Brentuximab vedotin with chemotherapy for Stage 3/4 classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study

David J. Straus,[1] Monika Dlugosz-Danecka,[2] Sergiy Alekseev,[3] Arpad Illes,[4] Marco Picardi,[5] Ewa Lech-Maranda,[6] Tatyana Feldman,[7] Piotr Smolewski,[8] Kerry J. Savage,[9] Nancy L. Bartlett,[10] Jan Walewski,[11] Andrea Gallamini,[12] Radhakrsihnan Ramchandren,[13] Pier L. Zinzani,[14] Joseph M. Connors,[9] Hina A. Jolin,[15] Rachael Liu,[15] Keenan Fenton,[16] Andres Ferero-Torres,[16] John Radford[17]

1 Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, 2 the Department of Hematology, Jagiellonian University, Krakow, 3 N.N. Petrov Scientific Research Institute of Oncology, Russia, 4 the Department of Hematology, Faculty of Medicine, University of Debrecen, Debrecen, 5 the Department of Advanced Biomedical Science, Federico II University Hospital, Naples, 6 the Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, 7 John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ 8 the Department of Experimental Hematology, Medical University of Lodz, Lodz, 9 University of British Columbia and the Department of Medical Oncology, BC Cancer Centre for Lymphoid Cancer, Vancouver, Canada 10 the Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, 11 the Department of Lymphoid Malignancy, the Maria Sklodowska-Curie Institute and Oncology Center, Warsaw 12 Research Innovation and Statistics, Antoine-Lacassagne Cancer Centre, Nice, France, 13 the Department of Hematology–Oncology, Barbara Ann Karmanos Cancer Center, Detroit 14 the Institute of Hematology Seragnoli, University of Bologna, Bologna, 15 Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals, Cambridge, MA 16 Seattle Genetics, Inc, Bothell, WA, 17 the Department of Medical Oncology, University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

American Society of Clinical Oncology 2019, Chicago, IL, May 31–June 4, 2018, Abstract No. 252445

ASCO Poster: Timeline (FYI slide not part of poster)

- Abstract notifications: March 29
- Shell review (full team): April 8-12
- Draft 1 review (core writing team): April 24-26
- Draft 2 review: May 1-6 (full team)
- Approval of final poster: May 14-16
- ASCO starts May 31

Please let me know of any OOO dates to be aware of

Background

- Approximately 30% of advanced stage HL patients are refractory or relapse following frontline treatment with ABVD[1-3]
- The phase 3 ECHELON-1 study demonstrated that BV with AVD (A+AVD) was superior to ABVD for the previously untreated of Stage 3/4 cHL (NCT01712490).[4]

Background

- Maturing data from clinical trials utilizing PET2-adapted escalation/de-escalation strategies suggest limitations of this treatment approach, including:
  - Risk of relapse in PET2-negative patients after frontline treatment (~25%)
  - Risk of secondary malignancies, treatment related mortality, and other toxicities were observed in PET2-positive patients switched to BEACOPP
- Reported relapse rates for contemporary front-line trials:
  - 3-yr PFS of 79.8% (82.1% PET2-) for patients in the RATHL trial[6] with Stage 3/4 disease and ≤60 yrs (**Table 1**)
  - 5-yr PFS of 74% (76% PET2-) in patients ≤60 yrs in the SWOG S0816 trial[7]
- Here we present a 3-year update of the ECHELON-1 study—a non-PET-adapted therapy (six cycles of A+AVD versus ABVD)—including ITT PFS per investigator and extended safety follow-up

Background

Table 1: Summary of key results from the RATHL and SWOG S0816 trials for stage 3/4 patients

RATHL[6]

	ABVD (N=470)	AVD (N=465)	BEACOPP (N=172)	Overall
Status at cycle 2 PET (all pts)	Negative: 83.7%		Positive: 16.3%	-
3-year PFS (Stage 3/4)	NR	NR	NR	NR
3-year PFS (Stage 3/4, ≤60 yrs)	82.1%	82.1%	63.9%	79.8%

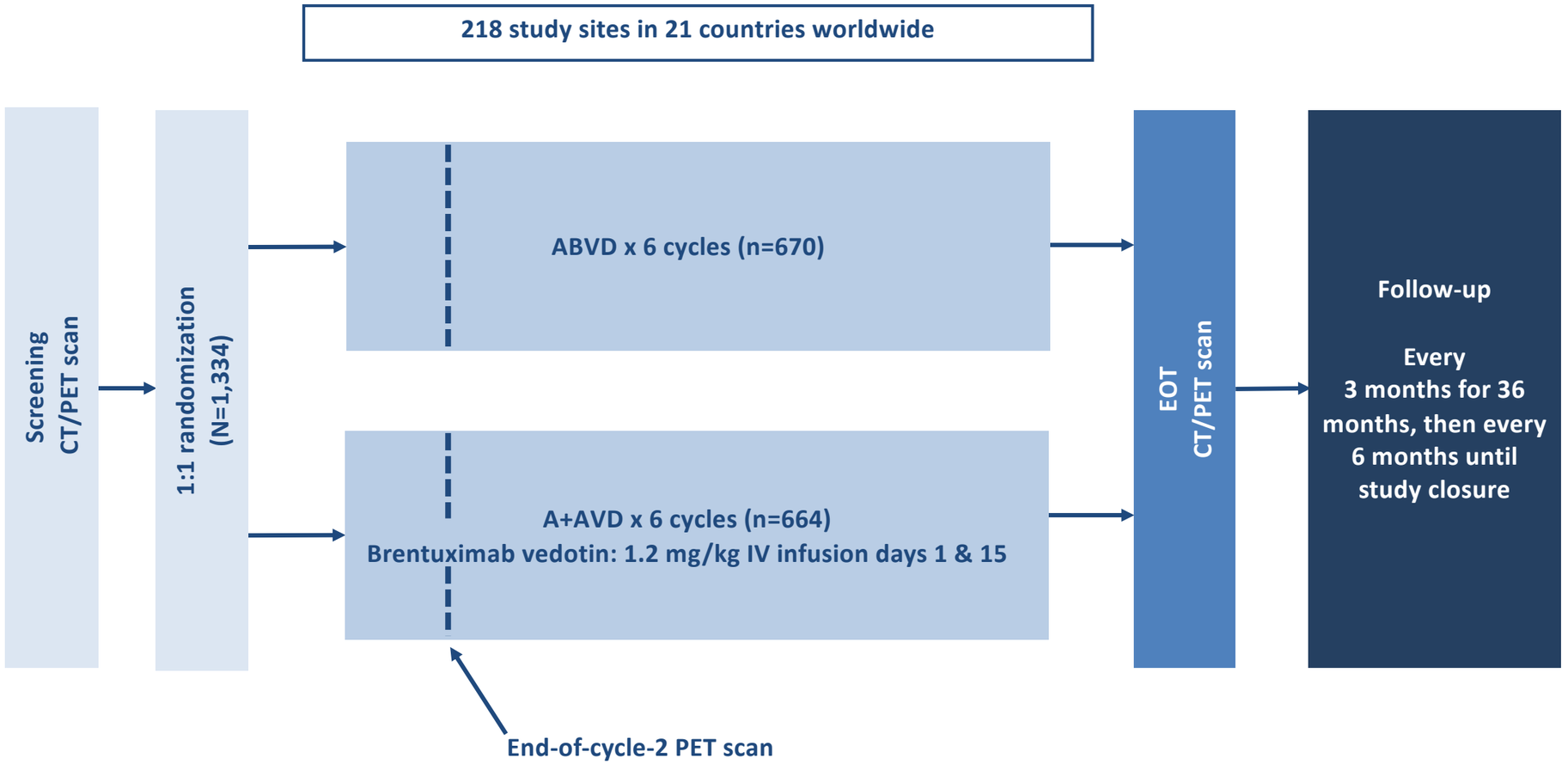
SWOG S0816[7]

	ABVD (N=271)	escBEACOPP (N=60)	Overall
Status at cycle 2 PET (all pts)	Negative: 82%	Positive: 18%	-
2-year PFS (Stage 3/4, ≤60 yrs)	82%	64%	79%
5-year PFS (Stage 3/4, ≤60 yrs)	76%	66%	74%

NR = not reported

Methods:

Figure 1: ECHELON-1 study design



- A+AVD, brentuximab vedotin + doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CT, computerized tomography; EOT, end of treatment; IV, intravenous; PET, positron emission tomography.

Methods

- ECHELON-1 was an open-label, international, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced (stage III and IV) cHL
  - The study design has been previously described (Figure 1)[4, 8]
  - A+AVD or ABVD were administered on days 1 and 15 of a 28 day cycle for up to 6 cycles
- All analyses of PFS are exploratory and per investigator assessment (INV)
- A PFS event was defined as the first of disease progression (per Cheson 2007)[9] or death from any cause
- End-of-cycle 2 PET (PET2) scans were conducted and were evaluated using the Deauville criteria:
  - PET2-negative was defined as Deauville score of 1, 2, or 3
  - PET2-positive was defined as Deauville score of 4 or 5
- Resolution and improvement of peripheral neuropathy (PN) was monitored during extended follow-up[4, 5]

Results

- From November 19, 2012, through January 13, 2016, a total of 1,334 patients at 218 sites in 21 countries were randomly assigned to receive A+AVD (n=664) or ABVD (n=670)[4, 8]
- Baseline patient demographics and disease characteristics for the ITT population and by PET2 status were well balanced and have been previously described,[4,10] (**Table 2**).
- In the A+AVD arm, 588 patients (89%) were PET2-negative and 47 (7%) were PET2-positive. In the ABVD arm, 577 (86%) were PET2-negative and 58 (9%) were PET2-positive
- PFS per INV at 3 years for all patients (95% CI) (**Figure 2**)
  - A+AVD: 83.1% (79.9–85.9) versus ABVD: 76.0% (72.4–79.2); difference of 7.1%
- Benefit of A+AVD is also observed for patients <60 years of age, independent of PET2 status **(Table 3)**
- Consistent improvement in PFS per INV was observed for patients treated with A+AVD versus ABVD across all subgroups prespecified for the ITT population, including Stage 3 and 4 disease, age, and international prognostic score (IPS) (**Figure 4**)

Results

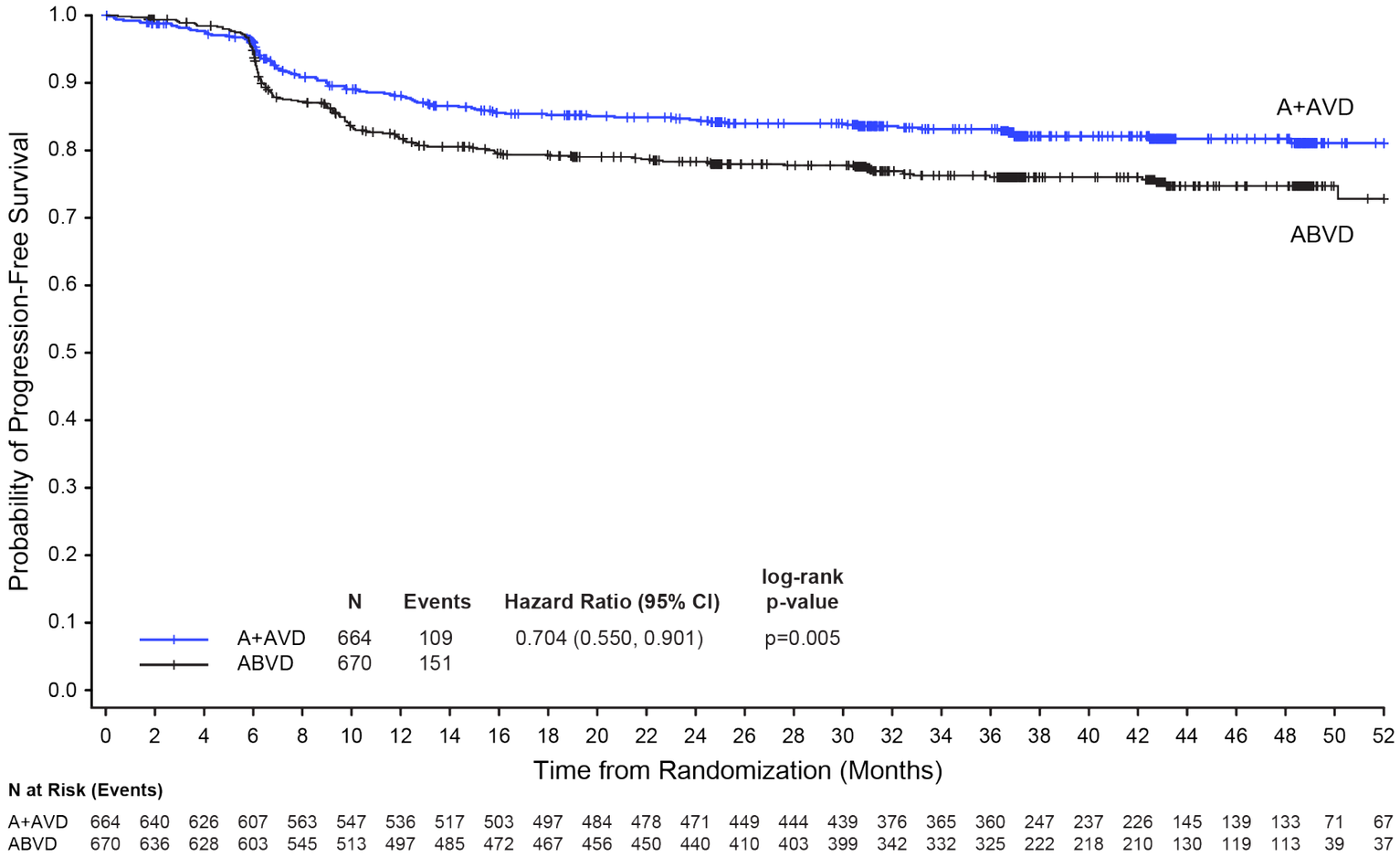
Table 2: Baseline patient demographics and disease characteristics (ITT population)

Baseline patient characteristics	A+AVD N=664	ABVD N=670
Male, %	57	59
Median age, years (range)	35 (18–82)	37 (18–83)
Age, years, %		
<45	68	63
45–59	19	22
60–64	4	6
≥65	9	9
Region, %		
Americas	39	39
Europe	50	50
Asia	11	11
Ann Arbor stage, %		
III	36	37
IV	64	63
IPS risk factors, %*		
0–1	21	21
2–3	53	52
4–7	25	27
ECOG PS, %		
0	57	57
≥1	43	43
B symptoms, %	60	57
Bone marrow involvement, %	22	23
Sites of extranodal involvement, %†		
None	33	34
1	33	33
>1	29	29

- *Percentages do not total 100% due to rounding; †Unknown/missing data for 5% and 4% in the A+AVD and ABVD groups, respectively; IPS, International Prognostic Score

Results

Figure 2: PFS per INV at 3 years shows a sustained benefit (ITT population)



- PFS per INV at 3 years for all patients (95% CI)
  - A+AVD: 83.1% (79.9–85.9) versus ABVD: 76.0% (72.4–79.2); difference of 7.1%

Results

Table 3: PFS per INV at 3 years shows benefit of A+AVD independent of PET2 status, including patients who are <60 yrs

% (95% CI)	A+AVD n=664	ABVD n=670	Difference (%)	HR (95% CI) p value	p value
All pts (ITT)	83.1 (79.9–85.9)	76.0 (72.4–79.2)	7.1	0.70 (0.55–0.90)	0.005
PET2(-)	85.8 (82.6–88.5) n=577	79.5 (75.8–82.7) n=573	6.3	0.69 (0.52–0.91)	0.009
PET2(+)	67.7 (53.8–78.3) n=58	51.5 (38.2–63.4) n=63	16.2	0.59 (0.33–1.07)	0.077
Pts <60 yrs	84.9 (81.6–87.7) n=580	77.8 (73.9–81.1) n=568	7.1	0.69 (0.52–0.91)	0.008
Pts <60 yrs, PET2(-)	87.2 (83.9–89.9) n=512	81.0 (77.1–84.4) n=489	6.2	0.71 (0.51–0.98)	0.034
Pts <60 yrs, PET2(+)	69.2 (54.1–80.1) n=51	54.7 (40.0–67.2) n=54	14.5	0.60 (0.32–1.15)	0.117

- Benefit of A+AVD is also observed for patients <60 years of age, independent of PET2 status **(Table 3)**

Results

Figure 4: Forest plot of PFS per INV at 3-year shows consistent improvement across all subgroups

Subgroup	Event / N (%) A+AVD	Event / N (%) ABVD	Hazard Ratio (95% CI)
Overall	109/664 (16.4)	151/670 (22.5)	0.704 (0.550, 0.901)
Age			
<60 years	86/580 (14.8)	116/568 (20.4)	0.689 (0.521, 0.910)
≥60 years	23/ 84 (27.4)	35/102 (34.3)	0.785 (0.464, 1.329)
<65 years	91/604 (15.1)	128/608 (21.1)	0.678 (0.518, 0.886)
≥65 years	18/ 60 (30.0)	23/ 62 (37.1)	0.800 (0.431, 1.484)
<45 years	63/451 (14.0)	81/423 (19.1)	0.686 (0.494, 0.954)
≥45 years	46/213 (21.6)	70/247 (28.3)	0.741 (0.511, 1.076)
Region			
Americas	33/261 (12.6)	57/262 (21.8)	0.547 (0.356, 0.839)
North America	30/250 (12.0)	56/247 (22.7)	0.490 (0.315, 0.764)
Europe	59/333 (17.7)	81/336 (24.1)	0.707 (0.505, 0.989)
Asia	17/ 70 (24.3)	13/ 72 (18.1)	1.256 (0.610, 2.587)
International Prognostic Score			
0–1	21/141 (14.9)	30/141 (21.3)	0.666 (0.381, 1.163)
2–3	53/353 (15.0)	63/351 (17.9)	0.804 (0.558, 1.158)
4–7	35/170 (20.6)	58/178 (32.6)	0.588 (0.386, 0.894)
Baseline cancer stage			
Stage III	32/237 (13.5)	49/246 (19.9)	0.643 (0.412, 1.004)
Stage IV	77/425 (18.1)	100/421 (23.8)	0.723 (0.537, 0.973)
Baseline B symptoms			
Present	74/400 (18.5)	89/381 (23.4)	0.760 (0.558, 1.035)
Absent	35/264 (13.3)	62/289 (21.5)	0.572 (0.378, 0.866)
Baseline extranodal sites			
0	35/217 (16.1)	50/228 (21.9)	0.689 (0.447, 1.062)
1	34/217 (15.7)	44/223 (19.7)	0.737 (0.471, 1.153)
>1	38/194 (19.6)	53/193 (27.5)	0.706 (0.465, 1.070)
Baseline ECOG status			
0	57/376 (15.2)	79/378 (20.9)	0.692 (0.492, 0.973)
1	44/260 (16.9)	63/263 (24.0)	0.681 (0.463, 1.001)
2	8/ 28 (28.6)	9/ 27 (33.3)	0.684 (0.264, 1.777)
Gender			
Male	66/378 (17.5)	94/398 (23.6)	0.699 (0.510, 0.958)
Female	43/286 (15.0)	57/272 (21.0)	0.684 (0.460, 1.016)

- Consistent improvement in PFS per INV was observed for patients treated with A+AVD versus ABVD across all subgroups prespecified for the ITT population, including Stage 3 and 4 disease, age, and IPS **(Figure 4)**

Results: Peripheral Neuropathy

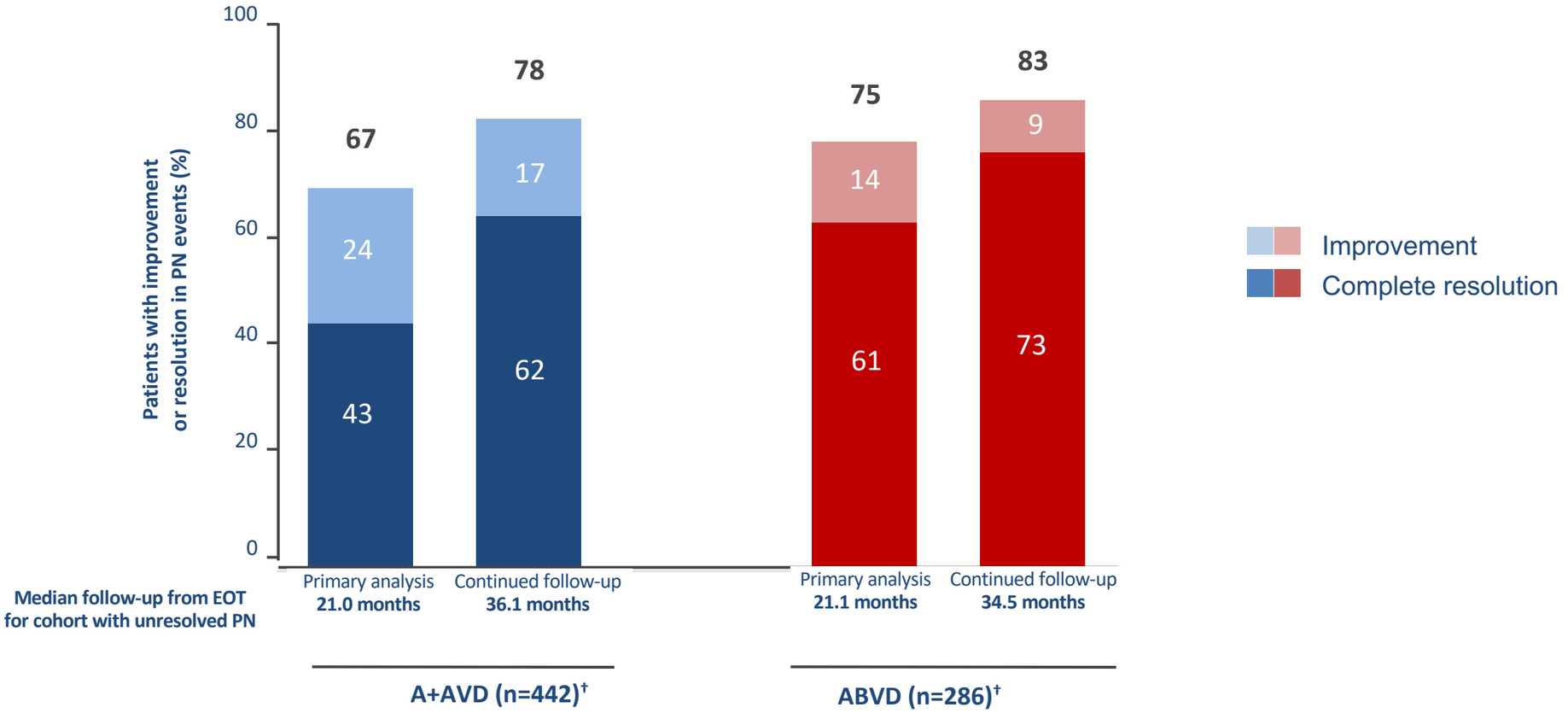
- At 3 years PN continues to resolve and improve in both arms; 78% of A+AVD patients and 83% of ABVD patients experience resolution or improvement **(Figure 5)**
- Among 170 patients in the A+AVD arm with ongoing PN after continued follow-up, 152 patients (89%) had ongoing grade 1/2 events
  - On the ABVD arm, 73/77 patients (95%) had ongoing grade 1/2 events
- Time to resolution and improvement following EOT:
  - Median time to complete resolution:

    A+AVD= 28 weeks (range: 0-167); ABVD=14 weeks (range: 0-188)
  - Median time to improvement:

    A+AVD= 40 weeks (8-129); ABVD= 32 weeks (2-70)

Results

Figure 5: PN events showed Resolution or improvement* with continued follow-up



- *Resolution is 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'.
- †Total patients with PN.

Conclusions

- At 3 years, frontline treatment of Stage 3/4 cHL with six cycles of A+AVD provides a durable treatment benefit versus ABVD that is independent of patient status at PET2
- A+AVD compares favorably to PET-adapted strategies without requiring interim PET assessment, escalation of therapy, or exposure to bleomycin
- The sustained PFS benefit of 7.1% at 3 years demonstrates a favorable benefit:risk profile for A+AVD versus ABVD

References

1. Canellos GP, et al. N Engl J Med 1992;327:1478-84.
2. Carda P, et al. J Clin Oncol 2016;34:2028-36.
3. Gordon LI, et al. J Clln Oncol 2013;31:684-91.
4. Connors JM, et al. N Engl J Med 2018;378:331-44.
5. ADCETRIS® (brentuximab vedotin) US Prescribing Information, November 2018.
6. Johnson P, et al. N Engl J Med 2016; 374: 2419-2429.
7. Stephens DM, et al. Blood 2018; 132: 292.
8. Connors JM, et al. ASH 2018; S624: 2904
9. Cheson BO, et al. J Clin Oncol 2007;25:579-86.
10. Chen, RW et al. J Clin Oncol 2018;36, no. 15_suppl 7539.

Acknowledgements

The authors would like to thank XXX, for writing support during the development of this poster which was funded by XXX, Inc., and complied with good Publication Practice 3 ethical guidelines (*Battisti WP, et al. Ann Intern Med 2015;163:461-4*)

Disclosures

This research was co-funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and Seattle Genetics, Inc., Bothell, WA, USA.

JS reports acting in a consulting or advisory role, and receipt of research funding from Seattle Genetics; MD reports serving in consulting or advisory role for Servier, Roche, and Janssen (China); AI reports research funding from Novartis, Roche, and AbbVie; EL reports serving in a consulting or advisory role for Amgen, Janssen-Cilag, Roche, Takeda, Novartis, Abbvie, and travel, accommodations and expenses from Roche and Amgen; TF reports acting in a consulting or advisory role for Seattle Genetics, Bayer, Bristol-Meyers Squibb, speaking for Seattle Genetics, Kite Pharma, Pharmacyclics, Abbvie, Janssen, Celgene, receipt of travel, accommodations, and expenses from Seattle Genetics, Kite Pharma, Pharmacyclics, Abbvie, and Takeda, honoraria from Seattle Genetics, Pharmacyclics/Janssen, Abbvie, Bristol-Meyers Squibb, Kite Pharma, Bayer, and Takeda, and research funding from Bristol-Meyers Squibb, Seattle Genetics, Portola Pharmaceuticals, Eisai, Kyowa Hakko Kirin, Amgen, Viracta Therapeutics, Cell Medica, Kyowa Hakko Kirin, Roche, Trillium Therapeutics, Pfizer, and Viracta Therapeutics; KS reports acting in a consulting or advisory role for Seattle Genetics, Bristol-Meyers Squibb, Merck, Servier, Novartis, Abbvie, Verastem, honoraria from Seattle Genetics, Bristol-Meyers Squibb, Merck, Novartis, Takeda, and research funding from Roche; PS reports receiving travel, accommodation and expenses from Roche; NB reports acting in a consulting or advisory role for Pfizer, Seattle Genetics, and ADC Therapeutics, research funding from Seattle Genetics, Genentech, Kite Pharma, Merck, Bristol-Meyers Squibb, Celgene, Immune Design, Forty Seven, Affimed Therapeutics, Janssen, Pharmacyclics, Millennium, and Gilead Sciences, AG reports receipt of honoraria from Takeda; JAW reports acting in a consulting or advisory role for Roche, Janssen-Cilag, Celgene, Amgen, Bristol-Meyers Squibb, Incyte, travel, accommodations, and expenses from Roche and Gilead Sciences, honoraria from Roche, Takeda, Celgene, Servier, Janssen-Cilag, and research funding from Roche, GlaxoSmithKline/Novartis, Takeda, and Janssen-Cilag; RR reports acting in a consulting or advisory role for Seattle Genetics, Sandoz-Novartis, Pharmacyclics/Janssen, Bristol-Meyers Squibb, research funding from Merck, Seattle Genetics, Janssen, and Genentech; PZ reports receiving honoraria, serving in a consulting or advisory role, and was paid to speak by MSD, Bristol-Myers Squibb, Servier, Janssen China R&D, and Gilead Sciences; JC reports receipt of patents, royalties and other intellectual property, research funding from Seattle Genetics, Bristol-Meyers Squibb, Amgen, Cephalon, Roche, Genentech/Roche, Janssen Oncology, Lilly, Merck, NanoString Technologies, Takeda, and Bayer; HJ and RL are employees of Millenium Pharmaceutics, a wholly owned Subsidiary of Takeda Pharmaceuticals, Inc., the company sponsor of ECHELON-1.; KF and AF-T are employees of Seattle Genetics. JR reports owning stock in AstraZeneca and GlaxoSmithKline, honoraria from Takeda, consulting or advisory roles at Takeda and ADC Therapeutics, speaking for Takeda and Gilead Sciences, research funding from ADC Therapeutics, and Kite Pharma, and travel, accommodations and expenses from ADC Therapeutics and Takeda.