October 23, 2018

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NCCN Guidelines Panel: Bladder Cancer

On behalf of Merck & Co., Inc., I respectfully request the NCCN Bladder Cancer Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V5.2018 for Bladder Cancer.

Specific changes requested:

We respectfully request the NCCN Bladder Cancer panel to consider adding KEYTRUDA (pembrolizumab) as a treatment option for patients with BCG unresponsive high-risk non-muscle invasive bladder cancer (HR NMIBC) who were considered ineligible for or have refused to undergo radical cystectomy.

FDA Approval:

KEYTRUDA (pembrolizumab) is not approved for the treatment of patients with HR NMIBC.

Please see enclosed prescribing information for other FDA-approved indications (PI).[1]

Rationale:
KEYNOTE-057 (NCT02625961) is an ongoing phase 2 study evaluating the efficacy and safety of pembrolizumab as monotherapy in BCG unresponsive HR NMIBC who are considered ineligible for or have refused to undergo radical cystectomy. Cohort A included patients with carcinoma in situ (CIS) with or without papillary disease high-grade Ta tumor or T1. Primary objective for cohort A is complete response (CR) defined as the absence of HR NMIBC. Secondary endpoints are CR defined as the absence of HR or low-risk NMIBC and duration of response (DOR).[2]

First interim analysis results from cohort A (n=103) were based on a median follow-up of 14 months with a data cutoff date of July 18, 2018:

- CR per central assessment at month 3 was 38.8% (40/103) (95% CI, 29.4-48.9). Of those patients who had CR, 72.5% (n=29) had an ongoing response at the time of analysis, 25% (n=10) had recurrent NMIBC after CR and no patients developed muscle invasive or metastatic disease.
- Median DOR was not reached (range, 0+ to 14.1+ months) with response ≥6 months in 80% of responders based on KM curve.
- Treatment related adverse events of any grade occurred in 63.1% of patients, with grade 3-5 occurring in 12.6%. Six patients (5.8%) discontinued treatment due to a treatment-related adverse event. Three patients died due to; respiratory failure from MRSA pneumonia (n=1), metastatic pancreatic cancer (n=1) and one death was due to TRAE (patient had recurrent grade 3 colitis during the survival follow-up that was not adequately treated with steroids and subsequently developed intestinal perforation during colonoscopy procedure, which led to fevers, hypotension and subsequent death).
- Safety profile in KEYNOTE-057 cohort A was consistent with the previously established safety/tolerability profile of pembrolizumab in other tumor types.

To assist the committee with their review, I have included the following resources:

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

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2. DeWit R, et al. Pembrolizumab for high-risk non-muscle invasive bladder cancer unresponsive to BCG): results from cohort A of KEYNOTE-057. Presented at the 2018 ESMO Annual Meeting; October 19-23, 2018; Munich, Germany.

Thank you for considering this request. Please contact me for any additional information.

Sincerely,

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