Drug Policy:

Opdivo™ (nivolumab)

POLICY NUMBER UM ONC_1274	SUBJECT Opdivo™ (nivolumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 8
DATES COMMITTEE REVIEWED 03/27/15, 10/14/15, 04/13/16, 06/22/16, 12/21/16, 03/08/17, 03/14/18, 03/13/19, 12/11/19, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 10/14/20, 11/11/20, 12/09/20, 02/10/21, 04/14/21, 05/12/21, 06/09/21, 09/08/21, 11/15/21, 02/09/22, 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, 08/09/23, 12/13/2023, 03/13/24, 04/10/24, 06/12/24, 09/18/24, 11/13/24	**APPROVAL DATE** November 13, 2024	**EFFECTIVE DATE** November 29, 2024	**COMMITTEE APPROVAL DATES** 03/27/15, 10/14/15, 04/13/16, 06/22/16, 12/21/16, 03/08/17, 03/14/18, 03/13/19, 12/11/19, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 10/14/20, 11/11/20, 12/09/20, 02/10/21, 04/14/21, 05/12/21, 06/09/21, 09/08/21, 11/15/21, 02/09/22, 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, 08/09/23, 12/13/2023, 03/13/24, 04/10/24, 06/12/24, 09/18/24, 11/13/24	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Evolent Specialty Services Clinical Guideline Review 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 Opdivo (nivolumab) 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. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab) 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 Carcinoma

1. Squamous Cell Carcinoma of Esophagus

a. The member has advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC), regardless of PD-L1 status AND

i. Opdivo (nivolumab) may be used as monotherapy in a member who has experienced disease progression on or after prior fluoropyrimidine based chemotherapy (e.g., fluorouracil or capecitabine) and platinum-based chemotherapy (e.g., cisplatin, carboplatin, or oxaliplatin) OR

ii. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab) OR in combination with fluoropyrimidine (e.g., fluorouracil or capecitabine) + platinum (e.g., cisplatin, carboplatin, or oxaliplatin) containing chemotherapy as first-line treatment.

- 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.

2. **Adenocarcinoma of Esophagus**: The member has advanced/metastatic esophageal adenocarcinoma with a PD-L1 CPS greater than or equal to 5 and Opdivo (nivolumab) may be used as primary/initial therapy in combination with an oxaliplatin containing chemotherapy (e.g., FOLFOX/CapeOX).
3. **Squamous Cell Carcinoma and Adenocarcinoma of Esophagus**: Opdivo (nivolumab) may be used as monotherapy, for a total duration of 1 year, for members with stage II or III esophageal carcinoma who are found to have residual disease after neoadjuvant chemoradiotherapy and surgery.

D. Gastric Cancer and Gastroesophageal Junction Cancer

1. The member has advanced/metastatic gastric or gastroesophageal junction cancer with a PD-L1 CPS greater than or equal to 5 AND
2. Opdivo (nivolumab) may be used as primary/initial therapy in combination with an oxaliplatin containing chemotherapy (e.g., FOLFOX/CapeOX

E. Head and Neck Cancer

1. The member has recurrent/metastatic non-nasopharyngeal squamous cell carcinoma of the head and neck cancer and Opdivo (nivolumab) is being used as a single agent following disease progression during or after platinum-based chemotherapy.

F. Hepatocellular Carcinoma (HCC)

1. 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.
2. 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 clinical trials and/or meta-analyses) showing superior outcomes and or lower toxicities of the above regimen in comparison to [bevacizumab + atezolizumab] or [tremelimumab + durvalumab] in the first line setting. Please refer to Evolent alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.

G. Hodgkin's Lymphoma

1. Opdivo may be used in a member with classical Hodgkin's Lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) AND post-transplantation Adcetris (brentuximab vedotin) OR has progressed after 3 or more prior lines of systemic therapy, and the member has not received prior therapy with an Immune Checkpoint Inhibitor.
2. NOTE: [Opdivo (nivolumab) + Adcetris (brentuximab vedotin)] is not supported by Evolent Policy for the treatment of Hodgkin's Lymphoma. This policy position is based on the lack of Level 1 evidence (randomized clinical trials and/or meta-analyses) to support superior outcomes with the above combination compared to either single agent Opdivo (nivolumab) or single agent Adcetris (brentuximab). Please refer to Evolent alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.

H. Malignant Pleural Mesothelioma

1. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab), as first line or subsequent line therapy (if not used previously) for members with metastatic/unresectable Malignant Pleural Mesothelioma. The dose of Opdivo (nivolumab) is 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks + Yervoy (ipilimumab) 1 mg/kg every 6 weeks until disease progression, unacceptable toxicities, or up to 24 months of therapy in the above setting.

I. Melanoma

1. As a single agent or in combination with Yervoy (ipilimumab) for recurrent/metastatic melanoma as initial therapy or as subsequent therapy (if the combination was not used previously).
2. NOTE 1: Yervoy (ipilimumab) +/- Opdivo (nivolumab) is not supported by Evolent Policy for the adjuvant treatment of high risk resected melanoma. This policy position is based on 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.
3. NOTE 2: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab) for metastatic/advanced/unresectable melanoma, 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 (up to 360 mg) every 3 weeks followed by maintenance Opdivo (nivolumab) 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 comparable Overall

Survival with Yervoy (ipilimumab) 1 mg/kg compared to 3 mg/kg, when used in combination with Opdivo (nivolumab) in patients with advanced or metastatic melanoma.

4. NOTE 3: In brain metastases, Opdivo (nivolumab) 1 mg/kg in combination with Yervoy (ipilimumab) 3 mg/kg every 3 weeks for a maximum of 4 cycles followed by maintenance Opdivo (nivolumab) 240 mg every 2 weeks or 480 mg every 4 weeks is recommended.

J. Non-Small Cell Lung Cancer (NSCLC)

1. Opdivo (nivolumab) may be used as neoadjuvant therapy in combination with platinum doublet chemotherapy for up to 4 cycles in members with early stage IB-IIIA NSCLC with tumor size greater than or equal to 4 cm that is negative for EGFR and ALK mutation, regardless of the tumor PD-L1 status, followed by single-agent Opdivo (nivolumab) after surgery as adjuvant treatment for a maximum of 13 cycles OR
2. Opdivo (nivolumab) may be used as a single agent as second line or subsequent line therapy for ANY of the following:
    a. For members with recurrent/metastatic NSCLC that is negative for EGFR and ALK genomic alterations, who have experienced disease progression on platinum-based chemotherapy, except for prior treatment failure with Opdivo (nivolumab) or another checkpoint inhibitor OR
    b. For members, whose cancer is positive for EGFR/ALK genomic alterations and who have experienced disease progression on targeted therapy and platinum-based therapy, except for prior treatment failure with Opdivo (nivolumab) or another checkpoint inhibitor OR
3. Opdivo (nivolumab) + Yervoy (ipilimumab) may be used in metastatic Non- Small Cell Lung Cancer (both squamous and non-squamous) with or without chemotherapy that is EGFR and ALK negative and has a PDL-1 expression less than 1%.
4. NOTE 1: [Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy] is a not supported by Evolent Policy for use in 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 and/or lower toxicities 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.
5. 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.

K. Renal Cell Carcinoma

1. The member has recurrent/metastatic/surgically unresectable stage IV disease and Opdivo (nivolumab) is being used for ONE of the following:
    a. As first line therapy as monotherapy or in combination with Yervoy (ipilimumab) for IMDC Intermediate or Poor Risk disease.
        i. NOTE: Per Evolent policy, the dosing of the 2 agents is as follows: In the above setting, ipilimumab is dosed at 1 mg/kg every 3 weeks x 4 cycles only, nivolumab is dosed at 3 mg/kg (up to 360 mg) every 3 weeks x 4 cycles followed by single agent 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.
    b. As first line treatment in combination with cabozantinib for IMDC Intermediate/Poor risk disease.

c. IMDC criteria: Please see table below.

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	

OR

d. As subsequent therapy as a single agent and the member has disease progression on prior therapy with one or more tyrosine kinase inhibitors [e.g., Nexavar (sorafenib), Sutent (sunitinib), Cabometyx (cabozantinib), or Votrient (pazopanib)] in members who have not received prior therapy with an Immune Checkpoint Inhibitor.

L. Small Cell Lung Cancer (SCLC)

1. NOTE: Single agent Opdivo (nivolumab) is not supported by Evolent policy for the treatment of metastatic Small Cell Lung Cancer. This policy position is based on the fact that the above indication was withdrawn by the FDA; confirmatory studies [CheckMate-451 and CheckMate-331] failed to meet the primary endpoint of overall survival compared with standard chemotherapy. Please refer to Evolent alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.

M. Urothelial Carcinoma including Upper Tract and Urethral Carcinomas

1. The member has locally advanced or metastatic urothelial carcinoma and has experienced disease progression during or after platinum-based chemotherapy OR
2. Opdivo (nivolumab) may be used as adjuvant treatment up to a maximum of 1 year duration in members with urothelial carcinoma (originating in the bladder, ureter, or renal pelvis) with a high risk for recurrence as defined by any of the following: a. Pathologic stage pT3,pT4a, or p Node+ and member not eligible for or declined adjuvant cisplatin-based chemotherapy b. Pathologic stage of ypT2 to ypT4, or ypNode+ for members who received neoadjuvant cisplatin-based chemotherapy OR
3. Opdivo (nivolumab) may be used as monotherapy for members with high-risk, non-muscle invasive bladder cancer, with Tis with or without papillary tumors, who are not eligible for cystectomy, and is refractory to/not responding to treatment with BCG.
4. Opdivo (nivolumab) may be used in combination with cisplatin and gemcitabine for first-line treatment in adult members with unresectable or metastatic urothelial carcinoma.

III. EXCLUSION CRITERIA

A. Disease progression while taking Opdivo (nivolumab) or other PD-1/PDL-1 therapy, except when member is being switched to combination Opdivo (nivolumab) + Yervoy (ipilimumab) for advanced/metastatic melanoma.

B. Dosing exceeds single dose limit of 240 mg every 2 weeks, 360 mg every 3 weeks, 480 mg every 4 weeks (regardless of weight).

C. For the adjuvant treatment of Melanoma, length of Opdivo (nivolumab) treatment is greater than 12 months.

D. Investigational use of Opdivo (nivolumab) 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 for details regarding these topics.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Van der Heijden M, et al. Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. N Engl J Med 2023; 389 (19): 1778-1789. DOI: 10.1056/NEJMoa2309863

B. Cascone T, et al; CheckMate 77T Investigators. Perioperative Nivolumab in Resectable Lung Cancer. N Engl J Med. 2024 May 16;390(19):1756-1769. doi: 10.1056/NEJMoa2311926

C. Tawbi HA, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med. 2018 Aug 23;379(8):722-730. doi: 10.1056/NEJMoa1805453

D. 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

E. 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

F. 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.

G. 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.

H. 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

I. 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.

J. 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.

K. 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.

L. 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.

M. Owonikoko TK, et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol. 2021 Apr 20;39(12):1349-1359.

N. Bajorin DF, et al. CheckMate 274 Clinical Trial. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102-2114.

O. Forde PM, et al. CHECKMATE 816 Clinical Trial. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer N Engl J Med. 2022 May 26;386(21):1973-1985.

P. Larkin J, et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol. 2018 Feb 1;36(4):383-390.

Q. Kelly RJ, et al. CheckMate 577 Trial. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021 Apr 1;384(13):1191-1203.

R. Choueiri TK, et al. CheckMate 9ER Trial. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021 Mar 4;384(9):829-841.

S. Fennell DA, et al. CONFIRM Trial. Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial. Lancet Oncol. 2021 Nov;22(11):1530-1540.

T. Opdivo prescribing information. Bristol-Myers Squibb Company. Princeton, NJ 2022.

U. Clinical Pharmacology Elsevier Gold Standard 2023.

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

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

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

Y. 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.

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