POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

Luca Arcaini

Linfomi indolenti

Divisione di Ematologia, Fondazione IRCCS Policlinico San Matte & Dipartimento di Medicina Molecolare, Università di Pavia

Disclosures of Luca Arcaini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
EUSA Pharma							
Novartis							
Roche						X	
Janssen-Cilag						X	
Incyte						X	
BMS						X	
Kite/Gilead						X	
ADC Ther						X	
Morphosys			X				

FOLLICULAR LYMPHOMA

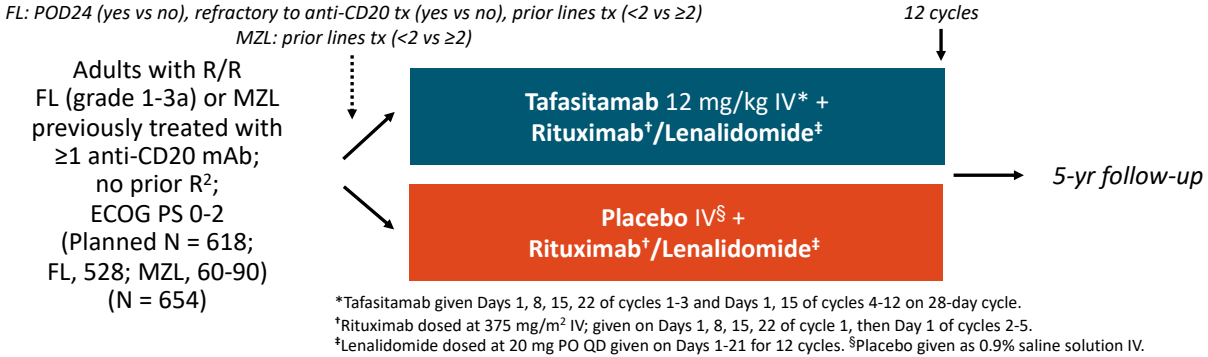
New chemo-free approaches

Sehn et al. *Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma: Results from a Phase 3 Study (inMIND)*

InMIND: Tafasitamab + R^2 vs R^2 Alone in R/R FL or MZL

ASH 2024; Abstract LBA-1

- Global, double-blind, placebo-controlled, randomized phase III trial
  - Tafasitamab: Fc-engineered humanized anti-CD19 mAb



*Tafasitamab given Days 1, 8, 15, 22 of cycles 1-3 and Days 1, 15 of cycles 4-12 on 28-day cycle.
†Rituximab dosed at 375 mg/m^2 IV; given on Days 1, 8, 15, 22 of cycle 1, then Day 1 of cycles 2-5.
‡Lenalidomide dosed at 20 mg PO QD given on Days 1-21 for 12 cycles. §Placebo given as 0.9% saline solution IV.

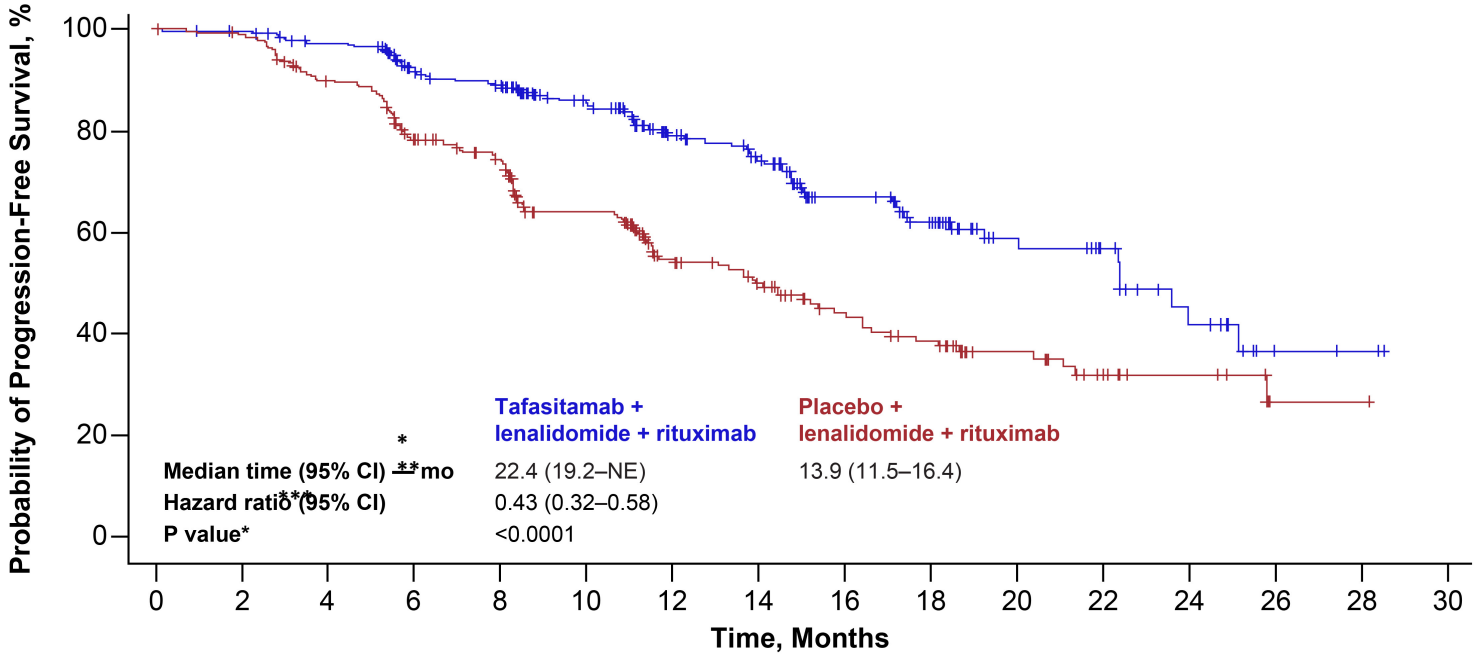
- **Primary endpoint:** PFS by investigator per Lugano 2014 criteria in FL population
- **Key secondary endpoints:** PFS in overall population, PET/CR at EOT and OS in FL population

Baseline characteristics

Variable	Tafasitamab + lenalidomide + rituximab (N = 273)	Placebo + lenalidomide + rituximab (N = 275)	Total (N = 548)
Median age, years (range)	64.0 (36, 88)	64.0 (31, 85)	64.0 (31, 88)
≥ 65	136 (49.8)	136 (49.5)	272 (49.6)
≥ 75	54 (19.8)	54 (19.6)	108 (19.7)
Male sex	150 (54.9)	149 (54.2)	299 (54.6)
ECOG PS at screening			
0	181 (66.3)	192 (69.8)	373 (68.1)
1	85 (31.1)	75 (27.3)	160 (29.2)
2	7 (2.6)	8 (2.9)	15 (2.7)
Bone marrow involvement			
Yes	66 (24.2)	65 (23.6)	131 (23.9)
No	126 (46.2)	122 (44.4)	248 (45.3)
Unknown	3 (1.1)	6 (2.2)	9 (1.6)
Missing	78 (28.6)	82 (29.8)	160 (29.2)
Ann Arbor Stage			
I or II	52 (19.0)	50 (18.2)	102 (18.6)
III or IV	221 (81.0)	225 (81.8)	446 (81.4)
GELF criteria	222 (81.3)	232 (84.4)	454 (82.8)
FL grade			
1 or 2	203 (74.4)	203 (73.8)	406 (74.1)
3A	67 (24.5)	71 (25.8)	138 (25.2)
B-symptoms	63 (23.1)	67 (24.4)	130 (23.7)
FLIPI score			
0 or 1	57 (20.9)	57 (20.7)	114 (20.8)
2	79 (28.9)	67 (24.4)	146 (26.6)
3-5	137 (50.2)	150 (54.5)	287 (52.4)

Variable	Tafasitamab + lenalidomide + rituximab (N = 273)	Placebo + lenalidomide + rituximab (N = 275)	Total (N = 548)
Median no. of prior lines of therapy (range)	1.0 (1, 7)	1.0 (1, 10)	1.0 (1, 10)
1	147 (53.8)	153 (55.6)	300 (54.7)
2	66 (24.2)	71 (25.8)	137 (25.0)
3	39 (14.3)	30 (10.9)	69 (12.6)
≥4	21 (7.7)	21 (7.6)	42 (7.7)
R/R status to last therapy			
Relapsed	148 (54.2)	164 (59.6)	312 (56.9)
Refractory	112 (41.0)	97 (35.2)	209 (38.1)
Undetermined	13 (4.8)	14 (5.1)	27 (4.9)
Refractory to prior CD20	118 (43.2)	115 (41.8)	233 (42.5)
POD24-positive	85 (31.1)	88 (32.0)	173 (31.6)
Time since last anti-lymphoma therapy			
≤2 years	147 (53.8)	157 (57.1)	304 (55.5)
>2 years	126 (46.2)	118 (42.9)	244 (44.5)
Median time since initial diagnosis of FL, years (range)	5.2 (0, 34)	5.5 (1, 33)	5.3 (0, 34)
FL diagnosis confirmed by central pathology	256 (93.8)	259 (90.5)	505 (92.2)

PFS by investigator assessment



No. at Risk																
Tafasitamab + lenalidomide + rituximab	273	261	250	212	200	164	119	103	71	57	30	22	12	3	2	0
Placebo + lenalidomide + rituximab	275	265	235	192	173	126	82	70	48	40	26	16	10	2	2	0

- Median follow-up for PFS was of 14.1 months

PFS details

mPFS, Mo (95% CI)	Tafasitamab + LEN/R (n = 273)	Placebo + LEN/R (n = 275)	HR (95% CI)	*P* Value
mPFS by investigator (primary endpoint)	22.4 (19.2-NE)	13.9 (11.5-16.4)	0.43 (0.32-0.58)	<.0001
mPFS by IRC	NR (19.3-NE)	16.0 (13.9-21.1)	0.41 (0.29-0.56)	<.0001

mPFS, Mo (95% CI, n)	Tafasitamab + LEN/R	Placebo + LEN/R	HR (95% CI)
POD24 ▪ Yes ▪ No	 19.2 (13.8-NE, n = 85) 23.6 (22.3-NE, n = 188)	 11.3 (8.3-13.6, n = 88) 16.0 (13.3-21.4, n = 187)	 0.43 (0.27-0.69) 0.45 (0.31-0.65)
Anti-CD20 refractory ▪ Yes ▪ No	 15.0 (14.1-25.1, n = 118) 24.0 (22.3-NE, n = 155)	 8.6 (7.9-11.6, n = 115) 18.2 (14.4-NE, n = 160)	 0.44 (0.30-0.65) 0.44 (0.28-0.68)

PFS benefit for 1 prior line of treatment (HR: 0.48; 95% CI: 0.32-0.74) and ≥0.41; 95% CI: 0.28-0.61)

PFS benefit of tafasitamab was observed in all prespecified subgroups

inMIND: Response, PET-CR, and OS

PET-CR (FDG-Avid Population)	Tafasitamab + LEN/R (n = 251)	Placebo + LEN/R (n = 254)
Postbaseline PET assessments, n (%)	201 (80.1)	205 (80.7)
Best metabolic response by PET, n (%) ▪ CMR ▪ PMR ▪ NMR/SD ▪ PMD ▪ Not done	124 (49.4) 37 (14.7) 19 (7.6) 19 (7.6) 50 (19.9)	101 (39.8) 39 (15.4) 12 (4.7) 51 (20.1) 46 (19.3)
PET-CR rate, % (95% CI)	49.4 (43.1-55.8)	39.8 (33.7-46.1)
Odds ratio (95% CI) Nominal *P* value	1.5 (1.04-2.13) .0286	

- Median DoR: 21.2 mo (95% CI: 19.5-NE) with tafasitamab vs 13.6 mo (95% CI: 12.4-18.6) with placebo (HR: 0.47; 95% CI: 0.33-0.68; *P* <.0001)

Result	Tafasitamab + LEN/R (n = 273)	Placebo + LEN/R (n = 275)
Best overall response, n (%) ▪ CR ▪ PR ▪ SD ▪ PD ▪ NE ▪ Not done	142 (52.0) 86 (31.5) 28 (10.3) 7 (2.6) 2 (0.7) 8 (2.9)	112 (40.7) 87 (31.6) 46 (16.7) 20 (7.3) 0 10 (3.6)
ORR, % (95% CI)	83.5 (78.6-87.7)	72.4 (66.7-77.6)
Odds ratio (95% CI) Nominal *P* value	2.0 (1.30-3.02) .0014	
Median time to next tx, mo (95% CI)	NR (NE-NE)	28.8 (20.7-NE)
HR (95% CI)	0.45 (0.31-0.64) P <.0001	
mOS, mo (95% CI)	NR (27.9-NE)	NR (NE-NE)
HR (95% CI)	0.59 (0.31-1.13)	

inMIND vs AUGMENT

	inMIND[1]		AUGMENT[2]
Variable	**Tafasitamab + LEN/R (n = 273)**	**Placebo + LEN/R (n = 275)**	**LEN/R (n = 147)**
Median age, yr	64	64	62
Male, %	55	54	42
Ann Arbor stage IV at enrollment, %	55	59	30
FL grade 3A, %	25	26	12
FLIPI high risk (score 3-5), %	50	55	37
ECOG PS 0, %	66	70	67
ECOG PS 1/2, %	34	30	33
B symptoms presence, %	23	24	8
GELF high tumor burden (y), %	81	84	52
Refractory to last prior regimen, %	41	35	18
Refractory to anti-CD20, %	43	42	-

- Outcomes of the inMIND placebo group were poorer than the AUGMENT study group, but inMIND patients were higher risk
  - Refractory to rituximab (anti-CD20 mAb) was an exclusion in AUGMENT[2]

Alderuccio et al. *Loncastuximab tesirine with rituximab induces robust and durable complete metabolic responses in high-risk relapsed/refractory follicular lymphoma*

Study Design

Phase II single arm and single center investigator-initiated study

Study design

- Simon's minimax two-stage design
- Sample size of 39 patients
- Clinically meaningful CR rate ≥50% (≤30% (H0))
- Type I error alpha 5% and power 80%

A total of ≥17 CRs among study cohort are required to reject the H0

Study endpoints

Primary endpoint:

- CR at week 12 by Lugano response criteria

Secondary endpoints:

- Overall response rate
- Safety and tolerability
- 2-year progression-free survival and overall survival

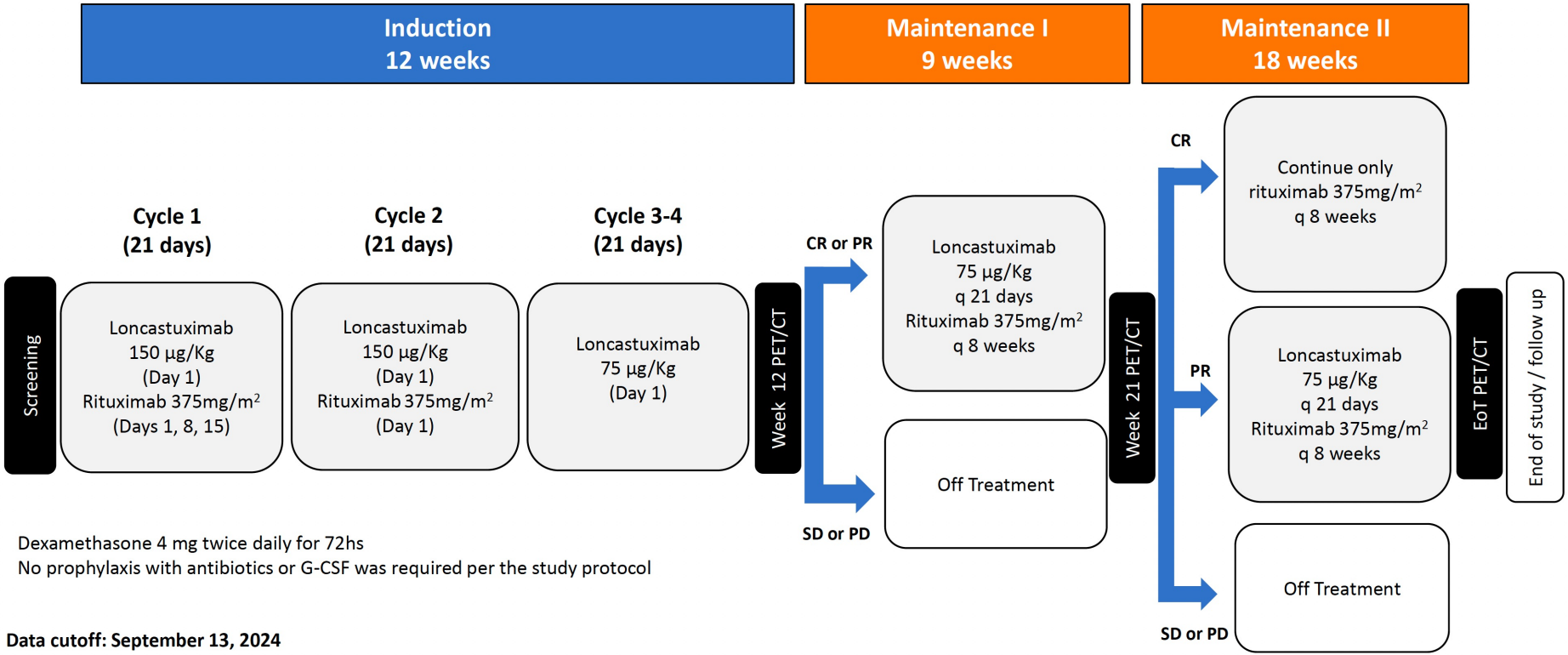
Key inclusion criteria

- R/R FL grade 1, 2 or 3A
- Previously treated with ≥1 line of systemic therapy
- Need for treatment based on GELF criteria, POD24, or second relapse
- ECOG PS 0 to 2
- Measurable disease by Lugano classification
- Adequate organ function

Safety analysis: ≥1 dose of loncastuximab
Efficacy analysis ≥3 doses of loncastuximab

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

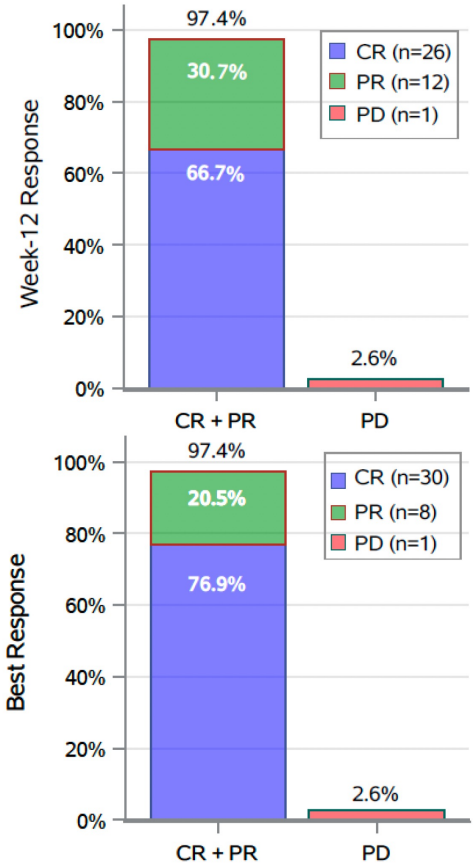
Study Schema

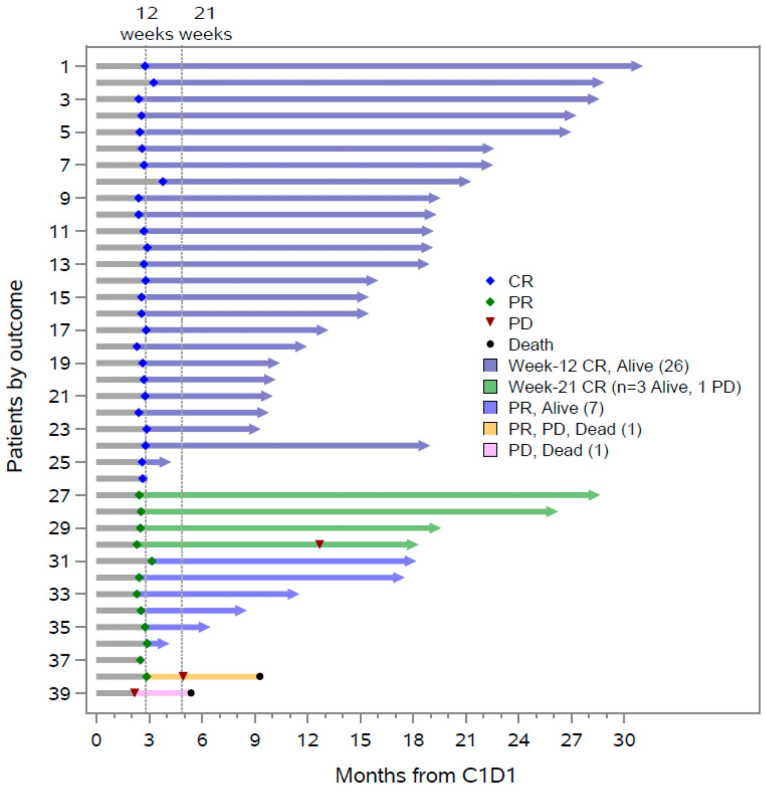


Dexamethasone 4 mg twice daily for 72hs
No prophylaxis with antibiotics or G-CSF was required per the study protocol

Data cutoff: September 13, 2024
Median follow-up: 18 (95% CI 12-19.3) months

Efficacy





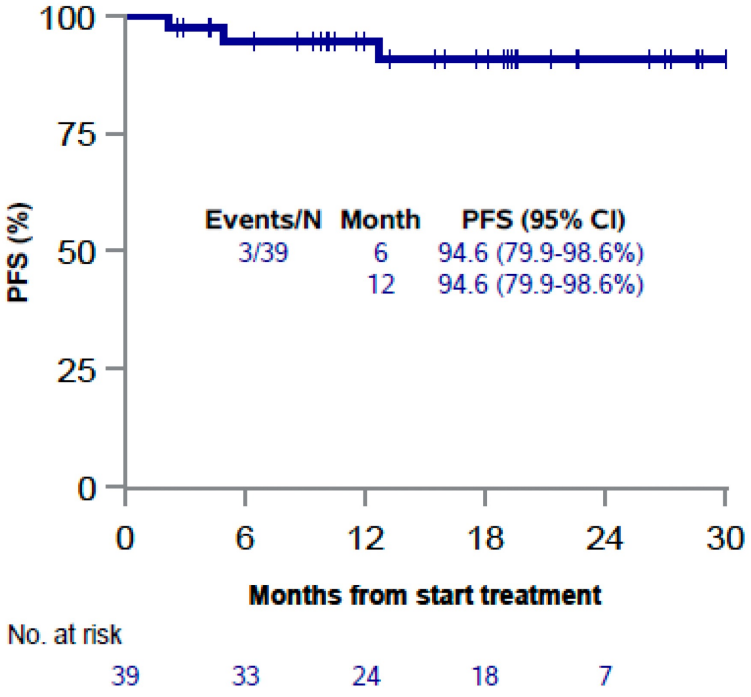
SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

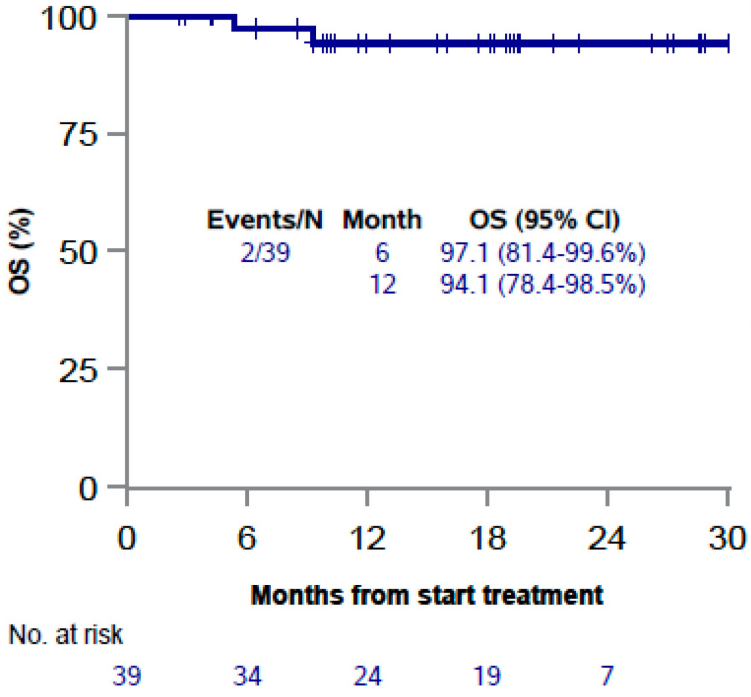
The null hypothesis was rejected (one-sided p<0.0001)

Post-hoc Efficacy Analyses

	n	Best ORR	Best CR rate
POD24	20	100%	85%
High risk FLIPI score	24	96%	67%
Prior transformed FL	11	100%	73%
Rituximab with an alkylating agent	32	100%	75%

Time-to-Event Endpoints





Falchi et al. *Single-agent mosunetuzumab produces high complete response rates in patients with newly diagnosed follicular lymphoma: Primary analysis of the MITHIC-FL1 trial*

Endpoints:

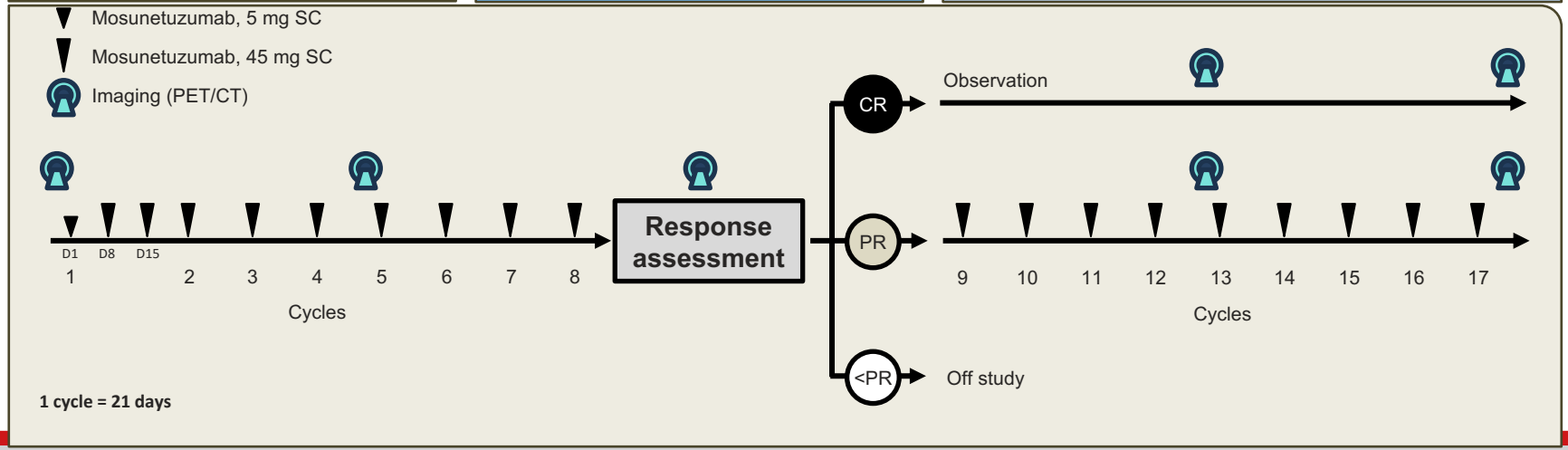
- **Primary:** CR rate per Lugano
- **Secondary:** ORR, safety, PFS, DOR, TTNT, OS
- **Exploratory:** PD, ctDNA monitoring

Eligibility:

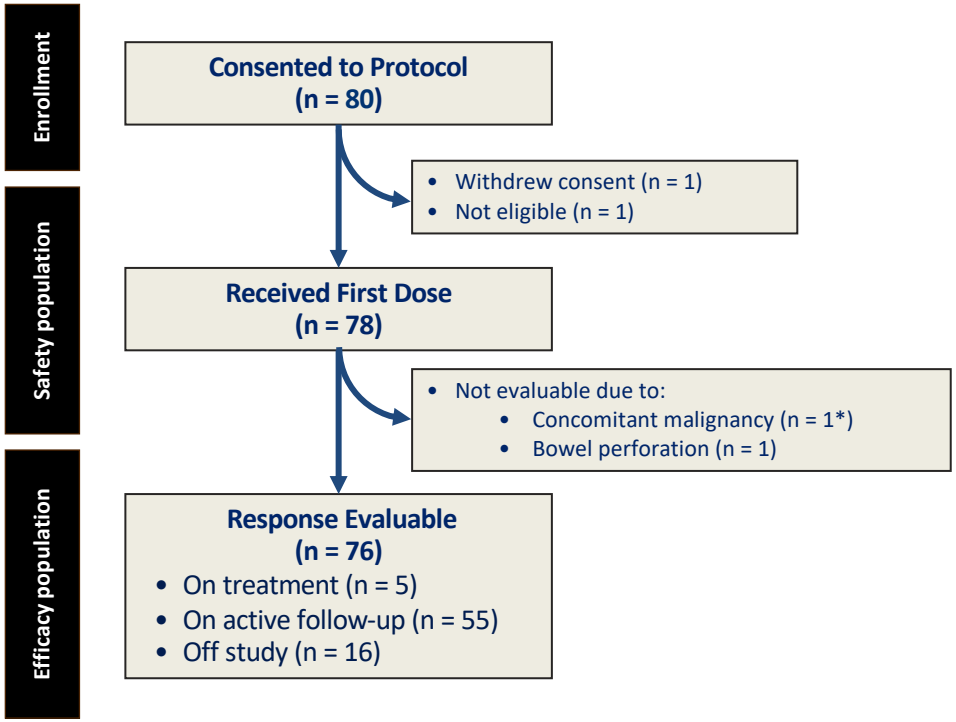
- ≥18 years; PS 0-2
- CD20+ previously untreated FL,
- G1-3A, stage II–IV
- **Need of therapy per GELF criteria**

Outpatient administration:

- Dexamethasone, anti H2, acetaminophen in C1 (and C2 if prior CRS)
- VZV and PJP prophylaxis and GCSF support per treating physician



Patient disposition

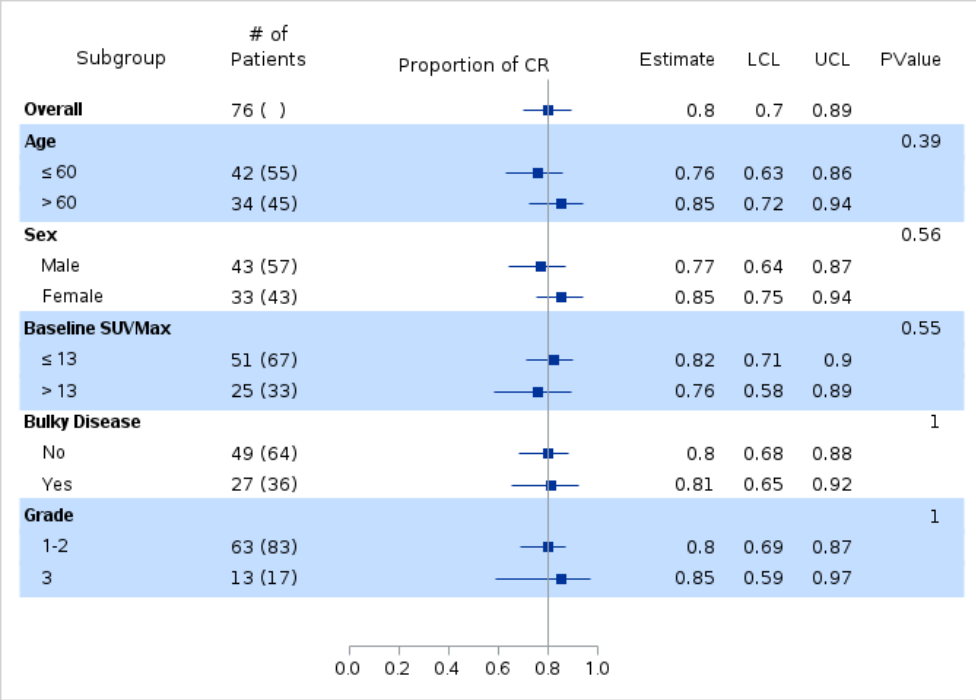


- Data cut-off date: November 1, 2024
- **Median follow-up: 14.8 months**
- **Median duration of therapy: 4.8 months**
- **Total n. patient-cycles: 694**
  - Delayed cycles: 33 (5%)
  - Median delay (days): 7 (6-29)
- **Discontinued therapy: 6 (8%)**
  - Progression: 1
  - Adverse events: 4
  - Physician decision: 1

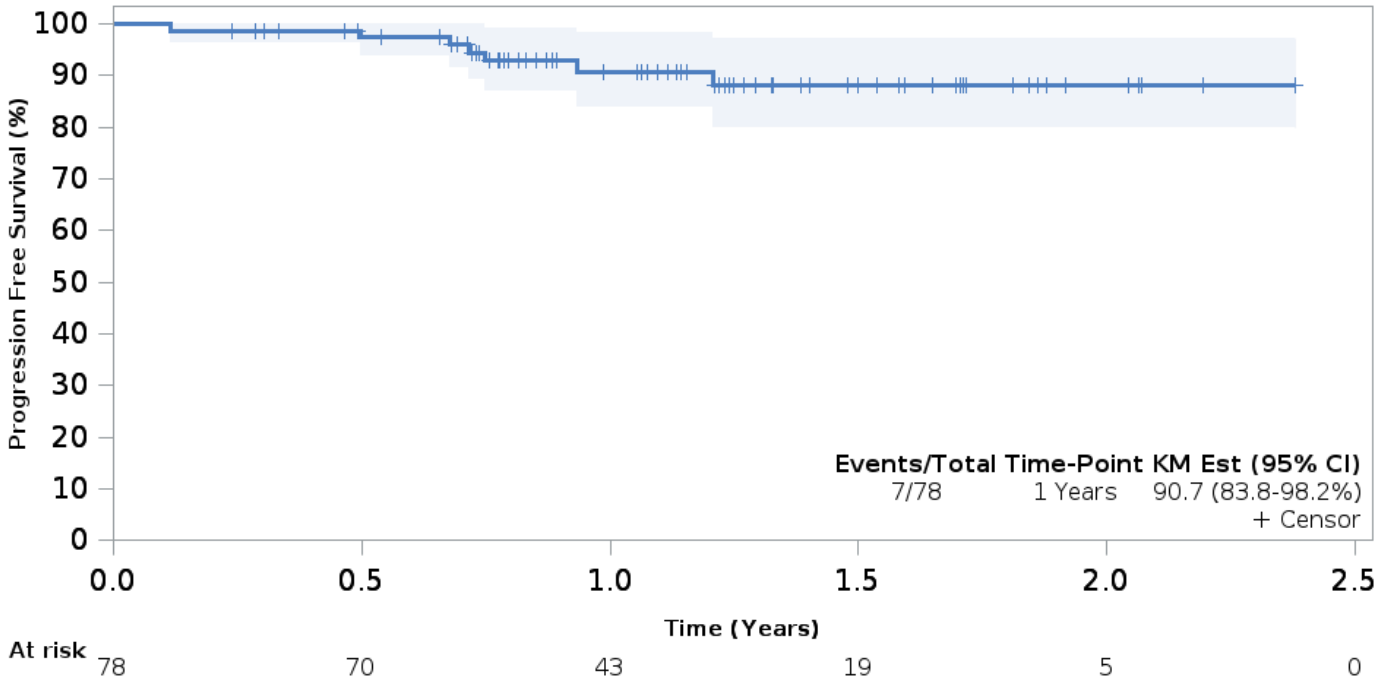
Safety population includes all patients who received at least one dose of mosunetuzumab. Efficacy population includes all patients who had at least one evaluable radiographic response scan; *1 patient discontinued due to persistent grade 2 neuropathy (“first-bite” syndrome) likely unrelated to study drug; 1 due to concurrent histiocytic sarcoma; 1 due to ventricular fibrillation in patient with pneumonia and COVID infection

Response rates

Response type	**Response evaluable (N=76)**	Intention-to-treat (N=78)
Overall response	**96%**	94%
Complete response	**80%**	78%
Partial response	16%	15%
Stable disease	3%	3%
Progressive disease	1%	1%
Non-evaluable	n/a	3%



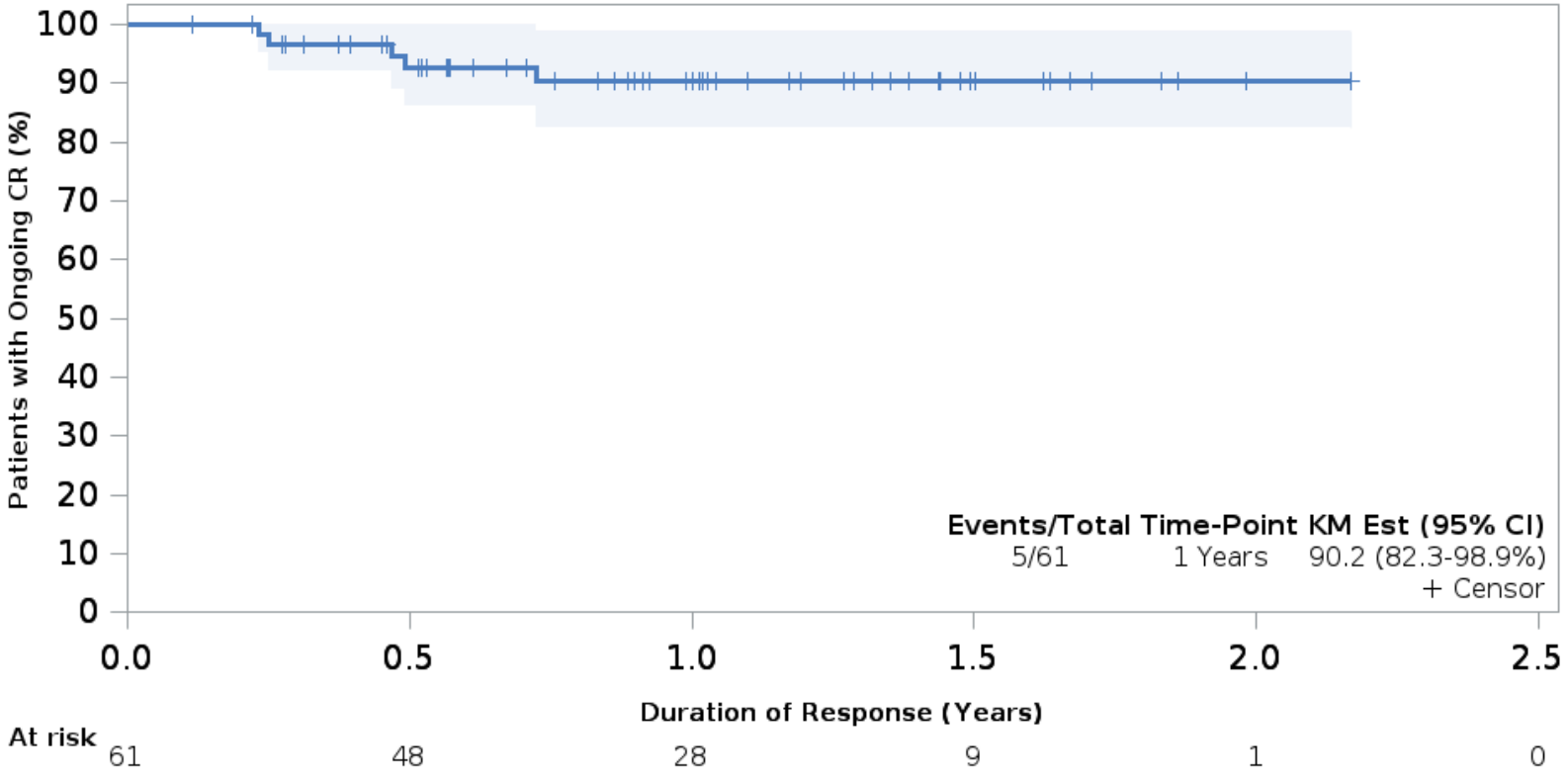
Progression-free survival



- **An estimated 91% of patients remained progression-free at 1 year**
- 7 patients progressed:
  - 3 patients had CD20-POD with FL histology
  - 3 patients had transformation to DLBCL (one of whom 6 weeks after study entry); all are in complete remission after i-CHT

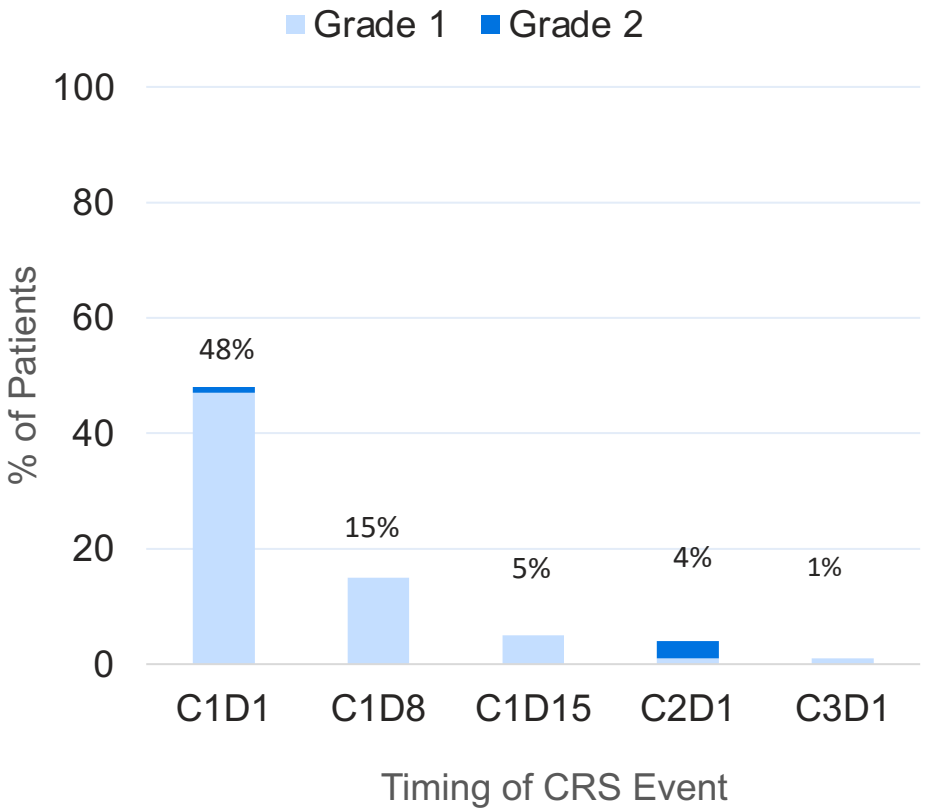
Duration of CR

An estimated 90% of patients who achieved CR, maintained their response at 1 year



Cytokine release syndrome

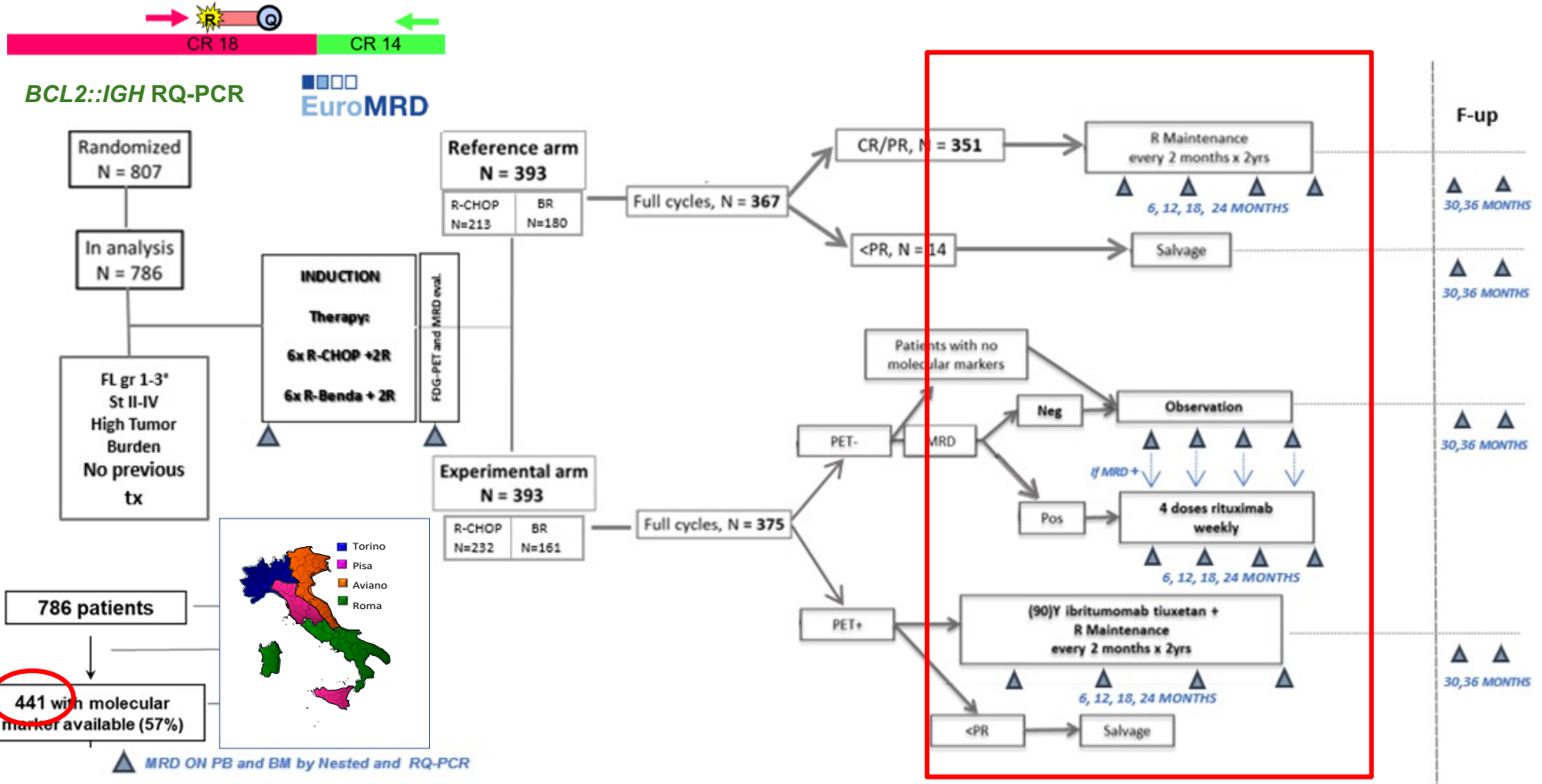
CRS*	All patients (N=78)
Incidence	42 (54%)
Grade 1	40 (51%)
Grade 2	2 (3%)
n. unique CRS episodes	59
Median time to onset, h (range)	
1st episode	24 (3 – 91)
2nd episode	44 (19 – 312)
3rd episode	80 (76 – 83)
Resolved	59 (100.0%)
Median time to resolution, h (range)	22 (2 – 264)
Corticosteroid use	12 (20%)
Tocilizumab use	3 (5%)
CRS leading to hospitalization	4 (7%)
CRS leading to SAE	4 (7%)



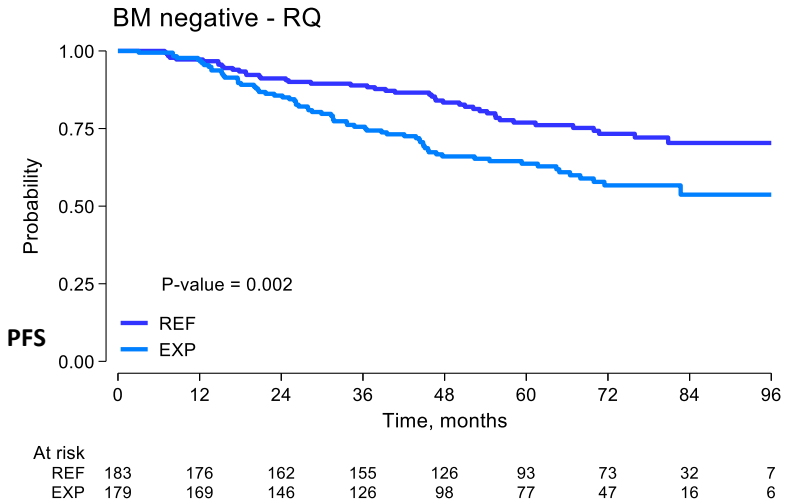
*Graded according to Lee et al. Biol Blood Marrow Transplant 2019 Apr;25(4):625-638

MRD and transplant

Ferrero et al. *Impact of MRD analysis in the era of rituximab maintenance in follicular lymphoma: Data from "FOLL12" phase III trial of the Fondazione Italiana Linfomi*

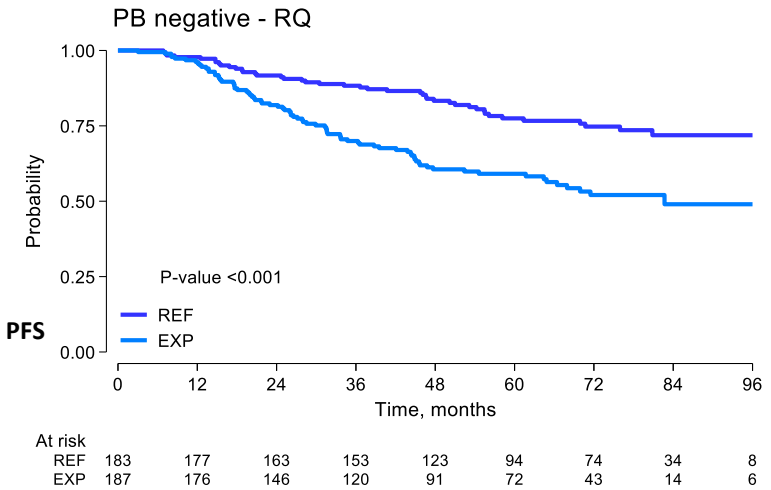


R maintenance benefited MRD- pts at EOI



REF

EXP

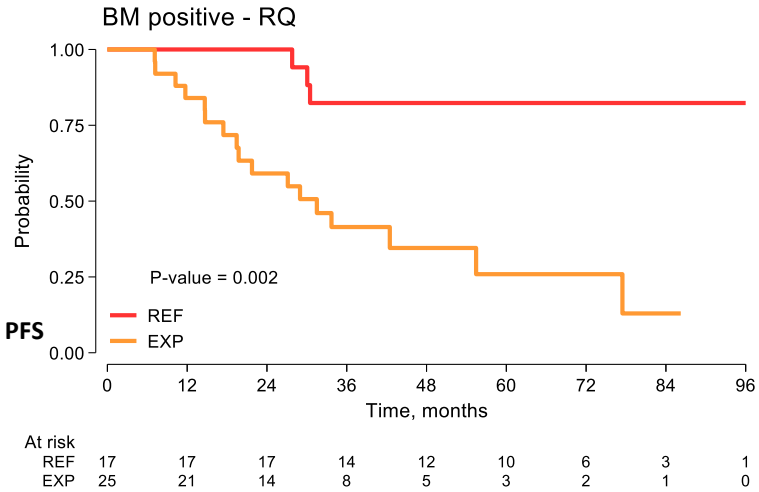


5-yr PFS REF vs EXP: 77% vs 64% (p=0.002)

Rituximab maintenance preserved persistent MRD negativity overtime, by halving the risk of MRD recurrence

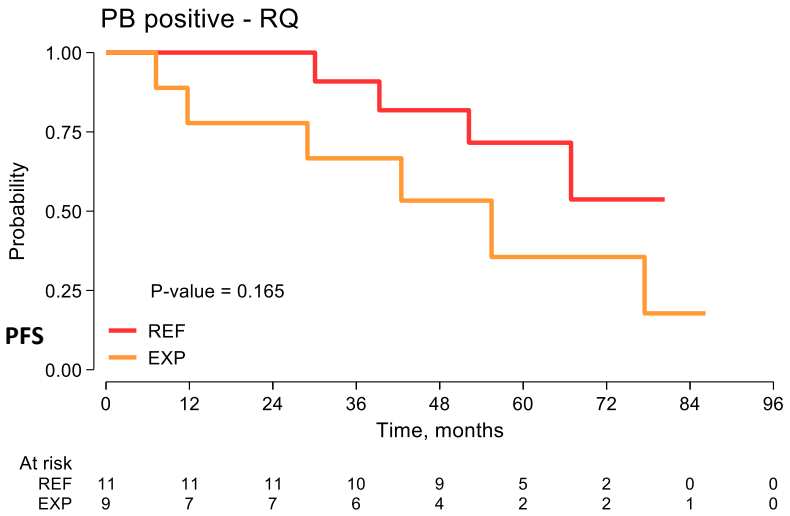
Median FU: 68 months

R maintenance benefited also MRD+ pts at EOI



REF

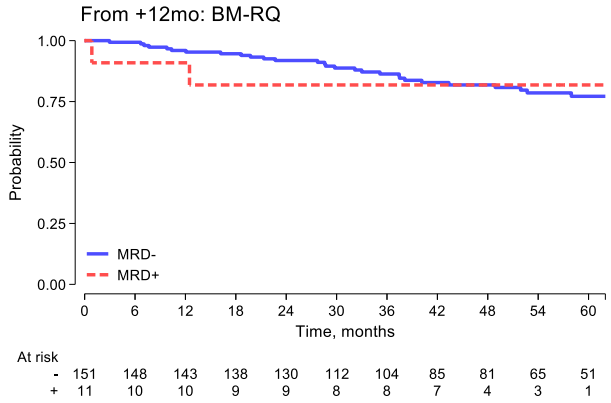
EXP

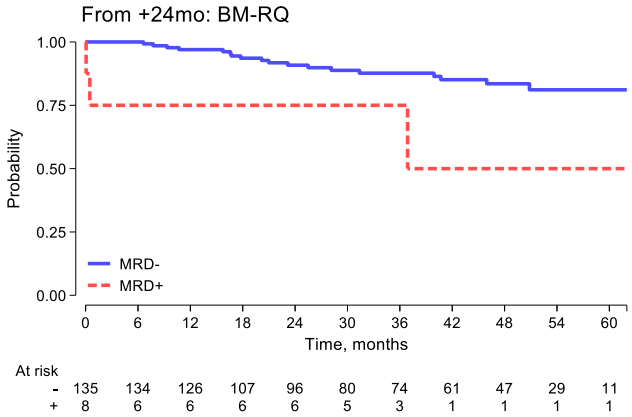


Rituximab maintenance mitigated the impact of MRD positivity, delaying the occurrence of clinical relapse

Median FU: 68 months

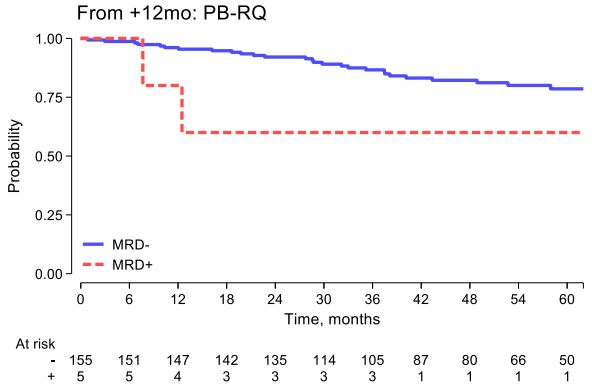
MRD+ after EOI predictive of PFS during RM

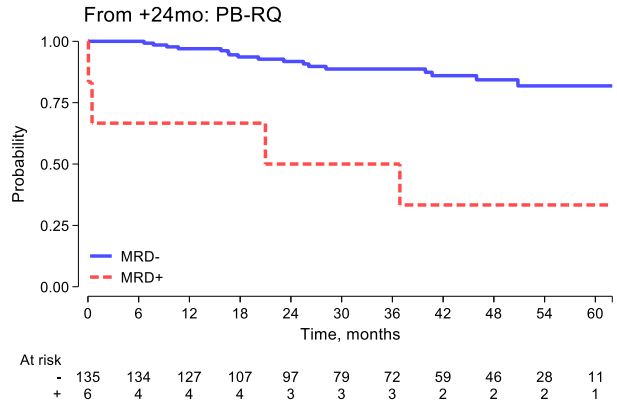




The persistence or reappearance of **MRD+ in PB** during rituximab maintenance predicted a worse PFS (**HR 2.58, p=0.003**)

MRD+ (REF)



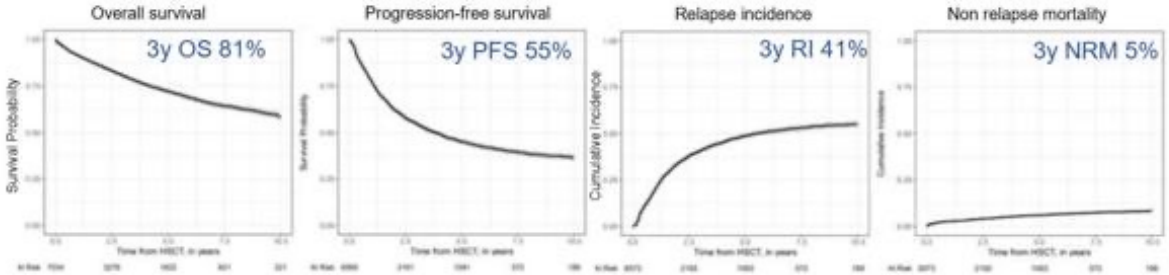


Serroukh et al. ***Outcome of Hematopoietic Stem Cell Transplantation for Follicular Lymphoma, a Benchmark Study from the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation***

2010-2022: 7330 ASCT patients ; transplant in CR 53%

Autologous stem cell transplantation

Median follow-up 3.2y



Multivariable analysis autologous stem cell transplantation (2016-2022)

Characteristic	Overall survival (n=2642)			Progression-free survival (n=2399)			Relapse incidence (n=2401)			Non Relapse Mortality (n=2401)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age at HSCT, 5y interval	1.23	1.15-1.31	<0.001	1.06	1.02-1.10	0.004	1.04	0.99-1.08	0.091	1.28	1.12-1.45	<0.001
Female vs Male sex	0.87	0.69-1.08	0.2	0.90	0.79-1.04	0.2	0.90	0.77-1.04	0.14	0.99	0.66-1.48	>0.9
≥3 vs <3 lines before SCT	1.26	1.01-1.56	0.038	1.26	1.10-1.44	0.001	1.28	1.10-1.48	<0.001	1.11	0.74-1.66	0.6
Disease status at SCT												
PR vs CR	1.90	1.52-2.38	<0.001	1.77	1.54-2.04	<0.001	1.80	1.55-2.09	<0.001	1.57	1.04-2.36	0.031
R/R vs CR	2.63	1.76-3.92	<0.001	1.86	1.40-2.47	<0.001	1.93	1.43-2.60	<0.001	1.39	0.55-3.50	0.5
Karnofsky ≥ 90 vs < 90	0.64	0.51-0.81	<0.001	0.71	0.61-0.83	<0.001	0.75	0.64-0.89	<0.001	0.50	0.33-0.76	0.001
TBI yes vs no	1.71	0.55-5.34	0.4	1.28	0.57-2.87	0.5	0.97	0.36-2.61	>0.9	3.15	0.77-12.9	0.11

Allogeneic stem cell transplantation

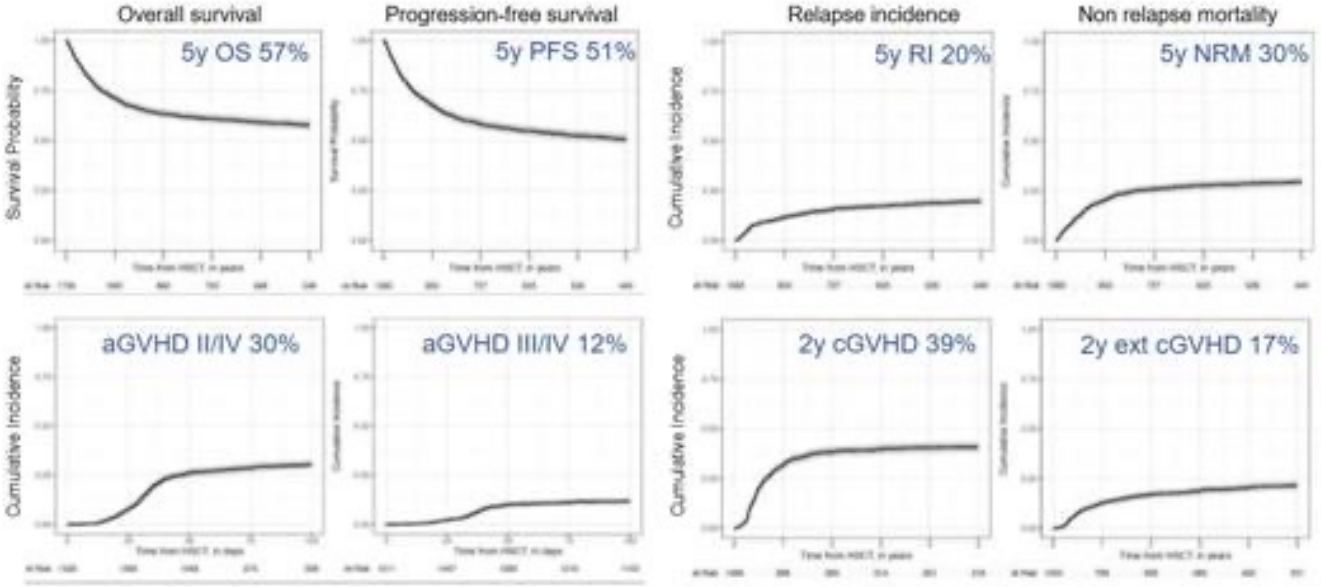
WHOLE COHORT 2010-2022	n = 1744
Age at allo	
Median (IQR)	54 (47-60)
Range	18-77
Male sex	62%
Time from diagnosis allo median (IQR)	54 mo (47-60)
Disease status at allo	
CR	45%
PR	33%
Refractory	22%
Previous ASCT	51%
Cell source PBSC	91%

WHOLE COHORT 2010-2022	n = 1744
Donor Type	
Haplo	**7%***
Sibling	34%
MUD	56%
Other or missing	3%
Conditioning	
MAC	28%
RIC	72%
TBI	22%
GVHD prophylaxis	
ATG	33%
PTCy	**11%***

Subgroup 2016-2022	n = 631
*Haplo	14%
*PTCy	24%

Allogeneic stem cell transplantation

Median follow-up 5.2y



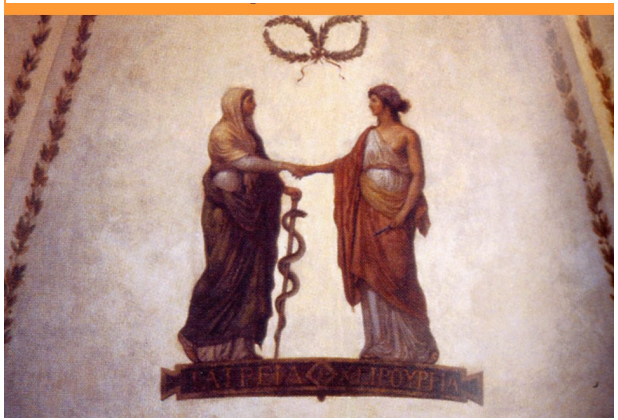
INDOLENT NON-FOLLICULAR LYMPHOMA

Buske et al. ***Bortezomib in combination with ibrutinib/rituximab is a highly effective and well tolerated first – line treatment for Waldenström's macroglobulinemia: results of the multicenter phase II trial (ECWM-2) of the European Consortium for Waldenström's macroglobulinemia***

- **Bortezomib** (1.6 mg/ m^2 s.c. d1,8,15)
- **Rituximab** (375 mg/m^2 i.v C1 d1, 1400 mg absolute s.c C2-6 d1)
- **Ibrutinib** (420 mg p.o. daily) 6 cycles

followed by RM (1400 mg s.c; d1 every 2nd mont) + Ibrutinib for 24 mo and subsequent ibrutinib treatment until progression or non-tolerated toxicity)

- 53 patients
- Median age 63 yrs (range 36-84)
- Primary endpoint **1y-PFS 93%**
- ORR 98% - MMR 70% after 3 cycles
- At best response 98% MRR
- Grade ≥3 AEs 45% (most common COVID-19)
- 8 deaths: 5 COVID-19, 3 respiratory tract infection



Aula Scarpa, Teatro Anatomico, Università di Pavia (1758)