

Drug Policy:

Keytruda™ (pembrolizumab)

POLICY NUMBER UM ONC_1263	SUBJECT Keytruda™ (pembrolizumab)	DEPT/PROGRAM UM Dept	PAGE 1 of 7
DATES COMMITTEE REVIEWED 11/12/14, 10/14/15, 07/26/16, 08/24/16, 03/08/17, 06/14/17, 06/13/18, 05/08/19, 09/11/19, 10/09/19, 12/11/19, 02/12/20, 03/11/20, 04/08/20, 05/13/20, 06/10/20, 08/12/20, 09/09/20, 12/09/20, 03/10/21, 04/14/21, 06/09/21, 07/14/21, 08/11/21, 09/08/21	APPROVAL DATE September 8, 2021	EFFECTIVE DATE September 24, 2021	COMMITTEE APPROVAL DATES 11/12/14, 10/14/15, 07/26/16, 08/24/16, 03/08/17, 06/14/17, 06/13/18, 05/08/19, 09/11/19, 10/09/19, 12/11/19, 02/12/20, 03/11/20, 04/08/20, 05/13/20, 06/10/20, 08/12/20, 09/09/20, 12/09/20, 03/10/21, 04/14/21, 06/09/21, 07/14/21, 08/11/21, 09/08/21
PRIMARY BUSINESS OWNER: UM		COMMITTEE/BOARD APPROVAL Utilization Management Committee	
URAC STANDARDS HUM 1	NCQA STANDARDS UM 2	ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS	APPLICABLE LINES OF BUSINESS Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Keytruda (pembrolizumab) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

New Century Health (NCH) is responsible for processing all medication requests from network ordering providers. Medications not authorized by NCH may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. PREFERRED MEDICATION GUIDANCE FOR INITIAL REQUEST:

1. When health plan Medicaid coverage provisions—including any applicable PDLs (Preferred Drug Lists)—conflict with the coverage provisions in this drug policy, health plan Medicaid coverage provisions take precedence per the [Preferred Drug Guidelines](#) OR

2. When health plan Exchange coverage provisions-including any applicable PDLs (Preferred Drug Lists)-conflict with the coverage provisions in this drug policy, health plan Exchange coverage provisions take precedence per the [Preferred Drug Guidelines](#) OR
3. For Health Plans that utilize NCH UM Oncology Clinical Policies as the initial clinical criteria, the [Preferred Drug Guidelines](#) shall follow [NCH L1 Pathways](#) when applicable, otherwise shall follow NCH drug policies AND
4. Continuation requests of previously approved, non-preferred medication are not subject to this provision AND
5. When applicable, generic alternatives are preferred over brand-name drugs.

B. Melanoma

1. Keytruda (pembrolizumab) will be used as single agent for [ONE](#) of the following:
 - a. Adjuvant therapy for high-risk Stage III melanoma following complete resection of the primary tumor (when identified) with or without a complete regional lymph node dissection. [NOTE: The maximum total duration of therapy is 1 year in the adjuvant setting](#) OR
 - b. For unresectable or metastatic melanoma and the member had no prior disease progression on a PD-L1/PD-1 inhibitor.
 - c. [NOTE: Preferred weight-based dosing: Keytruda \(pembrolizumab\) 200 mg \(if 50 kg or more\) or 2 mg/kg \(if less than 50 kg\) for every 3 weeks dosing.](#)

C. Recurrent/Metastatic Squamous and Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

1. [NOTE: The preferred agent, per NCH Policy and NCH Pathway, for first line and maintenance treatment of recurrent/metastatic NSCLC is Keytruda \(pembrolizumab\) over other PD-1 or PD-L1 inhibitors \[i.e., Opdivo \(nivolumab\), Tecentriq \(atezolizumab\)\].](#)
2. [NOTE: Keytruda \(pembrolizumab\) use in non-squamous/adenocarcinoma Non-Small Cell Lung Cancer, as a single agent or in combination with platinum-based chemotherapy REQUIRES that the member's NSCLC be negative for EGFR mutations and ALK rearrangements.](#)
3. Keytruda (pembrolizumab) will be used for [ONE](#) of the following:
 - a. As first line therapy:
 - i. As a single agent if member's NSCLC is negative for EGFR, ALK (biomarkers not required for squamous histology) [AND](#) the tumor PD-L1 expression (either CPS-Combined Positive Score, or TPS-Tumor Proportion Score) is $\geq 50\%$ OR
 - ii. As a single agent if member's NSCLC is negative for EGFR, ALK (biomarkers not required for squamous histology) [AND](#) the PDL1 is $\geq 1\%$ and concurrent chemotherapy cannot be given or is contraindicated OR
 - iii. In combination with pemetrexed and platinum chemotherapy in members with non-squamous histology if EGFR, ALK genomic alterations are negative (biomarkers not required for squamous histology regardless of the PD-L1 level OR
 - iv. In combination with carboplatin and paclitaxel or nab-paclitaxel (if there is a history of a severe allergic reaction, anaphylaxis, or intolerance to paclitaxel) in members with squamous cell histology. [NOTE: The NCH Preferred taxane in the above setting is paclitaxel unless there is a documented history of a severe allergic reaction/anaphylaxis/intolerance to paclitaxel.](#)
 - b. As continuation maintenance therapy, in combination with pemetrexed (non-squamous [ONLY](#)) or as a single agent, in members who have achieved complete response/partial

response/stable disease following first line therapy with a regimen that included chemotherapy + Keytruda (pembrolizumab).

- c. As subsequent therapy as a single agent for tumors with PD-L1 expression levels $\geq 1\%$ and the member had no prior progression on a PD-L1/PD-1 inhibitor.

D. Head and Neck Cancer

1. The member has unresectable, recurrent, or metastatic non-nasopharyngeal squamous cell carcinoma of the head and neck **AND** Keytruda (pembrolizumab) will be used for:
 - a. First line therapy
 - i. As a single agent for tumors that express PD-L1 (either CPS-Combined Positive Score or TPS-Tumor Proportion Score) $\geq 1\%$ **OR**
 - ii. In combination with chemotherapy, regardless of the PD-L1 expression score.
 - b. Subsequent therapy as a single agent for disease progression on or after platinum-based chemotherapy, regardless of the PD-L1 expression score.

E. Hodgkin's Lymphoma

1. The member has refractory or relapsed Hodgkin's Lymphoma and is not a candidate for HSCT and Keytruda (pembrolizumab) will be used as a single agent. **NOTE: In the above setting, Keytruda (pembrolizumab) is preferred over Adcetris (brentuximab) if the member has not had prior therapy with either of the above two agents.**

F. Urothelial Carcinoma including Upper Urinary Tract Carcinoma and Carcinoma of Urethra

1. **NOTE: Keytruda is a non-Preferred drug for recurrent, non-muscle invasive urothelial carcinoma. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support the use of Keytruda over other appropriate therapies for the above diagnosis.**
2. **NOTE: Per NCH Policy and NCH Pathway, Keytruda (pembrolizumab) is the preferred checkpoint inhibitor rather than Opdivo (nivolumab), Tecentriq (atezolizumab), Bavencio (avelumab) or Imfinzi (durvalumab), for subsequent therapy of metastatic/recurrent urothelial carcinoma.**
3. The member has recurrent/metastatic urothelial cancer and Keytruda (pembrolizumab) will be used for members who are not eligible for platinum-containing chemotherapy or who have disease progression during or after platinum containing chemotherapy.

G. Colorectal Cancer

1. Keytruda (pembrolizumab) may be used as a single agent for initial or subsequent therapy for members with unresectable/metastatic colorectal cancer whose tumors show deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]. **This requires confirmation of dMMR/MSI-High status by any standardized test.**

H. Gastric Cancer or Esophageal and Esophagogastric Junction Cancers

1. The member has unresectable locally advanced, recurrent, or metastatic gastric cancer or esophageal and EGJ adenocarcinoma **AND**
2. Keytruda (pembrolizumab) will be used as any of the following:
 - a. As first line therapy in combination with fluoropyrimidine and platinum containing chemotherapy +/- trastuzumab (if HER positive) **OR**
 - b. As second-line or subsequent therapy for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.

I. Cervical Cancer

1. The member has recurrent or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) cervical cancer or PD-L1 positive, CPS or TPS $\geq 1\%$, tumors **AND**
2. Keytruda (pembrolizumab) will be used as a single agent as subsequent therapy following disease progression on or after prior chemotherapy treatment.

J. Hepatobiliary Cancers

1. Keytruda use in this disease is limited to members with liver function of Child Pugh Class A only
2. Keytruda (pembrolizumab) will be used in members with hepatocellular carcinoma who have disease progression on or after Nexavar (sorafenib), Lenvima (Lenvatinib), or Stivarga (regorafenib) unless intolerance or contraindications exist to the above 3 agents **OR**
3. For subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or metastatic disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR).

K. Merkel Cell Carcinoma (MCC)

1. Keytruda (pembrolizumab) will be used as a single agent in members with recurrent/locally advanced/metastatic Merkel Cell Carcinoma regardless of the line of therapy.

L. Renal Cell Carcinoma (RCC)

1. **NOTE:** The preferred regimen for first line therapy if metastatic renal cell carcinoma- IMDC Intermediate and High Risk is Opdivo (nivolumab) with or without Yervoy (ipilimumab).
2. **NOTE:** Keytruda (pembrolizumab) + Lenvima (lenvatinib) is a non-preferred regimen for first line therapy of metastatic renal cell carcinoma. This position is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support that the above regimen is superior to the regimens recommended:
 - a. There was no OS benefit for the above regimen over sunitinib in the IMDC Favorable Risk Group (HR:1.15, CI=0.55-2.40) in the CLEAR trial.
 - b. There is no Level 1 evidence (randomized trials and/or meta-analyses) to show that [pembrolizumab + lenvatinib] is superior in terms of outcomes to [nivolumab + ipilimumab].
3. **NOTE:** Keytruda (pembrolizumab) + Inlyta (axitinib) combination therapy is non-preferred regimen for metastatic renal cell carcinoma for any line of therapy. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support superior outcomes with the above regimen over the regimen recommended by NCH policy, [Opdivo (nivolumab) + Yervoy (ipilimumab)], for IMDC Intermediate and Poor Risk disease. Furthermore, the above combination did not show an OS-Overall Survival benefit over the control arm of Sutent (sunitinib) in the IMDC favorable risk category.
4. Keytruda (pembrolizumab) will be used as a single agent for subsequent therapy if member has not received prior PD-1 inhibitor therapy.
5. Keytruda (pembrolizumab) may be used as adjuvant therapy in resected renal cell carcinoma if any of the following criteria are met:
 - a. Stage II disease with grade 4 histology or with sarcomatoid differentiation
 - b. Stage III or higher disease
 - c. Regional nodal metastases
 - d. M1 NED: Member with resectable metastases at diagnosis and surgical resection of the primary and of the metastatic lesions (within 1 year of nephrectomy) and No Evidence Of Metastatic disease prior to starting Keytruda (pembrolizumab).

M. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

1. Keytruda (pembrolizumab) will be used as a single agent in relapsed or refractory primary mediastinal large B-cell lymphoma.

N. Endometrial Carcinoma

1. Keytruda (pembrolizumab) will be used as a single agent as subsequent-line systemic therapy for unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor that has progressed following prior treatment **OR**
2. Keytruda (pembrolizumab) will be used with Lenvima (lenvatinib) as subsequent therapy after disease progression on prior chemotherapy, in members whose tumors are MSI-Stable or MMR-proficient. NOTE: For members with tumors that are MSI-High, single agent Keytruda (pembrolizumab) ALONE as monotherapy is recommended per policy in this clinical setting. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support superior outcomes with the above combination when compared with single agent Keytruda (pembrolizumab) in patients with MSI-High metastatic endometrial cancer.

O. Cutaneous Squamous Cell Carcinoma (CSCC)

1. NOTE: The preferred agent, per NCH Policy, for the treatment of members with recurrent or metastatic cutaneous squamous cell carcinoma is Libtayo (cemiplimab-rwlc) over Keytruda (pembrolizumab). Please refer to *UM Onc_1089 for Libtayo (cemiplimab-rwlc) policy*.

P. Microsatellite Instability-High or Mismatch Repair Deficient Cancer

1. Keytruda (pembrolizumab) may be used in members with a solid tumor that has progressed following prior treatment, including all satisfactory treatment alternatives and the solid tumor is positive for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) as confirmed by any standardized test for the above biomarker.

Q. Triple Negative Breast Cancer (TNBC)

1. Keytruda (pembrolizumab) may be used in combination with chemotherapy for any of the following:
 - a. As neoadjuvant or adjuvant therapy (if the member received pembrolizumab in the neoadjuvant setting) in members with newly diagnosed high-risk early-stage TNBC (a tumor size >1 cm, ≤2 cm in diameter with nodal involvement, or tumor size >2 cm in diameter regardless of nodal involvement) **AND** the members have not received prior checkpoint inhibitor (PD-1/PD-L1) therapy, regardless of tumor PD-L1 expression **OR**
 - b. In members with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 with a Combined Positive Score (CPS) ≥10.

R. Tumor Mutational Burden-High (TMB-H) Cancer

1. Keytruda (pembrolizumab) may be used as a single agent in members with unresectable or metastatic solid tumors with a high tumor mutational burden, TMB- H ≥10 mutations/megabase (mut/Mb), that have progressed following prior treatment and have no satisfactory alternative treatment options.

III. EXCLUSION CRITERIA

- A. Disease progression on Keytruda (pembrolizumab) containing regimen or prior checkpoint inhibitor (PD-1/PD-L1) therapy, except when Keytruda (pembrolizumab) is being used as part of neoadjuvant/adjuvant therapy in the treatment of early stage TNBC .

- B. Lack of EGFR & ALK test results when being used in the first line therapy (as a single agent or in combination with chemotherapy) of metastatic/recurrent non-squamous or adenocarcinoma Non-Small Cell Lung Cancer.
- C. Length of Keytruda (pembrolizumab) treatment is greater than 24 months (except for adjuvant therapy of resected stage III Melanoma or early stage TNBC for which the maximum treatment duration is up to 12 months).
- D. Specific exclusions detailed above under individual cancer types.
- E. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature.

IV. MEDICATION MANAGEMENT

- A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

- A. Review – Utilization Management Department
- B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

- A. None

VII. REFERENCES

- A. Choueiri et al. KEYNOTE-564 trial. N Engl J Med 2021;385:683-94. DOI:10.1016/NEJMoa2106391
- B. Schmid P, et al. KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.
- C. Motzer et al. CLEAR trial. N Engl J Med 2021;384:1289-1300. DOI:10.1056/NEJMoa2035716
- D. Chung HC, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol. 2021 Feb;17(5):491-501. doi: 10.2217/fon-2020-0737.
- E. Aurelien et al, KEYNOTE-158 trial, Lancet Oncol 2020;21:1353-65. DOI: [https://doi.org/10.1016/S1470-20145\(20\)30445-9](https://doi.org/10.1016/S1470-20145(20)30445-9)
- F. Leigh et al, CCR Drug Updates. Published Online First February 20, 2019; DOI:10.1158/1078-0432.CCR-18-4070
- G. Cortes J, et al. KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomized, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828. doi: 10.1016/S0140-6736(20)32531-9.
- H. Keytruda prescribing information. Merck & Co. Inc. 2020.
- I. Clinical Pharmacology Elsevier Gold Standard 2021.
- J. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO 2021.

- K. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2021.
- L. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs Bethesda, MD 2021.