Poster #2973

Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study

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OBJECTIVE OF THIS ANALYSIS

We report 5-year PFS per investigator, a prespecified exploratory analysis, and safety results for patients in the ECHELON-1 study after a median follow-up of 60.9 months

For more information, click the figures or icons

INVESTIGATION

- Adults (≥18 years)
- Histologically confirmed Stage III/IV cHL
- Previously untreated

Randomization 1:1 N=1,334

- **A+AVD infusion** *n=664*
- **ABVD infusion** *n=670*

6 cycles

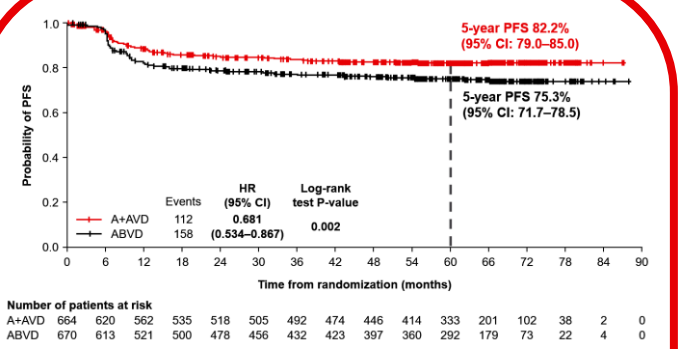
Follow-up Q3M for 36 months → Q6M until study closure

Study Assessments

Background

Patient characteristics

At 5 years PFS per investigator was significantly higher for A+AVD vs ABVD

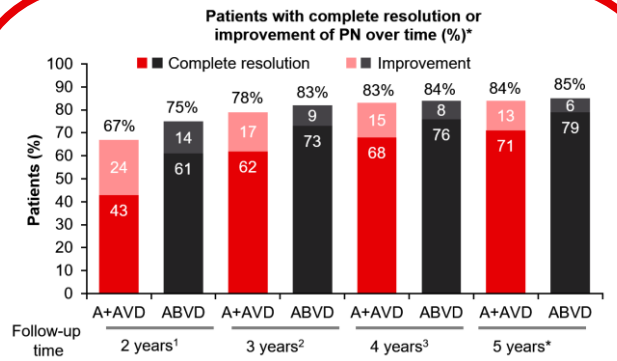


For subgroup analyses click the icons below

All subgroups | PET2 status + − | Disease stage III IV

Insufficient events have occurred to trigger an OS analysis for A+AVD versus ABVD

Most cases of PN had completely resolved or improved

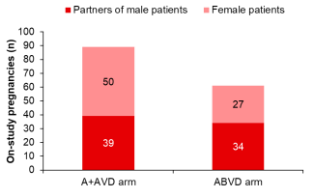


Low rate of secondary malignancies, no observed impact on pregnancy rate

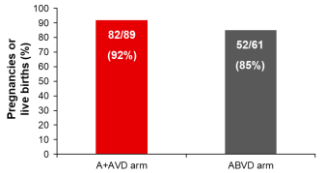
- Secondary malignancies were reported in 48 patients.
- 19 occurred in the A+AVD arm.
  - 9 hematological malignancies.
    - 2 cases of acute myeloid leukemia (patients aged 38 and 29 years).
  - 10 solid tumors.
- 29 occurred in the ABVD arm.
  - 15 hematological malignancies.
    - 1 case of myelodysplastic syndrome (patient aged 71 years).
    - 1 case of acute myeloid leukemia (patient aged 74).
  - 14 solid tumors.

- 150 on-study pregnancies were reported by participants and their partners.

On-study pregnancies in patients or their partners



Ongoing pregnancies or live births



CONCLUSIONS

With 5 years follow-up, **A+AVD** demonstrated a robust and **durable PFS improvement** versus ABVD, regardless of PET2 status, and a **consistent safety profile**

A+AVD should be considered a **preferred treatment option** for **all patients with previously untreated advanced cHL**

Abbreviations

Disclosures

- **DS:** Consulting role for Seattle Genetics, Inc., NY Lymphoma Rounds, Elsevier, and Karyopharm Therapeutics; research funding from Takeda; and membership of speaker's bureau for Imedex, Inc., Targeted Oncology, Takeda, and OncLive.
- **MDD:** Research Support for AbbVie, Acerta Pharma, Beigene, Bayer, Celgene, Celltrion, Gilead, Janssen, Mei-Pharma, Roche and Sandoz-Novartis; speakers' honoraria for Janssen, Roche, Servier and Takeda; scientific advisory board for AbbVie, Acerta, Janssen, Servier, Roche, and Takeda.
- **JMC:** Honoraria from Seattle Genetics, Inc., and Takeda
- **AI:** Consultancy for Janssen, Celgene, Takeda, Novartis, and Roche; research funding from Takeda, and Seattle Genetics; expenses from Novartis, Janssen, Pfizer, and Roche; consultancy and honoraria from Pfizer Pharmaceuticals Israel.
- **MP:** None.
- **ELM:** Consultancy for Roche, Novartis, Takeda, Janssen-Cilag, Amgen, Gilead, AbbVie, and Sanofi; speakers bureaus for Roche, Amgen, and Gilead.
- **TF:** Consultancy and speakers bureau for Seattle Genetics; consultancy, honoraria and speakers' bureaus for BMS/Celgene; honoraria and speakers bureaus for Takeda, KITE, AbbVie, Janssen, and Pharmacyclics; ad boards for AstraZeneca and Morphosis.
- **PS:** Consultancy and honoraria for Roche Poland and Takeda; honoraria from Sandoz and Morphosis.
- **KJS:** Consultancy for Merck, BMS, Seattle Genetics, Inc., Gilead, AstraZeneca, AbbVie, and Servier; research funding from Roche; honoraria from Merck, BMS, Seattle Genetics, Inc., Gilead, AstraZeneca, and AbbVie; steering committee for BeiGene.
- **NLB:** Consultancy for ADC Therapeutics, BTG, and Acerta; research funding from Autolus, BMS/Celgene, Forty Seven, Immune Design, Janssen, KITE, Merck, Millennium, Pharmacyclics, and Affimed Therapeutics; consultancy, advisory committees, and research funding from Pfizer; consultancy and research funding from Seattle Genetics and Roche/Genentech; advisory committees and research funding from Seattle Genetics.
- **JW:** Research funding from GSK; consultancy, honoraria, and research funding from Janssen and Takeda; consultancy, honoraria, travel support, and research funding from Roche; consultancy and honoraria from AbbVie, Amgen, BMS, Celgene, Gilead, and Servier.
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- **PLZ:** Honoraria, advisory committees, and speakers bureaus for Merck, AbbVie, Takeda, Incyte, and ADC Therapeutics; consultancy, honoraria, advisory committees, and speakers bureaus for BMS, Gilead, Roche, Servier, EUSA Pharma, and Verastem; honoraria and speakers bureaus for TG Therapeutics Inc.; consultancy, honoraria, and speakers bureaus for Janssen; consultancy and advisory committees for Sanofi; consultancy, advisory committees, and speakers bureaus for Celltrion, Janssen-Cilag, Sandoz, MSD, Immune Design, and Celgene; consultancy, advisory committees, research funding, and speakers bureaus for Portola; consultancy and speakers bureaus for Eusapharma and Kyowa Kirin; advisory committees and speakers bureaus for Immune Design.
- **MH:** Consultancy, honoraria, and advisory committees for Roche, Genmab, and Takeda; research funding from Celgene, Genmab, Janssen, Novartis, Roche, and Takeda.
- **JM:** Consultancy, honoraria, and speakers bureaus for Kyowa; consultancy, honoraria, research funding, and speakers bureaus for Seattle Genetics; consultancy, research funding, and speakers bureaus for Pharmacyclics, Bayer, Kite, Janssen, and Juno/Celgene/BMS; consultancy and speakers bureaus for Beigene; consultancy for Pfizer, Alexion, Fosunkite, and Innovent; speakers bureaus for Acrotech/Aurobindo, Verastem, and AstraZeneca; research funding and speakers bureaus for Genentech/Roche; consultancy and spears bureaus for AbbVie; research funding from Merck, Portola, Incyte, and Millennium.
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- **AY:** Employment with AstraZeneca; consultancy for BMS, Janssen, BioPath, Curis, Daiichi Sankyo, HCM, Epizyme, Takeda, and Novartis.
- **AG:** Speaker for Takeda.
- **RL:** Employment with Takeda Pharmaceuticals.
- **ML:** Employment and equity holder with Takeda Pharmaceuticals.
- **KF, MF:** Employment and equity ownership with Seattle Genetics, Inc.
- **JR:** Consultancy and speakers bureau from BMS, Takeda, Seattle Genetics, Inc., and Novartis; consultancy for ADC Therapeutics; equity ownership with AstraZeneca and GlaxoSmithKline; research funding from Celgene, ADC Therapeutics, Pfizer, and Millennium Pharmaceuticals Inc.

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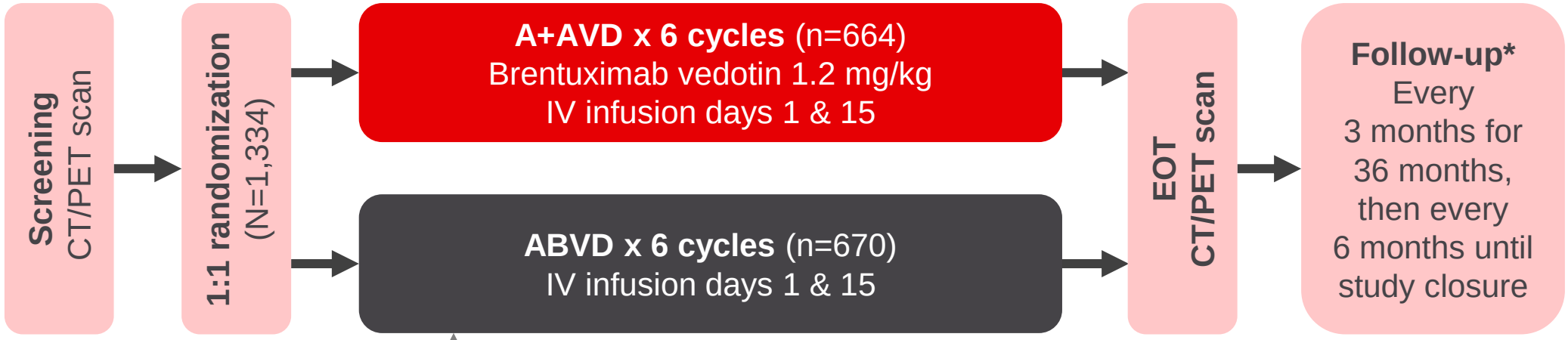
Background

- Historically, nearly all relapses in patients with cHL occured 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, and baseline disease IPI.[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.
  - These are exploratory analyses and p-values are unadjusted/descriptive.

A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine;
ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classical Hodgkin lymphoma;
CI, confidence interval; HR, hazard ratio; IPI, international prognostic index; IRF, independent review facility; ITT, intent-to-treat; PET, positron emission tomography; PFS, progression-free survival;
PN, peripheral neuropathy.

1. Radford J, et al. BMJ 1997;314:343–6;
2. Connors JM, et al. N Engl J Med 2018;378:331–44;
3. Straus DJ, et al. Blood 2020;135:735–42;
4. Bartlett NL, et al. Blood 2019;134(Suppl. 1):4026.

ECHELON-1 is an open-label, international, randomized, phase 3 trial comparing A+AVD vs ABVD in patients with advanced cHL



End-of-cycle-2 PET scan by IRF per Deauville 5-point scale

- PET (–): 1–3
- PET (+): 4–5

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' follow-up.
- 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 performed Q3M until 36 months after EOT, then Q6M.

*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.

CT, computed tomography; EOT, end of treatment; IV, intravenous; OS, overall survival; PET2, PET status after 2 cycles of treatment; Q3M, every 3 months; Q6M, every 6 months.

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, and CT scans are no longer required 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 one grade from worst grade with no higher grade thereafter.
- The incidence and outcomes of pregnancies among participants and their partners was assessed.

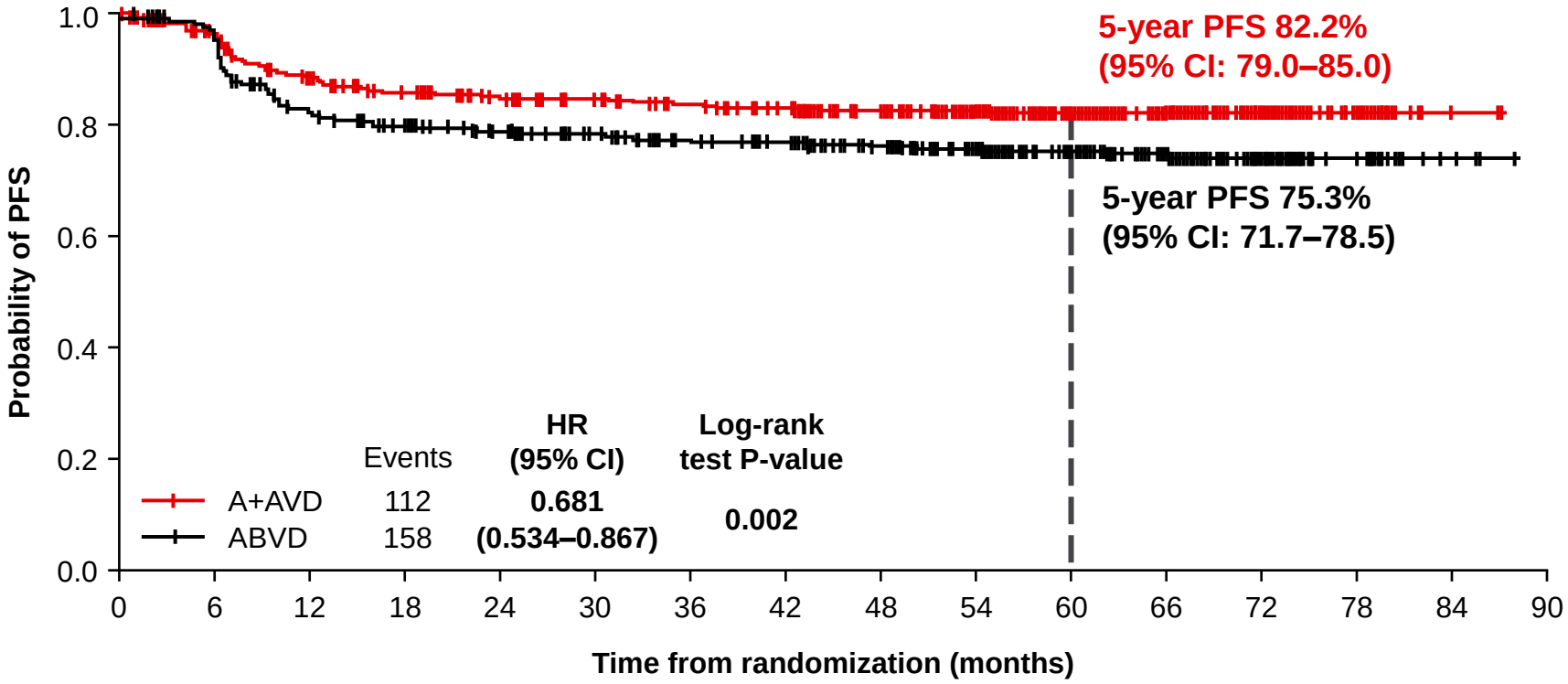
Key patient characteristics

- Median age of patients was 36 years, and 57.8% of patients were aged <40 years.[1]
- Median follow-up time was 60.9 months (95% CI: 60.8–61.0).

Characteristic[1]	A+AVD n=664	ABVD n=670	Total N=1,334
Male sex, n (%)	378 (57)	398 (59)	776 (58)
Median age, years (range)	35 (18–82)	37 (18–83)	36 (18–83)
Aged <60 years, n (%)	580 (87)	568 (85)	1148 (86)
Aged ≥60 years, n (%)	84 (13)	102 (15)	186 (14)
International Prognostic Score, n (%)			
0 or 1	142 (21)	141 (21)	283 (21)
2 or 3	355 (53)	357 (53)	712 (53)
4 to 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)

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

ECHELON-1: PFS per investigator at 5 years' follow-up*



Number of patients at risk

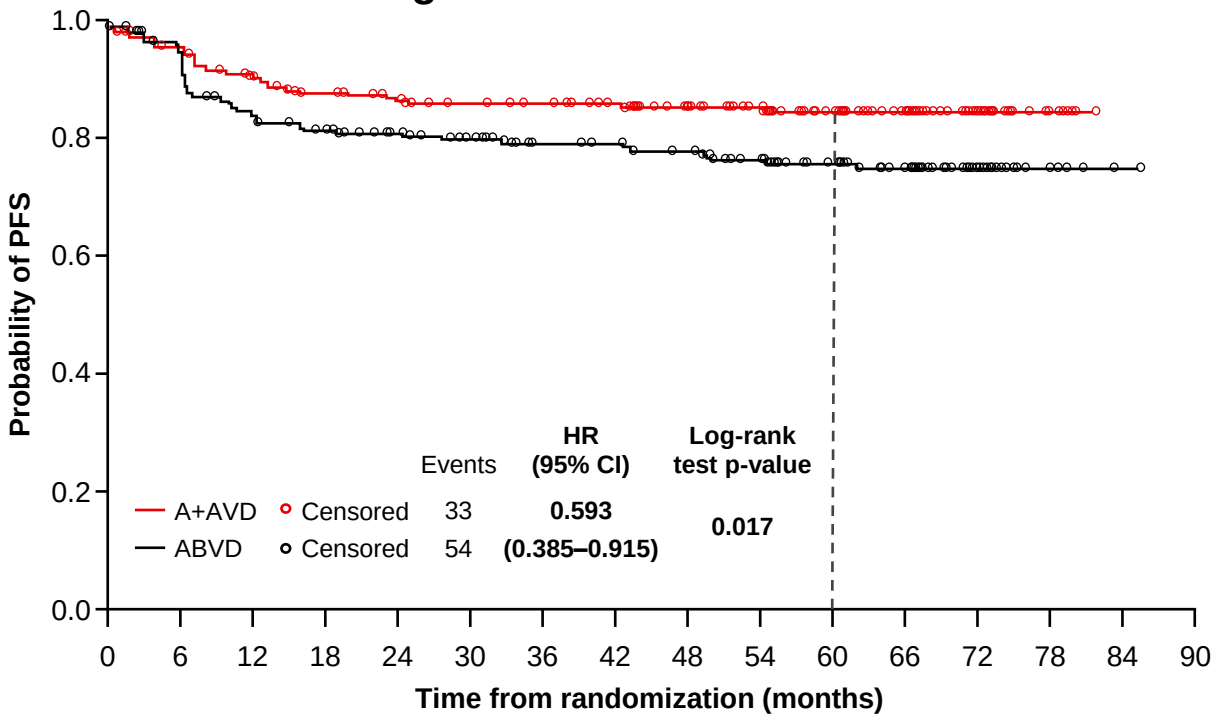
A+AVD	664	620	562	535	518	505	492	474	446	414	333	201	102	38	2	0
ABVD	670	613	521	500	478	456	432	423	397	360	292	179	73	22	4	0

- As of the 5-year follow-up, the prespecified number of events required to trigger an OS analysis have not been reached
- OS was a prespecified key secondary endpoint

*September 14, 2020 data cut-off.

ECHELON-1: PFS per investigator at 5 years in patients with Stage III/IV disease at enrollment

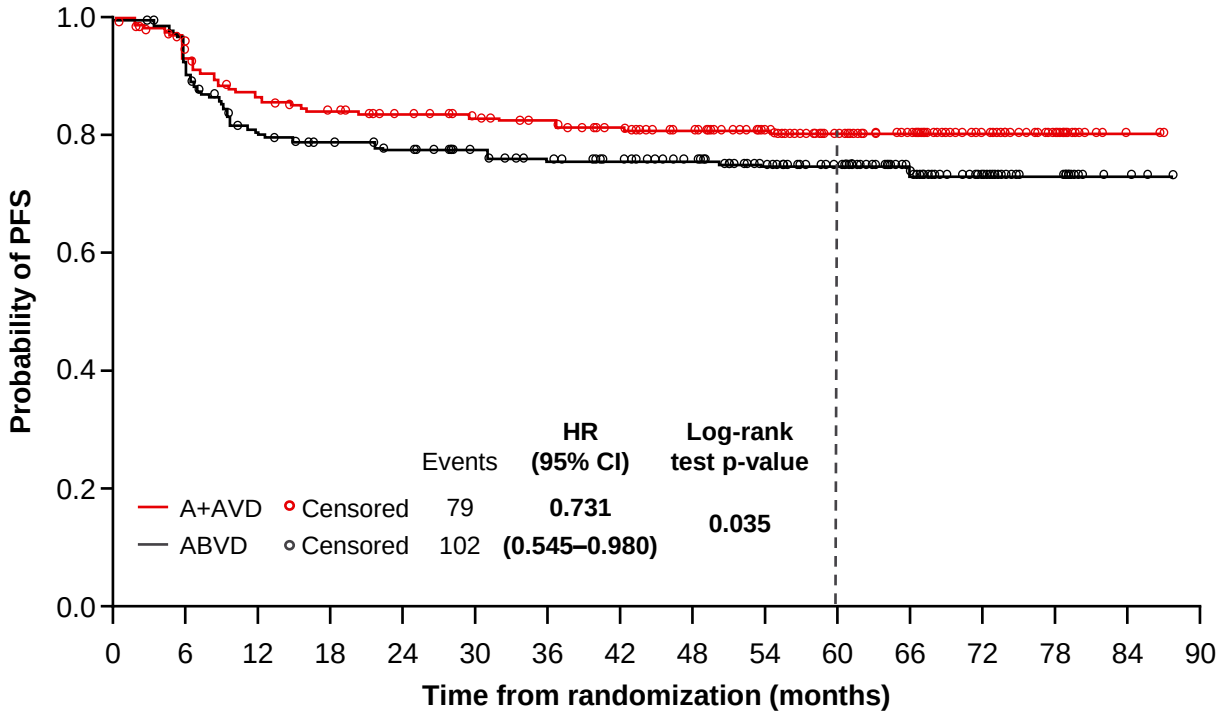
Stage III disease at enrollment



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

Stage IV disease at enrollment

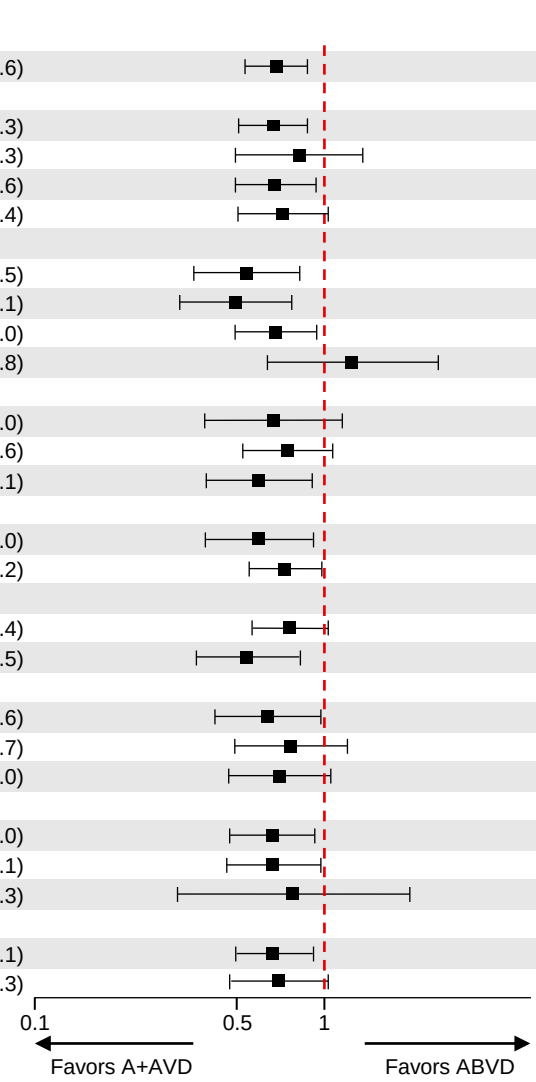


Number of patients at risk

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

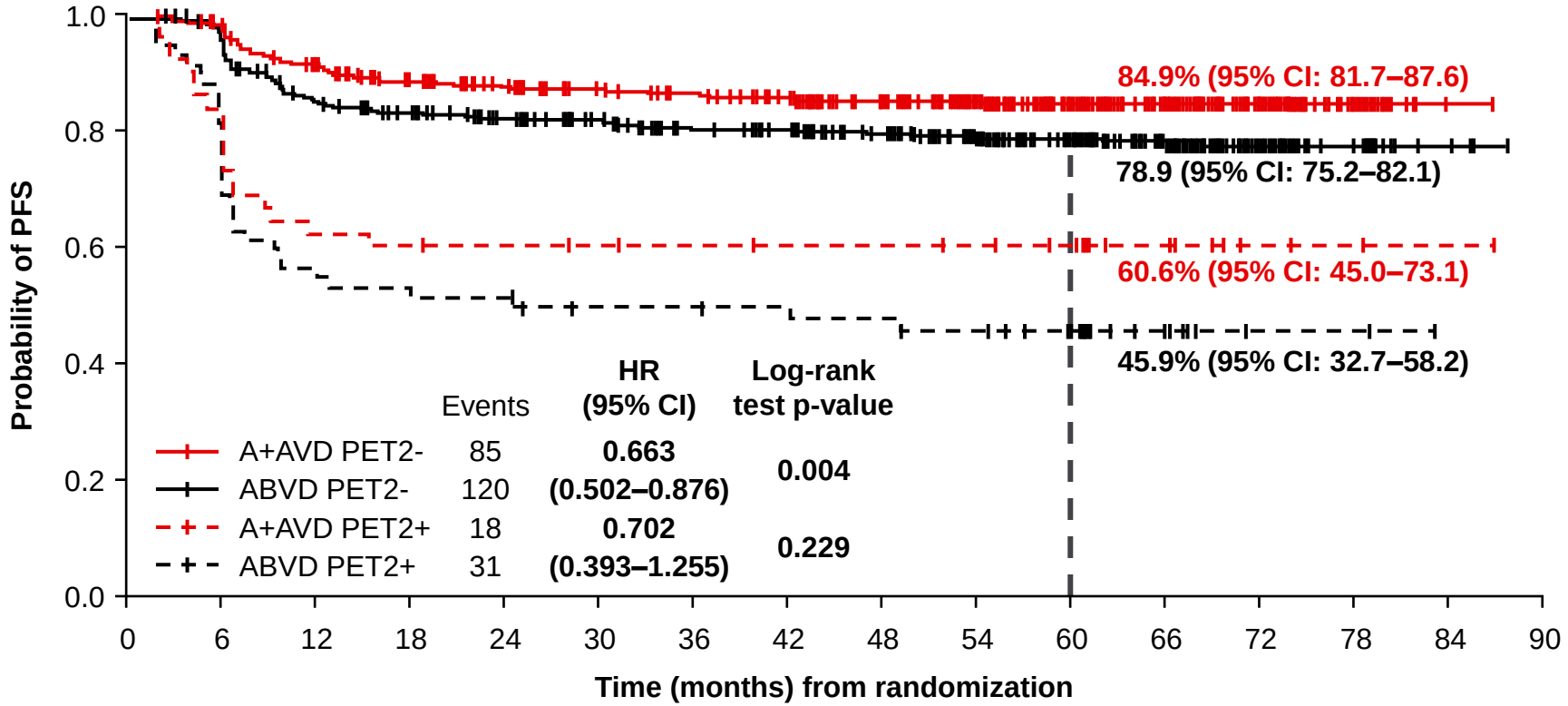
ECHELON-1: PFS subgroup analysis

Subgroup	Events/N (%) A+AVD	Events/N (%) ABVD	HR (95% CI)
Overall	112/664 (16.9)	158/670 (23.6)	0.681 (0.534–0.867)
Age			
<60 years	87/580 (15.0)	121/568 (21.3)	0.665 (0.505–0.876)
≥60 years	25/84 (29.8)	37/102 (36.3)	0.820 (0.494–1.362)
<45 years	64/451 (14.2)	83/423 (19.6)	0.680 (0.491–0.942)
≥45 years	48/213 (22.5)	75/247 (30.4)	0.720 (0.501–1.035)
Region			
Americas	34/261 (13.0)	59/262 (22.5)	0.540 (0.354–0.823)
North America	31/250 (12.4)	57/247 (23.1)	0.493 (0.318–0.764)
Europe	59/333 (17.7)	84/336 (25.0)	0.680 (0.487–0.948)
Asia	19/70 (27.1)	15/72 (20.8)	1.256 (0.638–2.472)
IPI score			
0–1	22/142 (15.5)	31/141 (22.0)	0.665 (0.385–1.148)
2–3	54/355 (15.2)	70/357 (19.6)	0.747 (0.524–1.065)
4–7	36/167 (21.6)	57/172 (33.1)	0.596 (0.392–0.904)
Baseline cancer stage			
Stage III	33/237 (13.9)	54/246 (22.0)	0.593 (0.385–0.915)
Stage IV	79/425 (18.6)	102/421 (24.2)	0.731 (0.545–0.980)
Baseline B symptoms			
Present	77/400 (19.3)	93/381 (24.4)	0.759 (0.561–1.026)
Absent	35/264 (13.3)	65/289 (22.5)	0.543 (0.360–0.819)
Baseline extra Nodal sites			
1	36/217 (16.6)	56/228 (24.6)	0.635 (0.418–0.965)
0	35/217 (16.1)	44/223 (19.7)	0.764 (0.490–1.190)
>1	39/194 (20.1)	54/193 (28.0)	0.699 (0.463–1.056)
Baseline ECOG status			
0	57/376 (15.2)	83/378 (22.0)	0.660 (0.471–0.924)
1	46/260 (17.7)	66/263 (25.1)	0.668 (0.458–0.974)
2	9/28 (32.1)	9/27 (33.3)	0.780 (0.309–1.969)
Gender			
Male	67/378 (17.7)	100/398 (25.1)	0.669 (0.491–0.912)
Female	45/286 (15.7)	58/272 (21.3)	0.698 (0.473–1.030)



ECOG, Eastern Cooperative Oncology Group.

ECHELON-1: 5-year PFS rates by PET2 status



Number of patients at risk

A+AVD PET2-	588	572	526	500	484	472	460	444	417	386	312	189	98	36	1	0
ABVD PET2-	578	558	483	463	442	424	400	392	368	334	271	170	70	20	4	0
A+AVD PET2+	47	39	28	27	26	25	24	23	23	22	18	10	3	2	1	0
ABVD PET2+	58	46	32	31	30	26	26	25	24	22	18	8	2	2	0	0

ECHELON-1: 5-year PFS rates by PET2 status and age groups (<60 years vs ≥60 years)

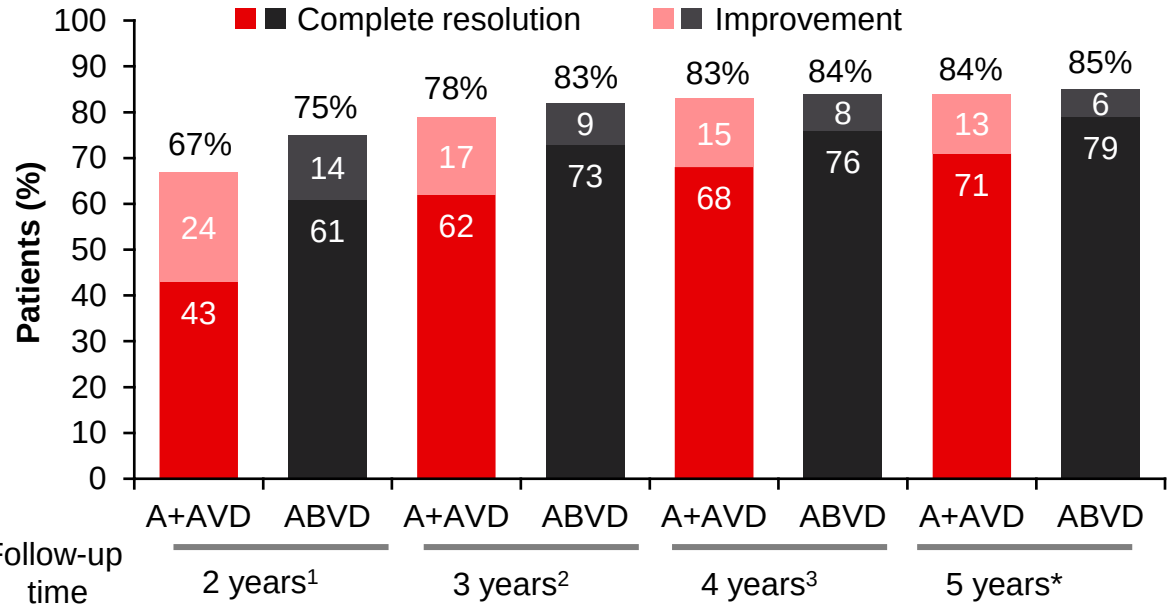
Group	A+AVD 5-year PFS, % (95% CI)	ABVD 5-year PFS, % (95% CI)	HR (95% CI)	P*
All patients	82.2 (79.0–85.0), n=664	75.3 (71.7–78.5), n=670	0.681 (0.534–0.867)	0.002
PET2–	84.9 (81.7–87.6), n=588	78.9 (75.2–82.1), n=578	0.663 (0.502–0.876)	0.004
PET2+	60.6 (45.0–73.1), n=47	45.9 (32.7–58.2), n=58	0.702 (0.393–1.255)	0.229
Aged <60 years	84.3 (81.0–87.1), n=580	77.8 (74.0–81.1), n=568	0.665 (0.505–0.876)	0.003
PET2–	86.6 (83.3–89.3), n=521	81.5 (77.7–84.7), n=493	0.675 (0.492–0.927)	0.014
PET2+	63.1 (46.4–75.9), n=42	49.3 (34.7–62.3), n=50	0.702 (0.370–1.331)	0.274
Aged ≥60 years	67.1 (55.1–76.5), n=84	61.6 (50.9–70.7), n=102	0.820 (0.494–1.362)	0.443
PET2–	71.9 (59.0–81.3), n=67	64.9 (53.5–74.2), n=85	0.720 (0.401–1.292)	0.268
PET2+	40.0 (5.2–75.3), n=5	25.0 (3.7–55.8), n=8	0.923 (0.229–3.715)	0.910

*P-values were descriptive and were calculated by stratified log-rank test to compare PFS between the two treatment groups. HRs (A+AVD/ABVD) and 95% CIs were based on a stratified Cox's proportional hazard regression model with stratification with treatment as the explanatory variable in the model.

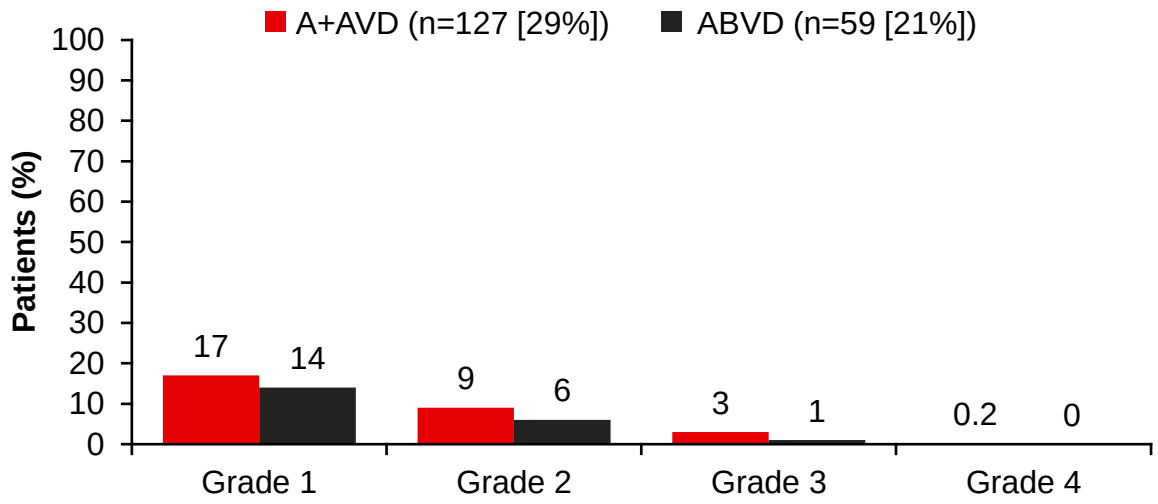
ECHELON-1: PN resolution and improvement

- At the primary analysis, 442 and 286 patients in A+AVD and ABVD arms, respectively, had experienced PN.

Patients with complete resolution or improvement of PN over time (%)*



Patients with ongoing PN by grade at last follow-up†



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; †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), and withdrawal from study (n=5).
Among the ABVD patients with grade 3 PN, two were lost to follow-up and two died prior to resolution of PN.

1. Connors JM, et al. N Engl J Med 2018;378:331–44;
2. Straus DJ, et al. Blood 2020;135:735–42;
3. Bartlett NL, et al. Blood 2019;134 (Suppl. 1):4026.

ECHELON-1: PN resolution and improvement over time

Patients with PN, n (%)		2 years[1]	3 years[2]	4 years[3]	5 years
A+AVD n=442	Complete resolution* or improvement†	295 (67)	345 (78)	365 (83)	375 (85)
	Complete resolution*	191 (43)	272 (62)	300 (68)	316 (71)
	Improvement†	104 (24)	73 (17)	65 (15)	59 (13)
	Ongoing at last follow-up‡	NA	NA	NA	127 (29)
ABVD n=286	Complete resolution* or improvement†	214 (75)	236 (83)	240 (84)	245 (86)
	Complete resolution*	174 (61)	209 (73)	217 (76)	227 (79)
	Improvement†	40 (14)	27 (9)	23 (8)	18 (6)
	Ongoing at last follow-up‡	NA	NA	NA	59 (21)

*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”.
‡Ongoing event at EOT is defined as an event with an end date that is 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).
NA, not appropriate.

1. Connors JM, et al. N Engl J Med 2018;378:331–44;
2. Straus DJ, et al. Blood 2020;135:735–42;
3. Bartlett NL, et al. Blood 2019;134(Suppl. 1):4026.

ECHELON-1: PN resolution and improvement after a median of 5 years' follow-up

	A+AVD	ABVD
Any grade on-study PN,[1] n (%)	443 (67)	286 (43)
Complete resolution, n (%)	316 (71)	227 (79)
Median time to resolution, weeks (range)	34 (0–262)	16 (0–267)
Improvement, n (%)	59 (13)	18 (6)
Median time to improvement, weeks (range)	49 (8–270)	12 (2–70)
Ongoing at last follow-up, n (%)	127 (29)	59 (21)
Grade 1	74 (17)	39 (14)
Grade 2	38 (9)	16 (6)
Grade 3	14 (3)	4 (1)
Grade 4	1 (<1)	0

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

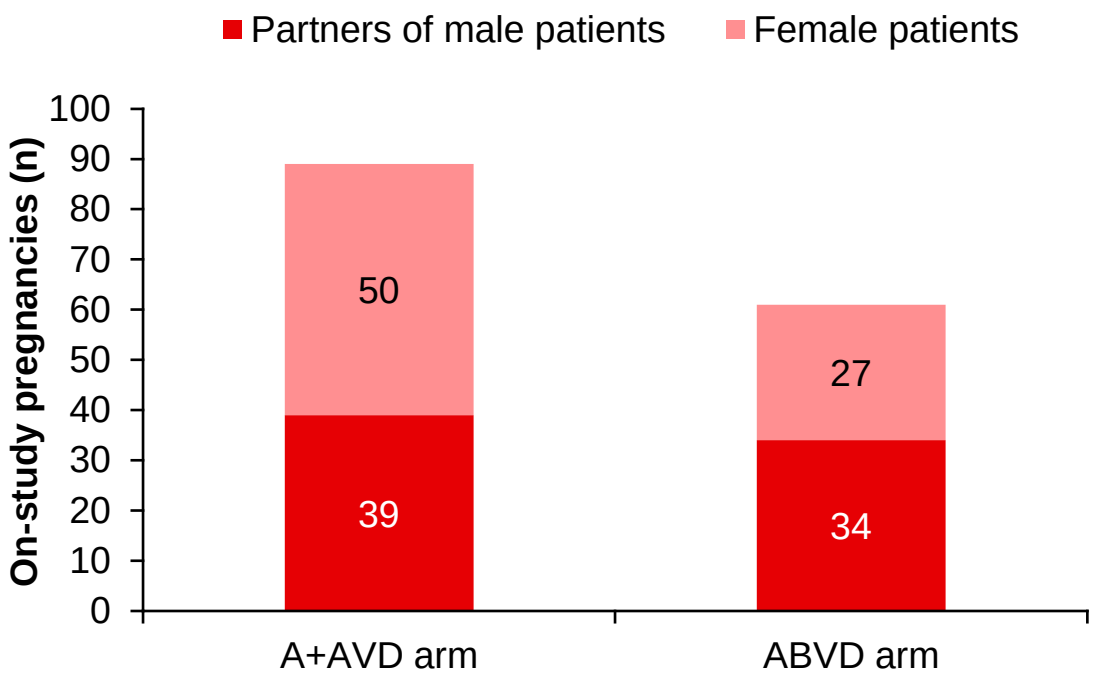
ECHELON-1: Secondary malignancies

- Secondary malignancies were reported in 48 patients.
- 19 occurred in the A+AVD arm:
  - 9 hematologic malignancies
    - 2 cases of acute myeloid leukemia (patients aged 38 and 29 years)
  - 10 solid tumors.
- 29 occurred in the ABVD arm:
  - 15 hematologic malignancies
    - 1 case of myelodysplastic syndrome (patient aged 71 years)
    - 1 case of acute myeloid leukemia (patient aged 74)
  - 14 solid tumors.

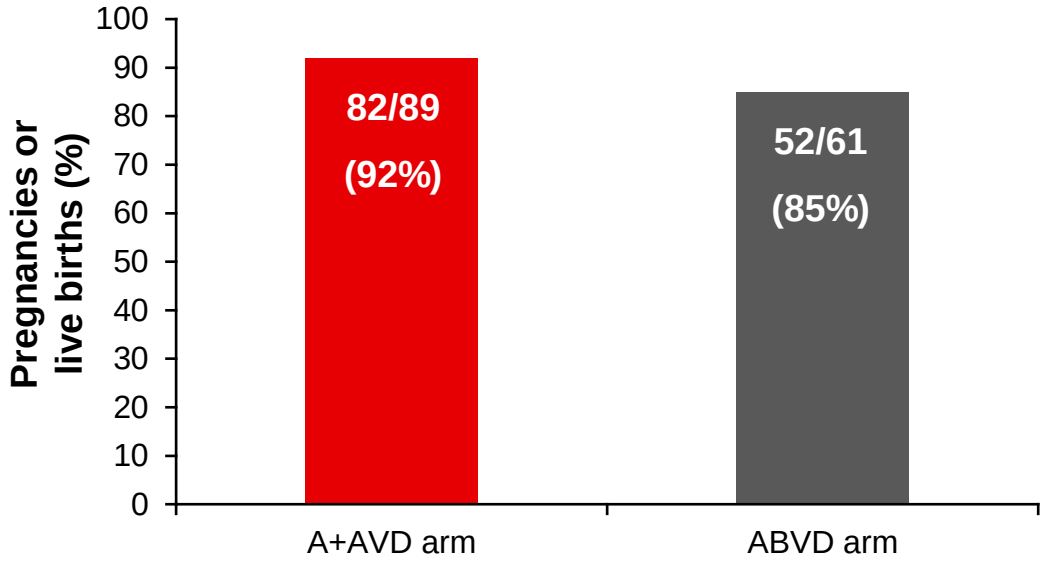
ECHELON-1: Pregnancies

- A total of 150 pregnancies were reported among study participants and their partners.

On-study pregnancies in patients or their partners



Ongoing pregnancies or live births



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 low rate of secondary malignancies
  - No observed impact on the rate of successful pregnancies compared with ABVD
  - A high rate of resolution and improvement of PN, with symptoms of PN resolving or improving over time.
- As most relapses in cHL occur within 5 years of frontline treatment, these long-term PFS data suggest that more patients may have been cured of their disease with A+AVD versus ABVD.
- A+AVD should be considered a preferred treatment option for all patients with previously untreated Stage III or IV cHL.

Abbreviations

A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine
ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine
cHL, classical Hodgkin lymphoma
CI, confidence interval
CT, computed tomography
ECOG, Eastern Cooperative Oncology Group
EOT, end of treatment
HR, hazard ratio
IPI, international prognostic index
IRF, independent review facility
ITT, intent-to-treat
IV, intravenous
NA, not appropriate
OS, overall survival
PET, positron emission tomography
PET2, PET status after 2 cycles of treatment
PET2+, PET2-positive
PET2–, PET2-negative
PFS, progression-free survival
PN, peripheral neuropathy
Q3M, every 3 months
Q6M, every 6 months