Selection and Sequencing of Therapies for Patients with Hodgkin Lymphoma

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Outline

- Long-term follow-up from the Phase III ECHELON-1 trial evaluating brentuximab vedotin (BV) in combination with AVD versus ABVD in patients with previously untreated advanced classical HL
- Role of BV-AVD as first-line therapy for advanced HL; potential factors (eg, age, stage/bulk of disease, IPS risk) affecting benefit
- Available data with and current role of BV in elderly patients with newly diagnosed HL
- Potential role of BV alone or in combination with immune checkpoint inhibition as a bridge to transplant in patients experiencing disease progression on up-front treatment
- Results from the Phase III KEYNOTE-204 trial evaluating pembrolizumab versus BV for patients with relapsed/refractory HL; implications for clinical practice
- Available activity and safety data with and ongoing evaluation of anti-PD-1/PD-L1 antibodies alone or in combination with other systemic approaches (eg, BV, chemotherapy) for patients with HL
- Other promising investigational strategies in newly diagnosed or relapsed/refractory HL

Courtesy of John Kuruvilla, MD

Brentuximab Vedotin with Chemotherapy for Stage III/IV Classical Hodgkin Lymphoma (cHL): 4-Year Update of the ECHELON-1 Study

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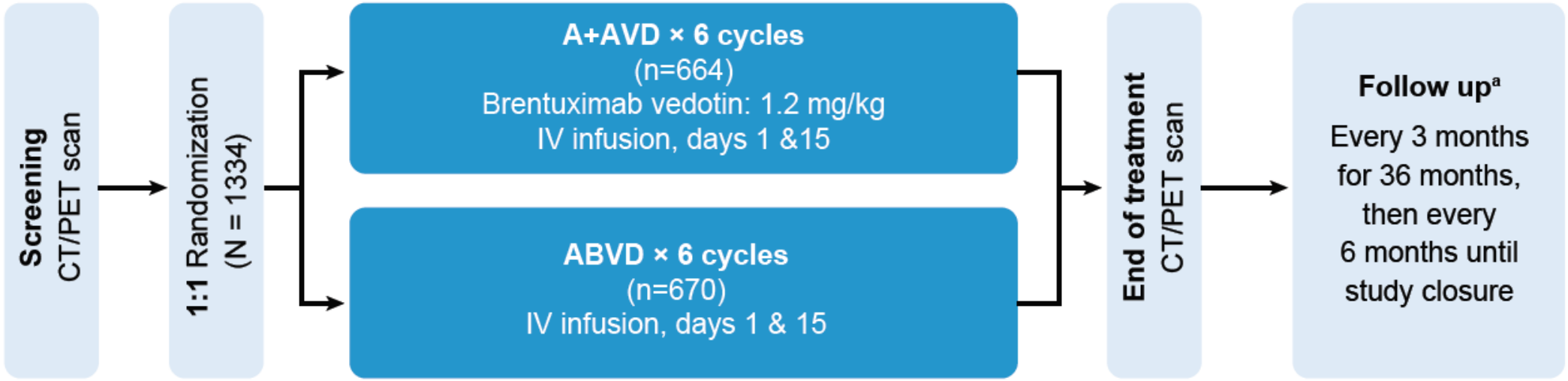
Study Design: ECHELON-1

- ECHELON-1 was an open-label, international, randomized, non–PET-adapted, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed, advanced (stage III/IV) cHL[4]



CT, computerized tomography; IV, intravenous; PET, positron emission tomography.

[a] Per protocol: During posttreatment follow-up, subjects are to be followed for survival disease status every 3 months for 36 months and then every 6 months 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.

Bartlett ASH 2019

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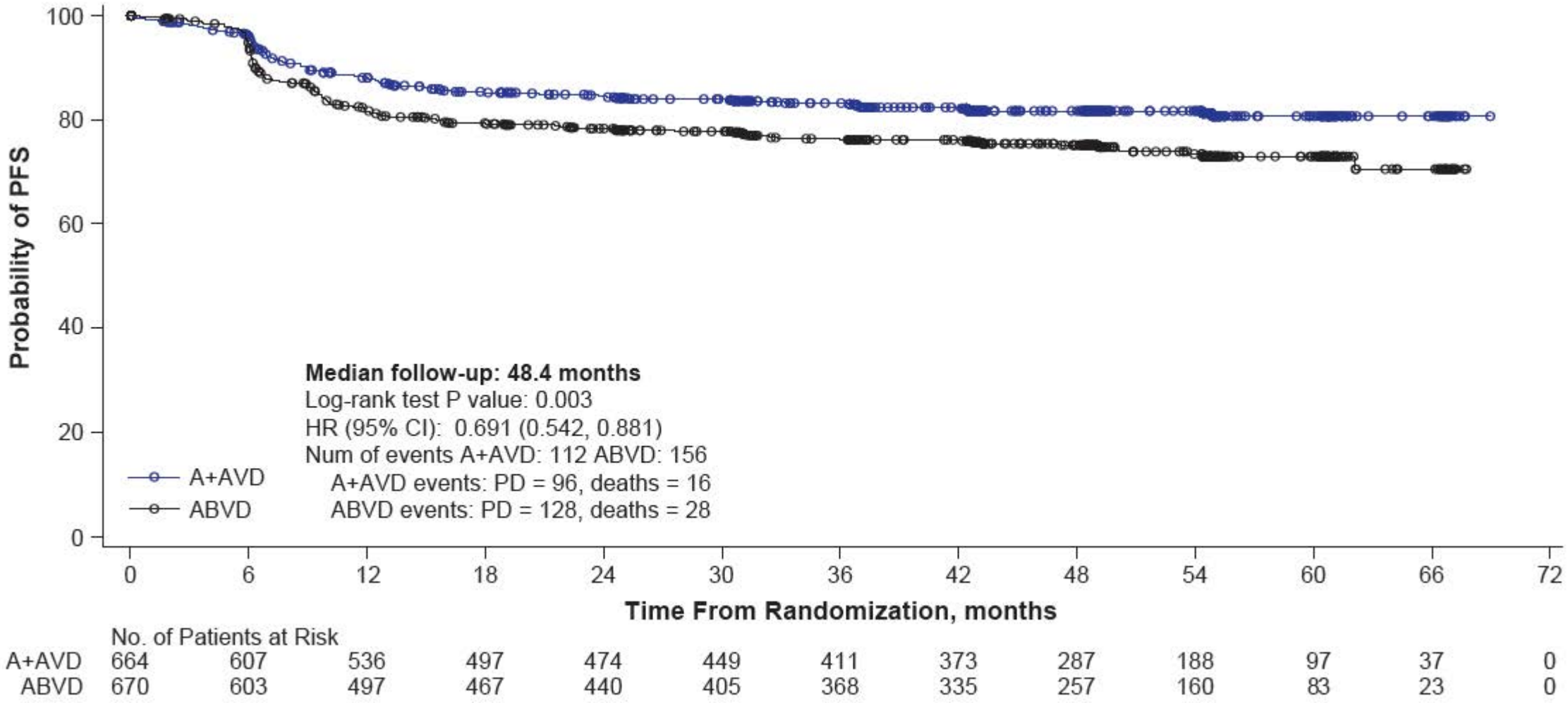
PFS per INV at 4 Years of Follow-Up (ITT)



PD, progressive disease.

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Landmark PFS per INV

Table 2. Landmark PFS per INV

PFS per INV	A+AVD (95% CI)	ABVD (95% CI)
2-Year follow up (primary analysis)[8]		
2-Year PFS rate (95% CI), %	n=332 84.2 (81.1, 86.9)	n=307 78.0 (74.4, 81.1)
HR (95% CI) P value	0.70 (0.54, 0.91) P=0.006	
3-Year follow up[5]		
3-Year PFS rate (95% CI), %	n=360 83.1 (79.9, 85.9)	n=325 76.0 (72.4, 79.2)
HR (95% CI) P value	0.70 (0.55, 0.90) P=0.005	
4-Year follow up		
4-Year PFS rate (95% CI), %	n=287 81.7 (78.3, 84.6)	n=257 75.1 (71.4, 78.4)
HR (95% CI) P value	0.69 (0.54, 0.88) P=0.003	

8. Connors JM, et al. ASH 2018 [abstract 2904].

Bartlett ASH 2019

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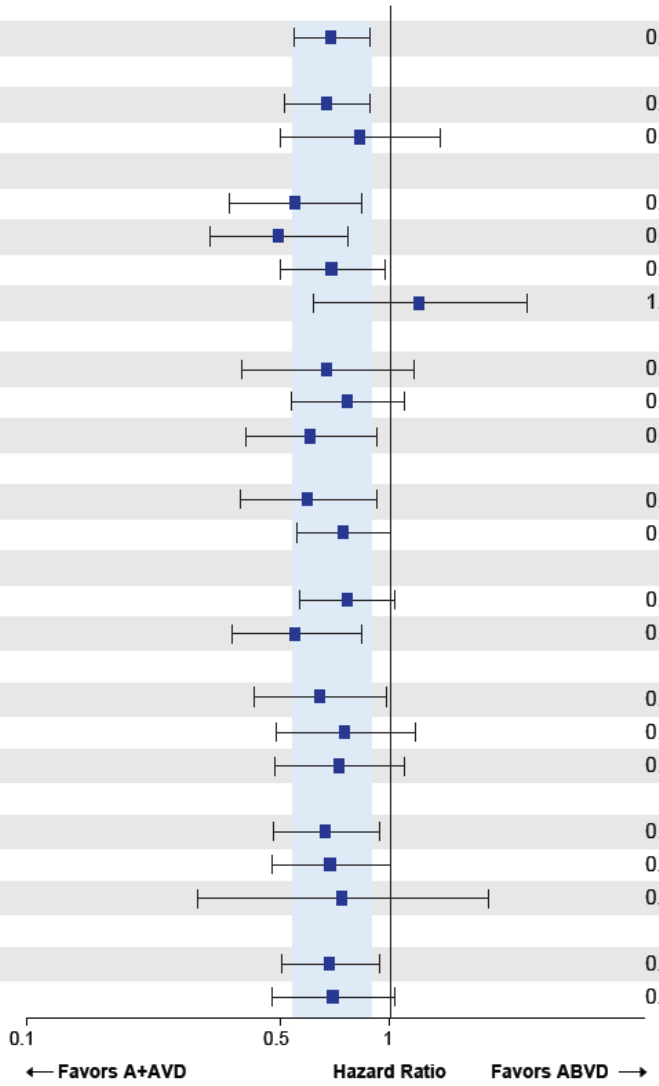
PFS per INV at 4 Years in Prespecified Subgroups

Subgroup	Events, n/N (%) A+AVD	Events, n/N (%) ABVD	HR (95% CI)
Overall	112/664 (16.9)	156/670 (23.3)	0.691 (0.542, 0.881)
Age			
<60 years	87/580 (15.0)	120/568 (21.1)	0.671 (0.509, 0.884)
≥60 years	25/84 (29.8)	36/102 (35.3)	0.827 (0.496, 1.379)
Region			
Americas	34/261 (13.0)	58/262 (22.1)	0.549 (0.359, 0.838)
North America	31/250 (12.4)	57/247 (23.1)	0.493 (0.319, 0.764)
Europe	59/333 (17.7)	83/336 (24.7)	0.693 (0.496, 0.967)
Asia	19/70 (27.1)	15/72 (20.8)	1.212 (0.616, 2.387)
International Prognostic Score			
0–1	22/141 (15.6)	31/141 (22.0)	0.674 (0.390, 1.163)
2–3	54/353 (15.3)	67/351 (19.1)	0.764 (0.534, 1.094)
4–7	36/170 (21.2)	58/178 (32.6)	0.606 (0.400, 0.918)
Baseline lymphoma stage			
Stage III	33/237 (13.9)	54/246 (22.0)	0.595 (0.386, 0.917)
Stage IV	79/425 (18.6)	100/421 (23.8)	0.745 (0.555, 1.001)
Baseline B symptoms			
Present	77/400 (19.3)	92/381 (24.1)	0.765 (0.565, 1.035)
Absent	35/264 (13.3)	64/289 (22.1)	0.551 (0.365, 0.832)
Baseline number of extranodal sites			
0	36/217 (16.6)	55/228 (24.1)	0.643 (0.422, 0.979)
1	35/217 (16.1)	44/223 (19.7)	0.755 (0.485, 1.177)
>1	39/194 (20.1)	53/193 (27.5)	0.726 (0.480, 1.097)
Baseline ECOG status			
0	57/376 (15.2)	82/378 (21.7)	0.666 (0.475, 0.934)
1	46/260 (17.7)	65/263 (24.7)	0.687 (0.471, 1.002)
2	9/28 (32.1)	9/27 (33.3)	0.742 (0.294, 1.874)
Gender			
Male	67/378 (17.7)	98/398 (24.6)	0.684 (0.501, 0.933)
Female	45/286 (15.7)	58/272 (21.3)	0.700 (0.474, 1.033)



IPFP, International Prognostic Factors Project.

Courtesy of John Kuruvilla, MD

Bartlett ASH 2019

PFS at 4 Years According to PET2 Status and Age (ITT population)

Group, % (95% CI)	A+AVD n=664	ABVD n=670	Difference at 4-Years, %	HR (95% CI)[a]	P Value[b]
All patients (ITT)	81.7 (78.3, 84.6)	75.1 (71.4, 78.4)	**6.6**	0.691 (0.542, 0.881)	0.003
PET2(-)	84.5 (81.1, 87.3) n=588	78.9 (75.2, 82.2) n=578	**5.6**	0.680 (0.515, 0.899)	0.006
PET2(+)	59.8 (43.9, 72.4) n=47	44.5 (30.8, 57.4) n=58	**15.3**	0.664 (0.371, 1.189)	0.164
Age <60 years	83.7 (80.3, 86.6) n=580	77.3 (73.3, 80.7) n=568	**6.4**	0.671 (0.509, 0.884)	0.004
<60 years, PET2(-)	86.2 (82.7, 89.0) n=521	81.0 (77.0, 84.3) n=493	**5.2**	0.686 (0.500, 0.942)	0.019
<60 years, PET2(+)	62.1 (45.2, 75.2) n=42	47.7 (32.5, 61.5) n=50	**14.4**	0.652 (0.343, 1.239)	0.187
Age ≥60 years	67.5 (55.4, 77.0) n=84	63.8 (52.9, 72.8) n=102	**3.7**	0.827 (0.496, 1.379)	0.466
≥60 years, PET2(-)	72.4 (59.3, 82.0) n=67	68.2 (56.7, 77.2) n=85	**4.2**	0.745 (0.414, 1.343)	0.326
≥60 years, PET2(+)	40.0 (5.2, 75.3) n=5	25.0 (3.7, 55.8) n=8	**15.0**	0.923 (0.229, 3.715)	0.910

- Among all enrolled patients, 89% (n=588) in the A+AVD arm and 86% (n=578) in the ABVD arm were PET2-negative; 7% (n=47) and 9% (n=58) were PET2-positive, respectively
  - PET2 status was unknown or unavailable in 29 patients (4%) in the A+AVD arm and 35 patients (5%) in the ABVD arm
- A PFS benefit favoring A+AVD was observed in all patients independent of PET2 status

PET2, PET scan after cycle 2.
[a] HRs (A+AVD/ABVD) and 95% CIs are based a Cox proportional hazard regression model, which is stratified for the ITT population and unstratified for subgroup analyses.
[b] *P* values are calculated using a log-rank test, which is stratified for the ITT population and unstratified for subgroup analyses.

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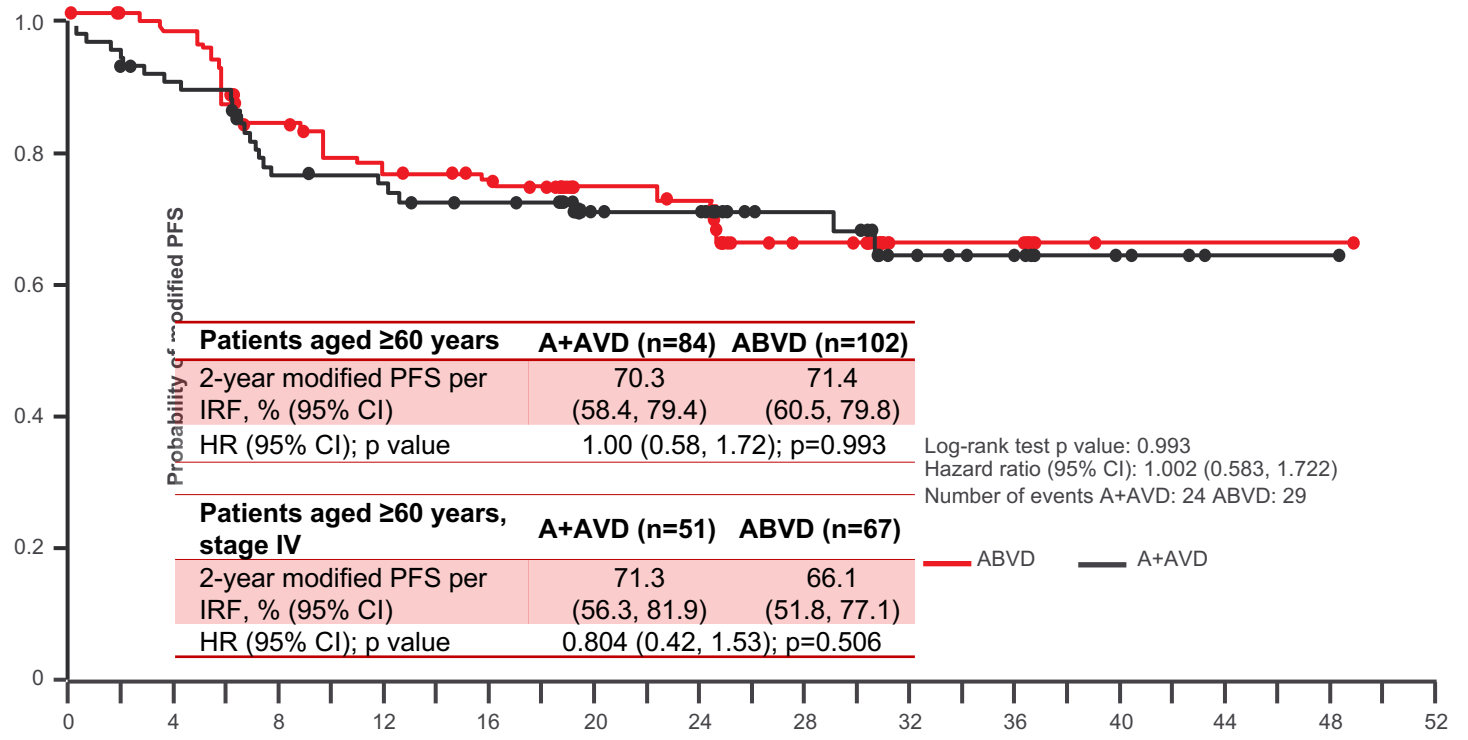
ECHELON-1: Patients Over Age 60

Modified PFS per IRF in patients aged ≥60 years



Patients aged ≥60 years	A+AVD (n=84)	ABVD (n=102)
2-year modified PFS per IRF, % (95% CI)	70.3 (58.4, 79.4)	71.4 (60.5, 79.8)
HR (95% CI); p value	1.00 (0.58, 1.72); p=0.993	

Log-rank test p value: 0.993
Hazard ratio (95% CI): 1.002 (0.583, 1.722)
Number of events A+AVD: 24 ABVD: 29

Patients aged ≥60 years, stage IV	A+AVD (n=51)	ABVD (n=67)
2-year modified PFS per IRF, % (95% CI)	71.3 (56.3, 81.9)	66.1 (51.8, 77.1)
HR (95% CI); p value	0.804 (0.42, 1.53); p=0.506	

Number at risk

A+AVD	84	74	69	68	56	55	54	51	50	49	38	37	37	25	24	23	13	11	10	5	4	3	1	1	1	0	0
ABVD	102	93	90	83	72	68	64	63	60	57	44	44	42	25	23	22	8	8	8	2	1	1	1	1	1	0	0

Evens ASH 2018

Courtesy of John Kuruvilla, MD

ECHELON-1 Older: Safety

Safety summary in older and younger patients

	Patients aged ≥60 years evaluable for safety* (n=181)		Patients aged <60 years evaluable for safety* (n=1140)		Safety population (n=1321)	
	A+AVD (n=83)	ABVD (n=98)	A+AVD (n=579)	ABVD (n=561)	A+AVD (n=662)	ABVD (n=659)
Grade ≥3 AEs, n (%)	73 (88)	78 (80)	476 (82)	356 (63)	549 (83)	434 (66)
Fatal AEs, n (%)	3 (4)	5 (5)	6 (1)	8 (1)	9 (1)	13 (2)
Grade ≥3 neutropenia, n (%)	58 (70)	58 (59)	372 (64)	259 (46)	430 (65)	317 (48)
Any-grade febrile neutropenia on study, n (%)	31 (37)	17 (17)	97 (17)	35 (6)	128 (19)	52 (8)
Any-grade pulmonary AEs, n (%)	2 (2)	13 (13)	10 (2)	31 (6)	12 (2)	44 (7)

*Received ≥1 dose of study therapy.

Safety profile according to receipt of G-CSF primary prophylaxis

	Patients aged ≥60 years evaluable for safety* (n=181)				Patients aged <60 years evaluable for safety* (n=1140)			
	A+AVD (n=83)		ABVD (n=98)		A+AVD (n=579)		ABVD (n=561)	
G-CSF received	Yes (n=10)	No (n=73)	Yes (n=9)	No (n=89)	Yes (n=73)	No (n=506)	Yes (n=34)	No (n=527)
Any-grade neutropenia, n	4	57	1	64	25	368	8	288
FN in cycle 1, n	1	20	2	8	0	41	0	16
Any-grade FN on study, n	3	28	2	15	6	91	1	34
Infections & infestations System Organ Class, n	8	43	5	60	31	279	14	252
Any SAE on study, n	5	53	2	44	22	204	5	127

*Received ≥1 dose of study therapy.

Evens ASH 2018

Courtesy of John Kuruvilla, MD

Other BV-based approaches in Older HL

Strategy	N	ORR (CR)	PFS	Toxicity
BV → ABVD	48	88 (81)	84% @ 24m	NRM: 2%
BV mono BV+Dacarbazine BV+Benda	27 22 20	92 (73) 100 (62) 100 (88)	mPFS 10.5m mPFS: 18m mPFS: NR	Grade 3 PN: 30% NRM:10% closed
BV 1.2 + Benda	59	92 (65)	83% @ 24m	
BV-CAP	49	98 (65)	94 @ 12 m	2 DC for infn 1 death

Evens JCO 2018; Forrero-Torres Blood 2015; Friedberg Blood 2017; de Colella ASCO 2020; Boll ASH 2018

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Sequential BV-chemotherapy Strategies pre-ASCT

Strategy	N	ORR (CR) BV	ORR (CR) post chemo	PFS	Toxicity
BV → augICE	46	NR (27)	NR (76)	2Y EFS: 80%	BV: G3-4: 7
BV → salvage	37	68 (35)	87 (65)	NR	

Sequential strategy allows less exposure to chemotherapy but conceptually is less likely to lead to very high CR rate

Note: No concerns with PBSC mobilization or engraftment post-ASCT

Moskowitz Lancet Oncol 2015, Chen BBMT 2016

Courtesy of John Kuruvilla, MD

Brentuximab-containing salvage Regimens

Regimen	N	ORR (CR)	PFS	Toxicity
BV-Bendamustine	55	93 (74)	2Y: 70%	IRR:56%
BV-ESHAP	66	93 (71)	NR	FN: 25%*
BV-DHAP	12	91 (91)	NR	Neutropenia DLT
BV-ICE	24	92 (85)	NR	FN: 17%

Conceptually should lead to high CR rates though with potential for increased toxicity

Note: No concerns with PBSC mobilization or engraftment post-ASCT

LaCasce Blood 2018 prepub, Garcia-Sanz EHA 2018, Hagenbeek ISHL 2016, Cassaday ASH 2017; *ASH 2017

Courtesy of John Kuruvilla, MD

Immune checkpoint inhibitor combinations pre ASCT

Regimen	N	ORR (CR)	PFS	Toxicity
Nivo + BV*	93	85 (67)	79% @ 24 m 92% @ 24 m (ASCT pp)	Gr3 PN and ANC (1) IrAE: GBS, pneumonia, diarrhea, AST (all n=1)
Nivo + BV + Ipi (E4412)	22	82 (68)	mPFS NR @ 6m	3 DLT (DKA, AST, rash)
Nivo / sequential NICE	43 N=8	90 (58) 100 (88)	74% @ 12 m	1 Gr5 sepsis 1 Grade 4 encephalitis

Note: No concerns with PBSC mobilization or engraftment post-ASCT
* pre-SCT

Moskowitz ASH 2019, Diefenbach ASH 2018; Herrera ASH 2019

Courtesy of John Kuruvilla, MD

KEYNOTE-204 Study Design (NCT02684292)

Key Eligibility Criteria

- Relapsed or Refractory cHL
- Relapse post−auto-SCT or ineligible for auto-SCT and failed one prior line of therapy
- Measurable disease per IWG 2007 criteria[1]
- ECOG PS 0-1
- BV-naive and BV-exposed patients eligible

Stratification Factors

- Prior auto-SCT (yes vs no)
- Status after 1L therapy (primary refractory vs relapsed <12 months vs relapsed ≥12 months after end of 1L therapy)

R
1:1

Pembrolizumab
200 mg IV Q3W
Up to 35 Cycles

Brentuximab Vedotin
1.8 mg/kg IV Q3W
Up to 35 Cycles

- Response assessed Q12W per IWG 2007 Revised Response Criteria for Malignant Lymphoma[1]
- AEs evaluated Q3W throughout the trial period, and Q12W during follow-up

Primary End Points: PFS per blinded independent central review (BICR) by IWG 2007 criteria including clinical and imaging data following auto-SCT or allogeneic stem cell transplant (allo-SCT); OS

Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

1. Cheson BD et al. *J Clin Oncol.* 2007;25:579-586.

Courtesy of John Kuruvilla, MD

Patient Characteristics

	Pembro n = 151	BV n = 153
Age, median (range)	36 (18-84)	35 (18-83)
≥65 years, n (%)	27 (17.9)	22 (14.4)
Male, n (%)	84 (55.6)	90 (58.8)
White, n (%)	119 (78.8)	115 (75.2)
ECOG PS 0, n (%)	86 (57.0)	100 (65.3)
Prior auto-SCT, n (%)		
Yes	56 (37.1)	56 (36.6)
No	95 (62.9)	97 (63.4)

	Pembro n = 151	BV n = 153
Disease status after frontline therapy, n (%)		
Primary refractory	61 (40.4)	62 (40.5)
Relapsed <12 months	42 (27.8)	42 (27.5)
Relapsed ≥12 months	48 (31.8)	49 (32.0)
Prior BV, n (%)	5 (3.3)	10 (6.5)
Prior radiation, n (%)	58 (38.4)	61 (39.9)
Bulky disease, n (%)	35 (23.2)	25 (16.3)
Baseline B-symptoms, n (%)	43 (28.5)	36 (23.5)
Baseline bone marrow involvement, n (%)	12 (7.9)	5 (3.3)

Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

Patient Characteristics (continued)

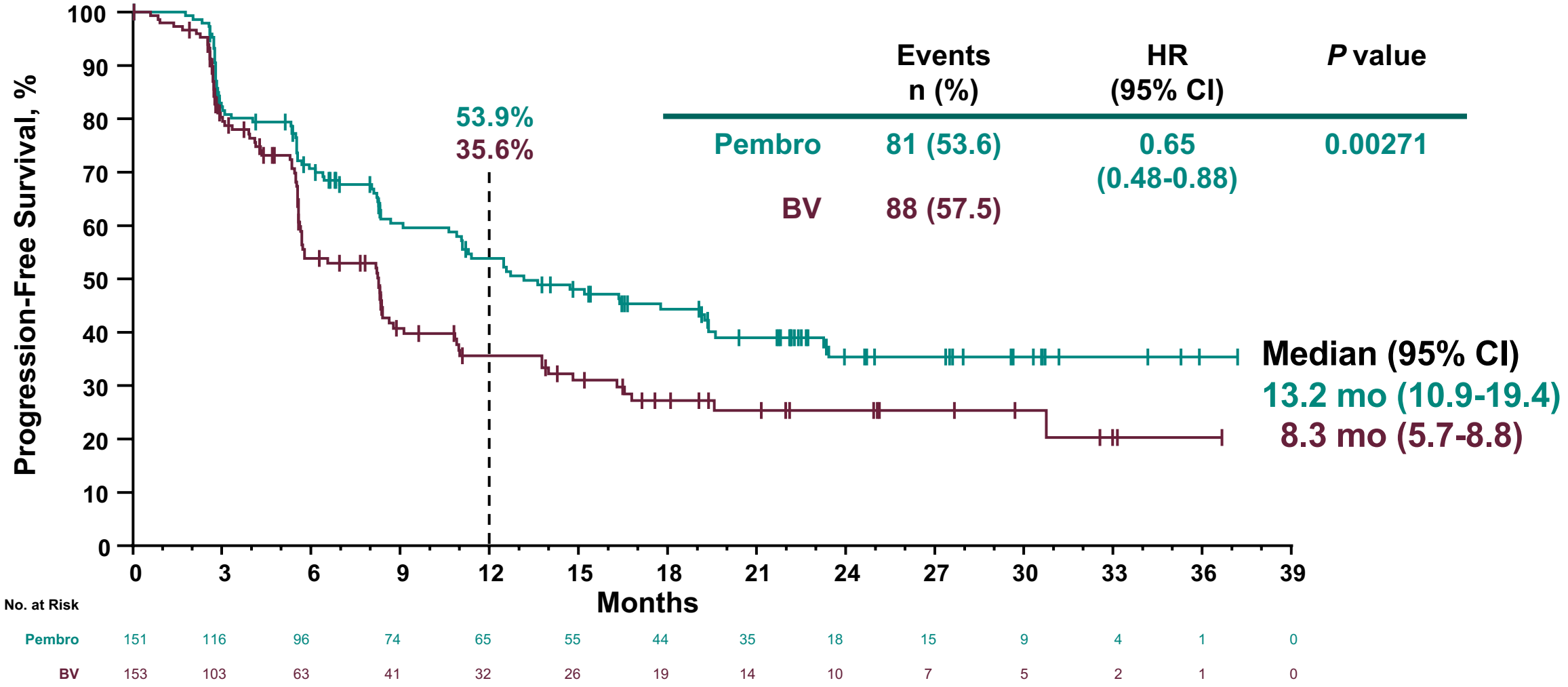
	Pembro n = 148	BV n = 152
Number of prior therapies, median (range)[a]	2 (1-10)	3 (1-11)
Subsequent SCT, n (%)		
Auto-SCT	30 (20.3)	34 (22.4)
Allo-SCT	14 (9.5)	13 (8.6)
Days on therapy, median (range)	305.0 (1-814)	146.5 (1-794)
Completed 2 years of treatment, n (%)	25 (16.9)	3 (2.0)
Treatment ongoing, n (%)	13 (8.8)	3 (2.0)

[a]Pembro: n = 151; BV: n = 153.
Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

Primary End Point: Progression-Free Survival Per Blinded Independent Central Review

Including Clinical and Imaging Data Following Auto-SCT or Allo-SCT

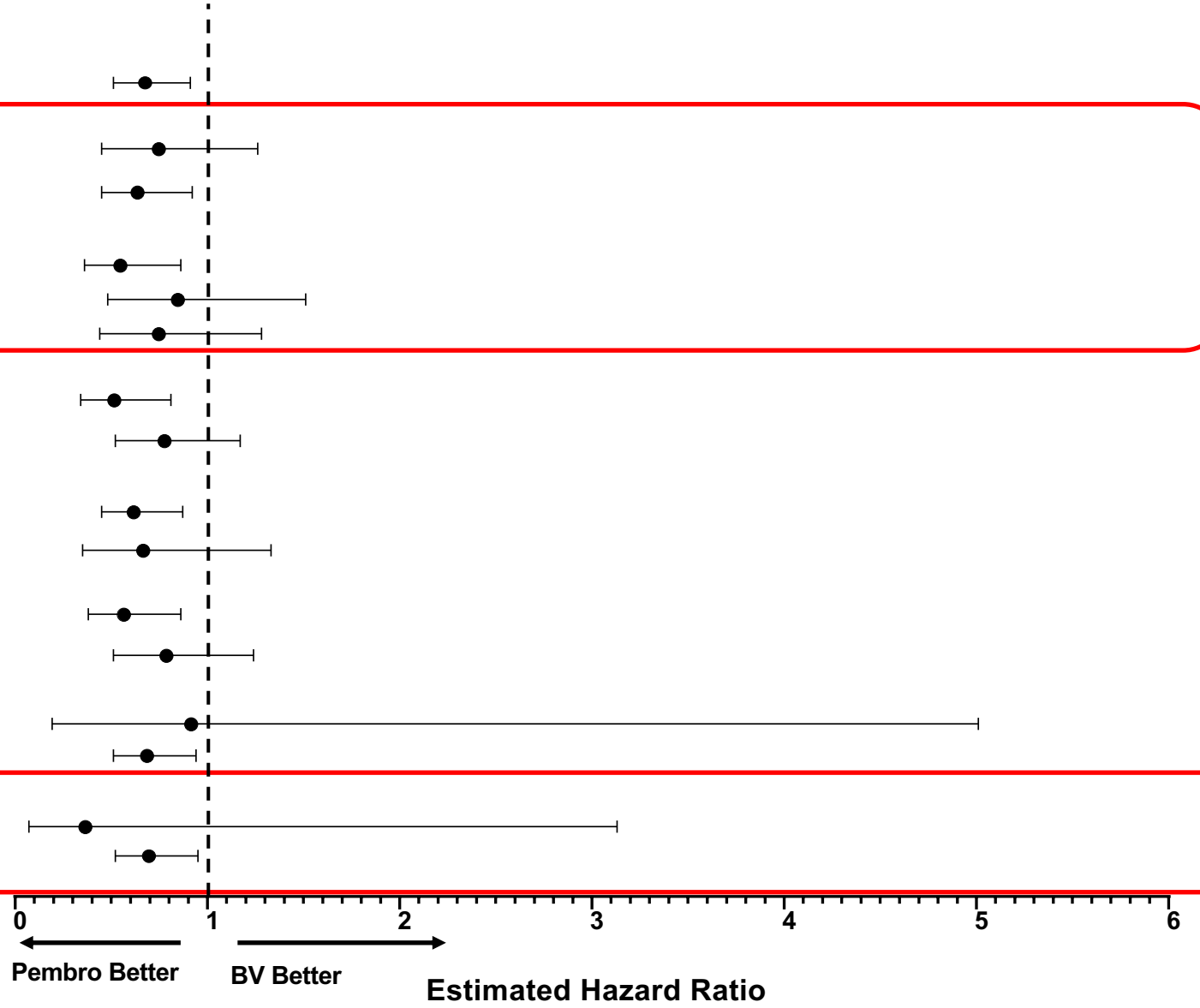


Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

Progression-Free Survival in Key Subgroups

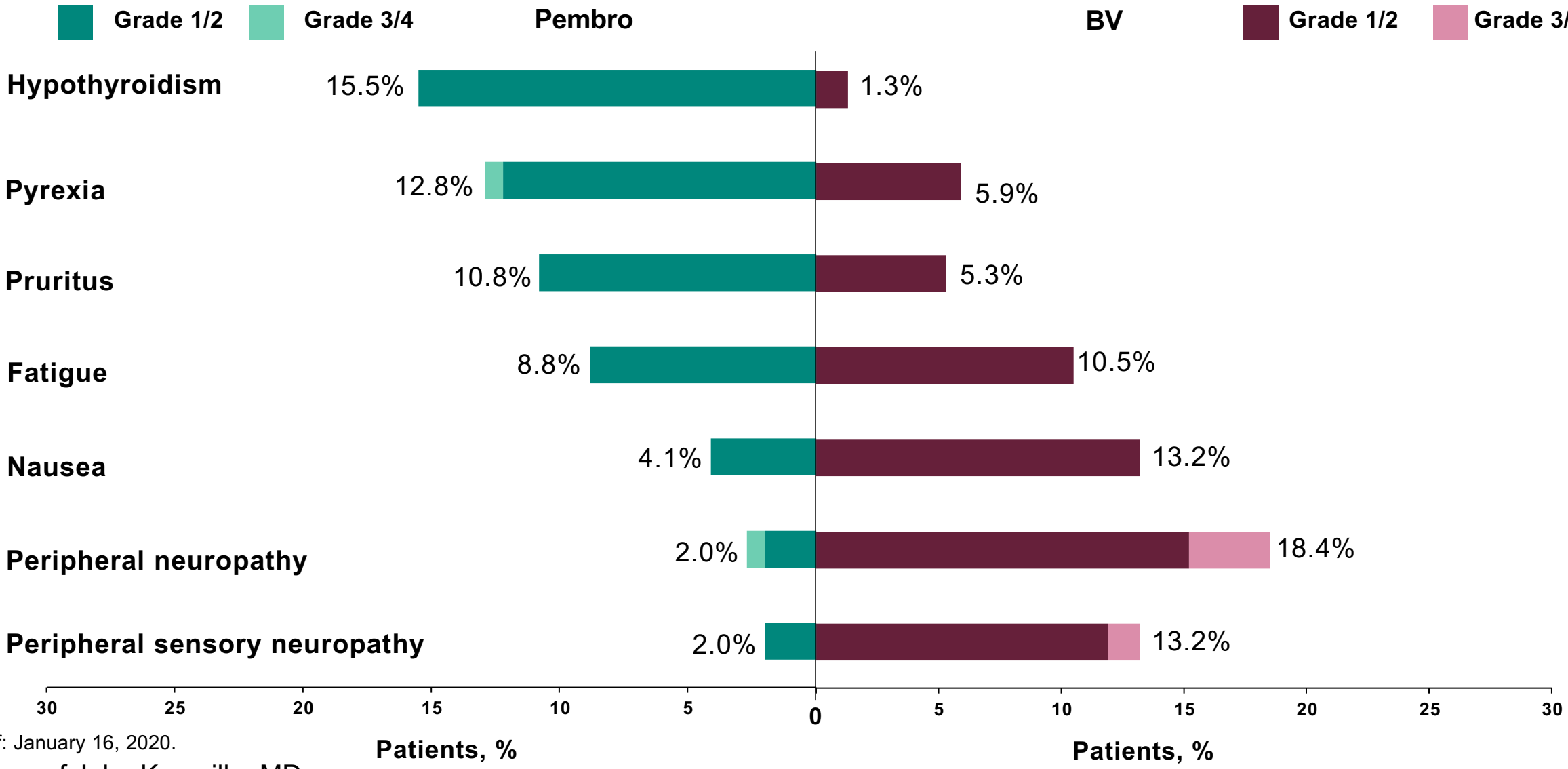
	No. of Events/N	HR (95% CI)
Overall	169/304	0.65 (0.48-0.88)
Prior auto-SCT		
Yes	57/112	0.72 (0.42-1.23)
No	112/192	0.61 (0.42-0.89)
Disease status after frontline therapy		
Primary refractory	72/123	0.52 (0.33-0.83)
Relapsed <12 months	46/84	0.82 (0.45-1.48)
Relapsed ≥12 months	51/97	0.72 (0.41-1.25)
Sex		
Female	81/130	0.49 (0.31-0.78)
Male	88/174	0.75 (0.49-1.14)
Age		
<65 years	132/255	0.59 (0.42-0.84)
≥65 years	37/49	0.64 (0.32-1.30)
ECOG PS		
0	91/186	0.54 (0.35-0.83)
1	77/117	0.76 (0.48-1.21)
Geographic region		
US	9/24	0.89 (0.16-4.98)
Ex-US	160/280	0.66 (0.48-0.91)
Prior BV		
Yes	7/15	0.34 (0.04-3.10)
No	162/289	0.67 (0.49-0.92)



Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

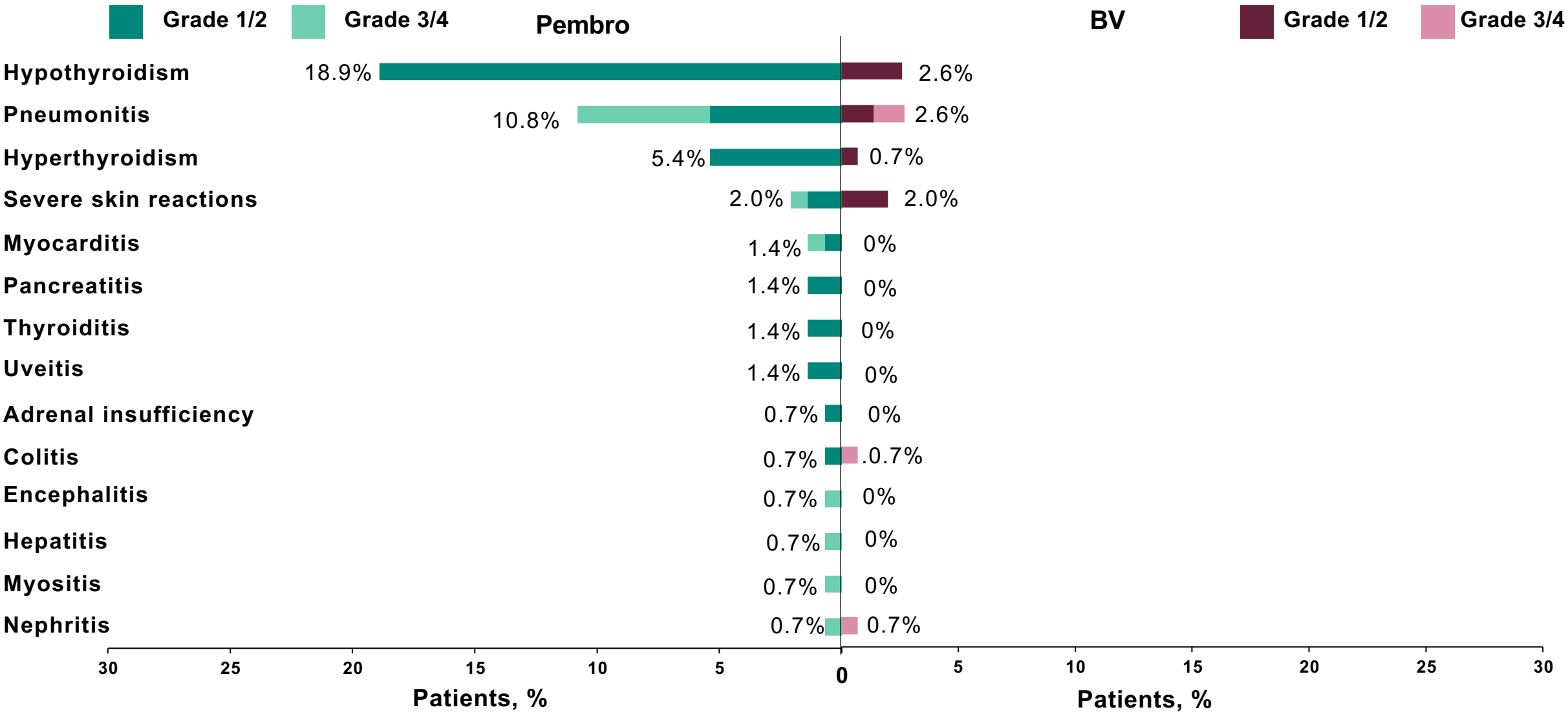
Treatment-Related AEs (≥10% Either Arm)



Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

Immune-Mediated AEs



Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness.
Data cutoff: January 16, 2020.

Courtesy of John Kuruvilla, MD

Selected Novel Strategies in RR-cHL

Regimen	N	ORR (%)	Comment
Camidanlumab Tesirine (ADCT-301)	77	71 (40 CR) 87 (higher dose)	GBS 6.5%, skin, liver Registrational trial underway
AFM-13 (CD30/CD16A)	28	12 (50 SD) 23 (higher dose)	Proof of concept trial
AFM-13 + Pembro	30	83 (37 CR)	Safety and proof of concept
Relatlimab + Nivo	Not published		Safety and proof of concept
MK4280 + Pembro	Not published		Safety and proof of concept
CD30 CAR-T therapy	41	62 (51) 72 (59)	UNC / BCM experience ORR in n=32 receiving fludarabine-based lymphodepletion

Collins ICML 2019;lRothe Blood 2015; Bartlett Blood 2020, Ramos JCO 2020

Courtesy of John Kuruvilla, MD

Patient 1: Approach to Primary of Advanced Stage HL

- You review a 25 year old male with newly diagnosed stage IV classical HL.
- He has no other medical comorbidity but has an IPS score of 4
  - Multiple bone sites
  - Male
  - WBC 24
  - ALC 0.5
- What is your choice of primary treatment?
  - PET-adapted ABVD (RATHL)
  - BEACOPP-based treatment (AHL2011 or GHSG)
  - BV-AVD (ECHELON-1)
  - PET-Adapted approach incorporating BV-AVD

Courtesy of John Kuruvilla, MD

Patient 2: Approach to Management of post-ASCT failure

- You are following a 32 year old patient who has relapsed HL (primary refractory disease, CR to second-line chemotherapy) and now with biopsy proven relapse approximately 3 months post-ASCT.
- Your next step in management is:
  - BV monotherapy
  - Pembrolizumab monotherapy
  - Combination BV+nivo therapy
  - One of the above but goal includes consolidation with allogeneic transplant

Courtesy of John Kuruvilla, MD