Update on Novel Therapies for Non-Hodgkin Lymphoma

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Discussion Topics:

1. **MCL: Triangle Trial Results (Auto PSCT, BTKi)**

2. **Bi-Specific Antibodies for NHL**
   - **Mosentuzumab**
   - **Glofitamab**

3. **Auto PSCT in Primary CNS Lymphoma**

4. **Pirtobrutinib: Non-Covalent BTK inhibitor**
   Recent FDA approval for relapsed MCL

TRIANGLE:

Autologous **T**ransplantation after a **R**ituximab/**I**brutinib/**A**ra-c Containing i**N**duction in **G**eneralized Mantle Cell **L**ymphoma – a Randomized **E**uropean MCL Network Trial

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Dreyling M, Doorduijn J, Giné E, Jerkeman M, Walewski J, Hutchings M, Mey U, Riise J, Trneny M, Vergote V, Celli M, Shpilberg O, Gomes da Silva M, Leppa S, Jiang L, Pott C, Klapper W, Gözel D, Schmidt C, Unterhalt M, Ladetto M*, Hoster E *

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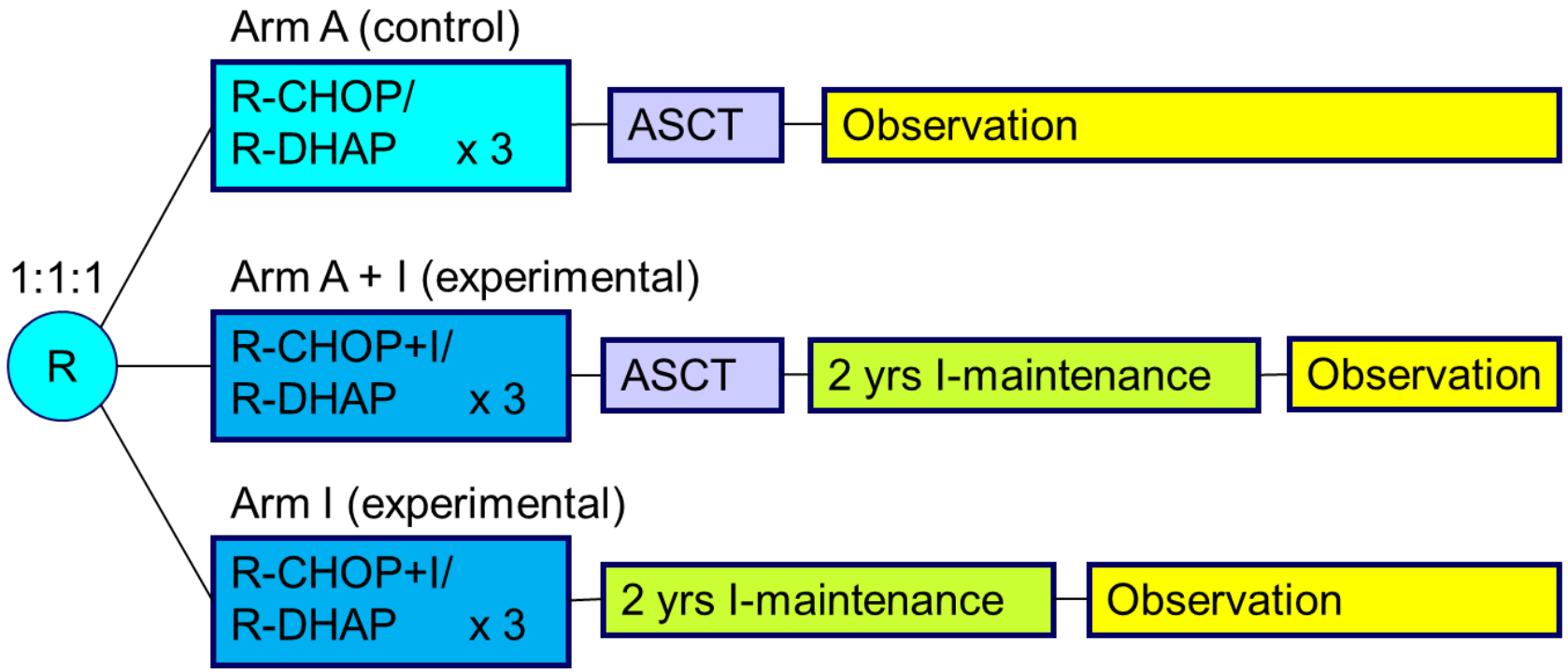
TRIANGLE: Trial Design

- MCL patients
- Previously untreated
- Stage II to IV
- Younger than 66 years
- Suitable for HA and ASCT
- ECOG 0 to 2

- Primary outcome: FFS

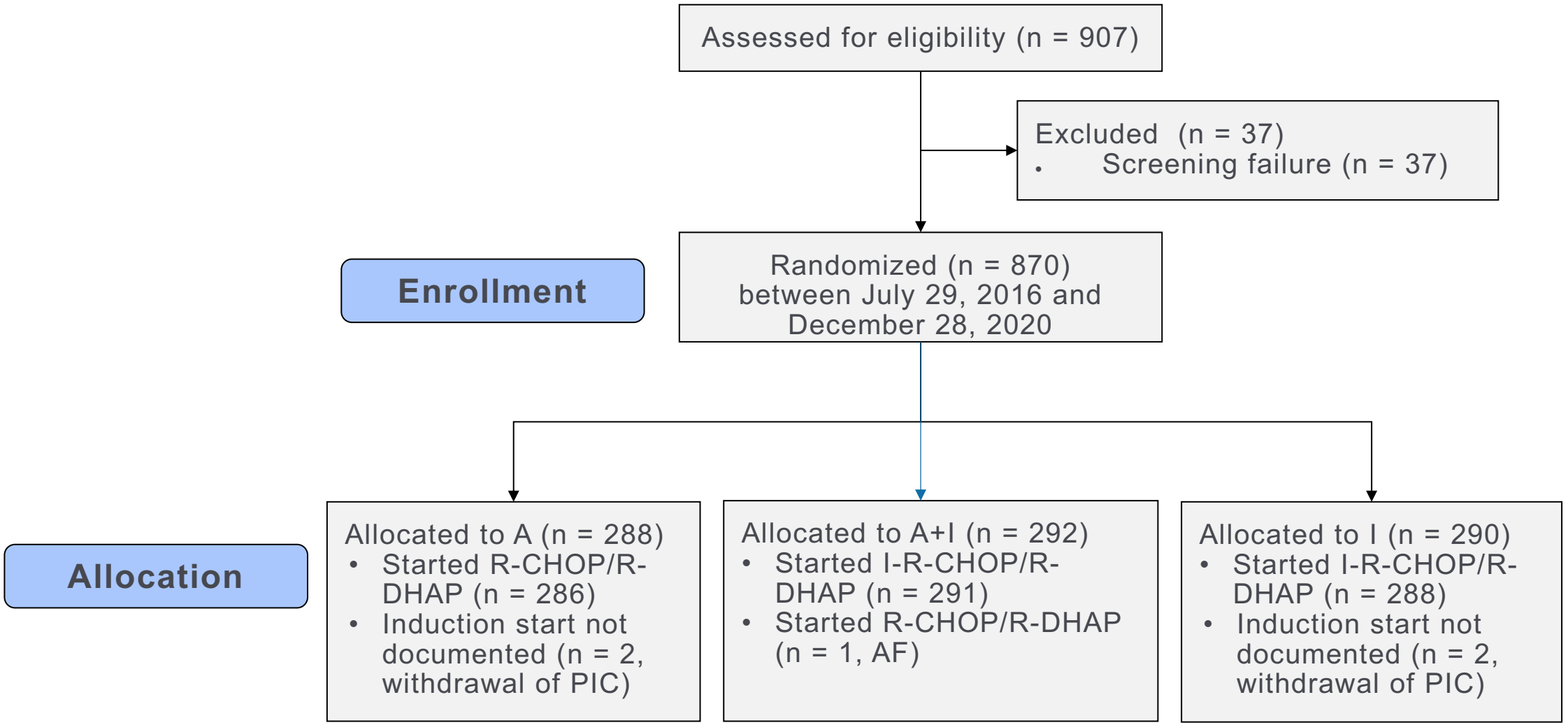
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58%)/165 (57%)/158 (54%) of A/A + I/I randomized patients

ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; FFS, failure-free survival; G-CSF, granulocyte-colony stimulating factor; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone; R-DHAP, rituximab, dexamethasone, Ara-C, cisplatine, G-CSF.

TRIANGLE: Patient Flow



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

TRIANGLE: Baseline Characteristics

Characteristic	Overall (n = 870)	A (n = 288)	A+I (n = 292)	I (n = 290)
Median age, years (range)	57 (27 to 68)	57 (31 to 65)	57 (36 to 68)*	58 (27 to 65)
Male sex	76%	76%	74%	79%
No MCL	8 (1%)	2 (CLL, FL)	4 (1 NHL NOS, 1 HD, 2 MZL)	2 (HCL, DLBCL)
Ann Arbor Stage (n = 864)				
I	0%	0%	0%	0%
II	5%	4%	4%	6%
III	9%	8%	7%	10%
IV	87%	88%	89%	84%
ECOG > 1	1%	2%	1%	2%
MIPI Low	58%	58%	58%	58%
MIPI Intermediate	27%	27%	27%	27%
MIPI High	15%	14%	15%	16%

MIPI, M
2 patie

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

- CR- and OR-Rates significantly higher in the combined I induction (A + I/I) vs control (A) (CR: *P* = .0203, OR: *P* = .0025)
- MCL Younger R-CHOP/R-DHAP group: 38% (CR), 94% (OR)

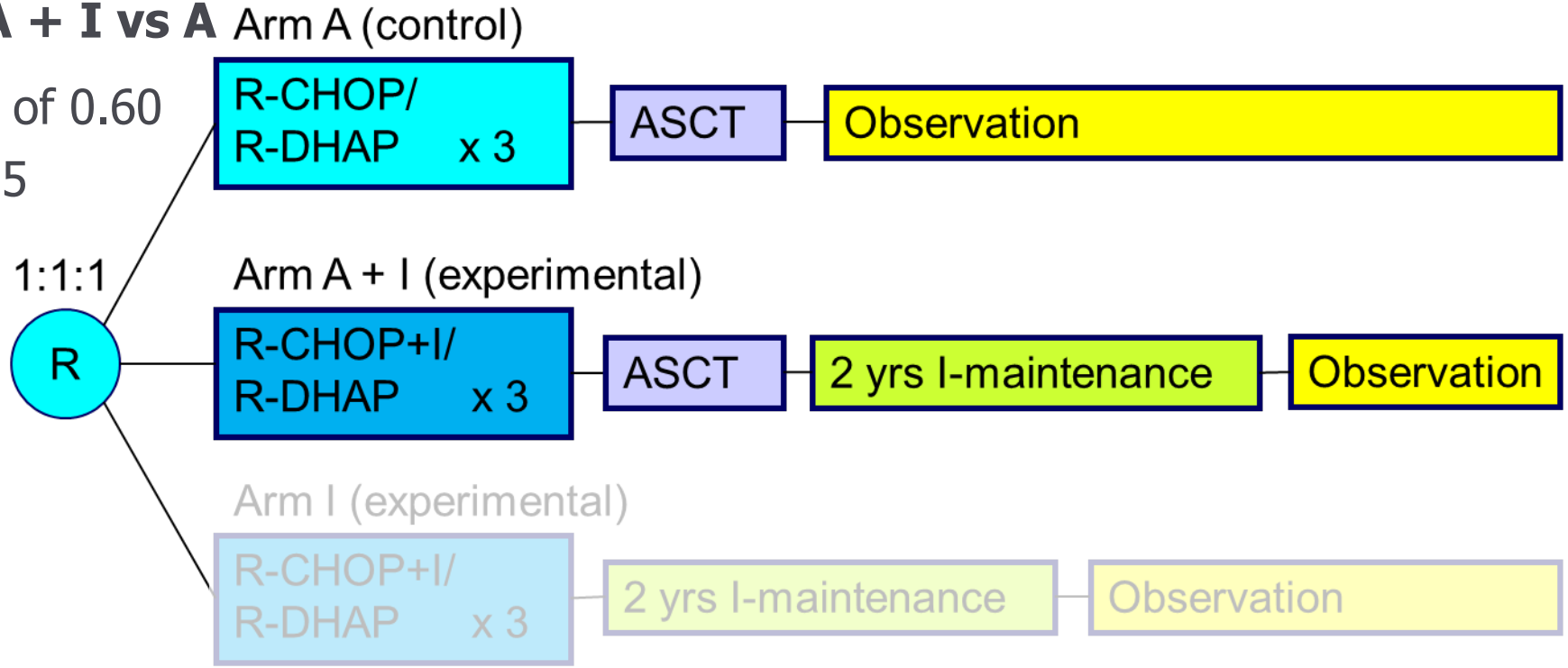
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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

TRIANGLE: Evaluation of Primary Endpoint FFS

Test 1: FFS Superiority of A + I vs A

- 90% power to detect HR of 0.60
- One-sided alpha 0.016665



All 3 hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, Whitehead, 1985)

TRIANGLE: FFS Superiority of A + I vs A

Superiority of A + I vs A (FFS) is confi

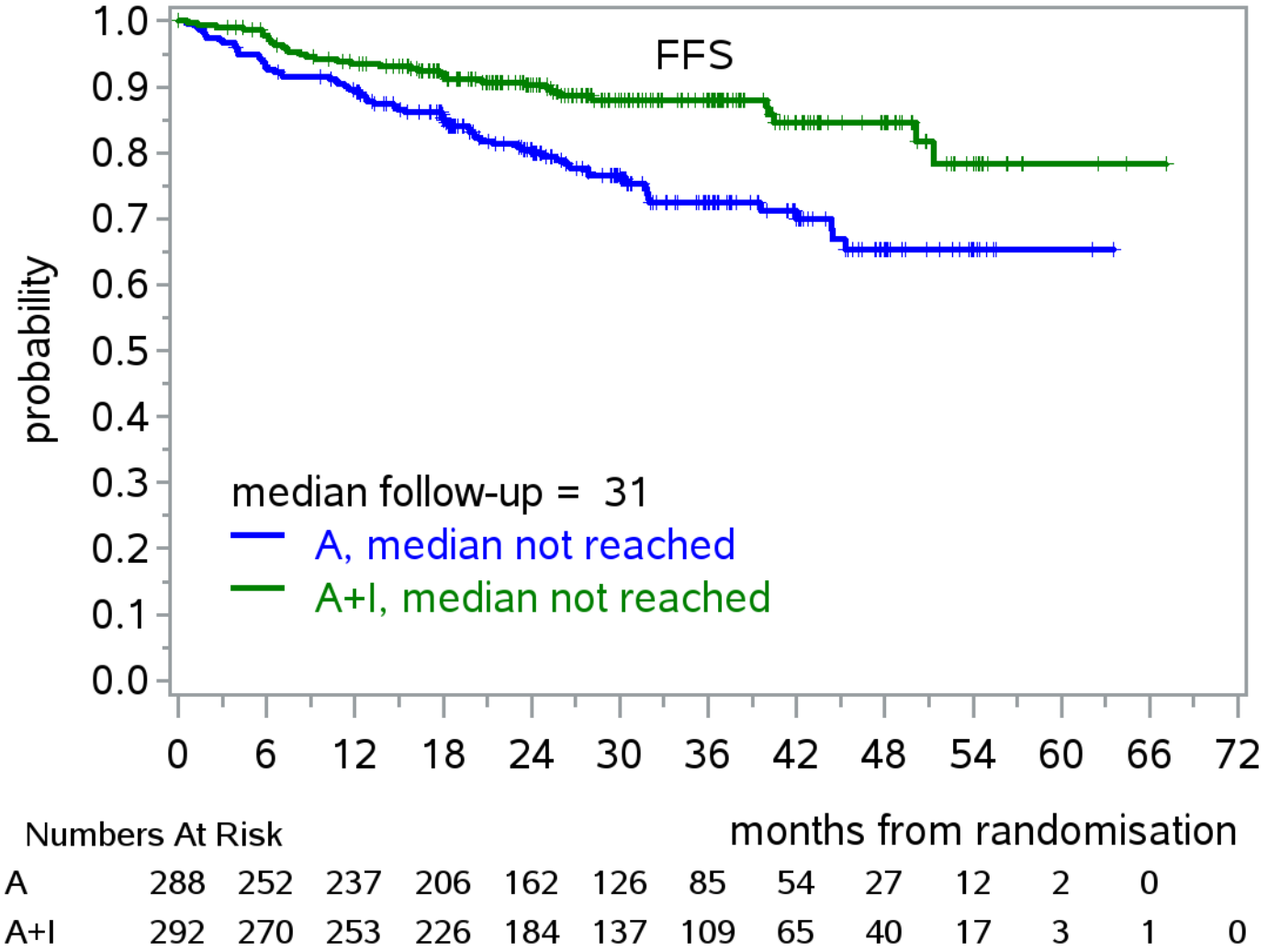
Kaplan-Meier plots:

- 3-year FFS A + I: 88%
- 3-year FFS A: 72%

***P*-value (corrected for sequential des**

***P* = .0008**

HR (A + I vs A): HR = 0.52

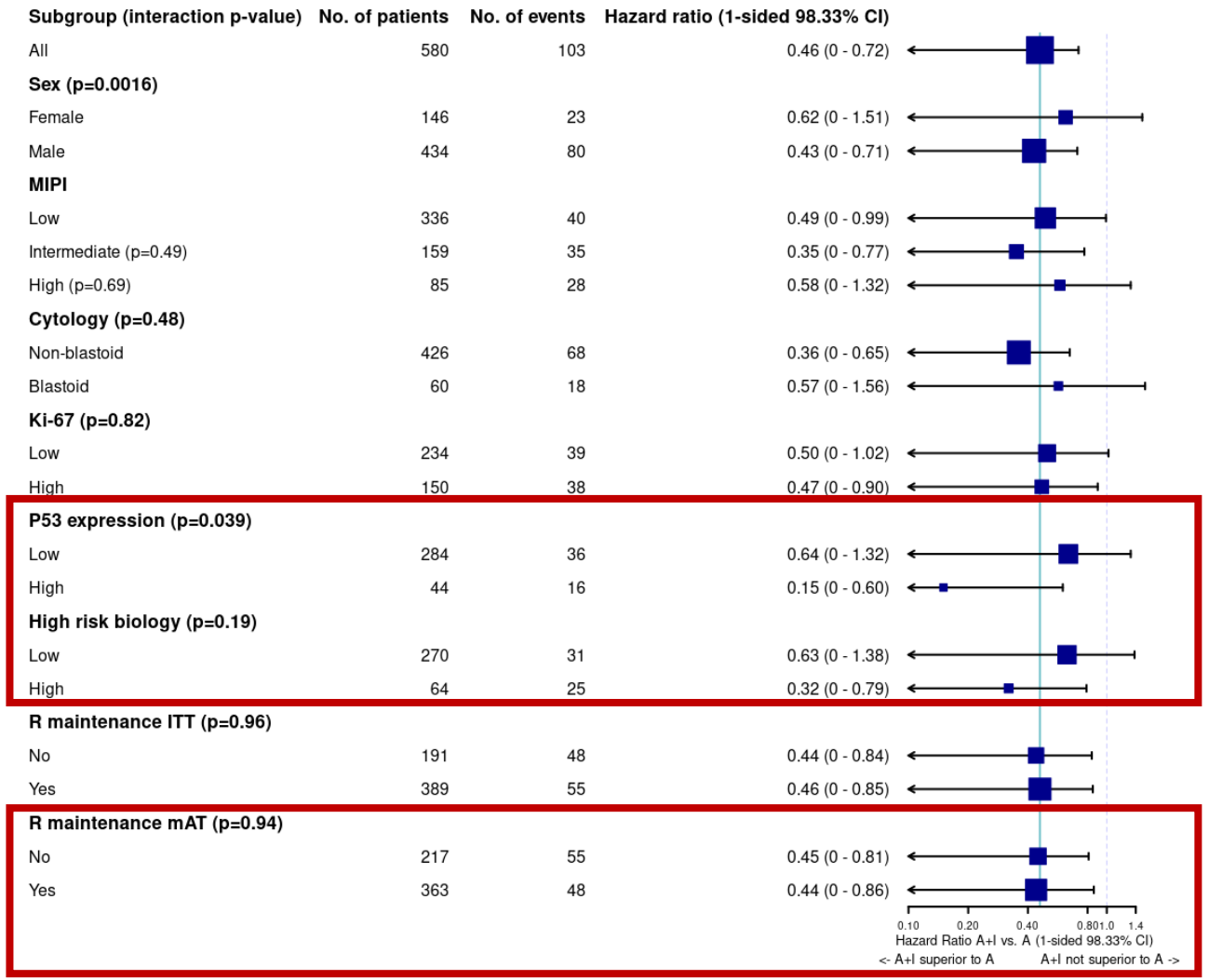


A arm: R-CHOP/R-DHAP + ASCT; A + I arm: IR-CHOP/R-DHAP + ASCT + I

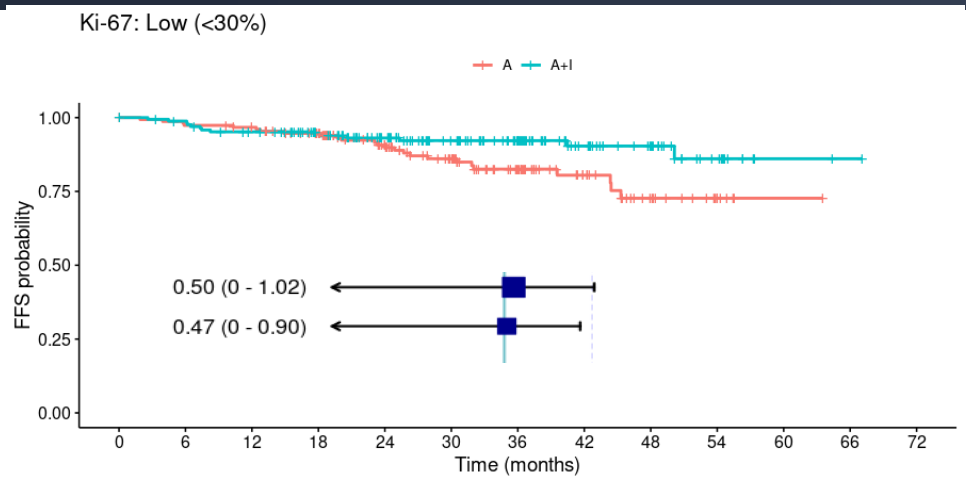
TRIANGLE: FFS Superiority of A + I vs A

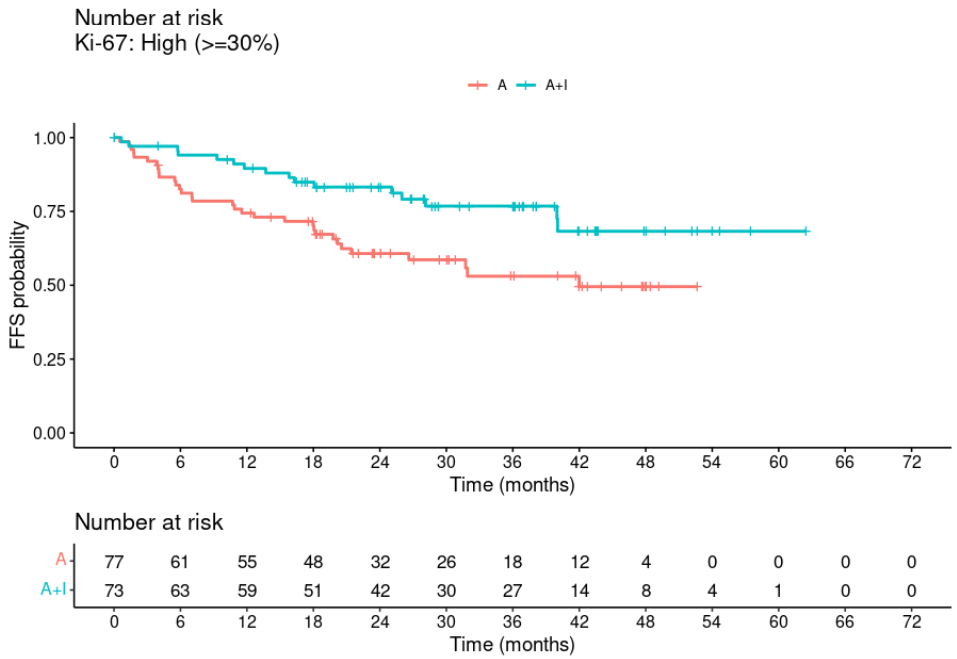
- Similar in all MIPI groups
- No differential efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend toward higher efficacy in high-risk biology
- No differential efficacy by rituximab maintenance

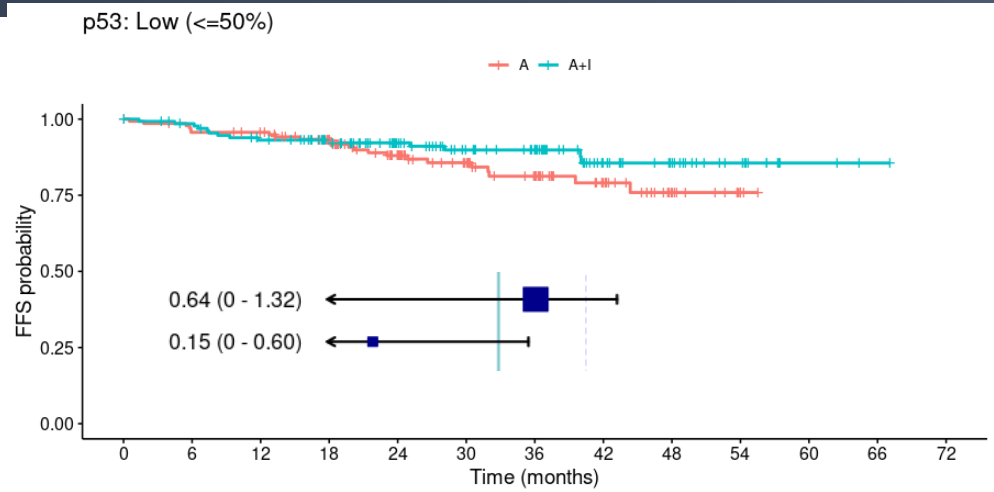
A arm: R-CHOP/R-DHAP + ASCT
A+I arm: IR-CHOP/R-DHAP + ASCT + I

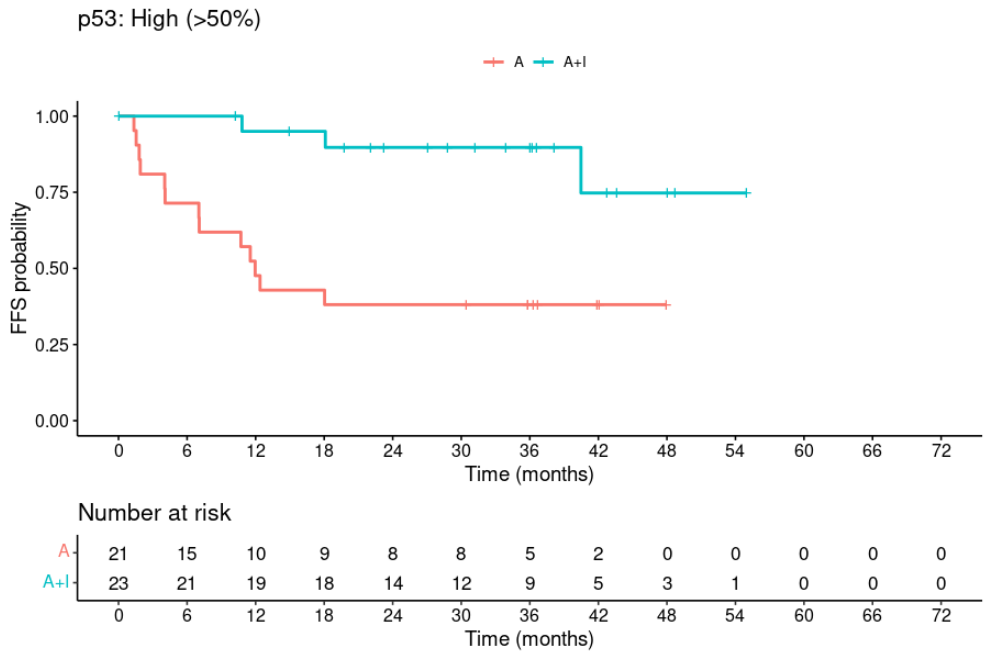


TRIANGLE: FFS Superiority of A + I vs A









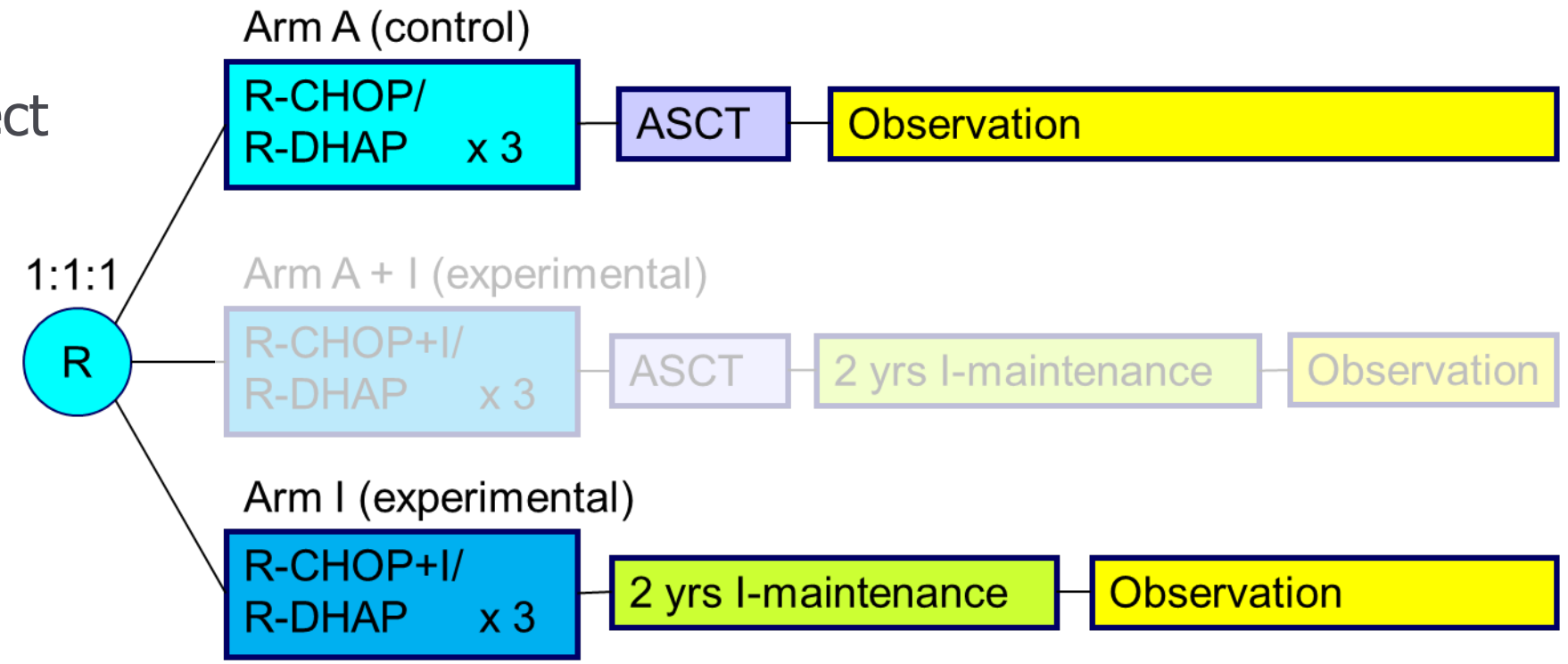
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: Evaluation of Primary Endpoint FFS

Test 2: FFS

Superiority of A vs I

- 95% power to detect HR of 0.60
- One-sided alpha 0.016665



All 3 hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, Whitehead, 1985)

TRIANGLE: No FFS Superiority of A vs I

Superiority of A vs I (FFS) was rejecte

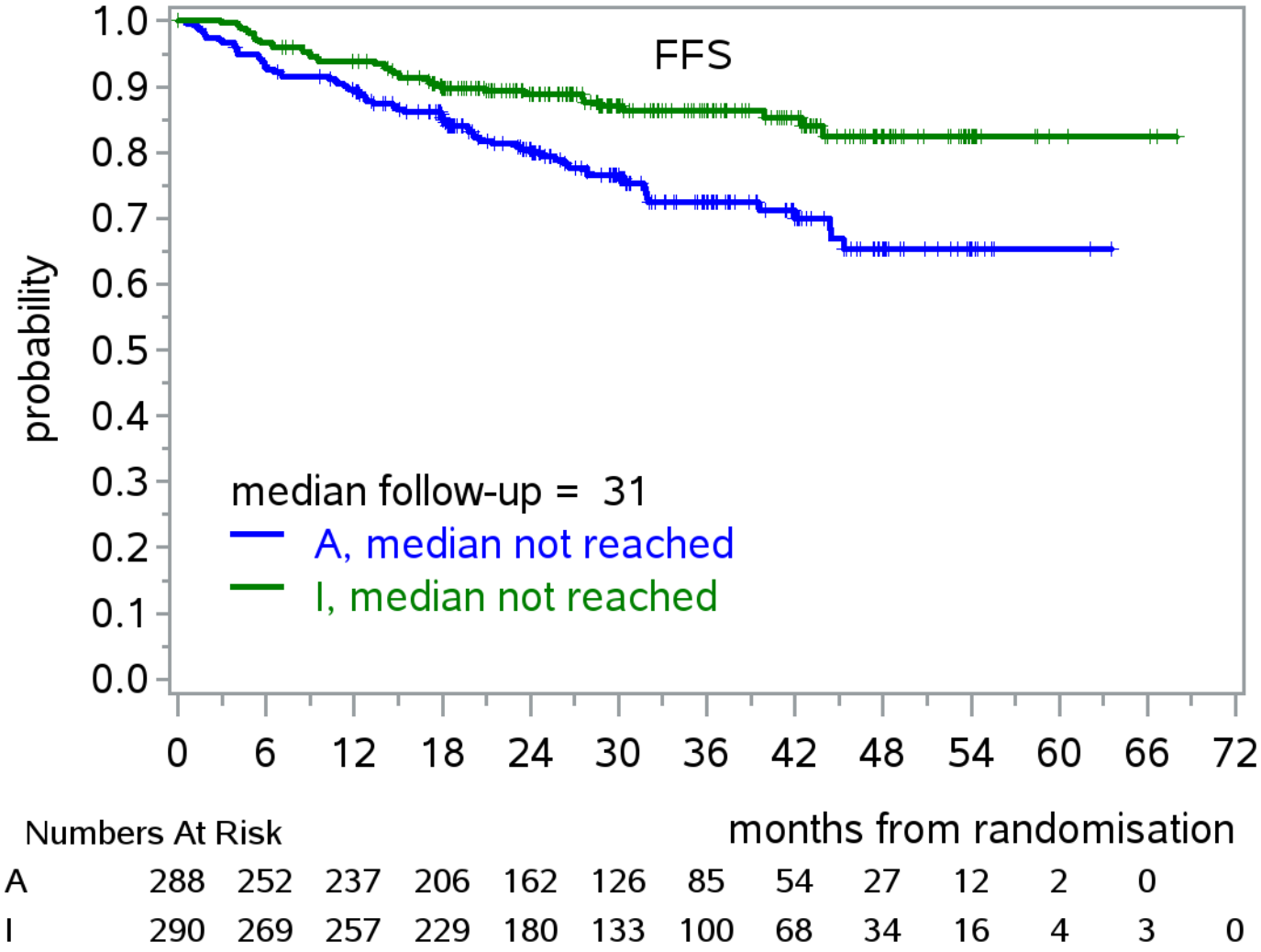
Kaplan-Meier plots:

- 3-year FFS A: 72% (MCL Younger: 75%)
- 3-year FFS I: 86%

***P*-value corrected for sequential desig**

***P* = .9979**

HR (A vs I): HR = 1.77

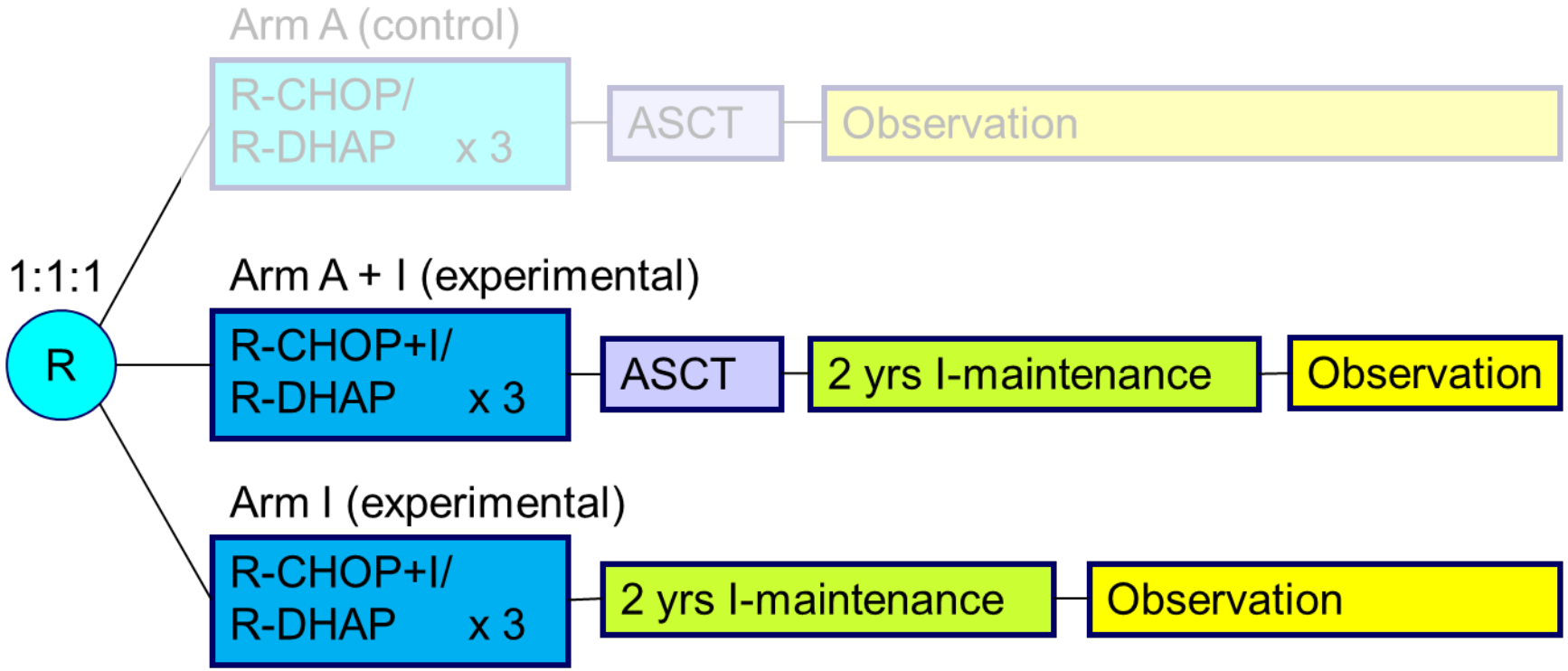


A arm: R-CHOP/R-DHAP+ASCT; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: Evaluation of Primary Endpoint FFS

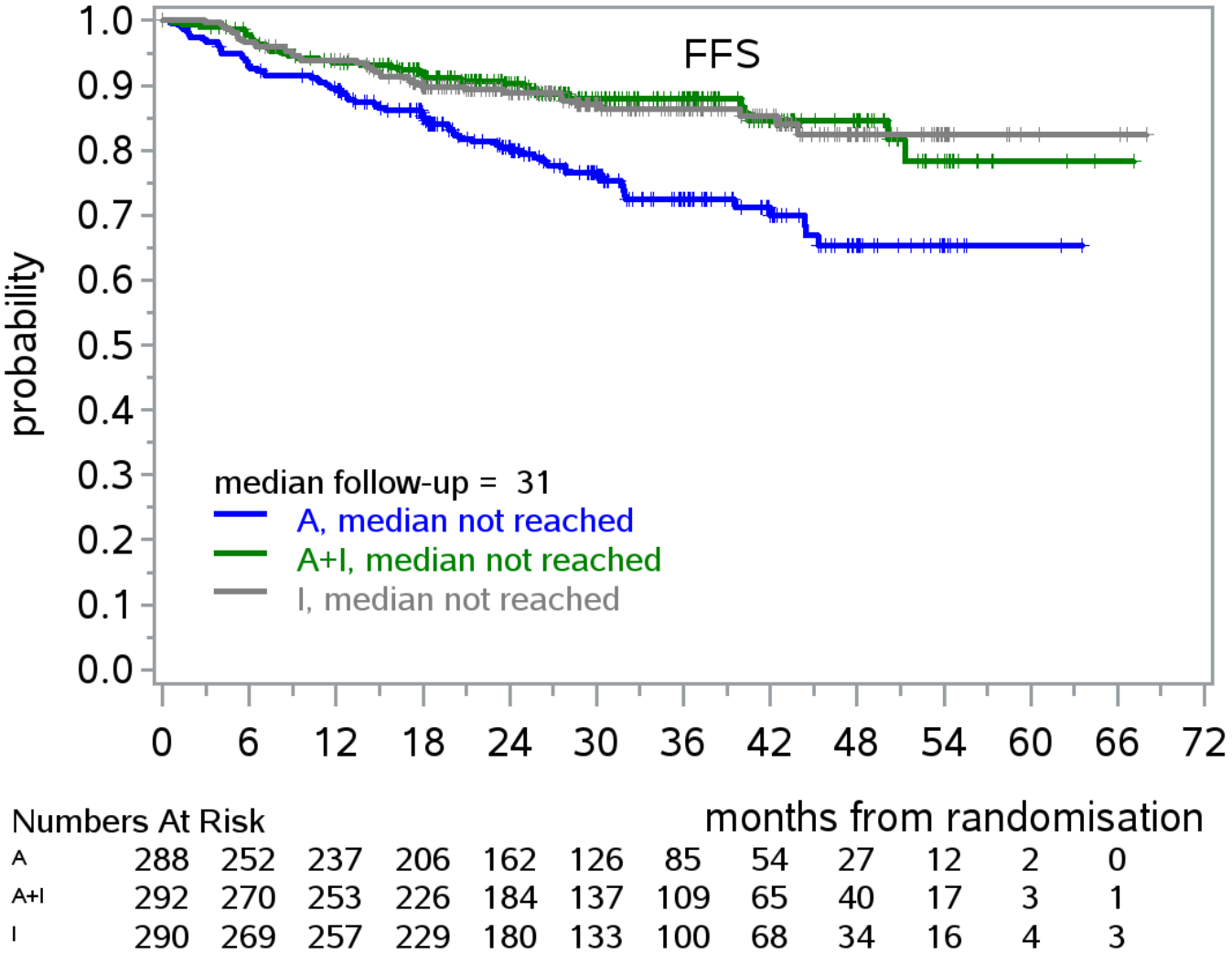
Test 3: FFS Superiority of A + I vs I

- 90% power to detect HR of 0.60
- One-sided alpha 0.016665



All 3 hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, Whitehead, 1985)

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

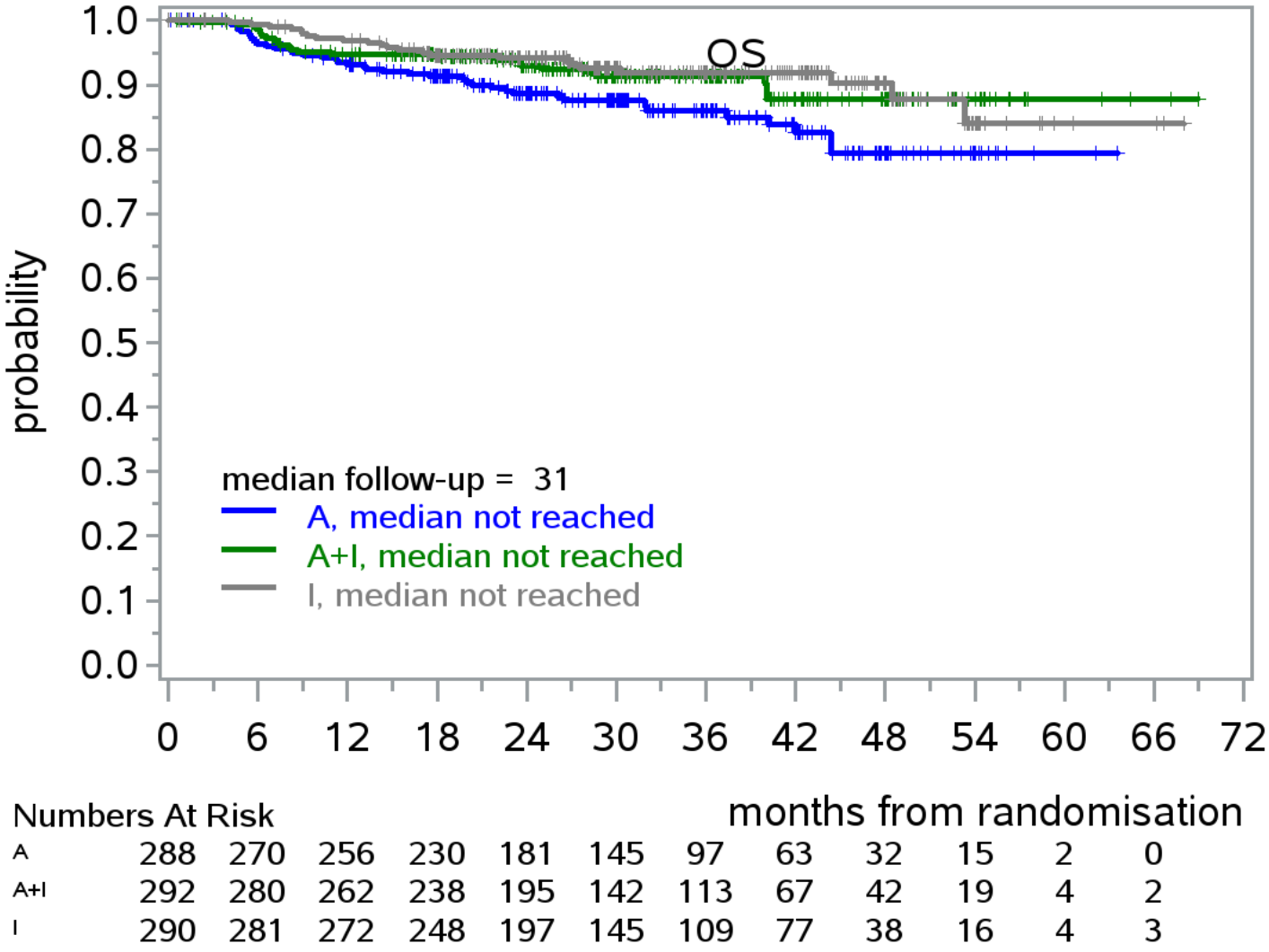
TRIANGLE: Overall Survival

3-year OS:

- A: 86% (MCL Younger exp: 84%)
- A + I: 91%
- I: 92%

Too early to evaluate statistical significance

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



TRIANGLE: Causes of Death

Cause of Death	A n = 39/288 (13.5%)		A+I N = 25/292 (8.6%)		I N = 23/290 (7.9%)	
Lymphoma	16	5.6%	4	1.4%	11	3.8%
Concomitant disease	11	3.8%	7	2.4%	5	1.7%
Lymphoma and concomitant disease	0	0%	1	0.3%	1	0,3%
Secondary malignancy	1	0.3%	2	0.7%	0	0%
Therapy	4	1.4%	3	1.0%	0	0%
Therapy and concomitant disease	1	0.3%	0	0%	0	0%
Unknown	6	2.1%	8	2.7%	6	2.1%

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

Conclusions: Current TRIANGLE Results

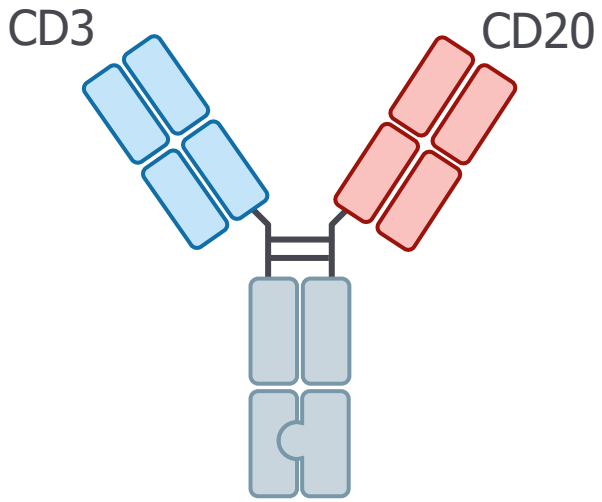
Based on FFS (primary endpoint):

- A + I (auto SCT + ibrutinib) is superior to A (auto SCT only)
- A (auto SCT) is not superior to I (ibrutinib without auto SCT)
- Currently, no decision whether autologous SCT adds to I (ibrutinib) but toxicity favors Ibrutinib only
- Numerical overall survival benefit in the ibrutinib arms (I, A + I)
- Unclear what this will do for Auto PSC – still useful in certain circumstances or relapsed patients

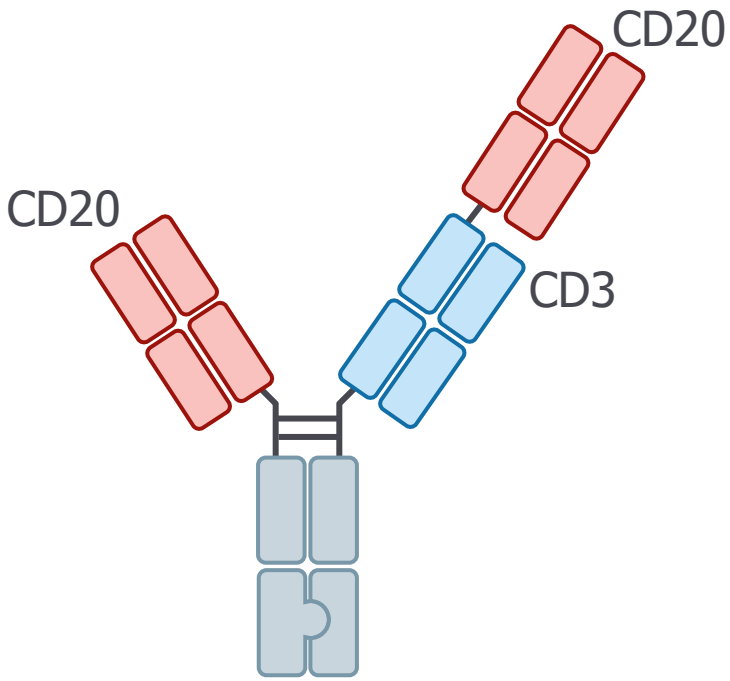
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Bispecifics in Late Stage Development in Non-Hodgkin Lymphoma

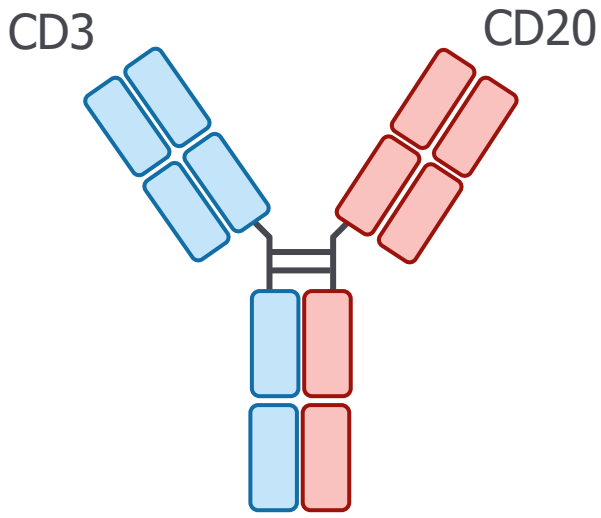
Mosunetuzumab
CD20xCD3



Glofitamab
$(CD20)_2$xCD3



Epcoritamab
CD20xCD3



Schuster SJ. Hematol Oncol. 2021;39:113-116.

610: Mosunetuzumab Monotherapy Demonstrates Durable Efficacy with a Manageable Safety Profile in Patients with Relapsed/Refractory Follicular Lymphoma who Received ≥ 2 Prior Therapies: Updated Results from a Pivotal Phase II Study

Nancy L. Bartlett, Laurie H. Sehn, Matthew Matasar, Stephen J. Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta Nastoupil, Michael C. Wei, Shen Yin, Iris To, Huang Huang, Juliana Min, Elicia Penuel, Christopher R. Bolen, L. Elizabeth Budde

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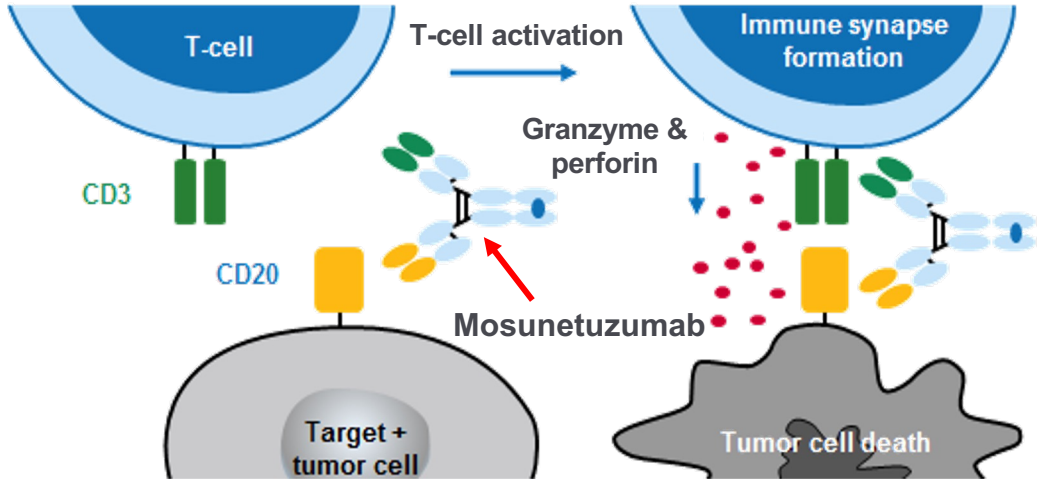
Background

Mosunetuzumab (first-in-class) is approved in the EU and US for the treatment of relapsed/refractory follicular lymphoma (R/R FL) after ≥ 2 prior systemic therapies[a,b]

- ORR 80%, CR 60%, majority maintaining response after 18 months[c]
- Consistent benefit in patients with double-refractory disease and POD24[c]
- Off-the-shelf, fixed-duration treatment that can be administered in the outpatient setting[c]

Mosunetuzumab: CD20 x CD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells[d,e]



We present updated results after a median 28.3 months of follow-up (cut-off: July 8, 2022)

a. Mosunetuzumab [PI]. Approved 2022. Revised December 2022; b FDA Drug Approvals and Databases https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma Accessed January 9, 2023; c. Budde LE, et al. Lancet Oncol 2022;23:1055-1065; d. Sun LL, et al: Sci Transl Med. 2015;7:287ra70; e. Hernandez G, et al. Blood. 2019;134: Poster 1585.

Study Design

Pivotal, Single-Arm, Multicenter, Phase II Expansion in Patients With R/R FL and ≥ 2 Prior Therapies

Key Inclusion Criteria

- FL Grade 1 to 3a
- ECOG PS 0 to 1
- ≥ 2 prior therapies including an anti-CD20 antibody and an alkylator

Data Analysis

Study met its primary endpoint: 60% CR rate vs 14% historical control ($P < .0001$)

Updated efficacy and safety analysis with median 28.3 months of follow up (10 months after the previous report)

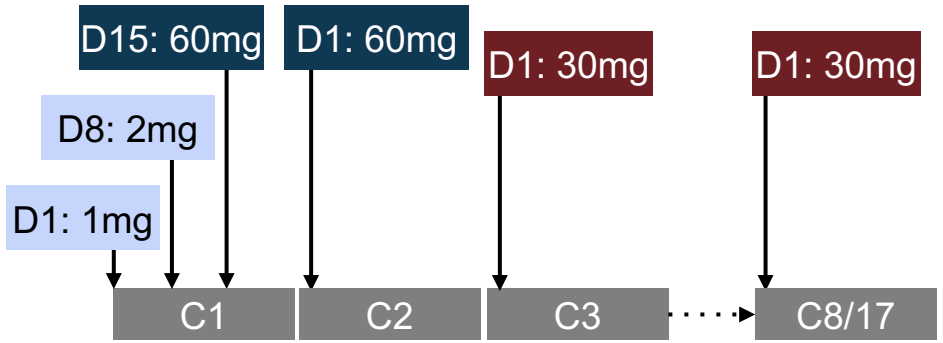
Mosunetuzumab Administration

IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1

Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8

Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR

No mandatory hospitalization



Response Rates

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

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

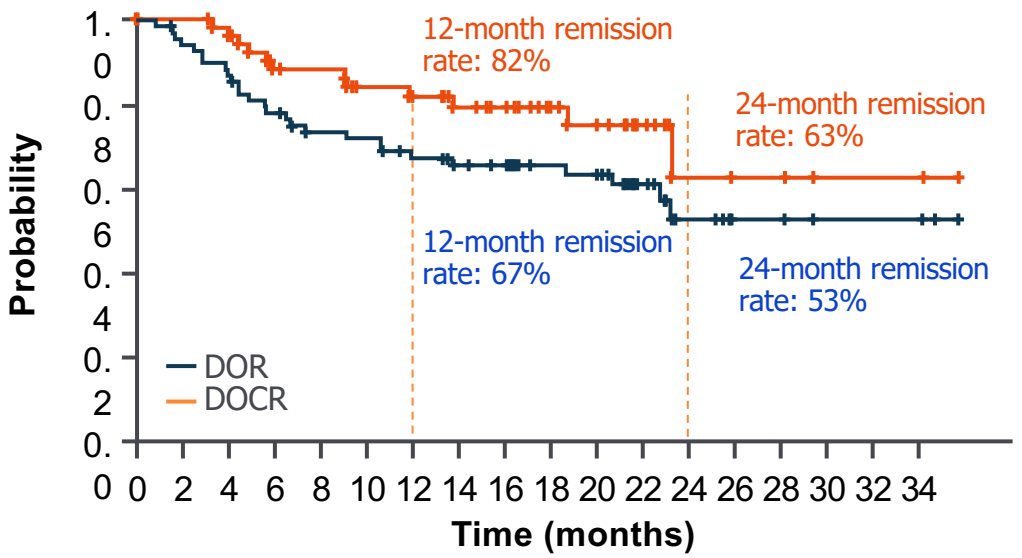
High ORR and CR rate were consistent with published results

Budde LE, et al. Lancet Oncol. 2022;23:1055-1065.

Durability of Responses

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

DOR and DOCR



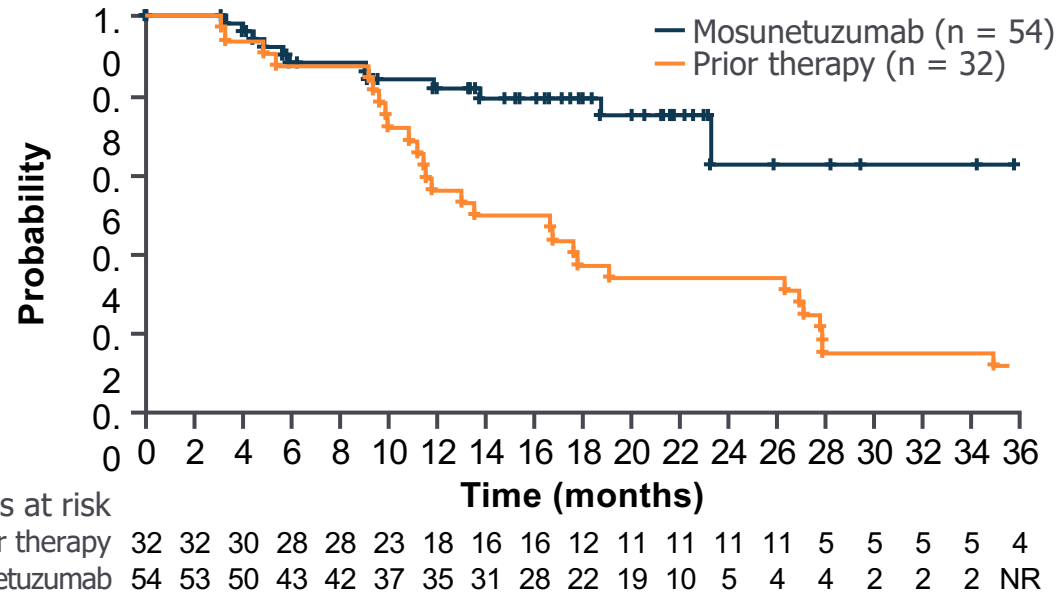
Patients at risk	70	65	60	52	48	47	42	39	37	30	29	18	9	5	5	3	3	3
Patients at risk	54	53	50	43	42	37	35	31	28	22	19	10	5	4	4	2	2	2

Durable responses: majority of patients in remission after 2 years

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

DOCR and PFS With Mosunetuzumab vs Last Prior Therapy

DOCR

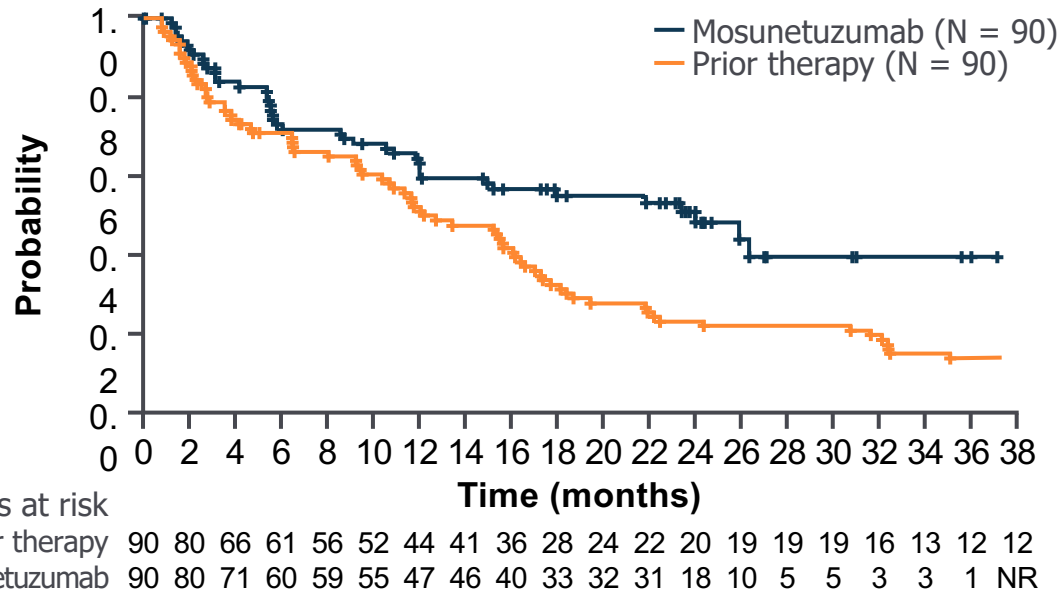


Patients at risk

Prior therapy	32	32	30	28	28	23	18	16	16	12	11	11	11	11	5	5	5	5	4
Mosunetuzumab	54	53	50	43	42	37	35	31	28	22	19	10	5	4	4	2	2	2	NR

	Mosunetuzumab (n = 54)	Last prior therapy (n = 32)
Median DOCR, months (95% CI)	**NR** (23, NR)	**15** (11 to 26)

PFS



Patients at risk

Prior therapy	90	80	66	61	56	52	44	41	36	28	24	22	20	19	19	19	16	13	12	12
Mosunetuzumab	90	80	71	60	59	55	47	46	40	33	32	31	18	10	5	5	3	3	1	NR

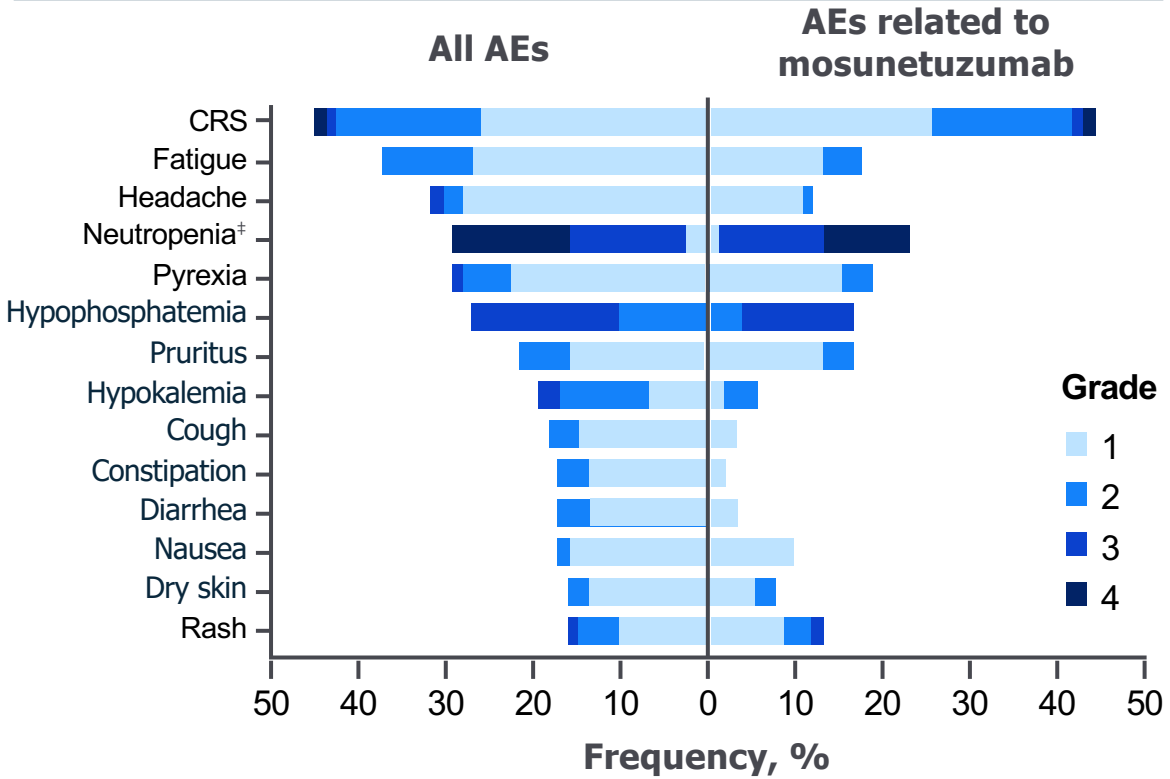
	Mosunetuzumab (N = 90)	Last prior therapy (N = 90)
Median PFS, months (95% CI)	**24** (12, NR)	**12** (10 to 16)

Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Safety Profile

Adverse Events (AEs)	N = 90
AE Mosunetuzumab-related	100% 92%
Grade 3/4 AE Mosunetuzumab-related	70% 51%
Serious AE Mosunetuzumab-related	47% 33%
Grade 5 (fatal) AE Mosunetuzumab-related	2%* 0
AE leading to treatment discontinuation Mosunetuzumab-related	4%† 2%

AEs (≥ 15%) by Grade and Relationship With Mosunetuzumab



No new serious AEs, Grade ≥ 3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up

*Malignant neoplasm progression (n=1) and unexplained death (n=1). †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each). ‡Grouped term including preferred term 'neutropenia' and 'neutrophil count decreased'.

Conclusions

Pivotal Phase II study of mosunetuzumab continues to demonstrate:

- Clinically meaningful outcomes in heavily pre-treated R/R FL patients, after more than 2 years of follow-up: CR rate, 60%; 24-month DOCR, 63%
- A manageable safety profile with no new CRS events and no late-onset or chronic toxicities

Mosunetuzumab substantially improved tumor response and PFS vs patients' last prior therapy

Mosunetuzumab is a promising treatment option, as an off-the-shelf, outpatient therapy with a fixed duration of treatment

Recently FDA approved for R/R FL patients

Relapse is Uncommon in Patients With Large B-Cell Lymphoma Who Are in Complete Remission at the End of Fixed-Course Glofitamab Treatment

Martin Hutchings, Carmelo Carlo-Stella, Franck Morschhauser, Emmanuel Bachy, Paolo Corradini, Gloria Iacoboni, Cyrus Khan, Krish Patel, Mark Hertzberg, Lorenzo Falchi, Nancy L. Bartlett, Joshua Brody, Linda Lundberg, Yuying Xie, Estefania Mulvihill, Pauline Baumlin, James Relf, Emily Piccione, Kathryn Humphrey, Michael Dickinson

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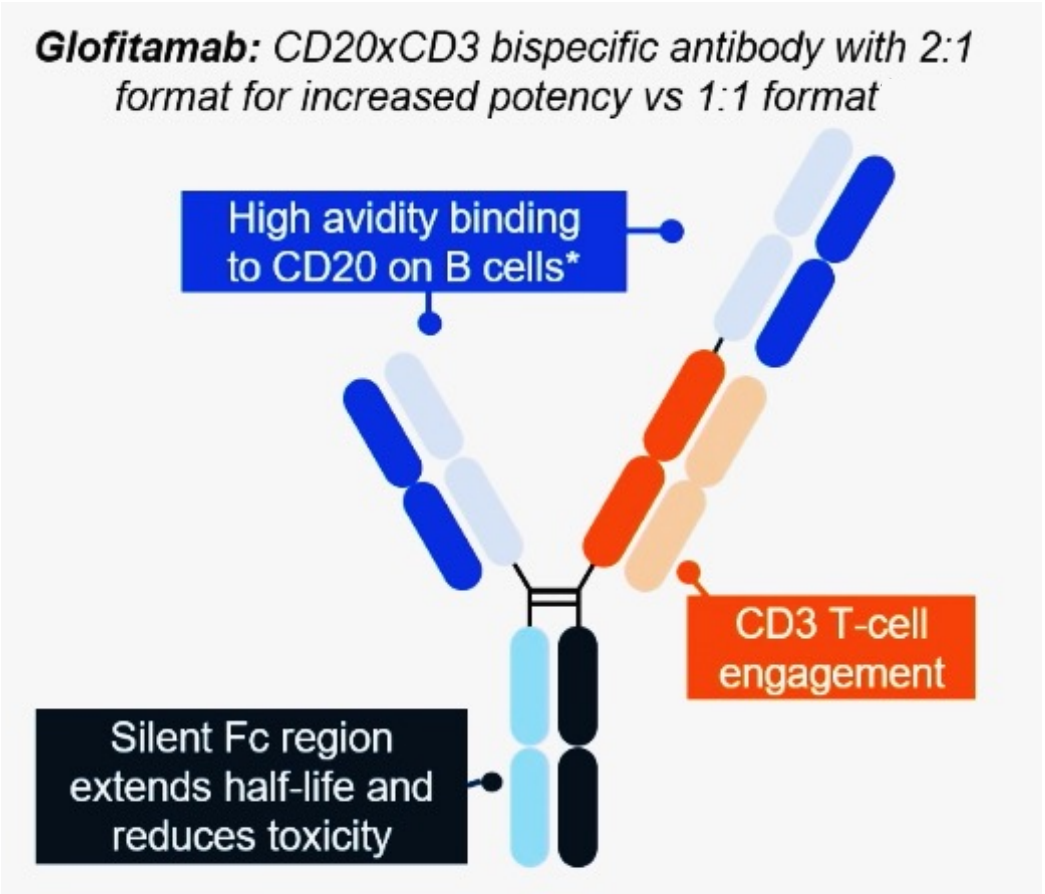
Background

Glofitamab

- Redirects T cells to eliminate B cells[a]
- Off-the-shelf treatment, administered for a fixed duration of up to 12 cycles[a,b]

Phase I/II experience (NCT03075696)[b]

- Glofitamab has induced frequent and durable complete responses (CRs) and demonstrated a manageable safety profile in patients with R/R LBCL and other B-cell NHL subtypes[c,d]



Aim: present data for the duration of remission from end-of-treatment (EOT) in patients with R/R LBCL†

*Obinutuzumab binds to the same CD20 epitope as glofitamab; †DLBCL NOS, HGBCL, PMBCL, trFL.
DLBCL, diffuse large a-cell lymphoma; HGBCL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; NOS, not otherwise specified; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

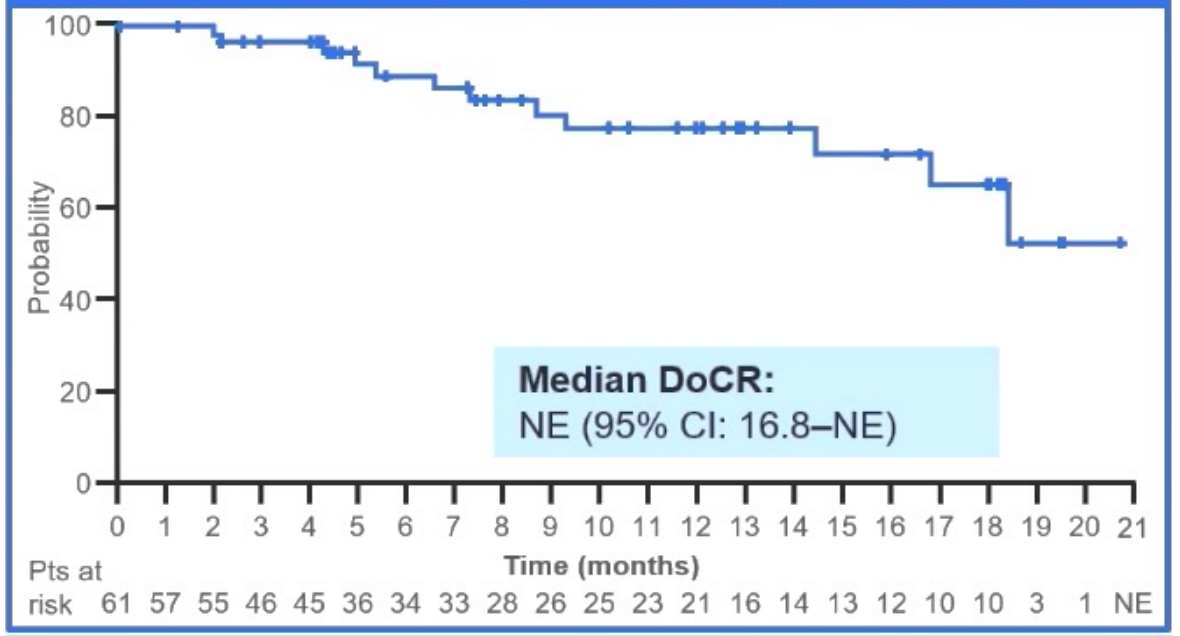
a. Bacac M, et al. Clin Cancer Res. 2018;24:4785-4797; b. ClinicalTrials.gov. Accessed December 28, 2022. https://www.clinicaltrials.gov/ct2/show/NCT03075696; c. Dickinson M, et al. J Clin Oncol. 2022;40(16_suppl):7500; d. Hutchings M, et al. J Clin Oncol. 2021;39:1959-1970.

Background: Glofitamab Monotherapy at RP2D Induces Durable Complete Responses

Pivotal Phase II results presented at ASCO 2022

- DLBCL NOS, HGBCL, trFL, or PMBCL; ≥ 2 prior therapies
- Glofitimab 2.5 mg/10 mg/30 mg (N = 155)
- Efficacy
  - **CR rate:** 39.4% (61/155)
  - **ORR:** 51.6% (80/155)
- Safety
  - Glofitimab was well-tolerated with a low rate of discontinuation
  - CRS was mostly low-grade

Pivotal Phase II cohort (ASCO 2022) – DoCR* 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)

Clinical cut-off date: March 14, 2022.
*Time from the initial occurrence of a CR until PD or death due to any cause, whichever occurs first. CRS, cytokine release syndrome; DoCR, duration of complete response; IRC, Independent Review Committee; PD, progressive disease.
Dickinson M, et al. J Clin Oncol. 2022;40(16_suppl):7500.

Study Overview

Phase I/II Dose Escalation and Expansion in Patients With R/R LBCL

- Glofitimab IV administration fixed dose (0.6 mg to 25 mg) or with step-up dosing during C1 (target dose: 16 mg or 30 mg) every three weeks, maximum 13 infusions
- Obinutuzumab pretreatment (1 × 1000 mg) to mitigate CRS
- Fixed duration treatment* maximum 12 cycles† (8.3 months)
- Optional re-treatment in patients with PD after prior response

*Earlier protocol version allowed treatment cessation after 8 cycles; †21-day cycles; ‡Response assessments at C3 and C6.

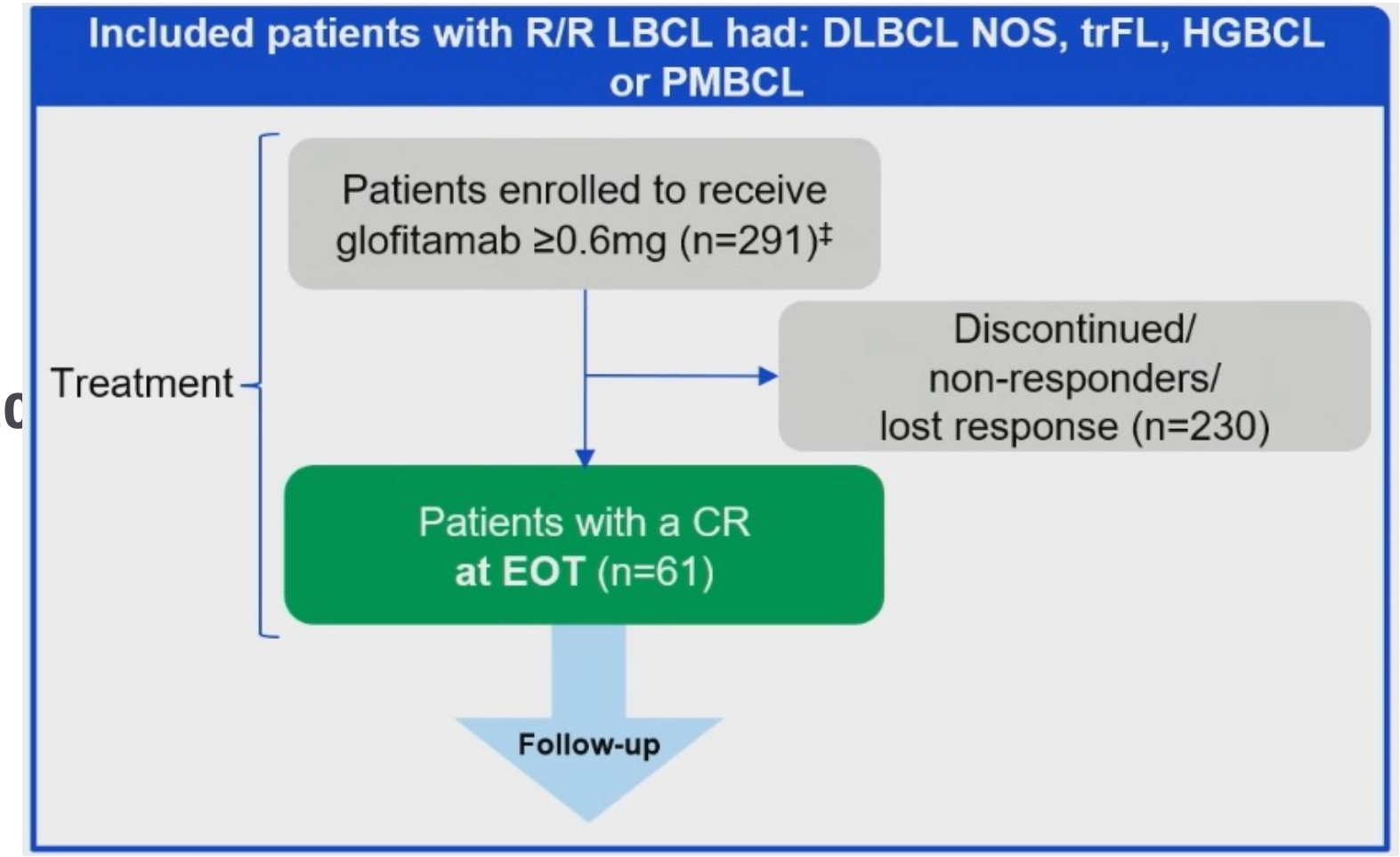
Outcomes in Patients With R/R LBCL

Best overall response*:

- CR: 35.4% (103/291)
- PR: 17.2% (50/291)
- ORR: 52.6% (153/291)

Median time to first CR (N = 10

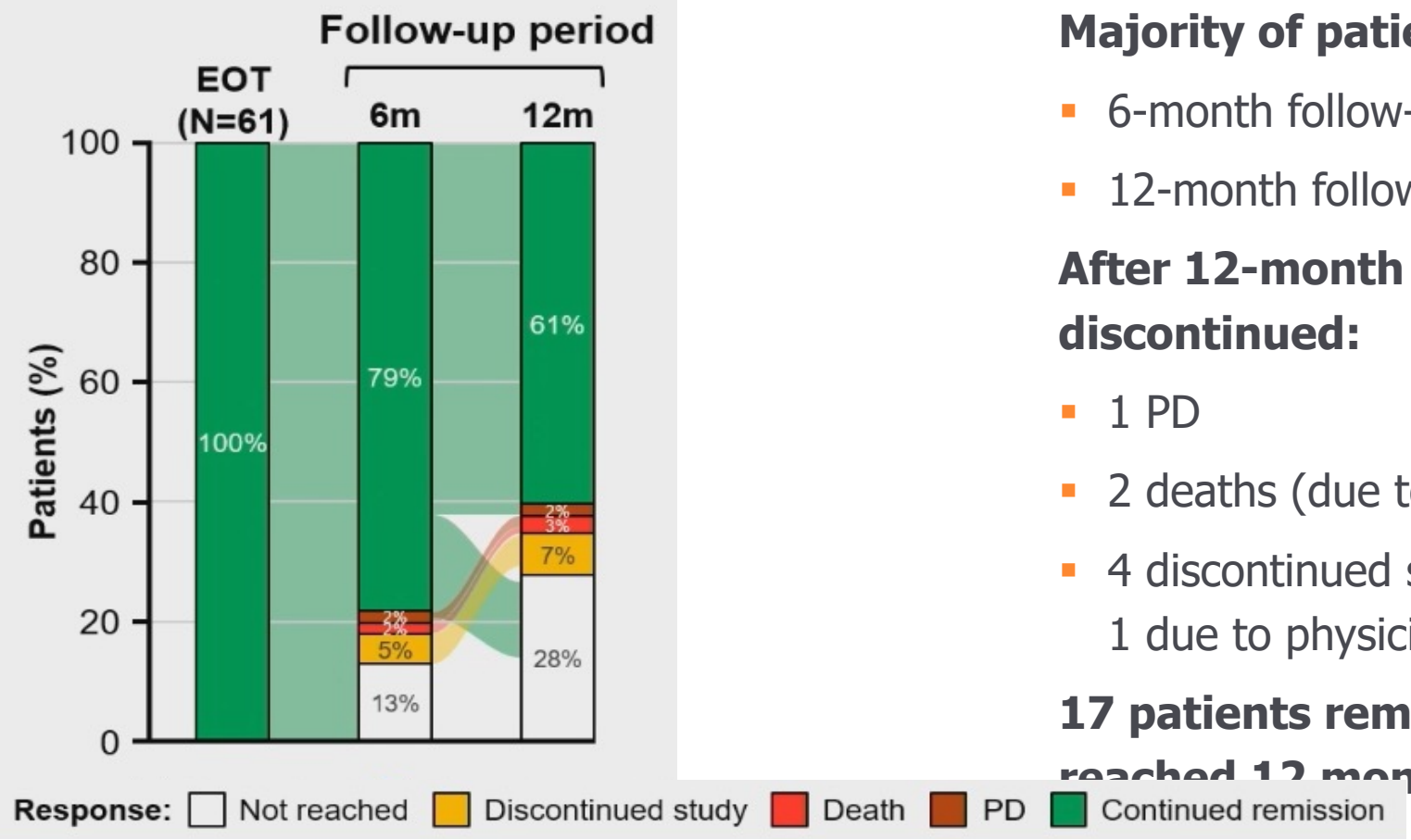
- 43 days



Complete remissions are achieved early in patients with R/R LBCL

*Investigator-assessed; †CR as best overall response on treatment; ‡Includes patients with ≥ 2 prior therapies enrolled to receive glofitimab 2.5/10/30 mg (n = 155)

Remission at 12 Months Post-EOT in Patients With CR at EOT



Majority of patients remain in remission:

- 6-month follow-up: 79% (48/61)
- 12-month follow-up: 61% (37/61)

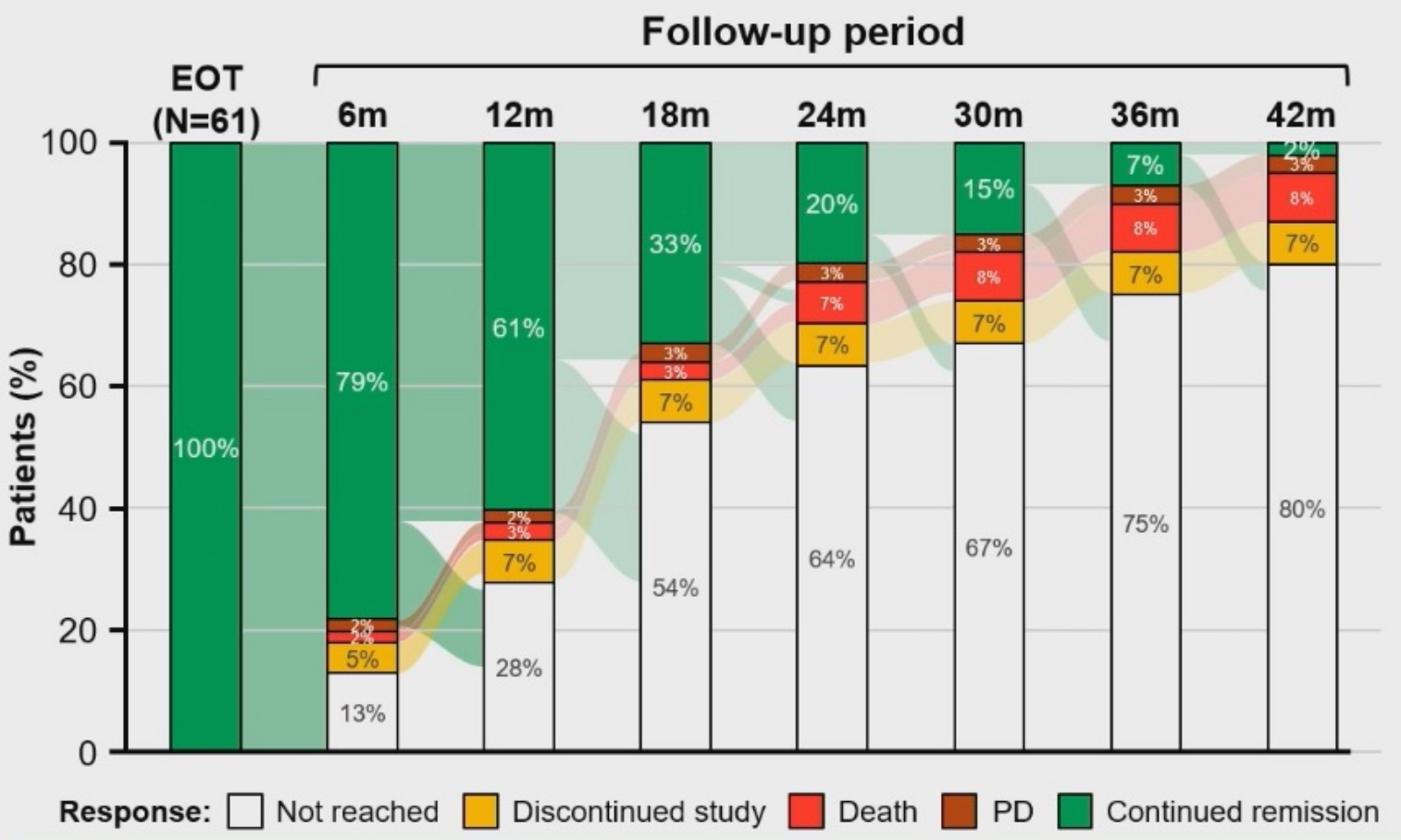
After 12-month follow-up, 12 patients had discontinued:

- 1 PD
- 2 deaths (due to lymphoma)
- 4 discontinued study (2 received allogeneic transplant, 1 due to physician decision, 1 lsot to follow-up)

17 patients remained in follow-up but had not yet reached 12 months

Majority of patients remain in remission 12 months after cessation of therapy

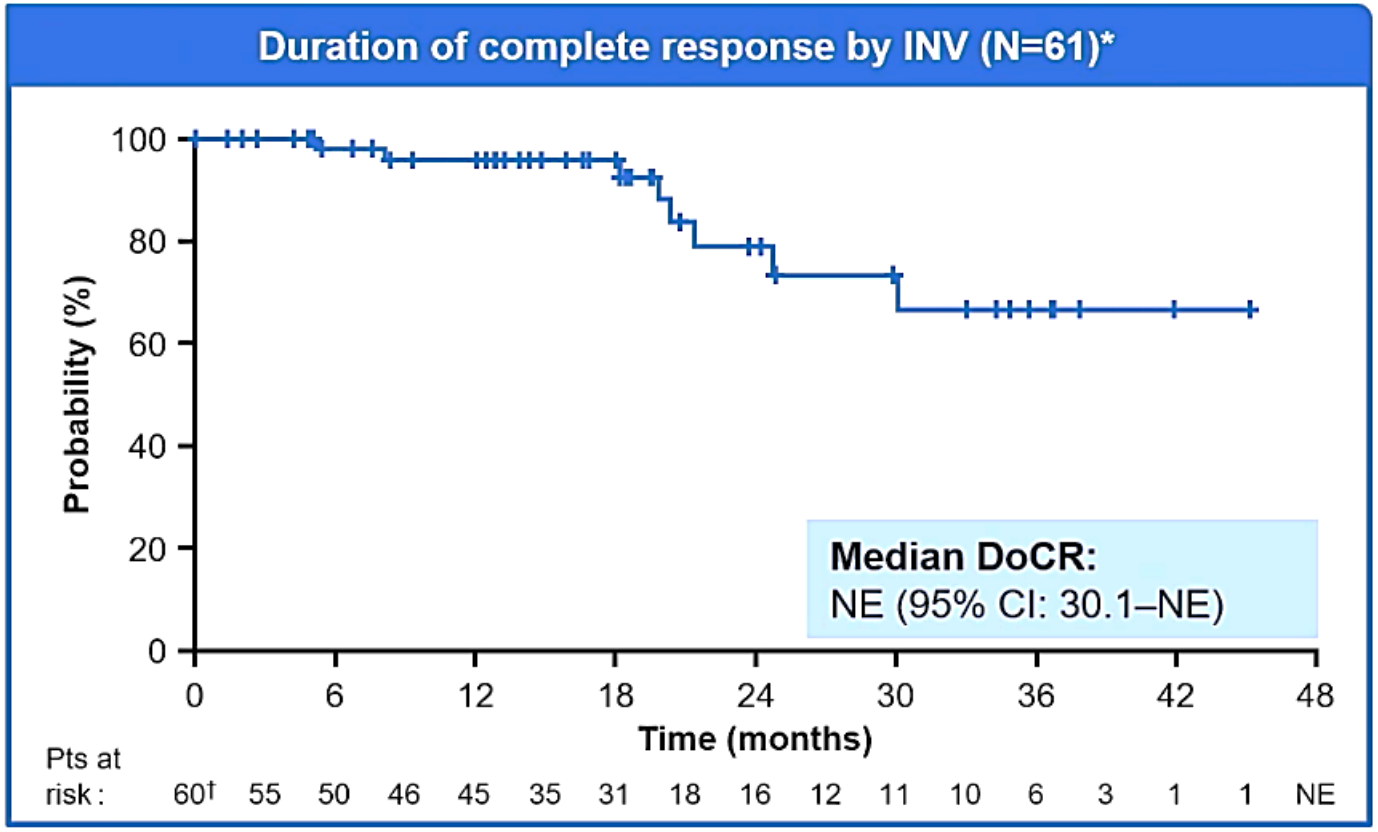
Remissions Beyond EOT in Patients With CR at EOT



- Longer follow-up is needed beyond 12 months after EOT
- Of the patients still in remissions at 12 months, 2 patients subsequently had PD
  - Both patients initiated re-treatment 12 to 18 months post-EOT and achieved a CR

Although longer follow-up is needed, the majority of patients remain in remission beyond EOT

Durable Response After First CR



	N=61
Median DoCR follow-up from first CR, months (95% CI)	18.1 (14.8–20.7)
Median DoCR follow-up from EOT, months (95% CI)	11.5 (10.5–16.4)
Median DoCR, months (95% CI)	NE (30.1–NE)
24-months DoCR, % (95% CI)	79.1 (63.3–95.0)
CRs ongoing at CCOD, n (%)	52 (85.2)

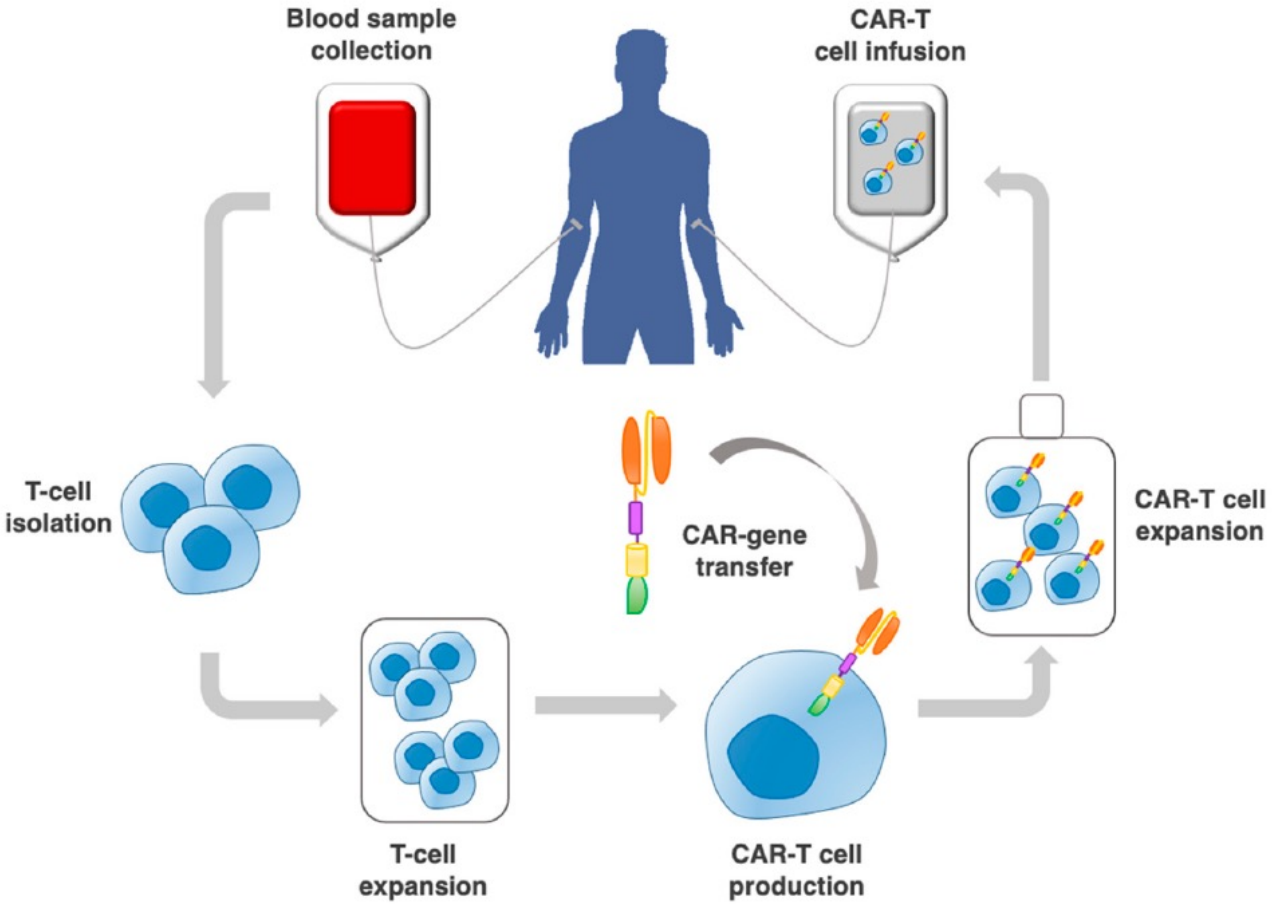
CRs remain durable with significant follow-up (11.5 months) post-EOT

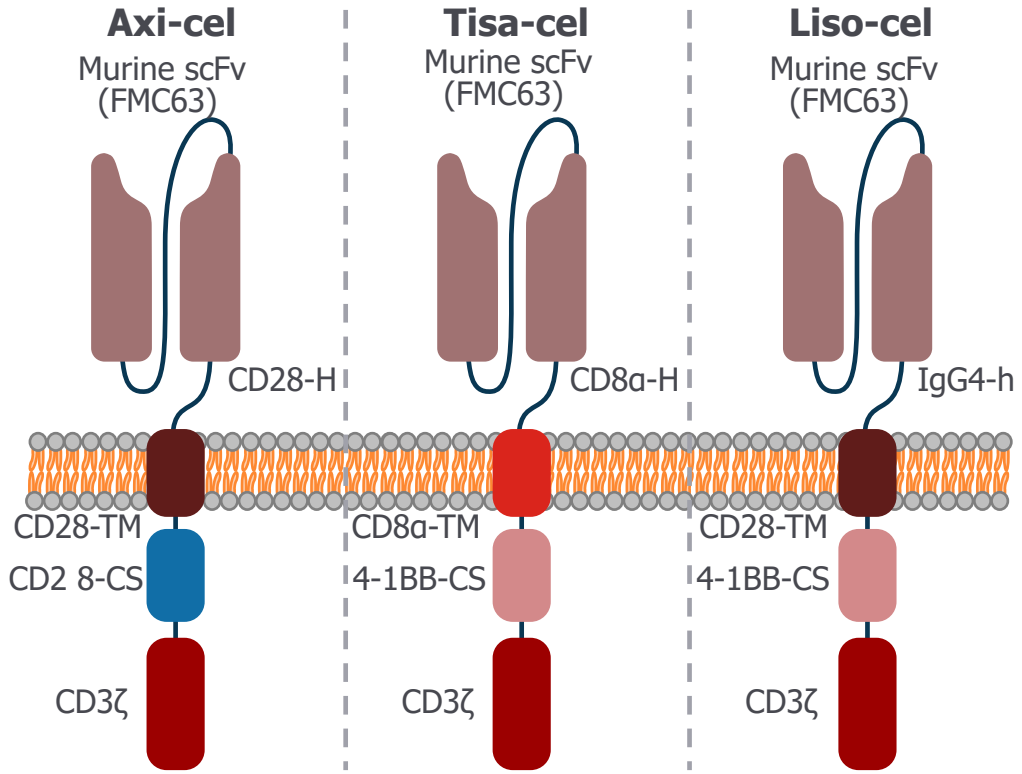
*Time from the initial occurrence of a CR until PD or death due to any cause. whichever occurs first; †1 patient had pseudoprogression prior to CR at EOT visit and is, by definition, excluded from DoCR analysis.

Conclusions

- Glofitamab is administered every 3 weeks for a fixed treatment duration of 12 cycles or 13 infusions (approximately 8.3 months)
- Off-treatment progression is uncommon in heavily pre-treated, highly refractory patients with LBCL who are in CR at the end of treatment
- Estimated rate of patients with a CR lasting a minimum of two years is 79%

CAR T-Cell Therapy





Axi-ce;, axicabtagene ciloleucel; Liso-cell, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel

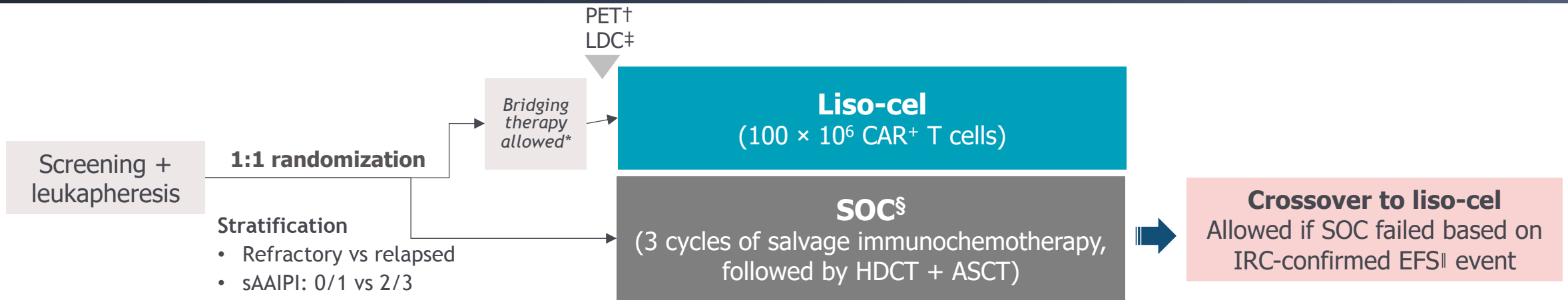
Guerra E, et al. Int J Mol Sci. 2021;23(1):405; Roex G, et al. Pharmaceutics. 2020;12:194.

Lisocabtagene Maraleucel Versus Standard of Care With Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients With Relapsed or Refractory Large B-Cell Lymphoma: Primary Analysis of the Randomized, Phase 3 TRANSFORM Study

Jeremy S. Abramson, Scott R. Solomon, Jon Arnason, Patrick B. Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Manali Kamdar

ASH 2022

TRANSFORM: Study Design



Key patient eligibility criteria

- Age 18 to 75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for ASCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count

Primary endpoint

- EFS‖ (per IRC)

Key secondary endpoints

- CR rate (per IRC), PFS (per IRC), OS

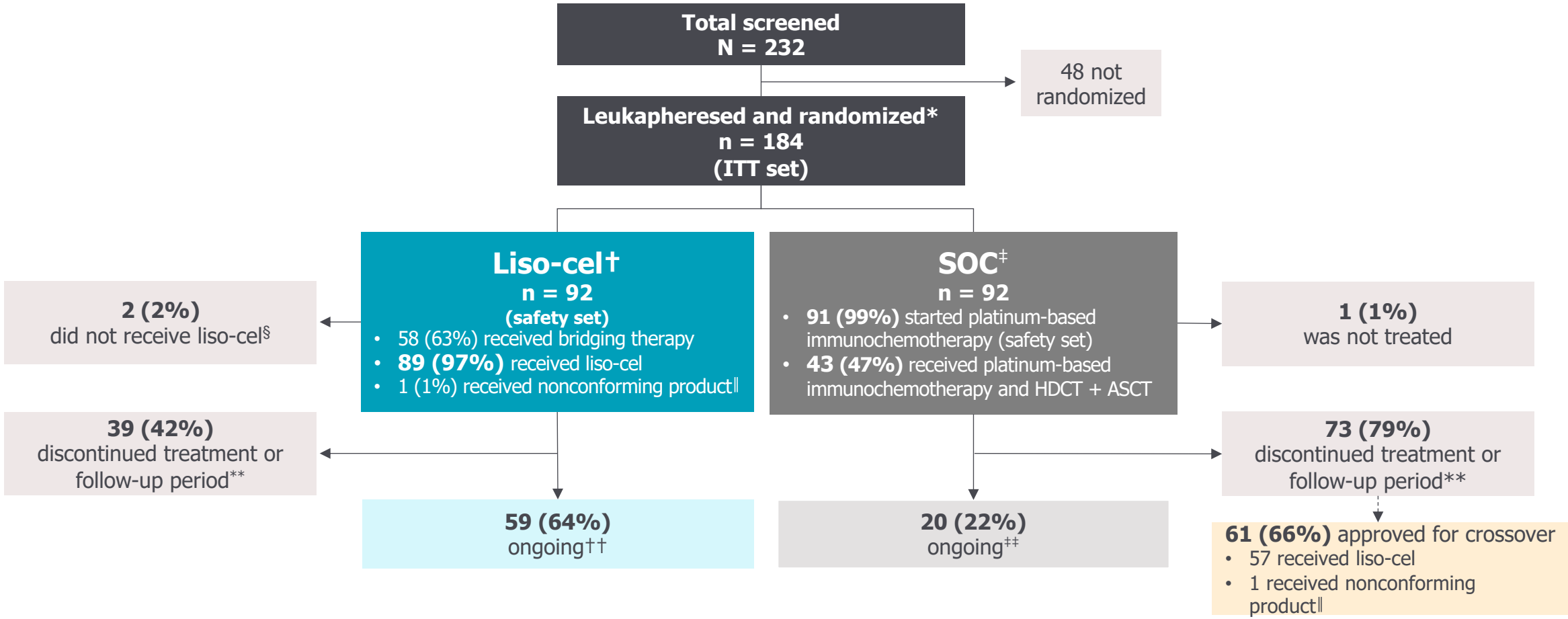
Other secondary endpoints

- Duration of response, ORR (per IRC), PFS on next line of treatment
- Safety, PROs

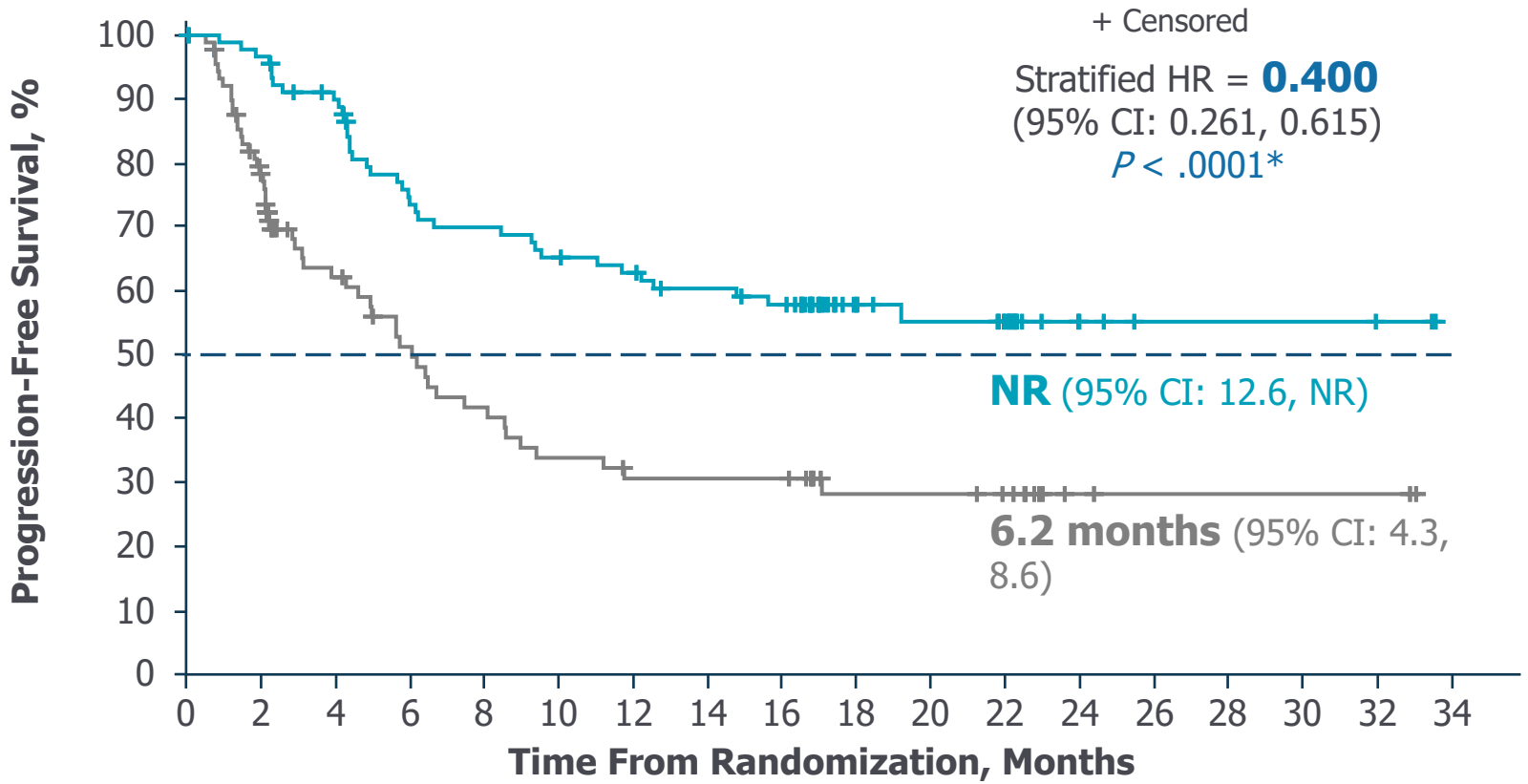
Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

TRANSFORM: Patient Disposition



TRANSFORM: PFS per IRC (ITT Set)



No. at risk

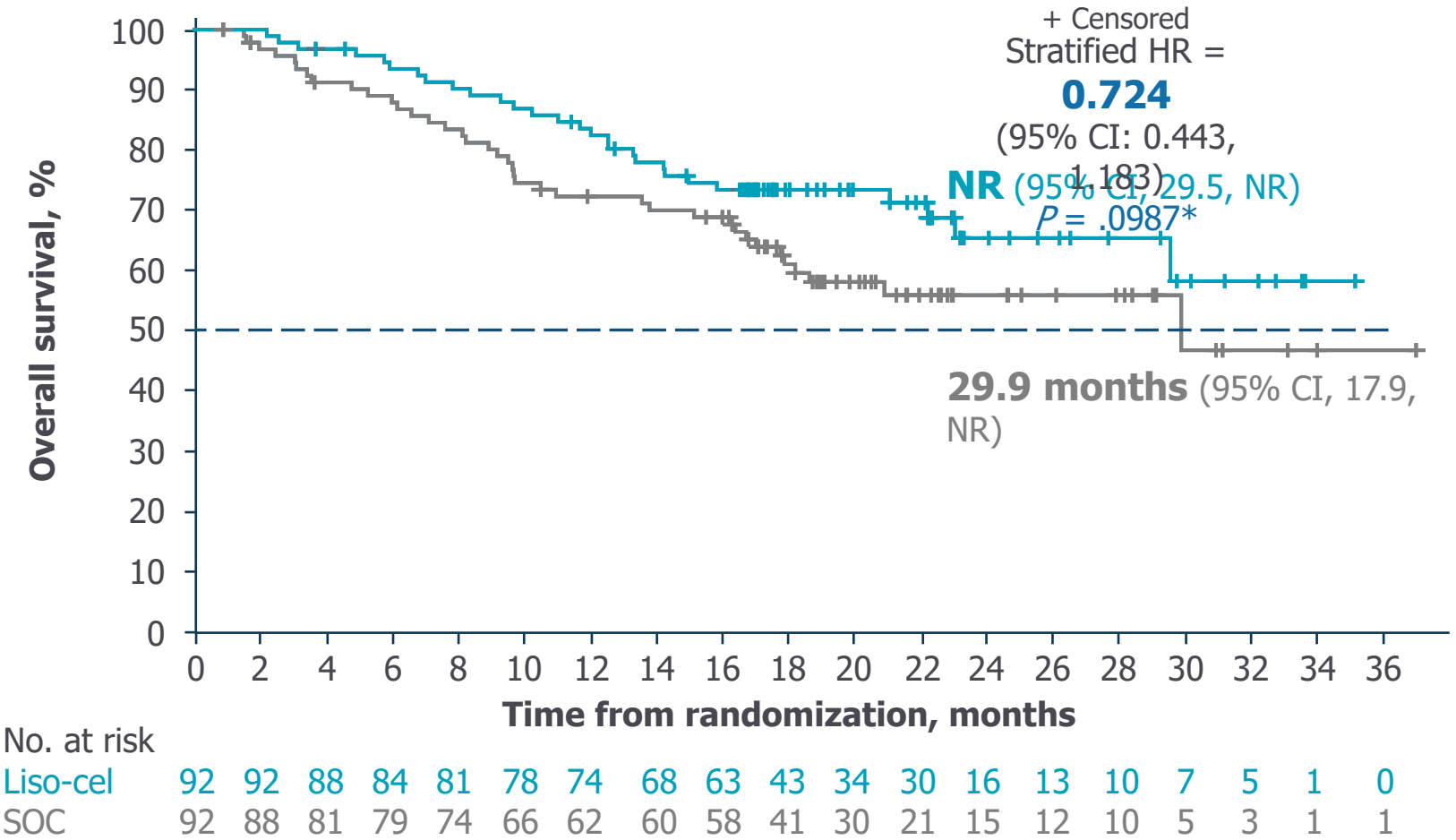
Liso-cel	92	88	79	63	60	56	53	49	46	25	21	18	6	3	3	3	3	0
SOC	92	66	42	33	27	22	19	19	19	12	12	10	3	2	2	2	2	0

18-month PFS rate	
Liso-cel	**SOC**
58.2%	**28.8%**
(95% CI: 47.7, 68.7)	(95% CI: 17.7, 40.0)

Median follow-up: 17.5 months

*One-sided *P* value significance threshold to reject the null hypothesis was ≤ 0.021.
PFS was defined as the time from randomization to death from any cause or PD, whichever occurred first.
Abramson JS, et al. Blood. 2022;140: Abstract 655.

TRANSFORM: Overall Survival (ITT Set)



18-month OS rate	
Liso-cel **73.1%** (95% CI: 63.9, 82.3)	**SOC** **60.6%** (95% CI: 50.2, 71.1)

Median follow-up: 17.5 months

- Patients in SOC arm who crossed over to receive liso-cel continue to be followed for OS in the SOC arm

*One-sided *P* value significance threshold to reject the null hypothesis was ≤ 0.021.
OS was defined as the time from randomization to death from any cause.
Abramson JS, et al. Blood. 2022;140: Abstract 655.

Summary

- With a median follow-up of 17.5 months, the primary analysis of the TRANSFORM study confirmed the superiority of liso-cel over SOC in patients with primary refractory or early relapsed LBCL
- Liso-cel resulted in significant improvements in EFS, CR rate, and PFS
  - At 18 months, EFS and PFS rates with liso-cel were more than double those with SOC
  - With longer follow-up, there was a deepening of response
- OS numerically favored liso-cel, despite allowing for crossover; however, the difference was not statistically significant
  - In a supportive OS analysis that adjusted for the impact of crossover to liso-cel, an OS benefit in favor of liso-cel was observed
- The incidence of CAR T cell therapy: specific adverse events was manageable and consistent with previous studies of liso-cel
  - Rates of grade ≥ 3 CRS (1%) and NEs (4%) were low (no grade 4 or 5 events), with no prophylactic corticosteroid use
- These data support the use of liso-cel as a preferred second-line treatment for patients with primary refractory or early relapsed LBCL

Abramson JS, et al. Blood. 2022;140: Abstract 655.

Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation As Consolidation Therapy in Patients with Primary CNS Lymphoma — Results of an International Randomized Phase III Trial (MATRix/IELSG43)

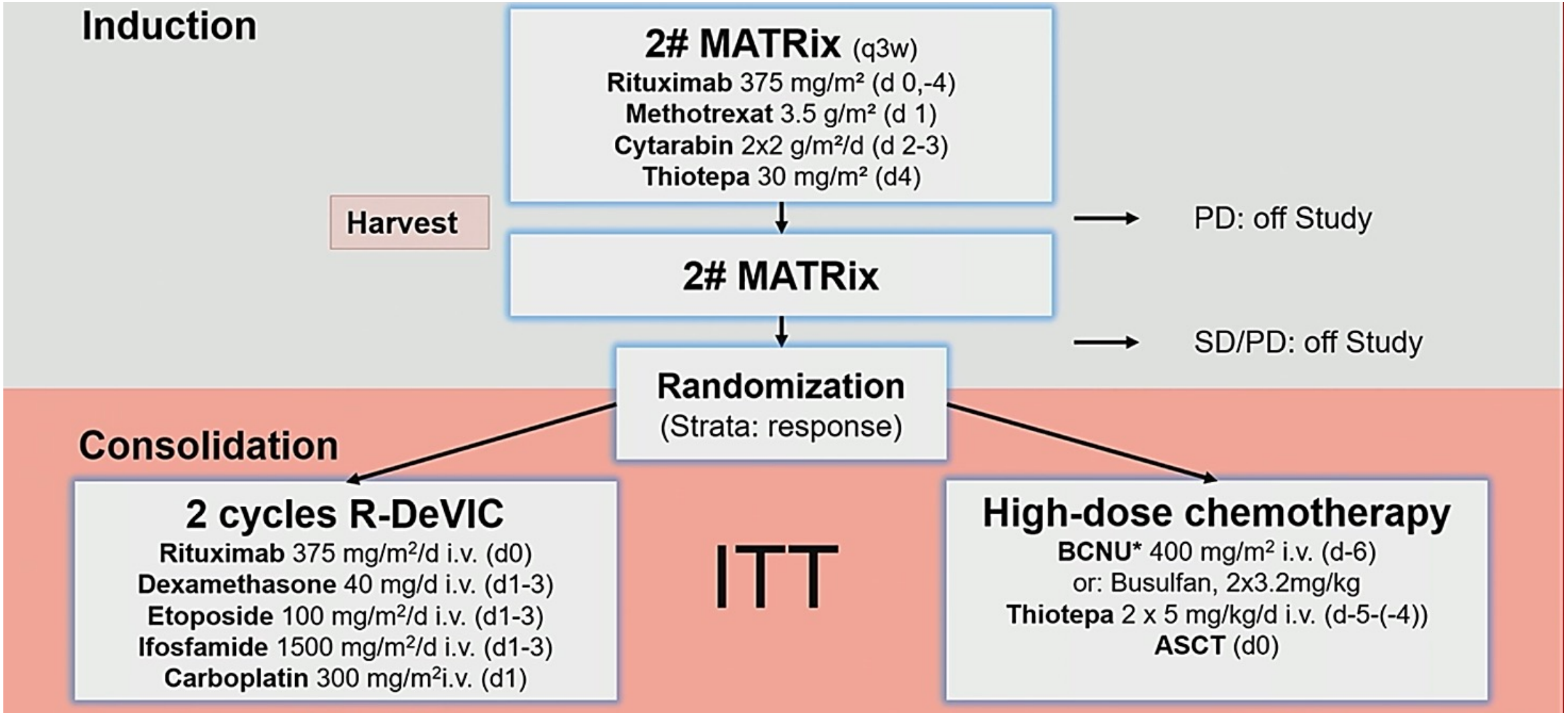
Gerald Illerhaus, AJM Ferreri, M Binder, P Borchmann, J Hasenkamp, S Stilgenbauer, A Roeth, T Weber, G Egerer, T Ernst, B Hertenstein, G Lenz, G Kobbe, U Brunnberg, C Schmidt, M Kneba, M Dreyling, R Möhle, J Panse, T Heinicke, S Schroll, TS Larsen, H Salwender, R Naumann, G Hess, L Thurner, T Pukrop, U Keller, AK Blystadt, FP Kroschinsky, F Re, E Pulczynski, L Orsucci, L Pospiech, M Deckert, M Ponzoni, J Wendler, E Valk, T Calimeri, B Kasenda, M Trepel, H Fricker, Pv Gottberg, E Burger, G Ihorst, O Grishina, C Hader, E Zucca, J Finke and Elisabeth Schorb

ASH 2022

Key Inclusion Criteria

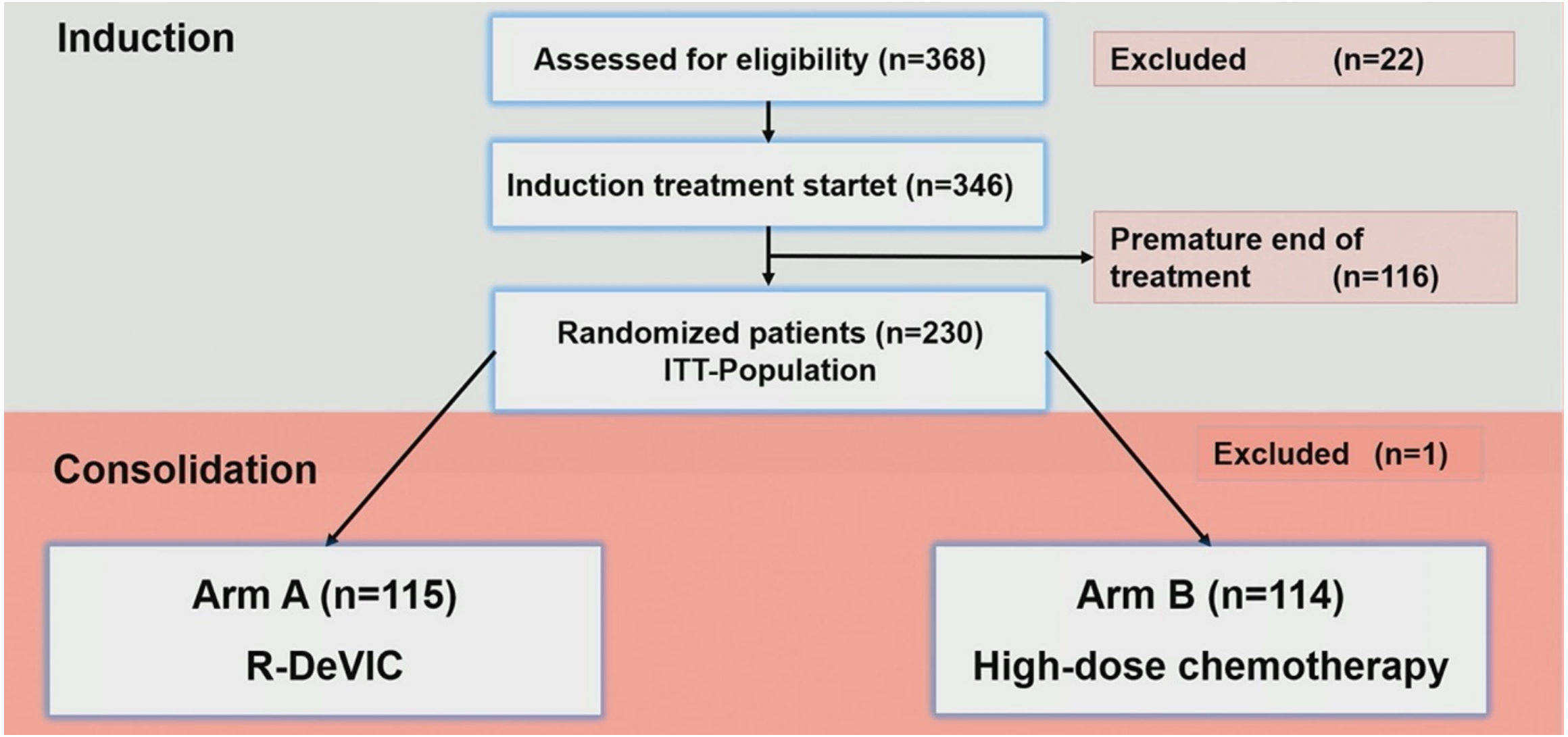
- Immunocompetent patients with newly diagnosed PCNSL
- Age 18 to 65 years irrespective of ECOG or 66 to 70 years (with ECOG PS ≤ 2)
- Histologically or cytologically assessed diagnosis of B-cell lymphoma
- At least 1 radiologically measurable lesion
- Adequate organ function (ie, creatinine clearance > 60 ml/min)

Treatment Algorithm

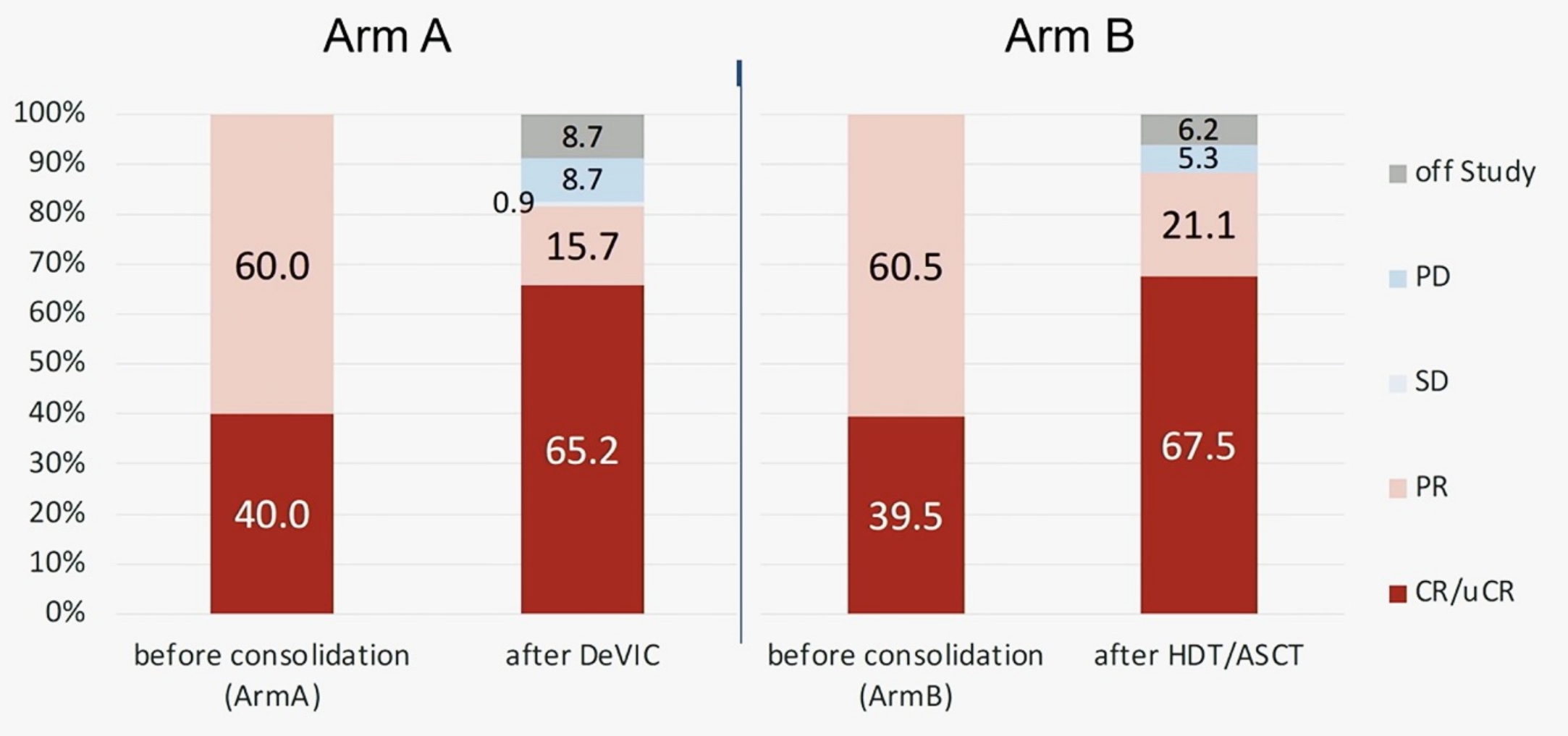


*If BCNU was not available
Accrual between 2012 and 2019.

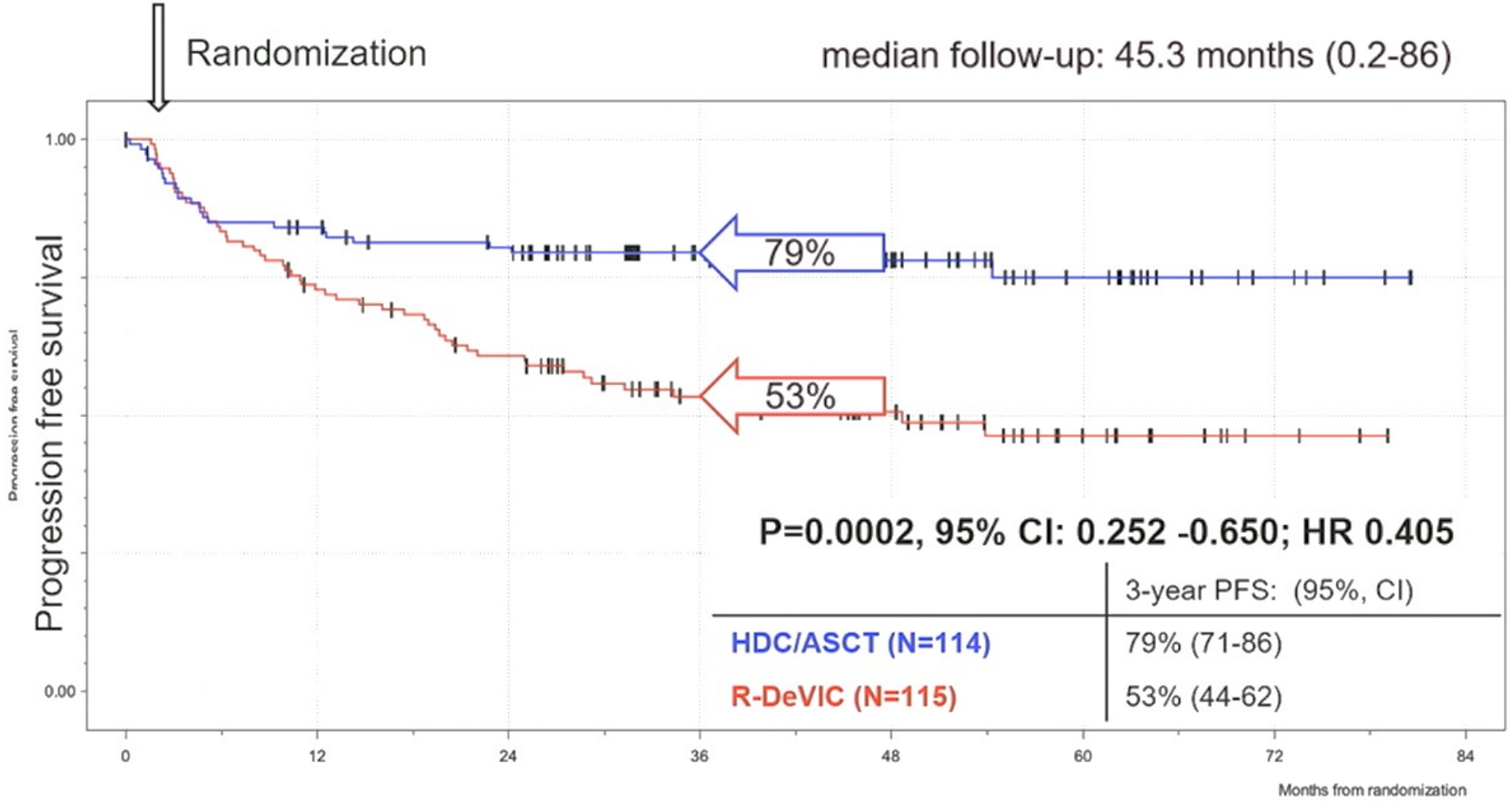
Treatment Algorithm



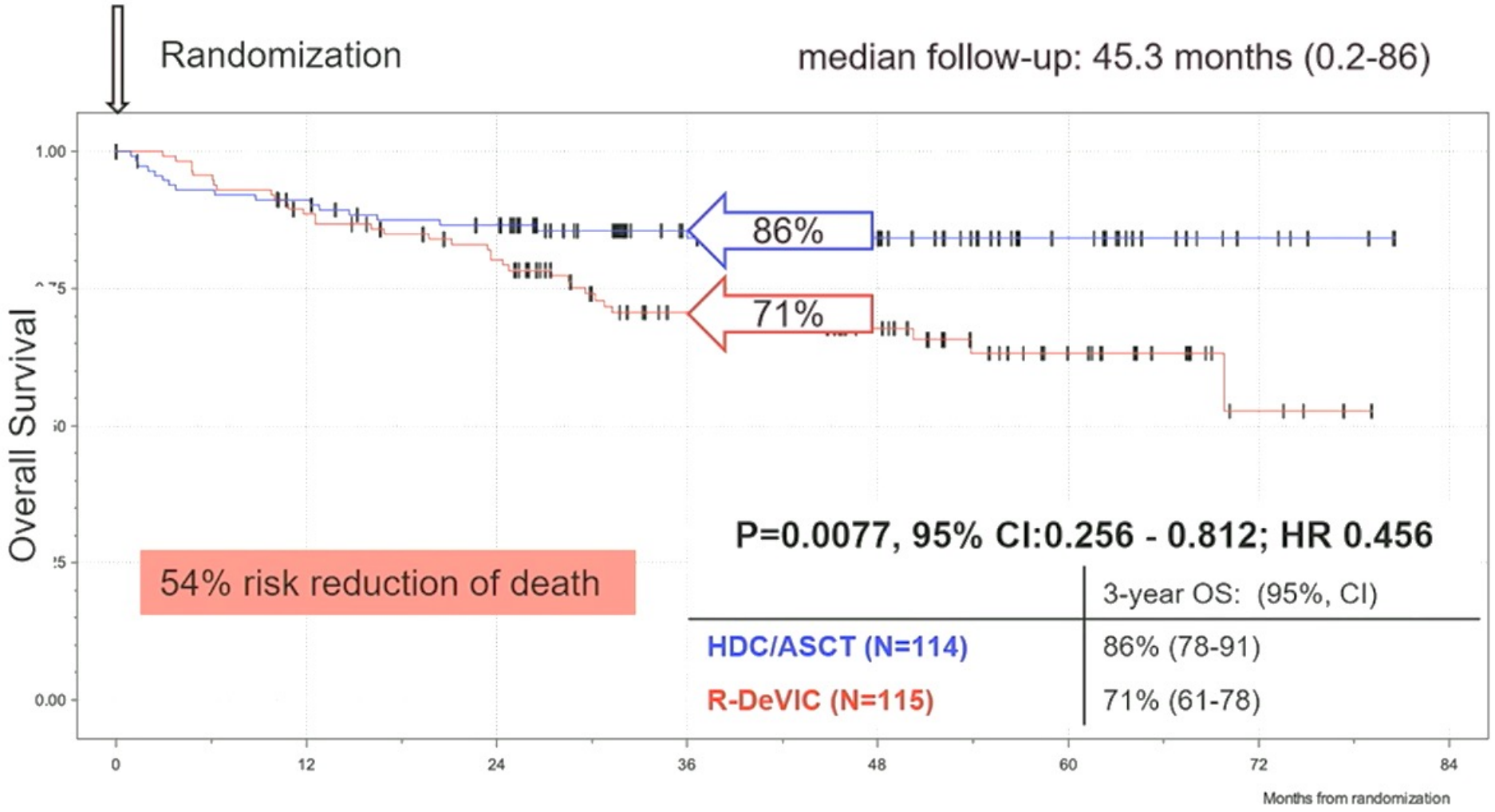
Response (Randomized Patients)



MATRix/IELSG43 Trial: PFS (ITT)



MATRis/IELSG43 Trial: OS (ITT)



Summary

- Largest randomized multicenter phase Ill trial investigating the impact of HCT/ASCT in untreated PCNSL patients 70years
- PFS and OS is significantly higher after HCT/ASCT compared to conventional immunochemotherapy with R-DeVlC…
- …despite similar remission-rates after consolidation!
- In order to reduce toxicity during induction therapy, a shorter induction therapy with R-MTX pre-treatment followed by 2 cycles of MATRix is being tested in the randomised OptiMATe trial

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

Michael L. Wang[1], Nirav N. Shah[2], Alvaro J. Alencar[3], James N. Gerson[4], Manish R. Patel[5], Bita Fakhri[6], Wojciech Jurczak[7], Xuan Tan[8], Katharine Lewis[8], Timothy Fenske[2], Catherine C. Coombs[9], Ian W. Flinn[10], David J. Lewis[11], Steven Le Gouill[12], M. Lia Palomba[13], Jennifer A. Woyach[14], John M. Pagel[15], Nicole Lamanna[16], Jonathon B. Cohen[17], Minal A. Barve[18], Paolo Ghia[19], Toby A. Eyre[20], Pier Luigi Zinzani[21], Chaitra S. Ujjani[22], Youngil Koh[23], Koji Izutsu[24], Ewa Lech-Maranda[25], Constantine S. Tam[26], Suchitra Sundaram[27], Ming Yin[28], Binoj Nair[28], Donald E. Tsai[28], Minna Balbas[28], Anthony R. Mato[13], Chan Y. Cheah[8]

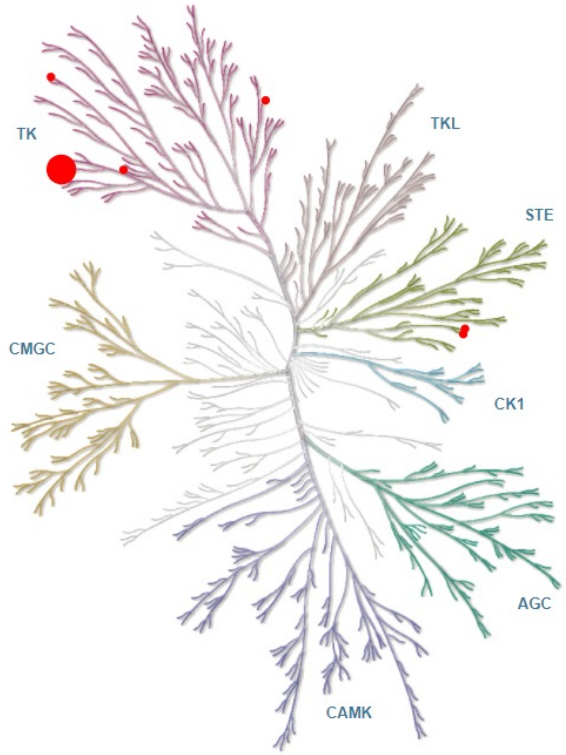
[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI; [3]Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, FL; [4]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [5]Florida Cancer Specialists / Sarah Cannon Research Institute, Sarasota, FL; [6]Division of Hematology and Oncology, University of California, San Francisco, CA; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [9]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [10]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [11]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, United Kingdom; [12]Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes, Nantes, France; [13]Memorial Sloan Kettering Cancer Center, New York, NY; [14]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [15]Center for Blood Disorders and Stem Cell Transplantation, Swedish Cancer Institute, Seattle, WA; [16]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [17]Winship Cancer Institute, Emory University, Atlanta, GA; [18]Mary Crowley Cancer Research, Dallas, TX; [19]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, MI, Italy; [20]Churchill Cancer Center, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [21]Institute of Hematology "Seràgnoli" University of Bologna, Bologna Italy; [22]Fred Hutchinson Cancer Research Center; [23]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [24]National Cancer Center Hospital, Tokyo, Japan; [25]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [26]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [27]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [28]Loxo Oncology at Lilly, Stamford, CT

Wang, et al: ASH 2021, abst 381

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

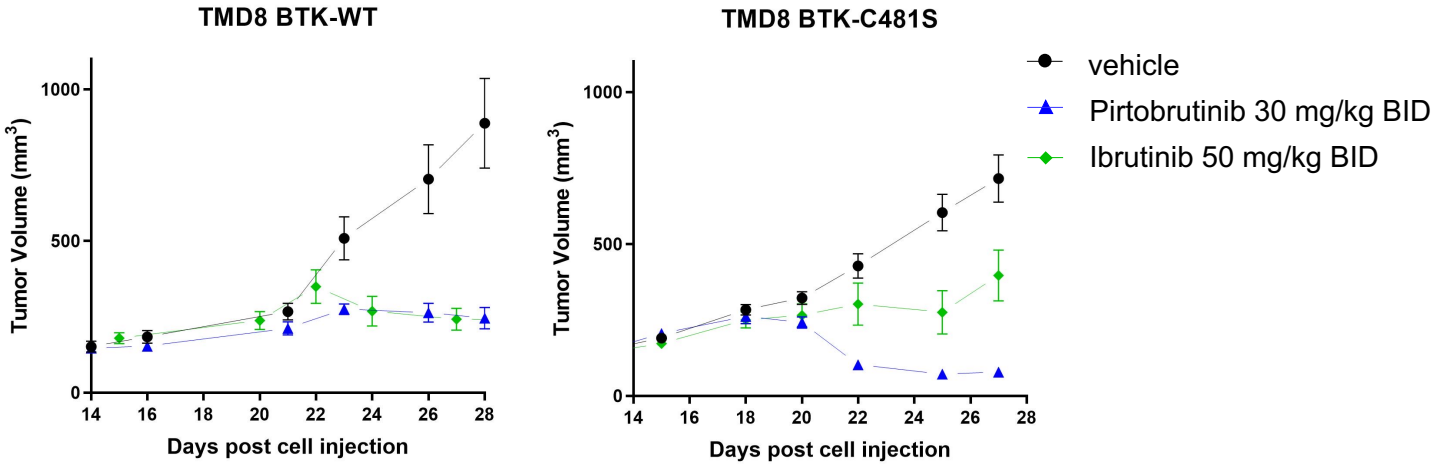
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

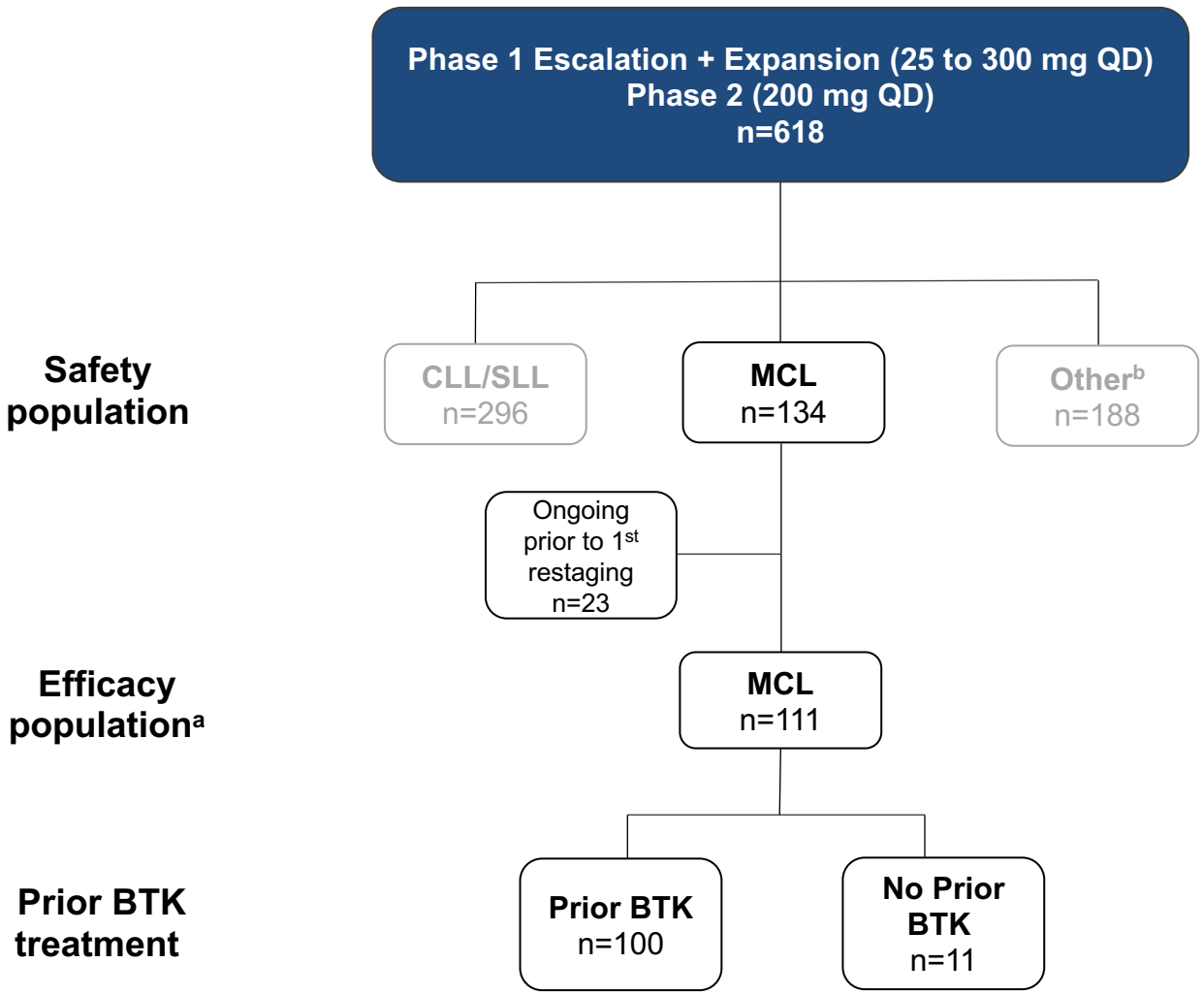
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

Wang, et al: ASH 2021, abst 381

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (Lugano, iwCLL, IWWM)

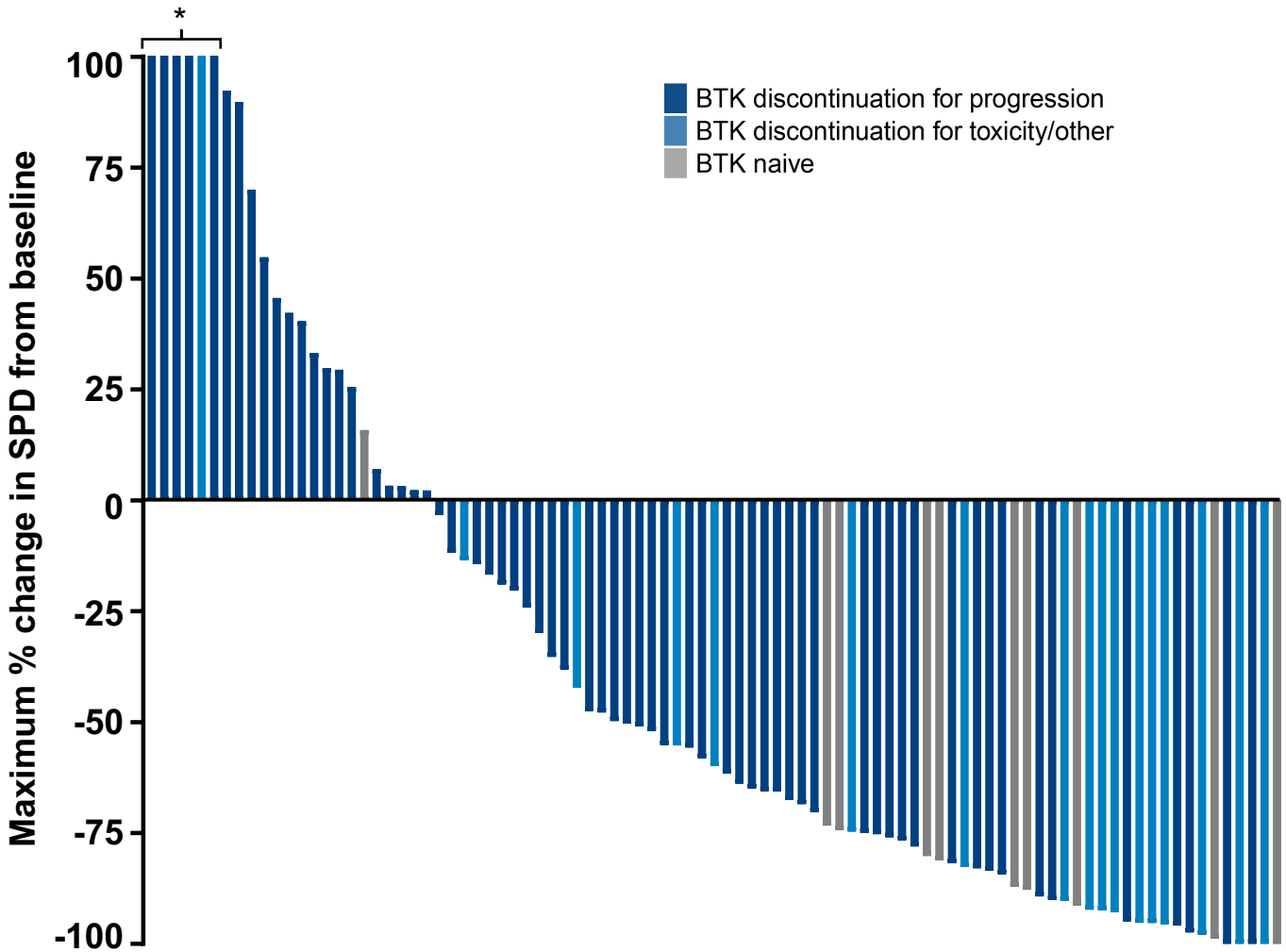
Wang, et al: ASH 2021, abst 381

Patient Characteristics

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Wang, et al: ASH 2021, abst 381

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



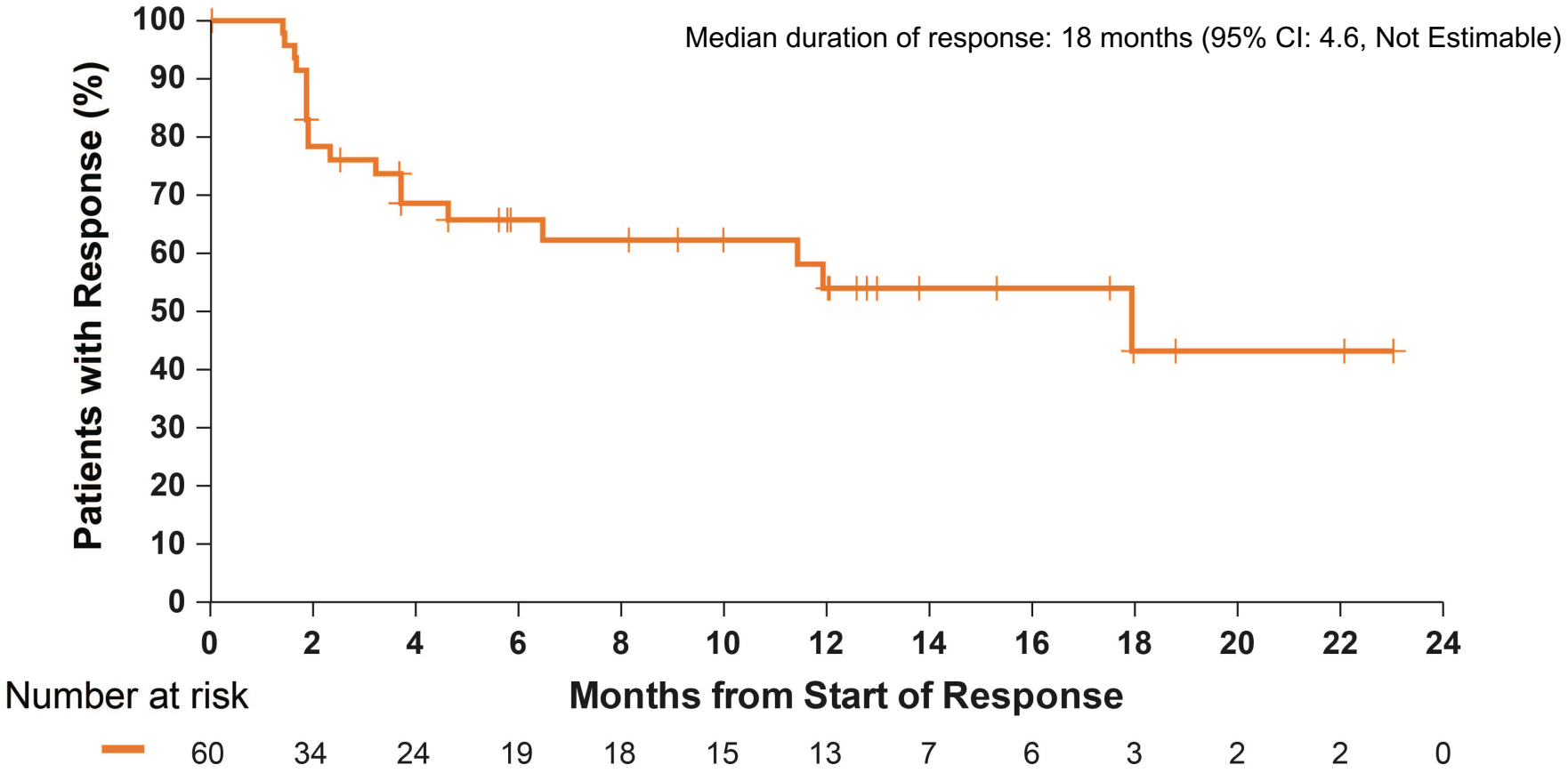
BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Wang, et al: ASH 2021, abst 381

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma

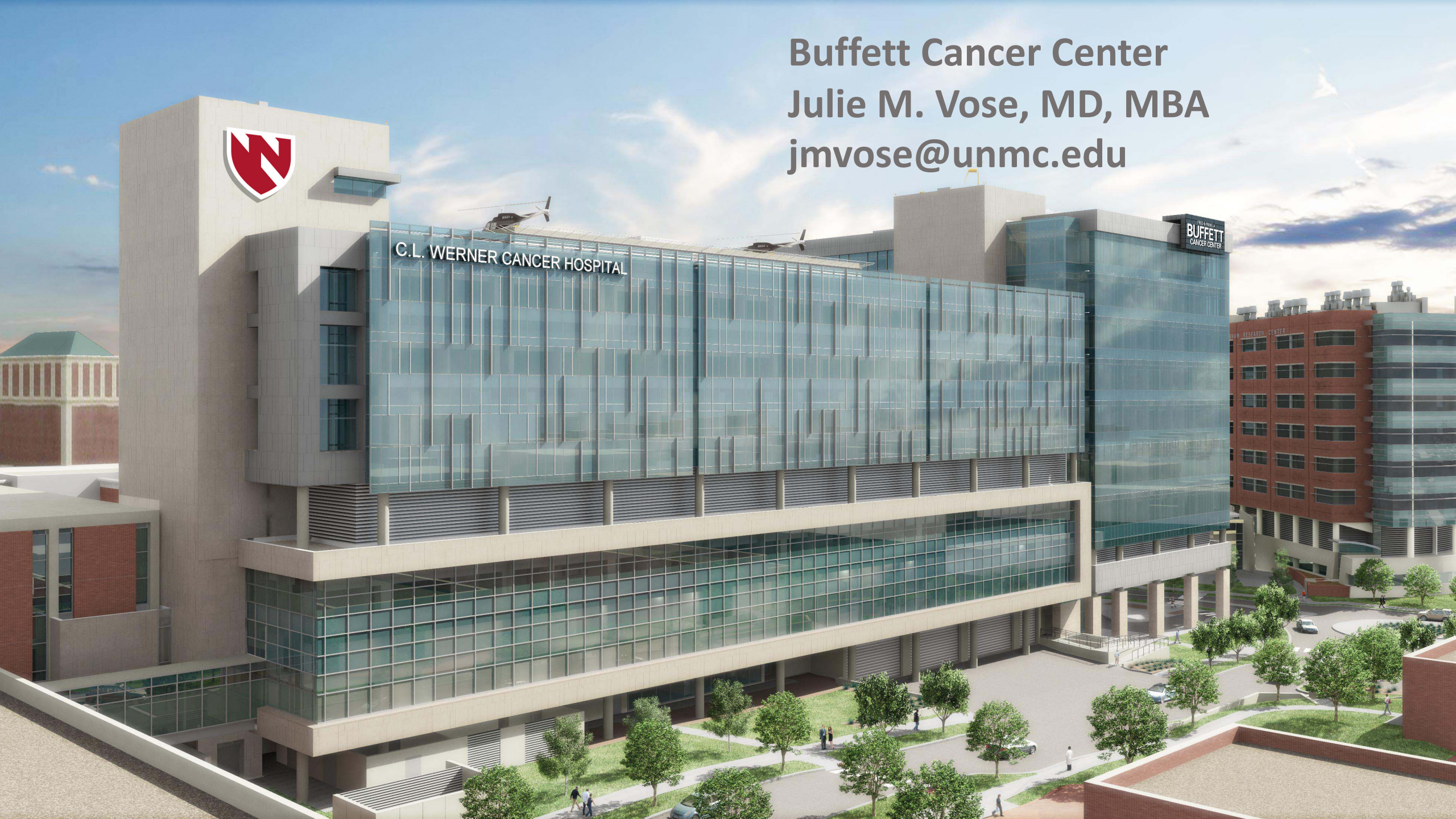


- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Wang, et al: ASH 2021, abst 381

Conclusions: Updates 2023

- 1. **Triangle Trial:** Induction and/or Maintenance with Ibrutinib had a better PFS. ? Auto PSCT necessary ? Other BTK inhibitors the same
- 2. **Bi-specific Antibodies**: Updates Mostentuzumab and Glofitamab
- 3**. PCNSL:** Auto PSCT in CR 1 beneficial for PFS and OS
- 4. **Pirtobrutinib:** Now approved for MCL failing another BTKi



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