Drug Policy:

Keytruda™ (pembrolizumab)

POLICY NUMBER UM ONC_1263	SUBJECT Keytruda™ (pembrolizumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 10
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, 05/11/22, 06/08/22, 07/13/22, 09/20/22, 11/09/22, 12/14/22, 01/11/23, 02/08/23, 03/08/23, 05/10/23, 07/12/23, 10/11/23, 12/13/23, 01/10/24, 02/14/24, 06/12/24, 07/10/24, 10/09/24, 12/12/24	**APPROVAL DATE** December 12, 2024	**EFFECTIVE DATE** December 27, 2024	**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, 12/08/21, 01/12/22, 03/09/22, 05/11/22, 06/08/22, 07/13/22, 09/20/22, 11/09/22, 12/14/22, 01/11/23, 02/08/23, 03/08/23, 05/10/23, 07/12/23, 10/11/23, 12/13/23, 01/10/24, 02/14/24, 06/12/24, 07/10/24, 10/09/24, 12/12/24	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Evolent Specialty Services Clinical Guideline Review Committee		
NCQA STANDARDS UM 2		**ADDITIONAL AREAS OF IMPACT**		
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Commercial, Exchange, Medicaid	

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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.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent 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. Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided:

1. The member has not experienced disease progression on the requested medication AND
2. The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
3. Additional medication(s) are not being added to the continuation request.

B. Cervical Cancer

1. Keytruda (pembrolizumab) + Carboplatin/Cisplatin + Taxol (paclitaxel) may be used as first line or subsequent therapy for members with advanced/recurrent/metastatic cervical carcinoma whose tumors express PD-L1 CPS greater than or equal to 1% OR
2. Keytruda (pembrolizumab) will be used in members with advanced/recurrent/metastatic cervical carcinoma whose tumors express PD-L1 CPS greater than or equal to 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. Bevacizumab/bevacizumab biosimilar + Keytruda (pembrolizumab) + cisplatin/carboplatin + paclitaxel may be used in members for the initial treatment of PD-L1 positive (PD-L1 greater than or equal to 1%) metastatic cervical cancer.
4. Keytruda (pembrolizumab) may be used in combination with chemoradiotherapy in members with newly diagnosed, previously untreated, high-risk locally advanced FIGO 2014 Stage III-IVA cervical cancer.

Table 1: International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging of Cancer of the Cervix Uteri (2018)

Stage			Description
I			The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
	IA		Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a]
		IA1	Measured stromal invasion ≤3 mm in depth
		IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
	IB		Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
		IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
		IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
		IB3	Invasive carcinoma >4 cm in greatest dimension
II			The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
	IIA		Involvement limited to the upper two-thirds of the vagina without parametrial invasion
		IIA1	IIA1 Invasive carcinoma ≤4 cm in greatest dimension
		IIA2	Invasive carcinoma >4 cm in greatest dimension
	IIB		With parametrial invasion but not up to the pelvic wall
III			The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
	IIIA		Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	IIIC		Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases),[c] irrespective of tumor size and extent (with r and p notations).
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Paraaortic lymph node metastasis
IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
	IVA		Spread of the growth to adjacent organs
	IVB		Spread to distant organs

[a] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. Pathological findings supersede imaging and clinical findings.
[b] The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
[c] Isolated tumor cells do not change the stage but their presence should be recorded.
[d] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

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C. 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 either dMMR OR MSI-High status by any standardized test.

D. Cutaneous Squamous Cell Carcinoma (CSCC)

1. Keytruda (pembrolizumab) may be used as monotherapy for the treatment of members with recurrent, advanced, or metastatic cutaneous squamous cell carcinoma and are not candidates for curative surgery and/or curative radiation.

E. Endometrial Carcinoma

1. Keytruda (pembrolizumab) may be used as first line therapy in combination with carboplatin and paclitaxel for members with recurrent/metastatic (stage III and IV) endometrial carcinoma
2. 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
3. Keytruda (pembrolizumab) may be used with Lenvima (lenvatinib) as subsequent therapy after disease progression on prior chemotherapy, in members who have not received prior therapy with an Immune Checkpoint Inhibitor and whose tumors are MSI-Stable or MMR-proficient (not MSI-High/deficient MMR).

F. 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 ONE of the following:
    a. As first line therapy in combination with fluoropyrimidine and platinum containing chemotherapy AND CPS of 1% or higher.
    b. As first line therapy in combination with fluoropyrimidine and platinum containing chemotherapy with trastuzumab for members with HER-2 positive disease, regardless of PD-L1 level.
    c. As second line or subsequent therapy as a single agent for esophageal squamous cell carcinoma with PD-L1 expression by CPS of 10 or higher.
    d. As second-line or subsequent therapy for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.

G. 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) greater than or equal to 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.
    c. NOTE: Keytruda (pembrolizumab) + Erbitux (cetuximab) combination is not supported by Evolent Keytruda policy for the initial and subsequent treatment of non-nasopharyngeal cancers. This policy position is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at

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http://pathways.newcenturyhealth.com.

H. Hepatocellular Carcinoma (HCC)

1. Keytruda (pembrolizumab) will be used in members with hepatocellular carcinoma who have not received prior therapy with an Immune Checkpoint Inhibitor, and have experienced 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. NOTE: Keytruda use in this disease is limited to members with liver function of Child Pugh Class A and B only, and members who have not received previous therapy with an immune checkpoint inhibitor [e.g., Tecentriq (atezolizumab)].

I. 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.

J. Malignant Pleural Mesothelioma (MPM)

1. Keytruda (pembrolizumab) may be used in combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult members with unresectable advanced or metastatic malignant pleural mesothelioma.

K. Melanoma

1. Keytruda (pembrolizumab) will be used as single agent for ONE of the following:
    a. In adult or pediatric members greater than or equal to 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.
    b. As neoadjuvant therapy for stage IIIB and IVC melanoma that is amenable to surgical resection; above neoadjuvant therapy (generally 3 cycles) may be followed by a total of 15 additional cycles of adjuvant Keytruda.
    c. For unresectable or metastatic melanoma and the member had no prior disease progression on a PD-L1/PD-1 inhibitor.

L. 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.

M. 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.

N. Non-Muscle Invasive Bladder Cancer

1. The member has high risk non-muscle invasive bladder cancer with carcinoma in situ (CIS), with or without papillary tumors, and Keytruda (pembrolizumab) will be used as monotherapy, for intravenous administration, in members who are refractory to local (intravesical) therapy with Bacillus Calmette-Guérin (BCG). Refractory is defined as a loss of response to treatment within 12 months of maintenance therapy with at least the first course of induction (5-6 doses) followed by at least 2 doses of maintenance BCG or the loss of response with the second

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induction course (of at least 2 doses) of BCG treatment.

O. Non-Small Cell Lung Cancer (NSCLC) – Squamous and Non-Squamous

1. Keytruda (pembrolizumab) will be used for ONE of the following:
    a. As first line therapy in advanced, recurrent, or metastatic disease:
        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 greater than or equal to 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 greater than or equal to 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.
    b. As continuation maintenance therapy in advanced, recurrent, or metastatic disease, 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 in advanced, recurrent, or metastatic disease as a single agent for tumors with PD-L1 expression levels greater than or equal to 1% and the member had no prior progression on a PD-L1/PD-1 inhibitor.
    d. As neoadjuvant therapy (with platinum-based chemotherapy) for 4 cycles for locally advanced- stages II, IIIA and IIB Non-Small Cell Lung Cancer; above may be followed by a maximum of 13 additional cycles of Keytruda as continuation/adjuvant therapy.
    e. As adjuvant monotherapy, up to 12 months, following complete resection and platinum-based chemotherapy for members with stage IB (tumors ≥4 cm in diameter), II, or IIIA NSCLC, regardless of PD-L1 status.
2. NOTE: [Keytruda (pembrolizumab) + Carboplatin + Abraxane (albumin-bound paclitaxel)] is not supported by Evolent Keytruda Policy for the treatment of NSCLC based on the results of the KEYNOTE- 407 trial which showed equivalent Progression Free Survival and Overall Survival with both Abraxane (albumin-bound paclitaxel) and Taxol (solvent-based paclitaxel). KEYNOTE-407 is referenced below. Please refer to alternative agents/regimens recommended by Evolent including but not limited to regimens available at http://pathways.newcenturyhealth.com.

P. 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.

Q. Renal Cell Carcinoma (RCC)

1. The member has advanced or metastatic RCC and Lenvima (lenvatinib) may be used in combination with Keytruda (pembrolizumab) as first line therapy.
2. Keytruda (pembrolizumab) may be used in combination with Inlyta (axitinib) as first line treatment for members with IMDC favorable risk advanced/metastatic RCC who have not experienced prior disease progression on Inlyta (axitinib) and/or PD-L1/PD-1 inhibitor (e.g., avelumab, pembrolizumab, nivolumab).

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3. Keytruda (pembrolizumab) may be used as a single agent for adjuvant therapy in resected renal cell carcinoma 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).

R. Small Cell Lung Cancer (SCLC)

1. NOTE: Single agent Keytruda (pembrolizumab) is not supported by Evolent Keytruda Policy for the treatment of metastatic SCLC following disease progression on platinum-based chemotherapy and/or at least one other line of therapy (e.g., topotecan, irinotecan, paclitaxel, docetaxel). The above indication was withdrawn by the FDA based on confirmatory study, KEYNOTE-604 failed to meet the primary endpoint of overall survival compared to chemotherapy. Please refer to alternative agents/regimens recommended by Evolent including but not limited to regimens available at http://pathways.newcenturyhealth.com.

S. Soft Tissue Sarcoma

1. NOTE: Single agent Keytruda (pembrolizumab) is not supported by Evolent Keytruda Policy for the following soft tissue sarcomas: cutaneous angiosarcoma, undifferentiated sarcomas, myxofibrosarcoma, undifferentiated pleomorphic sarcoma. This policy position is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes with Keytruda (pembrolizumab) compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.

T. Triple Negative Breast Cancer (TNBC)

1. Keytruda (pembrolizumab) may be used for the following:
    a. As a part of neoadjuvant therapy in combination with chemotherapy and subsequent adjuvant therapy in a member with newly diagnosed high-risk early-stage TNBC (a tumor size greater than 1 cm, less than or equal to 2 cm in diameter with nodal involvement, or tumor size greater than 2 cm in diameter regardless of nodal involvement. NOTE Keytruda may be used as a part of the member's adjuvant therapy ONLY if the member received pembrolizumab in the neoadjuvant setting.
    b. In members with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 with a Combined Positive Score (CPS) greater than or equal to 10.
2. NOTE: Keytruda (pembrolizumab) + Abraxane (nab-paclitaxel) regimen is not supported by Evolent Policies for Keytruda and Abraxane, for the treatment of recurrent unresectable or metastatic breast cancer. This policy position is based on the results of the KEYNOTE 355 trial (referenced below) which showed equivalent outcomes (PFS and OS) in patients treated with Abraxane(nab-paclitaxel) and Taxol (paclitaxel). Please refer to alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.

U. 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 greater than or equal to 10 mutations/megabase (mut/Mb), that have progressed following prior anti-cancer treatment and have no satisfactory alternative anti-cancer treatment options.

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

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1. Keytruda (pembrolizumab) monotherapy may be used in members with recurrent/metastatic urothelial cancer who are not eligible for platinum-based chemotherapy or who have disease progression during or after platinum containing chemotherapy.
2. Keytruda (pembrolizumab) and Padcev (enfortumab vedotin-ejfv) may be used as first line therapy for locally advanced/metastatic urothelial carcinoma

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. Dosing exceeds single dose limit of Keytruda (pembrolizumab) 200 mg every 3 weeks or 400 mg every 6 weeks,

D. Length of Keytruda (pembrolizumab) treatment is greater than 12 months for adjuvant therapy of resected Melanoma or NSCLC.

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 definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, considering 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. CODING INFORMATION

HCPCS Code	Description
J9271	Injection, pembrolizumab, 1 mg

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V. MEDICATION MANAGEMENT

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

VI. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VII. ATTACHMENTS

C. None

VIII. REFERENCES

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