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NCCN Guidelines® Panel: Hodgkin Lymphoma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I submit to the Hodgkin Lymphoma Panel the prescribing information for OPDIVO® (nivolumab) with an updated indication, and extended follow-up data from a Phase 1 study.

OPDIVO has received accelerated approval for the treatment of patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

Specific Changes: Please consider adding nivolumab with a Category 1 designation to the list of regimens in "Second-Line or Subsequent Therapy Options" for patients with cHL who have received autologous HSCT and post-transplantation brentuximab vedotin (page HODG-E).

FDA Clearance: On May 17, 2016, the FDA approved the use of nivolumab in patients with cHL, as stated above. Nivolumab is also approved in the treatment of patients with[1]:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
  This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Unresectable or metastatic melanoma, in combination with ipilimumab.
  This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Metastatic non-small cell lung cancer and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

Rationale: The FDA granted accelerated approval for the use of nivolumab in patients with cHL, as stated above. Clinical efficacy and safety data from the product label is described below.
In addition, extended follow-up data from the Phase 1 study presented at ASH 2015 as an oral presentation, is described below, and attached for consideration.

Clinical efficacy and safety data from product label[1]:
The efficacy and safety of nivolumab 3mg/kg every 2 weeks as a single agent in patients with cHL after failure of autologous HSCT and post-transplantation brentuximab vedotin was evaluated in a Phase 2 and a Phase 1 trial.

The Phase 2 trial was a single-arm, open-label, multicenter, multicohort study in cHL. The Phase 1 trial was an open-label, multicenter, dose escalation study that included cHL. Efficacy was evaluated on the basis of the objective response rate (ORR) as determined by an independent radiographic review committee per the 2007 revised International Working Group Criteria, and the additional outcome, duration of response.[1]

The efficacy was evaluated in 95 patients from the Phase 2 and Phase 1 trials combined who had received brentuximab vedotin after failure of autologous HSCT. Patients median age was 37 years (range: 18, 72) and had received a median of 5 prior systemic regimens (range: 3, 15). Patients received a median of 17 doses of nivolumab (range: 3, 48), with a median duration of therapy of 8.3 months (range: 1.9, 24). The efficacy results are:

- ORR: **65%** (n=62/95); [95% CI: 55, 75]
  - Complete remission rate: **7%** (n=7/95); [95% CI: 3, 15]
  - Partial remission rate: **58%** (n=55/95); [95% CI: 47, 68];
- Median duration of response: **8.7 months**, [95% CI: 6.8, not estimable]; range: 0.0+, 23.1+
- Median time to response: **2.1 months**; range: 0.7, 5.7

The safety was evaluated in 263 adult patients with cHL (240 patients in the Phase 2 trial and 23 patients in the Phase 1 trial). Patients received a median of 10 doses of nivolumab (range: 1, 48), with a median duration of therapy of 4.8 months (range: 0.3, 24). Safety information is described below:

- Serious adverse reactions occurred in 21% of patients. The most frequent serious adverse reactions reported in at least 1% of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash and pneumonitis.
- Nivolumab was discontinued in 4.2% of patients due to adverse reactions; 23% of patients had a dose delay for an adverse reaction.
- Ten patients died for causes other than disease progression, including 6 who died from complications of allogeneic HSCT.
- The most common adverse reactions (reported in at least 20% of patients) were fatigue, upper respiratory tract infection, pyrexia, diarrhea, and cough.

Please refer to Section 5. Warnings and Precautions, Section 6.1. Adverse Reactions, Clinical Trials Experience: Classical Hodgkin Lymphoma, and Section 14.4. Clinical Studies, Classical Hodgkin Lymphoma for additional information on clinical safety and efficacy of nivolumab in patients with cHL.

Clinical outcomes from extended follow-up of Phase 1 study[2]:

The extended follow-up (median 101 weeks) of 23 patients with relapsed or refractory cHL from the Phase 1 study described above showed:

- Investigator-assessed ORR: 87% (n = 20/23); [95% CI: 66.4, 97.2]
  - Complete response: 22% (n = 5/23); [95% CI: 7.5, 43.7]
  - Partial response: 65% (n = 15/23); [95% CI: 42.7, 83.6]
- Stable disease: 13% (n=3/23)
- Duration of Response (DOR):
  - Median DOR: Not reached, [95% CI: 15.5, NA]
- Median progression-free survival (PFS): Not reached, [95% CI: 18.6, NA]

- Overall survival (OS):
  - OS rate at 1 year: 91% (95% CI: 69.5, 97.8)
  - OS rate at 1.5 years: 83% (95% CI: 60.1, 93.1)

- Select treatment-related Grade 3 adverse events: colitis (n = 1) and pneumonitis (n = 1), which resolved
- Treatment-related serious adverse events: 13% (n = 3) including Grade 2 lymph node pain (n = 1), Grade 3 pancreatitis (n = 1), and Grade 3 myelodysplastic syndrome (n = 1)[3]
- Three patients discontinued due to adverse events, 2 of which were considered study drug related (1 case each of pancreatitis and myelodysplastic syndrome, both grade 3).

Citations:

1. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. May 2016
2. Ansell SM, Armand P, Timmerman J et al. Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin Lymphoma (R/R cHL): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039). Oral presentation at, The 57th American Society of Hematology annual meeting and exposition; December 5-8; Orlando, FL.
3. Ansell SM, Lesokhin AM, Borrello I et al. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *N Engl J Med.* 2015;372:311-9. DOI: 10.1056/NEJMoa1411087

Thank you for your consideration of this request.

Sincerely,

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