Indolent Non-Hodgkin lymphoma and Mantle Cell Lymphoma

Novel advances in 2023 in less than 40…

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Indolent Non-Hodgkin lymphomas

- Follicular lymphoma
- Marginal zone lymphoma
  - ✓ Primary cutaneous MZL
  - ✓ Nodal MZL
  - ✓ Splenic MZL
  - ✓ Extranodal MZL of the mucosa-associated lymphoid tissue (i.e. MALT lymphoma).
- Small lymphocytic lymphoma
- Lymphoplasmacytic lymphoma (WM)
- Nodular lymphocyte predominant B-cell lymphoma (prior NLPHL)

Mantle cell lymphoma

- In situ mantle cell neoplasm
- Mantle cell lymphoma (MCL)
- Leukemic non-nodal MCL

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Alaggio R et al. Leukemia. 2022 Jul;36(7):1720-1748

Follicular lymphoma

- Second most common NHL (35%) with a median age at diagnosis of 65 years.
- Most FL (85%) have overexpression on the anti-apoptotic protein BCL-2, via t(14;18). Epigenetic mutations are also important (i.e. EZH2).
- Indolent course but usually in advance stages at presentation (~50-70% BM) and but biologic behavior can be highly variable.
- Special FL subtypes: duodenal FL and Pediatric FL.
- **Currently not curable but very treatable. The goals should be:**
  - ✓ Treat only when it is appropriate.
  - ✓ Long lasting disease control with improvement of QoL.

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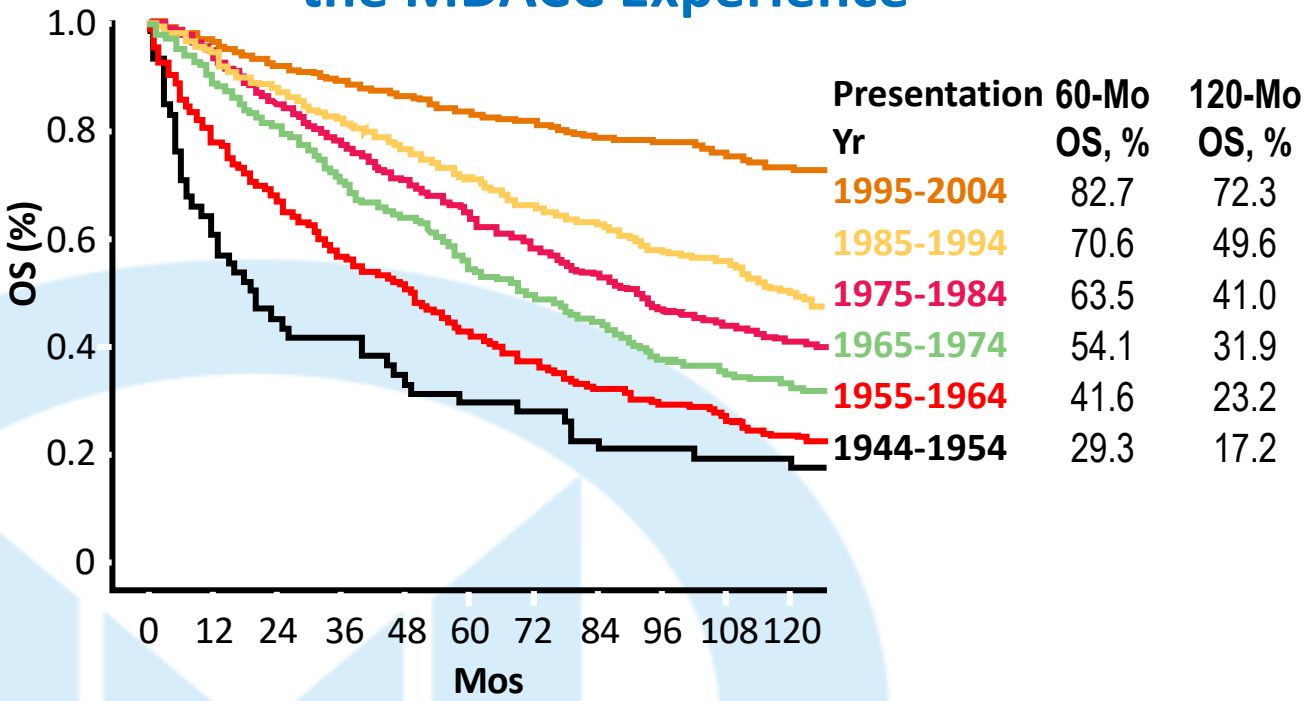
Jacobsen E et al. Am J Hematol. 2022;97:1638–1651.

FL: prognosis has improved but we need to do better

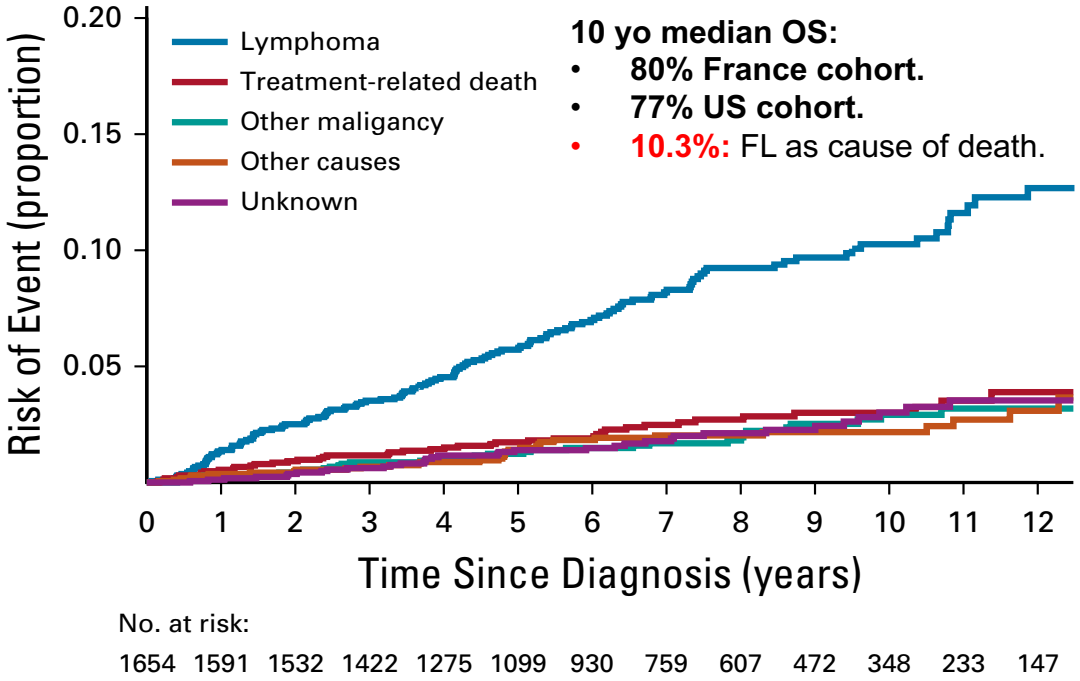
OS Improvement in Indolent B-Cell Lymphoma from 1944 to 2004: the MDACC Experience



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.

Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts



Sarkozy C et al. J Clin Oncol . 2018; 37:144-152.

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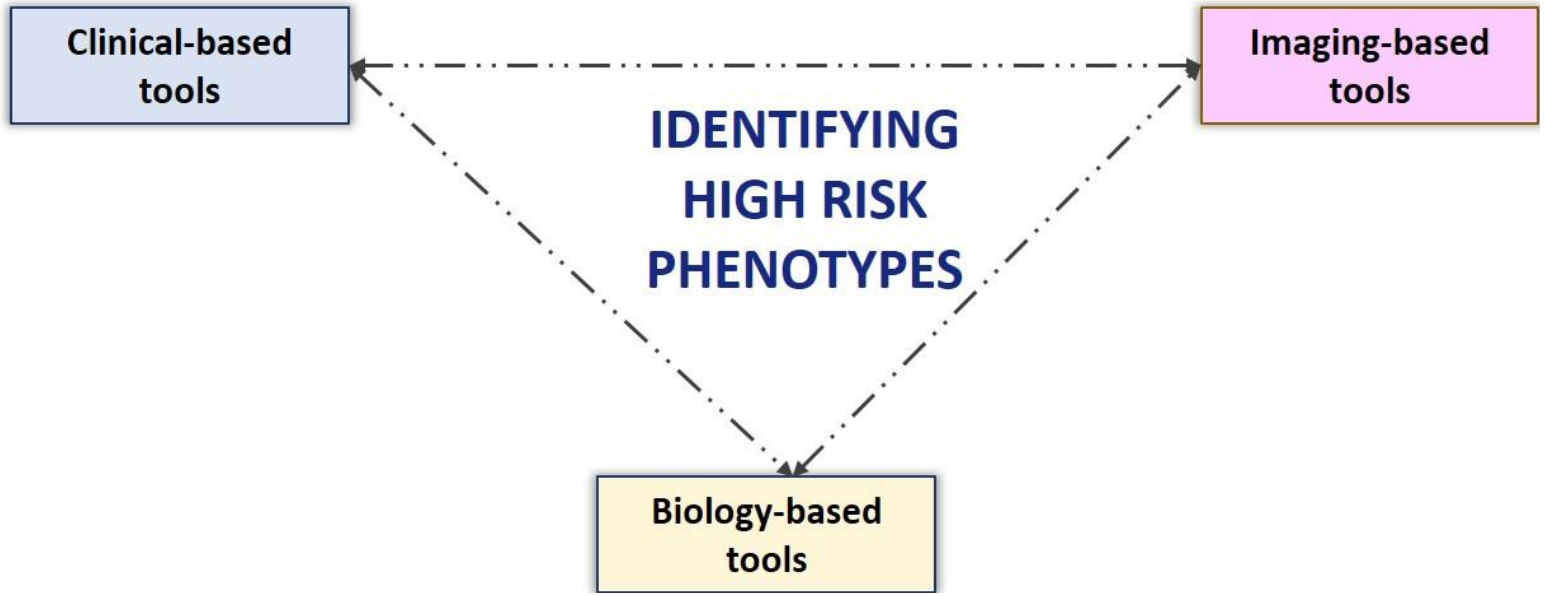
FL: but how to better assess prognosis?



At diagnosis/before treatment

- Clinical: FLIPI, FLIPI2, PRIMA-PI, FLEX
- Biology: m7-FLIPI, PRIMA 23-gene, PD-L2
- Imaging: Baseline PET metrics

After therapy

- Imaging: EOI PET
- Biology: MRD (*not standard*)
- Response-based: POD24, transformation

Biology: MRD, circulating tumor DNA (*research tools*)

At intervals

Nastoupil L. 27th Annul congress in Hem malignancies, Miami, FL , 2023

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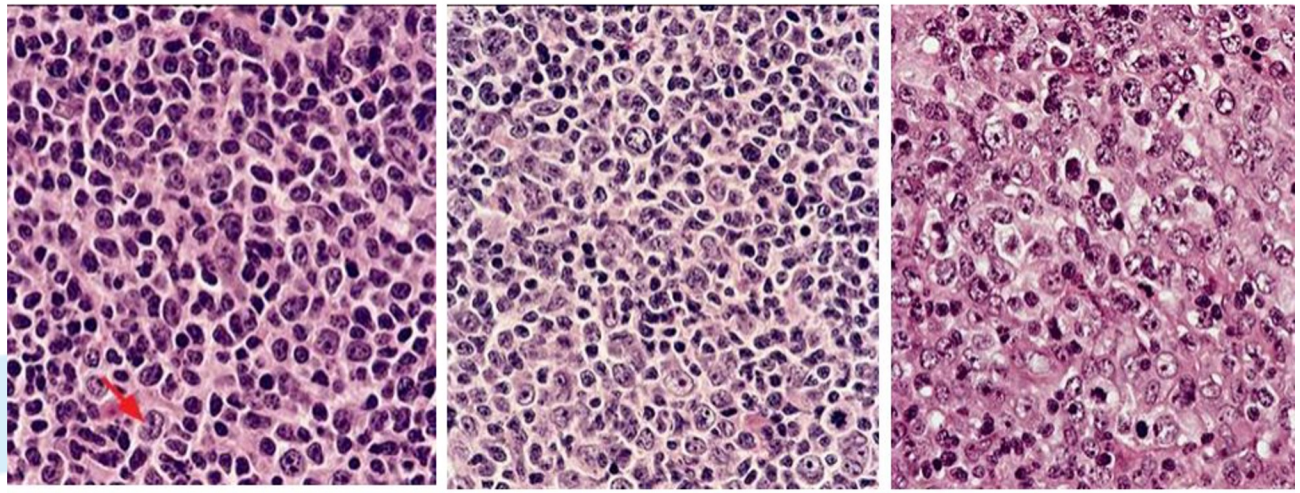
5th edition of the World Health Organization

"beta version"

Grade 1
0-5 centroblasts /HPF

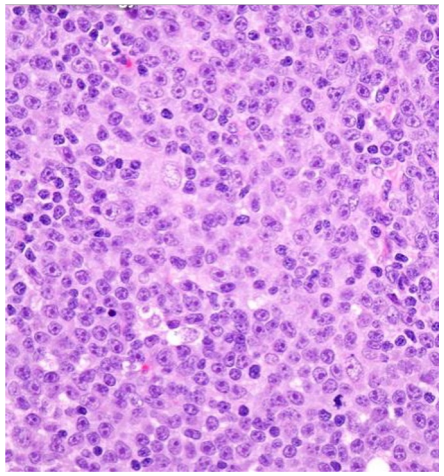
Grade 2
6-15 centroblasts /HPF

Grade 3a
>15 centroblasts /HPF
centrocytes present



Centrocytes present

Grade 3b
Sheets of centroblasts
without centrocytes



Centrocytes absent

Classic Follicular lymphoma (cFL)
Managed as follicular lymphoma

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

Courtesy of Dr. Sameh Gaballa, MCC Tampa

Alaggio R et al. Leukemia. 2022 Jul;36(7):1720-1748

Follicular lymphoma

When to treat?

✓Anemia (Hb < 10 g/dl) or thrombocytopenia (< 100 K)platelets due to BM infiltration by FL.

✓Lymph nodes or tumor mass > 7 cm.

✓Enlarged LN > 3cm in > 3 different areas.

✓Splenomegaly (> 16 cm).

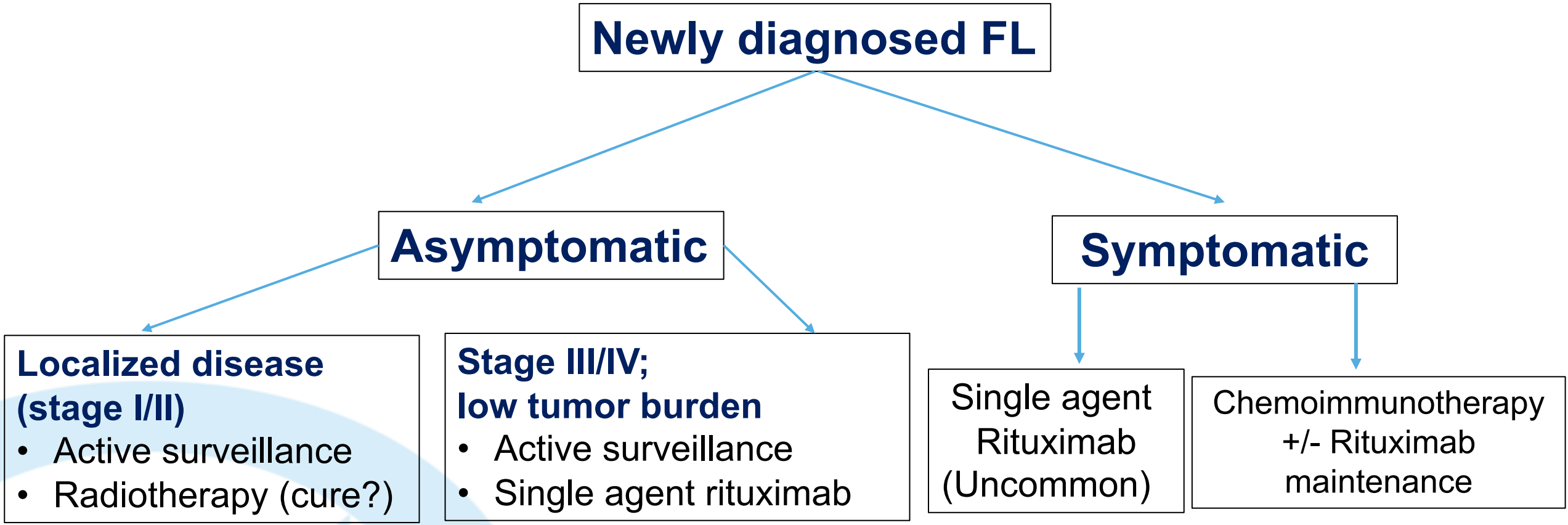
✓Symptoms related to LN/tumoral compression: airway, liver/biliary duct, GI tract, etc.

✓Pleura/pericardial effusions, or ascites.

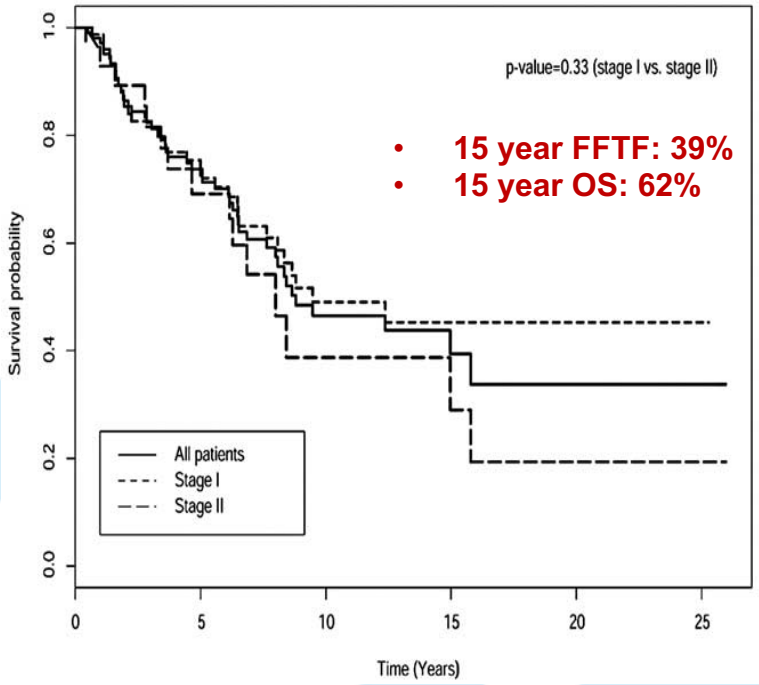
✓Constitutional symptoms.

✓Circulating FL cells (> 5 x 10^9/L)

High tumor burden

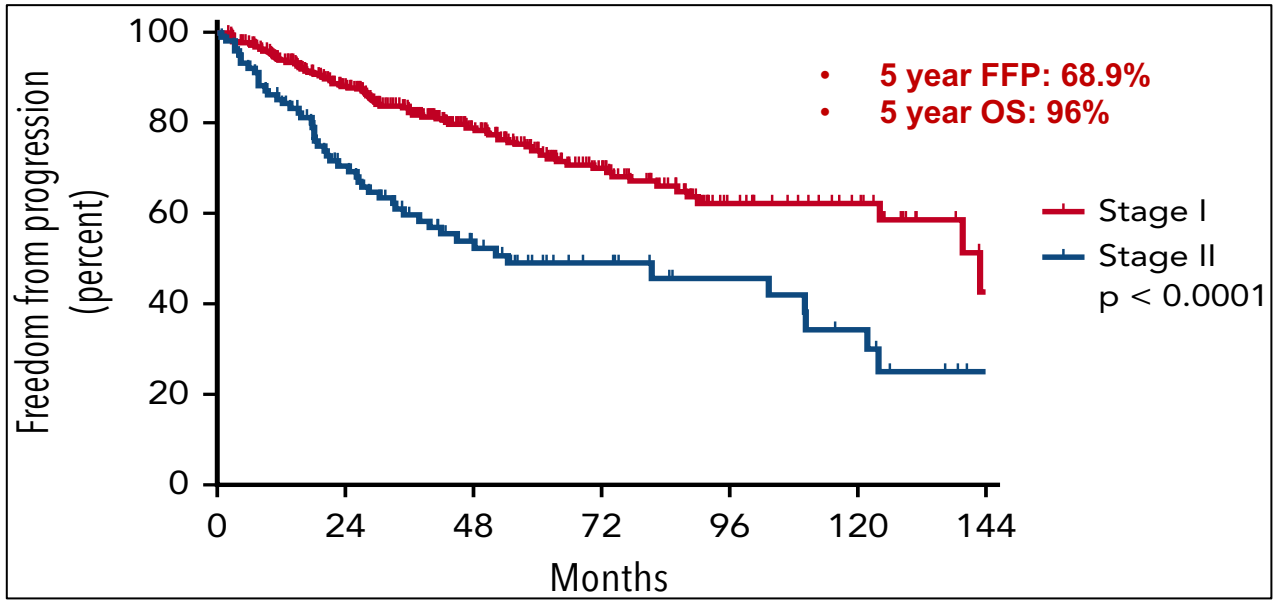

Newly diagnosed FL
Asymptomatic
Symptomatic
Localized disease (stage I/II)
• Active surveillance
• Radiotherapy (cure?)
Stage III/IV; low tumor burden
• Active surveillance
• Single agent rituximab
Single agent Rituximab (Uncommon)
Chemoimmunotherapy +/- Rituximab maintenance

Stage I and localized stage II (Curable?)



- 15 year FFTF: 39%
- 15 year OS: 62%

106 S I/II non-bulky FL patients treated with RT[1]



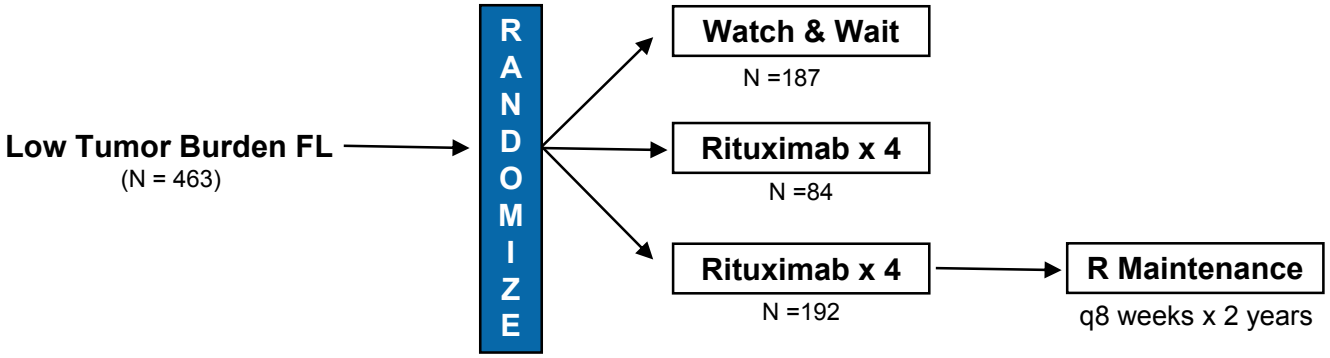
- 5 year FFP: 68.9%
- 5 year OS: 96%

512 stage I/II non-bulky FL patients treated with RT[2]

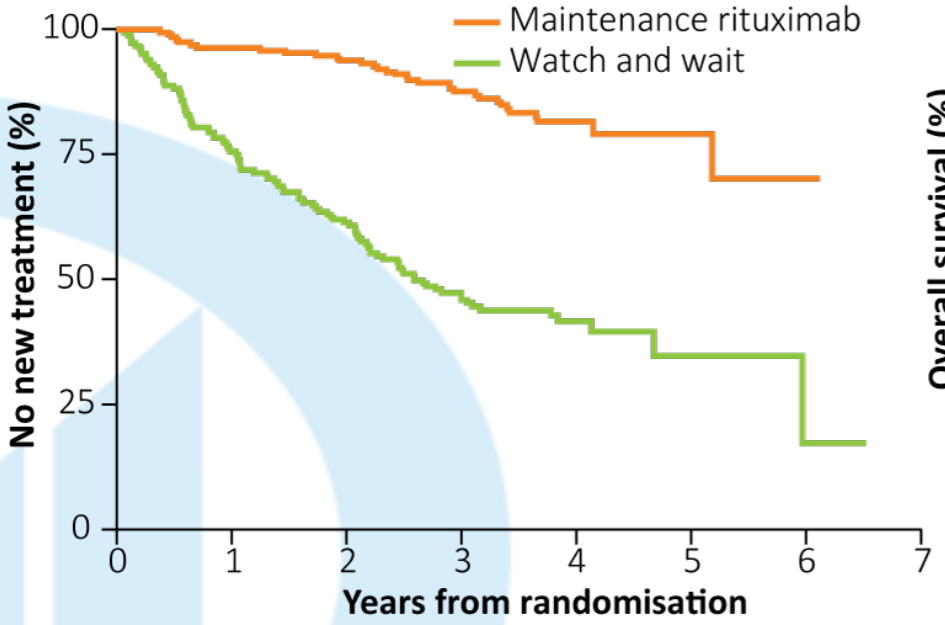
- **Stage I: 80.1%.**
- **Median RT dose: 30 Gy**

1. Guadagnolo et al. Int J. Rad Onc Biol Phys. 2006.
2. Brady JL et al. Blood. 2019;133(3):237-245

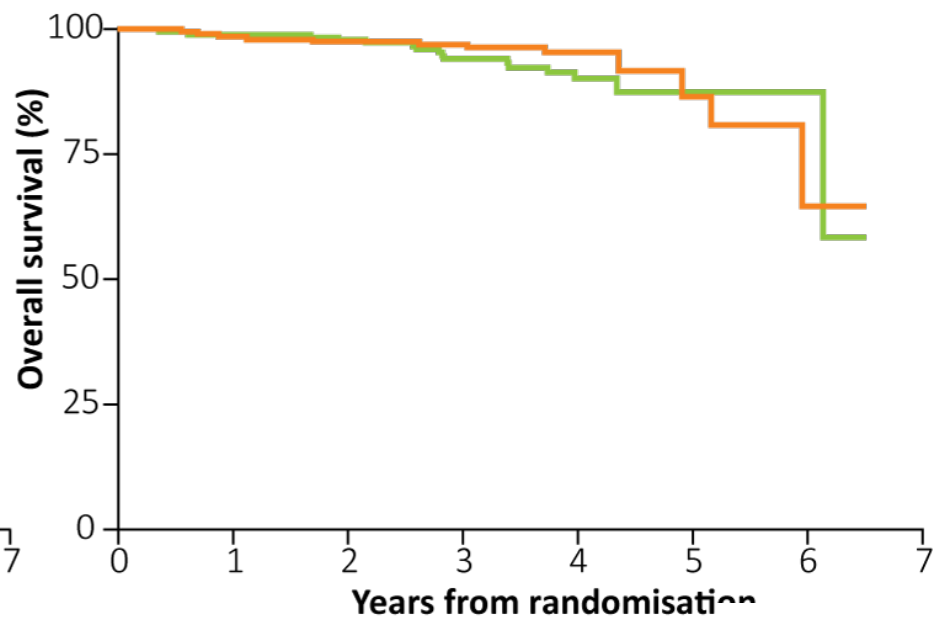
Stage III/IV FL with low tumor burden disease



Time to start of new treatment



Overall survival



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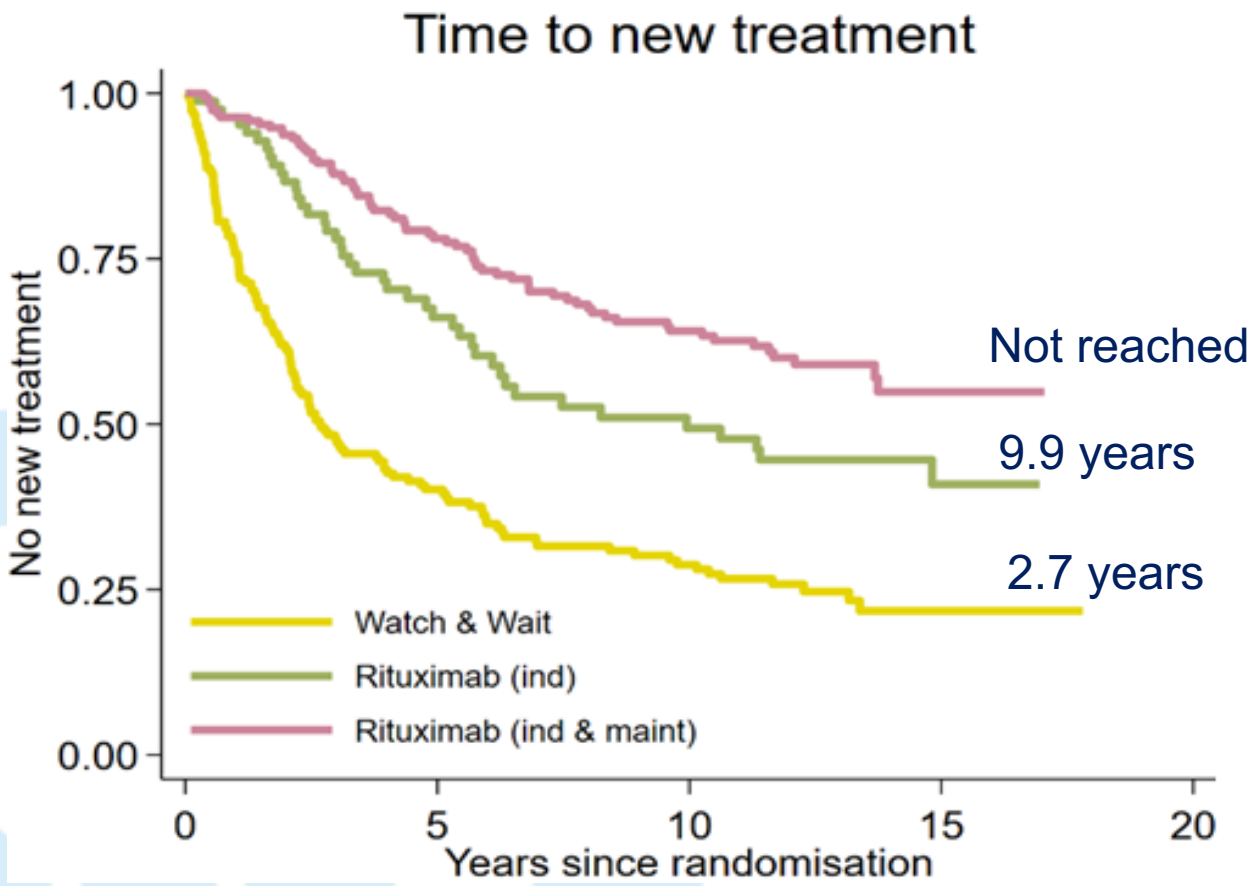
Ardeshna KM et al. Lancet Oncol 2014;15(4):424-35

12-year f/up the International phase III RCT of Rituximab Induction (RI), Rituximab maintenance (RM) vs. Watch and Wait



	Hazard ratio (95% CI)	p-value
RI vs W&W	0.48 (0.34-0.68)	p<0.001
RM vs W&W	0.31 (0.23-0.42)	p<0.001
RM vs RI	0.65 (0.44-0.96)	p=0.03

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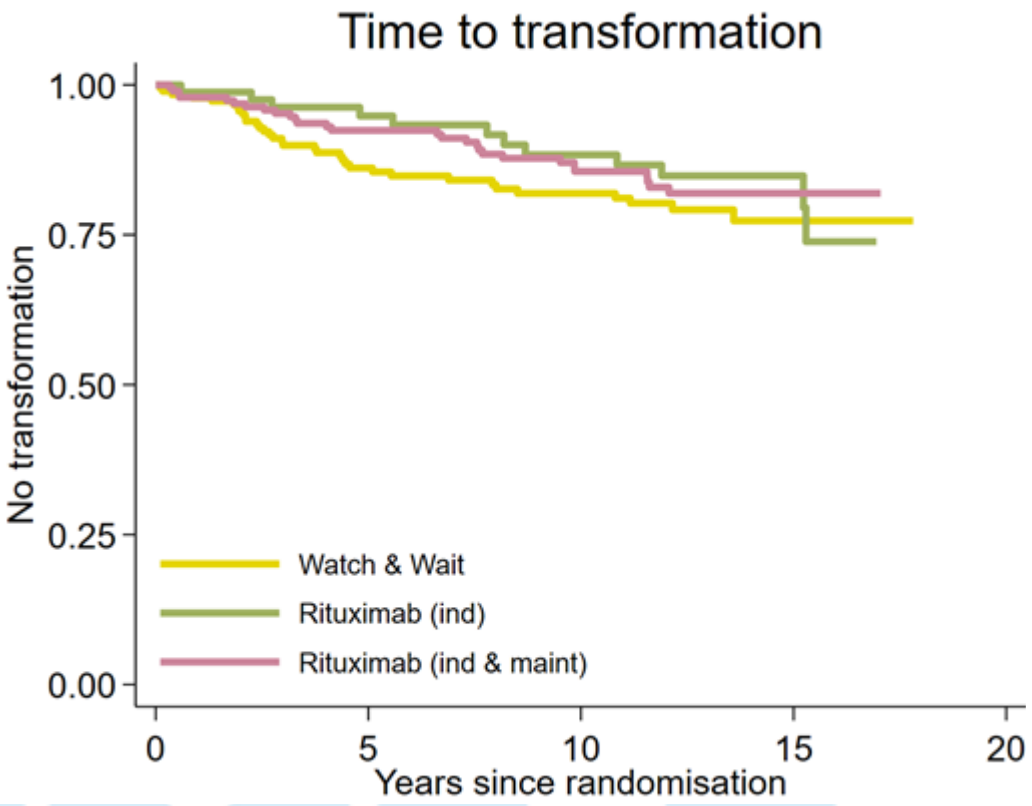
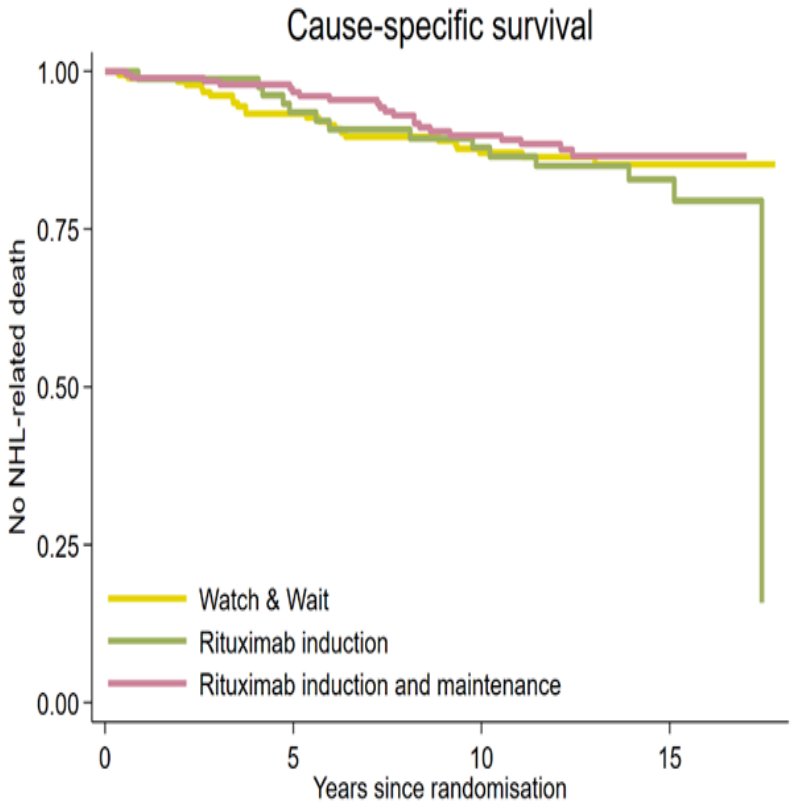
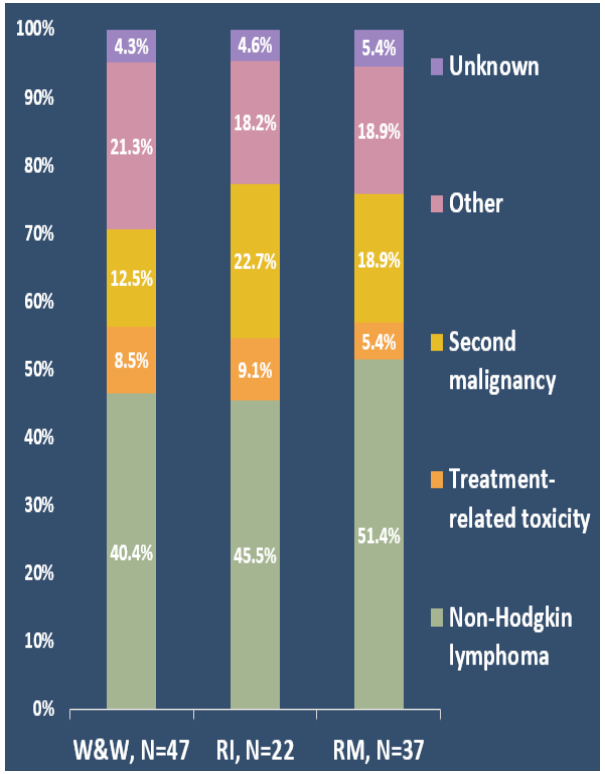
Northend M et al. 2022 ASH Annual Meeting. Abstract 607

No difference in time to transformation







Northend M et al. 2022 ASH Annual Meeting. Abstract 607

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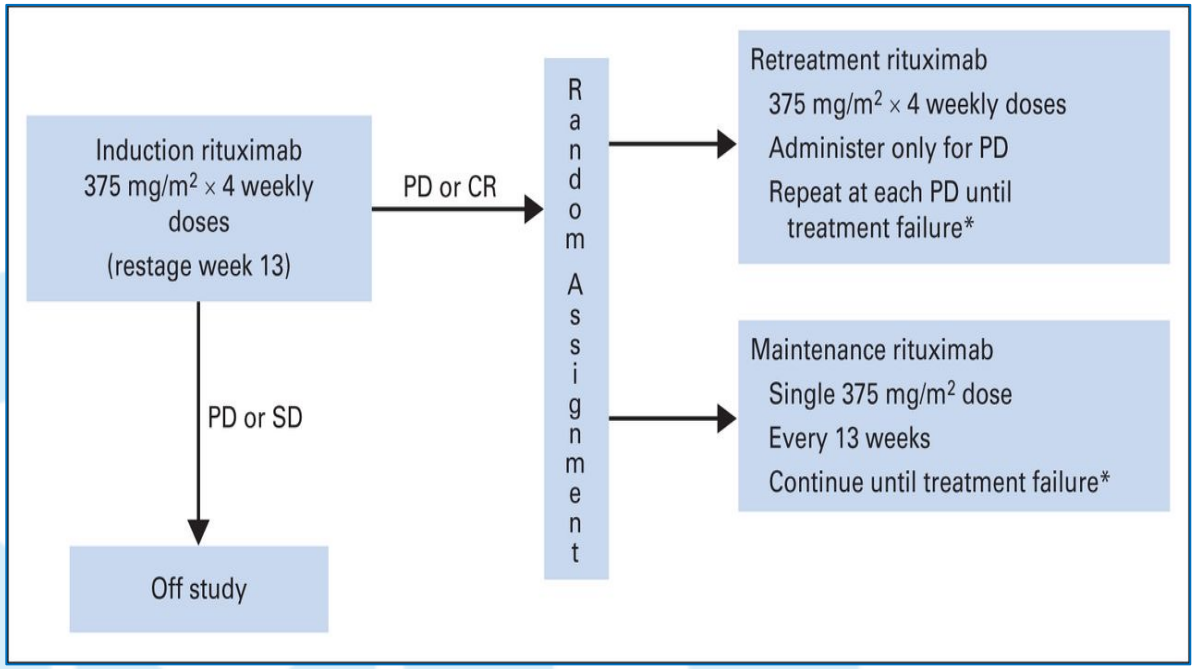
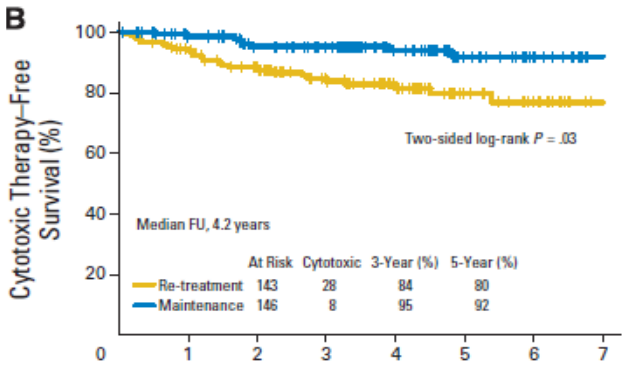
ECOG 4402 (RESORT) clinical trial

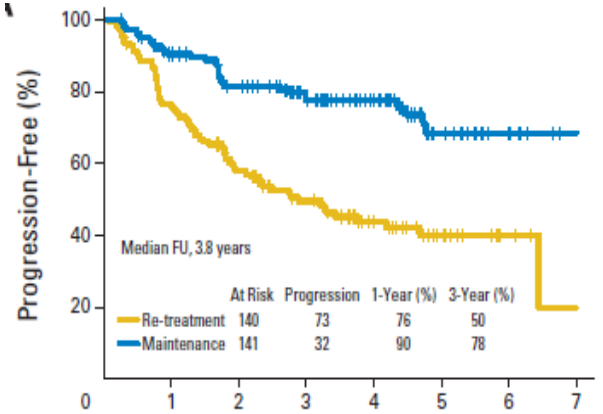


Kahl BS. Et al. JCO 2015; 32: 3096-3102

3 yo TFF: MR: 95% vs. RR: 84%

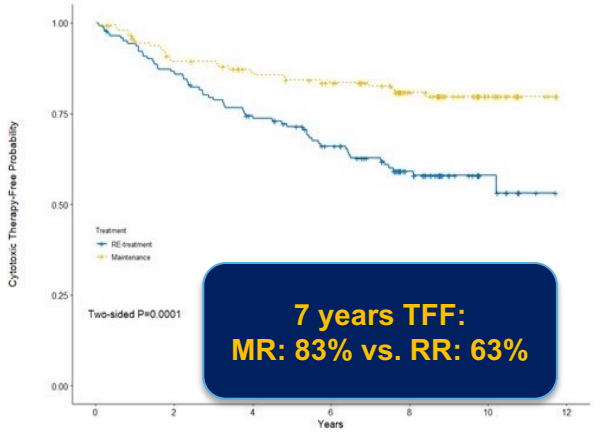


3 yo PFS: MR: 78% vs. RR 50%

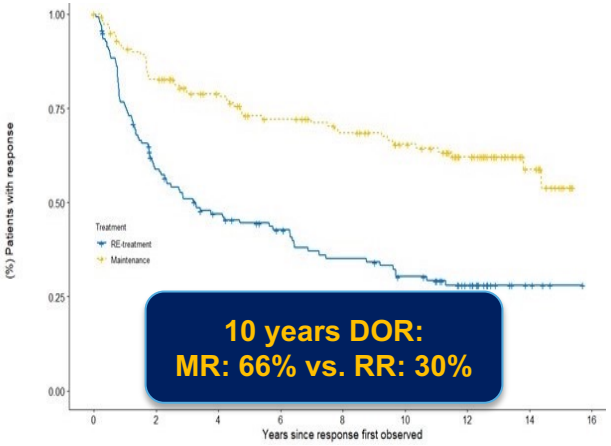


Long term follow up of RESORT (Kahl BS ASH 2022)

Time to cytotoxic tx (f/up 8.7 yo)



DOR (f/up 12.1 yo)



Stage III/IV FL with High tumor burden disease

Chemoimmunotherapy:

- Bendamustine-R (or Benda-Obi)
- RCHOP (or Obi-CHOP)
- RCVP (or Obi-CVP)

R^2 (Rituximab + Lenalidomide): in some cases

+/- Rituximab maintenance

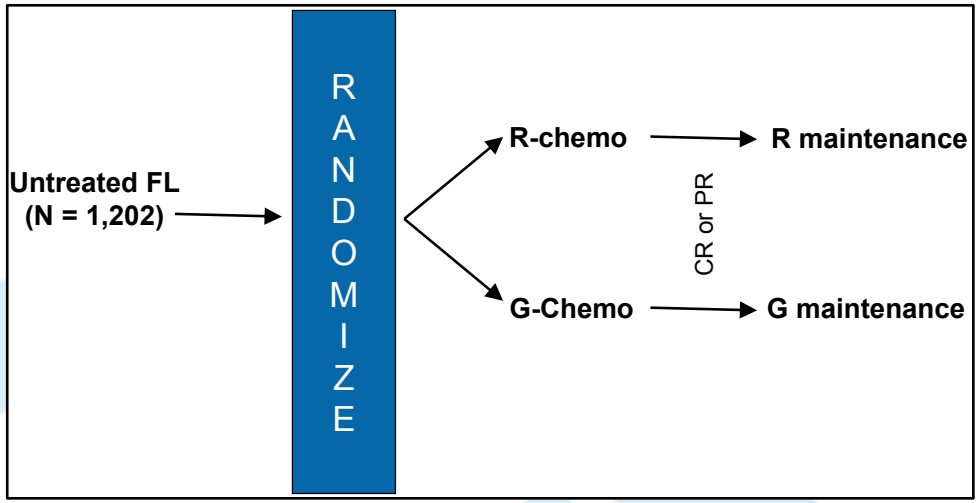
Ph III RCT

- STiLL
- BRIGHT
- GALLIUM

RELEVANCE

PRIMA

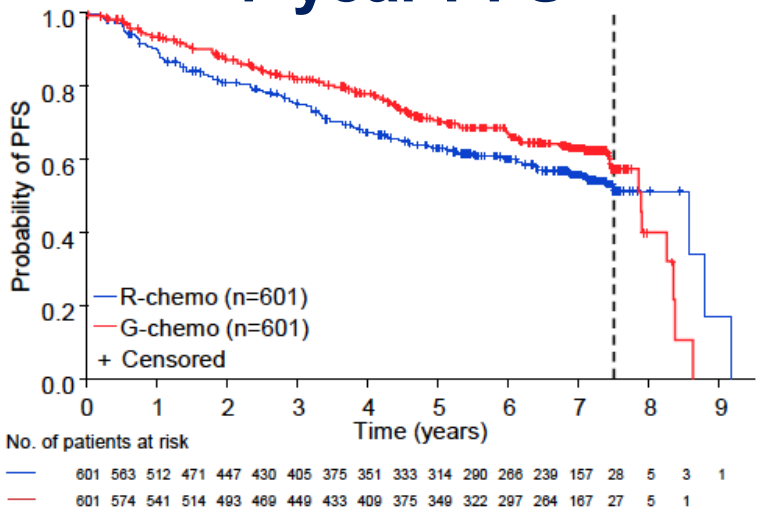
Gallium trial: Obi-chemo vs. R-chemo in untreated FL



8 year follow up

Median observation:
7.9 years (0.0 – 9.8)

7-year PFS

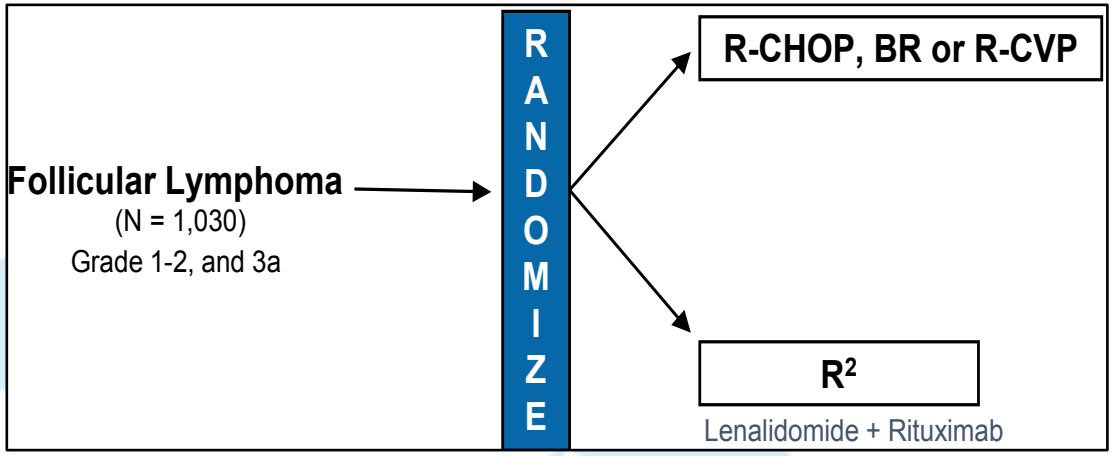


INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

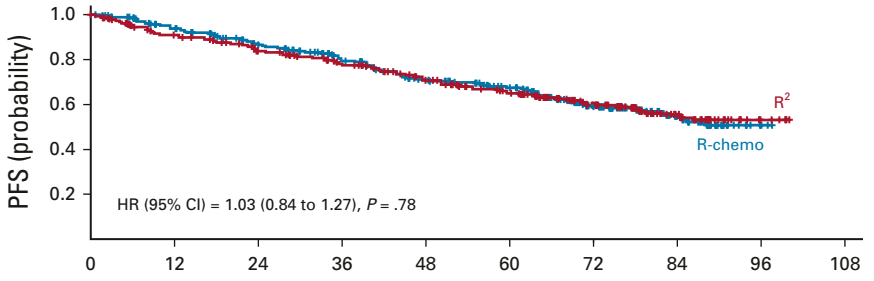
NO OS DIFFERENCE

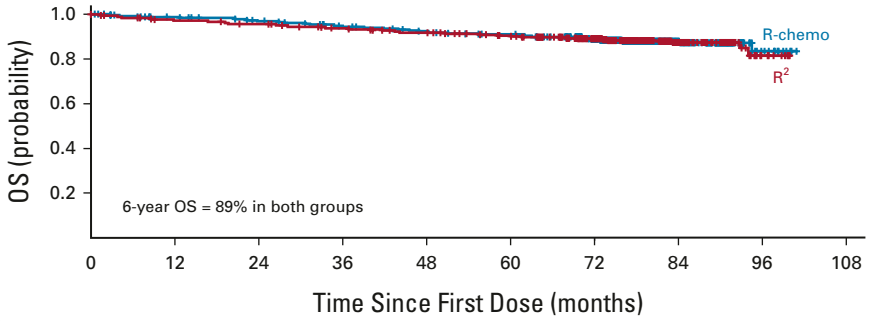
1. Marcus R et al. *N Engl J Med.* 2017;377:1331-1334.
2. Townsend W et al. EHA 2022

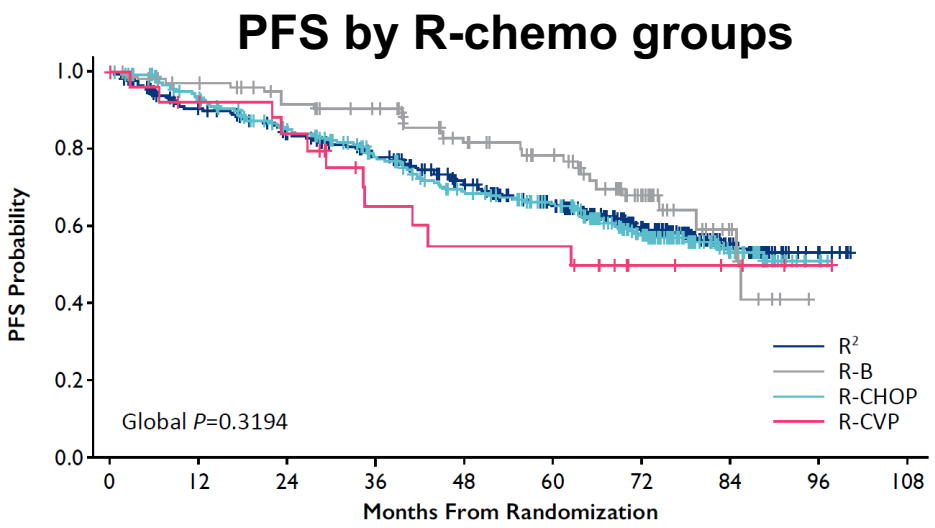
6 year follow of RELEVANCE: R^2 vs. R-chemo followed by RM



Median f/u: 72 mo





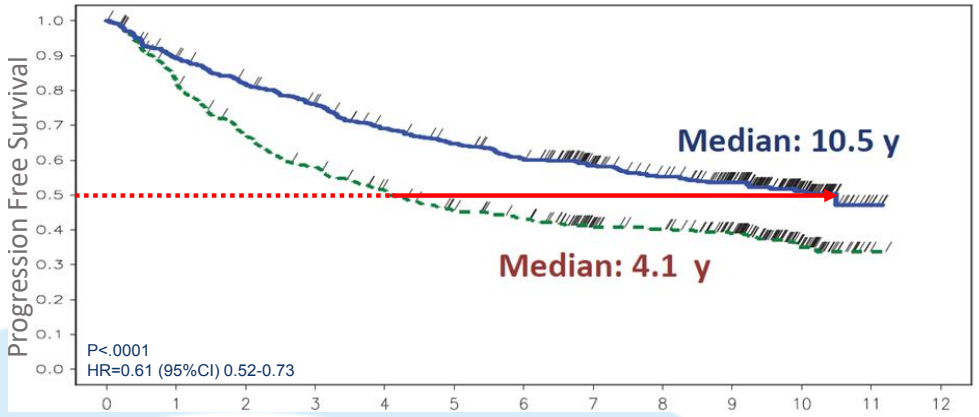


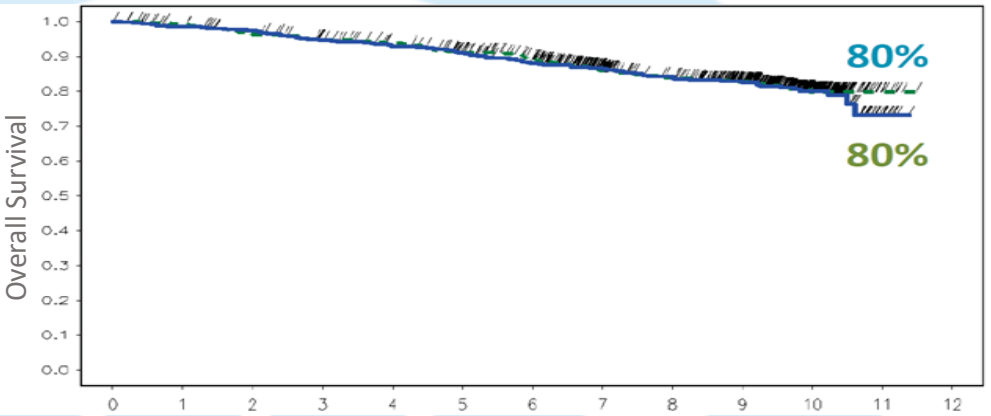
Morschhauser F, et al J Clin Oncol. 2022; 40:3239-3245.

Any changes in rituximab maintenance in FL?.. **NO!**

PRIMA trial:

- > 1,000 Pt tx with RCHOP/RCVP.
- Randomization: Obs vs. RM (Q8w x 2 years).

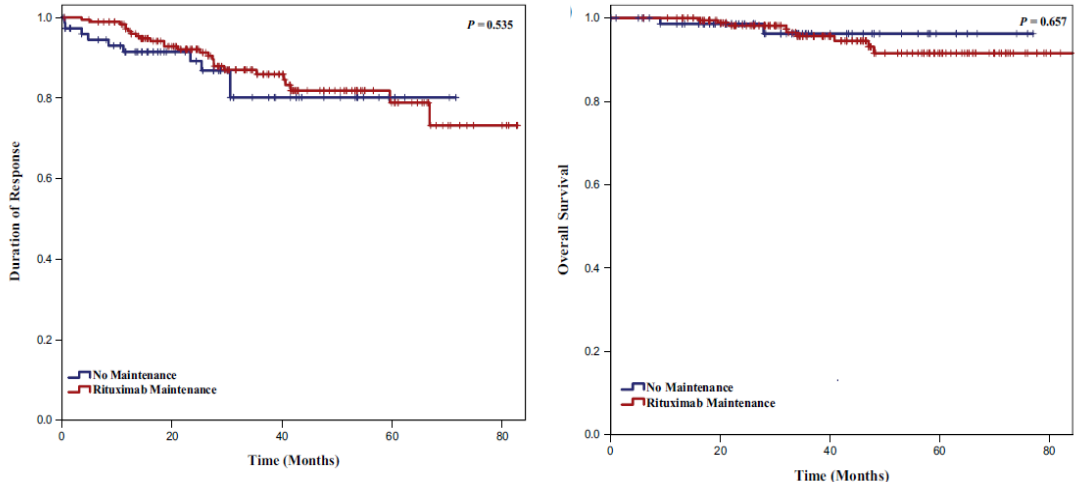




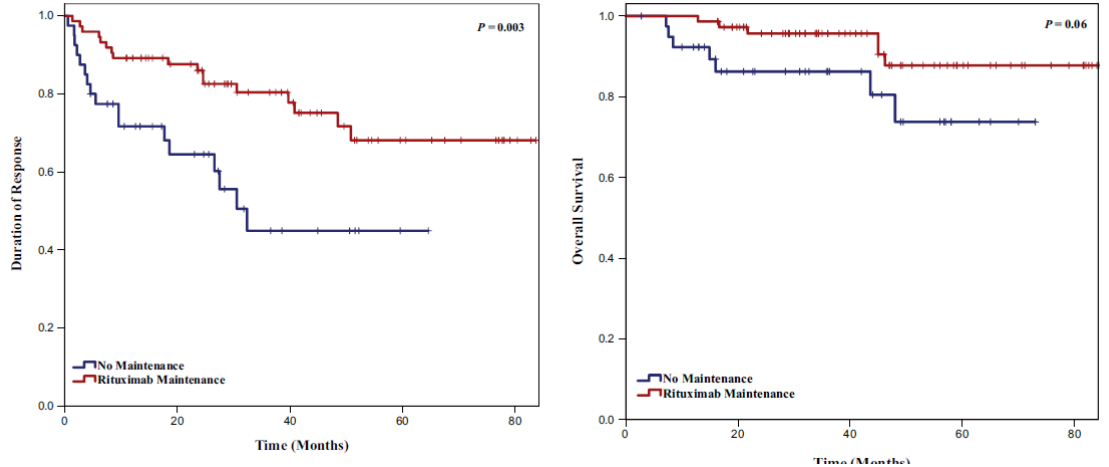
Salles GA et al. 2017 ASH Annual Meeting. Abstract 486.
Hill BT et al. Br J Haematol. 2019;184(4):524-535.

Retrospective cohort of pts treated with BR (N= 410)

Patients on CR

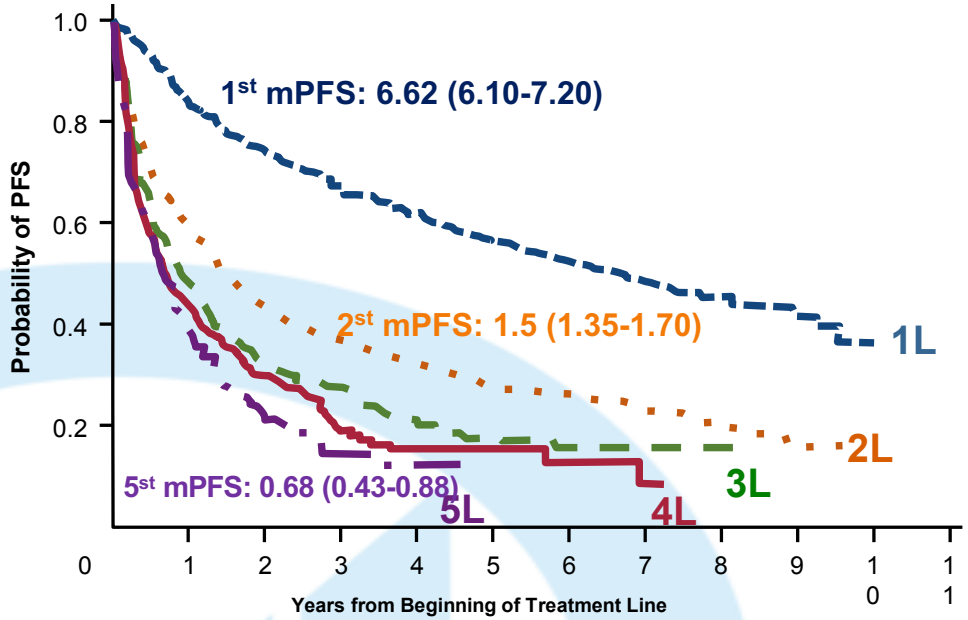


Patients on PR



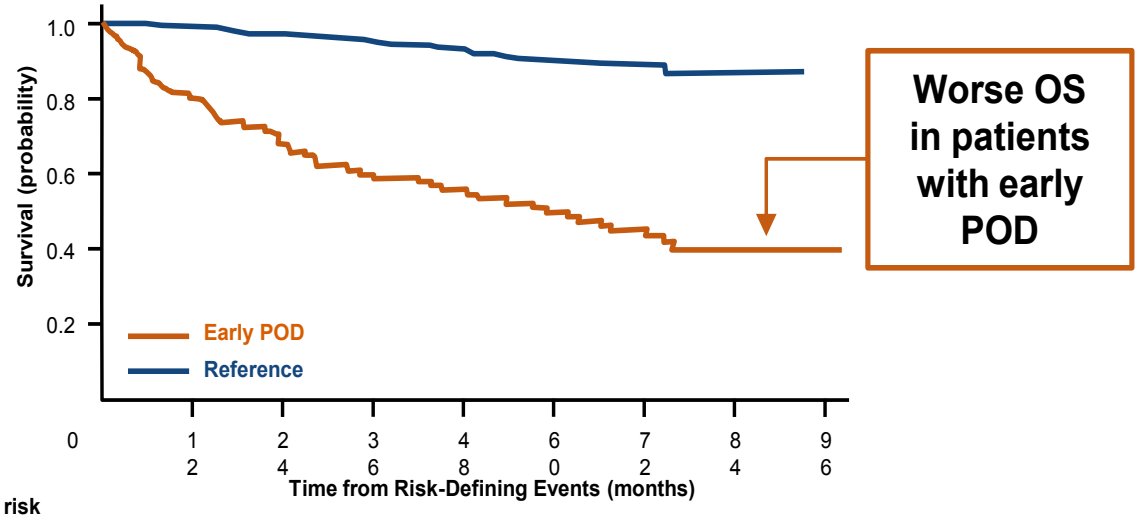
Relapsed/Refractory (R/R) FL

- Multiple relapses with shorter PFS after every event.
- The best response is usually the first one.



No. at risk												
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	
Third-line	438	181	109	78	50	30	18	5	1	0		
Fourth-line	229	91	49	24	14	8	3	1	0			
Fifth-line	123	42	19	9	5	0						

- Early progression of disease (<24 mo): 15-20% pts.
- POD24: worse PFS and OS.
- No accurate way to prognosticate POD24 cases.
- ALWAYS DO A BIOPSY AT TIME OF RELAPSE:
  - ✓ Assess for disease transformation!



No. at risk									
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

Link BK et al. *Br J Haematol.* 2019;184(4):660-663.
Casulo C et al. *J Clin Oncol.* 2015;33(23):2516-2522.
Casulo C et al. *Blood.* 2019;133(14):1540-1547.

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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 (as of 2022 only copanlisib is available).
- Tazemetostat
- Mosunetuzumab **(Approved Dec 22 2022)**
- CART cell therapy (Axi-cel, Tisa-cel)

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

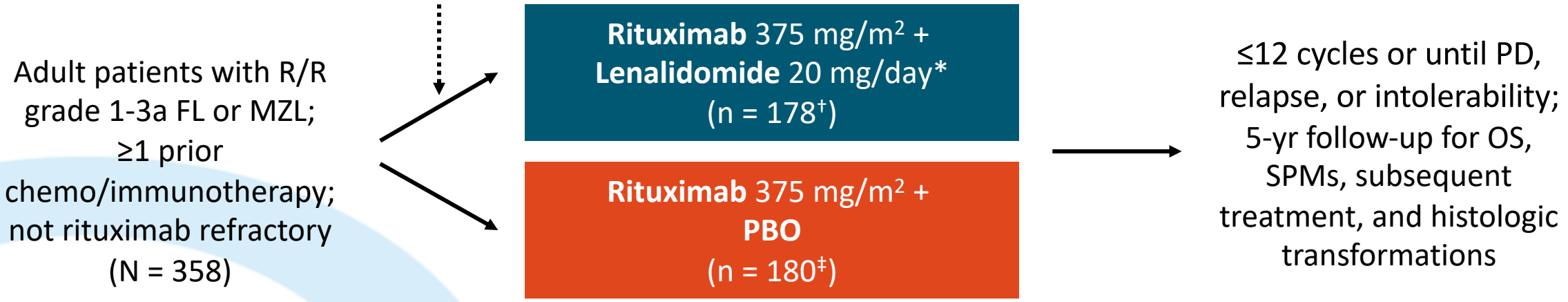
Courtesy of Dr. Sameh Gaballa, MCC Tampa

Partially adopted from NCCN.org

R+Len (R^2) vs. R for R/R "Rituximab sensitive" FL/MZL)

- Multicenter, placebo-controlled, randomized phase III trial

Stratified by prior rituximab (yes vs no), time since last therapy (≤ vs >2 yr), histology (FL vs MZL)



Rituximab: Days 1, 8, 15, 22 of cycle 1; Day 1 of cycles 2-5. Lenalidomide: Days 1-21 of 28. Prophylactic anticoagulation recommended for at-risk patients. Growth factor use allowed per ASCO/ESMO guidelines.
*10 mg/day if CrCl 30-59 mL/min. †FL, n = 147; MZL, n = 31. ‡FL, n = 148; MZL, n = 32.

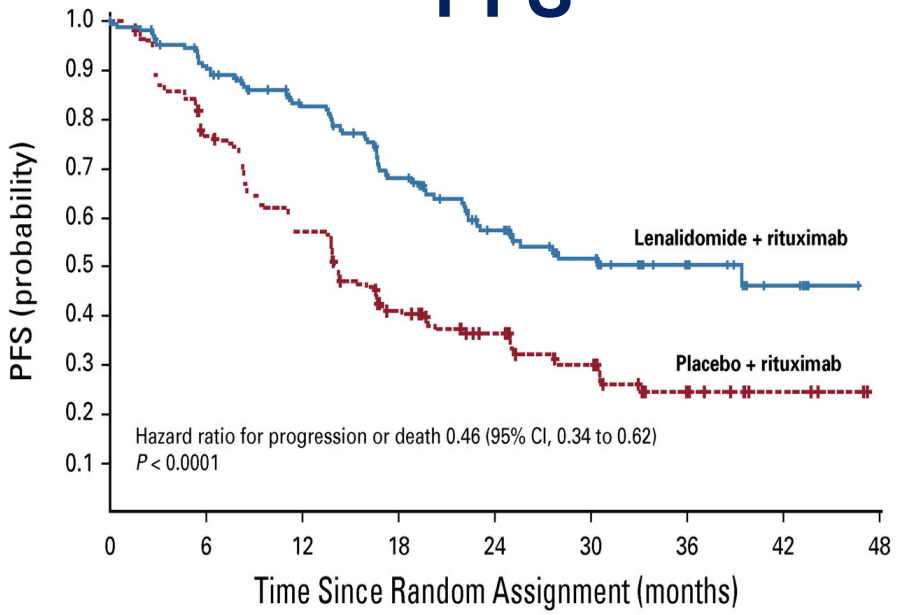
- Primary endpoint: PFS by IRC (2007 IWG criteria without PET)

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

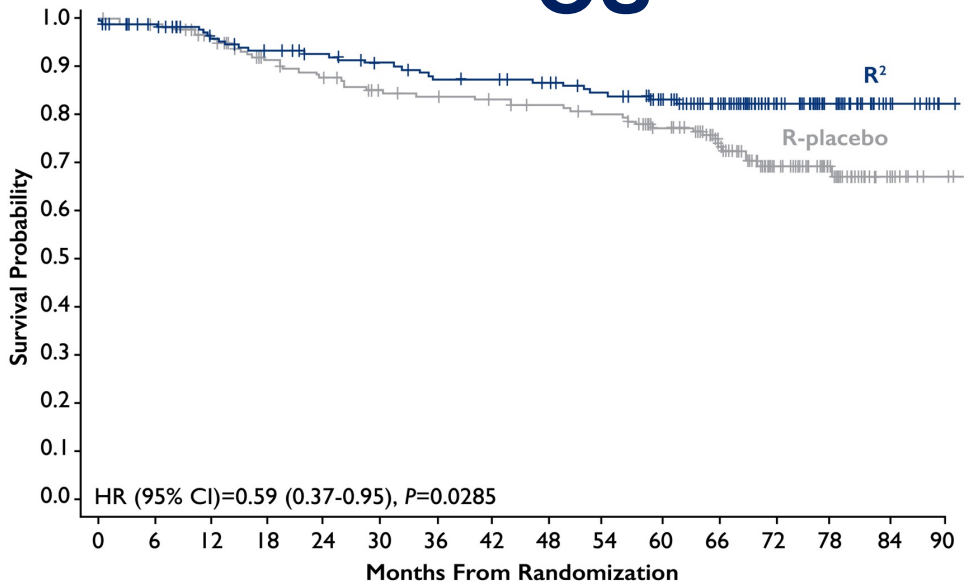
Leonard et al., ASH 2022 abstract #230

ASH 2022: 5.5 year f/up of the AUGMENT Phase III trial

PFS



OS



	R² (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

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

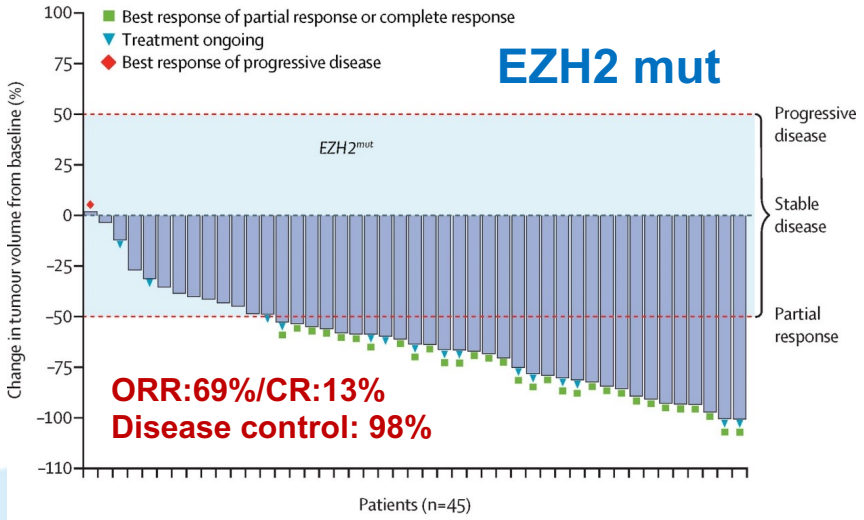
Leonard et al., ASH 2022 abstract #230

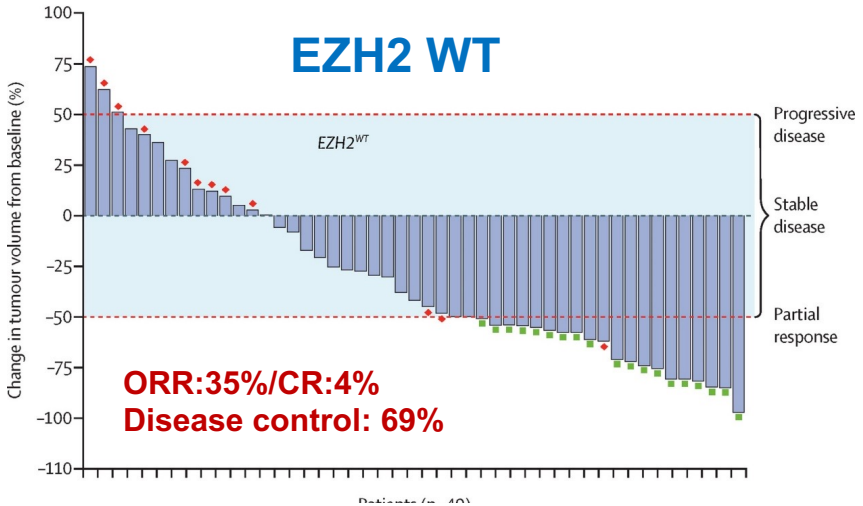
PI3K Inhibitors: Only one remaining

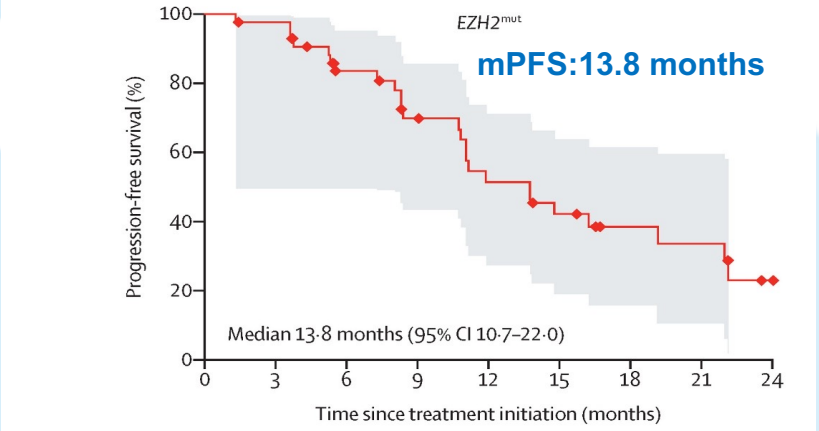
	Idelalisib	Duvalisib 	Copanlisib
Isoform Target	Delta	Delta and gamma	Alpha and delta
Evaluation Trial (patients)	Phase 2, refractory to R and an alkylator (125)	Phase 2, refractory to R and chemotherapy or radioimmunotherapy (129)	Phase 2, 2 prior therapies (142)
Approval (year)	**≥ 2 prior therapies (2014)**	**≥ 2 prior therapies (2018)**	**≥ 2 prior therapies (2018)**
ORR, n (%)	72 (54)	83 (42)	104 (59)
CR, %	N/A	1	20
Median PFS, months	11	9.5	12.5
Median OS, months	20.3	N/A	N/A
Grade ≥ 3 AEs	Diarrhea (13%), elevated ALT (13%), elevated AST (8%)	Diarrhea (15%), pneumonia (5%), fatigue (5%), elevated ALT (5.4%), elevated AST (3.1%)	Hyperglycemia (40%), pneumonia (11%), diarrhea (8.5%), elevated ALT (0.7%)

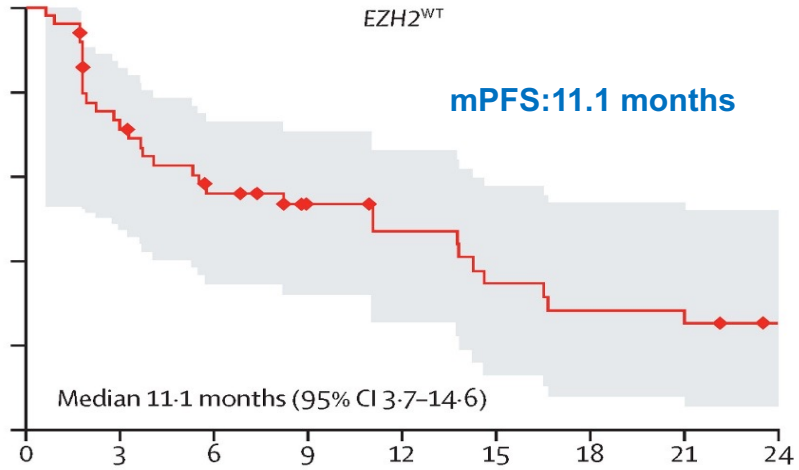
1. Gopal AK et al. *N Engl J Med*. 2014;370(11):1008-1018.
2. Flinn IW et al. *J Clin Oncol*. 2019;37(11):912-922.
3. Dreyling M et al. *Am J Hematol*. 2020;95(4):362-371.

Tazemetostat for R/R FL
Single arm open label phase II trial









- Outcomes in POD24 pts:

ORR:
- ✓ 63% (M)/25%(WT)

PFS:
- ✓ 13.8 months (M)
- ✓ 5.8 months (WT).

- Low rates of ≥ G3 AEs.
- Single oral agent.
- Approved after 2 of more Lines of tx.

Morschhauser F et al. *Lancet Oncol.* 2020;21(11):1433-1442.

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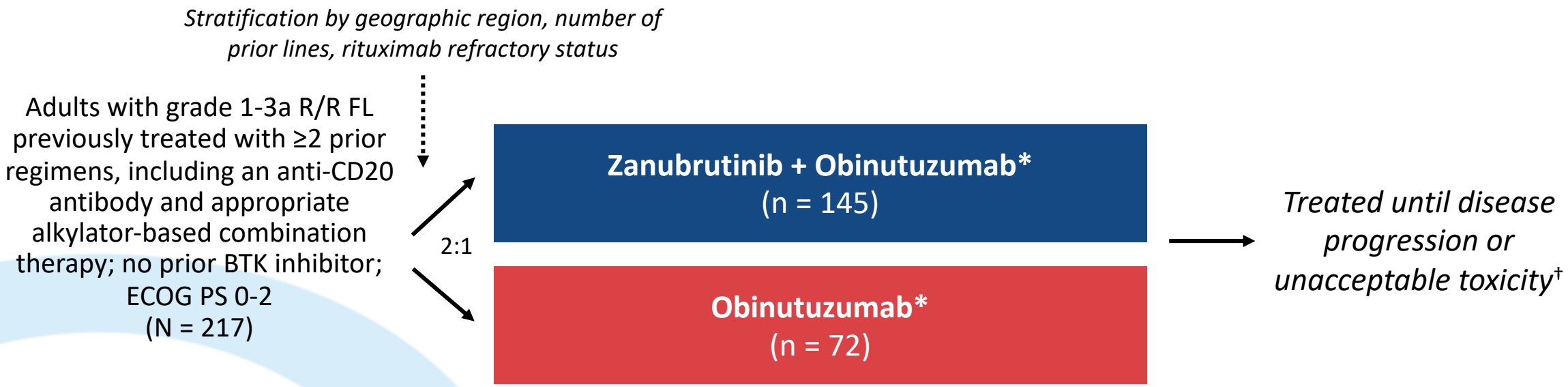
Zanubrutinib+Obi vs. Obi in R/R FL Phase II RCT ROSEWOOD trial



*Zanubrutinib dosed at 160 mg PO BID. Obinutuzumab dosed at 1000 mg IV on Days 1,8,15 of cycle 1 and Day 1 of cycles 2-6, then Q8W to ≥20 doses.
†Patients assigned to obinutuzumab with centrally confirmed PD or no response at 12 mo could crossover to receive combination therapy.

- **Primary endpoint:** IRC-assessed ORR according to Lugano classification
- **Key secondary endpoints:** investigator-assessed ORR, CR, DoR, PFS, OS, safety

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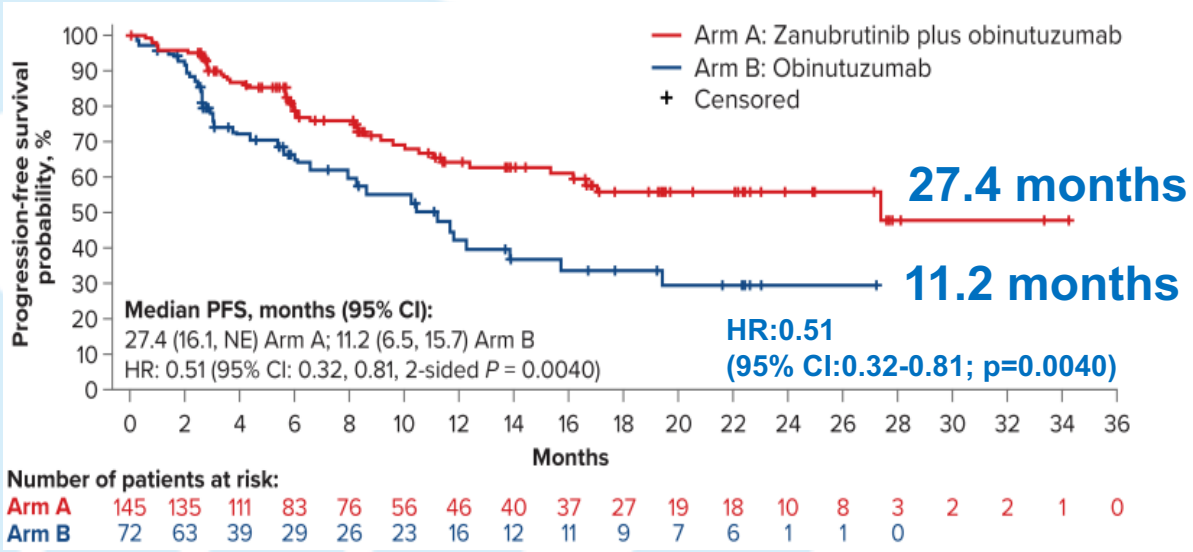
Zinzani PL et al. ASCO 2022; Abstract 7510

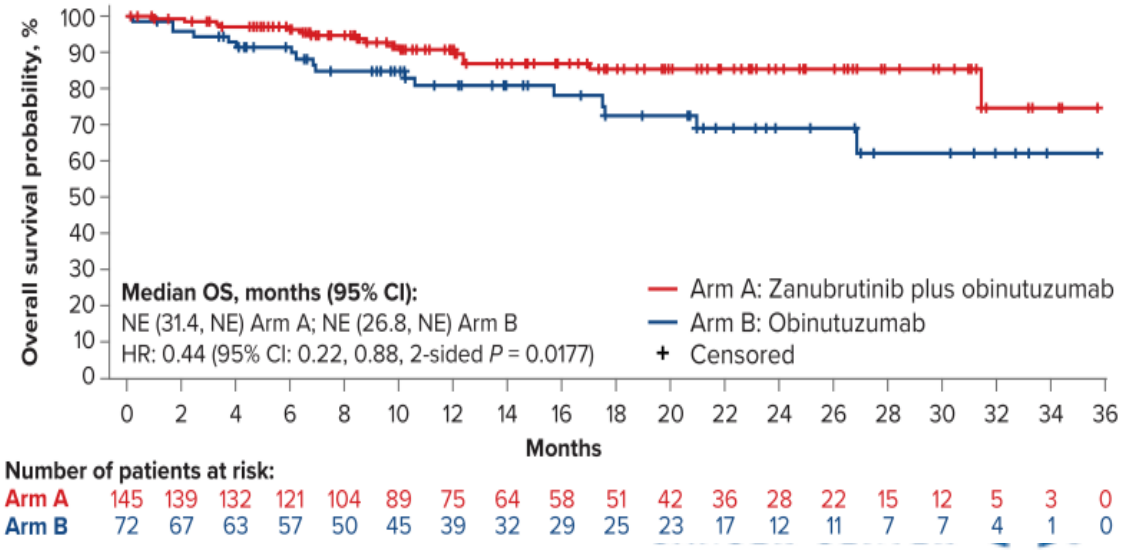
Zanubrutinib+Obi Vs. Obi in R/R FL Phase II RCT ROSEWOOD trial

	Zanu+Obi (n=145)	Obi (n=72)	P Value
ORR, % (95% CI)	68.3% (60-75.7%)	45.8% (34-58%)	0.0017
CR, % (95% CI)	37.2% (29.4-45.7%)	19.4% (11.1-30.5%)	0.0083

Progression-free survival (IRC)



Overall survival



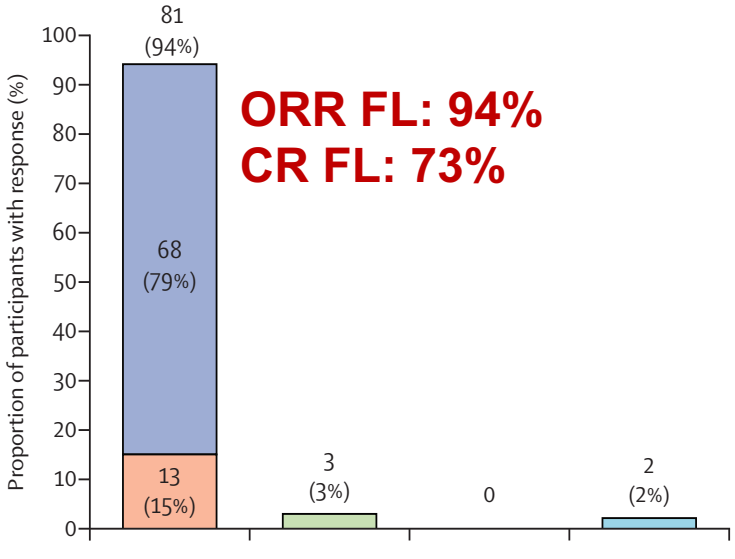
Zinzani PL et al. ASCO 2022; Abstract 7510

Chimeric Antigen Receptor (CAR) T cell therapy IN R/R FL

Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

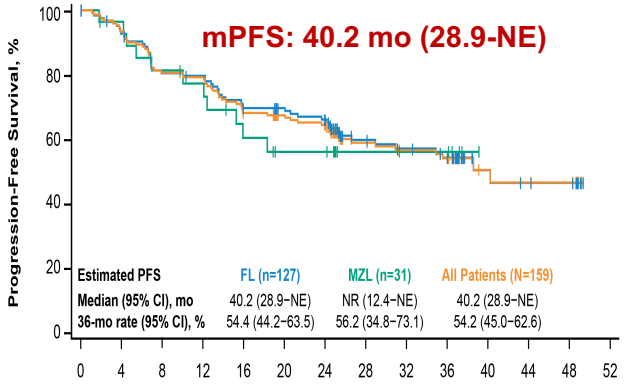
Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

ASH 2022: 3-Year F/up of ZUMA-5

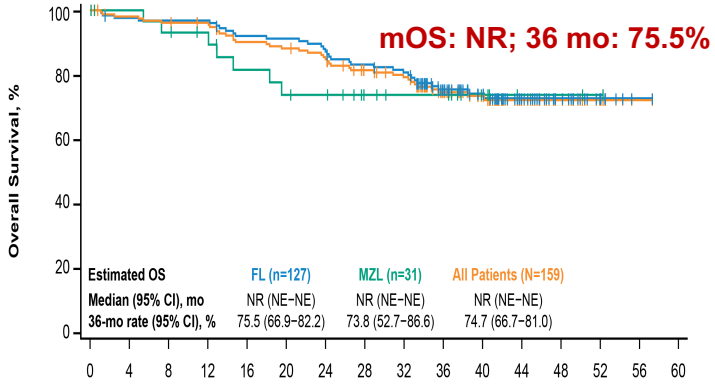


ORR FL: 94%
CR FL: 73%

PFS in FL



OS in FL



Parameter (95% CI)	Follicular Lymphoma (n=127)[a]	
	With POD24 (n=63)	Without POD24 (n=40)
Median DOR, months	NR (36.6–NE)	NR (24.7–NE)
36-month rate, %	64.6 (50.9–75.3)	52.7 (33.9–68.4)
Median PFS, months	40.2 (15.9–NE)	NR (25.4–NE)
36-month rate, %	59.2 (46.3–70.0)	52.2 (33.4–68.0)
Median OS, months	NR (NE–NE)	NR (NE–NE)
36-month rate, %	75.4 (63.4–83.9)	73.8 (56.5–85.0)

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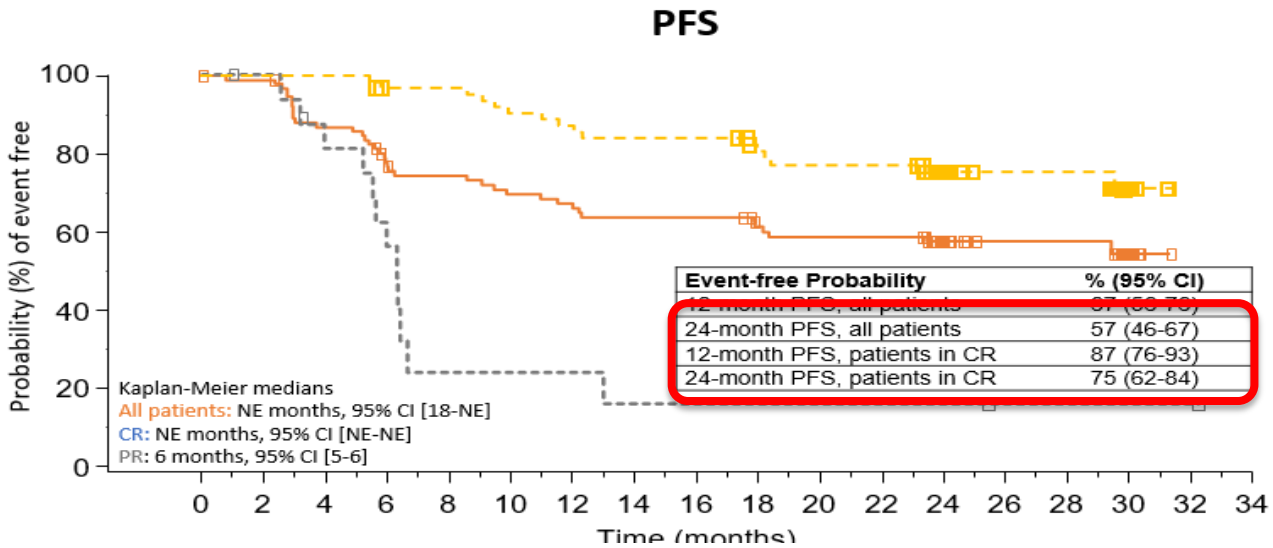
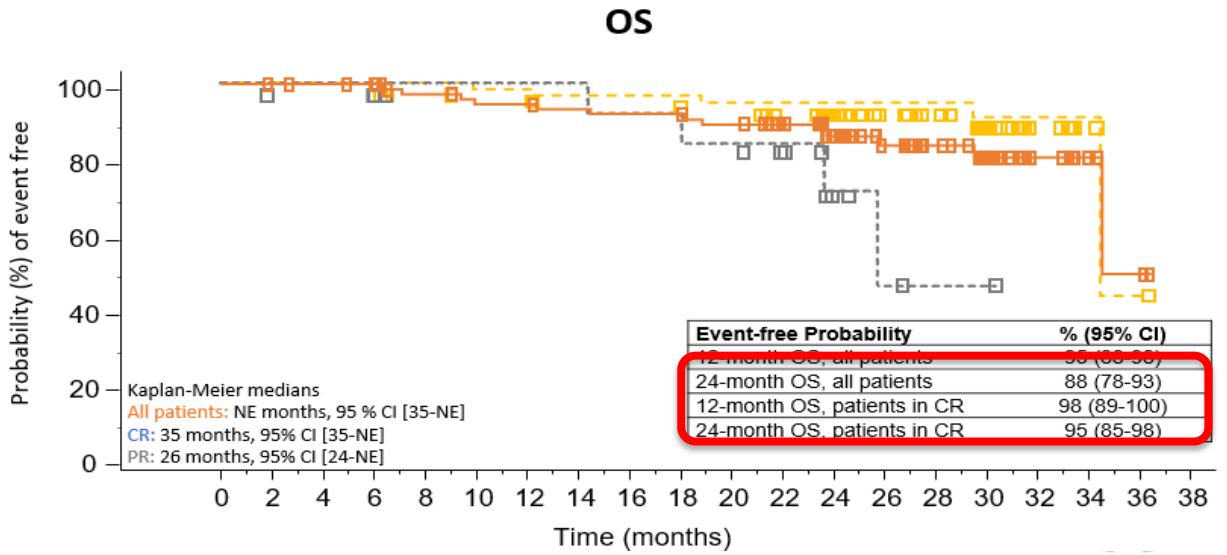
1.Jacobson C, Chavez JC et al. *Lancet Oncol* 2022; 23: 91–103 ; 2. Neelapu SS et al. ASH 2022. Abstract 4660

ASH 2022: 2-Year F/up of ELARA trial

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

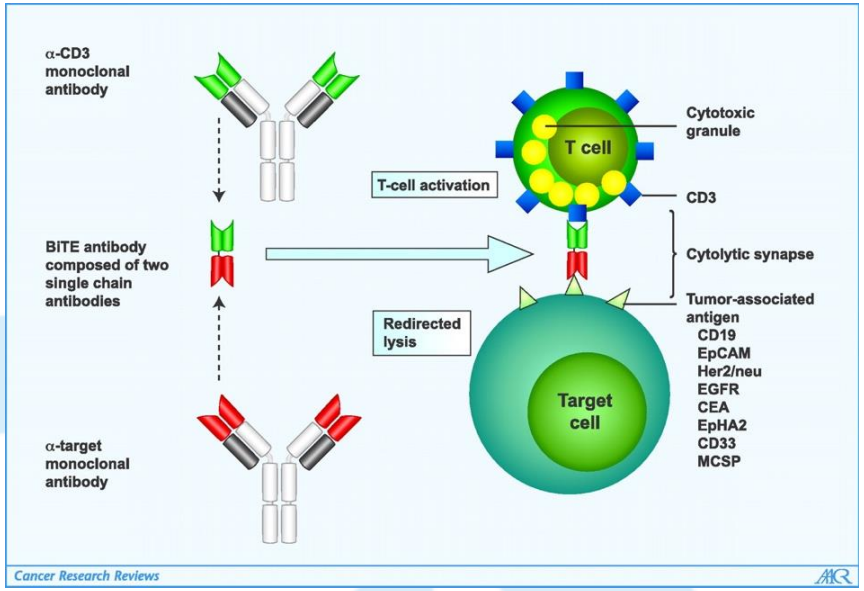
Characteristic	All Pts (N = 97)	CRR, %	ORR, %
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume	20 (21)	40 (19-64)	75 (51-91)
Bulky disease	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

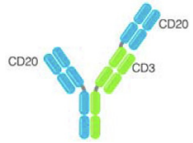
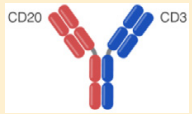
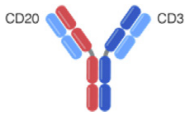
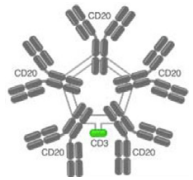




Dreyling M et al. ASH 2022. Abstract 608.

Bispecific antibodies in R/R FL



Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio
Mosunetuzumab[18] **FDA approved**		IgG1	Knobs-into-holes (different Fabs)	1:1
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1
Epcoritamab[16] **FDA granted orphan drugs status**		IgG1	Controlled Fab-arm exchange	1:1
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1
Plamotamab[90]		IgG1	Fab-Fc x scFv-Fc	1:1
IgM 2323[19]		IgM	IgM + modified J chain	10:1

Baeuerle PA et al. *Cancer Res.* 2009;69(12):4941-4944
Falchi L et al. *Blood* (2023) 141 (5): 467–480.

Mosunetuzumab (CD3xCD20 BsAb) in R/R FL

Phase 2 Pivotal Study

Adults with R/R FL (grades 1-3a) after ≥2 prior systemic tx including ≥1 anti-CD20 mAb and ≥1 alkylating agent; ECOG PS ≤1 (N = 90)

Cycle 1 (21-Day Cycles)*	Cycle 2	Cycles 3-8
Mosunetuzumab D1: 1 mg; D8: 2 mg; D15: 60 mg	Mosunetuzumab D1: 60 mg	Mosunetuzumab D1: 30 mg

*Cycle 1 step-up dosing for CRS mitigation.

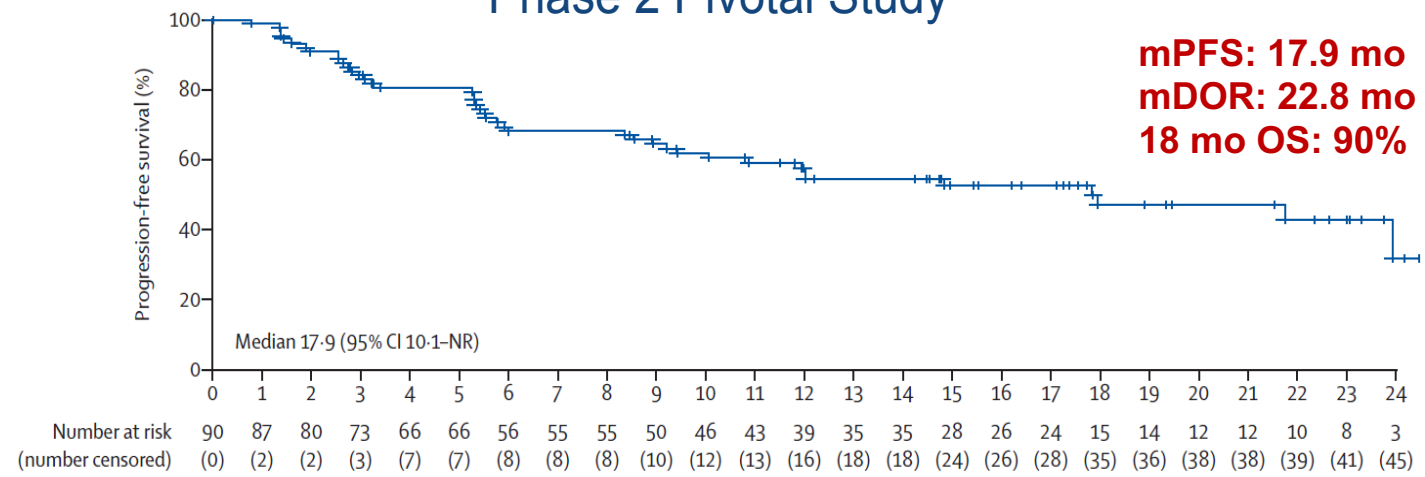
Discontinue if CR by cycle 8; if PR or SD, continue treatment for 17 cycles, unless PD or unacceptable toxicity occurs

Primary endpoints
CR (best response) rate by IRF, assessed vs 14% historical control CR rate
Secondary endpoints
ORR, DoR, PFS, safety and tolerability

- Fixed-duration Tx: 8 cycles if CR; 17 cycles if PR/SD after C8.
- Re-treatment was permitted at relapse for pt who achieved CR.
- No mandatory hospitalization

Median F/up (Mon)	28.3
ORR	78%
CR	60%
Double refractory	
• **ORR**	71%
• **CR**	50%
POD 24 mo	
• **ORR**	74%
• **CR**	63%

Phase 2 Pivotal Study

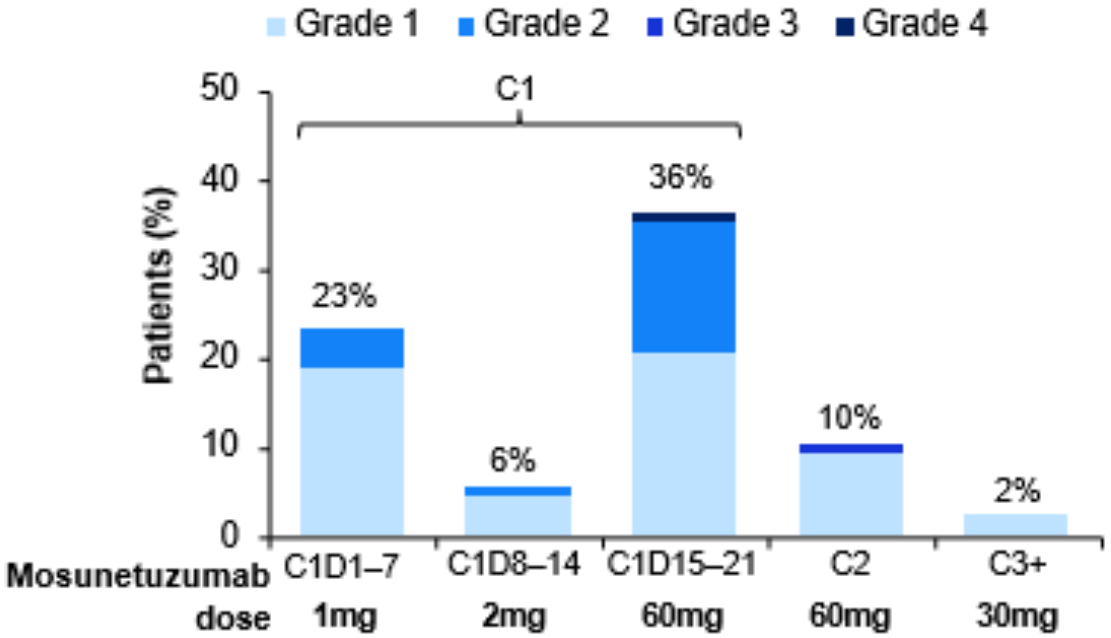


mPFS: 17.9 mo
mDOR: 22.8 mo
18 mo OS: 90%

Budde LE et al. *Lancet Oncol*. 2022;23(8):1055-1065.
Barlett N et al. ASH 2022

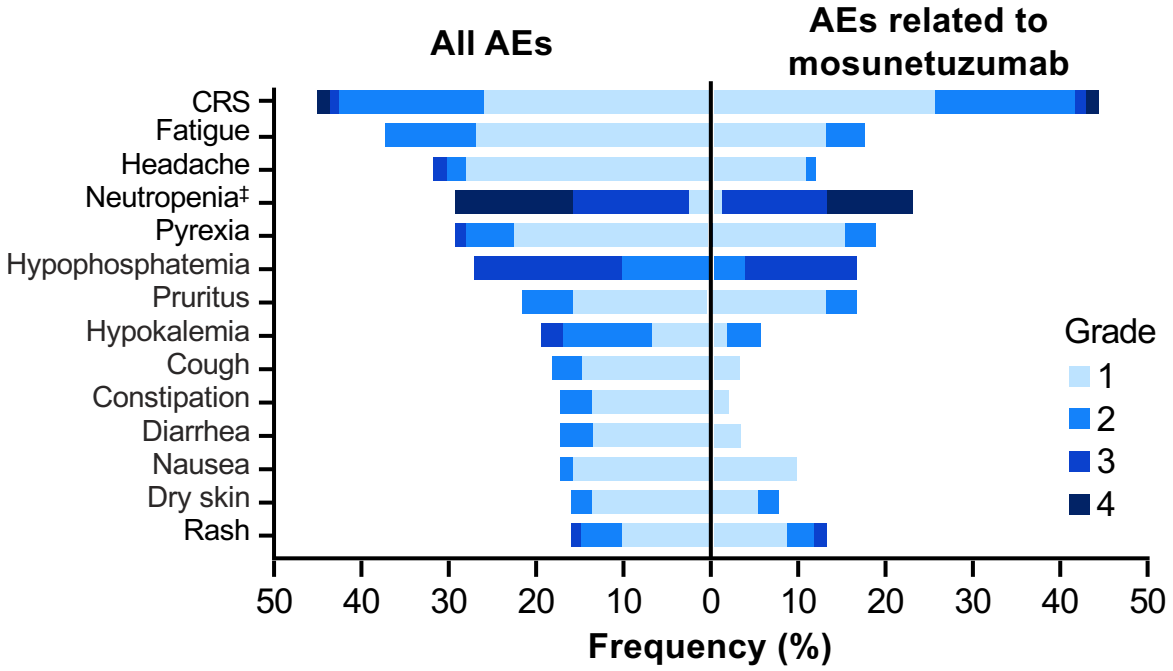
Mosunetuzumab (CD3xCD20 BsAb) in R/R FL: Safety

CRS by cycle and grade



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

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



Budde LE et al. *Lancet Oncol*. 2022;23(8):1055-1065.
Barlett N et al. ASH 2022

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Other BsAb (CD3xCD20) in R/R FL: single BsAb and in combinations

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)

Mantle cell lymphoma (MCL)

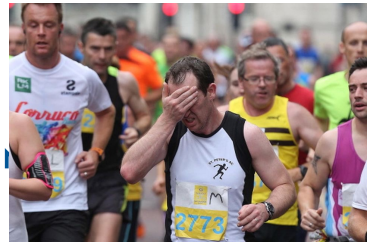
- Uncommon B-cell NHL (~6%) with a median age at diagnosis of 68 years and most prevalent in men.

- Most cases have cyclin-D1 overexpression via t(11;14) but there are other important pathogenic mutations affecting cell cycle (CDKN2), epigenetic regulation (KMT2D), DNA damage repair (TP53 and ATM mut), etc.

- For the most part presents with stage III-IV involving BM and GI tract (not always symptomatic).

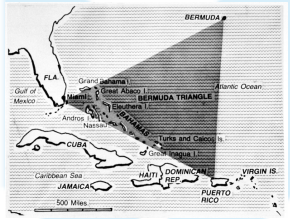
- Special subtype: Leukemic non-nodal MCL

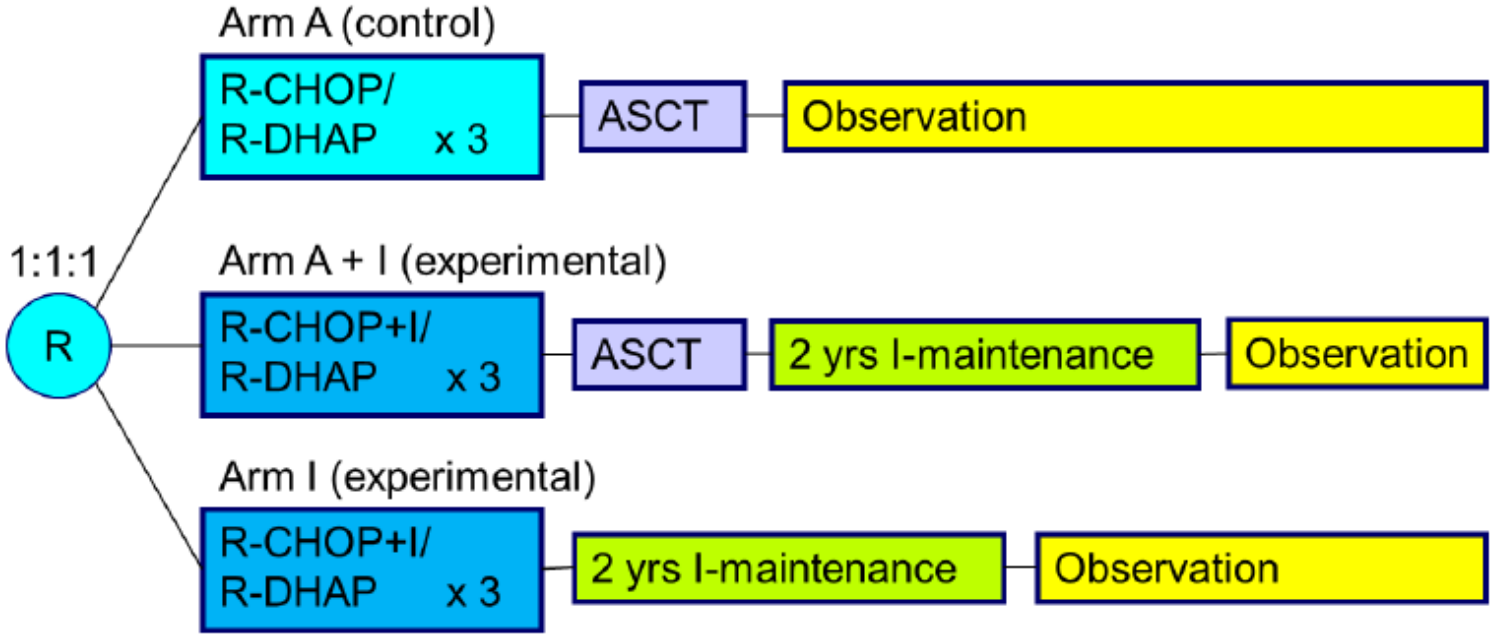
- **Currently not curable but very treatable, but usually more aggressive than FL. The goals should be:**
  - ✓ Treat when appropriate.
  - ✓ Long lasting disease control with improvement of QoL.



Updates in the frontline treatment for MCL:
TRIANGLE TRIAL (#1 2022 ASH abstract)

- Previously untread AutoHCT eligible stage II-IV MCL pts (≤ 65 yo).
- **Primary Outcome:** FFS
- **Secondary outcome:**
  - ✓ RR
  - ✓ PFS
  - ✓ 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.

Dreyling M et al/, ASH 2022

TRIANGLE TRIAL: Results

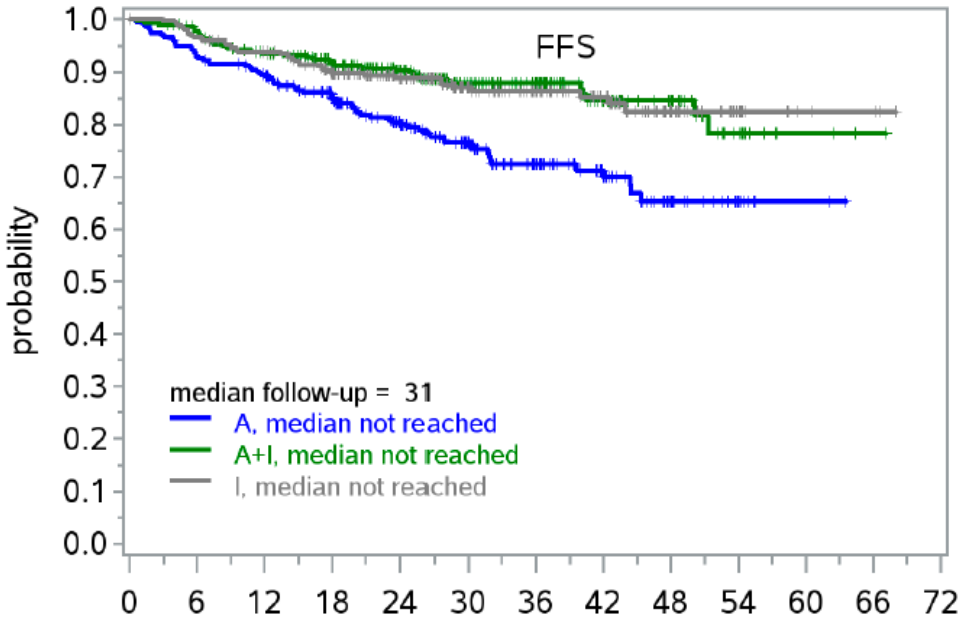
	Ibrutinib +/- AutoHCT (n=559)	AutoHCT (n=272)	P-Value
ORR, %	98%	94%	0.0025
CR, %	45%	36%	0.0203

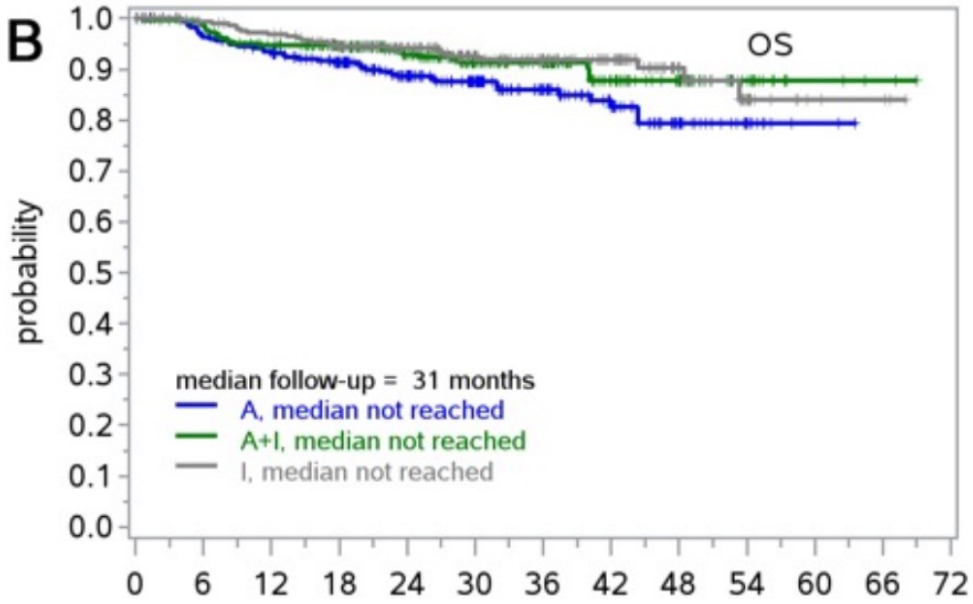
FFS and OS: Ibru+ AutoHCT vs. AutoHCT

	Ibrutinib + AutoHCT (n=292)	AutoHCT (n=288)	P-Value
3-yo FFS, %	88%	72%	0.0008
3-yo OS, %	91%	86%	-

FFS and OS: AutoHCT vs. Ibru w/o AutoHCT

	AutoHCT (n=288)	Ibrutinib (n=290)	P-Value
3-yo FFS, %	72%	86%	0.9979
3-yo OS, %	86%	92%	-

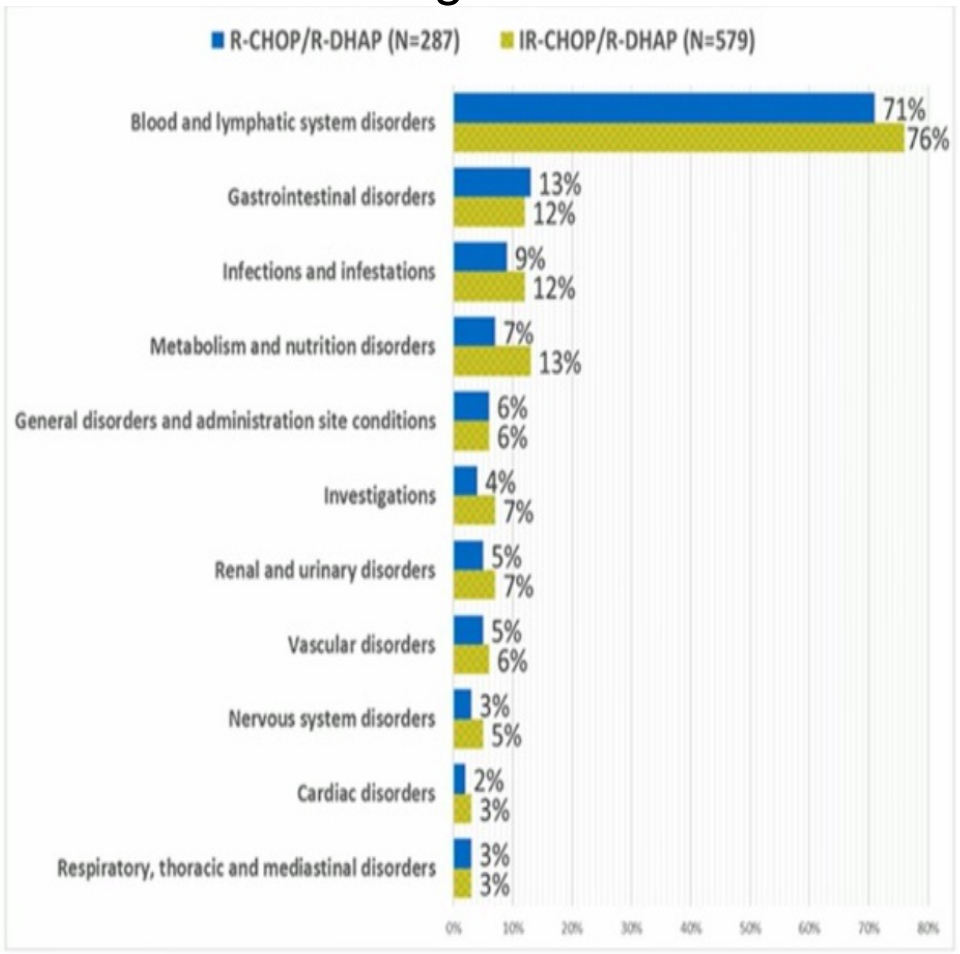




Dreyling M et al/, ASH 2022

TRIANGLE TRIAL: AEs and Causes of death

During induction tx, ibrutinib was associated with higher AEs.



Cause of death	A n=39/288 (13,5%)		A+I n=25/292 (8,6%)		I n=23/290 (7,9%)	
Lymphoma	16	5,6%	4	1,4%	11	3,8%
Concomitant disease	11	3,8%	7	2,4%	5	1,7%
Lymphoma and concomitant disease	0	0%	1	0,3%	1	0,3%
Secondary malignancy	1	0,3%	2	0,7%	0	0%
Therapy	4	1,4%	3	1,0%	0	0%
Therapy and concomitant disease	1	0,3%	0	0%	0	0%
Unknown	6	2,1%	8	2,7%	6	2,1%

Dreyling M et al/, ASH 2022

Updates in the frontline treatment for MCL:

Chemotherapy is “yesterday’s newspaper”?

Acalabrutinib + Venetoclax + R in TN MCL: 2 –year safety and efficacy analysis

Acalabrutinib	**Until PD**
+	
Rituximab	**24mo (monthly x6, then q2mo)**
+	
Venetoclax	**24mo (starting in c2)**

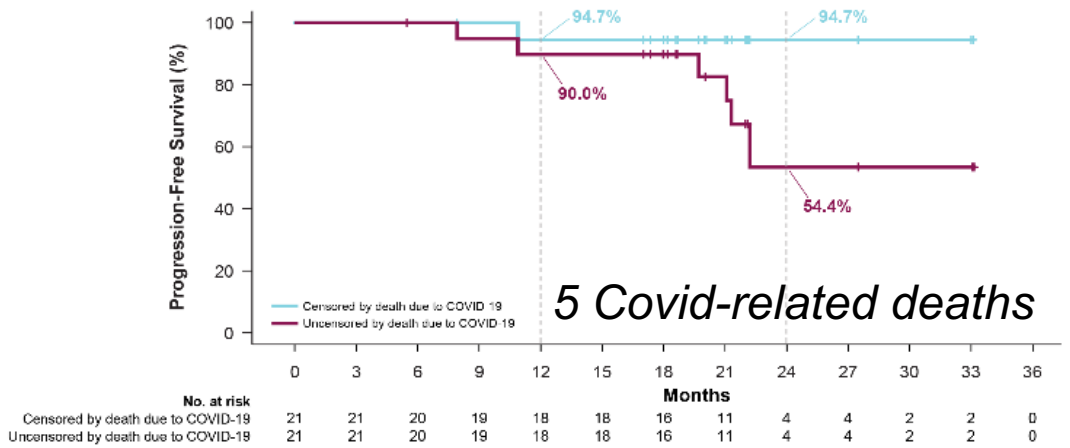
Median fup: 25.8 months
N=21

1º: Safety
2º: ORR, DOR/PFS/OS
Exploratory: MRD

Median Age: 66 (51-85)
sMIPI High: 19%
Ki67 ≥30%: 48%

AVR (n=21)	
ORR / CR	100% / 90%
6mo MRD^{neg}	12 of 12 evaluable (100%)
12mo MRD^{neg}	12 of 14 evaluable (86%)
24mo MRD^{neg}	Not reported

12 and 24 months PFS



5 Covid-related deaths

Wang M et al, ASH 2022

Updates in the frontline treatment for MCL:

Chemotherapy is “yesterday’s newspaper”?

Acalabrutinib + Lenalidomide + R with real-time monitoring of MRD in pts with TN MCL

Acalabrutinib	**Optional DC at 24mo if MRD negative**
+	
Rituximab	**Until PD (weekly x4, then 2mo)**
+	
Lenalidomide	**Optional DC at 24mo if MRD negative**

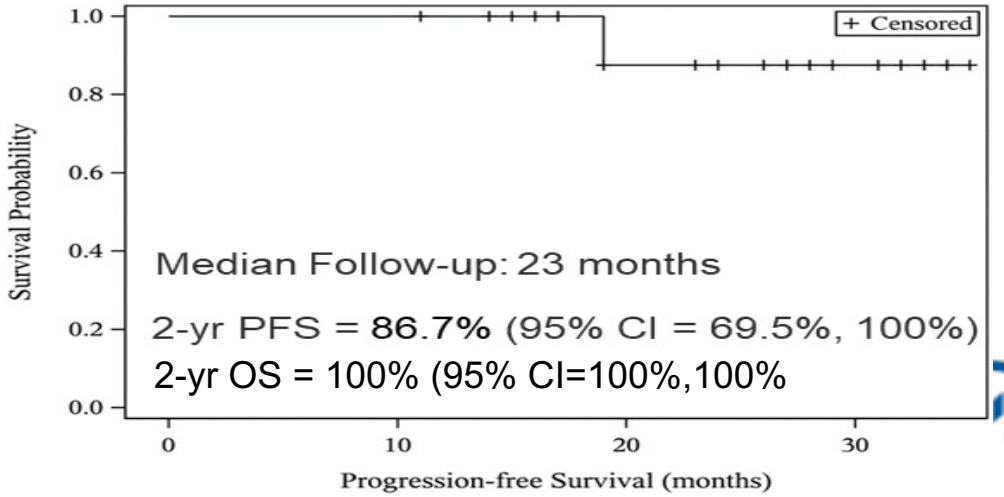
Median fup: 23 months
N=24

1º: 12mo CR Rate
2º: ORR, Safety, DOR/PFS/OS
Exploratory: MRD

Median Age: 64 (35-77)
MIPI High: 21%
Ki67 >30%: 29%

ALR (n=24)	
ORR / CR	100% / 83%
6mo MRD^{neg}	12 of 24 evaluable (50%)
12mo MRD^{neg}	16 of 24 evaluable (67%)
24mo MRD^{neg}	10 of 12 evaluable (83%)

PFS and OS



Relapsed/Refractory MCL:
Anti-CD3xCD20 BsAb (but of course!)

Glofitamab Monotherapy Induces High CR Rates in Patients with Heavily Pretreated R/R MCL: Phase I dose escalation study

Glofitamab IV administration

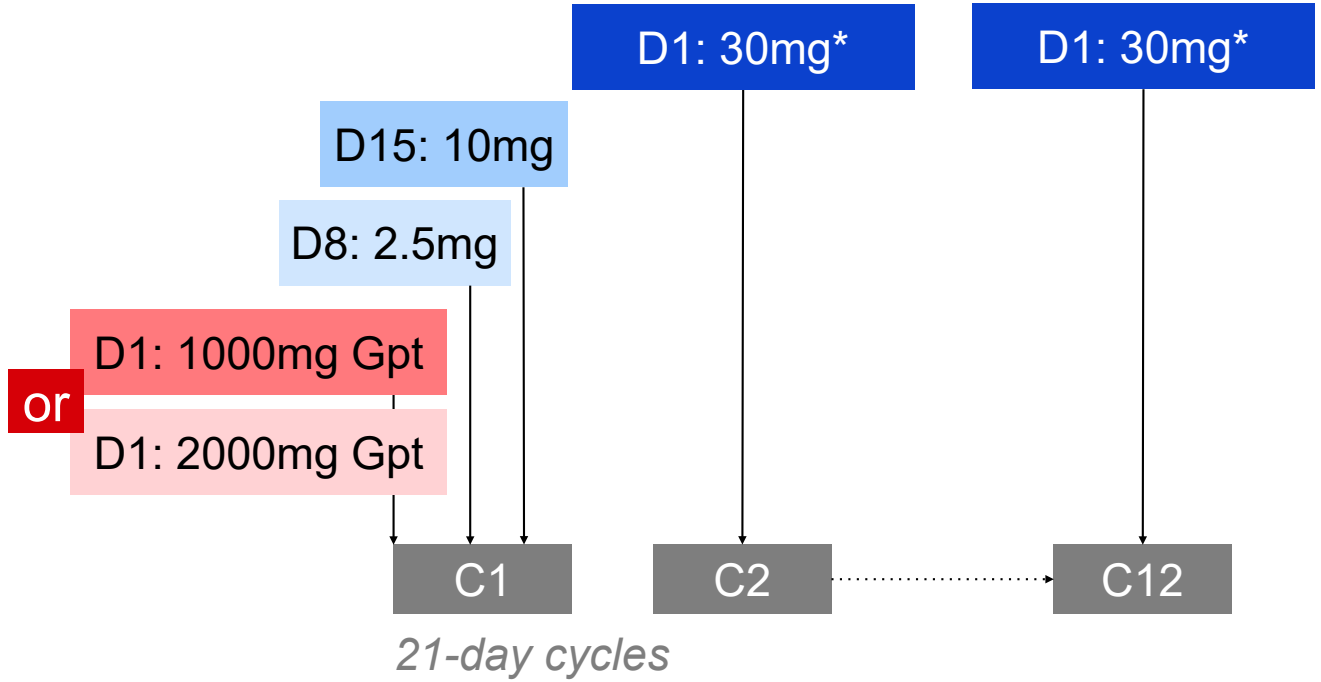
- Fixed-duration treatment: maximum 12 cycles

CRS mitigation

- Obinutuzumab pretreatment (1 x 1000mg or 1 x 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Population characteristics:

- Age ≥ 18 years
- ≥ 1 prior systemic therapy
- ECOG PS ≤ 1

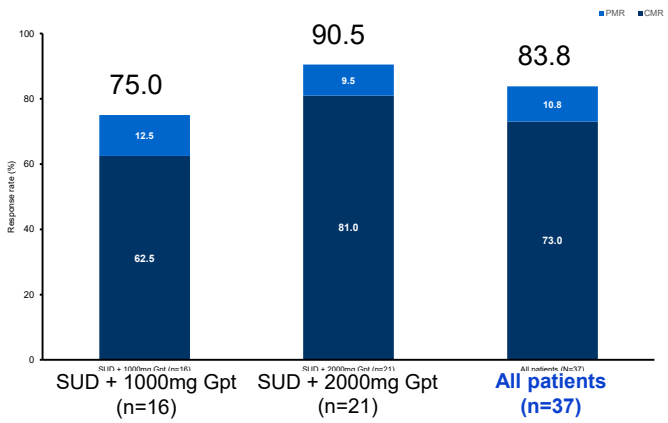


Philips T et al. ASH 2022

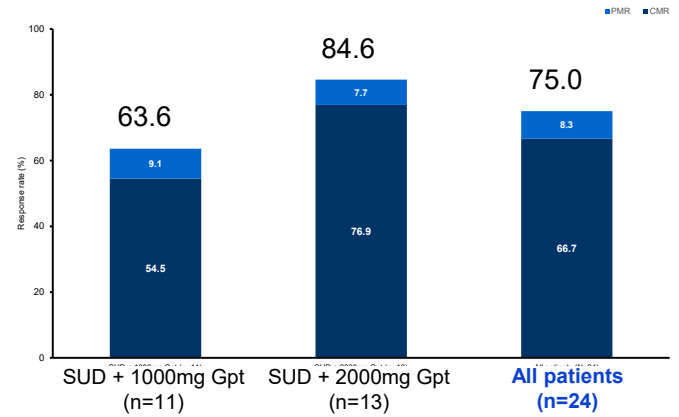
Relapsed/Refractory MCL:

Glofitamab in R/R MCL: Results

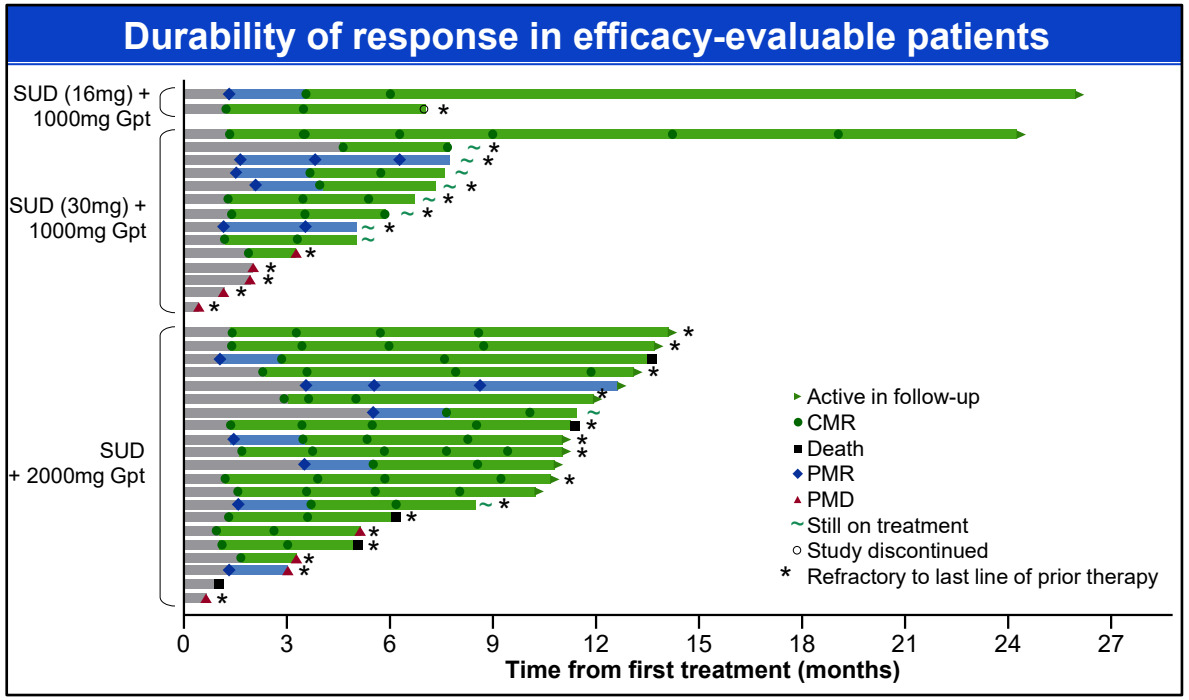
All patients*



Patients with prior BTKi



Durability of response in efficacy-evaluable patients



- Median f/up: 8 months; Median DORC: 5.1 mo (0.0-18.0)
- Response of first assessment: ORR=73%/CR:48.6%.
- Median DORC: 10 mo (95% CI: 4.9-NE).
- Durable CRs persistent s/p treatment cessation.
- Four COVID-19 related deaths.

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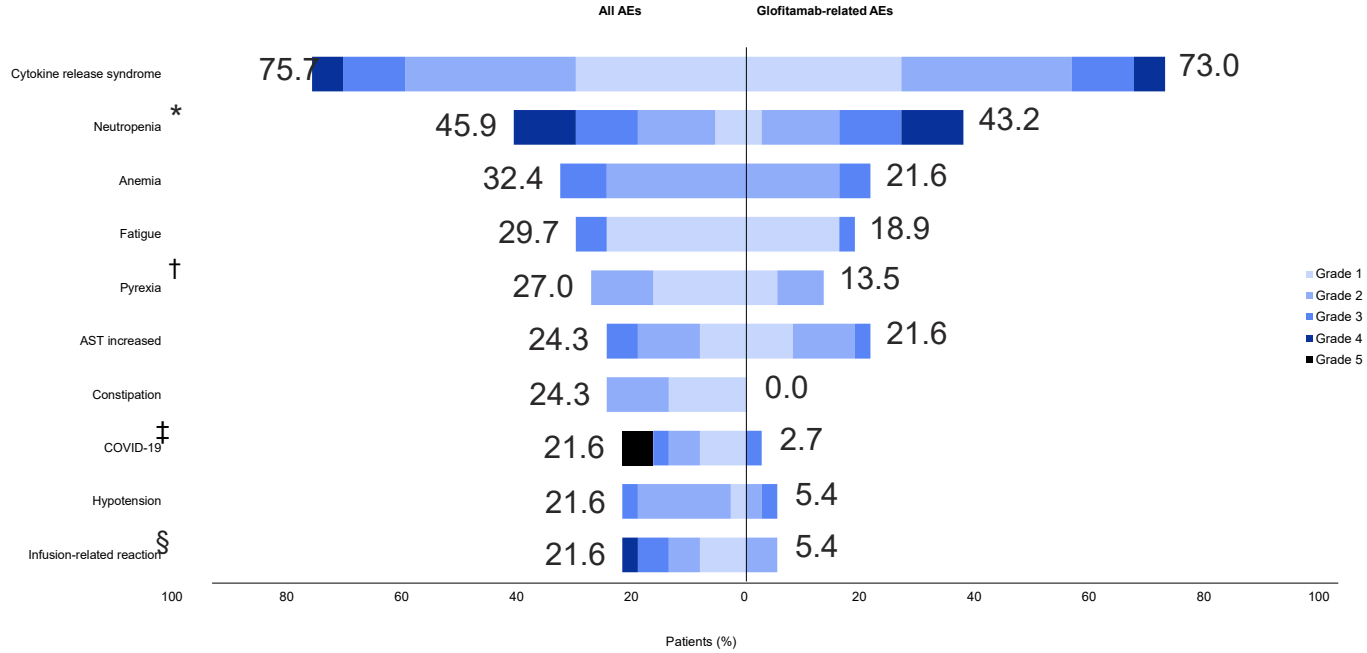
Philips T et al. ASH 2022

Relapsed/Refractory MCL:
Glofitamab in R/R MCL: Safety

AEs with an incidence of ≥20% in all patient (N=37)



CRS was the most common AE

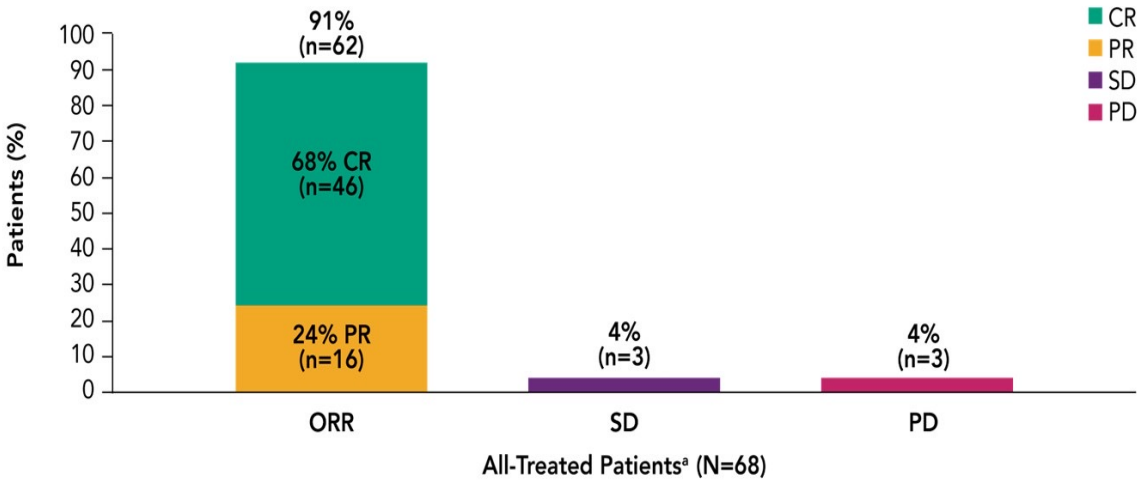
*Includes neutrophil count decrease. †Events occurred separately from CRS. ‡There were three serious COVID-19 AEs, Grade 3 (n=1), Grade 5 (n=2). An additional two patients had COVID-19 pneumonia. §IRR AEs related to glofitamab are reported as such if cytokine levels were normal. Most IRRs were related to obinutuzumab. AST, aspartate aminotransferase; IRR, infusion-related reaction.

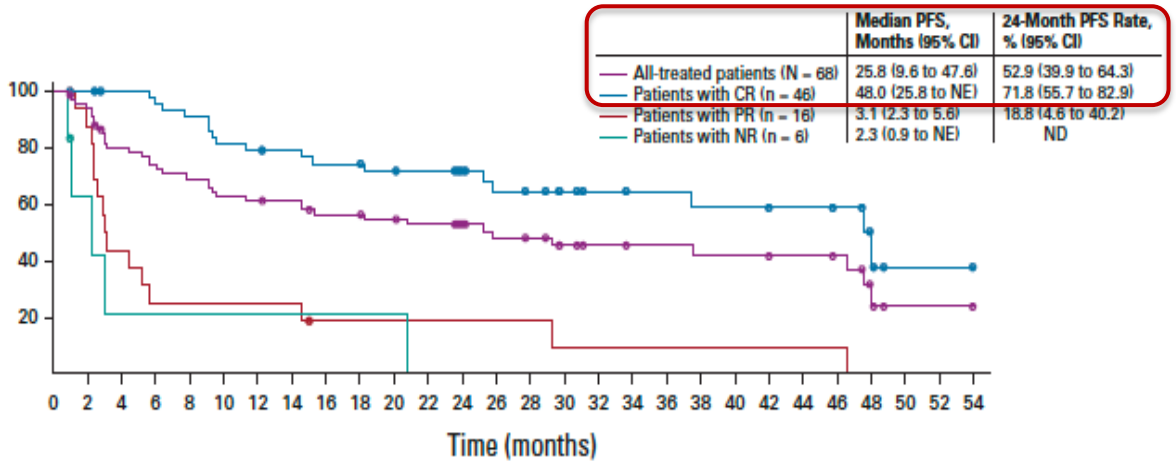
Philips T et al. ASH 2022

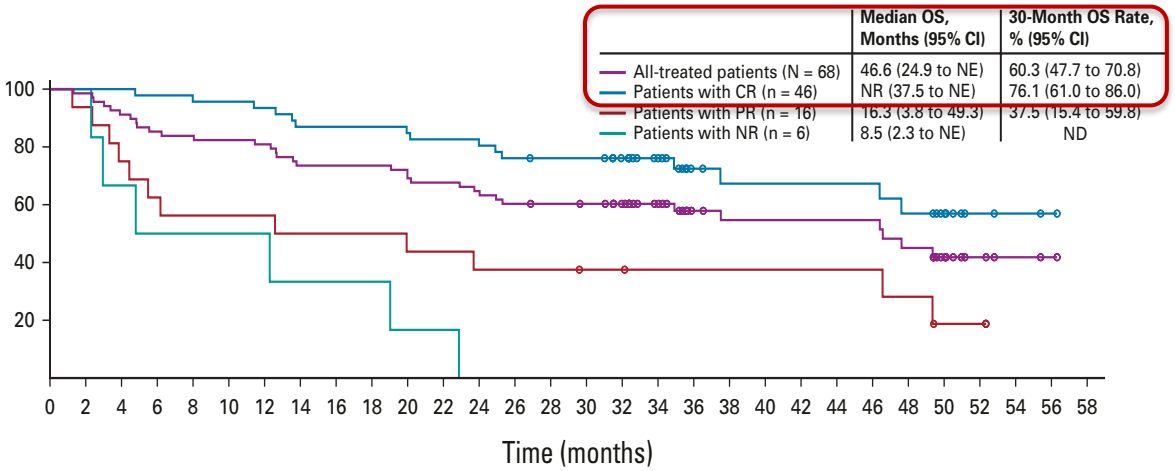
Relapsed/Refractory MCL:

Anti-CD19 CAR-T cell Tx (can't leave without mentioning them)

ZUMA-2: 3-year follow-up of outcomes with Brexucabtagene autoleucel in R/R MCL





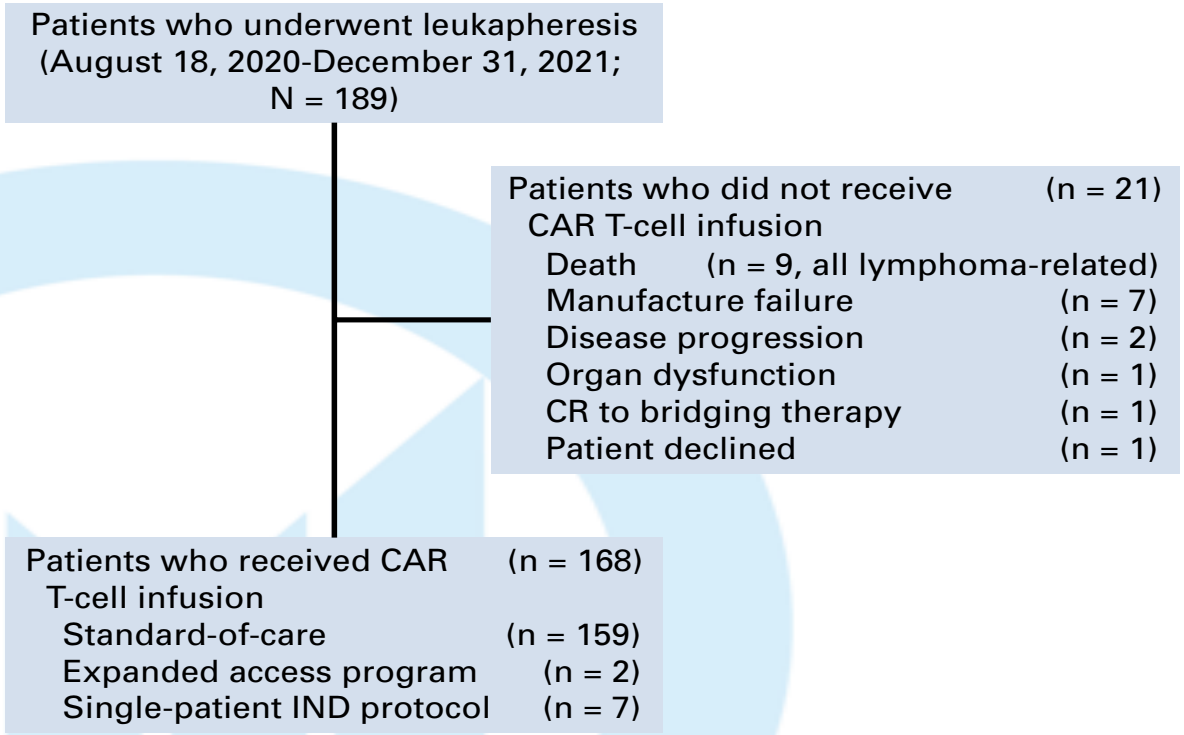


Wang M, Munoz J et al. JCO 2023; 37:144-152.

Relapsed/Refractory MCL:

Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)

- **189 pts underwent leukapheresis.**
- **168 (89%) received Brexu-cel.**
- **79% would not have met ZUMA-2 eligibility criteria.**



	Brexu-cel (n=168)
ORR, %	90%
CR, %	82%
6-mo PFS	69%
12-mo PFS	59%
1 yo NRM	9.1%
≥ G3 CRS	8% (1 G5)
≥ G3 ICANS	32%

Wang Y, Jain P, Locke F, et at. JCO 2023

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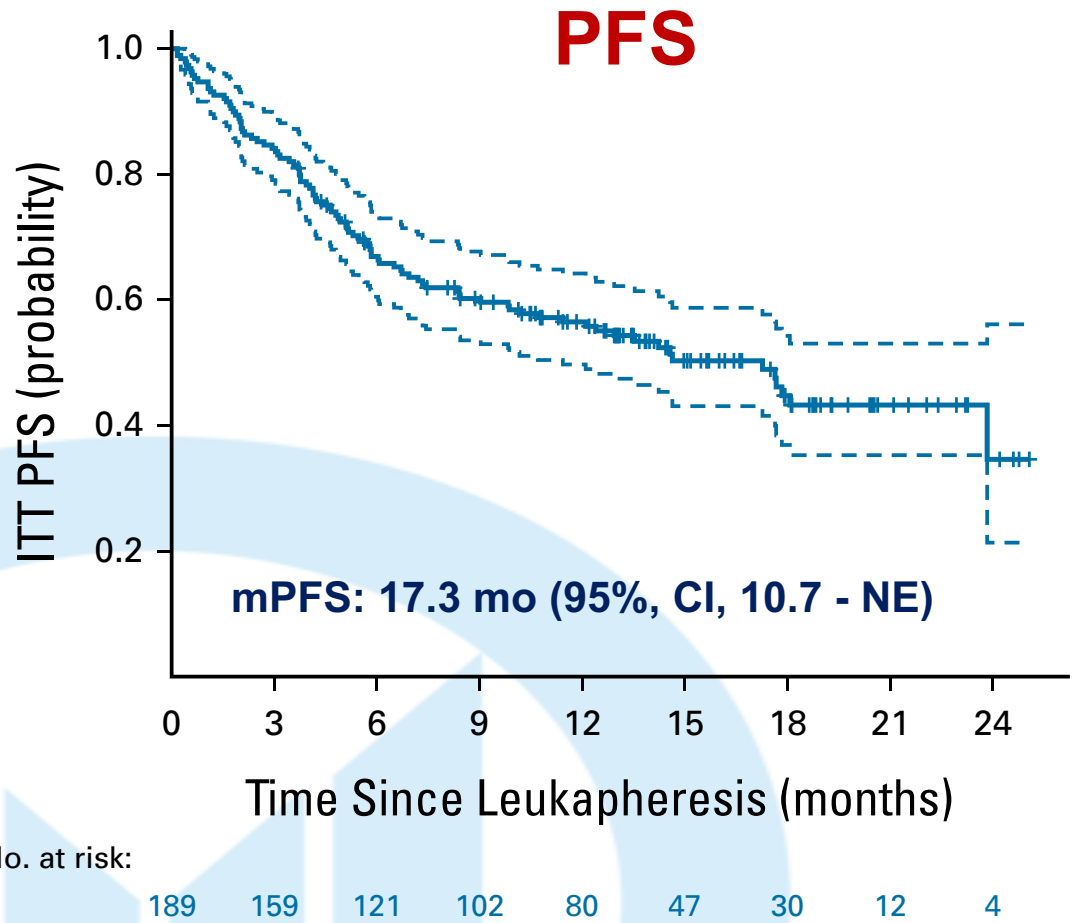
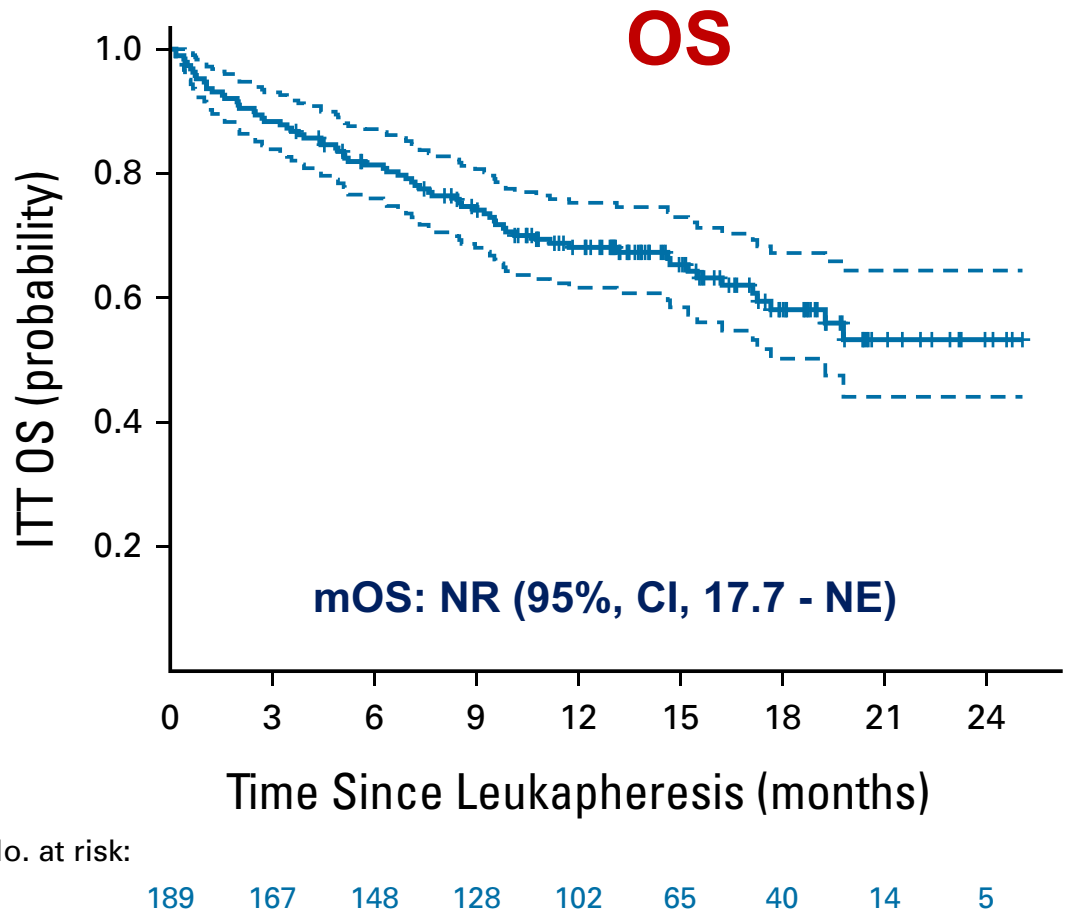
Relapsed/Refractory MCL:

Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)





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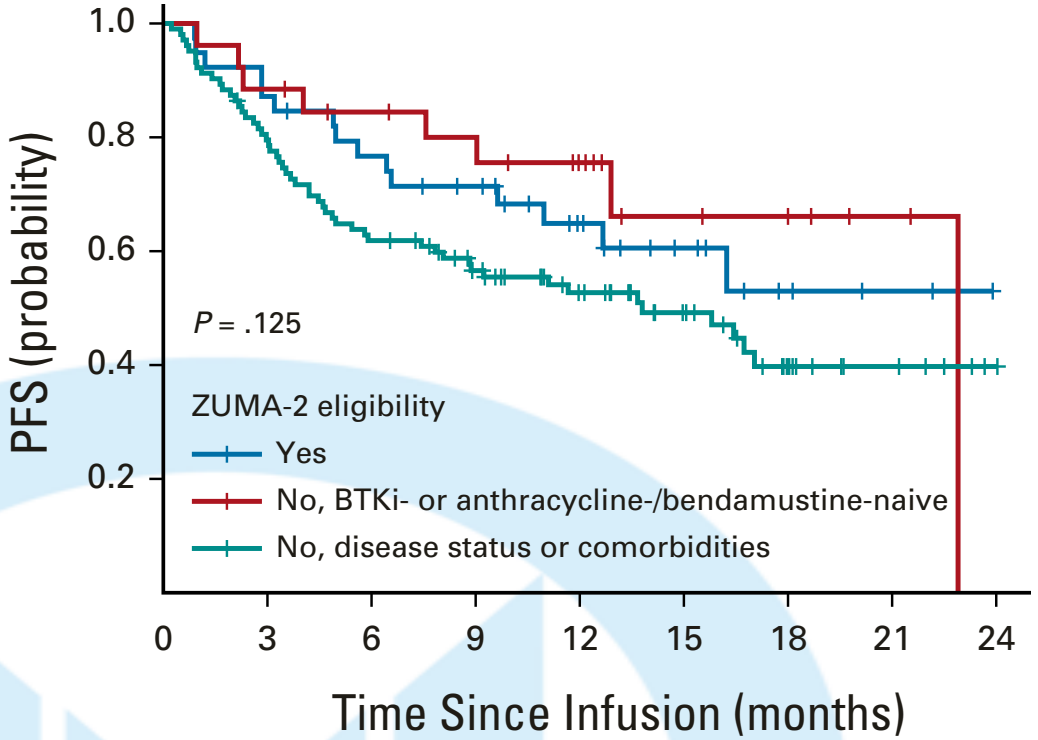
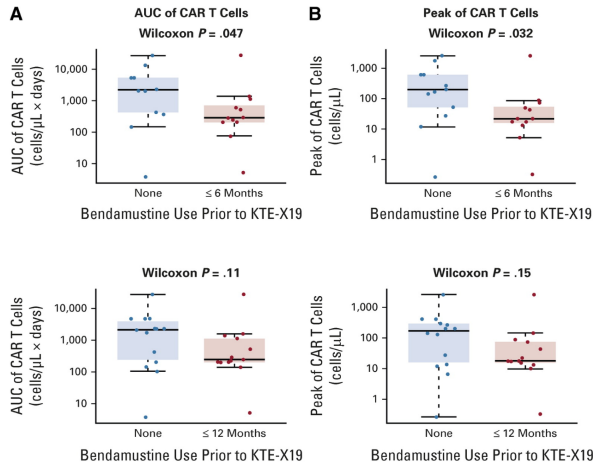
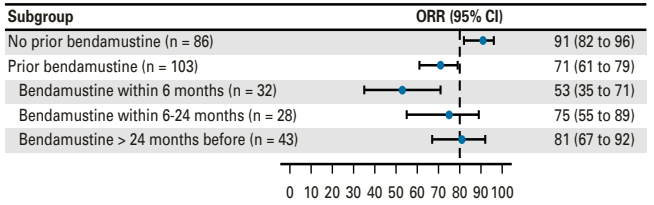
Wang Y, Jain P, Locke F, et at. JCO 2023

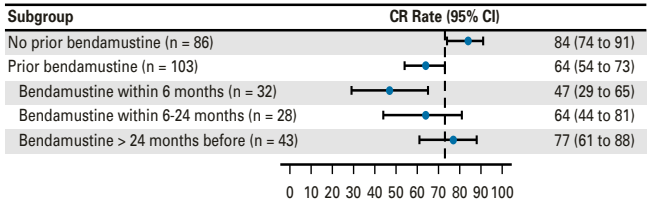
Relapsed/Refractory MCL:

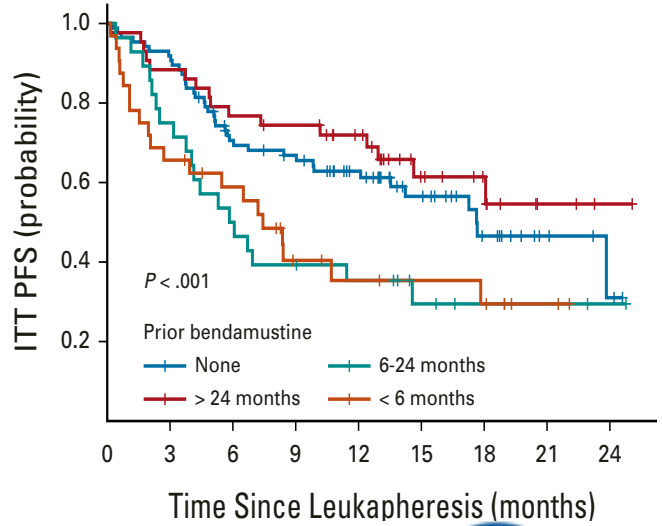
Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)











Wang Y, Jain P, Locke F, et at. JCO 2023

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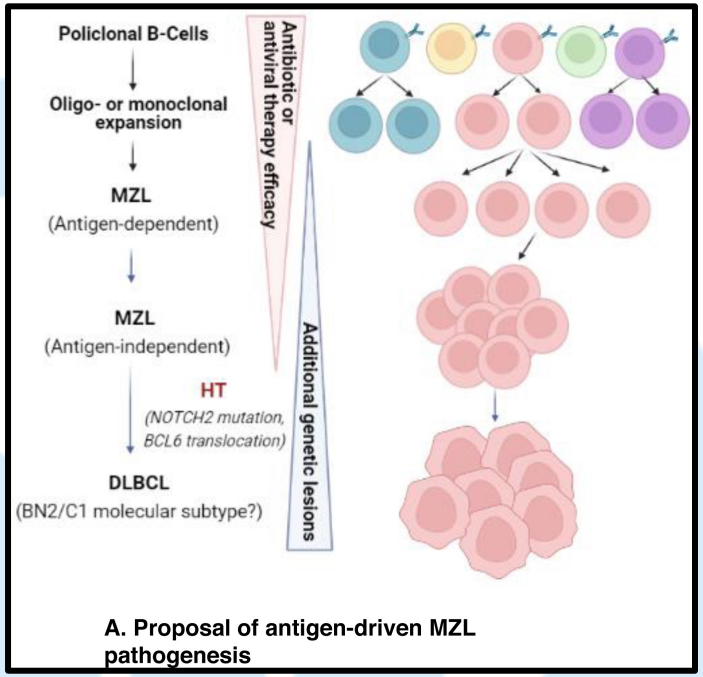
Marginal Zone lymphoma (MCL)

- Indolent B-cell NHL (~7%) originating from memory B- cell.
- Diagnosis of exclusion (CD20+, CD5-, CD23-).
- DDx:
  - ✓ Lymphoplasmacytic lymphoma (MYD88).
  - ✓ Hairy cell leukemia
  - ✓ Atypical CLL (rare).

Meeting 2020



A. Proposal of antigen-driven MZL pathogenesis

3 subtypes

Extranodal MZL:

- ✓ Most common
- ✓ Chronic antigen stimulation associated to its pathogenesis (i.e. infections, autoimmunity)
- ✓ Gastric MALT, skin, lungs, etc

Splenic MZL:

- ✓ Approx. 4% of cases
- ✓ Presents with splenomegaly and cytopenias reflecting involved areas.
- ✓ Can be associated to Hep C infection.

Nodal MZL:

- ✓ Approx. 6% of cases
- ✓ Presents with lymphadenopathy; like FL.

1. . Broccolli & Zinzani ASH Educ Program (2020) 2020 (1): 295–305.; 2. Merli M et al. ASH education Book. 2022; (1): 676-87; Cheah CY et al. Haematologica. 2022; 107(1): 35-43

Marginal Zone lymphoma (MCL)
General treatment approaches

Extranodal MZL/MALT

- Gastric: Antibiotic tx (+H.pylori).
- Non-gastric or gastric (- H.pylori):
  - Localized disease(stage I/II): definitive radiation Tx
  - Systemic disease (stage III/IV): Rituximab, R+chemotx, other agents at relapse.
- Primary cutaneous MZL: surgery, XRT, local steroids, rituximab.

Splenic MZL:

- + Hepatitis C: Hep C directed therapy
- Singe agent rituximab
- Splenomegaly
- Chemmoimmunotherapy, other agents at relapse.

Nodal MZL:

- Singe agent rituximab
- Chemmoimmunotherapy, other agents at relapse

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1. . Broccolli & Zinzani ASH Educ Program (2020) 2020 (1): 295–305.; 2. Merli M et al. ASH education Book. 2022; (1): 676-87; Cheah CY et al. Haematologica. 2022; 107(1): 35-43

Infectious etiologies and anti-infective regimens in MZL

Pathogen	MZL subtype, organ	Prevalence range (%)	Anti-infectious regimen	Type of evidence	ORR (CR)	PFS
Helicobacter pylori	EMZL, stomach	>90%	PPI, clarithromycin-based triple therapy with amoxicillin or metronidazole[a]	>30 retrospective or prospective studies; data from >1400 pts	75%	28 mo
Chlamydophila psittaci	EMZL, ocular adnexa	0%-80%	Doxycycline[b] or clarithromycin[c]	>10 retrospective and 3 prospective studies; data from >100 pts	45%-65%	55% at 5y
Borrelia burgdorferi	EMZL, skin	0%-40%	Ceftriaxone[d]	Case reports	40%	NA
Campylobacter jejuni	EMZL, small bowel (IPSID)	up to 60%	Tetracycline, metronidazole, or ampicillin	Case reports	NA	NA
Achromobacter xylosoxidans	EMZL, lung	2%-46%	NA	NA	NA	NA
Hepatitis C virus	EMZL, various nongastric sites; SMZL; NMZL	5%-20%	DAAs[e]	Retrospective studies, 1 prospective study	48% (26%)	73% at 3y

Merli M et al. ASH education Book. 2022; (1): 676-87

Role of chemoimmunotherapy in MZL

IELSG-19: Phase III EMZL R-Chlorambucil vs. Chlorambucil vs. Rituximab:

- At 7 years of f/up R+Chlorambucil was associated to better ORR, EFS and PFS compared to individual agents.
- OS was the same.
- Only Phase III RTC in MZL but not useful in the US.

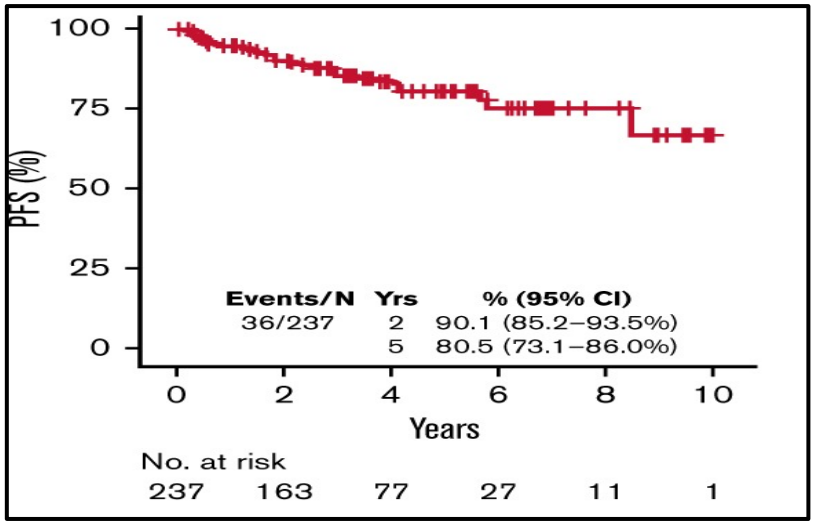
Study	Number of MZL pts	Phase	ORR (CR) %	Result
BRIGHT study [1] R-Bendamustine vs R-CHOP/R-CVP	**46** (28 BR vs 18 R-CHOP/R-CVP)	3	92% (20%)	BR is noninferior to R-CHOP/R-CVP
German StiL study [2] R-Bendamustine vs R-CHOP	**67** (37 BR vs 30 RCHOP)	3	Not reported for MZL	Better PFS with BR in FL only, no difference in MZL.
StiL NHL7-2008 MAINTAIN trial [3] 2 year rituximab maintenance after R-Bendamustine	**119** (Only nodal and splenic MZL, MALT was excluded)	2	91% (19%)	PFS improvement with maintenance vs observation

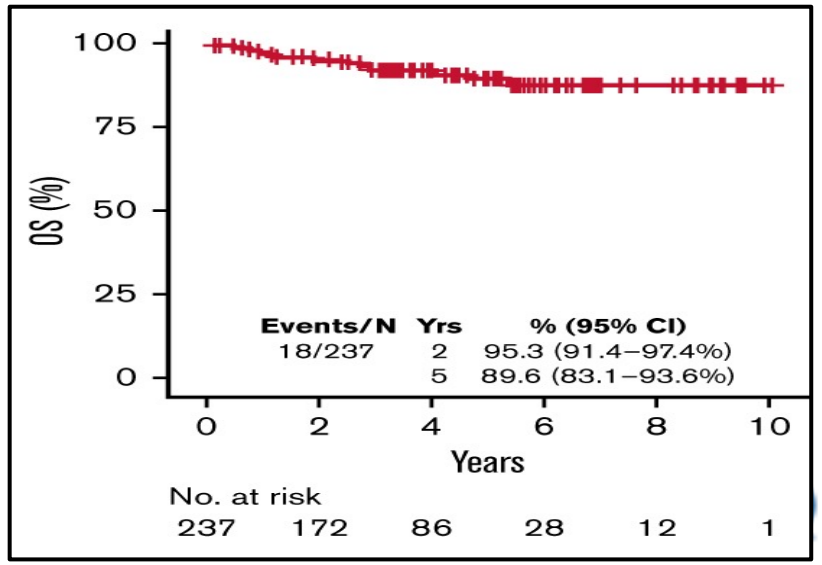
1. Zucca E et al. 2017 Jun 10;35(17):1905-19121; 2. Ian W. Flinn et al. JCO 2019; 3. Rummel MJ, et al. Lancet. 2013:381:1203-10. and updated ASCO 2017; 4 Rummel MJ ASCO 2018

An International analysis evaluating Frontline Bendamustine with Rituximab in Extranodal Marginal Zone Lymphoma

Retrospective cohort

- International retrospective cohort of 237 EMZL.
- Median age: 63 yo (21-85 years).
- Most pts had stage III/IV disease (75%) and intermediate and high MALT-IPI score.
- ORR: 93.2%/CR: 81%.
- 5-year PFS: 80.5%; 5-year OS: 89.6%.
- RM improved PFS but not OS.
- MALT-IPI did not predict outcomes.
- 13% infectious complications, most common was Herpes Zoster.





Alderuccio J , Arcaini L et al. Blood Advances 2022

An update in the treatment of R/R MZL

BTK inhibitors in R/R MZL

	Ibrutinib	Zanubrutinib	Acalabrutinib
Trial	**NCT01980628**	**MAGNOLIA**	**ACE-LY-003**
Population	Adult patients with R/R MZL, >1 prior therapy including anti-CD20 based antibody		
Median Rx	2 (1-9)	2 (1 – 6)	1 (1-4)
N	63 (32 MALT, 14 SMZL, 17 NMZL)	68 (26 NMZL, 26 EMZL, 12 SMZL, 4 mixed subtype)	43 (19 EMZL, 13 (NMZL, 11 SMZL)
ORR, %	48	68.2	52.5
CR, %	3	25.8	12.5
PFS, mo	14.2	NR	27.4
G≥ 3 TEAE	71%	38.2%	39.5%
A. Fib/hypertension	8%/5%	2.9%/0%	0/4.7%
Infections all G/G≥ 3	NR/22%	39.7%/13.2%	34.9%/7%
Bleeding all G/G≥ 3	68%/3%	32.4%/0%	23.3%/0%
Diarrhea G/G≥ 3	48%/NR	20.6%/2.9%	25.6%/0%

Noy A et Al, Blood Advances 2020, Opat et al, Clin Can Res 2021, Strati P at Al, Br J Haematol 2022

Zanubrutinib in R/R MZL: Final analysis of the MAGNOLIA trial (single arm phase 2 study)

Study identifier: BGB-3111-214, NCT03846427

Primary endpoint: ORR assessed by IRC according to Lugano classification 2014[3]
Key secondary endpoints: ORR by PI, PFS, OS, DOR, safety

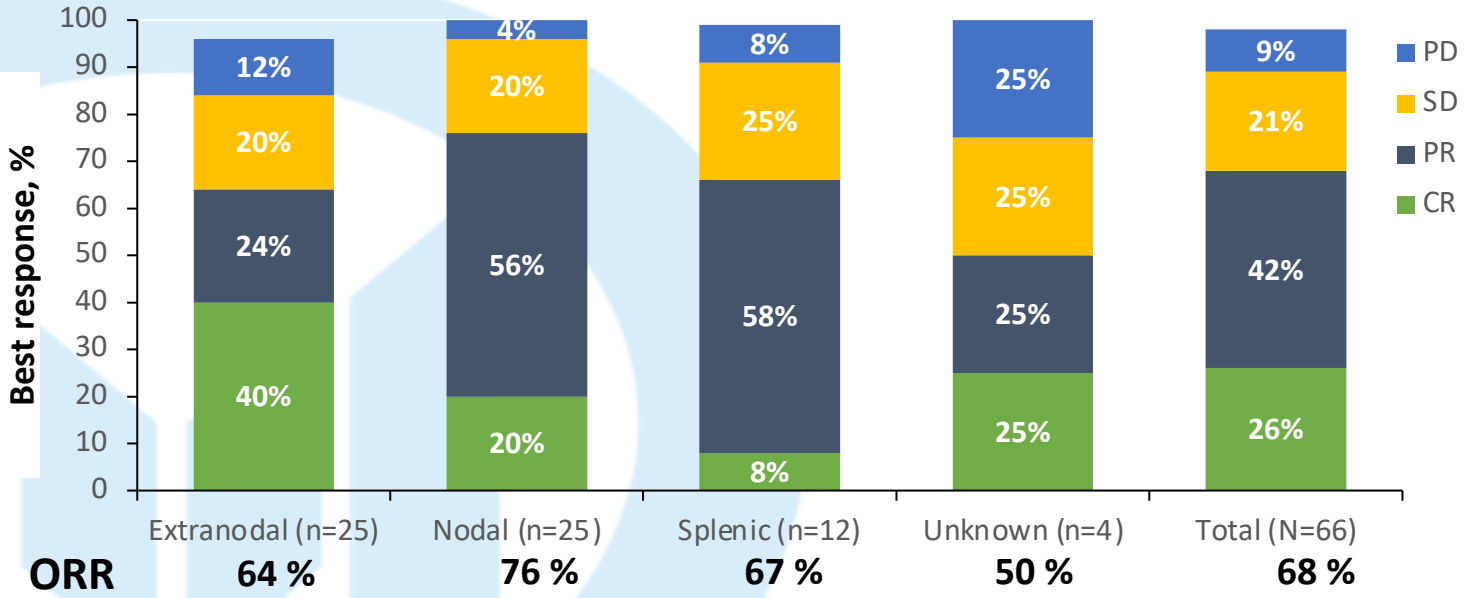
Key eligibility criteria

- R/R MZL patients who received at least one prior line of CD20-directed regimen

Treatment

Zanubrutinib 160 mg BID (N=68)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent or end of study



Enrolled/safety population (N=68)
Median study follow-up:
28 months (range, 1.6-32.9)

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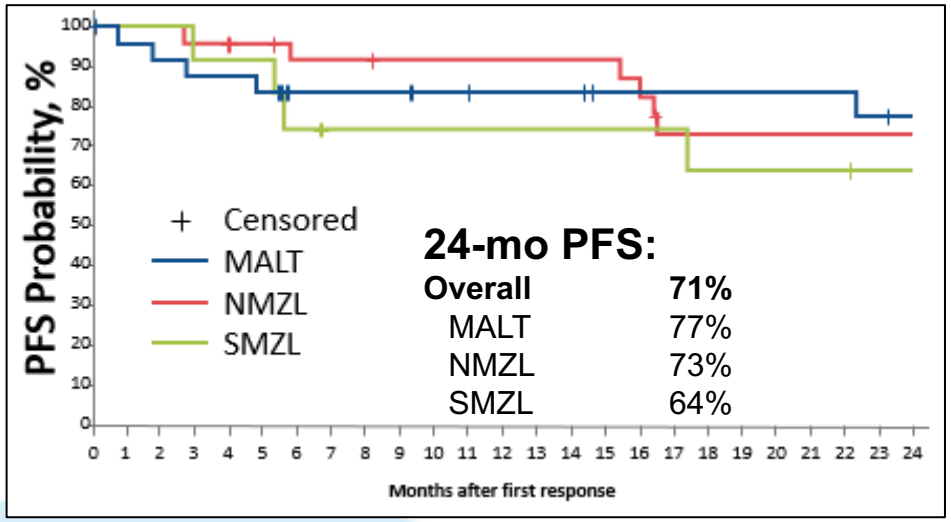
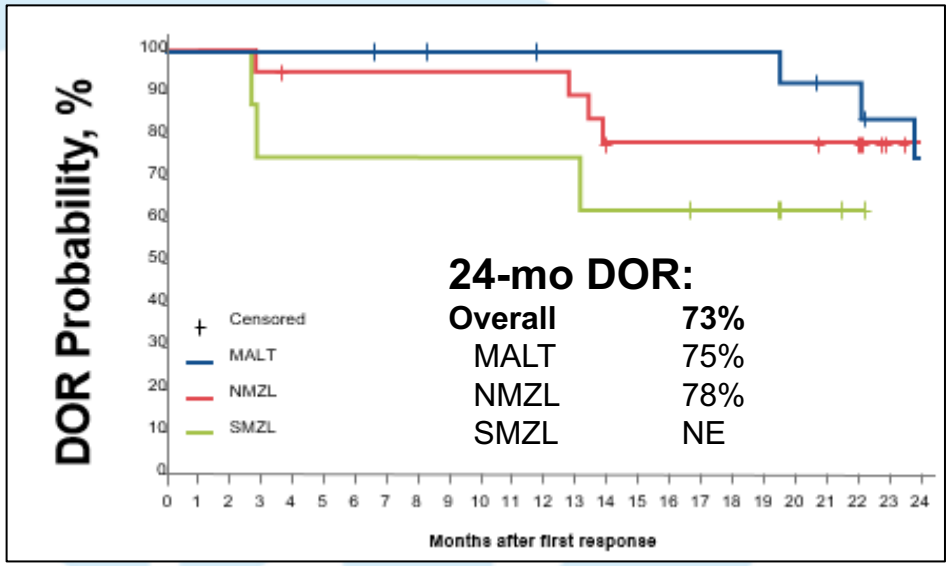
Opat S et al. ASH 2022, abstract 234

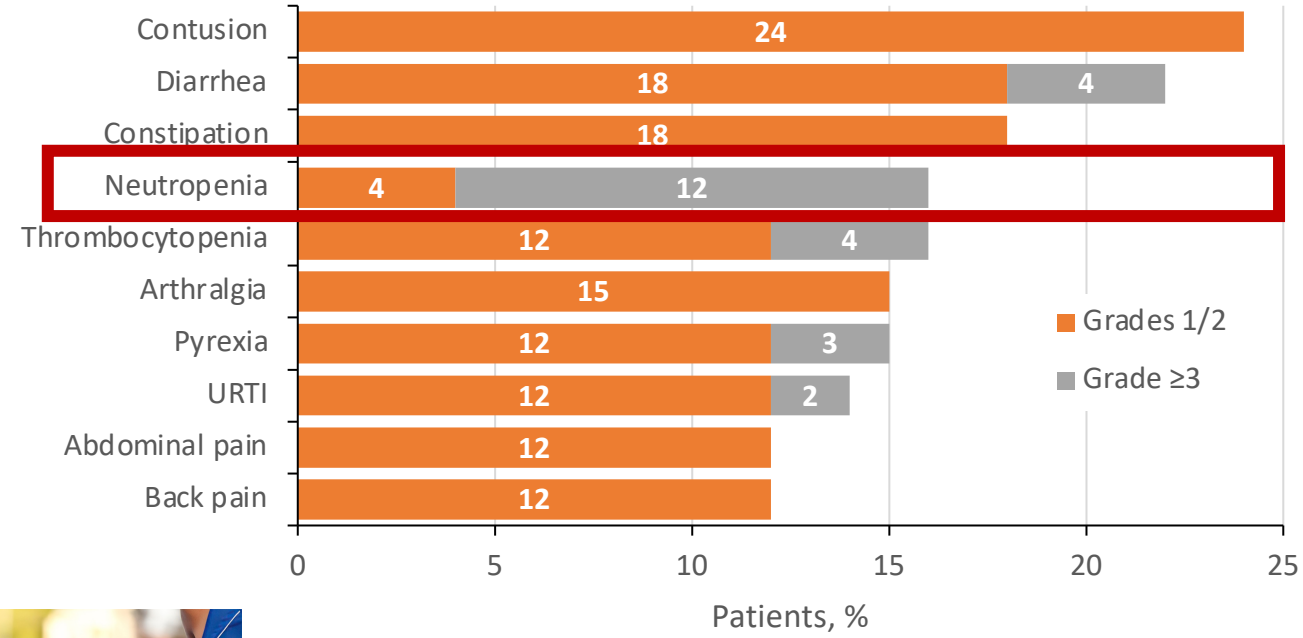
Zanubrutinib in R/R MZL: Final analysis of the MAGNOLIA trial

Outcomes based on MZL subtype





Most common treatment associated AEs



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Opat S et al. ASH 2022, abstract 234

R+Len (R^2) vs. R for R/R "Rituximab sensitive" FL/MZL)

- Multicenter, placebo-controlled, randomized phase III trial

Stratified by prior rituximab (yes vs no), time since last therapy (≤ vs >2 yr), histology (FL vs MZL)

Adult patients with R/R grade 1-3a FL or MZL; ≥1 prior chemo/immunotherapy; not rituximab refractory (N = 358)

Histology (FL/MZL), %	83/17%	82/18%	82/18%
MZL subtype (n=63)			
MALT	14	16	30
Splenic	9	6	15
Nodal	8	10	18

Rituximab: Days 1, 8, 15, 22 of cycle 1; Day 1 of cycles 2-5. Lenalidomide: Days 1-21 of 28. Prophylactic anticoagulation recommended for at-risk patients. Growth factor use allowed per ASCO/ESMO guidelines.
*10 mg/day if CrCl 30-59 mL/min. †FL, n = 147; MZL, n = 31. ‡FL, n = 148; MZL, n = 32.

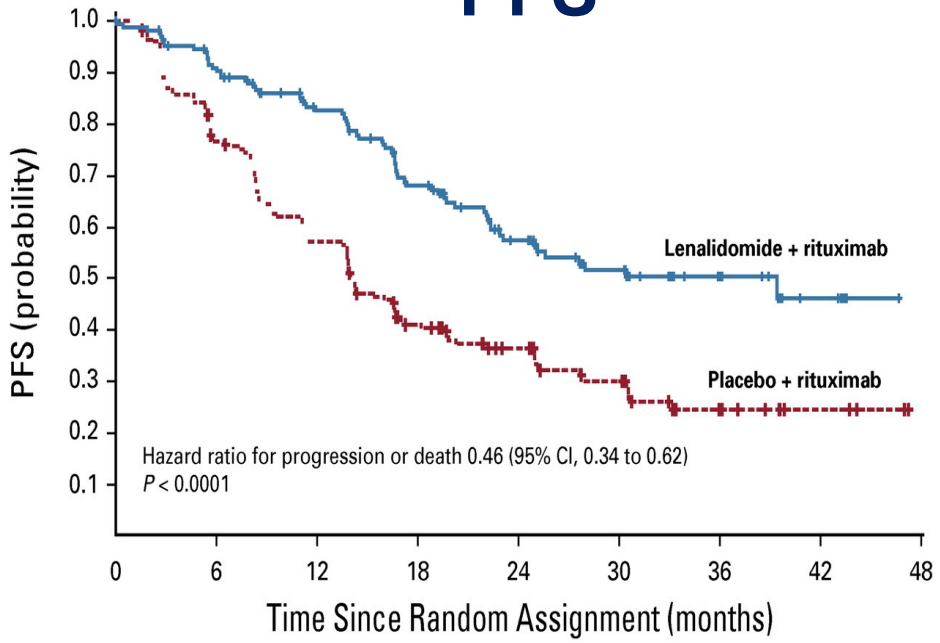
- Primary endpoint: PFS by IRC (2007 IWG criteria without PET)

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

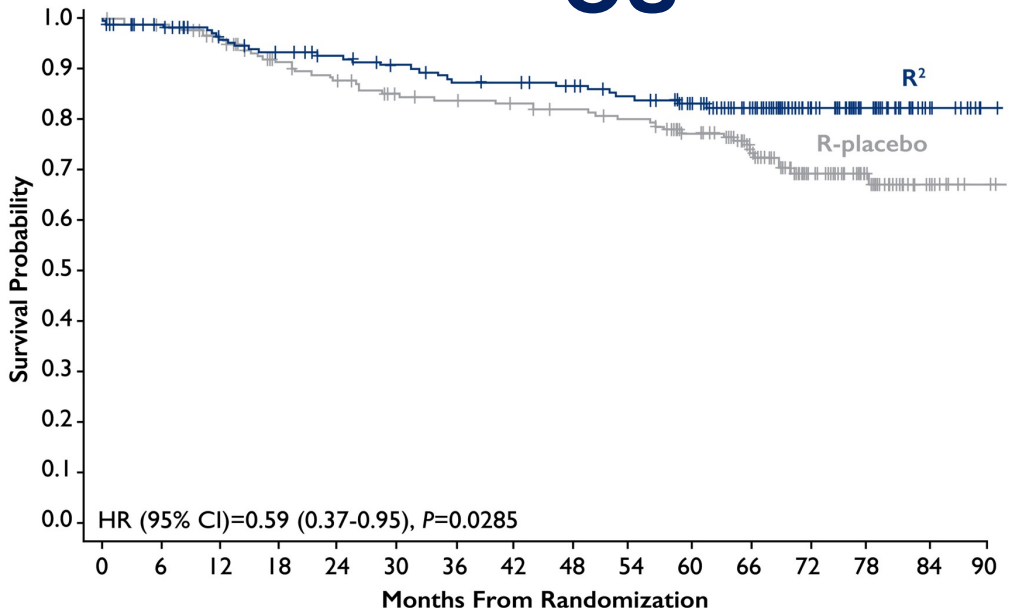
Leonard et al., ASH 2022 abstract #230

ASH 2022: 5.5 year f/up of the AUGMENT Phase III trial

PFS



OS



	All patients		MZL patients (n=63)	
	R2	Rituximab	R2	Rituximab
ORR	78%	53%	65%	44%
CR	34%	18%	29%	13%

	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
mPFS (MZL pts)	20.2 mo	25.2	1	1
5-year Overall Survival	83.2 %	77.3 %	0.59 (0.37-0.95)	0.0285

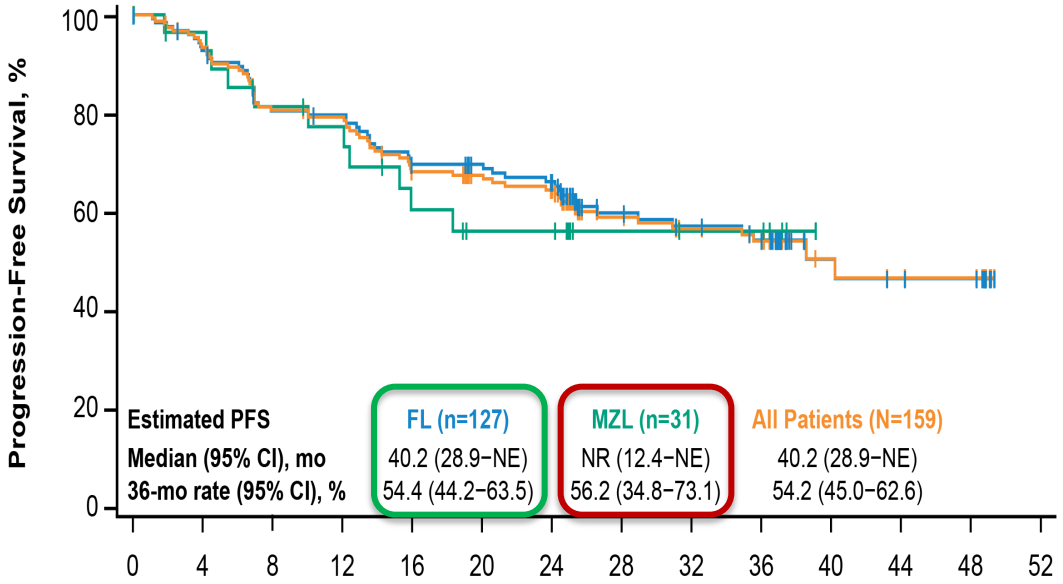
Leonard J, et al. Journal of Clinical Oncology 2019 37:14, 1188-1199.

Leonard et al., ASH 2022 abstract #230

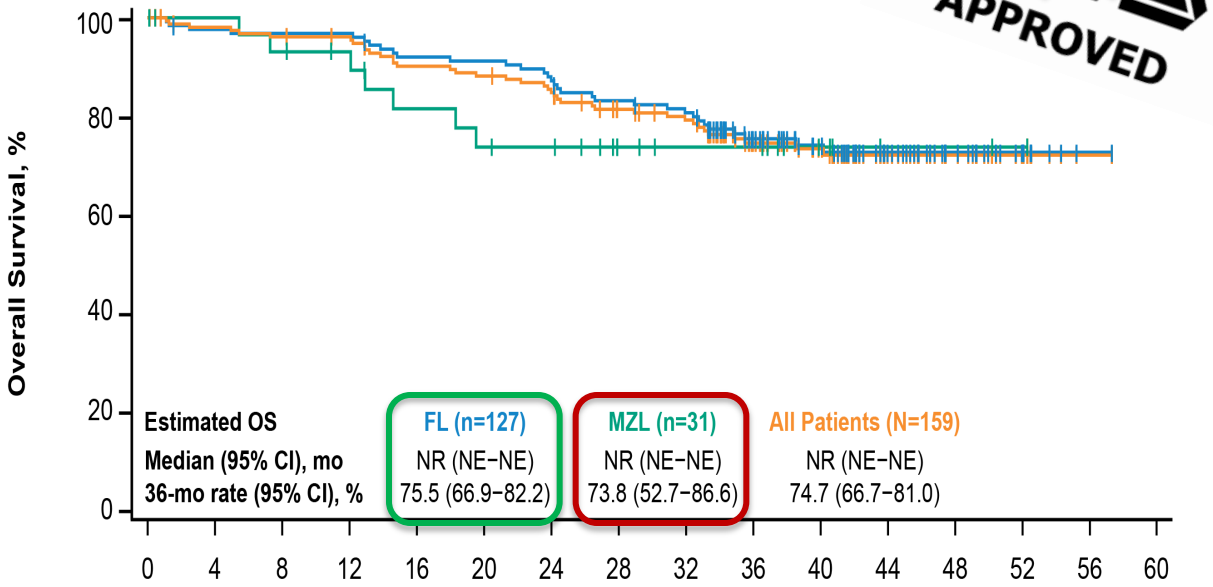
3-Year F/up Analysis of ZUMA-5: A Phase 2 Study of Axi-Cel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

- 159 pts were enrolled (127 FL**; 31 MZL**).
- 152 were treated with axi-cel (124 FL; **28 MZL**).
- Median f/up: 40.5 mo (FL: 41.7 mo/MZL: **31.8 mo**)
- ORR for MZL**: 83%;** CR for MZL**: 65%**

Progression-Free Survival



Overall Survival



1.Jacobson C, Chavez JC et al. *Lancet Oncol* 2022; 23: 91–103 ; 2. Neelapu SS et al. ASH 2022. Abstract 4660

Study/phase	Type of lymphoma	Regimen	Number of patients	ORR%/CR%	PFS, months	OS, months
P III	FL/MZL	B+O; O maintenance	164 FL/28 MZL	69.1/11.2	25.8 months	41 months
Leonard *et al.*[30]/P III	FL/MZL	Rituximab plus Lenalidomide	147 FL/31 MZL	78/34	39.4 months	2 years OS = 95% FL 2 years OS = 82% MZL
Gopal *et al.*[31]/P II	FL/MZL	Idelalisib	72 FL/15 MZL	57/6	11 months FL 7 months MZL	20.3 months
Flinn *et al.*[32]/P II	FL/MZL	Duvelisib	83 FL/18 MZL	40/20 FL 66.7/0 MZL	9.5 mo.	28.9 months
Dreyling *et al.*[33]/P II	FL/MZL	Copanlisib	104 FL/23 MZL	58.7/20.2 FL 78.3/13 MZL	12.5 months 24.1 months	42.6 months 83% at 2 years
Zinzani *et al.*[34]/P II	FL MZL	Umbralisib	117 FL 69 MZL	53/12 FL 55/10.5 MZL	16 months 71% at 12 months	NR NR
Gopal *et al.*[35]/P II Noy *et al.*[36]/P II	FL MZL	Ibrutinib	110 FL 63 MZL	20.9/11 48/3	4.6 months 14.2 months	78% at 2 years 81% at 18 months
Morschhauser *et al.*[37]/P II	FL	Tazemetostat	45 EZH2 mut FL 54 EZH2 wt FL	69/11 35/3	13.8 months 11.1 months	
Jacobson C et al./Phase II	FL/MZL	Axi-cel	124 FL/24 MZL	94/79 FL/ 83/65 MZL	**36 mo PFS: FL: 54% MZL: 56%**	**36 mo OS: All: 74.7% FL: 75.3% MZL: 73.8%**

Sandoval-Sus and Chavez JC. Ther Adv Hematol May 2021

Some of the upcoming trials in MZL

Population	Phase	Treatment regimen	Trial Status	Primary Endpoint(s)	NCT#
Frontline MZL	3	Ibrutinib+rituximab Vs. Rituximab	Recruiting	CR at 30 months	04212013
R/R MZL or FL	3	Zanubrutinib + R Vs. R^2	Recruiting	PFS	05100862
R/R NHL including MZL	1/2	Epcoritamab	Recruiting	Safety/ORR	03625037
R/R MZL or FL	3	Tafasitamab+R^2 Vs. R^2	Recruiting	PFS	04680052
R/R MZL	2	Tafasitamab+Acalabrutinib	Recruiting	CCR	04646395

Thank you for finishing this marathon with me!

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