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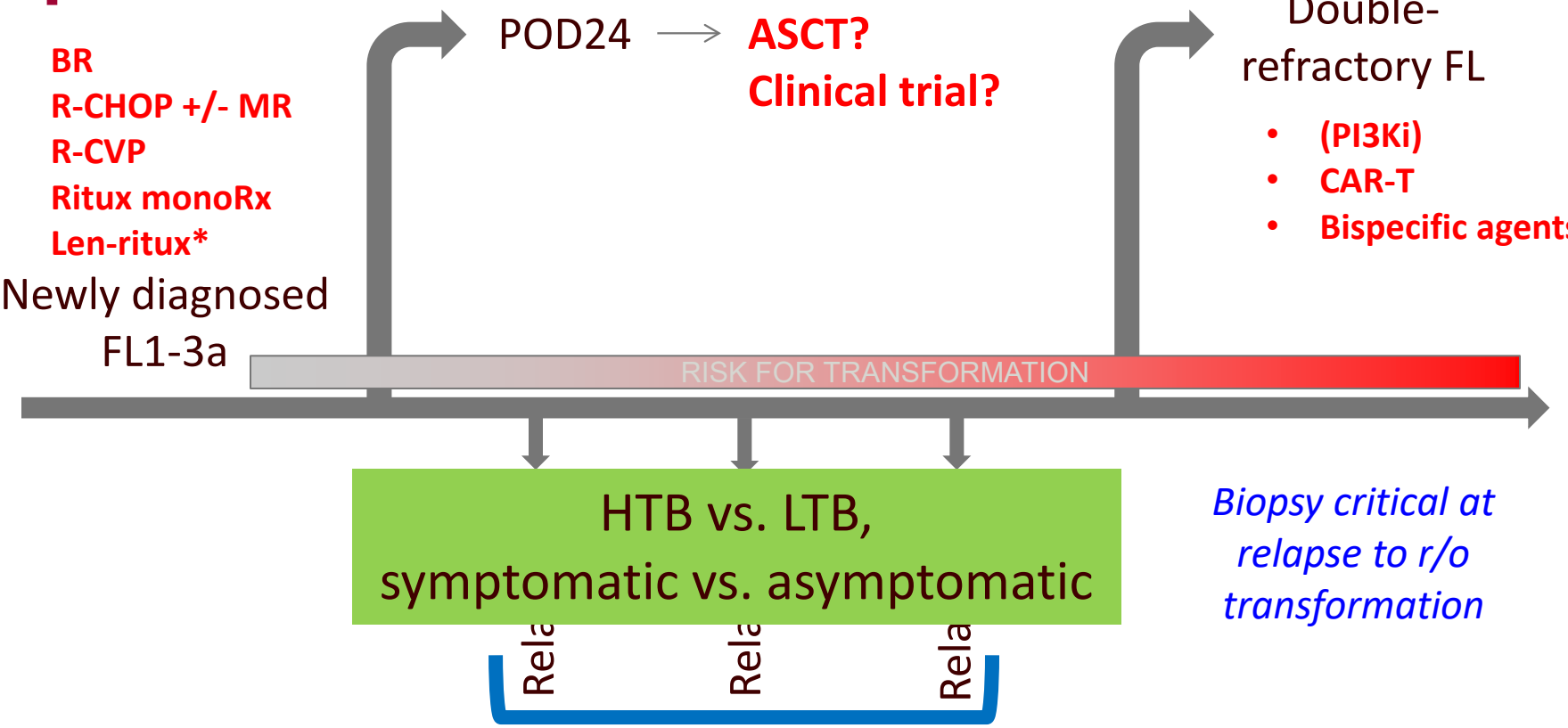
Non T-cell Engaging Options in RR FL

Sonali Smith, MD FASCO
Elwood V. Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line

Disclosures

Sonali Smith, MD serves as a consultant for Genmab, Ono Pharmaceuticals, and Regeneron.

FL: Clinical categories and treatment options



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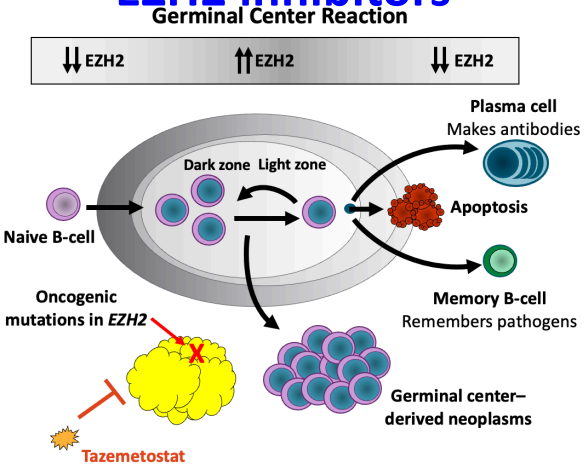
*not approved

NOVEL APPROACHES FOR R/R FL: A PREVIEW (approved and unapproved)

EZH2 inhibitors



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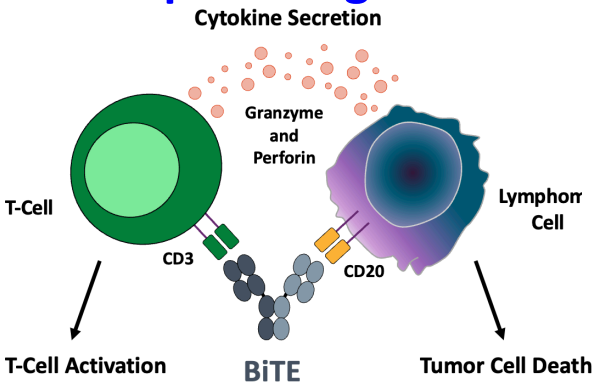
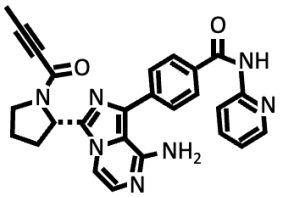
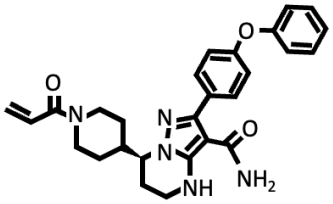


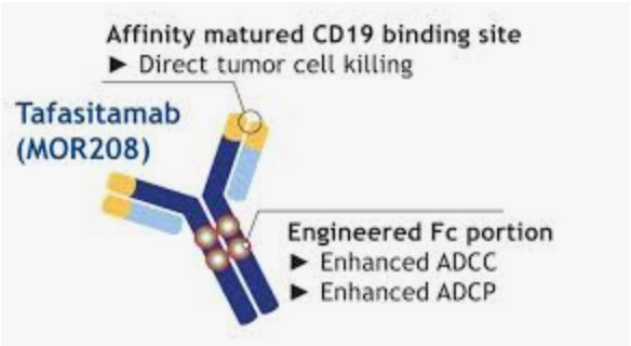
BTK inhibitors

Acalabrutinib

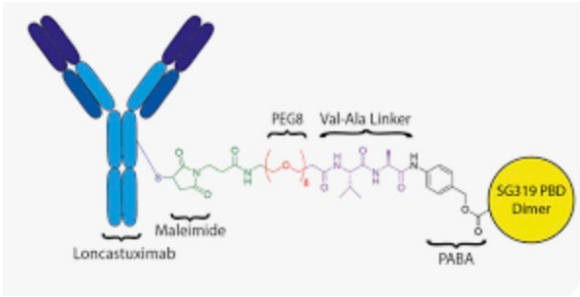


Zanubrutinib





antiCD19 moAb



antiCD19 ADC

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Chemoimmunotherapy in rel/ref FL

Trial/Agent	Key pt features	Design, Primary endpoint	Outcome	Comments
BR	Rel/ref 1-3 prior regimens	Ph 2 ORR	ORR 90% Med PFS 24m	
BR	Rituximab-sensitive	Ph 2	ORR 92% Med DR 21m Med PFS 23m	
BO	Rituximab-refractory	RP3 (BO + main O vs. B) PFS	Med PFS 25.8m vs. 14m (2018 update)	Overall survival benefit with longer f/u

Benda-based regimens yield med PFS 2 years

Can BR/BO be backbone for more agents?

-bortezomib XX

-lenalidomide XX

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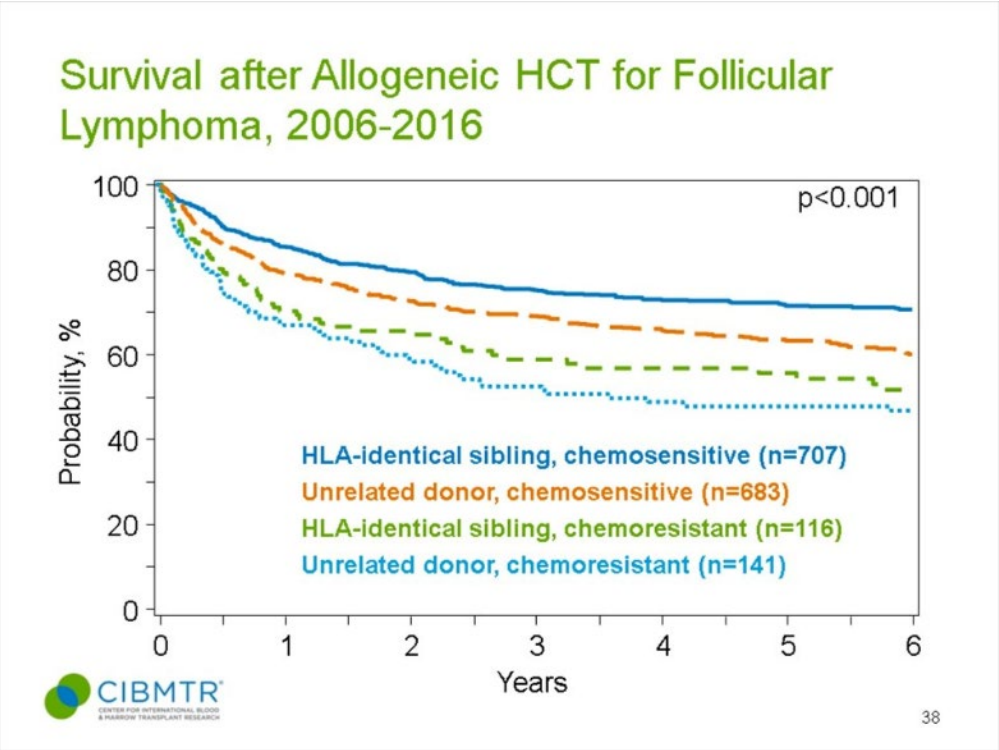
Rummel J Clin Oncol 2005 May 20;23(15):3383-9; Robinson, J Clin Oncol 2008 Sep 20;26(27):4473-9; Sehn Lancet Oncol. 2016 Aug;17(8):1081-1093

Autologous vs Allogeneic HCT in Early Relapsed FL

Auto = autologous HSCT

MSD = allogenic HSCT w/ matched sibling donor

MUD = allogenic HSCT w/ matched unrelated donor



Fewer than 2% of patients with FL undergo autoHCT

Smith. Cancer. 2018;124:2541. Slide courtesy of Mehdi Hamadani, MCW.

ASCT vs No ASCT for Early Progressing FL

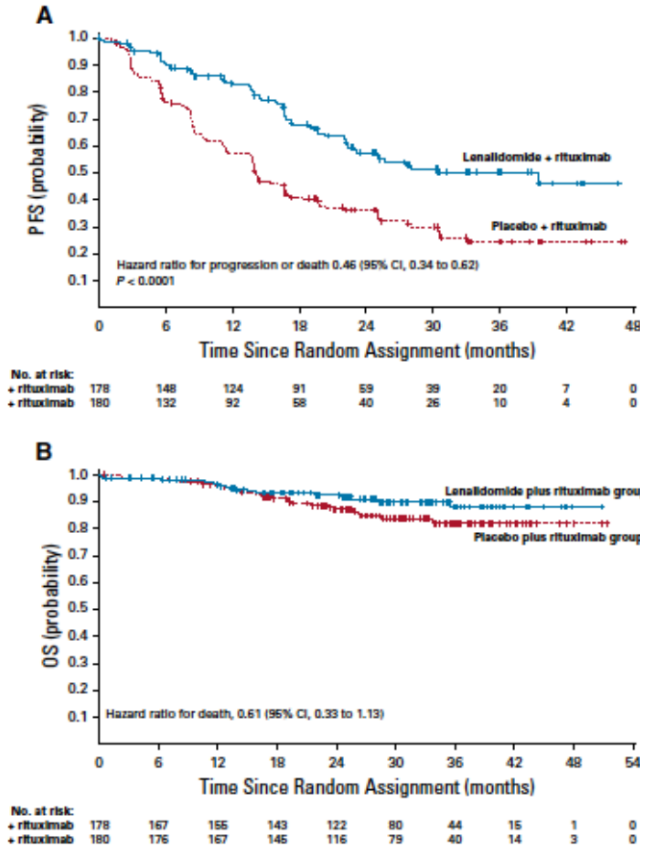
Study	Casulo et al[1]	Manna et al[2]	Jurunovic et al[3]
Patient cohorts	NLCS and CIBMTR	Calgary	GLSG
Patient population	Failure to achieve at least a PR or early relapse ≤ 2 yrs on frontline rituximab-based CIT	Early relapse ≤ 2 yrs following frontline CIT	Progressive, relapsed, or refractory disease ≤ 2 yrs on systemic frontline therapy*
N	349 ▪ ASCT cohort: 175 ▪ Non-ASCT cohort: 174	84 ▪ ASCT cohort: 50 ▪ Non-ASCT cohort: 34	113 ▪ ASCT cohort: 52 ▪ Non-ASCT cohort: 46†
5-Yr PFS, %	Not reported	Not reported	▪ ASCT cohort: 51% ▪ Non-ASCT cohort: 19% ▪ *P* < .0001
5-Yr OS, %	▪ ASCT cohort: 67% ▪ Non-ASCT cohort: 60% ▪ *P* = .16	▪ ASCT cohort: 85% ▪ Non-ASCT cohort: 58% ▪ *P* = .001	▪ ASCT cohort: 77% ▪ Non-ASCT cohort: 59% ▪ *P* = .031

1. Casulo. Biol Blood Marrow Transplant. 2018;24:1163. 2. Manna. Leuk Lymphoma. 2019;60:133. 3. Jurinovic. Biol Blood Marrow Transplant. 2018;24:1172.

*At ≤ 65 yrs of age. †Excludes patients with cytoreduction failure.

Lenalidomide in relapsed (not refractory) FL: AUGMENT RP3 Len-ritux vs. Pbo-ritux

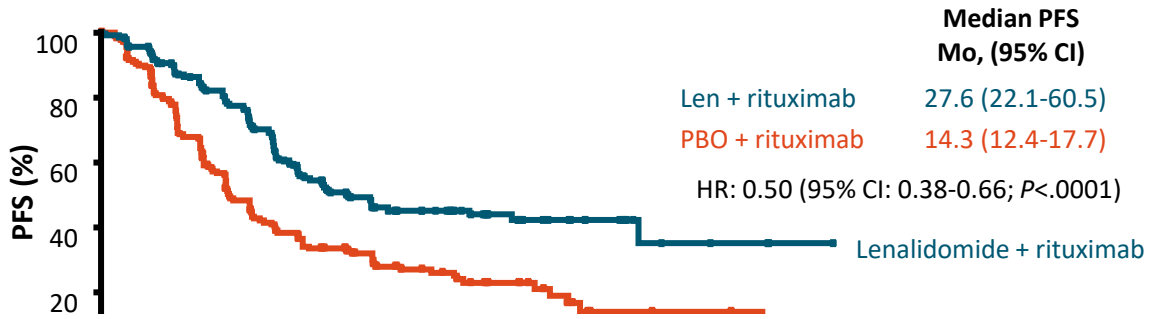
- N= 147 FL
- Disease characteristics:
  - ~30% relapsed within 2 years of initial Rx (POD24)
  - 50% progressed within 2 years of most recent therapy
  - 17% refractory to most recent regimen
- Results (R2 only):
  - Med PFS 39.4m (vs. 14m for R-pbo)
  - ORR 78%, CR 34%
  - Med DR 36.6m
  - Med OS NR



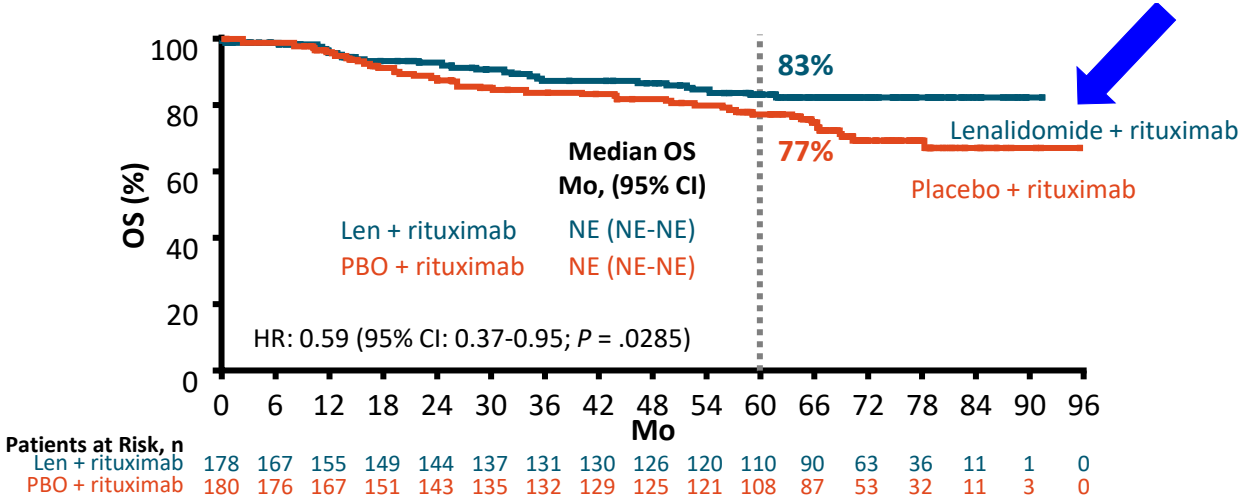
Leonard J Clin Oncol 2019 May 10;37(14):1188-1199

AUGMENT: 5-Yr Survival

- Median follow-up: 65.9 mo

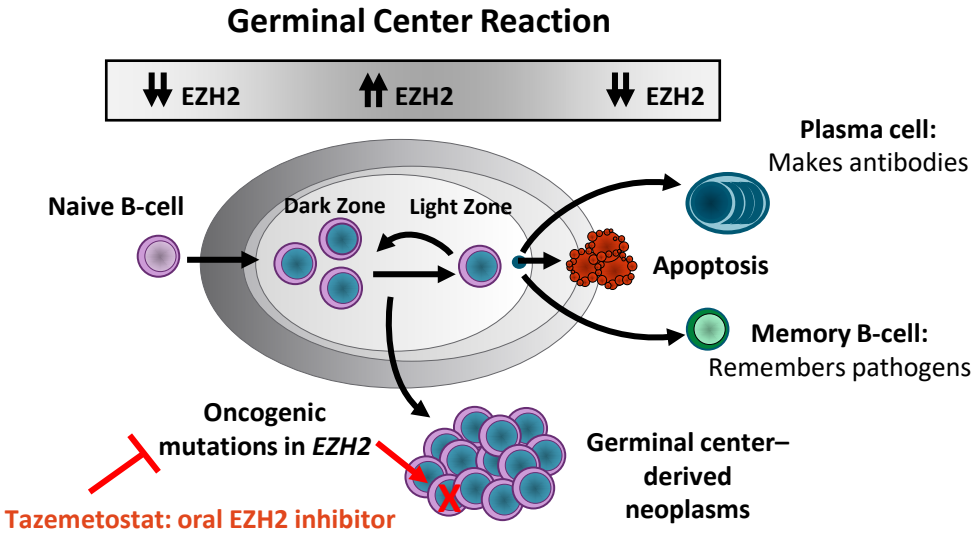


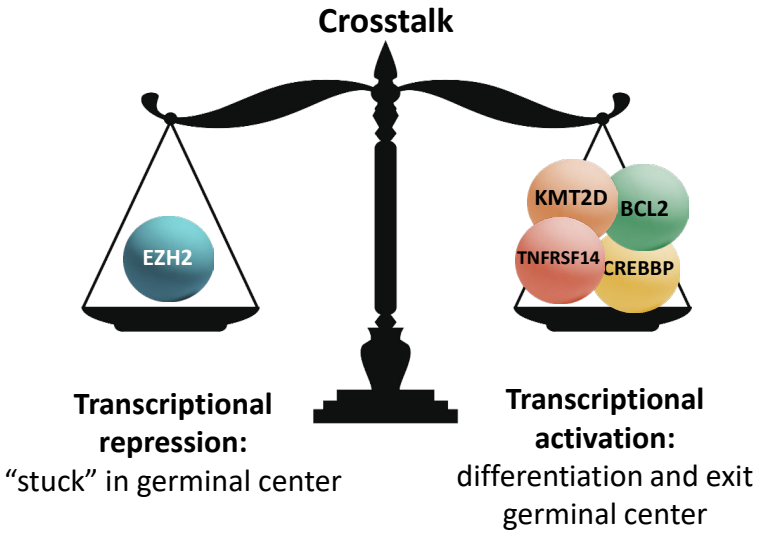
Can (and should) LenR be a backbone for future drug development?



Leonard. ASH 2022. Abstr 230.

Follicular Lymphoma and *EZH2*: Tazemetostat



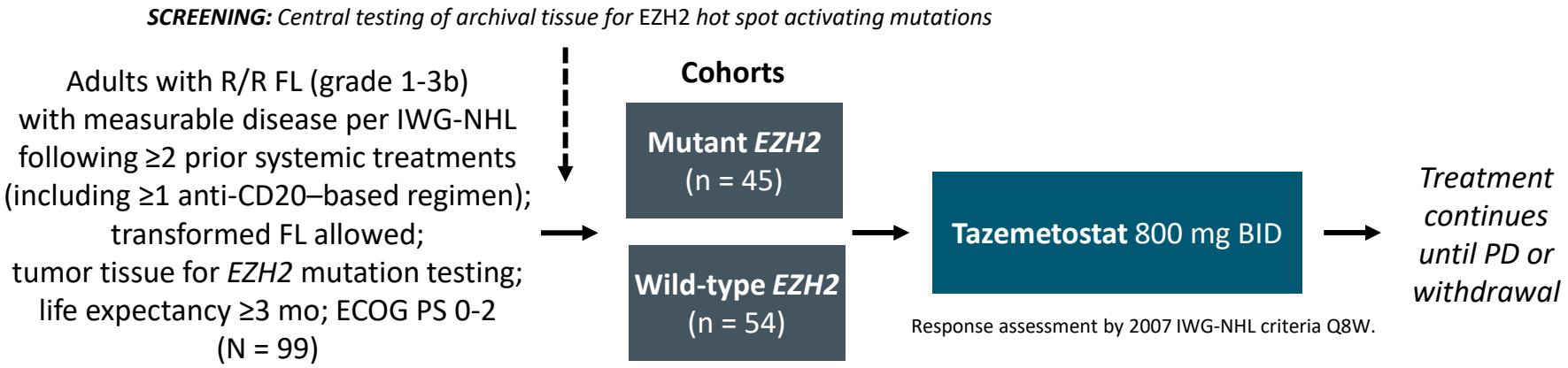


- EZH2: an epigenetic regulator of gene expression and cell fate decisions
  - In normal B-cell biology, EZH2 regulates germinal center formation
  - *EZH2* mutations can lead to oncogenic transformation by locking B-cells in germinal state and preventing terminal differentiation

Gan. Biomark Res. 2018;6:10. Béguelin. Cancer Cell. 2013;23:677. Tazemetostat PI.

Phase II Study: Tazemetostat in R/R FL

- Open label, multicohort, single-arm phase II study conducted at 38 sites across NA, Europe, Australia (data cutoff for efficacy: August 9, 2019; for safety: May 24, 2019)



- **Primary endpoint:** ORR
- **Secondary endpoints:** DoR, PFS, safety/tolerability

Morschhauser. Lancet Oncol. 2020;21:1433. NCT01897571.

Tazemetostat monotherapy: Activity in both mutant and wt EZH2 FL

- Tazemetostat was generally well tolerated
- No treatment-related deaths

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Morschhauser. Lancet Oncol. 2020;21:1433. Tazemetostat PI.

SYMPHONY-1 Phase Ib: Tazemetostat + R^2 in R/R FL

- Phase Ib safety run-in analysis (stage 1) of international, randomized, double-blind phase Ib/III trial (median follow-up: 11.2 mo)
  - Stage 2: phase III design comparing tazemetostat at RP3D + R^2 vs placebo + R^2 in patients with R/R FL
  - Stage 3 (to be executed if stage 2 futility analysis finds that efficacy fails in overall population but is promising for *EZH2*-mutated subpopulation): in patients with *EZH2*-mutated R/R FL

Adults with R/R FL grades 1-3A;
tumor tissue for *EZH2* mut testing;
≥1 prior systemic CT, IO, or CIT;
prior HSCT, CAR T-cell tx permitted;
no prior lenalidomide, tazemetostat, or other EZH2 inhibitor;
measurable disease per Lugano;
ECOG PS 0-2
(N = 44)

→

Phase Ib: Dose Escalation (3 + 3 Design)

Tazemetostat 400/600/800 mg BID x 28-d cycles +
Rituximab 375 mg/m^2 IV on D1,8,15,22 of cycle 1, then D1 of cycles 2-5 +
Lenalidomide 20 mg* PO QD on D1-21 of 28-d cycles x 12

*10 mg if CrCl <60 mL/min.

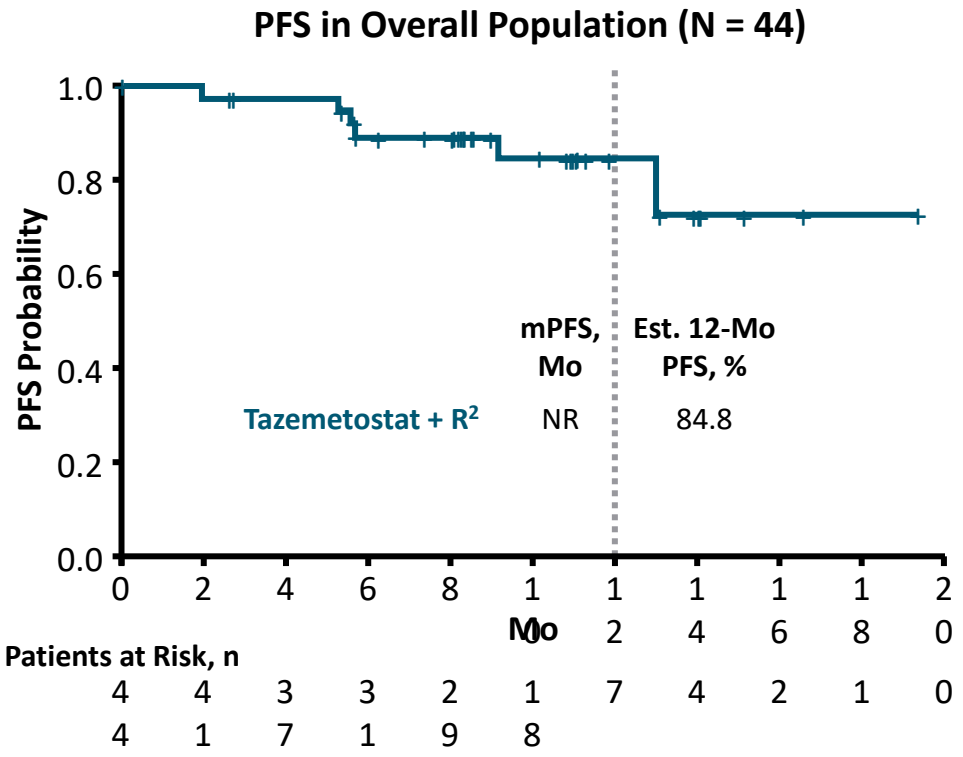
- **Primary endpoints:** safety/tolerability, tazemetostat RP3D
- **Secondary endpoint:** safety PK parameters

Batlevi. ASH 2022. Abstr 954. NCT04224493.

SYMPHONY-1 Phase Ib: Efficacy in Overall Population

Response	Tazemetostat + R² (n = 41)
ORR, n (%)	40 (97.6)
▪ CR	21 (51.2)
▪ PR	19 (46.3)
▪ SD	1 (2.4)
Median DoR, mo	NR

- At data cutoff (June 14, 2022), 56.8% (25/44) had treatment ongoing, 6.8% (3/44) had PD



Batlevi. ASH 2022. Abstr 954.

SYMPHONY-1 Phase Ib: Efficacy by Subgroup

RP2 is ONGOING
(including UChicago)

Batlevi. ASH 2022. Abstr 954.

ROSEWOOD: RP2 of Zanubrutinib plus Obinutuzumab vs. Obinutuzumab monotherapy in R/R FL

- Grade 1-3A RR FL
- 3L+
- No prior BTKi

2:1

- Zanu plus obinu (n=145)
  - Zanu until PD Obinu maintenance
- Obinu monotherapy (n=72)
  - Obinu maintenance

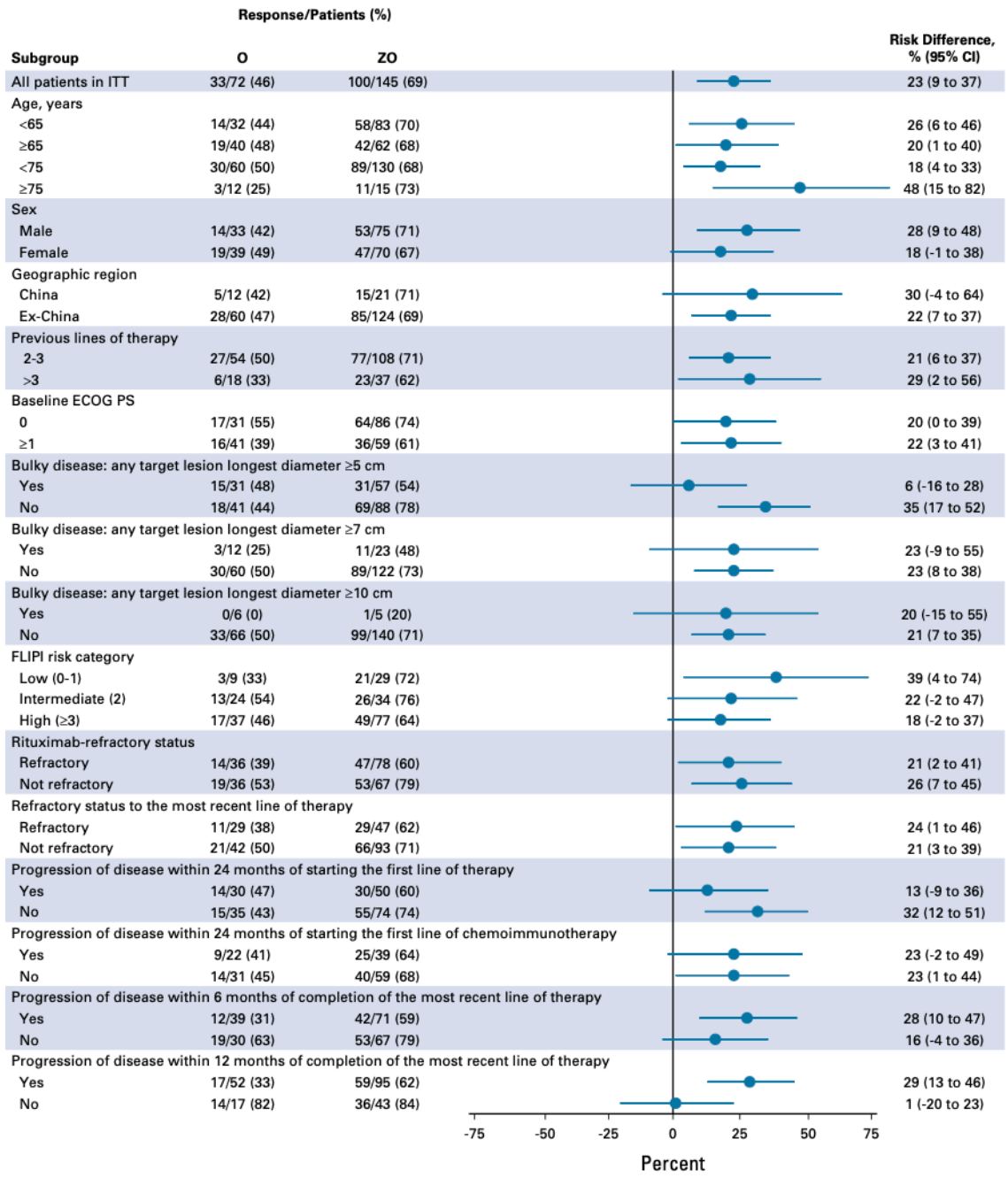
Dosing:
Zanubrutinib 160mg BID
Obinu 1000mg IV C1D1, C1D8, C1D15 then D1 of C2-6, then q8 weeks x 2y

Primary endpoint: ORR

Zinzani J Clin Oncol 2023 Nov 20;41(33):5107-5117

ROSEWOOD: Results

- Responses across most subgroups
- Lower response rates for bulky disease and early progressors



Zinzani J Clin Oncol 2023 Nov 20;41(33):5107-5117

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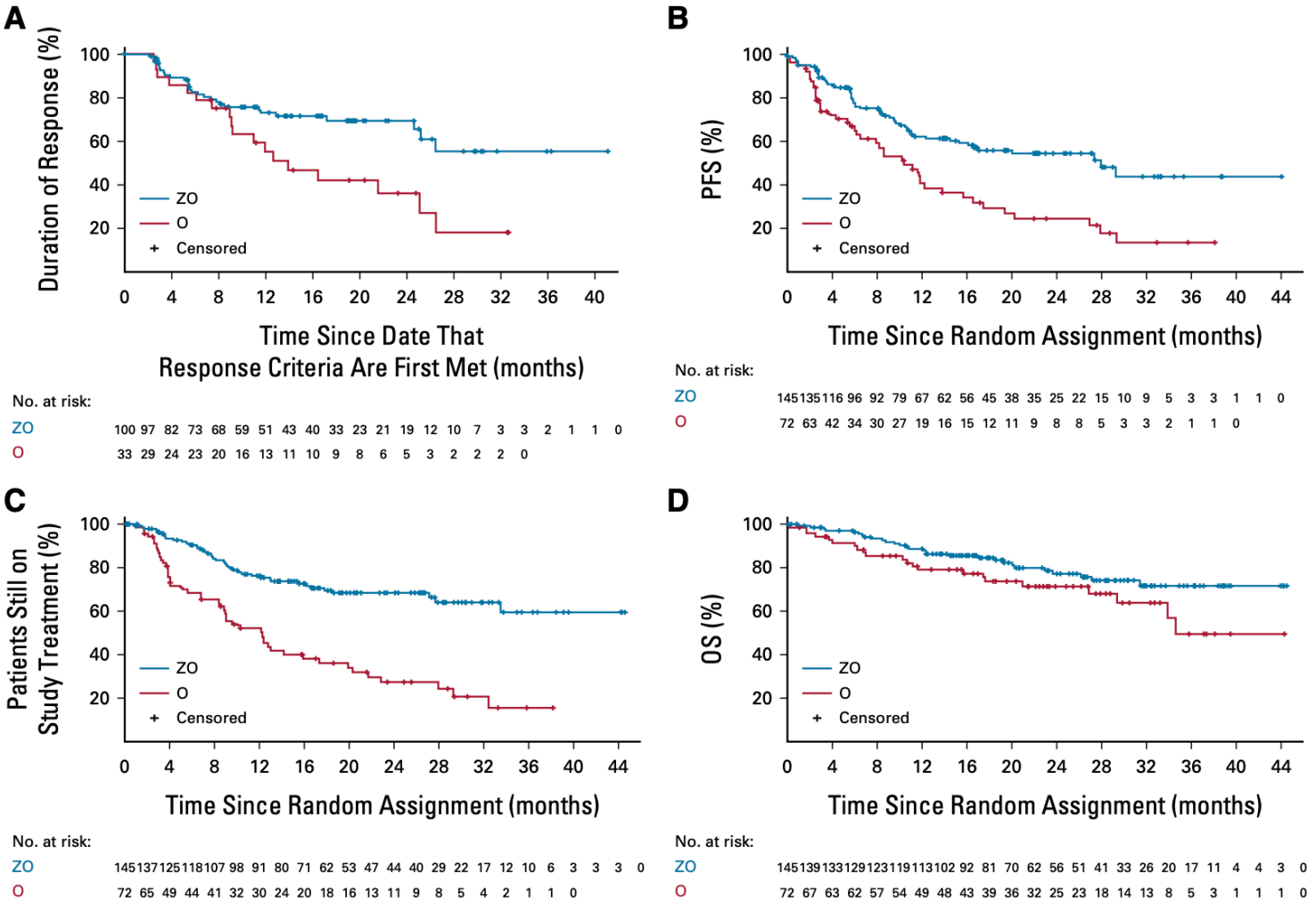
ROSEWOOD: DR, PFS, TTNT, OS



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Zinzani J Clin Oncol 2023 Nov 20;41(33):5107-5117

Targeting CD19 in RR FL

inMIND: RP3 Double-Blind, Placebo-Controlled, International, Multicenter Study

- FL gr 1-3A or MZL
- 2L+

Primary endpoint: PFS

Relapsed/refractory status to last therapy, n (%)			
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 anti-CD20 therapy, n (%)	118 (43.2)	115 (41.8)	233 (42.5)

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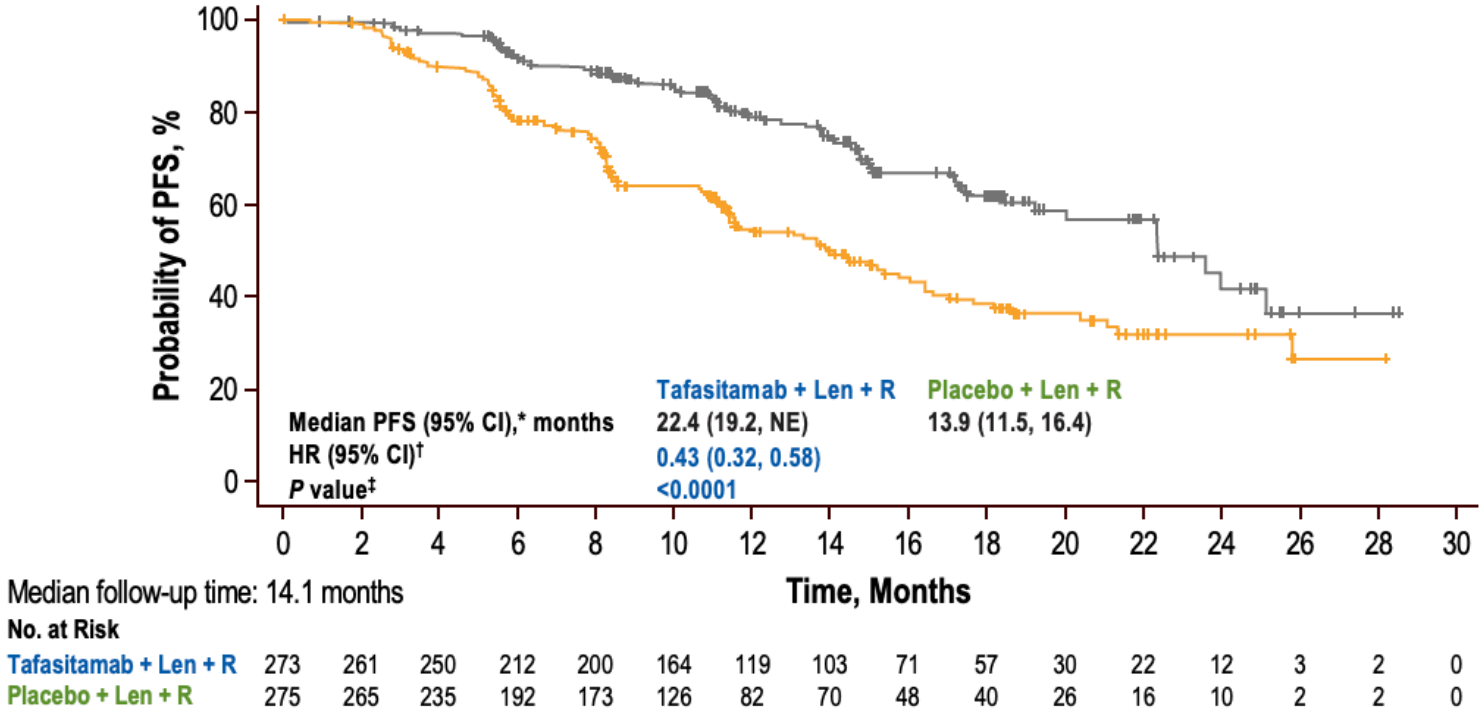
Sehn ASH 2024, LBA

inMIND: PET-CR and ORR

Higher PET-CR rate and ORR was observed with tafasitamab arm (~10% difference via PET)

Sehn ASH 2024, LBA

inMIND Primary Endpoint: PFS by Investigator Assessment



Med PFS 22.4m vs. 13.9m

(p < 0.0001)

No diff in OS

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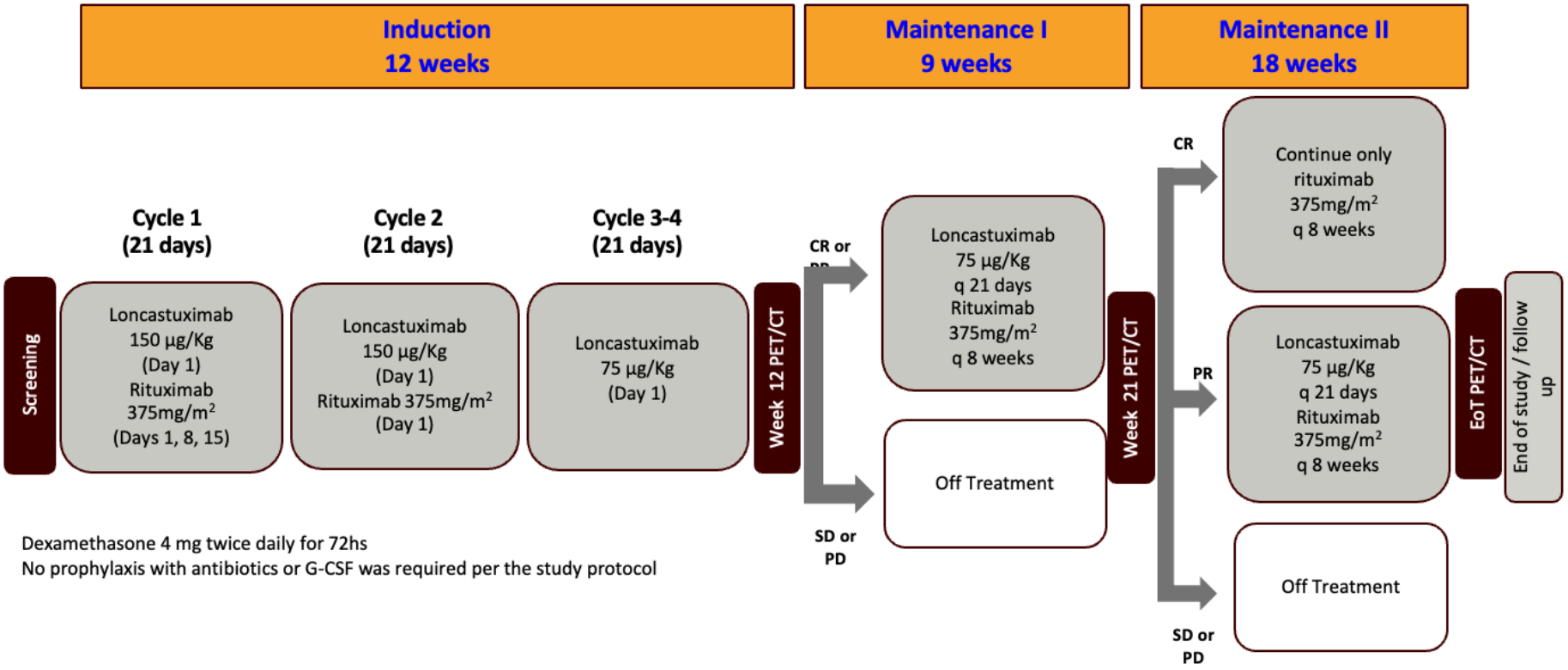
Loncastuximab teserine plus rituximab: single arm, single center phase 2 study



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

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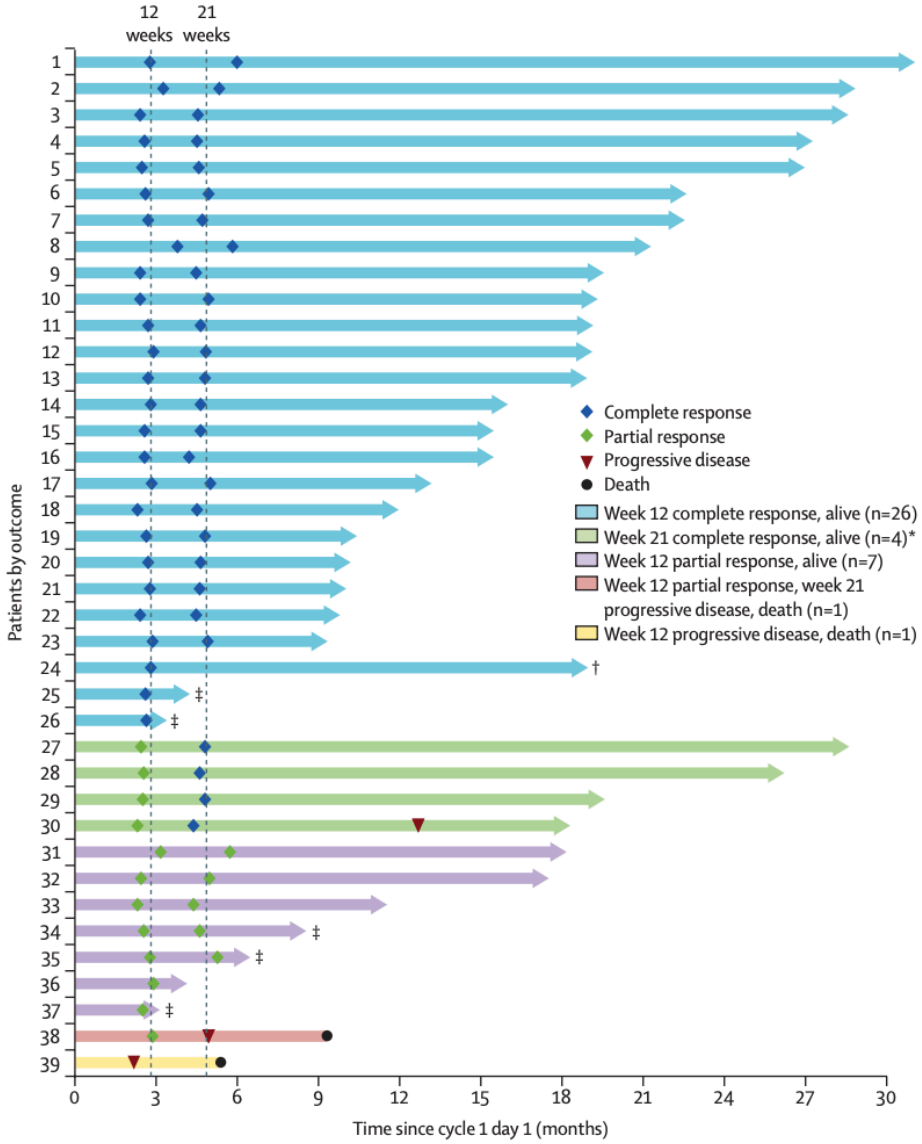
Alderuccio ASH 2024, abstract 337

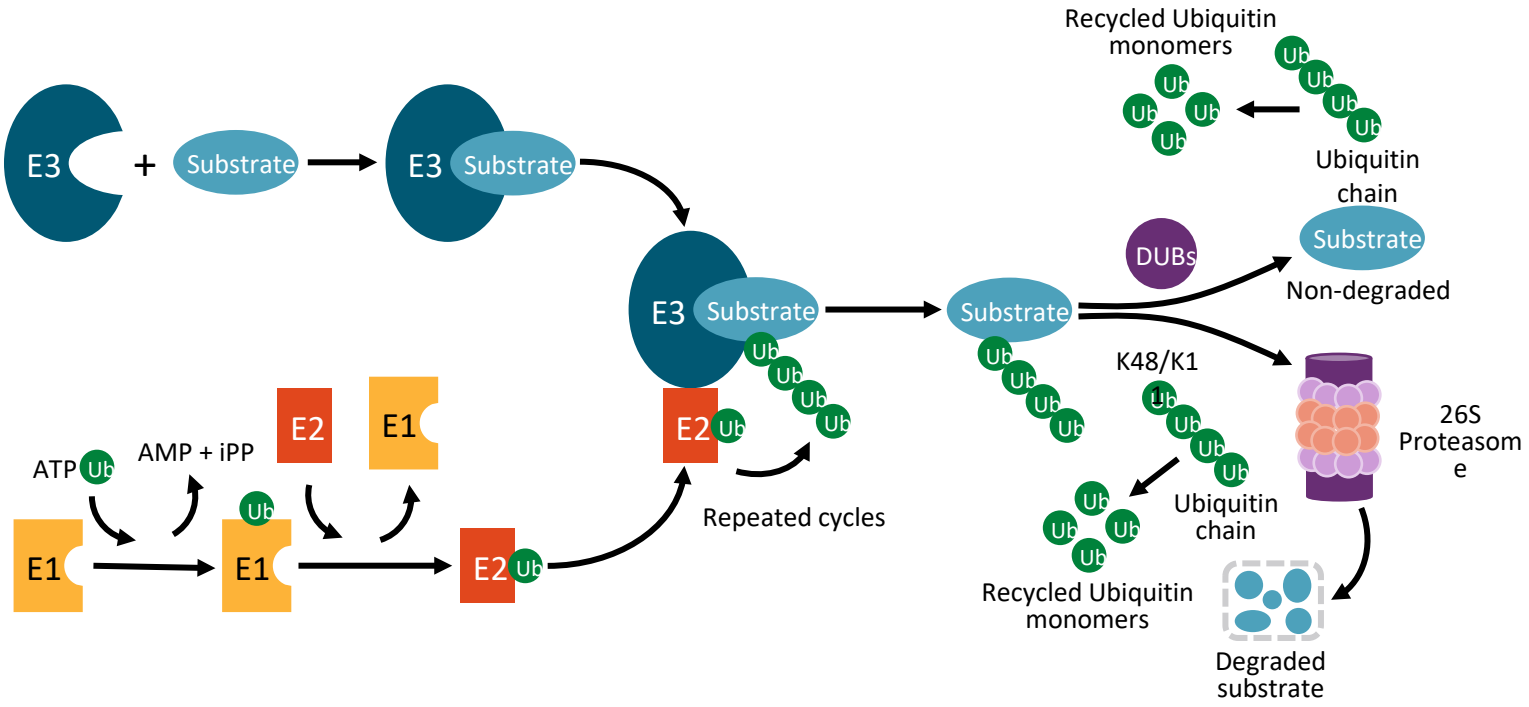
Loncastuximab plus rituximab in RR FL: Results



Alderuccio ASH 2024, abstract 337; Alderuccio Lancet Haematology 2025 Jan;12(1):e23-e34

CelMODs

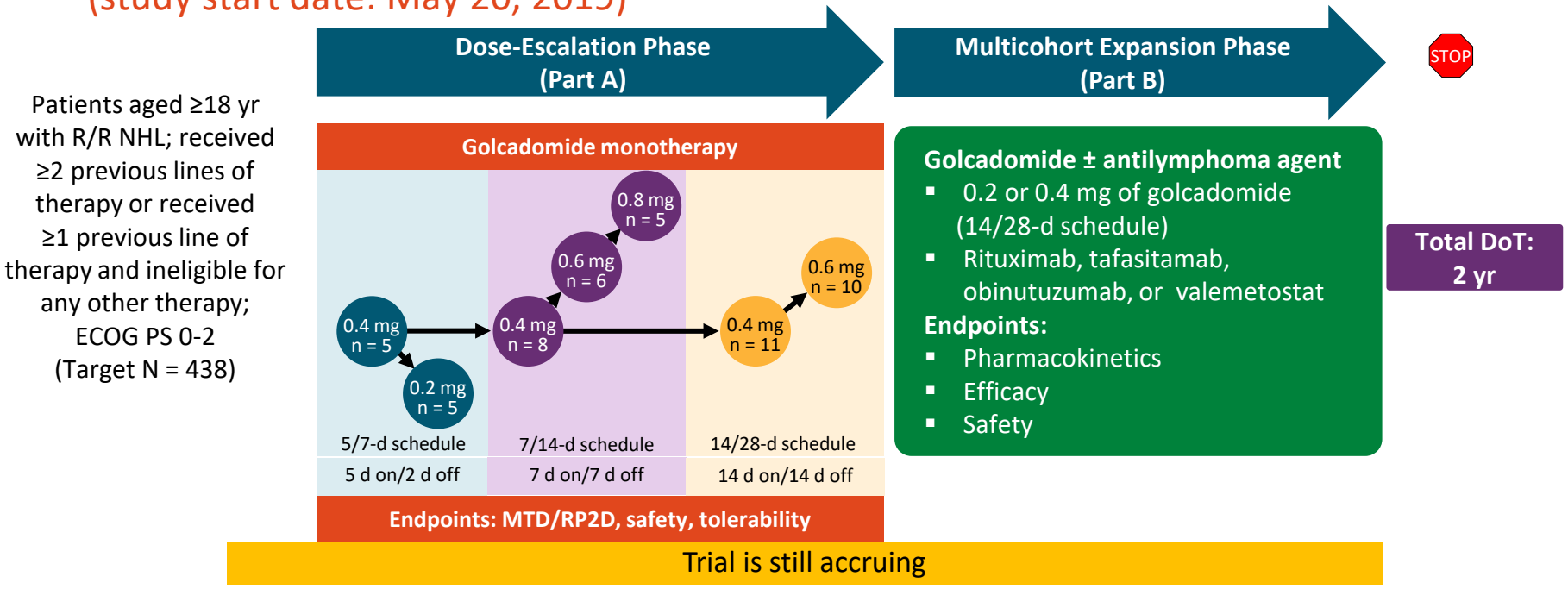
Ubiquitin-Proteasome System (UPS)



Bhat. Curr Opin Pharmacol. 2022;67:102310.

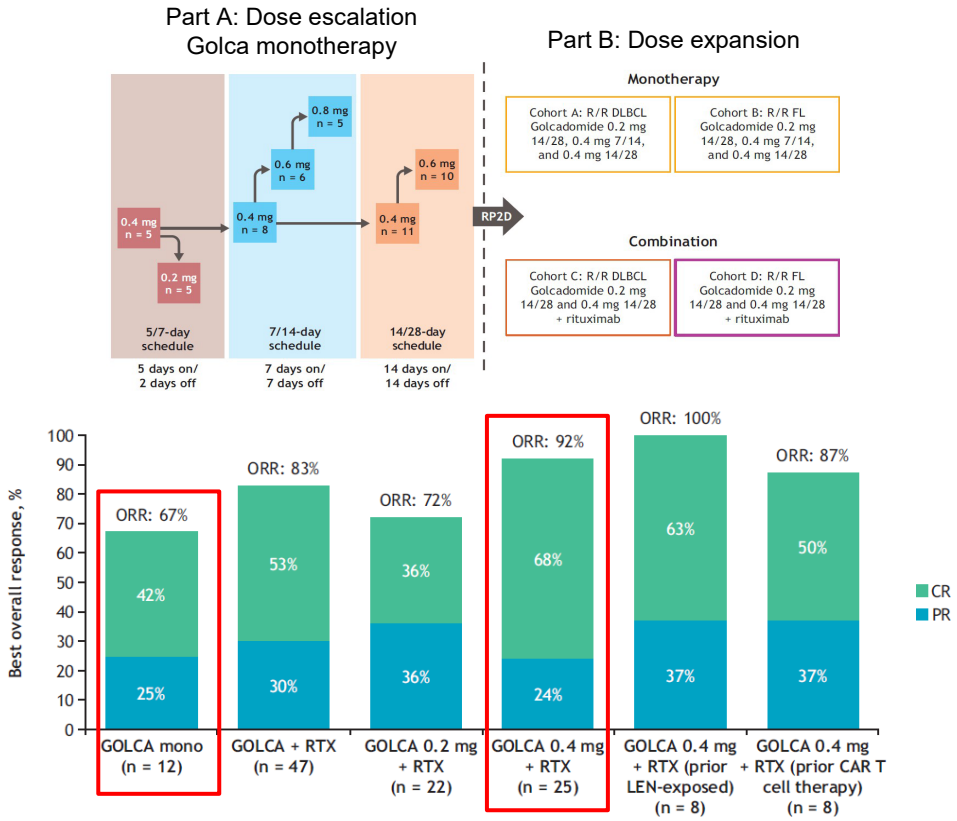
CC-99282-NHL-001: Phase I/II First-in-Human Trial of Golcadomide in R/R NHL

- Nonrandomized multicenter, 2-part, first-in-human, open-label phase I/II trial (study start date: May 20, 2019)



Chavez. ASH 2023. Abstr 4496. NCT03930953.

Golcadomide with or without rituximab R in 2L+ FL



TRAE, n (%)	Part B / Rituximab combination			
	Golcadomide 0.2 mg (n = 22)		Golcadomide 0.4 mg (n = 34)	
	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)	-

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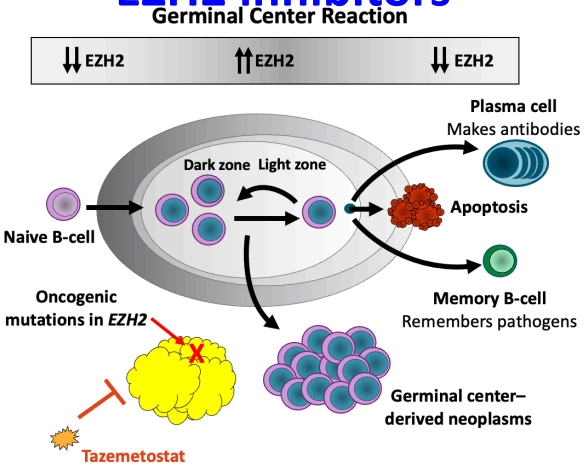

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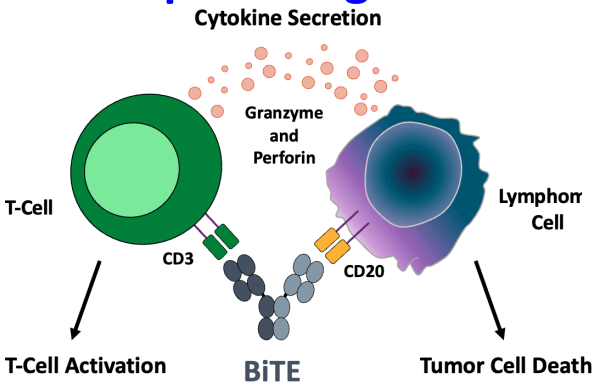

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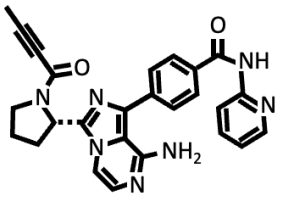

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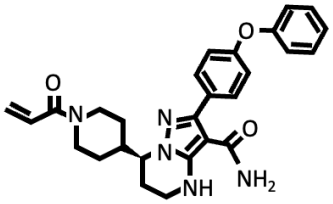

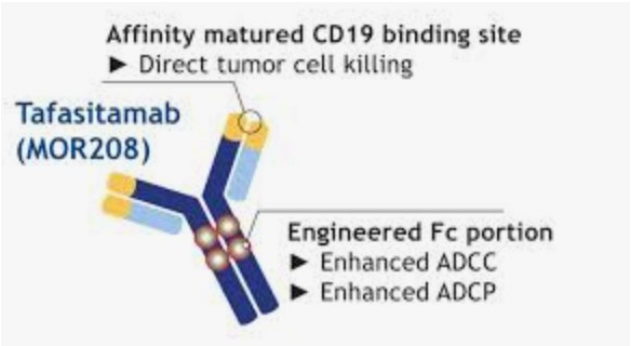

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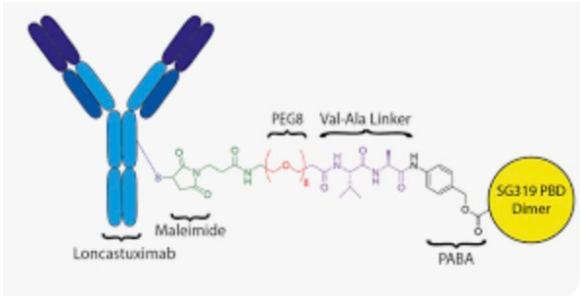

antiCD19 ADC

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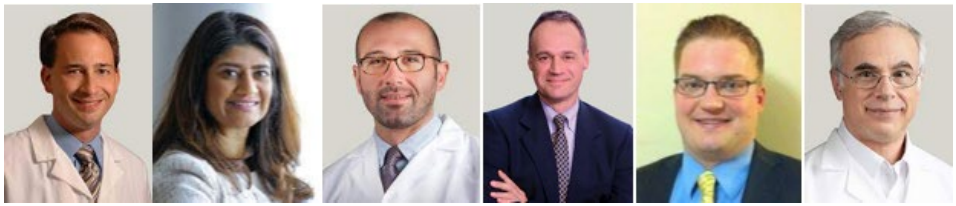
THANK YOU

Opening 2027



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cancer@uchospitals.edu