

Drug Policy:

Opdivo™ (nivolumab)

POLICY NUMBER UM ONC_1274	SUBJECT Opdivo™ (nivolumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 7
DATES COMMITTEE REVIEWED 03/27/15, 10/14/15, 04/13/16, 06/22/16, 12/21/16, 03/08/17, 03/14/18, 03/13/19, 12/11/19, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 10/14/20, 11/11/20, 12/09/20, 02/10/21, 04/14/21, 05/12/21, 06/09/21, 09/08/21, 11/15/21, 02/09/22, 04/13/22	APPROVAL DATE April 13, 2022	EFFECTIVE DATE April 29, 2022	COMMITTEE APPROVAL DATES 03/27/15, 10/14/15, 04/13/16, 06/22/16, 12/21/16, 03/08/17, 03/14/18, 03/13/19, 12/11/19, 03/11/20, 04/08/20, 06/10/20, 07/08/20, 10/14/20, 11/11/20, 12/09/20, 02/10/21, 04/14/21, 05/12/21, 06/09/21, 09/08/21, 11/15/21, 02/09/22, 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 Opdivo (nivolumab) 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. Opdivo (nivolumab) may be used in members with stage III or metastatic/recurrent melanoma as follows:
 - a. As a single agent for adjuvant therapy of high-risk Stage III melanoma following complete resection of the primary tumor with or without a complete regional lymph node dissection. Maximum duration of therapy is one year. [NOTE: 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 \(nivolumab\).](#)
 - b. As a single agent or in combination with Yervoy (ipilimumab) for recurrent/metastatic melanoma as initial therapy or as subsequent therapy (if the combination was not used previously).
2. [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 every 3 weeks followed by maintenance Opdivo \(nivolumab\).](#)
3. [NOTE: In the above clinical setting, nivolumab preferred dosing recommendations are: 240 mg \(if 67 kg or more\) or 3mg/kg \(if less than 67 kg\) for every 2 weeks dosing.](#)

C. Non-Small Cell Lung Cancer (NSCLC)

1. Opdivo (nivolumab) may be used as neoadjuvant therapy in combination with platinum doublet chemotherapy for up to 3 cycles in members with early stage (IB-III A) NSCLC with tumor size ≥ 4 cm that is negative for EGFR and ALK mutation, regardless of the tumor PD-L1 status.
2. Opdivo (nivolumab) may be used as a single agent as second line or subsequent line therapy for ANY of the following:
 - a. For members with recurrent/metastatic NSCLC that is negative for EGFR and ALK genomic alterations, who have experienced disease progression on platinum-based chemotherapy, except for prior treatment failure with Opdivo (nivolumab) or another checkpoint inhibitor OR
 - b. For members, whose cancer is positive for EGFR/ALK genomic alterations and who have experienced disease progression on targeted therapy and platinum-based therapy, except for prior treatment failure with Opdivo (nivolumab) or another checkpoint inhibitor.
3. [NOTE: Per NCH Policy & NCH Pathway, the combination of Opdivo \(nivolumab\) + Yervoy \(ipilimumab\), with or without chemotherapy, for the treatment of metastatic Non-Small Cell Lung Cancer is a non-preferred regimen. This recommendation is based on the lack of Level 1 evidence \(randomized trials and/or meta-analyses\) to show that either of the above listed regimens containing both ipilimumab & nivolumab are superior to the recommended regimens per NCH Policy and NCH Pathway. The recommended regimens are:](#)

[carboplatin/cisplatin + pemetrexed + pembrolizumab] for non-squamous NSCLC and [carboplatin/cisplatin + paclitaxel + pembrolizumab] for squamous NSCLC.

D. Renal Cell Carcinoma

1. The member has recurrent/metastatic/surgically unresectable stage IV disease and Opdivo (nivolumab) is being used for ONE of the following:
 - a. As first line therapy as monotherapy or in combination with Yervoy (ipilimumab) for IMDC Intermediate or Poor Risk disease.
 - b. NOTE: In the above setting, ipilimumab is dosed at 1 mg/kg every 3 weeks x 4 cycles only, nivolumab is dosed at 3 mg/kg every 3 weeks x 4 cycles followed by single agent nivolumab either as 240 mg every 2 weeks or 480 mg every 4 weeks.
 - c. IMDC criteria: Please see table below.

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	

OR

- d. As subsequent therapy as a single agent and the member has disease progression on prior therapy with one or more tyrosine kinase inhibitors [e.g., Nexavar (sorafenib), Sutent (sunitinib), Cabometyx (cabozantinib), or Votrient (pazopanib)].
2. NOTE: First line therapy with [Cabometyx (cabozantinib) + Opdivo (nivolumab)] for advanced/metastatic clear cell Renal Cell Carcinoma is not recommended per NCH Policy or NCH Pathway. This position is based on the following:
 - a. Our detailed review of the CheckMate9ER trial showed that the HR for OS for IMDC Favorable Risk disease was 0.84, with wide Confidence Intervals that crossed 1.0 (CI 0.35-1.97). The HR for PFS for IMDC Favorable Risk disease was 0.62, however, again the Confidence Intervals were wide and crossed 1.0 (CI 0.38-1.01).
 - b. For IMDC Intermediate and Poor risk disease, there is a lack of Level 1 evidence (randomized trials and/or meta-analysis) to support the superiority of [Cabometyx (cabozantinib) + Opdivo (nivolumab)] over [Opdivo (nivolumab) + Yervoy (ipilimumab)]- the recommended regimen per NCH Policy and NCH Pathway.
 - c. Additionally, for IMDC Intermediate and Poor Risk disease, Cabometyx (cabozantinib) has already been shown to be superior to Sutent (sunitinib) per the CABOSUN trial. Therefore, the control arm-in the CheckMate9ER trial- with single agent Sutent (sunitinib) is not optimal/standard.

E. Hodgkin’s Lymphoma

1. Opdivo may be used in a member with classical Hodgkin's Lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) AND post-transplantation Adcetris (brentuximab vedotin) OR has progressed after 3 or more prior lines of systemic therapy, and the member has not received prior therapy with an Immune Checkpoint Inhibitor.
2. NOTE: Opdivo (nivolumab) given in combination with Adcetris (brentuximab vedotin) is a non-preferred regimen per NCH Policy. This recommendation is based on the lack of Level 1

evidence (randomized clinical trial and/or meta-analyses) to support superior outcomes with the above combination compared to either single agent Opdivo (nivolumab) or single agent Adcetris (brentuximab).

F. Head and Neck Cancer

1. The member has recurrent/metastatic non-nasopharyngeal squamous cell carcinoma of the head and neck cancer and Opdivo (nivolumab) is being used as a single agent following disease progression during or after platinum-based chemotherapy.

G. Urothelial Carcinoma including Upper Tract and Urethral Carcinomas

1. The member has locally advanced or metastatic urothelial carcinoma and has experienced disease progression during or after platinum-based chemotherapy **OR**
2. Opdivo (nivolumab) may be used as adjuvant treatment up to a maximum of 1 year duration in members with urothelial carcinoma (excluding UTUC or tumors originating in the renal pelvis/ureter), at high risk for recurrence (defined as T3/T4 disease and/or positive node or margins), **AND** the member is not a candidate for cisplatin-based chemotherapy **OR**
3. Opdivo (nivolumab) may be used as monotherapy for members with high-risk, non-muscle invasive bladder cancer, with Tis with or without papillary tumors, who are not eligible for cystectomy, and is refractory to/not responding to treatment with BCG.
4. **NOTE: Unless contraindicated or not tolerated, Keytruda (pembrolizumab) is the preferred Checkpoint Inhibitor/Immunotherapy agent over Opdivo (nivolumab) for use in recurrent/metastatic urothelial cancer. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to show Opdivo (nivolumab) is superior to Keytruda (pembrolizumab). Please refer to UM ONC_1263 Keytruda (pembrolizumab) policy.**

H. Colorectal Cancer

1. Opdivo (nivolumab) may be used in a member that has unresectable/metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer that has progressed following prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan **AND**
2. Opdivo (nivolumab) will be used as a single agent or in combination with Yervoy (ipilimumab) **AND**
3. The member has not had disease progression on prior therapy with Opdivo (nivolumab) or another checkpoint inhibitor, e.g., Keytruda (pembrolizumab) or Jemperli (dostarlimab-gxly).
4. **NOTE: Per NCH Pathway & NCH Policy, Opdivo (nivolumab) +/- Yervoy (ipilimumab) is a Non-Preferred regimen for the treatment of metastatic MSI-High colorectal cancer, the preferred Checkpoint Inhibitor in this setting is Keytruda (pembrolizumab). Please refer to UM ONC_1263 Keytruda (pembrolizumab) policy.**

I. Esophageal Carcinoma

1. **Squamous Cell Carcinoma of Esophagus**
 - a. The member has advanced, recurrent, or metastatic esophageal squamous cell carcinoma **AND**
 - b. Has experienced disease progression on or after prior fluoropyrimidine based chemotherapy (e.g., fluorouracil or capecitabine) and platinum-based chemotherapy (e.g., cisplatin, carboplatin, or oxaliplatin) **AND**
 - c. Opdivo (nivolumab) will be used as a single agent as second line or subsequent therapy, regardless of PD-L1 status.
2. **Adenocarcinoma of Esophagus:** The member has advanced/metastatic esophageal adenocarcinoma with a PD-L1 CPS ≥ 5 and Opdivo (nivolumab) may be used as

primary/initial therapy in combination with an oxaliplatin containing chemotherapy (e.g., FOLFOX/CapeOX).

3. **Squamous Cell Carcinoma and Adenocarcinoma of Esophagus:** Opdivo (nivolumab) may be used as monotherapy, for a total duration of 1 year, for members with stage II or III esophageal carcinoma who are found to have residual disease after neoadjuvant chemoradiotherapy and surgery.

J. Gastric Cancer and Gastroesophageal Junction Cancer

1. The member has advanced/metastatic gastric or gastroesophageal junction cancer with a PD-L1 CPS \geq 5 **AND**
2. Opdivo (nivolumab) may be used as primary/initial therapy in combination with an oxaliplatin containing chemotherapy (e.g., FOLFOX/CapeOX).

K. Malignant Pleural Mesothelioma

1. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab), as first line therapy for members with non-epithelioid subtype (by histology) of metastatic/unresectable Malignant Pleural Mesothelioma. The recommended dose of Opdivo (nivolumab) is 360 mg every 3 weeks + Yervoy (ipilimumab) 1 mg/kg every 6 weeks until disease progression, unacceptable toxicities, or up to 24 months of therapy in the above setting.
2. Opdivo (nivolumab) may be used as monotherapy or in combination with Yervoy (ipilimumab) (if was not previously used) in metastatic/unresectable malignant pleural mesothelioma, in the 2nd line/subsequent line setting, regardless of the histologic sub-type, in members who experienced disease progression on prior first line chemotherapy.
3. **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 for the Epithelioid subtype compared to [platinum + pemetrexed] in the trial by Baas et al. referenced below.

III. EXCLUSION CRITERIA

- A. Disease progression while taking Opdivo (nivolumab) or other PD-1/PDL-1 therapy, except when member is being switched to combination Opdivo (nivolumab) + Yervoy (ipilimumab) for melanoma.
- B. For the adjuvant treatment of Melanoma, length of Opdivo (nivolumab) treatment is greater than 12 months.
- C. Investigational use of Opdivo (nivolumab) 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

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- D. Choueiri TK, et al. CheckMate 9ER Trial. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2021 Mar 4;384(9):829-841.
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- G. Clinical Pharmacology Elsevier Gold Standard 2022.
- H. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO 2022.
- I. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2022.
- J. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs Bethesda, MD 2022.

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