LYMPHOMA: STATE OF THE ART

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Presentation Outline

- Hodgkin Lymphoma
  - PD-1 blockade improves PFS for advanced stage cHL
- Diffuse Large B-cell Lymphoma
  - POLARIX: a new standard of care?
  - CART cells improve overall survival as 2nd line therapy
  - CD20-CD3 Bispecific Antibodies approved for relapsed/refractory disease
- Follicular Lymphoma
  - Mosunetuzumab (CD20-CD3 bispecific antibody) approved in 3rd line
- Mantle Cell Lymphoma
  - TRIANGLE and pirtobrutinib

HODGKIN LYMPHOMA

Hodgkin Lymphoma Management When My Career Started

Brentuximab vedotin: the first novel immunotherapy for Hodgkin lymphoma

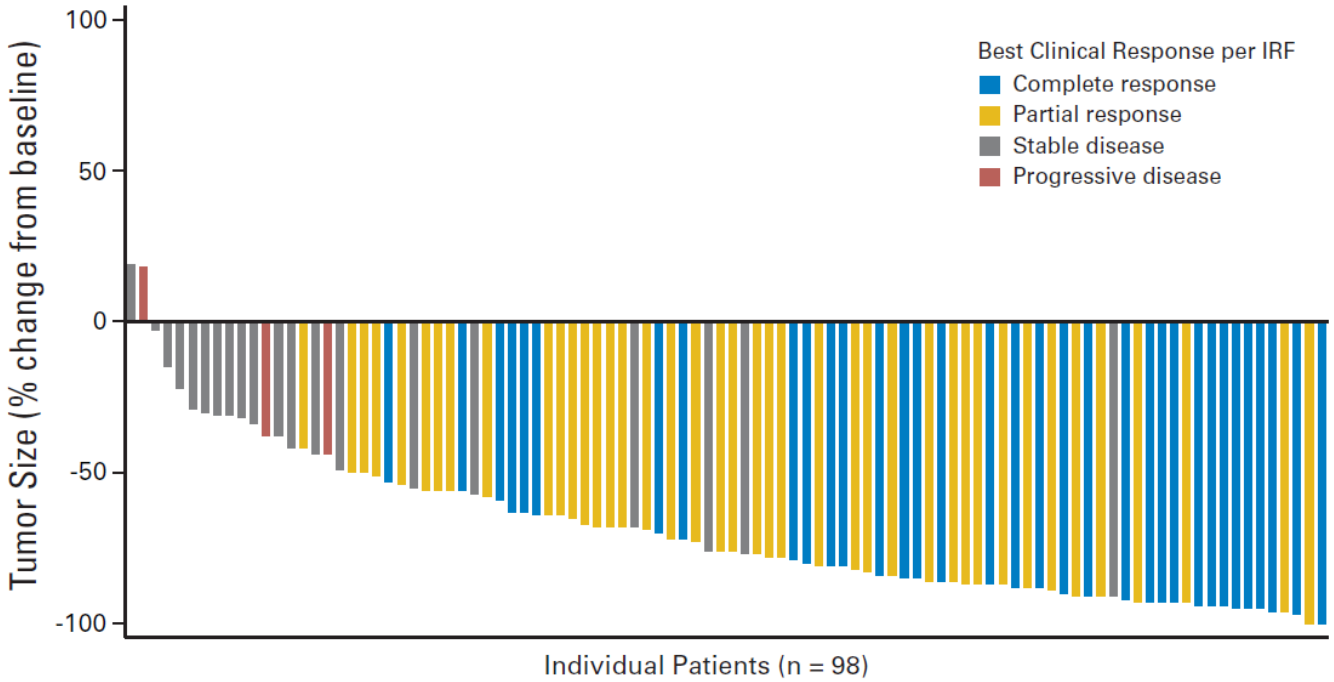
Late R/R HL, pivotal Ph 2

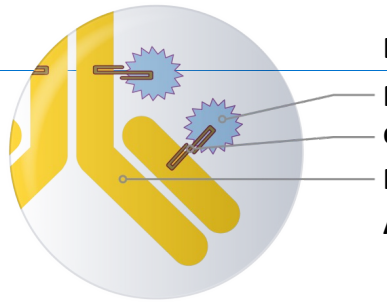
n = 102

ORR 75%

CR 34%

- **Safe as bridge to alloHCT**



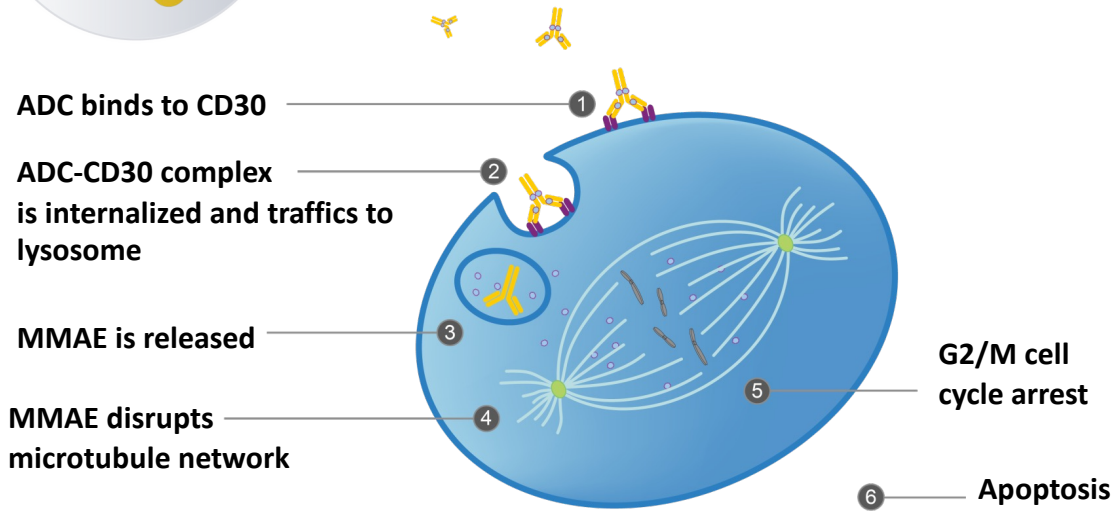


Brentuximab vedotin antibody-drug conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

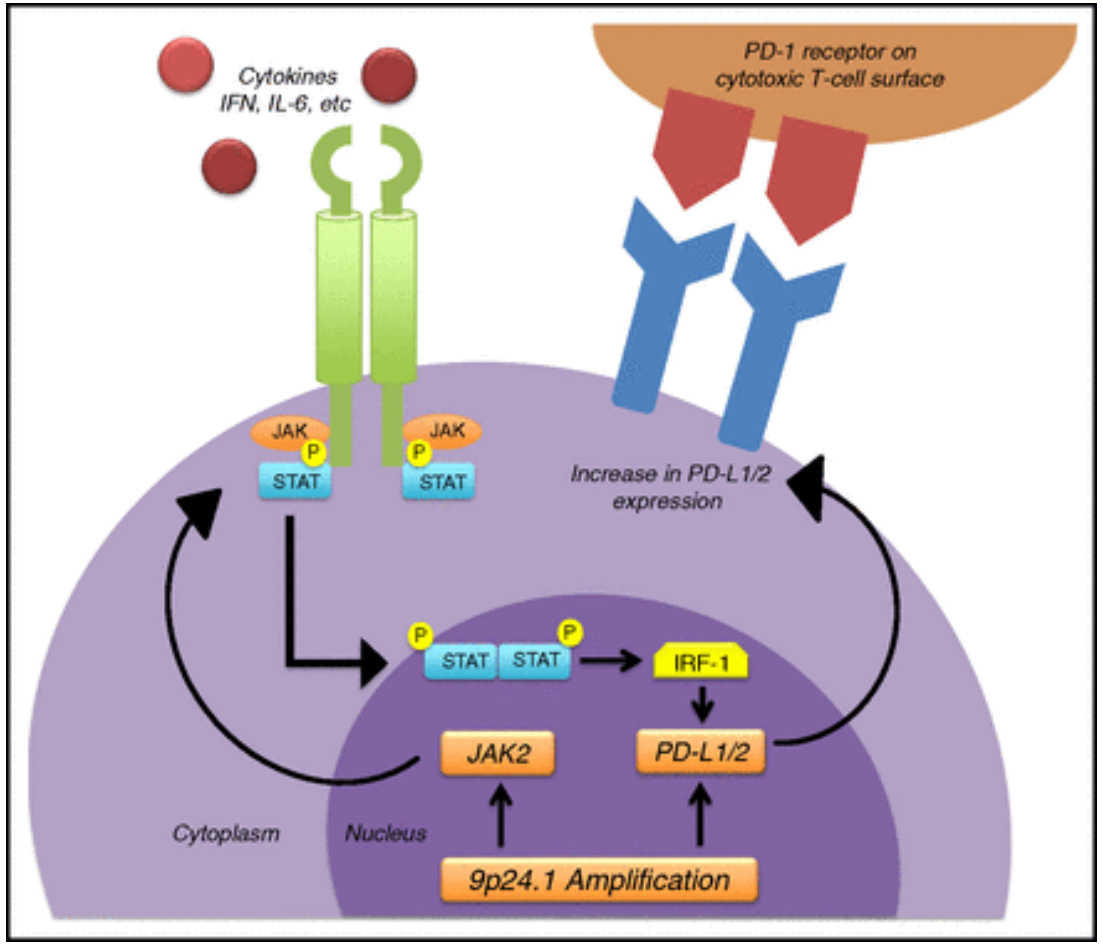
Anti-CD30 monoclonal antibody



Younes et al. *JCO* 2012

PD-1 in Hodgkin Lymphoma

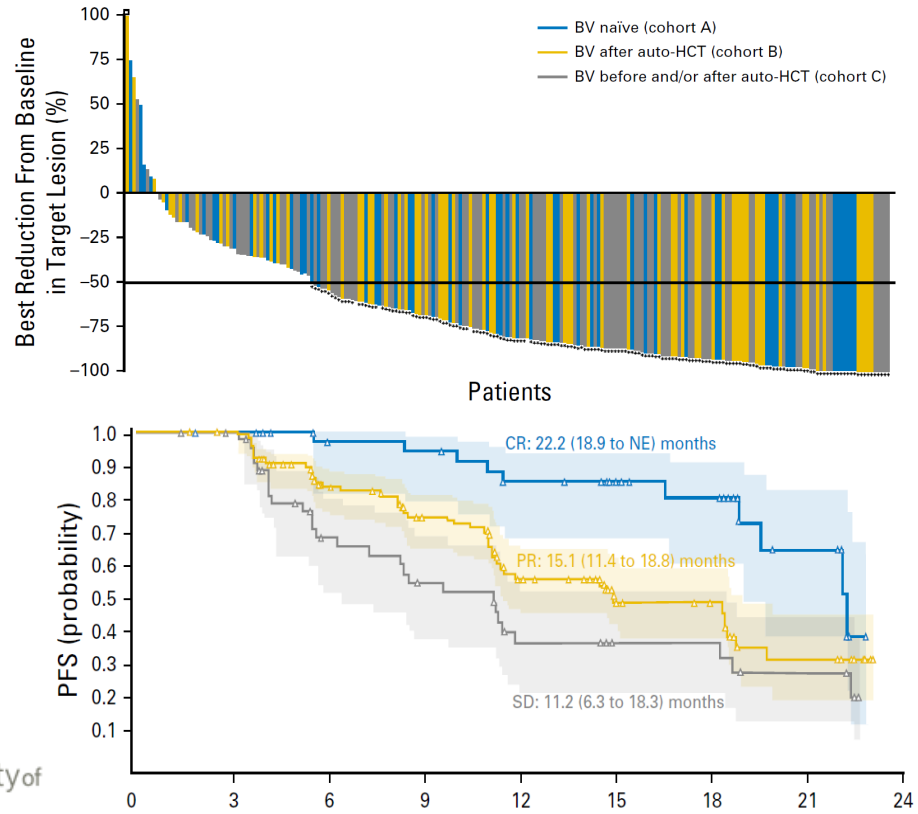
- 9p24.1 alteration directly results in PD-L1/2 expression on RS cells
- 9p24.1 alteration increases JAK2 expression, which can induce PD-L1/2 expression on RS cells
- EBV infection induces PD-L1 expression on RS cells
- Tumor-associated macrophages express PD-L1 in the HL TME



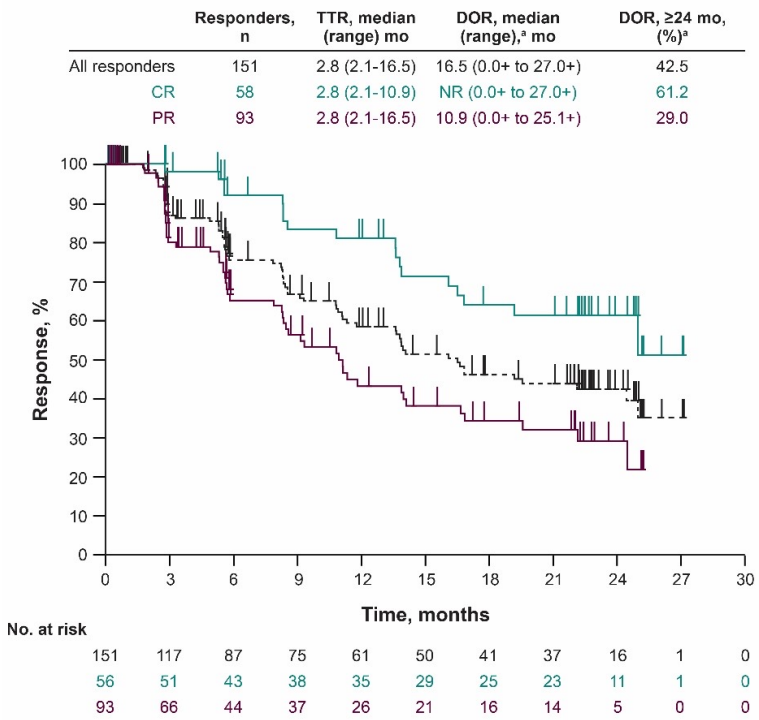
- Cabanillas F and Rivera N. Blood 2017, Green MR et al Blood 2010, Green MR et al. CCR 2012, Carey CD et al. Blood 2017

PD-1 blockade is effective in R/R HL

Nivolumab
Late R/R HL, pivotal Ph 2
n = 243
ORR 69%, CR 16%



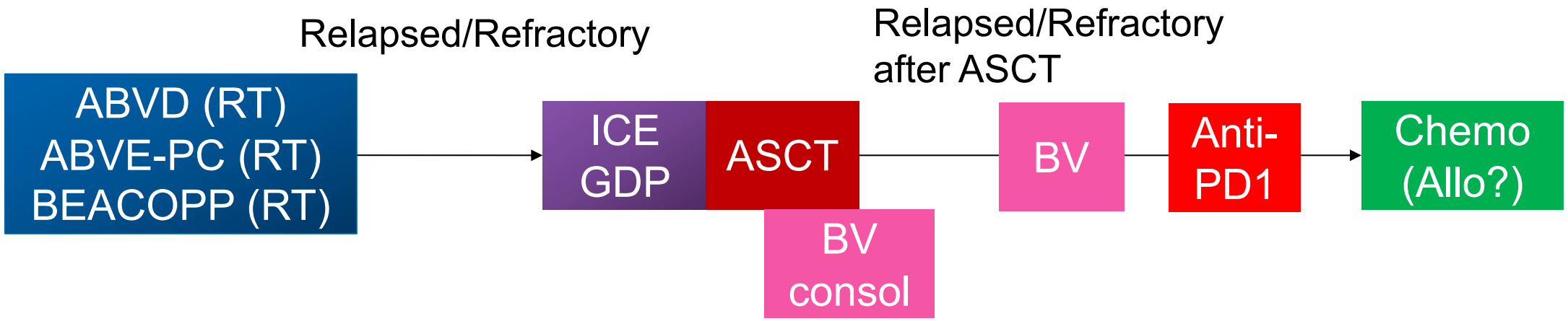
Pemrolizumab
Late R/R HL, pivotal Ph 2
n = 210
ORR 69%, CR 22%



	Responders, n	TTR, median (range) mo	DOR, median (range),[a] mo	DOR, ≥24 mo, (%)[a]
All responders	151	2.8 (2.1-16.5)	16.5 (0.0+ to 27.0+)	42.5
CR	58	2.8 (2.1-10.9)	NR (0.0+ to 27.0+)	61.2
PR	93	2.8 (2.1-16.5)	10.9 (0.0+ to 25.1+)	29.0

Armand P et al., JCO 2018
Chen R. et al, JCO 2017

Hodgkin Lymphoma Management circa 2016



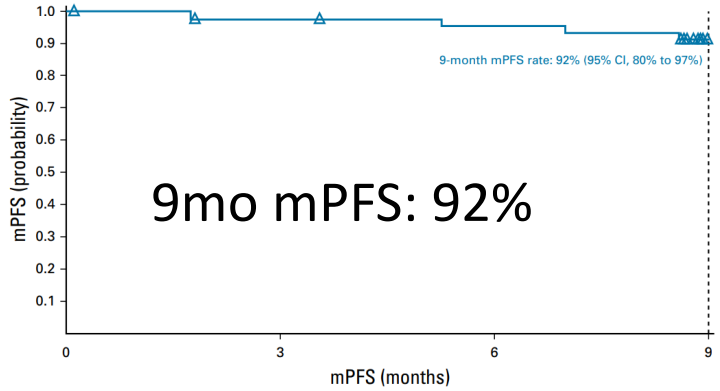
Novel Salvage Regimens for R/R cHL

	Regimen	% PET-neg	PFS	Reference
Sequential BV and chemo	BV->augICE	83% 27% (DS1-2)	82% @ 3 yrs	Moskowitz AJ, et al. Blood 2017; Lancet Oncol 2015
	BV->ICE/chemo	75% 43% (DS1-3)	67% @ 2 yrs	Chen R, et al. BBMT 2015 Herrera AF, et al. Ann Oncol 2018
BV Combos	BV-benda	74%	62.6% @ 2 yrs 69.8% (ASCT pts)	LaCasce A, et al. Blood 2018
	BV plus: ICE DHAP ESHAP	74% 79% 70%	80% @ 2 yrs 76% @ 2 yrs 71% @ 2.5 yrs	Lynch R, et al. Lancet Haematology 2021 Hagenbeek, et al. Haematologica 2020 Garcia-Sanz, et al. Ann Oncol 2019
BV+Nivo	BV+Nivo	67%	77% @ 3 yrs	Advani RH, et al. Blood 2021, Herrera AF et al. Blood 2018
Sequential PD1/chemo	Nivo->NICE	91%	72% @ 2 yrs	Mei MG, et al. Blood 2022
Anti-PD1 + Chemo	Pem+GVD Pem+ICE Nivo+ICE (hi-risk) Tisle+GemOx	95% 86.5% 88% 97%	100% @ 13.5m 88% @ 2 yrs 90% @ 1yr 96% @ 1yr	Moskowitz AJ, et al. JCO 2020 Bryan LJ, et al. JAMA Oncology 2023 Mei MG, et al. ASH 2022 Ding K, et al. Haematologica 2023

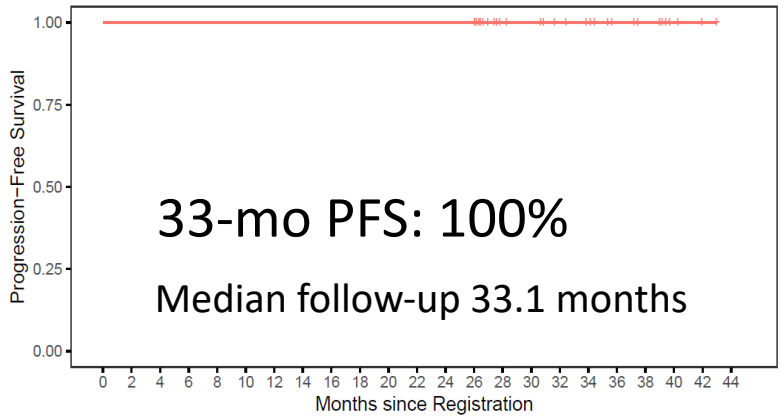
Incorporating PD-1 blockade into initial cHL therapy is well-tolerated and highly effective

- Studies of frontline PD-1 blockade in cHL have been promising[10,11,12,13]
  - N-AVD well-tolerated
  - Excellent PFS

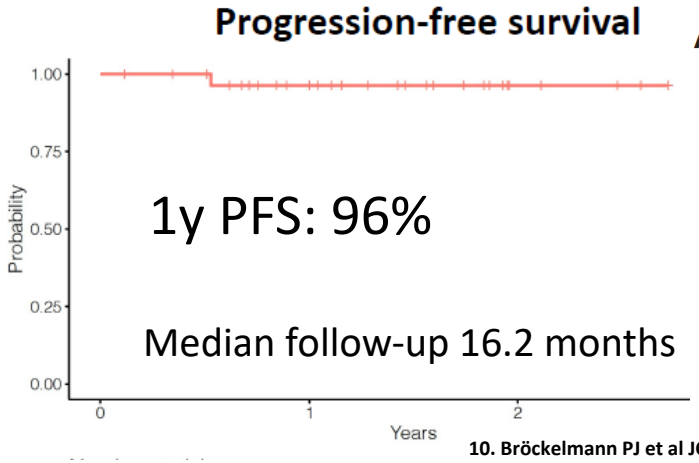
1L Nivolumab-AVD in advanced stage cHL



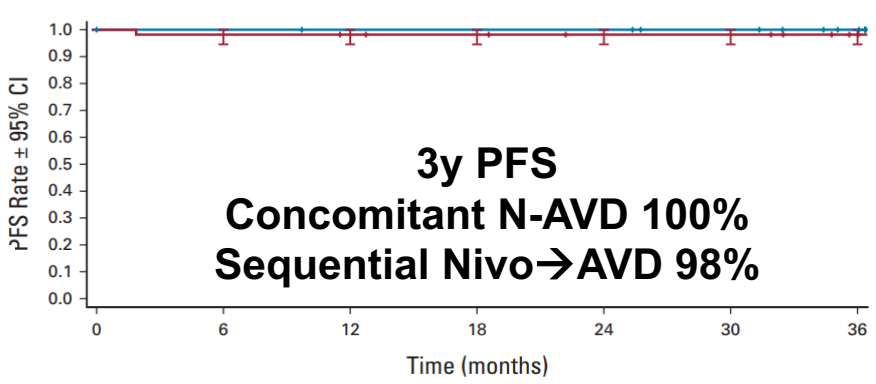
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL



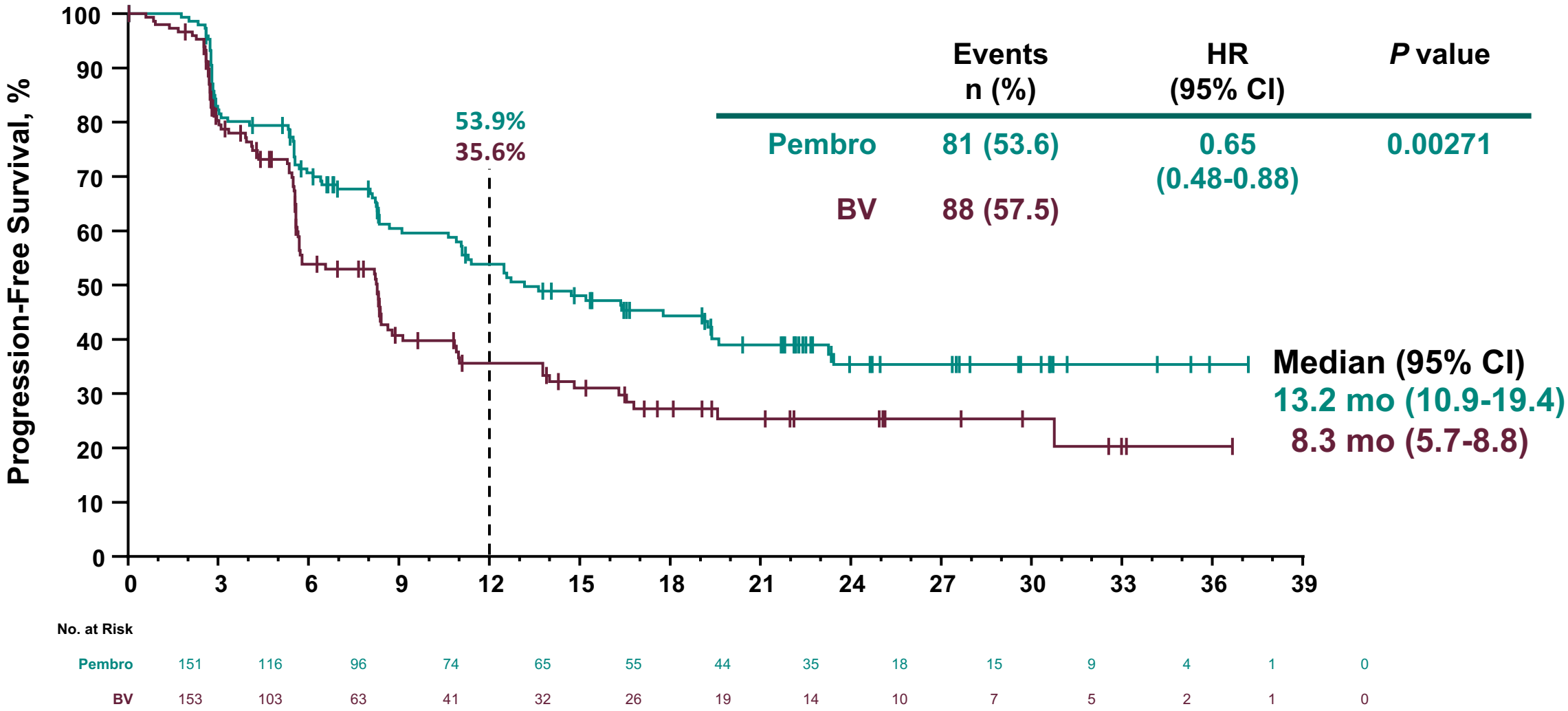
1L Nivolumab-AVD in early stage cHL



10. Bröckelmann PJ et al JCO. 2023 11. Ramchandren R et al JCO 2019 12. Allen PB, et al Blood. 2021 13. Lynch RC et al Blood 2023

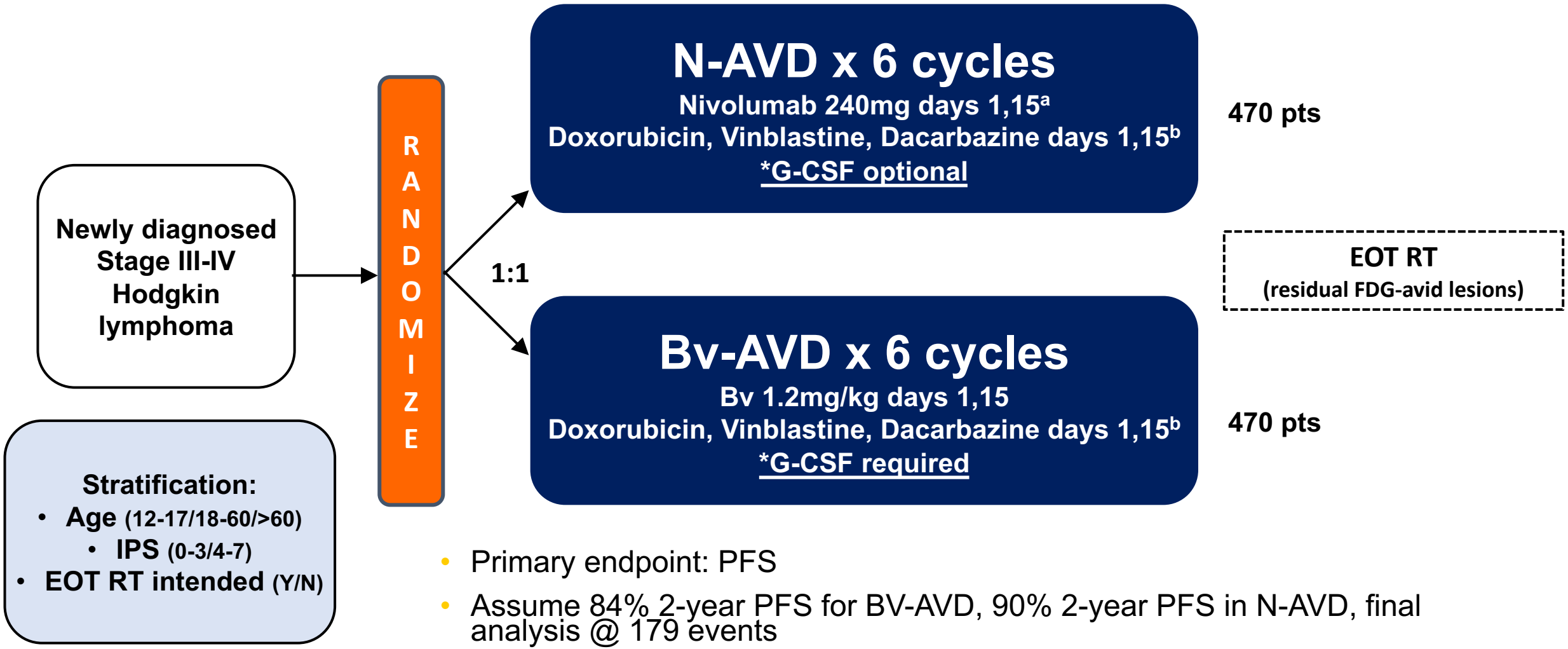
Presented by: Alex F. Herrera, MD

PD-1 superior to BV in R/R HL



Kuruvilla J et al ASCO 2020, Lancet Oncol 2021

S1826 Study Design



- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

Herrera, AF et al. ASCO 2023.

[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

S1826 Baseline Characteristics

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	120 (25%)	117 (24%)
18-60 years	323 (66%)	323 (66%)
≥ 61 years	46 (9%)	47 (10%)
Female Sex	218 (45%)	213 (44%)
Race		
White	375 (77%)	364 (75%)
Black	57 (12%)	56 (11%)
Asian	11 (2%)	17 (3%)
Other/Unknown	46 (9%)	50 (10%)
Hispanic	68 (14%)	59 (12%)

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Stage		
III	187 (38%)	167 (34%)
IV	301 (62%)	317 (65%)
Not reported	1 (0.2%)	3 (1%)
B symptoms present	286 (58%)	274 (56%)
IPS Score		
0-3	331 (68%)	330 (68%)
4-7	158 (32%)	157 (32%)
Bulky disease > 10cm	155 (32%)	131 (27%)
HIV+	10 (2%)	5 (1%)

Representative study, inclusive of high-risk pts

Herrera, AF et al. ASCO 2023.

AEs of interest: Hematologic

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	268 (55%)	227 (47%)	152 (32%)	118 (25%)
Anemia	185 (38%)	29 (6%)	207 (44%)	42 (9%)
Thrombocytopenia	48 (10%)	8 (2%)	82 (17%)	15 (3%)
Received G-CSF	265 (54%)		463 (95%)	
Bone pain	39 (8%)		94 (20%)	

More neutropenia after N-AVD

More growth factor use, bone pain in Bv-AVD arm

Herrera, AF et al. ASCO 2023.

AEs of interest: Infectious

Toxicity	N-AVD n = 483	Bv-AVD n = 473
Febrile Neutropenia	26 (5%)	32 (7%)
Sepsis	9 (2%)	16 (3%)
Infections/Infestations	22 (5%)	36 (8%)

No increased infectious toxicity in N-AVD arm

Herrera, AF et al. ASCO 2023.

AEs of Interest: Peripheral Neuropathy

Toxicity	N-AVD n = 483			Bv-AVD n = 473		
	Gr 1 (%)	Gr 2 (%)	Gr ≥ 3 N (%)	Gr 1 (%)	Gr 2 (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	97 (20%)	35 (7%)	6 (1%)	117 (25%)	108 (23%)	37 (9%)
Peripheral motor neuropathy	12 (2%)	7 (1%)	1 (0%)	12 (3%)	17 (4%)	6 (1%)

More and higher grade neuropathy in Bv-AVD arm

Herrera, AF et al. ASCO 2023.

AEs of Interest: Immune/Other

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	**156 (32%)**	**22 (5%)**	**194 (41%)**	**22 (5%)**
AST increased	**120 (25%)**	**12 (2%)**	**153 (32%)**	**13 (3%)**
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**33 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**14 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

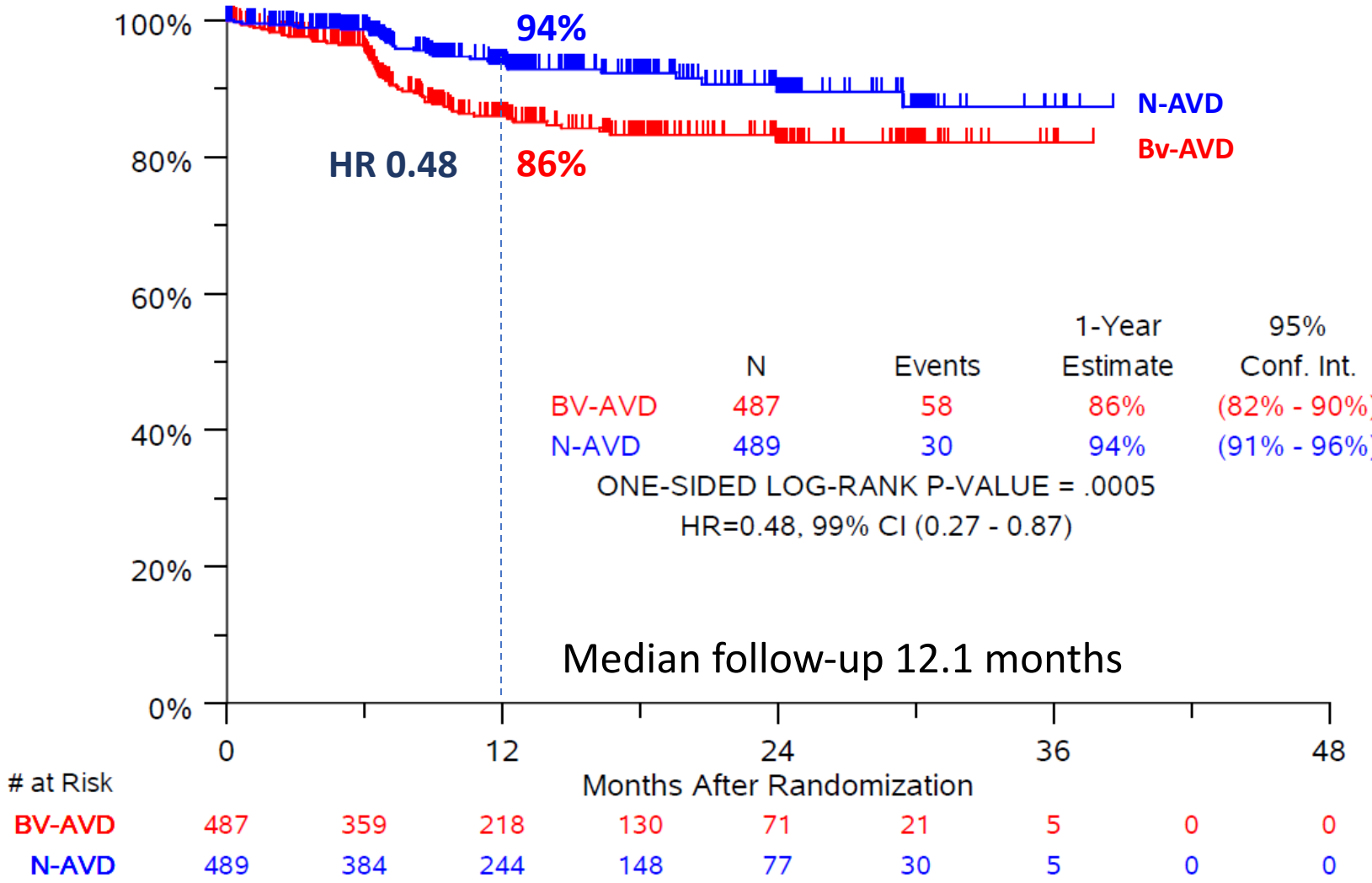
Herrera, AF et al. ASCO 2023.

Treatment Discontinuation and Deaths

Disposition	N-AVD (n=489) N (%)	Bv-AVD (n=487) N (%)
Treatment ongoing	22	30
Completed treatment	428	400
Discontinued all treatment early	**39 (8%)**	**57 (12%)**
Adverse event	22 (4%)	18 (4%)
Refusal unrelated to AE	10	14
Progression/relapse	**0 (0%)**	**7 (1.4%)**
Death on treatment	**2 (0.4%)**	**8 (1.6%)**
Other – not protocol specified	5	10
Discontinued Bv or Nivolumab	**53 (11%)**	**109 (22%)**
Received radiotherapy	**2 (0.4%)**	**4 (0.8%)**

Herrera, AF et al. ASCO 2023.

N-AVD improves PFS compared to Bv-AVD

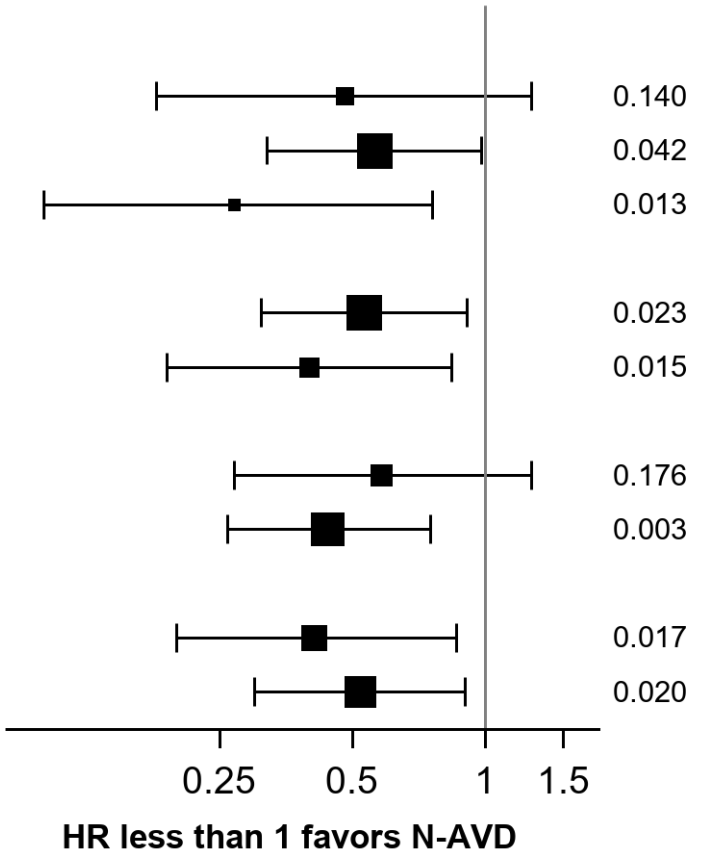


1-year PFS
N-AVD 94%
Bv-AVD 86%

Herrera, AF et al. ASCO 2023.

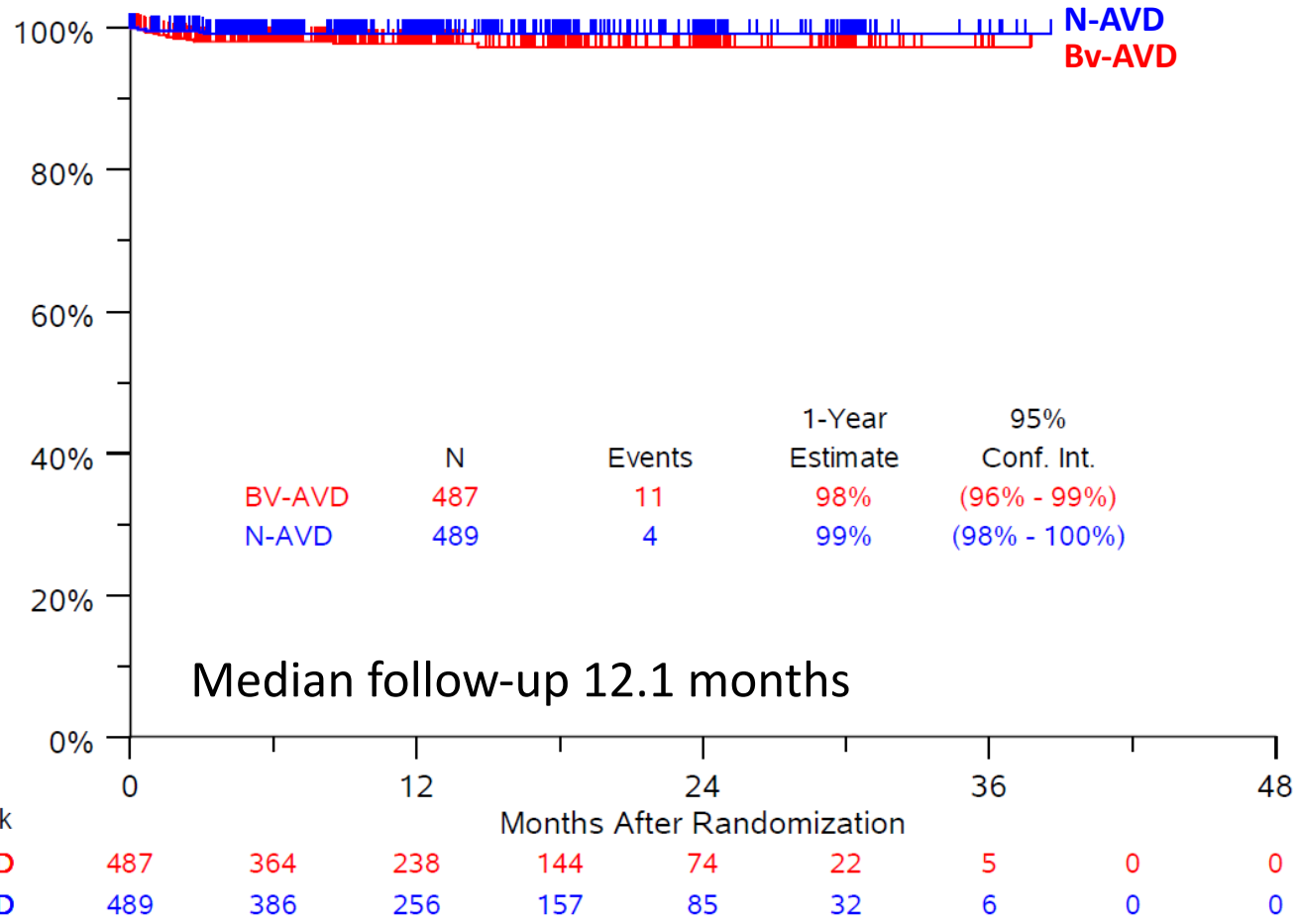
PFS benefit consistent across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera, AF et al. ASCO 2023.

Overall Survival



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

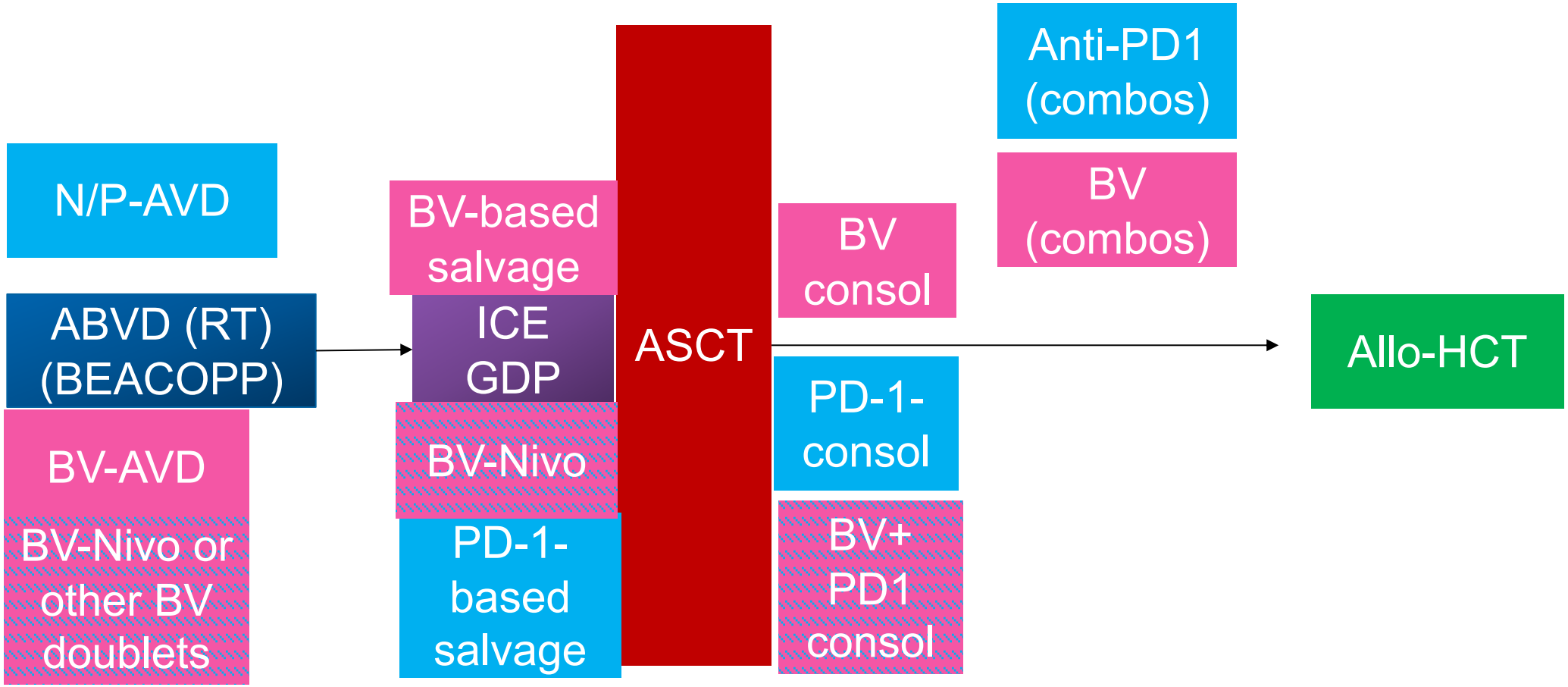
Herrera, AF et al. ASCO 2023.

S1826 Conclusions

- **N-AVD improved PFS compared to Bv-AVD in advanced stage cHL**
  - N-AVD improved EFS versus Bv-AVD
- N-AVD was well-tolerated
  - Few immune-related adverse events
- < 1% of patients received consolidative RT
  - May reduce late effects
- Follow-up ongoing to confirm durability of PFS, assess long-term safety, OS, and PROs
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard therapy for advanced stage cHL**

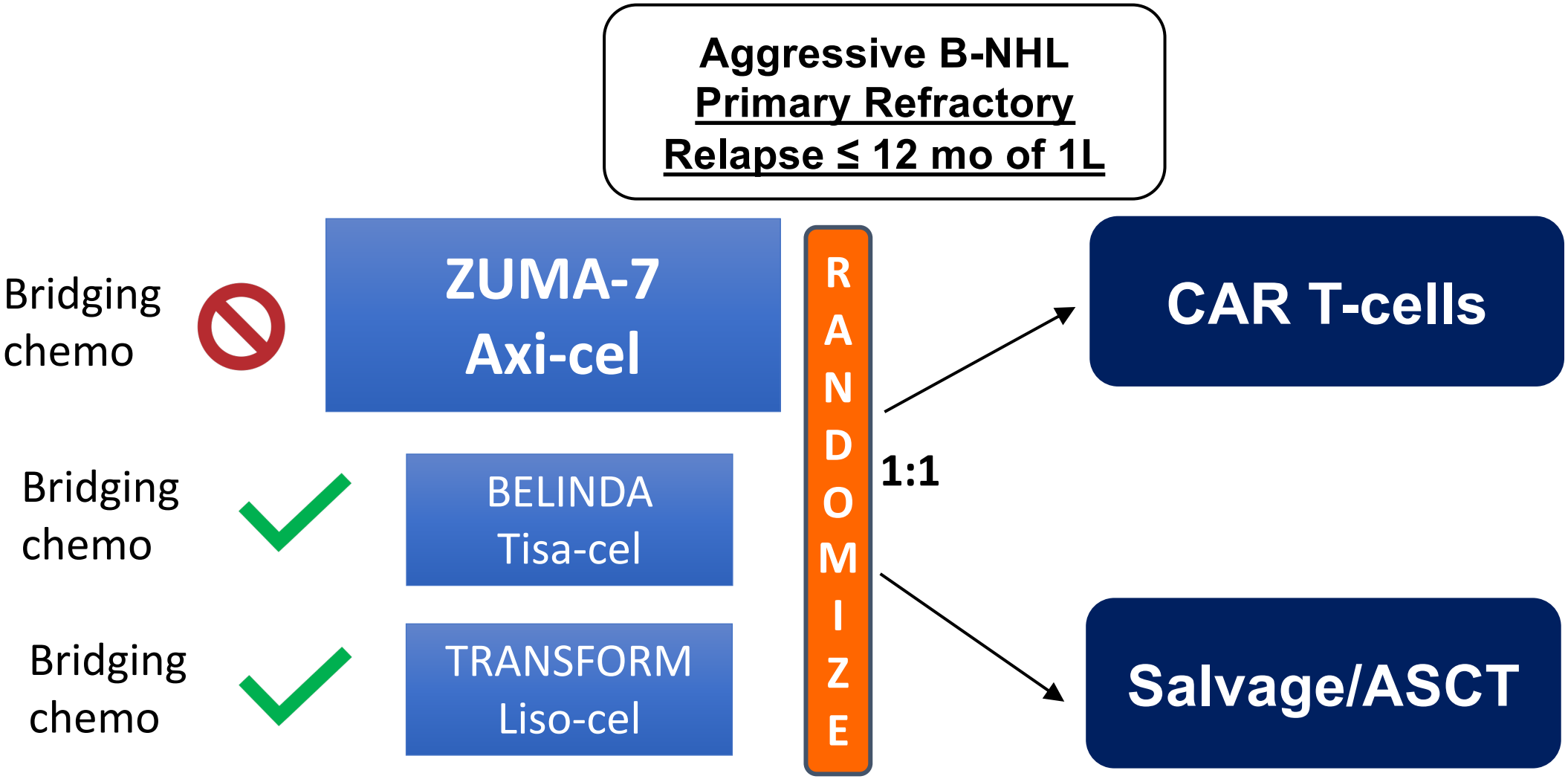
Herrera, AF et al. ASCO 2023.

Current Management of Hodgkin Lymphoma

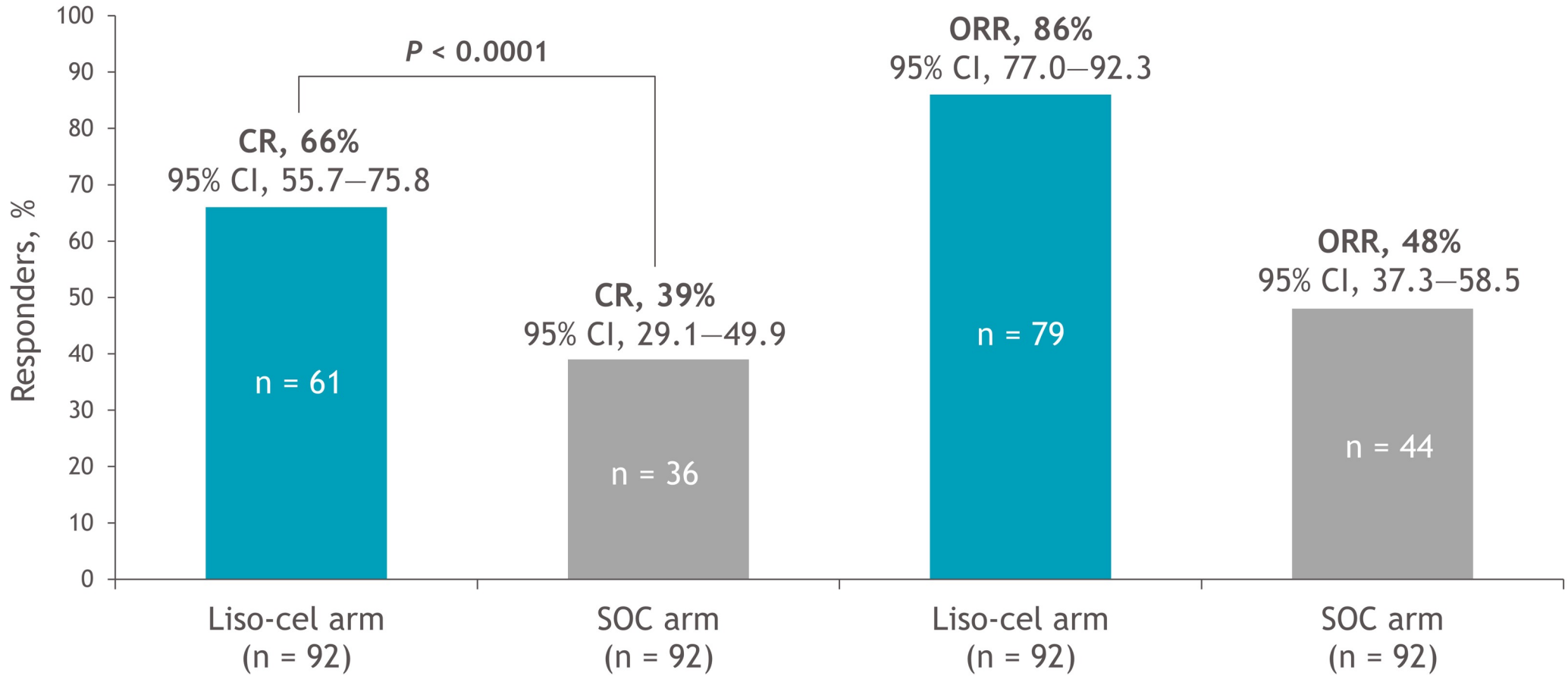


DIFFUSE LARGE B-CELL LYMPHOMA

CAR T-cells vs Salvage Chemotherapy/Transplant



TRANSFORM: Complete and objective response rates per IRC (ITT set)

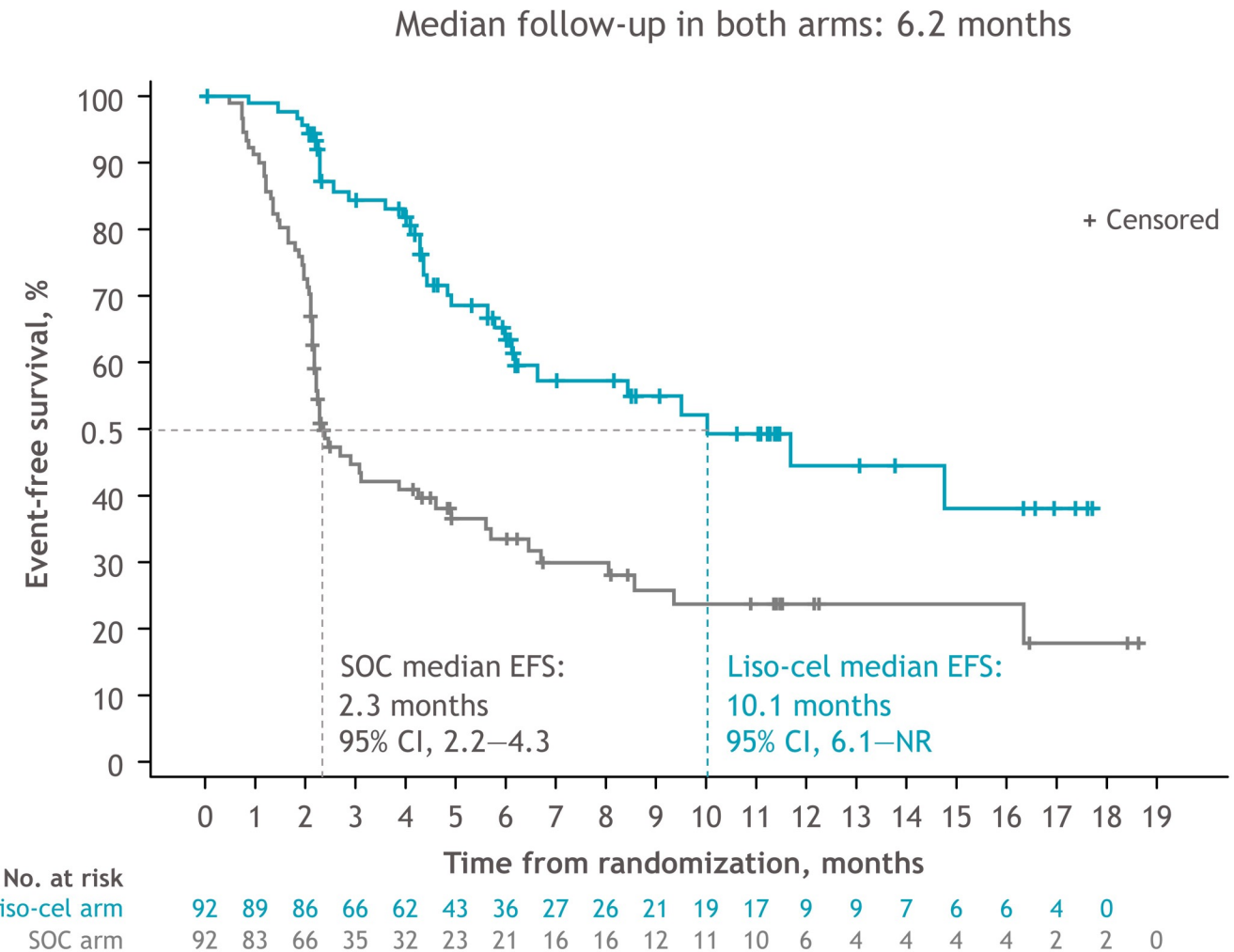


One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

CR rate was defined as the proportion of patients achieving a best overall response of CR.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)



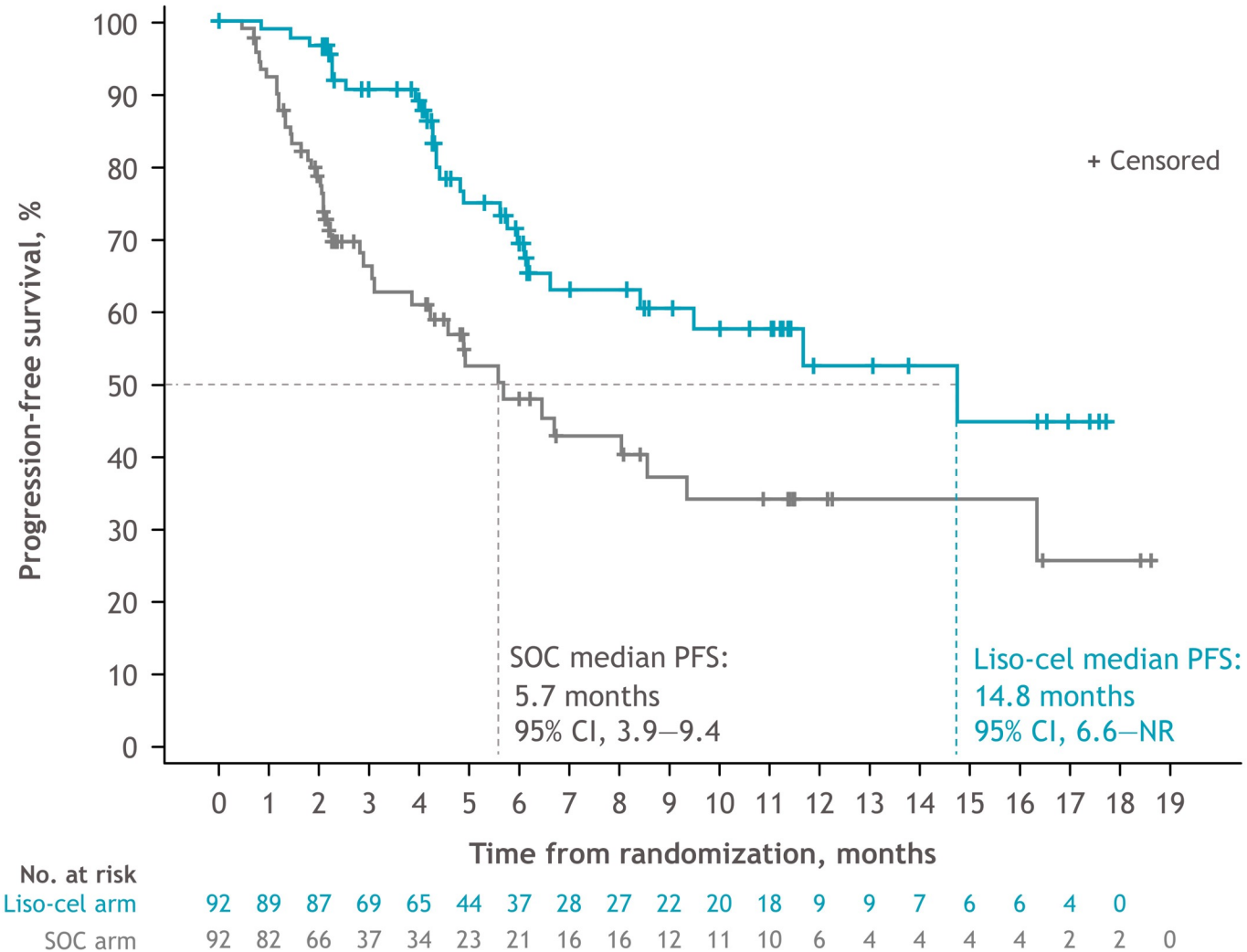
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	**0.349** (0.229—0.530) *P* < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Progression-free survival per IRC (ITT set)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	28	43
Stratified HR (95% CI)	**0.406** (0.250–0.659)	
	***P* = 0.0001**	
6-month PFS rate, % (SE)	69.4 (5.74)	47.8 (6.53)
Two-sided 95% CI	58.1–80.6	35.0–60.6
12-month PFS rate, % (SE)	52.3 (7.96)	33.9 (7.03)
Two-sided 95% CI	36.7–67.9	20.1–47.7

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

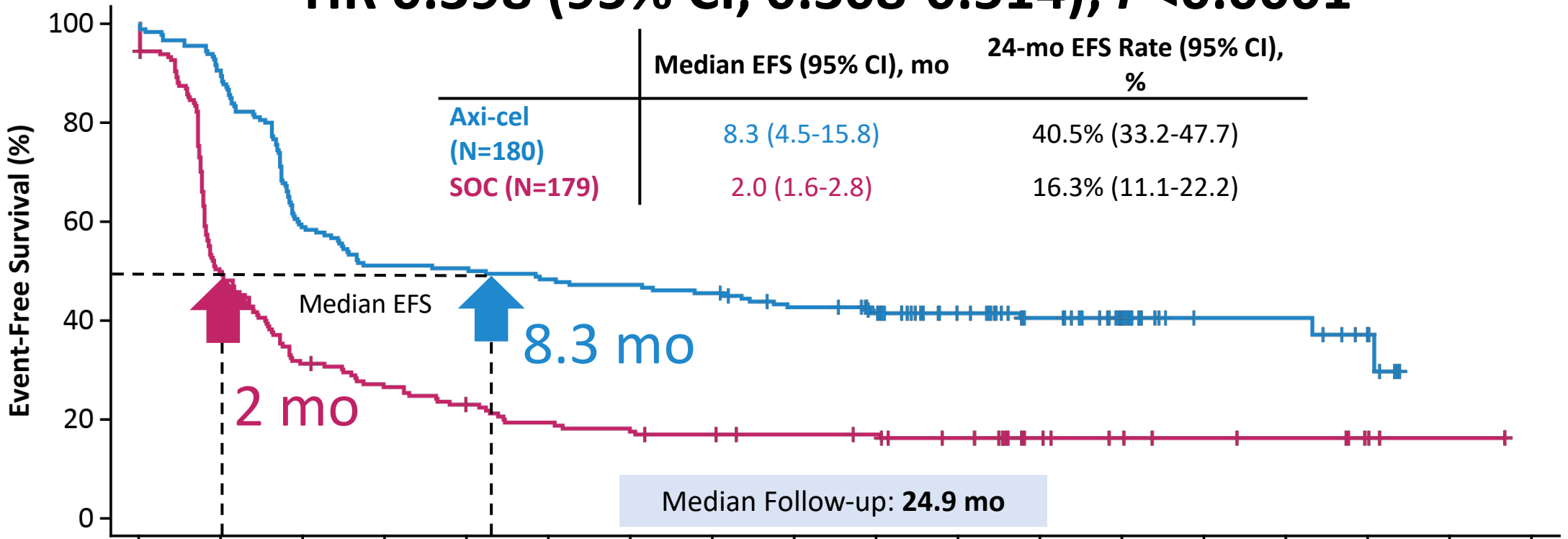
PFS is defined as the time from randomization to death from any cause or progressive disease, whichever occurs first.

Kamdar M, et al. ASH 2021 [Abstract #91]

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

HR 0.398 (95% CI, 0.308-0.514); *P*<0.0001

	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %
Axi-cel (N=180)	8.3 (4.5-15.8)	40.5% (33.2-47.7)
SOC (N=179)	2.0 (1.6-2.8)	16.3% (11.1-22.2)



No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
SOC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

City of Hope

Locke FL, et al ASH 2021. NEJM 2021

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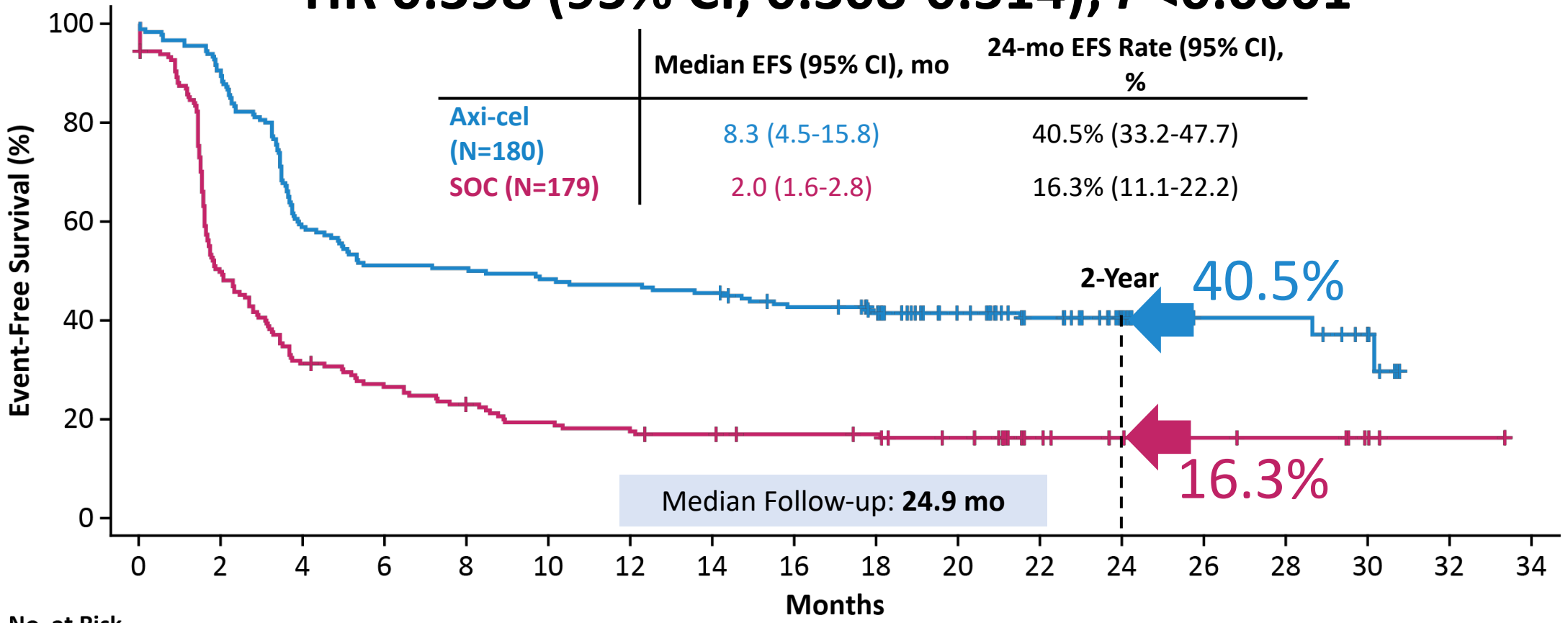

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SOC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

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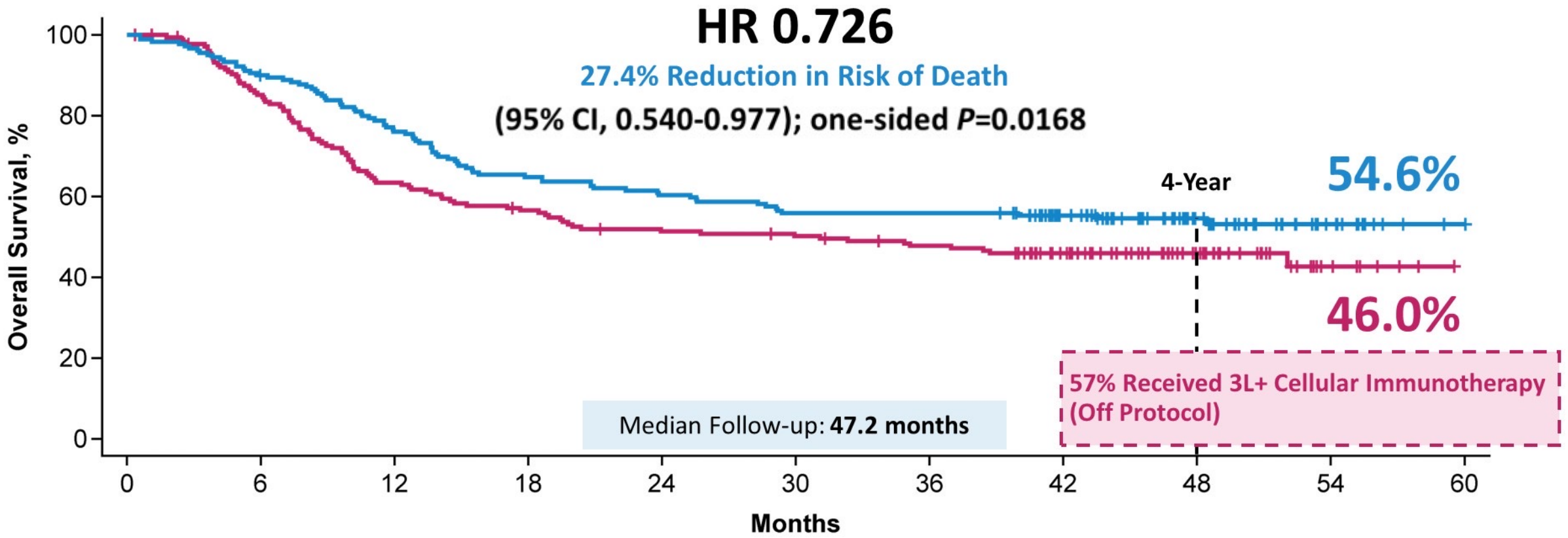
Axi-Cel Improved Overall Survival Versus Standard of Care



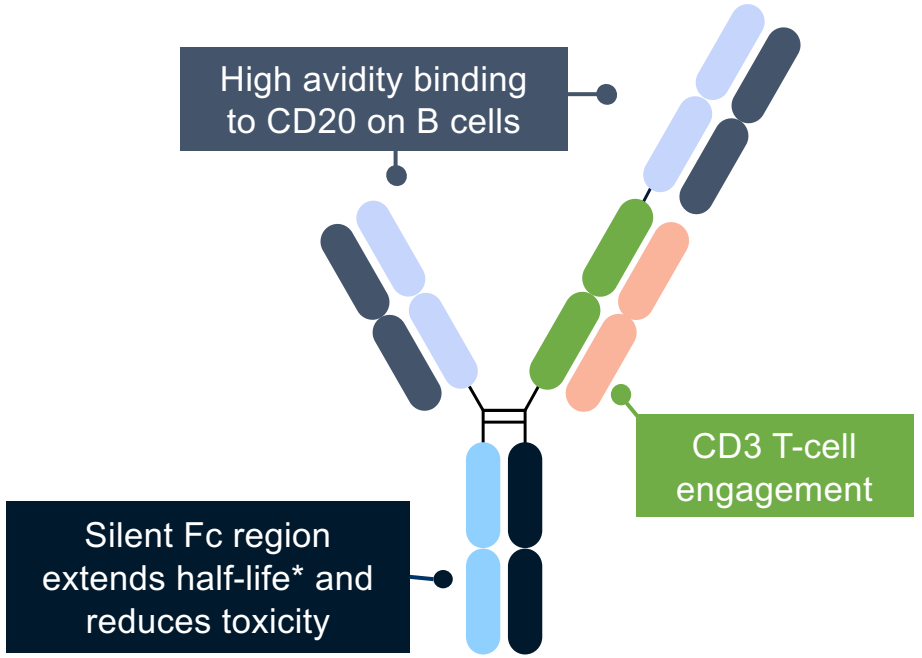
- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).
3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

Glofitamab: a 2:1 CD20xCD3 bispecific antibody

- **Glofitamab**
  - Off-the-shelf treatment delivered in a fixed course of 12 three-weekly cycles[1,2]
- **Phase II experience (NCT03075696)[2]**
  - Glofitamab has induced high CR rates and demonstrated manageable toxicity in patients with R/R LBCL[3]

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



Aim: to report an extended follow-up and landmark analyses in patients with R/R LBCL who achieved a CR after receiving glofitamab monotherapy

*Compared with non-Fc bearing T-cell engaging bispecific antibodies.[1,4] CR, complete response; Fc, fragment crystallized; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

1. Bacac, et al. Clin Cancer Res 2018; 2. NCT03075696. Available at: https://clinicaltrials.gov; 3. Dickinson MJ, et al. N Engl J Med 2022;387:2220–31; 4. Bacac M, et al. Oncoimmunol 2016;e1203498.

Glofitamab Pivotal Phase II Study overview

Pivotal Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, trFL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

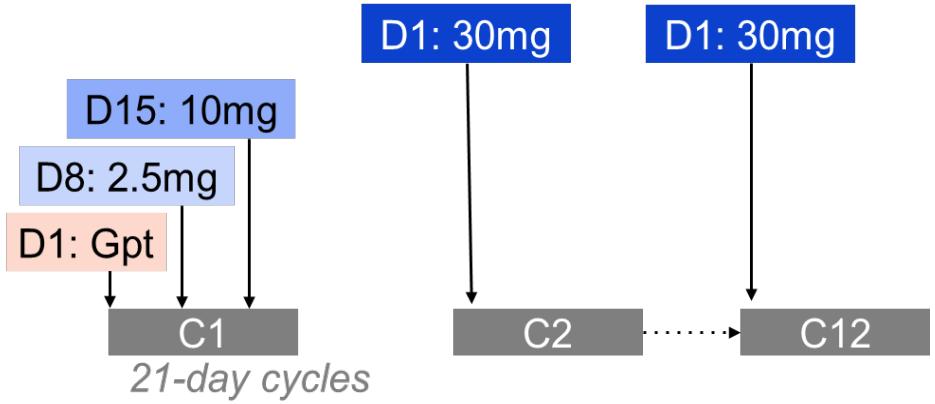
Glofitamab IV administration

Fixed-duration treatment

- Maximum 12 cycles

CRS* mitigation:

- Obinutuzumab pre-treatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

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

Landmark analyses

- PFS and OS post-hoc analysis were performed by response (landmark at C3, or EOT)

*By American Society for Transplantation and Cellular Therapy criteria.[1] †By PET-CT (Lugano criteria[2]). ‡By IRC and investigator. C, cycle; CRS, cytokine release syndrome; D, day; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; DoCR, duration of complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; Gpt, Obinutuzumab; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38;
2. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Dickinson M, et al. ICML 2023.

Glofitamab in R/R DLBCL: Baseline characteristics

Glofitamab RP2D

n (%)*		N=155†
Median age, years (range)		66.0 (21–90)
Male		101 (65)
ECOG PS	0 1	69 (45) 84 (54)
Ann Arbor stage	I II III IV	10 (7) 25 (16) 31 (20) 85 (55)
NHL subtype	DLBCL trFL HGBCL PMBCL	110 (71) 29 (19) 10 (7) 6 (4)
Bulky disease	>6cm >10cm	64 (41) 19 (12)

n (%)	N=155
Median no. of prior lines of therapy, n (range) 2 prior lines ≥3 prior lines	3 (2–7) 61 (39) 94 (61)
Prior anti-CD20 therapy	155 (100)
Prior anthracycline therapy	152 (98)
Prior CAR-T	52 (34)
Prior ASCT	29 (19)
Refractory to any prior therapy	139 (90)
Refractory to first prior therapy	91 (59)
Refractory to last prior therapy	131 (85)
Refractory to prior CAR-T	46/52 (88)
Refractory to any prior anti-CD20	129 (83)

The patient population was heavily pre-treated and highly refractory[1]

Clinical cut-off date: Jan 16, 2023. *Unless otherwise specified. †Intent-to-treat population. ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; NHL, non-Hodgkin's lymphoma; RP2D, recommended Phase II dose.

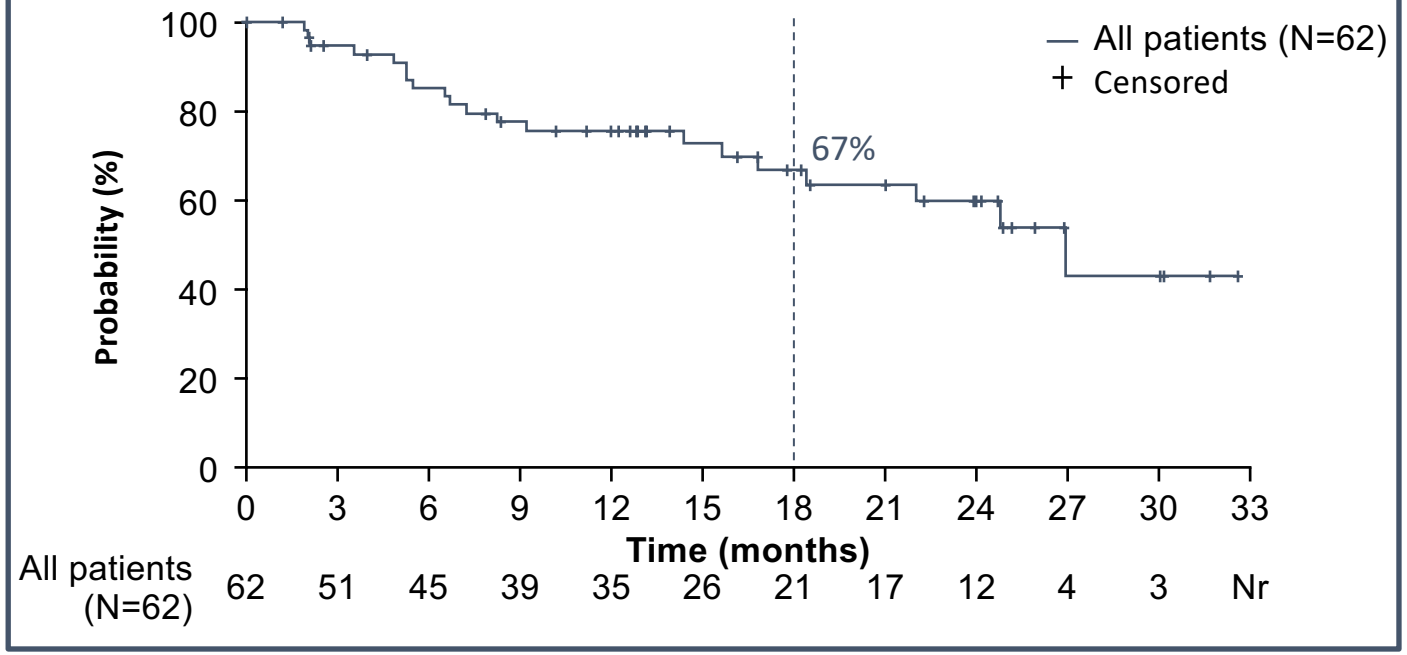
Dickinson M, et al. ICML 2023.

Complete responses to glofitamab were durable

Glofitamab RP2D

	IRC (N=155)*
CR rate†, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median CR follow-up, months (range)	18.2 (0–33)
18 months DoCR, n (%) [95% CI]	67.0 (53.3–80.8)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, months (95% CI)	26.9 (18.4–NR)

DoCR by IRC (n=62)



- The median time on study was 21.2 months (range: 0–34)

An estimated 67% of patients with a CR at any time remained in remission at 18 months

*Intent-to-treat population. †Best overall response. CI, confidence interval; NR, not reached.

Dickinson M, et al. ICML 2023.

Epcoritamab

Prior Treatments	DLBCL & HGBCL, n=148	LBCL, N=157
Median time from initial diagnosis to first dose, mo	19	19
Median time from end of last therapy to first dose, mo	2.4	2.4
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)
≥3 Lines of therapy, n (%)	104 (70)	110 (70)
Primary refractory[b] disease, n (%)	88 (59)	95 (61)
Refractory[b] to last systemic therapy, n (%)	122 (82)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	112 (76)	118 (75)
Prior ASCT, n (%)	27 (18)	31 (20)
Prior CAR T therapy, n (%)	58 (39)	61 (39)
Refractory[b] to CAR T therapy	43/58 (74)	46/61 (75)

Karimi Y, et al. ASCO 2023.

Epcoritamab is effective in R/R DLBCL

High Rates of Complete Response

Best Overall Response, n (%)	DLBCL & HGBCL, n=148[a]	LBCL, N=157[a]
Overall response	90 (61) [95% CI, 53–69]	99 (63) [95% CI, 55–71]
Complete response	57 (39) [95% CI, 31–47]	62 (39) [95% CI, 32–48]
Partial response	33 (22)	37 (24)
Stable disease	5 (3)	5 (3)
Progressive disease	37 (25)	37 (24)

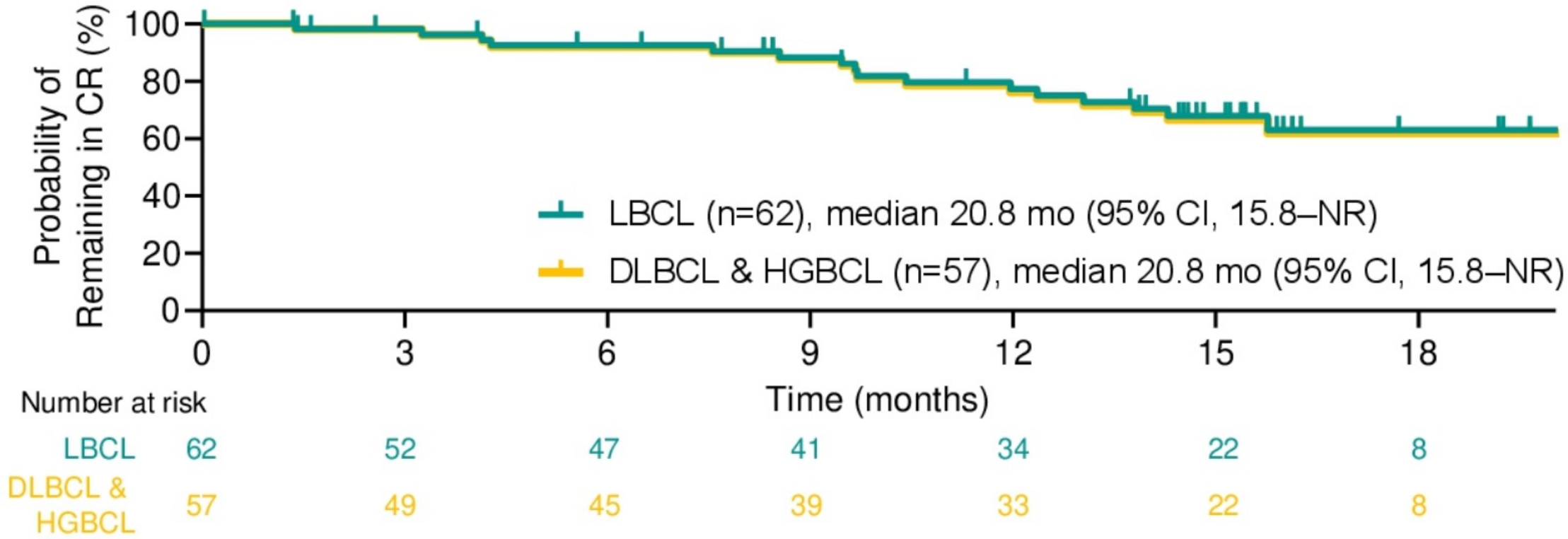
Based on IRC per Lugano criteria. [a]16 patients were not evaluable.

Karimi Y, et al. ASCO 2023.

Median Duration of CR almost 2 years

Median DOR: 15.5mo in all responders

Median DOCR: 20.8 mo among CR patients



Karimi Y, et al. ASCO 2023.

Cytokine release syndrome after Epcoritamab

	LBCL N=157
CRS, n (%)[a]	80 (51)
Grade 1	50 (32)
Grade 2	25 (16)
Grade 3	5 (3)
Median time to onset after first full dose, h	20
Treated with anticytokine therapy, n (%)	23 (15)
Leading to treatment discontinuation, n (%)	1 (1)
CRS resolution, n/n (%)	79/80 (99)
Median time to resolution, d (range)[b]	2 (1–27)

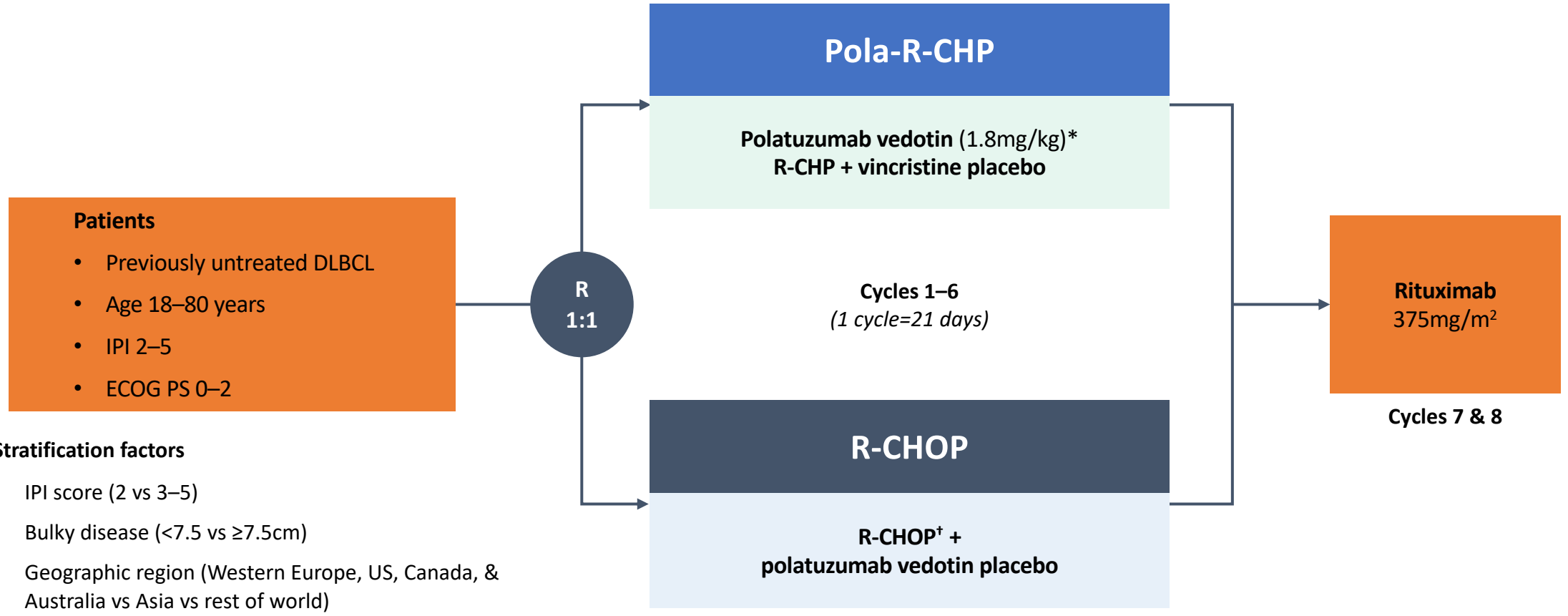
[a]Graded by Lee et al 2019 criteria.[9] [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.

Karimi Y, et al. ASCO 2023.

Initial R-CHOP therapy for DLBCL: Unbeatable for decades

- Dose adjusted R-EPOCH
- R-CHOP + lenalidomide
- R-CHOP + bortezomib
- R-CHOP + ibrutinib
- R-CHOP + vorinostat
- Obinutuzumab-CHOP
- Others…

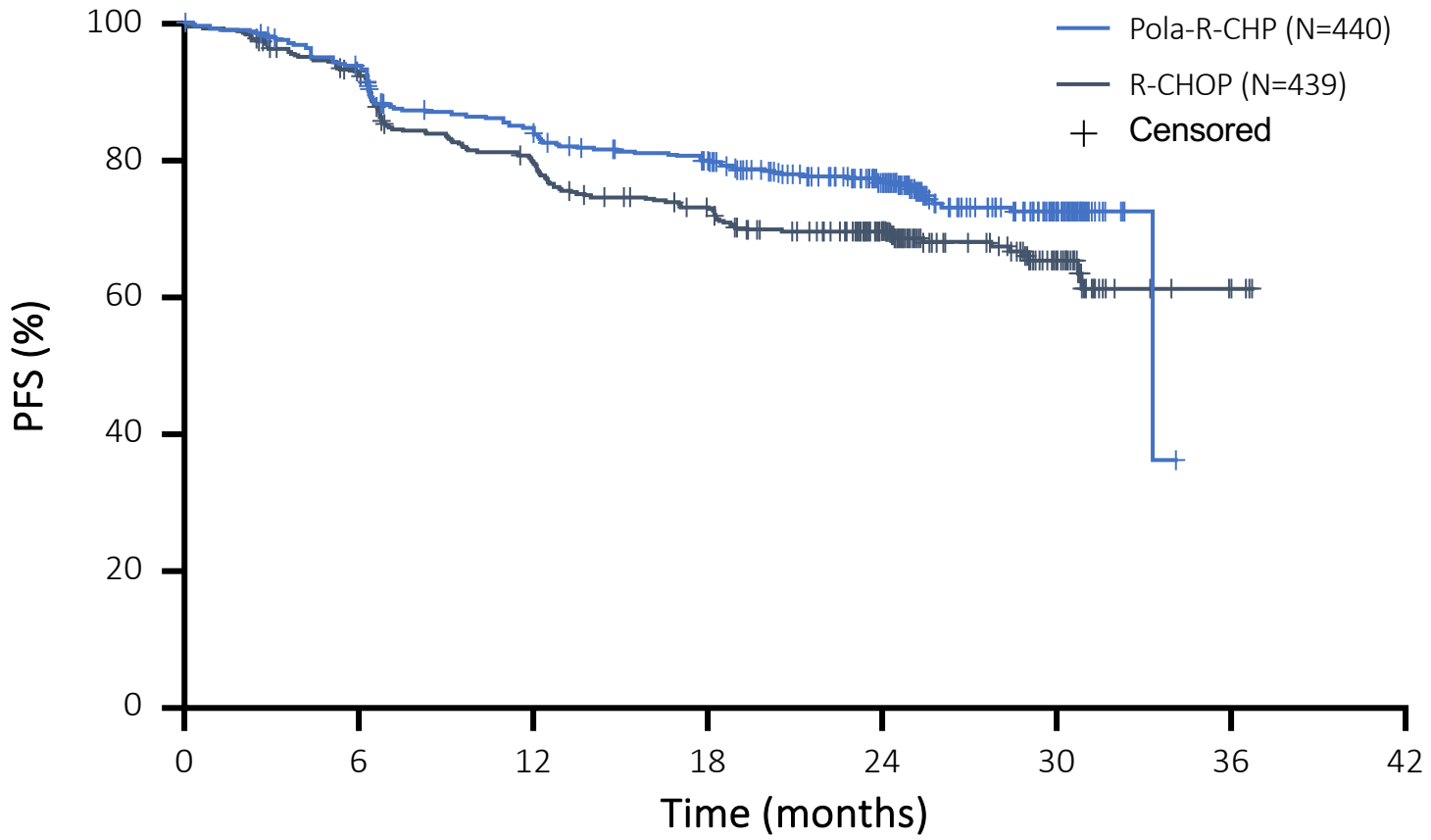
POLARIX: A randomized double-blinded study



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

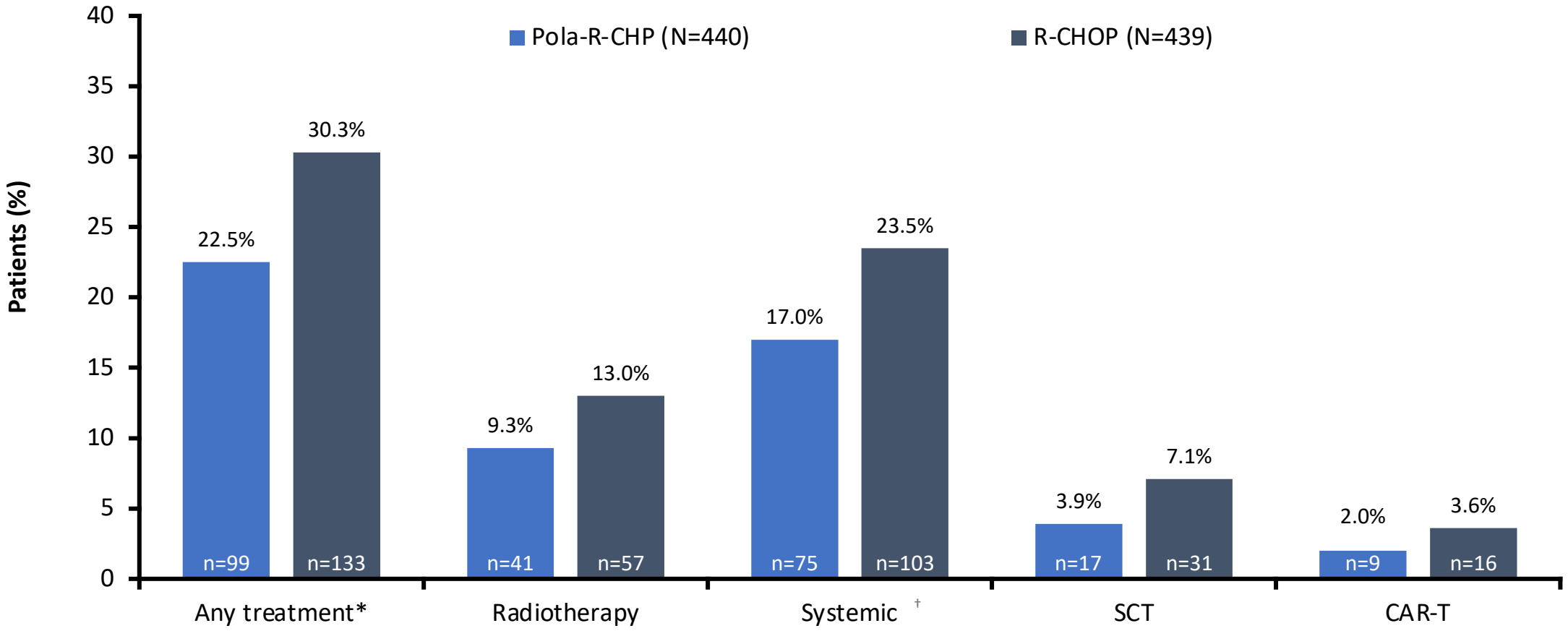
HR 0.73 **(P<0.02)**

95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP versus 70.2% with R-CHOP (**Δ=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Patients receiving subsequent treatments



Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.
CAR-T, chimeric antigen receptor T-cell therapy; SCT, stem cell transplant.

Safety summary

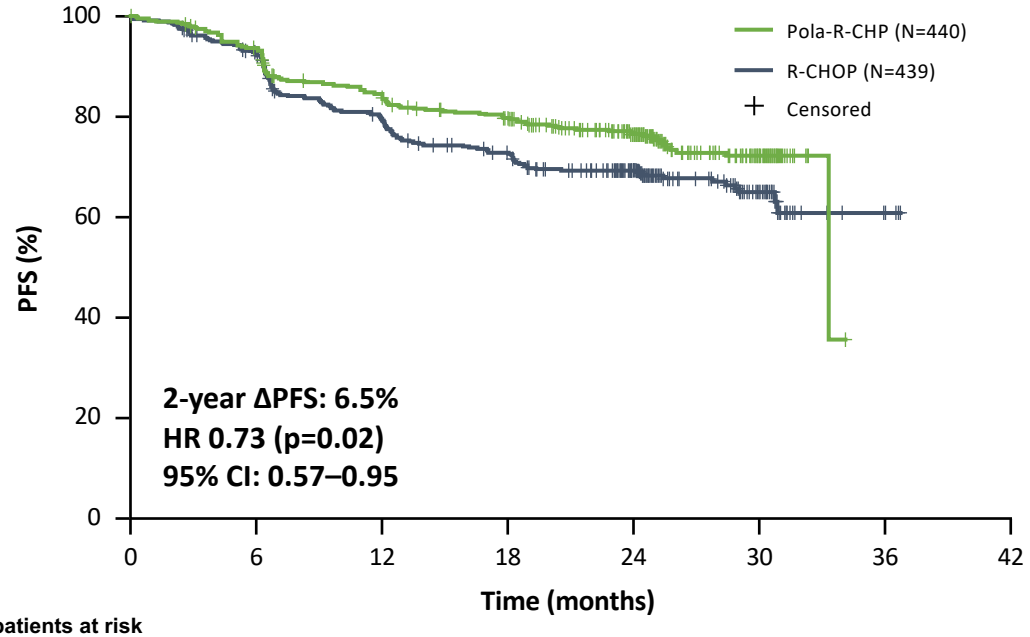
Safety profiles were similar with Pola-R-CHP and R-CHOP

n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

Data cut-off: June 28, 2021.

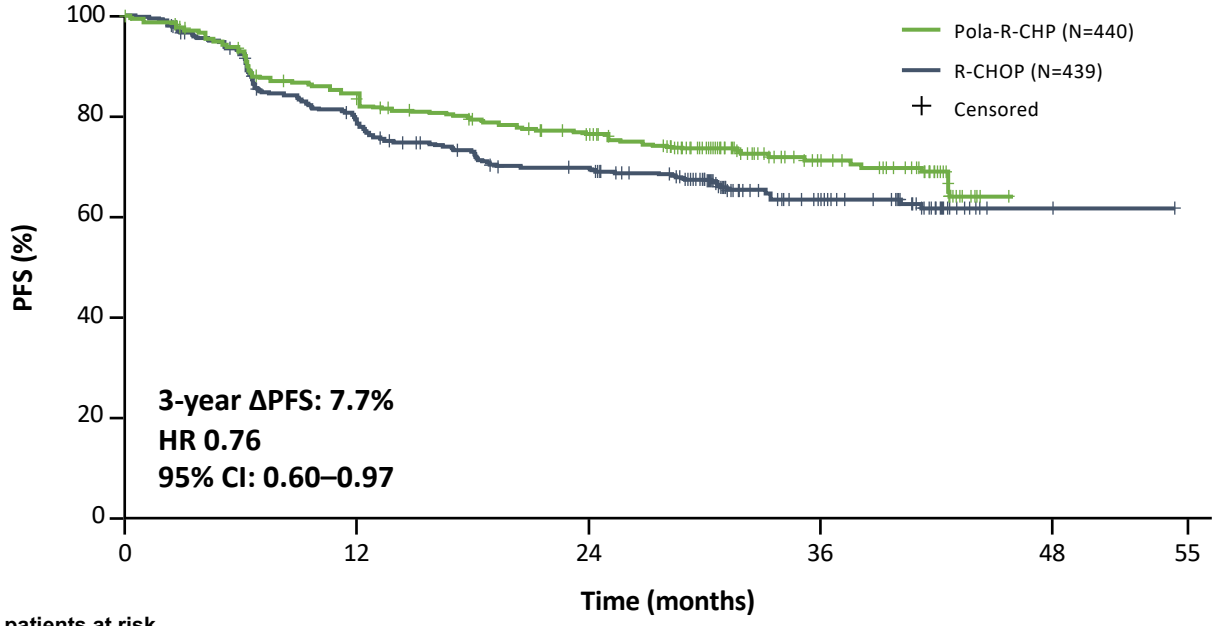
PFS benefit with Pola-R-CHP vs R-CHOP was maintained with longer follow-up

Primary analysis (CCOD: June 28, 2021)[1]
Median follow-up: 28.2 months



No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	0	0
R-CHOP	439	389	330	296	220	78	3	0

Updated results (CCOD: June 15, 2022)
Median follow-up: 39.7 months



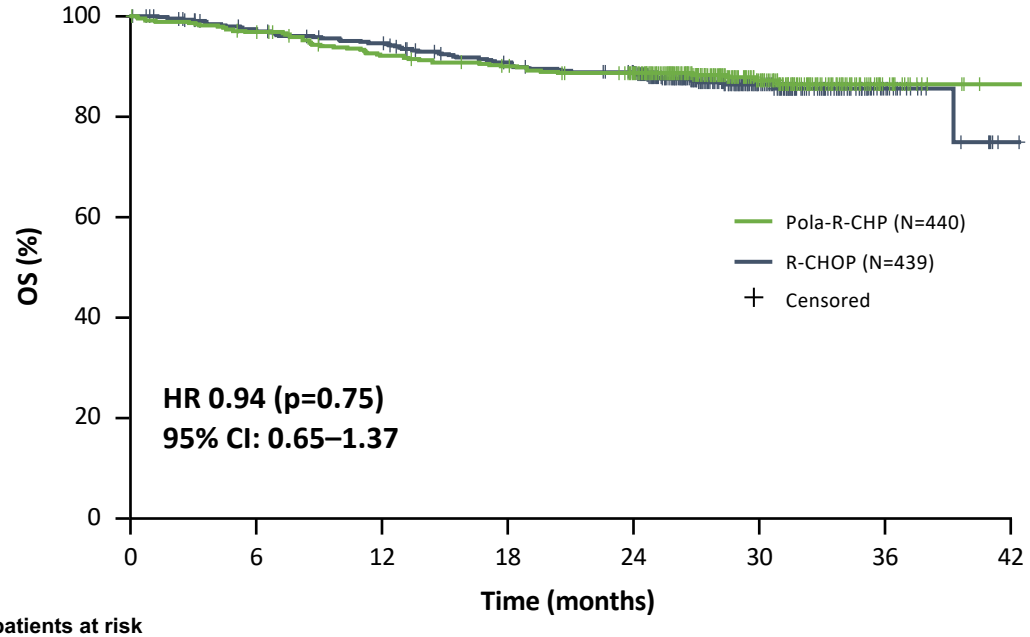
No. of patients at risk										
Pola-R-CHP	440	405	354	331	313	242	103	66	0	0
R-CHOP	439	390	331	300	284	222	94	59	2	1

Analysis based on the ITT population.
ITT, intention-to-treat; NE, not evaluable; no., number.

1. Tilly H, et al. N Engl J Med 2022;386:351–63.

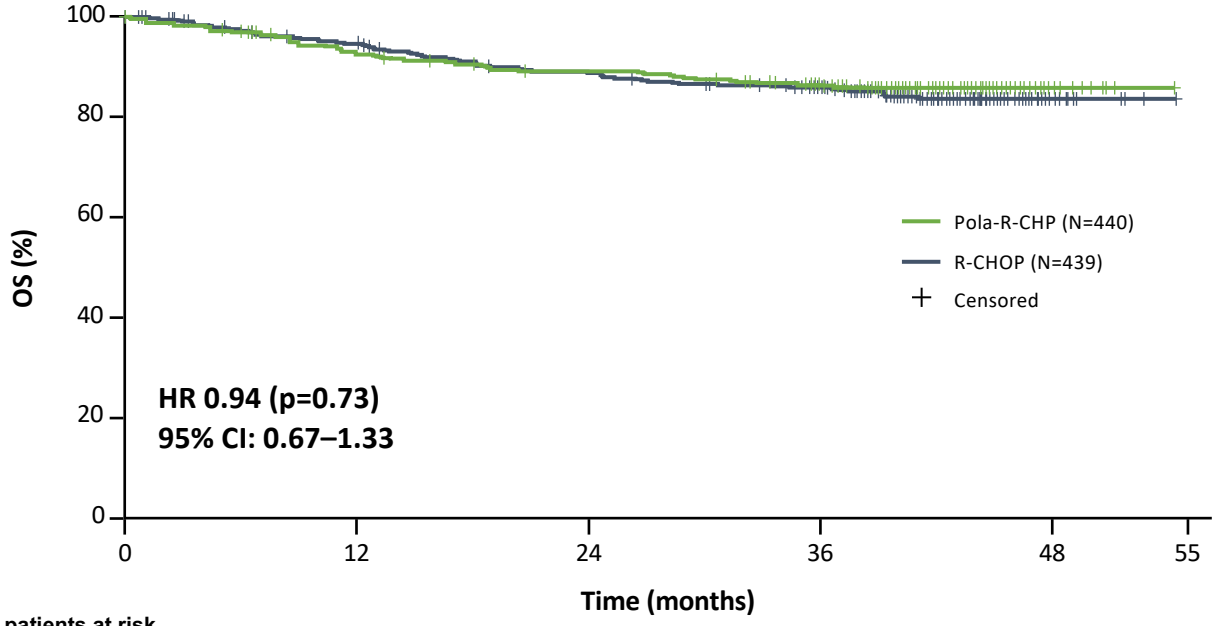
OS remained similar between treatment arms

Primary analysis (CCOD: June 28, 2021)[1]
Median follow-up: 28.2 months



No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

Updated results (CCOD: June 15, 2022)
Median follow-up: 39.7 months



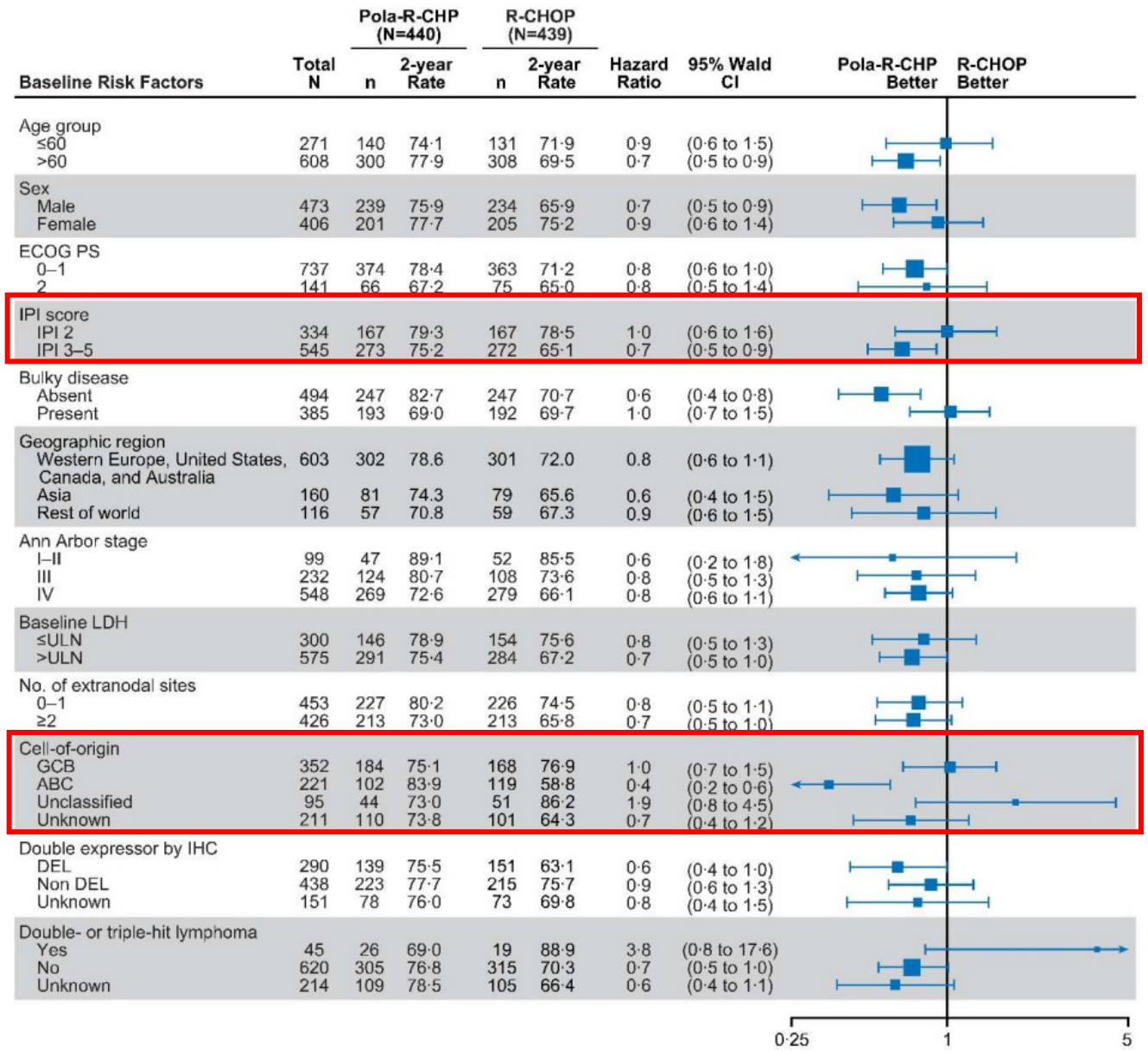
No. of patients at risk										
Pola-R-CHP	440	423	398	387	379	371	338	129	13	1
R-CHOP	439	415	403	382	372	361	329	124	18	1

No new safety signals have been identified with longer follow-up compared with the primary analysis

Analysis based on the ITT population. Analysis of OS was time-driven, and was a prespecified, statistically tested analysis.

1. Tilly H, et al. N Engl J Med 2022;386:351–63.

Should we limit Polatuzumab use to subsets?



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

1. Tilly H, et al. N Engl J Med 2022;386:351–63.

FOLLICULAR LYMPHOMA

Mosunetuzumab Response rates in R/R FL

Efficacy endpoint in the overall population by investigator assessment; % (95% CI)	N=90
ORR	**78%** (68–86)
CR	**60%** (49–70)

Time to first response (median [range]): **1.4 months** (1.0–11)
Time to first CR (median [range]): **3.0 months** (1.0–19)

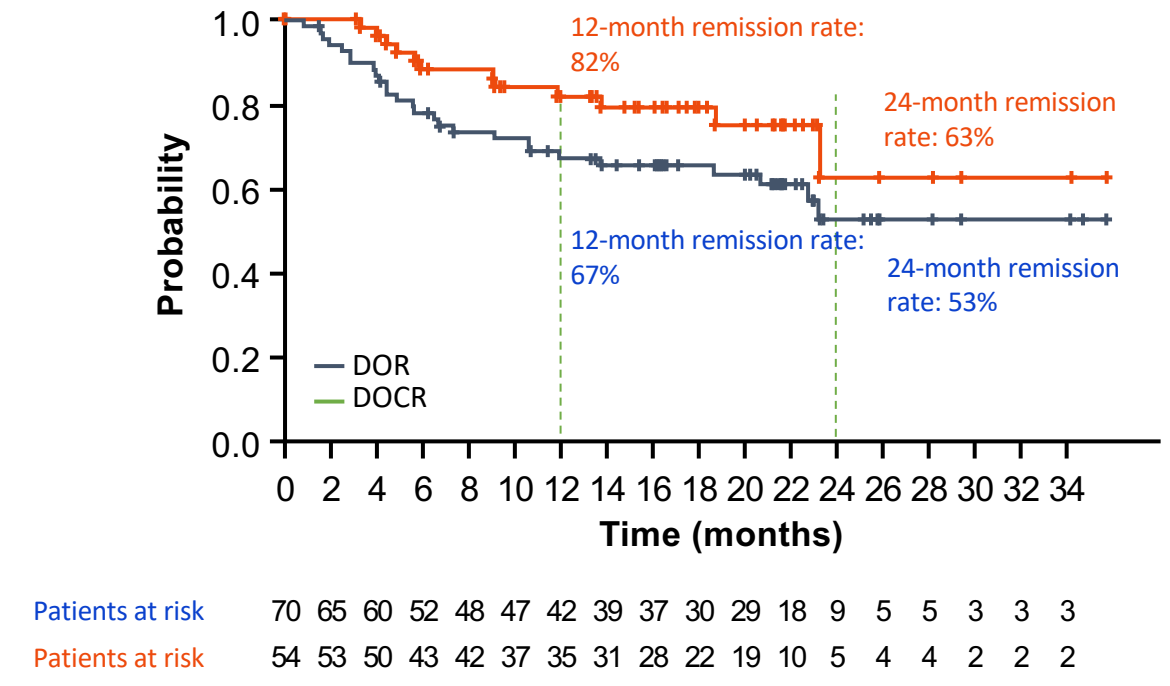
High ORR and CR rate were consistent with published results[1]

1. Budde LE, et al. Lancet Oncol 2022;23(8):1055–1065.

Mosunetuzumab: durable responses in FL

Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70	NR (21–NR)
24-month DOR (95% CI)	53% (38–68)
Median DOCR, months (range), n=54	NR (23–NR)
24-month DOCR (95% CI)	63% (38–88)
Median PFS, months (range)	24 (12–NR)
24-month PFS (95% CI)	48% (36–60)
Median TTNT, months (range)	NR (18–NR)
24-month TTNT (95% CI)	56% (45–67)
Median OS, months (range)	NR (NR–NR)
24-month OS (95% CI)	87% (80–94)

DOR and DOCR



Durable responses: majority of patients in remission after 2 years

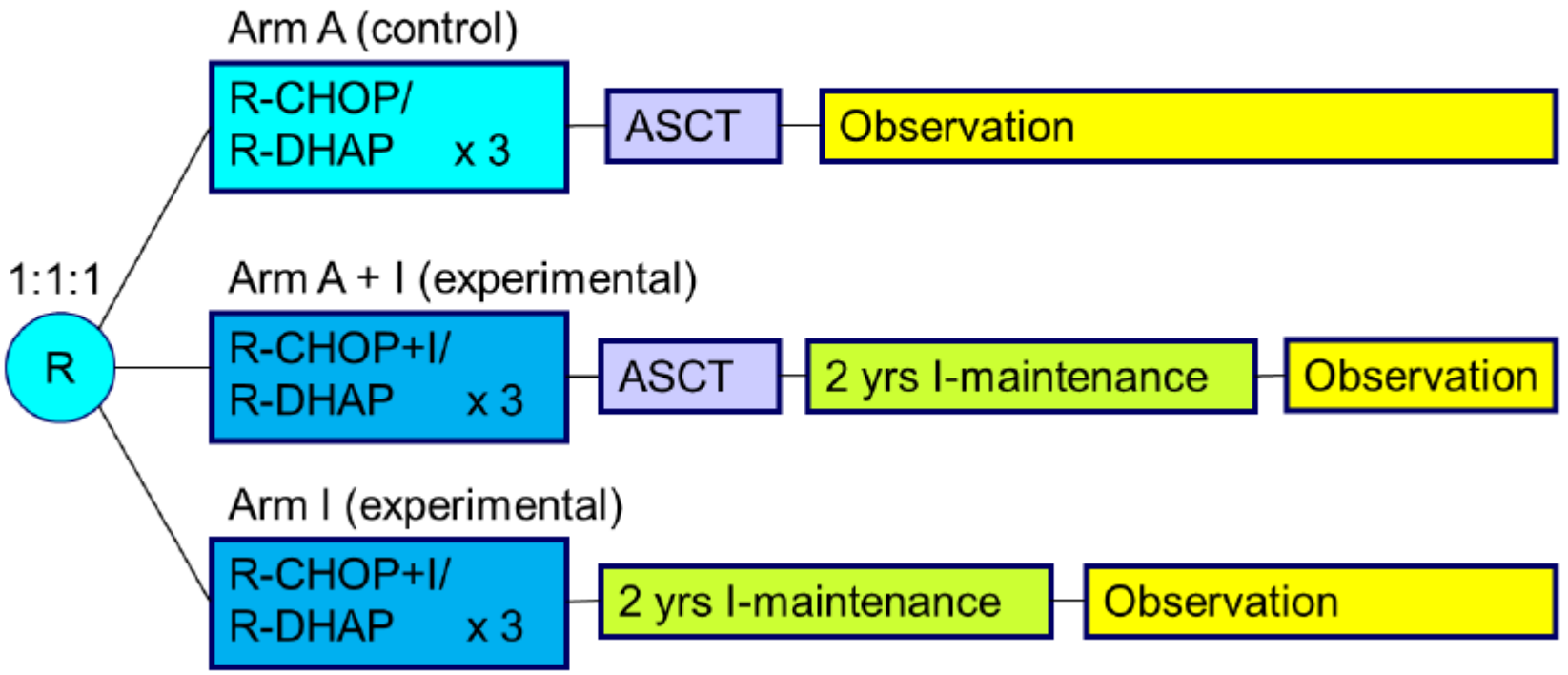
DOCR, duration of complete response; TTNT, time-to-next therapy.

MANTLE CELL LYMPHOMA

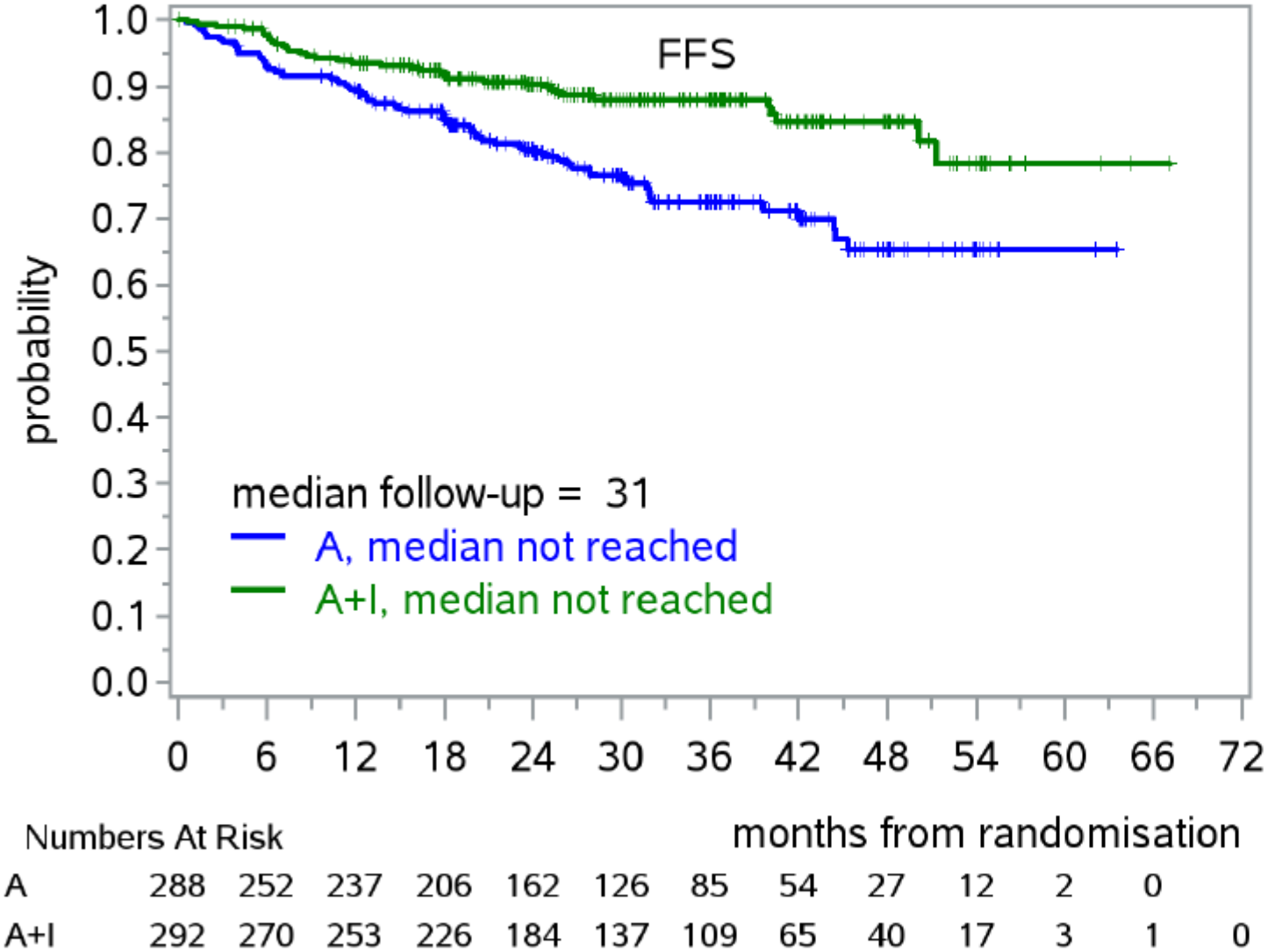
TRIANGLE: BTK inhibition during induction and maintenance

TRIANGLE: Trial Design

LMU KLINIKUM



TRIANGLE: FFS Superiority of A+I vs. A

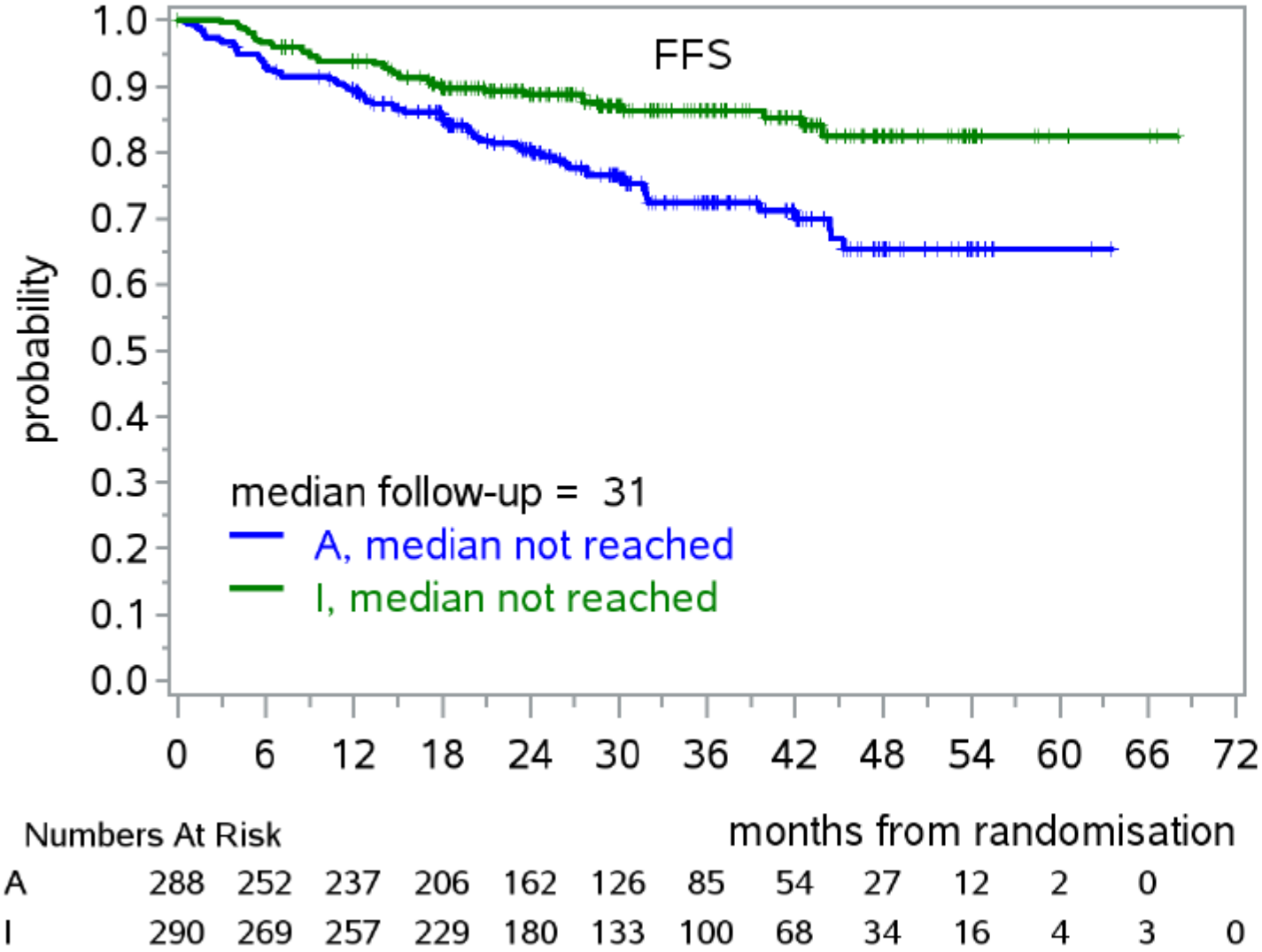


Numbers At Risk													
A	288	252	237	206	162	126	85	54	27	12	2	0	
A+I	292	270	253	226	184	137	109	65	40	17	3	1	0

- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

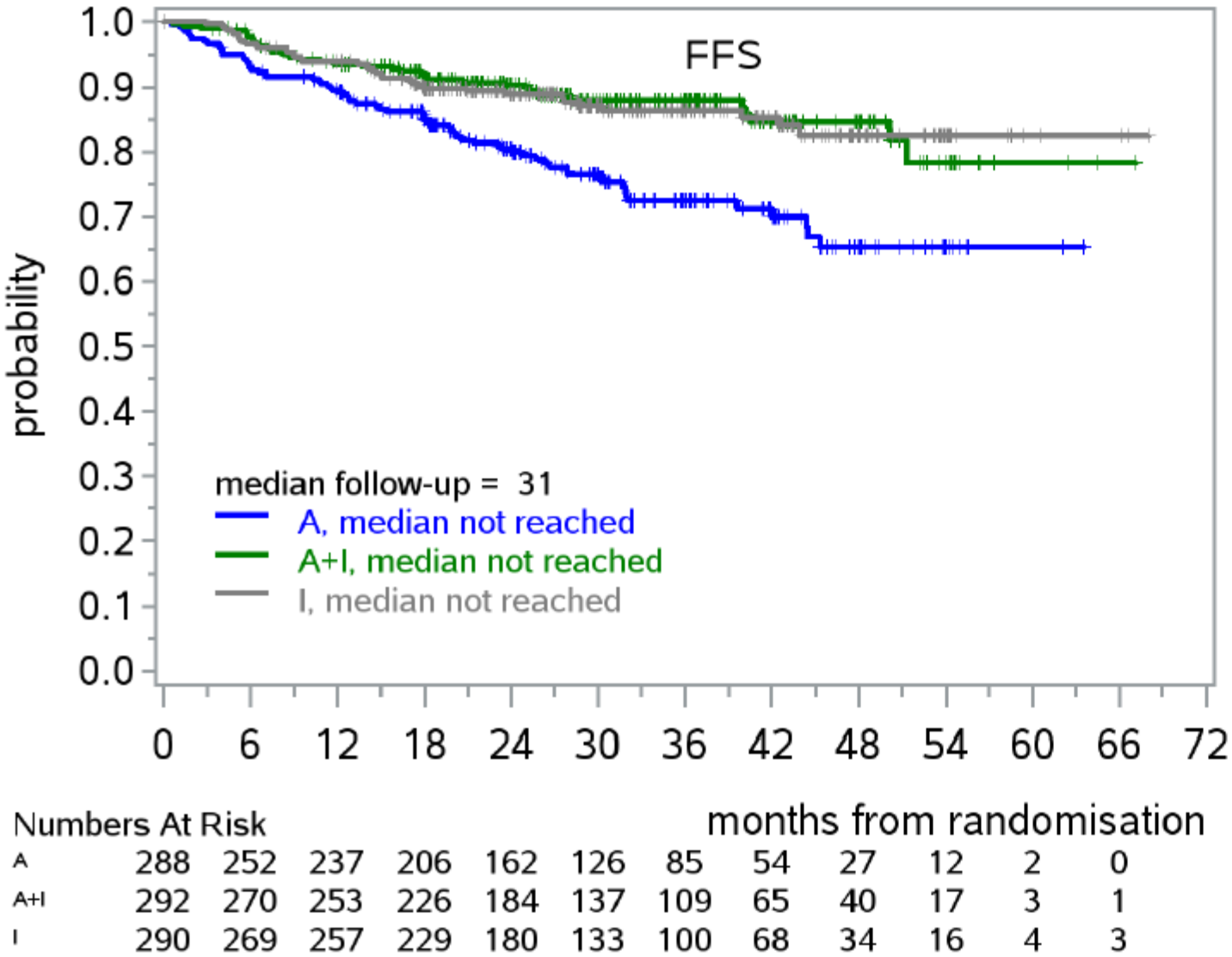
TRIANGLE: No FFS Superiority of A vs. I



- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- p-value corrected for sequential design: p=0.9979
- HR (A vs. I): HR=1.77

A arm: R-CHOP/R-DHAP+ASCT; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: FFS Superiority of A+I vs. I ?



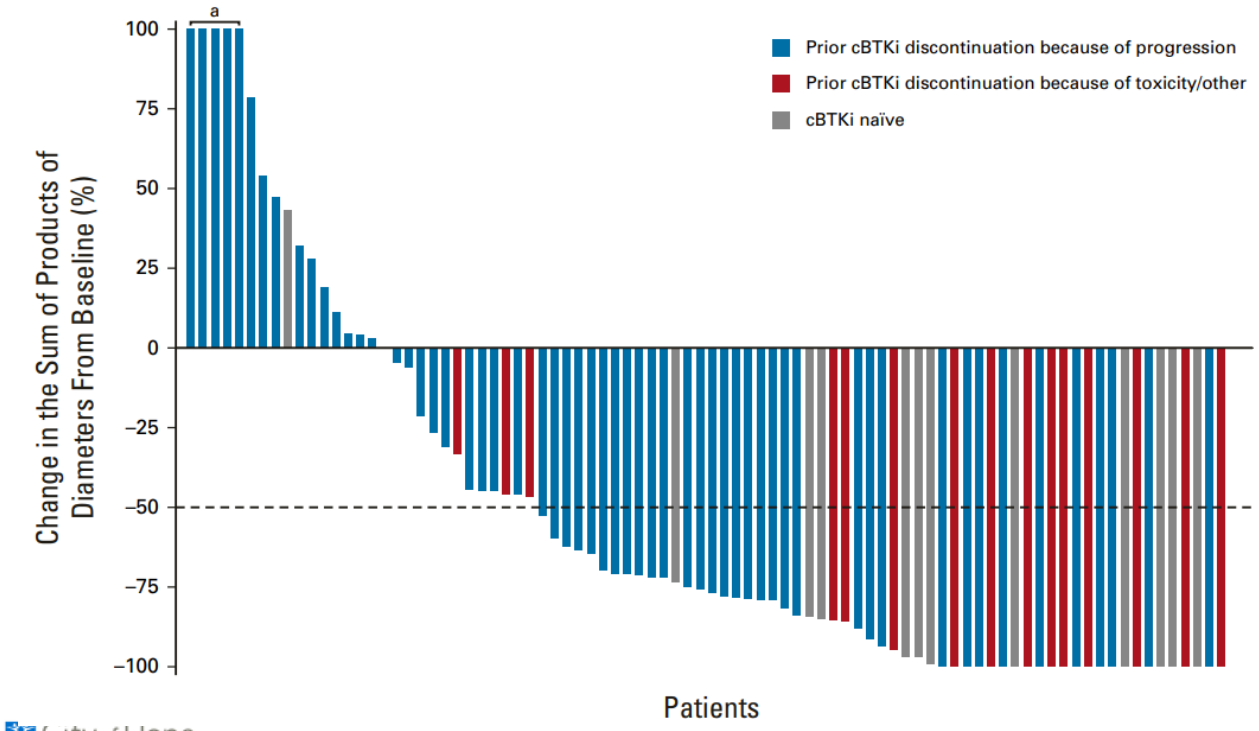
- Test A+I vs. I ongoing, no decision yet

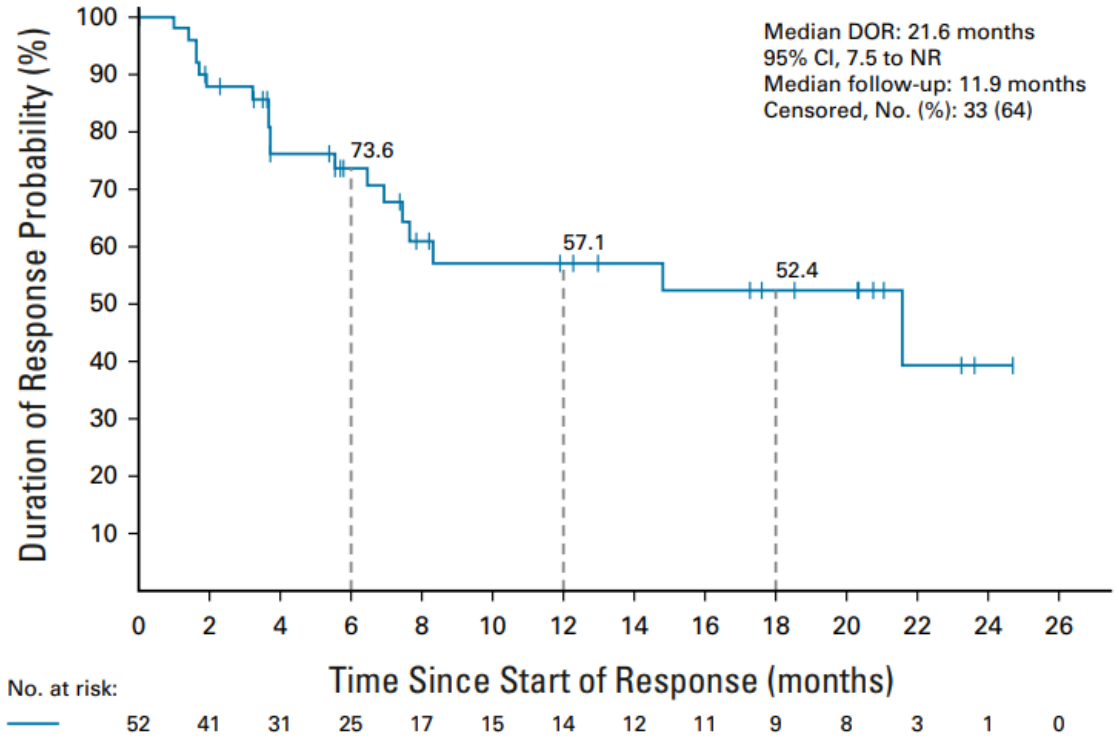
Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Pirtobrutinib for R/R MCL

N = 90
ORR 58%, CR 38%
Median DOR: 21.6 mo





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