Drug Policy:

Yervoy™ (ipilimumab)

POLICY NUMBER UM ONC_1201	SUBJECT Yervoy™ (ipilimumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 5
DATES COMMITTEE REVIEWED 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22	APPROVAL DATE April 13, 2022	EFFECTIVE DATE April 29, 2022	COMMITTEE APPROVAL DATES 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22	
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 Yervoy (ipilimumab) 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. NOTE 1: The preferred drugs, per NCH Policies & NCH Pathway, for the adjuvant therapy of completely resected stage III melanoma are Opdivo (nivolumab) OR Keytruda (pembrolizumab). Please refer to *UM ONC_1274 Opdivo (nivolumab)* policy or *UM ONC_1263 Keytruda (pembrolizumab)* policy. Adjuvant Yervoy (ipilimumab) + Opdivo (nivolumab) is not recommended in this setting. This recommendation is based on randomized data showing inferior outcomes with Yervoy (ipilimumab + Opdivo (nivolumab) compared to single agent Opdivo (nivolumab).
2. NOTE 2: Per NCH Pathway & NCH Policy, Yervoy (ipilimumab) + Keytruda (pembrolizumab) is a Non-Preferred regimen for first line treatment of unresectable or metastatic melanoma based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes compared to NCH preferred regimens [e.g., Opdivo (nivolumab) +/- Yervoy (ipilimumab)]. Please refer to NCH pathway for the preferred treatments for unresectable or metastatic melanoma.
3. The member has cutaneous melanoma and Yervoy (ipilimumab) may be used as any of the following:
    a. For unresectable or metastatic melanoma:
        i. First line therapy in combination with Opdivo (nivolumab) OR
        ii. Second line or subsequent therapy as a single agent or in combination with Opdivo (nivolumab) in members who have not received prior therapy with Yervoy (ipilimumab).
        iii. NOTE 3: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the recommended dose of Yervoy (ipilimumab) should not exceed 1 mg/kg every 3 weeks for a maximum of 4 cycles with Opdivo (nivolumab) dosed at 3 mg/kg every 3 weeks followed by maintenance Opdivo (nivolumab).

C. Renal Cell Carcinoma

1. The member has a relapsed/metastatic or surgically unresectable disease AND
2. Yervoy (ipilimumab) is being used in combination with Opdivo (nivolumab) for 4 cycles followed by single agent nivolumab for Intermediate or Poor risk disease (as defined by the IMDC criteria). The recommended dose of Yervoy (ipilimumab) in this setting is 1mg/kg IV every 3 weeks for a total of 4 cycles.
3. IMDC Criteria:

CRITERIA= Assign 1 point for each	**RISK CATEGORIES= RISK SCORE**
Time to systemic treatment less than 1 year from diagnosis	Favorable Risk = 0
Performance Status < 80% Karnofsky Scale	Intermediate Risk = 1-2
Hemoglobin < LLN; <12 g/dL	Poor Risk= 3-6

Calcium > ULN; > 12 mg/dL	
Neutrophils > ULN	
Platelets > ULN	

D. Colorectal Cancer

1. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not a preferredregimen per NCH Policy& NCH Pathway for unresectable/metastatic/recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient [dMMR] colorectal cancer. The preferred drug in this setting is single agent Keytruda (pembrolizumab). This recommendation is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes with Yervoy (ipilimumab) + Opdivo (nivolumab) over Keytruda (pembrolizumab) in the above setting. Please refer to *UMC ONC_1263 Keytruda (pembrolizumab)* policy.

E. Hepatocellular Carcinoma (HCC)

1. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not a preferred regimen per NCH Policy or NCH Pathway for the treatment of hepatocellular carcinoma. Please refer to the NCH Pathway document for the most current recommended therapies for hepatocellular carcinoma. This recommendation is based on the lack of Level 1 evidence (randomized trial and/or meta-analyses) showing superior outcomes with Yervoy (ipilimumab) over the preferred second line therapies recommended per the NCH Pathway.

F. Non-Small Cell Lung Cancer

1. NOTE: The combination of [Yervoy (ipilimumab + Opdivo (nivolumab)], [Opdivo (nivolumab + Yervoy (ipilimumab) + Alimta (pemetrexed) + carboplatin/cisplatin], or Opdivo (nivolumab + Yervoy (ipilimumab) +Taxol (paclitaxel) + carboplatin/cisplatin] are Non-Preferred regimens for the treatment of metastatic Non-Small Cell Lung Cancer. Please refer to the NCH Pathway document for the most current recommended regimens/agent for metastatic Non-Small Cell Lung Cancer. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or metanalyses) showing the superiority of the above combination over the recommended regimens for first line therapy of EGFR/ALK negative metastatic NSCLC: a.) [carboplatin/cisplatin + pemetrexed + pembrolizumab] for non-squamous NSCLC and b.) [carboplatin/cisplatin + paclitaxel + pembrolizumab] for squamous NSCLC.

G. Malignant Pleural Mesothelioma

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab), as first line therapy for members with Non-epithelioid subtype (by histology) of metastatic/unresectable Malignant Pleural Mesothelioma. Yervoy (ipilimumab) is dosed at 1 mg/kg every 6 weeks until disease progression or unacceptable toxicities, in the above setting.
2. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not recommended for use in Epithelioid metastatic/unresectable Malignant Pleural Mesothelioma. This recommendation is based on the lack of a survival benefit of the above regimen compared to [platinum + pemetrexed] in the trial by Baas et al referenced below.

III. EXCLUSION CRITERIA

A. Members who experience severe or life-threatening reactions to Yervoy (ipilimumab) including any moderate immune mediated adverse events or symptomatic endocrinopathy.

B. Disease progression during or following treatment with Yervoy (ipilimumab).

C. Dosing exceeds single dose limit of Yervoy (ipilimumab) 3mg/kg when Yervoy is being used as a single agent.

D. Dosing exceeds 1 mg/kg when Yervoy (ipilimumab) is being given in combination with Opdivo (nivolumab).

E. Investigational use of Yervoy (ipilimumab) 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 and/or ASCO guidelines for management of immunotherapy toxicities.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Baas P, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-386.

B. Weber J, et al. CheckMate 238 Collaborators. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-1835.

C. Motzer RJ, et al. CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277-1290.

D. Yervoy prescribing information. Princeton, NJ. Bristol-Myers Squibb Company 2021.

E. Clinical Pharmacology Elsevier Gold Standard 2022.

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

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

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

I. 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.

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