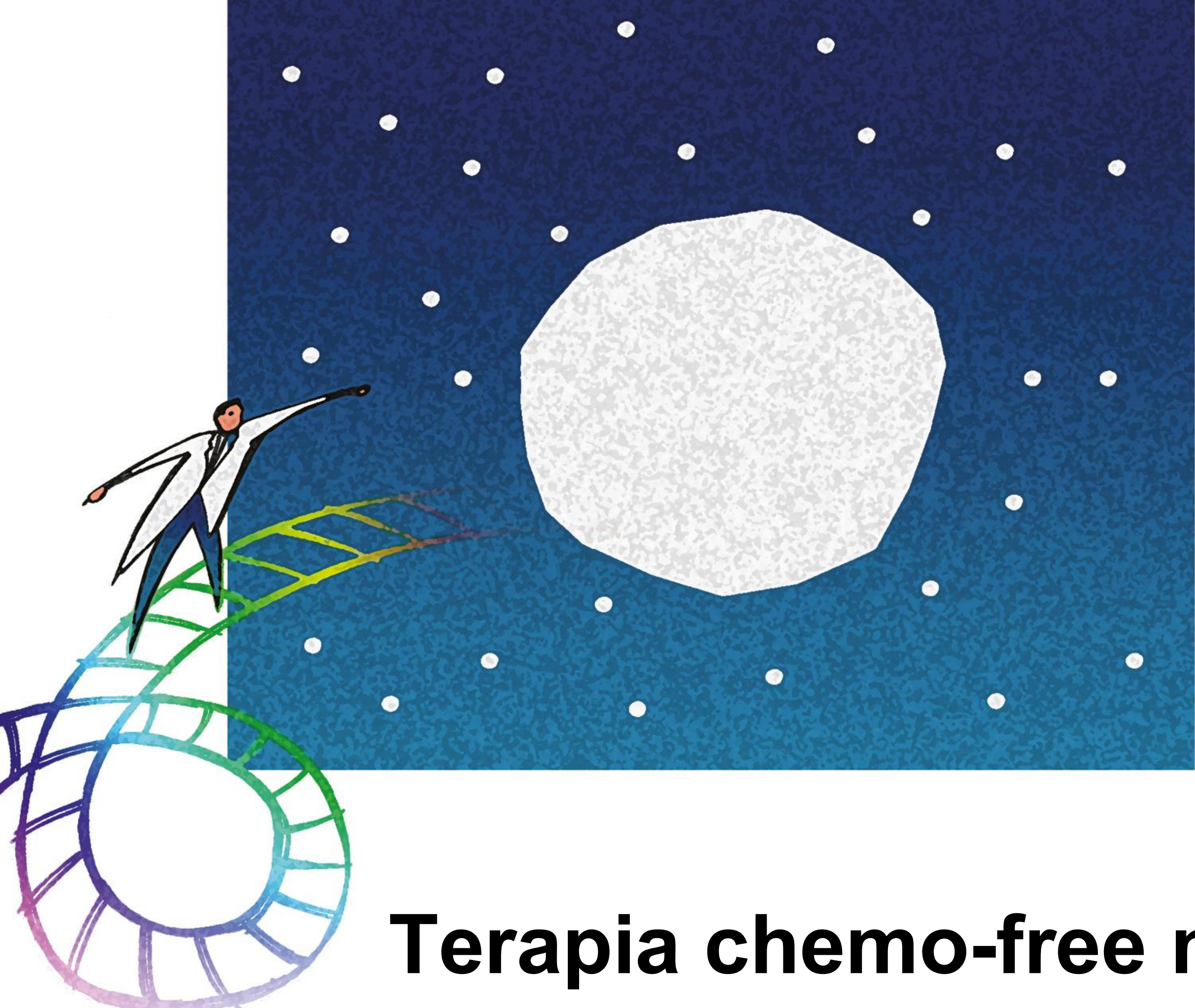




The young side of **LYMPHOMA**

gli under 40 a confronto

Reggio Emilia, Hotel Mercure Astoria
2-3 ottobre 2026

Terapia chemo-free nel Linfoma Follicolare 1L

*Dott.ssa Marika Porrazzo
AORR Villa Sofia Cervello, Oncoematologia, Palermo*



Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
/	/	/	/	/	/	/	/



Alla luce delle terapie di I Linea attualmente a disposizione che trattamento sceglieresti in un paziente con linfoma follicolare stadio IVA, FLIPI 2, high tumor burden, di 79 anni con anamnesi positiva per cardiopatia ischemica, insufficienza renale moderata e polmoniti ricorrenti?

- a) ICT (R-CHOP, R-mini CHOP, R COMP)
- b) R2
- c) Rituximab single agent
- d) R Bendamustina



**What Would
You Do?**

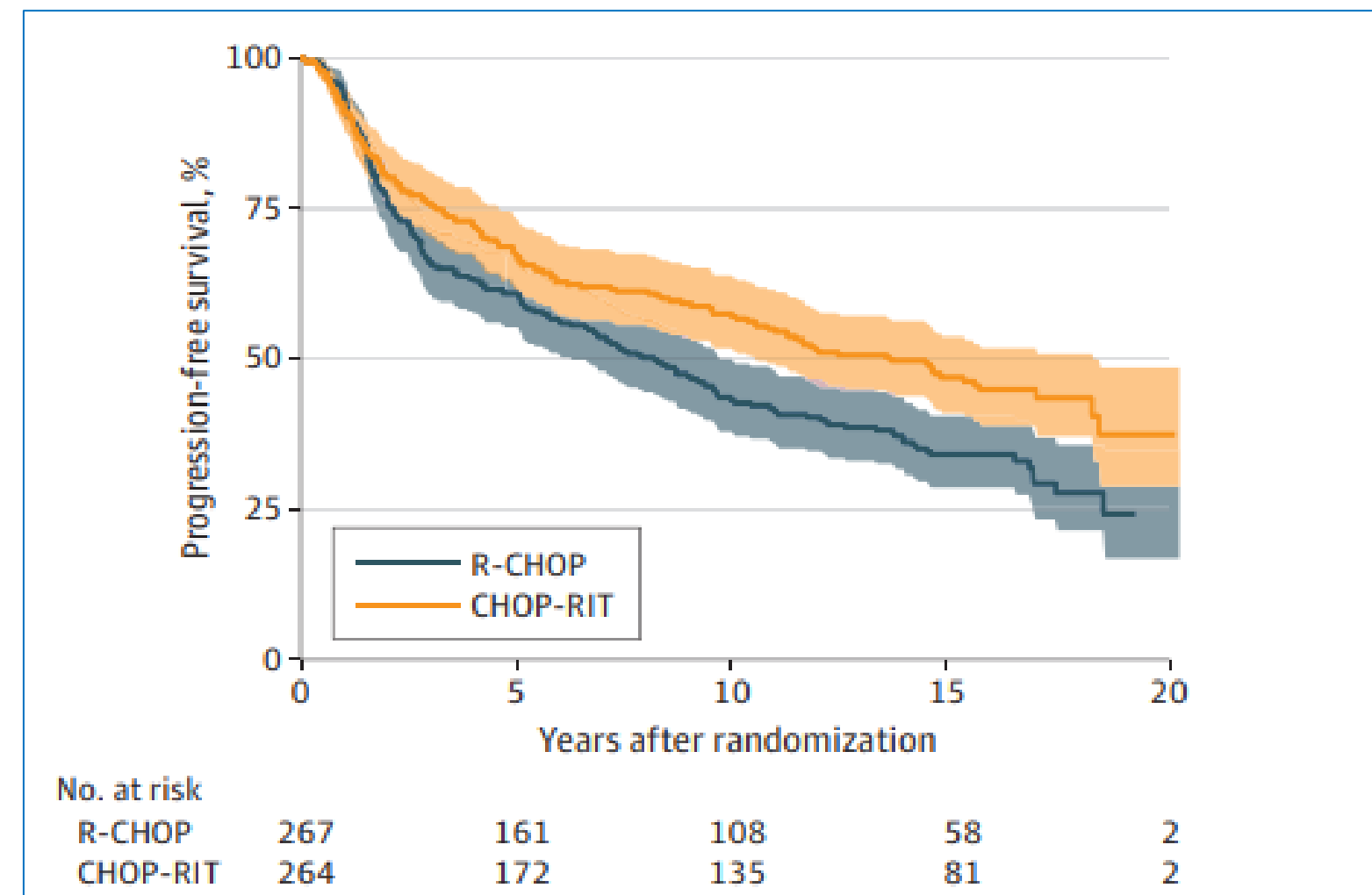
Nella scelta terapeutica relativa alla domanda precedente cosa hai tenuto principalmente in considerazione?

- a) Tossicità
- b) PFS
- c) Sequencing e terapie successive
- d) Tempo al successivo trattamento
- e) Tutte le precedenti

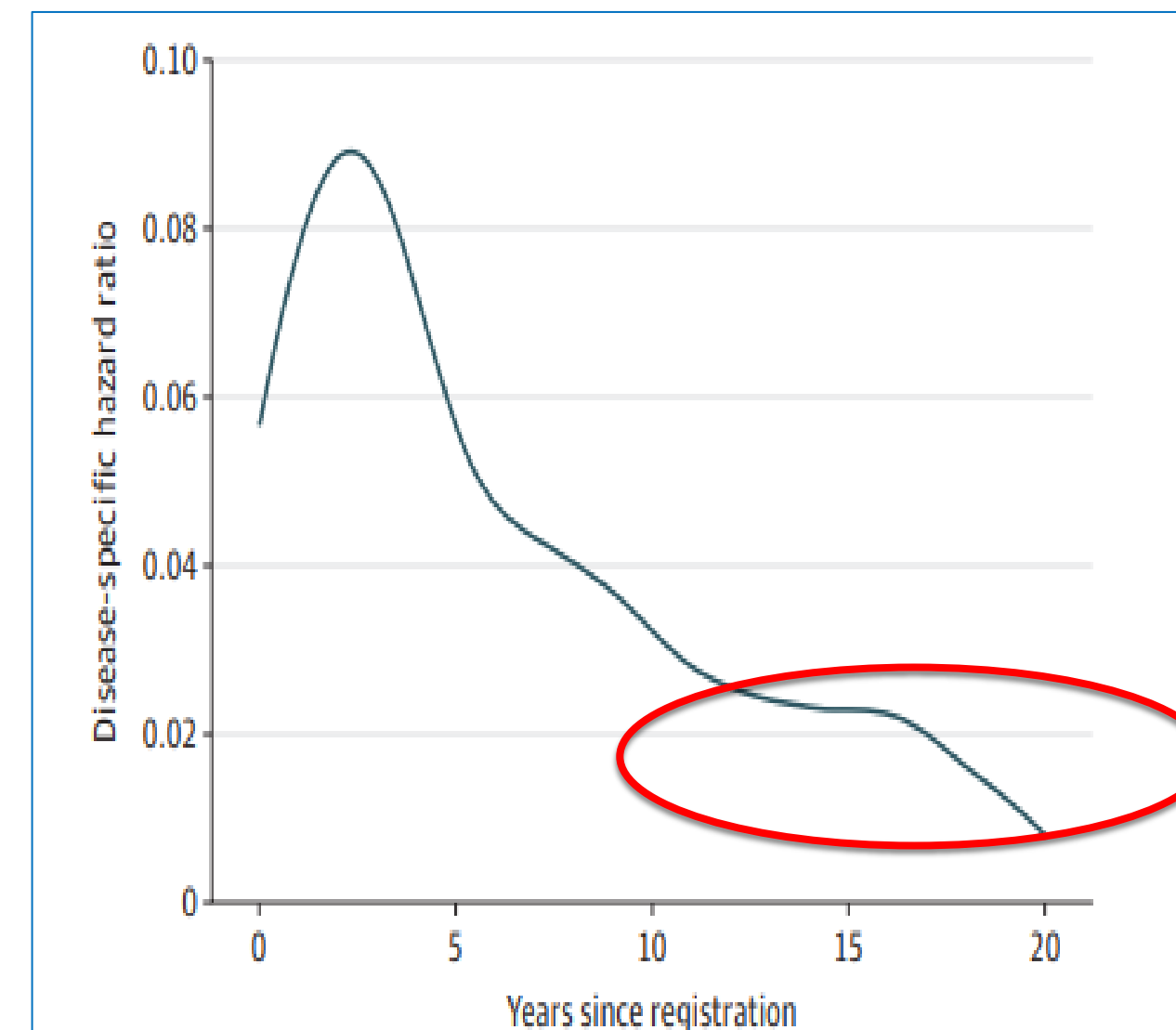
Shifting Paradigms in 1 L FL

Redefining «Cure»: where do we start and where are we going?

Treatment of Follicular Lymphoma With CHOP and Anti-CD20 Therapy 15-Year Follow-Up of the SWOG S0016 Trial



15y PFS 47% CHOP + RT

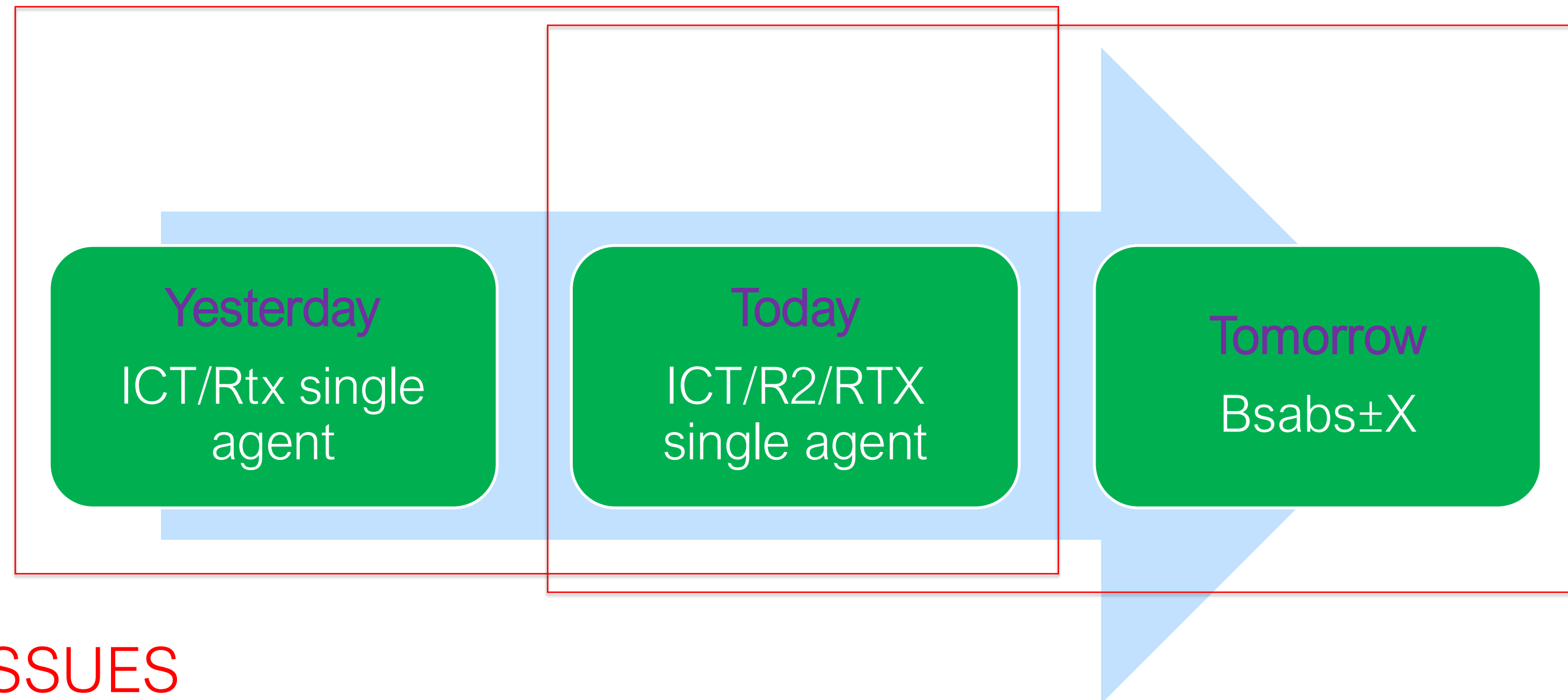


Overall Cure estimate: 42%

A subset of patients with advanced-stage FL can achieve cure with CHOP-based chemoimmunotherapy

Shifting Paradigms in 1 L FL

Redefining «Cure»: where do we start and where are we going?



MAIN ISSUES

- None of the currently available studies has shown that any single treatment was able to modify patient's overall risk of death
- Toxicities represent a major limitation

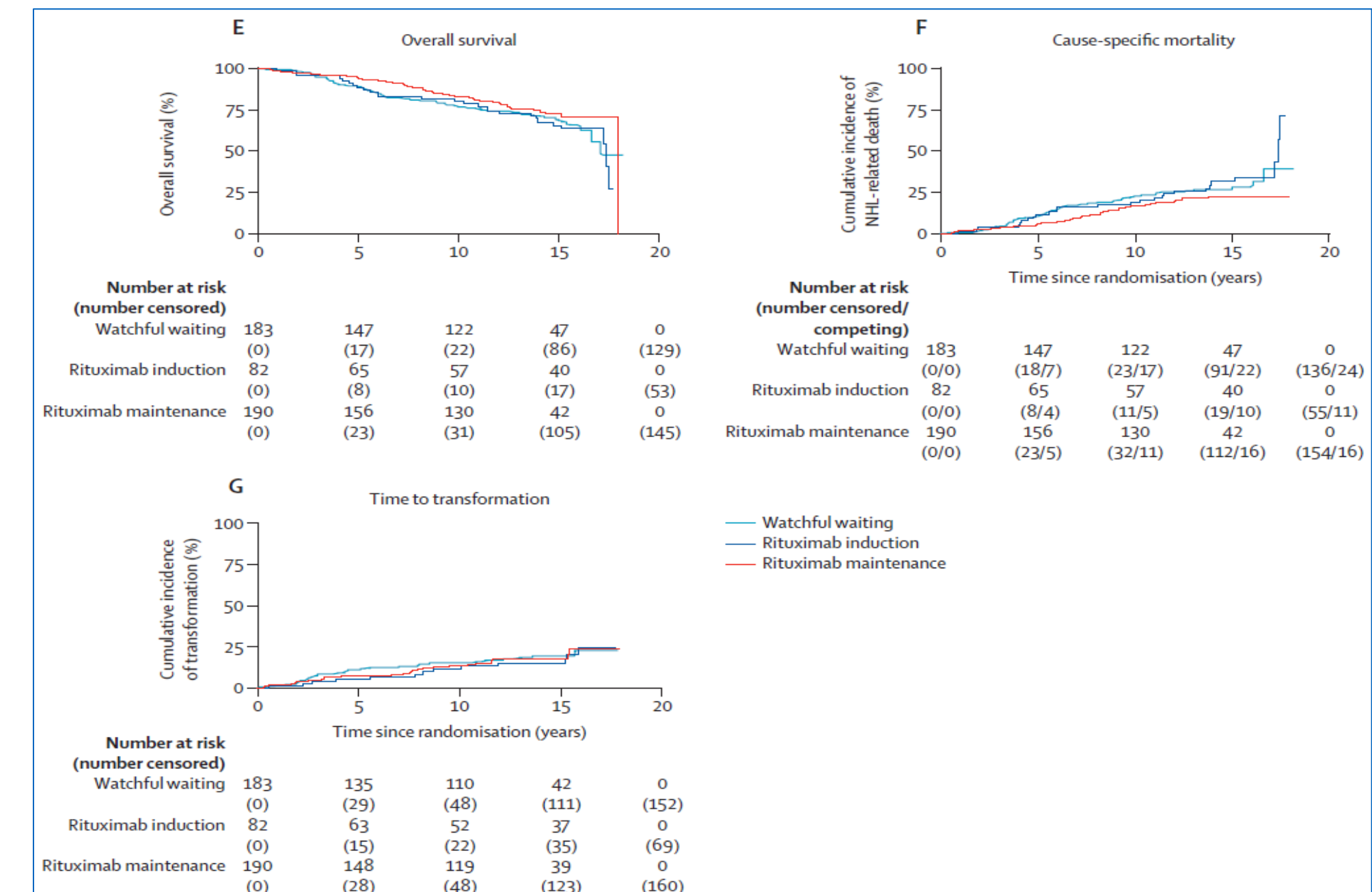
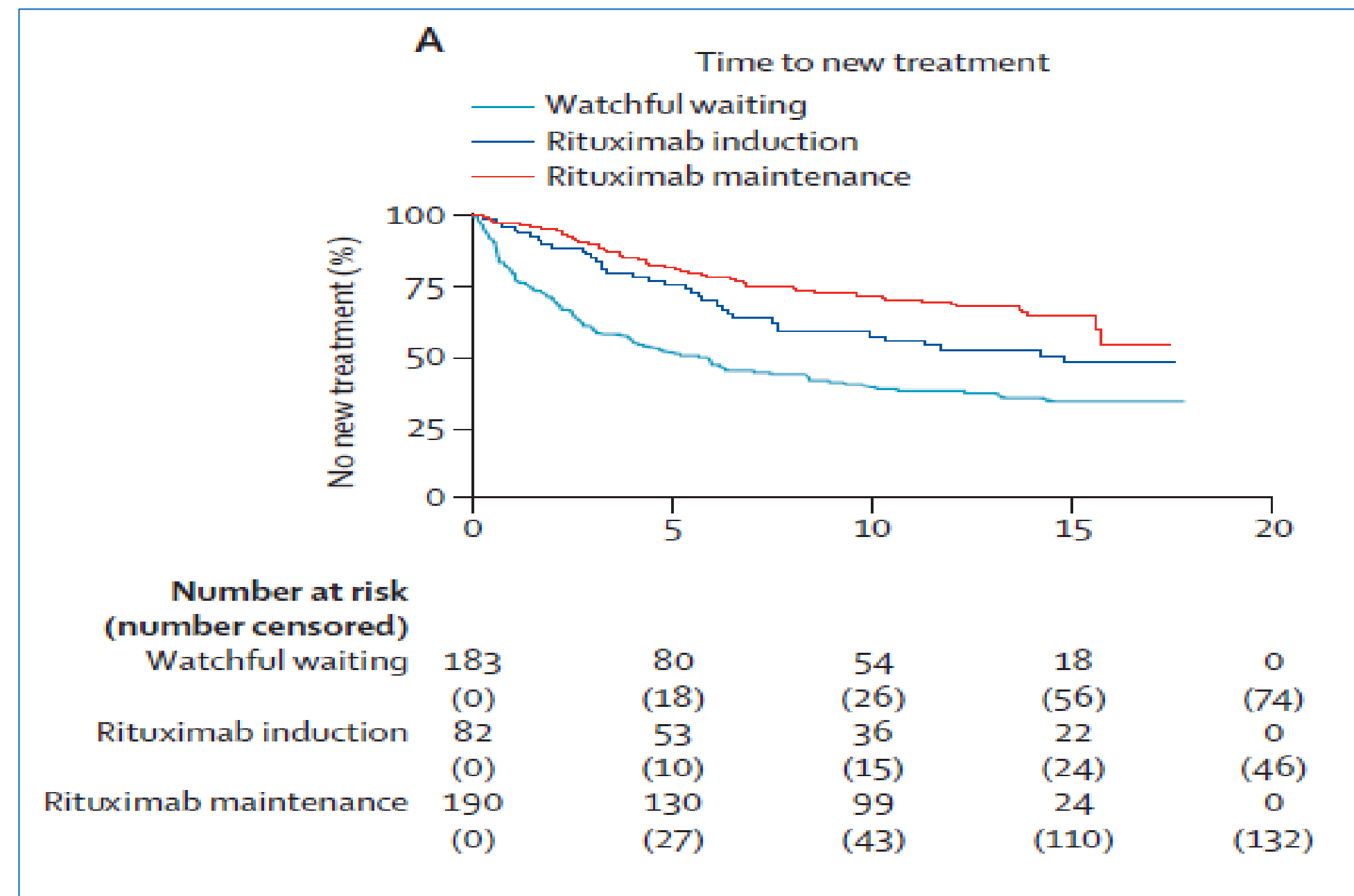
MAIN ISSUES

- Sequencing strategy
- Risk adapted therapy
- Better understanding of the biology (es. loss of CD20+ , risk of transformation)

Early rituximab monotherapy versus watchful waiting for advanced stage, asymptomatic, low tumour burden follicular lymphoma: long-term results of a randomised, phase 3 trial

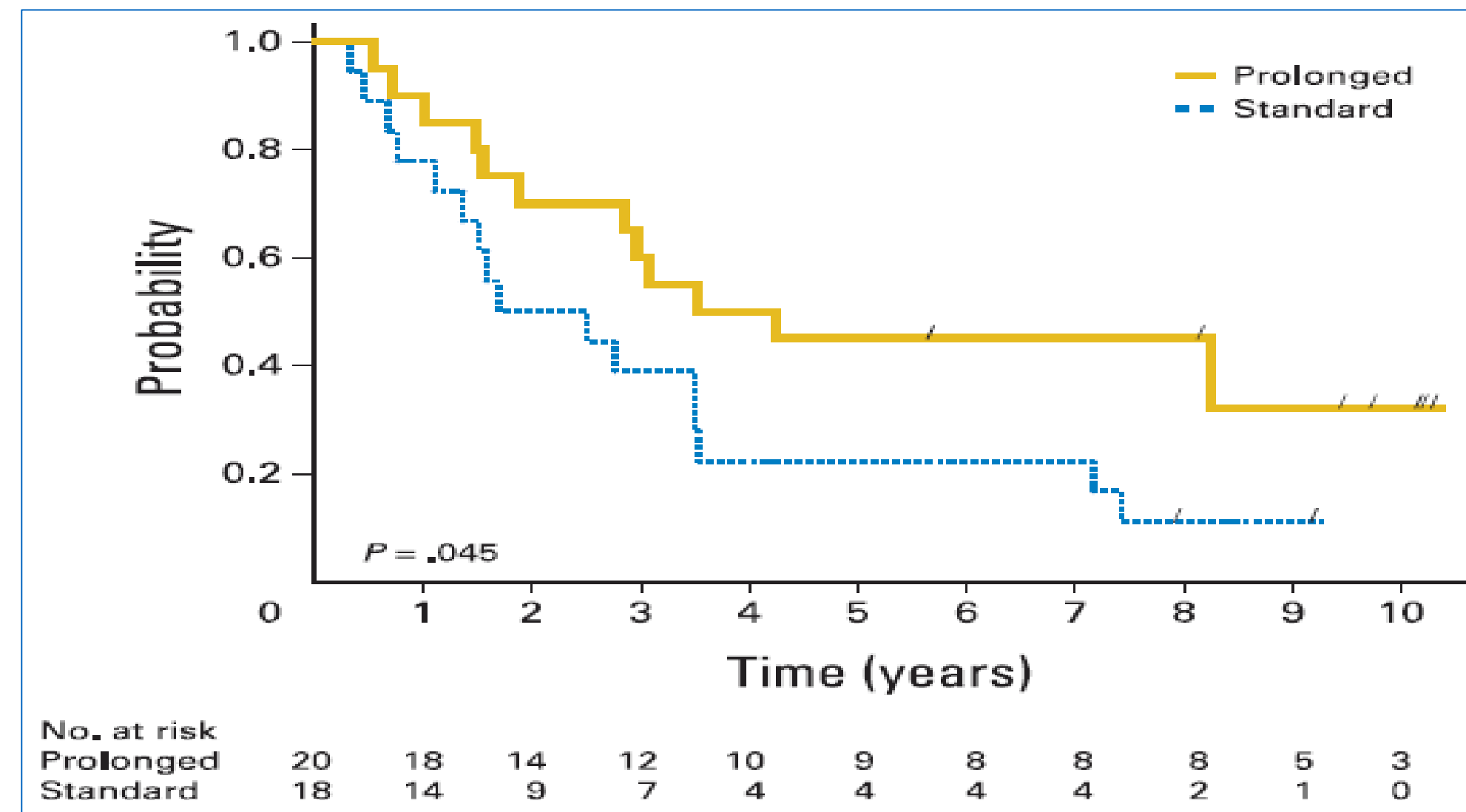
Time to new treatment 15 y FU

Outcomes 15 y FU



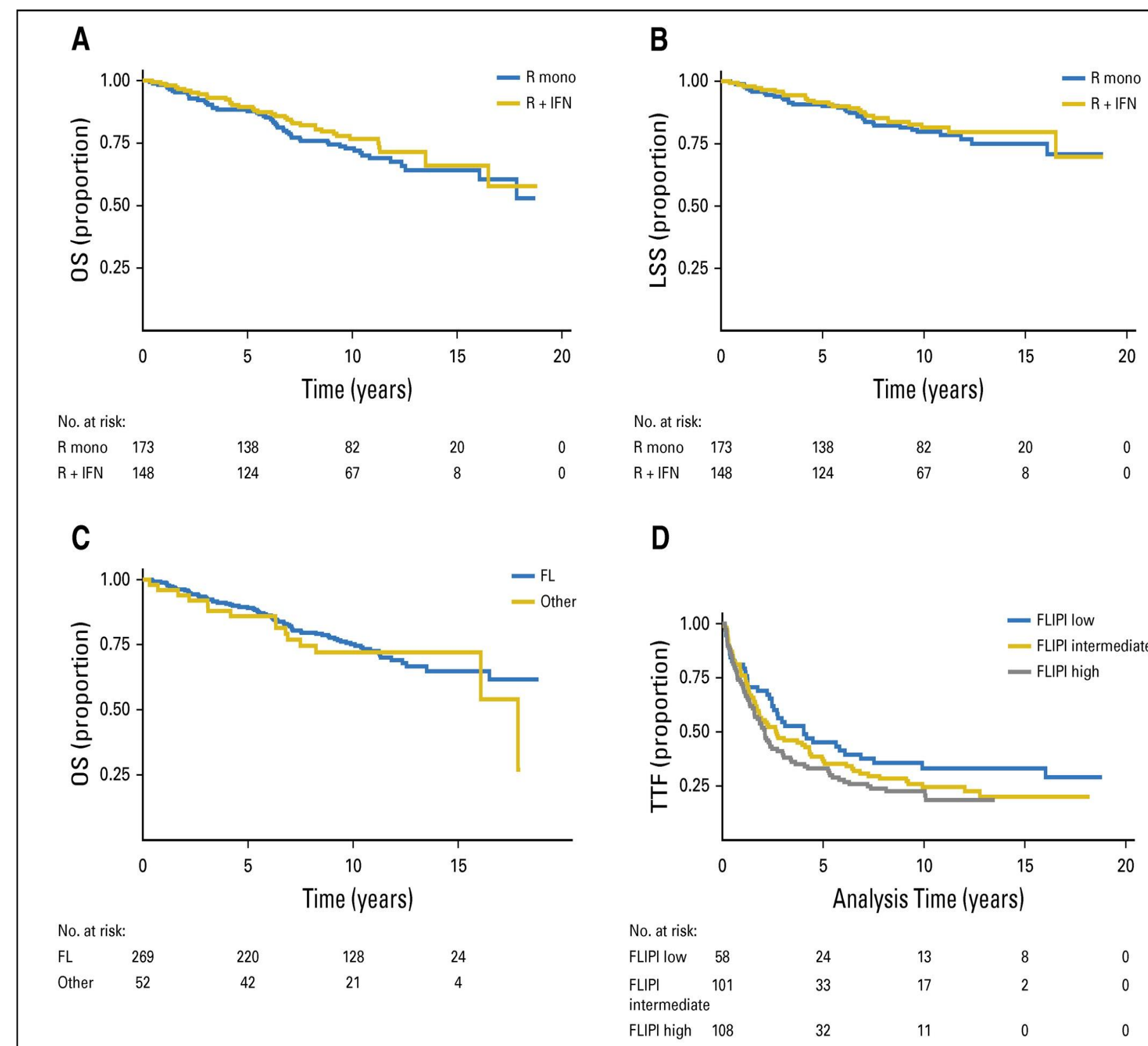
Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98

EFS 8 y Fu



45% of chemo-naive
Responders are in remission
at 8 years

Chemotherapy-Free Initial Treatment of Advanced Indolent Lymphoma Has Durable Effect With Low Toxicity: Results From Two Nordic Lymphoma Group Trials With More Than 10 Years of Follow-Up

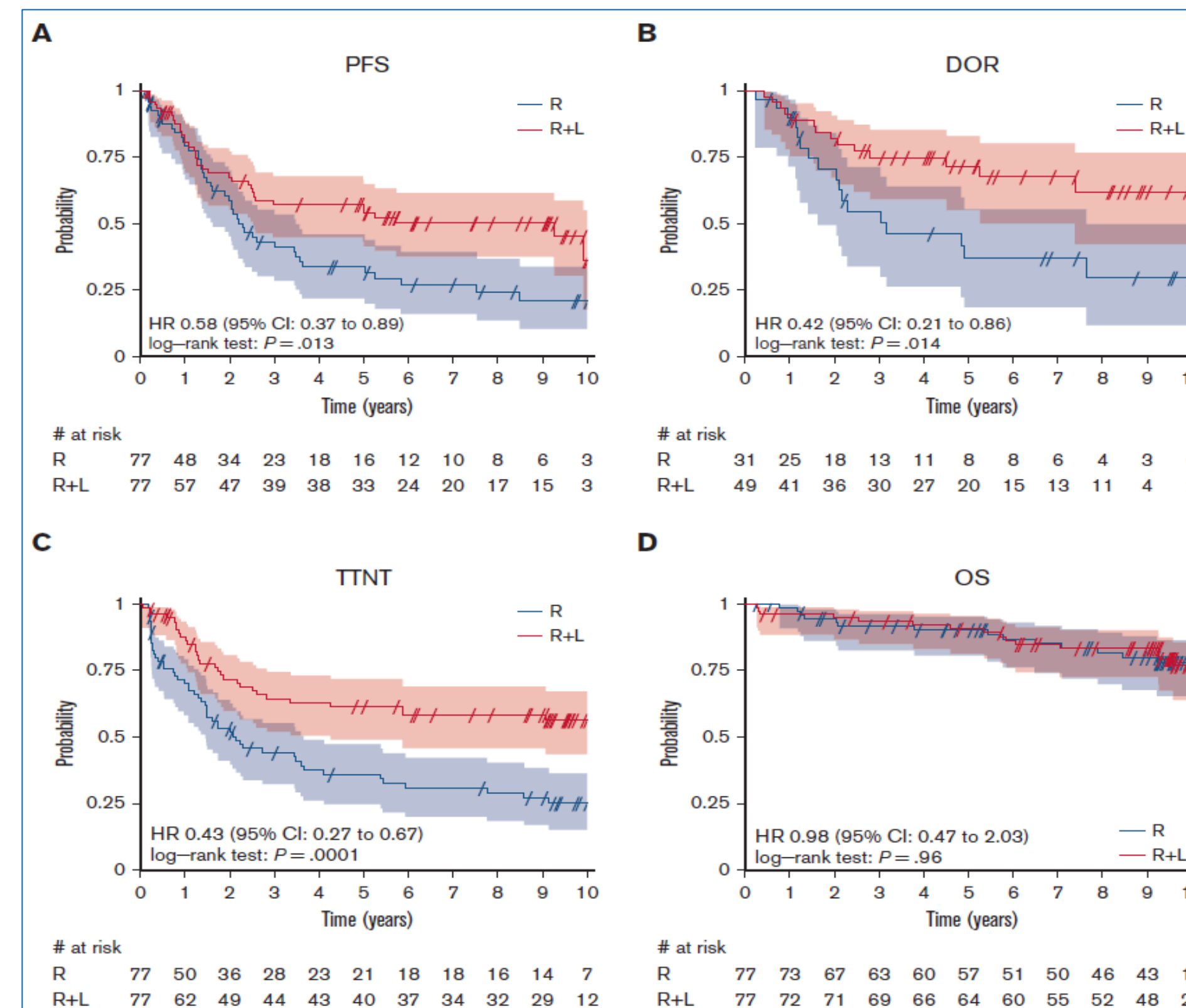


- N=321 (289 FL)
- Med F-up 10.6 years
- All pts recieved Rituximab (8 doses) +/- IFN upfront
- One out of three pts never required chemotherapy
- tFL in 20%
- Long term outcomes (OS, LSS) similar to those achieved with conventional approaches

Six-month rituximab-lenalidomide regimen in advanced untreated follicular lymphoma: SAKK 35/10 trial 10-year update

Response

	R	R2
ORR	61%	82%
CRR	25%	36%
CRR 30 m	19%	42%

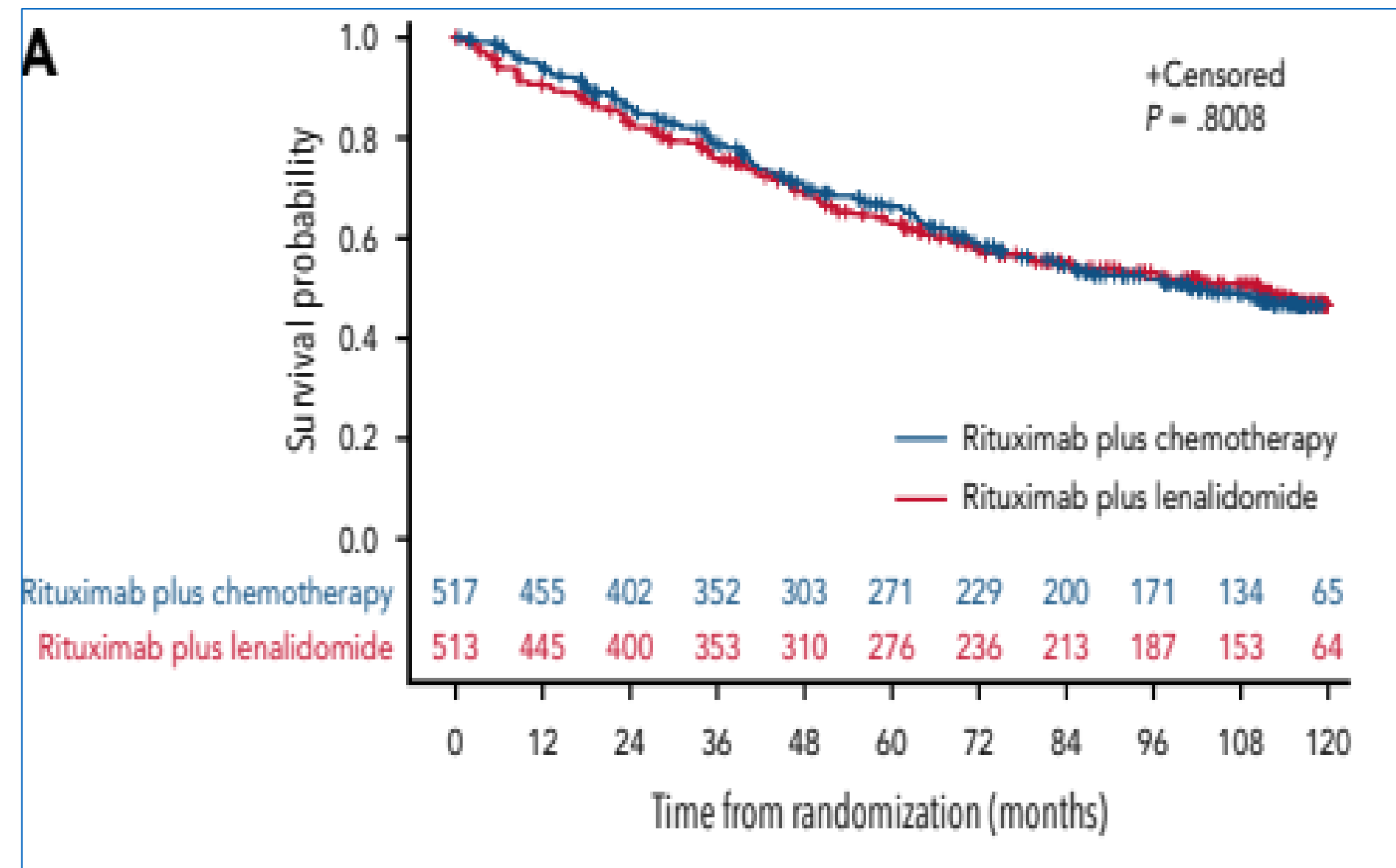


Median PFS (9.3 vs 2.3 years)

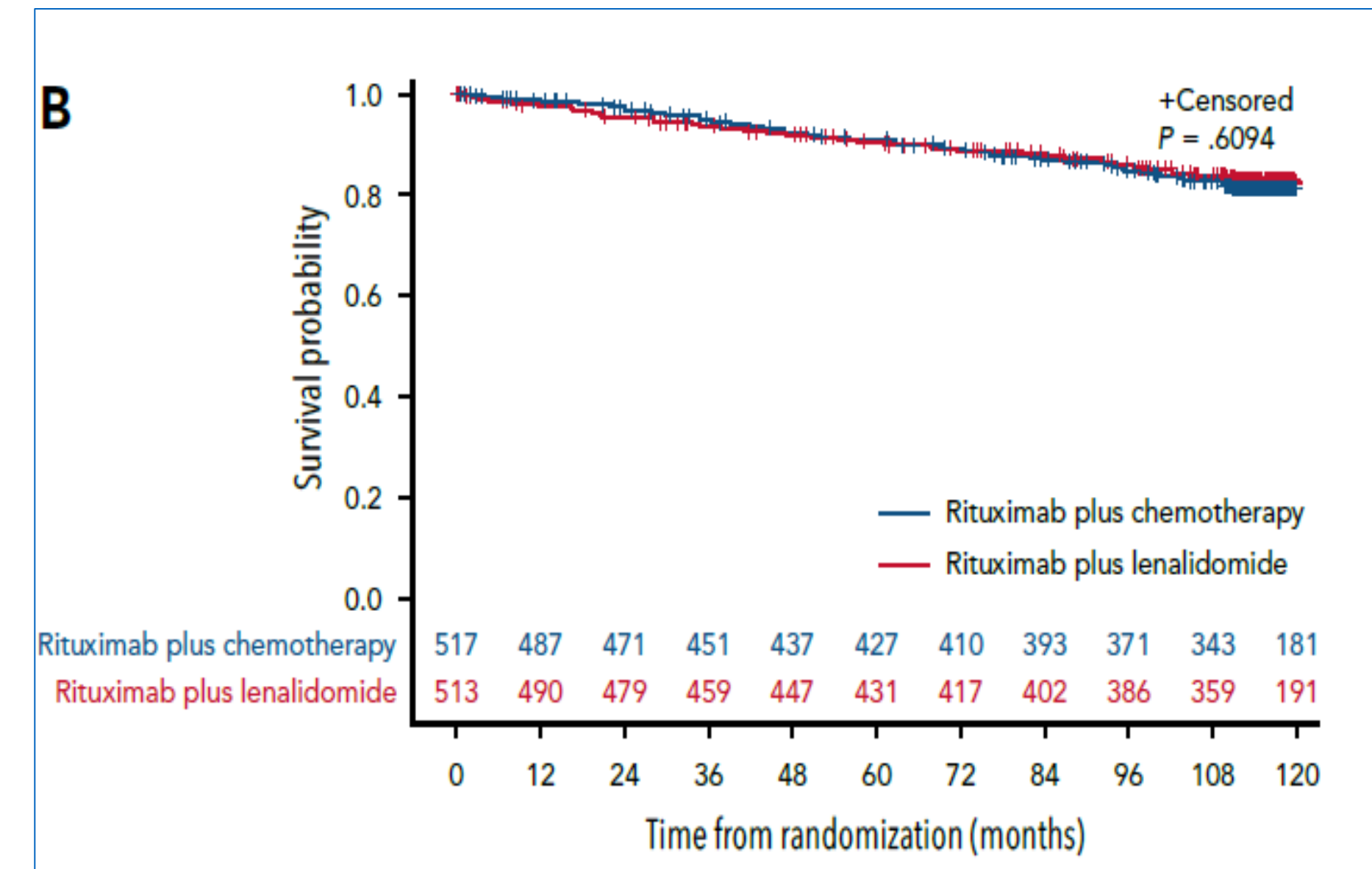
Median TTNT (not reached vs 2.1 years)

Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: the 10-year RELEVANCE trial analysis

PFS



OS



10 y PFS 46,4% R2 vs 46,6% R- chemo

- Transformation rates similar (2% range)
- Similar ORR and OS with subsequent therapy in both groups
- Similar rates of second primary malignancies

Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: Relevance trial safety

Table 3. Adverse Events during the Treatment Period in the Safety Population.				
Adverse Event	Rituximab–Lenalidomide Group (N = 507)		Rituximab–Chemotherapy Group (N = 503)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
number of patients (percent)				
Neutropenia*	381 (75)	160 (32)	386 (77)	252 (50)
Anemia*	333 (66)	0	446 (89)	0
Thrombocytopenia*	268 (53)	11 (2)	266 (53)	8 (2)
Cutaneous reactions†	220 (43)	36 (7)	120 (24)	5 (1)
Diarrhea	187 (37)	10 (2)	95 (19)	6 (1)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)
Rash	146 (29)	20 (4)	39 (8)	1 (<1)
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)
Nausea	100 (20)	0	209 (42)	8 (2)
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)
Myalgia	73 (14)	0	29 (6)	1 (<1)
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)
Peripheral edema	69 (14)	0	47 (9)	1 (<1)
Muscle spasms	68 (13)	0	21 (4)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)
Upper respiratory tract infection	47 (9)	0	55 (11)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)
Tumor flare reaction	30 (6)	7 (1)	1 (<1)	0
Leukopenia	21 (4)	8 (2)	48 (10)	30 (6)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)
Tumor lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)
Alopecia	5 (1)	0	45 (9)	3 (<1)

Fixed duration subcutaneous mosunetuzumab in patients with previously untreated high-tumor burden follicular lymphoma interim results from the Phase II MorningSun study

Ongoing Phase II basket study of mosunetuzumab subcutaneous monotherapy in patients with B-cell NHL, including FL

Key inclusion criteria

- Previously untreated FL
- HTB by GELF criteria
- ECOG performance status 0–2

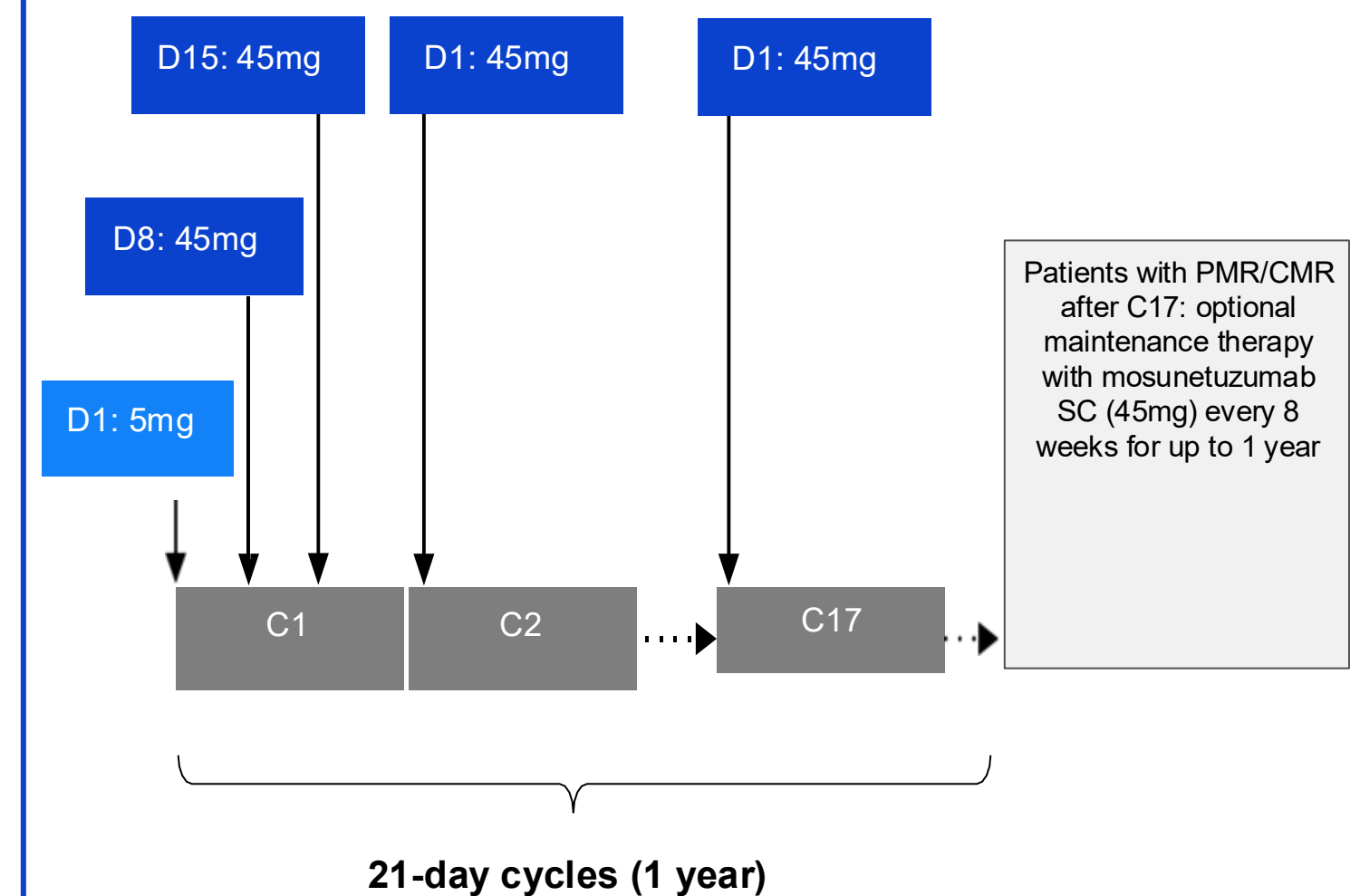
CRS mitigation

- Mosunetuzumab SC step-up dosing in C1
- Corticosteroid prophylaxis* was mandatory in C1–2 and optional thereafter
- Hospitalization was not mandatory

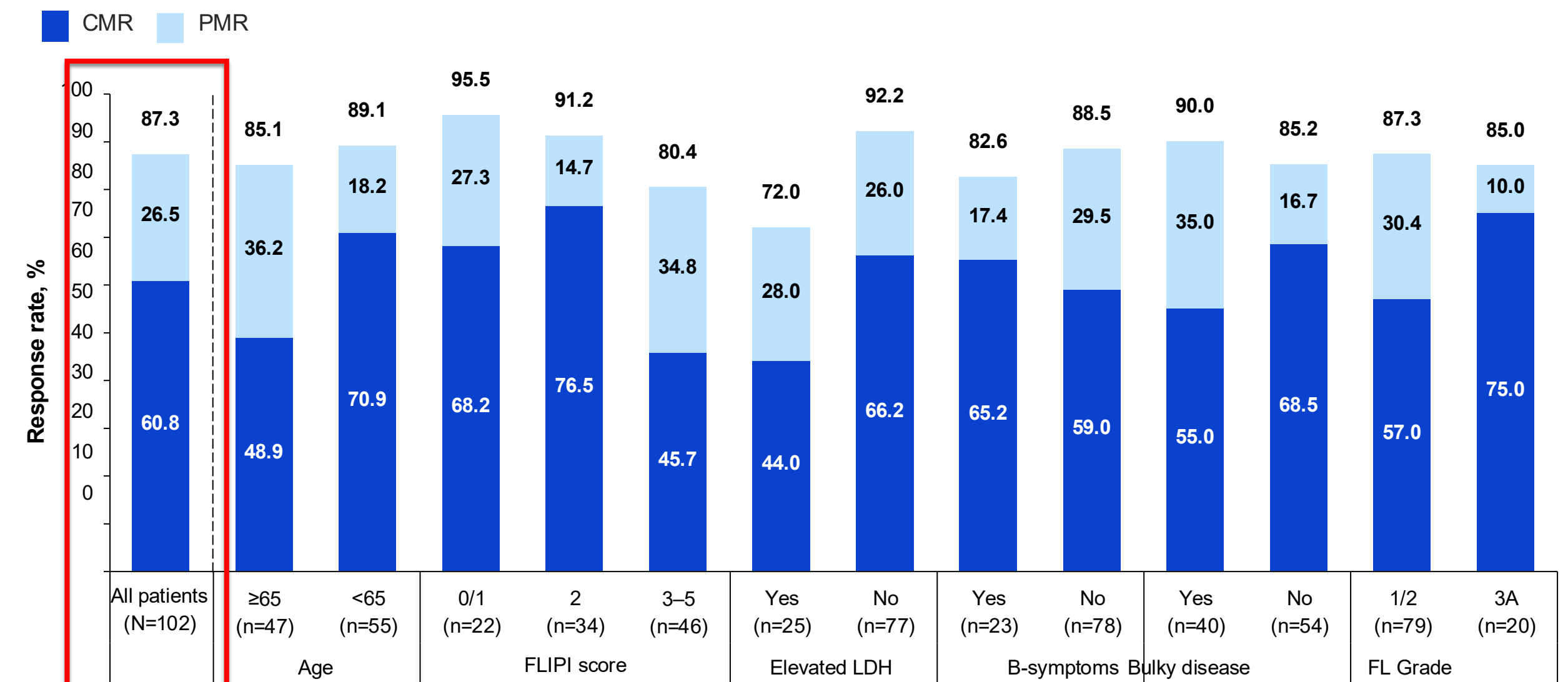
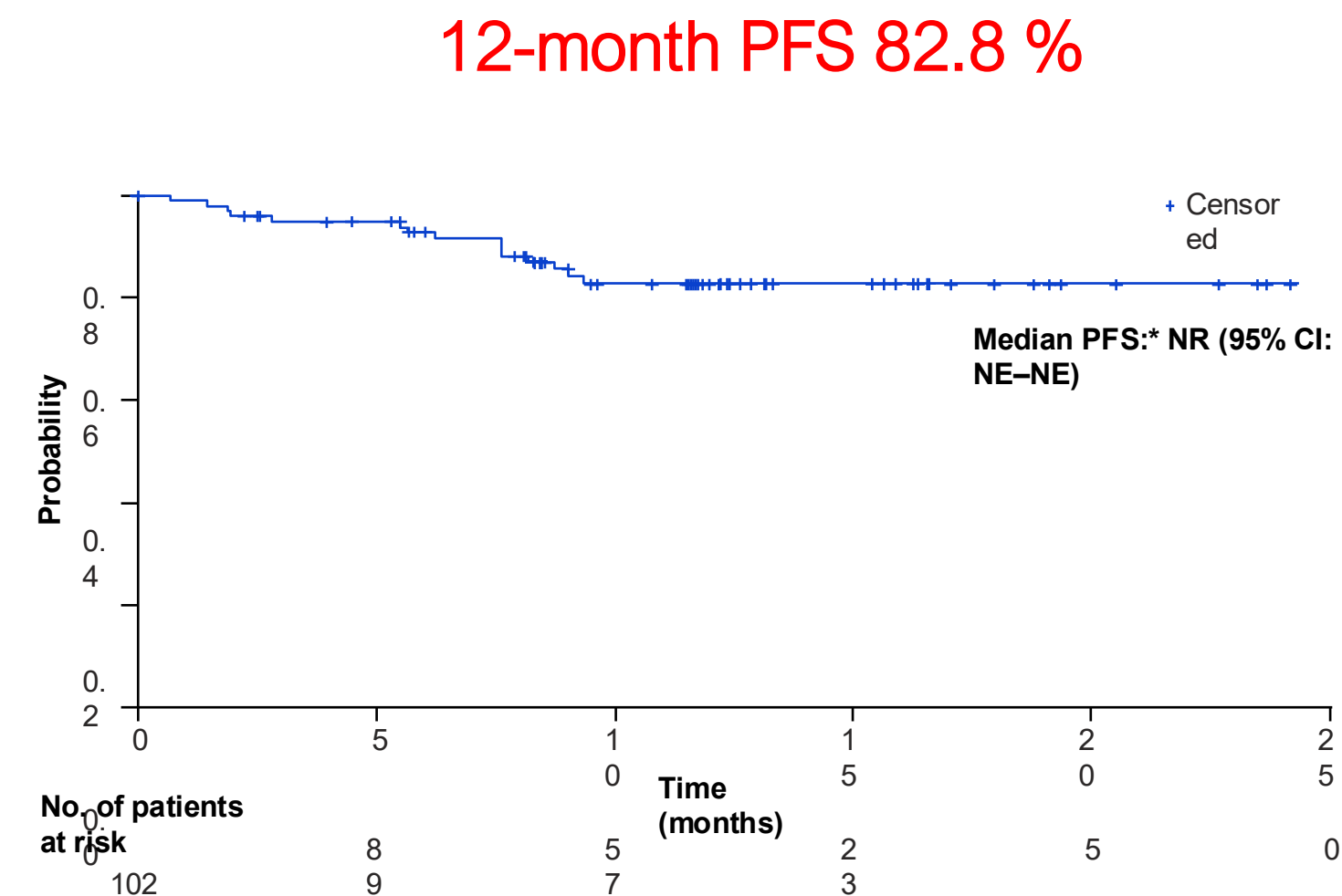
Endpoints

- Primary: PFS rate at 24 months
- Key secondary: ORR, time to response, safety

Mosunetuzumab SC administration



MorningSun study: interim results



MorningSun study: safety

Adverse Events

n (%)	N=102
Any grade AE	102 (100)
Most common any grade AEs ($\geq 30\%$)	
Injection site reaction	66 (64.7)
Fatigue	43 (42.2)
CRS	35 (34.3)
Headache	32 (31.4)
Nausea	31 (30.4)
AE leading to mosunetuzumab discontinuation	8 (7.8)*
Grade 3/4 AE	41 (40.2)
Most common Grade 3/4 AE ($\geq 10\%$)	
Neutrophil count decreased	12 (11.8)
Grade 5 AEs	4 (3.9)
COVID-19 pneumonia	2 (2.0)
Cardiogenic shock	1 (1.0)
Death (unexplained)	1 (1.0)

n (%)	N=102
Select AEs of interest	
Infections	75 (73.5) [†]
Grade 3	13 (12.7)
Grade 4	2 (2.0)
Grade 5	2 (2.0) [‡]
ICANS	1 (1.0)
Grade 4	1 (1.0)
Serious AE	30 (29.4)
Most common serious AEs ($\geq 10\%$)	
☐ Infections and infestations [§]	13 (12.7)
CRS	11 (10.8)

Injection site reaction, CRS and headache AEs were all Grade 1/2

Fatigue and nausea AEs were Grade 1–3

*Cardiogenic shock, COVID-19 pneumonia, upper respiratory tract infection, neutrophil count decreased, amnesia, ICANS, nasal congestion, pneumonitis (n=1 each).

[†]Most common infections ($\geq 10\%$): COVID-19/COVID-19 pneumonia (26.5%), sinusitis (13.7%), urinary tract infection (12.7%), and pneumonia (11.8%).

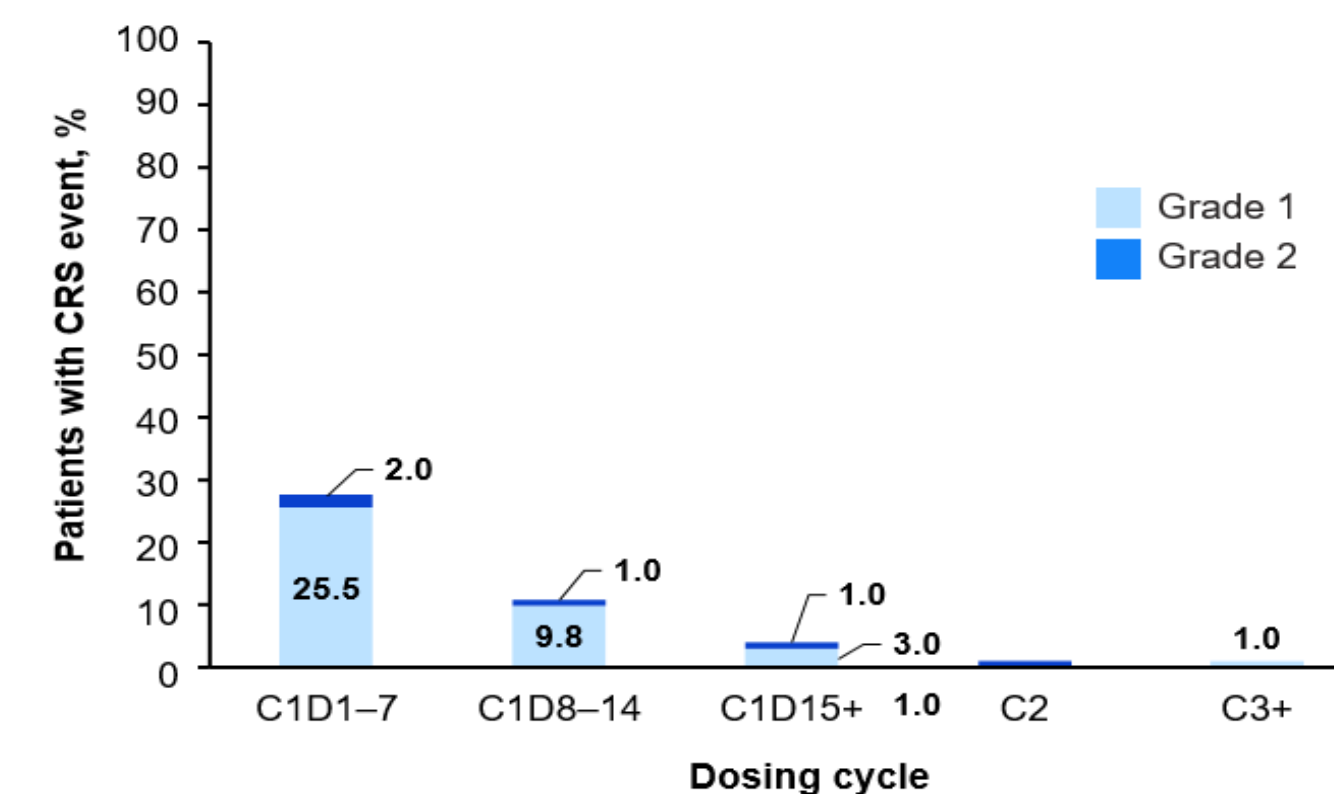
[‡]COVID-19 pneumonia (n=2). [§]Grouped term.

ICANS, immune effector cell-associated neurotoxicity syndrome.

CRS

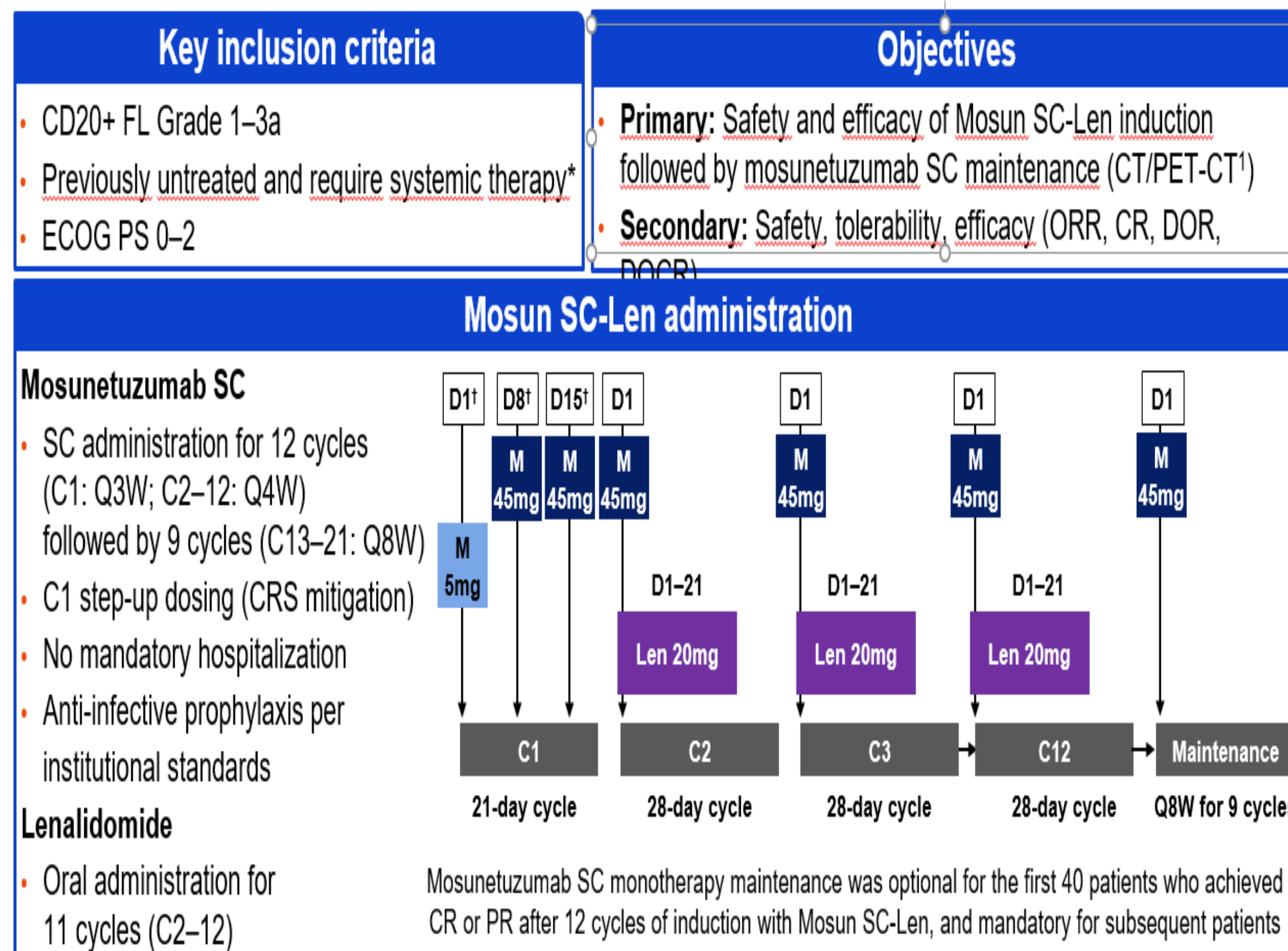
n (%) unless stated	N=102
Any grade CRS*	35 (34.3)
Grade 1	30 (29.4)
Grade 2	5 (4.9)
Median time to CRS onset, days (range)	2.0 (1–8)
Median CRS duration, days (range)	2.5 (1–15)
Corticosteroids for CRS management	8 (7.8)
Tocilizumab for CRS management	6 (5.9)
Corticosteroids + tocilizumab for CRS management	3 (2.9)
CRS resolution	35 (100)

CRS Frequency by cycles



Flinn IW; et al ASCO 2025 oral presentation (abstract #7014)

Safety and efficacy of subcutaneous mosunetuzumab plus lenalidomide induction therapy followed by mosunetuzumab maintenance in previously untreated follicular lymphoma



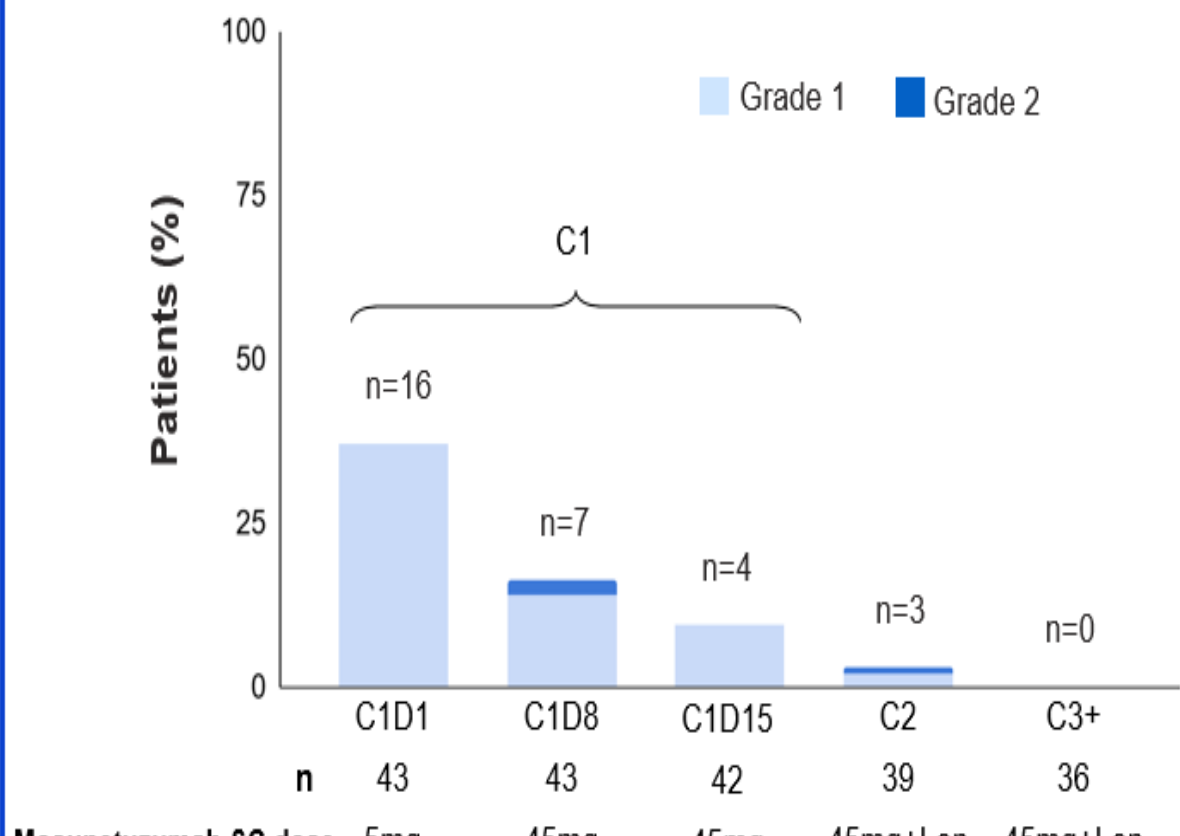
Safety and efficacy of subcutaneous mosunetuzumab plus lenalidomide induction therapy followed by mosunetuzumab maintenance in previously untreated follicular lymphoma

Adverse Events

Summary of AEs, n (%)	Induction phase N=43	Maintenance phase n=16
CRS	24 (55.8)	0
Grade 3/4	0	0
Neutropenia*	26 (60.5)	5 (31.3)
Grade 3/4	21 (48.8)	4 (25.0)
Febrile neutropenia	0	0
Infections†	28 (65.1)	8 (50.0)
Grade 3/4	5 (11.6)	0
Injection site reactions	31 (72.1)	3 (18.8)
Grade 3/4	0	0
ICANS	0	0

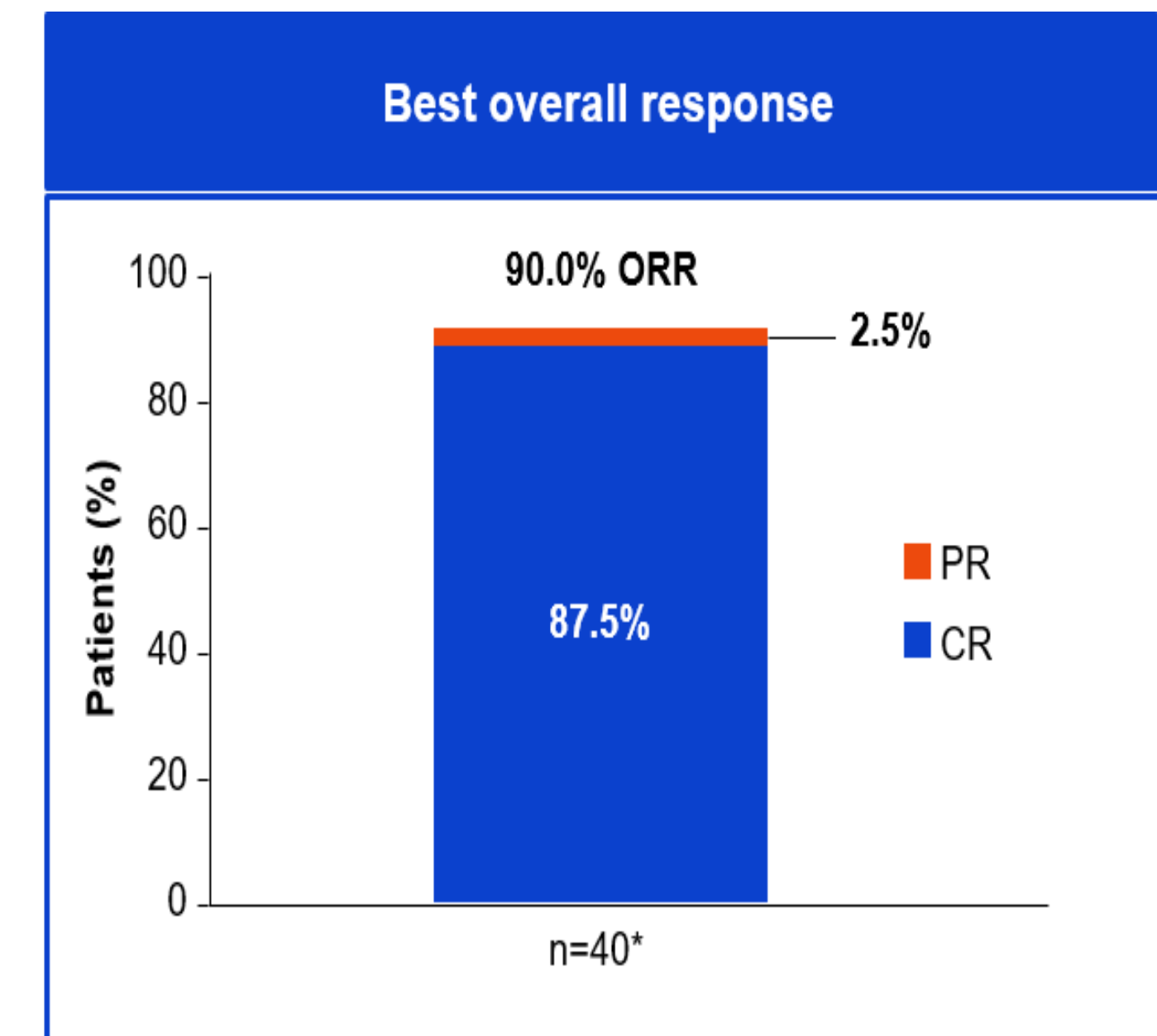
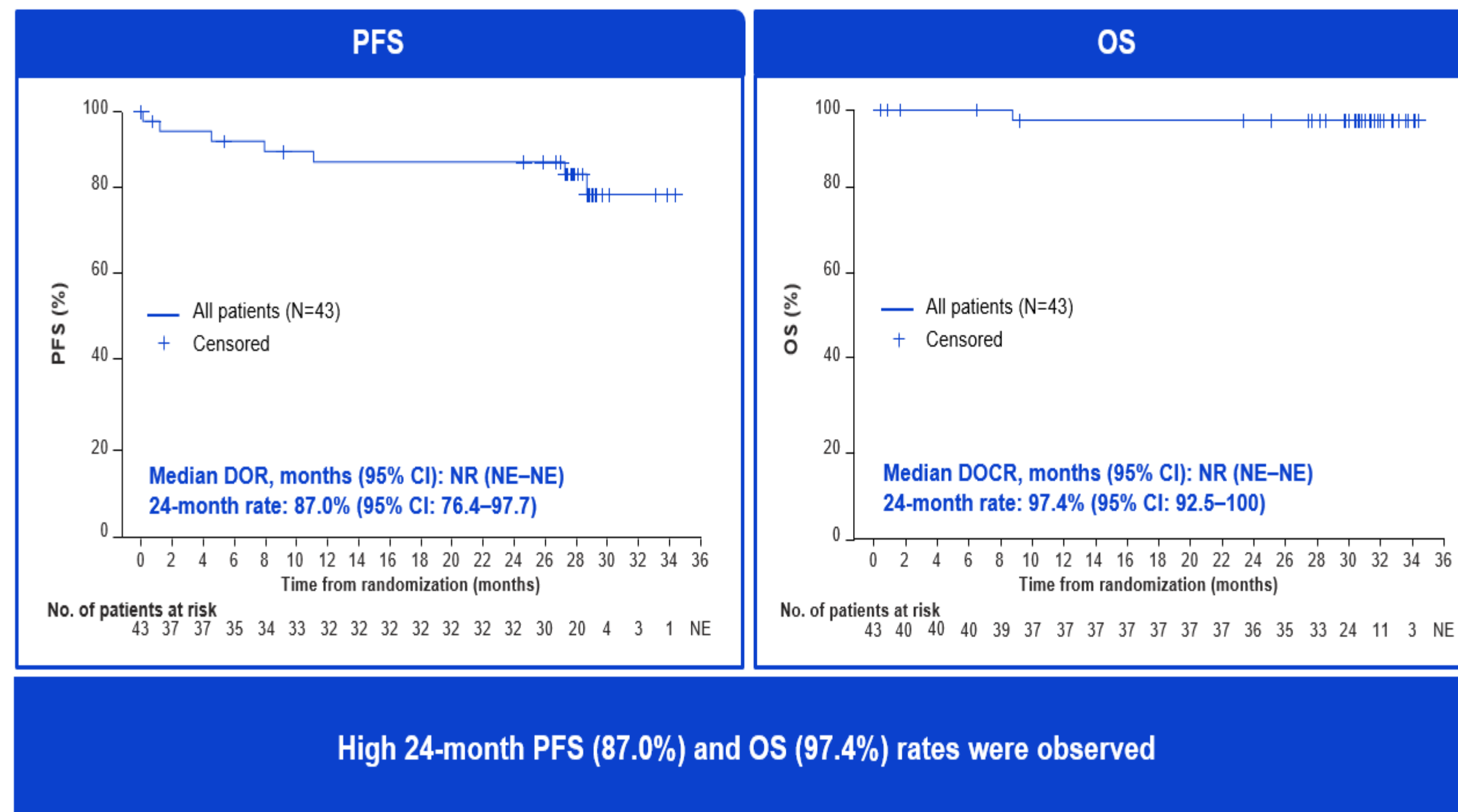
No CRS or Grade 3/4 infections occurred during maintenance;
no ICANS was reported during induction or maintenance

CRS

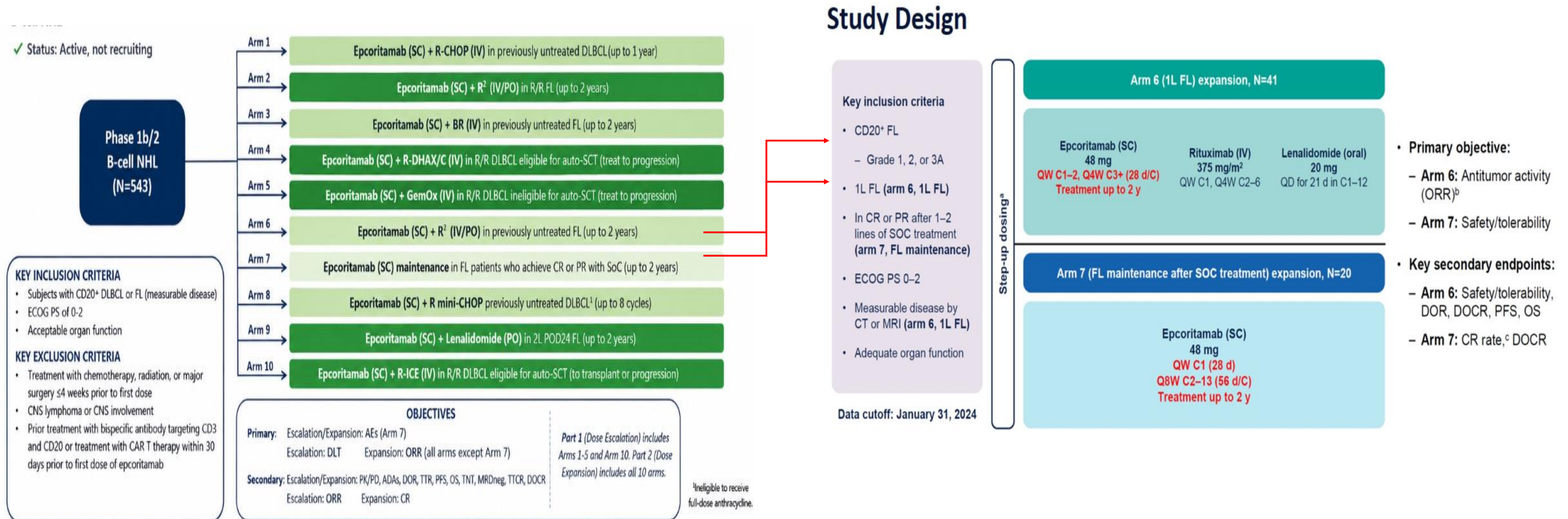
n (%), unless stated	1L FL cohort N=43	Patients with CRS* by cycle and grade	
CRS* (any grade)	24 (55.8)		
Grade 1	22 (51.2)		
Grade 2	2 (4.7)		
Serious AE of CRS† (any grade)	7 (16.3)		
Median time to first CRS onset,‡ days (range)	2 (1–27)		
Median CRS duration, days (range)	2 (1–11)		
CRS resolved	24 (100)		
Corticosteroids for CRS management	0		
Tocilizumab for CRS management§	3 (7.0)		
CRS leading to mosunetuzumab SC discontinuation	0		

CRS occurred in 56% of patients; it was predominantly Grade 1 and confined to C1–C2.
No CRS cases required vasopressors, supplemental oxygen, or ICU admission.
All events resolved

Safety and efficacy of subcutaneous mosunetuzumab plus lenalidomide induction therapy followed by mosunetuzumab maintenance in previously untreated follicular lymphoma



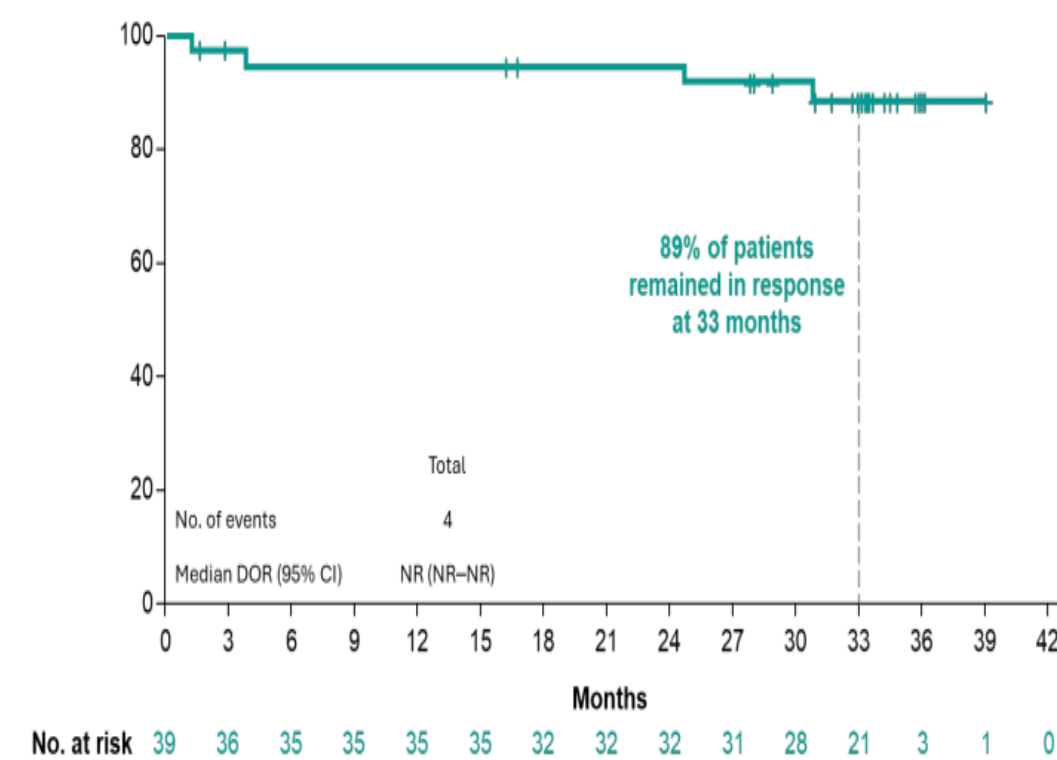
EPCORE NHL-2: Epcoritamab Combinations in B cell NHL



EPCORE NHL-2 Epcoritamab Combinations in B cell NHL ARM-6: efficacy

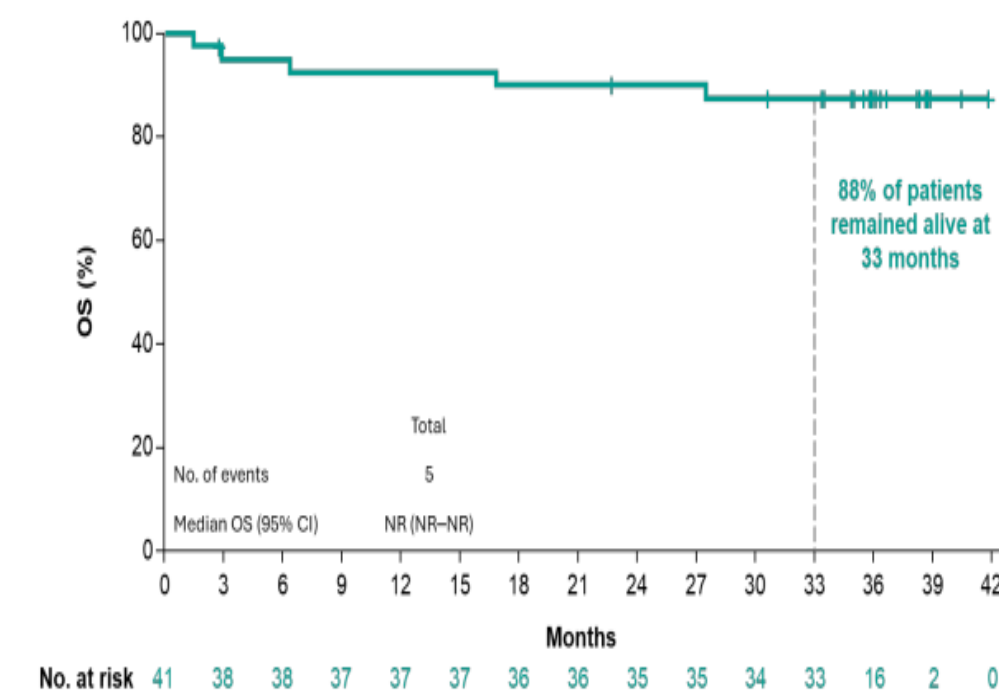
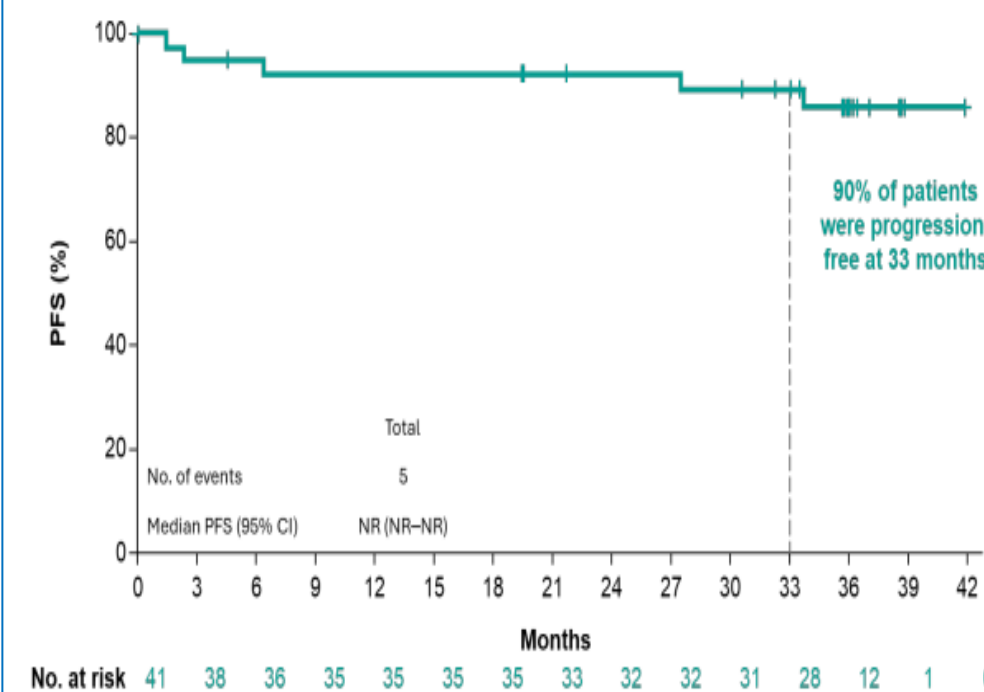
Arm 6 (1L FL): Deep and Durable Responses

	Epcoritamab + R ² N = 41
Overall response, n (%)	39 (95)
CR	36 (88)
PR	3 (7)
NE ^a	2 (5)



- Among 36 patients in CR:
 - 10 discontinued treatment for reasons other than PD or death^b
 - 90% (9/10) maintained CR^c
- Among 21 patients who completed treatment in CR
 - 95% (20/21) maintained CR
 - Median DOCR: NR^d
- MRD negativity^e (<10⁻⁶): 100%
 - 26/26 MRD-evaluable patients

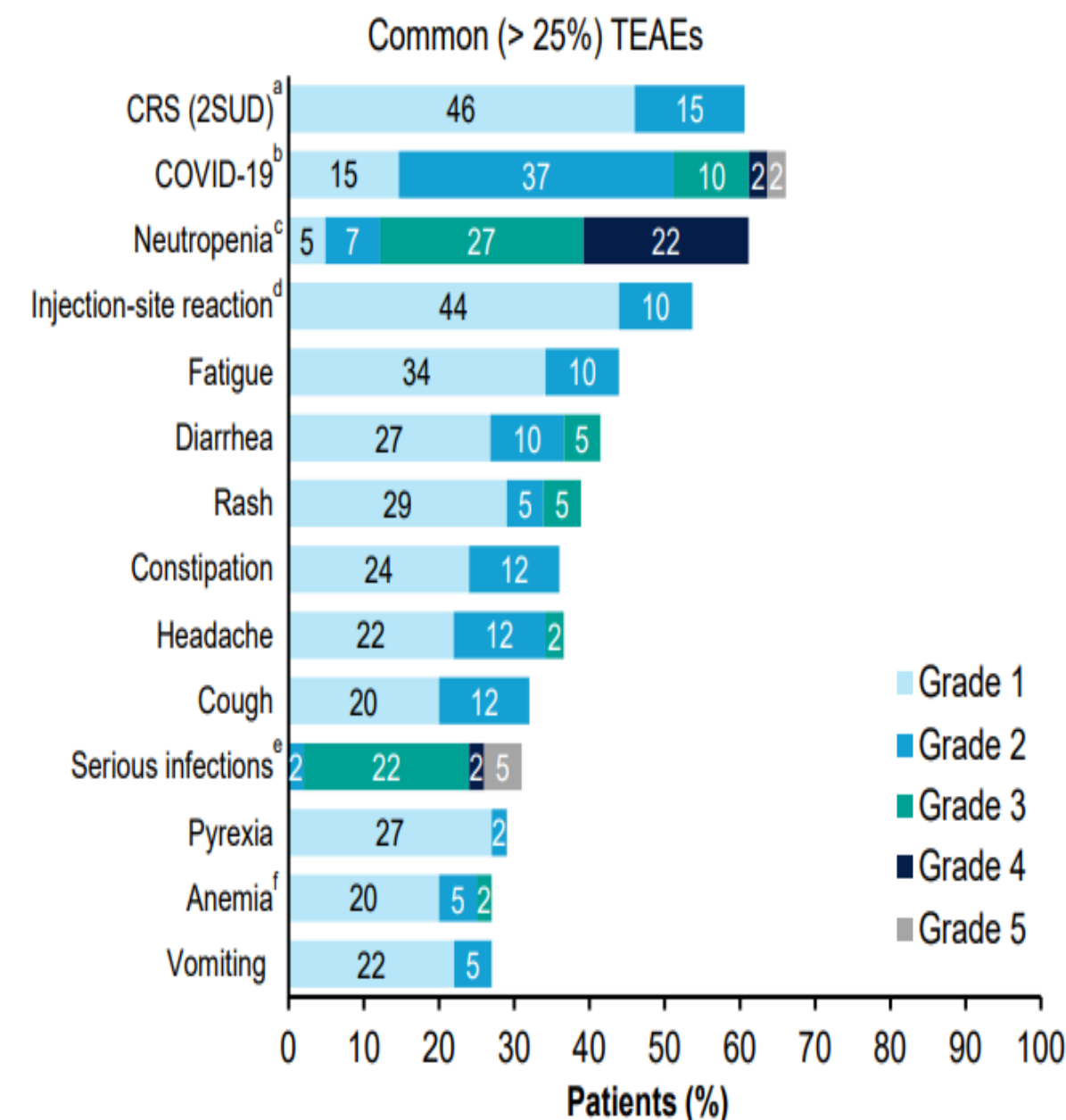
Arm 6 (1L FL): Favorable Long-Term Outcomes



- Median TTNT was NR; at 33 months, an estimated 97% (95% CI, 83–100) of patients had not received a new anti-lymphoma treatment

EPCORE NHL-2: ARM-6 Safety

Arm 6 (1L FL): Safety Profile



Overall

- Serious infections: 13 patients (32%); 7 occurred within the first 24 weeks
- Neutropenia: rates highest in the first 24 weeks; no febrile neutropenia observed
- CRS: all grade 1–2, resolved with supportive care, no discontinuations

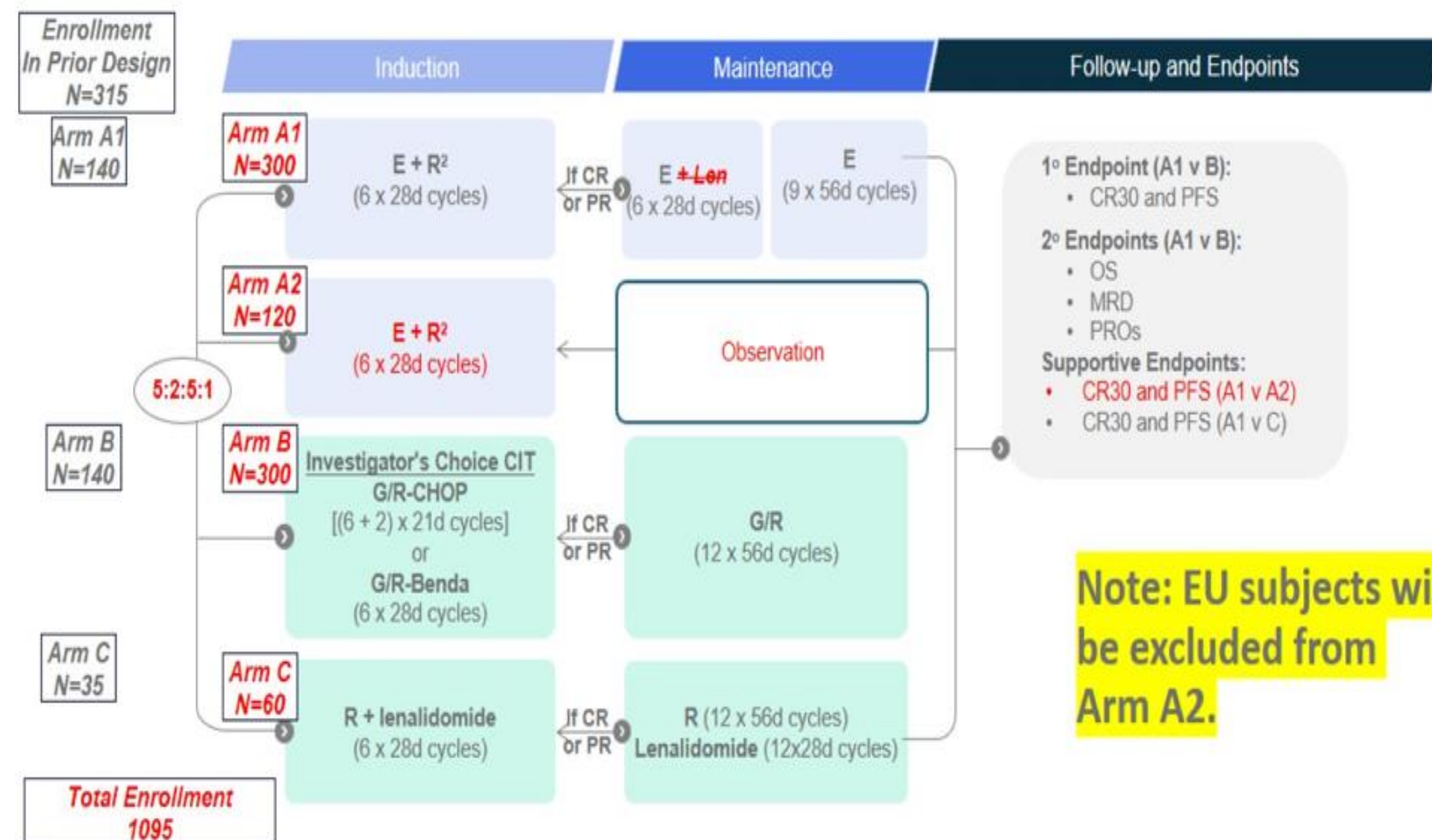
Long term

- TEAEs, including grade ≥3 events, declined over 2 years of epcoritamab treatment
- Since the last report with ~13 months of additional follow-up¹:
 - One new grade 3 COVID-19 TEAE
 - Two pneumonia TEAEs led to discontinuation
 - One death due to progressive multifocal leukoencephalopathy (PML)^g

^aCRS signs and symptoms included fever in 25 patients, hypotension in 8, hypoxia in 2 and other symptoms in 8 patients. Dose-optimization strategies from the NHL-1 FL optimization cohort, which included an additional SUD (including dexamethasone as the preferred steroid and adequate hydration), have shown significantly lower rates and severity of CRS. ^bCOVID-19 includes COVID-19 or COVID-19 pneumonia. ^cNeutropenia includes neutropenia or neutrophil count decreased. ^dLocal injection site reactions include injection site reactions as high-level group terms. ^eSerious infections include serious TEAEs in the system organ class of Infections and Infestations. ^fAnemia includes anemia, hemoglobin decreased, hemoglobin decreased, red blood cell count decreased, and serum ferritin decreased. ^gPrevious deaths were due to PD (n = 1), COVID-19 pneumonia (n = 1), septic shock (n = 1) and acute respiratory insufficiency (n = 1).
1. Falchi L, et al. *HemaSphere* 2024;8(Suppl 1). Abstract P1146. CRS, cytokine release syndrome.

7

A Phase 3, multicenter, randomized, open-label trial to evaluate the safety and efficacy of Epcor+ R2 versus CIT in previously untreated follicular lymphoma (EPCORE™FL-2)



Primary Endpoint

Complete Response rates at 30 months

Ongoing phase III trials in first line FL

STUDY	DRUGS	PATIENT N.	POPULATION	PRIMARY ENDPOINT
MorningLyte	Mosunetuzumab- lenalidomide vs R/G – CHOP/Benda	790	FLIPI 2-5 FL	PFS
SWOG 2308	Mosunetuzumab vs Rituximab	600	Low Tumor Burden stage 2-4 FL	PFS
M22-003	Epcoritamab-R2 vs R2 vs R/G –CHOP/Benda 900	900	Stage III –IV FL o bulky stage II	CR30
OLYMPIA-1	Odronextamab vs RCHOP/R Benda	473	Stage III –IV FL o bulky stage II	DLT, TEAE, CR30
OLYMPIA-2	Odronextamab- CHOP/CVP+/- manteinence vs R- CHOP	753	Stage III –IV FL o bulky stage II	DLT, TEAE, CR30
SOUNDTRACK –F1	AZD0486+RTX vs R- CHOP/CVP/Benda	1015	Stage III –IV FL and FLIPI 2-5	TEAE, RP3D,PFS

Evolving paradigms in FL therapy

Today FL stage III-IV, HTB	First line • ICT • Rituximab (full chemo-free program)	Second line POD24 • ICT + ASCT (?) • R2 Non-POD24 • R2	Third line + • BsAbs • CAR-T • Zanu-obinut. • Tazemetostat*
Tomorrow <i>Already anticipated Ph3 results</i> FL stage III-IV, HTB	• ICT • Rituximab	POD24 and non-POD24 • Len ± R + Tafa/BsAbs	• BsAbs • CAR-T • Zanu-obinut. • Tazemetostat*
Future view <i>Pending results of Ph3 ongoing trials</i> FL stage III-IV, HTB	• BsAbs ± X	• CAR-T (POD24) • Len ± R +Tafa/BsAbs • Zanu-obinut	• BsAbs • Novel agents • CAR-T • Zanu-obinut. • Len ± R +Tafa/BsAbs • Tazemetostat

FIGURE 1 Evolving paradigms in FL therapy. ASCT, autologous stem cell transplant; bsAbs, bispecific antibodies; FL, follicular lymphoma; HTB, high tumour burden; ICT, immunochemotherapy; Len, lenalidomide; Ph3, phase 3 trials; R2, rituximab-lenalidomide; Tafa, tafasitamab; Zanu-obinut, zanubrutinib obinutuzumab. *Only FDA approved.

Conclusions

First line therapy has a critical role in determining:

- «functional» cure
- long term events

First line is not just a matter of options but of strategy

Chemo free options are valid alternatives to ICT: Frail/old populations or other?

The increase number of chemo free options will be able to improve outcomes?

- OS?
- Risk of transformations
- Late events (SPM, Infections)