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NCCN Hodgkin Lymphoma Guideline Panel:

On behalf of Seattle Genetics, Inc., I respectfully request the NCCN Hodgkin Lymphoma Panel review the enclosed data and consider revising the Category of Evidence and Consensus to a Category 2A for the use of brentuximab vedotin (ADCETRIS®) in combination with nivolumab as a second-line treatment option for relapsed/refractory classic Hodgkin Lymphoma (cHL).

FDA Clearance: Brentuximab vedotin is indicated for use in multiple lines of therapy for the treatment of adult patients with cHL, including: previously untreated Stage 3 or 4 cHL in combination with doxorubicin, vinblastine, and dacarbazine; cHL at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation; and cHL after failure of auto-HSCT or at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates. Brentuximab vedotin is also approved for use for several indications of CD30-expressing peripheral T-cell lymphomas.[1]

Rationale: The NCCN Hodgkin Lymphoma panel has recently included the combination of brentuximab vedotin with nivolumab as a second-line treatment option for relapsed/refractory cHL in Version 1.2019 of the Hodgkin Lymphoma NCCN Guidelines as a Category 2B recommendation.[2] The recommendation was based on interim trial results evaluating the combination of brentuximab vedotin and nivolumab published in Blood 2018.[3] Since the publication of these interim data, Part 3 of the trial has enrolled an additional 30 patients. Additional analyses with longer term follow up, as well as data from Part 3 of the trial, were presented at the 2018 International Symposium for Hodgkin Lymphoma (ISHL) and the 2018 Annual Meeting of the American Society of Hematology (ASH).[4-6] Further, data from a second trial of brentuximab vedotin and nivolumab have recently been presented at ASH 2018.[7,8] Similar to the results reported by Herrera, et al this study demonstrated high complete response (CR) and overall response rates (ORR) in a pediatric, adolescent and young adult population. We submit data from these two trials as additional evidence for consideration by the NCCN Hodgkin Lymphoma Panel.

Clinical Evidence:
The combination of brentuximab vedotin and nivolumab for 4 cycles was evaluated in the Phase 1/2 SGN35-025 trial in patients with relapsed/refractory cHL following front-line treatment; Parts 1 and 2 administered staggered dosing for the first cycle followed by concurrent dosing for subsequent cycles, and Part 3 administered concurrent dosing beginning with the first cycle. Interim results for 61 patients from Parts 1 and 2 previously reported an ORR of 82%, CR of 61%, and an estimated 6-month progression-free survival (PFS) of 89%.[3]

Herrera, et al and Advani, et al have recently updated the results of the trial[4-6] Herrera, et al presented longer term follow up for Parts 1 and 2 (median follow up 21.8 months; N = 61) Investigators reported an estimated 21-month PFS of 82%, and an overall Survival (OS) of 95%. The estimated 21-month PFS was 97% for patients who achieved a CR and 97% for patients who proceeded directly to autologous stem cell transplantation (ASCT). Advani, et al presented the results of Part 3 of the trial (median follow up 12.7 months; N = 30); they reported an ORR of 95%, CR of 80%, and an estimated 12-month PFS of 89%. In addition, an estimated 18-month PFS of 84% for all treated patients (Parts 1, 2, and 3; N = 91) was reported.

The combination of brentuximab vedotin and nivolumab in 44 children, adolescent, and young adult patients with cHL prior to auto-HSCT has also been evaluated in CheckMate 744, a Phase 2, risk-stratified, response-adapted trial.[7,8] Following 4 cycles of brentuximab vedotin and nivolumab, Harker-Murray, et al reported an ORR of 82% (CMR 59%) and 91% (CMR 66%) by Blinded Independent Review Committee and Investigator, respectively. In a subset analysis of 24 patients with primary refractory disease a CMR of 83% prior to ASCT was also reported. The combination was well-tolerated with a limited incidence of immune-mediated adverse events and low rate of hematologic toxicity.

Summary: We respectfully request that the NCCN Hodgkin Lymphoma Panel review the additional analyses and longer-term follow-up data from the SGN35-025 trial, as well as data from the CheckMate 744 trial when considering the Category of Evidence for this NCCN-listed second line relapsed/refractory treatment option.

Sincerely,

Gerald Engley, PharmD
Executive Director, Medical Affairs
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References (**enclosed**):

1. **ADCETRIS. [prescribing information]. Bothell, WA: Seattle Genetics, Inc; Revised Nov 2018.**
2. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma Version 1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed April 15, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2019.
3. **Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood.* 2018;131(11):1183-1194.**
4. **Herrera AF, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma: follow-up results from the phase 1/2 study. *HemaSphere.* 2018;2(S3):T025 (0005).**
5. Advani RH, Moskowitz AJ, Bartlett NL, et al. Phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory classic Hodgkin lymphoma: part 3 (concurrent dosing) results and updated progression-free survival results from parts 1 and 2 (staggered dosing). *Blood.* 2018;132(Suppl 1):Abstract 1635.
6. **Advani RH, Moskowitz AJ, Bartlett NL, et al. (2018). Phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory classic Hodgkin lymphoma: part 3 (concurrent dosing) results and updated progression-free survival results from parts 1 and 2 (staggered dosing). Blood 132(Suppl 1): Abstract 1635. 2018 ASH, 60th Annual Meeting of the American Society of Hematology, San Diego, CA, Dec 01-04, 2018. Poster presentation.**
7. Harker-Murray P, Leblanc T, Mascarin M, et al. Response-adapted therapy with nivolumab and brentuximab vedotin (BV), followed by BV and bendamustine for suboptimal response, in children, adolescents, and young adults with standard-risk relapsed/refractory classical Hodgkin lymphoma. *Blood.* 2018;132(Suppl 1):Abstract 927.
8. **Harker-Murray P, Leblanc T, Mascarin M, et al. (2018). Response-adapted therapy with nivolumab and brentuximab vedotin (BV), followed by BV and bendamustine for suboptimal response, in children, adolescents, and young adults with standard-risk relapsed/refractory classical Hodgkin lymphoma. Blood 132(Suppl 1): Abstract 927. 2018 ASH, 60th Annual Meeting of the American Society of Hematology, San Diego, CA, Dec 01-04, 2018. Oral presentation.**