BRENTUXIMAB VEDOTIN WITH CHEMOTHERAPY FOR PATIENTS WITH PREVIOUSLY UNTREATED STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: 5-YEAR UPDATE OF THE ECHELON-1 STUDY

Radhakrishnan Ramchandren[1], Monika Długosz-Danecka[2], Joseph M. Connors[3], John Radford[4], Árpád Illés[5], Marco Picardi[6], Ewa Lech-Maranda[7], Tatyana Feldman[8], Piotr Smolewski[9], Kerry J. Savage[3], Jan Walewski[10], Pier Luigi Zinzani[11], Martin Hutchings[12], Javier Munoz[13], Won Seog Kim[14], Ranjana Advani[15], Stephen M. Ansell[16], Andrea Gallamini[17], Sergey Alekseev[18], Hun Ju Lee[19], Rachael Liu[20], Meredith Little[20], Keenan Fenton[21], Michelle Fanale[21], David J. Straus[22]

[1]The University of Tennessee Graduate School of Medicine, Knoxville, Tennessee, USA; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [3]BC Cancer Centre for Lymphoid Cancer, Vancouver, British Columbia, Canada; [4]University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [5]University of Debrecen, Debrecen, Hungary; [6]Federico II University, Naples, Italy; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Hackensack University Medical Center, Hackensack, New Jersey, USA; [9]Medical University of Lodz, Lodz, Poland; [10]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [11]Seràgnoli Institute of Hematology, Bologna University, Bologna, Italy; [12]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [13]Banner MD Anderson Cancer Center, Gilbert, Arizona, USA; [14]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [15]Stanford University, Stanford, California, USA; [16]Mayo Clinic, Rochester, Minnesota, USA; [17]Antoine-Lacassagne Cancer Centre, Nice, France; [18]Petrov Research Institute of Oncology, St Petersburg, Russia; [19]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [20]Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [21]Seagen Inc., Bothell, Washington, USA; [22]Memorial Sloan Kettering Cancer Center, New York, New York, USA.

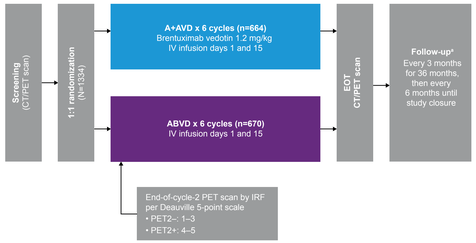
Background

- Historically, nearly all relapses in patients with cHL occurred within the first 5 years.[1]
- In the primary analysis of the phase 3 ECHELON-1 study (NCT01712490), treatment with A+AVD was superior to treatment with ABVD for patients with previously untreated Stage III or IV cHL.[2]
  - 2-year modified PFS per IRF: A+AVD=82.1%, ABVD=77.2%; HR=0.77 (95% CI: 0.60–0.98; P=0.04).
- Analyses after 3- and 4-years follow-up reported durable PFS per investigator with A+AVD versus ABVD in the ITT population that was consistent across most key patient subgroups, irrespective of interim PET scan status, disease stage, or baseline disease IPS.[3,4]
- We report updated efficacy and safety results for patients in the ECHELON-1 study after a median follow-up of 5 years, with safety data focusing on PN, secondary malignancies, and fertility.[5]
  - These are exploratory analyses and P values are unadjusted/descriptive.

Methods

- ECHELON-1 (NCT01712490) is an open-label, randomized, 2-arm, multicenter, phase 3 study (**Figure 1**).
- Adults with advanced untreated cHL were randomized 1:1 to receive 6 cycles of A+AVD or ABVD by IV infusion on days 1 and 15.

Figure 1: Study design



[a]Per protocol: During post-treatment follow-up, patients are to be followed for survival and disease status Q3M for 36 months and then Q6M until death/study closure. Investigators are requested to document response assessed from any scans performed either as standard of care or based on clinical judgement before initiation of any subsequent anticancer therapy for cHL. Investigators are also requested to document best response to any subsequent salvage anticancer therapies and any multimodality therapy that includes brentuximab vedotin as a component of the regimen.

Primary endpoint

- Modified PFS per IRF.

Key secondary endpoints

- OS, rate of PET2-negativity, safety.

Long-term follow-up assessments

- PFS per investigator in the ITT population was assessed at a median follow-up of approximately 5 years.
- Patients are followed for survival until death or for a minimum of 10 years after enrollment of the last patient.
- Post-treatment follow-up for secondary malignancies and other safety events was performed Q3M until 36 months after EOT, then Q6M.

Study assessments

- CT and PET scans were conducted at screening and after completion of cycle 2.
- PET2 status was assessed using the Deauville criteria with central review.
  - PET2– was defined as a Deauville score of 1, 2, or 3.
  - Deauville score of 4 or 5 was considered PET2+.
- Initially, CT scans were performed Q3M for the first year of follow-up and then Q6M.
  - The study protocol was amended (July 16, 2018) approximately 15 months after the primary analysis to remove the requirement for CT scans during the extended monitoring period.
- Safety was assessed using the Medical Dictionary for Regulatory Activities version 19.0 and National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
- PN was monitored for resolution and improvement; events were investigator assessed and reported.
  - Improvement was defined as a decrease of at least 1 grade from worst grade with no higher grade thereafter.
- The incidence and outcomes of pregnancies among participants and their partners was assessed.

Results

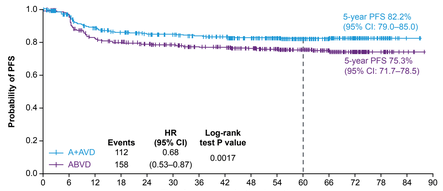
- Median age of patients was 36 years, and 58% of patients were aged <40 years (**Table 1**).[2]
- Median follow-up time was 60.9 months (95% CI: 60.8–61.0).

Table 1: Key baseline patient characteristics[2]

Characteristic	A+AVD n=664	ABVD n=670	Total N=1334
Male sex, n (%)	378 (57)	398 (59)	776 (58)
Median age, years (range)	35 (18–82)	37 (18–83)	36 (18–83)
Age <60 years, n (%)	580 (87)	568 (85)	1148 (86)
Age ≥60 years, n (%)	84 (13)	102 (15)	186 (14)
International Prognostic Score, n (%)			
0–1	142 (21)	141 (21)	283 (21)
2–3	355 (53)	357 (53)	712 (53)
4–7	167 (25)	172 (26)	339 (25)
PET2 status, n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

- At 5 years follow-up, PFS per investigator remained significantly higher for A+AVD at 82.2% vs 75.3% with ABVD (**Figure 2**).
- OS was a prespecified key secondary endpoint; the prespecified number of events required to trigger an OS analysis has not been reached.

Figure 2: PFS per investigator at 5 years follow-up[a]



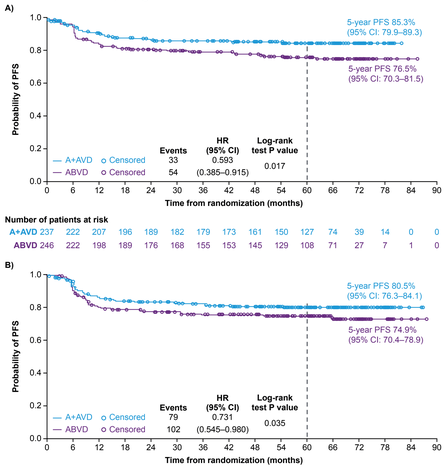
Number of patients at risk

A+AVD	664	620	562	535	518	505	492	474	446	414	333	201	102	38	2	0
ABVD	670	613	521	500	478	456	432	423	397	360	292	179	73	22	4	0

[a]Data cut-off: September 14, 2020.

- At 5 years, patients had significantly higher PFS per investigator with A+AVD versus ABVD, regardless of disease stage at enrollment (**Figure 3**).
- The PFS improvement with A+AVD was robust and durable versus ABVD, and was independent of disease stage, patient age, and baseline risk (**Figure 4**).
- Among PET2– patients, the PFS rate at 5 years was higher in the A+AVD arm than in the ABVD arm (**Figure 5**).
- Among PET2+ patients, the PFS rate at 5 years was numerically higher in the A+AVD arm than in the ABVD arm (**Figure 5**).
- At the primary analysis, 443 and 286 patients in A+AVD and ABVD arms, respectively, had experienced PN.
- After 5 years, most cases of PN had either completely resolved or improved (**Figure 6** and **Table 2**).
- Median time to complete resolution of PN events that were ongoing at EOT was 34 weeks (range 0–262) in the A+AVD arm and 16 weeks (range 0–267) in the ABVD arm; median time to improvement was 49 weeks (range 8–270) and 12 weeks (range 2–70), respectively.

Figure 3: PFS per investigator at 5 years in patients with (A) Stage III disease at enrollment and (B) Stage IV disease at enrollment



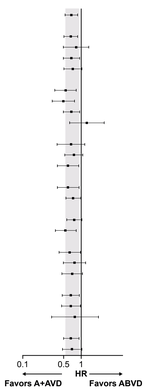
Number of patients at risk

A+AVD	237	222	207	196	189	182	179	173	161	150	127	74	39	14	0	0
ABVD	246	222	198	189	176	168	155	153	145	129	108	71	27	7	1	0

Number of patients at risk

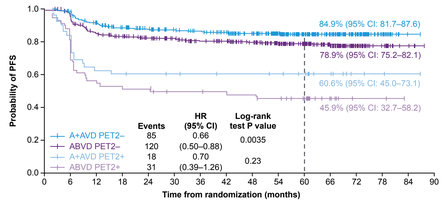
A+AVD	425	398	355	339	329	323	313	301	285	264	206	127	63	24	2	0
ABVD	421	390	322	310	302	288	277	270	252	231	184	108	46	15	3	0

Figure 4: PFS subgroup analysis



Subgroup	Events/N (%) A+AVD	ABVD	HR (95% CI)
Overall	112/664 (17)	158/670 (24)	0.68 (0.53–0.87)
Age			
<60 years	87/580 (15)	121/568 (21)	0.67 (0.50–0.88)
≥60 years	25/84 (30)	37/102 (36)	0.82 (0.49–1.36)
<45 years	64/451 (14)	83/423 (20)	0.68 (0.49–0.94)
≥45 years	48/213 (23)	75/247 (30)	0.72 (0.50–1.06)
Region			
Americas	34/261 (13)	59/262 (23)	0.54 (0.35–0.82)
North America	31/250 (12)	57/247 (23)	0.49 (0.32–0.76)
Europe	59/333 (18)	84/336 (25)	0.68 (0.49–0.95)
Asia	19/70 (27)	15/72 (21)	1.26 (0.64–2.47)
IPS			
0–1	22/142 (16)	31/141 (22)	0.67 (0.38–1.15)
2–3	54/355 (15)	70/357 (20)	0.75 (0.52–1.07)
4–7	36/167 (22)	57/172 (33)	0.60 (0.39–0.90)
Baseline cancer stage			
Stage III	33/237 (14)	54/246 (22)	0.59 (0.39–0.92)
Stage IV	79/425 (19)	102/421 (24)	0.73 (0.55–0.98)
Baseline B symptoms			
Present	77/400 (19)	93/381 (24)	0.76 (0.56–1.03)
Absent	35/264 (13)	65/289 (22)	0.54 (0.36–0.82)
Baseline extranodal sites			
1	36/217 (17)	56/228 (25)	0.64 (0.42–0.97)
0	35/217 (16)	44/223 (20)	0.76 (0.49–1.19)
>1	39/194 (20)	54/193 (28)	0.70 (0.46–1.06)
Baseline ECOG PS			
0	57/376 (15)	83/378 (22)	0.66 (0.47–0.92)
1	46/260 (18)	66/263 (25)	0.67 (0.46–0.97)
2	9/28 (32)	9/27 (33)	0.78 (0.31–1.97)
Sex			
Male	67/378 (18)	100/398 (25)	0.67 (0.49–0.91)
Female	45/286 (16)	58/272 (21)	0.70 (0.47–1.03)

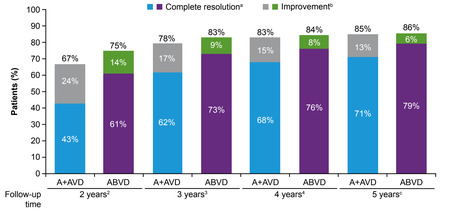
Figure 5: PFS by PET2 status at 5 years



Number of patients at risk

A+AVD	588	572	526	500	484	472	460	444	417	386	312	189	98	36	1	0
ABVD	578	558	483	463	442	424	400	392	368	334	271	170	70	20	4	0
A+AVD	47	39	28	27	26	25	24	23	23	22	18	10	3	2	1	0
ABVD	58	46	32	31	30	26	26	25	24	22	18	8	2	2	0	0

Figure 6: Patients with complete resolution or improvement of PN over time[2–4]



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

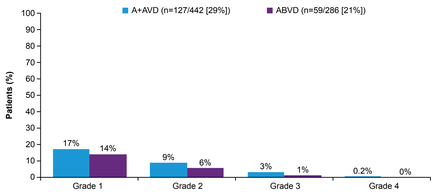
Table 2: PN resolution and improvement over time

Patients with PN, n (%)		2 years[2]	3 years[3]	4 years[4]	5 years
A+AVD n=443	Complete resolution[a] or improvement[b]	295 (67)	345 (78)	365 (83)	375 (85)
	Complete resolution[a]	191 (43)	272 (62)	300 (68)	316 (71)
	Improvement[b]	104 (24)	73 (17)	65 (15)	59 (13)
	Ongoing at last follow-up[c]	NA	NA	NA	127 (29)
ABVD n=286	Complete resolution[a] or improvement[b]	214 (75)	236 (83)	240 (84)	245 (86)
	Complete resolution[a]	174 (61)	209 (73)	217 (76)	227 (79)
	Improvement[b]	40 (14)	27 (9)	23 (8)	18 (6)
	Ongoing at last follow-up[c]	NA	NA	NA	59 (21)

[a]Resolution was defined as event outcome of "resolved" or "resolved with sequelae". [b]Improvement was defined as "improved by ≥1 grade from worst grade as of the latest assessment". [c]Ongoing event at EOT is defined as an event with an end date after the EOT date, and the event end date is "not missing", or the last follow-up date is on or after the EOT date and the event end date is missing. Median follow-up 236.9 weeks (range 0–344).

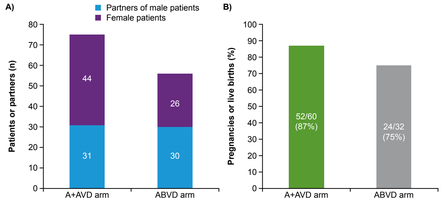
- Most ongoing cases of PN were grade 1 or 2 (**Figure 7**).
- A total of 125 live births were reported among study participants and their partners.
- There was no observable impact of study treatment on ongoing pregnancies or live births (**Figure 8**).
- Secondary malignancies were reported in 48 patients.
- Nineteen occurred in the A+AVD arm:
  - Nine hematologic malignancies.
    - Two cases of acute myeloid leukemia (patients aged 38 and 29 years).
  - Ten solid tumors.
- Twenty-nine occurred in the ABVD arm:
  - Fifteen hematologic malignancies.
    - One case of myelodysplastic syndrome (patient aged 71 years).
    - One case of acute myeloid leukemia (patient aged 74 years).
  - Fourteen solid tumors.

Figure 7: Patients with ongoing PN by grade at last follow-up



Median follow-up 236.9 weeks (range 0–344). Assessment of ongoing PN with maximum severity of grade 3/4 was confounded in 12 of the 15 A+AVD patients by death prior to resolution (n=3), loss to follow-up (n=4), or withdrawal from study (n=5). Among the ABVD patients with grade 3 PN, 2 were lost to follow-up and 2 died prior to resolution of PN.

Figure 8: (A) Number of patients or their partners reporting a pregnancy and (B) Ongoing pregnancies or live births in female patients



Conclusions

- At 5 years, A+AVD continues to demonstrate a robust and durable treatment benefit independent of disease stage, risk factor score, and PET2 status, without requiring change of therapy based on interim PET assessment and without exposure to bleomycin.
- The sustained PFS benefit with A+AVD is coupled with:
  - A manageable long-term safety profile.
  - A high rate of resolution and improvement of PN, with symptoms of PN resolving or improving over time.
  - A low rate of secondary malignancies.
  - No observed impact on the rate of successful pregnancies compared with ABVD.
- As most relapses in cHL occur within 5 years of frontline treatment, these long-term PFS data suggest that more patients may have been potentially cured of their disease with A+AVD versus ABVD.
- A+AVD should be considered as a preferred treatment option for all patients with previously untreated Stage III or IV cHL.

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Abbreviations: A+AVD, brentuximab vedotin + adriamycin, vinblastine and dacarbazine; ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; cHL, classical Hodgkin lymphoma; CI, confidence interval; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HR, hazard ratio; IPS, International Prognostic Score; IRF, independent review facility; ITT, intention-to-treat; IV, intravenous; NA, not applicable; OS, overall survival; PET, positron emission tomography; PET2, end-of-cycle-2 PET scan; PFS, progression-free survival; PN, peripheral neuropathy; Q3M, every 3 months; Q6M, every 6 months.

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