COMPENDIA TRANSPARENCY TRACKING FORM

DATE: August 30, 2022

OFF-LABEL ID #: 2398

DRUG NAME: Nivolumab

OFF-LABEL USE: Malignant tumor of cervix; Recurrent, persistent, or metastatic

COMPENDIA TRANSPARENCY REQUIREMENTS	
1	Provide criteria used to evaluate/prioritize the request (therapy)
2	Disclose evidentiary materials reviewed or considered
3	Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest
4	Provide meeting minutes and records of votes for disposition of the request (therapy)

EVALUATION/PRIORITIZATION CRITERIA: C, *to meet requirement 1

CODE	EVALUATION/PRIORITIZATION CRITERIA
A	Treatment represents an established standard of care or significant **advance** over current therapies
C	**Cancer** or cancer-related condition
E	Quantity and robustness of **evidence** for use support consideration
L	**Limited** alternative therapies exist for condition of interest
P	**Pediatric** condition
R	**Rare** disease
S	**Serious**, life-threatening condition

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Tamura, K, Hasegawa, K, Katsumata, N, et al: Efficacy and safety of nivolumab in Japanese patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma: Multicenter, open-label phase 2 trial. Cancer Sci Sep 2019; Vol 110, Issue 9; pp. 2894-2904.	This was a prospective multicenter single-arm phase 2 study that investigated treatment with nivolumab in Japanese patients with advanced or recurrent cervical cancer, uterine cancer, or soft tissue sarcoma. The risk of bias due to confounding, selection of participants, classification of intervention, deviation from intervention, missing data, and selective reporting were deemed low risk. The risk of bias associated with measurement of outcome was deemed moderate risk due to lack of central outcome assessment. Additional bias could be introduced due to small sample effects.	S
Santin, AD, Deng, W, Frumovitz, M, et al: Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002). Gynecol Oncol Apr 2020; Vol 157, Issue 1; pp. 161-166.	This was a prospective multicenter single-arm phase 2 study that investigated treatment with nivolumab in US American patients with persistent or recurrent cervical cancer. The risk of bias due to confounding, selection of participants, classification of intervention, deviation from intervention, missing data, and selective reporting were deemed low risk. The risk of bias associated with measurement of outcome was deemed moderate risk due to lack of central outcome assessment. Additional bias could be introduced due to small sample effects.	S
Naumann, RW, Hollebecque, A, Meyer, T, et al: Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 Trial. J Clin Oncol Nov 01, 2019; Vol 37, Issue 31; pp. 2825-2834.	This was an international prospective multicenter multiple-cohort phase 1/2 study that investigated treatment with nivolumab in patients with virus-associated solid tumors. This article analyzed the cohort of patients with metastatic or recurrent cervical, vaginal, or vulvar cancer. The risk of bias due to confounding, selection of participants, classification of intervention, deviation from intervention, missing data, and selective reporting were deemed low risk. The risk of bias associated with measurement of outcome was deemed moderate risk due to lack of central outcome assessment. Additional bias could be introduced due to small sample effects.	S
Naumann, RW, Oaknin, A, Meyer, T, et al: Efficacy and safety of nivolumab (Nivo)+ ipilimumab (Ipi) in patients (pts) with recurrent/metastatic (R/M) cervical cancer: results from CheckMate 358. Ann Oncol 2019; Vol 30, Issue Suppl 5; pp. v898-v899.		2

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Megan Smith	None		
Stacy LaClaire, PharmD	None		
Catherine Sabatos, PharmD	None		
		Howard Goodman	None
		Jeffrey Klein	None
		Richard LoCicero	Incyte Corporation Local PI for REVEAL. Study is a multicenter, non-interventional, non-randomized, prospective, observational study in an adult population for patients who have been diagnosed with clinically overt PV and are being followed in either community or academic medical centers in the US who will be enrolled over a 12-month period and observed for 36 months.

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
IBM MICROMEDEX	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases		B

Howard Goodman	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	There are few options available for treating patients with metastatic cervical cancer who have progressed after chemotherapy. In addition most cervical cancers arise from HPV suggesting that immune therapy may have a significant role in therapeutic options. In the study by Tamura et al. the overall response rate for the cohort with cervical cancer was 25%. When stratified by POL1 status, however, response rate was 33% in the positive patients and O in the negative patients certainly suggesting in this trial that there is a role for this drug in POL1 positive tumors. These findings are consistent to the Keynote trial that used a similar POL1 agent, Keytruda, in a similar cohort with a response rate of 17% in the POL1 positive cohort. Responses only seen in the POL1 positive subgroup. In the study by Nauman et al. the overall response rate was 26% consistent with the studies noted above. Responses were sustained in this trial with median duration of response not reached at 19 months in the responding group. This was a small study making subgroup analysis, POL1 positive vs negative, difficult. In the final study by Santin et al. the overall response rate was low at 4% with poor ability to correlate with POL1 status due to the low number of evaluable patients. Based on the papers presented and correlating with data from Keynote using Keytruda, it would appear that Nivolumab is sufficiently active in the POL1 positive patients to recommend its use in this cohort	
Jeffrey Klein	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	The use of Nivolumab to treat recurrent, persistent, or metastatic cervical cancer, demonstrated a good degree of efficacy and safety. The patient type chosen to receive this medication should be PD-L1 positive and MSI high with biomarker testing, as these patients respond much better.	
Richard LoCicero	Evidence is Inconclusive	Class III: Not Recommended	Three phase II trials have evaluated the efficacy of nivolumab in the treatment of cervix cancer. While some (~25%) responses were observed, insufficient clinical trial data exists to support clinical benefit (i.e., improvement in survival time). No unexpected toxicities were reported.	