



Optum Cancer Therapy Pathways Program

Effective Date: March 1, 2024

Optum is a registered trademark of Optum, Inc. in the U.S. and other jurisdictions. All other brand or product names are the property of their respective owners. Because we are continuously improving our products and services, Optum reserves the right to change specifications without prior notice. Optum is an equal opportunity employer.

© 2023 Optum, Inc. All rights reserved.

Table of contents

[Overview](#)

[B-Cell Lymphomas](#)

[Diffuse Large B-Cell Lymphoma](#)

[Follicular Lymphoma](#)

[Mantle Cell Lymphoma](#)

[Marginal Zone Lymphoma](#)

[Biliary Tract Cancers](#)

[Bladder Cancer](#)

[Breast Cancer](#)

[Colon/Rectal Cancer](#)

[Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma](#)

[Chronic Myeloid Leukemia](#)

[Esophageal Cancer](#)

[Gastric Cancer](#)

[Head and Neck Cancer](#)

[Hepatocellular Cancer](#)

[Hodgkin Lymphoma](#)

[Kidney Cancer](#)

[Non-Small Cell Lung Cancer](#)

[Melanoma](#)

[Multiple Myeloma](#)

[Ovarian, Fallopian and Primary Peritoneal Cancer](#)

[Pancreatic Cancer](#)

[Prostate Cancer](#)

[Small Cell Lung Cancer](#)

[Uterine \(Endometrial\) Cancer](#)

[Change Control](#)

Overview

Cancer Therapy Pathways Program

With the rapid approval of new therapies, along with the rising cost of cancer care, pathways serve a critical role in the delivery of high-quality and high-value cancer treatments while reducing an unwarranted variation in care.

The Optum Cancer Therapy Pathways Program aims to improve quality and value in cancer care by identifying anti-cancer regimens supported by evidence-based guidelines to help reduce total cost of care and improve outcomes.

The program's regimens are selected on the basis of clinical benefit (efficacy) and side-effect profile (toxicity). Among regimens with comparable efficacy and toxicity, additional consideration is given to the frequency of hospitalizations during therapy, duration of therapy, drug costs and total cost of care.

NOTE: This list of regimens and the drugs with in them are still subject to the relevant payer plan language and policy; inclusion here is not a guarantee that they will be authorized or reimbursed by an individual payer.

Care decisions are between the physician and the patient.

The Cancer Therapy Pathways Program is not a substitute for the experience and judgment of a physician or other health care professional. Any clinician participating in the program must use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. Care decisions are between the physician and patient.

B-Cell Lymphomas

Diffuse Large B-Cell Lymphoma (include histological transformation and follicular grade 3 (high-grade))**

1st Line of Therapy

- Rituximab-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
- Rituximab-mini-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)
- Rituximab-DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) (For Primary Mediastinal B-Cell Lymphoma (PMBCL) Only)

2nd + Subsequent Lines of Therapy

- Rituximab ± GDP (Gemcitabine, Dexamethasone, Cisplatin or Carboplatin)
- Rituximab ± ICE (Ifosfamide, Carboplatin, Etoposide)
- Rituximab ± DHAP (Dexamethasone, Cisplatin, Cytarabine)

Diffuse Large B-Cell Lymphoma with translocations of MYC and BCL2 and/or BCL6 (double-/triple-hit lymphoma)**

- Rituximab-DA-EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin)

***Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.*

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/dlbcl.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
3. Persky, D.O., Unger, J.M., Spier, C.M., et al. Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients with Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014. *J Clin Oncol* 2008;26:2258-2263
4. Coiffier, B., Thieblemont, C., Van Den Neste, E., et al. Long-Term Outcome of Patients in the LNH-98.5 Trial, the First Randomized Study Comparing Rituximab-CHOP to Standard CHOP Chemotherapy in DLBCL Patients: A Study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010;116:2040-2045
5. Feugier, P., Van Hoof, A., Sebban, C., et al. Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients with Diffuse Large B-Cell Lymphoma: A Study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005;23:4117-4126
6. Pfreundschuh, M., Trumper, L., Osterborg, A., et al. CHOP-Like Chemotherapy Plus Rituximab Versus CHOP-Like Chemotherapy Alone in Young Patients with Good-Prognosis Diffuse

- Large-B-Cell Lymphoma: A Randomised Controlled Trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7:379-391
7. Poeschel, V., Held, G., Ziepert, M., et al. Excellent Outcome of Young Patients (18–60 years) with Favorable Prognosis Diffuse Large B-Cell Lymphoma (DLBCL) Treated with 4 Cycles CHOP Plus 6 Applications of Rituximab: Results of the 592 Patients of the Flyer Trial of the DSHNHL/GLA. *Blood* 2018;132: Abstract 781
 8. Poeschel, V., Held, G., Ziepert, M., et al. Four Versus Six Cycles of CHOP Chemotherapy in Combination with Six Applications of Rituximab in Patients with Aggressive B-Cell Lymphoma with Favourable Prognosis (FLYER): A Randomized, Phase 3, Non-Inferiority Trial. *The Lancet* 2019;394:2271-2281
 9. Bartlett, N.L., Wilson, W.H., Jung, S.H., et al. Dose-Adjusted EPOCH-R Compared with R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. DOI: 10.1200/JCO.18.01994 *J Clin Oncol* 37, no. 21 (July 20, 2019) 1790–1799
 10. Purroy, N., Bergua, J., Gallur, L., et al. Long-Term Follow-Up of Dose-Adjusted EPOCH Plus Rituximab (DA- EPOCH-R) in Untreated Patients with Poor Prognosis Large B-Cell Lymphoma. A Phase II Study Conducted by the Spanish PETHEMA Group. *Br J Haematol* 2015;169:188-198
 11. Wilson, W.H., Dunleavy, K., Pittaluga, S., et al. Phase II Study of Dose-Adjusted EPOCH and Rituximab in Untreated Diffuse Large B-Cell Lymphoma with Analysis of Germinal Center and Post-Germinal Center Biomarkers. *J Clin Oncol* 2008;26:2717-2724
 12. Wilson, W.H., Jung, S.H., Porcu, P., et al. A Cancer and Leukemia Group B Multi-Center Study of DA-EPOCH-Rituximab in Untreated Diffuse Large B-Cell Lymphoma with Analysis of Outcome by Molecular Subtype. *Haematologica* 2012;97:758-765
 13. Dunleavy, K., Pittaluga, S., Maeda, L.S., et al. Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma. *N Engl J Med* 2013;368:1408-1416. Available at ncbi.nlm.nih.gov/pubmed/23574119
 14. Bartlett, N.L., Wilson, W.H., Jung, S.H., et al. Dose-Adjusted EPOCH-R Compared with R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. DOI: 10.1200/JCO.18.01994 *J Clin Oncol* 37, no. 21 (July 20, 2019) 1790-1799
 15. Martino, R., Perea, G., Caballero, M.D., et al. Cyclophosphamide, Pegylated Liposomal Doxorubicin (Caelyx), Vincristine and Prednisone (CCOP) in Elderly Patients with Diffuse Large B-Cell Lymphoma: Results From a Prospective Phase II Study. *Haematologica* 2002;87:822-827
 16. Zaja, F., Tomadini, V., Zaccaria, A., et al. CHOP-Rituximab with Pegylated Liposomal Doxorubicin for the Treatment of Elderly Patients with Diffuse Large B-Cell Lymphoma. *Leuk and Lymphoma* 2006;47:2174-2180
 17. Chao, N.J., Rosenberg, S.A., and Horning, S.J. CEPP(B): An Effective and Well-Tolerated Regimen in Poor- Risk, Aggressive Non-Hodgkin's Lymphoma. *Blood* 1990;76:1293-1298
 18. Moccia, A.A., Schaff, K., Hoskins, P., et al. R-CHOP with Etoposide Substituted for Doxorubicin (R-CEOP): Excellent Outcome in Diffuse Large B Cell Lymphoma for Patients with a Contraindication to Anthracyclines. *Blood* 2009; 114 (22): 408. DOI: DOI.org/10.1182/blood.V114.22.408.408
 19. Fields, P.A., Townsend, W., Webb, A., et al. De Novo Treatment of Diffuse Large B-Cell Lymphoma with Rituximab, Cyclophosphamide, Vincristine, Gemcitabine and Prednisolone in

- Patients with Cardiac Comorbidity: A United Kingdom National Cancer Research Institute trial. *J Clin Oncol* 2014;32:282-287
20. Peyrade, F., Jardin, F., Thieblemont, C., et al. Attenuated Immunochemotherapy Regimen (R-Mini CHOP) in Elderly Patients Older Than 80 Years with Diffuse Large B-Cell Lymphoma: A Multicentre, Single-Arm, Phase 2 Trial. *Lancet Oncol* 2011;12:460-468
 21. Peyrade, F., Fain, O., Fabiani, B., et al. Long-Term Follow-Up of the GELA LNH 03-7B Study: A Prospective Phase II Study of 150 Patients Over 80 Years with Diffuse Large B-Cell Lymphoma (DLBCL) Treated with RminiCHOP [abstract]. *J Clin Oncol* 2013;31(15_suppl): Abstract 8536
 22. Thieblemont, C., Tilly, H., Gomes da Silva, M., et al. Lenalidomide Maintenance Compared with Placebo in Responding Elderly Patients with Diffuse Large B-Cell Lymphoma Treated with First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone. *J Clin Oncol* 2017;35:2473-2481
 23. Crump, M., Kuruvilla, J., Couban, S., et al. Randomized Comparison of Gemcitabine, Dexamethasone and Cisplatin Versus Dexamethasone, Cytarabine and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12. *J Clin Oncol* 2014;32:3490-3496
 24. Gisselbrecht, C., Glass, B., Mounier, N., et al. Salvage Regimens with Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era. *J Clin Oncol*. 2010 Sep 20;28(27):4184-90. DOI: 10.1200/JCO.2010.28.1618. Epub 2010 Jul 26. Erratum in: *J Clin Oncol*. 2012 May 20;30(15):1896. PMID: 20660832; PMCID: PMC3664033
 25. Gisselbrecht, C., Schmitz, N., Mounier, N., et al. Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients with Relapsed CD20+ Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma. *J Clin Oncol* 2012;30:4462-4469
 26. Lignon, J., Sibon, D., Madelaine, I., et al. Rituximab, Dexamethasone, Cytarabine, and Oxaliplatin (R-DHAX) Is an Effective and Safe Salvage Regimen in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. *Clin Lymphoma Myeloma Leuk* 2010;10:262-269
 27. Rigacci, L., Fabbri, A., Puccini, B., et al. Oxaliplatin-Based Chemotherapy (Dexamethasone, High-Dose Cytarabine, and Oxaliplatin) +/- Rituximab Is an Effective Salvage Regimen in Patients with Relapsed or Refractory Lymphoma. *Cancer* 2010;116:4573-4579
 28. Crump, M., Kuruvilla, J., Couban, S., et al. Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12. *J Clin Oncol* 2014;32:3490-3496
 29. Gopal, A.K., Press, O.W., Shustov, A.R., et al. Efficacy and Safety of Gemcitabine, Carboplatin, Dexamethasone and Rituximab in Patients with Relapsed/Refractory Lymphoma: A Prospective Multi- Center Phase II Study by the Puget Sound Oncology Consortium. *Leuk Lymphoma* 2010;51:1523-1529
 30. Zelenetz, A.D., Hamlin, P., Kewalramani, T., et al. Ifosfamide, Carboplatin, Etoposide (ICE)-Based Second-Line Chemotherapy for the Management of Relapsed and Refractory Aggressive Non-Hodgkin's Lymphoma. *Ann Oncol*. 2003;14 Suppl 1:i5-10. DOI: 10.1093/annonc/mdg702. PMID: 12736224
 31. Kewalramani, T., Zelenetz, A.D., Nimer, S.D., et al. Rituximab and ICE (RICE) as Second-Line Therapy Prior to Autologous Stem Cell Transplantation for Relapsed or Primary Refractory Diffuse Large B-Cell Lymphoma. *Blood* 2004;103:3684-8

32. Velasquez, W.S., McLaughlin, P., Tucker, S., et al. ESHAP — an Effective Chemotherapy Regimen in Refractory and Relapsing Lymphoma: A 4-Year Follow-Up Study. *J Clin Oncol* 1994; 12:1169-1176
33. Martin, A., Conde, E., Arnan, M., et al. R-ESHAP as Salvage Therapy for Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The Influence of Prior Exposure to Rituximab on Outcome. A GEL/TAMO Study. *Haematologica* 2008;93:1829-1836
34. López, A., Gutiérrez, A., Palacios, A., et al. GEMOX-R Regimen Is a Highly Effective Salvage Regimen in Patients with Refractory/Relapsing Diffuse Large-Cell Lymphoma: A Phase II Study. *Eur J Haematol.* 2008 Feb;80(2):127-32. DOI: 10.1111/j.1600-0609.2007.00996.x. Epub 2007 Nov 20. PMID: 18005385
35. Mounier, N., El Gnaoui, T., Tilly, H., et al. Rituximab Plus Gemcitabine and Oxaliplatin in Patients with Refractory/Relapsed Diffuse Large B-Cell Lymphoma Who Are Not Candidates for High-Dose Therapy. A Phase II Lymphoma Study Association Trial. *Haematologica.* 2013 Nov;98(11):1726-31. DOI: 10.3324/haematol.2013.090597. Epub 2013 Jun 10. PMID: 23753028; PMCID: PMC3815173
36. Corazzelli, G., Capobianco, G., Arcamone, M., et al. Long-Term Results of Gemcitabine Plus Oxaliplatin with and without Rituximab as Salvage Treatment for Transplant-Ineligible Patients with Refractory/Relapsing B-Cell Lymphoma. *Cancer Chemother Pharmacol.* 2009 Oct;64(5):907-16. DOI: 10.1007/s00280-009-0941-9. Epub 2009 Feb 15. PMID: 19219604
37. Chang, S.H., Kim, Y.S., Eo, W.K. MINE (Mesna, Ifosfamide, Mitoxantrone, Etoposide) Chemotherapy as a Treatment of Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma. *Cancer Res Treat.* 2002 Apr;34(2):145-52. DOI: 10.4143/crt.2002.34.2.145. PMID: 26680856
38. Neelapu, S.S., Locke, F.L., Bartlett, N.L., et al. Axicabtagene Ciloleuce CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017;377:2531-2544
39. Locke, F.L., Ghobadi, A., Jacobson, C.A., et al. Long-Term Safety and Activity of Axicabtagene Ciloleuce in Refractory Large B-Cell Lymphoma (ZUMA-1): A Single-Arm, Multicentre, Phase 1-2 Trial. *Lancet Oncol* 2019;20:31-42
40. Schuster, S.J., Bishop, M.R., Tam, C.S., et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med* 2019;380:45-56
41. Bachanova, V., Westin, J., Tam, C. Correlative Analyses of Cytokine Release Syndrome and Neurological Events in Tisagenlecleucel-Treated Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients. Presented at: the SOHO 2019 Annual Meeting; Sept. 11–14, 2019; Houston, Texas. Abstract ABCL-278
42. Aribi, M., Mesli, N., Remla, N., et al. Gemcitabine and Treatment of Diffuse Large B-Cell Lymphoma in Relapsed or Refractory Elderly Patients: A Prospective Randomized Trial in Algeria. *J Cancer Res Ther.* 2010 Jan-Mar;6(1):41-6. DOI: 10.4103/0973-1482.63572. PMID: 20479546
43. Sehn, L.H., Herrera, A.F., Matasar, M.J., et al. Polatuzumab Vedotin (Pola) Plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase (Ph) Ib/II Study [abstract]. *Blood* 2018;132: Abstract 1683
44. Gutierrez, M., Chabner, B.A., Pearson, D., et al. Role of a Doxorubicin-Containing Regimen in Relapsed and Resistant Lymphomas: An 8-Year Follow-Up Study of EPOCH. *J Clin Oncol.* 2000 Nov 1;18(21):3633-42. DOI: 10.1200/JCO.2000.18.21.3633. PMID: 11054436

45. Jermann, M., Jost, L.M., Taverna, Ch., et al. Rituximab-EPOCH, an Effective Salvage Therapy for Relapsed, Refractory or Transformed B-Cell Lymphomas: Results of a Phase II Study. *Ann Oncol*. 2004 Mar;15(3):511-6. DOI: 10.1093/annonc/mdh093. PMID: 14998858
46. Coiffier, B., Haioun, C., Ketterer, N., et al. Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients with Relapsing or Refractory Aggressive Lymphoma: A Multicenter Phase II Study. *Blood*. 1998 Sep 15;92(6):1927-32. PMID: 9731049
47. Salles, G., et al. Tafasitamab Plus Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (L-MIND): A Multicentre, Prospective, Single-Arm, Phase 2 Study. *Lancet Oncol* 2020. Published online June 5, 2020
48. Jacobsen, E.D., Sharman, J.P., Oki, Y., et al. Brentuximab Vedotin Demonstrates Objective Responses in a Phase 2 Study of Relapsed/Refractory DLBCL with Variable CD30 Expression. *Blood* 2015;125:1394-1402
49. Weidmann, E., Kim, S.Z., Rost, A., et al. Bendamustine Is Effective in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma. *Ann Oncol* 2002;13:1285-1289
50. Vacirca, J.L., Acs, P.I., Tabbara, I.A., et al. Bendamustine Combined with Rituximab for Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma. *Ann Hematol* 2014;93:403-409
51. Ohmachi, K., Niitsu, N., Uchida, T., et al. Multicenter Phase II Study of Bendamustine Plus Rituximab in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2013;31:2103-2109
52. Wilson, W.H., Young, R.M., Schmitz, R., et al. Targeting B-Cell Receptor Signaling with Ibrutinib in Diffuse Large B Cell Lymphoma. *Nat Med* 2015;21:922-926
53. Wang, M., Fowler, N., Wagner-Bartak, N., et al. Oral Lenalidomide with Rituximab in Relapsed or Refractory Diffuse Large Cell, Follicular and Transformed Lymphoma: A Phase II Clinical Trial. *Leukemia* 2013;27:1902-1909
54. Czuczman, M.S., Trneny, M., Davies, A., et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Clin Cancer Res* 2017;23:4127-4137
55. Kalakonda, N., Maerevoet, M., Cavallo, F., et al. Selinexor in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (SADAL): A Single-Arm, Multinational, Multicentre, Open-Label, Phase 2 Trial. *Lancet Haematol*. 2020 Jul;7(7):e511-e522. DOI: 10.1016/S2352-3026(20)30120-4. PMID: 32589977
56. Cavallo, F., Follows, G.A., Goy, A., et al. Effect of Prior Therapy on the Efficacy and Safety of Oral Selinexor in Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): A Post-Hoc Analysis of the Sadal Study. *Blood* 2019; 134 (Supplement_1): Abstract 5333
57. Persky, D.O., Li, H., Stephens, D.M., et al. Positron Emission Tomography-Directed Therapy for Patients with Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001. *J Clin Oncol*. 2020 Sep 10;38(26):3003-3011. DOI: 10.1200/JCO.20.00999. Epub 2020 Jul 13. Erratum in: *J Clin Oncol*. 2020 Oct 10;38(29):3459. PMID: 32658627; PMCID: PMC7479758
58. Cazelles, C., Belhadj, K., Vellemans, H., et al. Rituximab Plus Gemcitabine and Oxaliplatin (R-GemOx) in Refractory/Relapsed Diffuse Large B-Cell Lymphoma: A Real-Life Study in Patients Ineligible for Autologous Stem-Cell Transplantation. *Leuk Lymphoma*. 2021 Sep;62(9):2161-2168. DOI: 10.1080/10428194.2021.1901090. Epub 2021 Mar 25. PMID: 33764240

59. Sehni, L.H., Herrera, A.F., Flowers, C.R., et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol*. 2020;38:155-165
60. Caimi, P.F., Ai, W., Alderuccio, J.P., et al. Loncastuximab Tesirine in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial. *Lancet Oncol*. 2021 Jun;22(6):790-800. DOI: 10.1016/S1470-2045(21)00139-X. Epub 2021 May 11. PMID: 33989558

Follicular Lymphoma (Grade 1–2)**

1st Line of Therapy

- Bendamustine + Rituximab (BR)

2nd + Subsequent Lines of Therapy (Non-Refractory Disease)

- Bendamustine + Rituximab (BR)
- CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab
- CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab
- Rituximab

2nd + Subsequent Lines of Therapy (Refractory Disease)

- Bendamustine + Obinutuzumab
- Bendamustine + Rituximab (BR)
- CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab
- CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab
- Rituximab

*** Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.*

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/follicular.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
3. Rummel, M.J., Niederle, N., Maschmeyer, G., et al. Bendamustine Plus Rituximab Versus CHOP Plus Rituximab as First-Line Treatment for Patients with Indolent and Mantle-Cell Lymphomas: An Open-Label, Multicentre, Randomised, Phase 3 Non-Inferiority Trial. *Lancet* 2013;381:1203-1210
4. Mathais, J., Rummel, Maschmeyer, G., et al. Bendamustine Plus Rituximab (B-R) Versus CHOP Plus Rituximab (CHOP-R) as First-Line Treatment in Patients with Indolent Lymphomas: Nine-Year Updated Results From the StiL NHL1 Study. *J Clin Oncol* 2017; 35, no. 15_suppl: 7501-7501. DOI: 10.1200/JCO.2017.35.15_suppl.7501
5. Flinn, I.W., van der Jagt, R., Kahl, B.S., et al. Open-Label, Randomized, Noninferiority Study of Bendamustine-Rituximab or R-CHOP/R-CVP in First-Line Treatment of Advanced Indolent NHL or MCL: The BRIGHT Study. *Blood* 2014;123:2944-2952
6. Flinn, I.W., van der Jagt, R., Kahl, B., et al. First-Line Treatment of Patients with Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma with Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *J Clin Oncol* 2019; 37: 984-991

7. Marcus, R., Davies, A., Ando, K., et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med* 2017;377:1331-1344
8. Czuczman, M.S., Weaver, R., Alkuzweny, B., et al. Prolonged Clinical and Molecular Remission in Patients with Low-Grade or Follicular Non-Hodgkin's Lymphoma Treated with Rituximab Plus CHOP Chemotherapy: 9-Year Follow-Up. *J Clin Oncol* 2004;22:4711-4716
9. Hiddemann, W., Kneba, M., Dreyling, M., et al. Frontline Therapy with Rituximab Added to the Combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) Significantly Improves the Outcome for Patients with Advanced-Stage Follicular Lymphoma Compared with Therapy with CHOP Alone: Results of a Prospective Randomized Study of the German Low-Grade Lymphoma Study Group. *Blood* 2005;106:3725-3732.
10. Marcus, R., Imrie, K., Solal-Celigny, P., et al. Phase III Study of R-CVP Compared with Cyclophosphamide, Vincristine and Prednisone Alone in Patients with Previously Untreated Advanced Follicular Lymphoma. *J Clin Oncol* 2008;26:4579-4586
11. Martin, P., Jung, S.H., Pitcher, B., et al. A Phase II Trial of Lenalidomide Plus Rituximab in Previously Untreated Follicular Non-Hodgkin's Lymphoma (NHL): CALGB 50803 (Alliance). *Ann Oncol* 2017;28:2806-2812
12. Fowler, N., Davis, R., Rawal, S., et al. Safety and Activity of Lenalidomide and Rituximab in Untreated Indolent Lymphoma: An Open-Label, Phase 2 Trial. *Lancet Oncol* 2014;15:1311-1318
13. Morschhauser, F., Fowler, N.H., Feugier, P., et al. Rituximab Plus Lenalidomide in Advanced Untreated Follicular Lymphoma. *N Engl J Med* 2018;379:934-947
14. Nastoupil, L.J., et al. Results of a Phase II Study of Obinutuzumab in Combination with Lenalidomide in Previously Untreated, High Tumor Burden Follicular Lymphoma (FL); 2019 Dec 7. Oral Abstract #125: 61st American Society of Hematology (ASH) Meeting & Exposition, Orlando, U.S.
15. Ghielmini, M., Schmitz, S.H., Cogliatti, S.B., et al. Prolonged Treatment with Rituximab in Patients with Follicular Lymphoma Significantly Increases Event-Free Survival and Response Duration Compared with the Standard Weekly x 4 Schedule. *Blood* 2004;103:4416-4423
16. Martinelli, G., Montoro, J., Vanazzi, A., et al. Chlorambucil-Rituximab as First-Line Therapy in Patients Affected by Follicular Non-Hodgkin's Lymphoma: A Retrospective Single-Centre Study. *Hematol Oncol*. 2015 Dec;33(4):129-35. DOI: 10.1002/hon.2154. Epub 2014 Jul 22. Erratum in: *Hematol Oncol*. 2016 Jun;34(2):117. PMID: 25047267
17. Scholz, C.W., Pinto, A., Linkesch, W., et al. (90)Yttrium-Ibritumomab-Tiuxetan as First-Line Treatment for Follicular Lymphoma: 30 Months of Follow-Up Data From an International Multicenter Phase II Clinical Trial. *J Clin Oncol* 2013;31:308-313
18. Bachy, E., Seymour, J.F., Feugier, P., et al. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients with Follicular Lymphoma: Long-Term Results of the PRIMA Study. *J Clin Oncol* 2019;37:2815-2824
19. Salles, G., Seymour, J.F., Fritz, O., et al. Rituximab Maintenance for 2 Years in Patients with High-Tumour Burden Follicular Lymphoma Responding to Rituximab Plus Chemotherapy (PRIMA): A Phase 3, Randomized Controlled Trial. *Lancet* 2011; 377: 42-51
20. Kahl, B.S., Hong, F., Williams, M.E., et al. Rituximab Extended Schedule or Re-Treatment Trial for Low-Tumor Burden Follicular Lymphoma: Eastern Cooperative Oncology Group Protocol E4402. *J Clin Oncol* 2014;32: 3096-3102
21. Morschhauser, F., Radford, J., Van Hoof, A., et al. 90Yttrium-Ibritumomab Tuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma:

- Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial. *J Clin Oncol* 2013;31:1977-1983
22. Cheson, B.D., Chua, N., Mayer, J., et al. Overall Survival Benefit in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. *J Clin Oncol* 2018 Aug 1;36(22):2259-2266. DOI: 10.1200/JCO.2017.76.3656. Epub 2018 Mar 27. PMID: 29584548
 23. Sakai, R., Ohmachi, K., Sano, F., et al. Bendamustine-120 Plus Rituximab Therapy for Relapsed or Refractory Follicular Lymphoma: A Multicenter Phase II Study. *Ann Hematol.* 2019 Sep;98(9):2131-2138. DOI: 10.1007/s00277-019-03750-7. Epub 2019 Jul 8. PMID: 31286196
 24. Rummel, M., Kaiser, U., Balsler, C., et al.; Study Group Indolent Lymphomas. Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab for Patients with Relapsed Indolent and Mantle-Cell Lymphomas: A Multicentre, Randomised, Open-Label, Non-Inferiority Phase 3 Trial. *Lancet Oncol.* 2016 Jan;17(1):57-66. DOI: 10.1016/S1470-2045(15)00447-7. Epub 2015 Dec 5. Erratum in: *Lancet Oncol.* 2016 Jan;17(1):e6. PMID: 26655425
 25. Robinson, K.S., Williams, M.E., van der Jagt, R.H., et al. Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients with Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma. *J Clin Oncol.* 2008 Sep 20;26(27):4473-9. DOI: 10.1200/JCO.2008.17.0001. Epub 2008 Jul 14. PMID: 18626004
 26. Radford, J., Davies, A., Cartron, G., et al. Obinutuzumab (GA101) Plus CHOP or FC in Relapsed/Refractory Follicular Lymphoma: Results of the GAUDI Study (BO21000). *Blood.* 2013 Aug 15;122(7):1137-43. DOI: 10.1182/blood-2013-01-481341. Epub 2013 Jul 10. PMID: 23843495
 27. van Oers, M.H., Van Glabbeke, M., Giurgea, L., et al. Rituximab Maintenance Treatment of Relapsed/Resistant Follicular Non-Hodgkin's Lymphoma: Long-Term Outcome of the EORTC 20981 Phase III Randomized Intergroup Study. *J Clin Oncol* 2010 Jun 10;28(17):2853-8. DOI: 10.1200/JCO.2009.26.5827. Epub 2010 May 3. PMID: 20439641; PMCID: PMC2903319
 28. Leonard, J.P., Jung, S.H., Johnson, J., et al. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients with Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). *J Clin Oncol* 2015;33:3635-3640
 29. Leonard, J.P., Trneny, M., Izutsu, K., et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2019;37:1188-1199
 30. Witzig, T.E., Gordon, L.I., Cabanillas, F., et al. Randomized Controlled Trial of Yttrium-90-Labeled Ibritumomab Tiuxetan Radioimmunotherapy Versus Rituximab Immunotherapy for Patients with Relapsed or Refractory Low-Grade, Follicular or Transformed B-Cell Non-Hodgkin's Lymphoma. *J Clin Oncol* 2002;20:2453-2463
 31. Witzig, T.E., Flinn, I.W., Gordon, L.I., et al. Treatment with Ibritumomab Tiuxetan Radioimmunotherapy in Patients with Rituximab-Refractory Follicular Non-Hodgkin's Lymphoma. *J Clin Oncol* 2002;20:3262-3269
 32. Witzig, T.E., Wiernik, P.H., Moore, T., et al. Lenalidomide Oral Monotherapy Produces Durable Responses in Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma. *J Clin Oncol* 2009;27:5404-5409
 33. Sacchi, S., Marcheselli, R., Bari, A., et al. Safety and Efficacy of Lenalidomide in Combination with Rituximab in Recurrent Indolent Non-Follicular Lymphoma: Final Results of a Phase II Study Conducted by the Fondazione Italiana Linfomi. *Haematologica.* 2016 May;101(5):e196-

9. DOI: 10.3324/haematol.2015.139329. Epub 2016 Feb 8. PMID: 26858355; PMCID: PMC5004354.
34. Morschhauser, F., Le Gouill, S., et al. Obinutuzumab Combined with Lenalidomide for Relapsed or Refractory Follicular B-Cell Lymphoma (GALEN): A Multicentre, Single-Arm, Phase 2 Study. *Lancet Haematol*. 2019 Aug;6(8):e429-e437. DOI: 10.1016/S2352-3026(19)30089-4. Epub 2019 Jul 8. PMID: 31296423
35. Coiffier, B., Osmanov, E.A., Hong, X., et al., LYM-3001 Study Investigators. Bortezomib Plus Rituximab Versus Rituximab Alone in Patients with Relapsed, Rituximab-Naive or Rituximab-Sensitive, Follicular Lymphoma: A Randomised Phase 3 Trial. *Lancet Oncol*. 2011 Aug;12(8):773-84. DOI: 10.1016/S1470-2045(11)70150-4. Epub 2011 Jul 1. PMID: 21724462
36. McLaughlin, P., Grillo-Lopez, A.J., Link, B.K., et al. Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program. *J Clin Oncol* 1998;16:2825-2833
37. Dreyling, M., Santoro, A., Mollica, L., et al. Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2017;35:3898-3905
38. Dreyling, M., Santoro, A., Mollica, L., et al. Long-Term Efficacy and Safety From the Copanlisib CHRONOS-1 Study in Patients with Relapsed or Refractory Indolent B-Cell Lymphoma. *Blood*. 2018;132:1595
39. Flinn, I., Miller, C., Ardesna, K., et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients with Refractory Indolent Non-Hodgkin Lymphoma. *J Clin Oncol* 2019;37:912-922
40. Gopal, A., Kahl, B., De Vos, S., et al. PI3K δ inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. *N Engl J Med* 2014;370:1008-1018
41. Salles, G., Schuster, S.J., de Vos, S., et al. Efficacy and Safety of Idelalisib in Patients with Relapsed, Rituximab- and Alkylating Agent-Refractory Follicular Lymphoma: A Subgroup Analysis of a Phase 2 Study. *Haematologica* 2017;102:e156-e159
42. Zinzani, P., Samaniego, F., Jurczak, W., et al. Umbralisib, the Once-Daily Dual Inhibitor of Pi3k δ and Casein Kinase-1 ϵ Demonstrates Clinical Activity in Patients with Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global UNITY-NHL Trial. *Blood*. 2020; 136 (suppl 1): 34-35. DOI: 10.1182/blood-2020-134851
43. Pastore, A., Jurinovic, V., Kridel, R., et al. Integration of Gene Mutations in Risk Prognostication for Patients Receiving First-Line Immunochemotherapy for Follicular Lymphoma: A Retrospective Analysis of a Prospective Clinical Trial and Validation in a Population-Based Registry. *Lancet Oncol*. 2015 Sep;16(9):1111-1122. DOI: 10.1016/S1470-2045(15)00169-2. Epub 2015 Aug 6. PMID: 26256760
44. Morschhauser, F., Tilly, H., Chaidos, A., et al. Phase 2 Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in Patients with Relapsed or Refractory Follicular Lymphoma [abstract]. *Blood* 2019;134:Abstract 123
45. Martinelli, G., Montoro, J., Vanazzi, A., et al. Chlorambucil-Rituximab as First-Line Therapy in Patients Affected by Follicular Non-Hodgkin's Lymphoma: A Retrospective Single-Centre Study. *Hematol Oncol*. 2015 Dec;33(4):129-35. DOI: 10.1002/hon.2154. Epub 2014 Jul 22. Erratum in: *Hematol Oncol*. 2016 Jun;34(2):117. PMID: 25047267
46. Bassi, S., Nassi, L., Pruneri, G., et al. Rituximab and Chlorambucil as Front-Line Treatment in Untreated Follicular Lymphoma: A Combination with a Durable Response and Low Toxicity Profile. *Blood*. 2009; 114 (22): 3754. DOI: DOI.org/10.1182/blood.V114.22.3754.3754
47. Forstpointner, R., Unterhalt, M., Dreyling, M., et al. German Low-Grade Lymphoma Study Group (GLSG). Maintenance Therapy with Rituximab Leads to a Significant Prolongation of Response Duration After Salvage Therapy with a Combination of Rituximab, Fludarabine,

- Cyclophosphamide and Mitoxantrone (R-FCM) in Patients with Recurring and Refractory Follicular and Mantle Cell Lymphomas: Results of a Prospective Randomized Study of the German Low-Grade Lymphoma Study Group (GLSG). *Blood*. 2006 Dec 15;108(13):4003-8. DOI: 10.1182/blood-2006-04-016725. Epub 2006 Aug 31. PMID: 16946304
48. Hainsworth, J.D., Litchy, S., Shaffer, D.W., et al. Maximizing Therapeutic Benefit of Rituximab: Maintenance Therapy Versus Re-Treatment at Progression in Patients with Indolent Non-Hodgkin's Lymphoma: A Randomized Phase II Trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2005 Feb. 20;23(6):1088-95. DOI: 10.1200/JCO.2005.12.191. Epub 2005 Jan 18. PMID: 15657401
 49. Sehn, L.H., Chua, N., Mayer, J., et al. Obinutuzumab Plus Bendamustine Versus Bendamustine Monotherapy in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma (GADOLIN): A Randomised, Controlled, Open-Label, Multicentre, Phase 3 Trial. *Lancet Oncol* 2016;17:1081-1093
 50. Casulo, C., Byrtek, M., Dawson, K.L., et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *J Clin Oncol*. 2015 Aug 10;33(23):2516-22. DOI: 10.1200/JCO.2014.59.7534. Epub 2015 Jun 29. Erratum in: *J Clin Oncol* 2016 Apr 20;34(12):1430. Erratum in: *J Clin Oncol*. 2016 Apr 20;34(12):1430. PMID: 26124482; PMCID: PMC4879714
 51. Townsend, W., Buske, C., Cartron, G., et al. Comparison of Efficacy and Safety with Obinutuzumab Plus Chemotherapy Versus Rituximab Plus Chemotherapy in Patients with Previously Untreated Follicular Lymphoma: Updated Results From the Phase III Gallium Study. *J Clin Oncol* 2020; 38: 8023-8023
 52. Fowler, N.H., Samaniego, F., Jurczak, W., et al. Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients with Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2021 May 20;39(15):1609-1618. DOI: 10.1200/JCO.20.03433. Epub 2021 Mar 8. PMID: 33683917; PMCID: PMC8148421
 53. Morschhauser, F., Tilly, H., Chaidos, A., et al. Tazemetostat for Patients with Relapsed or Refractory Follicular Lymphoma: An Open-Label, Single-Arm, Multicentre, Phase 2 Trial. *Lancet Oncol*. 2020 Nov;21(11):1433-1442. DOI: 10.1016/S1470-2045(20)30441-1. Epub 2020 Oct 6. PMID: 33035457; PMCID: PMC8427481

Mantle Cell Lymphoma**

1st Line of Therapy

- Alternating RCHOP/RDHAP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)/(Rituximab, Dexamethasone, Cytarabine, Cisplatin)
- Nordic Regimen (Dose-Intensified Induction Immunochemotherapy with Rituximab + Cyclophosphamide, Vincristine, Doxorubicin, Prednisone [Maxi-CHOP]) Alternating with Rituximab + High-Dose Cytarabine
- Hyper-CVAD (Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone Alternating with High-Dose Methotrexate and Cytarabine) + Rituximab
- Bendamustine + Rituximab
- VR-CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone)

Maintenance After 1st Line of Therapy

- Rituximab (after HDT/ASCR only)

2nd Line of Therapy

- Bendamustine + Rituximab (BR)
- Acalabrutinib
- Ibrutinib
- Zanubrutinib

3rd + Subsequent Lines of Therapy

- Bendamustine + Rituximab (BR)
- Acalabrutinib
- Ibrutinib
- Zanubrutinib
- Lenalidomide

** Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.

References:

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
2. Le Gouill, et al. Rituximab After Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med.* 2017;377:1250-1260. DOI: 10.1056/NEJMoa1701769
3. Hermine, O., Hoster, E., Walewski, J., et al. European Mantle Cell Lymphoma Network. Addition of High-Dose Cytarabine to Immunochemotherapy Before Autologous Stem-Cell Transplantation in Patients Aged 65 Years or Younger with Mantle Cell Lymphoma (MCL

- Younger): A Randomised, Open-Label, Phase 3 Trial of the European Mantle Cell Lymphoma Network. *Lancet*. 2016 Aug 6;388(10044):565-75. DOI: 10.1016/S0140-6736(16)00739-X. Epub 2016 Jun 14. PMID: 27313086
4. Romaguera, J.E., Fayad, L., Rodriguez, M.A., et al. High Rate of Durable Remissions After Treatment of Newly Diagnosed Aggressive Mantle-Cell Lymphoma with Rituximab Plus Hyper-CVAD Alternating with Rituximab Plus High-Dose Methotrexate and Cytarabine. *J Clin Oncol*. 2005 Oct 1;23(28):7013-23. DOI: 10.1200/JCO.2005.01.1825. Epub 2005 Sep 6. Erratum in: *J Clin Oncol* 2006 Feb 1;24(4):724. PMID: 16145068
 5. Merli, F., Luminari, S., Ilariucci, F., et al. Rituximab Plus Hyper CVAD Alternating with High-Dose Cytarabine and Methotrexate for the Initial Treatment of Patients with Mantle Cell Lymphoma, A Multicentre Trial From Gruppo Italiano Studio Linfomi. *Br J Haematol*. 2012 Feb;156(3):346-53. DOI: 10.1111/j.1365-2141.2011.08958.x. Epub 2011 Dec 7. PMID: 22145911
 6. Geisler, et al. Long-Term Progression-Free Survival of Mantle Cell Lymphoma After Intensive Front-Line Immunochemotherapy within Vivo-Purged Stem Cell Rescue: A Nonrandomized Phase 2 Multicenter Study by the Nordic Lymphoma Group. *Blood*. (2008) 112 (7): 2687–2693. <https://DOI.org/10.1182/blood-2008-03-147025>
 7. Eskelund, C.W., Kolstad, A., Jerkeman, M., et al. 15-Year Follow-Up of the Second Nordic Mantle Cell Lymphoma Trial (MCL2): Prolonged Remissions without Survival Plateau. *Br J Haematol*. 2016 Nov;175(3):410-418. DOI: 10.1111/bjh.14241. Epub 2016 Jul 5. PMID: 27378674
 8. Merryman, et al. Rituximab/Bendamustine and Rituximab/Cytarabine Induction Therapy for Transplant-Eligible Mantle Cell Lymphoma. *Blood Adv*. (2020) 4 (5): 858–867. Retrieved from DOI.org/10.1182/bloodadvances.2019001355
 9. Rummel, M.J., Niederle, N., Maschmeyer, G., et al. Bendamustine Plus Rituximab Versus CHOP Plus Rituximab as First-Line Treatment for Patients with Indolent and Mantle-Cell Lymphomas: An Open-Label, Multicentre, Randomised, Phase 3 Non-Inferiority Trial. *Lancet* 2013;381:1203-1210
 10. Mathais, J., Rummel, Maschmeyer, G., et al. Bendamustine Plus Rituximab (B-R) Versus CHOP Plus Rituximab (CHOP-R) as First-Line Treatment in Patients with Indolent Lymphomas: Nine-Year Updated Results from the Stil NHL1 Study. *J Clin Oncol*. 2017; 35, no. 15_suppl: 7501-7501. DOI: 10.1200/JCO.2017.35.15_suppl.7501
 11. Flinn, I.W., van der Jagt, R., Kahl, B.S., et al. Open-Label, Randomized, Noninferiority Study of Bendamustine-Rituximab or R-CHOP/R-CVP in First-Line Treatment of Advanced Indolent NHL or MCL: The BRIGHT Study. *Blood*. 2014;123:2944-2952
 12. Flinn, I.W., van der Jagt, R., Kahl, B., et al. First-Line Treatment of Patients with Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma with Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *J Clin Oncol*. 2019; 37: 984-991
 13. Robak, T., Huang, H., Jin, J., et al., LYM-3002 Investigators. Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma. *N Engl J Med*. 2015 Mar 5;372(10):944-53. DOI: 10.1056/NEJMoa1412096. PMID: 25738670
 14. Robak, T., Jin, J., Pylypenko, H., et al., LYM-3002 investigators. Frontline Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (VR-CAP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) in Transplantation-Ineligible Patients with Newly Diagnosed Mantle Cell Lymphoma: Final Overall Survival Results of a Randomised, Open-Label, Phase 3 Study. *Lancet Oncol*. 2018 Nov;19(11):1449-1458. DOI: 10.1016/S1470-2045(18)30685-5. Epub 2018 Oct 19.

15. Ruan, J., Martin, P., Shah, B., et al. Lenalidomide Plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma. *N Engl J Med*. 2015 Nov 5;373(19):1835-44. DOI: 10.1056/NEJMoa1505237. PMID: 26535512; PMCID: PMC4710541
16. Ruan, J., Martin, P., Christos, P., et al. Five-Year Follow-Up of Lenalidomide Plus Rituximab as Initial Treatment of Mantle Cell Lymphoma. *Blood*. 2018 Nov 8;132(19):2016-2025. DOI: 10.1182/blood-2018-07-859769. Epub 2018 Sep 4. PMID: 30181173; PMCID: PMC6634960
17. Kahl, B.S., Longo, W.L., Eickhoff, J.C., et al., Wisconsin Oncology Network. Maintenance Rituximab Following Induction Chemoimmunotherapy May Prolong Progression-Free Survival In Mantle Cell Lymphoma: A Pilot Study From the Wisconsin Oncology Network. *Ann Oncol*. 2006 Sep;17(9):1418-23. DOI: 10.1093/annonc/mdl127. Epub 2006 Jun 9. PMID: 16766582
18. Visco, C., Finotto, S., Zambello, R., et al. Combination of Rituximab, Bendamustine and Cytarabine for Patients with Mantle-Cell Non-Hodgkin Lymphoma Ineligible for Intensive Regimens or Autologous Transplantation. *J Clin Oncol*. 2013 Apr 10;31(11):1442-9. DOI: 10.1200/JCO.2012.45.9842. Epub 2013 Feb 11. PMID: 23401442
19. Visco, C., Chiappella, A., Nassi, L., et al. Rituximab, Bendamustine and Low-Dose Cytarabine as Induction Therapy in Elderly Patients with Mantle Cell Lymphoma: A Multicentre, Phase 2 Trial From Fondazione Italiana Linfomi. *Lancet Haematol*. 2017 Jan;4(1):e15-e23. DOI: 10.1016/S2352-3026(16)30185-5. Epub 2016 Dec 5. PMID: 27927586
20. Wang, M., Rule, S., Zinzani, P.L., et al. Acabrutinib in Relapsed or Refractory Mantle Cell Lymphoma (ACE-LY-004): A Single-Arm, Multicentre, Phase 2 Trial. *Lancet*. 2018 Feb 17;391(10121):659-667. DOI: 10.1016/S0140-6736(17)33108-2. Epub 2017 Dec 11. PMID: 29241979; PMCID: PMC7864374
21. Wang, M., Rule, S., Zinzani, P.L., et al. Long-Term Follow-up of Acabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma. *Blood*. 2018; 132 (Supplement 1): 2876. DOI: DOI.org/10.1182/blood-2018-99-110327
22. Wang, M.L., Rule, S., Martin, P., et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2013;369(6):507-516
23. Wang, M.L., Blum, K.A., Martin, P., et al. Long-Term Follow-Up of MCL Patients Treated with Single-Agent Ibrutinib: Updated Safety and Efficacy Results. *Blood*. 2015;126(6):739-745
24. Dreyling, M., Jurczak, W., Jerkeman, M., et al. Ibrutinib Versus Temsirolimus in Patients with Relapsed or Refractory Mantle-Cell Lymphoma: An International, Randomised, Open-Label, Phase 3 Study. *Lancet*. 2016 Feb 20;387(10020):770-8. DOI: 10.1016/S0140-6736(15)00667-4. Epub 2015 Dec 7. Erratum in: *Lancet*. 2016 Feb 20;387(10020):750. PMID: 26673811
25. Rule, S., Jurczak, W., Jerkeman, M., et al. Ibrutinib Versus Temsirolimus: 3-Year Follow-Up of Patients with Previously Treated Mantle Cell Lymphoma From the Phase 3, International, Randomized, Open-Label RAY Study. *Leukemia*. 2018 Aug;32(8):1799-1803. DOI: 10.1038/s41375-018-0023-2. Epub 2018 Feb 2. PMID: 29572505; PMCID: PMC6087720
26. Wang, M.L., Lee, H., Chuang, H., et al. Ibrutinib in Combination with Rituximab in Relapsed or Refractory Mantle Cell Lymphoma: A Single-Centre, Open-Label, Phase 2 Trial. *Lancet Oncol*. 2016 Jan;17(1):48-56. DOI: 10.1016/S1470-2045(15)00438-6. Epub 2015 Nov 28. PMID: 26640039
27. Jain, P., Romaguera, J., Srour, S.A., et al. Four-Year Follow-Up of a Single-Arm, Phase II Clinical Trial of Ibrutinib with Rituximab (IR) in Patients with Relapsed/Refractory Mantle Cell Lymphoma (MCL). *Br J Haematol*. 2018 Aug;182(3):404-411. DOI: 10.1111/bjh.15411. Epub 2018 May 22. PMID: 29785709
28. Song, Y., Zhou, K., Zou, D., et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. *Clin*

- Cancer Res.* 2020 Aug 15;26(16):4216-4224. DOI: 10.1158/1078-0432.CCR-19-3703. Epub 2020 May 27. PMID: 32461234
29. Habermann, T.M., Lossos, I.S., Justice, G., et al. Lenalidomide Oral Monotherapy Produces a High Response Rate in Patients with Relapsed or Refractory Mantle Cell Lymphoma. *Br J Haematol.* 2009 May;145(3):344-9. DOI: 10.1111/j.1365-2141.2009.07626.x. Epub 2009 Feb 24. PMID: 19245430
 30. Goy, A., Sinha, R., Williams, M.E., et al. Single-Agent Lenalidomide in Patients with Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study. *J Clin Oncol.* 2013 Oct 10;31(29):3688-95. DOI: 10.1200/JCO.2013.49.2835. Epub 2013 Sep 3. PMID: 24002500; PMCID: PMC4879693
 31. Zinzani, P.L., Vose, J.M., Czuczman, M.S., et al. Long-Term Follow-Up of Lenalidomide in Relapsed/Refractory Mantle Cell Lymphoma: Subset Analysis of the NHL-003 Study. *Ann Oncol.* 2013 Nov;24(11):2892-7. DOI: 10.1093/annonc/mdt366. Epub 2013 Sep 12. PMID: 24030098; PMCID: PMC3811905
 32. Trněný, M., Lamy, T., Walewski, J., et al., SPRINT Trial Investigators and in Collaboration with the European Mantle Cell Lymphoma Network. Lenalidomide Versus Investigator's Choice in Relapsed or Refractory Mantle Cell Lymphoma (MCL-002; SPRINT): A Phase 2, Randomised, Multicentre Trial. *Lancet Oncol.* 2016 Mar;17(3):319-331. DOI: 10.1016/S1470-2045(15)00559-8. Epub 2016 Feb 16. PMID: 26899778
 33. Wang, M., Schuster, S.J., Phillips, T., et al. Observational Study of Lenalidomide in Patients with Mantle Cell Lymphoma Who Relapsed/Progressed After or Were Refractory/Intolerant to Ibrutinib (MCL-004). *J Hematol Oncol.* 2017 Nov 2;10(1):171. DOI: 10.1186/s13045-017-0537-5. PMID: 29096668; PMCID: PMC5668956
 34. Wang, M., Fayad, L., Wagner-Bartak, N., et al. Lenalidomide in Combination with Rituximab for Patients with Relapsed or Refractory Mantle-Cell Lymphoma: A Phase 1/2 Clinical Trial. *Lancet Oncol.* 2012 Jul;13(7):716-23. DOI: 10.1016/S1470-2045(12)70200-0. Epub 2012 Jun 6. PMID: 22677155
 35. Robinson, K.S., Williams, M.E., van der Jagt, R.H., et al. Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients with Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma. *J Clin Oncol.* 2008 Sep 20;26(27):4473-9. DOI: 10.1200/JCO.2008.17.0001. Epub 2008 Jul 14. PMID: 18626004
 36. Rummel, M.J., Al-Batran, S.E., Kim, S.Z., et al. Bendamustine Plus Rituximab Is Effective and Has a Favorable Toxicity Profile in the Treatment of Mantle Cell and Low-Grade Non-Hodgkin's Lymphoma. *J Clin Oncol.* 2005 May 20;23(15):3383-9. DOI: 10.1200/JCO.2005.08.100. PMID: 15908650

37. Rummel, M., Kaiser, U., Balsler, C., et al., Study Group Indolent Lymphomas. Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab for Patients with Relapsed Indolent and Mantle-Cell Lymphomas: A Multicentre, Randomised, Open-Label, Non-Inferiority Phase 3 Trial. *Lancet Oncol.* 2016 Jan;17(1):57-66. DOI: 10.1016/S1470-2045(15)00447-7. Epub 2015 Dec 5. Erratum in: *Lancet Oncol.* 2016 Jan;17(1):e6. PMID: 26655425
38. Visco, C., Finotto, S., Zambello, R., et al. Combination of Rituximab, Bendamustine and Cytarabine for Patients with Mantle-Cell Non-Hodgkin Lymphoma Ineligible for Intensive Regimens or Autologous Transplantation. *J Clin Oncol.* 2013 Apr 10;31(11):1442-9. DOI: 10.1200/JCO.2012.45.9842. Epub 2013 Feb 11. PMID: 23401442
39. Goy, A., Younes, A., McLaughlin, P., et al. Phase II Study of Proteasome Inhibitor Bortezomib in Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma. *J Clin Oncol.* 2005 Feb 1;23(4):667-75. DOI: 10.1200/JCO.2005.03.108. Epub 2004 Dec 21. PMID: 15613697
40. Goy, A., Bernstein, S.H., Kahl, B.S., et al. Bortezomib in Patients with Relapsed or Refractory Mantle Cell Lymphoma: Updated Time-to-Event Analyses of the Multicenter Phase 2 PINNACLE Study. *Ann Oncol.* 2009 Mar;20(3):520-5. DOI: 10.1093/annonc/mdn656. Epub 2008 Dec 12. PMID: 19074748; PMCID: PMC4592328
41. Fisher, R.I., Bernstein, S.H., Kahl, B.S., et al. Multicenter Phase II Study of Bortezomib in Patients with Relapsed or Refractory Mantle Cell Lymphoma. *J Clin Oncol.* 2006 Oct 20;24(30):4867-74. DOI: 10.1200/JCO.2006.07.9665. Epub 2006 Sep 25. PMID: 17001068
42. Agathocleous, A., Rohatiner, A., Rule, S., et al. Weekly Versus Twice Weekly Bortezomib Given in Conjunction with Rituximab, in Patients with Recurrent Follicular Lymphoma, Mantle Cell Lymphoma and Waldenström Macroglobulinaemia. *Br J Haematol.* 2010 Nov;151(4):346-53. DOI: 10.1111/j.1365-2141.2010.08340.x. Epub 2010 Sep 29. PMID: 20880120
43. Baiocchi, R.A., Alinari, L., Lustberg, M.E., et al. Phase 2 Trial of Rituximab and Bortezomib in Patients with Relapsed or Refractory Mantle Cell and Follicular Lymphoma. *Cancer.* 2011 Jun 1;117(11):2442-51. DOI: 10.1002/cncr.25792. Epub 2010 Dec 14. PMID: 24048792; PMCID: PMC3116936
44. Lamm, W., Kaufmann, H., Raderer, M., et al. Bortezomib Combined with Rituximab and Dexamethasone Is an Active Regimen for Patients with Relapsed and Chemotherapy-Refractory Mantle Cell Lymphoma. *Haematologica.* 2011 Jul;96(7):1008-14. DOI: 10.3324/haematol.2011.041392. Epub 2011 Apr 12. PMID: 21486866; PMCID: PMC3128220
45. Lignon, J., Sibon, D., Madelaine, I., et al. Rituximab, Dexamethasone, Cytarabine and Oxaliplatin (R-DHAX) Is an Effective and Safe Salvage Regimen in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. *Clin Lymphoma Myeloma Leuk.* 2010;10:262-269
46. Rodríguez, J., Gutierrez, A., Palacios, A., et al. Rituximab, Gemcitabine and Oxaliplatin: An Effective Regimen in Patients with Refractory and Relapsing Mantle Cell Lymphoma. *Leuk Lymphoma.* 2007 Nov;48(11):2172-8. DOI: 10.1080/10428190701618268. PMID: 17990179
47. Gironella, M., Lopez, A., Merchan, B., et al. Rituximab Plus Gemcitabine and Oxaliplatin as Salvage Therapy in Patients with Relapsed/Refractory Mantle-Cell Lymphoma. *Blood.* 2012; 120 (21): 1627. DOI: <https://doi.org/10.1182/blood.V120.21.1627.1627>
48. Jerkeman, M., Eskelund, C.W., Hutchings, M., et al. Ibrutinib, Lenalidomide, and Rituximab in Relapsed or Refractory Mantle Cell Lymphoma (PHILEMON): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial. *Lancet Haematol.* 2018 Mar;5(3):e109-e116. DOI: 10.1016/S2352-3026(18)30018-8. Epub 2018 Jan 29. PMID: 29396091
49. Tam, C.S., Anderson, M.A., Pott, C., et al. Ibrutinib Plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. *N Engl J Med.* 2018 Mar 29;378(13):1211-1223. DOI: 10.1056/NEJMoa1715519. PMID: 29590547

50. Davids, M.S., Roberts, A.W., Seymour, J.F., et al. Phase I First In-Human Study of Venetoclax in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma. *J Clin Oncol*. 2017 Mar 10;35(8):826-833. DOI: 10.1200/JCO.2016.70.4320. Epub 2017 Jan 17. PMID: 28095146; PMCID: PMC5455685
51. Le Gouill, et al. Rituximab After Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med*. 2017;377:1250-1260. DOI: 10.1056/NEJMoa1701769
52. Kluijn-Nelemans, H.C., Hoster, E., Hermine, O., et al. Treatment of Older Patients with Mantle-Cell Lymphoma. *N Engl J Med*. 2012 Aug 9;367(6):520-31. DOI: 10.1056/NEJMoa1200920. PMID: 22873532
53. Kahl, B.S., Longo, W.L., Eickhoff, J.C., et al., Wisconsin Oncology Network. Maintenance Rituximab Following Induction Chemoimmunotherapy May Prolong Progression-Free Survival in Mantle Cell Lymphoma: A Pilot Study from the Wisconsin Oncology Network. *Ann Oncol*. 2006 Sep;17(9):1418-23. DOI: 10.1093/annonc/mdl127. Epub 2006 Jun 9. PMID: 16766582
54. Kenkre, V., Long, W., Eickhoff, J., et al. Maintenance Rituximab Following Induction Chemo-Immuno-therapy for Mantle Cell Lymphoma: Long-Term Follow-Up of a Pilot Study from the Wisconsin Oncology Network. *Leuk Lymphoma*. 2011;52(9): 1675–1680
55. Rummel, M.J., Knauf, W., Goerner, M., et al. Two Years Rituximab Maintenance Vs. Observation After First-Line Treatment with Bendamustine Plus Rituximab (BR) in Patients with Mantle Cell Lymphoma: First Results of a Prospective, Randomized, Multicenter Phase II Study (a Subgroup Study of the StiL NHL7-2008 MAINTAIN Trial) [Abstract]. *J Clin Oncol*. 2016; 34: abstract 7503
56. Klener, P., Salek, D., Pytlik, R., et al. Rituximab Maintenance Significantly Prolongs Progression-Free Survival of Patients with Newly Diagnosed Mantle Cell Lymphoma Treated with the Nordic MCL2 Protocol and Autologous Stem Cell Transplantation. *Am J Hematol*. 2019 Feb;94(2):E50-E53. DOI: 10.1002/ajh.25362. Epub 2018 Dec 13. PMID: 30474171
57. Hermine, O., Hoster, E., Walewski, J., et al. European Mantle Cell Lymphoma Network. Addition of High-Dose Cytarabine to Immunochemotherapy Before Autologous Stem-Cell Transplantation in Patients Aged 65 Years or Younger with Mantle Cell Lymphoma (MCL Younger): A Randomised, Open-Label, Phase 3 Trial of the European Mantle Cell Lymphoma Network. *Lancet*. 2016 Aug 6;388(10044):565-75. DOI: 10.1016/S0140-6736(16)00739-X. Epub 2016 Jun 14. PMID: 27313086
58. Robak, T., Jin, J., Pylypenko, H., et al. Frontline Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (VR-CAP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) in Transplantation-Ineligible Patients with Newly Diagnosed Mantle Cell Lymphoma: Final Overall Survival Results of a Randomized, Open-Label, Phase 3 Study. *Lancet Oncol*. 2018; 19(11):1449-1458
59. Doorduijn, J.K., Zijlstra, J.M., Lugtenburg, P.J., et al. Bortezomib Maintenance After R-CHOP, Cytarabine and Autologous Stem Cell Transplantation in Newly Diagnosed Patients with Mantle Cell Lymphoma, Results of a Randomised Phase II HOVON Trial. *Br J Haematol*. 2020 Aug;190(3):385-393. DOI: 10.1111/bjh.16567. Epub 2020 Mar 9. PMID: 32150297; PMCID: PMC7496560

Marginal Zone Lymphoma**

1st Line of Therapy

- Helicobacter Pylori (H. pylori) Eradication Therapy (Gastric MALT Lymphoma Only)
- Bendamustine + Rituximab (BR)
- Chlorambucil ± Rituximab
- Rituximab (weekly for 4 doses)

2nd + Subsequent Lines of Therapy (Non-Refractory Disease)

- Bendamustine + Rituximab (BR)
- CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab
- CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab
- Chlorambucil ± Rituximab
- Rituximab (Weekly for 4 Doses)

2nd Line of Therapy (Refractory Disease)

- Bendamustine + Obinutuzumab
- Bendamustine + Rituximab (BR)
- CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) + Rituximab
- CVP (Cyclophosphamide, Vincristine, Prednisone) + Rituximab
- Chlorambucil ± Rituximab
- Rituximab (Weekly for 4 Doses)

*** Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.*

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd5327/
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.

3. Andriani, A., Miedico, A., Tedeschi, L., et al. Management and Long-Term Follow-Up of Early Stage H. Pylori-Associated Gastric MALT-Lymphoma in Clinical Practice: An Italian, Multicentre Study. *Dig Liver Dis*. 2009 Jul;41(7):467-73. DOI: 10.1016/j.dld.2008.09.009. Epub 2008 Oct 21. PMID: 18945654
4. Nakamura, S., Sugiyama, T., Matsumoto, T., et al.; JAPAN GAST Study Group. Long-Term Clinical Outcome of Gastric MALT Lymphoma After Eradication of Helicobacter Pylori: A Multicentre Cohort Follow-Up Study of 420 Patients in Japan. *Gut*. 2012 Apr;61(4):507-13. DOI: 10.1136/gutjnl-2011-300495. Epub 2011 Sep 2. PMID: 21890816
5. Wündisch, T., Thiede, C., Morgner, A., et al. Long-Term Follow-Up of Gastric MALT Lymphoma After Helicobacter Pylori Eradication. *J Clin Oncol*. 2005 Nov 1;23(31):8018-24. DOI: 10.1200/JCO.2005.02.3903. Epub 2005 Oct 3. PMID: 16204012
6. Stathis, A., Chini, C., Bertoni, F., et al. Long-Term Outcome Following Helicobacter Pylori Eradication in a Retrospective Study of 105 Patients with Localized Gastric Marginal Zone B-Cell Lymphoma of MALT Type. *Ann Oncol*. 2009 Jun;20(6):1086-93. DOI: 10.1093/annonc/mdn760. Epub 2009 Feb 4. PMID: 19193705
7. Avilés, A., Nambo, M.J., Neri, N., et al. Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma of the Stomach: Results of a Controlled Clinical Trial. *Med Oncol*. 2005;22(1):57-62. DOI: 10.1385/MO:22:1:057. PMID: 15750197
8. Zullo, A., Hassan, C., Cristofari, F., et al. Effects of Helicobacter Pylori Eradication on Early-Stage Gastric Mucosa-Associated Lymphoid Tissue Lymphoma. *Clin Gastroenterol Hepatol*. 2010 Feb;8(2):105-10. DOI: 10.1016/j.cgh.2009.07.017. Epub 2009 Jul 22. PMID: 19631287
9. Rummel, M.J., Niederle, N., Maschmeyer, G., et al. Bendamustine Plus Rituximab Versus CHOP Plus Rituximab as First-Line Treatment for Patients with Indolent and Mantle-Cell Lymphomas: An Open-Label, Multicentre, Randomised, Phase 3 Non-Inferiority Trial. *Lancet* 2013;381:1203-1210
10. Rummel, M.J., Maschmeyer, G., Ganser, A., et al. Bendamustine Plus Rituximab (B-R) Versus CHOP Plus Rituximab (CHOP-R) as First-Line Treatment in Patients with Indolent Lymphomas: Nine-Year Updated Results From the Stii NHL1 Study. *J of Clin Oncol*. 2017; 35, no. 15_suppl: 7501-7501. DOI: 10.1200/JCO.2017.35.15_suppl.7501
11. Flinn, I.W., van der Jagt, R., Kahl, B.S., et al. Open-Label, Randomized, Noninferiority Study of Bendamustine-Rituximab or R-CHOP/R-CVP in First-Line Treatment of Advanced Indolent NHL Or MCL: The BRIGHT Study. *Blood*. 2014;123:2944-2952
12. Flinn, I.W., van der Jagt, R., Kahl, B., et al. First-Line Treatment of Patients with Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma with Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *J Clin Oncol*. 2019; 37: 984-991
13. Salar, A., Domingo-Domenech, E., Panizo, C., et al. Long-Term Results of a Phase 2 Study of Rituximab and Bendamustine for Mucosa-Associated Lymphoid Tissue Lymphoma. *Blood*. 2017. 130(15): 1772-1774
14. Tsimberidou, A.M., Catovsky, D., Schlette, E., et al. Outcomes in Patients with Splenic Marginal Zone Lymphoma and Marginal Zone Lymphoma Treated with Rituximab with or without Chemotherapy or Chemotherapy Alone. *Cancer*. 2006 Jul 1;107(1):125-35. DOI: 10.1002/cncr.21931. PMID: 16700034
15. Else, M., Marín-Niebla, A., de la Cruz, F., et al. Rituximab, Used Alone or in Combination, Is Superior to Other Treatment Modalities in Splenic Marginal Zone Lymphoma. *Br J Haematol*. 2012 Nov;159(3):322-8. DOI: 10.1111/bjh.12036. Epub 2012 Sep 27. PMID: 23016878

16. Kalpadakis, C., Pangalis, G.A., Angelopoulou, M.K., et al. Treatment of Splenic Marginal Zone Lymphoma with Rituximab Monotherapy: Progress Report and Comparison with Splenectomy. *Oncologist*. 2013;18(2):190-7. DOI: 10.1634/theoncologist.2012-0251. Epub 2013 Jan 23. PMID: 23345547; PMCID: PMC3579603
17. Zucca, E., Conconi, A., Martinelli, G., et al. Final Results of the IELSG-19 Randomized Trial of Mucosa-Associated Lymphoid Tissue Lymphoma: Improved Event-Free and Progression-Free Survival with Rituximab Plus Chlorambucil Versus Either Chlorambucil or Rituximab Monotherapy. *J Clin Oncol*. 2017 Jun 10;35(17):1905-1912. DOI: 10.1200/JCO.2016.70.6994. Epub 2017 Mar 29. Erratum in: *J Clin Oncol*. 2017 Jul 10;35(20):2342. PMID: 28355112
18. Fowler, N.H., Davis, R.E., Rawal, S., et al. Safety and Activity of Lenalidomide and Rituximab in Untreated Indolent Lymphoma: An Open-Label, Phase 2 Trial. *Lancet Oncol*. 2014 Nov;15(12):1311-8. DOI: 10.1016/S1470-2045(14)70455-3. Epub 2014 Oct 15. PMID: 25439689; PMCID: PMC4370362
19. Lossos, I.S., Fabregas, J.C., Koru-Sengul, T., et al. Phase II Study of (90)Y Ibritumomab Tiuxetan (Zevalin) in Patients with Previously Untreated Marginal Zone Lymphoma. *Leuk Lymphoma*. 2015 Jun;56(6):1750-5. DOI: 10.3109/10428194.2014.975801. Epub 2014 Nov 20. PMID: 25315074
20. Williams, M.E., Hong, F., Gascoyne, R.D., et al. Rituximab Extended Schedule or Retreatment Trial for Low Tumour Burden Non-Follicular Indolent B-Cell Non-Hodgkin Lymphomas: Eastern Cooperative Oncology Group Protocol E4402. *Br J Haematol*. 2016 Jun;173(6):867-75. DOI: 10.1111/bjh.14007. Epub 2016 Mar 11. PMID: 26970533; PMCID: PMC4900920
21. Cheson, B.D., Chua, N., Mayer, J., et al. Overall Survival Benefit in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. *J Clin Oncol*. 2018 Aug 1;36(22):2259-2266. DOI: 10.1200/JCO.2017.76.3656. Epub 2018 Mar 27. PMID: 29584548
22. Rummel, M., Kaiser, U., Balsler, C., et al., Study Group Indolent Lymphomas. Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab for Patients with Relapsed Indolent and Mantle-Cell Lymphomas: A Multicentre, Randomised, Open-Label, Non-Inferiority Phase 3 Trial. *Lancet Oncol*. 2016 Jan;17(1):57-66. DOI: 10.1016/S1470-2045(15)00447-7. Epub 2015 Dec 5. Erratum in: *Lancet Oncol*. 2016 Jan;17(1):e6. PMID: 26655425
23. Robinson, K.S., Williams, M.E., van der Jagt, R.H., et al. Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients with Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma. *J Clin Oncol*. 2008 Sep 20;26(27):4473-9. DOI: 10.1200/JCO.2008.17.0001. Epub 2008 Jul 14. PMID: 18626004
24. Leonard, J.P., Trneny, M., Izutsu, K., et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol*. 2019;37:1188-1199
25. Sacchi, S., Marcheselli, R., Bari, A., et al. Safety and Efficacy of Lenalidomide in Combination with Rituximab in Recurrent Indolent Non-Follicular Lymphoma: Final Results of a Phase II Study Conducted by the Fondazione Italiana Linfomi. *Haematologica*. 2016 May;101(5):e196-9. DOI: 10.3324/haematol.2015.139329. Epub 2016 Feb 8. PMID: 26858355; PMCID: PMC5004354
26. Witzig, T.E., Gordon, L.I., Cabanillas, F., et al. Randomized Controlled Trial of Yttrium-90-Labeled Ibritumomab Tiuxetan Radioimmunotherapy Versus Rituximab Immunotherapy for Patients with Relapsed or Refractory Low-Grade, Follicular or Transformed B-Cell Non-Hodgkin's Lymphoma. *J Clin Oncol*. 2002;20:2453-2463

27. Dreyling, M., Santoro, A., Mollica, L., et al. Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol.* 2017;35:3898-3905
28. Dreyling, M., Santoro, A., Mollica, L., et al. Long-Term Efficacy and Safety From the Copanlisib CHRONOS-1 Study in Patients with Relapsed or Refractory Indolent B-Cell Lymphoma. *Blood.* 2018;132:1595
29. Flinn, I., Miller, C., Ardeshta, K., et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients with Refractory Indolent Non-Hodgkin Lymphoma. *J Clin Oncol.* 2019;37:912-922
30. Gopal, A., Kahl, B., De Vos, S., et al. PI3K δ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. *N Engl J Med.* 2014;370:1008-1018.
31. Zinzani, P.L., Samaniego, F., Jurczak, W., et al. Umbralisib, the Once Daily Dual Inhibitor of PI3K δ and Casein Kinase-1 ϵ Demonstrates Clinical Activity in Patients with Relapsed or Refractory Indolent Non-Hodgkin Lymphoma: Results From the Phase 2 Global Unity-NHL Trial [Abstract]. *Blood.* 2020; 136:34-35
32. Noy, A., de Vos, S., Thieblemont, C., et al. Targeting Bruton Tyrosine Kinase with Ibrutinib in Relapsed/Refractory Marginal Zone Lymphoma. *Blood.* 2017 Apr 20;129(16):2224-2232. DOI: 10.1182/blood-2016-10-747345. Epub 2017 Feb 6. PMID: 28167659; PMCID: PMC5399483
33. Conconi, A., Martinelli, G., Thiéblemont, C., et al. Clinical Activity of Rituximab in Extranodal Marginal Zone B-Cell Lymphoma of MALT Type. *Blood.* 2003 Oct 15;102(8):2741-5. DOI: 10.1182/blood-2002-11-3496. Epub 2003 Jul 3. PMID: 12842999
34. Sehn, L.H., Chua, N., Mayer, J., et al. Obinutuzumab Plus Bendamustine Versus Bendamustine Monotherapy in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma (GADOLIN): A Randomised, Controlled, Open-Label, Multicentre, Phase 3 Trial. *Lancet Oncol.* 2016;17:1081-1093
35. Panayiotidis, P., Follows, G.A., Mollica, L., et al. Efficacy and Safety of Copanlisib in Patients with Relapsed or Refractory Marginal Zone Lymphoma. *Blood Adv.* 2021;5:823-828
36. Wagner-Johnston, N.D., Schuster, S.J., deVos, S., et al. Outcomes of Patients with Up to 6 Years of Follow-Up From a Phase 2 Study of Idelalisib for Relapsed Indolent Lymphomas. *Leuk Lymphoma.* 2021 May;62(5):1077-1087.
37. Fowler, N.H., Samaniego, F., Jurczak, W., et al. Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients with Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol.* 2021 May 20;39(15):1609-1618
38. Opat, S., Tedeschi, A., Linton, K., et al. The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. *Clin Cancer Res.* 2021;27(23): 6323-6332
39. Shadman, M., Sharman, J.P., Levy, M.Y., et al. Preliminary Results of the Phase 2 Study of Zanubrutinib in Patients with Previously Treated B-Cell Malignancies Intolerant to Ibrutinib and/or Acalabrutinib [Abstract]. *J Clin Oncol.* 2021;39: Abstract e19506

Biliary Tract Cancers (Gallbladder, Intrahepatic and Extrahepatic Cholangiocarcinoma)

Adjuvant Therapy

- Capecitabine

Unresectable/Metastatic

1st Line of Therapy

- Gemcitabine + Cisplatin
- Cisplatin + Durvalumab + Gemcitabine (regardless of PD-L1 status)

2nd + Subsequent Lines of Therapy

- Fluorouracil/Leucovorin + Oxaliplatin (FOLFOX)
- Ivosidenib (in IDH1 Mutation Cholangiocarcinoma)

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/livibd.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers (V1.2023, 2.17.2023)
3. Stein, A., Arnold, D., Bridgewater, J., et al; Adjuvant Chemotherapy with Gemcitabine and Cisplatin Compared to Observation After Curative Intent Resection of Cholangiocarcinoma and Muscle Invasive Gallbladder Carcinoma (ACTICCA-1 Trial) — A Randomized, Multidisciplinary, Multinational Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/26228433
4. Edeline, J., Bonnetain, F., Phelip, J.M., et al. (2017, Feb. 1). Gemox Versus Surveillance Following Surgery of Localized Biliary Tract Cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) Phase III Trial. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2017.35.4_suppl.225
5. Ben-Josef, E., Guthrie, K.A., El-Khoueiry, A.B., et al. (2015, Aug. 20). SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/25964250
6. Ebata, T., Hirano, S., Konishi, M., et al. (February 2018). Randomized Clinical Trial of Adjuvant Gemcitabine Chemotherapy Versus Observation in Resected Bile Duct Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/29405274

7. Primrose, J.N., Fox, R.P., Palmer, D.H., et al. (May 2019). Capecitabine Compared with Observation in Resected Biliary Tract Cancer (BILCAP): A Randomised, Controlled, Multicentre, Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/30922733](https://pubmed.ncbi.nlm.nih.gov/30922733)
8. Shroff, R.T., Kennedy, E.B., Bachini, M., et al. (2019, April 20). Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. Retrieved from [ncbi.nlm.nih.gov/pubmed/30856044](https://pubmed.ncbi.nlm.nih.gov/30856044)
9. Graham, J.S., Boyd, K., Coxon, F.Y., et al. (2016, March 12). A Phase II Study of Capecitabine and Oxaliplatin Combination Chemotherapy in Patients with Inoperable Adenocarcinoma of the Gall Bladder or Biliary Tract. Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC4788848](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC4788848)
10. Ducreux, M., Van Cutsem, E., Van Laethem, J.L., et al. (February 2005). A Randomised Phase II Trial of Weekly High-Dose 5-Fluorouracil with and without Folinic Acid and Cisplatin in Patients with Advanced Biliary Tract Carcinoma: Results of the 40955 EORTC Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/15691639](https://pubmed.ncbi.nlm.nih.gov/15691639)
11. Lamarca, A., Hubner, R.A., David Ryder, W., et al. (December 2014). Second-Line Chemotherapy in Advanced Biliary Cancer: A Systematic Review. Retrieved from [ncbi.nlm.nih.gov/pubmed/24769639](https://pubmed.ncbi.nlm.nih.gov/24769639)
12. Eckel, F., Schmid, R.M. (2007, March 26). Chemotherapy in Advanced Biliary Tract Carcinoma: A Pooled Analysis of Clinical Trials. Retrieved from [ncbi.nlm.nih.gov/pubmed/17325704](https://pubmed.ncbi.nlm.nih.gov/17325704)
13. Ghidini, M., Pizzo, C., Botticelli, A., et al. (2018, Dec. 28). [Full text] Biliary Tract Cancer: Current Challenges and Future Prospects: CMAR. Retrieved from dovepress.com/biliary-tract-cancer-current-challenges-and-future-prospects-peer-reviewed-fulltext-article-CMAR
14. Valle, J., Wasan, H., Palmer, D.H., et al. (2010, April 8). Cisplatin Plus Gemcitabine Versus Gemcitabine for Biliary Tract Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/20375404](https://pubmed.ncbi.nlm.nih.gov/20375404)
15. Okusaka, T., Nakachi, K., Fukutomi, A., et al. (2010, Aug. 10). Gemcitabine Alone or in Combination with Cisplatin in Patients with Biliary Tract Cancer: A Comparative Multicentre Study in Japan. Retrieved from [ncbi.nlm.nih.gov/pubmed/20628385](https://pubmed.ncbi.nlm.nih.gov/20628385)
16. André, T., Reyes-Vidal, J.M., Fartoux, L., et al. (2008, Sept. 16). Gemcitabine and Oxaliplatin in Advanced Biliary Tract Carcinoma: A Phase II Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/19238628](https://pubmed.ncbi.nlm.nih.gov/19238628)
17. Sharma, A., Dwary, A.D., Mohanti, B.K., et al. (2010, Oct. 20). Best Supportive Care Compared with Chemotherapy for Unresectable Gall Bladder Cancer: A Randomized Controlled Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/20855823](https://pubmed.ncbi.nlm.nih.gov/20855823)
18. Lee, J., Park, S.H., Chang, H.-M., et al. (February 2012). Gemcitabine and Oxaliplatin with or without Erlotinib in Advanced Biliary-Tract Cancer: A Multicentre, Open-Label, Randomised, Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/22192731](https://pubmed.ncbi.nlm.nih.gov/22192731)
19. Knox, J.J., Hedley, D., Oza, A., et al. (2005, April 1). Combining Gemcitabine and Capecitabine in Patients with Advanced Biliary Cancer: A Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/15800324](https://pubmed.ncbi.nlm.nih.gov/15800324)
20. Riechelmann, R.P., Townsley, C.A., Chin, S.N., et al. (2007, Sept. 15). Expanded Phase II Trial of Gemcitabine and Capecitabine for Advanced Biliary Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/17628484](https://pubmed.ncbi.nlm.nih.gov/17628484)
21. Iqbal, S., Rankin, C., Lenz, H.J., et al. (December 2011). A Phase II Trial of Gemcitabine and Capecitabine in Patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma: Southwest Oncology Group Study S0202. Retrieved from [ncbi.nlm.nih.gov/pubmed/21556747](https://pubmed.ncbi.nlm.nih.gov/21556747)

22. Kim, T.W., Chang, H.M., Kang, H.J., et al. (July 2003). Phase II Study of Capecitabine Plus Cisplatin as First-Line Chemotherapy in Advanced Biliary Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/12853355](https://pubmed.ncbi.nlm.nih.gov/12853355)
23. Nehls, O., Oettle, H., Hartmann, J.T., et al. (2008, Jan. 29). Capecitabine Plus Oxaliplatin as First-Line Treatment in Patients with Advanced Biliary System Adenocarcinoma: A Prospective Multicentre Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/18182984](https://pubmed.ncbi.nlm.nih.gov/18182984)
24. Ducreux, M., Van Cutsem, E., Van Laethem, J.L., et al. (February 2005). A Randomised Phase II Trial of Weekly High-Dose 5-Fluorouracil with and without Folinic Acid and Cisplatin in Patients with Advanced Biliary Tract Carcinoma: Results of the 40955 EORTC Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/15691639](https://pubmed.ncbi.nlm.nih.gov/15691639)
25. Nehls, O., Klump, B., Arkenau, H.T., et al. (2002, Sept. 23). Oxaliplatin, Fluorouracil and Leucovorin for Advanced Biliary System Adenocarcinomas: A Prospective Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/12232749](https://pubmed.ncbi.nlm.nih.gov/12232749)
26. Moehler, M., Maderer, A., Schimanski, C., et al. (December 2014). Gemcitabine Plus Sorafenib Versus Gemcitabine Alone in Advanced Biliary Tract Cancer: A Double-Blind Placebo-Controlled Multicentre Phase II AIO Study with Biomarker and Serum Programme. Retrieved from [ncbi.nlm.nih.gov/pubmed/25446376](https://pubmed.ncbi.nlm.nih.gov/25446376)
27. Abou-Alfa, G.K., Sahai, V., Hollebecque, A., et al. Pemigatinib for Previously Treated, Locally Advanced or Metastatic Cholangiocarcinoma: A Multicentre, Open-Label, Phase 2 Study. *Lancet Oncol.* 2020;21(5):671-684. DOI:10.1016/S1470-2045(20)30109-1
28. Abou-Alfa, G.K., Macarulla, T., Javle, M.M., et al. Ivosidenib in IDH1-Mutant, Chemotherapy-Refractory Cholangiocarcinoma (ClarIDHy): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study. *Lancet Oncol.* 2020;21(6):796-807. DOI:10.1016/S1470-2045(20)30157-1
29. Shroff, R.T., Kennedy, E.B., Bachini, M., et al. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. *J Clin Oncol.* 2019 Apr 20;37(12):1015-1027. DOI: 10.1200/JCO.18.02178. Epub 2019 Mar 11. PMID: 30856044
30. Sun, W., Patel, A., Normolle, D., et al. A Phase 2 Trial of Regorafenib as a Single Agent in Patients with Chemotherapy-Refractory, Advanced and Metastatic Biliary Tract Adenocarcinoma. *Cancer.* 2019 Mar 15;125(6):902-909. DOI: 10.1002/cncr.31872. Epub 2018 Dec 18. PMID: 30561756; PMCID: PMC6402964
31. Caparica, R., Lengelé, A., Bekolo, W., et al. FOLFIRI as Second-Line Treatment of Metastatic Biliary Tract Cancer Patients. *Autops Case Rep.* 2019 Jun 24;9(2): e2019087. DOI: 10.4322/acr.2019.087. PMID: 31528622; PMCID: PMC6738847
32. Andre, T. et al. Safety and Efficacy of Anti-PD1 Antibody Dostarlimab in Patients (Pts) with Mismatch Repair-Deficient (dMMR) Solid Cancers: Results from GARNET— Study [Abstract]. *J Clin Oncol.* 2021; 39: Abstract 9
33. Berton, D. et al. Antitumor Activity of Dostarlimab in Patients with Mismatch Repair-Deficient/Microsatellite Instability-High Tumors: A Combined Analysis of Two Cohorts in the GARNET Study [Abstract]. *J Clin Oncol.* 2021; 39: Abstract 2564
34. Zhu, A.X., Macarulla, T., Javle, M.M., et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients with Advanced Cholangiocarcinoma with IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. *JAMA Oncol.* 2021; 7(11):1669–1677
35. Subbiah, V., et al. Dabrafenib Plus Trametinib in Patients with BRAFV600E-Mutated Biliary Tract Cancer (ROAR): A Phase 2, Open-Label, Single-Arm, Multicentre Basket Trial. *Lancet Oncol.* 2020 Sep; 21(9):1234-1243. Epub 2020 Aug 17. PMID: 32818466

36. Salama, A.K.S., et al. Dabrafenib and Trametinib in Patients with Tumors with BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol.* 2020 Nov 20; 38(33):3895-3904. Epub 2020 Aug 6. PMID: 32758030
37. Kim, R.D., et al. A Phase 2 Multi-institutional Study of Nivolumab for Patients with Advanced Refractory Biliary Tract Cancer. *JAMA Oncol.* 2020 Jun 1; 6(6):888-894. PMID: 32352498
38. Lwin, Z., et al. LEAP-005: Phase II study of Lenvatinib (len) Plus Pembrolizumab (Pembro) in Patients (Pts) with Previously Treated Advanced Solid Tumors. *Ann Oncol.* 2020; 31:S1142-S1215
39. Villanueva, L., Lwin, Z., Chung, H.C., et al. Lenvatinib Plus Pembrolizumab for Patients with Previously Treated Biliary Tract Cancers in the Multicohort Phase II LEAP-005 Study. *J Clin Oncol.* 2021; 39(suppl_3):321-321
40. Javle, M., Lowery, M., Shroff, R.T., et al. Phase II Study of BGJ398 in Patients with FGFR-Altered Advanced Cholangiocarcinoma. *J Clin Oncol.* 2018 Jan 20; 36(3):276-282. DOI: 10.1200/JCO.2017.75.5009. Epub 2017 Nov 28. PMID: 29182496; PMCID: PMC6075847
41. Javle, M., Roychowdhury, S., Kelley, R.K., et al. Final Results From a Phase II Study of Infigratinib (BGJ398), an FGFR-Selective Tyrosine Kinase Inhibitor, in Patients with Previously Treated Advanced Cholangiocarcinoma Harboring an FGFR2 Gene Fusion or Rearrangement. *J Clin Oncol.* 2021 Jan 20; 39(3_suppl):265-265. DOI: 10.1200/JCO.2021.39.3_suppl.265
42. Do-Youn Oh, Aiwu Ruth He, Shukui Qin, et.al. A Phase 3 Randomized, Double-blind, Placebo-controlled Study of Durvalumab in Combination with Gemcitabine Plus Cisplatin (GemCis) in Patients (pts) with Advanced Biliary Tract Cancer (BTC); TOPAZ-. *J Clin Oncol.* 2022 40:4_suppl, 378-378

Bladder Cancer

Non-Muscle Invasive, Neoadjuvant/Adjuvant

- Intravesical BCG (Bacillus Calmette-Guerin)
- Intravesical Gemcitabine

Non-Muscle Invasive, Maintenance

- Intravesical BCG (Bacillus Calmette-Guerin)

Muscle Invasive, Neoadjuvant/Adjuvant

- Gemcitabine + Cisplatin
- Nivolumab PD-L1 \geq 1% (high-risk, adjuvant only)

Radiosensitizing Chemotherapy for Organ-Preserving Chemoradiation

- Cisplatin + Fluorouracil (5FU)
- Gemcitabine

Locally Advanced or Metastatic

1st Line of Therapy

- Gemcitabine + Cisplatin or Carboplatin

Maintenance Post 1st Line of Therapy and No Progression

- Avelumab

2nd Line of Therapy

- Pembrolizumab (if IO not used previously)
- Nivolumab (if IO not used previously)
- Avelumab (if IO not used previously)
- Gemcitabine + Cisplatin or Carboplatin (if platinum-based therapy not used previously)

3rd + Subsequent Lines of Therapy

- Enfortumab Vedotin-ejfv
- Gemcitabine + Cisplatin or Carboplatin (if platinum-based therapy not used previously)

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/urinb.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer (V3.2023, May 25, 2023) Accessed August 2023. Retrieved from nccn.org/professionals/physician_gls/pdf/bladder.pdf
3. Grossman, H.B., Natale, R.B., Tangen, C.M., et al. Neoadjuvant Chemotherapy Plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. *NEJM*. 2003;349:859-866
4. Sternberg, C.N., de Mulder, P.H., Schornagel, J.H., et al.; European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized Phase III Trial of High-Dose-Intensity Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol*. 2001 May 15;19(10):2638-46. DOI: 10.1200/JCO.2001.19.10.2638. PMID: 11352955
5. Sternberg, C.N., de Mulder, P., Schornagel, J.H., et al.; EORTC Genito-Urinary Cancer Group. Seven-year Update of an EORTC Phase III Trial of High-Dose Intensity M-VAC Chemotherapy and G-CSF Versus Classic M-VAC in Advanced Urothelial Tract Tumours. *Eur J Cancer*. 2006 Jan;42(1):50-4. DOI: 10.1016/j.ejca.2005.08.032. Epub 2005 Dec 5. PMID: 16330205
6. Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. *Eur Urol*. 2005 Aug;48(2):202-5; discussion 205-6. DOI: 10.1016/j.eururo.2005.04.006. Epub 2005 Apr 21. PMID: 15939524
7. Plimack, E.R., Hoffman-Censits, J.H., Viterbo, R., et al. Accelerated Methotrexate, Vinblastine, Doxorubicin and Cisplatin Is Safe, Effective and Efficient Neoadjuvant Treatment for Muscle-Invasive Bladder Cancer: Results of a Multicenter Phase II Study with Molecular Correlates of Response and Toxicity. *J Clin Oncol*. 2014 Jun 20;32(18):1895-901. DOI: 10.1200/JCO.2013.53.2465. Epub 2014 May 12. PMID: 24821881; PMCID: PMC4050203
8. Choueiri, T.K., Jacobus, S., Bellmunt, J., et al. Neoadjuvant Dose-Dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin with Pegfilgrastim Support in Muscle-Invasive Urothelial Cancer: Pathologic, Radiologic and Biomarker Correlates. *J Clin Oncol*. 2014 Jun 20;32(18):1889-94. DOI: 10.1200/JCO.2013.52.4785. Epub 2014 May 12. PMID: 24821883; PMCID: PMC7057274
9. Pfister, C., Gravis, G., Fléchon, A., et al.; VESPER Trial Investigators. Randomized Phase III Trial of Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin, or Gemcitabine and Cisplatin as Perioperative Chemotherapy for Patients with Muscle-invasive Bladder Cancer. Analysis of the GETUG/AFU V05 VESPER Trial Secondary Endpoints: Chemotherapy Toxicity and Pathological Responses. *Eur Urol*. 2021 Feb;79(2):214-221. DOI: 10.1016/j.eururo.2020.08.024. Epub 2020 Aug 28. PMID: 32868138
10. Flaig, T.W., Tangen, C.M., Daneshmand, S., et al. Randomized Phase II Study of Coexpression Extrapolation (COXEN) with Neoadjuvant Chemotherapy for Bladder Cancer (SWOG S1314; NCT02177695). *Clin Cancer Res*. 2021 May 1;27(9):2435-2441. DOI: 10.1158/1078-0432.CCR-20-2409. Epub 2021 Feb 10. PMID: 33568346; PMCID: PMC8219246
11. Galsky, M.D., Pal, S.K., Chowdhury, S., et al. Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. Comparative Effectiveness of Gemcitabine Plus

- Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer. *Cancer*. 2015 Aug 1;121(15):2586-93. DOI: 10.1002/cncr.29387. Epub 2015 Apr 14. PMID: 25872978
12. Zargar, H., Espiritu, P.N., Fairey, A.S., et al. Multicenter Assessment of Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer. *Eur Urol*. 2015 Feb;67(2):241-9. DOI: 10.1016/j.eururo.2014.09.007. Epub 2014 Sep 23. PMID: 25257030; PMCID: PMC4840190
 13. Dash, A., Pettus, J.A. 4th, Herr, H.W., et al. A Role for Neoadjuvant Gemcitabine Plus Cisplatin in Muscle-Invasive Urothelial Carcinoma of the Bladder: A Retrospective Experience. *Cancer*. 2008 Nov 1;113(9):2471-7. DOI: 10.1002/cncr.23848. PMID: 18823036; PMCID: PMC2585515
 14. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group; Australian Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; Finnbladder; Norwegian Bladder Cancer Study Group; Club Urologico Espanol de Tratamiento Oncologico Group, Griffiths, G., Hall, R., Sylvester, R., Raghavan D, Parmar, M.K. International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial. *J Clin Oncol*. 2011 Jun 1;29(16):2171-7. DOI: 10.1200/JCO.2010.32.3139. Epub 2011 Apr 18. PMID: 21502557; PMCID: PMC3107740
 15. Bajorin, D.F., Witjes, J.A., Gschwend, J.E., et al. Adjuvant Nivolumab Versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med*. 2021 Jun 3;384(22):2102-2114. DOI: 10.1056/NEJMoa2034442. PMID: 34077643; PMCID: PMC8215888
 16. Bellmunt, J., Hussain, M., Gschwend, J.E., et al.; IMvigor010 Study Group. Adjuvant Atezolizumab Versus Observation in Muscle-Invasive Urothelial Carcinoma (Imvigor010): A Multicentre, Open-Label, Randomised, Phase 3 Trial. *Lancet Oncol*. 2021 Apr;22(4):525-537. DOI: 10.1016/S1470-2045(21)00004-8. Epub 2021 Mar 12. PMID: 33721560
 17. de Reijke, T.M., Kurth, K.H., Sylvester, R.J., et al.; European Organization for the Research and Treatment of Cancer-Genito-Urinary Group. Bacillus Calmette-Guerin Versus Epirubicin for Primary, Secondary or Concurrent Carcinoma in Situ of the Bladder: Results of a European Organization for the Research and Treatment of Cancer — Genito-Urinary Group Phase III Trial (30906). *J Urol*. 2005 Feb;173(2):405-9. DOI: 10.1097/01.ju.0000150425.09317.67. PMID: 15643181
 18. Lamm, D.L., Blumenstein, B.A., Crissman, J.D., et al. Maintenance Bacillus Calmette-Guerin Immunotherapy for Recurrent TA, T1 and Carcinoma in Situ Transitional Cell Carcinoma of the Bladder: A Randomized Southwest Oncology Group Atudy. *J Urol*. 2000;163(4):1124-9. PMID: 10737480
 19. Böhle, A., Bock, P.R. Intravesical Calmette-Guérin Versus Mitomycin C in Superficial Bladder Cancer: Formal Meta-Analysis of Comparative Studies on Tumor Progression. *Urology*. 2004 Apr;63(4):682-6; discussion 686-7. DOI: 10.1016/j.urology.2003.11.049. PMID: 15072879
 20. Shelley, M.D., Wilt, T.J., Court, J., et al. Intravesical Bacillus Calmette-Guérin Is Superior to Mitomycin C in Reducing Tumour Recurrence in High-Risk Superficial Bladder Cancer: A Meta-Analysis of Randomized Trials. *BJU Int*. 2004;93(4):485-90. PMID: 15008714
 21. Sylvester, R.J., van der Meijden, A.P., Witjes, J.A., et al. Bacillus Calmette-Guerin Versus Chemotherapy for the Intravesical Treatment of Patients with Carcinoma in Situ of the Bladder: A Meta-Analysis of the Published Results of Randomized Clinical Trials. *J Urol*. 2005 Jul;174(1):86-91; discussion 91-2. DOI: 10.1097/01.ju.0000162059.64886.1c. PMID: 15947584

22. Addeo, R., Caraglia, M., Bellini, S., et al.; Randomized Phase III Trial on Gemcitabine Versus Mytomicin in Recurrent Superficial Bladder Cancer: Evaluation of Efficacy and Tolerance. *J Clin Oncol*. 2010 Feb 1;28(4):543-8. DOI: 10.1200/JCO.2008.20.8199. Epub 2009 Oct 19. PMID: 19841330
23. Mitin, T., Hunt, D., Shipley, W.U., et al. Transurethral Surgery and Twice-Daily Radiation Plus Paclitaxel-Cisplatin or Fluorouracil-Cisplatin with Selective Bladder Preservation and Adjuvant Chemotherapy for Patients with Muscle Invasive Bladder Cancer (RTOG 0233): A Randomised Multicentre Phase 2 Trial. *Lancet Oncol*. 2013 Aug;14(9):863-72. DOI: 10.1016/S1470-2045(13)70255-9. Epub 2013 Jul 1. PMID: 23823157; PMCID: PMC3955198
24. Coen, J.J., Zhang, P., Saylor, P.J., et al. Bladder Preservation with Twice-a-Day Radiation Plus Fluorouracil/Cisplatin or Once Daily Radiation Plus Gemcitabine for Muscle-Invasive Bladder Cancer: NRG/RTOG 0712-A Randomized Phase II Trial. *J Clin Oncol*. 2019 Jan 1;37(1):44-51. DOI: 10.1200/JCO.18.00537. Epub 2018 Nov 15. Erratum in: *J Clin Oncol*. 2021 Apr 10;39(11):1309. PMID: 30433852; PMCID: PMC6354769
25. James, N.D., Hussain, S.A., Hall, E., et al.; BC2001 Investigators. Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. *N Engl J Med*. 2012 Apr 19;366(16):1477-88. DOI: 10.1056/NEJMoa1106106. PMID: 22512481
26. Tester, W., Caplan, R., Heaney, J., et al. Neoadjuvant Combined Modality Program with Selective Organ Preservation for Invasive Bladder Cancer: Results of Radiation Therapy Oncology Group Phase II Trial 8802. *J Clin Oncol*. 1996 Jan;14(1):119-26. DOI: 10.1200/JCO.1996.14.1.119. PMID: 8558186
27. Kent, E., Sandler, H., Montie, J., et al. Combined-Modality Therapy with Gemcitabine and Radiotherapy as a Bladder Preservation Strategy: Results of a Phase I Trial. *J Clin Oncol*. 2004 Jul 1;22(13):2540-5. DOI: 10.1200/JCO.2004.10.070. PMID: 15226322
28. Choudhury, A., Swindell, R., Logue, J.P., et al. Phase II Study of Conformal Hypofractionated Radiotherapy with Concurrent Gemcitabine in Muscle-Invasive Bladder Cancer. *J Clin Oncol*. 2011 Feb 20;29(6):733-8. DOI: 10.1200/JCO.2010.31.5721. Epub 2011 Jan 4. PMID: 21205754
29. von der Maase, H., Hansen, S.W., Roberts, J.T., et al. Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. *J Clin Oncol*. 2000 Sep;18(17):3068-77. DOI: 10.1200/JCO.2000.18.17.3068. PMID: 11001674
30. Powles, T., Park, S.H., Voog, E., et al. Avelumab Maintenance + Best Supportive Care (BSC) Versus BSC Alone After Platinum-Based First-Line (1L) Chemotherapy in Advanced Urothelial Carcinoma (UC): JAVELIN Bladder 100 Phase III Interim Analysis. *N Engl J Med* 2020; 383:1218-30
31. Balar, A.V., Galsky, M.D., Rosenberg, J.E., et al.; IMvigor210 Study Group. Atezolizumab as First-Line Treatment in Cisplatin-Ineligible Patients with Locally Advanced and Metastatic Urothelial Carcinoma: A Single-Arm, Multicentre, Phase 2 Trial. *Lancet*. 2017 Jan 7;389(10064):67-76. DOI: 10.1016/S0140-6736(16)32455-2. Epub 2016 Dec 8. Erratum in: *Lancet*. 2017 Aug 26;390(10097):848. PMID: 27939400; PMCID: PMC5568632
32. Galsky, M.D., Arija, J.Á.A., Bamias, A., et al.; IMvigor130 Study Group. Atezolizumab with or without Chemotherapy in Metastatic Urothelial Cancer (Imvigor130): A Multicentre, Randomised, Placebo-Controlled Phase 3 Trial. *Lancet*. 2020 May 16;395(10236):1547-1557. DOI: 10.1016/S0140-6736(20)30230-0. PMID: 32416780
33. Vuky, J., Balar, A.V., Castellano, D., et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients with Locally

- Advanced or Metastatic Urothelial Cancer. *J Clin Oncol*. 2020 Aug 10;38(23):2658-2666. DOI: 10.1200/JCO.19.01213. Epub 2020 Jun 17. PMID: 32552471
34. Powles, T., Csőszi, T., Özgüroğlu, M., et al.; KEYNOTE-361 Investigators. Pembrolizumab Alone or Combined with Chemotherapy Versus Chemotherapy as First-Line Therapy for Advanced Urothelial Carcinoma (KEYNOTE-361): A Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol*. 2021 Jul;22(7):931-945. DOI: 10.1016/S1470-2045(21)00152-2. Epub 2021 May 26. PMID: 34051178
 35. Stadler, W.M., Kuzel, T., Roth, B., et al. Phase II Study of Single-Agent Gemcitabine in Previously Untreated Patients with Metastatic Urothelial cancer. *J Clin Oncol*. 1997 Nov;15(11):3394-8. DOI: 10.1200/JCO.1997.15.11.3394. PMID: 9363871
 36. Calabrò, F., Lorusso, V., Rosati, G., et al. Gemcitabine and Paclitaxel Every 2 Weeks in Patients with Previously Untreated Urothelial Carcinoma. *Cancer*. 2009 Jun 15;115(12):2652-9. DOI: 10.1002/cncr.24313. PMID: 19396817
 37. Siefker-Radtke, A.O., Dinney, C.P., Shen Y, et al. A Phase 2 Clinical Trial of Sequential Neoadjuvant Chemotherapy with Ifosfamide, Doxorubicin, and Gemcitabine Followed by Cisplatin, Gemcitabine, and Ifosfamide in Locally Advanced Urothelial Cancer: Final Results. *Cancer*. 2013 Feb 1;119(3):540-7. DOI: 10.1002/cncr.27751. Epub 2012 Aug 22. PMID: 22914978; PMCID: PMC3828072
 38. Bellmunt, J., de Wit, R., Vaughn, D.J., et al.; KEYNOTE-045 Investigators. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med*. 2017 Mar 16;376(11):1015-1026. DOI: 10.1056/NEJMoa1613683. Epub 2017 Feb 17. PMID: 28212060; PMCID: PMC5635424
 39. Powles, T., Durán, I., van der Heijden, M.S., et al. Atezolizumab Versus Chemotherapy in Patients with Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma (Imvigor211): A Multicentre, Open-Label, Phase 3 Randomised Controlled Trial. *Lancet*. 2018 Feb 24;391(10122):748-757. DOI: 10.1016/S0140-6736(17)33297-X. Epub 2017 Dec 18. Erratum in: *Lancet*. 2018 Oct 20;392(10156):1402. PMID: 29268948
 40. Sharma, P., Retz, M., Siefker-Radtke, A., et al. Nivolumab in Metastatic Urothelial Carcinoma After Platinum Therapy (Checkmate 275): A Multicentre, Single-Arm, Phase 2 Trial. *Lancet Oncol*. 2017 Mar;18(3):312-322. DOI: 10.1016/S1470-2045(17)30065-7. Epub 2017 Jan 26. PMID: 28131785
 41. Apolo, A.B., Infante, J.R., Balmanoukian, A., et al. Avelumab, an Anti-Programmed Death-Ligand 1 Antibody, in Patients with Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase IB Study. *J Clin Oncol*. 2017 Jul 1;35(19):2117-2124. DOI: 10.1200/JCO.2016.71.6795. Epub 2017 Apr 4. PMID: 28375787; PMCID: PMC5493051
 42. Patel, M.R., Ellerton, J., Infante, J.R., et al. Avelumab in Metastatic Urothelial Carcinoma After Platinum Failure (JAVELIN Solid Tumor): Pooled Results From Two Expansion Cohorts of an Open-Label, Phase 1 Trial. *Lancet Oncol*. 2018 Jan;19(1):51-64. DOI: 10.1016/S1470-2045(17)30900-2. Epub 2017 Dec 5. Erratum in: *Lancet Oncol*. 2018 Jul;19(7):e335. PMID: 29217288; PMCID: PMC7984727
 43. Yu, E.Y., Petrylak, D.P., O'Donnell, P.H., et al. Enfortumab Vedotin After PD-1 Or PD-L1 Inhibitors in Cisplatin-Ineligible Patients with Advanced Urothelial Carcinoma (EV-201): A Multicentre, Single-Arm, Phase 2 Trial. *Lancet Oncol*. 2021 Jun;22(6):872-882. DOI: 10.1016/S1470-2045(21)00094-2. Epub 2021 May 12. Erratum in: *Lancet Oncol*. 2021 Jun;22(6):e239. PMID: 33991512
 44. Powles, T., Rosenberg, J.E., Sonpavde, G., et al: Primary Results of EV-301: A Phase III Trial of Enfortumab Vedotin Versus Chemotherapy in Patients with Previously Treated Locally

- Advanced or Metastatic Urothelial Carcinoma. 2021 Genitourinary Cancers Symposium. Abstract 393. Presented Feb. 12, 2021
45. Sideris, S., Aoun, F., Zanaty, M., et al. Efficacy of Weekly Paclitaxel Treatment as a Single Agent Chemotherapy Following First-Line Cisplatin Treatment in Urothelial Bladder Cancer. *Mol Clin Oncol*. 2016 Jun;4(6):1063-1067. DOI: 10.3892/mco.2016.821. Epub 2016 Mar 17. PMID: 27284445; PMCID: PMC4887921
 46. McCaffrey, J.A., Hilton, S., Mazumdar, M., et al. Phase II Trial of Docetaxel in Patients with Advanced or Metastatic Transitional-Cell Carcinoma. *J Clin Oncol*. 1997 May;15(5):1853-7. DOI: 10.1200/JCO.1997.15.5.1853. PMID: 9164195
 47. Loriot, Y., Necchi, A., Park, S.H., et al.; BLC2001 Study Group. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med*. 2019 Jul 25;381(4):338-348. DOI: 10.1056/NEJMoa1817323. PMID: 31340094
 48. Li, Q., Bagrodia, A., Cha, E.K., Coleman, J.A. Prognostic Genetic Signatures in Upper-Tract Urothelial Carcinoma. *Curr Urol Rep*. 2016; 17:12-12
 49. Knowles, M.A., Hurst, C.D. Molecular Biology of Bladder Cancer: New Insights into Pathogenesis and Clinical Diversity. *Nat Rev Cancer*. 2015; 15:25-41
 50. Tagawa, S.T., Balar, A.V., Petrylak, D.P., et al.; TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients with Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol*. 2021 Aug 1;39(22):2474-2485. DOI: 10.1200/JCO.20.03489. Epub 2021 Apr 30. PMID: 33929895; PMCID: PMC8315301
 51. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol*. 2021;22(1):107-117. doi:10.1016/S1470-2045(20)30540-4
 52. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study [published correction appears in *Lancet Oncol*. 2021 Aug;22(8):e347]. *Lancet Oncol*. 2021;22(7):919-930. doi:10.1016/S1470-2045(21)00147-9
 53. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab for the treatment of patients with high-risk (HR) non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guérin: extended follow-up of KEYNOTE-057 cohort A. *J Clin Oncol*. 2021;39:6s (suppl; abstr 451)
 54. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J Clin Oncol* 2016;34:1935–44. <https://doi.org/10.1200/JCO.2015.64.4070>.
 55. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma [published correction appears in *N Engl J Med*. 2021 Aug 26;385(9):864]. *N Engl J Med*. 2021;384(22):2102-2114. doi:10.1056/NEJMoa2034442
 56. Galsky M, Witjes AA, Gschwend JE. Extended follow-up results from the CheckMate 274 trial. *J Clin Oncol*. 2023; 41 (no.6_suppl):LBA443. doi:10.1200/JCO.2023.41.6_suppl.LBA443
 57. Joshi M, Atlas SJ, Beinfeld M, et al. Cost-Effectiveness of Nadofaragene Firadenovec and Pembrolizumab in Bacillus Calmette-Guérin Immunotherapy Unresponsive Non-Muscle Invasive Bladder Cancer. *Value Health*. 2023;26(6):823-832. doi:10.1016/j.jval.2022.12.005

58. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J Clin Oncol.* 2016;34(16):1935-1944.
59. Hoimes CJ, Flaig TW, Milowsky MI, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. *J Clin Oncol.* 2023;41(1):22-31. doi:10.1200/JCO.22.01643
60. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. *J Clin Oncol.* 2021;39(22):2474-2485. doi:10.1200/JCO.20.03489
61. Loriot Y, Matsubara N, Park SH et al. Phase 3 THOR study: Results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (FGFRalt). *JCO* 41:17_suppl (June 10, 2023) LBA4619-LBA4619. DOI: 10.1200/JCO.2023.41.17_suppl.LBA4619
62. Sayegh N, Tripathi N, Agarwal N, Swami U. Clinical Evidence and Selecting Patients for Treatment with Erdafitinib in Advanced Urothelial Carcinoma. *Onco Targets Ther.* 2022;15:1047-1055. Published 2022 Sep 25. doi:10.2147/OTT.S318332

Breast Cancer

Neoadjuvant/Adjuvant

HER2 Negative:

- Doxorubicin + Cyclophosphamide (dose dense) → Paclitaxel weekly (ddAC → weekly T)
- Doxorubicin + Cyclophosphamide (dose dense) → Paclitaxel every 2 weeks (ddAC → q2w T)
- Docetaxel + Cyclophosphamide (TC)
- Olaparib (for BRCA 1/2 mutation positive; adjuvant therapy only)

HER2 Positive:

- Doxorubicin + Cyclophosphamide → Paclitaxel weekly + Trastuzumab (AC → TH)
- Docetaxel + Carboplatin + Trastuzumab (TCH)
- Paclitaxel + Trastuzumab

Adjuvant (Residual Disease Post-Neoadjuvant Treatment)

Triple negative breast cancer (TNBC):

- Capecitabine

HER2 Positive (to completion of 1 yr of HER2 therapy):

- Ado-trastuzumab Emtansine (T-DM1)
- Trastuzumab

Adjuvant (No Residual Disease Post-Neoadjuvant Treatment)

HER2 Positive:

- Trastuzumab to completion 1 yr of HER2 therapy

Metastatic and Recurrent — Endocrine Therapy

HER2 Negative: 1st Line of Therapy

- Fulvestrant + Anastrozole
- Anastrozole + Palbociclib
- Letrozole + Palbociclib
- Exemestane + Palbociclib
- Anastrozole + Abemaciclib
- Letrozole + Abemaciclib

- Exemestane + Abemaciclib
- Anastrozole + Ribociclib
- Letrozole + Ribociclib
- Exemestane + Ribociclib

HER2 Negative: 1st + Subsequent Lines of Therapy

- Anastrozole
- Letrozole
- Exemestane
- Tamoxifen
- Fulvestrant

HER2 Negative: 2nd + Subsequent Lines of Therapy

- Anastrozole
- Letrozole
- Exemestane
- Tamoxifen
- Fulvestrant
- Fulvestrant + Palbociclib
- Fulvestrant + Abemaciclib
- Fulvestrant + Ribociclib

HER2 positive

- Anastrozole + Trastuzumab
- Letrozole + Trastuzumab
- Exemestane + Trastuzumab
- Anastrozole + Lapatinib
- Letrozole + Lapatinib
- Exemestane + Lapatinib

Metastatic and Recurrent — Chemotherapy

HER2 Negative: 1st + Subsequent Lines of Therapy

- Doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine

- Gemcitabine
- Vinorelbine
- Olaparib or talzoparib (Germline BRCA 1/2 Mutation Positive)
- Fam-trastuzumab deruxtecan--nxki (For patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative, who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.)

HER2 Negative: Triple Negative Breast Cancer (TNBC)

- Cisplatin or Carboplatin (PD-L1 CPS < 10 and germline BRCA 1/2 mutation)
- Pembrolizumab + Paclitaxel (CPS ≥ 10)
- Pembrolizumab + Gemcitabine + Carboplatin (CPS ≥ 10)
- Sacituzumab Govitecan-hziy (after 2 prior therapies for metastatic disease)

HER2 Positive: 1st Line of Therapy

- Docetaxel + Trastuzumab + Pertuzumab
- Paclitaxel + Trastuzumab + Pertuzumab

HER2 Positive: 2nd + Subsequent Lines of therapy

- Ado-Trastuzumab Emtansine (T-DM1)
- Fam-trastuzumab deruxtecan-nxki

HER2 Positive: 4th + Subsequent Lines of therapy

- Capecitabine + Lapatinib
- Paclitaxel + Trastuzumab
- Vinorelbine + Trastuzumab
- Gemcitabine + Trastuzumab
- Capecitabine + Trastuzumab

References:

1. National Comprehensive Cancer Network. Breast Cancer (V4.2023, March 23,2023). Accessed April 2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
2. Citron, M.L., Berry, D.A., Cirrincione, C., et al. (2003, April 15). Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/12668651](https://pubmed.ncbi.nlm.nih.gov/12668651)
3. Mamounas, E.P., Bryant, J., Lembersky, B., et al. (2005, June 1). Paclitaxel After Doxorubicin Plus Cyclophosphamide as Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28. *Journal of Clinical Oncology: Official Journal of the American Society of*

- Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/15897552](https://pubmed.ncbi.nlm.nih.gov/15897552)
4. Budd, G.T., Barlow, W.E., Moore, H.C.F. et al. SWOG S0221: Comparison of Two Schedules of Paclitaxel as Adjuvant Therapy for Breast Cancer ASCO Meeting Library (suppl; abstr CRA1008). Accessed May 20, 2019. Retrieved from meetinglibrary.asco.org/record/82186/abstract
 5. Jones, S.E., Savin, M.A., Holmes, F.A., et al. (2006, Dec. 1). Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide with Docetaxel Plus Cyclophosphamide as Adjuvant Therapy for Operable Breast Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/17135639](https://pubmed.ncbi.nlm.nih.gov/17135639)
 6. Jones, S., Holmes, F.A., O'Shaughnessy, J., et al. (2009, March 10). Docetaxel with Cyclophosphamide Is Associated with an Overall Survival Benefit Compared with Doxorubicin and Cyclophosphamide: Seven-Year Follow-Up of U.S. Oncology Research Trial 9735. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=19204201](https://pubmed.ncbi.nlm.nih.gov/?term=19204201)
 7. Preethi, J., Bannuru, R.R., Cohen, J.T., et al. Cost-Effectiveness of Adjuvant Chemotherapy in Early-Stage Breast Cancer. *Journal of Clinical Oncology*. Accessed May 20, 2019. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2018.36.15_suppl.e18887
 8. Fisher, B., Brown, A.M., Dimitrov, N.V., et al. (September 1990). Two Months of Doxorubicin-Cyclophosphamide with and without Interval Reinduction Therapy Compared with Six Months of Cyclophosphamide, Methotrexate and Fluorouracil in Positive-Node Breast Cancer Patients with Tamoxifen-Nonresponsive Tumors: Results From the National Surgical Adjuvant Breast and Bowel Project B-15. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=2202791](https://pubmed.ncbi.nlm.nih.gov/?term=2202791)
 9. Sparano, J.A., Wang, M., Martino, Silvana, et al. (2008, April 17). Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer. *N Engl J Med*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/18420499](https://pubmed.ncbi.nlm.nih.gov/18420499)
 10. Von Minckwitz, G., Raab, G., Caputo, A., et al. (2005, April 20). Doxorubicin with Cyclophosphamide Followed by Docetaxel Every 21 Days Compared with Doxorubicin and Docetaxel Every 14 Days as Preoperative Treatment in Operable Breast Cancer: The GEPAR DUO Study of the German Breast Group. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=15837982](https://pubmed.ncbi.nlm.nih.gov/?term=15837982)
 11. Hutchins, L.F., Green, S.J., Ravdin, P.M., et al. (2005, Nov. 20). Randomized, Controlled Trial of Cyclophosphamide, Methotrexate, and Fluorouracil Versus Cyclophosphamide, Doxorubicin, and Fluorouracil with and without Tamoxifen for High-Risk, Node-Negative Breast Cancer: Treatment Results of Intergroup Protocol INT-0102. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/16293862](https://pubmed.ncbi.nlm.nih.gov/16293862)
 12. Fisher, B., Anderson, S., Tan-Chiu, E., et al. (2001, Feb. 15). Tamoxifen and Chemotherapy for Axillary Node-Negative, Estrogen Receptor-Negative Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-23. Retrieved from [ncbi.nlm.nih.gov/pubmed/11181655](https://pubmed.ncbi.nlm.nih.gov/11181655)
 13. Mackey, J.R., Pieńkowski, T., Crown, J., et al. (June 2016). Long-Term Outcomes After Adjuvant Treatment of Sequential Versus Combination Docetaxel with Doxorubicin and Cyclophosphamide in Node-Positive Breast Cancer: BCIRG-005 Randomized Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/26940688](https://pubmed.ncbi.nlm.nih.gov/26940688)

14. Martin, M., Pienkowski, T., Mackey, J., et al. (2005, June 2). Adjuvant Docetaxel for Node-Positive Breast Cancer. *The New England Journal of Medicine*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=15930421](https://pubmed.ncbi.nlm.nih.gov/?term=15930421)
15. Piccart, M.J., Di Leo, A., Beauduin, M., et al. (2001, June 15). Phase III Trial Comparing Two Dose Levels of Epirubicin Combined with Cyclophosphamide with Cyclophosphamide, Methotrexate and Fluorouracil in Node-Positive Breast Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=11408507](https://pubmed.ncbi.nlm.nih.gov/?term=11408507)
16. Masuda, N., Lee, S., Ohtani, S., et al. (2017, June 1). Adjuvant Capecitabine for Breast Cancer After Preoperative Chemotherapy. *N Engl J Med*. Accessed May 20, 2019. Retrieved from [ncbi.nlm.nih.gov/pubmed/28564564](https://pubmed.ncbi.nlm.nih.gov/28564564)
17. Kosaka, Y., Rai, Y., Masuda, N., et al. (2015). Phase III Placebo-Controlled, Double-Blind, Randomized Trial of Pegfilgrastim to Reduce the Risk of Febrile Neutropenia in Breast Cancer Patients Receiving Docetaxel/Cyclophosphamide Chemotherapy. Retrieved from [ncbi.nlm.nih.gov/pubmed/25576433](https://pubmed.ncbi.nlm.nih.gov/25576433)
18. Jones, R.L., Walsh, G., Ashley, S., et al. (2009, Jan. 27). A Randomised Pilot Phase II Study of Doxorubicin and Cyclophosphamide (AC) or Epirubicin and Cyclophosphamide (EC) Given Two Weekly with Pegfilgrastim (Accelerated) vs. Three Weekly (Standard) for Women with Early Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=19165198](https://pubmed.ncbi.nlm.nih.gov/?term=19165198)
19. Romond, E.H., Perez, E.A., Bryant, J., et al. Trastuzumab Plus Adjuvant Chemotherapy for Operable HER2 Positive Breast Cancer. *The New England Journal of Medicine*. 2005;353:1673-1684. Retrieved from pubmed.ncbi.nlm.nih.gov/16236738
20. Perez, E.A., Romond, E.H., Suman, V.J., et al. Trastuzumab Plus Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Planned Joint Analysis of Overall Survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-52. Retrieved from pubmed.ncbi.nlm.nih.gov/25332249
21. Piccart-Gebhart, M.J., Procter, M., Leyland-Jones, B., et al. Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Breast Cancer. *N Engl J Med*. 2005;353:1659-72. Retrieved from pubmed.ncbi.nlm.nih.gov/16236737
22. Cameron, D., Piccart-Gebhart, M.J., Gelber, R.D., et al. Eleven Years' Follow-Up of Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer: Final Analysis of the HERceptin Adjuvant (HERA) Trial. *Lancet*. 2017;389(10075):1195-205. Retrieved from pubmed.ncbi.nlm.nih.gov/28215665
23. Gianni, L., et al. Neoadjuvant and Adjuvant Trastuzumab in Patients with HER2-Positive Locally Advanced Breast Cancer (NOAH): Follow-Up of a Randomized Controlled Superiority Trial with a Parallel HER2-Negative Cohort. *Lancet Oncol*. 2014;15(6): 640-647. Retrieved from pubmed.ncbi.nlm.nih.gov/24657003
24. Von Minckwitz, G., Procter, M., Azambuja, E., et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017;377:122-31. Retrieved from pubmed.ncbi.nlm.nih.gov/28581356
25. Tolaney, S.M., Barry, W.T., Dang, C.T., et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. *N Engl J Med*. 2015;372:134-41. Retrieved from pubmed.ncbi.nlm.nih.gov/25564897
26. Slamon, D., Eiermann, W., Robert, N., et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. *N Engl J Med*. 2011;365:1273-1283. Retrieved from pubmed.ncbi.nlm.nih.gov/21991949

27. Burstein, H.J., Piccart-Gebhart, M., Perez, E.A., et al. Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracycline? *J Clin Oncol.* 2012;30(18): 2179-2182. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/22614986/>
28. Schneeweiss, A., Chia, S., Hickish, T., et al. Pertuzumab Plus Trastuzumab in Combination with Standard Neoadjuvant Anthracycline-Containing and Anthracycline-Free Chemotherapy Regimens in Patients with HER2-Positive Early Breast Cancer: A Randomized Phase II Cardiac Safety Study (TRYPHAENA). *Ann Oncol.* 2013;24:2278-2284. Retrieved from <pubmed.ncbi.nlm.nih.gov/23704196>
29. Hurvitz, S.A., Martin, M., Symmans, W.F., et al. Neoadjuvant Trastuzumab, Pertuzumab and Chemotherapy Versus Trastuzumab Emtansine Plus Pertuzumab in Patients with HER2-Positive Breast Cancer (KRISTINE); A Randomised, Open-Label, Multicenter, Phase 3 Trial. *Lancet Oncol.* 2018;19(1):115-126. Retrieved from <pubmed.ncbi.nlm.nih.gov/29175149>
30. Von Minckwitz, G., Huang, C.S., Mano, M.S., et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med.* 2019;380(7):617-628. Retrieved from <pubmed.ncbi.nlm.nih.gov/30516102>
31. Jones, S.E., Collea, R., Paul, D., et al. Adjuvant Docetaxel and Cyclophosphamide Plus Trastuzumab in Patients with HER2-Amplified Early Stage Breast Cancer: A Single-Group, Open-Label, Phase 2 Study. *Lancet Oncol.* 2013;14:1121-8. Retrieved from <pubmed.ncbi.nlm.nih.gov/24007746>
32. Dang, C., Fournier, M., Sugarman, S., et al. The Safety of Dose-Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel with Trastuzumab in HER-2/Neu Over-Expressed/Amplified Breast Cancer. *J Clin Oncol.* 2008;26(8):1216-22. Retrieved from <pubmed.ncbi.nlm.nih.gov/18323546>
33. Chan, A., Delaloge, S., Holmes, F.A., et al. Neratinib After Trastuzumab-Based Adjuvant Therapy in Patients with HER2-Positive Breast Cancer (ExteNET): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol.* 2016 Mar;17(3):367-77. Retrieved from <pubmed.ncbi.nlm.nih.gov/26874901>
34. Martin, M., Holmes, F.A., Ejlertsen, B., et al. Neratinib After Trastuzumab-Based Adjuvant Therapy in HER2-Positive Breast Cancer (ExteNET): Five-Year Analysis of a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol.* 2017 Dec;18(12):1688-1700. Retrieved from <pubmed.ncbi.nlm.nih.gov/29146401>
35. Bonnetterre, J., Thürlimann, B., Robertson, J.F., et al. (2000, Nov. 15). Anastrozole Versus Tamoxifen as First-Line Therapy for Advanced Breast Cancer in 668 Postmenopausal Women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability Study. Retrieved from <ncbi.nlm.nih.gov/pubmed/11078487>
36. Nabholz, J.M., Buzdar, A., Pollak, M., et al. (2000, Nov. 15). Anastrozole Is Superior to Tamoxifen as First-Line Therapy for Advanced Breast Cancer in Postmenopausal Women: Results of a North American Multicenter Randomized Trial. Arimidex Study Group. Retrieved from <ncbi.nlm.nih.gov/pubmed/?term=11078488>
37. Bonnetterre, J., Buzdar, A., Nabholz, J.M., et al. Anastrozole Is Superior to Tamoxifen as First-Line Therapy in Hormone Receptor Positive Advanced Breast Carcinoma: Results of Two Randomized Trials Designed for Combined Analysis. *Cancer* 2001; 92:2247–2258. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/11745278/>
38. Llombart-Cussac, A., Ruiz, A., Antón, A., et al. (2012, Jan. 1). Exemestane Versus Anastrozole as Front-Line Endocrine Therapy in Postmenopausal Patients with Hormone Receptor-Positive, Advanced Breast Cancer: Final Results From the Spanish Breast Cancer Group 2001-03 Phase 2 Randomized Trial. Retrieved from <ncbi.nlm.nih.gov/pubmed/21717449>

39. Ding, H., Fang, L., Xin, W., et al. (November 2017). Cost-Effectiveness Analysis of Fulvestrant Versus Anastrozole as First-Line Treatment for Hormone Receptor-Positive Advanced Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/28675545](https://pubmed.ncbi.nlm.nih.gov/28675545)
40. Mouridsen, H., Gershanovich, M., Sun, Y., et al. (2003, June 1). Phase III Study of Letrozole Versus Tamoxifen as First-Line Therapy of Advanced Breast Cancer in Postmenopausal Women: Analysis of Survival and Update of Efficacy from the International Letrozole Breast Cancer Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=12775735](https://pubmed.ncbi.nlm.nih.gov/?term=12775735)
41. Finn, R.S., Crown, J.P., Lang, I., et al. (January 2015). The Cyclin-Dependent Kinase 4/6 Inhibitor Palbociclib in Combination with Letrozole Versus Letrozole Alone as First-Line Treatment of Oestrogen Receptor-Positive, HER2-Negative, Advanced Breast Cancer (PALOMA-1/TRIO-18): A Randomised Phase 2 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=25524798](https://pubmed.ncbi.nlm.nih.gov/?term=25524798)
42. Finn, R.S., Martin, M., Rugo, H.S., et al. (2016, Nov. 17). Palbociclib and Letrozole in Advanced Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/27959613](https://pubmed.ncbi.nlm.nih.gov/27959613)
43. Hortobagyi, G.N., Stemmer, S.M., Burris, H.A., et al. (2018, July 1). Updated Results From MONALEESA-2, a Phase III Trial of First-Line Ribociclib Plus Letrozole Versus Placebo Plus Letrozole in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/29718092](https://pubmed.ncbi.nlm.nih.gov/29718092)
44. Paridaens, R.J., Dirix, L.Y., Beex, L.V., et al. (2008, Oct. 20). Phase III Study Comparing Exemestane with Tamoxifen as First-Line Hormonal Treatment of Metastatic Breast Cancer in Postmenopausal Women: The European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group. Retrieved from [ncbi.nlm.nih.gov/18794551/](https://pubmed.ncbi.nlm.nih.gov/18794551/)
45. Robertson, J.F., Llombart-Cussac, A., Rolski, J., et al. (2009, Sept. 20). Activity of Fulvestrant 500 mg Versus Anastrozole 1 mg as First-Line Treatment for Advanced Breast Cancer: Results From the FIRST Study. Retrieved from [ncbi.nlm.nih.gov/19704066/](https://pubmed.ncbi.nlm.nih.gov/19704066/)
46. Robertson, J.F., Bondarenko, I.M., Trishkina, E., et al. (2016, Dec. 17). Fulvestrant 500 mg Versus Anastrozole 1 mg for Hormone Receptor-Positive Advanced Breast Cancer (FALCON): An International, Randomised, Double-Blind, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/27908454](https://pubmed.ncbi.nlm.nih.gov/27908454)
47. Di Leo, A., Jerusalem, G., Petruzelka, L., et al. (2010, Oct. 20). Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg with Fulvestrant 500 mg in Postmenopausal Women with Estrogen Receptor-Positive Advanced Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/20855825](https://pubmed.ncbi.nlm.nih.gov/20855825)
48. Di Leo, A., Jerusalem, G., Petruzelka, L., et al. (January 2014). Final Overall Survival: Fulvestrant 500 mg vs. 250 mg in the Randomized CONFIRM Trial. Retrieved from [ncbi.nlm.nih.gov/24317176/](https://pubmed.ncbi.nlm.nih.gov/24317176/)
49. Slamon, D.J., Neven, P., Chia, S., et al. (2018, Aug. 20). Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Retrieved from [ncbi.nlm.nih.gov/pubmed/29860922](https://pubmed.ncbi.nlm.nih.gov/29860922)
50. Tripathy, D., Im, S., Colleoni, M., et al. (July 2018). Ribociclib Plus Endocrine Therapy for Premenopausal Women with Hormone-Receptor-Positive, Advanced Breast Cancer (MONALEESA-7): A Randomised Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/29804902](https://pubmed.ncbi.nlm.nih.gov/29804902)
51. Mistry, R., May, J.R., Suri, G., et al. (June 2018). Cost-Effectiveness of Ribociclib Plus Letrozole Versus Palbociclib Plus Letrozole and Letrozole Monotherapy in the First-Line Treatment of Postmenopausal Women with HR/HER2-Advanced or Metastatic Breast Cancer: A U.S. Payer Perspective. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=29799329](https://pubmed.ncbi.nlm.nih.gov/?term=29799329)

52. Goetz, M.P., Toi, M., Campone, M., et al. (2017, Nov. 10). MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/28968163
53. Johnston, S.R., Kilburn, L.S., Ellis, P., et al. (September 2013). Fulvestrant Plus Anastrozole or Placebo Versus Exemestane Alone After Progression on Non-Steroidal Aromatase Inhibitors in Postmenopausal Patients with Hormone-Receptor-Positive Locally Advanced or Metastatic Breast Cancer (SoFEA): A Composite, Multicentre, Phase 3 Randomised Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=23902874
54. Cristofanilli, M., Turner, N.C., Bondarenko, I., et al. (April 2016). Fulvestrant Plus Palbociclib Versus Fulvestrant Plus Placebo for Treatment of Hormone-Receptor-Positive, HER2-Negative Metastatic Breast Cancer That Progressed on Previous Endocrine Therapy (PALOMA-3): Final Analysis of the Multicentre, Double-Blind, Phase 3 Randomised Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/26947331
55. Yardley, D.A., Noguchi, S., Pritchard, K.I., et al. (2013). Everolimus Plus Exemestane in Postmenopausal Patients with HR(+) Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis. Retrieved from ncbi.nlm.nih.gov/pubmed/24158787
56. Piccart, M., Hortobagyi, G.N., Campone, M., et al. (December 2014). Everolimus Plus Exemestane for Hormone-Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Advanced Breast Cancer: Overall Survival Results From BOLERO-2†. Retrieved from ncbi.nlm.nih.gov/pubmed/25231953
57. Chia, S., Gradishar, W., Mauriac, L., et al. (2008, April 1). Double-Blind, Randomized Placebo-Controlled Trial of Fulvestrant Compared with Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women with Hormone Receptor-Positive, Advanced Breast Cancer: Results From EFACT. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=18316794
58. Kornblum, N., Zhao, F., Manola, J., et al. (2018, June 1). Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. Retrieved from ncbi.nlm.nih.gov/pubmed/29664714
59. Sledge, G.W., Toi, M., Neven, P., et al. (2017, Sept. 1). MONARCH 2: Abemaciclib in Combination with Fulvestrant in Women with HR/HER2-Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. Retrieved from ncbi.nlm.nih.gov/pubmed/28580882
60. Dickler, M.N., Tolaney, S.M., Rugo, H.S., et al. (2017, Sept. 1). MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR/HER2- Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/28533223
61. Bachelot, T., Bourgier, C., Cropet, C., et al. (2012, Aug. 1). Randomized Phase II Trial of Everolimus in Combination with Tamoxifen in Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors: A GINECO Study. Retrieved from ncbi.nlm.nih.gov/pubmed/22565002
62. Turner, N.C., Slamon, D.J., Ro, J., et al. (2018, Nov. 15). Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1810527
63. Li, N., Hao, Y., Xie, J., et al. (2016, Feb. 6). Effectiveness of Everolimus Versus Endocrine Monotherapy or Chemotherapy Among HR+/HER2-mBC Patients with Multiple Metastatic Sites. Retrieved from ncbi.nlm.nih.gov/pubmed/26078883

64. Jerusalem, G., De Boer, R.H., Hurvitz, S., et al. (October 2018). Everolimus Plus Exemestane vs. Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/29862411](https://pubmed.ncbi.nlm.nih.gov/29862411)
65. Kaufman, B., Mackey, J.R., Clemens, M.R., et al. (2009, Nov. 20). Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women with Human Epidermal Growth Factor Receptor 2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=19786670](https://pubmed.ncbi.nlm.nih.gov/?term=19786670)
66. Rimawi, M., Ferrero, J., De la Haba-Rodriguez, J., et al. (2018, Oct. 1). First-Line Trastuzumab Plus an Aromatase Inhibitor, with or without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30106636](https://pubmed.ncbi.nlm.nih.gov/30106636)
67. Johnston, S.R., Hegg, R., Im, S.A., et al. (2018, March 10). Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade with Lapatinib Plus Trastuzumab in Combination with an Aromatase Inhibitor in Postmenopausal Women with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=29244528](https://pubmed.ncbi.nlm.nih.gov/?term=29244528)
68. Huober, J., Fasching, P.A., Barsoum, M., et al. (February 2012). Higher Efficacy of Letrozole in Combination with Trastuzumab Compared to Letrozole Monotherapy as First-Line Treatment in Patients with HER2-Positive, Hormone-Receptor-Positive Metastatic Breast Cancer — Results of the eLEcTRA Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/21862331](https://pubmed.ncbi.nlm.nih.gov/21862331)
69. Johnston, S., Pippen, J., Pivov, X., et al. (2009, Nov. 20). Lapatinib Combined with Letrozole Versus Letrozole and Placebo as First-Line Therapy for Postmenopausal Hormone Receptor-Positive Metastatic Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/19786658](https://pubmed.ncbi.nlm.nih.gov/19786658)
70. Mahmoud, C., Elyse, L., Diane, K., et al. (2017, Jan. 31). The Effect of Trastuzumab Therapy on Clinical Benefit From Fulvestrant Treatment for Metastatic Estrogen Receptor-Positive Breast Cancer Patients. Retrieved from ascopubs.org/DOI/abs/10.1200/jco.2014.32.26_suppl.155
71. Burstein, H.J., Cirrincione, C.T., Barry, W.T., et al. (2014, Dec. 10). Endocrine Therapy with or without Inhibition of Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Fulvestrant with or without Lapatinib for Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer-CALGB 40302 (Alliance). Retrieved from [ncbi.nlm.nih.gov/pubmed/25348000](https://pubmed.ncbi.nlm.nih.gov/25348000)
72. Chan, S., Friedrichs, K., Noel, D., et al. (August 1999). Prospective Randomized Trial of Docetaxel Versus Doxorubicin in Patients with Metastatic Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=10561296](https://pubmed.ncbi.nlm.nih.gov/?term=10561296)
73. Paridaens, R., Biganzoli, L., Bruening, P., et al. (February 2000). Paclitaxel Versus Doxorubicin as First-Line Single-Agent Chemotherapy for Metastatic Breast Cancer: A European Organization for Research and Treatment of Cancer Randomized Study with Cross-Over. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=10673513](https://pubmed.ncbi.nlm.nih.gov/?term=10673513)
74. O'Brien, M.E., Wigler, N., Inbar, M., et al. (March 2004). Reduced Cardiotoxicity and Comparable Efficacy in a Phase III Trial of Pegylated Liposomal Doxorubicin HCl (CAELYX/Doxil) Versus Conventional Doxorubicin for First-Line Treatment of Metastatic Breast Cancer. Retrieved from [hncbi.nlm.nih.gov/pubmed/?term=14998846](https://pubmed.ncbi.nlm.nih.gov/?term=14998846)

75. Gradishar, W.J., Krasnojon, D., Cheporov, S., et al. (2009, Aug. 1). Significantly Longer Progression-Free Survival with Nab-Paclitaxel Compared with Docetaxel as First-Line Therapy for Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/19470941
76. Seidman, A.D., Tiersten, A., Hudis, C., et al. (October 1995). Phase II Trial of Paclitaxel by 3-Hour Infusion as Initial and Salvage Chemotherapy for Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=7595709
77. Miller, K., Wang, M., Gralow, J., et al. (2007, Dec. 27). Paclitaxel Plus Bevacizumab Versus Paclitaxel Alone for Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/18160686
78. Perez, E.A., Vogel, C.L., Irwin, D.H., et al. (2001, Nov. 15). Multicenter Phase II Trial of Weekly Paclitaxel in Women with Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/11709565
79. Stockler, M.R., Harvey, V.J., Francis, P.A., et al. (2011, Dec. 1). Capecitabine Versus Classical Cyclophosphamide, Methotrexate and Fluorouracil as First-Line Chemotherapy for Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/22025143
80. Bajetta, E., Procopio, G., Celio, L., et al. (2005, April 1). Safety and Efficacy of Two Different Doses of Capecitabine in the Treatment of Advanced Breast Cancer in Older Women. Retrieved from ncbi.nlm.nih.gov/pubmed/15710946
81. Carmichael, J., Possinger, K., Phillip, P., et al. (November 1995). Advanced Breast Cancer: A Phase II Trial with Gemcitabine. Retrieved from ncbi.nlm.nih.gov/pubmed/7595731
82. Fumoleau, P., Delgado, F.M., Delozier, T., et al. (July 1993). Phase II Trial of Weekly Intravenous Vinorelbine in First-Line Advanced Breast Cancer Chemotherapy. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=8315421
83. Weber, B.L., Vogel, C., Jones, S., et al. (November 1995). Intravenous Vinorelbine as First-Line and Second-Line Therapy in Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=7595730
84. Langkjer, S.T., Ejlertsen, B., Mouridsen, H., et al. (2008). Vinorelbine as First-Line or Second-Line Therapy for Advanced Breast Cancer: A Phase I-II Trial by the Danish Breast Cancer Cooperative Group. Retrieved from ncbi.nlm.nih.gov/pubmed/18465342
85. Maeda, S., Saimura, M., Minami, S., et al. (April 2017). Efficacy and Safety of Eribulin as First- to Third-Line Treatment in Patients with Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes. Retrieved from ncbi.nlm.nih.gov/pubmed/28056400
86. Kimura, K., Iwamoto, M., Tanaka, S., et al. (May 2018). A Phase II, Multicenter, Single-Arm Trial of Eribulin as First- or Second-Line Chemotherapy for HER2-Negative Advanced or Metastatic Breast Cancer: Evaluation of Efficacy, Safety and Patient-Reported Outcomes. Retrieved from ncbi.nlm.nih.gov/pubmed/29594360
87. Gradishar, W.J., Tjulandin, S., Davidson, N., et al. (2005, Nov. 1). Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared with Polyethylated Castor Oil-Based Paclitaxel in Women with Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/16172456
88. Bastholt, L., Dalmark, M., Gjedde, S.B., et al. (April 1996). Dose-Response Relationship of Epirubicin in the Treatment of Postmenopausal Patients with Metastatic Breast Cancer: A Randomized Study of Epirubicin at Four Different Dose Levels Performed by the Danish Breast Cancer Cooperative Group. Retrieved from ncbi.nlm.nih.gov/pubmed/8648369
89. Nabholz, J., Falkson, C., Campos, D., et al. (2003, March 15). Docetaxel and Doxorubicin Compared with Doxorubicin and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer: Results of a Randomized, Multicenter, Phase III trial. Retrieved from ncbi.nlm.nih.gov/pubmed/12637459

90. Langley, R.E., Carmichael, J., Jones, A.L., et al. (2005, Nov. 20). Phase III Trial of Epirubicin Plus Paclitaxel Compared with Epirubicin Plus Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer: United Kingdom National Cancer Research Institute Trial AB01. Retrieved from ncbi.nlm.nih.gov/pubmed/16293863
91. Stockler, M.R., Harvey, V.J., Francis, P.A., et al. (2011, Dec. 1). Capecitabine Versus Classical Cyclophosphamide, Methotrexate and Fluorouracil as First-Line Chemotherapy for Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/22025143
92. Mavroudis, D., Papakotoulas, P., Ardavanis, A., et al. (January 2010). Randomized Phase III Trial Comparing Docetaxel Plus Epirubicin Versus Docetaxel Plus Capecitabine as First-Line Treatment in Women with Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/19906761
93. Albain, K.S., Nag, S.M., Calderillo-Ruiz, G., et al. (2008, Aug. 20). Gemcitabine Plus Paclitaxel Versus Paclitaxel Monotherapy in Patients with Metastatic Breast Cancer and Prior Anthracycline Treatment. Retrieved from ncbi.nlm.nih.gov/pubmed/18711184
94. Bontenbal, M., Andersson, M., Wildiers, J., et al. (1998). Doxorubicin vs. Epirubicin, Report of a Second-Line Randomized Phase 11/111 Study in Advanced Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pmc/articles/PMC2150384/pdf/brjcancer00088-0203.pdf
95. Gasparini, G., Dal, S., Panizzoni, G.A., et al. (February 1991). Weekly Epirubicin Versus Doxorubicin as Second-Line Therapy in Advanced Breast Cancer. A Randomized Clinical Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=1987737
96. Rha, S.Y., Moon, Y.H., Jeung, H.C., et al. (April 2005). Gemcitabine Monotherapy as Salvage Chemotherapy in Heavily Pretreated Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=15830134
97. Spielmann, M., Llombart-Cussac, A., Kalla, S., et al. (2001). Single-Agent Gemcitabine Is Active in Previously Treated Metastatic Breast Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=11408796
98. Zelek, L., Barthier, S., Riofrio, M., et al. (2001, Nov. 1). Weekly Vinorelbine Is an Effective Palliative Regimen After Failure with Anthracyclines and Taxanes in Metastatic Breast Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=11745280
99. Cortes, J., O'Shaughnessy, J., Loesch, D., et al. (2011, March 12). Eribulin Monotherapy Versus Treatment of Physician's Choice in Patients with Metastatic Breast Cancer (EMBRACE): A Phase III Open-Label Randomised Study. Retrieved from ncbi.nlm.nih.gov/pubmed/21376385
100. Vahdat, L.T., Garcia, A.A., Vogel, C., et al. (July 2013). Eribulin Mesylate Versus Ixabepilone in Patients with Metastatic Breast Cancer: A Randomized Phase II Study Comparing the Incidence of Peripheral Neuropathy. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=23877339
101. Perez, E.A., Lerzo, G., Pivot, X., et al. (2007, Aug. 10). Efficacy and Safety of Ixabepilone (BMS-247550) in a Phase II Study of Patients with Advanced Breast Cancer Resistant to an Anthracycline, a Taxane and Capecitabine. Retrieved from ncbi.nlm.nih.gov/pubmed/17606974
102. Litton, J.K., Rugo, H.S., Ettl, J., et al. (2018, Aug. 23). Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. Retrieved from ncbi.nlm.nih.gov/pubmed/30110579
103. Robson, M., Im, S., Senkus, E., et al. (2017, Aug. 10). Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. Retrieved from ncbi.nlm.nih.gov/pubmed/28578601

104. Tutt, A., Tovey, H., Cheang, M.C., et al. (May 2018). Carboplatin in BRCA1/2-Mutated and Triple-Negative Breast Cancer BRCAness Subgroups: The TNT Trial. Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC6372067](https://pubmed.ncbi.nlm.nih.gov/36372067/)
105. Isakoff, S.J., Mayer, E.L., He, L., et al. (2015, June 10). TBCRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy with Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=tbcrc009](https://pubmed.ncbi.nlm.nih.gov/25693012/)
106. Byrski, T., Dent, R., Blecharz, P., et al. (2012, July 20). Results of a Phase II Open-Label, Non-Randomized Trial of Cisplatin Chemotherapy in Patients with BRCA1-Positive Metastatic Breast Cancer. Retrieved from breast-cancer-research.biomedcentral.com/articles/10.1186/bcr3231
107. Schmid, P., Adams, S., Rugo, H.S., et al. (2018, Nov. 29). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/30345906](https://pubmed.ncbi.nlm.nih.gov/30345906/)
108. Carrick, S., Parker, S., Wilcken, N., et al. (2005, April 18). Single Agent Versus Combination Chemotherapy for Metastatic Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/15846660](https://pubmed.ncbi.nlm.nih.gov/15846660/)
109. Jones, S.E., Erban, J., Overmoyer, B., et al. (2005, Aug. 20). Randomized Phase III Study of Docetaxel Compared with Paclitaxel in Metastatic Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/16110015](https://pubmed.ncbi.nlm.nih.gov/16110015/)
110. Yuan, P., Hu, X., Sun, T., et al. (May 2019). Eribulin Mesilate Versus Vinorelbine in Women with Locally Recurrent or Metastatic Breast Cancer: A Randomised Clinical Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30928806](https://pubmed.ncbi.nlm.nih.gov/30928806/)
111. Baselga, J., Cortes, J., Kim, S.B., et al. Pertuzumab Plus Trastuzumab Plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med.* 2012;366:109-119. Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC5705202](https://pubmed.ncbi.nlm.nih.gov/22547504/)
112. Swain, S.M., Baselga, J., Kim, S.B., et al. Pertuzumab Plus Trastuzumab Plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med.* 2015;372(8):724-34. Retrieved from pubmed.ncbi.nlm.nih.gov/25693012
113. Dang, C., Iyengar, N., Datko, F., et al. Phase II Study of Paclitaxel Given Once per Week Along with Trastuzumab and Pertuzumab in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *J Clin Oncol.* 2015;33(5): 442-47. Retrieved from pubmed.ncbi.nlm.nih.gov/25547504
114. Smyth, L.M., Iyengar, N.M., Chen, M.F., et al. Weekly Paclitaxel with Trastuzumab and Pertuzumab in Patients with HER2-Overexpressing Metastatic Breast Cancer: Overall Survival and Updated Progression-Free Survival Results From a Phase II Study. *Breast Cancer Res Treat.* 2016;158(1):91-97. Retrieved from pubmed.ncbi.nlm.nih.gov/27306421
115. Wang, R., Smyth, L.M., Iyengar, N., et al. (2019). Phase II Study of Weekly Paclitaxel with Trastuzumab and Pertuzumab in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: Five-Year Follow-Up. *Oncologist.* Retrieved from pubmed.ncbi.nlm.nih.gov/30602614
116. Verma, S., Miles, D., Gianni, L., et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer [Supplementary Appendix Available Online]. *N Engl J Med.* 2012;367:1783-1791. Retrieved from pubmed.ncbi.nlm.nih.gov/23020162
117. Perez, E.A., Barrios, C., Eiermann, W., et al. Trastuzumab Emtansine with or without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. *J Clin Oncol.* 2017;35(2):141-148. Retrieved from pubmed.ncbi.nlm.nih.gov/28056202

118. A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Participants with Metastatic Breast Cancer (MARIANNE). Retrieved from clinicaltrials.gov/ct2/show/results/NCT01120184
119. Leyland-Jones, B., Gelmon, K., Ayoub, J.P., et al. Pharmacokinetics, Safety, and Efficacy of Trastuzumab Administered Every Three Weeks in Combination with Paclitaxel. *J Clin Oncol.* 2003;21:3965-3971. Retrieved from pubmed.ncbi.nlm.nih.gov/14507946
120. Robert, N., Leyland-Jones, B., Asmar, L., et al. Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared with Trastuzumab and Paclitaxel in Women with HER2-Overexpressing Metastatic Breast Cancer. *J Clin Oncol.* 2006;24:2786-2792. Retrieved from pubmed.ncbi.nlm.nih.gov/16782917
121. Perez, E.A., Suman, V.J., Rowland, K.M., et al. Two Concurrent Phase II Trials of Paclitaxel/Carboplatin/ Trastuzumab (Weekly or Every-Three-Week Schedule) as First-Line Therapy in Women with HER2-Overexpressing Metastatic Breast Cancer. NCCTG study 983252. *Clin Breast Cancer.* 2005;6:425-432. Retrieved from pubmed.ncbi.nlm.nih.gov/16381626
122. Giordano, S.H., Temin, S., Chandarlapaty, S., et al. Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol.* 2018; 36(26): 2736-2740. Retrieved from pubmed.ncbi.nlm.nih.gov/29939838
123. Seidman, A., Berry, D.A., Cirrincione, C., et al. Randomized Phase III Trial of Weekly Compared with Every-Three-Weeks Paclitaxel for Metastatic Breast Cancer, with Trastuzumab for All HER2 Overexpressors and Random Assignment to Trastuzumab or Not in HER2 Non-Overexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840. *J Clin Oncol.* 2008;26:1642-1649. Retrieved from pubmed.ncbi.nlm.nih.gov/18375893
124. Marty, M., Cognetti, F., Maraninchi, E., et al. Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined with Docetaxel in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered as First-Line Treatment: the M77001 Study Group. *J Clin Oncol.* 2005;23:4265-4274. Retrieved from pubmed.ncbi.nlm.nih.gov/15911866
125. Esteva, F.J., Valero, V., Booser, D., et al. Phase II Study of Weekly Docetaxel and Trastuzumab for Patients with HER-2-Overexpressing Metastatic Breast Cancer. *J Clin Oncol.* 2002;20:1800-1808. Retrieved from pubmed.ncbi.nlm.nih.gov/11919237
126. Andersson, M., Lidbrink, E., Bjerre, K., et al. Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab with Vinorelbine Plus Trastuzumab as First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: the HERNATA Study. *J Clin Oncol.* 2011;29:264-271. Retrieved from pubmed.ncbi.nlm.nih.gov/21149659
127. Burstein, H.J., Keshaviah, A., Baron, A.D., et al. Trastuzumab Plus Vinorelbine or Taxane Chemotherapy for HER2-Overexpressing Metastatic Breast Cancer: The Trastuzumab and Vinorelbine or Taxane Study. *Cancer.* 2007; 110:965-972. Retrieved from pubmed.ncbi.nlm.nih.gov/17614302
128. Andersson, M., Lidbrink, E., Bjerre, K., et al. Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab with Vinorelbine Plus Trastuzumab as First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The HERNATA Study. *J Clin Oncol.* 2011;29:264-271. Retrieved from pubmed.ncbi.nlm.nih.gov/21149659
129. Papaldo, P., Fabi, A., Ferretti, G., et al. A Phase II Study on Metastatic Breast Cancer Patients Treated with Weekly Vinorelbine with or without Trastuzumab According to HER2 Expression:

- Changing the Natural History of HER2-Positive Disease. *Ann Oncol*. 2006; 17(4):630-636. Retrieved from pubmed.ncbi.nlm.nih.gov/16410363
130. Yardley, D.A., Burris, H.A., Hanson, S., et al. Weekly Gemcitabine and Trastuzumab in the Treatment of Patients with HER2-Overexpressing Metastatic Breast Cancer. *Clin Breast Cancer*. 2009; 9(3): 178-83. Retrieved from pubmed.ncbi.nlm.nih.gov/19661042
 131. von Minchwitz, G., du Bois, A., Schmidt, M., et al. Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study. *J Clin Oncol*. 2009;27:1999-2006. Retrieved from pubmed.ncbi.nlm.nih.gov/19289619
 132. Cobleigh, M.A., Vogel, C.L., Tripathy, D., et al. Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease. *J Clin Oncol*. 1999;17:2639-2648. Retrieved from pubmed.ncbi.nlm.nih.gov/1056133
 133. Bartsch, R., Wenzel, C., Altorjai, G., et al. Capecitabine and Trastuzumab in Heavily Pretreated Metastatic Breast Cancer. *J Clin Oncol*. 2007;25:3853-3858. Retrieved from pubmed.ncbi.nlm.nih.gov/17679724
 134. Geyer, C., Forster, J., Lindquist, D., et al. Lapatinib Plus Capecitabine for HER2-Positive Advanced Breast Cancer. *N Engl J Med*. 2006;255:2733-2743. Retrieved from pubmed.ncbi.nlm.nih.gov/17192538
 135. Verma, S., Miles, D., Gianni, L., et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer [Supplementary Appendix Available Online]. *N Engl J Med*. 2012;367:1783-1791. Retrieved from pubmed.ncbi.nlm.nih.gov/23020162
 136. Blackwell, K.L., Burstein, H., Storniolo, A., et al. Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer. *J Clin Oncol*. 2010;28(7):1124-30. Retrieved from pubmed.ncbi.nlm.nih.gov/20124187
 137. Blackwell, K.L., Burstein, H.J., Storniolo, A.M., et al. Overall Survival Benefit with Lapatinib in Combination with Trastuzumab for Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: Final Results From the EGF104900 Study. *J Clin Oncol*. 2012 Jul 20;30(21):2585-2592. Retrieved from pubmed.ncbi.nlm.nih.gov/22689807
 138. 2019 ASP Files. [cms.gov](https://www.cms.gov). Centers for Medicare & Medicaid Services. (2019, March 19). Accessed May 20, 2019. Retrieved from [cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html](https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html)
 139. Medi-Span Price Rx. Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; May 31, 2019
 140. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Accessed July 8, 2020. Retrieved from [nccn.org/professionals/physician_gls/default.aspx#breast](https://www.nccn.org/professionals/physician_gls/default.aspx#breast)
 141. Schmid, P., Cortes, J., Pusztai, L., et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med*. 2020;382(9):810-821. DOI:10.1056/NEJMoa1910549
 142. Piccart, M., et al. Interim OS Analysis of APHINITY (BIG 4-11): A Randomized Multicenter, Double-Blind, Placebo-Controlled Trial Comparing Chemotherapy Plus Trastuzumab Plus Pertuzumab Versus Chemotherapy Plus Trastuzumab Plus Placebo as Adjuvant Therapy in Patients with Operable HER2-Positive eBC. Presented at SABCs, 2019, Dec. 10-14; San Antonio, Texas. Abstract #GS1-04

143. André, F., Ciruelos, E., Rubovszky, G., et al. (2019, May 16). Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/31091374?dopt=Abstract](https://pubmed.ncbi.nlm.nih.gov/pubmed/31091374?dopt=Abstract)
144. Hurvitz, S.A., Im, S.A., Lu, Y.S., et al. Phase III MONALEESA-7 Trial of Premenopausal Patients with HR+/HER2- Advanced Breast Cancer Treated with Endocrine Therapy with and without Ribociclib: Overall Survival Results. 2019 ASCO Annual Meeting. Abstract LBA1008. Presented June 4, 2019
145. Wegener, W., et al. ASCENT – Study of Sacituzumab Govitecan in Refractory/Relapsed Triple-Negative Breast Cancer (ASCENT). Retrieved from clinicaltrials.gov/ct2/show/NCT02574455
146. Modi, S., Saura, C., Yamashita, T., et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med*. 2020;382(7):610-621. DOI:10.1056/NEJMoa1914510
147. Martin, M., Bonnetterre, J., Geyer, C.E. Jr., et al. A Phase Two Randomised Trial of Neratinib Monotherapy Versus Lapatinib Plus Capecitabine Combination Therapy in Patients with HER2+ Advanced Breast Cancer. *Eur J Cancer*. 2013;49(18):3763-3772. DOI:10.1016/j.ejca.2013.07.142
148. Saura, C., Oliveira, M., Feng, Y.H., et al. Neratinib + Capecitabine vs. Lapatinib + Capecitabine in Patients with HER2+ Metastatic Breast Cancer Previously Treated with ≥ 2 HER2-Directed Regimens: Findings From the Multinational, Randomized, Phase III NALA trial. 2019 ASCO Annual Meeting. Abstract 1002. Presented June 4, 2019
149. Murthy, R.K., Loi, S., Okines, A., et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer [published correction appears in *N Engl J Med*. 2020 Feb 6;382(6):586]. *N Engl J Med*. 2020;382(7):597-609. DOI:10.1056/NEJMoa1914609
150. Schmid, P., Cortes, J., Puzstai, L., et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med*. 2020;382(9):810-821. DOI:10.1056/NEJMoa1910549
151. Tutt, A.N.J., Garber, J.E., Kaufman, B., et al.; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. 2021 Jun 24;384(25):2394-2405. DOI: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848
152. Piccart, M., Procter, M., Fumagalli, D., et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *J Clin Oncol* 2021;39(13):1448-1457
153. Swain, S.M., Ewer, M.S., Viale, G., et al. Pertuzumab, Trastuzumab and Standard Anthracycline- and Taxane-Based Chemotherapy for the Neoadjuvant Treatment of Patients with HER2-Positive Localized Breast Cancer (BERENICE): A Phase II, Open-Label, Multicenter, Multinational Cardiac Safety Study. *Ann Oncol*. 2018; 29(3): 646-653
154. Cortes, J., Cescon, D.W., Rugo, H.S., et al.; KEYNOTE-355 Investigators. Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (KEYNOTE-355): A Randomised, Placebo-Controlled, Double-Blind, Phase 3 Clinical Trial. *Lancet*. 2020 Dec 5;396(10265):1817-1828. DOI: 10.1016/S0140-6736(20)32531-9. PMID: 33278935
155. Rugo, H.S., Im, S.A., Cardoso, F., et al.; SOPHIA Study Group. Efficacy of Margetuximab vs. Trastuzumab in Patients with Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2021 Apr 1;7(4):573-584. DOI: 10.1001/jamaoncol.2020.7932. PMID: 33480963; PMCID: PMC7823434

156. Cortes, J., et al, LBA1 – Trastuzumab Deruxtecan (T-DXd) vs. Trastuzumab Emtansine (T-DM1) in Patients (Pts) with HER2+ Metastatic Breast Cancer (mBC): Results of the Randomized Phase III DESTINY-Breast03 study. *Annals of Oncology* (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741
157. Rugo H.S., Cortes, J., Cescon, D.W., et al.; KEYNOTE-355 Investigators. Final Results From a Randomized, Double-Blind Phase III Study of First-Line Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy for Metastatic Triple-Negative Breast Cancer. ESMO Congress 2021. Abstract LBA16. Presented Sept. 19, 2021
158. Bardia, A., Hurvitz, S.A., Tolaney, S.M., et al.; ASCENT Clinical Trial Investigators. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med*. 2021 Apr 22;384(16):1529-1541. DOI: 10.1056/NEJMoa2028485. PMID: 33882206
159. Schmid, P., Cortes, J., Dent, R., et al; KEYNOTE-522 Investigators. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med*. 2022 Feb 10;386(6):556-567. DOI: 10.1056/NEJMoa2112651. PMID: 35139274.
160. Modi S, et al. DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. 2022 Jul 7;387(1):9-20. DOI: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782.
161. Rugo HS, et al. Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast CancerTROPiCS02 *J Clin Oncology* 2022. DOI: 10.1200/JCO.22.01002 *Journal of Clinical Oncology*
162. Hortobagyi GN, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2022 Mar 10;386(10):942-950. DOI: 10.1056/NEJMoa2114663. PMID: 35263519.
163. Finn RS, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2– ABC): Analyses from PALOMA-2.10.1200/JCO.2022.40.17_suppl.LBA1003 *J Clin Oncol* 40, no. 17_suppl (June 10, 2022) LBA1003-LBA1003
164. Isakoff SJ, Mayer EL, He L, et al. TBCRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy with Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. *J Clin Oncol*. 2015;33(17):1902-1909. DOI:10.1200/JCO.2014.57.6660

Colon/Rectal Cancer

Adjuvant

- Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX)
- Capecitabine + Oxaliplatin (CAPEOX)
- Fluorouracil (5-FU)/Leucovorin

Metastatic — pMMR/ MSS

RAS/BRAF Wild Type or Mutant

1st and 2nd Lines of Therapy

- Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX) +/- Bevacizumab
- Fluorouracil + Leucovorin + Irinotecan (FOLFIRI) +/- Bevacizumab
- Fluorouracil + Leucovorin +/- Bevacizumab
- Capecitabine

RAS/BRAF Wild Type -Left-sided Tumor Only

1st and 2nd Lines of Therapy

- Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX) + Cetuximab
- Fluorouracil + Leucovorin + Irinotecan (FOLFIRI) + Cetuximab
- Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX) + Panitumumab
- Fluorouracil + Leucovorin + Irinotecan (FOLFIRI) + Panitumumab

Metastatic — dMMR/ MSI-H

RAS/BRAF Wild Type or Mutant

1st Line of Therapy

- Pembrolizumab

2nd and Subsequent Lines of Therapy

- FOLFOX +/- Bevacizumab
- FOLFIRI +/- Bevacizumab
- 5-FU + Leucovorin +/- Bevacizumab
- Capecitabine

RAS/BRAF Wild Type - Left-sided Tumor Only

2nd and Subsequent Lines of Therapy

- FOLFOX + Cetuximab*
- FOLFIRI + Cetuximab*
- FOLFOX + Panitumumab*
- FOLFIRI + Panitumumab*

* If no prior progression on KRAS/NRAS/BRAF WT therapy

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/colorect.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer (V2.2023, April 25, 2023). Accessed August 2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer (V4.2023, July 25, 2023). Accessed August 2023. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf
4. Andre, T., Boni, C., Mounedji-Boudiaf, L., et al. Oxaliplatin, Fluorouracil and Leucovorin as Adjuvant Treatment for Colon Cancer. *N Engl J Med.* 2004; 350:2343-2351. Retrieved from pubmed.ncbi.nlm.nih.gov/15175436
5. Andre, T., Boni, C., Navarro, M., et al. Improved Overall Survival with Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. *J Clin Oncol.* 2009; 27(19): 3109-3116. Retrieved from pubmed.ncbi.nlm.nih.gov/19451431
6. Andre, T., de Gramont, A., Vemerey, D., et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. *J Clin Oncol.* 2015; 33(35): 4176-4187
7. Haller, D.G., Tabernero, J., Maroun, J., et al. Capecitabine Plus Oxaliplatin Compared with Fluorouracil and Folinic Acid as Adjuvant Therapy for Stage III Colon Cancer. *J Clin Oncol.* 2011; 29: 1465-1471. Retrieved from pubmed.ncbi.nlm.nih.gov/21383294
8. Schmoll, H.J., Cartwright, T., Tabernero, J., et al. Phase III Trial of Capecitabine Plus Oxaliplatin as Adjuvant Therapy for Stage III Colon Cancer: A Planned Safety Analysis in 1,864 Patients. *J Clin Oncol.* 2007; 25: 102-109. Retrieved from pubmed.ncbi.nlm.nih.gov/17194911
9. Twelves, C., Wong, A., Nowacki, M.P., et al. Capecitabine as Adjuvant Treatment for Stage III Colon Cancer. *N Engl J Med.* 2005; 352:2696-2704. Retrieved from pubmed.ncbi.nlm.nih.gov/15987918
10. Grothy, A., Sobrero, A.F., Shields, A.F., et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N Engl J Med.* 2018; 378: 1177-1188. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1713709
11. Amlani, A., Kumar, A., Ruan, J., Cheung, W.Y. Compliance with Adjuvant Capecitabine in Patients with Stage II and III Colon Cancer: Comparison of Administrative Versus Medical Record Data. *Cancer Medicine* 2016; 5(8): 1776-1782. Retrieved from pubmed.ncbi.nlm.nih.gov/27228415

12. Colucci, G., Gebbia, V., Paoletti, G., et al. (2005, Aug. 1). Phase III Randomized Trial of FOLFIRI Versus FOLFOX4 in the Treatment of Advanced Colorectal Cancer: A Multicenter Study of the Gruppo Oncologico Dell'Italia Meridionale. Retrieved from [ncbi.nlm.nih.gov/pubmed/15939922](https://pubmed.ncbi.nlm.nih.gov/15939922)
13. Tournigand, C., André, T., Achille, E., et al. (2004, Jan. 15). FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/14657227](https://pubmed.ncbi.nlm.nih.gov/14657227)
14. Maindrault-Goebel, F., de Gramont, A., Louvet, C., et al. (November 2000). Evaluation of Oxaliplatin Dose Intensity in Bimonthly Leucovorin and 48-Hour 5-Fluorouracil Continuous Infusion Regimens (FOLFOX) in Pretreated Metastatic Colorectal Cancer. Oncology Multidisciplinary Research Group (GERCOR). Retrieved from [ncbi.nlm.nih.gov/pubmed/11142489](https://pubmed.ncbi.nlm.nih.gov/11142489)
15. Emmanouilides, C., Sfakiotaki, G., Androulakis, N., et al. (2007, May 30). Front-Line Bevacizumab in Combination with Oxaliplatin, Leucovorin and 5-Fluorouracil (FOLFOX) in Patients with Metastatic Colorectal Cancer: A Multicenter Phase II Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/17537235](https://pubmed.ncbi.nlm.nih.gov/17537235)
16. Yamazaki, K., Nagase, M., Tamagawa, H., et al. (August 2016). Randomized Phase III Study of Bevacizumab Plus FOLFIRI and Bevacizumab Plus mFOLFOX6 as First-Line Treatment for Patients with Metastatic Colorectal Cancer (WJOG4407G). Retrieved from [ncbi.nlm.nih.gov/pubmed/27177863](https://pubmed.ncbi.nlm.nih.gov/27177863)
17. Porschen, R., Arkenau, H.T., Kubicka, S., et al. (2007, Sept. 20). Phase III Study of Capecitabine Plus Oxaliplatin Compared with Fluorouracil and Leucovorin Plus Oxaliplatin in Metastatic Colorectal Cancer: A Final Report of the AIO Colorectal Study Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/17548840](https://pubmed.ncbi.nlm.nih.gov/17548840)
18. Cassidy, J., Clarke, S., Díaz-Rubio, E., et al. (2008, April 20). Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared with Fluorouracil/Folinic Acid Plus Oxaliplatin as First-Line Therapy for Metastatic Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/18421053](https://pubmed.ncbi.nlm.nih.gov/18421053)
19. Saltz, L.B., Clarke, S., Díaz-Rubio, E., et al. (2008, April 20). Bevacizumab in Combination with Oxaliplatin-Based Chemotherapy as First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/18421054](https://pubmed.ncbi.nlm.nih.gov/18421054)
20. Schmiegel, W., Reinacher-Schick, A., Arnold, D., et al. (June 2013). Capecitabine/Irinotecan or Capecitabine/Oxaliplatin in Combination with Bevacizumab Is Effective and Safe as First-Line Therapy for Metastatic Colorectal Cancer: A Randomized Phase II Study of the AIO Colorectal Study Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/23463625](https://pubmed.ncbi.nlm.nih.gov/23463625)
21. Colucci, G., Gebbia, V., Paoletti, G., et al. (2005, Aug. 1). Phase III Randomized Trial of FOLFIRI Versus FOLFOX4 in the Treatment of Advanced Colorectal Cancer: A Multicenter Study of the Gruppo Oncologico Dell'Italia Meridionale. Retrieved from [ncbi.nlm.nih.gov/pubmed/15939922](https://pubmed.ncbi.nlm.nih.gov/15939922)
22. Fuchs, C.S., Marshall, J., Mitchell, E., et al. (2007, Oct. 20). Randomized, Controlled Trial of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Results from the BICC-C Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/17947725](https://pubmed.ncbi.nlm.nih.gov/17947725)
23. Van Cutsem, E., Tabernero, J., Lakomy, R., et al. (2012, Oct. 1). Addition of Aflibercept to Fluorouracil, Leucovorin and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients with Metastatic Colorectal Cancer Previously Treated with an Oxaliplatin-Based regimen. Retrieved from [ncbi.nlm.nih.gov/pubmed/22949147](https://pubmed.ncbi.nlm.nih.gov/22949147)

24. Tabernero, J., Van Cutsem, E., Lakomý, R., et al. (January 2014). Afibercept Versus Placebo in Combination with Fluorouracil, Leucovorin and Irinotecan in the Treatment of Previously Treated Metastatic Colorectal Cancer: Pre-Specified Subgroup Analyses From the VELOUR Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/24140268](https://pubmed.ncbi.nlm.nih.gov/24140268)
25. Tabernero, J., Yoshino, T., Cohn, A.L., et al. (May 2015). Ramucirumab Versus Placebo in Combination with Second-Line FOLFIRI in Patients with Metastatic Colorectal Carcinoma That Progressed During or After First-Line Therapy with Bevacizumab, Oxaliplatin, and a Fluoropyrimidine (RAISE): A Randomised, Double-Blind, Multicentre, Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/25877855](https://pubmed.ncbi.nlm.nih.gov/25877855)
26. Falcone, A., Ricci, S., Brunetti, I., et al. (2007, May 1). Phase III Trial of Infusional Fluorouracil, Leucovorin, Oxaliplatin and Irinotecan (FOLFOXIRI) Compared with Infusional Fluorouracil, Leucovorin and Irinotecan (FOLFIRI) as First-Line Treatment for Metastatic Colorectal Cancer: The Gruppo Oncologico Nord Ovest. Retrieved from [ncbi.nlm.nih.gov/pubmed/17470860](https://pubmed.ncbi.nlm.nih.gov/17470860)
27. Souglakos, J., Androulakis, N., Syrigos, K., et al. (2006, March 27). FOLFOXIRI (Folinic Acid, 5-Fluorouracil, Oxaliplatin and Irinotecan) vs. FOLFIRI (Folinic Acid, 5-Fluorouracil and Irinotecan) as First-Line Treatment in Metastatic Colorectal Cancer (MCC): A Multicentre Randomised Phase III Trial from the Hellenic Oncology Research Group (HORG). Retrieved from [ncbi.nlm.nih.gov/pubmed/16508637](https://pubmed.ncbi.nlm.nih.gov/16508637)
28. Loupakis, F., Cremolini, C., Masi, G., et al. (October 2014). Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer. Retrieved from pubmed.ncbi.nlm.nih.gov/25337750
29. Cremolini, C., Loupakis, F., Antoniotti, C., et al. (October 2015). FOLFOXIRI Plus Bevacizumab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment of Patients with Metastatic Colorectal Cancer: Updated Overall Survival and Molecular Subgroup Analyses of the Open-Label, Phase 3 TRIBE Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/26338525](https://pubmed.ncbi.nlm.nih.gov/26338525)
30. Cremolini, C., Loupakis, F., Masi, G., et al. (May 2016). FOLFOXIRI or FOLFOXIRI Plus Bevacizumab as First-Line Treatment of Metastatic Colorectal Cancer: A Propensity Score-Adjusted Analysis From Two Randomized Clinical Trials. Retrieved from [ncbi.nlm.nih.gov/pubmed/26861604](https://pubmed.ncbi.nlm.nih.gov/26861604)
31. Van Cutsem, E., Hoff, P.M., Harper, P., et al. (2004, March 22). Oral Capecitabine vs. Intravenous 5-Fluorouracil and Leucovorin: Integrated Efficacy Data and Novel Analyses From Two Large, Randomised, Phase III Trials. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=15026800](https://pubmed.ncbi.nlm.nih.gov/?term=15026800)
32. Cunningham, D., Lang, I., Marcuello, E., et al. (October 2013). Bevacizumab Plus Capecitabine Versus Capecitabine Alone in Elderly Patients with Previously Untreated Metastatic Colorectal Cancer (AVEX): An Open-Label, Randomised Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/24028813](https://pubmed.ncbi.nlm.nih.gov/24028813)
33. Fuchs, C.S., Moore, M.R., Harker, G., et al. (2003, March 1). Phase III Comparison of Two Irinotecan Dosing Regimens in Second-Line Therapy of Metastatic Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/12610178](https://pubmed.ncbi.nlm.nih.gov/12610178)
34. Pitot, H.C., Wender, D.B., O'Connell, M.J., et al. (August 1997). Phase II Trial of Irinotecan in Patients with Metastatic Colorectal Carcinoma. Retrieved from ascopubs.org/DOI/pdfdirect/10.1200/JCO.1997.15.8.2910
35. Kuramochi, H., Ando, M., Itabashi, M., et al. (March 2017). Phase II Study of Bevacizumab and Irinotecan as Second-Line Therapy for Patients with Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidines, Oxaliplatin and Bevacizumab. Retrieved from [ncbi.nlm.nih.gov/pubmed/28213683](https://pubmed.ncbi.nlm.nih.gov/28213683)

36. de Gramont, A., Figer, A., Seymour, M., et al. (August 2000). Leucovorin and Fluorouracil with or without Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/10944126
37. Hurwitz, H.I., Fehrenbacher, L., Hainsworth, J.D., et al. (2005, May 20). Bevacizumab in Combination with Fluorouracil and Leucovorin: An Active Regimen for First-Line Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15908660
38. Grothey, A., Van Cutsem, E., Sobrero, A., et al. (2013, Jan. 26). Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer (CORRECT): An International, Multicentre, Randomised, Placebo-Controlled, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/23177514
39. Mayer, R.J., Van Cutsem, E., Falcone, A., et al. (2015, May 14). Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/25970050
40. Bennouna, J., Sastre, J., Arnold, D., et al. (January 2013). Continuation of Bevacizumab After First Progression in Metastatic Colorectal Cancer (ML18147): A Randomised Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/23168366
41. Qin, S., Li, J., Wang, L., et al. (2018, Oct. 20). Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients with RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/30199311
42. Bokemeyer, C., Bondarenko, I., Makhson, A., et al. (2009, Feb. 10). Fluorouracil, Leucovorin and Oxaliplatin with and without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/19114683
43. Douillard, J.Y., Siena, S., Cassidy, J., et al. (2010, Nov. 1). Randomized, Phase III Trial of Panitumumab with Infusional Fluorouracil, Leucovorin and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone as First-Line Treatment in Patients with Previously Untreated Metastatic Colorectal Cancer: The PRIME Study. Retrieved from ncbi.nlm.nih.gov/pubmed/20921465
44. Rivera, F., Karthaus, M., Hecht, J.R., et al. (August 2017). Final Analysis of the Randomised PEAK Trial: Overall Survival and Tumour Responses During First-Line Treatment with mFOLFOX6 Plus Either Panitumumab or Bevacizumab in Patients with Metastatic Colorectal Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/28424871
45. Heinemann, V., von Weikersthal, L.F., Decker, T., et al. (September 2014). FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment for Patients with Metastatic Colorectal Cancer (FIRE-3): A Randomised, Open-Label, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/25088940
46. Peeters, M., Price, T.J., Cervantes, A., et al. (2010, Nov. 1). Randomized Phase III Study of Panitumumab with Fluorouracil, Leucovorin and Irinotecan (FOLFIRI) Compared with FOLFIRI Alone as Second-Line Treatment in Patients with Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/20921462
47. Hecht, J.R., Cohn, A., Dakhil, S., et al. (June 2015). SPIRITT: A Randomized, Multicenter, Phase II Study of Panitumumab with FOLFIRI and Bevacizumab with FOLFIRI as Second-Line Treatment in Patients with Unresectable Wild Type KRAS Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/25982297
48. Cunningham, D., Humblet, Y., Siena, S., et al. (2004, July 22). Cetuximab Monotherapy and Cetuximab Plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15269313

49. André, T., Blons, H., Mabro, M., et al. (February 2013). Panitumumab Combined with Irinotecan for Patients with KRAS Wild-Type Metastatic Colorectal Cancer Refractory to Standard Chemotherapy: A GERCOR Efficacy, Tolerance and Translational Molecular Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/23041588](https://pubmed.ncbi.nlm.nih.gov/23041588)
50. Nishi, T., Hamamoto, Y., Nagase, M., et al. (June 2016). Phase II Trial of Panitumumab with Irinotecan as Salvage Therapy for Patients with Advanced or Recurrent Colorectal Cancer (TOPIC study). Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC4888220](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC4888220)
51. Seymour, M.T., Brown, S.R., Middleton, G., et al. (July 2013). Panitumumab and Irinotecan Versus Irinotecan Alone for Patients with KRAS Wild Type, Fluorouracil-Resistant Advanced Colorectal Cancer (PICCOLO): A Prospectively Stratified Randomised Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=23725851](https://pubmed.ncbi.nlm.nih.gov/?term=23725851)
52. Cunningham, D., Humblet, Y., Siena, S., et al. (2004, July 22). Cetuximab Monotherapy and Cetuximab Plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/15269313](https://pubmed.ncbi.nlm.nih.gov/15269313)
53. Jonker, D.J., O'Callaghan, C.J., Karapetis, C.S., et al. (2007, Nov. 15). Cetuximab for the Treatment of Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/18003960](https://pubmed.ncbi.nlm.nih.gov/18003960)
54. Price, T.J., Peeters, M., Kim, T.W., et al. (May 2014). Panitumumab Versus Cetuximab in Patients with Chemotherapy-Refractory Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer (ASPECCT): A Randomised, Multicentre, Open-Label, Non-Inferiority Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/24739896](https://pubmed.ncbi.nlm.nih.gov/24739896)
55. Van Cutsem, E., Peeters, M., Siena, S., et al. (2007, May 1). Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared with Best Supportive Care Alone in Patients with Chemotherapy-Refractory Metastatic Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/17470858](https://pubmed.ncbi.nlm.nih.gov/17470858)
56. Venook, A.P., Niedzwiecki, D., Lenz, H.J., et al. (2017, June 20). Effect of First-Line Chemotherapy Combined with Cetuximab or Bevacizumab on Overall Survival in Patients with KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28632865](https://pubmed.ncbi.nlm.nih.gov/28632865)
57. Bennouna, J., Hiret, S., Bertaut, A., et al. (2019, Jan. 1). Continuation of Bevacizumab vs. Cetuximab Plus Chemotherapy After First Progression in KRAS Wild-Type Metastatic Colorectal Cancer: The UNICANCER PRODIGE18 Randomized Clinical Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30422156](https://pubmed.ncbi.nlm.nih.gov/30422156)
58. Shitara, K., Yonesaka, K., Denda, T., et al. (December 2016). Randomized Study of FOLFIRI Plus Either Panitumumab or Bevacizumab for Wild-Type KRAS Colorectal Cancer – WJOG 6210G. Retrieved from [ncbi.nlm.nih.gov/pubmed/27712015](https://pubmed.ncbi.nlm.nih.gov/27712015)
59. Zheng, B., Wang, X., Wei, M., et al. (2019, March 28). First-Line Cetuximab Versus Bevacizumab for RAS and BRAF Wild-Type Metastatic Colorectal Cancer: A Systematic Review and Meta-Analysis. Retrieved from [ncbi.nlm.nih.gov/pubmed/30922269](https://pubmed.ncbi.nlm.nih.gov/30922269)
60. Peeters, M., Forget, F., Karthaus, M., et al. (2018, Feb. 24). Exploratory Pooled Analysis Evaluating the Effect of Sequence of Biological Therapies on Overall Survival in Patients with RAS Wild-Type Metastatic Colorectal Carcinoma. Retrieved from [ncbi.nlm.nih.gov/pubmed/29531837](https://pubmed.ncbi.nlm.nih.gov/29531837)
61. Kopetz, S., Grothey, A., Yaeger, R., et al. Encorafenib, Binimetinib and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med.* 2019;381(17):1632-1643. DOI:10.1056/NEJMoa1908075

62. Kopetz, S., Grothey, A., Van Cutsem, E., et al. Encorafenib Plus Cetuximab with or without Binimetinib for BRAF V600E-Mutant Metastatic Colorectal Cancer: Quality-of-Life Results From a Randomized, Three-Arm, Phase III Study Versus the Choice of Either Irinotecan or FOLFIRI Plus Cetuximab (BEACON CRC) [abstract]. *J Clin Oncol*. 2020; 38, (suppl 4; abstr8)
63. Le, D., et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *NEJM*. 2015 Jun 25;372:2509-20
64. Le, D.T., Durham, J.N., Smith, K.N., et al. Mismatch-Repair Deficiency Predicts Response of Solid Tumors to PD-1 Blockade. Retrieved from [ncbi.nlm.nih.gov/pubmed/28596308](https://pubmed.ncbi.nlm.nih.gov/28596308). *Science* 2017 Jul 28;357(6349):409-13
65. Diaz, L., Marabelle, A., et al. Efficacy of Pembrolizumab in Phase 2 KEYNOTE-164 and KEYNOTE-158 Studies of Microsatellite Instability High Cancers Presented at the European Society for Medical Oncology Congress; Madrid, Spain; 8-12 September 2017. Poster 386P
66. Overman, M.J., Lonardi, S., Wong, K.Y.M., et al. (2018, March 10). Durable Clinical Benefit with Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/29355075](https://pubmed.ncbi.nlm.nih.gov/29355075)
67. Lenz, H.J., Van Cutsem, E., Limon, M.L., et al. (October 2018). Durable Clinical Benefit with Nivolumab (NIVO) Plus Low-Dose Ipilimumab (IPI) as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC). Retrieved from oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/Durable-Clinical-Benefit-with-Nivolumab-NIVO-Plus-Low-Dose-Ipilimumab-IPI-as-First-Line-Therapy-in-Microsatellite-Instability-High-Mismatch-Repair-Deficient-MSI-H-dMMR-Metastatic-Colorectal-Cancer-mCRC
68. Andre, T., Shiu, K.K., Kim, T.W., et al. Pembrolizumab vs. Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study. ASCO20 Virtual Scientific Program. Abstract LBA4. Presented in pre-meeting press briefing on May 26, 2020
69. André, T., et al. Effect of Duration of Adjuvant Chemotherapy for Patients with Stage III Colon Cancer (IDEA Collaboration): Final Results From a Prospective, Pooled Analysis of Six Randomised, Phase 3 Trials. *Lancet Oncol* 2020 Dec; 21:1620. ([https://DOI.org/10.1016/S1470-2045\(20\)30527-1](https://doi.org/10.1016/S1470-2045(20)30527-1))
70. Iveson, T.J., Sobrero, A.F., Yoshino, T., et al. Duration of Adjuvant Doublet Chemotherapy (3 or 6 Months) in Patients with High-Risk Stage II Colorectal Cancer. *J Clin Oncol*. 2021 Feb 20;39(6):631-641. DOI: 10.1200/JCO.20.01330. Epub 2021 Jan 13. Erratum in: *J Clin Oncol*. 2021 May 20;39(15):1691. PMID: 33439695; PMCID: PMC8078416
71. Pfeiffer, P., Yilmaz, M., Möller, S., et al. TAS-102 with or without Bevacizumab in Patients with Chemorefractory Metastatic Colorectal Cancer: An Investigator-Initiated, Open-Label, Randomised, Phase 2 Trial. *Lancet Oncol*. 2020 Mar;21(3):412-420. DOI: 10.1016/S1470-2045(19)30827-7. Epub 2020 Jan 27. PMID: 31999946
72. Andre, T., Berton, D., Curigliano, G., et al. Safety and Efficacy of Anti-PD-1 Antibody Dostarlimab in Patients (Pts) with Mismatch Repair-Deficient (Dmmr) Solid Cancers: Results From GARNET Study. *J Clin Oncol*. 2021 Jan 22; DOI: 10.1200/JCO.2021.39.3_suppl.9 *Journal of Clinical Oncology* 39, no. 3_suppl
73. Takayuki Yoshino, et al. PARADIGM study: A multicenter, randomized, phase III study of mFOLFOX6 plus panitumumab or bevacizumab as first-line treatment in patients with RAS (KRAS/NRAS) wild-type metastatic colorectal cancer. *J Clin Oncol*. 2021 39:3_suppl, 85-85.
74. Sartore-Bianchi, A., Trusolino, L., Martino, C., et al (2016, June). Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive

- metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/27108243>.
75. Okamura, R., Boichard, A., Kato, S., et al (2018). Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Malignancies: Implications for NTRK-Targeted Therapeutics. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329466/>.
 76. Verschoor YL, van den Berg J, Beets G, et al. Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study. *JCO* 40, no. 16_suppl (June 01, 2022) 3511-3511. DOI: 10.1200/JCO.2022.40.16_suppl.3511
 77. Chalabi, M, Verschoor YL, van den Berg J, et al. LBA7 - Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. *Annals of Oncology* (2022) 33 (suppl_7): S808-S869. DOI: 10.1016/annonc/annonc1089
 78. Ludford K, Ho WJ, Thomas JV, et al. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. *J Clin Oncol*. 2023;41(12):2181-2190. doi:10.1200/JCO.22.01351
 79. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med*. 2022;386(25):2363-2376. doi:10.1056/NEJMoa2201445
 80. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. *J Clin Oncol*. 2022;40(23):2546-2556. doi:10.1200/JCO.22.00032
 81. Schrag D, Shi Q, Weiser MR, et al. Preoperative Treatment of Locally Advanced Rectal Cancer. *N Engl J Med*. 2023;389(4):322-334. doi:10.1056/NEJMoa2303269
 82. Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. 2022;23(5):659-670. doi:10.1016/S1470-2045(22)00197-8
 83. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet*. 2011;377(9783):2103-2114. doi:10.1016/S0140-6736(11)60613-2
 84. Leone F, Artale S, Marino D, et al. Panitumumab in combination with infusional oxaliplatin and oral capecitabine for conversion therapy in patients with colon cancer and advanced liver metastases. The MetaPan study. *Cancer*. 2013;119(19):3429-3435. doi:10.1002/cncr.28223
 85. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2023;24(5):496-508. doi:10.1016/S1470-2045(23)00150-X
 86. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of seliperatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol*. 2022;23(10):1261-1273. doi:10.1016/S1470-2045(22)00541-1
 87. Santos C, Sanz-Pamplona R, Salazar R. RET-fusions: a novel paradigm in colorectal cancer. *Ann Oncol*. 2018;29(6):1340-1343. doi:10.1093/annonc/mdy132

Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

1st line of therapy

- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- Venetoclax + Obinutuzumab
- Bendamustine + Rituximab (without del(17p)/TP53 mutation)

2nd + Subsequent lines of therapy

- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- Venetoclax + Rituximab
- Bendamustine + Rituximab (without del(17p)/TP53 mutation)

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from <https://seer.cancer.gov/statfacts/html/clyl.html>
2. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/ Small Lymphocytic Leukemia (V2.2023, January 25, 2023). Accessed June 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
3. 2023 ASPFiles. Centers for Medicare & Medicaid Services. April 1, 2023. Accessed June 5, 2023. Retrieved from cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2023ASPFiles.html
4. Sharman J.P., Egyed M., Jurczak W., et al. Acabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020;395:1278-1291.
5. Sharman J.P., Egyed M., Jurczak W., et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. *Leukemia*. 2022;36:1171-1175.
6. Burger J.A., Tedeschi A., Barr P.M., et al. Ibrutinib as therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373:2425-37.
7. Burger J.A., Barr P.M., Robak T., et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34:787-798.

8. Barr P.M., Owen C., Robak T., et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia [abstract]. *J Clin Oncol.* 2021;39:Abstract 7523.
9. Woyach J.A., Ruppert A.S., Heerema N.A., et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med.* 2018;379:2517-2528.
10. Woyach JA, Ruppert A.S., Heerema N.A., et al. Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy [abstract]. *Blood* 2021;138:Abstract 639.
11. Shanafelt T.D., Wang X.V., Kay N.E., et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *N Engl J Med.* 2019;381:432-443.
12. Hillmen P., Pitchford A., Bloor A., et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: Results of the phase III NCRI FLAIR trial [abstract]. *Blood.* 2021;138:Abstract 642.
13. Fischer K., Al-Sawaf O., Bahlo J., et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med.* 2019;380:2225-2236.
14. Al-Sawaf O., Zhang C., Tandon M., et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21:1188-1200.
15. Eichhorst B., Fink A.M., Bahlo J., et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2016;17:928-942.
16. Kutsch N., Bahlo J., Robrecht S., et al. Long Term Follow-up Data and Health-Related Quality of Life in Frontline Therapy of Fit Patients Treated with FCR Versus BR (CLL10 Trial of the GCLLSG). *Hemasphere* 2020;4:e336.
17. Moreno C., Greil R., Demirkan F., et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20:43-56.
18. Tam C.S., Giannopoulos K., Jurczak W., et al. SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab (BR) in patients with treatment-naïve (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [abstract]. *Blood.* 2021;138:Abstract 396.
19. Tam C.S., Robak T., Ghia P., et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. *Haematologica.* 2020;106:2354-2363.
20. Ghia P., Pluta A., Wach M., et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2020;38:2849-2861.
21. Jurczak W., Pluta A., Wach M., et al. Three-year follow-up of the Ascend trial: Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia [abstract]. *Blood.* 2021;138:Abstract 393.
22. Byrd J.C., Hillmen P., Ghia P., et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. *J Clin Oncol.* 2021;39:3441-3452.

23. Byrd J.C., Brown J.R., and O'Brien S., et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *N Engl J Med.* 2014; 371:213-223 DOI: 10.1056/NEJMoa1400376
24. Munir T., Brown J.R., O'Brien S., et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94:1353-1363.
25. Hillmen P., Eichhorst B., Brown J.R., et al. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. EHA Virtual Congress; 2021:Abstract LB1900
26. Seymour J.F., Kipps T.J., Eichhorst B., et al: Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 378:1107-1120, 2018.
27. Kater A.P., Seymour J.F., Hillmen P., et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III STUDY. *J Clin Oncol.* 2018;37:269-277.
28. Kater A.P., Wu J.Q., Kipps T., et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO Phase III Study. *J Clin Oncol.* 2020;38:4042-4054.
29. Kater A.P., Kipps T.J., Eichhorst B., et al. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx) [abstract]. *Blood.* 2020;136:19-21.
30. Flinn I.W., Hillmen P., Montillo M., et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood.* 2018;132:2446-2455.
31. Sharman J.P., Coutre S.E., Furman R.R., et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol.* 2019;37:1391-1402
32. Sharman J.P., Egyed M., Jurczak W., et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395:1278-1291.
33. Sharman J.P., Egyed M., Jurczak W., et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. *Leukemia.* 2022;36:1171-1175.
34. Burger J.A., Tedeschi A., Barr P.M., et al. Ibrutinib as therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373:2425-37.
35. Burger J.A., Barr P.M., Robak T., et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia.* 2020;34:787- 798.
36. Barr P.M., Owen C., Robak T., et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia [abstract]. *J Clin Oncol.* 2021;39:Abstract 7523.
37. Woyach J.A., Ruppert A.S., Heerema N.A., et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med.* 2018;379:2517-2528.

38. Woyach JA, Ruppert A.S., Heerema N.A., et al. Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy [abstract]. *Blood*. 2021;138:Abstract 639.
39. Shanafelt T.D., Wang X.V., Kay N.E., et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *N Engl J Med*. 2019;381:432-443.
40. Hillmen P., Pitchford A., Bloor A., et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: Results of the phase III NCRI FLAIR trial [abstract]. *Blood*. 2021;138:Abstract 642.
41. Fischer K., Al-Sawaf O., Bahlo J., et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med*. 2019;380:2225-2236.
42. Al-Sawaf O., Zhang C., Tandon M., et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1188-1200.
43. Eichhorst B., Fink A.M., Bahlo J., et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17:928-942.
44. Kutsch N., Bahlo J., Robrecht S., et al. Long Term Follow-up Data and Health-Related Quality of Life in Frontline Therapy of Fit Patients Treated with FCR Versus BR (CLL10 Trial of the GCLLSG). *Hemasphere*. 2020;4:e336.
45. Moreno C., Greil R., Demirkan F., et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:43-56.
46. Tam C.S., Giannopoulos K., Jurczak W., et al. SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab (BR) in patients with treatment-naïve (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [abstract]. *Blood*. 2021;138:Abstract 396.
47. Tam C.S., Robak T., Ghia P., et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. *Haematologica*. 2020;106:2354-2363.
48. Ghia P., Pluta A., Wach M., et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38:2849-2861.
49. Jurczak W., Pluta A., Wach M., et al. Three-year follow-up of the Ascend trial: Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia [abstract]. *Blood*. 2021;138:Abstract 393.
50. Byrd J.C., Hillmen P., Ghia P., et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. *J Clin Oncol*. 2021;39:3441-3452.
51. Byrd J.C., Brown J.R., and O'Brien S., et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *N Engl J Med*. 2014; 371:213-223 DOI: 10.1056/NEJMoa1400376
52. Munir T., Brown J.R., O'Brien S., et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94:1353-1363.

53. Hillmen P., Eichhorst B., Brown J.R., et al. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. EHA Virtual Congress; 2021:Abstract LB1900
54. Seymour J.F., Kipps T.J., Eichhorst B., et al: Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 378:1107-1120, 2018.
55. Kater A.P., Seymour J.F., Hillmen P., et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post Treatment Follow-Up of the MURANO Phase III STUDY. *J Clin Oncol.* 2018;37:269-277.
56. Kater A.P., Wu J.Q., Kipps T., et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO Phase III Study. *J Clin Oncol.* 2020;38:4042-4054.
57. Kater A.P., Kipps T.J., Eichhorst B., et al. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx) [abstract]. *Blood.* 2020;136:19-21.
58. Flinn I.W., Hillmen P., Montillo M., et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood.* 2018;132:2446-2455.
59. Sharman J.P., Coutre S.E., Furman R.R., et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol.* 2019;37:1391-1402.
60. Al-Sawaf, O., Zhang, C., Jin, H.Y. et al. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun.* 14, 2147 (2023). <https://DOI.org/10.1038/s41467-023-37648-w>
61. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. *J Clin Oncol.* 2021;39(34):3853-3865. DOI:10.1200/JCO.21.00807
62. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood.* 2022;139(22):3278-3289. DOI:10.1182/blood.2021014488
63. Eichhorst B, Niemann CU, Kater AP, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. *N Engl J Med.* 2023;388(19):1739-1754. DOI:10.1056/NEJMoa2213093
64. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv.* 2022;6(11):3440-3450. DOI:10.1182/bloodadvances.2021006434
65. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood.* 2022;140(2):112-120. DOI:10.1182/blood.2021014960
66. Sharman J, Egyed M, Jurczak E, et al. *JCO*;2022 40:16_suppl, 7539-7539
67. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2023;24(5):535-552. DOI:10.1016/S1470-2045(23)00144-4

68. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial [published correction appears in *Lancet Oncol*. 2023 Mar;24(3):e106]. *Lancet Oncol*. 2022;23(8):1031-1043. DOI:10.1016/S1470-2045(22)00293-5
69. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients with Chronic Lymphocytic Leukemia with 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial [published correction appears in *J Clin Oncol*. 2019 Sep 1;37(25):2299]. *J Clin Oncol*. 2018;36(19):1973-1980. DOI:10.1200/JCO.2017.76.6840
70. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med*. 2023;388(4):319-332. DOI:10.1056/NEJMoa2211582
71. Sharman JP, Egyed M, Jurczak W, et al. Acabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial [published correction appears in *Lancet*. 2020 May 30;395(10238):1694]. *Lancet*. 2020;395(10232):1278-1291. DOI:10.1016/S0140-6736(20)30262-2

Chronic Myeloid Leukemia

Chronic Phase

1st Line Therapy, Low Risk

- Imatinib

1st Line Therapy, Intermediate or High Risk

- Dasatinib
- Imatinib
- Nilotinib

2nd Line of Therapy or Greater

- Omacetaxine (T313I mutation only)
- Ponatinib

References:

1. National Comprehensive Cancer Network. Chronic Myeloid Leukemia (V2.2024, December 2, 2023). Accessed December 2023.
2. Kantarjian HM, Hughes TP, et. al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021 Feb;35(2):440-453. DOI: 10.1038/s41375-020-01111-2. Epub 2021 Jan 7. Erratum in: *Leukemia*. 2021 Jul;35(7):2142-2143. PMID: 33414482; PMCID: PMC7862065. Kantajarian et al, *N Engl J Med*. 2010; 362:2260-2270.
3. Jorge E. Cortes, Hagop M. Kantarjian, et al, Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome–positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011; 118 (17): 4567–4576. DOI: <https://DOI.org/10.1182/blood-2011-05-355594>
4. Elias Jabbour, Hagop M. Kantarjian, et.al, Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014; 123 (4): 494–500. DOI: <https://DOI.org/10.1182/blood-2013-06-511592>
5. Hagop Kantarjian, Guillermo Garcia-Manero, et. Al, Survival and Efficacy of Decitabine in Myelodysplastic Syndromes (MDS), Analysis of the 5-Day IV Dosing Regimen. *Blood*. 2007; 110 (11): 115. DOI: <https://DOI.org/10.1182/blood.V110.11.115.115>
6. Cortes E, Kim DW, et.al, A Phase 2 Trial of Ponatinib in Philadelphia Chromosome–Positive Leukemias. *N Engl J Med*. 2013; 369:1783-1796. DOI: 10.1056/NEJMoa1306494
7. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132(4):393-404. doi:10.1182/blood-2016-09-739086
8. Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol*. 2012 Oct

- 1;30(28):3486-92. DOI: 10.1200/JCO.2011.38.7522. Epub 2012 Sep 4. PMID: 22949154; PMCID: PMC4979199.
9. Cortes JE, Gambacorti-Passerini C, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. *J Clin Oncol*. 2018 Jan 20;36(3):231-237. DOI: 10.1200/JCO.2017.74.7162. Epub 2017 Nov 1. PMID: 29091516; PMCID: PMC5966023.
 10. Cortes JE, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. *Blood* 2021;138:2042-2050.
 11. Cortes JE, Deininger MW, Lomaia E, et al. Three-Year Update from the Optic Trial: A Dose-Optimization Study of 3 Starting Doses of Ponatinib. *Blood* 2022; 140 (Supplement 1): 1495–1497. doi.org/10.1182/blood-2022-157822
 12. Khoury HJ, Cortes J, Bacarani M, Wetzler M, Masszi T, Digumarti R, Craig A, Benichou AC, Akard L. Omacetaxine mepesuccinate in patients with advanced chronic myeloid leukemia with resistance or intolerance to tyrosine kinase inhibitors. *Leuk Lymphoma*. 2015 Jan;56(1):120-7. doi: 10.3109/10428194.2014.889826. Epub 2014 Apr 28. PMID: 24650054.
 13. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012;120(13):2573-2580. doi:10.1182/blood-2012-03-415307
 14. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood*. 2021;138(21):2031-2041. doi:10.1182/blood.2020009984
 15. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. *N Engl J Med*. 2019;381(24):2315-2326. doi:10.1056/NEJMoa1902328
 16. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. *Am J Hematol*. 2016;91(12):1206-1214. doi:10.1002/ajh.24536
 17. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase I/II study. *Haematologica*. 2018;103(8):1298-1307. doi:10.3324/haematol.2017.171249
 18. Yeung DT, Osborn MP, White DL, et al. TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. *Blood*. 2015;125(6):915-923. doi:10.1182/blood-2014-07-590315
 19. Cortes JE, Jiang Q, Wang J, et al. Dasatinib vs. imatinib in patients with chronic myeloid leukemia in chronic phase (CML-CP) who have not achieved an optimal response to 3 months of imatinib therapy: the DASCERN randomized study. *Leukemia*. 2020;34(8):2064-2073. doi:10.1038/s41375-020-0805-1
 20. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. *Blood*. 2009;113(10):2154-2160. doi:10.1182/blood-2008-04-154344
 21. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia* 2013;27:107-112.
 22. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. *Am J Hematol* 2016;91:1206-1214.

23. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044-1054. doi:10.1038/leu.2016.5
24. Hughes TP, Saglio G, Larson RA, et al; Long-Term Outcomes in Patients with Chronic Myeloid Leukemia in Chronic Phase Receiving Frontline Nilotinib Versus Imatinib: Enestnd 10-Year Analysis. *Blood* 2019; 134 (Supplement_1): 2924. doi.org/10.1182/blood-2019-128761
25. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol*. 2016;34(20):2333-2340. doi:10.1200/JCO.2015.64.8899
26. Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med*. 2017;376(10):917-927. doi:10.1056/NEJMoa1609324

Esophageal Cancer

Perioperative

- Capecitabine + Oxaliplatin
- Fluorouracil +/- Leucovorin, Cisplatin
- Fluorouracil +/- Leucovorin, Oxaliplatin
- Fluorouracil + Leucovorin + Oxaliplatin + Docetaxel (FLOT)

Preoperative or Definitive Chemoradiotherapy

- Capecitabine + Cisplatin + RT
- Capecitabine + Oxaliplatin + RT
- Carboplatin + Paclitaxel + RT
- Fluorouracil +/- Leucovorin + Cisplatin + RT
- Fluorouracil +/- Leucovorin + Oxaliplatin + RT

Recurrent or Metastatic Disease

HER2 Positive (HER2+) Disease: 1st Line of Therapy

- Capecitabine + Cisplatin + Trastuzumab
- Capecitabine + Oxaliplatin + Trastuzumab
- Fluorouracil +/- Leucovorin + Oxaliplatin + Trastuzumab
- Fluorouracil +/- Leucovorin + Cisplatin + Trastuzumab

HER2 Negative (HER2-) or Unknown Disease: 1st Line of Therapy

- Capecitabine + Cisplatin
- Capecitabine + Oxaliplatin
- Capecitabine + Cisplatin + Nivolumab (Squamous Cell CPS ≥ 1)
- Capecitabine + Oxaliplatin + Nivolumab (Adenocarcinoma CPS ≥ 5 or Squamous Cell CPS ≥ 1)
- Fluorouracil +/- Leucovorin + Oxaliplatin
- Fluorouracil +/- Leucovorin + Cisplatin
- Fluorouracil +/- Leucovorin + Oxaliplatin + Nivolumab (Adenocarcinoma CPS ≥ 5 or Squamous Cell CPS ≥ 1)
- Fluorouracil +/- Leucovorin + Cisplatin + Nivolumab (Squamous Cell CPS ≥ 1)
- Capecitabine + Oxaliplatin + Pembrolizumab (CPS ≥ 10)
- Fluorouracil \pm Leucovorin + Cisplatin + Pembrolizumab (CPS ≥ 10)
- Fluorouracil \pm Leucovorin + Oxaliplatin + Pembrolizumab (CPS ≥ 10)

- Capecitabine + Cisplatin + Pembrolizumab (CPS \geq 10)

HER2- and HER2+ Disease: 2nd + Subsequent Lines of Therapy

- Docetaxel
- Irinotecan
- Paclitaxel
- Paclitaxel + Ramucirumab (for adenocarcinoma)
- Fam-trastuzumab deruxtecan (HER2+ Disease and adenocarcinoma only)

References:

1. National Comprehensive Cancer Network. Gastric Cancer (V2.2023, March 10th, 2023 and V3.2023, August 29th, 2023). Accessed September 2023. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
2. Van Hagen P, Hulshof MC, et al. CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012 May 31;366(22):2074-84. DOI: 10.1056/NEJMoa1112088. PMID: 22646630.
3. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol*. 2014;15:305-314.
4. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012;30:2327-2333.
5. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1389-1396.
6. Kelly RJ, Ajani JA, Kuzdzal J, et al. CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021 Apr 1;384(13):1191-1203. DOI: 10.1056/NEJMoa2032125. Erratum in: *N Engl J Med*. 2023 Feb 16;388(7):672. PMID: 33789008.
7. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687- 697
8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398:27-40.
9. Doki et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med*. 2022; 386:449-462
10. Shitara K, Bang YJ, Iwasa S, et al. DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med*. 2020 Jun 18;382(25):2419-2430. DOI: 10.1056/NEJMoa2004413. Epub 2020 May 29. PMID: 32469182.
11. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction

- adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1224-1235
12. Shitara K, DOI T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19:1437-1448.
 13. Andre T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. *J Clin Oncol* 2023;41:255-265. doi:10.1200/JCO.22.00686
 14. Ludford K, Ho WJ, Thomas JV, et al. Neoadjuvant pembrolizumab in localized microsatellite instability high/deficient mismatch repair solid tumors. *J Clin Oncol* 2023;41:2181-2190. doi:10.1200/JCO.22.01351
 15. Liu L, Woo Y, D'Apuzzo M, et al. Immunotherapy based neoadjuvant treatment of advanced microsatellite instability-high gastric cancer: a case series. *J Natl Compr Canc Netw* 2022;20:857-865. doi:10.6004/jnccn.2022.7023
 16. Kelly RJ, Lee J, Bang YJ, et al. Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma. *Clin Cancer Res* 2020;26:846-854.
 17. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/ GEJAC). *Journal of Clinical Oncology* 2023;41:358- 358.
 18. Raimondi A, Palermo F, Prisciandaro M, et al. Tremellmumab and Durvalumab Combination for the Non-Operative Management (NOM) of Microsatellite Instability (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study. *Cancers (Basel)*. 2021;13(11):2839. Published 2021 Jun 7. doi:10.3390/
 19. Ciombor KK, Eng C. Immunotherapy in Localized Microsatellite Instability–High/Mismatch Repair Deficient Solid Tumors: Are We Ready for a New Standard of Care? *Journal of Clinical Oncology* 2023;41:2138- 2140. doi:10.1200/JCO.22.02564
 20. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature*. 2021;600(7890):727-730. doi:10.1038/s41586-021-04161-3
 21. Shitara K, Ozguroglu M, Bang YJ, et al; KEYNOTE-061 Investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet.* 2018;392(10142):123-133. doi:10.1016/S0140-6736(18)31257-1
 22. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol.* 2020;38(33):3895-3904. doi:10.1200/JCO.20.00762
 23. Fong C, Cunningham, D. Chemotherapy with nivolumab in advanced gastro-oesophageal adenocarcinoma. *Lancet.* 2021; 398 (10294):2-3. doi:10.1016/S0140-6736(21)00988-0
 24. Rha SY, Oh D, Yanez, P et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomized, double-blind, phase 3 trial. *Lancet Oncol.* 2023;24:1181-95. doi.org/10.1016/S1470-2045(23)00515-6

25. Janjigian YY, Kawazoe A, Bai Y, et al. Lancet. 2023; Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomized placebo-controlled trial. Lancet. 2023; doi.org/10.1016/S0140-6736(23)02033-0
26. Chao J, Fuchs CS, Shitara K, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA Oncol. 2021;7(6):895-902. doi:10.1001/jamaoncol.2021.0275
27. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. Aug 28 2021;398(10302):759-771. doi:10.1016/S0140-6736(21)01234-4

Gastric Cancer

Perioperative

- Capecitabine + Oxaliplatin
- Fluorouracil +/- Leucovorin + Cisplatin
- Fluorouracil +/-Leucovorin + Oxaliplatin
- Fluorouracil + Leucovorin + Oxaliplatin + Docetaxel (FLOT)

Postoperative Chemoradiotherapy

- Capecitabine + RT
- Fluorouracil + RT

Postoperative Chemotherapy

- Capecitabine
- Capecitabine + Oxaliplatin
- Fluorouracil

Recurrent or Metastatic Disease

HER2 Positive (HER2+) Disease: 1st Line of Therapy

- Fluorouracil +/- Leucovorin + Cisplatin + Trastuzumab
- Fluorouracil +/- Leucovorin + Oxaliplatin + Trastuzumab
- Capecitabine + Cisplatin + Trastuzumab
- Capecitabine + Oxaliplatin + Trastuzumab

HER2 Negative (HER2-) Disease: 1st Line of Therapy

- Capecitabine + Cisplatin
- Capecitabine + Oxaliplatin
- Capecitabine + Oxaliplatin + Nivolumab (CPS \geq 5)
- Cisplatin +/- Leucovorin, Fluorouracil
- Fluorouracil +/- Leucovorin, Oxaliplatin
- Fluorouracil +/- Leucovorin, Oxaliplatin, Nivolumab, (CPS \geq 5)

HER2- and HER2+ Disease: 2nd + Subsequent Lines of Therapy

- Docetaxel
- Irinotecan

- Paclitaxel
- Paclitaxel + Ramucirumab
- Fam-trastuzumab deruxtecan (HER2+ disease only)

Addition to HER2 Negative (HER2-) Disease: 1st Line of Therapy Effective: TBD upon NCCN addition

- Capecitabine + Oxaliplatin + Pembrolizumab (CPS ≥ 10)
- Fluorouracil ± Leucovorin + Cisplatin+ Pembrolizumab (CPS ≥ 10)
- Fluorouracil ± Leucovorin + Oxaliplatin + Pembrolizumab (CPS ≥ 10)
- Capecitabine + Cisplatin + Pembrolizumab (CPS ≥ 10)

References:

1. National Comprehensive Cancer Network. Gastric Cancer (V1.2023, March 10th, 2023 and V2.2023, August 29th, 2023). Accessed September 2023. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
2. Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29:1715-1721.
3. Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393:1948-1957
4. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074- 2084.
5. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol*. 2014;15:305-314.
6. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012;30:2327-2333.
7. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1389-1396.
8. Kelly RJ, Ajani JA, et al. CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021 Apr 1;384(13):1191-1203. DOI: 10.1056/NEJMoa2032125. Erratum in: *N Engl J Med*. 2023 Feb 16;388(7):672. PMID: 33789008.
9. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687- 697
10. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal

- adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398:27-40.
11. Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, Ogata T, Kawakami H, Hsu CH, Adenis A, El Hajbi F, Di Bartolomeo M, Braghiroli MI, Holtved E, Ostoich SA, Kim HR, Ueno M, Mansoor W, Yang WC, Liu T, Bridgewater J, Makino T, Xynos I, Liu X, Lei M, Kondo K, Patel A, Gricar J, Chau I, Kitagawa Y; CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med*. 2022 Feb 3;386(5):449-462. DOI: 10.1056/NEJMoa2111380. PMID: 35108470.
 12. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235
 13. Shitara K, DOI T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19:1437-1448.
 14. Andre T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. *J Clin Oncol* 2023;41:255-265. doi:10.1200/JCO.22.00686
 15. Ludford K, Ho WJ, Thomas JV, et al. Neoadjuvant pembrolizumab in localized microsatellite instability high/deficient mismatch repair solid tumors. *J Clin Oncol* 2023;41:2181-2190. doi:10.1200/JCO.22.01351
 16. Liu L, Woo Y, D'Apuzzo M, et al. Immunotherapy based neoadjuvant treatment of advanced microsatellite instability-high gastric cancer: a case series. *J Natl Compr Canc Netw* 2022;20:857-865. doi:10.6004/jnccn.2022.7023
 17. Kelly RJ, Lee J, Bang YJ, et al. Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma. *Clin Cancer Res* 2020;26:846-854.
 18. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/ GEJAC). *Journal of Clinical Oncology* 2023;41:358- 358.
 19. Raimondi A, Palermo F, Prisciandaro M, et al. Tremellmumab and Durvalumab Combination for the Non-Operative Management (NOM) of Microsatellite Instability (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study. *Cancers (Basel)*. 2021;13(11):2839. Published 2021 Jun 7. doi:10.3390/cancers13112839 □ this is a study design, no results
 20. Ciombor KK, Eng C. Immunotherapy in Localized Microsatellite Instability–High/Mismatch Repair Deficient Solid Tumors: Are We Ready for a New Standard of Care? *Journal of Clinical Oncology* 2023;41:2138- 2140. doi:10.1200/JCO.22.02564
 21. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature*. 2021;600(7890):727-730. doi:10.1038/s41586-021-04161-3
 22. Janjigian YY, Kawazoe A, Bai Y, et al. *Lancet*. 2023; Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomized placebo-controlled trial. *Lancet*. 2023; doi.org/10.1016/S0140-6736(23)02033-0

23. Shitara K, Ozguroglu M, Bang YJ, et al; KEYNOTE-061 Investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018;392(10142):123-133. doi:10.1016/S0140-6736(18)31257-1
24. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol*. 2020;38(33):3895-3904. doi:10.1200/JCO.20.00762
25. Fong C, Cunningham, D. Chemotherapy with nivolumab in advanced gastro-oesophageal adenocarcinoma. *Lancet*. 2021; 398 (10294):2-3. doi:10.1016/S0140-6736(21)00988-0
26. Chao J, Fuchs CS, Shitara K, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. *JAMA Oncol*. 2021;7(6):895-902. doi:10.1001/jamaoncol.2021.0275
27. Rha SY, Oh D, Yanez, P et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomized, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24:1181-95. doi.org/10.1016/S1470-2045(23)00515-6

Head and Neck Cancer

Primary Definitive Therapy

Non-Nasopharyngeal

- Cisplatin + Concurrent Radiation Therapy

Nasopharyngeal

- Cisplatin + Concurrent Radiation Therapy
- Cisplatin + Gemcitabine

Adjuvant Therapy

Non-Nasopharyngeal

- Cisplatin + Concurrent Radiation Therapy

Nasopharyngeal

- Cisplatin + Fluorouracil (5FU)
- Carboplatin + Fluorouracil (5FU)

Recurrent/Metastatic/Unresectable

Non-Nasopharyngeal: 1st Line of Therapy

- Cisplatin or Carboplatin + Fluorouracil (5FU) + Cetuximab
- Cisplatin + Fluorouracil (5FU)
- Cisplatin or Carboplatin + Docetaxel
- Cisplatin or Carboplatin + Paclitaxel
- Cisplatin or Carboplatin + Fluorouracil (5FU) + Pembrolizumab (CPS \geq 1 only)
- Pembrolizumab (for combined positive score (CPS) \geq 1 only)

Non-Nasopharyngeal: Maintenance

- Cetuximab
- Pembrolizumab (for combined positive score (CPS) \geq 1 only)

Non-Nasopharyngeal: 2nd + Subsequent Lines of Therapy

- Nivolumab (if IO not used previously)
- Pembrolizumab (if IO not used previously)
- Cisplatin or Carboplatin + Fluorouracil (5FU) + Cetuximab

- Cisplatin + Fluorouracil (5FU)
- Cisplatin or Carboplatin + Docetaxel
- Cisplatin or Carboplatin + Paclitaxel

Nasopharyngeal: 1st Line of Therapy

- Cisplatin + Gemcitabine

References:

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
2. Adelstein, D.J., Li, Y., Adams, G.L., et al. An Intergroup Phase III Comparison of Standard Radiation Therapy and Two Schedules of Concurrent Chemoradiotherapy in Patients with Unresectable Squamous Cell Head and Neck Cancer. *J Clin Oncol.* 2003;21(1):92-98. DOI:10.1200/JCO.2003.01.008
3. Forastiere, A.A., Zhang, Q., Weber, R.S., et al. Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients with Locally Advanced Larynx Cancer. *J Clin Oncol.* 2013;31(7):845-852. DOI:10.1200/JCO.2012.43.6097
4. Forastiere, A.A., Goepfert, H., Maor, M., et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. *N Engl J Med.* 349:2091-2098, 2003
5. Pignon, J.P., le Maître, A., Maillard, E., Bourhis, J., MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): An Update on 93 Trials and 17,346 Patients. *Radiother Oncol.* 2009;92(1):4-14. DOI:10.1016/j.radonc.2009.04.014
6. Denis, F., Garaud, P., Bardet, E., et al. Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone with Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma. *J Clin Oncol.* 2004;22(1):69-76. DOI:10.1200/JCO.2004.08.021
7. Bourhis, J., Sire, C., Graff, P., et al. Concomitant Chemoradiotherapy Versus Acceleration of Radiotherapy with or without Concomitant Chemotherapy in Locally Advanced Head and Neck Carcinoma (GORTEC 99-02): An Open-Label Phase 3 Trial. *Lancet Oncol.* 2012;13(2):145-153. DOI:10.1016/S1470-2045(11)70346-1
8. Garden, A.S., Harris, J., Vokes, E.E., et al. Preliminary Results of Radiation Therapy Oncology Group 97-03: A Randomized Phase II Trial of Concurrent Radiation and Chemotherapy for Advanced Squamous Cell Carcinomas of the Head and Neck. *J Clin Oncol.* 2004;22(14):2856-2864. DOI:10.1200/JCO.2004.12.012
9. Suntharalingam, M., Haas, M.L., Conley, B.A., et al. The Use of Carboplatin and Paclitaxel with Daily Radiotherapy in Patients with Locally Advanced Squamous Cell Carcinomas of the Head and Neck. *Int J Radiat Oncol Biol Phys.* 2000;47(1):49-56. DOI:10.1016/s0360-3016(00)00408-9
10. Bonner, J.A., Harari, P.M., Giralt, J., et al. Radiotherapy Plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med.* 2006;354(6):567-578. DOI:10.1056/NEJMoa053422
11. Gillison, M.L., Trotti, A.M., Harris, J., et al. Radiotherapy Plus Cetuximab or Cisplatin in Human Papillomavirus-Positive Oropharyngeal Cancer (NRG Oncology RTOG 1016): A Multicentre, Non-Inferiority Trial [published correction appears in *Lancet.* 2020 Mar 7;395(10226):784]. *Lancet.* 2019;393(10166):40-50. DOI:10.1016/S0140-6736(18)32779-X

12. Taylor, S.G., Murthy, A.K., Vannetzel, J.M., et al. Randomized Comparison of Neoadjuvant Cisplatin and Fluorouracil Infusion Followed by Radiation Versus Concomitant Treatment in Advanced Head and Neck Cancer. *J Clin Oncol*. 1994;12(2):385-395. DOI:10.1200/JCO.1994.12.2.385
13. Medina, J.A., Rueda, A., de Pasos, A.S., et al. A Phase II Study of Concomitant Boost Radiation Plus Concurrent Weekly Cisplatin for Locally Advanced Unresectable Head and Neck Carcinomas. *Radiother Oncol*. 2006;79(1):34-38. DOI:10.1016/j.radonc.2006.03.010
14. Bachaud, J.M., Cohen-Jonathan, E., Alzieu, C., et al. Combined Postoperative Radiotherapy and Weekly Cisplatin Infusion for Locally Advanced Head and Neck Carcinoma: Final Report of a Randomized Trial. *Int J Radiat Oncol Biol Phys*. 1996;36(5):999-1004. DOI:10.1016/s0360-3016(96)00430-0
15. Bernier, J., Dometge, C., Ozsahin, M., et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. *N Engl J Med*. 2004;350(19):1945-1952. DOI:10.1056/NEJMoa032641
16. Harari, P.M., Harris, J., Kies, M.S., et al. Postoperative Chemoradiotherapy and Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. 2014;32(23):2486-2495. DOI:10.1200/JCO.2013.53.9163
17. Cooper, J.S., Zhang, Q., Pajak, T.F., et al. Long-Term Follow-Up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head and Neck. *Int J Radiat Oncol Biol Phys*. 2012;84(5):1198-1205. DOI:10.1016/j.ijrobp.2012.05.008
18. Cooper, J.S., Pajak, T.F., Forastiere, A.A., et al. Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2004;350(19):1937-1944. DOI:10.1056/NEJMoa032646
19. Noronha, V., Joshi, A., Patil, V.M., et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. *J Clin Oncol*. 2018;36(11):1064-1072. DOI:10.1200/JCO.2017.74.9457
20. Janoray, G., Pointreau, Y., Garaud, P., et al. Long-Term Results of a Multicenter Randomized Phase III Trial of Induction Chemotherapy with Cisplatin, 5-Fluorouracil, ± Docetaxel for Larynx Preservation. *J Natl Cancer Inst*. 2015;108(4):djv368. Published 2015 Dec 16. DOI:10.1093/jnci/djv368
21. Pointreau, Y., Garaud, P., Chapet, S., et al. Randomized Trial of Induction Chemotherapy with Cisplatin And 5-Fluorouracil with or without Docetaxel for Larynx Preservation. *J Natl Cancer Inst*. 2009;101(7):498-506. DOI:10.1093/jnci/djp007
22. Posner, M.R., Hershock, D.M., Blajman, C.R., et al. Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer. *N Engl J Med*. 2007;357(17):1705-1715. DOI:10.1056/NEJMoa070956
23. Hitt, R., López-Pousa, A., Martínez-Trufero, J., et al. Phase III Study Comparing Cisplatin Plus Fluorouracil to Paclitaxel, Cisplatin and Fluorouracil Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Head and Neck Cancer [published correction appears in *J Clin Oncol*. 2006 Feb. 20;24(6):1015]. *J Clin Oncol*. 2005;23(34):8636-8645. DOI:10.1200/JCO.2004.00.1990
24. Haddad, R., O'Neill, A., Rabinowits, G., et al. Induction Chemotherapy Followed by Concurrent Chemoradiotherapy (Sequential Chemoradiotherapy) Versus Concurrent Chemoradiotherapy Alone in Locally Advanced Head and Neck Cancer (PARADIGM): A Phase 3 Trial. *Lancet Oncol*. 2013;14(3):257-264. DOI:10.1016/S1470-2045(13)70011-1

25. Lefebvre, J.L., Pointreau, Y., Rolland, F., et al. Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLEIN Randomized Phase II Study [Published Correction Appears in *J Clin Oncol.* 2013 May 1;31(13):1702]. *J Clin Oncol.* 2013;31(7):853-859. DOI:10.1200/JCO.2012.42.3988
26. Chitapanarux, I., Lorvidhaya, V., Kamnerdsupaphon, P., et al. Chemoradiation Comparing Cisplatin Versus Carboplatin in Locally Advanced Nasopharyngeal Cancer: Non-Inferiority, Open Trial. *Eur J Cancer.* 2007;43(9):1399-1406. DOI:10.1016/j.ejca.2007.03.022
27. Vermorken, J.B., Remenar, E., van Herpen, C., et al. Cisplatin, Fluorouracil and Docetaxel in Unresectable Head and Neck Cancer. *N Engl J Med.* 2007;357(17):1695-1704. DOI:10.1056/NEJMoa071028
28. Hanemaaijer, S.H., Kok, I.C., Fehrmann, R.S.N., et al. Comparison of Carboplatin with 5-Fluorouracil vs. Cisplatin as Concomitant Chemoradiotherapy for Locally Advanced Head and Neck Squamous Cell Carcinoma. *Front Oncol.* 2020;10:761. Published 2020 Jun 5. DOI:10.3389/fonc.2020.00761
29. Al-Sarraf, M., LeBlanc, M., Giri, P.G., et al. Chemoradiotherapy Versus Radiotherapy in Patients with Advanced Nasopharyngeal Cancer: Phase III Randomized Intergroup Study 0099. *J Clin Oncol.* 1998; 16: 1310-1317
30. Chan, A.T., Leung, S.F., Ngan, R.K., et al. Overall Survival After Concurrent Cisplatin-Radiotherapy Compared with Radiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma. *J Natl Cancer Inst.* 2005; 97:536-539
31. Lee, A.W., Tung, S.Y., Ng, W.T., et al. A Multicenter, Phase 3, Randomized Trial of Concurrent Chemoradiotherapy Plus Adjuvant Chemotherapy Versus Radiotherapy Alone in Patients with Regionally Advanced Nasopharyngeal Carcinoma: 10-Year Outcomes for Efficacy and Toxicity. *Cancer.* 2017; 123(21):4147-4157
32. Dechaphunkul T., Pruegsanusak, K., Sangthawan, D., et al. Concurrent Chemoradiotherapy with Carboplatin Followed by Carboplatin and 5-Fluorouracil in Locally Advanced Nasopharyngeal Carcinoma. *Head Neck Oncol.* 2011; 3:30
33. Chen, L., Hu, C.S., Chen, X.Z., et al. Concurrent Chemoradiotherapy Plus Adjuvant Chemotherapy Versus Concurrent Chemoradiotherapy Alone in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma: A Phase 3 Multicentre Randomized Controlled Trial. *Lancet Oncol.* 2012; 13:163-171
34. Zhang, Y., Chen, L., Hu, G.Q., et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. *N Engl J Med.* 2019; 381:1124-1135
35. Chen, Y.P., Tang, L.L., Yang, Q., et al. Induction Chemotherapy Plus Concurrent Chemoradiotherapy in Endemic Nasopharyngeal Carcinoma: Individual Patient Data Pooled Analysis of Four Randomized Trials. *Clin Cancer Res.* 2018; 24:1824-1833
36. Bae, W.K., Hwang, J.E., Shim, H.J., et al. Phase II Study of Docetaxel, Cisplatin and 5-FU Induction Chemotherapy Followed by Chemoradiotherapy in Locoregionally Advanced Nasopharyngeal Cancer. *Cancer Chemother Pharmacol.* 2010; 65: 589-595
37. Sun, Y., Li, W.F., Chen, N.Y., et al. Induction Chemotherapy Plus Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma: A Phase 3, Multicenter, Randomized Controlled Trial. *Lancet Oncol.* 2016; 17:1509-1520
38. Fountzilas, G., Tolis, C., Kalogera-Fountzila, A., et al. Induction Chemotherapy with Cisplatin, Epirubicin and Paclitaxel (CEP), Followed by Concomitant Radiotherapy and Weekly Paclitaxel for the Management of Locally Advanced Nasopharyngeal Carcinoma. A Hellenic Cooperative Oncology Group Phase II Study. *Strahlenther Onkol.* 2005; 181(4): 223-30

39. Hui, E.P., Ma, B.B., Leung, S.F., et al. Randomized Phase II Trial of Concurrent Cisplatin-Radiotherapy with or without Neoadjuvant Docetaxel and Cisplatin in Advanced Nasopharyngeal Carcinoma. *J Clin Oncol*. 2009; 27: 242-249
40. Blanchard, P., Lee, A., Marguet, S., et al. Chemotherapy and Radiotherapy in Nasopharyngeal Carcinoma: An Update of the MAC-NPC Meta-Analysis. *Lancet Oncol*. 2015; 16: 645-655
41. Ribassin-Majed, L., Marguet, S., Lee, A., et al. What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. *J Clin Oncol*. 2017; 35(5): 498-505
42. Vermorken, J.B., Mesia, R., Rivera, F., et al. Platinum-Based Chemotherapy Plus Cetuximab in Head and Neck Cancer. *N Engl J Med*. 2008;359(11):1116-1127. DOI:10.1056/NEJMoa0802656
43. Burtneess, B., Harrington, K.J., Greil, R., et al. Pembrolizumab Alone or with Chemotherapy Versus Cetuximab with Chemotherapy for Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (KEYNOTE-048): An Open-Label, Phase 3 Study [published correction appears in *Lancet*. 2020 Jan 25;395(10220):272] [published correction appears in *Lancet*. 2020 Feb 22;395(10224):564]. *Lancet*. 2019;394(10212):1915-1928. DOI:10.1016/S0140-6736(19)32591-7
44. Burtneess, B., Goldwasser, M.A., Flood, W., et al., Eastern Cooperative Oncology Group. Phase III Randomized Trial of Cisplatin Plus Placebo Compared with Cisplatin Plus Cetuximab in Metastatic/Recurrent Head and Neck Cancer: An Eastern Cooperative Oncology Group Study [published correction appears in *J Clin Oncol*. 2006 Feb 1;24(4):724]. *J Clin Oncol*. 2005;23(34):8646-8654. DOI:10.1200/JCO.2005.02.4646
45. Samlowski, W.E., Moon, J., Kuebler, J.P., et al. Evaluation of the Combination of Docetaxel/Carboplatin in Patients with Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN): A Southwest Oncology Group Phase II Study. *Cancer Invest*. 2007;25(3):182-188. DOI:10.1080/07357900701209061
46. Gibson, M.K., Li, Y., Murphy, B., et al. Randomized Phase III Evaluation of Cisplatin Plus Fluorouracil Versus Cisplatin Plus Paclitaxel in Advanced Head and Neck Cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;23(15):3562-3567. DOI:10.1200/JCO.2005.01.057
47. Guigay, J., Fayette, J., Dillies, A.F., et al. Cetuximab, Docetaxel and Cisplatin as First-Line Treatment in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Multicenter, Phase II GORTEC Study. *Ann Oncol*. 2015;26(9):1941-1947. DOI:10.1093/annonc/mdv268
48. Forastiere, A.A., Metch, B., Schuller, D.E., et al. Randomized Comparison of Cisplatin Plus Fluorouracil and Carboplatin Plus Fluorouracil Versus Methotrexate in Advanced Squamous-Cell Carcinoma of the Head and Neck: A Southwest Oncology Group Study. *J Clin Oncol*. 1992;10(8):1245-1251. DOI:10.1200/JCO.1992.10.8.1245
49. Guigay, J., Fayette, J., Mesia, R., et al. TPEXtreme Randomized Trial: TPEX Versus Extreme Regimen in 1st Line Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC). *J Clin Oncol*. 37, 2019 (suppl; abstr 6002). DOI: 10.1200/JCO.2019.37.15_suppl.6002
50. Vermorken, J.B., Stöhlmacher-Williams, J., Davidenko, I., et al. Cisplatin and Fluorouracil with or without Panitumumab in Patients with Recurrent or Metastatic Squamous-Cell Carcinoma of the Head and Neck (SPECTRUM): An Open-Label Phase 3 Trial. *Lancet Oncol*. 2013;14(8):697-710. DOI:10.1016/S1470-2045(13)70181-5
51. Martinez-Trufero, J., Isla D., Adansa, J.C., et al. Phase II Study of Capecitabine as Palliative Treatment for Patients with Recurrent and Metastatic Squamous Head and Neck Cancer After

- Previous Platinum-Based Treatment. *Br J Cancer*. 2010;102(12):1687-1691.
DOI:10.1038/sj.bjc.6605697
52. Stewart, J.S., Cohen, E.E., Licitra, L., et al. Phase III Study of Gefitinib Compared with Intravenous Methotrexate for Recurrent Squamous Cell Carcinoma of the Head and Neck [corrected] [published correction appears in *J Clin Oncol*. 2009 Jul 10;27(20):3410]. *J Clin Oncol*. 2009;27(11):1864-1871. DOI:10.1200/JCO.2008.17.0530
 53. Vermorken, J.B., Trigo, J., Hitt, R., et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab as a Single Agent in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. *J Clin Oncol*. 2007;25(16):2171-2177.
DOI:10.1200/JCO.2006.06.7447
 54. Bossi, P., Miceli, R., Locati, L.D., et al. A Randomized, Phase 2 Study of Cetuximab Plus Cisplatin with or without Paclitaxel for the First-Line Treatment of Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck. *Ann Oncol*. 2017;28(11):2820-2826. DOI:10.1093/annonc/mdx439
 55. Ferris, R.L., Blumenschein, Jr., G., Fayette, J., et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016;375(19):1856-1867.
DOI:10.1056/NEJMoa1602252
 56. Ferris, R.L., Blumenschein, Jr., G., Fayette, J., et al. Nivolumab vs. Investigator's Choice in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: 2-Year Long-Term Survival Update of Checkmate 141 with Analyses by Tumor PD-L1 Expression. *Oral Oncol*. 2018;81:45-51. DOI:10.1016/j.oraloncology.2018.04.008
 57. Cohen, E.E.W., Soulières, D., Le Tourneau, C., et al. Pembrolizumab Versus Methotrexate, Docetaxel, or Cetuximab for Recurrent or Metastatic Head-and-Neck Squamous Cell Carcinoma (KEYNOTE-040): A Randomized, Open-Label, Phase 3 Study [published correction appears in *Lancet*. 2019 Jan 12;393(10167):132]. *Lancet*. 2019;393(10167):156-167. DOI:10.1016/S0140-6736(18)31999-8
 58. Machiels, J.P., Haddad, R.I., Fayette, J., et al. Afatinib Versus Methotrexate as Second-Line Treatment in Patients with Recurrent or Metastatic Squamous-Cell Carcinoma of the Head and Neck Progressing On or After Platinum-Based Therapy (LUX-Head & Neck 1): An Open-Label, Phase 3 Trial. *Lancet Oncol*. 2015;16(5):583-594. DOI:10.1016/S1470-2045(15)70124-5
 59. Jacobs, C., Lyman, G., Velez-García, E., et al. A Phase III Randomized Study Comparing Cisplatin and Fluorouracil as Single Agents and in Combination for Advanced Squamous Cell Carcinoma of the Head and Neck. *J Clin Oncol*. 1992;10(2):257-263.
DOI:10.1200/JCO.1992.10.2.257
 60. Catimel, G., Verweij, J., Mattijssen, V., et al. Docetaxel (Taxotere®): An Active Drug for the Treatment of Patients with Advanced Squamous Cell Carcinoma of the Head and Neck. EORTC Early Clinical Trial Group. *Ann Oncol*. 1994; 5:533–537
 61. Guardiola, E., Peyrade, F., Chaigneau, L., et al. Results of a Phase II Study Comparing Docetaxel with Methotrexate in Patients with Recurrent Head and Neck Cancer. *Eur J Cancer*. 2004;40(14):2071-2076. DOI:10.1016/j.ejca.2004.05.019
 62. Grau, J.J., Caballero, M., Verger, E., et al. Weekly Paclitaxel for Platin-Resistant Stage IV Head and Neck Cancer Patients. *Acta Otolaryngol*. 2009;129(11):1294-1299.
DOI:10.3109/00016480802590451
 63. Al-Sarraf, M., Metch, B., Kish, J., et al. Platinum Analogs in Recurrent and Advanced Head and Neck Cancer: A Southwest Oncology Group and Wayne State University Study. *Cancer Treat Rep*. 1987;71(7-8):723-726

64. Jin, Y., Cai, X.Y., Shi, Y.X., et al. Comparison of Five Cisplatin-Based Regimens Frequently Used as the First-Line Protocols in Metastatic Nasopharyngeal Carcinoma. *J Cancer Res Clin Oncol*. 2012;138:1717-1725
65. Zhang, L., Huang, Y., Hong, S., et al. Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Recurrent or Metastatic Nasopharyngeal Carcinoma: A Multicentre, Open-Label, Phase 3 Trial. *Lancet*. 2016;388:1883-1892
66. Gibson, M.K., Li, Y., Murphy, B., et al. Randomized Phase III Evaluation of Cisplatin Plus Fluorouracil Versus Cisplatin Plus Paclitaxel in Advanced Head and Neck Cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;23:3562-3567
67. Jacobs, C., Lyman, G., Velez-Garcia, E., et al. A Phase III Randomized Study Comparing Cisplatin and Fluorouracil as Single Agents and in Combination for Advanced Squamous Cell Carcinoma of the Head and Neck. *J Clin Oncol*. 1992;10:257-263
68. Samlowski, W.E., Moon, J., Kuebler, J.P., et al. Evaluation of the Combination of Docetaxel/Carboplatin in Patients with Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN): A Southwest Oncology Group Phase II Study. *Cancer Invest*. 2007;25:182-188
69. Chan, A.T.C., Hsu, M.-M., Goh, B.C., et al. Multicenter, Phase II Study of Cetuximab in Combination with Carboplatin in Patients with Recurrent or Metastatic Nasopharyngeal Carcinoma. *J Clin Oncol*. 2005;23:3568-3576
70. Leong, S.S., Wee, J., Tay, M.H., et al. Paclitaxel, Carboplatin and Gemcitabine in Metastatic Nasopharyngeal Carcinoma: A Phase II Trial Using a Triplet Combination. *Cancer*. 2005;103:569-575
71. Burtneß, B., Goldwasser, M.A., Flood, W., et al. Phase III Randomized Trial of Cisplatin Plus Placebo Compared with Cisplatin Plus Cetuximab in Metastatic/Recurrent Head and Neck Cancer: An Eastern Cooperative Oncology Group Study. *J Clin Oncol*. 2005;23:8646-8654
72. Zhang, L., Zhang, Y., Huang, P.-Y., et al. Phase II Clinical Study of Gemcitabine in the Treatment of Patients with Advanced Nasopharyngeal Carcinoma After the Failure of Platinum-Based Chemotherapy. *Cancer Chemother Pharmacol*. 2008;61:33-38
73. Delord, J.P., Hollebecque, A., de Boer, J.P., et al. An Open-Label, Multicohort, Phase I/II Study to Evaluate Nivolumab in Patients with Virus-Associated Tumors (Checkmate 358): Efficacy and Safety in Recurrent or Metastatic (R/M) Nasopharyngeal Carcinoma (NPC). *J Clin Oncol*. 2017;35(suppl 15): Abstract 6025
74. Ma, B.B.Y., Lim, W.T., Goh, B.C., et al. Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). *J Clin Oncol*. 2018;36:1412-1418
75. Hsu, C., Lee, S.H., Ejadi, S., et al. Safety and Antitumor Activity of Pembrolizumab in Patients with Programmed Death-Ligand 1-Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study. *J Clin Oncol*. 2017; 35:4050-4056
76. Marabelle, A., Le, D.T., Ascierto, P.A., et al. Efficacy of Pembrolizumab in Patients with Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38: 1–10
77. Chen, Y.P., Liu, X., Zhou, Q., et al. Metronomic Capecitabine as Adjuvant Therapy in Locoregionally Advanced Nasopharyngeal Carcinoma: A Multicentre, Open-Label, Parallel-Group, Randomised, Controlled, Phase 3 Trial. *Lancet*. 2021 Jul 24; 398(10297):303-313. DOI: 10.1016/S0140-6736(21)01123-5. Epub 2021 Jun 7. PMID: 34111416
78. Yang, Y., Qu, S., Li, J., et al. Camrelizumab Versus Placebo in Combination with Gemcitabine and Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Carcinoma

- (CAPTAIN-1st): A Multicentre, Randomised, Double-Blind, Phase 3 Trial. *Lancet Oncol.* 2021 Aug; 22(8):1162-1174. DOI: 10.1016/S1470-2045(21)00302-8. Epub 2021 Jun 23. PMID: 34174189
79. Mai, H.Q., Chen, Q.Y., Chen, D., et al. Toripalimab or Placebo Plus Chemotherapy as First-Line Treatment in Advanced Nasopharyngeal Carcinoma: A Multicenter Randomized Phase 3 Trial. *Nat Med.* 2021 Sep; 27(9):1536-1543. DOI: 10.1038/s41591-021-01444-0. Epub 2021 Aug 2. Erratum in: *Nat Med.* 2022 Jan;28(1):214. PMID: 34341578
 80. Sacco, A.G., Chen, R., Worden, F.P., et al. Pembrolizumab Plus Cetuximab in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: An Open-Label, Multi-Arm, Non-Randomised, Multicentre, Phase 2 Trial. *Lancet Oncol.* 2021 Jun; 22(6):883-892. DOI: 10.1016/S1470-2045(21)00136-4. Epub 2021 May 11. PMID: 33989559

Hepatocellular Carcinoma

Unresectable, Not a Transplant Candidate, Metastatic Disease, Inoperable by PS or Comorbidity

1st Line of Therapy

- Sorafenib
- Lenvatinib
- Atezolizumab + Bevacizumab*
- Durvalumab + Tremelimumab

2nd + Subsequent Lines of Therapy

- Regorafenib
- Cabozantinib
- Sorafenib
- Lenvatinib

*For patients that have not received treatment with a checkpoint inhibitor.

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/livibd.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatocellular Carcinoma (V1.2023, 2.17.2023)
3. Cheng, A.-L., Kang, Y.-K., Chen, Z., et al. (January 2009). Efficacy and Safety of Sorafenib in Patients in the Asia-Pacific Region with Advanced Hepatocellular Carcinoma: A Phase III Randomised, Double-Blind, Placebo-Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/19095497
4. Llovet, J.M., Ricci, S., Mazzaferro, V., et al. (2008, July 24). Sorafenib in Advanced Hepatocellular Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/18650514
5. Zhu, A.X., Rosmorduc, O., Evans, T.R.J., et al. (2015, Feb. 20). SEARCH: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sorafenib Plus Erlotinib in Patients with Advanced Hepatocellular Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/25547503
6. Kudo, M., Finn, R.S., Qin, S., et al. (2018, March 24). Lenvatinib Versus Sorafenib in First-Line Treatment of Patients with Unresectable Hepatocellular Carcinoma: A Randomised Phase 3 Non-Inferiority Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=29433850
7. Qin, S., Bai, Y., Lim, H.Y., et al. (2013, Oct. 1). Randomized, Multicenter, Open-Label Study of Oxaliplatin Plus Fluorouracil/Leucovorin Versus Doxorubicin as Palliative Chemotherapy in Patients with Advanced Hepatocellular Carcinoma from Asia. Retrieved from ncbi.nlm.nih.gov/pubmed/23980077

8. Bruix, J., Qin, S., Merle, P., et al. (2017, Jan. 7). Regorafenib for Patients with Hepatocellular Carcinoma Who Progressed on Sorafenib Treatment (RESORCE): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/27932229
9. Abou-Alfa, G.K., Meyer, T., Cheng, A.L., et al. (2018, July 5). Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=29972759
10. Zhu, A.X., Kang, Y.-K., Yen, C.-J., et al. (February 2019). Ramucirumab After Sorafenib in Patients with Advanced Hepatocellular Carcinoma and Increased α -Fetoprotein Concentrations (REACH-2): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/30665869
11. El-Khoueiry, A.B., Sangro, B., Yau, T., et al. (2017, June 24). Nivolumab in Patients with Advanced Hepatocellular Carcinoma (CheckMate 040): An Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28434648
12. Yau, T., Park, J.W., Finn, R.S., et al. (2019, Sept. 27). CheckMate 459: A Randomized, Multi-Center Phase 3 Study of Nivolumab (NIVO) vs. Sorafenib (SOR) as First-Line (1L) Treatment in Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC). Retrieved from oncologypro.esmo.org/Meeting-Resources/ESMO-2019-Congress/CheckMate-459-A-Randomized-Multi-Center-Phase-3-Study-of-Nivolumab-NIVO-vs-Sorafenib-SOR-as-First-Line-1L-Treatment-in-Patients-pts-with-Advanced-Hepatocellular-Carcinoma-aHCC
13. Zhu, A.X., Finn, R.S., Edeline, J., et al. (July 2018). Pembrolizumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib (KEYNOTE-224): A Non-Randomised, Open-Label Phase 2 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/29875066
14. Finn, R.S., Ryoo, B.-Y., Merle, P., et al. (2019, Dec. 2). Pembrolizumab As Second-Line Therapy in Patients with Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/31790344
15. Finn, R.S., Qin, S., Ikeda, M., et al. Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020 May 14;382(20):1894-1905. DOI: 10.1056/NEJMoa1915745. PMID: 32402160
16. Finn, R.S., Qin, S., Ikeda, M., et al. IMbrave150: Updated Overall Survival (OS) Data From a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) vs. Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC). *J Clin Oncol*. 2021;39(suppl 3):267. Retrieved from bit.ly/2LVd9Mu
17. Yau, T., Hsu, C., Kim, T.Y., et al. Nivolumab in Advanced Hepatocellular Carcinoma: Sorafenib-Experienced Asian Cohort Analysis. *J Hepatol*. 2019 Sep;71(3):543-552. DOI: 10.1016/j.jhep.2019.05.014. Epub 2019 Jun 7. Erratum in: *J Hepatol*. 2019 Dec;71(6):1278
18. Sangro, B., Melero, I., Wadhawan, S., et al. Association of Inflammatory Biomarkers with Clinical Outcomes in Nivolumab-Treated Patients with Advanced Hepatocellular Carcinoma. *J Hepatol*. 2020 Dec;73(6):1460-1469. DOI: 10.1016/j.jhep.2020.07.026. Epub 2020 Jul 22
Yau, T., Kang, Y.K., Kim, T.Y., et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol*. 2020 Oct 1;6(11):e204564. DOI: 10.1001/jamaoncol.2020.4564. Epub ahead of print. PMID: 33001135; PMCID: PMC7530824.040
19. Andre, T. et al. Safety and Efficacy of Anti-PD1 Antibody Dostarlimab in Patients (Pts) with Mismatch Repair-Deficient (dMMR) Solid Cancers: Results from GARNET- Study [Abstract]. *J Clin Oncol*. 2021; 39: Abstract 9

20. Berton, D. et al. Antitumor Activity of Dostarlimab in Patients with Mismatch Repair-Deficient/Microsatellite Instability-High Tumors: A Combined Analysis of Two Cohorts in the GARNET Study [Abstract]. *J Clin Oncol.* 2021; 39: Abstract 2564
21. Salama, A.K.S., et al. Dabrafenib and Trametinib in Patients with Tumors with BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol.* 2020 Nov 20; 38(33):3895-3904. Epub 2020 Aug 6. PMID: 32758030
22. Lwin, Z., et al. LEAP-005: Phase II study of Lenvatinib (len) Plus Pembrolizumab (Pembro) in Patients (Pts) with Previously Treated Advanced Solid Tumors. *Ann Oncol.* 2020; 31:S1142-S1215
23. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evidence.* 2022;1(8). DOI:10.1056/EVIDoa2100070.

Hodgkin Lymphoma (HL)

1st Line of Therapy

- Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)
- Doxorubicin + Vinblastine + Dacarbazine (AVD)
- Escalated bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisone (escBEACOPP)

References:

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
2. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363:640-652.
3. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372:1598-1607.
4. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35:1786-1794.
5. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol*. 2010;28:4199-4206.
6. Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. *Blood*. 2018;132:1013- 1021.
7. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37:2835-2845.
8. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's Lymphoma. *N Engl J Med*. 2016;374: 2419-2429.
9. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379:1791-1799.
10. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): A randomised, multicentre, noninferiority, phase 3 study. *Lancet Oncol*. 2019;20:202-215.
11. Casasnovas RO, Bouabdallah R, Brice P, et al. Positron Emission Tomography-Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study. *J Clin Oncol*. 2022 Apr 1;40(10):1091-1101. PMID: 34990281.
12. Borchmann P, Goergen H, Kobe C et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2017 Dec 23;390(10114):2790-2802. DOI: 10.1016/S0140-6736(17)32134-7. Epub 2017 Oct 20. PMID: 29061295.

13. Kreissl S, Goergen H, Buehnen I et al. German Hodgkin Study Group. PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021 Jun;8(6):e398-e409.
14. von Tresckow B, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30:907-913.
15. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021;8:e410-e421.
16. Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. *Blood*. 2011 Oct 27;118(17):4585-90. DOI: 10.1182/blood-2011-07-365932. Epub 2011 Aug 26. PMID: 21873543.
17. Canellos GP, Mauch P. What is the appropriate systemic chemotherapy for lymphocyte-predominant Hodgkin's lymphoma? *J Clin Oncol*. 2010 Jan 1;28(1):e8. DOI: 10.1200/JCO.2009.26.3293. Epub 2009 Nov 23. PMID: 19933898.
18. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. *Blood*. 2017 Jul 27;130(4):472-477. DOI: 10.1182/blood-2017-02-766121. Epub 2017 May 18. PMID: 28522441; PMCID: PMC5578726.
19. Shankar A, Hall GW, Gorde-Grosjean S, et al. Treatment outcome after low intensity chemotherapy [CVP] in children and adolescents with early stage nodular lymphocyte predominant Hodgkin's lymphoma - an Anglo-French collaborative report. *Eur J Cancer*. 2012 Jul;48(11):1700-6. DOI: 10.1016/j.ejca.2011.10.018. Epub 2011 Nov 15. PMID: 22093944.
20. Advani RH, Horning SJ, Hoppe RT, Daadi S, Allen J, Natkunam Y, Bartlett NL. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol*. 2014 Mar 20;32(9):912-8. DOI: 10.1200/JCO.2013.53.2069. Epub 2014 Feb 10. PMID: 24516013.
21. Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. *Blood*. 2013 Dec 19;122(26):4182-8. DOI: 10.1182/blood-2013-07-453241. Epub 2013 Nov 8. PMID: 24215035.
22. Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood*. 2011 Oct 20;118(16):4363-5. DOI: 10.1182/blood-2011-06-361055. Epub 2011 Aug 9. PMID: 21828141.
23. Eichenauer DA, Plütschow A, Fuchs M, et al. Long-Term Course of Patients with Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group. *J Clin Oncol*. 2015 Sep 10;33(26):2857-62. DOI: 10.1200/JCO.2014.60.4363. Epub 2015 Aug 3. PMID: 26240235.
24. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood*. 2008 Jan 1;111(1):109-11. DOI: 10.1182/blood-2007-03-078725. Epub 2007 Oct 15. PMID: 17938252.
25. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010 Aug 12;363(7):640-52. DOI: 10.1056/NEJMoa1000067. PMID: 20818855.

26. Stamatoullas A, Brice P, Bouabdallah R, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. *Br J Haematol*. 2015 Jul;170(2):179-84. DOI: 10.1111/bjh.13419. Epub 2015 Apr 19. PMID: 25891777.
27. Behringer K, Goergen H, Hitz F, et al; German Hodgkin Study Group; Swiss Group for Clinical Cancer Research; Arbeitsgemeinschaft Medikamentöse Tumortherapie. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet*. 2015 Apr 11;385(9976):1418-27. DOI: 10.1016/S0140-6736(14)61469-0. Epub 2014 Dec 22. Erratum in: *Lancet*. 2015 Apr 11;385(9976):1396. PMID: 25539730.
28. Kolstad A, Nome O, Delabie J, et al. Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. *Leuk Lymphoma*. 2007 Mar;48(3):570-6. DOI: 10.1080/10428190601126610. PMID: 17454601.
29. Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients with Untreated Classical Hodgkin Lymphoma. *J Clin Oncol*. 2018 Oct 20;36(30):3015-3022. DOI: 10.1200/JCO.2018.79.0139. Epub 2018 Sep 4. PMID: 30179569.
30. Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥ 60 years with HL. *Blood*. 2017 Dec 28;130(26):2829-2837. DOI: 10.1182/blood-2017-06-787200. Epub 2017 Oct 16. PMID: 29038340.
31. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183-2189.
32. O' Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial. *Lancet Oncol*. 2018;19:257-266.
33. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131:1183-1194.
34. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/ cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol*. 2002;13:1628-1635.
35. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. *Ann Oncol*. 1999;10:593-595.
36. Labrador J, Cabrero-Calvo M, Perez-Lopez E, et al. ESHAP as salvage therapy for relapsed or refractory Hodgkin's lymphoma. *Ann Hematol*. 2014;93:1745-1753.
37. Fernández de Larrea C, Martínez C, et al. Salvage chemotherapy with alternating MINE-ESHAP regimen in relapsed or refractory Hodgkin's lymphoma followed by autologous stem cell transplantation. *Ann Oncol*. 2010;21:1211-1216.
38. Santoro A, Mazza R, Pulsoni A, et al. Bendamustine in combination with gemcitabine and vinorelbine is an effective regimen as induction chemotherapy before autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma: final results of a multicenter phase II study. *J Clin Oncol*. 2016;34:3293-3299.
39. Bartlett N, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol*. 2007;18:1071-1079.

40. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2021;39:3109-3117.
41. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97:616-623.
42. Hertzberg MS, Crombie C, Benson W, et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma. *Ann Oncol*. 2006;17 Suppl 4:iv25-30.
43. Abali H, Urün Y, Oksüzoğlu B, Budakoğlu B, et al. Comparison of ICE (ifosfamide, carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. *Cancer Invest*. 2008;26:401-406. Santoro 2007
44. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35:2125-2132.
45. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22:512-524.

Kidney Cancer

Relapsed or Metastatic (Clear Cell)

1st Line of Therapy

- Axitinib + Avelumab
- Axitinib + Pembrolizumab
- Cabozantinib + Nivolumab
- Lenvatinib + Pembrolizumab

2nd + Subsequent lines of therapy

- Axitinib
- Cabozantinib
- Pazopanib
- Sunitinib
- Tivozanib (who received ≥ 2 prior systemic therapies)
- Nivolumab (if immune checkpoint inhibitor not received previously)

References:

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology.
2. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomized, phase 3 trial. *Lancet*. 2016 May 14;387(10032):2008-16. Epub 2016 Mar 9. Erratum in: *Lancet*. 2016 May 14;387(10032):1998. PMID: 26969090.
3. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med*. 2016 Dec 8;375(23):2246-2254. Epub 2016 Oct 9. PMID: 27718781.
4. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. *N Engl J Med*. 2021 Aug 19;385(8):683-694. PMID: 34407342.
5. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380:1116-1127.
6. Powles T, Plimack ER, Soulieres D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2020;21:1563-1573.
7. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021.
8. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2021;384:829-841.

9. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018;378:1277-1290.
10. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380:1103-1115.
11. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*. 2020;31:1030-1039.
12. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients with Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *J Clin Oncol*. 2017;35:591-597.
13. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722-731.
14. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med*. 2014;370:1769-1770.
15. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124.
16. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:3584-3590.
17. Hammers HJ, Plimack ER, Infante JR, et al. Safety and Efficacy of Nivolumab in Combination with Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. *J Clin Oncol*. 2017;35:3851-3858.
18. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16:1473-1482.
19. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. *Lancet Oncol*. 2016;17:e4-5.
20. Lee CH, Shah AY, Rasco D, et al. Lenvatinib plus pembrolizumab in patients with either treatment-naïve or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study. *Lancet Oncol*. 2021;22:946-958.
21. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373:1814-1823.
22. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:917-927.
23. Motzer RJ, Escudier B, Powles T, et al. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. *Br J Cancer*. 2018;118:1176-1178.
24. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373:1803-1813.
25. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378:1931-1939.
26. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14:552-562.

27. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol.* 2020;21:95-104.
28. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med.* 2003 Jul 31;349(5):427-34. DOI: 10.1056/NEJMoa021491. PMID: 12890841; PMCID: PMC2275324.
29. Apolo AB, Nadal R, Girardi DM, et al. Phase I Study of Cabozantinib and Nivolumab Alone or with Ipilimumab for Advanced or Metastatic Urothelial Carcinoma and Other Genitourinary Tumors. *J Clin Oncol.* 2020;38:3672-3684.
30. Final results from a phase I trial and expansion cohorts of cabozantinib and nivolumab (CaboNivo) alone or with ipilimumab (CaboNivolpi) for metastatic genitourinary tumors. ASCO; 2021. Available at: <https://meetinglibrary.asco.org/record/194730/abstract>. A
31. Pal SK, Tangen C, Thompson IM, Jr., et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:695-703.
32. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol.* 2016;17:378-388.
33. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. *Eur Urol.* 2016;69:866- 874
34. Blank C, Bono P, Larkin JMG, et al. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy: Subgroup analysis of REACT. *J Clin Oncol.* 30, no. 5_suppl (February 10, 2012) 402-402.
35. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. *Ann Oncol.* 2013;24:1026- 1031.
36. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer.* 2016;69:226-235.
37. Hutson TE, Michaelson MD, Kuzel TM, et al. A Single-arm, Multicenter, Phase 2 Study of Lenvatinib Plus Everolimus in Patients with Advanced Non-Clear Cell Renal Cell Carcinoma. *Eur Urol.* 2021;80:162- 170.
38. Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. *J Immunother Cancer.* 2018;6:9.
39. McKay RR, Bosse D, Xie W, et al. The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma. *Cancer Immunol Res.* 2018;6:758-765.
40. McDermott DF, Lee JL, Ziobro M, et al. Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients with Advanced Non-Clear Cell Renal Cell Carcinoma. *J Clin Oncol.* 2021;39:1029-1039.
41. Park I, Lee SH, Lee JL. A Multicenter Phase II Trial of Axitinib in Patients with Recurrent or Metastatic Non-clear-cell Renal Cell Carcinoma Who Had Failed Prior Treatment with Temsirolimus. *Clin Genitourin Cancer.* 2018;16:e997-e1002.
42. Jung KS, Lee SJ, Park SH, et al. Pazopanib for the Treatment of Non-clear Cell Renal Cell Carcinoma: A Single-Arm, Open-Label, Multicenter, Phase II Study. *Cancer Res Treat.* 2018;50:488-494.

43. Buti S, Bersanelli M, Maines F, et al. First-Line Pazopanib in Non-clear-cell Renal cArcinoMA: The Italian Retrospective Multicenter PANORAMA Study. *Clin Genitourin Cancer*. 2017;15:e609-e614.

Non-Small Cell Lung Cancer

Neoadjuvant/Adjuvant

Nonsquamous

- Nivolumab + Carboplatin or Cisplatin + Paclitaxel (Neoadjuvant only)
- Nivolumab + Carboplatin or Cisplatin + Pemetrexed (Neoadjuvant only)
- Cisplatin + Vinorelbine
- Cisplatin or Carboplatin + Pemetrexed ± Concurrent Radiation Therapy (RT)
- Carboplatin + Paclitaxel ± Concurrent Radiation Therapy (RT)
- Cisplatin + Etoposide + Concurrent Radiation Therapy (RT)
- Osimertinib (in completely resected stage IB – IIIA EGFR (exon 19del, L858R) directly following completion of adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy)

Squamous

- Nivolumab + Carboplatin or Cisplatin + Paclitaxel (Neoadjuvant only)
- Nivolumab + Carboplatin or Cisplatin + Gemcitabine (Neoadjuvant only)
- Cisplatin + Vinorelbine
- Carboplatin + Paclitaxel ± Concurrent Radiation Therapy (RT)
- Cisplatin + Etoposide + Concurrent Radiation Therapy (RT)
- Osimertinib (in completely resected stage IB — IIIA EGFR (exon 19del, L858R) directly following completion of adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy)

Consolidation after chemoradiation, Stage III Unresectable, No Progression, and PS 0–1

- Durvalumab

Advanced/Metastatic: EGFR exon 19 deletion, L858R, S768I, L861Q, and/or G719X Mutation Positive

1st + Subsequent Lines of Therapy

- Dacomitinib
- Osimertinib

Advanced/Metastatic: ALK Rearrangement Positive

1st + Subsequent Lines of Therapy

- Alectinib
- Brigatinib

- Lorlatinib

Advanced/Metastatic (EGFR, ALK, RET Wild Type)

Nonsquamous: 1st Line of Therapy

- Pembrolizumab Single Agent (PD-L1 \geq 50% only)
- Atezolizumab (PD-L1 \geq 50% only)
- Cemiplimab-rwlc (PD-L1 \geq 50% only)
- Carboplatin/Cisplatin + Pemetrexed + Pembrolizumab (regardless of PD-L1)
- Carboplatin/Cisplatin + Pemetrexed + Cemiplimab-rwlc, (regardless of PD-L1)
- Carboplatin/Cisplatin + Paclitaxel + Cemiplimab-rwlc (regardless of PD-L1)
- Carboplatin/Cisplatin + Pemetrexed (IO Ineligible)
- Carboplatin/Cisplatin + Paclitaxel (IO Ineligible)

Nonsquamous: Maintenance

- Cemiplimab-rwlc +/- Pemetrexed
- Pemetrexed
- Pembrolizumab +/- Pemetrexed

Nonsquamous: 2nd + Subsequent Lines of Therapy

- Docetaxel
- Pemetrexed
- Gemcitabine

Squamous: 1st Line of Therapy

- Pembrolizumab Single Agent (PD-L1 \geq 50% only)
- Atezolizumab (PD-L1 \geq 50% only)
- Cemiplimab-rwlc (PD-L1 \geq 50% only)
- Carboplatin + Paclitaxel + Pembrolizumab (regardless of PD-L1)
- Carboplatin/Cisplatin + Paclitaxel + Cemiplimab-rwlc (regardless of PD-L1)
- Carboplatin/Cisplatin + Paclitaxel (IO Ineligible)
- Carboplatin/Cisplatin + Gemcitabine (IO Ineligible)

Squamous: Maintenance

- Cemiplimab-rwlc
- Pembrolizumab

Squamous: 2nd + Subsequent Lines of Therapy

- Docetaxel
- Gemcitabine

References:

1. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (V1.2024, December 21, 2023). Accessed January 2023.
2. Winton, T., Livingston, R., Johnson, D., et al. (2005, June 23). Vinorelbine Plus Cisplatin vs. Observation in Resected Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15972865
3. Douillard, J.-Y., Rosell, R., De Lena, M., et al. (September 2006). Adjuvant Vinorelbine Plus Cisplatin Versus Observation in Patients with Completely Resected Stage IB-III A Non-Small-Cell Lung Cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A Randomised Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/16945766
4. Arriagada, R., Bergman, B., Dunant, A., et al. (2004, Jan. 22). Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/14736927
5. Sandler, A.B., Nemunaitis, J., Denham, C., et al. (January 2000). Phase III Trial of Gemcitabine Plus Cisplatin Versus Cisplatin Alone in Patients with Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/10623702
6. Fossella, F., Pereira, J.R., von Pawel, J., et al. (2003, Aug. 15). Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=12837811
7. Kreuter, M., Vansteenkiste, J., Fischer, J.R., et al. (April 2013). Randomized Phase 2 Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy with Cisplatin and Pemetrexed Versus Cisplatin and Vinorelbine: The TREAT Study. Retrieved from ncbi.nlm.nih.gov/pubmed/23161898
8. Zhang, L., Ou, W., Liu, Q., et al. (January 2014). Pemetrexed Plus Carboplatin as Adjuvant Chemotherapy in Patients with Curative Resected Non-Squamous Non-Small Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pmc/articles/PMC4704276
9. Strauss, G.M., Herndon, J.E., Maddaus, M.A., et al. (2008, Nov. 1). Adjuvant Paclitaxel Plus Carboplatin Compared with Observation in Stage IB Non-Small-Cell Lung Cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group and North Central Cancer Treatment Group Study Groups. Retrieved from ncbi.nlm.nih.gov/pubmed/18809614
10. Usami, N., Yokoi, K., Hasegawa, Y., et al. (December 2010). Phase II Study of Carboplatin and Gemcitabine as Adjuvant Chemotherapy in Patients with Completely Resected Non-Small Cell Lung Cancer: A Report From the Central Japan Lung Study Group, CJLSG 0503 trial. Retrieved from ncbi.nlm.nih.gov/pubmed/20714770
11. Pignon, J.-P., Tribodet, H., Scagliotti, G.V., et al. (2008, July 20). Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group. Retrieved from ncbi.nlm.nih.gov/pubmed/18506026

12. Scagliotti, G., Parikh, P., von Pawel, J., et al. (2008) Phase III Study Comparing Cisplatin Plus Gemcitabine with Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients with Advanced-Stage Non-Small-Cell Lung Cancer. *J Clin Oncol.* 26: 3543–3551
13. Albain, K.S., Crowley, J.J., Turrisi, A.T., et al. Concurrent Cisplatin, Etoposide and Chest Radiotherapy in Pathologic Stage IIIB Non-Small-Cell Lung Cancer: A Southwest Oncology Group Phase II study, SWOG 9019. *J Clin Oncol.* 2002; 20: 3454-3460
14. Curran, W.J., Paulus, R., Langer, C.J., et al. Sequential vs. Concurrent Chemoradiation for Stage III Non-Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410. *J Natl Cancer Inst.* 2011; 103: 1452-1460
15. Senan, S., Brade, A., Wang, L.H., et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous NSCLC. *J Clin Oncol.* 2016; 34: 953-962
16. Govindan, R., Bogart, J., Stinchcombe, T., et al. Randomized Phase II Study of Pemetrexed, Carboplatin and Thoracic Radiation with or without Cetuximab in Patients with Locally Advanced Unresectable Non-Small Cell Lung Cancer. Cancer and Leukemia Group B Trial 30407. *J Clin Oncol.* 2011; 29: 3120-3125
17. Bradley, J.D., Paulus, R., Komaki, R., et al. Standard-Dose Versus High-Dose Conformal Radiotherapy with Concurrent and Consolidation Carboplatin Plus Paclitaxel with or without Cetuximab for Patients with Stage IIIA or IIIB NSCLC (RTOG 0617): A Randomized, Two-by-Two Factorial Phase 3 Study. *Lancet Oncol.* 2015; 16: 187-199
18. Antonia, S.J., Villegas, A., Daniel, D., et al. Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med.* 2017; 377: 1919-1929
19. Antonia, S.J., Villegas, A., Daniel, D., et al. Overall Survival with Durvalumab After Chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* 2018; 379: 2342-2550
20. Rosell, R., Carcereny, E., Gervais, R., et al. (March 2012). Erlotinib Versus Standard Chemotherapy as First-Line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (EURTAC): A Multicentre, Open-Label, Randomised Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/22285168](https://pubmed.ncbi.nlm.nih.gov/22285168)
21. Zhou, C., Wu, Y.L., Chen, G., et al. (September 2015). Final Overall Survival Results From a Randomised, Phase III Study of Erlotinib Versus Chemotherapy as First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer (OPTIMAL, CTONG-0802). Retrieved from [ncbi.nlm.nih.gov/pubmed/26141208](https://pubmed.ncbi.nlm.nih.gov/26141208)
22. Soria, J.-C., Ohe, Y., Vansteenkiste, J., et al. (2018, Jan. 11). Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer: *N Engl J Med.* Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1713137](https://pubmed.ncbi.nlm.nih.gov/30000000)
23. Ramalingam, S.S., Gray, J.E., Ohe, Y., et al. (2019, Sept. 28). Osimertinib vs. Comparator EGFR-TKI as First-Line Treatment for EGFRm Advanced NSCLC (FLAURA): Final Overall Survival Analysis. Retrieved from [oncologypro.esmo.org/Meeting-Resources/ESMO-2019-Congress/Osimertinib-vs-comparator-EGFR-TKI-as-first-line-treatment-for-EGFRm-advanced-NSCLC-FLAURA-Final-overall-survival-analysis](https://www.esmo.org/Meeting-Resources/ESMO-2019-Congress/Osimertinib-vs-comparator-EGFR-TKI-as-first-line-treatment-for-EGFRm-advanced-NSCLC-FLAURA-Final-overall-survival-analysis)
24. Mok, T.S., Wu, Y.-L., Thongprasert, S., et al. (2009, Sept. 3). Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. Retrieved from [ncbi.nlm.nih.gov/pubmed/19692680](https://pubmed.ncbi.nlm.nih.gov/19692680)
25. Inoue, A., Kobayashi, K., Maemondo, M., et al. (January 2013). Updated Overall Survival Results From a Randomized Phase III Trial Comparing Gefitinib with Carboplatin-Paclitaxel for Chemo-Naïve Non-Small Cell Lung Cancer with Sensitive EGFR Gene mutations (NEJ002). Retrieved from [ncbi.nlm.nih.gov/pubmed/22967997](https://pubmed.ncbi.nlm.nih.gov/22967997)

26. Wu, Y.-L., Cheng, Y., Zhou, X., et al. (November 2017). Dacomitinib Versus Gefitinib as First-Line Treatment for Patients with EGFR-Mutation-Positive Non-Small-Cell Lung Cancer (ARCHER 1050): A Randomised, Open-Label, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28958502](https://pubmed.ncbi.nlm.nih.gov/28958502)
27. Mok, T.S., Cheng, Y., Zhou, X., et al. (2018, June 4). Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib with Gefitinib in Patients with Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. Retrieved from ascopubs.org/DOI/10.1200/JCO.2018.78.7994
28. Urata, Y., Katakami, N., Morita, S., et al. (2016, Sept. 20). Randomized Phase III Study Comparing Gefitinib with Erlotinib in Patients with Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. Retrieved from [ncbi.nlm.nih.gov/pubmed/27022112](https://pubmed.ncbi.nlm.nih.gov/27022112)
29. Sequist, L.V., Yang, J.C.-H., Yamamoto, N., et al. (2013, Sept. 20). Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients with Metastatic Lung Adenocarcinoma with EGFR Mutations. Retrieved from [ncbi.nlm.nih.gov/pubmed/23816960](https://pubmed.ncbi.nlm.nih.gov/23816960)
30. Wu, Y.-L., Zhou, C., Hu, C.-P., et al. (February 2014). Afatinib Versus Cisplatin Plus Gemcitabine for First-Line Treatment of Asian Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations (LUX-Lung 6): An Open-Label, Randomised Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/24439929](https://pubmed.ncbi.nlm.nih.gov/24439929)
31. Yang, J.C.-H., Wu, Y.-L., Schuler, M., et al. (February 2015). Afatinib Versus Cisplatin-Based Chemotherapy for EGFR Mutation-Positive Lung Adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of Overall Survival Data From Two Randomised, Phase 3 Trials. Retrieved from [ncbi.nlm.nih.gov/pubmed/25589191](https://pubmed.ncbi.nlm.nih.gov/25589191)
32. Paz-Ares, L., Tan, E.-H., O'Byrne, K., et al. (2017, Feb. 1). Afatinib Versus Gefitinib in Patients with EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer: Overall Survival Data From the Phase IIb LUX-Lung 7 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28426106](https://pubmed.ncbi.nlm.nih.gov/28426106)
33. Planchard, D., Boyer, M.J., Lee, J.-S., et al. (2019, April 1). Postprogression Outcomes for Osimertinib Versus Standard-of-Care EGFR-TKI in Patients with Previously Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/30659024](https://pubmed.ncbi.nlm.nih.gov/30659024)
34. Mok, T.S., Wu, Y.-L., Ahn, M.-J., et al. (2017, May 18). Osimertinib or Platinum — Pemetrexed in EGFR T790M — Positive Lung Cancer: *N Engl J Med*. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1612674
35. Nakagawa, K., Garon, E.B., Seto, T., et al. (December 2019). Ramucirumab Plus Erlotinib in Patients with Untreated, EGFR-Mutated, Advanced Non-Small-Cell Lung Cancer (RELAY): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/31591063](https://pubmed.ncbi.nlm.nih.gov/31591063)
36. Saito, H., Fukuhara, T., Furuya, N., et al. (May 2019). Erlotinib Plus Bevacizumab Versus Erlotinib Alone in Patients with EGFR-Positive Advanced Non-Squamous Non-Small-Cell Lung Cancer (NEJ026): Interim Analysis of an Open-Label, Randomised, Multicentre, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30975627](https://pubmed.ncbi.nlm.nih.gov/30975627)
37. Peters, S., Camidge, R., Shaw, A.T., et al. (2019, Dec. 26). Alectinib Versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1704795
38. Hida, T., Nokihara, H., Kondo, M., et al. (2017, July 1). Alectinib Versus Crizotinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer (J-ALEX): An Open-Label, Randomised Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28501140](https://pubmed.ncbi.nlm.nih.gov/28501140)

39. Camidge, D.R., Kim, H.R., Ahn, M.-J., et al. (2018, Nov. 22). Brigatinib Versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1810171](https://doi.org/10.1056/NEJMoa1810171)
40. Soria, J.-C., Tan, D.S.W., Chiari, R., et al. (2017, March 4). First-Line Ceritinib Versus Platinum-Based Chemotherapy in Advanced ALK-Rearranged Non-Small-Cell Lung Cancer (ASCEND-4): A Randomised, Open-Label, Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/28126333](https://pubmed.ncbi.nlm.nih.gov/28126333)
41. Solomon, B.J., Mok, T., Kim, D.-W., et al. (2014, Dec. 4). First-Line Crizotinib Versus Chemotherapy in ALK-Positive Lung Cancer: *N Engl J Med*. Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1408440](https://doi.org/10.1056/NEJMoa1408440)
42. Solomon, B.J., Besse, B., Bauer, T.M., et al. (December 2018). Lorlatinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer: Results From a Global Phase 2 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/30413378](https://pubmed.ncbi.nlm.nih.gov/30413378)
43. Shaw, A.T., Gandhi, L., Gadgeel, S., et al. (February 2016). Alectinib in ALK-Positive, Crizotinib-Resistant, Non-Small-Cell Lung Cancer: A Single-Group, Multicentre, Phase 2 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/26708155](https://pubmed.ncbi.nlm.nih.gov/26708155)
44. Ou, S.-H.I., Ahn, J.S., De Petris, L., et al. (2016, March 1). Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/26598747](https://pubmed.ncbi.nlm.nih.gov/26598747)
45. Kim, D.-W., Tiseo, M., Ahn, M.-J., et al. (2017, Aug. 1). Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28475456](https://pubmed.ncbi.nlm.nih.gov/28475456)
46. Shaw, A.T., Kim, T.M., Crinò, L. (July 2017). Ceritinib Versus Chemotherapy in Patients with ALK-Rearranged Non-Small-Cell Lung Cancer Previously Given Chemotherapy and Crizotinib (ASCEND-5): A Randomised, Controlled, Open-Label, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28602779](https://pubmed.ncbi.nlm.nih.gov/28602779)
47. Reck, M., Grosshansdorf, Johnson, B.E., et al. (2016, Nov. 10). Pembrolizumab Versus Chemotherapy for PD-L1 — Positive Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1606774](https://doi.org/10.1056/NEJMoa1606774)
48. Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al. (2019, Jan. 8). Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score of 50% or Greater. Retrieved from [ascopubs.org/DOI/10.1200/JCO.18.00149](https://doi.org/10.1200/JCO.18.00149)
49. Mok, T.S.K., Wu, Y.-L., Kudaba, I., et al. (2019, May 4). Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30955977](https://pubmed.ncbi.nlm.nih.gov/30955977)
50. Paz-Ares, L., Luft, A., Vicente, D., et al. (2018, Nov. 22). Pembrolizumab Plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/30280635](https://pubmed.ncbi.nlm.nih.gov/30280635)
51. Hellmann, M.D., Paz-Ares, L., Bernabe Caro, R., et al. (2019, Nov. 21). Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/31562796](https://pubmed.ncbi.nlm.nih.gov/31562796)
52. Gandhi, L., Rodríguez-Abreu, D., Gadgeel, S., et al. (2018, May 31). Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/29658856](https://pubmed.ncbi.nlm.nih.gov/29658856)

53. Gadgeel, S.M., Garassino, M.C., Esteban, E., et al. (2019, May 20). KEYNOTE-189: Updated OS and Progression After the Next Line of Therapy (PFS2) with Pembrolizumab (Pembro) Plus Chemo with Pemetrexed and Platinum vs. Placebo Plus Chemo for Metastatic Nonsquamous NSCLC. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2019.37.15_suppl.9013
54. Langer, C.J., Gadgeel, S.M., Borghaei, H., et al. (November 2016). Carboplatin and Pemetrexed with or without Pembrolizumab for Advanced, Non-Squamous Non-Small-Cell Lung Cancer: A Randomised, Phase 2 Cohort of the Open-Label KEYNOTE-021 Study. Retrieved from ncbi.nlm.nih.gov/pubmed/27745820
55. Borghaei, H., Langer, C.J., Gadgeel, S., et al. (January 2019). 24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/30138764
56. Socinski, M.A., Jotte, R.M., Cappuzzo, F., et al. (2018, June 14). Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. Retrieved from ncbi.nlm.nih.gov/pubmed/29863955
57. Socinski, M.A., Jotte, R.M., Capuzzo, F., et al. (2019, May 26). IMpower150: Analysis of Efficacy in Patients (pts) with Liver Metastases (mets). Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2019.37.15_suppl.9012
58. West, H., McCleod, M., Hussein, M., et al. (July 2019). Atezolizumab in Combination with Carboplatin Plus Nab-Paclitaxel Chemotherapy Compared with Chemotherapy Alone as First-Line Treatment for Metastatic Non-Squamous Non-Small-Cell Lung Cancer (IMpower130): A Multicentre, Randomised, Open-Label, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/31122901
59. Sandler, A., Gray, R., Perry, M.C., et al. (2006, Dec. 14). Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/17167137
60. Patel, J.D., Socinski, M.A., Garon, E.B., et al. (2013, Dec. 1). PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/24145346
61. Ramalingam, S.S., Dahlberg, S.E., Belani, C.P., et al. (2019, Sept. 10). Pemetrexed, Bevacizumab or the Combination as Maintenance Therapy for Advanced Nonsquamous Non-Small-Cell Lung Cancer: ECOG-ACRIN 5508. Retrieved from ncbi.nlm.nih.gov/pubmed/31361535
62. Barlesi, F., Scherpereel, A., Rittmeyer, A., et al. (2013, Aug. 20). Randomized Phase III Trial of Maintenance Bevacizumab with or without Pemetrexed After First-Line Induction with Bevacizumab, Cisplatin and Pemetrexed in Advanced Nonsquamous Non-Small-Cell Lung Cancer: AVAPERL (MO22089). Retrieved from ncbi.nlm.nih.gov/pubmed/23835708
63. Barlesi, F., Scherpereel, A., Gorbunova, V., et al. (May 2014). Maintenance Bevacizumab-Pemetrexed After First-Line Cisplatin-Pemetrexed-Bevacizumab for Advanced Nonsquamous Non-Small-Cell Lung Cancer: Updated Survival Analysis of the AVAPERL (MO22089) Randomized Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/24585722
64. Socinski, M.A., Bondarenko, I., Karaseva, N.A., et al. (2012, June 10). Weekly Nab-Paclitaxel in Combination with Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients with Advanced Non-Small-Cell Lung Cancer: Final Results of a Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/22547591

65. Fossella, F., Pereira, J.R., von Pawel, J., et al. (2003, Aug. 15). Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. Retrieved from ncbi.nlm.nih.gov/pubmed/12837811
66. Frasci, G., Comella, P., Panza, N., et al. (October 1998). Carboplatin-Oral Etoposide Personalized Dosing in Elderly Non-Small-Cell Lung Cancer Patients. Gruppo Oncologico Cooperativo Sud-Italia. Retrieved from ncbi.nlm.nih.gov/pubmed/9893657
67. Danson, S., Middleton, M.R., O'Byrne, K.J., et al. (2003, Aug. 1). Phase III Trial of Gemcitabine and Carboplatin Versus Mitomycin, Ifosfamide and Cisplatin or Mitomycin, Vinblastine and Cisplatin in Patients with Advanced Non-Small-Cell Lung Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/12879472
68. Ohe, Y., Ohashi, Y., Kubota, K., et al. (February 2007). Randomized Phase III Study of Cisplatin Plus Irinotecan Versus Carboplatin Plus Paclitaxel, Cisplatin Plus Gemcitabine, and Cisplatin Plus Vinorelbine for Advanced Non-Small-Cell Lung Cancer: Four-Arm Cooperative Study in Japan. Retrieved from ncbi.nlm.nih.gov/pubmed/17079694
69. Belani, C.P., Lee, J.S., Socinski, M.A., et al. (July 2005). Randomized Phase III Trial Comparing Cisplatin-Etoposide to Carboplatin-Paclitaxel in Advanced or Metastatic Non-Small Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15860487
70. Schiller, J.H., Harrington, D., Belani, C.P., et al. (2002, Jan. 10). Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/11784875
71. Zukin, M., Barrios, C.H., Pereira, J.R., et al. (2013, Aug. 10). Randomized Phase III Trial of Single-Agent Pemetrexed Versus Carboplatin and Pemetrexed in Patients with Advanced Non-Small-Cell Lung Cancer and Eastern Cooperative Oncology Group Performance Status of 2. Retrieved from ascopubs.org/DOI/full/10.1200/JCO.2012.48.1911?rss=1
72. Scagliotti, G.V., Kortsik, C., Dark, G.G., et al. (2005, Jan. 15). Pemetrexed Combined with Oxaliplatin or Carboplatin as First-Line Treatment in Advanced Non-Small-Cell Lung Cancer: A Multicenter, Randomized, Phase II Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/15701857
73. Cardenal, F., López-Cabrerizo, M.P., Antón, A., et al. (January 1999). Randomized Phase III Study of Gemcitabine-Cisplatin Versus Etoposide-Cisplatin in the Treatment of Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/10458212
74. Scagliotti, G.V., Parikh, P., von Pawel, J., et al. (2008, July 20). Phase III Study Comparing Cisplatin Plus Gemcitabine with Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients with Advanced-Stage Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/18506025
75. Smit, E.F., van Meerbeeck, J.P.A.M., Lianes, P., et al. (2003, Nov. 1). Three-Arm Randomized Study of Two Cisplatin-Based Regimens and Paclitaxel Plus Gemcitabine in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group – EORTC 08975. Retrieved from ncbi.nlm.nih.gov/pubmed/14581415
76. Pujol, J.-L., Breton, J.-L., Gervais, R., et al. (April 2005). Gemcitabine-Docetaxel Versus Cisplatin-Vinorelbine in Advanced or Metastatic Non-Small-Cell Lung Cancer: A Phase III Study Addressing the Case for Cisplatin. Retrieved from ncbi.nlm.nih.gov/pubmed/15741225
77. Tan, E.H., Szczesna, A., Krzakowski, M., et al. (August 2005). Randomized Study of Vinorelbine —Gemcitabine Versus Vinorelbine — Carboplatin in Patients with Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/16022917

78. Green, M.R., Manikhas, G.M., Orlov, S., et al. (August 2006). Abraxane, a Novel Cremophor-Free, Albumin-Bound Particle Form of Paclitaxel for the Treatment of Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/16740598
79. Hanna, N., Shepherd, F.A., Fossella, F.V., et al. (2004, May 1). Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients with Non-Small-Cell Lung Cancer Previously Treated with Chemotherapy. Retrieved from ncbi.nlm.nih.gov/pubmed/15117980
80. Zatloukal, P., Kanitz, E., Magyar, P., et al. (December 1998). Gemcitabine in Locally Advanced and Metastatic Non-Small Cell Lung Cancer: The Central European Phase II Study. Retrieved from ncbi.nlm.nih.gov/pubmed/10048477
81. Ceresoli, G.L., Gregorc, V., Cordio, S., et al. (May 2004). Phase II Study of Weekly Paclitaxel as Second-Line Therapy in Patients with Advanced Non-Small Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15084388
82. Lilenbaum, R.C., Herndon, J.E., List, M.A., et al. (2005, Jan. 1). Single-Agent Versus Combination Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The Cancer and Leukemia Group B (Study 9730). Retrieved from ncbi.nlm.nih.gov/pubmed/15625373
83. Rosell, R., Carcereny, E., Gervais, R., et al. (March 2012). Erlotinib Versus Standard Chemotherapy as First-Line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (EURTAC): A Multicentre, Open-Label, Randomised Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/22285168
84. Zhou, C., Wu, Y.L., Chen, G., et al. (September 2015). Final Overall Survival Results From a Randomised, Phase III Study of Erlotinib Versus Chemotherapy as First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer (OPTIMAL, CTONG-0802). Retrieved from ncbi.nlm.nih.gov/pubmed/26141208
85. Soria, J.-C., Ohe, Y., Vansteenkiste, J., et al. (2018, Jan. 11). Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1711317
86. Ramalingam, S.S., Gray, J.E., Ohe, Y., et al. (2019, Sept. 28). Osimertinib vs. Comparator EGFR-TKI as First-Line Treatment for EGFRm Advanced NSCLC (FLAURA): Final Overall Survival Analysis. Retrieved from oncologypro.esmo.org/Meeting-Resources/ESMO-2019-Congress/Osimertinib-vs-comparator-EGFR-TKI-as-first-line-treatment-for-EGFRm-advanced-NSCLC-FLAURA-Final-overall-survival-analysis
87. Mok, T.S., Wu, Y.-L., Thongprasert, S., et al. (2009, Sept. 3). Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/19692680
88. Inoue, A., Kobayashi, K., Maemondo, M., et al. (January 2013). Updated Overall Survival Results From a Randomized Phase III Trial Comparing Gefitinib with Carboplatin-Paclitaxel for Chemo-Naïve Non-Small- Cell Lung Cancer with Sensitive EGFR Gene Mutations (NEJ002). Retrieved from ncbi.nlm.nih.gov/pubmed/22967997
89. Wu, Y.-L., Cheng, Y., Zhou, X., et al. (November 2017). Dacomitinib Versus Gefitinib as First-Line Treatment for Patients with EGFR-Mutation-Positive Non-Small-Cell Lung Cancer (ARCHER 1050): A Randomised, Open-Label, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28958502
90. Mok, T.S., Cheng, Y., Zhou, X., et al. (2018, June 4). Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib with Gefitinib in Patients with Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. Retrieved from ascopubs.org/DOI/10.1200/JCO.2018.78.7994

91. Urata, Y., Katakami, N., Morita, S., et al. (2016, Sept. 20). Randomized Phase III Study Comparing Gefitinib with Erlotinib in Patients with Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. Retrieved from ncbi.nlm.nih.gov/pubmed/27022112
92. Sequist, L.V., Yang, J.C.-H., Yamamoto, N., et al. (2013, Sept. 20). Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients with Metastatic Lung Adenocarcinoma with EGFR Mutations. Retrieved from ncbi.nlm.nih.gov/pubmed/23816960
93. Wu, Y.-L., Zhou, C., Hu, C.-P., et al. (February 2014). Afatinib Versus Cisplatin Plus Gemcitabine for First-Line Treatment of Asian Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations (LUX-Lung 6): An Open-Label, Randomised Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/24439929
94. Yang, J.C.-H., Wu, Y.-L., Schuler, M., et al. (February 2015). Afatinib Versus Cisplatin-Based Chemotherapy for EGFR Mutation-Positive Lung Adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of Overall Survival Data From Two Randomised, Phase 3 Trials. Retrieved from ncbi.nlm.nih.gov/pubmed/25589191
95. Paz-Ares, L., Tan, E.-H., O'Byrne, K., et al. (2017, Feb. 1). Afatinib Versus Gefitinib in Patients with EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer: Overall Survival Data From the Phase IIb LUX-Lung 7 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28426106
96. Planchard, D., Boyer, M.J., Lee, J.-S., et al. (2019, April 1). Post-Progression Outcomes for Osimertinib Versus Standard-of-Care EGFR-TKI in Patients with Previously Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/30659024
97. Mok, T.S., Wu, Y.-L., Ahn, M.-J., et al. (2017, May 18). Osimertinib or Platinum — Pemetrexed in EGFR T790M — Positive Lung Cancer: NEJM. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1612674
98. Nakagawa, K., Garon, E.B., Seto, T., et al. (December 2019). Ramucirumab Plus Erlotinib in Patients with Untreated, EGFR-Mutated, Advanced Non-Small-Cell Lung Cancer (RELAY): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/31591063
99. Saito, H., Fukuhara, T., Furuya, N., et al. (May 2019). Erlotinib Plus Bevacizumab Versus Erlotinib Alone in Patients with EGFR-Positive Advanced Non-Squamous Non-Small-Cell Lung Cancer (NEJ026): Interim Analysis of an Open-Label, Randomised, Multicentre, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/30975627
100. Peters, S., Camidge, R., Shaw, A.T., et al. (2019, Dec. 26). Alectinib Versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1704795
101. Holleman, M.S., van Tinteren, H., Groen, H.J., et al. (2019, Feb. 20). First-Line Tyrosine Kinase Inhibitors in EGFR Mutation-Positive Non-Small-Cell Lung Cancer: A Network Meta-Analysis. Retrieved from ncbi.nlm.nih.gov/pubmed/30863108
102. Hida, T., Nokihara, H., Kondo, M., et al. (2017, July 1). Alectinib Versus Crizotinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer (J-ALEX): An Open-Label, Randomised Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28501140
103. Camidge, D.R., Kim, H.R., Ahn, M.-J., et al. (2018, Nov. 22). Brigatinib Versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer: NEJM. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1810171
104. Soria, J.-C., Tan, D.S.W., Chiari, R., et al. (2017, March 4). First-Line Ceritinib Versus Platinum-Based Chemotherapy in Advanced ALK-Rearranged Non-Small-Cell Lung Cancer

- (ASCEND-4): A Randomised, Open-Label, Phase 3 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/28126333](https://pubmed.ncbi.nlm.nih.gov/28126333)
105. Solomon, B.J., Mok, T., Kim, D.-W., et al. (2014, Dec. 4). First-Line Crizotinib Versus Chemotherapy in ALK-Positive Lung Cancer: *N Engl J Med*. Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1408440](https://pubmed.ncbi.nlm.nih.gov/24844044)
 106. Solomon, B.J., Besse, B., Bauer, T.M., et al. (December 2018). Lorlatinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer: Results From a Global Phase 2 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/30413378](https://pubmed.ncbi.nlm.nih.gov/30413378)
 107. Shaw, A.T., Gandhi, L., Gadgeel, S., et al. (February 2016). Alectinib in ALK-Positive, Crizotinib-Resistant, Non-Small-Cell Lung Cancer: A Single-Group, Multicentre, Phase 2 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/26708155](https://pubmed.ncbi.nlm.nih.gov/26708155)
 108. Ou, S.-H.I., Ahn, J.S., De Petris, L., et al. (2016, March 1). Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/26598747](https://pubmed.ncbi.nlm.nih.gov/26598747)
 109. Kim, D.-W., Tiseo, M., Ahn, M.-J., et al. (2017, Aug. 1). Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28475456](https://pubmed.ncbi.nlm.nih.gov/28475456)
 110. Shaw, A.T., Kim, T.M., Crinò, L. (July 2017). Ceritinib Versus Chemotherapy in Patients with ALK-Rearranged Non-Small-Cell Lung Cancer Previously Given Chemotherapy and Crizotinib (ASCEND-5): A Randomised, Controlled, Open-Label, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28602779](https://pubmed.ncbi.nlm.nih.gov/28602779)
 111. Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al. (2016, Nov. 10). Pembrolizumab Versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer: *N Engl J Med*. Retrieved from [nejm.org/DOI/full/10.1056/NEJMoa1606774](https://pubmed.ncbi.nlm.nih.gov/26677444)
 112. Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al. (2019, Jan. 8). Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score of 50% or Greater. Retrieved from ascopubs.org/DOI/10.1200/JCO.18.00149
 113. Mok, T.S.K., Wu, Y.-L., Kudaba, I., et al. (2019, May 4). Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/30955977](https://pubmed.ncbi.nlm.nih.gov/30955977)
 114. Paz-Ares, L., Luft, A., Vicente, D., et al. (2018, Nov. 22). Pembrolizumab Plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/30280635](https://pubmed.ncbi.nlm.nih.gov/30280635)
 115. Hellmann, M.D., Paz-Ares, L., Bernabe Caro, R., et al. (2019, Nov. 21). Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/31562796](https://pubmed.ncbi.nlm.nih.gov/31562796)
 116. Gandhi, L., Rodríguez-Abreu, D., Gadgeel, S., et al. (2018, May 31). Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/29658856](https://pubmed.ncbi.nlm.nih.gov/29658856)
 117. Gadgeel, S.M., Garassino, M.C., Esteban, E., et al. (2019, May 20). KEYNOTE-189: Updated OS and Progression After the Next Line of Therapy (PFS2) with Pembrolizumab (Pembro) Plus Chemo with Pemetrexed and Platinum vs. Placebo Plus Chemo for Metastatic Nonsquamous NSCLC. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2019.37.15_suppl.9013

118. Langer, C.J., Gadgeel, S.M., Borghaei, H., et al. (November 2016). Carboplatin and Pemetrexed with or without Pembrolizumab for Advanced, Non-Squamous Non-Small-Cell Lung Cancer: A Randomised, Phase 2 Cohort of the Open-Label KEYNOTE-021 Study. Retrieved from ncbi.nlm.nih.gov/pubmed/27745820
119. Borghaei, H., Langer, C.J., Gadgeel, S., et al. (January 2019). 24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/30138764
120. Socinski, M.A., Jotte, R.M., Cappuzzo, F., et al. (2018, June 14). Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. Retrieved from ncbi.nlm.nih.gov/pubmed/29863955
121. Socinski, M.A., Jotte, R.M., Capuzzo, F., et al. (2019, May 26). IMpower150: Analysis of Efficacy in Patients (pts) with Liver Metastases (mets). Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2019.37.15_suppl.9012
122. West, H., McCleod, M., Hussein, M., et al. (July 2019). Atezolizumab in Combination with Carboplatin Plus Nab-Paclitaxel Chemotherapy Compared with Chemotherapy Alone as First-Line Treatment for Metastatic Non-Squamous Non-Small-Cell Lung Cancer (IMpower130): A Multicentre, Randomised, Open-Label, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/31122901
123. Sandler, A., Gray, R., Perry, M.C., et al. (2006, Dec. 14). Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/17167137
124. Patel, J.D., Socinski, M.A., Garon, E.B., et al. (2013, Dec. 1). PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/24145346
125. Ramalingam, S.S., Dahlberg, S.E., Belani, C.P., et al. (2019, Sept. 10). Pemetrexed, Bevacizumab, or the Combination as Maintenance Therapy for Advanced Nonsquamous Non-Small-Cell Lung Cancer: ECOG-ACRIN 5508. Retrieved from ncbi.nlm.nih.gov/pubmed/31361535
126. Barlesi, F., Scherpereel, A., Rittmeyer, A., et al. (2013, Aug. 20). Randomized Phase III Trial of Maintenance Bevacizumab with or without Pemetrexed After First-Line Induction with Bevacizumab, Cisplatin and Pemetrexed in Advanced Nonsquamous Non-Small-Cell Lung Cancer: AVAPERL (MO22089). Retrieved from ncbi.nlm.nih.gov/pubmed/23835708
127. Barlesi, F., Scherpereel, A., Gorbunova, V., et al. (May 2014). Maintenance Bevacizumab-Pemetrexed After First-Line Cisplatin-Pemetrexed-Bevacizumab for Advanced Nonsquamous Non-Small-Cell Lung Cancer: Updated Survival Analysis of the AVAPERL (MO22089) Randomized Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/24585722
128. Socinski, M.A., Bondarenko, I., Karaseva, N.A., et al. (2012, June 10). Weekly Nab-Paclitaxel in Combination with Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients with Advanced Non-Small-Cell Lung Cancer: Final Results of a Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/22547591
129. Fossella, F., Pereira, J.R., von Pawel, J., et al. (2003, Aug. 15). Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. Retrieved from ncbi.nlm.nih.gov/pubmed/12837811

130. Frasci, G., Comella, P., Panza, N., et al. (October 1998). Carboplatin-Oral Etoposide Personalized Dosing in Elderly Non-Small Cell Lung Cancer Patients. Gruppo Oncologico Cooperativo Sud-Italia. Retrieved from ncbi.nlm.nih.gov/pubmed/9893657
131. Danson, S., Middleton, M.R., O'Byrne, K.J., et al. (2003, Aug. 1). Phase III Trial of Gemcitabine and Carboplatin Versus Mitomycin, Ifosfamide and Cisplatin or Mitomycin, Vinblastine and Cisplatin in Patients with Advanced Non-Small Cell Lung Carcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/12879472
132. Ohe, Y., Ohashi, Y., Kubota, K., et al. (February 2007). Randomized Phase III Study of Cisplatin Plus Irinotecan Versus Carboplatin Plus Paclitaxel, Cisplatin Plus Gemcitabine, and Cisplatin Plus Vinorelbine for Advanced Non-Small-Cell Lung Cancer: Four-Arm Cooperative Study in Japan. Retrieved from ncbi.nlm.nih.gov/pubmed/17079694
133. Belani, C.P., Lee, J.S., Socinski, M.A., et al. (July 2005). Randomized Phase III Trial Comparing Cisplatin-Etoposide to Carboplatin-Paclitaxel in Advanced or Metastatic Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15860487
134. Schiller, J.H., Harrington, D., Belani, C.P., et al. (2002, Jan. 10). Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/11784875
135. Zukin, M., Barrios, C.H., Pereira, J.R., et al. (2013, Aug. 10). Randomized Phase III Trial of Single-Agent Pemetrexed Versus Carboplatin and Pemetrexed in Patients with Advanced Non-Small-Cell Lung Cancer and Eastern Cooperative Oncology Group Performance Status of 2. Retrieved from ascopubs.org/DOI/full/10.1200/JCO.2012.48.1911?rss=1
136. Scagliotti, G.V., Kortsik, C., Dark, G.G., et al. (2005, Jan. 15). Pemetrexed Combined with Oxaliplatin or Carboplatin as First-Line Treatment in Advanced Non-Small Cell Lung Cancer: A Multicenter, Randomized, Phase II Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/15701857
137. Cardenal, F., López-Cabrerizo, M.P., Antón, A., et al. (January 1999). Randomized Phase III Study of Gemcitabine-Cisplatin Versus Etoposide-Cisplatin in the Treatment of Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/10458212
138. Scagliotti, G.V., Parikh, P., von Pawel, J., et al. (2008, July 20). Phase III Study Comparing Cisplatin Plus Gemcitabine with Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients with Advanced-Stage Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/18506025
139. Smit, E.F., van Meerbeeck, J.P.A.M., Lianes, P., et al. (2003, Nov. 1). Three-Arm Randomized Study of Two Cisplatin-Based Regimens and Paclitaxel Plus Gemcitabine in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group – EORTC 08975. Retrieved from ncbi.nlm.nih.gov/pubmed/14581415
140. Pujol, J.-L., Breton, J.-L., Gervais, R., et al. (April 2005). Gemcitabine-Docetaxel Versus Cisplatin-Vinorelbine in Advanced or Metastatic Non-Small-Cell Lung Cancer: A Phase III Study Addressing the Case for Cisplatin. Retrieved from ncbi.nlm.nih.gov/pubmed/15741225
141. Tan, E.H., Szczesna, A., Krzakowski, M., et al. (August 2005). Randomized Study of Vinorelbine —Gemcitabine Versus Vinorelbine — Carboplatin in Patients with Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/16022917
142. Green, M.R., Manikhas, G.M., Orlov, S., et al. (August 2006). Abraxane, a Novel Cremophor-Free, Albumin-Bound Particle Form of Paclitaxel for the Treatment of Advanced Non-Small-Cell Lung Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/16740598

143. Hanna, N., Shepherd, F.A., Fossella, F.V., et al. (2004, May 1). Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients with Non-Small-Cell Lung Cancer Previously Treated with Chemotherapy. Retrieved from [ncbi.nlm.nih.gov/pubmed/15117980](https://pubmed.ncbi.nlm.nih.gov/15117980)
144. Zatloukal, P., Kanitz, E., Magyar, P., et al. (December 1998). Gemcitabine in Locally Advanced and Metastatic Non-Small-Cell Lung Cancer: The Central European Phase II Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/10048477](https://pubmed.ncbi.nlm.nih.gov/10048477)
145. Ceresoli, G.L., Gregorc, V., Cordio, S., et al. (May 2004). Phase II Study of Weekly Paclitaxel as Second-Line Therapy in Patients with Advanced Non-Small-Cell Lung Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/15084388](https://pubmed.ncbi.nlm.nih.gov/15084388)
146. Lilenbaum, R.C., Herndon, J.E., List, M.A., et al. (2005, Jan. 1). Single-Agent Versus Combination Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The Cancer and Leukemia Group B (Study 9730). Retrieved from [ncbi.nlm.nih.gov/pubmed/15625373](https://pubmed.ncbi.nlm.nih.gov/15625373)
147. Gray, J.E., Villegas, A., Daniel, D., et al. Three-Year Overall Survival with Durvalumab After Chemoradiotherapy in Stage III NSCLC-Update From PACIFIC. *J Thorac Oncol.* 2020 Feb;15(2):288-293. DOI: 10.1016/j.jtho.2019.10.002. Epub 2019 Oct 14. PMID: 31622733; PMCID: PMC7244187
148. Wu, Y.-L., Tsuboi, M., He, J., et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med* 2020;383:1711-1723
149. Herbst, R.S., Giaccone, G., de Marinis, F., et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med.* 2020 Oct 1;383(14):1328-1339. DOI: 10.1056/NEJMoa1917346. PMID: 32997907
150. Sezer, A., Kilickap, S., Gümüş, M., et al. Cemiplimab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer with PD-L1 of at Least 50%: A Multicentre, Open-Label, Global, Phase 3, Randomised, Controlled Trial. *Lancet.* 2021 Feb 13;397(10274):592-604. DOI: 10.1016/S0140-6736(21)00228-2. PMID: 33581821
151. Paz-Ares, L., Ciuleanu, T.E., Cobo, M., et al. First-Line Nivolumab Plus Ipilimumab Combined with Two Cycles of Chemotherapy in Patients with Non-Small-Cell Lung Cancer (CheckMate 9LA): An International, Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol.* 2021 Feb;22(2):198-211. DOI: 10.1016/S1470-2045(20)30641-0. Epub 2021 Jan 18. Erratum in: *Lancet Oncol.* 2021 Mar;22(3):e92. PMID: 33476593
152. Gadgeel, S., Rodríguez-Abreu, D., Speranza, G., et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2020 May 10;38(14):1505-1517. DOI: 10.1200/JCO.19.03136. Epub 2020 Mar 9. PMID: 32150489
153. Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al. Five-Year Outcomes with Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score \geq 50. *J Clin Oncol.* 2021 Apr 19;JCO2100174. DOI: 10.1200/JCO.21.00174. Epub ahead of print. PMID: 33872070
154. Ramalingam, S.S., Ciuleanu, T.E., Pluzanski, A., et al. Nivolumab + Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update From CheckMate 227 Part 1. 2020 ASCO Virtual Scientific Program. 10.1200/JCO.2020.38.15_suppl.9500. *J Clin Oncol.* 38: 2020 (suppl; abstr 9500)
155. Shaw, A.T., Bauer, T.M., de Marinis, F., et al.; CROWN Trial Investigators. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. *N Engl J Med.* 2020 Nov 19;383(21):2018-2029. DOI: 10.1056/NEJMoa2027187. PMID: 33207094
156. Park, K., Haura, E.B., Leigh, N.B., et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the

- CHRYSLIS Phase I Study. *J Clin Oncol*. 2021 Oct 20;39(30):3391-3402. DOI: 10.1200/JCO.21.00662. Epub 2021 Aug 2. PMID: 34339292; PMCID: PMC8791812.
157. Ramalingam, S.S., Zhou, C., Kim, T.M., et al. Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase ½ study. DOI: 10.1200/JCO.2021.39.15_suppl.9014 *J Clin Oncol*. 39, no. 15_suppl (May 20, 2021) 9014-9014.
 158. Skoulidis, F., Li B.T., Dy G.K., et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *N Engl J Med*. 2021 Jun 24;384(25):2371-2381. DOI: 10.1056/NEJMoa2103695. Epub 2021 Jun 4. PMID: 34096690.
 159. Felip, E., Altorki, N., Zhou, C., et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021 Oct 9;398(10308):1344-1357.
 160. Castro, G.D., Kudaba, I., Wu, Y., et al. 363 KEYNOTE-042 5-year survival update: pembrolizumab versus chemotherapy in patients with previously untreated, PD-L1–positive, locally advanced or metastatic non–small-cell lung cancer. *J Immunother Cancer* 2021;9:DOI: 10.1136/jitc-2021-SITC2021.363
 161. Jassem, J., de Marinis, F., Giaccone, G., et al. Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC. *J Thorac Oncol*. 2021 Nov;16(11):1872-1882. DOI: 10.1016/j.jtho.2021.06.019. Epub 2021 Jul 12. PMID: 34265434.
 162. Paz-Ares, L.G., Ciuleanu, T.E., Lee, J.S., et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. *J Clin Oncol*. 2021. DOI: 10.1200/JCO.2021.39.15_suppl.9016 *J Clin Oncol*. 39, no. 15_suppl
 163. Gray, J., Rodrigues-Abreu, D., Powell, S.F., et al. FP13.02 Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. 2021. *J Thorac Oncol*. DOI: https://doi.org/10.1016/j.jtho.2021.01.141_suppl.S224; 16;3
 164. Forde P, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386:1973-85.
 165. Johnson ML, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol*. 2022; 23:279-91
 166. Gogishvili, M., Melkadze, T., Makharadze, T. et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nat Med* 28, 2374–2380 (2022).
 167. Makharadze T, Gogishvili M, Melkadze T, et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial [published correction appears in *J Thorac Oncol*. 2023 Oct 12;:]. *J Thorac Oncol*. 2023;18(6):755-768. doi:10.1016/j.jtho.2023.03.008
 168. Remon J, Hendriks LEL, Reck M. The POSEIDON Trial: Will Secondary End Points Change Our Clinical Practice?. *J Clin Oncol*. 2023;41(6):1176-1179. doi:10.1200/JCO.22.01737
 169. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIa Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial [published correction appears in *J Clin Oncol*. 2023 Aug 1;41(22):3877]. *J Clin Oncol*. 2023;41(10):1830-1840. doi:10.1200/JCO.22.02186

170. Tsuboi M, Herbst RS, John T, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. *N Engl J Med.* 2023;389(2):137-147. doi:10.1056/NEJMoa2304594
171. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *N Engl J Med.* 2023;389(6):491-503. doi:10.1056/NEJMoa2302983
172. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIa non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* 2022;23(10):1274-1286. doi:10.1016/S1470-2045(22)00518-6
173. Felip E, Altorki N, Zhou C, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol.* 2023;34(10):907-919. doi:10.1016/j.annonc.2023.07.001
174. Akinboro O, Drezner N, Amatya A, et al. US Food and Drug Administration Approval Summary: Nivolumab Plus Platinum-Doublet Chemotherapy for the Neoadjuvant Treatment of Patients With Resectable Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2023;41(17):3249-3259. doi:10.1200/JCO.22.02509
175. Oselin K, Shim BY, Okada M, et al. Pembrolizumab vs placebo for early-stage non-small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of patients who received adjuvant chemotherapy in the phase 3 PEARLS/KEYNOTE-091 studyDOI: 10.1200/JCO.2023.41.16_suppl.8520 *Journal of Clinical Oncology* 41, no. 16_suppl (June 01, 2023) 8520-8520.
176. de Castro Jr G, Kudaba I, Wu Y-L et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score \geq 1% in the KEYNOTE-042 Study. *JCO*; Published online 28 October 2022. DOI: 10.1200/JCO.21.02885
177. Spicer J.D., Gao S, Liberman M, et al. LBA56 Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC). DOI:<https://doi.org/10.1016/j.annonc.2023.10.052>
178. Planchard D, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Eng J Med* 2023;389:1935-1948. doi: 10.1056/NEJMoa2306434. Epub 2023 Nov 8. PMID: 37937763.
179. Kawashima Y, Fukuhara T, Saito H, et al. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Respir Med.* 2022;10(1):72-82. doi:10.1016/S2213-2600(21)00166-1
180. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. *J Clin Oncol.* 2023;41(11):1992-1998. doi:10.1200/JCO.22.01989

Melanoma

Adjuvant (Resectable)

- Nivolumab
- Pembrolizumab

Adjuvant (Resectable) — (BRAF Mutated)

- Dabrafenib + Trametinib
- Nivolumab
- Pembrolizumab

Metastatic/Unresectable (BRAF Mutated/Symptomatic)

1st + Subsequent Lines of Therapy

- Dabrafenib + Trametinib
- Encorafenib + Binimetinib
- Vemurafenib + Cobimetinib

Metastatic/Unresectable (BRAF Wild-Type/Mutated/Unknown)

1st + Subsequent Lines of Therapy

- Nivolumab*
- Pembrolizumab*
- Nivolumab (3mg/kg) + Ipilimumab (1mg/kg)

**For patients that have not received treatment with a checkpoint inhibitor, had a history of progression on a checkpoint inhibitor < 3 months after treatment discontinuation.*

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/melan.html
2. National Comprehensive Cancer Network. *Melanoma*. (V2.2023, March 10, 2023). Accessed June 2023. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf
3. Weber, J., Mandala, M., Del Vecchio, M., et al. (2017, Nov. 9). Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III or IV Melanoma. Retrieved from [ncbi.nlm.nih.gov/pubmed/28891423](https://pubmed.ncbi.nlm.nih.gov/pubmed/28891423)

4. Weber, J., Mandala, M., Del Vecchio, M., et al. (2018, June 1). Adjuvant Therapy with Nivolumab (NIVO) Versus Ipilimumab (IPI) After Complete Resection of Stage III/IV Melanoma: Updated Results From a Phase III Trial (CheckMate 238). Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2018.36.15_suppl.9502
5. ClinicalTrials.gov. An Investigational Immuno-Therapy Study of Nivolumab Combined with Ipilimumab Compared to Nivolumab by Itself After Complete Surgical Removal of Stage IIIb/c/d or Stage IV Melanoma. Retrieved from clinicaltrials.gov/ct2/show/NCT03068455
6. Eggermont, A.M., Blank, C., Mandala, M., et al. (2018, May 10). Adjuvant Pembrolizumab Versus Placebo in Resected Stage III Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/296584309
7. Gossman, K.F., Othus, M., Tarhini, A.A., et al. (2017, May 11). SWOG S1404: A Phase III Randomized Trial Comparing Standard of Care Adjuvant Therapy to Pembrolizumab in Patients with High-Risk Resected Melanoma. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2016.34.15_suppl.e21032
8. Eggermont, A.M., Chiarion-Sileni, V., Grob, J., et al. (May 2015). Adjuvant Ipilimumab Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (EORTC 18071): A Randomized, Double-Blind, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/25840693
9. Weber, J., Mandala, M., Del Vecchio, M., et al. (2017, Nov. 9). Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III or IV Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/28891423
10. Weber, J., Mandala, M., Del Vecchio, M., et al. (2018, June 1). Adjuvant Therapy with Nivolumab (NIVO) Versus Ipilimumab (IPI) After Complete Resection of Stage III/IV Melanoma: Updated Results From a Phase III Trial (CheckMate 238). Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2018.36.15_suppl.9502
11. Tarhini, A.A., Lee, S.J., Hodi, S.F., et al. (2017, May 30). A Phase III Randomized Study of Adjuvant Ipilimumab (3 or 10 mg/kg) Versus High-Dose Interferon Alfa-2b for Resected High-Risk Melanoma (U.S. Intergroup E1609): Preliminary Safety and Efficacy of the Ipilimumab Arms. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2017.35.15_suppl.9500
12. Long, Z.V., Hauschild, A., Santinami, M., et al. (2017, Nov. 9). Adjuvant Dabrafenib Plus Trametinib in Stage III BRAF-Mutated Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/28891408
13. Hauschild, A., Dummer, R., Schadendorf, D., et al. (2018, Oct. 22). Longer Follow-Up Confirms Relapse-Free Survival Benefit with Adjuvant Dabrafenib Plus Trametinib in Patients with Resected BRAF V600-Mutant Stage III Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed?term=30343620
14. Maio, M., Lewis, K., Demidov, L., et al. (April 2018). Adjuvant Vemurafenib in Resected, BRAFV600 Mutation-Positive Melanoma (BRIM8): A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/29477665
15. Hauschild, A., Grob, J., Demidov, L.V., et al. (2012, July 28). Dabrafenib in BRAF-Mutated Metastatic Melanoma: A Multicentre, Open-Label, Phase 3 Randomised Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/22735384

16. Hauschild, A., Grob, J., Demidov, L.V., et al. (2013, May 20). An Update on BREAK-3, a Phase III, Randomized Trial: Dabrafenib (DAB) Versus Dacarbazine (DTIC) in Patients with BRAF V600E-Positive Mutation Metastatic Melanoma (MM). Retrieved from ascopubs.org/DOI/abs/10.1200/jco.2013.31.15_suppl.9013
17. McArthur, G.A., Chapman, P.B., Robert, C., et al. (March 2014). Safety and Efficacy of Vemurafenib in BRAF (V600E) and BRAF (V600K) Mutation-Positive Melanoma (BRIM-3): Extended Follow-Up of a Phase 3, Randomised, Open-Label Study. Retrieved from ncbi.nlm.nih.gov/pubmed/24508103
18. Chapman, P.B., Hauschild, A., Robert, C., et al. (2011, June 30). Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. Retrieved from ncbi.nlm.nih.gov/pubmed/21639808
19. Chapman, P.B., Robert, C., Larkin, J., et al. (2017, Oct. 1). Vemurafenib in Patients with BRAFV600 Mutation-Positive Metastatic Melanoma: Final Overall Survival Results of the Randomized BRIM-3 Study. Retrieved from ncbi.nlm.nih.gov/pubmed/28961848
20. Delord, J., Robert, C., Nyakas, M., et al. (2017, Jan. 1). Phase I Dose-Escalation and Expansion Study of the BRAF Inhibitor Encorafenib (LGX818) in Metastatic BRAF-Mutant Melanoma. Retrieved from clincancerres.aacrjournals.org/content/early/2017/06/13/1078-0432.CCR-16-2923
21. Long, G.V., Stroyakovskiy, D., Gogas, H., et al (2015, Aug. 1). Dabrafenib and Trametinib Versus Dabrafenib and Placebo for Val600 BRAF-Mutant Melanoma: A Multicentre, Double-Blind, Phase 3 Randomised, Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/26037941
22. Long, G.V., Flaherty, K.T., Stroyakovskiy, D., et al. (2017, May 5). Dabrafenib Plus Trametinib Versus Dabrafenib Monotherapy in Patients with Metastatic BRAF V600E/K-Mutant Melanoma: Long-Term Survival and Safety Analysis of a Phase 3 Study. Retrieved from academic.oup.com/annonc/article/28/7/1631/3798688
23. Robert, C., Karaszewska, B., Schachter, J., et al. (2015, Jan. 1). Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. Retrieved from ncbi.nlm.nih.gov/pubmed/25399551
24. Robert, C., Grob, J.J., Stroyakovskiy, D., et al. (2019, June 4). Five-Year Outcomes with Dabrafenib Plus Trametinib in Metastatic Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/31166680
25. Ascierto, P.A., McArthur, G.A., Dréno, B., et al. (September 2016). Cobimetinib Combined with Vemurafenib in Advanced BRAF (V600)-Mutant Melanoma (coBRIM): Updated Efficacy Results From a Randomised, Double-Blind, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/27480103
26. Dréno, B., Ribas, A., Larkin, J., et al. (2017, May 1). Incidence, Course and Management of Toxicities Associated with Cobimetinib in Combination with Vemurafenib in the coBRIM Study. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=28444112
27. Dummer, R., Ascierto, P.A., Gogas, H.J., et al. (May 2018). Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients with BRAF-Mutant Melanoma (COLUMBUS): A Multicentre, Open-Label, Randomised Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/29573941
28. Dummer, R., Ascierto, P.A., Gogas, H.J., et al. (October 2018). Overall Survival in Patients with BRAF-Mutant Melanoma Receiving Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib (COLUMBUS): A Multicentre, Open-Label, Randomised, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/30219628

29. Robert, C., Schachter, J., Long, G.V., et al. Pembrolizumab Versus Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2015; 372:2521-2532. Retrieved from pubmed.ncbi.nlm.nih.gov/25891173
30. Robert, C., Ribas, A., Schachter, J., et al. Pembrolizumab Versus Ipilimumab in Advanced Melanoma (KEYNOTE-006): Post-Hoc 5-Year Results From an Open-Label, Multicenter, Randomized, Controlled, Phase 3 Study. *Lancet Oncol.* 2019; Epub ahead of print. Retrieved from [thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(19\)30388-2.pdf](http://thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(19)30388-2.pdf)
31. Robert, C., Long, G.V., Brady, B., et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med.* 2015; 372(4): 320-329. Retrieved from pubmed.ncbi.nlm.nih.gov/25399552
32. Ascierto, P.A., Long, G.V., Robert, C., et al. Survival Outcomes in Patients with Previously Untreated BRAF Wild-Type Advanced Melanoma Treated with Nivolumab Therapy: Three-Year Follow-Up of a Randomized Phase 3 Trial. *JAMA Oncol.* 2018. Epub. Retrieved from pubmed.ncbi.nlm.nih.gov/30422243
33. Wolchok, J.D., Chiarion-Sileni, V., Gonzalez, R., et al. (2017, Oct. 5). Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/28889792
34. ESMO 2018: CheckMate 067: 4-Year Follow-Up of Nivolumab Plus Ipilimumab in Advanced Melanoma. Retrieved from ascopost.com/News/59415
35. Hodi, F.S., Chesney, J., Pavlick, A.C., et al. (November 2016). Combined Nivolumab and Ipilimumab Versus Ipilimumab Alone in Patients with Advanced Melanoma: 2-Year Overall Survival Outcomes in a Multicentre, Randomised, Controlled, Phase 2 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/27622997
36. Robert, C., Thomas, L., Bondarenko, I., et al. (2011, June 30). Ipilimumab Plus Dacarbazine for Previously Untreated Metastatic Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/21639810
37. Maio, M., Grob, J.J., Aamdal, S., et al. (2015, April 1). Five-Year Survival Rates for Treatment-Naive Patients with Advanced Melanoma Who Received Ipilimumab Plus Dacarbazine in a Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pmc/articles/PMC5795709
38. Ascierto, P.A., Del Vecchio, M., Robert, C., et al. (May 2017). Ipilimumab 10 mg/kg Versus Ipilimumab 3 mg/kg in Patients with Unresectable or Metastatic Melanoma: A Randomised, Double-Blind, Multicentre, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28359784
39. Ribas, A., Puzanov, I., Dummer, R., et al. Pembrolizumab Versus Investigator-Choice Chemotherapy for Ipilimumab-Refractory Melanoma (KEYNOTE-002): A Randomized, Controlled, Phase 2 Trial. *Lancet Oncol.* 2015; 16:908-918. Retrieved from pubmed.ncbi.nlm.nih.gov/26115796
40. Hamid, O., Puzanov, I., Dummer, R., et al. Final Analysis of a Randomized Trial Comparing Pembrolizumab Versus Investigator-Choice Chemotherapy for Ipilimumab-Refractory Advanced Melanoma. *Eu J Cancer.* 2017; 86: 37-45. Retrieved from pubmed.ncbi.nlm.nih.gov/28961465
41. Weber, J.S., D'Angelo, S.P., Minor, D., et al. (April 2015). Nivolumab Versus Chemotherapy in Patients with Advanced Melanoma Who Progressed After Anti-CTLA-4 Treatment (CheckMate 037): A Randomised, Controlled, Open-Label, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/25795410

42. Larkin, J., Minor, D., D'Angelo, S., et al. (2018, Feb. 1). Overall Survival in Patients with Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28671856
43. Chesney, J., Puzanov, I., Collichio, F., et al. (2018, June 10). Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination with Ipilimumab Versus Ipilimumab Alone in Patients with Advanced, Unresectable Melanoma. Retrieved from ncbi.nlm.nih.gov/pubmed/28981385
44. Ribas, A., Puzanov, I., Dummer, R., et al. (August 2015). Pembrolizumab Versus Investigator-Choice Chemotherapy for Ipilimumab-Refractory Melanoma (KEYNOTE-002): A Randomised, Controlled, Phase 2 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=26115796
45. Andtbacka, R.H.I., Collichio, F., Harrington, K.J., et al. Final Analyses of OPTiM: A Randomized Phase III Trial of Talimogene Laherparepvec Versus Granulocyte-Macrophage Colony-Stimulating Factor in Unresectable Stage III-IV Melanoma. *J Immunother Cancer*. 2019;7(1):145. Published 2019 Jun 6. DOI:10.1186/s40425-019-0623-z
46. Ascierto, P.A., Del Vecchio, M., Mandalá, M., et al. Adjuvant Nivolumab Versus Ipilimumab in Resected Stage IIIB-C and Stage IV Melanoma (Checkmate 238): 4-Year Results From a Multicentre, Double-Blind, Randomised, Controlled, Phase 3 Trial. *Lancet Oncol*. 2020 Nov;21(11):1465-1477. DOI: 10.1016/S1470-2045(20)30494-0. Epub 2020 Sep 19. PMID: 32961119
47. Dummer, R., Hauschild, A., Santinami, M., et al. Five-Year Analysis of Adjuvant Dabrafenib Plus Trametinib in Stage III Melanoma. *N Engl J Med*. 2020 Sep 17;383(12):1139-1148. DOI: 10.1056/NEJMoa2005493. Epub 2020 Sep 2. PMID: 32877599
48. Eggermont, A.M.M., Blank, C.U., Mandalà, M., et al.; EORTC Melanoma Group. Adjuvant Pembrolizumab Versus Placebo in Resected Stage III Melanoma (EORTC 1325-MG/KEYNOTE-054): Distant Metastasis-Free Survival Results From a Double-Blind, Randomised, Controlled, Phase 3 Trial. *Lancet Oncol*. 2021 May;22(5):643-654. DOI: 10.1016/S1470-2045(21)00065-6. Epub 2021 Apr 12. PMID: 33857412
49. Gutzmer, R., Stroyakovskiy, D., Gogas, H., et al. Atezolizumab, Vemurafenib, and Cobimetinib as First-Line Treatment for Unresectable Advanced BRAFV600 Mutation-Positive Melanoma (IMspire150): Primary Analysis of the Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet*. 2020 Jun 13;395(10240):1835-1844. DOI: 10.1016/S0140-6736(20)30934-X. Erratum in: *Lancet*. 2020 Aug 15;396(10249):466. PMID: 32534646.
50. Ferrucci, P.F., Di Giacomo, A.M., Del Vecchio, M., et al.; KEYNOTE-022 International Team. KEYNOTE-022 Part 3: A Randomized, Double-Blind, Phase 2 Study of Pembrolizumab, Dabrafenib, and Trametinib in BRAF-Mutant Melanoma. *J Immunother Cancer*. 2020 Dec;8(2):e001806. DOI: 10.1136/jitc-2020-001806. PMID: 33361337; PMCID: PMC7768966
51. Ascierto, P.A., Ferrucci, P.F., Fisher, R., et al. Dabrafenib, Trametinib and Pembrolizumab or Placebo in BRAF-Mutant Melanoma. *Nat Med*. 2019;25:941-46
52. Carlino, M.S., Menzies, A.M., Atkinson, V., et al. Long-Term Follow-Up of Standard-Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in Patients with Advanced Melanoma: KEYNOTE-029 Part 1B. *Clin Cancer Res*. 2020 Oct 1;26(19):5086-5091. DOI: 10.1158/1078-0432.CCR-20-0177. Epub 2020 Jun 30. PMID: 32605909
53. Olson, D.J., Eroglu, Z., Brockstein, B., et al. Pembrolizumab Plus Ipilimumab Following Anti-PD-1/L1 Failure in Melanoma. *J Clin Oncol*. 2021 Aug 20;39(24):2647-2655. DOI: 10.1200/JCO.21.00079. Epub 2021 May 4. PMID: 33945288; PMCID: PMC8376314

54. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet*. 2022;399(10336):1718-1729. DOI:10.1016/S0140-6736(22)00562-1
55. Long GV, Luke JJ, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(11):1378-1388. DOI:10.1016/S1470-2045(22)00559-9
56. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med*. 2018;378(19):1789-1801. Eggermont AMM, Blank CU, Mandala M, et al. Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial. *J Clin Oncol*. 2020;38(33):3925-3936. DOI:10.1200/JCO.20.02110
57. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(5):643-654. DOI:https://DOI.org/10.1016/S1470-2045(21)00065-6
58. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma *N Engl J Med*. 2022;386(1):24-34. DOI:10.1056/NEJMoa2109970
59. Long G, Hodi S, Lipson E, et al. Overall Survival and Response with Nivolumab and Relatlimab in Advanced Melanoma. *N Engl J Med. Evidence*. 2023;2(4):pages unknown. DOI: 10.1056/EVIDoa2200239
60. Wolchok JD, Chiarion-Sileni V, Gonzalez R; CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. *JCO*; 2021 39:15_suppl, 9506-9506. DOI: 10.1200/JCO.2021.39.15_suppl.9506.
61. Ascierto PA, Lipson EJ, Dummer R, et al. Nivolumab and Relatlimab in Patients with Advanced Melanoma That Had Progressed on Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy: Results From the Phase I/IIa RELATIVITY-020 Trial. *J Clin Oncol*. 2023;41(15):2724-2735. DOI:10.1200/JCO.22.02072
62. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in *Lancet*. 2020 Aug 15;396(10249):466]. *Lancet*. 2020;395(10240):1835-1844. DOI:10.1016/S0140-6736(20)30934-X
63. Ascierto PA, Stroyakovskiy D, Gogas H, et al. Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. *Lancet Oncol*. 2023;24(1):33-44. DOI:10.1016/S1470-2045(22)00687-8
64. Ferrucci PF, Di Giacomo AM, Del Vecchio M, et al. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma. *J Immunother Cancer*. 2020;8(2):e001806. DOI:10.1136/jitc-2020-001806
65. Ribas A, Ferruci PF, Atkinson V, et al. Pembrolizumab plus dabrafenib and trametinib in BRAFv600E/Kmutant melanoma: Long-term follow-up of KEYNOTE-022 parts 1, 2, and 3. Presented at: American Society of Clinical Oncology Annual Meeting; 3-7 June 2022; Chicago, IL.

66. Arance A, de la Cruz-Merino L, Petrella TM, et al. Phase II LEAP-004 Study of Lenvatinib Plus Pembrolizumab for Melanoma with Confirmed Progression on a Programmed Cell Death Protein-1 or Programmed Death Ligand 1 Inhibitor Given as Monotherapy or in Combination [published correction appears in *J Clin Oncol*. 2023 May 1;41(13):2454]. *J Clin Oncol*. 2023;41(1):75-85. DOI:10.1200/JCO.22.00221
67. DOI: 10.1200/JCO.2021.39.15_suppl.9504 *J Clin Oncol*. 39, no. 15_suppl (May 20, 2021) 9504-9504.
68. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(4):435-445. DOI:10.1016/S1470-2045(17)30180-8
69. Atkins MB, Lee SJ, Chmielowski B, et al. Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients with Advanced BRAF-Mutant Melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134. *J Clin Oncol*. 2023;41(2):186-197. DOI:10.1200/JCO.22.01763
70. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2021;22(6):836-847. DOI:10.1016/S1470-2045(21)00097-8
71. Lebbé C, Meyer N, Mortier L, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination with Ipilimumab in Patients with Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. *J Clin Oncol*. 2019;37(11):867-875. DOI:10.1200/JCO.18.01998
72. Lebbe C, Meyer N, Mortier L, et al. Two dosing regimens of nivolumab (NIVO) plus ipilimumab (IPI) for advanced (adv) melanoma: Three-year results of CheckMate 511. *JCO*. 2021 39:15_suppl, 9516-9516. DOI: 10.1200/JCO.2021.39.15_suppl.9516

Multiple Myeloma: Primary Therapy**

Transplant Eligible and Ineligible

- Bortezomib + Lenalidomide + Dexamethasone (VRD)
- Bortezomib + Cyclophosphamide + Dexamethasone (CyBorD or VCD)

Maintenance Therapy**

Transplant Eligible or Ineligible

- Lenalidomide
- Bortezomib

Relapsed or Refractory**

1st Relapse

- Daratumumab + Lenalidomide + Dexamethasone (DRD)
- Daratumumab + Bortezomib + Dexamethasone (DVD)
- Bortezomib + Lenalidomide + Dexamethasone (VRD)
- Bortezomib + Cyclophosphamide + Dexamethasone (CyBorD or VCD)

2nd Relapse

- Daratumumab + Lenalidomide + Dexamethasone (DRD)
- Daratumumab + Bortezomib + Dexamethasone (DVD)
- Isatuximab-irfc + Pomalidomide + Dexamethasone (Isa-PD)
- Elotuzumab + Pomalidomide + Dexamethasone (EPD)
- Carfilzomib + Lenalidomide + Dexamethasone (KRD)
- Pomalidomide + Bortezomib + Dexamethasone (PVD)
- Bortezomib + Lenalidomide + Dexamethasone (VRD)
- Bortezomib + Cyclophosphamide + Dexamethasone (CyBorD or VCD)

*** Therapies that are administered at Centers of Excellence, including stem cell transplant or CAR T-cell therapy, are not included in pathways. Patients eligible for transplant or CAR T-cell therapy should be referred appropriately for evaluation.*

References:

1. National Comprehensive Cancer Network. Multiple Myeloma. (V2.2024, November 1, 2023). Accessed February 2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

2. Richardson, P.G., Weller, E., Lonial, S., et al. Lenalidomide, Bortezomib and Dexamethasone Combination Therapy in Patients with Newly Diagnosed Multiple Myeloma. *Blood*. 2010;116(5):679-686. DOI: 10.1182/blood-2010-02-268862
3. Kumar, S., Flinn, I., Richardson, P.G., et al. Randomized, Multicenter, Phase 2 Study (EVOLUTION) of Combinations of Bortezomib, Dexamethasone, Cyclophosphamide and Lenalidomide in Previously Untreated Multiple Myeloma. *Blood*. 2012;119(19):4375-4382. DOI: 10.1182/blood-2011-11-395749
4. Durie, B.G.M., Hoering, A., Abidi, M.H., et al. Bortezomib with Lenalidomide and Dexamethasone Versus Lenalidomide and Dexamethasone Alone in Patients with Newly Diagnosed Myeloma without Intent for Immediate Autologous Stem-Cell Transplant (SWOG S0777): A Randomised, Open-Label, Phase 3 Trial. *Lancet*. 2017;389(10068):519-527. DOI: 10.1016/S0140-6736(16)31594-X
5. Moreau, P., Hulin, C., Macro, M., et al. VTD Is Superior to VCD Prior to Intensive Therapy in Multiple Myeloma: Results of the Prospective IFM2013-04 Trial. *Blood*. 2016;127(21):2569-2574. DOI: 10.1182/blood-2016-01-693580
6. Reeder, C.B., Reece, D.E., Kukreti, V., et al. Cyclophosphamide, Bortezomib and Dexamethasone Induction for Newly Diagnosed Multiple Myeloma: High Response Rates in a Phase II Clinical Trial. *Leukemia*. 2009;23(7):1337-1341. DOI: 10.1038/leu.2009.26
7. Einsele, H., Engelhardt, M., Tapprich, C., et al. Phase II Study of Bortezomib, Cyclophosphamide and Dexamethasone as Induction Therapy in Multiple Myeloma: DSMM XI Trial. *Br J Haematol*. 2017 Nov;179(4):586-597. DOI: 10.1111/bjh.14920. Epub 2017 Sep 29. PMID: 28961309
8. Knop, S., Liebisch, P., Wandt, H., et al. Bortezomib, IV Cyclophosphamide and Dexamethasone (Velcade) as Induction Therapy in Newly Diagnosed Multiple Myeloma: Results of an Interim Analysis of the German DSMM Trial. *Blood*. 2009;27:8516-8516. Retrieved from DOI.org/10.1182/blood.V112.11.2776.2776
9. Reeder, C.B., Reece, D.E., Kukreti, V., et al. Long-Term Survival with Cyclophosphamide, Bortezomib and Dexamethasone Induction Therapy in Patients with Newly Diagnosed Multiple Myeloma. *Br J Haematol*. 2014;167(4):563-565. Retrieved from DOI.org/10.1111/bjh.13004
10. Reeder, C.B., Reece, D.E., Kukreti, V., et al. Once- Versus Twice-Weekly Bortezomib Induction Therapy with Cybord in Newly Diagnosed Multiple Myeloma. *Blood*. 2010;115(16):3416-3417. DOI: 10.1182/blood-2010-02-271676

11. Korde, N., Zingone, A., Kwok, M., et al. Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide and Dexamethasone Followed by Lenalidomide Extended Dosing (CRD-R) Induces High Rates of MRD Negativity in Newly Diagnosed Multiple Myeloma (MM) Patients [Abstracts]. *Blood*. 2013;122:538. Retrieved from DOI.org/10.1182/blood.V122.21.538.538
12. Korde, N., Roschewski, M., Zingone, A., et al. Treatment with Carfilzomib-Lenalidomide-Dexamethasone with Lenalidomide Extension in Patients with Smoldering or Newly Diagnosed Multiple Myeloma. *JAMA Oncol*. 2015;1(6):746-754. DOI: 10.1001/jamaoncol.2015.2010
13. Jakubowiak, A.J., Dytfeld, D., Griffith, K.A., et al. A Phase 1/2 Study of Carfilzomib in Combination with Lenalidomide and Low-Dose Dexamethasone as a Frontline Treatment for Multiple Myeloma. *Blood*. 2012;120(9):1801-1809. DOI: 10.1182/blood-2012-04-422683
14. Jasieliec, J., Kubicki, T., Raje, N., et al. Carfilzomib, Lenalidomide, and Dexamethasone Plus Transplant in Newly Diagnosed Multiple Myeloma. *Blood*. 2020 Jul 31;blood.2020007522. DOI: 10.1182/blood.2020007522. Epub ahead of print. PMID: 32735641
15. Voorhees, P.M., Kaufman, J.L., Laubach, J., et al. Daratumumab, Lenalidomide, Bortezomib and Dexamethasone for Transplant-Eligible Newly Diagnosed Multiple Myeloma: The GRIFFIN Trial. *Blood*. 2020 Aug 20;136(8):936-945. DOI: 10.1182/blood.2020005288. PMID: 32325490; PMCID: PMC7441167
16. Sonneveld, P., Broijl, A., Gay, F., et al. Bortezomib, Lenalidomide and Dexamethasone (Vrd) +/- Daratumumab (DARA) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM); A Multicenter, Randomized, Phase III Study (PERSEUS). *J Clin Oncol*. 2019;37(15 suppl)
17. Kumar, S.K., Berdeja, J.G., Niesvizky, R., et al. Safety and Tolerability of Ixazomib, an Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma: An Open-Label Phase 1/2 Study [published correction appears in *Lancet Oncol*. 2019 Jul;20(7):e346]. *Lancet Oncol*. 2014;15(13):1503-1512. DOI: 10.1016/S1470-2045(14)71125-8
18. Kumar, S.K., Berdeja, J.G., Niesvizky, R., et al. Ixazomib, Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Long-Term Follow-Up Including Ixazomib Maintenance. *Leukemia*. 2019;33(7):1736-1746. DOI:10.1038/s41375-019-0384-1
19. Sonneveld, P., Schmidt-Wolf, I.G., van der Holt, B., et al. Bortezomib Induction and Maintenance Treatment in Patients with Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/GMMG-HD4 Trial [published correction appears in *J Clin Oncol*. 2012 Oct 10;30(29):3654]. *J Clin Oncol*. 2012;30(24):2946-2955. DOI: 10.1200/JCO.2011.39.6820
20. Bringhen, S., Petrucci, M.T., Larocca, A., et al. Carfilzomib, Cyclophosphamide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: A Multicenter, Phase 2 Study. *Blood*. 2014;124(1):63-69. DOI:10.1182/blood-2014-03-563759
21. Kumar, S.K., et al. Phase 1/2 Trial of Ixazomib, Cyclophosphamide and Dexamethasone in Patients with Previously Untreated Symptomatic Multiple Myeloma. *Blood Cancer J*. 2018 Jul 30;8(8):70. DOI: 10.1038/s41408-018-0106-3
22. Moreau, P., Avet-Loiseau, H., Facon, T., et al. Bortezomib Plus Dexamethasone Versus Reduced-Dose Bortezomib, Thalidomide Plus Dexamethasone as Induction Treatment Before Autologous Stem Cell Transplantation in Newly Diagnosed Multiple Myeloma. *Blood*. 2011;118(22):5752-5982. DOI: 10.1182/blood-2011-05-355081

23. Cavo, M., Tacchetti, P., Patriarca, F., et al. Bortezomib with Thalidomide Plus Dexamethasone Compared with Thalidomide Plus Dexamethasone as Induction Therapy Before, and Consolidation Therapy After, Double Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Randomised Phase 3 Study [Published Correction Appears in *Lancet*. 2011 Nov 26;378(9806):1846]. *Lancet*. 2010;376(9758):2075-2085. DOI: 10.1016/S0140-6736(10)61424-9
24. Rosiñol, L., Oriol, A., Teruel, A.I., et al. Superiority of Bortezomib, Thalidomide and Dexamethasone (VTD) as Induction Pretransplantation Therapy in Multiple Myeloma: A Randomized Phase 3 PETHEMA/GEM Study. *Blood*. 2012;120(8):1589-1596. DOI: 10.1182/blood-2012-02-408922
25. Kumar, S.K., Lacy, M.Q., Hayman, S.R., et al. Lenalidomide, Cyclophosphamide and Dexamethasone (CrD) for Newly Diagnosed Multiple Myeloma: Results From a Phase 2 Trial. *Am J Hematol*. 2011;86(8):640-645. DOI: 10.1002/ajh.22053
26. Moreau, P., Attal, M., Hulin, C., et al. Bortezomib, Thalidomide and Dexamethasone with or without Daratumumab Before and After Autologous Stem-Cell Transplantation for Newly Diagnosed Multiple Myeloma (CASSIOPEIA): A Randomised, Open-Label, Phase 3 Study. *Lancet*. 2019;394(10192):29-38. DOI: 10.1016/S0140-6736(19)31240-1
27. Yimer, H., Melear, J., Faber, E., et al. Daratumumab, Bortezomib, Cyclophosphamide and Dexamethasone in Newly Diagnosed and Relapsed Multiple Myeloma: LYRA Study. *Br J Haematol*. 2019;185(3): 492-502
28. Barlogie, B., Anaissie, E., van Rhee, F., et al. Incorporating Bortezomib into Upfront Treatment for Multiple Myeloma: Early Results of Total Therapy. *Br J Haematol*. 2007;138(2):176-185. DOI: 10.1111/j.1365-2141.2007.06639
29. Huang, J., Phillips, S., Byrne, M., et al. Lenalidomide vs. Bortezomib Maintenance Choice Post-Autologous Hematopoietic Cell Transplantation for Multiple Myeloma. *Bone Marrow Transplant* 53, 701–707 (2018). Retrieved from DOI.org/10.1038/s41409-018-0177-6
30. Roussel, M., Lauwers-Cances, V., Robillard, N., et al. Front-Line Transplantation Program with Lenalidomide, Bortezomib and Dexamethasone Combination as Induction and Consolidation Followed by Lenalidomide Maintenance in Patients with Multiple Myeloma: A Phase II Study by the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2014;32(25):2712-2717. DOI: 10.1200/JCO.2013.54.8164
31. Jackson, H.G., Davies, F.E., Pawlyn, C., et al. Lenalidomide Maintenance Versus Observation for Patients with Newly Diagnosed Multiple Myeloma (Myeloma XI): A Multicentre, Open-Label, Randomised, Phase 3 Trial. *Lancet Oncol*. 2019;20(1):57-73
32. Attal, M., Lauwers-Cances, V., Marit, G., et al. Lenalidomide Maintenance After Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med*. 2012;366(19):1782-1791. DOI:10.1056/NEJMoa1114138
33. McCarthy, P.L., Owzar, K., Hofmeister, C.C., et al. Lenalidomide After Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med*. 2012;366(19):1770-1781. DOI:10.1056/NEJMoa1114083
34. Holstein, S.A., Jung, S.H., Richardson, P.G., et al. Updated Analysis of CALGB (Alliance) 100104 Assessing Lenalidomide Versus Placebo Maintenance After Single Autologous Stem-Cell Transplantation for Multiple Myeloma: A Randomised, Double-Blind, Phase 3 Trial. *Lancet Haematol*. 2017 Sep;4(9):e431-e442. DOI: 10.1016/S2352-3026(17)30140-0. Epub 2017 Aug 17. Erratum in: *Lancet Haematol*. 2018 Aug;5(8):e332. Erratum in: *Lancet Haematol*. 2018 Dec;5(12):e608. PMID: 28826616; PMCID: PMC5718627

35. Palumbo, A., Cavallo, F., Gay, F., et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. *N Engl J Med*. 2014;371(10):895-905. DOI:10.1056/NEJMoa1402888
36. McCarthy, P.L., et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol*. 35, 3279–3289 (2017)
37. Dimopoulos, M.A., Gay, F., Schjesvold, F., et al. Oral Ixazomib Maintenance Following Autologous Stem Cell Transplantation (TOURMALINE-MM3): A Double-Blind, Randomised, Placebo-Controlled Phase 3 Trial. *Lancet*. 2019;393(10168):253-264. DOI: 10.1016/S0140-6736(18)33003-4
38. Zhang, S., Kulkarni, A.A., Xu, B., et al. Bortezomib-Based Consolidation or Maintenance Therapy for Multiple Myeloma: A Meta-Analysis. *Blood Cancer J*. 10, 33 (2020). Retrieved from DOI.org/10.1038/s41408-020-0298-1
39. Goldschmidt, H., et al. Bortezomib Before and After High-Dose Therapy in Myeloma: Long-Term Results From the Phase III HOVON-65/GMMG-HD4 Trial. *Leukemia*. 32, 383–390 (2018)
40. Niesvizky, R., Flinn, I.W., Rifkin, R., et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol*. 2015;33(33):3921-3929. DOI: 10.1200/JCO.2014.58.7618
41. Mikhael, J., Ismaila, N., Cheung, M.C., et al. ASCO and CCO Joint Clinical Practice Guideline. *J Clin Oncol*. 2019 May 10;37(14):1228-1263. DOI: 10.1200/JCO.18.02096. Epub 2019 Apr 1. Erratum in: *J Clin Oncol*. 2020 Jul 20;38(21):2469. PMID: 30932732 Cavo, M., Rajkumar, S.V., Palumbo, A., et al. International Myeloma Working Group. International Myeloma Working Group Consensus Approach to the Treatment of Multiple Myeloma Patients Who Are Candidates for Autologous Stem Cell Transplantation. *Blood*. 2011 Jun 9;117(23):6063-73. DOI: 10.1182/blood-2011-02-297325. Epub 2011 Mar 29. PMID: 21447828; PMCID: PMC3293742
42. Kumar, S.K., Jacobus, S.J., Cohen, A.D., et al. Carfilzomib or Bortezomib in Combination with Lenalidomide and Dexamethasone for Patients with Newly Diagnosed Multiple Myeloma without Intention for Immediate Autologous Stem-Cell Transplantation (ENDURANCE): A Multicentre, Open-Label, Phase 3, Randomised, Controlled Trial. *Lancet Oncol*. 2020 Aug 28:S1470-2045(20)30452-6. DOI: 10.1016/S1470-2045(20)30452-6. Epub ahead of print. PMID: 32866432
43. Facon, T., Kumar, S., Plesner, T., et al. Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med*. 2019 May 30;380(22):2104-2115. PMID: 31141632
44. Benboubker, L., Dimopoulos, M.A., Dispenzieri, A., et al. Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma. *N Engl J Med*. 2014;371:906–917
45. Rajkumar, S.V., Jacobus, S., Callander, N.S., et al. Eastern Cooperative Oncology Group. Lenalidomide Plus High-Dose Dexamethasone Versus Lenalidomide Plus Low-Dose Dexamethasone as Initial Therapy for Newly Diagnosed Multiple Myeloma: An Open-Label Randomised Controlled Trial. *Lancet Oncol*. 2010 Jan;11(1):29-37. DOI: 10.1016/S1470-2045(09)70284-0. Epub 2009 Oct 21. Erratum in: *Lancet Oncol*. 2010 Jan;11(1):14. PMID: 19853510; PMCID: PMC3042271
46. Gay, F., Hayman, S.R., Lacy, M.Q., et al. Lenalidomide Plus Dexamethasone Versus Thalidomide Plus Dexamethasone in Newly Diagnosed Multiple Myeloma: A Comparative Analysis of 411 Patients. *Blood*. 2010; 115:1343-1350. PMID: 20008302
47. Zepeda, V.H.J., Duggan, P., Neri, P.E., et al. Cyclophosphamide, Bortezomib and Dexamethasone (Cybord) Is a Feasible and Active Regimen for Non-Transplant Eligible Multiple Myeloma Patients [Abstract]. *Blood*. 2014;124:5751

48. Jakubowiak, A.J., Dytfield, D., Griffith, K.A., et al. A Phase 1/2 Study of Carfilzomib in Combination with Lenalidomide and Low-Dose Dexamethasone as a Frontline Treatment for Multiple Myeloma. *Blood*. 2012;120:1801–1809
49. Kumar, S.K., Berdeja, J.G., Niesvizky, R., et al. Safety and Tolerability of Ixazomib, an Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma: An Open-Label Phase 1/2 Study. *Lancet Oncol*. 2014;15:1503–1512
50. Mateos, M.V., Dimopoulos, M.A., Cavo, M., et al.; ALCYONE Trial Investigators. Daratumumab Plus Bortezomib, Melphalan and Prednisone for Untreated Myeloma. *N Engl J Med*. 2018 Feb 8;378(6):518-528. DOI: 10.1056/NEJMoa1714678. Epub 2017 Dec 12. PMID: 29231133
51. Yimer, H., Melear, J., Faber, E., et al. Daratumumab, Bortezomib, Cyclophosphamide and Dexamethasone in Newly Diagnosed and Relapsed Multiple Myeloma: LYRA Study. *Br J Haematol*. 2019 May;185(3):492-502. DOI: 10.1111/bjh.15806. Epub 2019 Mar 3. PMID: 30828799; PMCID: PMC6593455
52. Niesvizky, R., Flinn, I.W., Rifkin, R., et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol*. 2015 Nov 20;33(33):3921-3929. PMID: 26056177
53. Kumar, S.K., Lacy, M.Q., Hayman, S.R., et al. Lenalidomide, Cyclophosphamide and Dexamethasone (Crd) for Newly Diagnosed Multiple Myeloma: Results From a Phase 2 Trial. *Am J Hematol*. 2011 Aug;86(8):640-5. DOI: 10.1002/ajh.22053. Epub 2011 May 31. PMID: 21630308; PMCID: PMC3901994
54. Mina, R., Bonello, F., Petrucci, M.T., et al. Carfilzomib, Cyclophosphamide and Dexamethasone for Newly Diagnosed, High-Risk Myeloma Patients Not Eligible for Transplant: A Pooled Analysis of Two Studies. *Haematologica*. 2020;105(4):243428. DOI: 3324/haematol.2019.243428
55. Jackson, G.H., Davies, F.E., Pawlyn, C., et al. UK NCRI Haemato-Oncology Clinical Studies Group. Lenalidomide Maintenance Versus Observation for Patients with Newly Diagnosed Multiple Myeloma (Myeloma XI): A Multicentre, Open-Label, Randomised, Phase 3 Trial. *Lancet Oncol*. 2019 Jan;20(1):57-73. DOI: 10.1016/S1470-2045(18)30687-9. Epub 2018 Dec 14. PMID: 30559051; PMCID: PMC6318225
56. Singh, P.P., Kumar, S.K., LaPlant, B.R., et al. Lenalidomide Maintenance Therapy in Multiple Myeloma: A Meta-Analysis of Randomized Trials. *Blood*. 2013;122 (21): 407. Retrieved from DOI.org/10.1182/blood.V122.21.407.407
57. Palumbo, A., Hajek, R., Delforge, M., et al. MM-015 Investigators. Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma. *N Engl J Med*. 2012 May 10;366(19):1759-69. DOI: 10.1056/NEJMoa1112704. Erratum in: *N Engl J Med*. 2012 Jul 19;367(3):285
58. Palumbo, A., Cavallo, F., Gay, F., et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. *N Engl J Med*. 2014 Sep 4;371(10):895-905. DOI: 10.1056/NEJMoa1402888. PMID: 25184862
59. Isoda, A., Murayama, K., Ito, S., et al., Kanshinetsu Multiple Myeloma Study Group. Bortezomib Maintenance Therapy in Transplant-Ineligible Myeloma Patients Who Plateaued After Bortezomib-Based Induction Therapy: A Multicenter Phase II Clinical Trial. *Int J Hematol*. 2018 Jul;108(1):39-46. DOI: 10.1007/s12185-018-2448-9. Epub 2018 Mar 28. PMID: 29594921

60. Palumbo, A., Sezer, O., Kyle, R., et al., IMWG. International Myeloma Working Group Guidelines for the Management of Multiple Myeloma Patients Ineligible for Standard High-Dose Chemotherapy with Autologous Stem Cell Transplantation. *Leukemia*. 2009 Oct;23(10):1716-30. DOI: 10.1038/leu.2009.122. Epub 2009 Jun 4. PMID: 19494840
61. Richardson, P.G., Xie, W., Jagannath, S., et al. A Phase 2 Trial of Lenalidomide, Bortezomib, and Dexamethasone in Patients with Relapsed and Relapsed/Refractory Myeloma. *Blood*. 2014 Mar 6;123(10):1461-9. DOI: 10.1182/blood-2013-07-517276. Epub 2014 Jan 15. PMID: 24429336; PMCID: PMC4123434.
62. Stewart, A.K., Rajkumar, S.V., Dimopoulos, M.A., et al., ASPIRE Investigators. Carfilzomib, Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma. *N Engl J Med*. 2015 Jan. 8;372(2):142-52. DOI: 10.1056/NEJMoa1411321. Epub 2014 Dec 6. PMID: 25482145
63. Siegel, D.S., Dimopoulos, M.A., Ludwig, H., et al. Improvement in Overall Survival with Carfilzomib, Lenalidomide and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. *J Clin Oncol*. 2018 Mar 10;36(8):728-734. DOI: 10.1200/JCO.2017.76.5032. Epub 2018 Jan 17. PMID: 29341834
64. Palumbo, A., Chanan-Khan, A., Weisel, K., et al. CASTOR Investigators. Daratumumab, Bortezomib and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016 Aug 25;375(8):754-66. DOI: 10.1056/NEJMoa1606038. PMID: 27557302
65. Spencer, A., Lentzsch, S., Weisel, K., et al. Daratumumab Plus Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Analysis of CASTOR. *Haematologica*. 2018 Dec;103(12):2079-2087. DOI: 10.3324/haematol.2018.194118. Epub 2018 Sep 20. PMID: 30237264; PMCID: PMC6269293
66. Mateos, M.V., Sonneveld, P., Hungria, V., et al. Daratumumab, Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients with Previously Treated Multiple Myeloma: Three-Year Follow-up of CASTOR. *Clin Lymphoma Myeloma Leuk*. 2020 Aug;20(8):509-518. DOI: 10.1016/j.clml.2019.09.623. Epub 2019 Oct 9. PMID: 32482541
67. Chari, A., Martinez-Lopez, J., Mateos, M.V., et al. Daratumumab Plus Carfilzomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. *Blood*. 2019 Aug 1;134(5):421-431. DOI: 10.1182/blood.2019000722. Epub 2019 May 21. PMID: 31113777; PMCID: PMC6676132
68. Dimopoulos, M., Quach, H., Mateos, M.V., et al. Carfilzomib, Dexamethasone and Daratumumab Versus Carfilzomib and Dexamethasone for Patients with Relapsed or Refractory Multiple Myeloma (CANDOR): Results From a Randomised, Multicentre, Open-Label, Phase 3 Study. *Lancet*. 2020 Jul 18;396(10245):186-197. DOI: 10.1016/S0140-6736(20)30734-0. Erratum in: *Lancet*. 2020 Aug 15;396(10249):466. PMID: 32682484
69. Dimopoulos, M.A., Oriol, A., Nahi, H., et al. POLLUX Investigators. Daratumumab, Lenalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016 Oct 6;375(14):1319-1331. DOI: 10.1056/NEJMoa1607751. PMID: 27705267
70. Kaufman, J.L., Usmani, S.Z., San-Miguel, J., et al. Four-Year Follow-Up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). *Blood*. 2019; 134 (Supplement_1): 1866. Retrieved from DOI.org/10.1182/blood-2019-123483
71. Attal, M., Richardson, P.G., Rajkumar, S.V., et al., ICARIA-MM Study Group. Isatuximab Plus Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma (ICARIA-MM): A Randomised, Multicentre, Open-Label, Phase 3 Study. *Lancet*. 2019 Dec 7;394(10214):2096-2107. DOI: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. Erratum in: *Lancet*. 2019 Dec 7;394(10214):2072. PMID: 31735560

72. Moreau, P., Masszi, T., Grzasko, N., TOURMALINE-MM1 Study Group, et al. Oral Ixazomib, Lenalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016 Apr 28;374(17):1621-34. DOI: 10.1056/NEJMoa1516282. PMID: 27119237
73. Krishnan, A., Kapoor, P., Palmer, J.M., et al. Phase I/II Trial of the Oral Regimen Ixazomib, Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma. *Leukemia*. 2018 Jul;32(7):1567-1574. DOI: 10.1038/s41375-018-0038-8. Epub 2018 Feb 23. PMID: 32082000; PMCID: PMC6005710
74. Richardson, P.G., Oriol, A., Beksac, M., et al., OPTIMISMM Trial Investigators. Pomalidomide, Bortezomib and Dexamethasone for Patients with Relapsed or Refractory Multiple Myeloma Previously Treated with Lenalidomide (OPTIMISMM): A Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol*. 2019 Jun;20(6):781-794. DOI: 10.1016/S1470-2045(19)30152-4. Epub 2019 May 13. PMID: 31097405
75. Lonial, S., Lee, H.C., Badros, A., et al. Belantamab Mafodotin for Relapsed or Refractory Multiple Myeloma (DREAMM-2): A Two-Arm, Randomised, Open-Label, Phase 2 Study. *Lancet Oncol*. 2020 Feb;21(2):207-221. DOI: 10.1016/S1470-2045(19)30788-0. Epub 2019 Dec 16. PMID: 31859245
76. Offidani, M., Corvatta, L., Maracci, L., et al. Efficacy and Tolerability of Bendamustine, Bortezomib and Dexamethasone in Patients with Relapsed-Refractory Multiple Myeloma: A Phase II Study. *Blood Cancer J*. 2013 Nov 22;3(11):e162. DOI: 10.1038/bcj.2013.58. PMID: 24270324; PMCID: PMC3880441
77. Lentzsch, S., O'Sullivan, A., Kennedy, R.C., et al. Combination of Bendamustine, Lenalidomide and Dexamethasone (BLD) in Patients with Relapsed or Refractory Multiple Myeloma Is Feasible and Highly Effective: Results of Phase 1/2 Open-Label, Dose Escalation Study. *Blood*. 2012 May 17;119(20):4608-13. DOI: 10.1182/blood-2011-12-395715. Epub 2012 Mar 26. PMID: 22451423; PMCID: PMC3392072
78. Orlowski, R.Z., Nagler, A., Sonneveld, P., et al. Randomized Phase III Study of Pegylated Liposomal Doxorubicin Plus Bortezomib Compared with Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression. *J Clin Oncol*. 2007 Sep 1;25(25):3892-901. DOI: 10.1200/JCO.2006.10.5460. Epub 2007 Aug 6. PMID: 17679727
79. Davies, F.E., Wu, P., Jenner, M., et al. The Combination of Cyclophosphamide, Velcade and Dexamethasone Induces High Response Rates with Comparable Toxicity to Velcade Alone and Velcade Plus Dexamethasone. *Haematologica*. 2007 Aug;92(8):1149-50. DOI: 10.3324/haematol.11228. PMID: 17650451
80. Kropff, M., Bisping, G., Schuck, E., et al., Deutsche Studiengruppe Multiples Myelom. Bortezomib in Combination with Intermediate-Dose Dexamethasone and Continuous Low-Dose Oral Cyclophosphamide for Relapsed Multiple Myeloma. *Br J Haematol*. 2007 Aug;138(3):330-7. DOI: 10.1111/j.1365-2141.2007.06656.x. PMID: 17614819
81. Yong, K., Brown, S., Hinsley, S., et al. Carfilzomib, Cyclophosphamide and Dexamethasone Is Well Tolerated in Patients with Relapsed/Refractory Multiple Myeloma Who Have Received One Prior Regimen. 2015;126:1840. Retrieved from ash.confex.com/ash/2015/webprogramscheduler/Paper82080.html
82. Dimopoulos, M.A., Moreau, P., Palumbo, A., et al. Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Patients with Relapsed or Refractory Multiple Myeloma (ENDEAVOR): A Randomised, Phase 3, Open Label, Multicentre Study. *Lancet Oncol*. 2016;17:27-38. Retrieved from ncbi.nlm.nih.gov/pubmed/26671818

83. Dimopoulos, M.A., Goldschmidt, H., Niesvizky, R., et al. Carfilzomib or Bortezomib in Relapsed or Refractory Multiple Myeloma (ENDEAVOR): An Interim Overall Survival Analysis of an Open Label, Randomised, Phase 3 Trial. *Lancet Oncol.* 2017;18:1327-1337. Retrieved from [ncbi.nlm.nih.gov/pubmed/28843768](https://pubmed.ncbi.nlm.nih.gov/28843768)
84. Orłowski, R.Z., Moreau, P., Niesvizky, R., et al. Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety and Subgroups. *Clin Lymphoma Myeloma Leuk.* 2019 Aug;19(8):522-530.e1. DOI: 10.1016/j.clml.2019.04.018. Epub 2019 May 2. PMID: 31160237
85. Morgan, G.J., Schey, S.A., Wu, P., et al. Lenalidomide (Revlimid), in Combination with Cyclophosphamide and Dexamethasone (RCD), Is an Effective and Tolerated Regimen for Myeloma Patients. *Br J Haematol.* 2007;137:268-269. Retrieved from [ncbi.nlm.nih.gov/pubmed/17408469](https://pubmed.ncbi.nlm.nih.gov/17408469)
86. Chari, A., Suvannasankha, A., Fay, J.W., et al. Daratumumab Plus Pomalidomide and Dexamethasone in Relapsed and/or Refractory Multiple Myeloma. *Blood.* 2017;130:974-981. Retrieved from [ncbi.nlm.nih.gov/pubmed/28637662](https://pubmed.ncbi.nlm.nih.gov/28637662)
87. Jakubowiak, A., Offidani, M., Pegourie, B., et al. Randomized Phase 2 Study: Elotuzumab Plus Bortezomib/Dexamethasone vs. Bortezomib/Dexamethasone for Relapsed/Refractory MM. *Blood.* 2016;127:2833-2840. Retrieved from [ncbi.nlm.nih.gov/pubmed/27091875](https://pubmed.ncbi.nlm.nih.gov/27091875)
88. Lonial, S., Dimopoulos, M., Palumbo, A., et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2015;373:621-631. Retrieved from [ncbi.nlm.nih.gov/pubmed/26035255](https://pubmed.ncbi.nlm.nih.gov/26035255)
89. Dimopoulos, M.A., Lonial, S., White, D., et al. Elotuzumab Plus Lenalidomide/Dexamethasone for Relapsed or Refractory Multiple Myeloma: ELOQUENT-2 Follow-Up and Post-Hoc Analyses on Progression-Free Survival and Tumour Growth. *Br J Haematol.* 2017;178:896-905. Retrieved from [ncbi.nlm.nih.gov/pubmed/28677826](https://pubmed.ncbi.nlm.nih.gov/28677826)
90. Dimopoulos, M.A., Lonial, S., White, D., et al. Elotuzumab, Lenalidomide and Dexamethasone in RRMM: Final Overall Survival Results From the Phase 3 Randomized ELOQUENT-2 Study. *Blood Cancer J.* 2020;10:91. Retrieved from [ncbi.nlm.nih.gov/pubmed/32887873](https://pubmed.ncbi.nlm.nih.gov/32887873)
91. Dimopoulos, M.A., Dytfeld, D., Grosicki, S., et al. Elotuzumab Plus Pomalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2018;379:1811-1822. Retrieved from [ncbi.nlm.nih.gov/pubmed/30403938](https://pubmed.ncbi.nlm.nih.gov/30403938)
92. Kumar, S.K., Grzasko, N., Delimpasi, S., et al. Phase 2 Study of All-Oral Ixazomib, Cyclophosphamide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma. *Br J Haematol.* 2019;184:536-546. Retrieved from [ncbi.nlm.nih.gov/pubmed/30460684](https://pubmed.ncbi.nlm.nih.gov/30460684)
93. San-Miguel, J.F., Hungria, V.T., Yoon, S.S., et al. Overall Survival of Patients with Relapsed Multiple Myeloma Treated with Panobinostat or Placebo Plus Bortezomib and Dexamethasone (The PANORAMA 1 Trial): A Randomised, Placebo-Controlled, Phase 3 Trial. *Lancet Haematol.* 2016 Nov;3(11):e506-e515. DOI: 10.1016/S2352-3026(16)30147-8. Epub 2016 Oct 14
94. Richardson, P.G., Schlossman, R.L., Alsina, M., et al. PANORAMA 2: Panobinostat in Combination with Bortezomib and Dexamethasone in Patients with Relapsed and Bortezomib-Refractory Myeloma. *Blood.* 2013;122:2331-2337. Retrieved from [ncbi.nlm.nih.gov/pubmed/23950178](https://pubmed.ncbi.nlm.nih.gov/23950178)
95. Baz, R.C., Martin, T.G., Lin, H.Y., et al. Randomized Multicenter Phase 2 Study of Pomalidomide, Cyclophosphamide and Dexamethasone in Relapsed Refractory Myeloma. *Blood.* 2016;127:2561-2568. Retrieved from [ncbi.nlm.nih.gov/pubmed/26932802](https://pubmed.ncbi.nlm.nih.gov/26932802)

96. Garderet, L., Kuhnowski, F., Berge, B., et al. Pomalidomide, Cyclophosphamide and Dexamethasone for Relapsed Multiple Myeloma. *Blood*. 2018; 132 (24): 2555–2563. Retrieved from DOI.org/10.1182/blood-2018-07-863829
97. Shah, J.J., Stadtmauer, E.A., Abonour, R., et al. Carfilzomib, Pomalidomide and Dexamethasone for Relapsed or Refractory Myeloma. *Blood*. 2015;126:2284-2290. Retrieved from ncbi.nlm.nih.gov/pubmed/26384354
98. Rosenbaum, C.A., Stephens, L.A., Kukreti, V., et al. Phase 1/2 Study of Carfilzomib, Pomalidomide and Dexamethasone (Kpd) in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM): A Multiple Myeloma Research Consortium Multicenter Study. ASCO Meeting Abstracts 2016;34:8007. Retrieved from meeting.ascopubs.org/cgi/content/abstract/34/15_suppl/8007
99. Goldsmith, S., Fiala, M.A., Wang, B.B., et al. Bendamustine in Patients with Quad- and Penta-Refractory Multiple Myeloma. *Blood*. 2018; 132 (Supplement 1): 5627. Retrieved from DOI.org/10.1182/blood-2018-99-112258
100. Mikhael, J.R., Belch, A.R., Prince, H.M., et al. High Response Rate to Bortezomib with or without Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma: Results of a Global Phase 3b Expanded Access Program. *Br J Haematol*. 2009 Jan;144(2):169-75. DOI: 10.1111/j.1365-2141.2008.07409.x. Epub 2008 Nov 19. PMID: 19036114
101. Mikhael, J.R., Reeder, C.B., Libby, E.N., et al. Phase Ib/II Trial of CYKLONE (Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone) for Newly Diagnosed Myeloma. *Br J Haematol*. 2015 Apr;169(2):219-27. DOI: 10.1111/bjh.13296. Epub 2015 Feb 13. PMID: 25683772; PMCID: PMC4521972
102. Usmani, S.Z., Nahi, H., Plesner, T., et al. Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma: Final Results From the Phase 2 GEN501 and SIRIUS Trials. *Lancet Haematol*. 2020 Jun;7(6):e447-e455. DOI: 10.1016/S2352-3026(20)30081-8. PMID: 32470437
103. Park, S., Lee, S.J., Jung, C.W., et al. DCEP for Relapsed or Refractory Multiple Myeloma After Therapy with Novel Agents. *Ann Hematol*. 2014 Jan;93(1):99-105. DOI: 10.1007/s00277-013-1952-5. Epub 2013 Nov 16. PMID: 24240976
104. Lee, C.K., Barlogie, B., Munshi, N., et al. DTPACE: An Effective, Novel Combination Chemotherapy with Thalidomide for Previously Treated Patients with Myeloma. *J Clin Oncol*. 2003 Jul 15;21(14):2732-9. DOI: 10.1200/JCO.2003.01.055. Erratum in: *J Clin Oncol*. 2008 Apr 20;26(12): 2066. PMID: 12860952
105. Srikanth, M., Davies, F.E., Wu, P., et al. Survival and Outcome of Blastoid Variant Myeloma Following Treatment with the Novel Thalidomide Containing Regime DT-PACE. *Eur J Haematol*. 2008 Dec;81(6):432-6. DOI: 10.1111/j.1600-0609.2008.01131.x. Epub 2008 Aug 6. PMID: 18691254
106. Lakshman, A., Singh, P.P., Rajkumar, S.V., et al. Efficacy of VDT PACE-Like Regimens in Treatment of Relapsed/Refractory Multiple Myeloma. *Am J Hematol*. 2018 Feb;93(2):179-186. DOI: 10.1002/ajh.24954. Epub 2017 Nov 10. PMID: 29067723
107. Buda, G., Orciuolo, E., Galimberti, S., et al. VDTPACE as Salvage Therapy for Heavily Pretreated MM Patients. *Blood*. 2013; 122 (21): 5377. Retrieved from DOI.org/10.1182/blood.V122.21.5377.5377
108. Kumar, S.K., LaPlant, B., Roy, V., et al. Phase 2 Trial of Ixazomib in Patients with Relapsed Multiple Myeloma Not Refractory to Bortezomib. *Blood Cancer J*. 2015 Aug 14;5(8):e338. DOI: 10.1038/bcj.2015.60. PMID: 26275080; PMCID: PMC4558585

109. Kumar, S.K., Laplant, B.R., Reeder, C.B., et al. Randomized Phase 2 Trial of Two Different Doses of Ixazomib in Patients with Relapsed Multiple Myeloma Not Refractory to Bortezomib. *Blood*. 2015; 126 (23): 3050. Retrieved from DOI.org/10.1182/blood.V126.23.3050.3050
110. Berdeja, J.G., Hart, L.L., Mace, J.R., et al. Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma. *Haematologica*. 2015 May;100(5):670-6. DOI: 10.3324/haematol.2014.119735. Epub 2015 Feb 20. PMID: 25710456; PMCID: PMC4420216
111. Kaufman, J.L., Mina, R., Jakubowiak, A.J., et al. Combining Carfilzomib and Panobinostat to Treat Relapsed/Refractory Multiple Myeloma: Results of a Multiple Myeloma Research Consortium Phase I Study. *Blood Cancer J*. 2019 Jan 4;9(1):3. DOI: 10.1038/s41408-018-0154-8. PMID: 30610196; PMCID: PMC6320362
112. Chari, A., Cho, H.J., Dhadwal, A., et al. A Phase 2 Study of Panobinostat with Lenalidomide and Weekly Dexamethasone in Myeloma. *Blood Adv*. 2017 Aug 21;1(19):1575-1583. DOI: 10.1182/bloodadvances.2017007427. PMID: 29296798; PMCID: PMC5728465
113. San Miguel, J., Weisel, K., Moreau, P., et al. Pomalidomide Plus Low-Dose Dexamethasone Versus High-Dose Dexamethasone Alone for Patients with Relapsed and Refractory Multiple Myeloma (MM-003): A Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol*. 2013;14:1055–66
114. Dimopoulos, M.A., Palumbo, A., Corradini, P., et al. Safety and Efficacy of Pomalidomide Plus Low-Dose Dexamethasone in STRATUS (MM-010): A Phase 3b Study in Refractory Multiple Myeloma. *Blood*. 2016;128:497–503
115. Chari, A., Vogl, D.T., Gavriatopoulou, M., et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med*. 2019 Aug 22;381(8):727-738. DOI: 10.1056/NEJMoa1903455. PMID: 31433920
116. Kumar, S., Kaufman, J.L., Gasparetto, C., et al. Efficacy of Venetoclax as Targeted Therapy for Relapsed/Refractory T(11;14) Multiple Myeloma. *Blood*. 2017; 130 (22): 2401–2409. Retrieved from DOI.org/10.1182/blood-2017-06-788786
117. Basali, D., Chakraborty, R., Rybicki, L., et al. Real-World Data on Safety and Efficacy of Venetoclax-Based Regimens in Relapsed/Refractory T(11;14) Multiple Myeloma. *Br J Haematol*. 2020 Jun;189(6):1136-1140. DOI: 10.1111/bjh.16454. Epub 2020 Feb 3. PMID: 32012228
118. Giri, S., Grimshaw, A., Bal, S., et al. Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients with High-Risk Cytogenetic Factors: A Systematic Review and Meta-Analysis. *JAMA Oncol*. 2020 Sep 24;6(11):1–8. DOI: 10.1001/jamaoncol.2020.4338. Epub ahead of print. PMID: 32970151; PMCID: PMC7516804
119. Dimopoulos, M., Quach, H., Mateos, M.V., et al. Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Efficacy and Safety Results of the Phase 3 Candor Study. ASH. 2020, Abstract 2325. Retrieved from ash.confex.com/ash/2020/webprogram/Paper137602.html
120. Richardson, P.G., Perrot, A., Sang-Miguel, J.F., et al. Updates From ICARIA-MM, a Phase 3 Study of Isatuximab (Isa) Plus Pomalidomide and Low-Dose Dexamethasone (Pd) Versus Pd in Relapsed and Refractory Multiple Myeloma (RRMM). *J Clin Oncol*. 2021 39:15_suppl, 8017-8017
121. Moreau, P., Dimopoulos, M.A., Mikhael, J., et al.; IKEMA Study Group. Isatuximab, Carfilzomib, and Dexamethasone in Relapsed Multiple Myeloma (IKEMA): A Multicentre, Open-Label, Randomised Phase 3 Trial. *Lancet*. 2021 Jun 19;397(10292):2361-2371. DOI: 10.1016/S0140-6736(21)00592-4. Epub 2021 Jun 4. PMID: 34097854

122. Richardson, P.G., Kumar, S.K., Masszi, T., et al. Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. *J Clin Oncol*. 2021 Aug 1;39(22):2430-2442. DOI: 10.1200/JCO.21.00972. Epub 2021 Jun 11. PMID: 34111952
123. Dimopoulos, M., Weisel, K., Moreau, P., et al. Pomalidomide, Bortezomib, and Dexamethasone for Multiple Myeloma Previously Treated with Lenalidomide (OPTIMISMM): Outcomes by Prior Treatment at First Relapse. *Leukemia*. 2021 Jun;35(6):1722-1731. DOI: 10.1038/s41375-020-01021-3. Epub 2020 Sep 7. PMID: 32895455; PMCID: PMC8179841
124. Lonial, S., Lee, H.C., Badros, A., et al. Longer Term Outcomes with Single-Agent Belantamab Mafodotin in Patients with Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study. *Cancer*. 2021 Nov 15;127(22):4198-4212. DOI: 10.1002/cncr.33809. Epub 2021 Jul 27. PMID: 34314018
125. Dimopoulos, M.A., Dytfeld, D., Grosicki, S., et al. Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Efficacy Results After Additional Follow-Up of the Phase 2, Randomized ELOQUENT-3 Study. Presented at: 2019 EHA Congress; June 13-16, 2019; Amsterdam, Netherlands. Abstract PS1370
126. Gasparetto, C., Lentzsch, S., Schiller, G., et al. Selinexor, Daratumumab, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma. *eJHaem*. 2021; 2: 56– 65. <https://DOI.org/10.1002/jha2.122>
127. Grosicki, S., Simonova, M., Spicka, I., et al. Once-Per-Week Selinexor, Bortezomib, and Dexamethasone Versus Twice-per-Week Bortezomib and Dexamethasone in Patients with Multiple Myeloma (BOSTON): A Randomised, Open-Label, Phase 3 Trial. *Lancet*. 2020 Nov 14;396(10262):1563-1573. DOI: 10.1016/S0140-6736(20)32292-3. PMID: 33189178.
128. Dimopoulos, M.A., Špička, I., Quach, H., et al.; TOURMALINE-MM4 Study Group. Ixazomib as Postinduction Maintenance for Patients with Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial. *J Clin Oncol*. 2020 Dec 1;38(34):4030-4041. DOI: 10.1200/JCO.20.02060. Epub 2020 Oct 6. PMID: 33021870; PMCID: PMC7768338
129. Facon, T., Venner, C.P., Bahlis, N.J., et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma. *Blood*. 2021 Jul 1;137(26):3616-3628. DOI: 10.1182/blood.2020008787. PMID: 33763699; PMCID: PMC8462404
130. Durie, B.G.M., Hoering, A., Sexton, R., et al. Longer-Term Follow-Up of the Randomized Phase III Trial SWOG S0777: Bortezomib, Lenalidomide and Dexamethasone vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT). *Blood Cancer J*. 2020 May 11;10(5):53. DOI: 10.1038/s41408-020-0311-8. PMID: 32393732; PMCID: PMC7214419
131. Landgren et al, Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial, *JAMA Oncology* 7:862-68;2021.
132. Yimer H, Melear J, Faber E, et al. Daratumumab, cyclophosphamide, bortezomib, and dexamethasone for multiple myeloma: final results of the LYRA study. *Leuk Lymphoma*. 2022;63(10):2383-2392. doi:10.1080/10428194.2022.2076847
133. Sidana S, Kumar S, Fraser R, et al. Impact of Induction Therapy with VRD versus VCD on Outcomes in Patients with Multiple Myeloma in Partial Response or Better Undergoing Upfront

- Autologous Stem Cell Transplantation. *Transplant Cell Ther.* 2022;28(2):83.e1-83.e9.
doi:10.1016/j.jtct.2021.10.022Eso
134. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* 2020;21(2):207-221. doi:10.1016/S1470-2045(19)30788-0

Ovarian, Fallopian and Primary Peritoneal Cancer

Neoadjuvant Therapy

- Carboplatin + Paclitaxel**

Adjuvant or Primary Therapy

- Carboplatin + Paclitaxel**

Maintenance Therapy After Primary Therapy

- Olaparib (Germline/Somatic BRCA Mutation Only)
- Niraparib
- Rucaparib

Platinum – Sensitive Recurrent Disease

1st + Subsequent Lines of Therapy

- Carboplatin + Gemcitabine
- Carboplatin + Liposomal Doxorubicin
- Carboplatin + Paclitaxel

Maintenance Therapy After Platinum — Sensitive

- Olaparib
- Niraparib

Platinum — Resistant Recurrent Disease

1st + Subsequent Lines of Therapy

- Gemcitabine
- Liposomal Doxorubicin
- Liposomal Doxorubicin + Bevacizumab
- Paclitaxel (weekly)
- Paclitaxel (weekly) + Bevacizumab
- Tamoxifen

***Only intravenous carboplatin + paclitaxel are pathway regimens.*

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/livibd.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (V2.2023, June 2, 2023). Accessed July 2023. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
3. Wright, A.A., Bohlke, K., Armstrong, D.K., et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016. 34(28): 3460-3473
4. Coleridge, S.L., Bryant, A., Lyons, T.J., et al. Chemotherapy Versus Surgery for Initial Treatment in Advanced Ovarian Epithelial Cancer. *Cochrane Database Syst Rev*. 2019;2019(10):CD005343. Published 2019 Oct 31. DOI:10.1002/14651858.CD005343.pub4
5. Pignata, S., Scambia, G., Ferrandina, G., et al. Carboplatin Plus Paclitaxel Versus Carboplatin Plus Pegylated Liposomal Doxorubicin as First-Line Treatment for Patients with Ovarian Cancer: The MITO-2 Randomized Phase III Trial. *J Clin Oncol*. 2011 Sep 20;29(27):3628-35. DOI: 10.1200/JCO.2010.33.8566. Epub 2011, Aug. 15
6. Bell, J., Brady, M.F., Young, R.C., et al. Randomized Phase III Trial of Three Versus Six Cycles of Adjuvant Carboplatin and Paclitaxel in Early Stage Epithelial Ovarian Carcinoma: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 2006 Sep;102(3):432-9. Epub 2006 Jul 24
7. Vasey, P.A., Jayson, G.C., Gordon, A., et al. Phase III Randomized Trial of Docetaxel-Carboplatin Versus Paclitaxel-Carboplatin as First-Line Chemotherapy for Ovarian Carcinoma. *J Natl Cancer Inst*. 2004 Nov 17;96(22):1682-91. PMID: 15547181 DOI: 10.1093/jnci/djh323
8. Armstrong, D.K., Bundy, B., Wenzel, L., et al. Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. *N Engl J Med*. 2006 Jan 5;354(1):34-43. PMID: 16394300
9. Ozols, R.F., Bundy, B.N., Greer, B.E., Phase III Trial of Carboplatin and Paclitaxel Compared with Cisplatin and Paclitaxel in Patients with Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2003 Sep 1;21(17):3194-200. Epub 2003 Jul 14
10. Bookman, M.A., Brady, M.F., McGuire, W.P., et al. Evaluation of New Platinum-Based Treatment Regimens in Advanced-Stage Ovarian Cancer: A Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol*. 2009 Mar 20;27(9):1419-25. DOI: 10.1200/JCO.2008.19.1684. Epub 2009 Feb 17
11. Clamp, A.R., James, E.C., McNeish, I.A., et al. Weekly Dose-Dense Chemotherapy in First-Line Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma Treatment (ICON8): Primary Progression Free Survival Analysis Results From a GCIG Phase 3 Randomised Controlled Trial. *Lancet*. 2019;394:2084-95
12. Pignata, S., Scambia, G., Katsaros, D., et al. Carboplatin Plus Paclitaxel Once a Week Versus Every 3 Weeks in Patients with Advanced Ovarian Cancer (MITO-7): A Randomised, Multicentre, Open-Label, Phase 3 Trial. *Lancet Oncol*. 2014 Apr;15(4):396-405. DOI: 10.1016/S1470-2045(14)70049-X. Epub 2014 Feb 28
13. Katsumata, N., Yasuda, M., Isonishi, S., et al. Long-Term Results of Dose-Dense Paclitaxel and Carboplatin Versus Conventional Paclitaxel and Carboplatin for Treatment of Advanced Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (JGOG 3016): A Randomised, Controlled, Open-Label Trial. *Lancet Oncol*. 2013 Sep;14(10):1020-6. DOI: 10.1016/S1470-2045(13)70363-2. Epub 2013 Aug 13

14. Perren, T.J., Swart, A.M., Pfisterer, J., et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *N Engl J Med*. 2011 Dec 29;365(26):2484-96. DOI: 10.1056/NEJMoa1103799
15. Oza, A.M., Cook, A.D., Pfisterer, J., Standard Chemotherapy with or without Bevacizumab for Women with Newly Diagnosed Ovarian Cancer (ICON7): Overall Survival Results of a Phase 3 Randomised Trial. *Lancet Oncol*. 2015 Aug;16(8):928-36. DOI: 10.1016/S1470-2045(15)00086-8. Epub 2015 Jun 23
16. Burger, R.A., Brady, M.F., Bookman, M.A., et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. *N Engl J Med*. 2011 Dec 29;365(26):2473-83. DOI: 10.1056/NEJMoa1104390
17. Burger, R.A., Brady, M.F., Rhee, J., et al. Independent Radiologic Review of the Gynecologic Oncology Group Study 0218, a Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer. *Gynecol Oncol*. 2013 Oct;131(1):21-6. DOI: 10.1016/j.ygyno.2013.07.100. Epub 2013 Jul 29
18. Monk, B.J., Huang, H.Q., Burger, R.A., et al. Patient-Reported Outcomes of a Randomized, Placebo-Controlled Trial of Bevacizumab in the Front-Line Treatment of Ovarian Cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 2013 Mar;128(3):573-8. DOI: 10.1016/j.ygyno.2012.11.038. Epub 2012 Dec 4
19. Tewari, K.S., Burger, R.A., Enserro, D., et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. *J Clin Oncol*. 2019; 37: 2317-2328
20. Von Gruenigen, V.E., Huang, H.Q., Beumer, J.H., et al. Chemotherapy Completion in Elderly Women with Ovarian, Primary Peritoneal or Fallopian Tube Cancer — an NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. 2017; 144(3): 459-467
21. Gonzalez-Martin, A., Pothuri, B., Vergote, I., et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019; 381: 2391-2402
22. Moore, K., Colombo, N., Scambia, G., et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018; 379: 2495-2505
23. Ray-Coquard, I., Pautier, P., Pignata, S., et al. Olaparib Plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019; 381: 2416-2428
24. Falandry, C., Savoye, A.M., Stefani, L., et al. EWOC-1: A Randomized Trial to Evaluate the Feasibility of Three Different First-Line Chemotherapy Regimens for Vulnerable Elderly Women with Ovarian Cancer (OC): A GCIG-ENGOT-GINECO Study. *J Clin Oncol*. 2019; 37: 5508-5508
25. Walker, J.L., Brady, M.F., Wenzel, L., et al. Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study [published correction appears in *J Clin Oncol*. 2019 Sep 1;37(25):2299]. *J Clin Oncol*. 2019;37(16):1380-1390. DOI:10.1200/JCO.18.01568
26. Alsop, K., Fereday, S., Meldrum, C., et al. BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation-Positive Women with Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012; 30: 2654–63
27. Spellman, et al., Cancer Genome Atlas Research Network. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature*. 2011; 474: 609–15
28. Zhang, S., Royer, R., Li, S., et al. Frequencies of BRCA1 and BRCA2 Mutations Among 1,342 Unselected Patients with Invasive Ovarian Cancer. *Gynecol Oncol*. 2011; 121: 353–57
29. Dann, R.B., DeLoia, J.A., Timms, K.M., et al. BRCA1/2 Mutations and Expression: Response to Platinum Chemotherapy in Patients with Advanced Stage Epithelial Ovarian Cancer. *Gynecol Oncol*. 2012; 125: 677–82

30. Pfisterer, J., Plante, M., Vergote, I., et al. Gemcitabine Plus Carboplatin Compared with Carboplatin in Patients with Platinum-Sensitive Recurrent Ovarian Cancer: An Intergroup Trial of the AGO-OVAR, the NCIC CTG and the EORTC GCG. *J Clin Oncol.* 2006;24(29):4699–4707. DOI:10.1200/JCO.2006.06.0913
31. Aghajanian, C., Blank, S.V., Goff, B.A., et al. OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy with or without Bevacizumab in Patients with Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer. *J Clin Oncol.* 2012;30(17):2039–2045. DOI:10.1200/JCO.2012.42.0505
32. Sehouli, J., Chekerov, R., Reinthaller, A., et al. Topotecan Plus Carboplatin Versus Standard Therapy with Paclitaxel Plus Carboplatin (PC) or Gemcitabine Plus Carboplatin (GC) or Pegylated Liposomal Doxorubicin Plus Carboplatin (PLDC): A Randomized Phase III Trial of the NOGGO-AGO-Study Group-AGO Austria and GEICO-ENGOT-GCIG Intergroup Study (HECTOR). *Ann Oncol.* 2016;27(12):2236–2241. DOI:10.1093/annonc/mdw418
33. Pujade-Lauraine, E., Wagner, U., Aavall-Lundqvist, E., et al. Pegylated Liposomal Doxorubicin and Carboplatin Compared with Paclitaxel and Carboplatin for Patients with Platinum-Sensitive Ovarian Cancer in Late Relapse. *J Clin Oncol.* 2010;28(20):3323–3329. DOI:10.1200/JCO.2009.25.7519
34. Wagner, U., Marth, C., Largillier, R., et al. Final Overall Survival Results of Phase III GCIG CALYPSO Trial of Pegylated Liposomal Doxorubicin and Carboplatin vs. Paclitaxel and Carboplatin in Platinum-Sensitive Ovarian Cancer Patients. *Br J Cancer.* 2012;107(4):588–591. DOI:10.1038/bjc.2012.307
35. Pfisterer, J., Dean, A.P., Baumann, K., et al. Carboplatin/Pegylated Liposomal Doxorubicin/Bevacizumab (CD-BEV) vs. Carboplatin/Gemcitabine/Bevacizumab (CG-BEV) in Patients with Recurrent Ovarian Cancer: A Prospective Randomized Phase III ENGOT/GCIG-Intergroup Study (AGO study group, AGO-Austria, ANZGOG, GINECO, SGCTG). *Ann Oncol.* 2018;29 Suppl 8:viii332–viii333. DOI:10.1093/annonc/mdy285.142
36. Parmar, M.K., Ledermann, J.A., Colombo, N., et al. Paclitaxel Plus Platinum-Based Chemotherapy Versus Conventional Platinum-Based Chemotherapy in Women with Relapsed Ovarian Cancer: The ICON4/AGO-OVAR-2.2 trial. *Lancet.* 361:2099-2106, 2003
37. Coleman, R.L., Brady, M.F., Herzog, T.J., et al. Bevacizumab and Paclitaxel-Carboplatin Chemotherapy and Secondary Cytoreduction in Recurrent, Platinum-Sensitive Ovarian Cancer (NRG Oncology/Gynecologic Oncology Group Study GOG-0213): A Multicentre, Open-Label, Randomised, Phase 3 Trial. *Lancet Oncol.* 2017;18(6):779–791. DOI:10.1016/S1470-2045(17)30279-6
38. Rose, P.G., Mossbrugger, K., Fusco, N., et al. Gemcitabine Reverses Cisplatin Resistance: Demonstration of Activity in Platinum- and Multidrug-Resistant Ovarian and Peritoneal Carcinoma. *Gynecol Oncol.* 2003;88(1):17–21. DOI:10.1006/gyno.2002.6850
39. Strauss, H.G., Henze, A., Teichmann, A., et al. Phase II Trial of Docetaxel and Carboplatin in Recurrent Platinum-Sensitive Ovarian, Peritoneal and Tubal Cancer. *Gynecol Oncol.* 2007;104(3):612–616. DOI:10.1016/j.ygyno.2006.09.023
40. Kushner, D.M., Connor, J.P., Sanchez, F., et al. Weekly Docetaxel and Carboplatin for Recurrent Ovarian and Peritoneal Cancer: A Phase II Trial. *Gynecol Oncol.* 2007;105(2):358–364. DOI:10.1016/j.ygyno.2006.12.018
41. Alvarez Secord, A., Berchuck, A., Higgins, R.V., et al. A Multicenter, Randomized, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of Combination Docetaxel and Carboplatin and Sequential Therapy with Docetaxel Then Carboplatin in Patients with Recurrent Platinum-Sensitive Ovarian Cancer. *Cancer.* 2012;118(13):3283–3293. DOI:10.1002/cncr.26610

42. Burger, R.A., Sill, M.W., Monk, B.J., et al. Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study [published correction appears in *J Clin Oncol*. 2014 Nov 10;32(32):3686]. *J Clin Oncol*. 2007;25(33):5165–5171. DOI:10.1200/JCO.2007.11.5345
43. Moore, K.N., Secord, A.A., Geller, M.A., et al. Niraparib Monotherapy for Late-Line Treatment of Ovarian Cancer (QUADRA): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial [published correction appears in *Lancet Oncol*. 2019 May;20(5):e242]. *Lancet Oncol*. 2019;20(5):636–648. DOI:10.1016/S1470-2045(19)30029-4
44. Mirza, M.R., Monk, B., Herrstedt, J., et al. (2016, Dec. 1). Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer: *N Engl J Med*. Retrieved from nejm.org/DOI/full/10.1056/NEJMoa1611310
45. Domchek, S.M., Aghajanian, C., Shapira-Frommer, R., et al. Efficacy and Safety of Olaparib Monotherapy in Germline BRCA1/2 Mutation Carriers with Advanced Ovarian Cancer and Three or More Lines of Prior Therapy. *Gynecol Oncol*. 2016;140(2):199–203. DOI:10.1016/j.ygyno.2015.12.020
46. Kaufman, B., Shapira-Frommer, R., Schmutzler, R.K., et al. Olaparib Monotherapy in Patients with Advanced Cancer and a Germline BRCA1/2 Mutation. *J Clin Oncol*. 2015;33(3):244–250. DOI:10.1200/JCO.2014.56.2728
47. Pujade-Lauraine, E., Ledermann, J.A., Selle, F., et al. Olaparib Tablets as Maintenance Therapy in Patients with Platinum-Sensitive, Relapsed Ovarian Cancer and a BRCA1/2 Mutation (SOLO2/ENGOT-Ov21): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial [published correction appears in *Lancet Oncol*. 2017 Sep;18(9):e510]. *Lancet Oncol*. 2017;18(9):1274–1284. DOI:10.1016/S1470-2045(17)30469-2
48. Coleman, R.L., Oza, A.M., Lorusso, D., et al. Rucaparib Maintenance Treatment for Recurrent Ovarian Carcinoma After Response to Platinum Therapy (ARIEL3): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial [published correction appears in *Lancet*. 2017 Oct 28;390(10106):1948]. *Lancet*. 2017;390(10106):1949–1961. DOI:10.1016/S0140-6736(17)32440-6
49. Swisher, E.M., Lin, K.K., Oza, A.M., et al. Rucaparib in Relapsed, Platinum-Sensitive High-Grade Ovarian Carcinoma (ARIEL2 Part 1): An International, Multicentre, Open-Label, Phase 2 Trial. *Lancet Oncol*. 2017;18(1):75–87. DOI:10.1016/S1470-2045(16)30559-9
50. Friedlander, M., Hancock, K.C., Rischin, D., et al. A Phase II, Open-Label Study Evaluating Pazopanib in Patients with Recurrent Ovarian Cancer. *Gynecol Oncol*. 2010;119(1):32–37. DOI:10.1016/j.ygyno.2010.05.033
51. Mirza, M.R., Ávall Lundqvist, E., Birrer, M.J., et al. Niraparib Plus Bevacizumab Versus Niraparib Alone for Platinum-Sensitive Recurrent Ovarian Cancer (NSGO-AVANOVA2/ENGOT-ov24): A Randomised, Phase 2, Superiority Trial. *Lancet Oncol*. 2019;20(10):1409–1419. DOI:10.1016/S1470-2045(19)30515-7
52. Sugiyama, T., Okamoto, A., Enomoto, T., et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared with Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial. *J Clin Oncol*. 2016;34(24):2881–2887. DOI:10.1200/JCO.2016.66.9010
53. Benigno, B.B., Burrell, M.O., Daugherty, P., et al. (2016). A Phase II Nonrandomized Study of Nab-Paclitaxel Plus Carboplatin in Patients with Recurrent Platinum-Sensitive Ovarian or Primary Peritoneal Cancer. Retrieved from ascopubs.org/DOI/abs/10.1200/jco.2010.28.15_suppl.5011

54. Wolf, J.K., Bodurka, D.C., Verschraegen, C., et al. A Phase II Trial of Oral Capecitabine in Patients with Platinum — and Taxane — Refractory Ovarian, Fallopian Tube or Peritoneal Cancer. *Gynecol Oncol.* 2006;102(3):468–474. DOI:10.1016/j.ygyno.2005.12.040
55. Ferrandina, G., Corrado, G., Mascilini, F., et al. Metronomic Oral Cyclophosphamide (MOC) in the Salvage Therapy of Heavily Treated Recurrent Ovarian Cancer Patients: A Retrospective, Multicenter Study. *BMC Cancer* 14, 947 (2014). Retrieved from DOI.org/10.1186/1471-2407-14-947
56. Markman, M., Hakes, T., Reichman, B., et al. Ifosfamide and Mesna in Previously Treated Advanced Epithelial Ovarian Cancer: Activity in Platinum-Resistant Disease. *J Clin Oncol.* 1992;10(2):243–248. DOI:10.1200/JCO.1992.10.2.243
57. Matsumoto, K., Katsumata, N., Yamanaka, Y., et al. The Safety and Efficacy of the Weekly Dosing of Irinotecan for Platinum- and Taxanes-Resistant Epithelial Ovarian Cancer. *Gynecol Oncol.* 2006;100(2):412–416. DOI:10.1016/j.ygyno.2005.10.013
58. Wadler, S., Yeap, B., Vogl, S., et al. Randomized Trial of Initial Therapy with Melphalan Versus Cisplatin-Based Combination Chemotherapy in Patients with Advanced Ovarian Carcinoma: Initial and Long-Term Results — Eastern Cooperative Oncology Group Study E2878. *Cancer.* 1996;77(4):733–742
59. Chollet, P., Bensmaïne, M.A., Brienza, S., et al. Single-Agent Activity Of Oxaliplatin in Heavily Pretreated Advanced Epithelial Ovarian Cancer. *Ann Oncol.* 1996;7(10):1065–1070. DOI:10.1093/oxfordjournals.annonc.a010500
60. Omura, G.A., Brady, M.F., Look, K.Y., et al. Phase III Trial of Paclitaxel at Two Dose Levels, the Higher Dose Accompanied by Filgrastim at Two Dose Levels in Platinum-Pretreated Epithelial Ovarian Cancer: An Intergroup Study. *J Clin Oncol.* 2003;21(15):2843–2848. DOI:10.1200/JCO.2003.10.082
61. Teneriello, M.G., Tseng, P.C., Crozier, M., et al. Phase II Evaluation of Nanoparticle Albumin-Bound Paclitaxel in Platinum-Sensitive Patients with Recurrent Ovarian, Peritoneal, or Fallopian Tube Cancer. *J Clin Oncol.* 2009;27(9):1426–1431. DOI:10.1200/JCO.2008.18.9548
62. Miller, D.S., Blessing, J.A., Krasner, C.N., et al. Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group. *J Clin Oncol.* 2009;27(16):2686–2691. DOI:10.1200/JCO.2008.19.2963
63. Rothenberg, M.L., Liu, P.Y., Wilczynski, S., et al. Phase II Trial of Vinorelbine for Relapsed Ovarian Cancer: A Southwest Oncology Group Study. *Gynecol Oncol.* 2004;95(3):506–512. DOI:10.1016/j.ygyno.2004.09.004
64. Bajetta, E., Di Leo, A., Biganzoli, L., et al. Phase II Study of Vinorelbine in Patients with Pretreated Advanced Ovarian Cancer: Activity in Platinum-Resistant Disease. *J Clin Oncol.* 1996;14(9):2546–2551. DOI:10.1200/JCO.1996.14.9.2546
65. Smyth, J.F., Gourley, C., Walker, G., et al. Antiestrogen Therapy Is Active in Selected Ovarian Cancer Cases: The Use of Letrozole in Estrogen Receptor-Positive Patients. *Clin Cancer Res.* 2007;13(12):3617–3622. DOI:10.1158/1078-0432.CCR-06-2878
66. Ramirez, P.T., Schmeler, K.M., Milam, M.R., et al. Efficacy of Letrozole in the Treatment of Recurrent Platinum- and Taxane-Resistant High-Grade Cancer of the Ovary or Peritoneum. *Gynecol Oncol.* 2008;110(1):56–59. DOI:10.1016/j.ygyno.2008.03.014
67. del Carmen, M.G., Fuller, A.F., Matulonis, U., et al. Phase II Trial of Anastrozole in Women with Asymptomatic Müllerian Cancer. *Gynecol Oncol.* 2003;91(3):596–602. DOI:10.1016/j.ygyno.2003.08.021

68. Bonaventura, A., O'Connell, R.L., Mapagu, C., et al. Paragon (ANZGOG-0903): Phase 2 Study of Anastrozole in Women with Estrogen or Progesterone Receptor-Positive Platinum-Resistant or Refractory Recurrent Ovarian Cancer. *Int J Gynecol Cancer*. 2017;27(5):900–906. DOI:10.1097/IGC.0000000000000978
69. Williams, C., Simer, I., Bryant, A., et al. Tamoxifen for Relapse of Ovarian Cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD001034. DOI: 10.1002/14651858.CD001034.pub2
70. Sikic, B.I., Scudder, S.A., Ballon, S.C., et al. High-Dose Megestrol Acetate Therapy of Ovarian Carcinoma: A Phase II Study by the Northern California Oncology Group. *Semin Oncol*. 1986;13(4 Suppl 4):26–32
71. Argenta, P.A., Thomas, S.G., Judson, P.L., et al. A Phase II Study of Fulvestrant in the Treatment of Multiply-Recurrent Epithelial Ovarian Cancer. *Gynecol Oncol*. 2009;113(2):205–209. DOI:10.1016/j.ygyno.2009.01.012
72. Jin, W. Roles of TrkC Signaling in the Regulation of Tumorigenicity and Metastasis of Cancer. *Cancers*. 2020, 12, 147
73. Gershenson, D.M., Miller, A., Brade, W., et al. (2019). LBA61A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer. Retrieved from researchgate.net/publication/336195140_LBA61A_randomized_phase_IIIII_study_to_assess_the_efficacy_of_trametinib_in_patients_with_recurrent_or_progressive_low_grade_serous_ovarian_or_peritoneal_cancer
74. Le, D.T., Durham, J.N., Smith, K.N., et al. Mismatch Repair Deficiency Predicts Response of Solid Tumors to PD-1 Blockade. *Science*. 2017;357(6349):409–413. DOI:10.1126/science.aan6733
75. Diaz, L., Marabelle, A., et al. Efficacy of Pembrolizumab in Phase 2 KEYNOTE-164 and KEYNOTE-158 Studies of Microsatellite Instability High Cancers Presented at the European Society for Medical Oncology Congress; Madrid, Spain; 8-12 September 2017. Poster 386P
76. Falandry, C., Savoye, A.M., Stefani, L., et al. EWOC-1: A Randomized Trial to Evaluate the Feasibility of Three Different First-Line Chemotherapy Regimens for Vulnerable Elderly Women with Ovarian Cancer (OC): A GCIG-ENGOT-GINECO Study. *J Clin Oncol*. 2019; 37: 5508-5508
77. Walker, J.L., Brady, M.F., Wenzel, L., et al. Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study [published correction appears in *J Clin Oncol*. 2019 Sep 1;37(25):2299]. *J Clin Oncol*. 2019;37(16):1380-1390. DOI:10.1200/JCO.18.01568
78. Barber, E.L., Zsiros, E., Lurain, J.R., et al. The Combination of Intravenous Bevacizumab and Metronomic Oral Cyclophosphamide Is an Effective Regimen for Platinum-Resistant Recurrent Ovarian Cancer. *J Gynecol Oncol*. 2013;24(3):258-264. DOI:10.3802/jgo.2013.24.3.258
79. Garcia, A.A., Hirte, H., Fleming, G., et al. Phase II Clinical Trial of Bevacizumab and Low-Dose Metronomic Oral Cyclophosphamide in Recurrent Ovarian Cancer: A Trial of the California, Chicago and Princess Margaret Hospital Phase II Consortia. *J Clin Oncol*. 2008;26(1):76-82. DOI:10.1200/JCO.2007.12.1939
80. Rose, P.G., Blessing, J.A., Ball, H.G., et al. A Phase II Study of Docetaxel in Paclitaxel-Resistant Ovarian and Peritoneal Carcinoma: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 2003;88(2):130-135. DOI:10.1016/s0090-8258(02)00091-4
81. Verschraegen, C.F., Sittisomwong, T., Kudelka, A.P., et al. Docetaxel for Patients with Paclitaxel-Resistant Müllerian Carcinoma. *J Clin Oncol*. 2000;18(14):2733-2739. DOI:10.1200/JCO.2000.18.14.2733

82. Kavanagh, J.J., Kudelka, A.P., de Leon, C.G., et al. Phase II Study of Docetaxel in Patients with Epithelial Ovarian Carcinoma Refractory to Platinum. *Clin Cancer Res.* 1996;2(5):837-842
83. Rose, P.G., Blessing, J.A., Mayer, A.R., et al. Prolonged Oral Etoposide as Second-Line Therapy for Platinum-Resistant and Platinum-Sensitive Ovarian Carcinoma: A Gynecologic Oncology Group Study. *J Clin Oncol.* 1998;16(2):405-410. DOI:10.1200/JCO.1998.16.2.405
84. Mutch, D.G., Orlando, M., Goss, T., et al. Randomized Phase III Trial of Gemcitabine Compared with Pegylated Liposomal Doxorubicin in Patients with Platinum-Resistant Ovarian Cancer. *J Clin Oncol.* 2007;25(19):2811-2818. DOI:10.1200/JCO.2006.09.6735
85. Ferrandina, G., Ludovisi, M., Lorusso, D., et al. Phase III Trial of Gemcitabine Compared with Pegylated Liposomal Doxorubicin in Progressive or Recurrent Ovarian Cancer. *J Clin Oncol.* 2008;26(6):890-896. DOI:10.1200/JCO.2007.13.6606
86. Gordon, A.N., Fleagle, J.T., Guthrie, D., et al. Recurrent Epithelial Ovarian Carcinoma: A Randomized Phase III Study of Pegylated Liposomal Doxorubicin Versus Topotecan. *J Clin Oncol.* 2001;19(14):3312-3322. DOI:10.1200/JCO.2001.19.14.3312
87. Pujade-Lauraine, E., Hilpert, F., Weber, B., et al. Bevacizumab Combined with Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial [published correction appears in *J Clin Oncol.* 2014 Dec 10;32(35):4025]. *J Clin Oncol.* 2014;32(13):1302-1308. DOI:10.1200/JCO.2013.51.4489
88. Gynecologic Oncology Group, Markman, M., Blessing, J., et al. Phase II Trial of Weekly Paclitaxel (80 Mg/M2) in Platinum and Paclitaxel-Resistant Ovarian and Primary Peritoneal Cancers: A Gynecologic Oncology Group Study. *Gynecol Oncol.* 2006;101(3):436-440. DOI:10.1016/j.ygyno.2005.10.036
89. Pignata, S., Lorusso, D., Scambia, G., et al. Pazopanib Plus Weekly Paclitaxel Versus Weekly Paclitaxel Alone for Platinum-Resistant or Platinum-Refractory Advanced Ovarian Cancer (MITO 11): A Randomized, Open-Label, Phase 2 Trial. *Lancet Oncol.* 2015;16(5):561-568. DOI:10.1016/S1470-2045(15)70115-4
90. Coleman, R.L., Brady, W.E., McMeekin, D.S., et al. A Phase II Evaluation of Nanoparticle, Albumin-Bound (Nab) Paclitaxel in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol.* 2011;122(1):111-115. DOI:10.1016/j.ygyno.2011.03.036
91. McGonigle, K.F., Muntz, H.G., Vuky, J., et al. Combined Weekly Topotecan and Biweekly Bevacizumab in Women with Platinum-Resistant Ovarian, Peritoneal or Fallopian Tube Cancer: Results of a Phase 2 Study. *Cancer.* 2011;117(16):3731-3740. DOI:10.1002/cncr.25967
92. Wolf, J.K., Bodurka, D.C., Verschraegen, C., et al. A Phase II Trial of Oral Capecitabine in Patients with Platinum — and Taxane — Refractory Ovarian, Fallopian Tube or Peritoneal Cancer. *Gynecol Oncol.* 2006;102(3):468-474. DOI:10.1016/j.ygyno.2005.12.040
93. Ferrandina, G., Corrado, G., Mascilini, F., et al. Metronomic Oral Cyclophosphamide (MOC) in the Salvage Therapy of Heavily Treated Recurrent Ovarian Cancer Patients: A Retrospective, Multicenter Study. *BMC Cancer* 14, 947 (2014). Retrieved from DOI.org/10.1186/1471-2407-14-947
94. Markman, M., Hakes, T., Reichman, B., et al. Ifosfamide and Mesna in Previously Treated Advanced Epithelial Ovarian Cancer: Activity in Platinum-Resistant Disease. *J Clin Oncol.* 1992;10(2):243-248. DOI:10.1200/JCO.1992.10.2.243
95. Matsumoto, K., Katsumata, N., Yamanaka, Y., et al. The Safety and Efficacy of the Weekly Dosing of Irinotecan for Platinum- and Taxanes-Resistant Epithelial Ovarian Cancer. *Gynecol Oncol.* 2006;100(2):412-416. DOI:10.1016/j.ygyno.2005.10.013

96. Fracasso, P.M., Blessing, J.A., Morgan, M.A., et al. Phase II Study of Oxaliplatin in Platinum-Resistant and Refractory Ovarian Cancer: A Gynecologic Group Study. *J Clin Oncol*. 2003;21(15):2856–2859. DOI:10.1200/JCO.2003.03.077
97. Miller, D.S., Blessing, J.A., Krasner, C.N., et al. Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group. *J Clin Oncol*. 2009;27(16):2686–2691. DOI:10.1200/JCO.2008.19.2963
98. Chekerov, R., Hilpert, F., Mahner, S., et al. Sorafenib Plus Topotecan Versus Placebo Plus Topotecan for Platinum-Resistant Ovarian Cancer (TRIAS): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial. *Lancet Oncol*. 2018;19(9):1247–1258. DOI:10.1016/S1470-2045(18)30372-3
99. Rothenberg, M.L., Liu, P.Y., Wilczynski, S., et al. Phase II Trial of Vinorelbine for Relapsed Ovarian Cancer: A Southwest Oncology Group Study. *Gynecol Oncol*. 2004;95(3):506–512. DOI:10.1016/j.ygyno.2004.09.004
100. Bajetta, E., Di Leo, A., Biganzoli, L., et al. Phase II Study of Vinorelbine in Patients with Pretreated Advanced Ovarian Cancer: Activity in Platinum-Resistant Disease. *J Clin Oncol*. 1996;14(9):2546–2551. DOI:10.1200/JCO.1996.14.9.2546
101. Moore, K.N., Secord, A.A., Geller, M.A., et al. Niraparib Monotherapy for Late-Line Treatment of Ovarian Cancer (QUADRA): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial [published correction appears in *Lancet Oncol*. 2019 May;20(5):e242]. *Lancet Oncol*. 2019;20(5):636–648. DOI:10.1016/S1470-2045(19)30029-4
102. Kaufman, B., Shapira-Frommer, R., Schmutzler, R.K., et al. Olaparib Monotherapy in Patients with Advanced Cancer and a Germline BRCA1/2 Mutation. *J Clin Oncol*. 2015;33(3):244–250. DOI:10.1200/JCO.2014.56.2728
103. Swisher, E.M., Lin, K.K., Oza, A.M., et al. Rucaparib in Relapsed, Platinum-Sensitive High-Grade Ovarian Carcinoma (ARIEL2 Part 1): An International, Multicentre, Open-Label, Phase 2 Trial. *Lancet Oncol*. 2017;18(1):75–87. DOI:10.1016/S1470-2045(16)30559-9
104. Dal Molin, G.Z., Westin, S.N., Coleman, R.L. Rucaparib in Ovarian Cancer: Extending the Use of PARP Inhibitors in the Recurrent Disease. *Future Oncol*. 2018;14(30):3101-3110. DOI:10.2217/fo-2018-0215
105. Burger, R.A., Sill, M.W., Monk, B.J., et al. Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study [published correction appears in *J Clin Oncol*. 2014 Nov 10;32(32):3686]. *J Clin Oncol*. 2007;25(33):5165–5171. DOI:10.1200/JCO.2007.11.5345
106. Cannistra, S.A., Matulonis, U.A., Penson, R.T., et al. Phase II Study of Bevacizumab in Patients with Platinum-Resistant Ovarian Cancer or Peritoneal Serous Cancer [published correction appears in *J Clin Oncol*. 2008 Apr 1;26(10):1773]. *J Clin Oncol*. 2007;25(33):5180–5186. DOI:10.1200/JCO.2007.12.0782
107. Friedlander, M., Hancock, K.C., Rischin, D., et al. A Phase II, Open-Label Study Evaluating Pazopanib in Patients with Recurrent Ovarian Cancer. *Gynecol Oncol*. 2010;119(1):32–37. DOI:10.1016/j.ygyno.2010.05.033
108. Jin, W. Roles of TrkC Signaling in the Regulation of Tumorigenicity and Metastasis of Cancer. *Cancers*. 2020, 12, 147
109. Gershenson, D.M., Miller, A., Brade, W., et al. (2019). LBA61A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer. Retrieved from researchgate.net/publication/

- 336195140_LBA61A_randomized_phase_III_study_to_assess_the_efficacy_of_trametinib_in_patients_with_recurrent_or_progressive_low-grade_serous_ovarian_or_peritoneal_cancer
110. Argenta, P.A., Thomas, S.G., Judson, P.L., et al. A Phase II Study of Fulvestrant in the Treatment of Multiply-Recurrent Epithelial Ovarian Cancer. *Gynecol Oncol.* 2009;113(2):205–209. DOI:10.1016/j.ygyno.2009.01.012
 111. Smyth, J.F., Gourley, C., Walker, G., et al. Antiestrogen Therapy Is Active in Selected Ovarian Cancer Cases: The Use of Letrozole in Estrogen Receptor-Positive Patients. *Clin Cancer Res.* 2007;13(12):3617–3622. DOI:10.1158/1078-0432.CCR-06-2878
 112. del Carmen, M.G., Fuller, A.F., Matulonis, U., et al. Phase II Trial of Anastrozole in Women with Asymptomatic Müllerian Cancer. *Gynecol Oncol.* 2003;91(3):596–602. DOI:10.1016/j.ygyno.2003.08.021
 113. Bonaventura, A., O'Connell, R.L., Mapagu, C., et al. Paragon (ANZGOG-0903): Phase 2 Study of Anastrozole in Women with Estrogen or Progesterone Receptor-Positive Platinum-Resistant or Refractory Recurrent Ovarian Cancer. *Int J Gynecol Cancer.* 2017;27(5):900–906. DOI:10.1097/IGC.0000000000000978
 114. Lindemann, K., Gibbs, E., Åvall-Lundqvist, E., et al. Chemotherapy vs. Tamoxifen in Platinum-Resistant Ovarian Cancer: A Phase III, Randomised, Multicentre Trial (Ovaresist). *Br J Cancer.* 2017;116(4):455–463. DOI:10.1038/bjc.2016.435
 115. Marinaccio, M., D'Addario, V., Serrati, A., et al. Leuprolide Acetate as a Salvage-Therapy in Relapsed Epithelial Ovarian Cancer. *Eur J Gynaecol Oncol.* 1996;17(4):286–288
 116. Sikic, B.I., Scudder, S.A., Ballon, S.C., et al. High-Dose Megestrol Acetate Therapy of Ovarian Carcinoma: A Phase II Study by the Northern California Oncology Group. *Semin Oncol.* 1986;13(4 Suppl 4):26–32
 117. Falandry, C., Savoye, A.M., Stefani, L., et al. EWOC-1: A Randomized Trial to Evaluate the Feasibility of Three Different First-Line Chemotherapy Regimens for Vulnerable Elderly Women with Ovarian Cancer (OC): A GCIG-ENGOT-GINECO Study. *J Clin Oncol.* 2019; 37: 5508-5508
 118. Walker, J.L., Brady, M.F., Wenzel, L., et al. Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study [published correction appears in *J Clin Oncol.* 2019 Sep 1;37(25):2299]. *J Clin Oncol.* 2019;37(16):1380-1390. DOI:10.1200/JCO.18.01568
 119. Banerjee, S., Moore, K.N., Colombo, N., et al. Maintenance Olaparib for Patients with Newly Diagnosed, Advanced Ovarian Cancer and a BRCA Mutation: 5-Year Follow-Up from SOLO-1. ESMO Virtual Congress 2020. Abstract 811MO. Presented Sept. 18, 2020
 120. Hardesty, M.M., Krivak, T., Wright, G.S., et al. Phase 2 OVARIO Study of Niraparib Plus Bevacizumab Therapy in Advanced Ovarian Cancer Following Frontline Platinum-Base Chemotherapy with Bevacizumab. Society of Gynecologic Oncology Virtual Annual Meeting on Women's Cancer. Poster 22. Presented March 19, 2021
 121. Matulonis, U.A., Herrstedt, J., Oza, A., et al. Long-Term Safety and Secondary Efficacy Endpoints in the ENGOT-OV16/NOVA Phase 3 Trial Of Niraparib in Recurrent Ovarian Cancer. Presented at: Society of Gynecological Oncology 2021 Virtual Annual Meeting on Women's Cancer; March 19–21, 2021; Virtual. Abstract 37.
 122. Ledermann, J.A., Oza, A.M., Lorusso, D., et al. Rucaparib for Patients with Platinum-Sensitive, Recurrent Ovarian Carcinoma (ARIEL3): Post-Progression Outcomes and Updated Safety Results From a Randomised, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol.* 2020 May;21(5):710-722. DOI: 10.1016/S1470-2045(20)30061-9. PMID: 32359490

123. Kristeleit, R., Lisyanskaya, A., Fedenko, A., et al. Rucaparib Versus Chemotherapy in Patients with Advanced, Relapsed Ovarian Cancer and a Deleterious BRCA Mutation: Efficacy and Safety From ARIEL4, a Randomized Phase 3 Study. Presented at: Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women's Cancer; March 19–25, 2021; Virtual. Abstract 11479
124. Herzog TJ, Monk BJ, Rose PG, et al. A phase II trial of oxaliplatin, docetaxel, and bevacizumab as first-line therapy of advanced cancer of the ovary, peritoneum, and fallopian tube. *Gynecol Oncol*. 2014;132(3):517-525. DOI:10.1016/j.ygyno.2014.01.035
125. Khemapech N, Oranratanaphan S, Termrungruanglert W, Lertkhachonsuk R, Vasurattana A. Salvage chemotherapy in recurrent platinum-resistant or refractory epithelial ovarian cancer with Carboplatin and distearoylphosphatidylcholine pegylated liposomal Doxorubicin (lipo-dox®). *Asian Pac J Cancer Prev*. 2013;14(3):2131-2135. DOI:10.7314/apjcp.2013.14.3.2131
126. Havrilesky LJ, Alvarez AA, Sayer RA, et al. Weekly low-dose carboplatin and paclitaxel in the treatment of recurrent ovarian and peritoneal cancer. *Gynecol Oncol*. 2003;88(1):51-57. DOI:10.1006/gyno.2002.6859
127. Sharma R, Graham J, Mitchell H, Brooks A, Blagden S, Gabra H. Extended weekly dose-dense paclitaxel/carboplatin is feasible and active in heavily pre-treated platinum-resistant recurrent ovarian cancer. *Br J Cancer*. 2009;100(5):707-712. DOI:10.1038/sj.bjc.6604914
128. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699-4707
129. Parmar MK, Ledermann JA, Colombo N, et al: Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. *Lancet*. 361::2099,2003-2106
130. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol*. 2010;28:3323- 3329.
131. Pfisterer J, Dean AP, Baumann K, et al. Carboplatin/pegylated liposomal doxorubicin/bevacizumab (CD-BEV) vs. carboplatin/gemcitabine/bevacizumab (CGBEV) in patients with recurrent ovarian cancer. A prospective randomized phase III ENGOT/GCIG-Intergroup study (AGO Study Group, AGO-Austria, ANZGOG, GINECO, SGCTG). Presented at: 2018 ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 9330.
132. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:779-791.
133. Rose PG. Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. *Int J Gynecol Cancer*. 2005;15:18-22.
134. Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. *Gynecol Oncol*. 2007;105:358-364.
135. Strauss HG, Henze A, Teichmann A, et al. Phase II trial of docetaxel and carboplatin in recurrent platinum-sensitive ovarian, peritoneal and tubal cancer. *Gynecol Oncol*. 2007;104:612-616
136. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol*. 2003;88(1):35-39. DOI:10.1006/gyno.2002.6855

137. Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and Safety of Mirvetuximab Soravtansine in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha Expression: Results From the SORAYA Study. *J Clin Oncol*. 2023;41(13):2436-2445. DOI:10.1200/JCO.22.01900
138. O'Malley DM, Matulonis UA, Birrer MJ, et al. Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FR α)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol*. 2020;157(2):379-385. DOI:10.1016/j.ygyno.2020.01.037
139. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol*. 2022;23(10):1261-1273. DOI:10.1016/S1470-2045(22)00541-1
140. Roque DM, Siegel ER, Buza N, et al. Randomised phase II trial of weekly ixabepilone \pm biweekly bevacizumab for platinum-resistant or refractory ovarian/fallopian tube/primary peritoneal cancer. *Br J Cancer*. 2022;126(12):1695-1703. DOI:10.1038/s41416-022-01717-6
141. Nagao S, Kogiku A, Suzuki K, et al. A phase II study of the combination chemotherapy of bevacizumab and gemcitabine in women with platinum-resistant recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Ovarian Res*. 2020;13(1):14. Published 2020 Feb 7. DOI:10.1186/s13048-020-0617-y
142. Roque DM, Ratner ES, Silasi DA, et al. Weekly ixabepilone with or without biweekly bevacizumab in the treatment of recurrent or persistent uterine and ovarian/primary peritoneal/fallopian tube cancers: A retrospective review. *Gynecol Oncol*. 2015;137(3):392-400. DOI:10.1016/j.ygyno.2015.03.008
143. Shoji T, Enomoto T, Abe M, et al. Efficacy and safety of standard of care with/without bevacizumab for platinum-resistant ovarian/fallopian tube/peritoneal cancer previously treated with bevacizumab: The Japanese Gynecologic Oncology Group study JGOG3023. *Cancer Sci*. 2022;113(1):240-250. DOI:10.1111/cas.15185

Pancreatic Cancer (Adenocarcinoma)

Neoadjuvant (Resectable/Borderline Resectable)

- Fluorouracil/Leucovorin + Oxaliplatin + Irinotecan (FOLFIRINOX/mFOLFIRINOX)
- Gemcitabine + Albumin-Bound Paclitaxel (G-nP)

Adjuvant (Resectable)

- Fluorouracil/Leucovorin + Oxaliplatin + Irinotecan (mFOLFIRINOX)
- Gemcitabine + Capecitabine
- Gemcitabine

Locally Advanced/Metastatic

1st Line of Therapy

- Fluorouracil/Leucovorin + Oxaliplatin + Irinotecan (FOLFIRINOX/mFOLFIRINOX)
- Gemcitabine + Albumin-Bound Paclitaxel (G-nP)
- Gemcitabine

2nd + Subsequent Lines of Therapy

- Gemcitabine + Albumin-Bound Paclitaxel (G-nP)
- Gemcitabine
- Fluorouracil +/- Leucovorin
- Fluorouracil/Leucovorin + Oxaliplatin (OFF)
- Fluorouracil/Leucovorin + Oxaliplatin (FOLFOX)
- Fluorouracil/Leucovorin + Irinotecan (FOLFIRI)
- Fluorouracil/Leucovorin + Oxaliplatin + Irinotecan (FOLFIRINOX/mFOLFIRINOX)

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/pancreas.html
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. [nccn.org/professionals/physician_gls/pdf/pancreatic.pdf](https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf)
3. Murphy, J.E., Wo, J.Y., Ryan, D.P., et al. (2018, July 1). Total Neoadjuvant Therapy with FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=29800971](https://pubmed.ncbi.nlm.nih.gov/29800971/)

4. Dhir, M., Zenati, M.S., Hamad, A., et al. (July 2018). FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel for Neoadjuvant Treatment of Resectable and Borderline Resectable Pancreatic Head Adenocarcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=29761331
5. Blazer, M., Wu, C., Goldberg, R.M., et al. (April 2015). Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas. Retrieved from ncbi.nlm.nih.gov/pubmed/25358667?dopt=Abstract
6. Peterson, S.L., Husnain, M., Pollack, T., et al. (July 2018). Neoadjuvant Nab-Paclitaxel and Gemcitabine in Borderline Resectable or Locally Advanced Unresectable Pancreatic Adenocarcinoma in Patients Who Are Ineligible for FOLFIRINOX. Retrieved from ncbi.nlm.nih.gov/pubmed/29970528
7. Ielpo, B., Duran, H., Diaz, E., et al. (September 2016). Preoperative Treatment with Gemcitabine Plus Nab-Paclitaxel Is a Safe and Effective Chemotherapy for Pancreatic Adenocarcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/?term=26899943
8. Neoptolemos, J.P., Palmer, D.H., Ghaneh, P., et al. (2017, March 11). Comparison of Adjuvant Gemcitabine and Capecitabine with Gemcitabine Monotherapy in Patients with Resected Pancreatic Cancer (ESPAC-4): A Multicentre, Open-Label, Randomised, Phase 3 Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28129987
9. Conroy, T., Hammel, P., Hebbar, M., et al. (2018, Dec. 20). FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/30575490
10. Oettle, H., Neuhaus, P., Hochhaus, A., et al. (2013, Oct. 9). Adjuvant Chemotherapy with Gemcitabine and Long-Term Outcomes Among Patients with Resected Pancreatic Cancer: The CONKO-001 Randomized Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/24104372
11. Neoptolemos, J.P., Stocken, D.D., Bassi, C., et al. (2010, Sept. 8). Adjuvant Chemotherapy with Fluorouracil Plus Folinic Acid vs. Gemcitabine Following Pancreatic Cancer Resection: A Randomized Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/20823433
12. Sinn, M., Bahra, M., Liersch, T., et al. (2017, Oct. 10). CONKO-005: Adjuvant Chemotherapy with Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/28817370
13. Neoptolemos, J.P., Stocken, D.D., Friess, H., et al. (2004, March 18). A Randomized Trial of Chemoradiotherapy and Chemotherapy After Resection of Pancreatic Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/15028824
14. Regine, W.F., Winter, K.A., Abrams, R.A., et al. (2008, March 5). Fluorouracil vs. Gemcitabine Chemotherapy Before and After Fluorouracil-Based Chemoradiation Following Resection of Pancreatic Adenocarcinoma: A Randomized Controlled Trial. Retrieved from ncbi.nlm.nih.gov/pubmed/18319412
15. Conroy, T., Desseigne, F., Ychou, M., et al. (2011, May 12). FOLFIRINOX Versus Gemcitabine for Metastatic Pancreatic Cancer. Retrieved from ncbi.nlm.nih.gov/pubmed/21561347
16. Mahaseth, H., Brucher, E., Kauh, J., et al. (November 2013). Modified FOLFIRINOX Regimen with Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma. Retrieved from ncbi.nlm.nih.gov/pubmed/24152956
17. Pacheco-Barcia, V., France, T., Zogopoulos, G., et al. (June 2018). Gemcitabine Plus Nab-Paclitaxel Versus Modified FOLFIRINOX as First-Line Chemotherapy in Metastatic Pancreatic Cancer: A Comparison of Toxicity and Survival. Retrieved from academic.oup.com/annonc/article/29/suppl_5/mdy151.163/5039455

18. Von Hoff, D.D., Ervin, T., Arena F.P., et al. (2013, Oct. 31). Increased Survival in Pancreatic Cancer with Nab-Paclitaxel Plus Gemcitabine. Retrieved from [ncbi.nlm.nih.gov/pubmed/24131140](https://pubmed.ncbi.nlm.nih.gov/24131140)
19. Moore, M.J., Goldstein, D., Hamm, J., et al. (2007, May 20). Erlotinib Plus Gemcitabine Compared with Gemcitabine Alone in Patients with Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/17452677](https://pubmed.ncbi.nlm.nih.gov/17452677)
20. Sinn, M., Bahra, M., Liersch, T., et al. (2017, Oct. 10). CONKO-005: Adjuvant Chemotherapy with Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/28817370](https://pubmed.ncbi.nlm.nih.gov/28817370)
21. Cunningham, D., Chau, I., Stocken, D.D., et al. (2009, Nov. 20). Phase III Randomized Comparison of Gemcitabine Versus Gemcitabine Plus Capecitabine in Patients with Advanced Pancreatic Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/19858379](https://pubmed.ncbi.nlm.nih.gov/19858379)
22. Herrmann, R., Bodoky, G., Ruhstaller, T., et al. (2007, June 1). Gemcitabine Plus Capecitabine Compared with Gemcitabine Alone in Advanced Pancreatic Cancer: A Randomized, Multicenter, Phase III Trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/17538165](https://pubmed.ncbi.nlm.nih.gov/17538165)
23. Colucci, G., Labianca, R., Di Costanzo, F., et al. (2010, April 1). Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared with Single-Agent Gemcitabine as First-Line Treatment of Patients with Advanced Pancreatic Cancer: The GIP-1 Study. Retrieved from [ncbi.nlm.nih.gov/pubmed/20194854](https://pubmed.ncbi.nlm.nih.gov/20194854)
24. Rothenberg, M.L., Moore, M.J., Cripps, M.C., et al. A Phase II Trial of Gemcitabine in Patients with 5-FU Refractory Pancreas Cancer. *Ann of Oncology*. 1996;7:347-353. Retrieved from pubmed.ncbi.nlm.nih.gov/8805925
25. Fine, R.L., Fogelman, D.R., Schreiber, S.M., et al. (January 2008). The Gemcitabine, Docetaxel, and Capecitabine (GTX) Regimen for Metastatic Pancreatic Cancer: A Retrospective Analysis. Retrieved from [ncbi.nlm.nih.gov/pubmed/17440727](https://pubmed.ncbi.nlm.nih.gov/17440727)
26. Dakik, H.K., Moskovic, D.J., Carlson, P.J., et al. (February 2012). The Use of GTX as Second-Line and Later Chemotherapy for Metastatic Pancreatic Cancer: A Retrospective Analysis. Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC3923586](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC3923586)
27. Cartwright, T.H., Cohn, A., Varkey, J.A., et al. (2002, Jan. 1). Phase II Study of Oral Capecitabine in Patients with Advanced or Metastatic Pancreatic Cancer. Retrieved from [ncbi.nlm.nih.gov/pubmed/11773165](https://pubmed.ncbi.nlm.nih.gov/11773165)
28. Burris, H.A., Moore, M.J., Andersen, J., et al. (June 1997). Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy for Patients with Advanced Pancreas Cancer: A Randomized Trial. Retrieved from [ncbi.nlm.nih.gov/pubmed/9196156](https://pubmed.ncbi.nlm.nih.gov/9196156)
29. Pelzer, U., Schwane, I., Stieler, J. (July 2011). Best Supportive Care (BSC) Versus Oxaliplatin, Folinic Acid and 5-Fluorouracil (OFF) Plus BSC in Patients for Second-Line Advanced Pancreatic Cancer: A Phase III-Study From the German CONKO-Study Group. Retrieved from [ncbi.nlm.nih.gov/pubmed/?term=21565490](https://pubmed.ncbi.nlm.nih.gov/?term=21565490)
30. Xiong, H.Q., Varadhachary, G.R., Blais, J.C., et al. Phase 2 Trial of Oxliplatin Plus Capecitabine (XELOX) as Second-Line Therapy for Patients with Advanced Pancreatic Cancer. *Cancer*. 2008;113:2046-52. Retrieved from pubmed.ncbi.nlm.nih.gov/18756532
31. Yoo, C., Hwang, J.Y., Kim, J.E., et al. A Randomized Phase II Study of Modified FOLFIRI-3 vs. Modified FOLFOX as Second-Line Therapy in Patients with Gemcitabine-Refractory Advanced

- Pancreatic Cancer. *Br J Cancer*. 2009;101(10):1658-63. Retrieved from pubmed.ncbi.nlm.nih.gov/19826418
32. Neuzillet, C., Hentic, O., Rousseau, B., et al. FOLFIRI Regimen in Metastatic Pancreatic Adenocarcinoma Resistant to Gemcitabine and Platinum-Salts. *World J Gastroenterol*. 2012;18(33):4533-41. Retrieved from ncbi.nlm.nih.gov/pmc/articles/PMC3435778
 33. Zaniboni, A., Aitini, E., Barni, S., et al. FOLFIRI as Second-Line Chemotherapy for Advanced Pancreatic Cancer: A GISCAD Multicenter Phase II Study. *Cancer Chemother Pharmacol*. 2012;69(6):1641-5. Retrieved from pubmed.ncbi.nlm.nih.gov/22576338
 34. Wang-Gillam, A., Li, C.P., Bodoky, G., et al. Nanoliposomal Irinotecan with Fluorouracil and Folinic Acid in Metastatic Pancreatic Cancer After Previous Gemcitabine-Based Therapy (NAPOLI-1): A Global, Randomized, Open-Label, Phase 3 Trial. *Lancet*. 2016; 387:545-557. Retrieved from pubmed.ncbi.nlm.nih.gov/26615328
 35. Boeck, S., Wilkowsi, R., Bruns, C., et al. Oral Capecitabine in Gemcitabine-Pretreated Patients with Advanced Pancreatic Cancer. *Oncology*. 2007;73:221-227. Retrieved from pubmed.ncbi.nlm.nih.gov/18424886
 36. Mita, N., Iwashita, T., Uemura, S., et al. (2019). Second-Line Gemcitabine Plus Nab-Paclitaxel for Patients with Unresectable Advanced Pancreatic Cancer After First-Line FOLFIRINOX Failure. *J Clin Med*. Retrieved from pubmed.ncbi.nlm.nih.gov/31146420
 37. Hammel, P., Lacy, J., Portales, F., et al. Phase II LAPACT Trial of Nab-Paclitaxel Plus Gemcitabine for Patients with Locally Advanced Pancreatic Cancer. 2018 Gastrointestinal Cancers Symposium. Abstract 204. Presented Jan. 19, 2018
 38. Le, D.T., Uram, J.N., Wang, H., et al. (2015, June 25). PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. Retrieved from ncbi.nlm.nih.gov/pubmed/26028255
 39. O'Reilly, E.M., Lee, J.W., Zalupski, M., et al. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin with or without Veliparib in Patients with Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. *J Clin Oncol*. 2020; 38: 1378-88
 40. Golan, T., Hammel, P., Reni, M., et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N Engl J Med*. 2019; 381: 317-327
 41. Gill, S., Ko, Y., Cripps, C., et al. PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin with or without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. *J Clin Oncol*. 2016; 34(32): 3914–3920
 42. Chung, M.J., Kang, H., Kim, H.G., et al. Multicenter Phase II Trial of Modified FOLFIRINOX in Gemcitabine-Refractory Pancreatic Cancer. *World J of Gastrointestinal Oncology*. 2018; 10(12): 505-515
 43. Kim, J.H., Lee, S., Oh, S.Y., et al. Attenuated FOLFIRINOX in the Salvage Treatment of Gemcitabine-Refractory Advanced Pancreatic Cancer: A Phase II Study. *Cancer Comm*. 2018; 38:32
 44. Pointet, A.L., Tougeron, D., Pernot, S., et al. Three Fluoropyrimidine-Based Regimens in Routine Clinical Practice After Nab-Paclitaxel Plus Gemcitabine for Metastatic Pancreatic Cancer: An AGEO Multicenter Study. Retrieved from DOI: 10.1016/j.clinre.2019.08.009
 45. Zhang, H., Kellett, C., Lambert, P., et al. Efficacy and Tolerability of Second-Line Nab-Paclitaxel and Gemcitabine After Failure of First-Line FOLFIRINOX for Advanced Pancreas Cancer: A Single-Institution Experience. Retrieved from ncbi.nlm.nih.gov/pubmed/29631907

46. Tsang, E.S., Spratlin, J., Cheung, W.Y., et al. Real-World Outcomes Among Patients Treated with Gemcitabine-Based Therapy Post-FOLFIRINOX Failure in Advanced Pancreatic Cancer. *Am J Clin Oncology*. 2019; 42(12): 903-908
47. Palacio, S., Hosein, R.J., Reis, I., et al. The Nab-Paclitaxel/Gemcitabine Regimen for Patients with Refractory Advanced Pancreatic Adenocarcinoma. Retrieved from [dx.DOI.org/10.21037/jgo.2017.10.12](https://doi.org/10.21037/jgo.2017.10.12)
48. Janssen, Q.P., Buettner, S., Suker, M., et al. Neoadjuvant FOLFIRINOX in Patients with Borderline Resectable Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis. *J Natl Cancer Inst*. 2019;111(8):782-794. DOI:10.1093/jnci/djz073
49. Versteijne, E., Suker, M., Groothuis, K., et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. Retrieved from ascopubs.org/DOI/full/10.1200/JCO.19.02274

Prostate Cancer

Androgen Deprivation Therapy (ADT)

- Goserelin
- Leuprolide (HCPCS: J9217: Eligard, Lupron Depot)
- Triptorelin

Castration Sensitive

Neoadjuvant, Adjuvant in lieu of local therapy

- ADT

Recurrent or Metastatic

- ADT
- Abiraterone (Zytiga®), Prednisone + ADT
- Abiraterone (Zytiga®), Prednisone + Docetaxel + ADT

Castration Resistant

Recurrent or Metastatic

- Abiraterone (Zytiga®), Prednisone + ADT
- Docetaxel + ADT
- Olaparib + Abiraterone (Zytiga®), Prednisone + ADT (BRCA 1/2, no prior novel hormone)
- Cabazitaxel + ADT (after prior docetaxel therapy)
- Enzalutamide + ADT (after prior abiraterone therapy)

References:

1. National Comprehensive Cancer Network. Prostate Cancer (V4.2023, September 7, 2023) Accessed December 2023.
2. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-60. PMID: 28578607
3. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24. PMID: 31150574
4. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132-42. PMID: 35179323
5. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a

- multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022 Apr 30;399(10336):1695-1707.
6. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-46. PMID: 30763142
 7. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-9. PMID: 32905676
 8. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018; 378:2465-74.
 9. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020 Jun 4;382(23):2197-2206. DOI: 10.1056/NEJMoa2003892.
 10. Oudard S, Fizazi K, Sengeløv L, et al. Cabazitaxel Versus Docetaxel as First-Line Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. *J Clin Oncol*. 2017 Oct 1;35(28):3189-3197. DOI: 10.1200/JCO.2016.72.1068. Epub 2017 Jul 28. PMID: 28753384.
 11. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. *N Engl J Med*. 2019 Dec 26;381(26):2506-2518. DOI: 10.1056/NEJMoa1911206. Epub 2019 Sep 30. PMID: 31566937.
 12. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, Hug EB, Asbell SO, Grignon D. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005 Apr 1;61(5):1285-90. DOI: 10.1016/j.ijrobp.2004.08.047. PMID: 15817329.
 13. Mason MD, Parulekar WR, Sydes MR, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. *J Clin Oncol*. 2015 Jul 1;33(19):2143-50. DOI: 10.1200/JCO.2014.57.7510. Epub 2015 Feb 17. PMID: 25691677; PMCID: PMC4477786.
 14. Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. *Lancet Oncol*. 2015 Jul;16(7):787-94. DOI: 10.1016/S1470-2045(15)00011-X. Epub 2015 May 28. PMID: 26028518.
 15. Rosenthal SA, Hu C, Sartor O, et al. Effect of Chemotherapy with Docetaxel with Androgen Suppression and Radiotherapy for Localized High-Risk Prostate Cancer: The Randomized Phase III NRG Oncology RTOG 0521 Trial. *J Clin Oncol*. 2019 May 10;37(14):1159-1168. DOI: 10.1200/JCO.18.02158. Epub 2019 Mar 12. Erratum in: *J Clin Oncol*. 2021 Jun 10;39(17):1949. PMID: 30860948; PMCID: PMC6506419.
 16. James ND, Sydes MR, Clarke NW, et al. STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016 Mar 19;387(10024):1163-77. DOI: 10.1016/S0140-6736(15)01037-5. Epub 2015 Dec 21. PMID: 26719232; PMCID: PMC4800035.
 17. James ND, de Bono JS, Spears MR, et al. STAMPEDE Investigators. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med*. 2017 Jul 27;377(4):338-351. DOI: 10.1056/NEJMoa1702900. Epub 2017 Jun 3. PMID: 28578639; PMCID: PMC5533216.
 18. Sydes MR, Spears MR, Mason MD, et al. STAMPEDE Investigators. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the

- STAMPEDE multi-arm, multi-stage platform protocol. *Ann Oncol*. 2018 May 1;29(5):1235-1248. DOI: 10.1093/annonc/mdy072. PMID: 29529169; PMCID: PMC5961425.
19. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007 Apr 20;25(12):1596-605. DOI: 10.1200/JCO.2006.10.1949. Epub 2007 Apr 2. PMID: 17404365.
 20. Shore ND, Saad F, Cookson MS, et al. HERO Study Investigators. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. *N Engl J Med*. 2020 Jun 4;382(23):2187-2196. DOI: 10.1056/NEJMoa2004325. Epub 2020 May 29. PMID: 32469183.
 21. Schulze H, Senge T. Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. *J Urol*. 1990 Oct;144(4):934-41. DOI: 10.1016/s0022-5347(17)39625-8. PMID: 2144596.
 22. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019 May;20(5):686-700. DOI: 10.1016/S1470-2045(19)30082-8. Epub 2019 Apr 12. PMID: 30987939.
 23. Chi KN, Agarwal N, Bjartell A, et al. TITAN Investigators. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med*. 2019 Jul 4;381(1):13-24. DOI: 10.1056/NEJMoa1903307. Epub 2019 May 31. PMID: 31150574.
 24. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in Patients with Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. *J Clin Oncol*. 2021 Jul 10;39(20):2294-2303. DOI: 10.1200/JCO.20.03488. Epub 2021 Apr 29. PMID: 33914595.
 25. Davis ID, Martin AJ, Stockler MR, et al. ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med*. 2019 Jul 11;381(2):121-131. DOI: 10.1056/NEJMoa1903835. Epub 2019 Jun 2. PMID: 31157964.
 26. Ryan CJ, Smith MR, Fizazi K, et al. COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015 Feb;16(2):152-60. DOI: 10.1016/S1470-2045(14)71205-7. Epub 2015 Jan 16. PMID: 25601341.
 27. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol*. 2016 Feb;17(2):153-163. DOI: 10.1016/S1470-2045(15)00518-5. Epub 2016 Jan 14. PMID: 26774508.
 28. Tombal B, Saad F, Penson D, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019 Apr;20(4):556-569. DOI: 10.1016/S1470-2045(18)30898-2. Epub 2019 Feb 12. PMID: 30770294.
 29. Smith MR, Saad F, Chowdhury S, et al. SPARTAN Investigators. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. 2018 Apr 12;378(15):1408-1418. DOI: 10.1056/NEJMoa1715546. Epub 2018 Feb 8. PMID: 29420164.
 30. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB

- 9583). *J Clin Oncol*. 2004 Mar 15;22(6):1025-33. DOI: 10.1200/JCO.2004.06.037. PMID: 15020604.
31. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*. 2008 Jan 10;26(2):242-5. DOI: 10.1200/JCO.2007.12.4008. PMID: 18182665.
 32. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*. 2015 Aug 20;373(8):737-46. DOI: 10.1056/NEJMoa1503747. Epub 2015 Aug 5. PMID: 26244877; PMCID: PMC4562797.
 33. Gravis G, Boher JM, Joly F, et al. GETUG. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. *Eur Urol*. 2016 Aug;70(2):256-62. DOI: 10.1016/j.eururo.2015.11.005. Epub 2015 Nov 21. PMID: 26610858.
 34. Tucci M, Bertaglia V, Vignani F, et al. Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*. 2016 Apr;69(4):563-573. DOI: 10.1016/j.eururo.2015.09.013. Epub 2015 Sep 28. PMID: 26422676.
 35. Bahl A, Oudard S, Tombal B, et al. TROPIC Investigators. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol*. 2013 Sep;24(9):2402-8. DOI: 10.1093/annonc/mdt194. Epub 2013 May 30. PMID: 23723295; PMCID: PMC3755329.
 36. Oudard S, Fizazi K, Sengeløv L, et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. *J Clin Oncol*. 2017 Oct 1;35(28):3189-3197. DOI: 10.1200/JCO.2016.72.1068. Epub 2017 Jul 28. PMID: 28753384.
 37. Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Ann Oncol*. 2018 Aug 1;29(8):1807-1813. DOI: 10.1093/annonc/mdy232. PMID: 29992241.
 38. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients with Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. 2020 Jan 1;38(1):1-10. DOI: 10.1200/JCO.19.02105. Epub 2019 Nov 4. PMID: 31682550; PMCID: PMC8184060.
 39. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015 Jan 20;33(3):244-50. DOI: 10.1200/JCO.2014.56.2728. Epub 2014 Nov 3. PMID: 25366685; PMCID: PMC6057749.
 40. Bögemann M, Shore ND, Smith MR, et al. Efficacy and Safety of Darolutamide in Patients with Nonmetastatic Castration-resistant Prostate Cancer Stratified by Prostate-specific Antigen Doubling Time: Planned Subgroup Analysis of the Phase 3 ARAMIS Trial [published correction appears in *Eur Urol*. 2023 Feb;83(2):e60]. *Eur Urol*. 2023;83(3):212-221. doi:10.1016/j.eururo.2022.07.018
 41. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med*. 2017;377(4):338-351. doi:10.1056/NEJMoa1702900
 42. James ND, Clarke NW, Cook A, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). *Int J Cancer*. 2022;151(3):422-434. doi:10.1002/ijc.34018

43. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol*. 2019;20(12):1730-1739. doi:10.1016/S1470-2045(19)30688-6
44. Lai LY, Oerline MK, Caram MEV, et al. Risk of Metabolic and Cardiovascular Adverse Events With Abiraterone or Enzalutamide Among Men With Advanced Prostate Cancer. *J Natl Cancer Inst*. 2022;114(8):1127-1134. doi:10.1093/jnci/djac081
45. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. 2018;378(15):1408-1418. doi:10.1056/NEJMoa1715546
46. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and Overall Survival in Prostate Cancer. *Eur Urol*. 2021;79(1):150-158. doi:10.1016/j.eururo.2020.08.011
47. Cattrini C, Caffo O, De Giorgi U, et al. Apalutamide, Darolutamide and Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC): A Critical Review. *Cancers (Basel)*. 2022;14(7):1792. Published 2022 Mar 31. doi:10.3390/cancers14071792
48. Wenzel M, Nocera L, Collà Ruvolo C, et al. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis [published correction appears in *Prostate Cancer Prostatic Dis*. 2023 Mar 10;:]. *Prostate Cancer Prostatic Dis*. 2022;25(2):139-148. doi:10.1038/s41391-021-00395-487-2
49. Halabi S, Jiang S, Terasawa E, et al. Indirect Comparison of Darolutamide versus Apalutamide and Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer. *J Urol*. 2021;206(2):298-307. doi:10.1097/JU.0000000000001767
50. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154. doi:10.1016/S0140-6736(10)61389-X
51. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433. doi:10.1056/NEJMoa1405095
52. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol*. 2017;71(2):151-154. doi:10.1016/j.eururo.2016.07.032
53. Armstrong AJ, Lin P, Tombal B, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol*. 2020;78(3):347-357. doi:10.1016/j.eururo.2020.04.061
54. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy [published correction appears in *N Engl J Med*. 2013 Feb 7;368(6):584]. *N Engl J Med*. 2013;368(2):138-148. doi:10.1056/NEJMoa1209096

Small Cell Lung Cancer

Limited Stage – Primary Therapy

- Carboplatin + Etoposide
- Cisplatin + Etoposide

Extensive Stage – Primary Therapy

- Carboplatin + Etoposide + Atezolizumab
- Carboplatin + Etoposide + Durvalumab
- Cisplatin + Etoposide + Durvalumab
- Carboplatin + Etoposide
- Cisplatin + Etoposide

Extensive Stage – Maintenance after Primary Therapy

- Atezolizumab
- Durvalumab

Subsequent Therapy: Relapse \leq 6 months

- Topotecan (IV)
- Paclitaxel
- Irinotecan

Subsequent Therapy: Relapse $>$ 6 months

- Carboplatin + Etoposide
- Cisplatin + Etoposide
- Topotecan (IV)
- Irinotecan

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from seer.cancer.gov/statfacts/html/lungb.html
2. National Comprehensive Cancer Network. Small Cell Lung Cancer (V2.2024, November 21, 2023) Accessed December 2023.
3. Faivre-Finn, C., Snee, M., Ashcroft, L., et al. Concurrent Once-Daily Versus Twice-Daily Chemoradiotherapy in Patients with Limited-Stage Small Cell Lung Cancer (CONVERT): An Open-Label, Phase 3, Randomized, Superiority Trial. *Lancet Oncol.* 2017; 18:1116-1125. Retrieved from pubmed.ncbi.nlm.nih.gov/28642008

4. Sundstrom, S., Bremnes, R.M., Kaasa, S., et al. Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin and Vincristine Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial with 5 Years' Follow-Up. *J Clin Oncol.* 2002;20:4665-4672. Retrieved from pubmed.ncbi.nlm.nih.gov/12488411
5. Skarlos, D.V., Samantas, E., Briassoulis, E., et al. Randomized Comparison of Early Versus Late Hyperfractionated Thoracic Irradiation Concurrently with Chemotherapy in Limited Disease Small-Cell Lung Cancer: A Randomized Phase II Study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol.* 2001;12:1231-1238. Retrieved from pubmed.ncbi.nlm.nih.gov/11697833
6. Kosmidis, P.A., Samantas, E., Fountzilas, G., et al. Cisplatin/Etoposide Versus Carboplatin/Etoposide Chemotherapy and Irradiation in Small-Cell Lung Cancer: A Randomized Phase III Study. *Semin Oncol.* 1994;21(suppl 6):23-30. Retrieved from pubmed.ncbi.nlm.nih.gov/8052870
7. Rossi, A., Di Maio, M., Chiodini, P., et al. Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data. *J Clin Oncol.* 2012;14:1692-8. Retrieved from pubmed.ncbi.nlm.nih.gov/2247316
8. Horn, L., Mansfield, A.S., Szczesna, A., et al. (2018, Dec. 6). First-Line Atezolizumab Plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. Retrieved from pubmed.ncbi.nlm.nih.gov/30280641
9. Socinski, M.A., Smit, E.F., Lorigan, P., et al. (2009, Oct. 1). Phase III Study of Pemetrexed Plus Carboplatin Compared with Etoposide Plus Carboplatin in Chemotherapy-Naive Patients with Extensive-Stage Small-Cell Lung Cancer. Retrieved from pubmed.ncbi.nlm.nih.gov/19720897
10. Schmittel, A., Sebastian, M., Fischer von Weikersthal, L., et al. (August 2011). A German Multicenter, Randomized Phase III Trial Comparing Irinotecan-Carboplatin with Etoposide-Carboplatin as First-Line Therapy for Extensive-Disease Small-Cell Lung Cancer. Retrieved from pubmed.ncbi.nlm.nih.gov/21266516
11. Niell, H.B., Herndon, J.E., Miller, A.A., et al. (2005, June 1). Randomized Phase III Intergroup Trial of Etoposide and Cisplatin with or without Paclitaxel and Granulocyte Colony-Stimulating Factor in Patients with Extensive-Stage Small-Cell Lung Cancer: Cancer and Leukemia Group B Trial 9732. Retrieved from pubmed.ncbi.nlm.nih.gov/15923572
12. Zatloukal, P., Cardenal, F., Szczesna, A., et al. (September 2010). A Multicenter International Randomized Phase III Study Comparing Cisplatin in Combination with Irinotecan or Etoposide in Previously Untreated Small-Cell Lung Cancer Patients with Extensive Disease. Retrieved from pubmed.ncbi.nlm.nih.gov/20231298
13. Lara, P.N., Natale, R., Crowley, J., et al. (2009, May 20). Phase III Trial of Irinotecan/Cisplatin Compared with Etoposide/Cisplatin in Extensive-Stage Small-Cell Lung Cancer: Clinical and Pharmacogenomic Results From SWOG S0124. *J Clin Oncol.* Retrieved from pubmed.ncbi.nlm.nih.gov/19349543
14. Noda, K., Nishiwaki, Y., Kawahara, M., et al. (2002, Jan. 10). Irinotecan Plus Cisplatin Compared with Etoposide Plus Cisplatin for Extensive Small-Cell Lung Cancer. *N Engl J Med.* Retrieved from pubmed.ncbi.nlm.nih.gov/11784874
15. Hanna, N., Bunn, P.A., Langer, C., et al. (2006, May 1). Randomized Phase III Trial Comparing Irinotecan/Cisplatin with Etoposide/Cisplatin in Patients with Previously Untreated Extensive-Stage Disease Small-Cell Lung Cancer. *J Clin Oncol.* Retrieved from pubmed.ncbi.nlm.nih.gov/16648503
16. Paz-Ares, L., Dvorkin, M., Chen, Y., et al. (2019, Oct. 4). Durvalumab Plus Platinum-Etoposide Versus Platinum-Etoposide in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer

- (CASPIAN): A Randomised, Controlled, Open-Label, Phase 3 Trial. *Lancet*. Retrieved from pubmed.ncbi.nlm.nih.gov/31590988
17. Von Pawel, J., Schiller, J.H., Shepherd, F.A., et al. Topotecan Versus Cyclophosphamide, Doxorubicin and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer. *J Clin Oncol*. 1999; 17(2): 658-667. Retrieved from pubmed.ncbi.nlm.nih.gov/10080612
 18. O'Brien, M.E., Ciuleanu, T.E., Tsekov, H., et al. Phase III Trial Comparing Supportive Care Alone with Supportive Care with Oral Topotecan in Patients with Relapsed Small-Cell Lung Cancer. *J Clin Oncol*. 2006; 24(34): 5441-5447. Retrieved from pubmed.ncbi.nlm.nih.gov/17135646
 19. Eckardt, J.R., von Pawel, J., Pujol, J.L., et al. Phase III Study of Oral Compared with Intravenous Topotecan as Second-Line Therapy in Small-Cell Lung Cancer. *J Clin Oncol*. 2007; 25(15): 2086-2092. Retrieved from pubmed.ncbi.nlm.nih.gov/17513814
 20. Ready, N.E., Ott, P.A., Hellmann, M.D., et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small-Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. *J Thorac Oncol*. 2019 (Epub ahead of print). Retrieved from pubmed.ncbi.nlm.nih.gov/31629915
 21. Reck, M., Vicente, D., Ciuleanu, T., et al. Efficacy and Safety of Nivolumab (Nivo) Monotherapy Versus Chemotherapy (Chemo) in Recurrent Small Cell Lung Cancer (SCLC): Results from CheckMate 331. *Ann Oncol*. 2018; 29 (Supplement 10). Retrieved from [annalsofncology.org/article/S0923-7534\(19\)32761-9/abstract](https://annalsofncology.org/article/S0923-7534(19)32761-9/abstract)
 22. Chung, H.C., Lopez-Martin, J.A., Kao, S., et al. Phase 2 Study of Pembrolizumab in Advanced Small-Cell Lung Cancer (SCLC): KEYNOTE-158. *J Clin Oncol*. 2018; 36: Abstract 8506. Retrieved from ascopubs.org/DOI/abs/10.1200/JCO.2018.36.15_suppl.8506
 23. Smit, E.F., Fokkema, E., Biesma, B., et al. A Phase II Study of Paclitaxel in Heavily Pretreated Patients with Small-Cell Lung Cancer. *Br J Cancer*. 1998; 77: 347-351. Retrieved from pubmed.ncbi.nlm.nih.gov/9461009
 24. Yamamoto, N., Tsurutani, J., Yoshimura, N., et al. Phase II Study of Weekly Paclitaxel for Relapsed and Refractory Small Cell Lung Cancer. *Anticancer Res* 2006; 26:777-781. Retrieved from pubmed.ncbi.nlm.nih.gov/16739353
 25. Smyth, J.F., Smith, I.E., Sessa, C., et al. Activity of Docetaxel (Taxotere) in Small-Cell Lung Cancer. The Early Clinical Trials Group of the EORTC. *Eur J Cancer*. 1994; 20A: 1058-1060. Retrieved from pubmed.ncbi.nlm.nih.gov/7654428
 26. Masuda, N., Fukuoka, M., Kusunoki, Y., et al. CPT-11: A New Derivative of Camptothecin for the Treatment of Refractory or Relapsed Small-Cell Lung Cancer. *J Clin Oncol*. 1992; 10: 1225-1229. Retrieved from pubmed.ncbi.nlm.nih.gov/1321891
 27. Sevinc, A., Kalender, M.E., Altinbas, M., et al. Irinotecan as a Second-Line Monotherapy for Small-Cell Lung Cancer. *Asian Pacific J of Cancer Prevention*. 2011; 12:1055-1059. Retrieved from pubmed.ncbi.nlm.nih.gov/21790251
 28. Pallis, A.G., Agelidou, A., Agelaki, S., et al. A Multicenter Randomized Phase II Study of the Irinotecan/Gemcitabine Doublet Versus Irinotecan Monotherapy in Previously Treated Patients with Extensive Stage Small-Cell Lung Cancer. *Lung Cancer*. 2009; 65(2): 187-191. Retrieved from pubmed.ncbi.nlm.nih.gov/19100647
 29. Pietanza, M.C., Kadota, K., Huberman, K., et al. Phase II Trial of Temozolomide with Relapsed Sensitive or Refractory Small-Cell Lung Cancer, with Assessment of Methylguanine-DNA Methyltransferase as a Potential Biomarker. *Clin Cancer Res*. 2012; 18: 1138-1145. Retrieved from pubmed.ncbi.nlm.nih.gov/22228633

30. Zauderer, M.G., Drilon, A., Kadota, K., et al. Trial of a 5-Day Dosing Regimen of Temozolomide in Patients with Relapsed Small-Cell Lung Cancers with Assessment of Methylguanine-DNA Methyltransferase. *Lung Cancer*. 2014; 86: 237-240. Retrieved from [ncbi.nlm.nih.gov/pmc/articles/PMC4497567](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC4497567)
31. Johnson, D.H., Greco, F.A., Strupp, J., et al. Prolonged Administration of Oral Etoposide in Patients with Relapsed or Refractory Small-Cell Lung Cancer: A Phase II Trial. *J Clin Oncol*. 1990; 8: 1613-1617. Retrieved from pubmed.ncbi.nlm.nih.gov/2170589
32. Jassem, J., Karnicka-Mlodkowska, H., van Pottelsberghe, C., et al. Phase II Study of Vinorelbine (Navelbine) in Previously Treated Small-Cell Lung Cancer Patients. EORTC Lung Cancer Cooperative Group. *Eur J Cancer*. 1993; 29A: 1720-1722. Retrieved from pubmed.ncbi.nlm.nih.gov/8398301
33. Masters, G.A., Declerck, L., Blanke, C., et al. Phase II Trial of Gemcitabine in Refractory or Relapsed Small-Cell Lung Cancer: Eastern Cooperative Oncology Group Trial 1597. *J Clin Oncol*. 2003; 21: 1550-1555. Retrieved from pubmed.ncbi.nlm.nih.gov/12697880
34. van der Lee, I., Smit, E.F., van Putten, J.W.G., et al. Single-Agent Gemcitabine in Patients with Resistant Small-Cell Lung Cancer. *Ann Oncol*. 2001; 12: 557-561. Retrieved from pubmed.ncbi.nlm.nih.gov/11398892
35. Schmittel, A., Knödler, M., Hortig, P., et al. Phase II Trial of Second-Line Bendamustine Chemotherapy in Relapsed Small Cell Lung Cancer Patients. *Lung Cancer*. 2007; 55(1): 109-113. Retrieved from pubmed.ncbi.nlm.nih.gov/17097191
36. Liu, S.V., Reck, M., Mansfield, A.S., et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin and Etoposide (IMpower133). *J Clin Oncol*. 2021 Feb 20;39(6):619-630. DOI: 10.1200/JCO.20.01055. Epub 2021 Jan 13. PMID: 33439693; PMCID: PMC8078320
37. Goldman, J.W., Dvorkin, M., Chen, Y., et al.; CASPIAN Investigators. Durvalumab, with or without Tremelimumab, Plus Platinum-Etoposide Versus Platinum-Etoposide Alone in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): Updated Results From a Randomised, Controlled, Open-Label, Phase 3 Trial. *Lancet Oncol*. 2021 Jan;22(1):51-65. DOI: 10.1016/S1470-2045(20)30539-8. Epub 2020 Dec 4. PMID: 33285097
38. Subbiah, V., Paz-Ares, L., Besse, B., et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. *Lung Cancer*. 2020;150:90-96. PMID: 33096421.
39. Spigel, D.R., Vicente, D., Ciuleanu, T.E. et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. *Ann Oncol*. 2021;32(5):631-641. PMID: 33539946.
40. Keeping, S.T., Cope, S., Chan, K., et al. Comparative effectiveness of nivolumab versus standard of care for third-line patients with small-cell lung cancer. *J Comp Eff Res*. 2020;9(18):1275-1284. PMID: 33140652.

Uterine Carcinoma (Endometrial)

Adjuvant

- Carboplatin + Paclitaxel
- Dostarlimab + Carboplatin + Paclitaxel (stage III-IV tumors, dMMR/MSI-H only)

Metastatic or Recurrent

1st Line of Therapy

- Carboplatin + Paclitaxel
- Carboplatin + Paclitaxel + Trastuzumab (for stage III/IV or recurrent HER2-positive uterine serous carcinoma only)
- Dostarlimab + Carboplatin + Paclitaxel (stage III-IV tumors, dMMR/MSI-H only)*
- Lenvatinib + Pembrolizumab (pMMR only, after prior platinum-based therapy including neoadjuvant and adjuvant)*

2nd + Subsequent Lines of Therapy

- Lenvatinib + Pembrolizumab (pMMR only)*
- Docetaxel
- Paclitaxel
- Doxorubicin
- Liposomal Doxorubicin

*For patients that have not received treatment with a checkpoint inhibitor.

References:

1. National Cancer Institute. Cancer Statistics. Retrieved from <https://seer.cancer.gov/statfacts/html/corp.html>
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Endometrial Carcinoma (V2.2023, April 28, 2023). Accessed July 2023. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/uterine_blocks.pdf
3. de Boer SM, Powell ME, Mileskin L, et al; PORTEC study group. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018 Mar;19(3):295-309. DOI: 10.1016/S1470-2045(18)30079-2. Epub 2018 Feb 12. Erratum in: *Lancet Oncol*. 2018 Apr;19(4):e184. PMID: 29449189; PMCID: PMC5840256.
4. Hidaka T, Nakamura T, Shima T, Yuki H, Saito S. Paclitaxel/carboplatin versus cyclophosphamide/adriamycin/cisplatin as postoperative adjuvant chemotherapy for advanced

- endometrial adenocarcinoma. *J Obstet Gynaecol Res.* 2006 Jun;32(3):330-7. DOI: 10.1111/j.1447-0756.2006.00405.x. PMID: 16764625.
5. Mustea A, Koensgen D, Belau A, et al. Adjuvant sequential chemoradiation therapy in high-risk endometrial cancer: results of a prospective, multicenter phase-II study of the NOGGO (North-Eastern German Society of Gynaecological Oncology). *Cancer Chemother Pharmacol.* 2013 Nov;72(5):975-83. DOI: 10.1007/s00280-013-2276-9. Epub 2013 Sep 1. PMID: 23995698.
 6. Jutzi L, Hoskins P, Lim P, Aquino-Parsons C, Tinker A, Kwon JS. The importance of adjuvant chemotherapy and pelvic radiotherapy in high-risk early stage endometrial carcinoma. *Gynecol Oncol.* 2013 Dec;131(3):581-5. DOI: 10.1016/j.ygyno.2013.09.012. Epub 2013 Sep 19. PMID: 24055614.
 7. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2004;22:2159-2166.
 8. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study [abstract]. *Gynecologic Oncology.* 2012;125:771.
 9. Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *J Clin Oncol.* 2020 Nov 20;38(33):3841-3850. DOI: 10.1200/JCO.20.01076. Epub 2020 Sep 29. PMID: 33078978; PMCID: PMC7676887.
 10. Fader AN, Roque DM, Siegel E, et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu *J Clin Oncol.* 2018 Jul 10;36(20):2044-2051.
 11. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. *Gynecol Oncol.* 2009;112:543-552.
 12. Rose PG, Ali S, Moslemi-Kebria M, Simpkins F. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. *Int J Gynecol Cancer.* 2017;27:452-458.
 13. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2011;29:2259-2265.
 14. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol.* 2011;29:3278-3285.
 15. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25:526-531.
 16. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20:711-718.
 17. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol.* 2020;21:1353-1365.
 18. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. *J Clin Oncol.* 2020;38:1-10.

19. Azad NS, Gray RJ, Overman MJ, et al. Nivolumab is effective in mismatch repair-deficient noncolorectal cancers: Results from Arm Z1D-A Subprotocol of the NCI MATCH (EAY131) study. *J Clin Oncol*. 2020;38:214-222.
20. Oaknin A, Tinker AV, Gilbert L, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer a nonrandomized phase 1 clinical trial. *JAMA Oncol*. 2020;6:1766-1772.
21. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. *Lancet Oncol*. 2020; 21: 271–82.
22. Sidaway P. Targeted therapy: larotrectinib effective against TRK-fusion-positive cancers. *Nat Rev Clin Oncol*. 2018; 15: 264.
23. Geller MA, Ivy JJ, Ghebre R, Downs LS Jr, Judson PL, Carson LF, Jonson AL, Dusenbery K, Vogel RI, Boente MP, Argenta PA. A phase II trial of carboplatin and docetaxel followed by radiotherapy given in a "Sandwich" method for stage III, IV, and recurrent endometrial cancer. *Gynecol Oncol*. 2011 Apr;121(1):112-7. DOI: 10.1016/j.ygyno.2010.12.338. Epub 2011 Jan 15.
24. Glasgow M, Vogel RI, Burgart J, Argenta P, Dusenbery K, Geller MA. Long term follow-up of a phase II trial of multimodal therapy given in a "sandwich" method for stage III, IV, and recurrent endometrial cancer. *Gynecol Oncol Res Pract*. 2016 May 26;3:6. DOI: 10.1186/s40661-016-0027-4.
25. Katsumata N, Noda K, Nozawa S, et al. Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study. *Br J Cancer*. 2005 Oct 31;93(9):999-1004. DOI: 10.1038/sj.bjc.6602817. PMID: 16234823; PMCID: PMC2361676.
26. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1989 Apr;33(1):68-70. DOI: 10.1016/0090-8258(89)90605-7. PMID: 2703169.
27. Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P, Acquino-Parsons C, Lee N. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol*. 2001 Oct 15;19(20):4048-53. DOI: 10.1200/JCO.2001.19.20.4048. PMID: 11600606.
28. McMeekin S, Dizon D, Barter J, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. *Gynecol Oncol*. 2015 Jul;138(1):18-23. DOI: 10.1016/j.ygyno.2015.04.026. Epub 2015 Apr 26. PMID: 25925990.
29. Homesley HD, Blessing JA, Sorosky J, Reid G, Look KY. Phase II trial of liposomal doxorubicin at 40 mg/m(2) every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 2005 Aug;98(2):294-8. DOI: 10.1016/j.ygyno.2005.05.016. PMID: 15975638.
30. Wadler S, Levy DE, Lincoln ST, Soori GS, Schink JC, Goldberg G. Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group Study E3E93. *J Clin Oncol*. 2003 Jun 1;21(11):2110-4. DOI: 10.1200/JCO.2003.12.093. PMID: 12775736.
31. Sutton G, Kauderer J, Carson LF, Lentz SS, Whitney CW, Gallion H; Gynecologic Oncology Group. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005 Mar;96(3):630-4. DOI: 10.1016/j.ygyno.2004.11.022. PMID: 15721404.

32. Hensley ML. Role of chemotherapy and biomolecular therapy in the treatment of uterine sarcomas. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:773-782.
33. Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005;96:630-634.
34. Powell MA, Filiaci VL, Rose PG, Mannel RS, Hanjani P, Degeest K, Miller BE, Susumu N, Ueland FR. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. *J Clin Oncol*. 2010 Jun 1;28(16):2727-31. DOI: 10.1200/JCO.2009.26.8326. Epub 2010 Apr 26. PMID: 20421537; PMCID: PMC2881851.
35. Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. *Lancet Oncol*. 2009;10:1188-1198.
36. Novetsky AP, Powell MA. Management of sarcomas of the uterus. *Curr Opin Oncol*. 2013;25:546-552.
37. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, et al. ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021 Nov;32(11):1348-1365. DOI: 10.1016/j.annonc.2021.07.006. Epub 2021 Jul 22. PMID: 34303806.
38. Thanopoulou E, Judson I. Hormonal therapy in gynecological sarcomas. *Expert Rev Anticancer Ther*. 2012;12:885-894.
39. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol*. 2006;101:464-469
40. Reich O, Regauer S. Estrogen replacement therapy and tamoxifen are contraindicated in patients with endometrial stromal sarcoma. *Gynecol Oncol*. 2006;102:413-414; author reply 414.
41. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). *Cancer*. 2013;119:1555-1561
42. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25:2755-2763.
43. Davis EJ, Chugh R, Zhao L, et al. A randomised, open-label, phase II study of neo/adjuvant doxorubicin and ifosfamide versus gemcitabine and docetaxel in patients with localised, high-risk, soft tissue sarcoma. *Eur J Cancer*. 2015;51:1794-1802.
44. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. *Gynecol Oncol*. 2009;112:563-567.
45. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol*. 2015;33:1180-1185.
46. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol*. 2002;20:2824-2831.

47. Karavasilis V, Seddon BM, Ashley S, et al. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. *Cancer*. 2008;112:1585-1591.
48. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29:2528-2533.
49. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879-1886
50. Mancari R, Signorelli M, Gadducci A, et al. Adjuvant chemotherapy in stage I-II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. *Gynecol Oncol*. 2014;133:531-536.
51. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol*. 2009;27:3126-3132.
52. Rajendra R, Jones RL, Pollack SM. Targeted treatment for advanced soft tissue sarcoma: profile of pazopanib. *Onco Targets Ther*. 2013;6:217- 222.
53. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *Oncologist*. 2012;17:1213-1220.
54. van Hoesel QG, Verweij J, Catimel G, et al. Phase II study with docetaxel (Taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. *Ann Oncol*. 1994;5:539- 542.
55. Edmonson JH, Ebbert LP, Nascimento AG, et al. Phase II study of docetaxel in advanced soft tissue sarcomas. *Am J Clin Oncol*. 1996;19:574-576
56. Ferriss JS, Atkins KA, Lachance JA, et al. Temozolomide in advanced and recurrent uterine leiomyosarcoma and correlation with o6- methylguanine DNA methyltransferase expression: a case series. *Int J Gynecol Cancer*. 2010;20:120-125.
57. Anderson S, Aghajanian C. Temozolomide in uterine leiomyosarcomas. *Gynecol Oncol*. 2005;98:99-103.
58. Talbot SM, Keohan ML, Hesdorffer M, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. *Cancer*. 2003;98:1942-1946.
59. Oosten AW, Seynaeve C, Schmitz PI, et al. Outcomes of first-line chemotherapy in patients with advanced or metastatic leiomyosarcoma of uterine and non-uterine origin. *Sarcoma*. 2009;2009:348910.
60. Bernstein-Molho R, Grisaro D, Soyfer V, et al. Metastatic uterine leiomyosarcomas: a single-institution experience. *Int J Gynecol Cancer*. 2010;20:255-260.
61. Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. *Gynecol Oncol*. 2004;92:644-647.
62. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic

- soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer*. 2001;37:870-877.
63. Sutton G, Blessing J, Hanjani P, Kramer P. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2005;96:749-752.
 64. Gallup DG, Blessing JA, Andersen W, Morgan MA. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a gynecologic oncology group study. *Gynecol Oncol*. 2003;89:48-51.
 65. George S, Feng Y, Manola J, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. *Cancer*. 2014;120:738-743.
 66. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2009;27:4188-4196.
 67. Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol*. 2015;16:457-464.
 68. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2015.
 69. Hensley ML, Patel SR, von Mehren M, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: Subgroup analysis of a phase 3, randomized clinical trial. *Gynecol Oncol*. 2017;146:531-537.
 70. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016 Apr 16;387(10028):1629-37. DOI: 10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10. PMID: 26874885.
 71. Hanvic B, Ray-Coquard I. Gynecological sarcomas: literature review of 2020. *Curr Opin Oncol*. 2021 Jul 1;33(4):345-350. DOI: 10.1097/CCO.0000000000000753. PMID: 34009140.
 72. Rizzo A, Nannini M, Astolfi A, et al. Impact of Chemotherapy in the Adjuvant Setting of Early Stage Uterine Leiomyosarcoma: A Systematic Review and Updated Meta-Analysis. *Cancers (Basel)*. 2020 Jul 14;12(7):1899. DOI: 10.3390/cancers12071899. PMID: 32674439; PMCID: PMC7409135.
 73. Pautier P, Penel N, Ray-Coquard I et al. A phase II of gemcitabine combined with pazopanib followed by pazopanib maintenance, as second-line treatment in patients with advanced leiomyosarcomas: A unicancer French Sarcoma Group study (LMS03 study). *Eur J Cancer*. 2020 Jan;125:31-37. DOI: 10.1016/j.ejca.2019.10.028. Epub 2019 Dec 10. PMID: 31835236.
 74. Tap WD, Wagner AJ, Schöffski P, et al. ANNOUNCE Investigators. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients with Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. *JAMA*. 2020 Apr 7;323(13):1266-1276. DOI: 10.1001/jama.2020.1707. PMID: 32259228; PMCID: PMC7139275.
 75. Blay J-Y, Schöffski P, Bauer S, et al. Eribulin versus dacarbazine in patients with leiomyosarcoma: subgroup analysis from a phase 3, open-label, randomised study. *Br J Cancer*. 2019; 120:1026–1032.

76. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016; 387:1629–1637.
77. Seligson ND, Kautto E, Passen E, et al. BRCA1/2 functional loss defines a targetable subset in leiomyosarcoma. *Oncologist*. 2019; 24: 973–979
78. Post CCB, Westermann AM, Bosse T, Creutzberg CL, Kroep JR. PARP and PD-1/PD-L1 checkpoint inhibition in recurrent or metastatic endometrial cancer. *Crit Rev Oncol Hematol*. 2020 Aug;152:102973. DOI: 10.1016/j.critrevonc.2020.102973. Epub 2020 May 18. PMID: 32497971.
79. Musacchio L, Caruso G, Pisano C, Cecere SC, Di Napoli M, Attademo L, Tambaro R, Russo D, Califano D, Palaia I, Muzii L, Benedetti Panici P, Pignata S. PARP Inhibitors in Endometrial Cancer: Current Status and Perspectives. *Cancer Manag Res*. 2020 Jul 22;12:6123-6135. DOI: 10.2147/CMAR.S221001. PMID: 32801862; PMCID: PMC7383016.
80. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. *Lancet*. 2022 Apr 9;399(10333):1412-1428. DOI: 10.1016/S0140-6736(22)00323-3. PMID: 35397864.
81. Ray-Coquard I, Hatcher H, Bompas E, et al. A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in high-grade uterine sarcoma after stabilization or response to doxorubicin + ifosfamide following surgery or in metastatic first line treatment (EORTC62113). *Int J Gynecol Cancer*. 2020; 30:1633–1637.
82. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023;388(23):2159-2170. DOI:10.1056/NEJMoa2302312
83. Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. *N Engl J Med*. 2023;388(23):2145-2158. DOI:10.1056/NEJMoa2216334
84. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib Plus Pembrolizumab in Patients with Advanced Endometrial Cancer. *J Clin Oncol*. 2020;38(26):2981-2992. DOI:10.1200/JCO.19.02627
85. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. *J Immunother Cancer*. 2022;10(1):e003777. DOI:10.1136/jitc-2021-003777
86. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients with Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. *J Clin Oncol*. 2022;40(7):752-761. DOI:10.1200/JCO.21.01874
87. Andre T, Bertib D, Curigliano G, et al. Efficacy and safety of dostarlimab in patients (pts) with mismatch repair deficient (dMMR) solid tumors: Analysis of 2 cohorts in the GARNET study. *J Clin Oncol*. 40 (16_suppl):2587. DOI:10.1200/JCO.2022.40.16_suppl.2587
88. Wang L, Li S, Zhang Z, Jia J, Shan B. Prevalence and occult rates of uterine leiomyosarcoma. *Medicine (Baltimore)*. 2020;99(33):e21766. DOI:10.1097/MD.00000000000021766
89. Makker V, Aghajanian C, Cohn AL, et al. A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update. *J Clin Oncol*. 2023;41(5):974-979. DOI:10.1200/JCO.22.01021
90. Konstantinopoulos PA, Luo W, Liu JF, et al. Phase II Study of Avelumab in Patients with Mismatch Repair Deficient and Mismatch Repair Proficient Recurrent/Persistent Endometrial Cancer. *J Clin Oncol*. 2019;37(30):2786-2794. DOI:10.1200/JCO.19.01021

91. Pautier P, Italiano A, Piperno-Neumann S, et al. Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma (LMS-04): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol.* 2022;23(8):1044-1054. DOI:10.1016/S1470-2045(22)00380-1
92. Pautier P, Floquet A, Chevreau C, et al. A single-arm multicentre phase II trial of doxorubicin in combination with trabectedin in the first-line treatment for leiomyosarcoma with long-term follow-up and impact of cytoreductive surgery. *ESMO Open* 2021; 6: 100209.

Change control

Date	Changes
July 1, 2020	<p>Added change control</p> <p>New pathways — Small Cell Lung Cancer and Hepatobiliary Cancer</p> <p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Melanoma Pathways: <ul style="list-style-type: none"> – Removed “Stages IIIB and IIIC” from Adjuvant • Colon Pathways: <ul style="list-style-type: none"> – Updated name to “Colon/Rectal” to reflect pathways for rectal cancer – Removed FOLFOX/FOLFIRI + Cetuximab regimen from Colon Cancer: Metastatic KRAS/NRAS: Wild Type – 1st and 2nd Lines of Therapy
Aug. 1, 2020	<p>New pathways — Ovarian Cancer</p>
Oct. 1, 2020	<p>New pathways — Non-Small-Cell Lung Cancer</p> <p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Breast Pathways: <ul style="list-style-type: none"> – Added capecitabine + lapatinib to pathways for HER2 POSITIVE: 1st + Subsequent Lines of Therapy • Pancreatic Pathways: <ul style="list-style-type: none"> – Added fluorouracil/leucovorin to Locally Advanced/Metastatic: 2nd + Subsequent Lines of Therapy • Colon/Rectal Pathways: <ul style="list-style-type: none"> – Added capecitabine + oxaliplatin (CAPEOX) to pathways for Adjuvant – Added new category of pathways for Metastatic: MSI/dMMR: 1st + Subsequent Lines of Therapy
Nov. 1, 2020	<p>New pathways — Head and Neck Cancer</p> <p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Melanoma Pathways: <ul style="list-style-type: none"> – Removed Nivolumab single agent from Adjuvant and Metastatic/Unresectable

Date	Changes
Jan. 1, 2021	New pathways — Multiple Myeloma
March 1, 2021	<p>New pathways — Diffuse Large B-Cell Lymphoma</p> <p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Hepatocellular carcinoma: <ul style="list-style-type: none"> – Added Atezolizumab + Bevacizumab regimen to pathways as 1st Line of Therapy and 2nd + Subsequent Lines of Therapy – Added Sorafenib or Lenvatinib to 2nd + Subsequent Lines of Therapy • Biliary tract cancers: <ul style="list-style-type: none"> – Added FOLFOX, Pemigatinib (in FGFR2 mutation cholangiocarcinoma), and Ivosidenib (in IDH1 mutation cholangiocarcinoma) to pathways as 2nd + subsequent lines of therapy
May 1, 2021	New pathways — Follicular Lymphoma and Marginal Zone Lymphoma
June 1, 2021	<p>New pathways — Mantle Cell Lymphoma</p> <p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Follicular Lymphoma and Marginal Zone Lymphoma <ul style="list-style-type: none"> – Added pathway options for refractory disease
July 1, 2021	<p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Mantle Cell Lymphoma <ul style="list-style-type: none"> – Added pathway option for maintenance after first line of therapy • Lung Cancer
Sept. 1, 2021	<p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Ovarian Cancer <ul style="list-style-type: none"> – Added carboplatin to pathways as Primary/Adjuvant Therapy • Head and Neck Cancer <ul style="list-style-type: none"> – Added “Cisplatin/Carboplatin + 5FU + Cetuximab, followed by Cetuximab Maintenance (Extreme regimen),” “Cisplatin/Carboplatin + Docetaxel/Paclitaxel,” and “Cisplatin + 5FU” regimens to pathways as non-nasopharyngeal: recurrent/metastatic unresectable: 2nd + subsequent line of therapy
Oct. 1, 2021	New pathways — Bladder Cancer

Date	Changes
Dec. 1, 2021	<p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Breast Pathways: <ul style="list-style-type: none"> – Added olaparib (for BRCA 1/2 mutation positive) to pathways for Neoadjuvant/Adjuvant – HER2 Negative – Added trastuzumab to pathways for Adjuvant (residual disease post-neoadjuvant therapy) – HER2 Positive – Removed atezolizumab + nab-paclitaxel (in PD-L1 Positive and metastatic TNBC) from pathways • Pancreatic Pathways: <ul style="list-style-type: none"> – Added FOLFIRINOX/mFOLFIRINOX to pathways for locally advanced or metastatic — 2nd + Subsequent Lines of Therapy • Colon/Rectal Pathways: <ul style="list-style-type: none"> – Added fluorouracil + leucovorin ± bevacizumab to pathways for metastatic disease • Melanoma <ul style="list-style-type: none"> – Added pembrolizumab to pathways for Adjuvant (Resectable): BRAF Mutated
March 1, 2022	<p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Breast Pathways: <ul style="list-style-type: none"> – Added pembrolizumab + paclitaxel (mTNBC and PD-L1 expression threshold for positivity combined positive score ≥ 10) to pathways – Added pembrolizumab + gemcitabine + carboplatin (mTNBC and PD-L1 expression threshold for positivity combined positive score ≥ 10) to pathways – Added sacituzumab govitecan-hziy (mTNBC and after 2 prior therapies for metastatic disease) to pathways – Added fam-trastuzumab deruxtecan-nxki to pathways for 2nd + Subsequent Lines of Therapy in HER2 Positive metastatic disease • Multiple Myeloma <ul style="list-style-type: none"> – Removed Bortezomib + Thalidomide + Dexamethasone (VTD) from relapsed or refractory disease – Removed Carfilzomib + Pomalidomide + Dexamethasone (KPD) from relapsed or refractory disease: 2nd Line of Therapy • Lymphoma, Diffuse Large B-Cell <ul style="list-style-type: none"> – Added rituximab-mini-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) to pathways for 1st Line of Therapy • Lymphoma, Follicular <ul style="list-style-type: none"> – Removed 3rd + Subsequent Lines of Therapy (refractory disease) category and changed “2nd Line of Therapy (refractory disease)” to “2nd + Subsequent Lines of Therapy (refractory disease)” – Removed Duvelisib, Idelalisib, Umbralisib from pathways • Lymphoma, Marginal Zone <ul style="list-style-type: none"> – Removed 3rd + Subsequent Lines of Therapy (refractory disease) category and changed “2nd Line of Therapy (refractory disease)” to “2nd + Subsequent Lines of Therapy (refractory disease)” – Removed Duvelisib, Idelalisib, Umbralisib from pathways

Date	Changes
April 1, 2022	Updates to existing pathways <ul style="list-style-type: none"> • Multiple Myeloma <ul style="list-style-type: none"> – Removed Panobinostat + Bortezomib + Dexamethasone from relapsed or refractory disease • Small Cell Lung Cancer <ul style="list-style-type: none"> – Added topotecan, paclitaxel, and irinotecan to pathways for subsequent line(s), relapse > 6 months • Non-Small Cell Lung Cancer <ul style="list-style-type: none"> – Removed pathways for advanced/metastatic, ROS1 rearrangement, MET Exon 14 skipping, BRAF V600E, RET rearrangement, and NTRK gene fusion
May 1, 2022	Updates to existing pathways <ul style="list-style-type: none"> • Hepatobiliary Tract Cancers <ul style="list-style-type: none"> – Removed pemigatinib (for FGFR2 mutated cholangiocarcinoma) • Head and Neck Cancer <ul style="list-style-type: none"> – No change to current pathway
July 1, 2022	New Pathways — Hodgkin Lymphoma and Kidney Cancer
Aug. 1, 2022	New Pathways — Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
Sept. 1, 2022	New Pathways — Uterine (Endometrial) Cancer
Nov. 1, 2022	Updates to existing pathways <ul style="list-style-type: none"> • Breast Cancer <ul style="list-style-type: none"> – Added Ribociclib + anastrozole/letrozole/exemestane to Metastatic and Recurrent – Endocrine therapy, HER2 negative, first line – Added Ribociclib + fulvestrant to Metastatic and Recurrent – Endocrine therapy, HER2 negative, 2nd and subsequent lines of therapy – Added Fam-trastuzumab deruxtecan-nxki to HER2 IHC 1+ or 2+/ISH negative metastatic or recurrent disease: 2nd + subsequent lines of therapy – Removed Talazoparib (Germline BRCA 1/2 Mutation Positive) from Metastatic and Recurrent – Chemotherapy, HER2 NEGATIVE: 1st and subsequent lines of therapy • Bladder Cancer <ul style="list-style-type: none"> – Removed Cisplatin + Methotrexate + Vinblastine (CMV) from Neoadjuvant/Adjuvant • Colon Cancer <ul style="list-style-type: none"> – Added Fluorouracil + Leucovorin + Oxaliplatin (FOLFOX) + Cetuximab and Fluorouracil + Leucovorin + Irinotecan (FOLFIRI) + Cetuximab to Metastatic KRAS/NRAS: Wild Type: 1st and 2nd line of therapy and MSI-H/dMMR: 1st + subsequent lines of therapy for left-sided colon cancer
Feb. 1, 2023	New Pathways — Chronic Myeloid Leukemia (CML), Esophageal and Esophagogastric Cancers, Gastric Cancer, and Prostate Cancer

Date	Changes
<p>May 1, 2023</p>	<p>Update to existing pathways</p> <ul style="list-style-type: none"> • Non-Small Cell Lung Cancer <ul style="list-style-type: none"> – Added Carboplatin/Cisplatin + Pemetrexed/Paclitaxel + Cemiplimab-rwlc (PD-L1: < 1%, 1 – 49%, and ≥ 50%) to Advanced/Metastatic – Nonsquamous (EGFR, ALK, RET WT) – 1st line of therapy – Added Carboplatin + Paclitaxel + Cemiplimab-rwlc (PD-L1: < 1%, 1 – 49%, and ≥ 50%) to Advanced/Metastatic – Squamous (EGFR, ALK, RET WT) – 1st line of therapy – Added Cemiplimab-rwlc ± Pemetrexed to Advanced/Metastatic – Nonsquamous (EGFR, ALK, RET WT) – Maintenance – Added Cemiplimab-rwlc to Advanced/Metastatic – Squamous (EGFR, ALK, RET WT) – Maintenance • Ovarian <ul style="list-style-type: none"> – Rucaparib – added to maintenance therapy following primary therapy (voted upon by committee 8/2022, NCCN went live with it V1.2023, December 22, 2022 – published in CGP tool on 5.12.2023)
<p>June 1, 2023</p>	<p>Updates to existing pathway</p> <ul style="list-style-type: none"> • Breast Cancer <ul style="list-style-type: none"> – Added Cisplatin/Carboplatin to Metastatic and Recurrent – Chemotherapy, HER2 negative, 1st line and subsequent lines of therapy, TNBC
<p>June 23, 2023</p>	<p>Updates to existing pathways</p> <ul style="list-style-type: none"> • Hepatobiliary split into two cancers, Hepatocellular and Biliary Tract Cancers
<p>Aug. 1, 2023</p>	<p>Update to existing pathway</p> <ul style="list-style-type: none"> • Melanoma <ul style="list-style-type: none"> – Removed Nivolumab (1mg/kg) + Ipilimumab (3mg/kg); kept Nivolumab (3mg/kg) + Ipilimumab (1mg/kg) as pathway
<p>Sept. 1, 2023</p>	<p>Update to existing pathways</p> <ul style="list-style-type: none"> • Ovarian Cancer <ul style="list-style-type: none"> – Carboplatin single-agent is removed from adjuvant/primary therapy as it has been removed from NCCN guidelines. • Uterine/Endometrial Cancer <ul style="list-style-type: none"> – Add dostarlimab + carboplatin/paclitaxel to primary/ adjuvant in dMMR/MSI-H patients. – Add dostarlimab + carboplatin/paclitaxel to first-line therapy for recurrent disease in dMMR/MSI-H patients and if prior ICI therapy was not received. – Add pembrolizumab + lenvatinib to first line recurrent therapy in pMMR patients for patients who had not received prior ICI therapy. – Pembrolizumab + lenvatinib is 2nd line in pMMR patients, added the variable, for patients who had not received prior ICI therapy. – Remove nivolumab, avelumab, and dostarlimab from 2nd line pathways in patients that dMMR/MSI-H and pembrolizumab in TMB-H (≥10 mutations/mega-base) or dMMR/MSI-H tumors. – Move the following therapies to 2nd line recurrent: Docetaxel (2B), doxorubicin, liposomal doxorubicin, and paclitaxel.

Date	Changes
Oct. 1, 2023	<p>Update to existing pathways</p> <ul style="list-style-type: none"> • Bladder Cancer <ul style="list-style-type: none"> – Add nivolumab to adjuvant therapy in muscle invasive bladder cancer in patients who are high-risk and PD-L1 \geq 1%. – Carboplatin single-agent is removed from adjuvant/primary therapy as it has been removed from NCCN guidelines. • Colorectal Cancer <ul style="list-style-type: none"> – Changed pembrolizumab to the only first-line agent in patients who are dMMR/MSI-H. – The following regimens were moved to second and subsequent lines of therapy in patients who are dMMR/MSI-H: <ul style="list-style-type: none"> – FOLFOX \pm Bevacizumab – 5-FU + Leucovorin \pm Bevacizumab – Capecitabine – FOLFIRI \pm Bevacizumab – FOLFOX + Cetuximab* – FOLFIRI + Cetuximab* – FOLFOX + Panitumumab* – FOLFIRI + Panitumumab* – * KRAS/NRAS/BRAF WT and left-sided tumor only
Dec. 1, 2023	<p>Update to existing pathways</p> <ul style="list-style-type: none"> • Bladder Cancer <ul style="list-style-type: none"> – Add BCG maintenance for NMIBC • Esophageal, Esophagogastric Cancer <ul style="list-style-type: none"> – Addition of the following regimens in first-line recurrent or metastatic disease, HER2 negative or unknown disease <ul style="list-style-type: none"> – Capecitabine + Oxaliplatin + Pembrolizumab (CPS \geq 10) – Fluorouracil \pm Leucovorin + Cisplatin+ Pembrolizumab (CPS \geq 10) – Fluorouracil \pm Leucovorin + Oxaliplatin + Pembrolizumab (CPS \geq 10) – Capecitabine + Cisplatin + Pembrolizumab (CPS \geq 10) – Inclusion of “Unknown” to HER2 negative disease • Multiple Myeloma <ul style="list-style-type: none"> – Removal bortezomib + thalidomide + dexamethasone (VTD) due to removal from NCCN • Breast Cancer <ul style="list-style-type: none"> – The following regimens for HER2 positive moved to 4th line and subsequent due to NCCN updates: <ul style="list-style-type: none"> – Capecitabine + Lapatinib – Paclitaxel + Trastuzumab – Vinorelbine + Trastuzumab – Gemcitabine + Trastuzumab – Capecitabine + Trastuzumab

Date	Changes
March 1, 2024	<p>Update to existing pathways</p> <ul style="list-style-type: none"> • Prostate Cancer <ul style="list-style-type: none"> – Addition of the following regimen in castrate resistant metastatic recurrent prostate cancer with no prior novel hormone therapy, without and with prior docetaxel <ul style="list-style-type: none"> – Olaparib + Abiraterone (BRCA 1/2) • Non-Small Cell Lung Cancer <ul style="list-style-type: none"> – Addition of the following regimens in Neoadjuvant / Adjuvant therapy <ul style="list-style-type: none"> – Carboplatin + Pemetrexed +/- XRT – Nivolumab + Carboplatin or Cisplatin + Paclitaxel (Neoadjuvant only) – Nivolumab + Carboplatin or Cisplatin + Pemetrexed (Neoadjuvant only, Nonsquamous only) – Nivolumab + Carboplatin or Cisplatin + Gemcitabine (Neoadjuvant only, Squamous only) – Addition of the following regimens to Advanced/ Metastatic First-Line in “IO Ineligible” <ul style="list-style-type: none"> – Carboplatin or Cisplatin + Paclitaxel – Carboplatin or Cisplatin + Pemetrexed (Nonsquamous only) – Carboplatin + Cisplatin + Gemcitabine (Squamous only) – Addition of the following regimens to Advanced/ Metastatic Second-Line <ul style="list-style-type: none"> – Gemcitabine
Addition pending NCCN addition	<ul style="list-style-type: none"> • Gastric Cancer (10/2023) <ul style="list-style-type: none"> – Addition of the following regimens in first-line recurrent or metastatic disease, HER2 negative or unknown disease <ul style="list-style-type: none"> – Capecitabine + Oxaliplatin + Pembrolizumab (CPS ≥ 10) – Fluorouracil ± Leucovorin + Cisplatin+ Pembrolizumab (CPS ≥ 10) – Fluorouracil ± Leucovorin + Oxaliplatin + Pembrolizumab (CPS ≥ 10) – Capecitabine + Cisplatin + Pembrolizumab (CPS ≥ 10) – Inclusion of “Unknown” to HER2 negative disease • Prostate Cancer (1/2024) <ul style="list-style-type: none"> – Addition of the following regimen in castrate resistant metastatic recurrent prostate cancer with no prior novel hormone therapy, without and with prior docetaxel <ul style="list-style-type: none"> – Olaparib + Abiraterone + ADT (HRRm) • Non-Small Cell Lung Cancer (1/2024) <ul style="list-style-type: none"> – Addition of the following regimen to Advanced/ Metastatic First-Line <ul style="list-style-type: none"> – Atezolizumab + Carboplatin or Cisplatin + Paclitaxel (Nonsquamous only) – Addition of the following regimen to Advanced/ Metastatic Maintenance <ul style="list-style-type: none"> – Atezolizumab (Nonsquamous)