Pemetrexed:
Alimta®; Pemfexy™
(Intravenous)

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I. Length of Authorization [15]

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

- Thymomas/Thymic Carcinoma: Coverage will be provided for six 21-day cycles and may not be renewed.
- MPM: Coverage will be provided for six 21-day cycles and may not be renewed when used in combination with platinum therapy and bevacizumab

II. Dosing Limits

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

- Alimta 100 mg powder for injection: 4 vials every 21 days
- Alimta 500 mg powder for injection: 2 vials every 21 days
- Pemfexy 500 mg solution for injection: 4 vials every 21 days

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

- Ovarian Cancer: 230 billable units every 21 days
- All other indications: 130 billable units every 21 days

III. Initial Approval Criteria [1,2]

Coverage is provided in the following conditions:

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

Malignant Pleural* Mesothelioma † Φ [3-6,10,26,79e,80e]

- Used in combination with cisplatin or carboplatin; **AND**
  - Patient has stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors and used as first-line therapy with or without bevacizumab; **OR**
  - Patient has stage I-IIIA disease with epithelioid or biphasic histology; **AND**

        - Used as induction therapy; **OR**
        - Used as first-line therapy with or without bevacizumab for unresectable disease; **OR**
        - Patient has resected disease not treated with induction chemotherapy; **OR**
- Used as a single agent; **AND**
    - Patient has stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors and used as first-line therapy; **AND**
    - Patient has stage I-IIIA disease with epithelioid or biphasic histology; **AND**
        - Used as first-line therapy for unresectable disease; **OR**
    - Used as subsequent therapy, if not administered first-line; **OR**
    - Used as a re-challenge, if pemetrexed was administered first-line with a good sustained response at the time initial chemotherapy was interrupted

**peritoneal, pericardial, and tunica vaginalis testis mesothelioma will be evaluated on a case by case basis*

Non-Squamous Non-Small Cell Lung Cancer (NSNSCLC) † 3,7-9,11,12,28,50e,51e,54e,56e-58e,81e-83e

- Used in combination with carboplatin or cisplatin; **AND**
    - Used as induction, neoadjuvant, or adjuvant therapy for early-stage or locally advanced disease; **OR**
    - Used as concurrent chemoradiation for locoregional recurrence or symptomatic local disease in the mediastinal lymph nodes or for superior vena cava obstruction; **OR**
    - Used as initial therapy as definitive concurrent chemoradiation for unresectable, advanced, or metastatic disease; **OR**
- Used for 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; **AND**
        - Used for PD-L1 ≥1% tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative*****; **AND**
            - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-2; **OR**
            - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-2; **OR**
        - Used for one of the following:
            - PD-L1 <1% and EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative***** tumors
            - BRAF V600E-mutation, NTRK gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors; **AND**
            - Used as a single-agent in patients with PS 2; **OR**
            - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-1; **OR**

- Used in combination with cisplatin in patients with PS 0-1; **OR**
- Used in combination with carboplatin in patients with PS 0-2; **OR**
- Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1; **OR**

- Used as subsequent therapy; **AND**
  - Used as a single-agent for second-line therapy (if not previously given) in patients with a PS 0-2; **OR**
  - Used for one of the following:
    - EGFR, ALK, or ROS1 positive tumors who received prior targeted therapy§ for those aberrations
    - BRAF V600E-mutation, NTRK gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors
    - PD-L1 ≥ 1% tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative* with prior PD-1/PD-L1 inhibitor therapy but no prior platinum doublet chemotherapy; **AND**
      - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-1 *(excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy)*; **OR**
      - Used in combination with cisplatin in patients with PS 0-1; **OR**
      - Used in combination with carboplatin in patients with PS 0-2; **OR**
- Used as maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy; **AND**
  - Used as a single agent for continuation maintenance therapy; **OR**
  - Used as a single agent for switch maintenance therapy following a first-line platinum chemotherapy regimen without pemetrexed; **OR**
  - Used for continuation maintenance therapy in combination with pembrolizumab following a first-line pembrolizumab/pemetrexed/and either carboplatin or cisplatin regimen

** Note: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, 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.*

Thymomas/Thymic Carcinoma ‡ [3,14,15,25.68e]

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

Ovarian Cancer (epithelial ovarian/fallopian tube/primary peritoneal cancer) ‡ [3,13,24,74e,75e]

- Used for disease progression, stable or persistent disease (if not on maintenance therapy), disease relapse; **AND**

- Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 and no radiographic evidence of disease); **AND**
- Used as a single agent; **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 *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
RET rearrangement-positive tumors – Selpercatinib – Cabozantinib – Vandetanib

IV. Renewal Criteria [1,2]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet 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 the following: bone marrow suppression (e.g., neutropenia, febrile neutropenia, thrombocytopenia, anemia), renal impairment (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**

Continuation of Maintenance Therapy for Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

- *Refer to Section III for criteria*

MPM

- May not be renewed when used in combination with platinum therapy and bevacizumab

Thymomas/Thymic Carcinoma

- May not be renewed

V. Dosage/Administration [1,2,13,15,16]

Indication	Dose
Non-Squamous NSCLC	• Administer 500 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity
Malignant Pleural Mesothelioma	Administer 500 mg/m^2 intravenously every 21 days – For 6 cycles only when used in combination with platinum therapy and bevacizumab • All others until disease progression or unacceptable toxicity
Ovarian Cancer	• Administer 900 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity
Thymomas/Thymic Carcinoma	• Administer 500 mg/m^2 intravenously every 21 days for a maximum of 6 cycles in absence of disease progression or unacceptable toxicity
• Supplement with oral folic acid and intramuscular vitamin B_{12} • Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration in patients with CrCl <80 mL/min. • Do not dose in patients with CrCl <45 mL/min	

VI. Billing Code/Availability Information

HCPCS Code:

- J9305 – Injection, pemetrexed, 10 mg; 1 billable unit = 10mg
- J9304 – Injection, pemetrexed (pemfexy), 10 mg; 1 billable unit = 10mg *(Effective 10/1/20)*

NDC:

- Alimta 100 mg powder for injection; single-use vial: 00002-7640-xx
- Alimta 500 mg powder for injection; single-use vial: 00002-7623-xx
- Pemfexy 500 mg/20 mL solution for injection, single-use vial: 42367-0531-xx

VII. References (STANDARD)

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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

ICD-10	ICD-10 Description
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
C38.4	Malignant neoplasm of pleura
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
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
C56.9	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
D15.0	Benign neoplasm of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
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: 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): 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
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; pCR = pathologic complete response; SD = stable disease; DoR = duration of response; TTP = time to progression; TTF = time to treatment failure; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; PS = performance status; MTX = methotrexate; DCR = disease control rate; DFS = disease-free survival; RFS = recurrence-free survival

Primary CNS Lymphoma

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed	2A	No	Prospective, single-center study	N/A	----------	Relapsed or refractory disease	• Pemetrexed has single-agent activity in relapsed/ refractory primary CNS lymphoma with an ORR of 55%
MTX rechallenge	2A	No	Retrospective, multi-center study	N/A	ORR	Relapsed disease after a complete response after treatment with MTX-based therapy	• High-dose methotrexate remains effective fore relapsed CNS lymphoma in patients who initially respond to methotrexate.
Rituximab + TMZ	2A	No	Phase 2, multi-center	N/A	ORR	Recurrent disease	• Rituximab plus temozolomide demonstrated modest activity with a complete response rate or 14%.

Malignant pleural mesothelioma

Induction/Neoadjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed + cisplatin	1 preferred (with cisplatin) 2A other (with carboplatin)	No	Phase 2	N/A	pCR	Neoadjuvant	• This multicenter trial showed that trimodality therapy with neoadjuvant pemetrexed plus cisplatin is feasible with a reasonable long-term survival rate, particularly for patients who completed all therapy. Radiologic response to chemotherapy, but not sex, histology, disease stage, or nodal status, was associated with improved survival.
First-line							
Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pemetrexed + cisplatin	1 preferred (with cisplatin) 2A other (with carboplatin)	Yes (with cisplatin)	Phase 3, randomized	Cisplatin	OS	Chemo-naïve and not eligible for curative surgery	• Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma.
Pemetrexed + cisplatin	1 preferred (with cisplatin) 2A other (with carboplatin)	Yes (with cisplatin)	Expanded Access Program	Pemetrexed + carboplatin	-----	Chemo-naïve and not amenable to curative surgery	• This large study confirmed the activity of pemetrexed plus cisplatin and pemetrexed plus carboplatin in chemo-naïve patients with MPM, demonstrating clinically similar time to progressive disease and 1-year survival rates.

Pemetrexed	2A certain circumstances	No	Open-label study	N/A	-----	Chemo-naïve and pretreated not amenable to curative surgery	• Single-agent pemetrexed demonstrated promising activity in MPM in both chemo-naïve and pretreated patients, with TTP of 6.0 and 4.9 months, respectively, 1-year survival >or=54.7%, and mild hematologic toxicity.
Bevacizumab + cisplatin + pemetrexed, followed by maintenance bevacizumab	1 preferred (with cisplatin) 2A other (with carboplatin)	No	Phase 3 (MAPS), multi-center, randomized, controlled, open-label	Cisplatin + pemetrexed	OS	Chemo-naïve	• Addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it should be considered as a suitable treatment for the disease.
Bevacizumab + carboplatin + pemetrexed	1 preferred (with cisplatin) 2A other (with carboplatin)	No	Phase 2	N/A	PFS	First-line	• Bevacizumab, carboplatin, and pemetrexed achieved a 34.2% partial response and 57.9% stable disease. • The primary end point of the trial was not reached
Carboplatin + pemetrexed	2A other	No	Phase 2	N/A	--------	First-line	• This combination of carboplatin and pemetrexed is moderately active with an ORR of 25%
Carboplatin + pemetrexed	2A other	No	Phase 2, multi-center	N/A	ORR	Chemo-naïve	• Disease control rate, time to disease progression, and overall survival were similar to the results achieved with the standard regimen of pemetrexed and cisplatin, suggesting that the carboplatin combination could be an alternative option for these patients.
Nivolumab + ipilimumab	2A preferred	No	Phase 3 (CheckMate 743),	Pemetrexed + cisplatin	OS	First-line	• CheckMate 743 demonstrated a statistically significant improvement in OS for patients randomized to nivolumab in combination with ipilimumab compared to chemotherapy.

			randomized, open-label	or carboplatin			
Vinorelbine or Mitomycin + vinblastine + cisplatin (MVP)	2A certain circumstances	No	Randomized trial	Active symptom control (ASC)	OS	Chemo-naive	• The addition of chemotherapy to ASC offers no significant benefits in terms of overall survival however a trend in improved survival was seen with vinorelbine.
Gemcitabine + cisplatin	2A certain circumstances	No	Phase 2	N/A	-----	First-line	• Gemcitabine and cisplatin demonstrated an ORR of 33% in patient with previously untreated pleural malignant mesothelioma.
Gemcitabine + cisplatin	2A certain circumstances	No	Phase 2	N/A	-----	First-line	• A 16% ORR was observed with gemcitabine and cisplatin in patients with previously untreated malignant pleural mesothelioma.
Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed + best supportive case (P+BSC)	1 preferred	No	Phase 3, multi-center	Best supportive care (BSC)	OS	Second-line	• Second-line pemetrexed elicited significant tumor response and delayed disease progression compared with BSC alone in patients with advanced MPM. Improvement in OS was not seen in this study.
Pemetrexed	1 preferred	No	Retrospective study	N/A	-----	Second-line	• In selected patients, re-challenge with pemetrexed-based regimens, preferentially associated with platinum-compound, appears to be an option for second-line therapy.

Nivolumab ± ipilimumab	2A preferred	No	Phase 2 (MAPS2), randomized Updated results	N/A	12-week DCR	Second- or third-line	• Both nivolumab and nivolumab + ipilimumab reached their endpoint in 2nd/3rd line MPM patients without any unexpected toxicity, leading to meaningful progression-free and overall survivals.
Nivolumab + ipilimumab	2A preferred	No	Phase 2 (INITIATE), single-center	N/A	12-week DCR	After at least one platinum-containing chemotherapy	• In this single-center phase 2 trial, the combination of nivolumab plus ipilimumab showed a disease control rate of 68% at 12 weeks in patients with recurrent malignant pleural mesothelioma
Nivolumab	2A preferred	No	Phase 2	N/A	12-week DCR	Recurrent MPM	• Single-agent nivolumab has meaningful clinical efficacy with a 12-week disease control rate of 47% and a manageable safety profile in pre-treated patients with mesothelioma. PD-L1 expression does not predict for response in this population.
Pembrolizumab	2A preferred	No	Phase 1b (KEYNOTE-028) Updated results	N/A	Safety Response	Previously treated	• Single-agent pembrolizumab has significant clinical activity in patients with PD-L1–positive MPM. Responses from pembrolizumab in patients with MPM are durable with a 62.6% 12-month OS rate in this mostly pretreated patient population
Pembrolizumab	2A preferred	No	Phase 2	N/A	-----	Second-line	• Second-line therapy with pembrolizumab demonstrated and overall ORR of 37%. Greater clinical activity was associated with high PD-L1 expression.

Vinorelbine	2A other	No	Phase 2	N/A	-----	After prior chemotherapy	• Vinorelbine demonstrated an ORR of 16% in second-line treatment of MPM.
Gemcitabine	2A other	No	Retrospective study	N/A	-----	Second- or third-line	• Response to second- or third-line gemcitabine
Peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed + cisplatin *Pericardial*	1 (with cisplatin)	No	Case report	N/A	-----	----------	• A few case reports demonstrated that chemotherapy with pemetrexed and platinum may prolong survival in patients with pericardial mesothelioma.
Pemetrexed ± cisplatin or carboplatin *Peritoneal*	1 (with cisplatin) 2A (with carboplatin)	Yes (with cisplatin)	Open-label study	N/A	-----	Chemo-naïve or previously treated patients not amenable to surgery	• Pemetrexed with or without a platinum agent was active in patients with peritoneal mesothelioma demonstrating an ORR ranging from 12.5% to 24.1%.

Nonsquamous Non-small cell lung cancer (NSCLC)

Induction, neoadjuvant or adjuvant therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pemetrexed + carboplatin	2A	No	Phase 2	N/A	Regimen compliance DFS (secondary end-point)	Adjuvant therapy in patients with completely resected NSNSCLC	• Adjuvant therapy with pemetrexed plus carboplatin was an acceptable regimen in resected NSNSCLC. 85.4% of patients received all 4 cycles of therapy and median DFS ranged from 21-38mon.
Pemetrexed + cisplatin	2A	No	Phase 2 (TREAT), randomized	Vinorelbine + cisplatin	Safety Efficacy (secondary end-point)	Adjuvant therapy in patients with completely resected NSNSCLC	• Adjuvant therapy with pemetrexed plus cisplatin is associated with less toxicity than vinorelbine plus cisplatin.
Pemetrexed + cisplatin (Pem/Cis)	2A	No	Phase 3 (JIPANG), randomized	Vinorelbine + cisplatin (Vin/Cis)	RFS	Adjuvant therapy in patients with completely resected NSNSCLC	• Although this phase III study did not meet the primary endpoint, Pem/Cis had a similar efficacy to Vin/Cis with a better tolerability as postoperative adjuvant chemotherapy for Ns-NSCLC patients
Etoposide + cisplatin	2A		Randomized clinical trial	Observation	OS	Adjuvant therapy	• Cisplatin-based adjuvant chemotherapy (including regimens containing etoposide plus cisplatin) improves survival among patients with completely resected non-small-cell lung cancer. However, after 7.5 years of follow-up there were more deaths in the chemotherapy group and the

							benefit of chemotherapy decreased over time.
Gemcitabine + cisplatin	2A	No	Phase 3, randomized	No treatment	PFS	Neoadjuvant therapy	• Preoperative gemcitabine plus cisplatin followed by radical surgery improved survival in patients with clinical stage IIB/IIIA NSCLC.
Paclitaxel + carboplatin	2A	No	Randomized trial (CALGB 9633)	Observation	OS	Adjuvant therapy	• A statistically significant survival advantage for patients who had tumors > or = 4 cm supports consideration of adjuvant paclitaxel/carboplatin for stage IB patients who have large tumors.
Gemcitabine + carboplatin	2A	No	Phase2 (CJLSG 0503)	N/A	Completion rate of 4 cycles	Adjuvant therapy	• Adjuvant chemotherapy with a carboplatin and gemcitabine combination regimen has an acceptable toxicity profile, and the majority of patients completed 4 cycles of therapy.
Chemoradiation							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed + cisplatin + radiation therapy, followed by consolidation pemetrexed	2A	No	Phase 3 (PROCLAIM), randomized	Etoposide _ cisplatin + radiation therapy, followed by non-pemetrexed doublet consolidation therapy	OS	Chemo-radiation	• Pemetrexed-cisplatin combined with radiation therapy followed by consolidation pemetrexed was not superior to standard chemoradiotherapy for stage III unresectable nonsquamous non-small-cell lung cancer. The pemetrexed-cisplatin regimen was associated with less neutropenia and fewer grade 3 to 4 adverse events.

Cisplatin + vinblastine or Etoposide + cisplatin (with concurrent radiation)	2A	No	Phase 3 (RTOG 9410), randomized	Cisplatin + vinblastine (with sequential radiation)	OS	Chemo-radiation	• Concurrent delivery of cisplatin-based chemotherapy with radiation confers a long-term survival benefit compared with the sequential delivery of these therapies.
Paclitaxel (weekly) + carboplatin	2A	No	Phase 2	N/A	OS	Chemo-radiation	• Concurrent weekly paclitaxel, carboplatin, and TRT followed by consolidation is associated with a median survival of 16.3 months.
Locally advanced or metastatic disease – First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed + cisplatin	2A	Yes	Phase 3, randomized, non-inferiority trial	Gemcitabine + cisplatin	OS	Chemo-naive	• Patients with nonsquamous NSCLC had improved survival with pemetrexed plus cisplatin compared to gemcitabine plus cisplatin. The pemetrexed regimen was also associated with significantly lower rates of grade 3 or 4 adverse events.
Pemetrexed + cisplatin	2A	Yes	Phase 3 (LUX-Lung 3), randomized	Afatinib	PFS	First-line stage IIIB or IV adeno-carcinoma with **EGFR** mutation	• In patients with lung adenocarcinoma with EGFR mutations, first-line afatinib was associated with better control of cough and dyspnea compared with chemotherapy, although diarrhea, dysphagia, and sore mouth were worse. Global health status/QoL was also improved over time with afatinib compared with chemotherapy.

Pemetrexed + carboplatin	1 (PS 0-1) 2A (PS 2)	No	Phase 3, randomized	Gemcitabine + carboplatin	QOL	First-line	• Pemetrexed plus carboplatin provides similar quality of life and survival when compared with gemcitabine plus carboplatin with less hematologic toxicity and less need for supportive care.
Pemetrexed + carboplatin (for patients with PS 2)	2A	No	Phase 3, randomized, multi-center	Pemetrexed	OS	First-line	• Combination chemotherapy with carboplatin plus pemetrexed significantly improves survival in patients with advanced NSCLC and ECOG PS of 2.
Pemetrexed	2A (PS 2)	No	Phase 2, randomized, multi-center	Sequential pemetrexed, gemcitabine	-----	Chemo naïve	• Single-agent pemetrexed and sequential pemetrexed/gemcitabine have shown moderate activity and are well tolerated as first-line treatments for advanced NSCLC in elderly patients or patients unsuitable for platinum-based combination chemotherapy.
Pemetrexed	2A (PS 2)	No	Phase 2	N/A	-----	Chemo naïve	• Pemetrexed demonstrated an ORR of 23% as a single agent against advanced NSCLC.
Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed + bevacizumab (PemCBev)	2A (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (PointBreak), randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	• OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev
Bevacizumab + cisplatin + pemetrexed	2A (for adeno-	No	Phase 3 (AVAPERL	Bevacizumab + cisplatin + pemetrexed	PFS	First-line	• In patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus

followed by bevacizumab maintenance	carcinoma only; PS 0-1)		[MO22089]), randomized	followed by bevacizumab + pemetrexed maintenance			pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone
Pembrolizumab + carboplatin (or cisplatin) + pemetrexed, followed by pembrolizumab + pemetrexed (for up to 35 cycles)	1 preferred (for PD-L1 1-49%)	Yes	Phase 3 (KEYNOTE-189), double-blind, randomized (2:1)	Carboplatin (or cisplatin) + pemetrexed + placebo, followed by placebo + pemetrexed (for up to 35 cycles)	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
Pembrolizumab	1 preferred (for PD-L1 ≥ 50%)	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%.
Atezolizumab + carboplatin + paclitaxel + bevacizumab	1	Yes	Phase 3 (IMpower150), open-label,	Atezolizumab + carboplatin + paclitaxel (ACP) vs. bevacizumab +	PFS	First-line	• The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous

(ABCP), followed by atezolizumab + bevacizumab maintenance			randomized (1:1:1)	carboplatin + paclitaxel (BCP)			NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status
Cisplatin + etoposide	1 (for PS 0-1) 2A (PS 2)	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
Carboplatin + docetaxel (DCb) or Cisplatin + docetaxel (DC)	1 (for PS 0-1) 2A (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.
Gemcitabine	2A (PS 2)	No	Phase 2	N/A	-----	Chemo naïve	• This study confirms that single-agent gemcitabine is active in advanced NSCLC with an ORR of 21.1%.
Gemcitabine + docetaxel	2A (PS 2)	No	Phase 3, randomized, multi-center	Cisplatin + vinorelbine		Chemo naïve	• 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	2A (PS 2)	No	Randomized trial	Carboplatin + vinorelbine	ORR	Previously untreated	• VG compared to VC resulted in a similar overall response rate, favorable median survival and a better toxicity profile.
Continuation maintenance therapy							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pemetrexed	1	Yes (if no progression after 4 cycles of platinum-based first-line chemo)	Phase 3 (PARAMOUNT), randomized, double-blind Final OS results	Placebo	PFS	Maintenance therapy after 4 cycles of pemetrexed plus cisplatin	• Continuation maintenance with pemetrexed offers superior OS and PFS for patients with advanced non-squamous NSCLC with good performance status who have not progressed after induction therapy with pemetrexed plus cisplatin.
Pemetrexed (switch maintenance therapy)	2A	Yes	Phase 3, randomized, double-blind	Placebo	PFS	Maintenance therapy after no progression on 4 cycles of platinum-based chemo	• Maintenance therapy with pemetrexed offers improved progression-free and overall survival compared with placebo in patients with advanced non-small-cell lung cancer.
Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed + bevacizumab (PemCBev)	2A (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (PointBreak), randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	• OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (AVAPERL [MO22089]), randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab +	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

				pemetrexed maintenance			
Locally advanced or metastatic disease – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed	2A	No	Phase 3	Docetaxel	OS	Previously treated with chemotherapy (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
Nivolumab	1 (for first progression)	Yes	Phase 3 (CheckMate 057),	Docetaxel	OS	Subsequent	• Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival

	2A (for subsequent progression)		randomized, open-label				was longer with nivolumab than with docetaxel
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	After platinum-containing systemic therapy	• 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
Paclitaxel	2A (PS 2)	No	Phase 2	N/A	-----	Second-line after cisplatin-based therapy	• Weekly paclitaxel demonstrated an ORR of 15%. Patients with PS 0-1, non-squamous histology and with no progression within 4 months of first line cisplatin-based chemotherapy seem more likely to benefit from this treatment.

Thymomas/Thymic carcinoma

Thymoma – Second line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed	2A	No	Phase 2	N/A	-----	Previously treated	• Pemetrexed is an active agent in this heavily pretreated population of patients with recurrent thymic malignancies, especially thymoma. 2 complete responses and 3 partial responses were documented.
Gemcitabine + capecitabine	2A	No	Phase 2	N/A	-----	Previously treated	• Gemcitabine plus capecitabine is active in thymic epithelial tumors with 12 patients responding to treatment.
Sunitinib	2A (thymic carcinoma only)	No	Phase 2, open-label	N/A	ORR	Chemo-refractory	• Sunitinib is active in previously treated patients with thymic carcinoma with a partial response rate of 26% and stable disease rate of 65%.
Everolimus	2A	No	Phase 2, open-label, multi-center	N/A	DCR	After cisplatin-based therapy	• Everolimus may induce durable disease control in a high percentage of patients with thymoma or thymic carcinoma after cisplatin-based chemotherapy.
Octreotide	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Octreotide alone has modest activity in patients with octreotide scan-positive thymoma demonstrating an ORR of 30.3%.
Paclitaxel	2A	No	Case report	N/A	-----	After platinum-based therapy	• This is the first report to suggest that paclitaxel has anti-thymoma activity.
Etoposide	2A	No	Retrospective analysis	N/A	-----	Previously treated	• Oral etoposide monotherapy is an active option for pretreated patients with thymic epithelial tumors demonstrating an ORR of 15%.

Ovarian Cancer

Persistent or recurrent disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pemetrexed	2A	No	Phase 2	N/A	-----	Platinum-resistant	• Pemetrexed demonstrated clinical activity in the treatment of recurrent platinum-resistant ovarian cancer
Docetaxel	2A	No	Phase 2	N/A	---------	Second-line	• Docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer but, in view of significant hematologic toxicity
Etoposide (oral)	2A	No	Phase 2	N/A	---------	Second-line therapy	• Etoposide is active in platinum-resistant 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
Topotecan weekly (Tw)	2A	Yes	Phase 2 (TOWER), randomized	Topotecan conventional 5-day therapy (Tc)	ORR	Second-line and later	• Conventional dosing of topotecan was more effective than weekly dosing in terms of response. There was no difference in median PFS or median OS.