Chemo-Free* in Follicular Lymphoma

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Disclosures

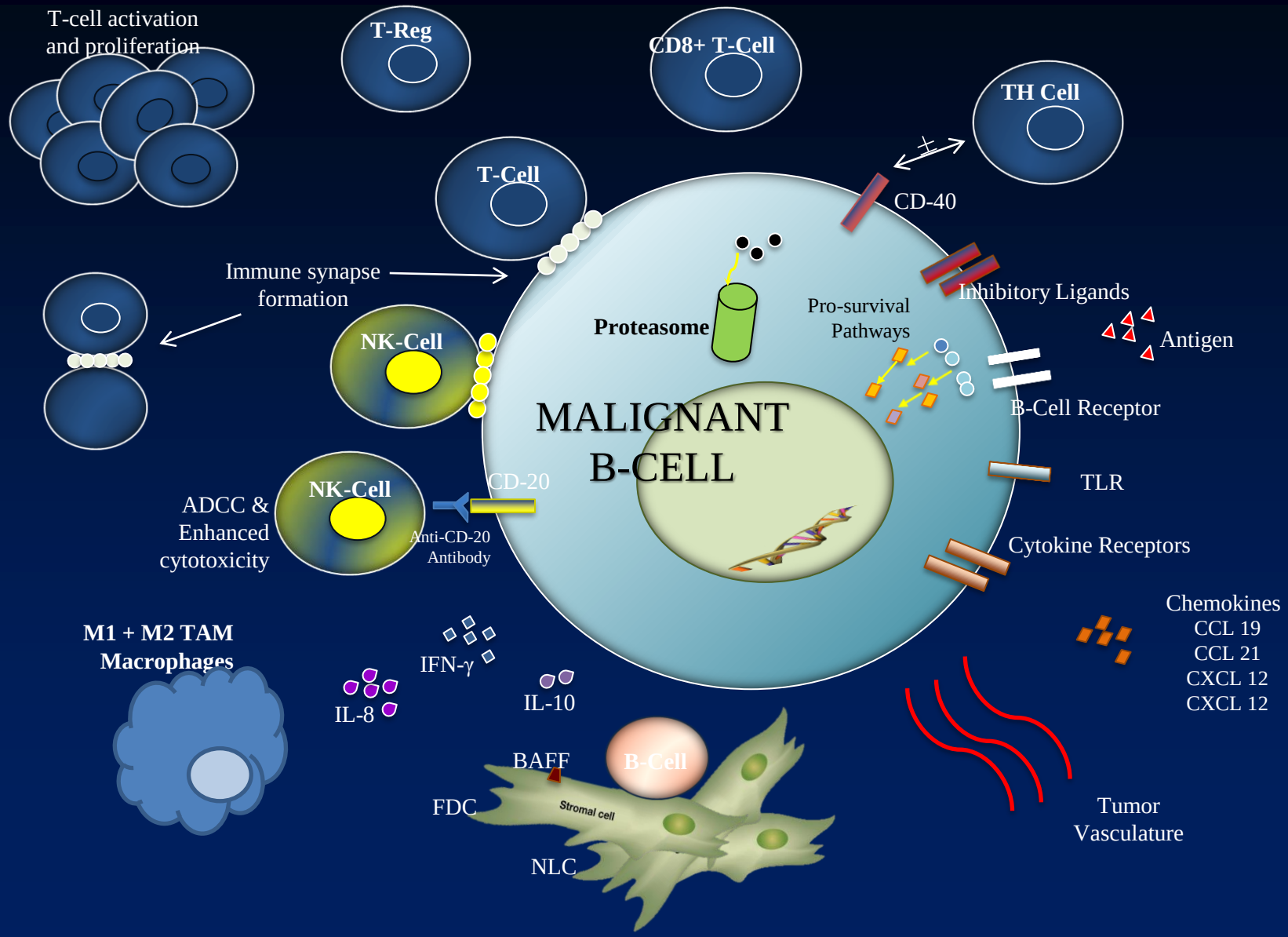
- Grants: Roche, Celgene, TG Therapeutics
- Advisory Board: Roche, TG Therapuetics, BMS, Novartis
- Employment: BostonGene

Why do we need more (*better?*) options?

- Chemotherapy is associated with short- and long-term toxicity[1-5]
  - Infection
  - Fatigue
  - Nausea
  - Cytopenias
  - Secondary malignancies
- Most patients are still not cured with traditional regimens[5-8]
- Unselected therapy does not benefit all populations

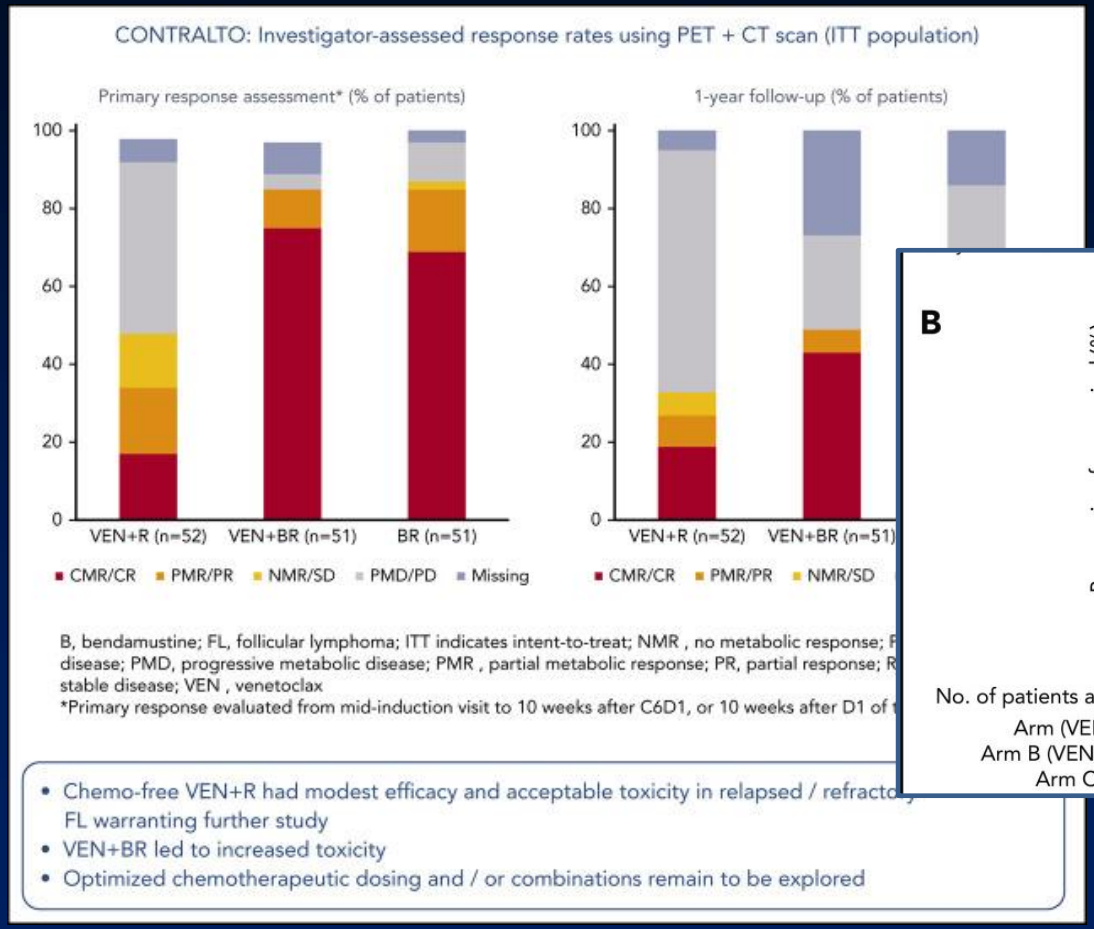
- 1. Green MR, et al. *Blood*. 2013;121(9):1604-1611; **2.** Hiddemann W, et al. At: ICML; 2017. Abstract 107; 3. National Cancer Institute. updated August 2018, www.cancer.gov/about cancer/treatment/side effects; 4. Federico M, et al. J Clin Oncol . 2013;31(12):1506 1513; 5. Marcus R, et al. N Engl J Med . 2017;377(14):1331 1344; 6. Fowler N. Hematology Am Soc Hematol Educ Program. 2016;2016(1):277 283; 7. Cabanillas F. J Clin Oncol . 2013; 31(1):14; 8. Alperovich A, *et al*. In: ASH Annual Meeting & Exposition; 2016. Abstract 2955.

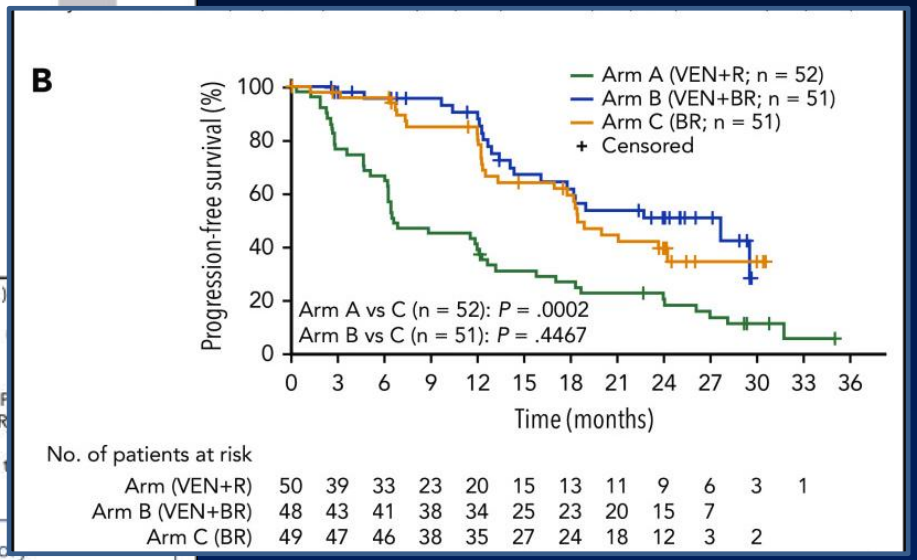
Survival Advantage in iNHL



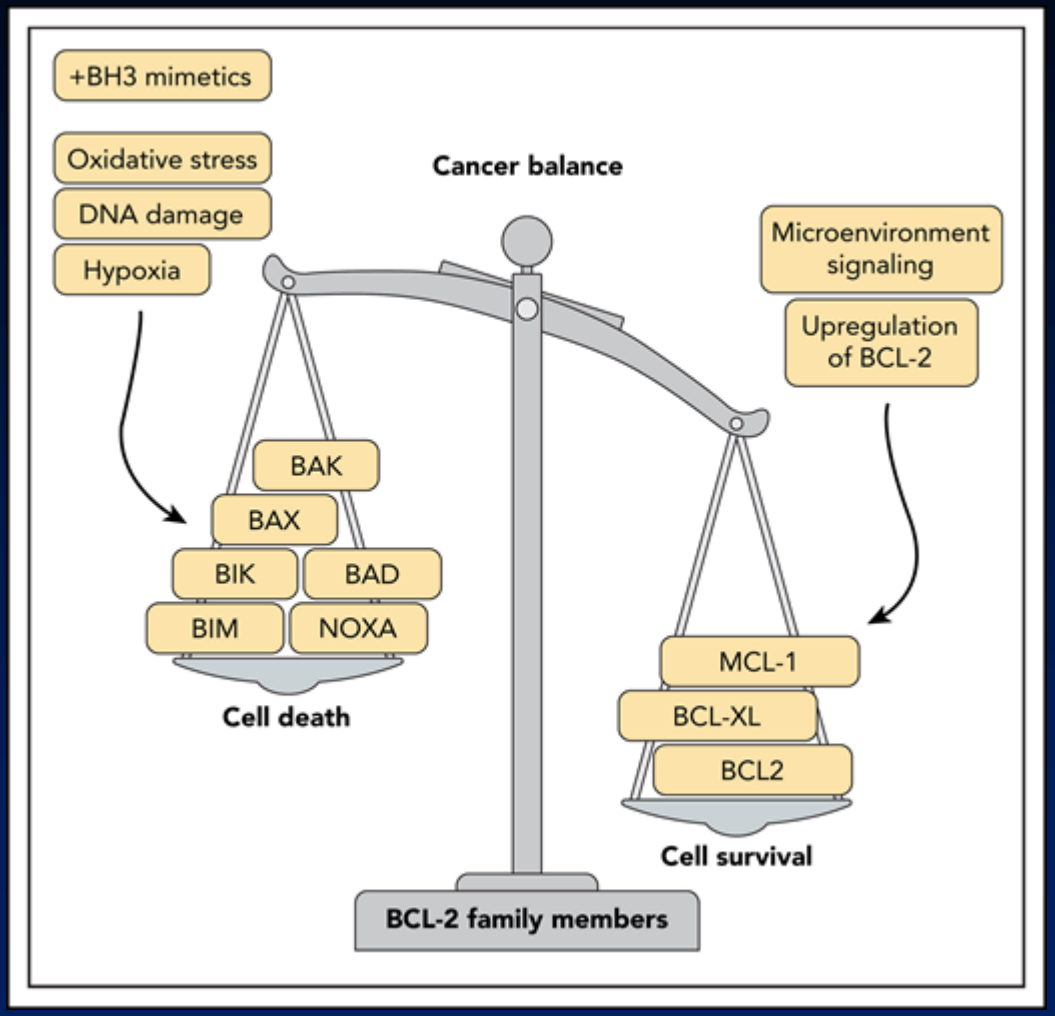
Fowler & Dunleavy; 2013 Dublin Summit on Immune Microenvironment

CONTRALTO: A Chemotherapy-Free Approach With Venetoclax in Relapsed/Refractory FL





Zinzani P et al. Blood 2020



Fowler N, *BCL-2 inhibition in follicular lymphoma: can we tip the scales?* Blood 2020

Phase II Multicenter Study of Tazemetostat, in R/R FL Patients- Results

Primary endpoint: ORR in Response Evaluable Population

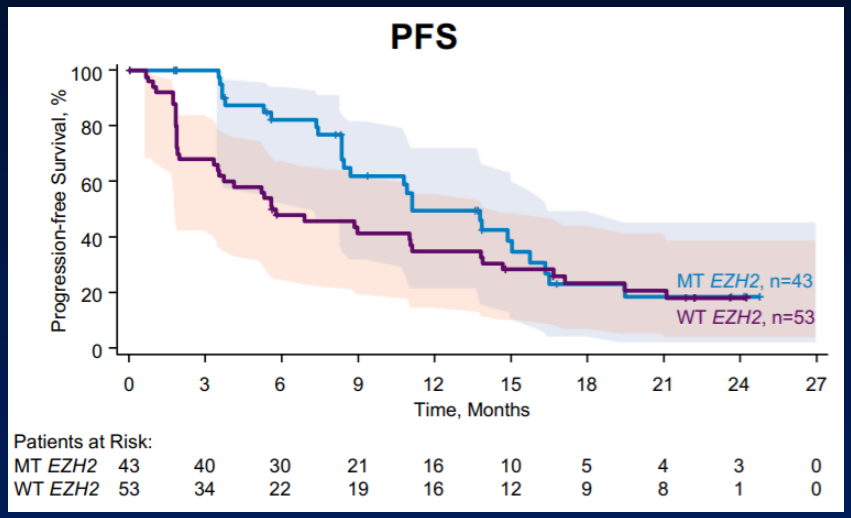
Endpoint n (%)	MT *EZH2* (n=43)	WT *EZH2* (n=53)
ORR [CR+PR]	33 (77%)	18 (34%)
95% CI[a]	(61.4–88.2)	(21.5–48.3)
CR	3 (7%)	3 (6%)
PR	30 (70%)	15 (28%)
SD	10 (23%)	16 (30%)
SD, treatment ongoing	4 (9%)	0
DCR (CR+PR+SD)	43 (100%)	34 (64%)
PD	0	19 (36%)

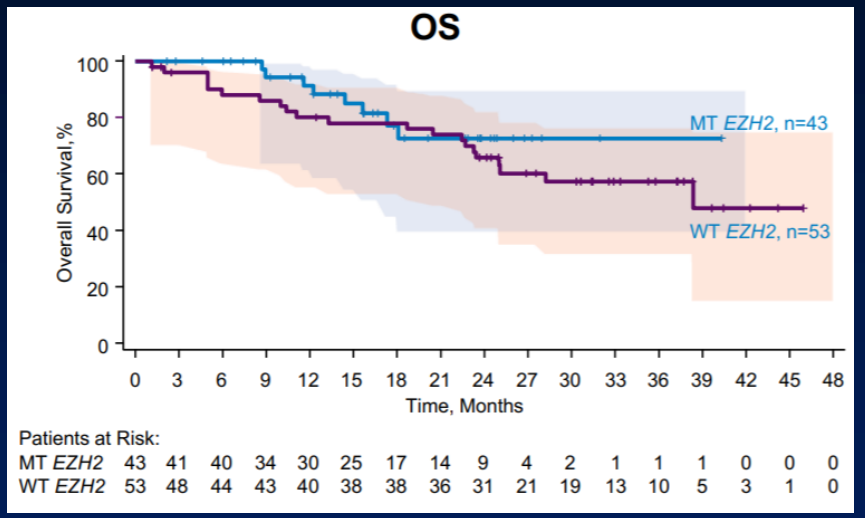
Best overall response based on Cheson (2007) criteria for lymphomas. a By Brookmeyer and Crowley method. CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; MT, mutant; PD, progressive disease; PR, partial response; SD, stable disease; WT, wild-type.

Morschhauser et al., ICML. 2019

Phase II Multicenter Study of Tazemetostat, in R/R FL Patients- Results

- Landmark Analysis for Responders in WT EZH2





Endpoint	Response Evaluable Population	
	MT *EZH2* (n=43)	WT *EZH2* (n=53)
Median PFS, months (95% CI)	11.1[a] (8.4–15.7)	5.7 (3.5–11.1)
Median OS, months (95% CI)	Not reached (NR) (NE–NE)	38.4 (25.0–NE)

a, Median PFS not mature for MT cohort; +, censored; CI, confidence interval; FL, follicular lymphoma; MT, mutant; NE, non-estimable; OS, overall survival; PFS, progression-free survival.

Morschhauser et al., ICML. 2019

Phase II Multicenter Study of Tazemetostat, in R/R FL Patients- Safety & AEs in ≥10% Patients

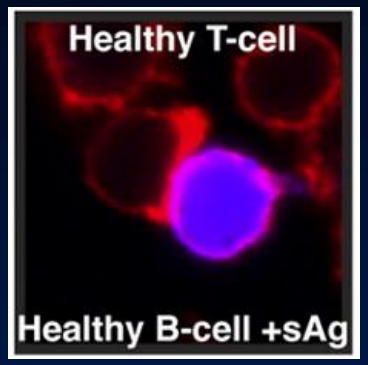
Category, n (%)	All Treatment-Emergent AEs (TEAEs) (N=99)		Treatment-related AEs (N=99)	
	All Grades[a]	Grade ≥3[b]	All Grades[a]	Grade ≥3[b]
Nausea	24 (24)	0 (0)	20 (20)	0 (0)
Asthenia	19 (19)	4 (4)	15 (15)	2 (2)
Diarrhea	18 (18)	0 (0)	12 (12)	0 (0)
Fatigue	17 (17)	2 (2)	12 (12)	1 (1)
Alopecia	17 (17)	0 (0)	14 (14)	0 (0)
Cough	16 (16)	0 (0)	2 (2)	0 (0)
Upper respiratory tract infection	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	12 (12)	1 (1)	2 (2)	0 (0)
Headache	12 (12)	0 (0)	5 (5)	0 (0)
Vomiting	12 (12)	2 (2)	6 (6)	1 (1)
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)

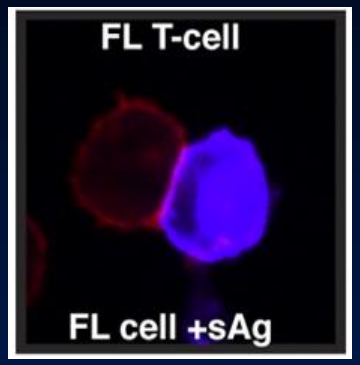
- Treatment with tazemetostat was generally well tolerated
  - 5% patients discontinued treatment due to a treatment-related AE
  - 9% patients had a dose reduction due to a treatment-related AE
  - Low rate of grade ≥3 treatment related AEs
- There were no treatment-related deaths

a All grades TEAEs reported as occurring in ≥10% of patients; b Grade ≥3 TEAEs reported in ≥5% patients

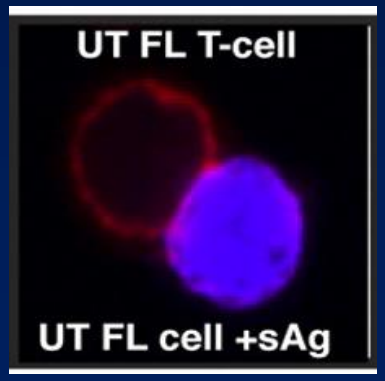
Morschhauser et al., ICML. 2019

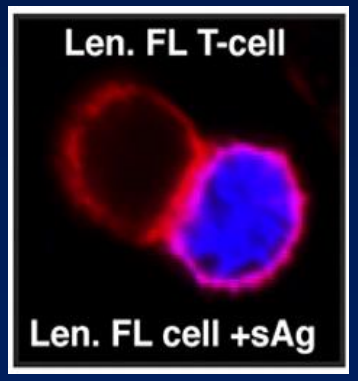
Lenalidomide may repair immune synapse





Follicular lymphoma cells exhibit defective T-cell synapse formation with autologous antigen-pulsed tumor cells

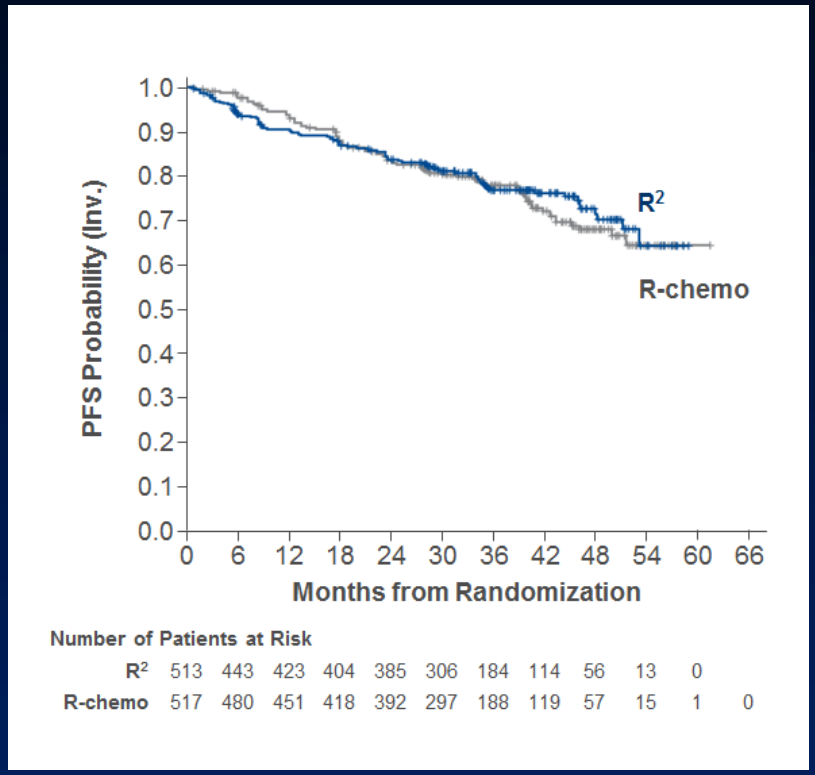




Lenalidomide repairs FL T-cell immunologic synapse dysfunction with autologous tumor cells.

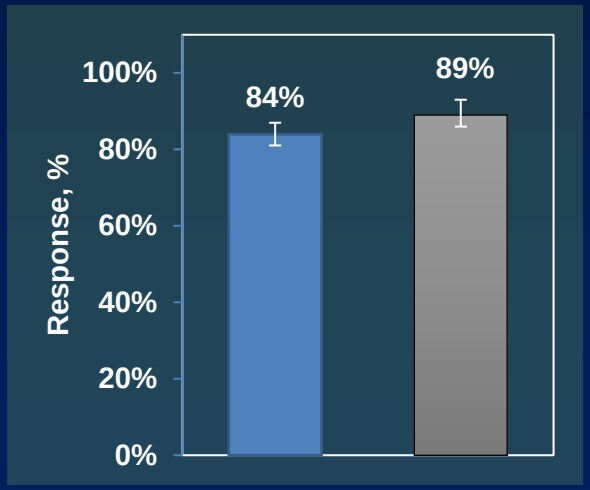
Ramsay A, et al Blood 2009; 114: 4713 - 4720

Lenalidomide plus Rituximab vs R-Chemo in Frontline FL



	R² (n = 513)	R-chemo (n = 517)
Events, n (%)	111 (22)	121 (23)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-81%)
HR (95% CI)	0.94 (0.73-1.22)	
P value	0.63	

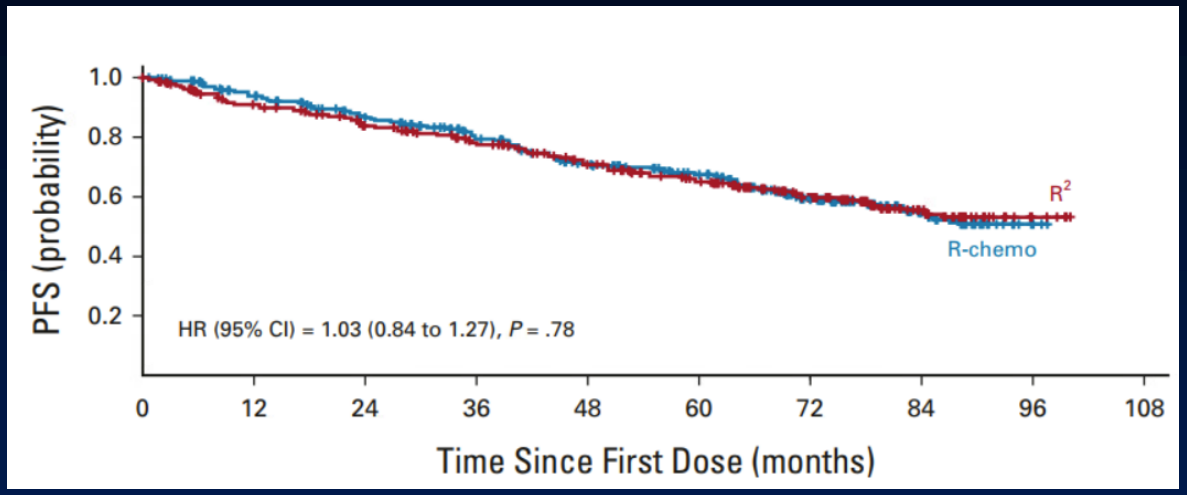
Best ORR

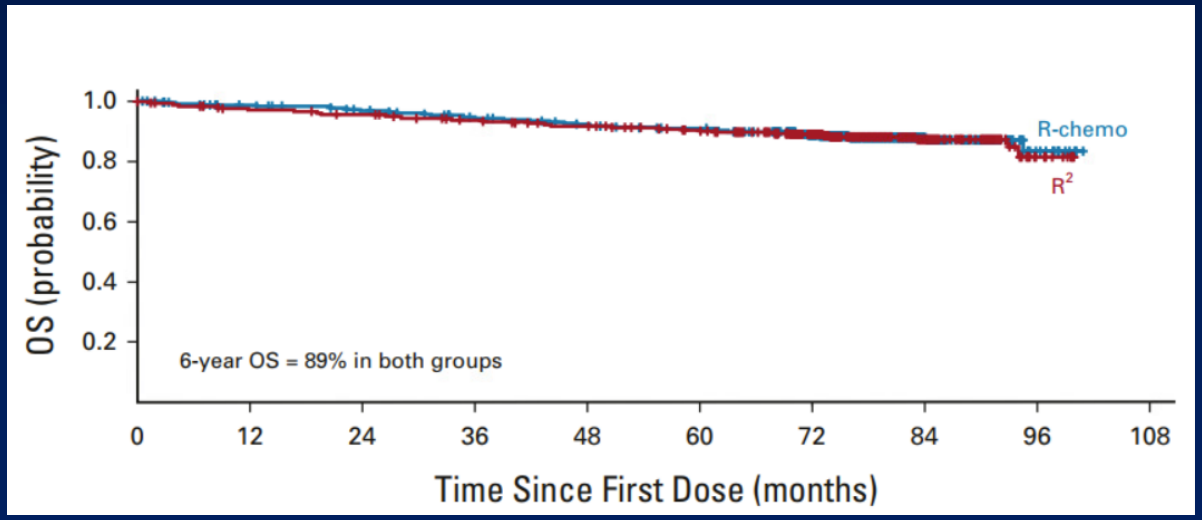


- 3-year DOR was 77% for R² vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

Morchauser F, Fowler N et al, NEJM 2019

RELEVANCE: 6 Year Follow up



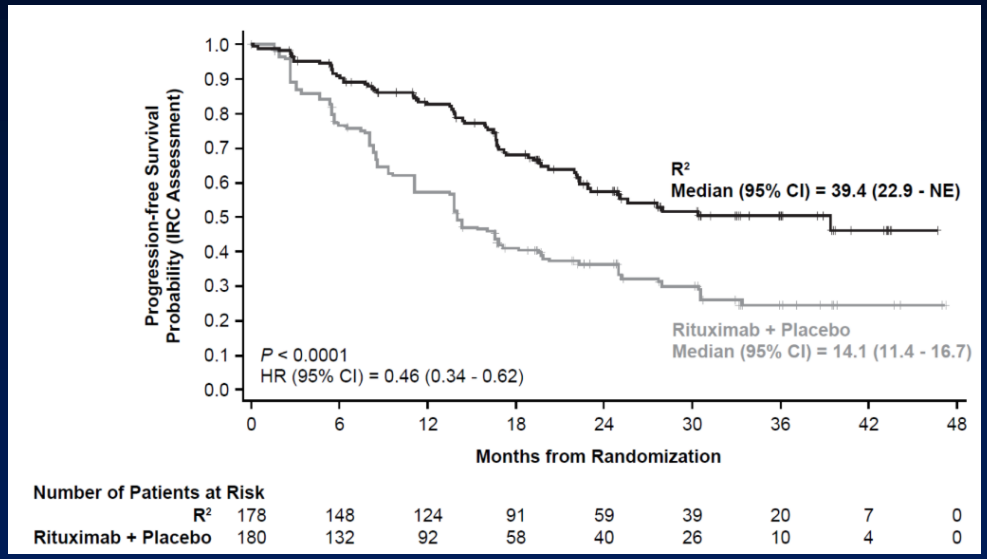


Morchhauser F, et al. JCO 2022

Adverse Events

Fowler N, et al. ASCO 2018

Phase 3 R^2 vs Rituximab + Placebo in R/R iNHL (AUGMENT)



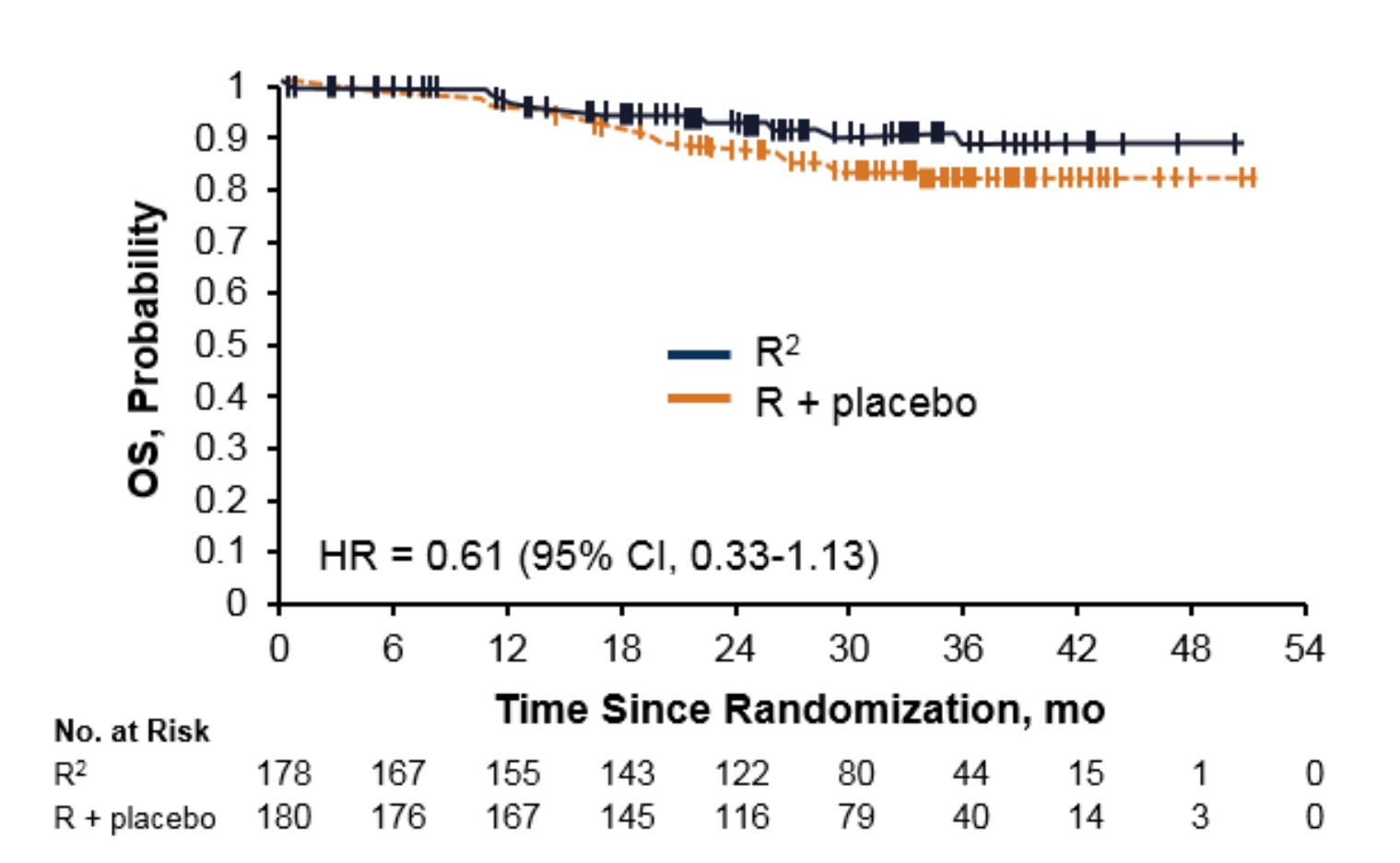
Efficacy, %	R^2	R + PBO
ORR by IRC	78	53
CR	34	18
PR	44	35
Median DOR, mo	36.6	21.7
2-y OS rate	93	87
Completion of all planned treatment	71	61

- **Median follow-up was 28.3 months**

- **Time to next lymphoma treatment was longer for the R^2 arm versus R + PBO (HR=0.54 [95% CI, 0.38-0.78]; *P*=0.0007**
- **OS data not mature, but at time of analysis:**
  - **16 deaths reported in R^2 arm**
  - **26 deaths reported in R + PBO arm**

Leonard J, [Fowler N] et al. ASH 2018. Abstract 445.

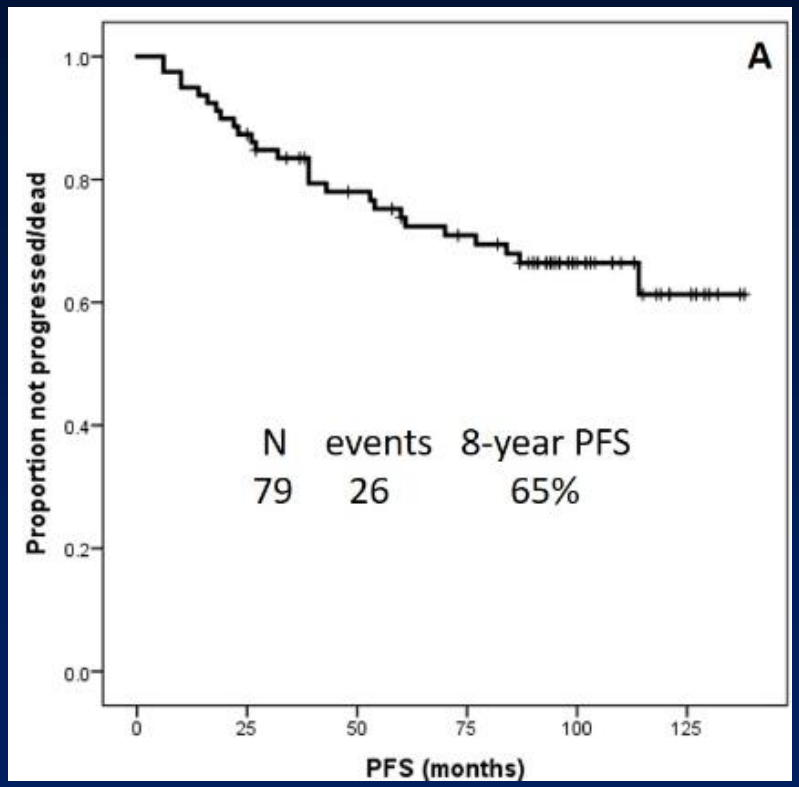
Augment: Overall Survival



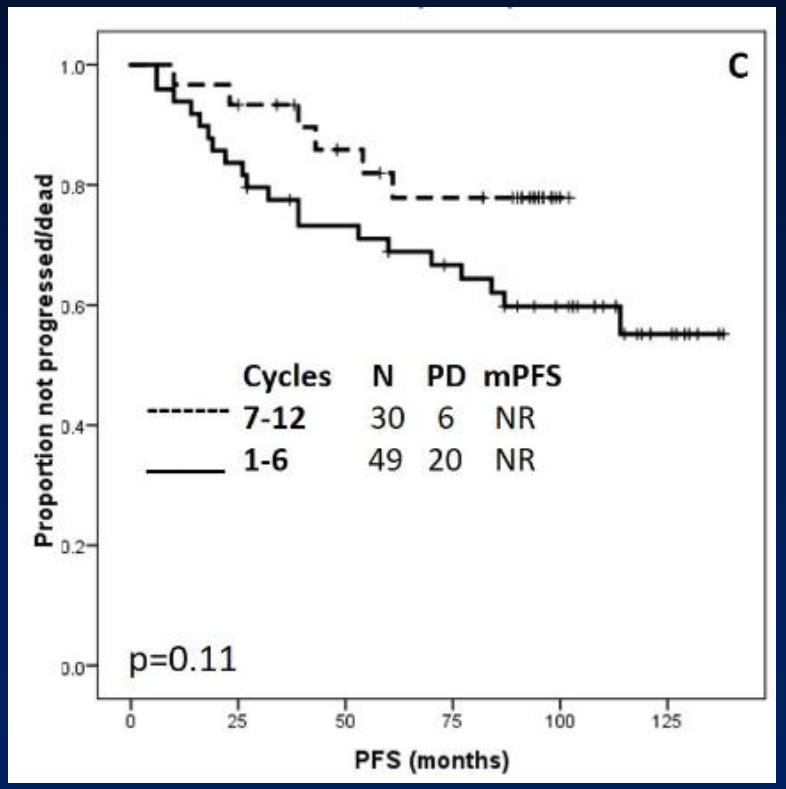
Leonard J, [Fowler N] et al. ASH 2018. Abstract 445.

How long should I give R2?

All Follicular Patients



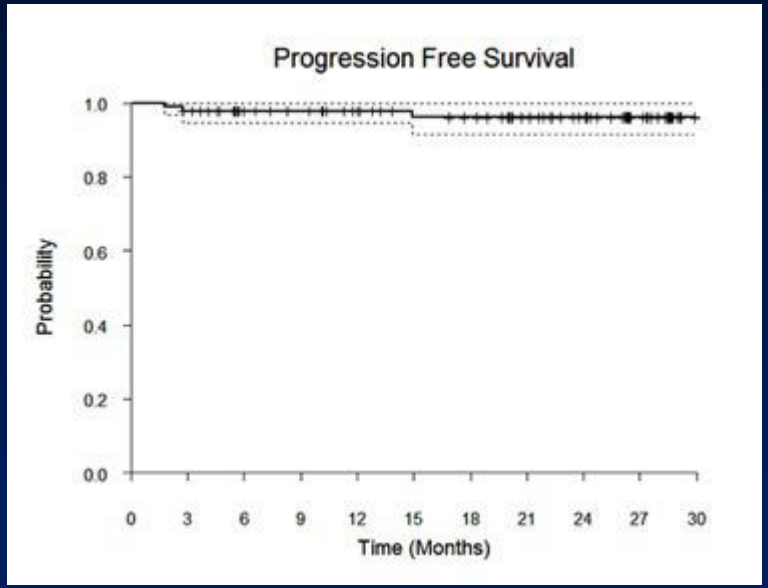
6 vs 12 Cycles



Strati P, [Fowler N], et al. Blood 2020. In press.

Lenalidomide plus Obinutuzimab in Untreated High Tumor Burden FL

Study	N	ORR/CR	PFS
MDACC	90	98%/92%	2 Yr 96%
LYSA	100	94%/80%	3 Yr 82%



Nastoupil L, et al. ASH 2020
Bachy E ,et al. ASH 2021

Selected Combination R2 Studies

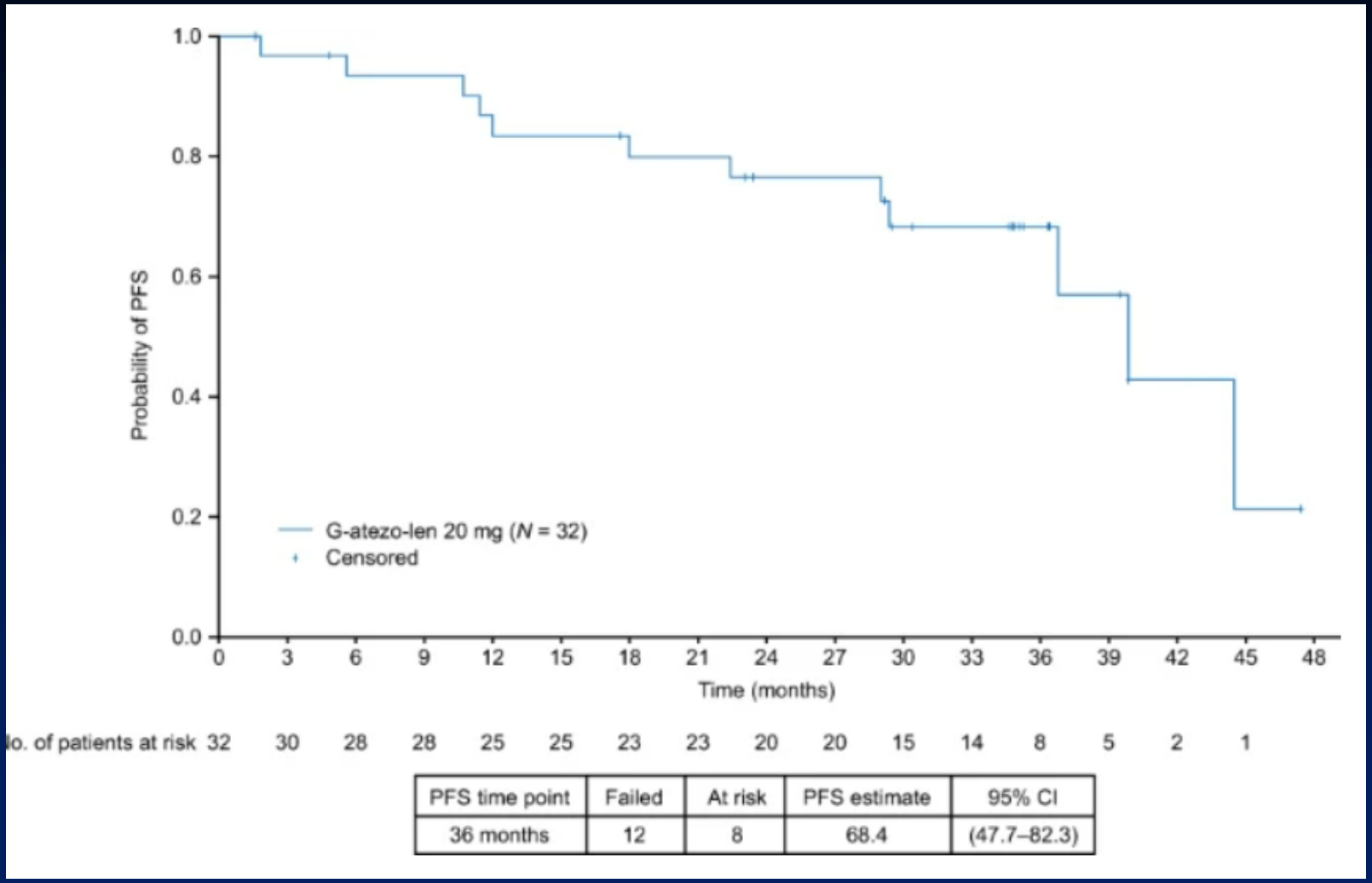
	R2 Partner	Sponsor/Lead	N	Setting	Results
PI3K	Idelalisib	MDACC	8	Relapsed indolent NHL	Closed due to toxicity, liver failure, colitis
PI3K	Idelalisib	Alliance	11	Relapsed indolent and Mantle cell lymphoma	Excessive toxicity, sepsis, pneumonia, rash
BTKi	Ibrutinib	MDACC	42	Relapsed indolent NHL	ORR 97%, CR 78% increased rash
BTKi	Ibrutinib	Alliance	22	Untreated indolent	Similar efficacy, increased toxicity and rash
BTKi	acalabrutinib	MDACC	40	Relapsed indolent NHL	ongoing
Chemo	CHOP	LYSA	80	Frontline indolent NHL	CR 74% 3yr PFS: 79% GR4 neutropenia: 65%
Chemo	Bendamustine	HOVON	18	Relapsed Follicular	GR4 neutropenia 50% Randomized phase II ongoing
BCL2i	venetoclox	Chan, Australia	61	Relapsed Follicular	Ongoing
EZH2i	tazometostat	Epizyme	15	Relapsed Follicular	ORR 92% CR 41%
PDL1i	atezolizumab (plus obin)	Roche	37	Relapsed Follicular	CR 75% 3Yr PFS 68%
BITE	Mosuntuzumab (no rituximab)	Roche	22	Relpased Follicular	ORR 90% CR 65%
CD19	Tafasitamab	Epizyme	528	Relpased Indolent	Randomized study ongoing

PDL-1 plus Lenalidomide and Rituximab

Characteristic, [*n* (%), unless stated]	Safety population (*N* = 38)
Median age, years (range)	61.5 (38–79)
Male	19 (50)
ECOG PS 0–1	38 (100)
Ann Arbor stage III/IV at diagnosis	30 (79)
FLIPI risk group [low (0–1); intermediate (2); high (≥3)]	6 (16); 22 (58); 10 (26)
Elevated LDH >1 × ULN	9 (24)
Prior lines of therapy [1; ≥2]	20 (53); 18 (47)
Prior treatment	
Bendamustine	12 (32)
CHOP	24 (63)
Obinutuzumab	1 (3)
Rituximab	35 (92)
Refractory to last line of treatment	17 (45)
Refractory to last line of anti-CD20 antibody	11 (29)
POD24 on first-line treatment	14 (37)
Bulky disease (≥7 cm)	6 (16)
Bone marrow infiltration	13 (35)*
Extranodal involvement	20 (53)

Morchhauser F, et al Blood Canc J. 2021

PDL-1 plus Lenalidomide and Rituximab



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

Morchhauser F, et al Blood Canc J. 2021

PDL-1 plus Lenalidomide and Rituximab

Patient, *n* (%)	G-atezo-len 15 mg (*n* = 4)	G-atezo-len 20 mg (*n* = 34)	All patients (*N* = 38)
Any AE	4 (100.0)	34 (100.0)	38 (100.0)
Grade 3–5 AE	4 (100.0)	28 (82.4)	32 (84.2)
Grade 5 (fatal) AE[a]	0	2 (5.9)	2 (5.3)
Serious AE	2 (50.0)	16 (47.1)	18 (47.4)
AE leading to discontinuation of any study drug[b]	1 (25.0)	10 (29.4)	11 (28.9)
AE leading to study discontinuation[c]	0	2 (5.9)	2 (5.3)
AE leading to dose interruption of any treatment	4 (100.0)	30 (88.2)	34 (89.5)
Atezolizumab-related AESI (≥5%)[d]			
Hyperthyroidism	0	5 (14.7)	5 (13.2)
Hypothyroidism	0	4 (11.8)	4 (10.5)
ALT increased	1 (25.0)	2 (5.9)	3 (7.9)
AST increased	1 (25.0)	2 (5.9)	3 (7.9)
Lipase increased	0	3 (8.8)	3 (7.9)
Hepatocellular injury	0	2 (5.9)	2 (5.3)
Rash	0	2 (5.9)	2 (5.3)
Rash maculopapular	0	2 (5.9)	2 (5.3)
Squamous cell carcinoma	0	2 (5.9)	2 (5.3)
Pneumonitis	1 (25.0)	0	1 (2.6)
Bronchiolitis	1 (25.0)	0	1 (2.6)

Should we switch to ‘chemo-free’ regimens in follicular lymphoma?

Chemotherapy Backbones

+ Long term data available
+ High efficacy rate
+ Known toxicities
+ Inexpensive*
+Limited duration

- **Mostly intravenous**
- **acute/late toxicity**
- **High Infection rate**
- **Unselected**
- **Genotoxic**
- **Rarely curative**

Biologic Backbones

+ Improved QOL?
+ Selected
+ Mostly Oral

- Expensive**
- Prolonged duration
- Unknown long term AEs
- Unpredictable toxicity
- No biomarkers (yet)

*Costs less than a Ferrari.

**Costs more than a Ferrari. (>1)

Should we switch to ‘chemo-free’ regimens in follicular lymphoma?

Yes, but…..

- Therapy choice should be driven by biologic predictors of risk,response and toxicity.
  - TME, BioFLIPI, EZH2, GEP Scoring etc
- Duration of therapy should be driven by response kinetics and depth.
  - MRD, Clonotyping in PB, CTDNA
- All patients should undergo banking of tissue and blood when feasible.