



Yervoy® (ipilimumab) (Intravenous)

Document Number: IC-0148

Last Review Date: 09/01/2020

Date of Origin: 11/28/2011

Dates Reviewed: 12/2011, 03/2012, 06/2012, 09/2012, 12/2012, 05/2013, 06/2013, 09/2013, 12/2013, 03/2014, 06/2014, 09/2014, 12/2014, 03/2015, 05/2015, 08/2015, 10/2015, 11/2015, 02/2016, 05/2016, 08/2016, 11/2016, 01/2017, 05/2017, 08/2017, 11/2017, 02/2018, 05/2018, 08/2018, 12/2018, 03/2019, 06/2019, 09/2019, 12/2019, 03/2020, 04/2020, 6/2020, 09/2020

I. Length of Authorization

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

Small Cell Lung Cancer (SCLC)/Renal Cell Carcinoma (RCC)/Cutaneous Melanoma (*excluding adjuvant therapy*)/Colorectal Cancer (CRC)/Small Bowel Adenocarcinoma/Hepatocellular Carcinoma (HCC)/Uveal Melanoma/CNS metastases from Melanoma (combination therapy with nivolumab) ^{1,6,9,10,11,17-19,20,27,29,33}

- Coverage will be provided for 12 weeks (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame) and may not be renewed*.

* *Requests for Cutaneous Melanoma may be renewed if the patient meets the provisions for re-induction therapy.*

Non-Small Cell Lung Cancer (NSCLC) ^{1,12,24}

- Coverage will be provided for up to a maximum of 2 years of therapy.

Cutaneous Melanoma (adjuvant therapy) ^{1,6,17}

- Coverage for adjuvant treatment will be provided for six months and may be renewed for up to a maximum of 3 years of therapy.

CNS metastases from Melanoma (single agent therapy) ^{8,28}

- Coverage will be provided for 12 weeks initially (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame). Coverage may be renewed in 6 month intervals thereafter.

II. Dosing Limits

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

- Yervoy 200 mg/40 mL injection:
 - 5 vials per 84 days (initially up to 5 vials per 21 days x 4 doses)
- Yervoy 50 mg/10 mL injection:

- 3 vials per 84 days (initially up to 3 vials per 21 days x 4 doses)

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

Indication	Billable Units (BU)	Per unit time (days)
Cutaneous Melanoma (excluding adjuvant therapy)	350 BU	21 days x 4 doses
Cutaneous Melanoma (adjuvant therapy), CNS metastases from melanoma	Initial: 1150 BU	Initial: 21 days x 4 doses
	Followed by: 1150 BU	Followed by: 84 days
Uveal Melanoma	1150 BU	21 days x 4 doses
CRC, RCC, SBA	115 BU	21 days x 4 doses
MPM, NSCLC	115 BU	42 days
SCLC, HCC	350 BU	21 days x 4 doses

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise indicated; **AND**

Cutaneous Melanoma † ⊕ ^{1,2,6,17}

- Patient has unresectable or metastatic disease OR disease with satellite/in-transit metastases or recurrence; **AND**
 - Used as first-line therapy in combination with nivolumab; **OR**
 - Used for disease previously treated with cytotoxic chemotherapy as a single agent in patients at least 12 years of age †; **OR**
 - Used as subsequent therapy after disease progression on first-line therapy or after maximum clinical benefit from BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
 - Used as a single agent or in combination with nivolumab if checkpoint inhibitor immunotherapy was not previously used; **OR**
 - Used as a single agent or in combination with nivolumab for patients who progressed on single agent checkpoint inhibitor immunotherapy; **OR**
 - Used for retreatment of disease as re-induction as a single agent or in combination with nivolumab in patients who experienced disease control (*i.e., complete or partial response or stable disease*) from prior checkpoint inhibitor therapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **AND**
 - Patient has completed initial induction (completion of 4 cycles within a 16 week period); **OR**
- Used as single-agent for adjuvant therapy; **AND**
 - Patient has pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †; **OR**
 - Patient has previously received anti-PD-1 therapy (e.g., nivolumab or pembrolizumab); **AND**

- Patient has local satellite/in-transit recurrence and has no evidence of disease (NED) after complete excision ‡; **OR**
- Patient has undergone therapeutic lymph node dissection (TLND) and/or complete resection of nodal recurrence ‡; **OR**
- Patient has undergone complete resection of distant metastatic disease ‡

Uveal Melanoma ‡ ^{2,20-23,32}

- Used as a single agent or in combination with nivolumab for distant metastatic disease

Renal Cell Carcinoma (RCC) † ^{1,2,18}

- Used in combination with nivolumab for clear cell histology; **AND**
 - Used as first-line therapy in patients with advanced, relapsed, or stage IV disease with poor or intermediate risk; **OR**
 - Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; **OR**
 - Used as subsequent therapy in patients with relapsed or stage IV disease

Small Cell Lung Cancer (SCLC) ‡ ^{2,3,9,33}

- Used as subsequent therapy in combination with nivolumab; **AND**
 - Used for relapse within 6 months following a complete response, partial response, or stable disease with initial treatment; **AND**
 - Patient did not relapse while on maintenance atezolizumab or durvalumab; **OR**
 - Used for primary progressive disease

Non-Small Cell Lung Cancer (NSCLC) † ^{2,16,24}

- Patient has metastatic disease with a high tumor mutational burden (TMB)* (i.e., ≥10 mutations per megabase); **AND**
 - Used in combination with nivolumab as first-line therapy; **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 one of the following:
 - Used in patients with PS 0-1 who have EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative** tumors and PD-L1 <1%
 - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E-mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements

- Used in patients with PS 0-2 for PD-L1 expression positive (PD-L1 $\geq 1\%$) tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET rearrangement negative**; **AND**
 - Used in combination with nivolumab; **OR**
 - Used in combination with nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, paclitaxel and carboplatin for squamous cell histology, etc.); **OR**
- Used as subsequent therapy; **AND**
 - Used for one of the following:
 - Used in patients with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and have received prior targeted therapy§
 - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements; **AND**
 - Used in combination with nivolumab; **OR**
 - Used in combination with nivolumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology; **OR**
 - Used in combination with nivolumab, paclitaxel and carboplatin for squamous cell histology

**TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.*

*** 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.*

Malignant Pleural Mesothelioma ‡ 2,5,25,26,34

- Used in combination with nivolumab as subsequent therapy

Central Nervous System (CNS) Cancer ‡ 2,4,8,10,11,27

- Used for the treatment of brain metastases in patients with melanoma; **AND**
- Used in combination with nivolumab or as a single agent; **AND**
 - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
 - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable treatment options; **OR**
 - Patient has recurrent limited brain metastases; **OR**
 - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

Colorectal Cancer † 1,2,19,31

- Patient is at least 12 years of age; **AND**
- Used in combination with nivolumab; **AND**
- Patient’s disease is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
 - Patient has advanced or metastatic disease that has progressed following a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based regimen; **OR**
 - Used as primary treatment for unresectable metastatic disease after previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months

Small Bowel Adenocarcinoma ‡ 2,19,29

- Patient has advanced or metastatic disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
- Used in combination with nivolumab in one of the following settings:
 - As subsequent therapy; **OR**
 - As initial therapy in patients with prior oxaliplatin exposure in the adjuvant setting or a contraindication

Hepatocellular Carcinoma (HCC) † 1,2,30

- Patient locally advanced, unresectable, inoperable, or metastatic disease; **AND**
- Used as subsequent therapy; **AND**
- Patient has Child-Pugh Class A disease; **AND**
- Used in combination with nivolumab; **AND**
- Patient has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.)

† FDA approved indication(s); ‡ Compendia recommended indication; Ⓞ 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 <ul style="list-style-type: none"> – Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib
<i>ALK</i> rearrangement-positive tumors <ul style="list-style-type: none"> – Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib
<i>ROS1</i> rearrangement-positive tumors <ul style="list-style-type: none"> – Ceritinib – Crizotinib

– Entrectinib
<i>BRAF</i> V600E-mutation positive tumors
– Dabrafenib ± Trametinib
– Vemurafenib
<i>NTRK</i> Gene Fusion positive tumors
– Larotrectinib
– Entrectinib
PD-1/PD-L1 expression-positive tumors ($\geq 1\%$)
– Pembrolizumab
– Atezolizumab
– Nivolumab ± ipilimumab
<i>MET</i> Exon-14 skipping mutations
– Capmatinib
– Crizotinib
<i>RET</i> rearrangement-positive tumors
– Selpercatinib
– Cabozantinib
– Vandetanib

IV. Renewal Criteria ^{1,2,6,9-12,17-29}

- Patient continues to meet universal and other 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: immune-mediated reactions (e.g. diarrhea/colitis, hepatitis, dermatitis/skin adverse reactions, neuropathies, pneumonitis, nephritis/renal dysfunction, encephalitis, endocrinopathies [i.e., hypophysitis, hypothyroidism, hyperthyroidism, adrenal insufficiency] and ocular toxicity, etc.), severe infusion reactions, complications of allogeneic hematopoietic stem cell transplant, etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Coverage may not be renewed for the following indications:
 - Small Cell Lung Cancer (SCLC)
 - Renal Cell Carcinoma (RCC)
 - Colorectal Cancer (CRC)
 - Small Bowel Adenocarcinoma (SBA)
 - Hepatocellular Carcinoma (HCC)
 - Cutaneous Melanoma (*excluding adjuvant therapy*)
 - Uveal Melanoma
 - CNS metastases from melanoma (combination therapy with nivolumab)

Cutaneous Melanoma Re-induction ‡

- *Refer to Section III for criteria (see Melanoma – Used for retreatment of disease as re-induction)*

Cutaneous Melanoma Maintenance therapy (adjuvant treatment)

- Patient has not exceeded a maximum of three (3) years of therapy

Non-Small Cell Lung Cancer (NSCLC)

- Patient has not exceeded a maximum of two (2) years of therapy

V. Dosage/Administration^{1,6,8-12,17-29,33,34}

Indication	Dose
Cutaneous Melanoma (excluding adjuvant therapy)	Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses
Cutaneous Melanoma (adjuvant therapy)	Administer 10 mg/kg intravenously every 3 weeks for 4 doses, followed by 10 mg/kg intravenously every 12 weeks for up to 3 years
Uveal Melanoma	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> – Administer 3 mg/kg or 10mg/kg intravenously every 3 weeks for 4 doses <p><u>In combination with nivolumab:</u></p> <ul style="list-style-type: none"> – Administer 3 mg/kg intravenously 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
CNS metastases from melanoma	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> – <u>Initial:</u> Administer 10 mg/kg intravenously every 3 weeks for 4 doses – <u>Subsequent (starting at week 24):</u> Administer 10 mg/kg intravenously every 12 weeks until disease progression or unacceptable toxicity <p><u>In combination with nivolumab:</u></p> <ul style="list-style-type: none"> – Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Small Cell Lung Cancer (SCLC), Hepatocellular Carcinoma (HCC)	Administer 3 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Non-Small Cell Lung Cancer (NSCLC)	<p><u>In combination with nivolumab:</u></p> <ul style="list-style-type: none"> – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 3 mg/kg every 2 weeks), until disease progression or unacceptable toxicity for up to 2 years <p><u>In combination with nivolumab and platinum-doublet chemotherapy:</u></p> <ul style="list-style-type: none"> – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 360 mg every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles), until disease progression or unacceptable toxicity for up to 2 years
Renal Cell Carcinoma (RCC), Colorectal Cancer	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)

(CRC), Small Bowel Adenocarcinoma (SBA)	
Malignant Pleural Mesothelioma	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease progression or unacceptable toxicity
<i>* All treatments given for a maximum of 4 doses must be administered within 16 weeks of the first dose.</i>	

VI. Billing Code/Availability Information

HCPCS code:

- J9228 – Injection, ipilimumab, 1 mg: 1 billable unit = 1 mg

NDC(s):

- Yervoy 200 mg/40 mL injection (single-use vial): 00003-2328-xx
- Yervoy 50 mg/10 mL injection (single-use vial): 00003-2327-xx

VII. References

1. Yervoy [package insert]. Princeton, NJ; Bristol Meyers Squib; June 2020. Accessed July 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ipilimumab. National Comprehensive Cancer Network, 2020. 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 July 2020.
3. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Small Cell Lung Cancer. Version 4.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
4. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Central Nervous System Cancers. Version 2.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
5. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Malignant Pleural Mesothelioma. Version 1.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.

6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010 Aug 19; 363(8):711-23.
7. Wilgenhof S, Du Four S, Vandenbroucke F, et al. Single-center experience with ipilimumab in an expanded access program for patients with pretreated advanced melanoma. *J Immunother*. 2013 Apr; 36(3):215-22.
8. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012 May; 13(5):459-65.
9. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016 Jul;17(7):883-895.
10. Tawbi HA, Forsyth PAJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. *Journal of Clinical Oncology* 35, no. 15_suppl (May 2017) 9507-9507.
11. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC). *Journal of Clinical Oncology* 35, no. 15_suppl (May 2017) 9508-9508.
12. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; 378:2093-2104.
13. 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.
14. 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
15. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. *BMJ*. 2016 Feb 29;352:i788.
16. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
17. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-

- blind, phase 3 trial. *Lancet Oncol.* 2015 May;16(5):522-30. doi: 10.1016/S1470-2045(15)70122-1. Epub 2015 Mar 31.
18. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2018 Apr 5;378(14):1277-1290. doi: 10.1056/NEJMoa1712126. Epub 2018 Mar 21.
 19. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol.* 2018 Mar 10;36(8):773-779. doi: 10.1200/JCO.2017.76.9901. Epub 2018 Jan 20.
 20. Piulats JM, Cruz-Merino LDL, Garcia MTC, et al. Phase II multicenter, single arm, open label study of nivolumab in combination with ipilimumab in untreated patients with metastatic uveal melanoma (GEM1402.NCT02626962). *Annals of Oncology*, Volume 29, Issue suppl_8, October 2018, mdy289.003, <https://doi.org/10.1093/annonc/mdy289.003>.
 21. 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 Mar 11;10(3):e0118564. doi: 10.1371/journal.pone.0118564. eCollection 2015.
 22. Danielli R, Ridolfi R, Chiarion-Sileni V, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. *Cancer Immunol Immunother.* 2012 Jan;61(1):41-8. doi: 10.1007/s00262-011-1089-0. Epub 2011 Aug 11.
 23. Luke JJ, Callahan MK, Postow MA, et al. Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience. *Cancer.* 2013 Oct 15;119(20):3687-95. doi: 10.1002/cncr.28282. Epub 2013 Aug 2.
 24. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med.* 2019 Nov 21;381(21):2020-2031. doi: 10.1056/NEJMoa1910231. Epub 2019 Sep 28.
 25. 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. doi: 10.1016/S1470-2045(18)30765-4. Epub 2019 Jan 16.
 26. 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. doi: 10.1016/S2213-2600(18)30420-X. Epub 2019 Jan 16.
 27. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* 2018 May;19(5):672-681. doi: 10.1016/S1470-2045(18)30139-6. Epub 2018 Mar 27.

28. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012 May;13(5):459-65. doi: 10.1016/S1470-2045(12)70090-6. Epub 2012 Mar 27.
29. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Small Bowel Adenocarcinoma. Version 2.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
30. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017 Jun 24;389(10088):2492-2502. doi: 10.1016/S0140-6736(17)31046-2. Epub 2017 Apr 20.
31. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Colon Cancer. Version 4.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
32. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Uveal Melanoma. Version 1.2020. National Comprehensive Cancer Network, 2020. 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 Guidelines, go online to NCCN.org. Accessed July 2020.
33. Hellmann M, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032. *J Clin Oncol* 2017; 35 Abstract 8503.
34. Zalcman G, Mazieres J, Greillier L, et al. Second- or third-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 [abstract]. *Ann Oncol* 2017; 28:Abstract LBA58_PR.
35. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231.
36. 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.

37. Palmetto GBA. Local Coverage Article (LCA): Billing and Coding: Chemotherapy (A56141). Centers for Medicare & Medicaid Services, Inc. Updated on 05/26/2020 with effective date 04/30/2020. Accessed July 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
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

YERVOY® (ipilimumab) Prior Auth Criteria

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

©2020, Magellan Rx Management

ICD-10	ICD-10 Description
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and 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
C38.4	Malignant neoplasm of pleura
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 melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part 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
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
C45.0	Mesothelioma of pleura
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis

YERVOY® (ipilimumab) Prior Auth Criteria

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

©2020, Magellan Rx Management

ICD-10	ICD-10 Description
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C7A.1	Malignant poorly differentiated neuroendocrine tumors
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.820	Personal history of malignant melanoma of skin

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): J&M	NCD/LCD/Article Document (s): A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAAA	

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

YERVOY® (ipilimumab) Prior Auth Criteria

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.

©2020, Magellan Rx Management

Medicare Part B Administrative Contractor (MAC) Jurisdictions

Jurisdiction	Applicable State/US Territory	Contractor
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