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Published in:
Journal of Clinical Oncology

DOI:
[10.1200/JCO.18.01830](https://doi.org/10.1200/JCO.18.01830)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Adams, H. J. A., & Kwee, T. C. (2019). A 73% Price Reduction Does Not Indisputably Justify Routine Application of Brentuximab Vedotin as First-Line Treatment of Hodgkin Lymphoma. *Journal of Clinical Oncology*, 37(10), 852-854. <https://doi.org/10.1200/JCO.18.01830>

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TO THE EDITOR:

A recent study by Huntington et al¹ aimed to determine the cost effectiveness of brentuximab vedotin (BV) combined with doxorubicin, vinblastine, and dacarbazine (AVD) compared with standard bleomycin-containing chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]) for first-line treatment of stage III or IV Hodgkin lymphoma. A Markov decision-analytic model was constructed to measure the costs and clinical outcomes for AVD plus BV compared with ABVD using the results of the recently published ECHELON-1 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01712490) identifier: NCT01712490) trial.² This trial reported a hazard ratio of 0.77 for modified progression-free survival (PFS) for patients receiving AVD plus BV versus standard ABVD. Using this hazard ratio, in combination with several other variables, Huntington et al¹ calculated the lifetime direct health care costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) for AVD plus BV versus ABVD. First-line treatment with AVD plus BV resulted in a gain of 0.56 QALYs but involved significantly higher lifetime health care costs (\$361,137 v \$184,291), leading to an ICER for AVD plus BV of \$317,254 per QALY. Huntington et al¹ concluded that AVD plus BV as first-line treatment was unlikely to be cost effective under current drug pricing but suggested that a price reduction of 73% would be acceptable to reduce ICERs to a more widely acceptable value (corresponding to \$100,000 investment per QALY).

However, in our opinion, this conclusion cannot be drawn because the ECHELON-1 trial (which provided the hazard ratio of 0.77, the most influential variable in the model of the study by Huntington et al¹) suffered from relevant methodologic shortcomings.² The ECHELON-1 trial used modified PFS as an outcome measure, which included progression of disease, death, and initiation of second-line treatment because of positive end-of-treatment ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) findings as events.² However, FDG-active residual lesions after treatment do not necessarily reflect viable lymphoma but are often the result of therapy-induced inflammation, as shown by several studies that used

tissue sampling and pathologic examination as a reference standard.³⁻⁵ Therefore, current guidelines^{6,7} recommend biopsy of residual FDG-active lesions after treatment, but this recommendation was not adopted in the ECHELON-1 trial.²

Another issue is that the results of the ECHELON-1² trial are not reproducible because of the strikingly different results between the investigator and the independent review committee. The independent review committee determined the 2-year modified PFS to be 82.1% for AVD plus BV and 77.2% for ABVD with a risk difference of 4.9% and a hazard ratio of 0.77 in favor of AVD plus BV.² Conversely, the investigator determined the 2-year modified PFS to be 81.0% for AVD plus BV versus 74.4% for ABVD with a risk difference of 6.6% and a hazard ratio of 0.72.² In the AVD plus BV group, the independent review committee determined 117 events (90 with disease progression, 18 deaths, and 9 with second-line treatment initiation after a positive end-of-treatment FDG-PET result), whereas the investigator reported 123 events in the same patient population (73 with disease progression, 15 deaths, and 35 with second-line treatment initiation after a positive end-of-treatment FDG-PET result).² An explanation for why the independent committee found 3 more deaths than the investigator (corresponding to 20% more deaths in the entire AVD plus BV arm) was not given in their report.² In the ABVD group, the independent review committee determined 146 events (102 with disease progression, 22 deaths, and 22 with initiation of second-line treatment after a positive end-of-treatment FDG-PET result), whereas the investigator reported 164 events in the same population (103 with disease progression, 22 deaths, 39 with second-line treatment initiation after a positive end-of-treatment FDG-PET result).

In conclusion, it is in our opinion that flawed data from the ECHELON-1 trial do not allow for a reliable cost-effectiveness analysis on the use of BV as first-line treatment of stage III and IV Hodgkin lymphoma. In fact, the superiority of AVD plus BV over standard ABVD in improving the outcome of patients with Hodgkin lymphoma has not yet convincingly been proven. Therefore, a commitment by pharmaceutical companies to cut the price of BV by 73% (corresponding to \$100,000 investment per QALY, according to the calculation of Huntington et al¹) does not indisputably justify routine application of BV as first-line treatment of Hodgkin lymphoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.18.01830>.

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DOI: <https://doi.org/10.1200/JCO.18.01830>; **Published at** [jco.org](https://www.jco.org) on **February 11, 2019.**



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