Drug Policy:

Keytruda™ (pembrolizumab)

POLICY NUMBER UM ONC_1263	**SUBJECT** Keytruda™ (pembrolizumab)		**DEPT/PROGRAM** UM Dept	**PAGE 1 OF 8**
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, 111/15/21, 12/8/21, 01/12/22, 03/09/22	**APPROVAL DATE** March 9, 2022	**EFFECTIVE DATE** March 25, 2022	**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, 11/15/21, 12/8/21, 01/12/22, 03/09/22	
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. In adult or pediatric members ≥12 years of age as adjuvant therapy for Stages IIb, IIc, and 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. The FDA approved pediatric dose is 2 mg/kg (up to a maximum of 200 mg) every three weeks.

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

1. 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 and ALK (biomarkers not required for squamous histology) AND the tumor PD-L1 expression (either CPS-Combined Positive Score, or TPS-Tumor Proportion Score) is ≥ 50% OR
      ii. As a single agent if member's NSCLC is negative for EGFR and ALK (biomarkers not required for squamous histology) AND the PDL1 is ≥ 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 and 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, regardless of the PD-L1 level. 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 histology 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 ≥ 1% and the member had no prior progression on a PD-L1/PD-1 inhibitor.
2. NOTE 1: Per NCH Pathway & NCH Policy, [Pembrolizumab + Carboplatin + Albumin-bound Paclitaxel] is a Non-Preferred regimen for the treatment of NSCLC based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes

compared to NCH Preferred regimens. Please refer to NCH Pathway for the preferred treatments.

3. NOTE 2: Keytruda (pembrolizumab) use as first line therapy for 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.

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) ≥ 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. Keytruda (pembrolizumab) monotherapy may be used in a member with recurrent/metastatic urothelial cancer who are not eligible for platinum-containing chemotherapy or who have disease progression during or after platinum containing chemotherapy.
2. NOTE 1: 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.
3. NOTE 2: 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.

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), AND CPS of 10 or higher. This position is supported by the lack of survival benefit of pembrolizumab monotherapy or pembrolizumab + chemotherapy for tumors expressing lower levels of PD-L1 OR

b. As second-line or subsequent therapy for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.

I. Cervical Cancer

1. Keytruda (pembrolizumab) + Carboplatin/Cisplatin + Taxol (paclitaxel) will be used as first line therapy for members with advanced/metastatic cervical carcinoma whose tumors express PD-L1 CPS ≥ 1% OR
2. Keytruda (pembrolizumab) will be used in members with advanced/metastatic cervical carcinoma whose tumors express PD-L1 CPS ≥ 1% as a single agent as second line or subsequent therapy following disease progression on or after prior chemotherapy treatment, with no exposure to prior Keytruda (pembrolizumab) or another Immune Checkpoint Inhibitor.
3. NOTE: Carboplatin/Cisplatin + Taxol + Pembrolizumab WITH Bevacizumab is a Non-Preferred regimen for advanced/metastatic cervical carcinoma in members whose tumors express PD-L1 CPS ≥ 1%. This recommendation is based on the findings of KEYNOTE 826 trial (see reference below). The latter trial showed NO additional benefit for patient outcomes (PFS and OS) with the addition of bevacizumab to the above 3-drug regimen, [Carboplatin/Cisplatin + Taxol (paclitaxel) + Keytruda (pembrolizumab)].

J. Hepatobiliary Cancers

1. 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
2. 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) AND
3. Keytruda use in this disease is limited to members with liver function of Child Pugh Class A only, and members who have not received previous therapy with an immune checkpoint inhibitor [e.g., Tecentriq (atezolizumab)].

K. Merkel Cell Carcinoma (MCC)

1. Keytruda (pembrolizumab) may 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. Keytruda (pembrolizumab) may be used as a single agent for subsequent therapy if member has not received prior PD-1 inhibitor therapy.
2. Keytruda (pembrolizumab) may be used as a single agent for adjuvant therapy in resected renal cell carcinoma that is positive for PD-L1 (CPS ≥1) if any ONE 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).
3. NOTE 1: 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).
4. NOTE 2: 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].

5. NOTE 3: 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.

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

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

N. Endometrial Carcinoma

1. Keytruda (pembrolizumab) may 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). This position is based on the lack of Level 1 Evidence (randomized trials and or meta-analyses) to show superior outcomes with Keytruda compared to Libtayo. 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 metastatic /unresectable 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 the following:

a. As neoadjuvant in a member 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 OR

b. As adjuvant therapy (ONLY if the member received pembrolizumab in the neoadjuvant setting) AND

c. The member has not received prior checkpoint inhibitor (PD-1/PD-L1) therapy

d. 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. Investigational use of Keytruda (pembrolizumab) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of < 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

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. Shitara K, 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 Oncol. 2020 Oct 1;6(10):1571-1580.

B. Makker V, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 2020 Sep 10;38(26):2981-2992.

C. Colombo N, et al. KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867.

D. Choueiri TK, et al. KEYNOTE-564 Investigators. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021 Aug 19;385(8):683-694.

E. 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.

F. Motzer R, et al. CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-1300.

G. 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.

H. Marabelle A, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020 Oct;21(10):1353-1365.

I. Marcus L, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res. 2019 Jul 1;25(13):3753-3758.

J. 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.

K. Keytruda prescribing information. Merck & Co. Inc. 2021.

L. Clinical Pharmacology Elsevier Gold Standard 2022.

M. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO 2022.

N. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2022.

O. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs Bethesda, MD 2022.

P. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

Q. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.