Day 3 – Sunday 1/21/24
Session XI: Lymphoma Session
B-Cell NHL (Low Grades)

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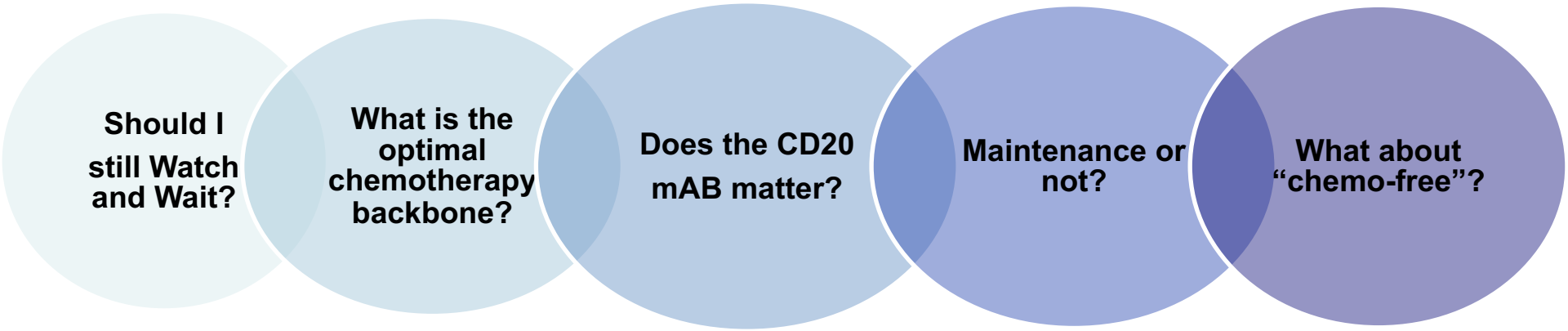
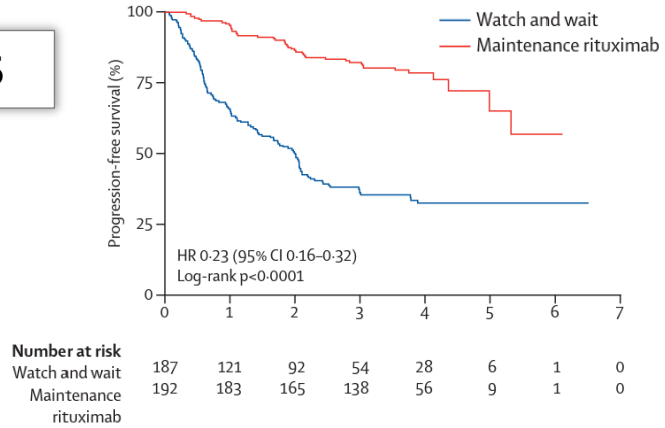
Treatment Dilemmas in 1st Line Advanced FL



Low Tumor Burden FL: Should I Still W&W?

Ardeshna Study[1]

PFS



Improved PFS and TTNT:
Rituximab compared to Watch and Wait

Arguments for W&W

- Treatment does not impact OS
- 15-20% not received treatment after 10 years
- 12% spontaneous disease reduction

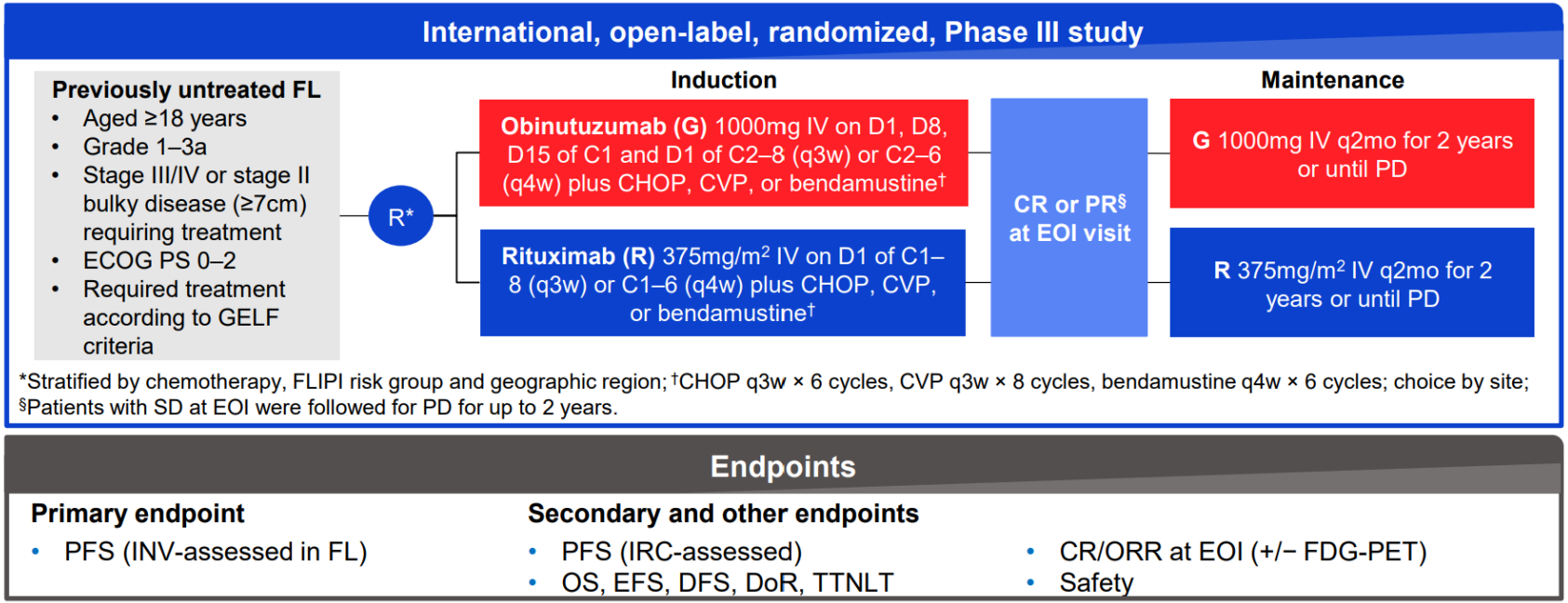
BUT:

- Median time to needing treatment: 2.5 years
- Psychological impact/QoL

Ardeshna KM et al. *Lancet Oncol.* 2014;15:424-435.

Which Anti-CD20? Rituximab (R) vs Obinutuzumab (G): Final Analysis of the GALLIUM Study

GALLIUM study design:

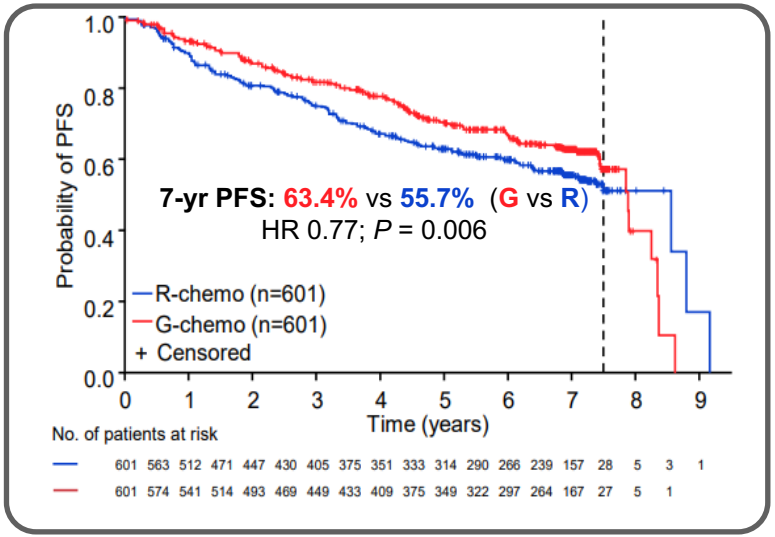


N =1202 previously untreated advanced FL patients

Marcus R et al. *N Engl J Med*. 2017;377:1331-1344.

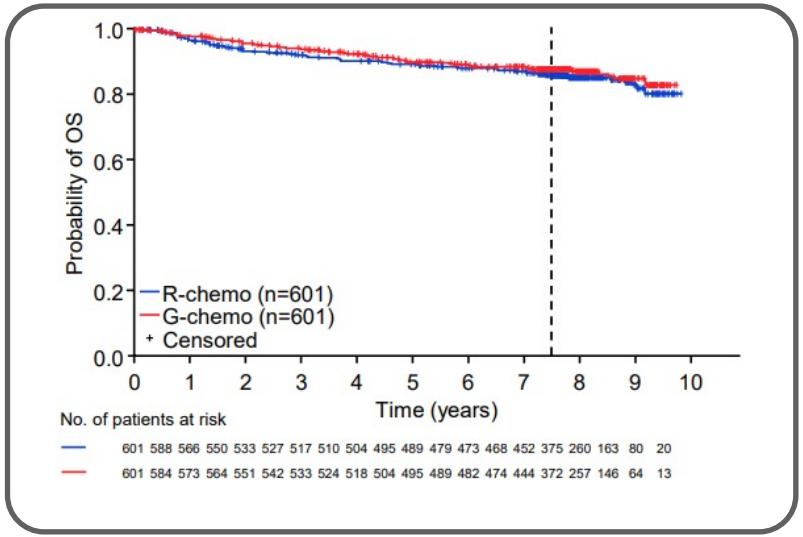
Final Analysis of the GALLIUM Study: PFS and OS

PFS: G-chemo vs R-chemo



PFS benefit maintained with
G-chemo vs **R-chemo**

OS: G-chemo vs R-chemo

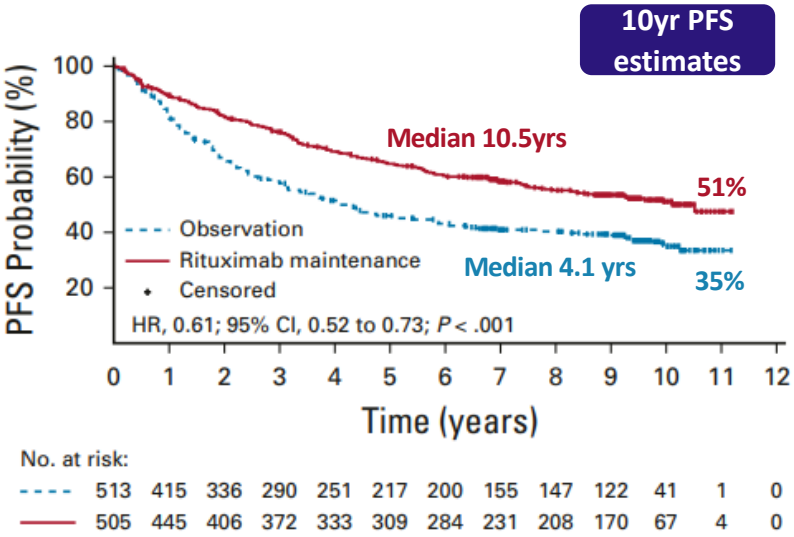


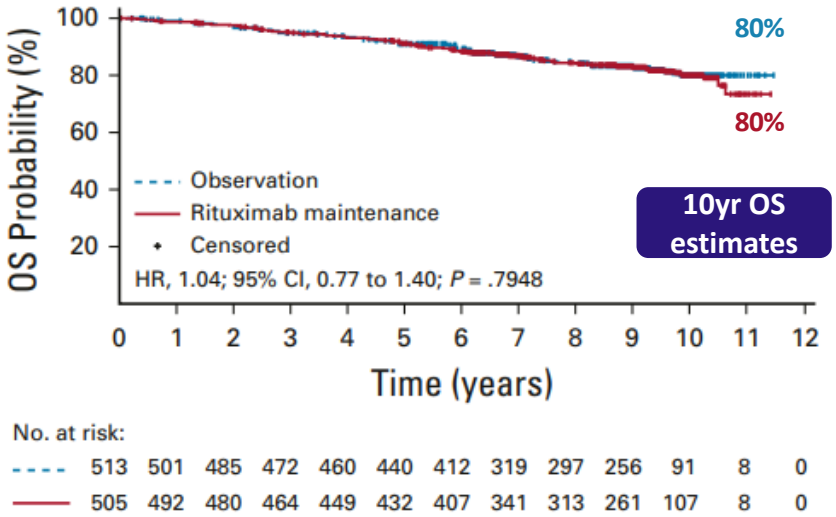
Overall survival similar between
G-chemo vs **R-chemo**

Townsend W et al. EHA 2022. Abstract S206.

Value in Adding Maintenance After 1st Line Rituximab-Chemotherapy?

Yes, it increases PFS: PRIMA study update





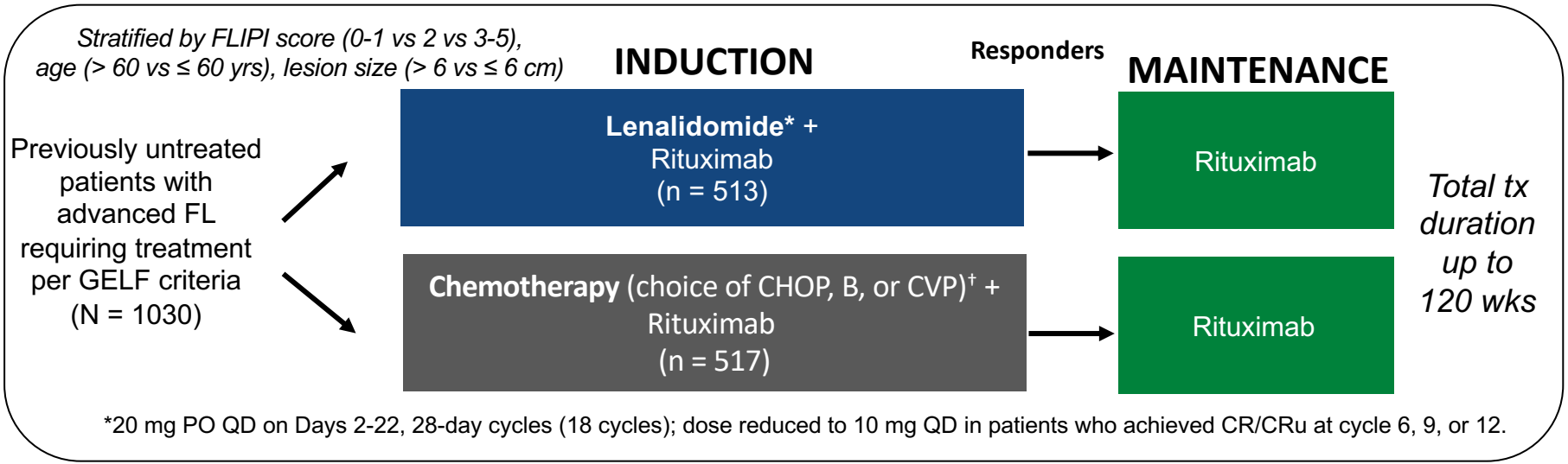
Comments:

- In PRIMA, no BR as induction
- No PET to assess EOI response
- Value in BR/OB-treated patients unclear

Salles G et al. *Lancet.* 2011;377:42-51. Bachy E et al. *J Clin Oncol.* 2019;37:2815-2824.

Can We Improve Upon First Line: Chemo-Free Combination?
RELEVANCE trial – R^2 (Rituximab + Lenalidomide) vs R-Chemo

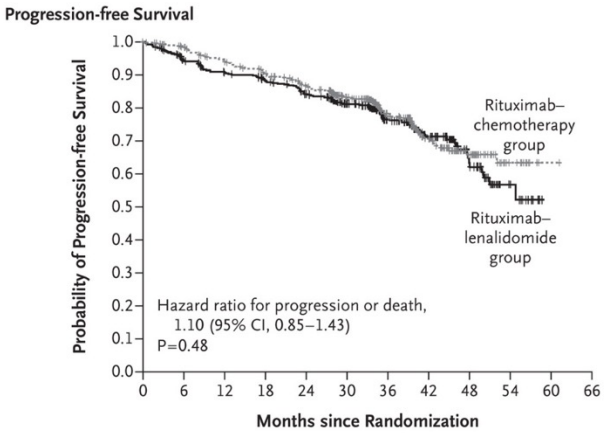
- International, randomized phase III study

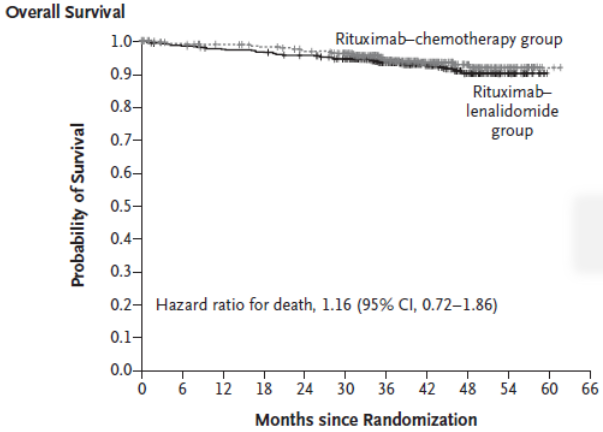


- Co-primary endpoints (superiority): CR/CRu at 120 wks, PFS

Morschhauser F et al. *N Engl J Med.* 2018;379:934-947.

Can We Improve Upon First Line: Chemo-Free Combination?
RELEVANCE trial – R^2 (Rituximab + Lenalidomide) vs R-Chemo





R^2 comparable to R-chemo

Safety

Higher gd 3-4 neutropenias in R-chemo (50% vs 32%)

Higher gd 3-4 cutaneous rxns in R^2 (7% vs 1%)

Outcomes

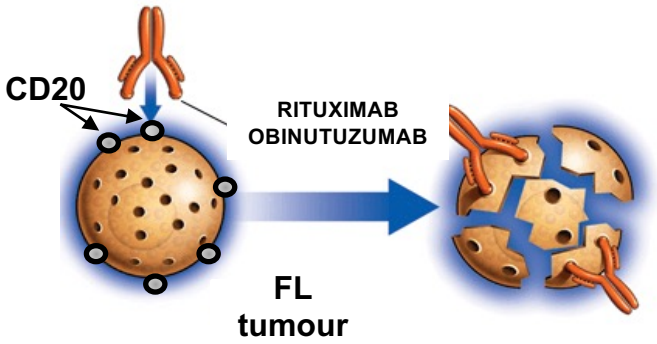
	R-chemo N = 517	R^2 N = 513
3yr PFS % (95% CI)	78 (74-82)	77 (72-80)
CR rates (%)	33	28
3yr OS %	94	94

Morschhauser F et al. *N Engl J Med.* 2018;379:934-947.

Summary of Frontline Treatment in Advanced Stage FL in 2024

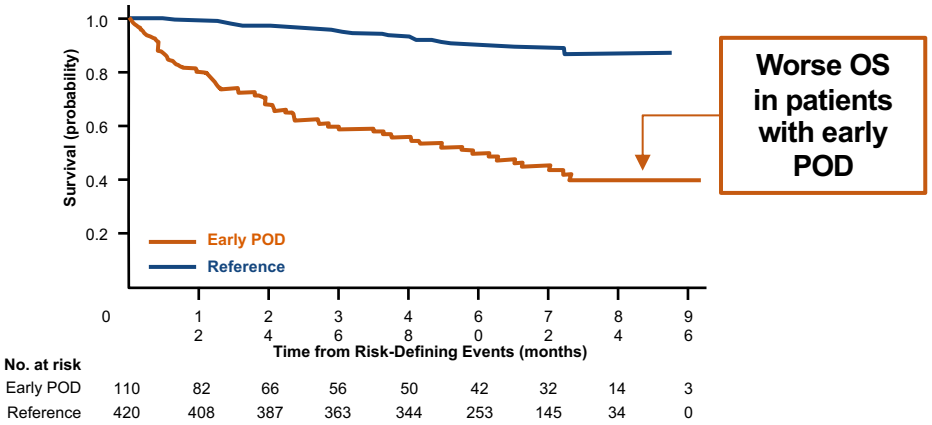
Anti-CD20 + chemotherapy remains the standard first line therapy

- BR, R-CHOP, R-CVP – choice is patient-specific
- Rituximab maintenance improves PFS, but no difference in OS
- Obinutuzumab-chemo improves PFS, but no difference in OS compared to R-chemo
- R2 – not superior to R-chemo, but appears comparable, potential option if the goal is to avoid chemotherapy
- Consider a clinical trial as there are several novel therapies moving into frontline vs. R-chemo



R/R FL: POD24 is associated with inferior survival

- Biopsy recommended to detect histologic transformation of FL, which is reported to occur at a rate of 2% per year[1]
  - If concerned for clinical transformation and biopsy is not pursued, would treat as DLBCL[2]
- Early progression of disease (≤2 years) after frontline chemoimmunotherapy (POD24) occurs in approximately 20% of patients
  - Associated with a poor prognosis[3]
  - Represents a population that should be targeted for trials.



1. Link BK, et al. *J Clin Oncol.* 2013;31:3272. 2. Casulo C, Barr PM. *Blood.* 2019;133:1540.
3. Casulo C, et al. *J Clin Oncol.* 2015;33:2516.

R^2 vs R in R/R FL and MZL
Phase III AUGMENT Study

N=358

- **R/R MZL and FL (grades 1-3a)**
- **≥1 prior chemotherapy, immunotherapy, or chemoimmunotherapy and ≥2 previous doses of rituximab**
- **Not rituximab-refractory**

1:1

≤12 cycles or until PD, relapse, intolerability, or withdrawal of consent

R-lenalidomide (R^2)
Rituximab: 375 mg/m^2 d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
Lenalidomide: 20 mg/d,* d1-21/28 (12 cycles)

*10 mg if CrCl between 30 and 59 mL/min.

R-placebo
Rituximab: 375 mg/m^2 d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
Placebo: matched capsules (12 cycles)

- *Prophylactic anticoagulation/antiplatelet Rx recommended for at-risk patients*

5-year follow-up for OS, SPMs, subsequent treatment, and response to next therapies

Primary endpoint

PFS by IRC (2007 IWG criteria without PET)

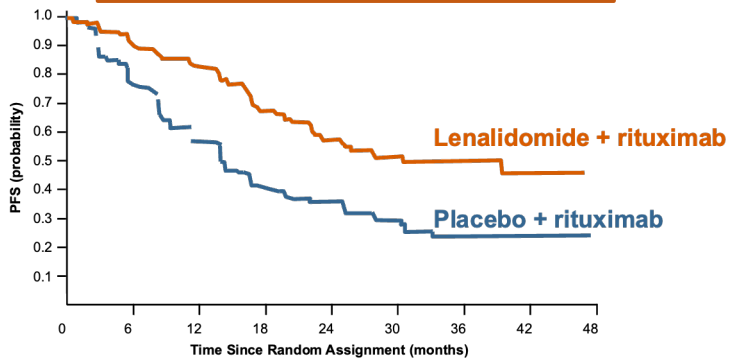
Stratification
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Leonard J et al. *J Clin Oncol*. 2019;37:1188-1199.

R^2 vs R in R/R FL and MZL
Phase III AUGMENT Study: PFS, OS

Progression-free Survival

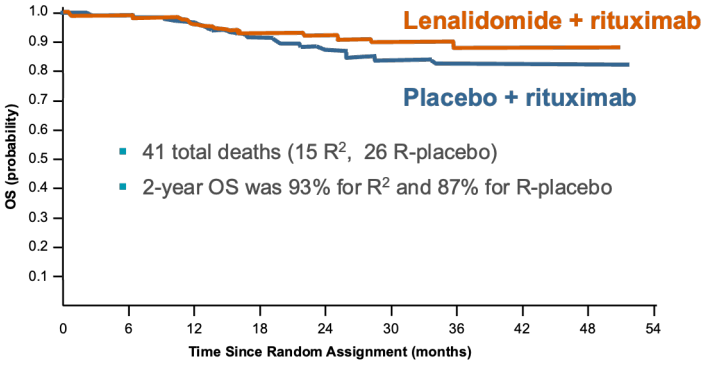
HR, 0.46 (95% CI, 0.34 to 0.62)
P < 0.0001



No. at risk									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

Overall Survival

HR, 0.61 (95% CI, 0.33 to 1.13)



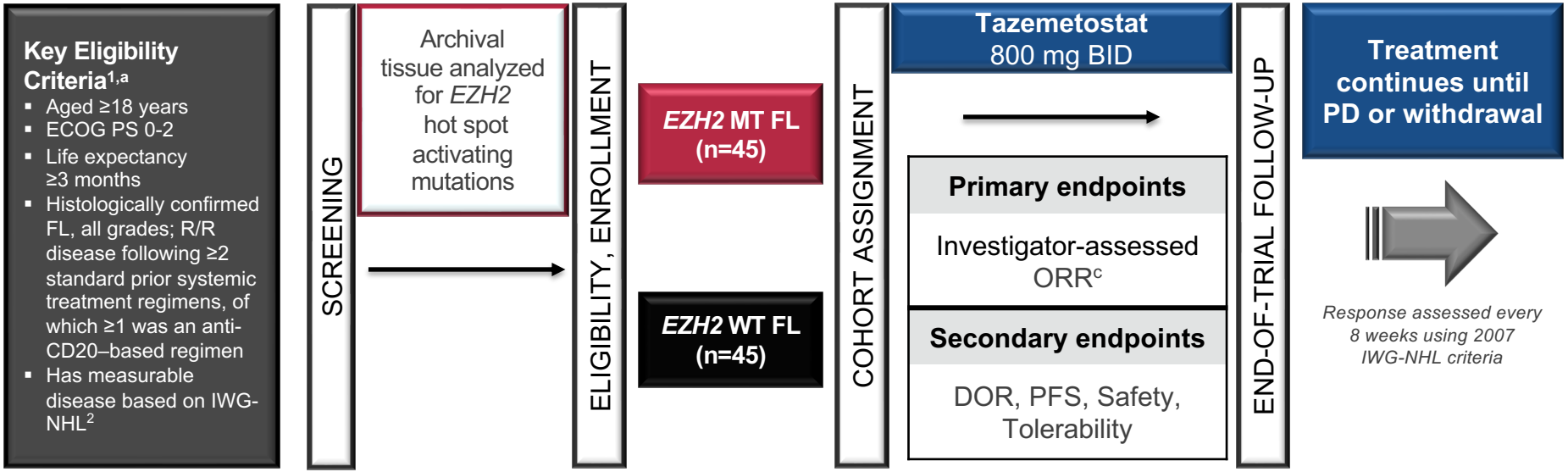
No. at risk										
Lenalidomide + rituximab	178	167	155	143	122	80	44	15	1	0
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0

Median PFS	R^2 (n=178)	R-Placebo (n=180)	HR	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	<0.0001
By INV, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	<0.0001

Median follow-up: 28.3 months

Leonard J et al. *J Clin Oncol*. 2019;37:1188-1199.

Tazemetostat for R/R FL
Phase 2, Open-Label, Multicenter Study



[a]For a full list of study eligibility criteria, please see Clinicaltrials.gov/ct2/show/NCT01897571. [b]Actual enrollment: n=54. cORR defined as the number of participants with a best objective response of CR or PR.

Morschhauser F et al. *Lancet Oncol.* 2020;21:1433-1442.

Tazemetostat for R/R FL
Phase 2, Open-Label, Multicenter Study

Response in the MT *EZH2* Cohort

Response in MT EZH2 (n=45)	IRC	INV
ORR, n (%) [95% CI[a]]	31 (69) [53, 82]	35 (78) [63, 89]
CR, n (%)	6 (13)	4 (9)
PR, n (%)	25 (56)	31 (69)
SD, n (%)	13 (29)	10 (22)
PD, n (%)	1 (2)	0

- 44 of 45[b] (98%) patients with evidence of tumor reduction, by IRC
- mPFS, 13.8 mos (95% CI, 10.7-22.0)

Response in the WT *EZH2* Cohort

Response in WT EZH2 (n=54)	IRC	INV
ORR, n (%) [95% CI[a]]	19 (35) [23, 49]	18 (33) [21, 48]
CR, n (%)	2 (4)	3 (6)
PR, n (%)	17 (31)	15 (28)
SD, n (%)	18 (33)	16 (30)
PD, n (%)	12 (22)	16 (30)
NE/missing/unknown,[b] n (%)	5 (9)	4 (7)

- 37 of 49[c] (69%) patients with evidence of tumor reduction, by IRC
- mPFS, 11.1 mos (95%CI, 3.7-`14.6)

[a]By Brookmeyer and Crowley method. [b]4 subjects with missing post-baseline values and 1 subject with poor image. [c]Best overall response based on Cheson (2007) criteria for lymphomas.

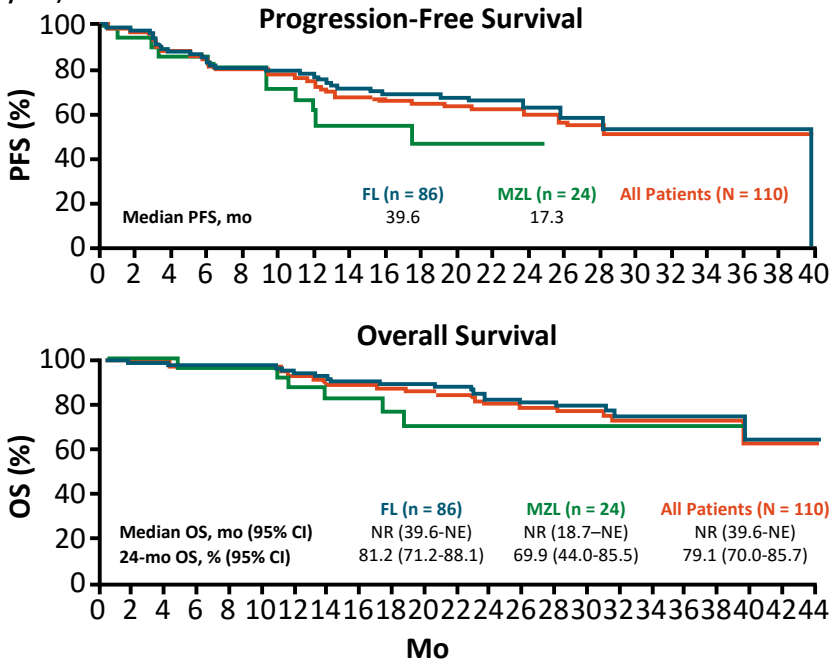
Morschhauser F et al. *Lancet Oncol.* 2020;21:1433-1444.

ZUMA-5: Axicabtagene Ciloleucel for Relapsed/Refractory Indolent NHL (FL or MZL)

- Single-arm phase II study of axicabtagene ciloleucel for patients with R/R indolent B-cell NHL (FL or MZL) **with ≥2 prior therapies** (N = 110 eligible for efficacy analysis)

Outcome	FL (n = 86)	MZL (n = 24)	All (N = 110)
ORR, n (%)	81 (94)	20 (83)	--
▪ CR	68 (79)	15 (63)	--
▪ PR	13 (15)	5 (21)	--
▪ SD	3 (3)	0	--
▪ PD	0	1 (4)	--
▪ ND	2 (2)	3 (13)	
Median DoR, mo (95% CI)	38.6 (24.7-NE)	NR (8.2-NE)	38.6 (24.7-NE)
24-mo DoR, % (95% CI)	66.1 (53.9-75.8)	NR (NE-NE)	63.5 (52.4-72.7)

- CRS grade ≥3, 7% (6% FL); neurotoxicity grade ≥3, 19% (15% FL); tocilizumab, 49%; corticosteroids, 36%



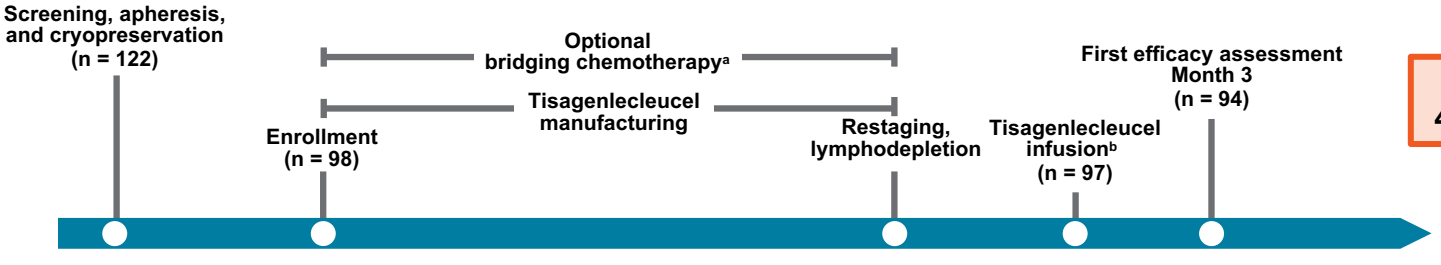
Neelapu SS et al. ASH 2021. Abstract 93.

ZUMA-5 CRS and Neurologic Events

Parameter	CRS[a]			Neurologic Events[a]		
	FL (n=124)	MZL (n=22)	All Patients (N=146)	FL (n=124)	MZL (n=22)	All Patients (N=146)
Any grade	97 (78)	22 (100)	119 (82)	70 (56)	17 (77)	87 (60)
Grade ≥3	8 (6)	2 (9)	10 (7)	19 (15)	9 (41)	28 (19)
Most common CRS symptoms of any grade, n/n (%)						
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)	–	–	–
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)	–	–	–
Most common neurologic events of any grade, n/n (%)						
Tremor	–	–	–	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	–	–	–	28/70 (40)	7/17 (41)	35/87 (40)
Tocilizumab use, n (%)	56 (45)	15 (68)	71 (49)	7 (6)	2 (9)	9 (6)
Corticosteroid use, n (%)	19 (15)	6 (27)	25 (17)	38 (31)	14 (64)	52 (36)
Median time to onset (range), days	4 (1–15)	4 (1–9)	4 (1–15)	7 (1–177)	7 (3–19)	7 (1–177)
Median duration of events (range), days	6 (1–27)	6 (2–14)	6 (1–27)	14 (1–452)	10 (2–81)	14 (1–452)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]	67/70 (96)	14/17 (82)	81/87 (93)

Jacobson CA et al. ASH 2020. Abstract 700.

ELARA Study Design



Median follow-up:
40.6 months (range, 34.2-49.7)

Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • Relapsed/refractory disease[d] • No evidence of histological transformation/FL3B • No prior anti-CD19 therapy or allogeneic HSCT	Tisagenlecleucel dose range (single IV infusion) was 0.6-6 × 10^8 CAR-positive viable T cells	**Primary:** CRR by IRC **Secondary:** ORR, DOR, PFS, OS, safety, cellular kinetics

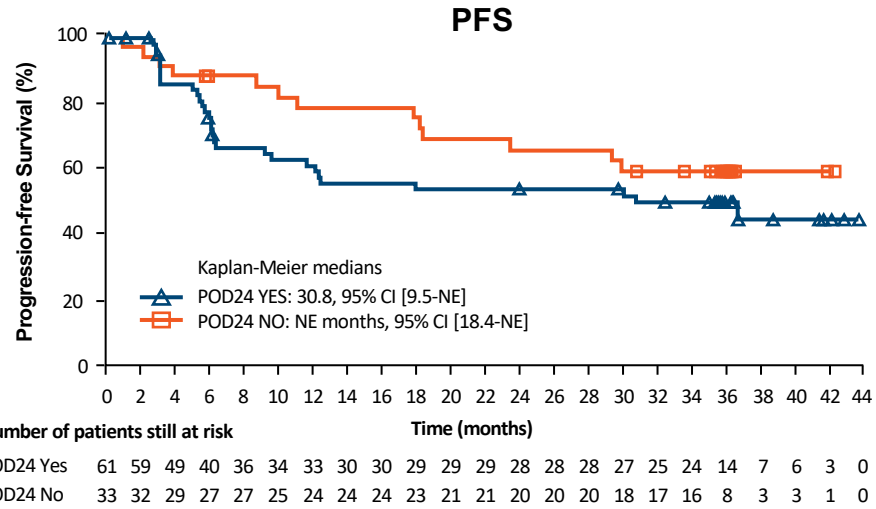
- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion

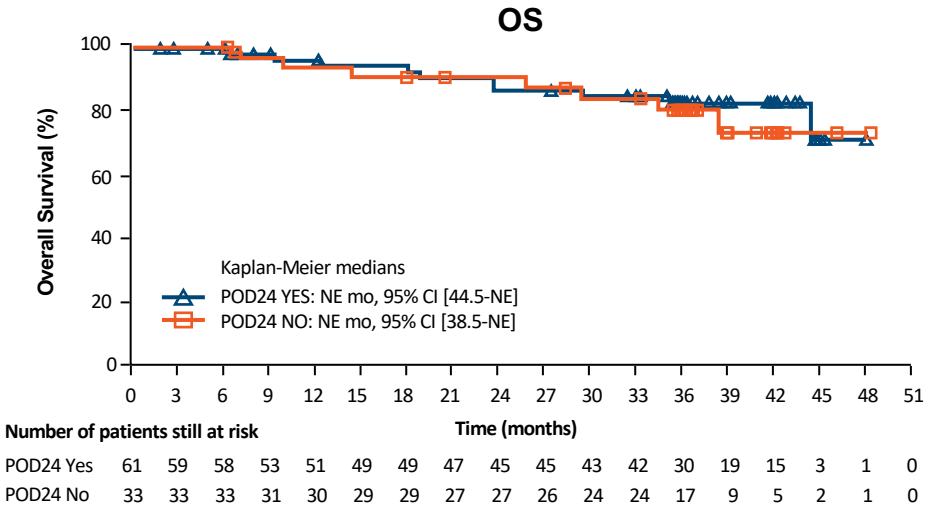
CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; FL3B, FL grade 3B; HSCT, hematopoietic stem cell transplant; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Every 3 months until Month 12, and every 6 months until end of study. [d]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT.

Presented at the 2023 ASH Annual Meeting and Exposition; December 9-12, 2023; San Deigo, CA, USA, and Online

36-Month PFS and OS Rates Were Consistent Among Patients With and Without POD24





- 36-month PFS rate was 50% (95% CI, 35.8-61.9) in the POD24 subgroup and 59% (95% CI, 39.5-73.5) in patients without POD24

- 36-month OS rate was 83% (95% CI, 69.1-90.5) in the POD24 subgroup and 80% (95% CI, 60.9-90.6) in patients without POD24

NE, not estimated; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years of frontline systemic therapy.

Presented at the 2023 ASH Annual Meeting and Exposition; December 9-12, 2023; San Deigo, CA, USA, and Online

Mosunetuzumab Monotherapy in 3L+ FL
Study design

Pivotal, single-arm, Phase II expansion study in patients with R/R FL and ≥2 prior therapies (NCT02500407)

Key inclusion criteria

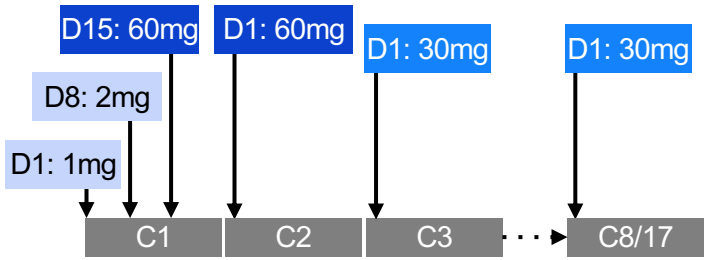
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historic control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with a median follow-up of 37.4 months

Mosunetuzumab administration

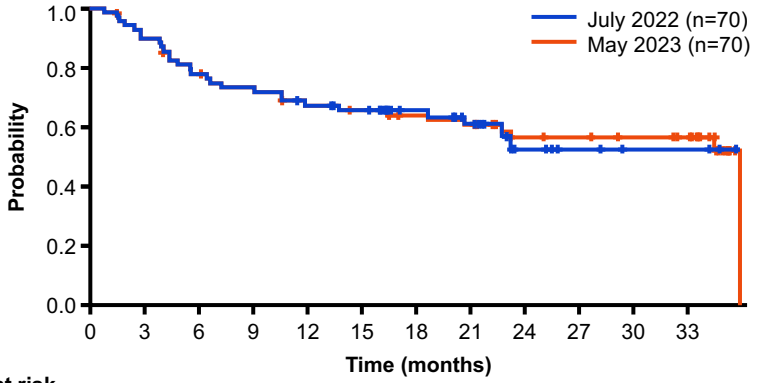
- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



1. Dreyling M, et al. J Clin Oncol 2017;35:3898–905;
2. Budde LE, et al. Lancet Oncol 2022;23:1055–65.

Durability of responses

DOR (July 2022 vs May 2023 data cut-off)

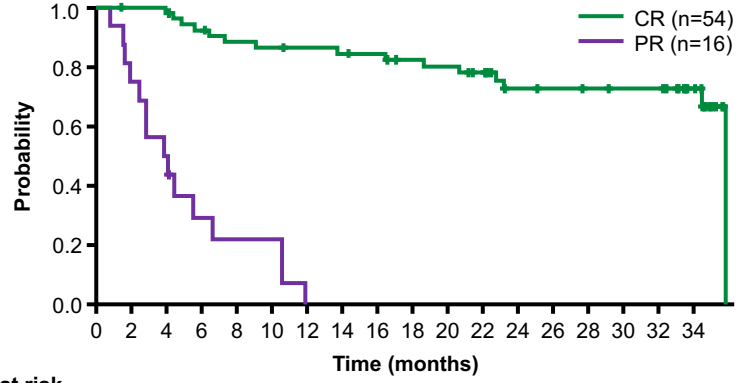


Patients at risk

July 2022	70	62	52	48	42	38	30	25	9	5	3	3
May 2023	70	62	52	48	43	41	38	36	26	25	23	21

	n=70
Median DOR, months (95% CI)	35.9 (20.7–NE)
30-month DOR rate, % (95% CI)	56.6% (44.2–68.9)

DOR for CR vs PR (May 2023 data cut-off)



Patients at risk

CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Median DOR in patients with CR, months (95% CI); n=54	35.9 (NE–NE)
Median DOR in patients with PR, months (95% CI); n=16	4.0 (2.5–6.7)

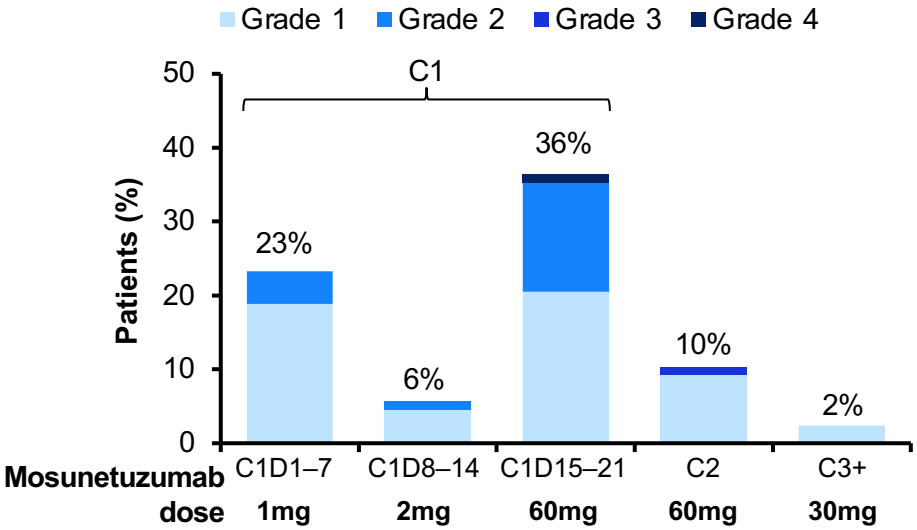
72.7% of the patients with a CR were estimated to remain alive and progression free 30 months after their first response

Presented by S. Schuster at the 65th ASH Annual Meeting | December 9–12, 2023

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

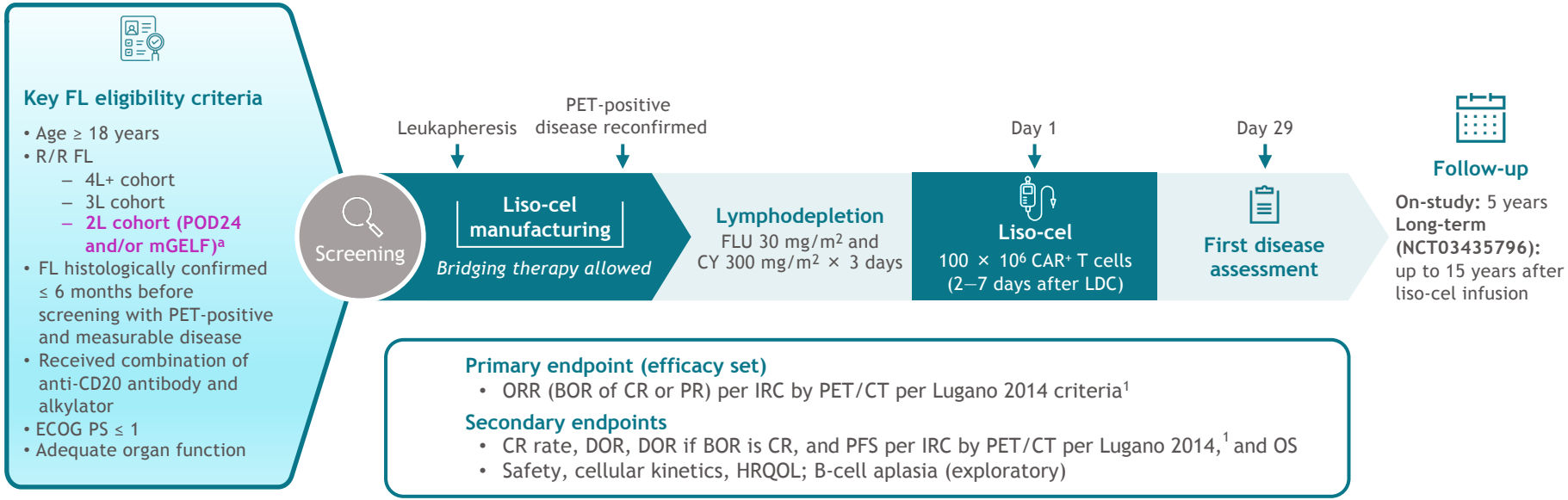
CRS by cycle and grade



CRS was predominantly low grade and occurred during C1
All CRS events resolved; no new events were reported in this extended follow-up

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

TRANSCEND FL: phase 2, open-label, multicenter Lisocabtagene maraleucel in R/R FL



- Study endpoints of ORR and CR rate were tested hierarchically with null hypotheses in the following order at 1-sided α = 0.025 significance:
  - Sequence 1: 3L+ FL (ORR ≤ 60%), 4L+ FL (ORR ≤ 50%), 3L+ FL (CR rate ≤ 30%), and 4L+ FL (CR rate ≤ 20%); sequence 2: 2L FL (ORR ≤ 50%) and 2L FL (CR rate ≤ 19%)

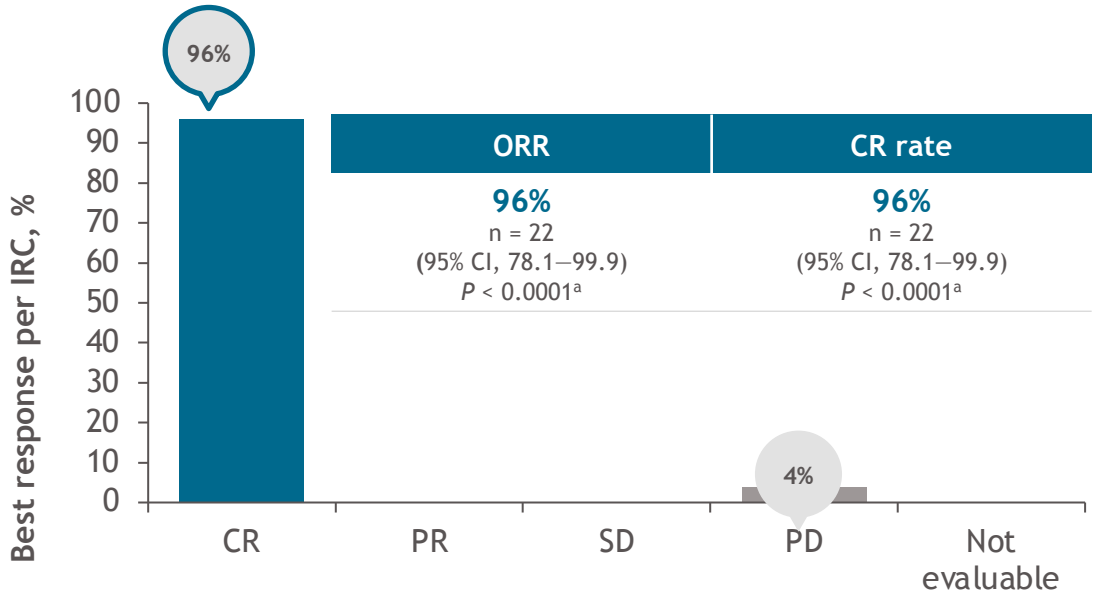
ClinicalTrials.gov identifier: NCT04245839.

[a]POD24 was defined as progression within 24 months of diagnosis after treatment with an anti-CD20 antibody and an alkylating agent within the first 6 months of initial FL diagnosis. Patients who did not meet criteria of POD24 had to meet at least 1 criterion of the mGELF criteria (symptoms attributable to FL; threatened end-organ function, or cytopenia secondary to lymphoma or bulky disease [single mass > 7 cm, or 3 or more masses > 3 cm]; splenomegaly; or steady progression over at least 6 months). 3L, third line; 4L+, fourth line or later; BOR, best overall response; CY, cyclophosphamide; DOR, duration of response; FLU, fludarabine; HRQOL, health-related quality of life; IRC, independent review committee; mGELF, modified Groupe d'Etude des Lymphomes Folliculaires. 1. Cheson BD, et al. *J Clin Oncol* 2014;32:3059–3068.

Morschhauser F, et al. ASH 2023 [Presentation #602]

Primary endpoint: ORR per IRC by best overall response

2L FL efficacy set (n = 23)



Primary and key secondary endpoints were met
All null hypotheses were rejected

ORR was 96%, with all responders achieving CR

In patients with 3L+ FL[1]

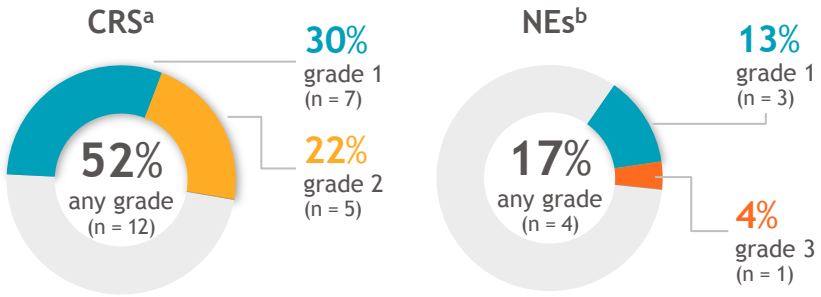
- ORR = 97%
- CR rate = 94%

[a]One-sided *P* value (H_0 of ORR ≤ 50%; H_0 of CR rate ≤ 19%).
H_0, null hypothesis; SD, stable disease.
1. Morschhauser F, et al. *Hematol Oncol* 2023;41(suppl 2):877–880.

Morschhauser F, et al. ASH 2023 [Presentation #602]

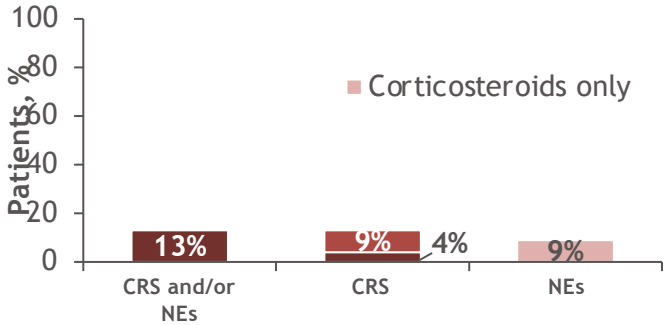
CRS and NE incidence and treatment summary in liso-cel—treated set

2L FL (n = 23)



No Grade 3—5 CRS
Median time to onset: 6 days
Median time to resolution: 3 days

No Grade 4—5 NEs
Median time to onset: 8.5 days
Median time to resolution: 2.5 days



CRS in 2L vs 3L+ FL

- 52% vs 59% with any-grade CRS
- Grade 1–2 CRS only vs 1% grade 3 CRS (all others grade 1–2)
- Median time to onset of 6 days in both cohorts
- Median time to resolution of 3 vs 4 days

NEs in 2L vs 3L+ FL

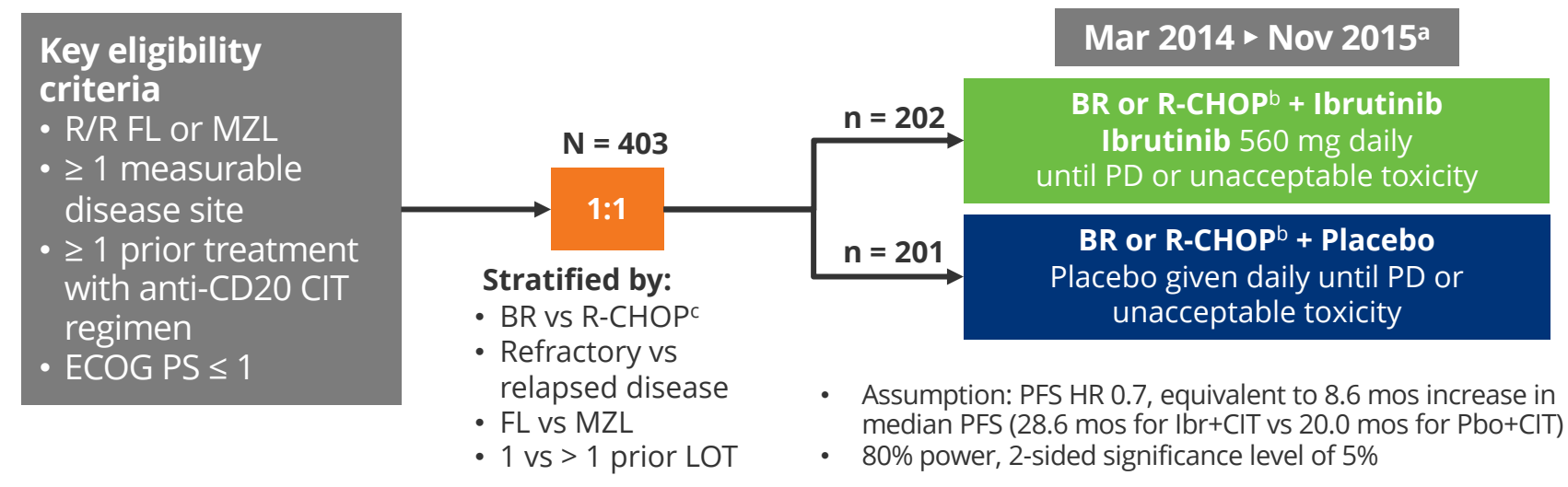
- 17% vs 15% with any-grade NEs
- No grade 4–5 NEs in either cohort
  - 4% vs 2% with grade 3 NEs
- Median time to onset of 8.5 days in both cohorts
- Median time to resolution of 2.5 vs 4.5 days

13% vs 31% received tocilizumab and/or corticosteroids to manage CRS/NEs

[a]Graded according to the Lee 2014 criteria; [b]Defined as investigator-identified neurological AEs related to liso-cel and graded per the NCI CTCAE, version 5.0; NE, neurological event.

Morschhauser F, et al. ASH 2023 [Presentation #602]

SELENE (NCT01974440): A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of BR/RCHOP +/- ibrutinib in R/R FL/MZL



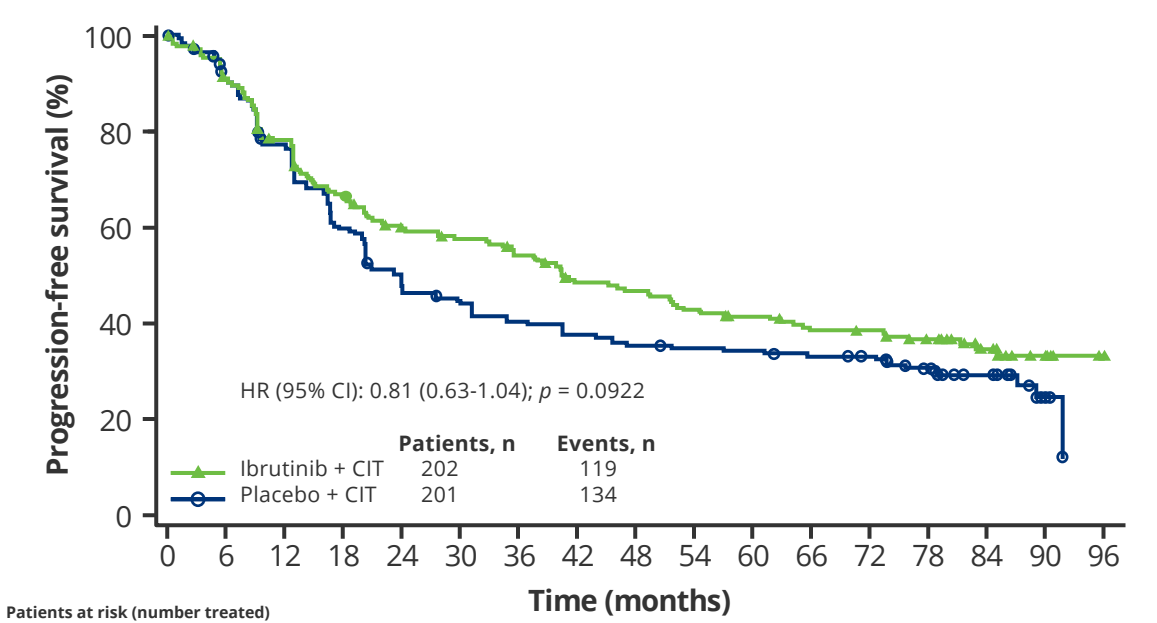
Primary end point: Progression-free survival (investigator-assessed)

Secondary end points: Overall survival, Complete Response Rate, Overall Response Rate, Duration of Response, Patient-Reported Outcomes (FACT-Lym); Safety

Nastoupil, ICML, LBA 2023

[a]Enrollment period. [b]Given for 6 cycles. [c]Investigator discretion.
BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HR, hazard ratio; Ibr, ibrutinib; LOT, line of therapy; mos, months; MZL, marginal zone lymphoma; Pbo, placebo; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R, relapsed/refractory.

Despite Favorable Median PFS With Ibrutinib + CIT, the Primary Study End Point Was Not Met



Patients at risk (number treated)

Ibrutinib + CIT	202(201)	174(149)	147(110)	125(93)	108(82)	103(77)	96(72)	84(62)	81(57)	74(52)	69(49)	63(46)	61(44)	55(39)	34(28)	15(12)	0(1)
Placebo + CIT	201(199)	172(167)	144(130)	112(99)	88(81)	81(69)	74(63)	69(58)	65(53)	63(48)	62(45)	59(44)	57(42)	46(38)	32(27)	6(7)	0(0)

ITT population: PFS at median follow-up of 84 months:

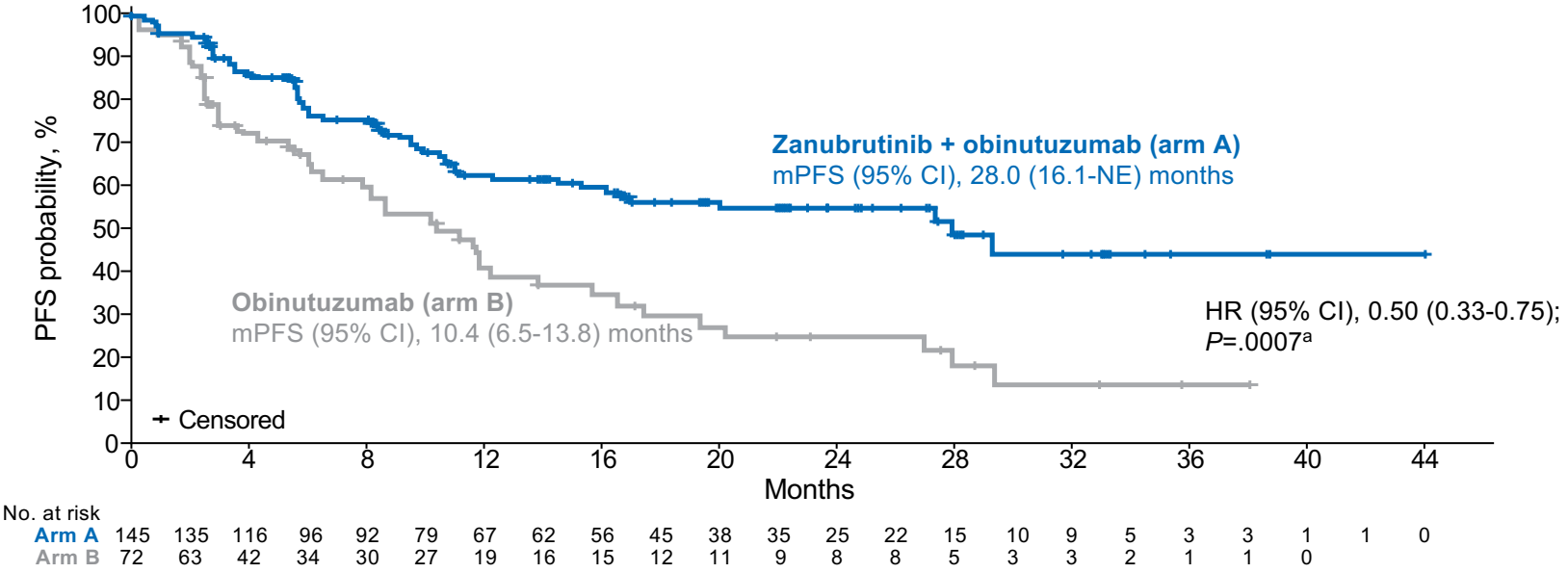
- Ibrutinib + CIT, 40.5 months
- Placebo + CIT, 23.8 months

CI, confidence interval; CIT, chemoimmunotherapy; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Nastoupil, ICML, LBA 2023

Phase 2 ROSEWOOD: Zanubrutinib + Obinutuzumab superior to Obinutuzumab alone

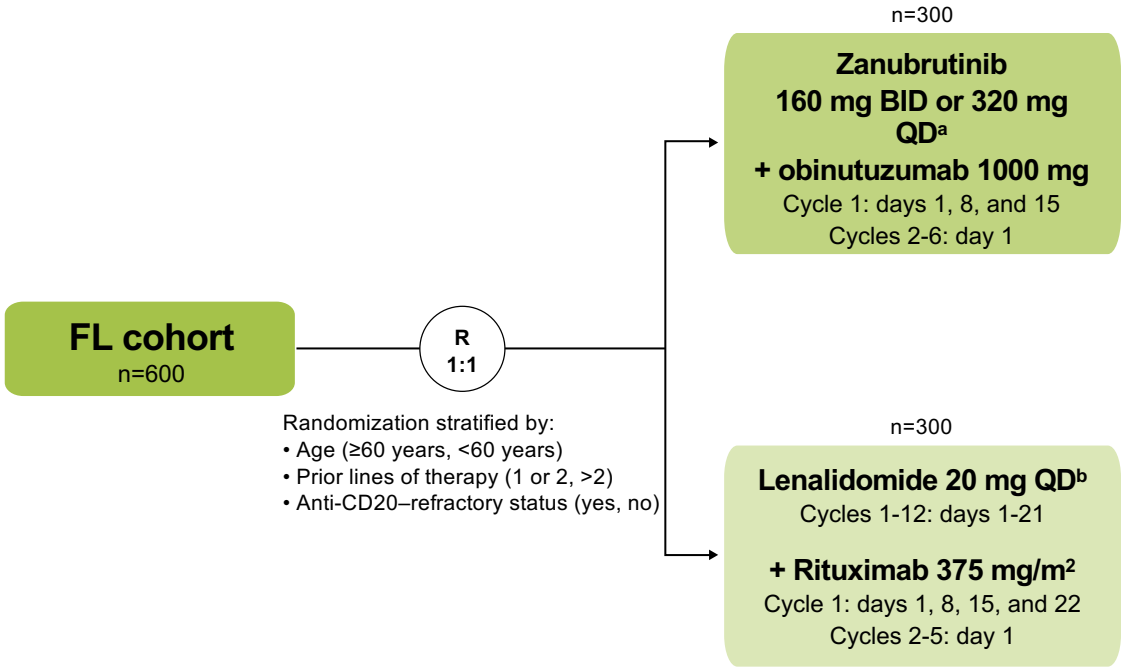
- In the randomized phase 2 ROSEWOOD study in R/R FL (NCT03332017), zanubrutinib + obinutuzumab led to an IRC-assessed ORR of 69.0% (CR rate, 39.3%); mPFS at 24 months of 28 months



Median follow-up, 20.2 months.
CR, complete response; FL, follicular lymphoma; HR, hazard ratio; IRC, independent review committee; mPFS, median PFS; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.
[a] Descriptive 2-sided *P* value. Zinzani PL, et al. Presented at: 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Abstract 81.

Sehn LH, et al. MAHOGANY: a phase 3 trial of zanubrutinib plus anti-CD20 antibodies vs lenalidomide plus rituximab in patients with relapsed or refractory follicular or marginal zone lymphoma. Presented at:17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Abstract 994. Correspondence: Laurie H. Sehn, MD, MPH; lsehn@bccancer.bc.ca

MAHOGANY: Phase 3 Study Design: FL Cohort



Primary endpoint

- PFS per IRC using PET/CT-based Lugano 2014 criteria[1]

Key secondary endpoints

- ORR per IRC using PET/CT-based Lugano 2014 criteria[1]
- OS

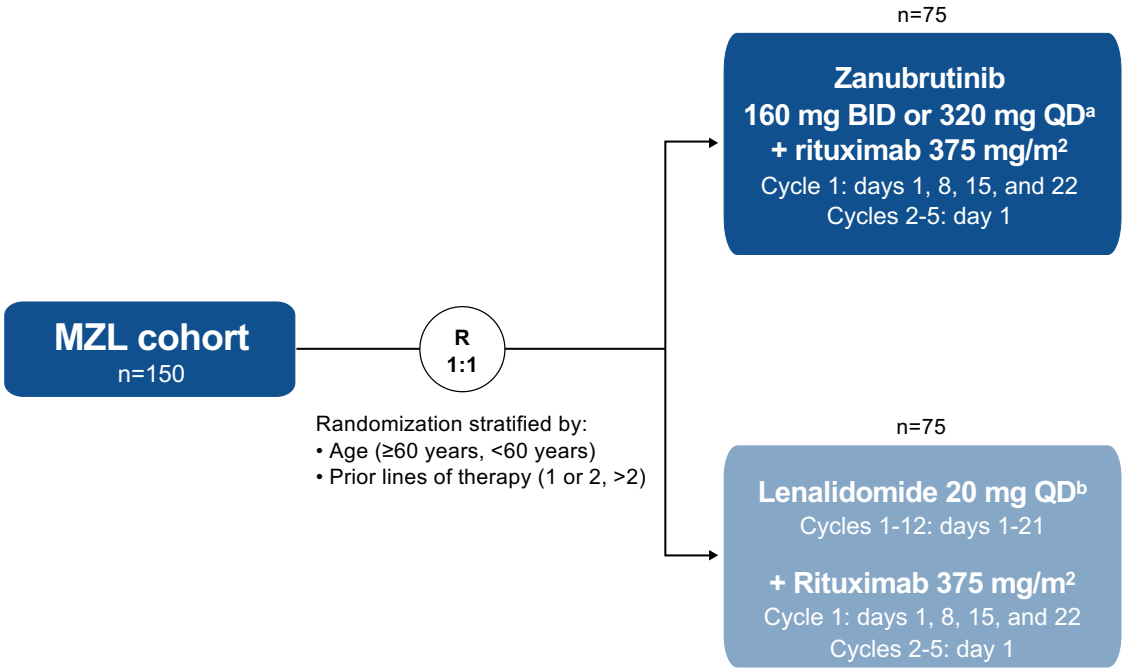
Secondary endpoints

- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

One cycle is 28 days.
BID, twice daily; CRR, complete response rate; CT, computed tomography; DOR, duration of response; FL, follicular lymphoma; IA, investigator assessment; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; QD, once daily; QOL, quality of life; R, randomized; TTR, time to response. [a] After completion of combination treatment, patients will receive zanubrutinib monotherapy until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination, whichever comes first. [b] Patients with creatinine clearance of ≥30 but <60 mL/min will receive 10 mg QD. If the patient remains free of lenalidomide-related grade 3 or 4 toxicities for ≥2 cycles, the dose may be increased to 15 mg QD on days 1 to 21 of a 28-day cycle at the discretion of the treating physician from cycles 3 to 12. 1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

Sehn LH, et al. MAHOGANY: a phase 3 trial of zanubrutinib plus anti-CD20 antibodies vs lenalidomide plus rituximab in patients with relapsed or refractory follicular or marginal zone lymphoma. Presented at:17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Abstract 994. Correspondence: Laurie H. Sehn, MD, MPH; lsehn@bccancer.bc.ca

MAHOGANY: Phase 3 Study Design: MZL Cohort



Primary endpoint

- PFS per IRC using CT-based Lugano 2014 criteria[1]

Key secondary endpoint

- ORR per IRC using CT-based Lugano 2014 criteria[1]

Secondary endpoints

- OS
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using CT- and PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

One cycle is 28 days.
BID, twice daily; CRR, complete response rate; CT, computed tomography; DOR, duration of response; IA, investigator assessment; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; QD, once daily; QOL, quality of life; R, randomized; TTR, time to response. [a] After completion of combination treatment, patients will receive zanubrutinib monotherapy until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination, whichever comes first. [b] Patients with creatinine clearance of ≥30 but <60 mL/min will receive 10 mg QD. If the patient remains free of lenalidomide-related grade 3 or 4 toxicities for ≥2 cycles, the dose may be increased to 15 mg QD on days 1 to 21 of a 28-day cycle at the discretion of the treating physician from cycles 3 to 12. 1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

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Conclusions

1. **Bispecifics are exciting, approved for 3rd line, how does this impact sequencing now and in the future?**
   - I would consider most for a bispecific in 3rd line
   - I eagerly await the randomized trials in 2nd line + to know if a combo is preferred over monotherapy

2. **When do you use CAR T-cell therapy?**
   - For concerns for transformed disease
   - Young fit patients with high-risk features
   - Will liso-cel change this given the favorable safety profile?

3. **Is there still a role for BTK inhibitors?**
   - Would not use ibrutinib in R/R FL or MZL
   - Single agent approval of zanubrutinib in MZL, anticipate an approval in combination with obin in R/R FL

4. **When will we have a new frontline approach?**
   - Bispecifics are the most exciting new therapy and will likely move into frontline
   - Do you need a combination approach?