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NCCN Hodgkin Lymphoma Guideline Panel

Request for review of recent FDA approval and updated clinical data for the recommendation for brentuximab vedotin (ADCETRIS®) as frontline therapy for classic Hodgkin Lymphoma (cHL)

In light of recent FDA approval[1] and updated clinical data[2] of brentuximab vedotin in combination with chemotherapy for previously untreated patients with advanced cHL, Seattle Genetics respectfully request the NCCN Panel to review the guideline recommendation for frontline BV+AVD.

FDA Clearance: On March 20, 2018, the FDA approved ADCETRIS for the treatment of adult patients with previously untreated Stage 3 or 4 classical Hodgkin lymphoma in combination with chemotherapy.[1]

Suggested Changes: We respectfully ask the NCCN Panel to consider the following modifications[1-3]:

- **HODG-10, "Classic Hodgkin Lymphoma Stage III-IV Primary Treatment":**
  Modify current recommendation to:
  "Brentuximab vedotin (BV) + AVD (category 2A)" with the following suggested footnote:
  - "BV plus chemotherapy is approved by the FDA as frontline treatment of patients with previously untreated stage III or IV cHL based on improved modified PFS over ABVD in the phase 3 ECHELON-1 study. Given that BV+AVD has a different safety profile than that of ABVD, patient-specific factors such as presence of neuropathy or bleomycin contraindication should be considered."

Rationale:
The recent FDA approval of BV plus chemotherapy[1] for previously untreated Stage 3 or 4 cHL extends the current frontline treatment options for patients with advanced cHL. Approval was supported by the global, phase 3, randomized, ECHELON-1 trial that demonstrated significantly higher modified PFS for BV+AVD compared with ABVD.[2,3] A prospectively planned subgroup analysis among North American patients demonstrated that BV+AVD significantly increased 2-year modified PFS by IRF by 10.6% (HR=0.596; *P*=0.012). Similarly, there was an increase in 2-yr modified PFS by investigator of 12.8% (HR=0.516; *P*=0.002) compared with ABVD.[2] Traditional PFS per Investigator (defined as progression or death) in the North American patient population also significantly favored BV+AVD with an increased in 2-year PFS of 11.7% (HR=0.500; *P*=0.012). The toxicity profiles differed, most notably with higher bleomycin-related pulmonary toxicity in the ABVD arm and higher neutropenia and peripheral neuropathy in the BV+AVD arm.[3] In the patients

receiving BV+AVD, myelotoxicity was significantly reduced with prophylactic G-CSF and neurotoxicity was largely reversible.[3]

Clinical Data:

Phase 3, randomized study data for patients with previously untreated stage III or IV cHL[2,3]

The phase 3 ECHELON-1 trial randomized 1334 patients with previously untreated stage III-IV cHL to BV+AVD versus ABVD as frontline therapy.[3] After a median follow-up of 24.9 months, BV+AVD was associated with a statistically significant 23% reduction in the risk of a modified PFS event versus ABVD in the overall population as assessed by independent review (hazard ratio [HR], 0.77; 95% CI, 0.60-0.98; *P*=0.04). Modified PFS was defined as time to progression, death, or receipt of additional anticancer therapy for patients who were not in complete remission after completion of frontline therapy. The 2-year modified PFS rate was 82.1% in the BV+AVD arm versus 77.2% in the ABVD arm. Results of the interim analysis of OS and all other secondary efficacy endpoints trended in favor of BV+AVD. Further, the benefit of BV+AVD was observed consistently in prespecified subgroups, including across all IPS groups (defined as IPS 0-1; 2-3; and 4-7).[3]

An analysis of the North American results of ECHELON-1 showed even stronger benefits of BV+AVD.[2] Among these 497 patients, 2-year modified PFS per independent review was 84.3% for BV+AVD versus 73.7% for ABVD (HR, 0.596; 95% CI, 0.395-0.899). Modified PFS per investigator review was similar: 86.4% for BV+AVD versus 73.6% for ABVD (HR, 0.516; 95% CI, 0.339-0.786). PFS per investigator review at 2 years was also higher with BV+AVD (88.1% vs 76.4%; HR, 0.500; 95% CI, 0.318-0.786). Again, the benefit over ABVD was consistent across all prespecified subgroups.[2]

The adverse event profiles differed between the BV+AVD and ABVD treatment groups.[3] Overall, pulmonary toxicity was reported in 2% of the patients in the BV+AVD group versus 7% in the ABVD group; pulmonary events of grade 3 or higher were reported in less than 1% of the BV+AVD group and 3% of the ABVD group. Peripheral neuropathy occurred in 67% of patients who received BV+AVD and 43% of patients who received ABVD; the majority of these were resolved or improved by the last visit. Neutropenia occurred in 58% of the patients receiving BV+AVD and in 45% of those receiving ABVD. G-CSF primary prophylaxis was administered at the investigators' discretion and recommended by an independent data monitoring committee for the BV+AVD group during protocol. Patients in the BV+AVD group who received G-CSF had lower rates of febrile neutropenia (11% vs 21%).[3]

Sincerely,

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References (**enclosed**):

1. ADCETRIS. [prescribing information]. Bothell, WA: Seattle Genetics, Inc; 2017.
2. Ramchandren R, Advani R, Ansell S, et al. Brentuximab Vedotin (BV) plus Chemotherapy in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma (HL): North American Results. 2018 ASCO Annual Meeting. June 4, 2018; Chicago, IL. Abstract 7534.
3. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *N Engl J Med*. 2017;378(4):331-344.