Anthem

Cancer Care Quality Program

Treatment Pathways

EFFECTIVE: NOVEMBER 12, 2018

LAST REVIEWED: AUGUST 21, 2018

AIM SpecialtyHealth
8600 West Bryn Mawr Avenue
South Tower – Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

Appropriate.Safe.Affordable

9074-1118

Review and updates during 3rd quarter 2018

Bladder Cancer (Urothelial)

- Intravesical gemcitabine regimen added as a pathway option for low-grade histology only in the following clinical scenario: **'Adjuvant Therapy | Stage 0 (Ta, Tis) or Stage I | After TURBT* or Following Resection of Recurrent or Persistent Disease'**

Colorectal Cancer

- Capecitabine and oxaliplatin (CAPOX) combination regimen added as a pathway option, specifically for the low-risk (T1-3, N1), stage III population, limited to 3 cycles, in the following clinical scenario: '**Adjuvant Therapy'**

Lung Cancer: Non-Small Cell Lung Cancer (NSCLC)

- Clinical scenarios without ALK, EGFR, or ROS mutations have been restructured as follows:
  - **'Metastatic Disease | Squamous | TPS ≥ 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2'** was added.
    - Pembrolizumab (Keytruda), carboplatin, and paclitaxel combination regimen was added as a pathway option
  - **'Metastatic Disease | Squamous | PD-L1 Expression <50% | First Line of Therapy (1st Line) | ECOG PS: 0-2'** was changed to **'Metastatic Disease | Squamous | TPS < 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2'**
    - Carboplatin and paclitaxel combination regimen was removed as a pathway option
    - Cisplatin and gemcitabine (Gemzar) combination regimen was removed as a pathway option
    - Pembrolizumab (Keytruda) was added as a pathway option
  - **'Metastatic Disease | ALK and EGFR Negative | PD-L1 Positive | First Line of Therapy (1st Line) | ECOG PS: 0-2'** was changed to **'Metastatic Disease | Nonsquamous | ALK/EGFR Negative (ROS1 Negative or Unknown) | PD-L1 Positive TPS > 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2'**
  - **'Metastatic Disease | Nonsquamous | ALK/EGFR Negative (ROS1 Negative or Unknown) | PD-L1 Positive TPS < 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2'** was added
    - Pembrolizumab (Keytruda), pemetrexed (Alimta), and carboplatin combination regimen was added as a pathway option
  - **'Metastatic Disease | Non-Squamous | First Line of Therapy (1st Line) | ECOG PS: 0-2'** was changed to **'Metastatic Disease | Squamous or Nonsquamous | Immunotherapy-Ineligible | First Line of Therapy (1st Line) | ECOG PS: 0-2'**
    - Carboplatin, pemetrexed (Alimta), and pembrolizumab (Keytruda) was removed as a pathway option
- Pemetrexed and pembrolizumab combination regimen added as a pathway option for patients previously treated with carboplatin, pemetrexed and pembrolizumab in the following clinical scenario: **'Metastatic Disease | Non-Squamous | Maintenance | ECOG PS: 0-2'**
- In the **'Metastatic Disease | Second or Subsequent Lines of Therapy (2nd Line+) | ECOG PS: 0-2'** the following pathway changes have been made:
  - Atezolizumab (Tecentriq) clarified to require "no prior checkpoint inhibitors"
  - Nivolumab (Opdivo) clarified to require "no prior checkpoint inhibitors"
  - Pemetrexed (Alimta) (non-squamous histology) was removed as a pathway option
  - Carboplatin and paclitaxel combination regimen was added as a pathway option
  - Carboplatin and gemcitabine (Gemzar) combination regimen was added as a pathway option
  - Carboplatin and pemetrexed (Alimta) combination regimen was added as a pathway option

NHL: Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL)

- Venetoclax (Venclexta) and rituximab combination regimen added as a pathway option in the following clinical scenarios:
  - **'Second and Subsequent Lines of Therapy (2nd Line+)| With 17 Deletion or TP53 Mutation Present'**
  - **'Second and Subsequent Lines of Therapy (2nd Line+)| Without 17p Deletion'**
- Bendamustine and rituximab (BR) regimen removed as a pathway option from the following clinical scenario: **'Second and Subsequent Lines of Therapy (2nd Line+)| Without 17p Deletion'**

NHL: Mantle Cell Lymphoma

- Acalabrutinib (Calquence) regimen added as a pathway option in the following clinical scenario: **'Second and Subsequent Lines of Therapy (2nd Line+)'**

Ovarian Cancer (Epithelial)

- Rucaparib (Rubraca) regimen added as a pathway option in the following clinical scenario: **'Recurrent Disease | Maintenance Therapy | Platinum Sensitive'**
- Olaparib (Lynparza) regimen added as a pathway option in the following clinical scenario: **'Recurrent Disease | Maintenance Therapy | Platinum Sensitive'**

Prostate Cancer (Adenocarcinoma)

- No updates at this time

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

CONTENTS

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

Cancer Care Quality Program

The goal of the Cancer Care Quality Program is to help provide access to quality and affordable cancer care. A key component of the Cancer Care Quality Program is Cancer Treatment Pathways ("Pathways").

The Pathways are developed using a rigorous process of evidence-based medicine. Pathways differ from clinical practice guidelines in that the objective of a Pathway is to identify a subset of regimens supported by clinical evidence and practice guidelines with the goal of further reducing unwarranted variation in care and cost. Pathways are selected based on: clinical benefit (efficacy), safety/side effects (especially those leading to hospitalizations & impacting quality of life), strength of national guideline recommendations, and cost of regimens. The Pathways developed for this Program are intended to support quality cancer care.

Selecting a Pathway depends upon a number of factors – the type of cancer, the stage of disease, and the biomarkers or specific genetic profile of the cancer. Within each cancer type, separate Pathways are usually available for early stage and advanced cancer, sub-types of cancer (e.g. HER2 positive) and different lines of therapy.

Pathways are not available for every medical condition but are intended to be applicable for 80%-90% of individuals with the most common types of cancer. Selecting the best cancer treatment depends upon a number of factors – the type of cancer, the stage, the biomarkers or specific genetic profile of the cancer, and unique aspects of each individual's medical condition. Given the complexity of cancer and all of the unique individual circumstances, it would not be possible to have a Pathway for every specific situation. The treating oncologist will determine if, in his/her medical opinion, a Pathway treatment regimen is the best option for a patient or whether, given his or her unique circumstances, another treatment regimen will be a better treatment for him or her.

It is important to note that we will review requested services in accordance with our medical policies and clinical guidelines. When a request is received from a provider that requires medical necessity review, whether it is a Pathway or non-pathway regimen it may be authorized if it is determined to be medically necessary pursuant to our medical policies and clinical guidelines.

Feedback to enhance the Cancer Care Quality Program, Pathways, and/or questions can be emailed to cancer.quality@anthem.com. Requests for the evidence summaries reviewed to develop individual Pathways can also be sent to the same email address.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

Bladder Cancer (Urothelial) Pathways

Neoadjuvant Therapy | Clinical Stage II, III, or IV Without Evidence of Metastases (cT2, cT3, cT4a, cT4b, M0)

CMV: cisplatin, methotrexate, and vinblastine 3 cycles[4,5]

Gemcitabine (Gemzar) and cisplatin 4 cycles[2]

Adjuvant Therapy | Stage 0 (Ta, Tis) or Stage I | After TURBT* or Following Resection of Recurrent or Persistent Disease

BCG: bacillus calmette-guerin, intravesical[20-24]

Gemcitabine (Gemzar), intravesical **(low-grade histology only)**[40] – Added effective 11/12/2018

Metastatic Disease | First Line of Therapy (1st Line)

Gemcitabine (Gemzar) and cisplatin†[6,17,18]

Metastatic Disease | Second Line of Therapy (2nd Line)

Gemcitabine (Gemzar)[9]

Paclitaxel[14]

Pembrolizumab (Keytruda)[37]

* TURBT: Transurethral resection of bladder tumor

† In the setting of recurrent/metastatic disease, a substitution of carboplatin for cisplatin will be considered a pathway option

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

BLADDER CANCER (UROTHELIAL) REFERENCES

NCCN Practice Guidelines: Bladder Cancer Version 5.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V5.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Plimack ER, Hoffman-Censits JH, 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;32(18):1895-901. PMID: 24821881
2. Dash A, Pettus JA, Herr HW, et al. A role of neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer. 2008;113(9):2471-7. PMID: 18823036
3. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859-66. PMID: 12944571
4. Griffiths G, Hall R, Sylvester R, et al. 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;29:2171-2177. PMID: 21502557
5. International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomized controlled trial. Lancet. 1999;354(9178):533-540. PMID: 10470696
6. Von der Maase H, Hansen SW, Roberts JT, 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;18(17):3068-3077. PMID: 11001674
7. Sternberg CN, de Mulder P, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor vs classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001 May;19(10):2638-46. PMID: 11352955
8. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity MVAC chemotherapy and GCSF versus classic MVAC in advanced urothelial tract tumours. Eur J Cancer. 2006 Jan;42(1):50-54. PMID: 16330205
9. Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer. 1998;34(8):1208-1212. PMID: 9849481
10. Papamichael D, Gallagher CJ, Oliver RT, et al. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. Br J Cancer. 1997;75(4):606-607. PMID: 9052419
11. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol. 1997;15(5):1853-1857. PMID: 9164195
12. Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol. 2006;24(21):3451-3457. PMID: 16849761
13. Witte RS, Elson P, Bono B, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol. 1997;15(2):589-593. PMID: 9053481
14. Vaughn DJ, Broome FM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol. 2002;20(4):937-940. PMID: 11844814
15. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer (Version 5.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed July 31, 2018
16. 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. Eur Urol. 2005;48(2):202-206. PMID: 15939524
17. Von der Maase H, Senglov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-4608. PMID: 16034041
18. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/ciplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-1113. PMID: 22370319
19. Kitamura H, Tsukamoto T, Shibata T, et al. Randomized phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine, and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. Ann Oncol. 2014;25(6):1192-1198. PMID: 24669010
20. Ojea A, Nogueira JL, Solsona E, et al. A multicenter, randomized prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low dose bacillus calmette-guerin (27mg) vs very low dose bacillus calmette-guerin (13.5mg) vs mitomycin C. Eur Urol. 2007;52:1398-1406. PMID: 17485161
21. Bohle A, Jocham D, and Bock PR. Intravesical bacillus calmette-guerin vs mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003; 169(1):90-95. PMID: 12478111

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Han RF and Pan JG. Can intravesical bacillus calmette-guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trial. Urology. 2006; 67(6):1216-1223. PMID: 16765182
23. Shelley MD, Wilt TJ, Court J, et al. Intravesical bacillus calmette-guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU International. 2004; 93(4):485-490. PMID: 15008714
24. Lamm DL, Blumenstein BA, Crissman JD, 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 study. J Urol. 2000; 163(4):1124-1129. PMID: 10737480
25. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of bacillus calmette-guein refractory carcinoma in situ of the bladder. J Urol. 2000; 163:761-767. PMID: 10687972
26. Bambury RM, Benjamin DJ, Chaim JL, et al. The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: a large single-institution experience. Oncologist. 2015 May;20(5):508-15. PMID: 25845990
27. Rosenberg, Jonathan E et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet.2016 ; 387 (10031): 1909 - 1920 PMID: 26952546
28. DeSantis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carbopatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012; 30:191-9.PMID: 22162575
29. Stadler WM, 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; 15:3394-8.. PMID: 9363871
30. Calabro F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer. 2009; 115:2652-9.PMID: 19396817
31. Siefker-Radtke AC, Dinney CR 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; 119:540-7. PMID: 22914978
32. Ko YJ, Canil CM, Mukherjee SD, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. Lancet Oncol. 2013;14:769-76. PMID:23706985
33. Milowsky MI, Rumble RB, Booth CM, et al. Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2016 Jun 1;34(16):1945-52. PMID: 27001593.
34. Balar AV, Galsky MD, Loriot Y, et al. Atezolizumab (atezo) as first-line (1L) therapy in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (mUC): Primary analysis of IMvigor210 cohort 1. JCO. 2016; 34:18 (suppl: LBA4500)
35. Apolo AB, Infante JR, 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;35(19):2117-24. PMID: 28375787.
36. Balar A, Bellmunt J, O'Donnell PH, et al. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. Ann Oncol. 2016;27(suppl_6):LBA32.
37. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. NEJM. 2017;376(11):1015-26. PMID: 28212060.
38. Massard C, Gordon MS, Sharma S, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol. 2016;34(26):3119-25. PMID: 27269937.
39. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol. 2016;17(11):1590-8. PMID: 27733243.
40. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. Jama. 2018;319(18):1880-8.PMID 29801011.

Breast Cancer Pathways: Neoadjuvant

Neoadjuvant Therapy | HER2 Negative

ddAC → weekly T: dose dense doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel[8,11,12,39]

TC: docetaxel (Taxotere) and cyclophosphamide[10,43]

Neoadjuvant Therapy | HER2 Positive

AC →TH: doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel and trastuzumab (Herceptin)*[1,14,23,24,26]

TCH: docetaxel (Taxotere), carboplatin, and trastuzumab (Herceptin)*[25,49]

Neoadjuvant Therapy | HER2 Positive | Hormone Receptor (ER/PR) Negative

TCH+P: docetaxel (Taxotere), carboplatin, trastuzumab (Herceptin)*, and pertuzumab (Perjeta)[50,51,54,55,57]

* Administration of trastuzumab (Herceptin) is limited to 1 year (maximum 18 cycles)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

BREAST CANCER NEOADJUVANT REFERENCES

NCCN Clinical Practice Guidelines: Breast Cancer V1.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2018. Available at: http://www.nccn.org. Accessed May 30, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005 Dec 29;353(26):2747-2757.
2. Howell A, Cuzick J, ATAC Trialists' Group, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005 Jan 1-7;365(9453):60-62.
3. Davies C, Pan H, Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013 Mar 9;381(9869):805-816.
4. Gray RG, Rea DW, aTTom Collaborators, et al. aTTom (adjuvant Tamoxifen—To offer more?): Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—Preliminary results. J Clin Oncol. 2008; 26(15S):513.
5. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007 Feb 10;25(5):486-492
6. Al-Mubarak M, Tibau A, Templeton AJ,et al. Extended adjuvant tamoxifen for early breast cancer: a meta-analysis. PLoS One. 2014 Feb 20;9(2):e88238.
7. Pagani O, Regan MM, SOFT and TEXT Investigators and International Breast Cancer Study Group, et al. Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) v tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC):v Joint analysis of IBCSG TEXT and SOFT trials. J Clin Oncol. 2014;32(15S):LBA1.
8. Cuzick J, Sestak I, ATAC/LATTE investigators, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010 Dec;11(12):1135-1141.
9. Coombes RC, Hall E, Intergroup Exemestane Study, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004 Mar 11;350(11):1081-1092.
10. Coombes RC, Kilburn LS, Intergroup Exemestane Study, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007 Feb 17;369(9561):559-5970.
11. Goss PE, Ingle JN, National Cancer Institute of Canada Clinical Trials Group MA.17, et al. Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17. J Clin Oncol. 2007 May 20;25(15):2006-2011.
12. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol. 2001 Jun 15;19(12):3103-3110.
13. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1998 Aug;16(8):2651-2658.
14. Poole CJ, Earl HM, NEAT Investigators and the SCTBG, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. N Engl J Med. 2006 Nov 2;355(18):1851-1862.
15. Martin M, Villar A, GEICAM Group (Spanish Breast Cancer Research Group), Spain, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol. 2003 Jun;14(6):833-842.
16. Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer. 1978 May;41(5):1649-1657.
17. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003 Mar 15;21(6):976-983.
18. Jones SE, Savin MA, Holmes FA,et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006 Dec 1;24(34):5381-5387.
19. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 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. J Clin Oncol. 1990 Sep;8(9):1483-1496.
20. Martín M, Rodríguez-Lescure A, GEICAM 9906 Study Investigators, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. J Natl Cancer Inst. 2008 Jun 4;100(11):805-814.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

21. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(16):1663-1671.
22. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(16 Supplemental Material):1-15.
23. Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 2006 Dec 20;24(36):5664-5671.
24. Mackey JR, Martin M, TRIO/BCIRG 001 investigators, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol. 2013 Jan;14(1):72-80.
25. Swain SM, Tang G, Geyer CE Jr, et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013 Sep 10;31(26):3197-3204.
26. Martín M, Seguí MA, GEICAM 9805 Investigators, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med. 2010 Dec 2;363(23):2200-2210.
27. Martin M, Pienkowski T, Breast Cancer International Research Group 001 Investigators, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005 Jun 2;352(22):2302-2313.
28. Bear HD, Anderson S, National Surgical Adjuvant Breast and Bowel Project Protocol B-27, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003 Nov 15;21(22):4165-4174.
29. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol. 2005 Sep 1;23(25):5983-92.
30. Buzdar AU, Singletary SE, Theriault RL, et al. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol. 1999 Nov;17(11):3412-7.
31. Citron ML, Berry DA, Cirrincione C, et al. 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. J Clin Oncol. 2003 Apr 15;21(8):1431-1439.
32. Budd GT, Barlow WE, Moore HCF, et al. S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. J Clin Oncol. 2013;31(1S): CRA1008.
33. Martín M, Ruiz A, Ruiz Borrego M, et al. Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study. J Clin Oncol. 2013 Jul 10;31(20):2593-2599.
34. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet. 2011 Jan 22;377(9762):3213-31.
35. Assikis V, Buzdar A, Yang Y, et al. A phase III trial of sequential adjuvant chemotherapy for operable breast carcinoma: final analysis with 10-year follow-up. Cancer. 2003 Jun 1;97(11):2716-2723.
36. Joensuu H, Kellokumpu-Lehtinen PL, FinHer Study Investigators, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006 Feb 23;354(8):809-820.
37. Coudert BP, Largillier R, Arnould L, et al. Multicenter phase II trial of neoadjuvant therapy with trastuzumab, docetaxel, and carboplatin for human epidermal growth factor receptor-2-overexpressing stage II or III breast cancer: results of the GETN(A)-1 trial. J Clin Oncol. 2007 Jul 1;25(19):2678-2684.
38. 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 Sep;24(9):2278-2284
39. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32.
40. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005 Jun 1;23(16):3676-3685.
41. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 30, 2018
42. Bear HD, Anderson S, National Surgical Adjuvant Breast and Bowel Project Protocol B-27, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003 Nov 15;21(22):4165-4174.
43. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol. 2009 Mar 10;27(8):1177-1783.
44. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011 Sep 1;29(25):3366-3373.
45. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1673-1684.
46. Burstein HJ, Piccart-Gebhart MJ, Perez EA, et al. Choosing the best trastuzumab-based adjuvant chemotherapy regimen: should we abandon anthracyclines? J Clin Oncol. 2012 Jun 20;30(18):2179-2182.
47. Slamon D, Eiermann W, Breast Cancer International Research Group, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-1283.

48. Cognetti F, Bruzzi P, De Placido S, et al: Epirubicin and cyclophosphamide followed by paclitaxel versus fluorouracil, epirubicin and cyclophosphamide followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer patients. Final results of the Gruppo Italiano Mammella (GIM)-2 randomized phase III study. 2013 San Antonio Breast Cancer Symposium. Abstract S5-06. Presented December 13, 2013.
49. von Minckwitz G, Kümmel S, German Breast Group, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst. 2008 Apr 16;100(8):552-562.
50. Sparano JA, Zhao F, Martino S, et la. [S3-03] Ten year update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk nodenegative breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-03. Presented December 11, 2014.
51. Samuel JA, Wilson JW, Bandos H, et al. [S3-02] NSABP B-36: A randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin and cyclophosphamide (AC) in patients (pts) with node-negative breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-02. Presented December 11, 2014.
52. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-172.
53. Briefing Book: Perjeta (pertuzumab) prepared for Oncology Drugs Advisory Committee Meeting. San Francisco: Genentech, Inc. August 9, 2013.
54. FDA Briefing Document for sBLA 125409/51, Pertuzumab (PERJETA®). Oncologic Drugs Advisory Committee Meeting, September 12, 2013.
55. Baselga J, Bradbury I, Eidtmann H, Det al. Lapatinib with trastuzumab for HER2- positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012; 379: 633–640.
56. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol. 2014 Sept;15(10):1137-1146.
57. Blackwell KL, Burstein HJ, Storniolo AM, 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; 30:2585-2592.
58. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First resultsfromthephase III ALTTOtrial (BIG 2-06; NCCTG[Alliance] N063D) comparingoneyearofanti-HER2 therapywithlapatinibalone(L), trastuzumabalone(T), their sequence(T→L), ortheircombination(T+L) in theadjuvanttreatmentof HER2-positiveearlybreast cancer(EBC). J Clin Oncol. 2014; 32(5S):LBA4.
59. Dang CT, D'Andrea GM, Moynahan ME, et al. Phase II study of feasibility of dose-dense FEC followed by alternating weekly taxanes in high-risk, four or more node-positive breast cancer. Clin Cancer Res. 2004 Sep 1;10(17):5754-5761.
60. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64. PMID: 25422488
61. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(Supplementary Appendix 1):58-64. PMID: 25422488
62. Del Mastro L, De Placido S, Gruppo Italiano Mammella (GIM) investigators, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet. 2015 May 9;385(9980):1863-1872. PMID: 25740286
63. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800. Epub 2016/05/18. PMID: 27179402
64. Schneeweiss A CS, Hickish T, et al. Pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: Efficacy analysis of a phase II cardiac safety study (TRYPHAENA). San Antonio Breast Cancer Symposium 2016. Abstract P4-21-02
65. Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17(3):345-56. Epub 2016/02/13. PMID: 26869049
66. Jones SE, 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(11):1121-8. Epub 2013/09/07. PMID: 24007746
67. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-41. Epub 2015/01/08. PMID: 25564897
68. Van Ramshorst M, van Werkhoven E, Mandjes I, et al. A phase III trial of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2+ breast cancer: The TRAIN-2 study (BOOG 2012-03). J Clin Oncol. 2017;35(15_suppl):507
69. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2017;23:23.PMID 29175149
70. Hahnen E, Lederer B, Hauke J, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol. 2017;3(10):1378-85.PMID 28715532
71. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-59.PMID 28564564

Breast Cancer Pathways: Adjuvant

Adjuvant Therapy | HER2 Negative*

ddAC → weekly T: dose dense doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel[8,9,11,12,60]

TC: docetaxel (Taxotere) and cyclophosphamide[10,19]

Adjuvant Therapy | HER2 Positive

AC → TH: doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel and trastuzumab (Herceptin)†[23-26,58]

TCH: docetaxel (Taxotere), carboplatin, and trastuzumab (Herceptin)†[25,26,58]

TH: paclitaxel and trastuzumab (Herceptin)†[34,58] **(Pathway for stage I, HER2 positive breast cancer only)**

Adjuvant Therapy | HER2 Negative | Hormone Receptor (ER/PR) Negative | Residual Disease following Neoadjuvant Therapy

Capecitabine (Xeloda)[56]

---

* Adjuvant chemotherapy pathways do NOT apply to individuals with hormone-receptor positive, lymph node negative, OncotypeDX™ LOW risk score

† Administration of trastuzumab (Herceptin) is limited to 1 year (maximum 18 cycles)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

BREAST CANCER ADJUVANT REFERENCES

NCCN Clinical Practice Guidelines: Breast Cancer V1.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2018. Available at: http://www.nccn.org. Accessed May 30, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 2006 Dec 20;24(36):5664-5671.
2. Martín M, Rodríguez-Lescure A, Ruiz A, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. J Natl Cancer Inst. 2008 Jun 4;100(11):805-814.
3. Martín M, Ruiz A, Ruiz Borrego M, et al. Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study. J Clin Oncol. 2013 Jul 10;31(20):2593-2599.
4. Swain SM, Tang G, Geyer CE Jr, et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013 Sep10;31(26):3197-3204.
5. Martín M, Seguí MA, Antón A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med. 2010 Dec 2;363(23):2200-2210.
6. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005 Jun 2;352(22):2302-2313.
7. Mackey JR, Martin M, Pienkowski T, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol. 2013 Jan;14(1):72-80.
8. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(16):1663-1671.
9. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(Supplemental Material):1-15.
10. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006 Dec 1;24(34):5381-7.
11. Budd GT, Barlow WE, Moore HCF, et al. S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. J Clin Oncol. 2013; 31(15): CRA1008.
12. Citron ML, Berry DA, Cirrincione C, et al. 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. J Clin Oncol. 2003 Apr 15;21(8):1431-1439.
13. Buzdar AU, Singletary SE, Theriault RL, et al. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol. 1999 Nov;17(11):3412-3417.
14. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003 Nov 15;21(22):4165-4174.
15. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol. 2001 Jun 15;19(12):3103-3110.
16. Martin M, Villar A, Sole-Calvo A, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol. 2003 Jun;14(6):833-842.
17. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003 Mar 15;21(6):976-983.
18. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 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. J Clin Oncol. 1990 Sep;8(9):1483-1496.
19. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol. 2009 Mar 10;27(8):1177-1183.
20. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1998 Aug;16(8):2651-2658.
21. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. N Engl J Med. 2006 Nov 2;355(18):1851-1862.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol. 2005 Sep 1;23(25):5983-5992.
23. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011 Sep 1;29(25):3366-3373.
24. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1673-1684.
25. Burstein HJ, Piccart-Gebhart MJ, Perez EA, et al. Choosing the best trastuzumab-based adjuvant chemotherapy regimen: should we abandon anthracyclines? J Clin Oncol. 2012 Jun 20;30(18):2179-2182.
26. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-1283.
27. Blackwell KL, Burstein HJ, Storniolo AM, 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 Mar 1;28(7):1124-1130
28. Cognetti F, Bruzzi P, De Placido S, et al: Epirubicin and cyclophosphamide followed by paclitaxel versus fluorouracil, epirubicin and cyclophosphamide followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer patients. Final results of the Gruppo Italiano Mammella (GIM)-2 randomized phase III study. 2013 San Antonio Breast Cancer Symposium. Abstract S5-06. Presented December 13, 2013.
29. Sparano JA, Zhao F, Martino S, et la. [S3-03] Ten year update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk nodenegative breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-03. Presented December 11, 2014.
30. Samuel JA, Wilson JW, Bandos H, et al. [S3-02] NSABP B-36: A randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin and cyclophosphamide (AC) in patients (pts) with node-negative breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-02. Presented December 11, 2014.
31. Joensuu H, Kellokumpu-Lehtinen PL, FinHer Study Investigators, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006 Feb 23;354(8):809-820.
32. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005 Jun 1;23(16):3676-3685.
33. Piccart-Gebhart M, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T->L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). J Clin Oncol. 2014; 32(18 Supp): LBA4.
34. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015 Jan 8;372(2):134-41.
35. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 30, 2018
36. Barcenas CH, Niu J, Zhang N, et la. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol. 2014 Jul 1; 32(19):2010-7
37. Slamon DJ, Swain SM, Buyse M, et al. [S1-03] Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab ± bevacizumab in patients with HER2-positive, node-positive or high risk node-negative breast cancer. Cancer Res. December 15, 2013 73; S1-03. Abstract S1-03
38. Barrios CE, Lluch A, Ruiz-Boreego M, et al. [OT3-1-06] CIBOMA/2004-01_GEICAM/2003-11: A randomised phase III trial assessing adjuvant capecitabine (Cap) maintenance therapy after standard chemotherapy for triple-negative early breast cancer (EBC). Cancer Res. 2013 December 15; 73:OT3-1-06. Abstract OT3-1-06
39. Von Minckwitz G, Reimer T, Potenberg J, et al. [S3-04] The phase III ICE study: Adjuvant Ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-04. Presented December 11, 2014. Abstract S3-04
40. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(1):58-64. PMID: 25422488
41. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol. 2015 Jan 1;33(Supplementary Appendix 1):58-64. PMID: 25422488
42. Del Mastro L, De Placido S, Gruppo Italiano Mammella (GIM) investigators, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet. 2015 May 9;385(9980):1863-1872. PMID: 25740286
43. 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 Feb 10;33(5):442-447. PMID: 25547504
44. 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 Sep;24(9):2278-2284
45. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32.
46. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005 Jun 1;23(16):3676-3685.
47. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-172.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

48. Briefing Book: Perjeta (pertuzumab) prepared for Oncology Drugs Advisory Committee Meeting. San Francisco: Genentech, Inc. August 9, 2013.
49. FDA Briefing Document for sBLA 125409/51, Pertuzumab (PERJETA®). Oncologic Drugs Advisory Committee Meeting, September 12, 2013.
50. Baselga J, Bradbury I, Eidtmann H, Det al. Lapatinib with trastuzumab for HER2- positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012; 379: 633–640.
51. Gianni, Luca, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 17.6 (2016): 791-800. PMID: 27179402
52. Schneeweiss A. Pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline free chemotherapy regimens in patients with HER2-positive early breast cancer: Efficacy analysis of a phase II cardiac safety study (TRYPHAENA). SABCS 2016
53. Jones, Stephen E., 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. 14.11 (2013): 1121-1128. PMID: 24007746
54. Tolaney, Sara M., et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Eng J Med. 372.2 (2015): 134-141. PMID: 25564897
55. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017;35(23):2647-55.PMID 28398846
56. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-59.PMID 28564564
57. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-700.PMID 29146401
58. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 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.PMID 28215665
59. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer.[Erratum appears in N Engl J Med. 2017 Aug 17;377(7):702; PMID: 28700263]. N Engl J Med. 2017;377(2):122-31.PMID 28581356
60. Bell R, Brown J, Parmar M, et al. Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer. Ann Oncol. 2017;28(4):754-60.PMID 27993816
61. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R, et al. Adjuvant Capecitabine in Combination With Docetaxel, Epirubicin, and Cyclophosphamide for Early Breast Cancer: The Randomized Clinical FinXX Trial. JAMA Oncol. 2017;3(6):793-800.PMID 28253390.

Breast Cancer Pathways: Advanced/Metastatic Disease

Advanced/Metastatic Disease | HER2 Negative | First and Subsequent Lines of Therapy (1st Line+)
Capecitabine (Xeloda)[4,24-26,28,60,65]
Doxorubicin (Adriamycin)[4,5,9,65]
Gemcitabine (Gemzar)[14,60]
Paclitaxel[18-20,65]
Vinorelbine (Navelbine)[15-17,65]
Advanced/Metastatic Disease | HER2 Negative | Deleterious Germline BRCA Mutation | First and Subsequent Lines of Therapy (1st Line+)
Olaparib (Lynparza)[87]
Advanced/Metastatic Disease | HER2 Positive | First Line of Therapy (1st Line)
Capecitabine (Xeloda) and trastuzumab (Herceptin)[40-43]
Gemcitabine (Gemzar) and trastuzumab (Herceptin)[44,45]
Paclitaxel and trastuzumab (Herceptin)[35,36]
Pertuzumab (Perjeta), trastuzumab (Herceptin), and docetaxel (Taxotere)[32,33,35]
Pertuzumab (Perjeta), trastuzumab (Herceptin), and paclitaxel[34]
Vinorelbine (Navelbine) and trastuzumab (Herceptin)[46,47]
Advanced/Metastatic Disease | HER2 Positive | Second and Subsequent Lines of Therapy (2nd Line+)
Ado-trastuzumab emtansine (Kadcyla)[59,61,62]
Capecitabine (Xeloda) and lapatinib (Tykerb)[51,52]
Capecitabine (Xeloda) and trastuzumab (Herceptin)[40-43]
Gemcitabine (Gemzar) and trastuzumab (Herceptin)[44,45]
Paclitaxel and trastuzumab (Herceptin)[35,36]
Pertuzumab (Perjeta), trastuzumab (Herceptin), and docetaxel (Taxotere)[32,33,35,82]
Pertuzumab (Perjeta), trastuzumab (Herceptin), and paclitaxel[34]
Trastuzumab (Herceptin) and lapatinib (Tykerb)[49,50]
Trastuzumab (Herceptin) monotherapy[37,48]
Vinorelbine (Navelbine) and trastuzumab (Herceptin)[46,47]

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

BREAST CANCER ADVANCED/METASTATIC REFERENCES

NCCN Clinical Practice Guidelines: Breast Cancer V1.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2018. Available at: http://www.nccn.org. Accessed May 30, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 2006 Dec 20;24(36):5664-5671. PMID: 17116941
2. O'Shaughnessy J, Gradishar WJ, Bhar P, Iglesias J. Nab-paclitaxel for first-line treatment of patients with metastatic breast cancer and poor prognostic factors: a retrospective analysis. Breast Cancer Res Treat. 2013 Apr;138(3):829-837. PMID: 23563958
3. Cortazar P, Justice R, Johnson J, Sridhara R, Keegan P, Pazdur R. US Food and Drug Administration approval overview in metastatic breast cancer. J Clin Oncol. 2012 May 10;30(14):1705-1711. PMID: 22430273
4. Gradishar WJ, Krasnojon D, Cheporov S, et al. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: final analysis of overall survival. Clin Breast Cancer. 2012 Oct;12(5):313-321. PMID: 22728026
5. O'Brien ME, Wigler N, Inbar M, et al. 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. Ann Oncol. 2004 Mar;15(3):440-449. PMID: 14998846
6. Norris B, Pritchard KI, James K, Myles J, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. J Clin Oncol. 2000 Jun;18(12):2385-2394. PMID: 10856098
7. Reyno L, Seymour L, Tu D, et al. Phase III study of N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA.19. J Clin Oncol. 2004 Jan 15;22(2):269-276. PMID: 14722035
8. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol. 1999 Aug;17(8):2341-2354. PMID: 10561296
9. Gundersen S, Kvinnsland S, Klepp O, Kvaløy S, Lund E, Høst H. Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. Eur J Cancer Clin Oncol. 1986 Dec;22(12):1431-1434. PMID: 3595668
10. Gundersen S, Kvinnsland S, Klepp O, Lund E, Høst H. Weekly Adriamycin vs. 4-epidoxorubicin every second week in advanced breast cancer. A randomized trial. The Norwegian Breast Cancer Group. Eur J Cancer. 1990 Jan;26(1):45-48. PMID: 2138477
11. Martín M, Díaz-Rubio E, Casado A, et al. Carboplatin: an active drug in metastatic breast cancer. J Clin Oncol. 1992 Mar;10(3):433-437. PMID: 1740682
12. O'Brien ME, Talbot DC, Smith IE. Carboplatin in the treatment of advanced breast cancer: a phase II study using a pharmacokinetically guided dose schedule. J Clin Oncol. 1993 Nov;11(11):2112-2117. PMID: 8229125
13. Dcatris MP, Sundar S, O'Byrne KJ. Platinum-based chemotherapy in metastatic breast cancer: current status. Cancer Treat Rev. 2004 Feb;30(1):53-81. PMID: 14766126
14. Ejlertsen B, Mouridsen HT, Langkjer ST, et al. Phase III study of intravenous vinorelbine in combination with epirubicin versus epirubicin alone in patients with advanced breast cancer: a Scandinavian Breast Group Trial (SBG9403). J Clin Oncol. 2004 Jun 15;22(12):2313-2320. PMID: 15197192
15. Rha SY, Moon YH, Jeung HC, et al. Gemcitabine monotherapy as salvage chemotherapy in heavily pretreated metastatic breast cancer. Breast Cancer Res Treat. 2005 Apr;90(3):215-221. PMID: 15830134
16. Fumoleau P, Delgado FM, Delozier T, et al. Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. J Clin Oncol. 1993 Jul;11(7):1245-1252. PMID: 8315421
17. Weber BL, Vogel C, Jones S, et al. Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. J Clin Oncol. 1995 Nov;13(11):2722-2730. PMID: 7595730
18. Zelek L, Barthier S, Riofrio M, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer. 2001 Nov 1;92(9):2267-22672. PMID: 11745280
19. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment totrastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. 2008 Apr 1;26(10):1642-1649. PMID: 18375893
20. Winer EP, Berry DA, Woolf S, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. J Clin Oncol. 2004 Jun 1;22(11):2061-2068. PMID: 15169793
21. Nabholtz JM, Gelmon K, Bontenbal M, et al. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol. 1996 Jun;14(6):1858-1867. PMID: 8656254
22. Tabernero J, Climent MA, Lluch A, et al. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. Ann Oncol. 2004 Sep;15(9):1358-1365. PMID: 15319242

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

23. Nabholtz JM, Senn HJ, Bezwoda WR, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol. 1999 May;17(5):1413-1424. PMID: 10334526
24. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002 Jun 15;20(12):2812-2823. PMID: 12065558
25. Crown JP, Diéras V, Staroslawska E, et al. Phase III trial of sunitinib in combination with capecitabine versus capecitabine monotherapy for the treatment of patients with pretreated metastatic breast cancer. J Clin Oncol. 2013 Aug 10;31(23):2870-2878. PMID: 23857972
26. O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. Oncologist. 2012;17(4):476-484. PMID: 22418569
27. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol. 2005 Apr 1;23(10):2155-2161. PMID: 15710946
28. Dear RF, McGeechan K, Jenkins MC, Barratt A, Tattersall MH, Wilcken N. Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2013 Dec 18;12:CD008792 PMID: 24347031
29. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-923 PMID: 21376385
30. Perez EA, Lerzo G, Pivot X, et al. 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. J Clin Oncol. 2007 Aug 10;25(23):3407-3414. PMID: 17606974
31. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012 May 10;30(14):1715-1724. PMID: 22493340
32. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug 19;363(8):733-742. PMID: 20818875
33. Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013 May;14(6):461-471. PMID: 23602601
34. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012 Jan 12;366(2):109-119. PMID: 22149875
35. Datko FM, D'Andrea G, Dickler MN, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with HER2-overexpressing metastatic breast cancer (MBC). J Clin Oncol. 2013; 31: 15 Suppl:Abstract 606.
36. 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 HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 2006 Jun 20;24(18):2786-2792. PMID: 16782917
37. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783-792. PMID: 11248153
38. Hamberg P, Bos MM, Braun HJ, et al. Randomized phase II study comparing efficacy and safety of combination-therapy trastuzumab and docetaxel vs. sequential therapy of trastuzumab followed by docetaxel alone at progression as first-line chemotherapy in patients with HER2+ metastatic breast cancer: HERTAX trial. Clin Breast Cancer. 2011 Apr;11(2):103-113. PMID: 21569996
39. Marty M, Cognetti F, Maraninchi D, 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 Jul 1;23(19):4265-4274. PMID: 15911866
40. Extra JM, Cognetti F, Maraninchi D, et al. Long-term survival demonstrated with trastuzumab plus docetaxel: 24-month data from a randomised trial (M77001) in HER2-positive metastatic breast cancer. J Clin Oncol. 2005;23(16S): 555.
41. von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011 Oct;47(15):2273-2281. PMID: 21741829
42. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol. 2007 Sep 1;25(25):3853-3858. PMID: 17679724
43. Schaller G, Fuchs I, Gonsch T, et al. Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. J Clin Oncol. 2007 Aug 1;25(22):3246-3250. PMID: 17577021
44. von Minckwitz 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 Apr 20;27(12):1999-2006. PMID: 19289619
45. Yardley DA, Burris HA 3rd, Hanson S, et al. Weekly gemcitabine and trastuzumab in the treatment of patients with HER2-overexpressing metastatic breast cancer. Clin Breast Cancer. 2009 Aug;9(3):178-183. PMID: 19661042
46. O'Shaughnessy JA, Vukelja S, Marsland T, Kimmel G, Ratnam S, Pippen JE. Phase II study of trastuzumab plus gemcitabine in chemotherapy-pretreated patients with metastatic breast cancer. Clin Breast Cancer. 2004 Jun;5(2):142-147. PMID: 15245619
47. Chan Ar, Martin M, Untch M, et al. Vinorelbine plus trastuzumab combination as first-line therapy for HER 2-positive metastatic breast cancer patients: an international phase II trial. Br J Cancer. 2006 Oct 9;95(7):788-793. PMID: 16969343
48. 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 Apr;17(4):630-636. PMID: 16410363
49. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002 Feb 1;20(3):719-726. PMID: 11821453
50. Blackwell KL, Burstein HJ, Storniolo AM, 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. PMID: 22689807

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

51. Blackwell KL, Burstein HJ, Storniolo AM, 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 Mar 1;28(7):1124-1130 PMID: 20124187
52. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006 Dec 28;355(26):2733-2743. PMID: 17192538
53. Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008 Dec;112(3):533-543. PMID: 18188694
54. Smorenburg CH, de Groot SM, van Leeuwen-Stok AE, et al. A randomized phase III study comparing pegylated liposomal doxorubicin with capecitabine as first-line chemotherapy in elderly patients with metastatic breast cancer: results of the OMEGA study of the Dutch Breast Cancer Research Group BOOG. Ann Oncol. 2014 Mar;25(3):599-605. PMID: 24504445
55. Awada A, Kaufman PA, Yelle L, et al. [P3-13-03] A phase III, open-label, randomized study of eribulin versus capecitabine in patients (pts) with metastatic breast cancer (MBC): Effect of post-progression anti-cancer treatments (PPT) and metastatic progression events on overall survival. 2013 San Antonio Breast Cancer Symposium. Abstract P3-13-03. Presented December 12, 2013.
56. Hurtvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2013 Mar 20;31(9):1157-63. PMID: 23382472
57. Tolaney SM, Najita J, Sperinde J, et al. A phase II study of ixabepilone and trastuzumab for metastatic HER2-positive breast cancer. Ann Oncol. 2013 Jul;24(7):1841-7. PMID: 23559151
58. Diéras V, Hardbeck N, Budd GT, et al. Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. J Clin Oncol. 2014 Sep 1;32(25):2750-7. PMID: 25024070
59. Krop I, Lin N, Blackwell K, et al. [P4-12-27] Efficacy and safety of trastuzumab emtansine (T-DM1) vs lapatinib plus capecitabine (XL) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastases: Results from a retrospective exploratory analysis of EMILIA. 2013 San Antonio Breast Cancer Symposium. Presented December 13, 2013.
60. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014 Oct 10;32(29):3307-3329. PMID: 25185096
61. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015 Feb 20;33(6):594-601 PMID: 25605862
62. Yardley DA, Brufsky A, Conte P, et al. [OT3-1-11] tnAcity: A phase 2/3 randomized study of weekly nab-paclitaxel in combination with either gemcitabine or carboplatin vs gemcitabine/carboplatin as first-line treatment for triple-negative metastatic breast cancer. 2013 San Antonio Breast Cancer Symposium. Presented December 13, 2013. Abstract [OT3-1-11]
63. De Gregorio N, Schochter F, Melcher C, et al. [OT1-1-11] DETECT III - A multicenter, randomized, phase III trial to compare standard therapy alone versus standard therapy plus lapatinib in patients with initially HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells. Cancer Res. 2013 December 15; 73: OT1-1-11. Abstract OT1-1-11
64. Mackey JR, Roms-Vazquez M, Lipatov O, et al. [S5-04] Primary results of ROSE/TRIO-12, a randomized placebo controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. Cancer Res. 2013 December 15: 73; S5-04. Abstract S5-04
65. Park IH, Lee KS, Im S-A, et al. [OT3-1-08] The PROCEED trial KCSG BR11-01: Phase III multicenter randomized open label study of irinotecan plus capecitabine versus capecitabine in patients previously treated with anthracycline and taxane for HER2 negative metastatic breast cancer. Cancer Res. 2013 December 15; 73: OT3-1-08. Abstract OT3-1-08
66. von Minckwitz G, Puglisi F, Cortes J, et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1269-1278 PMID: 25273342
67. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol. 2014 Dec 1;32(34):3840-3847PMID: 25349301
68. Gligorov J, Doval D, Bines J, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Nov;15(12):1351-1360 PMID: 25273343
69. Swain SM, Baselga J, Miles D, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. Ann Oncol. 2014 Jun;25(6):1116-1121.PMID: 24685829
70. Baselga J, Manikhas A, Cortes J, et al. Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel in HER2-positive metastatic breast cancer. Ann Oncol. 2014 Mar;25(3):592-598. PMID: 24401928
71. Llombart A, Espie M, Ranade A, et al. Phase III study of vinflunine plus gemcitabine versus paclitaxel plus gemcitabine in the first-line treatment of anthracycline pretreated advanced breast cancer. J Clin Oncol. 2014; 32(15S): 1011. Abstract 1011
72. Rochliz C, Moos R, Bigler M, et al. SAKK 24/09: Safety and tolerability of bevacizumab plus paclitaxel versus bevacizumab plus metronomic cyclophosphamide and capecitabine as first-line therapy in patients with HER2-negative advanced stage breast cancer—A multicenter, randomized phase III trial. J Clin Oncol. 2014; 32(5S): 518. Abstract 518
73. Tutt A, Ellis P, Kilburn L, et al. [S3-01] TNT: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). 2014 San Antonio Breast Cancer Symposium. Abstract S3-01. Presented December 11, 2014. Abstract S3-01
74. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med. 2012 Nov 8; 367:1783-1791. PMID: 23020162
75. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 30, 2018

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

76. Swain SM, Tang G, Geyer CE Jr, et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013 Sep10;31(26):3197-3204. PMID: 23940225
77. Swain SM, Baselga J, CLEOPATRA Study Group, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-734. PMID: 25693012
78. Durkee BY, Qian Y, Pollom EL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015 Sep 8 [Epub ahead of print] PMID: 26351332
79. Gelmon KA, Boyle FM, Kaufman B, et al. Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31. J Clin Oncol. 2015 May 10;33(14):1574-1583. PMID: 25779558
80. Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. Journal of Chemotherapy (Florence, Italy). 2010;22(3):201-4. Epub 2010/06/23. PMID: 20566427
81. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer. J Clin Oncol. 2010;28(7):1145-53. Epub 2010/01/27. PMID: 20100965
82. Ackland SP, Anton A, Breitbach GP, et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. J Clin Oncol. 2001;19(4):943-53. Epub 2001/02/22. PMID: 11181656
83. Langley RE, Carmichael J, Jones AL, et al. 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. J Clin Oncol. 2005;23(33):8322-30. Epub 2005/11/19. PMID: 16293863
84. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666-76. Epub 2007/12/28. PMID: 18160686
85. Arpino G FJ-M, de la Haba-Rodriguez J, et al. Primary analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer. San Antonio Breast Cancer Symposium 2016. Abstract S3-04
86. Bachelot T PF, Ciruelos E, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (PERUSE). San Antonio Breast Cancer Symposium 2016. Abstract P4-21-04
87. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.[Erratum appears in N Engl J Med. 2017 Oct 26;377(17):1700; PMID: 28792849]. N Engl J Med. 2017;377(6):523-33.PMID 28578601
88. Rugo HS, Barve A, Waller CF, et al. Effect of a Proposed Trastuzumab Biosimilar Compared With Trastuzumab on Overall Response Rate in Patients With ERBB2 (HER2)-Positive Metastatic Breast Cancer: A Randomized Clinical Trial. Jama. 2017;317(1):37-47.PMID 27918780
89. Perez EA, 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):141-8.PMID 28056202
90. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732-42.PMID 28526536
91. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743-54.PMID 28526538
92. Urruticoechea A, Rizwanullah M, Im SA, et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. J Clin Oncol. 2017;35(26):3030-8.PMID 28437161
93. Dickler MN, Barry WT, Cirrincione CT, et al. Phase III Trial Evaluating Letrozole As First-Line Endocrine Therapy With or Without Bevacizumab for the Treatment of Postmenopausal Women With Hormone Receptor-Positive Advanced-Stage Breast Cancer: CALGB 40503 (Alliance). J Clin Oncol. 2016;34(22):2602-9.PMID 27138575

Breast Cancer Pathways: Endocrine Therapy for Advanced/Metastatic Disease

Advanced/Metastatic Disease | Hormone Receptor Positive | First Line of Therapy (1st Line)
Anastrozole (Arimidex)*[1,6,7,10,11,22,33]
Anastrozole (Arimidex) and palbociclib (Ibrance)*[19,40,41]
Anastrozole (Arimidex) and ribociclib (Kisqali)*[19,40,41]
Fulvestrant (Faslodex)* high dose[5-7,22,26,33,42]
Letrozole (Femara)*[3,12-14,38]
Letrozole (Femara) and palbociclib (Ibrance)*[19,40,41]
Letrozole (Femara) and ribociclib (Kisqali)*[19,40,41,53]
Tamoxifen†[12,26]
Advanced/Metastatic Disease | Hormone Receptor Positive | Second and Subsequent Lines of Therapy (2nd Line+)
Anastrozole (Arimidex)*[1,6,7,10,11,22,33]
Exemestane (Aromasin)*[4,20,21,39]
Fulvestrant (Faslodex) high dose*
Fulvestrant (Faslodex) and palbociclib (Ibrance)*‡[40]
Letrozole (Femara)*[3,12-14,38]
Tamoxifen†[12,26]
Advanced/Metastatic Disease | Hormone Receptor Positive | HER2 Positive | First and Subsequent Lines of Therapy (1st Line+)
Anastrozole (Arimidex) and trastuzumab (Herceptin)*[46]
Letrozole (Femara) and trastuzumab (Herceptin)*[49]

* With ovarian suppression for premenopausal individuals. Ovarian suppression utilizes LHRH agonists given as monthly injections. 3-month depot dosing does not reliably suppress estrogen levels.

† Tamoxifen is considered pathway for premenopausal individuals with or without ovarian suppression

‡ Palbociclib regimens are not considered pathway when continued in the second line setting if the patient has received an available CDK4/6 inhibitor regimen in the first line setting

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

BREAST CANCER ENDOCRINE THERAPY FOR ADVANCED/METASTATIC DISEASE REFERENCES

NCCN Clinical Practice Guidelines: Breast Cancer V1.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2018. Available at: http://www.nccn.org. Accessed May 30, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Nabholtz JM, Buzdar A, Pollak M, et al. 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. J Clin Oncol. 2000 Nov 15;18(22):3758-67. PMID: 11078488
2. Buzdar AU. Advances in endocrine treatments for postmenopausal women with metastatic and early breast cancer. Oncologist. 2003;8(4):335-341. PMID: 12897330
3. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009 Nov 20;27(33):5538-46. PMID: 19786658
4. Chia S, Gradishar W, Mauriac L, et al. 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 EFECT. J Clin Oncol. 2008 Apr 1;26(10):1664-70. PMID: 18316794
5. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014 Jan;106(1):djt337. PMID: 24317176
6. Robertson JFR, Llombart-Cussac A, Rolski J, et al. Activity of Fulvestrant 500 mg Versus Anastrozole 1 mg As First-Line Treatment for Advanced Breast Cancer: Results From the FIRST Study. J Clin Oncol. 2009. 27(27): 4530-4535. PMID: 19704066.
7. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol. 2002 Aug 15;20(16):3396-3403. PMID: 12177099
8. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol. 2002 Aug 15;20(16):3386-3395. PMID: 12177098
9. Di Leo A, Jerusalem G, Petruzelka L, et al. Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg. Cancer Res. 2012 Dec 15; 72(24 Supplement): S1-4.
10. Bergh J, Jönsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol. 2012 Jun 1;30(16):1919-1925. PMID: 22370325
11. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med. 2012 Aug 2;367(5):435-444. PMID: 22853014
12. Mouridsen H, Gershanovich M, Sun Y, et al. 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. J Clin Oncol. 2003 Jun 1;21(11):2101-2109. PMID: 12775735
13. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 2001 Jul 15;19(14):3357-3366. PMID: 11454883
14. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol. 1998 Feb;16(2):453-461. PMID: 9469328
15. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol. 1996 Jul;14(7):2000-2011. PMID: 8683230
16. Westerberg H. Tamoxifen and fluoxymesterone in advanced breast cancer: a controlled clinical trial. Cancer Treat Rep. 1980 Jan;64(1):117-121. PMID: 6991101
17. Beex L, Pieters G, Smals A, Koenders A, Benraad T, Kloppenborg P. Tamoxifen versus ethinyl estradiol in the treatment of postmenopausal women with advanced breast cancer. Cancer Treat Rep. 1981 Mar-Apr;65(3-4):179-185. PMID: 7237448
18. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-2269. PMID: 24868023
19. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 30, 2018

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

20. Johnston SR, Kilburn LS, Ellis P, et al. 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. Lancet Oncol. 2013 Sep;14(10):989-998. PMID: 23902874
21. Yardley DA, Ismail-Khan RR, Melichar B, et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J Clin Oncol. 2013 Jun 10;31(17):2128-2135. PMID: 23650416
22. Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat. 2012 Nov;136(2):503-511. PMID: 23065000
23. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013 Oct;30(10):870-884. PMID: 24158787
24. Park IH, Ro J, Lee KS, et al. Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. J Clin Oncol. 2010 Jun 1;28(16):2705-2711. PMID: 20421538
25. Piccart M, et al. Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (BC): overall survival results from BOLERO-2. Oral Presentation Abstract #LBA1. European Breast Cancer Conference (EBCC-9), 2014, Glasgow, Scotland.
26. Howell A, Robertson JF, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol. 2004;22(9):1605. PMID: 15117982
27. Kaufmann M, Jonat W, Schachner-Wünschmann E, Bastert G, Maass H. The depot GnRH analogue goserelin in the treatment of premenopausal patients with metastatic breast cancer--a 5-year experience and further endocrine therapies. Cooperative German Zoladex Study Group. Onkologie. 1991 Feb;14(1):22-4,26-8,30. PMID: 1829149
28. Wolff AC, Lazar AA, Bondarenko I, Garin AM, Brincat S, Chow L, et al. Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer. J Clin Oncol. 2013 Jan 10; 31(2):195-202. PMID: 2323719
29. Carlson RW, Theriault R, Schurman CM, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol. 2010;28(25):3917. PMID: 20679610
30. Klijn JG, Beex LV, Mauriac L, et al. Combined Treatment With Buserelin and Tamoxifen in Premenopausal Metastatic Breast Cancer: a Randomized Study. J Natl Cancer Inst. 2000; 92: 903–11. PMID: 10841825
31. Santen RJ, Manni A, Harvey H, Redmond C. Endocrine treatment of breast cancer in women. Endocr Rev. 1990; 11:221–65. PMID: 2194783
32. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer. 2004; 90:590-4. PMID: 14760369
33. Robinson JFR, Llobmart-Cussac A, Feltl D, et al. [S6-04] Fulvestrant 500 mg versus anastrozole as first-line treatment for advanced breast cancer: overall survival from the phase II 'first' study. Presented at: 2014 San Antonio Breast Cancer Symposium; December 12, 2014.
34. Burris H, Gnant M, Hortobagyi G, et al. Abstract P2-16-17: Characterization of response to everolimus (EVE) in BOLERO-2: A phase 3 trial of EVE plus exemestane (EXE) in postmenopausal women with HR+, HER2- advanced breast cancer. Cancer Res. 2013 Dec 15;73:P2-16-17. http://cancerres.aacrjournals.org/content/73/24_Supplement/P2-16-17
35. Ellis MJ, Prahladan M, Green NL, Mari E, Robertson JFR. Abstract OT3-2-09: FALCON: A randomised, double-blind, multicentre, phase III study comparing fulvestrant 500 mg with anastrozole 1 mg for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy. Cancer Res. 2013 Dec 15;73:OT3-2-09. http://cancerres.aacrjournals.org/content/73/24_Supplement/OT3-2-09
36. Beck JT, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Breast Cancer Res Treat. 2014 Feb;143(3):459-467. PMID: 24362951
37. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012 Feb 9;366(6):520-529. PMID: 22149876
38. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005 Dec 29;353(26):2747-2757. PMID: 16382061
39. Pagani O, Regan MM, et al. SOFT and TEXT Investigators and International Breast Cancer Study Group. Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) v tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC):v Joint analysis of IBCSG TEXT and SOFT trials. J Clin Oncol. 2014;32(15S):LBA1.
40. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole v letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35. PMID: 25524798
41. Turner NC, Ro J, Andre F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. Engl J Med. 2015 Jul 16;373(3):209-219. PMID: 26030518
42. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg V Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol. 2015 Nov 10;33(32):3781-7. PMID: 26371134
43. Robertson JFR, Zefei J, Di Leo A, et al. [P51401] A meta analysis of clinical benefit rates for fulvestrant 500 mg v alternative therapies for treatment of postmenopausal, estrogen receptor positive advanced breast cancer. San Antonio Breast Cancer Symposium. December 11, 2015. P5-14-01
44. Cristofanili M, Bondarenko I, Ro, J, et al. [P41301] PALOMA3: Phase 3 trial of fulvestrant with or without palbociclib in pre and postmenopausal women with hormone receptor positive, HER2negative metastatic breast cancer that progressed on prior endocrine therapy—confirmed efficacy and safety. San Antonio Breast Cancer Symposium. December 11, 2015. Abstract P4-13-01

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

45. Hortobagyi GN, Stemmer SM, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-48. PMID: 27717303
46. Kaufman B, Mackey JR, Clemens MR, et al. 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. J Clin Oncol. 2009;27(33):5529-37. PMID: 19786670
47. Kornblum NS MJ, Klein P et al. . PrECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in post-menopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy. San Antonio Breast Cancer Symposium; San Antonio TX2016. SABCS Abstract S1-02
48. Robertson JF, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet (London, England). 2017;388(10063):2997-3005. PMID: 27908454
49. Rugo HS, Rumble RB, Macrae E, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016;34(25):3069-103. PMID: 27217461
50. Cristofanilli M, Turner NC, Bondarenko I, et al. 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. Lancet Oncol. 2016;17(4):425-39. PMID: 26947331
51. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375(20):1925-36.PMID 27959613
52. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017;35(32):3638-46.PMID 28968163
53. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-48.PMID 27717303
54. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination with Fulvestrant in Women with HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875-84.PMID 28580882
55. Cristofanilli M, Turner NC, Bondarenko I, et al. 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. Lancet Oncol. 2016;17(4):425-39.PMID 26947331

Chronic Myelogenous Leukemia (CML) Pathways

First Line of Therapy (1st Line) | Low Risk Disease
Imatinib (Gleevec)[1-4,6-8,30,33-35]
First Line of Therapy (1st Line) | Intermediate or High Risk Disease*
Dasatinib (Sprycel)[1,2,30,37-39]
Imatinib (Gleevec)[1-4,6-8,30,33-35]
Nilotinib (Tasigna)[6-8,31,32]
Second Line of Therapy (2nd Line) | Following Treatment Failure, Suboptimal Response† , or Intolerance to 1st Line
Bosutinib (Bosulif)[23,33]
Dasatinib (Sprycel)[1,2,9,10,12,36]
Nilotinib (Tasigna)[16-18,31,32]
Ponatinib (Iclusig)‡[26]
Third Line of Therapy (3rd Line)
Ponatinib (Iclusig)[26]

* For patients with intermediate or high risk disease based on Sokal or Hasford score:
  - Sokal: Intermediate Risk=0.8-1.2; High Risk>1.2
  - Hasford: Intermediate Risk=781-1480; High Risk>1480

† Defined as lack of complete hematologic response or BCR-ABL1 transcripts > 10% (IS) or lack of partial cytogenetic response on bone marrow cytogenetics.

‡ Pathway option for second line therapy only after failure, suboptimal response, or intolerance of a second generation TKI has been used in the first line setting, or T315I mutation has been identified.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

CHRONIC MYELOGENOUS LEUKEMIA (CML) REFERENCES

NCCN Clinical Practice Guidelines: Chronic Myelogenous Leukemia V4.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myelogenous Leukemia V4.2018. Available at: http://www.nccn.org. Accessed May 9, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Jabbour E, Kantarjian HM, Saglio G, 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 Jan 23;123(4):494-500. PMID: 24311723
2. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2260-2270. PMID: 20525995
3. Druker BJ, Guilhot F, IRIS Investigators, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006 Dec 7;355(23):2408-2417. PMID: 17151364
4. Deininger M, O'Brian SG, Guilhot F, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. Blood. 2009 114: Abstract: 1126
5. Cortes JE, Jones D, O'Brien S, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol. 2010 Jan 20;28(3):392-397. PMID: 20008621
6. Saglio G, Kim DW, ENESTnd Investigators, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010 Jun 17;362(24):2251-2259. PMID: 20525993
7. Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011 Sep;12(9):841-851. PMID: 21856226
8. Larson RA, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd 4-year (y) update. J Clin Oncol. 2013 ASCO Annual Meeting Abstracts. 31(15 May 20 Supplement), 2013: 7052. Abstract 7052
9. Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood. 2009 Jun 18;113(25):6322-9. PMID: 19369231
10. Shah NP, Kim DW, Kantarjian H, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica. 2010 Feb; 95(2):232-240. PMID: 20139391
11. Cortes J, Kim DW, Raffoux E, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia. 2008 Dec;22(12):2176-2183. PMID: 18754032
12. Shah NP, Kantarjian H, Kim KW, et al. Six-year follow-up of patients (pts) with imatinib-resistant or intolerant chronic-phase chronic myeloid leukemia (CML-CP) receiving dasatinib [Abstract]. J Clin Oncol. 2012;30 (suppl; Abstract 6506)
13. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008 Feb 15;111(4):1834-1839. PMID: 18048643
14. Giles FJ, Larson RA, Kantarjian HM, et al. Nilotinib in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in blast crisis (CML-BC) who are resistant or intolerant to imatinib. J Clin Oncol.2008; 26(15S): 7017. Abstract 7017
15. Kantarjian H, Giles F, Bhalla K, et al. Nilotinib in chronic myeloid leukemia patients in chronic phase (CML-CP) with imatinib (IM) resistance or intolerance: Longer follow-up results of a phase II study. J Clin Oncol. 2009; 27(15S): 7029. Abstract 7029
16. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood. 2007 Nov 15;110(10):3540-3546. PMID: 17715389
17. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011 Jan 27;117(4):1141-5. PMID: 21098399
18. 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 Jan;27(1):107-112. PMID: 22763385
19. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia. 2012 Jun;26(6):1189-1194.PMID: 22076466
20. Giles FJ, Kantarjian HM, le Coutre PD, et al. Nilotinib is effective in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blastic phase. Leukemia. 2012 May;26(5):959-962. PMID: 22157807
21. Gambacorti-Passerini C, Kantarjian HM, et al. Activity and tolerance of bosutinib in patients with AP and BP CML and Ph+ ALL.J Clin Oncol. 2008; 26(15S): 7049. Abstract 7049

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Gambacorti-Passerini C, Corets JE, Khoury H J, et al. Safety and efficacy of bosutinib in patients with AP and BP CML and ph+ ALL the following resistance/intolerance to imatinib and other TKIs: Update from study SKI-200. J Clin Oncol. 2010; 28(15S):A6509. Abstract 6509
23. Cortes JE, Kantarjian HM, Brümmendorf TH, 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 Oct 27;118(17):4567-76. PMID: 21865346
24. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012 Apr 12;119(15):3403-12. PMID: 22371878
25. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al . PACE: A pivotal phase II trial of ponatinib in patients with CML and Ph+ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation. J Clin Oncol. 2012;30(15S): 6503.Abstract 6503
26. Cortes JE, Kim DW, PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013 Nov 7;369(19):1783-1796.PMID: 24180494
27. Nicolini FE, Lipton JH, Kantarjian H, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) resistant/intolerant to two or three approved tyrosine-kinase inhibitors (TKIs). J Clin Oncol. 2012; 30(15S): 6513. Abstract 6513
28. Cortes J, Digumarti R, Omacetaxine 203 Study Group, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol. 2013 May;88(5):350-4.PMID: 23468307
29. 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 Jan;27(1):107-112. PMID: 22763385
30. Radich JP, Kopecky KJ, Appelbaum FR, et al A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood. 2012 Nov 8;120(19):3898-905.PMID: 22915637
31. Rea D, Mirault T,Cluzeau T, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. Haematologica 2014; 99(7):1197-1203 PMID: 24658819
32. Kim TD, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 2013;27:1316-1321. PMID: 23459449
33. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety of bosutinib versus imatinib in the phase 3 BELA trial in newly diagnosed chronic phase chronic myeloid leukemia. Am J Hematol. 2014 Jun 18. PMID: 24944159
34. Cortes J, Hochhaus A, Hughes T, and Kantarjian H. Front-line and Salvage Therapies with Tyrosine Kinase Inhibitors and Other Treatment in Chronic Myeloid Leukemia. J Clin Oncol. 2011;29:524-531. PMID: 21220597
35. Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol. 2015 Jan;168(1):69-81. PMID: 25196702
36. Shah NP, Guilhot F, Cortes JE, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014 Apr 10;123(15):2317-2324. PMID: 24569263
37. Cortes JE, Saglio G, Baccarani M, et al. Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). Blood. 2014; 124(21): 152. Abstract 152
38. O'Brien SG, Hedgley C, Adams S, et al. Spirit 2: An NCRI Randomised Study Comparing Dastinib with Imatinib in Patients with Newly Diagnosed CML. Blood. 2014;124(21): 517. Abstract 517
39. Deininger MW, Kopecky KJ, Radich JP, et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. Br J Haematol. 2014 Jan;164(2):223-32. PMID: 24383843
40. Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol. 2015 Jan;168(1):69-81. PMID: 25196702
41. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. Cancer. 2015 May 15;121(10):1637-44. PMID: 25586015
42. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Myelogenous Leukemia (Version 4.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 9, 2018
43. Cortes, Jorge E., et al. "Final study results of the phase 3 dasatinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) trial (DASISION, CA180-056)." Blood 124.21 (2014): 152-152. PMID: 27217448
44. Hochhaus, A., 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). PMID: 26837842
45. Hochhaus A, Larson RA, Guilhot F, et. al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017 Mar 9;376(10):917-927. PMID: 28273028
46. Khoury HJ, Cortes J, Baccarani M, et al. 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. PMID: 24650054
47. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018;36(3):231-7.PMID 29091516.

Colorectal Cancer Pathways

Adjuvant Therapy*

Capecitabine (Xeloda)[52,69]

CAPOX: capecitabine (Xeloda) and oxaliplatin (limited to 3 months duration)†[94] - Added effective 11/12/2018

FOLFOX: fluorouracil (5-FU), leucovorin, and oxaliplatin[7,8,50,51,60,69]

FULV: fluorouracil (5FU) and leucovorin[1,4,7,49,52,69]

Metastatic Disease | RAS Wild Type (WT) or Mutant (MT)‡ | First or Second Lines of Therapy (1st or 2nd Line)

Capecitabine (Xeloda)[27]

FOLFIRI: fluorouracil (5FU), leucovorin, and irinotecan (Camptosar)[18,23,30,32,34]

FOLFIRI + bevacizumab: fluorouracil (5FU), leucovorin, and irinotecan (Camptosar) with bevacizumab (Avastin)[21,23,31,36,44,45,58]

FOLFOX: fluorouracil (5FU), leucovorin, and oxaliplatin[24,26,28,30,34]

FOLFOX + bevacizumab: fluorouracil (5FU), leucovorin, oxaliplatin, with bevacizumab (Avastin)[25,26,28,33,44,45,70]

FOLFOXIRI + bevacizumab: fluorouracil (5FU), leucovorin, oxaliplatin, and irinotecan (Camptosar) with bevacizumab (Avastin)[25,26, 28,33,44,45,70]

FULV: fluorouracil (5FU) and leucovorin[22,27,35]

FULV: fluorouracil (5FU) and leucovorin with bevacizumab (Avastin)[22,35]

Metastatic Disease | RAS Wild Type (WT) | First or Second Lines of Therapy (1st or 2nd Line)

FOLFIRI + panitumumab: fluorouracil (5FU), leucovorin, and irinotecan (Camptosar) with panitumumab (Vectibix)§[11,62]

FOLFOX + panitumumab: fluorouracil (5-FU), leucovorin, and oxaliplatin with panitumumab (Vectibix)§[12,53,59]

Irinotecan (Camptosar) and panitumumab (Vectibix)§[47]

Metastatic Disease | MSI-H or dMMR | Second Line of Therapy (2nd Line)

Pembrolizumab (Keytruda)[91]

Metastatic Disease | RAS Wild Type (WT) |Third or Subsequent Lines of Therapy (3rd Line+)

Panitumumab (Vectibix) monotherapy§[13,61,56]

---

* Adjuvant Pathways do not apply to stage II MSI-H (microsatellite instability-high) disease

† Limited to low-risk (T1-3, N1), stage III only

‡ Exon 2 KRAS, non-exon 2 KRAS, and NRAS mutations; testing recommended for all patients with metastatic disease

§ Limit to one line of therapy

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

COLORECTAL CANCER REFERENCES

NCCN Clinical Practice Guidelines: Colon Cancer. Version 2.2018; Rectal Cancer. Version 2.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V2.2018 and Rectal Cancer V2.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Lembersky BC, Wieand HS, Petrelli NJ, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol. 2006;24(13):2059-2064. PMID: 16648506
2. Allegra CJ, Yothers G, O'Connell, et al. Initial safety report of NSABP C08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol. 2009;27(20):3385-90. PMID: 19414665
3. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696-2704. PMID: 15987918
4. Haller DG, 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(11):1465-1471. PMID: 21383294
5. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198-2204. PMID: 17470851
6. Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III 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(1):102-109. PMID: 17194911
7. André 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. PMID: 19451431
8. Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol. 2012;30(27):3353-3360. PMID: 22915656
9. Pessino A, Artale S, Sciallero S, et al. First-line single-agent cetuximab in patients with advanced colorectal cancer. Ann Oncol. 2008;19(4):711-716. PMID: 18073221.
10. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;260(14):1408-17. PMID: 19339720
11. Peeters M, Price TJ, Cervantes A, et al. 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. J Clin Oncol. 2010;28(31):4706-4713. PMID: 20921462
12. Douillard JY, Siena S, Cassidy J, et al. 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. J Clin Oncol. 2010;28(31):4697-705. PMID: 20921465
13. Van Cutsem E, Peeters M, Siena S, et al. 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. J Clin Oncol. 2007;25(13):1658-1664. PMID: 17470858
14. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomized phase 2 trial. Lancet Oncol. 2010;11(1):38-47. PMID: 19942479
15. Hofheinz R, Mineur L, Greil R, et al. Panitumumab (pmab) withFOLFIRI as first line treatment of patients with metastatic colorectal cancer (mCRC): resections and curative surgery in a phase II single arm, multicenter study (20060314). J Clin Oncol. 2010. 28(suppl15): Abstract 3545
16. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. Cancer Treat Rev. 2012;38(6):618-25. PMID: 22118887
17. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27(5):663-71. PMID: 19114683
18. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29(15):2011-2019. PMID: 21502544
19. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol. 2013;31(16):1931-8. PMID: 23569301
20. Falcone A, Ricci S, Brunetti L, et al. 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. J Clin Oncol. 2007;25(13):1670-1676. PMID: 17470860
21. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol. 2013;31(15S): 3505. Abstract 3505

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol. 2005;23(16):3697-3705. PMID: 15738537
23. Fuchs CS, Marshall J, Mitchell E, et al. 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. J Clin Oncol. 2007;25(30):4779-4786. PMID: 17947725
24. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30. PMID: 14665611
25. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013-2019. PMID: 18421054
26. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol. 2008;26(21):3523-3529. PMID: 18640933
27. Van Cutsem E, Twelves C, Xeloda Colorectal Cancer Study Group, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001;19(21):4097-4106. PMID: 11689577
28. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26(12):2006-2012. PMID: 18421053
29. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351(4):337-45. PMID: 15269313
30. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-237. PMID: 14657227
31. Kwon HC, Oh SY, Lee S, Kim SH, Kim HJ. Bevacizumab plus infusional 5-fluorouracil, leucovorin and irinotecan for advanced colorectal cancer that progressed after oxaliplatin and irinotecan chemotherapy: a pilot study. World J Gastroenterol. 2007;13(46):6231-6235. PMID: 18069765
32. Van Cutsem E, Tabernero J, Lakomy R, et al. 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. J Clin Oncol. 2012;30(28):3499-3506. PMID: 22949147
33. Giantonio BJ, Catalano PJ, Cooperative Oncology Group Study E3200, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-1544. PMID: 17442997
34. Colucci G, Gebbia V, Gruppo Oncologico Dell'Italia Meridionale, et al. 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. J Clin Oncol. 2005;23(22):4866-4875. PMID: 15939922
35. Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005;23(16):3706-3712. PMID: 15867200
36. Sobrero A, Ackland S, AVIRI Trial investigators, et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology. 2009;77(2):113-119. PMID: 19628950
37. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5FU, oxaliplatin and irinotecan) vs. FOLFIRI (folinic acid, 5FU, and irinotecan) as first line treatment in metastatic colorectal cancer (MCC). A multicenter randomized phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer. 2006;94(6):798-805. PMID: 16508637
38. Zhang C, Wang J, Gu H, et al. Capecitabine plus oxaliplatin compared with 5FU plus oxaliplatin in metastatic colorectal cancer. Metal-analysis of randomized controlled trials. Oncol Lett. 2012;3(4):831-838. PMID: 22741002
39. Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol. 2008;26(28):4544-50. PMID: 18824706
40. Borner MM, Dietrich D, Stupp R, et al. Phase II study of capecitabine and oxaliplatin in first and second line treatment of advanced or metastatic colorectal cancer. J Clin Oncol. 2002;20(7):1759-66. PMID: 11919232
41. Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second line therapy of metastatic colorectal cancer. J Clin Oncol. 2003;21(5):807-14. PMID: 12610178
42. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357(20):2040-8. PMID: 18003960
43. Sobrero AF, Peeters M, Price TJ, et al. Final results from study 181: Randomized phase III study of FOLFIRI with or without panitumumab (pmab) for the treatment of second-line metastatic colorectal cancer (mCRC). J Clin Oncol. 2012; 30(4S): 387. Abstract 387.
44. Masi G, Loupakis F, Salvatore L, et al. Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III "BEBYP" trial by the Gruppo Oncologico Nord Ovest (GONO). J Clin Oncol. 2013; 31(15S): 3615. Abstract 3615
45. Bennouna J, Sastre J, ML18147 Study Investigators, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14(1):29-37. PMID: 23168366
46. Grothey A, Van Cutsem E, CORRECT Study Group, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-312. PMID: 23177514
47. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol. 2013;14(8):749-759. PMID: 23725851
48. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757-1765. PMID: 18946061
49. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29(28):3768-3774. PMID: 21859995

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

50. André T, Boni C,Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343-2351. PMID: 15175436
51. Allegra CJ, Yothers G, O'Connell MJ, et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. J Clin Oncol. 2013;31(3):359-364. PMID: 23233715
52. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol. 2012;23(5):1190-1197. PMID: 21896539
53. Zhou SW, Huang YY, Wei Y, et al. No survival benefit from adding cetuximab or panitumumab to oxaliplatin-based chemotherapy in the first-line treatment of metastatic colorectal cancer in KRAS wild type patients: a meta-analysis. PLoS One. 2012;7(11):e50925. PMID: 23226426
54. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012;10(14):1715-1724. PMID: 22493340
55. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med. 2010;363(8):733-742. PMID: 20818875
56. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer (Version 2.2018) and for Rectal Cancer (Version 2.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed July 31, 2018.
57. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomized phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomizing postoperative adjuvant capecitabine plus oxaliplatin (XELOX) vs control. Ann Oncol. 2014;25(7):1356-1362. PMID: 24718885
58. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open label, phase 3 trial. Lancet Oncol. 2014;15:1065-1075. PMID: 25088940
59. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25:1346-1355. PMID: 24718886
60. Taieb J, Tabernero J, Mini E, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomized phase 3 trial. Lancet Oncol. 2014;15:862-873. PMID: 24928083
61. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomized, multicenter, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15:569-579. PMID: 24739896
62. Peeters M, Price TJ, Cervantes A, et al. Final results from a randomized phase 3 study of FOLFIRI +/- panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25:107-116. PMID: 24356622
63. Tabernero J, Cutsem ER, Lakomy R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: Pre-specified analyses from the VELOUR trial. Eur J Cancer. 2014;50:320-331. PMID: 24140268
64. Koopman M, Simkens, L, May AM, et al. Final results and subgroup analyses of the phase 3 CAIRO3 study: maintenance treatment with capecitabine+bevacizumab versus observation after induction treatment with chemotherapy+bevacizumab in metastatic colorectal cancer (mCRC). J Clin Oncol. 2014;32(15S):3504. Abstract 3504.
65. Primrose J, Flak S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable liver metastasis: the New EPOC randomized controlled trial. Lancet Oncol. 2014;15:601-611. PMID: 24717919
66. Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first line treatment of metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIBE trial. J Clin Oncol. 2013;31(suppl4). Abstract 336
67. Gruenberger T, Bredgewater JA, Chau I, et al. Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: resectability and safety in OLIVIA. J Clin Oncol. 2013;31(15s):A3619 Abstract 3619
68. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and Bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;317:1609-1618. PMID: 25337750
69. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219-3226. PMID: 20498393
70. Masi G, Salvatore L, on behalf of the BEBYP Study Investigators, et al. cancer: final results of the randomized BEBYP trial. Ann Oncol. 2015 Jan 18. pii: mdv012. PMID: 25600568
71. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. J Clin Oncol. 2009 Feb 10; 27: 663-671. PMID: 19114683
72. Venook AP, Niedzwiecki D, Lenz H, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol. 32:5s, 2014 (suppl; abstr LBA3).
73. Yasui H, Muro K, Shimada Y, Tsuji A, et al. A phase 3 non-inferiority study of 5-FU/l-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study. J Cancer Res Clin Oncol. 2015 Jan;141(1):153-160 PMID: 25106731
74. Yoshida M, Ishiguro M, Ikejiri K, et al. S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol. 2014 Sep;25(9):1743-1749 PMID: 24942277
75. Masi G, Salvatore L, on behalf of the BEBYP Study Investigators, et al. cancer: final results of the randomized BEBYP trial. Ann Oncol. 2015 Jan 18. pii: mdv012. PMID: 25600568
76. Tabernero J, Yoshino T, RAISE Study Investigators, et al. 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. Lancet Oncol. 2015 May;16(5):499-508. PMID: 25877855

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

77. Loupakis F, Cremolini C, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as initial treatment for metastatic colorectal cancer (TRIBE study): Updated survival results and final molecular subgroups analyses. J Clin Oncol. 2015;33 (20suppl): 3510. Abstract 3510
78. Schmoll HJ, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial. J Clin Oncol. 2015 Nov 10;33(32):3733-40. PMID: 26324362
79. Goldstein DA, Chen Q, Ayer T, et al. First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis. J Clin Oncol. 2015 Apr 1;33(10):1112-8 PMID: 25691669
80. Aparicio T, Lavau-Denes S, FFCD investigators, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02)†. Ann Oncol. 2016 Jan;27(1):121-7 (Supplementary) PMID: 26487578
81. Aparicio T, Lavau-Denes S, FFCD investigators, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02)†. Ann Oncol. 2016 Jan;27(1):121-7. PMID: 26487578
82. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet. 2015 May 9;385(9980):1843-52. PMID: 25862517
83. Cremolini C, Loupakis F, Antoniotti C, et al. 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. Lancet Oncol. 2015 Oct;16(13):1306-15. PMID: 26338525
84. Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. Ann Oncol. 2015 Jul;26(7):1427-33.
85. Mayer RJ, Van Cutsem E, RECOURSE Study Group, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19 PMID: 25970050
86. Cremolini C, Loupakis F, Masi G, et al. FOLFOXIRI or FOLFOXIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: a propensity score-adjusted analysis from two randomized clinical trials. Ann Oncol. 2016 Feb 9. pii: mdw052. PMID: 26861604
87. Segelov E, Thavaneswaran S, Waring PM et al. Response to Cetuximab With or Without Irinotecan in Patients With Refractory Metastatic Colorectal Cancer Harboring the KRAS G13D Mutation: Australasian Gastro-Intestinal Trials Group ICECREAM Study. J Clin Oncol. 2016 Apr 25. PMID: 27114605.
88. Ciardiello F, Normanno N, Martinelli E et al. Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. Ann Oncol. 2016 Jun;27(6):1055-61 PMID: 27002107.
89. Folprecht G, Pericay C, Saunders MP et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. Ann Oncol. 2016 Apr 18. PMID: 27091810.
90. Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. Ann Oncol. 2014;25(6):1172-8.PMID: 24608198.
91. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372(26):2509-20.PMID: 26028255.
92. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017.PMID: 28734759.
93. Cunningham D, Pyrhönen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet Oncol. 1998 Oct 31;352(9138):1413-8. PubMed PMID: 9807987.
94. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med. 2018;378(13):1177-88.PMID 29590544.

Gastric, Esophageal, and Gastroesophageal Junction Cancer (Adenocarcinoma) Pathways

Primary Therapy | Resectable and Unresectable Disease
Cisplatin and fluorouracil (5FU)[3,4]
Fluorouracil (5FU) and cisplatin with concurrent radiation therapy (RT)[35]
FLOT: Fluorouracil (5FU), leucovorin, oxaliplatin, and docetaxel (Taxotere)[47,48]
Paclitaxel and carboplatin with concurrent RT[5]
Post-Operative Treatment
Fluorouracil (5FU) and leucovorin with concurrent RT[38]
Recurrent/Metastatic or Locally Advanced/Inoperable Disease | HER2 Negative | First Line of Therapy (1st Line)
Cisplatin and fluorouracil (5FU)[15,19,21,26]
Fluorouracil (5FU) and irinotecan (Camptosar)[25,26]
FLO/FOLFOX: fluorouracil (5FU), leucovorin, and oxaliplatin[27]
FLP: fluorouracil (5FU), leucovorin, and cisplatin[27]
Recurrent/Metastatic or Locally Advanced/Inoperable Disease | HER2 Positive | First Line of Therapy (1st Line)
Cisplatin, fluorouracil (5FU), and trastuzumab (Herceptin)[15]
Recurrent/Metastatic or Locally Advanced/Inoperable Disease | Second Line of Therapy (2nd Line)
Irinotecan (Camptosar)[24,29]
Paclitaxel[33]

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

GASTRIC, ESOPHAGEAL, AND GASTROESOPHAGEAL JUNCTION (ADENOCARCINOMA) CANCERS REFERENCES

NCCN Clinical Practice Guidelines: Gastric Cancer. Version 5.2017; Esophageal and Esophagogastric Junction Cancers. Version 4.2017

References

1. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006; 355:11-20. PMID: 16822992
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer (Versions 5.2017) and for Esophageal Cancer (Version 4.2017). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2017. Accessed January 31, 2018.
3. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer. CALGB 9781. J Clin Oncol. 2008; 26:1086-92. PMID: 18309943
4. Heath EI, Burtness BA, Heitmiller RF, et al. Phase II evaluation of preoperative chemoradiation and postoperative adjuvant chemotherapy for squamous cell and adenocarcinoma of the esophagus. J Clin Oncol. 2000; 18:868-76. PMID: 10673530
5. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012; 366:2074-84. PMID: 22646630
6. Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. J Clin Oncol. 2007; 37;829-35. PMID: 17951334
7. Khushalani NI, Leichman CG, Proulx G, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. J Clin Oncol. 2002; 20:2844-50. PMID: 12065561
8. Javle MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. Cancer Invest. 2009; 27:193-200. PMID: 19235592
9. MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001; 345:725-30. PMID: 11547741
10. Jansen EP, Boot H, Saunders MP, et al. A phase I-II study of postoperative capecitabine-based chemoradiotherapy in gastric cancer. Int J Radiat Oncol Biol Phys. 2007; 69:1424-28. PMID: 17689023
11. Lee HS, Choi Y, Hur WJ, et al. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. World J Gastroenterol. 2006; 12:603-7. PMID: 16489675
12. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomized controlled trial. Lancet Oncol. 2014; 15:78-86. PMID: 24332238
13. Leong T, Joon DL, Willis D, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2011; 79:690-95. PMID: 20472363
14. Kim MM, Mansfield PF, Das P, et al. Chemoradiation therapy for potentially resectable gastric cancer: clinical outcomes among patients who do not undergo planned surgery. Int J Radiat Oncol Biol Phys. 2008; 71:167-72. PMID: 18406886
15. 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-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010; 376:687-97. PMID: 20728210
16. Shah MA, Shibata S, Stoller RG, et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma. Proc Amer Soc Clin Oncol 28:Abstract 4014;2010. Abstract 4014
17. Cunningham D, Starling N., Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008; 358:36-46. PMID: 18172173
18. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer. 1998; 78:511-14. PMID: 9716036
19. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. Ann Oncol. 2009; 20:666-73. PMID: 19153121
20. Van Meerten Em Eskens FA, van Gameren EC, et al. First-line treatment with oxaliplatin and capecitabine in patients with advanced or metastatic oesophageal cancer: a phase II study. Br J Cancer. 2009; 96:1348-52. PMID: 17437008
21. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2009; 20:1667-73. PMID: 19549707

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol. 2004; 15:955-59. PMID: 15151954
23. Shankaran V, Mulcahy MF, Hochster HS, et al. Docetaxel, oxaliplatin, and 5-fluorouracil for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinomas. Proc Amer Soc Clin Oncol Abstract 47;2009. Abstract 47
24. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013; 31:4438-4444. PMID: 24190112
25. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irniotecan versus epirubicin, cisplatin, and capecitabine ain advanced gastric adenocarcinoma: a French intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol. 2014; 32:3520-26. PMID: 25287828
26. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naïve patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol. 2008; 19:1450-57. PMID: 18558665
27. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008; 26:1435-42. PMID: 18349393
28. El-Rayes BF, Shields A, Zalupski M, et al. A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol. 2004; 15:960-65. PMID: 15151955
29. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011; 47:2306-14. PMID: 21742485
30. Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol. 1999; 17:3270-75. PMID: 10506629
31. Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology 18 (Suppl 14):22-25; 2004. PMID: 15685830
32. Ilson DH, Wadleigh RG, Leichman LP, et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol. 2007; 18:898-902. PMID: 17351256
33. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomized, multicenter, placebo-controlled phase 3 trial. Lancet. 2014; 383:31-39. PMID: 24094768
34. 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, randomized phase 3 trial. Lancet Oncol. 2014; 15:1224-35. PMID: 25240821
35. Ychou M, Boige V, Pignon JP, 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. PMID: 21444866
36. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST Trial. J Clin Oncol. 2012; 20:268-73. PMID: 22184384
37. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol. 2015; Jan 5. PMID: 25559811
38. 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; 30:2327-33. PMID: 22585691
39. Al-Batran SE, Van Cutsem E, Oh SC, et al. Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel vs. placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma. Ann Oncol. 2016; 27:673-679. PMID: 26747859
40. Tebbutt NC, Price TJ, Ferraro DA, et al. Panitumumab added to docetaxel, cisplatin, and 5FU in oesophagogastric cancer: ATTAX3 phase II trial. Cr J Cancer. 2016; 114:505-509. PMID: 26867157
41. Enzinger PC, Brutness CA, Niedzwiecki D, et al. CALGB 80143 (Alliance)/E1206: A randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol. 2016; pii: JCO655092. [Epub ahead of print] PMID: 27382098
42. Pavlakis N, Sjoquist KM, Martin AJ, et al. Regorafenib for the treatment of advanced gastric cancer (INTEGRATE): A multinational placebo controlled phase II trial. J Clin Oncol. 2016. Jun 20. pii: JCO651901. PMID: 27325864
43. Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016; 34:1448-1454. PMID: 26884585
44. Shah MA, Cho JY, Tan IB, et al. A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal Junction. Oncologist. 2016 Jul 8. pii: theoncologist.2016-0038. [Epub ahead of print]. PMID: 27401892
45. Yoon-Koo Kang TS, Min-Hee Ryu, et al. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial. 2017 Gastrointestinal Cancers Symposium Abstract 2
46. Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. Ann Oncol. 2016;27(12):2196-203. PMID: 27765757
47. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

(FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-708.PMID 27776843

48. Al-Batran SE, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. J Clin Oncol. 2017;35(15 Supplement 1):4004.
49. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol. 2017;18(9):1249-60.PMID 28784312
50. Fuchs CS, Niedzwiecki D, Mamon HJ, et al. Adjuvant Chemoradiotherapy With Epirubicin, Cisplatin, and Fluorouracil Compared With Adjuvant Chemoradiotherapy With Fluorouracil and Leucovorin After Curative Resection of Gastric Cancer: Results From CALGB 80101 (Alliance). J Clin Oncol. 2017;35(32):3671-7.PMID 28976791
51. Fuchs CS, Doi T, Jang RWJ, et al. KEYNOTE-059 cohort 1: Efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. J Clin Oncol. 2017;35(15 Supplement 1):4003.
52. Suntharalingam M, Winter K, Ilson D, et al. Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2017;3(11):1520-8.PMID 28687830.
53. Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1637-51.PMID 29103871
54. Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640-53.PMID 28343975
55. Suntharalingam M, Winter K, Ilson D, et al. Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2017;3(11):1520-8.PMID 28687830

Head and Neck Cancer Pathways

Non-Nasopharyngeal (Squamous Cell Carcinoma) | Candidate for Local Therapy (M0) | Primary Systemic Therapy or Post-Operative Systemic Therapy

High dose cisplatin* with concurrent RT[3,10,37]

Non-Nasopharyngeal (Squamous Cell Carcinoma) | Metastatic and Recurrent Disease | First Line of Therapy (1st line)

Carboplatin, fluorouracil (5FU), and cetuximab (Erbitux)[14]

Cisplatin, fluorouracil (5FU), and cetuximab (Erbitux)[14]

Non-Nasopharyngeal (Squamous Cell Carcinoma) | Metastatic and Recurrent Disease | Second and Subsequent Lines of Therapy (2nd line+)

Nivolumab (Opdivo)[35]

Paclitaxel[23]

Nasopharynx | Candidate for Local Therapy (M0) | Primary Systemic Therapy

High dose cisplatin* with concurrent RT[13,37]

Nasopharynx | Metastatic and Recurrent Disease | First and Subsequent Lines of Therapy (1st Line+)

Carboplatin[21]

Cisplatin[20,22]

Cisplatin† and gemcitabine (Gemzar)[29,39]

Cisplatin† and paclitaxel[18,22,29]

Fluorouracil (5FU)[22]

Gemcitabine (Gemzar)[31]

Methotrexate[24,26]

Paclitaxel[23]

---

* High dose cisplatin refers to dosing to achieve total dose of 200-300 mg/m^2 of cisplatin over the course of the radiotherapy. There are several different appropriate cisplatin schedules that may be used.

† Substitution of carboplatin for cisplatin, and vice-versa, is acceptable for metastatic disease

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

HEAD AND NECK CANCER REFERENCES

NCCN Clinical Practice Guidelines: Head and Neck Cancers V1.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers V1.2018. Available at: http://www.nccn.org. Accessed May 30, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Posner MR, Hershock DM, TAX 324 Study Group, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007 Oct 25;357(17):1705-1715. PMID: 17960013
2. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase 3 study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol. 2005 Dec 1;23(34):8636-8645. PMID: 16275937
3. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003 Nov 27;349(22):2091-2098. PMID: 14645636
4. Bonner JA, Harari PM, Cohen RB, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010 Jan;11(1):21-8. PMID: 19897418
5. Bonner JA, Harai PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006 Feb 9;354(6):567-578. PMID: 16467544
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 Jan 1;22(1):69-76. PMID: 14657228
7. Calais G, ALfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst. 1999; 91:2081-2086. PMID: 10601378
8. Garden AS, Harris J, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase 2 trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol. 2004 Jul 15;22(14):2856-2864. PMID: 15254053
9. Taylor SG 4th, Murthy AK, Vannetzel JM, 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 Feb;12(2):385-395. PMID: 8113846
10. Cooper JS, Pajak TF, Radiation Therapy Oncology Group 9501/Intergroup, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004 May 6;350(19):1937-1944. PMID: 15128893
11. Ghadjar P, Simcock M, Swiss Group for Clinical Cancer Research (SAKK), et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase 3 trial (SAKK 10/94). Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):524-531. PMID: 21300466
12. Chan AT, Hsu MM, Goh BC, et al. Multicenter, phase 2 study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. J Clin Oncol. 2005 May 20;23(15):3568-3576. PMID: 15809453
13. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase 3 randomized Intergroup study 0099. J Clin Oncol. 1998 Apr;16(4):1310-1317. PMID: 9552031
14. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-1127. PMID: 18784101
15. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin (TPEx) as firstline treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase 2 trial GORTEC 200803. J Clin Oncol. 2012; 30 (5505).
16. Glisson BS, Murphy BA, Frenette G, Khuri FR, Forastiere AA. Phase 2 Trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol. 2002 Mar 15;20(6):1593-1599. PMID: 11896109
17. Samlowski WE, Moon J, Kuebler JP, 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 2 study. Cancer Invest. 2007 Apr-May;25(3):182-188. PMID: 17530488
18. Gibson MK, Li Y, Eastern Cooperative Oncology Group, et al. Randomized phase 3 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 May 20;23(15):3562-3567. PMID: 15908667
19. Clark JI, Hofmeister C, Choudhury A, et al. Phase 2 evaluation of paclitaxel in combination with carboplatin in advanced head and neck carcinoma. Cancer. 2001 Nov 1;92(9):2334-2340. PMID: 11745288
20. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. Phase 3 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 Dec 1;23(34):8646-8654. PMID: 16314626
21. 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 Jul-Aug;71(7-8):723-726. PMID: 3300967

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Jacobs C, Lyman G, Velez-Garcia E, et al. A phase 3 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 Feb;10(2):257-263. PMID: 1732427
23. Grau JJ, Caballero M, Verger E, Monzó M, Blanch JL. Weekly paclitaxel for platin-resistant stage IV head and neck cancer patients. Acta Otolaryngol. 2009 Nov;129(11):1294-1299. PMID: 19863327
24. Guardiola E, Peyrade F, Chaigneau L, et al. Results of a randomised phase 2 study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 2004 Sep;40(14):2071-2076. PMID: 15341981
25. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase 2 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 Jun 1;25(16):2171-2177. PMID: 17538161
26. Forastiere AA, Metch B, Schuller DE, 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 Aug;10(8):1245-1251. PMID: 1634913
27. Martinez-Trufero J, Isla D, Adansa JC, et al. Phase 2 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 Jun 8;102(12):1687-1691. PMID: 20485287
28. Degardin M, Oliveira J, Geoffrois L, et al. An EORTC-ECSG phase 2 study of vinorelbine in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 1998 Oct;9(10):1103-1107. PMID:9834823
29. Jin Y, Shi YX, Cai XY, 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 Oct;138(10):1717-1725. PMID: 22684794
30. Chen C, Wang FH, Wang ZQ, et al. Salvage gemcitabine-vinorelbine chemotherapy in patients with metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol. 2012 Nov;48(11):1146-1151. PMID: 22748450
31. Zhang L, Zhang Y, Huang PY, Xu F, Peng PJ, Guan ZZ. Phase 2 clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. Cancer Chemother Pharmacol. 2008 Jan;61(1):33-38. PMID: 17909810
32. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers (V1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 30, 2018
33. Herbst RS, Arguette M, Shin DM, et al. Phase II multicenter study of epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol. 2005; 23:5578-87. PMID: 16009949
34. Chow LQ, Haddad R, Gupta S, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016 Nov; 34(32):3838-45. PMID: 27646946
35. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016. Epub 2016/10/11. PMID: 27718784
36. Seiwert TY, Burtness B, Mehra, R et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016 Jul;17(7):956-65. PMID: 27247226
37. Noronha V, Joshi A, Patil V, et al. Phase III randomized trial comparing weekly versus three-weekly (W3W) cisplatin in patients receiving chemoradiation for locally advanced head and neck cancer. J Clin Oncol. 2017;35.15_suppl.6007
38. Chen L, Hu CS, Chen XZ, et al. Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: Long-term results of a phase 3 multicentre randomised controlled trial. Eur J Cancer. 2017;75:150-8.PMID 28235726
39. Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial.[Erratum appears in Lancet. 2016 Oct 15;388(10054):1882 Note: ; PMID: 27751398]. Lancet. 2016;388(10054):1883-92.PMID 27567279
40. Liang H, Xia W-X, Xing Lv, et al. Concurrent chemoradiotherapy with 3-weekly versus weekly cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: A phase 3 multicentre randomised controlled trial (ChiCTR-TRC-12001979). J Clin Oncol. 2017;35:15_suppl.6006
41. Cao SM, Yang Q, Guo L, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase III multicentre randomised controlled trial. Eur J Cancer. 2017;75:14-23.PMID 28214653
42. Hsu C, Lee SH, 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. 2017.73.3675. [Epub ahead of print] PMID 28837405

Hodgkin Lymphoma Pathways

Classical Hodgkin Lymphoma | Early Stage (Stage I-IIA, Favorable and Unfavorable Risk)
ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (DTIC) ± ISRT*[1-5,30,35,36]
Classical Hodgkin Lymphoma | Advanced Stage (Stage IIB, III, and IV)
ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (DTIC) ± ISRT*[7-10,32]

* ISRT – Involved site radiation therapy

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

HODGKIN LYMPHOMA REFERENCES

NCCN Clinical Practice Guidelines: Hodgkin Lymphoma V1.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma V1.2018. Available at: http://www.nccn.org. Accessed February 27, 2018 © National Comprehensive Cancer Network, 2017. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol. 2004 Jul 15;22(14):2835-2841. PMID: 15199092
2. Meyer RM, NCIC Clinical Trials Group, Easter Cooperative Oncology Group, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012 Feb 2;366(5):399-408. PMID: 22149921
3. Von Tresckow B, Plutschow 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 Mar 20;30(9):907-913. PMID: 22271480
4. Engert A, Plutschow 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):640-652. PMID: 20818855
5. Radford J, Barrington S, Counsell N, et al. Involved Field Radiotherapy Versus No Further Treatment in Patients with Clinical Stages IA and IIA Hodgkin Lymphoma and a 'Negative' PET Scan After 3 Cycles ABVD. Results of the UK NCRI RAPID Trial. Blood. 2012 Nov 16; 120(21): Abstract 547. Abstract 547
6. Advani RH, Hong F, Fisher RI, et al. Randomized Phase III Trial Comparing ABVD Plus Radiotherapy With the Stanford V Regimen in Patients With Stages I or II Locally Extensive, Bulky Mediastinal Hodgkin Lymphoma: A Subset Analysis of the North American Intergroup E2496 Trial. J Clin Oncol. 2015 Mar 20;32(9):912-918. PMID: 25897153
7. Gordon LI, Hong F, Bartlett NL, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013 Feb 20;31(6):684-691. PMID: 23182987
8. Frederico M, Luminari S, HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009 Feb 10;27(5):805-811. PMID: 19124807
9. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol. 2003 Feb 15;21(4):607-614. PMID: 12586796
10. Merli F, Luminari S, Gobbi PG, et al. Long-Term Results of the HD2000 Trial Comparing ABVD Versus BEACOPP Versus COPP-EBV-CAD in Untreated Patients With Advanced Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi. J Clin Oncol. 2016 Apr 10;34(11):1175-1181. PMID: 26712220
11. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. Ann Oncol. 2010 Mar;21(3):574-581. PMID: 19759185
12. Savage KJ, Skinnider B, Al-Mansour M, Sehn LH, Gascoyne RD, Connors JM. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood. 2011 Oct 27;118(17):4585-4590. PMID: 21873543
13. Fanale MA, Lai CM, McLaughlin P, et al. Outcomes of Nodular Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL) Patients Treated with RCHOP. ASH. 2010 Dec 5. Abstract 2812. Abstract 2812
14. Ekstrand BC, Lucas JB, Horwitz S, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood. 2003 Jun 1;101(11):4285-4289. PMID: 12586628
15. 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):4363-4365. PMID: 21828141
16. 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):109-111. PMID: 17938252
17. 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 Jun 20;30(18):2183-2189. PMID: 22454421
18. Velasequez WS, McLaughlin P, Hagemeister FB, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol. 1994 Jun;12(6):1169-1176. PMID: 8201379
19. Gopal AK, Press OW, Shustov AR, 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 Aug;51(8):1523-1539. PMID: 20578815
20. Bartlett NL, Niedzwiecki D, Johnson LJ, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007 Jun;18(6):1071-1079. PMID: 17426059
21. Hertzberg MS, Crombie C, Benson W, Taper J, Gottlieb D, Bradstock KF. Outpatient-based ifosfamide, carboplatin and etoposide (ICE) chemotherapy in transplant-eligible patients with non-Hodgkin's lymphoma and Hodgkin's disease. Ann Oncol. 2003;14 Suppl 1:i11-6. PMID: 12736225

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Abali H, Urün Y, Oksüzoğlu 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 May;26(4):401-406. PMID: 18443961
23. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica. 2007 Jan;92(1):35-41. PMID: 17229633
24. Martin A, Fernández-Jiménez MC, Caballero MD, et al. Long-term follow-up in patients treated with Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease. Br J Haematol. 2001 Apr;113(1):161-171. PMID: 11328296
25. Colwill R, Crump M, Couture F, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. J Clin Oncol. 1995 Feb;13(2):396-402. PMID: 7844600
26. Rodrigeuz MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol. 1995 Jul;6(6):609-611. PMID: 8573542
27. Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-460. PMID: 23248254
28. Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol. 2010 May;85(5):320-324 PMID: 20229590
29. Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011 Nov 10;118(19):5119-5125. PMID: 21937701
30. 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 Sep 20;28(27):4199-206. PMID: 20713848
31. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. Ann Oncol. 2013 Apr;24(4):1044-8. PMID: 23136225.
32. Carde P, Karrasch M, Fortpied C, et al. Eight Cycles of ABVD Versus Four Cycles of BEACOPPescalated Plus Four Cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score ≥ 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial. J Clin Oncol. 2016 Apr 25. pii: JCO645648. PMID: 27114593
33. Engert A, German Hodgkin Study Group; Swiss Group for Clinical Cancer Research; Arbeitsgemeinschaft Medikamentöse Tumortherapie, 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 May 12;379(9828):1791-9. PMID: 22480758
34. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma (Version 1.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2017
35. Ferme C, Thomas J, Brice P, et al. ABVD or BEACOPP baseline along with involved-field radiotherapy in early-stage Hodgkin Lymphoma with risk factors: Results of the European Organisation for Research and Treatment of Cancer (EORTC)-Groupe d'Etude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. Eur J Cancer. 2017;81:45-55. PMID 28601705
36. Sasse S, Brockelmann PJ, Goergen H, et al. Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials. J Clin Oncol. 2017;35(18):1999-2007. PMID 28418763
37. Borchmann P, Haverkamp H, Lohri A, et al. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPP escalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. Lancet Oncol. 2017;18(4):454-63. PMID 28236583
38. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2018 Jan 25;378(4):331-344. PMID 29224502.
39. Longo DL, DeVita VT Jr. Progress in the Treatment of Hodgkin's Lymphoma. N Engl J Med. 2018 Jan 25;378(4):392-394 PMID 29224505

Kidney Cancer (Renal Cell Carcinoma) Pathways

Metastatic Disease | First Line of Therapy (1st Line)
High dose intravenous (IV) interleukin-2 (IL2, Proleukin)*[17,18]
Nivolumab (Opdivo) and ipilimumab (Yervoy)*[46]
Pazopanib (Votrient)[4,5,7]
Sunitinib (Sutent)[1-3,37]
Temsirolimus (Torisel)†[12,23]
Metastatic Disease |Second or Subsequent Lines of Therapy (2nd Line+) | Clear Cell Carcinoma
Nivolumab (Opdivo)[29,30,32]

* Indicated only for tumors with a significant clear cell histology component

† Indicated only for poor prognosis and non-clear cell histology. Poor prognosis is based on the Motzer criteria ((https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

KIDNEY CANCER (RENAL CELL CARCINOMA) REFERENCES

NCCN Practice Guideline: Kidney Cancer V4.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V4.2018. Available at: http://www.nccn.org. Accessed May 9, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. 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(22):3584-90. PMID: 19487381
2. Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol. 2012; 30(12):1371-7. PMID: 22430274
3. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal cell-carcinoma: an expanded-access trial. Lancet Oncol. 2009; 10(8):757-63. PMID: 19615940
4. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6):1061-8. PMID: 20100962
5. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomized, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer. 2013; 49(6):1287-96. PMID: 23321547
6. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol. 2014; 32(14):1412-8. PMID: 24687826
7. Garnick MB. How to Interpret patient preferences in selecting the best drug: are the current measurements up to the job? J Clin Oncol. 2014; 32(14):1392-3. PMID: 24687838
8. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomized open-label phase 3 trial. Lancet Oncol. 2013; 14(13):1287-94. PMID: 24206640
9. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006; 24(16):2505-12. PMID: 16636341
10. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol. 2013; 31(30):3791-9. PMID: 24019545
11. Rini BI, Szczylik C, Tannir NM, et al. AMG 386 in combination with sorarfenib in patients with metastatic clear cell carcinoma of the kidney: a randomized, double-blind, placebo-controlled, phase 2 study. Cancer. 2012; 118(24):6152-61. PMID: 22692704
12. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal cell-carcinoma. N Engl J Med. 2007; 356(22):2271-81. PMID: 17538086
13. Rini BI, Halabi S, Rosenbery JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008; 26(33):5422-8. PMID: 18936475
14. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010; 28(13):2137-43. PMID: 20368558
15. Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol. 2014; 32(8): 752-9. PMID: 24297945
16. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010; 28(13):2144-50. PMID: 20368553
17. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003; 21(16):3127-32. PMID: 12915604
18. McDermott DF, Cheng SC, Signoretti S, et al. The high-dose aldesleukin "select" trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res. 2015. 21(3):561-8. PMID: 25424850
19. Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(25):4068-75. PMID: 19652072
20. Rini BI, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol. 2008; 26(22):3743-8. PMID: 18669461
21. Hainsworth JD, Rubin MS, Arrowsmith ER, et al. Pazopanib as second-line treatment after sunitinib or bevacizumab in patients with advanced renal cell carcinoma: a Sarah Cannon Oncology Research Consortium Phase II Trial. Clin Genitourin Cancer. 2013; 11(3):270-5. PMID: 23665131
22. Motzer RJ, Escudier BI, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomized phase 3 trial. Lancet Oncol. 2013; 14(6):552-62. PMID: 23598172
23. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014; 32(8):760-7. PMID: 24297950
24. Motzer RJ, Porta C, Vogelzang NJ, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomized phase 3 trial. Lancet Oncol. 2014; 15(3):286-96. PMID: 24556040

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

25. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010; 116(18):4256-65. PMID: 20549832
26. Bracarda S, Hutson TE, Porta C, et al. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. Br J Cancer. 2012; 106(9):1475-80. PMID: 22441644
27. 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; 349(5):427-34. PMID: 12890841
28. Choueiri TK, Escudier B, METEOR Investigators, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Sep 25. [Epub ahead of print]. PMID: 26406150
29. Motzer RJ, Escudier B, CheckMate 025 Investigators, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Sep 25. [Epub ahead of print]. PMID: 26406148
30. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer (Version 4.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network 2018. Accessed May 9, 2018
31. 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(7):917-27. PMID: 27279544
32. Cella D, Grunwald V, Nathan P, et al. Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):994-1003. PMID: 27283863
33. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016. PMID: 27718781
34. 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, randomised, phase 3 trial. Lancet (London, England). 2016;387(10032):2008-16. PMID: 26969090
35. 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(15):1473-82. PMID: 26482279
36. 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(1):e4-5. PMID: 26758760
37. 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(3):378-88. PMID 26794930
38. 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(6):591-7.PMID 28199818.
39. Irshad T, Olencki T, Zynger DL, et al. Bevacizumab in metastatic papillary renal cell carcinoma (PRCC). J Clin Oncol. 2011;29(15 SUPPL. 1):e15158
40. Srinivasan R, Su D, Stamatakis L, et al. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: Interim results from a phase 2 study of bevacizumab and erlotinib. Eur J Cancer. 2014;50:8.
41. Voss MH, Molina AM, Chen YB, et al. Phase II Trial and Correlative Genomic Analysis of Everolimus Plus Bevacizumab in Advanced Non-Clear Cell Renal Cell Carcinoma. J Clin Oncol. 2016;06:06. PMID 27601542.
42. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol. 2009;27(34):5788-93. PMID 19884559.
43. Blank CU, 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. Feb 2012;30(5 SUPPL. 1):402.
44. Koh Y, Kim JY, Lim HY, et al. Phase II trial of RAD001 in renal cell carcinoma patients with non-clear cell histology. J Clin Oncol. 2012;30(15 SUPPL. 1):4544.
45. Motzer, RJ, Haas, NB, Donskov, F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. J Clin Oncol. 2017:JCO2017735324. [Epub ahead of print] PubMed PMID: 28902533
46. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;21:21.PMID 29562145.
47. Curti BD. Immunotherapy in Advanced Renal Cancer - Is Cure Possible? N Engl J Med. 2018;21:21.PMID 29562143.

Lung Cancer: Non-Small Cell Lung Cancer (NSCLC) Pathways

Neoadjuvant/Preoperative/Induction Therapy or Adjuvant/Definitive Therapy

Cisplatin and etoposide (Toposar) with concurrent XRT[88,89]

Paclitaxel and carboplatin with concurrent XRT[93]

Adjuvant Therapy

Carboplatin and paclitaxel[52]

Cisplatin and gemcitabine (Gemzar)

Cisplatin and vinorelbine (Navelbine)[53]

Metastatic Disease | Squamous | TPS ≥ 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Added effective 11/12/2018

Pembrolizumab (Keytruda)*[125] - Added effective 11/12/2018

Metastatic Disease | Squamous | PD-L1 Expression <50% | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Termed effective 11/12/2018

Metastatic Disease | Squamous | TPS < 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Added effective 11/12/2018

Carboplatin* and paclitaxel[7-16] – Termed effective 11/12/2018

Cisplatin* and gemcitabine (Gemzar)[8,11,13,22-25,75] – Termed effective 11/12/2018

Pembrolizumab (Keytruda), carboplatin, and paclitaxel[126] – Added effective 11/12/2018

Metastatic Disease | ALK and EGFR Negative | PD-L1 Positive† | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Termed effective 11/12/2018

Metastatic Disease | Nonsquamous | ALK/EGFR Negative (ROS1 Negative or Unknown) | PD-L1 Positive TPS ≥ 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Added Effective 11/12/2018

Pembrolizumab (Keytruda)*[102,125]

Metastatic Disease | Nonsquamous | ALK/EGFR Negative (ROS1 Negative or Unknown) | PD-L1 Positive TPS < 50% | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Added Effective 11/12/2018

Pembrolizumab (Keytruda), pemetrexed (Alimta), and carboplatin[124] – Added effective 11/12/2018

Metastatic Disease | Non-Squamous | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Termed effective 11/12/2018

Metastatic Disease | Squamous or Nonsquamous | Immunotherapy-Ineligible | First Line of Therapy (1st Line) | ECOG PS: 0-2 – Added effective 11/12/2018

Carboplatin† and paclitaxel[7-16,54]

Carboplatin, paclitaxel, and bevacizumab (Avastin)[13,14,31]

Carboplatin*, pemetrexed (Alimta), and pembrolizumab (Keytruda)[124] – Termed effective 11/12/2018

Cisplatin† and gemcitabine (Gemzar)[8,11,13,22-25]

Cisplatin† and pemetrexed (Alimta)[17,18]

---

* Administered at a dose of 2 mg/kg (up to a maximum of 200 mg)

† In the setting of recurrent/metastatic NSCLC, a substitution of carboplatin for cisplatin (or vice-versa) will be considered a pathway option.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

Lung Cancer: Non-Small Cell Lung Cancer (NSCLC) Pathways (continued)

Metastatic Disease | Non-Squamous | Maintenance | ECOG PS: 0-2

Continuation bevacizumab (Avastin)[36-38]

Continuation pemetrexed (Alimta)[39,94]

Pembrolizumab (Keytruda) and pemetrexed (Alimta) **(if previously treated with carboplatin, pemetrexed, and pembrolizumab)**[113] – Added effective 11/12/2018

Switch pemetrexed (Alimta)[41,94]

Metastatic Disease | Second or Subsequent Lines of Therapy (2nd Line+) | ECOG PS: 0-2

Atezolizumab (Tecentriq)[104] – Termed effective 11/12/2018

Atezolizumab (Tecentriq)[104] **(if no prior checkpoint inhibitors)** – Added effective 11/12/2018

Nivolumab (Opdivo)[59,61,72,78] – Termed effective 11/12/2018

Nivolumab (Opdivo)[59,61,72,78] **(if no prior checkpoint inhibitors)** – Added effective 11/12/2018

Pemetrexed (Alimta)[43,44] **(non-squamous histology)** – Termed effective 11/12/2018

Carboplatin† and paclitaxel[7-16,54] – Added effective 11/12/2018

Carboplatin† and gemcitabine (Gemzar) – Added effective 11/12/2018

Carboplatin† and pemetrexed (Alimta) – Added effective 11/12/2018

Metastatic Disease | ALK Positive | First Line of Therapy (1st Line)

Alectinib (Alecensa)[108]

Metastatic Disease | EGFR Positive| First Line of Therapy (1st Line)

Osimertinib (Tagrisso)[114]

Metastatic Disease | ALK or EGFR Positive | Second or Subsequent Lines of Therapy (2nd Line+) | ECOG PS: 0-2

Carboplatin† and paclitaxel[7-16,54]

Cisplatin† and gemcitabine (Gemzar)[8,11,13,22-25]

Cisplatin† and pemetrexed (Alimta)[17,18]

Metastatic Disease | EGFR Positive | ECOG PS: 3-4

Erlotinib (Tarceva)[42,48,50,51]

---

* Administered at a dose of 2 mg/kg (up to a maximum of 200 mg)

† In the setting of recurrent/metastatic NSCLC, a substitution of carboplatin for cisplatin (or vice-versa) will be considered a pathway option.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

LUNG CANCER: NON-SMALL CELL LUNG CANCER (NSCLC) REFERENCES

NCCN Clinical Practice Guidelines: Non-Small Cell Lung Cancer V6.2018

References

1. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013 Jun 20;368(25):2385-2394. PMID: 23724913
2. Jänne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol. 2012 Jun 10;30(17):2063-2069. PMID: 22547605
3. Drug Label: TARCEVA® (erlotinib) tablets, oral [Internet]. Melville: OSI Pharmaceuticals, Inc.; c2010 [cited 2017 Nov 09]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021743s14s16lbl.pdf
4. 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 multicenter, open-label, randomized phase 3 trial. Lancet Oncol. 2012;13(3):239-46. PMID: 22285168
5. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011 Aug;12(8):735-742. PMID: 21783417
6. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013 Sep 20;31(27):3327-3334. PMID: 23816960
7. Socinski MA, Bondarenko I, Karaseva NA, et al. 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. J Clin Oncol. 2012 Jun 10;30(17):2055-2062. PMID: 22547591
8. Schiller JH, Harrington D, Eastern Cooperative Oncology Group, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002 Jan 10;346(2):92-98. PMID: 11784875
9. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol. 2001 Jul 1;19(13):3210-3218. PMID: 11432888
10. Hirsh V, Paz-Ares L, Boyer M, et al. Randomized phase III trial of paclitaxel/carboplatin with or without PF-3512676 (Toll-like receptor 9 agonist) as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol. 2011 Jul 1;29(19):2667-2674. PMID: 21632509
11. Scagliotti GV, De Marinis F, Italian Lung Cancer Project. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002 Nov 1;20(21):4285-4291. PMID: 12409326
12. Quoix E, Zalcman G, Intergroupe Francophone de Cancérologie Thoracique, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet. 2011 Sep 17;378(9796):1079-1088. PMID: 21831418
13. Sandler A, Gray R, Perry MC, Braet al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-2550. PMID: 17167137
14. FDA review documents
15. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol. 2008 Jan 20;26(3):468-473. PMID: 18202422
16. Smit EF, van Meerbeeck JP, European Organization for Research and Treatment of Cancer Lung Cancer Group, et al. 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. J Clin Oncol. 2003 Nov 1;21(21):3909-3917. PMID: 14581415
17. Scagliotti GV, Parikh P, von Pawel J, et al. 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. 2008 Jul 20;26(21):3543-3551. PMID: 18506025
18. Socinski MA, Smit EF, Lorigan P, et al. Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. J Clin Oncol. 2009 Oct 1;27(28):4787-4792. PMID: 19720897
19. Fossella F, Pereira JR, von Pawel J, et al. 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. J Clin Oncol. 2003;21(16):3016-24. PMID: 12837811

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

20. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol. 2004;22(2):254-61. PMID: 14722033
21. Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase III trial. PMID: 15701857
22. Gronberg BH, Bremnes RM, Flotten O, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small cell lung cancer. J Clin Oncol. 2009;27(19):3217-24. PMID: 19433683.
23. Grigorescu AC, Draghici IN, Nitipir C, et al. Gemcitabine (GEM) and carboplatin (CBDCA) versus cisplatin (CDDP) and vinblastine (VLB) in advanced non-small cell lung cancer (NSCLC) stages III and IV: a phase III randomized trial. Lung Cancer. 2002;37(1):9-14. PMID: 12057861
24. Helbekkmo N, Sundstrøm SH, Norwegian Lung Cancer Study Group, et al. Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. Br J Cancer. 2007 Aug 6;97(3):283-289. PMID: 17595658
25. Masters GA, Argiris AE, Hahn EA, et al. A randomized phase II trial using two different treatment schedules of gemcitabine and carboplatin in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2006;1(1):19-24. PMID: 17409822
26. Georgoulias V, Ardavanis A, Tsiafaki X, et al. Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small cell lung cancer: a phase III randomized trial. J Clin Oncol. 2005;23(13);2937-45. PMID: 15728228
27. Booton R, Lorigan P, Anderson H, et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small cell lung cancer: a randomized multicenter trial of the British Thoracic Group (BTOG1). Ann Oncol. 2006;17(7):1111-9. PMID: 16603599
28. Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07681. J Clin Oncol. 1990;8(9):1556-62. PMID: 2167953
29. Doll D, Goutsou M, Graziano S, et al. Carboplatin and vinblastine in advanced non-small cell lung cancer: a phase II study. Cancer Chemother Pharmacol. 1991;29(1):71-4. PMID: 1660354
30. Patel JD, Socinski MA, Garon EB, et al. 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. J Clin Oncol. 2013 Dec 1;31(34):4349-4357. PMID: 24145346
31. Azzoli CG, Baker S Jr, American Society of Clinical Oncology, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009 Dec 20;27(36):6251-6266. PMID: 19917871
32. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol. 2005;16(4):602-10. PMID: 15741225
33. Binder D, Schweisfurth H, Grah C, et al. Docetaxel/gemcitabine or cisplatin/gemcitabine followed by docetaxel in the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC): results of a multicenter randomized phase II trial. Cancer Chemother Pharmacol. 2007;60(1):143-50. PMID: 17031643
34. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small cell lung cancer (FLEX): an open-label randomized phase III trial. Lancet. 2009;373(9674):1525-31. PMID: 19410716
35. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e341S-368S. PMID: 23649446
36. Lopez-Chavez A, Young T, Fages S, et al. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern Cooperative Oncology Group 4599 Study: results of an exploratory analysis. J Thorac Oncol. 2012 Nov;7(11):1707-1712. PMID: 23059774
37. Barlesi F, Scherpereel A, Rittmeyer A, et al. 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). J Clin Oncol. 2013 Aug 20;31(24):3004-3011. PMID: 23835708
38. Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2013 Nov 1;31(31):3926-3934. PMID: 24101054
39. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013 Aug 10;31(23):2895-2902. PMID: 23835707
40. Cappuzzo F, Ciuleanu T, SATURN investigators, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010 Jun;11(6):521-529. PMID: 20493771
41. Ciuleanu T, Brodowicz T, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009 Oct 24;374(9699):1432-40. PMID: 19767093
42. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med. 2010;363(8):733-42. PMID: 20818875
43. Hanna N, Shepherd FA, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004 May 1;22(9):1589-97. PMID: 15117980
44. Ciuleanu T, Stelmakh L, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012 Mar;13(3):300-8. PMID: 22277837
45. Kim ES, Hirsh V, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008 Nov 22;372(9652):1809-18. PMID: 19027483
46. Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol. 2010 Jul;11(7):619-26. PMID: 20570559

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

47. Garassino MC, Martelli O, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol. 2013 Sep;14(10):981-8. PMID: 23883922
48. Shepherd FA, Rodrigues Pereira J, National Cancer Institute of Canada Clinical Trials Group, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005 Jul 14;353(2):123-132. PMID: 16014882
49. Zhu CQ, da Cunha Santos G, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. 2008 Sep 10;26(26):4268-4275. PMID: 18626007
50. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 2012 May;13(5):528-538. PMID: 22452896
51. Schnipper LE, Smith TJ, Raghavan D, et al. Amercian Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012;30(14):1715-24. PMID: 22493340
52. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. 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. J Clin Oncol. 2008 Nov 1;26(31):5043-5051. PMID: 18809614
53. Arriagada R, Bergman B, International Adjuvant Lung Cancer Trial Collaborative Group, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004 Jan 22;350(4):351-360. PMID: 14736927
54. Winton T, Livingston R, National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005 Jun 23;352(25):2589-2597. PMID: 15972865
55. Leighl NB, Shepherd FA, Kwong R, Burkes RL, Feld R, Goodwin PJ. Economic analysis of the TAX 317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer. J Clin Oncol. 2002 Mar 1;20(5):1344-1352. PMID: 11870178
56. Shaw AT, Kim D-W, Mehra R, Tan DSW et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. N Engl J Med 2014; 370:1189-97.
57. Abe T, Takeda K, Ohe Y, et al. Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L. J Clin Oncol. 2015 Feb 20;33(6):575-581. PMID: 25584004
58. Solomon BJ, Mok T, PROFILE 1014 Investigators, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-2177. PMID: 25470694
59. Drug Label: OPDIVO (nivolumab) injection, for intravenous use [Internet]. Princeton: Bristol-Myers Squibb Company; c2014 [cited 2017 Nov 09]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf
60. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014 Aug 23;384(9944):665-73. PMID: 24933332
61. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015 Feb 19. pii: S1470-2045(15)70054-9. PMID: 25704439
62. Brahmer JR, Horn L, Gandhi L, et a. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis. J Clin Oncol. 2014;32(15S):8112. Abstract 8112
63. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 6.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed September 12, 2018
64. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. J Clin Oncol. 2004 Oct 1;22(19):3860-3867. PMID: 15326194
65. Heymach JV, Lockwood SJ, Herbst RS, Johnson BE, Ryan AJ. EGFR biomarkers predict benefit from vandetanib in combination with docetaxel in a randomized phase III study of second-line treatment of patients with advanced non-small cell lung cancer. Ann Oncol. 2014 Oct;25(10):1941-1948. PMID: 25057173
66. Cardenal F, Nadal E, Jové M, Faivre-Finn C. Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature. Ann Oncol. 2015 Feb;26(2):278-288. PMID: 24942274
67. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol. 2014 Jun 20;32(18):1902-1908. PMID: 24841974
68. Wislez M, Barlesi F, Besse B, et al. Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE. J Clin Oncol. 2014 Apr 20;32(12):1256-1261. PMID: 24638013
69. Yoshioka H, Mitsudomi T, Morita S, et al. Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). J Clin Oncol. 2014 May 20; 32(15 suppl):8117.
70. Ibata H, Ando M, Asami K, et al. Updated overall survival (OS) results of randomized phase III trial of erlotinib (E) versus (v) docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol. 2014 May 20; 32(15 suppl):e19003.
71. Perol M, Ciuleanu TE, Arrieta O, et al. REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy. J Clin Oncol. 2014 May 20; 32(15 suppl):LBA8006.
72. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab v Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123-35. PMID: 26028407
73. Wu TL, Zhou C, Liam CK, et al. First-line erlotinib v gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015 Sep;26(9):1883-9. PMID: 26105600

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

74. Langer CJ, Hirsh V, Okamoto I, et al. Survival, quality-adjusted survival, and other clinical end points in older advanced non-small-cell lung cancer patients treated with albumin-bound paclitaxel. Br J Cancer. 2015 Jun 30;113(1):20-9. PMID: 26035702
75. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin v gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2015 Jul;16(7):763-74. PMID: 26045340
76. Ou SI, Ahn JS, De Petris L, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol. 2015 Nov 23. PMID: 26598747
77. Schuler M, Yang JC, Park K, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. Ann Oncol. 2015 Dec 8. PMID: 26646759
78. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab v Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39. PMID: 26412456
79. Soria JC, Felip E, LUX-Lung 8 Investigators, et al. Afatinib v erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2015 Aug;16(8):897-907. PMID: 26156651
80. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. 2015 Aug 20;373(8):726-36. PMID: 26287849
81. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib V Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. 2015 Dec 1;33(34):4007-14. PMID: 26324372
82. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 20;33(30):3488-515. PMID: 26324367
83. O'Brien ME, Gaafar R, EORTC-LCG, et al. Maintenance pazopanib v placebo in Non-Small Cell Lung Cancer patients non-progressive after first line chemotherapy: A double blind randomised phase III study of the lung cancer group, EORTC 08092 (EudraCT: 2010-018566-23, NCT01208064). Eur J Cancer. 2015 Aug;51(12):1511-28. PMID: 26074395
84. Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):990-8. PMID: 26159065
85. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2015 Dec 18. pii: S0140-6736(15)01281-7. PMID: 26712084
86. Mitsudomi T, Tsai CM, Shepherd F, et al. MINI16.08 AZD9291 in Pre-Treated T790M Positive Advanced NSCLC: AURA2 Phase II Study. World Conference on Lung Cancer. 2015; abstract 1406.
87. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br J Cancer. 2014 Jan 7;110(1):55-62. PMID: 24263064
88. Albain, K. S., Crowley, J. J., Turrisi, A. T., 3rd, et al. (2002). 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, 20(16), 3454-3460. PMID: 12177106
89. Curran, W. J., Jr., Paulus, R., Langer, C. J., et al. (2011). Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst, 103(19), 1452-1460. PMID: 21903745
90. Govindan, R., Bogart, J., Stinchcombe, T., et al. (2011). 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, 29(23), 3120-3125. PMID: 21747084
91. Choy, H., Gerber, D. E., Bradley, J. D., et al. (2015). Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. Lung Cancer, 87(3), 232-240. PMID: 25650301
92. Belani, C. P., Choy, H., Bonomi, P., et al. (2005). Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol, 23(25), 5883-5891. PMID: 16087941
93. Bradley, J. D., Paulus, R., Komaki, R., et al. (2015). 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 non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol, 16(2), 187-199. PMID: 25601342
94. Kulkarni, S., Vella, E. T., Coakley, N., et al. (2016). The Use of Systemic Treatment in the Maintenance of Patients with Non-Small Cell Lung Cancer: A Systematic Review. J Thorac Oncol, 11(7), 989-1002. PMID: 27013406
95. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014 Nov 20;371(21):1963-71. PMID: 25264305
96. Barlesi F, Scherpereel A, Rittmeyer A, et al. 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). J Clin Oncol. 2013 Aug 20;31(24):3004-11. PMID: 23835708
97. Tan EH, Szczesna A, GLOB 2 group, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer. 2005 Aug; 49(2):233-40. PMID: 16022917.
98. Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol. 2006 Aug;17(8):1263-8. PMID: 16740598
99. Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. J Clin Oncol. 2005 Nov 20;23(33):8380-8. PMID: 16293868
100. Zatloukal P, Kanitz E, Magyar P, et al. Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. Lung Cancer. 1998 Dec;22(3):243-50. PMID: 10048477
101. Lilenbaum RC, Herndon JE 2nd, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol. 2005 Jan 1;23(1):190-6. PMID: 15625373

102. Reck M, Rodríguez-Abreu D, KEYNOTE-024 Investigators, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print] PMID: 27718847
103. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer--a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer. 2000 Aug;83(4):447-53. PMID: 10945489
104. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65. PMID 27979383.
105. Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017 Aug 14:JCO2017746065. [Epub ahead of print] PubMed PMID: 28806116.
106. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncol. 2013;24(4):986-92. PMID 23161898.
107. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;08:08. PMID 28885881.
108. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(9):829-38. PMID 28586279.
109. Soria JC, Tan DSW, Chiari R, et al. 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. Lancet. 2017;389(10072):917-29. PMID 28126333.
110. Ramalingam S RT, Chewaskulyong B, et al. Osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFRm advanced NSCLC: FLAURA. Ann Oncol. 2017 Sept 1;28(SUPPL. 5):635.
111. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. 2016;17(7):984-93. PMID 27283860.
112. Frasci G, Comella P, Panza N, et al. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. Eur J Cancer. 1998;34(11):1710-4. PMID 9893657.
113. Langer CJ, Gadgeel SM, Borghaei H, et al. 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. Lancet Oncol. 2016;17(11):1497-508.PMID 27745820.
114. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376(7):629-40. PMID 27959700.
115. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. J Clin Oncol. 2017;35(22):2490-8. PMID 28475456.
116. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discovery. 2014;4(9):1036-45. PMID 25074459.
117. Camidge DR, Ou SHI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). J Clin Oncol. 2014;32(15 SUPPL. 1). PMID 71526374.
118. Drilon AE, Sima CS, Somwar R, et al. Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers. J Clin Oncol. 2015;33(15 SUPPL. 1). PMID 72014666.
119. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol. 2017;28(2):292-7. PMID 27803005.
120. Wu Y-L, Zhong W, Wang Q, et al. Gefitinib (G) versus vinorelbine+cisplatin (VP) as adjuvant treatment in stage II-IIIA (N1-N2) non-small-cell lung cancer (NSCLC) with EGFR-activating mutation (ADJUVANT): A randomized, Phase III trial (CTONG 1104). J Clin Oncol. 2017.35.15_suppl.8500
121. Kris MG, Gaspar LE, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. J Clin Oncol. 2017 35(25):2960-2974, PMID # 28437162
122. Goldstein D, Gordon N, Davidescu M, et. al. A phamacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non–small cell lung cancer. J Natl Cancer Inst. 2017 June;109(11):1558-1568. Accessed June 5, 2017 Abstract
123. Drug Label: Keytruda (pembrolizumab) injection, for intravenous use [Internet}. Merck Sharp & Dohme Corp; c2015 [cited 2017 June 05]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf
124. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;z916). Epub ahead of print. PMID 29658856.
125. Lopes G, Wu Y, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol. 2018;36(Suppl):abstr LBA4.
126. Paz-Ares L, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab for patients with metastatic squamous non-small cell lung cancer (NSCLC). J Clin Oncol. 2018;36(Suppl):abstr 105.

Lung Cancer: Small Cell Lung Cancer Pathways

Limited Stage | Primary, Adjuvant, or First Line of Therapy (1st Line)
Carboplatin and etoposide (Toposar) ± XRT[3]
Cisplatin and etoposide (Toposar) ± XRT[1,2]
Extensive Stage | First Line of Therapy (1st Line)
Carboplatin and etoposide (Toposar)[9]
Second and Subsequent Lines of Therapy (2nd Line+) | Relapse Greater than Six (6) Months
Carboplatin and etoposide (Toposar)[9]

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

LUNG CANCER: SMALL CELL LUNG CANCER REFERENCES

NCCN Clinical Practice Guidelines: Small Cell Lung Cancer. Version 2.2018

References

1. Turrisi AT 3rd, Kim K, Blum R, Sause WT, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999 Jan 28;340(4):265-71. PMID: 9920950
2. Saito H, Takada Y, West Japan Thoracic Oncology Group 9902, 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. J Clin Oncol. 2006 Nov 20;24(33):5247-52. PMID: 17114657
3. Skarlos DV, 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 Sep;12(9):1231-8. PMID: 11697833
4. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol. 2011 Jun 1;29(16):2215-22. PMID: 21502556
5. Hanna N, Bunn PA Jr, 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. J Clin Oncol. 2006 May 1;24(13):2038-43. PMID: 16648503
6. Noda K, Nishiwaki Y, Japan Clinical Oncology Group, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002 Jan 10;346(2):85-91. PMID: 11784874
7. Niell HB, Herndon JE 2nd, Cancer and Leukemia Group, et al. 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. J Clin Oncol. 2005 Jun 1;23(16):3752-9. PMID: 15923572
8. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol. 1985 Nov;3(11):1471-7. PMID: 2997406
9. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol. 1999 Nov;17(11):3540-5. PMID: 10550152
10. Schmittel A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. Ann Oncol. 2006 Apr;17(4):663-7. PMID: 16423848
11. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer. 1998;77(2):347-51. PMID: 9461009
12. 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 Jan-Feb;26(1B):777-81. PMID: 16739353
13. Smyth JF, Smith IE, 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;30A(8):1058-60 PMID: 7654428
14. O'Brien ME, Ciuleanu TE, 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 Dec 1;24(34):5441-7. PMID: 17135646
15. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007 May 20;25(15):2086-92. PMID: 17513814
16. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999 Feb;17(2):658-67. PMID: 10080612
17. 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 Aug;10(8):1225-9. PMID: 1321891
18. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res. 2012 Feb 15;18(4):1138-45. PMID: 22228633
19. Zauderer MG, 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 Nov;86(2):237-40. PMID: 25194640
20. van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. Ann Oncol. 2001 Apr;12(4):557-61. PMID: 11398892
21. Masters GA, 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 Apr 15;21(8):1550-5. PMID: 12697880
22. Cantwell BM, Bozzino JM, Corris P, Harris AL. The multidrug resistant phenotype in clinical practice; evaluation of cross resistance to ifosfamide and mesna after VP16-213, doxorubicin and vincristine (VPAV) for small cell lung cancer. Eur J Cancer Clin Oncol. 1988 Feb;24(2):123-9. PMID: 2833398

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

23. Furuse K, Kubota K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Oncology. 1996 Mar-Apr;53(2):169-72. PMID: 8604245
24. Jassem J, Karnicka-Młodkowska 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(12):1720-2. PMID: 8398301
25. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol. 1990 Oct;8(10):1613-7. PMID: 2170589
26. Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. Semin Oncol. 1990 Feb;17(1 Suppl 2):32-5. PMID: 2154857
27. Antonia, Scott J., et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 17.7 (2016): 883-895. PMID: 27269741
28. Tiseo M, Boni L, Ambrosio F, et al. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The OIRC-AIFA FARM6PMFJM Trial. J Clin Oncol. 2017 Jan 30:JCO2016694844. PMID: 28135143
29. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2016;17(8):1147-57.PMID 27312053.
30. Hellmann MD. Impact of tumor mutation burden on the efficacy of nivolumab or nivolumab + ipilimumab in small cell lung cancer: and exploratory analysis of CheckMate 032. (2017) The IASLC 18th World Conference on Lung Cancer. Available from: https://library.iaslc.org/search-speaker?search_speaker=52814.

Melanoma Pathways: Metastatic Melanoma

Stage IIIB/IIIC (Resected) | Adjuvant Therapy

Nivolumab (Opdivo)[59]

Metastatic Disease | First and Subsequent Lines of Therapy (1st Line+) | Any BRAF Status | ECOG PS: 0-2

Pembrolizumab (Keytruda)*[35,45,55,56]

Nivolumab (Opdivo) and ipilimumab (Yervoy)[65]

Metastatic Disease | First Line of Therapy (1st Line) |BRAF Mutated‡ | Symptomatic Disease | ECOG PS: 0-2

Vemurafenib (Zelboraf) and cobimetinib (Cotellic)[26,40-42]

Metastatic Disease | Second and Subsequent Lines of Therapy (2nd Line+) | BRAF Mutated† | ECOG PS: 0-2

Vemurafenib (Zelboraf) and cobimetinib (Cotellic)[26,40-42]

Metastatic Disease | Second and Subsequent Lines of Therapy (2nd Line+) | Any BRAF Status | ECOG PS: 0-2

Ipilimumab (Yervoy)[1,14,15,35,36]

* Administered at a dose of 2 mg/kg (up to a maximum of 200 mg)

† BRAF mutations include V600E and V600K mutations

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

MELANOMA: METASTATIC MELANOMA REFERENCES

NCCN Clinical Practice Guidelines: Melanoma V2.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma V2.2018. Available at: http://www.nccn.org. Accessed May 9, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23. PMID: 20525992

2 Atkins MB, Lotze MT, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999 Jul;17(7):2105-16. PMID: 10561265

3 Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am. 2000 Feb;6 Suppl 1:S11-4. PMID: 10685652

4 Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000 Jan;18(1):158-66. PMID: 10623706

5 Kaufmann R, Spieth K, Leiter U, et al. Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. J Clin Oncol. 2005 Dec 10;23(35):9001-7. PMID: 16260697

6 Hersh EM, O'Day SJ, Ribas A, et al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naive patients with metastatic melanoma. Cancer. 2010 Jan 1;116(1):155-63.

7 Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012 Feb 23;366(8):707-14. PMID: 22356324

8 Chapman PB, Hauschild A, Robert C , et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun 30;364(26):2507-16. PMID: 21639808

9 Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28;380(9839):358-65. PMID: 22735384

10 Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012 Nov;367(18):1694-703. PMID: 23020132

11 Carvajal RD1, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011 Jun 8;305(22):2327-34. PMID: 21642685

12 Long GV, Stroyakovsky DL, Gogas H, et la. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. N Engl J Med 2014;371:1877-88.

13 Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012 Jul 12;367(2):107-14. PMID: 22663011

14 McDermott D, Haanen J, Chen T, et al. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20) Ann Oncol. 2013; 24: 2694–2698. PMID: 23942774

15 Robert C, Schadendorf D, Messina M, et al. Efficacy and Safety of Retreatment with Ipilimumab in Patients with Pretreated Advanced Melanoma Who Progressed after Initially Achieving Disease Control. Clin Cancer Res. 2013;19: 2232-2239. PMID: 23444228

16 Smith FO, Downey SG, Klapper JA, et al. Treatment of Metastatic Melanoma Using Interleukin-2 Alone or in Conjunction with Vaccines. Clin Cancer Res. 2008; 14(17): 5610–5618. PMID: 18765555

17 Hersh E, Vecchio MD, Brown M, et al. Phase 3, randomized, open-label, multicenter trial of nab-paclitaxel (nab-P) vs dacarbazine (DTIC) in previously untreated patients with metastatic malignant melanoma (MMM). Presented at Society for Melanoma Research 2012 Congress. Pigment Cell Melanoma Res. 2012; 25: 863.

18 Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for 1-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. Presented at ASCO 2012. J Clin Oncol 2012; 30:15s:8502. Abstract 8502

19 Hauschild A, Grob JJ, Demidov LV, et al. 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). Presented at ASCO 2013. J Clin Oncol 2013; 31:15s:9013. Abstract 9013

20 Topalian SL, Sznol M, McDermott DF, et al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol 2014; 32(10):1020-1030. PMID: 24590637

21 Wolchok JD, Kluger H, Callahan MKL, et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med 2013; 369:122-33. PMID: 23724867

22 Sznol M, Kluger HM, Callahan MK, Postow MA, Gordon RA. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). Presented at ASCO 2014. J Clin Oncol 2014; 32:5s:9003. Abstract 9003

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

23 Hamid O, Robert C, Daud A, Hodi FS, Hwu W, Kefford R et al. Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. N Engl J Med 2013; 369:134-44. PMID: 23724846
24 Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. Early Online Publication, 15 July 2014. Abstract
25 Johnson DB, Flaherty KT, Weber JS, et al. Combined BRAF (Dabrafenib) and MEK Inhibition (Trametinib) in Patients With BRAFV600-Mutant Melanoma Experiencing Progression With Single-Agent BRAF Inhibitor. J Clin Oncol 2014 Nov 20;32(33):3697-3704. PMID: 25287827
26 Larkin J, Ascierto PA, Dréno B, et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. N Engl J Med 2014;371:1867-1876. PMID: 25265494
27 Ribas A, Wolchok JD, Robert C, et al. Updated clinical efficacy of the anti-PD-1 monoclonal antibody pembrolizumab (pembro, MK-3475) in 411 patients (pts) with melanoma (MEL). Society for Melanoma Research 2014 International Congress. November 13-16, 2004, Zurich, Switzerland.
28 Ribas A, Pzanov I, Dummer R, et al. A Randomized Controlled Comparison of Pembrolizumab and Chemotherapy in Patients With Ipilimumab-Refractory (IPI-R) Melanoma (MEL). Society for Melanoma Research 2014 International Congress. November 13-16, 2004, Zurich, Switzerland.
29 Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. New Engl J Med. 2015 Jan 1;372(1):30-9. PMID: 25399551
30 Robert C, Ribas A, Wolchok J, et al. Anti-programmed death receptor-1 treatment with pembrolizumab in ipilumumab –refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109-17. PMID: 25034862
31 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-330. PMID: 25399552
32 Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-C TLA-4 treatment (CheckMate 037): a randomized, controlled, open-labeled phase 3 trial. Lancet Oncol. 2015 Apr;16(4):375-384. PMID: 25795410
33 McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF (V600E) and BRAF (V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomized, open-label study. Lancet Oncol. 2014;15(3):323-32. PMID: 24508103
34 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma Cancer (Version 2.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018.
35 Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jn 25;372(26):2521-2532. PMID: 25891173
36 Larkin J, Chiarion‐Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34. PMID: 26027431
37 Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015 May 29. pii: S0140-6736(15)60898-4. PMID: 26037941
38 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;16:908-18. PMID: 26115796
39 Postow M, Chesney J, Pavlick A, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372:2006-2017. PMID: 25891304
40 Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF (V600)-mutated melanoma: a phase 1b study. Lancet Oncol. 2014;15:954-965. PMID: 25037139
41 Pavlick A, Ribas A, Gonzalez R, et al. Extended follow-up results of phase 1b study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAF-mutated melanoma. ASCO Meeting Abstracts. 2015;33:Abstract 9020. Abstract 9020
42 Larkin J, Yan Y, McArthur G, et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced BRAF-mutated melanoma. ASCO Meeting Abstracts. 2015;33:Abstract 9006. Abstract 9006
43 Hersh EM, Vecchio M, Brown MP, et al. A randomized, controlled phase III trial of nab-paclitaxel versus dacrabazine in chemotherapy-naïve patients with metastatic melanoma. Ann Oncol. 2015;26:2267-2274. PMID: 26410620
44 Bowyer S, Prithviraj P, Lorigan P, et al. Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma after prior anti-PD-1 therapy. Br J Cancer. 2016 May 10;114(10):1084-9. PMID: 27124339
45 Ribas A, Hamid O, Daud A, et. al. Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. JAMA. 2016 Apr 19;315(15):1600-9. PMID: 27092830
46 Hodi FS, Chesney J, Pavlick AC, et. al. 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. Lancet Oncol. 2016 Nov;17(11):1558-1568. PMID: 27622997
47 Ascierto PA, McArthur GA, Dréno B, et. al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016 Sep;17(9):1248-60. PMID: 27480103
48 Ives NJ, Stowe RL, Lorigan P, et. al. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol. 2007 Dec 1;25(34):5426-34. PMID: 18048825
49 Atkins MB, Hsu J, Lee S, et. al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2008 Dec 10;26(35):5748-54. PMID: 19001327
50 Rao RD, Holtan SG, Ingle JN, et. al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer. 2006 Jan 15;106(2):375-82. PMID: 16342250
51 Hauschild A, Agarwala SS, Trefzer U, et. al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol. 2009 Jun 10;27(17):2823-30. PMID: 19349552.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

52 Wiernik PH, Einzig AI. Taxol in malignant melanoma. J Natl Cancer Inst Monogr. 1993;(15):185-7. PMID: 7912525
53 Schreuer M, Jansen Y, Planken S, et. al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAF(V600)-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol. 2017 Apr;18(4):464-472. PMID: 28268064
54 Hodi FS, Corless CL, Giobbie-Hurder A, et. al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013 Sep 10;31(26):3182-90. PMID: 23775962
55 Goldstein D, Gordon N, Davidescu M, et. al. A phamacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non–small cell lung cancer. J Natl Cancer Inst. 2017 June;109(11):1558-1568. Accessed June 5, 2017 Abstract
56 Drug Label: Keytruda (pembrolizumab) injection, for intravenous use [Internet}. Merck Sharp & Dohme Corp; c2015 [cited 2017 June 05]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf
57 Eggermont AM, Charion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med. 2016 Nov 10;375(19):1845-1855. PMID: 27717298
58 Schuchter LM. Adjuvant melanoma therapy – head-spinning progress. N Engl J Med. 2017 Nov 9;377(19):1888-1890. PMID: 29117487
59 Weber J, Mandala, M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-1835. PMID: 28891423
60 Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017 Nov 9;377(19):1813-1823. PMID: 28891408
61 Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018 Apr 15. doi: 10.1056/NEJMoa1802357. [Epub ahead of print] PMID: 29658430
62 Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017;18(5):611-22.PMID 28359784.
63 Devji T, Levine O, Neupane B, et al. Systemic Therapy for Previously Untreated Advanced BRAF-Mutated Melanoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials. JAMA Oncology. 2017;3(3):366-73.PMID 27787543.
64 Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017 ;390(10105):1853-62.PMID 28822576.
65 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377(14):1345-56.PMID 28889792.

Myeloma Pathways: Multiple Myeloma

Primary/First Line of Therapy (1st Line) | Transplant Candidates

VRD/VDR: bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone[10,12,79]

Primary/First Line of Therapy (1st Line) | Non-Transplant Candidates

CyBorD or VDC: bortezomib (Velcade), cyclophosphamide, and dexamethasone[9,10,84]

R-dex: lenalidomide (Revlimid) and low-dose dexamethasone[10,11,13,73]

VRD/VDR: bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone[10,12,79]

VD: bortezomib (Velcade) and dexamethasone[1,3,12,24,89]

Maintenance Therapy | Post-Transplant

Lenalidomide (Revlimid)[26,27,83,92]

Relapsed Disease | Second and Subsequent Lines of Therapy (2nd Line+)

CRd or KRd: carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone[82]

DRD: daratumumab (Darzalex), lenalidomide (Revlimid), and dexamethasone[100]

DVD: daratumumab (Darzalex), bortezomib (Velcade), and dexamethasone[103]

Relapsed Disease | Third and Subsequent Lines of Therapy (3rd Line+)

Daratumumab (Darzalex)[95]

Elotuzumab (Empliciti), lenalidomide (Revlimid), and dexamethasone[97]

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

MYELOMA: MULTIPLE MYELOMA REFERENCES

NCCN Clinical Practice Guidelines: Multiple Myeloma V3.2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V3.2018. Available at: http://www.nccn.org. Accessed: February 1, 2018. ©National Comprehensive Cancer Network, 2017. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

References

1. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica. 2006; 91:1498-1505. PMID: 17043025.
2. Harousseau JL, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): updated data from IFM 2005/01 trial. [Abstract 8505]. Blood. 2008. Accessed: Abstract 8505
3. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010; 28:4621-4629. PMID: 20823406.
4. Oakervee HE, Popat R, Curry N, et al. PAD combination therapy (PS-341/bortezomib, doxorubicin, and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol. 2005; 129:755-762. PMID: 15953001.
5. Sonneveld P, Schmidt-Wolf IG, 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. J Clin Oncol. 2012; 30:2946-2955. PMID: 22802322.
6. Cavo M, Patriarca F, Pantani L, et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcase-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. [Abstract 158]. Blood. 2008. Accessed. Abstract 158
7. Cavo M, Tacchetti P, Patriarca MT, 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 randomized phase 3 study. Lancet. 2010; 376:2075-2085. PMID: 21146205.
8. Rosinol L, Oriol A, Teruel AI, 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; 120:1589-1596. PMID: 22791289.
9. Reeder CB, Reece DE, 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; 23:1337-1341. PMID: 19225538.
10. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012; 119:4375-4385. PMID: 22422823.
11. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. Lancet Oncol. 2010; 11:29-37. PMID: 19853510.
12. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma (Version 3.2018). Available at http://www.nccn.org. Accessed February 1, 2018 ©National Comprehensive Cancer Network, 2017
13. Gay F, Hayman SR, Lacy MQ, 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.
14. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010; 116:679-686. PMID: 20385792.
15. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 of carfilzomib with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012; 120: 1801-1809. PMID: 22665938.
16. Korde N, Kwok M, Costello R, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed multiple myeloma (MM) patients. [Abstract 732]. Blood. 2012. Accessed: abstract 732
17. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: a randomized controlled trial. Lancet. 2006; 367:825-831. PMID: 16530576.
18. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008; 112:3107-3114. PMID: 18505783.
19. Hulin C, Facon R, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009; 27:3664-3670. PMID: 19451428.
20. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 study. J Clin Oncol. 2010; 28: 3160-3166. PMID: 20516439.
21. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008; 359:906-917. PMID: 18753647.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol. 2013; 31:448-455. PMID: 23233713.
23. Niesvizky R, Reeves J, Flinn IW, et al. Phase 3b UPFRONT study: interim results from a community practice-based prospective randomized trial evaluating three bortezomib-based regimens in elderly, newly diagnosed myeloma patients. [Abstract 129]. Blood. 2009.
24. Niesvizky R, Flinn I, Rifkin R, et al. Efficacy and safety of three bortezomib based combinations in elderly, newly diagnosed multiple myeloma patients: results from all randomized patients in the community-based, phase 3b UPFRONT study. [Abstract 478]. Blood. 2011. Accessed: Abstract 478
25. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA-Italian Multiple Myeloma Network. J Clin Oncol. 2007; 25:4459-4465. PMID: 17785703.
26. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012; 366:1782-1791. PMID: 22571202.
27. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012: 366:1770-1781. PMID: 22571201.
28. Brinker BR, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. Cancer. 2006; 106:2171-2180. PMID: 16598756.
29. Bruno B, Patriarca F, Sorasio R, et al. Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation. Haematologica. 2006; 91:837-839. PMID: 16769588.
30. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. Lancet Oncol. 2011; 15:431-440. PMID: 21507715.
31. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica. 2012; 97:1925-1928. PMID: 22689676.
32. Reece DE, Rodriguez GP, Chen C, et al. Phase I-II of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. J Clin Oncol. 2008; 26:4777-4783. PMID: 18645194.
33. Garderet L, Iacoblli S, Moreau P, et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 randomized phase III trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2012; 30:2475-2482. PMID: 22585692.
34. Weber DM, Chen C, Neisvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007; 357:2133-2142. PMID: 18032763.
35. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007; 357:2123-2132. PMID: 18032762.
36. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005; 352:2487-2498. PMID: 15958804.
37. Richardson PG, Sonneveld P, Schuster MW, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood. 2007; 110:3557-3560. PMID: 17690257.
38. Orlowski RZ, Nagler A, Sonneveld PG, 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; 25:3892-3901. PMID: 17679727.
39. Mikhael JR, Belch AR, Prince HM, 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; 144:169-175. PMID: 19036114.
40. Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica. 2006; 91:929-934. PMID: 16818280.
41. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004; 127:165-172. PMID: 15461622.
42. Anderson KC, Jagannath S, Jakubowiak A, et al. Phase II study of lenalidomide (Len), bortezomib (Bz), and dexamethasone (Dex) in patients (pts) with relapsed or relapsed and refractory multiple myeloma (MM). J Clin Oncol. 2008; 26(15S):A8545 Abstract 8545
43. Richardson PG, Jagannath S, Jakubowiak AJ, et al. Phase II trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory multiple myeloma (MM): updated efficacy and safety data after 2 years of follow-up. [Abstract 3049]. Blood. 2010. Abstract 3049.
44. Siegel D, Martin T, Wang M, et al. PX-171-003-A1 an open-label, single-arm, phase (Ph) II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (R/R MM): Long-term follow-up and subgroup analysis. [Abstract 8027]. J Clin Oncol. 2011;29(15S): 8027 Abstract 8027
45. Siegel D, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012; 120:2817-25. PMID: 22833546.
46. Kropff M, Bisping G, Schuck E, et al. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Br J Haematol. 2007;138:330-337. PMID: 17614819.
47. Davies FE, 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; 92:1149-1150. PMID: 17650451.
48. Morgan GJ, Schey SA, 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. PMID: 17408469.
49. Dadacaridou M, Papanicolaou X, Maltesas D, et al. Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) for relapsed or refractory multiple myeloma patients. J BUON. 2007; 12:41-44. PMID: 17436400.
50. Lee CK, Barlogie B, Munshi, N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol. 2003; 21:2732-2739. PMID: 12860952.

51. Barlogie B, Anaissie E, van Rhee R, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol. 2007; 138:176-185. PMID: 17593024.
52. Nair B, van Rhee F, Shaughnessy JD Jr, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. Blood. 2010; 115:4168-4173. PMID: 20124509.
53. Lenhard RE Jr, Oken MM, Barnes JM, et al. High-dose cyclophosphamide. An effective treatment for advanced refractory multiple myeloma. Cancer. 1984; 53:1456-1460. PMID: 6697291.
54. Dimopoulos MA, Lacy MQ, Moreau P, et al. Pomalidomide in combination with low-dose dexamethasone: demonstrates a significant progression free survival and overall survival advantage, in relapsed/refractory MM: A phase 3, multicentre, randomized, open-label study. [Abstract 6]. Blood. 2012. Accessed. Abstract 6
55. Richardson PG, Siegel DS, Vij R, et al. Randomized open-label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidoide (LEN) and brotezomib (BORT): Phase 2 results. [Abstract 634]. Blood. 2011. Accessed. Abstract 634
56. Dimopoulos MA, Zervas K, Kouvatseas G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001; 12:991-995. PMID: 11521808.
57. Palumbo A, Bertola A, Falco P, et al. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Hematol J. 2004; 5:318-324. PMID: 15297848.
58. Knop S, Straka C, Haen M, et al. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica. 2005; 90:1287-1288. PMID: 16154860.
59. Michael M, Bruns I, Boike E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. Eur J Med Res. 2010; 15:13-19. PMID: 20159666.
60. Lentzsch S, O'Sullivan A, Kennedy RC, 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; 119:4608-4613. PMID: 22451423.
61. Dimopoulos MA, Jagannath S, Yoon SS, et al. Vantage 88: Vorinostat in combination with boretzomib in patients with relapsed/refractory multiple myeloma: results of a global, randomized phase 3 trial. [Abstract 811]. Blood. 2011. Accessed. Abstract 811
62. Siegel DS, Dimopoulos MA, Yoon SS, et al. Vantage 095: Vorinostat in combination with bortezomib in salvage multiple myeloma patients: final results of a global phase 2B trial. [Abstract 480]. Blood. 2011. Accessed. Abstract 480
63. Wang M, Martin T, Bensinger W, et al. Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Blood. 2013; 122:3122-3128. PMID: 24014245.
64. Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood. 2006; 107:1292-1298. PMID: 16174762.
65. Siegel DS, Jagannath S, Yoon S, al. Vantage 088: Final results from the global phase 3 trial of the multi-histone deacetylase inhibitor vorinostat in combination with bortezomib in relapsed/refractory multiple myeloma. Haematologica. 2012;97(Suppl 1): Abstract 0281. Accessed; Abstract 0281
66. Siegel D, Dimopoulos M, Yoon S, et al. Vantage 095: Final results from a global, single-arm, phase 2B trial of vorinostat in combination with bortezomib in salvage multiple myeloma patients. Haematologica. 2012;97(Suppl 1): Abstract. 0294.. Accessed; Abstract 0294
67. Attal M, Horousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006; 108:3289-3294. PMID: 16873668.
68. Avet-Loiseau H, Attal M, Campion L, et al. Long-term analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t(4;14), del(17p), 1q gains] play a major role in defining long-term survival. J Clin Oncol. 2012; 30:1949-1952. PMID: 22547600.
69. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009; 27:1788-1793. PMID: 19273705.
70. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC myeloma IX results and meta-analysis. Blood. 2012; 119:7-15. PMID: 22021371.
71. Stewart KA, Trudel S, Bahlis NJ, et al. A randomized phase III trial of thalidomide and prednisone as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): the NCIC CTG MY10 Trial [Abstract 39]. Blood 2010;116(21).
72. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012; 119:3003-3015. PMID: 22271445.
73. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma. N Engl J Med. 2014; 371: 906-17. PMID: 25184863.
74. Baz R, Martin TG, Alsina M, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. Blood. 2014 Dec 6:124(21):303 Abstract 303
75. Dimopoulos MA, Palumbo A, Weisel K, et al. Safety and Efficacy in the Stratus (MM-010) Trial, a Single-Arm Phase 3b Study Evaluating Pomalidomide + Low-Dose Dexamethasone in Patients with Refractory or Relapsed and Refractory Multiple Myeloma. Blood. 2014 Dec 6:124(21):80 Abstract 80
76. Leiba M, Kedmi M, Duek A, et al. Bortezomib-cyclophosphamide-dexamethasone (VCD) versus bortezomib-thalidomide-dexamethasone (VTD) -based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. Blood.2014 Sept; 166(5):702-710. PMID: 24861981
77. Mateos MV, Oriol A, Martínez-López J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014 Sept 18;124(12):1887-1893. PMID: 25102853
78. Morgan G, Palumbo A, Dhanasiri S, et al. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone. Br J Haematol. 2015 Mar;168(6):820-3. PMID: 25403264

79. 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 Sep 1;32(25):2712-7. PMID: 25024076
80. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1195-206 PMID: 25242045
81. Scheid C, Sonneveld P, Schmidt-Wolf IG, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. Haematologica. 2014 Jan;99(1):148-54. PMID: 23996482
82. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015 Jan 8;372(2):142-52. PMID: 25482145
83. 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. PMID: 25184862
84. Mai EK, Bertsch U, Durig J, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015 Mar 19. PMID: 25787915
85. Niesvizky R, Flinn IW, Rifkin R, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015 Jun 8. PMID: 26056177
86. Straka C, Vogel M, Muller J, et al. Results from two phase III studies of bortezomib (BTZ) consolidation vs observation (OBS) post-transplant in patients (pts) with newly diagnosed multiple myeloma (NDMM). J Clin Oncol. 33, 2015 (suppl; abstr 8511). Abstract 8511
87. Dimopoulos MA, Moreau P, ENDEAVOR investigators, 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 Jan;17(1):27-38. PMID: 26671818
88. Durie B, Hoering A, Rajkumar SV, et al. 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):Results of the Randomized Phase III Trial SWOG S0777. ASH. December 5, 2015. Abstract 25
89. Niesvizky R, Flinn IW, 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
90. Mia EK, Bertsch U, Durig J, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015 Aug;29(8):1721-9. PMID: 25787915
91. Stewart AK, Jacobus S, Fonseca R, et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood. 2015 Sep 10;126(11):1294-1301. PMID: 26157076
92. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015 Dec;16(16):1617-1629. PMID: 26596670
93. San-Miguel, Hungria V TM, Yoon S-S, et al. 3026 Final Analysis of Overall Survival from the Phase 3 Panorama 1 Trial of Panobinostat Plus Bortezomib and Dexamethasone Versus Placebo Plus Bortezomib and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma. ASH. December 6, 2015. Abstract 3026
94. Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in relapsed/relapsed and refractory myeloma: outcomes by prior treatment. Blood. 2015 Dec 2. PMID: 26631116
95. Lonial S, Weiss BM, Usmani SZ, et al. Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). J Clin Oncol. 2015. 33; LBA8512. Abstract LBA8512
96. Moreau P, Masszi T, Grzasko N, et al. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (NCT01564537). ASH. December 7, 2015. Abstract 727
97. Lonial S, Dimpopoulos M, ELOQUENT-2 Investigators. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015 Aug 13;373(7):621-31. PMID: 26035255
98. Dimopoulos MA, Moreau P, ENDEAVOUR investigators, 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 Jan;17(1):27-38. PMID: 26671818
99. Wang Y, Yang F, Shen Y, et al. Maintenance Therapy With Immunomodulatory Drugs in Multiple Myeloma: A Meta-Analysis and Systematic Review. J Natl Cancer Inst. 2015 Nov 18;108(3). PMID: 26582244
100. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-31. Epub 2016/10/06. PMID: 27705267
101. Durie BG, Hoering A, Abidi MH, 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 (London, England). 2016. Epub 2016/12/27. PMID: 28017406
102. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;374(17):1621-34. Epub 2016/04/28. PMID: 27119237
103. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-66. Epub 2016/08/25. PMID: 27557302
104. Pawlyn CD, FE; Kaiser, MF; et al. Primary IMiD Refractory Myeloma; Results from 3894 Patients Treated in the Phase III Myeloma XI Study. Blood; San Diego CA2016. ASH Abstract 1144
105. Stewart AK, Dimopoulos MA, Masszi T, et al. Health-Related Quality of Life Results From the Open-Label, Randomized, Phase III ASPIRE Trial Evaluating Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma. J Clin Oncol. 2016. Epub 2016/09/08. PMID: 27601539

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

106. Rajkumar SV, Harousseau JL. Next-generation multiple myeloma treatment: a pharmacoeconomic perspective. Blood. 2016;128(24):2757-64. Epub 2016/10/16. PMID: 27742709
107. Rajkumar SV. The ENDEAVOR Trial: A Case Study in the Interpretation of Modern Cancer Trials. The ASCO Post. June 10, 2016. Available at http://ascopost.com Accessed February 8, 2017.
108. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2017;12:12.PMID 29231133.
109. Dimopoulos MA, 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(10):1327-37.PMID 28843768.
110. Holstein SA, Jung SH, Richardson PG, 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;4(9):e431-e42.PMID 28826616.
111. Waxman AJ, Clasen S, Hwang WT, et al. Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis. JAMA Oncology. 2017:e174519.PMID 29285538.

NHL: Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) Pathways

First Line of Therapy (1st Line) | With 17p Deletion or TP53 Mutation Present

Ibrutinib (Imbruvica)[28,37,41,46,47]

First Line of Therapy (1st Line) | Without 17p Deletion

BR: bendamustine (Bendeka, Treanda) and rituximab[13-15,39,51]

FCR: fludarabine (Fludara), cyclophosphamide, and rituximab*[1,2,39,51]

Ibrutinib (Imbruvica)[29,37,46,47]

Obinutuzumab (Gazyva) and chlorambucil (Leukeran)[16]

Second and Subsequent Lines of Therapy (2nd Line+) | With 17p Deletion or TP53 Mutation Present

Ibrutinib (Imbruvica)[28,37,41,46,47]

Idelalisib (Zydelig)[43]

Idelalisib (Zydelig) and rituximab*[38]

Venetoclax (Venclexta) and rituximab[59] – Added effective 11/12/2018

Second and Subsequent Lines of Therapy (2nd Line+) | Without 17p Deletion

BR: bendamustine (Bendeka, Treanda) and rituximab[13-15,42] – Termed effective 11/12/2018

Ibrutinib (Imbruvica)[28,37,41,46,47]

Idelalisib (Zydelig)[43]

Idelalisib (Zydelig) and rituximab[38]

Venetoclax (Venclexta) and rituximab[59] – Added effective 11/12/2018

Primary treatment for CLL should be initiated in accordance with the guidelines established by the Working Group on CLL[58]

* Rituximab may be administered as Rituxan or Rituxan Hycela. When Rituxan Hycela is chosen, treatment with SC rituximab (Rituxan Hycela) should only be initiated after patients have received at least one full dose of IV rituximab (Rituxan)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

NHL: CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA (SLL) REFERENCES

NCCN Practice Guidelines: Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma V5.2018

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma V5.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomized, open-label, phase 3 trial. Lancet. 2010; 376:1164-74. PMID: 20888994.
2. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol. 2005; 23:4070-4078. PMID: 15767647.
3. Foon KA, Boyiadzis M, Land SR, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009; 27:498-503. PMID: 19075274.
4. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol. 2005; 23:694-704. PMID: 15681517.
5. Eichhorst EF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood. 2006; 107:885-891. PMID: 16219797.
6. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009; 114:3382-3391. PMID: 19605849.
7. Boogaerts MA, Van Hoof A, Catovsky D, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2001; 19:4252-4258. PMID: 11709569.
8. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood. 2007; 109:405-411. PMID: 17008537.
9. Lamanna N, Kalaycia M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol. 2006; 24:1575-1581. PMID: 16520464.
10. Knauf WU, Lissichkov T, Adlaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009; 27:4378-4384. PMID: 19652068.
11. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol. 2008; 26:204-210. PMID: 18182663.
12. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol. 2012; 159:67-77. PMID: 22861163.
13. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012; 30:3209-3216. PMID: 22869884.
14. Leblond V, Kamel L, Osman I, et al. Rituximab in combination with bendamustine or chlorambucil for treating patients with chronic lymphocytic leukemia: Interim results of a phase IIIB study (MaBLe). [Abstract 2744]. ASH. Dec 2012.
15. Robinson KS, Williams ME, van der Jagt RH, 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; 26:4473-4479. PMID: 18626004.
16. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014; 370:1101-1110. PMID: 24401022
17. Hillmen P, Gribben J, Follows G, et al. Rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia (CLL): Final response analysis of an open-label phase II study. [Abstract 697]. ASH. 2010.
18. Raphael B, Andersen JW, Silber R, et al. Comparison of chlorambucil and prednisone versus cyclophosphamide, vincristine, and prednisone as initial treatment for chronic lymphocytic leukemia: long-term follow-up of an Eastern Cooperative Oncology Group randomized clinical trial. J Clin Oncol. 1991; 9:770-776. PMID: 2016618.
19. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol. 2003; 21:1746-51. PMID: 12721250.
20. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol. 2001; 16:2153-2164. PMID: 11304767.
21. Saven A, Lemon RH, Kosty M, et al. 2-Chlorodeoxyadenosine Activity in Patients With Untreated Chronic Lymphocytic Leukemia. J Clin Oncol 13:570-574; 1995. PMID: 7884417

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Juliuson G, Liliemark J. Long-term survival following cladribine (2-chlorodeoxyadenosine) therapy in previously treated patients with chronic lymphocytic leukemia. Ann Oncol 7: 373-379, 1996
23. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007; 25:5616-5623. PMID: 17984186
24. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood. 2002; 99:3554-3561. PMID: 11986207.
25. Stigenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2009; 27:3994-4001. PMID: 19597025.
26. Faderl S, Thomas DA, O'Brien, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood. 2003; 101:3413-3415. PMID: 12522009
27. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leuk. Lymphoma. 2007; 48:2412-2417. PMID: 18067017.
28. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013; 369:32-42. PMID: 23782158.
29. Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. Blood. 2011; 118:2085-2093. PMID: 21670470.
30. Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2008; 26:196-203. PMID: 18182662.
31. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010; 28:1749-1755. PMID: 20194866.
32. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008; 111:5291-5297. PMID: 18334676.
33. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006; 24:5343-5349. PMID: 17088571.
34. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2013; 31:584-591. PMID: 23270003.
35. Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol. 2005; 23:7024-7031. PMID: 16145065.
36. Arzerra Prescribing Information. FDA April 17, 2014. Accessed: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm393823.htm.
37. Byrd JC, Brown JR, O'Brien S, Barrientos JC. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. N Engl J Med 2014; 371:213-223. PMID: 24881631.
38. Furman RF, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014; 370:997-1007. PMID: 24450857.
39. Eichhorst B, Fink AM, Busch R, et al. Frontline Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Shows Superior Efficacy in Comparison to Bendamustine (B) and Rituximab (BR) in Previously Untreated and Physically Fit Patients (patients) with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study). Blood. 6 Dec 2014. 124(21):19. Abstract 19.
40. Hillmen P, Robak T, COMPLEMENT 1 Study Investigators, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015 May 9;385(9980):1873-1883. PMID: 25882396
41. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014 Jul 17;371(3):213-223. PMID: 24881631
42. Chanan-Khan AA, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study. J Clin Oncol. 33, 2015 (suppl; abstr LBA7005). Abstract LBA7005
43. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-18. PMID: 24450858
44. Carton G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014 Oct 2;124(14):2196-202. PMID: 25143487
45. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (V5.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed July 31, 2018.
46. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015 Apr 16;125(16):2497-506. PMID: 25700432
47. Burger JA, Tedeschi A, RESONATE-2 Investigators, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015 Dec 17;373(25):2425-2437. PMID: 26639149
48. Chanan-Khan A, Cramer P, HELIOS investigators, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016 Feb;17(2):200-211. PMID: 26655421
49. Van Oers MH, Kuliczkowski K, PROLONG study investigators, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. Lancet Oncol. 2015 Oct;16(13):1370-1379. PMID: 26377300.
50. Roberts AW, Davids MS, Pagel JM ,et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2016 Jan 28;374(4):311-322. PMID: 26639348

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

51. Eichhorst, Barbara, 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). PMID: 27216274
52. Fischer, Kirsten, et al. "Long term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial." Blood, 127(2), 208-215 PMID: 26486789
53. Greil, Richard, et al. "Rituximab maintenance versus observation alone in patients with chronic lymphocytic leukaemia who respond to first-line or second-line rituximab-containing chemoimmunotherapy: final results of the AGMT CLL-8a Maintenance randomised trial." Lancet Haematol 3.7 (2016): e317-e329. PMID: 27374465
54. Stilgenbauer, Stephan, et al. "Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study." Lancet Oncol. 17.6 (2016): 768-778. PMID: 27178240
55. Jones JA, Robak T, Brown JR, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol. 2017;4(3):e114-e26.PMID: 28257752.
56. Munir T, Howard DR, McParland L, et al. Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. Leukemia. 2017:e-publication.PMID: 28216660.
57. Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. Leuk. Lymphoma. 2017;58(5):1084-93.PMID: 27731748.
58. Hallek, Michael, et al. "Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia." Blood (2018).
59. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378(12):1107-20.PMID 29562156.

NHL: Diffuse Large B-Cell Lymphoma Pathways

First Line of Therapy (1st Line)

R-CHOP (21): cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab*[1-4,52,53]

First Line of Therapy (1st Line)| Contraindication to Anthracycline

R-CEOP: cyclophosphamide, etoposide (Toposar), vincristine (Vincasar), prednisone, and rituximab*[13,14,40,41,52,53]

Second and Subsequent Lines of Therapy (2nd Line+) | Transplant Candidates

R-GDP: gemcitabine (Gemzar), dexamethasone, cisplatin, and rituximab*[23,24,43,52,53]

R-GDP: gemcitabine (Gemzar), dexamethasone, carboplatin, and rituximab*[23,24,43,52,53]

R-ICE: ifosfamide (Ifex), carboplatin, etoposide (Toposar), and rituximab*[18,19,29,52,53]

Second and Subsequent Lines of Therapy (2nd Line+) | Non-Transplant Candidates

BR: bendamustine (Bendeka, Treanda) and Rituximab*[32,33,52,53]

R-GDP: gemcitabine (Gemzar), dexamethasone, cisplatin, and rituximab*[23,24,52,53]

R-GDP: gemcitabine (Gemzar), dexamethasone, carboplatin, and rituximab*[23,24,52,53]

R-GemOx: gemcitabine (Gemzar), oxaliplatin, and rituximab*[25-27,52,53]

* Rituximab may be administered as Rituxan or Rituxan Hycela. When Rituxan Hycela is chosen, treatment with SC rituximab (Rituxan Hycela) should only be initiated after patients have received at least one full dose of IV rituximab (Rituxan)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

NHL: DIFFUSE LARGE B CELL LYMPHOMA REFERENCES

NCCN Practice Guidelines: Non-Hodgkin Lymphomas: B-Cell Lymphomas Version 4.2018.

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas: B-Cell Lymphomas. V4.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). for Non-Hodgkin's Lymphomas: B-Cell Lymphomas.(Version 4.2018). Available at http://www.nccn.org © 2018 National Comprehensive Cancer Network, last accessed July 31, 2018
2. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002; 346:235-242. PMID: 11807147.
3. 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. PMID: 20548096.
4. 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 randomized controlled trial by the Mab Thera Internatnional Trial (MInT) Group. Lancet Oncol. 2006; 7:379-391. PMID: 16648042.
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. PMID: 15867204.
6. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood. 1990; 76:1293-1298. PMID: 2207307.
7. 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 Lymphoma. 2006;47:2174-2180. PMID: 17071492.
8. Martino R, Perea G, Caballero MD, 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. PMID: 12161358.
9. Sonneveld R, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol. 1995; 13:2530-2539. PMID: 7595704.
10. Bessell EM, Burton A, Haynes AP, et al. A randomized multicenter trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003; 14:258-267. PMID: 12562653.
11. Wilson WH, 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. PMID: 18378569.
12. Wilson WH, Jung SH, 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. PMID: 22133770.
13. Economopoulos T, Dimopoulos MA, Mellou S, et al. Treatment of intermediate and high-grade non-Hodgkin's lymphoma using CEOP versus CNOP. Eur J Haematol. 2002; 68:135-143. PMID: 12068793.
14. Moccia AA, 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. [Abstract 408]. Blood. 2009. Accessed: Abstract 408
15. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicenter, single-arm, phase 2 trial. Lancet Oncol. 2011 May;12(5):460-468. PMID: 21482186.
16. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood. 1988;71:117-122. PMID: 3334893.
17. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995; 333:1540-1545. PMID: 7477169.
18. 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; 28:4184-4190. PMID: 20660832.
19. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest. 2006; 24:593-600. PMID: 16982464.
20. Velasquez WS, 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. PMID: 8201379.
21. 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. PMID: 18945747.
22. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin's lymphoma: a phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer. 2004; 101:1835-1842. PMID: 15386331.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

23. Hou Y, Wang HQ, Ba Y. Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. Med Oncol. 2012; 29:2409-2416. PMID: 22476761.
24. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapse/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma. 2010; 51:1523-1529. PMID: 20578815.
25. 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; 64: 907-916. PMID: 19219604.
26. Lopez A, Gutierrez 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 Haematolo. 2008; 80:127-132. PMID: 18005385.
27. El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol. 2007; 18:1363-1368. PMID: 17496309.
28. Zelenetz AD, 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 Supp1:i5-i10. PMID: 12736224.
29. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004; 103:3684-3688. PMID: 14739217.
30. Rodriguez MA, Cabanillas FC, Hagemeister FB, et al. A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol. 1995; 6:609-611. PMID: 8573542.
31. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2002; 13:1285-1289. PMID: 12181253.
32. 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. PMID: 23650408.
33. Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B-cell lymphoma. Ann Hematol. 2014; 93: 403-409. PMID: 23955074.
34. Lambertenghi Deliliers G, Butti C, Baldini L, et al. A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. Haematologica. 1995; 80:318-324. PMID: 7590500.
35. Gutierrez M, Chabner BA, 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; 18:3633-3642. PMID: 11054436.
36. Jermann M, Jost LM, 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; 15:511-516. PMID: 14998858.
37. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008; 26:4952-4957. PMID: 18606983.
38. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011; 22:1622-1627. PMID: 21228334.
39. 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; 92:1927-1932. PMID: 9731049.
40. Li Y, Yimamu M, Wang X, et al. Addition of rituximab to a CEOP regimen improved the outcome in the treatment of non-germinal center immunophenotype diffuse large B-cell lymphoma cells with high Bcl-2 expression. Int J Hematol. 2014; 99:79-86. PMID: 24258714.
41. Nowakowski GS, LaPlant B, Macon WR, et al. Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non-Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study. J Clin Oncol. 2015 Jan 20;33(3):251-257. PMID: 25135992
42. Vitolo U, Chiappella A, Franceschetti S, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol. 2014 Jun;15(7):730-737. PMID: 24831981
43. 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 Nov 1;32(31):3490-3496. PMID: 25267740
44. Fields PA, 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 Feb 1;32(4):282-7. PMID: 24220559
45. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014 Oct 9;124(15):2354-61. PMID: 25161267
46. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol. 2015 Aug;170(4):504-14. PMID: 25907897
47. Haioun C, Mouiner N, Emile JF, et al. Rituximab versus observation after high-dose consolidative first-line chemotherapy with autologous stem-cell transplantation in patients with poor-risk diffuse large B-cell lymphoma. Ann Oncol. 2009 Dec;20(12):1985-92. PMID: 19567453
48. 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 Dec 20;30(36):4462-9. PMID: 23091101
49. Witzens-Harig M, Benner A, McClanahan F, et al. Rituximab maintenance improves survival in male patients with diffuse large B-cell lymphoma. Results of the HD2002 prospective multicentre randomized phase III trial. Br J Haematol. 2015 Dec;171(5):710-9. PMID: 26449739
50. Wilson W, Sin-Ho J, Pitcher, B, et. al. Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303. American Society of Hematology 58th Annual Meeting & Exposition. 2016 Dec 4;Abstract 469. Available at https://ash.confex.com/ash/2016/webprogram/Paper97112.html. Accessed May 9, 2017

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

51. Pfreundschuh M, Held G, Zeynalova S, et. al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL. J Clin Oncol. 2014; 32(15):suppl, 8501-8501.
52. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2017;35(31):3529-37.PMID 28796588.
53. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol. 2017;35(5):544-51.PMID 28029326.

NHL: Follicular and Marginal Zone Lymphoma Pathways

Gastric MALT (Mucosa-Associated Lymphoid Tissue) Lymphoma | Stage IE or IIE | *H. pylori* Positive*

Antibiotic therapy for *H. pylori* eradication[33,34]

Splenic Marginal Zone† or Gastric MALT Lymphoma | First Line of Therapy (1st Line)

Rituximab‡ monotherapy[27-29,52,53]

Follicular (Grade I-IIIA) and Other Marginal Zone Lymphomas | First Line of Therapy (1st Line)

BR: Bendamustine (Bendeka, Treanda) and rituximab‡[5,6,52,53]

R-CHOP(21): Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab‡[1-3,5,52,53]

R-CVP: Cyclophosphamide, vincristine (Vincasar), prednisone, and rituximab‡[1,4,52,53]

Rituximab‡ monotherapy[7,17,52,53]

Follicular and Other Marginal Zone Lymphomas | First Line of Therapy (1st Line) | Additional options for the elderly or infirm

Chlorambucil (Leukeran)[10]

Chlorambucil (Leukeran) and rituximab‡[10,11,52,53]

Cyclophosphamide[11-13]

Cyclophosphamide and rituximab‡[52,53]

Follicular Lymphoma (Grade III) | First Line of Therapy (1st Line)

R-CHOP(21): Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, and rituximab‡[1-5,52,53]

R-CEOP: Cyclophosphamide, etoposide (Toposar), vincristine (Vincasar), prednisone, and rituximab‡[13,35-37,52,53]

---

* Gastric MALT with translocation 11;18 (t11;18) (q21;q21) predicts a lower response rate to anti-*H.pylori* treatment. Radiation therapy or other local intervention may be indicated.

† Splenectomy is also a recommended option for splenic marginal zone lymphoma (NCCN 2A)

‡ Rituximab may be administered as Rituxan or Rituxan Hycela. When Rituxan Hycela is chosen, treatment with SC rituximab (Rituxan Hycela) should only be initiated after patients have received at least one full dose of IV rituximab (Rituxan)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

NHL: FOLLICULAR AND MARGINAL ZONE LYMPHOMA REFERENCES

NCCN Practice Guidelines: Non-Hodgkin Lymphomas: B-Cell Lymphomas Version 4.2018.

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas: B-Cell Lymphomas. V4.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013; 31:1506-1513. PMID: 23530110.
2. 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. PMID: 16123223.
3. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol. 2013; 31:314-320. PMID: 23233710.
4. Marcus R, Imrie K, Solal-Celigny, 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. PMID: 18662969.
5. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantel cell lymphomas: an open-label, multicenter, randomized, phase 3 non-inferiority trial. Lancet. 2013; 381:1203-1210. PMID: 23433739.
6. Robinson KS, Williams ME, van der Jagt RH, 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; 26:4473-4479. PMID: 18626004.
7. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with low tumor burden: clinical and molecular evaluation. Blood. 2001; 97:101-106. PMID: 11133748.
8. IIlidge TM, Mayes S, Pettengell R, et al. Fractionated Y-ibritumomab tiuxetan radioimmunotherapy as an initial therapy of follicular lymphoma: an international phase II study in patients requiring treatment according to GELF/BNLI criteria. J Clin Oncol. 2014; 32:212-218. PMID: 24297953.
9. Scholz CW, 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. PMID: 23233718.
10. Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomized study. J Clin Oncol. 2013; 31: 565-572. PMID: 23295789.
11. Martinelli G, Laszlo D, Bertolini F, et al. Chlorambucil in combination with induction and maintenance rituximab is feasible and active in indolent non-Hodgkin's lymphoma. Br J Haematol. 2003; 123:271-277. PMID: 14531908.
12. Petersen BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol. 2003; 21:5-15. PMID: 12506163.
13. Horning SJ. Something old, something few, something subjective, and something déjà vu. J Clin Oncol. 2003; 21:1-2. PMID: 12506161.
14. Rose AC, Shenoy PJ, Garrett G, et al. A systemic literature review and meta-analysis of radioimmunotherapy consolidation for patients with untreated follicular lymphoma. Clin Lymphoma Myeloma Leuk. 2012; 12:393-399. PMID: 23158095.
15. Salles G, Seymour JF, Offner F, et al Rituximab maintenance for 2 years in patients with high tumor burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomized controlled trial. Lancet. 2011; 377:42-51. PMID: 21176949.
16. van Oers HM, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood. 2006; 108:3295-3301. PMID: 16873669.
17. Hainsworth JD, Litchy S, Shaffer DW, 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; 23:1088-1095. PMID: 15657401.
18. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2004; 104:3064-3071. PMID: 15284112.
19. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol. 2005; 23:694-704. PMID: 15681517.
20. Witzig TE, Wiernik PH, 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. PMID: 19805688.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

21. Leonard J, Sin-Ho J, Johnson J, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma. [Abstract 8000] J Clin Oncol.2012. Accessed. http://meetinglibrary.asco.org/content/93509-114
22. Tuscano JM, Dutia M, Chee K, et al. Lenalidomide plus rituximab can produce durable clinical responses in patients with relapsed or refractory, indolent non-Hodgkin lymphoma. Br J Haematol. 2014; 165:375-381. PMID: 24606326.
23. Witzig TE, Gordon LI, 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. PMID: 12011122.
24. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x4 schedule. Blood. 2004; 103:4416-4423. PMID: 14976046.
25. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol. 2000; 27:37-41. PMID: 11225999.
26. McLaughlin P, Estey E, Glassman A, et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood. 2005; 105:4573-4575. PMID: 15741224.
27. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG =1496 study. J Clin Oncol. 2009; 27:1607-1614. PMID: 19522334.
28. Kalpadakis C, Pangalis GA, Angelopoulou MK, et al. Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy. Oncologist. 2013; 18:190-197. PMID: 23345547.
29. Tsimberidou AM, 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; 107:125-135. PMID: 16700034.
30. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin's 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. PMID: 23547079.
31. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after remission in advanced follicular lymphoma. J Clin Oncol. 2008; 26:5156-5164. PMID: 18854568.
32. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med. 2005; 352:441-449. PMID: 15689582.
33. Wundisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. J Clin Oncol. 2005; 23:8018-8024. PMID: 16204012
34. Andriani A, Miedico A, Tedeschi L, et al. Management of long-term follow-up of early stage H. pylori-associated gastric MALT-lymphoma in clinical practice: an Italian, multicenter study. Dig Liver Dis. 2009; 41:467-473. PMID: 18945654
35. Economopoulos T, Dimopoulos MA, Mellou S, et al. Treatment of intermediate and high-grade non-Hodgkin's lymphoma using CEOP versus CNOP. Eur J Haematol. 2002; 68:135-143. PMID: 12068793
36. Moccia AA, 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. [Abstract 408]. ASH. 2009. Accessed: http://abstracts.hematologylibrary.org/cgi/contrent/abstract/114/22/408
37. Li Y, Yimamu M, Wang X, et al. Addition of rituximab to a CEOP regimen improved the outcome in the treatment of non-germinal center immunophenotype diffuse large B-cell lymphoma cells with high Bcl-2 expression. Int J Hematol. 2014; 99:79-86. PMID: 24258714
38. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, et al. Rituximab Extended Schedule or Re-Treatment Trial for Low–Tumor Burden Follicular Lymphoma: Eastern Cooperative Oncology Group Protocol E4402. J Clin Oncol. 32:3096-3102. PMID: 25154829
39. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ Inhibition by idelalisib in patients with relapsed indolent lymphoma. New Engl J Med. 2014; 370:1008-18. PMID: 24450858
40. Leonard JP, Jung SH, 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 Aug 24. [Epub ahead of print]. PMID: 26304886
41. Sehn LH, 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 Aug;17(8):1081-93. PMID: 27345636
42. 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. PMID: 28167659
43. Marcus R, Davies A, Ando K et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study. American Society of Hematology 58th Annual Meeting & Exposition. 2016 Dec 4;Abstract 6. Available at https://ash.confex.com/ash/2016/webprogram/Paper94744.html. Accessed May 9, 2017.
44. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). for Non-Hodgkin's Lymphomas: B-Cell Lymphomas.(Version 4.2018). Available at http://www.nccn.org © 2018 National Comprehensive Cancer Network, last accessed July 31, 2018
45. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol. 2017;35(5):544-51.PMID 28029326.
46. 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;35(17):1905-12.PMID 28355112.

NHL: Mantle Cell Lymphoma Pathways

First Line of Therapy (1st Line) | ASCT Candidates

Alternating R-CHOP/R-DHAP: cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Vincasar), prednisone, rituximab* alternating with dexamethasone, cisplatin, cytarabine (Ara-C), and rituximab*[4,5,28,30,31]

Nordic Regimen: dose intensified rituximab*, cyclophosphamide, vincristine (Vincasar), doxorubicin (Adriamycin), prednisone alternating with rituximab* and high dose cytarabine (Ara-C)[3]

First Line of Therapy (1st Line) | Not an ASCT Candidate

BR: bendamustine (Bendeka, Treanda) and rituximab*[9,10]

Second and Subsequent Lines of Therapy (2nd Line+)

Acalabrutinib (Calquence)[42] – Added effective 11/12/2018

BR: bendamustine (Bendeka, Treanda) and rituximab*

Bortezomib (Velcade)[17]

Ibrutinib (Imbruvica)[19,20]

Lenalidomide (Revlimid)[20-23]

* Rituximab may be administered as Rituxan or Rituxan Hycela. When Rituxan Hycela is chosen, treatment with SC rituximab (Rituxan Hycela) should only be initiated after patients have received at least one full dose of IV rituximab (Rituxan)

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

NHL: MANTLE CELL LYMPHOMA REFERENCES

NCCN Practice Guidelines: Non-Hodgkin Lymphomas: B-Cell Lymphomas Version 4.2018.

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphomas: B-Cell Lymphomas. V4.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 © National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Romaguera JE, Fayad L, Rodriguez MA, 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):7013-7023. PMID: 16145068
2. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD 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):346-353. PMID: 22145911
3. Geisler CH, Kolstad A, Nordic Lymphoma Group, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008 Oct 1;112(7):2687-2693. PMID: 22145911
4. Delarue R, Haioun C, Groupe d'Etude des Lymphomes de l'Adulte (GELA), et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood. 2013 Jan 3;121(1):48-53. PMID: 22718839
5. Pott C, Hoster E, Delfau-Larue MH, Beldjord K, Böttcher S, Asnafi V, Plonquet A, Siebert R, Callet-Bauchu E, Andersen N, van Dongen JJ, Klapper W, Berger F, Ribrag V, van Hoof AL, Trneny M, Walewski J, Dreger P, Unterhalt M, Hiddemann W, Kneba M, Kluin-Nelemans HC, Hermine O, Macintyre E, Dreyling M. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood. 2010 Apr 22;115(16):3215-23.
6. Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol. 2010 Jan;21(1):133-139. PMID: 20019090
7. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005 Mar 20;23(9):1984-1992. PMID: 15668467
8. Kluin-Nelemans HC1, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012 Aug 9;367(6):520-531. PMID: 22873532
9. Rummel MJ, Niederle N, Study group indolent Lymphomas (StiL), 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 Apr 6;381(9873):1203-1210. PMID: 23433739
10. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-2952. PMID: 24591201
11. Robak T, Huang H, LYM-3002 Investigators, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015 Mar 5;372(10):944-953. PMID: 25738670
12. Kahl BS, Longo WL, Wisconsin Oncology Network, et al. 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):1418-1423. PMID: 16766582
13. Forstpointner R, Dreyling M, German Low-Grade Lymphoma Study Group, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2004 Nov 15;104(10):3064-3071. PMID: 15284112
14. Levine AM, Tulpule A, Smith L, Espina BM, Mohrbacher AF, Fienstine DI. Results of a Pilot Trial of Fludarabine, Mitoxantrone and Rituxan in Mantle Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 2005 106: Abstract 945.
15. Fisher RI, Bernstein SH, Kahl BS, 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):4867-4874. PMID: 17001068
16. Goy A, Bernstein SH, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma. Ann Oncol. 2009 Mar;20(3):520-5. PMID: 19074748
17. Baiocchi RA, Alinari L, Lustberg ME, 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):2442-2451. PMID: 24048792
18. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013 Aug 8;369(6):507-516. PMID: 23782157
19. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015 Aug 6;126(6):739-745. PMID: 26059948

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

20. Habermann TM, Lossos IS, 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):344-349. PMID: 19245430
21. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011 Jul;22(7):1622-1627. PMID: 21228334
22. Goy A, Sinha R, Williams ME, 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):3688-3695. PMID: 24002500
23. 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):716-723. PMID: 22677155
24. Rummel MJ, Chow KU, Jäger E, et al. Treatment of mantle-cell lymphomas with intermittent two-hour infusion of cladribine as first-line therapy or in first relapse. Ann Oncol. 1999 Jan;10(1):115-117. PMID: 10076731
25. Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer. 2008 Jul 1;113(1):108-116. PMID: 18470909
26. Cohen BJ, Moskowitz C, Straus D, Noy A, Hedrick E, Zelenetz A. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma. 2001 Sep-Oct;42(5):1015-1022. PMID: 11697618
27. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009 Dec 20;27(36):6101-108. PMID: 19917845
28. Coleman M, Martin P, Ruan J, et al. Low-dose metronomic, multidrug therapy with the PEP-C oral combination chemotherapy regimen for mantle cell lymphoma. Leuk Lymphoma. 2008;49:447–450.
29. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, 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. PMID: 25154829
30. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). for Non-Hodgkin's Lymphomas: B-Cell Lymphomas.(Version 4.2018). Available at http://www.nccn.org © 2018 National Comprehensive Cancer Network, last accessed July 31, 2018
31. Hermine, Olivier, et al. "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 388.10044 (2016): 565-575. PMID: 27313086
32. Le Gouil S, Thieblemont C, Oberic L, et al. Rituximab Maintenance after Autologous Stem Cell Transplantation Prolongs Survival in Younger Patients with Mantle Cell Lymphoma: Final Results of the Randomized Phase 3 LyMa Trial of the Lysa/Goelams Group. American Society of Hematology 58th Annual Meeting & Exposition. 2016 Dec 3;Abstract 145. Available at https://ash.confex.com/ash/2016/webprogram/Paper89500.html. Accessed August 10, 2017.
33. 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. PMID: 26535512.
34. Wang ML, 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. PMID: 26640039.
35. Graf SA, Stevenson PA, Holmberg LA, et al. Maintenance rituximab after autologous stem cell transplantation in patients with mantle cell lymphoma. Ann Oncol. 2015 Nov;26(11):2323-8. PMID: 26347113.
36. Kluin-Nelemans HC, 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. PMID: 22873532.
37. 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. PMID: 26673811.
38. Davids MS, Roberts AW, Seymour JF, 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. PMID: 28095146.
39. Robinson KS, Williams ME, van der Jagt RH, 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. PMID: 18626004.
40. Rummel MJ, Al-Batran SE, Kim SZ, 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. PMID: 15908650.
41. Goy A, Bernstein SH, Kahl BS, 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. PMID: 19074748.
42. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-67.PMID 29241979.

Ovarian Cancer (Epithelial) Pathways

Adjuvant Therapy | Stage IA/B (Grade 2 or 3) or IC (Grade 1-3)
Carboplatin and dose dense paclitaxel[6-8]
Carboplatin and paclitaxel[2-5,7]
Adjuvant or Primary Therapy | Stage II, III, IV
Carboplatin and paclitaxel[6-8,45] **(Administered weekly or every 3 weeks)**
Intravenous (IV) paclitaxel and Intraperitoneal (IP) cisplatin and IP paclitaxel[1,49] **(Stage III only)**
Recurrent Disease | First and Subsequent Lines of Therapy (1st Line+) | Platinum-Sensitive*
Carboplatin[8,9,12]
Carboplatin and gemcitabine (Gemzar)[12,13]
Carboplatin and paclitaxel[8,9,15]
Carboplatin and weekly paclitaxel
Recurrent Disease | Maintenance Therapy | Platinum-Sensitive*
Niraparib (Zejula)[54]
Olaparib (Lynparza)[55] – Added effective 11/12/2018
Rucaparib (Rubraca)[60] – Added effective 11/12/2018
Recurrent Disease | Second and Subsequent Lines of Therapy (2nd Line+) | Platinum Resistant
Bevacizumab (Avastin) monotherapy[42]
Docetaxel (Taxotere)[17]
Gemcitabine (Gemzar)[19,20]
Liposomal doxorubicin (Doxil or Lipodox)[19-21]
Paclitaxel (weekly)[22,23]
Paclitaxel and bevacizumab (Avastin)[36-38]
Tamoxifen[56]
Topotecan (Hycamtin)[21,24]
Topotecan (Hycamtin) and bevacizumab (Avastin)[36,37]
Vinorelbine (Navelbine)[34,35]

* Platinum sensitive disease is defined as recurrence of greater than 6 months after prior platinum-based therapy

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

OVARIAN CANCER (EPITHELIAL) REFERENCES

NCCN Clinical Practice Guidelines: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer V2.2018

References

1. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006; 354:34-43. PMID: 16394300
2. Bookman MA, Brady MF, McGuire WP, 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. PMID: 19224846
3. Chan JK, Tian C, Fleming GF, et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. Gynecol Oncol. 2010 Mar;116(3):301-6. PMID: 19945740
4. Bell J, Brady MF, Young RC, 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; 102:432-439. PMID: 16860852
5. Vasey PA, Jayson GC, 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
6. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1331-8. PMID: 19767092
7. 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. PMID: 23948349
8. Gonzalez-Martin AJ, Calvo E, Bover I, et al. Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. Ann Oncol. 2005; 16:749-755. PMID: 15817604
9. 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. 2003 Jun 21;361(9375):2099-106. PMID: 12826431
10. 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 Mar;104(3):612-6. PMID: 17069876
11. 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 May;105(2):358-6. PMID: 17258800
12. 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 Oct 10;24(29):4699-707. PMID: 16966687
13. Aghajanian C, Blank SV, Goff BA, 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 Jun 10;30(17):2039-45. PMID: 22529265
14. 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 Jul 10;28(20):3323-9. PMID: 20498395
15. Wagner U, Marth C, Largilier 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; 107:588-591. PMID: 22836511
16. Nagourney RA, Brewer CA, Radecki S, et al. Phase III trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. Gynecol Oncol. 2003; 88:35-39. PMID: 12504624
17. Rose PG, Blessing JA, Ball HG et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2003 Feb;88(2):130-5. PMID: 12586591
18. Rose PG, Blessing JA, Mayer AR, and Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 1998 Feb;16(2):405-10. PMID: 9469322
19. 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 Feb 20;26(6):890-6. PMID: 18281662
20. Mutch DG, 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 Jul 1;25(19):2811-8. PMID: 17602086
21. Gordon AN, Tonda M, Sun S, Rackoff W; Doxil Study 30-49 Investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol. 2004 Oct;95(1):1-8. PMID: 15385103

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Le T, Hopkins L, Baines KA, Rambout L, Al Hayki M, and Kee Fung MF. Prospective evaluations of continuous weekly paclitaxel regimen in recurrent platinum-resistant epithelial ovarian cancer. Gynecol Oncol. 2006 Jul;102(1):49-53. PMID: 16375951
23. Gynecologic Oncology Group1, 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 Jun;101(3):436-40. PMID: 16325893
24. Abushahin F, Singh DK, Lurain JR, Grendys EC, Rademaker AW, and Schink JC. Weekly topotecan for recurrent platinum resistant ovarian cancer. Gynecol Oncol. 2008 Jan;108(1):53-7. PMID: 17904208
25. Markman M, Blessing JA, Moore D, Ball H, and Lentz SS. Altretamine (hexamethylmelamine) in platinum-resistant and platinum-refractory ovarian cancer: a Gynecologic Oncology Group phase II trial. Gynecol Oncol. 1998 Jun;69(3):226-9. PMID: 9648592
26. Wolf JK, Bodurka DC, 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 Sep;102(3):468-74. PMID: 16516276
27. de Palo GM, de Lena M, Di Re F, Luciani L, Valagussa P, Bonadonna G. Melphalan versus adriamycin in the treatment of advanced carcinoma of the ovary. Surg Gynecol Obstet. 1975 Dec;141(6):899-902. PMID: 1103333
28. Bolis G, D'Incalci M, Gramellini F, and Mangioni C. Adriamycin in ovarian cancer patients resistant to cyclophosphamide. Eur J Cancer. 1978 Dec;14(12):1401-2. PMID: 738344
29. Markman M, Hakes T, Reichman B, et al. Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: activity in latinum-resistant disease. J Clin Oncol. 1992; 10:243-248. PMID: 1732425
30. 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 Feb;100(2):412-6. PMID: 16298422
31. Teneriello MG, Tseng PC, 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 Mar 20;27(9):1426-31. PMID: 19224848
32. Dieras V, Bougnoux P, Petit T, et al. Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. Ann Oncol. 2002 Feb;13(2):258-66. PMID: 11886003
33. Miller DS, Blessing JA, Krasner CN, 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 Jun 1;27(16):2686-91. PMID: 19332726
34. Rothenberg ML, Liu PY, Wilczynski S, et al. Phase II trial of vinorelbine for relapsed ovarian cancer: a Southwest Oncology Group study. Gynecol Oncol. 2004 Dec;95(3):506-12. PMID: 15581954
35. 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 Sep;14(9):2546-51. PMID: 8823334
36. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA Open-Labeled Randomized Phase III Trial. J Clin Oncol. 2014; 32:1302-1308. PMID: 24637997
37. Stockler MR< Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol. 2014; 32:1309-1316. PMID: 24687829
38. O'Malley DM, Richardson DL, Rheaume PS, et al. Addition of bevacizumab to weekly paclitaxel significantly improves progression-free survival in heavily pretreated recurrent epithelial ovarian cancer. Gynecol Oncol. 2011 May 1;121(2):269-72. PMID: 21315428
39. Verschraegen CF, Czok S, Muller CY, et al. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. Ann Oncol. 2012 Dec;23(12):3104-10. PMID: 22851407
40. Wenham RM, Lapolla J, Lin HY, et al. A phase II trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy. Gynecol Oncol. 2013 Jul;130(1):19-24. PMID: 23623830
41. Tillmanns TD, Lowe MP, Walker MS, Stepanski EJ, and Schwartzberg LS. Phase II clinical trial of bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. Gynecol Oncol. 2013 Feb;128(2):221-8. PMID: 22960352
42. Burger RA, Sill MW, Monk BJ, Greer BE, and Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007 Nov 20;25(33):5165-71. PMID: 18024863
43. Hagemann AR, Novetsky AP, Zighelboim I, et al. Phase II study of bevacizumab and pemetrexed for recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer. Gynecol Oncol. 2013 Dec;131(3):535-4. PMID: 24096113
44. Garcia AA, 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 Jan 1;26(1):76-82. PMID: 18165643
45. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks with advanced ovarian cancer (MITO-7): a randomized, multicenter, open-label, phase 3 trial. Lancet Oncol. 2014;15(4):396-405. PMID: 24582486
46. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer (Version 2.2018). Available at http://www.nccn.org. Accessed Date: July 31, 2018. ©National Comprehensive Cancer Network, 2018.
47. 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 randomised, open-label, phase 2 trial. Lancet Oncol. 2015 May;16(5):561-8. PMID: 25882986
48. Tewari D1, Java JJ1, Salani, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2015 May 1;33(13):1460-6. PMID: 25800756
49. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015 Oct;139(1):10-6. PMID: 26271155
50. Poveda AM, Selle F, Hipert F, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol. 2015 Nov 10;33(32):3836-8. PMID: 26282651

51. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomized, controlled, non-inferiority trial. Lancet. 2015 Jul 18;386(9990):249-57. PMID: 26002111
52. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010 Sep 2;363(10):943-53. PMID: 2081890
53. Rouzier R, Gouy S, Selle F, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: Results from the ANTHALYA trial. Eur J Cancer. 2017;70:133-42. PMID: 27914243
54. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.PMID: 27717299
55. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016 Nov; 17(11):1579-1589. PMID: 27617661
56. Lindemann K, Gibbs E, Avall-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):455-63.PMID: 28118323
57. Clamp AR, McNeish I, Dean A, et al. ICON8: A GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/fallopian tube/primary peritoneal carcinoma (EOC) treatment: Results of primary progression-free survival (PFS) analysis. Ann Oncol. 2017;28(SUPPL 5):627.
58. van Driel WJ, Koole SN, Sikorska K, et. al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med. 2018 Jan 18;378(3):230-240. PMID 29342393
59. Spriggs DR, Zivanovic O. Ovarian Cancer Treatment – Are we getting warmer?. N Engl J Med. 2018 Jan 18;378(3):293-294. PMID 29342385
60. Coleman RL, Oza AM, 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. Lancet. 2017;390(10106):1949-61.PMID 28916367.

Pancreatic Cancer (Adenocarcinoma) Pathways

Adjuvant Therapy
Capecitabine (Xeloda) and gemcitabine (Gemzar)[36,40]
FULV: fluorouracil (5FU) and leucovorin[4,6,9]
mFOLFIRINOX*: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin[46]
Gemcitabine (Gemzar)[1,3-7]
Locally Advanced/Unresectable and Metastatic Disease | First Line of Therapy (1st Line) | ECOG PS: 0-2
FOLFIRINOX: fluorouracil (5FU), leucovorin, irinotecan (Camptosar), and oxaliplatin[5,21]
Gemcitabine (Gemzar)[5,15-21]
Gemcitabine (Gemzar) and nab-paclitaxel (Abraxane)[5,15,33]
Locally Advanced/Unresectable and Metastatic Disease | Second Line of Therapy (2nd Line) | ECOG PS: 0-2
OFF: Fluorouracil (5FU), leucovorin, and oxaliplatin[32]
Gemcitabine (Gemzar)[21]

* Modified FOLFIRINOX: Bolus 5-FU not administered

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

PANCREATIC CANCER (ADENOCARCINOMA) REFERENCES

NCCN Clinical Practice Guidelines: Pancreatic Adenocarcinoma V3.2017

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V3.2017. Available at: http://www.nccn.org. Accessed November 10, 2017 © National Comprehensive Cancer Network, 2017. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

References

1 Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant Chemotherapy with Gemcitabine and Long-term Outcomes Among Patients with Resected Pancreatic Cancer. The CONKO-001 Randomized Trial. JAMA. 2013; 310(14):1473-1481. PMID: 24104372.

2 Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002; 20:3270-3275. PMID: 12149301.

3 Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007; 297:267-277. PMID: 17227978

4 Neoptolemos J, Stocken D, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection. JAMA. 2010; 304:1073-1081. PMID: 20823433

5 NCCN Clinical Practice Guidelines in Oncology™. © 2017 National Comprehensive Cancer Network, Inc. For additional information: http://www.nccn.org. Pancreatic Adenocarcinoma.V3.2017.

6 Regine W, Winter K, Abrams R, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma. JAMA. 2008; 299:1019-1026. PMID: 18319412.

7 Regine W, Winter K, Abrams R, et al. Fluorouracil based chemoradiation with either gemcitabine or fluorouracil chemotherapy following resection of pancreatic adenocarcinoma: 5-year analysis of the US Intergroup/RTOG 9704 Phase III Trial. Ann Surg Oncol. 2011; 18:1319-1326. PMID: 21499862.

8 Cartwright T, Cohn A, Varkey J, et al. Phase II Study of Oral Capecitabine in Patients With Advanced or Metastatic Pancreatic Cancer. J Clin Oncol. 2002; 20:160-164. PMID: 11773165.

9 Neoptoplemos J, Stocken D, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004; 350:1200-1210. PMID: 15028824.

10 Blackstock A, Tepper J, Niedwiecki D, et al. Cancer and Leukemia Group B (CALGB) 89805. Phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. Int J Gastrointest Cancer. 2003; 34:107-116. PMID: 15361643.

11 Loehrer P, Powell M, Wagner C, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201 [Abstract]. J Clin Oncol. 2008; 26 (May 20 Supp).4506.

12 Loehrer P, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: An Eastern Cooperative Oncology Group Trial. J Clin Oncol. 2011; 29:4105-12. PMID: 21969502.

13 Moertel C, Frytak S, Hahn R, et al. Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 Rads) radiation alone, moderate dose radiation (4000 Rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. The Gastrointestinal Tumor Study Group. Cancer. 1981; 48:1705-1710. PMID: 7284971.

14 Mukherjee S, Hurt C, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicenter, randomized, phase 2 trial. Lancet Oncol. 2013; 14:317-326. PMID: 23474363.

15 Von Hoff D, Ervin T, Arena F, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369:1691-1703. PMID: 24131140.

16 Moore M, Goldstein D, Hamm J, et al. 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. J Clin Oncol. 2007; 25:1960-1966. PMID: 17452677.

17 Cunningham D, Chau I, Stocken D, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009; 27:5513-5518. PMID: 19858379.

18 Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol. 2006; 24:3946-3952. PMID: 16921047.

19 Colucci G, Labianca R, Costanzo F, et al. 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. J Clin Oncol. 2010; 28:1645-1651. PMID: 20194854.

20 Oliver G, Sugar E, Laheru D, et al. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Gastrointestinal Cancers Symposium 2010:180.

21 Rothenberg M, Moore M, Cripps M, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol. 1996; 7:347-353. PMID: 8805925.

22 Pelzer U, Kubica K, Stieler J, et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO-003 study. [abstract] J Clin Oncol. 2008; 26 (May 20 Supp).4508.

23 Pelzer U, Schwaner I, Stieler J, et al. 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. Euro J Cancer. 2011; 47;1676-1681. PMID: 21565490.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

24 Xiong H, Varadhachary G, Blais J, et al. Phase 2 trial of oxaliplatin plus capecitbine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer. 2008; 113:2046-2052. PMID: 18756532.
25 Boeck S, Wilkowski R, Bruns C, et al. Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. Oncology. 2007; 73:221-227. PMID: 18424886.
26 Hammel P, Hugeut F, van Laethem J-L, et al. Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced [pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib. Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.
27 Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol. 2008; 19:1592-1599. PMID: 18467316.
28 Smeenk H, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007; 246:734-740. PMID: 17968163.
29 Kalser MH, Ellenerg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985; 120:899-903. PMID: 4015380.
30 Jsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol. 2010; 17:981-990. PMID: 20087786.
31 Liao WC, Chien KL, Lin YL, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systemic review and network meta-analysis. Lancet Oncol. 2013; 14:1095-1103. PMID: 24035532.
32 Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32(23):2423-9. PMID: 24982456
33 Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, Scheithauer W, Siena S, Tabernero J, Teixeira L, Tortora G, Van Laethem JL, Young R, Penenberg DN, Lu B, Romano A, Von Hoff DD. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst. 2015 Jan 31;107(2). PMID: 25638248
34 Tempero MA, Cardin DB, Biankin A, et al. nab-paclitaxel (nab-P) plus gemcitabine (Gem) vs Gem alone as adjuvant treatment for resected pancreatic cancer (PC) in a phase III trial (APACT). J Clin Oncol 33, 2015 (suppl; abstr TPS4153). Abstract 4153
35 Wang-Gillam A, Li CP, NAPOLI-1 Study Group, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016 Feb 6;387(10018):545-57. PMID: 26615328
36 Neoptolemos J, Palmer D, Ghaneh P, et al. ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma" J Clin Oncol 34, 2016 (supplement) Abstract LBA4006
37 Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016 Jun;17(6):801-10. PMID: 27160474.
38 Chiorean EG, Von Hoff DD, Tabernero J, et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer. 2016 Jul 12;115(2):188-94. PMID: 27351217
39 Gill S, Ko YJ, Cripps C, Beaudoin A, et al. PANCREOX: A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. J Clin Oncol. 2016 Sep 12. pii: JCO685776. PMID: 27621395.
40 Neoptolemos J, Palmer D, Ghaneh P, et al. 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, Lancet. 2017 Mar 11;389(10073):1011-1024. PMID: 28129987
41 Khorana AA, Mangu PB, Berlin J, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35(20):2324-8. PMID: 28398845
42 Petrelli F, Inno A, Ghidini A, et al. Second line with oxaliplatin- or irinotecan-based chemotherapy for gemcitabine-pretreated pancreatic cancer: A systematic review. Eur J Cancer. 2017;81:174-82. PMID: 28633088
43 Irigoyen A, Gallego J, Guillen Ponce C, et al. Gemcitabine-erlotinib versus gemcitabine-erlotinib-capecitabine in the first-line treatment of patients with metastatic pancreatic cancer: Efficacy and safety results of a phase IIb randomised study from the Spanish TTD Collaborative Group. Eur J Cancer. 2017;75:73-82. PMID: 28222309
44 Chen L-T, Li C-P, Chiu C-F, et al. 221PD Efficacy and safety of nanoliposomal irinotecan (nal-IRI, MM-398, PEP02, BAX-2398) in patients with metastatic pancreatic cancer in Asia: A subgroup analysis of the phase 3 NAPOLI-1 Study. Ann Oncol 2016; 27, suppl_9, mdw582.002
45 Beatty GL, Eghbali S, Kim R. Deploying Immunotherapy in Pancreatic Cancer: Defining Mechanisms of Response and Resistance. Am Soc Clin Oncol Educ Book. 2017;37:267-278., PMID # 28561678
46 Conroy T, Hammel P, Hebbar M, et al. Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. Presented at ASCO 2018. J Clin Oncol 36, 2018 (suppl; abstr LBA4001)

Prostate Cancer (Adenocarcinoma) Pathways

Adjuvant Therapy | Post-Prostatectomy | Lymph Node Positive (LN+)
Goserelin (Zoladex)[1,2]
Leuprolide (Eligard/Lupron)[1,2]
Triptorelin (Trelstar)[1,2]
Intermediate Risk | Primary Treatment with Radiotherapy (RT)
Goserelin (Zoladex)*[3,5]
Leuprolide (Eligard/Lupron)*[3,5]
Triptorelin (Trelstar)*[3,5]
High Risk (T3a or Gleason 8-10), Very High Risk (T3b-T4), and Locally Advanced Prostate Cancer (LN+) | Primary Treatment with Radiotherapy (RT)
Goserelin (Zoladex)*[4]
Goserelin (Zoladex)* with abiraterone (Zytiga)[41]
Leuprolide (Eligard/Lupron)*[4]
Leuprolide (Eligard/Lupron)* with abiraterone (Zytiga)[41]
Triptorelin (Trelstar)*[4]
Triptorelin (Trelstar) with abiraterone (Zytiga)*[41]
Recurrent and Metastatic Disease | Hormone Sensitive
Abiraterone (Zytiga) and prednisone with Androgen Deprivation Therapy (ADT)†[39,41]
Docetaxel (Taxotere) (every 3 weeks) with Androgen Deprivation Therapy (ADT)†[19]
Goserelin (Zoladex)[6]
Leuprolide (Eligard/Lupron)[6]
Triptorelin (Trelstar)[6]

Bilateral orchiectomy (surgical castration) is an equally effective alternative to medical castration

* May be coadministered with bicalutamide (Casodex) or flutamide (Eulexin) for up to 30-60 days in patients who are at risk of developing symptoms associated with testosterone flare

† ADT pathway options, when given as listed above: goserelin (Zoladex), leuprolide (Eligard/Lupron), triptorelin (Trelstar) or history of orchiectomy

‡ If neither abiraterone nor enzalutamide have been previously used

§ If not previously used in the first line (1st Line) setting

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

Prostate Cancer (Adenocarcinoma) Pathways (continued)

Recurrent and Metastatic Disease | Hormone Resistant | First Line of Therapy (1st Line)

Abiraterone (Zytiga) and prednisone with continued ADT†[8,12,25-27]

Docetaxel (Taxotere) (every 3 weeks) with continued ADT†[9,10,19]

Enzalutamide (Xtandi) with continued ADT†

Goserelin (Zoladex) with bicalutamide (Casodex)[6,7]

Leuprolide (Eligard/Lupron) with bicalutamide (Casodex)[6,7]

Triptorelin (Trelstar) with bicalutamide (Casodex)[6,7]

Recurrent and Metastatic Disease | Hormone Resistant | Second and Subsequent Lines of Therapy (2nd Line+)

Abiraterone (Zytiga)‡ and prednisone with continued ADT†[8,12,25-27]

Cabazitaxel (Jevtana) with ADT†[11]

Docetaxel (Taxotere) (every 3 weeks) with continued ADT†§[9,10,19]

Docetaxel (Taxotere) rechallenge with ADT†[21,22]

Goserelin (Zoladex) with bicalutamide (Casodex)§[6,7]

Leuprolide (Eligard/Lupron) with bicalutamide (Casodex)§[6,7]

Triptorelin (Trelstar) with bicalutamide (Casodex)§[6,7]

Continued ADT† with supportive care ± dexamethasone[13-16,24]

Bilateral orchiectomy (surgical castration) is an equally effective alternative to medical castration

* May be coadministered with bicalutamide (Casodex) or flutamide (Eulexin) for up to 30-60 days in patients who are at risk of developing symptoms associated with testosterone flare.

† ADT pathway options, when given as listed above: goserelin (Zoladex), leuprolide (Eligard/Lupron), triptorelin (Trelstar), or history of orchiectomy

‡ If neither abiraterone nor enzalutamide have been previously used

§ If not previously used in the first line (1st Line) setting

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

PROSTATE CANCER (ADENOCARCINOMA) REFERENCES

NCCN Clinical Practice Guidelines: Prostate Cancer. Version 3. 2018

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V3.2018. Available at: http://www.nccn.org. Accessed July 31, 2018 ©National Comprehensive Cancer Network, 2018. To view the most recent and complete version of the Guideline, go online to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006; 7:472-479. PMID: 16750497
2. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med. 1999; 34:1781-1788. PMID: 10588962
3. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA. 2004; 292:821-827. PMID: 15315996
4. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol. 2008; 26:2497-2504. PMID: 18413638
5. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet. 2002; 360:103-108. PMID: 12126818
6. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008; 102:1531-1538. PMID: 19035858
7. Schellhammer PF, Sharifi R, Block NL, et al. Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. Urology. 1997; 50:330-336. PMID: 9301693
8. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013; 368:138-148. PMID: 23228172
9. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. J Engl J Med. 2004; 351:1502-1512. PMID: 15470213
10. 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; 26:242-245. PMID: 18182665
11. 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 randomized open-label trial. Lancet. 2010; 376:1147-1154. PMID: 20888992
12. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011; 364:1995-2005. PMID: 21612468
13. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014; 371:424-433. PMID: 24881730
14. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363:411-422. PMID: 20818862
15. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006; 24:3089-3094. PMID: 16809734
16. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367:1187-1197. PMID: 22894553
17. Chiappino L, Destefanis P, Addeo A, et al. Activity of weekly paclitaxel in advanced hormone-refractory prostate cancer. Am J Clin Oncol. 2007; 30:234-238. PMID: 17551298
18. Turner SL, Gruenwald S, Spry N, et al. Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. Br J Cancer. 2001; 84:297-302. PMID: 11161391
19. Sweeney C, Chen Y, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (MPrCA) : An ECOG-led phase III randomized trial. J Clin Oncol 2014; 32(5s): LBA2. Abstract LBA4
20. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-Year Survival Outcomes Following Primary Androgen-Deprivation Therapy for Localized Prostate Cancer. JAMA Intern Med. 2014 Sep;174(9):1460-1467. PMID: 25023796
21. Fuxius S, Mueller A, Kleitz K, et al. Weekly docetaxel rechallenge in patients with hormone-resistant prostate cancer resistant to conventionally three weekly docetaxel. J Clin Oncol 2010; 28 (Supp):E15004. Abstract 15004
22. Heck MM, Talgott M, Retz M, et al. Rational indication for docetaxel rechallenge in metastatic castration-resistant prostate cancer. BJU Int. 2012; 110:E635-640. PMID: 22889368
23. Shamash J, Powles T, Sarker SJ, et al. A multi-centre randomized phase III trial of dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: immediate vs deferred diethylstilbestrol. BR J Cancer. 2011; 104:620-328. PMID: 21285990

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

24. 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; 22:1025-1033. PMID: 15020604
25. Ryan CJ, Smith MR, COU-AA-302 Investigators, et al. 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(6):152-160. PMID: 25601341
26. Sternberg CN, Castellano D, Abiraterone Global EAP Investigators, et al. Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial. Lancet Oncol. 2014 Oct;15(11):1263-1268. PMID: 25242048
27. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014 Oct 20;32 (30):3436-3648. PMID: 25199761
28. Sternberg CN, de Bono JS, Chi KN, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol. 2014 Feb;25(2):429-434. PMID: 24478320
29. Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, and Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. Ann Oncol. 2015 Jan;26(1):179-185. PMID: 25361992
30. Tombal B, Borre M, Rathenborg P, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 2014 May;15(6):592-600. PMID: 24739897
31. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer (Version 3.2018). Available at http://www.nccn.org ©National Comprehensive Cancer Network, 2018. Accessed July 31, 2018.
32. Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy naïve metastatic castration-resistant prostate cancer: results from PREVAIL. Ann Oncol. 2016; 27(2):286-294. PMID: 26578735
33. Sweeney, Christopher J., et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373.8 (2015): 737-746. PMID: 26244877
34. James, Nicholas D., et al. "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 387.10024 (2016): 1163-1177. PMID: 26719232
35. Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). J Clin Oncol 33, 2015. Abstract LBA5002
36. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009;360(24):2516-27. PMID: 19516032.
37. De Bono J, Hardy-Bessard A, Kim C, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m2 (C20) versus 25 mg/m2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). American Society of Clinical Oncology Annual Meeting; Chicago IL: American Society of Clinical Oncology; 2016 Abstract 5008
38. 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;16(7):787-94. PMID: 26028518.
39. 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.
40. Gravis G, Boher JM, Joly F, et al. 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;70(2):256-62. PMID: 26610858.
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):338-51. PMID: 28578639.
42. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med. 2011;365(2):107-18. PMID: 21751904.
43. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. J Cancer Clin Oncol. 2016;34(18):2098-106. PMID: 26811535.
44. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-20. PMID: 15470214.
45. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. J Cancer Clin Oncol. 2015;33(4):332-9. PMID: 25534388.
46. 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 Jul 28:JCO2016721068. [Epub ahead of print] PMID: 28753384.
47. 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;17(2):153-63. PMID: 26774508.
48. Wong YN, Freedland S, Egleston B, et al. Role of androgen deprivation therapy for node-positive prostate cancer. J Cancer Clin Oncol. 2009;27(1):100-5. PMID: 19047295.
49. Zapatero A, Guerrero A, Maldonado X, et al. Late Radiation and Cardiovascular Adverse Effects After Androgen Deprivation and High-Dose Radiation Therapy in Prostate Cancer: Results From the DART 01/05 Randomized Phase 3 Trial. Int J Radiat Oncol Biol Phys. 2016;96(2):341-8. PMID: 27598804.
50. Sartor AO, Tangen CM, Hussain MH, et al.; Southwest Oncology Group. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). Cancer. 2008 Jun;112(11):2393-400. PMID: 18383517.

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

51. Dupont A, Gomez JL, Cusan L, et. al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol. 1993 Sep;150(3):908-13. PMID: 7688437.
52. Parker CC, Coleman RE, Sartor O, et al. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial. Eur Urol. 2017 Jul 10. pii: S0302-2838(17)30516-X. PMID: 28705540.
53. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2018;378(26):2465-74.PMID 29949494.

Testicular (Germ Cell Tumors) Cancer Pathways

Seminoma | Stage II-IIIA | Primary Therapy

BEP: bleomycin, etoposide (Toposar), and cisplatin[5]

EP: etoposide (Toposar) and cisplatin[4]

Seminoma | Stage IIIB-C | Good and Intermediate Risk | Metastatic Disease

BEP: bleomycin, etoposide (Toposar), and cisplatin*[5,6]

Nonseminoma | Stage II-IIIA | Primary Therapy

BEP: bleomycin, etoposide (Toposar), and cisplatin[5,6]

EP: etoposide (Toposar) and cisplatin[4]

Nonseminoma | Stage IIIB-C | Primary Therapy

BEP: bleomycin, etoposide (Toposar), and cisplatin[5,6]

Nonseminoma | Adjuvant Therapy after RPLND†

EP: etoposide (Toposar) and cisplatin[8,9,26]

* BEP is typically given for 3 cycles in good risk seminoma, and 4 cycles in intermediate risk

† RPLND: Retroperitoneal lymph node dissection

TESTICULAR (GERM CELL TUMORS) CANCER REFERENCES

NCCN Practice Guidelines: Testicular Cancer V2.2018.

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) for Testicular Cancer V2.2018. Available at: http://www.nccn.org. Accessed May 09, 2018© National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Oliver RT, Mason MD, MRC TE19 collaborators and the EORTC 30982 collaborators, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomized trial. Lancet. 2005 Jul 23-29;366(9482):293-300. PMID: 16039331
2. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol. 2011 Mar 10;29(8):957-62. PMID: 21282539
3. Tandstad T1, Ståhl O, SWENOTECA, et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Ann Oncol. 2016 Jul;27(7):1299-304. PMID: 27052649
4. Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol. 1997 Jul;15(7):2553-8. PMID: 9215824
5. Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University experience. J Clin Oncol. 1998 Feb;16(2):702-6. PMID: 9469360
6. Culine S, Kramar A, ; Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP, et al. Randomized trial comparing bleomycin/etoposide/cisplatin with alternating cisplatin/cyclophosphamide/doxorubicin and vinblastine/bleomycin regimens of chemotherapy for patients with intermediate- and poor-risk metastatic nonseminomatous germ cell tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. J Clin Oncol. 2008 Jan 20;26(3):421-7. PMID: 18202419
7. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol. 1998 Apr;16(4):1287-93. PMID: 9552027
8. Kondagunta GV, Sheinfeld J, Mazumdar M, et al. Relapse-free and overall survival in patients with pathologic stage II nonseminomatous germ cell cancer treated with etoposide and cisplatin adjuvant chemotherapy. J Clin Oncol. 2004 Feb 1;22(3):464-7. PMID: 14752068
9. Motzer RJ, Sheinfeld J, Mazumdar M, et al. Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. J Clin Oncol. 1995 Nov;13(11):2700-4. PMID: 7595727
10. 1Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol. 1996 Apr;14(4):1106-13. PMID: 8648364
11. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol. 2005 Sep 20;23(27):6549-55. PMID: 16170162
12. Loehrer PJ Sr, Lauer R, Roth BJ, Williams SD, Kalasinski LA, Einhorn LH. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med. 1988 Oct 1;109(7):540-6. PMID: 2844110
13. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007 Jul 26;357(4):340-8. PMID: 17652649
14. Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol. 2010 Apr 1;28(10):1706-13. PMID: 20194867
15. Kondagunta GV, Bacik J, Sheinfeld J, et al. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol. 2007 Jan 1;25(1):85-90. PMID: 17194908
16. Motzer RJ, Mazumadar M, Sheinfeld J, et al. Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients. J Clin Oncol. 2000 Mar;18(6):1173-80. PMID: 10715285
17. Einhorn LH, Brames MJ, Juliar B, Williams SD. Phase II study of paclitaxel plus gemcitabine salvage chemotherapy for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. J Clin Oncol. 2007 Feb 10;25(5):513-6. PMID: 17290059
18. Mulherin BP, Brames MJ, Einhorn LH. Long-term survival with paclitaxel and gemcitabine for germ cell tumors after progression following high-dose chemotherapy with tandem transplants. J Clin Oncol. 2011;11 (Suppl; Abstract 4562). Abstract 4562
19. Hinton S, Catalano P, Einhorn LH, et al. Phase II study of paclitaxel plus gemcitabine in refractory germ cell tumors (E9897): a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2002 Apr 1;20(7):1859-63. PMID: 11919245
20. Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol. 2004 Jan 1;22(1):108-14. PMID: 14701772
21. De Giorgi U, Rosti G, Aieta M, et al. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor. Eur Urol. 2006 Nov;50(5):1032-8; discussion 1038-9. PMID: 16757095

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

22. Pectasides D, Pectasides M, Farmakis D, et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Ann Oncol. 2004 Mar;15(3):493-7. PMID: 14998855
23. Bokemeyer C, Oechsle K, German Testicular Cancer Study Group, et al. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. Ann Oncol. 2008 Mar;19(3):448-53. PMID: 18006893
24. Miller JC, Einhorn LH. Phase II study of daily oral etoposide in refractory germ cell tumors. Semin Oncol. 1990 Feb;17(1 Suppl 2):36-9. PMID: 2154858
25. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Testicular Cancer (Version 2.2018). Available at http://www.nccn.org. ©National Comprehensive Cancer Network, 2018. Accessed May 9, 2018.
26. Aparicio J, Maroto P, del Muro XG, et. al. Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. J Clin Oncol. 2011 Dec 10;29(35):4677-81. PMID: 22042940
27. Fizazi K, Delva R, Caty A, et. al. A risk-adapted study of cisplatin and etoposide, with or without ifosfamide, in patients with metastatic seminoma: results of the GETUG S99 multicenter prospective study. Eur Urol. 2014 Feb;65(2):381-6. PMID: 24094847
28. Behnia M, Foster R, Einhorn LH, et. al. Adjuvant bleomycin, etoposide and cisplatin in pathological stage II non-seminomatous testicular cancer. the Indiana University experience. Eur J Cancer. 2000 Mar;36(4):472-5. PMID: 10717522
29. Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, etoposide, and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. Cancer. 2003 Apr 15;97(8):1869-75, PMID: 12673712

Uterine (Endometrial) Cancer Pathways

Adjuvant Therapy | Stage III-IV or High Risk Histologies
Carboplatin and paclitaxel[5,6]
Recurrent /Metastatic | First and Subsequent Lines of Therapy (1st Line+)
Carboplatin and paclitaxel[5,27-29]
Cisplatin and doxorubicin (Adriamycin)[24,25]

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

UTERINE (ENDOMETRIAL) CANCER REFERENCES

NCCN Practice Guidelines: Uterine Neoplasms V1.2018.

Referenced with permission from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V1.2018. Available at: http://www.nccn.org. Accessed May 9, 2018© National Comprehensive Cancer Network, 2018. To view the most recent complete version of the Guideline, go to www.nccn.org.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinical seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care ore treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References

1. Wolfson AH, Brady MF, Rocereto T, et al. A gynecological oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol. 2007; 107:177-85. PMID: 17822748
2. 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. PMID: 17290061
3. 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. PMID: 19108877
4. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of the whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006; 24:36-44. PMID: 16330675
5. Miller D, Filiaci G, Fleming R, et al. Randomized phase III non-inferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2012; 125:771-773 Abstract
6. Hidaka T, Nakamura T, Shima T, et al. Paclitaxel/carboplatin versus cyclophosphamide/Adriamycin/cisplatin as postoperative adjuvant chemotherapy for advanced endometrial adenocarcinoma. J Obstet Gynecol Res. 2006; 32:330 -337. PMID: 16764625
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms (Version 1.2018). Available at http://www.nccn.org. Accessed May 9, 2018©National Comprehensive Cancer Network, 2018.
8. Rose PG, Brunetto VL, VanLe L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2000; 78:212-16; PMID: 10926805
9. Breast International Group (BIG) 1-98 Collaboration Group, Thurlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005; 353:2747-57. PMID: 16382061
10. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemastane after two or three years therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004; 350:1081-92. PMID: 15014181
11. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999; 17:1736-44. PMID: 10561210
12. Lentz SS, Brady MF, Major FJ, et al. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol. 1996; 14:357-61. PMID: 8636744
13. Thigpen T, Brady MF, Homsley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2001; 19:364-67. PMID: 11208827
14. van Wijk FH, Lhomme C, Bolis G, et al. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynaecological Cancer Group. Eur J Cancer. 2006; 39:78-85. PMID: 12504662
15. Seski JC, Edwards CL, Herson J, et al. Cisplatin chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1982; 59:225-28. PMID: 7043339
16. Katsumata N, Noda K, Nozawa S, et al. Phase II trial of docetaxel in advanced or metastatic endometrial cancer: Br J Cancer. 2005; 93:999-1004. PMID: 16234823
17. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial cancer. J Clin Oncol. 1994; 12:1408-14. PMID: 8021731
18. Lissoni A, Zanetta G, Losa G, et al. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996. 7:861-63. PMID: 8922203
19. Muggia FM, Blessing JA, Sorosky J, et al. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer. A Gynecologic Oncology Group study. J Clin Oncol. 2002; 20:2360-64. PMID: 11981008
20. 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; 29:3278-85. PMID: 21788564
21. Wadler S, Levy DE, Lincoln ST, et al. 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; 21:2110-14. PMID: 12775736
22. 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. 2001; 29:2259-2265. PMID: 21537039
23. Nomura H, Aoki D, Takahashi F, et al. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Ann Oncol. 2011; 22:636-42. .PMID: 20696677

Note: Pathways are independent of specific health plan medical policy coverage criteria. Health plan medical policy/clinical guidelines should be consulted to determine whether proposed services will be covered.

24. Fleming GF, Brunetta 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; 22:2159-66. PMID: 15169803
25. Cella D, Huang H, Homesley HD, et al. Patient-reported peripheral neuropathy of doxorubicin and cisplatin with and without paclitaxel in the treatment of advanced endometrial cancer: Results from GOG 184. Gynecol Oncol. 2010; 119:538-542. PMID: 20863554
26. 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; 25:526-31. PMID: 17290061
27. Pectasides D, Xiros N, Papaxoinis G, et al. Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol. 2008; 109:250-254. PMID: 18299146
28. Sovak MA, Dupont J, Hensley ML, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. Int J Gynecol Cancer. 2007; 17:197-203. PMID: 17291253
29. Secord AA, Havrilesky LJ, Carney ME, et al. Weekly low-dose paclitaxel and carboplatin in the treatment of advanced or recurrent cervical and endometrial cancer. Int J Clin Oncol. 2007; 12:31-36. PMID: 17380438
30. Altman AD, Thompson J, Nelson G, et al. Use of aromatase inhibitors as first- and second-line medical therapy in patients with endometrial adenocarcinoma: a retrospective study. J Obstet Gynaecol Can. 2012 Jul;34(7):664-72. PMID: 22742486
31. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004 Jan;92(1):10-4. PMID: 14751131
32. Sutton G, Brunetto VL, Kilgore L, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. Gynecol Oncol. 2000 Nov;79(2):147-53. PMID: 11063636