UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Opdivo Qvantig Utilization Management Medical Policy

- Opdivo Qvantig™ (nivolumab and hyaluronidase-nvhy subcutaneous injection – Bristol-Myers Squibb and Halozyme)

REVIEW DATE: 08/06/2025

OVERVIEW

Opdivo Qvantiq, a programmed death receptor-1 (PD-1) blocking antibody and hyaluronidase-nvhy, is indicated for the following uses:[1]

- **Colorectal cancer**, in adults with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or as monotherapy following treatment with Opdivo (nivolumab intravenous infusion) and Yervoy (ipilimumab intravenous infusion) combination therapy.
  Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of MSI-H or dMMR metastatic colorectal cancer.
  This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- **Esophageal cancer**:
  - In adults, with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemotherapy.
  - In adults for the first-line treatment of unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy whose tumors express programmed death-ligand 1 (PD-L1 [≥ 1%]).
    Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of unresectable advanced or metastatic esophageal squamous cell carcinoma.
  - In adults with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, as monotherapy.
- **Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma**, in adults with advanced or metastatic disease in combination with fluoropyrimidine- and platinum-containing chemotherapy whose tumors express PD-L1 (≥ 1%).
- **Head and neck squamous cell carcinoma**, in adults with recurrent or metastatic disease with progression on or after platinum-based therapy, as monotherapy.
- **Hepatocellular carcinoma**, in adults who have been previously treated with Nexavar® (sorafenib tablets) and following treatment with Opdivo and Yervoy, as monotherapy.
  Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of hepatocellular carcinoma.
  This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- **Melanoma**:
  - In adults with unresectable or metastatic disease, as monotherapy.
  - In adults with unresectable or metastatic melanoma following treatment with Opdivo and Yervoy combination therapy, as monotherapy.

Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of unresectable or metastatic melanoma.
  - For the adjuvant treatment of adults with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma, as monotherapy.
- **Non-small cell lung cancer**:
  - In adults, for the neoadjuvant treatment of resectable (tumors ≥ 4 cm or node positive) disease in combination with platinum-doublet chemotherapy.
  - In adults, for the neoadjuvant treatment of resectable (tumors ≥ 4 cm or node positive) disease with no known epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements in combination with platinum-doublet chemotherapy, followed by Opdivo Qvantig monotherapy in the adjuvant setting after surgical resection.
  - In adults with metastatic disease with disease progression on or after platinum-based chemotherapy as monotherapy. Patients with *EGFR* or *ALK* tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo Qvantig.
    Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of metastatic non-small cell lung cancer.
- **Renal cell carcinoma**:
  - In adults, for the first-line treatment of intermediate or poor risk advanced disease following treatment with Opdivo and Yervoy combination therapy.
    Limitation of use: Opdivo Qvantig is not indicated in combination with Yervoy for the treatment of renal cell carcinoma.
  - In combination with Cabometyx® (cabozantinib tablets), for the first-line treatment of adults with advanced disease.
  - In adults with advanced disease who have received prior anti-angiogenic therapy, as monotherapy.
- **Urothelial carcinoma**:
  - For the adjuvant treatment of adults with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection, as monotherapy.
  - In adults, for the first-line treatment of unresectable or metastatic disease in combination with cisplatin and gemcitabine.
  - In adults with locally advanced or metastatic disease who have disease progression during or following platinum-containing chemotherapy, as monotherapy.
  - In adults with locally advanced or metastatic disease who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, as monotherapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Opdivo Qvantig. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdivo Qvantig as well as the monitoring required for adverse events and long-term efficacy, approval requires Opdivo Qvantig to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Opdivo Qvantig is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Colon, Rectal, or Appendiceal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); OR
     - **ii.** The tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase); AND
   - **C)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has tried chemotherapy; OR

     Note: Examples of chemotherapy are fluoropyrimidine such as fluorouracil (5-FU), and capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
     - **ii.** Patient has unresectable, medically inoperable, advanced, or metastatic disease; OR
     - **iii.** The medication is used for neoadjuvant therapy; AND
   - **D)** The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
   - **E)** The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
   - **B)** 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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2. **Esophageal and Esophagogastric Junction Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient meets ALL of the following (a, b, and c):
       - **a)** Patient has completely resected esophageal or esophagogastric junction cancer with residual pathologic disease; AND
       - **b)** Patient received neoadjuvant chemotherapy; AND
       - **c)** The medication is used as monotherapy for adjuvant treatment; OR
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has unresectable, advanced, or metastatic disease; AND
       - **b)** Patient meets ONE of the following [(1) or (2)]:
         - **(1)** The medication is used first-line in combination with fluoropyrimidine- and platinum-containing chemotherapy; OR

           Note: Examples of a fluoropyrimidine included fluorouracil and capecitabine. Examples of platinum agents include cisplatin and oxaliplatin.
         - **(2)** The medication is used as monotherapy following prior fluoropyrimidine- and platinum-containing chemotherapy; OR

Note: Examples of a fluoropyrimidine included fluorouracil and capecitabine. Examples of platinum agents include cisplatin and oxaliplatin.

iii. Patient has advanced or metastatic disease AND meets ONE of the following (a or b):
- **a)** The medication is used in combination with fluoropyrimidine- and platinum-containing chemotherapy; OR
  Note: Examples of a fluoropyrimidine included fluorouracil and capecitabine. Examples of platinum agents include cisplatin and oxaliplatin.
- **b)** The medication is used as single-agent; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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3. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
- **i.** Patient meets ALL of the following (a, b, and c):
  - **a)** Patient has locoregional disease; AND
  - **b)** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
  - **c)** The medication is used as a single-agent for adjuvant therapy; OR
- **ii.** Patient has advanced or metastatic disease and meets ONE of the following (a or b):
  - **a)** The medication will be used in combination with fluoropyrimidine- and platinum-containing chemotherapy; OR
    Note: Examples of a fluoropyrimidine included fluorouracil and capecitabine. Examples of platinum agents include cisplatin and oxaliplatin.
  - **b)** The medication is used as a single-agent; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks.

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4. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
- **i.** Patient has non-nasopharyngeal disease; OR
- **ii.** Patient has mucosal melanoma; OR
- **iii.** Patient meets BOTH of the following conditions (a and b):
  - **a)** Patient has nasopharyngeal disease; AND

b) Patient has recurrent, unresectable, oligometastatic, or metastatic disease; AND

C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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5. Hepatocellular Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) The medication is being used for subsequent therapy; AND

C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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6. Melanoma. Approve for duration noted if the patient meets ALL of the following (A, B, C, and D):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.

A) Patient is ≥ 18 years of age; AND

B) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND

C) Patient meets ONE of the following (i, ii, or iii):

i. Approve for 1 year if the patient has unresectable, advanced, or metastatic disease; OR

ii. Approve for up to 3 months if Opdivo Qvantig will be used as neoadjuvant treatment; OR

iii. Approve for up to 1 year (total) if Opdivo Qvantig will be used as adjuvant therapy; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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7. Non-Small Cell Lung Cancer – Neoadjuvant and Adjuvant. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (*EGFR*) *exon 19 deletion* or *exon 21 L858R*, anaplastic lymphoma kinase (*ALK), RET,* or *ROS1*; AND

C) Patient has Stage II or Stage III disease and meets ONE of the following (i or ii):

i. The medication is used as neoadjuvant therapy in combination with platinum-doublet chemotherapy; OR

Note: Examples of platinum-doublet chemotherapy agents include cisplatin and carboplatin.

ii. The medication is used as adjuvant therapy and meets BOTH of the following (a and b):

a) The medication is used as a single-agent; AND

b) Patient has received neoadjuvant treatment with Opdivo or Opdivo Qvantig; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR

C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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8. Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor *(EGFR) exon 19 deletion* or *exon 21 L858R*, anaplastic lymphoma kinase *(ALK), RET,* and *ROS1*; AND

C) Patient meets ALL of the following (i, ii, and iii):

i. The medication is used as subsequent therapy; AND

ii. The medication is used as a single agent; AND

iii. Patient has not progressed on prior therapy with a programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitor; AND

Note: This includes previous therapy with either one of Opdivo, Keytruda (pembrolizumab intravenous infusion), or Tecentriq (atezolizumab intravenous infusion).

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR

C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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9. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has ONE of the following (i, ii, or iii):

   i. Stage IV disease; OR
   ii. Relapsed disease; OR
   iii. Hereditary leiomyomatosis and renal cell cancer; AND
C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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10. Urothelial Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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11. Ampullary Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
C) Patient meets ONE of the following (i or ii):
   i. The medication is used first-line for metastatic disease; OR
   ii. The medication is used for subsequent therapy; AND
D) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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12. Anal Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND
B) Patient has locally recurrent, metastatic, or progressive disease; AND
C) Patient meets ONE of the following (i or ii):
  i. Medication is administered before proceeding to abdominoperineal resection; OR
  ii. Patient meets BOTH of the following (a and b):
    a) The medication is used as subsequent therapy; AND
    b) Patient has NOT received prior checkpoint inhibitors; AND

    Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion), Zynyx (retifanlimab-dlwr intravenous infusion), Loqtorzi (toripalimab-tpzi intravenous infusion), Tevimbra (tislelizumab-jsgr intravenous infusion).
D) The medication is used as a single agent; AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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13. Biliary Tract Cancers. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, iii, or iv):
  i. Unresectable disease; OR
  ii. Resected gross residual disease; OR
  iii. Metastatic disease; OR
  iv. The tumor is tumor mutational burden-high (TMB-H); AND
C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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14. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent or metastatic disease; AND
C) Patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1); AND

D) The medication is used as second-line or subsequent therapy; AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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15. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent or metastatic disease; AND
C) The tumor is mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H); AND
D) The medication will be used as single-agent; AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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16. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient has multiagent chemotherapy-resistant disease; AND
Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
B) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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17. Kaposi Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed or refractory disease; AND

C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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18. Merkel Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient meets BOTH of the following (a and b):
  - **a)** Patient has primary or recurrent locally advanced disease; AND
  - **b)** According to the prescriber, curative surgery and curative radiation therapy are not feasible; OR
- **ii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient has primary or recurrent regional disease; AND
  - **b)** According to the prescriber, curative surgery and curative radiation therapy are not feasible; OR
- **iii.** Patient has metastatic (disseminated) disease; OR
- **iv.** The medication is used as neoadjuvant therapy; AND

C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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19. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, iii, or iv):
- **i.** Malignant pleural mesothelioma; OR
- **ii.** Malignant peritoneal mesothelioma; OR
- **iii.** Pericardial mesothelioma; OR
- **iv.** Tunica vaginalis testis mesothelioma; AND

C) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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20. Neuroendocrine Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has locoregional unresectable, advanced, or metastatic disease; AND
C) Patient meets ONE of the following (i, ii, iii, iv, or v):
  i. Patient has well differentiated, Grade 3 disease; OR
  ii. Patient has extrapulmonary poorly differentiated neuroendocrine carcinoma; OR
  iii. Patient has large or small cell disease; OR
  iv. Patient has mixed neuroendocrine-non-neuroendocrine neoplasm; OR
  v. Patient has adrenocortical carcinoma; AND
D) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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21. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally unresectable, medically inoperable, advanced, or metastatic disease; AND
C) Patients meets ONE of the following (i or ii):
  i. The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); OR
  ii. The tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase); AND
D) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR

B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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22. Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) The medication is used as second-line or subsequent therapy; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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23. Soft Tissue Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion); AND
C) Patient has ONE of the following (i or ii):
  i. Patient has advanced, unresectable, progressive, or metastatic disease and has ONE of the following (a, b, c, d, e, f, or g):
    a) Myxofibrosarcoma; OR
    b) Undifferentiated pleomorphic sarcoma; OR
    c) Dedifferentiated liposarcoma; OR
    d) Cutaneous angiosarcoma; OR
    e) Undifferentiated sarcoma; OR
    f) Rhabdomyosarcoma; OR
    g) Tumor mutation burden-high (TMB-H); OR
  ii. Angiosarcoma; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
D) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
E) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
F) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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24. Squamous Cell Skin Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
C) Patient is ≥ 18 years of age; AND
D) Patient has locally advanced, regional, or metastatic disease; AND

E) According to the prescriber, the patient is not a candidate for curative surgery or curative radiation therapy; AND
F) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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25. Thyroid Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has metastatic disease; AND
C) Patient has anaplastic carcinoma; AND
D) The medication will be used as a single agent; AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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26. Vaginal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent or metastatic disease; AND
C) Patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1); AND
D) The medication is used as second-line or subsequent therapy; AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

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27. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has human papilloma virus (HPV)-related disease; AND

C) The medication is used as subsequent therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 600 mg nivolumab and 10,000 units hyaluronidase administered subcutaneously no more frequently than once every 2 weeks; OR
B) 900 mg nivolumab and 15,000 units hyaluronidase administered subcutaneously no more frequently than once every 3 weeks; OR
C) 1,200 mg nivolumab and 20,000 units hyaluronidase administered subcutaneously no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opdivo Qvantig is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/08/2025
Early Annual Revision	**Colon, Rectal, or Appendiceal Cancer:** Added Appendiceal to Colon, Rectal, or Appendiceal cancer. The tumor is polymerase epsilon/delta mutation positive added as new option for approval. Patient has tried chemotherapy; or patient has unresectable, advanced, or metastatic disease; or medication is used for neoadjuvant therapy added as new requirement. The medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion) added as new requirement. **Head and Neck Squamous Cell Carcinoma:** Added unresectable, oligometastatic to patient has recurrent, unresectable, oligometastatic, or metastatic disease. Patient has non-nasopharyngeal disease; or patient has nasopharyngeal and has recurrent, unresectable, oligometastatic, or metastatic disease added as new options for approval. The medication will NOT be used in combination with Yervoy added as new requirement. **Hepatocellular Carcinoma:** Requirement patient has been previously treated with sorafenib was removed. Added liver-confined, unresectable disease and are deemed ineligible for transplant, or extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy added as new options for approval. Removed requirement that the medication will be administered as monotherapy following treatment with Opdivo (nivolumab intravenous infusion) and Yervoy. Added the medication will NOT be used in combination with Yervoy as new requirement. **Melanoma:** Added Note that this condition includes cutaneous melanoma and brain metastases due to melanoma. The medication will NOT be used in combination with Yervoy added as new requirement. Removed requirement that the medication is used as monotherapy. Added approve for up to 3 months of treatment if Opdivo Qvantig is used as neoadjuvant treatment as new option for approval. Removed Stage IIB, IIC, III, or IV disease from adjuvant option for approval. **Non-Small Cell Lung Cancer:** Added new options for approval for first-line or continuation maintenance therapy, first-line or subsequent therapy, first-line therapy, and subsequent therapy. Added Note defining resectable disease. Removed Note defining	02/12/2025

	platinum agents and Added Note with examples of platinum-doublet chemotherapy. Removed up to from approve for 1 year (total) if the patient meets BOTH of the following. Removed medication is used as monotherapy for adjuvant treatment as requirement and added patient has completely resected disease as requirement. Added Opdivo to patient has received neoadjuvant treatment with Opdivo or Opdivo Qvantig. Removed requirement that the patient is negative for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. Removed option for approval that the patient has metastatic disease, has progressed on or after platinum based chemotherapy, medication will be used as monotherapy, and if the patient has EGFR mutations or ALK rearrangements, the patient has progressed on FDA approved therapy for these aberrations. **Renal Cell Carcinoma:** Removed options for approval for intermediate or poor risk disease, advanced disease and the medication is used in combination with Cabometyx (cabozantinib tablets), and advanced disease and the patient has received prior anti-angiogenic therapy. Added requirement that the patient has advanced, relapsed, or metastatic disease. Added requirement that the medication will NOT be used in combination with Yervoy. **Urothelial Carcinoma:** Removed options for approval for patient is at high-risk of recurrence after radical resection, patient has unresectable or metastatic disease, and patient has locally advanced or metastatic disease. **Ampullary Adenocarcinoma:** Added new condition of approval. **Anal Carcinoma:** Added new condition of approval. **Biliary Tract Cancers:** Added new condition of approval. **Cervical Cancer:** Added new condition of approval. **Endometrial Carcinoma:** Added new condition of approval. **Gestational Trophoblastic Neoplasia:** Added new condition of approval. **Kaposi Sarcoma:** Added new condition of approval. **Merkel Cell Carcinoma:** Added new condition of approval. **Mesothelioma:** Added new condition of approval. **Neuroendocrine Tumors:** Added new condition of approval. **Small Bowel Adenocarcinoma:** Added new condition of approval. **Small Cell Lung Cancer:** Added new condition of approval. **Squamous Cell Skin Carcinoma:** Added new condition of approval. **Thyroid Carcinoma:** Added new condition of approval. **Vaginal Cancer:** Added new condition of approval.	
Selected Revision	**Melanoma:** Added uveal melanoma to the Note. **Vulvar Cancer:** Added new condition of approval.	03/26/2025
Early Annual Revision	**Colon, Rectal, or Appendiceal Cancer:** The requirement that the tumor is polymerase epsilon/delta (POLE/POLD1) mutation was changed to also require ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase). The requirement that the patient has unresectable, advanced, or metastatic disease was changed to also include medically inoperable. **Esophageal and Esophagogastric Junction Cancer:** The requirement that a patient with advanced or metastatic disease has esophagogastric junction cancer or esophageal adenocarcinoma was removed. For advanced or metastatic disease, use as a single-agent was added as an approval option. **Gastric Cancer:** For advanced or metastatic disease, use as a single-agent was added as an approval option. The requirement that the patient meets ONE of the following: advanced or metastatic disease or the patients meets ALL of the following: patient has locoregional disease; the tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND the medication is used as single-agent for adjuvant therapy were added as options for approval. An option for approval was added for a patient with microsatellite instability-high or mismatch repair deficient locoregional disease, if used as a single agent as adjuvant therapy. **Head and Neck Squamous Cell Carcinoma:** Mucosal melanoma was added as an option for approval. **Hepatocellular Carcinoma:** The requirement that the patient has liver-confined, unresectable disease in a patient who is not a transplant candidate or extrahepatic/metastatic disease deemed ineligible for resection, transplant, or locoregional therapy, was removed. A requirement was added that the medication is used for subsequent therapy.	08/06/2025

	Non-Small Cell Lung Cancer – Neoadjuvant and Adjuvant: The condition of approval was changed to as listed. Previously, all non-small cell lung cancer (NSCLC) was addressed more generally under NSCLC. A requirement was added that the tumor is negative for the following actionable biomarkers: epidermal growth factor receptor *(EGRF) exon 19 deletion* or *exon 21 L858R, anaplastic lymphoma kinase (ALK), RET*, and *ROS1*. The requirement that the patients has resectable disease, has been changed to patient has Stage II or Stage III disease. The approval duration was changed to 1 year for both adjuvant and neoadjuvant treatment therapy. **Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease:** This condition of approval was changed to as listed. Previously, all non-small cell lung cancer (NSCLC) was addressed more generally under NSCLC. A requirement was added that the "the tumor is negative for the following actionable biomarkers: epidermal growth factor receptor *(EGRF) exon 19 deletion* or *exon 21 L858R, anaplastic lymphoma kinase (ALK), RET*, and *ROS1*". The following approval options were removed: as first-line therapy or as continuation maintenance therapy; if the medication is used as first-line or subsequent therapy; if the medication is used as first-line therapy; and if the medication is used as subsequent therapy. **Renal Cell Carcinoma:** The requirement that the patient has advanced, relapsed, or metastatic disease was changed to be Stage IV, relapsed, or hereditary leiomyomatosis disease and renal cell cancer. **Anal Carcinoma:** The approval option "patient has not received prior immunotherapy" was modified to "patient has not received prior checkpoint inhibitors." The Note was modified to add Zynyx (retifanlimab-dlwr intravenous infusion), Loqtorzi (toripalimab-tpzi intravenous infusion), Tevimbra (tislelizumab-jsgr intravenous infusion) to the examples. **Endometrial Carcinoma:** The requirements that the patient has recurrent or metastatic disease and the medication will be used as a single-agent were added. The requirement that the patient has tried at least one prior systemic therapy was removed. **Kaposi Sarcoma:** The requirement that the patient is ≥ 18 years of age was added. **Merkel Cell Carcinoma:** Patient has primary or recurrent locally advanced disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible was added as an approval option. For regional disease a requirement that "according to the prescriber, curative surgery and curative radiation therapy are not feasible" was added. The requirement that the patient has disseminated Merkel cell carcinoma was changed to the patient has metastatic (disseminated) disease. A requirement that the medication will NOT be used in combination with Yervoy (ipilimumab intravenous infusion was added. **Neuroendocrine Tumors:** Locoregional unresectable disease was added as an approval option. The following were added as options of approval: extrapulmonary poorly differentiated neuroendocrine carcinoma; large or small cell disease; mixed neuroendocrine-non-neuroendocrine neoplasm; and adrenocortical carcinoma. Poorly differentiated, large or small cell disease (other than lung) was removed as an approval option. **Small Bowel Adenocarcinoma:** The requirement that the tumor is ultra hypermutated phenotype was moved to apply only to a tumor that is polymerase epsilon/delta (POLE/POLD1) mutation positive. Tumor mutation burden > 50 mutations/megabase was added as a descriptor of ultra-hypermutated phenotype. **Soft Tissue Sarcoma:** This was added as a new condition of approval. **Vulvar Cancer:** A requirement that the medication is used as subsequent therapy was added. The patient has tried at least one prior systemic therapy was removed.	