BRENTUXIMAB VEDOTIN WITH CHEMOTHERAPY IN ADOLESCENTS AND YOUNG ADULTS (AYA) WITH STAGE III OR IV HODGKIN LYMPHOMA: A SUBGROUP ANALYSIS FROM THE PHASE 3 ECHELON-1 STUDY

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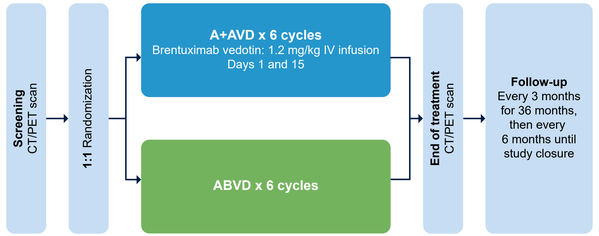
Background

- Hodgkin lymphoma (HL) is a rare disease that is most commonly diagnosed in adolescents and young adults (AYA), defined in the United States as patients aged 15 to 39 years[1–3]
  - AYA patients have unique biologic characteristics and psychosocial needs, including tolerance of therapies, adherence, financial toxicity, and access to care, that may impact their outcomes
  - The age definition of AYA varies geographically and may include non-pediatric patients aged <25 years (EUROCARE) or aged <40 years (NCI, SEER, JAYAO, AYAO PRG)
- Brentuximab vedotin is approved for adult patients with previously untreated stage III or IV classical HL (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy[4]
- ECHELON-1 is a global phase 3 trial comparing brentuximab vedotin in combination with AVD (A+AVD) versus ABVD in 1334 patients with newly diagnosed stage III or IV cHL
  - At 5 years, A+AVD demonstrated a robust and durable progression-free survival (PFS) benefit vs ABVD (hazard ratio [HR], 0.69; 95% CI, 0.54-0.9; P=0.003)[5] that was independent of disease stage, baseline risk, or interim positron emission tomography (PET) scan at Cycle 2 (PET2)-status without requiring exposure to bleomycin
  - A+AVD also demonstrated a promising long-term safety profile, with a low rate of secondary malignancies, no observed impact on the rate of pregnancies compared to ABVD, and a high rate of resolution and improvement of peripheral neuropathy (PN)
- We performed an updated analysis of AYA patients enrolled in ECHELON-1[6]

Methods

- ECHELON-1 (NCT01712490) was a phase 3, global, open-label, multicenter, randomized trial of patients with previously-untreated stage III or IV cHL (Figure 1)
- The current exploratory subgroup analysis presents key efficacy and safety results for AYA patients enrolled in ECHELON-1
- The exploratory endpoint was PFS per investigator (INV), defined as time from randomization to the earliest of:
  - Disease progression
  - Death due to any cause
- Outcomes of PFS per INV for A+AVD vs ABVD were compared in AYA patients:
  - <30 years (aged 18 to 29 years)
  - <40 years (aged 18 to 39 years)
- Correlation with PET2 status was assessed
- Incidence of secondary malignancies and pregnancies (as a surrogate for fertility) were also assessed

Figure 1. ECHELON-1 Study Design



CT, computed tomography; IV, intravenous; PET, positron emission tomography.

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Results

Baseline Demographics and Disease Characteristics

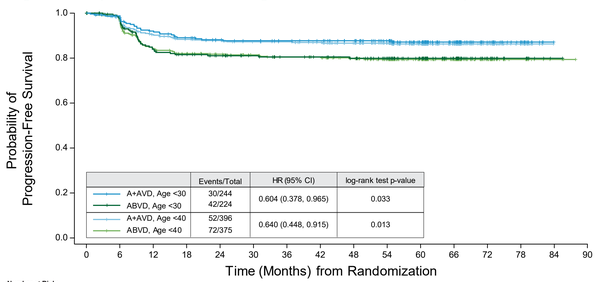
- The AYA population consisted of 771 patients comprising 57.8% of the total trial population who received either A+AVD (n=396) or ABVD (n=375) with PET2
  - Baseline demographics, disease characteristics, and regional distribution were similar across subgroups and to the overall population (Table 1)
  - Consistent with the overall trial population, median follow-up time was approximately 60.7 months

Table 1. Patient Demographics and Disease Characteristics in AYA Age Subgroups

	Age <30 Years		Age <40 Years	
	A+AVD (n=244)	ABVD (n=224)	A+AVD (n=396)	ABVD (n=375)
Age, median (range)	24 (18, 29)	24 (18, 29)	27 (18, 39)	28 (18, 39)
BMI, median (range)	23.01 (15.4, 59.6)	23.29 (15.4, 47.1)	23.05 (15.4, 59.6)	23.95 (15.4, 65.4)
Female, n (%)	112 (46)	99 (44)	188 (47)	155 (41)
Region, n (%)				
Americas	105 (43)	81 (36)	158 (40)	153 (41)
Europe	118 (48)	118 (53)	202 (51)	187 (50)
Asia	21 (9)	25 (11)	36 (9)	35 (9)
Ann Arbor Stage, n (%)				
Stage III	96 (39)	88 (39)	143 (36)	150 (40)
Stage IV	148 (61)	136 (61)	253 (64)	225 (60)
IPS Risk Factors, n (%)				
0–1	61 (25)	62 (28)	112 (28)	111 (30)
2–3	135 (55)	123 (55)	215 (54)	196 (52)
4–7	48 (20)	39 (17)	69 (17)	68 (18)
ECOG score, n (%)				
0	146 (60)	135 (60)	240 (61)	223 (59)
1	93 (38)	81 (36)	145 (37)	138 (37)
2	5 (2)	8 (4)	11 (3)	14 (4)
Extranodal disease, n (%)				
≥1 extranodal site	147 (60)	139 (62)	250 (63)	236 (63)
None	81 (33)	76 (34)	123 (31)	124 (33)
Marrow involvement, n (%)	48 (20)	48 (21)	78 (20)	78 (21)
B symptoms, n (%)	146 (60)	134 (60)	244 (62)	226 (60)
PET status at cycle 2				
PET2-positive	16 (7)	15 (7)	24 (6)	29 (8)
PET2-negative	224 (92)	197 (88)	366 (92)	324 (86)
Unknown or indeterminate	4 (2)	12 (5)	6 (2)	22 (6)

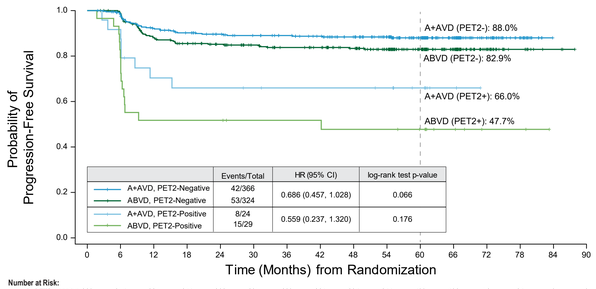
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score

Figure 2. PFS per INV in AYA Patients Ages <30 Years and <40 Years Population



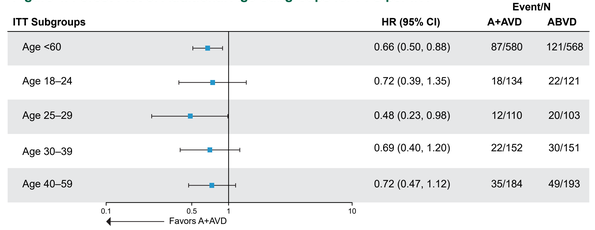
- Consistent with the intent-to-treat (ITT) population, AYA patients on the A+AVD arm showed improved PFS per INV compared with patients on the ABVD arm in the age <30 years and age <40 years groups (Figure 2)
  - For AYA patients <30 years: (HR 0.604; 95% CI, 0.378-0.965; P=0.033) with a 5-year PFS of 87.1% vs 79.9%, respectively
  - For AYA patients <40 years: (HR 0.640; 95% CI, 0.448-0.915; P=0.013) with a 5-year PFS of 86.3% vs 79.4%, respectively

Figure 3. PFS per INV by Treatment Group in Cycle 2 PET Status – AYA Age <40 Years



- Consistent with the ITT, a PFS benefit was observed with A+AVD vs ABVD independent of PET2 status in the <40 years age subgroup
- Similar outcomes were observed in the <30 years age subgroup: PET-negative (HR 0.502; 95% CI, 0.295, 0.854; P=0.009); PET-positive (HR 1.094; 95% CI, 0.334, 3.587; P=0.881)

Figure 4. Forest Plot of Additional Age Subgroups for PFS per INV



Multivariate Analysis

- A multivariate Cox regression analysis did not find association of age with treatment effect (P=0.907) or with increased risk of PFS events (P=0.412) after adjusting for IPS score, region, sex, disease stage, extranodal involvement, and body mass index (P values are nominal and not adjusted for multiplicity)

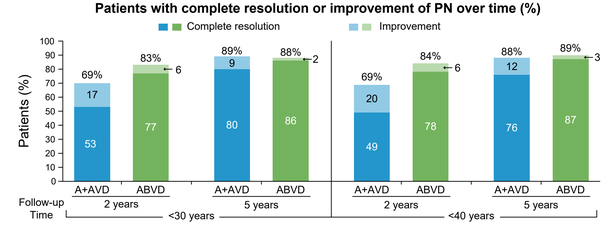
Table 2. Subsequent Anti-Cancer Therapy in AYA Age Subgroups (Safety Population)

	A+AVD	ABVD	Total
Patients with Age <30 years, n	244	219	463
Patients with at least 1 Subsequent Anti-Cancer Therapy	50 (20)	52 (24)	102 (22)
Type of Therapy,[a] n (%)			
Chemotherapy	24 (10)	38 (17)	62 (13)
Radiation	27 (11)	18 (8)	45 (10)
Autologous Stem Cell Transplant	14 (6)	22 (10)	36 (8)
Immunotherapy	4 (2)	9 (4)	13 (3)
Allogeneic Transplant	3 (1)	7 (3)	10 (2)
Chemotherapy+Radiation	1 (<1)	0	1 (<1)
Patients with Age <40 years, n	396	368	764
Patients with at least 1 Subsequent Anti-Cancer Therapy	81 (20)	96 (26)	177 (23)
Type of Therapy,[a] n(%)			
Chemotherapy	38 (10)	65 (18)	103 (13)
Radiation	41 (10)	36 (10)	77 (10)
Autologous Stem Cell Transplant	26 (7)	32 (9)	58 (8)
Immunotherapy	9 (2)	17 (5)	26 (3)
Allogeneic Transplant	6 (2)	10 (3)	16 (2)
Chemotherapy+Radiation	1 (<1)	0	1 (<1)

a Types of subsequent anti-cancer therapy are not exclusive (patients may have received more than 1 subsequent therapy and may be counted in multiple categories)

- The use of subsequent therapy, including transplant, was numerically lower for AYAs in both the <30 and <40 years age subgroups

Figure 5. PN Resolution and Improvement Over Time



Resolution was defined as event outcome of "resolved" or "resolved with sequelae". Improvement was defined as "improved by ≥1 Grade from worst Grade as of the latest assessment".
Percentages rounded to nearest integer

Table 3. Maximum Severity of Ongoing PN

	Patients with Age <30 Years (%)		Patients with Age <40 Years (%)	
	A+AVD (n=244)	ABVD (n=219)	A+AVD (n=396)	ABVD (n=368)
Incidence of PN	154 (63)	83 (38)	255 (64)	149 (40)
Ongoing at Last Follow-up (%)				
Grade 1	19 (12)	8 (10)	35 (14)	15 (10)
Grade 2	10 (6)	3 (4)	17 (7)	4 (3)
Grade 3	2 (1)	1 (1)	8 (3)	1 (<1)
Grade 4	0	0	1 (<1)	0

- Among AYA patients <40 years, assessment of ongoing PN with maximum severity of Grade 3/4 was confounded in 7 of 9 patients on the A+AVD arm and the 1 patient on the ABVD arm
  - A+AVD: 3 patients were lost to follow-up, 3 withdrew from the study, and 1 died prior to documentation of improvement or resolution
  - ABVD: the 1 patient with ongoing Grade 3 PN was lost to follow-up prior to documentation of improvement or resolution

Secondary Malignancies

- In the ITT population, 48 patients reported secondary malignancies, including 19 in the A+AVD arm and 29 in the ABVD arm
- Age <40 years subgroup:
  - A+AVD (7 total)
    - 4 hematologic malignancies (2 cases of AML [acute myeloid leukemia], patients aged 38 and 29)
    - 3 solid tumors
  - ABVD (5 total)
    - 4 hematologic malignancies
    - 1 solid tumor
- Age <30 years subgroup:
  - A+AVD (2 total)
    - 2 hematologic malignancies (1 case of AML [patient aged 29])
  - ABVD (1 total)
    - 1 hematologic malignancy

Pregnancy (Safety Population)

- A total of 131 female patients (44 A+AVD; 26 ABVD) or partners of male patients (31 A+AVD; 30 ABVD) reported a pregnancy
- 2+ live births were reported among 8 (A+AVD) and 3 (ABVD) female patients
- No stillbirths were reported
- All but 1 patient in each arm who reported a pregnancy was aged <40 years

Figure 6a. Female Patients or Partners of Male Patients Reporting a Pregnancy

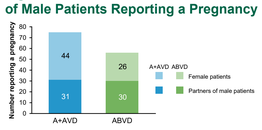
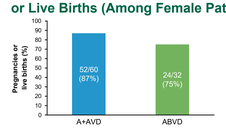


Figure 6b. Proportion of Ongoing Pregnancies or Live Births (Among Female Patients Only)



Conclusions

- Consistent with the ITT population,[5] this exploratory analysis of ECHELON-1 demonstrated that AYA patients age <30 years and age <40 years treated with A+AVD compared to ABVD had a robust and durable PFS benefit at this 5-year milestone
- A low rate of secondary malignancies and no apparent impact on the rate of pregnancies were observed, important considerations in this younger patient population
- Additionally, the majority of PN events improved or resolved over time
- As most relapses in cHL occur within 5 years of frontline treatment, these long-term PFS data suggest that more AYA patients are in long-term remission with A+AVD versus ABVD
- A+AVD should be considered a treatment option for AYA patients aged 18+ with stage III or IV cHL

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