FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
26-27 gennaio 2026

FL: I trattamenti chemo-free nella prima linea di terapia, studio Relevance e non solo

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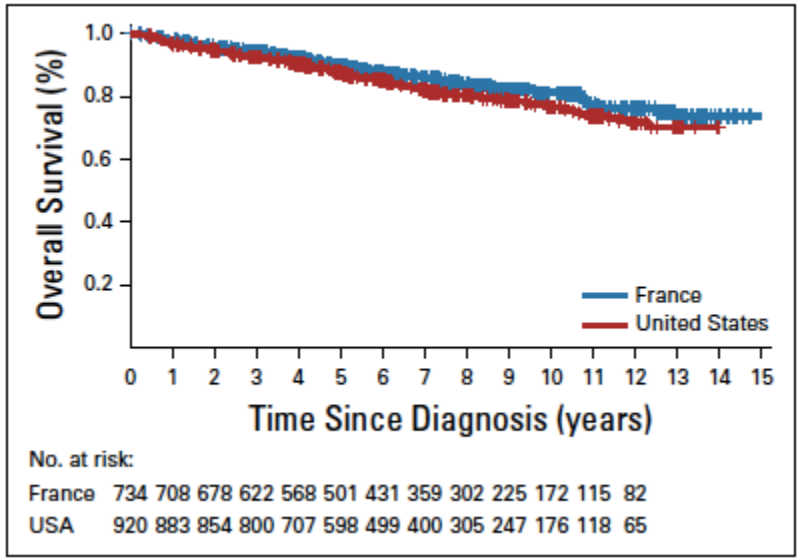
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x	x	
Lilly			x			x	
BeOne					x	x	
Roche						x	
Takeda						x	
J&J						x	
Kite						x	
Novartis						x	

FL patients are long survivors



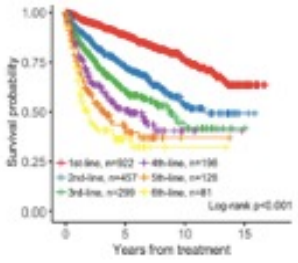
- The availability of very active therapies in first and subsequent relapse
- The adoption of more accurate diagnostic tools
- A better understanding of the biology of FL

Sarkozy, JCO 2017

Shared features of FL

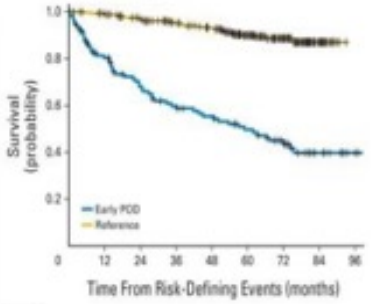
- Survival is improving — *Late effects matter; is cure a likely goal of therapy? Which are the risks for the patient (transformation, early failure, death)?*
- Can be asymptomatic — *W&W is an option/R mono*
- Can be localized — *RT is an option (+/- anti CD20)*
- Relapsing remitting course — *Strategy matters*

OS by line of therapy



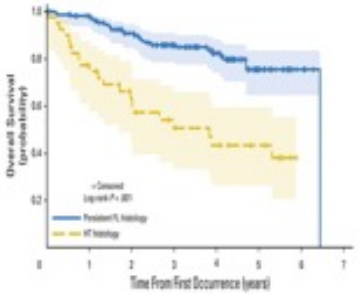
Batlevi et al
Blood Can Jour, 2020

OS according POD24



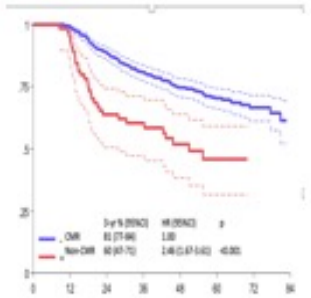
Casulo et al
JCO , 2015

OS according transformation



Sarkozy et al
JCO ,2016

PFS according EOT



Luminari et al
JCO, 2021

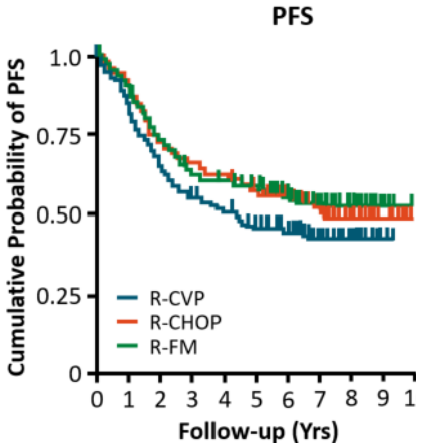
How to translate the prognostic model in a decisional tool for a risk-adapted therapy?


Se vogliamo che tutto rimanga come è, bisogna che tutto cambi.
Giuseppe Tomasi di Lampedusa

1st Line FL Treatment: Is There an Optimal Chemotherapy Backbone?

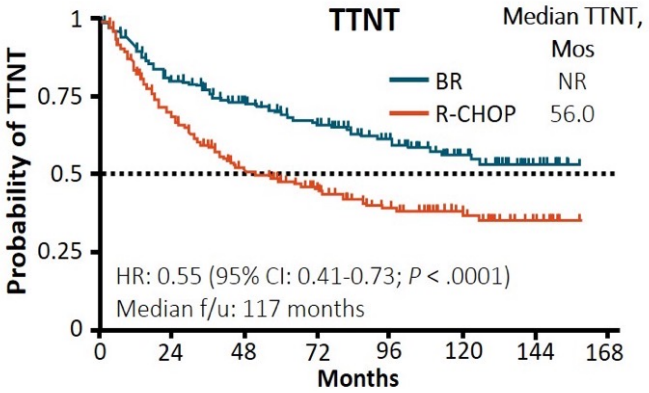
FOLL05 Trial[1,2]

R-CVP vs R-CHOP vs R-FM



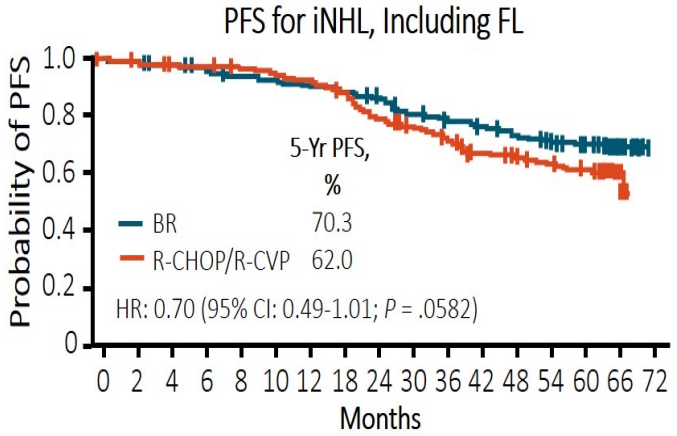
STiL NHL1 Trial[3,4]

BR vs R-CHOP



BRIGHT Trial[5,6]

BR vs R-CHOP or R-CVP



- R-CVP not as effective as R-CHOP/ R-FM
- 2º malignancies for R-FM-treated

- STiL: Improved PFS and fewer toxicities with BR
- BRIGHT: Similar ORR, PFS; different toxicities
- *No maintenance given in either study

1. Federico M et al. *J Clin Oncol.* 2013;2. Luminari S et al. *J Clin Oncol.* 2018;3. Rummel MJ et al. *Lancet.* 2013;. 4. Rummel MJ et al. ASCO 2017. 5. Flinn IW et al. *Blood.* 2014;. 6. Flinn IW et al. *J Clin Oncol.* 2019;.

Safety Profile of R-CHOP and R-Benda Randomized comparisons

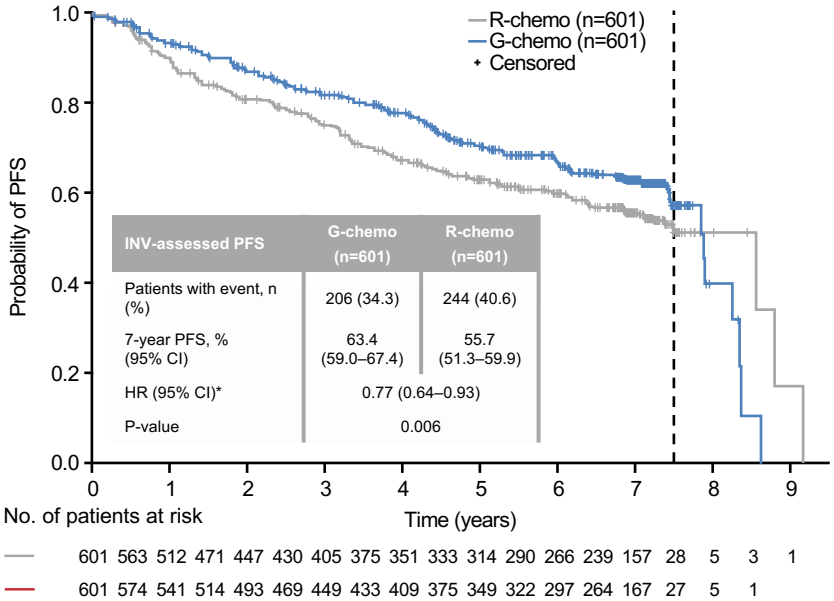
Stil (Rummel et al Lancet 2013, ASCO 2017)	R-CHOP	R-Benda
G3-4 Neutropenia	69%	29%
Infections	50%	37%
Skin reactions	9%	16%
Second malignancies	18.5%	18.6%
Bright (Flinn et al. Blood 2014, JCO 2019)	**R-CHOP/CVP**	**R-Benda**
G3-4 Neutropenia	87%	39%
Infections	5%	12%
Skin reactions	12%	20%
Second malignancies (Excl. non Melanoma skin cancers)	10%	6%
tFL	3.2%	2.2%

CHOP (1/3):
- More frequently used in young, High risk (FLIPI/FLIPI2), and FL g3a (Gallium, FOLL12)
- Reduced risk of tFL vs Benda (FOLL12 unpublished)
- Cardiac toxicity

Bendamustine (2/3):
- More frequently used in Old, Low risk (Gallium, FOLL12)
- Profound and persisting T-Cell depletion (Gallium)
- High risk of tFL for POD24 pts (up to 80%)
- Higher risk of SM (Bright, FOLL12)

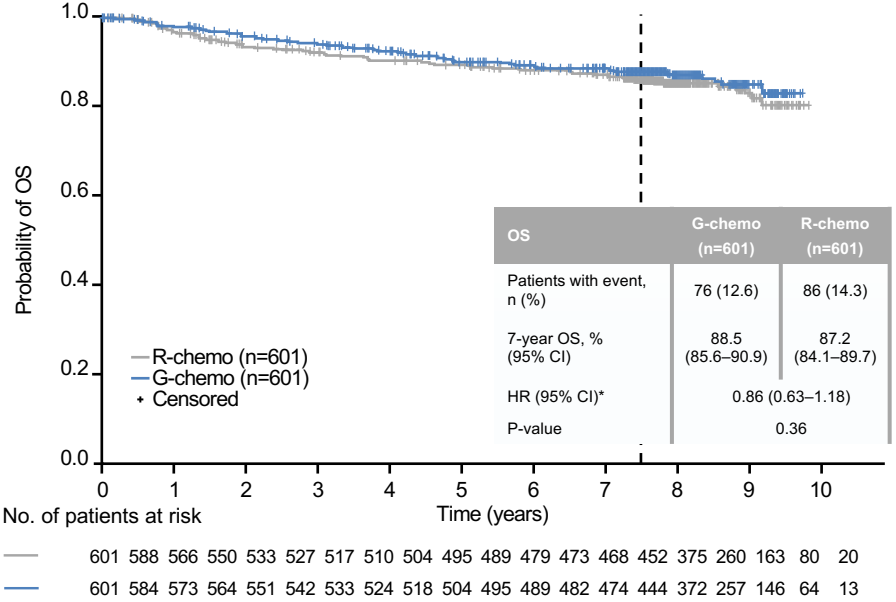
Unprecedented efficacy of immunochemotherapy in follicular lymphoma: Gallium Study

PFS



INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

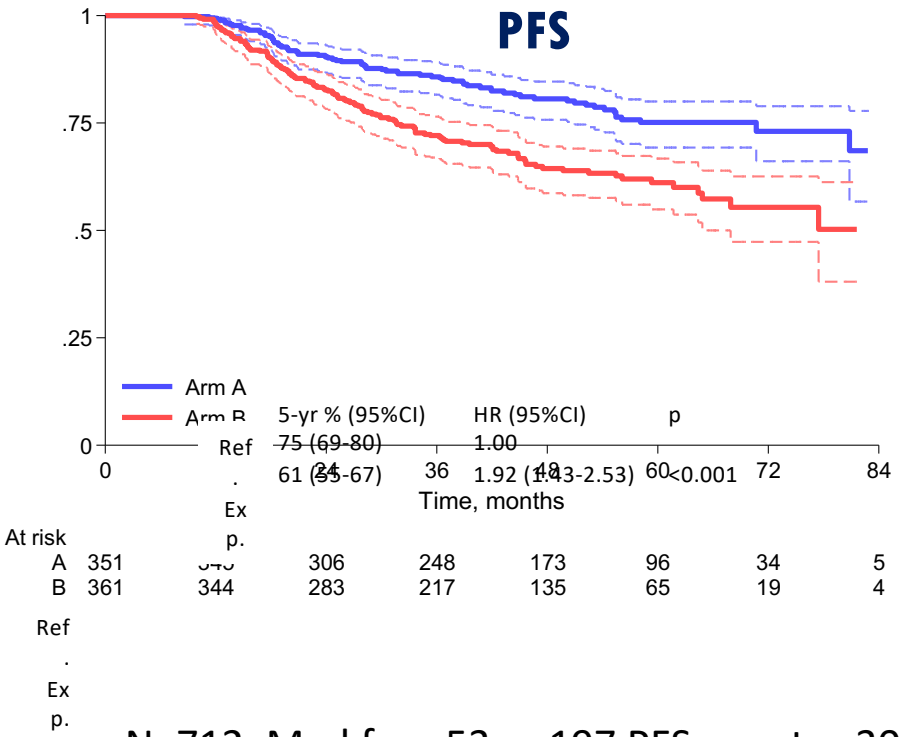
OS

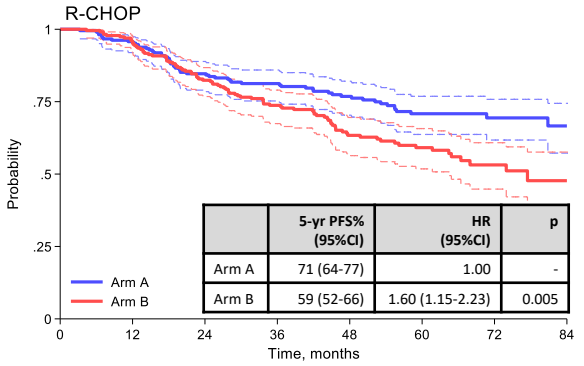


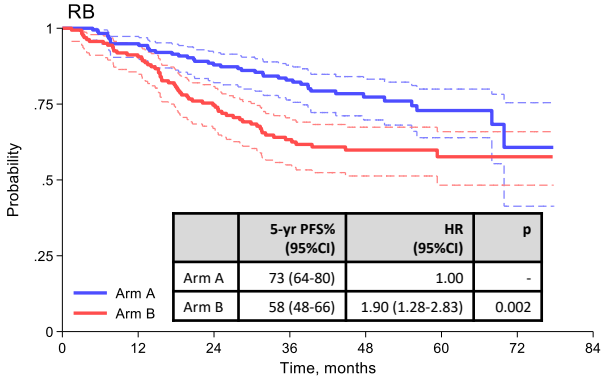
OS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	76 (12.6)	86 (14.3)
7-year OS, % (95% CI)	88.5 (85.6–90.9)	87.2 (84.1–89.7)
HR (95% CI)*	0.86 (0.63–1.18)	
P-value	0.36	

1. Marcus R, et al. N Engl J Med 2017;377:1331–1344
2. Townsend W, et al. EHA 2022

Standard maintenance is better than a response adapted therapy in adv. stage FL. Updated results of the FOLL12 trial







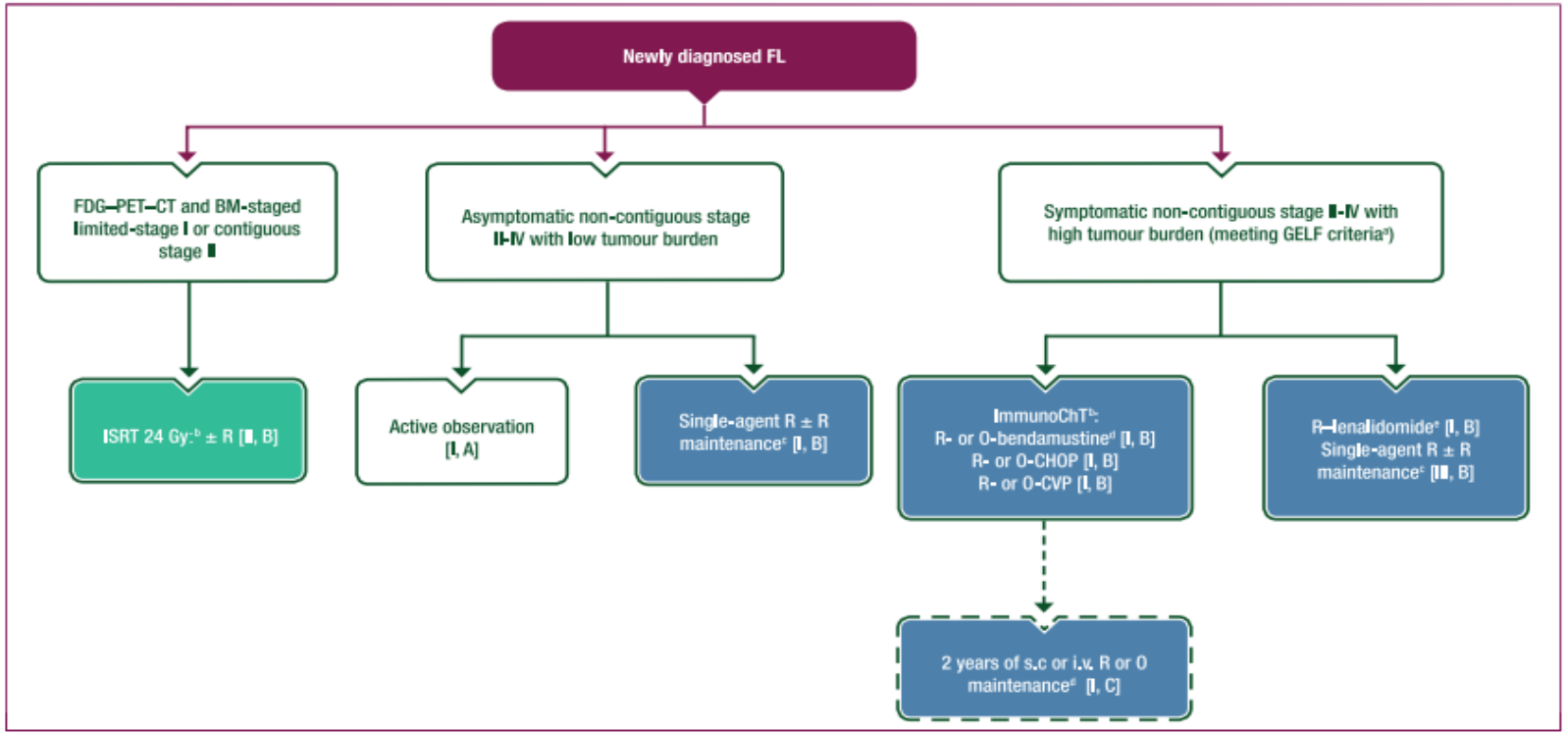
N=712, Med f-up 53m, 197 PFS events , 30 deaths

Luminari et al JCO 2022

2025 ESMO guidelines

Annals of Oncology

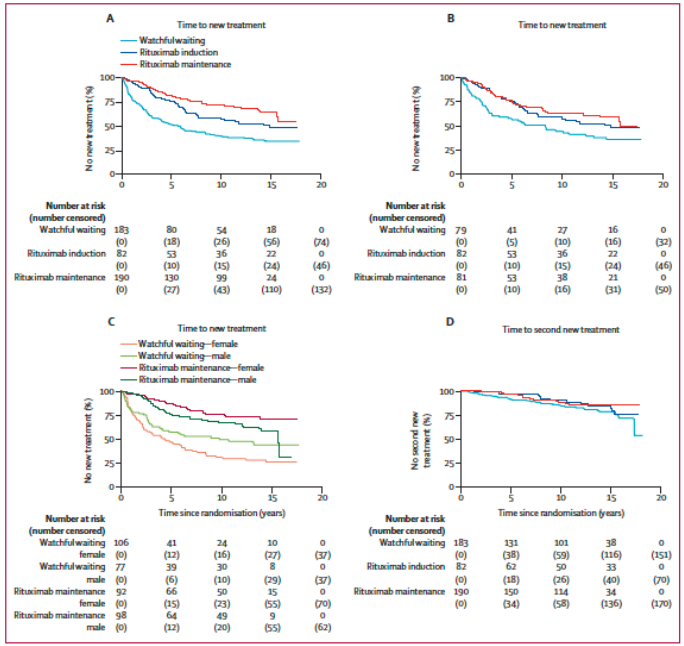
T. A. Eyre et al.

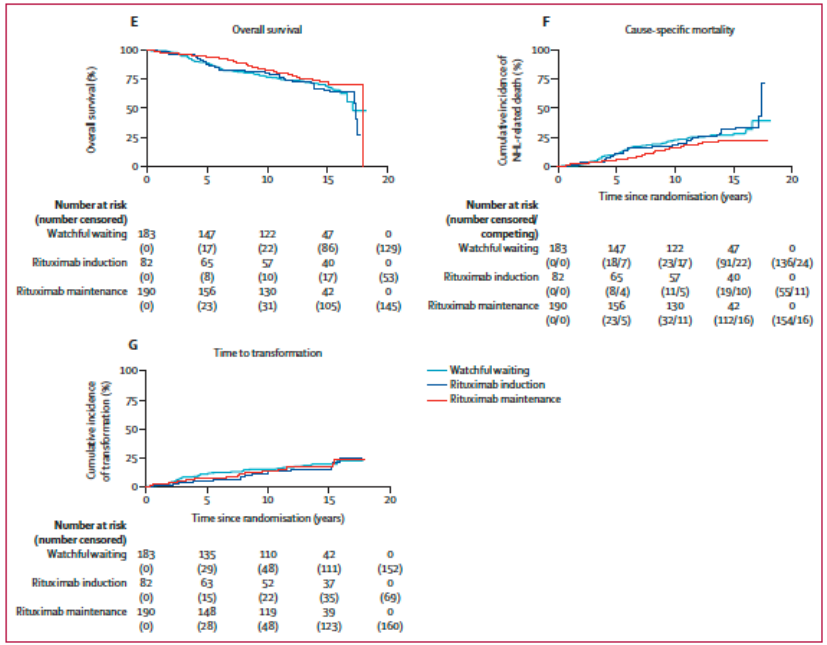


CHEMO FREE APPROACH

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

Michael Northend, William Wilson, Kushani Ediriwickrema, Laura Clifton-Hadley, Wendi Qian, Zaynab Rana, Tanya-Louise Martin, William Townsend, Moya Young, Fiona Miall, David Cunningham, Jan Walewski, Burhan Ferhanoglu, Kim Linton, Amanda Johnston, John F Seymour, David C Linch, Kirit M Ardeshna





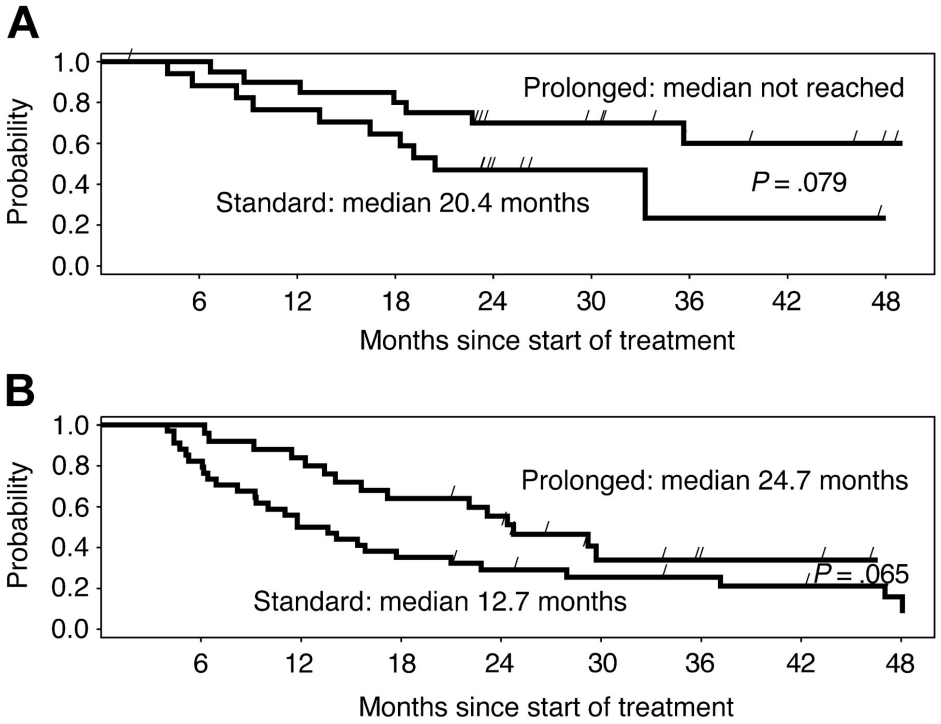
Median Follow up 14.7 years

15 year TTNT was 64% (R mant) 48% (R) 34% (OBS)

Lancet hem. 2025

Rituximab alone in the treatment of pts with FL

Duration of response by study arm in chemotherapy-naive (A) and pretreated patients (B)

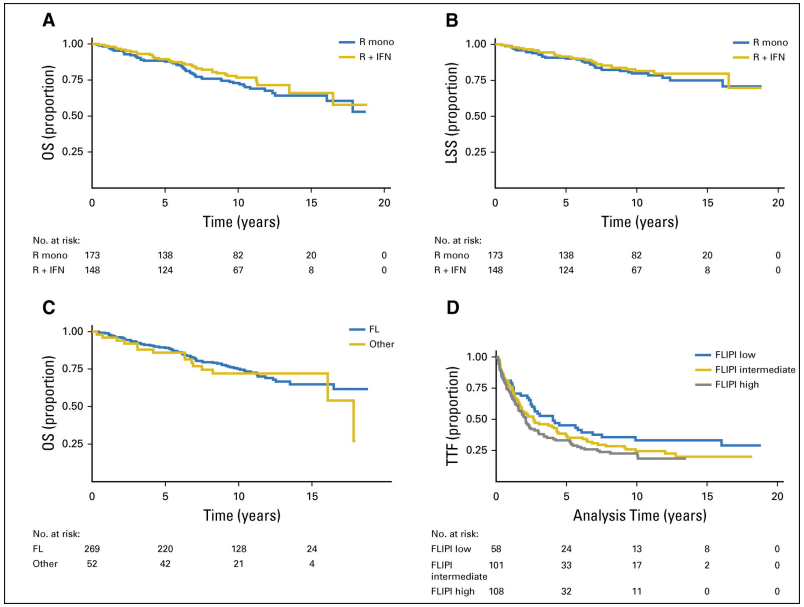


45% of chemo-naive responders in remission at 8 years
Martinelli et al. JCO 2010

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Ghielmini M, et al. *Blood*. 2004;103(12):4416-4423.

Long term outcomes of FL initially treated with Rituximab



- 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

Fig 2. (A) Kaplan-Meier overall survival (OS) estimate of all patients (n = 321) by treatment arm in years since random assignment. Log-rank P = .36. (B) Kaplan-Meier estimate of lymphoma-specific survival (LSS) by treatment arm in years since randomization. (C) Kaplan-Meier OS estimate for all patients (n = 321) in years since random assignment by indolent lymphoma subtype: follicular (FL) and other (non-FL). (D) Estimate of time to treatment failure (TTF) in patients with FL by Follicular Lymphoma International Prognostic Index (FLIPI) categories (log-rank P = .11) defined as the period between random assignment and either progressive disease while on study treatment, initiation of any new therapy because of relapse or intolerance, or death as a result of any cause. Patients with an unknown FLIPI score (n = 2) are omitted from the graph. R + IFN, rituximab plus interferon alfa-2a; R mono, single rituximab.

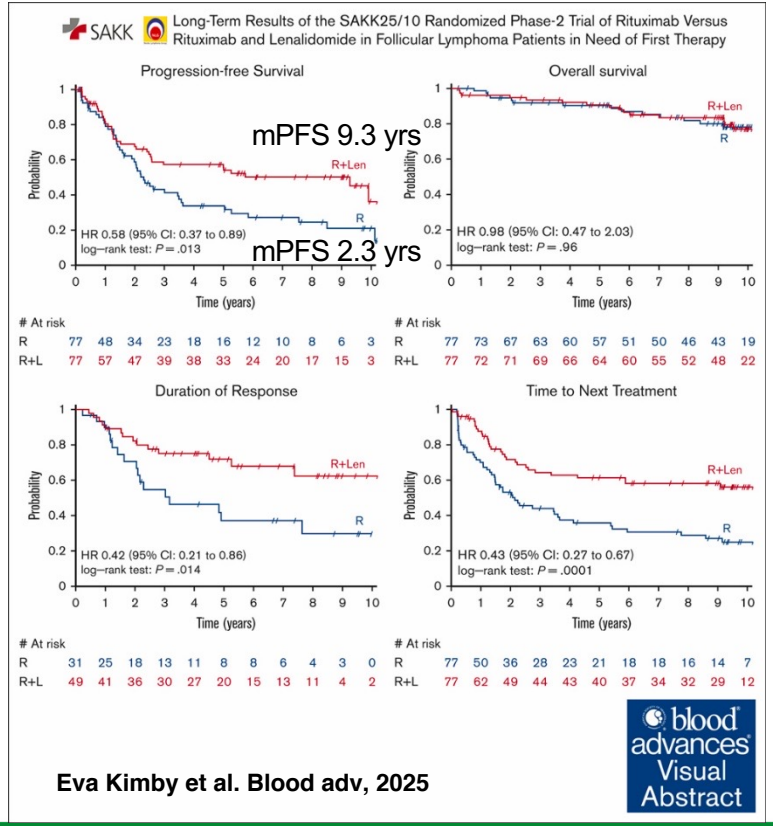
Sandra Lockmer; *Journal of Clinical Oncology* 2018 363315-3323.

DOI: 10.1200/JCO.18.00262

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

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

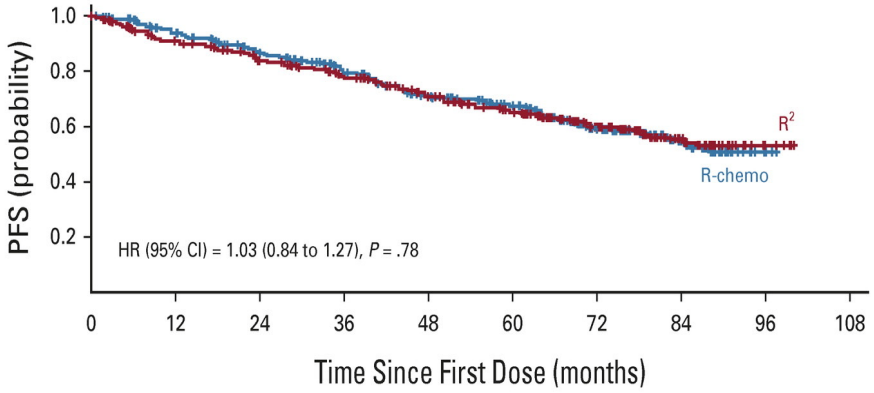
Grade 3/4 AEs	R (n = 76)	R2 (n = 77)
Fatigue	1 (1.3%)	2 (2.6%)
Allergic reaction		2 (2.6%)
Neutropenia	5 (6.6%)	18 (23.4%)
Thrombocytopenia		3 (3.9%)
Depression		1 (1.3%)
Psychosis		1 (1.3%)
Suicide attempt	1 (1.3%)	
Maculo-papular rash		4 (5.2%)
Hypertension	3 (3.9%)	7 (9.1%)
Discontinuation		12 (16%)

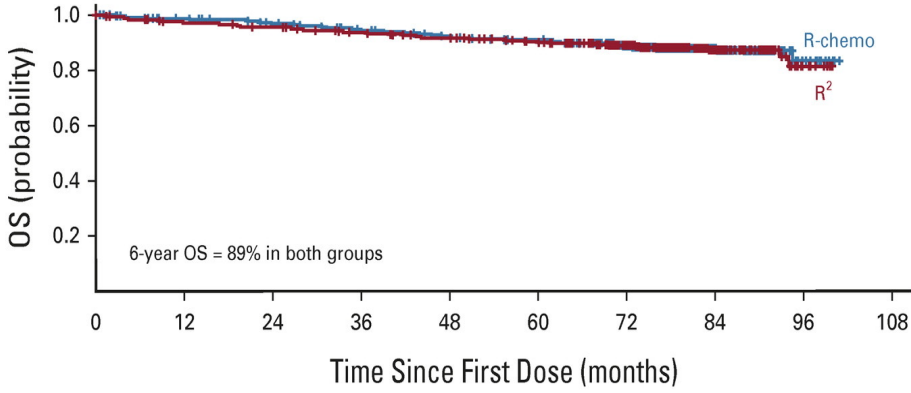


Eva Kimby et al. Blood adv, 2025

blood advances Visual Abstract

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma





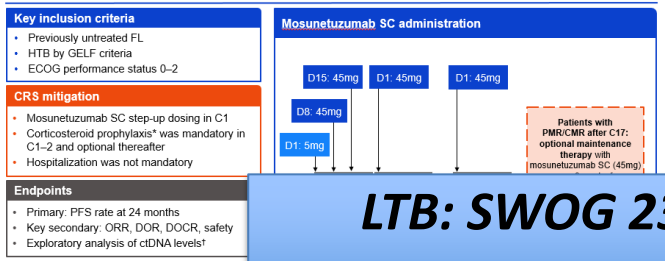
No. at risk:										
R-chemo	517	446	390	333	277	243	146	56	3	0
R2	513	412	370	328	281	242	157	51	5	0

at risk:										
hemo	517	487	471	451	435	424	330	130	13	0
	513	490	479	461	447	425	343	137	13	0

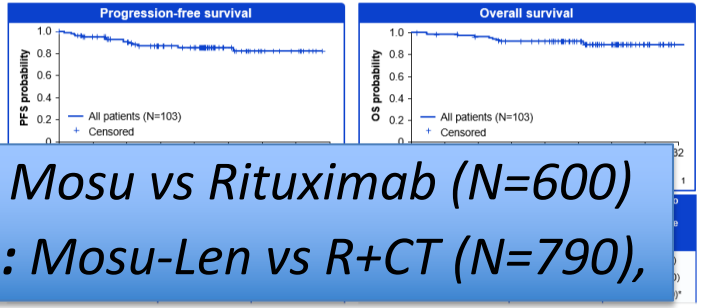
- 6-yr PFS: 60% R^2 vs 59% R-chemo
- Transformation rates similar (2% range)
- Similar ORR and OS with subsequent therapy in both groups
- Similar rates of second primary malignancies
- 6-yr OS: 89% in both groups

Morschhauser. JCO 2022

Morning SUN: HTB FL 1 line



Efficacy: PFS and OS

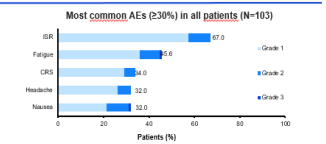


LTB: SWOG 2308: *Mosu vs Rituximab (N=600)*

HTB: MorningLyte: *Mosu-Len vs R+CT (N=790),*

Safety summary

AE summary, n (%)	All patients N=103	Patients who received maintenance treatment n=46
Patients with ≥1 AE	103 (100)	38 (82.6)
Grade 3/4 AE	48 (46.6)	7 (15.2)
Serious AE	37 (35.9)	6 (13.0)
AEs of special interest	29 (28.2)	4 (8.7)
Infections*	81 (78.6)	21 (45.7)
ISR	69 (67.0)	15 (32.6)
CRS (by ASTCT criteria)	35 (34.0)	0
Neutropenia/neutrophil count decreased	23 (22.3)	2 (4.3)
Grade 5 AEs	5 (4.9)†	1 (2.2)‡
AE leading to mosunetuzumab discontinuation	11 (10.7)§	4 (8.7)¶

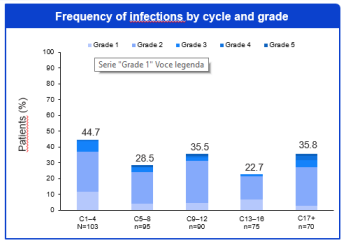


- CRS events were all Grade 1/2 and mostly observed within the first two cycles
  - CRS management included steroids (n=8), tocilizumab (n=6), steroids + tocilizumab (n=3) and fluids (n=3)
- No CRS events occurred during maintenance treatment
- One patient reported an ICANS event (Grade 4)** during C1

Infections and mild injection-site reactions were common; during maintenance, rates of Grade 3/4 and serious AEs were low, and CRS did not occur

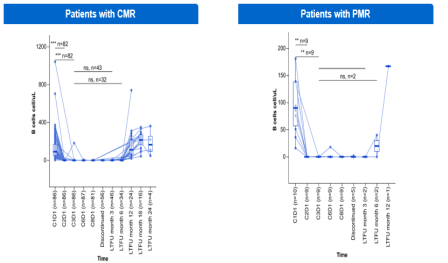
Infections: All patients

n (%) unless stated	N=103
Received antimicrobial prophylaxis	46 (44.7)
Any grade infection	81 (78.6)
Grade 1	12 (11.7)
Grade 2	49 (47.6)
Grade 3	13 (12.6)
Grade 4	4 (3.9)
Grade 5*	3 (2.9)
Serious infections	17 (16.5)
Median time from first mosunetuzumab dose to first infection, days (range)	84 (1–624)
Infections resolved, n/n (%)	77/81 (95.1)
Most common infections (≥10%)	
COVID-19/COVID-19 pneumonia†	28 (27.2)
Sinusitis	17 (16.5)
Urinary tract infection	15 (14.6)
Pneumonia	15 (14.6)
URTI	14 (13.6)



Infections were common and predominantly involved the respiratory tract; most events were resolved

B cell depletion and recovery



B-cell depletion was observed following the first dose of mosunetuzumab, with subsequent B-cell recovery observed within six months of treatment completion.

Ghosh N. et al, oral presentation ASH 2025;

Epcoritamab + R2 in 1L FL

Study Design

Key inclusion criteria

Overall
- CD20+ FL
  - Grade 1, 2, or 3A
- ECOG PS 0–2
- Adequate organ function

Arm 6, 1L FL
- 1L FL
- Measurable disease by CT or MRI
- Meet GELF criteria

Arm 7, FL maintenance
- In CR or PR after 1–2 lines of SOC treatment

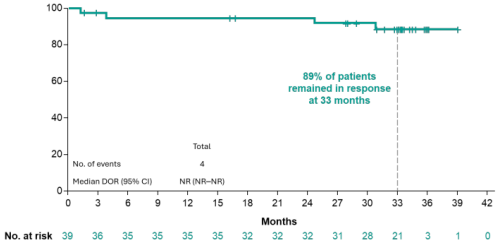
Data cutoff: Apr 9, 2025

Median follow-up: Arm 6, 36 months[e]; Arm 7, 35 months[f]

Arm 6 (1L FL) expansion	Arm 7 (FL maintenance after SOC treatment) expansion
Rituximab (IV) 375 mg/m² QW C1, Q4W C2–6 **Lenalidomide (oral) 20 mg** QD for 21 days in C1–12 **Epcoritamab (SC) 48 mg** 2 SUD[a], QW C1–2, Q4W C3+ (28-day cycles); treatment up to 2 years	**Epcoritamab (SC) 48 mg** 2 SUD[a], QW C1 (28 days) Q8W C2–13 (56-day cycles); treatment up to 2 years
Primary endpoint: ORR[b] **Key secondary endpoints:** Safety, DOR, DOCR, PFS, OS, MRD[c] **First patient first visit/last patient last visit** Oct 8, 2021/May 16, 2024	**Primary endpoint:** Safety **Key secondary endpoints:** CR rate,[d] DOCR **First patient first visit/last patient last visit:** Nov 8, 2021/Feb 22, 2024

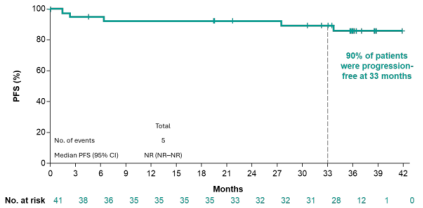
Arm 6 (1L FL): Deep and Durable Responses

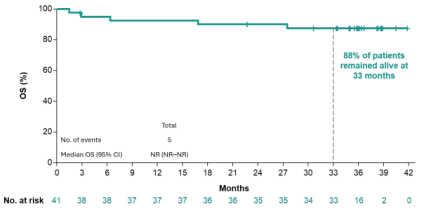
	Epcoritamab + R² N = 41
Overall response, n (%)	39 (95)
CR	36 (88)
PR	3 (7)
NE[a]	2 (5)



- 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

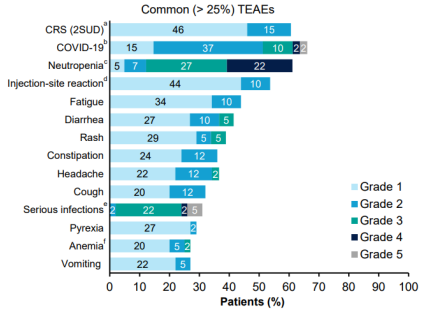
Arm 6 (1L FL): Favorable Long-Term Outcomes





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

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-up[1]:
  - One new grade 3 COVID-19 TEAE
  - Two pneumonia TEAEs led to discontinuation
  - One death due to progressive multifocal leukoencephalopathy (PML)[g]

[a]CRS 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. [b]COVID-19 includes COVID-19 or COVID-19 pneumonia. [c]Neutropenia includes neutropenia or neutrophil count decreased. [d]Local injection site reactions include injection site reactions as high-level group terms. [e]Serious infections include serious TEAEs in the system organ class of Infections and Infestations. [f]Anemia includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased, and serum ferritin decreased. [g]Previous 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.

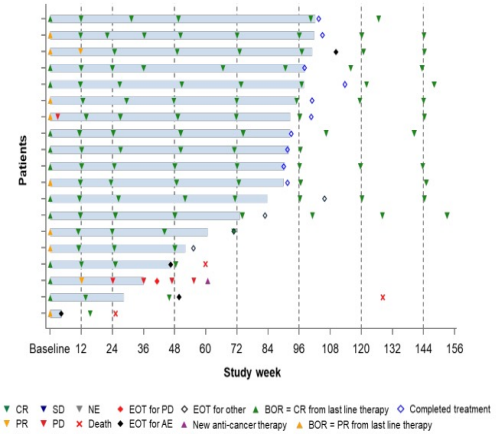
Leslie et al., ASH 2025;

Arm 7 (Maintenance After SOC): Baseline Characteristics, Treatment Exposure, and Follow-Up

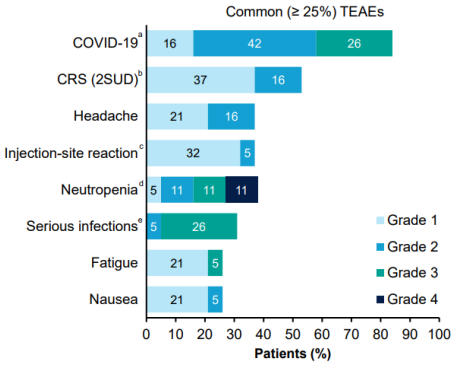
Characteristic	Epcoritamab N = 19
Age, median (range), years	56 (31–78)
Male, n (%)	11 (58)
ECOG PS, n (%)	
0	16 (84)
1	3 (16)
Treatment History	
Time from end of SOC induction therapy to first dose, months, median (range)	2.8 (1.2–6.0)
Prior systemic therapy received, n (%)	
Anti-CD20	19 (100)
Bendamustine-containing regimen	3 (16)
Prior lines of anti-lymphoma therapy, n (%)	19 (100)
1	16 (84)
2	3 (16)
Best response to last line of therapy, n (%)	
CR	11 (58)
PR	8 (42)

Treatment Exposure and Follow-Up	Epcoritamab N = 19
Follow-up, median (range), months	35 (6–39)
Epcoritamab treatment exposure	
Number of treatment cycles initiated, median (range)	11 (2–13)
Duration of treatment, months, median (range)	21 (1–24)
Completed treatment per protocol, n (%)	10 (53)
Discontinued treatment, n (%)	9 (47)
AE[a]	4 (21)
Patient withdrawal[b]	3 (16)
PD	1 (5)
Other[c]	1 (5)

- Prior SOC treatments included anti-CD20 mAb-containing regimens (100%), alkylating agent-containing regimens (79%), and anthracyclines (53%)



- All 8 patients with PR from last line of therapy converted to CR after a median of 2.8 months (range, 2.5–5.7)
- Median DOR and DOCR were NR; at 33 months, an estimated 84% of patients remained in response and 84% were alive
- All 10 patients who completed treatment per protocol had CR at EOT and all maintained their CR at the data cutoff (median follow-up, 12.2 months)
- Median PFS and OS were NR



Overall

- Safety was consistent with prior reports[1]
- Six out of 8 serious infection events were COVID-19
- Neutropenia
  - Primarily occurred in the first 48 weeks of treatment and decreased thereafter
  - No febrile neutropenia was reported
- CRS
  - All grade 1/2, resolved with supportive care
  - There were no discontinuations

Long term

- Since the last report with ~13 months of additional follow-up[1,f]
  - One grade 3 COVID-19 TEAE
  - One death due to unknown cause (non-TEAE-related) reported outside the treatment period[g]

1L

CR, 88%

33-month DOCR, 93%

33-month OS, 88%

Maintenance

CR, 100%

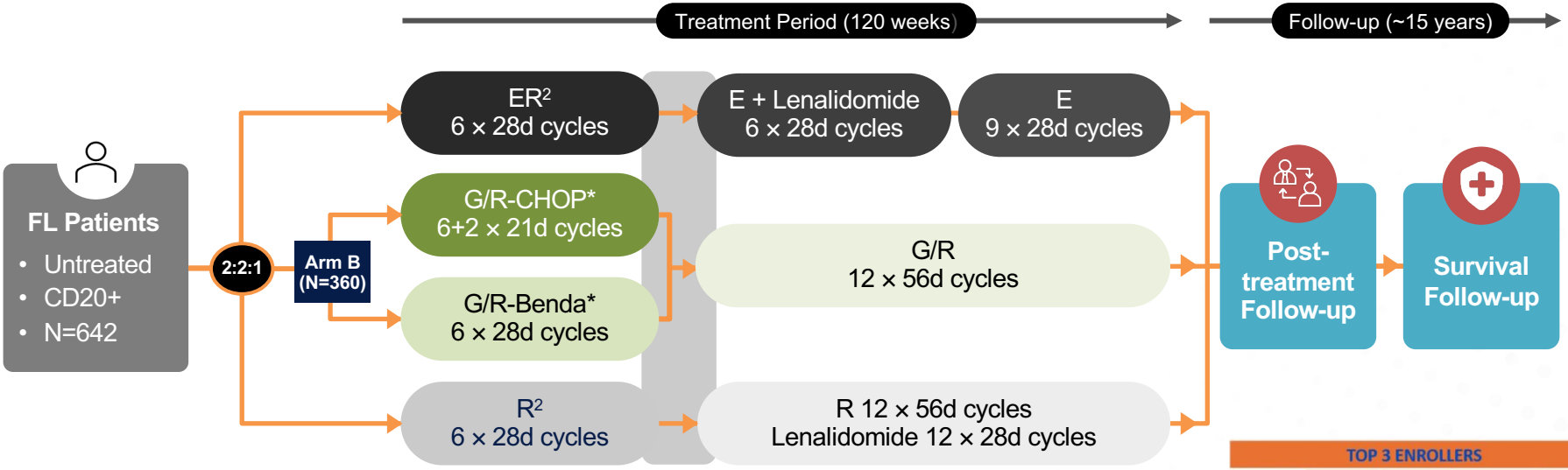
33-month DOR, 84%

33-month OS, 84%

[a]COVID-19 includes COVID-19 or COVID-19 pneumonia. [b]CRS signs and symptoms included fever in 10 patients, hypotension in 3, hypoxia in 1 and other symptoms in 4 patients. Dose-optimization strategies from other epcoritamab studies, such as the EPCORE 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, a learning incorporated into the approved dosing regimen for enhanced mitigation.[2] [c]Local injection site reactions include injection site reactions as high-level group terms. [d]Neutropenia includes neutropenia or neutrophil count decreased. [e]Serious infections include serious TEAEs in the system organ class of Infections and Infestations. [f]Median follow-up 19.7 months. [g]Previous deaths were due to acute respiratory failure in the context of pneumonia (n = 1) and post-acute COVID syndrome (n = 1). 1. Falchi L, et al. *HemaSphere* 2024;8(Suppl 1). Abstract P1146.

Leslie et al., ASH 2025;

Phase 3 multicenter, randomized, open-label trial to evaluate the safety and efficacy of epcoritamab + rituximab and lenalidomide compared to CIT in previously untreated FL



Primary Endpoint: CR rate at Month 30 or Week 120

TOP 3 ENROLLERS

	Country	PI Name	Site Name	Patients Enrolled
TOP 3	China	Rong Tao	Fudan University Cancer Hospital	42
2	Italy	Caterina Patti	Azienda Ospedaliera Ospedali Riuniti Villa Sofia Cervello	18
3	Australia	Joshua Tobin	Princess Alexandra Hospital	17

Other Key Endpoints: PFS, OS, MRD negativity, PROs, incidence and severity of AEs and changes in laboratory values, incidence of dose interruptions, reductions, and discontinuations

Ongoing phase 3 studies

Table 3. Ongoing phase 3 randomized studies with anti-CD3/CD20 bispecific antibodies in first-line FL

	EPCORE FL-2 (NCT06191744)	MorningLyte (NCT06284122)	OLYMPIA-1 (NCT06091254)	OLYMPIA-2 (NCT06097364)
Experimental agent	Epcoritamab	Mosunetuzumab	Odronextamab	Odronextamab
Route of admnistration	SC	SC	IV	IV
Experimental arm(s)	Epcoritamab + R^2 followed by epcoritamab maintenance (ratio 1:1 with control arm)	Mosunetuzumab + lenalidomide followed by mosunetuzumab maintenance (ratio 1:1 with control arm)	Odronextamab induction and maintenance (ratio 1:1 with control arm)	Odronextamab + CHOP/CVP followed by odronextamab maintenance or odronextamab + CHOP/CVP without maintenance (ratio 1:1:1 with control arm)
Control arm	R/O + CHOP/bendamustine followed by anti-CD20 maintenance	R/O + CHOP/bendamustine followed by anti-CD20 maintenance	R + CHOP/CVP/ bendamustine followed by anti-CD20 maintenance	R + CHOP/CVP followed by R maintenance
Primary end point	CR30 (PET-CT Lugano 2014) and PFS (dual end point)	PFS	CR30	PFS
Supplementary arm(s)*	R^2 only and epcoritamab + R^2 without maintenance	None	None	None
Patient population	Stage II to IV disease with at least one GELF high tumor burden criterion (any FLIPI)	Stage I to IV disease with at least 1 GELF high tumor burden criterion FLIPI 2-5	Stage II bulky or stage III/IV (any FLIPI)	Stage II bulky or stage III/IV (any FLIPI)
Planned enrollment	~1080 patients	~790 patients	~446 patients	~669 patients

The studies were included based on the data available at the ClinicalTrials.gov website and conference abstracts by end of 2024 (subject to amendments).

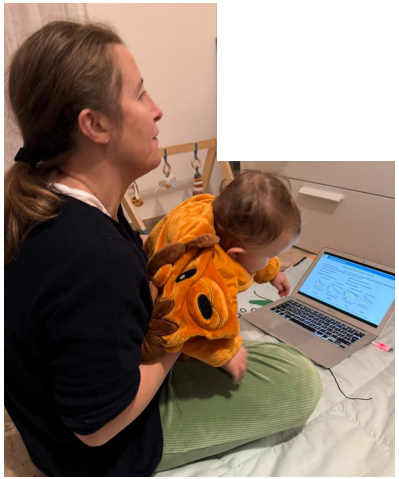
CR30, CRR at 30 months; NA, not available; SC, subcutaneous.

*Not directly powered for primary end point statistical comparison (exploratory arm of treatment).

Conclusions

- Overall survival not modified by initial choice
- First line therapy has a critical role in determining:
  - «functional» cure
  - long term events
  - Not just a matter of options, strategy matters
- Chemo free options are valid alternatives to ICT: Frail/old populations or other?
- Expected changes in 1L with incresing number of chemo free options
- Should be able to improve outcomes
  - OS?
  - Risk profiling/mechanisms of resistance
  - Transformations
  - Late events (SPM, Infections)

«Trasforming the current treatment paradigm in first line by moving from prognostic markers to predictive biomarkers will be achieved through further research into the biology of follicular tumoral B cells and their microenviroment «



Grazie per l’attenzione