Drug Policy:

Yervoy™ (ipilimumab)

POLICY NUMBER UM ONC_1201	**SUBJECT** Yervoy™ (ipilimumab)		**DEPT/PROGRAM** UM Dept	**PAGE 1 of 6**
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, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22	**APPROVAL DATE** December 16, 2022	**EFFECTIVE DATE** December 30, 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, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
URAC STANDARDS HUM v8: UM 1-2; UM 2-1	**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. When Health Plans utilize NCH UM Oncology Clinical Policies as the initial clinical criteria, and there is no Health Plan PDL applicable, the Preferred Drug Guidelines shall follow NCH recommended agents/regimens/preferred drugs 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 AND
6. When there is a documented drug shortage, disease progression, contraindication, or confirmed intolerance to a preferred drug/regimen, per NCH Policy and Pathway, the available alternative product may be used if deemed medically appropriate and the indication is listed in a standard reference compendia or accepted peer review literature. For a list of current drug shortages, please refer to FDA drug shortage website in the reference section.

B. Colorectal Cancer

1. NOTE: Per NCH Policy, Yervoy (ipilimumab) + Opdivo (nivolumab) is not a preferred regimen for unresectable/metastatic/recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient [dMMR] colorectal cancer. This recommendation is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes compared to NCH recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.

C. Esophageal Squamous Cell Carcinoma (ESCC)

1. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab) as first-line treatment of unresectable advanced/recurrent/metastatic squamous cell esophageal carcinoma, regardless of PD-L1 status.
2. NOTE: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the recommended dose of Yervoy (ipilimumab) is 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years. When the above combination is used with chemotherapy, chemotherapy may continue until disease progression or unacceptable toxicity.

D. Hepatocellular Carcinoma (HCC)

1. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not a preferred regimen per NCH Policy for the first line treatment of unresectable/metastatic recurrent hepatocellular carcinoma; the preferred regimen in this setting is [Avastin (bevacizumab) + Tecentriq (atezolizumab)]. This recommendation is based on the lack of Level 1 evidence (randomized trial and/or meta-analyses) showing superior outcomes in compared to NCH recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.
2. Yervoy (ipilimumab) + Opdivo (nivolumab) may be used as subsequent line therapy for members with unresectable/metastatic hepatocellular carcinoma if the member has not been previously treated with a checkpoint inhibitor. This recommendation is based on the lack of peer-reviewed literature/data to support the use of the above regimen in patients previously treated with a checkpoint inhibitor (e.g., atezolizumab with or without bevacizumab).

E. Malignant Pleural Mesothelioma

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab), as first line therapy for members with metastatic/unresectable Malignant Pleural Mesothelioma. Yervoy (ipilimumab) is dosed at 1 mg/kg every 6 weeks and Opdivo (nivolumab) may be dosed at 3

mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

F. Melanoma

1. NOTE: The preferred drugs, per NCH Policies, 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) or single agent Keytruda (pembrolizumab).
2. 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: 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 (360 mg) every 3 weeks followed by maintenance Opdivo (nivolumab) the latter may be dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks.

G. Non-Small Cell Lung Cancer

1. Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy may be used in metastatic Non- Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression less than 1%.
2. NOTE 1: Per NCH Policy, Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy is a non-preferred regimen when used in metastatic Non-Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression 1% or higher. 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), with or without chemotherapy, compared to NCH recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.
3. NOTE 2: The recommended dose of Yervoy (ipilimumab) should not exceed 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

H. 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).
    a. NOTE: The recommended dose of Yervoy (ipilimumab) in this setting is 1mg/kg IV every 3 weeks for a total of 4 cycles. Opdivo (nivolumab) may be dosed at 3 mg/kg (up to 360 mg) every 3 weeks for 4 cycles followed by single agent Opdivo (nivolumab)

maintenance therapy dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks, until disease progression or unacceptable toxicity.

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	

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). The single dose limit of Opdivo (nivolumab) is 240 mg every 2 weeks, 360 mg every 3 weeks, 480 mg every 4 weeks (regardless of weight).

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 less than 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

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F. 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.

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

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

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

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

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

O. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

P. NCQA UM 2022 Standards and Elements.