Evolent Clinical Guideline 3018 for Opdivo™ and Opdivo Qvantig™ (nivolumab IV/SC)

Guideline Number: Evolent_CG_3018	**Applicable Codes**	
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STATEMENT

Purpose

To define and describe the accepted indications for Opdivo and Opdivo Qvantig (nivolumab IV/SC) 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.

INDICATIONS

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

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Colorectal Cancer

- 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, or recurrent colorectal cancer.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Esophageal Carcinoma

- Squamous Cell Carcinoma of Esophagus
  - The member has advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC), regardless of PD-L1 status AND
  - 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

- 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.

- 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).
- 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Gastric Cancer and Gastroesophageal Junction Cancer

- The member has advanced/metastatic gastric or gastroesophageal junction cancer 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).
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab).

Head and Neck Cancer

- 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab).

Hepatocellular Carcinoma (HCC)

- Opdivo (nivolumab) + Yervoy (ipilimumab) may be used as first line therapy for adult members with unresectable/metastatic hepatocellular carcinoma (Child-Pugh Class A score only) for up to 4 cycles, followed by single-agent Opdivo (nivolumab) for up to 24 cycles.

CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

- Opdivo (nivolumab) + Yervoy (ipilimumab) may be used as subsequent line therapy in adult members with unresectable/metastatic/recurrent hepatocellular carcinoma if the member has not been previously treated with a checkpoint inhibitor.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Hodgkin's Lymphoma

- Opdivo (nivolumab) may be used in combination with doxorubicin, vinblastine, and dacarbazine as first line therapy for members with newly diagnosed, stage III-IV classical Hodgkin's Lymphoma.

HODGKIN LYMPHOMA STAGING[1]

Table 1

Definitions of Stages in Hodgkin Lymphoma[2]

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A No systemic symptoms present

B Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1861.

[1] For additional information regarding the staging of Hodgkin lymphoma, refer to: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification. J Clin Oncol 2014;32:3059-3068.

[2] FDG-PET scans are useful for upstaging in stage I–II disease. If there is FDG-PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. FDG-PET scans may demonstrate increased avidity in lymphoid tissue unrelated to lymphoma in persons with HIV, particularly if HIV is not well-controlled (i.e. acute/subacute HIV infection, advanced immunosuppression and or viremia) and in the presence of opportunistic infections.

- Opdivo (nivolumab) 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.
- 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 **Evolent Pathways**.

Malignant Pleural Mesothelioma

- 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Melanoma

- 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).
- 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 **Evolent Pathways**.
- 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.

- 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Non-Small Cell Lung Cancer (NSCLC)

- 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
- Opdivo (nivolumab) may be used as a single agent as second line or subsequent line therapy for ANY of the following:
    - 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
    - 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
- Opdivo (nivolumab) + Yervoy (ipilimumab) with or without chemotherapy may be used in metastatic NSCLC (both squamous and non-squamous) that is EGFR and ALK negative and has a PD-L1 expression less than 1%.
- Opdivo (nivolumab) + Yervoy (ipilimumab) with or without chemotherapy may be used in metastatic NSCLC (both squamous and non-squamous) that is positive for STK11 or KEAP1 mutations, regardless of PD-L1 expression.
- NOTE 1: Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy is not supported by Evolent Policy for use in metastatic NSCLC (both squamous and non-squamous) that is EGFR and ALK negative and has a PD-L1 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 **Evolent Pathways**.
- 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Renal Cell Carcinoma

- The member has recurrent/metastatic/surgically unresectable stage IV disease and Opdivo (nivolumab) is being used for ONE of the following:
  - As first line therapy as monotherapy or in combination with Yervoy (ipilimumab) for IMDC Intermediate or Poor Risk disease.
    - 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.
  - As first line treatment in combination with cabozantinib for IMDC Intermediate/Poor risk disease.
  - 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

  - 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.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Small Cell Lung Cancer (SCLC)

- 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 **Evolent Pathways**.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab) EXCEPT when it is used in combination with Yervoy (ipilimumab).

Urothelial Carcinoma including Upper Tract and Urethral Carcinomas

- The member has locally advanced or metastatic urothelial carcinoma and has experienced disease progression during or after platinum-based chemotherapy OR
- 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
- 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.
- Opdivo (nivolumab) may be used in combination with cisplatin and gemcitabine for first-line treatment in adult members with unresectable or metastatic urothelial carcinoma.
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be substituted for Opdivo (nivolumab).

CONTRAINDICATIONS/WARNINGS

- None

EXCLUSION CRITERIA

- Disease progression while taking Opdivo and Opdivo Qvantig (nivolumab IV/SC) or other PD-1/PD-L1 therapy, except when member is being switched to combination Opdivo (nivolumab) + Yervoy (ipilimumab) for advanced/metastatic melanoma.
- Dosing exceeds single dose limit of Opdivo (nivolumab) 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks (regardless of weight).

- Dosing exceeds single dose limit of Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) 600 mg/10,000 units every 2 weeks, 900 mg/15,000 units every 3 weeks, or 1200 mg/20,000 units every 4 weeks.
- For the adjuvant treatment of Melanoma, length of Opdivo and Opdivo Qvantig (nivolumab IV/SC) treatment is greater than 12 months.
- Use of Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) in combination with Yervoy (ipilimumab) in any cancer.
- Investigational use of Opdivo and Opdivo Qvantig (nivolumab IV/SC) 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:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
    - 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.
    - 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).
    - 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.
    - That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
    - 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.

CODING AND STANDARDS

Codes

- J9299 - Injection, nivolumab, 1 mg
- J9289 - Injection, nivolumab, 2 mg and hyaluronidase-nvhy

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
July 2026	• Updated NSCLC indication • Updated references
April 2026	• Updated NSCLC indication • Updated references
February 2026	• Updated references
October 2025	• Removed nivolumab + ipilimumab as a low-value regimen in subsequent line setting of metastatic hepatocellular carcinoma • Updated policy history section • Updated references
July 2025	• Under metastatic hepatocellular carcinoma indication, updated subsequent line therapy with nivolumab as a low-value regimen, and added use with ipilimumab in first line setting • Added Child-Pugh Score table to hepatocellular carcinoma indication • Updated HCPC code
February 2025	• Converted to new Evolent policy template • This guideline replaces UM ONC_1274 Opdivo (nivolumab) • Added new formulation to approved indications

Date	Summary
	• Updated references
January 2025	• Updated colorectal cancer indication verbiage to state the following: “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, or recurrent colorectal cancer”
December 2024	• Added use in combination with doxorubicin, vinblastine, and dacarbazine as first line therapy for members with newly diagnosed, stage III-IV classical Hodgkin’s Lymphoma • Added staging table for Hodgkin’s Lymphoma • Added Evolent disclaimer language • Added Coding Information section with HCPCS code • Added new reference
November 2024	• Updated NSCLC indication with: “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” • Updated references

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of

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