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Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Bispecific Therapy in Relapsed/Refractory FL

Reem Karmali, MD, MS
Associate Professor of Medicine
Northwestern University
Robert H. Lurie Comprehensive Cancer Center

Disclosures

- **Consulting Fees:** BMS, Gilead / Kite, Janssen, Genentech, GenMab, Abbvie, AvenCell
- **Speakers Bureau:** AstraZeneca, BeiGene, BMS
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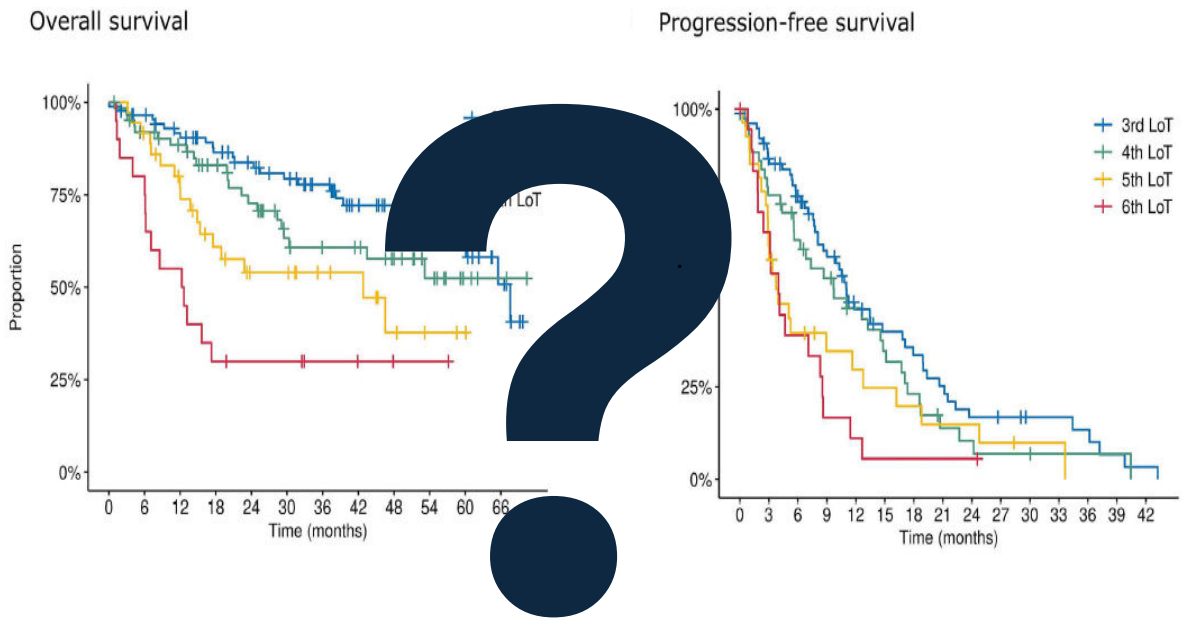
Objectives

- Overview of treatment landscape and where bispecifics fit in the treatment algorithm for relapsed/refractory FL currently
- Discuss pivotal trial data for bispecifics
- Compare outcomes of bispecifics with alternatives for 3L+ treatment of FL
- Discuss practical considerations that place bispecifics ahead of these alternatives

Survival Patterns in Follicular Lymphoma: Pre-BITE era

Outcomes with 3L and beyond

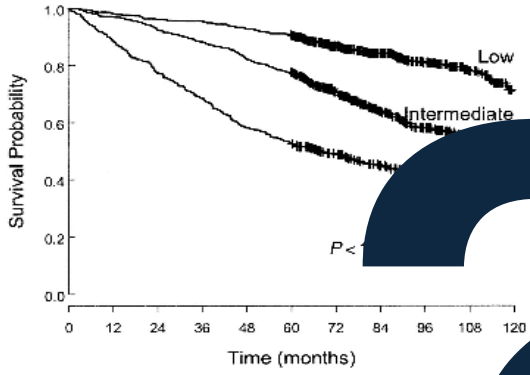


Diminishing returns with each line of therapy

Prognostic Tools

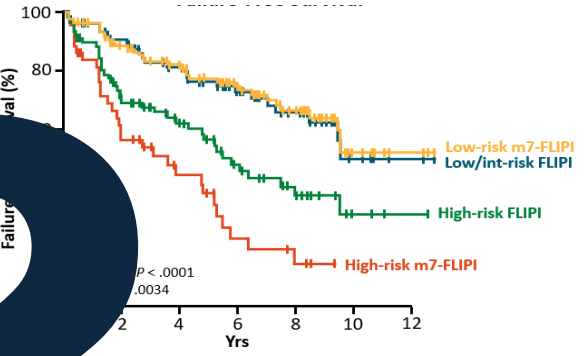
CLINICAL

OS According to FLIPI



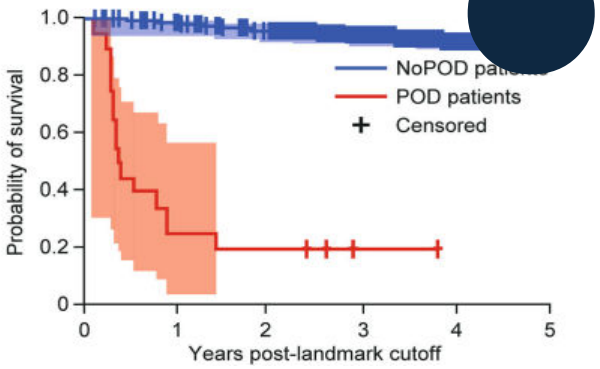
BIOLOGIC

FFS According to M-7 FLIPI

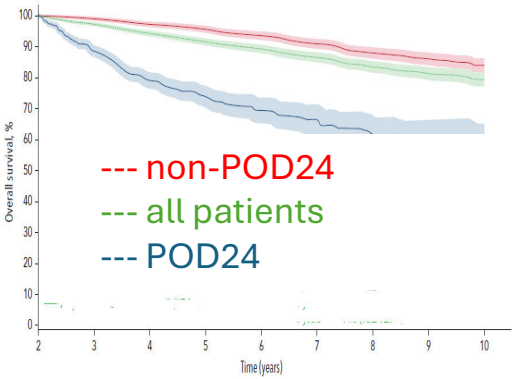


RESPONSE BASED

OS for Primary Refractory Disease

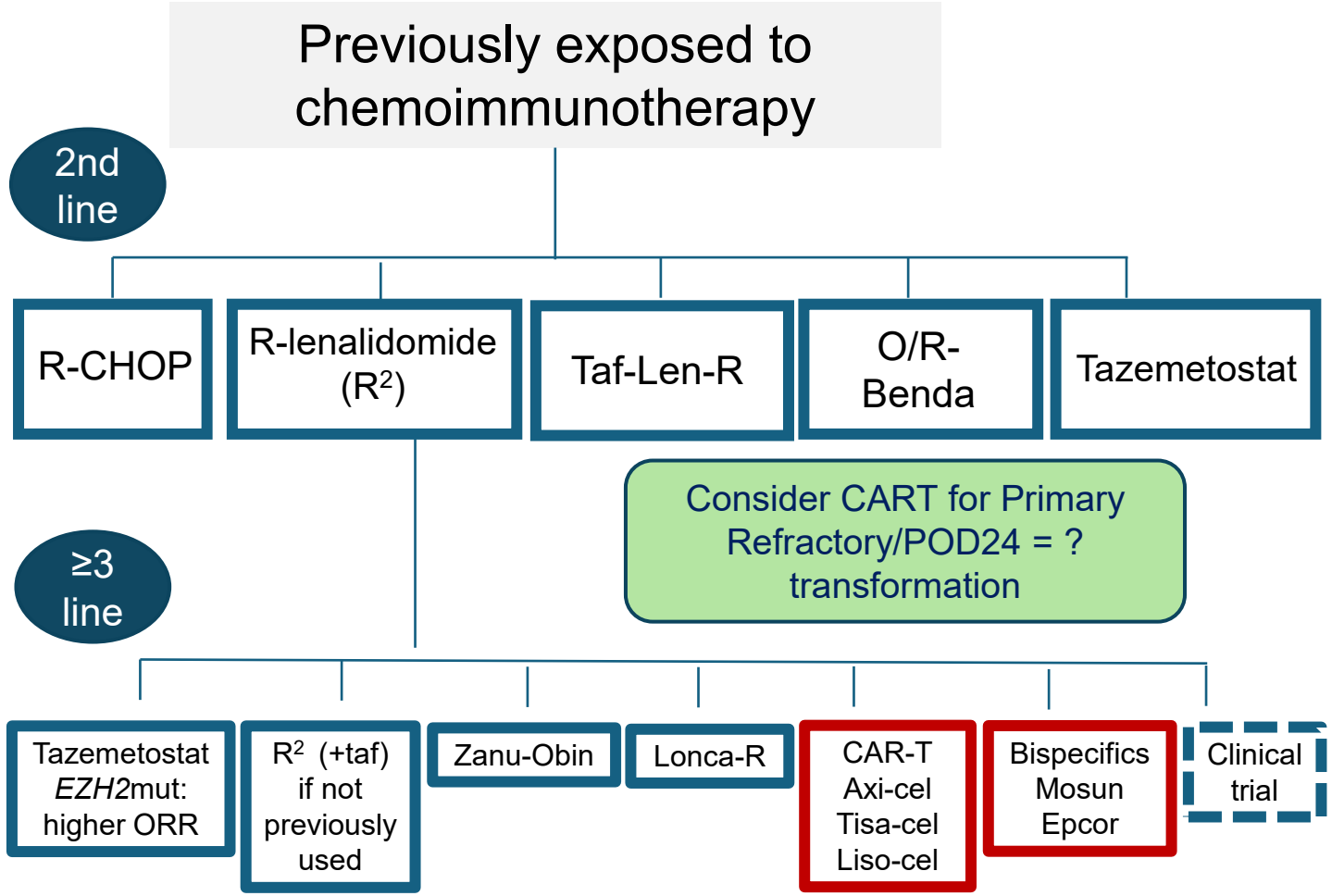


OS by POD24



Ghione et al., Haematologica, 2022; Solal-Céligny et al, 2004; Pastore. Lancet Oncol. 2015;16:1111; Seymour JF et al. Haematologica 2019;104:1202–8; Casulo et al. Blood 2022;139(11):1684-1693

Treatment Options and Sequencing in 2025



Considerations for Frontline

- BR generally still favored for high burden

Considerations for 2L

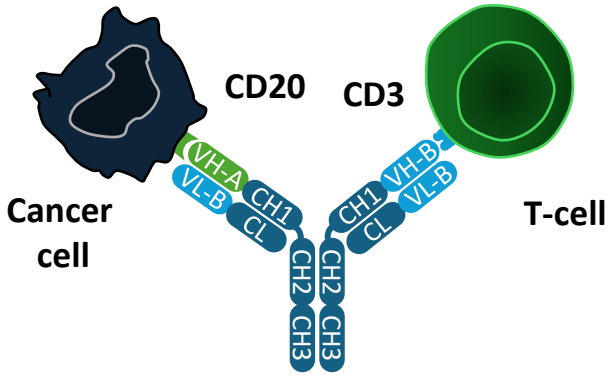
- R2 was generally favored
- Now consideration for adding tafasitamab
- POD24 /Primary Refractory - more frequently with underlying transformation
  - CART in 2nd line for curative intent?

Considerations for 3L+

- Decisions based on:
  - disease trajectory
    - POD24/short durations of prior response
    - Double Refractory
    - Clinical picture suggestive of more aggressive biology (rapid progression) vs transformation
  - prior exposures
  - logistics

CD20-CD3 Bispecifics in R/R FL 3L+

Anti-CD20/CD3 Bispecific Antibody



MoA: simultaneously bind CD20 on malignant B-cells and CD3 on cytotoxic T-cells, resulting in crosslinking of CD3, activation of T-cells, and cancer cell killing

Bispecific antibody	N	ORR %	CR %	mPFS (mo)	Any Grade CRS/NT (%)	CRS Gr≥3	NT Gr≥3
Glofitamab[1,2]	44	71	48	11.8	50/5	4	0
Odronextamab[3]	121	82	75	20.2	57/NR	2	NR
Epcoritamab[4]	128	82	63	18	49/NR	0	NR
Mosunetuzumab[5]	90	78	60	24	44/5	2	2

1. Hutchings 2021: JCO 39:1959-1970; 2. Morschhauser et al, ASH 2021; 3. Kim, Ann Onc 2024; 4. Linton Lancet Haem 2024; 5. Sehn, Blood 2025

Do High-Risk FL Patients Benefit from BITEs?

Characteristic	Mosunetuzumab N=90	Epcoritamab N=128	Odronextamab N=128
Median age, yr (range)	60 (53-67)	64 (39-84)	61 (22-84)
FLIPI ≥3 at study entry, (%)	44	61	58
Median lines of therapy, n	3	3	3
Bulky disease at study entry, (%)	34	26	14
Double Refractory Disease	53	70	41
POD24 from first anti-CD20 mAb-containing therapy (%)	52	42	49
Prior CART (%)	3	5	excluded
Prior autologous HSCT	21	19	30

3 Year Data for Fixed Duration Mosunetuzumab

FL with >2 lines therapy (N=90)

Cycle 1: Step-up Dosing

Mosunetuzumab IV
D1: 1 mg > D8: 2 mg > D15: 60 mg

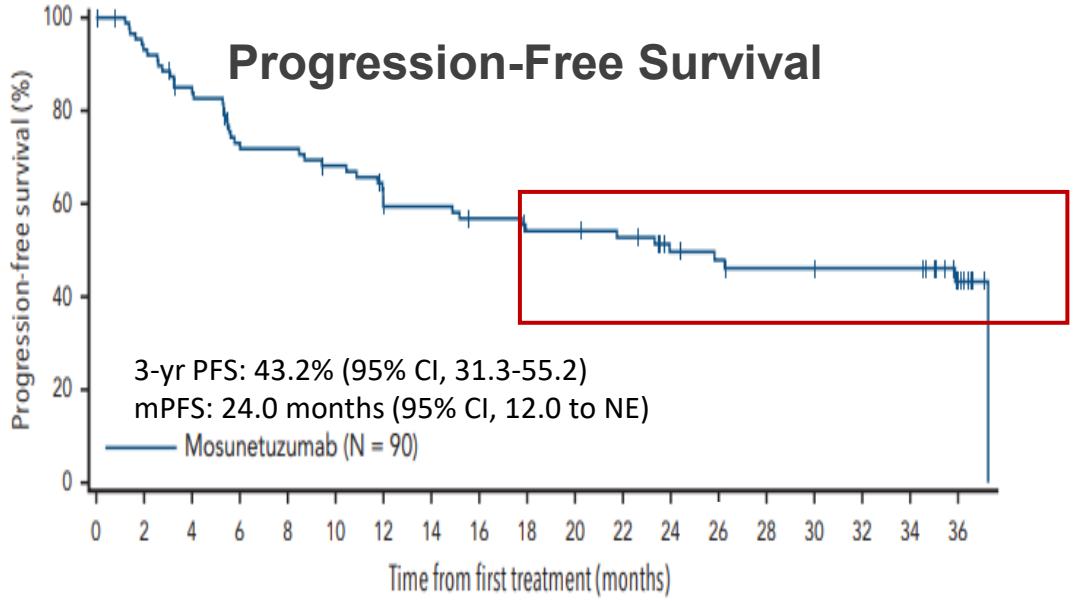
Cycle 2

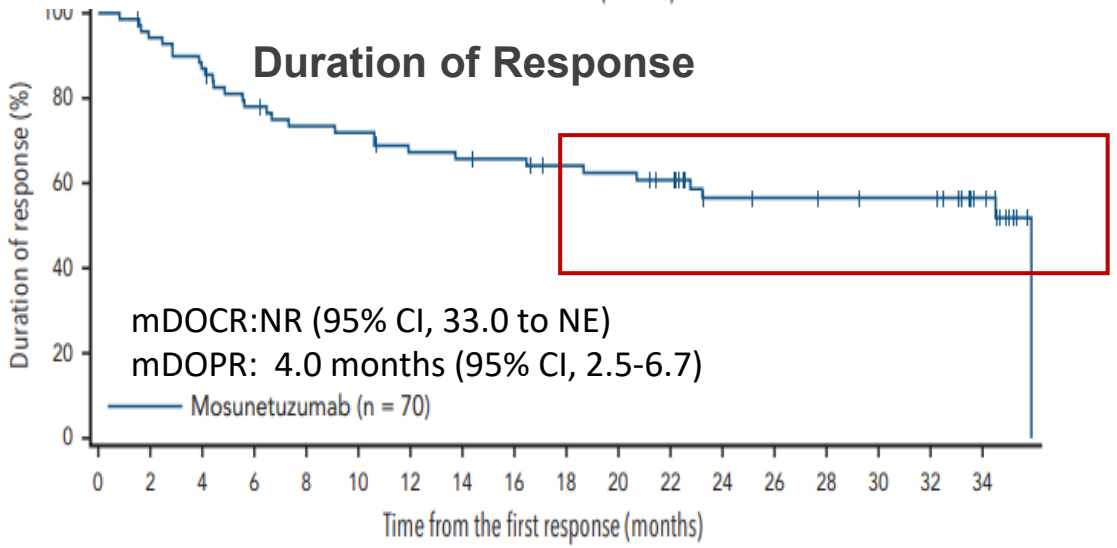
Mosunetuzumab IV
D1: 60 mg

Cycles 3-8

Mosunetuzumab IV
D1: 30 mg

Discontinue if CR by cycle 8;
if PR or SD, continue for 17 cycles
**Retreatment allowed if relapse after CR*





*5 patients retreated; 3 with CR2

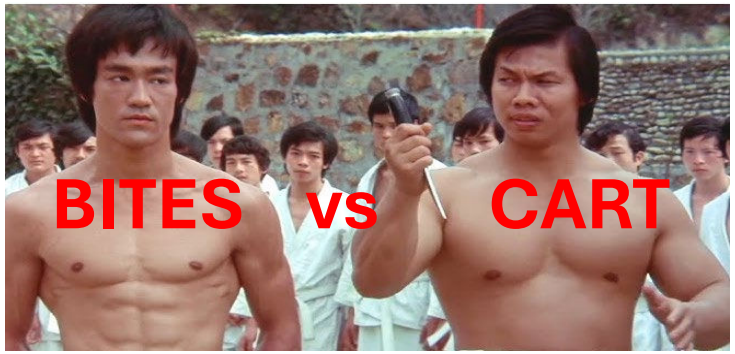
Sehn et al. *Blood 2025*

How Do BITEs Compare to CART and Other Alternatives

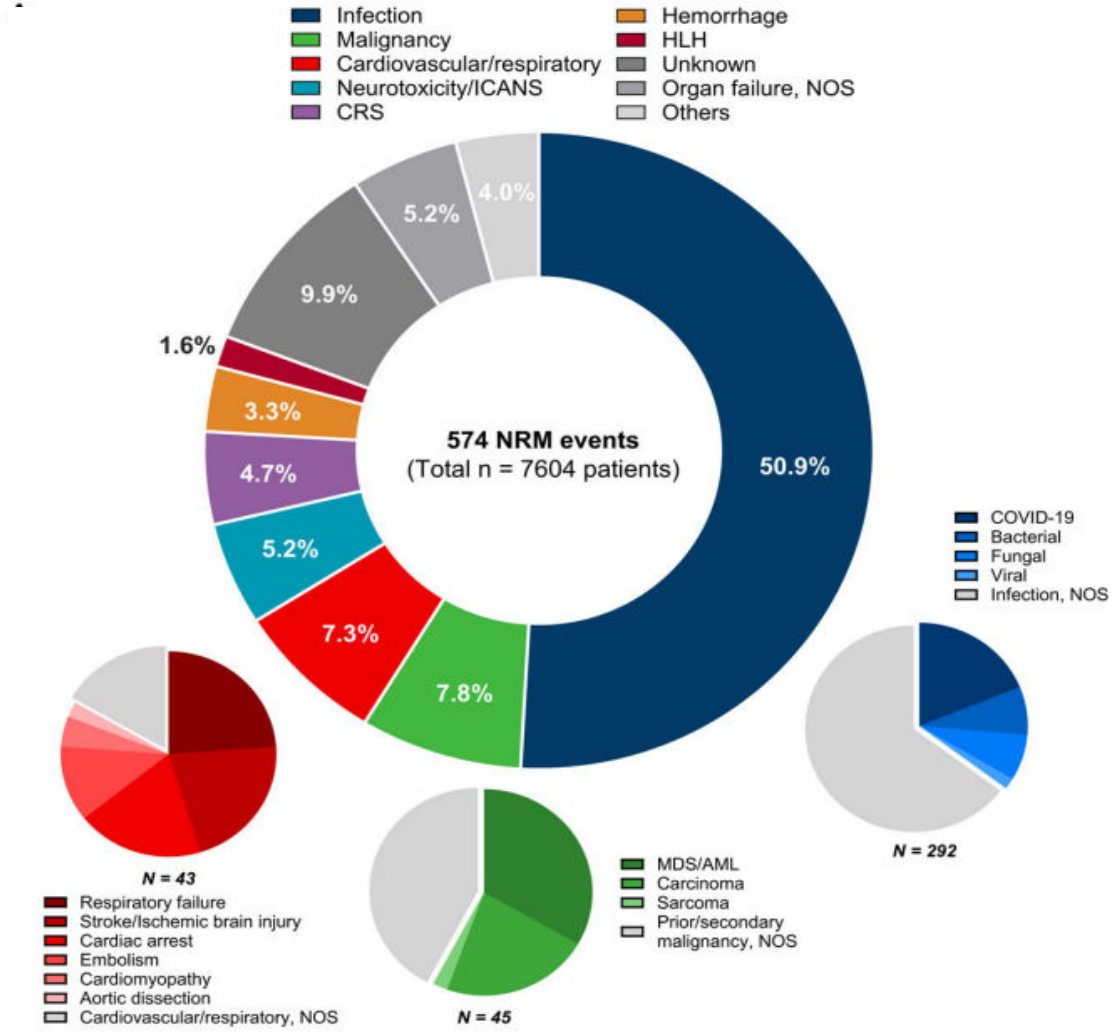
		ORR	CR	DOCR	CR in POD24	CR in double refractory	PFS	CRS		ICANS		Infections
		%	%		%	%		All	≥G3	All	≥G3	≥G3
CART	Axi-cel (ZUMA-5)[1]	94	79	60-mo DOCR: 53%	72	NR	60-mo PFS: 50%	78	6	56	15	15
CART	Liso-cel (TRANSCEND-FL)[2]	97	94	12-mo DOCR: 82%	95	93	24-mo PFS: 83%	58	1	15	2	5
CART	Tisa-cel (ELARA)[3]	86	68	24-mo DOCR: 78%	59	66	24-mo PFS: 57%	49	0	4	1	9
BsAbs	Mosunetuzumab (fixed duration)[4]	78	60	30-mo DOCR: 72%	55	42	36-mo PFS: 43%	44	2	5	2	13
BsAbs	Epocoritamab[5]	82	63	18-mo DOCR: 72%	61	56	18-mo PFS: 50%	49	0	0	0	At least 18%
BsAbs	Odronextamab[6]	81	73	24-mo DOCR: 48%	73	ORR: 73	24-mo PFS: 45%	57	1	1	0	41
Other targeted tx	Loncatuximab + R[7]	97	77	mDOCR: 16 mo	85	NR	12-mo PFS: 95%	-	-	-	-	Any grade: 26
Other targeted tx	Tafasitamab-R2 (2L included)[8]	84	49	mDOR: 21 mo	NR	NR	mPFS: 22 mo	-	-	-	-	not reported (> 10% COVID)
Other targeted tx	Zanubrutinib-Obinutuzumab[9]	69	57	18-mo DOCR: 87%	ORR: 64 CR NR	NR	mPFS: 28 mo	-	-	-	-	Any grade: 55
Other targeted tx	Tazemetostat EZH2 mutated[10]	69	13	mDOR: 11 mo	11	22	mPFS: 14 mo	-	-	-	-	<5

1. Neelapu, ASH 2024; 2. Morschhausser Nature Med 2024; 3. Dreyling Blood 2024; 4. Sehn, Blood 2025; 5. Linton Lancet Haem 2024; 6. Kim, Ann Onc 2024; 7. Alderuccio, Lancet Haem 2025; 8. Sehn ASH 2024; 9. Zinzani JCO 2023; 10. Morschhausser Lancet Oncol 2020

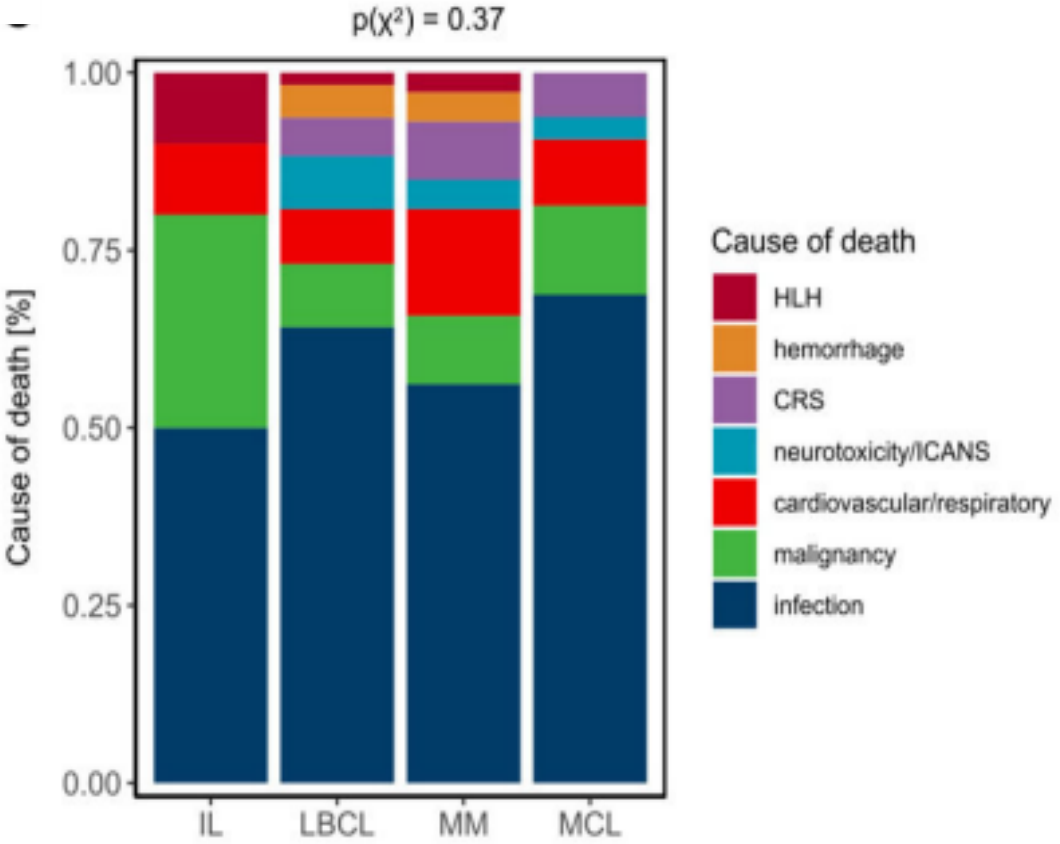
The DARK SIDE of CART



Causes of NRM following CART



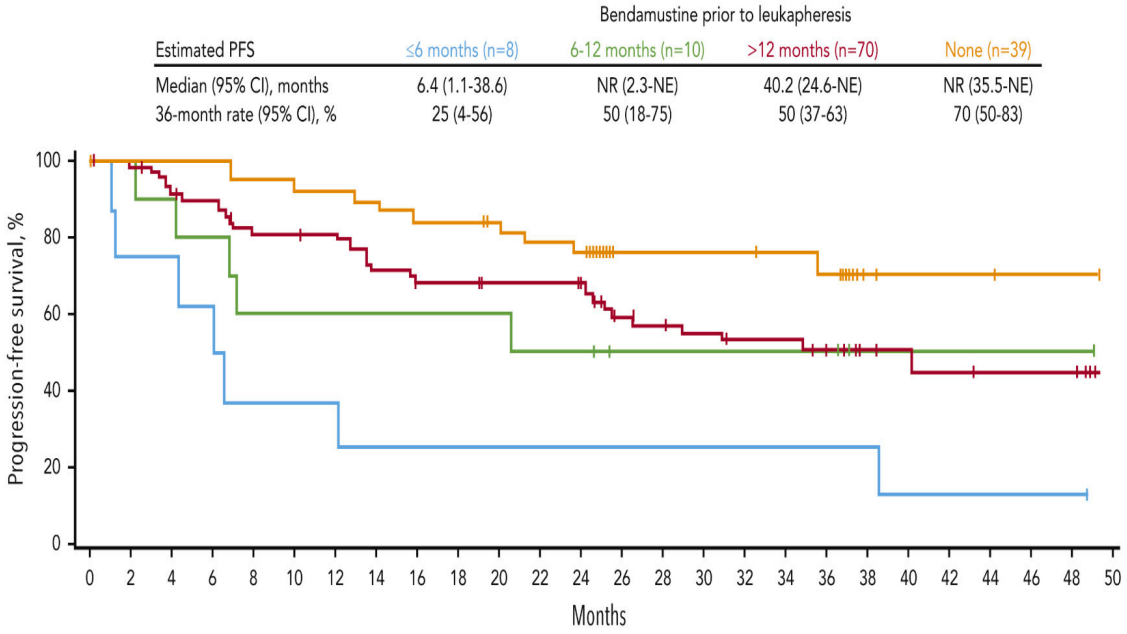
NRM in indolent lymphoma (IL) = 6%



Morabito et al., Eur J Haemtology, 2025

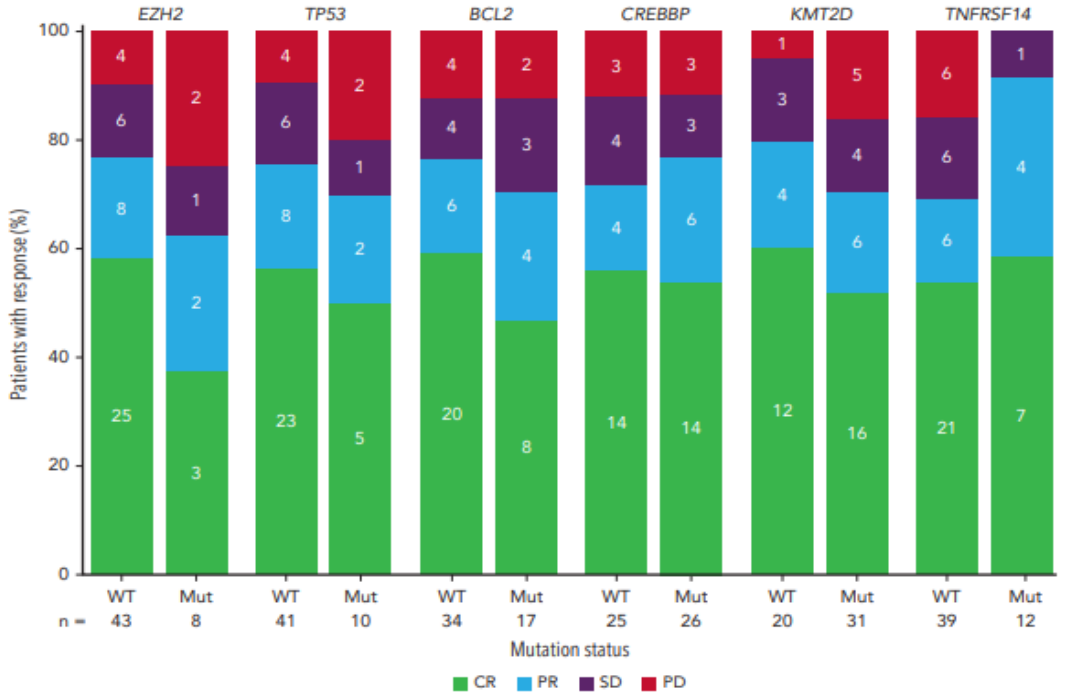
Practical Considerations on Sequencing

Prior bendamustine exposure



- CART outcomes with prior bendamustine exposure < 12 months poor
- The impact on efficacy of BITEs is not as clear

High risk mutations/biology



- Efficacy of BITEs seem to be unaffected by high-risk mutations

1. Neelapu, Blood 2024; 2. Sehn, Blood 2025

Practical Considerations on Sequencing in R/R FL

Patient fitness and logistics

BITEs	CART	
Patient Fitness		
Generally older and ECOG 2 allowed	Generally younger and ECOG 0-1 only	
Dosing Frequency		
Repeated dosing but as little as 6 months	One and done (but vein-to-vein time long)	? winner
Accessibility		
More widely available/outpatient	Limited to specialized centers	
Care Giver Support		
Generally minimal	More intensive support (2 months)	
Sequencing Data		
Less data for BITE pre-CART	Minimal data for BITE post-CART	? winner

Upfront studies with BITEs +/- adjunct

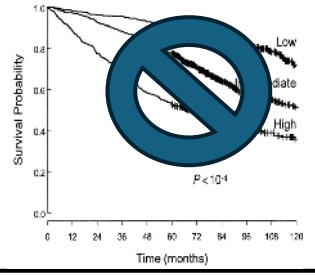
Trial	Phase	N	Treatment Arms
NCT05389293	II	76	Mosunetuzumab monotherapy
NCT05410418	II	34	Mosunetuzumab + polatuzumab vedotin
NCT05169658	II	42	Mosunetuzumab ± polatuzumab vedotin/obinutuzumab
NCT04792502	II	52	Mosunetuzumab + lenalidomide
NCT05994235	II	50	Mosunetuzumab + tazemetostat
NCT06112847	II	27	Epcoritamab + lenalidomide
NCT06191744	III	~1080	Epcoritamab + R2 vs R2 or CIT
NCT06091254	III	478	Odronextamab vs CIT

Ex – EPCORE-NHL2: epcoritamab + R^2 in 1L FL: CR rate = 85% (Lori et al., ASCO 2024)

Prognostic & Predictive Tools for BITE Era - Now & Future

CLINICAL

OS According to FLIPI



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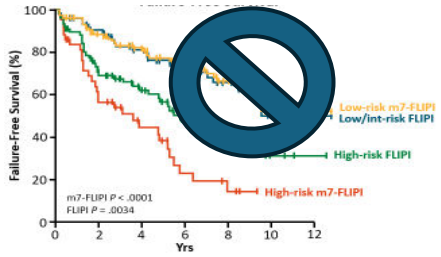
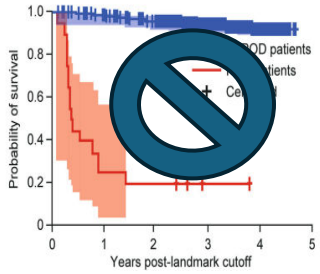
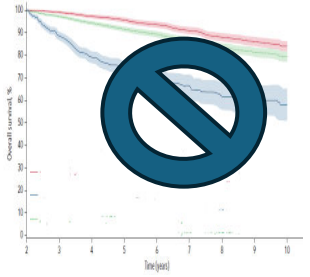


RESPONSE BASED

OS for Primary Refractory Disease



OS by POD24



What we know:

1. Response based prognostic tools exist for BITEs → but we don't have a strategy for these patients
   - MRD status as soon as 3 months post
   - Early response vs late response
   - Depth of response (CR vs PR)

Gaps:

1. Need for better risk stratification in the BITE era
2. Biomarkers to guide optimal sequencing /treatment choices
3. Optimization of treatment exposure for efficacy vs toxicities
4. Mechanisms of resistance unknown

1. Sehn, Blood 2025; 2. Linton Lancet Haem 2024; 3. Kim, Ann Onc 2024

Treatment for R/R FL in the BITE Era – Summary

- Easier logistics and toxicity profile with short fixed duration BITEs as compared to alternatives
- BITEs = simple = one size fits all
  - reasonable if dual refractory, POD24, high risk mutations, question of patient fitness
- BITE combinations underway in frontline →

? validity in relapsed setting may change

  - Retreatment with BITEs vs using an alternative may become a more pertinent question

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Thanks!