# Cost-Effectiveness analysis of Brentuximab Vedotin in combination with Doxorubicin, Vinblastine and Dacarbazine (AVD) in newly-diagnosed, stage III Hodgkin Lymphoma in Italy

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## BACKGROUND

- Advanced classical Hodgkin's lymphoma (cHL) is a rare severe neoplasm that particularly affects young adults and older people that significantly limits their ability to carry out daily activities among other impacts.
- Historically, first-line (FL) treatment with doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) has been the standard of care in Advanced stage (AS) cHL in Italy. Nevertheless, a considerable proportion of patients with AS disease relapse and/or become refractory to ABVD therapy.
- The most recent evidence from the ECHELON-1 study, which compares brentuximab vedotin (BV)+AVD vs ABVD, has shown the superiority of BV+AVD as FL treatment in AScHL and has been recognized as the most recent indication approved for brentuximab vedotin by EMA (as of 12 October 2023) [1].
- In the 6-year follow-up of the ECHELON-1 study, the superiority of BV+AVD for PFS and OS in the stage III population was demonstrated (PFS: HR 0.60 , 95% CI: 0.39 to 0.93 ; OS: HR 0.86, 95% CI: 0.45 to 1.65).
- A basis of the economic evidence in FL AScHL has been established, demonstrating the cost benefit of BV+AVD in AScHL patients in first-line and its positive implications for costs in subsequent lines of treatment [2, 3].

## OBJECTIVES

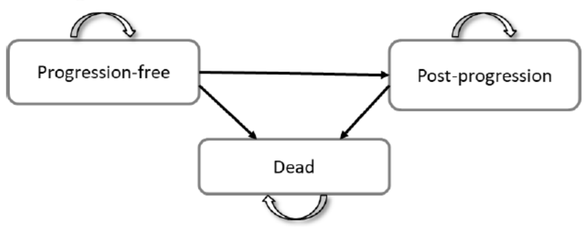
This analysis investigates the cost-effectiveness of BV+AVD versus ABVD for the treatment of stage III Hodgkin's lymphoma in Italy given the most recent approval in FL AScHL and its potential uptake locally.

## METHODS

### Overall Model Design and Analysis Approach

- The analysis was conducted from the National Health Service (NHS) perspective using a Markov model structure with three mutually exclusive health states: progression-free (PF), post-progression (PP) and dead (Figure 1). This structure was selected based on previous economic analyses in cHL [4-7] and best practice guidance.
- The model considers weekly cycles and a lifetime time horizon with half-cycle correction. Transition probabilities were derived from the ECHELON-1 six-year survival data, for the stage III subgroup [1].
- Cost inputs were obtained primarily from published literature and cited national tariffs [8, 9]. Costs, life years (LYs) and quality-adjusted life years (QALYs) were discounted by 3% according to Italian guidelines for economic analyses [10].
- One-way and probabilistic sensitivity analyses were conducted to explore model drivers and to account for joint uncertainty of the underlying parameter estimates.

**Figure 1: Transition-State Model Structure**




### Clinical Parameters

- Studies of HL suggest that patients can be "cured" by their FL treatment [11-13]; this is also supported by the long, flat plateau of the KM curves for PFS and OS curves in the ECHELON-1 six-year data [1], suggesting that a proportion of patients may have achieved long-term remission. Based on this evidence, a cure timepoint was specified in the model at 73 months (median follow-up time of ECHELON-1 trial). The model assumes that the cured patients are no longer at risk of experiencing the event of interest (i.e., progression and death due to disease). Table 1 shows the survival outcomes used in the model to inform the transition probabilities between the health state and Table 2 describes key clinical inputs.
- Rates of grade 3+ adverse events occurring in >5% of patients (see Table 1) and rates of secondary malignancies were based on those reported in ECHELON-1 [1].

**Table 1: Survival Outcomes and Health State Transitions**

| Survival curve | Definition | Data Source and Extrapolations |
|---|---|---|
| Time To Progression (TTP) | From the PFS curve by censoring the death events before progression and exit from follow-up<br><br>(Transition from "PF" to "PP" state) | Data: ECHELON-1 PFS KM<br>Censored: Pre-progression death<br>Extrapolation: from cure point based on last observed value indefinitely<br>Reasoning: extended plateau of events |
| Time To Death (TTD) | From the PFS curve by censoring the progression events before death and exit from follow-up<br><br>(from "PF" to "death" state) | Data: ECHELON-1 PFS KM<br>Censored: progression events<br>Extrapolation: the general population survival data [14] with SMR acceleration [15] |
| Post-Progression Survival (PPS) | From the time from disease progression to death<br><br>(from "PP" to "death" state) | Data: Derived from ECHELON-1 using TTP subtracted from OS time<br>Censored: Not applicable<br>Extrapolation: Exponential, single distribution<br>Reasoning: to address the "memoryless" nature of Markov models and account for the likelihood of death to be not solely determined by first-line treatment (i.e. no treatment effect) |

### Quality of Life (QoL) and Health State Utilities Applied

- Utility values were derived from EQ-5D-3L data collected in the ECHELON-1 trial for the PF health state (on randomized treatment vs off treatment) and the PP health state. For patients considered "cured", general population utility values for Italy were applied after the "cure" time point [16].

### Subsequent Therapy Proportions

- Later lines of therapy used after the conclusion of FL therapy were based on from the ECHELON-1 trial for each arm of treatment and organized by category of therapy (e.g chemotherapy autologous/ allogenic/undefined SCT, nivolumab, pembrolizumab, brentuximab, bendamustine, radiotherapy).

### Applied Cost Parameters

- All costs applied for administration, monitoring costs, adverse events, and pre-progression radiotherapy were informed by the DRG tariff list [24] and the national tariff on outpatient services [29]. Costs associated with secondary malignancies were based on an average cost identified in published literature [32].
- The acquisition cost for BV was estimated based on dosage, mean treatment cycles received (5.4) and median weight (73.9 kg) observed in the ECHELON-1 for the stage III population. The acquisition cost of AVD and ABVD were similarly calculated based on the median BSA observed in the ECHELON-1 for the stage III population.
- As reported in Russo et al. [17], confidential prices may affect the estimated value of the ICER of a new medicine and, consequently, its interpretation. In line with this purpose, it was considered appropriate to use the BV price net after the mandatory reductions required by law (5%+5%) and the negotiated discount. For all other drugs, ex-factory prices net of the mandatory reductions required by law (5%+5%) were used.
- Disease monitoring costs were estimated for PF and PP health states based on the follow-up and monitoring cadence for each health service as recommended in the ESMO Guidelines [18] and from clinical expert opinion.
- The cost of concomitant therapies was calculated considering the antiemetic and anti-infectious drugs, growth factors and pain management drugs. Correlated management scheme and dosing was obtained from published guidelines or literature [19-22]. Where appropriate, costs were weighted by length of stay (LOS).
- The acquisition cost for subsequent treatments was calculated considering the therapies used in PP status in the ECHELON-1 clinical trial for stage III patients. Individual regimen dosage and mean duration of treatment were informed by clinical trial specifications [23-29] and AIOM guidelines when necessary [30]. Chemotherapy regimens administration defined through expert opinions were then costed per DRG tariffs [24], whereas for all other treatments were costed based on the outpatient service tariff [25]).

**Table 2: Main Clinical Inputs**

| **Adverse Events (Grade 3+ at >5% incidence)*** | **BV+AVD [1]** | **ABVD [1]** |
|---|---|---|
| Anaemia | 8% | 4% |
| Febrile neutropenia | 19% | 8% |
| Neutropenia | 54% | 39% |
| Neutrophil count decreased | 13% | 10% |
| Peripheral neuropathy | 9% | 1% |
| Pulmonary Toxicity^ | 1% | 3% |
| **HRQoL*** | **Utility [1]** | |
| Progression Free On Treatment: BV-AVD | 0.753 | |
| Progression Free On Treatment: ABVD | 0.820 | |
| Progression Free Off Treatment: BV-AVD | 0.854 | |
| Progression Free Off Treatment: ABVD | 0.879 | |
| Progressed Disease | 0.821 | |
| **Subsequent Treatments*** | **BV+AVD [1]** | **ABVD [1]** |
| Chemotherapy | 105% | 128% |
| Autologous stem cell transplantation | 16% | 21% |
| Allogeneic stem cell transplantation | 0% | 11% |
| Stem cell transplantation (not defined) | 7% | 11% |
| Nivolumab | 5% | 17% |
| Pembrolizumab | 0% | 6% |
| Brentuximab | 9% | 55% |
| Bendamustine | 5% | 4% |
| Radiotherapy | 32% | 42% |

^Pulmonary toxicity was included despite being <5% given it is of particular interest for Bleomycin use, which is a key differentiator between the BV+AVD regimen versus the ABVD regimen.
*All inputs above were either derived through IPD analysis of ECHELON-1 and/or reported in the ECHELON1 trial.

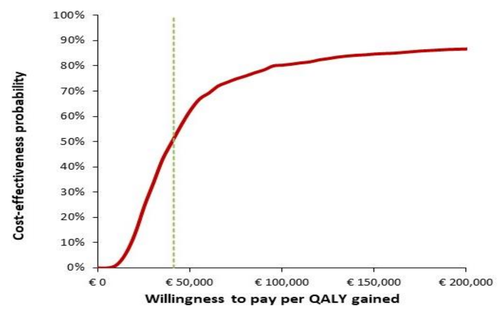
## RESULTS

- Base case results can be found in *Table 3* below. BV+AVD was associated with a total cost increase of € 25,523, as well as an incremental 0.75 LYs and 0.62 QALYs gained compared with ABVD. Thus, the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) were estimated to be € 34,162/LY and € 41,095/QALY respectively.
- Please refer to Figure 2 which describes that BV+AVD represents the treatment option most likely to be cost-effective compared to ABVD at any threshold of willingness at or above € 41,411/QALY [33] as determined for severe pathologies within recent assessments.

**Table 3. Base- Case results of BV+AVD vs ABVD**

| Outcome | Incremental (BV+AVD – ABVD) | ICER | ICUR |
|---|---|---|---|
| Total Costs | € 25,523 | | |
| Years of life | 0.75 | € 34,162 | - |
| QALYs | 0.62 | - | € 41,095 |

**Figure 2: Cost-Effectiveness Acceptability Curve**




### Sensitivity and Scenario Analysis Results

- Variables within the model that asserted an inherent variability (e.g trial variables) or potential impact on the final outcome (e.g. costs, utilities) were assessed within plausible value ranges. The most influential value drivers included the outcomes-related discount rate, average time on treatment, and subsequent treatments included.

## CONCLUSIONS

Previous analyses have established a basis of evidence for cost-savings in first-line therapy from the BV+AVD regimen with positive cost implications in subsequent lines of therapy with respect to regimen use, adverse events, secondary malignancies, and of life [2, 3]. Considering the average value of ICER for QALY observed at national level for severe pathologies equal to € 41,411/QALY [33], this analysis demonstrates BV+AVD can be considered a cost-effective treatment option compared to ABVD for the treatment of patients with stage III cHL, further contributing to this growing evidence base.

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