Supplemental Online Content

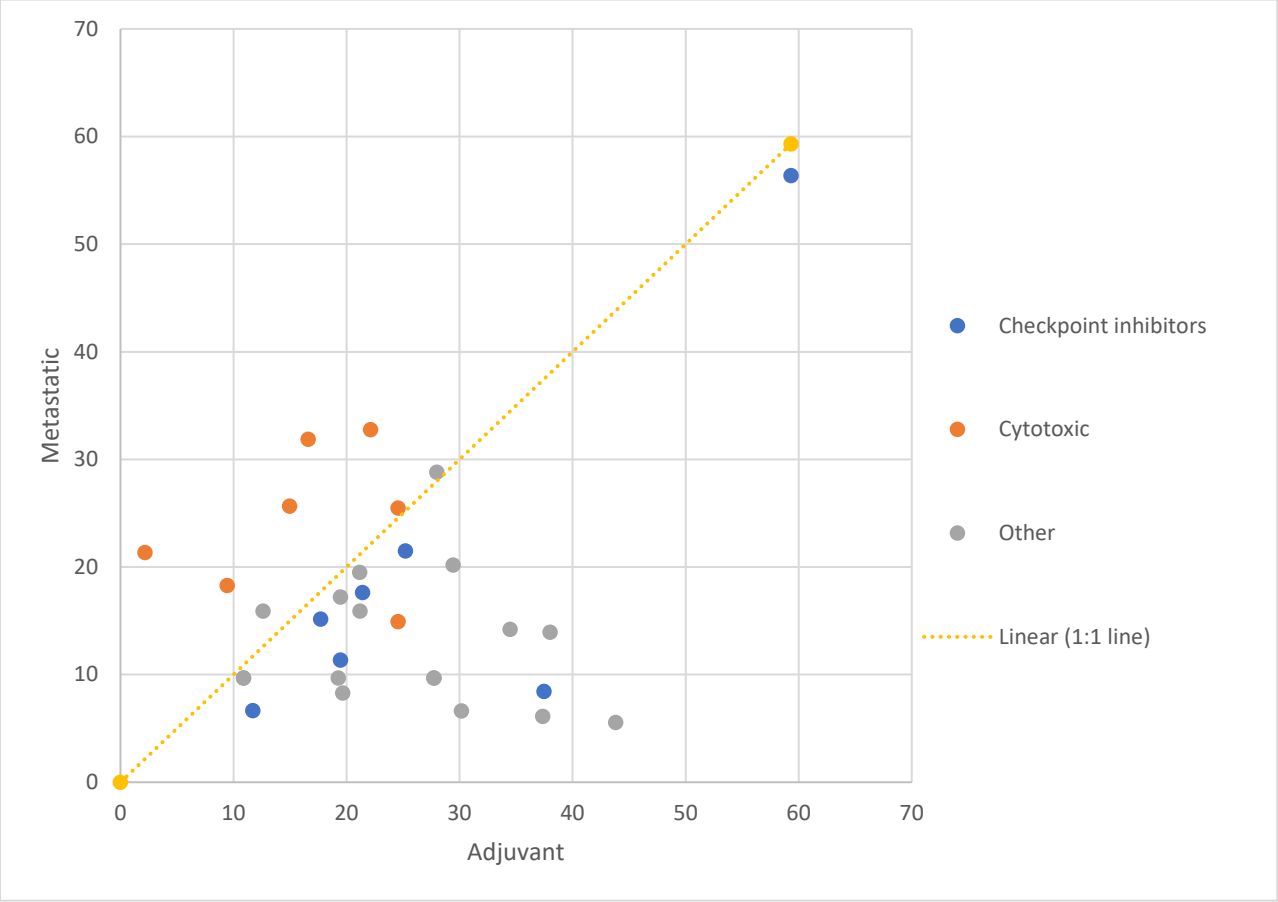
Ahmed N, Vengalasetti Y, Haslam A, Prasad V. Association of adjuvant or metastatic setting with discontinuation of cancer drugs in clinical trials. *JAMA Netw Open.* 2022;5(5):e2212327. doi:10.1001/jamanetworkopen.2022.12327

This supplemental material has been provided by the authors to give readers additional information about their work.

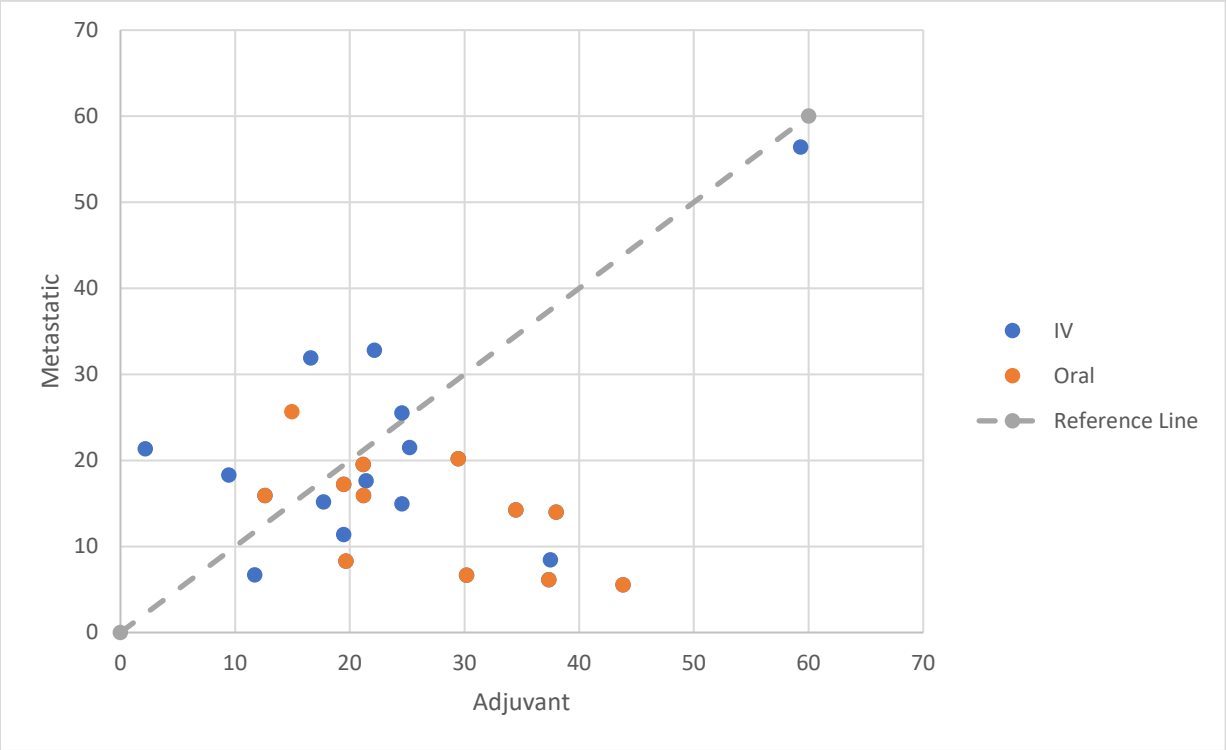
eTable. Study Trials

Drug	Tumor	Adjuvant study	Metastatic Study
Pembrolizumab	Melanoma	KEYNOTE-054 trial[1]	KEYNOTE-006[2]
Atezolizumab	Urothelial	IMvigor010 study[3]	IMvigor211[4]
Palbociclib	Breast	PALLAS trial[5]	PALOMA-3[6]
nivolumab	Melanoma	CheckMate 238 trial[7]	CheckMate 066[8]
Nivolumab plus ipilimumab	Melanoma	IMMUNED trial[9]	CheckMate 069[10]
Imatinib	GIST	PERSIST-5 Trial[11]	No name[12]
Afatinib	SCCHN	LUX-Head & Neck 2[13]	No name[14]
Olaparib	Breast	OlympiA[15]	OlympiAD[16]
Nivolumab	Gastric	CheckMate 577 trial[17]	CheckMate 649[18]
Nivolumab	Urothelial	CheckMate 274[19]	CheckMate 275[20]
Osimertinib	NSCLC	ADAURA[21]	FLAURA[22]
Trastuzumab emtansine	Breast	KATHERINE[23]	EMILIA[24]
Pertuzumab plus trastuzumab	Breast	APHINITY Trial[25]	CLEOPATRA[26]
Abemaciclib	Breast	monarchE[27]	MONARCH 3[28]
Ipilimumab	Melanoma	E1609 trial[29]	No name[30]
Erlotinib	NSCLC	SELECT trial[31]	EURTAC[32]
Sorafenib	RCC	SORCE trial[33]	TARGET[34]
Trastuzumab emtansine	Breast	ATEMPT trial[35]	EMILIA[24]
Bevacizumab	Breast	E5103 trial[36]	No name[37]
Dabrafenib plus trametinib	Melanoma	COMBI-AD trial[38]	COMBI-d[39]
Paclitaxel plus carboplatin	Breast	PATTERN[40]	BROCADE3[41]
Modified FOLFIRINOX regimen with gemcitabine	Pancreatic	PRODIGE 24–ACCORD[42]	No name[43]
Capecitabine	Breast	GEICAM/2003-11_CIBOMA/2004-01[44]	No name[45]
Gefitinib	NSCLC	CTONG1104[46]	WJTOG3405[47]
Gefitinib	NSCLC	IMPACT[48]	WJTOG3405[47]
Pemetrexed plus Cisplatin	NSCLC	JIPANG[49]	INSPIRE[50]
Carboplatin plus gemcitabine	Urothelial	POUT Trial[51]	EORTC 30986[52]
Irinotecan plus Cisplatin	SCLC - extensive	JCOG1205/1206[53]	No name[54]
Irinotecan plus Cisplatin	SCLC - limited	JCOG1205/1206[53]	WJTOG 9902[55]

eFigure 1. Discontinuation Percentages (Adverse Events and Withdrawal) for Drugs in the Metastatic vs Adjuvant Settings, by Drug Type



eFigure 2. Discontinuation Percentages (Adverse Events and Withdrawal) for Drugs in the Metastatic vs Adjuvant Settings, by Route of Administration



eReferences.

1. Eggermont AMM, Blank CU, Mandalà 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: 10.1016/s1470-2045(21)00065-6.
2. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *New England Journal of Medicine.* 2015;372(26):2521-2532. doi: 10.1056/NEJMoa1503093. Accessed 2021/12/15.
3. Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(4):525-537. doi: 10.1016/s1470-2045(21)00004-8.
4. Powles T, Durán I, van der Heijden MS, 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. *The Lancet.* 2018;391(10122):748-757. doi: https://doi.org/10.1016/S0140-6736(17)33297-X.
5. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2021;22(2):212-222. doi: 10.1016/s1470-2045(20)30642-2.
6. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *New England Journal of Medicine.* 2018;379(20):1926-1936. doi: 10.1056/NEJMoa1810527. Accessed 2021/12/15.
7. Ascierto PA, 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;21(11):1465-1477. doi: 10.1016/s1470-2045(20)30494-0.
8. Robert C, Long GV, Brady B, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *New England Journal of Medicine.* 2014;372(4):320-330. doi: 10.1056/NEJMoa1412082. Accessed 2021/12/15.
9. Zimmer L, Livingstone E, Hassel JC, et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet.* 2020;395(10236):1558-1568. doi: 10.1016/s0140-6736(20)30417-7.
10. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. *New England Journal of Medicine.* 2015;372(21):2006-2017. doi: 10.1056/NEJMoa1414428. Accessed 2021/12/15.
11. Raut CP, Espat NJ, Maki RG, et al. Efficacy and Tolerability of 5-Year Adjuvant Imatinib Treatment for Patients With Resected Intermediate- or High-Risk Primary Gastrointestinal Stromal Tumor: The PERSIST-5 Clinical Trial. *JAMA Oncology.* 2018;4(12):e184060-e184060. doi: 10.1001/jamaoncol.2018.4060. Accessed 12/14/2021.
12. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004;364(9440):1127-1134. doi: 10.1016/s0140-6736(04)17098-0.
13. Burtness B, Haddad R, Dinis J, et al. Afatinib vs Placebo as Adjuvant Therapy After Chemoradiotherapy in Squamous Cell Carcinoma of the Head and Neck: A Randomized Clinical

Trial. *JAMA Oncology.* 2019;5(8):1170-1180. doi: 10.1001/jamaoncol.2019.1146. Accessed 12/14/2021.
14. Seiwert TY, Fayette J, Cupissol D, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck†. *Annals of Oncology.* 2014;25(9):1813-1820. doi: https://doi.org/10.1093/annonc/mdu216.
15. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med.* 2021;384(25):2394-2405. doi: 10.1056/NEJMoa2105215.
16. Robson M, Im S-A, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *New England Journal of Medicine.* 2017;377(6):523-533. doi: 10.1056/NEJMoa1706450. Accessed 2021/12/15.
17. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *New England Journal of Medicine.* 2021;384(13):1191-1203. doi: 10.1056/NEJMoa2032125. Accessed 2021/12/14.
18. 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(10294):27-40. doi: 10.1016/s0140-6736(21)00797-2.
19. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *New England Journal of Medicine.* 2021;384(22):2102-2114. doi: 10.1056/NEJMoa2034442. Accessed 2021/12/14.
20. 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. *The Lancet Oncology.* 2017;18(3):312-322. doi: https://doi.org/10.1016/S1470-2045(17)30065-7.
21. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. *New England Journal of Medicine.* 2020;383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Accessed 2021/12/14.
22. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;378(2):113-125. doi: 10.1056/NEJMoa1713137.
23. von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *New England Journal of Medicine.* 2018;380(7):617-628. doi: 10.1056/NEJMoa1814017. Accessed 2021/12/14.
24. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *New England Journal of Medicine.* 2012;367(19):1783-1791. doi: 10.1056/NEJMoa1209124. Accessed 2021/12/15.
25. 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. *Journal of Clinical Oncology.* 2021;39(13):1448-1457. doi: 10.1200/JCO.20.01204. Accessed 2021/12/14.
26. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *New England Journal of Medicine.* 2011;366(2):109-119. doi: 10.1056/NEJMoa1113216. Accessed 2021/12/15.
27. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *Journal of Clinical Oncology.* 2020;38(34):3987-3998. doi: 10.1200/JCO.20.02514. Accessed 2021/12/14.
28. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *Journal of Clinical Oncology.* 2017;35(32):3638-3646. doi: 10.1200/JCO.2017.75.6155. Accessed 2021/12/15.

29. Tarhini AA, Lee SJ, Hodi FS, et al. Phase III Study of Adjuvant Ipilimumab (3 or 10 mg/kg) Versus High-Dose Interferon Alfa-2b for Resected High-Risk Melanoma: North American Intergroup E1609. *Journal of Clinical Oncology.* 2019;38(6):567-575. doi: 10.1200/JCO.19.01381. Accessed 2021/12/14.

30. Hodi FS, O'Day SJ, McDermott DF, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine.* 2010;363(8):711-723. doi: 10.1056/NEJMoa1003466. Accessed 2021/12/15.

31. Pennell NA, Neal JW, Chaft JE, et al. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer. *Journal of Clinical Oncology.* 2018;37(2):97-104. doi: 10.1200/JCO.18.00131. Accessed 2021/12/14.

32. Rosell R, Carcereny E, Gervais R, et al. 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. *The Lancet Oncology.* 2012;13(3):239-246. doi: https://doi.org/10.1016/S1470-2045(11)70393-X.

33. Eisen T, Frangou E, Oza B, et al. Adjuvant Sorafenib for Renal Cell Carcinoma at Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase III Intergroup Trial. *Journal of Clinical Oncology.* 2020;38(34):4064-4075. doi: 10.1200/JCO.20.01800. Accessed 2021/12/14.

34. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. *New England Journal of Medicine.* 2007;356(2):125-134. doi: 10.1056/NEJMoa060655. Accessed 2021/12/15.

35. Tolaney SM, Tayob N, Dang C, et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial. *Journal of Clinical Oncology.* 2021;39(21):2375-2385. doi: 10.1200/JCO.20.03398. Accessed 2021/12/14.

36. Miller KD, O'Neill A, Gradishar W, et al. Double-Blind Phase III Trial of Adjuvant Chemotherapy With and Without Bevacizumab in Patients With Lymph Node–Positive and High-Risk Lymph Node–Negative Breast Cancer (E5103). *Journal of Clinical Oncology.* 2018;36(25):2621-2629. doi: 10.1200/JCO.2018.79.2028. Accessed 2021/12/14.

37. Miller K, Wang M, Gralow J, et al. Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer. *New England Journal of Medicine.* 2007;357(26):2666-2676. doi: 10.1056/NEJMoa072113. Accessed 2021/12/15.

38. Hauschild A, Dummer R, Schadendorf D, et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600–Mutant Stage III Melanoma. *Journal of Clinical Oncology.* 2018;36(35):3441-3449. doi: 10.1200/JCO.18.01219. Accessed 2021/12/14.

39. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. *New England Journal of Medicine.* 2014;371(20):1877-1888. doi: 10.1056/NEJMoa1406037. Accessed 2021/12/15.

40. Yu K-D, Ye F-G, He M, et al. Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncology.* 2020;6(9):1390-1396. doi: 10.1001/jamaoncol.2020.2965. Accessed 12/16/2021.

41. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2020;21(10):1269-1282. doi: https://doi.org/10.1016/S1470-2045(20)30447-2.

42. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *New England Journal of Medicine.* 2018;379(25):2395-2406. doi: 10.1056/NEJMoa1809775. Accessed 2021/12/15.

43. Ozaka M, Ishii H, Sato T, et al. A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *Cancer Chemotherapy and Pharmacology.* 2018;81(6):1017-1023. doi: 10.1007/s00280-018-3577-9.

44. Lluch A, Barrios CH, Torrecillas L, et al. Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01). *Journal of Clinical Oncology.* 2019;38(3):203-213. doi: 10.1200/JCO.19.00904. Accessed 2021/12/15.

45. Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(20):3256-3263. doi: 10.1200/JCO.2009.24.4244.

46. Zhong W-Z, Wang Q, Mao W-M, et al. Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC: Final Overall Survival Analysis of CTONG1104 Phase III Trial. *Journal of Clinical Oncology.* 2020;39(7):713-722. doi: 10.1200/JCO.20.01820. Accessed 2021/12/15.

47. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 2010;11(2):121-128. doi: 10.1016/s1470-2045(09)70364-x.

48. Tada H, Mitsudomi T, Misumi T, et al. Randomized Phase III Study of Gefitinib Versus Cisplatin Plus Vinorelbine for Patients With Resected Stage II-IIIA Non–Small-Cell Lung Cancer With EGFR Mutation (IMPACT). *Journal of Clinical Oncology.* 2021:JCO.21.01729. doi: 10.1200/JCO.21.01729. Accessed 2021/12/15.

49. Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized Phase III Study of Pemetrexed Plus Cisplatin Versus Vinorelbine Plus Cisplatin for Completely Resected Stage II to IIIA Nonsquamous Non–Small-Cell Lung Cancer. *Journal of Clinical Oncology.* 2020;38(19):2187-2196. doi: 10.1200/JCO.19.02674. Accessed 2021/12/15.

50. Paz-Ares L, Mezger J, Ciuleanu TE, et al. Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. *Lancet Oncol.* 2015;16(3):328-337. doi: 10.1016/s1470-2045(15)70046-x.

51. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet.* 2020;395(10232):1268-1277. doi: 10.1016/s0140-6736(20)30415-3.

52. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(2):191-199. doi: 10.1200/JCO.2011.37.3571.

53. Kenmotsu H, Niho S, Tsuboi M, et al. Randomized Phase III Study of Irinotecan Plus Cisplatin Versus Etoposide Plus Cisplatin for Completely Resected High-Grade Neuroendocrine Carcinoma of the Lung: JCOG1205/1206. *Journal of Clinical Oncology.* 2020;38(36):4292-4301. doi: 10.1200/JCO.20.01806. Accessed 2021/12/15.

54. Hanna N, Bunn PA, Langer C, et al. Randomized Phase III Trial Comparing Irinotecan/Cisplatin With Etoposide/Cisplatin in Patients With Previously Untreated Extensive-Stage Disease Small-Cell Lung Cancer. *Journal of Clinical Oncology.* 2006;24(13):2038-2043. doi: 10.1200/JCO.2005.04.8595. Accessed 2021/12/15.

55. Saito H, Takada Y, Ichinose Y, et al. Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902. *Journal of Clinical Oncology.* 2006;24(33):5247-5252. doi: 10.1200/JCO.2006.07.1605. Accessed 2021/12/15.