Abraxane® (paclitaxel protein-bound particles)
(Intravenous)

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I. Length of Authorization

Coverage is provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Abraxane 100 mg powder for injection SDV: 9 vials per 21 day supply

B. Max Units (per dose and over time) [HCPCS Unit]:

- 900 billable units per 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Breast Cancer † [1-3,9,21,16e,18e-20e,22e,30e,121e,126e,130e]

- Used as a single agent after failure on combination chemotherapy for metastatic disease or relapsed within 6 months of adjuvant therapy **†**; **AND**
  - Previous chemotherapy included an anthracycline unless clinically contraindicated; **OR**
- Patient has recurrent unresectable (local or regional) or metastatic (stage IV [M1]) disease **‡**; **AND**
  - Used as a single agent for previously treated disease; **AND**
    - Disease is HER2-negative; **AND**
      - Disease is hormone receptor-negative; **OR**
      - Disease is hormone receptor-positive and patient is refractory to endocrine therapy or has a visceral crisis; **OR**

- Used in combination with carboplatin as first-line therapy in patients with triple negative breast cancer with high tumor burden, rapidly progressing disease, and visceral crisis; **AND**
  - Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**
- Used in combination with pertuzumab and trastuzumab as first-line therapy for disease that is HER2-positive; **AND**
  - Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**
- Used as first-line therapy for PD-L1 positive triple negative disease ‡; **AND**
  - Used in combination with one of the following:
    - Atezolizumab in patients with PD-L1 ≥1% on tumor-infiltrating cells; **OR**
    - Pembrolizumab in patients with a Combined Positive Score (CPS) ≥10

-OR- ‡

- Used in neoadjuvant therapy; **OR**
- Used in adjuvant therapy; **AND**
  - *(For adjuvant therapy only)* Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications

Non-Small Cell Lung Cancer (NSCLC) † [1,2,4,10,26e,27e,30e,43e,122e,129e,131e,134e]

- Used as first-line therapy for locally advanced or metastatic disease, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy †; **AND**
  - Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**
- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease with no evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used as first-line therapy; **AND**
    - Used in combination with carboplatin AND pembrolizumab (for squamous cell histology) or atezolizumab (for non-squamous histology); **AND**
      - Used in patients with EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement negative* tumors and one of the following:
        - PD-L1 <1% with performance status (PS) score of ≤1
        - PD-L1 expression positive (≥1%) tumors with PS ≤2; **AND**

- *(In combination with carboplatin and pembrolizumab ONLY):* Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**

➢ Used in patients with BRAF V600E-mutation, NTRK1/2/3 gene fusion, or MET exon 14 skipping mutation AND PS score of ≤1; **AND**

- *(In combination with carboplatin and pembrolizumab ONLY):* Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**

▪ Used in combination with carboplatin in patients with contraindications to PD-1 or PD-L1 inhibitors (PS score of ≤2) or as a single agent (PS 2); **AND**

➢ Used for one of the following:

– Patients with EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement negative* tumors AND PD-L1 <1%

– Patients with BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors; **AND**

➢ Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**

○ Used as subsequent therapy; **AND**

▪ Used in combination with carboplatin AND pembrolizumab (for squamous cell histology) or atezolizumab (for non-squamous histology) in patients with PS score of ≤1; **AND**

➢ Used for one of the following:

– Patients with BRAF V600E-mutation, NTRK1/2/3 gene fusion, or MET exon 14 skipping mutation positive tumors

– Patients with ROS1 rearrangement positive tumors who received prior targeted therapy**§** for those aberrations; **AND**

➢ *(In combination with carboplatin and pembrolizumab ONLY):* Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications; **OR**

▪ Used in combination with carboplatin in patients with contraindications to PD-1 or PD-L1 inhibitors (PS score of ≤2) or as a single agent (PS 2) AND one of the following; **AND**

➢ Used for one of the following:

- Patients with BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors
- Patients with EGFR, ALK, or ROS1 rearrangement positive tumors who received prior targeted therapy§ for those aberrations
- Patients with PD-L1 expression-positive (≥1%) tumors that are EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement negative* with prior PD-1/PD-L1 inhibitor therapy but no prior platinum-doublet chemotherapy; **AND**

➢ Patient experienced a hypersensitivity reaction to paclitaxel or docetaxel despite premedication or the patient has contraindications to standard hypersensitivity premedications

** Note: If there is insufficient tissue to allow testing for all of EGFR, ALK, ROS1, BRAF, **NTRK1/2/3,** MET, and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

Ovarian Cancer (Epithelial Ovarian/Fallopian Tube/Primary Peritoneal) ‡ [2,8,22,52e,59e,61e]

- Patient has recurrent or persistent disease; **AND**
- Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
  - Used as a single agent; **AND**
    - Patient has platinum-resistant disease and one of the following:
      - ➢ Used for progression on primary, maintenance, or recurrence therapy; **OR**
      - ➢ Used for stable or persistent disease if not currently on maintenance therapy; **OR**
      - ➢ Used for relapsed disease <6 months following complete remission from prior chemotherapy; **OR**
    - Patient has platinum-sensitive disease; **AND**
      - ➢ Used for radiographic and/or clinical relapse ≥6 months after complete remission from prior chemotherapy; **OR**
  - Used in combination with carboplatin if platinum-sensitive with confirmed taxane hypersensitivity; **AND**
    - Used for relapse ≥6 months after complete remission from prior chemotherapy

Pancreatic Adenocarcinoma † Φ [1,2,5-7,24,68e,69e,72e]

- Used in combination with gemcitabine; **AND**
  - Patient has locally advanced or metastatic disease; **AND**
    - Used as first-line therapy; **AND**

        - Patient must not be a candidate for treatment with FOLFIRINOX (i.e., has a contraindication, intolerance, or ECOG 2); **OR**
      - Used as induction therapy followed by chemoradiation *(locally advanced disease only)*; **AND**
        - Patient must not be a candidate for treatment with FOLFIRINOX (i.e., has a contraindication, intolerance, or ECOG 2); **OR**
      - Used as subsequent therapy after progression with a fluoropyrimidine-based therapy; **OR**
    - Patient has recurrent disease in the pancreatic operative bed or metastatic disease post-resection; **AND**
      - Used after completion of primary therapy with a fluoropyrimidine-based regimen; **OR**
    - Used as neoadjuvant therapy; **AND**
      - Patient has resectable with high-risk features (i.e., very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain); **AND**
        - Patient must not be a candidate for treatment with FOLFIRINOX (i.e., has a contraindication, intolerance, or ECOG 2); **OR**
      - Patient has biopsy positive borderline resectable disease; **AND**
        - Patient must not be a candidate for treatment with FOLFIRINOX (i.e., has a contraindication, intolerance, or ECOG 2)

Melanoma ‡ [2,15,16,78e,80e,81e]

- Patient has cutaneous melanoma; **AND**
  - Used as a single agent or in combination with carboplatin for metastatic or unresectable disease; **AND**
  - Used after maximum clinical benefit from BRAF targeted therapies

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Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s), ‡ Compendia recommended indication(s); Φ Orphan Drug

Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*) §
Sensitizing *EGFR* mutation-positive tumors

– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib
ALK rearrangement-positive tumors – Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib
ROS1 rearrangement-positive tumors – Ceritinib – Crizotinib – Entrectinib
BRAF V600E-mutation positive tumors – Dabrafenib ± Trametinib – Vemurafenib
NTRK Gene Fusion positive tumors – Larotrectinib – Entrectinib
PD-1/PD-L1 expression-positive tumors (≥1%) – Pembrolizumab – Atezolizumab – Nivolumab ± ipilimumab
MET Exon-14 skipping mutations – Capmatinib – Crizotinib – Tepotinib
RET rearrangement-positive tumors – Selpercatinib – Cabozantinib – Vandetanib – Pralsetinib

IV. Renewal Criteria [1,2]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: bone marrow suppression (e.g., severe neutropenia [absolute neutrophil count < 1,500

cell/mm^3] or thrombocytopenia), sensory neuropathy, sepsis, pneumonitis, severe hypersensitivity reactions including anaphylactic reactions, myelosuppression, etc.

V. Dosage/Administration [1,3,9,11,15-23,25,26]

Indication	Dose
Breast Cancer	260 mg/m² intravenously every 21 days until disease progression or unacceptable toxicity OR 100 mg/m² OR 125 mg/m² intravenously days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity ***NOTE:** If substituted for weekly paclitaxel or docetaxel, the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m²*
NSCLC	100 mg/m² intravenously days 1, 8, and 15 of a 21-day cycle until disease progression or unacceptable toxicity
Melanoma and Ovarian Cancer	100 mg/m² intravenously days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity
Pancreatic Adenocarcinoma	125 mg/m² intravenously days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity
All other indications	260 mg/m² intravenously every 21 days until disease progression or unacceptable toxicity OR 100 mg/m² intravenously days 1, 8, and 15 of a 21-day cycle until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9264 – Injection, paclitaxel protein-bound particles, 1 mg; 1 billable unit = 1 mg

NDC:

- Abraxane 100 mg powder for injection; single-use vial: 68817-0134-xx

VII. References (STANDARD)

1. Abraxane [package insert]. Summit, NJ; Celgene Corporation; August 2020. Accessed May 2021.
2. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) paclitaxel, albumin bound. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed May 2021.

3. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase Ill trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794-7803.
4. 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 Ill trial. J Clin Oncol. 2012;30(17):2055-2062.
5. Tabernero J, Chiorean EG, Infante JR, et al. Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine alone in patients with metastatic pancreatic cancer. Oncologist. 2015;20(2):143-150.
6. Goldstein D, El-Maraghi RH, Hammel P, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst. 2015;107(2):1-10.
7. Scheithauer W, Ramanathan RK, Moore M, et al. Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. J Gastrointest Oncol. 2016;7(3):469-478.
8. 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. Epub 2009 Feb 17.
9. Gradishar WJ, Krasnojon D, Cheporov S, et al, "Significantly Longer Progression-Free Survival With nab-paclitaxel Compared With Docetaxel as First-Line Therapy for Metastat*ic Breast Ca*ncer," *J Clin Oncol*, 2009, 27(22):3611-9.
10. Rizvi NA, Riely GJ, Azzoli CG, et al, "Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel as Initial Chemotherapy in Patients With Stage IV Non-Small-Cell Lung Cancer," *J Clin Oncol*, 2008, 26(4):639-43.
11. Sahai V, Catalano PJ, Zalupski MM, et al. Nab-Paclitaxel and Gemcitabine as First-line Treatment of Advanced or Metastatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(12):1707–1712. doi:10.1001/jamaoncol.2018.3277.
12. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
13. Hematology/Oncology Pharmacy Association (2019). Intravenous Cancer Drug Waste Issue Brief. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
14. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
15. 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.

16. Kottschade LA, Suman VJ, Amatruda T 3rd, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma : a North Central Cancer Treatment Group Study, N057E(1). Cancer. 2011 Apr 15;117(8):1704-10.
17. Overman MJ, Adam L, Raghav K, et al. Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol. 2018 Jan 1;29(1):139-144.
18. Aldrich JD, Raghav KPS, Varadhachary GR, et al. Retrospective Analysis of Taxane-Based Therapy in Small Bowel Adenocarcinoma. Oncologist. 2019 Jun;24(6):e384-e386.
19. Fortino S, Santoro M, Luliano E, et al. Treatment of Kaposi's Sarcoma (KS) with nab-paclitaxel. Ann Oncol 2016;27:suppl_4: iv124.
20. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms 2.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2021.
21. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer, Version 4.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.
22. Benigno BB, Burrell MO, Daugherty P, et al. A phase II nonrandomized study of nab-paclitaxel plus carboplatin in patients with recurrent platinum-sensitive ovarian or primary peritoneal cancer. DOI: 10.1200/jco.2010.28.15_suppl.5011 *Journal of Clinical Oncology* 28, no. 15_suppl (May 20, 2010) 5011-5011.
23. Coleman RL, Brady WE, McMeekin DS, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol. 2011 Jul;122(1):111-5. doi: 10.1016/j.ygyno.2011.03.036. Epub 2011 Apr 15.
24. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16.
25. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Kaposi Sarcoma, Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.

26. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Small Bowel Adenocarcinoma, Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.
27. National Government Services, Inc. Local Coverage Article: Billing and Coding: Paclitaxel (e.g., Taxol®/Abraxane™) (A52450). Centers for Medicare & Medicaid Services, Inc. Updated on 04/23/2021 with effective date of 05/01/2021. Accessed May 2021.

VIII. References (ENHANCED)

1e. 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 Jul;14(8):769-76.
2e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer, Version 4.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.
3e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.
4e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pancreatic Adenocarcinoma, Version 2.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.
5e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma: Cutaneous, Version 2.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.

6e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma: Uveal, Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.

7e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatobiliary Cancers, Version 2.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2021.

8e. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003 Feb 15;21(4):588-92.

9e. Jones SE, Erban J, Overmoyer B, et al. Randomized Phase III Study of Docetaxel Compared With Paclitaxel in Metastatic Breast Cancer. Journal of Clinical Oncology 2005 23:24, 5542-5551.

10e. 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;33(6):594-601.

11e. Twelves C, Awada A, Cortes J, et al. Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer (Auckl). 2016;10:77-84. Published 2016 Jun 28. doi:10.4137/BCBCR.S39615.

12e. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol. 2015;33(21):2361-9.

13e. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004 Mar;40(4):536-42.

14e. Blackstein M, Vogel CL, Ambinder R, et al. Gemcitabine as first-line therapy in patients with metastatic breast cancer: a phase II trial. Oncology. 2002;62(1):2-8.

15e. Martín M, Ruiz A, Muñoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007 Mar;8(3):219-25.

16e. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2011;366(2):109-19.

17e. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.

18e. 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. Journal of Clinical Oncology 2006 24:18, 2786-2792.

19e. Andersson M, Lidbrink E, Bjerre K, et al. Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab With Vinorelbine Plus Trastuzumab As First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The HERNATA Study. Journal of Clinical Oncology 2011 29:3, 264-271.

20e. Anthony Ellis P, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. Journal of Clinical Oncology 2015 33:15_suppl, 507-507.

21e. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.

22e. Mirtsching, Barry, Cosgriff T, Harker G, et al. A Phase II Study of Weekly Nanoparticle Albumin-Bound Paclitaxel With or Without Trastuzumab in Metastatic Breast Cancer. Clinical Breast Cancer 2011 11:2, 121 – 128.

23e. 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 Mar;17(3):345-56. doi: 10.1016/S1470-2045(15)00542-2. Epub 2016 Feb 8.

24e. Loibl S, Jackisch C, Schneeweiss A, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Annals of Oncology 2017 28:3, 497–504.

25e. Gianni L, Mansutti M, Anton A, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. JAMA Oncol. 2018 Mar 1;4(3):302-308. doi: 10.1001/jamaoncol.2017.4612.

26e. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. N Engl J Med 2018; 379:2040-2051.

27e. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med 2018; 378:2078-2092.

28e. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018; 378:2288-2301

29e. Sandler A, Gray R, Perry MC, et al. Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. N Engl J Med 2006; 355:2542-2550.

30e. Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. J Allergy Clin Immunol. 2016 Apr;137(4):1154-1164.e12. doi: 10.1016/j.jaci.2015.

31e. 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 Aug 15;21(16):3016-24. Epub 2003 Jul 1.

32e. 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 07861. J Clin Oncol. 1990 Sep;8(9):1556-62.

33e. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003;98:542–53.

34e. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Annals of Oncology 2007 18:2, 317–323.

35e. 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 II Trial. Clin Cancer Res January 15 2005; 11(2); 690-696.

36e. Cardenal F, López-Cabrerizo MP, Antón A,et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 1999 Jan;17(1):12-8.

37e. 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. Journal of Clinical Oncology 2008 26:21, 3543-3551.

38e. Schiller JH, Harrington D, Belani CP, et al. Comparison of Four Chemotherapy Regimens for Advanced Non–Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

39e. 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. Annals of Oncology, Volume 16, Issue 4, 1 April 2005, 602–610.

40e. Tan EH, Szczesna A, Krzakowski M, 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.

41e. 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). Journal of Clinical Oncology 2013 31:24, 3004-3011.

42e. 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.

43e. 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. Annals of Oncology, Volume 17, Issue 8, 1 August 2006, 1263–1268.

44e. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.

45e. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-35.

46e. 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. 2016 Apr 9;387(10027):1540-50.

47e. Barlesi F, Park K, Ciardiello F, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC. Annals of Oncology, Volume 27, Issue suppl_6, 1 October 2016, LBA44_PR.

48e. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000 May;18(10):2095-103.

49e. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000 Jun;18(12):2354-62.

50e. Hanna N, Shepherd FA, Fossella FV, et al. Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy. Journal of Clinical Oncology 2004 22:9, 1589-1597.

51e. 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. British Journal of Cancer (2000) 83(4), 447–453.

52e. 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. Journal of Clinical Oncology 2006 24:29, 4699-4707.

53e. 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. Journal of Clinical Oncology 2010 28:20, 3323-3329.

54e. 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.

55e. 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;30(17):2039-45.

56e. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(6):779-791.

57e. 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.

58e. Rose PG, Blessing JA, Mayer AR, et al. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 1998 Feb;16(2):405-10.

59e. Gordon AN, Tonda M, Sun S, et al. 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.

60e. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001 Jul 15;19(14):3312-22.

61e. 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. Journal of Clinical Oncology 2007 25:19, 2811-2818.

62e. Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III Trial of Gemcitabine Compared With Pegylated Liposomal Doxorubicin in Progressive or Recurrent Ovarian Cancer. Journal of Clinical Oncology 2008 26:6, 890-896.

63e. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial. Journal of Clinical Oncology 2014 32:13, 1302-1308.

64e. 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.

65e. Markman M, Blessing J, Rubin SC, 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. Epub 2005 Dec 2.

66e. 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.

67e. Burger RA, Sill MW, Monk BJ, et al. Phase II Trial of Bevacizumab in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study. Journal of Clinical Oncology 2007 25:33, 5165-5171.

68e. Katz MH, Shi Q, Ahmad SA, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg. 2016;151(8):e161137.

69e. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med 2011; 364:1817-1825.

70e. Moore MJ, 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. Journal of Clinical Oncology 2007 25:15, 1960-1966.

71e. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997 Jun;15(6):2403-13.

72e. Portal A, Pernot S, Tougeron D, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer. 2015;113(7):989-95.

73e. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-413.

74e. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.

75e. Larkin J, Del Vecchio M, Ascierto PA, et al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. Lancet Oncol. 2014 Apr;15(4):436-44.

76e. Ascierto PA, Minor D, Ribas A, et al. Phase II Trial (BREAK-2) of the BRAF Inhibitor Dabrafenib (GSK2118436) in Patients With Metastatic Melanoma. Journal of Clinical Oncology 2013 31:26, 3205-3211.

77e. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372:2521-2532.

78e. Agarwala SS, Keilholz U, Hogg D, et al. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma. Journal of Clinical Oncology 2007 25:18_suppl, 8510-8510.

79e. 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.

80e. 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.

81e. Einzig AI, Hochster H, Wiernik PH, et al. A phase II study of taxol in patients with malignant melanoma. Invest New Drugs. 1991 Feb;9(1):59-64.

82e. Kottschade LA, McWilliams RR, Markovic SN,et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. Melanoma Res. 2016 Jun;26(3):300-3.

83e. Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. Cancer. 2016;122(21):3344-3353.

84e. Piulats Rodriguez JM, De La Cruz Merino L, Espinosa E, et al. Phase II multicenter, single arm, open label study of Nivolumab in combination with Ipilimumab in untreated patients with metastatic uveal melanoma. Annals of Oncology (2018) 29 (suppl_8): viii442-viii466.

85e. Zimmer L, Vaubel J, Mohr P, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. PLoS One. 2015;10(3):e0118564. Published 2015 Mar 11. doi:10.1371/journal.pone.0118564.

86e. Bedikian AY, Papadopoulos N, Plager C, et al. Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma Res. 2003 Jun;13(3):303-6.

87e. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015-1026.

88e. Rosenberg JE, Hoffman-Censits J, Powles T, 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):1909-20.

89e. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017 Mar;18(3):312-322.

90e. 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.

91e. 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.

92e. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018 Jan;19(1):51-64.

93e. 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 Jul;34(8):1208-12.

94e. Meluch AA, Greco FA, Burris HA 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol. 2001 Jun 15;19(12):3018-24.

95e. 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. Journal of Clinical Oncology 2000 18:17, 3068-3077.

96e. 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 May;15(5):1853-7.

97e. Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol. 2002 Feb 15;20(4):937-40.

98e. Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. Lancet. 2017 Nov 18;390(10109):2266-2277.

99e. Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. Journal of Clinical Oncology 2006 24:21, 3451-3457.

100e. 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 Feb;15(2):589-93.

101e. Siefker-Radtke AO, Dinney CP, 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. 2012;119(3):540-7.

102e. Sternberg CN, de Mulder PH, 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 versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001 May 15;19(10):2638-46.

103e. Miller D, Filiaci V, Gleming G, et al. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecologic Oncology 2012;125(3):771-3.

104e. Fleming GF, Brunetto VL, Cella D, et al. Phase III Trial of Doxorubicin Plus Cisplatin With or Without Paclitaxel Plus Filgrastim in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. Journal of Clinical Oncology 2004 22:11, 2159-2166

105e. 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 May 1;20(9):2360-4.

106e. Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1–Positive Endometrial Cancer: Results From the KEYNOTE-028 Study. Journal of Clinical Oncology 2017 35:22, 2535-2541.

107e. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011;29(16):2259-65.

108e. 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(24):3278-85.

109e. 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. Journal of Clinical Oncology 2007 25:5, 526-531.

110e. Rose PG, Ali S, Moslemi-Kebria M, et al. Paclitaxel, Carboplatin, and Bevacizumab in Advanced and Recurrent Endometrial Carcinoma. Int J Gynecol Cancer. 2017 Mar;27(3):452-458.

111e. Northfelt DW, Dezube BJ, Thommes JA, et al. Efficacy of pegylated-liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy. J Clin Oncol. 1997 Feb;15(2):653-9.

112e. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for Symptomatic Kaposi's Sarcoma in People With and Without HIV Infection: A Phase I/II Study. J Clin Oncol. 2016;34(34):4125-4131.

113e. Stebbing J, Wildfire A, Portsmouth S, et al. Paclitaxel for anthracycline-resistant AIDS-related Kaposi's sarcoma: clinical and angiogenic correlations. Ann Oncol. 2003 Nov;14(11):1660-6.

114e. Uldrick TS, Wyvill KM, Kumar P, et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol. 2012;30(13):1476-83.

115e. Evans SR, Krown SE, Testa MA, et al. Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: an AIDS Clinical Trials Group clinical study. J Clin Oncol. 2002 Aug 1;20(15):3236-41.

116e. Busakhala NW, Waako PJ, Strother MR, et al. Randomized Phase IIA Trial of Gemcitabine Compared With Bleomycin Plus Vincristine for Treatment of Kaposi's Sarcoma in Patients on Combination Antiretroviral Therapy in Western Kenya. J Glob Oncol. 2018;4(4):1-9.

117e. Koon HB, Krown SE, Lee JY, et al. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. J Clin Oncol. 2013;32(5):402-8.

118e. Shepherd FA, Beaulieu R, Gelmon K, et al. Prospective randomized trial of two dose levels of interferon alfa with zidovudine for the treatment of Kaposi's sarcoma associated with human immunodeficiency virus infection: a Canadian HIV Clinical Trials Network study. J Clin Oncol. 1998 May;16(5):1736-42.

119e. Little RF, Wyvill KM, Pluda JM, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol. 2000 Jul;18(13):2593-602.

120e. Nasti G, Errante D, Talamini R, et al. Vinorelbine is an effective and safe drug for AIDS-related Kaposi's sarcoma: results of a phase II study. J Clin Oncol. 2000 Apr;18(7):1550-7.

121e. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81.

122e. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol. 2005 Apr 1;23(10):2332-8.

123e. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med 2018; 379:2108-2121.

124e. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016; 375:1823-1833.

125e. Zaanan A, Gauthier M, Malka D, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer. 2011 Apr 1;117(7):1422-8. doi: 10.1002/cncr.25614.

126e. Suenaga M, Mizunuma N, Chin K, et al. Chemotherapy for small-bowel Adenocarcinoma at a single institution. Surg Today. 2009;39(1):27-31. doi: 10.1007/s00595-008-3843-2.

127e. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. N Engl J Med 2018; 378:731-739.

128e. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol. 2018;29(8):1763–1770. doi:10.1093/annonc/mdy201.

129e. Mavroudis D, Papakotoulas P, Ardavanis A, et al. Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. Ann Oncol. 2010 Jan;21(1):48-54. doi: 10.1093/annonc/mdp498.

130e. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008 Aug 20;26(24):3950-7. doi: 10.1200/JCO.2007.11.9362.

131e. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jul;20(7):924-937. doi: 10.1016/S1470-2045(19)30167-6.

132e. Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). Ann Oncol. 2019;30(5):766-773. doi:10.1093/annonc/mdz061.

133e. Spigel D et al. IMpower110: Interim OS Analysis of a Phase III Study of Atezolizumab (atezo) vs Platinum-Based Chemotherapy (chemo) as 1L Treatment (tx) in PD-L1–selected NSCLC [ESMO 2019 Abstract LBA78].

134e. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828. doi: 10.1016/S0140-6736(20)32531-9.

135e. Reid EG, Suazo A, Lensing SY, et al. Pilot Trial AMC-063: Safety and Efficacy of Bortezomib in AIDS-associated Kaposi Sarcoma. Clin Cancer Res. 2020;26(3):558-565. doi:10.1158/1078-0432.CCR-19-1044.

136e. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet. 2021 Feb 13;397(10274):592-604.

137e. Magellan Health, Magellan Rx Management. Abraxane Clinical Literature Review Analysis. Last updated May 2021. Accessed May 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C24.1	Malignant neoplasm of ampulla of Vater
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of the pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas

ICD-10	ICD-10 Description
C25.9	Malignant neoplasm of pancreas, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant neoplasm of right ear and external auricular canal
C43.22	Malignant neoplasm of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified parts of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin

ICD-10	ICD-10 Description
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast

ICD-10	ICD-10 Description
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast

ICD-10	ICD-10 Description
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): 6, K	**NCD/LCD/LCA Document (s):** A52450
https://www.cms.gov/medicare-coverage-database/new-search/search-results.aspx?keyword=a52450&areaId=all&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; pCR = pathological complete response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; OR = odds ratio; AE = adverse event; QoL = quality of life; TTF = time to treatment failure; TNBC = triple negative breast cancer

Breast Cancer

HER2-negative recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Doxorubicin	2A preferred	Yes	Phase 3	Paclitaxel vs. doxorubicin + paclitaxel (AT)	----------	First-line	• Doxorubicin and paclitaxel have similar activity • Combination of doxorubicin + paclitaxel resulted superior ORR and TTF however, did not improve survival compared to single agent therapy
Docetaxel	2A other	Yes	Phase 3, randomized, controlled, multicenter, open-label	Paclitaxel	ORR Toxicity	Second-line therapy for metastatic breast cancer or progression within 12 months of adjuvant or neoadjuvant therapy (prior anthracycline therapy required)	• Docetaxel was superior to paclitaxel in terms of OS and TTP • Hematologic and non-hematologic toxicities occurred more frequently in the docetaxel group
Eribulin	2A preferred	Yes (After 2 or more chemotherapy regimens for metastatic	Phase 3, randomized	Capecitabine	OS and PFS	First-, second-, or third-line therapy for metastatic disease (in patients with prior	• Overall, eribulin was not shown to be superior to capecitabine with regard to OS or PFS

		disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.)	Subgroup analysis			anthracycline- and taxane-based therapy)	• In HER2-negative and triple-negative disease, OS advantage was observed with eribulin over capecitabine
Nab-paclitaxel (no premedication)	2A other	Yes (after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy)	Phase 3, 1:1, randomized, open-label	Paclitaxel (with premedication)	ORR	All lines of therapy for metastatic disease (59% after at least one prior therapy; 77% with prior exposure to anthracycline)	• Nab-paclitaxel demonstrated greater efficacy in ORR and a favorable safety profile compared with standard paclitaxel • No statistically significant difference was observed in first-line patients however, the difference was statistically significant in patients who received nab-paclitaxel as second-line or greater therapy.
Nab-paclitaxel + bevacizumab	2A certain circumstances	Yes	Phase 3, randomized	Ixabepilone + bevacizumab vs. paclitaxel + bevacizumab	PFS	First-line	• PFS and OS for nab-paclitaxel was not superior to paclitaxel with a trend toward inferiority • Toxicity was increased for nab-paclitaxel
Nab-paclitaxel (300 mg/m^2 q3w, 100 mg/m^2 weekly, or 150 mg/m^2 weekly)	2A other	Yes (after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy)	Phase 2, open-label, randomized	Docetaxel	ORR	First-line for metastatic disease	• Weekly nab-paclitaxel demonstrated superior efficacy and safety compared with docetaxel with a statistically significantly prolongation of PFS

Capecitabine	2A preferred	Yes (after paclitaxel/ anthracycline-containing regimens or resistant to paclitaxel and not a candidate for anthracycline)	Phase 2, open-label	N/A	ORR	Pretreated with anthracycline and taxane	• Capecitabine demonstrated clinical activity with an ORR of 28% in patients with prior anthracycline and taxane therapy.
Gemcitabine	2A	No	Phase 2	N/A	---------	First-line	• Single-agent gemcitabine is active with an ORR of 37.1% and well tolerated as first-line treatment in patients with metastatic breast cancer
Vinorelbine + gemcitabine	None	No	Phase 3 (GEICAM), multicenter, open-label, randomized	Vinorelbine	PFS	Subsequent therapy after previous anthracycline and taxane treatment	• Patients with metastatic breast cancer assigned gemcitabine and vinorelbine had better progression-free survival compared with those assigned vinorelbine alone. However, this finding did not translate into a difference in overall survival.
Nab-paclitaxel + atezolizumab	1 preferred first-line 2A subsequent therapy	Yes (for PD-L1-positive triple negative breast cancer; PD-L1 ≥1% on tumor infiltrating cells)	Phase 3 (IMpassion130), randomized	Nab-paclitaxel + placebo	PFS OS	Treatment naïve metastatic TNBC	• Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup.
Nab-paclitaxel + pembrolizumab	1 preferred first-line 2A subsequent therapy	Yes for PD-L1 (CPS ≥10) TNBC	Phase 3 (KEYNOTE-355), randomized, double-blind	Placebo + chemotherapy (nab-paclitaxel; paclitaxel; or	PFS	First-line; ≥6 months disease free interval	• Pembrolizumab combined with several chemotherapy partners showed a statistically significant and clinically meaningful improvement in PFS versus

				gemcitabine plus carboplatin)			chemotherapy alone in patients with previously untreated locally recurrent inoperable or metastatic TNBC whose tumors expressed PD-L1 (CPS ≥10). Pembrolizumab plus chemotherapy was generally well tolerated, with no new safety concerns.
Nab-paclitaxel + carboplatin (nab-P/C)	2A certain circumstances	Yes (after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy)	Phase 2/3 (tnAcity), multi-center, open-label, randomized, study	Nab-paclitaxel + gemcitabine (nab-P/G) vs. gemcitabine + carboplatin (G/C)	PFS	First-line	• First-line nab-paclitaxel + carboplatin was active in mTNBC and resulted in a significantly longer PFS compared to nab-paclitaxel + gemcitabine and gemcitabine + carboplatin.
Docetaxel + capecitabine (DC)	2A certain circumstances	No	Phase 3, randomized	Docetaxel + epirubicin (DE)	TTP	First-line	• Docetaxel plus either capecitabine or epirubicin have similar efficacy but different toxicity.
Gemcitabine + paclitaxel (GT)	2A certain circumstances	No	Phase 3, randomized	Paclitaxel	OS	Relapsed after adjuvant anthracyclines	• Gemcitabine added to paclitaxel demonstrated a statistically significant improvement in OS and TTP compared to paclitaxel alone for women with advanced breast cancer who previously received anthracyclines.
HER2-positive recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pertuzumab+ trastuzumab + docetaxel	1 preferred	Yes	Phase 3 (CLEOPATRA), randomized, double-blind, placebo-controlled Second interim analysis	Docetaxel + trastuzumab+ placebo	PFS	First-line in metastatic breast cancer (patients with prior adjuvant or neoadjuvant therapy, with or without trastuzumab, must have an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer)	• Pertuzumab group significantly prolonged PFS and OS
Pertuzumab+ trastuzumab + docetaxel (or paclitaxel or nab-paclitaxel)	1 preferred with docetaxel or paclitaxel 2A with nab-paclitaxel	Yes	Phase 3 (PERUSE), multi-center, single-arm	N/A	Safety	No prior systemic therapy except endocrine therapy for locally recurrent or metastatic breast cancer	• Preliminary findings from PERUSE suggest that the safety and efficacy of first-line pertuzumab, trastuzumab and taxane (including nab-paclitaxel) for HER2-positive locally recurrent or metastatic breast cancer are consistent with results from CLEOPATRA.
Trastuzumab+ paclitaxel	2A	Yes	Phase 3, randomized, multicenter	Trastuzumab+ paclitaxel + carboplatin	ORR	First-line for metastatic disease (taxane not used in neoadjuvant or adjuvant therapy)	• Trastuzumab+ paclitaxel + carboplatin improved ORR and PFS • Trend toward improved OS with trastuzumab+ paclitaxel +

							carboplatin however, not statistically significant • Increased rates of neutropenia was associated with TPC
Trastuzumab+ vinorelbine	2A	No	Phase 3 (HERNATA), randomized	Trastuzumab+ docetaxel	TTP	First-line	• Neither arm demonstrated significant improvement in survival • However, vinorelbine combination was better tolerated than trastuzumab+ docetaxel
Ado- trastuzumab emtansine (T-DM1)	2A	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy)	Phase 3 (MARIANNE), randomized	(Docetaxel or paclitaxel)+ trastuzumab vs T-DM1 + pertuzumab (T-DM1 + P)	PFS Safety	First-line therapy in locally advanced or metastatic breast cancer with ≥ 6-month treatment-free interval since completion of adjuvant therapy	• No significant difference in PFS • T-DM1 is an effective and tolerable alternative first-line treatment for HER2-positive metastatic breast cancer
Ado- trastuzumab emtansine (T-DM1)	2A	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease	Phase 3 (EMILIA), randomized, open-label	Lapatinib+ capecitabine	PFS OS Safety	Previous treatment with trastuzumab and a taxane (in any setting) • First-line with progression within 6-months after adjuvant therapy	• T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane

		recurrence during or within 6 months of completing adjuvant therapy)				• Second-line therapy or later for locally advanced or metastatic disease	
Nab-paclitaxel +/- trastuzumab	2A	No	Phase 2, open-label multicenter	N/A	ORR	First-line	• Nab-paclitaxel demonstrated clinical activity with an ORR of 42%, particularly in patients with HER2-positive disease (ORR 52.4%)
Neoadjuvant Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel followed by epirubicin + cyclophosphamide (concurrent trastuzumab + pertuzumab for HER2-positive disease)	----------	No	Phase 3 (GeparSepto), randomized, 1:1	Paclitaxel followed by epirubicin + cyclophosphamide (concurrent trastuzumab + pertuzumab for HER2-positive disease)	pCR	Neoadjuvant	• Nab-paclitaxel improved pCR rates compared to standard paclitaxel but is associated with greater toxicity
Nab-paclitaxel (followed by anthracycline)	----------	No	Phase 3 (ETNA), multicenter, open-label	Paclitaxel (followed by anthracycline)	pCR	Neoadjuvant	• Improved rate of pCR after nab-paclitaxel was not statistically significant • Nab-paclitaxel was associated with higher incidence of severe neuropathy

Non-Small Cell Lung Cancer

First-line therapy in patients with recurrent, advanced, or metastatic disease and squamous cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel (or paclitaxel) + pembrolizumab + carboplatin	1 preferred	No	Phase 3 (KEYNOTE-407), double-blind, randomized (1:1)	Nab-paclitaxel (or paclitaxel) + carboplatin + placebo	OS PFS	First-line	• In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone regardless of PD-L1 expression • No difference between paclitaxel or nab-paclitaxel was observed
Pembrolizumab	1 preferred (if PD-L1 ≥50%) 2B (if PD-L1 1%-49%)	Yes	Phase 3 (KEYNOTE-024), open-label, randomized	Platinum-based chemotherapy	PFS	First-line	• In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy
Atezolizumab	1 preferred for PD-L1 ≥50%	Yes for TC ≥50% or IC ≥10%	Phase 3 (IMpower110), randomized, open-label	Carboplatin or cisplatin + pemetrexed (non-squamous) or gemcitabine (squamous)	OS	First-line	• IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful improvement as first-line therapy in patients with TC ≥50% or IC ≥10%.

Nab-paclitaxel + carboplatin	1 certain circumstances (for PS 0-1) 2A other (for PS 2)	Yes (for patients who are not candidates for curative surgery or radiation)	Phase 3, randomized (1:1) – FDA approval	Paclitaxel + carboplatin	ORR	First-line	• Nab-paclitaxel resulted in a significantly improved ORR versus paclitaxel • No significant difference was observed in PFS or OS • Nab-paclitaxel also produced less grade ≥ 3 adverse events than paclitaxel.
Nab-paclitaxel + carboplatin	1 certain circumstances (for PS 0-1) 2A other (for PS 2)	Yes (for patients who are not candidates for curative surgery or radiation)	Phase 1/2, open-label, single-arm	N/A	----------	First-line	• Nab-paclitaxel 125 mg/m^2 administered on days 1, 8, and 15 of a 28-day cycle was well tolerated and demonstrated encouraging single-agent activity with an ORR of 30%/
Carboplatin + docetaxel (DCb) or Cisplatin + docetaxel (DC)	1 certain circumstances (for PS 0-1) 2A other (for PS 2)	No	Phase 3 (TAX 326), randomized, multinational	Cisplatin + vinorelbine (VC)	----------	First-line	• DC resulted in a more favorable ORR and OS rate than VC. Both DC and DCb were better tolerated and provided patients with consistently improved QoL compared with VC. These findings demonstrate that a docetaxel plus platinum combination is an effective treatment option with a favorable therapeutic index for first-line treatment of advanced or metastatic NSCLC.
Carboplatin + etoposide	1 certain circumstances (for adeno-carcinoma only; PS 0-1)	No	Randomized trial	Cisplatin + etoposide	----------	----------	• Carboplatin + etoposide is less active than cisplatin + etoposide and less toxic

	2A other (for PS 2)						
Carboplatin + gemcitabine (GC)	1 certain circumstances (for PS 0-1) 2A other (for PS 2)	No	Phase 3, randomized	Mitomycin + ifosfamide + cisplatin (MIC) or mitomycin + vinblastine + cisplatin (MVP)	OS	First-line	• The results of the current study failed to demonstrate any difference in efficacy between the newer regimen of GC and the older regimens of MIC and MVP
Carboplatin + paclitaxel (TC)	1 certain circumstances (for PS 0-1) 2A other (for PS 2)	No	Phase 3, randomized	Cisplatin + irinotecan (IP) vs. cisplatin + gemcitabine (GP) vs. cisplatin + vinorelbine (NP)	OS	First-line	• The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Cisplatin + etoposide	1 certain circumstances (for PS 0-1)	No	Phase 3, randomized	Cisplatin + gemcitabine	ORR	First-line	• Compared with etoposide-cisplatin, gemcitabine-cisplatin provides a significantly higher response rate and a delay in disease progression
Cisplatin + gemcitabine	1 certain circumstances (for PS 0-1)	Yes	Phase 3, randomized	Cisplatin + pemetrexed	OS	First-line	• Cisplatin + pemetrexed provides similar efficacy to cisplatin + gemcitabine, with better tolerability
Cisplatin + paclitaxel	1 certain circumstances (for PS 0-1)	Yes	Randomized comparison study	Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + paclitaxel	OS	First-line	• None of four chemotherapy regimens offered a significant advantage over the others in the treatment of advanced non-small-cell lung cancer

Gemcitabine + docetaxel (GD)	1 certain circumstances (for PS 0-1) 2A certain circumstances (for PS 2)	No	Phase 3, multicenter, randomized	Cisplatin + vinorelbine (CV)	PFS	First-line	• There was no advantage in PFS with GD compared with CV; however, the CV regimen had higher rate of toxic events, mainly myelosuppression
Gemcitabine + vinorelbine (VG)	1 certain circumstances (for PS 0-1) 2A certain circumstances (for PS 2)	No	Randomized study	Carboplatin + vinorelbine (VC)	ORR	First-line	• VG compared to VC resulted in a similar overall response rate, favorable median survival and a better toxicity profile
Docetaxel	2A certain circumstances (for PS 2)	No	References in NCCN are for subsequent therapy				
Gemcitabine	2A certain circumstances (for PS 2)	No	Phase 2	N/A	----------	First-line	• Single-agent gemcitabine is active in advanced NSCLC with an ORR of 21.1% and is well-tolerated
Nab-paclitaxel	2A certain circumstances (for PS 2)	No	Phase 2, multicenter	N/A	ORR	First-line	• Abraxane administered without premedication was well tolerated. An ORR of 16% and prolonged disease control rates were documented.
Paclitaxel (or carboplatin)	2A certain circumstances (for PS 2)	No	References in NCCN are for subsequent therapy				
Pemetrexed	2A certain circumstances (for adeno-	No	Reference in NCCN are for subsequent therapy				

	carcinoma only; PS 2)						
First-line therapy in patients with recurrent, advanced, or metastatic disease and with PD-L1 ≥ 50% and EGFR, ALK negative and NON-squamous cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	• **Conclusion**
Atezolizumab + carboplatin + nab-paclitaxel, followed by maintenance atezolizumab	2A other	Yes	Phase 3 (IMpower130), randomized, multi-center, open-label	Carboplatin + paclitaxel	PFS OS	First-line for stage IV disease	• IMpower130 showed a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no ALK or EGFR mutations.
Pembrolizumab	1 preferred (if PD-L1 ≥50%) 2B (if PD-L1 1%-49%)	Yes	Phase 3 (KEYNOTE-024), open-label, randomized	Platinum-based chemotherapy	PFS	First-line	• In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy
Atezolizumab	2A preferred for PD-L1 ≥50%	Yes for TC ≥50% or IC ≥10%	Phase 3 (IMpower110), randomized, open-label	Carboplatin or cisplatin + pemetrexed (non-squamous) or gemcitabine (squamous)	OS	First-line	• IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful improvement as first-line therapy in patients with TC ≥50% or IC ≥10%.

Cemiplimab-rwlc	1 preferred for PD-L1 ≥50%	Yes for TPS ≥50%	Phase 3 (EMPOWER-Lung 1), randomized, multi-center, open-label, controlled	Platinum-doublet chemotherapy	OS PFS	First-line	• Cemiplimab monotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in patients with advanced non-small-cell lung cancer with PD-L1 of at least 50%.
Pembrolizumab + carboplatin (or cisplatin) + pemetrexed	1 preferred (for adeno-carcinoma only; PS 0-1)	Yes	Phase 3 (KEYNOTE-189), double-blind, randomized (2:1)	Carboplatin (or cisplatin) + pemetrexed + placebo	OS PFS	First-line	• In patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone
Atezolizumab + carboplatin + paclitaxel + bevacizumab (ABCP)	1 other (for adeno-carcinoma only; PS 0-1)	Yes	Phase 3 (IMpower150), open-label, randomized (1:1:1)	Atezolizumab + carboplatin + paclitaxel (ACP) vs. bevacizumab + carboplatin + paclitaxel (BCP)	PFS	First-line	• The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status
Bevacizumab + carboplatin + paclitaxel	1 certain circumstances (for adeno-carcinoma only; PD-L1 <1%; PS 0-1)	Yes	Phase 2/3 (ECOG 4599), randomized	Carboplatin + paclitaxel	OS	First-line	• The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non-small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths

Bevacizumab + carboplatin + pemetrexed	2A certain circumstances (for adeno-carcinoma only; PS 0-1)	No	Phase 3, randomized	Carboplatin + pemetrexed	OS	First-line	• The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non-small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A certain circumstances (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (AVAPERL [MO22089]), randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab + pemetrexed maintenance	PFS	First-line	• In patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone
Carboplatin + pemetrexed (PemCb)	1 certain circumstances (for adeno-carcinoma only; PS 0-1) 2A preferred(for PS 2)	No	Phase 2, multicenter, randomized	Pemetrexed + oxaliplatin (PemOx)	ORR	First-line	• Combining pemetrexed with either oxaliplatin or carboplatin demonstrated similar efficacy measures for the first-line treatment of locally advanced or metastatic NSCLC
Cisplatin + pemetrexed	1 certain circumstances (for adeno-carcinoma only; PS 0-1)	Yes	Phase 3, randomized	Cisplatin + gemcitabine	OS	First-line	See data for cisplatin + gemcitabine above
Generic regimens	1 or 2A	See squamous cell histology above					
Subsequent therapy in patients with recurrent, advanced, or metastatic disease							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Nab-paclitaxel	2A (for PS 2)	No	No data in subsequent therapy				
Nab-paclitaxel + carboplatin	1 (for PS 0-1) 2A (for PS 2)	No	No data in subsequent therapy				
Nab-paclitaxel + pembrolizumab + carboplatin	1 preferred (for PS 0-1 and squamous cell histology)	No	No data in subsequent therapy				
Nab-paclitaxel + pembrolizumab + cisplatin	2A (for PS 0-1 and squamous cell histology)	No	No data in subsequent therapy				
Nivolumab	1 (for first progression) 2A (for subsequent progression)	Yes	Phase 3 (CHECKMATE 057), randomized, open-label	Docetaxel	OS	Subsequent	• Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel
Nivolumab	1 (for first progression) 2A (for subsequent progression)	Yes	Phase 3 (CHECKMATE 017), randomized, open-label	Docetaxel	OS	Second-line	• Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level

Pembrolizumab (2mg/kg or 10mg/kg)	1 preferred (for PS 0-2; PD-L1 ≥ 1%)	Yes (after platinum therapy)	Phase 2/3 (KEYNOTE-010), randomized (1:1:1), open-label	Docetaxel	OS PFS	Previously treated	• Pembrolizumab prolongs overall survival compared to docetaxel and has a favorable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.
Atezolizumab	1 (for first progression) 2A (for subsequent progression)	Yes (after platinum therapy)	Phase 3 (OAK), open-label, multicenter randomized (1:1)	Docetaxel	OS	Second- or third-line	• Atezolizumab treatment results in a statistically significant and clinically relevant improvement in OS versus docetaxel in second- and third-line NSCLC, regardless of PD-L1 expression and histology
Ramucirumab + docetaxel	2A (first progression only)	Yes (after platinum therapy)	Phase 3 (REVEL), multicenter, double-blind, randomized (1:1)	Docetaxel + placebo	OS	Second-line after platinum-based regimen	• Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC
Docetaxel	2A (for first progression)	Yes	Prospective randomized trial	Best supportive care (BSC)	OS	Second-line or later after platinum therapy	• Treatment with docetaxel is associated with significant prolongation of survival
Docetaxel (100mg/m^2 or 75mg/m^2)	2A (for first progression)	Yes	Phase 3 (TAX 320), randomized	Vinorelbine or ifosfamide (V/I)	---------	Second-line after platinum therapy	• Single-agent docetaxel demonstrated clinical activity with an ORR of 10.8% for D100 and 6.7% for D75.
Pemetrexed	2A (for first progression; non-squamous)	Yes (non-squamous only)	Phase 3, randomized	Docetaxel	OS	Second-line	• Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in the

							second-line treatment of patients with advanced NSCLC
Gemcitabine + best supportive care	2A (for first progression)	No	Randomized multicenter trial	Best supportive care (BSC)	Change in patient assessment of a predefined subset of commonly reported symptoms (SS14) from the EORTC QLQ-C30 and LC13 scales	----------	• Patients treated with gemcitabine + BSC reported better QoL and reduced disease-related symptoms compared with those receiving BSC alone

Ovarian Cancer (Epithelial/Fallopian Tube/Primary Peritoneal)

Recurrent or persistent disease, platinum-sensitive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Carboplatin + gemcitabine	2A preferred	Yes (for patients who relapsed at least 6 months after platinum-based therapy)	Phase 3, open-label, randomized	Carboplatin	PFS	Second-line; recurrence after at least 6 months of first-line platinum-based therapy	• Gemcitabine plus carboplatin significantly improves PFS and response rate without worsening quality of life for patients with platinum-sensitive recurrent ovarian cancer
Carboplatin + liposomal doxorubicin	2A preferred	Yes (progressed or recurred after platinum-based chemotherapy)	Phase 3, randomized, multicenter	Carboplatin + paclitaxel	PFS	Second- or third-line therapy with recurrence after more than 6 months since first- or second-line platinum-based therapy	• Carboplatin + liposomal doxorubicin demonstrated superiority in PFS compared to carboplatin + paclitaxel.
Carboplatin + paclitaxel	2A preferred	Yes	Phase 3 (ICON4/AGO-OVAR-2.2),	Platinum-based chemotherapy	----------	Second-line or later; relapsing after 6 months of being treatment-free	• Paclitaxel plus platinum chemotherapy trended towards improvement in survival and PFS among patients with relapsed

			randomized, multicenter				platinum-sensitive ovarian cancer compared with conventional platinum-based chemotherapy
Carboplatin + gemcitabine + bevacizumab, followed by bevacizumab until progression	2A preferred	Yes	Phase 3 (OCEANS), randomized, multicenter, blinded, placebo-controlled	Carboplatin + gemcitabine + placebo	PFS	Second-line; recurrence after at least 6 months of first-line platinum-based therapy	• Carboplatin, gemcitabine, plus bevacizumab followed by bevacizumab until progression resulted in a statistically significant improvement in PFS compared with carboplatin, gemcitabine, plus placebo
Carboplatin + paclitaxel + bevacizumab	2A preferred	Yes	Phase 3 (GOG-0213), multicenter, open-label, randomized	Carboplatin + paclitaxel	OS	Second-line or later; relapsing after 6 months of being treatment-free	• The addition of bevacizumab to standard chemotherapy, followed by maintenance therapy until progression, improved the median OS in patients with platinum-sensitive recurrent ovarian cancer, although not statistically significant
Nab-paclitaxel + carboplatin	2A (for clinical relapse and patients with taxane hypersensitivity)	No	Phase 2, non-randomized	N/A	ORR	Recurrent disease in platinum-sensitive disease (after prior taxane/ platinum therapies)	• With a 97% disease control rate, the combination of nab-paclitaxel plus carboplatin had significant antitumor activity
Carboplatin + docetaxel	2A	No	Phase 2	N/A	ORR	Second-line or later; relapsing after 6 months of being treatment-free	• Carboplatin in combination with docetaxel is highly active with an ORR of 72.0% and well tolerated in patients with recurrent platinum-sensitive ovarian, peritoneal and tubal cancer
Nab-paclitaxel	2A	No	Phase 2	N/A	ORR	Second-line in platinum-sensitive disease	• Nab-paclitaxel is active in patients with recurrent ovarian, peritoneal, or fallopian tube

							cancer. The ORR was 64% and toxicities were manageable.
Etoposide (oral)	2A	No	Phase 2	N/A	---------	Second-line therapy	• Etoposide is active in platinum-sensitive ovarian cancer with an ORR of 26.8%
Topotecan	2A	Yes	Phase 3, randomized, multicenter	Liposomal doxorubicin	--------	Second-line or later	• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and refractory epithelial ovarian cancer by almost 7 weeks • Survival benefit is pronounced in patients with platinum-sensitive disease
Liposomal doxorubicin	2A	Yes	Phase 3, randomized	Topotecan	----------	Second-line after platinum-based therapy	• Liposomal has comparable efficacy and favorable safety profile compared to topotecan
Recurrent or persistent disease, platinum-resistant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Gemcitabine	2A preferred	No	Phase 3, centrally randomized, multicenter, open-label comparative trial	Liposomal doxorubicin	PFS	Second- to third-line; progression within 6 months of platinum-based therapy	• Gemcitabine and liposomal doxorubicin demonstrated to have comparable outcomes
Gemcitabine	2A preferred	No	Phase 3 randomized multicenter	Liposomal doxorubicin	TTP	Second-line; treatment-failure after platinum/	• Gemcitabine does not provide an advantage compared with liposomal doxorubicin in terms of TTP in ovarian cancer who

						paclitaxel-containing regimen	experience recurrence within 12 months after primary treatment
Liposomal doxorubicin	2A preferred	Yes	Phase 3, randomized	Topotecan	----------	Second-line after platinum-based therapy	• Liposomal has comparable efficacy and favorable safety profile compared to topotecan
Topotecan	2A preferred	Yes	Phase 3, randomized, multicenter	Liposomal doxorubicin	--------	Second-line or later	• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and refractory epithelial ovarian cancer by almost 7 weeks • Survival benefit is pronounced in patients with platinum-sensitive disease
Liposomal doxorubicin (or paclitaxel or topotecan) + bevacizumab	2A preferred	Yes	Phase 3 (AURELIA), open-label randomized	Paclitaxel, topotecan, or liposomal doxorubicin alone	PFS	Refractory disease with progression < 6 months after completing platinum-based therapy	• Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant
Paclitaxel + bevacizumab	2A preferred	Yes	See above (liposomal doxorubicin + bevacizumab)				
Topotecan + bevacizumab	2A preferred	No	See above (liposomal doxorubicin + bevacizumab)				
Paclitaxel + pazopanib	2A preferred	No	Phase 2 (MITO 11), randomized (1:1), open-label	Paclitaxel	PFS	Platinum-resistant or platinum-refractory ovarian cancer previously treated with a maximum of two lines of chemotherapy	• Adding pazopanib to paclitaxel for the treatment of platinum-resistant ovarian cancer demonstrated a statistically significant improvement in PFS by almost 3 months

Paclitaxel	2A preferred	Yes	Phase 2	N/A	---------	Platinum and paclitaxel-resistant ovarian cancer	• Paclitaxel demonstrated clinical activity with an ORR of 20.9%
Docetaxel	2A preferred	No	Phase 2	N/A	---------	Second-line therapy; platinum- and paclitaxel-resistant	• Docetaxel demonstrated clinical activity with an ORR of 22.4% however hematologic toxicity was significant
Etoposide (oral)	2A preferred	No	Phase 2	N/A	---------	Second-line therapy	• Etoposide is active in platinum-resistant ovarian cancer with an ORR of 26.8%
Bevacizumab	2A preferred	No	Phase 2	N/A	PFS	Second- or third-line	• Bevacizumab demonstrated clinical activity with an ORR of 21.0% in second- and third-line treatment
Nab-paclitaxel	2A	No	Phase 2	N/A	ORR	Second-line in platinum-resistant disease	• Nab-paclitaxel demonstrated clinical activity with an ORR of 23%

Pancreatic Adenocarcinoma

Neoadjuvant therapy resectable disease with high-risk features or borderline resectable							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel + gemcitabine	2A preferred	No	None. NCCN recommendation is based on clinical literature for metastatic disease.				
FOLFIRINOX	2A preferred	No	Phase 1, prospective, multicenter, single-arm trial	N/A	Accrual rate; safety; rate of completion of all preoperative	Preoperative	• Neoadjuvant therapy with FOLFIRINOX demonstrated clinical activity with 68% of patients undergoing pancreatectomy

					and operative therapy		
First-line therapy for patients with locally advanced or metastatic disease and good performance status (ECOG PS 0-2) in combination with gemcitabine							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel + gemcitabine	1 preferred (for metastatic disease) 2A preferred (for locally advanced disease)	Yes (for metastatic disease)	Phase 3 (MPACT), open-label, randomized	Gemcitabine	OS	First-line	• In patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved OS, PFS, and response rate, but rates of peripheral neuropathy and myelosuppression were increased
FOLFIRINOX	1 preferred (for metastatic disease, good performance status) 2A preferred (for locally advanced disease)	No	Phase 2-3 (PRODIGE), multicenter, randomized	Gemcitabine	OS	First-line	• FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status
Gemcitabine + erlotinib	1 (for metastatic disease) 2A (for locally advanced disease)	Yes	Phase 3 (NCIC CTG PA.3), randomized (1:1), double-blind, placebo-controlled	Gemcitabine + placebo	OS	First-line for advanced or metastatic disease	• Gemcitabine + erlotinib reduced the risk of death by 18% in patients with advanced pancreatic cancer. • Modest improvement in OS (0.33mon)
Gemcitabine	1 (for metastatic disease) 2A (for locally advanced disease)	Yes	Randomized trial	Fluorouracil (5-FU)	Clinical benefit response (pain, performance status, weight)	First-line	• Gemcitabine is more effective than 5-FU in obtaining a clinical benefit response and also demonstrated a modest survival advantage over treatment with 5-FU

Second-line therapy for locally advanced or metastatic disease for patients with previous treatment with fluoropyrimidine-based therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel + gemcitabine	2A (if prior fluoropyrimidine-based therapy)	No	Prospective multicenter cohort	N/A	----------	Second-line after FOLFIRINOX failure	• Nab-paclitaxel + gemcitabine has clinical activity after FOLFIRINOX failure in patients with metastatic pancreatic adenocarcinoma
Gemcitabine	1 (for poor performance status) 2A (for good performance status)	No	Recommendation is based on evidence in first-line therapy. No clinical trial data in second-line therapy.				
Gemcitabine + erlotinib	2A	No	Recommendation is based on evidence in first-line therapy. No clinical trial data in second-line therapy.				
5-FU + leucovorin + liposomal irinotecan	2A (if no prior irinotecan)	No	No clinical trial data to support use after prior fluoropyrimidine-based therapy				
Pembrolizumab (for MSI-H or dMMR tumors)	2A	Yes	Phase 2	N/A	----------	Second-line or later	• Mismatch repair-deficient cancers, including pancreatic cancer, demonstrated sensitivity to immune checkpoint blockade with an ORR of 62%

Melanoma

Second-line or subsequent therapy for metastatic or unresectable cutaneous melanoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Nab-paclitaxel	2A	No	Phase 2	N/A	----------	Previously-treated and chemotherapy naive	• Nab-paclitaxel demonstrated activity in both previously treated and chemotherapy-naive patients with metastatic melanoma with ORR of 2.7% and 21.6%, respectively.
Nab-paclitaxel + carboplatin	2A	No	Phase 2, parallel study	N/A	ORR	Previously-treated and chemotherapy naive	• Nab-paclitaxel plus carboplatin demonstrated clinical activity in both chemo-naïve and previously treated patients (ORR 25.6% and 8.8%, respectively)
Ipilimumab + placebo	2A	Yes	Phase 3 (CA184-002), randomized (3:1:1), double-blind	Ipilimumab + gp100 peptide vaccine vs. gp100 peptide vaccine + placebo	OS	Previously treated	• Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma
Vemurafenib	2A	Yes (BRAF V600E mutation positive)	Phase 4 (BRIM-3), open-label	----------	Safety	All lines of therapy	• Vemurafenib demonstrated a PFS of 5.6 months and OS of 12.0 months in patients with advanced melanoma
Dabrafenib	2A	Yes (BRAF V600E mutation positive)	Phase 2 (BREAK-2), open-label	----------	ORR	All lines of therapy	• Dabrafenib demonstrated a PFS of 6.3 months and OS of 13.1 months in patients with metastatic melanoma
Pembrolizumab (every 2 weeks vs. every 3 weeks)	2A	Yes	Phase 3 (KEYNOTE-006), randomized, open-label	Ipilimumab	PFS OS	All lines of therapy	• Pembrolizumab prolonged PFS and OS than ipilimumab in patients with advanced melanoma

Paclitaxel + carboplatin + placebo	2A	No	Phase 3, randomized	Paclitaxel + carboplatin + sorafenib	PFS	Second-line (after dacarbazine or temozolomide-regimen)	• Addition of sorafenib to paclitaxel + carboplatin did not improve PFS or ORR in this second-line patient population
Paclitaxel + carboplatin	2A	No	Retrospective analysis	N/A	----------	Second-line	• Paclitaxel + carboplatin demonstrated clinical activity 26% partial responses and 19% having stable disease
Temozolomide	2A	No	Phase 3	Dacarbazine (DTIC)	----------	----------	• Temozolomide demonstrates efficacy equal to that of DTIC and is an oral alternative for patients with advanced metastatic melanoma
Dacarbazine	2A	Yes	See temozolomide above				
Paclitaxel (with premedication)	2A	No	Phase 2	N/A	----------	----------	• Taxol has activity in melanoma with an ORR of 14%
Metastatic or unresectable uveal melanoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel	2A	No	No clinical trial data specific for uveal melanoma				
Pembrolizumab	2A	No	Case report	N/A	----------	After prior ipilimumab therapy	• Although cohort of patients was small, treatment with pembrolizumab demonstrated to be effective in patients with metastatic uveal melanoma
PD-1 and PD-L1 inhibitor therapy (nivolumab, pembrolizumab, ipilimumab, atezolizumab)	2A	No	Retrospective study	N/A	----------	All lines of therapy	• The ORR, median PFS, and median OS were substantially lower than seen in cutaneous melanoma

Nivolumab + ipilimumab	2A	No	Phase 2 (GEM1402), multicenter, single-arm, open-label	N/A	----------	Previously untreated	• Combination of nivolumab and ipilimumab demonstrated an ORR of 12% with grade ≥ 3 adverse events occurring 54%
Ipilimumab	2A	No	Phase 2 (DeCOG-Study), multicenter	N/A	----------	Pretreated and treatment naïve	• Ipilimumab has very limited clinical activity in patient with metastatic uveal melanoma with 47% of patient having stable disease. None experienced partial or complete response.
Dacarbazine	2A	No	No clinical trial data specific for uveal melanoma				
Temozolomide	2A	No	Phase 2	N/A	----------	----------	• Temozolomide is not effective for the control of metastatic melanoma of uveal origin
Paclitaxel + carboplatin	2A	No	No clinical trial data specific for uveal melanoma				
Paclitaxel (with premedication)	2A	No	No clinical trial data specific for uveal melanoma				

Uterine Cancer (endometrial carcinoma)

Adjuvant treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Carboplatin + paclitaxel (TC)	2A preferred	No	Phase 3 (GOG 209), randomized	Cisplatin + doxorubicin + paclitaxel (TAP)	OS	Chemo-therapy naive	• Demonstrated that carboplatin + paclitaxel results in an equivalent ORR, PFS, and is less toxic
Nab-paclitaxel	2A	No	No data				
Recurrent, metastatic, or high-risk disease							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Nab-paclitaxel	2A	No	No data				
Carboplatin + paclitaxel (TC)	2A preferred	No	Phase 3 (GOG 209), randomized	Cisplatin + doxorubicin + paclitaxel (TAP)	OS	Chemo-therapy naive	• Demonstrated that carboplatin + paclitaxel results in an equivalent ORR, PFS, and is less toxic
Cisplatin + doxorubicin + paclitaxel (TAP)	2A	No	Phase 3 (GOG 177)	Cisplatin + doxorubicin (AP)	OS	Chemo-therapy naive	• TAP significantly improves ORR, PFS, and OS compared with AP
Cisplatin + doxorubicin	2A	No	Phase 3 (GOG 177)	Cisplatin + doxorubicin + paclitaxel (TAP)	OS	Chemo-therapy naive	See cisplatin + doxorubicin + paclitaxel above
Liposomal doxorubicin	2A	No	Phase 2	N/A	----------	Second-line	• Liposomal doxorubicin has only limited activity (ORR 9.5%) in pretreated advanced, recurrent endometrial cancer
Pembrolizumab	2A (for MSI-H or dMMR tumors)	Yes (for MSI-H or dMMR solid tumors that have progressed following prior treatment)	Phase 1b (KEYNOTE-028)	N/A	ORR	Second-line	• Pembrolizumab demonstrated a favorable safety profile and durable antitumor activity in a subgroup of patients with heavily pretreated advanced PD-L1-positive endometrial cancer
Bevacizumab	2A	No	Phase 2	N/A	PFS ORR	Second- or third-line	• Bevacizumab is well tolerated and active based on PFS at 6 months in recurrent or persistent endometrial cancer

Temsirolimus	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Temsirolimus demonstrated clinical activity with ORR higher in chemo-naïve patients than in chemo-treated patients
Ifosfamide + paclitaxel	1 (for carcino-sarcoma) 2A	No	Phase 3, randomized	Ifosfamide	OS	First-line	• Ifosfamide + paclitaxel significantly improved OS compared to ifosfamide alone
Carboplatin + paclitaxel + bevacizumab	2A	No	Retrospective analysis	N/A	---------	First- and second-line	• A high response rate, PFS, and OS was observed with the bevacizumab, paclitaxel, and carboplatin regimen

Hepatobiliary Adenocarcinoma (Intrahepatic/Extrahepatic Cholangiocarcinoma)

Primary therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel + gemcitabine	2A	No	Phase 2, single-arm	N/A	6-mon PFS rate	First-line	• This study did not meet its primary efficacy endpoint of a 6-month PFS rate of 70%. 6-month PFS rate was 61%.
Gemcitabine + cisplatin	1	No	Phase 3 (ABC-02), multi-center	Gemcitabine	OS	First-line	• As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity.
Gemcitabine + capecitabine	2A	No	Phase 2	N/A	ORR	First-line	• Gemcitabine plus capecitabine demonstrate anti-tumor activity with

							an ORR of 31% and a mild toxicity profile

Small Bowel Adenocarcinoma (SBA)/Advanced Ampullary Cancer

Advanced or Metastatic Disease – Initial Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel	2A (prior oxaliplatin in the adjuvant setting or contraindication)	No	No clinical literature to support use in initial therapy.				
Nab-paclitaxel + gemcitabine	2A (prior oxaliplatin in the adjuvant setting or contraindication)	No	No clinical literature to support use in initial therapy.				
FOLFIRI (5-FU + leucovorin + irinotecan)	2A (prior oxaliplatin in the adjuvant setting or contraindication)	No	No clinical literature to support use in initial therapy.				
Advanced or Metastatic Disease – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel	2A	No	Phase 2, open-label, single-center	N/A	ORR	Subsequent therapy after a fluoropyrimidine and oxaliplatin	• Nab-paclitaxel demonstrated a disease control rate of 50% with 2 patients with partial responses and 3 with stable disease.
Nab-paclitaxel + gemcitabine	2A	No	Retro analysis of taxanes either SA or in combo	N/A	-----	----------	• Taxane-based therapy is clinically active as demonstrated by a response rate of 30%.

FOLFIRI (5-FU + leucovorin + irinotecan)	2A (for dMMR/MSI-H with progression through pembrolizumab, nivolumab, or clinical trial)	No	Retro multi-center study (AGEO)	N/A	-----	Second-line after platinum-based chemotherapy	• Second-line chemotherapy with FOLFIRI produced disease control in half of patients with advanced SBA after failure with first-line platinum-based chemotherapy
Irinotecan	2A (for patient not appropriate for intensive therapy with dMMR/MSI-H with progression through pembrolizumab, nivolumab, or clinical trial)	No	Retro single-institution study	N/A	------	Second-line after fluoropyrimidine therapy	• Fluoropyrimidines as the first-line and CPT-11 as the second-line chemotherapy yielded low response
Larotrectinib	2A (NTRK gene fusion positive)	Yes (for NTRK gene fusion positive solid tumors with no satisfactory alternative treatments or that have progressed following treatment)	Pooled analysis of a phase 1, phase 1/2, and phase 2	N/A	ORR	After standard therapy	• Larotrectinib had marked and durable antitumor activity in patients with TRK fusion–positive cancer, regardless of the age of the patient or of the tumor type

Kaposi Sarcoma

Subsequent therapy (third-line and later) for relapsed/refractory advanced, cutaneous, oral, visceral, or nodal disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Nab-paclitaxel	2A other	No	Phase 2	N/A	----------	----------	• Nab-paclitaxel demonstrated efficacy in all patients
Bortezomib	2A other	No	Pilot Trial AMC-063	N/A	-----	Subsequent therapy	• Bortezomib is well-tolerated and active in AIDS-Kaposi sarcoma with a partial response rate of 60% in patients with relapsed or refractory AIDS-related Kaposi Sarcoma.
Liposomal doxorubicin	2A (first or second-line)	Yes	Phase 2	N/A	----------	After doxorubicin + bleomycin + vincristine (ABV) or bleomycin + vincristine (BV) chemotherapy	• Liposomal doxorubicin is effective in treating patients who have experienced failure of standard chemotherapy for AIDS-KS
Pomalidomide	2A preferred	No	Phase 1/2	N/A	ORR	All lines of therapy	• Pomalidomide demonstrated an ORR of 73% and is active regardless of HIV status.
Paclitaxel	2A (first or second-line)	Yes	Phase 2	N/A	----------	Second-line after anthracycline	• Paclitaxel demonstrated an ORR of 71% with responses that correlate to a fall in plasma IL-6 levels
Etoposide	2A certain circumstances	No	Phase 2	N/A	----------	Subsequent therapy after prior combination chemo or anthracycline therapy	• Etoposide has an ORR of 36.1%
Gemcitabine	2A other	No	Phase IIA, randomized	Bleomycin + vincristine (BV)	----------	Subsequent therapy after anti-retroviral therapy	• Gemcitabine demonstrated clinical activity with a CR rate of 33.3% in chemotherapy-naïve patients
Imatinib	2A certain circumstances	No	Phase 2	N/A	ORR	Subsequent therapy after chemo or anti-retroviral therapy	• Imatinib has clinical activity in AIDS-KS with a PR of 33.3%

Interferon alpha-2b (1 million units per day) + zidovudine	None	No	Prospective randomized trial	Interferon alpha-2b (8 million units per day) + zidovudine	----------	----------	• Zidovudine + interferon alpha demonstrated clinical activity with dose-related responses and toxicity
Thalidomide	2A certain circumstances	No	Phase 2 dose-escalation study	N/A	ORR Safety	----------	• Thalidomide was found to induce an ORR of 40%.
Vinorelbine	2A other	No	Phase 2	N/A	----------	Second-line or later	• Vinorelbine is safe and effective in the treatment of patients with advanced KS who have been previously treated with one or more chemotherapy regimens (ORR 43%).