An Oncology Simulation Model to Estimate 10-year Progression-free Survival and Stem Cell Transplantation for Frontline Stage III or IV Classical Hodgkin Lymphoma Based on the 5-Year Update of the ECHELON-1 Trial: A United States Perspective

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Background

- Patients with stage III and IV classical Hodgkin lymphoma (cHL) are primarily treated in the frontline (1L) setting with a multi-agent chemotherapy regimen such as[1]
  - ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)
  - A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine)
  - eBEACOPP (escalated dosing regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)
- Although ABVD is the predominant 1L regimen for treating cHL, about 30% of patients with advanced disease will be refractory to or relapse following ABVD treatment[2,3]
- The 5-year update of the ECHELON-1 trial, which compared A+AVD with ABVD in newly diagnosed patients with stage III or IV cHL,[4] demonstrated a robust and durable improvement in progression-free survival (PFS) with A+AVD (82.2% [95% CI: 79.0–85.0]) vs ABVD (75.3% [CI: 71.7–78.5]), with a 32% reduction in the risk of disease progression or death (hazard ratio 0.68 [95% CI: 0.53–0.87]; nominal *P*=0.002)[4]
- The benefits observed with A+AVD compared with ABVD in ECHELON-1[4]
  - Were independent of disease stage, age, baseline risk, or interim positron emission tomography (PET) status
  - Compared favorably to contemporary PET-adapted strategies without requiring a change in therapy based on interim PET assessment or exposure to bleomycin

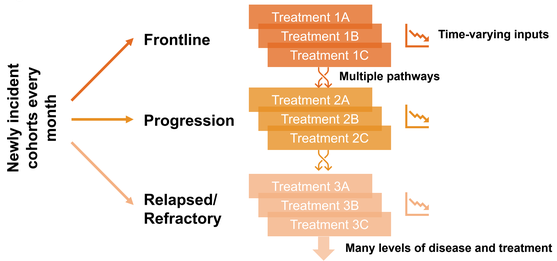
Objective

- To estimate the future annual number of patients with stage III or IV cHL who will be alive and progression free over 10 years in scenarios without and with 1L A+AVD therapy, based on the 5-year follow-up results from ECHELON-1

Methods

- A dynamic oncology simulation model (OSM) was developed from a United States perspective that estimates population-level outcomes based on the annual incidence of cHL (**Figure 1**)
  - The continuous dynamic Markov model considered disease incidence and treatment patterns for stage III and IV cHL, as well as PFS and overall survival (OS) reported for commonly used treatment regimens in stage III and IV cHL
  - The model cycle length was 1 month

Figure 1. Example Model Framework



Population inputs

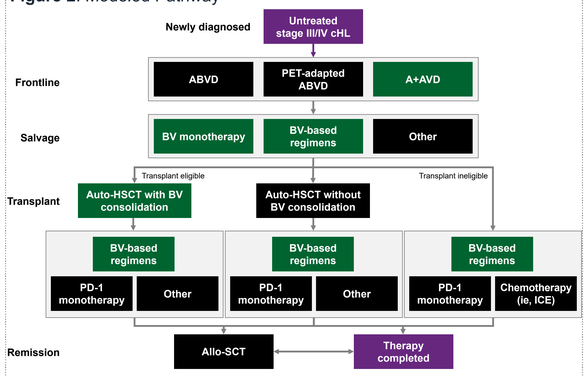
- Incidence of cHL was derived from the 2019 Surveillance, Epidemiology, and End Results (SEER) Program, assuming that 95% of HL cases are cHL cases, of which 41% are stage III or IV cHL[5]

Methods (cont'd)

Treatment patterns and utilization

- The modeled treatment pathway was informed by NCCN guidelines and expert clinicians' opinion on commonly used regimens for stage III or IV cHL (**Figure 2**)
  - The model assumed stem cell transplantation (SCT) was available at a single point, after salvage therapy

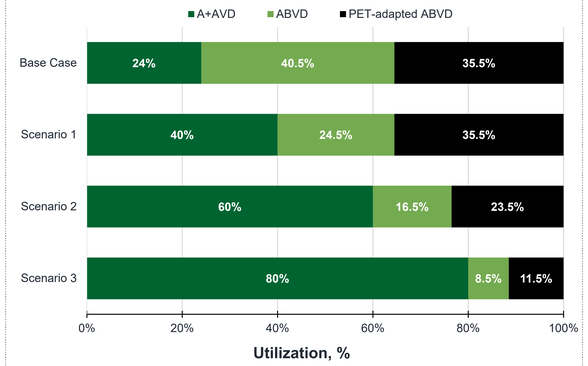
Figure 2. Modeled Pathway



Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; Allo-SCT, allogenic stem cell transplantation; Auto-HSCT, autologous hematopoietic stem cell transplantation; AVD, doxorubicin, vinblastine, dacarbazine; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; ICE, ifosfamide, carboplatin, etoposide; PD-1, programmed cell death protein 1; PET, positron emission tomography

- In the base case model, treatment patterns following 1L use of ABVD (64.5%) and PET-adapted ABVD (35.5%) were varied over time and compared to a scenario with A+AVD (24%)
  - For every model cycle, patients who experienced disease progression on 1L therapy discontinued their current treatment and transitioned to second-line (salvage) therapy
  - A transition from salvage therapy to SCT was also included in the model based on patient eligibility
- Scenario analyses varied A+AVD utilization from 24% to 80%, as recommended by expert clinicians (**Figure 3**)

Figure 3. A+AVD Utilization for the Base Case and Sensitivity Analyses



Abbreviations: A+AVD, brentuximab vedotin in combination with doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron emission tomography

Methods (cont'd)

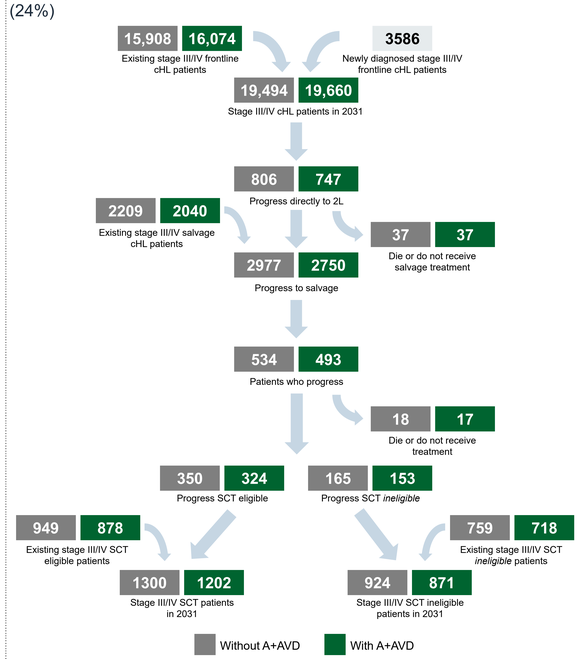
Clinical inputs

- Model inputs were informed by[4,6-16]
  1. Real-world treatment utilization
  2. Treatment-specific clinical trial data, including data from the 5-year ECHELON-1 update,[4] with 5-year PFS rates of 75.3% for ABVD (95% CI: 71.7–78.5) and 82.2% for A+AVD (95% CI: 79.0–85.0)
  3. Expert clinicians' opinions
- Annual prevalence of patients with cHL alive and progression free in the 1L setting was estimated for 10 years (year 2031) for scenarios without and with the availability of A+AVD

Results

- The estimated annual number of patients with newly diagnosed stage III or IV cHL in 2031 was 3586
- The number of patients alive and progression free in the 1L setting was 19,494 in the scenario without A+AVD and 19,660 in the scenario with A+AVD (Δ+166, 0.85% increase) in 2031 (**Figure 4**)

Figure 4. Patient Flow in 2031 for the Base Case Without and With A+AVD (24%)



Abbreviations: 2L, second-line therapy; A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; cHL, classical Hodgkin lymphoma; SCT, stem cell transplantation

- Overall, for every 100 patients prescribed 1L A+AVD, the model predicted an additional 6.5 patients per year would achieve at least 5 years' PFS and 3.1 fewer patients per year would require an SCT

Results (cont'd)

- In the scenario analyses, varying 1L treatment with A+AVD from 24% to 80% added 166 (0.85% increase) to 440 (2.26% increase) patients with cHL remaining alive and progression free (**Table 1**)

Table 1. Number of Patients with Stage III or IV cHL Progression Free in 2031 with Varying Frontline A+AVD Utilization, Scenario Analyses

	No. of patients	
	Progression free	Additional patients progression free[a]
A+AVD at 24% (base case)	19,660	166
A+AVD at 40%	19,805	311
A+AVD at 60%	19,862	368
A+AVD at 80%	19,934	440

[a] Compared to a scenario without 1L A+AVD
Abbreviation: A+AVD, brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine

Limitations

- This model was streamlined by combining treatment regimens; mean PFS and OS values for various regimens were calculated to represent the broader treatment groups
- The model includes SCT at only one time point (post second-line therapy in remission)
  - In clinical practice, SCT is utilized beyond second-line therapy and for patients with disease in partial remission
- An exponential function was assumed for PFS and OS based on a key model assumption of constant hazards; therefore, different functions (e.g., Weibull distribution) were not examined

Conclusions

- In this OSM for cHL, the durable improvement in PFS observed with A+AVD vs. ABVD in the 5-year follow-up data from ECHELON-1 translated to an increased prevalence of patients with stage III or IV cHL who remain alive and progression free over 10 years and reduced the number of patients treated with SCT
- The significant improvement in PFS observed in the 5-year ECHELON-1 trial update with A+AVD compared with ABVD may lead to fewer patients with stage III or IV cHL developing primary refractory or relapsed disease and reduce the need for patients to receive additional therapies that can be associated with significant morbidity, including long-term complications such as infertility and secondary malignancies, as well as costs

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