Follicular lymphoma: Defining Best 1L and 2L Treatment in the Era of Personalized Medicine

Nakhle Saba, MD
Associate Professor of Medicine
Tulane University
Annual New Orleans Summer Cancer Meeting
July 16, 2023

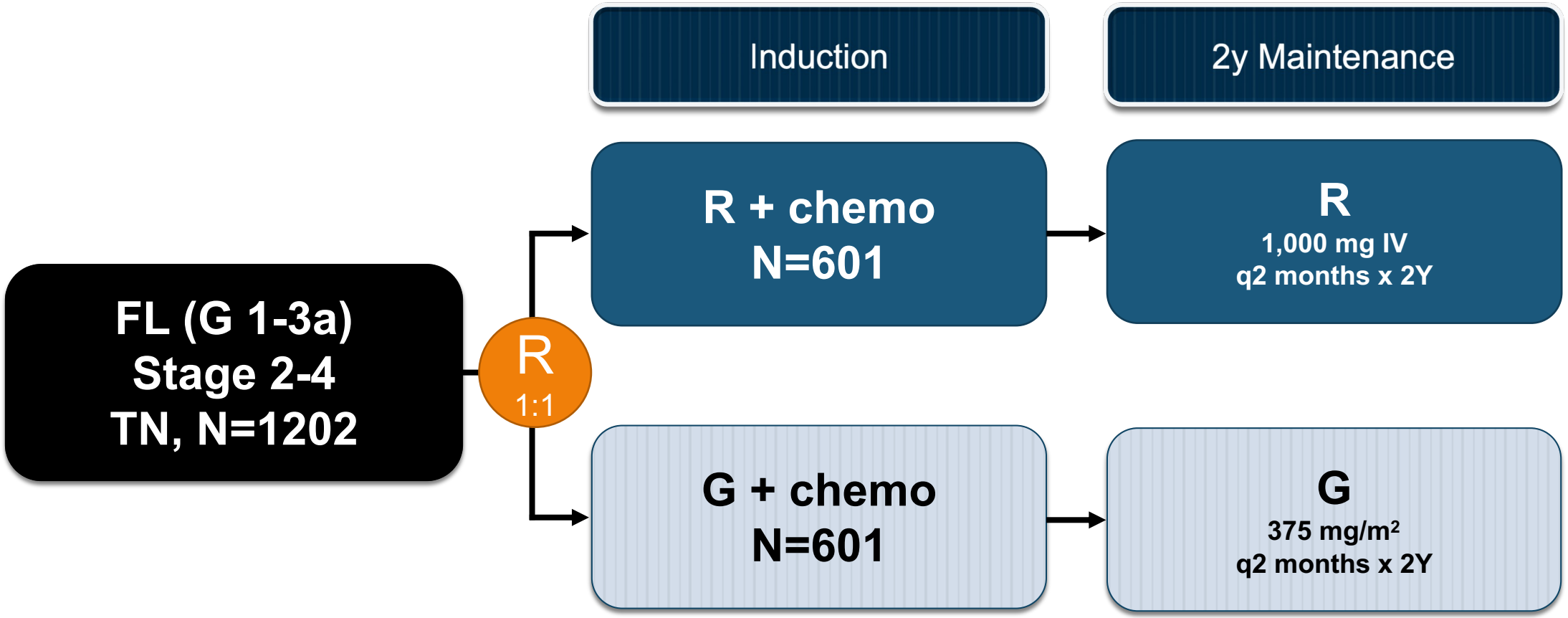
What we've learned from frontline trials

CIT			R^2 as a chemo-free option	R maintenance improves PFS but not OS
StiL[1] Phase 3 BR vs R-CHOP	**BRIGHT[2] Phase 3 BR vs R-CHOP/R-CVP**	**GALLIUM[3,4] Phase 3 G- vs R-chemo**	**RELEVANCE[5] Phase 3 R^2 (lenalidomide + R) vs R-chemo**	**PRIMA[6,7]: Phase 3 Rituximab maintenance FOLL12[8]: Phase 3 Rituximab maintenance**
▪ BR is safer and superior to R-CHOP (PFS and CR)	▪ BR is safer and superior to R-CHOP (Trend PFS, ORR)	▪ Superior PFS with G- vs R-chemo, but no difference in OS ▪ More grade 3-5 AEs with G (75% vs 68%)	▪ Efficacy: R^2 is equivalent to CIT ▪ Safety: Less hematologic toxicity with R^2, but more grade 3/4 cutaneous toxicity (7% vs 1%)	▪ Superior PFS (and TTNT), but not OS, with R maintenance ▪ Post R-CHOP or post BR

1. Rummel MJ, et al. *Lancet.* 2013; 2. Flinn IW, et al. *J Clin Oncol.* 2019; 3. Marcus R, et al. *N Engl J Med.* 2017; 4. Townsend W, et al. *EHA* 2022; 5. Morschhauser F, et al. *N Engl J Med.* 2018; 6. Salles G, et al. *Lancet.* 2011; 7. Bachy E, et al. *J Clin Oncol.* 2019. 8. Luminari S, et al. *J Clin Oncol. 2021.*

GALLIUM trial: R-chemo vs. G-chemo in TN FL

A phase III randomized trial



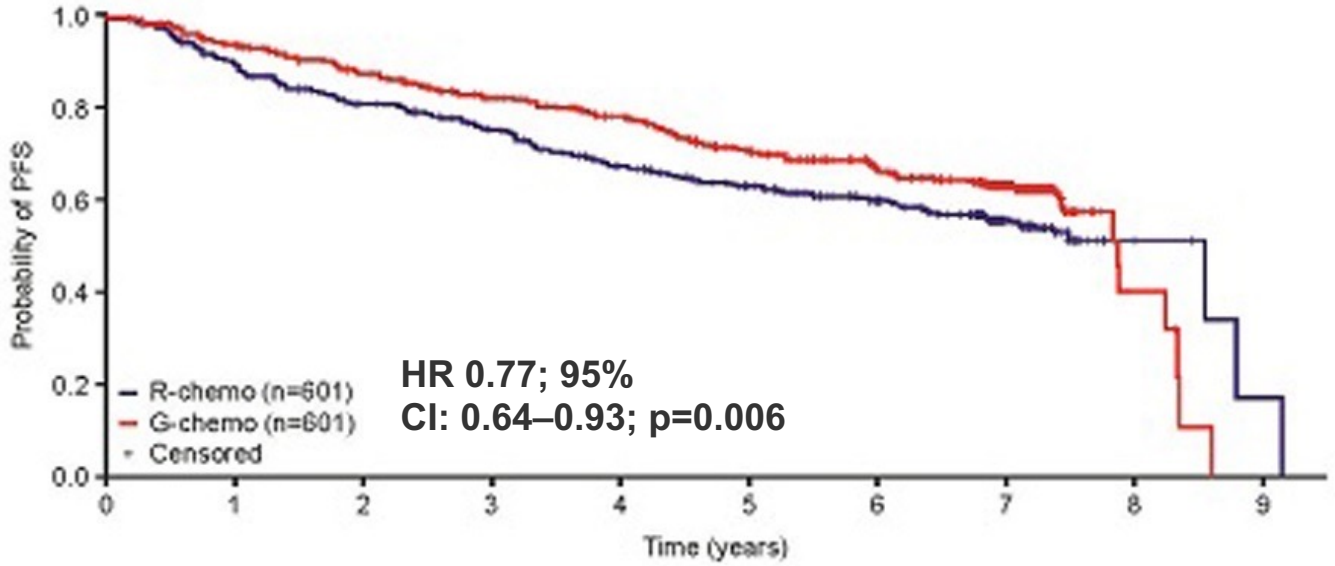
Chemo: CHOP, Bendamustine, CVP
Primary endpoints: investigator-assessed PFS
Secondary endpoints include: OS, TTNT, safety

Marcus et al. NEJM 2017
Townsend et al. EHA 2022

GALLIUM trial, R-chemo vs. G-chemo in TN FL

Final analysis, median F/U 8 years

Figure. Investigator-assessed PFS in the FL intent-to-treat population



No. of pts at risk

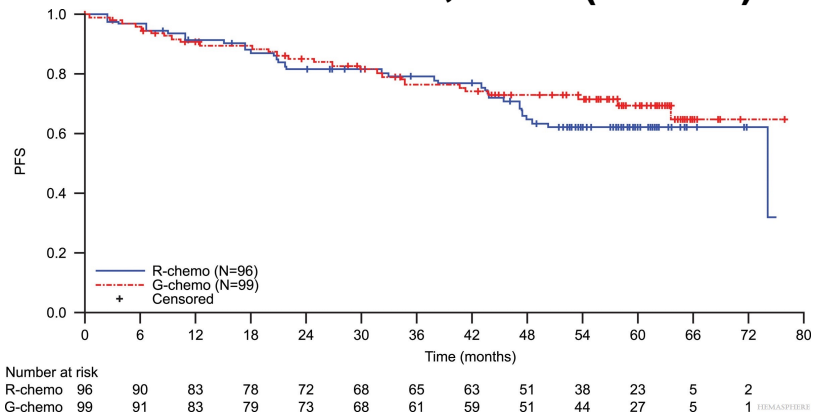
R-chemo	601	563	512	471	447	430	405	375	351	333	314	290	266	239	157	28	5	3	1
G-chemo	601	574	541	514	493	469	449	433	409	375	349	322	297	264	167	27	5	1	

Event-free probabilities became unreliable beyond 7 years as only around 10–20% of patients remained in follow-up, i.e. less than 60–120 patients were left at risk in one arm (Pocock, et al. 2002)

HEMASPHERE

7-year OS was similar in both arms:
88.5% with G-chemo *vs.*
87.2% with R-chemo
(HR, 0.86; 95% CI: 0.63–1.18; p=0.36)

GALLIUM trial, MZL (N=195)



Herold et al. HemaSphere, 2022

Chemo: CHOP, Bendamustine, CVP
Primary endpoints: PFS
Secondary endpoints include: OS, EFS, DoR, safety

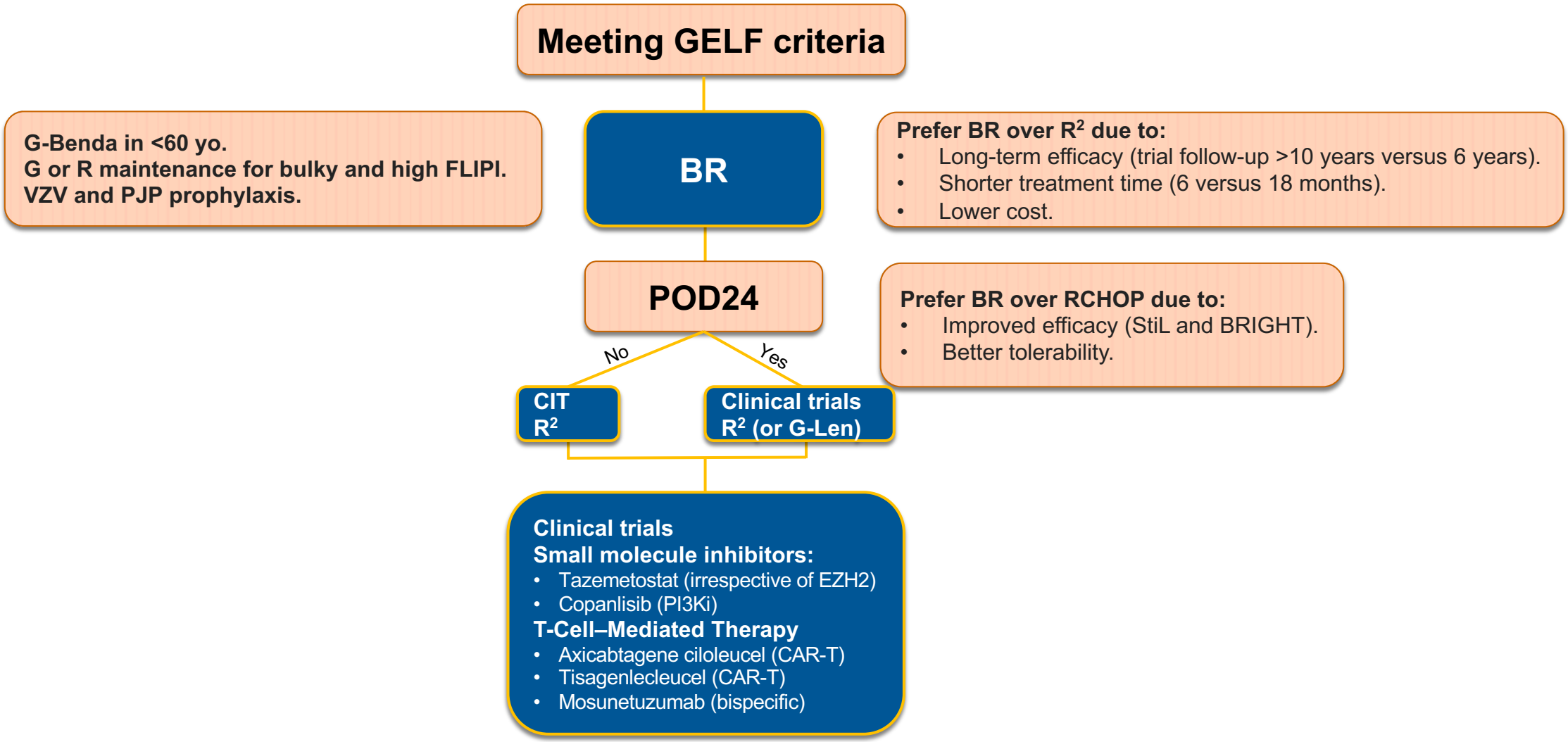
Marcus et al. NEJM 2017
Townsend et al. EHA 2022

RELEVANCE Trial: R-chemo vs. R^2

RELEVANCE, H2H	R^2	R-chemo	Comparison
CR rate (%)	48	53	No difference
6Y PFS (%)	60	59	No difference
6Y OS (%)	89	89	No difference
Histologic transformation	4.4	3.3	No difference
Second primary malignancy	11	13	No difference
Dose reduction (%)	36	14	Higher in R^2
Dose interruption (%)	59	35	Higher in R^2
Early discontinuation (%)	11	3	Higher in R^2
Treatment duration (w/o R maint)	18 months	4-6 months	Higher in R^2
AEs	More rash, diarrhea and tumor flare	More neutropenia, N/V, neuropathy	

Morschhauser F, et al. *N Engl J Med.* 2018

Advanced Stage FL



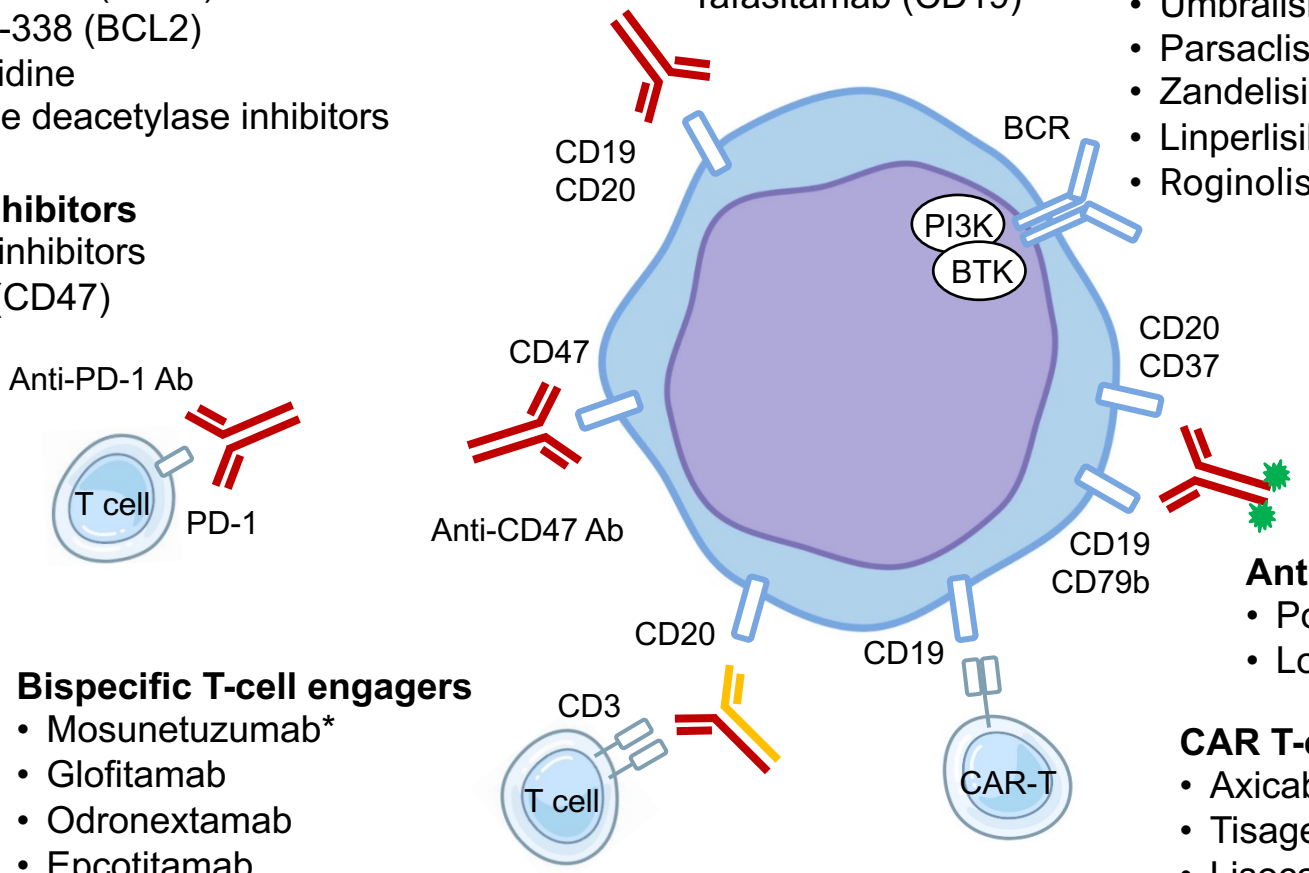
Targeted therapeutic agents in FL

Apoptosis & epigenetic targeting
- Tazemetostat (EZH2)*
- Venetoclax (BCL2)
- BGB-11417 (BCL2)
- LOXO-338 (BCL2)
- Azacitidine
- Histone deacetylase inhibitors

Checkpoint inhibitors
- PD-1/PD-L1 inhibitors
- Magrolimab (CD47)

Monoclonal antibodies
- Rituximab (CD20)*
- Obinutuzumab (CD20)*
- Ublituximab (CD20)
- Tafasitamab (CD19)

BCR pathway inhibitors
- Copanlisib (PI3Kα/δ)*
- Idelalisib (PI3Kδ)
- Duvelisib (PI3Kδ/γ)
- Umbralisib (PI3Kδ/CK1ε)
- Parsaclisib (PI3Kδ)
- Zandelisib (PI3Kδ)
- Linperlisib (PI3Kδ)
- Roginolisib (PI3Kδ)
- Ibrutinib (BTK)
- Acalabrutinib (BTK)
- Zanubrutinib (BTK)
- Orelabrutinib (BTK)



Immunomodulator
- Lenalidomide*

Radioimmunotherapy
- ^{90}Y-Ibritunomab tiuxetan (CD20)*
- ^{177}Lu-Lilotomab satetraxetan (CD37)

Antibody-drug conjugates
- Polatuzumab vedotin (CD79b)
- Loncastuximab tesirine (CD19)

Bispecific T-cell engagers
- Mosunetuzumab*
- Glofitamab
- Odronextamab
- Epcotitamab
- TNB-486

CAR T-cell therapy
- Axicabtagene ciloleucel*
- Tisagenlecleucel*
- Lisocabtagene maraleucel

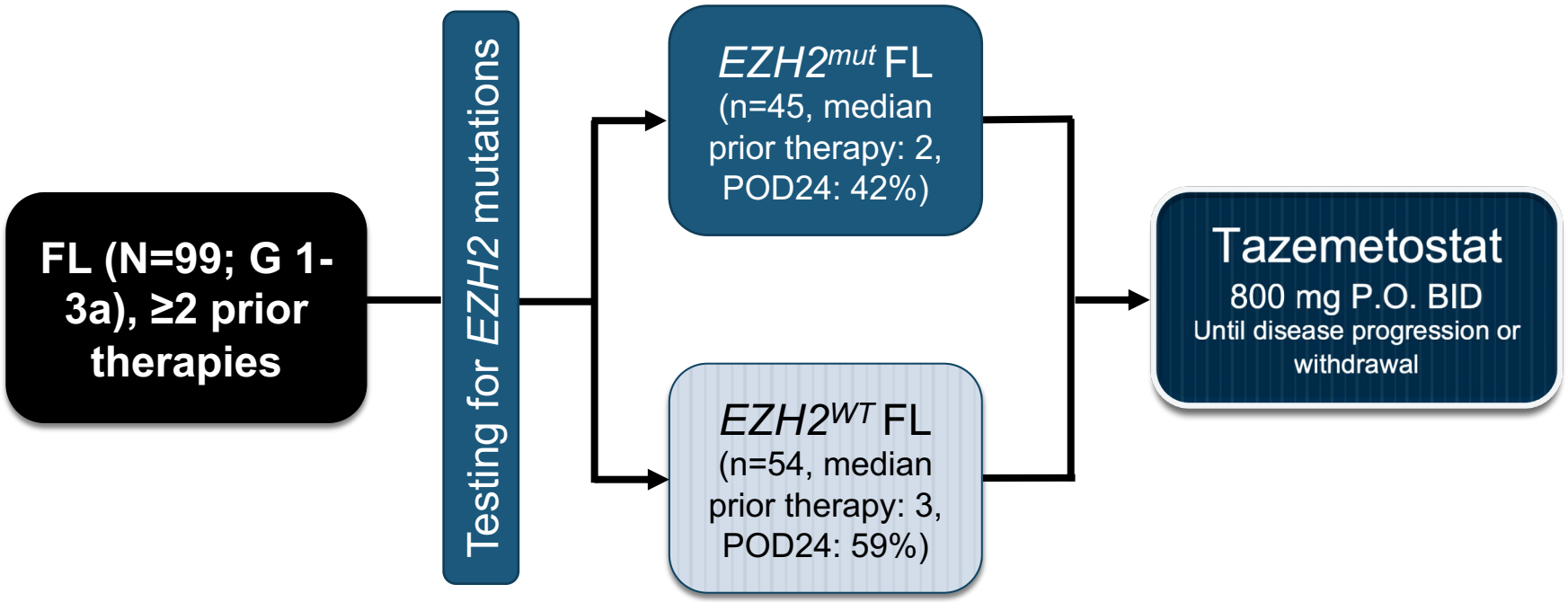
*FDA-approved agents. Ab, antibody; BCR, B-cell receptor; BTK, Burton's tyrosine kinase; FL, follicular lymphoma.

Copanlisib is the only PI3Ki available for FL

FL Subset Data	Copanlisib[1-4]
Isoform Target	PI3Kα and δ
Dosing and administration	60 mg IV on days 1, 8, and 15 of a 28-day treatment cycle
Evaluation Trial (patients)	**CHRONOS-1:** Phase 2, refractory to R and alkylating agents (104) **CHRONOS-3:** phase 3 C+R vs. C+P, relapsed after R or CIT
Approval (year)	≥2 prior therapies (2017)
ORR, (%)	59
CR, %	20
Median PFS	11 mo
Grade ≥3 AEs	Diarrhea (8.5%) Elevated ALT/AST(<1%) Colitis (<1%) Pneumonitis (1.4%) Hyperglycemia (40-56%)

1. Dreyling M, et al. *J Clin Oncol*. 2017; 2. Dreyling M, et al. *Am J Hematol.* 2020; 3. Matasar et al. The Lancet 2021; 4. Dreyling et al. *ASCO* 2023.

Phase 2, Open-Label, Multicenter Study of Tazemetostat in R/R FL

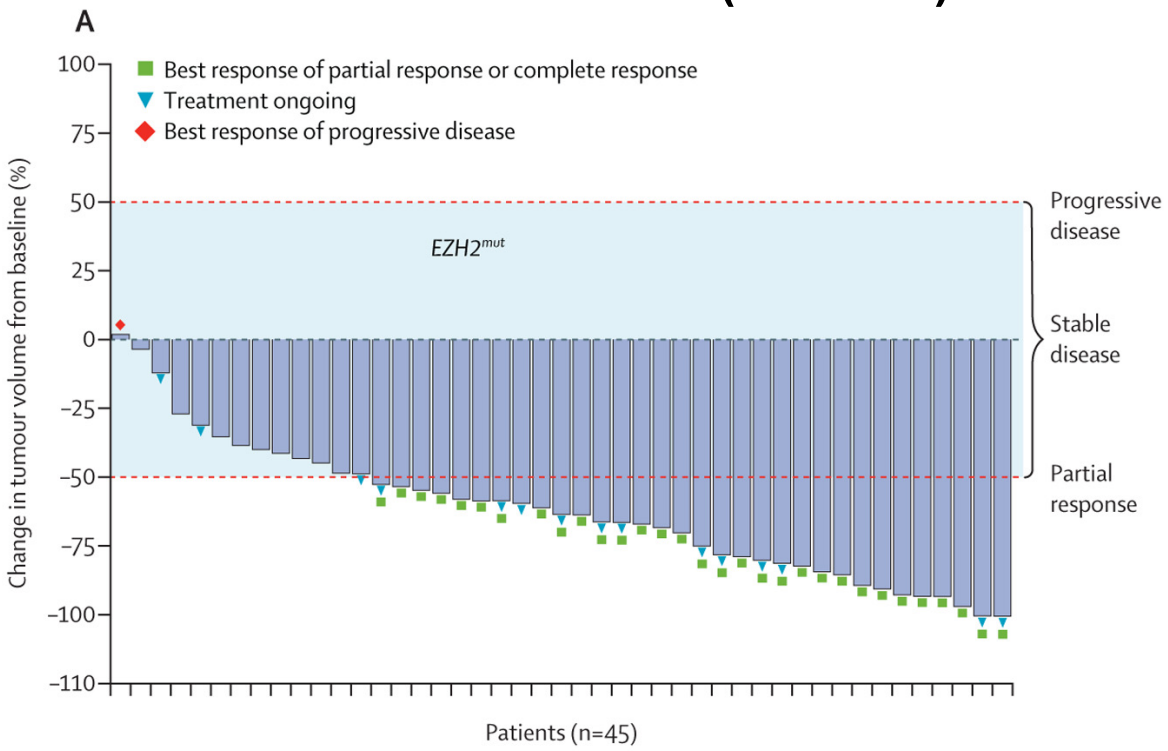


Primary endpoint: ORR
Secondary endpoints include: DOR, PFS, safety, tolerability

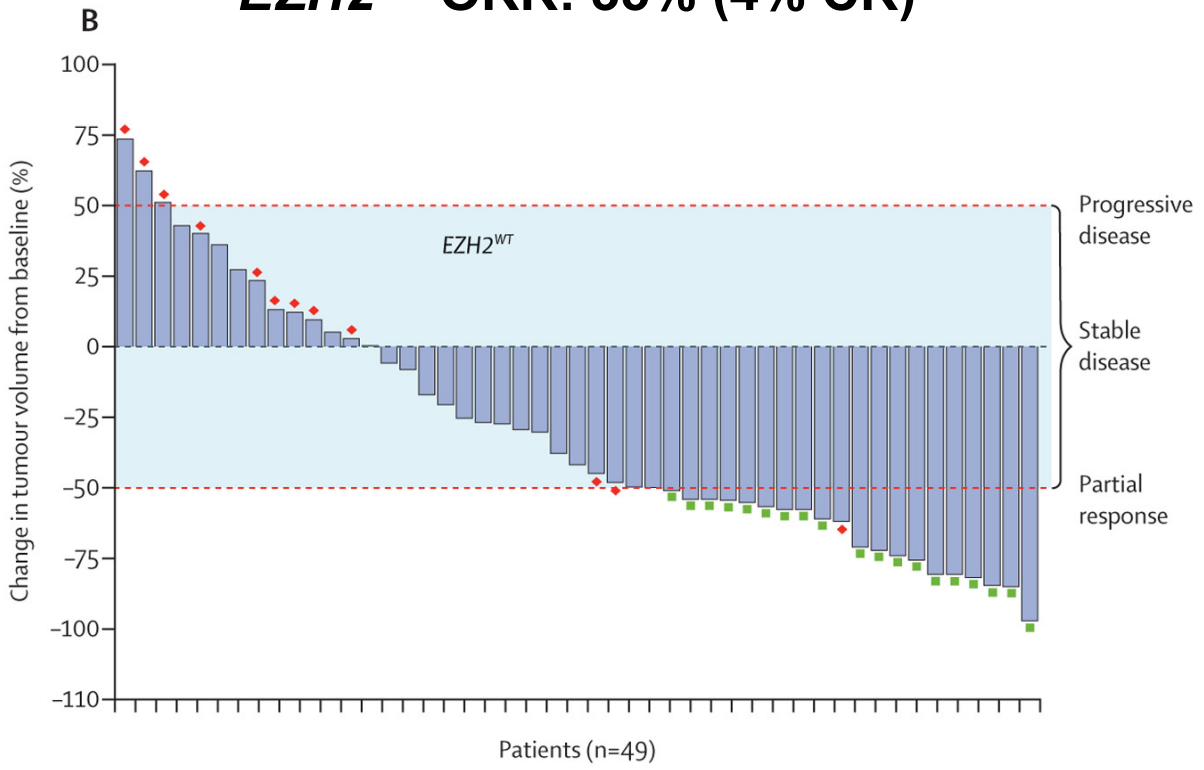
Morschhauser F, et al. *Lancet Oncol.* 2020

Tazemetostat is more efficacious in *EZH2*^{mut} compared to *EZH2*^{WT}

EZH2^{mut} ORR: 69% (13% CR)



EZH2^{WT} ORR: 35% (4% CR)



Morschhauser F, et al. *Lancet Oncol.* 2020

Tazemetostat is safe and well tolerated

TEAEs, n (%)	Treatment-Related TEAE (N=99)	
	All Grades	Grade ≥3
Nausea	19 (19)	0 (0)
Asthenia	14 (14)	1 (1)
Diarrhea	12 (12)	0 (0)
Fatigue	12 (12)	1 (1)
Alopecia	14 (14)	0 (0)
Cough	2 (2)	0 (0)
URTI	1 (1)	0 (0)
Bronchitis	3 (3)	0 (0)
Anemia	9 (9)	2 (2)
Abdominal pain	2 (2)	0 (0)
Headache	5 (5)	0 (0)
Vomiting	6 (6)	0 (0)
Back pain	0 (0)	0 (0)
Pyrexia	2 (2)	0 (0)
Thrombocytopenia	8 (8)	3 (3)

- Discontinuation rate due to TEAE: 8%
- Dose reduction due to TEAE: 9%
- Dose interruption due to TEAE: 27%
- No treatment related deaths

Approved by FDA for R/R FL:

- *EZH2* mutation-positive, relapsed/refractory FL and ≥2 prior therapies
- Relapsed/refractory FL with no satisfactory alternative treatment options

Morschhauser F, et al. *Lancet Oncol.* 2020

Phase 1b/3 study of Tazemetostat + R^2 in R/R FL

SYMPHONY-1 (EZH-302; NCT04224493)

Patients

- 44 patients enrolled, *EZH2*^{mut}: 17%
- Median # prior therapies: 1
- Refractory to rituximab: 34%; POD24: 27%

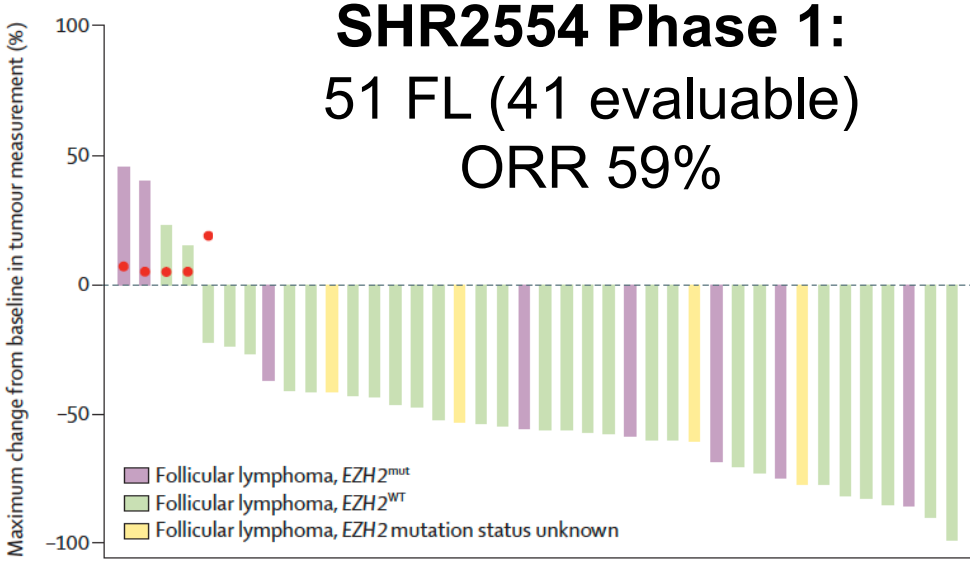
Efficacy (41 evaluable)

- ORR: 97.5% (CR: 51%)
- POD24 (ORR: 100%; CR: 55%)
- Median PFS: NR

Toxicity

- G3-4 TEAE: neutropenia (30%)
- RP3D: TAZ 800 mg + R^2 *vs.* Placebo+ R^2 in ≈500 patients with R/R FL

SHR2554 Phase 1:
51 FL (41 evaluable)
ORR 59%



Song, et al. *Lancet hematol.* 2022
Batlevi, et al. *ASH* 2022

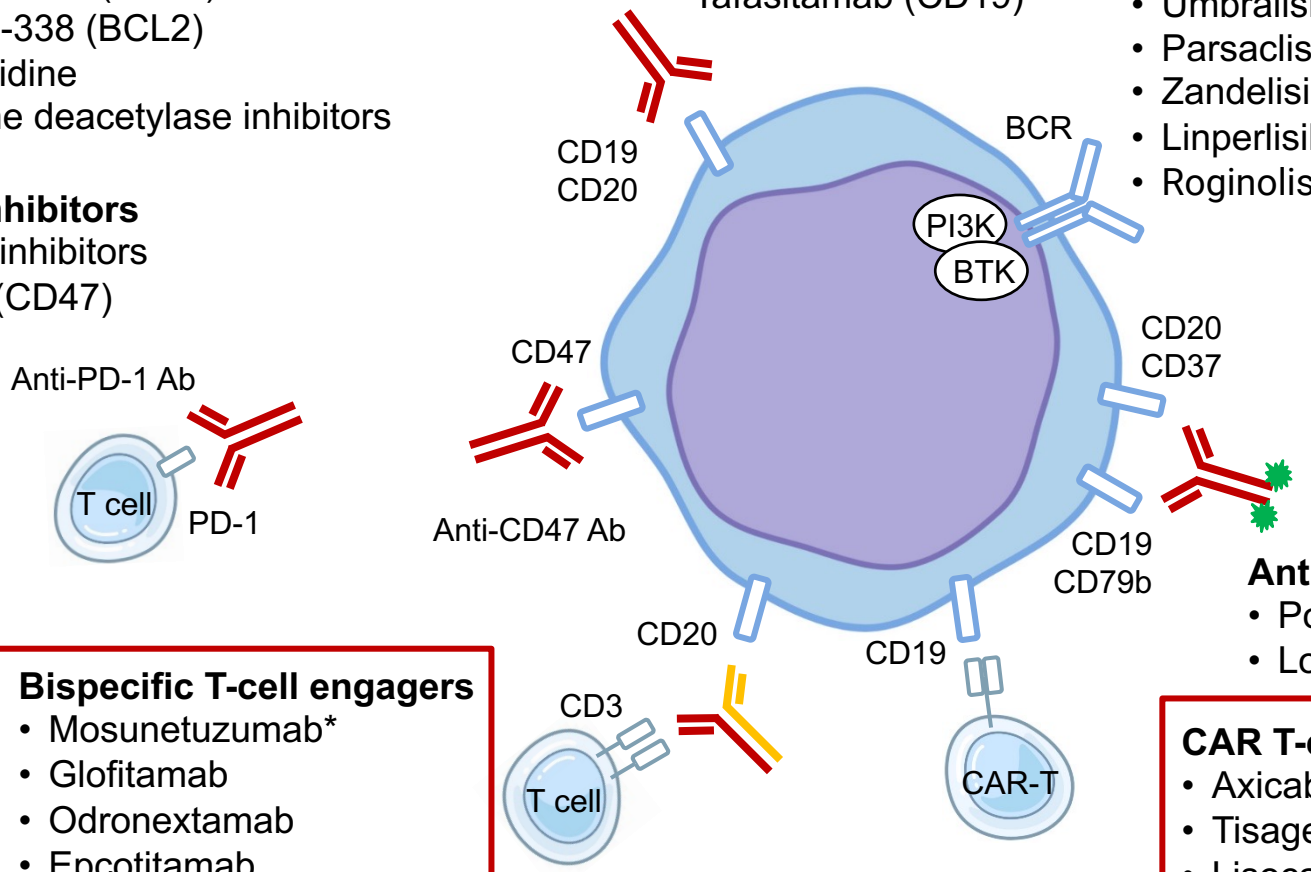
Targeted therapeutic agents in FL

Apoptosis & epigenetic targeting
- Tazemetostat (EZH2)*
- Venetoclax (BCL2)
- BGB-11417 (BCL2)
- LOXO-338 (BCL2)
- Azacitidine
- Histone deacetylase inhibitors

Checkpoint inhibitors
- PD-1/PD-L1 inhibitors
- Magrolimab (CD47)

Monoclonal antibodies
- Rituximab (CD20)*
- Obinutuzumab (CD20)*
- Ublituximab (CD20)
- Tafasitamab (CD19)

BCR pathway inhibitors
- Copanlisib (PI3Kα/δ)*
- Idelalisib (PI3Kδ)
- Duvelisib (PI3Kδ/γ)
- Umbralisib (PI3Kδ/CK1ε)
- Parsaclisib (PI3Kδ)
- Zandelisib (PI3Kδ)
- Linperlisib (PI3Kδ)
- Roginolisib (PI3Kδ)
- Ibrutinib (BTK)
- Acalabrutinib (BTK)
- Zanubrutinib (BTK)
- Orelabrutinib (BTK)



Immunomodulator
- Lenalidomide*

Radioimmunotherapy
- ^{90}Y-Ibritunomab tiuxetan (CD20)*
- ^{177}Lu-Lilotomab satetraxetan (CD37)

Antibody-drug conjugates
- Polatuzumab vedotin (CD79b)
- Loncastuximab tesirine (CD19)

Bispecific T-cell engagers
- Mosunetuzumab*
- Glofitamab
- Odronextamab
- Epcotitamab
- TNB-486

CAR T-cell therapy
- Axicabtagene ciloleucel*
- Tisagenlecleucel*
- Lisocabtagene maraleucel

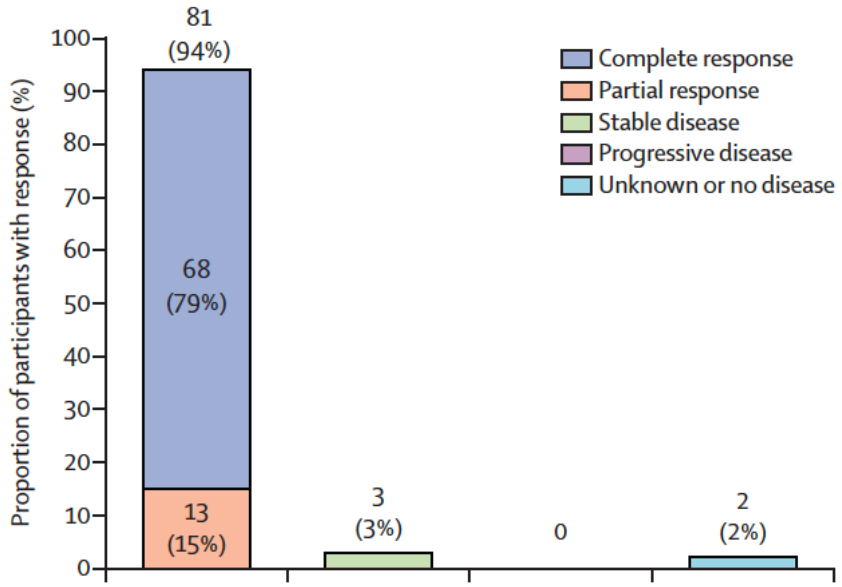
*FDA-approved agents. Ab, antibody; BCR, B-cell receptor; BTK, Burton's tyrosine kinase; FL, follicular lymphoma.

ZUMA-5: Axicabtagene Ciloleucel (Axi-Cel)

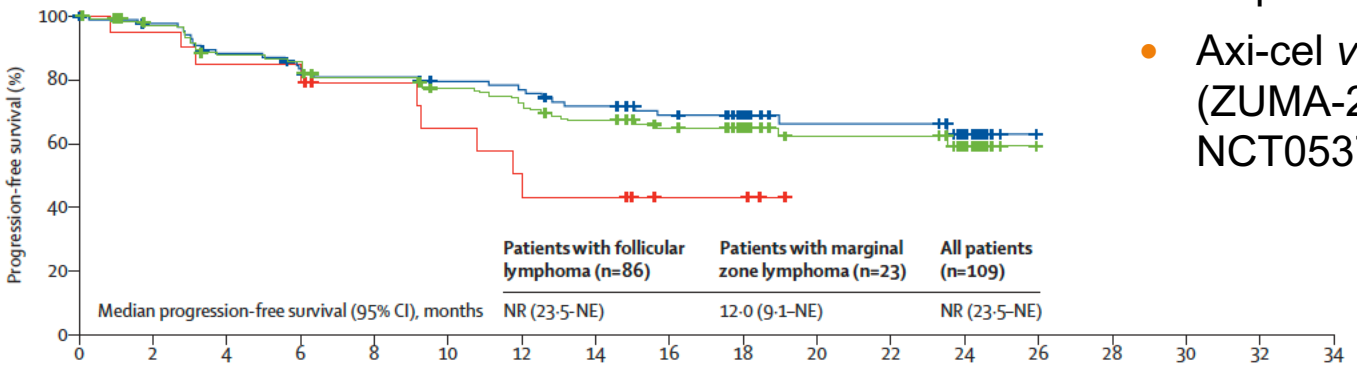
Single-arm, phase 2 study of axi-cel in patients with R/R iNHL (FL or MZL) after ≥2 lines of therapy

FL, N=124

Age, years	
Median	60 (53–67)
Previous lines of therapy	
Median†	3 (2–4)
≥3 previous lines of therapy	78 (63%)
Previous PI3K inhibitor	34 (27%)
Previous autologous stem-cell transplantation	30 (24%)
Previous anti-CD20 mAb and alkylating agent	123 (99%)
Previous anti-CD20 mAb single agent	39 (31%)
Previous alkylating single agent	16 (13%)
Previous lenalidomide	38 (31%)
Relapsed or refractory subgroup‡	
Refractory to last previous therapy	84 (68%)
POD24 from initiating first anti-CD20 mAb-containing therapy§	68 (55%)
Positive CD19 status¶	93/103 (90%)



Media F/U ~2Y



- The most common G≥3 AE: cytopenias (70%) and infections (18%)
- CRS G≥3: 7%
- ICANS G≥3: 19%
- SAE: 50%
- Deaths due to AE: 3%, one of which was deemed to be treatment-related
- Accelerated FDA approval (March 5, 2021) for patients after ≥2 prior lines of systemic therapy
- Axi-cel *vs.* SOC in R/R FL (ZUMA-22, Phase III) NCT05371093

Jacobson et al. *Lancet Oncol.* 2022

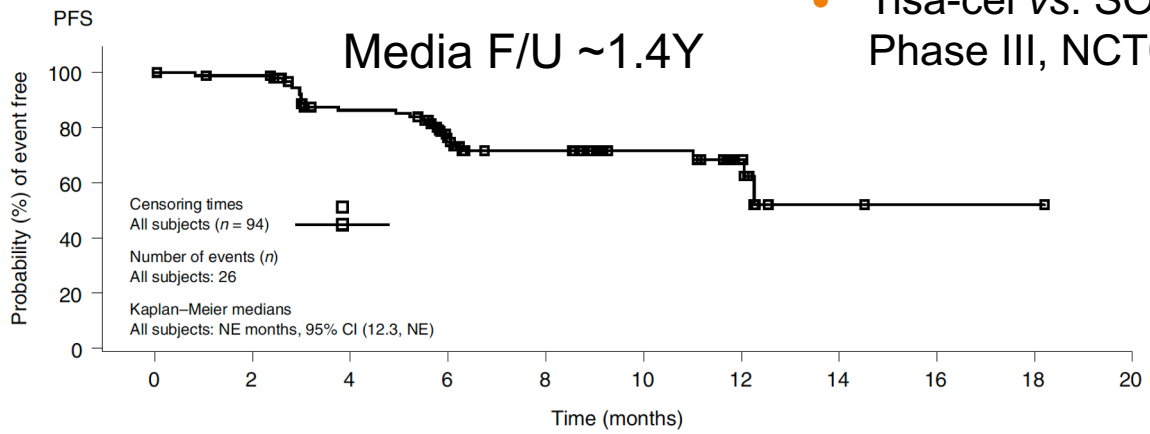
ELARA: Tisagenlecleucel (Tisa-Cel)

Single-arm, phase 2 study of Tisa-cel in patients with R/R FL after ≥2 lines of therapy

FL, N=97

Median age (IQR), years	57.0 (49–64)
≥65 Years, *n* (%)	24 (24.7)
Median no. of previous therapies (range)	4 (2–13)
>4 lines of therapy, *n* (%)	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy, *n* (%)	61 (62.9)
Previous therapy to which the disease was refractory,[a] *n* (%)	
Anti-CD20 mAb	84 (86.6)
Alkylating agents	69 (71.1)
Anti-CD20 mAb + alkylating agent combination (same regimen)	61 (62.9)
Anthracyclines	43 (44.3)
Lenalidomide	18 (18.6)
Lenalidomide + anti-CD20 mAb (same regimen)	18 (18.6)
PI3K inhibitors	14 (14.4)
Refractory disease to last line of therapy, *n* (%)	76 (78.4)
Best response SD/PD	54 (55.7)
Relapse within 6 months	22 (22.7)
Previous autologous HSCT, *n* (%)	35 (36.1)
Relapsed ≤12 months after HSCT, n (%)	15 (15.5)
Refractory[a] to at least two regimens, *n* (%)	69 (71.1)
Double refractory,[b] *n* (%)	66 (68.0)

	Local assessment	IRC assessment
Best overall response, *n* (%)		
CR	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	17 (18.1)	16 (17.0)
SD	3 (3.2)	3 (3.2)
PD	6 (6.4)	9 (9.6)
UNK		1 (1.1)
Overall response rate (CR + PR), *n* (%)	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4



- The most common G≥3 AE: cytopenias (69%) and infections (5%)
- CRS G≥3: 0%
- ICANS G≥3: 1%
- SAE: 29%
- Deaths due to AE: 0%
- Accelerated FDA approval (May 27, 2022) for patients after ≥2 prior lines of systemic therapy.
- Tisa-cel *vs*. SOC in R/R FL Phase III, NCT05888493

Fowler N, et al. *Nat. Med.* 2022

Mosunetuzumab-axgb Monotherapy in R/R

Pivotal Results from a Phase II Study

R/R FL
N=90; G1-3A; ≥2 prior line of therapy (median 3), ECOG 0-1

Mosun Q3W
C1: 1mg D1, 2mg D8; 60mg D15;
C2D1: 60mg; C3-17, D1: 30mg

CR: Stop after C8
PR/SD: Continue up to C17

Premed: Dex 20 mg IV 1 h before each dose in cycles 1 and 2, optional C3-17. **Hospitalization optional**

Primary Endpoint:
CR (by IRC)

Patients

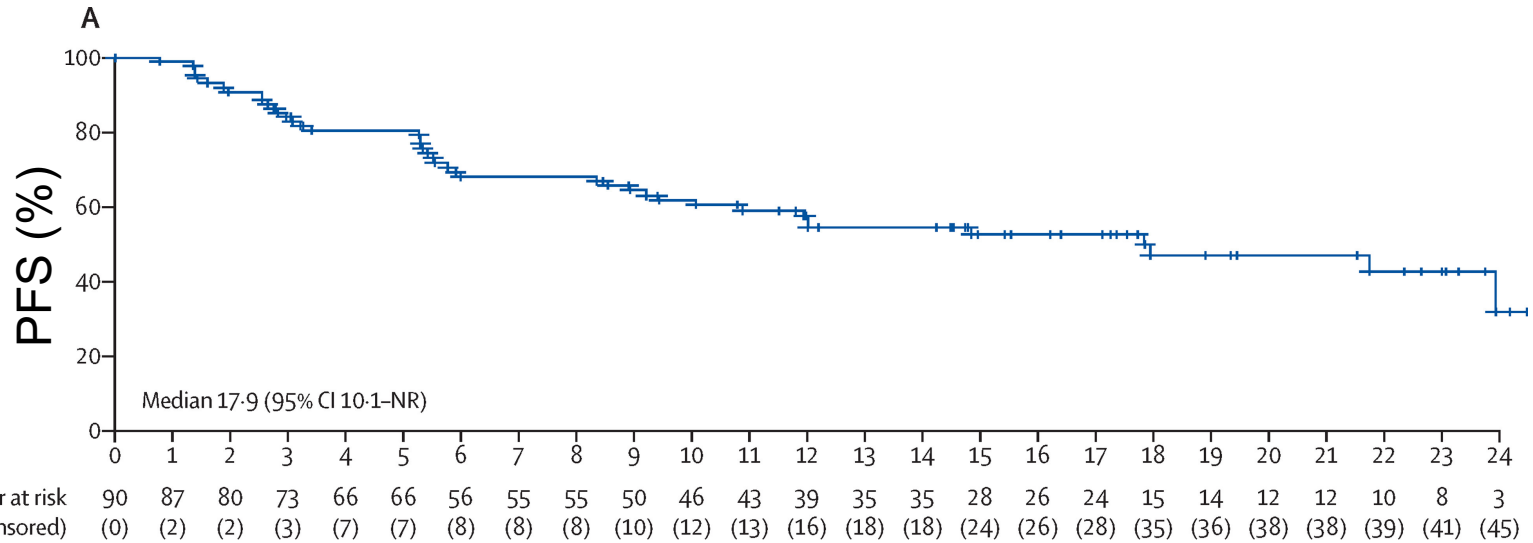
- 69% refractory to prior therapy
- 79% refractory to anti-CD20
- POD24: 52%

Efficacy

- Median F/U: 18.3 months
- ORR: 80% (CR: 60%)
- POD24 (ORR: 83%; CR: 55%)
- Median time to response 1.4 mo
- Median PFS:18 mo

Toxicity

- CRS: 42% (G3-4: 2%)
- G3-4: Neutropenia (26%), Hypophos (17%)
- AE leading to discontinuation: 4%



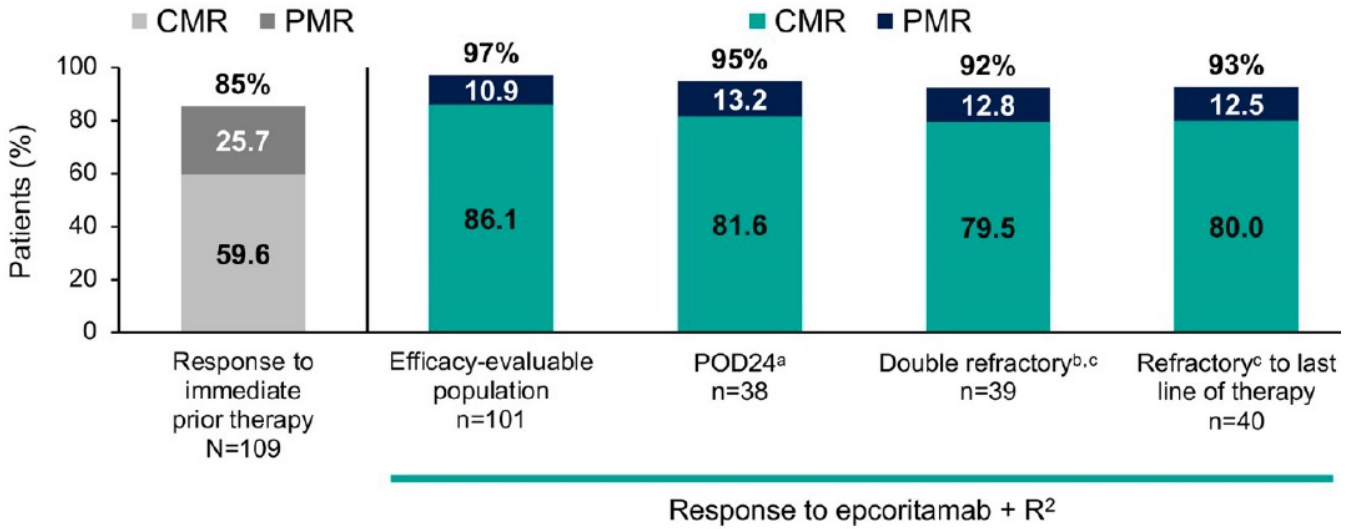
CELESTIMO, randomized phase III:
Mosun + Len *vs.* R^2 in R/R FL
NCT04712097

Budde, et al. *Lancet Oncol 2022*

CD3xCD20 Bispecific Antibodies in R/R FL

EPCORE NHL-2: Epcoritamab +R² phase I/II trial 109 R/R FL (101 evaluable, Median #PT) Median F/U 8.8 months	
6 months PFS	93%
CRS (G1-2/G3)	G1-2: 46% G3: 2%
ICANS (G1-2/G3)	G1-2: 2% G3-4: 0
6 months PFS	93%

Figure. Response rates, overall and among high-risk R/R FL subgroups, including POD24



[a]POD24 indicates progression within 2 y of first-line treatment with chemoimmunotherapy. [b]Double refractory indicates refractory to both anti-CD20 and an alkylating agent. [c]Refractory indicates no response or relapse within 6 mo after therapy.

Hutchings, et al. *The Lancet* 2021; Bannerji, et al. *Lancet Haematol.* 2022; Merryman et al. ASCO 2023; Sureda et al. EHA 2023. Morschhauser, et al. *ASH* 2021; Jacobs et al. EHA 2023; Taszner et al. EHA 2023.

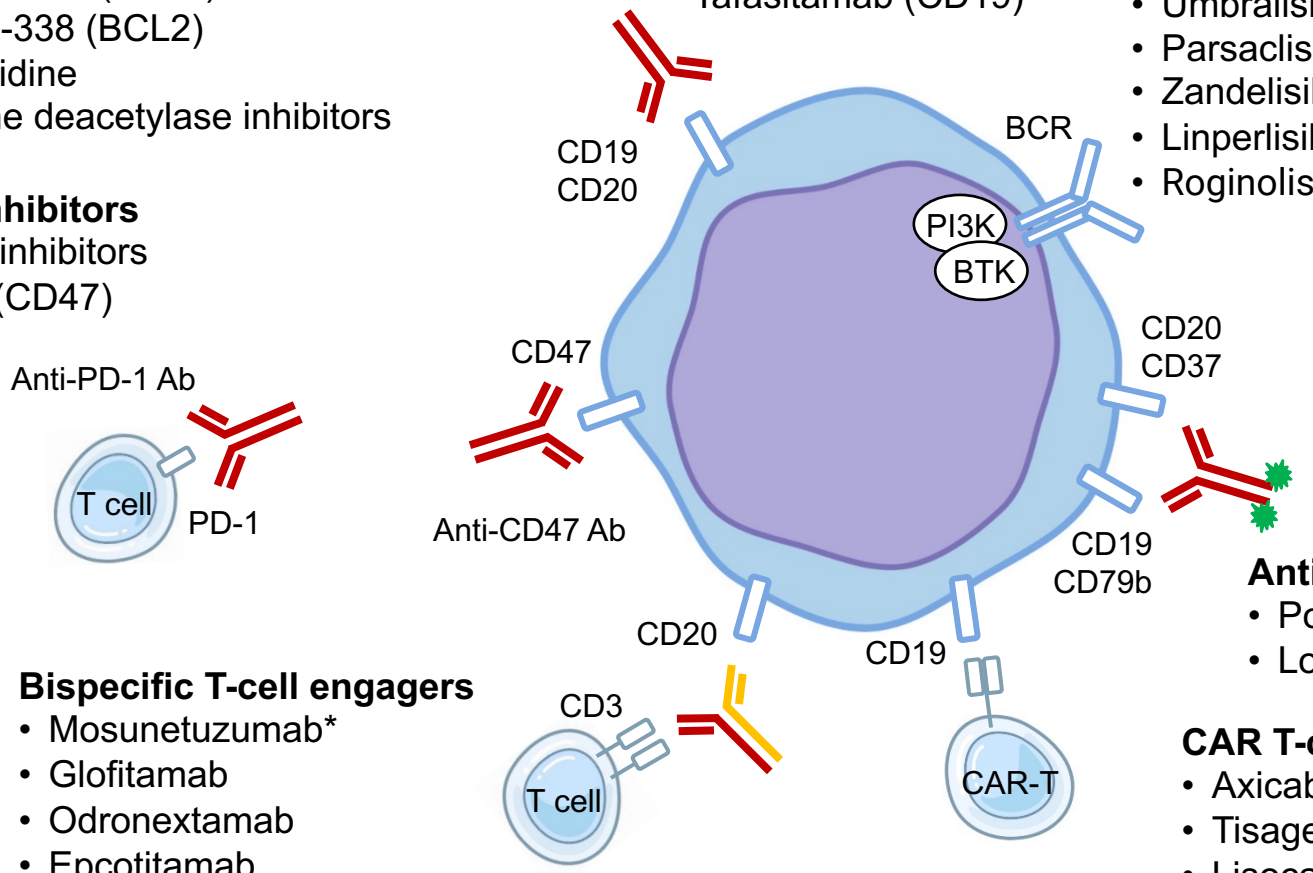
Targeted therapeutic agents in FL

Apoptosis & epigenetic targeting
- Tazemetostat (EZH2)*
- Venetoclax (BCL2)
- BGB-11417 (BCL2)
- LOXO-338 (BCL2)
- Azacitidine
- Histone deacetylase inhibitors

Checkpoint inhibitors
- PD-1/PD-L1 inhibitors
- Magrolimab (CD47)

Monoclonal antibodies
- Rituximab (CD20)*
- Obinutuzumab (CD20)*
- Ublituximab (CD20)
- Tafasitamab (CD19)

BCR pathway inhibitors
- Copanlisib (PI3Kα/δ)*
- Idelalisib (PI3Kδ)
- Duvelisib (PI3Kδ/γ)
- Umbralisib (PI3Kδ/CK1ε)
- Parsaclisib (PI3Kδ)
- Zandelisib (PI3Kδ)
- Linperlisib (PI3Kδ)
- Roginolisib (PI3Kδ)
- Ibrutinib (BTK)
- Acalabrutinib (BTK)
- Zanubrutinib (BTK)
- Orelabrutinib (BTK)



Immunomodulator
- Lenalidomide*

Radioimmunotherapy
- ^{90}Y-Ibritunomab tiuxetan (CD20)*
- ^{177}Lu-Lilotomab satetraxetan (CD37)

Antibody-drug conjugates
- Polatuzumab vedotin (CD79b)
- Loncastuximab tesirine (CD19)

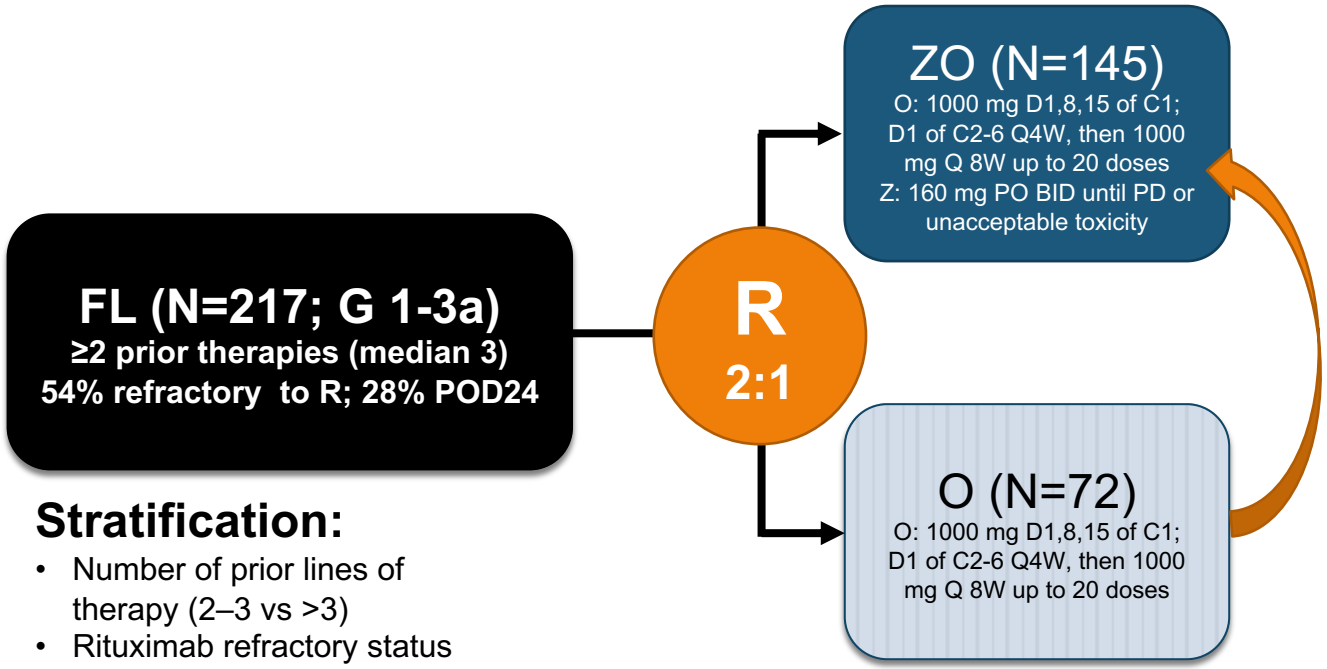
Bispecific T-cell engagers
- Mosunetuzumab*
- Glofitamab
- Odronextamab
- Epcotitamab
- TNB-486

CAR T-cell therapy
- Axicabtagene ciloleucel*
- Tisagenlecleucel*
- Lisocabtagene maraleucel

*FDA-approved agents. Ab, antibody; BCR, B-cell receptor; BTK, Burton's tyrosine kinase; FL, follicular lymphoma.

ROSEWOOD: Zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) in R/R FL

Phase II randomized trial



Stratification:

- Number of prior lines of therapy (2–3 vs >3)
- Rituximab refractory status (yes/no)
- Geographic region (China vs ex-China

Primary endpoint:
ORR

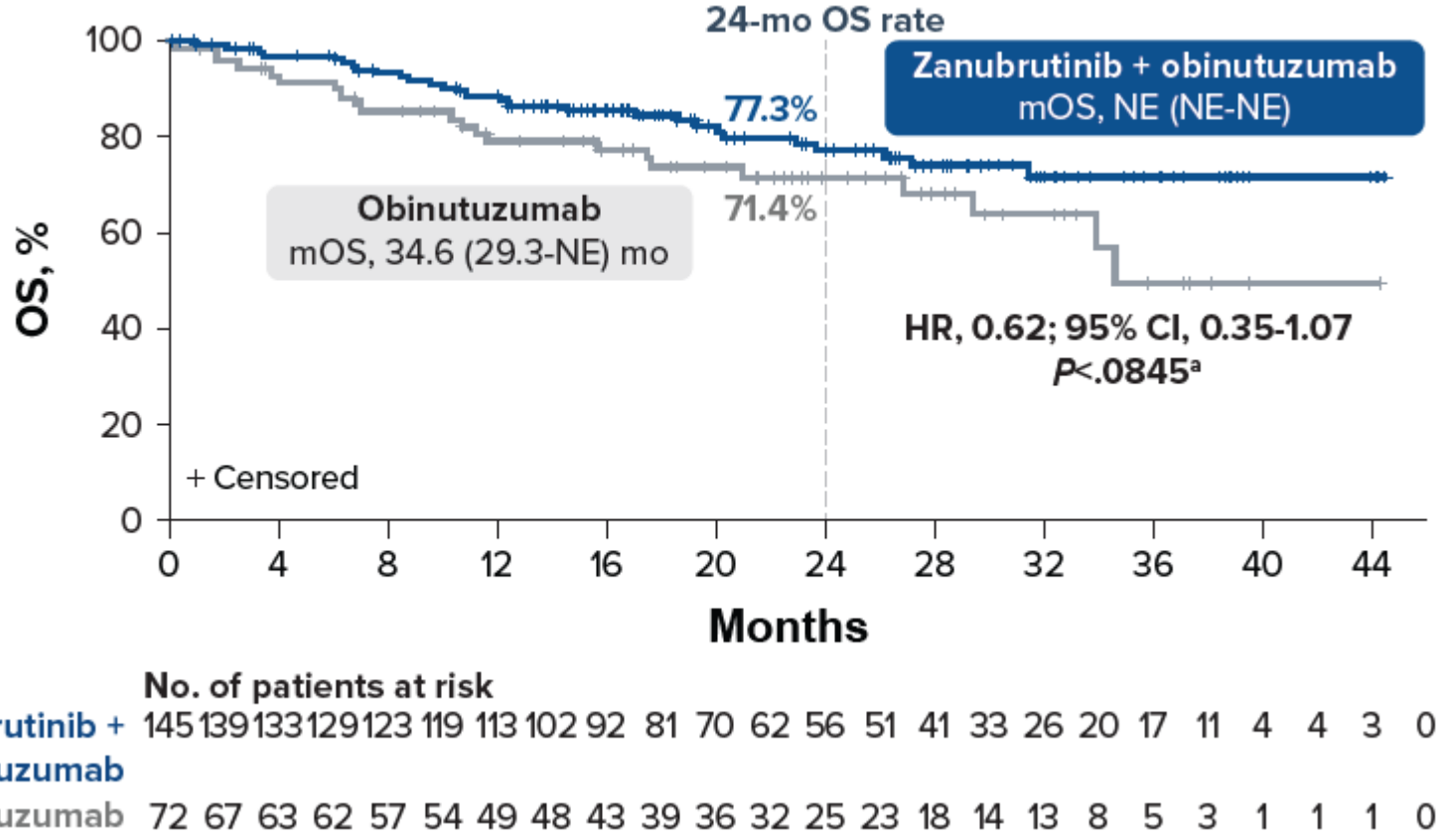
Secondary endpoints:
CR, DOR, PFS, OS

Flowers, et al. *ASCO* 2023

ROSEWOOD, Results

Median F/U 20.2 months

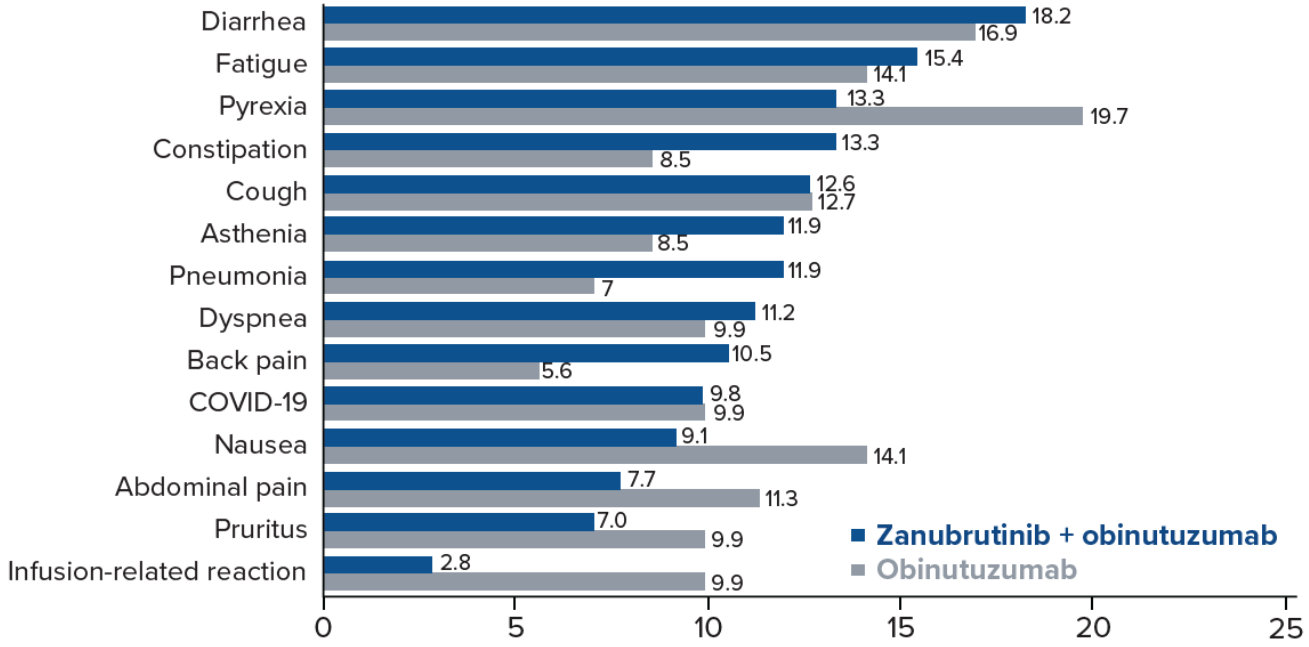
Characteristic	ZO (n=145)	O (n=72)
Age, median (range), years	63.0 (31-84)	65.5 (32-88)
ECOG PS ≥1, n (%)	59 (40.6)	41 (57.0)
FLIPI score ≥3, n (%)	77 (53.1)	37 (51.4)
Ann Arbor stage III-IV, n (%)	119 (82.1)	60 (83.3)
Bulky disease (≥7 cm), n (%)	23 (15.9)	12 (16.7)
Number of prior lines of therapy, median (range)	3 (2-11)	3 (2-9)
Refractory to rituximab, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent line of therapy, n (%)	47 (32.4)	29 (40.3)
POD24, n (%)	50 (34.5)	30 (41.7)
Prior therapy		
CIT	143 (98.6)	71 (98.6)
Anthracyclines	118 (81.4)	57 (79.2)
Cyclophosphamide	136 (93.8)	68 (94.4)
Bendamustine	79 (54.5)	40 (55.6)



Flowers, et al. *ASCO* 2023

ROSEWOOD, Results

Median F/U 20.2 months



	ZO (n=143)	O (n=71)
Pneumonia	14 (9.8)	3 (4.2)
COVID-19	8 (5.6)	2 (2.8)
COVID-19 pneumonia	5 (3.5)	2 (2.8)
Diarrhea	4 (2.8)	1 (1.4)
Febrile neutropenia	3 (2.1)	1 (1.4)
Atrial fibrillation	2 (1.4)	0 (0)
Infusion-related reaction	1 (0.7)	3 (4.2)
Hypertension	1 (0.7)	1 (1.4)

MAHOGANY Trial: Phase 3, randomized, open label.

ZO *vs.* R^2 in R/R FL (NCT05100862)

Nastoupil et al. ASCO 2023

Flowers, et al. *ASCO* 2023

Acalabrutinib and R^2 (aR^2) in High-Tumor Burden TN FL

Phase II investigator initiated single arm study

FL (N=24; G 1-3a)
Previously untreated
Stage III-IV

Acala+R^2
Acala: 100 mg po BID (C1-13)
Len: 20 mg po D1-21 (28-d cycle, C2-13)
Ritux: 375 mg/m2 IV (weekly C2, d1 C3-13)

Primary endpoint: CR

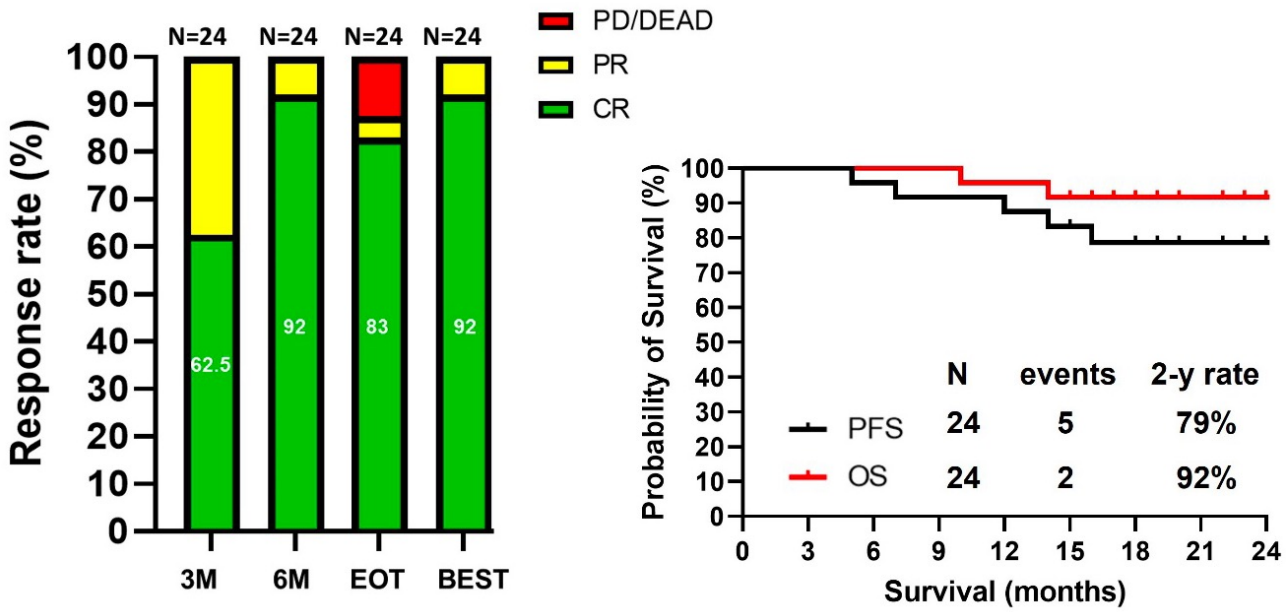
Patients

Median age: 62 years (range, 40-82).
Median largest LN size: 6.2 cm (range, 1.9-15).
Median SUVmax was 14 (range, 6-36).
intermediate-high FLIPI: 61%.
Median F/U: 22 months.

Safety (G3-4)

Neutropenia (58%), LFT increase (17%), infection (12.5%), anemia (8%), rash (8%).

One patient had atrial fibrillation and none had severe bleeding.



Strati et al, EHA 2023

SUMMARY

- Treatment landscape is evolving rapidly in FL.
- Big red-flag on Pi3K inhibitor safety.
- We are (will be) able to overcome major challenges (refractory, POD24).
- Who will win the race (BiTEs or CARs). Different target (CD20 vs. CD19), could they be use sequentially or even concurrently?
- Challenges:
  - Finding the magic recipe (long-term disease control, cure?).
  - Sequencing novel agents.

Thank you

nsaba@tulane.edu
Clinic: 504-988-6460
Cell: 423-946-1366