Follicular Lymphoma: Novel Advances and Pathways

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Agenda

- Overview of frontline options in advanced FL
- Approved and investigational agents in FL
- Overview of FDA-approved options in R/R FL
  - PI3Ki
  - EZH2i
  - CAR-T
- Investigational agents and landscape of future therapies
  - BiTE
  - ADC
  - PD-L1 blockade
  - BCL2i
  - BTKi
- Summary

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] Phase 3 G- vs R-chemo**	**RELEVANCE[4] Phase 3 R^2 (lenalidomide + R) vs R-chemo**	**PRIMA[5,6]: Phase 3 Rituximab maintenance FOLL12[7]: 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. Morschhauser F, et al. *N Engl J Med.* 2018; 5. Salles G, et al. *Lancet.* 2011; 6. Bachy E, et al. *J Clin Oncol.* 2019. 7. Luminari S, et al. *J Clin Oncol. 2021.*

Targeted therapeutic agents in FL

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

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

BCR pathway inhibitors
- Idelalisib (PI3Kδ)*
- Copanlisib (PI3Kα/δ)*
- Duvelisib (PI3Kδ/γ)*
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- Zandelisib (PI3Kδ)
- Ibrutinib (BTK)
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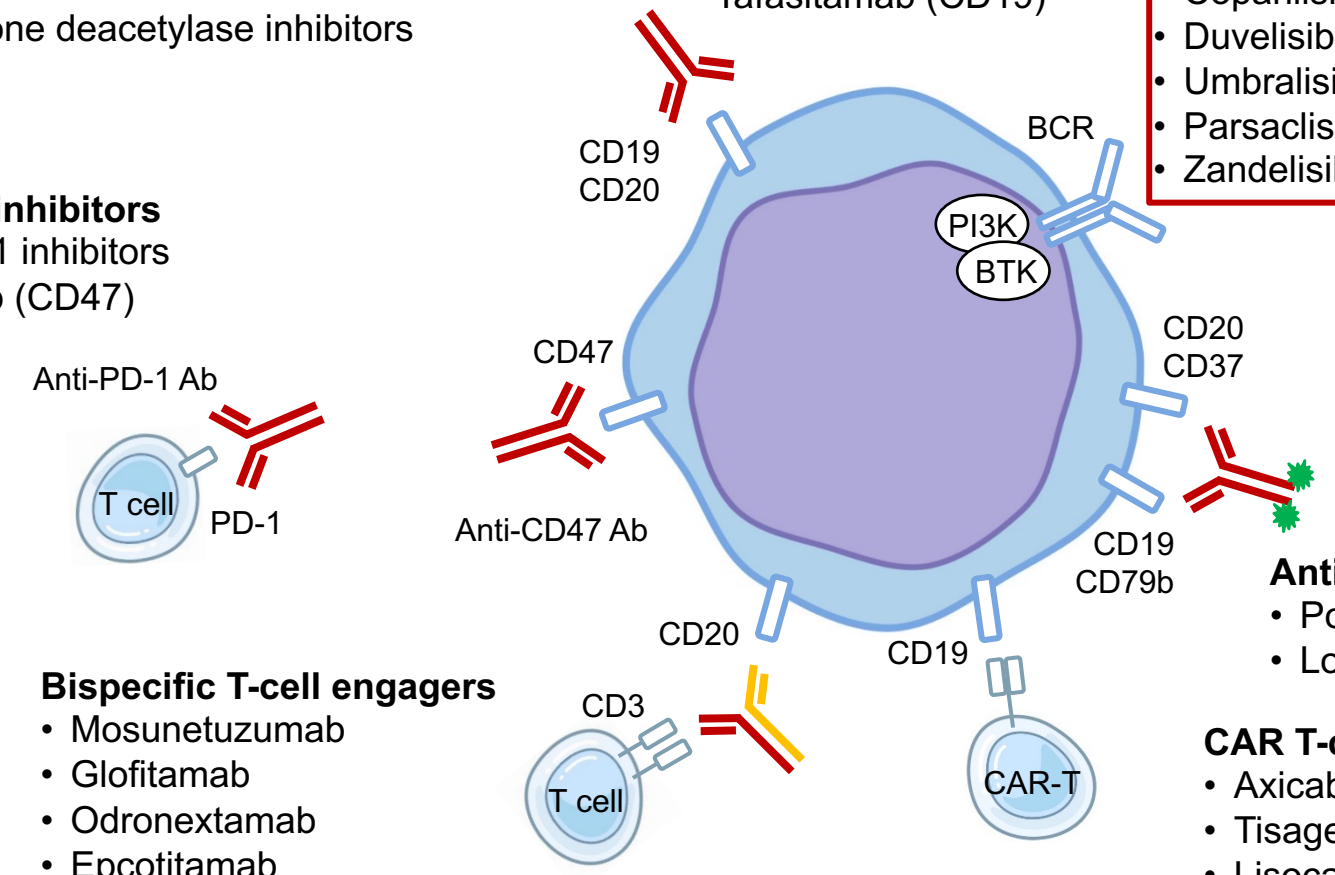
- Orelabrutinib (BTK)

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



Immunomodulator
- Lenalidomide*

Radioimmunotherapy
- ^{90}Y-Ibritunomab tiuxetan (CD20)*
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Antibody-drug conjugates
- Polatuzumab vedotin (CD79b)
- Loncastuximab tesirine (CD19)

Bispecific T-cell engagers
- Mosunetuzumab
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- Epcotitamab

CAR T-cell therapy
- Axicabtagene ciloleucel*
- Tisagenlecleucel
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*FDA-approved agents. Ab, antibody; BCR, B-cell receptor; BTK, Burton's tyrosine kinase; FL, follicular lymphoma.

PI3K Inhibitors: A dramatic safety drift

FL Subset Data	Idelalisib[1,2]	Duvelisib[3]	Copanlisib[4-6]	Umbralisib[7]
Isoform Target	PI3Kδ	PI3Kδ and γ	PI3Kα and δ	PI3Kδ and CK1ε
Route of Admin	PO	PO	IV	PO
Evaluation Trial (patients)	DE Ph 2, ref ry R and ar (72)	DYN D: P e 2, refra y and che y or radioimm apy (83)	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	UN NHL ase 2, refract o rior lines o 208)
Approval (year)	≥2 prior th s (2014)	≥2 prior th es (2018)	≥2 prior therapies (2017)	≥3 prior pies (2021)
ORR, (%)			59	
CR, %			20	
Median PFS			11 mo	o
Grade ≥3 AEs	Dia %) Elevat T (8- %) s (4 Pn onitis)	Dia 7%) Elevate T/A (3-5%), C s (5 Pn onitis %)	Diarrhea (8.5%) Elevated ALT/AST(<1%) Colitis (<1%) Pneumonitis (1.4%) Hyperglycemia (40-56%)	D 0%) Eleva AL T (7%), itis %) P mon %)

Head-to-head studies between these regimen are lacking. Therefore, direct comparisons cannot be made.

1. Gopal AK, et al. *N Engl J Med*. 2014; 2. Salles et al. Haematologica 2017; 3. Flinn I, et al. *J Clin Oncol.* 2019; 4. Dreyling M, et al. *J Clin Oncol*. 2017; 5. Dreyling M, et al. *Am J Hematol.* 2020; 6. Matasar et al. The Lancet 2021; 7. Fowler et al. *J Clin Oncol*. 2021.

PI3Ki: Shift in FDA's position from phase 2 data

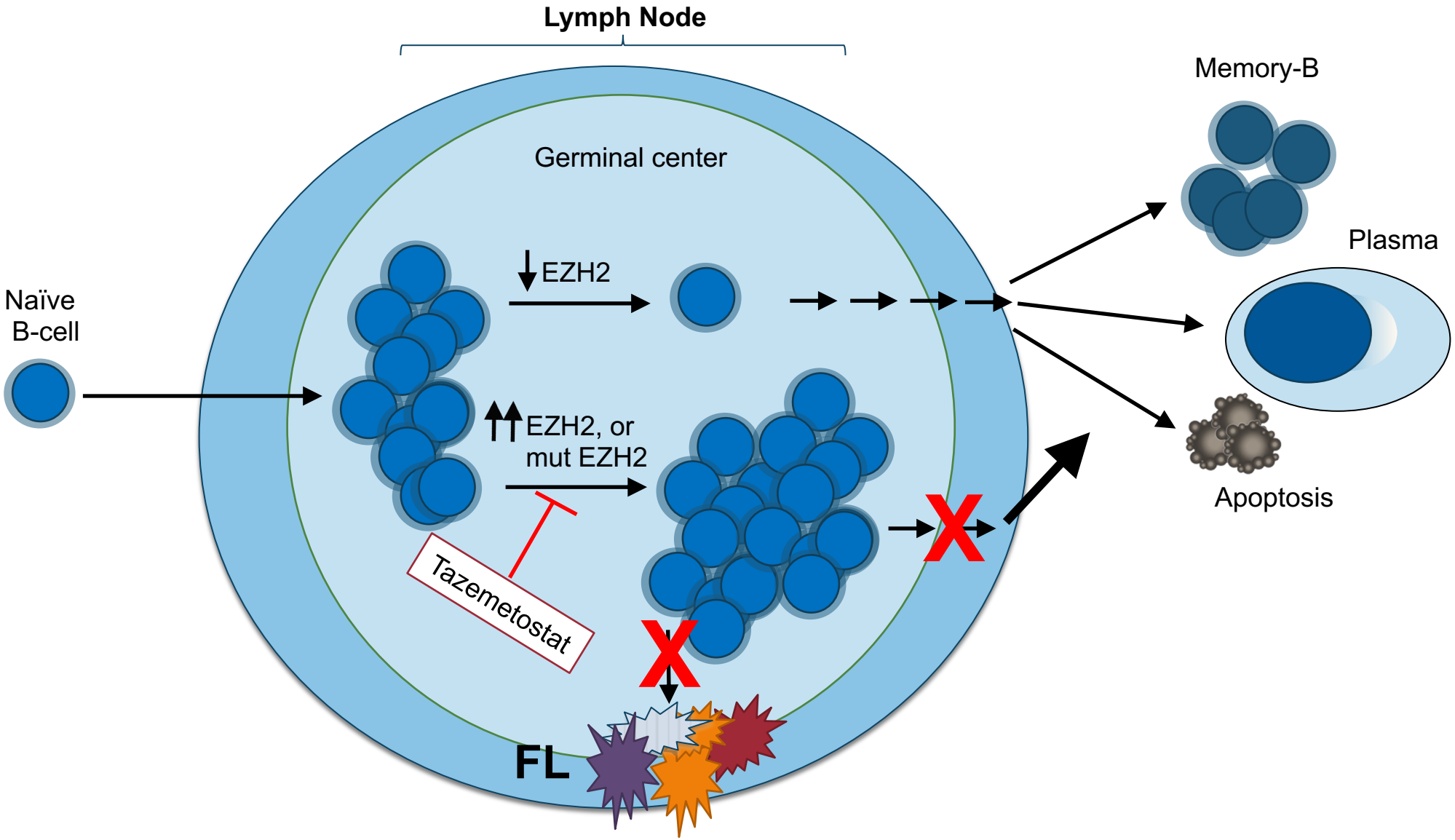
FL Subset Data	Copanlisib[1-3]	Zandelisib[4]
Isoform Target	PI3Kα and δ	PI3Kδ
Route of Admin	IV	PO
Evaluation Trial (patients)	CHRONOS-1: Phase 2, refractory to R and alkylating agents (104) CHRONOS-3: phase 3 C+R vs. C+P, relapsed after R or CIT	TIDAL: Phase 2, R/R to ≥ 2 prior lines of therapy (121)
Approval (year)	≥2 prior therapies (2017)	Not approved
ORR, (%)	59	70
CR, %	20	35
Median PFS	11 mo	N/A
Grade ≥3 AEs	Diarrhea (8.5%) Elevated ALT/AST(<1%) Colitis (<1%) Pneumonitis (1.4%) Hyperglycemia (40-56%)	Diarrhea (5%) Elevated ALT/AST (1.6%), Colitis (1.7%) Rash (3.3%) Stomatitis (2.5%)

The randomized, phase 3 COASTAL study (NCT04745832) is ongoing: Zandelisib + R vs CIT in patients with iNHL in first relapse.

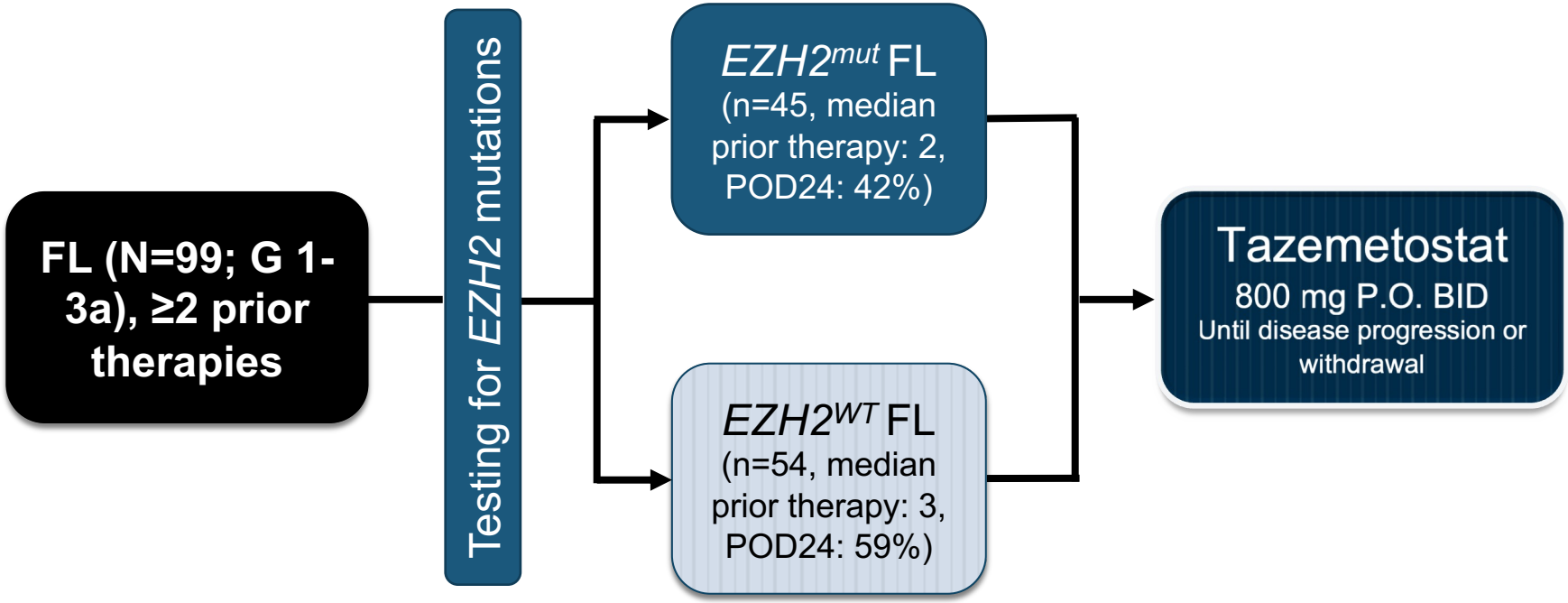
Head-to-head studies between these regimen are lacking. Therefore, direct comparisons cannot be made.

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. Zelenetz A, et al. ASCO 2022, A#7511.

Role for EZH2 in FL Pathology



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

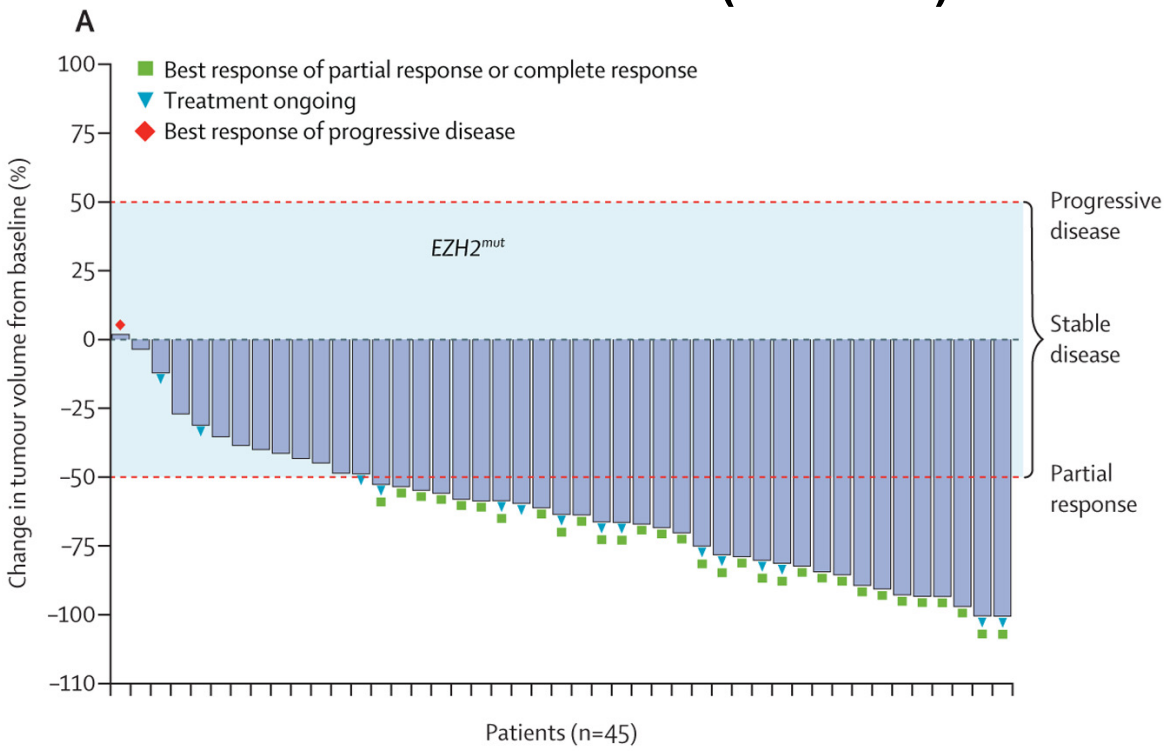


Primary endpoint: ORR
Secondary endpoints include: DOR, PFS, safety, tolerability

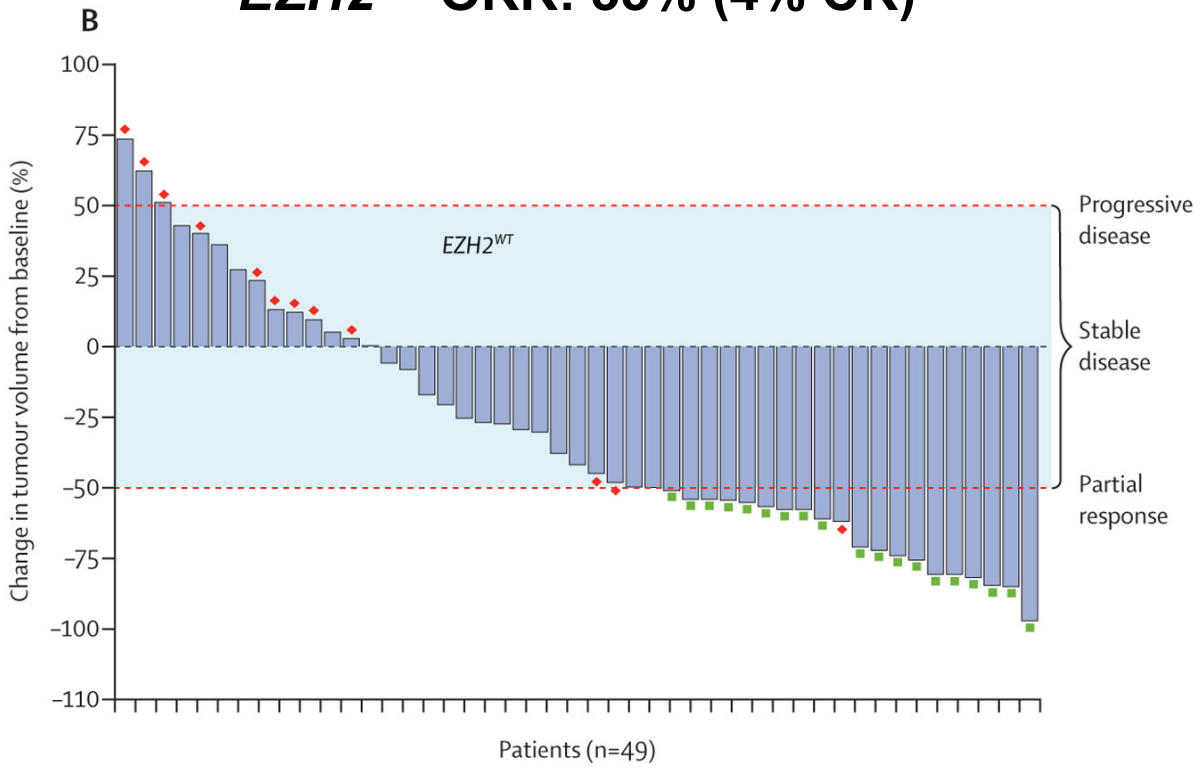
Morschhauser F, et al. *Lancet Oncol.* 2020

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

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



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



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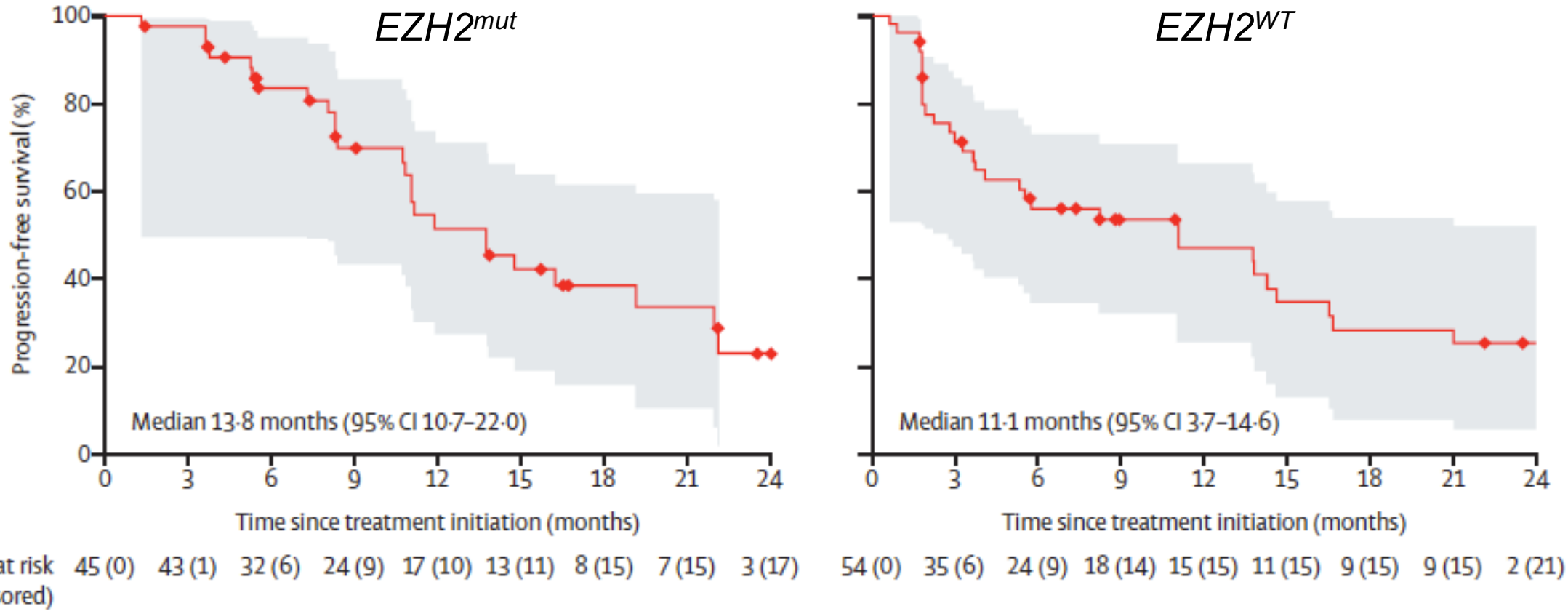

Morschhauser F, et al. *Lancet Oncol.* 2020

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

Patients

- 43 patients enrolled, *EZH2*^{mut}: 15%
- Median # prior therapies: 1
- Refractory to rituximab: 35%; POD24: 26%

Efficacy (38 evaluable)

- ORR: 95% (CR: 50%)
- POD24 (ORR: 83%; CR: 55%)
- Median PFS: NR

Toxicity

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

SHR2554 Phase 1:
41 FL
ORR 58.5%
Song ASCO 2022; A#7525

Batlevi, et al. *ASCO* 2022; A#7572

Available and pipeline agents in FL

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- Venetoclax (BCL2)
- Azacitidine
- Histone deacetylase inhibitors

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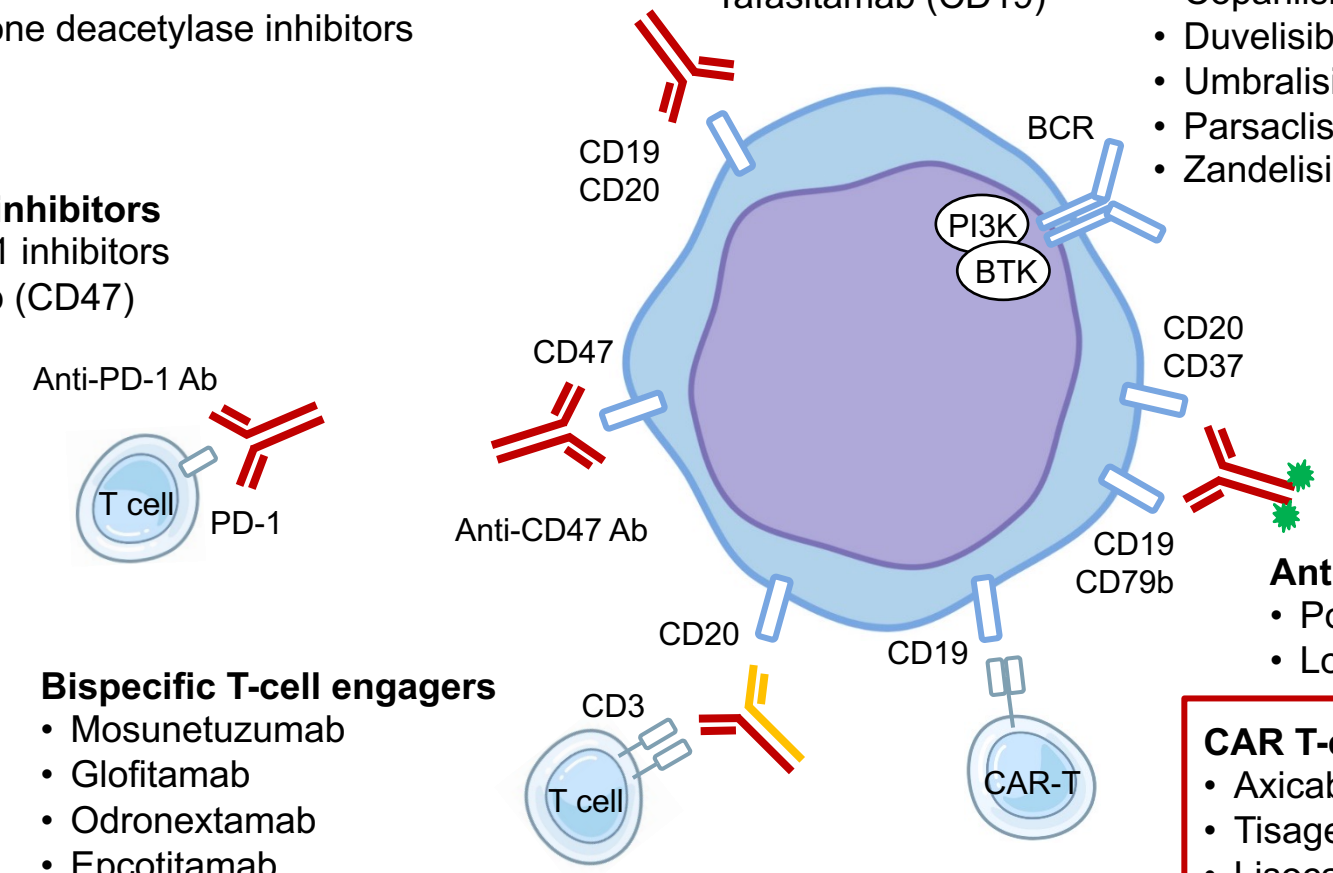

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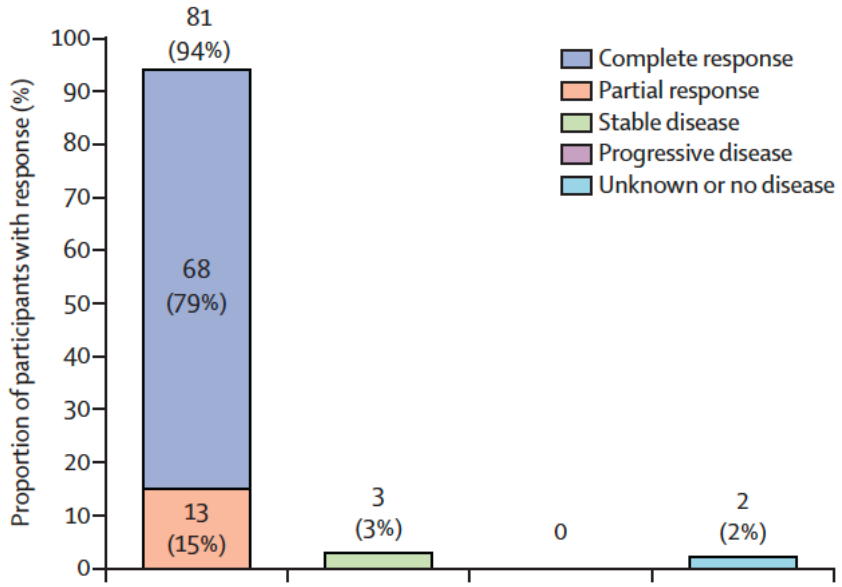
ZUMA-5: Axicabtagene Ciloleucel (Axi-Cel)

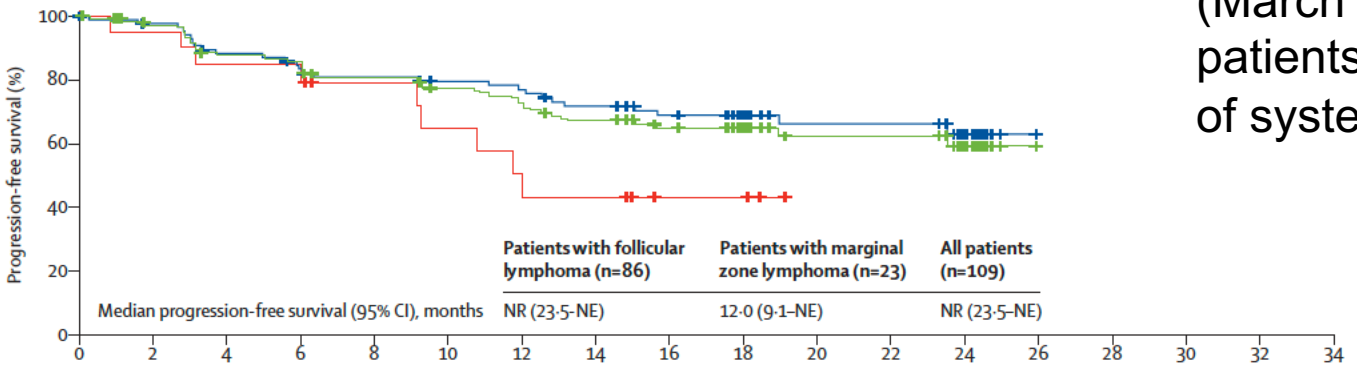
Single-arm, phase 2 study of axi-cel in patients with R/R iNHL (FL or MZL) after ≥2 lines of therapy

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

Jacobson et al. *Lancet Oncol.* 2022

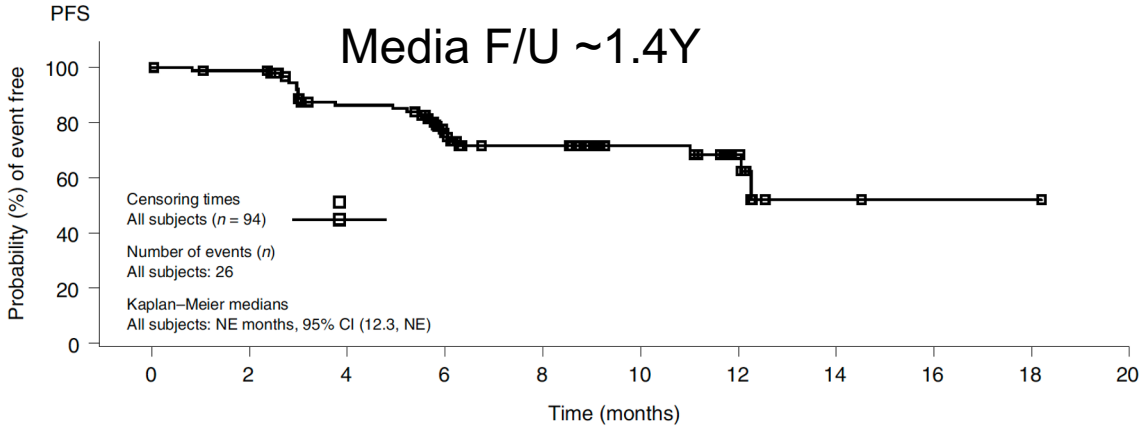
ELARA: Tisagenlecleucel (Tisa-Cel)

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%

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

Challenges associated with CAR-T

- Cost
- Manufacturing failure
- Time to infusion, need for bridge therapy
- CRS
- ICANS

Alternative: BiTE?

Mosunetuzumab, Glofitamab, Epcoritamab, Odronextamab

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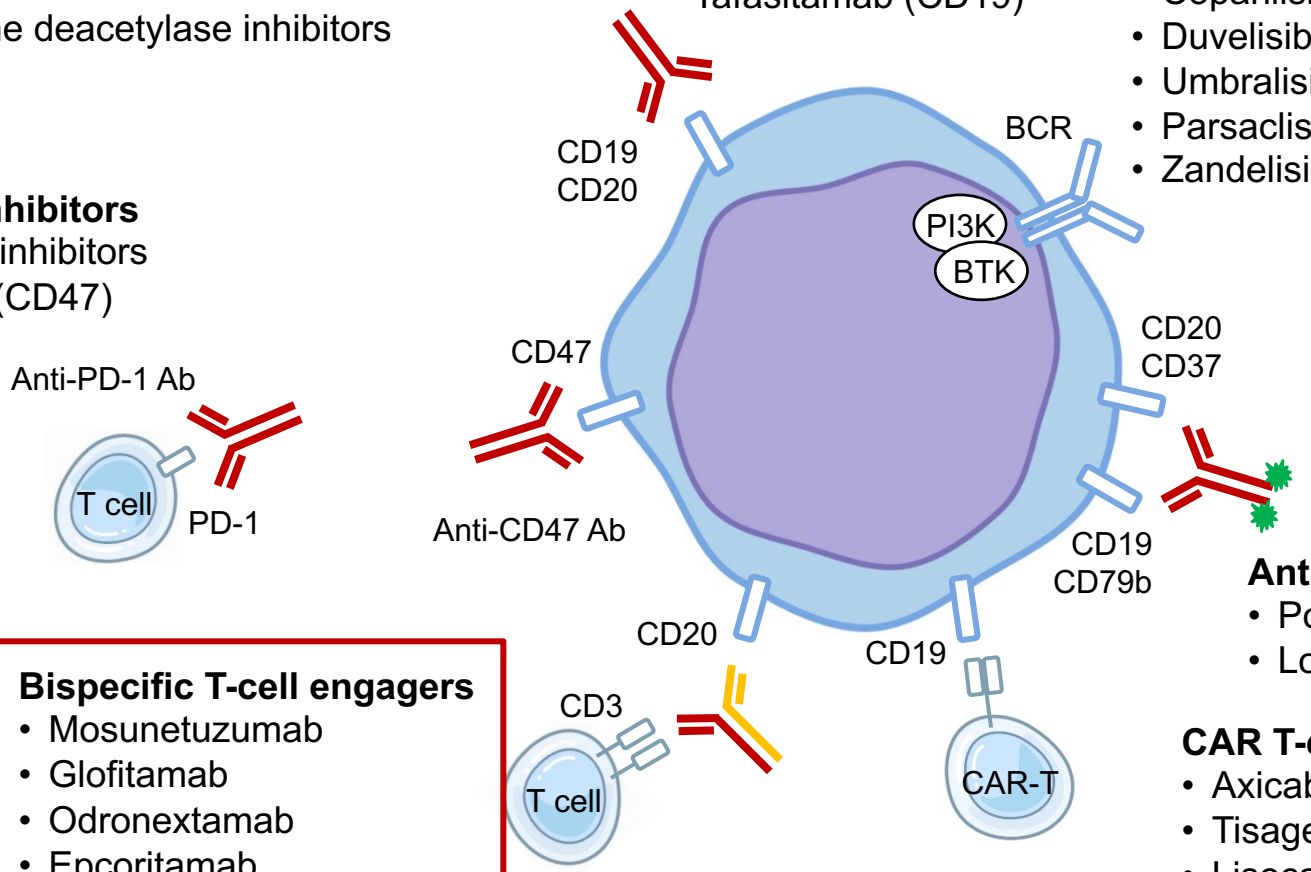

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Mosunetuzumab Monotherapy in R/R

Pivotal Results from a Phase I/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

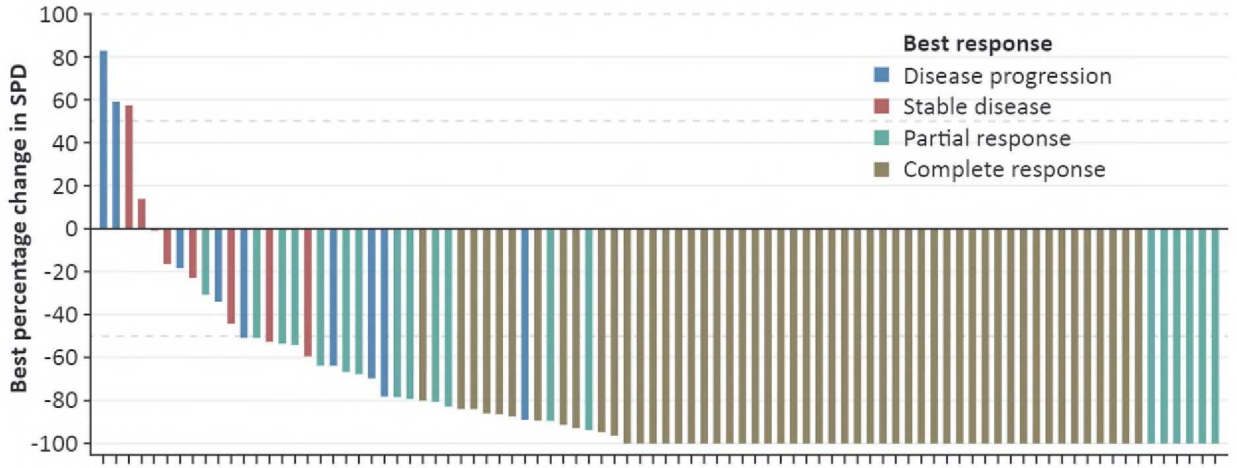
Primary Endpoint: CR

Patients
- 68% refractory to prior therapy
- 78% refractory to anti-CD20
- POD24: 52%

Efficacy
- ORR: 79% (CR: 58%)
- POD24 (ORR: 83%; CR: 55%)
- Median time to response 1.4 mo
- Median PFS:18 mo

Toxicity
- CRS: 42% (G3-4: 2%)
- Most common G3-4: Neutropenia (22%), Hypophos (13%)
- AE leading to discontinuation: 4%

Figure. Waterfall plot of best percentage change in SPD as assessed by PET/CT and independent review facility in all 3L+ R/R FL pts

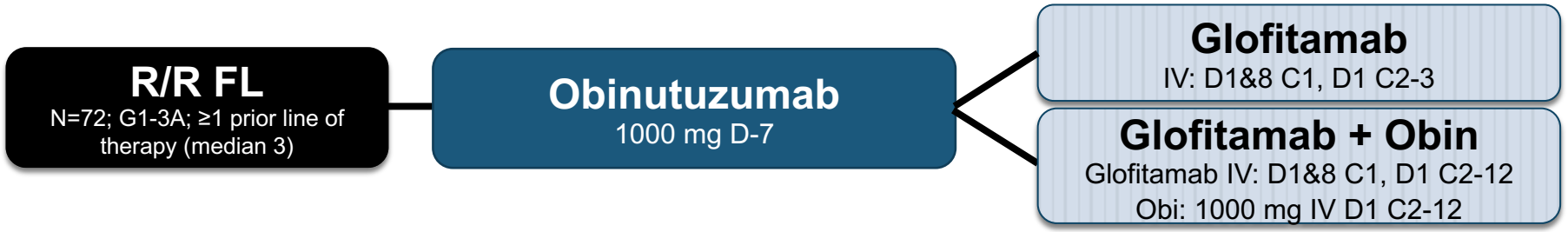


Mosun + Len: Phase 1b, N=27
No G3-4 CRS
ORR 92%, CR 77%

Budde, et al. *ASH* 2021, A#127

Glofitamab + Obinutuzumab in R/R FL

Pivotal Results from a Phase I/II Study



Patients

- ~50% refractory to prior therapy
- ~33% refractory to anti-CD20
- POD24: 62%

Efficacy

- ORR: 81-100% (CR: 70-74%)

Toxicity

- CRS: 66-79% (G3-4: 0%)
- No ICANS
- All grade neutropenia (26-58%), anemia (37%) and thrombocytopenia (32%)

Morschhauser, et al. *ASH* 2021, A#128

More BiTE in R/R B-NHL

Epcoritamab

CD20×CD3 BiTE; phase 1/2

- Subcutaneous 28-day cycles
- 73 patients
- No MTD, RP2D: 48 mg
- CRS: 48% (G3-4: 0%)
- TRAE discontinuation: 0%
- R/R FL:
  - ORR: 90%
  - CR: 50%

Epcoritamab + R2 in R/R FL 30% ref; 40% POD24; #prior therapy 1 Falchi ASCO 2022, A#7524	Total (%) N=30
Evaluable pts	27
Overall response	27 (100)
Complete metabolic response (CMR)	25 (93)
Partial metabolic response	2 (7)
Stable disease	0
Progressive disease	0

Hutchings, et al. *The Lancet* 2021; Bannerji, et al. *Lancet Haematol.* 2022

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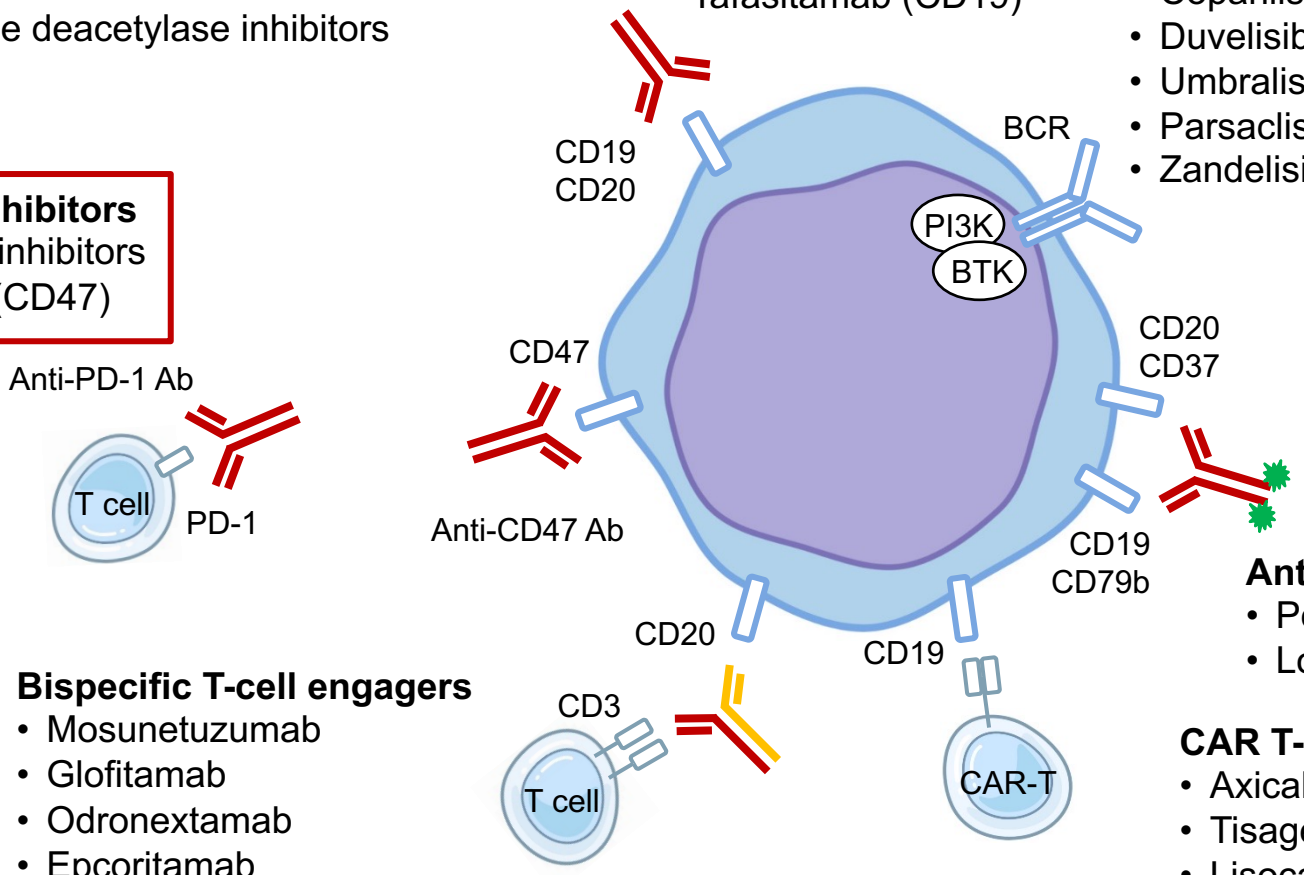

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G-atezo-len in R/R FL

An open-label, multicenter phase Ib/II study

FL (G1-3a)
N=38; ≥ 1 prior line of therapy (≥2 47%); ECOG 0-1

Induction
Up to 6 cycles, Q28D unless PD, relapse, intolerance, or withdrawal of consent

G-atezo-len
Obin: 1000 mg IV D1,8,15 of C1; D1 of C2-6
Atezo 840 mg IV D1&15 C2-6,
Len 15 or 20 mg po D1-21, C1-6

CR/PR/SD

Maintenance
24 months

G-atezo-len
Obin: 1000 mg IV D1 Q 2 mo
Atezo 840 mg IV D1&2 Q mo
Len 10 mg po D1-21, Q mo

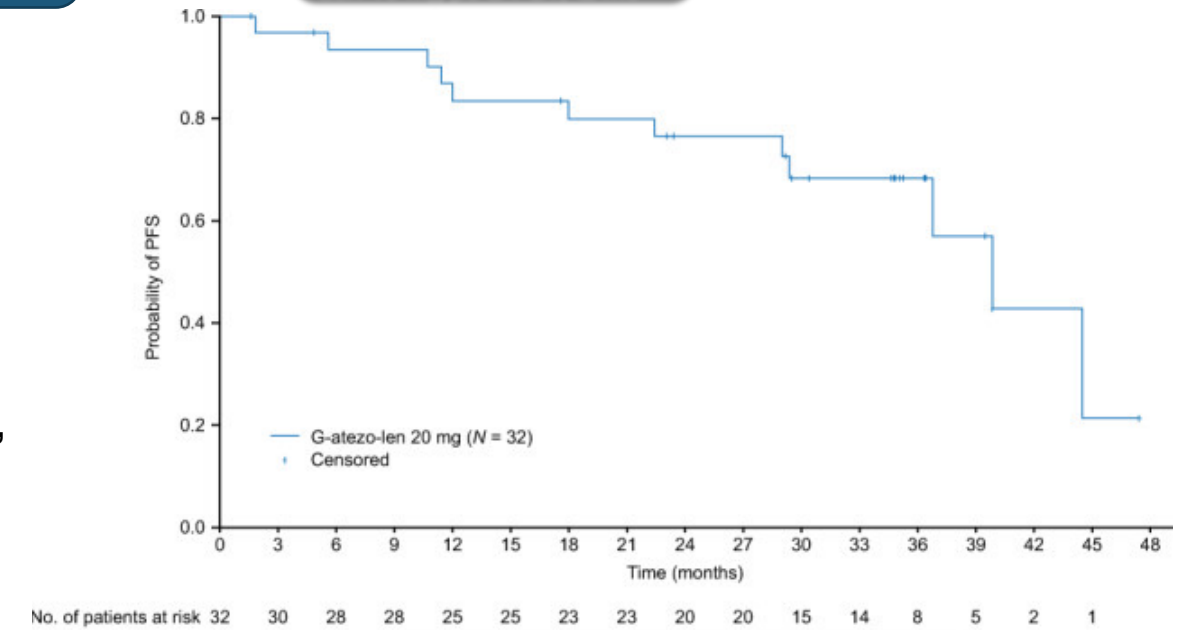
Primary Endpoints:
RP2D; EOI RR

Efficacy

- ORR: 78 % (25/38); CR: 72 % (23/38)
- 3Y PFS: 68%; 3Y OS: 90%
- EOI MRD-neg: 76% (21 evaluable)

Toxicity

- Most common G≥3 AE: Neutropenia (42%), thrombocytopenia (18%), ALT increase (5%)
- AI: Mostly G1-2, thyroid and liver (8-13%)

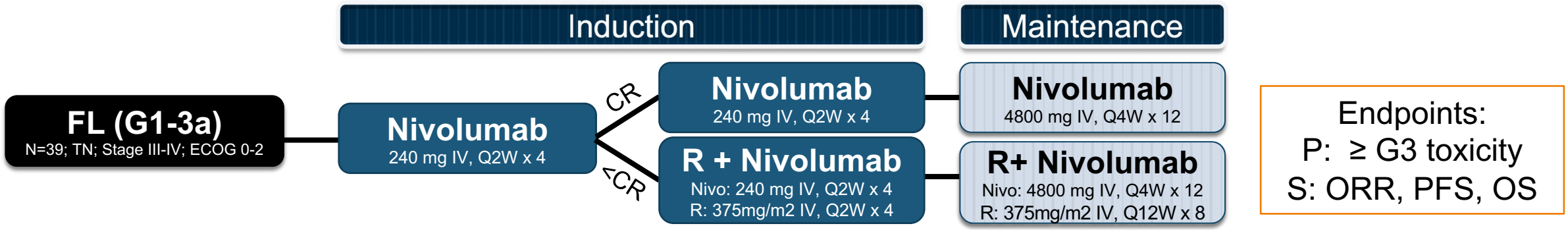


PFS time point	Failed	At risk	PFS estimate	95% CI
36 months	12	8	68.4	(47.7–82.3)

Morschhauser, et al. *Blood* Cancer J. 2021

1st FLOR

An open-label, multicenter phase II study



Endpoints:
P: ≥ G3 toxicity
S: ORR, PFS, OS

Efficacy

- Median F/U: 17.5 mo
- ORR: 92% (CR: 54 %)
- 1Y PFS: 72%; 1Y OS: 96%
- EOI MRD-neg: 76% (21 evaluable)

Toxicity

- ≥ G3 toxicity at EOI: 41% (16 pts)
- AI: Mostly G1-2

Overall promising frontline, immune-priming, chemo-free option to be tested in a phase 3 trial

Hawkes, et al. *ASCO* 2021, A#7560

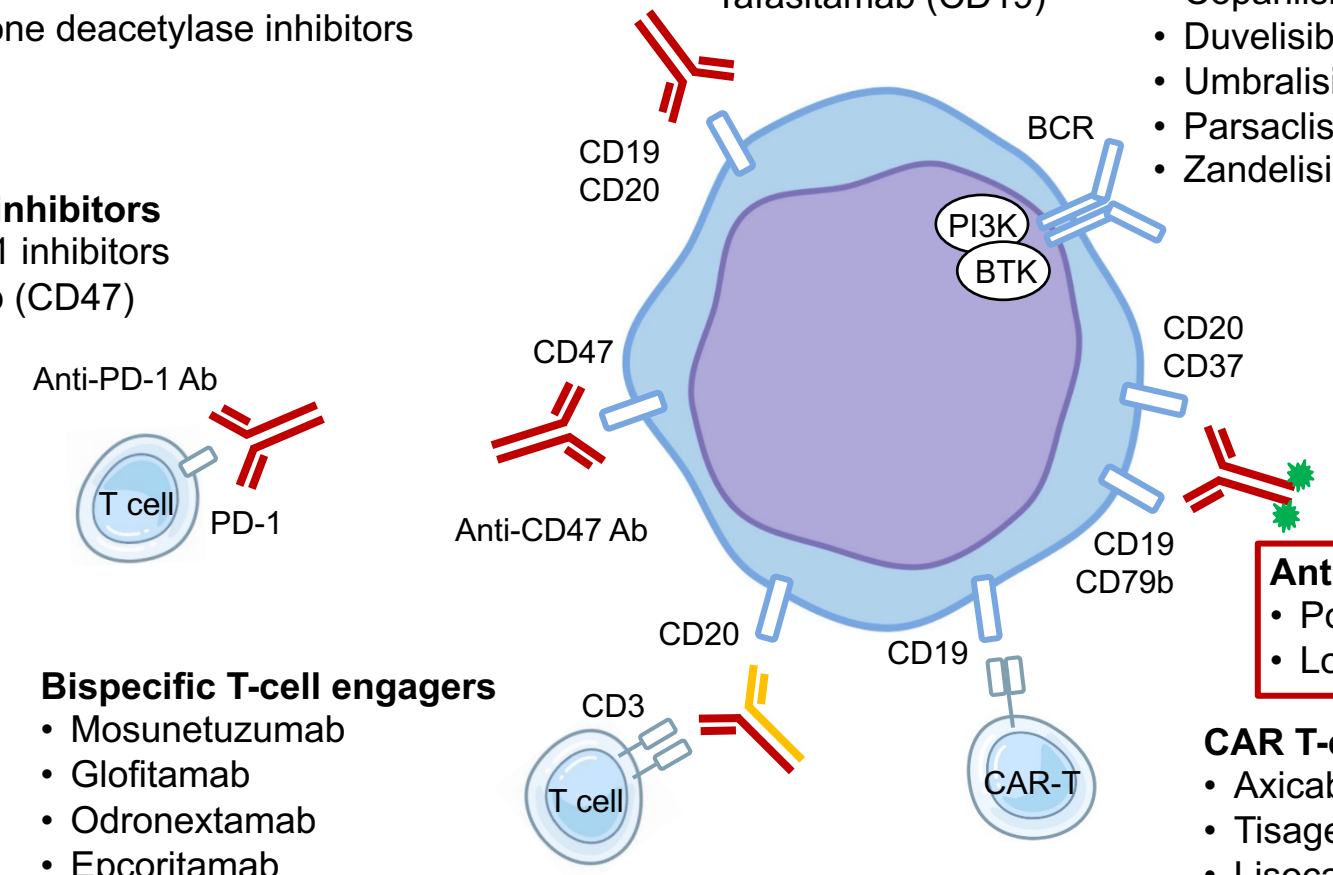
Available and pipeline agents in FL

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

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

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

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



Immunomodulator
- Lenalidomide*

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

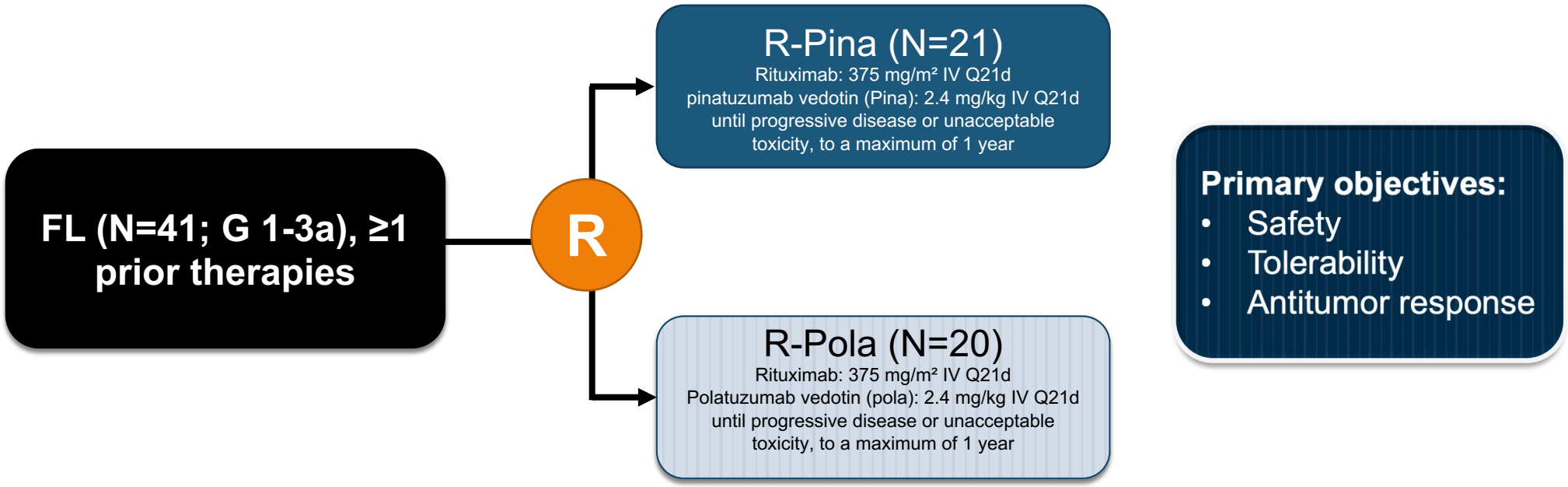
Antibody-drug conjugates
- Polatuzumab vedotin (CD79b)
- Loncastuximab tesirine (CD19)

Bispecific T-cell engagers
- Mosunetuzumab
- Glofitamab
- Odronextamab
- Epcoritamab

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.

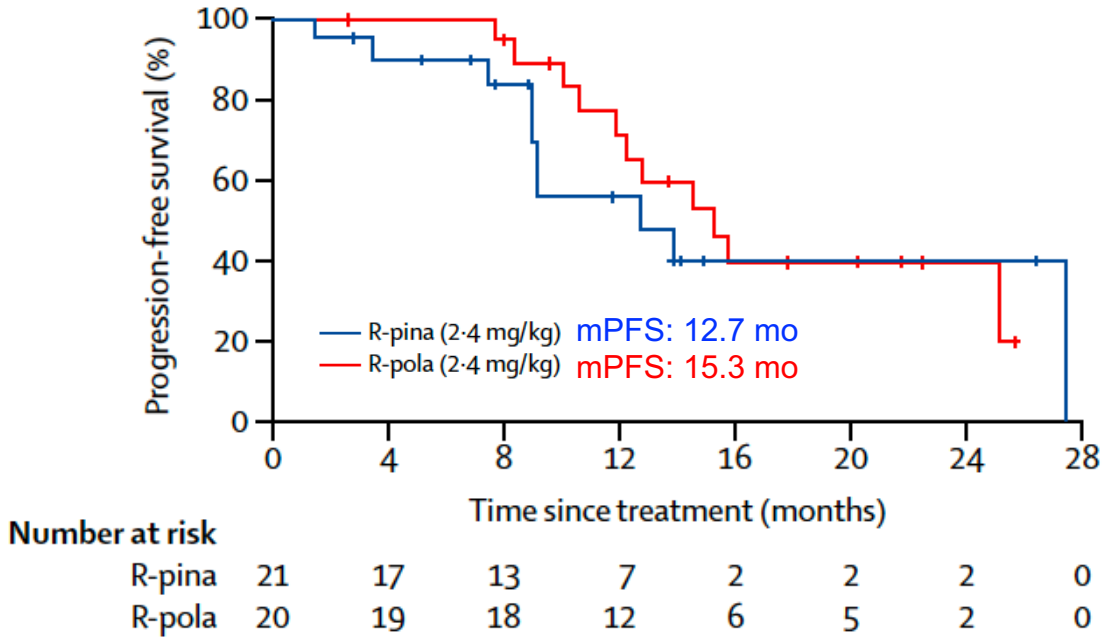
ROMULUS: Phase 2, Open-Label, Randomized, Multicenter Study of R-Pola vs. R-Pina in R/R FL



Morschhauser F, et al. *Lancet Haematol.* 2019

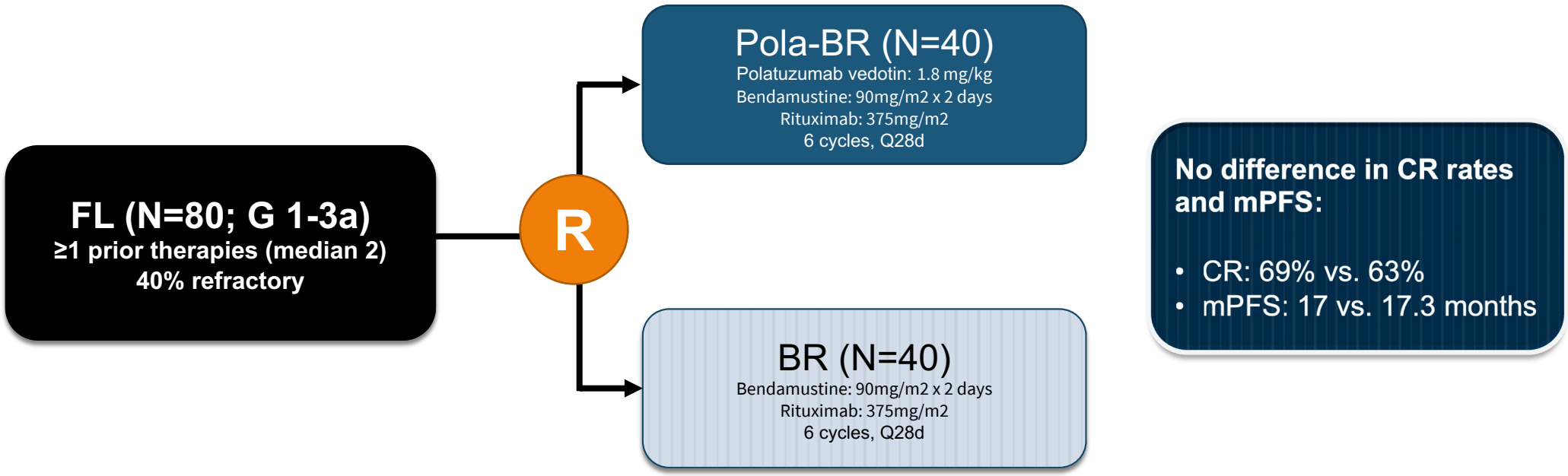
ROMULUS: Phase 2, Safety & Efficacy

- R-Pina
  - PN: 31% (G3-4: 2%)
  - G3-4 AEs occurred in13 (62%)
    - neutropenia (29%)
    - hyperglycemia (14%)
- R-Pola
  - PN: 36% (G3-4: 0%)
  - G3-5 AEs occurred in 10 (50%)
    - neutropenia (15%)
    - diarrhea (10%)
    - one grade 5 adverse event



Morschhauser F, et al. *Lancet Haematol.* 2019

Phase 1b/2: Randomized, Multicenter Study of Pola-BR vs. BR in R/R FL



Sehn LH, et al. *ASCO* 2018 A#7507

Pola-G-Len in R/R FL

A multicenter, single-arm Phase 1b/2 study

FL (G1-3a)
N=46; ≥ 1 prior line of therapy (median 3); ECOG 0-2

Induction
Up to 6 cycles, Q28D unless PD, relapse, intolerance, or withdrawal of consent

Pola-G-Len
Pola: 1.4-1.8 mg/kg IV D1; G: 1000 mg IV D1, 8, 15 C1 then D1 C2-6; Len: 10-20 mg PO D1-21

CR/PR/SD

Maintenance
24 months

G-Len
G: 1000 mg IV D1 Q2mo, x12
Len: 10 mg PO D1-21 Q28D x12

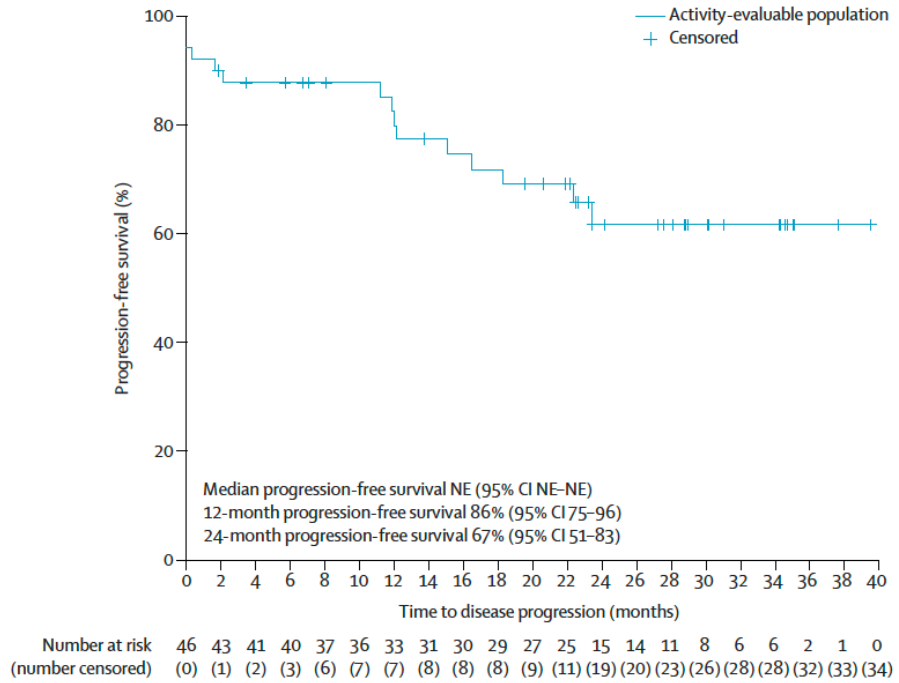
Primary Endpoints:
EOI CR, safety

Efficacy

- Median F/U: 26.7 mo
- Completed induction: 77%
- ORR: 76% (CR: 63%)
- mPFS: NR

Toxicity

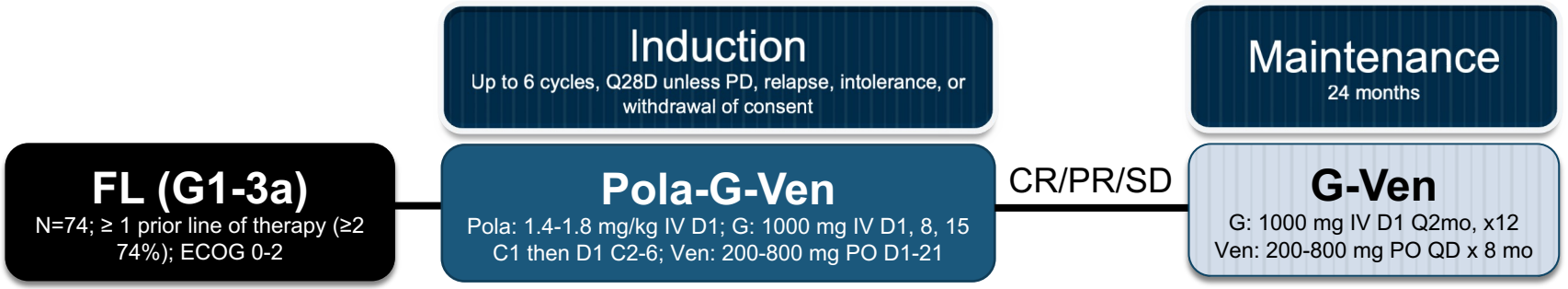
- Most common G≥3 TEAE: Neutropenia (55%), thrombocytopenia (25%), infection (25%), diarrhea (4%).



Diefenbach C, et al. *Lancet Haematol.* 2021

Pola-G-Ven in R/R FL

A multicenter, single-arm Phase 1b/2 study



Primary Endpoints:
EOI CR, safety

Efficacy (49 evaluable)

- Median F/U: 14.4 mo
- ORR: 71% (CR: 57%)
- mPFS: NR
- 12 mo PFS: 73%

Toxicity

- Most common G≥3 TEAE: neutropenia (39%), thrombocytopenia (19%), infection (16%).

Bannerji R, et al. *ASCO* 2021, A#7534

Loncastuximab in R/R B-NHL including FL

Final results of a single-arm, phase 1 trial

R/R NHL (FL, 14)
N=183 (FL, 14); ≥ 1 prior line of therapy (median 3)

Loncastuximab tesirine
IV D1 Q21D-cycle, at 15-200 µg/kg

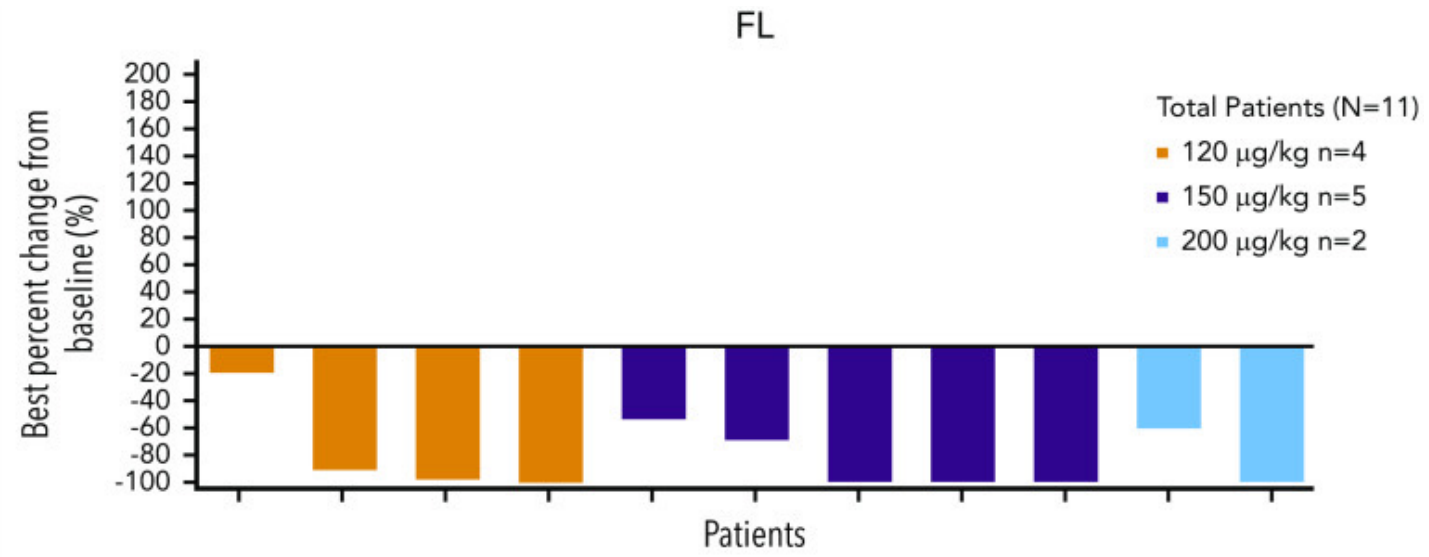
Tolerability, Safety

Efficacy

- ORR: 78.6% (11/14)
- CR: 64.3 % (9/14)
- Median time to response 43 days (full cohort)

Toxicity

- Most common G≥3 TEAE: neutropenia (39%), thrombocytopenia (26%), and increased GGT (21%)
- Edema/effusion (any grade 31%, 21%)

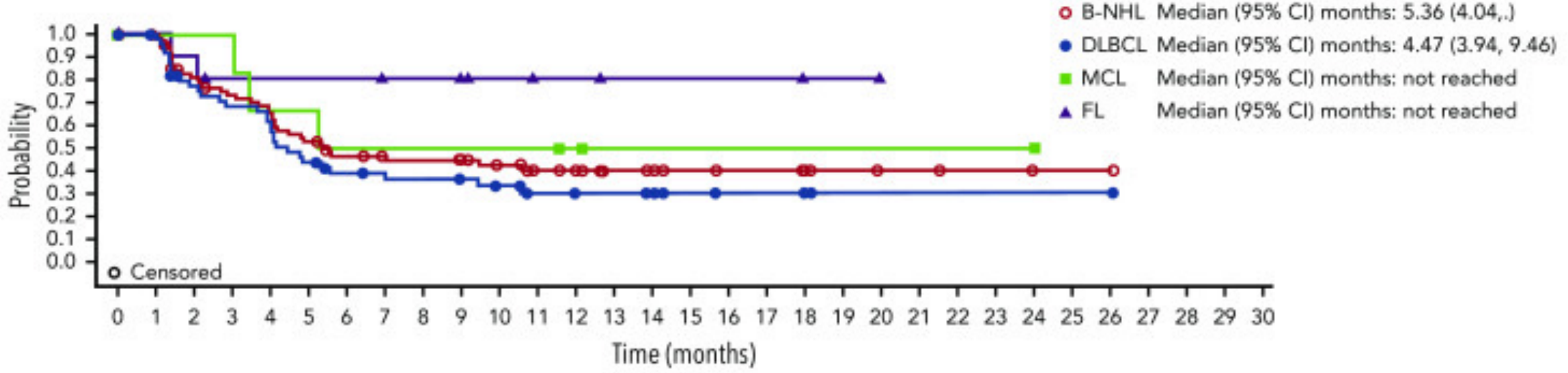


Hamadani, et al. *Blood* 2021

Loncastuximab in R/R B-NHL including FL

Final results of a single-arm, phase 1 trial

DOR



At risk

B-NHL	82	71	53	47	42	34	28	26	25	24	20	16	14	11	10	8	7	7	6	4	3	3	2	2	1	1	1	0
DLBCL	58	50	35	31	28	20	16	15	14	13	11	8	7	7	6	4	3	3	3	1	1	1	1	1	1	1	1	0
MCL	7	6	6	6	4	4	3	3	3	3	3	3	2	1	1	1	1	1	1	1	1	1	1	1	0			
FL	11	10	9	7	7	7	7	6	6	6	4	3	3	2	2	2	2	2	1	1	0							

Hamadani, et al. *Blood* 2021

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- Tisagenlecleucel
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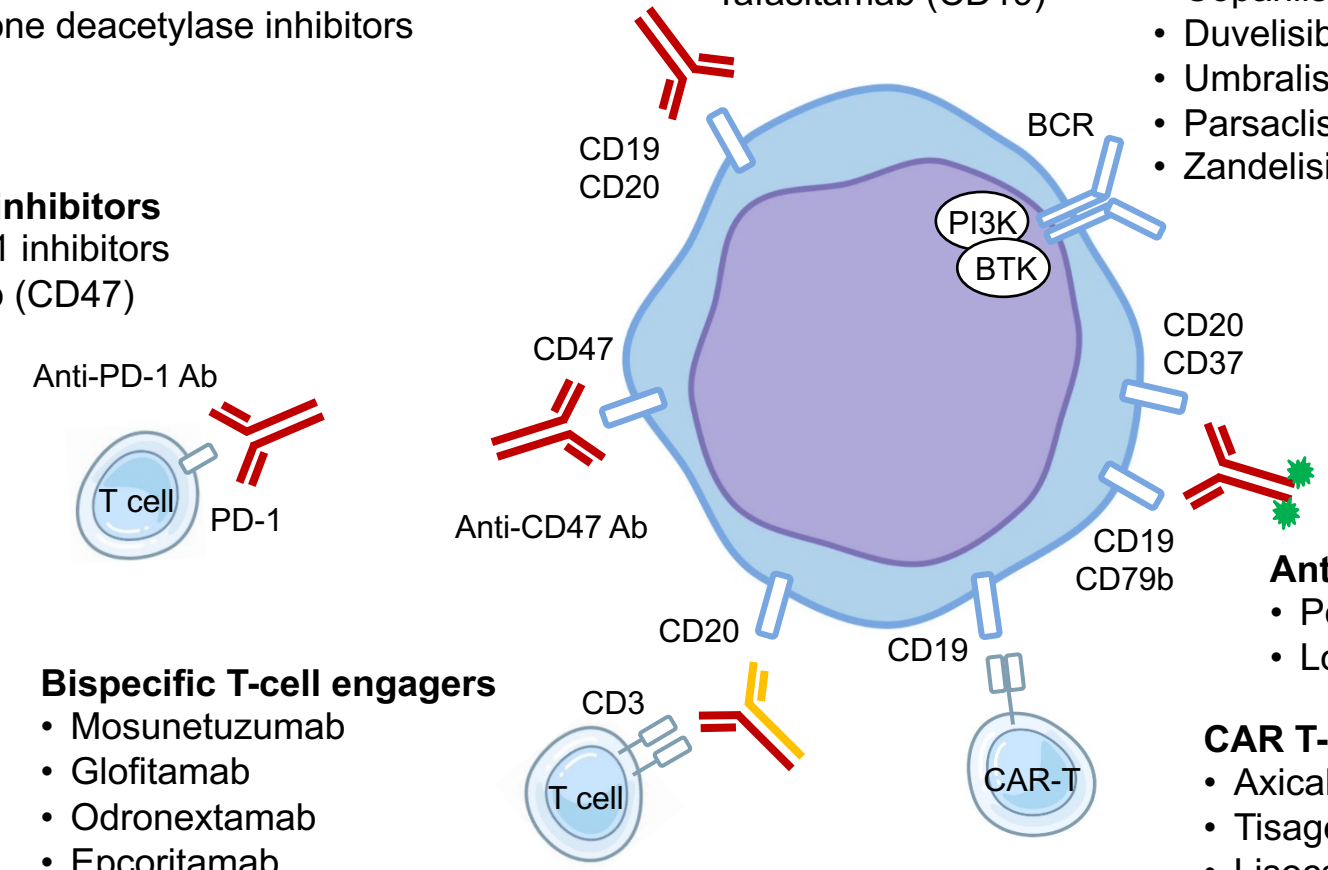
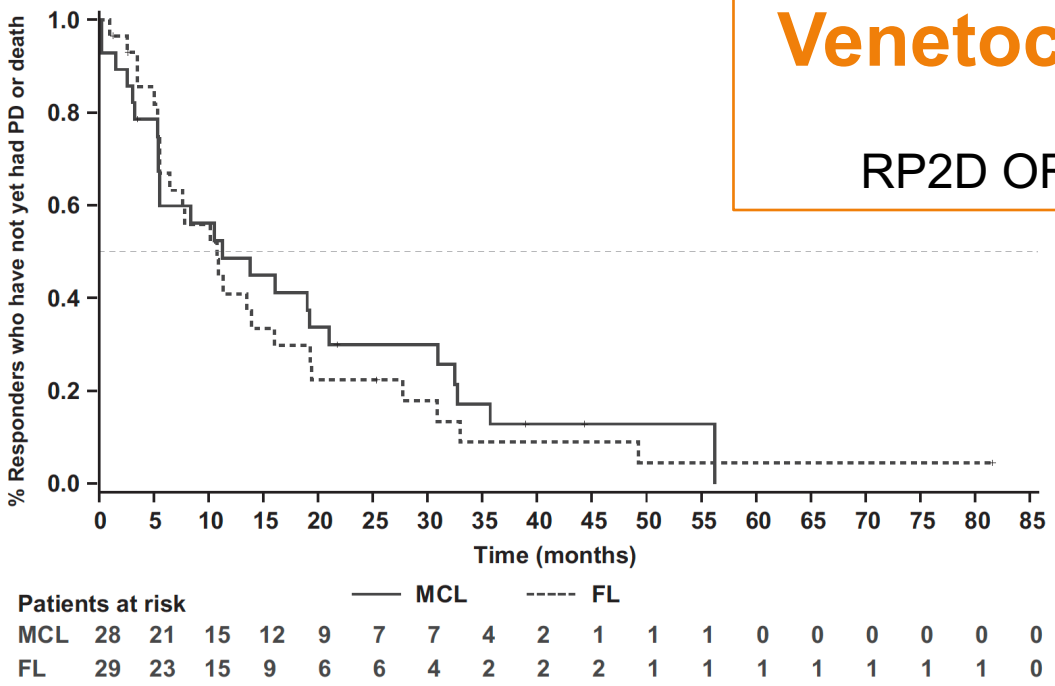


*FDA-approved agents. Ab, antibody; BCR, B-cell receptor; BTK, Burton's tyrosine kinase; FL, follicular lymphoma.

Combination strategies with venetoclax

Venetoclax

- ORR: 38% (CR: 17%)
- mPFS: 10.8 mo

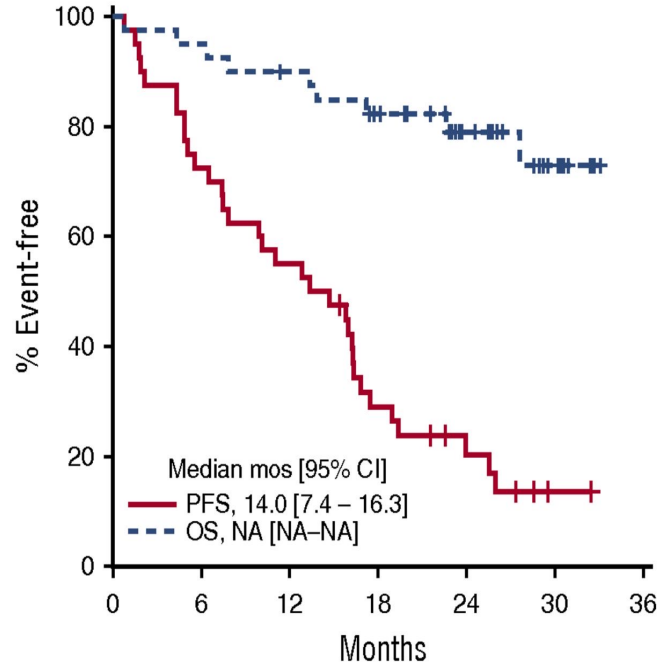


Venetoclax + Ibrutinib

RP2D ORR: 83% (CR: 33%)

Ibrutinib

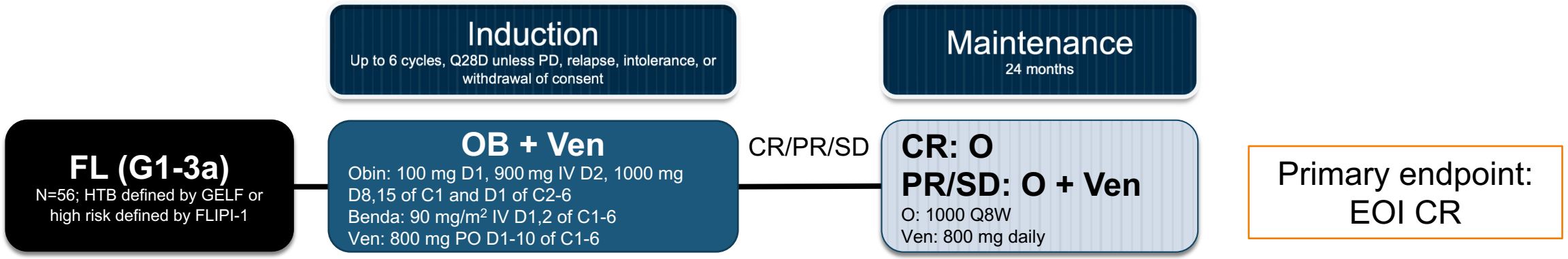
- ORR: 37.5% (CR: 12.5%)
- mPFS: 14 mo



1. Davis, et al. *Clin Cancer Res*. 2020; 2. Bartlett, et al. *Blood* 2018; Ujjani, et al. ASH 2020

Venetoclax + Obin + Benda in frontline FL

PrECOG 0403: Phase II, high tumor burden or high-risk



Efficacy

- Median F/U: 21 mo
- ORR: 93% (CR: 73%)
- 2Y PFS and OS: 86 % and 94%

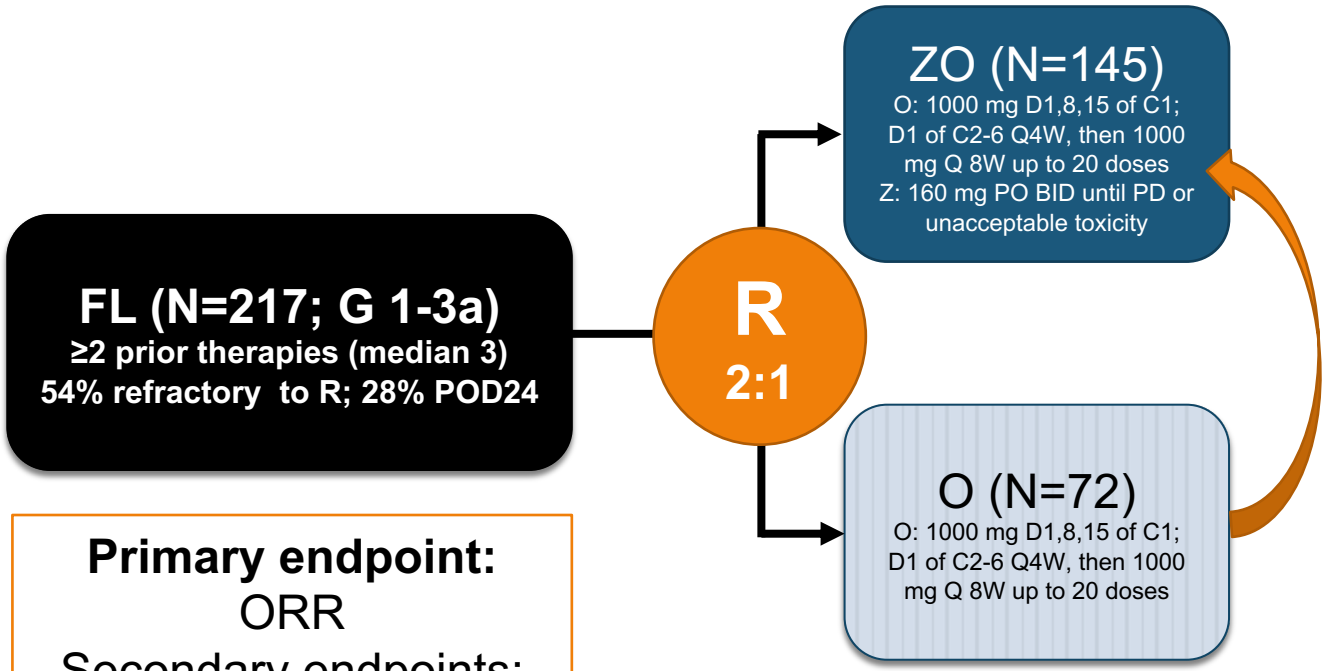
Toxicity

- Grade ≥3 AE of 83.9% (compared to 69% for OB in GALLIUM)
- Opportunistic infections: CMV encephalitis, PJP pneumonia and BK nephropathy
  Combination is highly immunosuppressive and unacceptable

Portell, et al. *ASH* 2021, A#814

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

Phase II randomized trial



Primary endpoint:
ORR
Secondary endpoints:
CR, DOR, PFS, OS

Efficacy

ORR: 68.3% vs 45.8% (*p*= 0.0017)
ORR for 29 pts who crossed over to ZO: 24.1%
CR: 37.2% vs 19.4%
mPFS: 27.4 mo vs 11.2 mo (HR 0.51, *p*= 0.0040)

Safety (ZO arm)

Thrombocytopenia (34%), neutropenia (27%), diarrhea (16%), fatigue (14%), atrial fibrillation (0.7%), and major bleeding (1.4%)

Zinzani, et al. *ASCO* 2022, A#7510

SUMMARY

- Treatment landscape is evolving rapidly in FL
- Big red-flag on Pi3K inhibitor safety
- We are (will be) able to over 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

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