Comparison of Survival Extrapolations Using Early Vs Late Data Cuts from the ECHELON-1 Trial in Frontline Advanced Hodgkin Lymphoma

Li S[1], Mittal M[2], Zou D[3], Paly VF[4]

[1]Evidera, Waltham, MA, USA, [2]Evidera, Gurugram, India, [3]Evidera, San Francisco, CA, USA, [4]Takeda Pharmaceuticals America, Inc., Lexington, MA, USA

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Background

- Hodgkin lymphoma (HL) is a cancer of the lymphatic system that is characterized by the presence of Hodgkin and Reed-Sternberg cells. Advanced-stage HL is associated with more unstable cure rates, which vary between 70% and 80% compared with early-stage HL, where approximately 90% of patients can be cured.[1,2]
- Brentuximab vedotin, an antibody-drug conjugate, has been investigated in ECHELON-1, a randomized, open-label phase III study comparing brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with treatment-naïve, advanced, classical HL (ClinicalTrials.gov # NCT01712490).
- In 2018, brentuximab vedotin in combination with AVD was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in adult patients with previously untreated Stage III or IV classical HL, and in adult patients with previously untreated CD30+ Stage IV HL, respectively. The approvals were based on ECHELON-1 trial that demonstrated superior progression-free survival (PFS) for A+AVD versus ABVD in patients with frontline stage III/IV HL with a median follow-up of two years (hazard ratio [HR] 0.77, p=0.04).[3] The two-year overall survival (OS) analysis did not demonstrate a significant difference.[3]
- After approximately six years of follow up, ECHELON-1 demonstrated a significantly better OS for A+AVD versus ABVD in patients with frontline stage III/IV HL (HR 0.59; p=0.009).[4]

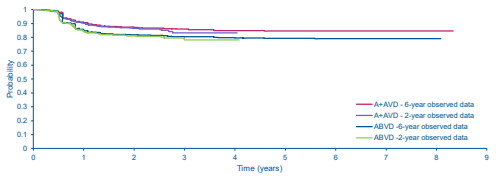
Objectives

- This study compared the lifetime survival extrapolations using ECHELON-1 trial data from the two-year vs. six-year data cuts.

Methods

- A Markov cohort model with three health states (pre-, post-progression, and death) was developed to extrapolate survival of A+AVD vs. ABVD over a 70-year time horizon. Life-years (LYs) were discounted at 3.5% per year to align with common practice in cost-effectiveness analyses.
- In this Markov cohort model, direct transition probabilities between the health states were estimated from treatment-specific time to progression (TTP), time to death (TTD), and post-progression survival (PPS) curves from the intention-to-treat (ITT) population of ECHELON-1. The OS was then derived by aggregating mortality from the pre-progression and post-progression health states.
- All patients enter the model in the pre-progression health state when they begin their frontline treatment. A cure timepoint was specified in the model at 73 months, which was aligned with the median follow-up time of ECHELON-1 trial.[4] This approximately aligns with the most recent ESMO[5] and NCCN guidelines.[6] Both guidelines reduced frequency of history, physical examination and laboratory analysis to once a year after 5 years from diagnosis if the patient does not experience progression. The model assumes that the cured patients are no longer at risk of experiencing progression events and death due to disease.
- Before the specified cure timepoint, the probabilities of transitioning to the post-progression and death health states were obtained from the observed treatment-specific TTP (**Figure 1**) and TTD (**Figure 2**) data from the two-year and six-year data cuts, respectively. After the cure timepoint, extrapolation was based on the last observed follow-up point for TTP and general population mortality (UK) accelerated by an excess mortality rate for TTD.
- Once patients enter the post-progression health state, the transition probabilities of death were informed by a constant transition probability using a joint exponential model fit to the two-year and six-year data cuts (**Figure 3**).
  - Six-year data was analyzed with and without a PPS treatment effect given the more consistent separation of the PPS curves between A+AVD and ABVD over time than seen in the two-year data.
- The treatment-specific TTP (**Figure 1**), TTD (**Figure 2**), and PPS curves (**Figure 3**) derived from the six-year data cut show improved survival outcomes favoring A+AVD over ABVD compared with the two-year data cut.

Figure 1: Kaplan-Meier Curves Based on Observed Data for TTP



Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; TTP = time to progression

Results

Extrapolation based on the two-year data underestimated five-year and seven-year OS and PFS for both treatments when compared with the observed data (Figure 6 and Figure 7) and underestimated the difference in landmark OS and PFS between treatments (Table 1, Figure 4, and Figure 5). When the six-year data were used, incremental OS and PFS more closely matched the observed data.

Table 1: Landmark OS and PFS

Outcome	A+AVD (with PPS Treatment Effect)			ABVD			Incremental (A+AVD with PPS Treatment Effect vs. ABVD)		
	Latest Observed Data	2-year Data Cut Extrapolation	6-year Data Cut Extrapolation	Latest Observed Data	2-year Data Cut Extrapolation	6-year Data Cut Extrapolation	Latest Observed Data	2-year Data Cut Extrapolation	6-year Data Cut Extrapolation
5-year OS	94.76%	92.45%	95.00%	91.17%	89.39%	91.80%	3.58%	3.06%	3.20%
7-year OS	93.31%	89.89%	93.60%	88.67%	86.34%	89.24%	4.64%	3.55%	4.36%
5-year PFS	82.28%	80.90%	82.27%	75.37%	74.74%	75.30%	6.91%	6.16%	6.97%
7-year PFS	82.28%	80.33%	82.04%	74.48%	74.21%	74.21%	7.80%	6.12%	7.84%

Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; OS = overall survival; PFS = progression-free survival; PPS = post-progression survival

Figure 4: Landmark OS

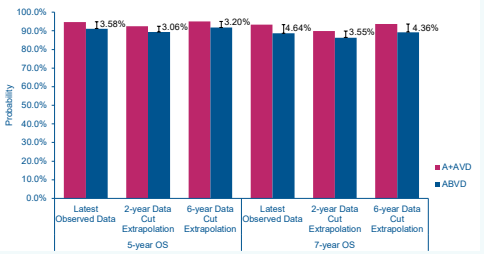


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Figure 5: Landmark PFS

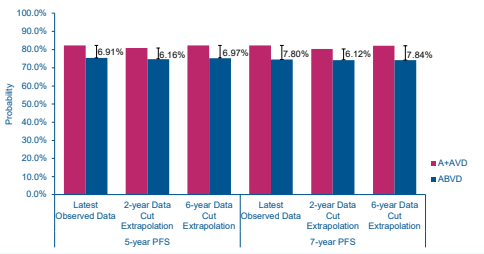

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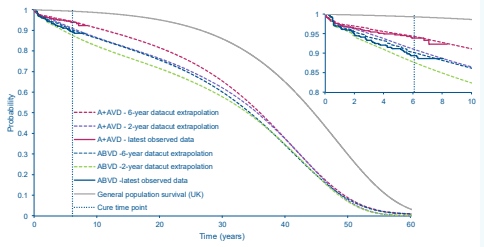
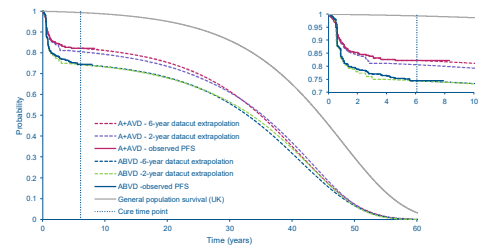
Figure 6: OS Curves



Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; OS = overall survival; UK = United Kingdom

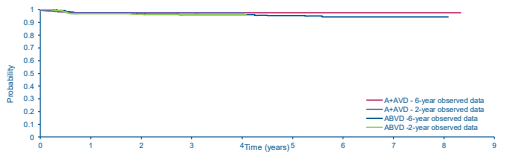
Figure 7: PFS Curves



Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; PFS = progression-free survival; UK = United Kingdom

Key Take Away Over the lifetime horizon, longer absolute LYs were generated with extrapolations based on six-year versus two-year data (Table 2 and Figure 8). Incremental LYs for A+AVD vs ABVD also improved with longer follow up.

Figure 2: Kaplan-Meier Curves Based on Observed Data for TTD



Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; TTD = time to death

Figure 3: Kaplan-Meier Curves Based on Observed Data for PPS

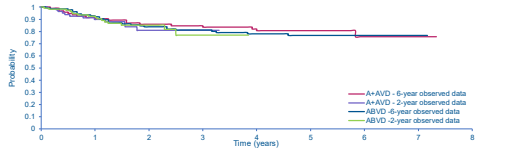


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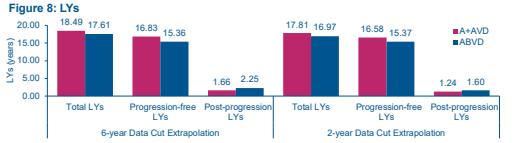
Table 2: LYs

Outcome	A+AVD		ABVD		Incremental (A+AVD vs. ABVD)	
	6-year Data Cut Extrapolation (with/without PPS Treatment Effect)	2-year Data Cut Extrapolation (without PPS Treatment Effect)	6-year Data Cut Extrapolation	2-year Data Cut Extrapolation	6-year Data Cut Extrapolation (with/without PPS Treatment Effect)	2-year Data Cut Extrapolation (without PPS Treatment Effect)
Total LYs	18.60/18.49	17.81	17.61	16.97	0.99/0.88	0.84
Progression-free LYs	16.83	16.58	15.36	15.37	1.47	1.21
Post-progression LYs	1.77/1.66	1.24	2.25	1.60	-0.48/-0.59	-0.36

Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; LY = life year; PPS = post-progression survival

Figure 8: LYs



Abbreviations: A+AVD = brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; LY = life year; PPS = post-progression survival

Conclusions

- This analysis shows that when based on the 6-year data cut from ECHELON-1, the absolute and incremental survival estimates for A+AVD improved vs. the 2-year data cut, indicating that survival extrapolations based on the 2-year data cut from ECHELON-1 underestimated the survival.
- While the modeling approach presented here is just one approach to survival extrapolation for A+AVD over a lifetime time horizon, it highlights the importance of incorporating long-term data to provide further context on the clinical benefit of A+AVD.

References **1.** Armitage JO. *N Engl J Med*. 2010;363(7):653-662. **2.** Allen PB, Gordon LI. *Clin Med Insights Oncol*. 2017;11. **3.** Connors JM, et al. *N Engl J Med*. 2018;378:331-344. **4.** Ansell SM, et al. *N Engl J Med*. 2022;387:310-320. **5.** Eichenauer DA, et al. *Annals of Oncology*. 2018;29:19-29. **6.** NCCN.*NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma*. 2022. **7.** Ara R, Brazier JE. *Value Health*. 2010;13(5):509-518.

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