Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study

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Supplementary material

Table S1. Summary of responses.

	Aged ≥60 years (n=186)		Aged <60 years (n=1,148)		ITT population (N=1,334)[1]	
	A+AVD (n=84)	**ABVD (n=102)**	**A+AVD (n=580)**	**ABVD (n=568)**	**A+AVD (n=664)**	**ABVD (n=670)**
CR at end of randomized regimen,* n (%)	51 (61)	62 (61)	437 (75)	410 (72)	488 (73)	472 (70)
Difference (95% CI)[†]	-0.1 (-14.5–14.3)		3.2 (-2.6–9.0)		3.0 (-2.3–8.4)	
ORR at end of randomized regimen,[‡] n (%)	59 (70)	76 (75)	510 (88)	477 (84)	569 (86)	553 (83)
Difference (95% CI)[†]	-4.3 (-18.6–10.2)		4.0 (-1.9–9.7)		3.2 (-2.2–8.6)	
CR at end of frontline regimen,[§] n (%)	50 (60)	62 (61)	438 (76)	412 (73)	488 (73)	474 (71)
Difference (95% CI)[†]	-1.3 (-15.6–13.1)		3.0 (-2.8–8.8)		2.7 (-2.6–8.1)	
CR at cycle 2, n (%)	50 (60)	66 (65)	408 (70)	385 (68)	458 (69)	451 (67)
Difference (95% CI)[†]	-5.2 (-19.5–9.3)		2.6 (-3.3–8.3)		1.7 (-3.7–7.1)	
PET-negative at cycle 2,[¶] n (%)	67 (80)	84 (82)	521 (90)	493 (87)	588 (89)	577 (86)

Difference (95% CI)[†]	-2.6 (-17.0–11.9)		3.0 (-2.8–8.8)		2.4 (-2.9–7.8)	
Deauville score[#]						
≤3 after completion of frontline therapy, n (%)	60 (71)	75 (74)	510 (88)	476 (84)	570 (86)	551 (82)
Difference (95% CI)[†]	-2.1 (-16.5–12.3)		4.1 (-1.7–9.9)		3.6 (-1.8–9.0)	
≤2 after completion of frontline therapy, n (%)	60 (71)	73 (72)	503 (87)	464 (82)	563 (85)	537 (80)
Difference (95% CI)[†]	-0.1 (-14.5–14.3)		5.0 (-0.8–10.8)		4.6 (-0.8–10.0)	

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence intervals; CR: complete response; ITT: intention-to-treat; IRF: independent review facility; ORR: overall response rate; PR: partial response. *CR at the end of the randomized regimen was defined as the proportion of patients with a CR at the end of treatment with either regimen (A+AVD or ABVD), as determined by an IRF assessment. [†]CI were calculated from the exact CI, have not been adjusted for the multiple comparisons, and should not be used for definitive comparisons. [‡]ORR at the end of the randomized regimen was defined as the proportion of patients with a CR or PR at the end of treatment with either regimen (A+AVD or ABVD), as determined by an IRF assessment. [§]CR at the end of frontline therapy was defined as the proportion of patients with a CR after completion of either the randomized regimen (A+AVD or ABVD) or alternate frontline therapy, as determined by an IRF assessment. [¶]PET negativity rate at cycle 2 was defined as the proportion of patients with negative cycle 2 PET results defined as a Deauville score of ≤3 at cycle 2. [#]The Deauville score is a 5-point scale on which higher scores indicate greater uptake of ^{18}F-fluorodeoxyglucose at involved sites on PET. A score of 1 indicates no uptake, a score of 2 indicates uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 indicates uptake at an initial site that is greater than uptake at the mediastinum but less than or equal to uptake at the liver, a score of 4 indicates uptake at an initial site that is moderately increased as compared with uptake at the liver, and a score of 5 indicates markedly increased uptake at any site or uptake at a new site of disease. The absence of a CR at the end of primary chemotherapy was defined as a Deauville score of 3, 4, or 5.

Table S2. Five-year progression-free survival per investigator in the two treatment arms by PET2 status and age.

60-month PFS* per INV, % (95% CI)	**A+AVD**	**ABVD**	**HR (95% CI) *P*-value**
ITT population	n=664 82.2 (79.0–85.0)	n=670 75.3 (71.7–78.5)	0.681 (0.53–0.87) 0.0017
PET2-negative	n=588 84.9 (81.7–87.6)	n=578 78.9 (75.2–82.1)	0.663 (0.50–0.88) 0.004
PET2-positive	n=47 60.6 (45.0–73.1)	n=58 45.9 (32.7–58.2)	0.702 (0.39–1.26) 0.229
Aged ≥60 years	n=84 67.1 (55.1–76.5)	n=102 61.6 (50.9–70.7)	0.820 (0.49–1.36) 0.443
PET2-negative	n=67 71.9 (59.0–81.3)	n=85 64.9 (53.5–74.2)	0.720 (0.40–1.29) 0.268
PET2-positive	n=5 40.0 (5.2–75.3)	n=8 25.0 (3.7–55.8)	0.923 (0.23–3.72) 0.910
Aged <60 years	n=580 84.3 (81.0–87.1)	n=568 77.8 (74.0–81.1)	0.665 (0.51–0.88) 0.003
PET2-negative	n=521 86.6 (83.3–89.3)	n=493 81.5 (77.7–84.7)	0.675 (0.49–0.93) 0.014
PET2-positive	n=42 63.1 (46.4–75.9)	n=50 49.3 (34.7–62.3)	0.702 (0.37–1.33) 0.274

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; INV: investigator; ITT: intention-to-treat; PET2, positron emission tomography status after cycle 2; PFS: progression-free survival. *5-year PFS per INV based on a median of 60.9 months extended follow-up.

Table S3. Mean relative dose intensity in patients aged ≥60 years.

	Patients aged ≥60 years	
Mean RDI, % (SD)	**A+AVD (n=83)**	**ABVD (n=98)**
Brentuximab vedotin	92.3 (14.0)	NA
Bleomycin	NA	88.7 (21.1)
Doxorubicin	96.6 (7.7)	97.3 (7.1)
Vinblastine	93.3 (13.6)	93.3 (14.8)
Dacarbazine	97.9 (5.4)	95.9 (11.9)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; NA: not applicable; RDI: relative dose intensity; SD: standard deviation.

Table S4. Cause of death in patients aged ≥60 years.

Age (years)/ gender	Cycle day of last dose	Days from first dose	Days from last dose	Cause of death*	Disease related?†	Treatment related?
A+AVD (n=83)						
On-study deaths‡						
62/F	C1D1	12	12	AE (histiocytosis hematophagic)	Yes	Yes
73/M	C1D15	41	25	AE (multiple organ dysfunction)	No	Yes
79/M	C1D1	3	3	AE (myocardial infarction)	Yes	No
ABVD (n=98)						
On-study deaths‡						
61/M	C5D15	168	19	AE (pneumonia)	No	No
63/M	C6D15	200	25	AE (cardiac arrest)	No	No
78/F	C3D15	109	29	AE (pulmonary toxicity – interstitial lung disease)	No	Yes
80/M	C3D1	83	27	AE (respiratory disorder)	No	Yes
83/F	C5D15	160	21	AE (pneumonia)	Yes	Yes

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AE: adverse event; C: cycle; D: day; F: female; M: male. *AE are described by their Medical Dictionary for Regulatory Activities (MedDRA) preferred term. †Related to the disease under study or complications thereof. ‡On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.

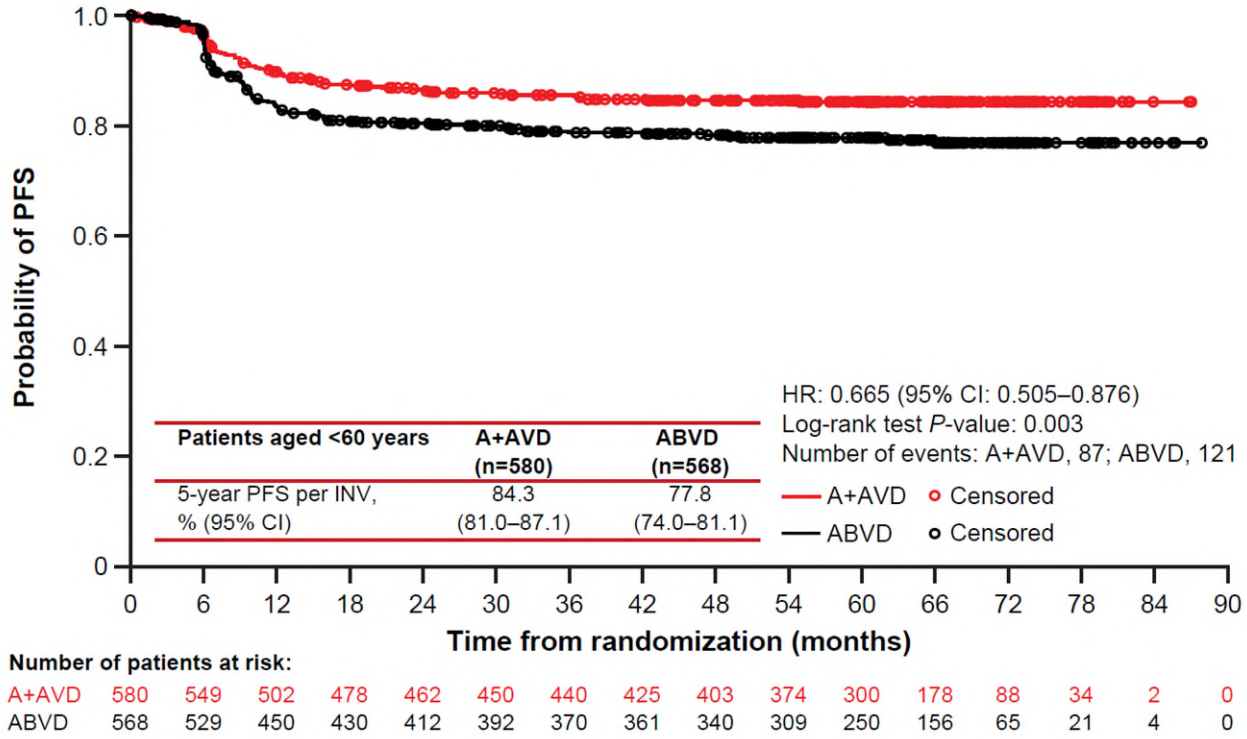
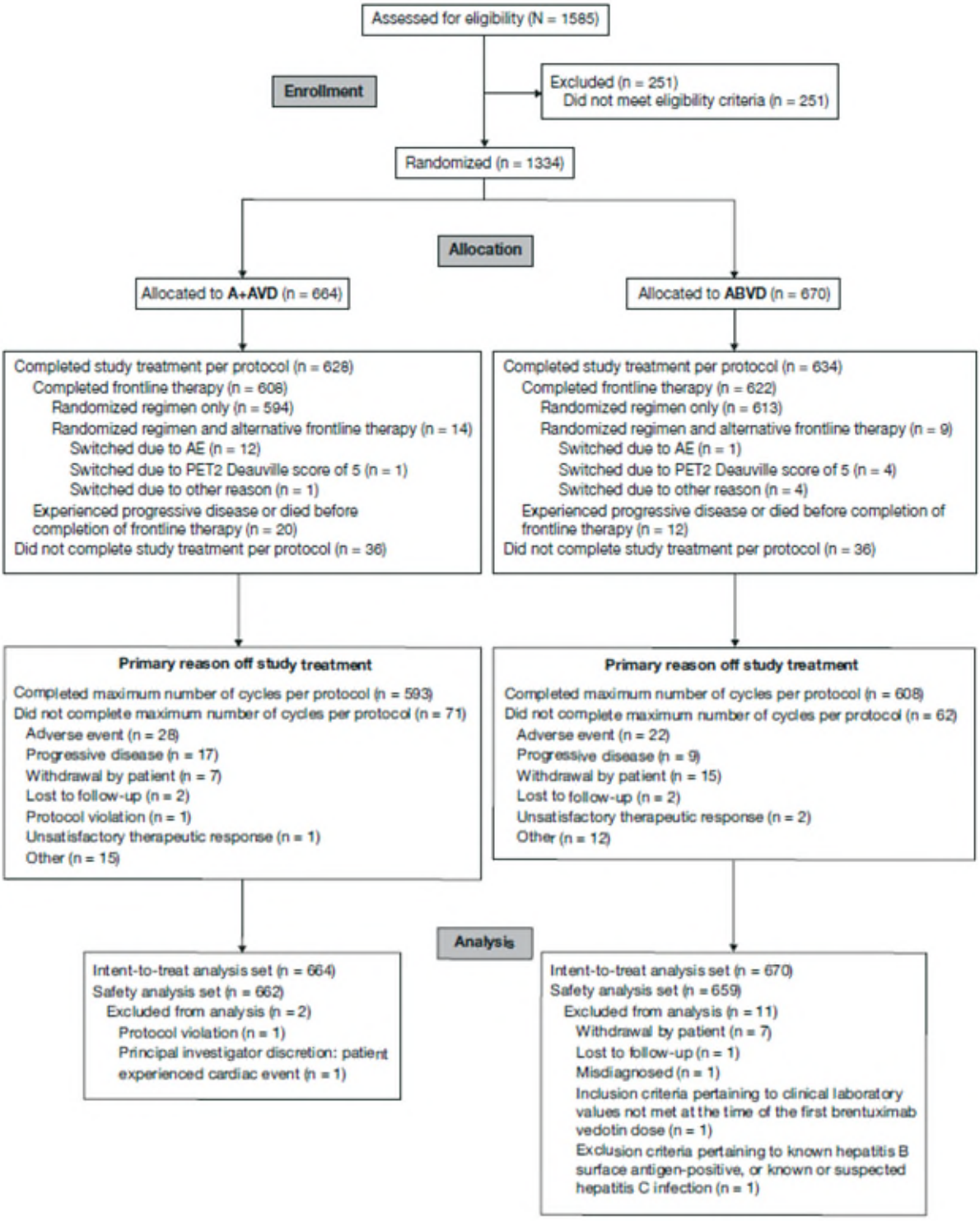


Figure S1. Progression-free survival (PFS) per independent review facility (IRF) in patients aged <60 years.

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; HR: hazard ratio; INV: investigator; IRF: independent review facility; PFS: progression-free survival.



ECHELON-1 CONSORT diagram.

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AE: adverse event; PET2: end-of-cycle-2 positron-emission tomography.

References

1. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331–344.