Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018;378:331-44. DOI: 10.1056/NEJMoa1708984

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Supplementary Appendix

Supplement to: Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

Contents

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Methods Text Not Included in Main Paper

Text S1. Modified Progression-free Survival.

Clinical trials evaluating the effectiveness of potentially curative systemic chemotherapy require definition of events considered to reveal failure of the regimens used to accomplish that goal. In advanced Hodgkin's lymphoma, two outcomes exposing failure of the primary treatment are straightforward to define: progression of the disease or death from any cause. However, a third possible outcome representing failure of the primary intervention has been variably identified in clinical trials: persistence of the disease despite completion of the planned primary treatment, a situation which then prompts additional rapid intervention. This latter situation clearly represents failure of the primary treatment even though neither progression nor death has occurred. Moreover, because delivery of subsequent treatment, which often includes salvage chemotherapy and an autologous hematopoietic stem cell transplant, is effective at preventing future progression the failure of frontline therapy in this scenario is not reflected by standard progression-free survival. To capture all events that reflect a failure of frontline chemotherapy in advanced Hodgkin's lymphoma the ECHELON-1 study primary end point of modified progression-free survival also included modified progression events, defined as a response that was less than complete at the end of primary chemotherapy (an end-of-treatment positron-emission tomography [PET] scan score Deauville 3, 4, or 5) ***AND*** the delivery of subsequent treatment. Both conditions had to be present to consider the patient to have experienced a modified progression event. Neither one in isolation was sufficient so that patients with false positive end-of-treatment PET scans that did not progress without additional therapy or those who received subsequent therapy in the absence of evidence of residual disease were not considered to have had a modified progression event. Furthermore, potential investigator bias for the modified end point was minimized in the ECHELON-1 study by the use of a blinded independent review committee

to read the end-of-treatment PET scans; results from the independent review committee read were not available to investigators.

Supplementary Figures S1 and S2

Figure S1. CONSORT Diagram.

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

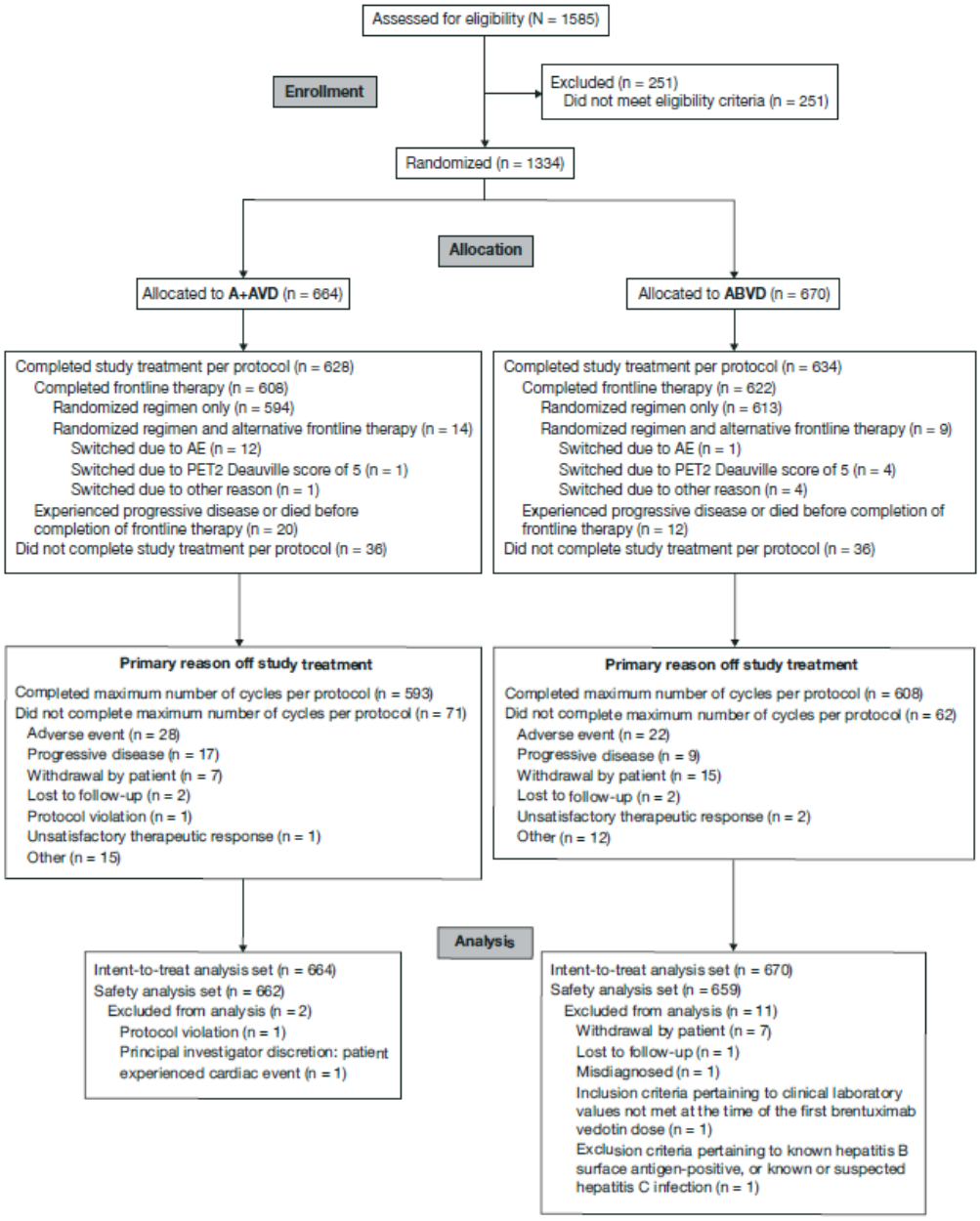
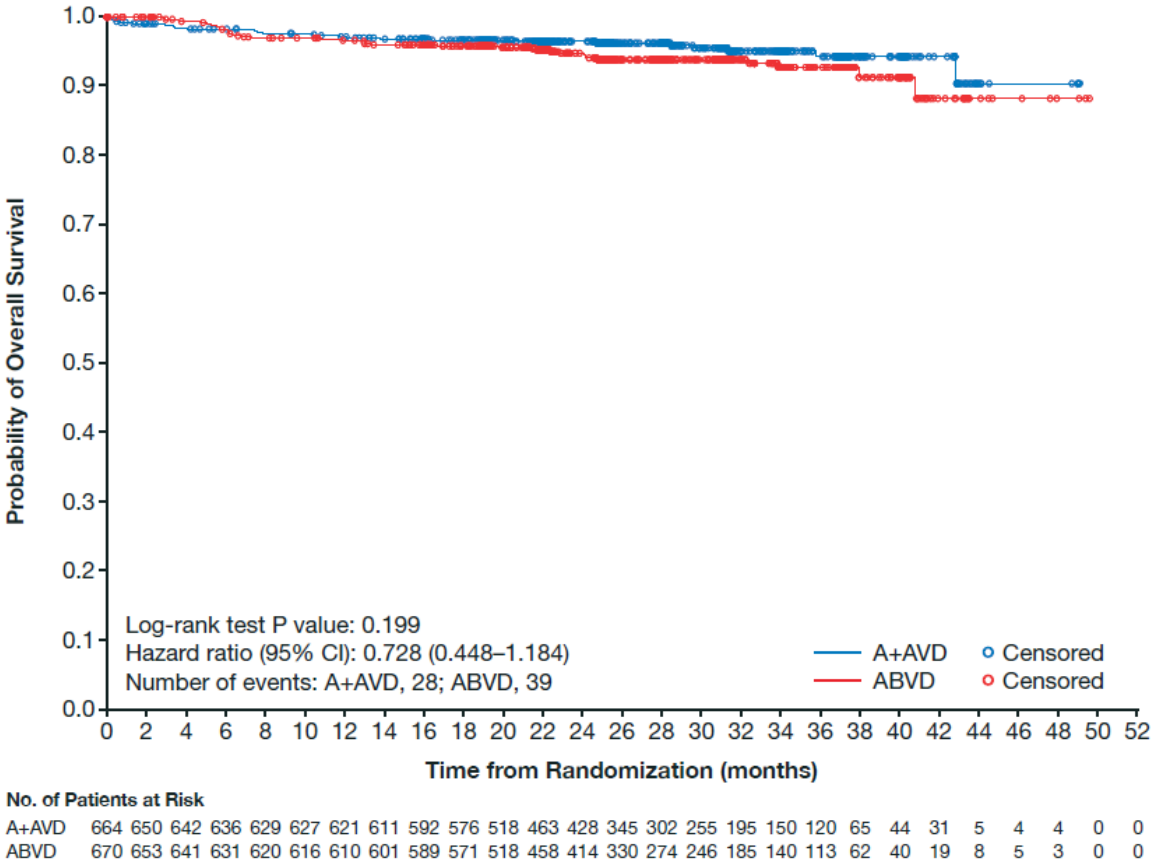


Figure S2. Kaplan–Meier Analysis of Overall Survival in the Intention-to-treat Population.

A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CI, confidence interval.



Supplementary Tables S1–S8

Table S1. Details of Brentuximab Vedotin Dose Modifications.

Toxicity	≤Grade 2		≥Grade 3	
Non-hematologic (excluding neuropathy)	Continue at same dose level		Hold A+AVD dosing until toxicity has resolved to ≤Grade 2 or has returned to baseline*	
Hematologic	Continue at same dose level		For neutropenia, manage with growth factors (G-CSF or GM-CSF) per institutional guidelines. For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines. For anemia, manage per institutional guidelines	
Peripheral neuropathy	**Grade 1** Continue at same dose level	**Grade 2** Reduce dose to 0.9 mg/kg and resume treatment; if already at 0.9 mg/kg, continue dosing at that level	**Grade 3** Withhold brentuximab vedotin until toxicity is ≤Grade 2, then reduce dose to 0.9 mg/kg and resume treatment. If already at 0.9 mg/kg, consult with sponsor (AVD may be continued or held concurrently at physician's discretion)	**Grade 4** Discontinue brentuximab vedotin

*Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Table S2. International Prognostic Score for Hodgkin's Lymphoma.

Risk factor
Male sex
Age ≥ 45 yr
Stage IV disease
Hemoglobin <10.5 g/dL
White-cell count ≥15 $x10^9$/L
Lymphocyte count <0.6 $x10^9$/L or <8% of white-cell count
Serum albumin <4 g/dL

The International Prognostic Score[1] ranges from 0 to 7, with higher scores indicating increased risk of treatment failure. Patients score one point for each factor present. Scores of 0 to 1 denote low risk, scores of 2 to 3 intermediate risk, and scores of 4 to 7 high risk.

Table S3. Patient Demographics and Clinical Characteristics at Baseline (Intention-to-treat Population).

Characteristic	A+AVD N = 664	ABVD N = 670	Total N = 1334
Sex — no. (%)			
Male	378 (57)	398 (59)	776 (58)
Female	286 (43)	272 (41)	558 (42)
Median age (range) — yr	35.0 (18–82)	37.0 (18–83)	36.0 (18–83)
Age categories (yr) — no. (%)			
<45	451 (68)	423 (63)	874 (66)
45–59	129 (19)	145 (22)	274 (21)
60–64	24 (4)	40 (6)	64 (5)
≥65	60 (9)	62 (9)	122 (9)
Race — no. (%)			
White	560 (84)	554 (83)	1114 (84)
Asian	56 (8)	57 (9)	113 (8)
Black or African American	20 (3)	25 (4)	45 (3)
Other	18 (3)	17 (3)	35 (3)
Not reported	10 (2)	17 (3)	27 (2)
Regions — no. (%)			
Americas	261 (39)	262 (39)	523 (39)
Europe	333 (50)	336 (50)	669 (50)
Asia	70 (11)	72 (11)	142 (11)
Ann Arbor stage at initial diagnosis — no. (%)*			
Stage I	0	0	0
Stage II†	1 (<1)	0	1 (<1)
Stage III	237 (36)	246 (37)	483 (36)
Stage IV	425 (64)	421 (63)	846 (64)
Not applicable, unknown, or missing	1 (<1)	3 (<1)	4 (<1)
IPS — no. (%)‡			
0 or 1	141 (21)	141 (21)	282 (21)
2 or 3	354 (53)	351 (52)	705 (53)
4 to 7	169 (25)	178 (27)	347 (26)
ECOG performance status — no. (%)§			
0	376 (57)	378 (57)	754 (57)
1	260 (39)	263 (39)	523 (39)
2	28 (4)	27 (4)	55 (4)
3 or 4	0	0	0
Not obtained or missing	0	2 (<1)	2 (<1)
Bone marrow involvement at diagnosis or study entry — no. (%)			
Yes	147 (22)	151 (23)	298 (22)
No	502 (76)	509 (76)	1011 (76)
Unknown or missing	15 (2)	10 (1)	25 (2)
Extranodal involvement at diagnosis — no. (%)			
Yes	411 (62)	416 (62)	827 (62)
1 extranodal site	217 (33)	223 (33)	440 (33)
>1 extranodal sites	194 (29)	193 (29)	387 (29)
No	217 (33)	228 (34)	445 (33)
Unknown or missing	36 (5)	26 (4)	62 (5)
Patients with any B symptom — no. (%)¶	400 (60)	381 (57)	781 (59)

Percentages may not total 100 because of rounding.
*The Ann Arbor staging system[2] ranges from I to IV, with higher stages indicating more widespread disease.
†Patients in this category have major protocol violation.
‡The IPS[1] ranges from 0 to 7, with higher scores indicating increased risk of treatment failure. Scores of 0 to 1 denote low risk, scores of 2 to 3 intermediate risk, and scores of 4 to 7 high risk.
§Values for ECOG performance status[3] range from 0 to 5, with higher scores indicating greater disability.
¶B symptoms consist of night sweats, unexplained fever (temperature >38°C), or loss of more than 10% of body weight.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score.

Table S4. Summary of First Subsequent Chemotherapy as Part of Salvage Treatment for Patients Failing to Achieve a Complete Response at the Completion of Frontline Therapy.

First subsequent chemotherapy — no. (%)	A+AVD N = 9	ABVD N = 22	Total N = 31
Overall	7 (78)	15 (68)	22 (71)
Cisplatin + cytarabine + dexamethasone	3 (33)	3 (14)	6 (19)
Carboplatin + etoposide + ifosfamide	2 (22)	2 (9)	4 (13)
Cisplatin + cytarabine + etoposide + methylprednisolone	1 (11)	3 (14)	4 (13)
Brentuximab vedotin	0	1 (5)	1 (3)
Brentuximab vedotin + bendamustine + ASCT	0	1 (5)	1 (3)
Carboplatin + etoposide + ifosfamide + ASCT	1 (11)	0	1 (3)
Carboplatin + etoposide + ifosfamide + rituximab + ASCT	0	1 (5)	1 (3)
Carboplatin + etoposide + ifosfamide + SCT	0	1 (5)	1 (3)
Dexamethasone + cisplatin + gemcitabine	0	1 (5)	1 (3)
Dexamethasone + cytarabine + procarbazine	0	1 (5)	1 (3)
Rituximab + bendamustine	0	1 (5)	1 (3)

A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplant; SCT, stem cell transplant.

Table S5. Summary of Reasons for Switching to Alternative Chemotherapy during Frontline Therapy (Safety Population).

Reason for switching to alternative chemotherapy — no. (%)	A+AVD N = 15	ABVD N = 9	Total N = 24
Adverse event	12 (80)	1 (11)	13 (54)
Deauville score assessment of 5*	1 (7)	4 (44)	5 (21)
Other	2 (13)†	4 (44)‡	6 (25)

These changes to alternative frontline therapy prior to completion of treatment with the randomized regimen were not considered events as they occurred in the absence of disease progression.

*The Deauville score[4] 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 uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 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 uptake at an initial site that is moderately increased as compared with uptake at the liver, and a score of 5 markedly increased uptake at any site or uptake at a new site of disease. The absence of complete response at the end of primary chemotherapy was defined as a Deauville score of 3, 4, or 5.

†Reason was unspecified for both patients.

‡Reasons included toxicity (n = 1), unsatisfactory response (n = 3).

A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, positron-emission tomography.

Table S6. Exposure to, and Dose Modifications of, Individual Regimen Components.

	A+AVD N = 662			
	Brentuximab vedotin (n = 662)	**Doxorubicin (n = 656)**	**Vinblastine (n = 661)**	**Dacarbazine (n = 661)**
Duration of treatment (weeks)				
Mean (standard deviation)	23.19 (5.646)	23.88 (5.362)	23.60 (5.600)	23.89 (5.335)
Median	24.21	24.57	24.43	24.57
Min, max	2.0, 35.0	2.0, 48.9	2.0, 48.9	2.0, 48.9
Total number of doses received				
Mean (standard deviation)	10.8 (2.60)	11.2 (2.38)	11.0 (2.50)	11.2 (2.37)
Median	12.0	12.0	12.0	12.0
Min, max	1, 12	1, 12	1, 12	1,12
Number of treated cycles				
Mean (standard deviation)	5.5 (1.21)	5.6 (1.13)	5.6 (1.18)	5.6 (1.12)
Median	6.0	6.0	6.0	6.0
Min, max	1, 6	1, 6	1, 6	1, 6
Action on study drug— no. (%)	434 (66)	355 (54)	378 (57)	350 (53)
Dose reduced prescribed	170 (26)	25 (4)	58 (9)	29 (4)
Dose reduced non-prescribed	3 (<1)	2 (<1)	1 (<1)	2 (<1)
Dose increased prescribed	0	0	0	0
Dose increased non-prescribed	0	0	0	0
Dose held	41 (6)	2 (<1)	12 (2)	1 (<1)
Dose missed	0	0	1 (<1)	0
Dose interrupted	12 (2)	8 (1)	1 (<1)	11 (2)
Dose delayed	315 (48)	323 (49)	319 (48)	317 (48)
Dose discontinued permanently	71 (11)	38 (6)	52 (8)	38 (6)
	ABVD N = 659			
	Bleomycin (n = 659)	**Doxorubicin (n = 649)**	**Vinblastine (n = 659)**	**Dacarbazine (n = 659)**
Duration of treatment (weeks)				
Mean (standard deviation)	22.38 (5.694)	23.88 (4.669)	23.65 (4.880)	23.86 (4.658)
Median	24.00	24.00	24.00	24.00
Min, max	2.0, 39.1	2.0, 45.4	2.0, 45.4	2.0, 45.4
Total number of doses received				
Mean (standard deviation)	10.7 (2.64)	11.4 (2.00)	11.3 (2.13)	11.4 (2.02)
Median	12.0	12.0	12.0	12.0
Min, max	1, 12	1, 12	1, 12	1, 12
Number of treated cycles				
Mean (standard deviation)	5.4 (1.24)	5.7 (0.95)	5.7 (1.01)	5.7 (0.96)
Median	6.0	6.0	6.0	6.0
Min, max	1, 6	1, 6	1, 6	1, 6
Action on study drug— no. (%)	315 (48)	250 (38)	281 (43)	256 (39)
Dose reduced prescribed	17 (3)	24 (4)	61 (9)	19 (3)
Dose reduced non-prescribed	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Dose increased prescribed	0	0	1 (<1)	0
Dose increased non-prescribed	1 (<1)	1 (<1)	0	1 (<1)
Dose held	32 (5)	1 (<1)	9 (1)	1 (<1)
Dose missed	2 (<1)	2 (<1)	3 (<1)	2 (<1)
Dose interrupted	6 (<1)	11 (2)	3 (<1)	28 (4)
Dose delayed	211 (32)	218 (33)	219 (33)	215 (33)
Dose discontinued permanently	106 (16)	22 (3)	34 (5)	22 (3)

A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

Table S7. Summary of Adverse Events in the Safety Population.

Safety summary — no. (%)	A+AVD N = 662		ABVD N = 659	
Any adverse event	653 (99)		646 (98)	
Drug-related adverse event	641 (97)		617 (94)	
Grade ≥3 adverse event	549 (83)		434 (66)	
Drug-related Grade ≥3 adverse event	525 (79)		389 (59)	
Serious adverse event	284 (43)		178 (27)	
Drug-related serious adverse event	240 (36)		125 (19)	
Adverse event resulting in drug discontinuation	88 (13)		105 (16)	
Adverse event resulting in dose modification	423 (64)		293 (44)	
Dose held	44 (7)		32 (5)	
Dose interrupted	22 (3)		33 (5)	
Dose reduced	191 (29)		65 (10)	
Dose delayed	318 (48)		217 (33)	
Death during treatment*	9 (1)		13 (2)	
Death due to drug-related adverse events	8 (1)		7 (1)	
Hospitalizations	242 (37)		186 (28)	
Common adverse events — no. (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia	382 (58)	357 (54)	295 (45)	260 (39)
Nausea	348 (53)	20 (3)	371 (56)	7 (1)
Constipation	279 (42)	11 (2)	241 (37)	4 (<1)
Vomiting	216 (33)	23 (3)	183 (28)	9 (1)
Fatigue	211 (32)	19 (3)	211 (32)	7 (1)
Peripheral sensory neuropathy	189 (29)	31 (5)	111 (17)	3 (<1)
Diarrhea	181 (27)	19 (3)	121 (18)	5 (<1)
Pyrexia	179 (27)	19 (3)	147 (22)	13 (2)
Peripheral neuropathy	174 (26)	27 (4)	85 (13)	6 (<1)
Alopecia	173 (26)	1 (<1)	146 (22)	0
Weight decreased	148 (22)	6 (<1)	40 (6)	1 (<1)
Abdominal pain	142 (21)	21 (3)	65 (10)	4 (<1)
Anemia	140 (21)	54 (8)	67 (10)	25 (4)
Stomatitis	138 (21)	10 (2)	104 (16)	3 (<1)
Febrile neutropenia	128 (19)	128 (19)	52 (8)	52 (8)
Bone pain	126 (19)	6 (<1)	66 (10)	1 (<1)
Insomnia	126 (19)	4 (<1)	82 (12)	1 (<1)
Decreased appetite	118 (18)	5 (<1)	76 (12)	2 (<1)
Cough	97 (15)	0	123 (19)	0
Headache	95 (14)	2 (<1)	94 (14)	2 (<1)
Arthralgia	89 (13)	2 (<1)	78 (12)	0
Neutrophil count decreased	86 (13)	83 (13)	79 (12)	67 (10)
Dyspepsia	84 (13)	1 (<1)	75 (11)	0
Paresthesia	84 (13)	0	73 (11)	0
Back pain	83 (13)	4 (<1)	49 (7)	0
Dyspnea	82 (12)	9 (1)	124 (19)	11 (2)
Myalgia	81 (12)	3 (<1)	71 (11)	3 (<1)
Pain in extremity	81 (12)	2 (<1)	67 (10)	1 (<1)
Oropharyngeal pain	72 (11)	2 (<1)	55 (8)	3 (<1)
Upper respiratory tract infection	70 (11)	5 (<1)	70 (11)	3 (<1)
Alanine aminotransferase increased	68 (10)	22 (3)	26 (4)	1 (<1)
G-CSF primary prophylaxis — no. (%)	**No (n = 579)**	**Yes (n = 83)**	**No (n = 616)**	**Yes (n = 43)**
Febrile neutropenia in Cycle 1	61 (11)	1 (1)	24 (4)	2 (5)
Febrile neutropenia during treatment	119 (21)	9 (11)	49 (8)	3 (7)
Any neutropenia†	425 (73)	29 (35)	352 (57)	9 (21)
Neutropenia Grade ≥3†	406 (70)	24 (29)	309 (50)	8 (19)
Grade ≥3 adverse event	502 (87)	47 (57)	414 (67)	20 (47)
Infections and infestations (SOC)	322 (56)	39 (47)	312 (51)	19 (44)
Grade ≥3 infections and infestations (SOC)	107 (18)	9 (11)	63 (10)	3 (7)
Serious adverse event	257 (44)	27 (33)	171 (28)	7 (16)
Serious adverse events of febrile neutropenia, neutropenia, sepsis,	190 (33)	20 (24)	107 (17)	4 (9)

neutropenic sepsis, pyrexia, or infections and infestations (SOC)				
Death during treatment*	8 (1)	1 (1)‡	12 (2)	1 (2)

*Defined as a death that occurred within 30 days after the last dose of frontline therapy.
†Neutropenia and neutropenia Grade ≥3 (neutrophil count <1000 per cubic millimeter) include the preferred terms of 'neutropenia' and 'neutrophil count decreased'.
‡The patient in the A+AVD group who had G-CSF primary prophylaxis received G-CSF for treatment of neutropenia, which occurred before day 5.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; G-CSF, granulocyte colony-stimulating factor; SOC, system organ class for the noted event.

Table S8. Summary of Peripheral Neuropathy (SMQ) (Safety Population).

Patients with event — no. (%)	A+AVD N = 662	ABVD N = 659	Total N = 1321
Any peripheral neuropathy (SMQ) event	442 (67)	286 (43)	728 (55)
Peripheral motor neuropathy (SSQ)*‡	74 (11)	29 (4)	103 (8)
Peripheral motor neuropathy	42 (6)	8 (1)	50 (4)
Muscular weakness	36 (5)	18 (3)	54 (4)
Peroneal nerve palsy	1 (<1)	2 (<1)	3 (<1)
Muscle atrophy	2 (<1)	0	2 (<1)
Hypotonia	0	1 (<1)	1 (<1)
Autonomic neuropathy	1 (<1)	2 (<1)	3 (<1)
Peripheral sensory neuropathy (SSQ)†‡	429 (65)	273 (41)	702 (53)
Peripheral sensory neuropathy	189 (29)	111 (17)	300 (23)
Neuropathy peripheral	174 (26)	85 (13)	259 (20)
Paraesthesia	84 (13)	73 (11)	157 (12)
Hypoaesthesia	33 (5)	27 (4)	60 (5)
Polyneuropathy	10 (2)	6 (<1)	16 (1)
Neuralgia	8 (1)	1 (<1)	9 (<1)
Burning sensation	2 (<1)	4 (<1)	6 (<1)
Dysaesthesia	4 (<1)	1 (<1)	5 (<1)
Gait disturbance	3 (<1)	0	3 (<1)
Toxic neuropathy	3 (<1)	0	3 (<1)
Neurotoxicity	2 (<1)	0	2 (<1)
Sensory disturbance	0	1 (<1)	1 (<1)

*Includes the preferred terms of peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, muscular weakness, hypotonia, or muscle atrophy.
†Includes all other preferred terms except for autonomic neuropathy, and the six preferred terms for peripheral motor neuropathy.
‡Numbers in individual categories exceed total because some patients experienced more than one type of neuropathy.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; SMQ, standardized Medical Dictionary for Regulatory Activities query; SSQ, special search query.

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