



Submitted by:

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NCCN Guidelines® Panel: Hodgkin Lymphoma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully submit to the Hodgkin Lymphoma Panel the Opdivo clinical data from the Phase 2 study (Nivolumab for classical Hodgkin lymphoma after autologous stem-cell transplantation and brentuximab vedotin failure) that was recently published in Lancet Oncology 20 July 2016.

These data are being submitted in response to a standing request from the NCCN for new data.

FDA Clearance (cHL indication): Opdivo is the only PD-1 inhibitor approved 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:

1. Please consider changing the recommendation for nivolumab “as an option for CHL that has relapsed or progressed following HDT/ASCR and brentuximab vedotin *maintenance therapy*” to “an option for CHL that has relapsed or progressed following HDT/ASCR and *post-transplantation brentuximab vedotin*” in both the Guidelines (HODG-E) and Compendia, to be consistent with the labeled indication.
2. Please also consider including nivolumab as an option for relapsed or refractory disease for the management of older patients rather than as palliative therapy, in both the Guidelines (HODG-F) and Compendia.

Rationale:

1. The current statement around the use of nivolumab after brentuximab vedotin maintenance therapy implies that nivolumab is only an option in patients who have received brentuximab vedotin as maintenance therapy post-transplant. The label and clinical data indicate that patients who have received brentuximab vedotin after failure of ASCT are also eligible to receive nivolumab.
2. Nivolumab’s approval in patients with cHL does not include any limitations or precautions regarding older patients, and there are no data with nivolumab that indicate worse outcomes or worse tolerability in older adults with cHL. The nivolumab monotherapy trials in cHL did not include a sufficient number of patients aged 65 years and older to prove that they respond differently from younger patients. In addition, data for nivolumab monotherapy across trials in multiple tumor types show no overall differences in safety or efficacy were reported between elderly patients and younger patients (please refer to section 8.5, Geriatric Use, of the product label).

The clinical data from the Phase 2 study recently published in Lancet Oncology is described below for your information. This data set includes response rates in 43 patients who had no prior response to brentuximab vedotin.

Clinical efficacy and safety data from CheckMate 205:

The clinical data from the CheckMate 205 was previously shared (May 18, 2016) as part of an integrated analysis with a Phase 1 trial that was the basis of approval of Opdivo in cHL. Data published in Lancet Oncology is specific to the Phase 2 trial-Cohort B and is summarized below.

This phase 2 trial was a single-arm, open-label, multicenter, multicohort study in cHL. Cohort B, for which we present the data, evaluated the efficacy and safety of nivolumab 3mg/kg every 2 weeks as a single agent in patients with cHL after failure of both autologous HSCT and subsequent brentuximab vedotin. The primary endpoint was objective response rate (ORR) per 2007 International Working Group criteria based on independent radiologic review committee (IRRC) assessment. Secondary endpoints based on IRRC assessment included duration of objective response, complete and partial remission rates and their duration, and ORR and duration of objective response based on investigator assessment. Exploratory endpoints included IRRC-assessed progression-free survival (PFS), overall survival (OS), safety and tolerability (adverse events, AEs, reported between the first dose and 30 days after the last dose), quality of life, and analyses of 9p24.1 alterations and PD-1 ligand expression.

The efficacy and safety was evaluated in 80 patients who had received brentuximab vedotin after failure of autologous HSCT. Patients median age was 37 (IQR 28-48) years, and had received a median of 4 prior lines of therapy (IQR 4-7); 49% (39/80) received ≥ 5 prior lines of therapy. Patients received a median of 17 doses of nivolumab (IQR 13-20), with a median follow-up duration of 8.9 (IQR 7.8-9.9) months. The efficacy results are:

- ORR: **66.3%** (n=53/80); [95% CI: 54.8, 76.4]
 - Complete remission: **9%** (n=7/80)
 - Partial remission: **58%** (n=46/80)
- Median duration of response: **7.8 months**, [95% CI: 6.6, not reached]
- Median time to response: **2.1 months** (IQR 1.9-3.0)
- 6-month PFS rate: **76.9%** (95% CI: 64.9, 85.3)
- 6-month OS rate: **98.7%** (95% CI: 91.0, 99.8)
- Median PFS: **10 months** (95% CI: 8.41, not reached)

There were 43 patients who had no prior response to most recent prior brentuximab vedotin. The ORR in these patients was 72% (n=31/43).

Safety information is described below:

- The most common drug-related AEs were fatigue (25%), infusion-related reaction (20%), rash (16%), arthralgia (14%), pyrexia (14%), nausea (13%), diarrhea (10%), and pruritus (10%).
- Grade 3 and 4 AEs occurred in 33% and 8% of patients, respectively; the most common drug-related grade 3-4 AEs being neutropenia (5% grade 3) and increased lipase (3% grade 3, and 3% grade 4).
- Serious AEs of any cause were reported in 25% of patients, the most common being pyrexia (4%); serious drug-related AEs occurred in 6% (5/80) of patients, the most common being infusion-related reaction (3%).
- One grade 5 AE occurred (1%; multi-organ failure)
- Among the 6 patients who underwent stem-cell transplantation (5 allogeneic and 1 autologous), acute graft-versus-host disease (GVHD) was reported in 3 patients (two grade 1, one grade 2). At time of this analysis, no cases of chronic GVHD had been reported. All patients who underwent transplantation following nivolumab treatment were alive at the time of analysis.
- Nivolumab was discontinued in 5% (4/80) of patients due to treatment-related adverse reactions.

- The most frequently reported select adverse events of special interest included:
 - skin abnormalities (41%; 33/80)
 - gastrointestinal abnormalities (26%; 21/80)
 - hypersensitivity/infusion-related reaction (21%, 17/80)
 - endocrine (18%, 14/80)
 - hepatic (10%, 8/80)
 - renal (5%, 4/80)
 - pulmonary (1%, 1/80)

The following resources are submitted for your review:

1. Opdivo Prescribing Information
2. Younes A, Santoro A, Shipp M et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial [published online July 20, 2016]. *Lancet Oncology*. [http://dx.doi.org/10.1016/S1470-2045\(16\)30167-X](http://dx.doi.org/10.1016/S1470-2045(16)30167-X).

Thank you for your attention to this submission.

Sincerely,

A handwritten signature in black ink, appearing to read "Awny Farajallah". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology
Bristol-Myers Squibb Company