March 18th 2023

T. Howard Lee Keynote Lecture:
20 Years of Indy Hematology Review and The Cure is in:

Managing Indolent and Mantle Cell Lymphomas with Targeted and Cellular Therapies in 2023

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Conflicts of interest (Nov 2022)

Gilles Salles has received in the last 24 months financial compensations for participating to advisory boards or consulting from :

Consulting fees: *Abbvie, Atbtherapeutics, Beigene, BMS/Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Milteniy, Molecular Partners, Morphosys, Nordic Nanovector, Novartis, Rapt, Takeda*

Honoraria: *Abbvie, Bayer, Incyte, Janssen, Kite/Gilead, Morphosys, Novartis, Regeneron,*

Shareholder: Owkin

Memorial Sloan Kettering Cancer Center

1. New Options for the Management of Patients with Follicular Lymphoma

2. New Agents for Marginal Zone Lymphoma

3. Paradigm Shifts in Mantle Cell Lymphoma

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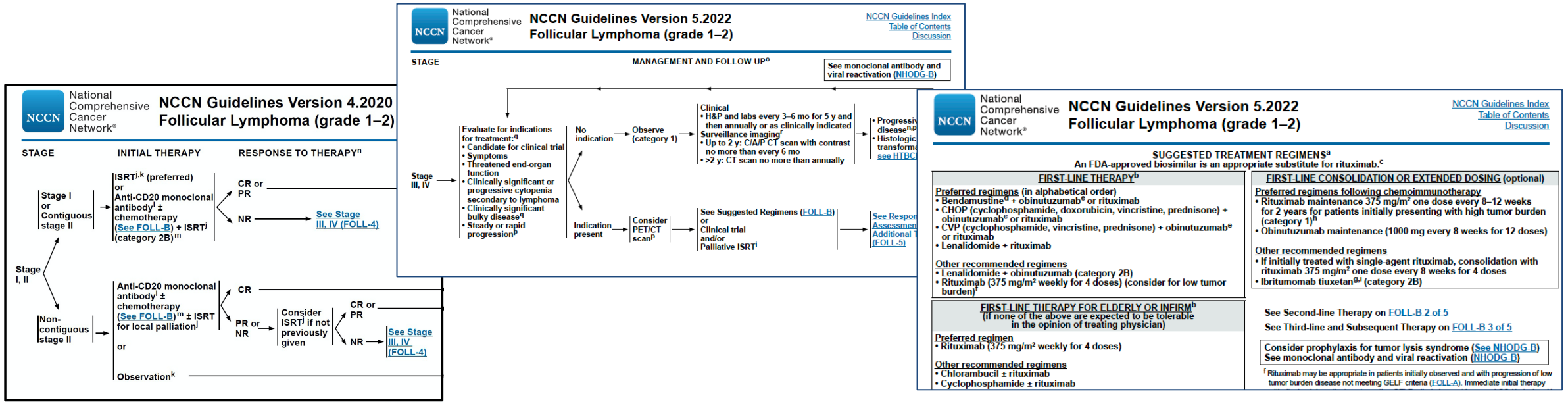
Follicular Lymphoma: First line of therapy

First line management of FL patients in 2023

1) In patients with localized disease
   radiation therapy, anti-CD20 (+/-chemo), observation,…
2) In patients with low tumor burden and/or asymptomatic disease
   observation
1) For other patients with high tumor burden in need of systemic treatment
   anti-CD20+chemo, anti-CD20+lenalidomide, anti-CD20, +/- maintenance



R-chemo + R-maintenance (PRIMA): 10-year updated results

10-year PFS estimates

Observation 35%

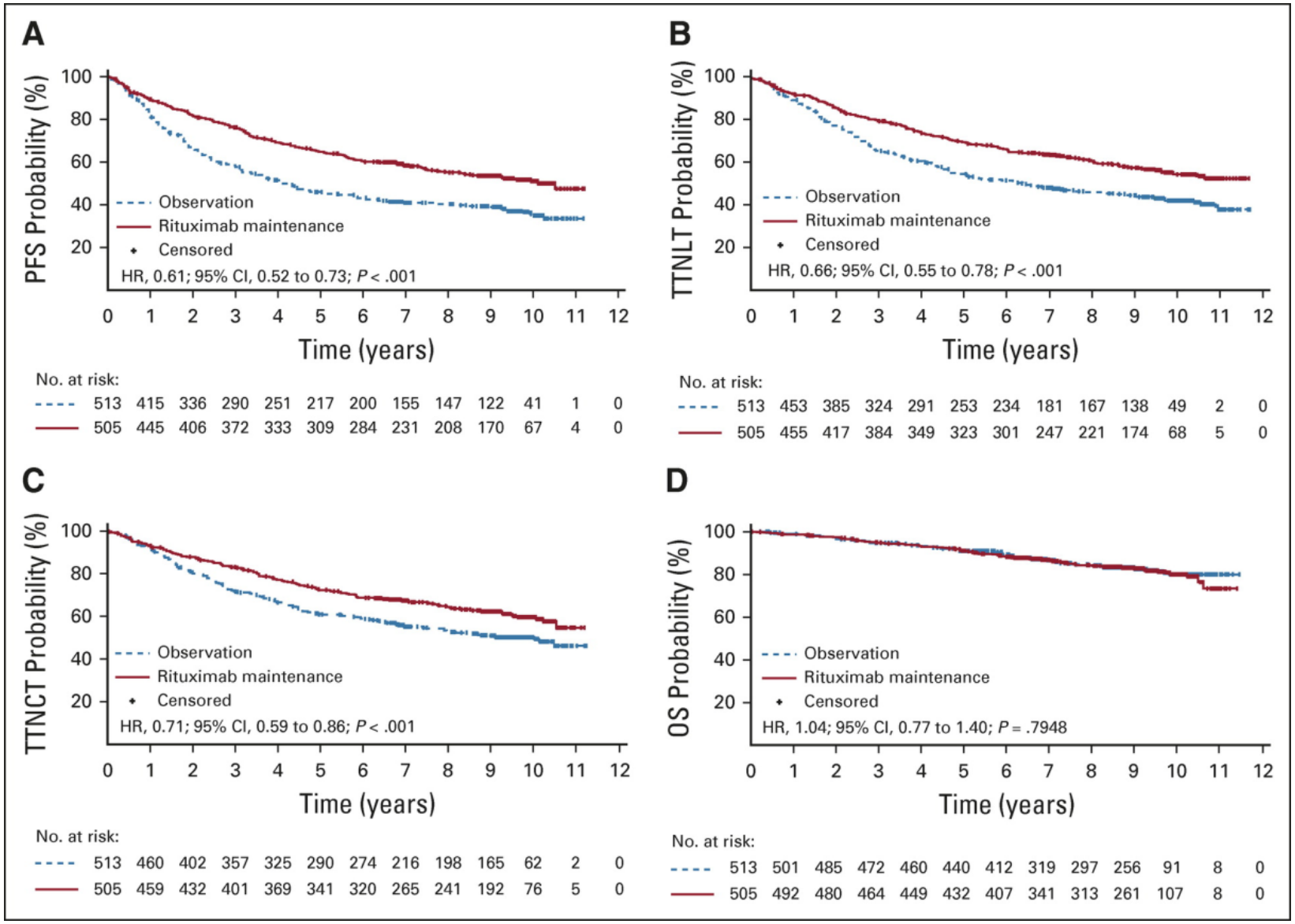
R Maintenance 51%

Median time to new treatment initiation

Observation 6.1 y

R Maintenance > 10 y (not reached)

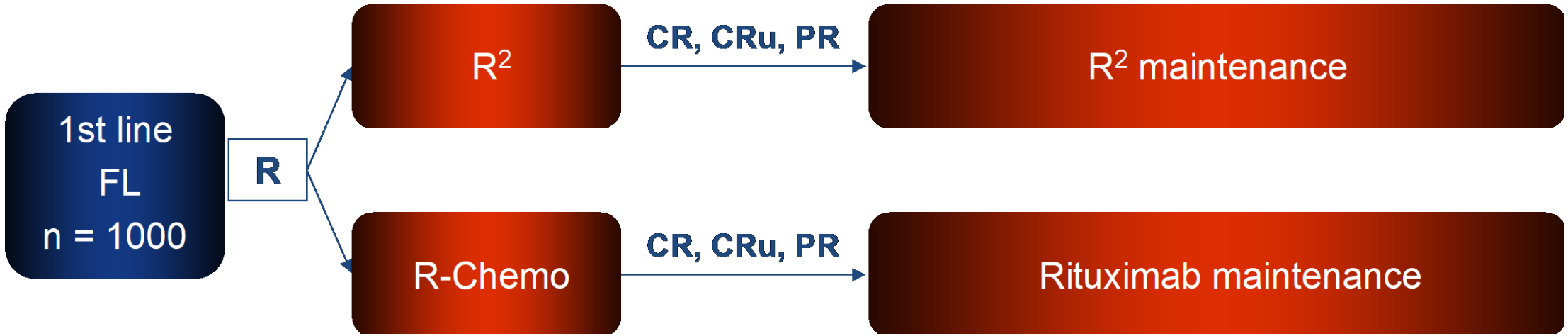
DRIVE RANK SCORE: Unkown



Bachy et al. JCO 2019

RELEVANCE : phase 3 study design

(Rituximab and LEnalidomide Versus ANy ChEmotherapy, FL-001)



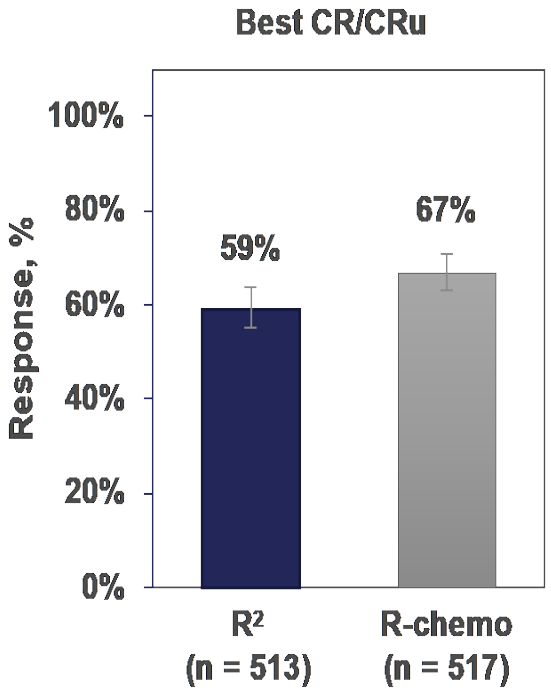
- R-Chemo
  - ➢ investigator choice of R-CHOP, R-CVP, R-Benda
- Lenalidomide
  - ➢ 20 mg x 6 cycles, if CR then 10 mg every 12 months

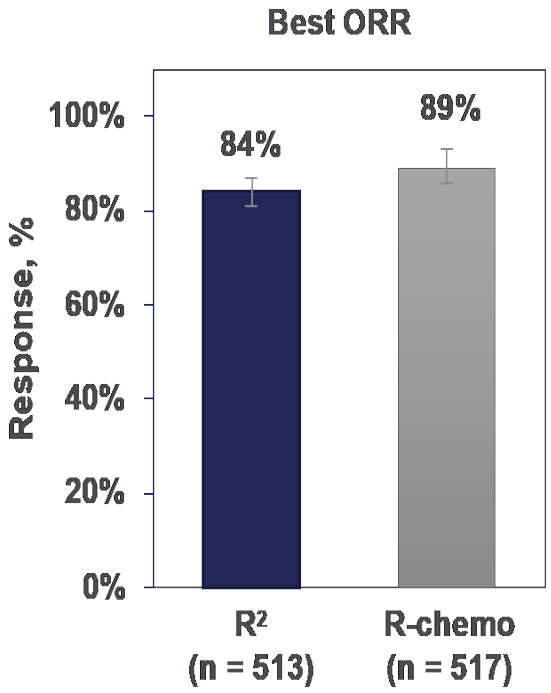
- Co-primary endpoints
  - ➢ CR/CRu rate at 2.5 years
  - ➢ PFS

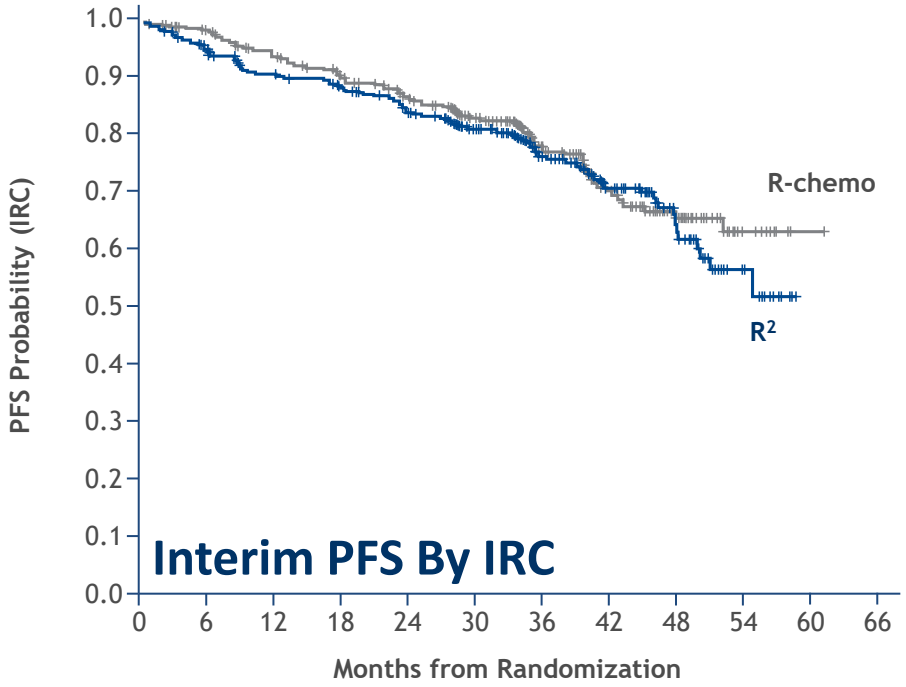
DRIVE RANK SCORE: Unkown

Morschhauser F et al, NEJM 2018

RELEVANCE (R2 versus R-chemo): initial results





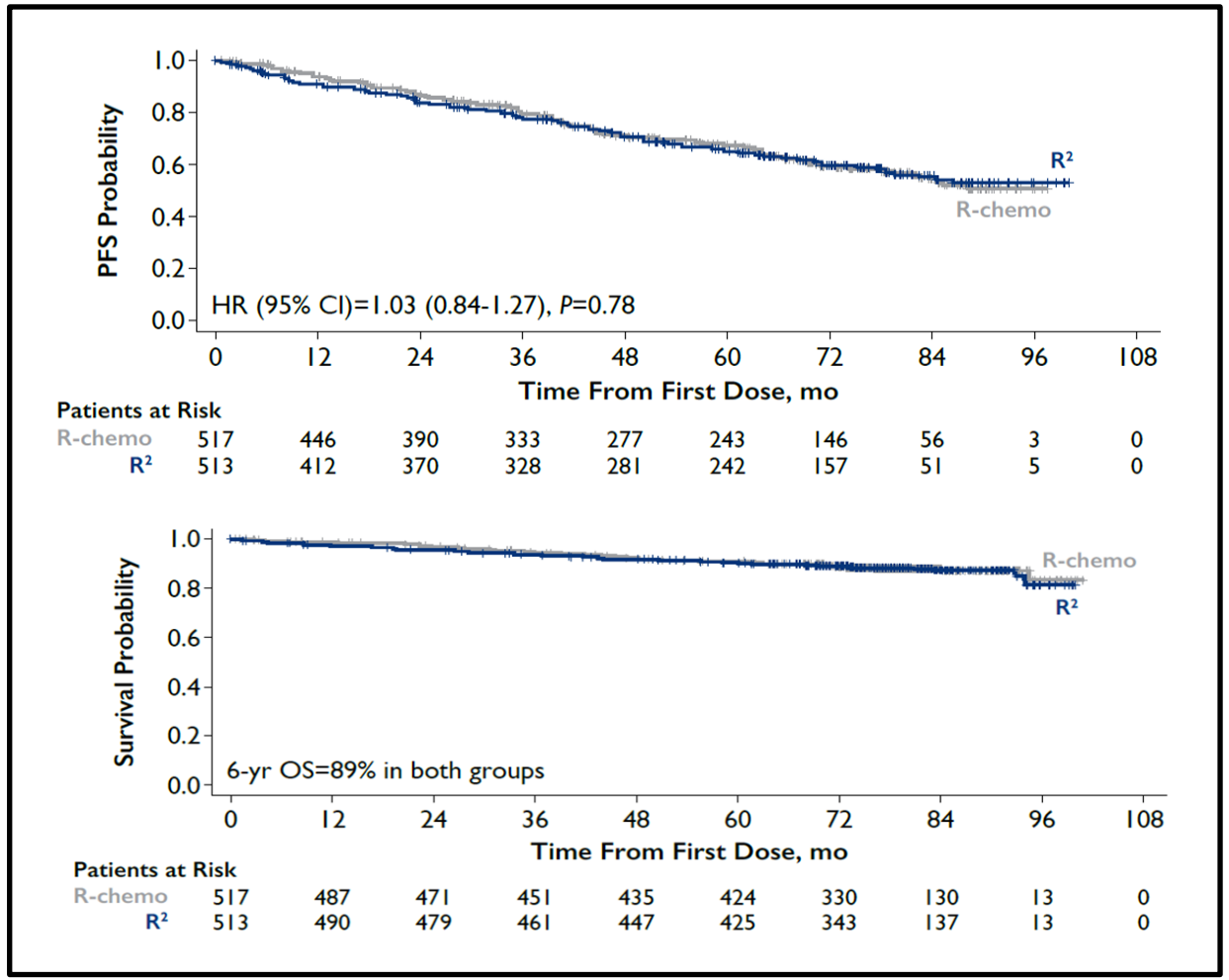


Number of Patients at Risk

R²	513	435	409	393	364	282	174	107	49	13	0	
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

Morschhauser F et al, NEJM 2018

RELEVANCE (R2 versus R-chemo): 6-year update



Gr 3-4 neutropenia and febrile neutropenia
- more frequent with R-chemo

Gr 3-4 Cutaneous reactions
- More frequent with R-Len

One of the "preferred options" in NCCN guidelines

Morschhauser F et al, JCO 2022

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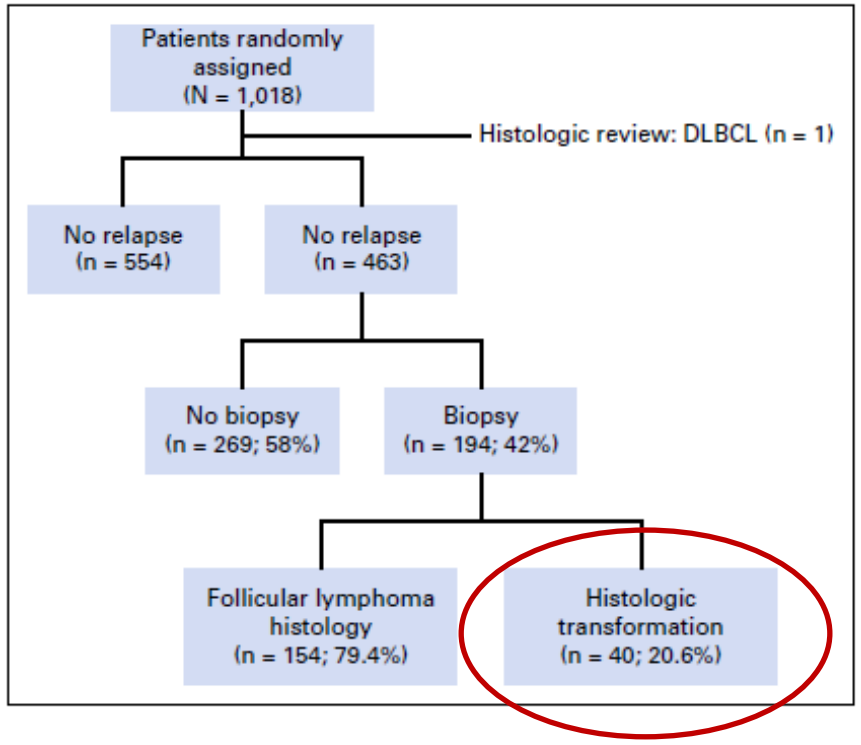
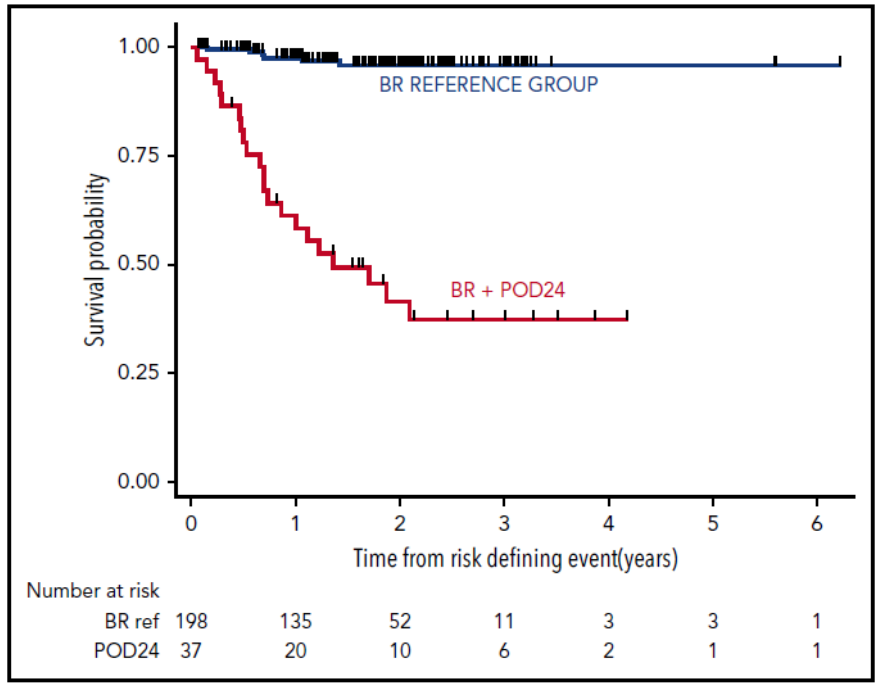
Follicular Lymphoma: Relapsed/Refractory Disease

POD24 patients have a worse outcome
-- > Biopsy is critical at time of progression



But 37% of progressions observed during the first year after EOI



BCA: 75% of early progressing patients after BR had transformed disease

But only ~ 19% of POD24 in Gallium

Sarkozy. *J Clin Oncol.* 2016;34(22):2575-2582; Freeman. *Blood.* 2019;134(9):761-764 ; Seymour JF, *Haematologica* 2019 Jun;104(6):1202-1208

Is there a standard in patients with R/R disease?

Figure 1: **Sankey plot of treatment patterns across lines of therapy**
CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone. CVP=cyclophosphamide, vincristine, and prednisolone.

After a median follow-up of 71 months from index therapy, 5-year overall survival was:

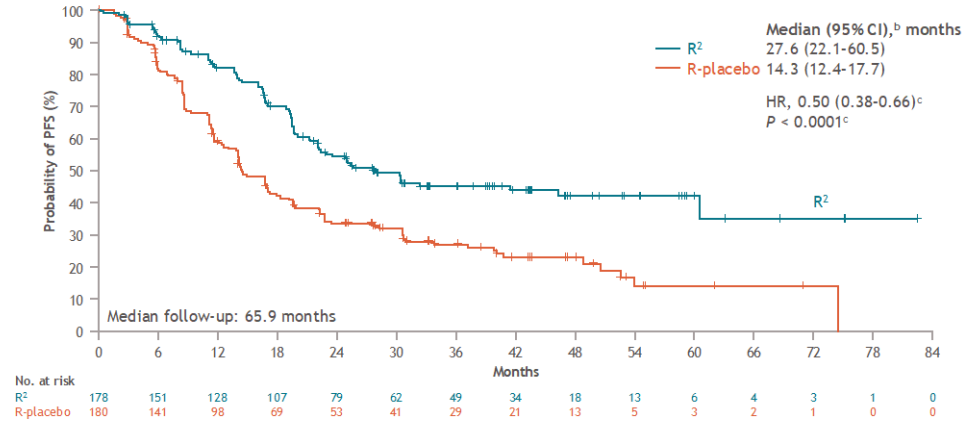
- 75% (95% CI 70-79)

Casulo C, et al. Lancet Haematol. 2022 Apr;9(4):e289-e300.

Five-year results and overall survival update from the phase 3 randomized study AUGMENT: lenalidomide plus rituximab versus rituximab plus placebo in patients with relapsed/refractory indolent non-Hodgkin lymphoma

Leonard J et al. ASH 2022

Progression-free survival[a] (ITT population)



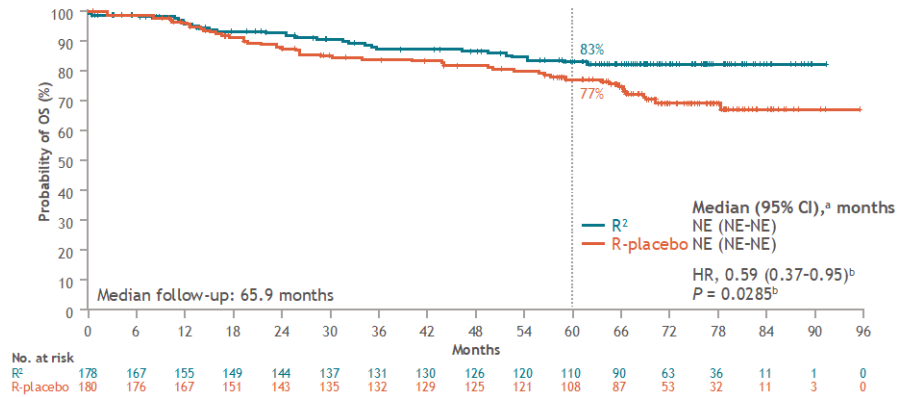
- Median PFS was 27.6 months for R² versus 14.3 months for R-placebo (HR, 0.50; *P* < 0.0001)

Treatment-emergent adverse events (safety population)

Patients with TEAE, n (%)	R² (n = 176)	R-placebo (n = 180)
Any-grade TEAE	174 (99)	173 (96)
Any-grade TEAE related to lenalidomide or placebo	159 (90)	118 (66)
Any-grade TEAE related to rituximab	134 (76)	105 (58)
Grade 3/4 TEAE[a]	121 (69)	58 (32)
Grade 3/4 TEAE related to lenalidomide or placebo	101 (57)	38 (21)
Grade 3/4 TEAE related to rituximab	57 (32)	20 (11)
Grade 5 TEAE[a,b]	2 (1)	2 (1)
Serious any-grade TEAE	45 (26)	25 (14)
Any-grade TEAE related to lenalidomide or placebo	23 (13)	8 (4)
Any-grade TEAE related to rituximab	13 (7)	4 (2)

- Grade 3/4 TEAEs were more common in patients who received R² versus R-placebo (69% vs 32%); the most common was neutropenia (R², 50%; R-placebo, 13%)

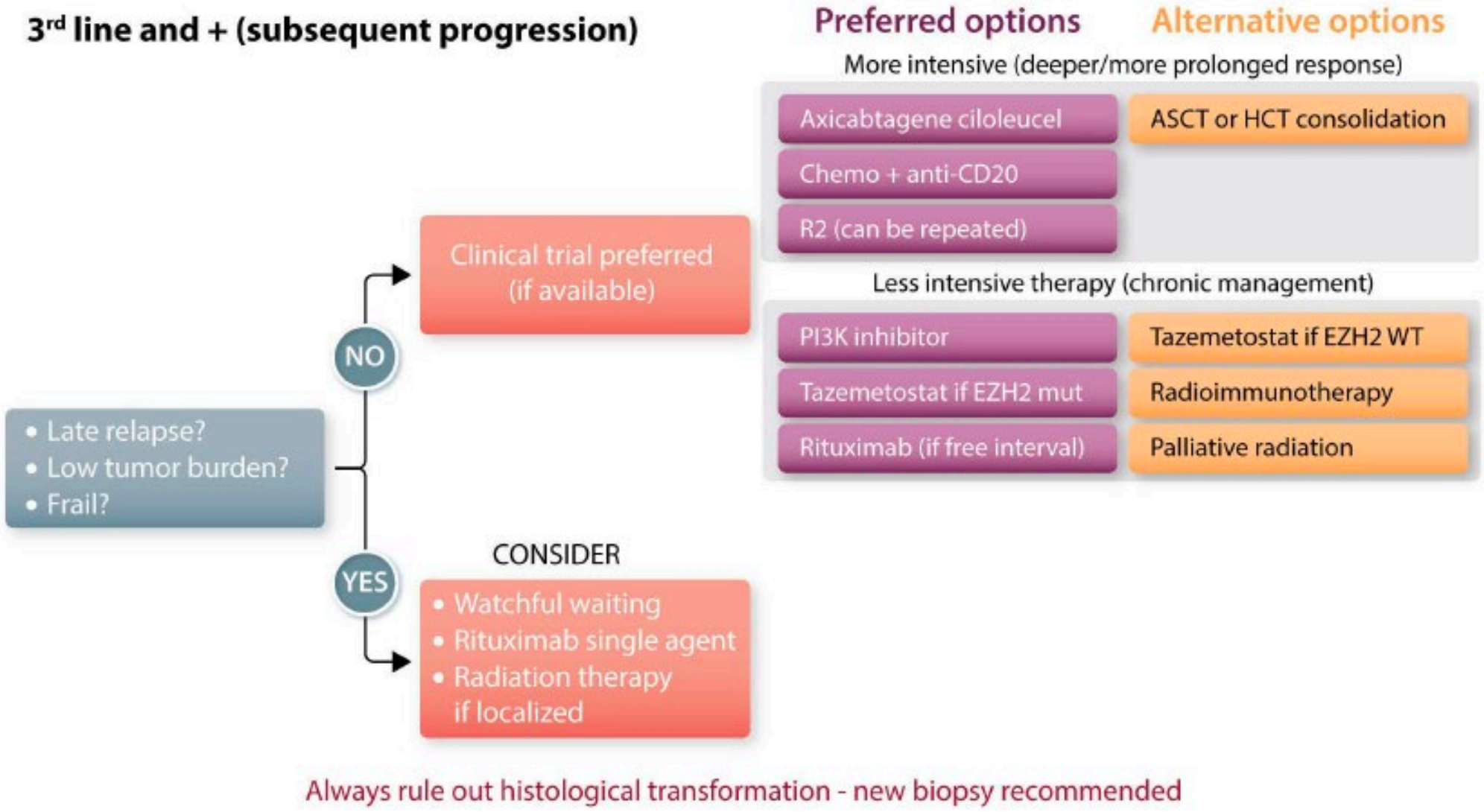
Overall survival (ITT population)



- Although median OS was not reached for either arm, there was an improvement in OS with R² compared with R-placebo (HR, 0.59; *P* = 0.0285)
  - 5-year OS rates for R² versus R-placebo were 83.2% and 77.3%, respectively

DRIVE RANK SCORE: Unkown

Options at later lines (3+)



Qualls D & Salles G, Haematologica 2022

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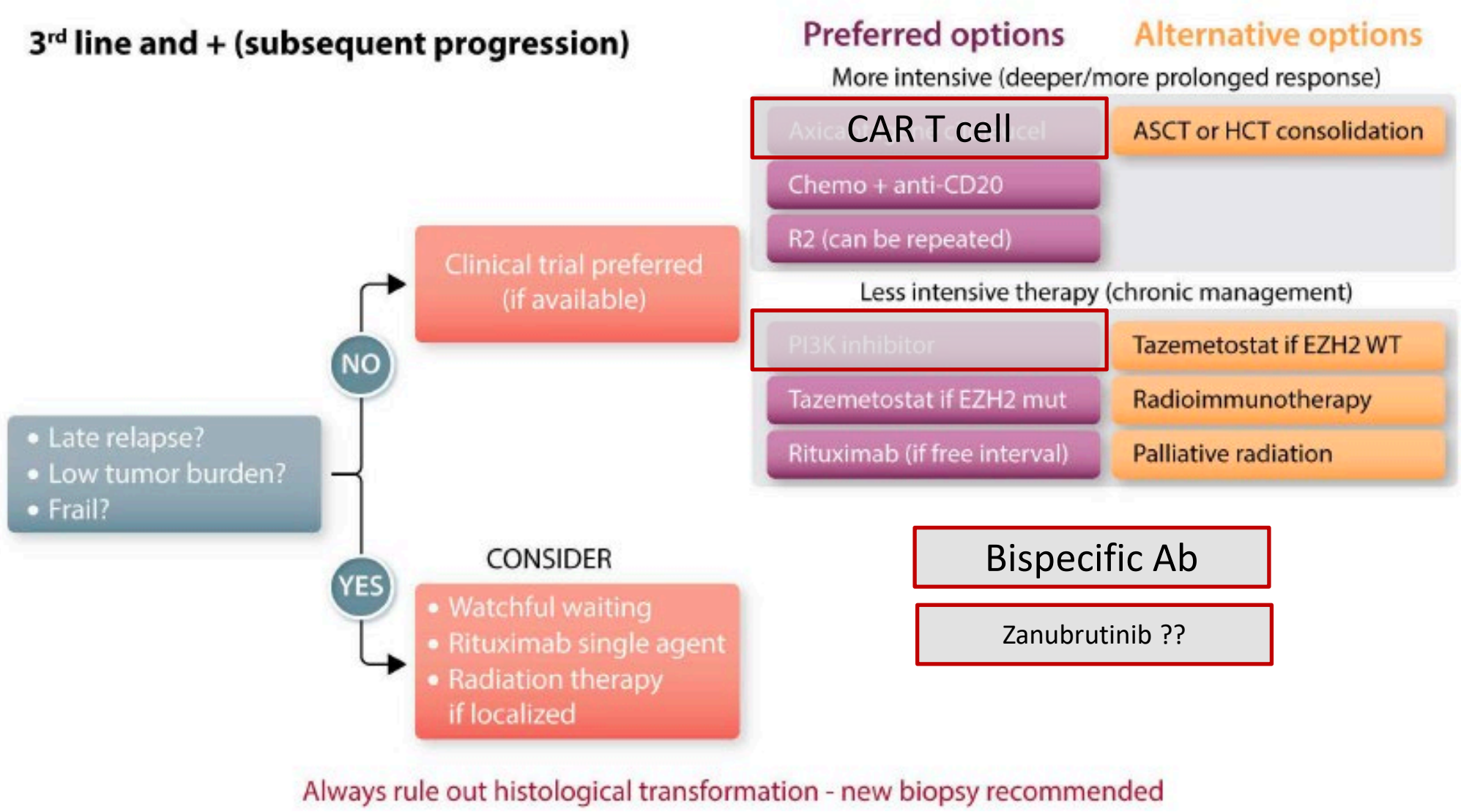

Qualls D & Salles G, Haematologica 2022

Activity of different PI3K inhibitors in patients with follicular lymphoma

Compound	Patient characteristics	No. of pts (FL/total)	ORR	CR	PFS in months (median)	DOR in months (median)	Time on drug in months (median)	Most frequent grade 3-4 AE (5% or more of the pts)*
Idelalisib[1] (oral; δ specific)	Double refractory	72/125	56	**14%**	**11**	11	**7**	Neutropenia (27%); transaminitis (13%); diarrhea (13%); pneumonia (7%); thrombocytopenia (6%)
Duvelisib[2] (oral; γ δ specific)	Double refractory	83/129	42%	**1%**	**10***	10*	**7***	Neutropenia (25%); diarrhea (15%); anemia (15%); thrombocytopenia (12%); febrile neutropenia (9%); lipase increased (7%); transaminitis (5%); pneumonia (5%); colitis (5%)
Copanlisib[3] (IV; α δ specific)	Relapsed or refractory (80%)	104/142	59%	**20%**	**13***	14*	**6***	Hyperglycemia (40%); hypertension (24%); neutropenia (24%); pneumonia (11%); diarrhea (9%); anemia (5%); thrombocytopenia (5%)
Umbralisib [4] (oral, δ and CK1ε specific)	Relapsed (32% rituximab refractory)	117/208	45%	**5%**	**11**	11	**8**	Neutropenia (12%); diarrhea (10%); transaminitis (20%); opportunistic infections (3%); rash (2%)

*Patients with follicular and other iNHL.

1. Salles G, et al. *Haematologica.* 2017;102(4):e156-e159; 2. Flinn I, et al. *J Clin Oncol.* 2019;37(11):912-922; 3. Dreyling, M, et al. *Am J Hematol.* 2020;95:362-371; 4. Fowler NH, et al. *J Clin Oncol.* 2021. Epub ahead of print.

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WITHDRAWN

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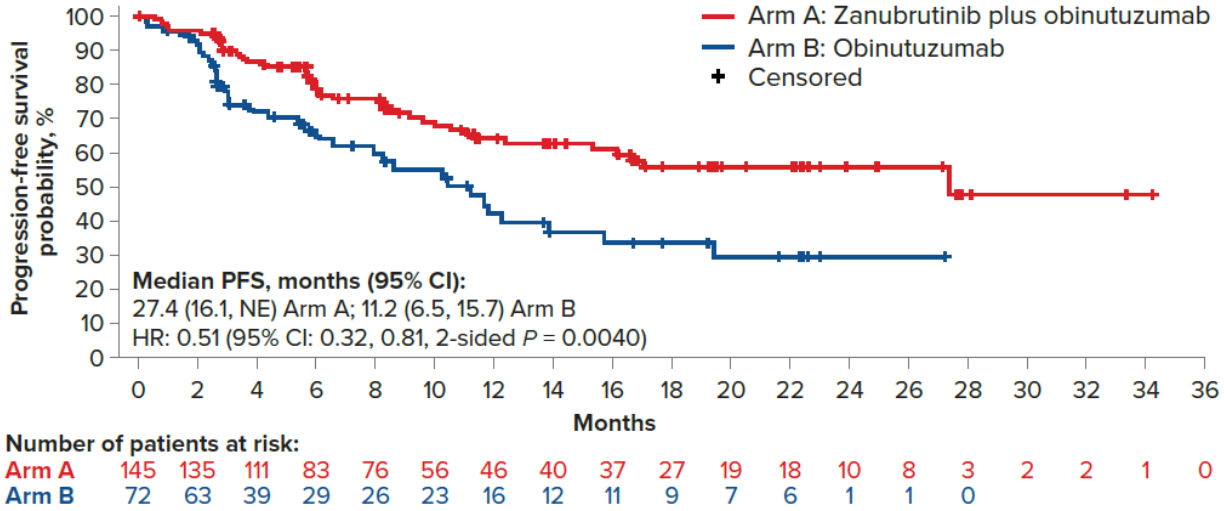
1. Salles G, et al. *Haematologica.* 2017;102(4):e156-e159; 2. Flinn I, et al. *J Clin Oncol.* 2019;37(11):912-922; 3. Dreyling, M, et al. *Am J Hematol.* 2020;95:362-371; 4. Fowler NH, et al. *J Clin Oncol.* 2021. Epub ahead of print.

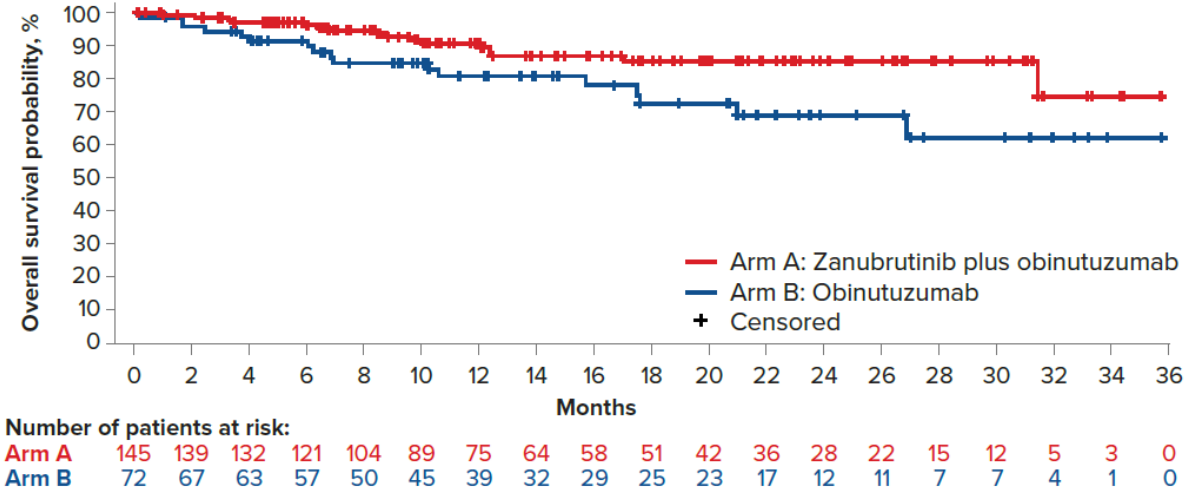
Obinutuzumab vs. Zanubrutinib-Obinutuzumab in the R/R FL

ORR: 45.8% vs. 68.3% and CR rate 19.4% vs. 37.2%

Progression-Free Survival by ICR



Overall Survival



Median PFS, months (95% CI):
27.4 (16.1, NE) Arm A vs 11.2 (6.5, 15.7) Arm B

Median OS*, months (95% CI):
NE (31.4, NE) Arm A vs NE (26.8, NE) Arm B

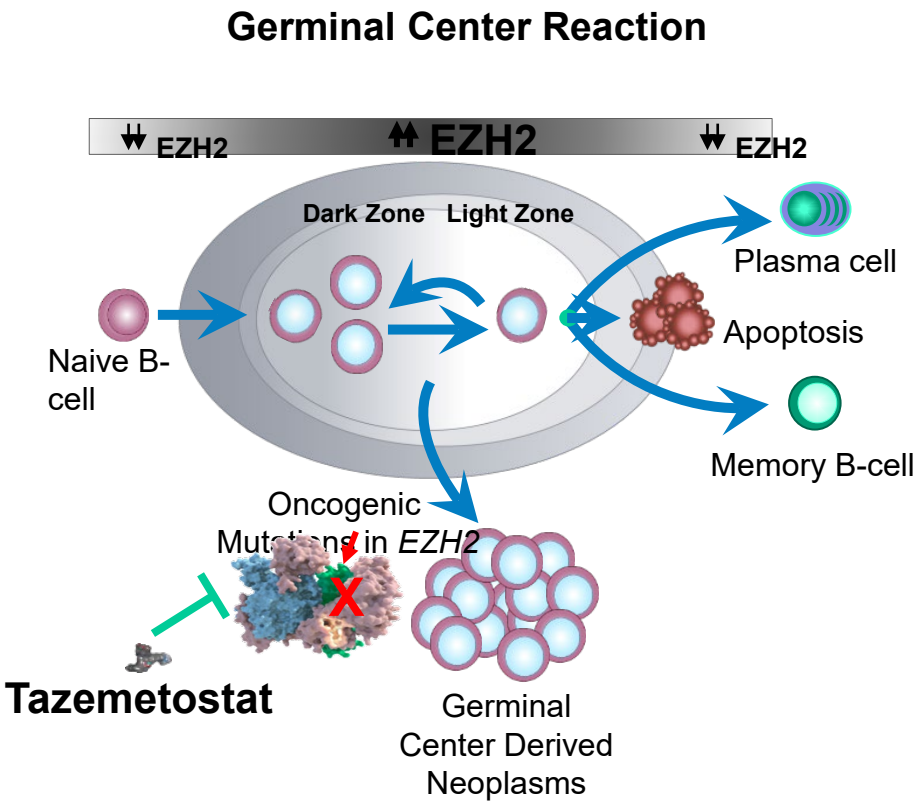
DRIVE RANK SCORE: Unkown

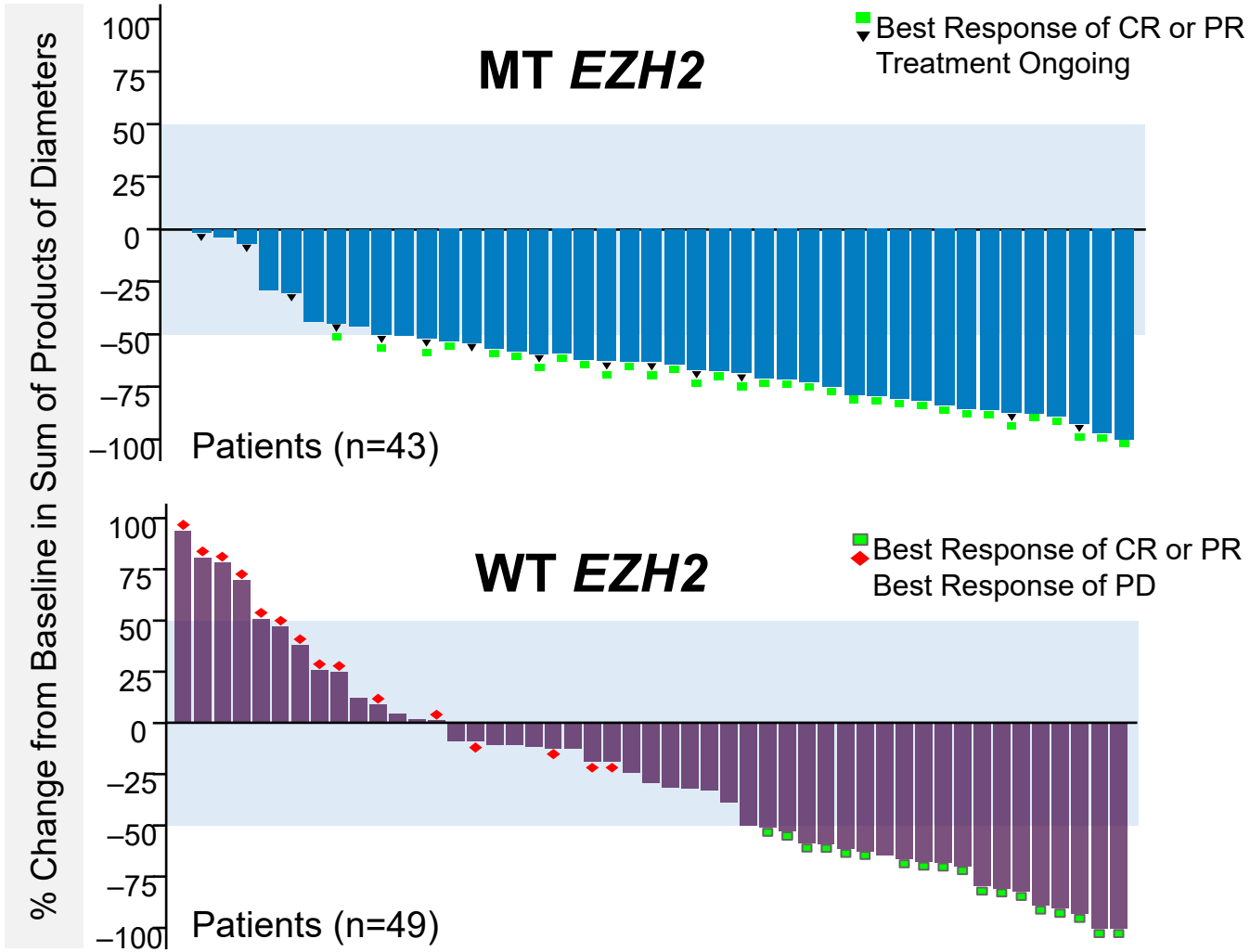
*Not powered to detect difference in OS

CI, confidence interval; DOR, duration of response; ICR, independent central review; NE, not evaluable; PD, progressive disease; PFS, progression-free survival.

Pier Luigi Zinzani PL et al. JCO 2022 40:16_suppl, 7510-7510

Targeting the epigenetic





Morschhauser F et al., Lancet Oncol 2020

Tazemetostat (EZH2 inhibitor): Key results

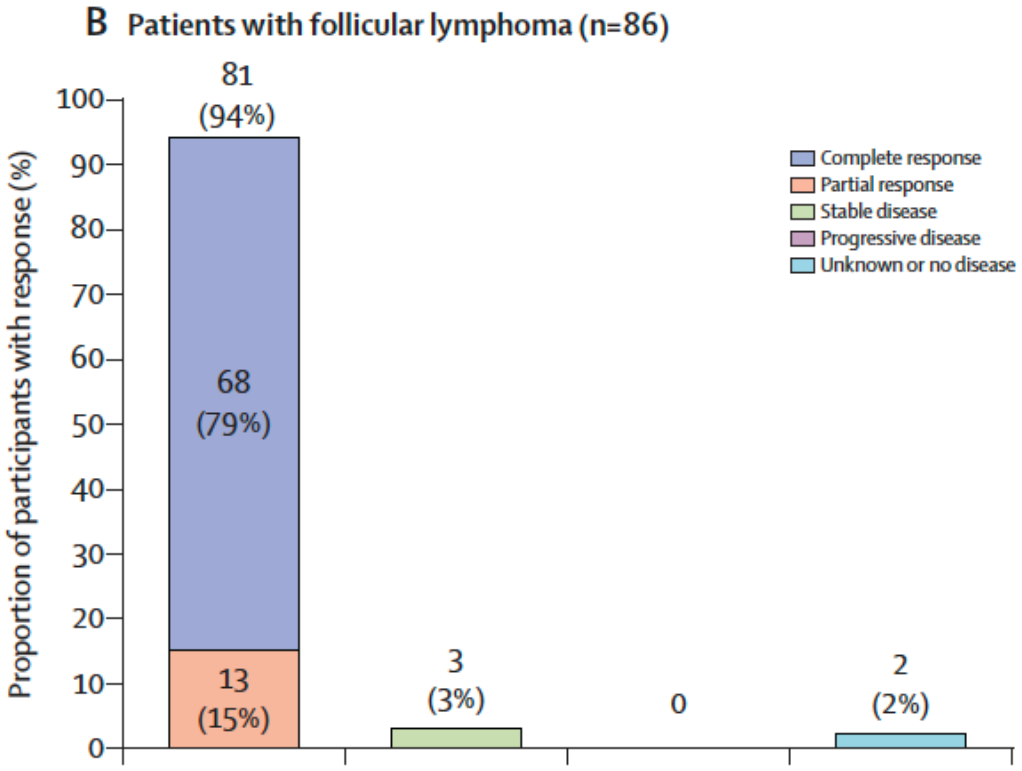
Patient cohort	Number of patients	ORR (by IRC)	CRR	PFS, median (mo)	DOR, median (mo)	Treatment-related adverse events (any grade) in ≥10% of patients	Treatment-related adverse events (grade 3-4) in ≥2% of patients
EZH2 mutated	45	69%	13%	14	11	Nausea (19%)	Anemia (2%)
EZH2 wild-type	54	35%	4%	11	13	Diarrhea (12%) Alopecia (14%) Asthenia (14%) Fatigue (12%)	Thrombocytopenia (3%) Leukopenia (3%)

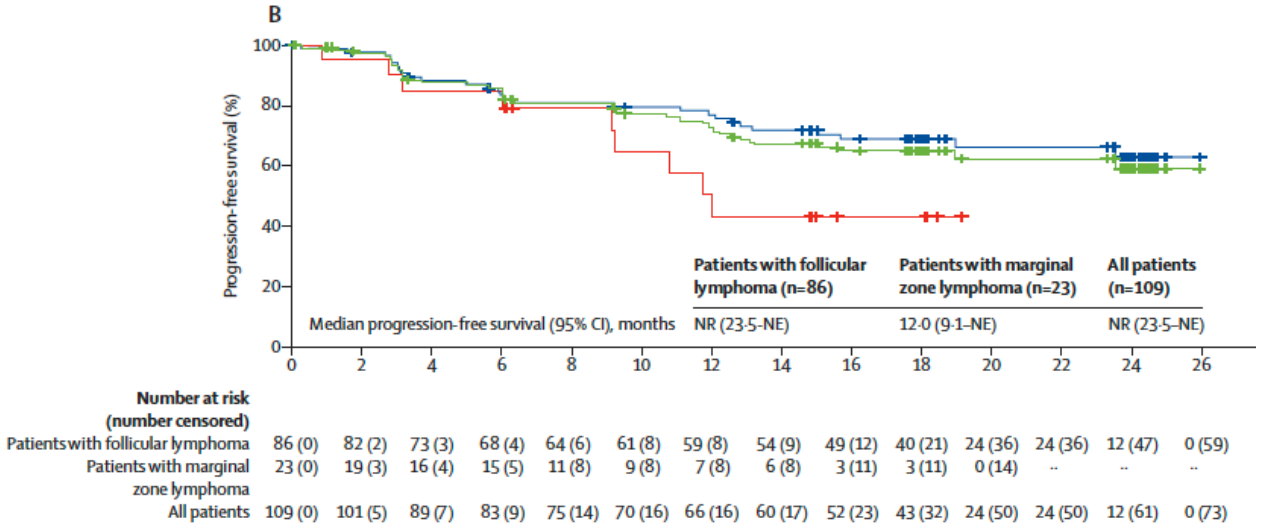
CRR, complete response rate; DOR, duration of response; IRC, independent review committee; ORR, overall response rate.

. . . for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test 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.

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

CAR-T cells: ZUMA-5 – Axicabtagene-Ciloleucel in iNHL



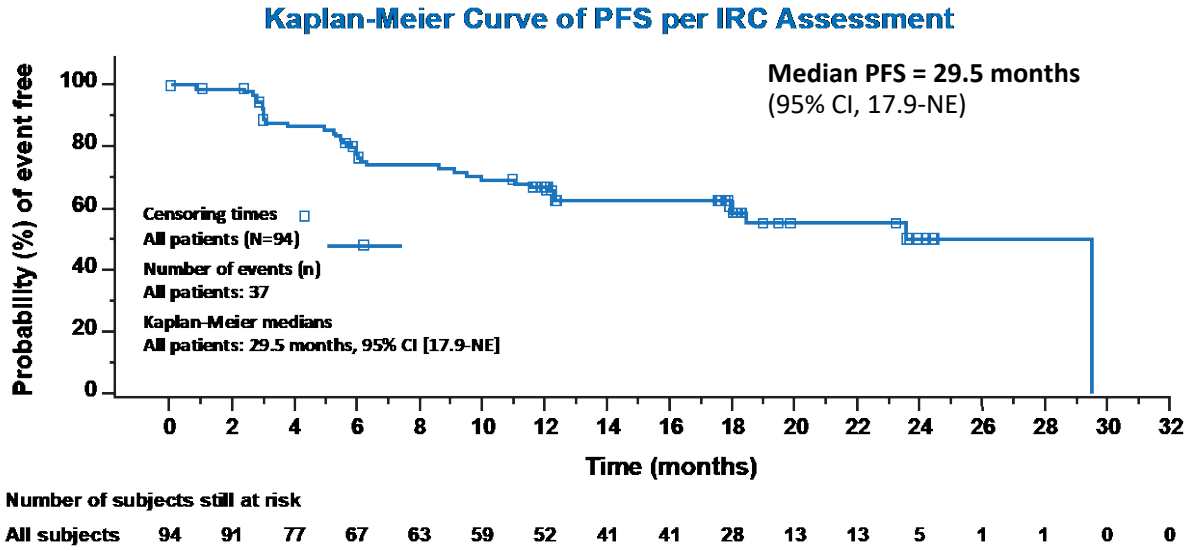


	Cytokine Release Syndrome (CRS)	Neurological Events (ICANS)
Total	**78%**	**56%**
Grade 3-4	**6%**	**15%**
	Tociluzumab 50% ; steroids 18%; ICU 5%	

Jacobson C et al, Lancet Onc 2021

CAR-T cells: tisagenlecleucel: ELARA study

Efficacy Results of Extended Follow-up Analysis	
Endpoint	**% (95% CI)**
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**76.0** (64.6-84.2)

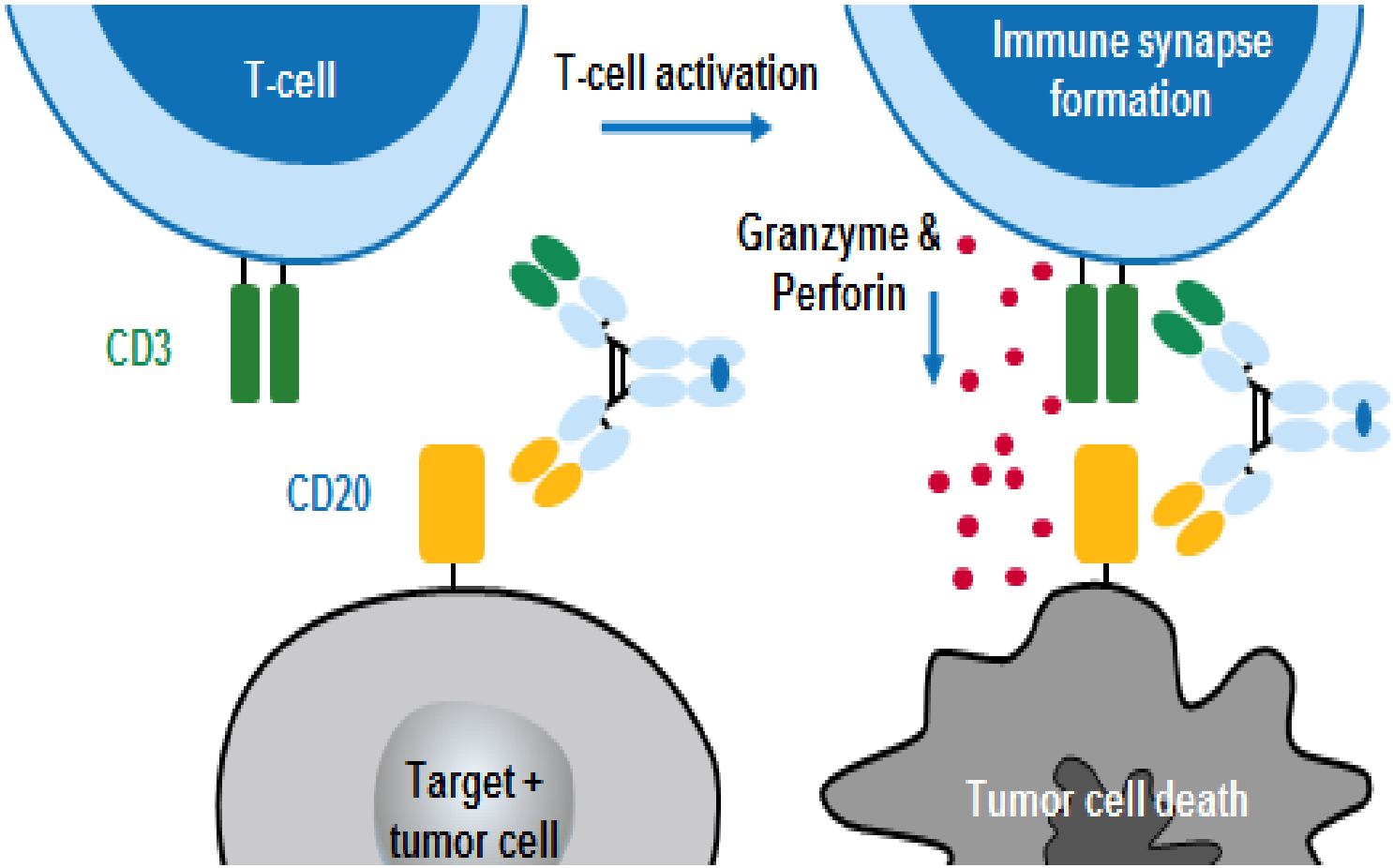


	Cytokine Release Syndrome (CRS)	Neurological Events (ICANS)
Total	**48.5%**	**4.1%**
Grade 3-4	**0%**	**4%**
	Tociluzumab 34% ; steroids 6.4%; ICU 8.5%	

[a]Median PFS should be interpreted with caution due to the low number of patients at risk after Month 24.
CI, confidence interval; NE, not estimable; PFS, progression-free survival.

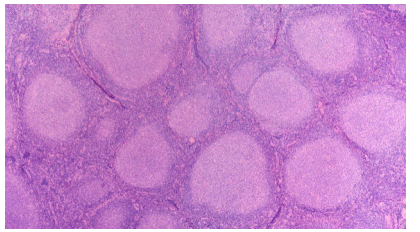
Fowler NH et al., Nat Med 2022; update Dreyling M et al, ASH2022

Bispecific CD3xCD20 MoAb :



No ex-vivo T cell manipulation required (‘off-the-shelf’ and no delay in treatment)

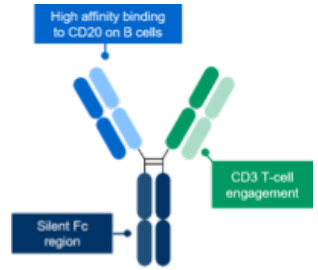
Bi-Specifics CD3 x CD20 in patients with R/R FL (updated January 2023)



	Mosunetuzumab (RG7828) [1]	Odronextumab (REGN1979) [2]	Glofitamab (RG6026) [3]	Epcoritamab (GEN3013) [4]
Patients	90	131	53	10
ORR	78%	82%	81 %	90%
CR	60%	75%	70 %	50%
Median PFS	24 months	20 months	NA	NA

1. Budde L et al, Lancet Oncology 2022; updated Bartlett N et al, ASH 2022; abstract 610
2. Kim TM et al. ASH 2022, abstract 949
3. Morschhauser F et al. ASH 2021 ;
4. Hutchings M, et al. Lancet Onc 2021

Mosunetuzumab: Study overview



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

Key inclusion criteria

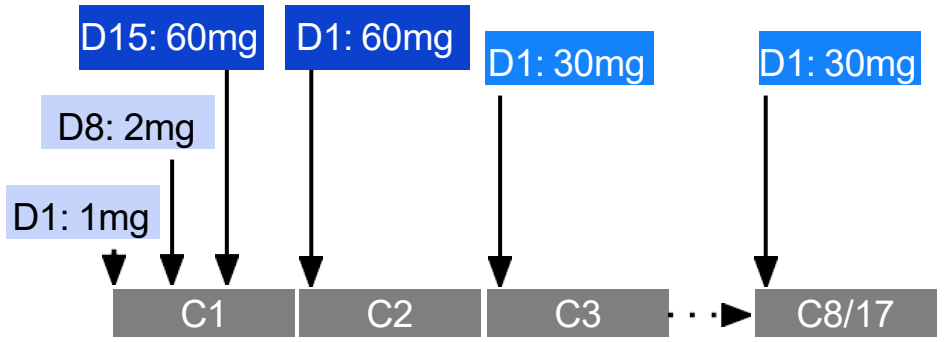
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

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

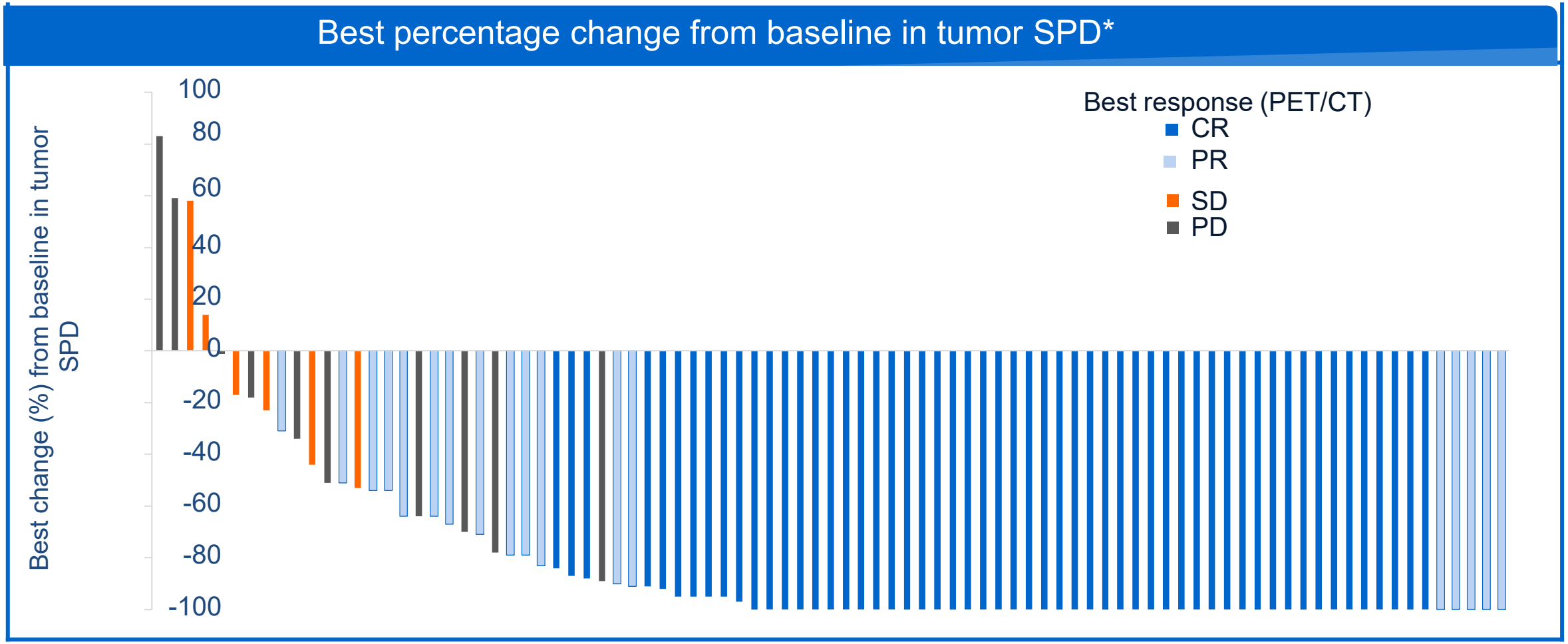
- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



1. Dreyling M, et al. J Clin Oncol 2017;35:3898–3905; 2. Budde LE, et al. Lancet Oncol 2022;23:1055–1065.

Mosun: Anti-tumor efficacy

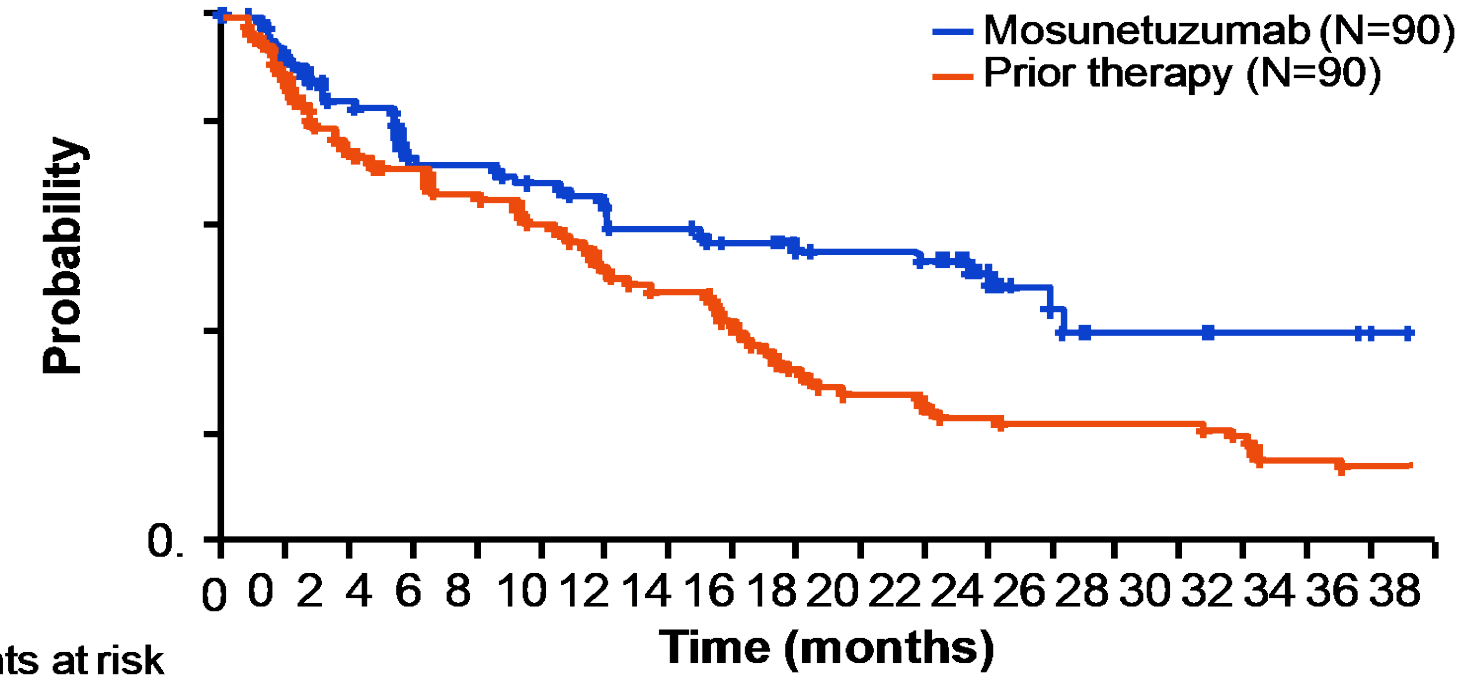
ORR 80%
CR rate 60%
Time to response 1.1 months



*in all patients with a baseline and ≥1 post-baseline SPD available; PD, progressive disease; SPD, sum of product diameters

Budde L et al, Lancet Oncology 2022

Mosunetuzumab: Progression-free survival



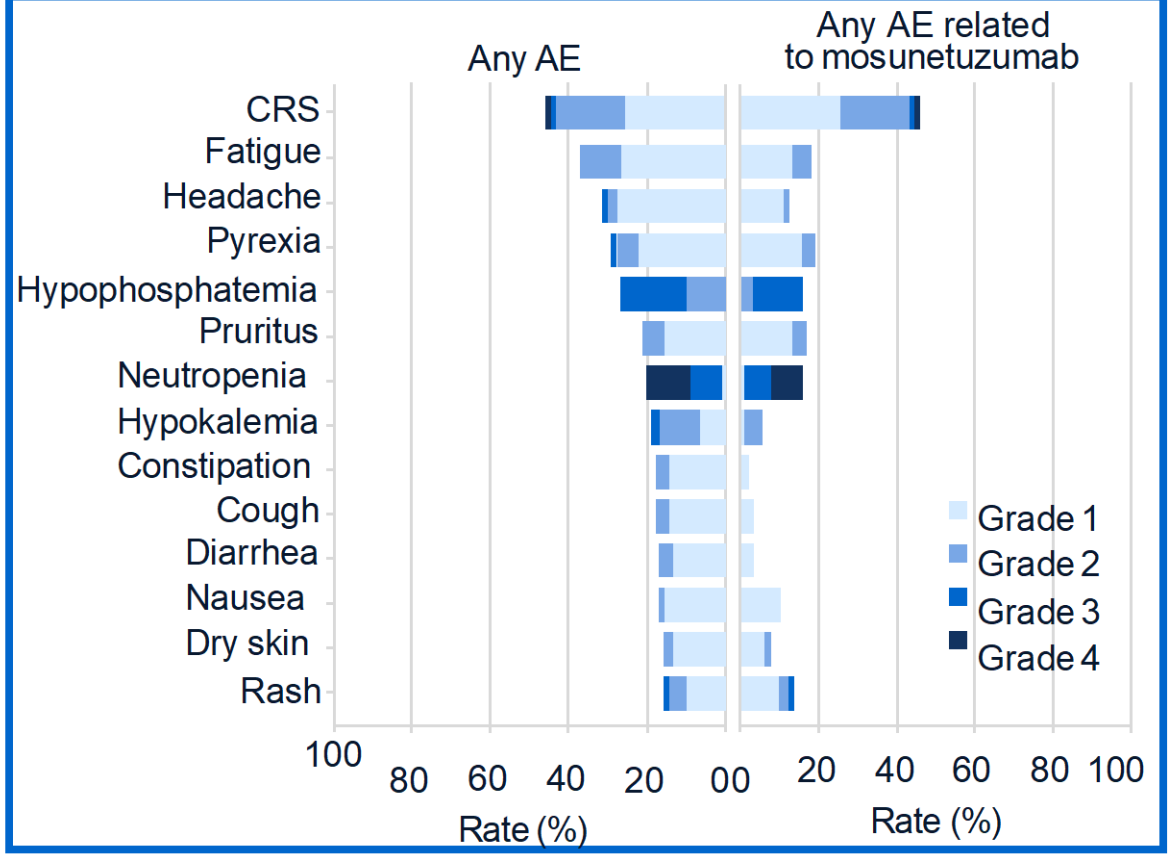
	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	**24** (12–NR)	**12** (10–16)

Bartlett N et al, ASH 2022

Mosunetuzumab :safety profile

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 3–4 AE	63 (70.0%)
Mosunetuzumab related*	46 (51.1%)
Serious AE	42 (46.7%)
Mosunetuzumab related*	30 (33.3%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡

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



*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade

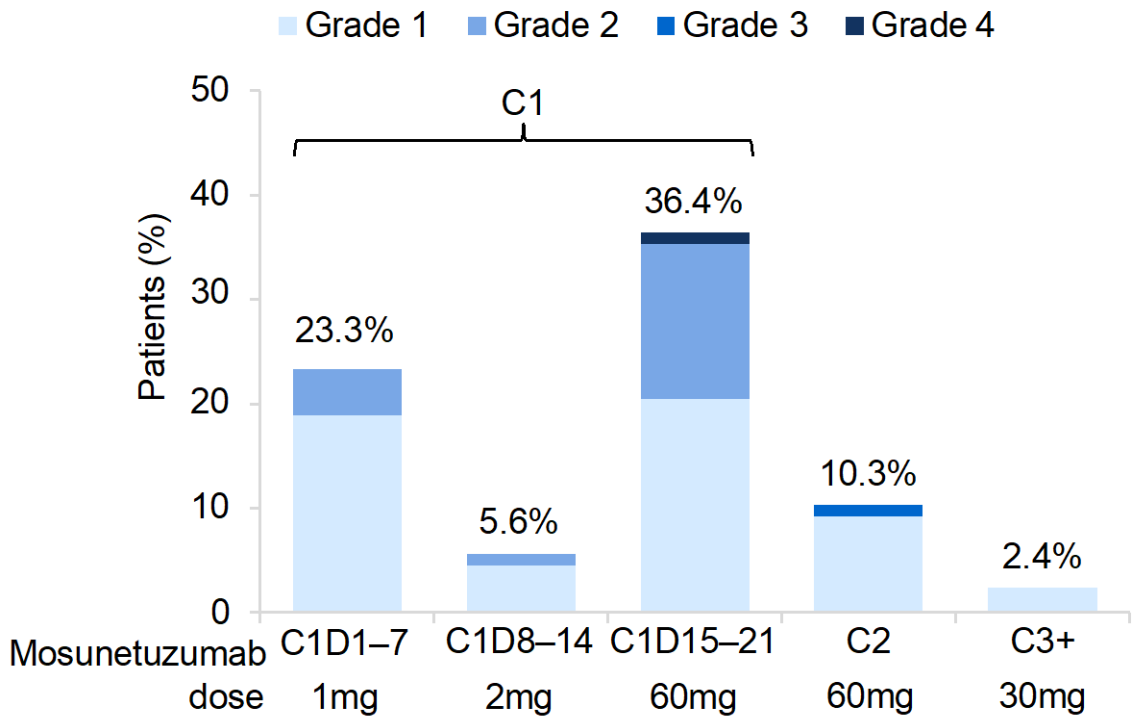
;

Budde L et al, ASH 2021

Mosunetuzumab: Cytokine release syndrome

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)

CRS by Cycle and Grade



- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

*assessed using ASTCT criteria[1]; †patient with leukemic phase FL

1. Lee et al. Biol Blood Marrow Transplant 20192019;25:625–38

Mosunetuzumab: other adverse events of interest

N (%)	N=90	Additional details
ICANS* Grade 3	4 (4.4%) 0	• Confusional state (3.3%; all Grade 1–2†), disturbance in attention and cognitive disorder (1.1% each; all Grade 1†); all resolved • No cases of aphasia, seizures, encephalopathy, or cerebral edema
Neutropenia‡ Grade 3–4 Febrile neutropenia	26 (28.9%) 24 (26.7%) 0	• 98.1% resolved • Serious AE of infection concurrent with Grade 3–4 neutropenia in 2 patients
Serious AE of infection (any Grade)§ Grade 3–4	18 (20.0%) 13 (14.4%)	• UTI (3.3%), pneumonia, COVID-19, Epstein-Barr viremia, septic shock (2.2% each)

- **ICANS events were infrequent and all Grade 1–2**

*mosunetuzumab-related neurological AEs potentially consistent with ICANS; †graded per CTCAE V4; ‡grouped term including Preferred Term 'neutropenia' and 'neutrophil count decreased'; §System Organ Class 'infections and infestations'; ICANS, immune effector cell-associated neurotoxicity syndrome; UTI, urinary tract infection;

Budde L et al, ASH 2021

Synopsis of areas of uncertainty in BsAb research and relative specific challenges

Areas of uncertainty	Challenges
Management of T-cell overactivation syndromes	Identifying risk factors for CRS Optimal step-up dosing, drug formulation, prophylaxis Outpatient administration Patient and provider education
DOR	Optimal duration of BsAb therapy Predictors of durable response
Moving BsAb to earlier lines of therapy	Competitive landscape Selecting the most appropriate patient populations (eg, high-risk disease)
Optimal combinations	Moving beyond cytotoxic agents as partners Rational (rather than expedient) combinations
Understanding mechanisms of resistance	Identifying actionable tumor-intrinsic resistance mechanisms Detailed characterization of T-cell function (and dysfunction) during BsAb therapy Dissecting the role of other players in the lymphoma immune microenvironment

Falchi L et al., Blood 2023

Follicular lymphoma takeaways

Choices of therapy at different steps are important

→ *Achieving long-term disease-free intervals is possible*

Not all patients with follicular lymphoma progression need to re-initiate therapy

→ *Assess patient needs and wishes*

With prolonged survival expectancy, short- and long-term toxicities are of concern

→ *Individualize therapy*

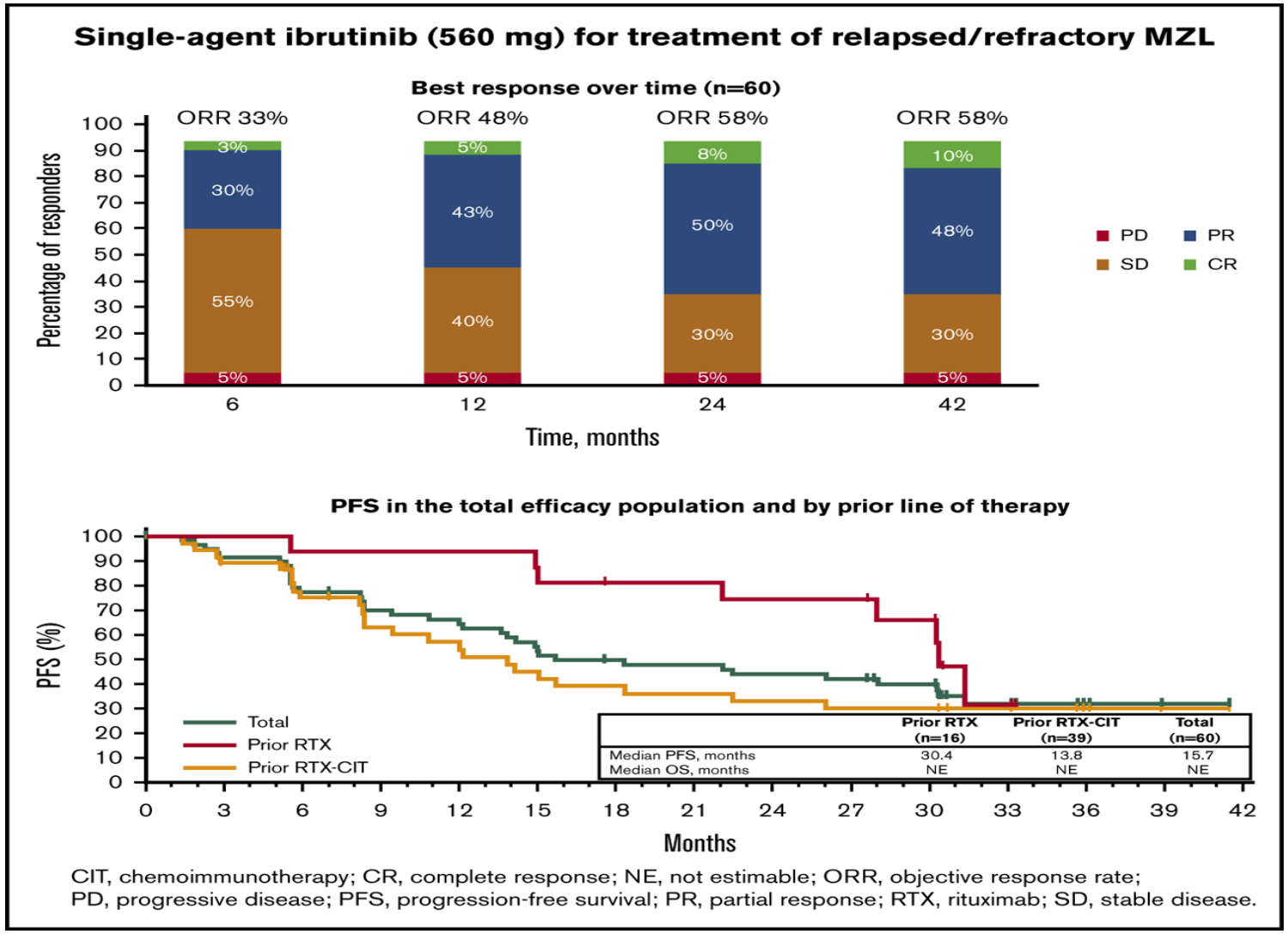
While many patients will still succumb to their disease, this is mainly the case when histologic transformation occur

→ *Re-biopsy is important*

Memorial Sloan Kettering Cancer Center

New Agents for Marginal Zone Lymphoma

Durable ibrutinib responses in relapsed/refractory MZL



Noy A et al. , Blood 2017 and Blood Adv, 2020

Zanubrutinib in R/R MZL:

Best Overall Response by Independent Review by MZL Subtypes

Best response, n (%)	Extranodal (N=25)	Nodal (N=25)	Splenic (N=12)	Unknown (N=4)	Total (N=66)[a]
ORR (CR or PR), n (%) 95% CI[b]	**16 (64) (42.5, 82)**	**19 (76) (54.9, 90.6)**	**8 (67) (34.9, 90.1)**	**2 (50) (6.8, 93.2)**	**45 (68) (55.6, 79.1)**
Complete response	10 (40)	5 (20)	1 (8)	1 (25)	17 (26)
Partial response	6 (24)	14 (56)	7 (58)	1 (25)	28 (42)
Stable disease	4 (16)	5 (20)	3 (25)	1 (25)	13 (20)
Progressive disease (PD)	3 (12)	1 (4)	1 (8)	1 (25)	6 (9)
Non-PD[c]	1 (4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Withdrew consent prior to 1st assessment	1 (4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)

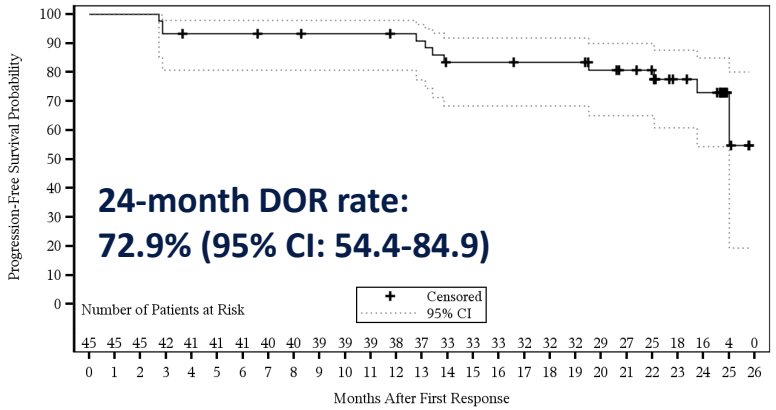
[a] Two patients were excluded from the efficacy population due to lack of central confirmation of MZL
[b] 2-sided Clopper-Pearson 95% CI

Opat S et al. . 2022 ASH Annual Meeting and Exposition. Abstract 234. Presented December 10, 2022.

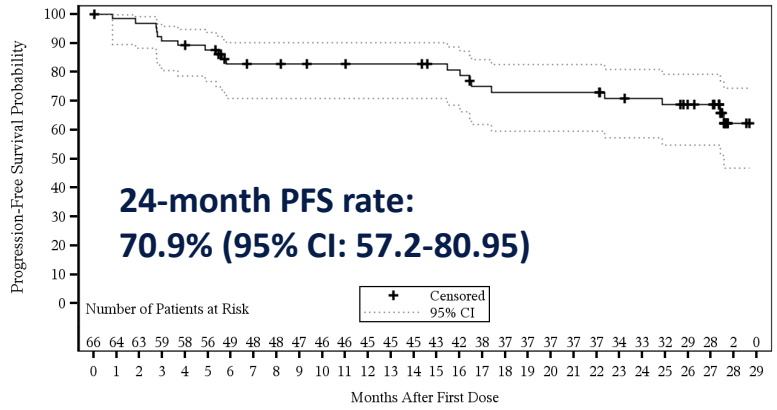
Zanubrutinib in R/R MZL:

Efficacy endpoints

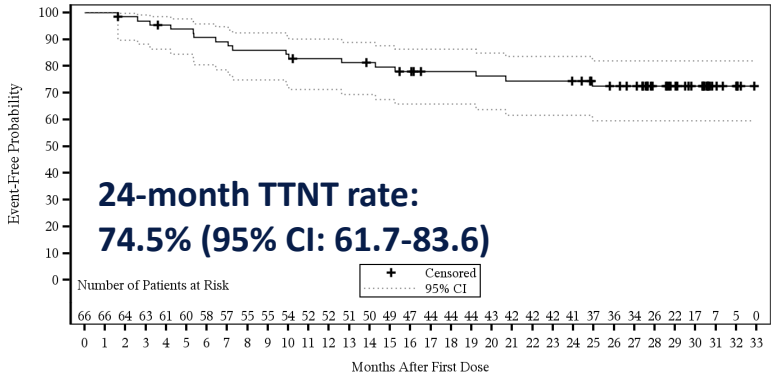
Duration of Response (IRC)



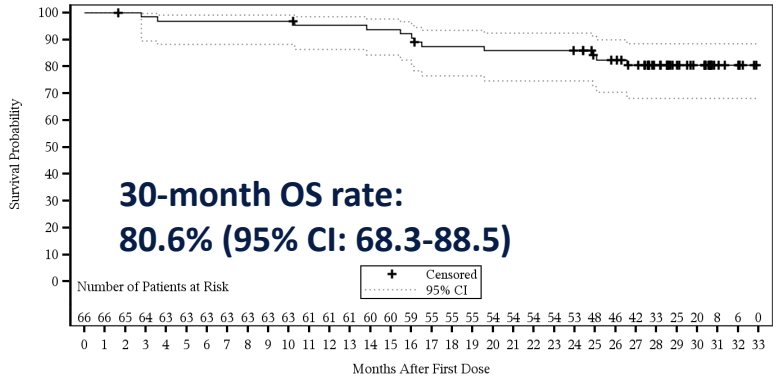
Progression-free survival (IRC)



Time to Next Antilymphoma Treatment



Overall survival



CI: confidence interval; DOR: duration of response; IRC: independent review committee; OS: overall survival; PFS: progression-free survival; TTNT: time to next anti-lymphoma treatment

Opat S et al. . 2022 ASH Annual Meeting and Exposition. Abstract 234. Presented December 10, 2022.

Zanubrutinib in R/R MZL:

Treatment emergent adverse events

Any grade, >10% of patients

	N=68
Diarrhea	15 (22.1)
Constipation	12 (17.6)
Abdominal pain	8 (11.8)
Nausea	7 (10.3)
Upper respiratory tract infection	9 (13.2)
Arthralgia	10 (14.7)
Back pain	8 (11.8)
Pyrexia	10 (14.7)
Contusion	16 (23.5)
Cough	7 (10.3)
Thrombocytopenia	7 (10.3)

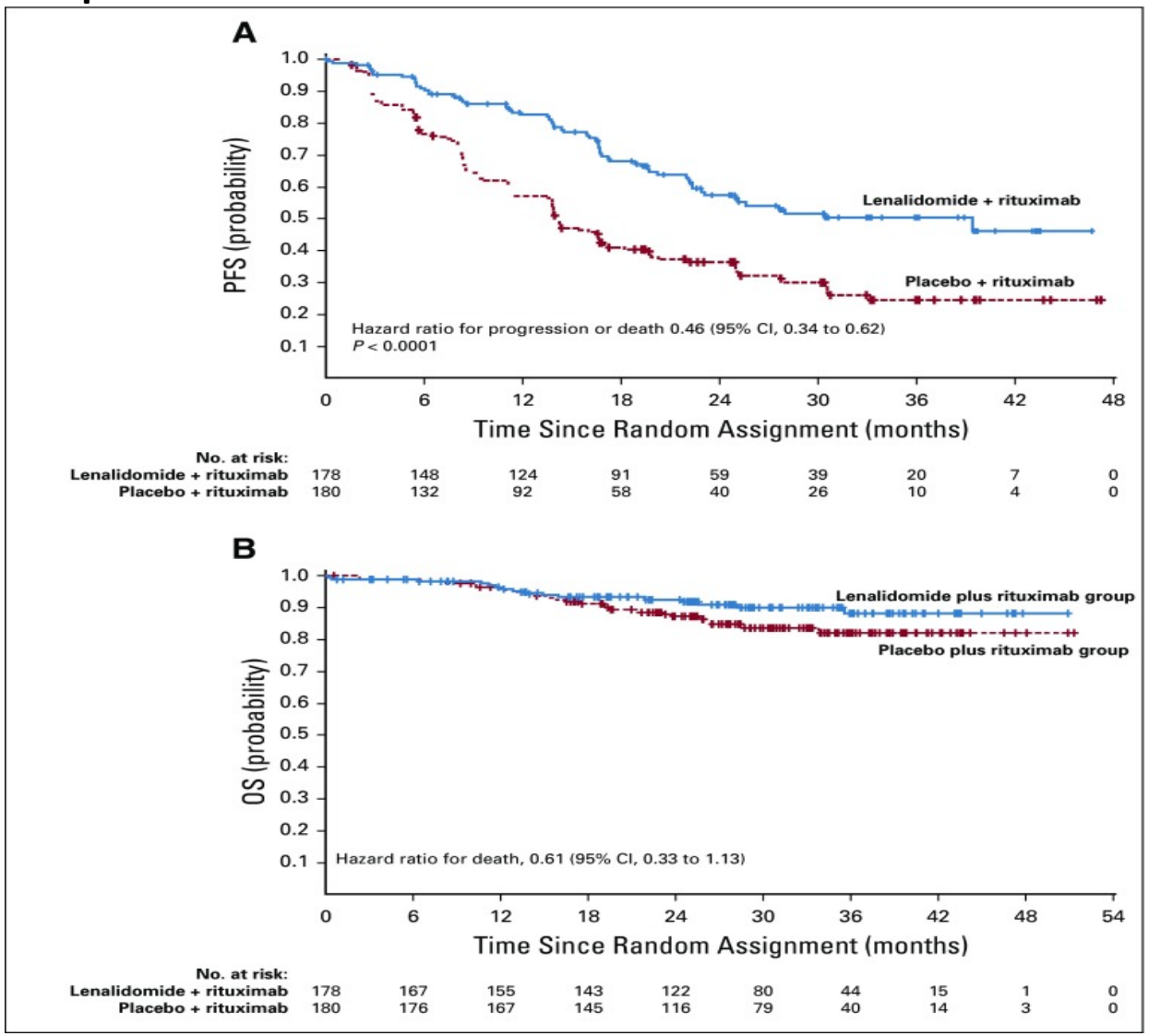
Grade 3-5, >1 patient

	N=68
COVID-19 pneumonia	4 (5.9)
Pneumonia	3 (4.4)
Diarrhea	3 (4.4)
Neutropenia	6 (8.8)
Anemia	2 (2.9)
Thrombocytopenia	2 (2.9)
Syncope	3 (4.4)
Neutrophil count decreased	2 (2.9)
Pyrexia	2 (2.9)
Hypertension	2 (2.9)

Opat S et al. . 2022 ASH Annual Meeting and Exposition. Abstract 234. Presented December 10, 2022.

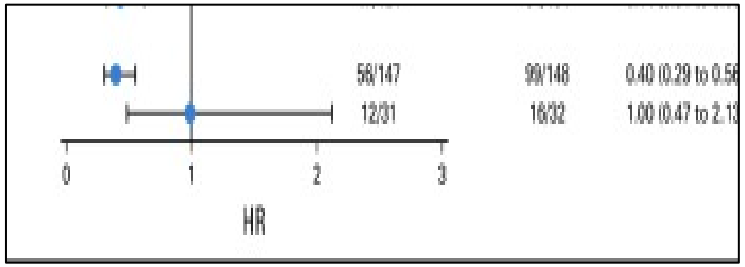
Augment: Randomized Phase III rituximab +/- lenalidomide beyond first line in FL and MZL

All patients: n=359



MZL subset: n= 63

Disease histology
Follicular lymphoma
Marginal zone lymphoma



For MZL: n=32 ritux/len vs ritux/placebo
PFS no difference: 20 vs 25 months

2 yr OS in MZL:
No difference:
82% (95% CI, 61% to 92%)
vs.
Ritux: 94% (95% CI, 77% to 98%)

Leonard J et al, JCO, 2019

MZL and CAR-T: axicabtagene ciloleucel

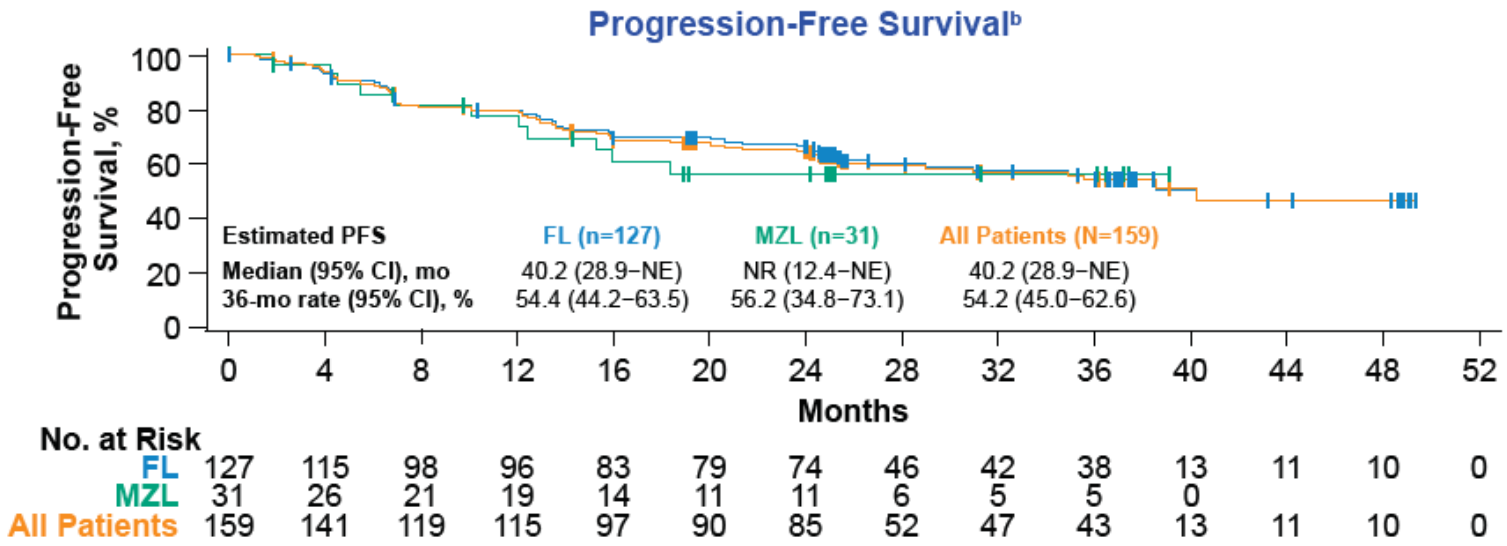
Zuma-5 updated results

MZL patients:

- 31 patients
- 77% ORR
- 65% CR rate

Toxicities c/w other CAR-T studies of axi-cel including

- 7% CRS >=grade 3
- 19% grade 3 or 4 ICANS 19%).
- SAEs (any grade) 50.
- Deaths 3%.



Neelapu SN et al. *Blood* 2023; blood.2022018893

Marginal Zone Lymphoma Takeaways

Different diseases with distinct clinical presentations and biologically heterogeneous

→ *Need to individualize management*

→ *Difficulties in interpreting clinical study results*

Rituximab remains the pivotal agent in first-line for disseminated disease

→ *Many options available for specific presentations*

→ *Rituximab-bendamustine for patients with poor prognostic features?*

New agents are progressively assessed with promising results

→ *BTK inhibitors (FDA approved)*

→ *Lenalidomide and rituximab (FDA approved)*

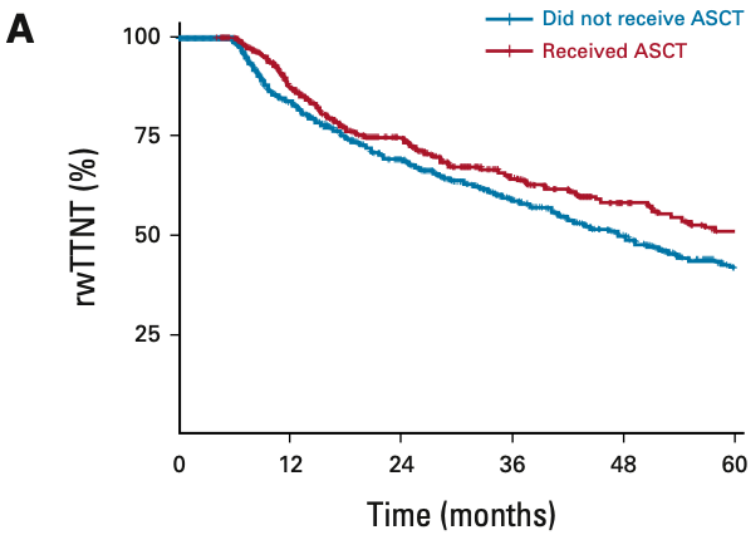
→ *Cellular therapies remain experimental*

Memorial Sloan Kettering Cancer Center

Paradigm Shifts in Mantle Cell Lymphoma

Real World Data: Flatiron Health Database Analysis

Only 29% of eligible younger patients received ASCT: no difference in rwTNTT or OS

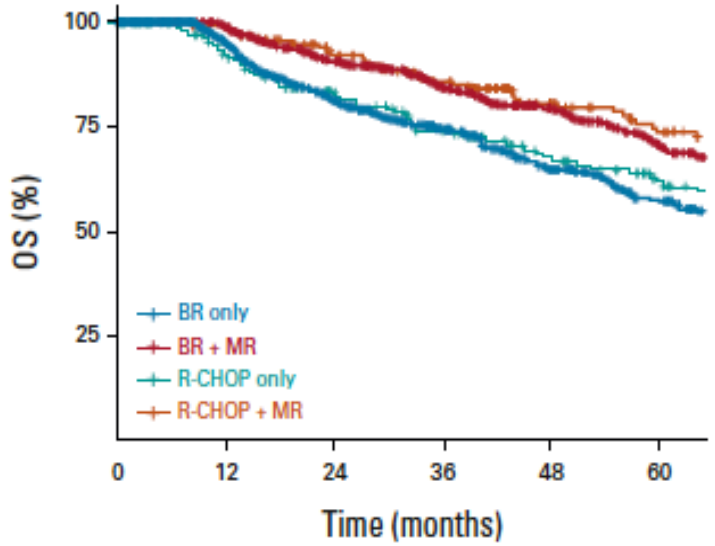


No. at risk:

Did not receive ASCT	680	451	331	228	164	106
Received ASCT	282	222	160	112	81	59

	Age < 65 Years and ASCT-Eligible n = 962	
	Received ASCT n = 282	Did Not Receive ASCT n = 680
Median rwTTNT (95% CI), months	59.9 (51.3 to 75.6)	48.3 (41.9 to 53.6)
rwTTNT rate at 3 years, % (95% CI)	65 (59 to 71)	59 (55 to 64)
HR (95% CI)	0.84 (0.68 to 1.03)	
Log-rank test *P*	.10	

Rituximab maintenance showed a benefit after R-CHOP and B-R in rwTNTT or OS



No. at risk:

BR only	679	458	317	225	156	106
BR + MR	427	409	330	235	179	113
R-CHOP only	195	144	120	99	75	61
R-CHOP + MR	160	155	129	108	85	71

	BR Only n = 679	BR + MR n = 427	R-CHOP Only n = 195	R-CHOP + MR n = 160
Median OS (95% CI), months	78.1 (62.9 to 93.5)	89.5 (80.0 to 108.6)	81.9 (67.6 to 105.0)	99.0 (82.1 to NE)
OS rate at 3 years, % (95% CI)	74 (70 to 79)	84 (80 to 88)	70 (68 to 82)	86 (80 to 92)
HR (95% CI)	1.51 (1.19 to 1.92)		1.53 (1.06 to 2.20)	
Log-rank test *P*	< .001		.023	

Martin P et al. JCO 2022

SHINE: A Randomized Double-Blinded Phase 3 Study

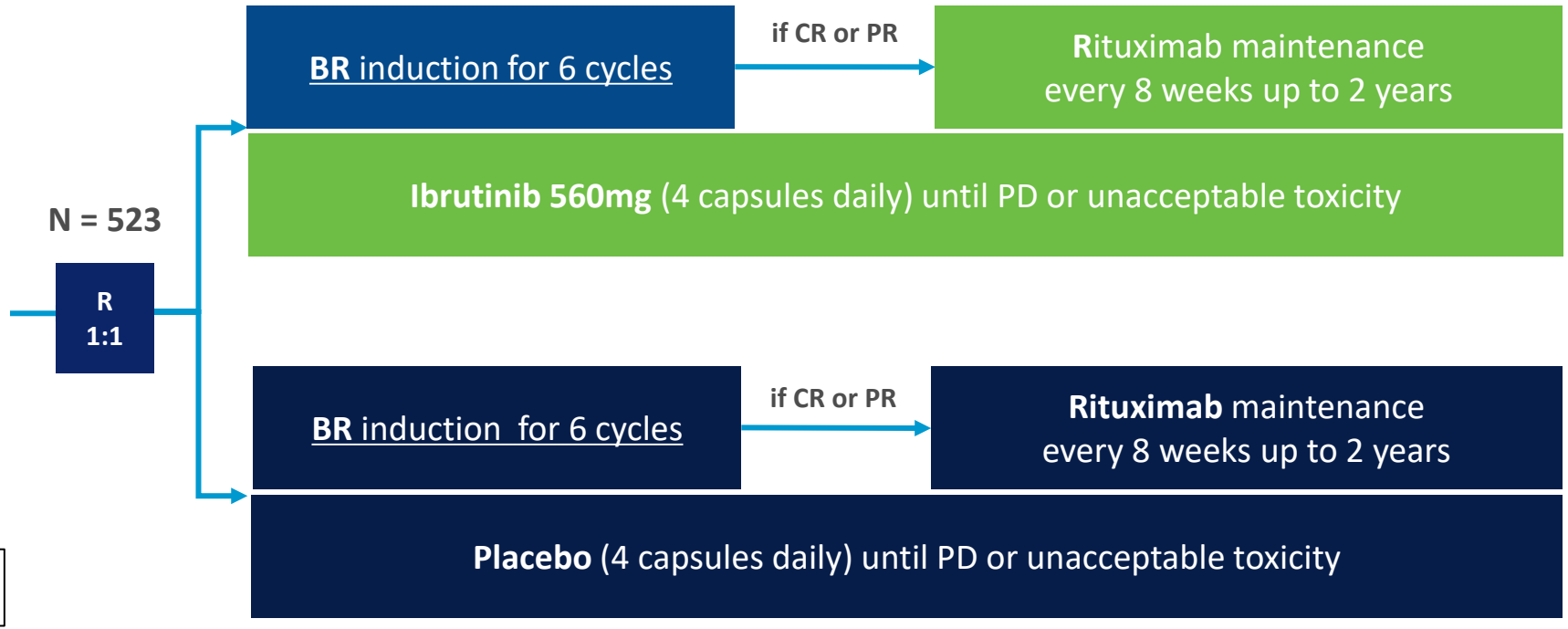
Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II-IV disease
- No stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

Enrolled between May 2013 and November 2014 at 183 sites



Primary endpoint: PFS (investigator-assessed)

Key Secondary endpoints: response rate, time to next treatment, overall survival, safety

DRIVE RANK SCORE: 2

Induction: **B**endamustine 90 mg/m^2 Days 1 and 2, **R**ituximab 375 mg/m^2 Day 1, Q4W. A cycle is defined as 28 days.

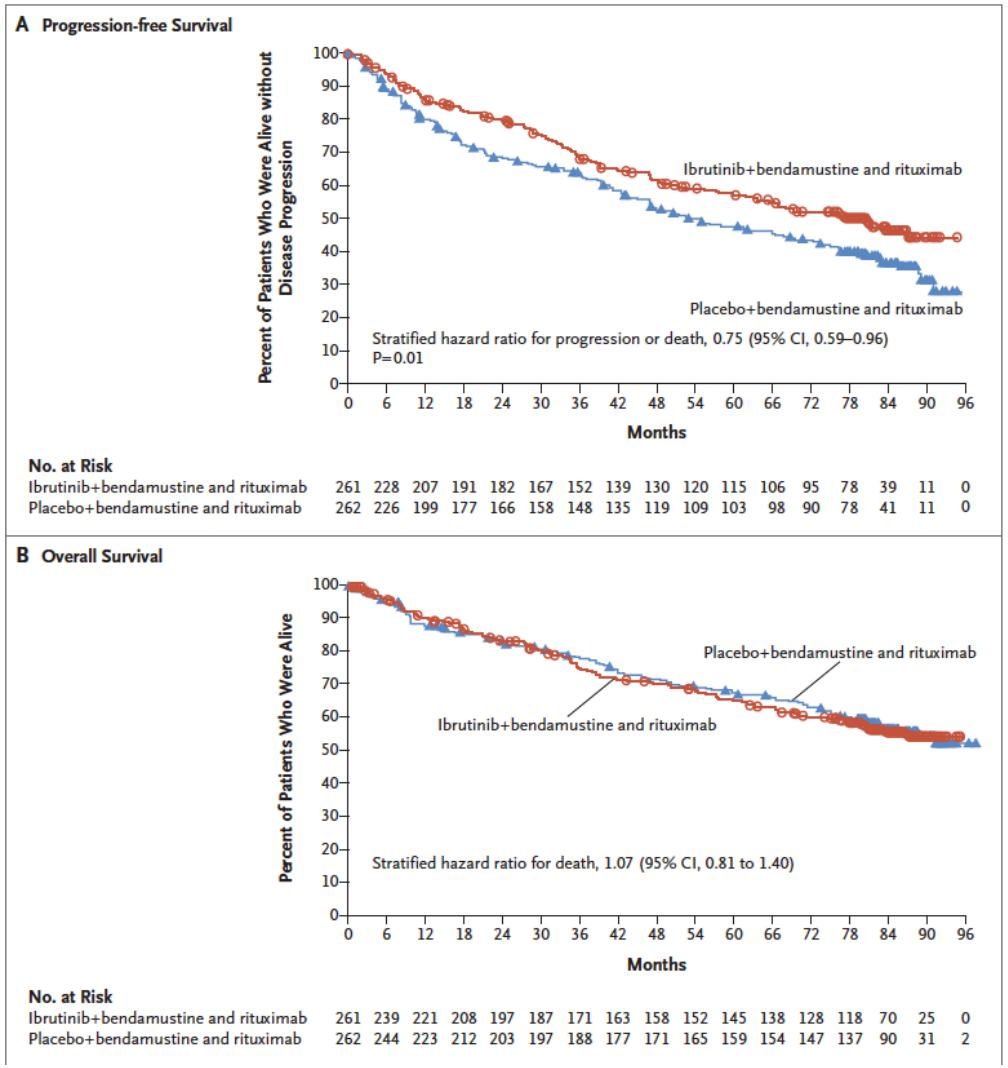
Wang ML et al., NEJM 2022

SHINE: A Randomized Double-Blinded Phase 3 Study

Key results

Progression-free sSurvival

	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	



Overall Survival

	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median OS, months	NR	NR
HR (95% CI)	**1.07 (0.81-1.40)**	

Wang ML et al., NEJM 2022

SHINE: TEAEs of Clinical Interest With BTKis

	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any bleeding*	42.9%	3.5%	21.5%	1.5%
Major bleeding	5.8%	--	4.2%	--
Atrial fibrillation*	13.9%	3.9%	6.5%	0.8%
Hypertension	13.5%	8.5%	11.2%	5.8%
Arthralgia	17.4%	1.2%	16.9%	0

- These adverse events were generally not treatment-limiting.
- During the entire study period, second primary malignancies: 20.8% in the ibrutinib arm and 18.8% in the placebo arm. MDS/AML in 2 and 3 patients, respectively.

*Difference of ≥5% in any grade TEAE.

Any bleeding is based on Haemorrhage Standardized MedDRA Query (SMQ) (excluding laboratory terms). Major bleeding includes any Grade 3 or higher bleeding and serious or CNS bleeding of any grade.

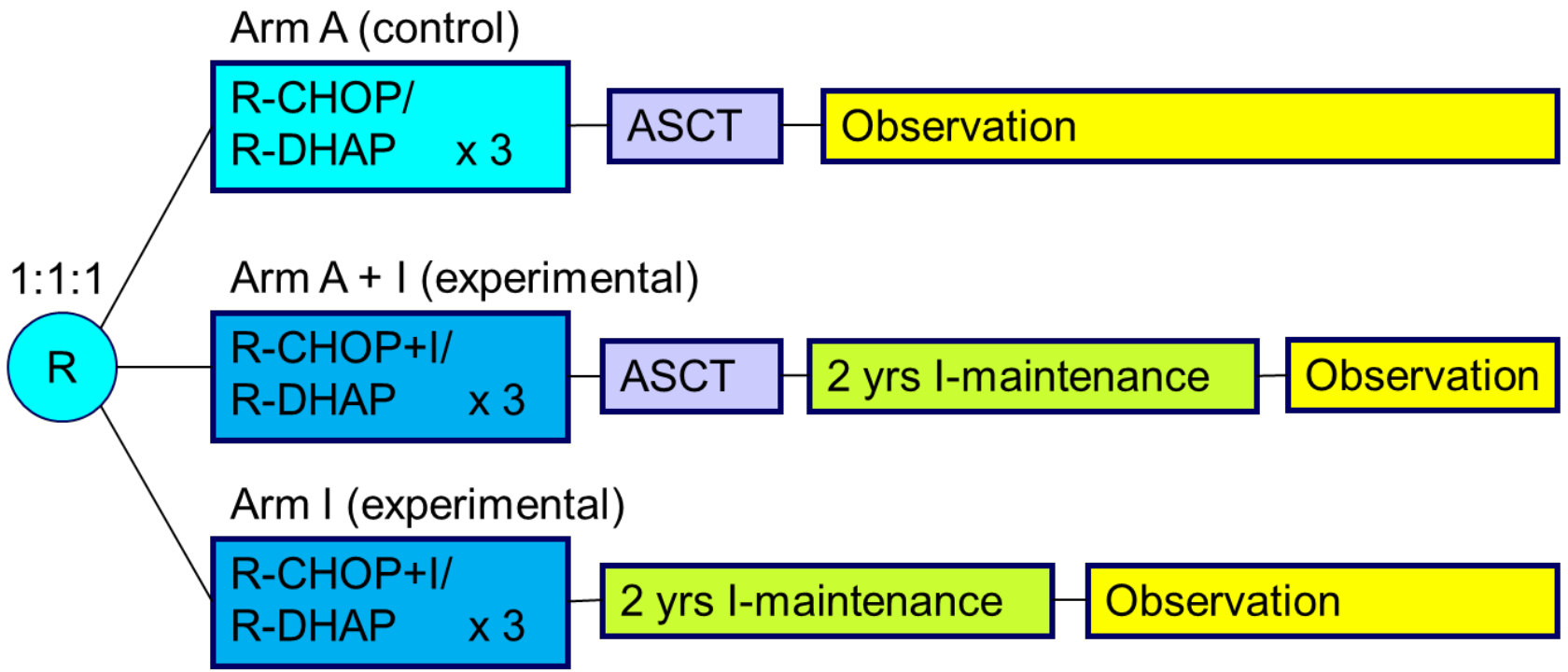
Wang ML et al., NEJM 2022

TRIANGLE: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA andASCT
- ECOG 0-2

- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

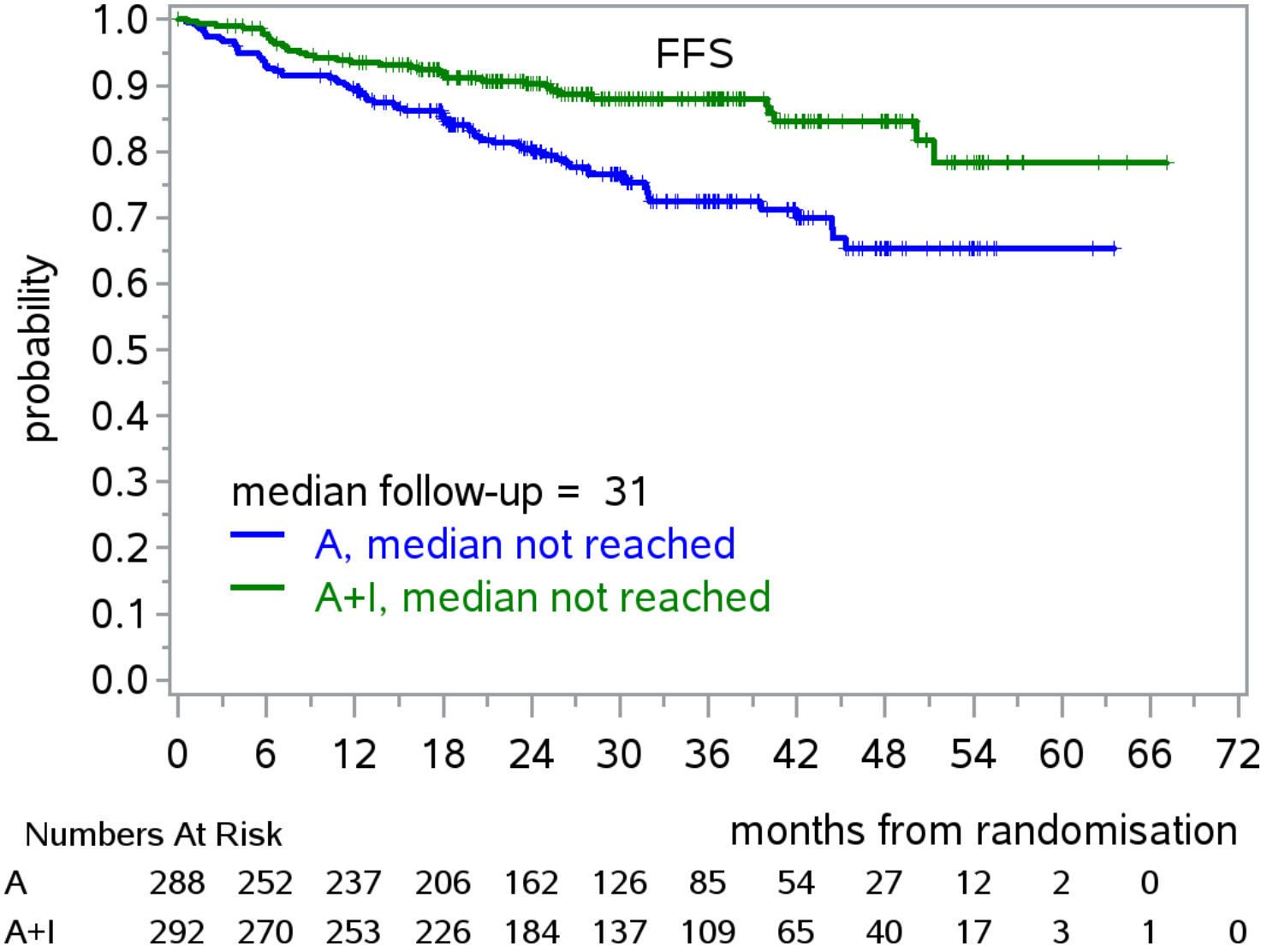


- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

DRIVE RANK SCORE: Unkown

Dreyling M et al., 2022 ASH Annual Meeting and Exposition. Abstract 1

TRIANGLE: FFS Superiority of A+I vs. A

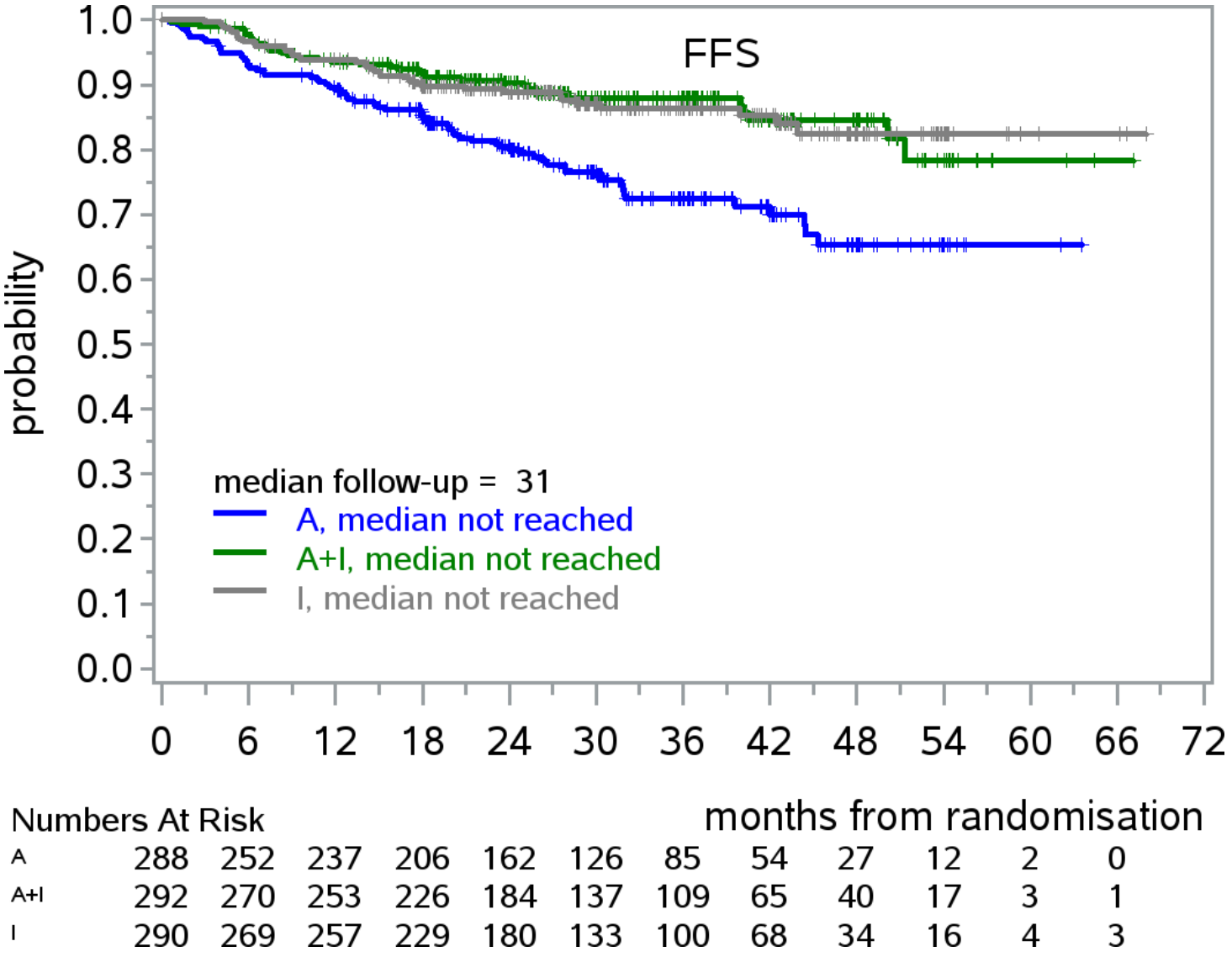


- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

Dreyling M et al., 2022 ASH Annual Meeting and Exposition. Abstract 1

TRIANGLE: FFS Superiority of A+I vs. I ?



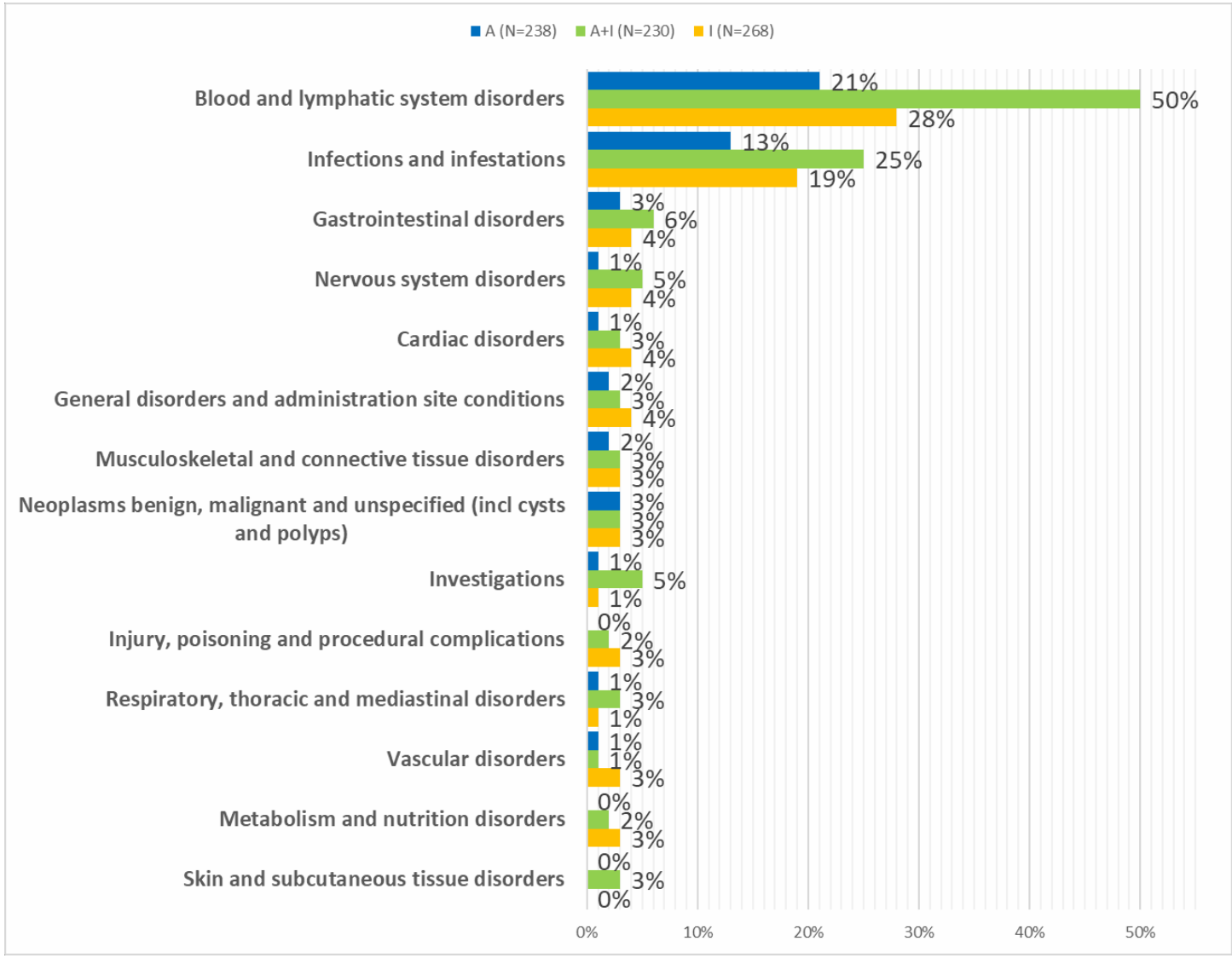
- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling M et al., 2022 ASH Annual Meeting and Exposition. Abstract 1

TRIANGLE: Grade 3-5 AEs (maintenance/follow-up, >2%)



Grade 3-5

Adverse Events by Preferred Term	A (N=238)		A+I (N=230)		I (N=268)	
Neutropenia	40	17%	101	44%	62	23%
Febrile neutropenia	6	3%	14	6%	7	3%
Thrombocytopenia	5	2%	13	6%	8	3%
Leukopenia	4	2%	10	4%	6	2%
Anaemia	4	2%	6	3%	4	1%
Lymphopenia	3	1%	1	0%	5	2%

Grade 5

Patients with at least one grade 5 AE by SOC

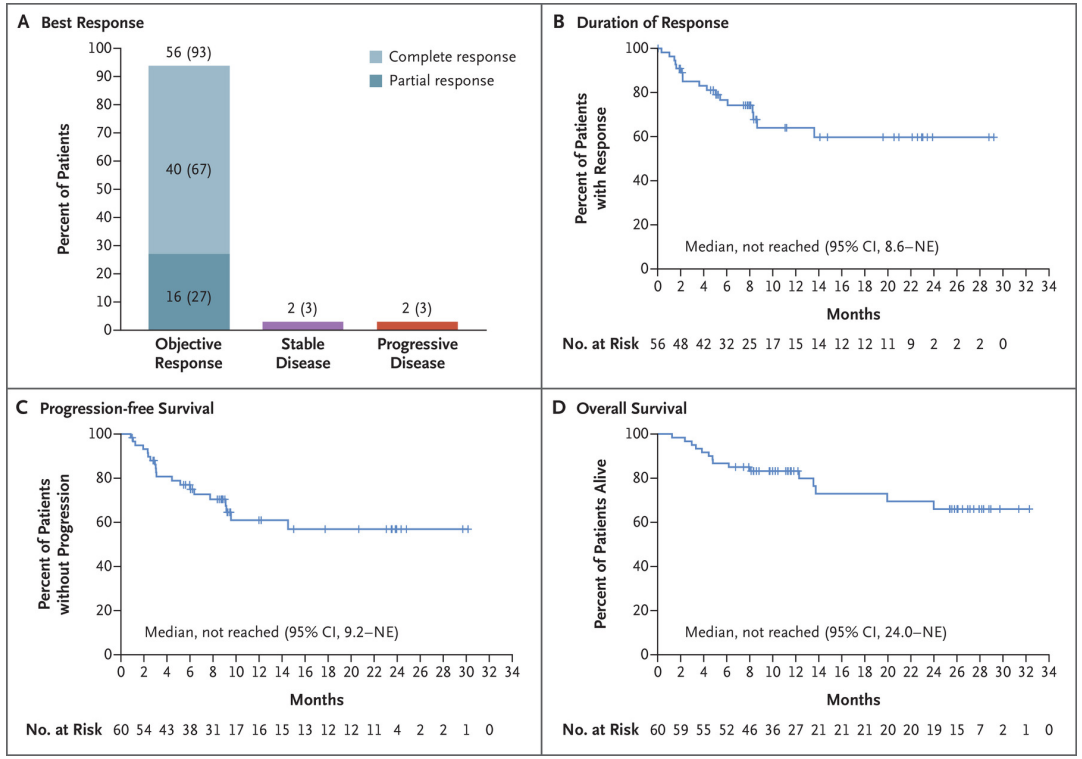
Adverse Events by System Organ Class	A (N=238)		A+I (N=230)		I (N=268)	
Infections and infestations	3	1%	2	1%	2	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0%	1	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Respiratory, thoracic and mediastinal disorders	0	0%	1	0%	0	0%
Vascular disorders	1	0%	0	0%	0	0%

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

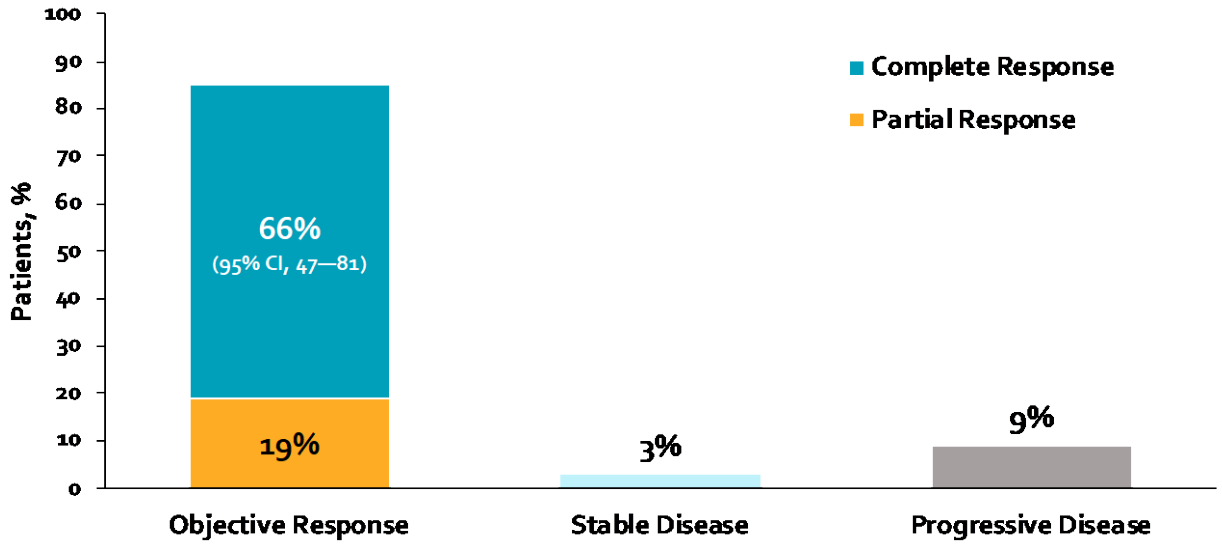
Dreyling M et al., 2022 ASH Annual Meeting and Exposition. Abstract 1

CAR T-cell in Mantle cell lymphoma (1)

ZUMA-2



Transcend



Wang M et al. NEJM 2020

Palomba LM et al. ASH 2020

CAR T-cell in Mantle cell lymphoma (2)

Cytokine Release Syndrome

- No Grade 5 CRS occurred

Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

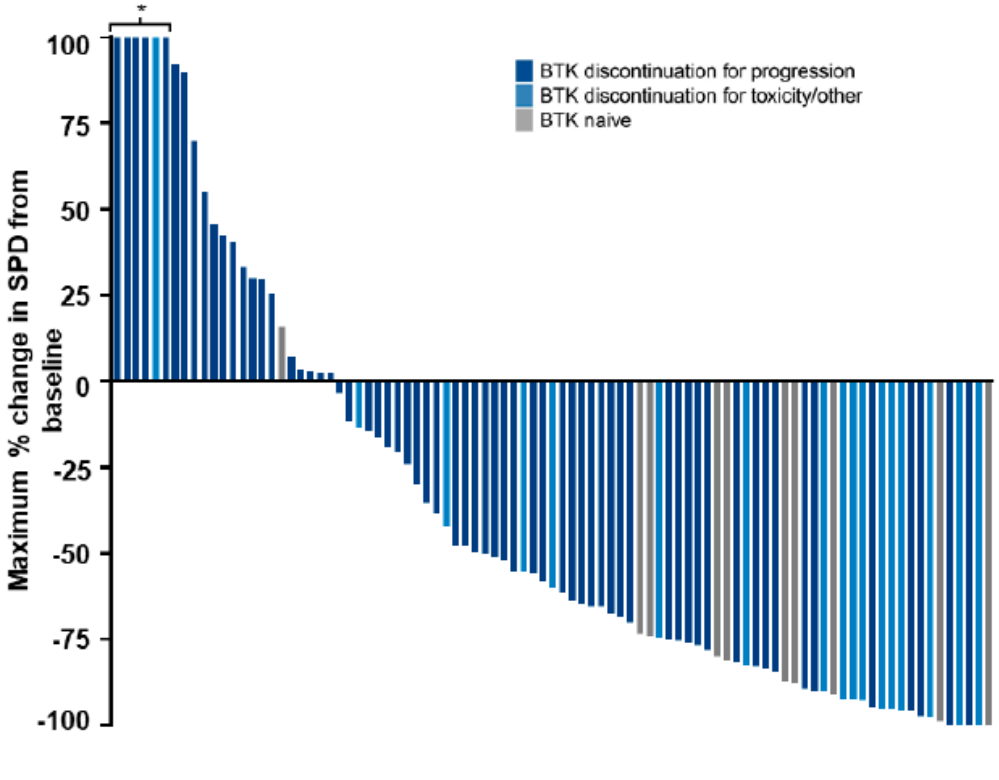
Neurologic Events

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

Wang M et al. NEJM 2020

A new BTK inhibitor in MCL (1)

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

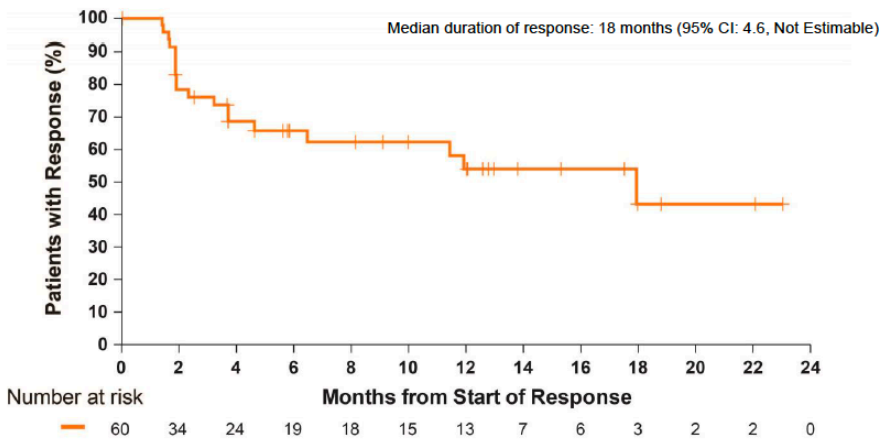
- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Mato A et al. Lancet 2021

A new BTK inhibitor in MCL (2)

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Data cutoff date of 16 July 2021. Response status per Lugano 2014 criteria based on investigator assessment.

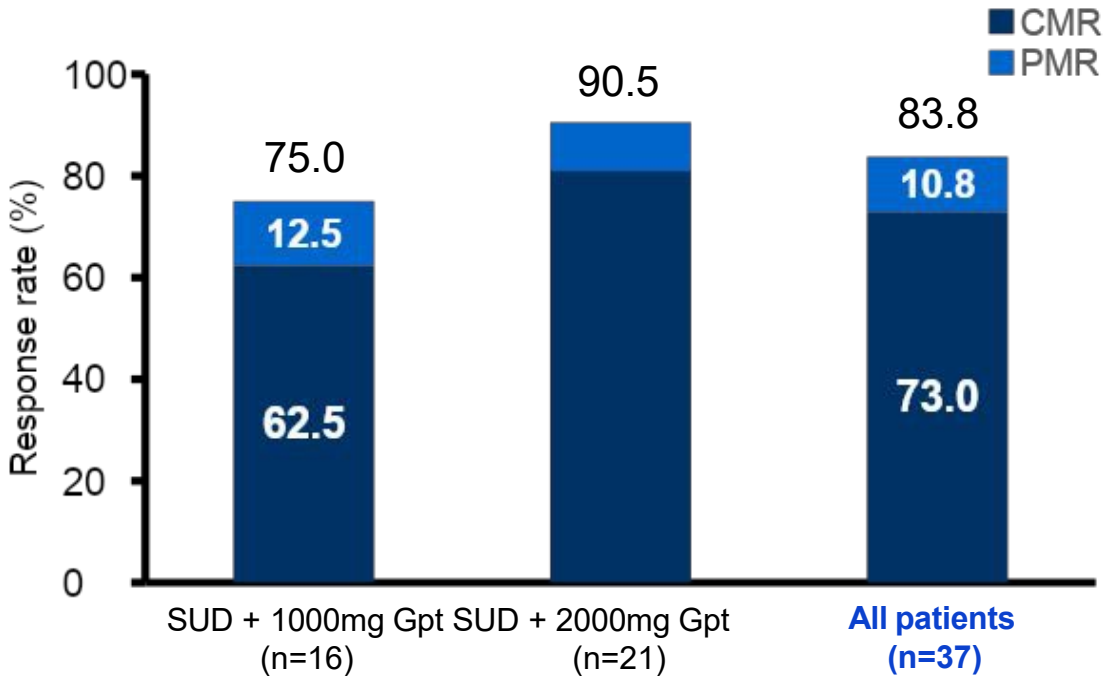
Pirtobrutinib: AE of special interest

AEs of special interest[b]	Gr. 1.	Gr. 2.	Gr. 3.	Gr. 4.	Total
Bruising[c]	20%	2%	-	-	22%
Rash[d]	9%	2%	<1%	-	11%
Arthralgia	8%	3%	<1%	-	11%
Hemorrhage[e]	5%	2%	1%[g]	-	8%
Hypertension	1%	4%	2%	-	7%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]

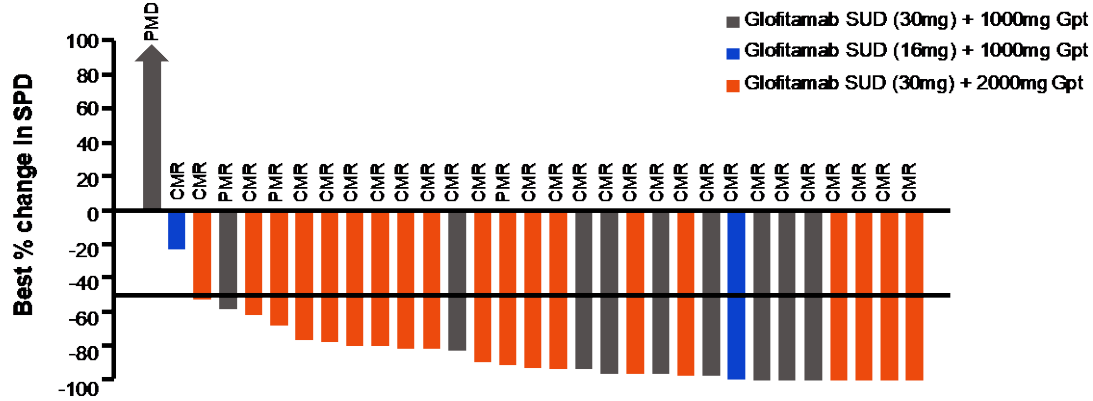
From Mato A et al. Lancet 2021

Glofitamab: Response rates in R/R MCL

All patients*



Best percentage change from baseline SPD*



CRS was the most common AE

*Efficacy results are reported for the secondary efficacy population (includes all patients who had a response assessment performed, withdrew early from treatment or study, or are on still on treatment at the time of their first scheduled response assessment). Prior lines of therapy ranged from 1–5 in both the responder and non-responder groups. CMR, complete metabolic response; PMR, partial metabolic response.

Phillips T et al., ASH 2022

Mantle Cell Lymphoma Takeaways

Introduction of BTKi (ibrutinib) in the first line setting

→ *Might alleviate ASCT need in young patients*

→ *Prolongs PFS (but not OS) in combination with B-R and R-maintenance*

New therapies become available in 2nd and 3rd+ line

→ *non-covalent BTK-inhibitor*

→ *CAR T cells*

Future developments include

→ *Combination of BTKi and BCL2i in patients with R/R disease*

→ *Triple combinations (anti-CD20, BTKi and BCL2i) in patients with TP53mut*

→ *Bispecific antibodies*

Conclusions

In B-cell malignancies, immunotherapies have significantly improved patients' outcome

→ *Anti-CD20; Lenalidomide with anti-CD20; Chimeric Antigen Receptor T-cell*

→ *may be T-cell engagers (bispecific antibodies) tomorrow*

Targeted agents alone or in combination have become standard of care

→ *BTK-inhibitors; BCL2-inhibitor; EZH2-inhibitor*

→ *lessons from the removal of PI3kinase inhibitors?*

Important challenges

→ *Optimal combination and sequencing of new therapies*

→ *Generalization of clinical results in minority groups unknown*