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NCCN Guidelines: Uterine Neoplasms

On behalf of Merck & Co., Inc., I respectfully request the **NCCN Uterine Neoplasms Panel** to review the enclosed data for the inclusion of KEYTRUDA (pembrolizumab) as a systemic therapy treatment option for unresectable or metastatic microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.

Specific changes requested:

Recommend the addition of Keytruda (pembrolizumab) as a systemic treatment option for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that has progressed following prior treatment and who have no satisfactory alternative treatment options or with colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

FDA approval:

KKEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.6)

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.6)

Rationale:

The presence of high levels of MSI (MSI-H) or dMMR signifies an underlying problem in a cell's ability to repair errors that occur during the DNA replication process. Tumor cells determined to have MSI-H or dMMR, harbor

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thousands of mutations and signals that may be particularly susceptible to treatment with immunotherapy. Patients with advanced or metastatic disease that progresses after initial therapy have limited treatment options with no optimal therapy in the majority of the cases.

Keytruda was recently approved by the FDA for the treatment of patients with MSI-H or dMMR unresectable or metastatic solid cancers that didn't respond to standard treatments and who have no satisfactory alternative treatment options.

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression [see Clinical Studies (14.6)].

The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

The efficacy of KEYTRUDA was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks until unacceptable toxicity; or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status; or a maximum of 24 months. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST 1.1 and duration of response.

A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% patients with other solid tumors received two or more prior lines of therapy.

Table 23: MSI-H Trials

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

Efficacy results are summarized in Table 24 and 25 of the PI.

Table 24. Efficacy Results for Patients with MSI-H/ dMMR

Endpoint	**n=149**
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 25. Response by tumor type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

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There is limited experience with KEYTRUDA in pediatric patients. In a study, 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab; toxicities that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%) and hyponatremia (18%).

Efficacy for pediatric patients with cHL or MSI-H cancers is extrapolated from the results in the respective adult populations [see Clinical Studies (14.4, 14.6)].

The following resources are submitted to assist the committee with the review:

KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,



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