9th POSTGRADUATE
Lymphoma
Conference

The new attack on the front line after "Relevance" study: Competitors and pretenders

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Hotel Brunelleschi

President:
P.L. Zinzani

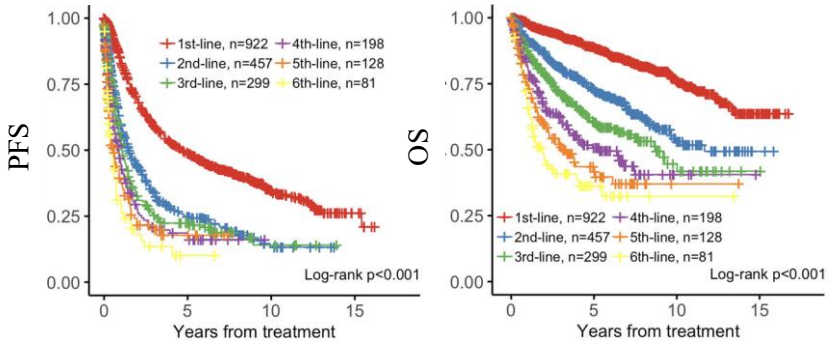
Disclosures

Disclosures of Lorenzo Falchi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Genmab	X		x				
AbbVie	x		x				
Genentech	x		x				
Roche	x		x				
Innate Pharma	x						
Beigene	x						
AstraZeneca	x		x				
Sanofi			x				
Merck			x				
ADC therapeutics						X	
Johnson & Johnson						X	
Kite			x				

FL outcomes over time

Old “dogma”



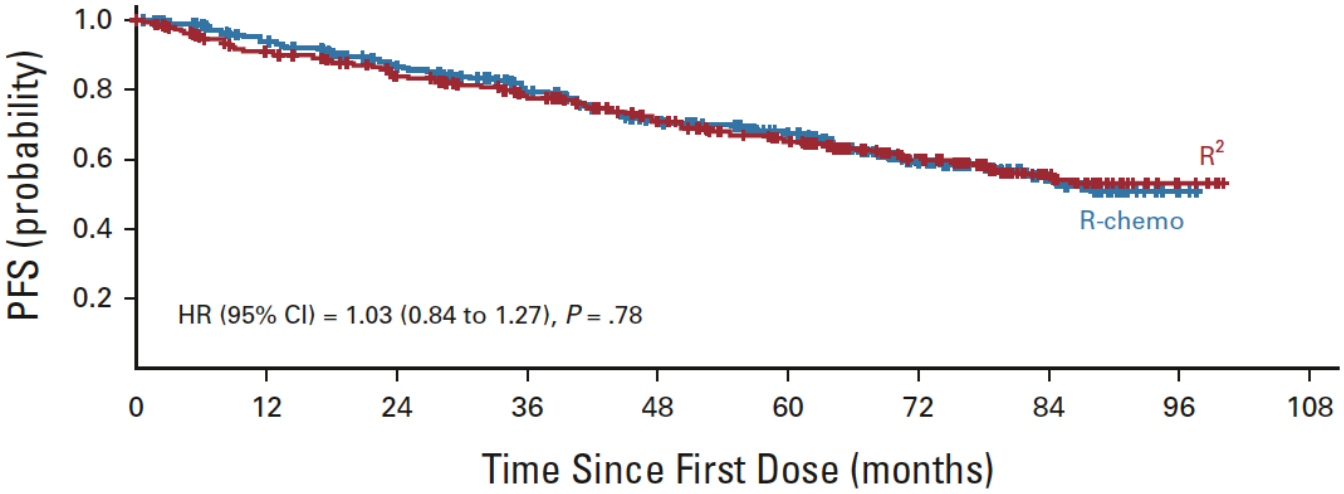
Vs.

Novel agents → New paradigms?

- Lenalidomide
- Tazemetostat
- Tisa-cel
- Mosunetuzumab
- Obinutuzumab-Zanubrutinib
- Liso-cel
- Epcoritamab

Batlevi et al. Blood Cancer J 2020

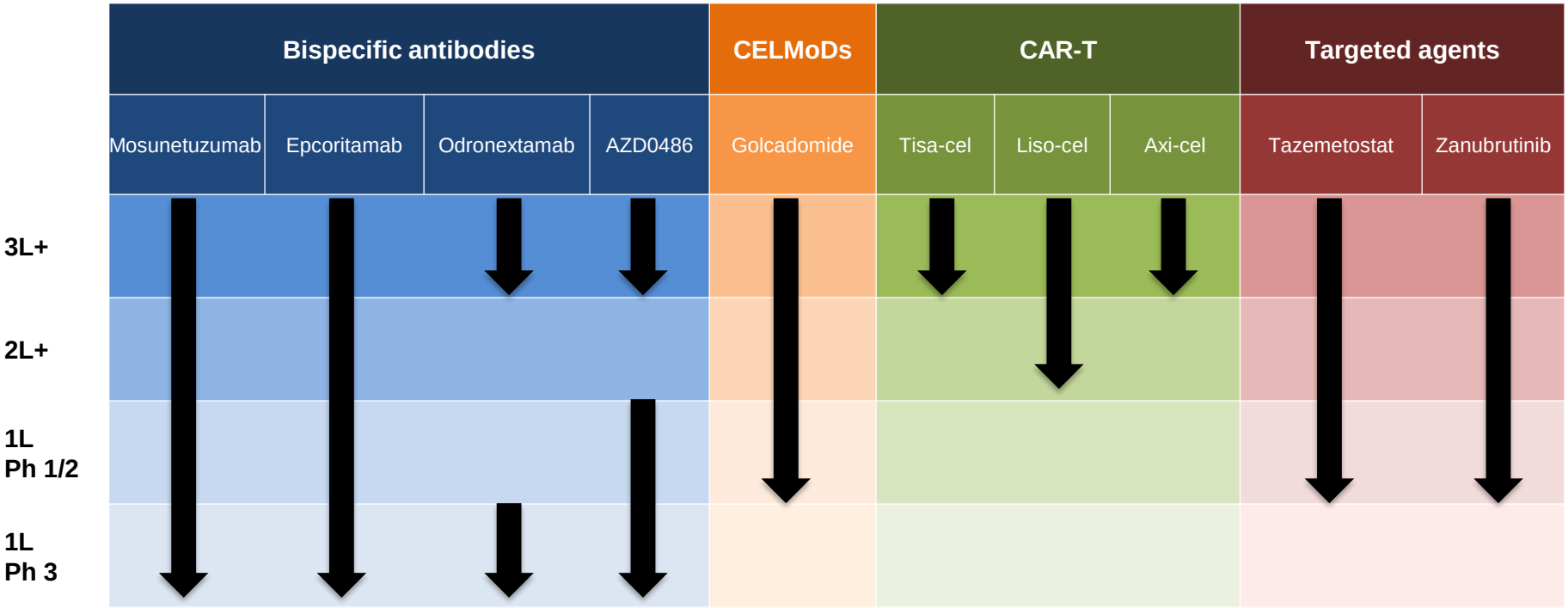
RELEVANCE: a “non-positive” study



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

Morschhauser et al. JCO 2022

A thematic approach to understanding current trial landscape in high-burden FL



Current standard of care: Chemoimmunotherapy

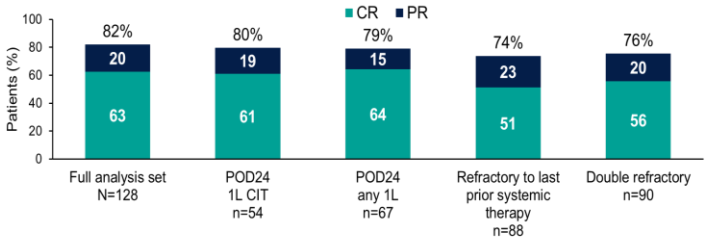
Competitors

(data available in 3L+, 2L+, 1L)

EPCORE NHL-1: Epcoritamab in pts with R/R FL, Phase 1/2

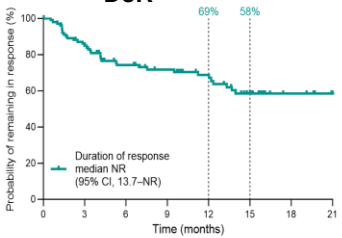
Efficacy Results

High ORRs and CR Rates Across High-Risk Subgroups

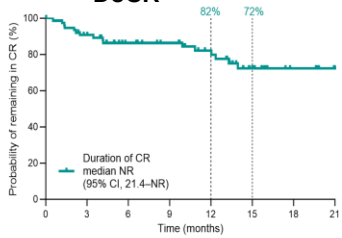


- Median time to response was 1.4 mo (range, 1.0–3.0)
- Median time to complete response was 1.5 mo (range, 1.2–11.1)
- Median time to next antilymphoma therapy was NR (range, 0.2+ to 30.0+)

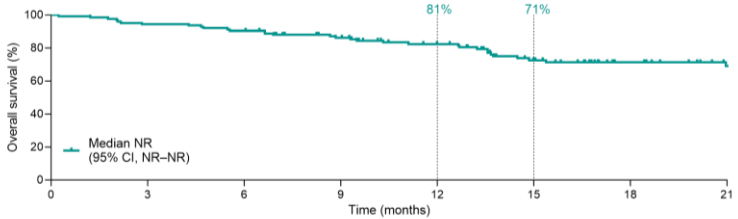
DoR



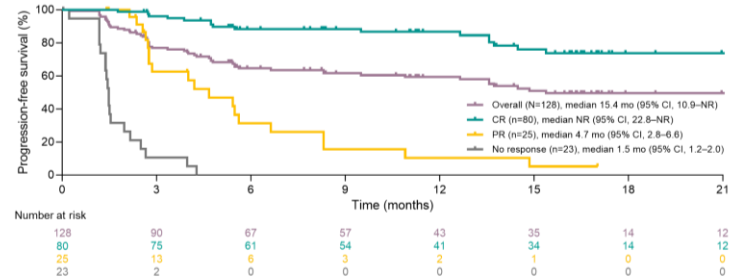
DoCR



Overall Survival Curve Plateaus, With Median NR



Progression-Free Survival Median NR in Complete Responders



- Of 100 MRD-evaluable patients, MRD negativity was achieved in 68 patients and was associated with improved PFS and OS

- Median follow-up: 17.4 months (IQR 9.1 – 20.9)

Linton et al. ASH 2023

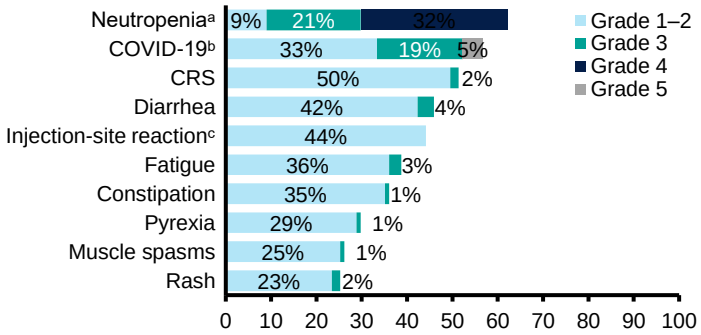
Building upon single-agent epcor: EPCORE NHL-2, Arm 2, Epcor-R^2 Responses and Safety

Study Schema

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						

Best Response, n (%)[a]	N=111
Overall response	**107 (96)**
Complete response	**97 (87)**
Partial response	10 (9)
Progressive disease	2 (2)

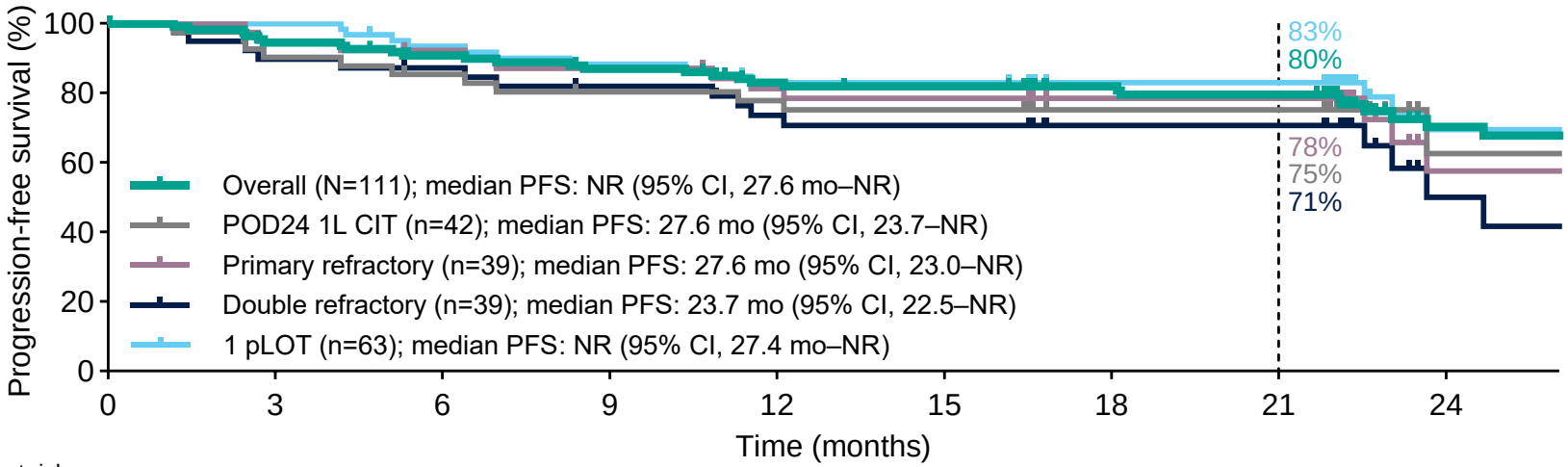
Treatment-emergent adverse events



MRD Negativity, n/n (%)	MRD Evaluable
MRD negativity at any time[b]	66/75 (88)
MRD negative and complete response[c]	63/68 (93)
MRD negativity in high-risk subgroups[d]	
POD24 (1L CIT)	26/30 (87)
Primary refractory	25/28 (89)
Double refractory	23/27 (85)

Falchi et al. ASH 2024

PFS Observed in Most Patients, Highest With 1 pLOT



Patients at risk									
Overall	111	102	95	90	82	80	68	66	29
POD24 1L CIT	42	37	34	31	30	29	21	21	5
Primary refractory	39	37	35	32	28	27	22	22	7
Double refractory	39	35	33	30	26	25	18	18	6
1 pLOT	63	61	55	52	45	45	38	38	13

- Median follow up overall: 25.3 months; Median follow-up for PFS: 22.3 months.

Falchi et al. ASH 2024

Epcor-R^2 in 1L FL (EPCORE NHL-2, Arm 6): Frequent, Durable Responses

Key inclusion criteria
- 1L CD20$^+$ FL, G1-3a
- ECOG PS 0–2
- Measurable disease
- Adequate organ function

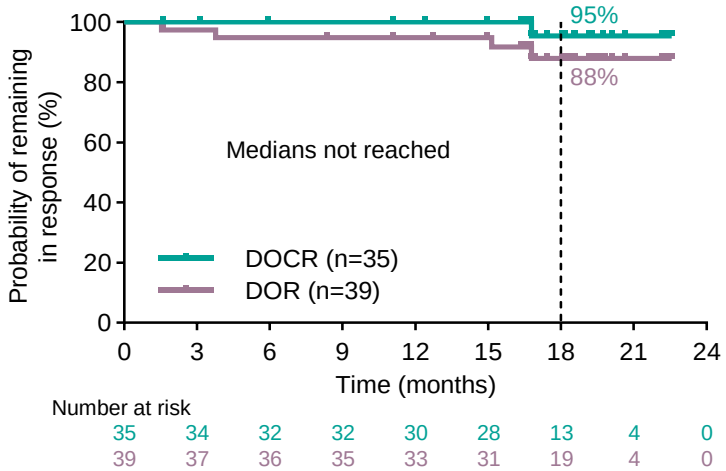
Arm 6 (1L FL) expansion, N=41

Epcoritamab (SC)	Rituximab (IV)	Lenalidomide (oral)
48 mg	**375 mg/m^2**	**20 mg**
QW C1–2, Q4W C3+ (28 d/C)	QW C1, Q4W C2–6	QD for 21 d in C1–12
Treatment up to 2 y		

Median follow-up: 22.8 mo
Primary objective: Antitumor activity (ORR)
Key secondary endpoints: Safety, DOR, DOCR, PFS, OS

	N=41[a]
Overall response, n (%)	**39 (95)**
Complete response, n (%)	**35 (85)**
Partial response, n (%)	4 (10)
Progressive disease, n	0
Median time to response, mo (range)	2.7 (1.2–5.5)
Median time to CR, mo (range)	2.8 (1.4–11.4)

1L, previously untreated; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; mo, month(s); R^2, rituximab + lenalidomide. Kaplan–Meier estimates of DOR and DOCR assessed by investigator. [a]A total of 2 patients were not evaluable.



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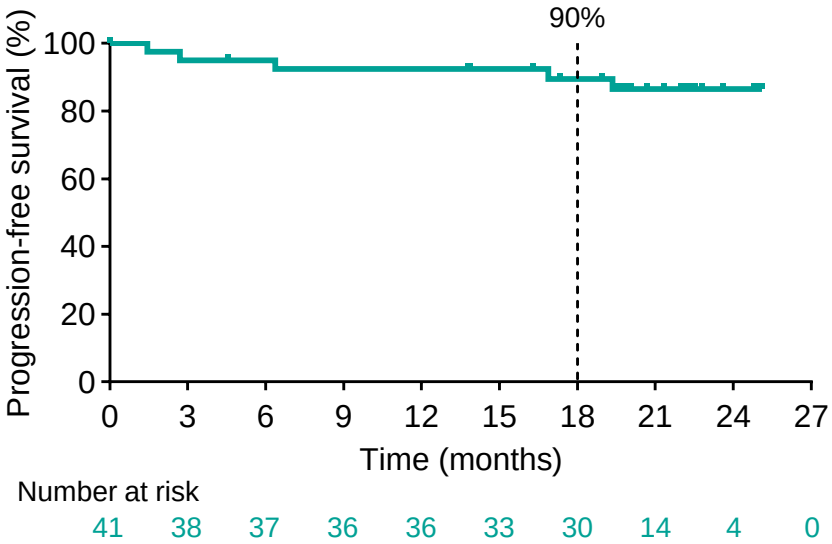
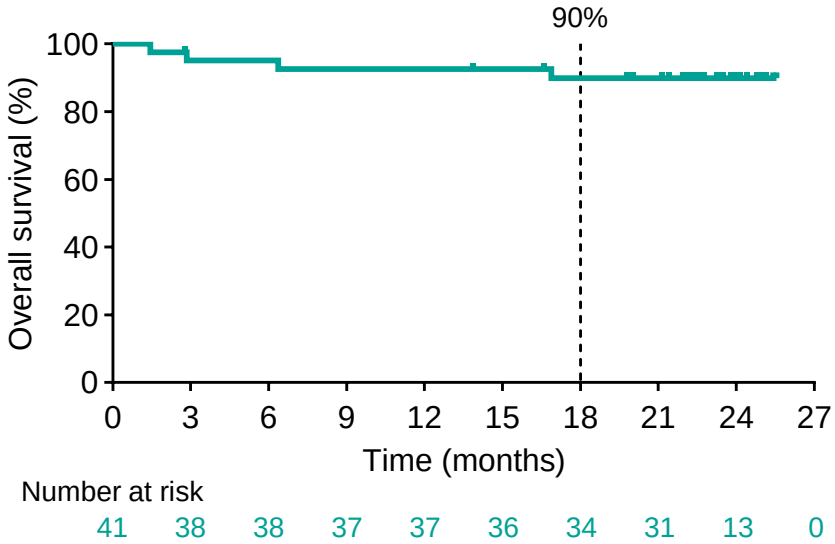
EPCORE NHL-2, Arm 6 (1L FL): PFS and OS





1L, previously untreated; FL, follicular lymphoma. Kaplan–Meier estimate of progression-free survival assessed by investigator.

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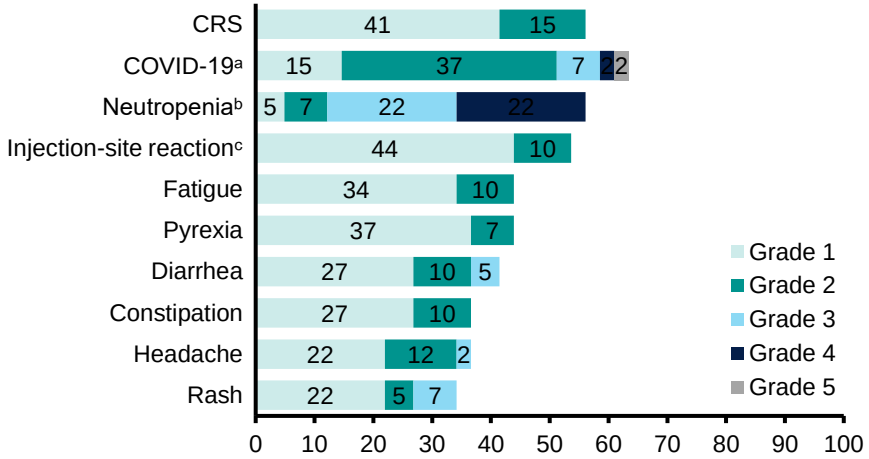
EPCORE NHL-2 Arm 6 (1L FL): Safety



- Common TEAEs were mostly low grade
- TEAEs leading to epcoritamab discontinuation were COVID-19 (n=5), CMV reactivation (n=1), ovarian epithelial cancer and pleural effusion (n=1), pneumonitis (n=1), and toxic skin eruption (n=1)
  - Pleural effusion and ovarian epithelial cancer were not deemed to be related to epcoritamab by the investigator
- Fatal TEAEs were COVID-19 pneumonia and septic shock (n=1 each)

1L, previously untreated; CMV, cytomegalovirus; CRS, cytokine release syndrome; FL, follicular lymphoma; TEAE, treatment-emergent adverse event. [a]Combined term includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 syndrome. [b]Combined term includes neutropenia and decreased neutrophil count. [c]Combined term includes injection-site reaction, erythema, rash, pain, hypersensitivity, and swelling.

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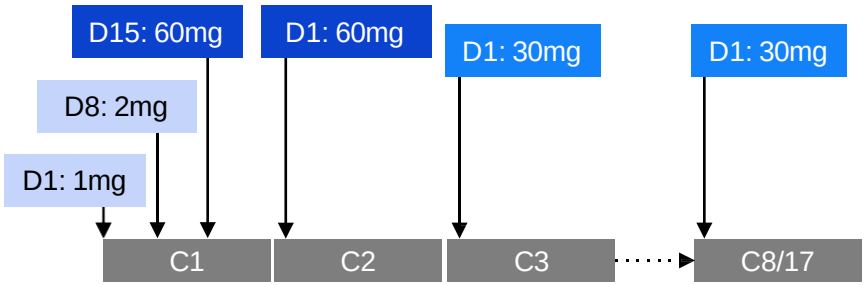
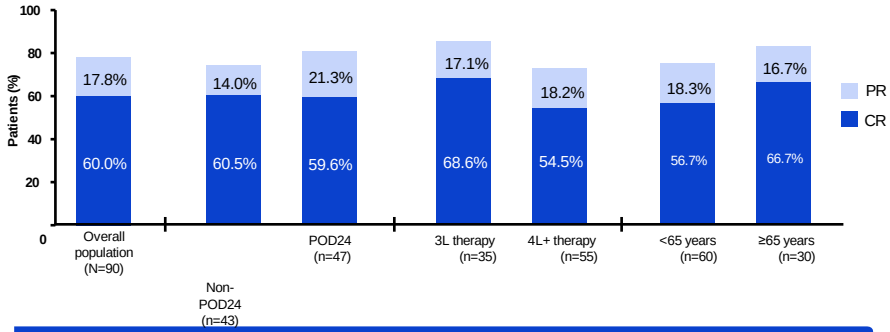
IV mosunetuzumab in 3L+ FL: Key findings

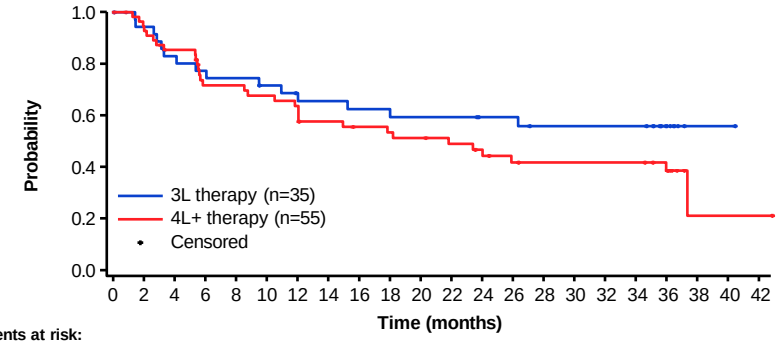
Treatment schema



Responses



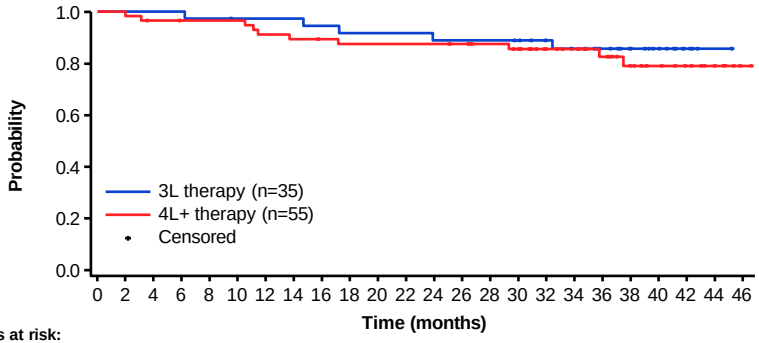
PFS



Patients at risk:

3L therapy	35	32	28	26	25	23	20	20	19	18	18	18	16	16	14	14	14	14	6	1	1	NE
4L+ therapy	55	49	43	34	34	32	27	26	24	23	22	20	17	15	14	14	14	14	10	1	1	1

OS



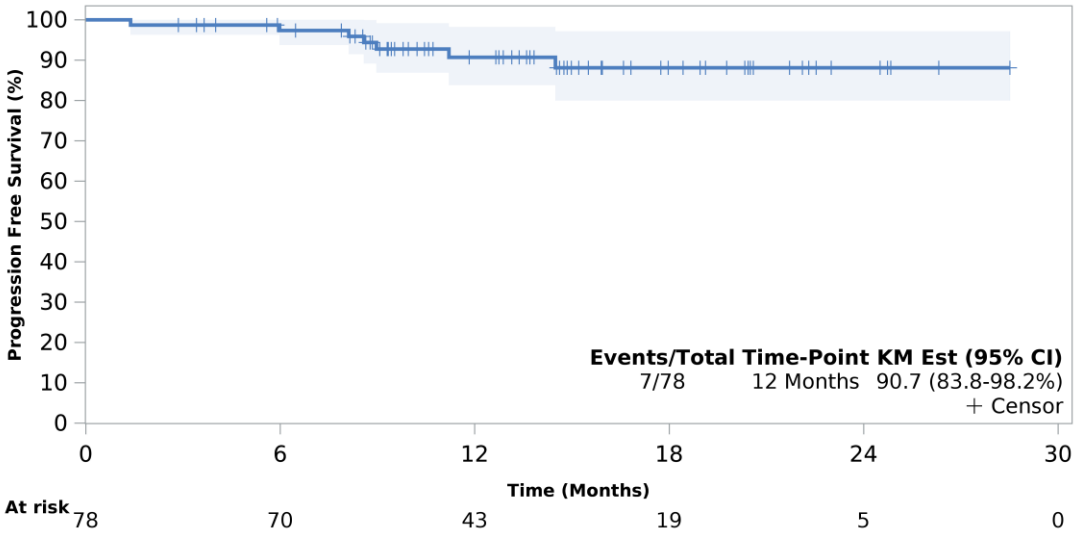
Patients at risk:

3L therapy	35	35	35	35	34	33	33	33	32	31	31	31	30	30	30	28	26	24	19	14	10	3	1	NE
4L+ therapy	55	54	52	51	51	51	48	47	46	45	45	45	45	44	42	38	33	31	26	20	15	13	6	1

Assouline EHA 2024

Moving mosunetuzumab in 1L FL: MITHIC-FL1 trial results

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%



- **An estimated 91% of patients remained progression-free at 1 year**
- 7 patients progressed (3 with CD20- FL, 1, CD20+ FL, 3 with CD20+ DLBCL (one 6 weeks after study entry)

Data cutoff: November 1, 2024; response assessed per the 2014 Lugano criteria and integrated with the 2016 LYRIC criteria; evaluable = patients who received at least one dose of study drug and underwent at least one response assessment;

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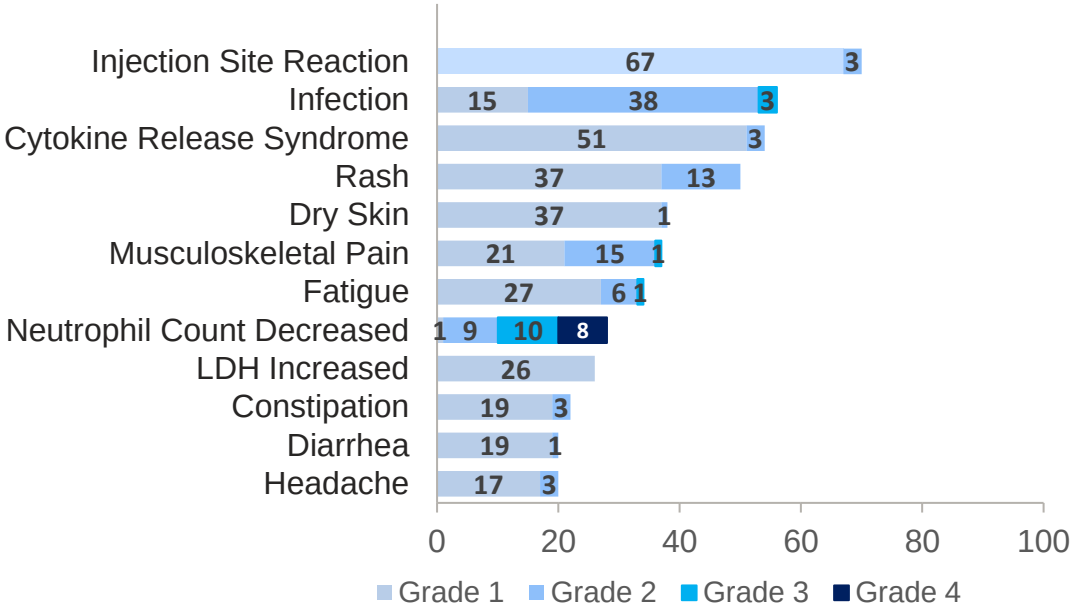
SC mosun in 1L FL: Treatment-emergent adverse events



- **No new safety signal observed**
  Median number of mosunetuzumab cycles: 8 (1-17)
- No ICANS-like toxicities
- No tumor lysis syndrome
- One episode of G2 tumor flare reaction

Less common TEAEs: Febrile neutropenia G3 (4%); ventricular tachycardia in setting of COVID19 pneumonia G5 (1%), dyspnea (G1-2 10%, G3 1%), platelet count decreased (G1-2 14%, G3 1%), syncope G3 (1%), hyperglycemia (G1-2 11%, G3 1%), ALC decreased (G1-2 3%, G3 1%), peritonitis (G3 1%), fracture (G3 1%), anemia (G1-2 12%, G3 1%).

Adverse events are stratified by CTCAE grade. AEs of grade 1-2 occurring in at least 20% of patients and all AEs of grade ≥3 regardless of frequency are reported

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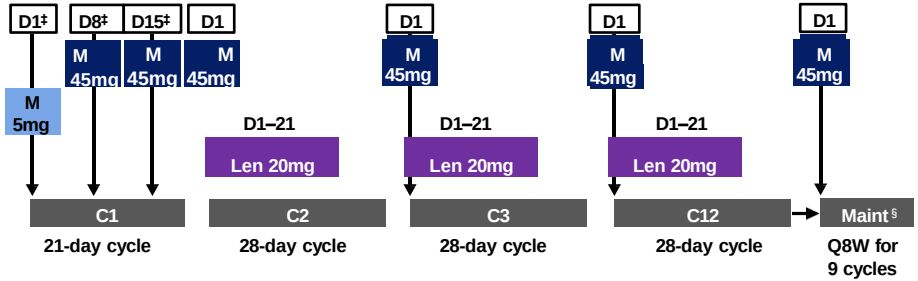
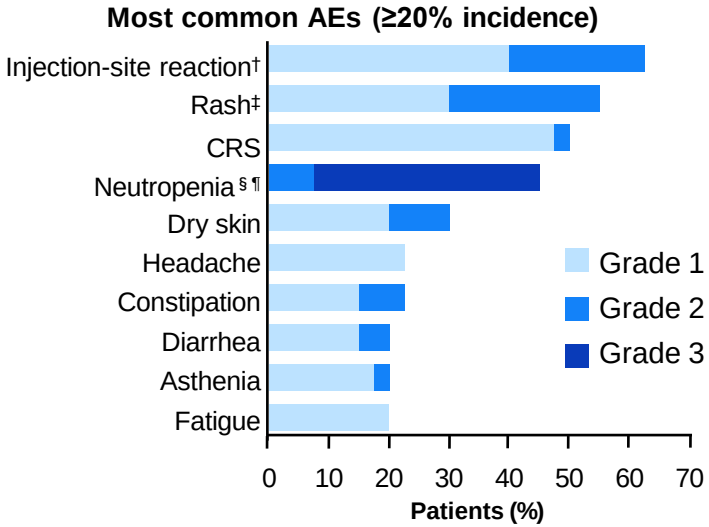
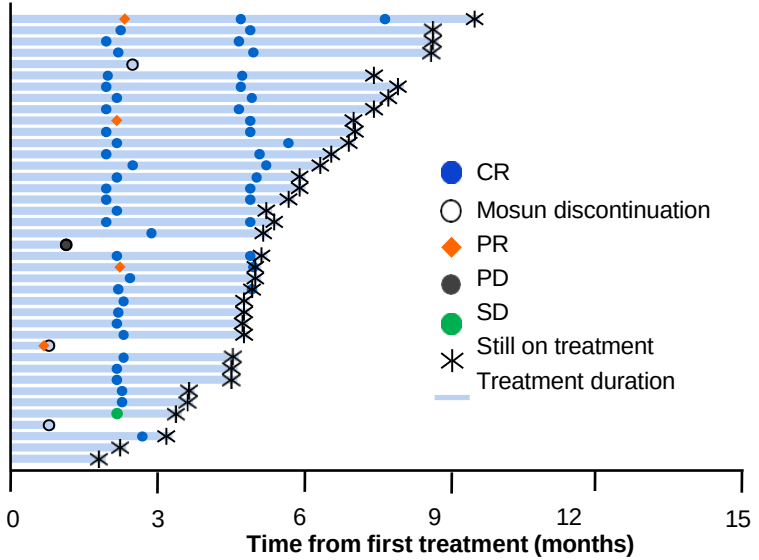
Phase 2 study of 1st line mosunetuzumab and lenalidomide in patients with FL (N=40)





- Median duration of follow-up: 5.2 months (range: 1–10)
- **Best ORR 92%; best CR 89%**



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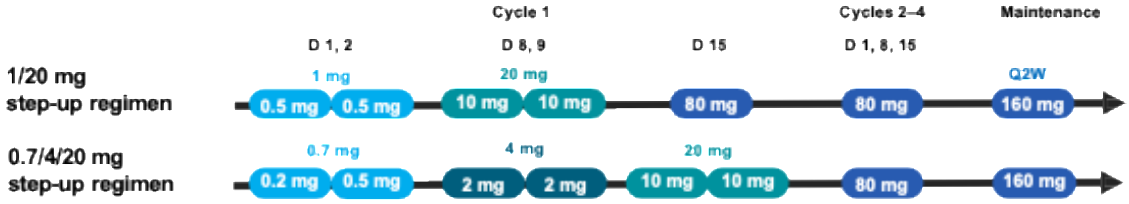
Pretenders

(data not available in 2L+ and/or 1L)

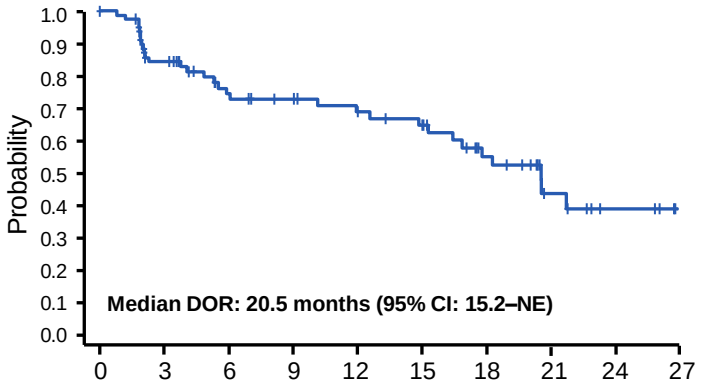
Odronextamab in 3L+ FL: Responses and outcomes



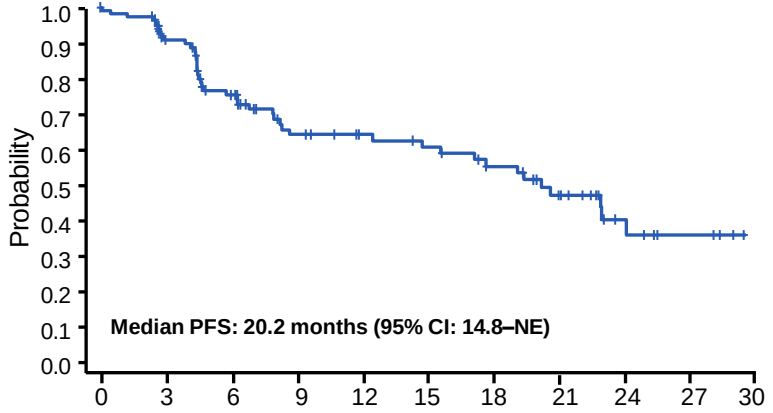
- Initial step-up regimen: 1/20/80 mg; changed to 0.7/4/20 mg based on safety.
- Median follow up 22.4 months (2.6-33)
- Treatment duration: Indefinite

Best response	Independent central review (N=121)
ORR	**81.8%** [95% CI: 73.8–88.2%]
CR	**75.2%**
PR	6.6%
SD	5.8%
PD	4.1%

Duration of response – Independent central review

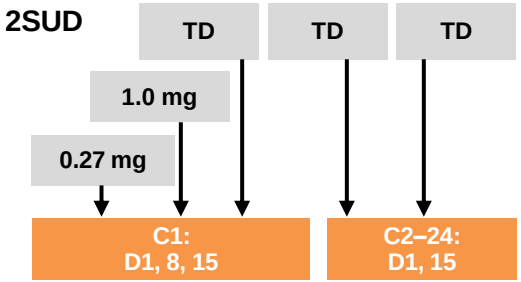


Progression-free survival – Independent central review



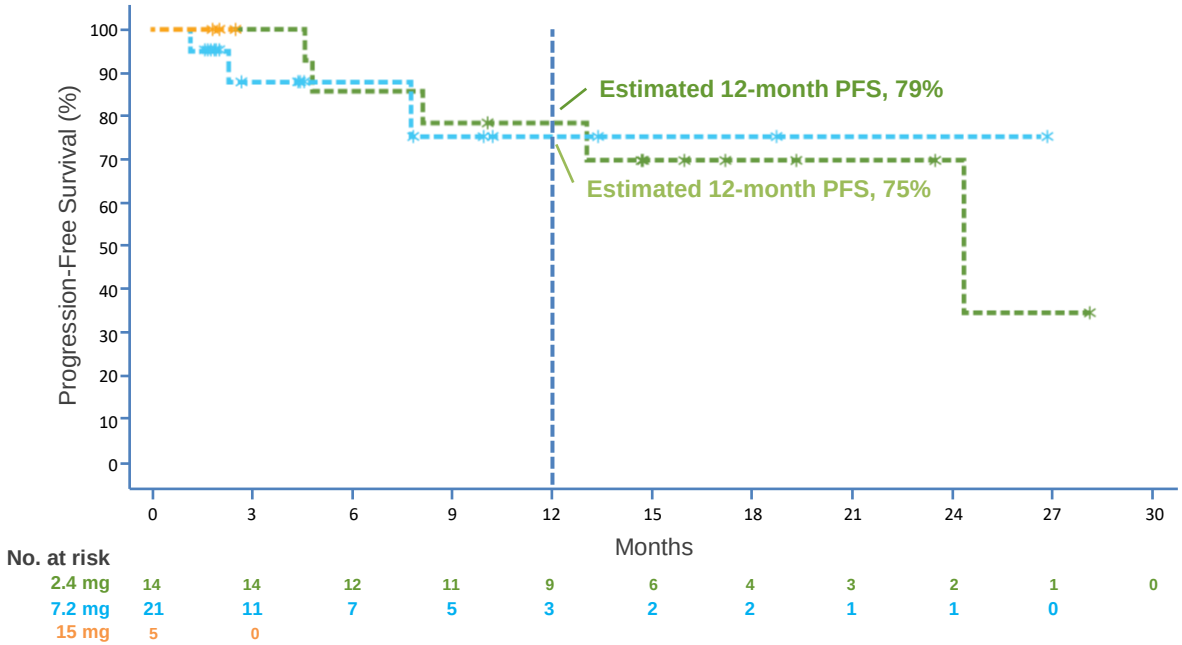
Kim TM et al. ASH 2022

AZD0486 in 3L+ FL: Responses and PFS by Target Dose

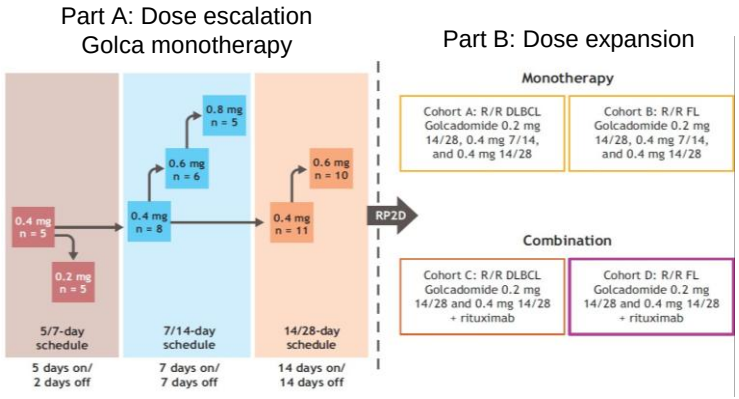


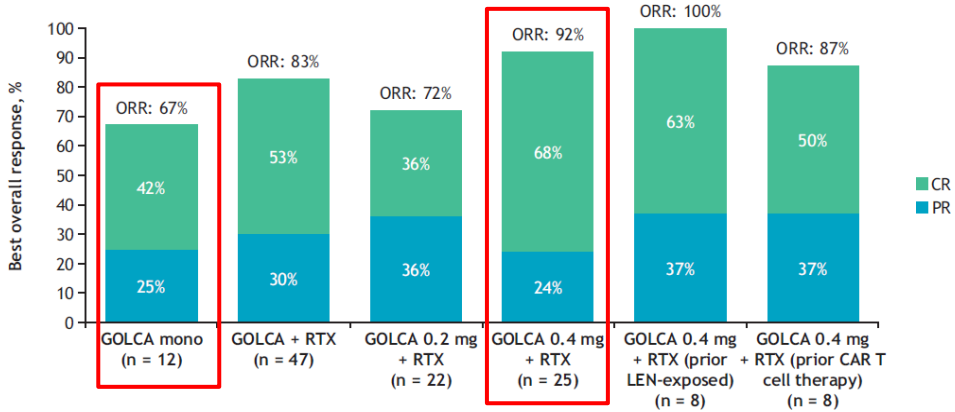
- **ORR 95% and CR 85%** in patients who received AZD0486 ≥2.4 mg (n=41)
- Activity in patients with POD24, prior BsAb, or prior CAR-T
- MRD negativity = 96% at doses ≥2.4 mg (PhasED-seq)

- Median study follow up: 8.4 months (range, 0.5–39.4)



Golcadomide with or without rituximab R in 2L+ FL





	Part B / Rituximab combination			
	Golcadomide 0.2 mg (n = 22)		Golcadomide 0.4 mg (n = 34)	
TRAE, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
Patient with ≥ 1 TRAE	22 (100)	16 (73)	30 (88)	20 (59)
Neutropenia	15 (68)	12 (55)	17 (50)	15 (44)
Febrile neutropenia	1 (5)	1 (5)	3 (9)	3 (9)
Anemia	2 (9)	1 (5)	8 (24)	3 (9)
Thrombocytopenia	4 (18)	1 (5)	6 (18)	-
Pneumonia	3 (14)	2 (9)	3 (9)	1 (3)
Constipation	3 (14)	-	4 (12)	1 (3)
Vomiting	1 (5)	-	-	-
Nausea	3 (14)	-	1 (3)	-
Diarrhea	3 (14)	-	3 (9)	-
Fatigue	2 (9)	-	4 (12)	-
Asthenia	2 (9)	-	4 (12)	-
Pyrexia	-	-	1 (3)	-
Pruritus	2 (9)	-	4 (12)	-

Ongoing comparative trials in 1L FL

NCT	Name	Phase	N.	Experimental arm	Control arm	Duration of therapy	Primary endpoint
NCT04663347	EPCORE FL-2	3	1095	Epcoritamab R^2	G/R-CHOP G/R-benda R^2	2.5 y	CR30, PFS
NCT06284122	MorningLyte	3	790	Mosunetuzumab-Lenalidomide	G/R-CHOP G/R-benda	1.5 y	PFS
NCT06091254	OLYMPIA-1	3	478	Odronextamab	R-CHOP R-CVP R-benda	2 y	CR30
NCT06097364	OLYMPIA-2	3	733	Odronextamab-CHOP/ CVP +/- O-maintenance	R-CHOP/CVP + R-maintenance	6 m vs 2.5 y	CR30
NCT06549595	SOUNDTRACK-F1	3	1015	AZD0486-rituximab +/- AZD0486 maintenance	R-CHOP/CVP + R-maintenance R-benda	6-12 m vs. up to 2.5 y	PFS
NCT06425302	Golseek 2	2	90	Rituximab-golcadomide (0.2 mg or 0.4 mg)	R-CHOP R-benda	Up to 2 y	CR

Competitors and Pretenders in 1L FL: Concluding remarks

- We are at an important juncture where BsAb-based regimens may challenge the role of standard CIT in 1L FL
- Ongoing 1L FL studies raise questions:
  - Prolonged duration of therapy (most ≥2 years), prolonged immunosuppression
  - Lack of robust 2L data (except for epcoritamab)
  - What would the choice of 1L be based on? (Efficacy? Ease of administration? Experience? Length of therapy? Availability?)
- The 2L+ landscape is likely going to be reshaped (R^2 used upfront, CD20 loss; T-cell dysfunction)

Acknowledgements

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