New Therapies for Follicular lymphoma

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FL: Overview

Indolent clinical course but clinical behavior can be widely variable.

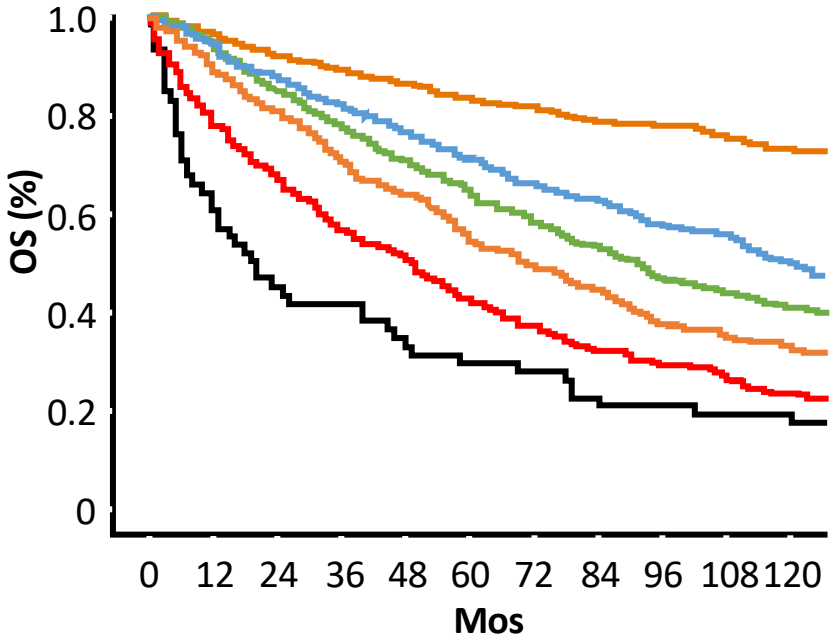
Treatable, but not curable with current therapies.

Rituximab significantly improved outcomes in last 2 decades.

Good response to initial therapy, but with eventual relapses and a shorter duration of response to each subsequent treatment

Current goal of treatment: delay disease progression/control disease.

OS Improvement in Indolent B-Cell Lymphoma from 1944 to 2004: the MDACC Experience[9]



Presentation Yr	60-Mo OS, %	120-Mo OS, %
1995-2004	82.7	72.3
1985-1994	70.6	49.6
1975-1984	63.5	41.0
1965-1974	54.1	31.9
1955-1964	41.6	23.2
1944-1954	29.3	17.2

Neelapu S. 60 Years of Survival Outcomes at the MD Anderson Cancer Center. New York, NY: Springer; 2013. p. 241-250.

5th edition "New" WHO classification

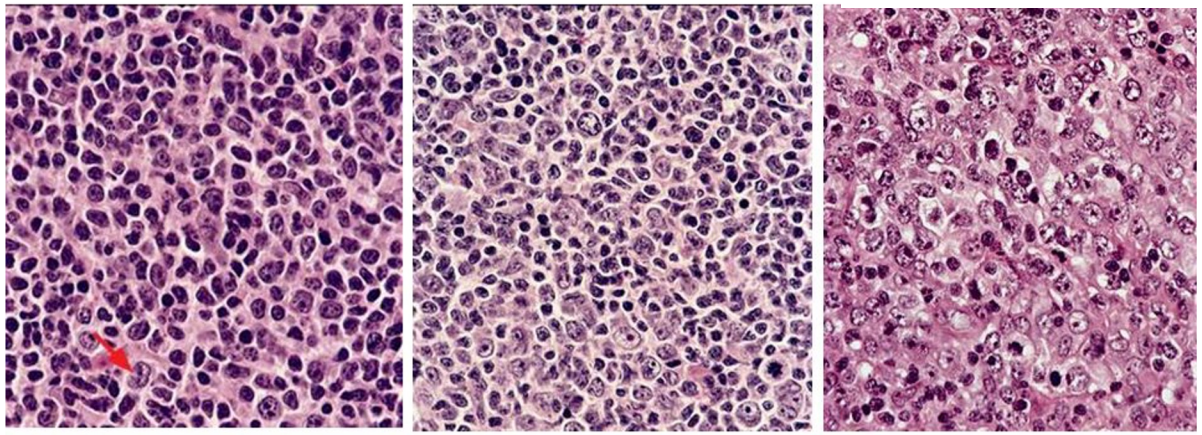
Follicular Lymphoma Grading

Grade 1
0-5 centroblasts /HPF

Grade 2
6-15 centroblasts /HPF

Grade 3a
>15 centroblasts /HPF
centrocytes present

Grade 3b
Sheets of centroblasts
without centrocytes



Centrocytes

"Small cleaved follicle cells"

Mixed

Centrocytes present

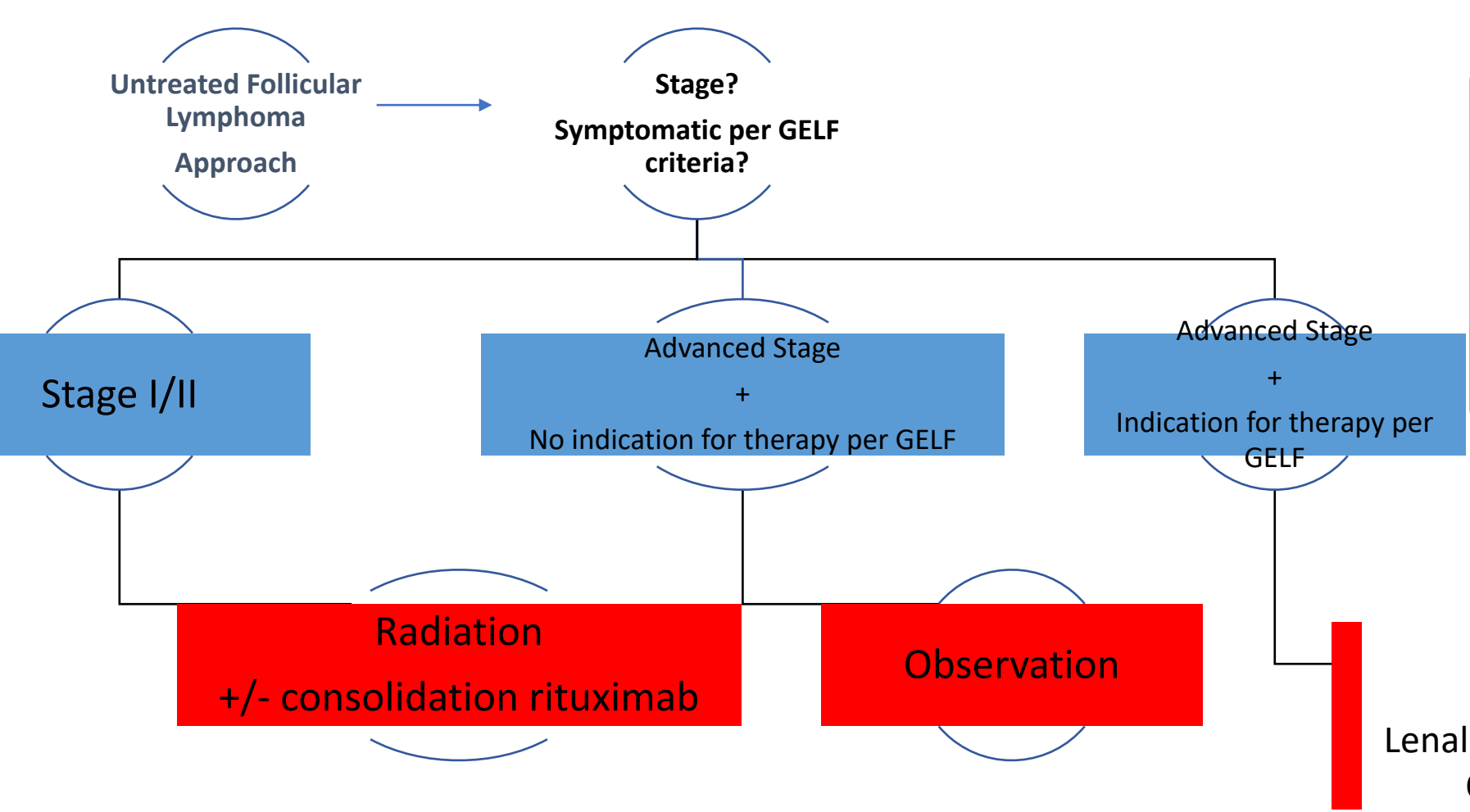
Centrocytes absent

Classic Follicular lymphoma (cFL)
(Indolent clinical course)

Follicular large B-cell lymphoma (FLBCL)
Managed as DLBCL

Alaggio, et al. Leukemia 2022

Current Management approach of untreated FL



GELF criteria:

- ❑ Any nodal or extranodal tumor mass ≥ 7 cm.
- ❑ ≥ 3 nodal sites, each >3 cm
- ❑ Presence of B symptoms
- ❑ Splenomegaly
- ❑ Compression or vital organ compromise
- ❑ Significant serous effusions
- ❑ Leukemia (>5 x 10^9/L)
- ❑ Cytopenias (leucocytes <1000, Pla <100k.

R-Benda (or O-Benda)
R-CHOP (or O-CHOP)
R-CVP (or O-CVP)
Lenalidomide/Rituximab can be considered
Optional: maintenance rituximab

Partially adopted from NCCN.org

12 year follow up to intergroup randomized study: Watch and Wait vs Rituximab induction vs Rituximab maintenance

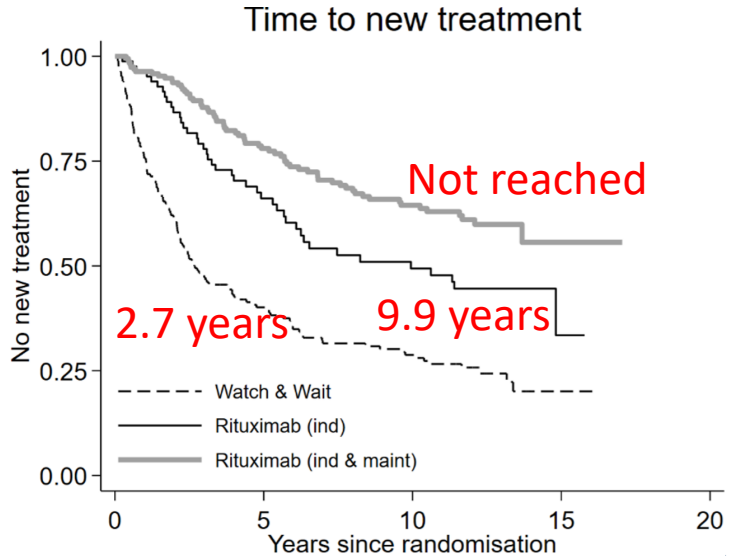
Study design:

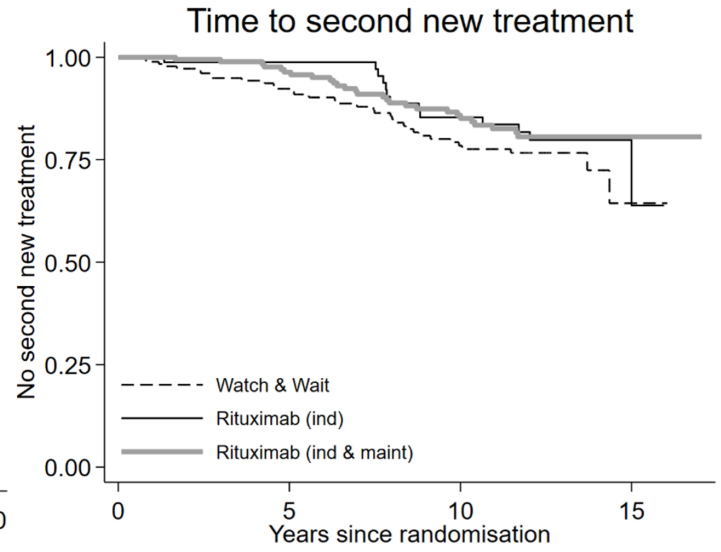
- Low burden asymptomatic patients with untreated, stage II-IV follicular lymphoma
- 1:1:1 randomization:

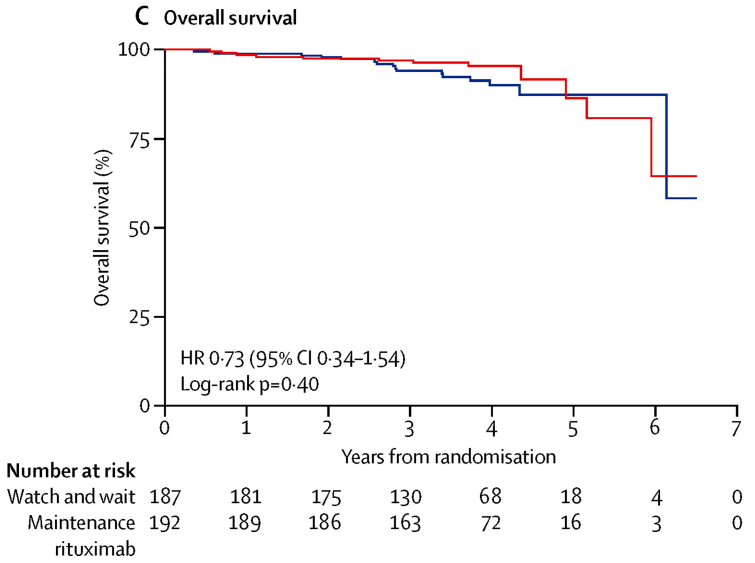
watch and wait vs Rituximab x4 vs Rituximab x4 followed by maintenance.

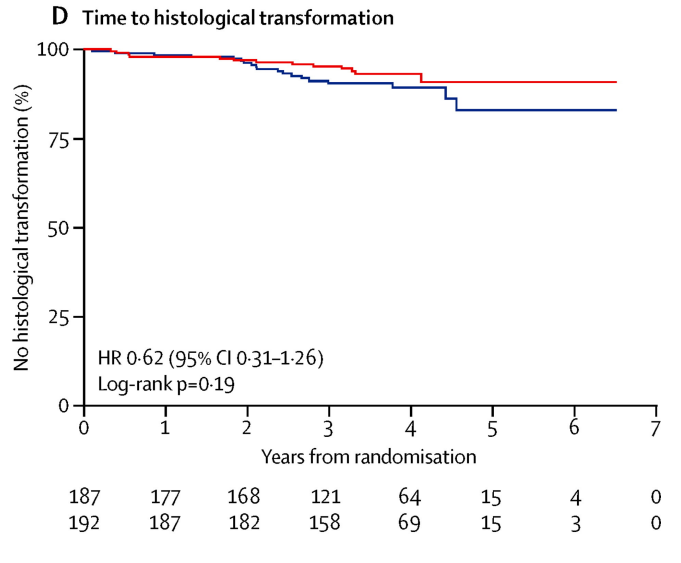
Key findings:

- At 10 years, **28.8% in W&W group required no therapy** vs 49% in rituximab vs 64.5% in maintenance group.
- **Time to start new treatment and PFS longer in rituximab groups (not surprising).**
- **Time to second new treatment** was not significantly different between the groups.
- **No difference in Overall survival**
- Histologic transformation and time to transformation not significantly different between the groups.









Adreshna K et al. Lancet Oncol. 2014 Apr;15(4):424-35.

Northend et al. ASH 2022 Abstract #607

Relapsed Follicular lymphoma is very heterogenous

Late Relapse FL	POD24 FL
60-year-old male diagnosed with stage IV follicular lymphoma grade 1-2 with bulky adenopathy.	60-year-old male diagnosed with stage IV follicular lymphoma grade 1-2 with bulky adenopathy.
Receives first line **R-Bendamustine** and achieves **CR1 for 5 years.**	Receives first line **R-Bendamustine** and achieves **CR1 for 18 months.**
Receives second line **Rituximab-Lenalidomide** and achieves **CR2 which lasts another 3 years**.	Receives second line **Rituximab-Lenalidomide** and achieves **CR2 which lasts 8 months**.
Patient now has progressive disease and presents to clinic for treatment recommendations.	Patient now has progressive disease and presents to clinic for treatment recommendations.

CART vs ‘non-cellular’ therapies? There is no ‘One size fits all’ approach

Need a more personalized approach to patients with R/R FL in third or subsequent lines.

Current Treatment Options for R/R FL

Observation for low bulky asymptomatic patients with late relapse is reasonable

Second line

- Lenalidomide + Rituximab/Obinutuzumab
- Bendamustine + R/O (if no prior Bendamustine)
- R/O CHOP (if concern for transformation)
- R/O CVP
- R/O single agent (low bulk)
- Tazemetostat (no other satisfactory options)

Third line and Beyond

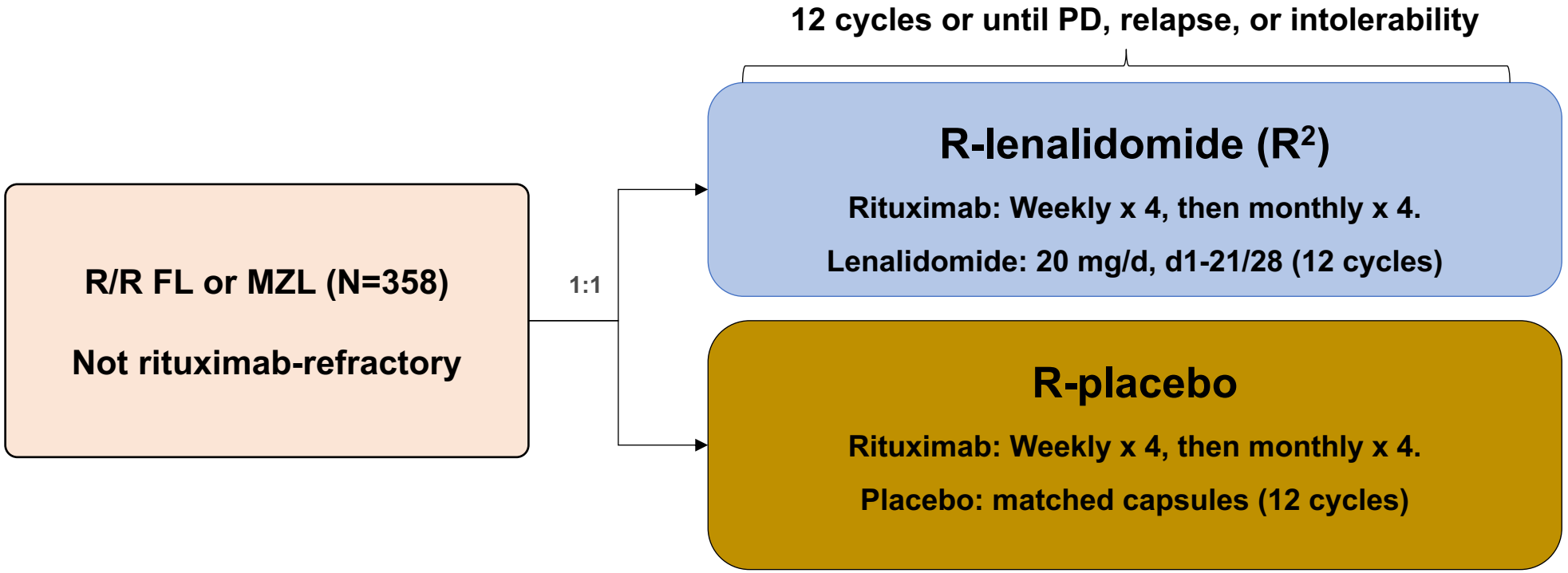
Additional options:

- Clinical Trial
- PI3K inhibitors (withdrawn 2022)
- Tazemetostat
- **Mosunetuzumab (Approved Dec 22 2022)**
- CART cell therapy (Axi-cel, Tisa-cel)

Optional Consolidation: Maintenance Rituximab/Obinutuzumab or Autologous or Allogeneic SCT

Partially adopted from NCCN.org

AUGMENT: Phase 3 Study of R^2 vs R in R/R FL and MZL

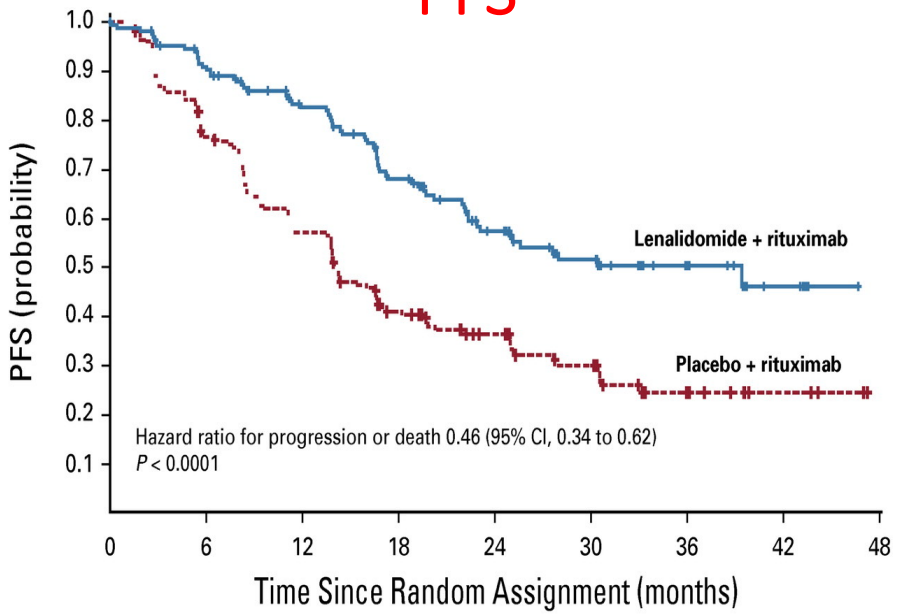


- Primary endpoint: PFS by IRC (2007 IWG criteria without PET)
- Prophylactic anticoagulation/antiplatelet agents were recommended for patients at risk of DVT
- Len dose was decreased to 10mg for patients with impaired renal function (CrCl 30-59 mL/min)

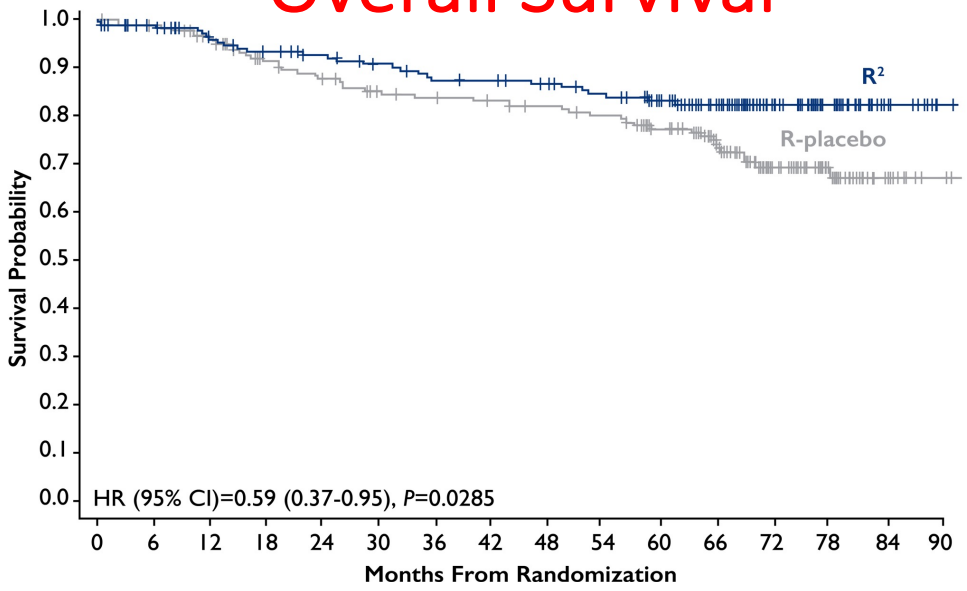
Leonard J, et al. Journal of Clinical Oncology 2019 37:14, 1188-1199.

Augment study: 5.5 year Follow-up PFS and OS advantage with R2

PFS



Overall Survival



	R2	Rituximab
ORR	78%	53%
CR	34%	18%

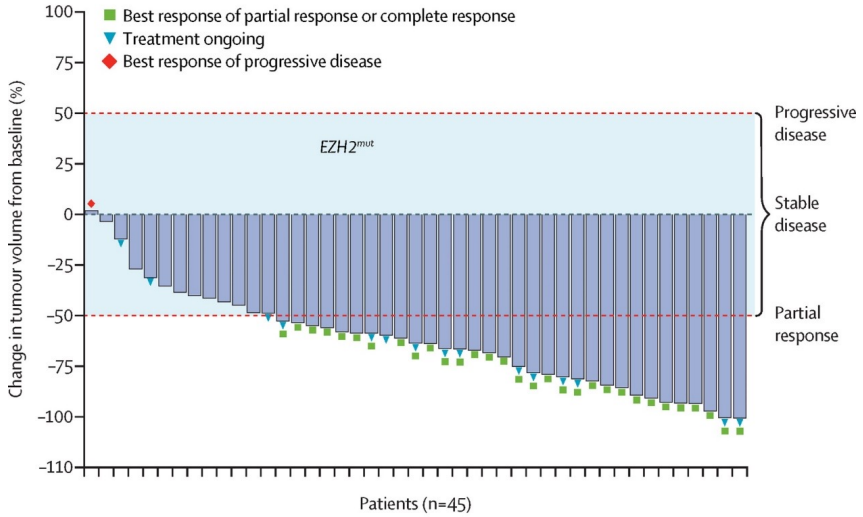
	R^2 (n=178)	R-Placebo (n=180)	HR	P Value
Median PFS	27.6 mo	14.3 mo	0.50 (0.38-0.66)	<0.0001
5-year Overall Survival	83.2 %	77.3 %	0.59 (0.37-0.95)	0.0285

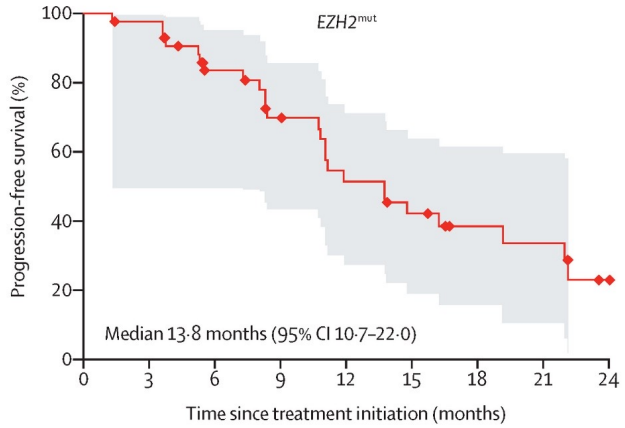
- Approved in second line or subsequent relapse
- Favorable toxicity profile
- Most common regimen in second line

Leonard J, et al. Journal of Clinical Oncology 2019 37:14, 1188-1199; Leonard et al., ASH 2022 abstract #230

Tazemetostat

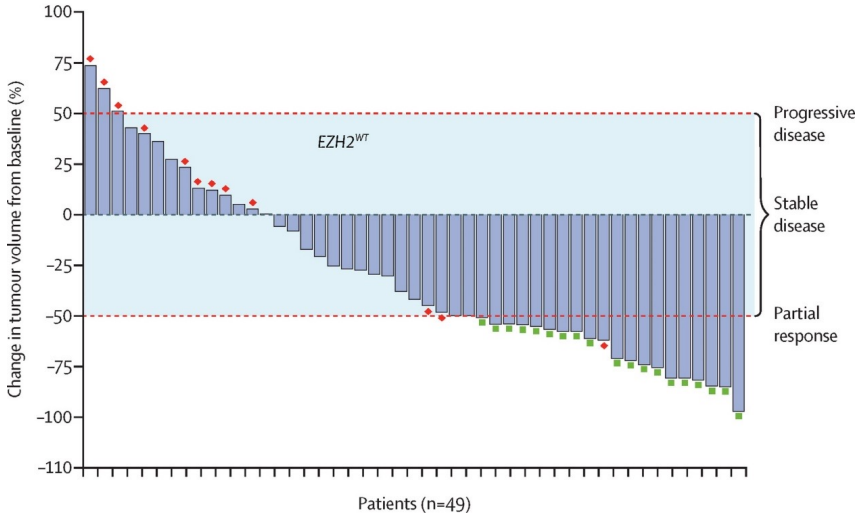
MT EZH2

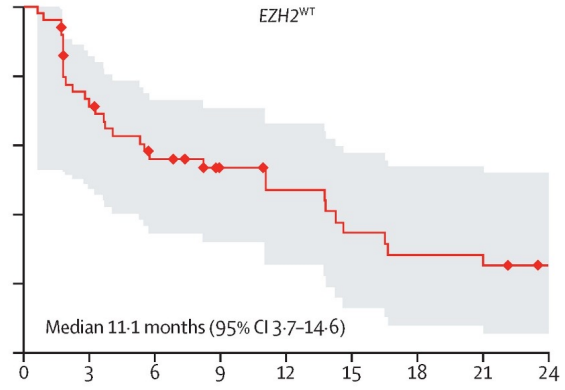




Median PFS 13.8 months

WT EZH2





Median PFS 11.1 months

- Approved for 3rd line, or earlier if no other satisfactory options.
- Oral therapy
- Superior safety profile
- Efficacy better if EZH2 mutation present
- Disease control rate (SD/PR/CR):
  - 98% for EZH2 MT
  - 65% for EZH2 WT

Morschhauser et al, Lancet Oncology 2020, Pages 1433-1442

Favorable Toxicity profile

TEAEs,[a] n (%)	All TEAEs (N=99)		Treatment-Related TEAEs (N=99)	
	All Grades[b]	Grade ≥3	All Grades	Grade ≥3
Nausea	23 (23)	0 (0)	19 (19)	0 (0)
Asthenia	19 (19)	3 (3)	15 (15)	1 (1)
Diarrhea	18 (18)	0 (0)	12 (12)	0 (0)
Fatigue	17 (17)	2 (2)	12 (12)	1 (1)
Alopecia	17 (17)	0 (0)	14 (14)	0 (0)
Cough	16 (16)	0 (0)	2 (2)	0 (0)
URTI	15 (15)	0 (0)	1 (1)	0 (0)
Bronchitis	15 (15)	0 (0)	3 (3)	0 (0)
Anemia	14 (14)	5 (5)	9 (9)	2 (2)
Abdominal pain	13 (13)	1 (1)	2 (2)	0 (0)
Headache	12 (12)	0 (0)	5 (5)	0 (0)
Vomiting	12 (12)	1 (1)	6 (6)	0 (0)
Back pain	11 (11)	0 (0)	0 (0)	0 (0)
Pyrexia	10 (10)	0 (0)	2 (2)	0 (0)
Thrombocytopenia	10 (10)	5 (5)	8 (8)	3 (3)

- Low rate of grade ≥3 AEs
- No treatment related deaths.

Morschhauser et al, Lancet Oncology 2020, Pages 1433-1442

Trial in progress: SYMPHONY-1
Tazemetostat + R2 vs R2

This international, multicenter, randomized, double-blind, active-controlled, 3-stage, biomarker-enriched, phase 1b/3 study (NCT04224493) is evaluating TAZ + R² in patients with R/R FL

Phase 1b (Stage 1: Safety Run-in)

Dose Escalation Using 3+3 Design[a]

Patients with R/R FL
N≈3–18[a]

TAZ (dose escalation; 3+3 design) + R²
Enrolled N=44

Phase 1b Dosing	
Tazemetostat	400 mg, 600 mg, 800 mg orally BID × 28-day cycles
Rituximab	375 mg/m² intravenously on days 1, 8, 15, and 22 of cycle 1, then on day 1 of cycles 2 to 5
Lenalidomide	20 mg (CrCl ≥60 mL/min) or 10 mg (CrCl <60 mL/min) orally QD on days 1 to 21 every 28 days for 12 cycles

Primary Endpoints
- Safety and tolerability
- TAZ RP3D

Secondary Endpoint
- Safety PK parameters

Phase 3 (Stage 2[b])

Patients with R/R FL
N≈500

R
1:1

Arm 1
TAZ RP3D + R²

Continue arm 1 treatment for up to 12 cycles or until relapse or intolerability[c]

Continue TAZ as maintenance therapy for up to 2 years

Arm 2
Placebo + R²

Continue arm 2 treatment for up to 12 cycles or until relapse or intolerability[c]

Continue placebo as maintenance therapy for up to 2 years

Stratified by *EZH2* mutation status (MT vs WT), sensitivity to prior treatment (sensitive vs refractory), and number of lines of therapy (1 vs ≥2)

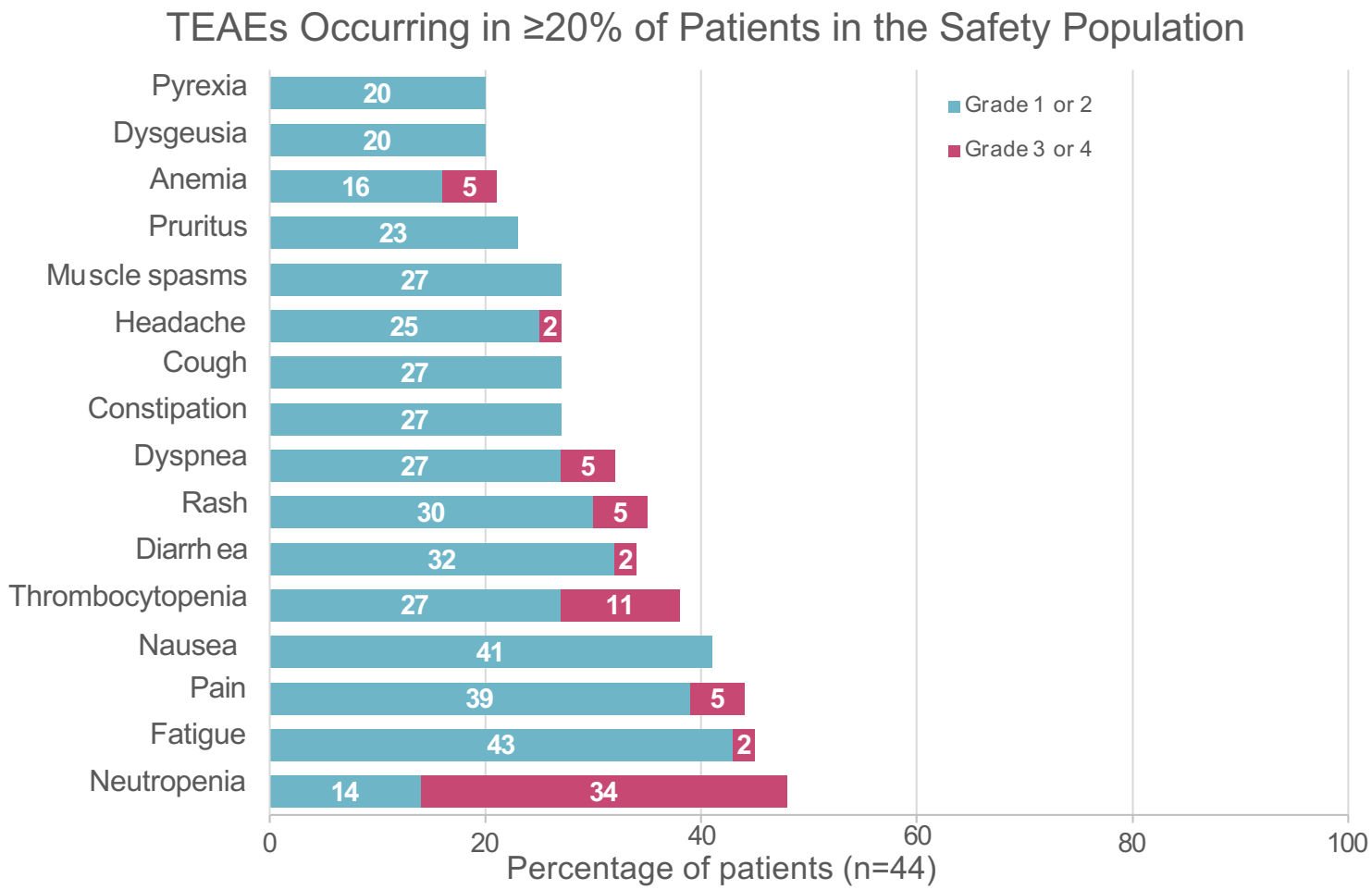
Primary Endpoint
- PFS (by Investigator)

Secondary Endpoints
- PFS (by IRC)
- ORR
- DOR
- DOCR
- DCR
- OS
- QoL
- Population PK
- Safety and tolerability

Batlevi et al. ASH 2022

Results of Phase Ib

Best Overall Response,[a] % (n)	WT (n=33)	MT (n=7)
ORR	97.0 (32)	100 (7)
Complete response	45.5 (15)	71.4 (5)
Partial response	51.5 (17)	28.6 (2)
Stable disease	3.0 (1)	0



Batlevi et al. ASH 2022

Trial Design

Phase 2

Study Identifier: BGB-3111-212, NCT03332017

Primary Endpoint: ORR by ICR per Lugano Classification[3]

Key Secondary Endpoints: ORR by investigator, DOR and PFS by ICR, OS, CR and CMR rate

Key eligibility criteria

- R/R FL (received ≥2 prior treatments)
- Must have received prior anti-CD20 antibody and an alkylator
- Grade 1, 2, or 3a FL
- Measurable disease
- ECOG PS 0-2
- Adequate organ functions
- No prior BTK inhibitor

Stratification factors

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

Treatment

Screening

R 2:1

Zanubrutinib[a] 160 mg PO BID + obinutuzumab IV until PD (n=145)

Obinutuzumab[b] IV until PD (n=72)

Follow-up

Safety and survival

Zinzani PL et al. ASCO 2022; Abstract 7510

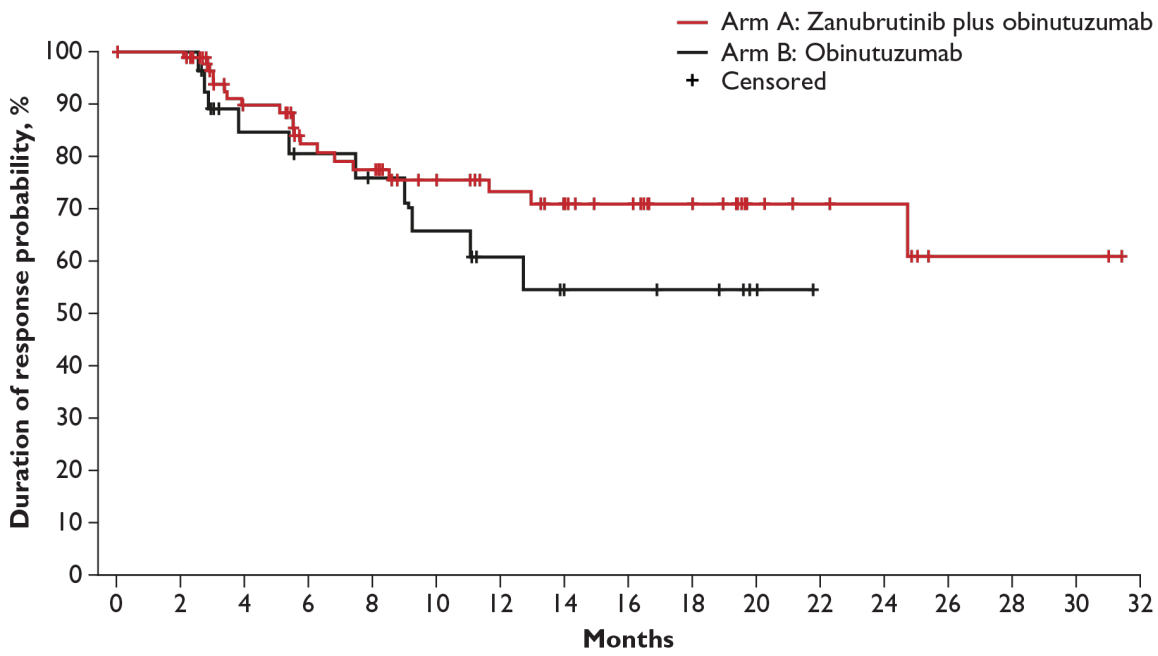
Response by Independent Central Review

Response by ICR	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
ORR, % (95% CI)	68.3 (60.0, 75.7)	45.8 (34.0, 58.0)
Risk difference, % (95% CI)	22.0 (8.3, 35.8)	
2-sided *P* value	0.0017	
BOR, n (%)		
CR	54 (37.2)	14 (19.4)
PR	45 (31.0)	19 (26.4)
SD	25 (17.2)	14 (19.4)
Nonprogressive disease	3 (2.1)	4 (5.6)
PD	13 (9.0)	15 (20.8)
Discontinued prior to first tumor assessment	4 (2.8)	6 (8.3)
NE	1 (0.7)	0 (0.0)
Complete response rate, % (95% CI)	37.2 (29.4, 45.7)	19.4 (11.1, 30.5)
2-sided *P* value	0.0083	

Zinzani PL et al. ASCO 2022; Abstract 7510

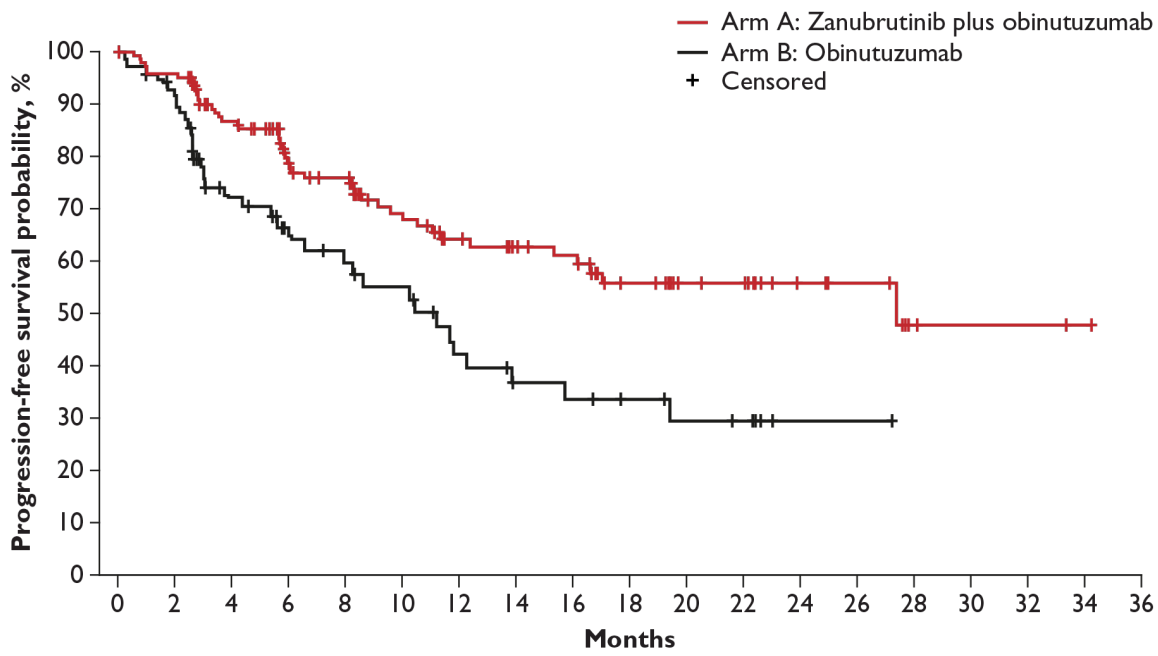
Efficacy

Duration of Response by ICR



DOR rate at 18 months:
70.9% Arm A vs 54.6% Arm B

Progression-Free Survival by ICR

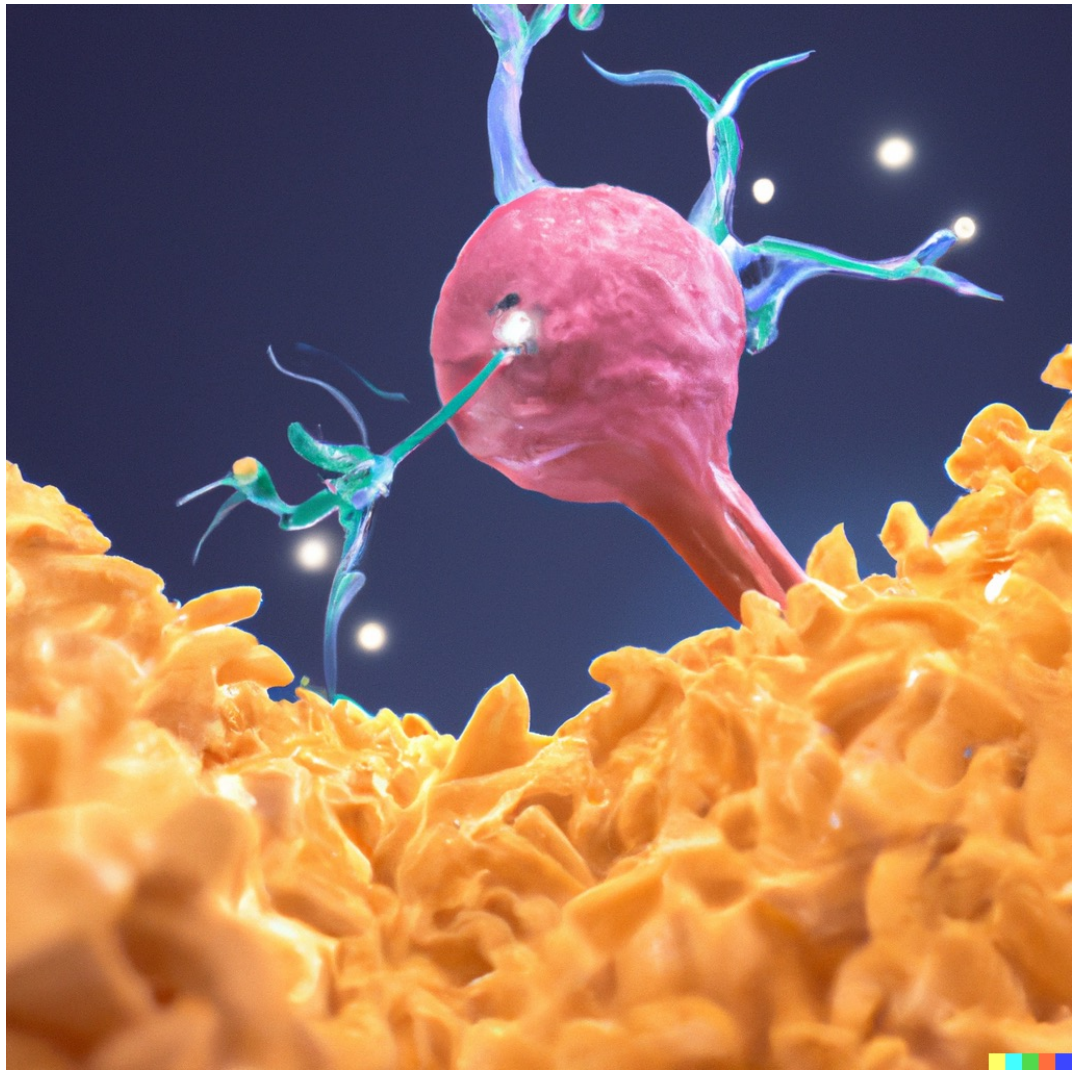


Median PFS, months (95% CI):
27.4 months Arm A vs 11.2 months Arm B

Median study follow-up 12.5 months

Zinzani PL et al. ASCO 2022; Abstract 7510

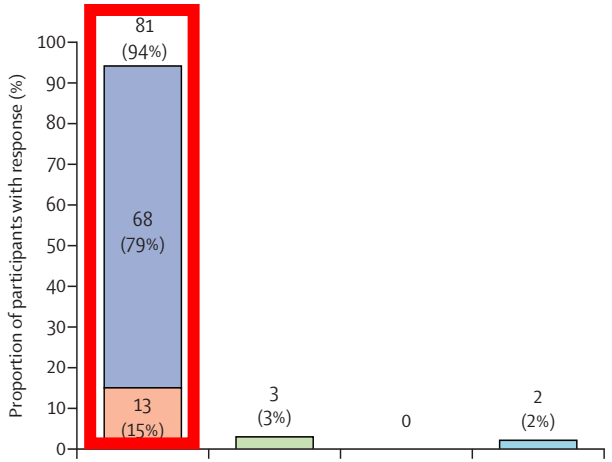
Chimeric antigen receptor T-cell updates



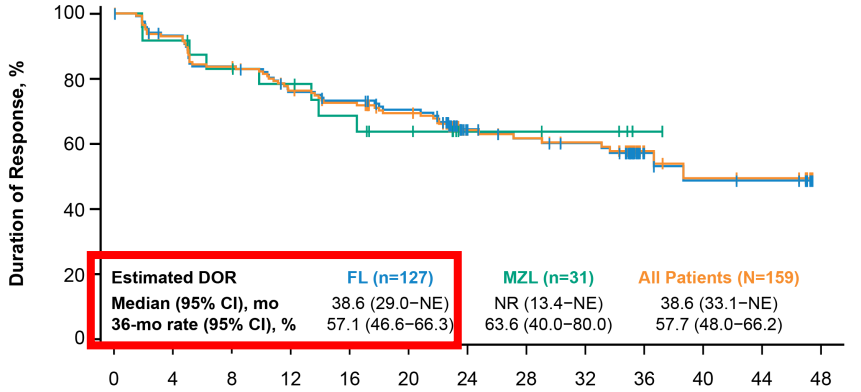
Artwork by “DALL.E” 2023, Artificial Intelligence

3-Year Follow-Up Analysis of ZUMA-5: A Phase 2 Study of Axi-Cel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

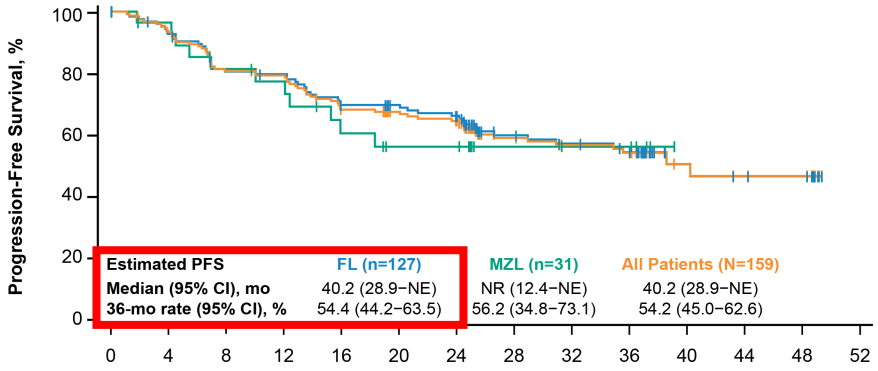
Response rates in Follicular lymphoma:
ORR: 94%
CR: 73%



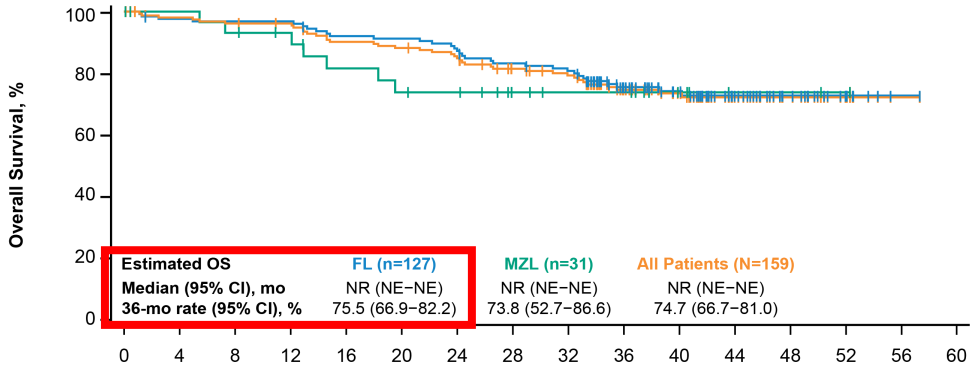
Duration of Response



Progression-Free Survival



Overall Survival

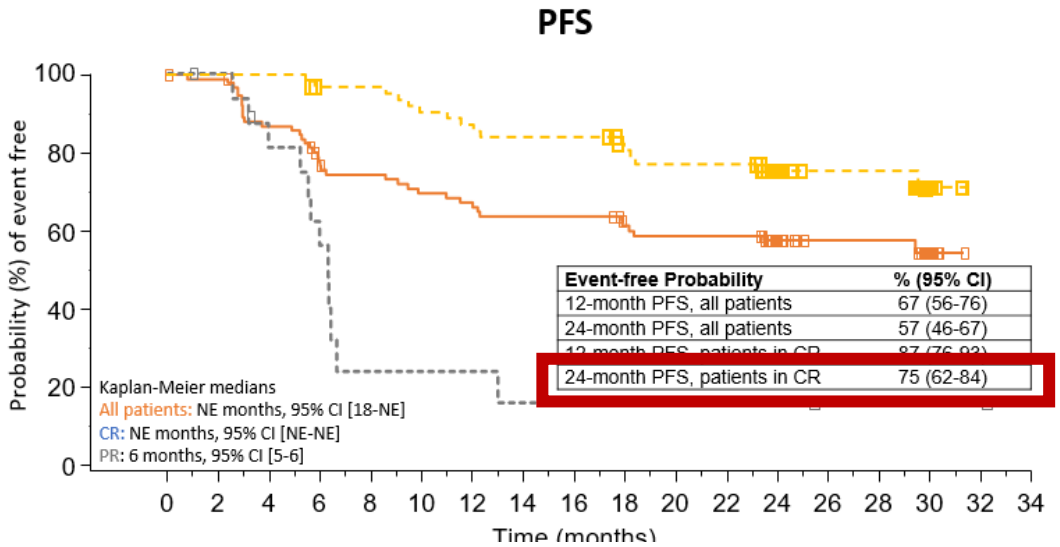


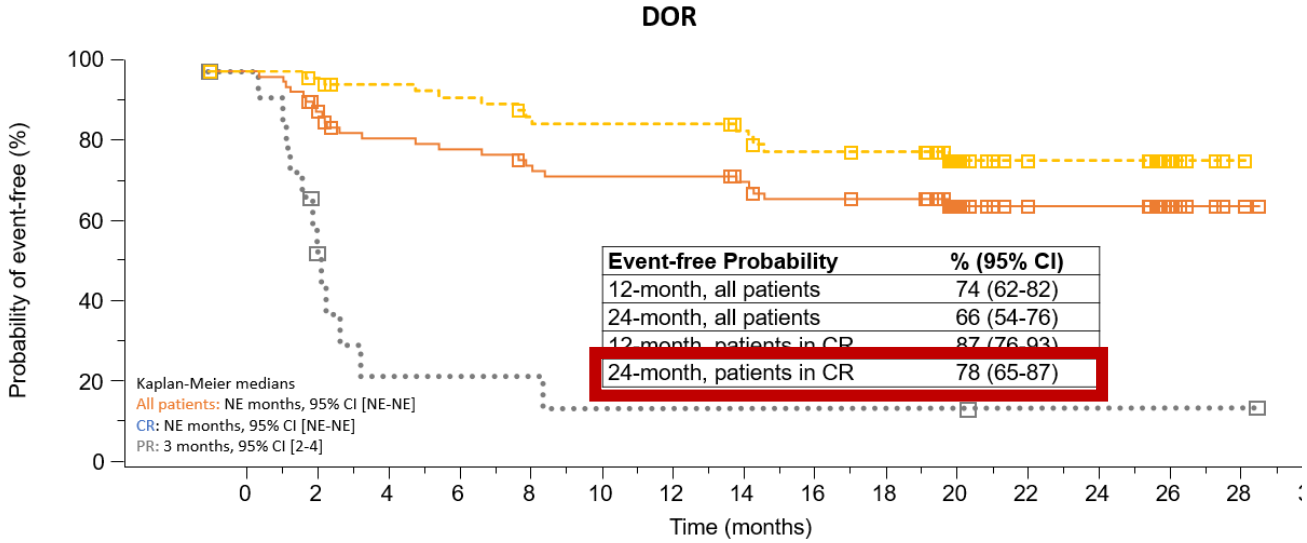
Yakoub-Agha, et al., ASH 2022

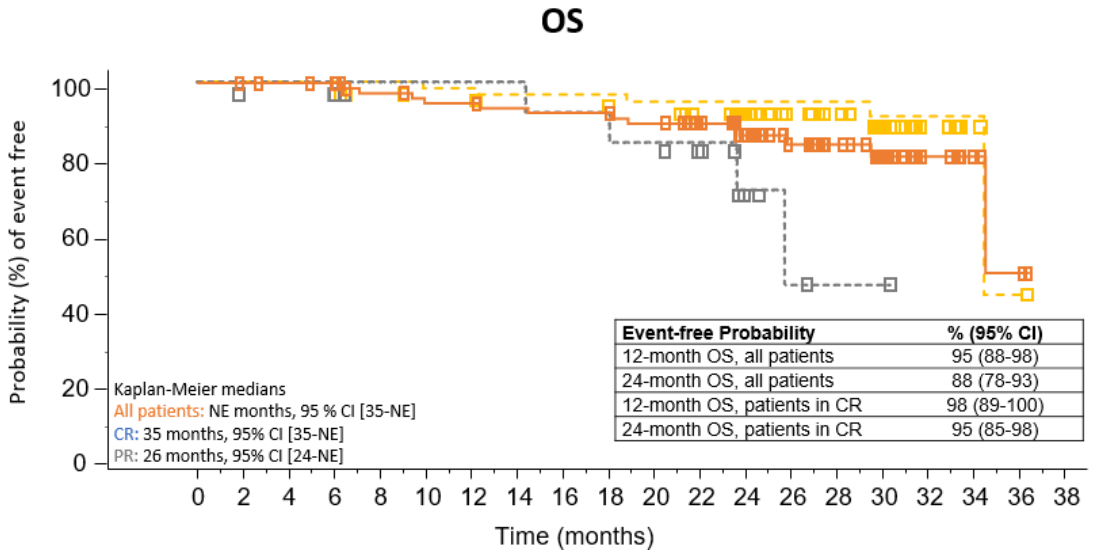
29 Follow-up Analysis of ELARA Trial: Tisagenlecleucel in patients with R/R Follicular lymphoma ELARA Trial.

Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR	68 (58-77)
ORR	86 (78-92)

Median DOR, PFS, and OS were **not reached** in the ELARA trial after >2 years of follow-up



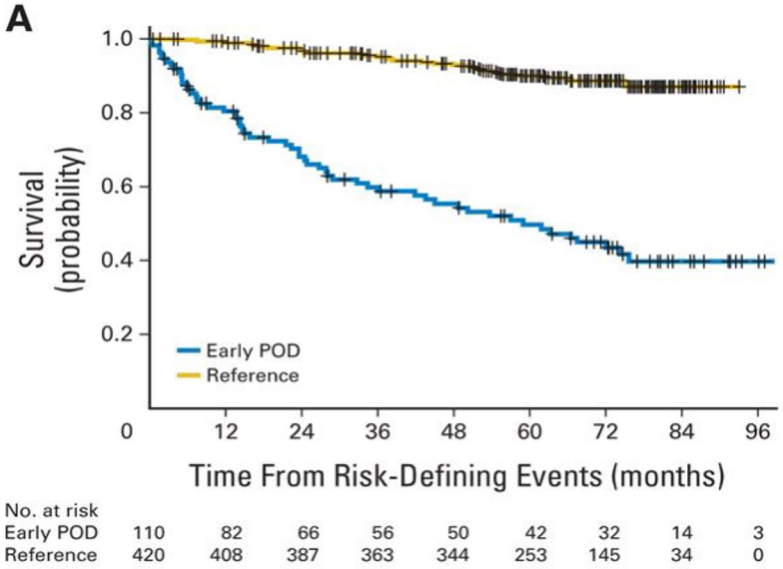


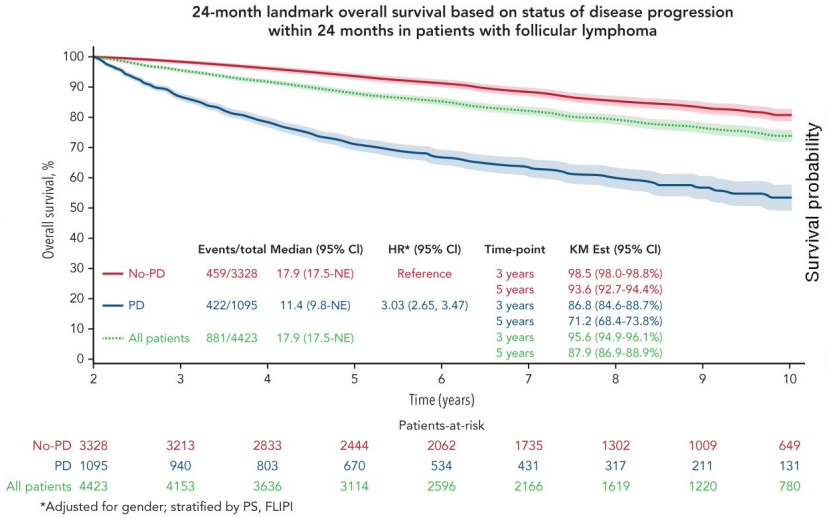


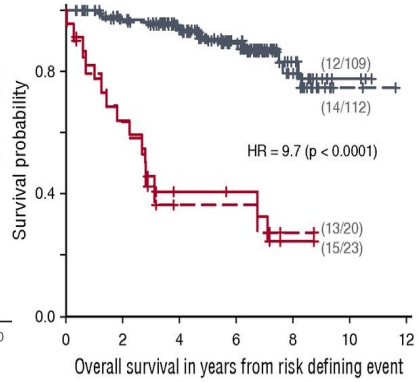
Dreyling et al., EBMT-EHA European CART Meeting 2023. Abstract #23

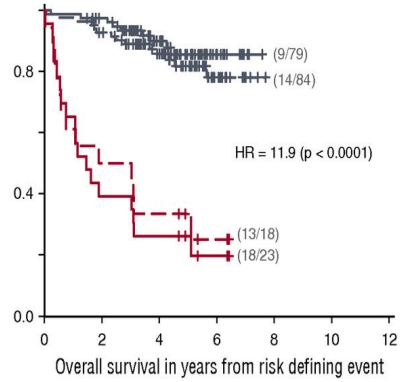
Where does CAR-T fit in for R/R FL?

POD24 (Progression Of Disease within 24 months of chemoimmunotherapy) have worse prognosis









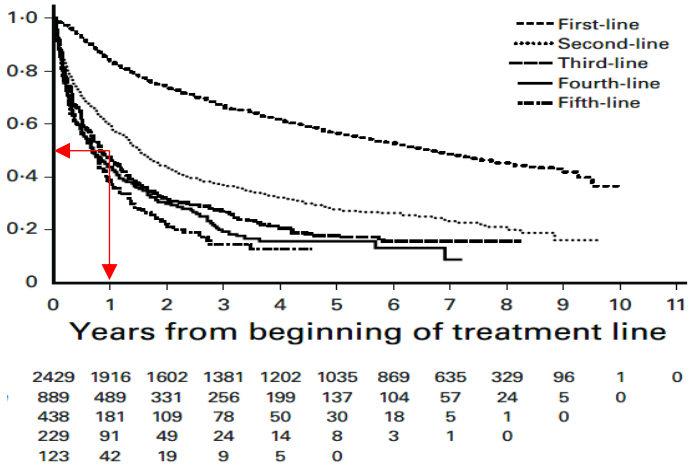
- Represent 20% of patients with FL
- Have lower OS (~50% at 5 years)
- Biopsy should be considered to detect histologic transformation of FL (higher incidence in POD24)
- High risk group needing better therapies

Casulo et al. JCO 2015, 33, 2516-2522; Casulo et al. Blood (2022) 139 (11): 1684–1693; Jurinovic et al. Blood (2016) 128 (8): 1112–1120.

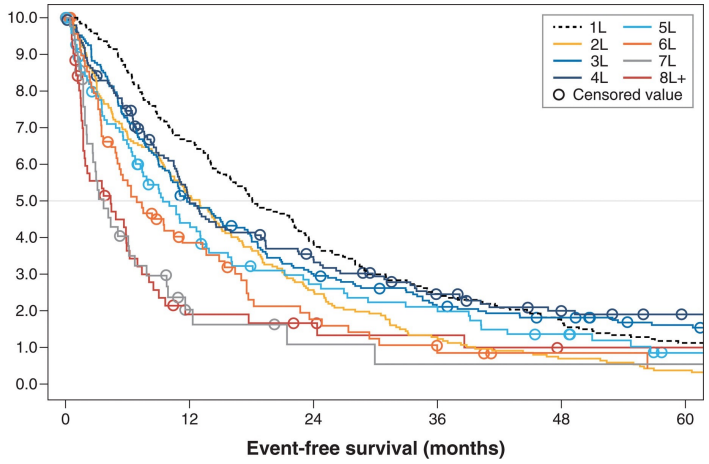
Where does CAR-T fit in for R/R FL?

Multiple relapses beyond third line have worse outcomes

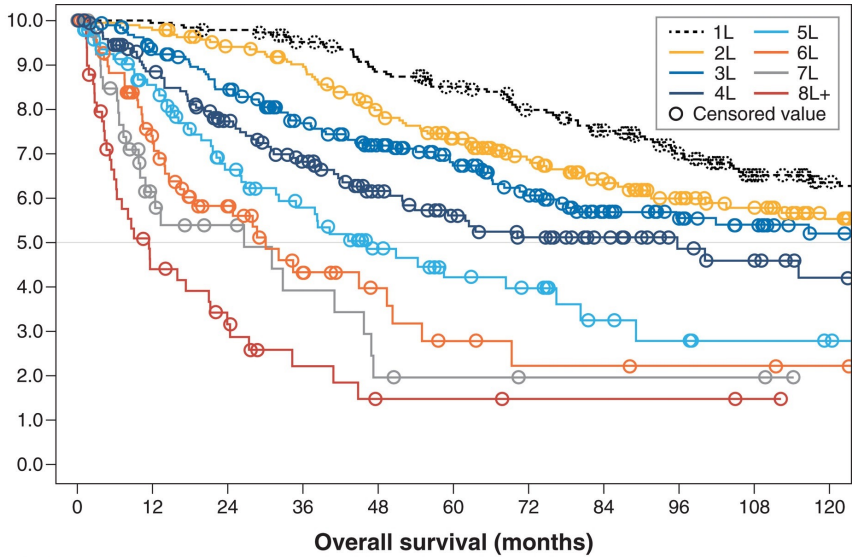
PFS



Treatment Line	Median PFS, Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)



Median Survival in years still



PFS and duration of remission fall with each subsequent relapse

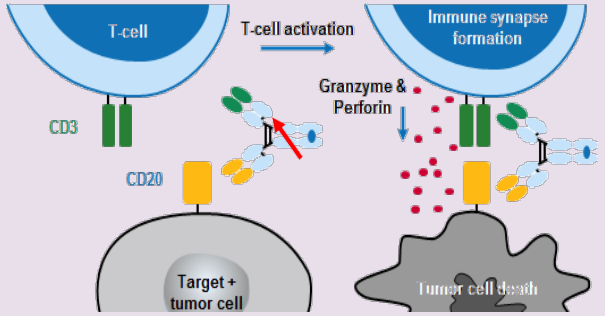
Median PFS typically <12 months in 3rd line and beyond

Link BK, et al. Br J Haematol. 2019;184:660; Salles, et al. HemaSphere 6(7):p e745, July 2022

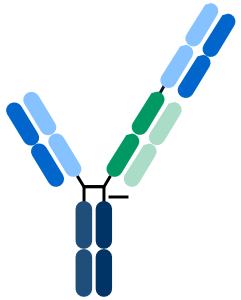
Bispecific antibodies in development

Mosunetuzumab (CD3xCD20)

FDA Approved Dec 2022

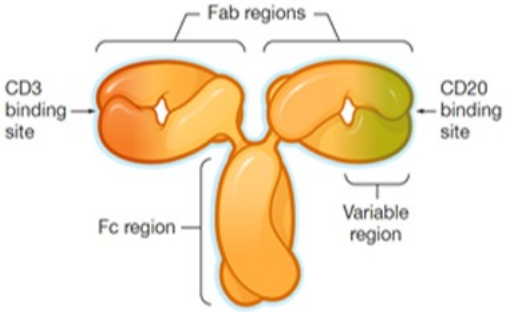


Glofitamab (CD3xCD20)

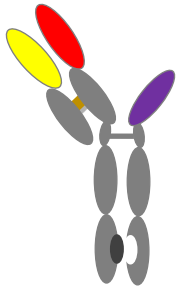


Epcoritamab (CD3xCD20)

Odronextamab (CD3xCD20)



TNB-486 (CD3x**CD19**)

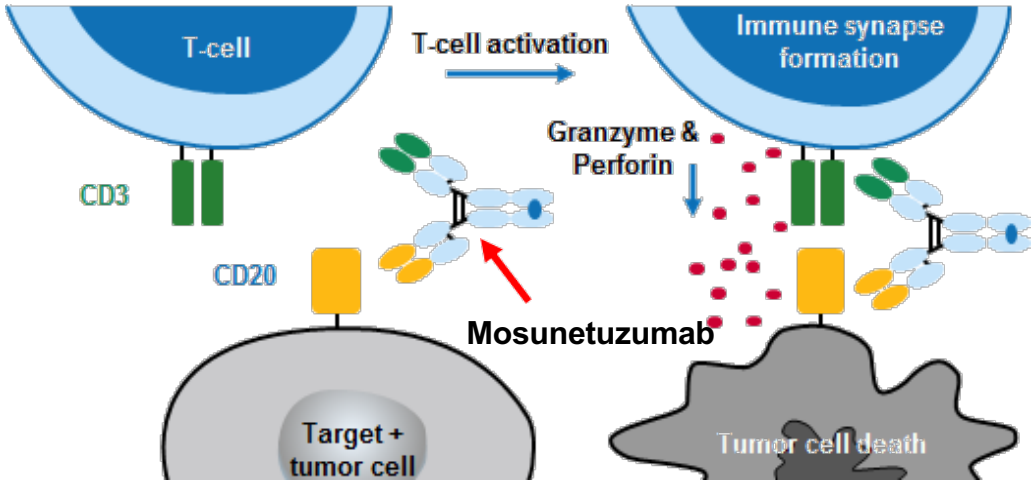


Fc Tail

Plamotamab (CD3xCD20)

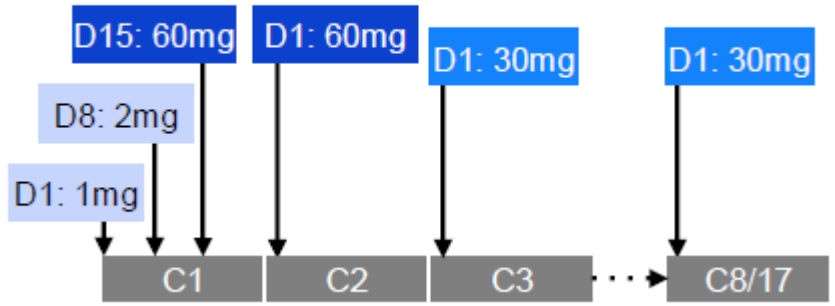
Mosunetuzumab (CD20 x CD3 T-cell Engager: First FDA approved bispecific antibody for R/R FL (Dec 2022)

- Mosunetuzumab **(first-in-class)** is now FDA approved for the treatment of **relapsed/refractory follicular lymphoma (R/R FL)** after ≥2 prior systemic therapies.
- Redirects T cells to engage and eliminate malignant B cells
- Off the Shelf outpatient treatment



Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



Bartlett et al. ASH 2022; Budde et al. The Lancet Oncology 2022; Sun LL, et al: Sci Transl Med 2015;7:287ra70; Hernandez G, et al. ASH 2019

Mosunetuzumab:
Baseline characteristics: Heavily pretreated patients

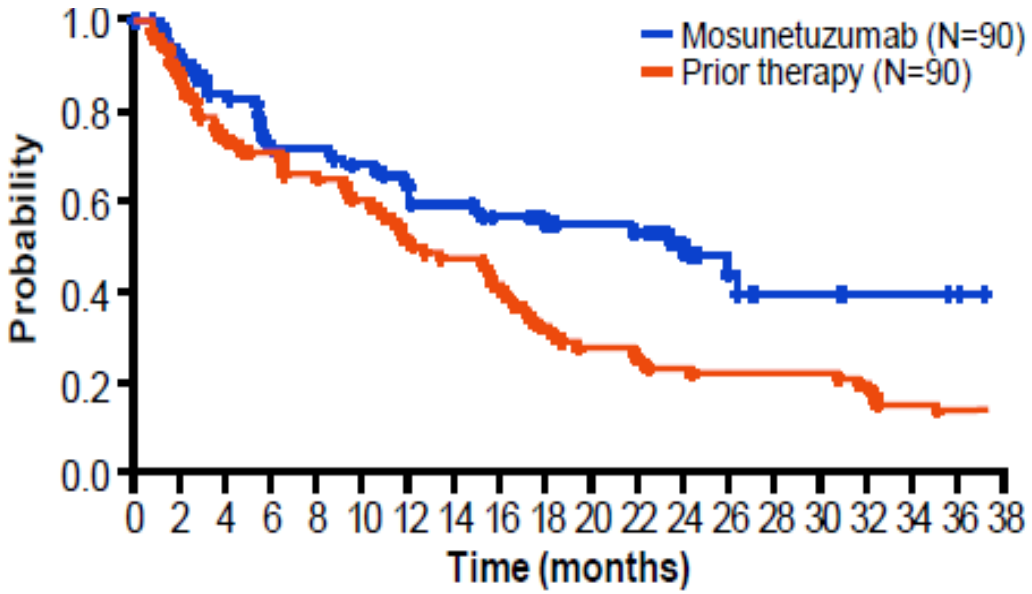
	N=90
Median age, years (range)	60 (29–90)
Male	61%
ECOG PS	
0	59%
1	41%
Ann Arbor stage	
I/II	23%
III/IV	77%
Median lines of prior therapy, n (range)	3 (2–10)
Refractory to last prior therapy	69%
Refractory to any prior anti-CD20 therapy	79%
Progression of disease within 24 months from start of first-line therapy (POD24)	52%
Double refractory to prior anti-CD20 and alkylator therapy	53%
Prior autologous stem cell transplant	21%

Bartlett et al. ASH 2022; Budde et al. The Lancet Oncology 2022;

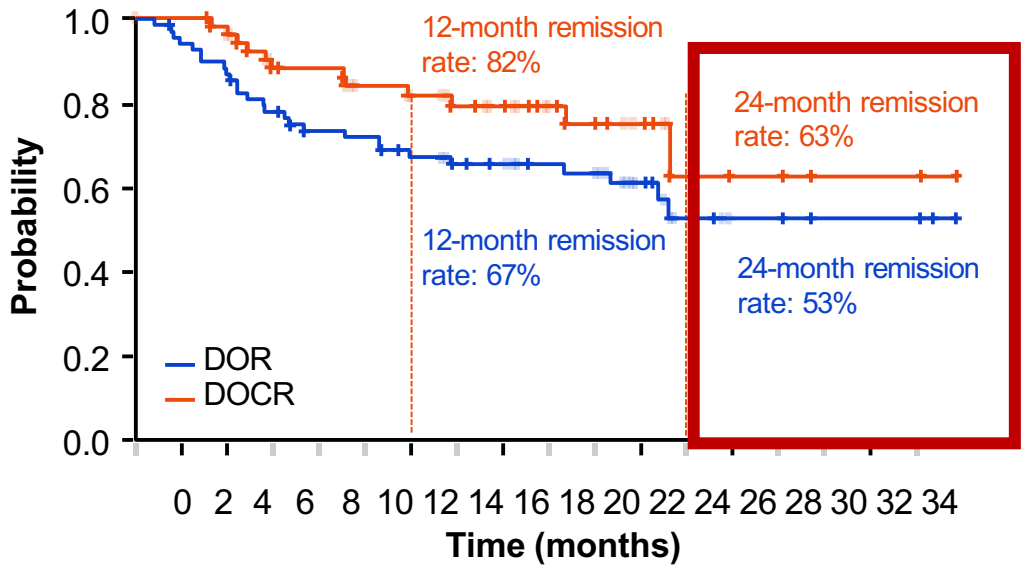
Mosunetuzumab: Efficacy Analysis

ORR	**78%**
CR	**60%**
Median FU	**28.3**

mPFS: 24 months



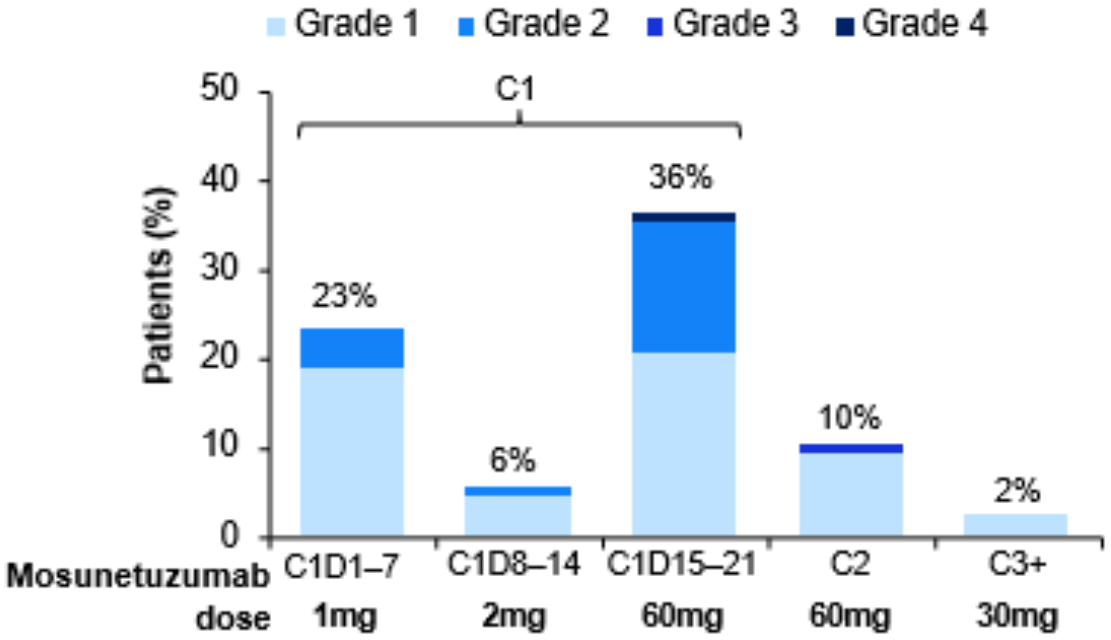
mDOR: NR and mDOCR: NR



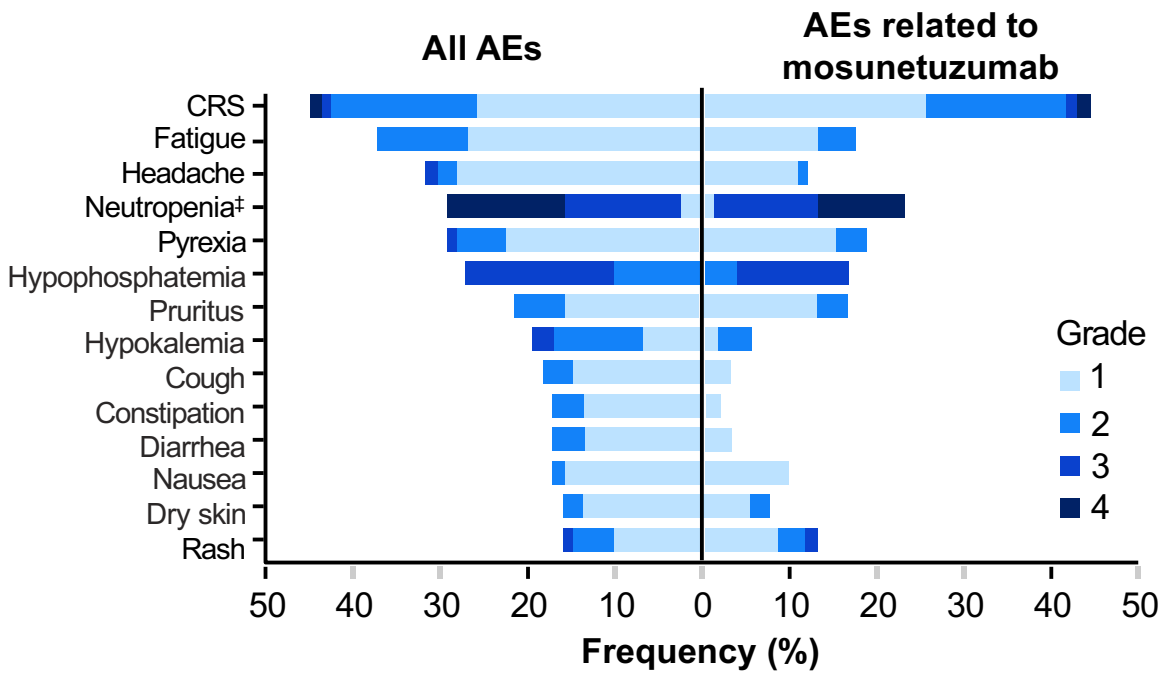
Bartlett et al. ASH 2022; Budde et al. The Lancet Oncology 2022

Mosunetuzumab: Safety profile

CRS by cycle and grade



AEs (≥15%) by grade and relationship with mosunetuzumab



CRS mostly low grade (Grade 3/4: 2%) and occurred during Cycle 1
ICANs 3% (all grade 1-2)

Bartlett et al. ASH 2022; Budde et al. The Lancet Oncology 2022;

Other Bispecifics (CD3/CD20)

Glofitamab in R/R FL	Epcoritamab + Rituximab + Lenalidomide in R/R FL	Odronextamab in R/R FL
Phase I/II	Phase I/II (EPCORE NHL-2)	Phase 2 (ELM-2)
Monotherapy or combination with obinutuzumab	Combined with R2	Monotherapy
Intravenous	Subcutaneous	Intravenous
C1: D1, 8, 15 then q21 days	Weekly first 2 cycles Afterwards Q21 days	C1: D1/2, 8/9, 15 Cycles 2-4: D1,8,15 then maintenance Q2w
Fixed duration: 12 cycles	Up to 2 years	Till disease progression

Morschhauser et al. ASH 2021 (Glofitamab); kim et al. ASH 2022 (Odronextamab); Falchi et al. ASH 2022 (Epcoritamab)

CAR-T vs Bispecifics

	Axi-cel	Tisa-cel	Mosunetuzumab (CD3xCD20)	Odronextamab (CD3xCD20)	Epcoritamab + R2 (CD3xCD20)	Glofitamab (CD3xCD20)
ORR %	94%	86%	78%	82%	95%	81%
CR %	79%	68%	60%	75%	80%	70%
mPFS	39.6%	Not reached	24 mo	20.2 mo	Not reached	Not reported
mDOR	38.6%	Not reached	Not reached	20.5 mo	Not reached	Not reported
CRS **Gr 1-2** **Gr 3-4**	 72% (1-2) 6% (3-4)	 48.5% (1-2) 0% (3-4)	 43% (1-2) 2% (3-4)	 56% (1-2) 1.6% (3)	 43% (1-2) 0% (3-4)	 55% (1-2) 0% (3-4)
ICAN (Neuro toxicity) **Gr 1-2** **Gr ≥ 3**	 41% 15%	 12% 1 %	 3% (1-2) 0%	 1.5% 0%	 1/76 pts (Gr 1) 0%	 0% 0%
Duration of therapy	One time!	One time!	8-17 cycles	Till PD	Up to 2 years	12 cycles
Median follow-up	31 mo	28.9%	28.3 mo	17.3 mo	6.4 mo	4.4

Neelapu et al. ASH 2021 (Axi-cel); Dreyling et al. ASH 2022 (Tisa-cel); Budde et al. The Lancet Oncology 2022 (Mosunetuzumab); Morschhauser et al. ASH 2021 (Glofitamab); kim et al. ASH 2022 (Odronextamab); Falchi et al. ASH 2022 (Epcoritamab)

How do I treat patients with R/R Follicular lymphoma

Pro-CAR-T

- ✓ **Consideration:**
  - ❑ Most effective, but relatively more toxic
  - ❑ Complicated Logistics
  - ❑ Age, Performance status, comorbid conditions
  - ❑ Access to close by CAR-T Center
  - ❑ Insurance coverage
  - ❑ Adequate social support
  - ❑ Patient commitment for 'intense workup and inpatient stay.
  - ❑ Patient preference: one time vs more extended therapy
- ✓ **Ideal CAR-T Candidate:**
  - ❑ POD 24, primary refractory, multiple relapses with short remission duration, concern for occult transformation
  - ❑ Relatively young, fit, motivated patient
  - ❑ Patient prefers a one-time treatment

Pro-Conventional/Novel therapies

- ✓ **Considerations:**
  - ❑ Older patient, comorbid conditions, poor performance status: Tazemetostat → R-Len → Bispecifics
  - ❑ Lack of access to CAR-T (insurance, logistics, social support, etc.): Bispecifics → R-Len → Tazemetostat
  - ❑ Patient preference (?oral vs IV; one time vs extended therapy), No commitment to CAR-T intensive workup and hospital stay, Patients refusing chemo-depletion: Bispecifics → R-Len → Tazemetostat
  - ❑ "Late relapse": R-Len or Bispecifics → Tazemetostat → CAR-T.

Thank you!!

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