Bristol-Myers Squibb

April 19, 2019

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NCCN Guidelines® Panel: Colon/Rectal/Anal Cancers

Dear Panel Members:

On behalf of Bristol-Myers Squibb Company, I respectfully submit the enclosed OPDIVO® (nivolumab) prescribing information and clinical data which supports the most recent label change that occurred on April 18, 2019, for your consideration. The updated prescribing information reflects the approved new dosing option for nivolumab for treatment of dMMR/MSI-H metastatic colorectal cancer after prior therapy with fluoropyrimindine, oxaplatin, and irinotecan, as follows:

- Single-agent nivolumab 480 mg administered intravenously every 4 weeks
- Nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 480 mg every 4 weeks

Specific Changes:

- NCCN Guideline for Colon Cancer
  - Request to update nivolumab dosing information on page COL-D 9 of 10 to include:
    - *Nivolumab 480 mg IV every 4 weeks*
    - Nivolumab 3 mg/kg (30 min IV infusion) and ipilimumab 1 mg/kg once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks *or nivolumab 480 mg every 4 weeks*
- NCCN Guideline for Rectal Cancer
  - Request to update nivolumab dosing information on page REC-F 9 of 10 to include:
    - *Nivolumab 480 mg IV every 4 weeks*
    - Nivolumab 3 mg/kg (30 min IV infusion) and ipilimumab 1 mg/kg once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks *or nivolumab 480 mg every 4 weeks*

FDA Clearance of OPDIVO® (nivolumab) (indication in metastatic colorectal cancer):

- Adult and pediatric (12 years and older) patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.[2]

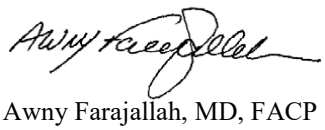
Rationale: The Opdivo Prescribing Information was updated to reflect the new dosing of OPDIVO, as single agent and as maintenance therapy when used in combination with ipilimumab, for treatment of dMMR/MSI-H mCRC after prior therapy to 480 mg IV every 4 weeks. The dosing recommendation stated in the product label is different than the dose that was administered in the registrational clinical studies that supported the current approved indication.

As part of this submission, the published literature that support the pharmacokinetic analyses for the dosing of 480 mg is enclosed for your review.

1. Product information, OPDIVO® (nivolumab) injection. Bristol-Myers Squibb Company, Princeton, NJ. April 2019.
2. Long GV, Tykodi SS, Schneider JG et al. Assessment of nivolumab exposure and clinical safety of 480mg every 4 weeks flat-dosing schedule in patients with cancer. *Annals of Oncology* 2018; 29:2208–2213

Thank you for your consideration of this request.

Sincerely,



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