Canada's Drug Agency
L'Agence des médicaments du Canada

Nivolumab in Combination With Doxorubicin (Adriamycin), Vinblastine, and Dacarbazine for Hodgkin Lymphoma

Formulary Management Expert Committee Responses to Questions From the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response (clinical experts act as guest specialists for FMEC)	FMEC response
Relevant comparators		
The phase III clinical trial compared N + AVD to BV + AVD for stage III and IV Hodgkin lymphoma. At the time of this input, BV + AVD is currently funded and used for the treatment of stage IV Hodgkin lymphoma. ABVD is the current standard of care for stage III Hodgkin lymphoma. BV + AVD is currently under review by the drug plans. Other regimens that could be considered are escalated BEACOPP for adults and BV + AVEPC for pediatric Hodgkin lymphoma.	With regard to the pediatric population, 1 clinical expert highlighted that BV + AVEPC (as per AHOD1331 trial) is the relevant comparator. Although stage IIIA disease was not included in the AHOD1331 trial, it is appropriate to include all stage III and IV disease as advanced-stage for this review. In the adult population, the other clinical expert noted that BV + AVD is an appropriate comparator for both stage III and IV diseases. CDA-AMC has recently updated the recommendations to include BV + AVD for patients with advanced-stage Hodgkin lymphoma, including stage III and IV, based on longer follow-up of the ECHELON-1 trial. Other regimens suitable for patients aged 60 years or younger would be BrECADD (results from the HD21 trial showed improvement with BrECADD over eBEACOPP) or eBEACOPP (PET2 guided based on HD18). For patients older than age 60, sequential BV + AVD is often used.[a]	FMEC defers to the clinical experts.
Considerations for initiation of therapy		
Can patients whose disease recurs after treatment with N + AVD be re-treated with downstream pembrolizumab or nivolumab? If yes, what is the minimum disease-free interval requirement?	Both clinical experts agree that re-treatment with pembrolizumab or nivolumab should be an option following disease recurrence with treatment with N + AVD. One clinical expert noted that there is evidence of response to checkpoint inhibitors at the time of disease recurrence for patients who have previously received N + AVD.	This is outside the scope of this review.

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	There is a lack of high-quality data to support a recommendation for disease-free interval. Because the disease is considered to be "primary refractory" if there is a relapse within 3 months of the completion of therapy, it is reasonable, perhaps, to use a time interval of greater than 3 months for re-treatment, given that there is a lack of evidence in terms of the time interval. Another clinical expert also pointed out that if a patient receives N + AVD and then relapses later after a significant period, there is no reason to believe this individual would not respond to the treatment again, especially if this individual had demonstrated a good response the first time. However, the time interval remains unclear. In clinical practice, we use the term "primary refractory," particularly in Hodgkin lymphoma, to describe patients whose disease progresses within 3 months of treatment.	
Considerations for prescribing of therapy		
Jurisdictions will use nivolumab 3 mg/kg (up to 240 mg).	While 1 clinical expert agreed with this dosing, the other clinical expert expressed that dosing is not weight-based for adults. This clinical expert supports using the dosing from the trial. For adults, the standard dose is 240 mg.	FMEC is aware that jurisdictions implement weight-based dosing to a cap. However, no data were reviewed regarding this particular issue as part of this review.
Nivolumab is administered as a 30-minute infusion.	The clinical experts have reviewed this information.	FMEC acknowledges this information.
Special implementation issues		
Patients with stage IIB Hodgkin lymphoma are often treated similarly to those with stage III and stage IV Hodgkin lymphoma. Should patients with stage IIB Hodgkin lymphoma be eligible for N + AVD?	Both clinical experts highlighted that patients with stage IIB or stage II Hodgkin lymphoma with bulky disease are treated as if they have advanced-stage disease, similar to stage III or IV. Although this subgroup was not included in this trial, it is often included in trials of advanced- stage Hodgkin lymphoma (e.g., HD21 trial comparing BrECADD vs. eBEACOPP). This clinical expert noted that, in North America, patients are generally classified into limited or advanced-stage disease. However, in Europe and some other centres, a different system is used with a 3-group classification that includes an "early unfavourable" stage, which is treated more similarly to advanced-stage disease.	FMEC defers to the clinical experts.

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	This is the classification in which these patients (stage IIB/with bulky disease) would fall. In clinical practice, we treat these patients the same way that we treat patients with advanced-stage disease, so we agree that patients with stage IIB or stage II with bulky disease should be eligible for N + AVD. For the pediatric population, it is recommended that patients with stage IIB or stage II Hodgkin lymphoma with bulky disease be eligible for N + AVD. These patients were included as high-risk patients in the AHOD1331 trial, and all of them would have received radiation to the mediastinum for large mediastinal adenopathy with the concern for late effects. Having the option of N + AVD, noting that fewer than 1% of patients received radiation, is significantly beneficial for our patients.	
Should patients with either CNS Hodgkin lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma be considered for N + AVD?	Both clinical experts indicate that there is insufficient evidence to recommend N + AVD for nodular lymphocyte-predominant Hodgkin lymphoma. CNS involvement is thankfully rare in cHL, and both clinical experts think these patients should be considered for N + AVD.	FMEC agrees with the clinical experts.
Should patients currently on BV + AVD or other first-line regimens be switched to N + AVD?	Both clinical experts indicated that for pediatric patients, the option should be available with the usual caveat regarding the lack of specific evidence on the related outcomes. Clinicians have always had to make changes based on individual toxicities with the same caveat.	FMEC defers to the clinical experts.
Care provision issues		
Jurisdictions are familiar with the preparation and administration of nivolumab because it is used for many tumour types.	Both clinical experts acknowledged this information.	FMEC acknowledges this information.
In the clinical trial, pegfilgrastim or filgrastim primary prophylaxis was optional for patients who received N + AVD, but it was mandatory for patients who received BV + AVD. If N + AVD receives a positive recommendation, is the use of growth factor support required for all patients who receive N + AVD?	Both clinical experts indicated that the use of growth factor support is not required for all patients. However, depending on the clinical course or other factors, the use of growth factor support may be recommended for some patients.	FMEC defers to the clinical experts.
A CD30 antigen test is completed as part of the diagnosis of cHL and	Both clinical experts agree with and support this statement.	FMEC defers to the clinical experts.

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should not be a barrier for implementation.		
System and economic issues		
BV has been negotiated and has confidential pricing. Doxorubicin, vinblastine, and dacarbazine have confidential prices.	Both clinical experts have acknowledged this information.	FMEC acknowledges this information.

ABVD = doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; AVEPC = doxorubicin (Adriamycin), vincristine, etoposide, prednisone, and cyclophosphamide; BEACOPP = bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone; BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin (Adriamycin), dacarbazine, and dexamethasone; BV = brentuximab vedotin; BV + AVD = brentuximab vedotin plus doxorubicin (Adriamycin), vinblastine, and dacarbazine; BV + AVEPC = brentuximab vedotin plus doxorubicin (Adriamycin), vincristine, etoposide, prednisone, and cyclophosphamide; CDA-AMC = Canada's Drug Agency; cHL = classic Hodgkin lymphoma; CNS = central nervous system; eBEACOPP = escalated doses of bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone; FMEC = Formulary Management Expert Committee; N + AVD = nivolumab in combination with doxorubicin (Adriamycin), vinblastine, and dacarbazine; PET2 = PET scan after 2 cycles of chemotherapy; vs. = versus.

[a]Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma. *J Clin Oncol*. 2018;36(30):3015-3022. doi:10.1200/JCO.2018.79.0139