Drug Policy:

Yervoy™ (ipilimumab)

POLICY NUMBER UM ONC_1201	SUBJECT Yervoy™ (ipilimumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 6
DATES COMMITTEE REVIEWED 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22, 02/08/23, 03/08/23, 05/10/23, 06/12/24	**APPROVAL DATE** June 12, 2024	**EFFECTIVE DATE** June 28, 2024	**COMMITTEE APPROVAL DATES** 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22, 02/08/23, 03/08/23, 05/10/23, 06/12/24	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
NCQA STANDARDS UM 2		**ADDITIONAL AREAS OF IMPACT**		
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Yervoy (ipilimumab) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided:

1. The requested medication was used within the last year, AND
2. The member has not experienced disease progression and/or no intolerance to the requested medication, AND
3. Additional medication(s) are not being added to the continuation request.

B. Colorectal Cancer

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab) for the treatment of adult and pediatric members 12 years and older with microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR), or polymerase epsilon/delta (POLE/POLD1) mutation unresectable/metastatic/recurrent colorectal cancer that has progressed following treatment with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, and irinotecan.

C. Esophageal Squamous Cell Carcinoma (ESCC)

1. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab) as first-line treatment of unresectable advanced/recurrent/metastatic squamous cell esophageal carcinoma, regardless of PD-L1 status.
2. NOTE: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the dose of Yervoy (ipilimumab), supported by Evolent policy, is 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years. When the above combination is used with chemotherapy, chemotherapy may continue until disease progression or unacceptable toxicity.

D. Hepatocellular Carcinoma (HCC)

1. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not supported by Evolent Policy for the first line treatment of unresectable/metastatic recurrent hepatocellular carcinoma. This policy position is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) showing superior outcomes compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.
2. Yervoy (ipilimumab) + Opdivo (nivolumab) may be used as subsequent line therapy for members with unresectable/metastatic hepatocellular carcinoma if the member has not been previously treated with a checkpoint inhibitor. This recommendation is based on the lack of peer-reviewed literature/data to support the use of the above regimen in patients previously treated with a checkpoint inhibitor (e.g., atezolizumab with or without bevacizumab).

E. Malignant Pleural Mesothelioma

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab), as first line therapy for members with metastatic/unresectable Malignant Pleural Mesothelioma. Evolent policy supports a Yervoy (ipilimumab) dose of 1 mg/kg every 6 weeks; Opdivo (nivolumab) may be dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

F. Melanoma

1. NOTE: Yervoy (ipilimumab) +/- Opdivo (nivolumab) is not supported by Evolent Policy for the adjuvant treatment of resected melanoma. This policy position is based on the results of the CheckMate 915 randomized trial showing inferior outcomes with Yervoy (ipilimumab) + Opdivo (nivolumab) compared to single agent Opdivo (nivolumab). Please refer to Evolent alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.
2. The member has cutaneous melanoma and Yervoy (ipilimumab) may be used as any of the following:
    a. For unresectable or metastatic melanoma:
        i. First line therapy in combination with Opdivo (nivolumab) OR
        ii. Second line or subsequent therapy as a single agent or in combination with Opdivo (nivolumab) in members who have not received prior therapy with Yervoy (ipilimumab).

iii. NOTE: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the use of Yervoy (ipilimumab) 3 mg/kg is not supported by Evolent Policy. The dose of Yervoy (ipilimumab), supported by Evolent policy, should not exceed 1 mg/kg every 3 weeks for a maximum of 4 cycles with Opdivo (nivolumab) dosed at 3 mg/kg (360 mg) every 3 weeks followed by maintenance Opdivo (nivolumab), the latter may be dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks. The above policy position is based on the results of the CheckMate 511 trial which demonstrated a significantly lower incidence of treatment-related adverse events and equivalent survival with Ipilimumab 1 mg/kg compared to 3 mg/kg, when used in combination with Opdivo (nivolumab) in patients with advanced or metastatic melanoma.

G. Non-Small Cell Lung Cancer

1. Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy may be used in metastatic Non- Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression less than 1%.
2. NOTE 1: Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy is a not supported by Evolent Policy when used for the treatment of metastatic Non-Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression 1% or higher. This policy position is based on the lack of Level 1 Evidence (randomized clinical trials and/or meta-analyses) to show superior outcomes with Yervoy (ipilimumab) + Opdivo (nivolumab), with or without chemotherapy, compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.
3. NOTE 2: The dose of Yervoy (ipilimumab), supported by Evolent policy, should not exceed 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

H. Renal Cell Carcinoma

1. The member has a relapsed/metastatic or surgically unresectable disease AND
2. Yervoy (ipilimumab) is being used in combination with Opdivo (nivolumab) for 4 cycles followed by single agent nivolumab for Intermediate or Poor risk disease (as defined by the IMDC criteria).
   a. NOTE: The dose of Yervoy (ipilimumab), supported by Evolent policy, in this setting is 1mg/kg IV every 3 weeks for a total of 4 cycles. Opdivo (nivolumab) may be dosed at 3 mg/kg (up to 360 mg) every 3 weeks for 4 cycles followed by single agent Opdivo (nivolumab) maintenance therapy dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks, until disease progression or unacceptable toxicity.

IMDC Criteria:

CRITERIA= Assign 1 point for each	**RISK CATEGORIES= RISK SCORE**
Time to systemic treatment less than 1 year from diagnosis	Favorable Risk = 0
Performance Status < 80% Karnofsky Scale	Intermediate Risk = 1-2
Hemoglobin < LLN; <12 g/dL	Poor Risk= 3-6
Calcium > ULN; > 12 mg/dL	

Neutrophils > ULN	
Platelets > ULN	

III. EXCLUSION CRITERIA

A. Members who experience severe or life-threatening reactions to Yervoy (ipilimumab) including any moderate immune mediated adverse events or symptomatic endocrinopathy.

B. Disease progression during or following treatment with Yervoy (ipilimumab).

C. Dosing exceeds single dose limit of Yervoy (ipilimumab) 3mg/kg when Yervoy is being used as a single agent.

D. Dosing exceeds 1 mg/kg when Yervoy (ipilimumab) is being given in combination with Opdivo (nivolumab). The single dose limit of Opdivo (nivolumab) is 240 mg every 2 weeks, 360 mg every 3 weeks, 480 mg every 4 weeks (regardless of weight).

E. Investigational use of Yervoy (ipilimumab) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

A. Please refer to the FDA label/package insert and/or ASCO guidelines for management of immunotherapy toxicities.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Weber JS, et al. Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915). J Clin Oncol. 2023 Jan 20;41(3):517-527.

B. Overman MJ, 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

C. Lenz HJ, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol. 2022 Jan 10;40(2):161-170. doi: 10.1200/JCO.21.01015

D. Brahmer JR, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2022 Oct 12:101200JCO2201503.

E. Paz-Ares LG, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients (pts) with metastatic non–small cell lung cancer (NSCLC): 3-year update from CheckMate 9LA. J Clin Oncol. 2022;40(17_suppl):LBA9026. doi:10.1200/JCO.2022.40.17_suppl.LBA9026

F. Lebbe C, Meyer N, Mortier L, et al: Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 trial. J Clin Oncol 2019; 37(11):867-875.

G. Lebbe C, et al. Two dosing regimens of nivolumab (NIVO) plus ipilimumab (IPI) for advanced (adv) melanoma: Three-year results of CheckMate 511. Journal of Clinical Oncology 2021 39:15_suppl, 9516-9516.

H. Yau T, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA Oncol. 2020 Nov 1;6(11):e204564.

I. Doki Y et al. CheckMate 648 Clinical Trial. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022 Feb 3;386(5):449-462.

J. Baas P, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-386.

K. Weber J, et al. CheckMate 238 Collaborators. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-1835.

L. Motzer RJ, et al. CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277-1290.

M. Yervoy prescribing information. Princeton, NJ. Bristol-Myers Squibb Company 2021.

N. Clinical Pharmacology Elsevier Gold Standard 2023.

O. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2023.

P. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2023.

Q. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2023.

R. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

S. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.