Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

63rd ASH Meeting 2021

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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Follikuläres Lymphom (FL)

Offenlegung potentieller Interessenskonflikte

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Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
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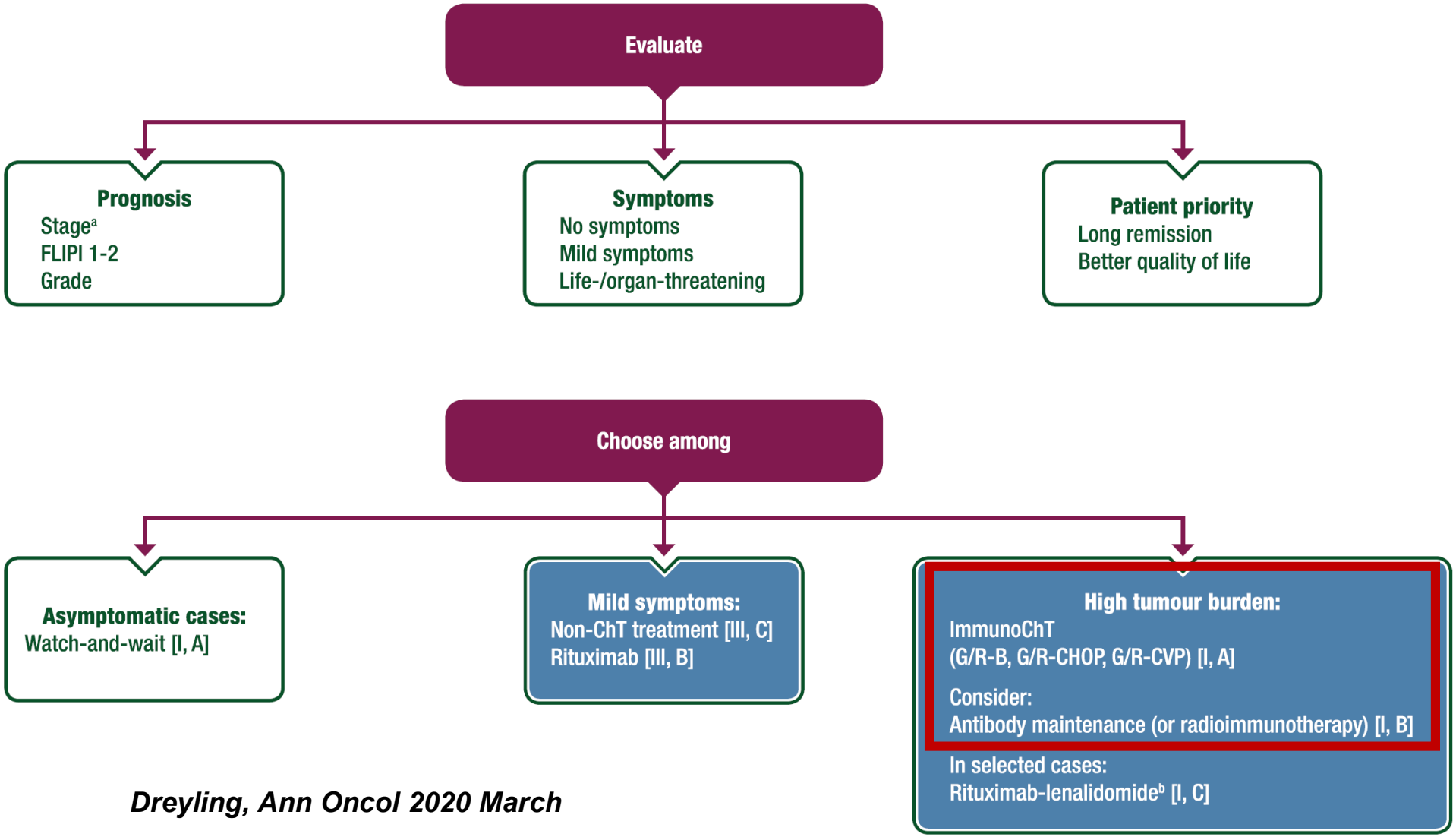
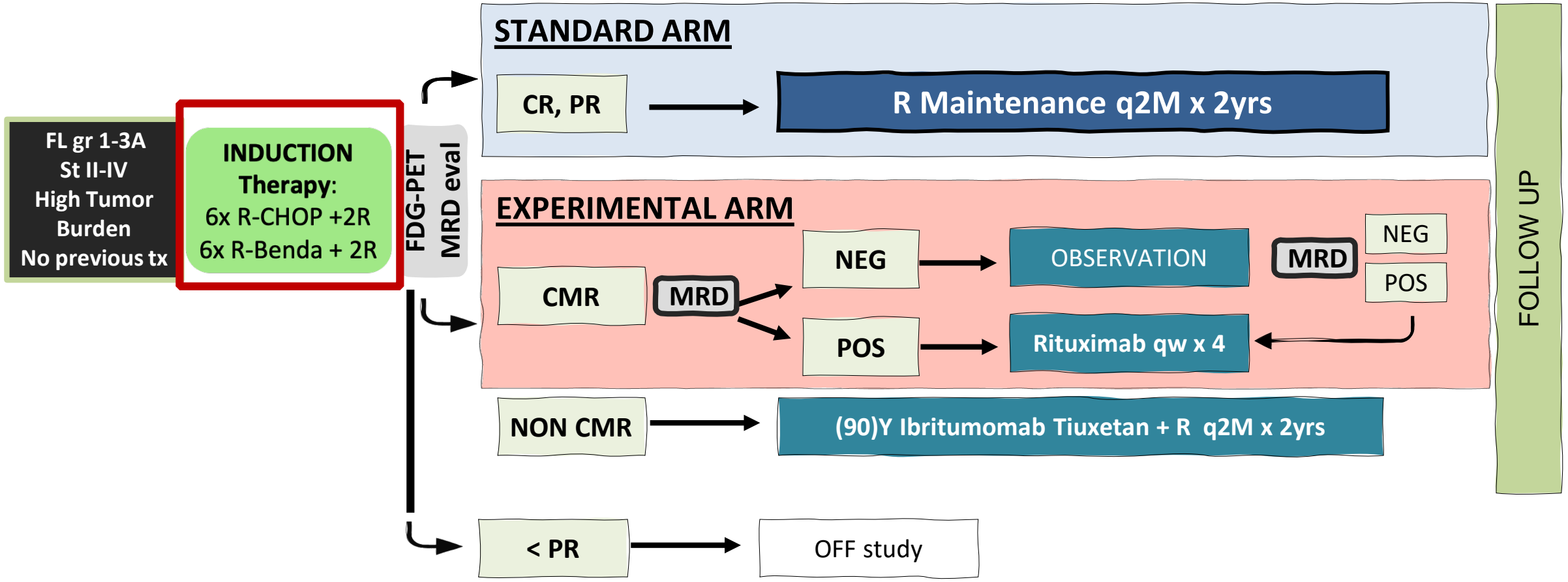
Follicular lymphoma
ESMO/EHA therapeutic algorithm



Dreyling, Ann Oncol 2020 March

Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

EUDRACT N° : 2012-003170-60



Luminari et al JCO 2021.

Patients Characteristic (n=786)

Treatment choice was allowed after amend#1 (N> 227) and was done on a patient basis

Factor	R-CHOP (N=445)	RB (N=341)	Total (N=786)			
	n (%)	n (%)	n (%)	P-value *	OR (95%CI)	Missing
Age >60	189 (42)	202 (59)	391 (50)	<0.001	1.97 (1.48-2.62)	-
Female sex	212 (48)	202 (59)	414 (53)	0.002	1.60 (1.20-2.12)	-
Grade 3a	123 (28)	68 (20)	191 (24)	0.015	0.65 (0.46-0.91)	-
B-symptoms	116 (26)	41 (12)	157 (20)	<0.001	0.39 (0.27-0.58)	6
Bone Marrow+	256 (58)	181 (53)	437 (56)	0.219	0.84 (0.63-1.11)	-
Stage III-IV	402 (91)	295 (87)	697 (89)	0.134	0.70 (0.45-1.10)	3
Hb <12 g/dL	69 (16)	58 (17)	127 (16)	0.625	1.12 (0.76-1.64)	-
LodLIN >6 cm	266 (60)	169 (50)	435 (55)	0.005	0.66 (0.50-0.88)	-
B2M >ULN	240 (54)	187 (55)	427 (54)	0.829	1.04 (0.78-1.38)	-
Nodal sites >4	190 (43)	129 (39)	319 (41)	0.239	0.83 (0.62-1.12)	10
LDH >ULN	106 (24)	67 (20)	173 (23)	0.256	0.81 (0.57-1.14)	20
FLIPI-2 3/5	172 (39)	144 (42)	316 (40)	0.340	1.16 (0.87-1.55)	-
Experim. arm	232 (52)	161 (47)	393 (50)	0.195	0.82 (0.62-1.09)	-

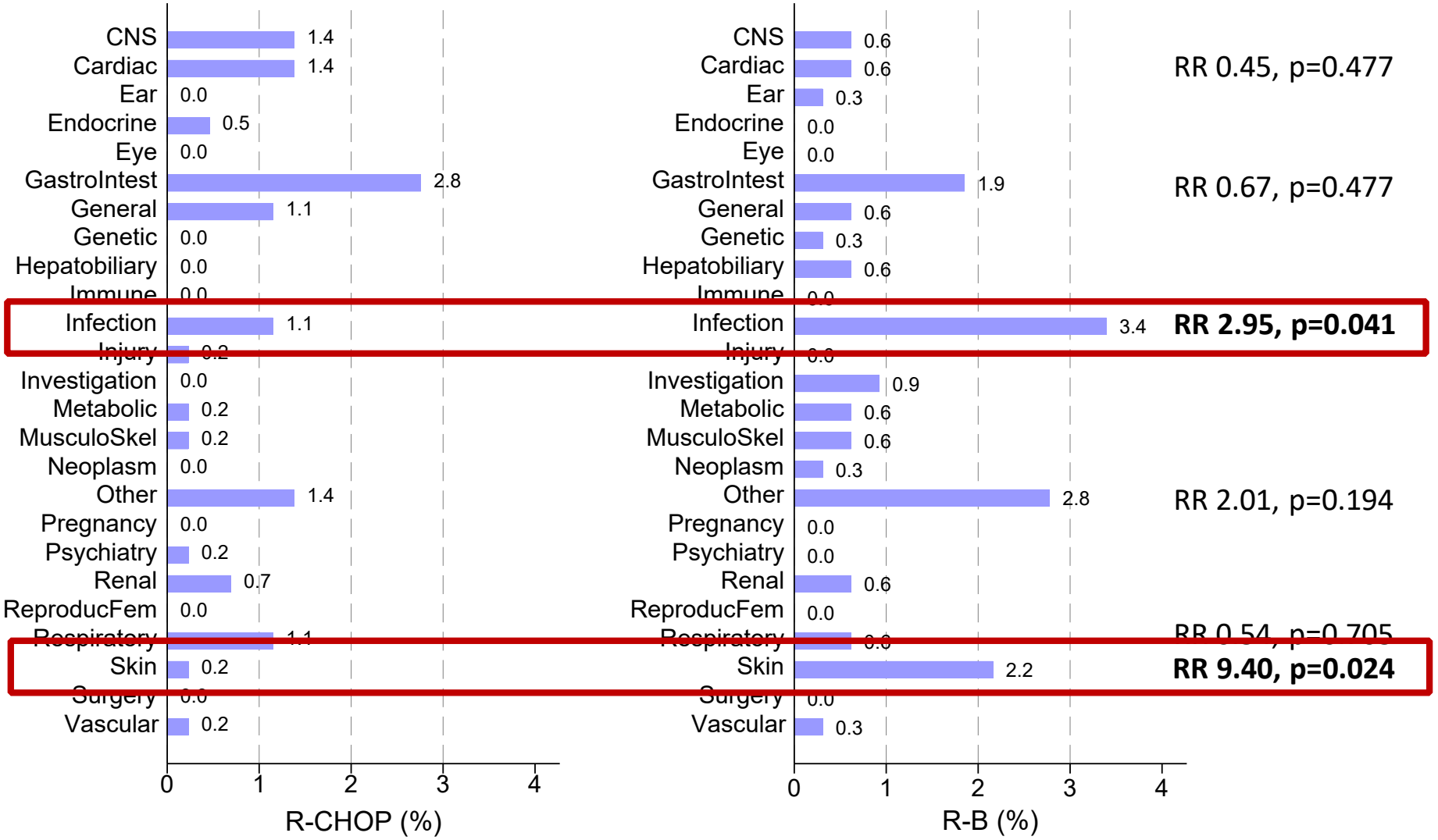
* Fisher's exact test

OR:odds ratio, association with RB vs RCHOP

Extra-hematological Adverse Events during Induction

CTCAE >2

Patients with SAE's by treatment: R-CHOP 29 (6.5%) vs R-B 42 (12.3%)p=0.006

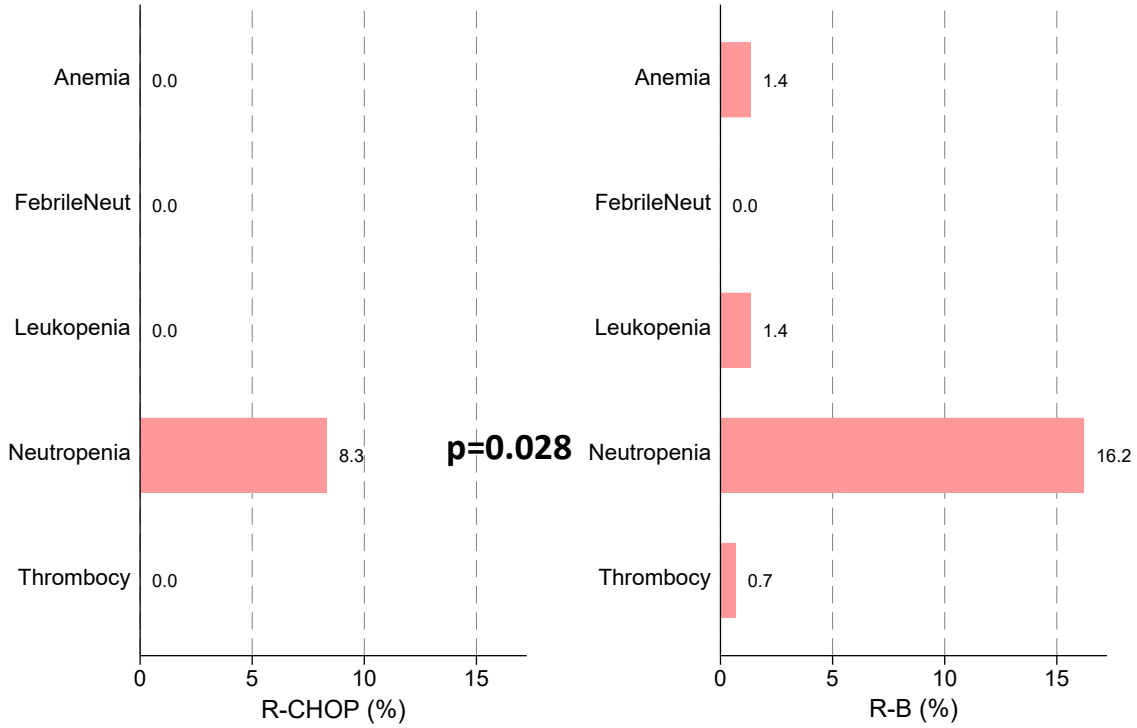


RR: risk ratio R-B vs R-CHOP; p: Fisher's exact test.

Adverse Events Post-induction. Full doses

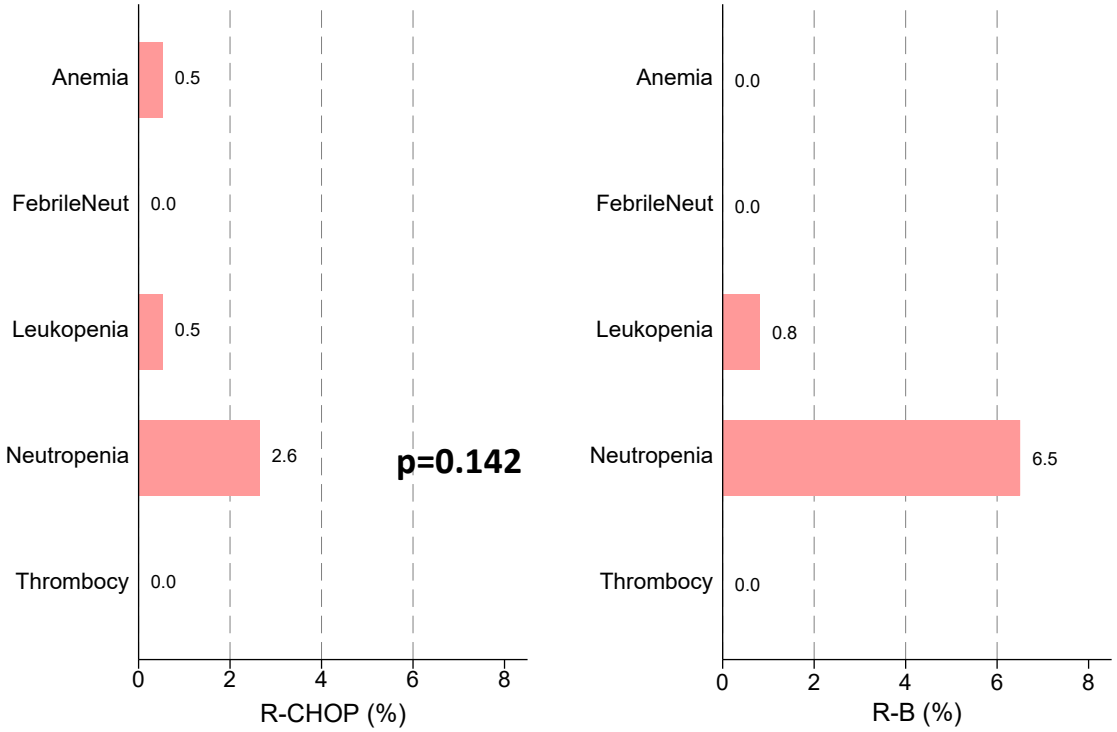
Hematological CTCAE >2

Maintenance (Excluded zevalin)



N=340
N=353

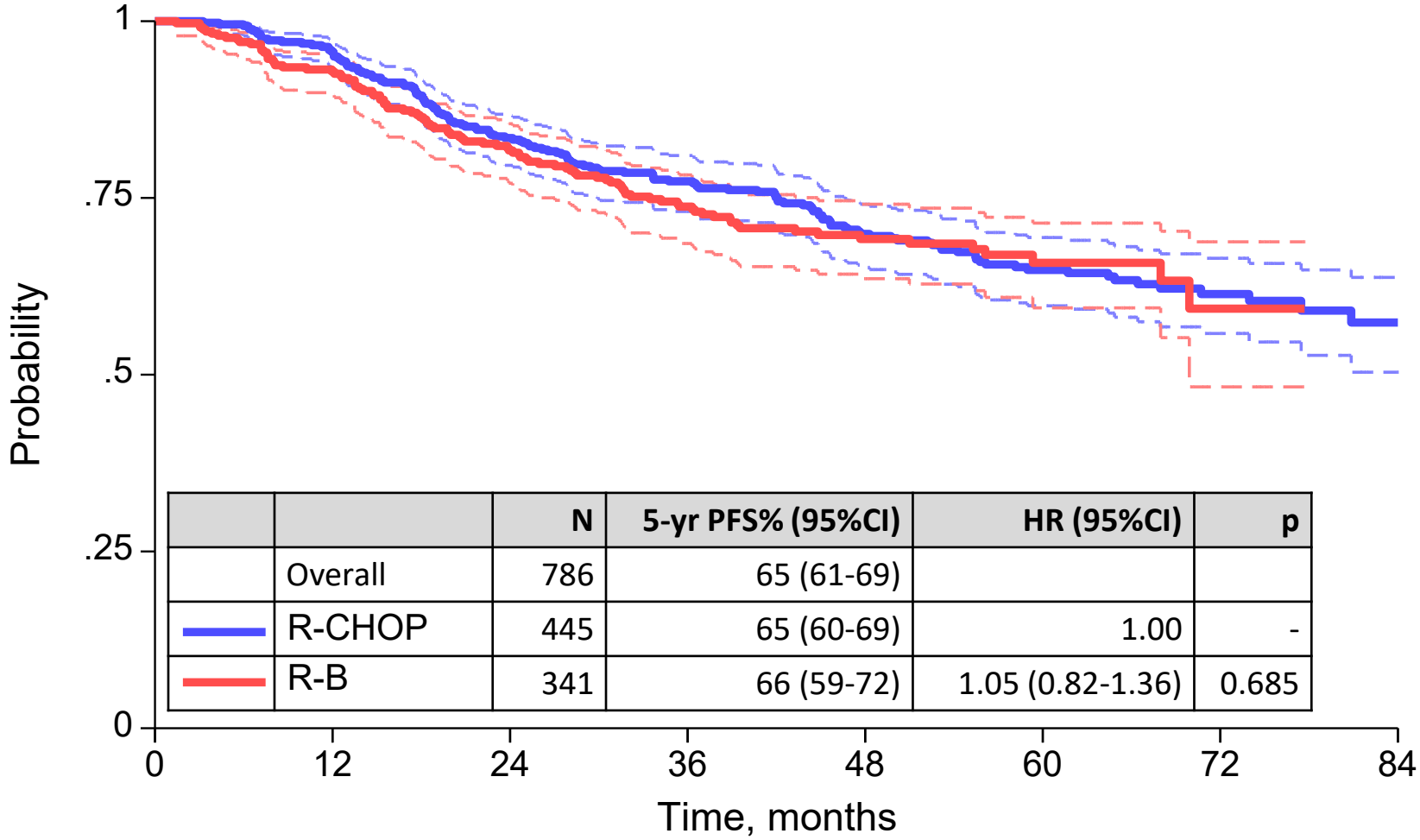
Observational



N=312
M=331

Progression Free Survival (n=786)

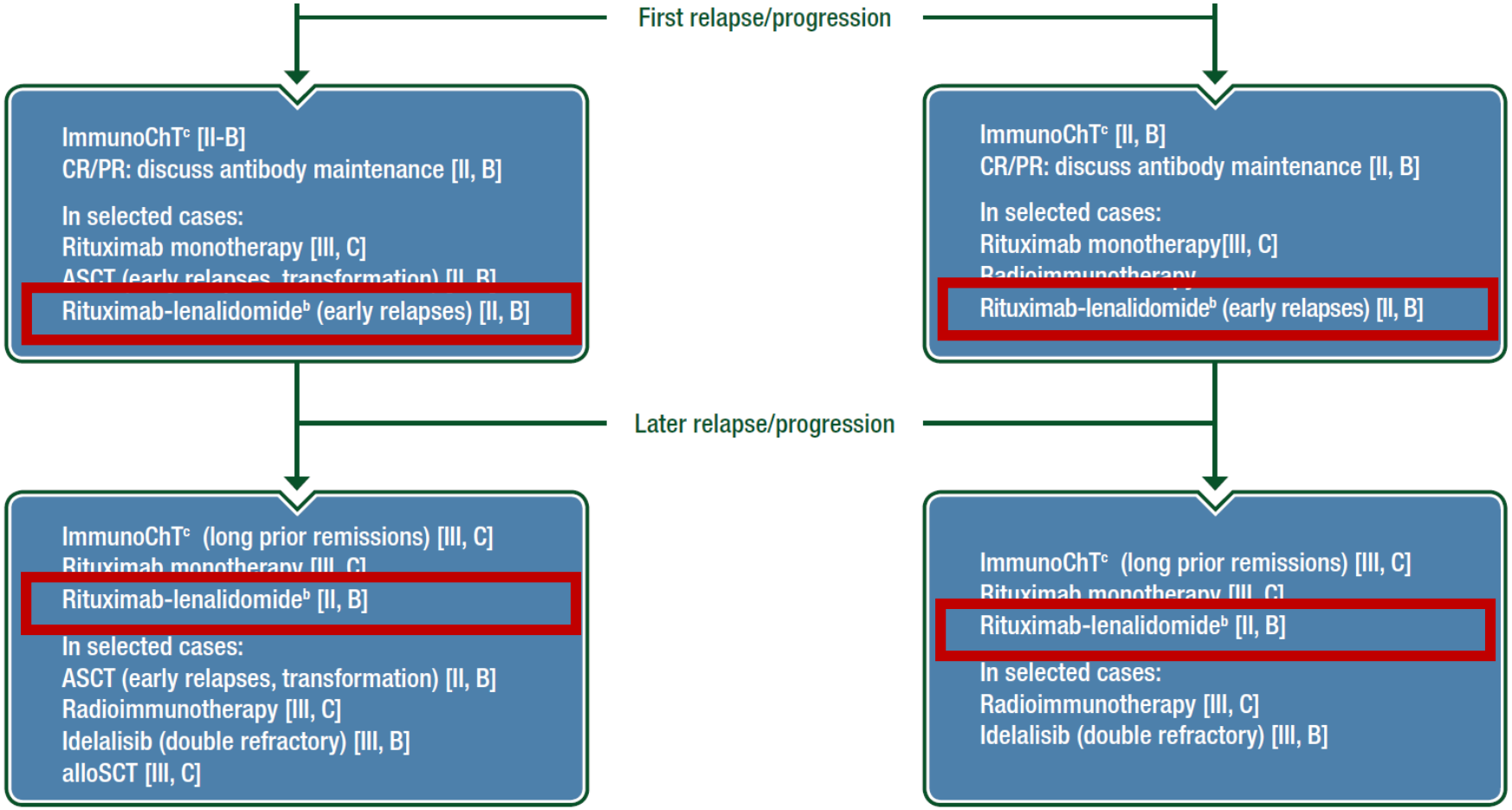
Non randomized comparison



		N	5-yr PFS% (95%CI)	HR (95%CI)	p
	Overall	786	65 (61-69)		
	R-CHOP	445	65 (60-69)	1.00	-
	R-B	341	66 (59-72)	1.05 (0.82-1.36)	0.685

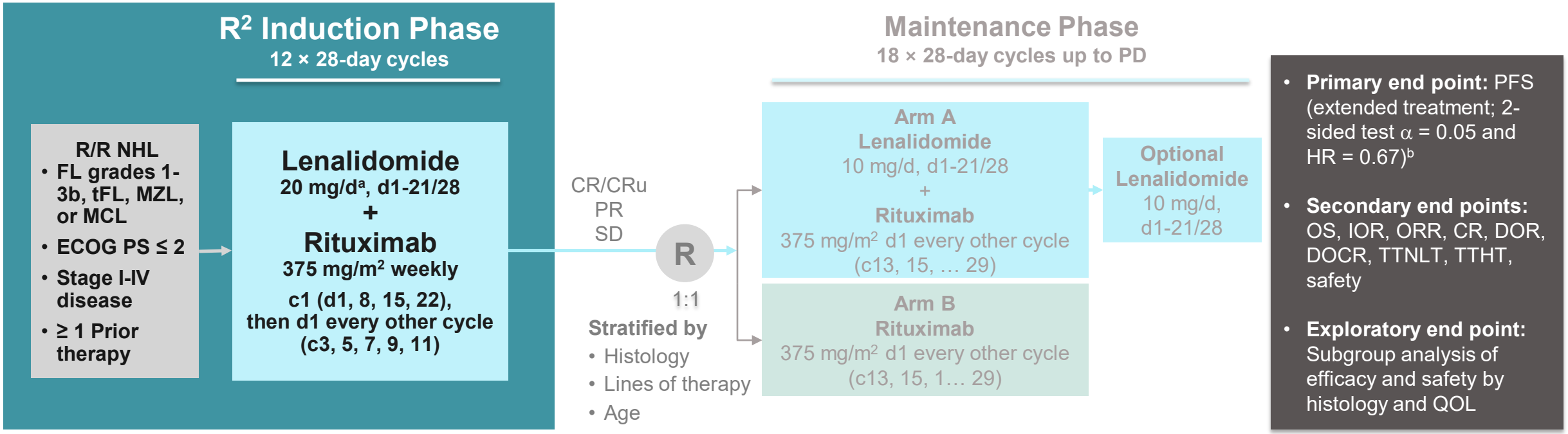
At risk								
RCHOP	445	417	360	316	235	159	76	21
RB	341	306	257	203	119	57	10	0

Follicular lymphoma
ESMO/EHA therapeutic algorithm



Dreyling, Ann Oncol 2021 March

MAGNIFY Study Design



- Data presented here are the complete analysis from the induction phase in patients with FL grades 1–3a or MZL (FL grade 3b, tFL, and MCL not included)[c]
- The focus of this current interim analysis was ORR, DOR, PFS, and safety
  - Response was assessed by 1999 IWG criteria

NCT01996865.
ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; tFL, transformed FL.
[a]Lenalidomide is administered at 10 mg if creatinine clearance is ≥ 30 to < 60 mL/min. [b]Assessed per computed tomography/magnetic resonance imaging and 1999 International Working Group criteria with modifications to include extranodal disease. [c]Data cutoff 05Mar2021.

Lansigan F, et al. ASH 2021 [Abstract #812]

Baseline Characteristics and Treatment History

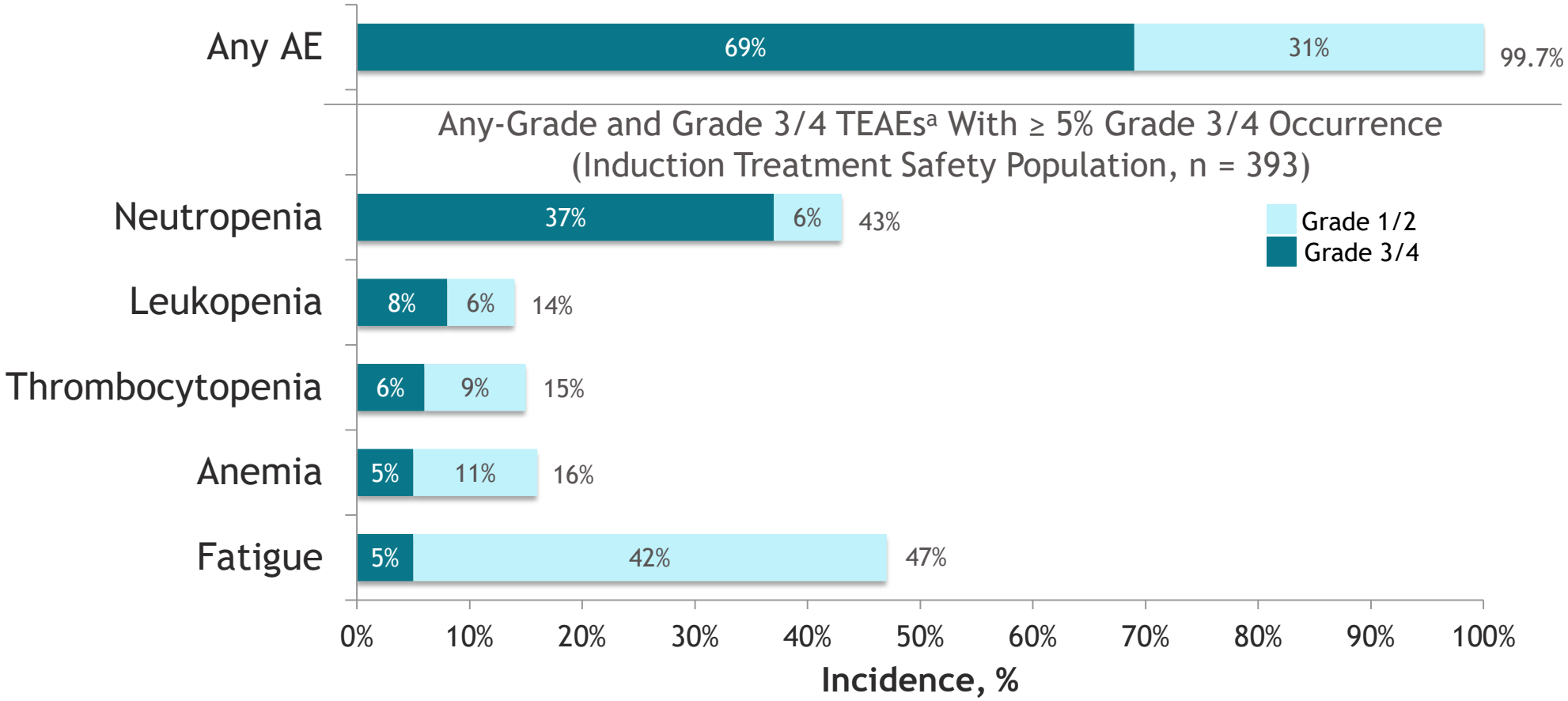
Characteristic, n (%)	Total (n = 394)
Age, median (range), y	66 (35-91)
≥ 65 y	221 (56)
Male	210 (53)
ECOG PS at enrolment	
0	193 (49)
1	192 (49)
2	9 (2)
Positive bone marrow involvement	123 (31)
Ann Arbor disease stage at enrollment	
I/II	66 (17)
III	99 (25)
IV	229 (58)
Bulky disease (> 7 cm or > 3 cm x 3)	161 (41)

Characteristic, n (%)	Total (n = 394)
FL	318 (81)
Grade 1	116 (29)
Grade 2	147 (37)
Grade 3a	55 (14)
MZL	76 (19)
MALT[a]	15 (4)
Nodal	44 (11)
Splenic	17 (4)
Prior lines of antilymphoma treatment, median (range)	2 (1-8)
Prior therapies	
Rituximab containing	372 (94)
Rituximab + chemotherapy	289 (73)
Rituximab monotherapy	159 (40)
Rituximab refractory[b]	140 (36)
Double refractory[c]	85 (22)
Early relapse[d]	133 (34)

MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.
[a]Three patients had gastric MALT. [b]Defined as experiencing a best response of PD or SD to rituximab or rituximab-containing regimen or a response lasting < 6 months after last rituximab dose. [c]Defined as being refractory to both rituximab and an alkylating agent. [d]Defined as progressing or relapsing within 2 years of initial diagnosis.

Lansigan F, et al. ASH 2021 [Abstract #812]

Treatment Emergent Adverse Events



- Other any-grade and grade 3/4 TEAEs of interest included rash maculopapular (17% and 1%), infusion-related reaction (12% and 1%), tumor flare reaction (4% and 1%), febrile neutropenia (3% and 3%), and tumor lysis syndrome (1% and < 1%)
- Concomitant growth factors (G-CSF/GM-CSF) were administered in 63 patients (16%)

[a]Assessed per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. TEAEs include any AEs occurring on or after first dose date of induction treatment through 28 days after the last dosing date of study treatment.

Lansigan F, et al. ASH 2021 [Abstract #812]

Dose Modifications Due to TEAEs

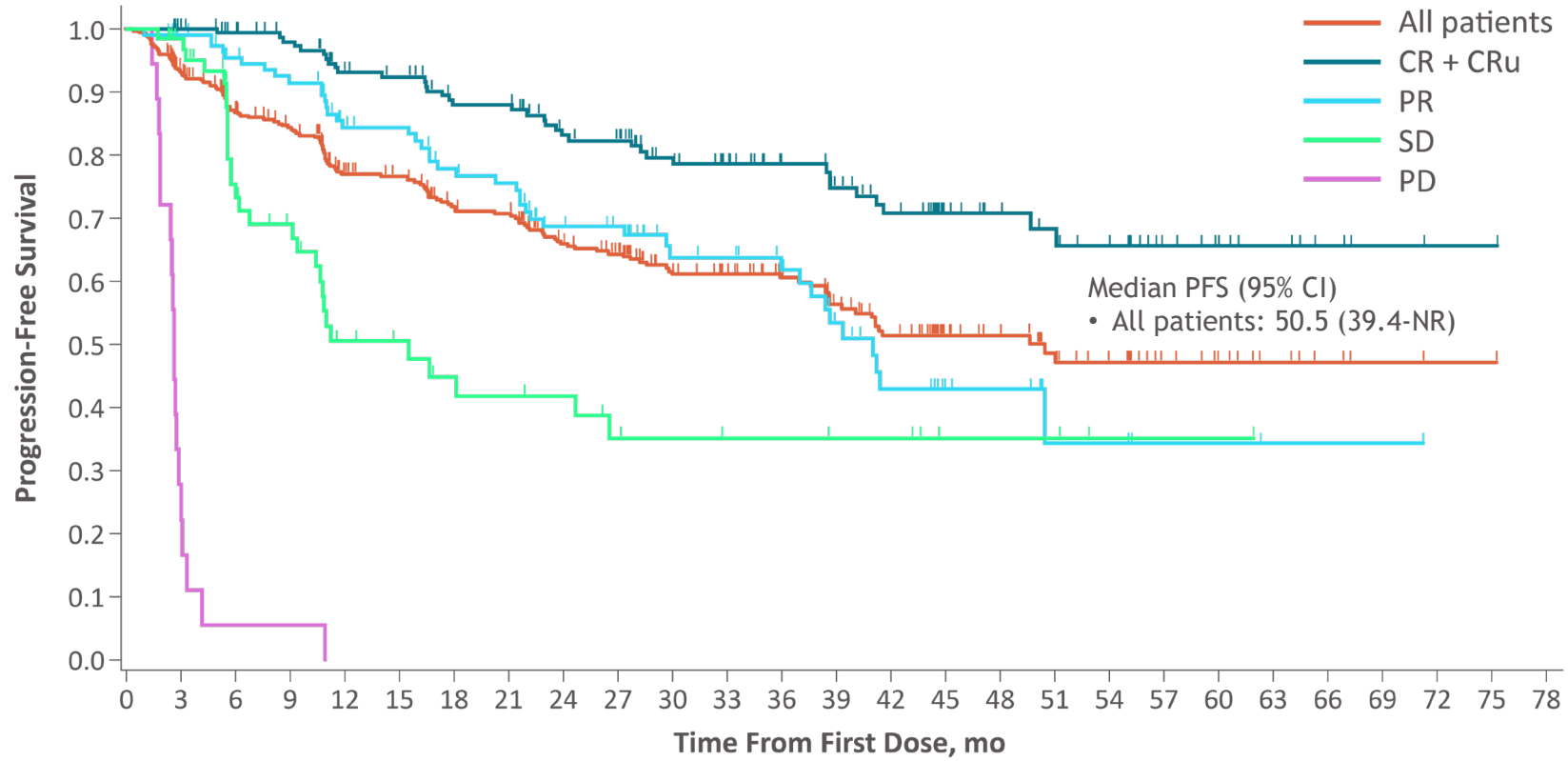
Patients with ≥ 1 TEAE leading to dose modification in induction period, n (%)	Total (n = 393)
Early lenalidomide discontinuation	75 (19)
Early rituximab discontinuation	46 (12)
Lenalidomide dose reduction/interruption	252 (64)
Rituximab dose interruption	116 (30)

- Neutropenia was the most common TEAE leading to lenalidomide discontinuation (n = 22, 6%) and reduction/interruption (n = 125, 32%), and rituximab discontinuation (n = 10, 3%)
- Infusion-related reaction was the most common TEAE leading to rituximab interruption (n = 32, 8%)

Lansigan F, et al. ASH 2021 [Abstract #812]

Progression-Free Survival[a] (OR/CR: 71%/42%)

PFS by Best Overall Response



Patients at risk

All:	393	335	289	272	232	225	203	199	171	160	128	118	104	86	73	47	41	33	26	16	13	8	5	3	1	1	0
CR + CRu:	164	160	151	144	130	127	116	116	102	99	83	76	66	58	51	34	29	26	21	13	10	7	4	2	1	1	0
PR:	115	108	99	94	80	78	70	67	55	51	36	35	31	22	16	10	9	4	4	2	2	1	1	1	0	0	0
SD:	65	59	36	31	20	18	15	14	13	10	9	7	7	6	6	3	3	3	1	1	1	0	0	0	0	0	0
PD:	18	5	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a]Induction treatment ITT population. If patients were already in maintenance at data cutoff, then response assessments also contributed to PFS.

Lansigan F, et al. ASH 2021 [Abstract #812]

Follicular lymphoma
Immunotherapy

- **Car T-lymphocytes**

  (Chimeric antigen-receptor)

- **bispecific antibodies**

- **checkpoint inhibitors**

Study overview

Key inclusion criteria

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2

Objectives

- Primary: safety and tolerability of M-Len
- Other: efficacy (response, durability of response) and pharmacokinetics

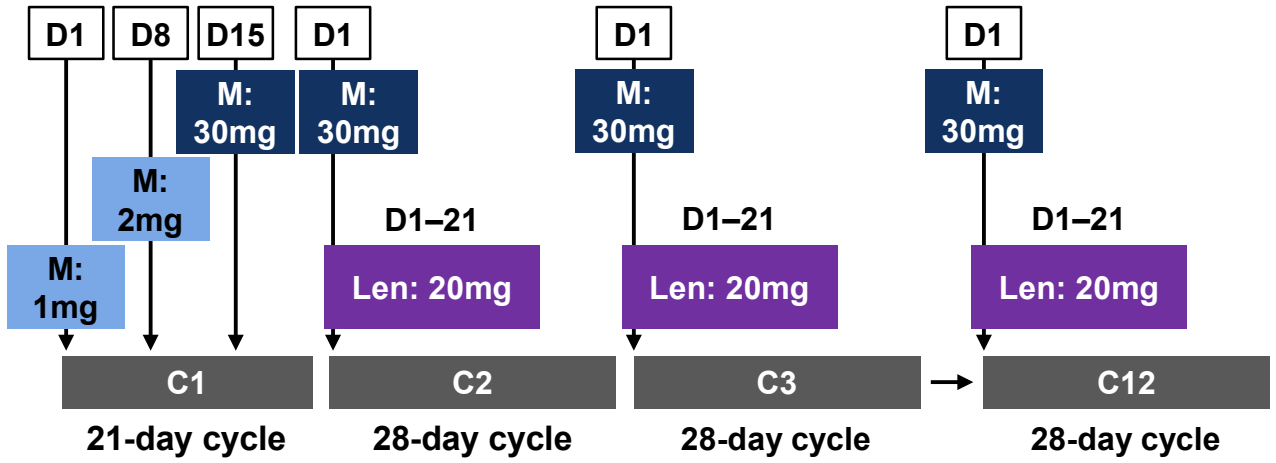
M-Len administration

Mosunetuzumab

- IV administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)



C, Cycle; CRS, cytokine release syndrome; D, Day; IV, intravenous; Q3W, once every 3 weeks; Q4W, once every 4 weeks

Baseline patient and disease characteristics

	N=29
Age in years, median (range)	59 (30–79)
Male	13 (44.8%)
Ann Arbor stage at study entry	
I–II	2 (6.8%)
III–IV	27 (93.1%)
FLIPI risk factors at study entry	
0–1	7 (24.1%)
2	8 (27.6%)
3–5	14 (48.3%)
Number of prior lines of therapy, median (range)	1 (1–6)
1 prior line	16 (55.2%)
≥2 prior lines	13 (44.8%)
Refractory to any prior aCD20 therapy	9 (31.0%)
Refractory to any prior aCD20 therapy AND an alkylating agent (double refractory)	7 (24.1%)
POD24	3 (10.3%)

- **Most patients had advanced stage disease**
- **31.0% were refractory to aCD20 therapy**

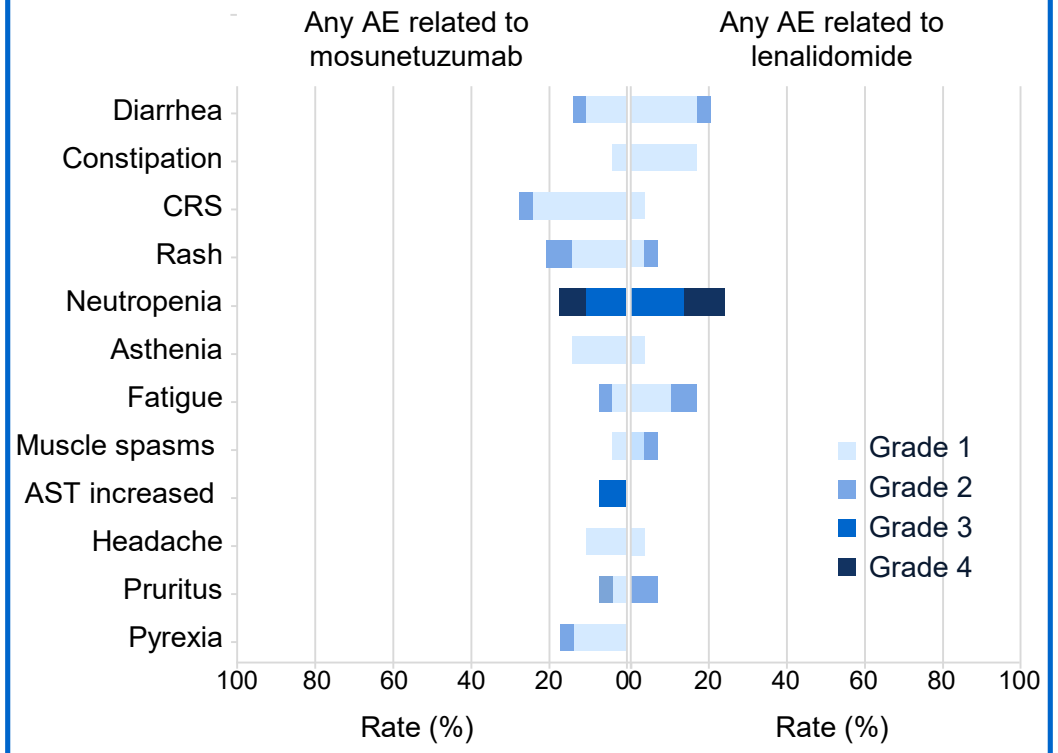
All patients had Grade 1–3a FL at entry; ECOG PS at entry was 0 in 19 patients (67.9%) and 1 in 9 patients (32.1%); no patient had received prior lenalidomide; cut-off date: Sept 13, 2021j; FLIPI, follicular lymphoma International Prognostic Index

Adverse event summary

- Median duration of follow-up: 5.4 months (range: 3–12)

	N=29
AE Related to mosunetuzumab / lenalidomide	29 (100%) 27 (93.1%) / 23 (79.3%)
Grade 3–4 AE Related to mosunetuzumab / lenalidomide	13 (44.8%) 1 (3.4%) / 1 (3.4%)
Serious AE Related to mosunetuzumab / lenalidomide	9 (31.0%) 6 (20.7%) / 1 (3.4%)
Grade 5 (fatal) AE	0
AE leading to mosunetuzumab / lenalidomide discontinuation	0 / 1 (3.4%)
AE leading to mosunetuzumab dose delay	6 (20.7%)
AE leading to lenalidomide dose reduction	2 (6.9%)
AE leading to lenalidomide temporary dose interruption	6 (20.7%)
AE leading to lenalidomide dose reduction AND temporary dose interruption	4 (13.7%)

AEs with ≥15% incidence overall and corresponding rates of treatment-related events by Grade



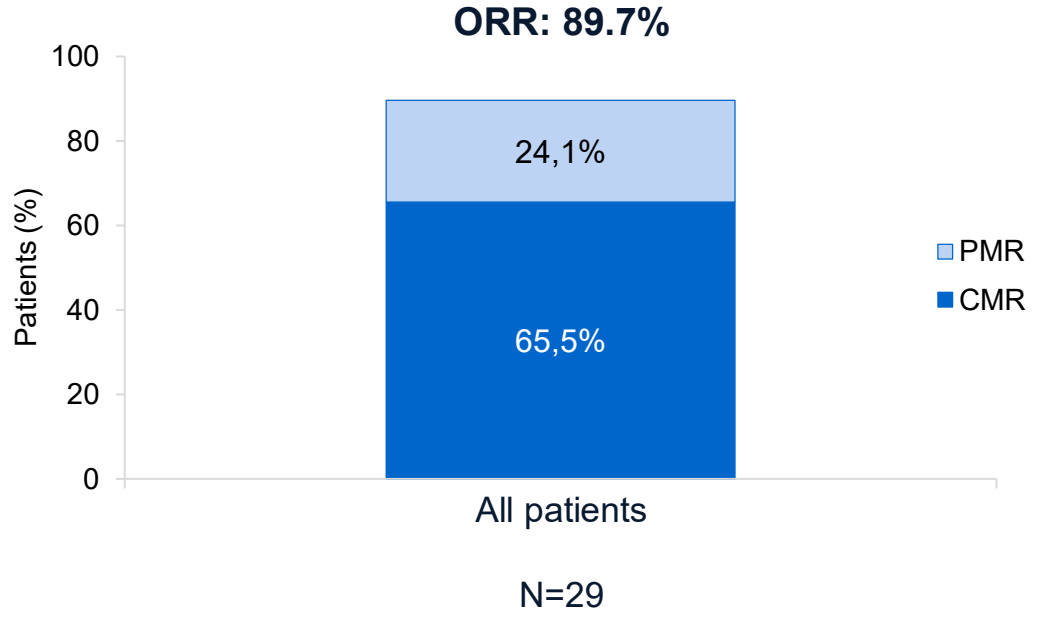
- **M-Len had a favorable safety profile. No AEs led to mosunetuzumab discontinuation.**

AE, adverse event; AST, aspartate aminotransferase

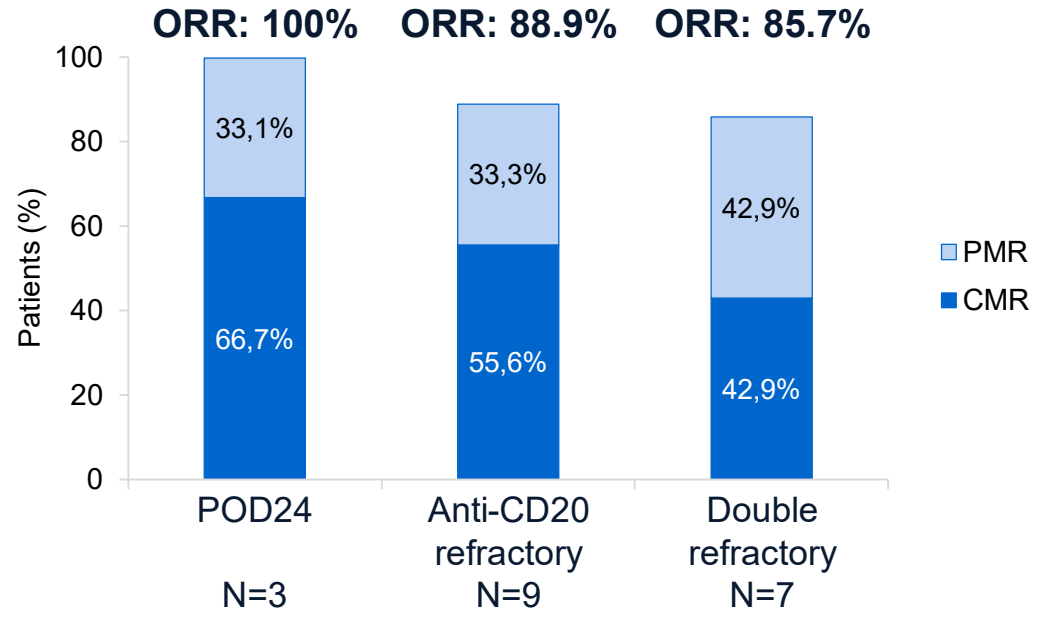
Response

- Median time to first / best response: 2.5 mo (range: 1.4–5.3) / 2.5 mo (range: 1.4–10.7)

Best response by PET-CT in all patients*



Best response by PET-CT in patient subgroups*



- **High ORR and CMR rate in overall population and in patients with high-risk disease**

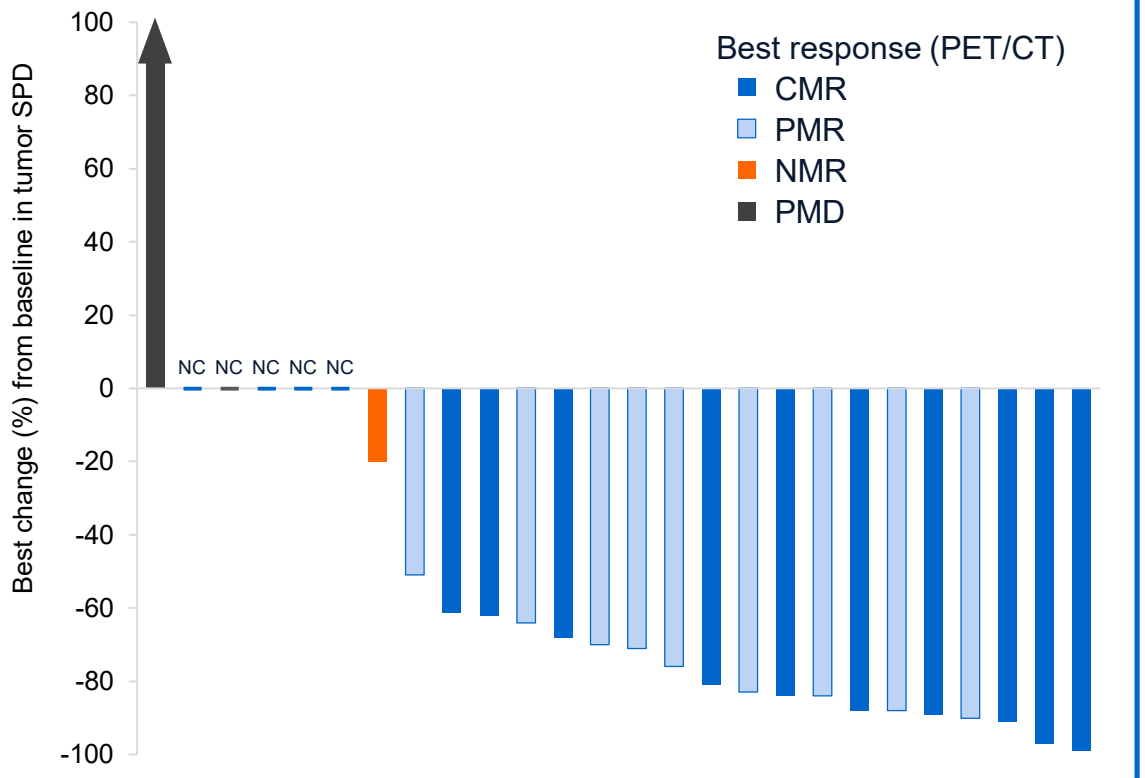
*assessed by investigators using Lugano 2014 criteria[1]; CMR, complete metabolic response; mo, months;
ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; PMR, partial metabolic response

1. Cheson et al. J Clin Oncol 2014;32:3059–67

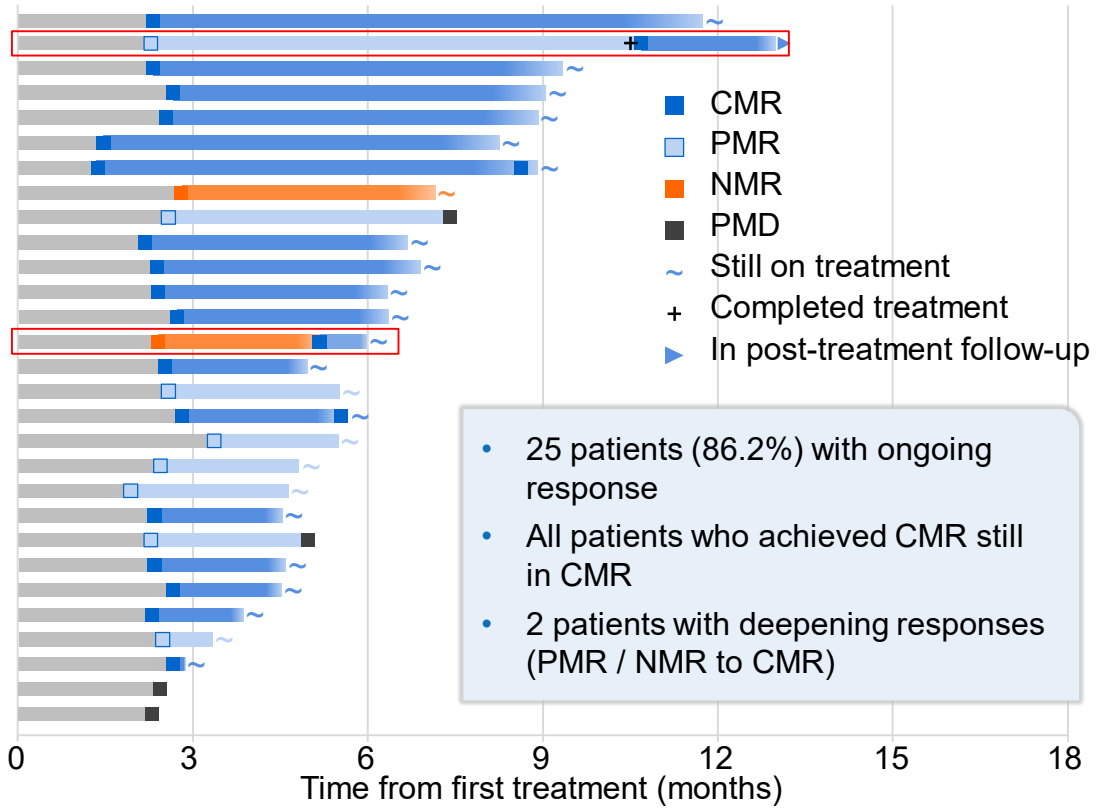
Change in tumor SPD and duration of response

- Median duration of follow-up: 5.4 months (range: 3–12)

Best percentage change from baseline in tumor SPD*



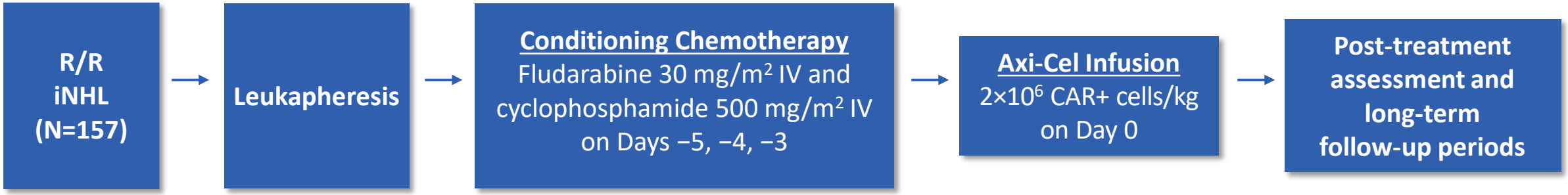
Duration of response



- 25 patients (86.2%) with ongoing response
- All patients who achieved CMR still in CMR
- 2 patients with deepening responses (PMR / NMR to CMR)

*in all patients with ≥1 diagnostic CT scan at response assessment (N=26);
NC, no change; NMR, no metabolic response; PMD, progressive metabolic disease; SPD, sum of product diameters

ZUMA-5 Study Design



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Safety Results

- Consistent with prior reports, the most common Grade ≥3 AEs were neutropenia (33%), decreased neutrophil count (28%), and anemia (25%)

- Grade ≥3 CRS and NEs occurred in 7% of patients (6% FL; 8% MZL) and 19% of patients (15% FL; 36% MZL), respectively
  - Most CRS cases (120 of 121) and NEs (82 of 87) of any grade resolved by data cutoff[a]
  - Nearly half of NEs (49%) resolved ≤2 weeks after onset; most NEs (76%) resolved ≤8 weeks after onset

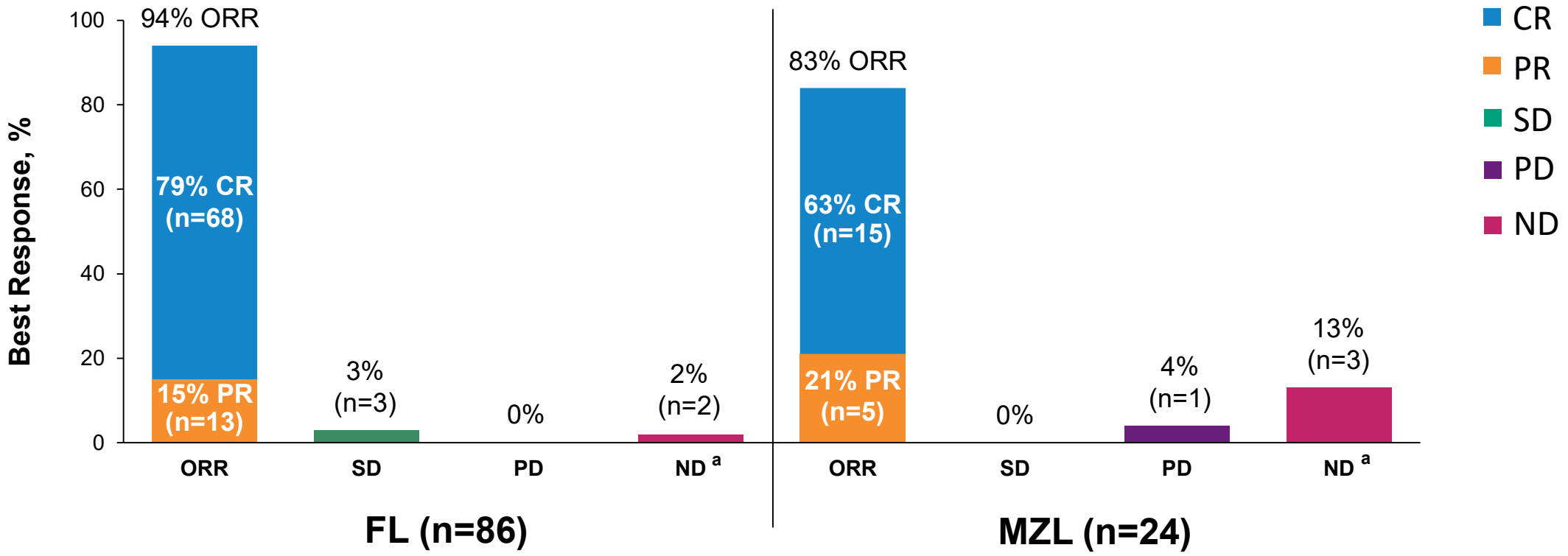
- Grade ≥3 cytopenias present ≥30 days post-infusion were reported in 34% of patients (33% FL; 36% MZL), most commonly neutropenia in 29% of patients (27% FL; 36% MZL)

CRS was graded according to Lee DW, et al. *Blood*. 2014;124:188-195. NEs were identified using the modified blinatumomab registrational study (Topp MS, et al. *Lancet Oncol.* 2015; 16;57-66). The severity of all AEs, including NEs and symptoms of CRS, was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

[a] One patient with FL died of multisystem organ failure in the context of CRS (Day 7) prior to the resolution of CRS. Ongoing NEs in FL included Grade 1 attention disturbance, Grade 1 memory impairment, and Grade 1 paresthesia. Ongoing NEs in patients with MZL included Grade 2 facial paresthesia, and Grade 1 memory impairment.

AE, adverse event; CRS, cytokine release syndrome; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, neurologic event.

ORR by Central Review

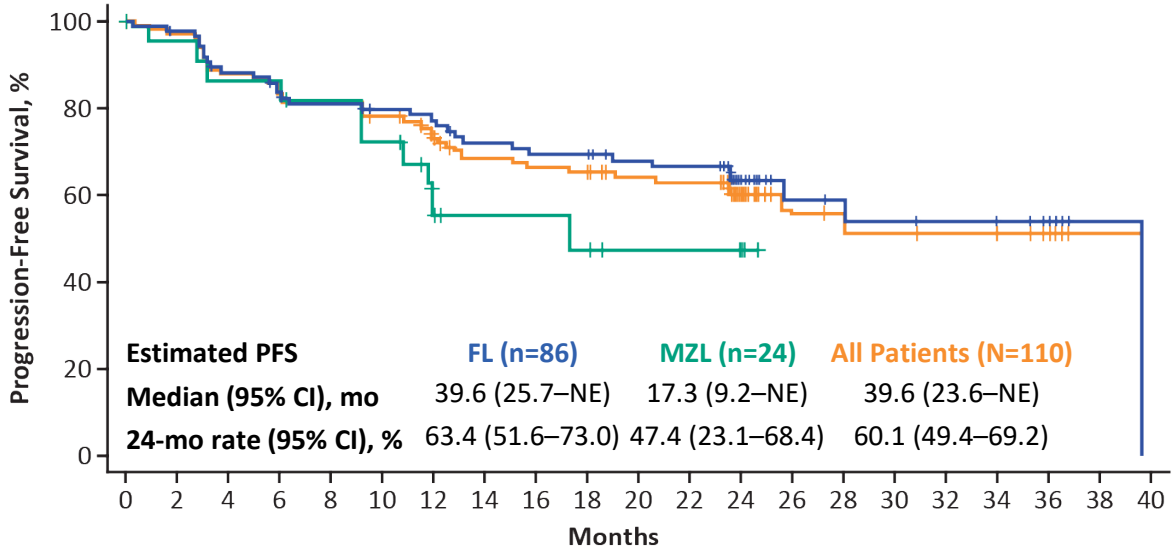


- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

Assessed in efficacy-eligible patients (n=110) by an IRRC according to the Lugano Classification (Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068).
[a] Among the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and post-baseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.
CR, complete response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, not done/undefined; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

PFS and OS

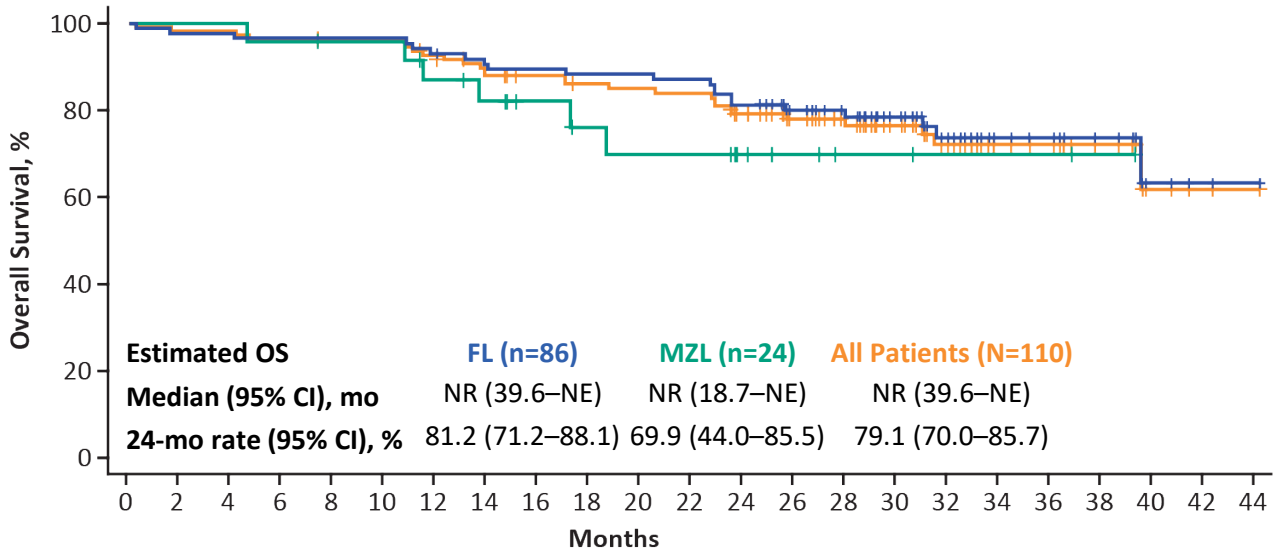
Progression-Free Survival



No. at Risk

FL	86	83	74	69	65	62	60	55	53	53	49	48	27	13	12	11	10	9	7	1	0
MZL	24	21	19	19	17	15	10	7	7	6	4	4	3	0							
All Patients	110	104	93	88	82	77	70	62	60	59	53	52	30	13	12	11	10	9	7	1	0

Overall Survival



No. at Risk

FL	86	84	84	83	83	83	80	77	76	75	75	74	69	60	53	40	28	17	15	11	4	2	1
MZL	24	24	24	23	22	22	19	17	14	12	11	11	8	6	3	3	2	2	2	1	0		
All Patients	110	108	108	106	105	105	99	94	90	87	86	85	77	66	56	43	30	19	17	12	4	2	1

- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24[a]; no disease progression events occurred after Month 24

[a] Of the 3 deaths, 2 were from COVID-19 and 1 was from sepsis.

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Follicular lymphoma
GLA Studien 2021

LMU KLINIKUM

Alternative 1:	*Alternative 2:*	*medically non-fit:*
G-Ibru	G-Copanlisib	G +/- Bendamustine
↓	↓	↓
G-Ibru maintenance	G-Copanlisib maintenance	G maintenance

Relapse

R2 +/- Tazemetostat	R2 +/- Tafasitamab	R2 vs Mosunetuzumab-R

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Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2021

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