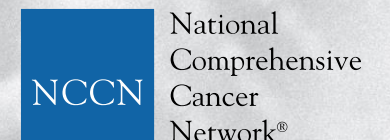


Follicular Lymphoma –How do I deal with relapse?

Brad Kahl, MD



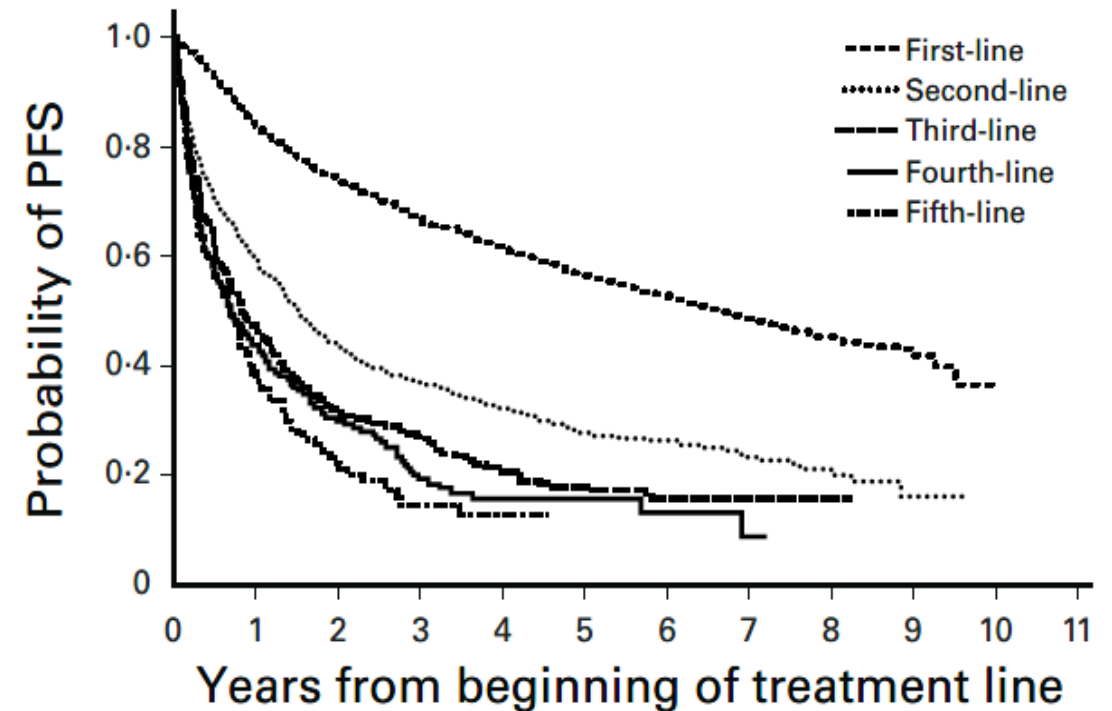
Disclosures

- Consulting
 - Genentech/Roche, ADC Therapeutics, Abbvie, AstraZeneca, BeiGene, Celgene/BMS, Kite, Genmab, Lilly, GSK
- Research Funding
 - Genentech/Roche, Abbvie, AstraZeneca, BeiGene

Relapsed/Refractory (R/R) FL

- Patients with FL will experience multiple relapses
- Sharply decreasing length of PFS after first relapse

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)



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11
First-line	2429	1916	1602	1381	1202	1035	869	635	329	96	1	0
Second-line	889	489	331	256	199	137	104	57	24	5	0	0
Third-line	438	181	109	78	50	30	18	5	1	0	0	0
Fourth-line	229	91	49	24	14	8	3	1	0	0	0	0
Fifth-line	123	42	19	9	5	0	0	0	0	0	0	0

Recurrent Follicular Lymphoma

CONVENTIONAL STRATEGIES

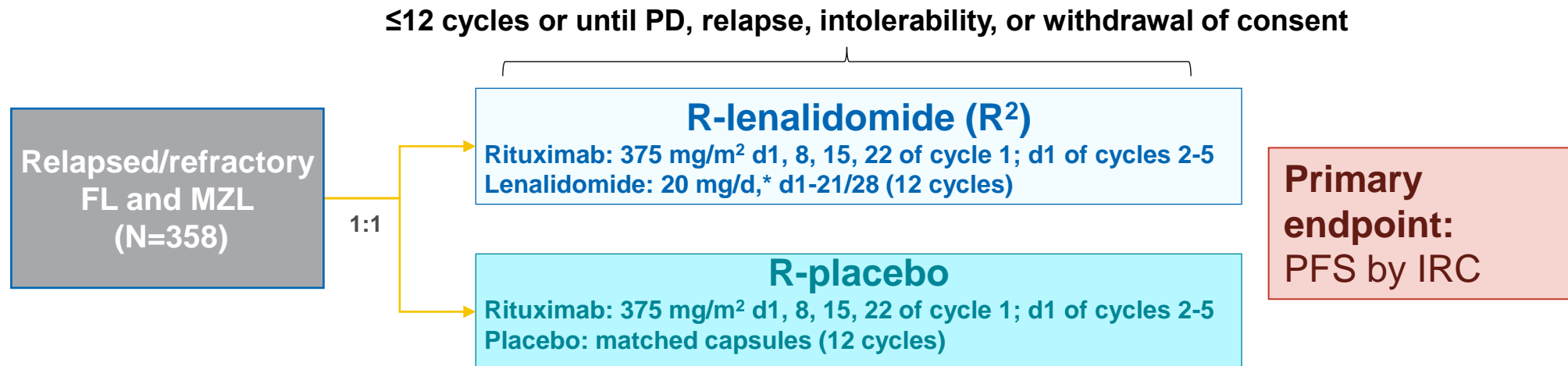
1. Chemoimmunotherapy
2. Rituximab
3. External beam XRT
4. Radioimmunotherapy
5. Autologous transplant
6. Allogeneic transplant

NEWER STRATEGIES

1. Lenalidomide based therapy
2. EZH2 inhibitors
3. CAR-T Cellular Therapy
4. Bi-Specific MoAb's
5. BTK inhibitors

AUGMENT

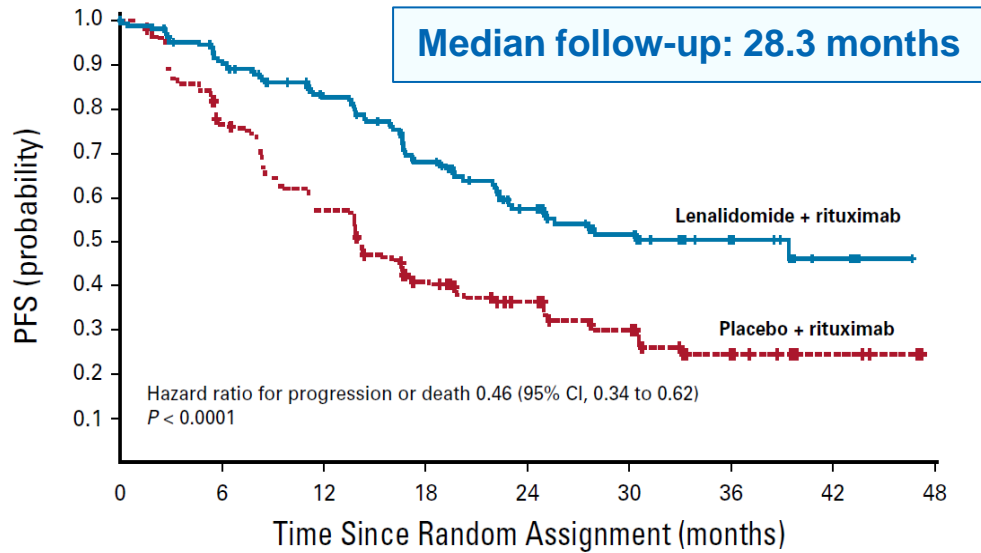
Phase 3 Study of R² vs R in R/R FL and MZL



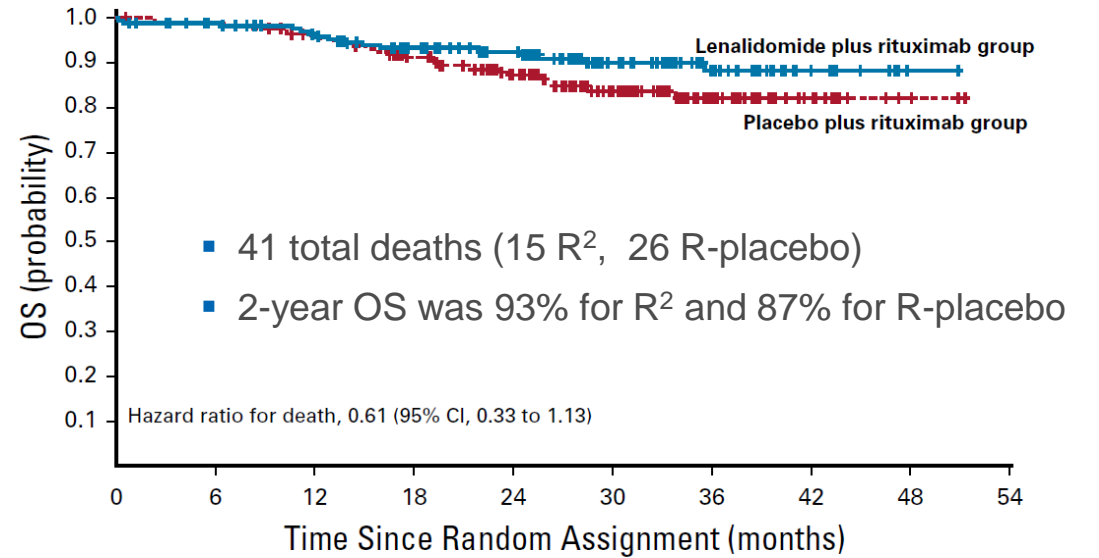
Key eligibility criteria

- R/R MZL or FL (grades 1-3a) in need of treatment
- ≥1 prior chemotherapy, immunotherapy, or chemoimmunotherapy and ≥2 previous doses of rituximab
- Not rituximab-refractory

R² vs R: PFS and OS



	No. at risk:								
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0



- 41 total deaths (15 R², 26 R-placebo)
- 2-year OS was 93% for R² and 87% for R-placebo

	No. at risk:										
Lenalidomide + rituximab	178	167	155	143	122	80	44	15	1	0	
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0	

Median PFS	R ² (n=178)	R-Placebo (n=180)	HR	P Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	<0.0001
By INV, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	<0.0001

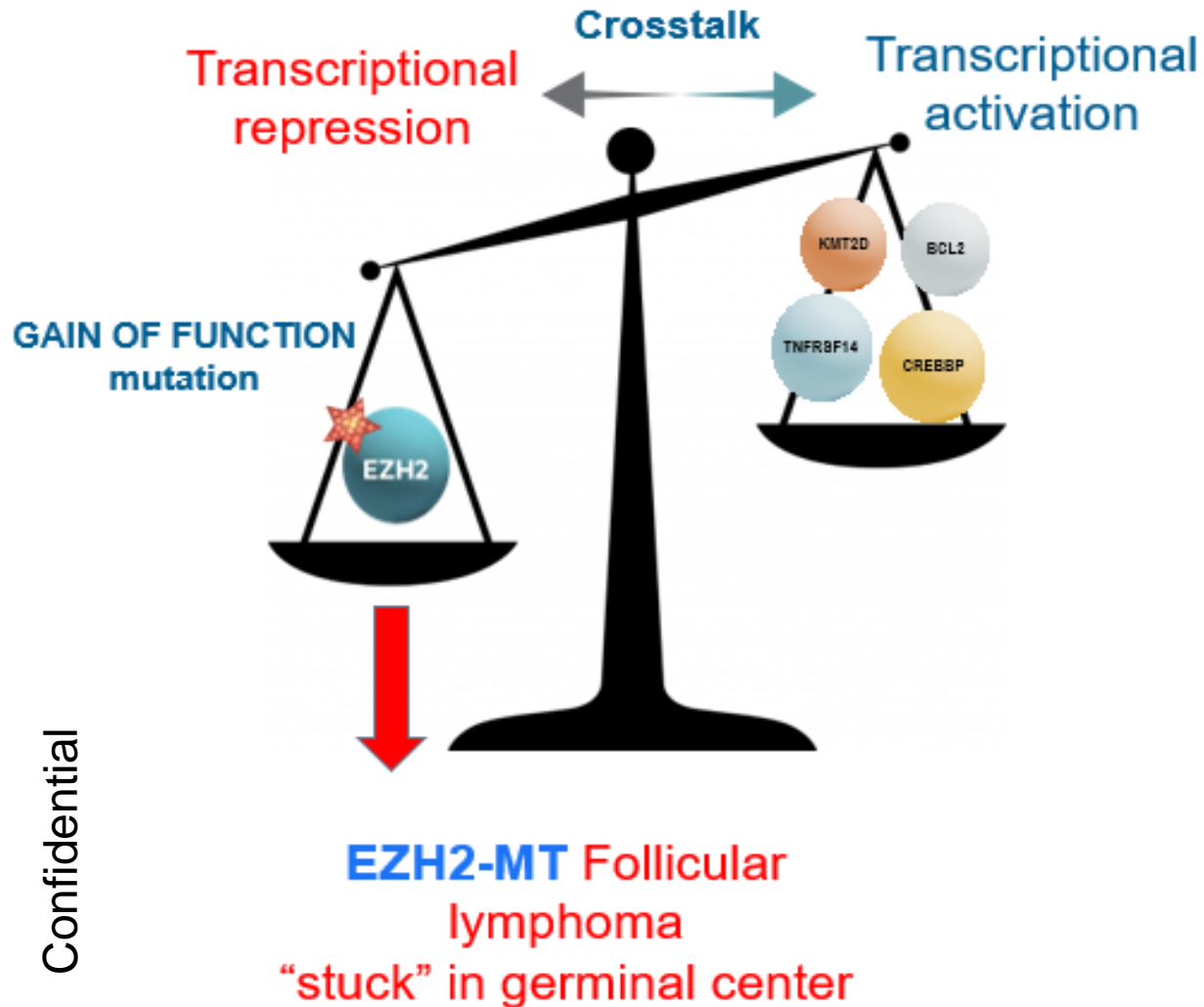
Tazemetostat in R/R FL: Approval

Approval Date	June 18, 2020*
Indication	Adult patients with R/R FL whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options
Mechanism of Action	Inhibitor of methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X, A682G, and A692V
Treatment	800 mg po BID
Clinical Trial	Cohorts 4 and 5 of E7438-G000-101, a multicenter, open-label, single-arm, phase 1/2 study (NCT01897571)
Primary Endpoints	MTD, ORR

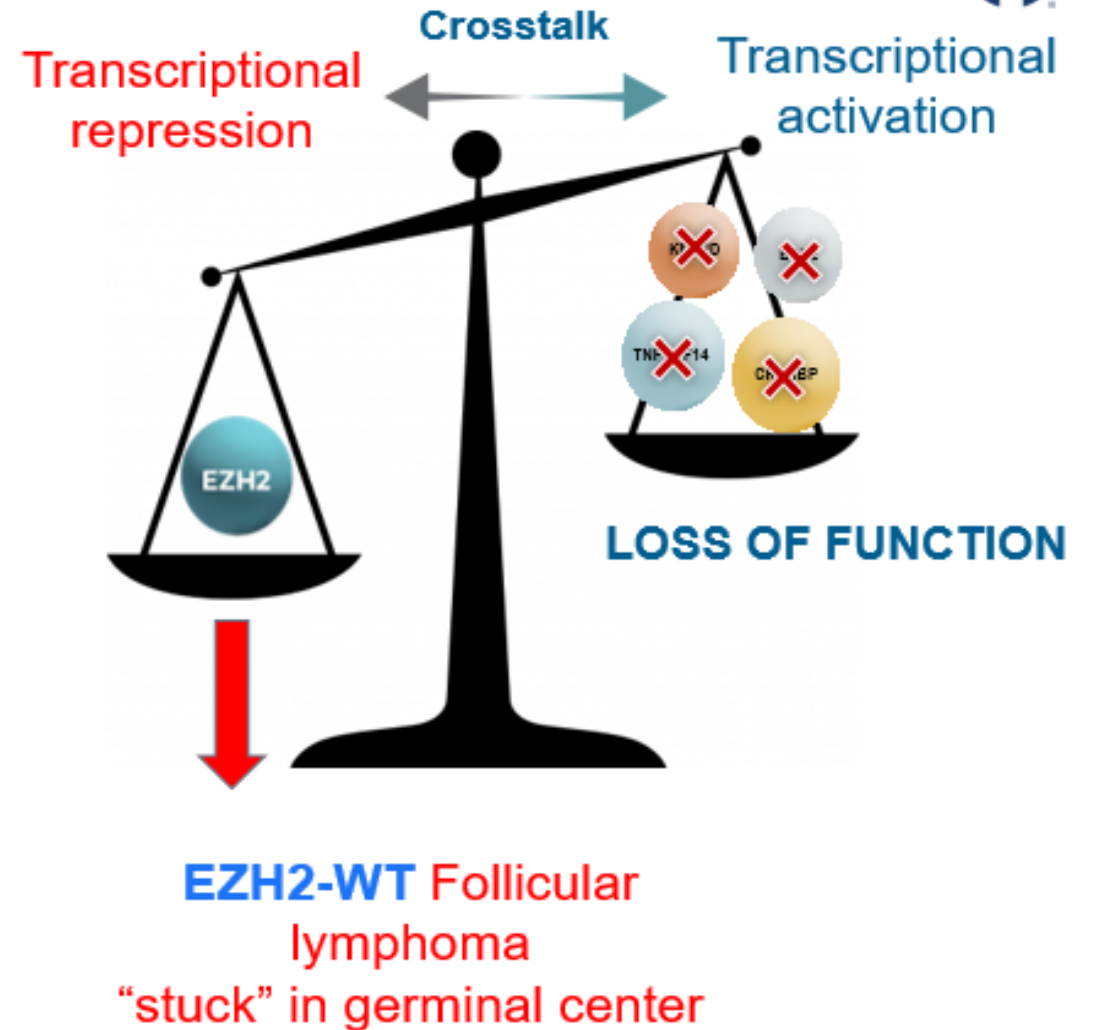
*Based on accelerated approval.

* https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211723s0001bl.pdf

EZH2-MT FL



EZH2-WT FL



EZH2 biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
~20% of patients with FL also have *EZH2* gain of function mutations

Confidential

Tazemetostat: Summary of efficacy and toxicity

EZH2 Mutated Cohort (n=45)

- ORR 69%
- mPFS 13.8 months

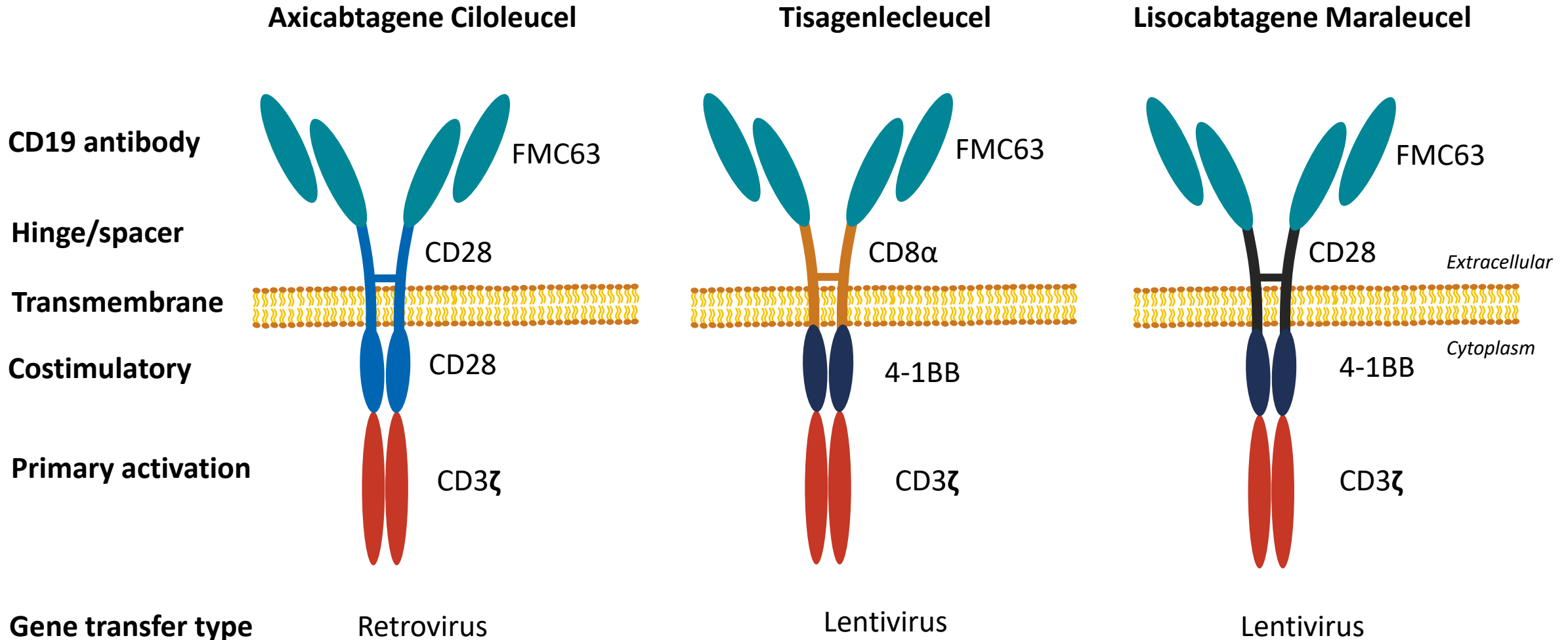
EZH2 Wild Type Cohort (n=54)

- ORR 35%
- mPFS 11.1 months

Extremely well tolerated

TEAEs, n (%)	All TEAEs (N=99)		Treatment-Related TEAEs (N=99)	
	All Grades ^a	Grade ≥3	All Grades	Grade ≥3
Nausea	23 (23)	0 (0)	19 (19)	0 (0)
Asthenia	18 (18)	3 (3)	14 (14)	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)

CAR T-Cell Therapy in the Clinic for FL



Summary of CART in FL

	Axi-Cel	Tisa-Cel	Liso-Cel
Trial	Zuma 5*	ELARA**	TRANSCEND FL***
Number of patients	127	94	107
ORR	94%	86%	97%
CR	80%	69%	94%
Durability	36 mos PFS: 54%	24 mos PFS: 57%	12 mos PFS: 80%
≥ Grade 3 CRS	6%	0%	1%
≥ Grade 3 ICANS	15%	3%	2%
FDA approved	March 2021	May 2022	TBD

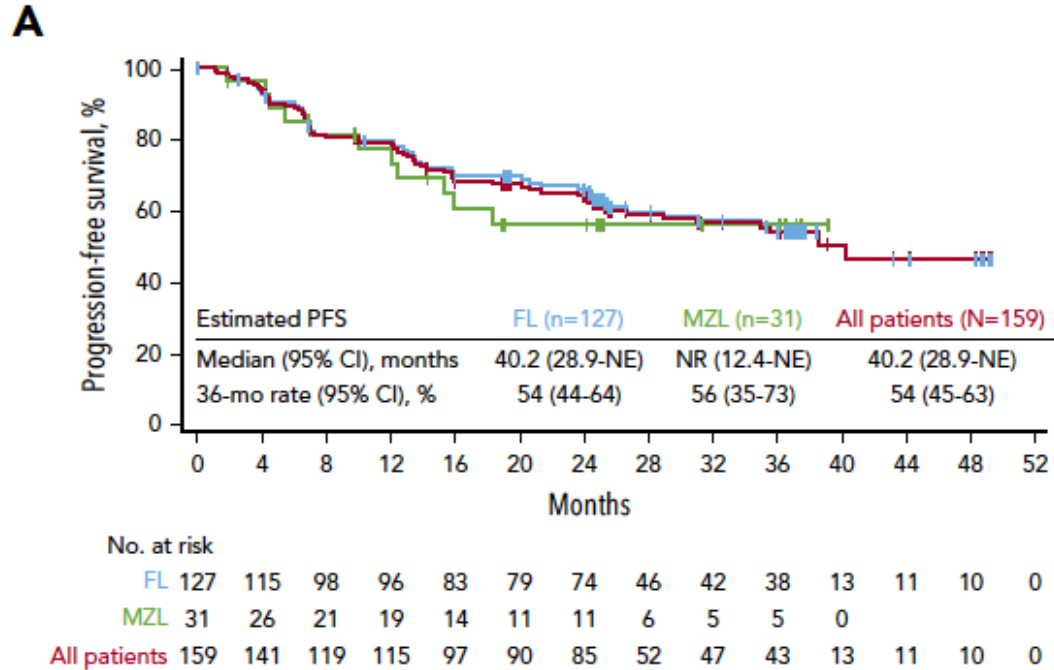
*Jacobson et al, Lancet 2022. Neelapu Blood 2024.

**Fowler et al, Nature Medicine 2022

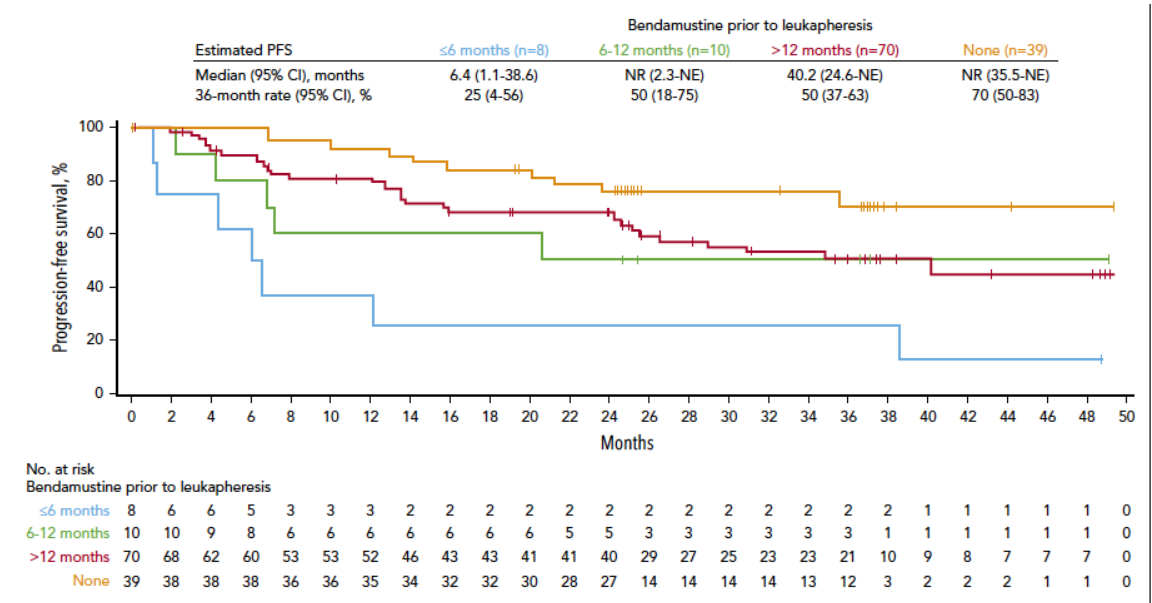
***Morschauer et al, ICML 2023

Axi-Cel in FL. 3-year follow up from Zuma 5

PROGRESSION FREE SURVIVAL

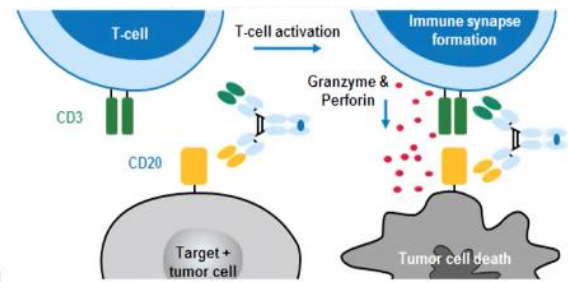


Impact of Recent Bendamustine

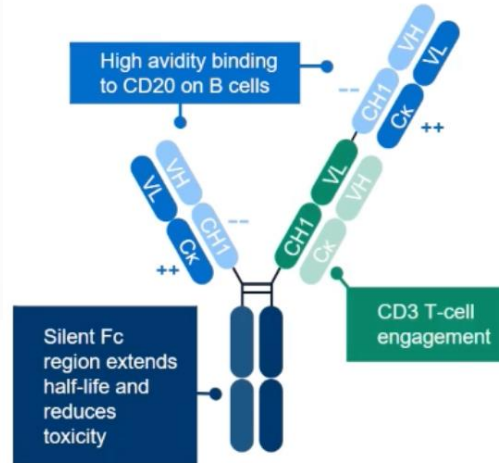


CD3/CD20 Bispecific Antibodies in B-NHL

Mosunetuzumab



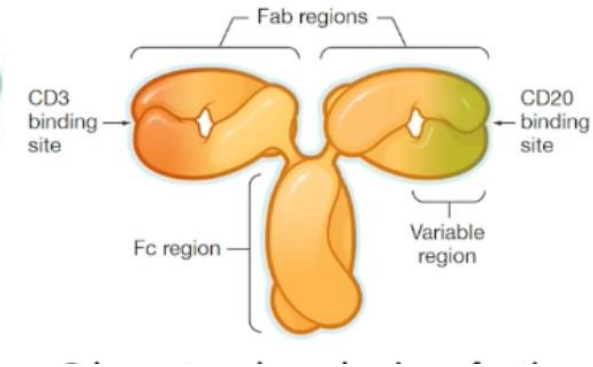
Glofitamab



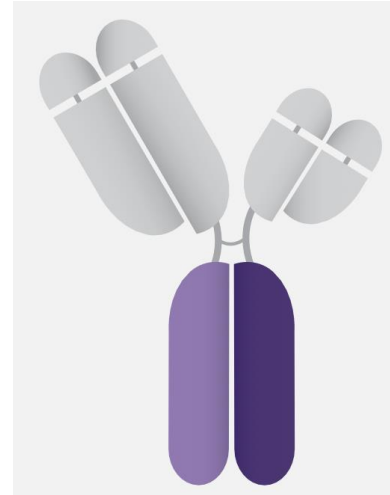
Epcoritamab



Odronextamab



Plamotamab

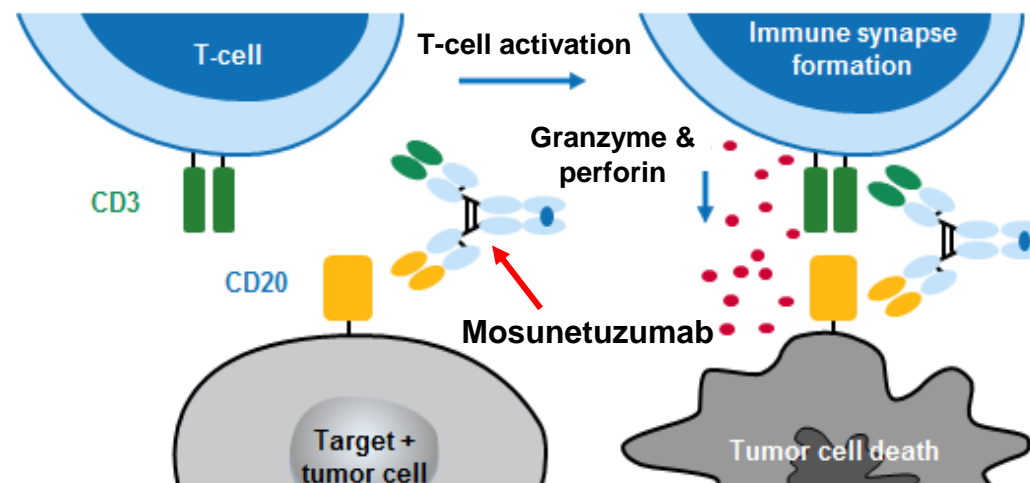


- "Off the shelf" therapy
- Route of administration: IV or SC
- Being explored as single-agents and combinatorial therapy in a multitude of B-cell NHL subtypes

Mosunetuzumab

- Mosunetuzumab (**first-in-class**) is approved in the EU and by the FDA, for the treatment of **relapsed/refractory follicular lymphoma (R/R FL)** after ≥ 2 prior systemic therapies^{1,2}
- **Off-the-shelf, fixed-duration** treatment that can be administered in the **outpatient** setting³

Mosunetuzumab: CD20xCD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells^{4,5}



FDA approved December 2022

1. Lunsumio SmPC: <https://www.ema.europa.eu/en/medicines/human/EPAR/lunsumio>;

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf 3. Budde LE, et al. Lancet Oncol 2022;23:1055–1065;

4. Sun LL, et al: Sci Transl Med 2015;7:287ra70; 5. Hernandez G, et al. ASH 2019; poster presentation (P-1585).

Study design

Pivotal, single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥ 2 prior therapies

Key inclusion criteria

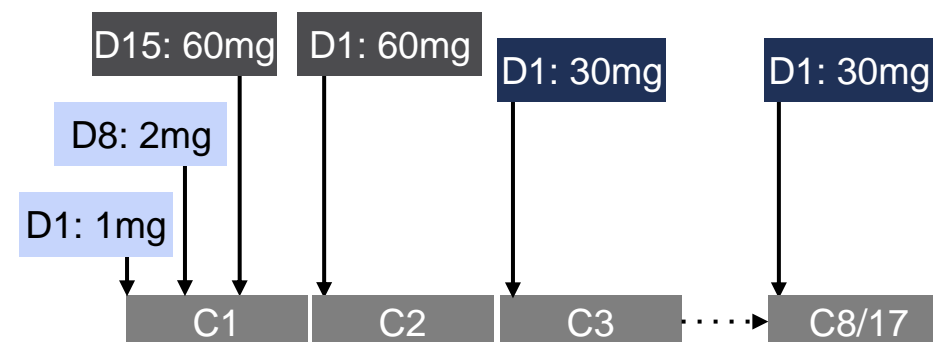
- FL Grade 1–3a
- ECOG PS 0–1
- ≥ 2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historical control ($p < 0.0001$)^{1,2}
- Updated efficacy and safety analysis with median 28.3 months of follow up (10 months after the previous report)

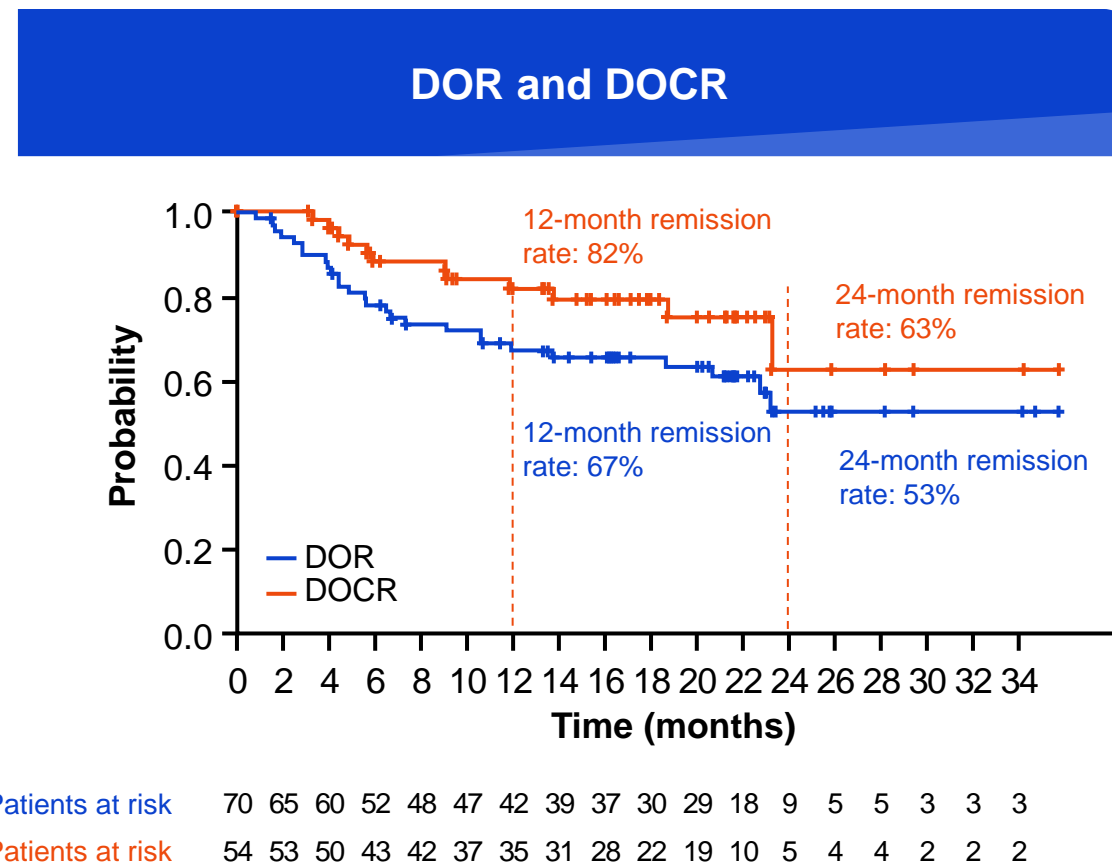
Mosunetuzumab administration

- 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



ORR 78%. CR 60%. Durability of responses

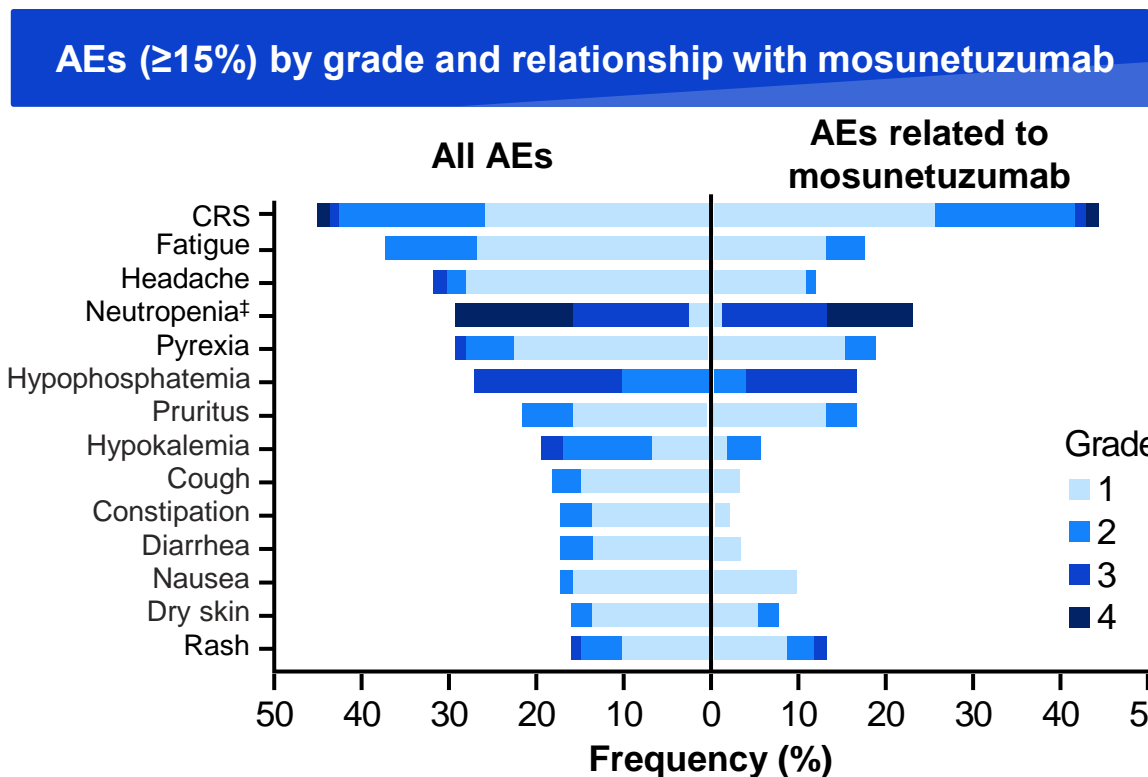
Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70 24-month DOR (95% CI)	NR (21–NR) 53% (38–68)
Median DOCR, months (range), n=54 24-month DOCR (95% CI)	NR (23–NR) 63% (38–88)
Median PFS, months (range) 24-month PFS (95% CI)	24 (12–NR) 48% (36–60)
Median TTNT, months (range) 24-month TTNT (95% CI)	NR (18–NR) 56% (45–67)
Median OS, months (range) 24-month OS (95% CI)	NR (NR–NR) 87% (80–94)



Durable responses: majority of patients in remission after 2 years

Safety profile

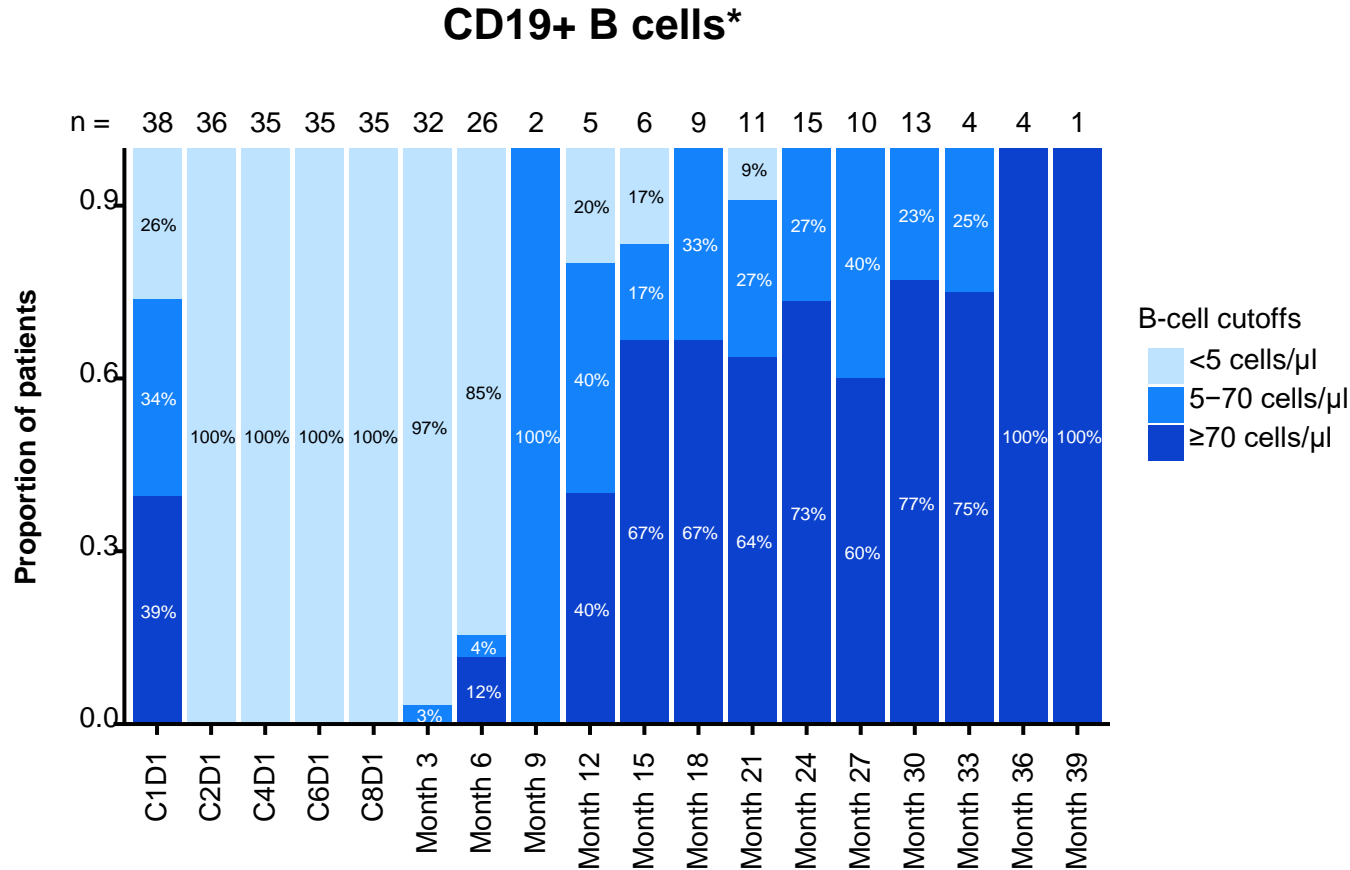
Adverse events (AEs)	N=90
AE	100%
Mosunetuzumab related	92%
Grade 3/4 AE	70%
Mosunetuzumab related	51%
Serious AE	47%
Mosunetuzumab related	33%
Grade 5 (fatal) AE	2%*
Mosunetuzumab related	0
AE leading to treatment discontinuation	4%†
Mosunetuzumab related	2%



No new serious AEs, Grade ≥3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up

*Malignant neoplasm progression (n=1) and unexplained death (n=1). †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Epstein-Barr viremia and Hodgkin's disease (1 patient each). ‡Grouped term including preferred term 'neutropenia' and 'neutrophil count decreased'.

B-cell depletion and recovery



- Peripheral blood B-cell depletion following treatment with mosunetuzumab occurred rapidly by the initiation of C2 dosing in all patients (n=74)
- Time-to-event analysis in patients with end-of-treatment (C8) and follow-up samples (n=38) was performed to assess B-cell recovery
 - Median time to recovery to quantitative levels was 18.4 months (95% CI: 12.8–25.0)
 - Median time to recover to the lower level of normal was 25.1 months (95% CI: 19.0–NE)

*CD19+ B cells were monitored by flow cytometry at C1, C2, C4, and C8, and every 3 months during follow-up or until progression or next lymphoma treatment. The lower limit of quantitation was 5 cells/μl and the lower limit of normal was 70 cells/μl. Depletion was analyzed in all patients with a pre-dose and at least one on-treatment sample. Recovery was analyzed in patients with a CR and at least one follow-up sample.

Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab: Primary Analysis of the Phase 2 Randomized ROSEWOOD Trial

Key Eligibility Criteria

- Adults with grade 1-3a FL
- R/R disease, previously treated with ≥ 2 systemic treatments including an anti-CD20 antibody and an appropriate alkylator-based combination therapy
- Measurable disease
- ECOG PS 0-2
- Adequate organ functions
- No prior BTK inhibitor

ClinicalTrials.gov: NCT03332017

Arm A
Zanubrutinib^a plus
obinutuzumab^b
N=145
Until PD/unacceptable toxicity

Randomization 2:1

Stratification factors

- Number of prior lines
- Rituximab refractory status
- Geographic region

Arm B
Obinutuzumab^b
N=72
Option to crossover to combination if PD centrally confirmed or no response at 12 months

Primary Endpoint

- ORR assessed by ICR according to Lugano classification¹

Select Secondary Endpoints

- ORR assessed by investigator
- DOR and PFS determined by ICR and investigator assessment
- Overall survival

- Patients were randomized between November 2017 and June 2021
- Median study follow-up: 20.2 months

1. Cheson et al. *J Clin Oncol* 2014;32(27):3059-68.

^aZanubrutinib was given orally at 160 mg twice a day; ^bObinutuzumab was given in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and then every 8 weeks up to 20 doses maximum.

BTK, Bruton tyrosine kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma;

ICR, independent central review; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R/R, relapsed or refractory; ~~SD, stable disease.~~

Disease Response by Independent Central Review (ICR)

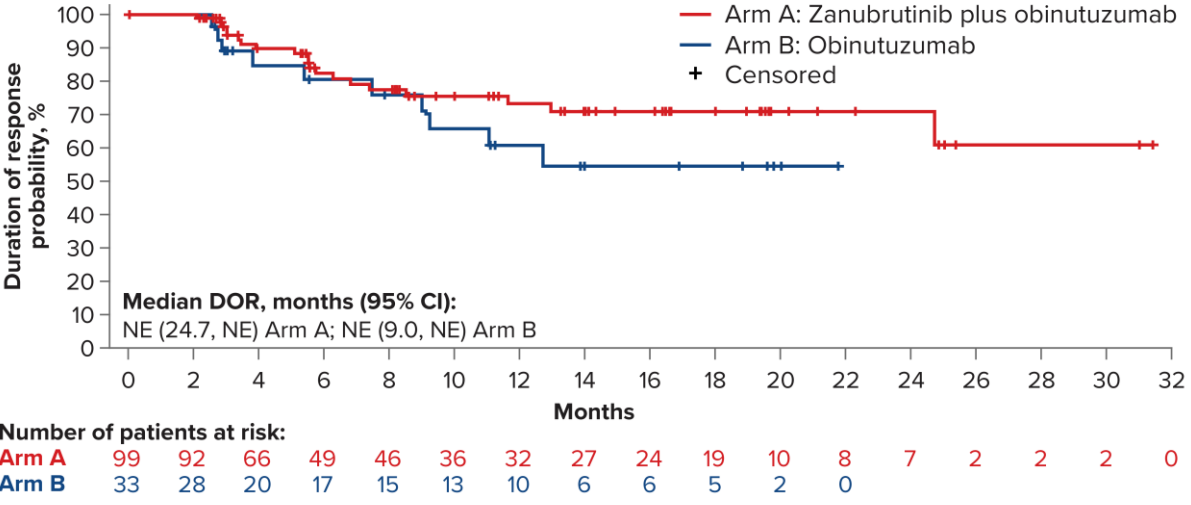
- The study met its primary endpoint
 - ORR per ICR was **68.3%** with zanubrutinib plus obinutuzumab vs **45.8%** with obinutuzumab

Response rate	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 <i>P</i> value	0.0017	
Best Response, 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 assessment	4 (2.8)	6 (8.3)
NE	1 (0.7)	0 (0.0)
CR rate, % (95% CI)	37.2 (29.4, 45.7)	19.4 (11.1, 30.5)
2-sided <i>P</i> value	0.0083	

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

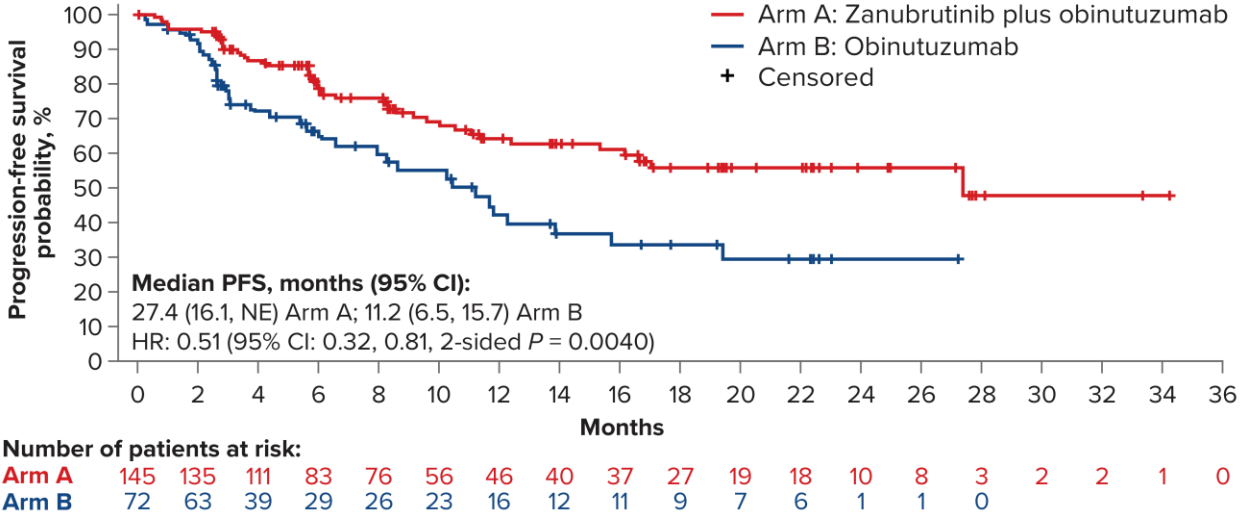
Duration of Response and Progression-Free Survival by ICR

Duration of Response



- The 18-month DOR rate was **70.9%** in the zanubrutinib plus obinutuzumab arm vs **54.6%** in the obinutuzumab arm

Progression-free survival



- Zanubrutinib plus obinutuzumab was associated with a **49%** reduction of risk of progression or death compared with obinutuzumab

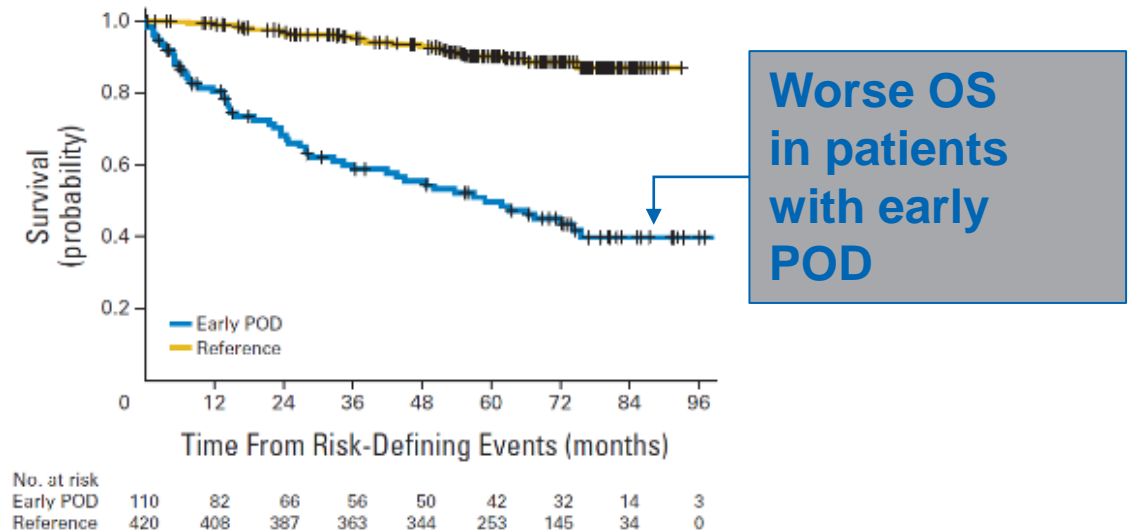
DOR, duration of response; ICR, independent central review; NE, not evaluable; PFS, progression-free survival.

CONCLUSIONS

- The ROSEWOOD (BGB-3111-212) trial met its primary endpoint, ORR was 68.3% with zanubrutinib plus obinutuzumab vs 45.8% with obinutuzumab ($P = 0.0017$)
- Median PFS was 27.4 months in the zanubrutinib plus obinutuzumab arm vs 11.2 months in the obinutuzumab arm (HR: 0.51 [95% CI: 0.32, 0.81], $P = 0.0040$)
- The safety profile of the zanubrutinib plus obinutuzumab arm was generally comparable to the obinutuzumab arm, with no unexpected safety findings
- Zanubrutinib plus obinutuzumab received accelerated FDA approval in March 2024
- Note: Treatment is prolonged. Obinutuzumab for 2.5 years. Zanubrutinib until PD.

POD 24: Important Considerations

- Early progression of disease (≤ 2 years) after frontline chemoimmunotherapy (POD24) occurs in approximately 20% of patients
 - Associated with a poor prognosis and represents an unmet medical need in FL³
 - Represents a population requiring novel intervention with novel agents



- Biopsy recommended to detect histologic transformation of FL, which is reported to occur at a rate of 2% per year¹
 - Treated as DLBCL²

Autologous SCT in early progressor FL

- Retrospective analysis NLCS/CIBMTR
- 349 early progressors on rituximab-based ICT (2 years)
- Matched, half received auto-SCT, half did not
- 5-year OS 60 and 67% ($p = 0.16$)

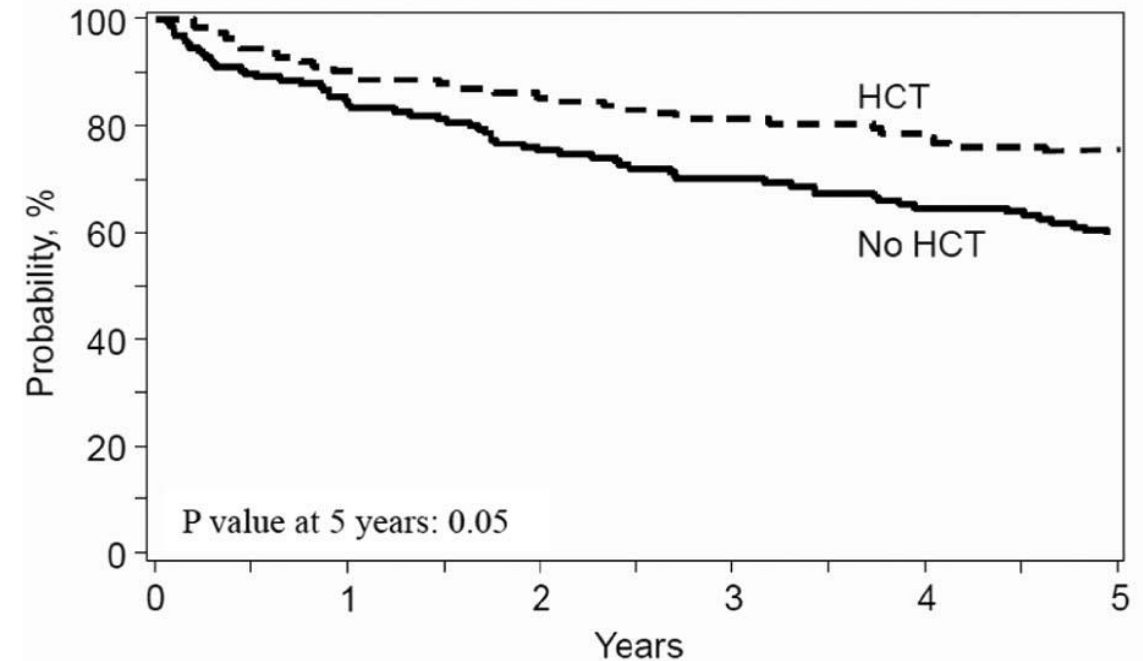
Improved OS when receiving auto-SCT within 1 year of treatment failure

5 yr OS with auto-HCT 73%

5 yr OS without auto-HCT 60%

$P=0.05$

Overall Survival of Patients Receiving HCT Within 1 year of Therapy Failure Compared to no HCT (n = 123)

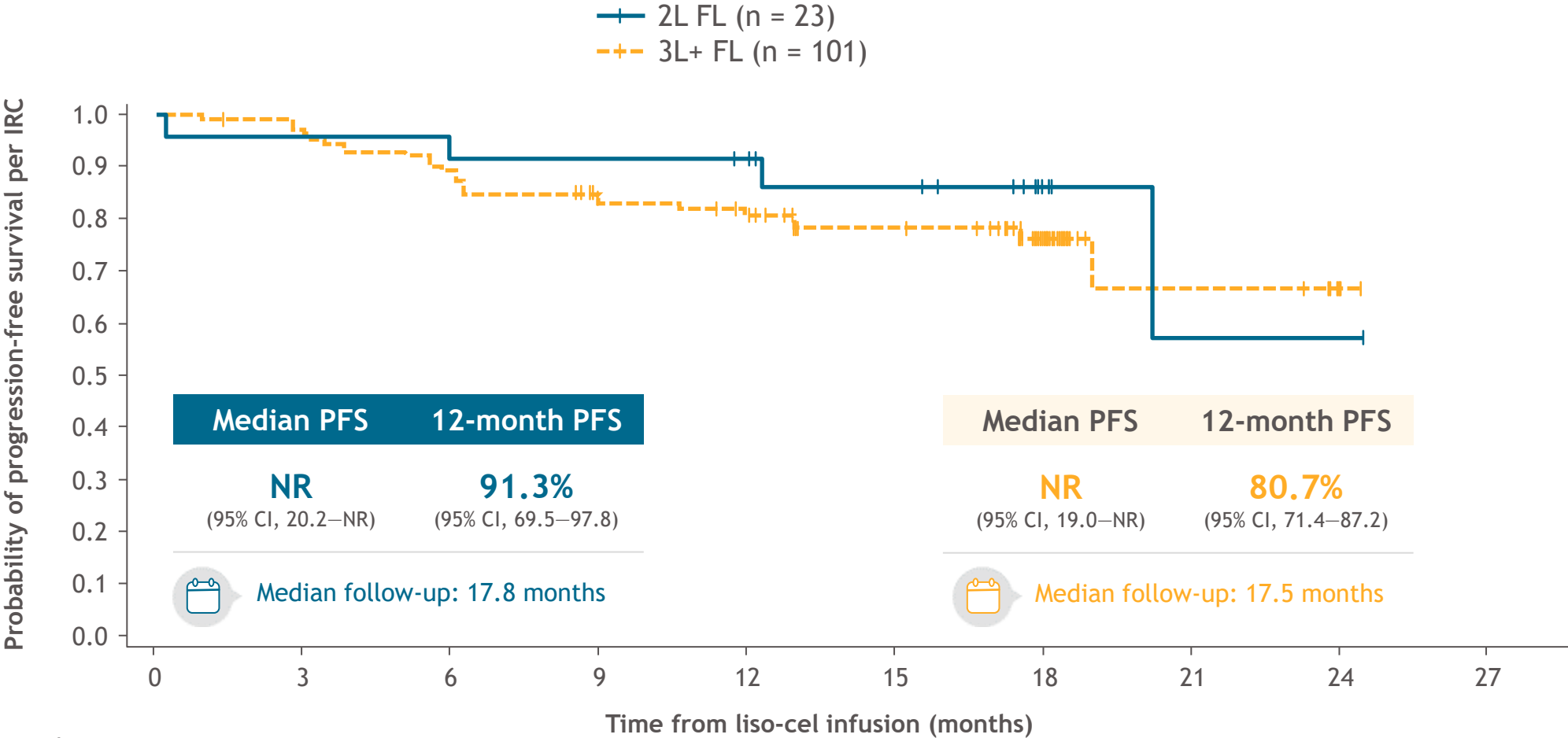


TRANSCEND FL: Phase 2 Study Primary Analysis of Lisocabtagene Maraleucel as Second-Line Therapy in Patients with High-risk Relapsed or Refractory Follicular Lymphoma

Franck Morschhauser,¹ Saurabh Dahiya,² M. Lia Palomba,³ Alejandro Martin Garcia-Sancho,⁴ Juan Luis Reguera Ortega,⁵ John Kuruvilla,⁶ Ulrich Jäger,⁷ Guillaume Cartron,⁸ Koji Izutsu,⁹ Martin Dreyling,¹⁰ Brad Kahl,¹¹ Hervé Ghesquieres,¹² Kirit Ardeshta,¹³ Hideki Goto,¹⁴ Anna Maria Barbui,¹⁵ Jeremy S. Abramson,¹⁶ Peter Borchmann,¹⁷ Isabelle Fleury,¹⁸ Stephan Mielke,¹⁹ Alan Skarbnik,²⁰ Sven de Vos,²¹ Manali Kamdar,²² Reem Karmali,²³ Andreas Viardot,²⁴ Thalia Farazi,²⁵ Omotayo Fasan,²⁶ James Lymp,²⁷ Min Vedal,²⁷ Rina Nishii,²⁶ Ariel Avilion,²⁷ Jessica Papuga,²⁸ Loretta J. Nastoupil²⁹

¹Centre Hospitalier Universitaire de Lille, Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; ²Stanford University School of Medicine, Stanford, CA, and University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; ³Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁴Hospital Universitario de Salamanca, IBSAL, CIBERONC, Universidad de Salamanca, Salamanca, Spain; ⁵Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS)/CSIC, Universidad de Sevilla, Seville, Spain; ⁶Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁷Medical University of Vienna, Vienna, Austria; ⁸Montpellier University Hospital Center, Montpellier, France; ⁹National Cancer Center Hospital, Tokyo, Japan; ¹⁰Medizinische Klinik III, Klinikum der Universität, LMU München, München, Germany; ¹¹Washington University School of Medicine in St. Louis, St. Louis, MO, USA; ¹²Hôpital Lyon Sud, Lyon, France; ¹³University College London Hospitals NHS Trust, London, UK; ¹⁴Hokkaido University Hospital, Sapporo, Japan; ¹⁵Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; ¹⁶Massachusetts General Hospital Cancer Center, Boston, MA, USA; ¹⁷Universität zu Köln, Köln, Germany; ¹⁸Hôpital Maisonneuve – Rosemont, Montreal, QC, Canada; ¹⁹Karolinska Institutet and University Hospital, Karolinska Comprehensive Cancer Center, Stockholm, Sweden; ²⁰Novant Health Cancer Institute, Charlotte, NC, USA; ²¹UCLA Santa Monica Medical Centre, Santa Monica, CA, USA; ²²University of Colorado Cancer Center, Aurora, CO, USA; ²³Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ²⁴University Hospital, Ulm, Germany; ²⁵Bristol Myers Squibb, Brisbane, CA, USA; ²⁶Bristol Myers Squibb, Princeton, NJ, USA; ²⁷Bristol Myers Squibb, Seattle, WA, USA; ²⁸Bristol Myers Squibb, Boudry, Switzerland; ²⁹The University of Texas MD Anderson Cancer Center, Houston, TX, USA

TRANSCEND: Progression-free survival per IRC in efficacy set



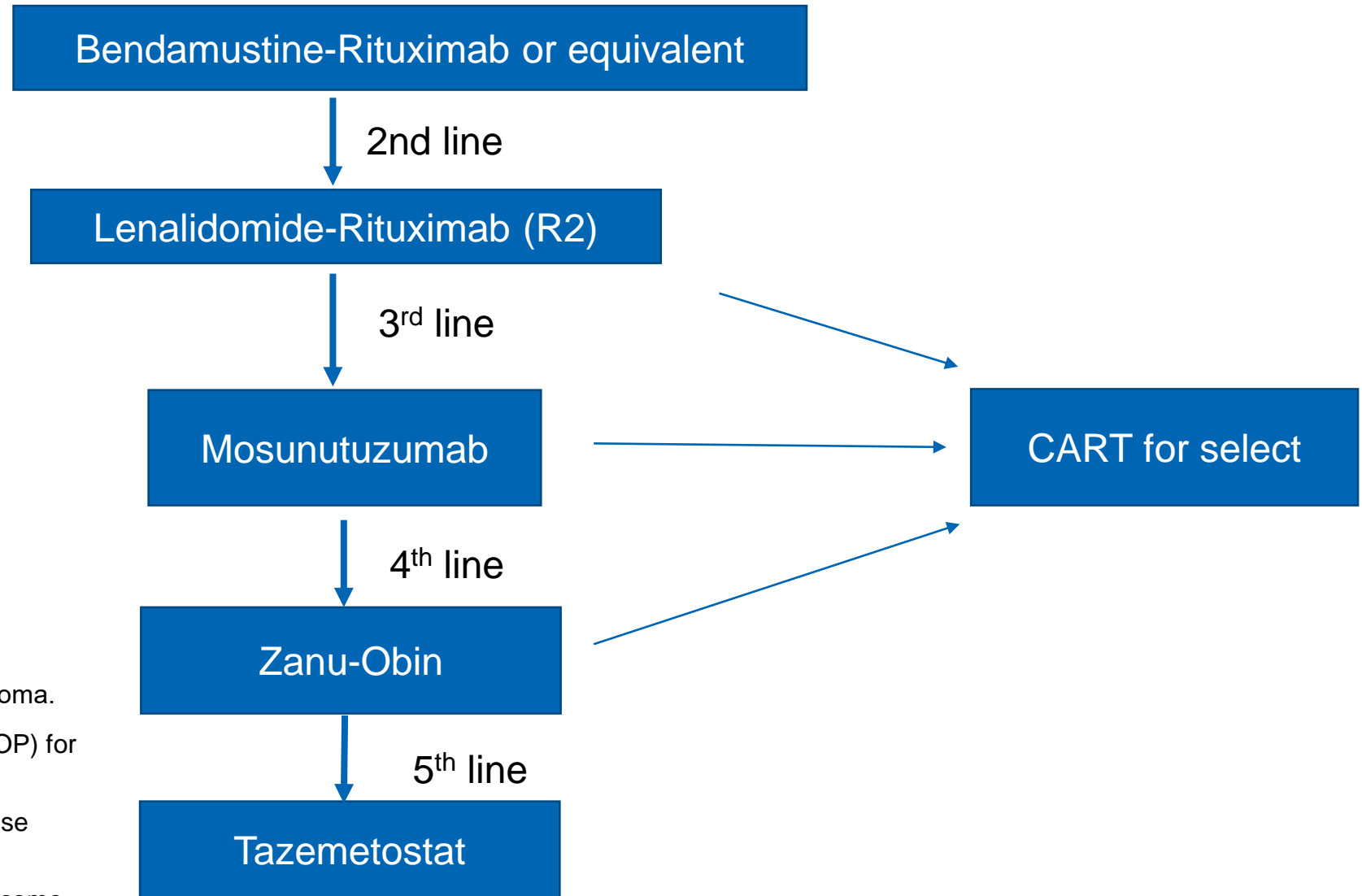
No. at risk (censored)

2L FL	23 (0)	22 (0)	21 (0)	21 (0)	20 (1)	16 (3)	5 (11)	2 (2)	2 (0)	0 (2)
3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)

Efficacy data for approved agents

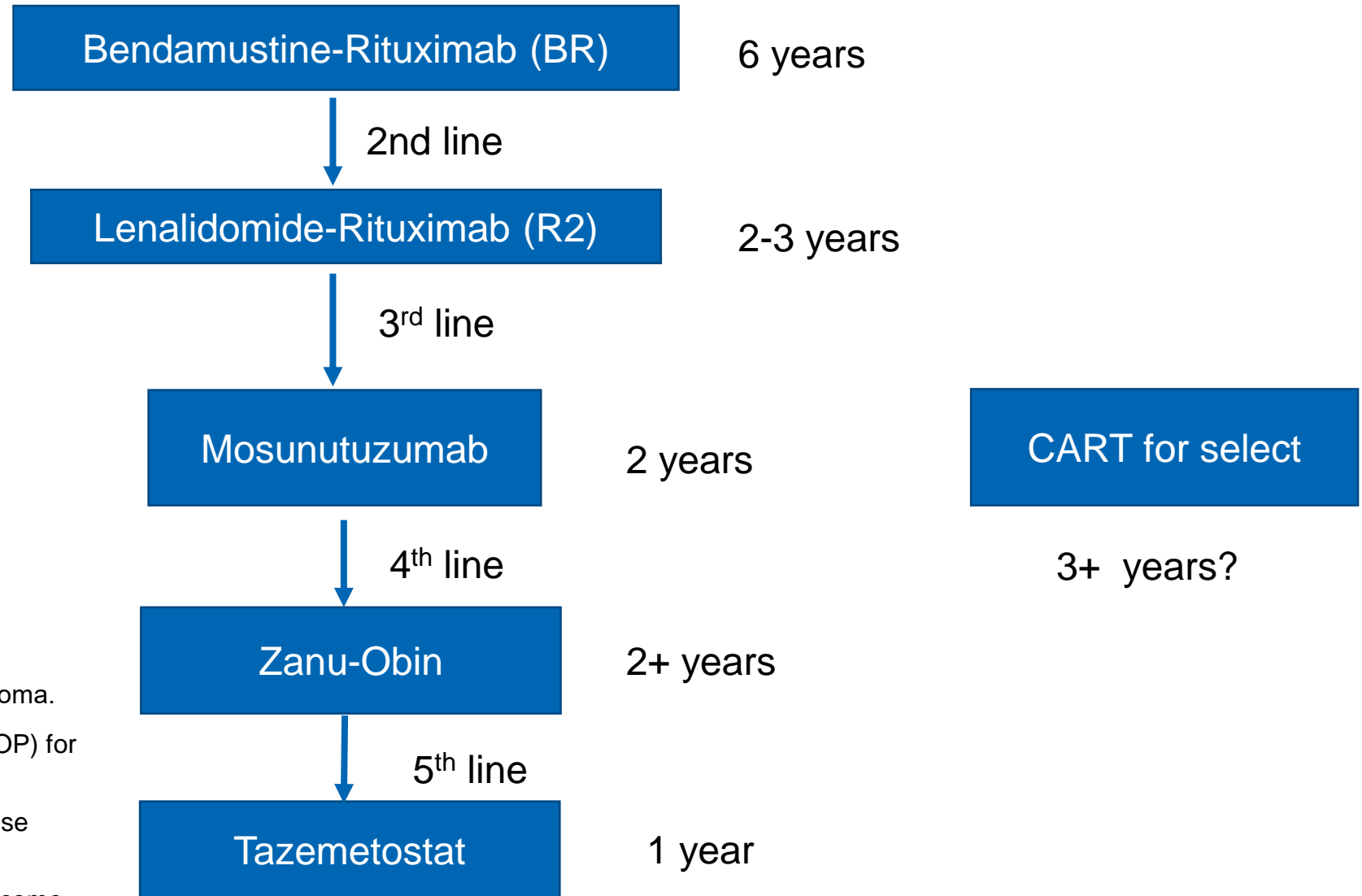
Regimen	MOA/Target	N	ORR	CR	mPFS
Lenalidomide-Rituximab	IMiD	147	78%	34%	25-39 months
Rituximab	antiCD20 MoAb	148	53%	18%	14 months
Tazemetostat (mutated)	EZH2 inhibitor	45	69%	13%	14 months
Tazemetostat (wild type)	EZH2 inhibitor	54	35%	4%	11 months
Axi-Cel	antiCD19 CAR-T	127	94%	80%	40 months
Tisa-Cel	antiCD19 CAR-T	94	86%	69%	?
Mosunutuzumab	Bi-specific MoAb	90	78%	60%	24 months
Zanubrutinib-Obin	BTK inhibitor	143	69%	39%	28 months

An approach to the Management of High Tumor Burden FL in 2024



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Follicular Lymphoma in Relapse: Conclusions

- Many effective disease management strategies
 - Recycling older, established therapies
 - Several newer strategies emerging
- Bi-specific MoAbs getting lots of attention currently
 - Several combination studies underway
- Optimal sequence unclear, requires some individualization
- Optimal management of POD24 population TBD



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