

The young side of
LYMPHOMA

gli under 40 a confronto

Reggio Emilia, Hotel Mercure Astoria
2-3 ottobre 2026

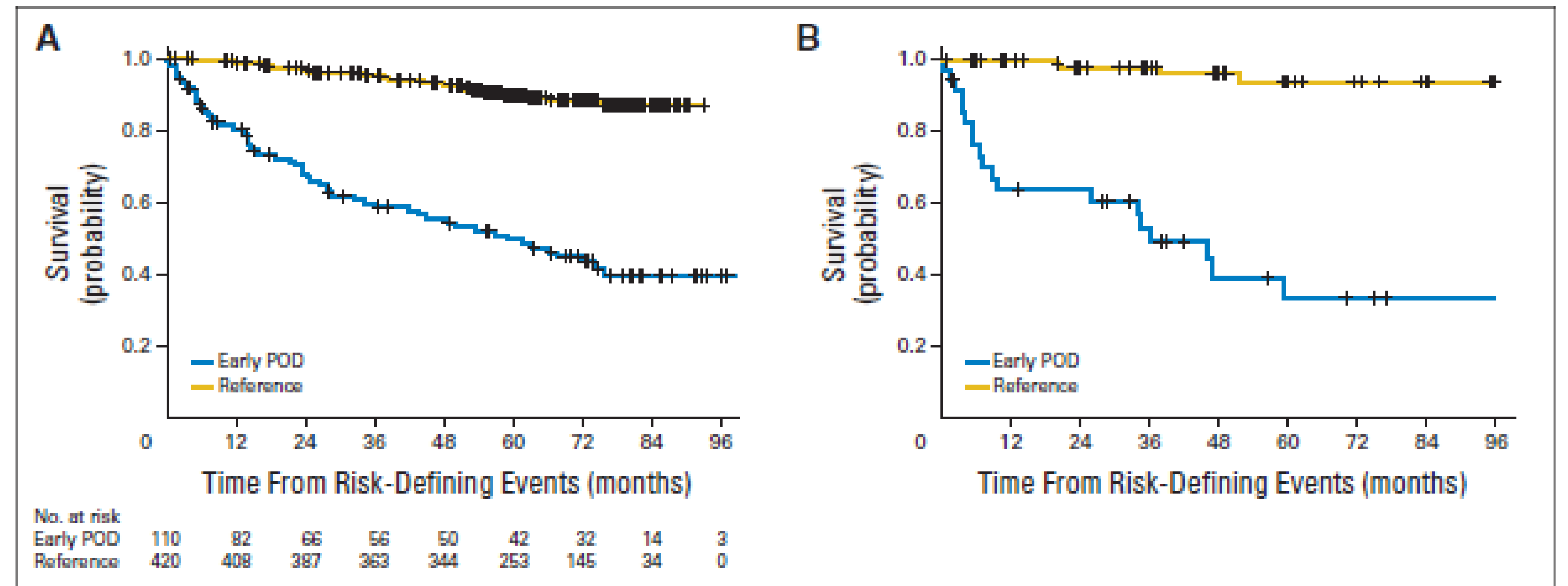
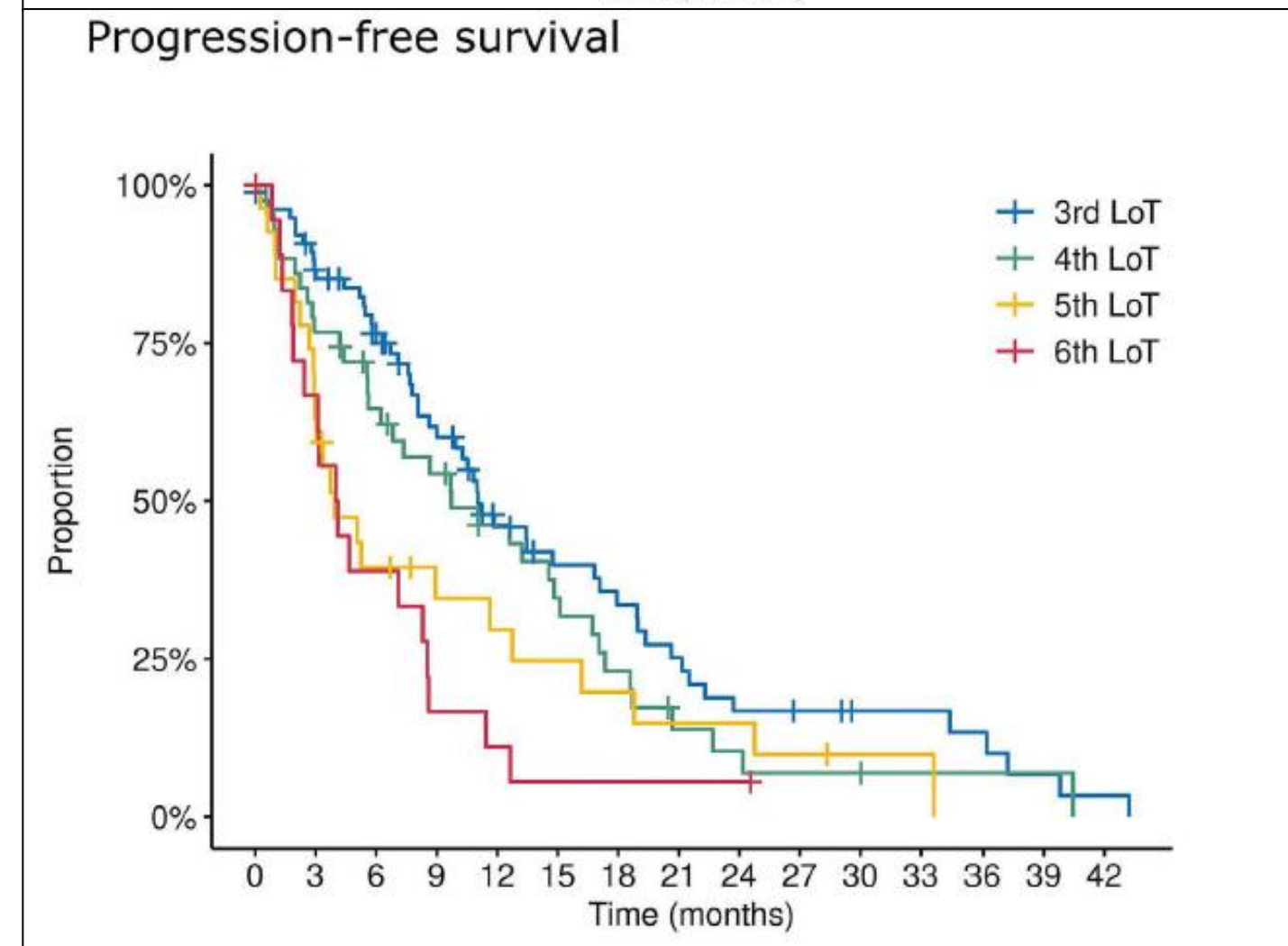
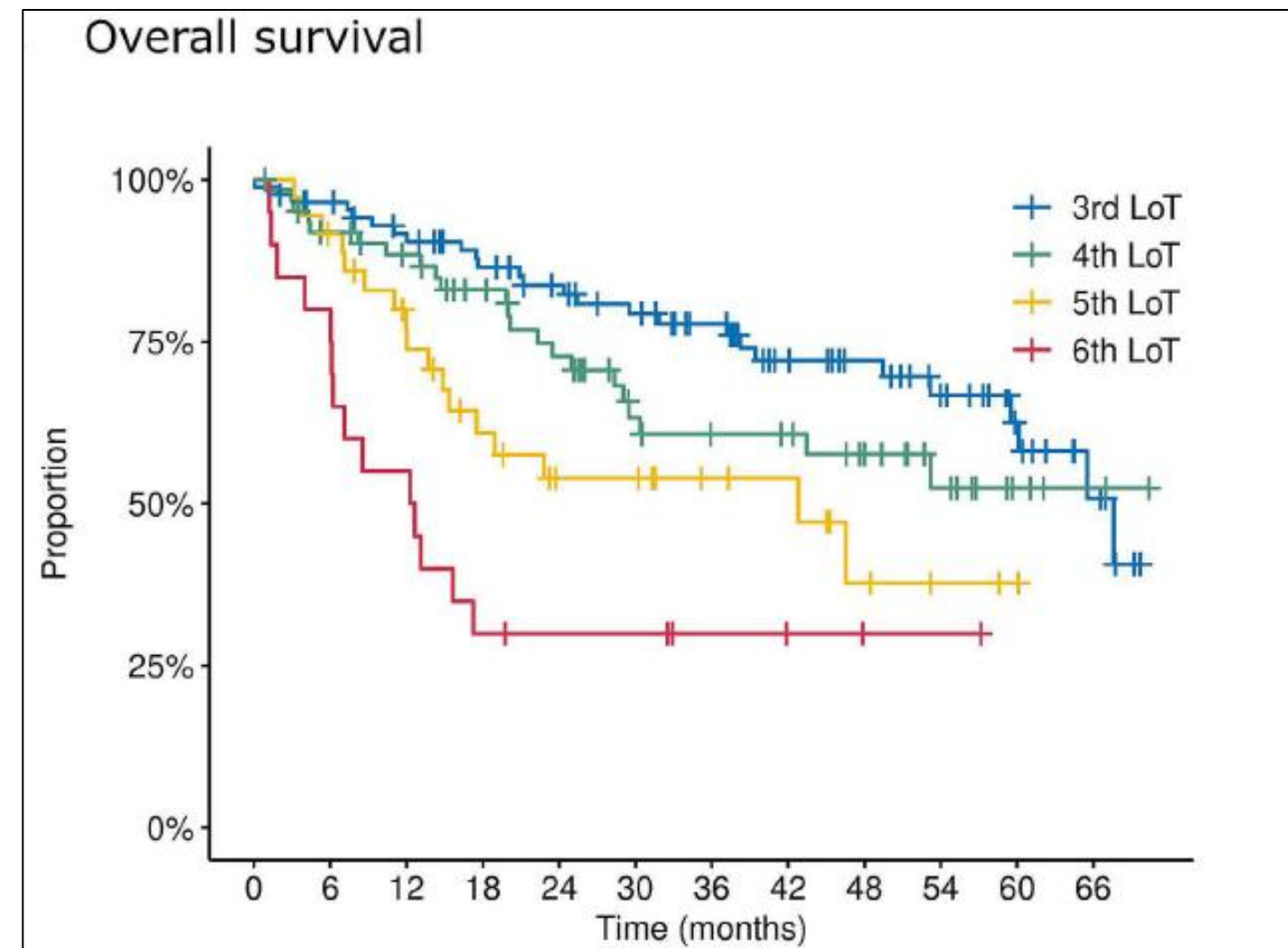
Terapia chemo-free nel linfoma follicolare r/r

Dott.ssa Elena Flospergher

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
none							

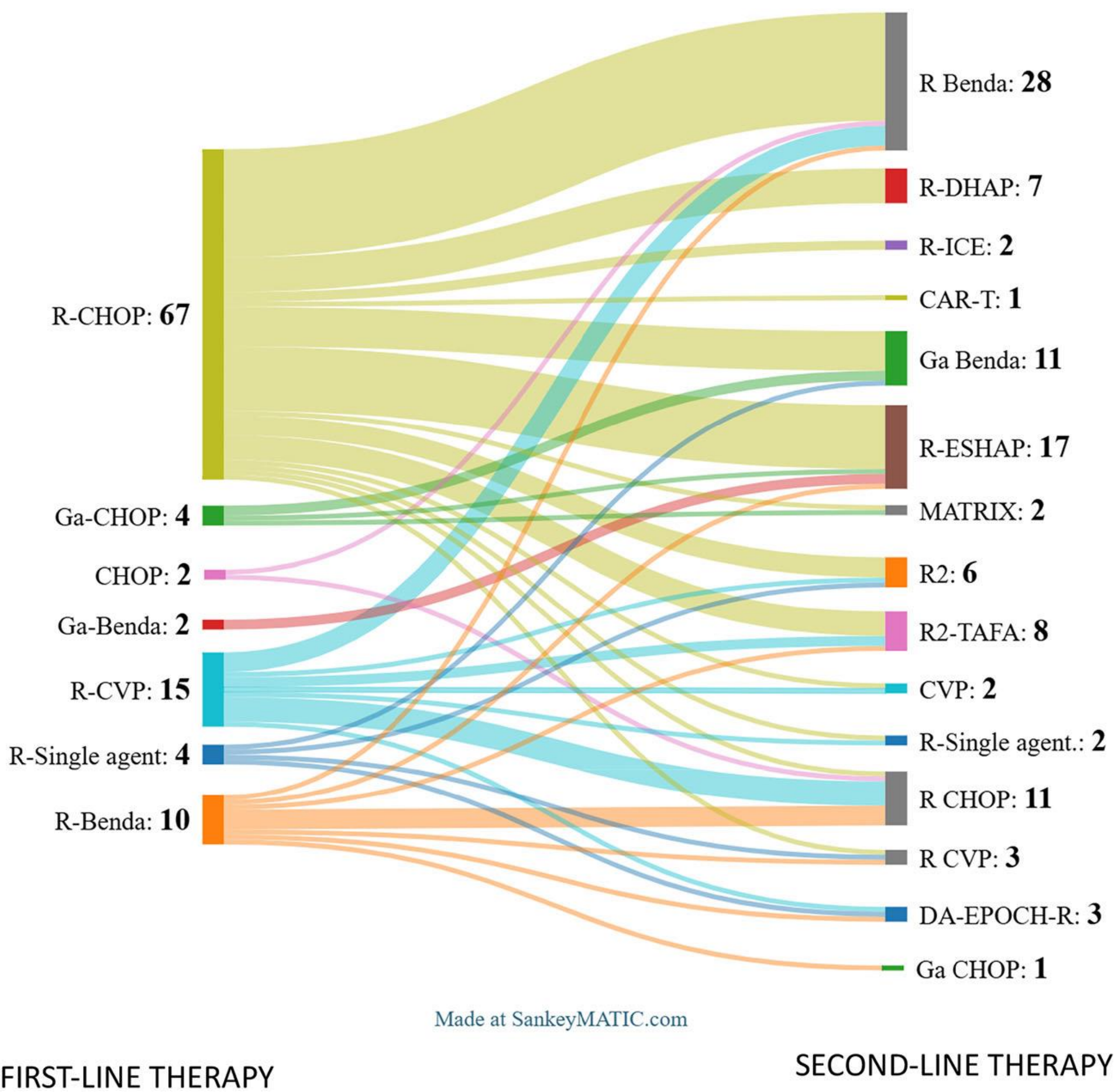
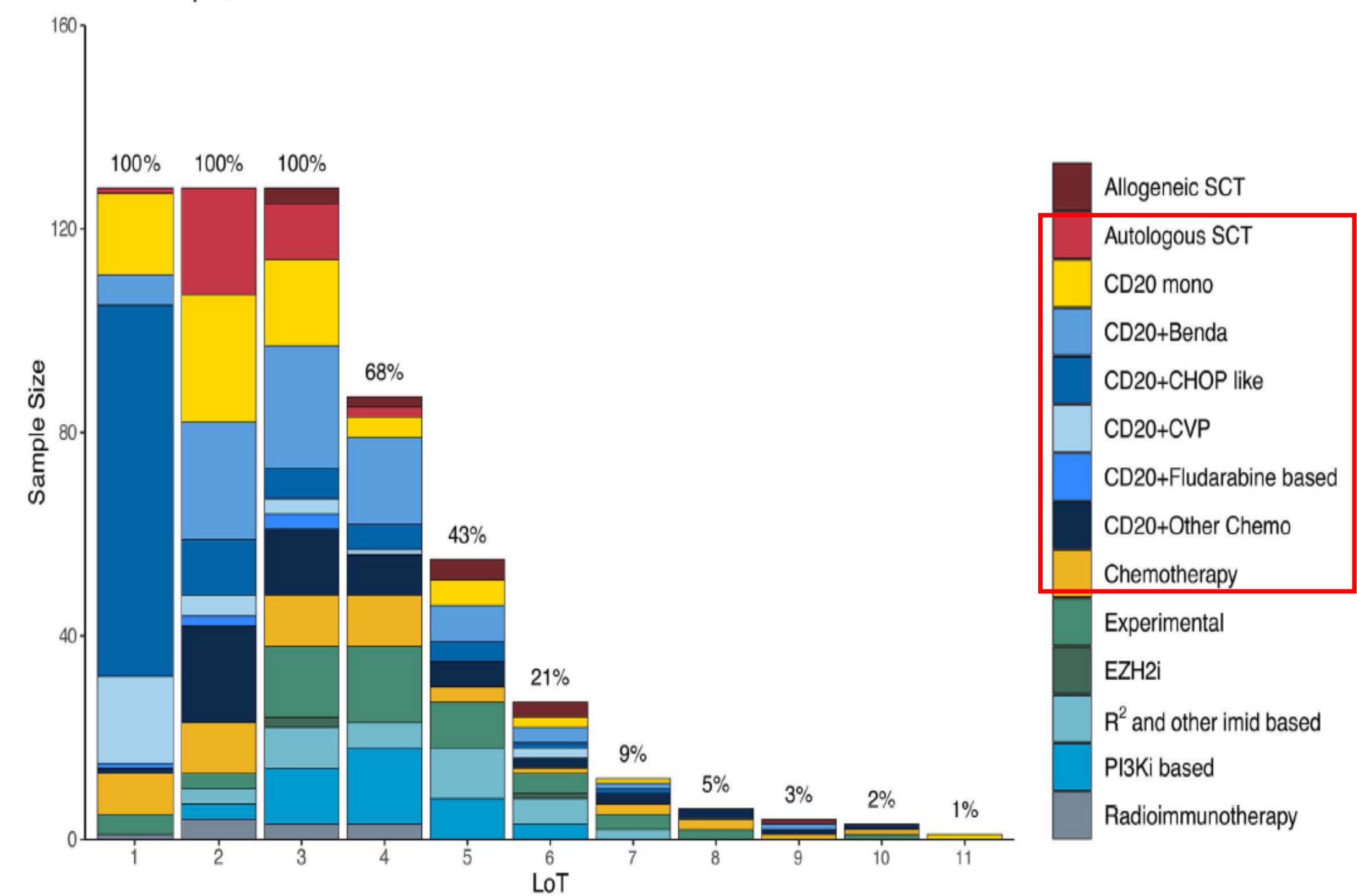
DA COSA PARTIVAMO...



- nessuna terapia standard
- outcomes peggiori a ogni linea successiva
- 20% POD24 (dopo CIT) outcomes peggiori: 5y OS 50% vs 90%!

DA COSA PARTIVAMO...

A Treatment patterns across all LoT



CASO CLINICO 1: F, 1961

02/2015: FL G2, stadio III, FLIPI low, diagnosi su biopsia In inguinale

APR: DM2 dal 2007 in terapia insulinica, ipertensione arteriosa dal 2015 in terapia, pregressa safenectomia sx nel 2007, ipercolesterolemia, pregressa eradicazione HP 12/2014 e 01/2023

R-CHOP x6 (ultimo 09/2015)>RP

R mantenimento 8 cicli trimestrali (fino 10/2017)>RC

02/2020 recidiva FL variante diffusa (biopsia In sovraclaveare dx), non criteri GELF→FU

06/2021 PD (biopsia In inguinale dx: FL variante diffusa) stadio IV (BOM+), GELF+

R-CVP x6 (ultimo 01/2022) >RP dopo 3 cicli, PD dopo 6 cicli >biopsia In inguinale dx 03/2022: FL variante diffusa, CD20+ > proposto arruolamento a trial con Epcoritamab, la paziente rifiutava

Idelalisib 04/2022-08/2023 iniziale RP poi PD 08/2023

Cosa fareste?

Opzioni disponibili c/ o HSR 09/2023:

- **RB**
- **ASCT**
- **R2**
- **mosunetuzumab CUP**
- **CAR-T (Tisacel)**
- **protocollo sperimentale: ZUMA22 (Axicel vs SOC)**
- **protocollo sperimentale: M20-638 (epco-R2 vs R2)**

CASO CLINICO 2: F, 1946

02/2016: FL G1 stadio IV BOM+, diagnosi su biopsia In inguinale

APR: ipertensione arteriosa in terapia, pregressa TBC nel 1972 trattata con terapia non specificata, appendicectomia, pregressa asportazione fibromi uterini, osteoporosi con cedimenti vertebrali 2019, 09/2024 carcinoma infiltrante mammario sottoposto a quadrantectomia+letrozolo

no GELF: **W&W**

08/2017 PD linfonodale sopra e sottodiaframmatica (GELF+) e SVP+

R-CHOP x6 (ultimo 01/2018)>RC (BOM-)

R mantenimento 12 cicli bimestrali (ultimo 01/2020) >RC

09/2020 iniziale PD: proseguito FU

03/2022 ulteriore PD+sudorazioni notturne+LDH 380: biopsia In ascellare FL> proposto arruolamento a trial con Epcoritamab, la paziente rifiutava

R-Benda x6 (ultimo 11/2022)> RC

06/2023 recidiva, no GELF: FU

03/2024 PD: biopsia In inguinale LF G2 > proposta terapia con CAR-T, la paziente rifiutava

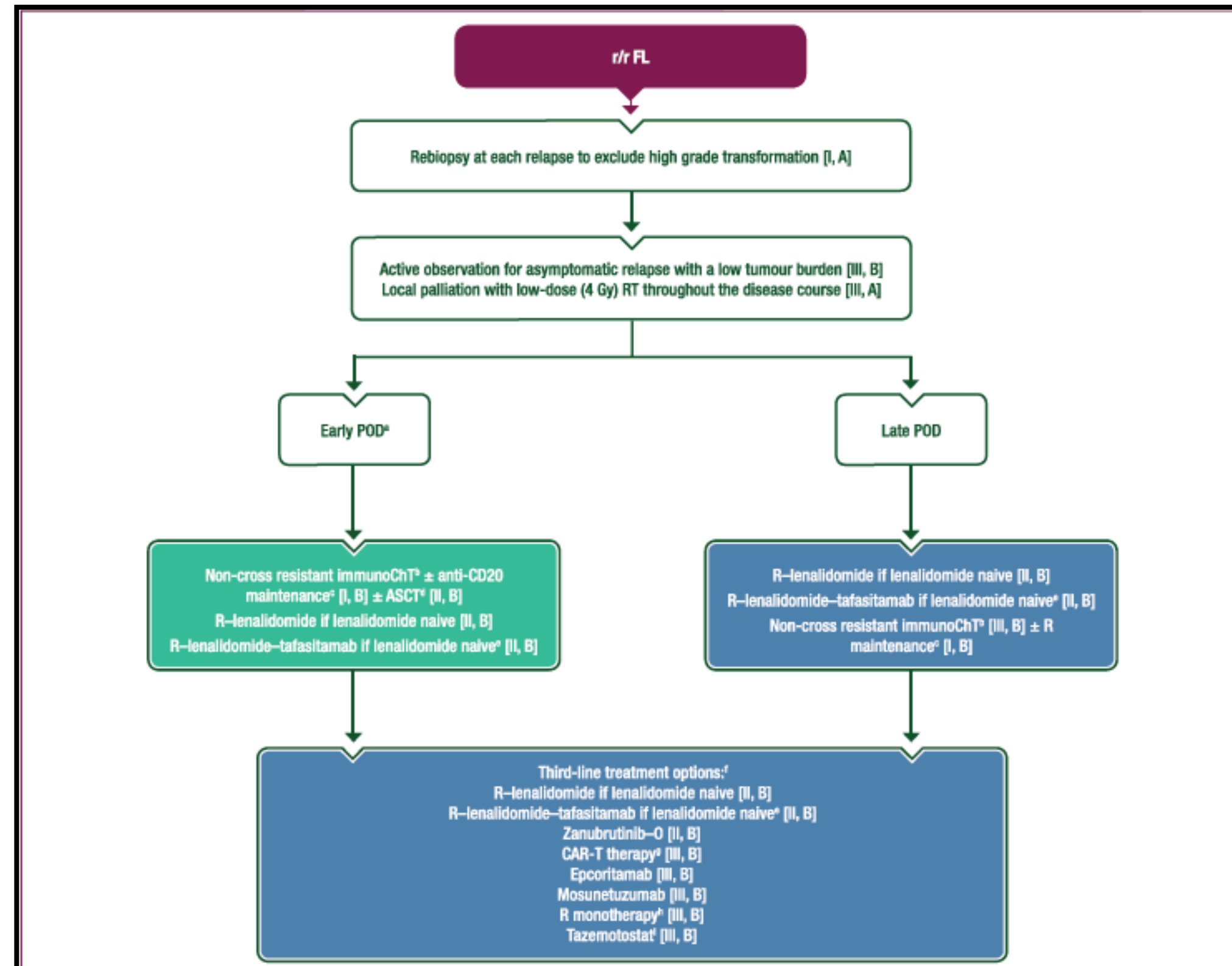
R2 dal 10/05/2024, durante C1 polmonite con FA, ripresa terapia alla risoluzione, impostata supplementazione IgEV. Alla rivalutazione dopo C2 mRP.

C5 09/2024 poi stop per intervento per carcinoma mammario

11/2024 PD

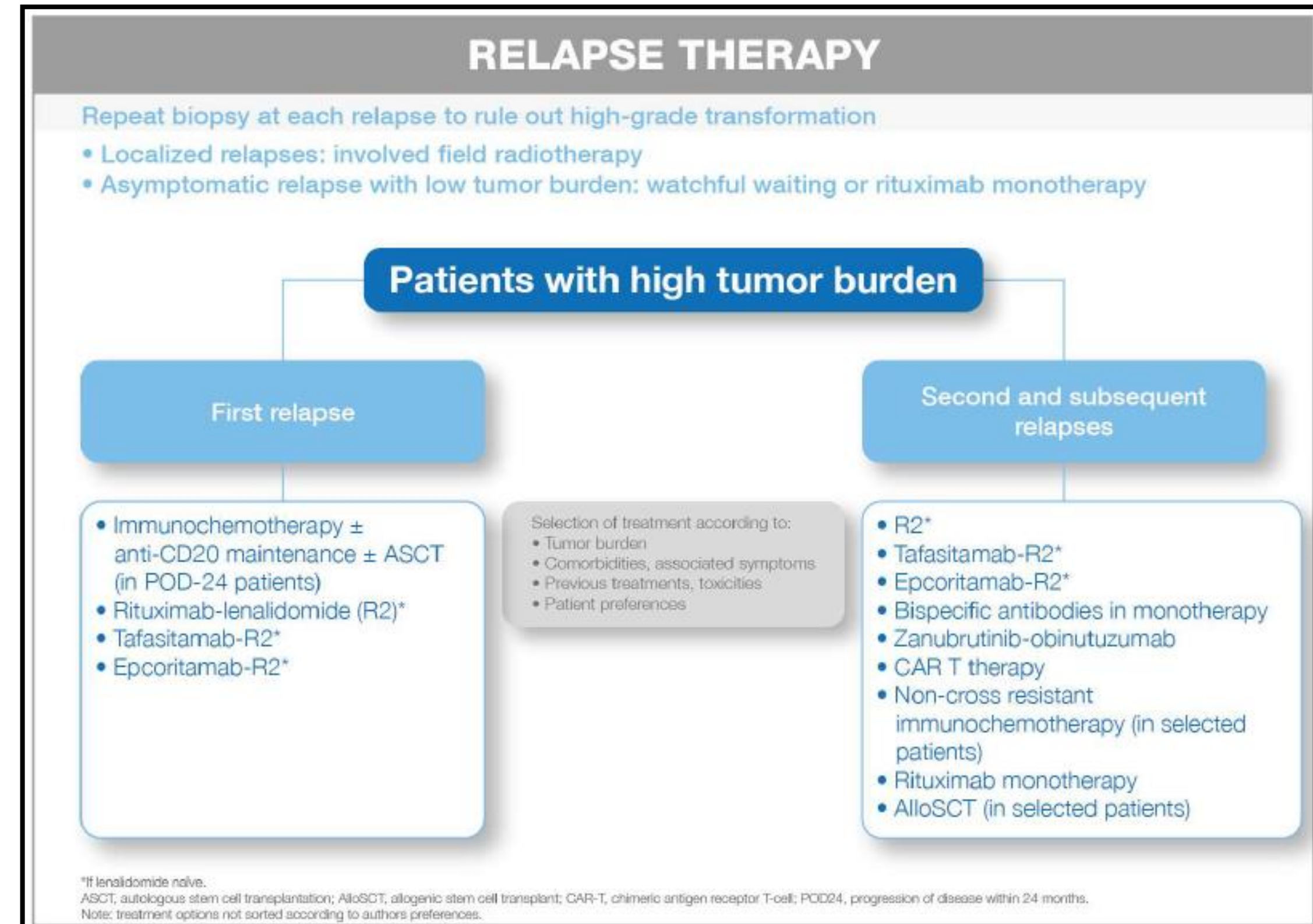
Cosa fareste?

COSA POSSIAMO FARE OGGI/FAREMO A BREVE



SUGGESTED TREATMENT REGIMENS^{a,b,c}

SECOND-LINE THERAPY ⁱ
Preferred (in alphabetical order) • Bendamustine^{d,j} + Obinutuzumab^{e,f} or Rituximab (not recommended if treated with prior Bendamustine) • CHOP + Obinutuzumab^{e,f} or Rituximab • CVP + Obinutuzumab^{e,f} or Rituximab • Lenalidomide + Rituximab + Epcoritamab-bysp^{k,l} (category 1) • Lenalidomide + Rituximab + Tafasitamab-cxix^{l,m} (≥1 prior systemic therapy including an anti-CD20 mAb) (category 1)
Other recommended (in alphabetical order) • Lenalidomide (if not a candidate for anti-CD20 mAb therapy) • Lenalidomide + Obinutuzumab or Rituximab • Obinutuzumab • Rituximab
SECOND-LINE THERAPY FOR OLDER OR INFIRM (if none of the therapies are expected to be tolerable in the opinion of treating physician)
Preferred • Rituximab (375 mg/m² weekly for 4 doses)
SECOND-LINE EXTENDED THERAPY (optional)
Preferred • Rituximab maintenance 375 mg/m² one dose every 12 weeks for 2 years (category 1) • Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

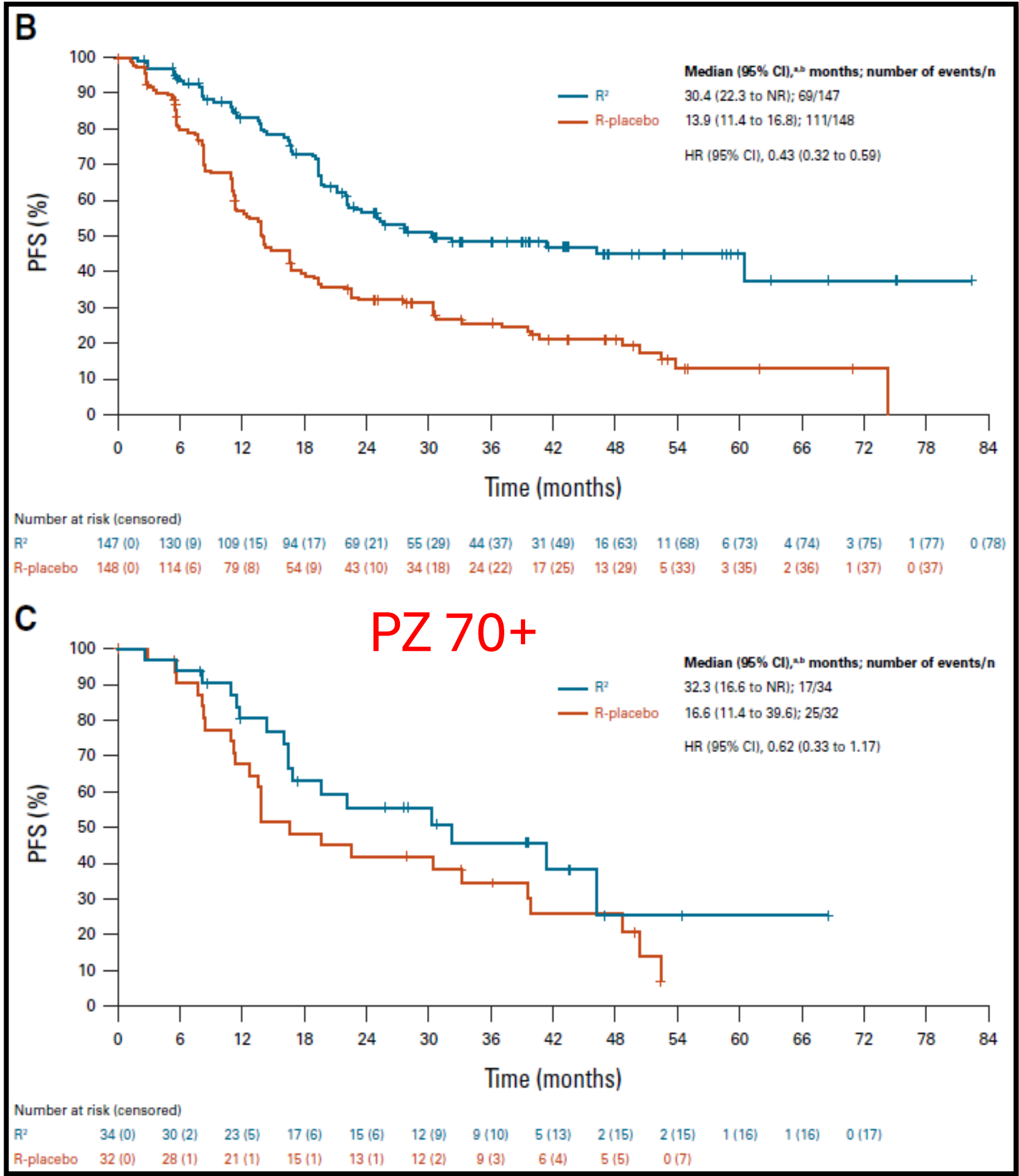


SUGGESTED TREATMENT REGIMENS^{a,b,c}

THIRD-LINE AND SUBSEQUENT THERAPY	
Second-line therapy regimens (FOLL-B 2 of 6) that were not previously given can also be used as options for third-line and subsequent therapy	
Preferred (in alphabetical order) • T-cell mediated therapy^k ▶ Bispecific antibody therapy^l ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb (IV or SC)^m ▶ Chimeric antigen receptor (CAR) T-cell therapy^{n,o} ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	Other recommended • BTK inhibitor (BTKi) ▶ Zanubrutinib^l + Obinutuzumab • Loncastuximab tesirine-lpyl^{l,n} + Rituximab (category 2B)

THIRD-LINE CONSOLIDATION THERAPY
Useful in Certain Circumstances • Allogeneic hematopoietic cell transplantation (HCT) in selected cases^p

AUGMENT: RITUXIMAB-LENALIDOMIDE(R2) vs R 2L+

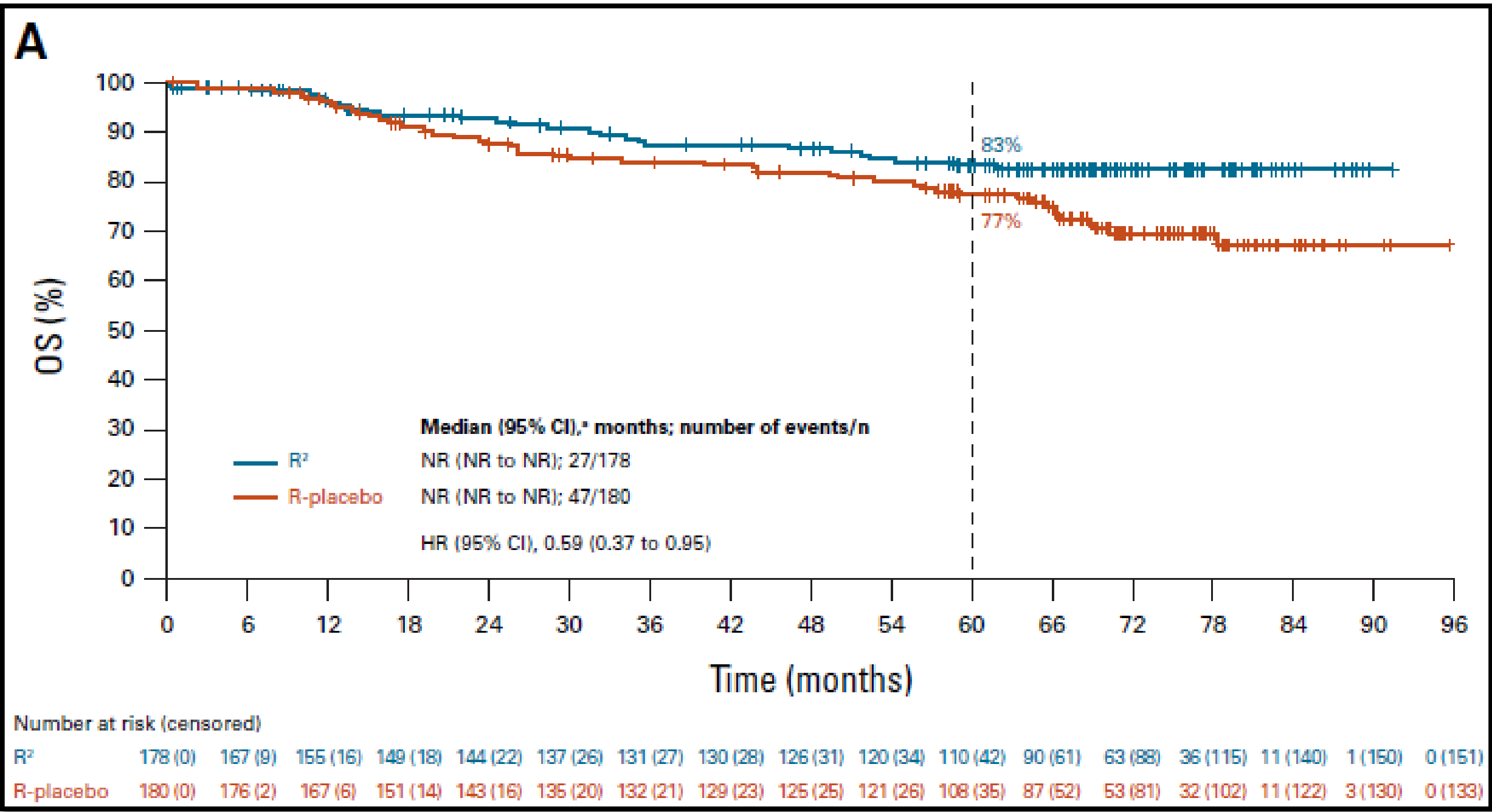


358 pazienti (FL 80%), GELF+ solo 50%, esclusi refrattari a R

ORR 78% vs 53%, CR 34% vs 18%

mPFS 30 m vs 14m (identica nei pz 70+): **R2 riduce il rischio di PD del 50% rispetto a R**

Benefit confermato anche in OS



REAL LIFE: 84 pz (inclusi refrattari a R)

ORR 82% CR 52% mPFS 22 m

Poorer PFS: refrattari a R, bulky, NO POD24

Meno tossicità vs AUGMENT

Leonard JP, AUGMENT Trial, J Clin Oncol. 2019

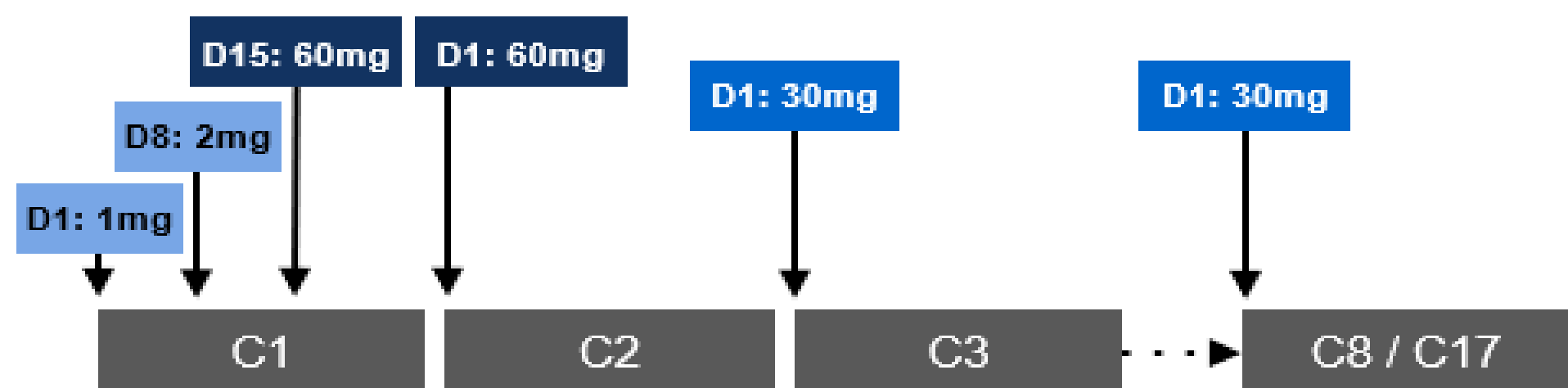
Leonard JP, 5y AUGMENT Trial. J Clin Oncol. 2026

Cassanello G, Haematologica 2025

GO29781: MOSUNETUZUMAB 3L+

Mosunetuzumab administration (N=90)

- Q3W IV administration
 - 8 cycles if CR after C8
 - 17 cycles if PR/SD after C8



21-day cycles

- Fixed duration treatment
- C1 step-up dosing for CRS mitigation
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR

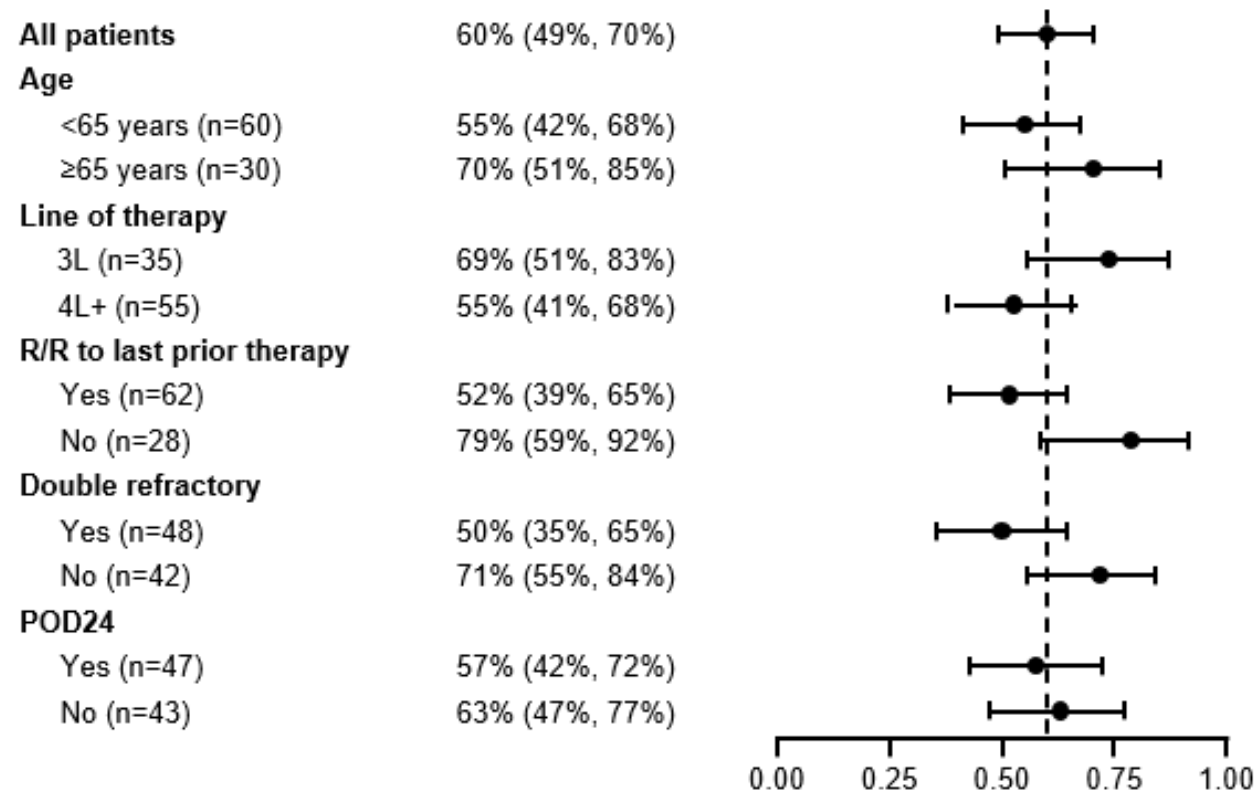
- Mediana linee di terapia 3
- Refrattari ad antiCD20 79%
- Double ref 53%
- POD24 52%

CR 60% ORR 80%
tempo alla risp 1.4 mesi

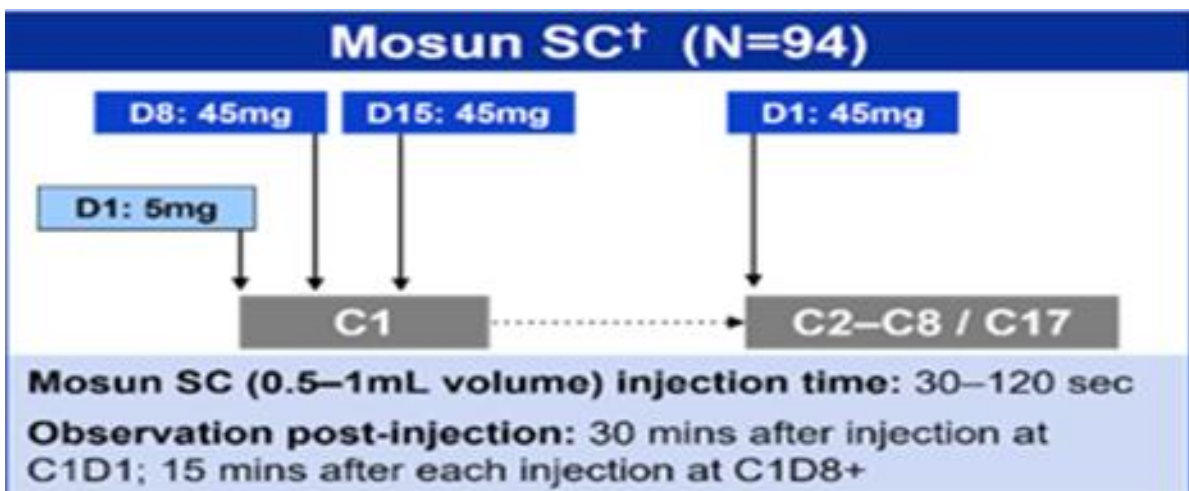
DOCR 5y 52%
PFS 5y 36% pz in CR 57%
OS 5y 78% pz in CR 92%

- CRS 40% G3 2%
- Recurrent CRS 21%
- ICANS 4.4% G3+ 0%
- Neutropenia G3-4 27%
- No neutropenia febbrile
- Infez 50% G3+ 16%

CR rate (95% CI) by IRF



GO29781: mosu sc 3L+



CRS meno
frequente e meno
grave vs mosu iv

Budde LE, Lancet Oncol. 2022

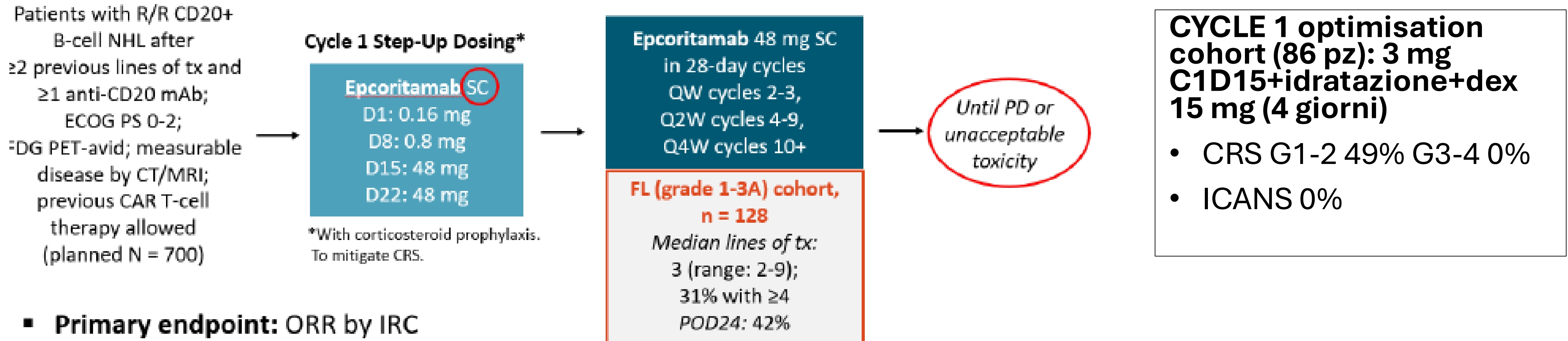
Budde LE, 3y FU, Blood. 2025

Buddle LE, 5y FU, ASH 2025

Bartlett NL, Am J Hematol. 2026

EPCORE NHL-1: EPCORITAMAB 3L+

- Phase I/II open-label, dose escalation/expansion study



- Primary endpoint: ORR by IRC

ORR 82% CR 63% MRDneg 67% **pneumoniae)**

Tempo mediano alla risp 1.4 mesi

meno efficace nelle linee 4+ e nei pazienti ad alto rischio

mDOR 36m, 3y PFS 51%, 3y OS 82%

3y discount 63%: PD 34%, AE 19%(COVID19/COVID19

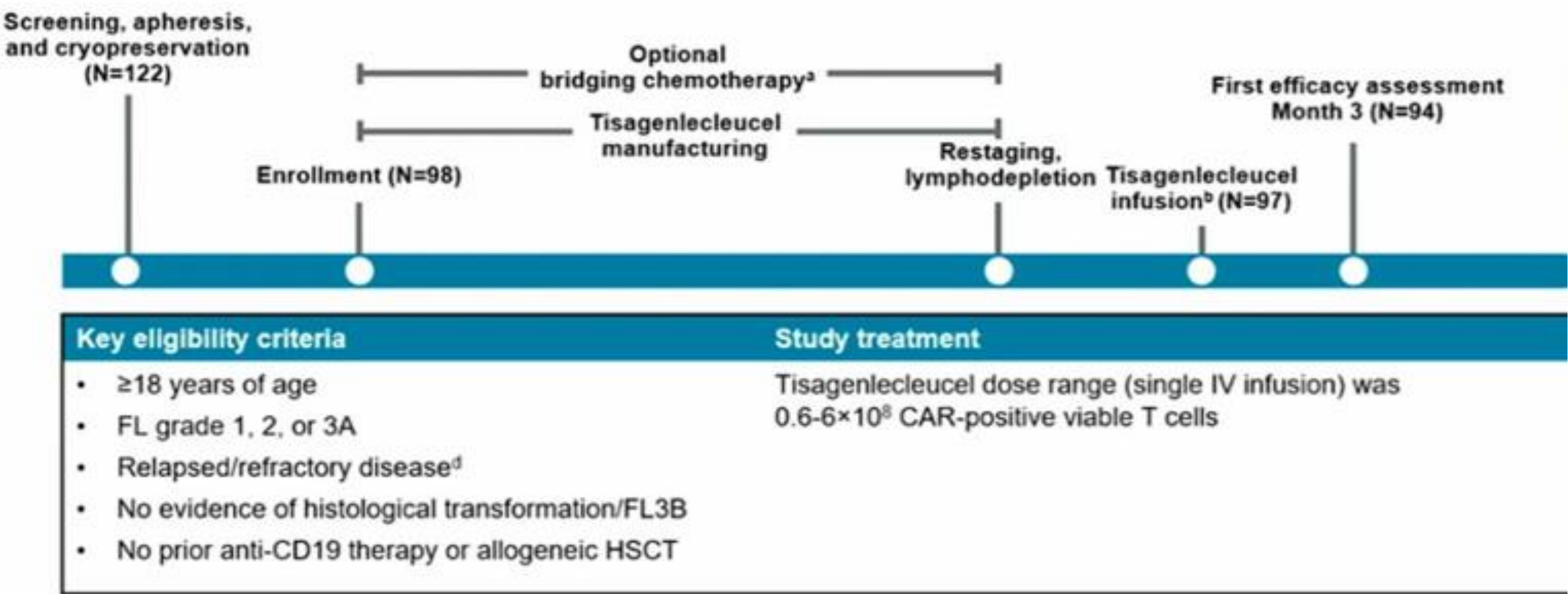
CRS G1-2 65% G3 2% G4 0%

ICANS 6% G3-4 0%

Neutropenia 30%, neutropenia febbrile 3%

Infezioni 69% G3-4 20% fatali 2% (2 polmoniti COVID, 1 PML)

ELARA: TISACEL 3L+



	ORR	CRR
POD24	82%	59%
High TMTV	75%	40%
Bulky Disease	86%	65%
High FLIPI	81%	61%
Double Refractory	85%	66%

ORR 86% CR 69% MRDneg 75% 3m
mDOR NR, 4y DOR 61%
mPFS 53m, 4y PFS 50% (nei CR 66%)
4y OS 79% (anche in POD24 e double ref.)

CRS 48% G3+ 0%
ICANS 4% G3+ 1%
Neutropenia 43%, febbre 8%
SPM 6%

Età mediana 57y
Mediana linee precedenti 4 (2-13)
68% double ref
65% POD24
64% bulky

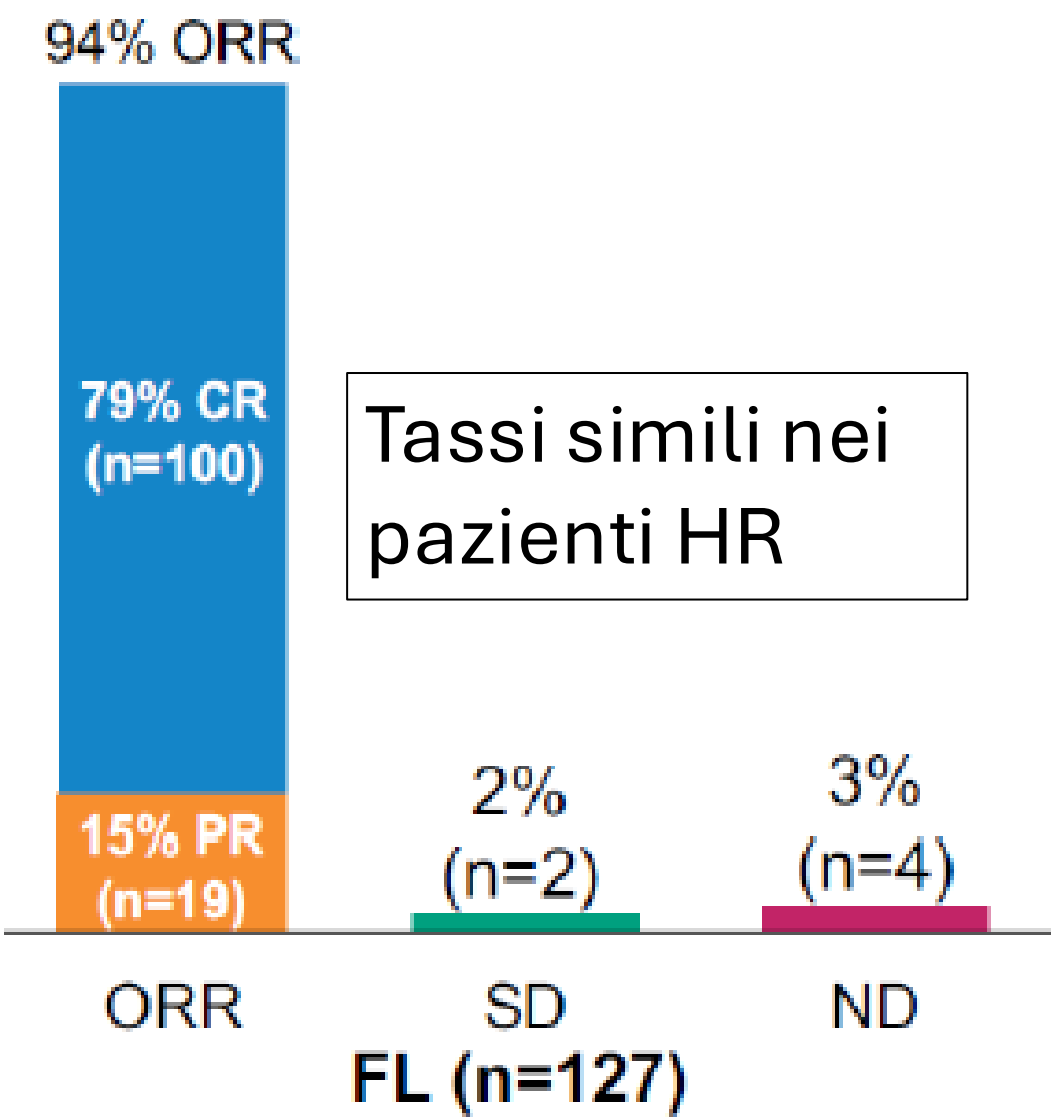
45% tp bridge
Tempo mediano da arruolamento a
infusione 46d

Fowler NH, ELARA trial, Nat Med. 2022
Dreyling M, ELARA update, Blood 2024
Thieblemont, update 4y, abstract ICML 2025

ZUMA-5: AXICEL 3L+

Characteristic	FL (n = 127)
Age, years, median (range)	60 (34-79)
≥65 years, No. (%)	40 (31)
Male sex, No. (%)	75 (59)
ECOG PS 1, No. (%)	48 (38)
Stages II-IV disease, No. (%)	109 (86)
High-risk FLIPI (≥3), No. (%)	56 (44)
High tumor bulk (GELF criteria), No. (%) ^b	65 (51)
Prior therapies, No., median (range) ^c	3 (1-10)
≥3 prior lines of therapy, No. (%)	80 (63)
R/R subgroup, No. (%)	
Refractory to last prior therapy	87 (69)
POD24 from initiating first anti-CD20 mAb-containing therapy ^d	70 (56)
Lymphoma present in bone marrow, No. (%) ^e	35 (28)

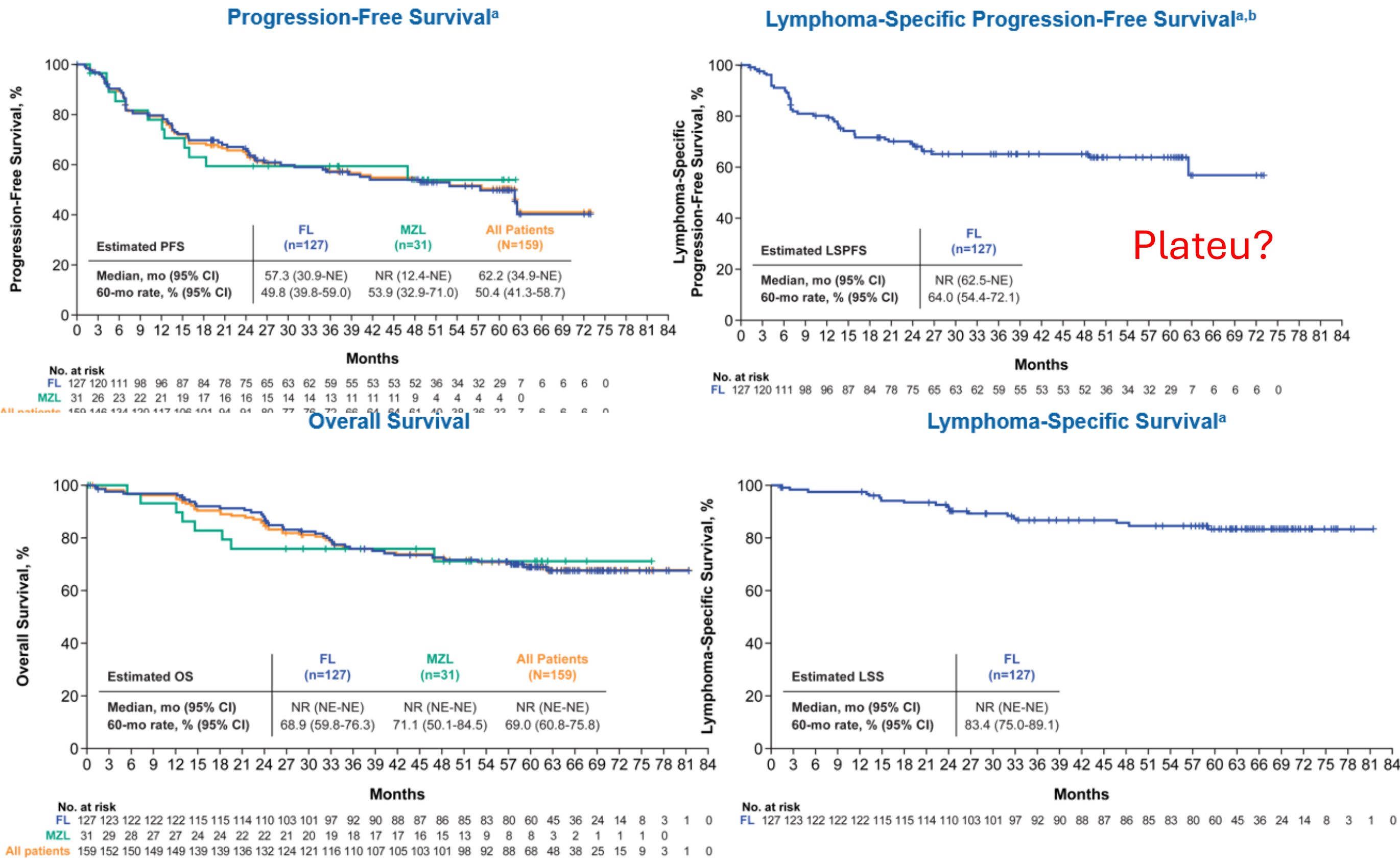
3% tp bridge
Tempo mediano da arruolamento a infusione 31d



60m DOR 53% DOCR 58%
mTTNT NR
60m PFS 50%: 61% se CR vs 9% se PR
60m OS 69%

CRS 78% G3+ 6% G5 1

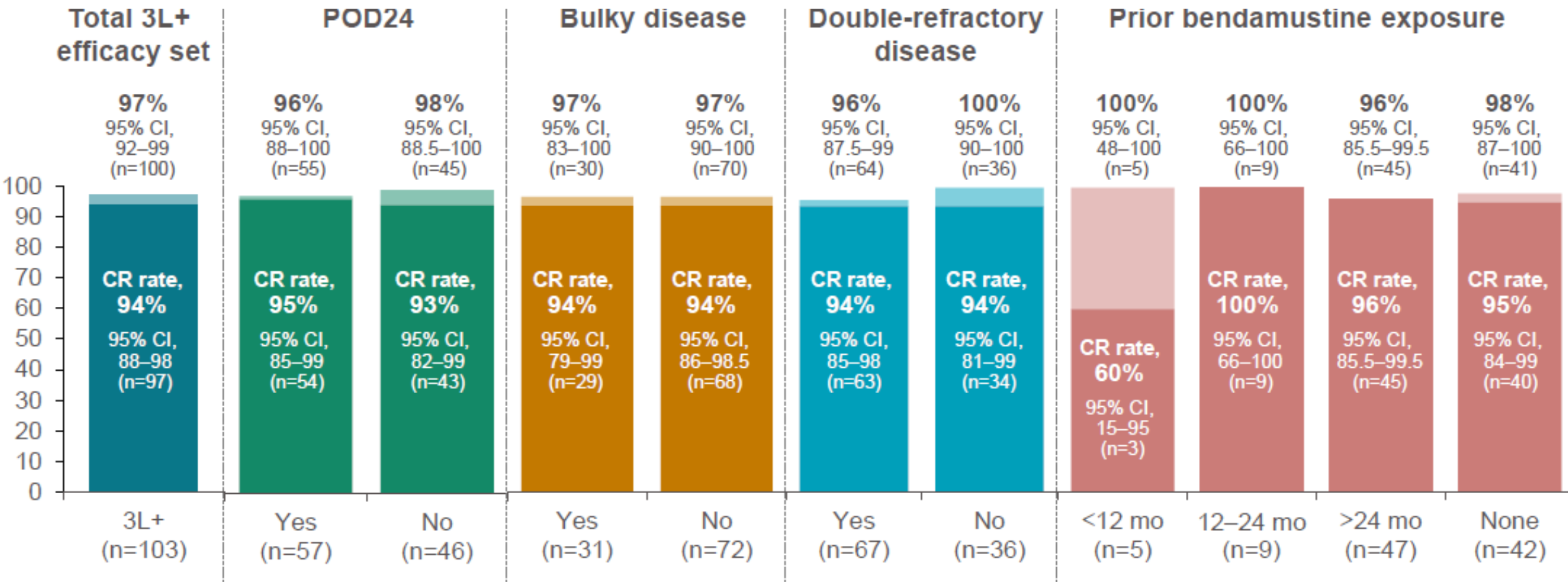
NE 50% CR 15% G5 20%



Jacobson CA, Lancet Oncol. 2022
Neelapu SS, 3y FU, Blood 2024
Neelapu SS, 5y FU, J Clin Oncol. 2025

TRASCEND FL: LISOCEL 2L+

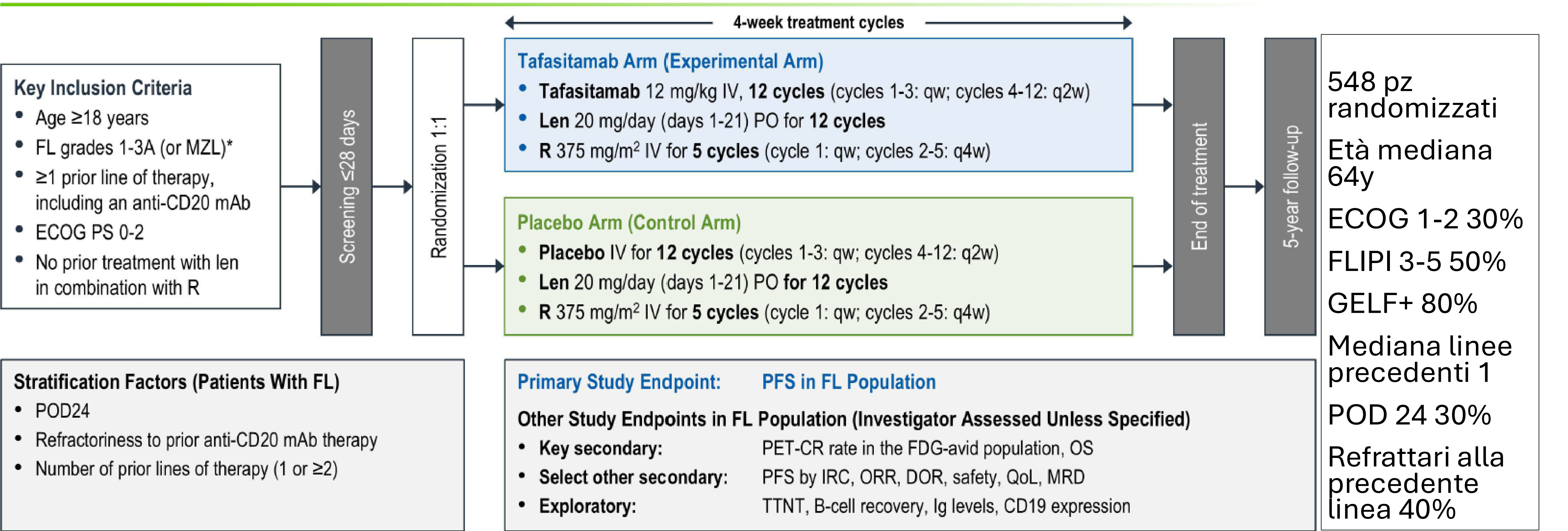
	3L+ FL (n=107)	2L FL (n=23)	2L+ FL (n=130)
Median age (range), years	62 (23–80)	53 (34–69)	60 (23–80)
Ann Arbor stage at screening, n (%)			
Stage I/II	12 (11)	6 (26)	18 (14)
Stage III	39 (36)	6 (26)	45 (35)
Stage IV	56 (52)	11 (48)	67 (52)
FLIPI at screening, n (%)			
Low risk (0–1)	12 (11)	11 (48)	23 (18)
Intermediate risk (2)	34 (32)	4 (17)	38 (29)
High risk (3–5)	61 (57)	8 (35)	69 (53)
mGELF criteria met at time of most recent relapse, n (%)	57 (53)	16 (70)	73 (56)
Median prior lines of systemic therapy (range)	3 (2–10)	1 (1–1)	2 (1–10)
Prior HSCT ^a , n (%)	33 (31)	0	33 (25)
Received prior rituximab and lenalidomide, n (%)	23 (21)	0	23 (18)
Prior bendamustine, n (%)			
No prior bendamustine	42 (39)	17 (74)	59 (45)
Prior bendamustine ≤6 months before leukapheresis	4 (4)	1 (4)	5 (4)
Prior bendamustine >6 months and ≤12 months before leukapheresis	4 (4)	2 (9)	6 (5)
Prior bendamustine >12 months before leukapheresis	57 (53)	3 (13)	60 (46)
Refractory to systemic therapy ^d , n (%)	38 (36)	3 (13)	41 (32)
PD while on the last LOT or ≤6 months of completing the last LOT, n (%)	69 (64)	15 (65)	84 (65)
POD24 from diagnosis ^e , n (%)	46 (43)	12 (52)	58 (45)
FL progression ≤24 months of first-line therapy with anti-CD20 antibody and alkylator, n (%)	58 (54)	15 (65)	73 (56)
Double refractory (anti-CD20 + alkylator) ^f , n (%)	69 (64)	11 (48)	80 (62)



- median 29d availability, 49d infusion
- Bridging therapy 38%
- 2L HR (POD24/mGELF) ORR 96% CR 96%
- **3L+ ORR 97% CR 94%: tassi uguali POD24 (axi e tisa no!)**
- mDOR/mPFS/mTTNT NR
- 3L+: 3y DOR 70% PFS 68% OS 86%
- CRS 58% G3 1%
- ICANS 15% G3 2%
- **Infezioni G3+ 5%**, infez tardive (29d+) 1%
- prolonged citopenia (29d+) 22% maggior parte risolte entro d90
- **Meno infezioni G3+, prolonged citopenia e necessita di toci/cs in 2L vs 3L+**
- 2 related deaths: 1 G5 MAS/HLH, 1 PML after d90

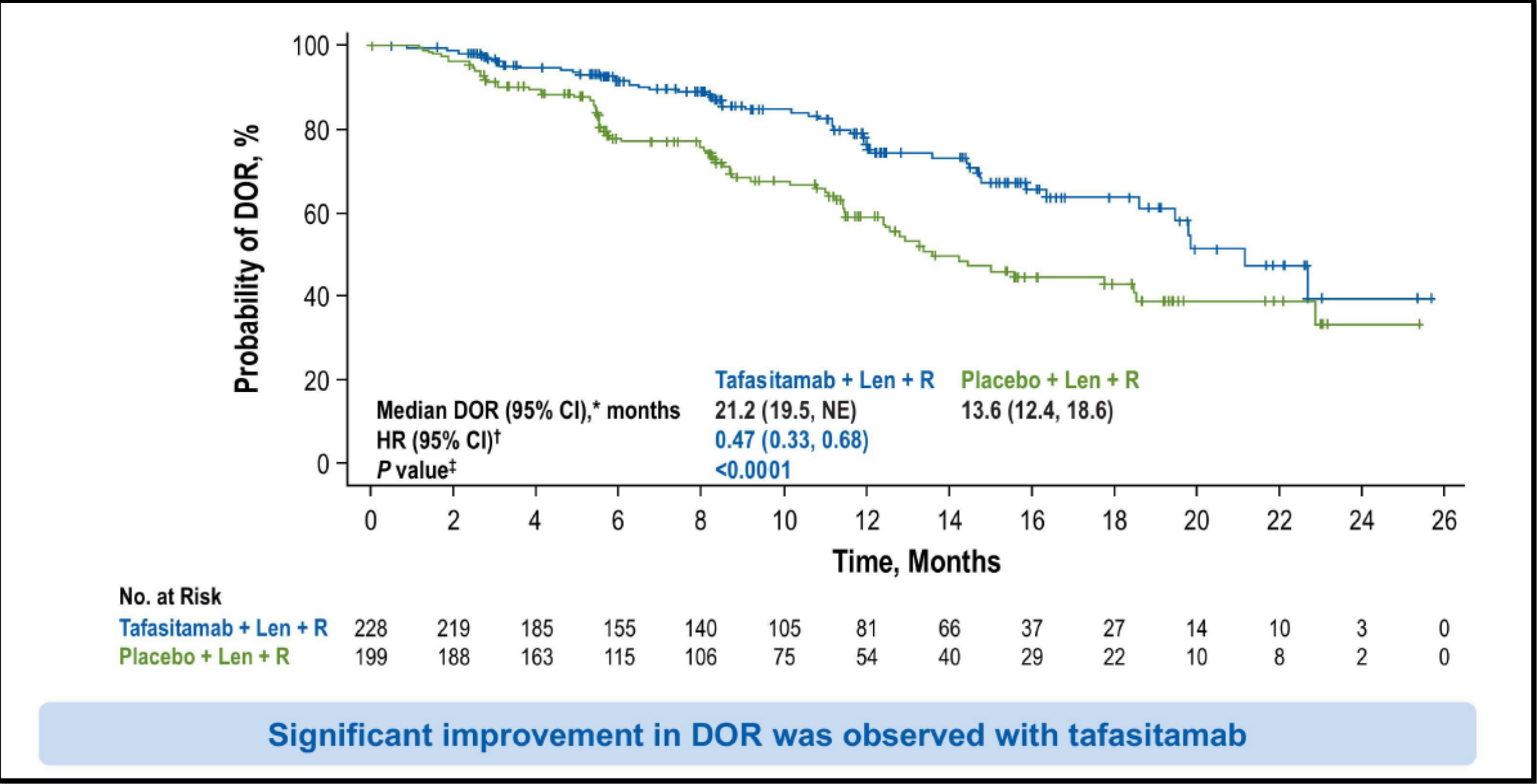
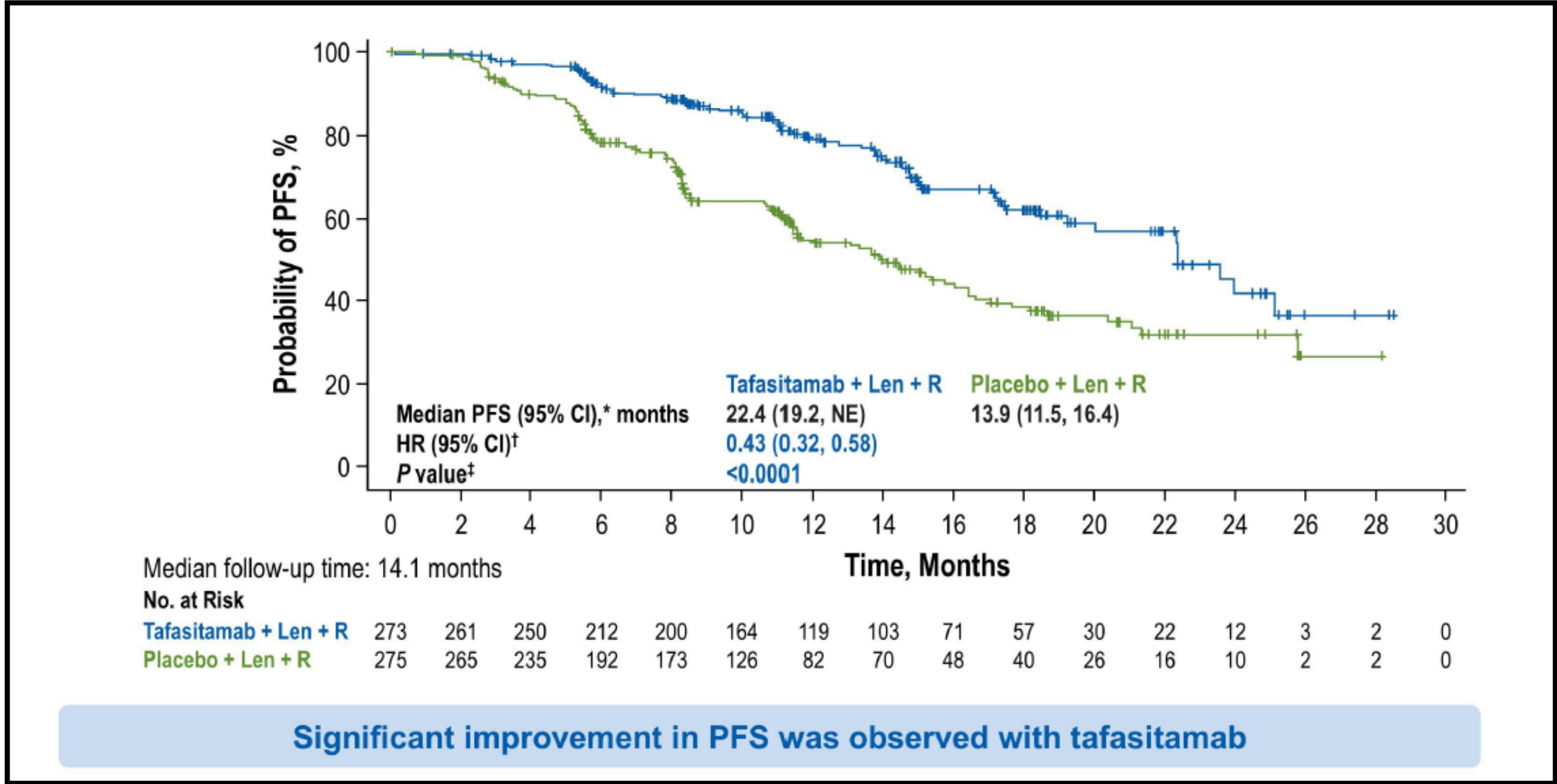
inMIND: TAFASITAMAB+R2 vs R2

inMIND: Phase 3, Double-Blind, Placebo-Controlled, International, Multicenter, Randomized Study

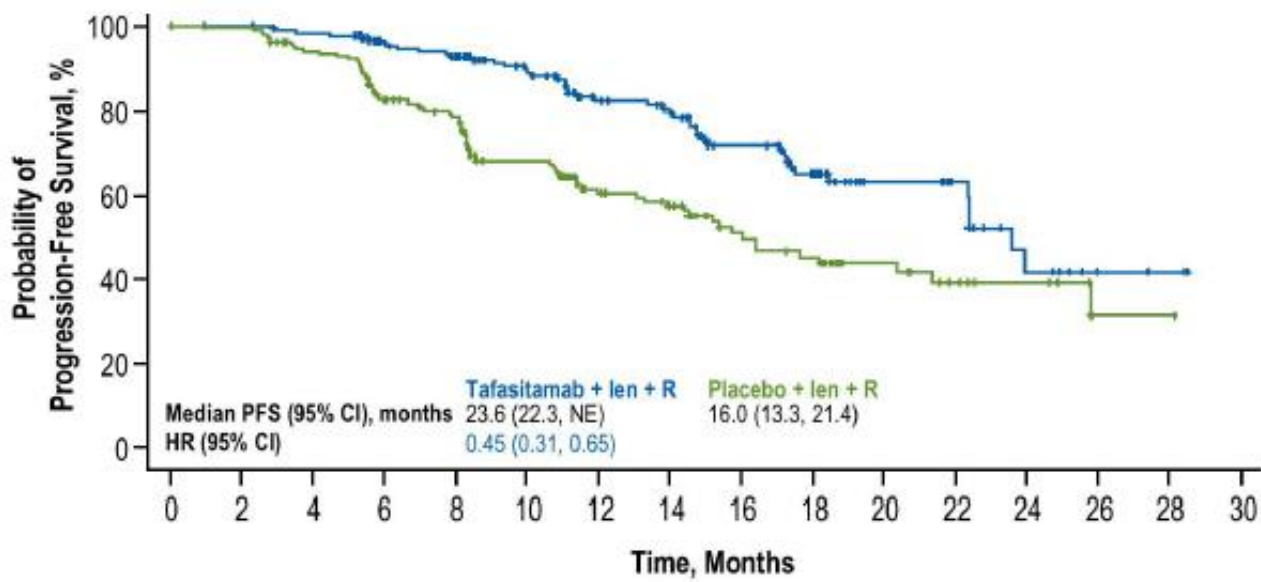


- Powered to assess PFS in the FL population, triggered when 174 investigator-assessed events occurred
- OS analysis planned after 5 years of follow-up

inMIND: TAFASITAMAB+R2 vs R2



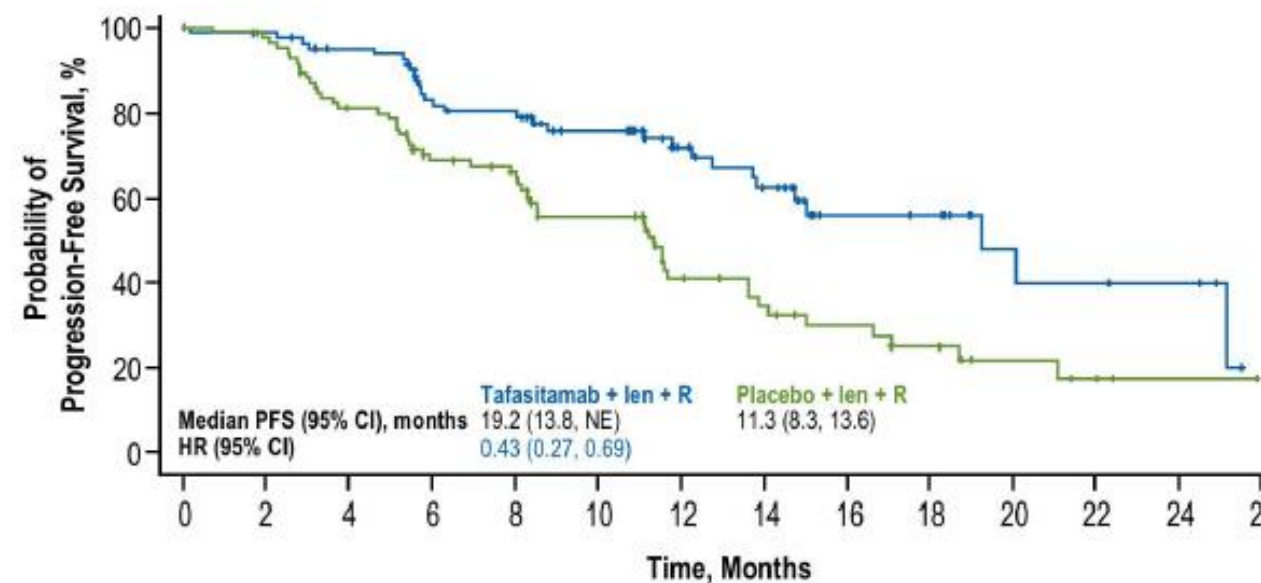
POD24: No



Vantaggio PFS anche in:

- POD24
- refrattarietà a anti-CD20
- L3+
- GELF+

POD24: Yes



PFS R2 peggio dell'atteso:
14m vs 26m (AUGMENT)

ORR (ITT Population)	Tafasitamab + Len + R	Placebo + Len + R
Patients, n	273	275
Best overall response,** n (%)		
CR	142 (52.0)	112 (40.7)
PR	86 (31.5)	87 (31.6)
SD	28 (10.3)	46 (16.7)
PD	7 (2.6)	20 (7.3)
NE	2 (0.7)	0
Not done	8 (2.9)	10 (3.6)
ORR, % (95% CI)	83.5 (78.6, 87.7)	72.4 (66.7, 77.6)
Odds ratio (95% CI)	2.0 (1.30, 3.02)	
Nominal P value	0.0014	

inMIND: TAFASITAMAB+R2 vs R2

Most Common Grade 3 or 4 TEAEs (≥5% in Any Group)			
Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†	Total (n=546)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
Anemia	12 (4.4)	16 (5.9)	28 (5.1)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)
15 patients (6%) in tafasitamab arm and 23 (9%) in placebo arm died during the study - Disease progression: 5 patients (2%) tafasitamab; 17 patients (6%) placebo Fatal adverse events: 6 patients (2%) in each treatment arm (most commonly due to infection)			

-Discontinuazione/interruzione di tafa/placebo, lena o rituximab per AE è analoga nei due bracci
 -Riduzione dose di lena analoga nei due bracci

Interruzione per PD: 18% tafa vs 30% placebo

EPCORE NHL-2 arm 2:EPCO-R2 fixed-duration

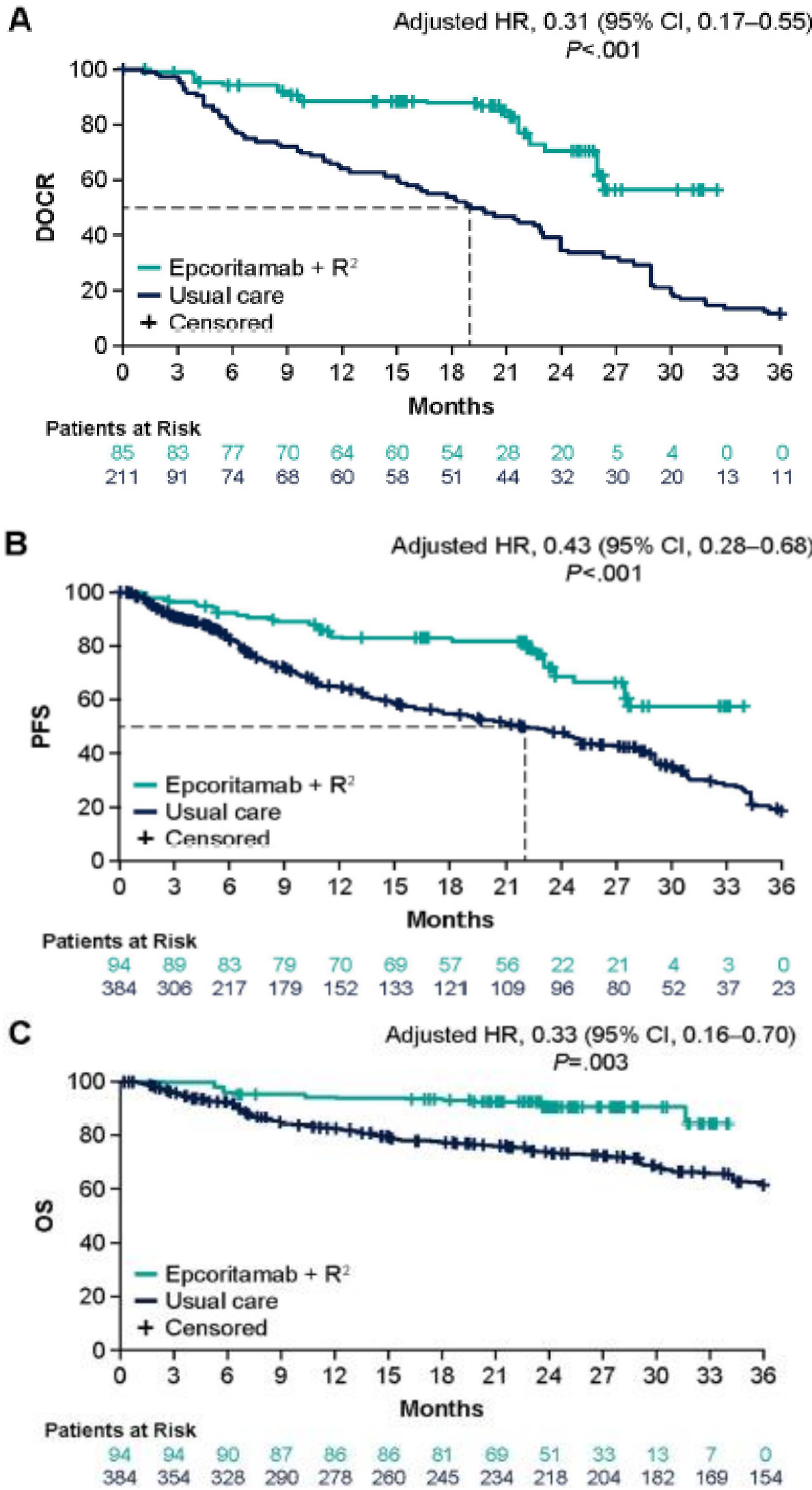
2 step-up dose

Agent	C1	C2	C3	C4–5	C6–9	C10–12	C13+
Epcoritamab SC 48 mg							
Cohort A ^b	QW			Q2W		Q4W	
Cohort B ^b	QW		Q4W				
Rituximab IV 375 mg/m ²	QW	Q4W					
Lenalidomide PO 20 mg/d	D1–21 of each cycle						

Fixed-duration 24 mesi

111 pz
GELF+ 96%
Bulky 27%
FLIPI 3-5 56%
2L 57% 3L 25%
POD24 26%
Primary ref 36%
Double ref 39%

ORR 96% CR 88% MRDneg 86%
-primary ref CR90%
-double ref CR82%
-POD24 CR83%
CR rate meglio 2L vs 3+
peggio se Benda entro 9 mesi
2y DoCR 82%
PFS 76% OS 90%
CRS 51% (G3 2% G4 0%): meno che in monotp
Neutropenia 65%
Covid19 59%

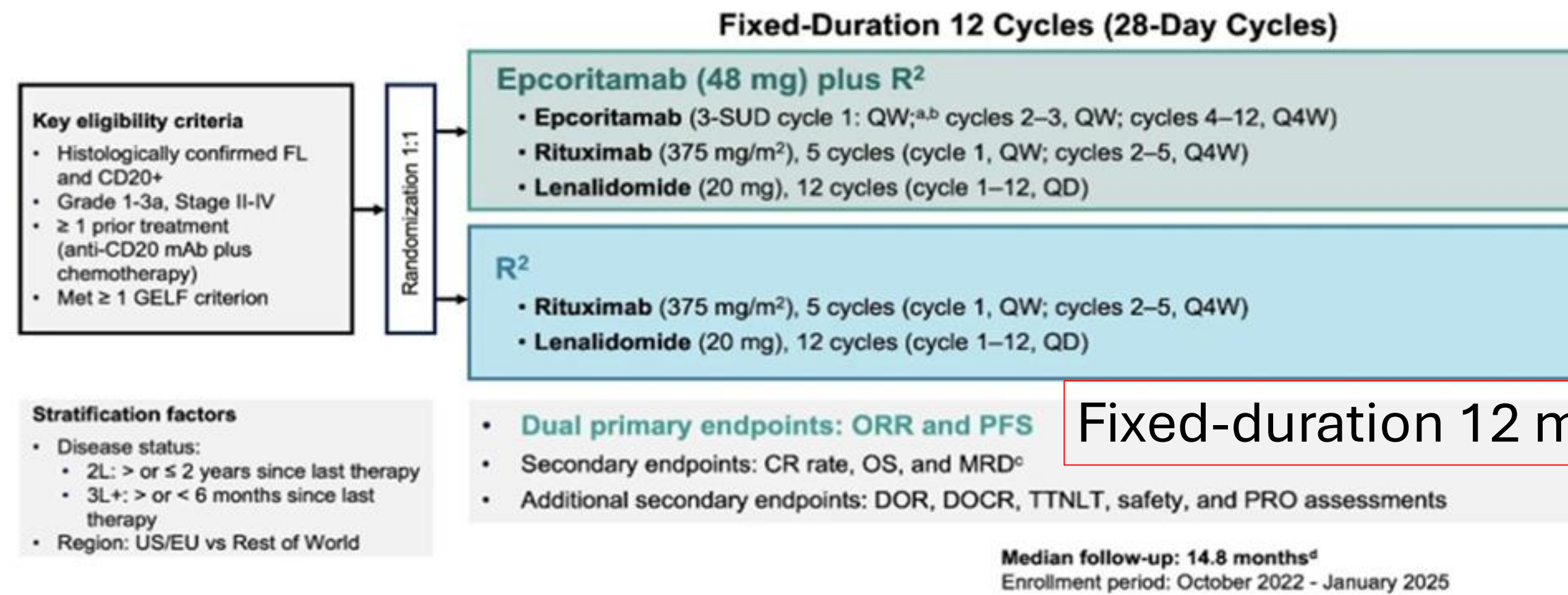


Falchi L, EPCORE NHL2 arm2, Blood 2025
Falchi L, OncoImmunology 2026

EPCORE FL-1: EPCO-R2 fixed-duration vs R2

EPCORE FL-1: Phase 3, Global, Randomized, Open-Label Study

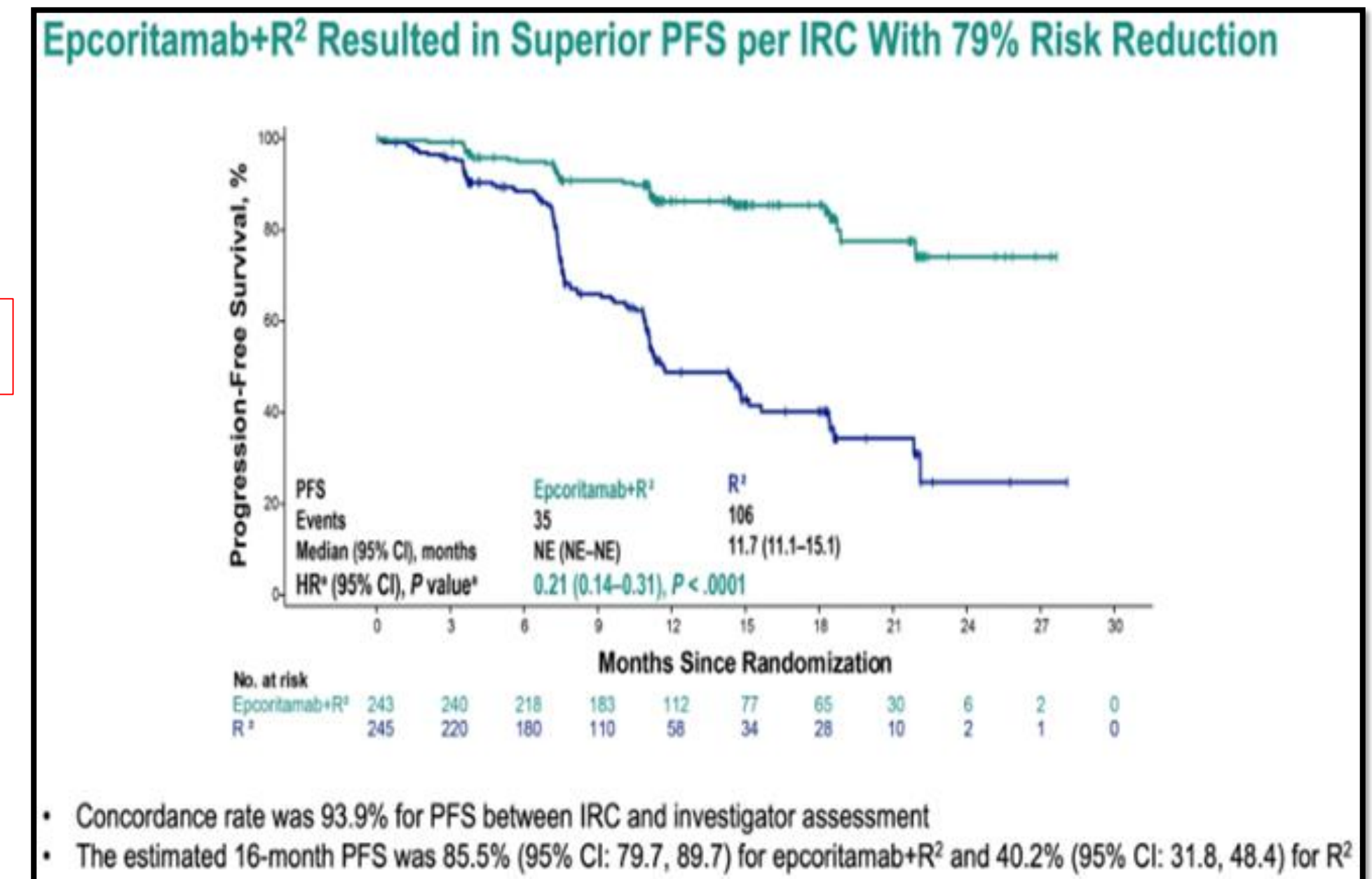
3 step-up dose



Fixed-duration 12 mesi

488 pz
ORR 95.7 vs 81%
CR 83 vs 50%
(anche HR)
 Aumenta TTNT
 16m OS 95.8 vs
 88.8%

Più tox G3+ braccio epco:
 -neutropenia 69 vs 42%
 -neutropenia febbrile 6 vs 3%
 -infezioni 33 vs 15%
Più morti per PD braccio R2
CRS G1-2 26% G3+ 0%
 1 pz ICANS G1



MOSU-R2

CO41942: fase Ib/II 2L+

Eligibility

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

Mosun-Len administration (n=29)*

Mosunetuzumab

- Intravenous administration for 12 cycles (C1: Q3W; C2–12: Q4W)

Lenalidomide

- Oral administration for 11 cycles (C2–12)

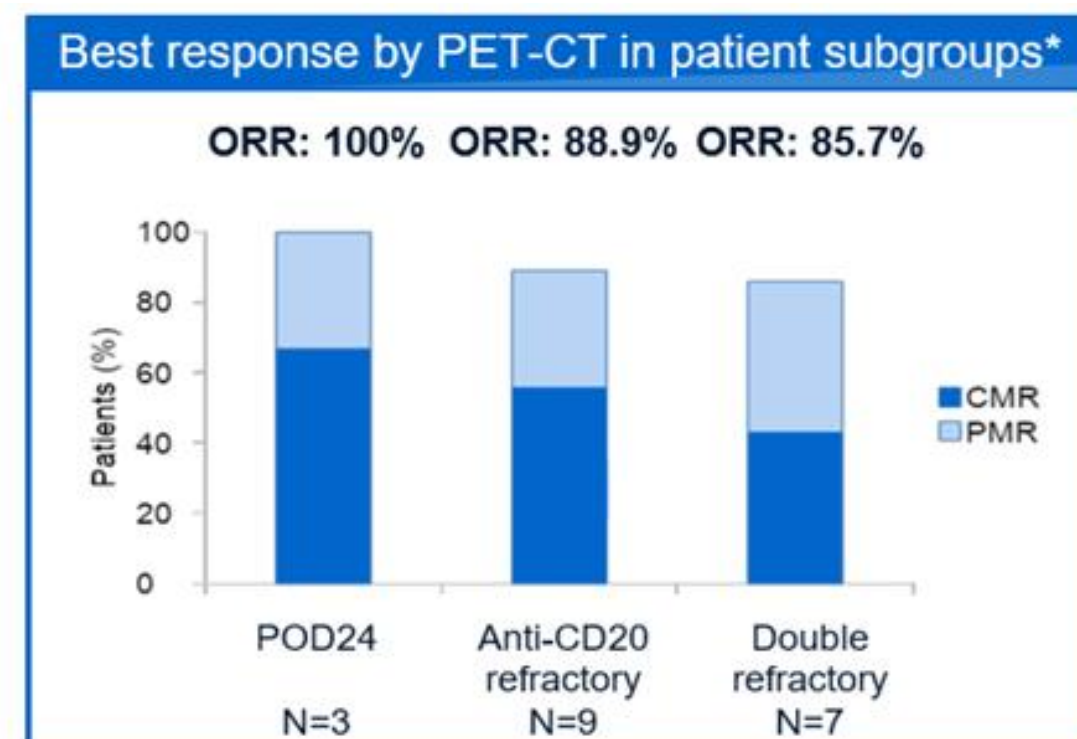
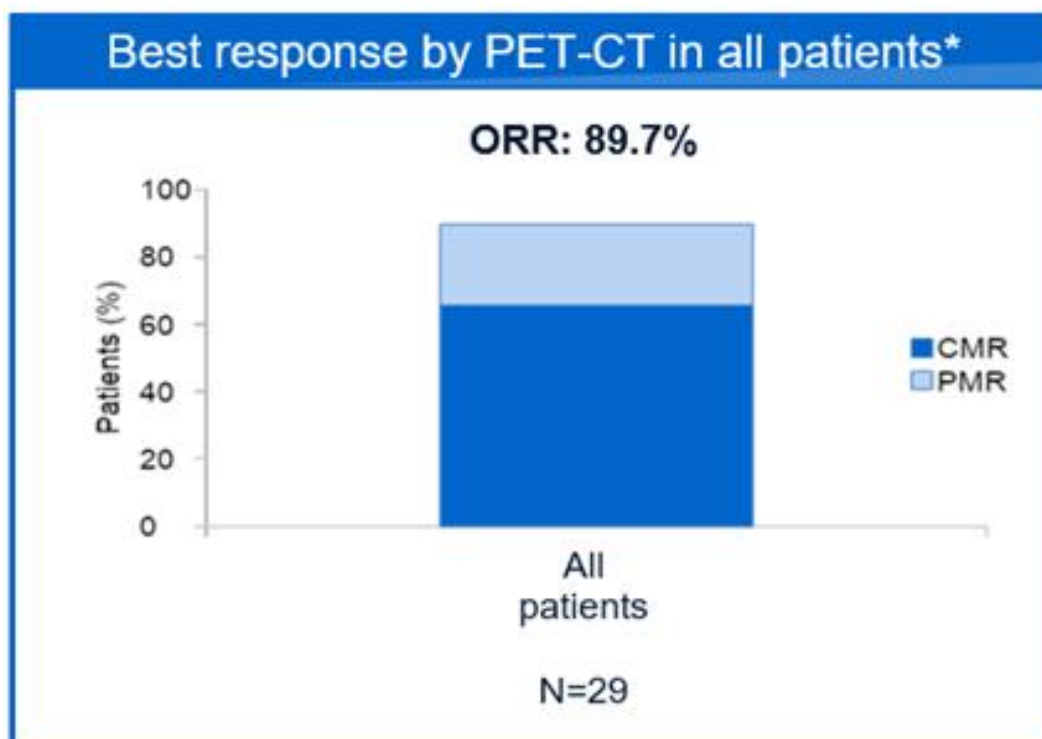
- C1 step-up dosing for CRS mitigation
- No mandatory hospitalization

Double ref 24%

POD24 10%

-No increase in rate or severity of CRS with addition of lenalidomide

-Neutropenia 24% G4 10%



CELESTIMO: fase III randomizzato

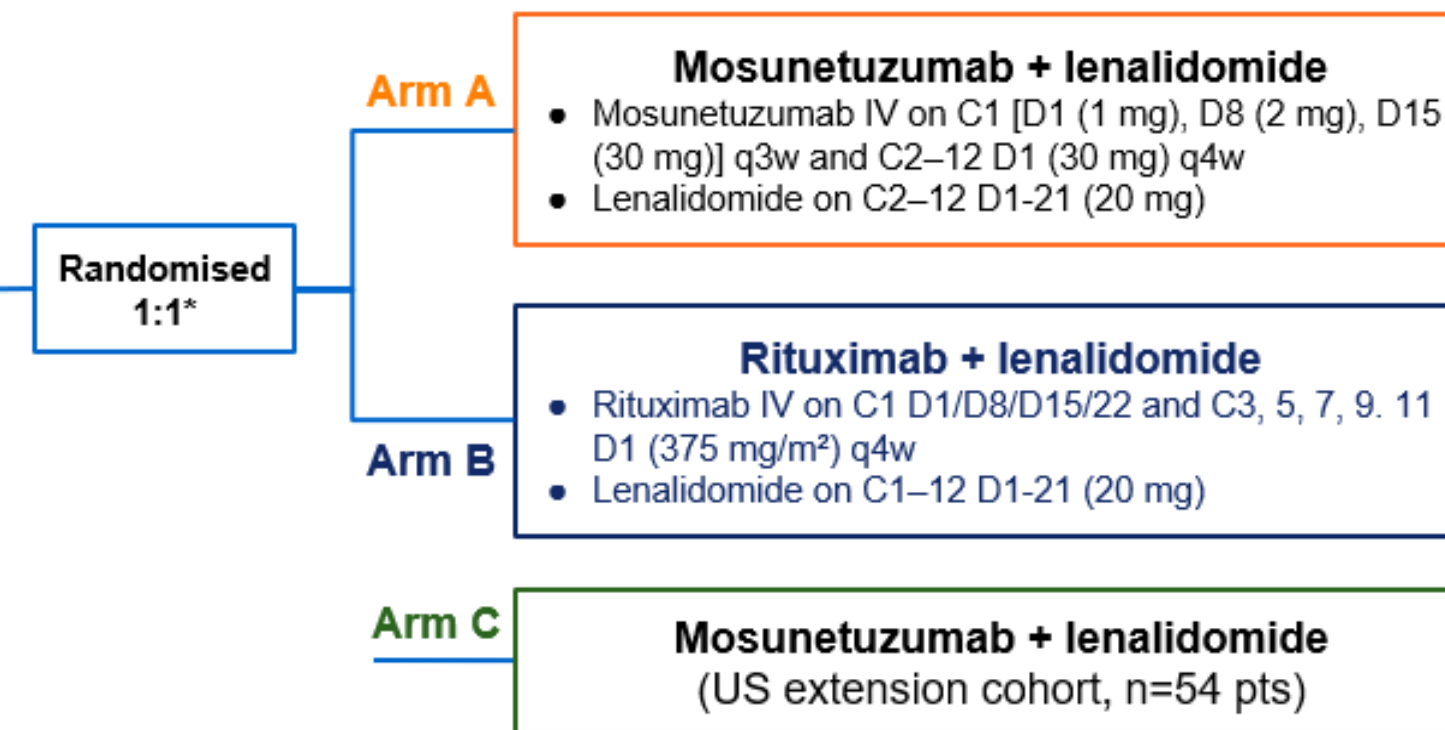
Randomised, open-label, multicentre Phase III study of mosunetuzumab (IV) and lenalidomide compared with rituximab and lenalidomide in patients with R/R FL

Eligibility

- Age ≥ 18 years
- Grade 1–3a CD20+ FL
- ECOG PS 0–2
- ≥ 1 prior systemic anti-lymphoma therapy
- Target enrolment (Randomised cohort): 400

Stratification factors

- POD 24 status
- Prior lines of therapy (1 vs ≥ 2)
- Refractoriness to anti-CD20 therapy



1° endpoint

PFS (IRC-assessed) in ITT

Efficacy follow-up: 5 years from time of randomisation

Secondary and other endpoints†

- PFS (INV-assessed) in ITT, CR rate (by PET-CT), ORR, OS, DOR, DOCR, time to deterioration in physical functioning and fatigue by EORTC QLQC30, safety, PK, immunogenicity, biomarker

ELM-2: ODRONEXTAMAB 3L+

-EV

-Step up dose: C1D1
0.7mg (split 0.2, 0.5) C1D8
4mg C1D15 20mg C1D22
80 mg; C2-4 80mg QW;
C5+160mg Q2W; se CR da
9 mesi 160mg Q4W

-Premed: dex 20 mg
durante C1, dex 10mg dal
C2 se CRS

-Fino a PD/tox

128 pz: 74% POD24, 78%
double ref, 34% bulky

median FU 22m

ORR 80% CR 73%
confermato in HR

2y PFS 48% OS 70%

- CRS 56% G3+ 2% ICANS
1 caso (G2)
- Neutropenia 39% G3-4
27%
- Infezioni G3-4 21%
- Sosp per AE 16% (causa
più freq COVID19)

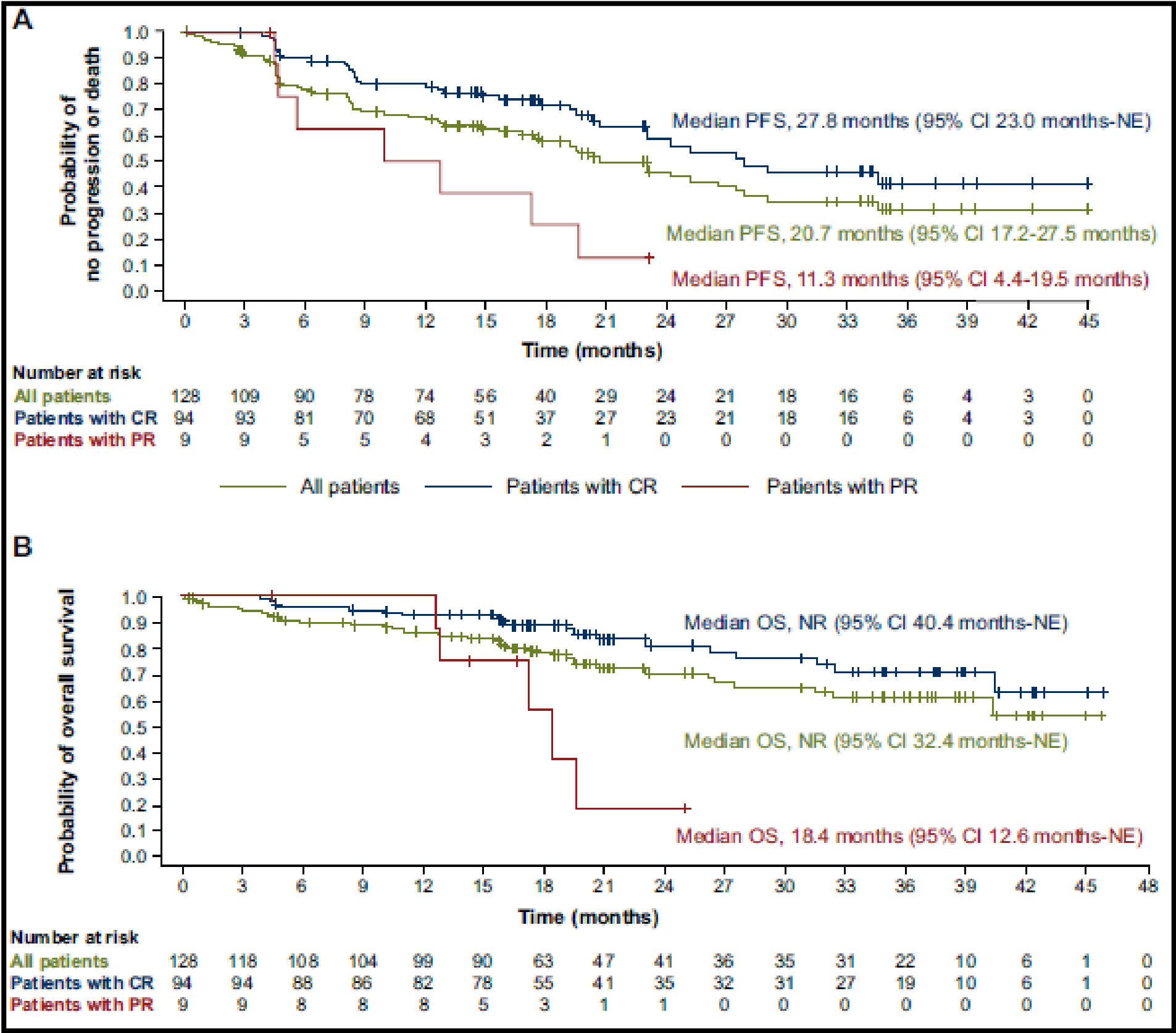
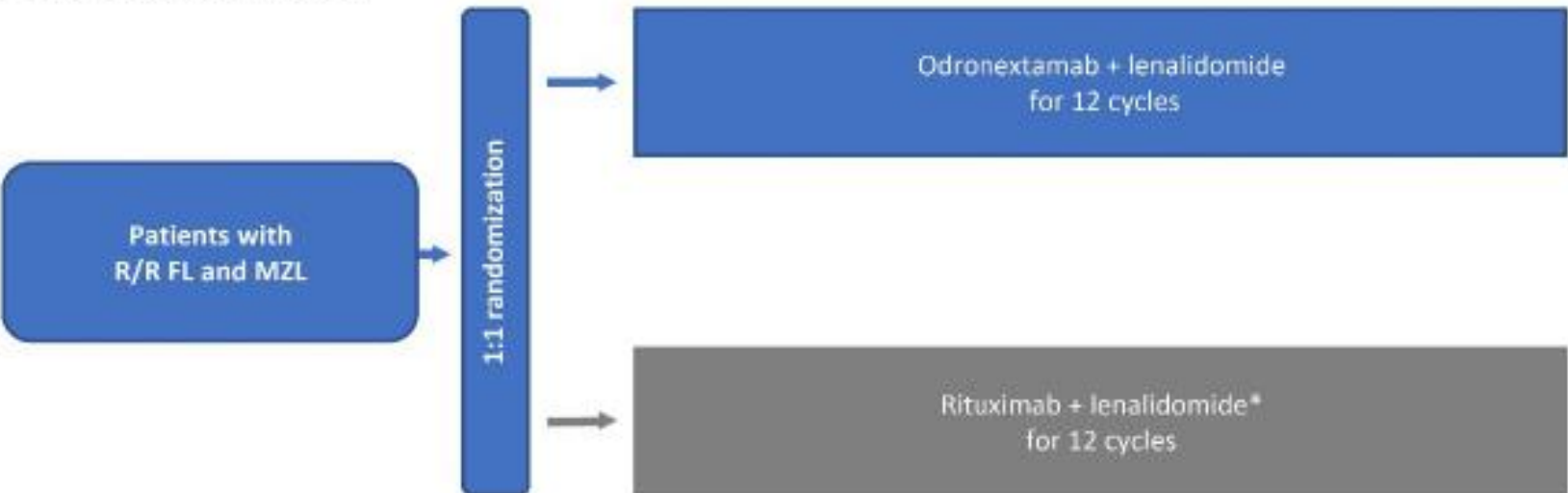


Figure. Phase 3 OLYMPIA-5 study design

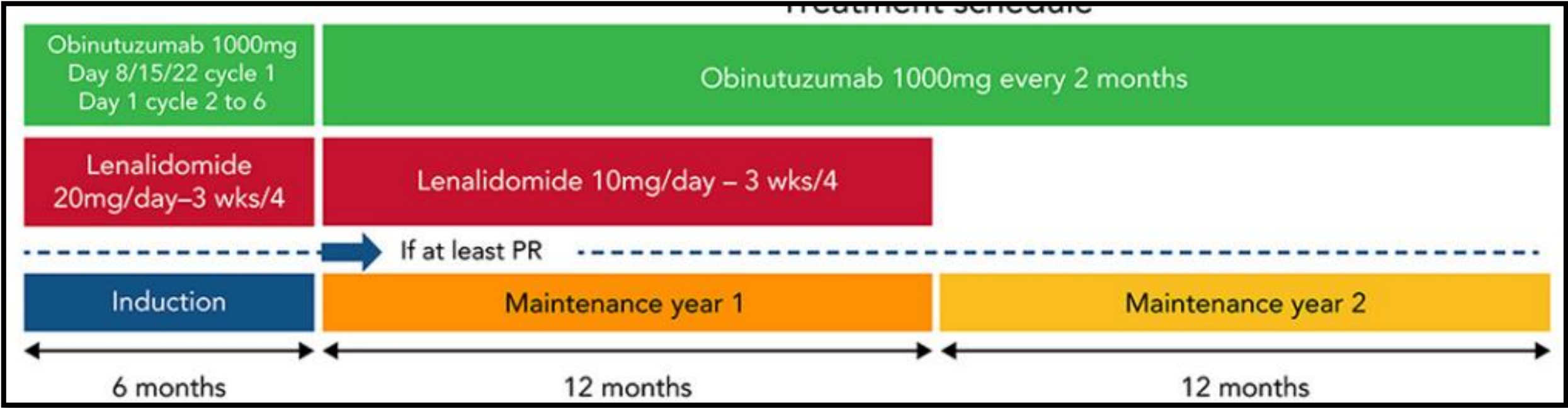
Part 1: Safety run-in

Part 2: Randomization



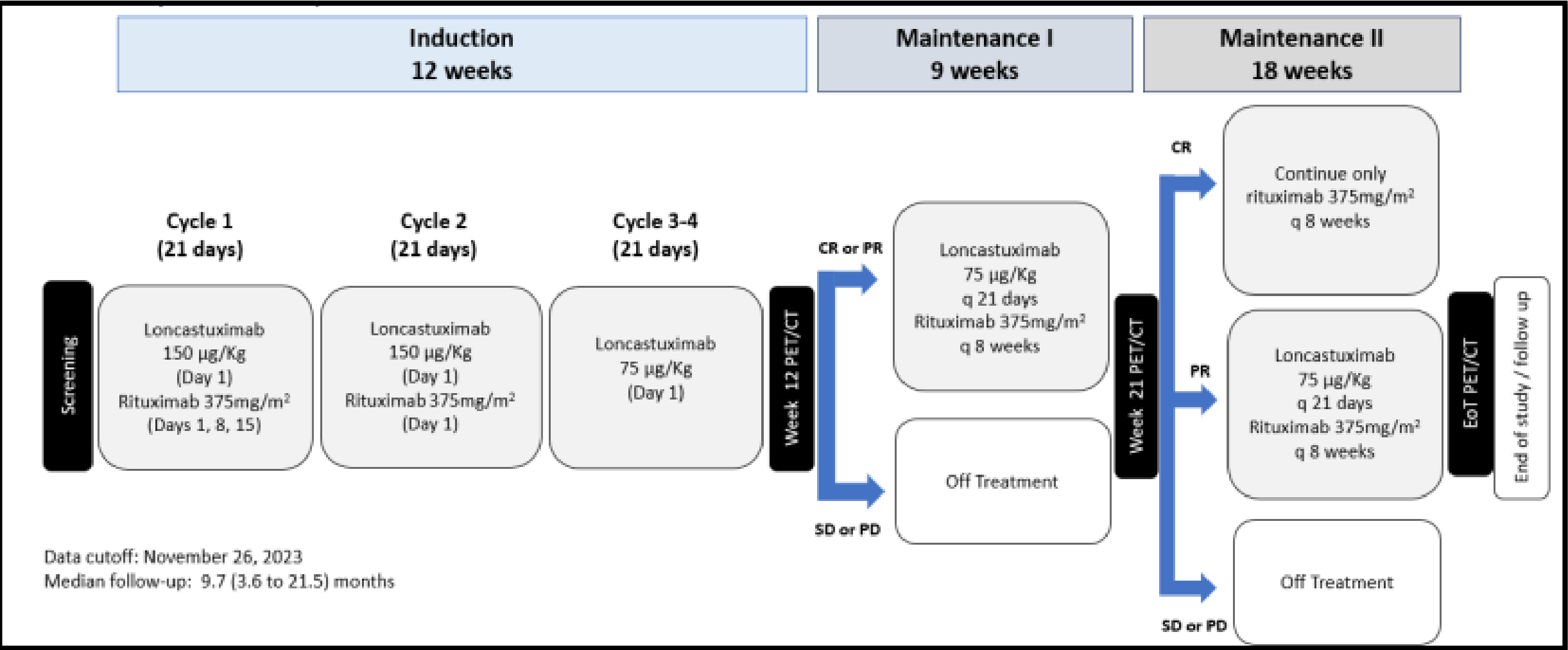
Kim T, ELM-2, Annals of Oncology, 2024
Vitolo U, OLYMPIA-5 study (abstract) ASH 2025

GALEN: OBINO-LENA

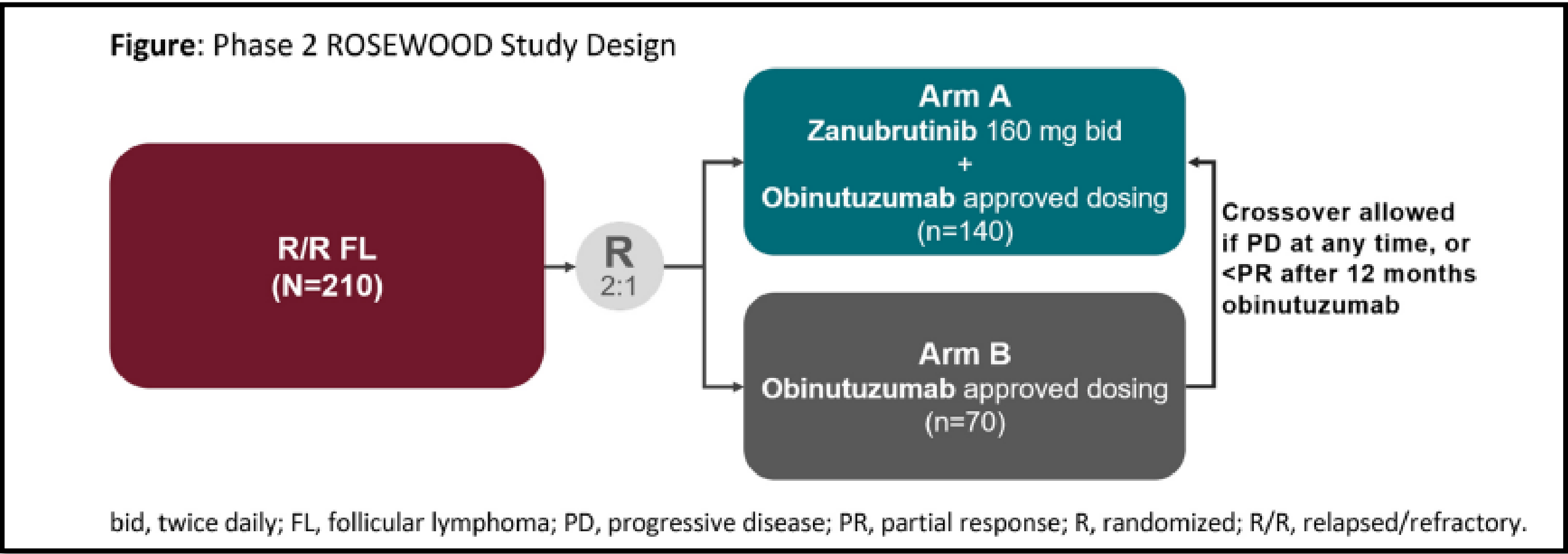


88 pazienti
ORR 79% CR 38%
2y PFS 65%
2y DOR 70%
2y OS 79%

LONCASTUXIMAB+R



ROSEWOOD: ZANU-OBINO vs OBINO



217 pazienti, mFU 20m
ORR 69 vs 46% CR 39 vs 19%
18m DOR 69 vs 42%
mPFS 28 vs 10m

39 pz: età 68y GELF+ 92% POD24 51%
2L+ (67%): POD24 o GELF+
W12 ORR 97% CR 67% W21CR 77%
CR uguale nei POD24
Tox: iperglicemia, aumento ALT, rash
Neutropenia 38% G3+ 13%

Morschhauser F, GALEN, Lancet Haematol 2019
Zinzani PL, ROSEWOOD, JCO 2023
Alderuccio JP, LONCA+R, Lancet Haematol 2025

CASI CLINICI

F, 1961

11/10/2023 randomizzata a braccio sperimentale (Axicel) protocollo ZUMA22

15/11/2023 infusione CAR-T previa terapia con Flu-Cy

-CRS G2: tocilizumab x3 (1 dose d3)

-ICANS G3: dex 10x4 dal d5 per ICANS G1, rapido peggioramento+crisi tonico clonica, intubazione orotracheale il 21/11/23, boli MP 1 g die per 3 giorni. Estubazione il 22/11/23 e risoluzione completa del quadro di ICANS in data 24/11/23

Rivalutazioni successive: mRC

-B-cell aplasia fino m18

09/2026 TAC: RC

F, 1946

08/01/2025 Mosunetuzumab

-CRS G1 C1D15: toci x2 + dex

TAC/PET dopo C8 mRC → stop

Da 01/2026 supplementa IgEV per ipogamma+infezioni ricorrenti

06/2026 (+12 mesi da mosu) PD linfonodo sottomandibolare: citologico non conclusivo (negativo per ca mammario)

Programmata TAC tra 1 mese...

Se PD cosa fareste?

-R mono

-R-CVP

-Epcoritamab

-Tafa-R2

-CAR-T

CONCLUSIONI