Chemotherapy-Free Treatments in cHL

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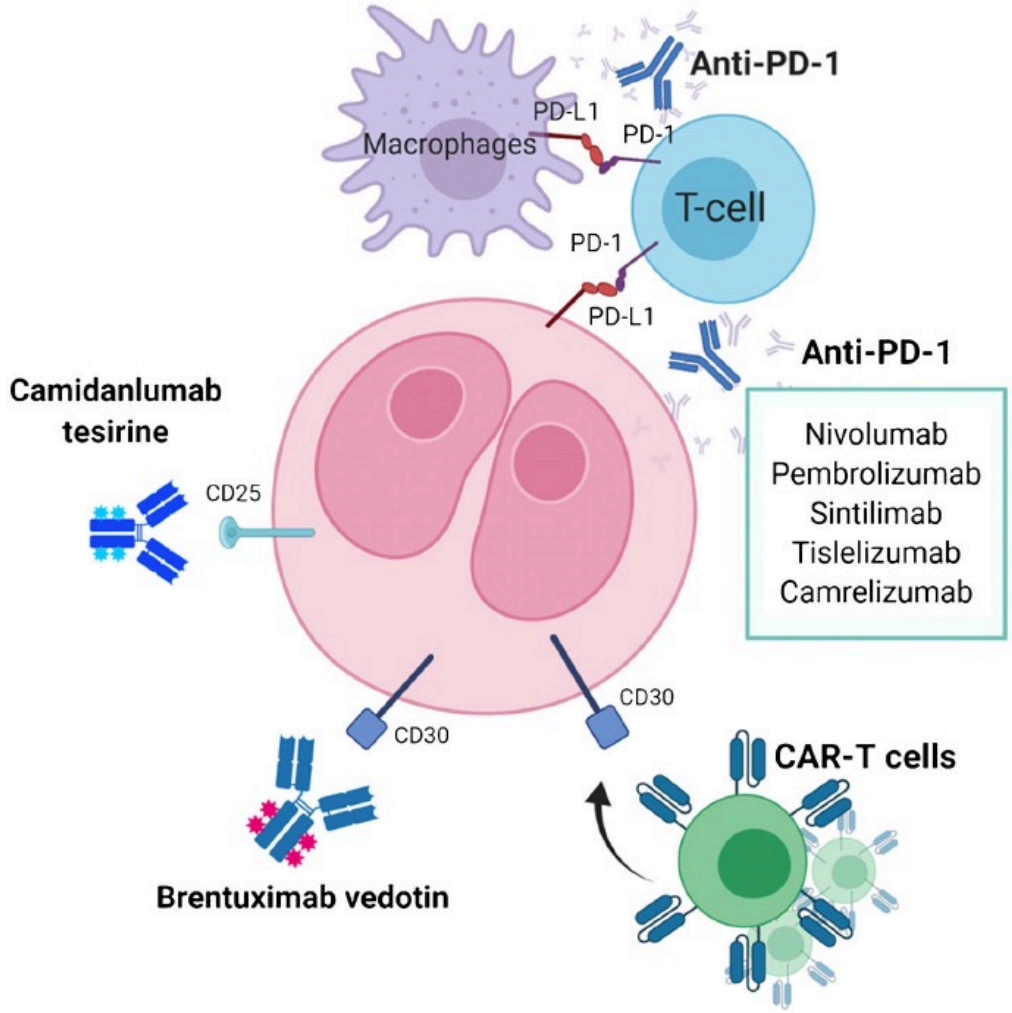
Disclosures of Carmelo Carlo-Stella

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi	X		X			X	
ADC Therapeutics	X		X			X	
Karyopharm Therapeutics						X	
Celgene/Bristol-Myers Squibb						X	Honoraria
Incyte					X		
F. Hoffmann-La Roche Ltd	X					X	Travel grants
Janssen Oncology							Travel grants, honoraria
Takeda							Travel grants, honoraria
Merck Sharp & Dohme					X		Honoraria
AstraZeneca							Honoraria
Gilead					X		Honoraria

Novel Therapeutic Agents in cHL



Brentuximab

Multi-Cohort Phase II study of BV as monotherapy or in combination in treatment-naive elderly patients

Primary End Point: ORR

	BV (N=26)	BV+DTIC (N=21)	BV+Benda (N=17)	BV+Nivo (N=21)
ORR (CR+PR), (%)	92	100	100	95
CR, (%)	72	68	88	79
Median PFS, mos	**10.5**	**46.8**	**40.3**	Not reached
Median OS, mos	77.5	64	46.9	Not reached
Median FW, mos	59.4	58.6	51.3	19.4
AE leading to treatment discontinuation, n (%)	42	42	40	30
Death within 30-day safety period, n (%)	0	0	0	0
Peripheral neuropathy (%)	30	26	20	35
Any SAE, (%)	12	11	40	5
Gr ≥3 treatment-related AE, n (%)	50	37	70	60

BV= 1.8 mg/Kg q 3wks; BV+DTIC: BV 1.8 mg/Kg + 375 mg/mq x 12 cycles; BV+ Benda: 1.8 mg/kg + 70/90 mg/mq

Forero-Torres, Blood 2015; Friedberger, Blood 2017; Yasenchak ASH 2019; Yasenchak ASH 2020

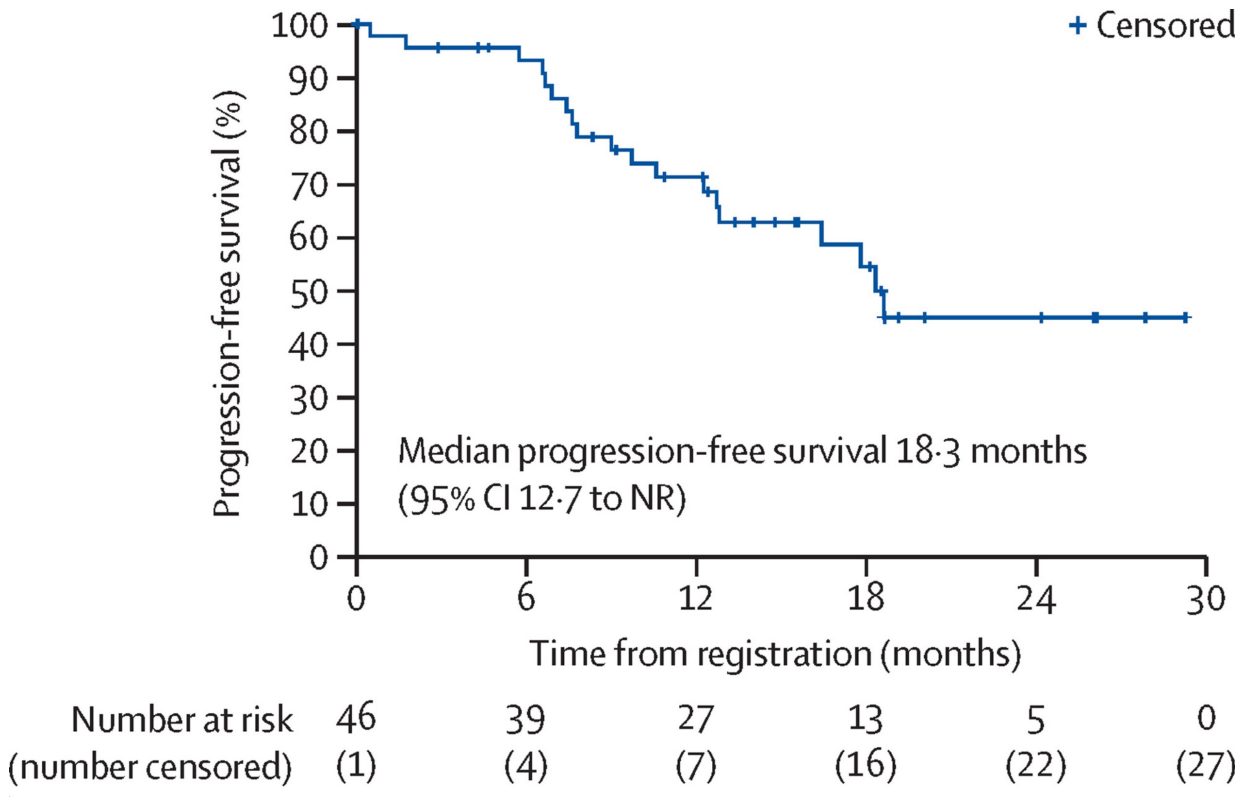
Brentuximab + Nivolumab

Multicentre, single-arm, phase 2 trial

Patients outcome and response therapy

	Total (n=46)
Cycle 8 metabolic rate	61% (45–75)
Complete metabolic response	22 (48%)
Partial metabolic response	6 (13%)
Progressive Metabolic Disease	7 (15%)
Off before cycle 8	11 (24%)
Best overall response rate (all cycles)	91% (79–98)
Complete metabolic response	30 (65%)
Partial metabolic response	12 (26%)
No metabolic response	1 (2%)
Progressive metabolic disease	1 (2%)
Not evaluated	2 (4%)
Median duration of response	NR (11·1–NR)
Median overall survival	NR (NR–NR)
Median progression-free survival (months)	18·3 (12·7 to NR)

Data are median or % (95% CI) or n (%), unless otherwise specified. NR=not reached.



Cheson, Lancet 2020

2L Therapy of r/r Classical Hodgkin Lymphoma

Regimen	No. of Patients	ORR (%)	CR Rate (%)	Imaging Modality	PFS or EFS (all patients)	PFS or EFS (SLT plus ASCT)	Reference
DHAP	241	70	24	CT	NR	72% (3-year)	Josting et al[21]
ESHAP	22	73	41	CT	27% (3-year)	NR	Aparicio et al[22]
GDP	23	70	17	CT	NR	NR	Baetz et al[23]
GVD	41	61	20	CT	52% (4-year)	NR	Bartlett et al[24]
ICE	65	88	26	CT	58% (3.5-year)	68% (3.5-year)	Moskowitz et al[25]
IGEV	91	81	54	CT	53% (3-year)	NR	Santoro et al[26]
BEGEV	59	83	75	PET	59% (5-year)	77% (5-year)	Santoro et al[27]

Bartlett N, JCO, 2021

Newer Options

- Brentuximab Vedotin
  - Prior to autoHSCT in case of induction failure
    - If CR, the patients are addressed to autoHSCT
  - AutoHSCT failure
  - High-risk of relapse after autoHSCT

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen,[1,*] Ajay K. Gopal,[2,*] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Dirk Huebner,[9] Abraham Fong,[8] and Anas Younes[10]

Blood. 2016;128(12):1562-1566

	%
All Patients (n = 102)	100%
CR as Best Response (n = 34)	33%
CR at End-of-Study (n = 13)	13%
No further therapy	9%
Allo-SCT	4%
Peripheral Neuropathy	42%
Resolution	73%
Improvement	14%

Newer Options

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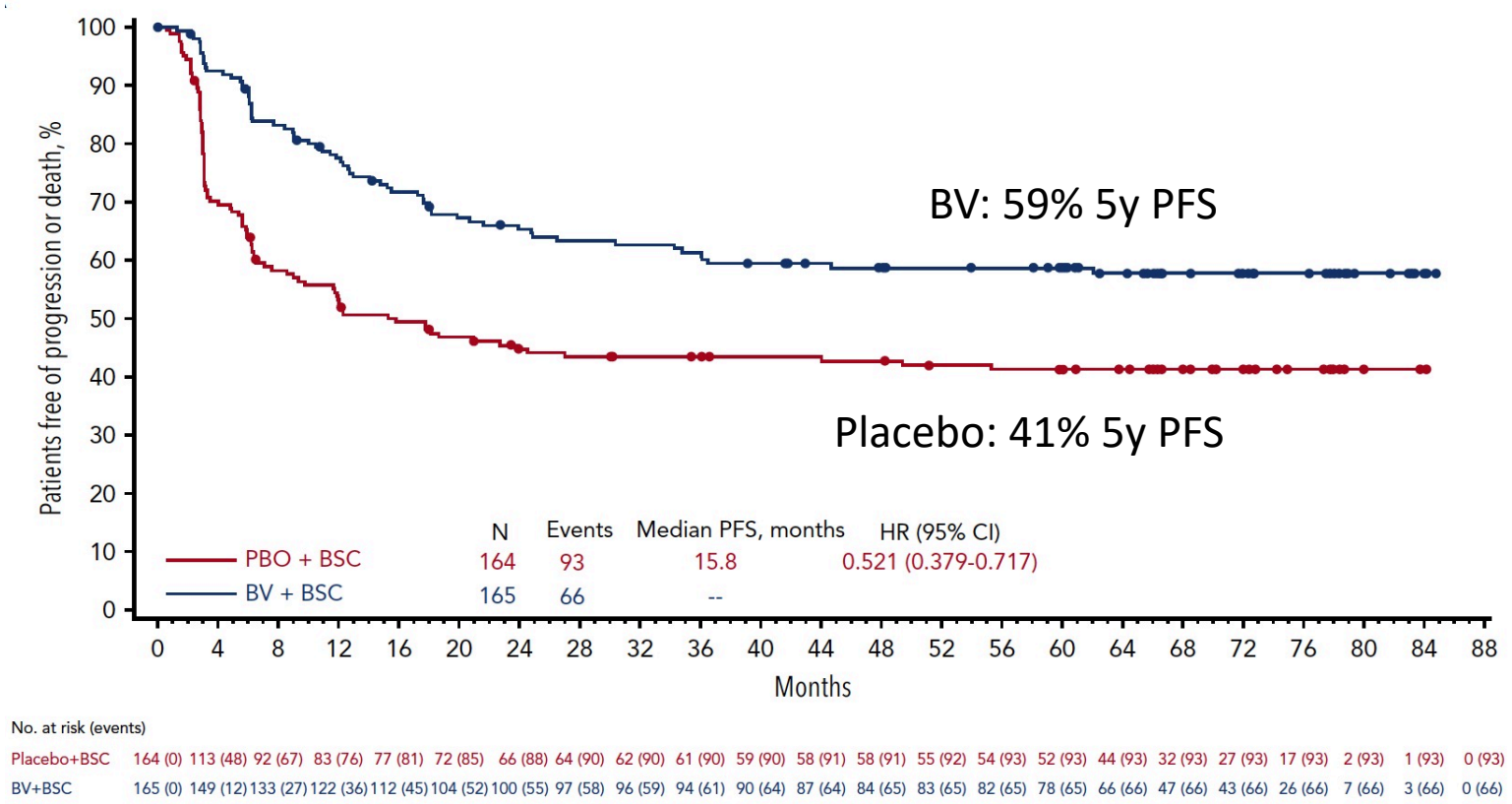
Consolidation with BV After AutoHSCT in cHL at High-Risk of Relapse



- Relapsed <12 months
- Primary refractory
- Extranodal disease
- PR/SD after salvage Tx
- B symptoms

Moskowitz, Blood 2018

Newer Options

- Nivolumab, Pembrolizumab
  - Prior to autoHSCT in case of induction failure (Pembro only)
    - If CR/PR, the patients are addressed to autoHSCT
  - AutoHSCT failure
  - [High-risk of relapse after autoHSCT]

Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma

Reid W. Merryman,[1] Robert A. Redd,[2] Taiga Nishihori,[3] Julio Chavez,[3] Yago Nieto,[4] Justin M. Darrah,[5,6] Uttam Rao,[7] Michael T. Byrne,[7] David A. Bond,[8] Kami J. Maddocks,[8] Michael A. Spinner,[9] Ranjana H. Advani,[9] Hatcher J. Ballard,[10] Jakub Svoboda,[10] Anurag K. Singh,[11] Joseph P. McGuirk,[11] Dipenkumar Modi,[12] Radhakrishnan Ramchandren,[13] Jason Romancik,[14] Jonathon B. Cohen,[14] Matthew J. Frigault,[15] Yi-Bin Chen,[15] Anthony V. Serritella,[16] Justine Kline,[16] Stephen Ansell,[17] Sunita Nathan,[18] Maryam Rahimian,[19] Robin M. Joyce,[19] Mansi Shah,[20] Kevin A. David,[20] Steven Park,[21] Anne W. Beaven,[22] Alma Habib,[23] Veronika Bachanova,[23] Shazia Nakhoda,[24] Nadia Khan,[24] Ryan C. Lynch,[25] Stephen D. Smith,[25] Vincent T. Ho,[1] Ann LaCasce,[1] Philippe Armand,[1] and Alex F. Herrera[5]

Blood Advances 5:1648-1659, 2021

- **Hypothesis**: Anti-PD-1 therapy before ASCT would result in acceptable outcomes among high-risk patients who progressed on or responded insufficiently to ≥1 salvage regimen, including chemorefractory patients
- **Included** were 78 HL patients who underwent ASCT after an anti-PD-1 mAb as ≥3L therapy.
- **Forty-two patients** (54%) refractory to ≥2 consecutive systemic therapies immediately before anti-PD-1 treatment.
- **Fifty-eight** (74%) patients underwent ASCT after anti-PD-1 treatment, while **20 patients** (26%) received additional therapy after PD-1 blockade and before ASCT.

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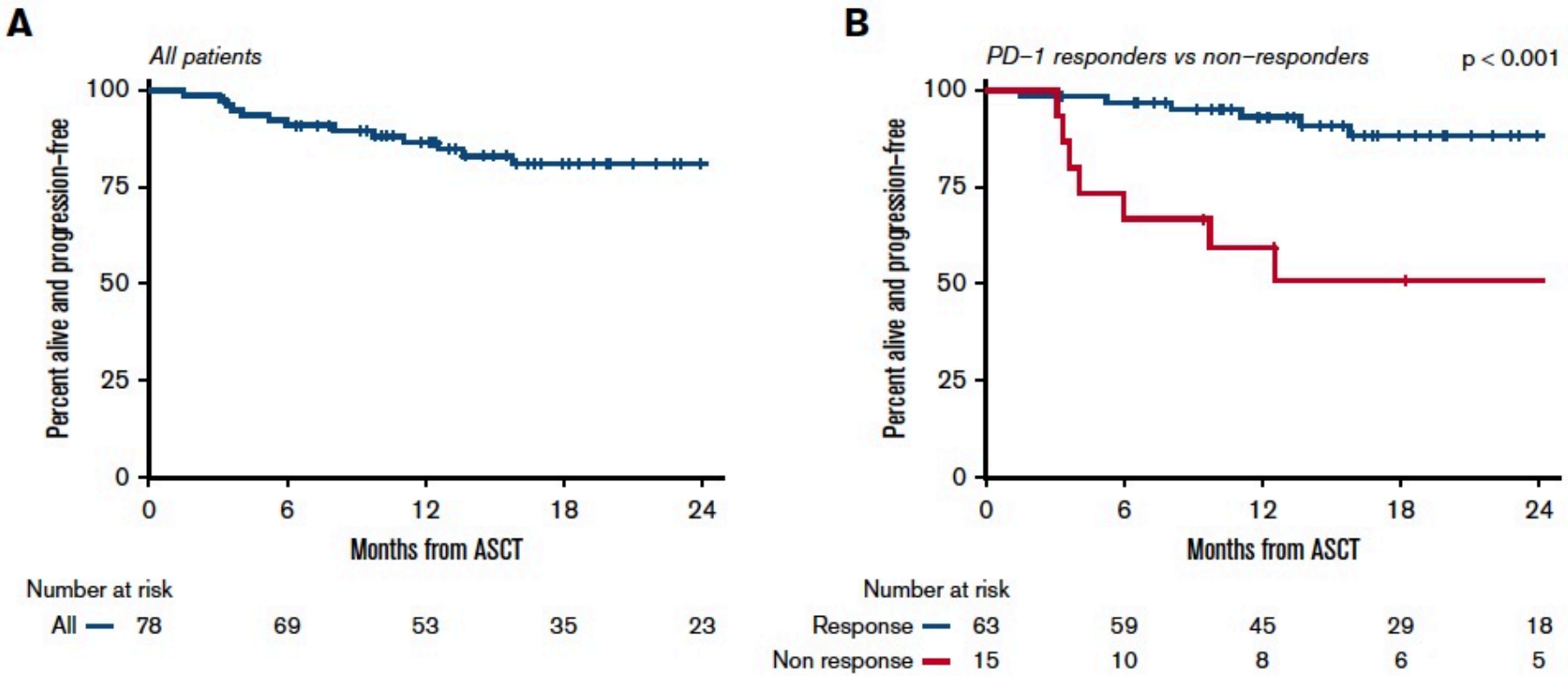

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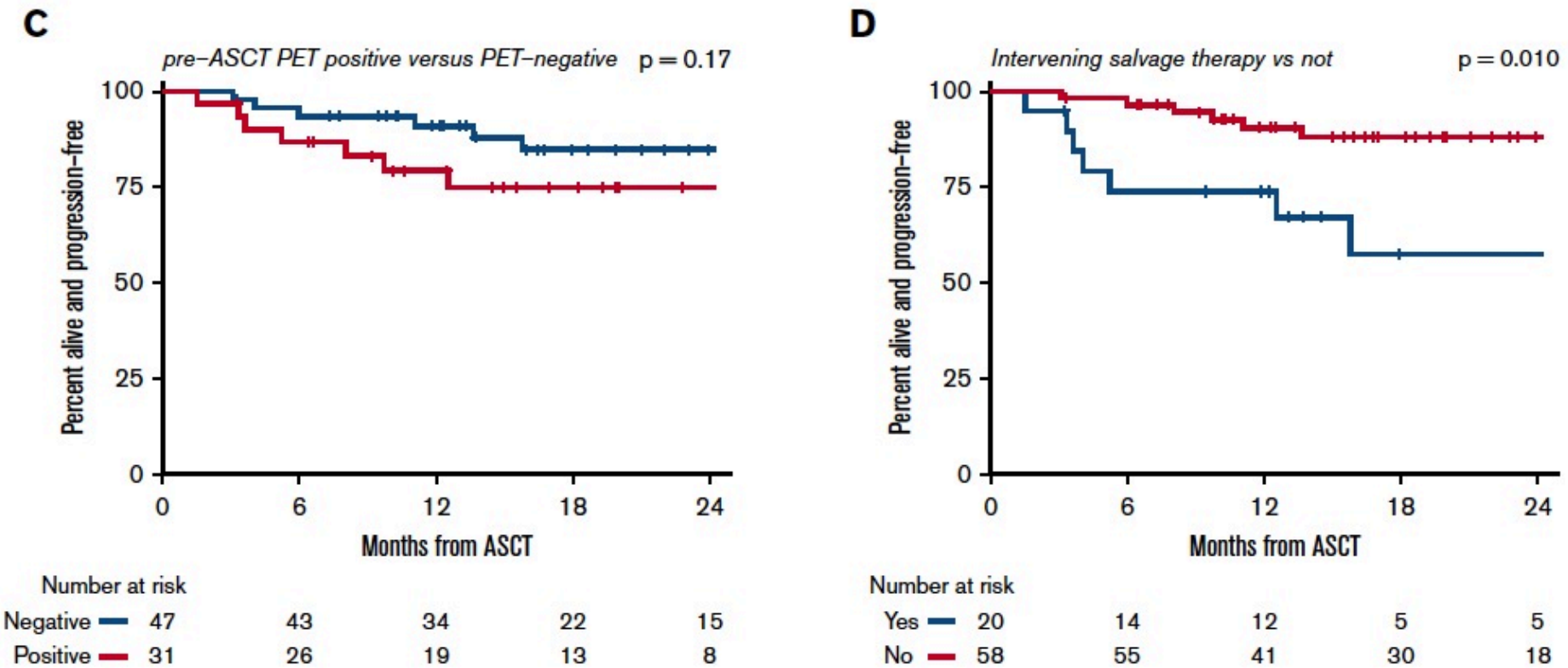

Newer Options

- Nivolumab, Pembrolizumab
  - Prior to autoHSCT in case of induction failure (Pembro only)
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  - [High-risk of relapse after autoHSCT]

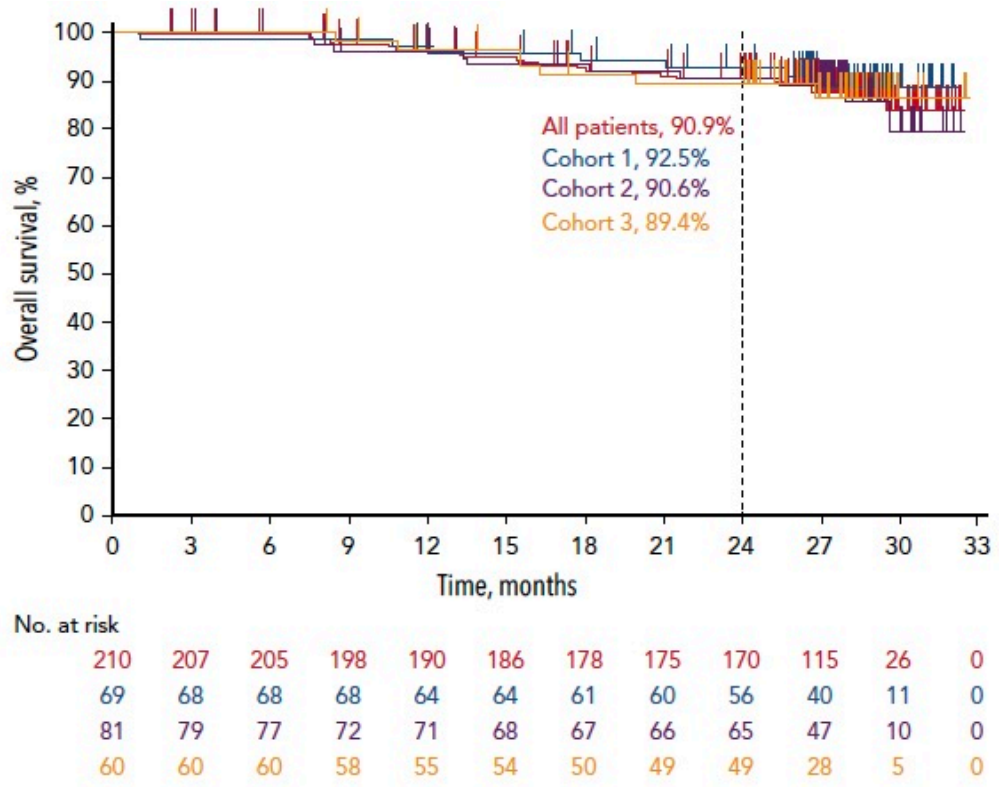
Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087

Robert Chen,[1,*] Pier Luigi Zinzani,[2,*] Hun Ju Lee,[3] Philippe Armand,[4] Nathalie A. Johnson,[5] Pauline Brice,[6] John Radford,[7] Vincent Ribrag,[8] Daniel Molin,[9] Theodoros P. Vassilakopoulos,[10] Akihiro Tomita,[11] Bastian von Tresckow,[12] Margaret A. Shipp,[4] Jianxin Lin,[13] Eunhee Kim,[13] Akash Nahar,[13] Arun Balakumaran,[13] and Craig H. Moskowitz[14]

Blood 134:1144-1153, 2019

KEYNOTE-087 - single-arm phase II study - 3 cohorts of patients with R/R HL

1. After Auto-SCT and BV (n = 69)
2. After salvage chemotherapy and BV, but ineligible for ASCT (n = 81)
3. After ASCT but without BV after transplant (n = 60)



mFollow-up: 27.6 months

ORR: 72%; CR: 27.6%, PR: 44%

mOS: NR in all patients or in any cohort

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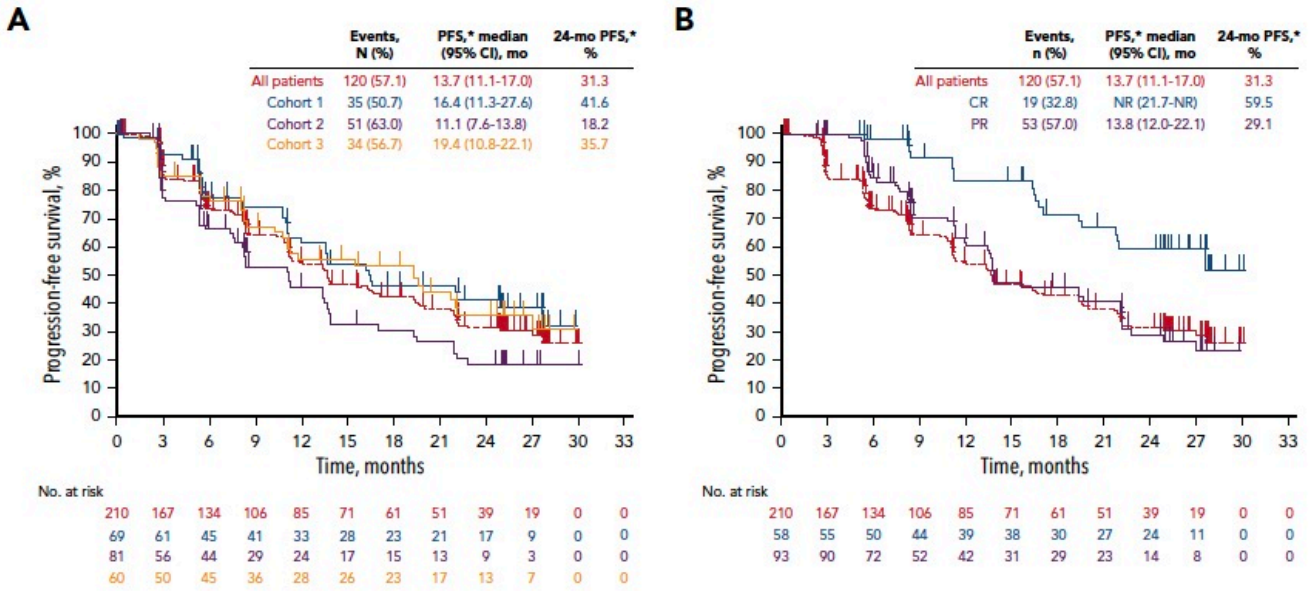

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PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation

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Blood 134:22-29, 2019

- **Hypothesis**: Pembrolizumab as consolidation after ASCT would improve the PFS at 18 months after ASCT (primary end point) from 60% to 80%
- R/R HL patients (n= 30) deemed at *high-risk by clinical criteria* were enrolled
- They had received ASCT and had chemosensitive disease, i.e., they had achieved PMR or CMR after salvage therapy and prior to ASCT
- Pembrolizumab at 200 mg IV every 3 weeks for up to 8 cycles, starting within 21 days of post-ASCT discharge
- **Toxicity** was manageable, with 30% of patients experiencing at least 1 grade 3 or higher AE, and 40% at least 1 grade 2 or higher immune-related AE.

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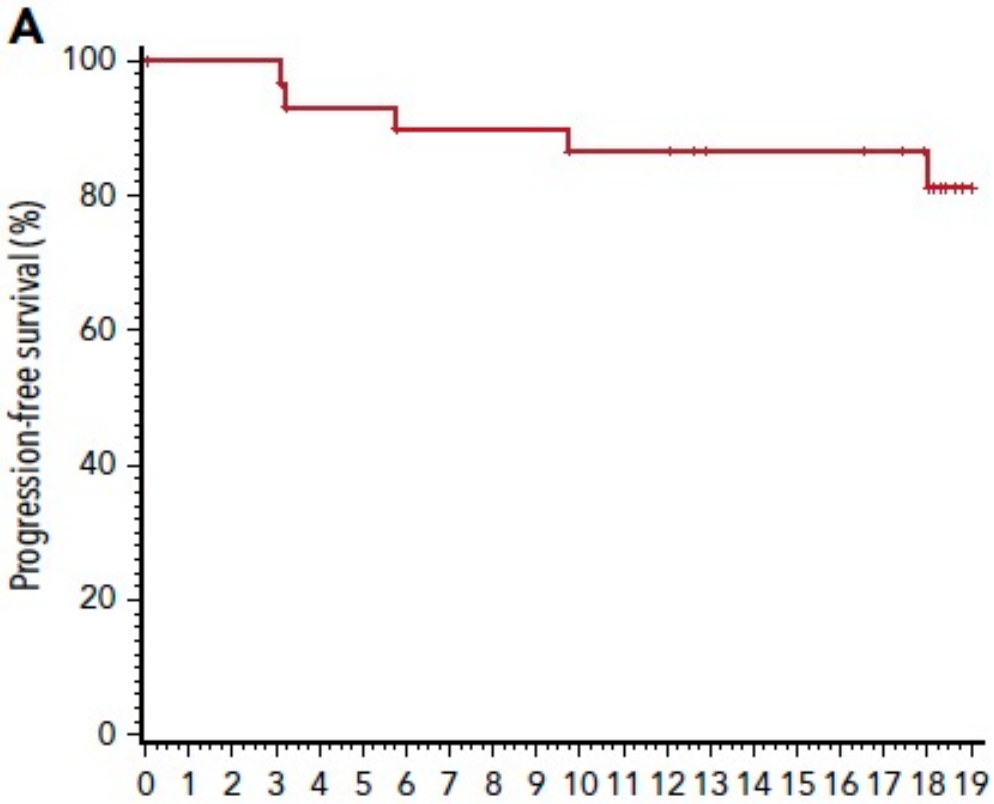


- **The 18 months PFS** = 82% (5 pts had relapsed)
- **The 18-month OS was 100%**

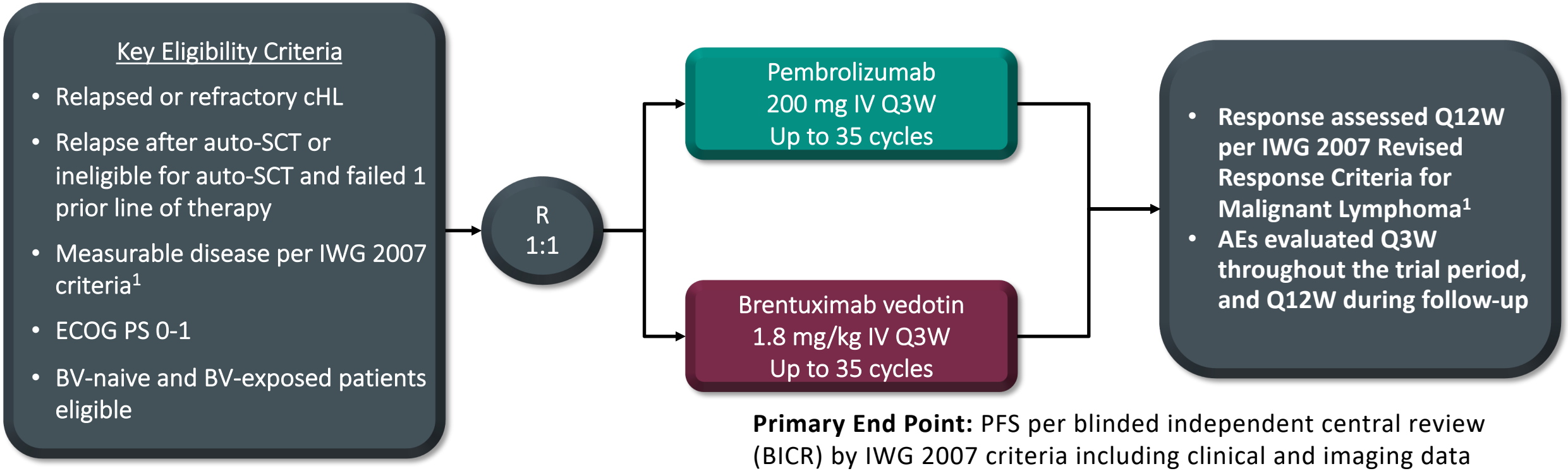
Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study

*John Kuruvilla, Radhakrishnan Ramchandren, Armando Santoro, Ewa Paszkiewicz-Kozik, Robin Gasiorowski, Nathalie A Johnson, Laura Maria Fogliatto, Iara Goncalves, Jose S R de Oliveira, Valeria Buccheri, Guilherme F Perini, Neta Goldschmidt, Iryna Kriachok, Michael Dickinson, Mieczyslaw Komarnicki, Andrew McDonald, Muhit Ozcan, Naohiro Sekiguchi, Ying Zhu, Akash Nahar, Patricia Marinello, Pier Luigi Zinzani, on behalf of the KEYNOTE-204 investigators**

Lancet Oncol 22:512-524, 2021

Interpretation Pembrolizumab showed statistically significant and clinically meaningful improvement in progression-free survival compared with brentuximab vedotin, with safety consistent with previous reports. These data support pembrolizumab as the preferred treatment option for patients with relapsed or refractory classical Hodgkin lymphoma who have relapsed post-autologous HSCT or are ineligible for autologous HSCT.

KEYNOTE-204 Study Design (NCT02684292)



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)

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

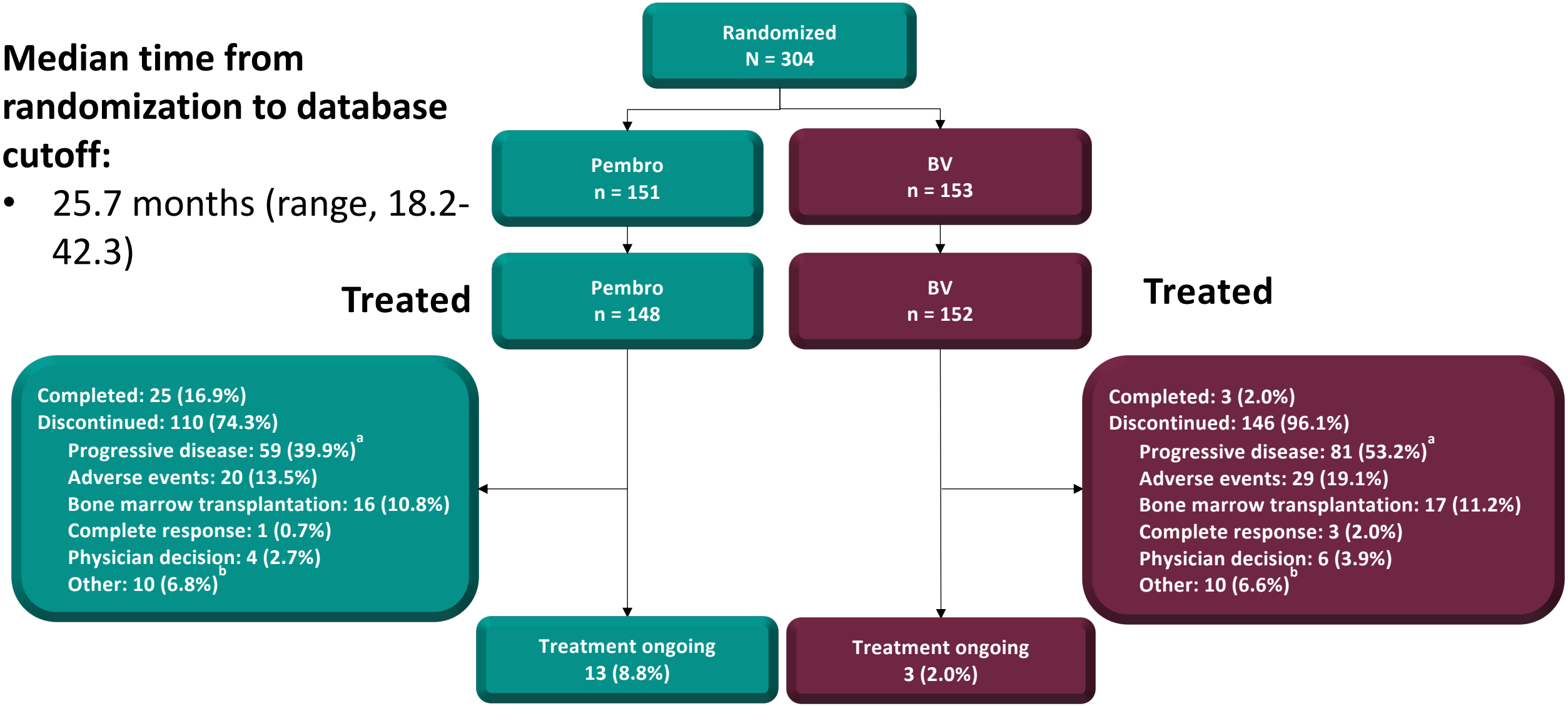
Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

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

Disposition

Median time from randomization to database cutoff:

- 25.7 months (range, 18.2-42.3)



[a]Includes clinical progression.
[b]Other included nonstudy anticancer therapy, excluded medication, noncompliance, withdrawal by patient, and protocol deviations.
Data cutoff: January 16, 2020.

Patient Characteristics

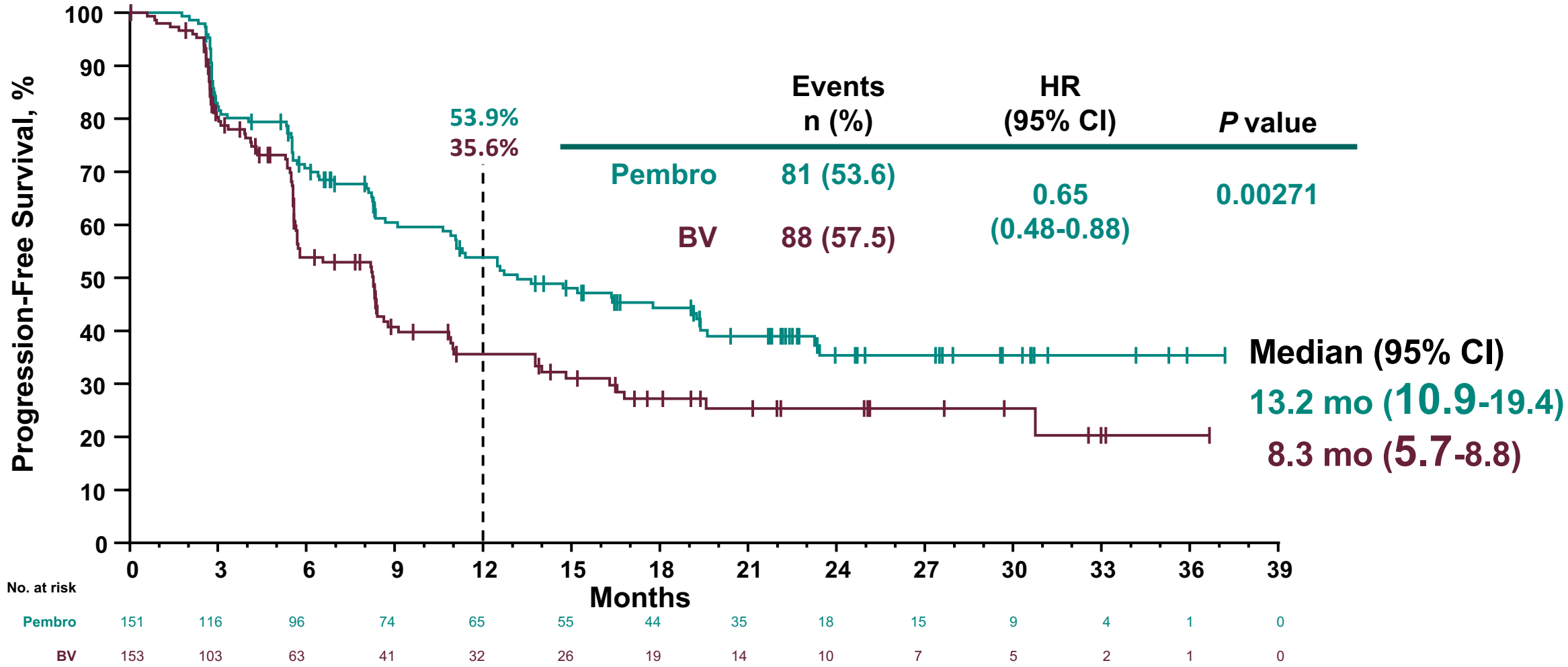
	Pembro n = 151	BV n = 153
Age, median (range)	36 (18-84)	35 (18-83)
≥65 years, n (%)	27 (17.9)	22 (14.4)
Male, n (%)	84 (55.6)	90 (58.8)
White, n (%)	119 (78.8)	115 (75.2)
ECOG PS 0, n (%)	86 (57.0)	100 (65.3)
Prior auto-SCT, n (%)		
Yes	56 (37.1)	56 (36.6)
No	95 (62.9)	97 (63.4)

	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.

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.

Take Home Messages

- Chemo-free regimens still to demonstrate their efficacy