Tycel Phillips, MD

Associate Professor

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Updates in Lymphoma

Disclosures

- Research Support
  - Abbvie, Bayer, BMS, Genentech, Incyte
- Advisory Board
  - Abbvie, ADC Therapeutics, AstraZeneca, Bayer, Beigene, BMS, Genmab, Genentech, Gilead, Eli Lily, Epizyme, Incyte, Pharmacyclics, TG Therapeutics, Seattle Genetics
- Strategic Counsel
  - Epizyme
- Scientific Board
  - Genentech

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Agenda

- Diffuse Large B cell Lymphoma
  - 1L
  - 2L and beyond
- Follicular Lymphoma
  - POD24
  - 2L and beyond
- MCL/CLL
  - New options
- T-cell lymphoma

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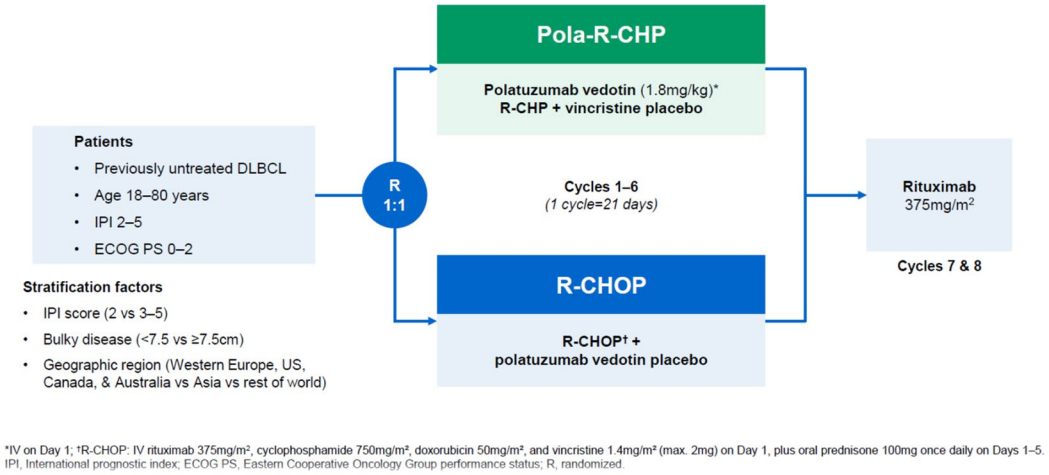
DLBCL

- Currently the SOC for 1L remains R-CHOP but recent NCCN update places R-CHP + Pola as category 1 recommendation.
- Recently Data from Polarix indicated an PFS benefit from the addition of polatuzumab to the CHOP backbone in place of vincristine.
  - Still without an OS benefit.
- Smart Start
  - Novel regimen from MD Anderson that provides a chemo-free lead in with rituximab-lenalidomide and ibrutinib prior to introduction of CHOP for non-GCB patients
  - Potential utility to safely incorporate these oral regimens in 1L therapy

POLARIX (Study Schema/Racial Breakdown)

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.

- DRIVE Score 0

Table S9. Race and ethnicity of patients enrolled in the US.

	Pola-R-CHP N = 106	R-CHOP N = 128
American Indian or Alaska Native, n (%)	1 (1)	0
Asian, n (%)	3 (3)	3 (2)
Black or African American, n (%)	8 (8)	8 (6)
Native Hawaiian or other Pacific Islander, n (%)	0	0
White, n (%)	79 (75)	98 (77)
Other, n (%)	1 (1)	3 (2)
Unknown, n (%)	14 (13)	16 (13)
Hispanic or Latino, n (%)*	5 (5)	12 (9)
American Indian or Alaska Native, n (%)	1 (1)	0

*Hispanic or Latino patients are also included in applicable race categories.

Pola-R-CHP, polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone.

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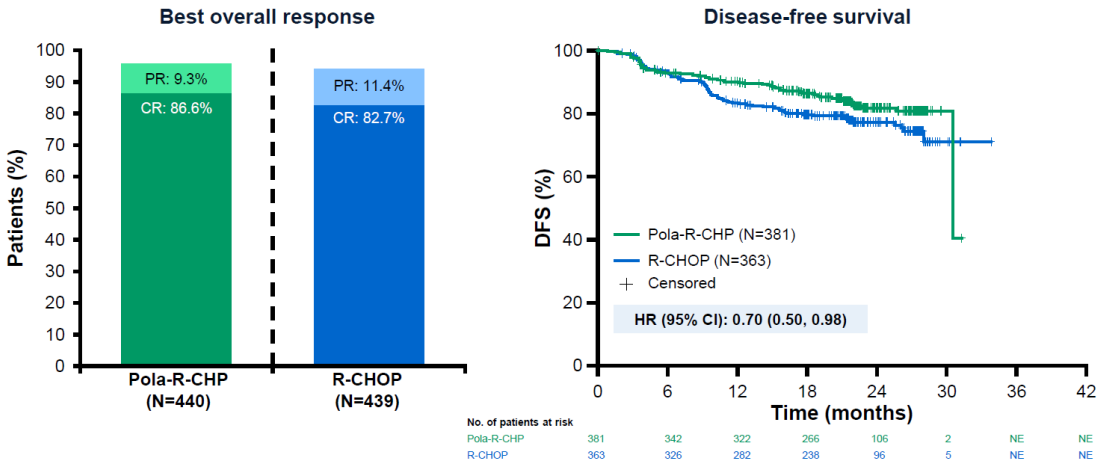
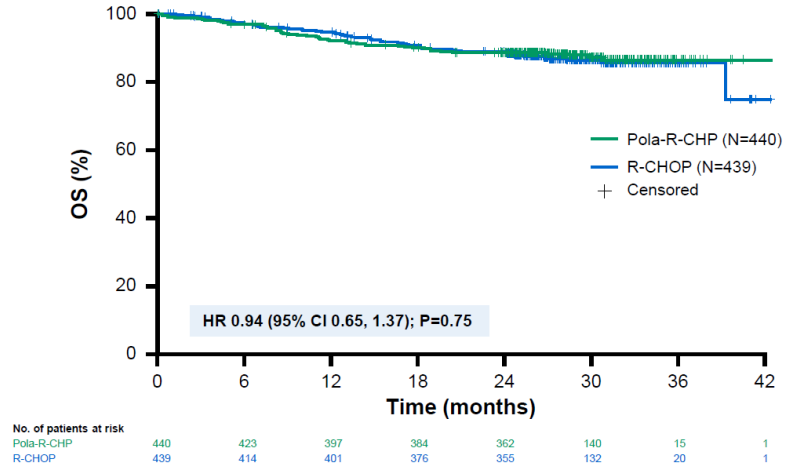
POLARIX (Outcomes)

Response rates and disease-free survival



ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up. Disease-free survival (DFS) defined as the time from the date of the first occurrence of a documented complete response to the date of progression, relapse, or death from any cause for the subgroup of patients with a best overall response of CR.

Overall survival



ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.

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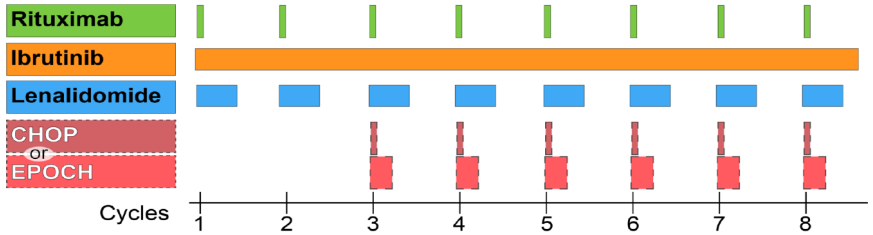
SMART START

- Enrolled 60 patients at MD Anderson with Non-GCB DLBCL – DRIVE (NA)
  - Defined by IHC
- All patients started therapy with rituximab, lenalidomide 25 mg D1-10, ibrutinib 560 mg daily (reduced to 420 with later amendment) in 21-day cycles for 1st two cycles.
- Combined with Chemotherapy for cycles 3-8
  - Originally EPOCH then amended to allow EPOCH or CHOP

1. **Supplemental Figure 1 Schema**



Supplemental Figure 1 Legend: A cycle of therapy was 21 days. Therapy on cycle 1 and 2 consisted of rituximab 375mg/m2 IV on day 1, ibrutinib 560mg orally daily (amended to 420mg orally daily if >65 years old), and lenalidomide 25mg orally days 1-10 (RLI). Therapy on cycles 3 – 8 consisted of RLI with either CHOP (cyclophosphamide 750mg/m^2 IV on day 1, doxorubicin 50mg/m^2 IV on day 1, Vincristine 2mg IV on day 1, and Prednisone 100mg orally days 1-5) **or** EPOCH (etoposide 50mg/m^2/day IV continuous days 1-4, Prednisone 100mg orally days 1-5, vincristine 0.4mg/m^2/day IV continuous days 1-4, cyclophosphamide 750mg/m2 IV on day 5, and Doxorubicin 10mg/m^2/day IV continuously days 1-4).

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SMART START – Response/Toxicity

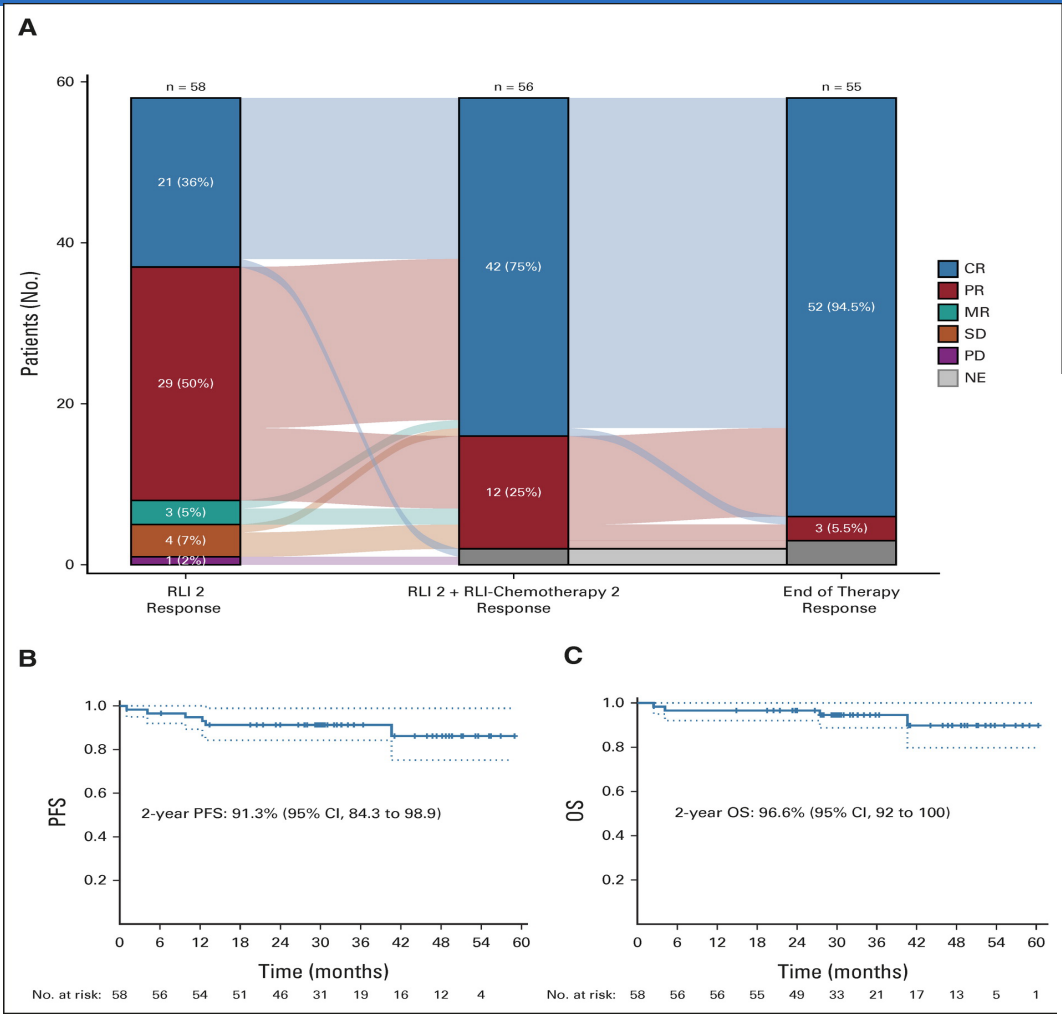

FIG 1. Clinical efficacy. (A) Response to RLI alone and with chemotherapy in a Sankey diagram. After two cycles of RLI, 58 patients were evaluable. Twenty-one (36%) had CR, 29 (50%) had PR, four (7%) had SD, three (5%) had MR, and one (2%) had PD. After two cycles of RLI and two cycles of RLI-chemotherapy, 56 patients were evaluable. Forty-two (75%) had CR and 12 (25%) had PR. At the end of therapy, 55 patients were evaluable. Fifty-two (94.5%) had CR and three (5.5%) had PR. Kaplan-Meier survival curves for (B) PFS and (C) OS. CR, complete response; MR, mixed response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RLI, rituximab, lenalidomide, and ibrutinib; SD, stable disease.

TABLE 2. Adverse Events

	No. (%)			
AE	Any Grade (N = 60)	Grade 3 or Higher (N = 60)	Any Grade CHOP (N = 25)	Any Grade EPOCH (N = 31)
Nausea	51 (85.0)	2 (3.0)	22 (88)	28 (90)
Peripheral sensory neuropathy	50 (83.0)	5 (8.0)	21 (84)	28 (90)
Diarrhea	47 (78.0)	8 (13.0)	18 (72)	28 (90)
Mucositis	45 (75.0)	2 (3.0)	19 (76)	25 (81)
Thrombocytopenia grade 2-4	35 (58.0)	28 (47.0)	14 (56)	21 (68)
Rash	32 (53.0)	9 (15.0)	13 (52)	17 (55)
Neutropenia grade 3-4	32 (53.0)	32 (53.0)	14 (56)	18 (58)
Anemia grade 2-4	32 (53.0)	23 (38.0)	12 (48)	19 (61)
Dyspnea	26 (43.0)	3 (5.0)	6 (24)	19 (61)
Febrile neutropenia	22 (37.0)	22 (37.0)	6 (24)	16 (52)
Vomiting	20 (33.0)	1 (1.7)	7 (28)	13 (42)
Atrial fibrillation	7 (12.0)	2 (3.0)	4 (16)	3 (10)
Syncope	6 (10.0)	6 (10.0)	3 (12)	3 (10)
Invasive fungal infection	1 (1.7)	1 (1.7)	—	—
Clostridium difficile	1 (1.7)	1 (1.7)	—	1 (3)

Abbreviations: AE, adverse event; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH, infusional etoposide, doxorubicin, vincristine, with prednisone and cyclophosphamide.

Published in: Jason Westin; R. Eric Davis; Lei Feng; Fredrick Hagemeister; Raphael Steiner; Hun Ju Lee; Luis Fayad; Loretta Nastoupil; Sairah Ahmed; Alma Rodriguez; Michelle Fanale; Felipe Samaniego; Swaminathan P. Iyer; Ranjit Nair; Yasuhiro Oki; Nathan Fowler; Michael Wang; Man Chun John Ma; Francisco Vega; Timothy McDonnell; Chelsea Pinnix; Donna Griffith; Yang Lu; Sanjit Tewari; Ryan Sun; David W. Scott; Christopher R. Flowers; Sattva Neelapu; Michael R. Green; *Journal of Clinical Oncology* 2023 41745-755.
DOI: 10.1200/JCO.22.00597

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R/R DLBCL

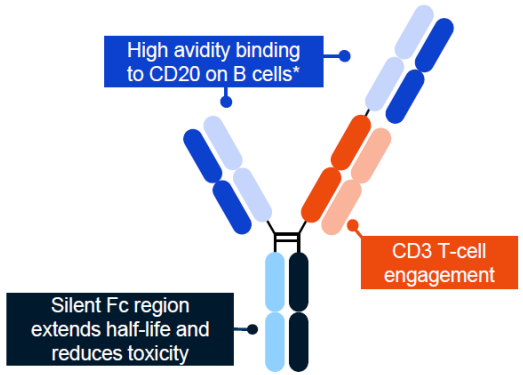
- Outcomes in R/R DLBCL while improved still with room for improvement.
- Primary refractory patients historically with worse outcomes
  - Two CAR-T products approved based on ZUMA-7 and TRANSFORM study
    - Both showed benefit over ASCT in primary refractory DLBCL
    - Still majority of patients don’t receive CAR-T either due to access to center or progression prior to receipt of cells
- Bispecific antibodies potential to be options for these patients given ability to be given in community
  - Glofitamab
  - Epcoritamab

Glofitamab

ailure
ase[3]
-BCL

amab

Glofitamab: *CD20xCD3 bispecific monoclonal antibody with 2:1 format for increased potency vs 1:1 format[6]*



glofitamab in R/R DLBCL and ≥2 prior therapies

1. Chien, et al. Future Oncol 2020; 2. Crump, et al. Blood 2017; 3. Sehn and Salles. NEJM 2021; al. Pharmaceuticals 2022; 5. Roschewski, et al. NEJM 2022; 6. Bacac, et al. Clin Cancer Res 2018; 7. NCT03075696. Available at: https://clinicaltrials.gov; 8. Hutchings, et al. J Clin Oncol 2021.

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

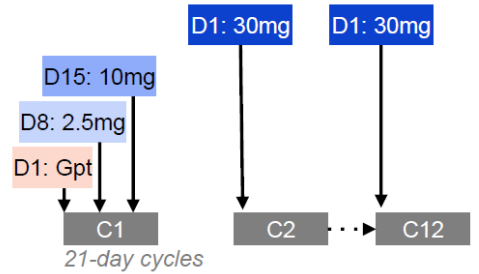
Glofitamab IV administration

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

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Glofitamab Response Data

Response rates – primary endpoint met

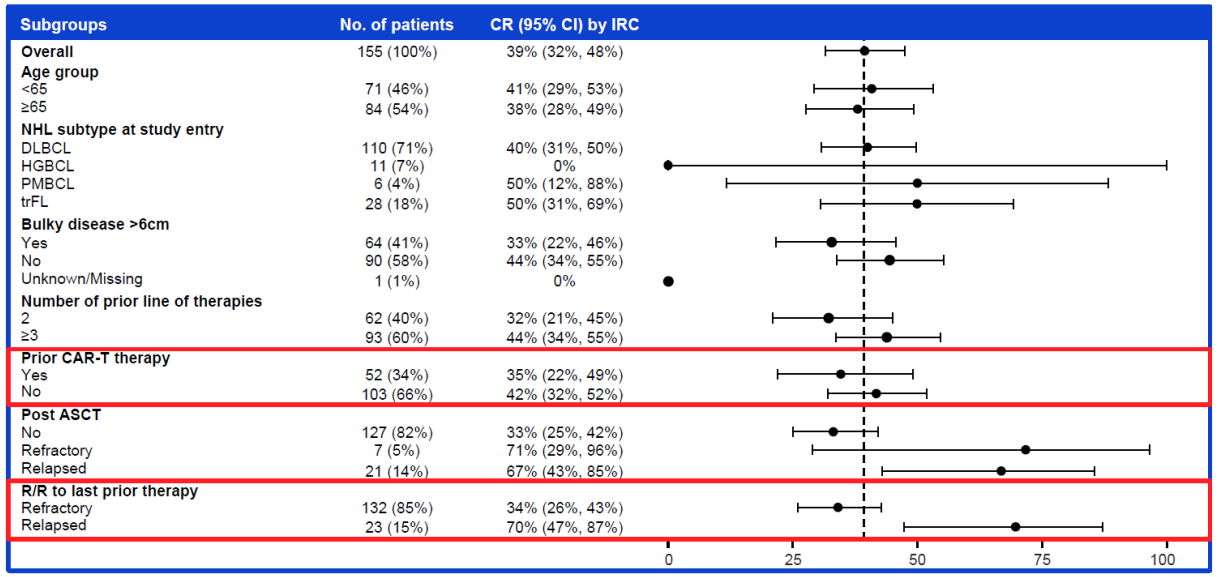
Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- 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‡

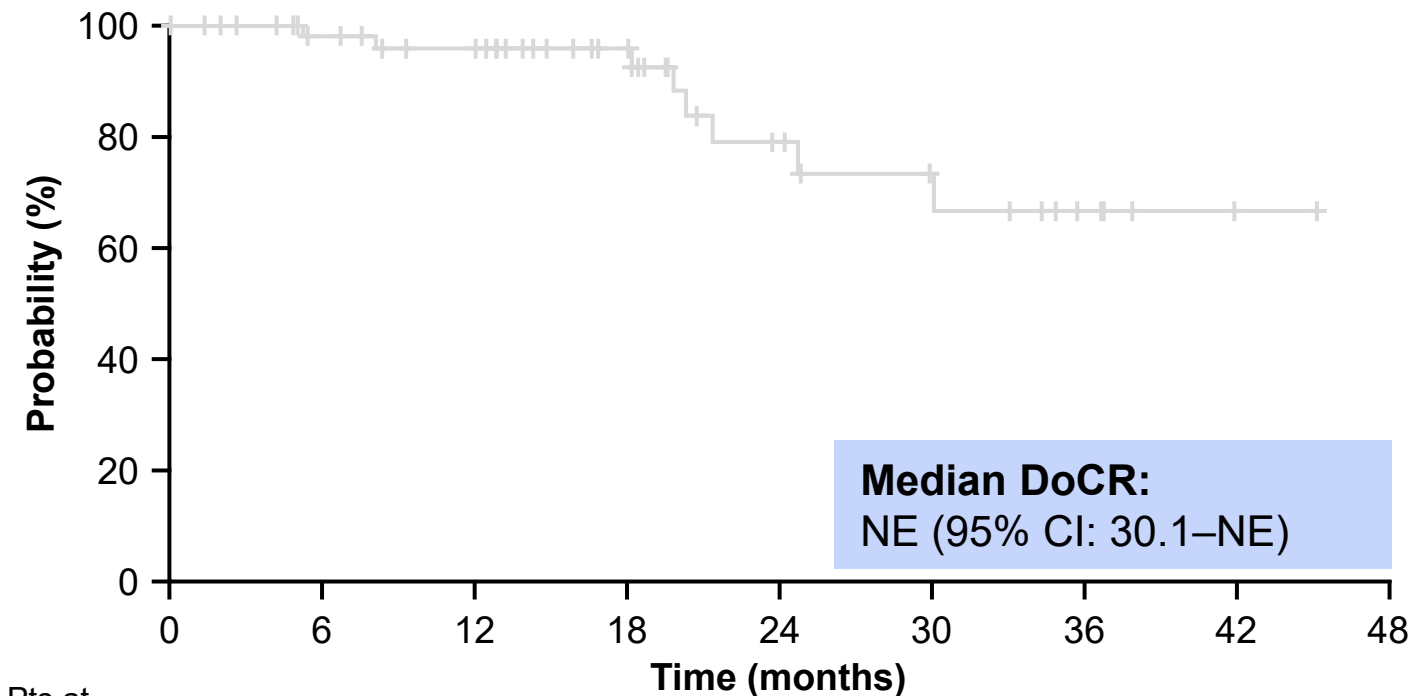
High CR/ORR rate at RP2D

Complete response rates by IRC in pre-specified subgroups



Durable responses after first CR

Duration of complete response by INV (N=61)*



	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; †One patient had pseudoprogression prior to CR at EOT visit and is by definition excluded from DoCR analysis.

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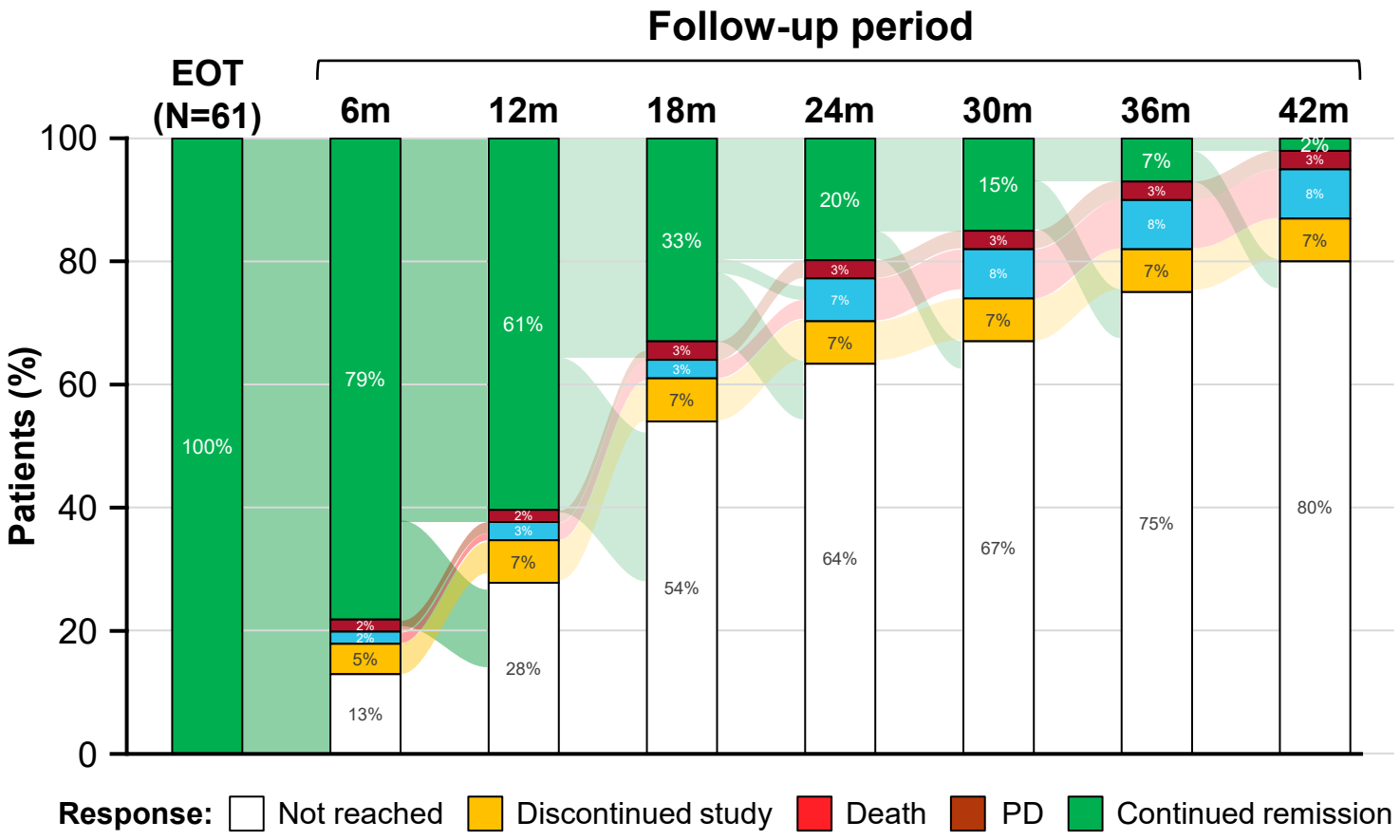
Remission beyond EOT in patients with CR at EOT



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

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

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EPCORE NHL-1: LBCL Expansion Cohort

Dose escalation

Dose expansion data cutoff: January 31, 2022
Median follow-up: 10.7 mo

B-NHL:

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→

Treatment until PD[b,c] or unacceptable toxicity

→

LBCL Cohort N=157
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

[a]**Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose)** and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG PET scan that demonstrates positive lesion(s) compatible with CT-defined (or MRI-defined) anatomical tumor sites for FDG-avid lymphomas. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

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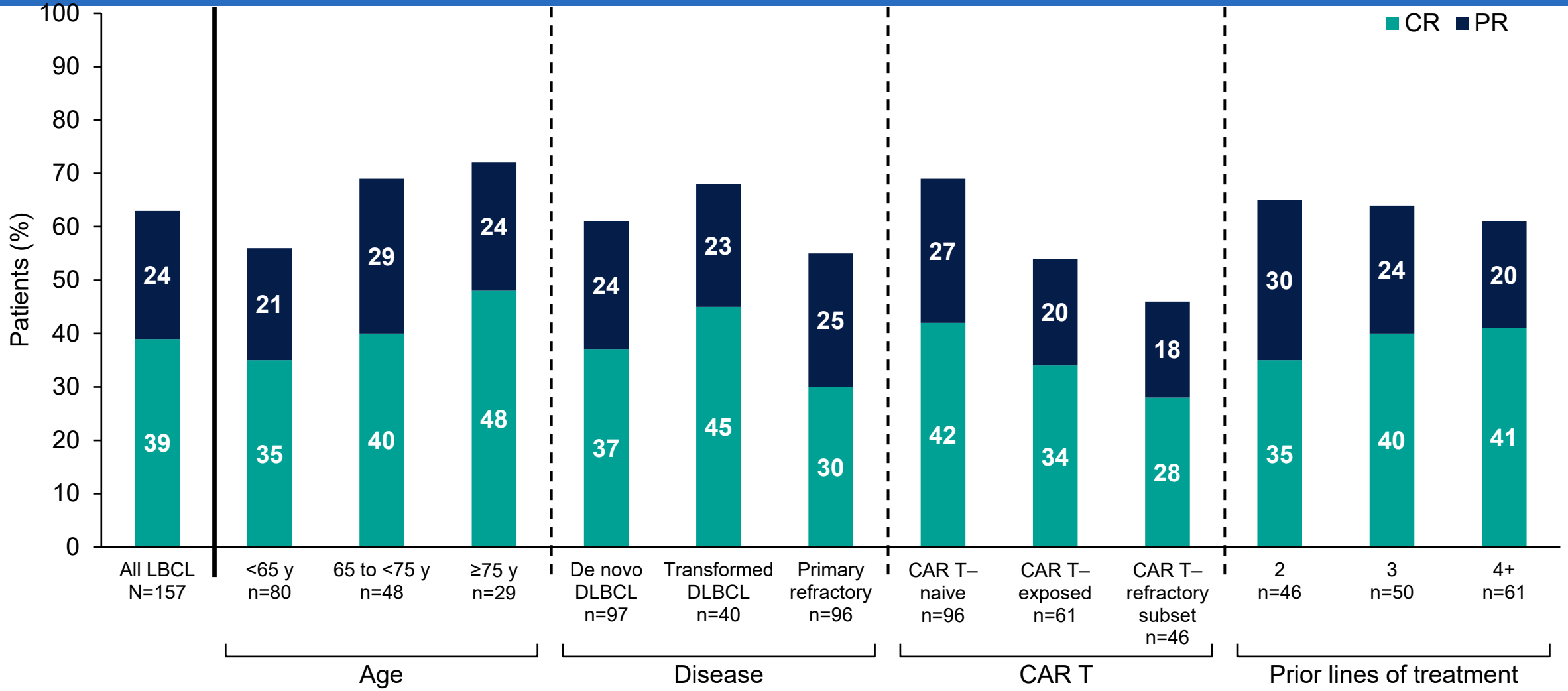
Deep Responses Consistent Across Key Subgroups



Based on IRC assessment and Lugano criteria.

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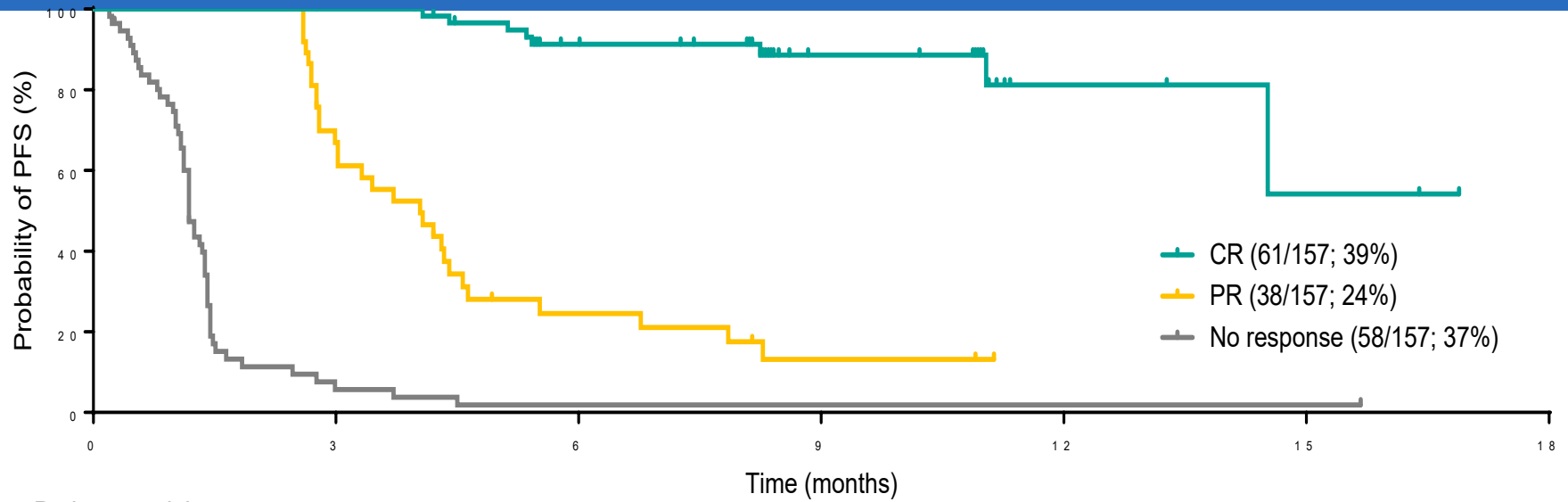
PFS by Best Response per IRC



Patients at risk

61	60	43	24	4	2	0
38	23	7	3	0	0	0
58	3	1	1	1	1	0

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

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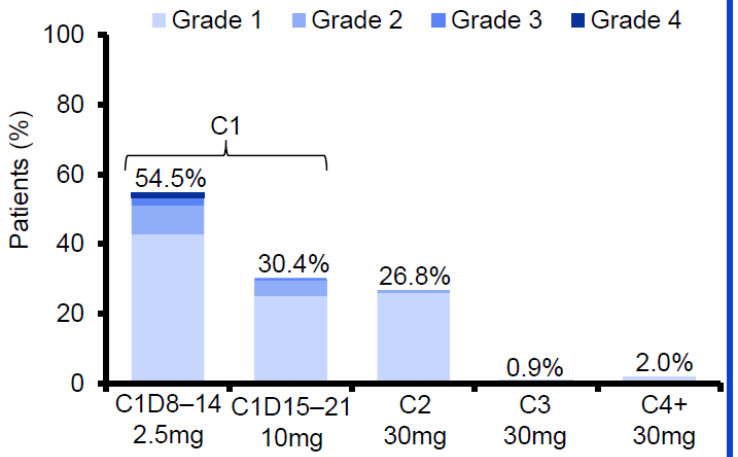
CRS

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†



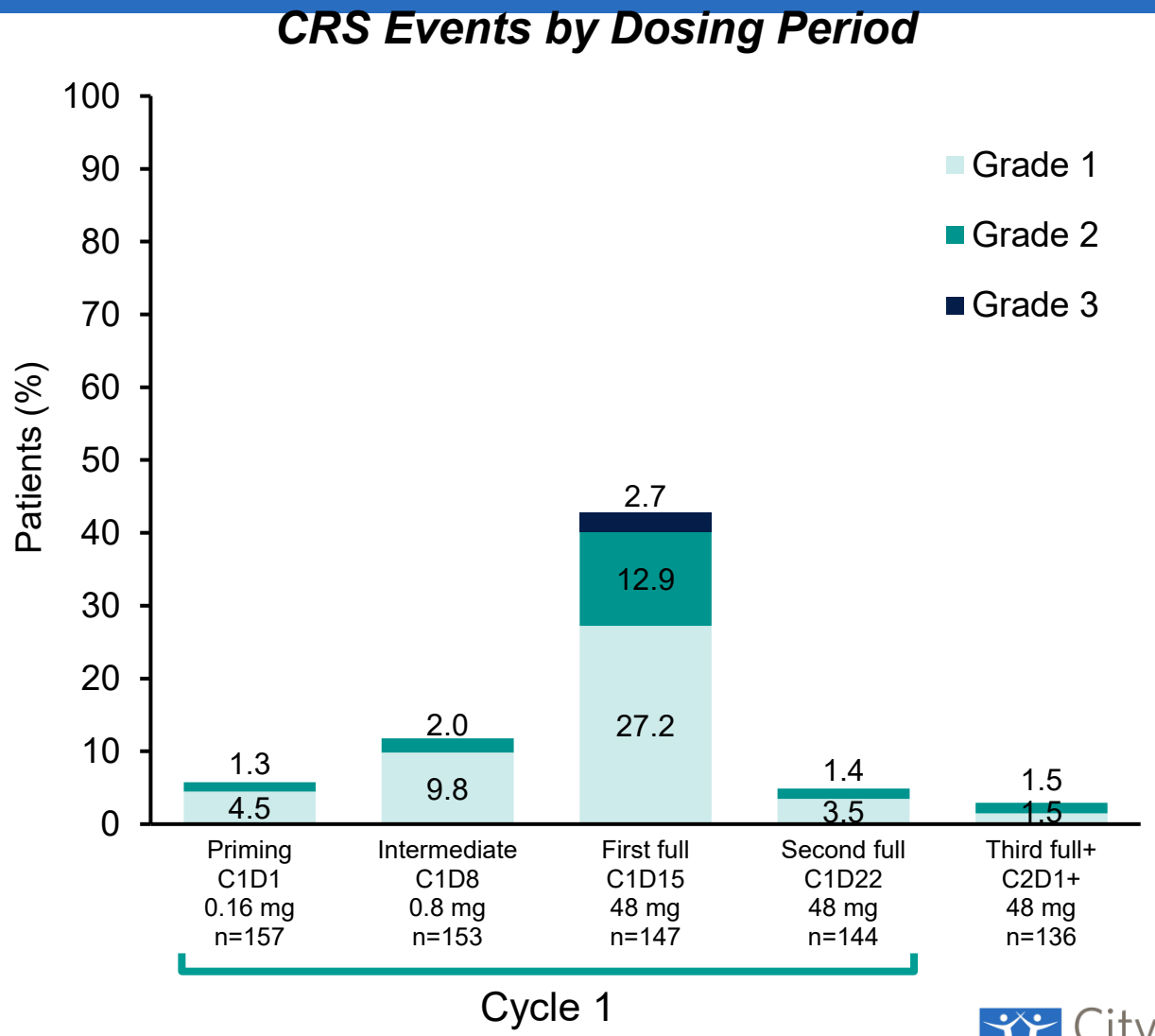
CRS was mostly low grade, time of onset was predictable, and most events occurred during C1

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



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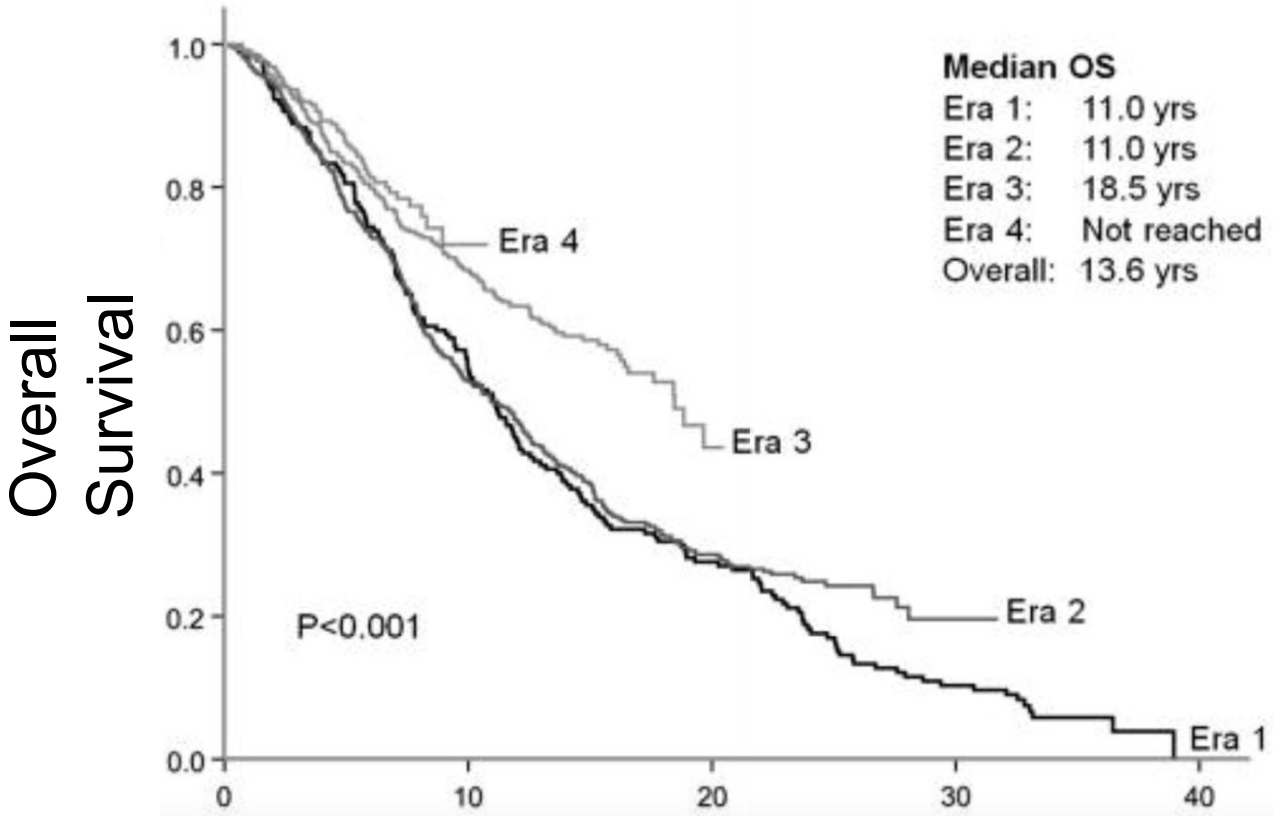
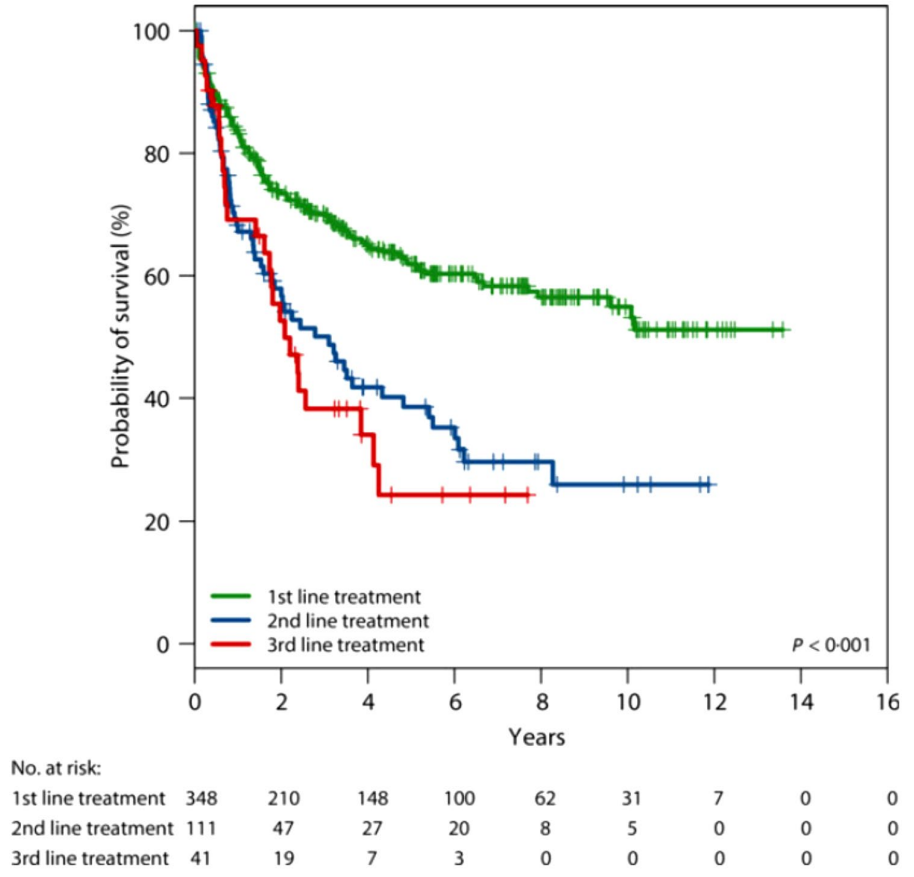
Follicular Lymphoma

- Follicular lymphoma is the most common indolent lymphoma in US and Western Europe accounting for approximately 22% of all cases of Non-Hodgkin Lymphoma
- Currently the disease is incurable with variable patient disease course and outcomes
- Several viable frontline options but currently no clear standard of care.
- Pattern of diminishing returns with successive lines of therapy
  - Worse outcomes in patients who relapse within 24 months of chemoimmunotherapy
- Novel agents have moved to the forefront of options in relapsed/refractory (R/R) disease

Treatment by Era and by Line of Therapy





Era 1: Pre-Antracycline (1960-1975) **Era 2: Antracycine. (1976-1986)**
Era 3: Agg. Chemo/Purine Analogs (1987-1996) **Era 4: Rituximab (1996-2003)**

Link et al. *BJH,* 2018; 184: 660-63
Rivas-Delgado et al. *BJH* 2018; 184: 753-59

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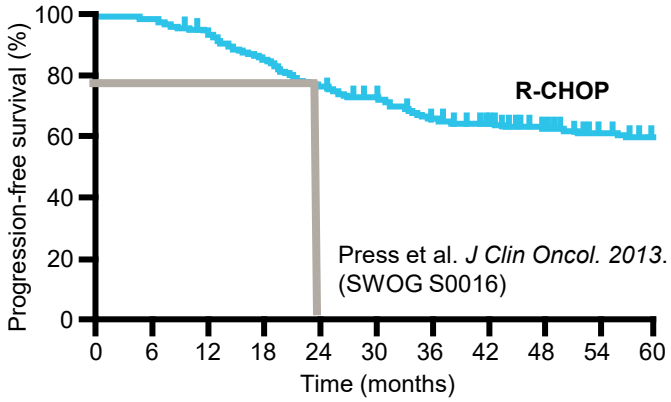
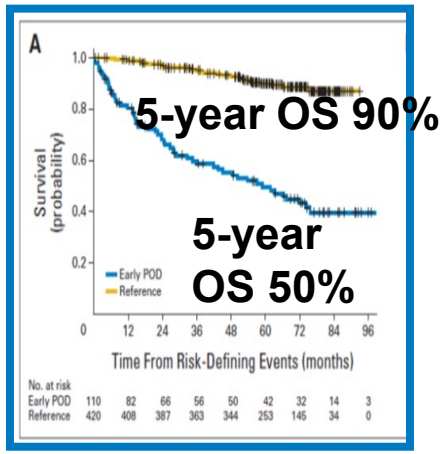
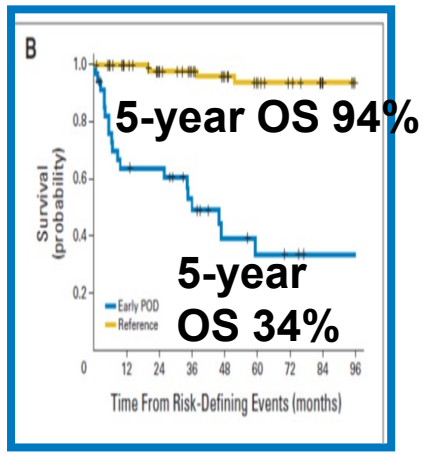
POD24/Transformation

- Despite worsening outcomes with subsequent therapy most patients with FL will live a considerable amount of time with disease.
- This does not appear to be the case with those who relapse early (within 24 months of receipt of chemo-immunotherapy for 1L treatment)
- Patients who fall into the POD24 category tend to have poor outcomes to subsequent therapy and shortened overall survival
  - Appears to be irrespective of regimen received in the frontline setting.

20% of Patients With FL Experience Disease Progression Within 2 years of Chemo-immunotherapy

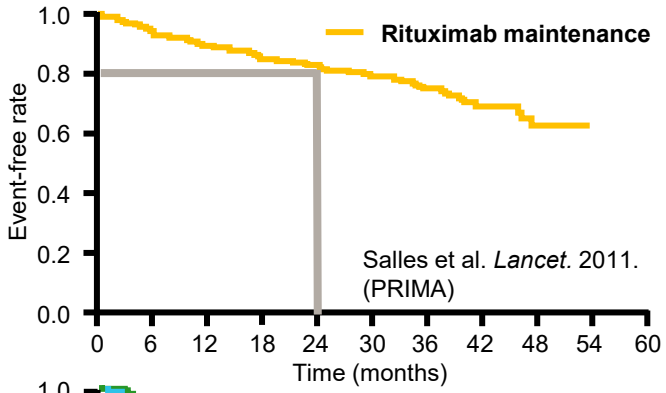


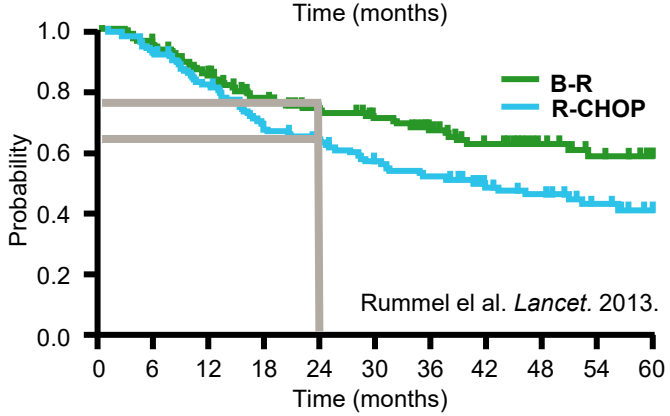




Casulo et al. JCO 2015

Original NLCS Cohort **Validation Cohort**





This suggests a high-risk group of patients who will relapse early despite different treatment approaches; maintenance

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POD24/Transformation (Continued)

- Data suggests that a portion of early relapsing patients have transformed DLBCL (tDLBCL).
- Highlights the need to biopsy early relapsing patients to confirm/rule out transformation
- Patients with transformed disease have historically had poor survival outcomes but more contemporary data suggests outcomes are more promising[1-3].
- If transformation noted, then patients should be treated like de novo DLBCL
  - Treatment should depend on receipt of chemotherapy prior to transformation.
    - Amount of prior anthracycline exposure
    - Most advocate consolidation with ASCT if response to chemotherapy used to treat tDLBCL

1. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic Transformation of low-grade follicular lymphoma. *J Clin Oncol*. 1995;13(7):1726-1733.
2. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(32):5165-5169.
3. Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *J Clin Oncol*. 2013;31(26):3272-3278.

Options 2L and Beyond

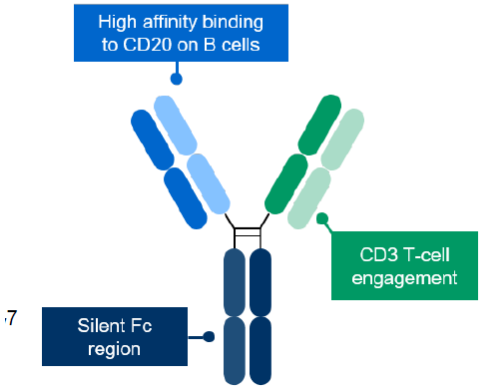
- Chemotherapy
  - Pending what was received in 1L setting and duration of remission.
- R2
  - AUGMENT and MAGNIFY Studies highlight benefit of agents in 2L+
    - MAGNIFY with higher risk patient population as compared to AUGMENT but ORR similar
- CAR-T (Axi-cel and Tisa-cel)
  - Access issues similar to DLBCL
- Tazemetostat
  - ORR higher in EZH2 mutant patients but PFS similar in both groups

Mosunetuzumab

- Recent approval for 3L beyond FL based on study by Budde et al.
  - CD20/CD3 bispecific antibody
- Drive Score - 0

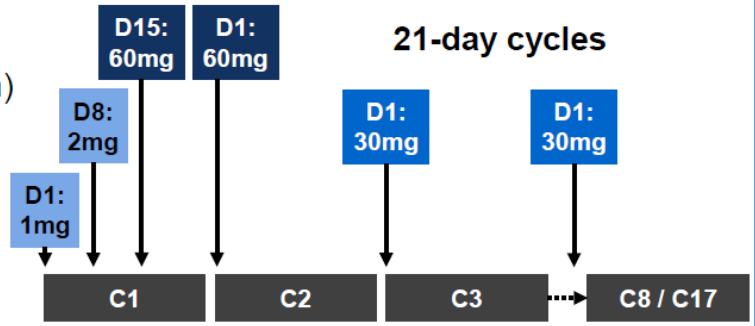
		N=90
Median number of prior lines, n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior aCD20 therapy		71 (78.9%)
Refractory to any prior aCD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

***Mosunetuzumab**:*
CD20xCD3 bispecific antibody[4]



Mosunetuzumab administration

- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



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Bispecific Antibodies (Mosunetuzumab)

Primary endpoint met: CR rate greater than historical control

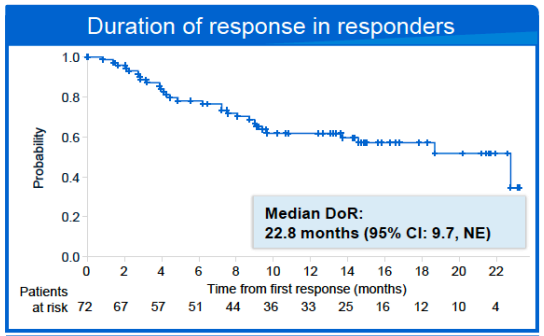
Efficacy endpoint[1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]	93%
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]	96%

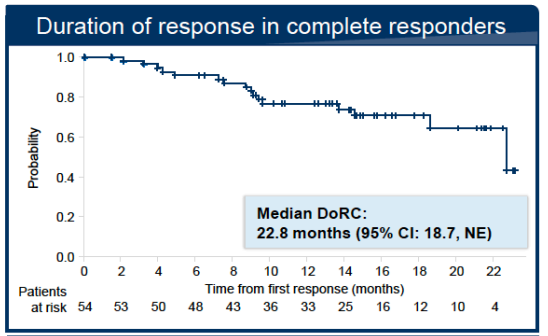
- **60% CR rate significantly greater (p<0.0001)* than 14% historical control CR rate[2]**

*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

1. Cheson et al. J Clin Oncol 2007;25:579–86
2. Dreyling et al. J Clin Oncol 2017;35:3898–905

Duration of response

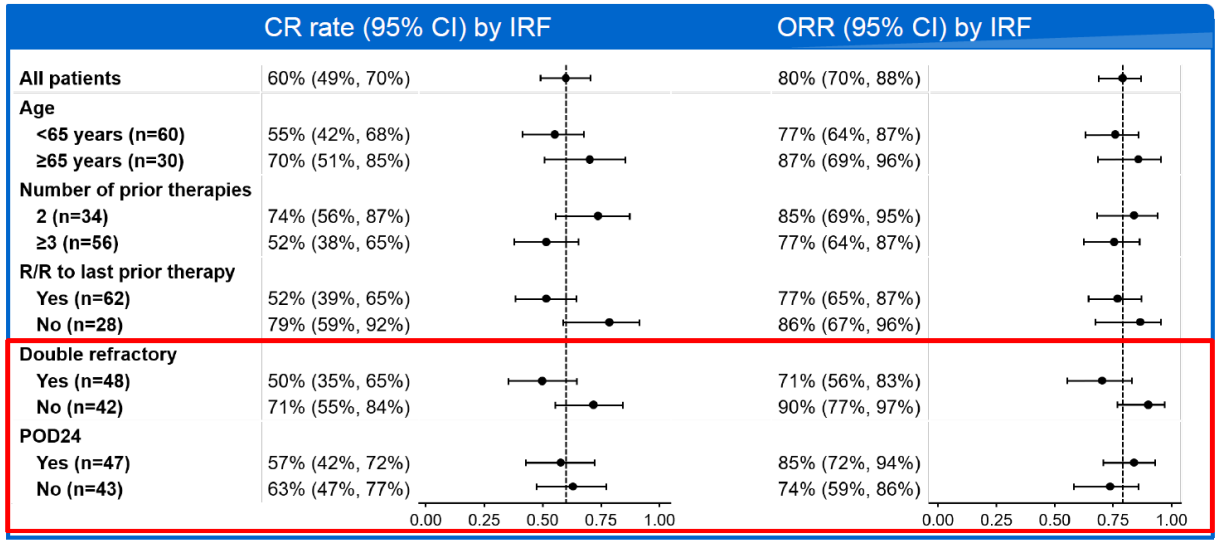




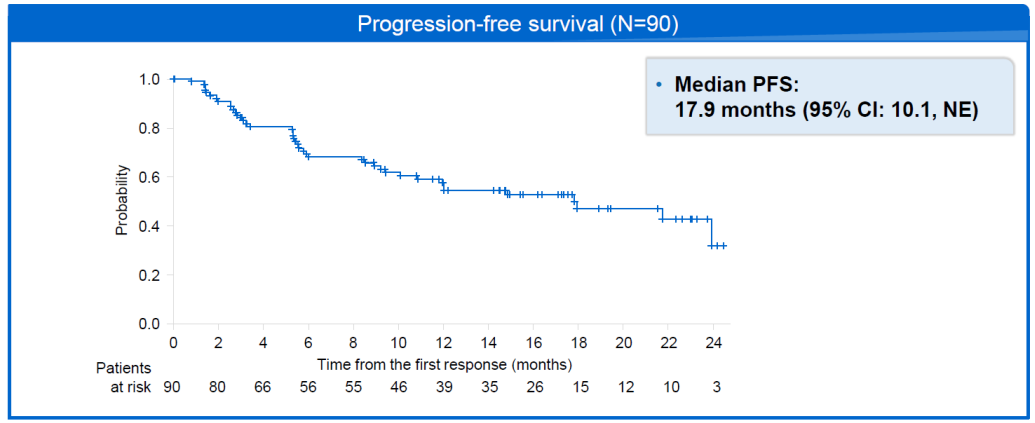
Median time to first response, mo (range)	1.4 (1.1, 8.9)
12-month event-free rate, % (95% CI)	62% (50%, 74%)
18-month event-free rate, % (95% CI)	57% (44%, 70%)

Median time to first CR, mo (range)	3.0 (1.1, 18.9)
12-month event-free rate, % (95% CI)	76% (65%, 88%)
18-month event-free rate, % (95% CI)	70% (57%, 84%)

DoRC, duration of response in complete responders; mo, month; NE, not estimable



Progression-free survival



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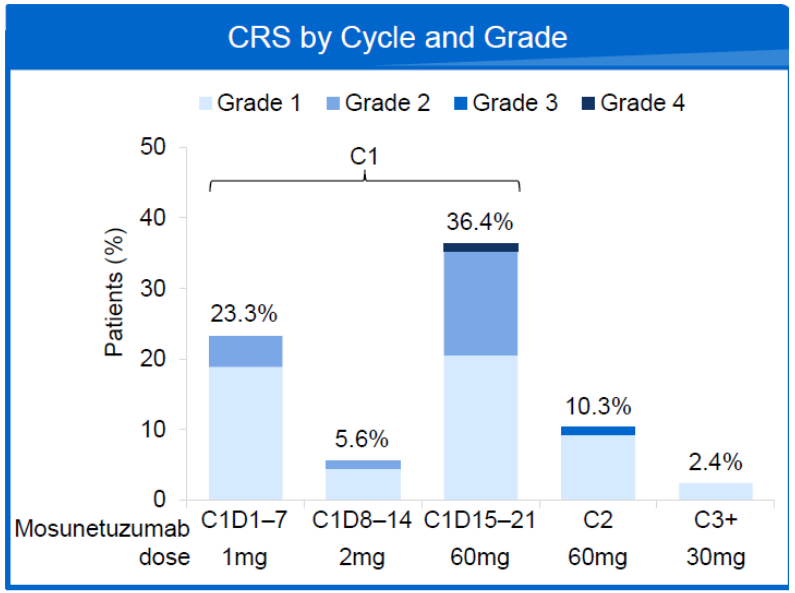
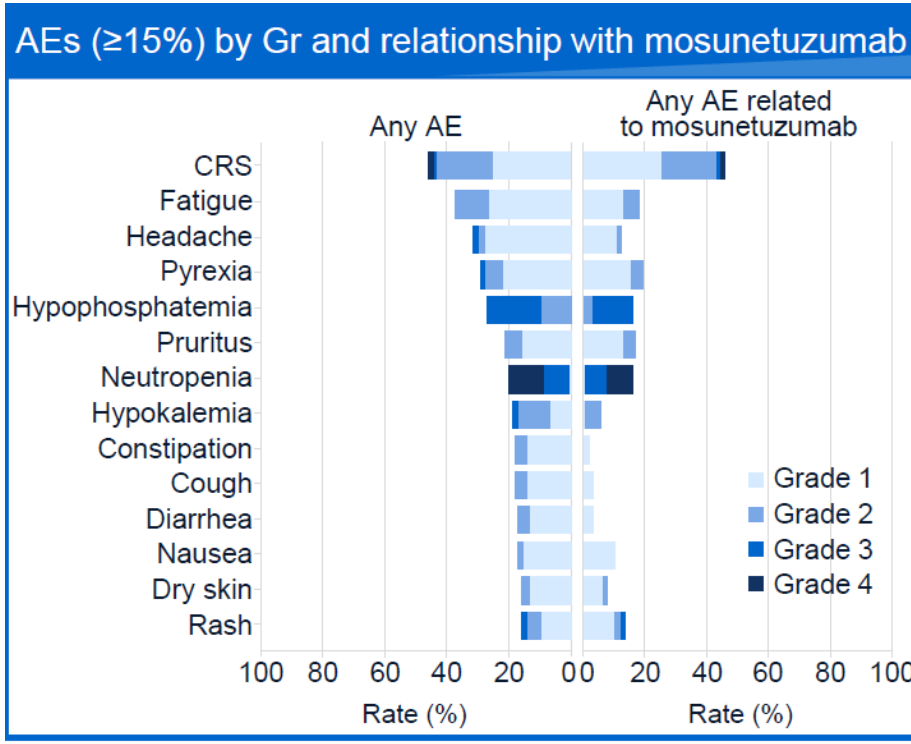
Mosunetuzumab AE profile

Cytokine release syndrome

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)





- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

ICANS*	4 (4.4%)
Grade 3	0

- Confusional state (3.3%; all Grade 1–2†), disturbance in attention and cognitive disorder (1.1% each; all Grade 1†); all resolved
- No cases of aphasia, seizures, encephalopathy, or cerebral edema

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MCL

- Rare NHL that is currently incurable.
  - Several 1L options but no true SOC
  - Clinical trials preferred for most if available
- Several exciting studies at ASH
  - Triangle
  - BRUIN – recent approval

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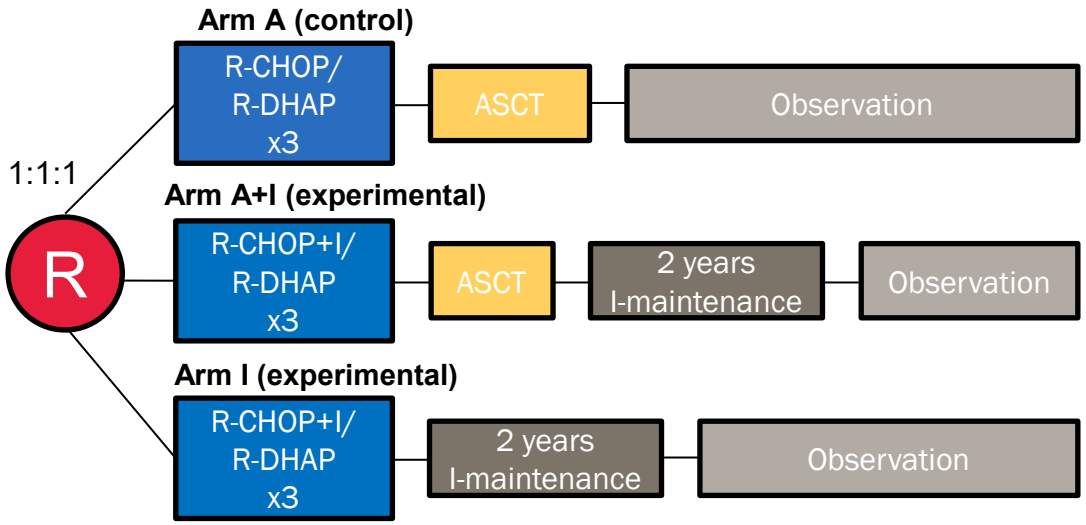
TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Study Design and Patients

Key Eligibility Criteria
- Previously untreated stage II-IV MCL
- Age <66 years
- Suitable for HA and ASCT
- ECOG PS 0-2



Primary endpoint: FFS
Secondary endpoints: Response rates, PFS, RD, OS, safety

Patient Characteristics		A (n=288)	A+I (n=292)	I (n=290)
Median age (range), years		57 (31-65)	57 (36-68)[a]	58 (27-65)
Male, %		76	74	79
No MCL, n		2[b]	4[c]	2[d]
Ann Arbor Stage, % (n=864)	I	0	0	0
	II	4	4	6
	III	8	7	10
	IV	88	89	84
ECOG >1%		2	1	2
MIPI, %	Low	58	58	58
	Intermediate	27	27	27
	High	14	15	16

- R maintenance (± I) was added in all 3 trial arms, following national guidelines. It was initiated in 168 (58%) patients in Arm A; 165 (57%) patients in Arm A+I; and 158 (54%) patients in Arm I

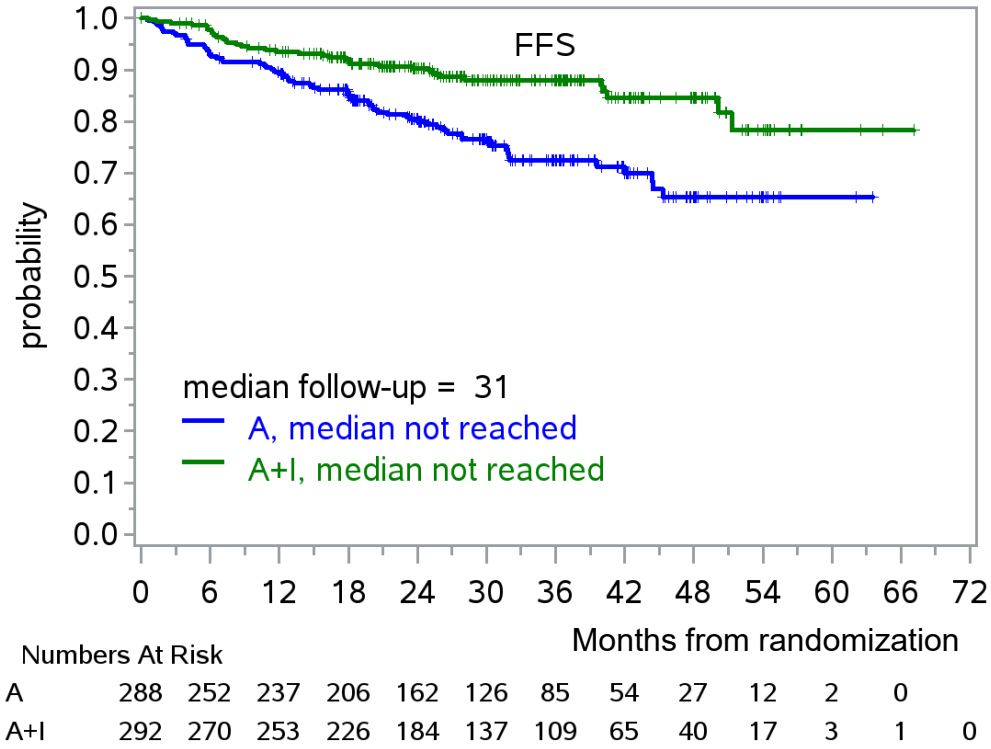
[a]2 patients aged 66 & 68 years were randomized. [b]1 CLL, 1 FL. [c]1 NHL NOS, 1 HD, 2 MZL. [d]1 HCL, 1 DLBCL.
Dreyling M, et al. ASH 2022. Abstract 1.

TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Efficacy

Responses at End of Induction, n (%)	Overall	A	A+I/I	A+I	I
ED	2 (0.2)	1 (0.4)	1 (0.2)	1 (0.4)	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 were significantly higher for combined I induction (A+I/I) vs control (A): CR *P*=0.0203; OR *P*=0.0025

FFS of A+I vs A

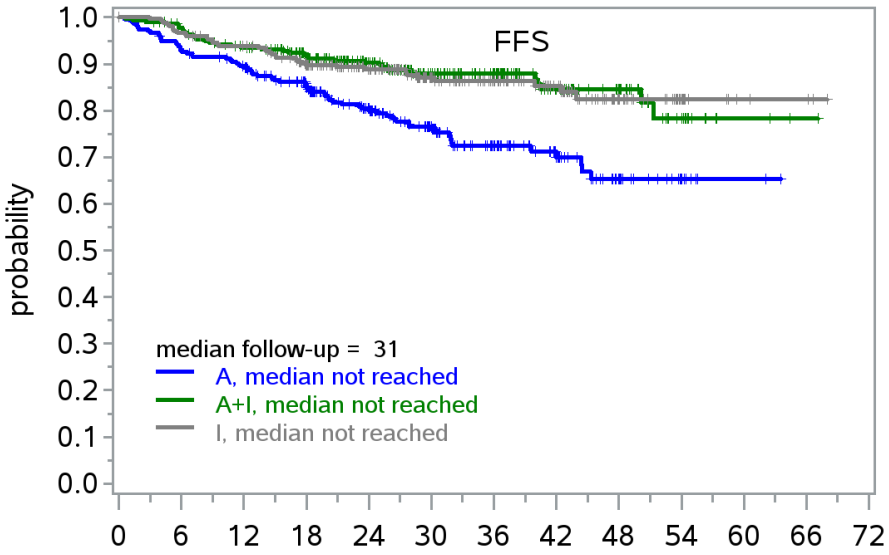


- 3-year FFS: A+I 88% vs A 72%; HR 0.52; *P*=0.0008

Dreyling M, et al. ASH 2022. Abstract 1.

TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Efficacy (cont'd)

FFS of A vs A+I vs I



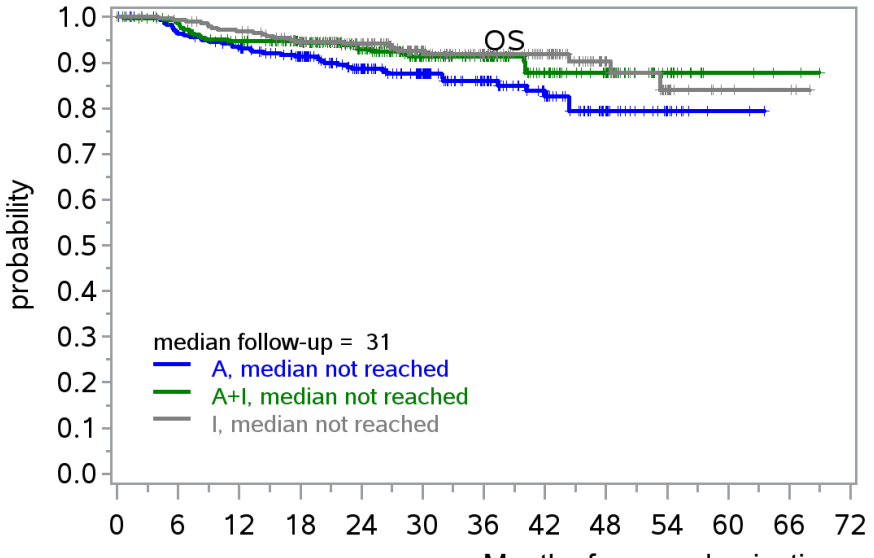
Numbers At Risk

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
I	290	269	257	229	180	133	100	68	34	16	4	3

- Test for A+I vs I FFS is ongoing

Next Lymphoma Treatment After 1st Treatment Failure, n (%)	A (n=68)	A+I (n=35)	I (n=37)
With ibrutinib	34 (79)	4 (24)	3 (11)
Without ibrutinib	9 (21)	13 (76)	24 (89)
No treatment	25	18	10

Overall Survival



Numbers At Risk

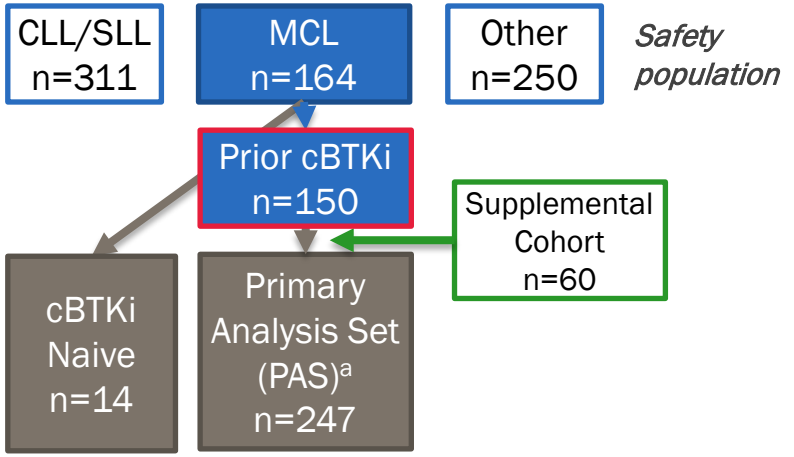
A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

- 3-year OS: A 86%; A+I 91%; I 92%
- Too early to determine statistical significance

Extended Follow-Up From the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With Covalent BTKi Pretreated R/R MCL: Study Design and Patients

Key Eligibility Criteria
- R/R MCL
- ECOG PS ≤2

Phase 1 Escalation + Expansion (25-300 mg QD)
Phase 2 (200 mg QD)
(N=725)



Key endpoints: safety/tolerability, MTD and RP2D, PK, efficacy (IRC-assessed ORR/DOR by Lugano)

Patient Characteristics		Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median age (range), years		70 (46-87)	67 (60-86)
Histology, n (%)	Classic	70 (78)	11 (79)
	Blastoid	20 (22)	3 (21)
ECOG PS, n (%)	0	61 (68)	5 (36)
	1	28 (31)	8 (57)
	2	1 (1)	1 (7)
sMIPI risk, n (%)	Low (0-3)	20 (22)	3 (21)
	Intermed. (4-5)	50 (56)	5 (36)
	High (6-11)	20 (22)	6 (43)
Tumor bulk, n (%)	<5 cm	66 (73)	9 (64)
	≥5 cm	24 (27)	5 (36)
	<10 cm	87 (97)	12 (86)
	≥10 cm	3 (3)	2 (14)
BM involvement, n (%)		46 (51)	4 (29)

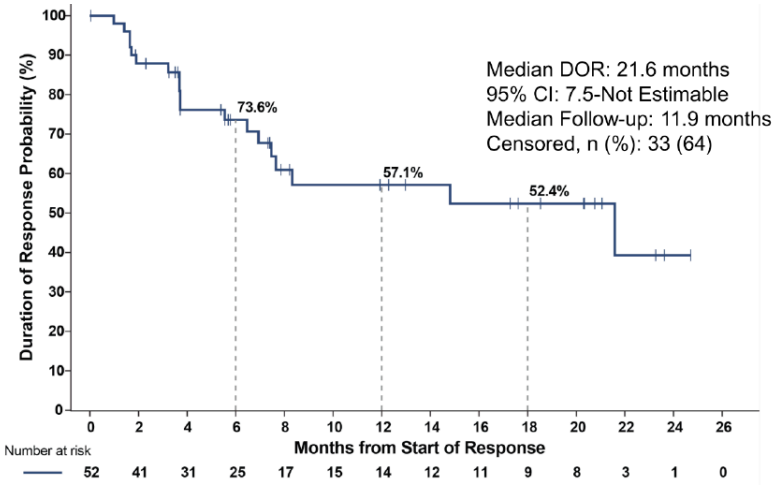
Prior Treatment	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median prior lines of therapy (range), n	3 (1-8)	2 (1-3)
Prior therapy, n (%)		
BTKi	90 (100)	0 (0)
Anti-CD20 mAb	86 (96)	14 (100)
Chemotherapy	79 (88)	14 (100)
Immunomodulator	19 (21)	1 (7)
SCT	19 (21)	7 (50)
BCL2i	14 (16)	0 (0)
CAR T	4 (4)	0 (0)
PI3Ki	3 (3)	1 (7)

- Reasons for prior cBTKi discontinuation
  - PD: 74 (82%)
  - Toxicity/other: 16 (18%)

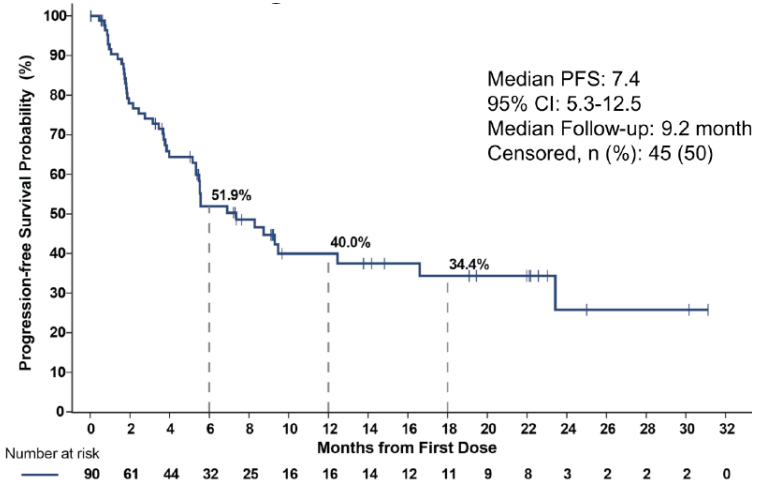
[a]To ensure adequate follow-up, a cutoff of January 31, 2022, was used, which allowed the vast majority (>90%) of responders in the PAS to be followed for ≥9 months from onset of initial response to the data cutoff date.
Wang ML, et al. ASH 2022. Abstract 4218.

Extended Follow-Up From the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With Covalent BTKi Pretreated R/R MCL: Efficacy (cont'd)

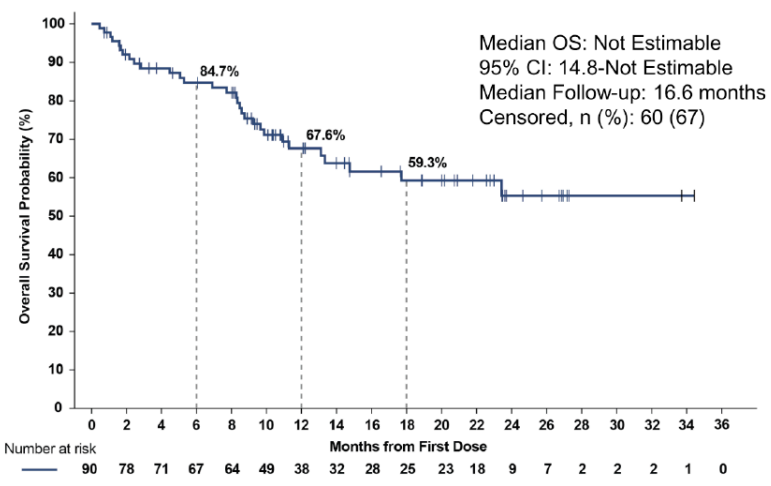
DOR in Prior cBTKi Patients



PFS in Prior cBTKi Patients



OS in Prior cBTKi Patients

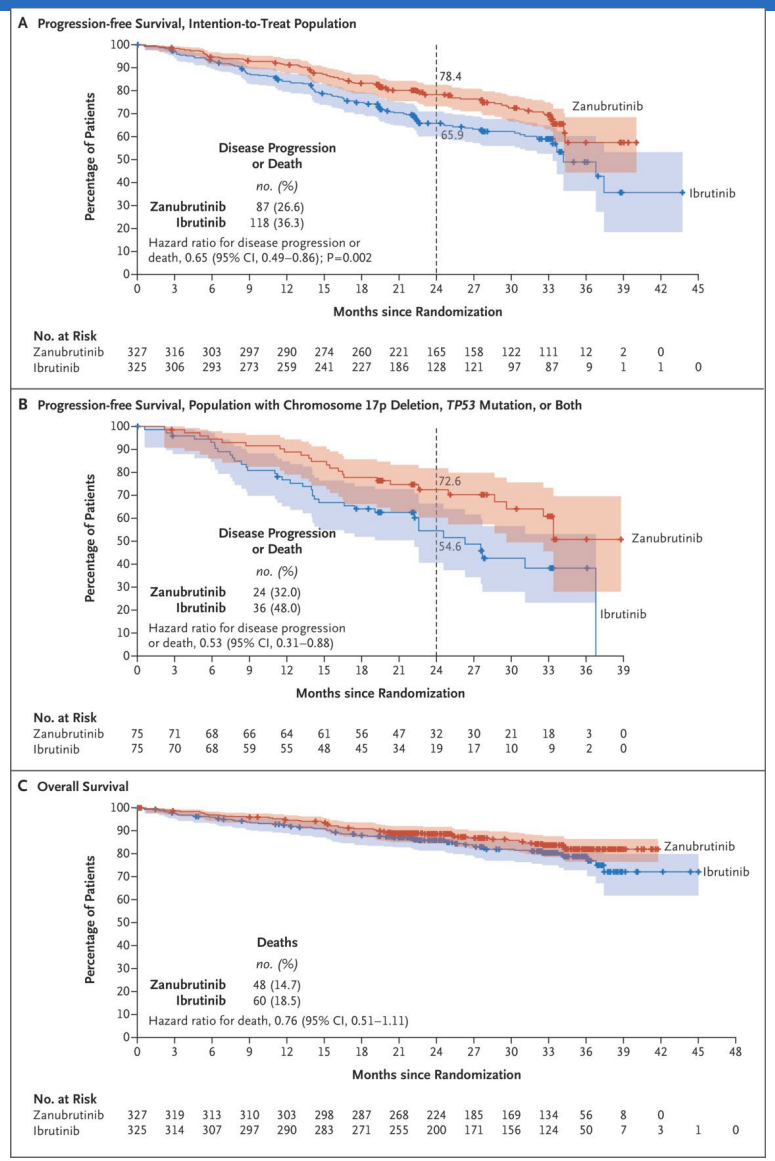


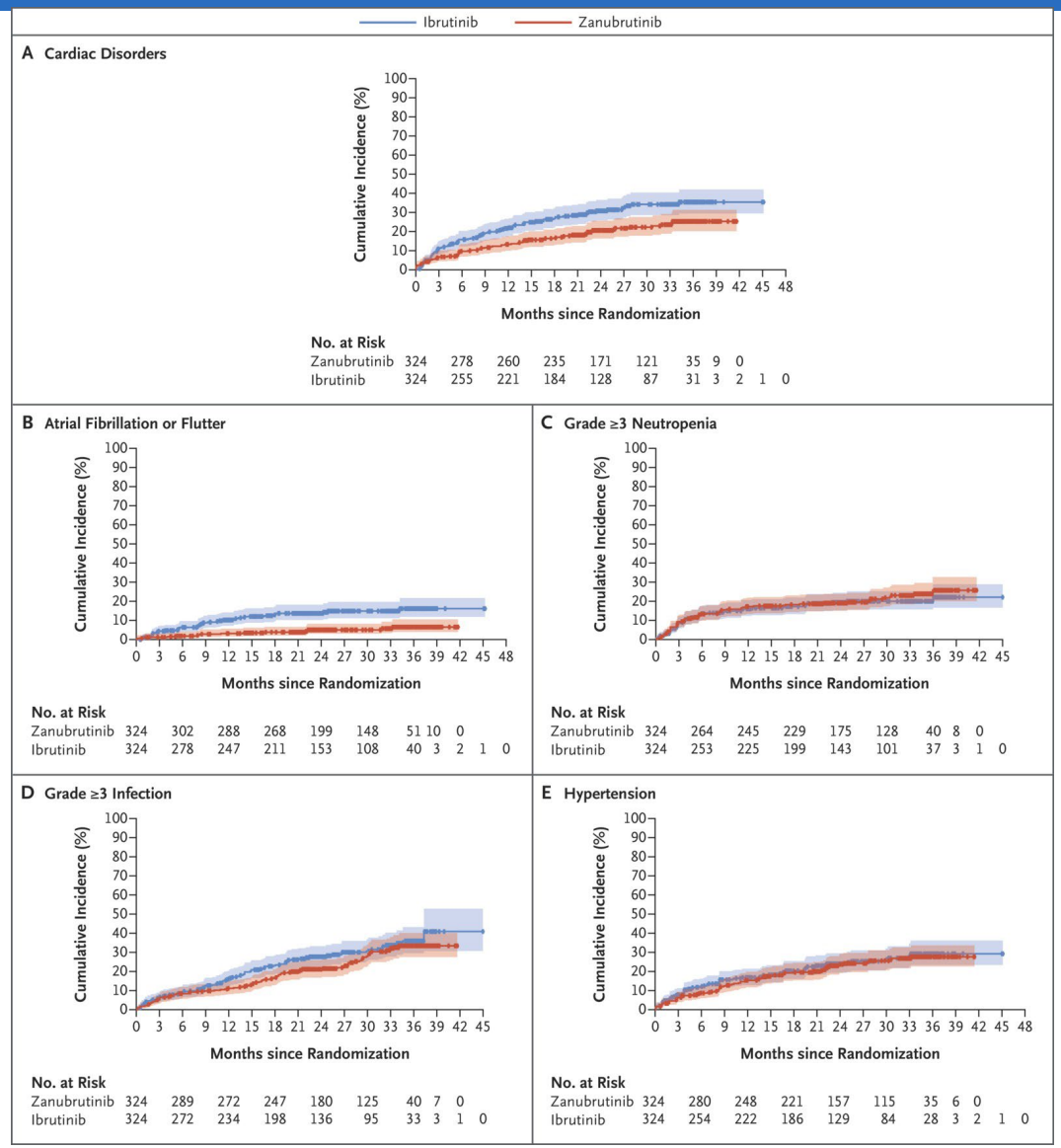
Wang ML, et al. ASH 2022. Abstract 4218.

CLL- ALPINE STUDY

- Most Common Leukemia
  - BTKi have revolutionized treatment landscape and are 1L option for most.
  - Currently two approved ibrutinib and acalabrutinib
  - Study evaluated ibrutinib vs. zanubrutinib (2^{nd} gen covalent BTKi)
  - DRIVE SCORE - 0

ALPINE –Results/Tox of interest





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T-Cell

- Rare in US
  - For ALCL reasonable to consider BV-CHP SOC from Echelon-2
    - ALK – with DUSP22 and TP63 mutations with favorable outcomes
  - Data for other subtypes less clear with respect to Echelon-2 especially those with low/no CD30 expression
    - CHOP/CHOEP + ASCT still reasonable options for these patients.
  - Limited options for R/R disease but some newer options include
  - PTCL
    - Duvelisib (while still available)
  - CTCL
    - Mogamulizumab

Summary

- DLBCL
  - R-CHOP still on 1L option approved for DLBCL in US.
  - Await further follow up of POLARIX
  - R/R disease
  - Bispecifics soon to be available and alternative to those who can’t get to or relapse after CAR
- FL
  - POD remains troublesome
  - Mosunetuzumab now available
- MCL/CLL
  - Triangle encouraging but need for long term data
  - Zanubrutinib now an option for 1L CLL
- T-Cell
  - No major changes on horizon

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