

## Pemetrexed: **Alimta®; Pemfexy™; Pemetrexed Ψ** (Intravenous)

**-E-**

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### **I. Length of Authorization** <sup>15,26,28-30</sup>

Coverage will be provided for 6 months and may be renewed, unless otherwise specified.

- Thymomas: Coverage will be provided for six (6) 21-day cycles and may NOT be renewed.
- MPM in combination with bevacizumab AND either cisplatin or carboplatin: Coverage will be provided for six (6) cycles and may NOT be renewed.

### **II. Dosing Limits**

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

- Alimta 100 mg powder for injection in a single-use vial: 4 vials every 21 days
- Alimta 500 mg powder for injection in a single-use vial: 4 vials every 21 days
- Pemfexy 500 mg solution for injection in a multi-dose vial: 4 vials every 21 days
- Pemetrexed 750 mg powder for injection: 2 vials every 21 days
- Pemetrexed 1000 mg powder for injection: 2 vials every 21 days
- Pemetrexed 100 mg/4 mL solution for injection: 4 vials every 21 days
- Pemetrexed 500 mg/20 mL solution for injection: 4 vials every 21 days
- Pemetrexed 850 mg/34 mL solution for injection: 2 vials every 21 days
- Pemetrexed 1000 mg/40 mL solution for injection: 2 vials every 21 days

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

- Pemfexy (500 mg MDV):
  - Ovarian Cancer: 225 billable units every 21 days
  - All other indications: 125 billable units every 21 days
- All other manufacturers (100 mg, 500 mg, 750 mg, 850 mg, and 1000 mg SDV):
  - Ovarian Cancer: 230 billable units every 21 days
  - All other indications: 130 billable units every 21 days

### III. Initial Approval Criteria <sup>1,2</sup>

Coverage is provided in the following conditions:

- Patient must have a contraindication, intolerance, or failure to ALL alternative pemetrexed products prior to consideration of Pempfexy (J9304); **AND**

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

#### **Malignant Pleural Mesothelioma (MPM) † ‡ ⊕ <sup>1-6,10,26,31,79e,80e</sup>**

- Used as induction therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible) in patients with clinical stage I-IIIa disease and epithelioid histology; **OR**
- Used as first-line therapy; **AND**
  - Used in combination with bevacizumab **AND** either cisplatin or carboplatin (if cisplatin ineligible) for unresectable disease; **OR**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Disease is unresectable or patient is not a candidate for curative surgery; **OR**
- Used as subsequent therapy; **AND**
  - Used as a single agent **OR** in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab; **AND**
    - Immunotherapy was administered as first-line treatment; **OR**
    - Used as a rechallenge if pemetrexed-based treatment was administered first-line with good response

#### **Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) † ‡ ⊕ <sup>1-3,7-9,11,12,28,30,50e,51e,54e,56e-58e,81e-83e</sup>**

- Used in combination with carboplatin or cisplatin; **OR**
- Used in combination with bevacizumab, pembrolizumab, cemiplimab, or durvalumab for continuation maintenance therapy if previously used first-line and patient achieved a tumor response or stable disease following initial therapy; **OR**
- Used in combination with cisplatin and nivolumab as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- Used in combination with one of the following:
  - Pembrolizumab and either cisplatin or carboplatin
  - Cemiplimab and either cisplatin or carboplatin
  - Tremelimumab, durvalumab, and either cisplatin or carboplatin; **OR**
- Used in combination with nivolumab, ipilimumab, and either cisplatin or carboplatin; **OR**
- Used as a single agent; **AND**

- Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used as first-line therapy for tumors that are negative for actionable molecular biomarkers\*; **OR**
  - Used as first-line therapy for EGFR exon 20 mutation, KRAS G12C mutation, BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, RET rearrangement, or ERBB2 (HER2) mutation positive tumors; **OR**
  - Used as subsequent therapy; **OR**
  - Used as continuation or switch maintenance therapy in patients who have achieved a tumor response or stable disease following initial therapy

*\* Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2). If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), 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.*

#### **Thymomas †<sup>3,14,15,25,68e</sup>**

- Used as a single agent; **AND**
- Used as second-line therapy for unresectable or metastatic disease

#### **Ovarian, Fallopian Tube, and Primary Peritoneal Cancer †<sup>3,13,24,74e,75e</sup>**

- Used as a single agent; **AND**
  - Patient has recurrent or persistent Grade 1 Endometrioid Carcinoma, Carcinosarcoma (Malignant Mixed Müllerian Tumors), Mucinous Carcinoma of the Ovary, Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer, or Clear Cell Carcinoma of the Ovary; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
    - Patient has platinum-resistant disease; **OR**
  - Patient has recurrent Low-Grade Serous Carcinoma; **AND**
    - Patient has platinum-resistant disease

**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 <i>EGFR</i> mutation-positive tumors	<i>ALK</i> rearrangement-positive tumors	<i>ROS1</i> rearrangement-positive tumors	<i>BRAF</i> V600E-mutation positive tumors	<i>NTRK1/2/3</i> gene fusion positive tumors
<ul style="list-style-type: none"> <li>– Afatinib</li> <li>– Erlotinib</li> <li>– Dacomitinib</li> <li>– Gefitinib</li> <li>– Osimertinib</li> <li>– Amivantamab (<i>exon-20 insertion</i>)</li> <li>– Mobocertinib (<i>exon-20 insertion</i>)</li> </ul>	<ul style="list-style-type: none"> <li>– Alectinib</li> <li>– Brigatinib</li> <li>– Ceritinib</li> <li>– Crizotinib</li> <li>– Lorlatinib</li> </ul>	<ul style="list-style-type: none"> <li>– Ceritinib</li> <li>– Crizotinib</li> <li>– Entrectinib</li> <li>– Lorlatinib</li> </ul>	<ul style="list-style-type: none"> <li>– Dabrafenib ± trametinib</li> <li>– Vemurafenib</li> </ul>	<ul style="list-style-type: none"> <li>– Larotrectinib</li> <li>– Entrectinib</li> </ul>
PD-L1 tumor expression ≥ 1%	<i>MET</i> exon-14 skipping mutations	<i>RET</i> rearrangement-positive tumors	<i>KRAS G12C</i> mutation positive tumors	<i>ERBB2 (HER2)</i> mutation positive tumors
<ul style="list-style-type: none"> <li>– Pembrolizumab</li> <li>– Atezolizumab</li> <li>– Nivolumab + ipilimumab</li> <li>– Cemiplimab</li> <li>– Tremelimumab + durvalumab</li> </ul>	<ul style="list-style-type: none"> <li>– Capmatinib</li> <li>– Crizotinib</li> <li>– Tepotinib</li> </ul>	<ul style="list-style-type: none"> <li>– Selpercatinib</li> <li>– Cabozantinib</li> <li>– Pralsetinib</li> </ul>	<ul style="list-style-type: none"> <li>– Sotorasib</li> <li>– Adagrasib</li> </ul>	<ul style="list-style-type: none"> <li>– Fam-trastuzumab deruxtecan-nxki</li> <li>– Ado-trastuzumab emtansine</li> </ul>

#### IV. Renewal Criteria <sup>1,2</sup>

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: myelosuppression (e.g., neutropenia, febrile neutropenia, thrombocytopenia, anemia), renal toxicity (CrCl < 45 mL/min), bullous and exfoliative skin toxicity (e.g., Stevens-Johnson Syndrome/Toxic epidermal necrolysis), interstitial pneumonitis, radiation recall, etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**

#### MPM <sup>26,29</sup>

- Coverage may NOT be renewed when used in combination with bevacizumab AND either cisplatin or carboplatin

#### Thymomas <sup>15</sup>

- Coverage may NOT be renewed

#### V. Dosage/Administration <sup>1,2,10,13,15,16,26,28-33</sup>

Indication	Dose
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Non-Squamous NSCLC	Administer up to 500 mg/m <sup>2</sup> intravenously every 21 days
MPM	Administer 500 mg/m <sup>2</sup> intravenously every 21 days – For 6 cycles only when used in combination with bevacizumab AND either cisplatin or carboplatin – All others until disease progression or unacceptable toxicity
Ovarian Cancer	Administer 900 mg/m <sup>2</sup> intravenously every 21 days, until disease progression or unacceptable toxicity
Thymomas	Administer 500 mg/m <sup>2</sup> intravenously every 21 days for a maximum of 6 cycles or until disease progression or unacceptable toxicity
<ul style="list-style-type: none"> <li>• Supplement with oral folic acid and intramuscular vitamin B<sub>12</sub>.</li> <li>• Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration in patients with CrCl &lt;80 mL/min.</li> <li>• Do not administer in patients with CrCl &lt;45 mL/min.</li> </ul>	

## VI. Billing Code/Availability Information

Product Formulation	Drug	Manufacturer	Type	HCPCS Code	NDC
Pemetrexed Disodium Lyophilisate for injection	Alimta 100 mg powder for inj. SDV *	Lilly	Brand	J9305	00002-7640-xx
	Alimta 500 mg powder for inj. SDV *				00002-7623-xx
	Pemetrexed 100 mg powder for inj. SDV ψ	Hospira	Brand	J9294	00409-1060-xx
	Pemetrexed 500 mg powder for inj. SDV ψ				00409-1061-xx
	Pemetrexed 750 mg powder for inj. SDV *	N/A	Generic	J9305	N/A
	Pemetrexed 1000 mg powder for inj. SDV *				
	Pemetrexed 100 mg powder for inj. SDV ψ	BluePoint	Brand	J9322	68001-0543-xx
	Pemetrexed 500 mg powder for inj. SDV ψ				68001-0544-xx
Pemetrexed 750 mg powder for inj. SDV ψ	68001-0545-xx				
Pemetrexed 1000 mg powder for inj. SDV ψ	68001-0546-xx				
Pemetrexed Disodium Solution for injection	Pemetrexed 100 mg/4 mL inj. SDV ψ	Sandoz	Brand	J9297	00781-3518-xx
		Accord	Brand	J9296	16729-0522-xx
		Hospira	Brand	J9294	00409-1045-xx
	Pemetrexed 500 mg/20 mL inj. SDV ψ	Sandoz	Brand	J9297	00781-3519-xx
		Accord	Brand	J9296	16729-0522-xx
		Hospira	Brand	J9294	00409-2188-xx
	Pemetrexed 850 mg/34mL inj. SDV ψ	Accord	Brand	J9296	16729-0522-xx
	Pemetrexed 1000 mg/40 mL inj. SDV ψ	Accord	Brand	J9296	16729-0522-xx
Hospira		Brand	J9294	00409-3532-xx	
Pemetrexed Solution for injection	Pemfexy 500 mg/20 mL inj. MDV	Eagle	Brand	J9304	42367-0531-xx
	Pemetrexed 100 mg/4mL inj. SDV ψ	Teva	Brand	J9314	00480-4516-xx
	Pemetrexed 500 mg/20 mL inj. SDV ψ	Teva	Brand	J9314	00480-4514-xx
	Pemetrexed 1000 mg/40 mL inj. SDV ψ	Teva	Brand	J9314	00480-4515-xx
Pemetrexed Ditromethamine for injection	Pemetrexed 100 mg powder for inj. SDV ψ	Hospira	Brand	J9323	00409-1060-xx
	Pemetrexed 500 mg powder for inj. SDV ψ				00409-1061-xx
<p><b>*Multiple manufacturers produce ANDA generics</b>  ψ Designated products approved by the FDA as a 505(b)(2) NDA of the innovator product. These products are not rated as therapeutically equivalent to their reference listed drug in the Food and Drug Administration's (FDA) Orange Book and are therefore considered single source products based on the statutory definition of "single source drug" in section 1847A(c)(6) of the Act. For a complete list of all approved 505(b)(2) NDA products please reference the latest edition of the Orange Book: <a href="#">Approved Drug Products with Therapeutic Equivalence Evaluations / Orange Book / FDA</a></p>					

J9294 – Injection, pemetrexed (hospira) not therapeutically equivalent to J9305, 10 mg  
 J9296 – Injection, pemetrexed (accord) not therapeutically equivalent to J9305, 10 mg  
 J9297 – Injection, pemetrexed (sandoz), not therapeutically equivalent to J9305, 10 mg  
 J9304 – Injection, pemetrexed (pemfexy), 10 mg  
 J9305 – Injection, pemetrexed, not otherwise specified, 10 mg  
 J9314 – Injection, pemetrexed (teva) not therapeutically equivalent to J9305, 10 mg  
 J9322 – Injection, pemetrexed (bluepoint) not therapeutically equivalent to J9305, 10 mg  
 J9323 – Injection, pemetrexed ditromethamine, 10 mg  
 J9324 – Injection, pemetrexed (pemrydi rtu), 10 mg (*Effective 01/01/2024*)  
 J9999 – Injection, pemetrexed various (shipla, etc.), 10 mg

## VII. References (STANDARD)

1. Alimta [package insert]. Indianapolis, IN; Eli Lilly; August 2022. Accessed September 2023.
2. Pemfexy [package insert]. Woodcliff Lake, NJ; Eagle Pharmaceuticals, Inc; December 2022. Accessed September 2023.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for pemetrexed. National Comprehensive Cancer Network, 2023. 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 September 2023.
4. Castagneto B, Botta M, Aitini E, et al, “Phase II Study of Pemetrexed in Combination With Carboplatin in Patients With Malignant Pleural Mesothelioma (MPM),” *Ann Oncol*, 2008, 19(2):370-3.
5. Ceresoli GL, Zucali PA, Favaretto AG, et al, “Phase II Study of Pemetrexed plus Carboplatin in Malignant Pleural Mesothelioma,” *J Clin Oncol*, 2006, 24(9):1443-8.
6. Taylor P, Castagneto B, Dark G, et al, “Single-Agent Pemetrexed for Chemo-naïve and Pretreated Patients With Malignant Pleural Mesothelioma: Results of an International Expanded Access Program,” *J Thorac Oncol*, 2008, 3(7):764-71.
7. Ciuleanu T, Brodowicz T, Zielinski C, et al, “Maintenance Pemetrexed Plus Best Supportive Care versus Placebo Plus Best Supportive Care for Non-Small-Cell Lung Cancer: A Randomised, Double-Blind, Phase 3 Study,” *Lancet*, 2009, 374(9699):1432-40.
8. Grønberg BH, Bremnes RM, Fløtten O, et al, “Phase III Study by the Norwegian Lung Cancer Study Group: Pemetrexed Plus Carboplatin Compared With Gemcitabine Plus Carboplatin as First-Line Chemotherapy in Advanced Non-Small-Cell Lung Cancer,” *J Clin Oncol*, 2009, 27(19):3217-24.
9. 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,” *J Clin Oncol*, 2004, 22(9):1589-97.
10. Jassem J, Ramlau R, Santoro A, et al, “Phase III Trial of Pemetrexed Plus Best Supportive Care Compared With Best Supportive Care in Previously Treated Patients With Advanced Malignant Pleural Mesothelioma,” *J Clin Oncol*, 2008, 26(10):1698-704. [PubMed 18375898]

11. Scagliotti GV, Parikh P, von Pawel J, et al, "Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer," *J Clin Oncol*, 2008, 26(21):3543-51.
12. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508.
13. Miller DS, Blessing JA, Krasner CN, et al, "Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group," *J Clin Oncol*, 2009, 27(16):2686-91.
14. Liang Y, Padda SK, Riess JW, et al. Pemetrexed in patients with thymic malignancies previously treated with chemotherapy. *Lung Cancer*. 2015 Jan;87(1):34-8.
15. Gbolahan OB, Porter RF, Salter JT, et al. A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma. *J Thorac Oncol*. 2018 Dec;13(12):1940-1948.
16. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer*. 2012 Aug 1;118(15):3743-8.
17. 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.
18. 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](http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf)
19. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. *BMJ*. 2016 Feb 29;352:i788.
20. 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(22):2078-2092. doi:10.1056/NEJMoa1801005.
21. Wu YL, Lu S, Cheng Y, et al. Efficacy and safety of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment in Chinese patients with advanced nonsquamous non-small cell lung cancer. *Lung Cancer*. 2014;85(3):401-407. doi:10.1016/j.lungcan.2014.07.007.
22. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;13(3):247-255. doi:10.1016/S1470-2045(12)70063-3.

23. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21(14):2636-2644. doi:10.1200/JCO.2003.11.136.
24. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 2.2023. National Comprehensive Cancer Network, 2023. 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 September 2023.
25. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Thymomas and Thymic Carcinomas. Version 1.2023. National Comprehensive Cancer Network, 2023. 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 September 2023.
26. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Mesothelioma: Pleural Version 1.2023. National Comprehensive Cancer Network, 2023. 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 September 2023.
27. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Central Nervous System Cancers Version 1.2023. National Comprehensive Cancer Network, 2023. 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 September 2023.
28. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Non-Small Cell Lung Cancer Version 3.2023. National Comprehensive Cancer Network, 2023. 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 September 2023.
29. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Mesothelioma: Peritoneal Version 2.2023. National Comprehensive



Cancer Network, 2023. 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 September 2023.

30. Forde P, Spicer J, Provencio M, et al. Abstract CT003: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-III A) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. *Cancer Res* (2021) 81 (13\_Supplement): CT003. <https://doi.org/10.1158/1538-7445.AM2021-CT003>
31. Miller DS, Blessing JA, Bodurka DC, et al. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol*. 2008 Jul;110(1):65-70. doi: 10.1016/j.ygyno.2008.03.009.
32. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016 Apr 2;387(10026):1405-1414. doi: 10.1016/S0140-6736(15)01238-6.
33. Fan C, Zhao Q, Li L, et al. Efficacy and Safety of Intrathecal Pemetrexed Combined With Dexamethasone for Treating Tyrosine Kinase Inhibitor-Failed Leptomeningeal Metastases From EGFR-Mutant NSCLC-a Prospective, Open-Label, Single-Arm Phase 1/2 Clinical Trial (Unique Identifier: ChiCTR1800016615). *J Thorac Oncol*. 2021 Aug;16(8):1359-1368. doi: 10.1016/j.jtho.2021.04.018.

## VIII. References (ENHANCED)

- 1e. Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol*. 2006 Jul 20;24(21):3451-7.
- 2e. 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.
- 3e. 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):1909–1920.
- 4e. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2018 Feb 24;391(10122):748-757.
- 5e. 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.

- 6e. 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):3119–3125.
- 7e. Patel MR, Ellerton J, Infante J, 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.
- 8e. Ko YJ, 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.
- 9e. Lorusso V, 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.
- 10e. Meluch AA, 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.
- 11e. von der Maase H, 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.
- 12e. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *J Clin Oncol.* 2009;27(33):5634–5639.
- 13e. McCaffrey JA, 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.
- 14e. Vaughn DJ, 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.
- 15e. Petrylak DP, 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.
- 16e. Witte RS, 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.
- 17e. 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.

- 18e. Sternberg CN, 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.
- 19e. Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res*. 2004 Sep 1;10(17):5643-6.
- 20e. Nayak L, Abrey LE, Drappatz J, et al. Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. *Leuk Lymphoma*. 2013;54(1):58–61.
- 21e. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol*. 2009;27(18):3007–3013.
- 22e. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol*. 2008 Jul;3(7):756-63.
- 23e. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016 Apr 2;387(10026):1405-1414.
- 24e. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. *Br J Cancer*. 2013;109(3):552–558.
- 25e. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet*. 2008;371(9625):1685–1694.
- 26e. Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. *Lung Cancer*. 2012 Mar;75(3):360-7.
- 27e. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol*. 2019 Feb;20(2):239-253.
- 28e. Scherpereel A, Mazieres J, Greillier L, et al. Second or 3rd line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Updated results of the IFCT-1501 MAPS2 randomized phase 2 trial. *Ann Oncol*. 2017 Sept;28(5):mdx440.074.
- 29e. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. *Lancet Respir Med*. 2019 Mar;7(3):260-270.

- 30e. Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed Death 1 Blockade With Nivolumab in Patients With Recurrent Malignant Pleural Mesothelioma. *J Thorac Oncol*. 2018 Oct;13(10):1569-1576.
- 31e. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 2017 May;18(5):623-630.
- 32e. Alley EW, Lopez J, Santoro A, et al. Long-Term Overall Survival for Patients with Malignant Pleural Mesothelioma on Pembrolizumab Enrolled in KEYNOTE-028. *J Thorac Oncol*. 2017 Jan;12(1):S294.
- 33e. Metaxas Y, Rivalland G, Mauti LA, et al. Pembrolizumab as Palliative Immunotherapy in Malignant Pleural Mesothelioma. *J Thorac Oncol*. 2018 Nov;13(11):1784-1791.
- 34e. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer*. 2009 Jan;63(1):94-7.
- 35e. Zauderer MG, Kass SL, Woo K, Sima CS, Ginsberg MS, Krug LM. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer*. 2014;84(3):271-274.
- 36e. Kim JS, Lim SY, Hwang J, Kang EJ, Choi YJ. A Case Report of Primary Pericardial Malignant Mesothelioma Treated with Pemetrexed and Cisplatin. *J Korean Med Sci*. 2017;32(11):1879-1884.
- 37e. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. *Lung Cancer*. 2009 May;64(2):211-8.
- 38e. Zhang L, Ou W, Liu Q, Li N, Liu L, Wang S. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. *Thorac Cancer*. 2014;5(1):50-56.
- 39e. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol*. 2013 Apr;24(4):986-92.
- 40e. Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized phase III study of pemetrexed/cisplatin (Pem/Cis) versus vinorelbine /cisplatin (Vnr/Cis) for completely resected stage II-IIIa non-squamous non-small-cell lung cancer (Ns-NSCLC): The JIPANG study. *J Clin Oncol*, 2019; 37(15\_suppl):8501.
- 41e. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004 Jan 22;350(4):351-60.
- 42e. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *J Clin Oncol*. 2012 Jan 10;30(2):172-8.

- 43e. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31):5043–5051.
- 44e. Usami N, Yokoi K, Hasegawa Y, et al. Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial. *Int J Clin Oncol*. 2010 Dec;15(6):583-7.
- 45e. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2016 Mar 20;34(9):953-62.
- 46e. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410 [published correction appears in *J Natl Cancer Inst*. 2012 Jan 4;104(1):79]. *J Natl Cancer Inst*. 2011;103(19):1452–1460.
- 47e. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 2005 Sep 1;23(25):5883-91.
- 48e. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013 Sep 20;31(27):3342-50.
- 49e. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol*. 2013 Aug 10;31(23):2849-53.
- 50e. Gridelli C, Kaukel E, Gregorc V, et al. Single-agent pemetrexed or sequential pemetrexed/gemcitabine as front-line treatment of advanced non-small cell lung cancer in elderly patients or patients ineligible for platinum-based chemotherapy: a multicenter, randomized, phase II trial. *J Thorac Oncol*. 2007 Mar;2(3):221-9.
- 51e. Rusthoven JJ, Eisenhauer E, Butts C, et al. Multitargeted antifolate LY231514 as first-line chemotherapy for patients with advanced non-small-cell lung cancer: A phase II study. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1999 Apr;17(4):1194.
- 52e. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31(34):4349–4357.

- 53e. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013 Aug 20;31(24):3004-11.
- 54e. 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.
- 55e. Socinski MA, Jotte RM, Capuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018; 378:2288-2301.
- 56e. 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.
- 57e. 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.
- 58e. 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.
- 59e. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol*. 2005 Apr;16(4):602-10.
- 60e. 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.
- 61e. Paz-Ares L, de Marinis F, Dediu M, et al. PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer. *J Clin Oncol*. 2013 Aug 10;31(23):2895-902.
- 62e. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer--a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. *Non-Small Cell Lung Cancer*. *Br J Cancer*. 2000;83(4):447–453.
- 63e. 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):1627–1639.
- 64e. 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.
- 65e. 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. *Ann Oncol*. 2016 Oct;27(6):LBA44\_PR.

- 66e. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014 Aug 23;384(9944):665-73.
- 67e. Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer*. 2004 May;44(2):231-9.
- 68e. Palmieri G, Buonerba C, Ottaviano M, et al. Capecitabine plus gemcitabine in thymic epithelial tumors: final analysis of a Phase II trial. *Future Oncol*. 2014 Nov;10(14):2141-7.
- 69e. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial [published correction appears in *Lancet Oncol*. 2015 Mar;16(3):e105]. *Lancet Oncol*. 2015;16(2):177-186.
- 70e. Zucali PA, De Pas T, Palmieri G, et al. Phase II Study of Everolimus in Patients With Thymoma and Thymic Carcinoma Previously Treated With Cisplatin-Based Chemotherapy. *J Clin Oncol*. 2018 Feb 1;36(4):342-349.
- 71e. Loehrer PJ Sr, Wang W, Johnson DH, et al. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. *J Clin Oncol*. 2004 Jan 15;22(2):293-9.
- 72e. Umemura S, Segawa Y, Fujiwara K, et al. A case of recurrent metastatic thymoma showing a marked response to paclitaxel monotherapy. *Jpn J Clin Oncol*. 2002 Jul;32(7):262-5.
- 73e. Bluthgen MV, Boutros C, Fayard F, et al. Activity and safety of oral etoposide in pretreated patients with metastatic or recurrent thymic epithelial tumors (TET): A single-institution experience. *Lung Cancer*. 2016 Sep;99:111-6.
- 74e. 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.
- 75e. Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 1998 Feb;16(2):405-10.
- 76e. 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.
- 77e. Sehouli J, Stengel D, Harter P, et al. Topotecan Weekly Versus Conventional 5-Day Schedule in Patients With Platinum-Resistant Ovarian Cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol*. 2011 Jan 10;29(2):242-8.

- 78e. Kindler, HL, Ismaila N, Armato III, SG, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018 Jan;36(13):1343-1373.
- 79e. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer*. 2002;87(5):491-496.
- 80e. van Haarst JM, Baas P, Manegold Ch, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer*. 2002;86(3):342-345.
- 81e. 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].
- 82e. Reck M, Ciuleanu T-E, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA [abstract]. *J Clin Oncol* 2020;38:Abstract 9501-9501.
- 83e. 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;20(7):924-937.
- 84e. Zalcman G, Peters S, Mansfield AS, et al. Checkmate 743: A phase 3, randomized, open-label trial of nivolumab (nivo) plus ipilimumab (ipi) vs pemetrexed plus cisplatin or carboplatin as first-line therapy in unresectable pleural mesothelioma. *Journal of Clinical Oncology* 2017 35:15\_suppl, TPS8581-TPS8581.
- 85e. 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.
- 86e. Scagliotti GV, Shin DM, Kindler HL, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. *J Clin Oncol*. 2003 Apr 15;21(8):1556-61.
- 87e. Jänne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer*. 2005 Jul;7(1):40-6.
- 88e. Gogishvili M, Melkadze T, Makharadze T, et al. LBA51 EMPOWER-Lung 3: Cemiplimab in combination with platinum doublet chemotherapy for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC). *Annals of Oncology*, ISSN: 0923-7534, Vol: 32, SUPPLEMENT 5, S1328, SEPTEMBER 01, 2021. DOI10.1016/j.annonc.2021.08.2130.
- 89e. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol*. 2023 Feb 20;41(6):1213-1227.



## Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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
C37	Malignant neoplasm of thymus
C45.0	Mesothelioma of pleura
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
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
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

ICD-10	ICD-10 Description
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
D15.0	Benign neoplasm of thymus
D38.4	Neoplasm of uncertain behavior of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.238	Personal history of other malignant neoplasm of thymus
Z85.43	Personal history of malignant neoplasm of ovary

## 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: <https://www.cms.gov/medicare-coverage-database/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): N/A

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,	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp
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
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC

<b>Medicare Part B Administrative Contractor (MAC) Jurisdictions</b>		
<b>Jurisdiction</b>	<b>Applicable State/US Territory</b>	<b>Contractor</b>
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