Lymphomas

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Disclosure of Conflicts of interest

Sabarish Ayyappan MD has the following financial relationships to disclose:

Research Support - Genmab, Regeneron , Astrazeneca, Innate Pharmaceuticals, Beigene, Pfizer, Xencor, Roche/Genentech

Consultant- Fate therapeutics, TG therapeutics, Beigene, ADC therapeutics, Seattle genetics, Intellisphere LLC, Total CME, Astrazeneca, Morphosys, Abbvie

Learning Objectives

- Summarize updates and evidence-based therapy for management of indolent and aggressive lymphoma
- List the implications of clinical trial data regarding B-cell lymphoma therapies

Updates from ASCO and EHA

- Hodgkin Lymphoma
  - Brentuximab+ AVD
- DLBCL
  - Bispecific Antibodies
- Follicular Lymphoma
  - Bispecific Antibodies
- Mantle cell lymphoma
  - BR-Ibrutinib(SHINE Trial)
  - CAR T cell therapy Update

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FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IMPROVES OVERALL SURVIVAL IN PATIENTS WITH STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: AN UPDATED ANALYSIS OF ECHELON-1

ORIGINAL ARTICLE FREE PREVIEW

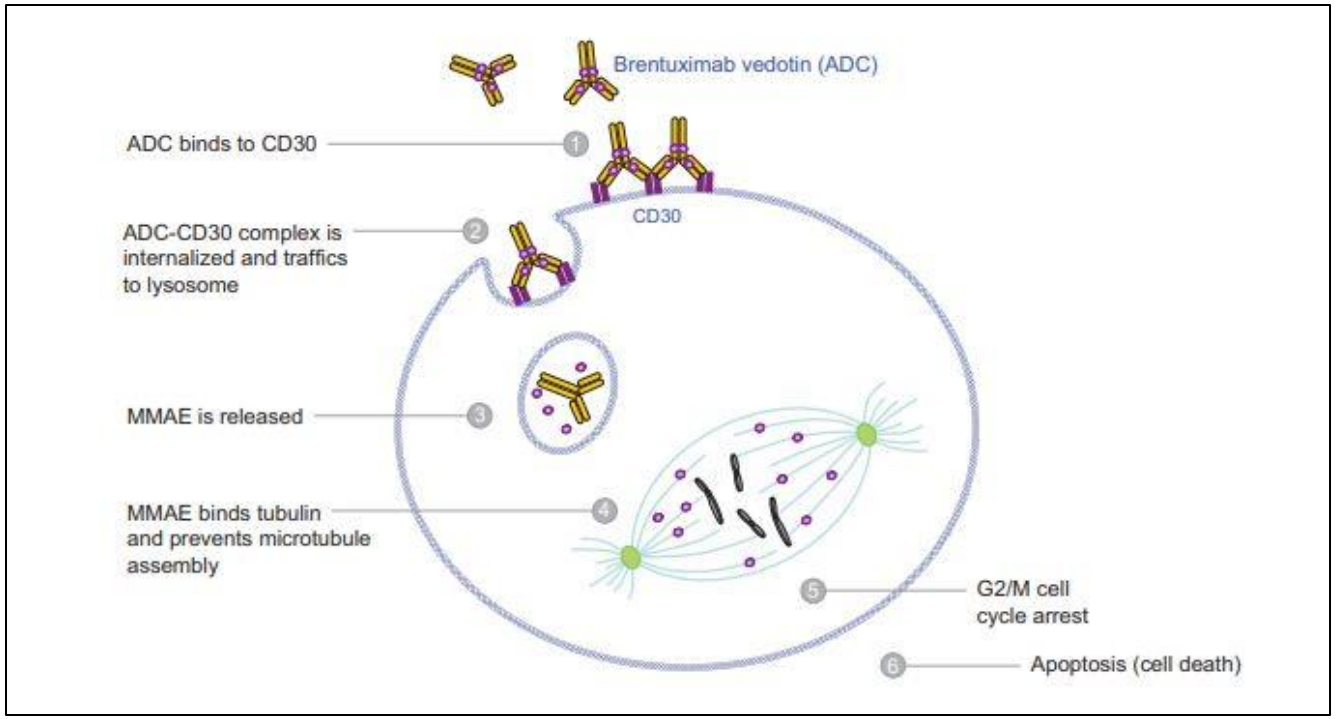
Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., John Radford, M.D., Joseph M. Connors, M.D., Monika Długosz-Danecka, M.D., Ph.D., Won-Seog Kim, M.D., Andrea Gallamini, M.D., Radhakrishnan Ramchandren, M.D., Lorenz H. Trümper, M.D., Ranjana Advani, M.D., Martin Hutchings, Ph.D., Andrew M. Evens, D.O., Pier Luigi Zinzani, M.D., Ph.D., et al., for the ECHELON-1 Study Group*

Ansell ASCO 2022 Abstract 7503, Ansell et al NEJM 2022

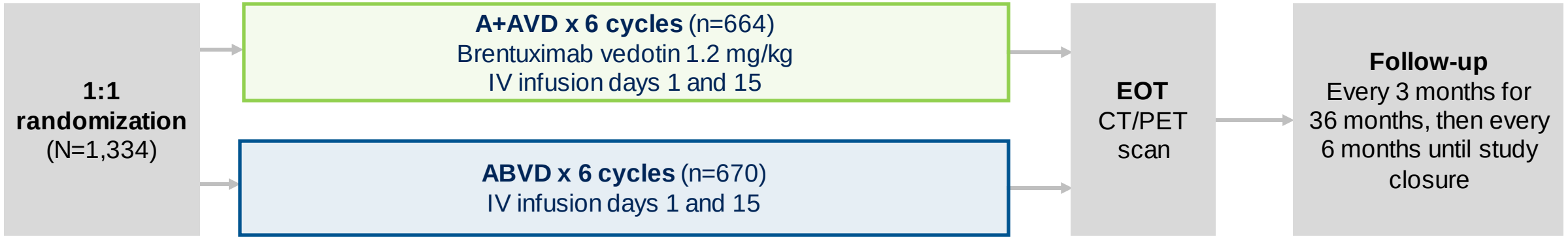
Brentuximab

- Phase 1 experience with brentuximab vedotin + AVD (A+AVD) (N=25)
  - Well tolerated
  - CR : 96%
  - 5-year FFS: 92%
  - 5-year OS : 100%



Younes A, et al. NEJM 2010
Younes A, et al. Lancet Oncol 2013
Connors et al Blood 2017

Phase 3 ECHELON-1 study design



Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

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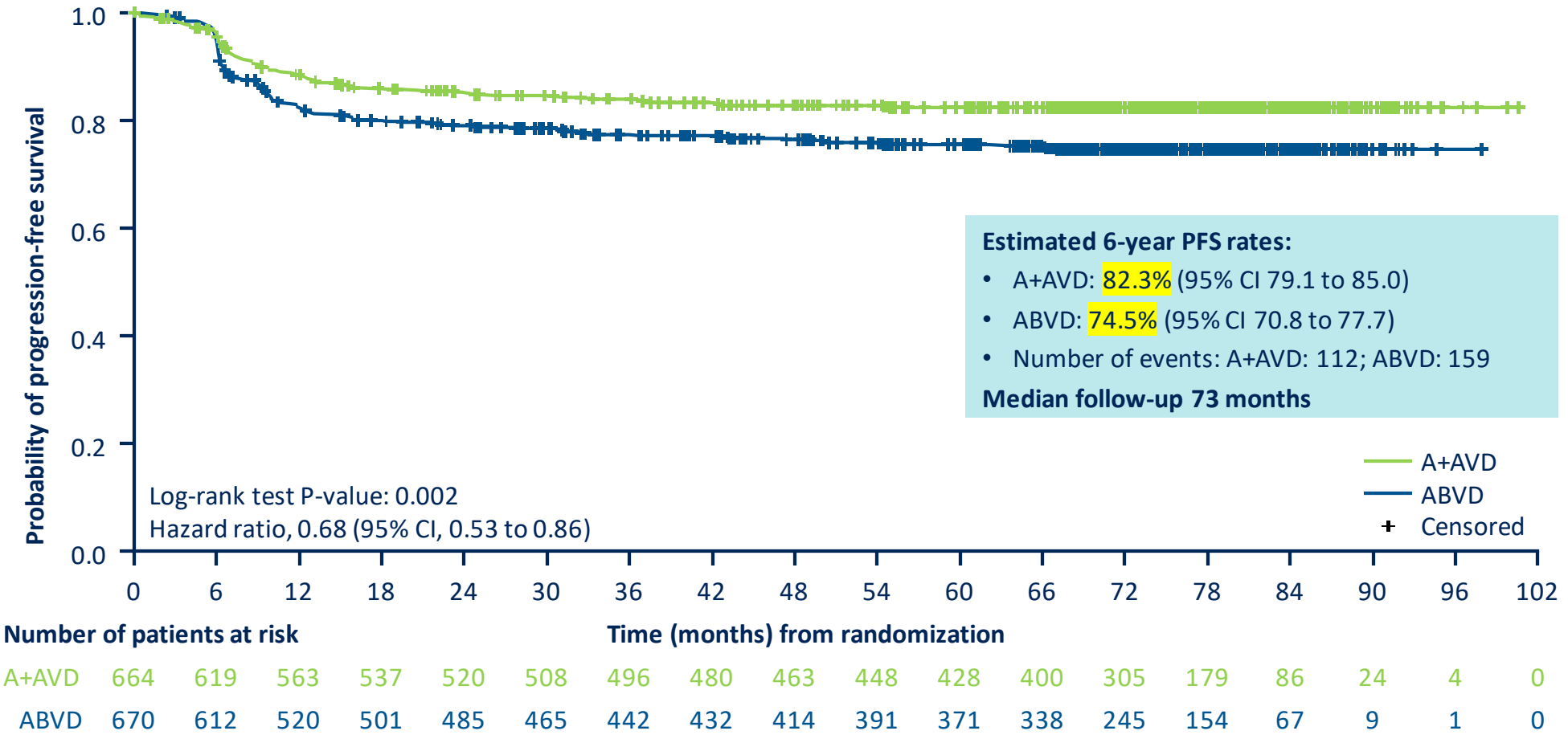
PFS benefit



Number of patients at risk

A+AVD	664	619	563	537	520	508	496	480	463	448	428	400	305	179	86	24	4	0
ABVD	670	612	520	501	485	465	442	432	414	391	371	338	245	154	67	9	1	0

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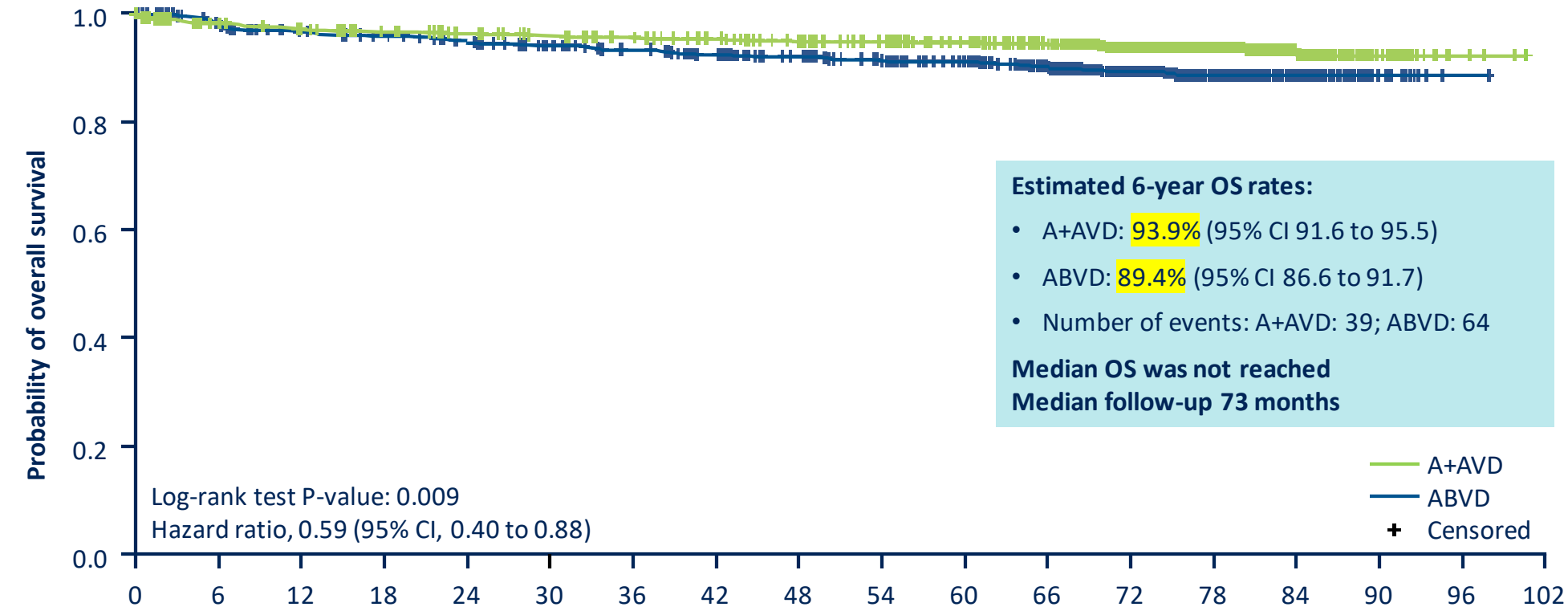
Overall Survival comparison



CI, confidence interval.

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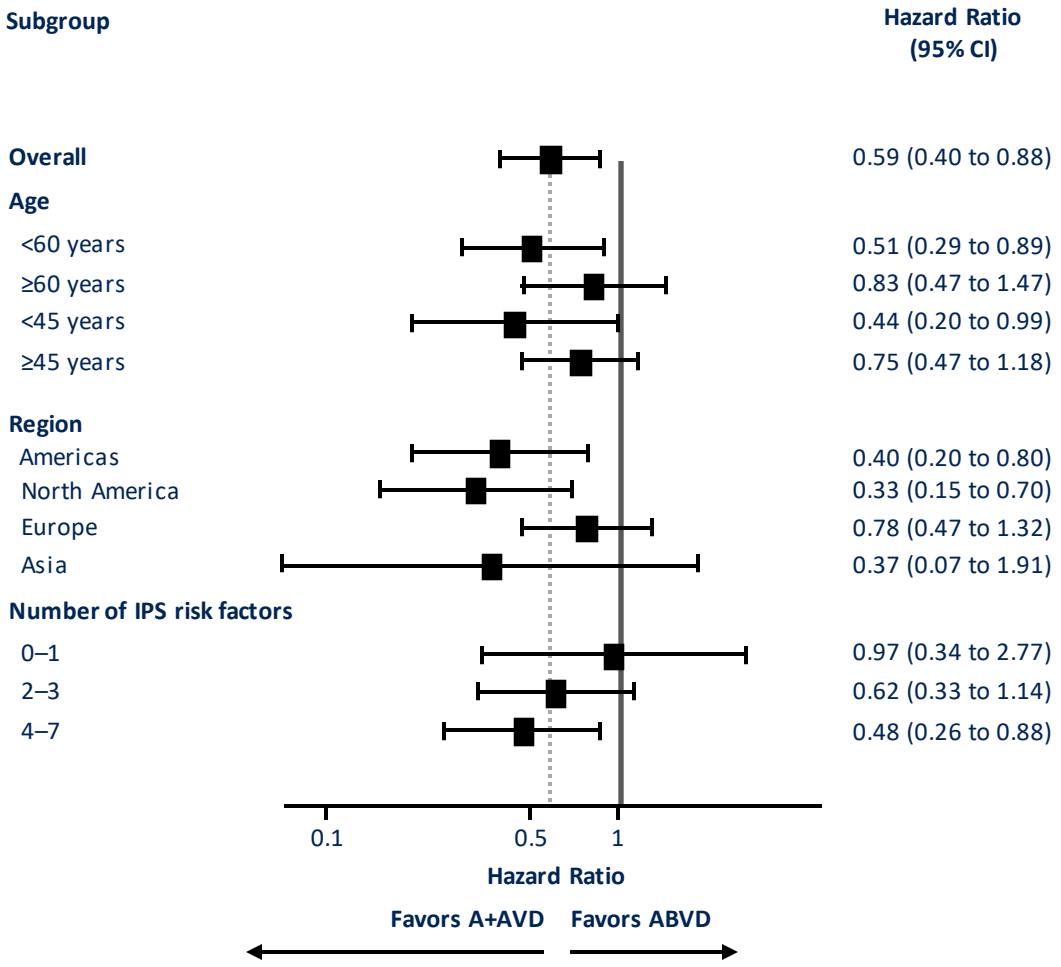
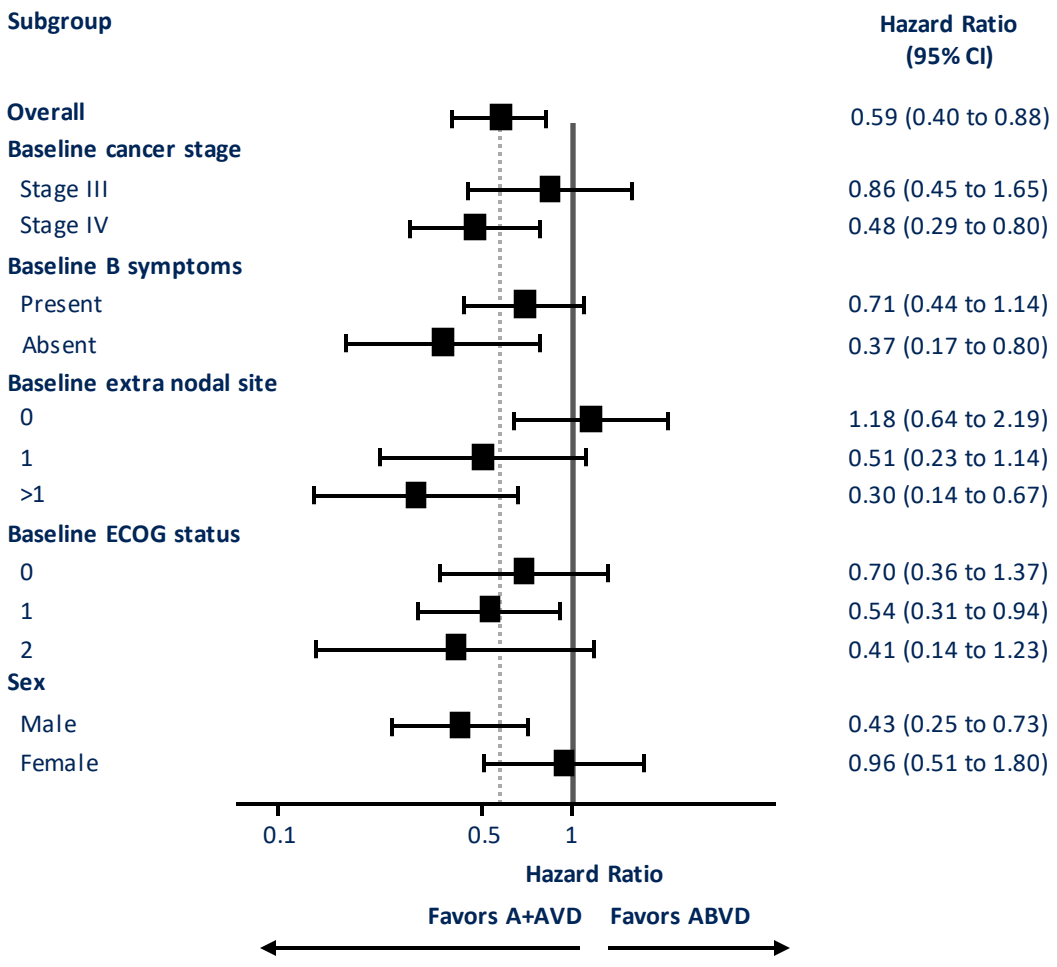
OS benefit was generally consistent across subgroups





ECOG, Eastern Cooperative Oncology Group.

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Fewer patients died from HL and disease- or treatment-related complications with A+AVD vs ABVD

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

- Among those who died:
  - A+AVD: 19 patients had prior disease progression (not always the cause of death); 18 received subsequent therapy
  - ABVD: 28 patients had prior disease progression, 25 received a subsequent therapy (13 received brentuximab vedotin)

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Use of subsequent therapy was less common with A+AVD versus ABVD (safety population)

	A+AVD n=662	ABVD n=659	Total N=1,321
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Brentuximab vedotin or chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)
Other	0 (0)	1 (<1)	1 (<1)

*Immunotherapy was based predominantly on anti-PD-1 agents.

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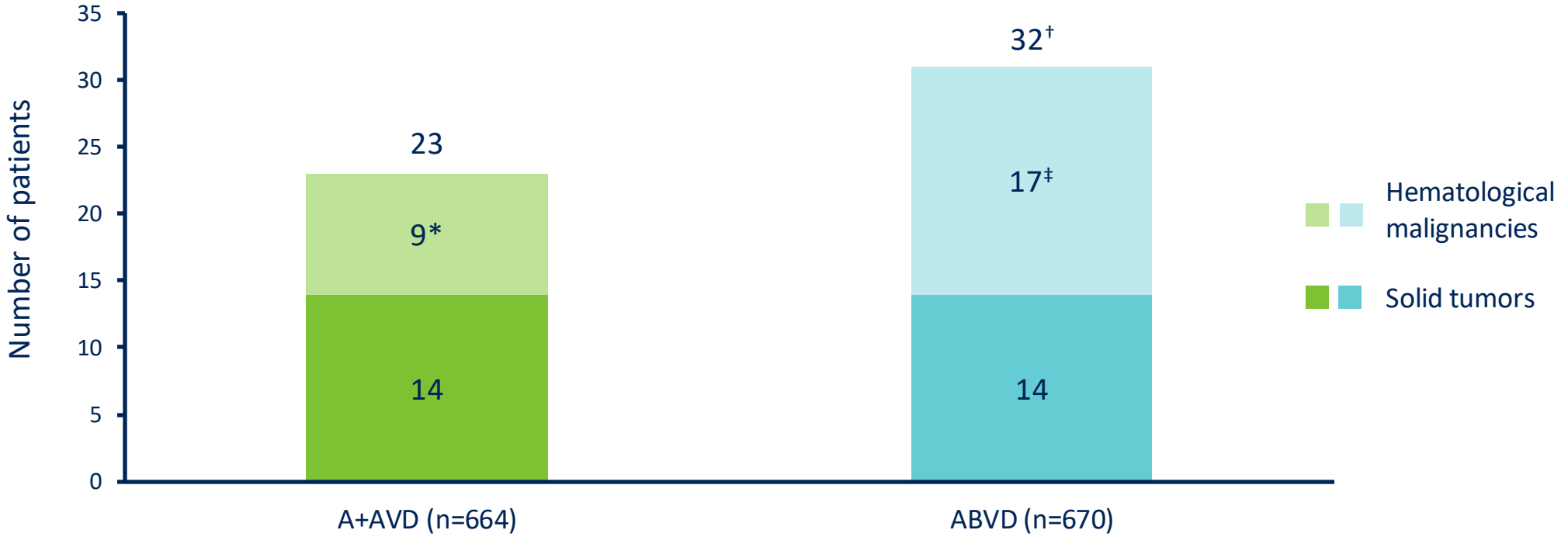
Fewer second malignancies were reported in the A+AVD vs ABVD arm, consistent with prior reports[1]



*Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas; †Includes 1 unknown malignancy; ‡Includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.

- Among patients with second malignancies:
  - Two patients on each arm received transplant
  - Three patients on the ABVD arm received prior radiation (none with A+AVD)

1. Straus DJ, et al. Lancet Haematol 2021;8:e410–21.

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Pregnancy and peripheral neuropathy data consistent with prior reports

Pregnancies

- Fertility was not formally assessed
- A total of 191 pregnancies were reported among patients and their partners (A+AVD: 113; ABVD: 78)
  - Among female patients with A+AVD and ABVD:
    - Pregnancies: 49 and 28
    - Live births*: 56 and 23
  - Among partners of male patients with A+AVD and ABVD:
    - Pregnancies: 33 and 33
    - Live births*: 40 and 36
  - No still births were reported in either arm

Peripheral neuropathy

- Incidence of PN at 2 years of follow-up was greater with A+AVD (67%) vs ABVD (43%)[1]
- In patients with PN in the A+AVD and ABVD arms, after 6 years follow-up:
  - Treatment-emergent PN either resolved or continued to improve[†] in 86% and 87%
  - Median time to resolution was 16 and 10 weeks

Safety population	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing PN at last follow-up, n (%)	125 (19)	59 (9)
Grade 1	71 (11)	39 (6)
Grade 2	38 (6)	16 (2)
Grade 3[‡]	15 (2)	4 (<1)
Grade 4[‡]	1 (<1)	0

*Some female patients (13 on the A+AVD arm and 3 on the ABVD arm)/partners of male patients (8 on the A+AVD arm and 7 on the ABVD arm) recorded more than one live birth; [†]Resolution was defined as resolved/recovered with or without sequelae or return to baseline or lower severity as of the latest assessment for pre-existing events. Improvement was defined as resolution or a decrease by at least 1 grade from the worst grade with no higher grade thereafter; [‡]Patients who were lost to follow-up or died prior to resolution or improvement were not censored (11/16 patients [including the 1 patient with Grade 4 PN] on the A+AVD arm; 4/4 on the ABVD arm).

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

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Advanced stage Hodgkin in 2022

- Brentuximab + AVD
- ABVD x 2 -->(PET response Deauville 1-3)-->AVD x 4 for elderly Hodgkin patients [RATHL study[1]]
- Sequential Brentuximab with AVD (Evens et al, JCO 2018)
  - Brentuximab x 2 cycles--> AVD x6 → Brentuximab x 4
- Clinical Trial : S1826 (NCT 03907488)
  - Brentuximab + AVD vs Nivolumab + AVD- phase 3 , randomized study

[1] Johnson et al NEJM 2016

Updates from ASCO and EHA

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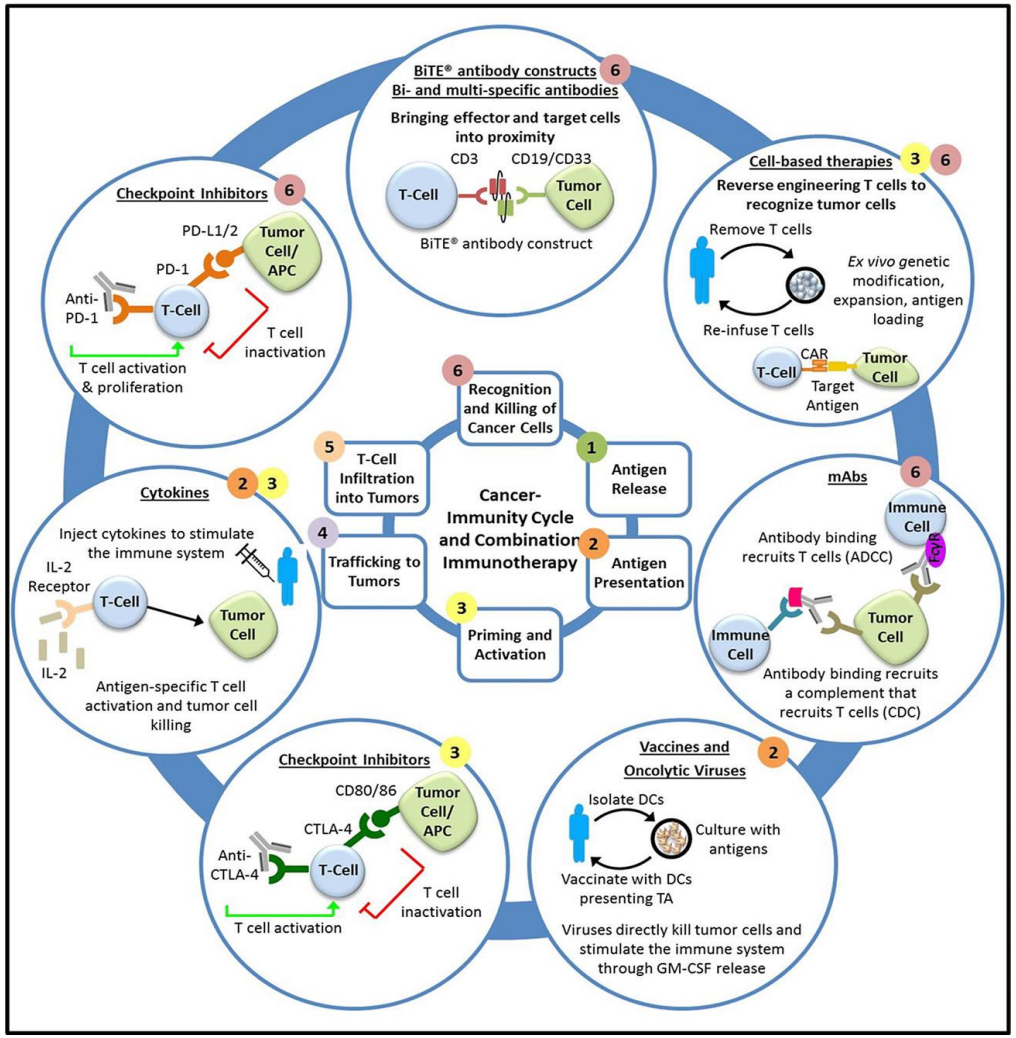
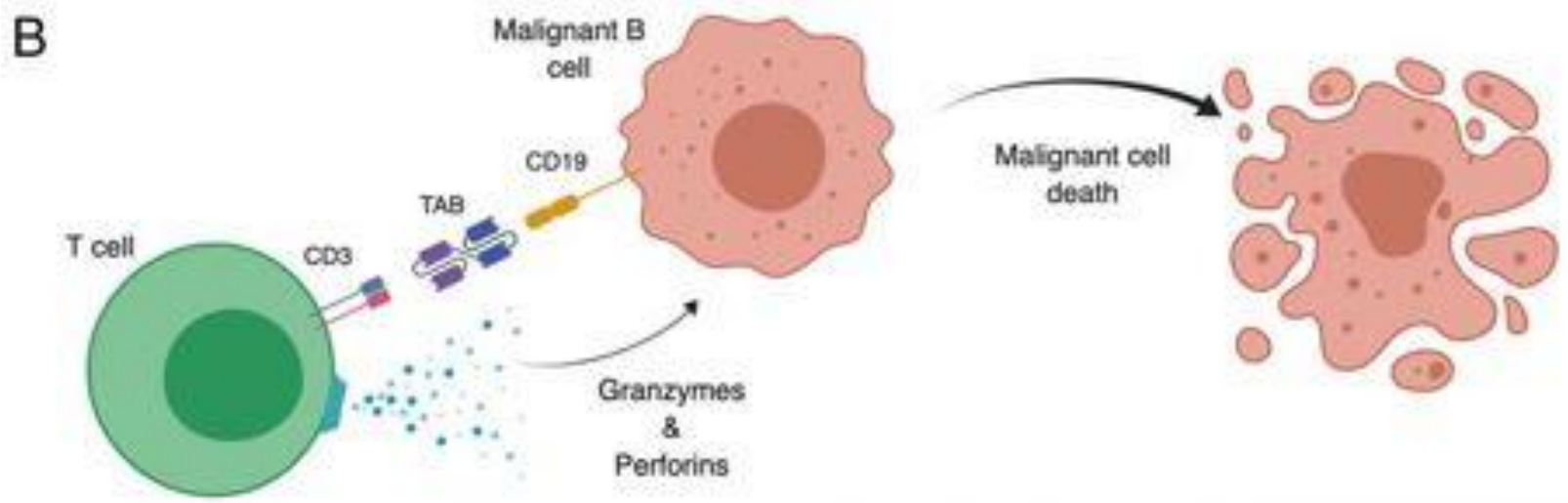
Immunotherapy in oncology



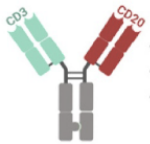
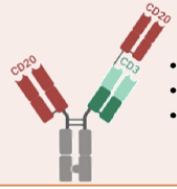
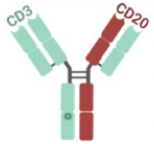
Morrissey et al, Clinical and Translational Science 2016

Bispecific antibodies mechanism



Asaad Trabolsi et al. J Immunol 2019

Bispecific antibodies in Lymphoma

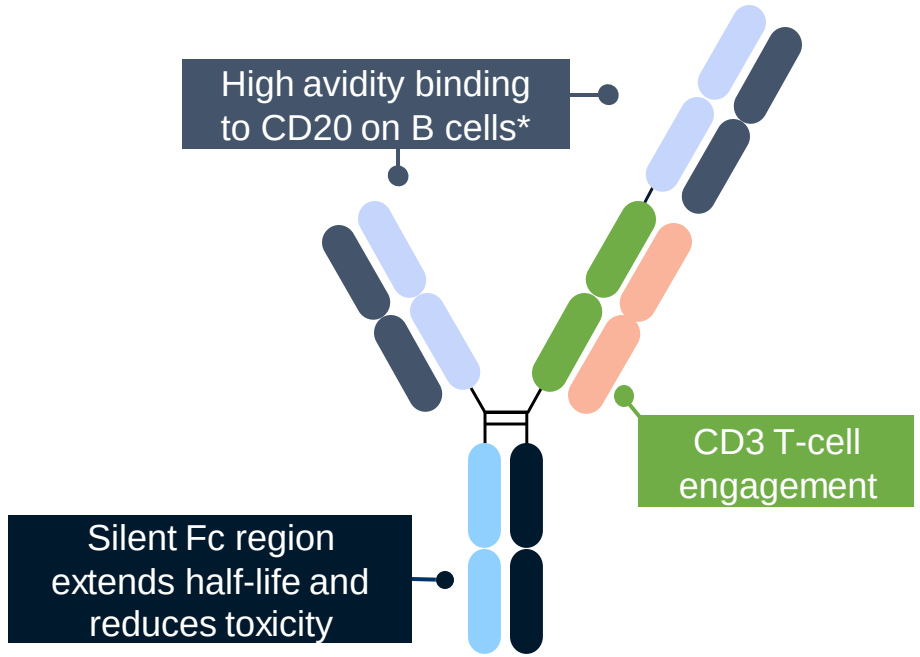
Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	
[illegible]	[illegible]	murine mAbs	• two murine scFv joined by a glycine-serine linker	[illegible]
umab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	mosunetuz
	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	glofitamab
nab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	odronextan
b	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	epcoritama

Schuster J Hemat Oncol 2021

Glofitamab

- **Glofitamab**
  - off-the-shelf and fixed duration treatment[1,2]
- **Phase I experience (NCT03075696)[7]**
  - encouraging efficacy and manageable safety with glofitamab monotherapy in patients with R/R B-cell NHL[2,3]
  - established a step-up dosing schedule and target dose (30mg) in patients with B-cell NHL in multiple cohorts[3]

Glofitamab: CD20xCD3 bispecific monoclonal antibody with 2:1 format for increased potency vs 1:1 format[1]



1.Bacac, et al. Clin Cancer Res 2018; 2. NCT03075696 3. Hutchings, et al. J Clin Oncol 2021.

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Study overview

Pivotal Phase II expansion in patients with R/R DLBCL and ≥2 prior therapies (NP30179)

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

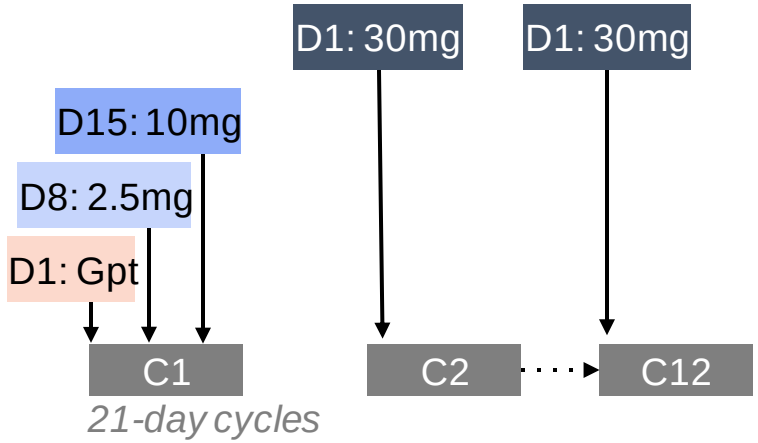
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



Endpoints

- **Primary: CR (best response) rate by IRC***
- **Key secondary:** ORR rate,† DoR, DoCR,† PFS, and OS

*by PET-CT (Lugano criteria[1]); †by IRC and investigator. BCL, B-cell lymphoma; FL, follicular lymphoma; Gpt, obinutuzumab pretreatment; HGBCL, high-grade BCL; IRC, Independent Review Committee; NOS, not otherwise specified; PMBCL, primary mediastinal large BCL.

1. Cheson, et al. J Clin Oncol 2014.

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Baseline characteristics

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Heavily pre-treated, highly refractory population

Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients); ‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

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Response rates – primary endpoint met

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

– At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate‡

High CR/ORR rate at RP2D

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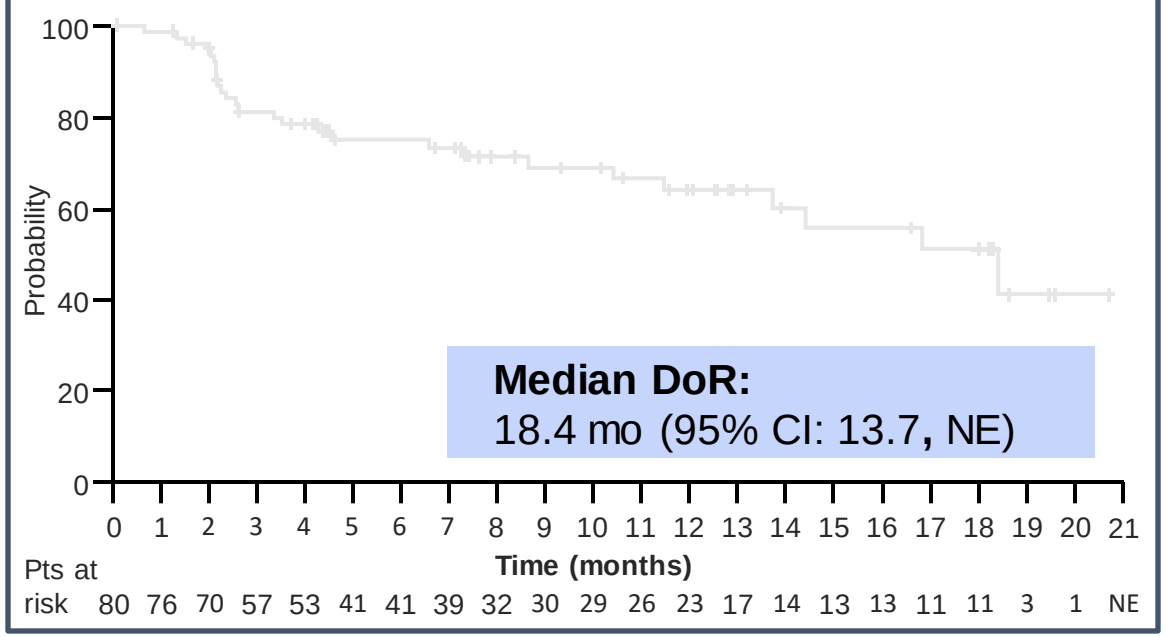
1. Cheson, et al. J Clin Oncol 2014.

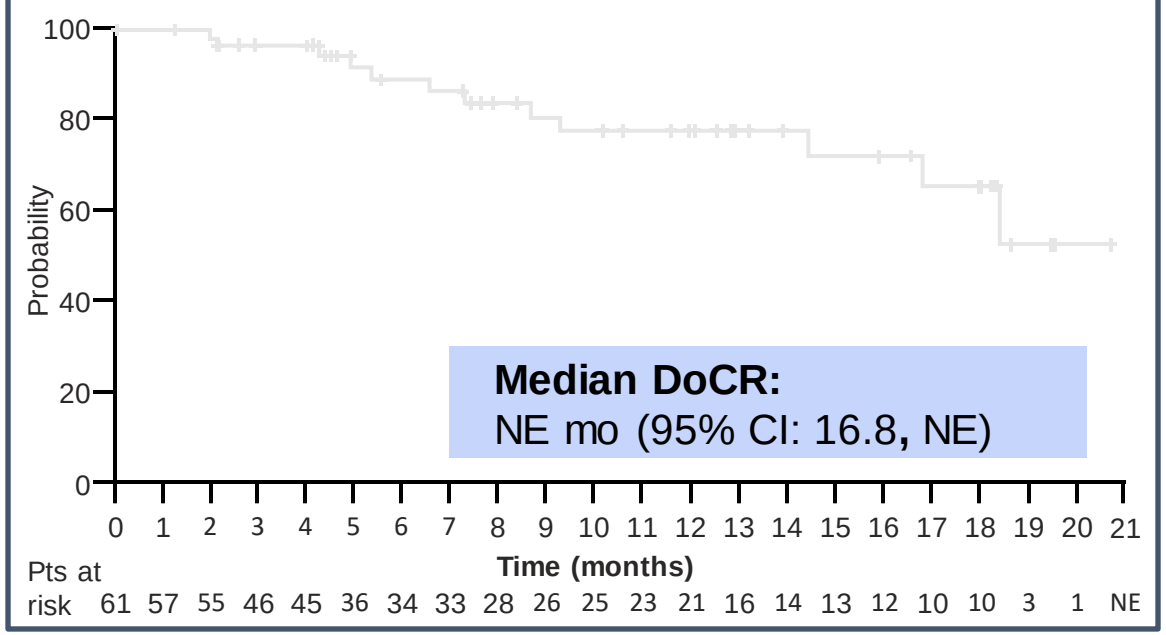
Durable responses maintained after cessation of therapy

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

CCOD, clinical cut-off date; mo, months; NE, not estimable.

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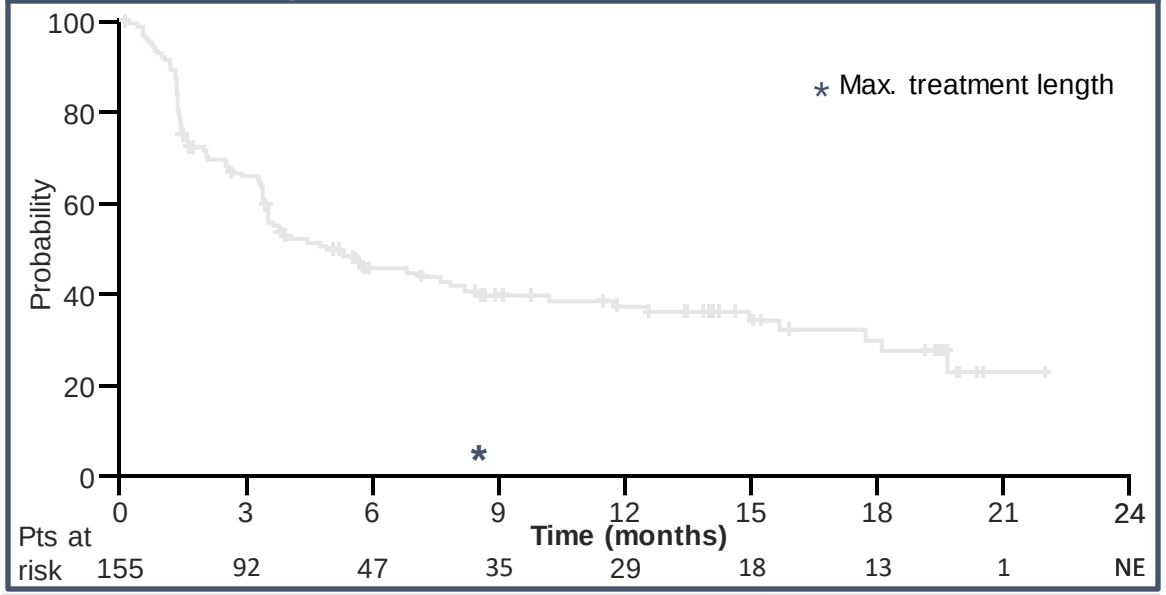
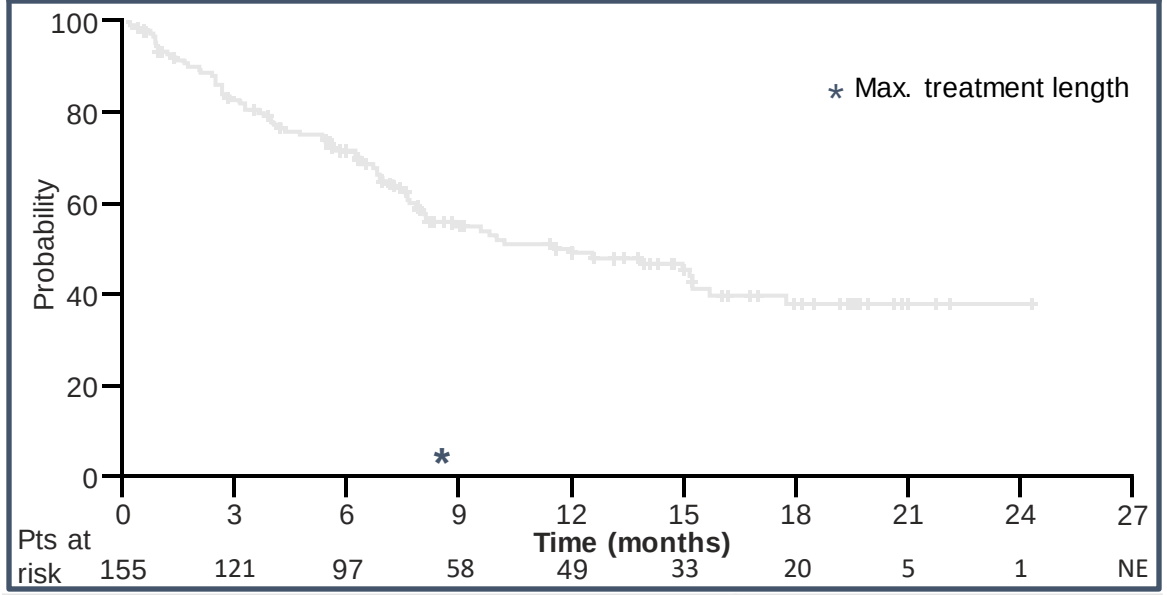
Time-to-event endpoints

Progression-free survival by IRC



	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)‡	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

Overall survival†



	N=155
Median OS, months (95% CI)‡	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

Clinically significant freedom from progression at 12 months and long-term overall survival

†including five deaths due to COVID-19; ‡KM estimates.

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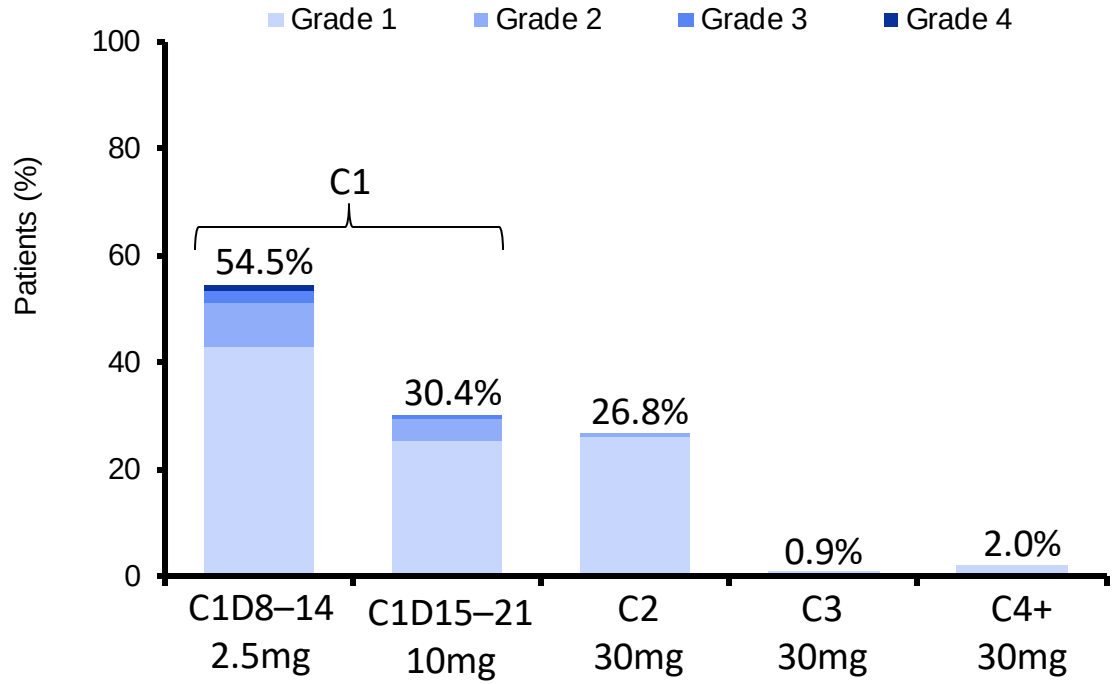
Cytokine release syndrome

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)

CRS by cycle and grade†



CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

*CRS reported by ASTCT grade (American Society for Transplantation and Cellular Therapy criteria) derived based on reported data and INV graded CRS according to Lee 2014 criteria[1,2]; †one patient had Grade 1 CRS following obinutuzumab pretreatment due to CART-T re-expansion.

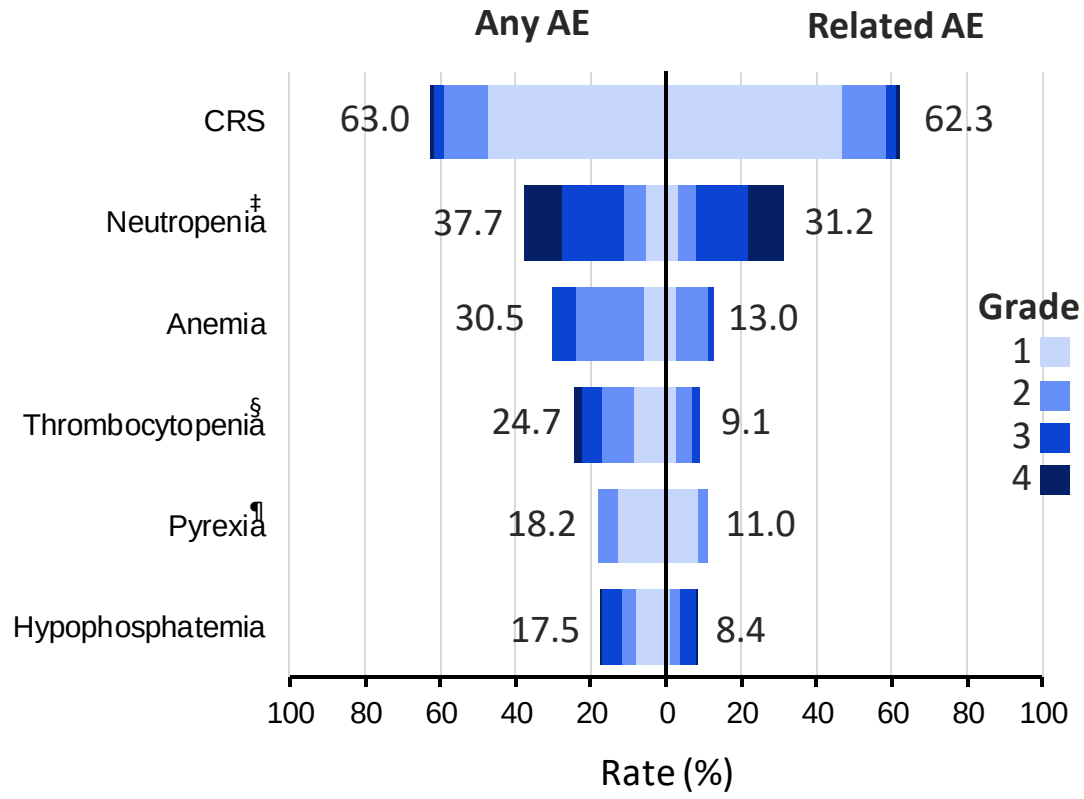
1. Lee, at al. Blood 2014;
2. Lee, et al. Biol Blood Marrow Transplant 2019.

Dickinson ASCO 2022 Abstract 7500

Glofitamab safety profile

n (%)*	N=154
Median no. of cycles received (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
AE	152 (98.7)
Related AE	140 (90.9)
Grade 3–4 AE	87 (56.5)
Related AE	64 (41.6)
Serious AE	73 (47.4)
Related AE	46 (29.9)
Grade 5 (fatal AE)	8 (5.2)†
Related AE	0
AE leading to treatment discontinuation	14 (9.1)
Related AE	5 (3.2)

AEs (≥15%) by grade and relationship with glofitamab

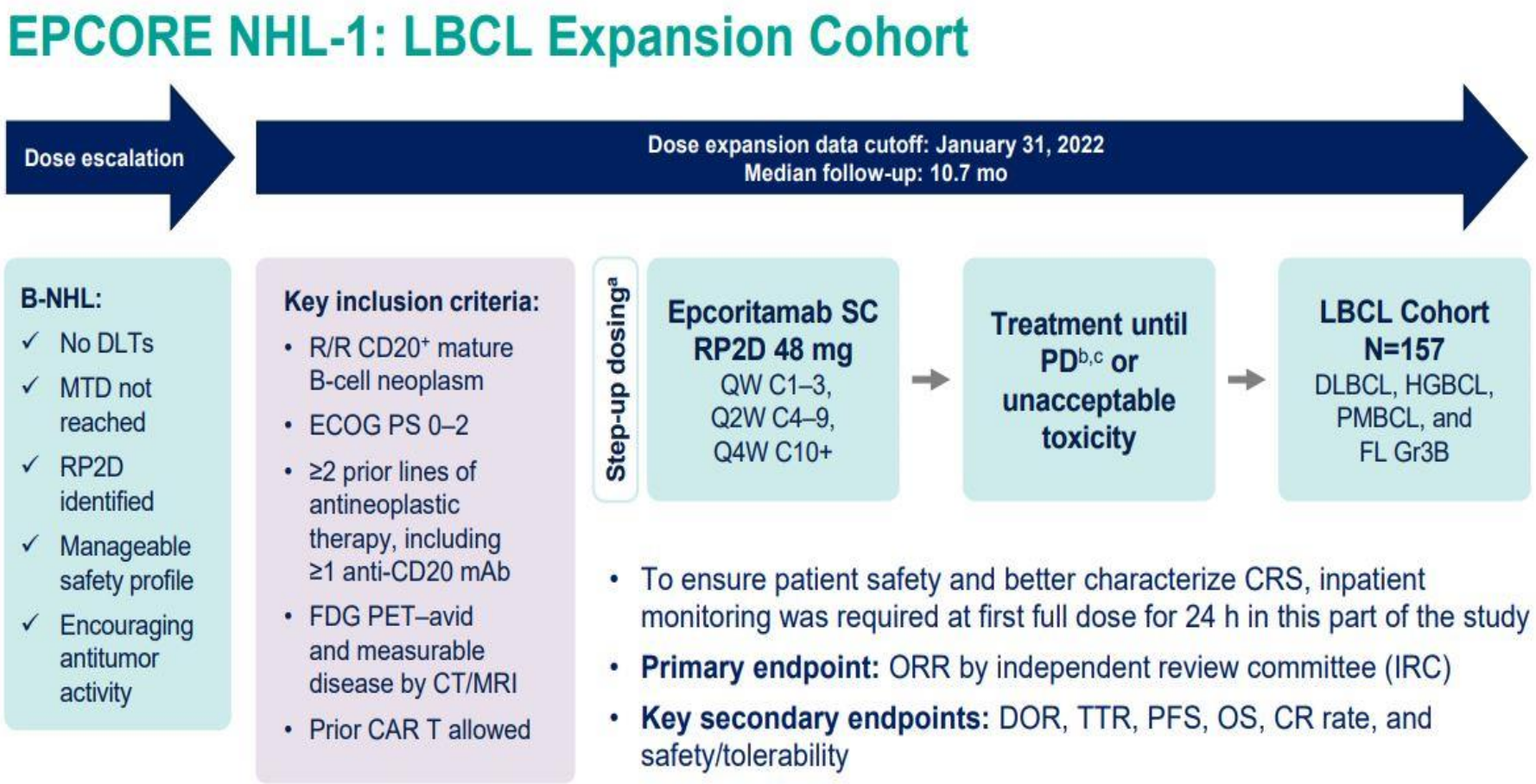


Glofitamab was well tolerated

*unless otherwise specified; †COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1);
‡includes neutrophil count decreased; §includes platelet count decreased; ¶pyrexia events separate from CRS.

Dickinson ASCO 2022 Abstract 7500

Epcoritamab - DLBCL



Thieblemont EHA 2022 LBA Abstract 2364

Patient characteristics

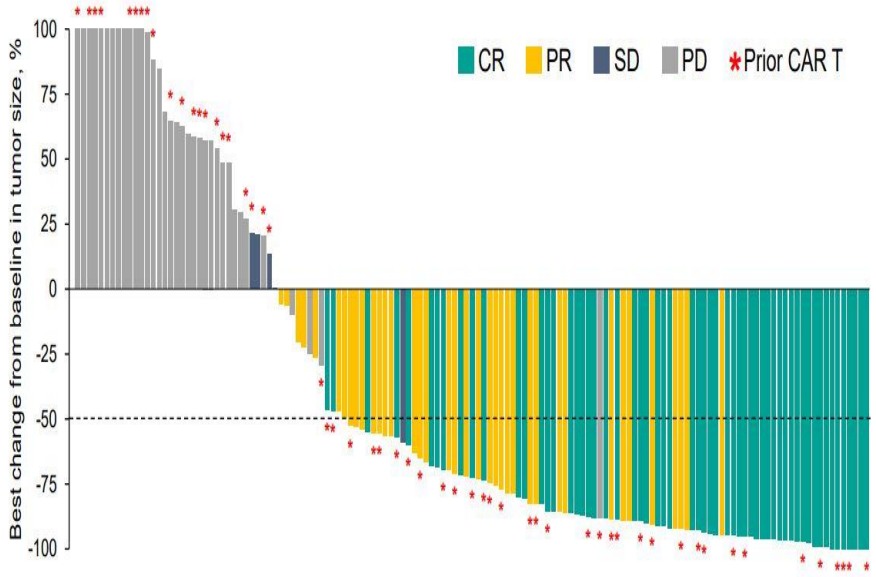
Demographics	LBCL, N=157
Median age (range), y	64 (20–83)
<65 y, n (%)	80 (51)
65 to <75 y, n (%)	48 (31)
≥75 y, n (%)	29 (18)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)
Disease Characteristics[a]	**LBCL, N=157**
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)

Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[b] disease, n (%)	96 (61)
Refractory[b] to last systemic therapy, n (%)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Progressed within 6 mo of CAR T therapy	46/61 (75)

Thieblemont EHA 2022 LBA Abstract 2364

Response Rates

Best Overall Response by IRC	DLBCL (N= 157)
Overall response	99 (63) [95% CI :55-71]
Complete response	61 (39) [95% CI :31-47]
Partial response	38 (24)
Stable disease	5 (3)
Progressive disease	37 (24)



Thieblemont EHA 2022 LBA Abstract 2364

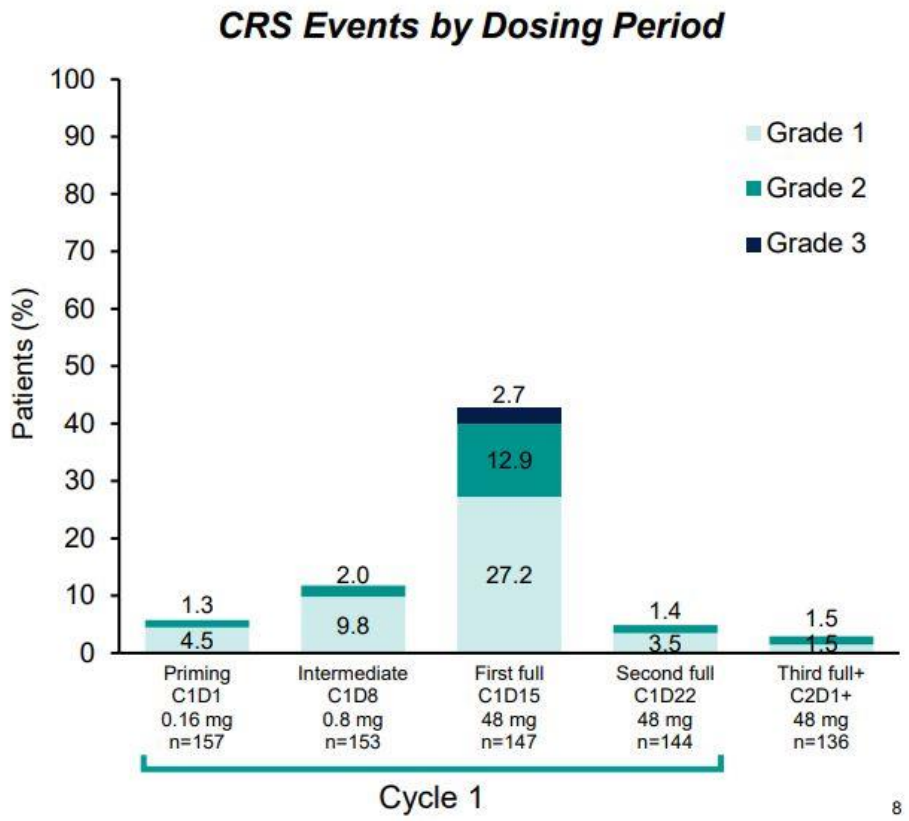
CRS mitigation

SC Administration and Step-up Dosing May Mitigate CRS

	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**

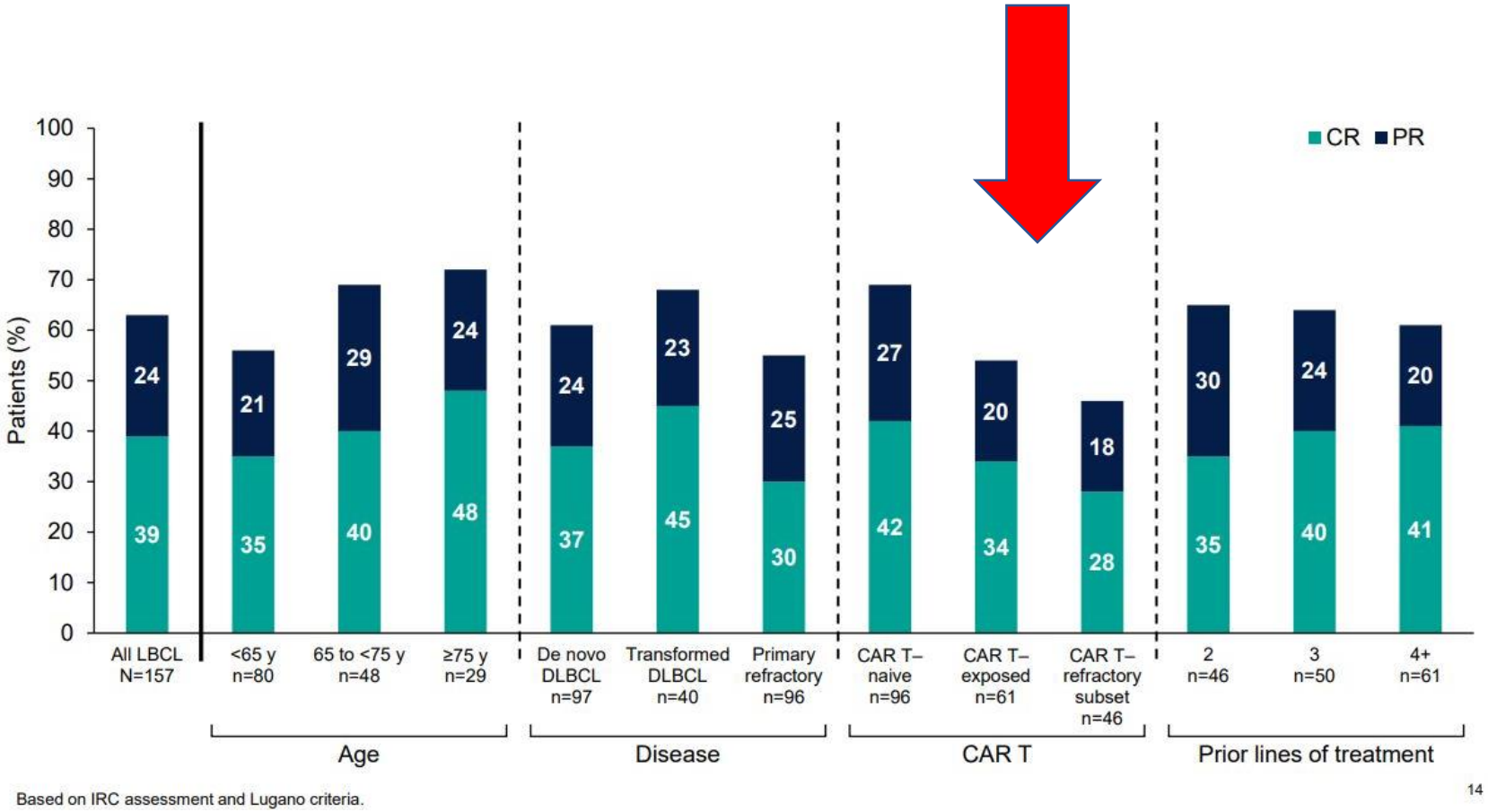
[a]Graded by Lee et al. 2019 criteria.

CRS was primarily low grade and predictable: most events occurred following the first full dose



Thieblemont EHA 2022 LBA Abstract 2364

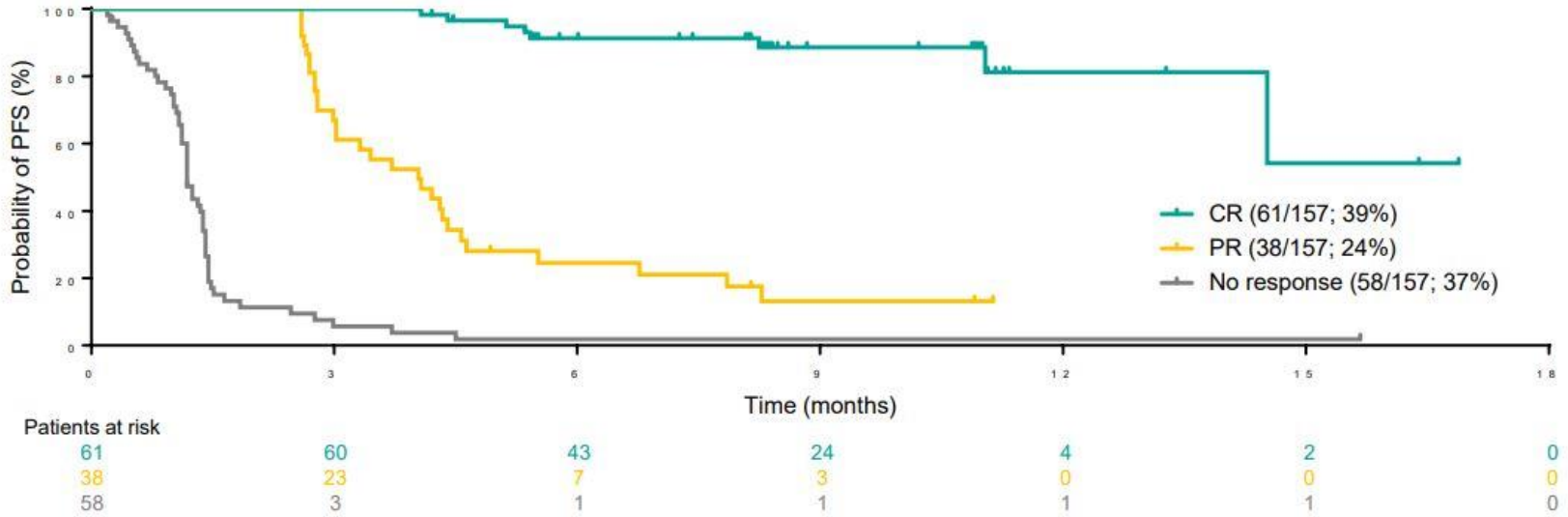
Subgroup comparison



Thieblemont EHA 2022 LBA Abstract 2364

Progression free survival

PFS by Best Response per IRC

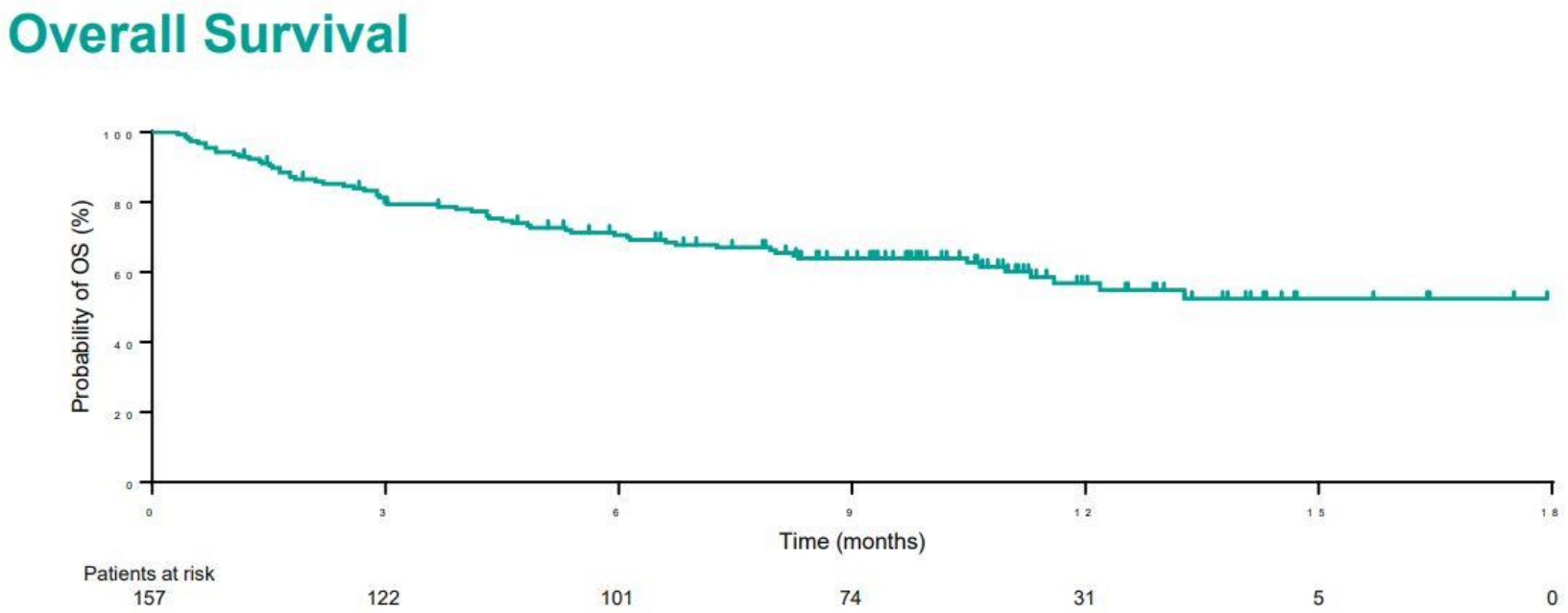


Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

A correlation between depth of response and PFS was observed

Thieblemont EHA 2022 LBA Abstract 2364

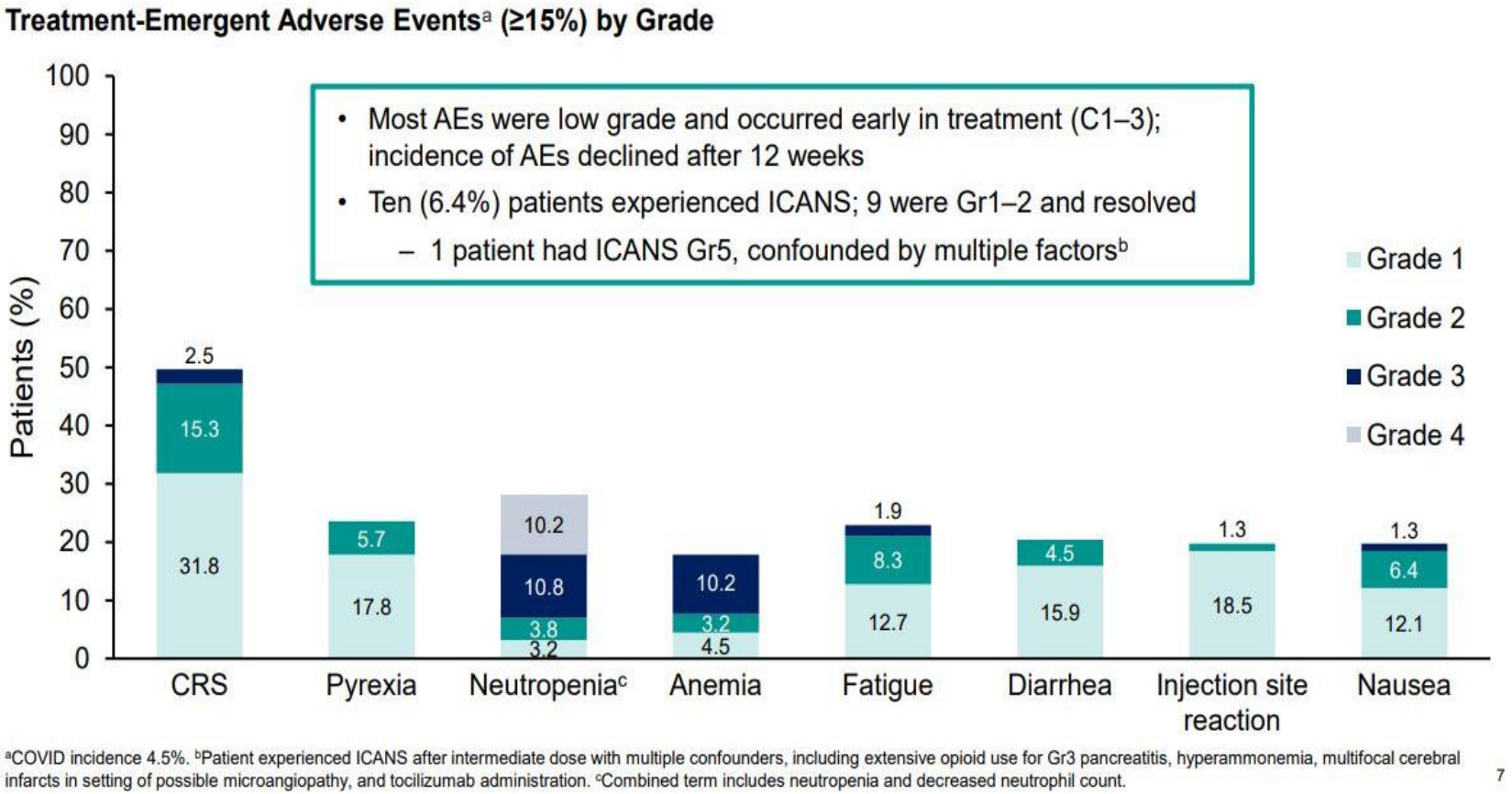
Overall Survival



Kaplan–Meier Estimate	N=157
Median OS	**Not reached**
OS at 6 mo, % (95% CI)	70.6 (62.7–77.2)
OS at 12 mo, % (95% CI)	56.9 (47.3–65.4)

Thieblemont EHA 2022 LBA Abstract 2364

Adverse events



Thieblemont EHA 2022 LBA Abstract 2364

Bispecific antibodies lymphoma

	blinatumomab[1,2,3]		mosunetuzumab[4]	glofitamab[5]		odronextumab[6]		epcoritamab[7]	
Design	Phase 1 (≥ MTD cohort[1])	Phase 2[3]	Phase 1/1b (dose escalation/expansion)	Phase 1 (dose escalation and expansion)		Phase 1 (dose escalation and expansion)		Phase 1 (dose escalation and expansion)	
Patients	r/r NHL (N=38) (DLBCL, n=5)	r/r DLBCL (N=25) (Evaluable, n=21)	r/r NHL (N=270) (DLBCL/tFL, n=116)	r/r NHL N=52 (DLBCL, n=10)		r/r NHL N=136 (DLBCL, n=78)		r/r NHL N=68 (DLBCL, n=46)	
Dosing	Dose escalation to 90 µg/m²/day	Stepwise escalation (9-28-112 µg/day or flat 112 µg/day)	aggressive NHL: 2.8 - 40.5 mg indolent NHL: 2.8 - 13.5 mg	Two target dose cohorts (C1D1, 2.5 mg; C1D8, 10 mg; C2D1 [target dose], 16 or 30 mg)		Dose range: 0.03-320 mg Weekly x 12, then every 2 weeks		Dose range: 0.0128 - 60 mg SC step-up, then every 28 days RP2D = 48 mg	
ORR	≥ 60 µg/m²/day N=25 (n=1 DLBCL) **64%**	(DLBCL, n=21) **43%**	indolent / aggressive n=124 / n=67 **62.7% / 37.1%**	16+30 mg cohorts combined, n=52 **63.5%**	indolent / aggressive n=24 / n=28 **66.7% / 60.7%**	DLBCL ≥ 80 mg *no CAR T* **55%** (n=6/11)	DLBCL ≥ 80 mg *prior CAR T* **33%** (n=8/24)	DLBCL 12-60 mg: **68%** (n=15/22) 48-60 mg: **91%** (n=10/11)	Follicular NHL 0.76-48 mg: **90%** (n=9/10) 12-48 mg: **80%** (n=4/5)
CR	**36%**	**19%**	indolent / aggressive **43.3% / 19.4%**	all NHL **53.8%**	indolent / aggressive **54.2% / 53.6%**	DLBCL ≥80mg, no CAR **55%** (n=6/11)	DLBCL ≥80mg, CAR **21%** (n=5/24)	DLBCL 12-60 mg: **46%** (n=10/22) 48-60 mg: **55%** (n=6/11)	Follicular NHL 0.76-48 mg: **50%** (n=5/10) 12-48 mg: **60%** (n=3/5)
PFS	median PFS 1.5 yrs. for ≥ 60 µg/m²/day (range, 0-10.3) median follow-up 4.6 years	median PFS 3.7 mos. (95% CI: 1.4-7.7) median follow-up 15 months	not reported 82% indolent ongoing responses to 26 months; 70% aggressive ongoing responses to 16 months	not reported median follow-up 1.8 months for indolent and 3.7 months for aggressive		not reported 83% CR ongoing at 3-21 months	not reported 100% CR ongoing at 3-20 months	not reported DLBCL 12-60 mg: 72% in remission at 6 months	not reported Follicular NHL: 100% CR ongoing at 3-13 months
CRS	not reported (20% ≥ Grade 3 CRP increase; n=76)[2]	not reported (13% ≥ Grade 3 CRP increase)	28.9% (All Grades) 1.1% Grade 3; no ≥ Gr. 4	63.5% (All Grades) 3.8% ≥ Grade 3		61% (All Grades) 7% ≥ Grade 3		59% (All Grades) no events ≥ Grade 3	
ICANS-like	22% Grade 3 (no 4/5)[2]	22% Grade 3	1.1% Grade 3	not reported (< 10%)		3.7% Grade 3 (no Grade 4)		2 (3%) Grade 1; 2 (3%) Grade 3	

[1]Dufner V, *et al*. Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al*. J Clin Oncol (2016) 34:1104; [3]Viardot *et al*. Blood (2016) 127(11):1410; [4]Schuster SJ, *et al*. ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al*. ASH 2020, Abstract 403; [6]Bannerji R, *et al*. ASH 2020, Abstract 400; [7]Hutchings M, *et al*. ASH 2020, Abstract 406

Schuster J Hemat Oncol 2021

Updates from ASCO and EHA

- Hodgkin Lymphoma
  - Brentuximab+ AVD
- DLBCL
  - Bispecific Antibodies
- Follicular Lymphoma
  - Bispecific Antibodies
- Mantle cell lymphoma
  - BR-Ibrutinib(SHINE Trial)
  - CAR T cell therapy Update

Mosunetuzumab is efficacious and well tolerated in patients aged <65 years and > 65 years with relapsed and refractory follicular lymphoma and > 2prior therapies : sub group analysis of a pivotal phase II study (Poster 1126)

Efficacy	< 65 years (N=60)	>65 years (N=30)
CR Rate ,% (95% CI)	55 (41.6-67.9)	70 (50.6-85.3)
ORR Rate ,% (95% CI)	76.7 (64-86.6)	86.7(69.3-96.2)
Duration of response Median Months	22.8(8.7-NE)	18.7(9.4- NE)
Duration of CR Median Months	NE (9.1-NE)	18.7(13.7- NE)
18-month PFS	45.4% (22.4-68.4)	48.1% (34.1-62)

Matasar et al , Abstract 1126 EHA 2022

Mosunetuzumab is efficacious and well tolerated in patients aged <65 years and > 65 years with relapsed and refractory follicular lymphoma and > 2prior therapies : sub group analysis of a pivotal phase II study (Poster 1126)

CRS event	< 65 years (N=60)	>65 years (N=30)
Patients with CRS	31 (52)	9 (30)
CRS Grade, n (%) Grade 1 Grade 2 Grade 3 Grade 4	 17 (28) 13 (22) 0 1 (2)	 6 (20) 2 (7) 1 (3) 0
Median duration of CRS, days (range)	3 (1-29)	3 (1-8)
Management approach Tocilizumab Steroids	 5/31 (16) 7/31 (23)	 2/9 (22) 3/9 (33)

Matasar et al , Abstract 1126 EHA 2022

Epcoritamab, a CD3 x CD20 Bispecific Antibody, Plus R^2 in R/R Follicular Lymphoma: Updated Analysis of Phase I/II EPCORE NHL-2 Trial (Poster 7524)

- Analysis of arm 2 in ongoing multicenter, open-label phase Ib/II trial (median follow-up for arm 2a: 8.6 mo; data cutoff: March 25, 2022)

Adults with R/R CD20+ FL; grade 1-3A; stage II-IV; treatment needed based on symptoms or disease burden per GELF criteria; measurable disease by CT/MRI; adequate organ function; ECOG PS 0-2 (N = 74)

→

Dose Escalation (n = 6)

Cohort 2a
Epcoritamab 24 or 48 mg SC*
QW for C1-3, Q2W for C4-9, Q4W for C10+
+
R^2 for C1-12†

→

Dose Expansion (n = 68)

Cohort 2a
Epcoritamab 48 mg SC*
QW for C1-3, Q2W for C4-9, Q4W for C10+
+
R^2 for C1-12†

Cohort 2b
Epcoritamab 48 mg SC*
QW C1-2, Q4W for C3+
+
R^2 for C1-12†

Primary endpoints:
DLT/safety and tolerability; key secondary objective, antitumor activity, **Expansion cohort** : efficacy

Falchi et al, EHA 2022 Abstract 7524

Response rate and CRS

Response	2A (n=28)	2B (n=28)
ORR	25 (93)	26 (93)
CR	19 (70)	17 (61)
PR	6 (22)	9(32)
Stable Disease	2 (7)	1 (4)
Progressive Disease	0	1 (4)

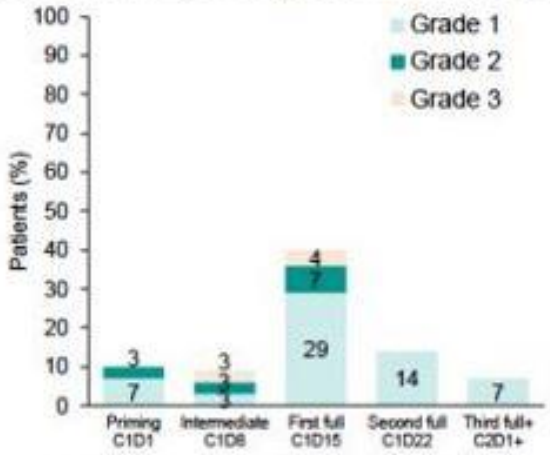
CRS Graded by Lee et al[10] 2019 Criteria in Arm 2a

	Arm 2a N=30
CRS, n (%)	15 (50)
Grade 1	9 (30)
Grade 2	4 (13)
Grade 3	2 (7)
CRS resolution, n (%)	15 (100)
Median time to resolution, d (range)[a]	4 (1–15)
CRS leading to treatment discontinuation, n (%)	1 (3)
Tocilizumab use, n (%)	3 (10)

Data cutoff: March 25, 2022. [a]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS; range is defined by shortest and longest CRS duration.

- CRS was mostly low grade; all cases resolved

CRS Events by Dosing Period in Arm 2a



Data cutoff: March 25, 2022. Priming dose: n=30; intermediate dose: n=29; first full dose and later: n=28.

- CRS occurrence was predictable; most cases occurred following the first full dose with a median time to onset of 2 days (range, 1–5)

Falchi et al, EHA 2022 Abstract 7524

Updates from ASCO and EHA

- Hodgkin Lymphoma
  - Brentuximab+ AVD
- DLBCL
  - Bispecific Antibodies
- Follicular Lymphoma
  - Bispecific Antibodies
- Mantle cell lymphoma
  - BR-Ibrutinib (SHINE Trial)
  - CAR T cell therapy Update

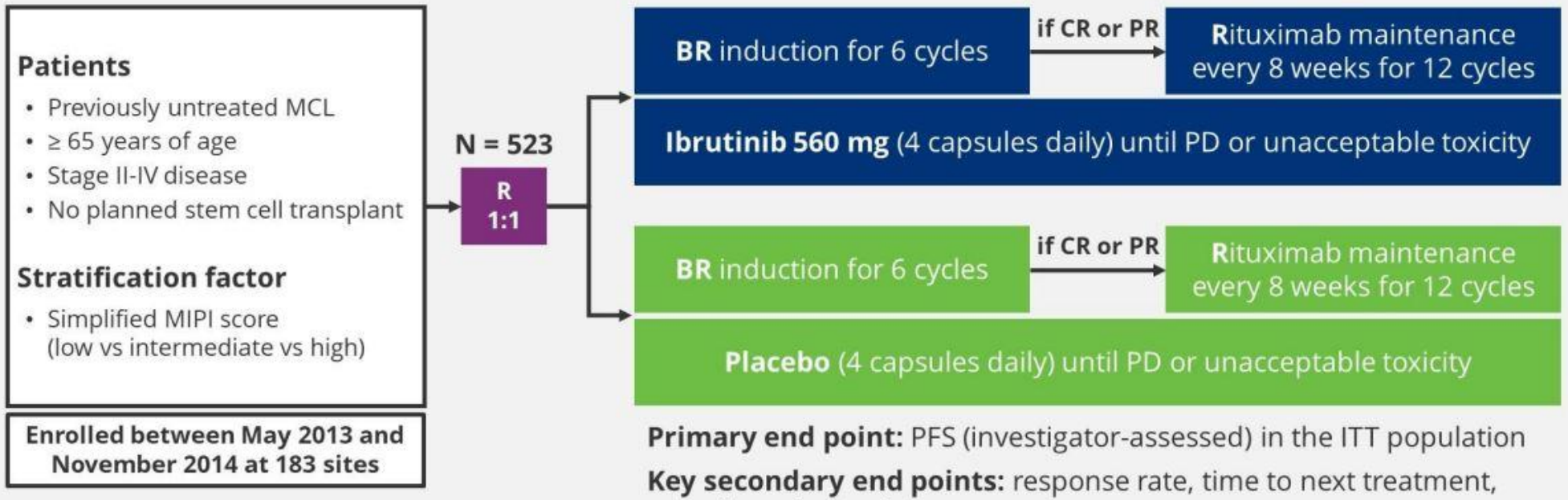
ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, M.D., Ph.D., José-Ángel Hernández-Rivas, M.D., Ph.D., Xiaonan Hong, M.D., Seok Jin Kim, M.D., Ph.D., David Lewis, F.R.C.Path., Ph.D., Yuko Mishima, M.D., Ph.D., Muhit Özcan, M.D., Guilherme F. Perini, M.D., Christopher Pocock, M.D., Ph.D., Yuqin Song, M.D., Ph.D., Stephen E. Spurgeon, M.D., John M. Storring, M.D., Jan Walewski, M.D., Jun Zhu, M.D., Ph.D., Rui Qin, Ph.D., Todd Henninger, Ph.D., Sanjay Deshpande, M.D., Angela Howes, Ph.D., Steven Le Gouill, M.D., Ph.D., and Martin Dreyling, M.D., for the SHINE Investigators*

Wang NEJM 2022

SHINE: A Randomized, Double-Blind, Phase III Study



Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

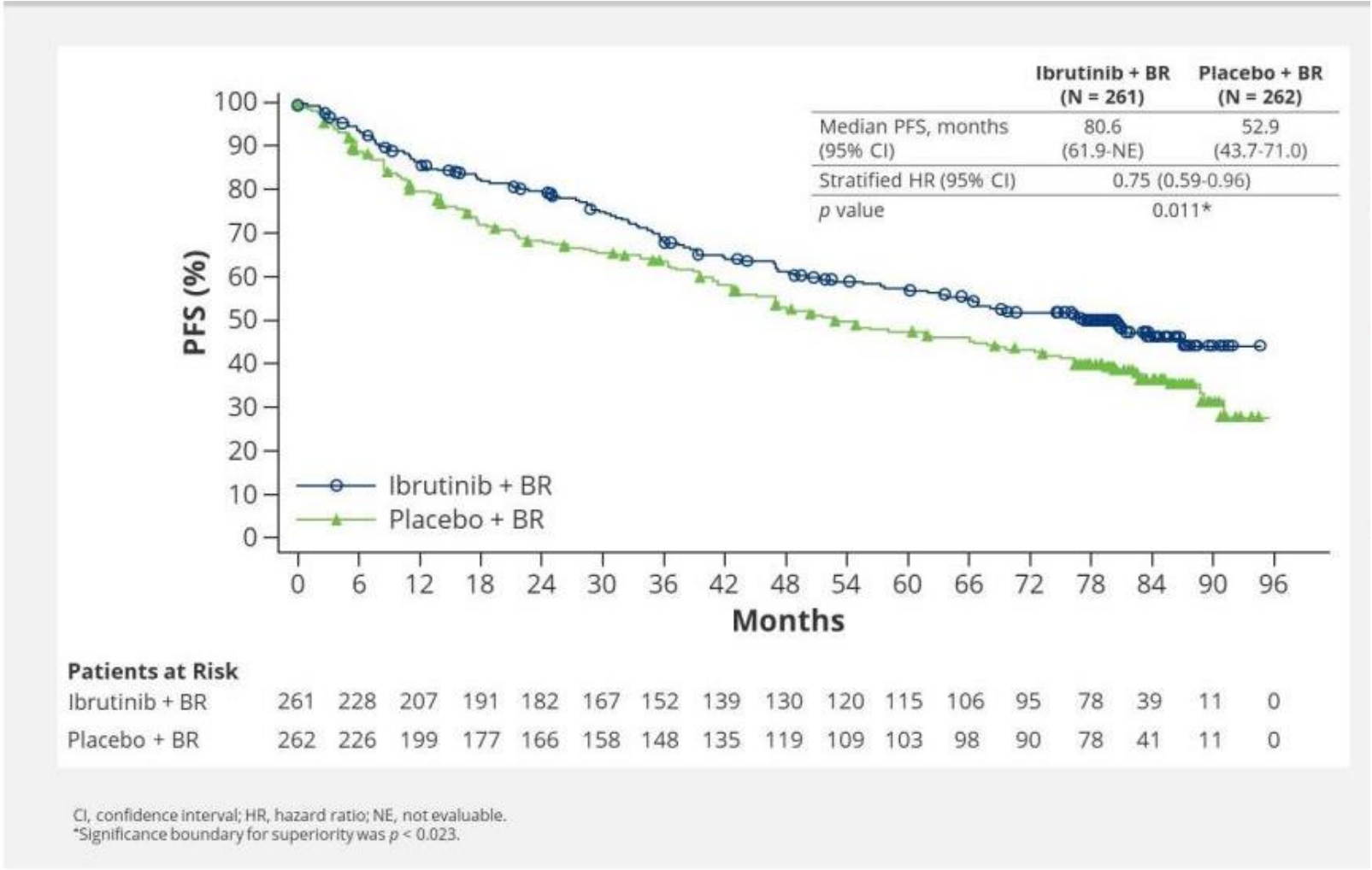
Wang ASCO 2022 Abstract LBA 7502

Baseline characteristics

Characteristic	Ibrutinib Group (N=261)	Placebo Group (N=262)
Age		
Median (range) — yr	71 (65–86)	71 (65–87)
≥70 yr — no. (%)	162 (62.1)	154 (58.8)
≥75 yr — no. (%)	74 (28.4)	82 (31.3)
Male sex — no. (%)	178 (68.2)	186 (71.0)
Race — no. (%)†		
White	199 (76.2)	206 (78.6)
Black	2 (0.8)	1 (0.4)
Asian	47 (18.0)	42 (16.0)
Other or multiple	3 (1.1)	4 (1.5)
Not reported	10 (3.8)	9 (3.4)
Median time from initial diagnosis to randomization (range) — mo	1.4 (0.2–116.1)	1.5 (0.1–66.1)
ECOG performance-status score — no. (%)‡		
0	134 (51.3)	141 (53.8)
1 or 2	127 (48.7)	121 (46.2)
Disease stage — no. (%)		
II	9 (3.4)	14 (5.3)
III	19 (7.3)	22 (8.4)
IV	233 (89.3)	226 (86.3)

Wang NEJM 2022

Progression free survival (PFS)

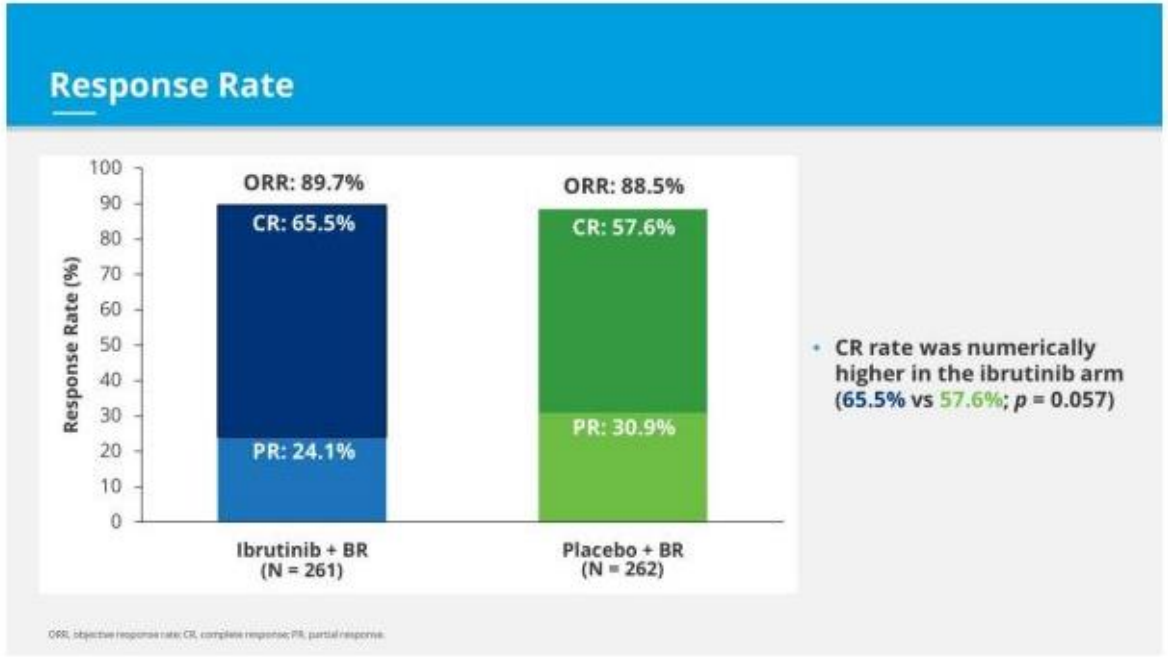


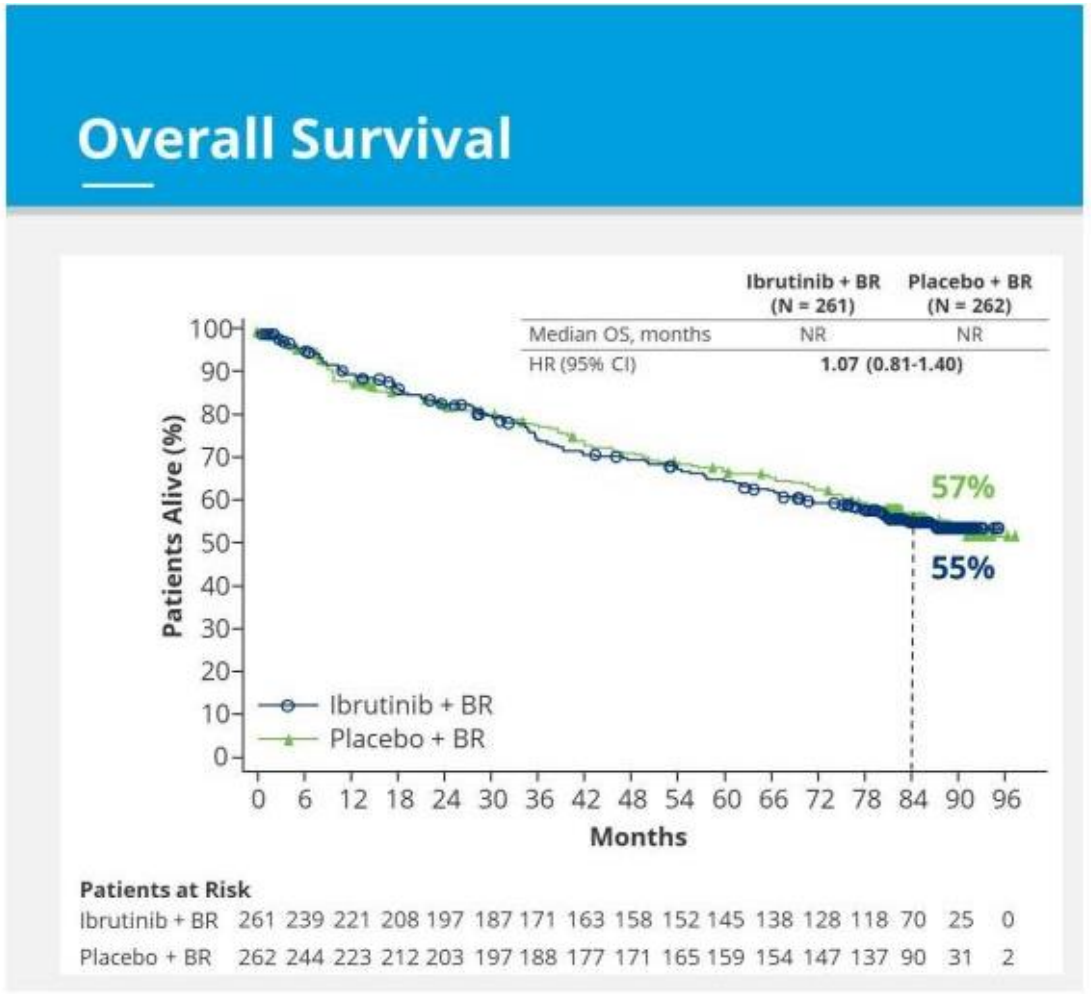
CI, confidence interval; HR, hazard ratio; NE, not evaluable.
*Significance boundary for superiority was $p < 0.023$.

Improvement in PFS by 2.3 years

Wang ASCO 2022 Abstract LBA 7502

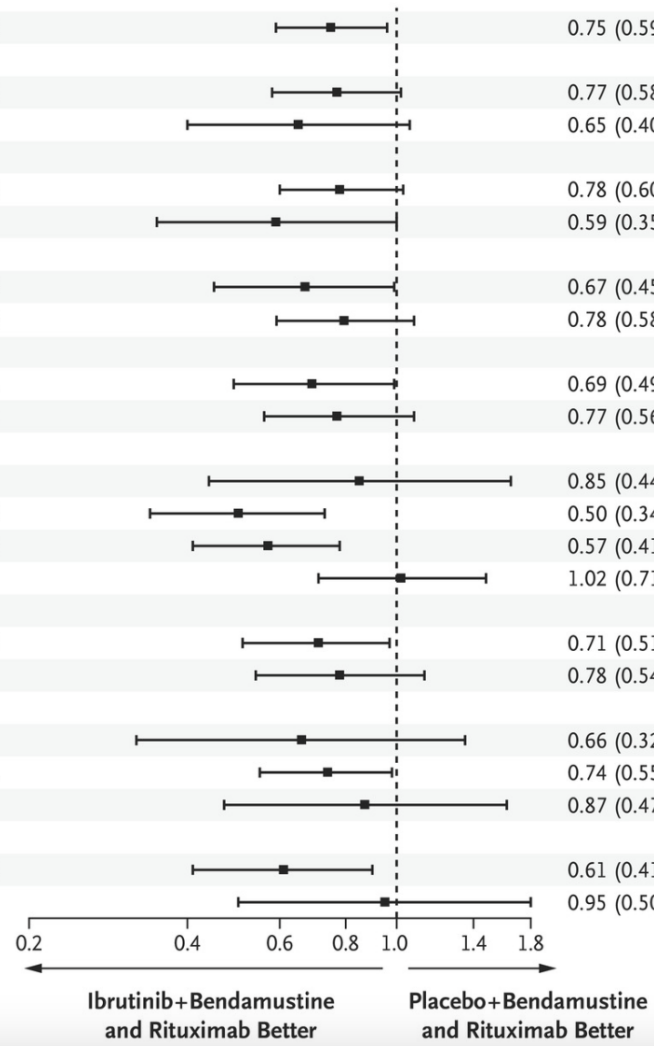
Response Rate and Overall survival





Wang ASCO 2022 Abstract LBA 7502

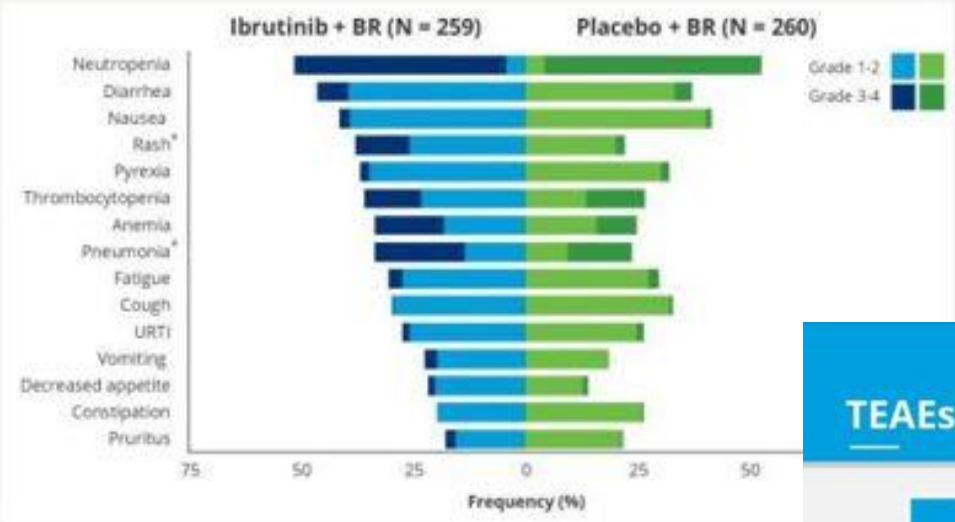
Subgroup	Ibrutinib Group	Placebo Group	Hazard Ratio for Progression or Death (95% CI)
	no. of events/no. of patients		
All patients	116/261	152/262	0.75 (0.59–0.96)
Sex			
Male	88/178	111/186	0.77 (0.58–1.02)
Female	28/83	41/76	0.65 (0.40–1.06)
Race			
White	92/199	118/206	0.78 (0.60–1.03)
Non-White	24/62	34/56	0.59 (0.35–1.00)
Age			
<70 yr	39/99	62/108	0.67 (0.45–0.99)
≥70 yr	77/162	90/154	0.78 (0.58–1.06)
ECOG performance-status score			
0	53/134	72/141	0.69 (0.49–0.99)
1–2	63/127	80/121	0.77 (0.56–1.08)
Simplified MIPI score category at baseline			
Low risk	15/44	21/46	0.85 (0.44–1.65)
Intermediate risk	42/124	76/129	0.50 (0.34–0.73)
Low or intermediate risk	57/168	97/175	0.57 (0.41–0.78)
High risk	59/93	55/87	1.02 (0.71–1.48)
Tumor bulk			
<5 cm in largest diameter	64/165	90/163	0.71 (0.51–0.97)
≥5 cm in largest diameter	51/95	62/98	0.78 (0.54–1.13)
Histologic features			
Blastoid or pleomorphic	12/19	20/26	0.66 (0.32–1.35)
Nonblastoid or nonpleomorphic	86/211	110/201	0.74 (0.55–0.98)
Unknown	18/31	22/35	0.87 (0.47–1.62)
TP53 status			
Nonmutated	42/114	62/105	0.61 (0.41–0.90)
Mutated	21/26	17/24	0.95 (0.50–1.80)



Wang NEJM 2022

Adverse event profile

Common Treatment-Emergent Adverse Events (≥ 20%)



TEAEs of Clinical Interest With BTKis

	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any bleeding*	42.9%	3.5%	21.5%	1.5%
Major bleeding	5.8%	–	4.2%	–
Atrial fibrillation*	13.9%	3.9%	6.5%	0.8%
Hypertension	13.5%	8.5%	11.2%	5.8%
Arthralgia	17.4%	1.2%	16.9%	0

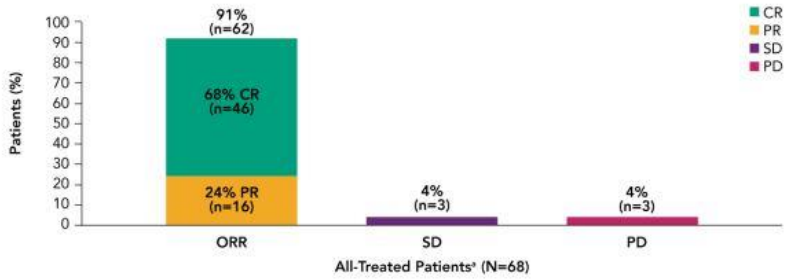
Wang ASCO 2022 Abstract LBA 7502

SHINE – Is it Shiny enough?

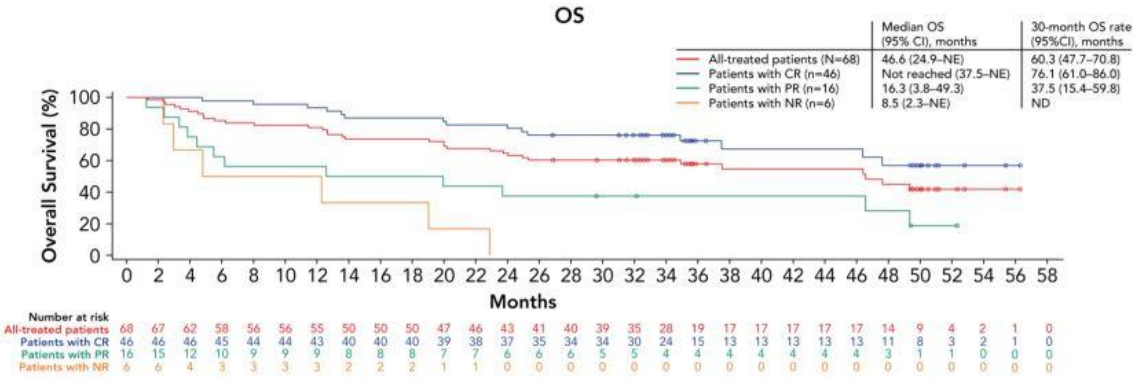
- Improved PFS for combination but more toxicities compared with bendamustine/rituximab alone.
- No improvement in overall survival: sequential therapy with ibrutinib at time of relapse - similar long-term outcomes.
- Combination with next generation BTKi being explored
- Explore role of chemotherapy free approach in combination regimens

Zuma -2: CART cell therapy for mantle cell lymphoma - 3 year follow up

Zuma-2: Objective Response Rate (ORR) in All Treated Patients (N=68)
Overall Survival according to response

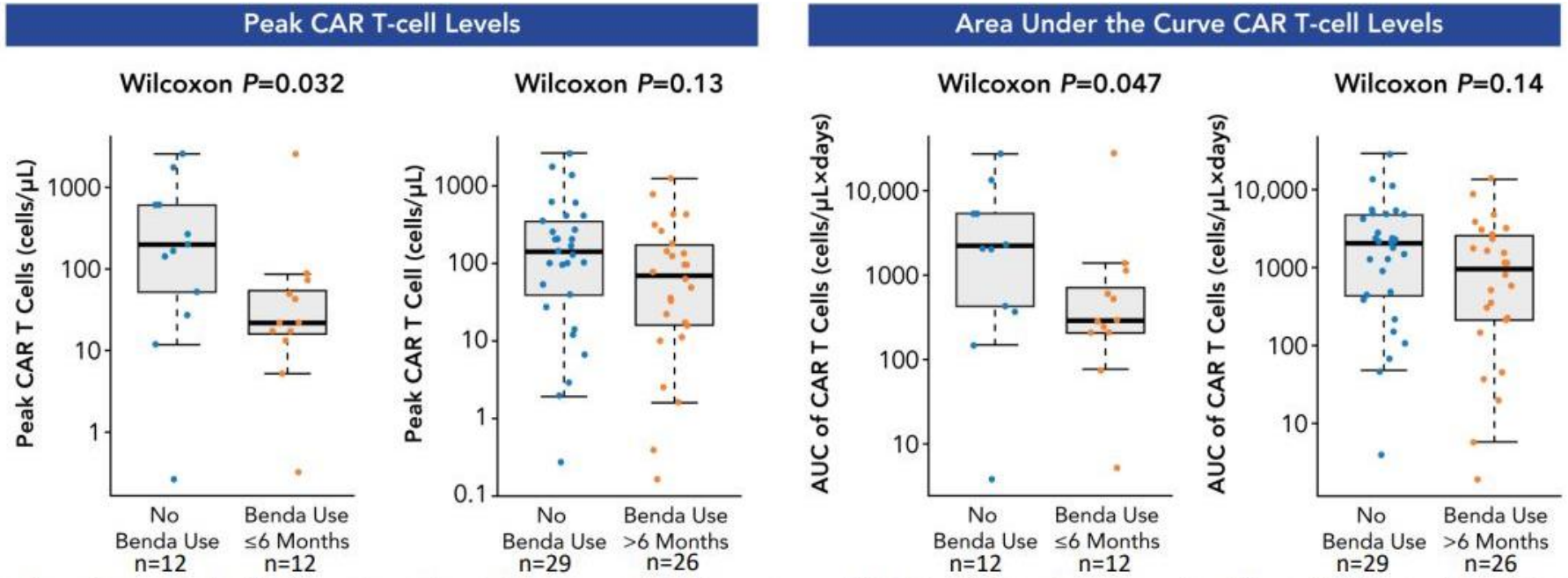


The median progression-free survival (PFS) was 25.8 months



Wang ASCO 2022 Abstract 7502

CAR-T Pharmacokinetics in relation to bendamustine



- An exploratory analysis found peak and area under the curve CAR T-cell levels were significantly lower in patients with prior bendamustine use within 6 months of CAR T-cell infusion compared to patients with no prior bendamustine use. Results were consistent when analyzed using propensity score matching

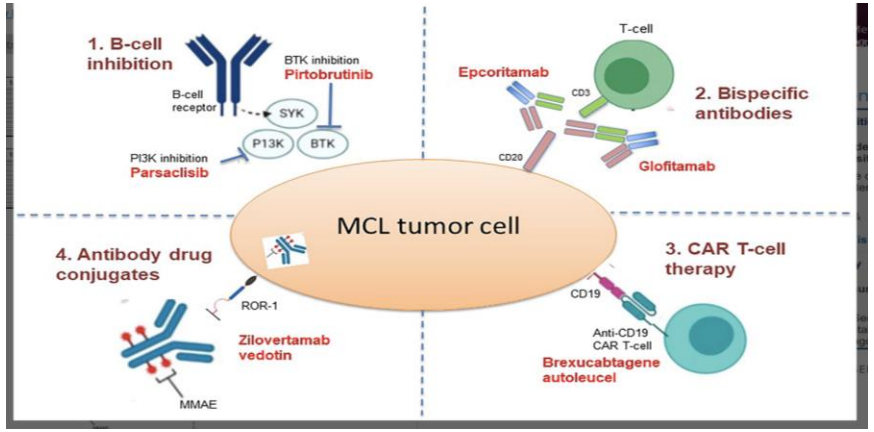
Patients could benefit from longer time spans between prior bendamustine and cell therapy, though further analyses are warranted.

AUC, area under the curve; Benda, bendamustine; CAR, chimeric antigen receptor.

Wang ASCO 2022 Abstract 7502

Mantle cell lymphoma in 2022

- Newly diagnosed
  - Induction chemotherapy based on various factors including biology of disease, high risk features, intention to transplant, age, functional status, comorbidities
  - Role of addition of novel agents like BTK inhibitor unclear
- Relapsed/Refractory disease
  - Novel agents: BTKi, in combination or sequentially with venetoclax
  - CAR-T cell therapy
  - Clinical trial



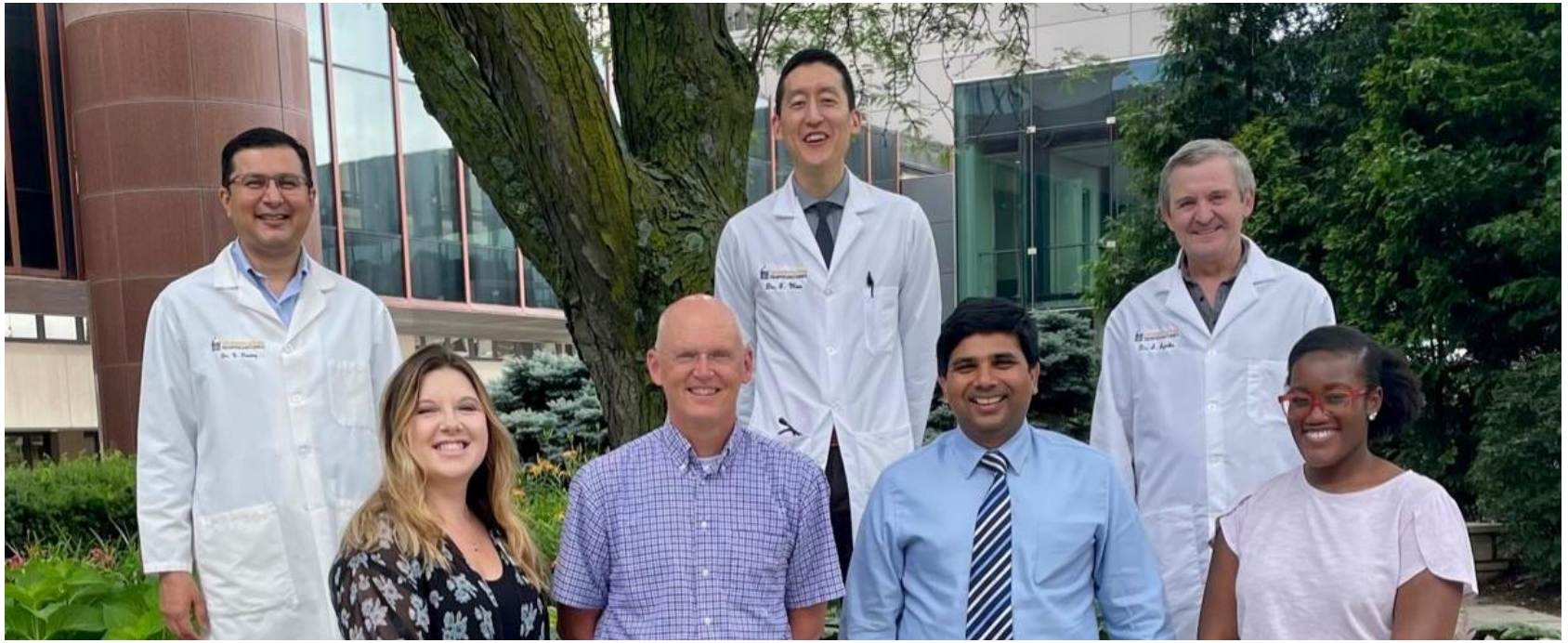
Kumar et al, American Society of clinical Oncology Educational Book 42 (May 13, 2022) 614-628

Clinical trials open at UlHC

- Newly Diagnosed DLBCL- Safety & Efficacy of Glofitamab in Combination with Rituximab + CHOP in ctDNA Untreated DLBCL
- Newly Diagnosed CD 30 negative T cell lymphoma – Duvelisib or azacitidine in combination with chemotherapy
- Newly Diagnosed Primary mediastinal lymphoma- Nivolumab in combination with chemotherapy
- Newly diagnosed Hodgkin – S1826 : Nivolumab or Brentuximab in combination with chemotherapy for advanced stage Hodgkin
- Relapsed T cell lymphoma- Lacutamab for KIR3DL2 expressing T cell lymphoma

- Relapsed Non-Hodgkin Lymphoma
  - Bispecific antibody studies: Epcoritamab, Odronextamab, Plamotamab in combination with tafasitmab and lenalidomide
  - Cellular therapy: CD 20 CAR T , Allogenic CD 19 CART, NK cell study with rituximab.
  - Autologous CD19 CART for relapsed Richter and Burkitt , Waldenstrom macroglobulinemia and Hairy cell leukemia

Acknowledgement and Questions



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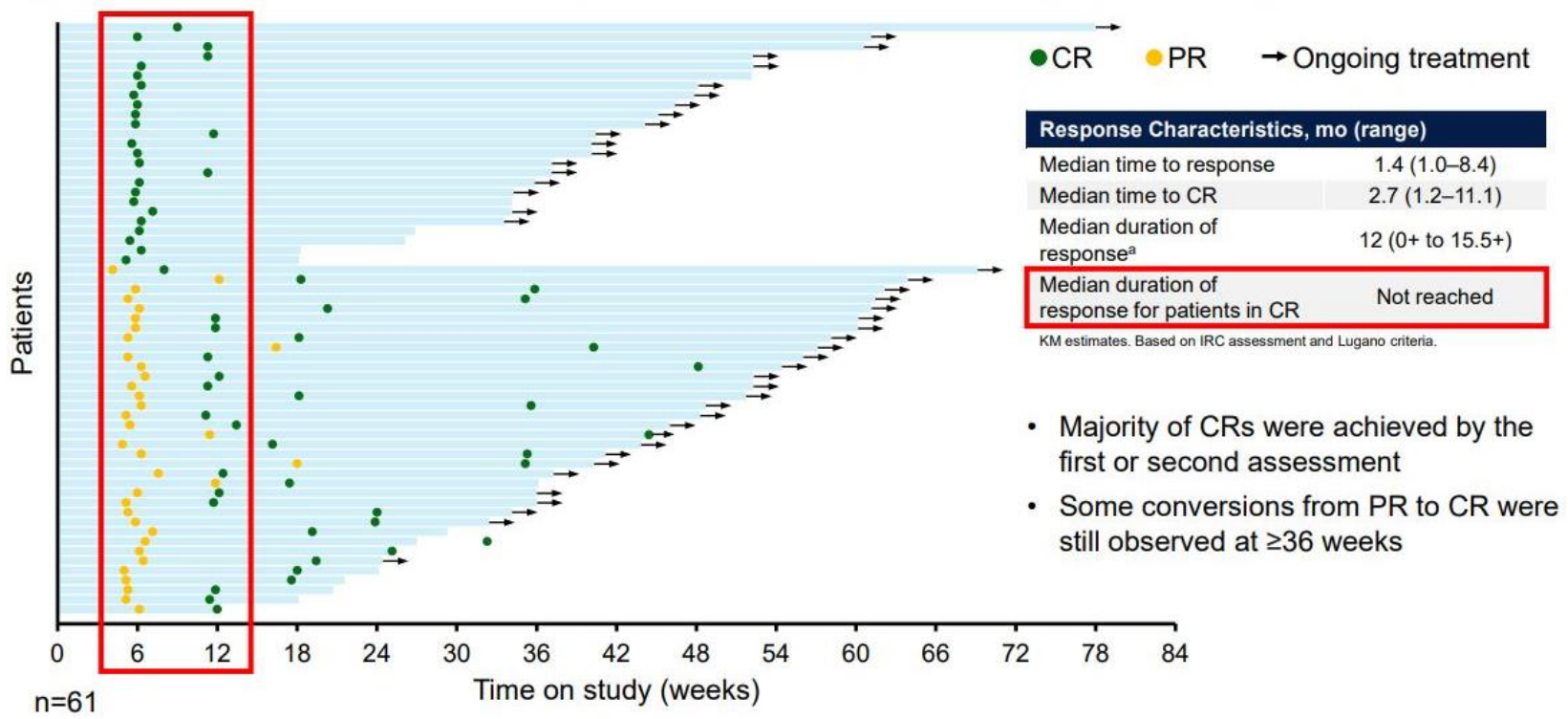
Deeper and Durable responses



Response Characteristics, mo (range)	
Median time to response	1.4 (1.0–8.4)
Median time to CR	2.7 (1.2–11.1)
Median duration of response[a]	12 (0+ to 15.5+)
Median duration of response for patients in CR	Not reached

KM estimates. Based on IRC assessment and Lugano criteria.

- Majority of CRs were achieved by the first or second assessment
- Some conversions from PR to CR were still observed at ≥36 weeks

[a]Median duration of response data not yet mature.

Thieblemont EHA 2022 LBA Abstract 2364