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Medication Policy Manual

Policy No: dru797

Topic: PD-1 and PD-L1 Inhibitor Monoclonal Antibody Therapies

Date of Origin: February 1, 2025

- Bavencio, avelumab
- Imfinzi, durvalumab
- Jemperli, dostarlimab
- Keytruda, pembrolizumab IV
- Keytruda Qlex, pembrolizumab-berahyaluronidase alfa-pmph SC
- Libtayo, cemiplimab-rwlc
- Loqtorzi, toripalimab-tpzi
- Opdivo, nivolumab IV
- Opdivo Qvantig, nivolumab-hyaluronidase-nvhy SC
- Opdualag, nivolumab-relatlimab-rmbw
- Penpulimab (unbranded)
- Tecentriq, atezolizumab IV
- Tecentriq Hybreza, atezolizumab- hyaluronidase-tqjs SC
- Tevimbra, tislelizumab-jsgr
- Unloxcyt, cosibelimab
- Zynyz, retifanlimab-dlwr

Committee Approval Date: June 4, 2026

Next Review Date: 2026

Effective Date: August 1, 2026

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description: Programmed death receptor-1 (PD-1) inhibitors and programmed death-ligand 1 (PD-L1) inhibitors are intravenous (IV) or subcutaneous (SC) immunotherapies used to treat specific types of cancer.

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Policy/Criteria

Most contracts require pre-authorization approval of PD-1 and PD-L1 Inhibitor Monoclonal Antibody Therapies ("PD-1 and PD-L1 Inhibitors," including all drugs as listed in *Table 1*) prior to coverage.

I. Continuation of therapy (COT): PD-1 and PD-L1 Inhibitors may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

PLEASE NOTE: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): PD-1 and PD-L1 Inhibitors (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (such as chart notes) that the indication-based criteria below are met.

A. Alveolar soft part sarcoma (ASPS)

Coverable medication(s)	ALL of the following diagnostic criteria for the requested coverable medication(s) are met:
Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**A.** A diagnosis of **alveolar soft part sarcoma (ASPS)**, **unresectable** or **metastatic**, when all criteria (1 through 3) below are met: **1.** Prior surgical resection, unless the tumor is unresectable (attestation). **2.** Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs) will be used as monotherapy. **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

B. Anal squamous cell carcinoma (aSCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **anal squamous cell carcinoma (aSCC)**, **recurrent** or **metastatic**, when all criteria (1 through 3) below are met: **1.** Disease progression on or after first-line cytotoxic chemotherapy. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **anal squamous cell carcinoma (aSCC)**, **recurrent** or **metastatic**, when all criteria (1 through 3) below are met: **1.** Disease progression on or after cytotoxic chemotherapy. **2.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Zynyz (retifanlimab-dlwr)	**C.** A diagnosis of **anal squamous cell carcinoma (aSCC)**, when both criteria (1 and 2) below are met: **1.** Use in one of the following settings: **a.** First line: for inoperable locally recurrent or metastatic aSCC **i.** No prior systemic therapy for advanced aSCC. **ii.** Used initially in combination with cytotoxic chemotherapy. **OR** **b.** Subsequent line: for recurrent or metastatic aSCC **i.** Disease progression on or after cytotoxic chemotherapy. **ii.** Zynyz (retifanlimab) will be used as monotherapy. **2.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

C. Basal cell carcinoma (BCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Libtayo (cemiplimab-rwlc)	**A.** A diagnosis of **basal cell carcinoma (BCC)**, **locally advanced** or **metastatic**, when both criteria (1 and 2) below are met: **1.** Prior hedgehog pathway inhibitor therapy [e.g., Odomzo (sonidegib), or Erivedge (vismodegib)] was not effective or was not tolerated, unless use of hedgehog pathway inhibitor therapy is not appropriate. **2.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

D. Biliary tract cancer (BTC)

PLEASE NOTE: Biliary tract cancer includes intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, gallbladder cancer, and ampulla of Vater cancer.

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Imfinzi (durvalumab)	**A.** A diagnosis of **biliary tract cancer (BTC)**, **unresectable locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** No prior systemic treatment in the advanced or metastatic disease setting. **2.** Imfinzi (durvalumab) will be used in combination with gemcitabine plus cisplatin. **3.** No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**B.** A diagnosis of **biliary tract cancer (BTC)**, **unresectable locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** No prior systemic therapy in the advanced disease setting. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with gemcitabine and cisplatin. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

E. Breast cancer, triple-negative (TNBC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **triple-negative breast cancer (TNBC)** when one of the following criteria (1 or 2) below is met: **1.** Will be used in <u>one</u> of the following settings (a or b): **a.** **High-risk**, **early-stage (stage II or III) TNBC** in combination with cytotoxic chemotherapy as a neoadjuvant therapy and then continued as a single agent as an adjuvant therapy after surgical excision <u>AND</u> no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **b.** **Recurrent** or **metastatic TNBC** when <u>all</u> criteria (i through iv) below are met: **i.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10). **ii.** No prior systemic therapy in the advanced disease setting. **iii.** Will be given in combination with cytotoxic chemotherapy. **iv.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** **In combination with Trodelvy (sacituzumab govitecan-hziy): First line TNBC** advanced disease (locally advanced or metastatic) when <u>all</u> criteria (a through c) below are met: **a.** First line therapy (no prior treatment in the advanced setting) **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10). **c.** No progression while on, or within six months, of any prior PD1/PD-L1 blocking antibody therapy (such as neoadjuvant/adjuvant therapy) (see *Appendix 1*).

F. Cervical cancer

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **cervical cancer** when <u>one</u> of the following criteria (1 or 2) below is met: **1.** Diagnosis of **cervical cancer**, **recurrent** or **metastatic**, when <u>all</u> criteria (a through c) below are met: **a.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 1 or more (CPS ≥ 1). **b.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in <u>one</u> of the following two settings (criterion i or ii) is met: **i.** As monotherapy when there has been disease progression on or after chemotherapy. **OR** **ii.** In combination with chemotherapy when used in patients who have had no prior systemic therapy for advanced disease. **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** Diagnosis of **cervical cancer**, **unresectable**, **locally advanced**, **International Federation of Gynecology and Obstetrics (FIGO) 2014 Stage III to IVA** when <u>all</u> criteria (a through d) below are met: **a.** One of the following histologies: squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma. **b.** No prior definitive surgery, radiation, or systemic therapy in the advanced disease setting. **c.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with chemoradiation [e.g., a platinum plus external beam radiation therapy (EBRT)]. **d.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

G. Classical Hodgkin lymphoma (cHL)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **classical Hodgkin Lymphoma (cHL)**, **relapsed/refractory**, when both criteria (1 and 2) below are met: **1.** Disease progression on or after one or more lines of systemic therapy [such as chemotherapy or a hematopoietic stem cell transplant (HSCT, BMT)]. **2.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **classical Hodgkin lymphoma (CHL)** when both criteria (1 and 2) are met: **1.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **2.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be used in one of the following settings (criterion a or b): **a.** **Relapsed/refractory**, when i and ii are met: **i.** Relapse or disease progression in one of the following two settings (criterion 1 or 2) is met: **1.** After a hematopoietic stem cell transplant [HSCT; bone marrow transplant (BMT)] and post-transplant Adcetris (brentuximab vedotin). **OR** **2.** Disease progression on or after three or more lines of therapy that includes an HSCT (BMT). **ii.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy. **OR** **b.** **Previously-untreated**, when i through iii are met: **i.** Advanced Stage (III or IV), or high-risk IIB with bulky disease. **ii.** No prior chemotherapy or radiation for cHL. **iii.** Will be used in combination with AVD (doxorubicin, vinblastine, and dacarbazine).

H. Colorectal cancer (CRC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **colorectal cancer (CRC)**, **locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** The tumor is microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) CRC by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **colorectal cancer (CRC)**, when all criteria (1 through 3) below are met: **1.** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing. **2.** **Unresectable** or **metastatic** CRC, when criterion a or b is met **a.** Opdivo (nivolumab) [IV only] is used initially in combination with Yervoy (ipilimumab), followed by monotherapy Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy). **OR** **b.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy after progression on or after cytotoxic chemotherapy for metastatic disease (2nd line for metastatic disease). **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).

I. Cutaneous squamous cell carcinoma (cSCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **cutaneous squamous cell carcinoma (cSCC)**, when all criteria (1 through 3) below are met: **1.** Documentation that the disease is metastatic or is not curable with surgical excision or radiation therapy. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Libtayo (cemiplimab-rwlc)	**B.** A diagnosis of **cutaneous squamous cell carcinoma (cSCC)** when both criteria (1 and 2) below are met: **1.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **2.** Libtayo (cemiplimab-rwlc) will be used in one of the following settings (criterion a or b): **a.** **Advanced cSCC**, when i and ii are met: **i.** Documentation that the disease is metastatic or is not curable with surgical excision or radiation therapy. **ii.** Libtayo (cemiplimab-rwlc) will be used as monotherapy. **OR** **b.** **Resectable cSCC**, when i and ii are met: **i.** Documentation of very high-risk nodal or non-nodal features (see *Appendix 4*). **ii.** Use of Libtayo (cemiplimab-rwlc) after surgical excision and adjuvant radiation therapy.
Unloxcyt (cosibelimab)	**C.** A diagnosis of **cutaneous squamous cell carcinoma (cSCC)** when all criteria (1 through 3) below are met: **1.** Documentation that the disease is metastatic or is not curable with surgical excision or radiation therapy. **2.** Unloxcyt (cosibelimab) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

J. Endometrial cancer

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Imfinzi (durvalumab)	**A.** A confirmed diagnosis of **endometrial carcinoma**, **locally advanced** or **metastatic (Stage III/IV)**, when all criteria (1 through 4) below are met: **1.** First-line: No prior systemic therapy for endometrial carcinoma in the advanced disease setting. **2.** The tumor is mismatch repair deficient (dMMR). **3.** Imfinzi (durvalumab) will be initiated in combination with carboplatin and paclitaxel. **4.** No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Jemperli (dostarlimab)	**B.** A confirmed diagnosis of **endometrial carcinoma**, **locally advanced or metastatic (Stage III/IV)**, when all other criteria (1 and 2) are met: **1.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1).* **2.** Jemperli (dostarlimab) will be used in one of the following two settings (criterion a or b): **a.** First-line: As part of a front-line regimen, when both criteria below are met (criterion i and ii): **i.** No prior systemic therapy for endometrial carcinoma in the advanced treatment setting. **ii.** Jemperli (dostarlimab) will be initiated in combination with carboplatin and paclitaxel. **OR** **b.** Subsequent line: When all criteria below are met (i through iii): **i.** Disease progression on or following prior treatment with a platinum-based chemotherapy regimen. **ii.** The tumor is mismatch repair deficient (dMMR) by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing. **iii.** Jemperli (dostarlimab) will be used as monotherapy.
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase	**C.** A diagnosis of **endometrial carcinoma**, **locally advanced or metastatic (Stage III/IV)**, when both criteria (1 and 2) below are met: **1.** Keytruda (pembrolizumab) or Keytruda Qlex

alfa-pmph)	(pembrolizumab- berahyaluronidase alfa-pmph) will be used in one of the following two settings (criterion a or b) is met: **a.** First-line: when both criteria (i and ii) below are met: **i.** No prior systemic therapy for endometrial carcinoma in the advanced treatment setting. **ii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) is initiated in combination with carboplatin and paclitaxel. **OR** **b.** Subsequent line: there has been disease progression on or after at least one prior systemic therapy. **AND** **2.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

K. Esophageal cancer

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **esophageal cancer** when one criterion (1 or 2) below is met: **1.** A diagnosis of **esophageal cancer**, **squamous cell carcinoma of the esophagus (ESCC)**, **recurrent unresectable locally advanced** or **metastatic**, when used in one of the following two settings (a or b): **a.** **First-line**: when all criteria (i through v) below are met: **i.** The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT). **ii.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10). **iii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with platinum (e.g., cisplatin or oxaliplatin) and fluoropyrimidine (e.g., fluorouracil or capecitabine) based chemotherapy. **iv.** No prior systemic therapy in the advanced disease setting. **v.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see Appendix *1*). **OR** **b.** **Subsequent line**: when all criteria (i through iv) below are met: **i.** Disease progression on or after prior systemic therapy. **ii.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10). **iii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **iv.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see Appendix *1*). **OR** **2.** A diagnosis of **esophageal adenocarcinoma**,

	unresectable locally advanced or **metastatic**, when all criteria (a through e) below are met: **a.** The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT). **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 1 or more (CPS ≥ 1). **c.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with platinum (e.g., cisplatin or oxaliplatin) and fluoropyrimidine (e.g., fluorouracil or capecitabine) based chemotherapy. **d.** **First-line**: No prior systemic therapy in the advanced disease setting. **e.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **esophageal cancer** when one of the following criteria (1, 2, or 3) below is met: **1.** A diagnosis of **esophageal squamous cell carcinoma (ESCC)**, **unresectable advanced** or **metastatic** when used in one of the following two settings (a or b): **a.** **First-line**: when all criteria (i through v) below are met: **i.** The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT). **ii.** One of the following (1 or 2): **1.** Opdivo (nivolumab) [IV only] will be used in combination with fluoro-pyrimidine (e.g., fluorouracil, capecitabine)- and platinum (e.g., cisplatin, carboplatin)-containing chemotherapy or Yervoy (ipilimumab) **OR** **2.** Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be used in combination with fluoropyrimidine (e.g., fluorouracil, capecitabine)- and platinum (e.g., cisplatin, carboplatin)-containing chemotherapy. **iii.** The tumor expresses PD-L1 (≥ 1%). **iv.** No prior systemic therapy in the advanced disease setting.

	v. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **b.** **Subsequent-line**: when all criteria (i through iii) below are met: **i.** Disease progression on or after, or intolerance to at least one fluoropyrimidine- and platinum-containing chemotherapy regimen. **ii.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy. **iii.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** A diagnosis of **esophageal adenocarcinoma**, locally advanced or metastatic when all criteria (a through d) below are met: **a.** **First-line**: No prior systemic therapy in the advanced disease setting. **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 5 or more (CPS ≥ 5). **c.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be administered in combination with a fluoropyrimidine (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy. **d.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3.** A diagnosis of **esophageal (adenocarcinoma** or **ESCC)** or **gastro-esophageal junction (GEJ) cancer**, **resectable (stage II or III)**, when all criteria (a through e) below are met: **a.** Completion of prior neoadjuvant chemoradiotherapy (must have received both chemotherapy and radiation in neoadjuvant setting). **b.** The tumor was completely resected. **c.** There is residual pathologic disease (absence of complete pathological response). [Note: POST OP notes required to establish absence of complete

	pathological response.] **d.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be used as monotherapy. **e.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).
Tevimbra (tislelizumab)	**C.** A diagnosis of **esophageal squamous cell carcinoma (ESCC)**, **unresectable locally advanced** or **metastatic** when all other criteria are met: (1, 2, and 3). **1.** **Subsequent-line**: Disease progression on or after at least one prior systemic therapy for advanced disease (locally advanced or metastatic). [Note: This includes disease recurring within 6 months of completing neoadjuvant or neoadjuvant chemotherapy.] **2.** Tevimbra (tislelizumab) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1).*

L. Gastric or gastroesophageal junction (GEJ) cancer, locally advanced (unresectable) or metastatic

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **gastric** or **gastroesophageal junction (GEJ) cancer** when <u>one</u> criterion (1, 2, or 3) below is met: **1.** A diagnosis of **<u>HER2-positive</u> gastric** or **gastroesophageal junction (GEJ) adenocarcinoma**, **unresectable locally advanced** or **metastatic**, when <u>all</u> criteria (a through d) below are met: **a.** The tumor expresses PD-L1 as defined by a Combined Positive Score of 1 or more (CPS ≥1). **b.** **First-line**: No prior systemic therapy in the advanced disease setting. **c.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with trastuzumab plus fluoropyrimidine- (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy. **d.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** A diagnosis of **<u>HER2-negative</u> gastric** or **gastroesophageal junction (GEJ) adenocarcinoma**, **unresectable locally advanced** or **metastatic**, when <u>all</u> criteria (a through d) below are met: **a.** The tumor expresses PD-L1 as defined by a Combined Positive Score of 1 or more (CPS ≥1). **b.** **First-line**: No prior systemic therapy in the advanced disease setting. **c.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with fluoropyrimidine- (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy. **d.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3.** A diagnosis of **gastroesophageal junction (GEJ) squamous cell carcinoma**, when <u>all</u> criteria (a through

	e) below are met: **a.** The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT). **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10). **c.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in combination with platinum (e.g., cisplatin or oxaliplatin) and fluoropyrimidine (e.g., fluorouracil or capecitabine) based chemotherapy. **d.** **First-line**: No prior systemic therapy in the advanced disease setting. **e.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Imfinzi (durvalumab)	**B.** A diagnosis of **gastric** or **gastroesophageal junction (GEJ) cancer** when all the following criteria (1 through 6) are met. **1.** Resectable disease, defined as Stage II to IVA [>T2 N0-3 M0 or T0-4 N1-3 M0]. **2.** PD-L1 expressing (TAP ≥1% or CPS ≥ 1). **3.** Non-diffuse type histology (such as intestinal). **4.** Planned surgical resection. **5.** Use in combination with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) neoadjuvant/adjuvant chemotherapy, followed by durvalumab monotherapy. **6.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**C.** A diagnosis of **gastric** or **gastroesophageal junction (GEJ) cancer** when one criterion (1 or 2) below is met: **1.** A diagnosis of **gastric** or **gastroesophageal junction (GEJ) cancer**, **locally advanced** or **metastatic**, when all criteria (a through d) below are met: **a.** **First-line**: No prior systemic therapy in the advanced disease setting. **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 5 or more (CPS ≥ 5). **c.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be administered in combination with a fluoropyrimidine (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy. **d.** No prior therapy with PD-1/PD-L1 blocking

	antibody therapy (see *Appendix 1*). **OR** **2.** A diagnosis of **gastro-esophageal junction (GEJ) cancer**, **stage II** or **III <u>resectable</u>**: see criteria under *Esophageal cancer - resectable*
Tevimbra (tislelizumab)	**D.** A diagnosis of **<u>HER2-negative</u> gastric** or **gastroesophageal junction (GEJ) adenocarcinoma**, **unresectable locally advanced** or **metastatic**, when <u>all</u> criteria (1 through 4) below are met: **1.** The tumor expresses PD-L1 as defined by a Tumor Area Positivity (TAP) score of 1 or more (TAP ≥ 1) OR a Combined Positive Score of 1 or more (CPS ≥ 1). **2.** **First-line**: No prior systemic therapy in the advanced disease setting. **3.** Tevimbra (tislelizumab) will be used in combination with fluoropyrimidine- (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy. **4.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

M. Head and neck squamous cell cancer (HNSCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **head and neck squamous cell cancer (HNSCC)**, for use in one of the following settings (criteria 1 or 2 below are met): **1.** **Recurrent** or **metastatic**, and no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** **Resectable**, and all the following are met (a through e): **a.** Documented stage III or IVA disease **b.** The tumor is PD-L1 positive as defined by a Combined Positive Score of 1 or more (CPS ≥ 1). **c.** The patient is eligible for/planning to undergo primary surgical resection. **d.** No prior radiation or systemic anticancer therapy for HNSCC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*). **e.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy in the neoadjuvant setting (prior to surgical resection) and in combination with radiation therapy +/- chemotherapy in the adjuvant setting (after surgical resection).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **head and neck squamous cell cancer (HNSCC)**, recurrent or metastatic, when all criteria (1 through 3) below are met: **1.** Disease progression on or after a platinum-containing chemotherapy regimen. **2.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

N. Hepatocellular carcinoma (HCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Imfinzi (durvalumab)	**A.** A diagnosis of **hepatocellular carcinoma (HCC), unresectable or metastatic,** when all criteria (1 through 4) below are met: **1.** First-line: There has been no prior systemic therapy for unresectable or metastatic HCC. **2.** Confirmation of one of the following (a or b): [provider attestation] **a.** Child-Pugh score of 5 to 6 (class A). **OR** **b.** Child-Pugh Class B AND good performance status (ECOG 0-1) **3.** Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab). **4.** No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). *Note: use as part of transarterial chemoembolization (TACE) is not coverable.*
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**B.** A diagnosis of **hepatocellular carcinoma (HCC)** when all criteria (1 through 5) below are met: **1.** The HCC is secondary to hepatitis B virus (HBV) infection. **2.** Confirmation of one of the following (a or b): [provider attestation] **a.** Child-Pugh score of 5 to 6 (class A). **OR** **b.** Child-Pugh Class B AND good performance status (ECOG 0-1) **3.** Subsequent line: Disease progression on, or intolerance to at least one prior non-PD-1/PD-L1 inhibitor systemic therapy for HCC (e.g., sorafenib or lenvatinib). **4.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **5.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). *Note: use as part of transarterial chemoembolization (TACE) is not coverable.*
Opdivo (nivolumab), Opdivo Qvantig	**C.** A diagnosis of **hepatocellular carcinoma (HCC)** when all criteria (1 through 4) below are met:

(nivolumab-hyaluronidase-nvhy)	**1.** Confirmation of one of the following (a or b): [provider attestation] **a.** Child-Pugh score of 5 to 6 (class A). **OR** **b.** Child-Pugh Class B AND good performance status (ECOG 0-1) **2.** Use in one of the following settings (a or b): **a.** Subsequent-line: There has been disease progression on, or intolerance to an HCC-active oral tyrosine kinase inhibitor (TKI) [such as Nexavar (sorafenib) or Lenvima (lenvatinib)]. **OR** **b.** First-line: unresectable or metastatic HCC, when both criteria i and ii are met **i.** No prior systemic therapy for unresectable or metastatic HCC. **ii.** Use of lower-cost Imfinzi (durvalumab)/Imjudo (tremelimumab) is not an option (not tolerated/medically contraindicated). **3.** Opdivo (nivolumab) [IV only] is used initially in combination with Yervoy (ipilimumab), followed by nivolumab monotherapy (Opdivo IV or Opdivo Qvantig SC) **4.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).
Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**D.** A diagnosis of **hepatocellular carcinoma (HCC)**, **unresectable** or **metastatic**, when all criteria (1 through 4) below are met: **1.** Confirmation of one of the following (a or b): [provider attestation] **a.** Child-Pugh score of 5 to 6 (class A) **OR** **b.** Child-Pugh Class B AND good performance status (ECOG 0-1) **2.** First-line: No prior systemic therapy for unresectable HCC. **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

	4.	Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab- hyaluronidase-tqjs) will be used in combination with bevacizumab.

O. Malignant pleural mesothelioma (MPM)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Opdivo (nivolumab)	**A.** A diagnosis of **malignant pleural mesothelioma (MPM)**, **unresectable**, when all criteria (1 through 3) below are met: **1.** First-line: No prior use of systemic therapy for advanced disease. **2.** Opdivo (nivolumab) [IV only] is used in combination with Yervoy (ipilimumab). **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**B.** A diagnosis of **malignant pleural mesothelioma (MPM)**, **unresectable**, when all criteria (1 through 4) below are met: **1.** First-line: No prior use of systemic therapy for advanced disease. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) is used in combination with pemetrexed plus platin-based chemotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **4.** **If epithelioid histology**: bevacizumab in combination with pemetrexed plus platin-based chemotherapy is not tolerated or is contraindicated.

P. Melanoma

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **melanoma** when all criteria (1 through 3) below are met: **1.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in one of the following settings (criterion a or b) is met: **a.** **Unresected**: unresectable locally advanced or metastatic melanoma (stage III or IV). **OR** **b.** **As adjuvant therapy (after surgery)**: stage IIB, IIC, or III melanoma after complete tumor resection. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **melanoma** when one criterion (1, 2, or 3) below is met: **1.** **Unresected Advanced (stage III** or **IV) melanoma,** when both criteria (a and b) below are met: **a.** One of the following is met (i or ii) is met: **i.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy **OR** **ii.** Opdivo (nivolumab) [IV only] is used in combination with Yervoy (ipilimumab) and no prior therapy with Yervoy (ipilimumab) **b.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** **Adjuvant (after surgery), for resected melanoma,** when all criteria (a through c) below are met **a.** One of the following is met (i or ii) is met: **i.** Stage III or IV **OR** **ii.** Early-stage (IIB or IIC): The tumor is

	completely resected with negative margins and a negative sentinel lymph node (adjuvant setting). **b.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy **c.** No prior systemic therapy, including no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3. For Opdivo (nivolumab) [IV only], neoadjuvant (before surgery), followed by adjuvant (after surgery) for resectable Stage III melanoma**: when <u>all</u> criteria (a through d) below are met **a.** Use as a <u>neoadjuvant</u> treatment (prior to complete surgical resection) in combination with Yervoy (ipilimumab) for the first two doses, followed by monotherapy in the adjuvant setting. **b.** Documentation of pathologic involvement of regional lymph nodes. **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **d.** No prior therapy with Yervoy (ipilimumab). *NOTE: Continued use of Opdivo (nivolumab) after surgery (adjuvant) is based on pathologic response, as detailed in the reauthorization criteria.* **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).
Opdualag (nivolumab-relatlimab-rmbw)	**C.** A diagnosis of **melanoma**, **unresectable** or **metastatic**, when <u>both</u> criteria (1 and 2) below are met: **1.** No prior systemic therapy (including but not limited to prior use of PD-1 inhibitors or PD-L1 inhibitors) in the advanced disease setting (see *Appendix 1*). **2.** Opdualag (nivolumab-relatlimab-rmbw) will be used as monotherapy.
Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**D.** A diagnosis of **cutaneous melanoma**, **unresectable** or **metastatic**, when <u>all</u> criteria (1 through 3) below are met: **1.** The cancer is BRAF V600 mutation-positive. **2.** Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab- hyaluronidase-tqjs) will be administered in combination with Zelboraf (vemurafenib) and Cotellic

	(cobimetinib). **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

Q. Merkel cell carcinoma (MCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Bavencio (avelumab)	**A.** A diagnosis of **Merkel cell carcinoma**, **metastatic**, when both criteria (1 and 2) below are met: **1.** Bavencio (avelumab) will be used as monotherapy. **2.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1)*.
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**B.** A diagnosis of **Merkel cell carcinoma (MCC)**, **unresectable locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** No prior systemic therapy (chemotherapy or immunotherapy) used in the advanced setting. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1)*.
Zynyz (retifanlimab-dlwr)	**C.** A diagnosis of **Merkel cell carcinoma (MCC)**, **recurrent locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** No prior systemic therapy (chemotherapy or immunotherapy) was used in the advanced disease setting. **2.** Zynyz (retifanlimab-dlwr) will be used as monotherapy. **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1)*.

R. Nasopharyngeal carcinoma (NPC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Loqtorzi (toripalimab)	**A.** A diagnosis of **nasopharyngeal carcinoma (NPC)**, **recurrent locally advanced** (unresectable) or **metastatic** when both criteria (1 and 2) below are met: **1.** Loqtorzi (toripalimab) will be used in one of the following settings (criterion a or b) is met: **a.** **First-line**: when both criteria (i and ii) are met: **i.** Used in combination with cisplatin and gemcitabine. **ii.** No prior systemic therapy for recurrent or metastatic disease. **OR** **b.** **Subsequent-line**: when both criteria (i and ii) are met: **i.** Loqtorzi (toripalimab) is used as monotherapy. **ii.** There has been disease progression on or after a platinum-containing chemotherapy regimen. **2.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1).*
Penpulimab (unbranded)	**B.** A diagnosis of **nasopharyngeal carcinoma (NPC)**, **recurrent locally advanced** (unresectable) or **metastatic** when both criteria (1 and 2) below are met: **1.** Penpulimab will be used in one of the following settings (criterion a or b) is met: **a.** **First-line**: when both criteria (i and ii) are met: **i.** Used in combination with either cisplatin or carboplatin and gemcitabine. **ii.** No prior systemic therapy for recurrent or metastatic disease. **OR** **b.** **Subsequent-line**: when both criteria (i and ii) are met: **i.** Penpulimab is used as monotherapy. **ii.** There has been disease progression on or after a platinum-containing chemotherapy regimen and at least one other prior line of therapy. **2.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1).*

S. Non-small cell lung cancer (NSCLC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Imfinzi (durvalumab)	**A.** A diagnosis of **NSCLC**, when one criterion (1, 2, or 3) below is met: **1.** **Locally advanced (unresectable stage III) NSCLC**, when all criteria (a through d) below are met: **a.** The patient has received 2 or more cycles of definitive concurrent platinum-containing chemotherapy and radiation therapy. **b.** There has been no disease progression during or following platinum-containing chemotherapy and radiation therapy. **c.** Imfinzi (durvalumab) is used as monotherapy. **d.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1).* **OR** **2.** **Metastatic NSCLC**, when all criteria (a through d) below are met: **a.** There has been no prior systemic therapy for metastatic NSCLC. **b.** There are no sensitizing epidermal growth factor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. **c.** Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab) AND platin doublet chemotherapy. **d.** No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3.** **Earlier-stage**, **resectable NSCLC**, as **neoadjuvant therapy followed by adjuvant therapy**, when all criteria (a through c) below are met: **a.** Documented stage II, IIIA, or IIIB disease (tumors ≥ 4 cm and/or node positive) **b.** Imfinzi (durvalumab) is used as follows (both criteria i and ii are met): **i.** In combination with platinum-containing chemotherapy in the neoadjuvant setting (prior to surgical resection) for up to four cycles. **ii.** As monotherapy in the adjuvant setting (after surgical resection) for up to 12 cycles.

	c. No prior systemic anticancer therapy for NSCLC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**B.** A diagnosis of **NSCLC**, when one criterion (1, 2, or 3) below is met: **1.** **Metastatic NSCLC (stage IV disease)**, when one of the following criteria below is met (a or b): **a.** There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*). **OR** **b.** Documented prior use of Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph) with NO progression of disease while on Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) adjuvant therapy. **OR** **2.** **Earlier-stage**, **resected NSCLC**, as adjuvant therapy only, when all criteria (a through e) below are met: **a.** Documented stage IB (T2a ≥4 cm), II, or IIIA disease **b.** Used in the adjuvant setting, after complete tumor resection. **c.** Used as a monotherapy. **d.** There is clinical documentation of previous adjuvant platinum- containing chemotherapy unless the patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin). **e.** There is no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*), including but not limited to use of Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) in the neoadjuvant setting or Tecentriq (atezolizumab) in the adjuvant setting. **PLEASE NOTE**: Platinum ineligibility may include poor kidney function, poor performance status (Eastern Cooperative Oncology Group [ECOG] score ≥ 2), heart failure, other comorbidities, etc.). **OR** **3.** **Earlier-stage**, **resectable NSCLC**, as neoadjuvant therapy followed by adjuvant therapy, when all criteria (a through c) below are met: **a.** Documented stage II, IIIA, or IIIB disease (tumors ≥

	4 cm and/or node positive) **b.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) is used as follows (<u>both</u> criteria i and ii are met): **i.** In combination with platinum-containing chemotherapy in the neoadjuvant setting (prior to surgical resection) for up to four cycles. **ii.** As monotherapy in the adjuvant setting (after surgical resection) for up to 13 cycles. **c.** No prior systemic anticancer therapy for NSCLC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).
Libtayo (cemiplimab)	**C.** A diagnosis of **NSCLC**, **locally advanced** (not candidates for surgical resection or definitive chemoradiation) or **metastatic**, when <u>all</u> criteria (1 through 3) below are met: **1.** No prior use of systemic therapy for locally advanced or metastatic disease. **2.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **3.** Libtayo (cemiplimab) will be used in <u>one</u> of the following settings (criterion a or b) is met: **a.** As monotherapy for tumors that express PD-L1 with a Tumor Proportion Score of at least 50% (TPS ≥ 50%). **OR** **b.** In combination with platinum-based chemotherapy for tumors that do not have EGFR, ALK, or ROS1 aberrations.
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**D.** A diagnosis of **NSCLC**, when <u>one</u> criterion (1, 2, or 3) below is met: **1.** **Earlier-stage**, **resectable NSCLC**, as <u>neoadjuvant therapy</u>, (with or without adjuvant therapy), when <u>all</u> criteria (a through c) below are met: **a.** Documented stage II, IIIA, or IIIB disease (defined as tumors ≥ 4 cm and/or node positive) **b.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as follows (<u>both</u> criteria i and ii are met): **i.** **For neoadjuvant doses**: In combination with platinum-containing chemotherapy in the neoadjuvant setting (prior to surgical resection) for up to four cycles. **ii.** **If adjuvant therapy is planned**: As

	monotherapy in the adjuvant setting (after surgical resection) for up to 13 cycles. **c.** No prior systemic anticancer therapy for NSCLC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*). **OR** **2.** **Advanced** or **metastatic NSCLC**, first-line setting, when all criteria (a through c) below are met. **a.** Opdivo (nivolumab) [IV only] is used in combination with Yervoy (ipilimumab) AND one of the following (criterion i or ii) is met: **i.** The tumor expresses PD-L1 (≥ 1%). **OR** **ii.** Given in combination with two cycles of platinum-doublet chemotherapy (regardless of PD-L1 status). **b.** No prior systemic therapy for advanced disease. **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3.** **Advanced** or **metastatic NSCLC**, subsequent therapy, when all criteria (a through c) below are met: **a.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is used as monotherapy. **b.** Disease progression on or after a platinum-containing chemotherapy regimen (such as cisplatin or carboplatin). **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**E.** A diagnosis of **NSCLC**, when one criterion (1 or 2) below is met: **1.** **NSCLC**, **metastatic (stage IV)**, when both criteria (a and b) below are met. **a.** One of the following criteria is met (criterion i or ii): **i.** There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*). **OR** **ii.** Documented prior use of Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab- hyaluronidase-tqjs) with NO progression of disease while on Tecentriq (atezolizumab) or Tecentriq Hybreza

	(atezolizumab- hyaluronidase-tqjs) adjuvant therapy. **b.** Tecentriq (atezolizumab) will be used in <u>one</u> of the following settings (criterion i, ii, or iii) below is met: **i.** As <u>monotherapy</u> in the <u>first-line setting</u> when the tumor has high PD-L1 expression. High PD-L1 expression is defined as PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]). **OR** **ii.** As <u>combination-therapy</u> in the <u>first-line setting</u> when <u>both</u> criteria (1 and 2) below are met: **1.** The tumor is an adenocarcinoma (non-squamous). **2.** Use is initiated in combination with chemotherapy, such as a platin and taxane. **OR** **iii.** As <u>monotherapy</u> in the <u>recurrent setting</u> when there has been disease progression on or after a platin-containing chemotherapy regimen. **OR** **2.** **NSCLC**, **stage II-IIIA disease**, as **adjuvant therapy**, when <u>all</u> criteria (a through e) below are met: **a.** Used in the adjuvant setting, after complete tumor resection. **b.** Used as a monotherapy. **c.** Documentation of PDL1 expression is provided. PD-L1 expression is defined as PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%]. **d.** There is clinical documentation of previous adjuvant platinum- containing chemotherapy, unless the patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin). **e.** There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*), including but not limited to use of Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) in the neoadjuvant setting.

	PLEASE NOTE: Any platinum ineligibility may include poor kidney function, poor performance status (Eastern Cooperative Oncology Group [ECOG] score ≥ 2), heart failure, other comorbidities, etc.).

T. Primary mediastinal B-cell lymphoma (PMBCL)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **primary mediastinal B-cell lymphoma (PMBCL)** when all criteria (1 through 3) below are met: **1.** Disease progression on or after two or more lines of therapy [such as chemotherapy or hematopoietic stem cell transplant (HSCT); a.k.a. ASCT or bone marrow transplant (BMT)]. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

U. Renal cell carcinoma (RCC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** A diagnosis of **renal cell carcinoma (RCC)** when both criteria (1 and 2) below are met: **1.** Clear cell histology. **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in one of the following settings (criterion a or b) below is met: **a.** A diagnosis of **recurrent** or **metastatic** disease when all criteria (i through iii) below are met: **i.** No prior systemic therapy for advanced disease. **ii.** Use in combination with Inlyta (axitinib) or Lenvima (lenvatinib). **iii.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **b.** **As adjuvant therapy** (after surgery) when all criteria (i through iii) below are met: **i.** No prior systemic therapy for RCC. **ii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be administered as monotherapy. **iii.** Use in one of the following settings (criterion 1 or 2) below is met: **1.** The tumor was **completely resected with clear margins** (the patient is tumor free based on MRI/CT scan) but there is intermediate-high or high-risk of RCC recurrence (per attestation or *Appendix 2*). **OR** **2.** The patient has RCC with stage M1 metastasis but there is **no evidence of disease (M1 NED) after nephrectomy** and **resection of metastatic lesions** (per attestation or *Appendix 2*).

Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**B.** A diagnosis of **renal cell cancer (RCC)**, **unresectable locally advanced**, or **metastatic**, with clear cell histology and no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **PLEASE NOTE**: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not indicated for concomitant use with Yervoy (ipilimumab).

V. Small cell lung cancer (SCLC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Imfinzi (durvalumab)	**A.** A diagnosis of **small cell lung cancer (SCLC)**, when one criterion (1 or 2) below is met: **1.** A diagnosis of **small cell lung cancer**, **extensive-stage (ES-SCLC)**, when all criteria (a through c) below are met: **a.** No prior systemic treatment for extensive stage SCLC (ES-SCLC) [not including any systemic treatment for early/limited-stage SCLC]. **b.** Imfinzi (durvalumab) is initiated in combination with etoposide and either cisplatin or carboplatin. **c.** No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** A diagnosis of **small cell lung cancer**, **limited-stage (LS-SCLC) [unresectable stage I to III]**, when all criteria (a through f) below are met: **a.** *For Stage I-II*: documented as medically inoperable disease. **b.** The patient has a documented good performance status (ECOG 0-1). **c.** The patient has received 3 or more cycles of concurrent etoposide/platinum-containing chemotherapy and radiation therapy. **d.** There has been no disease progression during or following platinum-containing chemotherapy and radiation therapy. **e.** Imfinzi (durvalumab) is used as monotherapy. **f.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1).*

Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**B.** A diagnosis of **small cell lung cancer**, **extensive-stage (ES-SCLC)**, when all criteria (1, through 4) below are met: **1.** No prior systemic treatment for extensive-stage SCLC (not including any systemic treatment for early/limited-stage SCLC). **2.** Use will be initiated in combination with carboplatin and etoposide (induction chemoimmunotherapy). **3.** No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*). **4.** If there has been no disease progression during or following induction chemoimmunotherapy, plan for maintenance therapy as one of the following (a or b): **a.** As monotherapy **OR** **b.** In combination with Zepzelca (lurbinectedin)

W. Urothelial carcinoma (UC)

Coverable medication(s)	ALL of the following diagnostic criteria are met:
Bavencio (avelumab)	**A.** A diagnosis of **urothelial carcinoma (bladder cancer)**, **locally advanced** or **metastatic**, when all criteria (1 through 3) below are met: **1.** Prior treatment with platinum-containing chemotherapy. **2.** Bavencio (avelumab) will be used as monotherapy. **3.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).
Imfinzi (durvalumab)	**B.** A diagnosis of **resectable muscle-invasive bladder cancer (MIBC)**, when all criteria (1 through 4) below are met: **1.** Pathological stage T2, T3, or T4a, N0 or N1, and M0. **2.** Planned radical cystectomy. **3.** Imfinzi (durvalumab) will be used in combination with gemcitabine/cisplatin neoadjuvant therapy followed by adjuvant monotherapy. **4.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). *Note: use in patients ineligible for cystectomy and/or cisplatin is not coverable.*
Keytruda (pembrolizumab), Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**C.** A diagnosis of **urothelial carcinoma (UC**, **bladder cancer)**, when both criteria (1 and 2) below are met: **1.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **2.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in one of the following settings (criterion a, b, or c) below is met: **a.** **First-line**: A diagnosis of **unresectable locally advanced (stage III)** or **metastatic (stage IV) bladder cancer**, when both criteria (i and ii) below are met: **i.** The patient has not had prior systemic therapy (chemotherapy or immunotherapy) in the advanced disease setting (locally advanced or metastatic disease). **ii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used in one of the following settings (criteria a or b below are met): **a.** In combination with Padcev (enfortumab

	vedotin). **b.** As a monotherapy **AND** the patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin). [Note: Any platinum ineligibility may include poor kidney function (CrCl<60), poor performance status (≥2), significant hearing loss (≥ 25 dB), grade 2-4 peripheral neuropathy, heart failure, other comorbidities, etc.] **OR** **b.** **Subsequent-line**: A diagnosis of **unresectable locally advanced (stage III)** or **metastatic (stage IV) bladder cancer**, when both (criteria i and ii) below are met: **i.** There is clinical documentation of disease progression during or following platinum-containing chemotherapy, **ii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy. **OR** **c.** A diagnosis of **non-muscle invasive bladder cancer (NMIBC)** when all criteria (i through iii) below are met: **i.** The tumor is carcinoma in situ (CIS, stage Tis) OR recurrent Ta/T1 disease within 12 months of BCG therapy. **ii.** Prior use of Bacillus Calmette-Guerin (BCG) therapy documented. **iii.** Keytruda (pembrolizumab) or Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) will be used as monotherapy.
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	**D.** A diagnosis of **urothelial carcinoma (UC**, **bladder cancer)** in one of the following settings (criterion 1, 2, or 3) below is met: **1.** **Subsequent line:** A diagnosis of **unresectable locally advanced (stage III)** or **metastatic (stage IV)**, , when all criteria (a through c) below are met: **a.** Disease progression during or following platinum-containing chemotherapy (such as cisplatin or carboplatin). **b.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-

	hyaluronidase-nvhy) is used as monotherapy. **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **2.** **First-line:** A diagnosis of **unresectable locally advanced** or **metastatic**, when all criteria (a through c) below are met: **a.** No prior systemic therapy in the advanced disease setting. **b.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be initiated in combination with cisplatin and gemcitabine. **c.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*). **OR** **3.** **Resected muscle-invasive urothelial carcinoma (MIUC)**, when all criteria (a through d) below are met: **a.** The patient has undergone radical resection of the bladder. **b.** There is high risk of recurrence as defined by one of the following (criterion i or ii) below is met: **i.** Patient received no prior neoadjuvant cisplatin-based chemotherapy: Pathological stage of pT3-pT4a, or pN+. **OR** **ii.** Patient received prior neoadjuvant cisplatin-based chemotherapy: Pathological stage of ypT2-ypT4a, or ypN+. **c.** Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) will be used as an adjuvant monotherapy. **d.** No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period:

A. Regence Pharmacy Services considers PD-1 and PD-L1 Inhibitors (as listed in *Table 1*) coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, PD-1 and PD-L1 Inhibitors will be authorized in the following quantities and for the following authorization periods outlined in *Table 1*.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks (unless otherwise specified in *Table 1*) for documented benefit, as detailed below.

1. *For initial reauthorization after neoadjuvant therapy*: Clinical documentation that the patient is following the treatment plan (such as completion of surgical resection +/- adjuvant radiation therapy) and the reauthorization request is for ongoing use in the adjuvant setting, as specified in the disease-specific coverage criteria. [Subsequent reauthorization will be reviewed for general reauthorization, detailed below]

2. *General reauthorization*: Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of confirmed disease progression (iCPD), based on an assessment of change in tumor burden. If there is documentation of potential disease progression [unconfirmed progressive disease (iUPD)], a shortened authorization (up to three months) may be approved to allow time for clarification of response to the PD-1/PD-L1 inhibitor, including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of the PD-1/PD-L1 inhibitor will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

Table 1. Administration – Quantity Limit (QL) and Authorization Period

Drug	Quantity Limit
Bavencio (avelumab)	For up to 24 weeks in doses up to 800 mg every 2 weeks, until disease progression.
Imfinzi (durvalumab)	For up to 24 weeks (unless otherwise specified), as follows: - ***Gastric/GEJ cancer***, ***earlier-stage - Neoadjuvant/adjuvant***: Neoadjuvant: up to 2 doses [up to 1500 mg every 4 weeks] pre-surgical resection, until disease progression or for up to a maximum of 8 weeks [one-time authorization]. Adjuvant: up to 12 doses [up to 1500 mg every 4 weeks] post-surgical resection, until disease progression or for up to a maximum of 48 weeks [one-time authorization]. - ***MIBC***, ***earlier-stage - Neoadjuvant/adjuvant***: Neoadjuvant: up to 4 doses [up to 1500 mg every 3 weeks] pre-surgical resection, until disease progression or for up to a maximum of 12 weeks [one-time authorization]. Adjuvant: up to 8 doses [up to 1500 mg every 4 weeks] post-surgical resection, until disease progression or for up to a maximum of 32 weeks [one-time authorization]. - ***NSCLC***, ***earlier-stage - Neoadjuvant/adjuvant***: Neoadjuvant: up to 4 doses [up to 1500 mg every 3 weeks] pre-surgical resection, until disease progression or for up to a maximum of 12 weeks [one-time authorization]. Adjuvant: up to 12 doses [up to 1500 mg every 4 weeks] post-surgical resection, until disease progression or for up to a maximum of 48 weeks, as follows: Initial Adjuvant: up to 6 doses (24 weeks). Continued Adjuvant: up to 6 doses (24 weeks). - ***NSCLC, locally advanced (unresectable, Stage 3) – consolidation therapy***: For up to 24 weeks, up to two, 10 mg/kg infusions every 28 days OR 1500 mg every 4 weeks until disease progression or for up to a maximum of 12 months. - ***NSCLC, metastatic (in combination with Imjudo)***: For up to 24 weeks, up to 1500 mg every 3 weeks for up to 4 cycles, then 1500 mg every 4 weeks until disease progression. - ***ES-SCLC***: For up to 24 weeks, up to 1500 mg every 3 weeks for up to 6 cycles then 1500 mg every 4 weeks until disease progression. - ***LS-SCLC – consolidation therapy***: For up to 24 weeks, up to 1500 mg every 4 weeks until disease progression or for up to a maximum of 24 months. - ***BTC***: For up to 24 weeks, up to 1500 mg every three weeks for up to 8 cycles

Drug	Quantity Limit
	then 1500 mg every 4 weeks until disease progression. - ***HCC***: For up to 24 weeks, up to 1500 mg every four weeks until disease progression. - ***Endometrial carcinoma***: For up to 24 weeks, up to 1,120 mg every 3 weeks for up to 6 cycles then 1,500 mg every four weeks until disease progression.
Jemperli (dostarlimab)	For up to 24 weeks, as follows: - ***Endometrial cancer***, ***front-line setting initiated with chemotherapy***: Initial: 500 mg IV every three weeks for six doses, followed by 1,000 mg IV every six weeks [7 doses over 24 weeks]. Continued: 1,000 mg IV every six weeks [4 doses over 24 weeks] until disease progression. - ***Endometrial cancer***, ***subsequent-line setting as monotherapy***: Initial: 500 mg IV every three weeks for four doses, followed by 1,000 mg IV every six weeks [6 doses over 24 weeks]. Continued: 1,000 mg IV every six weeks [4 doses over 24 weeks], until disease progression.
Keytruda (pembrolizumab)	*See Table 1a below*.
Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	*See Table 1a below*.
Libtayo (cemiplimab)	For up to 24 weeks, as follows: - ***Resected cSCC - adjuvant***: for up to 48 weeks of total therapy, in doses up to 350 mg every 3 weeks [Alternative dosing: 700 mg every 6 weeks]. - ***All other uses:*** For up to 24 weeks in doses up to 350 mg every three weeks, until disease progression.
Loqtorzi (toripalimab)	- ***In combination with chemotherapy***: For up to 24 weeks in doses up to 240 mg every three weeks until disease progression. - ***As monotherapy***: For up to 24 weeks in doses up to 3 mg/kg every two weeks until disease progression.
Opdivo (nivolumab)	*See Table 1b and Table 1c below.*
Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)	*See Table 1b and Table 1c below.*
Opdualag (nivolumab-relatlimab-rmbw)	For up to 24 weeks in doses up to one, 480 mg/160 mg infusion per 4 weeks until disease progression.
penpulimab	- ***In combination with chemotherapy***: For up to 24 weeks in doses up to 200

Drug	Quantity Limit
	mg every three weeks until disease progression. - ***As monotherapy***: For up to 24 weeks in doses up to 200 mg every two weeks until disease progression.
Tecentriq, atezolizumab (IV and SC)	*See Table 1d below*
Tevimbra (tislelizumab)	For up to 24 weeks in doses up to 150 mg every two weeks until disease progression. [Alternative dosing: 200 mg every three weeks or 300 mg every 4 weeks or 400 mg every 6 weeks].
Unloxcyt (cosibelimab)	For up to 24 weeks in doses up to 1,200 mg every three weeks, until disease progression.
Zynyz (retifanlimab)	For up to 24 weeks in doses up to 500 mg every four weeks, until disease progression. [Alternative dosing for anal squamous cell carcinoma (aSCC): 375 mg every three weeks].

Table 1a: Keytruda (pembrolizumab) and Keytruda Qlex (pembrolizumab- berahyaluronidase alfa-pmph) QL and Authorization Period[1]

Diagnosis	Keytruda/ Keytruda Qlex Dose	Treatment Period(s) [a]	Total Coverable Doses and/or Duration of Therapy [a]
Earlier stage disease (resected or planned resection)			
➢ Neoadjuvant followed by adjuvant			
Neoadjuvant/adjuvant TNBC, early-stage	Up to the FDA-approved dose	Neoadjuvant: up to 24 weeks Adjuvant: up to 27 weeks	Until disease progression, or until a total of 51 weeks
Neoadjuvant/adjuvant HNSCC, resectable			
Neoadjuvant/adjuvant NSCLC, earlier-stage	Up to the FDA-approved dose	Neoadjuvant: up to 12 weeks Initial Adjuvant: up to 24 weeks Continued Adjuvant: up to 15 weeks	Until disease progression, or a total of 51 weeks
➢ Adjuvant only			
Adjuvant ONLY: - NSCLC, earlier-stage - Melanoma - RCC	Up to the FDA-approved dose	Initial Adjuvant: up to 8 doses (24 weeks) Continued Adjuvant: up to 10 doses (30 weeks)	Until disease progression, up to 18 doses (54 weeks)
Advanced disease (non-resectable)			
Melanoma, unresectable or metastatic	Up to the FDA-approved dose	Initial / Continued: up to 8 doses (24 weeks)	Until disease progression
All other covered diagnoses [b]			

NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; TNBC: triple-negative breast cancer

[a] Total time on treatment, for example 200 mg every 3 weeks for 10 doses is a 30 week treatment period.

[b] Including advanced forms of diagnoses in the coverage criteria, except as specifically noted above in this table.

Table 1b: Opdivo (nivolumab) and Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) QL and Authorization Period

Monotherapy or in Combination with Chemotherapy			
Diagnosis	**Opdivo/ Opdivo Qvantig Dose**	**Treatment Period(s)** [a]	**Total Duration** [a]
Neoadjuvant therapy for RESECTABLE cancer (earlier stage NSCLC)	Up to the FDA-approved dose	n/a	One Time: up to up to 12 weeks.
Adjuvant therapy for RESECTABLE cancer (esophageal cancer, GEJ cancer, muscle-invasive urothelial carcinoma, melanoma, or NSCLC)	Up to the FDA-approved dose	Initial Adjuvant: up to 24 weeks. Continued Adjuvant: up to 28 weeks.	Until disease progression, or up to a total of 52 weeks
Classical Hodgkin lymphoma (cHL), first-line	Up to the FDA-approved dose	n/a	One Time: up to 24 weeks in 6 cycles (28-day cycle).
Other (non-resectable): NSCLC, aSCC, advanced melanoma, RCC, UC (bladder cancer), MSI-H/dMMR CRC, r/r classical HL, HNSCC, advanced esophageal, gastric, GEJ cancer	Up to the FDA-approved dose	Initial / Continued: up to 24 weeks.	Until disease progression.
Combination Therapy with Cabometyx (cabozantinib)			
Diagnosis	**Dose**	**Treatment Period(s)** [a]	**Total Duration** [a]
RCC	Up to the FDA-approved dose	Initial / Continued: up to 24 weeks.	Until disease progression.

[a] Total time on treatment, for example 240 mg every 2 weeks for 12 doses is a 24 week treatment period.

Table 1c: Opdivo (nivolumab) or Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) with Yervoy (ipilimumab) QL and Authorization Period

Opdivo IV with Yervoy				
Diagnosis	**Quantity Limit**		**Authorization Period(s)**	**Total Duration** [a]
	Initial, Opdivo IV in combination with Yervoy [b]	**Subsequent, Opdivo IV or Opdivo Qvantig as monotherapy**		
Melanoma, Neoadjuvant therapy for RESECTABLE Stage III	Up to the FDA-approved dose [based on NADINA]	Reauthorization: Up to the FDA-approved dose may be authorized with documentation of Major Pathologic Response (MPR) and no BRAF mutation, as determined by lymph node dissection.	Initial neoadjuvant: up to 6 weeks. Continued, as adjuvant, if reauthorization criteria are met: up to 24 weeks. Final authorization, Adjuvant: up to 20 weeks	Neoadjuvant only: 6 weeks If adjuvant is indicated: Until disease progression, up to 50 weeks total therapy.
Melanoma, advanced (not resected)	Up to 3 mg/kg every 3 weeks [based on CheckMate 511]	Up to the FDA approved dose.	Initial: up to 12 weeks. Continued: up to 24 weeks.	Until disease progression.
HCC CRC (MSI-H/dMMR), RCC	Up to the FDA-approved dose			
ESCC, NSCLC (PD-L1 ≥1), NSCLC (with 2 cycles platins), MPM	Up to the FDA-approved dose	Not applicable (used with Yervoy in maintenance phase)	Initial / Continued: up to 24 weeks.	Until disease progression.

[a] Total time on treatment, for example 240 mg every 2 weeks for 12 doses is a 24 week treatment period.

[b] Limitation of use: Opdivo Qvantig SC is not indicated for concomitant use with Yervoy (ipilimumab).

aSCC: anal squamous cell carcinoma; CRC: colorectal cancer; dMMR: mismatch repair deficient; GEJ: gastro-esophageal junction; HL: Hodgkin lymphoma; HNSCC: head and neck squamous cell cancer; IV=intravenous; MPM: malignant pleural mesothelioma; MPR: major pathological response (defined as ≤10% residual viable tumor, based on results of lymph node dissection); MSI-H: microsatellite instability-high; NSCLC: non-small cell lung cancer; RCC: renal cell cancer; SC=subcutaneous; UC: urothelial carcinoma

Table 1d: Tecentriq (atezolizumab) QL and Authorization Period [2]

Diagnosis	Dose	Authorization Period(s)	Total Coverable Duration of Therapy
Adjuvant NSCLC	IV dosing: Up to a maximum of 420 mg IV per 7 days (as 840 mg IV every 14 days, 1200 mg IV every 21 days, or 1680mg IV every 28 days). SC dosing: Up to a maximum of 1,875 mg atezolizumab/30,000 units hyaluronidase (Tecentriq Hybreza) SC every 21 days.	Initial Adjuvant: up to 24 weeks. Continued Adjuvant: up to 28 weeks.	Until disease progression, up to 12 months.
All other covered diagnoses	IV dosing: Up to a maximum of 420 mg IV per 7 days (as 840 mg IV every 14 days, 1200 mg IV every 21 days, or 1680mg IV every 28 days). SC dosing: Up to a maximum of 1,875 mg atezolizumab/30,000 units hyaluronidase (Tecentriq Hybreza) SC every 21 days.	Initial/Continued: up to 24 weeks.	Until disease progression.

Key: NSCLC: non-small cell lung cancer

IV. Not Medically Necessary Uses:

PD-1 and PD-L1 Inhibitors (as listed in *Table 1*) are considered not medically necessary when used for the following conditions:

Drug	Not Medically Necessary Uses
Bavencio, avelumab	Bavencio (avelumab) in combination with Inlyta (axitinib) for first-line advanced clear cell RCC.
Libtayo, cemiplimab	Cervical cancer.
Tecentriq, atezolizumab (IV and SC)	EGFR- or ALK-mutated NSCLC as a second-line therapy, after progression on EGFR-or ALK-directed therapy.
Tevimbra, tislelizumab	As an add-on to chemotherapy for first-line treatment of locally advanced (unresectable) or metastatic ESCC.

V. Investigational Uses:

PD-1 and PD-L1 Inhibitors (as listed in *Table 1*) are considered investigational when used for all other conditions, including but not limited to:

Drug	Investigational Uses
Bavencio (avelumab)	**A.** Gastric or gastroesophageal junction (GEJ) adenocarcinoma. **B.** Non-small cell lung cancer (NSCLC). **C.** Renal cell carcinoma (RCC), when used in the subsequent-line treatment setting.
Imfinzi (durvalumab)	**A.** Non-small cell lung cancer (NSCLC) [other than specified in the criteria above]. **B.** Biliary tract cancer (BTC) in the second- and subsequent-line setting. **C.** Cervical cancer. **D.** Endometrial sarcoma. **E.** Head and Neck cancer (HNSCC). **F.** HCC, as monotherapy after transarterial chemoembolization (TACE) **G.** Advanced urothelial carcinoma (bladder cancer).
Jemperli (dostarlimab)	**A.** Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the sections above]. **B.** Pancreatic cancer
Keytruda (pembrolizumab) and Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph)	**A.** Triple negative breast cancer (TNBC) [except as specified in the sections above]. **B.** Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the sections above]. **C.** HCC, as monotherapy after transarterial chemoembolization (TACE) **D.** Multiple myeloma. **E.** Neuroendocrine tumors (NETs) **F.** Ovarian cancer. **G.** Pancreatic cancer **H.** Prostate cancer **I.** Small cell lung cancer (SCLC). **J.** Soft tissue sarcomas (STS), including uterine leiomyosarcoma (LMS). **K.** TMB-H tumors (solid tumors with high mutational burden).

Drug	Investigational Uses
Opdivo (nivolumab) and Opdivo Qvantig (hyaluronidase-nvhy)	**A.** The use of Opdivo (nivolumab) or Opdivo Qvantig (hyaluronidase-nvhy) in combination with other targeted anti-cancer medications [except with Cabometyx (cabozantinib) for RCC, Yervoy (ipilimumab) for melanoma, CRC, RCC, NSCLC, and HCC, or as specified per the coverage criteria above] are considered investigational. **B.** Glioblastoma multiforme. **C.** Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the coverage criteria sections above]. **D.** Multiple myeloma. **E.** Ovarian cancer. **F.** Neuroendocrine tumors (NETs) **G.** Pancreatic cancer **H.** Small cell lung cancer (SCLC).
Opdualag (nivolumab-relatlimab-rmbw)	**A.** Subsequent therapy for previously treated advanced melanoma: Use for disease progression/recurrence on/after use of systemic therapy in the advanced setting, including but not limited to, PD-1 inhibitors or PD-L1 inhibitors in the advanced setting (see *Appendix 1*). **B.** Sequential use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).
Tecentriq (atezolizumab) and Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs)	**A.** Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs) is considered investigational when administered concomitantly with other anti-cancer immuno-, and targeted-therapies, with the exception of those specifically addressed in the coverage criteria above. **B.** Renal cell carcinoma (RCC). **C.** Breast cancer (including TNBC and HER-2 positive). **D.** Urothelial carcinoma (bladder cancer). **E.** Prostate cancer. **F.** Neuroendocrine tumors (NETs) **G.** Ovarian cancer. **H.** Soft tissue sarcoma (STS), other than specifically listed above in the coverage criteria.
Tevimbra (tislelizumab)	**A.** Esophageal adenocarcinoma.

Position Statement

- Medications in this policy ("PD-1 and PD-L1 Inhibitors") include human programmed death receptor-1 (PD-1) blocking monoclonal antibodies and programmed death-ligand (PD-L1) blocking antibodies. They are immunotherapies used in the treatment of several types of cancers.
- The intent of this policy is to cover PD-1 and PD-L1 Inhibitors in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of PD-1 and PD-L1 Inhibitors alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- PD-1 and PD-L1 Inhibitors are also FDA approved for use in the following conditions; however, the health plan considers these uses to be "investigational" (not covered) as the specific PD-1/PD-L1 inhibitor has not demonstrated to provide any health benefit, based on the currently available evidence:
    * Keytruda (pembrolizumab)
        - Adjuvant therapy for Stage IIB and IIC (completely resectable) melanoma.
        - MSI-H Tumors, other than CRC and endometrial carcinoma *(as described in the Clinical Efficacy section below).*
        - Tumor Mutational Burden-High (TMB-H) Solid Tumors (any).
    * Jemperli (dostarlimab)
        - MSI-H tumors, other than endometrial carcinoma (*as described in the Clinical Efficacy section below*).
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- *PD-L1 expression testing*: is required for coverage of many clinical indications for PD-1 and PD-L1 inhibitors.
    * There are several ways in which PD-L1 expression can be defined. In addition, how PD-L1 expression is defined varies by tumor type and setting.
    * PD-L1 expression is determined by the FDA-approved companion diagnostic testing, based on both the specific PD-1/PD-L1 inhibitor and the tumor type.
    * However, PD-L1 test results are not interchangeable across PD-1/PD-L1 inhibitors and/or indications. There is no conversion available from one type of test to another, such as combined positive score (CPS) versus tumor proportion score (TPS) versus percent of tumor cells (TC). Therefore, the correct test must be conducted for proper selection of patient populations for a given use.

- National Comprehensive Cancer Network (NCCN) guidelines recommend each PD-1/PD-L1 inhibitor as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- PD-1/PD-L1 inhibitor therapy is coverable for up to the dose and quantity as specified in the coverage criteria.
    * It is administered until disease progression or unacceptable toxicity, unless specified in the coverage criteria as a finite course.
    * For neoadjuvant/adjuvant therapy for very specific resectable cancers, a pre-specified number of doses (per the clinical trials) are administered as neoadjuvant therapy before surgery and, specific number of doses of adjuvant therapy after surgery (or until disease recurrence or unacceptable toxicity).
    * For other advanced, non-resectable indications, it is given until disease progression, unacceptable toxicity, or for up to a specific timeframe, such as Keytruda (pembrolizumab) for 24 months in patients without disease progression. Given that trials of Keytruda (pembrolizumab) for most indications were specifically designed for a 24-month course of therapy, there is no conclusive additional benefit with higher doses or when given for longer durations.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- Subcutaneous (SC) dosing: There are several PD-1/PD-L1s with subcutaneously administered formulations. The indications for the SC formulations generally mirror the indications for the IV formulation. However, when used in combination with other immunotherapy, such as CTLA4 Yervoy (ipilimumab), there may not be established dosing for the SC PD-1/PD-L1 formulation. While Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) may be used after completion of Opdivo (nivolumab) IV plus Yervoy (ipilimumab) combination therapy, it is not indicated for concomitant use with Yervoy (ipilimumab) per prescribing information, as there is no established dosing of the SC form.
- There are ongoing studies using PD-1/PD-L1 inhibitor therapies in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated. Therefore, use in settings other than that which is described in the coverage criteria above are considered investigational.
- Various FDA indications have been withdrawn after confirmatory trials failed to demonstrate an improvement in any health outcome when used in the specified setting, and these uses are considered investigational. [*note: this is not an all-inclusive list*]:
    * Cervical cancer, recurrent or metastatic: Libtayo (cemiplimab-rwlc)
    * Hepatocellular carcinoma (HCC): Opdivo (nivolumab)

    * Small cell lung cancer (SCLC), recurrent or metastatic: Keytruda (pembrolizumab) and Opdivo (nivolumab)
    * Urothelial carcinoma (bladder cancer), subsequent therapy: Imfinzi (durvalumab) and Tecentriq (atezolizumab)
    * Triple negative breast cancer (TNBC), locally advanced or metastatic, PD-L1-positive, front-line, in combination with Abraxane (nab-paclitaxel): Tecentriq (atezolizumab)
- *Reauthorization Criteria*: When coverage criteria are met, PD-1/PD-L1 inhibitor therapy is authorized for up to six months (up to 24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medical necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing equally efficacious potentially higher-value treatment options, considering effectiveness, safety, and cost. NCCN is a CMS recognized compendium that is considered a reference standard, rather than a gold standard, of care. NCCN compendia are not strictly evidence-based and therefore may not be supported by the best available evidence or meet benefit contract definitions of medical necessity. Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Alveolar soft part sarcoma (ASPS)

Background

- Alveolar soft part sarcoma (ASPS) is a very rare type of soft tissue sarcoma (STS) (less than 1% of all STS).[3]

Tecentriq (atezolizumab)

- The approval of Tecentriq (atezolizumab) in advanced ASPS is based one unpublished, non-randomized, multicenter, single-arm phase 2 trial in 49 patients with ASPS not curable by surgery (ML39345). [2 4]
    * All enrolled patients had prior surgery and were stage IV at the time of diagnosis.
    * A majority had prior other treatments (55% more than one), including radiation therapy (55%), chemotherapy (53%).
    * The primary outcome was overall response rate (ORR) (24%). Twelve patients (24%) had a partial response (PR), and none had a complete response (CR).
    * Subsequently, the trial was published with the results from a total of 52 patients [5], reporting ORR 37% (19 of 52 patients), 18 PR, and one CR.

Guidelines:

- The NCCN soft tissue sarcoma guideline includes the use of Tecentriq (atezolizumab) among preferred recommended options for unresectable or metastatic ASPS. [3]

Anal squamous cell carcinoma (aSCC)

Background[6]

- Squamous cell carcinoma of the anal canal (SCAC), also called anal squamous cell carcinoma (aSCC), is a relatively rare cancer, accounting for approximately 3% of all GI cancers, with approximately 11,000 new cases in the US in 2025.
- Risk factors for aSCC include human papilloma virus (HPV) infection (anal-genital warts, >90%), female gender, HIV infection, anal intercourse, immunosuppression, and smoking. High-risk forms of HPV include HPV-16 and HPV-18. HPV vaccination prevents persistent infection with nine strains: HPV-6, -11, -16, -18, -33, -45, -52, and -58.
- Anal cancer includes cancer of the anus, anal canal (SCAC), and anorectum. Histology subtypes include large-cell keratinizing, large-cell non-keratinizing (transitional), and basaloid. However, for the purposes of drug therapy treatment, the guidelines consider all subtypes to be aSCC (a.k.a. SCAC). Anal cancer (SCAC) is a more general term. However, perianal cancer, from the anal verge to the perianal skin, is not considered “SCAC” as it arises from the skin.
- Approximately 30% of HPV-positive and 40% of HPV-negative aSCC is programmed death-ligand 1 (PD-L1) expressing.
- aSCC is typically a chemosensitive tumor; however, responses to chemotherapy are not usually durable.

Zynyz (retifanlimab)

- Zynyz (retifanlimab) received FDA approval for the first-line setting based on meeting its primary endpoint of progression-free survival (PFS), a surrogate endpoint with unknown clinical value in one fair confidence phase 3 study (POD1UM-303/InterAACT-2) in patients with locally recurrent or metastatic SCAC (n=308).[7] The FDA approval in the subsequent line setting was based on one lower quality (phase 2 trial) evidence (POD1UM-202), with overall response rate (ORR) as the endpoint, similar to existing evidence for multiple other PD1/PD-L1 inhibitors.[8 9]
- First-line Efficacy [vs placebo, as add-on to standard of care (SOC) cytotoxic chemotherapy]:

    * Marginal response rate is not clinically meaningful endpoint, when SOC therapy has a high cure rate.
    * 1.9 mo difference in PFS vs placebo (PBO); p-value 0.006.
    * Interim median OS 29.2 [24.2 to NE] vs. 23.0 mo [15.1 to 27.9], with notable high rate of crossover from PBO to Zynyz (retifanlimab).
    * Limitations: OS not mature (interim analysis), missingness of baseline data (HPV status).
- Subsequent line Efficacy (single-arm) [8]
    * The majority of patients with anal SCC respond well to 1st line standard cytotoxic chemotherapy, with a cure.
    * In the phase 2 POD1UM-202 trial: ORR 14%; however, a not clinically meaningful endpoint. Similar to other PD1/PDL1s in this setting. [9] Specifically, there is phase 2 trial evidence for Opdivo (nivolumab), Keytruda (pembrolizumab), Bavencio (avelumab), Tecentriq (atezolizumab)/bevacizumab, and Zynyz (retifanlimab) in aSCC that is refractory to or recurs on front-line chemotherapy is limited to preliminary data (ORR, ranging from 11 to 24%, variable with patient population studied). However, cytotoxic chemotherapy has higher ORR, as well as PFS data.
    * Limitations: lack of comparator, unknown clinical outcome, generalizability to platin-eligible patients.

Keytruda (pembrolizumab)

- Although not FDA-approved for this use, Keytruda (pembrolizumab) and Opdivo (nivolumab) have been used in anal squamous cell carcinoma that is refractory to or recurs on front-line chemotherapy based on the lack of effective therapies for refractory disease. The majority of patients with anal SCC respond well to standard cytotoxic chemotherapy.
- Preliminary studies suggest these therapies have potential activity in this setting:
    * A manufacturer-funded study reported an ORR of 17% (all partial responses) in 24 patients with recurrent PD-L1-positive (> 1%) advanced anal SCC who received Keytruda (pembrolizumab).[10]
    * A National Institutes of Health (NIH) funded study reported an ORR of 24% (two complete and seven partial responses) in 37 patients with treatment refractory metastatic anal SCC who received Opdivo (nivolumab).[11]
    * Additional studies are needed to establish whether there is a lasting clinical benefit with these PD-1 inhibitors in this treatment setting. However, given the lack of treatment alternatives in a relatively small patient population, the use of Keytruda (pembrolizumab) and Opdivo (nivolumab) are considered medically necessary and coverable in chemotherapy-refractory disease.
- Given the lack of treatment alternatives in a relatively small patient population, the use of Keytruda (pembrolizumab) is considered medically necessary and coverable in chemotherapy-refractory disease.

Opdivo (nivolumab)

- Although not FDA-approved for this use, Opdivo (nivolumab) and Keytruda (pembrolizumab) have been used in anal squamous cell carcinoma that is refractory to or recurs on front-line chemotherapy due to the lack of other effective therapies.

- The majority of patients with aSCC respond well to standard cytotoxic chemotherapy.
- Preliminary studies suggest these therapies have potential activity in this setting:
    * There was a reported ORR of 17% (all partial responses) in 24 patients with recurrent PD-L1-positive (> 1%) advanced anal squamous cell carcinoma who received Keytruda (pembrolizumab).[10]
    * There was a reported ORR of 24% (two complete and seven partial responses) in 37 patients with treatment refractory metastatic anal squamous cell carcinoma who received Opdivo (nivolumab).[11]
    * Additional studies are needed to establish whether there is a lasting clinical benefit with these PD-1 inhibitors in this treatment setting.
- Given the lack of treatment alternatives in a relatively small patient population, the use of Opdivo (nivolumab) is considered medically necessary and coverable in chemotherapy-refractory disease.

Guidelines:

- Treatment options for aSCC (SCAC) include surgery, radiation, and chemotherapy (fluoropyrimidine with mitomycin or cisplatin). Most locally advanced aSCC responds to chemoradiation, but with significant recurrence.
- Refractory aSCC is difficult to treat and has a lack of effective treatment options.
- The NCCN Anal Cancer Guidelines recognize the following (all category 2A, unless noted): [3]
    * First-line Therapy: Zynyz (retifanlimab) with carboplatin/paclitaxel as a "preferred". "Other Recommended" include carboplatin/paclitaxel, FOLFCIS, and mFOLFOX6.
    * Subsequent Therapy: several PD-1/PD-L1s, if no prior immunotherapy used, as a "preferred" – Opdivo (nivolumab), Keytruda (pembrolizumab), Zynyz (retifanlimab), based on phase 2 trial data. More recently, NCCN also endorsed Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), and Loqtorzi (toripalimab), based on extrapolation of data from colorectal cancer (CRC). However, guidelines recognize there is insufficient clinical trial data to support the use of any of these other PD-1/PD-L1 inhibitors for aSCC. "Other Recommended" include carboplatin/paclitaxel, FOLFCIS, and mFOLFOX6.
- All cases of aSCC should be screened for HIV infection and treated with antiretrovirals, if HIV-positive.

Basal Cell Carcinoma (BCC)

Libtayo (cemiplimab)

- The available evidence for Libtayo (cemiplimab-rwlc) as a monotherapy in BCC is based on a small, single-arm trial (low-quality evidence) that enrolled 84 patients with locally advanced BCC (laBCC) and 48 patients with metastatic BCC (mBCC). [12-14]
    * All patients had prior therapy with a hedgehog inhibitor (HHI), the current standard of care for advanced BCC. Seventy-six percent had disease progression on a prior HHI, 34% had intolerance to a prior HHI, and 10% had no better than stable disease while on HHI therapy.
    * The primary endpoint of the study was objective response rate (ORR). ORRs ranged from 21% in the mBCC population, to 29% in the laBCC population. There were no complete responses in the mBCC population, while five patients (6%) were considered to have a

complete response in the laBCC group.

* ORR is a surrogate endpoint that does not necessarily predict clinical benefit, such as improved overall survival or improved quality of life.

- Of note, the part of the FDA BCC indication for Libtayo (cemiplimab-rwlc) that refers to "or in whom a HHI is not appropriate" is not part of a population that was defined or enrolled in the clinical trial. There are no known objective parameters used to define this subpopulation.
- All patients in the trial were naïve to prior PD-1/PD-L1 inhibitor therapy. To date, there is no evidence to support the benefit of sequential PD-1/PD-L1 inhibitor therapy after disease has progressed on a prior therapy with these agents.

Guidelines:

- HHIs and cemiplimab are the only systemic therapies available for the treatment of laBCC and mBCC. The NCCN Basal Cell Skin Cancer guideline recommends Libtayo (cemiplimab-rwlc) for patients who have been previously treated with a HHI or for whom a HHI is not appropriate. [3]

Biliary Tract Cancer (BTC)

Imfinzi (durvalumab)

- FDA approval of Imfinzi (durvalumab) as a front-line therapy for locally advanced and metastatic BTC was based on a single phase 3 randomized, double-blind, placebo-controlled trial [TOPAZ-1] that compared the addition of Imfinzi (durvalumab) to gemcitabine plus cisplatin versus gemcitabine and cisplatin alone.[15]

* Patients had no prior treatment in the advanced disease setting and had no prior exposure to immune-mediated therapy (e.g., PD-1/PD-L1 inhibitors).

* Eighty-six percent of the population had metastatic adenocarcinoma of the biliary tract, which included intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancer. The remainder of the population had unresectable, locally advanced disease.

* There was a small (~ 5 weeks), but statistically significant difference in OS advantage favoring the Imfinzi (durvalumab) treatment arm.

Keytruda (pembrolizumab)

- An RCT [KEYNOTE-966] evaluated Keytruda (pembrolizumab) in patients with unresectable locally advanced or metastatic biliary tract cancer (BTC) as an add-on to front-line chemotherapy.[16]

* Patients had histologically confirmed extra- or intrahepatic cholangiocarcinoma (CCA) or gall bladder cancer and had not received prior therapy for their advanced disease. Patients treated with neoadjuvant or adjuvant therapy for resectable, non-metastatic disease were allowed to enroll if their disease recurred at least 6 months after completing these therapies.

* The study compared Keytruda (pembrolizumab) plus gemcitabine/cisplatin with placebo plus gemcitabine/cisplatin (chemotherapy alone). Cisplatin was given for up to eight cycles, and Keytruda (pembrolizumab) was given for up to 35 cycles.

* Sixty-eight percent of the tumors had PD-L1 CPS $\geq$ 1, though PD-L1 status was not a condition for enrollment.

    * The median OS was 12.7 months and 10.9 months in the Keytruda (pembrolizumab) and placebo treatment arms, respectively.
- Imfinzi (durvalumab) is also approved in this treatment setting with similar evidence and outcomes; however, there is no evidence directly comparing the two therapies.

Guidelines:

- National Comprehensive Cancer Center (NCCN) guidelines list gemcitabine/cisplatin plus either Imfinzi (durvalumab) or Keytruda (pembrolizumab) among preferred, category 1 recommendations for the front-line treatment of unresectable or metastatic BTC. [3]

Bladder Cancer

- See Urothelial Carcinoma

Breast Cancer

- See Triple negative breast cancer

Cervical cancer

Keytruda (pembrolizumab)

Recurrent or metastatic

- Keytruda (pembrolizumab) received FDA Accelerated approval for use in recurrent or metastatic cervical cancer when tumors express PD-L1 (CPS ≥ 1) based on tumor response rates from a single-arm, open-label study [KEYNOTE-158]. To date, there is no evidence that it improves any clinically relevant outcome [e.g., improved overall survival (OS), symptom control, function, or quality of life (QOL)] in this disease setting.[17]
    * The current available evidence is limited to two small, uncontrolled, open-label Phase 1b/2 studies evaluated subjects with metastatic cervical cancer who had between one and four prior systemic therapies. Nearly all tumors expressed PD-L1 with a Combined Positive Score (CPS) of at least 1%. [18-20]
    * The reported objective response rate (ORR) in the pivotal study was 14.6%. Three patients (3.6%) had a complete response.
    * ORR has not been shown to accurately predict improvement in clinical endpoints in cervical cancer.
- A phase 3, double-blind RCT [KEYNOTE-826] evaluated the addition of Keytruda (pembrolizumab) to a platinum-based chemotherapy regimen in patients with carcinoma of the cervix that had not been treated with prior systemic chemotherapy and which was not amenable to curative treatment.[21]
    * Patients had persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous cell carcinoma of the cervix. Patients were naïve to prior systemic chemotherapy and PD-1/PD-L1 inhibitor therapy.
    * Patients were enrolled without regard to PD-L1 status; however, all patients were tested after enrolling in the study. Eighty-nine percent of patients in the study had a PD-L1

combined positive score (CPS) of at least 1.

* Patients received either Keytruda (pembrolizumab) or placebo plus a platinum and paclitaxel (with or without bevacizumab). Chemotherapy was given for up to six cycles and Keytruda (pembrolizumab) was given for up to 35 cycles.
* OS was significantly longer in the Keytruda (pembrolizumab) versus the placebo arm among patients with a PD-L1 CPS ≥ 1 (primary analysis population). The HR for death was 0.64 [95% CI: 0.50 to 0.81] with p < 0.001. There was also a statistically significant survival benefit in the entire population, which included patients with PD-L1 CPS < 1 ("All comers"). However, patients with a PD-L1 CPS ≥ 1 made up the vast majority (~90%) of the study population which likely confounded the "All comers" analysis by enriching the population with potential responders. A sub analysis in patients with PD-L1 CPS < 1 showed no survival benefit which supports this conclusion.

High-risk, locally advanced (FIGO 2014 Stage III/IVA)

- Keytruda (pembrolizumab) was also evaluated as an add-on therapy to chemoradiation for high-risk, locally advanced cervical cancer in a large placebo-controlled RCT [KEYNOTE A-18]. The current indication in this population is based on a subgroup from this study that had International Federation of Gynecology and Obstetrics (FIGO) 2014 stage III to IVA disease (tumor involvement in the lower vagina with or without extension into the pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs). Patients with FIGO stage IVB disease were excluded from the study.[1]
  * The study enrolled patients with the following disease histologies: Squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma of the cervix.
  * Patients enrolled in the study had no prior definitive surgery, radiation, or systemic therapy.
  * The study compared Keytruda (pembrolizumab) 200 mg IV Q3W for 5 cycles plus cisplatin (5 to 6 cycles) and radiotherapy, followed by Keytruda (pembrolizumab) 400 mg IV Q6W as monotherapy for an additional 15 cycles with matching placebo plus chemoradiotherapy as described above.
  * Ninety-three percent of the tumors had PD-L1 CPS ≥ 1.
  * The median PFS was not reached in either treatment arm. The hazard ratio for progression or death was 0.59 [95% CI: 0.43, 0.82] in favor of Keytruda (pembrolizumab). At the time of FDA approval, the impact of this therapy on clinically relevant outcomes was unknown as the OS data was not mature.
  * Results from the final OS analysis reported a small difference in 3-year OS [82.6% with Keytruda (pembrolizumab) vs. 74.8% with placebo [HR 0.67 (CI 0.50, 0.90); p=0.004].[22]
- See 'Guidelines' for information on use in patients with FIGO 2018 staging.

Guidelines:

- The NCCN cervical cancer guideline recommends the following: [3]
  * ***Recurrent or metastatic disease:*** Front-line platinum-based chemotherapy with or without bevacizumab. Keytruda (pembrolizumab) can be added for PD-L1-expressing tumors (CPS ≥ 1%).

* ***FIGO 2014 stage IIIA, IIIB, IVA disease:*** Cisplatin or carboplatin plus external beam radiation therapy (EBRT) plus Keytruda (pembrolizumab). "Select" FIGO 2018 Stage III-IVA is a lower category 2B, given the FIGO 2018 stage IIIC is nodal metastasis without other high-risk tumor features per FIGO 2014 (tumor size and extent). However, when the FIGO 2018 staging (III) overlaps with FIGO 2014 Stage IIIA/IIIB, the higher-level recommendation applies.

  Note: NCCN workup and recommendations are based primarily on FIGO 2018 staging. However, some recommendations refer to the FIGO 2014 staging used in clinical trials. Therefore, some recommendations note "select" FIGO 2018 Stage III-IVA.

Classical Hodgkin lymphoma (cHL)

Keytruda (pembrolizumab)

- Keytruda (pembrolizumab) was FDA-approved in classical Hodgkin lymphoma based on a single-arm trial [KEYNOTE-087] that evaluated tumor response rates in patients with relapsed or refractory disease. Patients in the study were heavily treatment-experienced.[1 23] To date, there is no evidence that Keytruda (pembrolizumab) improves any clinical outcome in this population.
  * Subjects enrolled in the trial had received a median of four prior therapies, including prior autologous hematopoietic stem cell transplant (61%) and/or Adcetris (brentuximab vedotin) 83%.
  * The ORR reported in the study was 69%, with 22% complete responses.
- Subsequently, the Keytruda (pembrolizumab) was studied in an open-label (not blinded) phase 3 RCT in an earlier line of therapy for relapsed or refractory cHL, after chemotherapy and/or hematopoietic stem cell transplant (HSCT), or in patients ineligible for HSCT in one unblinded Phase 3 trial [KEYNOTE-204]. [1]
  * Keytruda (pembrolizumab) was superior to brentuximab vedotin (BV, Adcetris), based on an improvement in PFS (13.2 months with pembrolizumab vs. 8.3 months with BV).
  * Overall survival data, a co-primary endpoint, was not mature at the time of the interim data analysis and the FDA approval. Therefore, the clinical benefit is unknown. Of note, a significant number of subjects received subsequent SCT (30% and 21% in the pembrolizumab and BV arms, respectively), which will confound future OS results.
- A small (N=38), single-arm, phase 2 study evaluated pembrolizumab plus gemcitabine/ vinorelbine/liposomal doxorubicin (GVD) given for two to four cycles prior to autologous stem cell transplant as a second-line therapy for patients with relapsed/refractory cHL. [24]
  * Ninety-five percent of patients achieved a complete remission and 36 of 38 patients went on to receive an ASCT.
  * It is unknown how pembrolizumab + GVD compares with other regimens used in this setting, or if it improves long-term outcomes such as overall survival.

Opdivo (nivolumab)

- Refractory/relapsed cHL: Opdivo (nivolumab) received FDA Accelerated approval for as a monotherapy relapsed or refractory CHL based on two, small, single-arm, trials that measured tumor response rate [CHECKMATE-205 and -039]. Clinical benefit in this setting has not been established.[25 26]

* Subjects had relapsed or refractory disease and had prior high-dose chemotherapy followed by autologous stem cell transplant rescue, and post-transplantation Adcetris (brentuximab vedotin). The median number of prior systemic regimens was four. *[Note: PD-1 inhibitors, such as Opdivo (nivolumab), should NOT be given after an allogeneic stem cell transplant as it may cause serious and potentially fatal immunologic reactions].*
* ORR, the primary endpoint, not been shown to correlate with clinical outcomes such as improved symptom control, function, or quality of life, or prolonged OS.

- Previous-untreated cHL (first-line): The evidence for Opdivo (nivolumab) [as N+AVD] as a potential therapy for first-line cHL is based on one large NCI/NIH-sponsored phase 3, open-label, randomized controlled trial (S1826) that reported a progression-free survival (PFS) benefit relative to Adcetris (brentuximab vedotin) [as BV+AVD] (n=940).[27] Overall survival (OS) was a secondary endpoint, along with safety. Due to the introduction of several potential sources of bias in the study it is difficult to precisely define a treatment benefit.
  * The trial enrolled subjects ≥ 12 years with histologically confirmed advanced (stage III or IV) cHL and were previously untreated (no prior chemotherapy or radiation).
  * Subjects were randomized to one of the following, added to the backbone AVD (doxorubicin, vinblastine, and dacarbazine)
    - Nivolumab 240 mg (or 3 mg/kg for age 12-18) [N+AVD] IV on Days 1 & 15 of each 28-day cycle for up to 6 cycles (n =487)
    - Brentuximab vedotin 1.2mg/kg [BV+AVD] IV as above (n = 483)
  * At the interim analysis (median follow up 12.1 months), the median PFS was not yet reached; however, the hazard ratio (HR) was 0.48 [0.27, 0.87] and statistically significant (p= 0.001).
  * The primary endpoint of PFS, a surrogate endpoint, has not been validated to be an accurate indicator of clinically meaningful benefit; however, the 2-year overall survival reported efficacy consistent with that known of the BV-AVD therapy.
  * Despite elements of bias in the trial design (open-label, investigator assessment), the OS endpoint is clinically meaningful. However, a 2-year OS follow up is relatively short given the high rate of very long-term survival in cHL.
  * Potential harms associated with the use of Opdivo (nivolumab) are well described and generally tolerable. For 1st line treatment of cHL, N+AVD is potentially better tolerated than existing BV+AVD. Tolerability is a key factor for long term quality of life in patients with cHL.
  * Longer term follow up is warranted for both safety and efficacy of this place in therapy, given the younger average patient population and very high long-term survival.
- Combination with Adcetris (brentuximab): There is interest in the use of Opdivo (nivolumab) in combination with Adcetris (brentuximab vedotin) for cHL. However, there is insufficient evidence at this time to establish the safety or efficacy of this combination. The evidence for use in the relapsed/refractory setting is limited to phase 1 and 2 trial interim data.[28 29] Additional trials are ongoing. In the front-line setting in chemotherapy-ineligible patients, the primary endpoint (ORR) was not met with the use of Opdivo (nivolumab) in combination with Adcetris (brentuximab vedotin).[30]

Guidelines:

The NCCN Hodgkin lymphoma guideline lists the following: [3]

- Keytruda (pembrolizumab) as a treatment option for relapsed/refractory Hodgkin lymphoma. Opdivo (nivolumab) is listed among several single-agent treatment options for relapsed or refractory CHL after high-dose chemotherapy with autologous stem cell rescue and Adcetris (brentuximab vedotin).
- Category 1 first-line treatment options for cHL include check point inhibitor (CPI)-containing regimens [nivolumab + AVD (doxorubicin, vinblastine, dacarbazine)] and brentuximab vedotin (BV)-based regimens [BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) and BV+AVD]. Bleomycin-containing regimen (ABVD) is now reserved for those unable to use CPI- or BV-containing regimens [also Category 1]. BV-based regimens are used in combination with prophylactic granulocyte colony stimulating factor (GCSF, such as pegfilgrastim, filgrastim) for prevention of febrile neutropenia.

Colorectal cancer (CRC), MSI-H/dMMR

Keytruda (pembrolizumab)

- Subsequent-line therapy: Keytruda (pembrolizumab) was initially approved for CRC as a subsequent therapy for locally advanced or metastatic MSI-H/dMMR CRC, when there is progression of disease on or after standard front-line therapy with fluoropyrimidine, oxaliplatin, and irinotecan, based on a combined cohort of 90 patients from several single-arm studies (a "basket" trial).[1 31]
    * The accelerated approval of Keytruda (pembrolizumab) was for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors was based on preliminary tumor response [overall response rate (ORR)] and duration of response (DOR) data from a "basket trial" pooled analysis of 149 patients across five different early phase, open-label trials (90 patients with CRC and 59 non-CRC patients).
    * Subjects enrolled in the basket trial had advanced solid tumors and at least one prior chemotherapy regimen. CRC-specific trials required prior CRC therapy.
    * In 90 CRC patients, tumor response rate was 36%. However, no other outcomes were measured, and, at the time of FDA approval, clinical benefit had not been established.
    * Results from the final OS analysis reported a median OS of 77.8 months with Keytruda (pembrolizumab) vs. 36.7 months with chemotherapy [HR 0.73].[32]
    * Despite the low level of evidence, Keytruda (pembrolizumab) may be a reasonable treatment alternative in patients with in MSI-H/dMMR CRC when there is progressive disease on or after standard CRC therapies.
- First-line therapy: Subsequently, the FDA approved Keytruda (pembrolizumab) for use as an initial therapy for MSI-H/dMMR CRC, based on an improvement in PFS in a single unblinded Phase 3 trial [KEYNOTE-177].[31] Keytruda (pembrolizumab) was superior to investigator's choice of chemotherapy (fluorouracil-based chemotherapy with or without bevacizumab or cetuximab) for PFS. However, overall survival data, a secondary endpoint, was not mature at the time of FDA approval. Therefore, the clinical benefit is unknown. Of note, high crossover to Keytruda (pembrolizumab) will confound interpretation of future OS results.

Opdivo (nivolumab)

- Subsequent-line therapy Opdivo (nivolumab) [as monotherapy or plus low-dose Yervoy (ipilimumab)] received FDA Accelerated approval for progressive MSI-H/dMMR metastatic CRC based on tumor response from an uncontrolled, single-arm (observational) study in cohort of subjects (N = 53) whose disease had progressed during or after treatment with all standard options: fluoropyrimidine, oxaliplatin, and irinotecan [CHECKMATE-142].[25 33] To date, there is no evidence that it provides any clinical benefit in this setting.
  - ORR was 28% (1.9% were considered to have a complete tumor response).
  - PD-L1 expression was not a condition for enrollment in the trial.
  - ORR has not been shown to accurately predict clinically relevant outcomes. Additional confirmatory studies are needed to establish clinical benefit.
- The confirmatory trial [CHECKMATE-8HW] found an improvement in PFS for the combination of Opdivo (nivolumab) plus low-dose Yervoy (ipilimumab) induction, followed by Opdivo (nivolumab) as compared to Opdivo (nivolumab) monotherapy in MSI-H/dMMR metastatic CRC, including both previously-treated progressive CRC (61% of enrolled subjects), as well as 1st line (39% of subjects).[34] Median PFS for "all lines" in the nivolumab plus ipilimumab arm was not reached (95% CI: 53.8, NE) and nivolumab alone arm was 39·3 months (95% CI: 22.1, NE).
- First-line therapy: Opdivo (nivolumab)/Yervoy (ipilimumab) was later FDA approved for MSI-H/dMMR unresectable or metastatic CRC in the 1st-line setting based on a pre-defined subset evaluation of the phase 3 open-label RCT [CHECKMATE-8HW].[35] Opdivo (nivolumab)/Yervoy (ipilimumab) was superior to investigator's choice of chemotherapy (fluorouracil-based chemotherapy with or without bevacizumab or cetuximab) for PFS. However, overall survival data, a secondary endpoint, was not mature at the time of FDA approval. Therefore, the clinical benefit is unknown.
- Sequential Immunotherapy: Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable. Trials of Opdivo (nivolumab)/Yervoy (ipilimumab) excluded those with prior use of immunotherapy (including PD-1/PD-L1 inhibitors and CTLA4s).

Guidelines:

The National Comprehensive Cancer Network (NCCN) guideline recommends: [3]

- Against the use of Keytruda (pembrolizumab) for MSI-H CRC in the adjuvant setting, meaning after surgery, but before any progression of disease. Standard therapies with fluoropyrimidine (fluorouracil, capecitabine), oxaliplatin, and irinotecan are recommended (with regimens such as FOLFOX, CAPEOX, or FOLFIRI).
- All of the following as first-line or subsequent-line options for unresectable dMMR/MSI-H CRC (candidate for immunotherapy and no prior immunotherapy received): Opdivo (nivolumab) ± Yervoy (ipilimumab), Keytruda (pembrolizumab), based on clinical trial data. More recently, dostarlimab, cemiplimab, retifanlimab, toripalimab, or tislelizumab were added, as the panel felt all checkpoint inhibitors are interchangeable for this indication, despite the lack of RCT data for their use. Of note: Opdivo (nivolumab) + Yervoy (ipilimumab) is a lower-level category 2B

recommendation in the first line setting, due to toxicity concerns.

Cutaneous Squamous Cell Carcinoma (cSCC)

Keytruda (pembrolizumab)

- Keytruda (pembrolizumab) was evaluated in a single-arm, non-blinded, multi-cohort, phase 2 trial in patients with cSCC [KEYNOTE-629].[36]
  - The cohort evaluated for the FDA accelerated approval included metastatic cSCC (55) and advanced recurrent disease that was not curable with surgery or radiation.
  - All subjects had prior systemic therapy, and 87% had ≥ 2 prior therapies.
  - An ORR of 34% was reported, with 3.8% complete response (CR) and 30% partial response (PR). However, health outcomes are unknown.
- ORR is an unvalidated surrogate endpoint that has not been shown to accurately predict clinical outcomes. ORR is a measure of tumor size (visible by physical observation or on x-ray) and is a combination of complete and partial responses. In advanced disease, ORR may not be representative of disease that has traveled to lymph nodes of other parts of the body, so it may not be an accurate measure of clinical benefit.

Libtayo (cemiplimab)

- Advanced (not curable with surgery/radiation): Two small low-quality, single-arm, non-comparative open-label trials evaluated Libtayo (cemiplimab-rwlc) in patients with cutaneous squamous cell carcinoma (cSCC) who were not candidates for curative surgical resection or radiation therapy. [13 37]
  - One trial (phase 1) included 16 patients with metastatic cSCC, and 10 patients with disease that had recurred after two or more prior surgical procedures and the investigator expected that curative resection would be unlikely, or surgery would result in substantial complications or deformity. The second trial (phase 2) included 59 patients with metastatic cSCC.
  - Approximately 57% of the subjects in the trials had prior systemic therapy, and about 82% had prior radiotherapy.
  - In the phase 1 trial, the objective response rate (ORR), the primary endpoint, was 50% [95% CI: 30, 70]. There were no complete responses.
  - In the phase 2 trial, the ORR was 47% [95% CI: 34, 61]. There were four (7%) complete responses.
  - The Libtayo (cemiplimab-rwlc) trials evaluated objective response rate (ORR) as a surrogate endpoint. ORR is a measure of tumor size (visible by physical observation or on x-ray) and is a combination of complete and partial responses. In advanced disease, ORR may not be representative of disease that has traveled to lymph nodes of other parts of the body, so it may not be an accurate measure of clinical benefit. To further complicate interpretation of these results, there were only four complete responses reported out of the 85 patients enrolled in the trial. The remainder were partial responses. There is currently no way to predict in advance who might achieve a complete response.
- Resectable cSCC with high risk of recurrence: Libtayo (cemiplimab) received FDA approval in the adjuvant setting based on meeting its primary endpoint of disease-free survival (DFS), a

surrogate endpoint with unknown clinical value, in one fair confidence trial in patients with resected cSCC, with high risk of recurrence (n=415) [C-POST].[38] DFS has not been validated to accurately predict clinical benefit such as reduction in need for subsequent therapy, improved quality of life, or overall survival.

* The trial enrolled subjects with local or regional cSCC (83% in the head and neck area)
* All had completed both curative-intent surgery and postoperative radiotherapy (RT) [or concurrent chemoradiotherapy (CRT)] and had high-risk of recurrence (nodal, non-nodal, or both). [See *Appendix 4*]
* Subjects were randomized to one of the following, added after surgery and adjuvant RT:
    - Placebo IV every 3 weeks for up to 48 weeks (n =206)
    - Cemiplimab 350 mg IV every 3 weeks for up to 48 weeks (n = 209)
      [use of consolidated 700 mg IV every 6 weeks was allowed after the initial 12 weeks]
* At a median follow-up of 24 months, the median disease-free survival (DFS) was not reached for Libtayo (cemiplimab) and 49.4 months for placebo [HR 0.32 (0.20, 0.51); p<0.001]. OS results are not yet mature. Estimated 24-month DFS difference of 23%.
* Despite a statistically significant difference in DFS, the upper bounds for the 95% CI for the placebo remains 'not estimable' such that the clinical significance of the finding is unclear. Independent of the available data, DFS does not accurately predict improvement in any clinically relevant outcome. DFS is a surrogate marker with different components of varying clinical importance: recurrence vs death. Longer term follow up is needed.
* The trial allowed for unblinded cemiplimab after disease recurrence. All of subsequent-treated placebo arm and 50% of cemiplimab arm patients received subsequent cemiplimab. Use of subsequent cemiplimab for disease recurrence confounds interpretation of future OS data.

- It has not yet been determined if Libtayo (cemiplimab-rwlc) provides clinically meaningful benefit in cSCC (any setting) as current studies have used surrogate measures such as overall tumor response rate (ORR) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- There is no evidence that compares the safety and effectiveness of Libtayo (cemiplimab-rwlc) with any other therapy that may be used in the advanced (inoperable/metastatic) or resectable cSCC setting. Libtayo (cemiplimab-rwlc) was only studied as a monotherapy (not in combination with other systemic therapy).
- Libtayo (cemiplimab-rwlc) has not been studied in patients who have received prior PD-1 inhibitor therapy.
- The quality of the currently available evidence is low. Additional evidence is needed to establish the clinical benefit (e.g., improved survival, improved quality of life) and the durability of effect of Libtayo (cemiplimab-rwlc).

Unloxcyt (cosibelimab)

- Unloxcyt (cosibelimab) was evaluated in a single-arm, non-blinded, multi-cohort, phase 2 trial in patients with cSCC [CK-301-101].[39]
    * The cohorts evaluated for the FDA accelerated approval included subjects with metastatic

cSCC (n=78) and locally advanced cSCC (n=31) that was not curable with surgical resection or radiation.

  * Sixty-five to 77% percent of the subjects in the study had prior radiation therapy and 3% to 9% had prior cytotoxic chemotherapy.
  * An ORR of 48% was reported, with 9% complete responses (CR) and 39% partial responses (PR). However, whether this therapy improves health outcomes is not yet known as ORR is not a validated surrogate marker for meaningful outcomes such as overall survival. Additional higher quality evidence is needed to confirm whether Unloxcyt (cosibelimab) provides any clinically relevant benefit.

- Unloxcyt (cosibelimab) has not been compared with any other therapy, including other PD-1 inhibitor therapies. It has also not been studied in subjects who received prior PD-1 inhibitor therapy. Subjects who had prior PD-1 inhibitor therapy were excluded from the clinical study due to the identical mechanism of action of these medications.

Guidelines

The National Comprehensive Cancer Center (NCCN) cSCC guideline lists the following recommendations, by risk, resectability/curability, and response to resection: [All are category 2A unless noted otherwise]: [3]

- Very-high risk cSCC, with risk of extensive local recurrence, nodal, or in-transit metastasis: consider sentinel lymph node biopsy (SLNB) for staging, then surgery (or definitive RT for non-surgical candidates). Treat based on surgical margins.
  * Positive margins: re-resection, RT, or, if surgery ± RT not curative, manage as locally advanced cSCC.
  * Negative margins: RT. If extremely high risk nodal and non-nodal features:[a] RT then Libtayo (cemiplimab) [Cat 1]

    [a] See *Appendix 4* - Mirrors trial criteria
- Locally advanced or metastatic cSCC (laCSCC or mCSCC) when curative RT or curative surgery is not feasible: Preferred: Libtayo (cemiplimab), Keytruda (pembrolizumab), clinical trial. 'Other:' Unloxcyt (cosibelimab) [2A mCSCC; 2B laCSCC]

Endometrial Cancer (EC)

Background [3]

- Endometrial cancer (EC) is the most commonly occurring gynecologic cancer in the U.S. Most cases (75%) are diagnosed at an early stage and can be cured with surgery. However, approximately 25% are diagnosed in advanced stages.
- Surgery is used for staging. Therefore, treatment is classified as "Primary" or "Adjuvant" for new diagnoses. For previously treated endometrial cancer, treatment is referred to as "Recurrent" or "Subsequent."
- For advanced disease, first-line therapy with surgery and platinum-containing chemotherapy (standard of care) results in overall survival ranging between 13 and 29 months with tumor response rates of 40 to 62%.
- Upon disease progression in the advanced disease setting, tumor response rates are generally in the 7 to 14% range with single-agent chemotherapy.

- It is estimated that approximately 25% to 30% of endometrial tumors may have a high frequency of somatic mutations which are attributable to deficiencies in DNA mismatch repair (dMMR) making these tumors a possible target of immunotherapies such as programmed death receptor-1 inhibitors.

Imfinzi (durvalumab)

- First-line: A double-blind RCT [DUO-E] evaluated Imfinzi (durvalumab) versus placebo in combination with chemotherapy (carboplatin/paclitaxel) followed by maintenance therapy with Imfinzi (durvalumab) or placebo after completion of chemotherapy in patients with newly diagnosed stage III (unresectable) or stage IV (metastatic) endometrial carcinoma. The trial also enrolled patients with recurrent disease if there was a low potential for cure with radiation therapy or surgery.[40 41]
    * For patients with recurrent disease, prior chemotherapy in the adjuvant setting was allowed only if at least 12 months had passed from the time of completion of adjuvant chemotherapy to the time of relapse.
    * The trial included patients with all histologies of endometrial carcinomas (including carcinosarcomas) but excluded those with endometrial sarcoma.
    * Randomization was stratified by tumor mismatch repair status [deficient (dMMR) vs. proficient (pMMR) tumors].
    * The trial demonstrated a statistically significant improvement in progression-free survival (PFS) in the overall population; however, a preplanned subgroup analysis showed that this improvement was primarily due to patients with dMMR tumors. For this reason, Imfinzi (durvalumab) was FDA-approved in and is only covered in patients with dMMR tumors.
    * The study also employed an Imfinzi (durvalumab) plus Lynparza (olaparib) treatment arm; however, the relative PFS values for Imfinzi (durvalumab) vs. placebo and for Imfinzi (durvalumab) plus Lynparza (olaparib) vs. placebo were similar in patients with dMMR tumors suggesting no added benefit with the addition of Lynparza (olaparib) to the regimen in this population.

Jemperli (dostarlimab)

- Subsequent-line: The efficacy of Jemperli (dostarlimab) was evaluated in a small, non-comparative, non-blinded study [GARNET] that evaluated tumor response in patients with advanced EC.[42 43] The quality of this data is poor due to the lack of randomization, blinding, and comparator. Furthermore, tumor response is not predictive of improvement in any clinically relevant outcome.
    * The population evaluated for the EC indication was a specific cohort from a larger study that included patients with many different types of solid tumors. All patients in the EC cohort had mismatch repair deficient (dMMR) EC that could not be cured with surgery (advanced or metastatic disease) and had progressed on or after platinum doublet therapy.
    * Tumor response (objective response rate) was 42% with 12.7% complete responses. Seventy-three percent of patients had a duration of response of 6 months or longer.

* The following patients were excluded from the study: Patients with endometrial sarcoma and patients who had prior therapy with a PD-1/PD-L1 inhibitor.

- First-line: Subsequently, Jemperli (dostarlimab) was evaluated in a large, randomized, double-blind, placebo-controlled trial [ENGOT-EN6/GOG-3031/RUBY] as part of a front-line regimen for patients with advanced endometrial cancer for tumors that are dMMR or microsatellite instability-high (MSI-H). [44]
  * Patients enrolled in the study had no prior systemic therapy in the advanced disease setting, including no prior PD-1/PD-L1 inhibitor therapy. More specifically, patients included in the study had:
    - Primary advanced stage III or IV disease,
    - Initial recurrent disease without prior systemic therapy, or
    - Recurrent disease previously treated with neoadjuvant or adjuvant systemic therapy with recurrence or progression at least 6 months after completion or treatment (first recurrence).
  * Jemperli (dostarlimab) or placebo was initiated in combination with carboplatin plus paclitaxel chemotherapy for six cycles and was then continued as a single agent until disease progression.
  * The study enrolled patients with both mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR) tumors. Though an initial interim analysis of progression-free survival (PFS) concluded that any benefit was attributable to the dMMR subgroup, a later analysis of the mature overall survival (OS) endpoint demonstrated a statistically significant and clinically relevant OS advantage that extended to patients with tumor that were MMR proficient (pMMR tumors).[45]
  * The median OS reported in the study was 44.6 months and 28.2 months in the Jemperli (dostarlimab) and placebo treatment arms, respectively (HR 0.69 [95% CI 0.54, 0.89]; p = 0.002).

Keytruda (pembrolizumab)

- Subsequent-line:
  * *With lenvatinib*: Keytruda (pembrolizumab) received Accelerated FDA-approval for use in patients with metastatic endometrial carcinoma, in combination with Lenvima (lenvatinib), in patients whose disease progressed on prior therapy in any treatment setting and curative surgery or radiation is not an option. It was approved in this setting based on a cohort of patients from a small, single-arm trial that evaluated tumor response rate [KEYNOTE-146).[46] Clinical benefit has not been established.
  * *As monotherapy*: The evidence supporting the use of Keytruda (pembrolizumab) as a single agent in unresectable or metastatic, MSI-H/dMMR endometrial carcinoma after progression on standard front-line therapies is of poor quality. It is derived from a multi-cohort, single-arm trial that reported tumor response rate as the endpoint [KEYNOTE-158]. There is currently no comparative data or information related to improvement in any clinical outcome.[47]
- First-line: Subsequently, Keytruda (pembrolizumab) was evaluated in a large (N=816), randomized, double-blind, placebo-controlled trial [NRG-GY018] as part of a front-line regimen

for advanced endometrial cancer where it was found to improve PFS.[48]

* Patients enrolled in the trial had no prior systemic therapy in the advanced disease setting, including no prior PD-1/PD-L1 inhibitor therapy.
* Keytruda (pembrolizumab) was initiated in combination with carboplatin plus paclitaxel chemotherapy for six cycles and was then continued as a single agent until disease progression.
* Patients in the Keytruda (pembrolizumab) treatment arm had improved median PFS relative to those who received placebo. This PFS benefit extended to both mismatch repair proficient and deficient tumors (pMMR and dMMR).
* PFS has not been shown to accurately predict any beneficial clinical outcome (it is an unvalidated surrogate endpoint).
* The overall survival data from this study are not mature; however, interim results have not yet detected any survival difference between treatment groups.

Guidelines

The NCCN Uterine Cancer guideline, which includes endometrial carcinoma, lists the following:[3]

- First-line, primary or adjuvant (Stage III-IV): Imfinzi (durvalumab) [dMMR only], Jemperli (dostarlimab), or Keytruda (pembrolizumab), in combination with carboplatin/paclitaxel as preferred, category 1 for stage III and stage IV endometrial carcinomas, as well as for "First-line for Recurrent Disease." For Stage I-IV, carboplatin/paclitaxel (with or without prior chemoradiation with cisplatin) is the preferred regimen.
- Second-line or Subsequent: many single-agent and combination chemotherapy regimens as recommended regimens, including the following "Useful in Certain Circumstances."
    * For MSI-H/dMMR: Keytruda (pembrolizumab) monotherapy. Jemperli (dostarlimab) monotherapy.
    * For pMMR: Keytruda (pembrolizumab) plus Lenvima (lenvatinib)

Esophageal Cancer [including esophageal adenocarcinoma, esophageal squamous cell carcinoma (ESCC)]

Background

- Esophageal cancers are classified by histology as either squamous cell carcinoma (ESCC) or adenocarcinoma.
- There are differences in the treatment pathways based on disease histology, resectability, PD-L1 expression, or other tumor markers.

Imfinzi (durvalumab)

See Gastric and gastroesophageal junction (GEJ) Cancer (adenocarcinoma)

Keytruda (pembrolizumab)

Advanced Esophageal (Adenocarcinoma or ESCC) Cancer - First-line setting, High-PD-L1 expressing:

- A double-blind RCT [KEYNOTE-590] evaluated the addition of Keytruda (pembrolizumab) to standard first-line chemotherapy relative to placebo plus chemotherapy in patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma. The coprimary

endpoints were PFS and OS. [1 49]

* The trial included patients with esophageal cancer with either squamous cell carcinoma or adenocarcinoma histology. GEJ cancers were included if they had an epicenter 1 to 5 centimeters above the GEJ.
* Therapy was continued until disease progression, unacceptable toxicity, or for up to a maximum of two years.
* Patients enrolled in the trial were not candidates for surgical excision of their tumor or for definitive chemoradiation (CRT) and had no prior treatment in the advanced disease setting. The majority (54%) of patients enrolled had tumors that had a PD-L1 CPS ≥ 10.
* The median OS in the overall population was 12.4 months and 9.8 months in the Keytruda (pembrolizumab) and placebo treatment arms, respectively; and the median OS in the PD-L1 CPS ≥ 10 population was 13.5 months and 9.4 months, respectively. An exploratory analysis found there was no difference in median OS in the PD-L1 CPS < 10 population (10.5 months and 10.6 months, respectively), suggesting that efficacy of Keytruda (pembrolizumab) was being driven by PD-L1 expression.

Advanced Esophageal Cancer (ESCC) - Subsequent-line setting:

- Keytruda (pembrolizumab) was evaluated in a randomized, controlled trial in patients with recurrent locally advanced, or metastatic esophageal carcinoma who progressed on or after on prior systemic therapy [KEYNOTE-181].[50] The trial included both squamous cell carcinoma (ESCC) and adenocarcinoma. However, the primary efficacy endpoint was OS in patients with ESCC, patients with tumors expressing PD-L1 CPS ≥ 10, and all randomized patients.
  * Keytruda (pembrolizumab) as a single agent was compared with investigator's choice of chemotherapy.
  * Patients with HER2/neu-positive disease were required to have received treatment with an approved HER2/neu targeted therapy [e.g., trastuzumab].
  * The primary analysis for this study was in the subgroup of patients with PD-L1 expressing ESCC (CPS ≥ 10) found an overall survival advantage with Keytruda (pembrolizumab) relative to cytotoxic chemotherapy. There was no survival difference between the groups when the intent-to-treat population was analyzed so the FDA-approval excluded PD-L1 negative tumors.
  * Subpopulations with tumor histologies other than ESCC (e.g., patients with esophageal adenocarcinoma) were not part of the primary analysis so are not included as part of the FDA indication.
  * Randomization was not stratified by PD-L1 status which is a potential limitation of this data.
- The use of Keytruda (pembrolizumab) for advanced esophageal adenocarcinoma in the subsequent line setting is considered investigational.

Opdivo (nivolumab)

Early-Stage (Resectable) Esophageal (Adenocarcinoma or ESCC) or GEJ Cancer – as ADJUVANT therapy

- The efficacy of Opdivo (nivolumab) in esophageal or gastroesophageal junction (GEJ) cancer is

based on a phase 3, randomized, double-blind controlled trial [CheckMate-577] that compared adjuvant treatment with Opdivo (nivolumab) versus placebo in patients with stage II or III (resectable) esophageal or GEJ. [25 51]

* The trial included tumors with both adenocarcinoma (71%) and squamous cell carcinoma (29%) histology.
* All patients had to have completed neoadjuvant chemoradiotherapy (CRT) followed by a complete resection where the patient was rendered free of disease.
* Additionally, all patients had residual pathological disease (absence of pathological complete response) after their initial treatment. Patients with resectable metastatic disease were not eligible to participate in the study.
* Patients were randomized to either nivolumab or placebo for a total duration of up to one year of adjuvant therapy.
* Efficacy was based on disease-free survival, an unvalidated surrogate endpoint. Median DFS was 22.4 months and 11.0 months in the Opdivo (nivolumab) and placebo treatment arms, respectively. OS results are not mature.

Advanced Esophageal Squamous Cell Cancer (ESCC) - Subsequent-line setting:

- The efficacy of Opdivo (nivolumab) in refractory, unresectable advanced, recurrent, or metastatic ESCC is based on a phase 3, open label, randomized controlled trial that compared Opdivo (nivolumab) with investigator's choice of taxane (paclitaxel or docetaxel). There was a modest OS improvement with Opdivo (nivolumab) relative to chemotherapy [ATTRACTION-3].[52]
  * Patients were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen.
  * At a minimum follow-up time (i.e., time from random assignment of the last patient to data cutoff) of 17.6 months, OS was statistically significantly improved with Opdivo (nivolumab) versus chemotherapy (median 10.9 *vs* 8.4 months).
- Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.

Advanced Esophageal Squamous Cell Cancer (ESCC) - First-line setting:

- Opdivo (nivolumab) was approved as a potential first-line therapy in combination with fluoropyrimidine- and platin-based chemotherapy or ipilimumab for unresectable advanced or metastatic ESCC based on a large randomized, open-label trial that demonstrated a 2- to 2.5-month improvement in median OS relative to chemotherapy alone.[53] This is likely an overestimate of expected survival benefit in the general population due to the following:
  * The trial was enriched with patients whose tumors overexpressed PD-L1 (PD-L1 ≥ 1%) and were therefore more likely to respond to this immunotherapy combination. Subgroup analyses support this analysis as there was a 6-month improvement in median OS relative to standard chemotherapy in the PD-L1 ≥ 1% population; however, there was no survival benefit relative to chemotherapy in the PD-L1 < 1% population. *(Note: 49% of the study population had PD-L1 expression ≥ 1%)*

* Only 16% of patients in the chemotherapy arm received a PD-(L)1 inhibitor after disease progression. Follow-on therapy with a PD-(L)1 inhibitor is standard of care in the US based on current guidelines. There are currently two PD-1 inhibitors approved as monotherapy for ESCC in the second-line setting (after progression on chemotherapy).

- Optimal sequencing of therapies in esophageal carcinomas has not yet been determined.

Advanced Esophageal Adenocarcinoma - First-line setting:

- The efficacy of Opdivo (nivolumab) in advanced esophageal adenocarcinoma is based on a phase 3, open-label, randomized controlled trial [CheckMate-649] that compared first-line treatment with Opdivo (nivolumab) plus chemotherapy versus chemotherapy alone in patients with unresectable advanced, or metastatic gastric or GEJ cancer, or esophageal adenocarcinoma. [25 54] *Note: This same trial was used for the approval of Opdivo (nivolumab) in advanced gastric and GEJ cancer. (See "Gastric and GEJ cancer (adenocarcinoma)")*

Tevimbra (tislelizumab)

- *Advanced ESCC - Subsequent therapy*: The efficacy of Tevimbra (tislelizumab) as a single agent in recurrent (previously treated) locally advanced (unresectable) or metastatic esophageal squamous cell carcinoma (ESCC) was evaluated in a randomized controlled trial (RCT) where it was compared with single-agent chemotherapy [RATIONALE-302 Study; N=512].[55]
  * Patients enrolled in the study had disease progression on or after prior systemic therapy in the advanced or metastatic disease setting. The study also included patients whose disease recurred within 6 months of completing a course of neoadjuvant or adjuvant chemotherapy or chemoradiotherapy.
  * Patients with active brain metastases, histology other than ESCC, or who had prior PD-1/PD-L1 inhibitor therapy were excluded from the study.
  * The study compared Tevimbra (tislelizumab) 200 mg IV every 3 weeks versus investigator's choice of single agent chemotherapy (paclitaxel, docetaxel, or irinotecan).
  * Median overall survival (OS) was 8.6 months and 6.3 months in the Tevimbra (tislelizumab) and chemotherapy treatment arms, respectively. This is a statistically significant difference.
  * *Advanced ESCC - First-line therapy*: A second RCT [RATIONALE-306; N=649] studied Tevimbra (tislelizumab) as an add-on to standard front-line chemotherapy in patients with locally advanced (unresectable) or metastatic ESCC where it was compared with placebo plus standard front-line chemotherapy. [56] The study enrolled patients who had no prior therapy for their locally advanced or metastatic ESCC and the disease was not amenable to definitive therapies (curative intent) including surgery and radiation. If patients had received prior neoadjuvant or adjuvant platinum-based chemotherapy, a treatment-free interval (no disease progression) of at least 6 months was required.
  * Patients with active brain metastases, histology other than ESCC, or who had prior PD-1/PD-L1 inhibitor therapy were excluded from the study.
  * The study compared Tevimbra (tislelizumab) plus a platinum doublet with placebo plus a platinum doublet. The platinum (cisplatin or oxaliplatin) was stopped after six cycles.

Tevimbra (tislelizumab) was continued until disease progression.

* An OS benefit was observed with Tevimbra (tislelizumab) relative to placebo with median OS of 17.2 months and 10.6 months, respectively.
* Opdivo (nivolumab), Keytruda (pembrolizumab), and Tevimbra (tislelizumab) are now FDA approved in this first-line treatment setting. Although there is no directly comparative evidence, all three PD-1/PD-L1 inhibitor therapies appear similar with respect to safety and efficacy. However, the cost of Tevimbra (tislelizumab) is significantly higher. Therefore, Tevimbra (tislelizumab) is considered 'not medically necessary' in the front-line setting for advanced ESCC as it is not proven to be safer or more effective, but is more costly than alternatives.

Guidelines:

The NCCN Esophageal/Esophagogastric Junction Cancer and Gastric Cancer guidelines list the following recommendations, based on histology, resectability, and line of therapy: [3]

- *Resectable esophageal or GEJ cancer (adenocarcinoma), in those medically fit:*
  * Staging is based on clinical and pathological findings [TNM; tumor size, nodal involvement, and metastases], using AJCC staging system. Risk is based on lymphovascular invasion (LVI), histology, and staging.
  * Primary treatment for resectable <u>esophageal/GEJ adenocarcinoma</u>, high-risk lesions (LVI, >3 cm, poorly differentiated; cT1b-cT2,N+ or cT3-cT4a, any N): [cat 2A, unless noted] - Perioperative chemotherapy (preferred) [category 1 option]:
    - Preferred: fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), based on evidence for overall survival
    - Preferred: FLOT + durvalumab for PD-L1 CPS≥1 (or TAP≥1%) [cat 1 for gastric/GEJ; cat 2A for esophageal] (footnote: no EFS advantage in diffuse-type gastric/GEJ cancer).
    - 'Other Recommended': fluorouracil/cisplatin; fluoropyrimidine/oxaliplatin [2A]
  * Adjuvant therapy is based on surgical outcomes/pathological findings, including extent of LN resection (D1 vs. D2 dissection for GC). In those who received systemic therapy:
    - R0: systemic therapy, if preoperative chemotherapy [cat 1]; For esophageal/GEJ yp T+ and/or N+: nivolumab adjuvant [*see below*]
    - R1: CRT, observation, or consider re-resection.
    - R2: CRT or palliative care

    R0 resection (no cancer at resection margins); R1 (microscopic residual cancer); R2 (macroscopic residual cancer or M1)
- *Resected esophageal or GEJ cancer (adenocarcinoma or squamous cell carcinoma):*
  * <u>Adjuvant</u>: Opdivo (nivolumab) is listed as preferred, category 1 for adjuvant use in resected esophageal or esophagogastric junction cancer with residual disease, after pre-operative chemoradiation (CRT).
- *Squamous cell carcinoma (ESCC or gastric SCC) - unresectable locally advanced, recurrent, or metastatic:*
  * <u>First-line:</u> for-PD-L1 CPS ≥ 1: Opdivo (nivolumab), Keytruda (pembrolizumab), or

Tevimbra (tislelizumab) in combination with fluoropyrimidine/oxaliplatin (or cisplatin) are listed as preferred, category 1. [nivolumab/ipilimumab is a category 2A]

* Second- and subsequent-line: Single agent Opdivo (nivolumab), Keytruda (pembrolizumab), or Tevimbra (tislelizumab); OR single agent docetaxel, paclitaxel, or irinotecan [all preferred, category 1]. Keytruda (pembrolizumab) is only recommended for tumors with PD-L1 CPS ≥ 10.
* The use of PD-1 inhibitors [such as Opdivo (nivolumab) or Keytruda (pembrolizumab)] is only recommended if there has been no prior tumor progression on checkpoint inhibitor therapy (e.g., PD-1 or PD-L1 inhibitor).

- *Adenocarcinoma (esophageal, gastric or GEJ cancer) - unresectable locally advanced, recurrent* – first-line
  * First-line:
    - *HER2-positive disease:* Fluoropyrimidine/oxaliplatin (or cisplatin) plus trastuzumab is a preferred regimen. Keytruda (pembrolizumab) may be added for PD-L1 CPS ≥ 1 (also preferred, category 1).
    - *HER2-negative disease:*
      - PD-L1 CPS ≥ 5: Opdivo (nivolumab), Keytruda (pembrolizumab), or Tevimbra (tislelizumab) in combination with fluoropyrimidine/oxaliplatin (or cisplatin) are listed as preferred, category 1 recommendations.
      - PD-L1 CPS ≥ 1: These combination therapy recommendations drop to category 2A for CPS ≥ 1.
  * Subsequent-line: The use of PD-1/PD-L1s as subsequent therapy for esophageal or gastric/GEJ adenocarcinoma is not supported by guidelines.

Gastric and Gastroesophageal junction (GEJ) Cancer (adenocarcinoma)

Imfinzi (durvalumab)

Resectable gastric (GC) and GEJ cancer (GEJC), adenocarcinoma – perioperative (neoadjuvant/adjuvant):

- Imfinzi (durvalumab) received FDA approval in the perioperative setting based on meeting its primary endpoint of event-free survival (EFS), a surrogate endpoint with unknown clinical value, in one low confidence multinational, randomized, double-blind, placebo-controlled trial [MATTERHORN] in patients with previously untreated, resectable GC/GEJC (Stage II to Stage IVA) [n=948].[57]
  * Included resectable adenocarcinoma, Stage II to IVA [>T2 N0-3 M0 or T0-4 N1-3 M0 per AJCC 8th Edition]. GEJC includes Siewert type 2 and 3 tumor (type 1 was also eligible, as long as treated as 2/3).
  * All patients were medically fit for FLOT chemotherapy and surgical resection.
  * The trial evaluated the addition of Imfinzi (durvalumab) to standard of care (SOC) perioperative FLOT chemotherapy (cycles every 4 weeks), as follows:
    - Durvalumab/FLOT x 2 neoadjuvant, surgery, then adjuvant durvalumab/FLOT x 2, durvalumab monotherapy x 10 (up to 12 total adjuvant cycles)
    - Placebo/FLOT x 2 neoadjuvant, surgery, then adjuvant placebo/FLOT x 2, then placebo monotherapy x 10 (up to 12 total adjuvant cycles)

* At a median follow-up of 31.5 months, the median EFS was not reached for Imfinzi (durvalumab) and 32.2 months for placebo [HR 0.68 (0.56, 0.84); p<0.001]. At this time, health outcomes are unknown, as the overall survival results are not yet mature. 24-month EFS difference of 8.9%.
* The trial enrolled subjects independent of PD-L1 expression or histologic type. However, post-hoc analyses found better response (EFS) in those with PD-L1 expressing tumors (TAP ≥1% or CPS ≥ 1) as compared to those with TAP<1 (or CPS<1). Additionally, there was no EFS benefit in diffuse histology tumors as compared to placebo. Therefore, Imfinzi (durvalumab) in this setting is coverable only for those with PD-L1 expressing tumors with a non-diffuse histology type (such as intestinal or indeterminate).

Keytruda (pembrolizumab)

Advanced HER2-positive gastric and GEJ adenocarcinoma – First line:

- A multicenter, randomized, double-blind, placebo-controlled trial [KEYNOTE-811] evaluated the addition of Keytruda (pembrolizumab) to standard of care (SOC) trastuzumab plus chemotherapy relative to placebo plus SOC in patients with ***HER2-positive***, locally advanced unresectable, or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. [1 58 59]
  * All patients enrolled in this study had no prior therapy for metastatic disease, no prior PD-1/PD-L1 inhibitor therapy and had good performance status (PS).
  * Patients received SOC trastuzumab plus chemotherapy [either CAPEOX (87%) or fluorouracil plus cisplatin (13%)] in addition to either Keytruda (pembrolizumab) or placebo.
  * Approximately 87% of patients had a PD-L1 CPS of 1% or more.
  * There was no difference in median OS between the Keytruda (pembrolizumab) and placebo treatment arms in the intent-to-treat population. A subgroup analysis suggests a significant improvement in median OS in the patients with PD-L1-expressing tumors (CPS ≥ 1). Based on this information, the FDA updated the indication for Keytruda (pembrolizumab) in HER2-positive, advanced/metastatic gastric or GEJ adenocarcinoma to limit use to the PD-L1 CPS ≥ 1 subpopulation.

Advanced HER2-negative gastric and GEJ adenocarcinoma – First line:

- A second, similarly designed trial [KEYNOTE-859] evaluated Keytruda (pembrolizumab) as an add-on to SOC chemotherapy as a front-line therapy for ***HER2-negative***, locally advanced unresectable, or metastatic gastric or GEJ adenocarcinoma.[60]
  * As in the study above, all patients enrolled in this study had no prior therapy for metastatic disease, no prior PD-1/PD-L1 inhibitor therapy and had good PS.
  * Patients received SOC chemotherapy [either CAPEOX (86%) or fluorouracil plus cisplatin (14%)] in addition to either Keytruda (pembrolizumab) or placebo.
  * Approximately 78% of patients had a PD-L1 CPS of 1% or more and 35% had a CPS ≥ 10.
  * There was a significant improvement in median OS in the Keytruda (pembrolizumab) treatment arm relative to the placebo arm in the intent-to-treat population (12.9 months and 11.5 months, respectively). The difference in median OS was greater in the subgroups with high levels of PD-L1 expression suggesting results may have been driven by PD-L1 expression. The median OS in patients with tumors that had PD-L1 CPS ≥ 10 was 15.7 months and 11.8 months in the Keytruda (pembrolizumab) and placebo arms, respectively.

Advanced Esophageal (Adenocarcinoma or ESCC) and GEJ Cancer - Front-line setting, High-PD-L1 expressing: see "Esophageal cancer"

Advanced gastric and GEJ adenocarcinomas – Subsequent line:

- Keytruda (pembrolizumab) received Accelerated approval as a monotherapy for recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma in tumors expressing PD-L1 (CPS ≥ 1) when disease progressed on or after two or more lines of therapy [KEYNOTE-059]. Subsequently, this indication was voluntarily withdrawn by the manufacturer because clinical benefit was not demonstrated in confirmatory trials. [1 61] Therefore, use of Keytruda (pembrolizumab) in the subsequent-line advanced gastric and GEJ adenocarcinoma settings is considered investigational.
- Several other Keytruda (pembrolizumab) trials have also failed to establish clinical benefit in various gastric cancer settings:
    * Keytruda (pembrolizumab) in the second-line setting failed to meet the primary endpoints of PFS and OS as compared to paclitaxel in a phase 3 trial [KEYNOTE-061].[62] All subjects had gastric/GEJ cancer with a PD-L1 CPS of 1 or higher that progressed on first-line chemotherapy with a platinum and fluoropyrimidine.
    * In the first-line setting, Keytruda (pembrolizumab), as a monotherapy or in combination with chemotherapy, failed to improve PFS and OS as compared to chemotherapy alone in a phase 3 trial [KEYNOTE-062].[63] All subjects had gastric/GEJ cancer with a PD-L1 CPS of 1 or higher. Among patients with a CPS of ≥ 10, Keytruda (pembrolizumab) was numerically, but not statistically, superior to chemotherapy. Of note, 15% of patients in the control arm were treated with post-trial immune checkpoint inhibitors.

Opdivo (nivolumab)

Advanced Gastric, GEJ, and Esophageal Adenocarcinoma - First-line setting

- The efficacy of Opdivo (nivolumab) in gastric, GEJ, and advanced esophageal cancer is based on a phase 3, open-label, randomized controlled trial [CheckMate-649] that compared front-line treatment with Opdivo (nivolumab) plus chemotherapy versus chemotherapy alone in patients with unresectable advanced, or metastatic gastric or GEJ cancer and esophageal adenocarcinoma.[25 54]
    - Seventy percent of the population had gastric cancer, 18% had GEJ cancer, and the remaining 12% had esophageal adenocarcinoma. Ninety-six percent of the population had metastatic disease.
    - Opdivo (nivolumab) was given in combination with fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin chemotherapy. Patients in the comparator arm received the same chemotherapy regimen given alone.
    - The trial initially enrolled patients regardless of PD-L1 CPS status; however, a protocol amendment was made when the trial was underway which required a PD-L1 CPS of 5% or more. This resulted in an overall population of patients with tumors that had a higher-than-average PD-L1 CPS expression (the population was enriched with high PD-L1-expressing tumors).
    - Efficacy was based on the primary efficacy population of patients with tumors with a PD-L1 CPS ≥ 5. The median OS was 14.4 months and 11.1 months in the Opdivo (nivolumab) and comparator arms, respectively.

- Results in the ITT population (all patients, regardless of tumor PD-L1 CPS expression) are not reliable as this population was enriched with patients whose tumors had high PD-L1 CPS expression and were more likely to respond to PD-1 inhibitor therapy.

Early-Stage (Resectable) GEJ Cancer – as ADJUVANT therapy – see Esophageal Cancer

Tevimbra (tislelizumab)

- First line: A phase 3 trial [RATIONALE-305] evaluated Tevimbra (tislelizumab) as an add-on to SOC chemotherapy as a first-line therapy for ***HER2-negative***, locally advanced unresectable, or metastatic gastric or GEJ adenocarcinoma. [64]
  - All patients enrolled in this study had no prior therapy for metastatic disease, no prior PD-1/PD-L1 inhibitor therapy and had good PS (ECOG 0-1).
  - Patients received SOC chemotherapy [either CAPEOX or fluorouracil plus cisplatin] in addition to either Tevimbra (tislelizumab) or placebo.
  - Patients were enrolled regardless of PD-L1 expression status. Approximately 45% of patients had a PD-L1 Tumor Area Positivity (TAP) of less than 5% and 55% had a TAP ≥ 5.
  - The primary endpoint was overall survival in the patients with TAP ≥ 5. There was a significant improvement in median OS in the Tevimbra (tislelizumab) treatment arm relative to the placebo arm in the TAP ≥ 5 population (16.4 months and 12.8 months, respectively as well as in the intent-to-treat population (15.0 months and 12.9 months, respectively). The difference in median OS was greater in the subgroups with high levels of PD-L1 expression suggesting results may have been driven by PD-L1 expression.
  - The prespecified determination of PD-L1 expression was done using TAP with the VENTANA PD-L1 (SP263) platform. However, Combined Positive Score (CPS) was also assessed post hoc using the samples from which the prespecified TAP score was assessed. The investigators reported high concordance of results (82%) between the test results from TAP and CPS. The ODAC recommended labeling the indication based on "PD-L1 expression ≥ 1," without a specific required testing method. Therefore, the coverage criteria allow for use of either the TAP or CPS testing for expression of PD-L1 expression.

Guidelines:

[see *Esophageal Cancer - Guidelines*]:

Head and neck squamous cell cancer (HNSCC, SCCHN)

Background[3 65 66]

- Head and neck cancers are divided into two categories: non-nasopharyngeal and nasopharyngeal (NPC). NPC cancers are not included in this section [See Nasopharyngeal carcinoma (NPC)].
- Non-NPC HNSCC includes oral cancers (of the oral cavity, oropharynx, hypopharynx) and laryngeal cancer.
- HNSCC is more prevalent in those with a history of tobacco (all), along with heavy alcohol use and human papillomavirus (HPV) infection for oral cancers.
- Most HNSCC is locally advanced (LA) at diagnosis. Treatment goals vary based on site of the tumor, disease categorization as well as site.

    - Oral cavity: buccal mucosa, floor of mouth, oral tongue, alveolar ridge, retromolar trigone, hard palate
    - Oropharynx: base of tongue, tonsil, posterior pharyngeal wall, soft palate
    - Hypopharynx
    - Larynx (glottic and supraglottic)
    - Sinus (ethmoid and maxillary)
- Most patients with LA HNSCC are treated with chemoradiotherapy or surgery, followed by radiotherapy with or without chemotherapy as the standard of care.
- HPV-negative (p16-negative) HNSCC are at higher risk of recurrence.

Keytruda (pembrolizumab)

- First-line, unresectable or metastatic: Keytruda (pembrolizumab) was FDA approved as a first-line treatment for unresectable or metastatic HNSCC as a monotherapy OR in combination with standard chemotherapy, based on small improvement in overall survival (OS) in an open-label phase 3 trial [KEYNOTE-048]:[67]
    - The combination of Keytruda (pembrolizumab) and a platin plus fluorouracil improved median OS relative to Erbitux (cetuximab) plus a platin and fluorouracil (13.0 months versus 10.7 months, respectively; p = 0.0067).
    - A small survival advantage (statistically significant) was noted with use of Keytruda (pembrolizumab) monotherapy relative to Erbitux (cetuximab) plus a platin and fluorouracil in PD-L1-positive tumors (CPS ≥ 1). Median OS was 12.3 months and 10.3 months in the Keytruda (pembrolizumab) and chemotherapy arms, respectively. The advantage did not extend to the overall population (OS superiority was only for tumors with CPS ≥ 1).
- Subsequent-line, recurrent or metastatic: Keytruda (pembrolizumab) also has approval (Accelerated) as a subsequent-line therapy for recurrent or metastatic HNSCC as a single agent when used after progression of disease on or after a platinum-containing chemotherapy.
    - Efficacy was based on improved tumor response rates in two uncontrolled, open-label studies [KEYNOTE-012], with a 16% objective response rate (ORR). A small proportion of complete responses (4.6%) was reported in one of the trials. The remainder were partial responses. To date, there is no evidence that it improves any clinically relevant outcome (e.g., improved survival, symptom control, function, or quality of life) in this setting. [1 68]
    - There is no evidence to support the use of Keytruda (pembrolizumab) as a second-line therapy in patients unable to use first-line platinum-based chemotherapy for HNSCC.
- Perioperative (neoadjuvant/adjuvant), resectable locally advanced (LA): Keytruda (pembrolizumab) received FDA approval in the perioperative setting based on meeting its primary endpoints of event free survival (EFS), a surrogate endpoint with unknown clinical value, in one low confidence open-label Phase 3 trial [KEYNOTE-689] in patients with resectable LA HNSCC (Stage III-IVA) (n=714).[69]
    - The trial enrolled adults with newly diagnosed, nonmetastatic, resectable LA HNSCC (26% stage III, 74% stage IVA).
    - Subjects had to be eligible for cisplatin-based chemotherapy (CrCl ≥ 60) and eligible for/planning to undergo primary surgery.

* No prior radiotherapy or systemic anticancer therapy (including PD1/PD-L1) for treatment of HNSCC was allowed.
* Although not required for trial enrollment, 96% of randomized subjects had PD-L1 expressing (CPS ≥1) HNSCC.
* Patients were randomized to perioperative add-on or standard of care (SOC) chemoradiotherapy (CRT).
    - Pembrolizumab: neoadjuvant 200 mg Q3W x 2 cycles, followed by resection, then adjuvant radiotherapy (RT) ± cisplatin plus pembrolizumab Q3W x 15 cycles (n =363)
    - Control: Placebo, followed by resection, a then adjuvant RT ± cisplatin [a] (n =351) [a] Addition of cisplatin to the adjuvant RT was based on risk for recurrence (in about half of the enrolled subjects):
        - High risk: positive margins (<1 mm) or extranodal extension; CRT (RT plus cisplatin Q3W x 3 cycles).
        - Low-risk disease: no positive margins or extranodal extension; RT (no cisplatin).
* Efficacy was based on a statistically significant difference in event-free survival (EFS). Although EFS is usually not considered a clinically meaningful endpoint, the difference in EFS (30 months) may be meaningful in a population where recurrence/progression is common and subsequent therapies (such as radiation) have significant morbidity.
* There was no difference in secondary endpoints of major pathological response (mPR) or clinical outcome, interim overall survival (OS).
* Limitations: unknown health outcome, lack of blinding introduces bias, high differential dropout rate.

- There is insufficient evidence for the use of Keytruda (pembrolizumab) in patients with LA HNSCC who are not a candidate for primary surgery. Keytruda (pembrolizumab) was studied in a phase 3 placebo-controlled RCT study [KEYNOTE-412] as add-on to concurrent CRT for locally advanced (LA) HNSCC in patients who were candidates for definitive chemoradiotherapy, but not for primary surgery. Both arms received standard CRT.[70] The study failed to meet its EFS endpoint.

Opdivo (nivolumab)

- Subsequent-line, recurrent or metastatic: Opdivo (nivolumab) received approval for recurrent or metastatic HNSCC based on improved overall survival (OS), a clinically relevant endpoint, relative to investigator's choice of Erbitux (cetuximab) or single-agent chemotherapy in an open-label randomized controlled trial (N = 361) [CHECKMATE-141].[25 71]
    * The trial included cancer of the oral cavity, pharynx, or larynx that was not amenable to curative therapy and progressive disease within 6 months of receiving platinum-based chemotherapy.
    * Median OS was 7.5 months and 5.1 months in the Opdivo (nivolumab) and investigator's choice of therapy treatment arms, respectively. A subgroup analysis demonstrated greater improvement in median OS with Opdivo (nivolumab) when at least 1% of the cells in the tumor expressed PD-L1 (tumor proportion score of > 1%).

Guidelines:

The National Comprehensive Cancer Network (NCCN) head and neck cancers guideline lists:[3]

- For recurrent, unresectable, or metastatic HNSCC:
  - Use of Keytruda (pembrolizumab) for recurrent, unresectable, or metastatic HNSCC when used in the front-line treatment setting, as well as when used in the subsequent-line treatment setting.
  - Opdivo (nivolumab) monotherapy among treatment options for non-nasopharyngeal HNSCC subsequent-line therapy, when there has been disease progression on or after platinum-containing chemotherapy.
- For resectable non-nasopharyngeal HNSCC:
  - Primary treatment is based on pathological risk (tumor stage and nodal status).
  - For less advanced/aggressive HNSCC, primary treatment is surgery, with the addition of pembrolizumab if CPS ≥1 (neoadjuvant + adjuvant with cisplatin for extranodal disease for Stage III/IVA), or radiotherapy (RT) [chemoradiotherapy (CRT) or definitive RT)]. Induction chemotherapy is recommended only in hypopharynx and larynx (select T 3-4a and/or node +).
  - Adjuvant RT or CRT is recommended for most HNSCC when there are adverse pathological features, extranodal extension, or positive margin after surgery. Addition of Keytruda (pembrolizumab) is recommended (if used neoadjuvant).

Hepatocellular Carcinoma (HCC)

Disease Background: Child Pugh Scoring

- Various rating scales may be used to estimate degree of hepatic dysfunction with chronic liver disease.
- In the trials for the use of PD1 and PD-L1 inhibitor therapy for HCC, the Child-Pugh (CP) score for cirrhosis mortality was used to screen for HCC patients with less severe liver disease.
- The CP score is an estimate of chronic liver disease and cirrhosis and is used as a prognostic indicator. Points are assigned for markers of hepatic dysfunction, including liver function tests, ascites, and encephalopathy. CP score is reported as a range, given it is an estimation assigned by the treating provider. Based on score, a CP class is assigned. The lower end of the reported range may be used as a marker for illness/prognosis (e.g., CP A6/B7 meets intent of coverage criteria of class A) (see Appendix 3).
- The evidence for use of systemic anticancer therapy in Child-Pugh class B HCC is limited to small numbers of patients across pivotal trials. All included patients had good performance status (ECOG 0-1). Additionally, patients with Child-Pugh class C were not included due to their poor performance status. Therefore, coverage of systemic therapies for HCC is limited to patients with good performance status (ECOG 0-1).

Imfinzi (durvalumab)

- First-line, unresectable or metastatic: A large, phase 3 RCT (HIMALAYA) compared the combination of Imjudo (tremelimumab) + Imfinzi (durvalumab) with sorafenib in adults with unresectable, previously untreated HCC not amenable to locoregional treatment. [72 73]

* The majority of patients (53%) had extrahepatic spread of their disease and nearly all (99%) had Child-Pugh Class A disease (score of A5, 73%; and score of A6, 26%). All enrolled patients had good performance status (ECOG 0-1).
* An overall survival (OS) advantage in favor of Imjudo (tremelimumab) + Imfinzi (durvalumab) was reported in the study.
* The study also employed a parallel Imfinzi (durvalumab) monotherapy arm. The median OS in the Imfinzi (durvalumab) monotherapy arm was numerically similar to the median OS in the Imjudo (tremelimumab) + Imfinzi (durvalumab) arm. However, a statistical difference was not demonstrated for the comparison between Imfinzi (durvalumab) monotherapy and sorafenib. A likely reason a statistical difference was not demonstrated is because of the lack of statistical power allocated to this secondary analysis (a non-inferiority analysis was done).

Endpoint	T+D (n=393)	D (n=389)	S (n=389)	HR [95% CI]; p-value
OS, median	16.4 mos	- - - - - -	13.8 mos	0.78 [0.66, 0.92]; 0.004
OS, median	- - - - - -	16.5 mos	13.8 mos	0.86 [0.73, 1.03]; non-inferior

D = durvalumab; T+D = tremelimumab+ durvalumab; S = sorafenib

* Based on this evidence it is unclear whether the addition of Imjudo (tremelimumab) to Imfinzi (durvalumab) results in a clinically relevant improvement in OS over sorafenib relative to Imfinzi (durvalumab) alone. *(Note: Durvalumab monotherapy has not been FDA approved for advanced HCC but is listed in NCCN guidelines as a potential treatment option).*

Keytruda (pembrolizumab)

Subsequent line, advanced (unresectable or metastatic):

- Keytruda (pembrolizumab) received Accelerated FDA approval for use in HCC after progression of disease on, or intolerance to, first-line Nexavar (sorafenib) based on a small, single-arm, open-label Phase 2 preliminary study [KEYNOTE-224] in patients with Child-Pugh (CP) Class A disease that evaluated tumor response rate. Clinical benefit in this setting has not been demonstrated.[74] The confirmatory phase 3 trial [KEYNOTE-240] failed to demonstrate PFS or OS benefit. A subsequent phase 3 trial [KEYNOTE-394] demonstrated a very small improvement in OS in a more limited population and the FDA narrowed the approved indication to relapsed/refractory HCC due to hepatitis B virus (HBV), in CP-Class A only.
  * Subjects enrolled in the trial had progressive disease while on Nexavar (sorafenib) or had intolerable adverse effects to Nexavar (sorafenib) therapy.
  * Nearly all of the patients were Child-Pugh Class A (score of A5 or A6); however, a small portion (6%) had a score of B7/B8 (Class B). All enrolled patients had good performance status (ECOG 0-1).
  * Most patients (64%) had disease that had spread beyond the liver.
  * An ORR of 17% was reported in the trial. ORR has not been shown to accurately predict clinically relevant outcomes. Additionally, it is not known how Keytruda (pembrolizumab) compares with other second-line HCC therapies.

- The confirmatory phase 3 RCT [KEYNOTE-240] evaluating Keytruda (pembrolizumab) relative to placebo (best supportive care) in the second-line advanced HCC setting failed to meet the primary endpoints of PFS and OS.[75] There is the potential for this indication to be withdrawn in the future based on FDA guidance for Accelerated approvals that states: "Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials".
- *Narrowed indication - HBV*: A subsequent RCT [KEYNOTE-394] intended as the confirmatory trial for Keytruda (pembrolizumab) in relapsed or refractory unresectable or metastatic HCC demonstrated a <1-month improvement in median OS relative to placebo. The trial evaluated Asian patients (primarily conducted in China) who had HCC secondary to hepatitis B virus (HBV) infection. All patients had Child-Pugh Class A disease, and all had prior systemic therapy for HCC, the majority (83%) with sorafenib. The FDA subsequently updated the Keytruda (pembrolizumab) HCC indication to reflect the population used in this study (more narrow than initially approved).[76]

Opdivo (nivolumab)

- Subsequent line, unresectable or metastatic:
  - *Combination therapy:* Opdivo (nivolumab) received FDA Accelerated approval for use in HCC after progression of disease on, or intolerance to, Nexavar (sorafenib) when given in combination with Yervoy (ipilimumab) based on a small, single-arm, preliminary study [CHECKMATE-040] that evaluated tumor response rate. Clinical benefit in this setting has not been demonstrated. [25 77]
    - Subjects had progressive disease while on, or had intolerance to, Nexavar (sorafenib) therapy.
    - Patients had Child-Pugh Class A disease (a score of A5 in 82%, and A6 in 18% of patients) and 80% had disease that had spread beyond the liver. All enrolled patients had good performance status (ECOG 0-1).
    - An ORRs of 33% was reported with this regimen. ORR has not been shown to accurately predict clinically relevant outcomes. Additionally, it is not known how Opdivo (nivolumab) plus Yervoy (ipilimumab) compares with other second-line HCC therapies.
  - *Monotherapy:* The Accelerated FDA indication for use of Opdivo (nivolumab) as a monotherapy in HCC after progression of disease on, or intolerance to, Nexavar (sorafenib) was withdrawn by the manufacturer in July of 2021 because clinical benefit was not demonstrated in confirmatory trials.
- First-line, unresectable or metastatic: A large, phase 3 RCT [CHECKMATE-9DW] compared the combination of Opdivo (nivolumab)/Yervoy (ipilimumab) with investigator's choice of TKI (lenvatinib or sorafenib) in adults with unresectable, previously untreated HCC not amenable to locoregional treatment (n=668).[78]
  - The majority of patients (54%) had extrahepatic spread of their disease and nearly all (97%) had Child-Pugh Class A disease (score of A5, 78%; and score of A6, 19%). All enrolled patients had good performance status (ECOG 0-1).

* An overall survival (OS) advantage in favor of Opdivo (nivolumab)/Yervoy (ipilimumab) was reported in the study (median +3.1 months). However, there was an early increase in death with Opdivo (nivolumab)/Yervoy (ipilimumab) and significantly higher rate of treatment-related adverse event (TRAE) discontinuations and hepatic related deaths.
* There was a potential safety signal for this new indication, with a 17% incidence of serious liver-related AEs, not seen in the lenvatinib/sorafenib arm. There were 12 treatment-related deaths in the Opdivo (nivolumab)/Yervoy (ipilimumab) arm, of which 11 occurred in the 1st 6 months after randomization, and 9 were attributed to fatal hepatic events in patients with underlying liver disease, as compared to three deaths in the TKI (lenvatinib or sorafenib) arm (one hepatic). This safety signal, in addition to the early deaths, lowers certainty in the overall health benefit of this regimen.
* In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) is significantly more costly than other established treatment options for 1st line unresectable HCC [such as Imfinzi (durvalumab)/Imjudo (tremelimumab)]. Therefore, Opdivo (nivolumab)/Yervoy (ipilimumab) is coverable only when other established treatment options [such as Imfinzi (durvalumab)/Imjudo (tremelimumab), or as detailed in the coverage criteria] are not a treatment option.

- Sequential Immunotherapy: Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable. Trials of Opdivo (nivolumab)/Yervoy (ipilimumab) excluded those with prior use of immunotherapy (including PD-1,/PD-L1 inhibitors and CTLA4s).

Tecentriq (atezolizumab)

- First-line, unresectable or metastatic: The initial approval in HCC was based on the results of one open-label, phase 3 RCT [IMbrave150] in patients with previously untreated, unresectable, or metastatic HCC.[2 79]
  * The trial compared Tecentriq (atezolizumab) given in combination with bevacizumab with Nexavar (sorafenib) as a monotherapy.
  * All patients included in the study had Child-Pugh (CP) class A disease. The trial excluded sicker patients (Class B and C; see Appendix 3). All enrolled patients had good performance status (ECOG 0-1).
  * An early analysis of overall survival (OS) favored Tecentriq (atezolizumab) plus bevacizumab over Nexavar (sorafenib), with median OS reached in the Nexavar (sorafenib) arm at 13.2 months but not been reached in the Tecentriq (atezolizumab) plus bevacizumab combination arm at 17 months.
  * Subsequently, an updated analysis after 12 additional months reported median OS of 19.2 months with Tecentriq (atezolizumab) plus bevacizumab and 13.4 months with Nexavar (sorafenib).[80]
  * It is unknown how Tecentriq (atezolizumab) plus bevacizumab compares to either agent alone in this setting. In addition, the safety and efficacy of Tecentriq (atezolizumab) in combination with medications other than noted above is unknown. A phase 3 trial of

Tecentriq (atezolizumab) in combination with Cometriq (cabozantinib) was non-inferior to Nexavar (sorafenib) monotherapy.[81]

- Adjuvant therapy: see *Investigational Uses*.

Guidelines:

The NCCN Hepatocellular Carcinoma guideline lists:

- First-line: all recommended therapies are the higher Category 1, except for Opdivo (nivolumab)/Yervoy (ipilimumab)
  - *Preferred*: Tecentriq (atezolizumab)/bevacizumab; Imfinzi (durvalumab)/ Imjudo (tremelimumab)
  - *Other recommended*: Imfinzi (durvalumab), Lenvima (lenvatinib), sorafenib; Opdivo (nivolumab)/Yervoy (ipilimumab)[2A]
  - It is not known how the front-line immunotherapy options compare with one another for unresectable HCC, given the lack of head-to-head trials.
- Subsequent therapy: several recommended therapies for subsequent therapy for HCC. Keytruda (pembrolizumab) monotherapy, Opdivo (nivolumab) monotherapy and in combination with Yervoy (ipilimumab) are listed as an options for patients who have not had prior checkpoint inhibitor therapy.
- Guidelines acknowledge that the evidence for use of immunotherapy is largely based on trials in patients with a Child-Pugh (CP) [or Child-Turcotte-Pugh (CTP)] score of A (5-6). However, use in patients with a higher degree of liver dysfunction, such as CP/CTP B (B7), may be considered with careful assessment of individual patient characteristics.

Malignant pleural mesothelioma (MPM)

Keytruda (pembrolizumab)

- First-line: Efficacy in MPM was studied in a phase 3, randomized, open-label trial in patients with unresectable advanced MPM and no prior systemic therapy for advanced/metastatic disease. Patients received either Keytruda (pembrolizumab) for up to two years in combination with pemetrexed and platinum-based chemotherapy for up to 6 cycles or pemetrexed and platinum-based chemotherapy for up to 6 cycles [KEYNOTE-483]. [1 82]
- The primary endpoint of median overall survival (OS) was 17.3 months for Keytruda (pembrolizumab) with chemotherapy versus 16.1 months for chemotherapy alone (hazard ratio [HR] 0.79 [95% CI: 0.64, 0.98]).

Opdivo (nivolumab)

- First-line: The efficacy of Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for unresectable MPM in the first-line setting is based on one randomized, open-label trial, which found improved OS relative to chemotherapy (platinum plus pemetrexed) alone (18.1 vs. 14.1 months) [CHECKMATE-743]. [83 84]
- Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.

Guidelines:

The NCCN guideline for MPM lists: [3]

- Platinum-based chemotherapy +/- bevacizumab; Keytruda (pembrolizumab) plus platinum-based chemotherapy; and Opdivo (nivolumab) plus Yervoy (ipilimumab) as first-line, preferred regimens.
- Opdivo (nivolumab) with or without Yervoy (ipilimumab) (if not used in 1st-line) is also listed as a second-line, treatment option. However, there are no high-quality trials for the use of Opdivo (nivolumab) with or without Yervoy (ipilimumab) as a second-line therapy. Therefore, the use of Opdivo (nivolumab) in the 2nd line setting is not coverable.

Melanoma

Keytruda (pembrolizumab)

Advanced (Unresectable or Metastatic) Melanoma

- The efficacy of Keytruda (pembrolizumab) in malignant melanoma (unresectable or metastatic) is based on two, multi-center, open-label, pivotal clinical trials; one in Yervoy (ipilimumab)-refractory subjects and the other in Yervoy (ipilimumab)-naïve subjects.
    * One trial [KEYNOTE-006] compared Keytruda (pembrolizumab) in doses of 10 mg/kg IV every 2 weeks or every 3 weeks with Yervoy (ipilimumab) 3 mg/kg IV every 3 weeks in progressive, unresectable, or metastatic disease. [1 85] Progression-free survival (PFS) and 12-month survival were superior in the Keytruda (pembrolizumab) treatment arms. Overall survival (OS) was not yet mature. [Note: The FDA-approved dosing of Keytruda (pembrolizumab) is 2 mg/kg IV every 3 weeks, so the applicability of these results is uncertain]
    * A second trial [KEYNOTE-002] compared Keytruda (pembrolizumab) 2 mg/kg or 10 mg/kg IV every 3 weeks with investigator's choice of chemotherapy in progressive, unresectable, or metastatic disease.[1 86] There was a statistically significant improvement in median PFS with Keytruda (pembrolizumab) relative to the chemotherapy arm; however, the clinical relevance of the small numerical difference (0.2 months) is uncertain. There was no difference in PFS between the two Keytruda (pembrolizumab) dosing arms. Overall survival is not mature.
    * There is no evidence to date that Keytruda (pembrolizumab) has any clinical benefit (improved overall survival, symptom control, function, or quality of life) in melanoma. Additionally, much of the available evidence is for doses that are much higher than the FDA-approved dose of Keytruda (pembrolizumab).

Adjuvant Therapy for Resectable Melanoma

- Stage IIIB, IIIC, IV: Keytruda (pembrolizumab) was evaluated as an adjuvant therapy in patients with resectable stage IIIB/C or stage IV (metastatic) melanoma after complete surgical resection [KEYNOTE-054].[87]
    * The study compared Keytruda (pembrolizumab) with placebo, dosed every 3 weeks for 18 cycles. Treatment was started within 13 weeks of tumor resection and was continued for up to one year.

    * There was a statistically significant improvement in recurrence-free survival (RFS) with Keytruda (pembrolizumab). At the time of FDA approval, it was unknown whether initial RFS would eventually translate to improvement in OS, a clinically relevant endpoint.
    * OS results are expected at 10 years (estimated November 2026).

- Stage IIB, IIC: Keytruda (pembrolizumab) was also evaluated as an adjuvant therapy for stage IIB and IIC (completely resectable) melanoma [KEYNOTE-716] where it was found to improve RFS and distant metastasis-free survival (DMFS) relative to placebo.[88] There is currently no evidence of clinical benefit, such as improved OS. Since there is a high cure rate with complete resection alone in early melanoma the potential for introducing serious side effects with adjuvant immunotherapy should be carefully considered, particularly in the absence of clinical outcomes data.
    * Mature survival data are not expected for many years because the prognosis for these early-stage melanoma patients is good, and life expectancy is relatively long with five-year survival rates approaching 99%.
    * Based on preliminary results, fourteen patients would need to be treated with Keytruda (pembrolizumab) for one patient to avoid disease relapse within the first year; however, only seven patients would need to be treated for one patient to discontinue Keytruda (pembrolizumab) due to a severe AE by one year.

Opdivo (nivolumab)

First-line Advanced (Unresectable or Metastatic) Melanoma Setting, Monotherapy

- The primary evidence of efficacy for Opdivo (nivolumab) in previously untreated (first-line setting) patients with unresectable (stage IIIB) or metastatic (stage IV) melanoma is based on a phase 3, double-blind randomized controlled trial that compared Opdivo (nivolumab) monotherapy with dacarbazine [CheckMate 066]. [25 89]
    * All enrolled subjects were without a BRAF mutation.
    * Progression-free survival (PFS), a secondary endpoint, was 5.1 months with Opdivo (nivolumab) and 2.2 months with dacarbazine.
    * Preliminary survival rates at 1 year were 72.9% and 42.1% with Opdivo (nivolumab) and dacarbazine, respectively. In a subsequent three-year analysis, median OS was substantially longer in the Opdivo (nivolumab) group in a subsequent analysis.[90]

First-line Advanced (Unresectable or Metastatic) Melanoma, in Combination with Yervoy (ipilimumab)

- The efficacy of Opdivo (nivolumab) when administered in combination with Yervoy (ipilimumab) for unresectable or metastatic melanoma in the first-line setting is based two RCTs [CheckMate 067], which found improved PFS relative to monotherapy with either drug alone. OS data was not yet mature at the time these trials were published.[25 91]
- A follow-on study [CheckMate 511] was conducted to determine whether adjustments in the dosing of Opdivo (nivolumab) and Yervoy (ipilimumab) might improve the tolerability of the combination. The currently approved dose is Opdivo (nivolumab) 1 mg/kg plus Yervoy (ipilimumab) 3 mg/kg IV every 3 weeks for 4 doses. The study found that Opdivo (nivolumab) 3 mg/kg plus Yervoy (ipilimumab) 1 mg/kg IV every 3 weeks for 4 doses was better tolerated without negatively impacting tumor response rate after a minimum of 12 months follow up. The median OS was not reached in either group.[92]

Subsequent Therapy for Advanced Melanoma, Monotherapy

- Opdivo (nivolumab) has also been evaluated in patients with advanced melanoma whose disease was refractory to therapy with Yervoy (ipilimumab) and, if BRAF mutation positive, BRAF inhibitor therapy.[25] [93]
    * Efficacy was based on improved tumor response rates relative to chemotherapy. There was no information with regard to improvement in any clinically relevant outcome in this setting at the time these trials were published.
    * Confirmatory evidence of efficacy in this melanoma setting was not yet mature at the time the trial was published.
- Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.

Adjuvant Only Therapy for Resectable Melanoma, Monotherapy

- Stage IIIB, IIIC, IV: Opdivo (nivolumab) was evaluated as an adjuvant therapy in patients with resectable stage IIIB/C or stage IV (metastatic) melanoma after complete surgical resection, as compared to Yervoy (ipilimumab) [CHECKMATE-238].[94]
    * Treatment was started within 12 weeks of tumor resection and was continued for up to one year.
    * There was a statistically significant improvement in recurrence-free survival (RFS) with Opdivo (nivolumab) relative to Yervoy (ipilimumab). However, improvement in OS, a clinically relevant endpoint, is unknown.
- Stage IIB, IIC: Opdivo (nivolumab) was evaluated as an adjuvant therapy in patients with early-stage (IIB/C) after complete surgical resection (negative margins and negative sentinel lymph node) where it was compared with placebo (best supportive care) [CHECKMATE-76K].[95]
    * Patients in the study were naïve to prior systemic therapy and treatment with Opdivo (nivolumab) was started within 12 weeks of tumor resection and was continued for up to one year.
    * There was a statistically significant improvement in recurrence-free survival (RFS) with Opdivo (nivolumab) relative to Yervoy (ipilimumab). However, improvement in OS, a clinically relevant endpoint, is unknown.

Neoadjuvant +/- Adjuvant Therapy for Resectable Melanoma, in Combination with Yervoy (ipilimumab)

- A multicenter, randomized, open-label, active-controlled trial [NADINA] evaluated Yervoy (ipilimumab) plus Opdivo (nivolumab) as a potential neoadjuvant therapy for resectable cutaneous melanoma.[96] *[Note: This is an interim analysis (preliminary evidence) and this use is not currently FDA approved]*
    * Patients enrolled in the trial had resectable cutaneous melanoma with one or more macroscopic lymph node metastases (clinically detectable) [Stage 3] and a maximum of three additional resectable in-transit metastases. Exclusion criteria included prior immunotherapy targeting CTLA-4, PD-1, PD-L1, or LAG-3; and prior therapy targeting BRAF and/or MEK.

* The study compared neoadjuvant therapy using Yervoy (ipilimumab) plus Opdivo (nivolumab) with standard adjuvant Opdivo (nivolumab) used as monotherapy.
    - *Neoadjuvant arm:* Yervoy (ipilimumab) 80 mg plus Opdivo (nivolumab) 240 mg every three weeks for 2 cycles, followed by therapeutic lymph node dissection (TLND). Adjuvant therapy was determined by pathologic response.
        - If a major pathologic response (MPR) was achieved (≤10% residual viable tumor), the patient was followed up with a CT scan every 12 weeks.
        - If an MPR was not achieved, one of the following was given:
            - BRAF V600E/K mutation-positive: Tafinlar (dabrafenib) plus Mekinist (trametinib) for up to 46 weeks
            - Without a BRAF V600E/K mutation: Opdivo (nivolumab) 480 mg every 4 weeks x 11 cycles
    - *Adjuvant arm:* TNLD was followed by standard Opdivo (nivolumab) monotherapy for up to twelve, 4-week cycles.
* The study evaluated event-free survival (EFS) as a surrogate endpoint. The median EFS was not reached in either treatment arm. The hazard ratio was 0.32 [99.9% CI: 0.15, 0.66] (p-value not reported) in favor of the neoadjuvant therapy arm. The MPR in the neoadjuvant therapy arm was 59%, including 47% pathologic complete responses (pCR).

- Although this preliminary analysis looks promising, results are only reported in relative terms which generally favors the new intervention, and the EFS endpoint has not been shown to correlate well with clinical benefit. There are no mature outcomes data to date.

Opdualag (nivolumab-relatlimab-rmbw)

- Opdualag (nivolumab-relatlimab-rmbw) is a combination of nivolumab, a programmed death receptor-1 (PD-1) blocking antibody and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody. Blocking these pathways inhibits tumor growth and promotes tumor regression.
- First-line for advanced (unresectable or metastatic) melanoma: The efficacy of Opdualag (nivolumab-relatlimab-rmbw) was studied in a fair quality randomized controlled trial [RELATIVITY-047] in patients with previously untreated, unresectable metastatic melanoma. The trial compared Opdualag (nivolumab-relatlimab-rmbw) with Opdivo (nivolumab) and evaluated progression-free survival (PFS) as the primary endpoint.[97]
    * Patients in the trial had no prior systemic therapy for their advanced disease. Approximately 8% of the population had prior neoadjuvant or adjuvant therapy which may have included immunotherapy or BRAF/MEK inhibitors; however:
        - Of the previously treated patients, the majority (6.3%) had interferon. Only one patient (0.14%) had a prior CTLA4/PD-1 inhibitor, and five patients (0.7%) had a prior PD-1 inhibitor.
        - The adjuvant therapy must have been completed at least 6 months prior to the current recurrence.
        - All previously treated patients must have returned to baseline or stabilized. Progressive disease was excluded.
    * Patients with uveal melanoma were excluded from the trial.

* Approximately 90% of patients had metastatic disease and all had good performance status.
* All patients were required to have a tumor tissue sample available for biomarker analysis. Randomization was stratified by PD-L1 expression, LAG-3 expression, BRAF status, and tumor stage.
* Seventy-five percent of tumors had LAG-3 expression of at least 1%. In an earlier phase 1 study, a greater than 3-fold increase in tumor response to Opdualag (nivolumab-relatlimab-rmbw) was observed when LAG-3 expression was ≥ 1% versus < 1%.
* The use of Opdualag (nivolumab-relatlimab-rmbw) after disease progression/recurrence on/after chemotherapy and/or immunotherapy for advanced melanoma is not coverable at this time. A small percent of patients enrolled in the RELATIVITY-047 trial received prior immunotherapy in the non-advanced adjuvant setting for resectable melanoma. Patients with prior use of systemic therapy for advanced melanoma were excluded from the trial. Therefore, the use of Opdualag (nivolumab-relatlimab-rmbw) is coverable only when there is no prior systemic therapy in the advanced setting.
* Median PFS was improved with Opdualag (nivolumab-relatlimab-rmbw) relative to Opdivo (nivolumab); however, at the time of FDA approval, there was no mature overall survival (OS) data available. OS is the clinical outcome of interest in this population. PFS has not been proven to be an accurate predictor of OS benefit. More information is needed before a better estimate of net health benefit can be made.[97] At four year interim OS analysis, median OS was 53.3 months with Opdualag (nivolumab-relatlimab-rmbw) versus 33.2 months with Opdivo (nivolumab) [HR 0.77 (0.64, 0.94)].[98]
* Additionally, similar to what was observed in an earlier phase 1 trial (Study CA224020), a subgroup analysis appears to show that tumors with a LAG-3 expression ≥ 1% show a better response to Opdualag (nivolumab-relatlimab-rmbw) than those with LAG-3 expression < 1%.[97] Whether this has any application in a clinical setting is yet to be determined.

- Subsequent therapy:
  * There is interest in the use of Opdualag (nivolumab-relatlimab-rmbw) as a subsequent therapy for metastatic melanoma. However, the use of Opdualag (nivolumab-relatlimab-rmbw) after disease progression/recurrence on/after chemotherapy and/or immunotherapy for advanced melanoma is not coverable at this time.
  * The evidence is limited to the Phase 1/2 RELATIVITY-020 trial, a single-arm, open-label trial in deeply pre-treated melanoma. [99]. Given the lack of controls in the trial, overall low response rate compared to serious treatment-related adverse reaction rate, it is not known if patients are likely to benefit from sequential therapy. Additional trials are ongoing.
  * As noted above, a small percent of patients enrolled in the pivotal RELATIVITY-047 trial [97] received prior immunotherapy in the non-advanced adjuvant setting for resectable melanoma. However, this trial does not support the use of sequential therapies for advanced melanoma.
  * Given the lack of available clinical trial evidence (and ongoing trials), use of Opdualag (nivolumab-relatlimab-rmbw) as a subsequent therapy for metastatic melanoma is considered investigational per this policy.

- Other therapies with higher levels of evidence include Opdivo (nivolumab), with or without concomitant Yervoy (ipilimumab), and Keytruda (pembrolizumab).

Tecentriq (atezolizumab)

Cutaneous Melanoma, BRAF mutation-positive

- The approval of Tecentriq (atezolizumab) in BRAF mutation-positive cutaneous melanoma is based on a large, double-blind, placebo-controlled RCT [IMspire150 study] that compared Tecentriq (atezolizumab) plus Zelboraf (vemurafenib) plus Cotellic (cobimetinib) with placebo plus Zelboraf (vemurafenib) plus Cotellic (cobimetinib).[2 100]
    * Subjects in the study had unresectable stage IIIC or stage IV (metastatic) cutaneous melanoma with a BRAF V600 mutation.
    * All patients were naïve to prior systemic therapy in the metastatic disease setting.
    * There was a PFS advantage of approximately four and a half months in the Tecentriq (atezolizumab) versus the placebo treatment arm [15.1 months and 10.6 months, respectively]. These results were statistically significant; however, the clinical meaningfulness of this difference is not known.
    * The OS data in this trial are not yet mature. No statistical difference in survival between the two therapy arms has been detected to date.
- Due to the design of this study and the current lack of proven clinical benefit, it is not known if adding Tecentriq (atezolizumab) to front-line BRAF inhibitors is superior to waiting to use anti-PD-1/PD-L1 therapies in the subsequent-line setting in BRAF mutation-positive melanoma. This should be considered in the decision when choosing a front-line therapy as sequential use of anti-PD-1/PD-L1 therapies is not covered by the health plan.

Guidelines

The NCCN Cutaneous Melanoma guideline includes the following: [3]

- For metastatic/unresectable melanoma, *BRAF V600* wild-type:
    * First-line: Keytruda (pembrolizumab), Opdivo (nivolumab) monotherapy, Opdivo (nivolumab) in combination with Yervoy (ipilimumab), or Opdualag (nivolumab-relatlimab-rmbw). Therapies with higher levels of evidence than Opdualag (nivolumab-relatlimab-rmbw) include Opdivo (nivolumab), with or without concomitant Yervoy (ipilimumab), and Keytruda (pembrolizumab).
    * Second/subsequent line:
        - Guidelines recommend that, following progression or poor response, subsequent lines of therapy should use different mechanisms of action.
        - Options include: Keytruda (pembrolizumab), Opdivo (nivolumab), as monotherapy or in combination with Yervoy (ipilimumab).
        - In addition, Opdualag (nivolumab-relatlimab-rmbw) is now also listed as an option for subsequent-line therapy of advanced melanoma. However, at this time, there is no robust comparative clinical trial evidence to support the use of Opdualag (nivolumab-relatlimab-rmbw) after progression on previous therapy, and as such this use is considered investigational per this policy.
- Uveal melanoma: Opdualag (nivolumab-relatlimab-rmbw) is not listed among the recommendation for uveal melanoma (the pivotal trial excluded patients with uveal melanoma).

- Adjuvant (after complete resection), based on stage:
  * Stage IIIB, IIIC, and IV disease: Keytruda (pembrolizumab), Opdivo (nivolumab)
  * Stage IIB and IIC disease: observation or adjuvant PD-1 therapy [Keytruda (pembrolizumab) or Opdivo (nivolumab)] are listed as recommendations. If Keytruda (pembrolizumab) or Opdivo (nivolumab) is considered, the guideline states the need for careful assessment of risk versus benefit as there is currently no information evaluating its impact on overall survival in this population.
- BRAF-mutated: the use of Tecentriq (atezolizumab) in combination with Zelboraf (vemurafenib) and Cotellic (cobimetinib) among recommended options for treatment of BRAF mutation-positive metastatic or unresectable melanoma.

Merkel Cell Carcinoma (MCC)

Background [3 101]

- Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin. It predominantly affects older adults (mean age of 75 years) with light skin types.
- Localized disease can generally be cured with surgical excision and radiotherapy. For patients with locally advanced or metastatic disease that is not amenable to curative surgery or radiation, systemic therapy may be used.

Bavencio (avelumab)

- Bavencio (avelumab) is approved for the treatment of metastatic MCC, regardless of prior therapy.
- Subsequent therapy: Initial FDA approval of Bavencio (avelumab) in MCC was based on results from a single-group, open-label (observational) trial [JAVELIN Merkel 200] that evaluated it in patients with stage IV (metastatic) MCC that had progressed after cytotoxic chemotherapy.[102 103]
  * All subjects in the study had progressed on at least one prior line of chemotherapy in the metastatic setting.
  * The study reported overall tumor response rate (ORR) as the primary endpoint. The clinical meaningfulness of this endpoint is unclear, as it has not been shown to accurately predict any clinically relevant outcome.
  * An overall ORR of 33% was reported in the trial. The duration of response ranged from 2.8 months to upwards of 23 months.
- First-line: Approval in treatment-naïve MCC patients was extrapolated from this initial study. However, there is now an ongoing study prospectively evaluating Bavencio (avelumab) in the first-line MCC setting.
- The relative safety and effectiveness of Bavencio (avelumab) in MCC is unknown as it has not been compared with either best supportive care, or with any other therapy. .

Keytruda (pembrolizumab)

- First-line:
  * Keytruda (pembrolizumab) was FDA-approved as a single agent for locally advanced or metastatic MCC, previously untreated with systemic therapy for advanced disease, based on a small, single-arm Phase 2 trial that evaluated tumor response rate [KEYNOTE-017].[104] [105]
  * One phase 3 open-label, single arm confirmatory trial [KEYNOTE-913] also reported ORR with use of pembrolizumab.

    * A clinically relevant benefit, such as improved OS relative to standard of care, has not been established.[106]
- The relative safety and effectiveness of Keytruda (pembrolizumab) in MCC is unknown as it has not been compared with either best supportive care, or with any other therapy.

Zynyz (retifanlimab-dlwr)

- First-line: The efficacy of Zynyz (retifanlimab-dlwr) was evaluated in a single-arm, open-label study in adults with recurrent locally advanced or metastatic MCC. The study evaluated tumor response as a primary surrogate endpoint. [107]
    * The MCC was not amenable to curable surgical resection or radiotherapy.
    * No prior systemic therapies, including prior programmed death receptor-1 (PD-1) blocking antibodies, were allowed in the study population.
    * Zynyz (retifanlimab-dlwr) was used as monotherapy.
    * The reported objective response rate (ORR) was 52% with 18% complete responses.
    * The duration of response was 6 months or longer in 76% of patients and 12 months or longer in 62% of patients.
- The evidence for Bavencio (avelumab) and Keytruda (pembrolizumab) in advanced MCC is also based on small, single-arm studies that evaluated ORR as a surrogate endpoint. There is no outcomes evidence for any of the PD-1 inhibitors approved for use in MCC. The relative safety and effectiveness of Zynyz (retifanlimab-dlwr) in MCC is unknown as it has not been compared with either best supportive care, or with any other therapy.

Guidelines

The NCCN Merkel Cell Carcinoma guideline includes the following:[3]

- Lists Bavencio (avelumab), Keytruda (pembrolizumab), and Zynyz (retifanlimab-dlwr) among potential systemic therapeutic options that can be used for locally advanced and metastatic MCC.
- Chemotherapy historically has been the standard approach for advanced MCC. Although MCC appears to be chemosensitive, the duration of response is limited. The impact of chemotherapy on survival in patients with metastatic MCC is unclear.

Nasopharyngeal carcinoma (NPC)

Background [3 108]

- Nasopharyngeal carcinoma (NPC) is classified as a head and neck cancer; however, it differs in epidemiology, histology, natural history, and response to treatment. Because it is generally more difficult to treat than head and neck cancer, patients with NPC have been historically excluded from enrollment in head and neck cancer clinical trials.
- NPC is most prevalent in Southeast Asia, especially Southern China. It is much less common in the U.S. and Western Europe.
- The two most common histological subtypes of NPC are keratinizing squamous cell carcinoma (SCC) and non-keratinizing SCC. NPC with keratinizing histology is less responsive to radiation therapy and is associated with lower survival rates. This more difficult to treat histology makes up only 2% of cases in SE Asia, but up to 25% of cases in North America.
- NPC tends to metastasize early. At the time of diagnosis lymph node metastasis is present in 75% to 90% of cases, and distant metastasis is present in 5% to 11% of cases.

Loqtorzi (toripalimab)

- The efficacy of Loqtorzi (toripalimab) in locally advanced (unresectable) or metastatic nasopharyngeal carcinoma (NPC) was evaluated in two pivotal studies:
- *Front-line setting in combination with chemotherapy [JUPITER-02]*[109]
    * This randomized, double-blind controlled trial enrolled patients with primary recurrent or metastatic NPC whose disease was not amenable to local/regional or curative treatment and who had no prior systemic therapy in this setting.
    * The study was conducted in Southeast Asia. Nearly all (99%) patients in the study had NPC with nonkeratinizing histology.
    * Seventy-five percent of patients had NPC tumors that were PD-L1 positive (≥ 1%).
    * Patients received either Loqtorzi (toripalimab) in combination with standard-of-care platinum-based chemotherapy or chemotherapy alone (placebo group) every 3 weeks for up to 6 cycles, followed by monotherapy (toripalimab or placebo) every 3 weeks, until disease progression or unacceptable toxicity or a maximum of 24 months.
    * Median progression-free survival (PFS) was 11.7 months and 8 months in the Loqtorzi (toripalimab) and placebo groups, respectively. The data for the overall survival endpoint is not mature.
    * Study limitations include lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S., the high proportion (75%) of PD-L1-postive tumors which may have driven the PFS results, and the use of a surrogate endpoint that has not been shown to predict improvement in clinical outcomes.
- *Subsequent-line setting as monotherapy [POLARIS-02]* [110]
    * This uncontrolled (single-arm) observational study enrolled patients with recurrent or metastatic (98%) NPC that progressed on or after standard-of-care platinum-based chemotherapy.
    * The study was conducted in China. Nearly all (96%) patients had NPC with nonkeratinizing histology, the predominant histology in this geographic region.
    * All patients received Loqtorzi (toripalimab) as monotherapy every two weeks until disease progression.
    * The study evaluated tumor response as the primary endpoint. The objective response rate (ORR) was 20.5% with a complete response rate of 2.6%.
    * Study limitations include high potential for bias due to single-arm study design, lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S. and generally has poorer outcomes, and use of a surrogate endpoint which is not predictive of clinical benefit.
- NPC is considered a head and neck cancer; however, because it is more difficult to treat, patients with NPC have historically been excluded from head and neck cancer clinical trials. Loqtorzi (toripalimab) is the first PD-1 inhibitor to specifically be studied in NPC. Though it shows promise in this treatment setting, there is no data to date showing that it improves clinical outcomes such as overall survival or quality of life.

Penpulimab (unbranded)

- The efficacy of penpulimab in locally advanced (unresectable) or metastatic nasopharyngeal carcinoma (NPC) was evaluated in two pivotal studies:
- *Front-line setting in combination with chemotherapy [AK 105-304]* [105 111]
    * This randomized, double-blind controlled trial enrolled patients with primary recurrent or metastatic NPC whose disease was not amenable to local/regional or curative treatment and who had no prior systemic therapy in this setting.
    * The study was conducted in Asia. Nearly all (96%) patients in the study had NPC with nonkeratinizing histology.
    * Thirty-eight percent of patients had NPC tumors with PD-L1 tumor proportion score (TPS) of 50% or greater and 50% of the tumors had a PD-L1 TPS of 1 to 49%.
    * Patients received either penpulimab in combination with standard-of-care platinum-based chemotherapy (cisplatin or carboplatin) and gemcitabine or chemotherapy alone (placebo group) every 3 weeks for up to 6 cycles, followed by monotherapy (penpulimab or placebo) every 3 weeks, until disease progression or unacceptable toxicity or a maximum of 24 months.
    * Median progression-free survival (PFS) was 9.6 months and 7 months in the penpulimab and placebo groups, respectively. The data for the overall survival endpoint is not mature.
    * Study limitations include lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S., the potential that PD-L1-postive tumors may have driven the PFS results, and the use of a surrogate endpoint (PFS) that has not been shown to predict improvement in clinical outcomes.
- *Subsequent-line setting as monotherapy [AK 105-202]* [105 111 112]
    * This uncontrolled (single-arm) observational study enrolled patients with recurrent or metastatic NPC that progressed on or after standard-of-care platinum-based chemotherapy **and** at least one additional systemic therapy.
    * The study was conducted in China. All patients had NPC with nonkeratinizing histology, the predominant histology in this geographic region.
    * All patients received penpulimab as monotherapy every two weeks until disease progression for up to 24 months.
    * The study evaluated tumor response as the primary endpoint. The objective response rate (ORR) was 28% with a complete response rate of 0.8%.
    * Study limitations include high potential for bias due to single-arm study design, lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S. and generally has poorer outcomes, and use of a surrogate endpoint (ORR) which is not predictive of clinical benefit.

Guidelines

The NCCN Head and Neck Cancer guideline lists Loqtorzi (toripalimab) among potential first- and subsequent-line therapy options for recurrent or metastatic NPC when surgery and radiation are not curative options. Penpulimab is also listed as an option in these settings; however, it is given a lower level of recommendation and is restricted to patients with non-keratinizing NPC. [3]

Non-small cell lung cancer (NSCLC)

Imfinzi (durvalumab)

Earlier stage NSCLC, resectable - Neoadjuvant therapy followed by adjuvant therapy

- A double-blind, placebo-controlled RCT [AEGEAN] evaluated Imfinzi (durvalumab) in resectable NSCLC as an add-on to platinum-containing chemotherapy used in the neoadjuvant setting (prior to surgical resection), and then continued as a monotherapy in the adjuvant setting (after surgical resection) (n=802).[113]
    * Patients had pathologically confirmed stage II (29%), IIIA (46%), or IIIB (25%) NSCLC. Approximately 50% were N2 stage, with involvement of ≥ 1 ipsilateral mediastinal lymph node or subcarinal lymph node.
    * Randomization was stratified by stage (II vs. III) and PD-L1 expression (≥1% or <1%). Patients with known EGFR mutations or ALK rearrangements were enrolled prior to a protocol amendment but excluded from the efficacy analyses (n=62).
    * Imfinzi (durvalumab) was given 1,500 mg every three weeks for 4 cycles (4 doses) prior to surgical resection, and then continued until disease progression or up to a maximum of 12 cycles (12 doses, as 1,500 mg every 4 weeks) after surgical resection.
    * The primary endpoints were event-free survival (EFS) and pathological complete response (pCR). The median EFS was not reached in the Imfinzi (durvalumab) treatment arm and was 25.9 months in the placebo arm with a hazard ratio of 0.68 [95% CI: 0.53, 0.88] and p-value 0.004. The results are based on the first interim analysis of EFS (with 31.9% data maturity). OS results are not available to date.
- EFS is not a validated surrogate endpoint. It has not been shown to accurately predict significant improvement in clinical endpoints of interest such as OS and quality of life.
- Currently, several PD-1 inhibitors are now approved in this population as a neoadjuvant/adjuvant. One of the outstanding questions from the currently available data is the extent to which continuing a PD-1 inhibitor as an adjuvant therapy may (or may not) contribute to the efficacy of this longer regimen. Additional evidence, including impact on clinical outcomes, is needed.

Unresectable, stage III disease as maintenance

- Imfinzi (durvalumab) was approved for use in unresectable, locally advanced (stage III) NSCLC that has not progressed after concurrent chemoradiation therapy. The FDA approval was based on one phase 3, randomized, double-blind, placebo-controlled trial that reported overall survival (OS) benefit at an interim analysis.[114]
    * Imfinzi (durvalumab) was given as monotherapy and was continued until disease progression (or until intolerable adverse effects) for a maximum of 12 months.
    * The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the Imfinzi (durvalumab) group, compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (p=0.005).
    * Median OS was not reached in the Imfinzi (durvalumab) group compared to 28.7 months in the placebo group (HR 0.68, 95% CI 0.53 to 0.87, p = 0.0025).

- It is unknown if there are any differences in safety or effectiveness relative to other therapies because the study did not employ any active comparators.
- Platinum-based chemotherapy is the standard of care for the first-line treatment of advanced NSCLC in tumors without driver mutations. However, the use of immunotherapy is becoming quickly adopted as an alternative in many first and second-line metastatic NSCLC settings.

Metastatic disease setting

- A large, phase 3 RCT (POSEIDON) compared the combination of Imfinzi (durvalumab) + Imjudo (tremelimumab) + platinum chemotherapy with platinum chemotherapy alone in adults with metastatic, previously untreated NSCLC. [115 116]
    * The trial excluded patients with sensitizing EGFR and ALK genetic alterations and symptomatic brain metastases. Approximately 64% of the population had tumors that were PD-L1-positive (PD-L1 TC ≥ 1%).
    * An OS advantage in favor of Imjudo (tremelimumab) + Imfinzi (durvalumab) + platinum chemotherapy was reported in the trial (HR 0.72 [95% CI: 0.65, 0.92]; p=0.003).
- Limitations of the evidence include but are not limited to: It is not known how Imjudo (tremelimumab) + Imfinzi (durvalumab) + platinum chemotherapy compares with Keytruda (pembrolizumab) + platinum chemotherapy which is the gold standard in this treatment setting based on NCCN guidelines. [3]
- There have been no direct comparisons of Imjudo (tremelimumab) and Yervoy (ipilimumab), the other commercially available CTLA-4 inhibitor.

Keytruda (pembrolizumab)

Advanced (unresectable or metastatic) NSCLC

- Keytruda (pembrolizumab) improves overall survival (OS) relative to cytotoxic chemotherapy in patients with metastatic NSCLC in the following treatment settings:
    * Front-line therapy for nonsquamous disease when administered with a platinum plus Alimta (pemetrexed) [KEYNOTE-021].[117]
    * First-line therapy for squamous disease when administered with carboplatin plus a taxane [KEYNOTE-407].[118]
    * First- or subsequent-line therapy for PD-L1-positive tumors [Tumor Proportion Score (TPS) ≥ 50% first-line; ≥ 1% subsequent] when used as a single agent [KEYNOTE-024, -010]. [119 120]
- An FDA-approved test (PD-L1 IHC 22C3 pharmDx) was developed in conjunction with Keytruda (pembrolizumab). The TPS measures the proportion of viable tumor cells that show partial or complete membrane staining on immunohistochemical (IHC) assay. [121]

Earlier stage NSCLC, resected - Adjuvant therapy

- Keytruda (pembrolizumab), as a single agent, demonstrated improved disease-free survival (DFS) relative to best supportive care in the adjuvant setting for patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC after complete tumor resection and standard adjuvant therapy with a platinum-based chemotherapy regimen, based on an interim analysis. [1 122]
    * Patients in the experimental arm received Keytruda (pembrolizumab) every 3 weeks for one year (up to 18 cycles) unless disease recurrence or unacceptable toxicity occurred.

* Patients in the trial received a median of four cycles of adjuvant cisplatin-based chemotherapy after complete resection.
* Prior use of PD-1/PD-L1 inhibitors was not allowed, such as in the neoadjuvant setting.
* Although patients with TC >1% PD-L1 expression demonstrated a DFS benefit, patients with a high PD-L1 expression (TC ≥ 50%) appeared to have the most significant DFS benefit based on a pre-determined subgroup analysis.
* DFS is not a validated endpoint in adjuvant NSCLC and has not been correlated to meaningful clinical outcomes such as overall survival.

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Earlier stage NSCLC, resectable - Neoadjuvant therapy followed by adjuvant therapy

- An RCT [KEYNOTE-671] evaluated Keytruda (pembrolizumab) in resectable NSCLC as an add-on to platinum-containing chemotherapy used in the neoadjuvant setting (prior to surgical resection) and then continued as a monotherapy in the adjuvant setting (after surgical resection). [123]
  * Patients had pathologically confirmed stage II, IIIA, or IIIB NSCLC [involvement of ≥1 ipsilateral mediastinal lymph node or subcarinal lymph node (N2 stage)].
  * Keytruda (pembrolizumab) was given 200 mg every three weeks for 4 cycles (4 doses) prior to surgical resection and then continued until disease progression or up to a maximum of 13 cycles (13 doses, as 200 mg every 3 weeks) after surgical resection.
  * The primary endpoint was event-free survival (EFS). The median EFS was not reached in the Keytruda (pembrolizumab) treatment arm and was 17 months in the placebo arm with a hazard ratio of 0.58 [95% CI: 0.46, 0.72] and p-value <0.001. OS results are not mature; however, no difference in OS has been detected to date.
- EFS is not a validated surrogate endpoint. It has not been shown to accurately predict significant improvement in clinical endpoints of interest such as OS and quality of life.
- Currently, several PD-1 inhibitors are now approved in this population as a neoadjuvant/adjuvant. One of the outstanding questions from the currently available data is the extent to which continuing a PD-1 inhibitor as an adjuvant therapy may (or may not) contribute to the efficacy of this longer regimen. Additional evidence, including impact on clinical outcomes, is needed.

Libtayo (cemiplimab)

Front-line therapy, as monotherapy – NSCLC

- The evidence for Libtayo (cemiplimab-rwlc) as a front-line monotherapy for advanced NSCLC when tumors have a PD-L1 of at least 50% [tumor proportion score (TPS) ≥ 50%] is derived from an open-label, randomized controlled trial (N = 710) that compared it with standard platinum doublet chemotherapy (EMPOWER-Lung 1).[124]
  * The population included patients with locally advanced (stage IIIB or IIIC, 15%) or metastatic (stage IV, 85%) NSCLC. Patients were naïve to prior therapy for advanced disease and had TPS ≥ 50%.
  * Patients with EGFR mutations, ALK translocations, or ROS1 fusions were excluded from the trial because therapy with targeted agents is the standard front-line therapy in these populations.

* The median overall survival (OS) in the Libtayo (cemiplimab-rwlc) treatment arm was superior to that in the cytotoxic chemotherapy arm (22.1 months and 14.3 months, respectively; HR 0.68 [95%CI: 0.53, 0.87], p = 0.0022).
* Libtayo (cemiplimab-rwlc) was found to improve median overall survival (OS) relative to standard of care cytotoxic chemotherapy when used as a front-line therapy for advanced NSCLC when the TPS > 50%. However, its relative effectiveness when compared to Tecentriq (atezolizumab) or Keytruda (pembrolizumab), which are also each approved as monotherapy in this setting, is not known. There is not head-to-head data that compares any of these agents with one another.

Front-line therapy, in combination with platin-based chemotherapy – NSCLC

- Libtayo (cemiplimab-rwlc) was also approved as part of a front-line regimen for advanced NSCLC based on a randomized, double blinded, phase 3 trial that compared Libtayo (cemiplimab-rwlc) and placebo. Both arms were given in combination with four cycles of platinum-doublet chemotherapy (followed by pemetrexed maintenance as indicated) (EMPOWER-Lung 3).[125]
  * The population included patients with locally advanced (stage III, 14.8%) or metastatic (stage IV, 85.2%) NSCLC. Patients were naïve to prior therapy for advanced disease.
  * Patients were negative for therapeutically actionable genetic mutations (EGFR mutations, ALK translocations, or ROS1 fusions).
  * Patients were enrolled irrespective of PD-L1 expression (29.8% PD-L1 <1%) or histology (57.1% non-squamous).
  * Libtayo (cemiplimab-rwlc) was initiated with investigators' choice of histology-specific platin-based chemotherapy as induction (four cycles) and then continued as monotherapy versus platin-based chemotherapy induction followed by pemetrexed switch maintenance or best supportive care (BSC).
  * The Libtayo (cemiplimab-rwlc) treatment arm demonstrated improved overall survival relative to the placebo arm, with an 8.9-month improvement in median OS, with 21.9 months [95% CI: 15.5, NE] and 13.0 months [95% CI: 11.9, 16.1] in the Libtayo (cemiplimab-rwlc) and placebo groups, respectively.
  * It was noted that the combination of Libtayo (cemiplimab-rwlc) with chemotherapy may add additional toxicity relative to either therapy alone.
- As with other PD-1/PD-L1 inhibitors in their many other treatment settings, there is no evidence to support the benefit of sequential PD-1/PD-L1 inhibitor therapy after disease has progressed on a prior therapy with these agents.

Opdivo (nivolumab)

Earlier NSCLC (resectable): Neoadjuvant (prior to surgical resection)

- The efficacy of Opdivo (nivolumab) as a neoadjuvant therapy for resectable NSCLC was evaluated in an open-label randomized controlled trial [CHECKMATE 816] that evaluated event-free survival (EFS) and pathological complete response (pCR) as surrogate endpoints. The trial compared the addition of Opdivo (nivolumab) to a platinum doublet with the platinum doublet alone. Therapy was given prior to surgical resection every three weeks for a total of 3 doses. [126]

    * Patients enrolled in the trial had resectable disease with tumors ≥ 4 cm and/or positive nodes.
    * Approximately 50% of the population had PD-L1 expression ≥ 1%.
    * The median EFS was 31.6 months and 20.8 months in the Opdivo (nivolumab)/platinum doublet and platinum doublet treatment arms, respectively [HR 0.63 (97.5% CI: 0.43, 0.91); p=0.005].
    * The rate of pCR was 24% and 2.2% in the Opdivo (nivolumab)/platinum doublet and platinum doublet treatment arms, respectively.
    * Data for overall survival (OS) were not mature in either treatment arm at the time of FDA approval.
- Limitations of the study include the use of surrogate endpoints which do not accurately reflect relevant clinical outcomes, and potential undertreatment of patients in the comparator arm as standard of care neoadjuvant therapy in this setting is generally four doses of platinum doublet therapy.
- At the final analysis of OS at 5 years, survival was statistically higher with Opdivo (nivolumab)/chemotherapy (65.4%) as compared to chemotherapy alone (55%) [HR 0.72; 95% CI, 0.52, 0.998; p=0.048].[127]

Neoadjuvant therapy followed by adjuvant therapy for earlier NSCLC

- An RCT [CHECKMATE 77T] evaluated Opdivo (nivolumab) in resectable NSCLC as an add-on to platinum-containing chemotherapy used in the neoadjuvant setting (prior to surgical resection), and then continued as a monotherapy in the adjuvant setting (after surgical resection).[128]
    * Patients had pathologically confirmed stage II, IIIA, or IIIB NSCLC [involvement of >1 ipsilateral mediastinal lymph node or subcarinal lymph node (N2 stage)], no EGFR mutations or known ALK translocations, and no prior systemic anticancer treatment.
    * Placebo or Opdivo (nivolumab) was given 360 mg every three weeks for 4 cycles (4 doses) prior to surgical resection, and then placebo or Opdivo (nivolumab) 480 mg every 4 weeks was continued until disease progression or up to a maximum of one year [up to 13 cycles (13 doses, as 360 mg every 4 weeks)] after surgical resection. All patients received neoadjuvant platinum-doublet chemotherapy every 3 weeks for 4 cycles.
    * The primary endpoint was event-free survival (EFS). The median EFS was not reached in the Opdivo (nivolumab) treatment arm and was 18.4 months in the placebo arm with a hazard ratio of 0.58 [97.63% CI: 0.42, 0.81] and p-value <0.001. OS results are not mature; however, no difference in OS has been detected to date.
- EFS is not a validated surrogate endpoint. It has not been shown to accurately predict significant improvement in clinical endpoints of interest such as OS and quality of life.
- Currently, several PD-1 inhibitors are now approved in this population as a neoadjuvant/adjuvant. One of the outstanding questions from the currently available data is the extent to which continuing a PD-1 inhibitor as an adjuvant therapy may (or may not) contribute to the efficacy of this longer regimen. Additional evidence, including impact on clinical outcomes, is needed.

Metastatic -Front-line use

In Combination with Yervoy (ipilimumab) and Platinum-Doublet for mNSCLC

- The efficacy of Opdivo (nivolumab) when administered in combination with Yervoy (ipilimumab)

and two cycles of platinum-doublet chemotherapy for recurrent or metastatic NSCLC in the first-line setting is based on one randomized, open-label trial, which found improved OS relative to chemotherapy alone [CHECKMATE-9LA].[25]

* Subjects received Opdivo (nivolumab) 360 mg IV every 3 weeks, Yervoy (ipilimumab) 1 mg/kg IV every 6 weeks, and platinum-doublet chemotherapy IV every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years.
* Patients received no prior systemic therapy for metastatic disease.
* OS was 14.1 months with the addition of nivolumab/ipilimumab versus 10.7 months with chemotherapy alone. These efficacy results are from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients in the treatment arm or control arm, respectively.

In Combination with Yervoy (ipilimumab) for mNSCLC

- The efficacy Opdivo (nivolumab) with Yervoy (ipilimumab) for metastatic NSCLC in the first-line setting is based on one open-label, phase 3 trial, which found improved OS versus chemotherapy in PD-L1 expressing tumors [CHECKMATE-227]. [129]
  * Patients had received no prior systemic therapy for metastatic disease.
  * Among the patients with a PD-L1 expression level of 1% or more, the median OS was 17.1 months with nivolumab plus ipilimumab vs. 14.9 months with chemotherapy, with 2-year overall survival rates of 40.0% and 32.8%, respectively.

Monotherapy for mNSCLC

- Front-line treatment of metastatic NSCLC with single agent Opdivo (nivolumab) was not superior to chemotherapy based on a phase 3 trial in this setting. The study failed to meet its primary endpoint of PFS [KEYNOTE-026].[130] No information on OS has been released to date.

Metastatic -Subsequent-line use

Opdivo (nivolumab) as Subsequent Therapy for Metastatic NSCLC

- The efficacy of Opdivo (nivolumab) in metastatic NSCLC is based on two RCTs, one in subjects with squamous histology and one in subjects with nonsquamous histology.[25 131 132]
  * Subjects enrolled in the trials had progression of disease during or after chemotherapy with a platinum doublet. Patients with a known EGFR mutation or ALK translocation were allowed to have one additional line of tyrosine kinase inhibitor therapy. The studies compared Opdivo (nivolumab) 3 mg/kg IV every two weeks with docetaxel 75 mg/m^2 IV every three weeks. Both were administered as monotherapy.
  * Median OS was statistically superior in the Opdivo (nivolumab) treatment arm relative to the docetaxel arm in both squamous and nonsquamous populations. The difference was considered to be clinically relevant.
  * In the population with nonsquamous histology, it was noted that there was a positive correlation between the level of PD-L1 expression and the efficacy of Opdivo (nivolumab) in metastatic NSCLC. Although Opdivo (nivolumab) therapy is currently not selected based on level of PD-L1 expression, future studies may help to clarify the role of testing in the selection of patients who are most likely to benefit from this therapy.

    * The clinical utility of nivolumab as a first-line therapy in NSCLC (nonsquamous or squamous) has not been demonstrated.
- Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.

Tecentriq (atezolizumab)

Adjuvant therapy – NSCLC

- Tecentriq (atezolizumab), as a single agent, demonstrated improved disease-free survival (DFS) relative to best supportive care in the adjuvant setting for patients with stage II-IIIA NSCLC after complete tumor resection and standard adjuvant therapy with a platinum-based chemotherapy regimen and, if the tumor is ≥1% PD-L1 positive, defined as PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%] [IMpower010]. Patients in the experimental arm received Tecentriq (atezolizumab) every 3 weeks for 16 cycles unless disease recurrence or unacceptable toxicity occurred.[2 133]
    * Patients in the trial received a median of four cycles of adjuvant cisplatin-based chemotherapy after complete resection.
    * Prior use of PD-1/PD-L1 inhibitors was not allowed, such as in the neoadjuvant setting.
    * Although patients with TC >1% PD-L1 expression demonstrated a DFS benefit, patients with a high PD-L1 expression (TC > 50%) appeared to have the most significant DFS benefit based on a pre-determined subgroup analysis.
    * DFS is not a validated endpoint in adjuvant NSCLC and has not been correlated to meaningful clinical outcomes such as overall survival.
    * At 5-year follow up, Tecentriq (atezolizumab) was superior to best supportive care across groups, including in patients with TC >1% PD-L1 expression [HR 0.76 (0.55, 1.04)] and high PD-L1 expression [HR 0.44 (0.26, 0.74)].[134]

Front-line therapy (as monotherapy) - mNSCLC

- The approval of Tecentriq (atezolizumab) as a front-line agent (as monotherapy) for metastatic NSCLC with high PD-L1 expression was based on an open-label (not blinded), phase 3 trial [IMpower110 study] that compared Tecentriq (atezolizumab) with platinum doublet chemotherapy.[2 135]
    * Patients previously treated with PD-1/PD-L1 inhibitors, including in the neoadjuvant, adjuvant, or advanced setting were excluded from inclusion in the trial.
    * The primary endpoint of OS was tested hierarchically according to PD-L1 expression status. Only those in the high PD-L1 expression group (defined as PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%] met the prespecified efficacy boundary.
    * At interim, a seven-month improvement in median OS was reported in the Tecentriq (atezolizumab) arm for patients with high PD-L1 expression.

* Patients with EGFR or ALK aberrations were enrolled in the trial after progression on ALK/EGFR-directed therapies but excluded from the primary analysis. In an exploratory analysis, monotherapy with Tecentriq (atezolizumab) was not superior to use of chemotherapy. Therefore, the use of Tecentriq (atezolizumab) for NSCLC after EGFR- or ALK-directed therapy is considered 'not medically necessary' and not coverable.

Front-line therapy, in combination with chemotherapy plus bevacizumab - mNSCLC

- The approval of Tecentriq (atezolizumab) as a front-line therapy for non-squamous metastatic NSCLC was based on a randomized, open-label (not blinded), phase 3 trial
- [IMpower150] that compared atezolizumab (A, Tecentriq)/ carboplatin (C)/ paclitaxel (P)/bevacizumab (B) [ABCP] with BCP alone in patients with metastatic, non-squamous NSCLC.[136]
  * Patients with EGFR or ALK aberrations were excluded from inclusion in the trial.
  * A 4-month survival advantage was reported in the ABCP group relative to the BCP group, with a median OS of 19.2 months, and 7.0 months, respectively [HR 0.71; 95% CI, 0.59, 0.85; p = 0.0002].
  * There were many threats to the reliability of these results, including the lack of blinding and numerous protocol changes during the trial which altered the predetermined efficacy analysis (high potential for bias in the results).
  * Despite the positive OS results, it is not known whether the addition of bevacizumab to Tecentriq (atezolizumab) plus platin-based chemotherapy is superior to Tecentriq (atezolizumab) plus platin-based chemotherapy alone, or whether the additional risks with this multi-drug regimen are acceptable, as ABCP was not formally compared with ACP. However, the median OS for these two groups was numerically similar suggesting a lack of any survival benefit (19.2 months and 19.4 months, respectively). Furthermore, it is not known if the addition of Tecentriq (atezolizumab) to platin-based chemotherapy is superior to platin-based chemotherapy alone. This is an area of ongoing investigation.
  * Additionally, the lack of formal comparison between the ABCP and ACP groups does not allow for an accurate assessment of the potential added safety risks when bevacizumab is added to an immunotherapy-based regimen.

Front-line therapy, in combination with a platinum plus a taxane – NSCLC

- Tecentriq (atezolizumab) was also approved as part of a front-line regimen for non-squamous metastatic NSCLC based on a randomized, open-label (not blinded), phase 3 trial that compared Tecentriq (atezolizumab) plus nab-paclitaxel and carboplatin with nab-paclitaxel and carboplatin with or without pemetrexed switch maintenance.[137]
  * Most patients had no EGFR or ALK aberrations.
  * Tecentriq (atezolizumab) was initiated with chemotherapy (carboplatin and nab-paclitaxel) as induction and then continued as monotherapy versus carboplatin plus nab-paclitaxel induction followed by pemetrexed switch maintenance or best supportive care (BSC).
  * The Tecentriq (atezolizumab) treatment arm demonstrated improved overall survival relative to the chemotherapy arm, with a 4.7-month improvement in median OS and 1.5-

month improvement in median PFS.

* It was noted that the combination of Tecentriq (atezolizumab) with chemotherapy may add additional toxicity relative to either therapy alone.
* Applicability of the results to patients with squamous histology or patients with EGFR or ALK genetic aberrations cannot be determined as the sample size for these groups was too small.

Subsequent-line therapy (after disease progression on platinum-based front-line therapy) - NSCLC

- Tecentriq (atezolizumab), as a single agent, demonstrated improved OS relative to docetaxel in patients with locally advanced or metastatic NSCLC who had disease progression after standard therapy with a platinum-based chemotherapy regimen and, if the tumor was EGFR- or ALK-positive, an appropriate tyrosine kinase inhibitor.[138 139]
  * A three- to four-month improvement in median overall survival was demonstrated with Tecentriq (atezolizumab) relative to docetaxel. Benefit was noted regardless of PD-L1 expression.
  * Prior treatment with PD-1/PD-L1 inhibitors was not allowed.

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC treatment guideline lists the following:[3]

- Subsequent therapy (dependent on PD-L1 expression and histology): Tecentriq (atezolizumab), Opdivo (nivolumab), and Keytruda (pembrolizumab) among preferred category 1 recommendations, for locally advanced or metastatic NSCLC that progressed on or after standard front-line therapy when there has been no prior use of anti-PD-1/PD-L1 therapy.
- First-line therapy: Level of recommendation and regimen (monotherapy or with chemotherapy) is based on PD-L1 expression and histology.
  * Preferred PD-1/PD-L1 regimens include Keytruda (pembrolizumab), Libtayo (cemiplimab-rwlc), Tecentriq (atezolizumab).
  * 'Other recommended' options include Imfinzi (durvalumab)/Imjudo (tremelimumab),Tecentriq (atezolizumab)/carboplatin/nab-paclitaxel, Tecentriq (atezolizumab)/carboplatin/paclitaxel/bevacizumab. Opdivo (nivolumab)/Yervoy (ipilimumab).
- Consolidation therapy for unresectable Stage III: Imfinzi (durvalumab) as consolidation therapy when there is no progression after 2 or more cycles of definitive concurrent platinum-based chemoradiation.
- For resectable NSCLC:
  * Neoadjuvant only: neoadjuvant therapy with Opdivo (nivolumab) among treatment options for resectable NSCLC (three cycles total). Platinum doublet therapy is also an option (four cycles total), as are various adjuvant therapies.
  * Neoadjuvant followed by adjuvant: neoadjuvant platinum-doublet therapy with addition of immunotherapy [Opdivo (nivolumab), Keytruda (pembrolizumab), or Imfinzi (durvalumab)] prior to surgical resection followed by adjuvant immunotherapy as monotherapy for up approximately one year (12-13 cycles; See "Quantity Limit").

* Adjuvant only: for completely resected NSCLC in patients who received previous adjuvant chemotherapy - Tecentriq (atezolizumab) [stage IIB-IIIA or high-risk stage IIA PD-L1 ≥ 1%] and Keytruda (pembrolizumab) [stage II-IIIA, with a note that the value of adjuvant therapy in PD-L1 negative NSCLC is unclear].

Primary mediastinal B cell lymphoma (PMBCL)

Keytruda (pembrolizumab)

- Keytruda (pembrolizumab) received FDA Accelerated approval for use in relapsed or refractory PMBCL based on tumor response rates from a single-arm, open-label study [KEYNOTE-170]. [1] To date, there is no evidence that it improves any clinically relevant outcome (e.g., improved survival, symptom control, function, or quality of life) in this disease setting.
  * Two small, uncontrolled, open-label studies evaluated patients with relapsed or refractory PMBCL who failed to achieve a complete remission after, or were ineligible for, an autologous stem cell transplant.[140-142]
  * Patients received a median of three prior therapies prior to Keytruda (pembrolizumab), and all had prior rituximab.
  * The reported objective response rate (ORR) was 45.3% and 47.6%. Six patients (11.3%) and seven patients (33.3%) had complete responses, respectively.
  * ORR has not been shown to accurately predict improvement in clinical endpoints in PMBCL.

Guidelines

The NCCN B-cell Lymphomas guideline lists rituximab-containing chemotherapy regimens among recommended therapy options for relapsed or refractory PMBCL when patients are not candidates for high-dose therapies with stem cell rescue. Keytruda (pembrolizumab) is listed as a treatment option for relapsed disease.[3]

Renal Cell Carcinoma (RCC)

Bavencio (avelumab)

- Bavencio (avelumab) is approved for the treatment of advanced (unresectable or metastatic) renal cell carcinoma (RCC) as a front-line therapy when used in combination with Inlyta (axitinib).
- First-line: The approval was based on interim results from a phase 3, open-label (not blinded), randomized controlled trial (RCT) in patients with advanced, clear cell RCC in the front-line treatment setting, comparing the combination of Bavencio (avelumab) plus Inlyta (axitinib) with sunitinib monotherapy [JAVELIN Renal 101 study].[143 144] Sunitinib, like Inlyta (axitinib), is an orally administered tyrosine kinase inhibitor.
  * All patients in the trial had a clear cell component (histology) and good performance status. The trial protocol allowed patients with advanced or metastatic disease. All enrolled subjects had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST). Most enrolled subjects (80%) had prior nephrectomy.
  * Median progression-free survival (PFS) was greater in the combination treatment arm [13.8 months and 8.4 months in the Bavencio (avelumab)/Inlyta (axitinib) and sunitinib

treatment arms, respectively].

* There was no difference in overall survival (OS) detected between groups at the time of the interim analysis, and it was not known if Bavencio (avelumab)/Inlyta (axitinib) improves any clinical outcome at this time.
* At the final analysis, there was no statistically significant difference between survival in the Bavencio (avelumab)/Inlyta (axitinib) and sunitinib arms (43 vs. 36 months, p=0.0755).[145] Therefore, the use of Bavencio (avelumab)/Inlyta (axitinib) for first-line advanced clear cell RCC is considered 'not medically necessary,' as it is not safer or more effective than low-cost generic sunitinib, but it is more costly.
* There was a slight increase in grade 3 and 4 adverse effects in the combination arm. Additionally, 11% of subjects in the combination arm had immune-mediated AEs that required 40 mg or more per day of prednisone.

- Subsequent: There is no evidence supporting the use of Bavencio (avelumab) in subsequent-line RCC settings, or as a monotherapy for RCC.
- The ideal sequencing of immunotherapies [such as Bavencio (avelumab), Opdivo (nivolumab), Keytruda (pembrolizumab), and Yervoy (ipilimumab)] and tyrosine kinase inhibitor (TKI) therapies [Inlyta (axitinib), Cabometyx (cabozantinib), Lenvima (Lenvatinib), Votrient (pazopanib), and sunitinib] in advanced RCC has not been established. Further study is needed.

Keytruda (pembrolizumab)

First-line -Advanced:

- FDA approval for Keytruda (pembrolizumab) in combination with Inlyta (axitinib) was based on interim PFS results from a phase 3, open-label (not blinded) randomized controlled trial (RCT) versus Sutent (sunitinib) monotherapy in patients with advanced, clear cell RCC in the front-line treatment [KEYNOTE-426].[146] Overall survival, the co-primary endpoint, was not mature at the time of approval.
    * All patients in the trial had a clear cell component (histology) and good performance status. The trial protocol allowed patients with locally advanced/metastatic disease (i.e., Stage IV RCC per American Joint Committee on Cancer) or have recurrent disease. More than 99% of enrolled subjects had metastatic disease.
    * Median progression-free survival (PFS) was greater in the combination treatment arm [15.1 months versus 11.1 months with sunitinib].
    * Median overall survival was not met in either treatment arm at the time of the interim analysis.
    * In a subsequent analysis of overall survival, the median OS was not reached with pembrolizumab/axitinib and was 35.7 months in the sunitinib treatment arm.[147]
    * There was a slight increase in grade 3 and 4 adverse effects in the combination arm. Additionally, 27% of subjects in the combination arm had immune-mediated AEs that required 40 mg or more per day of prednisone. [1]
- FDA approval of Keytruda (pembrolizumab) in combination with Lenvima (lenvatinib) is based on results from a phase 3, open-label (not blinded) RCT where this combination was found to show improved PFS relative to Sutent (sunitinib) monotherapy in patients with advanced, clear cell RCC in the front-line treatment [KEYNOTE-581/CLEAR Study]. [1 148]

- All patients in the trial had a clear cell component (histology) and good performance status. The trial protocol allowed unresectable, advanced or metastatic. More than 99% of enrolled subjects had metastatic disease
- The median PFS was 23.9 months versus 9.2 months in the Keytruda (pembrolizumab)-Lenvima (lenvatinib) and Sutent (sunitinib) treatment arms, respectively.
- Median OS was not met in either treatment arm.
- Limitations of this study include, but are not limited to:
  - PFS is a surrogate radiographic endpoint that may not accurately predict that a patient will live a longer or better life.
  - Front-line therapies for advanced RCC have evolved such that Sutent (sunitinib) is no longer considered a standard of care. The efficacy and safety of Keytruda (pembrolizumab) plus Lenvima (lenvatinib) relative to other available standards of care is not known.

- Adjuvant for Resected RCC: The use of Keytruda (pembrolizumab) as an adjuvant therapy for patients with resected RCC with a high risk of recurrence was based on a RCT [KEYNOTE-564] that compared it with best supportive care. Keytruda (pembrolizumab) or placebo was given every 3 weeks for a maximum of 17 cycles (one year).[149]
  - Patients had either localized, resectable RCC; or had RCC with a fully resectable metastatic lesion [M1 No Evidence of Disease (NED)] and had a high risk of disease recurrence (refer to *Appendix 2* for definitions).
  - Only patients with RCC with a clear cell component were included. No prior systemic therapy for RCC was allowed.
  - The primary endpoint was disease-free survival (DFS), a non-validated endpoint. At 24 months, 77% and 68% of patients in the Keytruda (pembrolizumab) and placebo arms were alive and recurrence free, respectively. Overall survival data is not yet mature.
- Subsequent therapy: Currently, there is no evidence supporting the use of Keytruda (pembrolizumab) in subsequent-line RCC settings, or as a monotherapy for advanced RCC.

Opdivo (nivolumab)

First-line use

In Combination with Yervoy (ipilimumab)

- A large, randomized, open-label trial compared the combination of Yervoy (ipilimumab) plus Opdivo (nivolumab) with Sutent (sunitinib) as initial therapy for patients with intermediate- to poor risk, unresectable or metastatic RCC [CHECKMATE-214].[150]
  - Yervoy (ipilimumab) was initiated for four doses with Opdivo (nivolumab) then Opdivo (nivolumab) monotherapy was continued until disease progression.
  - The population included favorable-, intermediate-, or poor-risk disease; however, only patients with intermediate- or poor risk disease were evaluated for efficacy.
  - There was no statistical difference in PFS between the two treatment groups. Efficacy was based on a modest improvement in survival at 18 months (interim analysis) relative to Sutent (sunitinib). Median survival had not been reached in either group at the time of approval. Therefore, it was too soon to make conclusions regarding its net health benefit in this setting. At 8 yr follow up, median OS was higher for nivolumab/ipilimumab with 46.7

months vs. sunitinib 26 months [HR 0.69, 95% CI 0.59-0.81]. However, there was no significant difference in OS for the favorable-risk disease group.[151]

In Combination with Cabometyx (cabozantinib)

- A large, open-label, randomized active-controlled trial compared the combination of Opdivo (nivolumab) plus cabozantinib with Sutent (sunitinib) in treatment-naïve patients with locally advanced (unresectable) or metastatic RCC with clear cell histology [CHECKMATE-9ER]. [25]
  - Patients were enrolled regardless of tumor PD-L1 expression.
  - The population included patients with favorable-, intermediate-, and poor-risk disease; however, approximately 75% had intermediate- to poor-risk disease.
  - The median PFS was 16.6 months and 8.3 months in the Opdivo (nivolumab)/Cabometyx (cabozantinib) and Sutent (sunitinib) treatment groups, respectively.
  - Median OS was not reached in either group; however, early results favor the Opdivo (nivolumab)/Cabometyx (cabozantinib) treatment arm.
- A more informative comparator would have been a monotherapy Cabometyx (cabozantinib) arm.

In combination with Yervoy (ipilimumab) and Cabometyx (cabozantinib)

- A large, phase 3, RCT [COSMIC-313] compared the combination of Opdivo (nivolumab)/ Yervoy (ipilimumab)/Cabometyx (cabozantinib) with Opdivo (nivolumab)/Yervoy (ipilimumab)/placebo in patients with intermediate- to poor-risk advanced or metastatic RCC with a clear cell component. An incremental improvement in PFS was noted in the 'triple therapy' group; however, there is no mature outcomes data from the study.[152]
- The risk of significant AEs was greater in the Opdivo (nivolumab)/Yervoy(ipilimumab)/ Cabometyx (cabozantinib) treatment arm with grade 3 or 4 AEs occurring in 79% of the patients in the 'triple therapy group' versus 56% in the control group.
- It is not known how Opdivo (nivolumab)/Yervoy (ipilimumab)/Cabometyx (cabozantinib) compares with Opdivo (nivolumab)/Cabometyx (cabozantinib) which is already FDA approved and coverable in this population.
- The NCCN guideline does not endorse the use of Opdivo (nivolumab)/Yervoy (ipilimumab)/Cabometyx (cabozantinib) for RCC. [3 153]

Subsequent-line use

- The primary evidence of efficacy in RCC is based on a phase 3, double-blind randomized controlled trial [CHECKMATE 025] that compared Opdivo (nivolumab) monotherapy with Afinitor (everolimus) in patients with refractory unresectable or metastatic RCC, after prior antiangiogenic therapy with bevacizumab or a multi-kinase inhibitor.[25 154]
  - Subjects were previously treated with at least one of the following: bevacizumab, Sutent (sunitinib), Votrient (pazopanib), Inlyta (axitinib), or Nexavar (sorafenib).
  - Efficacy was based on improved OS with Opdivo (nivolumab), a clinically relevant endpoint, relative to Afinitor (everolimus) at the time of the prespecified interim analysis (median OS of 25 months and 19.6 months, respectively).
- Although there is interest in the use of Opdivo (nivolumab)/Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab)/Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition,

the use of Opdivo (nivolumab)/Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.

Guidelines

The NCCN kidney guideline lists: [3]

- First-line treatment for advanced, clear cell RCC:
  - The recommendation ratings vary, based on risk assessment.
  - Immunotherapy options include: Keytruda (pembrolizumab) with Inlyta (axitinib) or Lenvima (lenvatinib); Opdivo (nivolumab) with Cabometyx (cabozantinib); Opdivo (nivolumab) with Yervoy (ipilimumab) are all category 1 preferred options. Bavencio (avelumab) with Inlyta (axitinib) is listed under 'Other Recommended'.
- Subsequent therapy for unresectable or metastatic RCC, after progression of disease on front-line therapy [e.g. multi-kinase inhibitors, bevacizumab]: Opdivo (nivolumab) among several treatment options.
- For resectable RCC with high risk of recurrence, Keytruda (pembrolizumab) as a single agent or surveillance are listed among recommendations for clear cell, previously untreated disease.

<u>Small Cell Lung Cancer (SCLC)</u>

Imfinzi (durvalumab)

<u>Extensive-stage SCLC (ES-SCLC) – First line</u>

- The initial FDA approval in SCLC was based on a single phase 3 randomized controlled trial that compared Imfinzi (durvalumab) plus chemotherapy (etoposide plus carboplatin or cisplatin) with chemotherapy alone (placebo arm) in patients with untreated extensive-stage SCLC (ES-SCLC).[155 156]
  - Subjects included in the study had no prior treatment for ES-SCLC. If they had prior treatment for limited-stage SCLC (LS-SCLC), they had to have been treated with curative intent and must have had a treatment-free interval of at least 6 months since their last chemotherapy, radiotherapy, or chemoradiotherapy. However, no prior use of anti-PD-1/PD-L1 therapy was allowed.
  - Patients with untreated or symptomatic CNS metastasis were not included in the study.
  - Imfinzi (durvalumab) was initiated with chemotherapy (given for four cycles) and was then continued as maintenance until disease progression.
  - After a median follow-up of 25.1 months. Median OS was 12.9 months [95% CI: 11.3 to 14.7] and 10.5 months [95% CI: 9.3 to 11.2], respectively.
- There was a small, but statistically significant difference in OS that favored patients in the Imfinzi (durvalumab) group.
- Optimal sequencing of chemotherapy and immunotherapy in SCLC has not been studied. Sequential use of immunotherapies (e.g., PD-1/PD-L1 inhibitors) is not supported by current evidence.

<u>Limited-stage SCLC (LS-SCLC) – Consolidation therapy, after concurrent chemoradiation (cCRT)</u>

- The FDA approval in limited-stage SCLC (LS-SCLC) was based on an interim analysis of phase 3 randomized placebo-controlled trial as consolidation therapy in patients with inoperable LS-SCLC

who did not have disease progression after concurrent chemoradiation therapy (cCRT).[157]

* All patients had stage I, II, or III LS-SCLC. Patients with stage I or II disease had to have medically inoperable disease.
* Enrollment was limited to patients with a good performance status (PS), defined as a WHO/ECOG PS score of 0 or 1. Patients with ECOG>1 were excluded from the trial.
* All patients received four cycles of definitive cCRT with etoposide plus a platinum (cisplatin or carboplatin). Three cycles of cCRT was allowed if the patient had disease control and the investigator documented no likely additional benefit from a fourth cycle. Only patients with no disease progression (partial response, complete response, or stable disease) were randomized.
* Patients were randomized to consolidation therapy with Imfinzi (durvalumab) monotherapy (n=264) or placebo (standard surveillance) (n=266), dosed every four weeks for up to 24 months or until disease progression. Prophylactic cranial irradiation (PCI) after cCRT was allowed, at the investigator's discretion. However, patients with untreated or symptomatic CNS metastasis were not included in the study.
* After a median follow-up of 37.2 months, median OS was 55.9 months [95% CI:37.3, not reported] with Imfinzi (durvalumab) and 33.4 months [95% CI: 25.5, 39.9] with placebo, based on an interim analysis.
* Of note: the trial also included a combination arm of Imfinzi (durvalumab) with Imjudo (tremelimumab) (n=200). However, enrollment in the combination arm was stopped based on a protocol amendment, given emerging OS data for ES-SCLC with the addition of PD-1 therapy to chemotherapy and the uncertain benefit of CTLA-4 therapy for ES-SCLC. The interim data analysis used for the FDA approval of Imfinzi (durvalumab) did not include the combination arm. Therefore, the use of Imfinzi (durvalumab) in combination with Imjudo (tremelimumab) for LS-ESCLC is considered investigational.
* There is no evidence to support the use of Imfinzi (durvalumab) in LS-SCLC in patients unable to tolerate prior concurrent chemoradiotherapy (cCRT) with etoposide plus a platinum, such as those with a poor performance status (ECOG>1). The trial only enrolled patients who had disease stability or response with cCRT (as detailed above). Therefore, Imfinzi (durvalumab) in LS-SCLC not previously treated with cCRT is considered investigational.

Tecentriq (atezolizumab)

Extensive-stage SCLC (ES-SCLC) – First line

- *Induction with chemotherapy, then maintenance monotherapy:* The initial approval in SCLC was based on the results of a phase 3 RCT [IMpower133] that compared Tecentriq (atezolizumab) plus chemotherapy (carboplatin plus etoposide) with chemotherapy alone (placebo arm) in patients with untreated, extensive-stage SCLC (ES-SCLC). There was a small, but statistically significant difference in the 1-year survival rate that favored patients in the Tecentriq (atezolizumab) treatment arm.[2 158]
    * Subjects included in the study had no prior treatment for extensive-stage SCLC. If they had prior treatment for limited-stage SCLC (LS-SCLC), they had to have been treated with curative intent and must have had a treatment-free interval of at least 6 months since their last chemotherapy, radiotherapy, or chemoradiotherapy. However, no prior use of

anti-PD-1/PD-L1 therapy was allowed.

* Patients with untreated or symptomatic CNS metastasis were not included in the study.
* Tecentriq (atezolizumab) was initiated with carboplatin plus etoposide (given for four cycles) and was then continued as maintenance until disease progression.
* Overall survival at 12 months was 51.7% and 38.2% in the Tecentriq (atezolizumab) and placebo arms, respectively [HR 0.70; 95% CI: 0.54, 0.91; p = 0.007]. Median OS was 12.3 months [95% CI: 10.8, 15.9] and 10.3 months [95% CI: 9.3, 11.3], respectively. No p-value was reported for the medians. Because the confidence intervals overlap, the meaningfulness of these findings is difficult to interpret.

- *Induction with chemotherapy, then maintenance in combination with Zepzelca (lurbinectedin)*: More recently, Tecentriq (atezolizumab) was studied in the front-line setting in a phase 3 trial [IMforte], when given as part of induction chemoimmunotherapy, followed by maintenance therapy with Zepzelca (lurbinectedin) in patients with ES-SCLC who had not progressed after induction therapy as compared to maintenance therapy with Tecentriq (atezolizumab) monotherapy.[159] Maintenance therapy with Tecentriq (atezolizumab) with Zepzelca (lurbinectedin) demonstrated improved overall survival (OS) relative to maintenance therapy with Tecentriq (atezolizumab) monotherapy. However, it was also associated with nearly double the adverse effects.
    * Patients in the trial completed four cycles of induction chemoimmunotherapy with Tecentriq (atezolizumab) combined with carboplatin and etoposide before being randomized into maintenance treatment of either Zepzelca (lurbinectedin) combined with Tecentriq (atezolizumab) or Tecentriq (atezolizumab) monotherapy. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of either 0 or 1 after induction.
    * The median overall survival (OS) for the combination arm was 13.2 months compared to 10.6 months with Tecentriq (atezolizumab) monotherapy (HR = 0.73, p=0.0174).
    * No new safety signals were identified but adverse events were observed at roughly double the incidence of Tecentriq (atezolizumab) alone despite pre-emptive filgrastim (G-CSF).
- Optimal sequencing of chemotherapy and immunotherapy in SCLC has not been studied. Sequential use of immunotherapies is not supported by current evidence.
- Other Neuroendocrine Tumors: Neuroendocrine tumors include a variety of tumor types, such as GI tract bronchopulmonary (including SCLC), thymic, and pancreatic, among others.[3] Although SCLC is classified as a neuroendocrine tumor. Tecentriq (atezolizumab) is coverable only for neuroendocrine that is "managed as SCLC" per guidelines or trial evidence. There is insufficient evidence at this time to conclude safety or efficacy of Tecentriq (atezolizumab) for any other type of neuroendocrine tumor, aside from SCLC.

Guidelines

The NCCN SCLC guidelines include the following:[3]

- For extensive-stage SCLC (ES-SCLC), initial therapy (first-line), preferred options include: Imfinzi (durvalumab) with chemotherapy for induction, followed by maintenance Imfinzi (durvalumab) monotherapy; Tecentriq (atezolizumab) with chemotherapy for induction, followed by maintenance Tecentriq (atezolizumab) monotherapy or in combination with Zepzelca (lurbinectedin).

- For limited-stage SCLC (LS-SCLC), initial therapy (first-line), preferred options include:
    * Primary therapy: surgical resection (preferred, when possible, for stage I-IIA), followed by concurrent chemoradiotherapy (cCRT) with thoracic radiation and platin/etoposide chemotherapy [performance status (PS) and stage dependent].
    * Consolidation therapy: Imfinzi (durvalumab) is a category 1 recommendation in patients with complete response, partial response, or stable disease after primary therapy with cCRT, limited to those with good PS and who are inoperable (or decision made to not pursue surgical resection). Other treatment options are limited to prophylactic cranial irradiation, in specific patients, or surveillance.

Squamous cell carcinoma of the head and neck (SCCHN)

- See HNSCC

Triple-negative breast cancer (TNBC)

Keytruda (pembrolizumab) [1]

- *Advanced (locally advanced or metastatic) triple-negative breast cancer (TNBC)*
    * FDA approval in TNBC is based on an RCT that studied the addition of Keytruda (pembrolizumab) to standard chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) relative to chemotherapy alone (placebo arm) in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting [KEYNOTE-355].[160] In patients with PD-L1 CPS ≥ 10, the addition of Keytruda (pembrolizumab) to standard chemotherapy improved OS, relative to chemotherapy alone.
        ▪ The trial enrolled patients regardless of their PD-L1 status. When it became apparent that there was no PFS difference between the treatment groups, the protocol was amended to change the primary analysis from all comers to the subpopulation with a PD-L1 combined positive score (CPS) ≥ 10.
        ▪ In subjects with a PD-L1 CPS of ≥ 10, the median PFS was 9.7 months and 5.6 months in the Keytruda (pembrolizumab)/chemotherapy and chemotherapy only treatment arms, respectively. The secondary endpoint was PFS in the PD-L1 CPS ≥ 1 subgroup. No difference in PFS was demonstrated in this population.
        ▪ A subsequent analysis reported a statistically significant improvement in median OS for the subpopulation with PD-L1 CPS ≥ 10. The median OS was 23.0 months and 16.1 months in the Keytruda (pembrolizumab)/chemotherapy and chemotherapy only treatment arms, respectively [HR 0.73 (95% CI: 0.55, 0.95)]. There was no difference in OS detected between the Keytruda (pembrolizumab) and placebo groups in the subgroup with PD-L1 CPS ≥ 1 or in the ITT population ('All comers' regardless of PD-L1 status).[161]
    * More recently, Keytruda (pembrolizumab) was studied in a phase 3 RCT for newly diagnosed PD-L1 expressing advanced TNBC in combination with Trodelvy (sacituzumab govitecan-hziy) vs. standard of care cytotoxic chemotherapy plus Keytruda (pembrolizumab) [(n=443); ASCENT04/KEYNOTE-D19].[162]

- All patients were previously untreated in the advanced (inoperable or metastatic) setting ("first-line advanced TNBC") and had PD-L1-positive tumors (CPS≥10).
  - 34% were metastatic at diagnosis.
  - For patients with previously treated TNBC in the non-advanced setting (neoadjuvant/adjuvant therapy), no prior systemic anticancer therapy was allowed within 6 months. At least 52% received previous neoadjuvant/adjuvant therapy (but only 1.3% had prior PD1/PDL1).
- The primary endpoint was progression-free survival (PFS) for both trials.
  - Median PFS was +2.4 months with sacituzumab govitecan versus standard cytotoxic chemotherapy (11.2 vs. 7/8 months), HR 0.65 [0.51, 0.84]. At this time, OS is unknown; however, high rates of crossover from the chemotherapy arm to sacituzumab govitecan limit interpretation of future OS data.
  - In addition, a very low percent of enrolled patients had prior PD1/PDL1 in the neoadjuvant/adjuvant setting. Therefore, generalizability of these results to a US patient population, where use of neoadjuvant/adjuvant pembrolizumab is standard of care, is uncertain.

* NCCN guidelines list the use of Keytruda (pembrolizumab) among recommended therapies for PD-L1-positive advanced TNBC, in combination with chemotherapy or Trodelvy (sacituzumab govitecan-hziy). [3]

- *Neoadjuvant/adjuvant triple-negative breast cancer (TNBC)*

FDA approval of Keytruda (pembrolizumab) in combination with chemotherapy as a neoadjuvant therapy and then continued as a single agent as an adjuvant therapy after surgical excision was based on a double-blind, placebo-controlled RCT that compared pembrolizumab (plus chemotherapy) with placebo (plus chemotherapy) and evaluated event-free survival (EFS) as a surrogate endpoint. [KEYNOTE-522] [1 163] The health benefit of the addition of Keytruda (pembrolizumab) to chemotherapy relative to alternatives (chemotherapy alone) for early TNBC is currently unknown. EFS is not a validated endpoint for predicting an OS benefit.

* Patients had newly diagnosed early-stage, high-risk TNBC who had no prior systemic therapy for their disease and were newly diagnosed. Patients with metastatic disease were excluded from the study.
* Keytruda (pembrolizumab) was given with chemotherapy for eight total 3-week cycles prior to surgical excision and was continued as monotherapy as a single agent for up to 9 additional, 3-week cycles [total of up to one year of Keytruda (pembrolizumab)].
* There was a relative improvement in EFS reported for patients in the Keytruda (pembrolizumab) arm of the study in a preliminary analysis. The OS data was not mature at the time of FDA approval.
* EFS is not a validated endpoint for predicting an OS benefit. Therefore, it is not currently known if Keytruda (pembrolizumab) contributes to a better or a longer life when used in this setting.
  - The FDA allows the use of EFS as a surrogate marker for the approval of drugs in early-stage breast cancer; however, its accuracy in predicting clinically relevant

outcomes is controversial.[164] This scenario is analogous to the use of PFS (another radiographic surrogate endpoint) for drug approvals for advanced breast cancer where several medications were found to improve PFS without confirmation of any clinical benefit in follow up trials.

- A recent publication analyzed EFS as a surrogate for OS in early breast cancer. The analysis included 7 studies for this surrogacy analysis. The authors concluded that although EFS moderately correlated with improved OS in early breast cancer in the neoadjuvant setting, the confidence intervals are wide, and the association was not significant.[164]

* Results from the final OS analysis reported a small difference in 5-year OS [86.6% with Keytruda (pembrolizumab) vs. 81.7% with placebo (p=0.002)].[165]
* The current NCCN guidelines list the use of adjuvant or neoadjuvant Keytruda (pembrolizumab) among potential treatment options for early-stage, high-risk TNBC. [3]

Urothelial Carcinoma (UC)

Background [3 166]

- UC can develop from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra. However, more than 90% of cases originate in the bladder.
- Bladder cancers are divided into three categories: Non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic bladder cancer.
- Most bladder cancer is non-muscle invasive at diagnosis. Approximately 10% to 15% of cases go on to become invasive, locally advanced, or metastatic (incidence estimated at 3.8 cases per 100,000).
- Treatment goals vary based on disease categorization:
  * NMIBC: Reduce recurrences and prevent progression to a more advanced stage.
  * MIBC (T2-4aN0M0): Determine whether bladder should be removed or if it can be preserved without compromising survival, and to determine if systemic therapy is required to improve the likelihood of a cure. Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy is the existing standard of care. Most recently, perioperative "sandwich therapy" with PD-1 (durvalumab) is being used as add-on to standard neoadjuvant cisplatin-based chemotherapy, then continued as adjuvant after cystectomy.
  * Metastatic bladder cancer: Prolong survival and maintain quality of life.
- Muscle-invasive bladder cancer (MIBC) is a more aggressive subset of bladder cancer, managed with surgery and systemic therapy, dependent on staging. Although radical resection for MIBC is done with curative intent, > 50% of patients w/ pathological evidence of cancer involving surrounding tissues or regional lymph nodes with have metastatic recurrence.

Bavencio (avelumab)

- Bavencio (avelumab) is approved in two advanced (locally advanced/metastatic) bladder cancer settings:[144]
  * As a subsequent-line therapy when there has been progression of locally advanced or metastatic disease after front-line platinum-containing chemotherapy.
  * As switch maintenance when there has been no progression of disease after front-line platinum-containing chemotherapy.

- Subsequent-line: The initial FDA approval for Bavencio (avelumab) in bladder cancer was based on a phase 1, non-blinded, single-arm cohort from a larger study in a variety of solid tumors.[167 168]
  * The study evaluated ORR as the primary endpoint. ORR is not a validated surrogate endpoint. It has not been shown to accurately predict any clinically relevant benefit in locally advanced or metastatic bladder cancer.
  * The reported ORR was 14.8% and the duration of response was not estimable.
- To date, Bavencio (avelumab) has only been studied after platinum-based therapy.
- Switch maintenance (first-line after induction chemotherapy): More recently, avelumab (Bavencio) was approved as switch maintenance therapy for locally advanced or metastatic bladder cancer after successful treatment with platinum-containing chemotherapy [JAVELIN Bladder 100 study].[169]
  * Subjects in the trial were initially treated with four to six cycles of a platinum plus gemcitabine. If the tumor decreased in size or did not progress on the initial chemotherapy, subjects were given Bavencio (avelumab) or best supportive care until disease progression.
  * Subjects in the Bavencio (avelumab) treatment arm were noted to have improved survival relative to those who received best supportive care with a median OS of 21.4 months and 14.3 months, respectively.
- Platinum-based chemotherapy is the standard of care for front-line treatment of advanced or metastatic bladder cancer as it is associated with improved OS. Ideal sequencing of therapies in bladder cancer is still under investigation. Because only 43% of subjects in the chemotherapy only arm of the JAVELIN Bladder 100 study received a PD-1 or PD-L1 inhibitor after disease progression, it cannot be determined whether Bavencio (avelumab) maintenance is superior to waiting until disease progression before beginning anti-PD-1/PD-L1 therapy.

Imfinzi (durvalumab)

- *Perioperative (neoadjuvant/adjuvant) for early-stage resectable MIBC*: In the perioperative setting, Imfinzi (durvalumab) has an unclear benefit improvement in pathological complete response (pCR) and event-free survival (EFS) as add-on to standard neoadjuvant chemotherapy, followed by radical cystectomy and adjuvant therapy, as compared to standard of care neoadjuvant chemotherapy, when used for resectable MIBC. Though there was reported improvement in this surrogate endpoint (pCR), there is uncertainty in the quality of the trial data, and it is still not known whether this will translate to a better or a longer life for the patient. Additional information demonstrating improvement in a clinically relevant outcome is needed. Although the safety surrounding Imfinzi (durvalumab) is generally acceptable in the advanced or metastatic disease setting, this may not hold in earlier disease settings where no proven benefit has been demonstrated. Specifically:
  * Imfinzi (durvalumab) received FDA approval in the perioperative setting based on meeting its co-primary endpoints of pathologic complete response (pCR) and event free survival (EFS), surrogate endpoints with unknown clinical value, in one low confidence Phase 3 open-label trial [NIAGARA] in patients with resectable MIBC (n=1063).[170]
    - The trial enrolled adults with resectable muscle-invasive urothelial carcinoma of the bladder stage T2-T4aN0-1M0 with transitional and mixed transitional cell histology
    - Subjects had to be eligible for cisplatin-based chemotherapy (CrCl ≥ 40) and

planning to undergo a radical cystectomy.

- No prior systemic chemotherapy or immunotherapy for treatment of MIBC was allowed. Exception: prior Bacillus-Calmette Guerin (BCG).
- Subjects were randomized to one of two arms:
  - Neoadjuvant durvalumab 1500 mg + gemcitabine-cisplatin every 3 weeks for 4 cycles, followed by cystectomy, then adjuvant durvalumab 1500 mg every 4 weeks for up to 8 cycles.
  - Neoadjuvant gemcitabine-cisplatin every 3 weeks for 4 cycles, followed by cystectomy.
- There was a marginal response rate in a not clinically meaningful endpoint. Specifically, 8% difference in pCR vs. SOC neoadjuvant chemotherapy; it was initially found to be a non-significant finding due to missing data but was found to be statistically significant (9.8%, p=0.001) upon re-analysis. EFS and overall survival (OS) results are not yet mature.

* Limitations of the available data include unknown health outcome at this time, lack of blinding in the trial introduces bias, and unclear integrity of the data. In addition, there is no comparison of this regimen to other available PD1/PD-L1 therapies for resectable MIBC, such as adjuvant Opdivo (nivolumab).

- *Advanced (locally advanced or metastatic) UC*: *See Investigational Uses*.

Keytruda (pembrolizumab)

- *Advanced disease (locally advanced or metastatic), first-line therapy (cisplatin ineligible) - as Monotherapy*: A single-arm, open-label trial [KEYNOTE-052] evaluated Keytruda (pembrolizumab) in subjects with locally advanced or metastatic urothelial carcinoma who were ineligible for treatment with a cisplatin-based regimen. Approval was based on tumor response. [1 171]
  * ORR was 29%, with 7% of the responses considered complete.
  * Response rate was higher in patients with a combined positive score (CPS) ≥ 10%.[171]
  * There is no evidence that Keytruda (pembrolizumab) improves any clinically relevant outcome in this population. Although a median OS was reported, this information is of little relevance as there was no comparator group to allow any conclusion of a health benefit relative any other therapy.
- *Advanced disease (locally advanced or metastatic), first-line therapy - In combination with Padcev (enfortumab vedotin):* Padcev (enfortumab vedotin) was also evaluated as a front-line therapy for locally advanced or metastatic UC in combination with Keytruda (pembrolizumab) [Study EV-302/KEYNOTE-A39]. The evidence is based on a large (N=886), open-label RCT that compared this combination with a platinum-based chemotherapy regimen.[172 173]
  * Patients enrolled in the study had no prior therapy for advanced disease and were eligible to receive platinum-based chemotherapy. Prior neoadjuvant or adjuvant chemotherapy was allowed if there had been no disease recurrence within 12 months after its completion.
  * Padcev (enfortumab vedotin) was given in 21-day cycles until disease progression. Keytruda (pembrolizumab) was given in 21-day cycles until disease progression or for a

maximum of 35 cycles (2 years).

* Ninety-five percent of the population had metastatic disease. Approximately 27% had upper tract UC while the remaining 73% had lower tract UC.
* The median OS was 33.8 months and 15.9 months in the Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) and chemotherapy treatment arms, respectively.
* The combination of Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) has not been compared to front-line platinum-based chemotherapy followed by maintenance therapy with a PD-1 inhibitor, such as gemcitabine/cisplatin followed by Bavencio (avelumab), a combination which has also been shown to improve median OS relative to platinum-based chemotherapy alone. Therefore, it is not known whether Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) is safer or more effective than the existing standard of care treatment of platinum-based chemotherapy followed by a PD-1 inhibitor.

- *Advanced disease (locally advanced or metastatic) - Subsequent therapy:* A randomized, active-controlled, open-label trial [KEYNOTE-045] evaluated Keytruda (pembrolizumab) versus investigator's choice of single-agent chemotherapy in subjects with locally advanced or metastatic urothelial carcinoma who had disease progression on or after platinum-containing chemotherapy. [1 174]
  * Fifteen percent of subjects enrolled in the trial had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy.
  * The median OS was statistically greater with pembrolizumab vs. chemotherapy (10.3 months versus 7.4 months, respectively).
- *For BCG-unresponsive non-muscle invasive bladder cancer (NMIBC):* A small, single-arm, non-blinded study evaluated Keytruda (pembrolizumab) in subjects with high-risk, recurrent or persistent NMIBC that was unresponsive to adequate treatment with Bacillus Calmette-Guerin (BCG) therapy who were either not eligible for a cystectomy (bladder removal), or did not elect to undergo cystectomy [KEYNOTE-057]. [1 175]
  * All patients had NMIBC with carcinoma *in situ* [stage Tis (63%), Ta (25%), or T1 (13%)].
  * Adequate BCG therapy was defined as having at least 5 of 6 induction intravesicular instillations AND either 2 of 3 maintenance instillations, or at least 2 of 6 doses of a second induction course. The median number of BCG instillations in the trial was 12.
  * Complete response (CR) was the study endpoint and was achieved in 41% of patients. The median duration of response was 16.2 months. Overall response rate (ORR) is an unvalidated surrogate endpoint that has not been shown to accurately predict clinical outcomes.

Opdivo (nivolumab)

- *Advanced (locally advanced or metastatic) UC, subsequent-line setting:* Opdivo (nivolumab) received FDA Accelerated approval for unresectable or metastatic bladder cancer based on a single-arm, observational trial that evaluated tumor objective response rates (ORR) [CHECKMATE-275].[25 176] Clinical benefit has not been established.

    * Subjects had disease that progressed during or following a platinum-containing chemotherapy regimen, or progressive disease within 12 months of treatment with a platinum-containing chemotherapy regimen administered in the adjuvant (after surgical resection) or neoadjuvant (prior to surgical resection) settings.
    * ORR was 19.6%, of which the vast majority (17%) were partial responders.
    * ORR has not been shown to accurately predict clinically relevant outcomes. Additional confirmatory studies are needed to establish a clinical benefit.

- *Advanced (unresectable locally advanced or metastatic) UC, first-line setting:* Opdivo (nivolumab) received FDA approval as a first-line therapy for unresectable locally advanced or metastatic bladder cancer when initiated in combination with cisplatin plus gemcitabine and then continued as monotherapy. Approval was based on a randomized, open-label trial [CheckMate-901] that compared this combination with cisplatin plus gemcitabine alone.[177]
    * Subjects were previously untreated in the advanced treatment setting; however, prior neoadjuvant or adjuvant chemotherapy was allowed as long as recurrence took place 12 or more months after completion of therapy. Patients who were not eligible for cisplatin-based chemotherapy were excluded from the study.
    * Opdivo (nivolumab) was initiated in combination with cisplatin plus gemcitabine which were given for up to six cycles, after which Opdivo (nivolumab) was continued every four weeks as monotherapy until disease progression, or for up to two years maximum from the first dose.
    * The study demonstrated a survival advantage with median OS of 21.7 months and 18.9 months in the Opdivo (nivolumab) and chemotherapy only treatment arms, respectively (HR 0.78 [95% CI: 0.63, 0.96]; p-value = 0.017).
- *Adjuvant therapy for early-stage resected MIUC*: Opdivo (nivolumab) received FDA approval as an adjuvant therapy (after complete surgical resection) for patients with early-stage muscle-invasive urothelial carcinoma (MIUC) [also known as muscle-invasive bladder cancer (MIBC)] with good performance status and a high risk of disease recurrence. Approval was based on a randomized, double-blind, placebo-controlled trial [CHECKMATE-274] that evaluated disease-free survival (DFS) as the primary endpoint (n=709).[178]
    * The population was primarily White, male, and with a median age of 66 years (generally younger than a typical patient which has a median age of 73 years at diagnosis). Forty percent had a PD-L1 > 1%.
    * Approximately 80% of patients had tumors originating in the bladder, with the remaining 20% originating in the renal pelvis or ureter.
    * Approximately 44% of subjects had prior neoadjuvant cisplatin-based chemotherapy.
    * Patients were randomized to either Opdivo (nivolumab) 240 mg or to placebo IV every 2 weeks for up to 1 year of adjuvant treatment.
    * The DFS was 20.8 months and 10.8 months in the Opdivo (nivolumab) and placebo arms, respectively (HR 0.70; [95% CI: 0.57, 0.86]; p = 0.0008).
    * DFS has not been shown to accurately predict improvement in any clinically relevant outcome in early-stage MIUC. It is not known if adjuvant therapy will ultimately improve overall survival (OS), the outcome of interest. In addition, the ideal sequencing of agents in this clinical setting has not been determined.

    - Results at 3 years were maintained, with a DFS of 22 months with nivolumab and 10.9 months with placebo.[179] Interim report of overall survival (74% mature) was 69.5 months (58.1, NE) with nivolumab and 50.1 months (38.2, NE) with placebo [HR 0.76, 95% CI (0.61, 0.96)].

Guidelines

The NCCN guideline lists the use of PD-1/PD-L1 immunotherapy for UC as follows:[3]

- *Advanced (locally advanced or metastatic disease):*
    - *Front-line:*
        - Category 1 recommendations for cisplatin-eligible patients include cisplatin plus gemcitabine followed by Bavencio (avelumab) maintenance, Opdivo (nivolumab) plus gemcitabine/cisplatin followed by Opdivo (nivolumab) maintenance, Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab), and dose-dense methotrexate/vinblastine/doxorubicin/cisplatin followed by Bavencio (avelumab) maintenance therapy.
        - Both Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab), and gemcitabine plus carboplatin followed by Bavencio (avelumab) maintenance therapy are also listed as category 1 recommendations for cisplatin-ineligible patients.
        - Of note - Ineligibility for cisplatin in clinical trials was defined as CrCl 30 to 60 mL/min, poor kidney function (CrCl < 60 mL/min), poor performance status (≥2), significant hearing loss (≥ 25 dB), grade 2-4 peripheral neuropathy, heart failure, other comorbidities.[171] Ineligibility for cisplatin is mentioned in NCCN as renal impairment (CrCl < 60 mL/minute) or comorbidities. Ineligibility for any platinum-containing chemotherapy is not explicitly defined by the clinical trials or NCCN. However, NCCN notes that carboplatin can be substituted for cisplatin for patients with a CrCl < 60 mL/min. Overall comorbidities should be considered for platinum eligibility (such as cardiac disease, advanced age, performance status, or "if the patient is unfit").
    - *Second- and subsequent-line:* Keytruda (pembrolizumab) after initial therapy with a platinum-containing regimen when used as monotherapy [preferred, category 1]; and Padcev (enfortumab vedotin) monotherapy is listed among several category 2A recommendations. Bavencio (avelumab) and Opdivo (nivolumab) are lower level (Cat 2B) options after prior chemotherapy.
- *NMIBC, BCG-unresponsive*: In patients with NMIBC, the NCCN lists Keytruda (pembrolizumab) as a recommended option for recurrent or persistent disease unresponsive to BCG and the patient is ineligible for a cystectomy or chooses not to have one.
- *Adjuvant therapy for newly diagnosed MIUC with a high risk of recurrence:* Opdivo (nivolumab), among potential therapy options.
- *Resectable MIBC* (category 2A, unless noted)
    - Primary treatment, Stage II/IIIA: neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy, based on evidence for OS.
    - Perioperative "sandwich therapy" preferred [Cat 1] with Imfinzi (durvalumab)/gemcitabine/cisplatin neoadjuvant prior to cystectomy, then Imfinzi

(durvalumab) after cystectomy.

* Adjuvant therapy based on pathological risk and prior therapy [if not using sandwich therapy]: Adjuvant cisplatin-based chemotherapy [preferred for some staging]. Adjuvant Opdivo (nivolumab) monotherapy may be considered.

Reauthorization Criteria

- When coverage criteria are met, PD-1 and PD-L1 inhibitor therapy is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Alternatively, if the request is for reauthorization after neoadjuvant treatment, the patient must have completed surgical resection +/- adjuvant radiation based on the specified disease specific coverage criteria, as well as standard follow up radiologic assessment.
  * The standard of care for evaluation of response to cancer immunotherapy, such as PD-1 and PD-L1 inhibitor therapy, is use of the iRECIST criteria for assessment of tumor burden.[180]
  * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions.[181]
    - Quantitative measurements for target lesions (tumor size and % change)
    - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
  * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, PD-1 and PD-L1 inhibitor therapy will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
  * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to PD-1 and PD-L1 inhibitor therapy, including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
  * If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional doses of PD-1 and PD-L1 inhibitor therapy is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Not Medically Necessary Uses

Bavencio (avelumab)

- See "Renal Cell Carcinoma – Bavencio (avelumab), First-line"

Libtayo (cemiplimab)

- Libtayo (cemiplimab-rwlc) was studied in recurrent cervical cancer where it was found to improve overall survival relative to single-agent chemotherapy. The manufacturer withdrew its application to expand use of Libtayo (cemiplimab-rwlc) in this population. Keytruda

(pembrolizumab) is already approved for use in cervical cancer.[182]

Tecentriq (atezolizumab)

- See "Non-small cell lung cancer (NSCLC) – Tecentriq (atezolizumab)"

Tevimbra (tislelizumab)

- See "Esophageal and GEJ Cancer [including Esophageal adenocarcinoma, Esophageal squamous cell carcinoma (ESCC)] - Tevimbra (tislelizumab)"

Investigational Uses

Bavencio (avelumab)

- Bavencio (avelumab) is actively being studied to determine if there is benefit in treating other types of cancers including gastric or gastroesophageal junction (GEJ) adenocarcinoma (including esophageal) and NSCLC.[105] To date, there are no studies establishing a clinical benefit in these settings.
- There is an early phase, published study evaluating Bavencio (avelumab) in NSCLC. However, larger, well-controlled studies are necessary to establish the safety and effectiveness of Bavencio (avelumab) in this setting.[183]

Imfinzi (durvalumab)

- *Urothelial carcinoma (UC, bladder cancer) Advanced (unresectable locally advanced or metastatic):*
  * *Subsequent-line setting:* Imfinzi (durvalumab) initially received Accelerated approval as a subsequent therapy (after disease progression on a cisplatin-based chemotherapy regimen) for unresectable or metastatic bladder cancer based on tumor response rate in a non-comparative (single-arm), observational study.
  * *First-line setting:* A subsequent phase 3 trial (DANUBE study) intended to confirm the efficacy of Imfinzi (durvalumab) in the unresectable, locally advanced or metastatic bladder cancer setting failed to demonstrate an OS advantage over standard chemotherapy. Based on this failed confirmatory trial the manufacturer voluntarily withdrew the bladder cancer indication. Because there is no proven net health benefit relative to the standard of care, the use of Imfinzi (durvalumab) for advanced bladder cancer is considered investigational.[184]
- *Head and neck squamous cell cancer (HNSCC):* Imfinzi (durvalumab) failed to show a benefit relative to standard of care for HNSCC in two different settings: a phase 3 trial (EAGLE study) in as a front-line therapy for PD-L1-postive advanced HNSCC [185] and in an open label phase 2/3 trial (NRG-HN004) as concurrent and adjuvant therapy for locoregionally advanced HNSCC, in patients with a contraindication to cisplatin.[186] Because there is no proven net health benefit relative to the standard of care, the use of Imfinzi (durvalumab) for HNSCC is considered investigational.
- *Cervical cancer*: A phase 3, double-blind RCT [CALLA study] compared Imfinzi (durvalumab) with placebo in patients with untreated, locally advanced cervical cancer.[187] Therapy was initiated with chemoradiotherapy, and then continued as maintenance after completion of the chemoradiotherapy. The primary endpoint was progression-free survival (PFS). However, there was no difference in PFS detected between the two treatment groups. There were five treatment-related deaths in the Imfinzi (durvalumab) treatment arm and one treatment-related death in the

placebo arm.

- *Hepatocellular carcinoma –for transarterial chemoembolization (TACE):* There is interest in the use of PD-1/PD-L1 therapy as follow-on therapy after TACE in patients with unresectable HCC that is amenable to chemoembolization (TACE). However, there is insufficient evidence to establish the superiority of the combination therapy with a PD-1/PD-L1 as compared to bevacizumab monotherapy. A phase 3 trial [EMERALD-1] studied Imfinzi (durvalumab)/bevacizumab vs. Imfinzi (durvalumab) monotherapy. [188] There was an improvement in PFS with the combination therapy, as compared to Imfinzi (durvalumab) monotherapy. However, the PFS with Imfinzi (durvalumab) monotherapy was numerically similar to PFS with placebo control arm. Therefore, the value of Imfinzi (durvalumab) in the combination regimen, relative to bevacizumab alone, is unclear and the use of Imfinzi (durvalumab) for TACE is considered investigational.
- There are also ongoing studies designed to evaluate Imfinzi (durvalumab) in other solid tumors.[105]

Jemperli (dostarlimab)

- Jemperli (dostarlimab) is actively being studied to determine if there is benefit in treating other types of cancers including non-small cell lung cancer and malignant melanoma.[105] To date, studies are preliminary and ongoing and the risk versus potential for clinical benefit remains under investigation.
- *dMMR Solid Tumors [other than endometrial carcinoma (EC)]* [189]
    - Jemperli (dostarlimab) is FDA approved as a treatment option for patients with any progressive dMMR solid tumor ("tumor agnostic") when no satisfactory treatment alternatives are available.
    - The Accelerated approval of Jemperli (dostarlimab) for all dMMR solid tumors was based on preliminary results from a 'basket trial' [GARNET] which included patients with any type of solid tumor as long as it was dMMR.
        - Fourteen types of solid tumors were represented in the non-EC cohort of 106 patients. Ten tumor types were represented by only one or two patients.
        - The sample size for most tumors was very small with most tumor types being represented in only one or two patients. Colon cancer was the most common tumor type (n=69), followed small intestine (n=11), gastric (n=6), and pancreatic (n=4). Additionally, the population did not include all types of solid tumors.
        - Subjects enrolled in the trial had advanced solid tumors, at least one prior chemotherapy regimen, and no acceptable treatment alternatives.
    - Although reported tumor response rates appear promising, it is not known if Jemperli (dostarlimab) improves tumor response in all dMMR solid tumors or positively impacts any clinically relevant outcome. Confirmatory studies are necessary to establish clinical benefit. Therefore, the use of Jemperli (dostarlimab) for dMMR tumors (other than EC) is considered investigational.

Keytruda (pembrolizumab)

- Keytruda (pembrolizumab) is actively being studied to determine if there is benefit in treating other types of cancers including multiple myeloma (MM), and ovarian cancer. To date, studies are preliminary and ongoing and the risk versus potential for clinical benefit remains under

investigation.[105]

- *Vulvar Cancer*
  - The evidence for Keytruda (pembrolizumab) in vulvar cancer is limited to an ongoing, single-arm, basket study (KEYNOTE-158) in multiple types of solid tumors. The cohort of patients with metastatic and/or unresectable vulvar squamous cell carcinoma consisted of 101 patients. The tumor response rate for this cohort was 10.9% with only 1 complete response. There is no comparative evidence or outcomes data available in this population.[190]
  - The NCCN vulvar cancer guideline lists Keytruda (pembrolizumab) as a potential biomarker-directed systemic therapy for recurrent or metastatic vulvar cancer for tumors that are TMB-H, MSI-H/dMMR, or PD-L1 (CPS) ≥ 1. [3]
- *Hepatocellular carcinoma –for transarterial chemoembolization (TACE):* There is interest in the use of PD-1/PD-L1 therapy as follow-on therapy after TACE in patients with unresectable HCC that is amenable to chemoembolization (TACE). However, there is insufficient evidence to establish the efficacy of Keytruda (pembrolizumab) in this setting. A phase 3 trial [LEAP-012] studied Keytruda (pembrolizumab)/Lenvima (lenvatinib) vs. placebo.[191] There was an improvement in PFS with the combination therapy, as compared to placebo. However, the OS was not met. Therefore, the use of Keytruda (pembrolizumab) for TACE is considered investigational.
- *MSI-H Tumors (other than CRC and endometrial carcinoma)*
  - Keytruda (pembrolizumab) is FDA approved as a treatment option for patients with any progressive MSI-H/dMMR solid tumor ("tumor agnostic") when no satisfactory treatment alternatives are available.[1] However, currently there is insufficient evidence to establish the efficacy or safety of Keytruda (pembrolizumab) in patients with other MSI-H/dMMR tumors.[1 192 193]
  - The Accelerated approval of Keytruda (pembrolizumab) for MSI-H or dMMR tumors was based on preliminary tumor response [overall response rate (ORR)] and duration of response (DOR) data from a "basket trial" pooled analysis of 149 patients across five different early phase, open-label trials (90 patients with CRC and 59 non-CRC patients). [192 194]
  - Subjects enrolled in the trial had advanced solid tumors and at least one prior chemotherapy regimen.
    - This tumor agnostic approval includes use in many cancer types that were either not tested in the "basket trial" or were only tested in very low numbers (n < 14) of patients.
    - Fourteen types of solid tumors were represented in the non-CRC cohort of 59 patients. Nine tumor types were represented by only one or two patients.

      No patients with uterine cancer (leiomyosarcoma) were represented in the sample.
  - Subsequently, one non-randomized, single-arm Phase 2 trial evaluated Keytruda (pembrolizumab) for non-CRC MSI-H/dMMR solid tumors.
    - The trial enrolled 233 patients with 27 tumor types.
    - Similar to the basket trial above, ORR was used as the primary endpoint.
    - An ORR of 34% was reported. However, health outcomes are unknown.

    - Endometrial cancer was the most common tumor type (n=49), followed by gastric (n=24), cholangiocarcinoma (n=22), and pancreatic (n=22). However, insufficient details were reported to establish if the endometrial tumors were sufficiently treated with standard therapies ("treatment alternatives").
  * Although reported tumor response rates appear promising, it is not known if Keytruda (pembrolizumab) improves tumor response in all MSI-H/dMMR solid tumors or positively impacts any clinically relevant outcome. Confirmatory studies are necessary to establish clinical benefit. Therefore, the use of Keytruda (pembrolizumab) for MSI-H/dMMR tumors (other than CRC and endometrial carcinoma, or as detailed in the coverage criteria) is considered investigational.

- *Ovarian cancer*
  * The evidence for the use of Keytruda (pembrolizumab) is limited to a non-randomized, non-comparative phase 2 trial for advanced recurrent ovarian cancer [KEYNOTE-100].[195] Although this initial evidence of overall response rate (ORR) is promising, along with other posters reporting single-arm data, there is insufficient data at this time to establish an improvement in clinically meaningful endpoints in ovarian cancer such as survival or quality of life. Therefore, the use of Keytruda (pembrolizumab) for ovarian cancer is considered investigational.
- *Neuroendocrine tumors (not covered in other indications, such as SCLC)*
  * The evidence for Keytruda (pembrolizumab) for locally advanced or metastatic NET is based on cohorts of patients from a single-arm, open-label trials [KEYNOTE-028, KEYNOTE-0158] that evaluated tumor response rates as an endpoint.[196 197] In previously-treated PD-L1 expressing well-differentiated or moderately-differentiated NETs [carcinoid (n=25) and pancreatic neuroendocrine tumors (n=16)], ORR was 12% and 6.3%. In a larger trial of previously-treated NETs of the lung, appendix, small intestine, colon, rectum, or pancreas (n=107). Keytruda (pembrolizumab) was ineffective with ORR of 3.7%
  * In one phase 2 pilot study of extrapulmonary poorly differentiated neuroendocrine carcinomas (EP-PDNECs), Keytruda (pembrolizumab) was ineffective, either as monotherapy (n=14) or in combination with chemotherapy (n=22). ORR was low in both groups (7% and 5%, respectively).[198]
- *Prostate cancer:* There is interest in the use of Keytruda (pembrolizumab) for prostate cancer. Trials of Keytruda (pembrolizumab) as add-on therapy for prostate cancer (various settings) have failed to demonstrate efficacy [KEYNOTE-921, KEYNOTE-991].[199 200]
- *Sarcoma (including STS, osteosarcoma)*
  * There is interest in the use of Keytruda (pembrolizumab) for various soft tissue sarcomas (STS) including liposarcoma, as well as osteosarcoma.
  * Keytruda (pembrolizumab) is included in the NCCN STS guidelines as an option for salvage therapy for certain types of STS, such as undifferentiated pleomorphic sarcoma (UPS).[3] However, the recommendation is based on one phase 2 trial in STS and osteosarcoma which did not meet the primary endpoint.[201]
  * A second trial in osteosarcoma also did not meet the primary endpoint.[202] Additional trials are ongoing.[105] Therefore, the use of Keytruda (pembrolizumab) for STS and

osteosarcoma is considered investigational.

- *Small cell lung cancer (SCLC)*
  - Keytruda (pembrolizumab) received Accelerated approval for metastatic SCLC, based on cohort of patients from single-arm, open-label trials that evaluated tumor response rates as an endpoint with pretreated metastatic (after a platinum-based chemotherapy and at least one other prior systemic regimen).[203]
  - However, subsequent trials [KEYNOTE-604] failed to demonstrate a proven health benefit and the company withdrew the FDA indication.[204] Therefore, the use of Keytruda (pembrolizumab) for SCLC is considered investigational at this time.
- *Tumor mutational burden-high (TMB-H) solid tumors*
  - Keytruda (pembrolizumab) received Accelerated FDA approval in patients with solid tumors that have high tumor mutational burden (TMB-H, based on genetic testing) and who have no remaining satisfactory treatment options, based on a 'basket trial' in a small number of patients with tumors that were found to be TMB-H.[1 205] Accelerated approval means that no clinical benefit has yet been demonstrated. The available evidence is of very poor quality. Additional clinical trials are needed to establish clinical benefit.
    - Patients were enrolled based on having TMB-H solid tumors. Inclusion was independent of tumor type or site. Pembrolizumab was given and tumor size monitored using x-rays, for overall response rate (ORR).
    - Small sample size, heterogeneity of tumor types, and lack of clinical outcomes limit interpretation of the data for estimation of clinical benefit.
      - A very small number of types of tumors were represented, only nine at the time of the initial data cut. ORR varied widely across tumor types with some types showing no response (e.g., salivary, thyroid, and mesothelioma).
      - ORR has not been shown to accurately predict clinical benefit such as improved survival, quality of life, or symptom control.
    - A high tumor mutational burden (TMB-H) was defined as having 10 or more mutations per megabase (mut/Mb) as determined by the FoundationOne CDx panel. The selection of 10 mut/Mb as a cutoff for administration of Keytruda (pembrolizumab) is arbitrary. Use of this definition is not associated with improvement in any clinically important outcome. Furthermore, this definition is based specifically on the FoundationOne CDx genetic test. Since there is no current standard for determining TMB-high status across different genetic tests, selection of appropriate patients may be confounded.
    - TMB is heterogeneous both within and across different tumor types. The extrapolation of this evidence from this small sample of tumors across all tumor types is not a valid predictor of potential for benefit.
  - The NCCN compendium generally aligns with the FDA label and recommends Keytruda (pembrolizumab) in TMB-high tumors when there are no other treatment options.[153] However, for the reasons stated above, the use of Keytruda (pembrolizumab) in TMB-H tumors is considered investigational.

Libtayo (cemiplimab)

- There is the potential for off-label use of Libtayo (cemiplimab-rwlc) based on its mechanism of action (immune checkpoint inhibition).
- There are currently no published clinical trials that evaluate Libtayo (cemiplimab-rwlc) outside of the settings described above.

Loqtorzi (toripalimab)

- Loqtorzi (toripalimab) is currently being studied in several other types of cancer including other head and neck cancers, such as squamous cell carcinoma of the head and neck (SCCHN), and small cell lung cancer (SCLC).[205] However, to date, Loqtorzi (toripalimab) has not been shown to be an effective therapy for any other type of cancer.

Opdivo (nivolumab)

- *Colorectal cancer (CRC), resectable:* Use of Opdivo (nivolumab)/ Yervoy (ipilimumab) as neoadjuvant therapy for resectable MSI-H/dMMR colorectal cancer (CRC) is considered investigational. Although there is interest in the use of neoadjuvant ipilimumab/nivolumab for resectable dMMR CRC, the evidence is limited to a single-arm, phase 2 trial (n=115) with interim 3-year disease-free survival data. Given the lack of comparator, interpretation of the disease-free survival endpoint is difficult. Benefit versus existing therapies (chemotherapy or no neoadjuvant therapy) is unknown at this time. Although the NCCN recommends the use of Yervoy (ipilimumab)/Opdivo (nivolumab) for "Clinical T4b or bulky nodal disease" as neoadjuvant therapy, the recommendation is one of three possible options: "Consider neoadjuvant therapy: Immunotherapy (preferred) OR chemotherapy (FOLFOX or CAPEOX) [both Category 2A]," or no neoadjuvant therapy, such that the use of any neoadjuvant therapy is not clearly defined.[206] In addition, the recommendation for neoadjuvant immunotherapy is not specific to ipilimumab/nivolumab. The footnote on the recommendation lists seven different PD-1/PD-L1 options, noting that combination PD-L1/CTLA4 therapy is associated with greater toxicity. For these reasons, the use of Yervoy (ipilimumab)/Opdivo (nivolumab) is considered investigational. Additional trials are ongoing.[207]
- *Hepatocellular carcinoma (HCC), with sorafenib:* A confirmatory phase 3 trial (CheckMate 459) comparing Opdivo (nivolumab) with Nexavar (sorafenib) as a front-line therapy for advanced HCC failed to show any overall survival advantage with Opdivo (nivolumab). Coverage is only provided for Opdivo (nivolumab) when it is given in combination with Yervoy (ipilimumab), as detailed in the coverage criteria.[208]
- *Glioblastoma:* Two open-label, phase 3 studies [CHECKMATE-489 (NCT02617589), NRG-BN007 (NCT04396860)] compared Opdivo (nivolumab) +/- Yervoy (ipilimumab) plus radiotherapy with temozolomide plus radiotherapy in patients with newly diagnosed glioblastoma multiforme. Temozolomide plus radiotherapy, the standard of care, demonstrated superior overall survival relative to Opdivo (nivolumab) plus radiotherapy.[209 210]
- *Melanoma, adjuvant Opdivo (nivolumab) plus Yervoy (ipilimumab):* A phase 3, double-blind RCT [CheckMate 915] compared Opdivo (nivolumab) plus Yervoy (ipilimumab) with Opdivo (nivolumab) plus placebo as an adjuvant therapy for up to one year after resection (with no evidence of residual disease) of their stage IIIB-D or IV cutaneous melanoma. The trial found that the addition of Yervoy (ipilimumab) to adjuvant Opdivo (nivolumab) did not improve relapse-free survival rates; however, the risk of grade 3 or 4 adverse effects (AEs) and discontinuation of therapy due to AEs was greater.[211]

- *Neuroendocrine tumors (not covered in other indications, such as SCLC)*
    * The evidence for Opdivo (nivolumab)/Yervoy (ipilimumab) for previously-treated, locally advanced or metastatic NET is based on various cohorts of patients from a single-arm, open-label basket trial [SWOG S1609 DART] that evaluated tumor response rates as an endpoint.
        - Neuroendocrine cohort (n=19) [unknown primary (21%), rectum, GEJ, cervix, and pancreas (11%)]. All were unfavorable biology, with a median Ki-67 of 80%. Reported ORR 26%.[212]
        - Nonpancreatic neuroendocrine cohort (n=32) [GI (47%), lung (19%)]. Reported ORR 25% [for high grade, ORR 44%].[213]
        - Adrenocortical carcinoma cohort (n=21) – Reported ORR 14%.[214]
    * For treatment-naïve advanced high-grade (Grade 3) digestive neuroendocrine neoplasms (NENs), the evidence is limited to one phase 2 single-arm trial [NICE-NEC] of Opdivo (nivolumab) plus carboplatin/etoposide (n=37) [pancreas (38%), stomach (16%), colon (11%)]. Two-thirds (67.6%) were poorly differentiated carcinomas (NECs) and/or had a Ki67 index >55%. The primary endpoint, 12-month OS, was not met.[215]
    * Given the lack of comparator and small sample size of various cohorts, evidence for efficacy remains insufficient. Additional trials are ongoing.
- *RCC, Adjuvant for Resected*: Two trials [CheckMate 914, PROSPER ECOG-ACRIN EA8143] of Opdivo (nivolumab) as an adjuvant therapy for patients with resected RCC with a high risk of recurrence failed to meet the primary endpoint of disease-free survival (DFS) or recurrence free survival (RFS).[216 217]
- *Sarcoma (including osteosarcoma):* The evidence for various soft tissue sarcomas (STS) including Ewing sarcoma, spindle cell sarcoma, and osteosarcoma, is limited to a single open-label, non-comparative phase 2 trial of Opdivo (nivolumab) with or without Yervoy (ipilimumab). The primary endpoint (ORR) was not met in the nivolumab monotherapy arm. Additional trials are ongoing with combination therapy.[105 218]
- *Small cell lung cancer (SCLC)*
    * Opdivo (nivolumab) received Accelerated approval for in metastatic SCLC, based on a small, single-arm, open label study that evaluated tumor response rate in a cohort of patients with pretreated metastatic SCLC [CHECKMATE-032].[219]
    * However, subsequent trials [CHECKMATE -451 and -331) failed to demonstrate a proven health benefit and the company withdrew the FDA indication.[220] Therefore, the use of Opdivo (nivolumab) for SCLC is considered investigational at this time.
- *TMB-H solid tumors, including pancreatic cancer*: The evidence for various TMB-H advanced solid tumors is limited to one small phase 2 basket trial [CheckMate 848] that investigated ORR with the use of Opdivo (nivolumab) plus Yervoy (ipilimumab) versus Opdivo (nivolumab). [221] ORR is a preliminary endpoint. Additional trials are needed to establish efficacy in this tumor type.
- *Other cancers*: PD-1 inhibitor medications, including Opdivo (nivolumab), are actively being studied in many different cancers. Ongoing areas of research include, but are not limited to, use in multiple myeloma, ovarian cancer, pancreatic (neoadjuvant), and DLBCL (other than listed in the coverage criteria).[222-224] Whether Opdivo (nivolumab) provides any clinical benefit in these settings is still being investigated. The evidence is limited to early phase trials. Larger trials are needed to

establish the safety and efficacy of Opdivo (nivolumab) in these conditions.

- Sequential therapy: The study of Opdivo (nivolumab) in combination and in sequence with other immunotherapies and targeted therapies is underway. Early results appear promising; however, the optimal sequencing, patient selection, and overall benefit of combination therapies has not yet been determined. [105]
  * There is an ongoing study of Opdivo (nivolumab) given sequentially with Yervoy (ipilimumab) in patients with advanced or metastatic melanoma [CHECKMATE-064 trial]. [225] The most recent trial result was from 2016.
  * There is a phase 2 trial in progress that combines Sutent (sunitinib) plus Opdivo (nivolumab) in KIT-mutated advanced melanoma.

Opdualag (nivolumab-relatlimab-rmbw)

- There is interest in using Opdualag (nivolumab-relatlimab-rmbw) in other tumors that express LAG-3; however, there are currently no well-controlled, published trials supporting its safety and efficacy in other cancers at this time.[105]
- For discussion of sequential use: see "Melanoma – Opdualag (nivolumab-relatlimab-rmbw)"
- There is no evidence to support the use of Opdualag (nivolumab-relatlimab-rmbw) in combination with any other melanoma therapy.

Tecentriq (atezolizumab)

Triple Negative Breast Cancer (TNBC)

Front-line advanced [locally advanced (unresectable) or metastatic] treatment setting: The FDA indication for use as a front-line therapy for locally advanced or metastatic, PD-L1-positive, triple negative breast cancer (TNBC) when used in combination with Abraxane (nab-paclitaxel) was approved on a modest improvement in in a surrogate endpoint (PFS) [IMpassion130 study] and later withdrawn after a confirmatory trial failed to demonstrate any clinical benefit in this treatment setting (no proven overall survival benefit). While post-hoc subgroup analyses suggested a potential benefit in the PD-L1 positive population, this result was not statistically significant by the predefined endpoints in the trial (using a priori study criteria).[226 227] As a result, the coverage of Tecentriq (atezolizumab) for TNBC is considered investigational. Further data in the metastatic setting from the IMpassion-132 trial has been delayed after a major expansion in the population was announced.[228]

- *Neoadjuvant TNBC:*
  * The IMpassion-031 trial found an improvement in of pathological complete response (cPR) rates, the co-primary endpoint, associated with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy [Abraxane (nab-paclitaxel)] as compared to use of Abraxane (nab-paclitaxel) alone in patients with early TNBC (58% vs. 41%, respectively). [229]
  * Subsequently, the NeoTRIPaPDL1 trial found no difference in the secondary pathological complete response (cPR) associated with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy [carboplatin/Abraxane (nab-paclitaxel)] versus chemotherapy alone. [230]

Other breast cancer

- One Phase 3 trial found no benefit with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy for HER2-positive BC (Impassion050).[231]

- Currently, there is insufficient evidence for the use of Tecentriq (atezolizumab) for breast cancer in all other BC settings, including adjuvant, and subsequent therapy (second-line or beyond) settings for breast cancer (TNBC or other).

Hepatocellular Carcinoma, Adjuvant Use

- A phase 3, open-label RCT [IMbrave050] evaluating Tecentriq (atezolizumab) in combination with bevacizumab as an adjuvant therapy (after surgical resection) in patients with high-risk, resectable hepatocellular carcinoma improved recurrence-free survival (RFS) relative to active surveillance; however, there are currently no mature outcomes data available. This is not an FDA-approved use for Tecentriq (atezolizumab).[232]

Neuroendocrine tumors (NETs): There is insufficient evidence for the use of Tecentriq (atezolizumab) in NETs. The evidence is limited to one phase 2 basket trial of Tecentriq (atezolizumab) plus bevacizumab. From the cohort of previously treated grade 1-2 neuroendocrine tumors (NET), including pancreatic (pNET; n=20) and extrapancreatic (epNET; n=20), ORR was low in both groups (20% for pNET and 15% for epNET). Additional trials are need to establish the efficacy of this regimen.[233]

Urothelial Carcinoma (UC, Bladder cancer)

- *Subsequent therapy*: Tecentriq (atezolizumab) initially received Accelerated approval as a subsequent therapy (after disease progression on a cisplatin-based chemotherapy regimen) for unresectable or metastatic bladder cancer based on tumor response rate in a non-comparative (single-arm), observational study [IMvigor-210 study].[234]
- A subsequent phase 3 trial [IMvigor-211 study] intended to confirm the efficacy of Tecentriq (atezolizumab) in the bladder cancer setting failed to demonstrate an OS advantage over standard chemotherapy in the second-line setting. [235] Based on this failed confirmatory trial the manufacturer voluntarily withdrew the bladder cancer indication. Because there is no proven net health benefit relative to the standard of care, the use of Tecentriq (atezolizumab) for bladder cancer is considered investigational.
- An additional follow-on, phase 3 trial of Tecentriq (atezolizumab) in the adjuvant muscle-invasive bladder cancer (MIBC) setting failed to meet its primary end-point (disease-free survival) versus best supportive care [IMvigor-010 study]. [236]

Renal Cell Carcinoma (RCC)

- A phase 3 study [IMmotion 151] of Tecentriq (atezolizumab) plus bevacizumab versus Sutent (sunitinib) in patients with clear cell or sarcomatoid, metastatic renal cell carcinoma (RCC) reported a PFS advantage for the combination therapy treatment arm in patients with PD-L1-positive tumors (PD-L1 $\geq$ 1%).[237] However, there was no OS benefit seen at the final analysis.[238]
- A phase 3 trial of adjuvant Tecentriq (atezolizumab) for high-risk RCC failed to meet the prespecified endpoints.[239] Tecentriq (atezolizumab) was studied in combination with Cabometyx (cabozantinib) in patients with advanced RCC who had progressed after immune checkpoint inhibitor therapy [CONTACT-03]. The addition of Tecentriq (atezolizumab) to Cabometyx (cabozantinib) did not improve clinical outcomes and led to increased toxicity versus Cabometyx (cabozantinib) alone.

Other phase 3 trials that did not demonstrate a clinical benefit: [105 240-246]

- Tecentriq (atezolizumab) failed to meet its prespecified endpoints, and/or overall survival, in several additional studies including colorectal cancer [IMblaze-370], HNSCC [IMvoke010], ovarian cancer

[IMagyn050, ENGOT-OV41/GEICO 69-O/ANITA], pleural mesothelioma [ETOP 13-18 BEAT-meso], and prostate cancer [IMbassador250, CONTACT-02].

- A phase 3, open-label RCT [IPSOS] evaluating Tecentriq (atezolizumab) as a front-line therapy in patients with stage IIIB or IV NSCLC who were deemed unsuitable to receive standard platinum-based chemotherapy due to an ECOG PS of 2 to 3 demonstrated an improvement in OS relative to single-agent chemotherapy. Though the OS difference was statistically significant it was not clinically relevant (median OS improvement of 1 month).[247]
- Multiple trials are ongoing in various soft tissue sarcomas (STS) (other than ASPS).

Tevimbra (tislelizumab)

- Tevimbra (tislelizumab) is currently being studied in several other types of cancers including non-small cell lung cancer (NSCLC), squamous cell cancer of the head and neck (SCCHN), ovarian cancer, and gastric cancer.[105] However, to date, Tevimbra (tislelizumab) has not been shown to be an effective therapy for these cancers.

Zynyz (retifanlimab)

- Zynyz (retifanlimab-dlwr) is currently being studied in several other types of cancer including gastroesophageal adenocarcinoma.[105] However, to date, Zynyz (retifanlimab-dlwr) has not been shown to be an effective therapy for any other type of cancer.

Safety **[248]**

- The primary adverse effects (AEs) of interest for PD-1 and PD-L1 inhibitors include immune-mediated reactions and infusion reactions. Immune-related AEs can affect any organ system or tissue (e.g., colitis, pneumonitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and dermatologic reactions).
- Overall, the safety of appears to be similar to among the available PD-1 and PD-L1 inhibitors.
- For the combination product, Opdualag (nivolumab-relatlimab-rmbw): Qualitatively, the adverse effects reported in the Opdualag (nivolumab-relatlimab-rmbw) clinical trial were similar to those reported with Opdivo (nivolumab). However, as relatlimab is a new entity and safety experience is limited, it cannot be ruled out that additional harms may become known in the future. Approximately one in two to three patients receiving Opdualag (nivolumab-relatlimab-rmbw) in the pivotal trial experienced a dose interruption, or permanent discontinuation due to AEs.[97]

Dosing **[248]**

- Dose interruptions: For patients who have the course of therapy interrupted or doses delayed, dose authorization periods (date range of the authorization) may be extended to allow the full course (such as 12- or 24-months) to be completed, not to exceed the number of doses that would be given in a contiguous period.
- Coverable doses mirror the FDA labeling and/or clinical trials.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies

FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda IV (pembrolizumab); Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) for SC use
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo IV (nivolumab); Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) for SC use
penpulimab (unbranded)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death ligand-1 (PD-L1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq IV (atezolizumab); Tecentriq Hybreza (atezolizumab- hyaluronidase-tqjs) for SC use
Unloxcyt (cosibelimab)
Combination Products
Opdualag (nivolumab-relatlimab-rmbw) [PD-1 plus a lymphocyte activation gene-3 (LAG-3) inhibitor]

[a] Or as listed on the FDA.gov website | KEY: IV=intravenous; SC=subcutaneous

Appendix 2: Definition for High-Risk of Renal Cell Carcinoma (RCC) Recurrence

Definition for High-Risk of Renal Cell Carcinoma (RCC) Recurrence[149]
Intermediate-High Risk
- pT2, Grade 4 (histology) or sarcomatoid, N0, M0 (nodes negative, no metastases) **OR** - pT3, Any Grade (histology), N0, M0 (nodes negative, no metastases)
High-Risk
- pT4, Any Grade 4 (histology), N0, M0 (nodes negative, no metastases) **OR** - pT Any Stage, Any Grade (histology), N+, M0 (nodes positive, no metastases)
M1 No Evidence of Disease (NED)
RCC is present not only with the primary kidney tumor but also solid, isolated, soft tissue metastasis that can be completely resected at the time of nephrectomy

T = tumor; N = lymph nodes; M = metastases

Appendix 3: Child Pugh (CP) Score [a.k.a. Child-Turcotte-Pugh (CTP)]

Child Pugh (CP) Score [a]	
Points	***Class***
5-6	Class A
7-9	Class B
10-15	Class C

[a] CP is reported as a range, given it is an estimation of chronic liver disease. The lower end of the reported range may be used as a marker for illness/prognosis (example: a CP score of A6/B7 meets intent of coverage criteria of "class A"). However, CP scoring was developed for use in determining surgical risk and not specifically as a marker for cancer.

Appendix 4: Very High-Risk Features for Cutaneous Squamous Cell Carcinoma (CSCC) Recurrence

Very High-Risk Nodal or Non-Nodal Features for CSCC Recurrence[38]	
Defined as at least one of the following (nodal, non-nodal, or both):	
Nodal	***Non-nodal***
• Extracapsular extension (ECE) with ≥1 LN, ≥20 mm in diameter • ≥3 involved LN regardless of ECE.	• In-transit metastases • Perineural invasion (PNI) • T4 primary tumor (with bone invasion) • Local recurrent disease with ≥1 other adverse feature: - ≥N2b - ≥T3 [diameter >4.0 cm] - Poorly differentiated with recurrent lesion ≥20 mm in diameter

Cross References

Cross References
Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Medical Policy Manual, Genetic Testing Policy No. 56
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Adcetris, brentuximab vedotin, Medication Policy Manual, Policy No. dru264
Inlyta, axitinib, Medication Policy Manual, Policy No. dru273
Cabozantinib-Containing Medications, Medication Policy Manual, Policy No. dru290
Abraxane, nab-paclitaxel (a.k.a. albumin bound paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, ABI-007), Medication Policy Manual, Policy No. dru310
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398
Padcev, enfortumab vedotin, Medication Policy Manual, Policy No. dru622
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
KRAS G12C Inhibitors, Medication Policy Manual, Policy No. dru683
BRAF Inhibitors, Medication Policy Manual, Policy No. dru728
Mitogen-Activated Extracellular Signal-Regulated Kinase (MEK) Inhibitors [Cotellic (cobimetinib), trametinib (Mekinist), Mektovi (binimetinib)], Medication Policy Manual, Policy No. dru727
Imjudo, tremelimumab, Medication Policy Manual, Policy No. dru737

Codes	Number	Description
HCPCS	J3490	Unclassified drugs
HCPCS	J9022	Injection, atezolizumab (Tecentriq), 10 mg
HCPCS	J9024	Injection, atezolizumab and hyaluronidase-tqjs (Tecentriq Hybreza), 5mg
HCPCS	J9023	Injection, avelumab (Bavencio), 10 mg
HCPCS	J9119	Injection, cemiplimab-rwlc (Libtayo), 1 mg
HCPCS	J9272	Injection, dostarlimab-gxly (Jemperli), 10mg
HCPCS	J9173	Injection, durvalumab (Imfinzi), 10 mg
HCPCS	J9299	Injection, nivolumab (Opdivo), 1 mg
HCPCS	J9289	Injection, nivolumab, (Opdivo Qvantig), 2 mg
HCPCS	J9298	Injection, nivolumab and relatlimab-rmbw (Opdualag), 3 mg/1 mg
HCPCS	J9271	Injection, pembrolizumab (Keytruda), 1 mg
HCPCS	J9345	Injection, retifanlimab-dlwr (Zynyz), 1mg
HCPCS	J9329	Injection, tislelizumab-jsgr (Tevimbra), 1mg
HCPCS	J3263	Injection, toripalimab-tpzi (Loqtorzi), 1 mg
HCPCS	J9275	Injection, cosibelimab-ipdl (Unloxcyt), 2 mg

References

1. Keytruda (pembrolizumab) [package insert]. Merck & Co., Inc.; Rahway, NJ; July 2025.
2. Tecentriq (atezolizumab) [package insert]. Genentech, Inc.; South San Francisco, CA; August 2025.
3. NCCN Clinical Practice Guidelines in Oncology™. (Updated periodically) [cited with updates]. 'Available from:' https://www.nccn.org/guidelines/category_1.
4. Naqash AR, Coyne GHOS, Moore N, et al. Phase II study of atezolizumab in advanced alveolar soft part sarcoma (ASPS). *Journal of Clinical Oncology*. 2021;39(15_suppl):11519-19. PMID:
5. Chen AP, Sharon E, O'Sullivan-Coyne G, et al. Atezolizumab for Advanced Alveolar Soft Part Sarcoma. *N Engl J Med*. 2023;389(10):911-21. PMID: 37672694
6. Ramos Santillan V, Kaur A, Menon G, et al. Anal Carcinoma. [Updated 2025 Apr 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441891/.
7. Rao S, Samalin-Scalzi E, Evesque L, et al. Retifanlimab with carboplatin and paclitaxel for locally recurrent or metastatic squamous cell carcinoma of the anal canal (POD1UM-303/InterAACT-2): a global, phase 3 randomised controlled trial. *Lancet*. 2025;405(10495):2144-52. PMID: 40517007
8. Rao S, Anandappa G, Capdevila J, et al. A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202). *ESMO open*. 2022;7(4):100529. PMID: 35816951
9. Pala L, De Pas T, Stucchi E, et al. Immune-checkpoint inhibitors in anal squamous cell carcinoma: a systematic review and meta-analysis. *Seminars in oncology*. 2023;50(6):140-43. PMID: 38065801
10. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. *Ann Oncol*. 2017;28(5):1036-41. PMID: 28453692
11. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *The Lancet Oncology*. 2017;18(4):446-53. PMID: 28223062
12. Product Dossier: Libtayo® (cemiplimab-rwlc), Basal Cell Carcinoma Supplement. Bridgewater, NJ; February 2021. Regeneron | Sanofi Genzyme. Date Reviewed: May 4, 2021.
13. Libtayo (cemiplimab-rwlc) [package insert], Regeneron Pharmaceuticals, Inc.; Tarrytown, NY; April 2024.
14. Stratigos AJ, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):848-57. PMID: 34000246
15. Oh DY, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. *NEJM Evid*. 2022;1(8):EVIDoa2200015. PMID: 38319896
16. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10391):1853-65. PMID: 37075781
17. Chung HC, Ros W, Delord JP, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. 2019;37(17):1470-78. PMID: 30943124
18. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1-Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial. *J Clin Oncol*. 2017;35(36):4035-41. PMID: 29095678
19. Chung, et al. Pembrolizumab for previously treated advanced cervical cancer: updated results from the phase 2 KEYNOTE-158 study. Presented at the 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. [NCT02628067].
20. Product Dossier: Keytruda (pembrolizumab), Cervical Cancer Supplement. North Wales, PA; June 2018. Merck & Co., Inc. 2018.
21. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med*. 2021. PMID: 34534429
22. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;404(10460):1321-32. PMID: 39288779

23. Chen R, Zinzani PL, Fanale MA, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *J Clin Oncol*. 2017;35(19):2125-32. PMID: 28441111
24. Moskowitz AJ, Shah G, Schoder H, et al. Phase II Trial of Pembrolizumab Plus Gemcitabine, Vinorelbine, and Liposomal Doxorubicin as Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma. *J Clin Oncol*. 2021;39(28):3109-17. PMID: 34170745
25. Opdivo (nivolumab) [package insert]. Bristol-Myers Squibb Company; Princeton, NJ; June 2025.
26. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *The New England journal of medicine*. 2015;372(4):311-9. PMID: 25482239
27. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma. *N Engl J Med*. 2024;391(15):1379-89. PMID: 39413375
28. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183-94. PMID: 29229594
29. Diefenbach CS, Hong F, Ambinder RF, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *The Lancet Haematology*. 2020;7(9):e660-e70. PMID: 32853585
30. Cheson BD, Bartlett NL, LaPlant B, et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. *The Lancet Haematology*. 2020;7(11):e808-e15. PMID: 33010817
31. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med*. 2020;383(23):2207-18. PMID: 33264544
32. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer: 5-year follow-up from the randomized phase III KEYNOTE-177 study. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2025;36(3):277-84. PMID: 39631622
33. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182-91. PMID: 28734759
34. Andre T, Elez E, Lenz HJ, et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial. *Lancet*. 2025;405(10476):383-95. PMID: 39874977
35. Andre T, Elez E, Van Cutsem E, et al. Nivolumab plus Ipilimumab in Microsatellite-Instability-High Metastatic Colorectal Cancer. *N Engl J Med*. 2024;391(21):2014-26. PMID: 39602630
36. Grob JJ, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629). *J Clin Oncol*. 2020;38(25):2916-25. PMID: 32673170
37. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med*. 2018;379(4):341-51. PMID: 29863979
38. Rischin D, Porceddu S, Day F, et al. Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma. *N Engl J Med*. 2025;393(8):774-85. PMID: 40454639
39. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review for BLA 761-297; UnloxcytTM (cosibelimab-ipdl). [cited 2/18/2025]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/761297Orig1s000MultidisciplineR.pdf.
40. Imfinzi (durvalumab) [package insert]. AstraZeneca Pharmaceuticals LP; Wilmington, DE; May 2025.
41. Westin SN, Moore K, Chon HS, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. *J Clin Oncol*. 2024;42(3):283-99. PMID: 37864337
42. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review BLA 761-174, dostarlimab-gxly (Jemperli). [cited 6/22/2021]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761174Orig1s000MultidisciplineR.pdf.
43. Oaknin A, Tinker AV, Gilbert L, et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. *JAMA oncology*. 2020;6(11):1766-72. PMID: 33001143
44. Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. *N Engl J Med*. 2023;388(23):2145-58. PMID: 36972026

45. Powell MA, Bjorge L, Willmott L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. *Ann Oncol.* 2024;35(8):728-38. PMID: 38866180
46. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol.* 2020;38(26):2981-92. PMID: 32167863
47. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. *J Clin Oncol.* 2022;40(7):752-61. PMID: 34990208
48. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med.* 2023;388(23):2159-70. PMID: 36972022
49. Product Dossier: Keytruda® (pembrolizumab), Esophageal Cancer Supplement. North Wales, PA; March 2021. Merck & Co., Inc. 2021.
50. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. *J Clin Oncol.* 2020;38(35):4138-48. PMID: 33026938
51. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med.* 2021;384(13):1191-203. PMID: 33789008
52. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(11):1506-17. PMID: 31582355
53. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med.* 2022;386(5):449-62. PMID: 35108470
54. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* 2021;398(10294):27-40. PMID: 34102137
55. Shen L, Kato K, Kim SB, et al. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. United States, 2022:3065-76.
56. Xu J, Kato K, Raymond E, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2023;24(5):483-95. PMID: 37080222
57. Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. *N Engl J Med.* 2025;393(3):217-30. PMID: 40454643
58. Janjigian YY, et al. Pembrolizumab Plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or Gastroesophageal Junction Cancer: Initial Findings of the Global Phase 3 KEYNOTE-811 Study. Presented at the 2021 ASCO Virtual Annual Meeting; June 4-8, 2021. [NCT03615326].
59. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet.* 2023;402(10418):2197-208. PMID: 37871604
60. Rha SY, Oh DY, Yanez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2023;24(11):1181-95. PMID: 37875143
61. Merck Press Release: Merck Provides Update on Keytruda® (pembrolizumab) Indication in Third-Line Gastric Cancer in the US; July 1, 2021. [cited 9/14/2021]. 'Available from:' https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-third-line-gastric-cancer-in-the-us/.
62. Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet.* 2018;392(10142):123-33. PMID: 29880231
63. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. *JAMA oncology.* 2020;6(10):1571-80. PMID: 32880601

64. Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *Bmj*. 2024;385:e078876. PMID: 38806195
65. National Cancer Institute (NCI); Surveillance, Epidemiology, and End Results Program (SEER); SEER Cancer Stat Facts: Laryngeal Cancer. [cited 10/2/2025]. Available from: https://seer.cancer.gov/statfacts/html/laryn.html.
66. National Cancer Institute (NCI); Surveillance, Epidemiology, and End Results Program (SEER); SEER Cancer Stat Facts: Oral Cavity and Pharynx Cancer. [cited 10/2/2025]. Available from: https://seer.cancer.gov/statfacts/html/oralcav.html.
67. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. 2019;394(10212):1915-28. PMID: 31679945
68. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. 2016;17(7):956-65. PMID: 27247226
69. Uppaluri R, Haddad RI, Tao Y, et al. Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer. *N Engl J Med*. 2025;393(1):37-50. PMID: 40532178
70. Machiels JP, Tao Y, Licitra L, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2024;25(5):572-87. PMID: 38561010
71. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016;375(19):1856-67. PMID: 27718784
72. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review BLA 761-289, tremelimumab-actl (Imjudo). [cited 12/22/2022]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761289Orig1s000MultidisciplineR.pdf.
73. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid*. 2022;1(8):EVIDoa2100070. PMID: 38319892
74. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19(7):940-52. PMID: 29875066
75. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol*. 2020;38(3):193-202. PMID: 31790344
76. Qin S, Chen Z, Fang W, et al. Pembrolizumab Versus Placebo as Second-Line Therapy in Patients From Asia With Advanced Hepatocellular Carcinoma: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. United States, 2023:1434-43.
77. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492-502. PMID: 28434648
78. Yau T, Galle PR, Decaens T, et al. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial. *Lancet*. 2025;405(10492):1851-64. PMID: 40349714
79. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894-905. PMID: 32402160
80. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-73. PMID: 34902530
81. Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2022;23(8):995-1008. PMID: 35798016
82. Chu Q, Perrone F, Greillier L, et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial. *Lancet*. 2023;402(10419):2295-306. PMID: 37931632
83. Product Dossier: Opdivo® (nivolumab). Princeton, NJ; January 2021. Bristol-Myers Squibb Company. Date reviewed: 2/3/2021.

84. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet.* 2021;397(10272):375-86. PMID: 33485464
85. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2015;372(26):2521-32. PMID: 25891173
86. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol.* 2015;16(8):908-18. PMID: 26115796
87. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med.* 2018;378(19):1789-801. PMID: 29658430
88. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet.* 2022;399(10336):1718-29. PMID: 35367007
89. Robert C, Long GV, Brady B, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med.* 2014. PMID: 25399552
90. Ascierto PA, Long GV, Robert C, et al. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. *JAMA oncology.* 2019;5(2):187-94. PMID: 30422243
91. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015. PMID: 26027431
92. 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):867-75. PMID: 30811280
93. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Medical Review BLA 125-554, Nivolumab (Opdivo) [cited 1/21/2015]. 'Available from:' http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000MedR.pdf.
94. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med.* 2017;377(19):1824-35. PMID: 28891423
95. Kirkwood JM, Del Vecchio M, Weber J, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. *Nature medicine.* 2023;29:2835-43. PMID: 37845511
96. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma. *The New England journal of medicine.* 2024;391(18):1696-708. PMID: 38828984
97. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med.* 2022;386(1):24-34. PMID: 34986285
98. Lipson EJ, Stephen Hodi F, Tawbi H, et al. Nivolumab plus relatlimab in advanced melanoma: RELATIVITY-047 4-year update. *Eur J Cancer.* 2025;225:115547. PMID: 40513285
99. Ascierto PA, Lipson EJ, Dummer R, et al. Nivolumab and Relatlimab in Patients With Advanced Melanoma That Had Progressed on Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy: Results From the Phase I/IIa RELATIVITY-020 Trial. *J Clin Oncol.* 2023;41(15):2724-35. PMID: 36780608
100. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020;395(10240):1835-44. PMID: 32534646
101. Tai P, Nghiem PT, Park SY. Pathogenesis, Clinical Features, and Diagnosis of Merkel Cell (Neuroendocrine) Carcinoma. In: UpToDate, Stern RS, Robinson JK, Corona R, Shah S (Eds). UpToDate, Waltham, MA, 2023.
102. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review, BLA 761049; Bavencio (avelumab). [cited 05/05/2017]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf.
103. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol.* 2016;17(10):1374-85. PMID: 27592805
104. Nghiem P, Bhatia S, Lipson EJ, et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. *J Clin Oncol.* 2019;37(9):693-702. PMID: 30726175

105. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. 'Available from:' www.clinicaltrials.gov.
106. Mortier L, Villabona L, Lawrence B, et al. Pembrolizumab for the First-Line Treatment of Recurrent Locally Advanced or Metastatic Merkel Cell Carcinoma: Results from the Single-Arm, Open-Label, Phase III KEYNOTE-913 Study. *American journal of clinical dermatology.* 2024;25(6):987-96. PMID: 39377880
107. Zynyz (retifanlimab-dlwr) [package insert]. Incyte Corporation; Wilmington, DE; May 2025.
108. Hui EO, Chan ATC. Epidemiology, etiology, and diagnosis of nasopharyngeal carcinoma. In: UpToDate, Brockstein BE, Brizel DM, Fried MP, Yushak M (Eds). UpToDate, Waltham, MA, 2023.
109. Mai HQ, Chen QY, Chen D, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nature medicine.* 2021;27:1536-43. PMID: 34341578
110. Wang FH, Wei XL, Feng J, et al. Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02). *J Clin Oncol.* 2021;39:704-12. PMID: 33492986
111. Penpulimab-kcqx [package insert]. Akeso BioPharma Co.; Ltd.; Zhongshan, Guangdong, China; April 2025.
112. Chen X, Wang W, Zou Q, et al. Penpulimab, an anti-PD-1 antibody, for heavily pretreated metastatic nasopharyngeal carcinoma: a single-arm phase II study. *Signal Transduct Target Ther.* 2024;9(1):148. PMID: 38890298
113. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. *N Engl J Med.* 2023;389(18):1672-84. PMID: 37870974
114. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-50. PMID: 30280658
115. Imjudo (tremelimumab-actl) [package insert]. AstraZeneca Pharmaceuticals LP; Wilmington, DE.
116. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol.* 2022:JCO2200975. PMID: 36327426
117. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497-508. PMID: 27745820
118. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;379(21):2040-51. PMID: 30280635
119. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2015. PMID: 26712084
120. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2016. PMID: 27718847
121. PD-L1 IHC22C3 pharmDx [package insert]. Carpinteria, CA: Dako North America, Inc.
122. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* 2022;23(10):1274-86. PMID: 36108662
123. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *N Engl J Med.* 2023;389(6):491-503. PMID: 37272513
124. Sezer A, Kilickap S, Gumus M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet.* 2021;397(10274):592-604. PMID: 33581821
125. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nature medicine.* 2022;28(11):2374-80. PMID: 36008722
126. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med.* 2022;386(21):1973-85. PMID: 35403841
127. Forde PM, Spicer JD, Provencio M, et al. Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer. *N Engl J Med.* 2025;393(8):741-52. PMID: 40454642
128. Cascone T, Awad MM, Spicer JD, et al. Perioperative Nivolumab in Resectable Lung Cancer. *N Engl J Med.* 2024;390(19):1756-69. PMID: 38749033

129. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med.* 2019;381(21):2020-31. PMID: 31562796
130. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med.* 2017;376(25):2415-26. PMID: 28636851
131. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015. PMID: 26028407
132. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015;373(17):1627-39. PMID: 26412456
133. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet.* 2021;398(10308):1344-57. PMID: 34555333
134. Felip E, Altorki N, Zhou C, et al. Five-Year Survival Outcomes With Atezolizumab After Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (IMpower010): An Open-Label, Randomized, Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2025;43(21):2343-49. PMID: 40446184
135. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med.* 2020;383(14):1328-39. PMID: 32997907
136. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med.* 2018;378(24):2288-301. PMID: 29863955
137. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):924-37. PMID: 31122901
138. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387(10030):1837-46. PMID: 26970723
139. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2016. PMID: 27979383
140. Product Dossier: Keytruda® (pembrolizumab), Hematologic Malignancies Supplement. North Wales, PA; July 2018. Merck & Co., Inc. 2018.
141. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood.* 2017;130(3):267-70. PMID: 28490569
142. Zinzani, et al. Efficacy and Safety of Pembroizumab in Relapsed/Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL): Updated Analysis of the KEYNOTE-170 Phase 2 Trial. Poster presented at the American Society of Hematology Conference; Atlanta, GA; December 9-12, 2017. [NCT02576990].
143. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2019;380(12):1103-15. PMID: 30779531
144. Bavencio (avelumab) [package insert]. EMD Serono, Inc.; Rockland, MA; June 2025.
145. Choueiri TK, Penkov K, Uemura H, et al. Avelumab + axitinib versus sunitinib as first-line treatment for patients with advanced renal cell carcinoma: final analysis of the phase III JAVELIN Renal 101 trial. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2025;36(4):387-92. PMID: 39706335
146. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2019;380(12):1116-27. PMID: 30779529
147. Powles T, Plimack ER, Soulieres D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2020;21(12):1563-73. PMID: 33284113
148. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med.* 2021;384(14):1289-300. PMID: 33616314
149. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. *N Engl J Med.* 2021;385(8):683-94. PMID: 34407342
150. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2018;378(14):1277-90. PMID: 29562145

151. Tannir NM, Albiges L, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 8-year follow-up results of efficacy and safety from the phase III CheckMate 214 trial. *Ann Oncol.* 2024;35(11):1026-38. PMID: 39098455
152. Choueiri TK, Powles T, Albiges L, et al. Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma. *N Engl J Med.* 2023;388(19):1767-78. PMID: 37163623
153. NCCN Drugs and Biologics Compendium (NCCN Compendium™) [Updated regularly]. [cited with policy updates and as necessary]. 'Available from:' https://www.nccn.org/professionals/drug_compendium/content/.
154. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015;373(19):1803-13. PMID: 26406148
155. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet.* 2019;394(10212):1929-39. PMID: 31590988
156. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. *Journal of Clinical Oncology.* 2020;38(15_suppl):9002-02. PMID:
157. Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. *N Engl J Med.* 2024;391(14):1313-27. PMID: 39268857
158. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med.* 2018;379(23):2220-29. PMID: 30280641
159. Paz-Ares L, Borghaei H, Liu SV, et al. Efficacy and safety of first-line maintenance therapy with lurbinectedin plus atezolizumab in extensive-stage small-cell lung cancer (IMforte): a randomised, multicentre, open-label, phase 3 trial. *Lancet.* 2025;405(10495):2129-43. PMID: 40473449
160. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet.* 2020;396(10265):1817-28. PMID: 33278935
161. Rugo HS, Cortes J, Cescon DW, et al. KEYNOTE-355: Final Results From a Randomized, Double-Blind, Phase 3 Study of First-Line Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy for Metastatic Triple-Negative Breast Cancer. Abstract LBA16. Poster Presentation at eh European Society for Medical Oncology (ESMO) Congress 2021; 16 to 21 September 2021.
162. Tolaney SM, de Azambuja E, Kalinsky K, et al. Sacituzumab Govitecan plus Pembrolizumab for Advanced Triple-Negative Breast Cancer. *N Engl J Med.* 2026;394(4):354-66. PMID: 41564397
163. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med.* 2020;382(9):810-21. PMID: 32101663
164. Gyawali B, D'Andrea E, Franklin JM, et al. A correlation analysis to assess event-free survival as a trial-level surrogate for overall survival in early breast cancer. *EClinicalMedicine.* 2021;32:100730. PMID: 33681740
165. Schmid P, Cortes J, Dent R, et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. *The New England journal of medicine.* 2024;391(21):1981-91. PMID: 39282906
166. National Cancer Institute (NCI); Surveillance, Epidemiology, and End Results Program (SEER); SEER Cancer Stat Facts: Bladder Cancer. [cited 9/24/2025]. Available from: https://seer.cancer.gov/statfacts/html/urinb.html.
167. Product Dossier: Bavencio® (avelumab). Rockland, MA; May 2017. EMD Serono, Inc. Date reviewed: May 31, 2017.
168. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol.* 2018;19(1):51-64. PMID: 29217288
169. Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med.* 2020;383(13):1218-30. PMID: 32945632
170. Powles T, Catto JWF, Galsky MD, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. *N Engl J Med.* 2024;391(19):1773-86. PMID: 39282910
171. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2017;18(11):1483-92. PMID: 28967485

172. Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *N Engl J Med.* 2024;390(10):875-88. PMID: 38446675
173. Powles TB, Van der Heijden MS, Loriot Y, et al. Enfortumab vedotin plus pembrolizumab in untreated locally advanced or metastatic urothelial carcinoma: 2.5-year median follow-up of the phase III EV-302/KEYNOTE-A39 trial. *Ann Oncol.* 2025;36(10):1212-19. PMID: 40460988
174. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med.* 2017;376(11):1015-26. PMID: 28212060
175. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol.* 2021;22(7):919-30. PMID: 34051177
176. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2017. PMID: 28131785
177. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. *N Engl J Med.* 2023;389(19):1778-89. PMID: 37870949
178. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med.* 2021;384(22):2102-14. PMID: 34077643
179. Galsky MD, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab in High-Risk Muscle-Invasive Urothelial Carcinoma: Expanded Efficacy From CheckMate 274. *J Clin Oncol.* 2025;43(1):15-21. PMID: 39393026
180. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017;18(3):e143-e52. PMID: 28271869
181. Persigehl T, Lennartz S,Schwartz LH. iRECIST: how to do it. Cancer Imaging. England, 2020:2.
182. Tewari KS, Monk BJ, Vergote I, et al. Survival with Cemiplimab in Recurrent Cervical Cancer. *N Engl J Med.* 2022;386(6):544-55. PMID: 35139273
183. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol.* 2017;18(5):599-610. PMID: 28373005
184. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2020;21(12):1574-88. PMID: 32971005
185. Ferris RL, Haddad R, Even C, et al. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. *Ann Oncol.* 2020;31(7):942-50. PMID: 32294530
186. Mell LK, Torres-Saavedra PA, Wong SJ, et al. Radiotherapy with cetuximab or durvalumab for locoregionally advanced head and neck cancer in patients with a contraindication to cisplatin (NRG-HN004): an open-label, multicentre, parallel-group, randomised, phase 2/3 trial. *The Lancet Oncology.* 2024;25(12):1576-88. PMID: 39551064
187. Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2023;24(12):1334-48. PMID: 38039991
188. Sangro B, Kudo M, Erinjeri JP, et al. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet.* 2025;405(10474):216-32. PMID: 39798579
189. Jemperli (dostarlimab) [package insert]. GlaxoSmithKline LLC; Philadelphia, PA; August 2024.
190. Shapira-Frommer R, Mileshkin L, Manzyuk L, et al. Efficacy and safety of pembrolizumab for patients with previously treated advanced vulvar squamous cell carcinoma: Results from the phase 2 KEYNOTE-158 study. *Gynecologic oncology.* 2022;166(2):211-18. PMID: 35361487
191. Kudo M, Ren Z, Guo Y, et al. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study. *Lancet.* 2025;405(10474):203-15. PMID: 39798578
192. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372(26):2509-20. PMID: 26028255

193. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. 2020;38(1):1-10. PMID: 31682550
194. Product Dossier: Keytruda® (pembrolizumab), MSI-H Supplement. Whitehouse Station, NJ; September 2017. Merck & Co., Inc. Date Reviewed: September 18, 2017.
195. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol*. 2019;30(7):1080-87. PMID: 31046082
196. Mehnert JM, Bergsland E, O'Neil BH, et al. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer*. 2020;126(13):3021-30. PMID: 32320048
197. Strosberg J, Mizuno N, Doi T, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase II KEYNOTE-158 Study. *Clin Cancer Res*. 2020;26(9):2124-30. PMID: 31980466
198. Raj N, Chan JA, Wang SJ, et al. Pembrolizumab alone and pembrolizumab plus chemotherapy in previously treated, extrapulmonary poorly differentiated neuroendocrine carcinomas. *Br J Cancer*. 2023;129(2):291-300. PMID: 37208512
199. Petrylak DP, Ratta R, Matsubara N, et al. Pembrolizumab Plus Docetaxel Versus Docetaxel for Previously Treated Metastatic Castration-Resistant Prostate Cancer: The Randomized, Double-Blind, Phase III KEYNOTE-921 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2025;43(14):1638-49. PMID: 40043230
200. Gratzke C, Ozguroglu M, Peer A, et al. Pembrolizumab plus enzalutamide and androgen deprivation therapy versus placebo plus enzalutamide and androgen deprivation therapy for metastatic hormone-sensitive prostate cancer: the randomized, double-blind, phase III KEYNOTE-991 study. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2025;36(8):964-75. PMID: 40383194
201. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(11):1493-501. PMID: 28988646
202. Le Cesne A, Marec-Berard P, Blay JY, et al. Programmed cell death 1 (PD-1) targeting in patients with advanced osteosarcomas: results from the PEMBROSARC study. *Eur J Cancer*. 2019;119:151-57. PMID: 31442817
203. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. *J Thorac Oncol*. 2020;15(4):618-27. PMID: 31870883
204. Merck Press Release: Merck Provides Update on Keytruda® (pembrolizumab) Indication in Metastatic Small Cell Lung Cancer in the US; March 1, 2021. [cited 3/12/2021]. 'Available from:' https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-metastatic-small-cell-lung-cancer-in-the-us/.
205. Product Dossier: Keytruda® (pembrolizumab), TMB-H Cancers Supplement. Whitehouse Station, NJ; June 2020. Merck & Co., Inc. Date Reviewed: July 20, 2020.
206. NCCN Clinical Practice Guidelines in Oncology™. (Updated periodically) [cited with updates]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
207. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. 'Available from:' https://www.nccn.org/guidelines/category_1.
208. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77-90. PMID: 34914889
209. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase III trial. *Neuro-oncology*. 2023;25:123-34. PMID: 35419607
210. Lassman AB, Polley MC, Iwamoto FM, et al. Dual Immune Check Point Blockade in MGMT-Unmethylated Newly Diagnosed Glioblastoma: NRG Oncology BN007, a Randomized Phase II/III Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2025;43(27):3032-40. PMID: 40779733

211. Weber JS, Schadendorf D, Del Vecchio M, 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;41:517-27. PMID: 36162037
212. Patel SP, Mayerson E, Chae YK, et al. A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. *Cancer.* 2021;127(17):3194-201. PMID: 33882143
213. Patel SP, Othus M, Chae YK, et al. A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2020;26(10):2290-96. PMID: 31969335
214. Patel SP, Othus M, Chae YK, et al. Phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors (DART) SWOG S1609: adrenocortical carcinoma cohort. *Journal for immunotherapy of cancer.* 2024;12(7). PMID: 39067873
215. Riesco-Martinez MC, Capdevila J, Alonso V, et al. Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 Neuroendocrine Neoplasms of gastroenteropancreatic or unknown origin: The multicenter phase 2 NICE-NEC trial (GETNE-T1913). *Nature communications.* 2024;15(1):6753. PMID: 39117670
216. Motzer RJ, Bex A, Russo P, et al. Adjuvant Nivolumab for Localized Renal Cell Carcinoma at High Risk of Recurrence After Nephrectomy: Part B of the Randomized, Placebo-Controlled, Phase III CheckMate 914 Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2025;43(2):189-200. PMID: 39303200
217. Allaf ME, Kim SE, Master V, et al. Perioperative nivolumab versus observation in patients with renal cell carcinoma undergoing nephrectomy (PROSPER ECOG-ACRIN EA8143): an open-label, randomised, phase 3 study. *The Lancet Oncology.* 2024;25(8):1038-52. PMID: 38942046
218. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol.* 2018;19(3):416-26. PMID: 29370992
219. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016;17(7):883-95. PMID: 27269741
220. Bristol Myers-Squibb Press Release: Bristol Myers-Squibb Statement on Opdivo® Small Cell Lung Cancer US Indication; December 29, 2020[cited 3/10/2021]. 'Available from:' https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Statement-on-Opdivo-nivolumab-Small-Cell-Lung-Cancer-US-Indication/default.aspx.
221. Schenker M, Burotto M, Richardet M, et al. Randomized, open-label, phase 2 study of nivolumab plus ipilimumab or nivolumab monotherapy in patients with advanced or metastatic solid tumors of high tumor mutational burden. *Journal for immunotherapy of cancer.* 2024;12(8). PMID: 39107131
222. Liu JF, Herold C, Gray KP, et al. Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer: A Phase 2 Clinical Trial. *JAMA oncology.* 2019. PMID: 31600397
223. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Patients Ineligible for or Having Failed Autologous Transplantation: A Single-Arm, Phase II Study. *J Clin Oncol.* 2019;37(6):481-89. PMID: 30620669
224. Grierson PM, Wolf C, Suresh R, et al. Neoadjuvant BMS-813160, Nivolumab, Gemcitabine, and Nab-Paclitaxel for Patients with Pancreatic Cancer. *Clin Cancer Res.* 2025;31(17):3644-51. PMID: 40125795
225. Weber JS, Gibney G, Sullivan RJ, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. *Lancet Oncol.* 2016;17(7):943-55. PMID: 27269740
226. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med.* 2018;379(22):2108-21. PMID: 30345906
227. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020;21(1):44-59. PMID: 31786121
228. Another disappointing result for Tecentriq in triple negative breast cancer; August 7, 2020. [cited 3/3/2021]. 'Available from:' https://www.evaluate.com/vantage/articles/news/snippets/another-disappointing-result-tecentriq-triple-negative-breast-cancer.

229. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet.* 2020;396(10257):1090-100. PMID: 32966830
230. Gianni L, Huang CS, Egle D, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. *Ann Oncol.* 2022;33(5):534-43. PMID: 35182721
231. Huober J, Barrios CH, Niikura N, et al. Atezolizumab With Neoadjuvant Anti-Human Epidermal Growth Factor Receptor 2 Therapy and Chemotherapy in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Primary Results of the Randomized Phase III IMpassion050 Trial. *J Clin Oncol.* 2022;40(25):2946-56. PMID: 35763704
232. Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;402(10415):1835-47. PMID: 37871608
233. Halperin DM, Liu S, Dasari A, et al. Assessment of Clinical Response Following Atezolizumab and Bevacizumab Treatment in Patients With Neuroendocrine Tumors: A Nonrandomized Clinical Trial. *JAMA oncology.* 2022;8(6):904-09. PMID: 35389428
234. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 2016;387(10031):1909-20. PMID: 26952546
235. Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2018;391(10122):748-57. PMID: 29268948
236. Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(4):525-37. PMID: 33721560
237. Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet.* 2019;393(10189):2404-15. PMID: 31079938
238. Motzer RJ, Powles T, Atkins MB, et al. Final Overall Survival and Molecular Analysis in IMmotion151, a Phase 3 Trial Comparing Atezolizumab Plus Bevacizumab vs Sunitinib in Patients With Previously Untreated Metastatic Renal Cell Carcinoma. *JAMA oncology.* 2022;8(2):275-80. PMID: 34940781
239. Pal SK, Albiges L, Tomczak P, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *Lancet.* 2023;402(10397):185-95. PMID: 37290461
240. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol.* 2019;20(6):849-61. PMID: 31003911
241. Moore KN, Bookman M, Sehouli J, et al. Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39). *J Clin Oncol.* 2021;39(17):1842-55. PMID: 33891472
242. Powles T, Yuen KC, Gillessen S, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nature medicine.* 2022;28(1):144-53. PMID: 35013615
243. Haddad R, Fayette J, Teixeira M, et al. Atezolizumab in High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A Randomized Clinical Trial. *Jama.* 2025;333(18):1599-607. PMID: 40079944
244. Gonzalez-Martin A, Rubio MJ, Heitz F, et al. Atezolizumab Combined With Platinum and Maintenance Niraparib for Recurrent Ovarian Cancer With a Platinum-Free Interval >6 Months: ENGOT-OV41/GEICO 69-O/ANITA Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2024;42(36):4294-304. PMID: 39292975
245. Felip E, Popat S, Dafni U, et al. A randomised phase III study of bevacizumab and carboplatin-pemetrexed chemotherapy with or without atezolizumab as first-line treatment for advanced pleural

mesothelioma: results of the ETOP 13-18 BEAT-meso trial. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2025;36(5):548-60. PMID: 39814199
246. Agarwal N, Azad AA, Carles J, et al. Cabozantinib plus atezolizumab in metastatic prostate cancer (CONTACT-02): final analyses from a phase 3, open-label, randomised trial. *The Lancet Oncology*. 2025;26(7):860-76. PMID: 40523369
247. Lee SM, Schulz C, Prabhash K, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. *Lancet*. 2023;402(10400):451-63. PMID: 37423228
248. Drug Facts and Comparisons. Facts and Comparisons. UpToDate Inc. https://fco.factsandcomparisons.com. Accessed periodically.

Revision History

Revision Date	Revision Summary
6/4/2026	Effective 8/1/26: - Added alternate dosing for Zynyz (retifanlimab-dlwr) for anal squamous cell carcinoma (aSCC). - Added coverage criteria for Keytruda (pembrolizumab) in combination with Trodelvy (sacituzumab govitecan-hziy) in newly diagnosed advanced TNBC (previously untreated advanced disease), PD-L1 expressing tumors (CPS ≥ 10).
4/2/2026	Effective 6/1/2026: - Updated quantity limit (QL) table for operational ease. - Clarified criteria for the following sections with no change to intent: Keytruda (pembrolizumab) for HNSCC, Opdivo (nivolumab)/Yervoy (ipilimumab) for neoadjuvant melanoma, and Opdivo (nivolumab)/Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) for CRC.
3/5/2026	Effective 5/1/2026: - Added coverage criteria for the following new FDA indications, based on clinical trial evidence: * Libtayo (cemiplimab) for resected cutaneous squamous cell carcinoma (CSCC), at very high risk of recurrence, as adjuvant therapy. * Imfinzi (durvalumab) for resectable gastric/GEJ cancer, as perioperative add-on therapy (neoadjuvant and adjuvant) to chemotherapy. - Added coverage criteria for Opdivo (nivolumab) in combination with AVD chemotherapy for classical Hodgkin lymphoma (cHL) in the first-line setting, based on evidence from the S1826 trial. - Updated dosing for Tevimbra (tislelizumab) to include every 6-week dosing (label). - Clarified Initial Reauthorization criteria for reauthorization after neoadjuvant dosing (no change to intent). - Updates made to drug name formatting within policy criteria with no change to intent.
12/4/2025	Effective 3/1/2026: - Clarified criteria for coverage of Tecentriq for HCC is limited to use in combination with bevacizumab. - Updated the use of Bavencio (avelumab)/Inlyta (axitinib) for first-line advanced clear cell

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	RCC to 'not medically necessary.' - Investigational Uses updated to include the use of PD-1/PD-L1s for unresectable HCC that is amenable to transarterial chemoembolization (TACE) [Imfinzi (durvalumab), Keytruda (pembrolizumab)].
12/4/2025	Effective 2/1/2026: - Added new subcutaneous product Keytruda Qlex (pembrolizumab-berahyaluronidase alfa-pmph) to policy. - Added coverage criteria for the following new FDA indications, based on clinical trial evidence outcomes: * Zynyz (retifanlimab) for recurrent or metastatic anal squamous cell carcinoma (aSCC) in the first-line in combination with cytotoxic chemotherapy as well as in the subsequent line setting as monotherapy. * Imfinzi (durvalumab) for resectable muscle invasive bladder cancer (MIBC), as perioperative add-on therapy (neoadjuvant and adjuvant) to standard of care neoadjuvant chemotherapy. * Keytruda (pembrolizumab) for resectable head and neck squamous cell carcinoma (HNSCC), as neoadjuvant therapy followed by add-on adjuvant therapy with standard of care chemoradiation (CRT). * Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for unresectable hepatocellular carcinoma (HCC) in the first-line setting, when lower-cost Imfinzi (durvalumab)/Imjudo (tremelimumab) is not a treatment option (not tolerated or use is contraindicated). * Opdivo (nivolumab) in combination with Yervoy (ipilimumab) unresectable MSI-H/dMMR colorectal cancer (CRC), in the first-line setting. - Added coverage of Opdivo (nivolumab) in the neoadjuvant melanoma setting when used in combination with Yervoy (ipilimumab) based on evidence from the NADINA study, to match existing the Yervoy (ipilimumab) policy coverage criteria. - Clarified criteria for the following for operational consistency: * Opdivo and Keytruda 1st line esophageal adenocarcinoma to mirror gastric/GEJ adenocarcinoma [no change to intent] * Simplified endometrial carcinoma criteria across covered options [no change to intent]. - Removed requirement for platin-ineligibility for first-line use of Keytruda plus Padcev in advanced UC. - Clarified Opdualag dosing for operational consistency (changed to every 4 weeks, rather than 'monthly'). - Investigational Uses clarified [pancreatic cancer for Jemperli, Keytruda, Opdivo; neuroendocrine tumors (NETs) for Tecentriq, Keytruda, Opdivo; prostate cancer for Keytruda].
9/4/2025	Effective 11/1/2025: - Added coverage criteria for penpulimab (unbranded) for patients with recurrent locally advanced (unresectable) or metastatic, nasopharyngeal carcinoma (NPC) in (1) the first-line setting when used in combination with a platin and gemcitabine; and, (2) in the

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	subsequent-line setting as a monotherapy when there has been disease progression on or after platinum-containing chemotherapy and at least on other line of therapy. - Added coverage for Tecentriq (atezolizumab) for ES-SCLC, when given as chemoimmunotherapy induction with carboplatin plus etoposide, then in combination with chemotherapy Zepzelca (lurbinectedin) as maintenance therapy.
6/5/2025	- Added coverage criteria for Unloxcyt (cosibelimab) in locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) when patients are not candidates for curative surgery or curative radiation. Criteria mirrors those for Keytruda (pembrolizumab) and Libtayo (cemiplimab). - Added coverage criteria for two new indications: * Tevimbra (tislelizumab) for HER-2-negative, PD-L1 expressing locally advanced unresectable, or metastatic gastric or GEJ adenocarcinoma, in the first-line setting. * Added coverage for Imfinzi (durvalumab) for inoperable limited-stage small cell lung cancer (LS-SCLC) (Stage I-III), if disease has not progressed following concurrent platinum/etoposide-based chemoradiotherapy, and good PS (0-1). - For Keytruda (pembrolizumab), moved coverage criteria for GEJ SCC from "Esophageal" to "Gastric or GEJ" section, for administrative consistency (no change to intent). - Updated dosing for Tevimbra (tislelizumab) based on prescribing information update (added every 2-week and every 4-week dosing options). - Clarified quantity limits [no change to intent].
3/6/2025	- Added coverage criteria for Keytruda (pembrolizumab) for malignant pleural mesothelioma (MPM) [new indication]. - Added coverage for Imfinzi (durvalumab) for neoadjuvant/adjuvant therapy for resectable earlier stage NSCLC. [new indication]. - Updated coverage criteria for PD1/PDL1s for hepatocellular carcinoma (HCC) to include Child-Pugh B with good performance status (ECOG 0-1).
2/15/2025	Added new subcutaneous product Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) to policy. Note: Opdivo Qvantig (nivolumab-hyaluronidase-nvhy) is not approved for concomitant use with Yervoy (ipilimumab).
12/12/2024	New policy effective 2/1/2025. - Combined 11 existing individual PD1/PDL1 policies: * Keytruda, pembrolizumab, dru367 * Opdivo, nivolumab, dru390 * Tecentriq, atezolizumab, dru463 * Bavencio, avelumab, dru499 * Imfinzi, durvalumab, dru500 * Libtayo, cemiplimab-rwlc, dru565 * Jemperli, dostarlimab, dru673 * Opdualag, nivolumab-relatlimab-rmbw, dru718 * Zynyz, retifanlimab-dlwr, dru751 * Loqtorzi, toripalimab, dru774

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	* Tevimbra, tislelizumab, dru785 - No change to intent to any of the existing policies. No change to coverage criteria. Re-wording for consistency/clarity across medications and within diagnoses. - Updated "Table 1. Administration – Quantity Limit (QL) and Authorization Period" for consistent administration of authorizations. - Added Tecentriq Hybreza, a new formulation for subcutaneous (SC) administration.

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