f. **Primary Mediastinal Large B-cell Lymphoma (PMBCL)**
   i. PMBCL presents with primary site of disease in the mediastinum, has unique clinical features, likely originates from thymic medullary B cells, and histology similar to diffuse large B-cell lymphoma (DLBCL).
   ii. Due to its unique nature and distinct clinical features, diagnoses are difficult and survival rates are varied, possibly because differentiating from DLBCL with mediastinal involvement is challenging.
   iii. Making up 2% of all NHL, PMBCL usually affects young women in their 30s and 40s
   iv. This cancer initially presents as aggressive mediastinal masses and respiratory symptoms with most cases featuring superior vena cava syndrome with facial edema, neck vein distention, and sometimes deep vein thrombosis. Spreading locally into the lung, chest wall, pleura, and pericardium is common, but further spread into bone marrow is unlikely at initial presentation.
   v. The role of chemoradiation for this condition is still unknown, but NCCN guidelines give 2A recommendations to EPOCH-R and RCHOP for first-line treatment, used with or without radiation. Observation is preferred over radiation therapy if PET/CT scans are negative following treatment and initial disease was considered non-bulky. NCCN recommends Keytruda (2A) for relapsed or refractory disease.

g. **Urothelial Carcinoma**
   i. Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis, which occur at a ratio of 50:3:1, respectively. Patients with cancer of the upper urinary tract have a 30% to 50% chance of developing cancer of the bladder at some point in their lives, and patients with bladder cancer have a 2% to 3% chance of developing cancer of the upper urinary tract. The National Cancer Institute (NCI) estimates there will be 79,000 new cases of urothelial carcinoma in 2017 with 16,870 deaths resulting from urothelial carcinoma in the United States. The 5 year survival rate for urothelial carcinoma was 77.3% between 2007-2013.
   ii. First line therapy options for metastatic or locally advanced urothelial carcinoma per NCCN include gemcitabine and cisplatin or DDMAC with growth factor support.
   iii. Subsequent therapy options for metastatic or locally advanced urothelial carcinoma per NCCN include Keytruda (category 1), Tecentriq, Imfinzi, gemcitabine, Opdivo, and Bavencio.

h. **Microsatellite instability-high cancers**
   i. Mutations in DNA mismatch repair genes (such as MLH1, MSH2 or MSH6) result in a failure to repair errors in repetitive sequences, leading to microsatellite instability (MSI) of the tumors. MSI can occur in tumors of many organs, but it is mainly the hallmark of colorectal cancer. Cancers with MSI account for approximately 15% of all colorectal cancers and 90% of colorectal cancers in patients with Lynch syndrome or hereditary non-polyposis colorectal carcinoma.
   ii. The tumor is termed MSI-high (MSI-H) if two or more of the five microsatellite sequences recommended by the National Cancer Institute (NCI) have been mutated. If only one of the microsatellite sequences has been mutated, the tumor is classified as MSI-low (MSI-L). The tumor is termed microsatellite stable (MSS) if there is no mutation in the microsatellite panel.
   iii. NCCN guidelines give 2A recommendations to Keytruda and Opdivo/Yervoy combination therapy for MSI-H/dMMR colorectal cancer following FOLFOX/CAPEOX within past 12 months.

i. **Gastric Cancer**
   i. Gastric (stomach) cancer is a disease in which malignant (cancer) cells form in the lining of the stomach. The stomach is in the upper abdomen and helps digest food. Almost all gastric cancers are adenocarcinomas (cancers that begin in cells that make and release mucus and other fluids). Other types of gastric cancer are gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, and lymphomas. Infection with bacteria called H. pylori is a common cause of gastric cancer. Gastric cancer is often diagnosed at an advanced stage because there are no early signs.
   ii. The American Cancer Society's estimates for stomach cancer in the United States for 2018 are: approximately 26,240 cases of stomach cancer will be diagnosed (16,520 in men and 9,720 in women) and about 10,800 people will die from this cancer (6,510 men and 4,290 women).

iii. Stomach cancer mostly affects older people. The average age of people when they are diagnosed is 68. About 6 of every 10 people diagnosed with stomach cancer each year are 65 or older. The risk that a man will develop stomach cancer in their lifetime is about 1 in 95. For women the chance is about 1 in 154. But each person's risk can be affected by certain other factors. In the US, new cases of stomach cancer have decreased about 1.5% each year over the last 10 years.
iv. Preferred therapy options for gastric cancer per NCCN include Cyramza with paclitaxel, taxanes, irinotecan ± fluorouracil. irinotecan with cisplatin or docetaxel, and Cyramza monotherapy.

j. **Esophageal Cancer**
i. The American Cancer Society estimates there will be 17,650 new esophageal cancer cases diagnosed and 16,080 deaths
ii. Overall, the rates of esophageal cancer in the United States have been fairly stable for many years, but over the past decade they have been decreasing slightly
iii. Esophageal cancer makes up about 1% of all cancers diagnosed in the United States
iv. About 20% of patients survive at least 5 years after diagnosis
v. NCCN guidelines recommend Keytruda as a second-line therapy for squamous cell carcinoma of the esophagus in with PD-L1 expression greater than 10 (category 1), for second-line or subsequent lines of therapy in MSI-H or dMMR tumors, and as a third-line agent or subsequent therapy for esophageal or esophagogastric junction adenocarcinomas with a PD-L1 expression greater than 1

k. **Cervical Cancer**
i. Cervical cancer occurs in cells of the cervix, the part of the uterus that connects to the vagina
ii. There are two main subtypes of cervical cancer: squamous cell carcinoma (majority of cases where cancer begins in the squamous cells lining the outer part of the cervix) and adenocarcinoma (where cancer begins in the glandular cells lining the cervical canal)
iii. Most cervical cancer is caused by human papillomavirus (HPV), a sexually transmitted infection that, in most cases, is managed by the immune system so the virus does not cause harm. In some women, however, the virus can survive for many years, resulting in the eventual transition of cells on the cervix surface from healthy cells into cancer cells.
iv. At one point, this cancer was one of the most common causes of cancer death in American women, but the increase of annual pap tests and vaccinations against HPV have resulted in significantly more cervical pre-cancers than invasive cervical cancer which allows for easier and proactive treatment.
v. The American Cancer Society estimates 13,240 new invasive cervical cancer diagnoses and 4,170 cervical cancer deaths in 2018. Diagnosis typically occurs between ages 35 and 44, but over 15% of cases occur in women over 65, usually not in women who have had screenings.
1. NCCN guidelines list Keytruda as a 2A recommendation for recurrent or metastatic cervical cancer as second-line therapy following first-line chemotherapy (primarily cisplatin, carboplatin, paclitaxel, topotecan alone or in combination with Avastin)

l. **Hepatocellular Carcinoma (HCC)**
i. American Cancer Society estimates over 30,000 deaths will be caused by liver and intrahepatic bile duct cancer in 2018. Hepatocellular carcinoma is the most common form of primary liver cancer. Risk factors include cirrhosis, hepatitis B and C infections, alcohol abuse, and nonalcoholic steatohepatitis (NASH). NASH is typically seen in patients with diabetes, obesity, dyslipidemia, and hypertension. Given the risk factors associated with HCC, it is expected that the incidence of HCC will continue to rise.
ii. HCC is more common in men than women. Those from Eastern and Southern Asia, Middle and Western Africa are at increased risk of HCC.
iii. Keytruda was approved for HCC under accelerated approval based on tumor response rate and durability of response. Continued approval for HCC may be contingent upon verification and description of clinical benefit in the confirmatory trials.

iv. NCCN recommends Keytruda as subsequent therapy after progression of HCC while on sorafenib or lenvatinib in Child-Pugh Class A.

m. **Merkle Cell Carcinoma**
   i. Merkel cell carcinoma (MCC) is an uncommon type of skin cancer
   ii. About 2,000 cases of MCC are diagnosed in the United States each year
   iii. The number of people diagnosed with MCC each year has been rising quickly over the past few decades most likely due to people living longer and more people living with compromised immune systems
   iv. It is much more likely to spread to other parts of the body and is difficult to treat
   v. NCCN guidelines state Keytruda should be considered for recurrent locally advance and regional disease is curative surgery and radiation are not feasible or in disseminated disease

n. **Renal Cell Carcinoma**
   i. About 9 out of 10 kidney cancers are renal cell carcinomas
   ii. There are several subtypes of RCC and knowing the subtype of renal cell carcinoma can be a factor in deciding treatment
   iii. The American Cancer Society's most recent estimates about 73,820 new cases of kidney cancer for 2019 with 14,770 deaths
   iv. Kidney cancer is among the 10 most common cancers in both men and women
   v. NCCN guidelines recommend use of Keytruda for those with clear cell histology in combination with axitinib as first-line or subsequent therapy in relapsed or stage 4 disease

o. **Endometrial Carcinoma**
   i. Endometrial cancer is the most common type of female reproductive cancer
   ii. It is estimated there will be 61,880 new cases and 12,160 deaths in 2019 from the disease
   iii. Endometrial cancer affects mainly post-menopausal women
   iv. NCCN guidelines recommend the use of Keytrude as a category 2B recommendation in those with recurrent, metastatic, or high risk disease

C. Efficacy

**Please refer to most recent prescribing information.*

D. Medication Safety Considerations

Black Box Warning: No

**Please refer to most recent prescribing information.*

E. Dosing and administration

a. Dosing:
   i. Pediatric microsatellite instability-high cancer, pediatric cHL, and pediatric PMBCL: 2 mg/kg (max 200 mg) every 3 weeks
   ii. NSCLC, melanoma, cHL, head and neck carcinoma, urothelial carcinoma, gastric cancer, cervical cancer, HCC: 200mg every 3 weeks

**Please refer to most recent prescribing information.*

F. How supplied

a. 100 mg vial

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Policy History		
#	Date	Change Description
1.0	Effective Date: 1/1/2022	Effective date of policy.

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm*