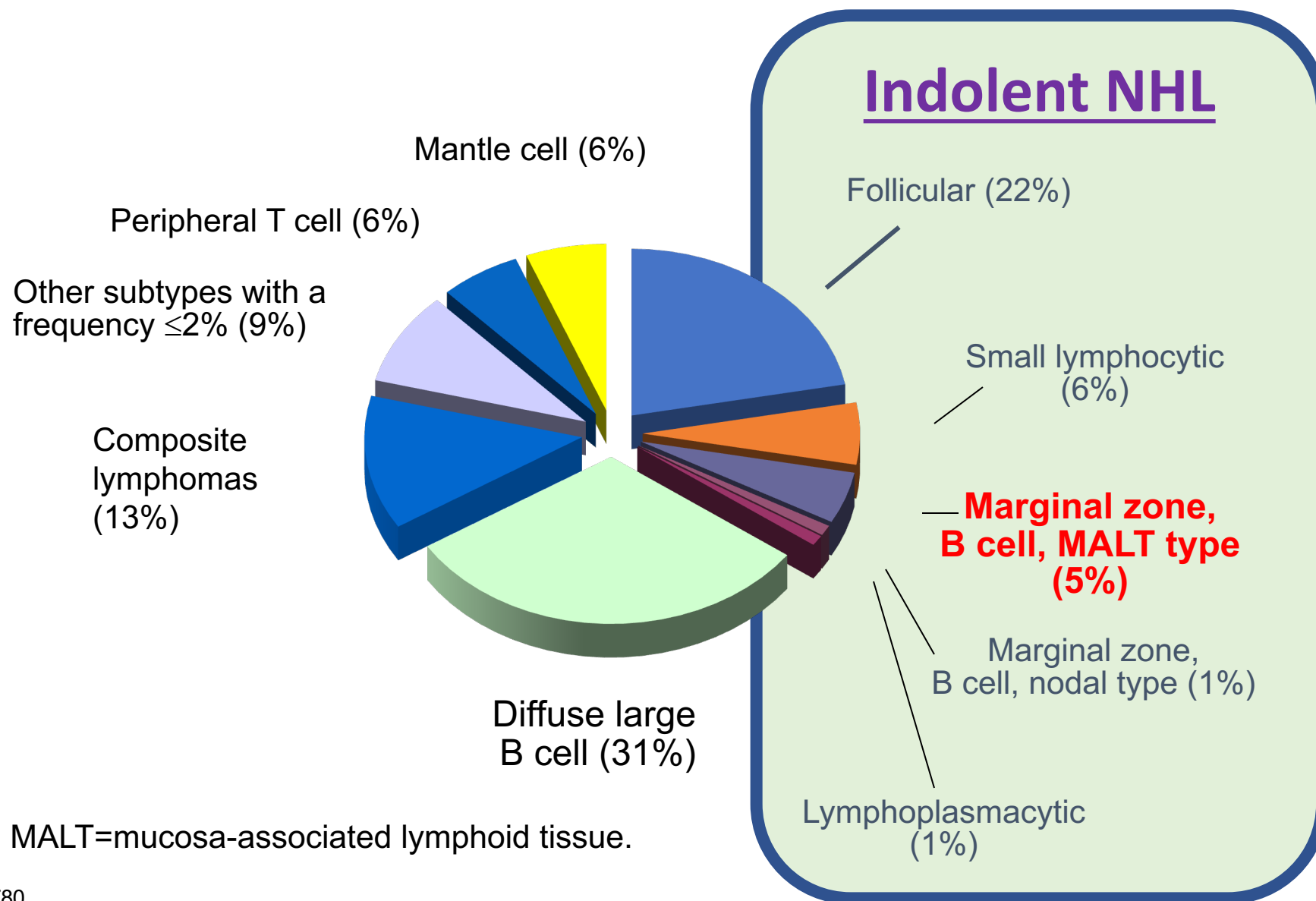


Marginal Zone Lymphoma

AKA... the STEPCHILD sibling of Follicular lymphoma

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The Frequency of Various Lymphoma Subtypes in Adults



Marginal Zone Lymphoma



Three distinct Entities

- Indolent lymphoma originating from memory B lymphocytes present in the marginal zone of secondary lymphoid follicles
- Often a diagnosis of 'exclusion' having no specific 'markers' (**CD5 –ve/ CD10 –ve monoclonal B-cells**).
- Differential: lymphoplasmacytic lymphoma (MYD88); Hairy cell leukemia (BRAF)

Extranodal MZL (MALT)

- Majority of cases
- Gastric
- Cutaneous
- Non-Gastric/Non-cutaneous (GI, lung, ocular adnexae, thyroid, etc)

Nodal MZL

- ~ 6% of cases
- Nodal presentation similar to follicular lymphoma

Splenic MZL

- ~ 4% of MZL
- Splenic, Marrow and peripheral blood involvement.
- Commonly presents with anemia and splenomegaly.

MZL Pathogenesis: Chronic Antigen Stimulation



Infections

Stomach: *Helicobacter Pylori*

Ocular adnexa: *Chlamydia psittaci*

Skin: *Borrelia Burgdorferi*

Lung: *Achromabacter xylosoxians*

Intestine: *Campylobacter jejuni*

Autoantigens

Sjogren's disease

Hashimoto's thyroiditis

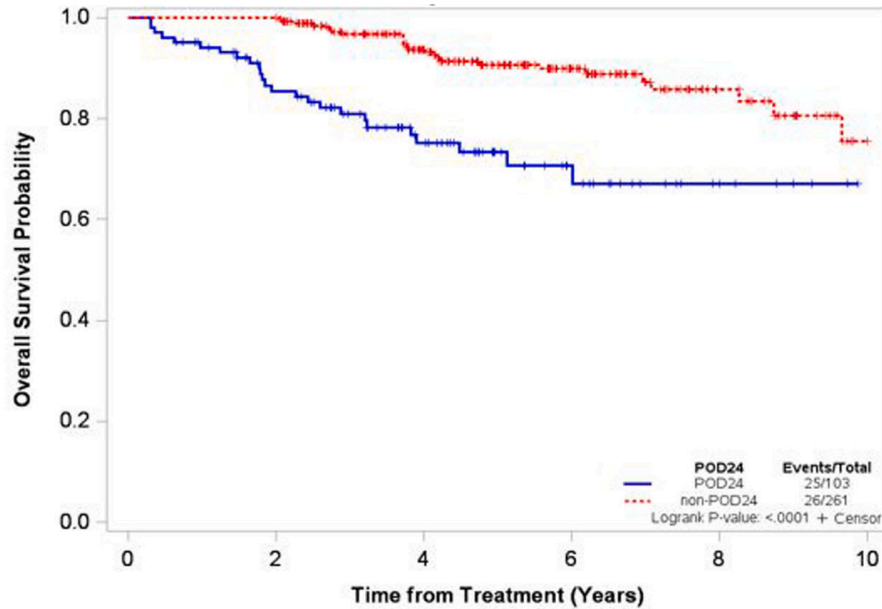
Systemic Lupus

Relapsing polychondritis

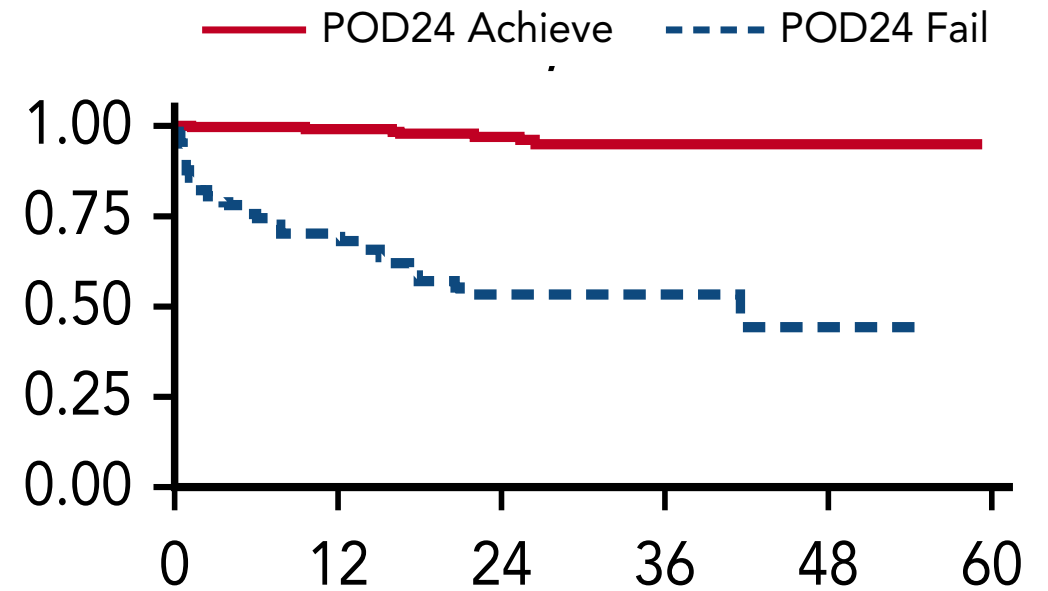
Splenic/Nodal MZL

Hepatitis C

Early Progression within 2 years (POD24) is associated with worse survival

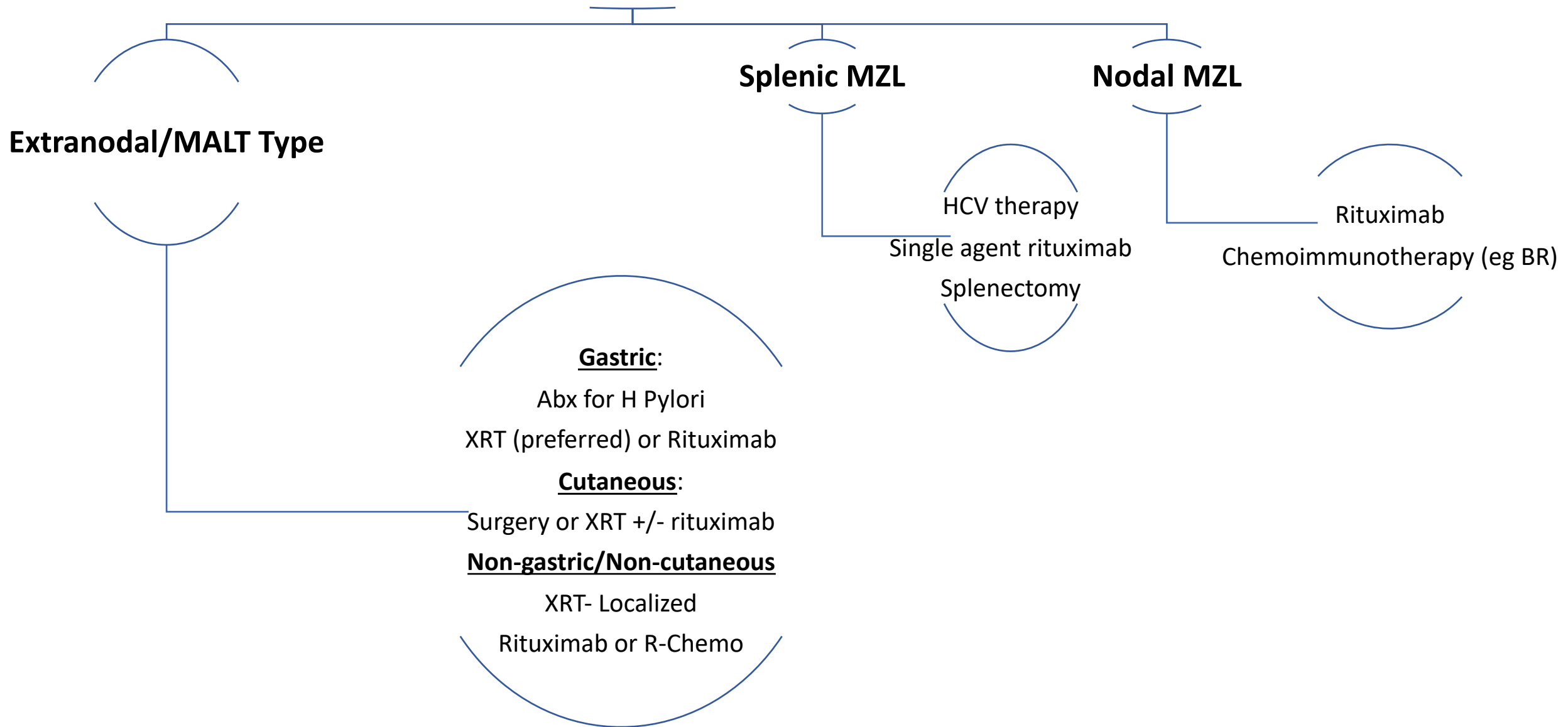


Overall Survival at 5 years:
POD24= 73%
Non-POD24= 91%



Overall Survival at 3 years
POD24 3-y: 53%
No POD24 3-y: 88%

Current Management approach of untreated MZL





Effectiveness of anti-infective therapy

Pathogen	Organ	Therapy	ORR
<i>H Pylori</i>	Stomach	PPI + clarithromycin based, triple therapy, metronidazole or amoxicillin	65- 77%
<i>C. Pstittaci</i>	Ocular Adnexa	Doxycycline or clarithromycin	45 – 52%
<i>B. Burgdorferi</i>	Skin	Ceftriaxone	40%
<i>C. Jejuni</i>	Small intestine	Various	NA
Hepatitis C	NA	Peg-IFN or IFN	1 st Line: 77% 2 nd Line: 85%

Gastric
MALT

Splenic
MZL

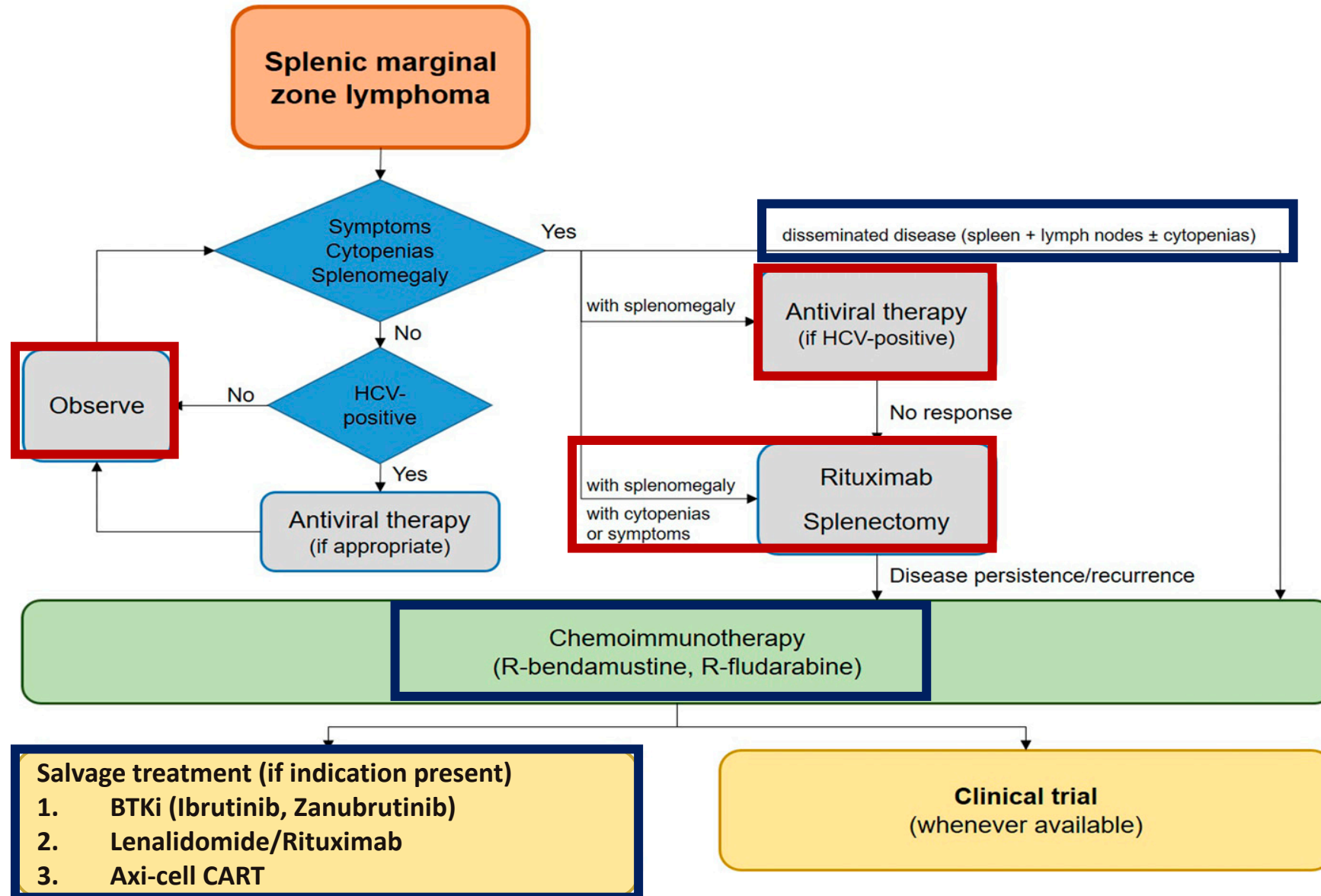
Gastric MALT: Radiation therapy



- SEER database study on 1134 gastric MALT patients
- Between 1997 – 2007
- 5-y lymphoma related death:
 - RT: 5.3% (95%CI 2.6– 9.4)
 - Chemo: 19.1% (95%CI 13.1 – 26.0)
- No differences between rituximab (R) single agent or R-chemo
- The freedom from treatment failure (FFTF) at 15-years is 88%!



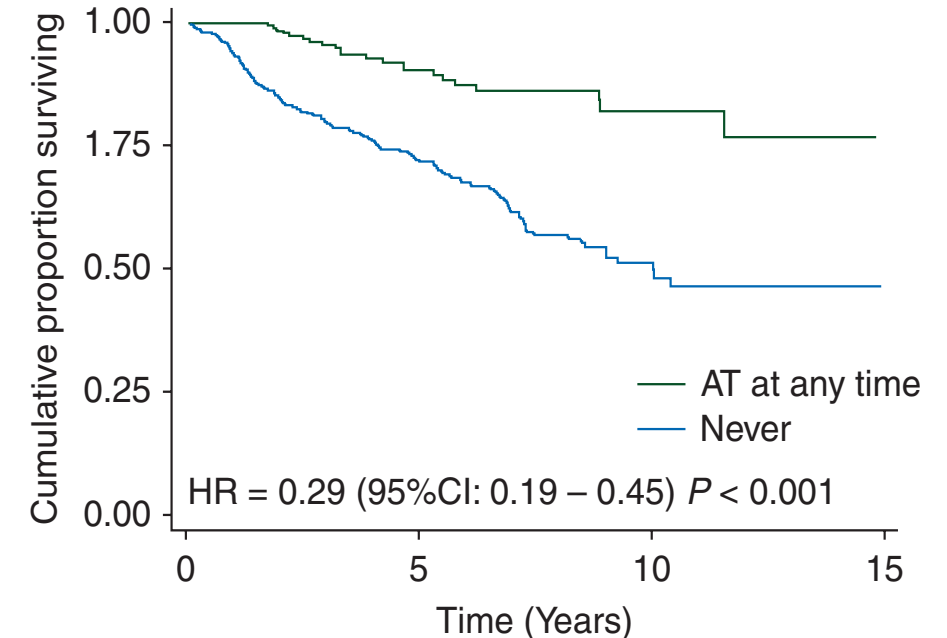
Splenic Marginal Zone Lymphoma





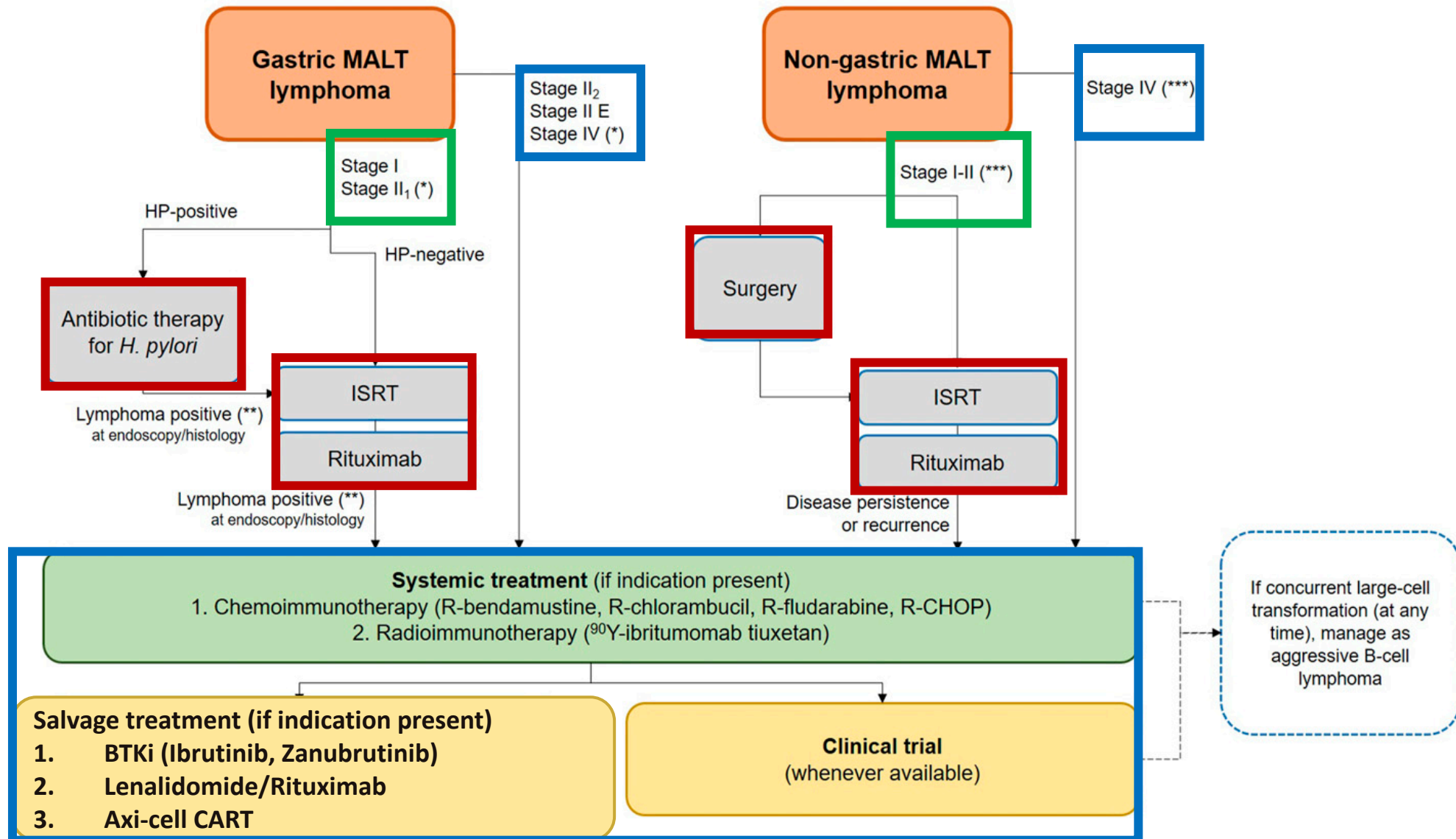
Hepatitis C and MZL: Effect of antiretroviral therapy

- Majority of studies were based on IFN-gamma regimens of antiviral therapies (AT)
- SMZL ORR between 50-75%
- Strong correlation with serologic viral responses (SVR)
- Antiviral therapy at any time is associated with improved survival



Number at risk				
AT at any time	225	102	32	6
Never	465	153	33	9

Extranodal Marginal Zone lymphoma management

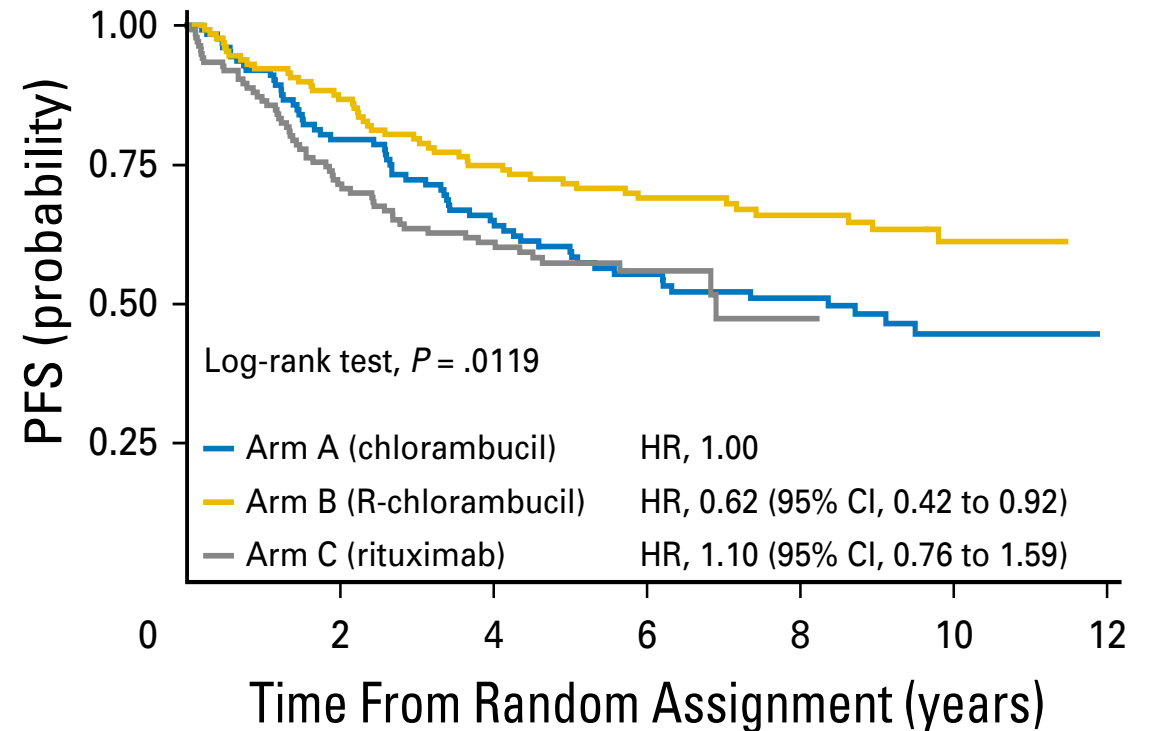
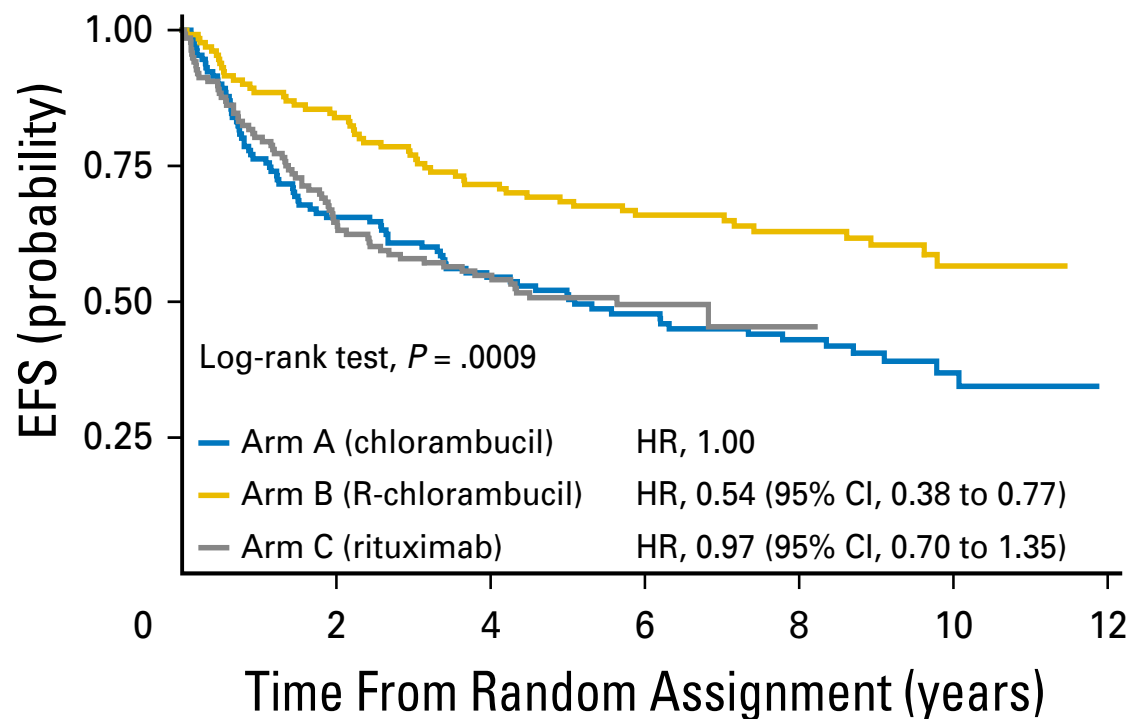


IELSG-19: Phase III EMZL R-Chlorambucil vs Chlorambucil vs R: 7- year follow up

The only frontline randomized phase III trial in MZL

Rituximab-Chlorambucil had better EFS and PFS compared to either agents alone

Rituximab-Chlorambucil rarely used in the United States



What about R-Bendamustine?

We lack prospective randomized trials dedicated to MZL



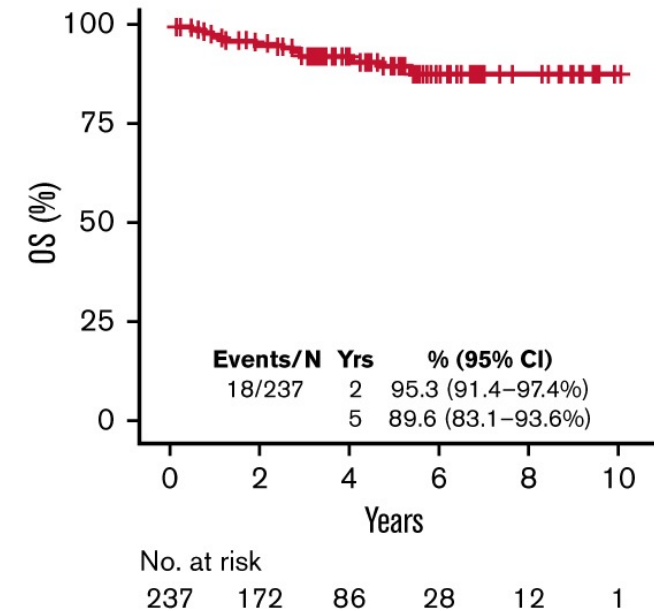
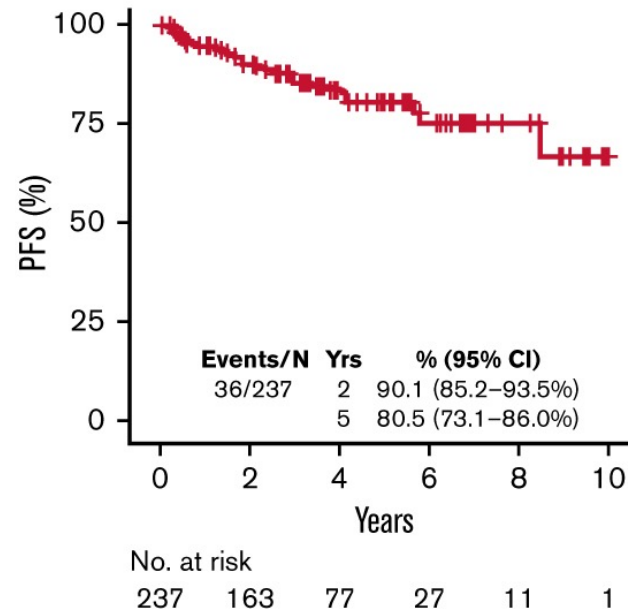
R-Bendamustine randomized trials included a small subset of MZL patients.

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

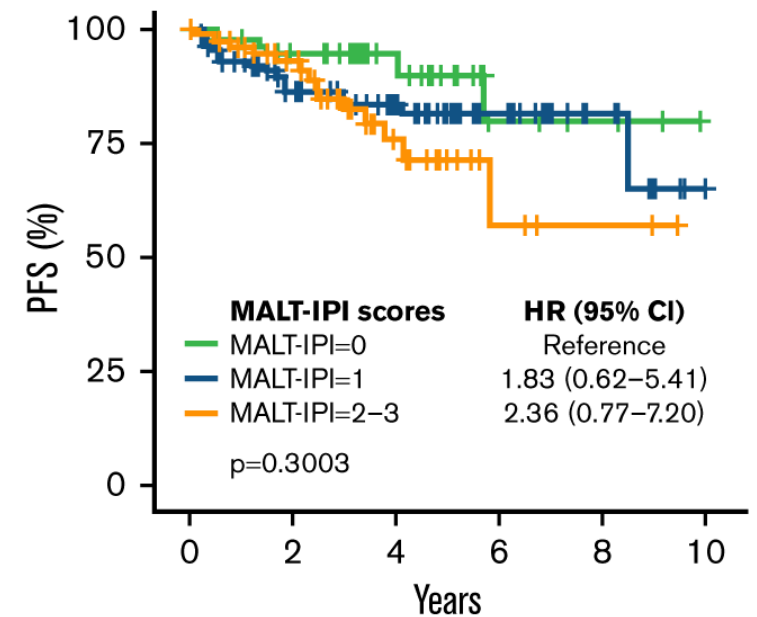
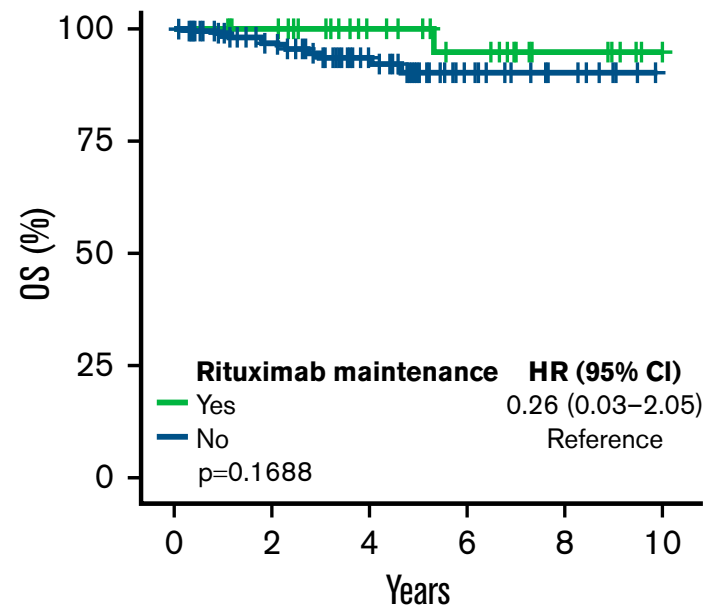
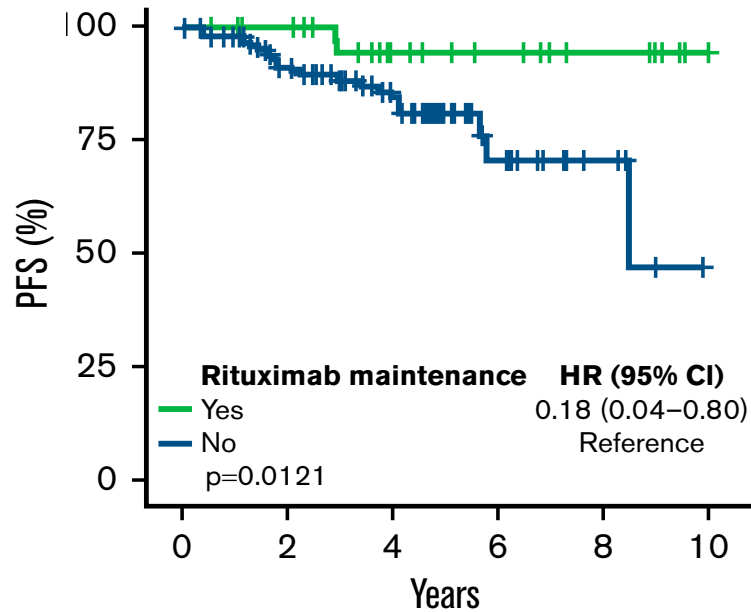
International Retrospective study: Frontline Bendamustine + Rituximab for EMZL

- # patients: 237
- Median age 63 (21 – 85)
- Stage III/IV: 75.5%
- Median follow up: 3.21 years
- More than 2 EN sites: 45%
- Efficacy (59% assessed by PET)
 - **ORR 93.2%**
 - **CR 81%**
 - **PFS at 5 years: 80.5%.**

Frontline bendamustine with rituximab in extranodal marginal zone lymphoma



International Retrospective study: Frontline BR for EMZL



Rituximab maintenance was associated with better PFS, but not OS.

MALT-IPI score was lacked predictive value

R/R MZL: Systemic Treatment options



Observation for low bulky asymptomatic patients with late relapse is reasonable

Second line

- Chemoimmunotherapy (RCHOP, R-CVP)
- Anti-CD20 agents: Rituximab, Obinutuzumab
- Lenalidomide/Rituximab (AUGMENT, MAGNIFY)
- BTK inhibitors:
 - Ibrutinib
 - Zanubrutinib
 - Acalabrutinib

Third line and Beyond

Second line options not previously used.

Additional options:

- Clinical Trial
- PI3K inhibitors (mostly withdrawn 2022)-
Copanlisib.
- CART cell therapy (Axi-cel) currently on NCCN

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

BTK Inhibitors in 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)
Dose	560 mg daily until PD	160 mg BID until PD	100 mg BID until PD
ORR, %	48	68.2	52.5
CR, %	3	25.8	12.5
PFS, mo	14.2	NR	27.4

BTK Inhibitors in MZL: Toxicities

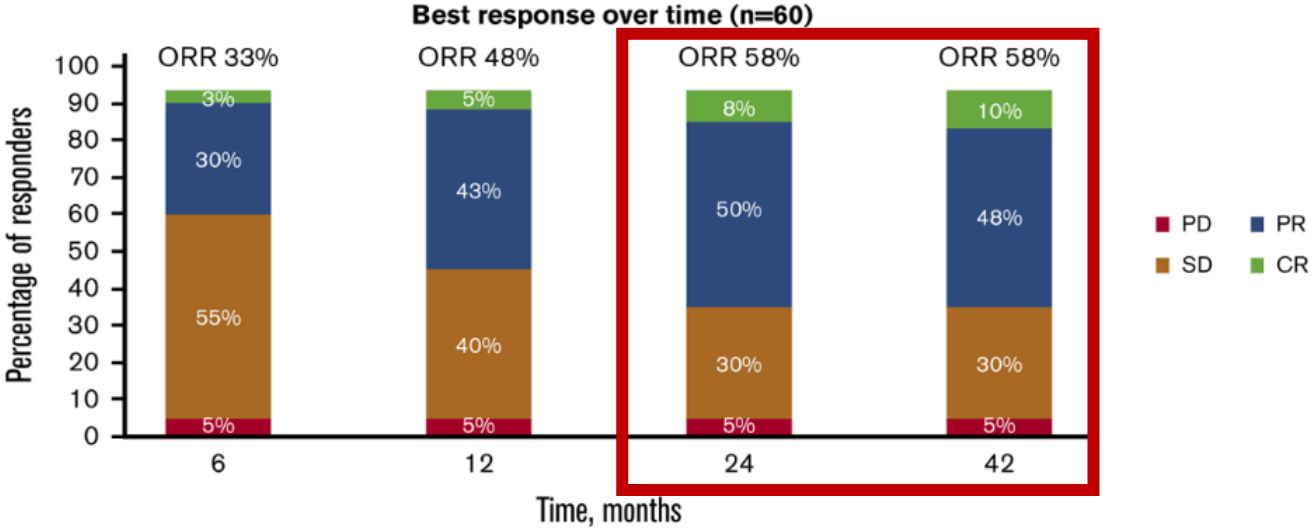


	Ibrutinib	Zanubrutinib	Acalabrutinib
Trial	PCYC-1121	MAGNOLIA	ACE-LY-003
Grade \geq 3 TEAE	71%	38.2%	39.5%
Drug interruption due to AE	17%	2.9%	7%
Atrial Fibrillation	8%	2.9%	0
Hypertension	NR (5%)	0	4.7% (0)
Infections all grades (G \geq 3)	NR (22%)	39.7% (13.2%)	34.9% (7%)
Bleeding all grades (G \geq 3)	68% (3%)	32.4% (0)	23.3% (0)
Diarrhea all grades (G \geq 3)	48%	20.6% (2.9%)	25.6% (0)
Neutropenia	NR (5%)	13.2% (10.9%)	14% (14%)

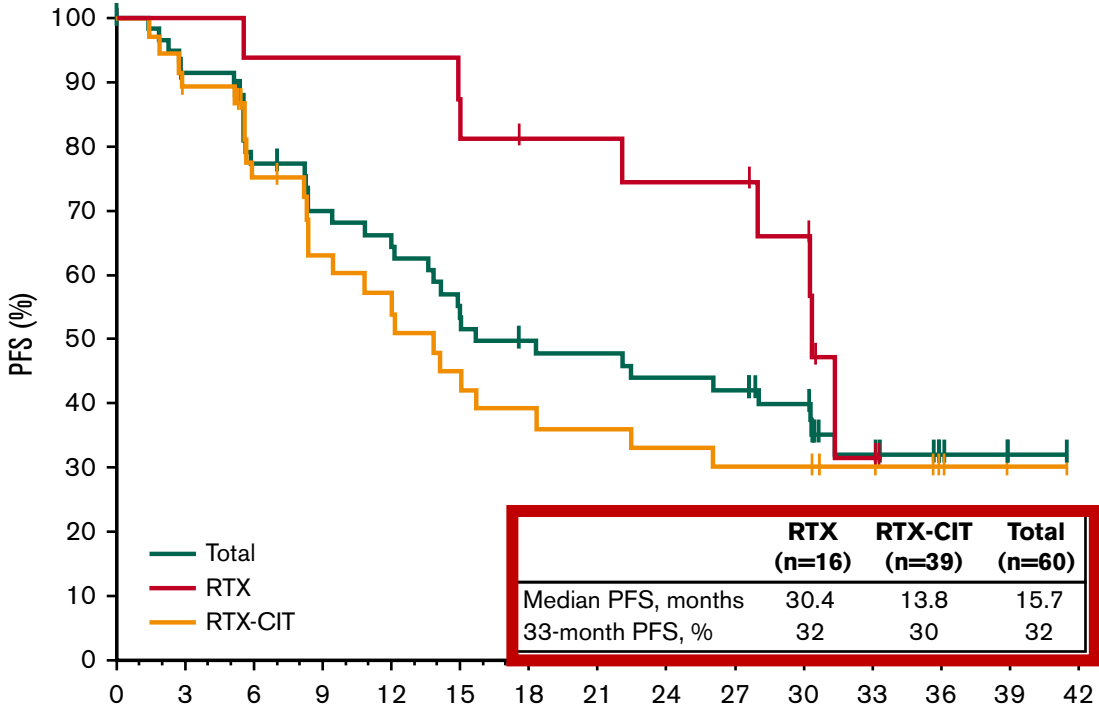
Ibrutinib for R/R MZL: PCYC-1121



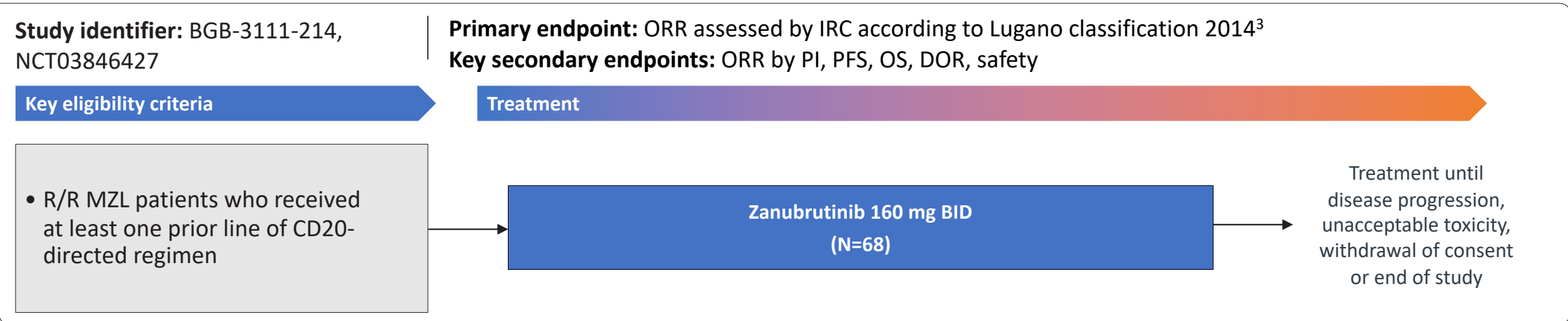
Single-agent ibrutinib (560 mg) for treatment of relapsed/refractory MZL



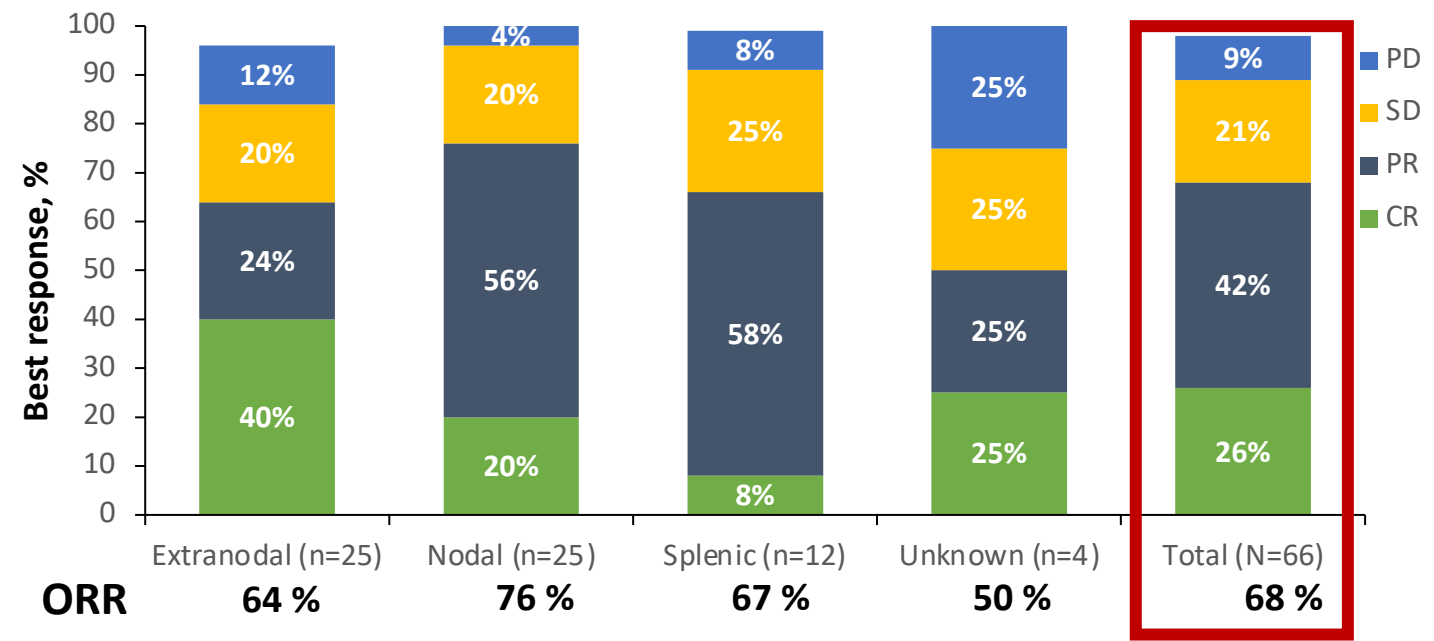
PFS in the total efficacy population and by prior line of therapy (Rituximab and chemoimmunotherapy)



Zanubrutinib for R/R MZL: Final analysis of the MAGNOLIA Trial

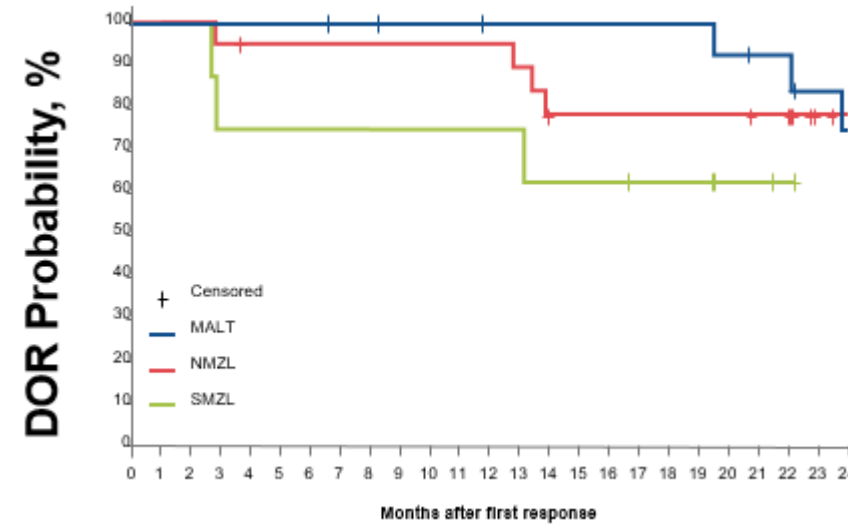
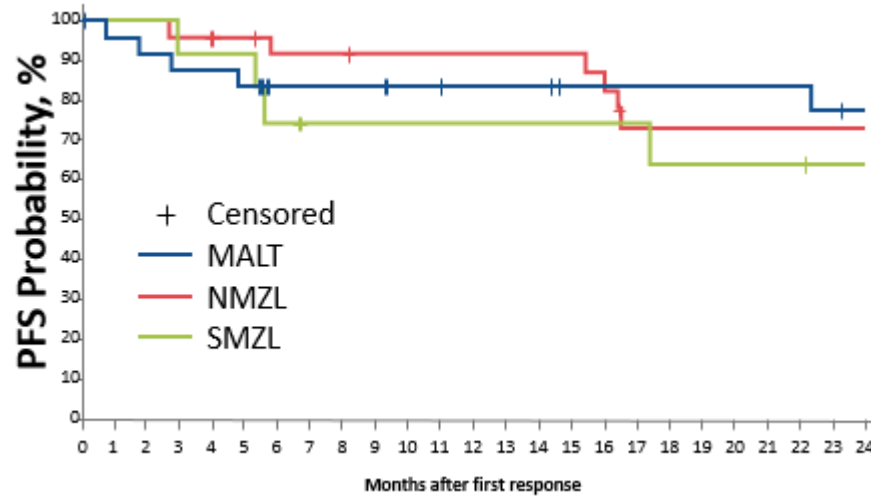


Enrolled/safety population (N=68)
Median study follow-up:
28 months (range, 1.6-32.9)



Zanubrutinib: MAGNOLIA

Efficacy by MZL Subtypes



PFS rate at 24 months:

Overall	71%
MALT	77%
NMZL	73%
SMZL	64%

DoR rate at 24 months:

Overall	73%
MALT	75%
NMZL	78%
SMZL	NE

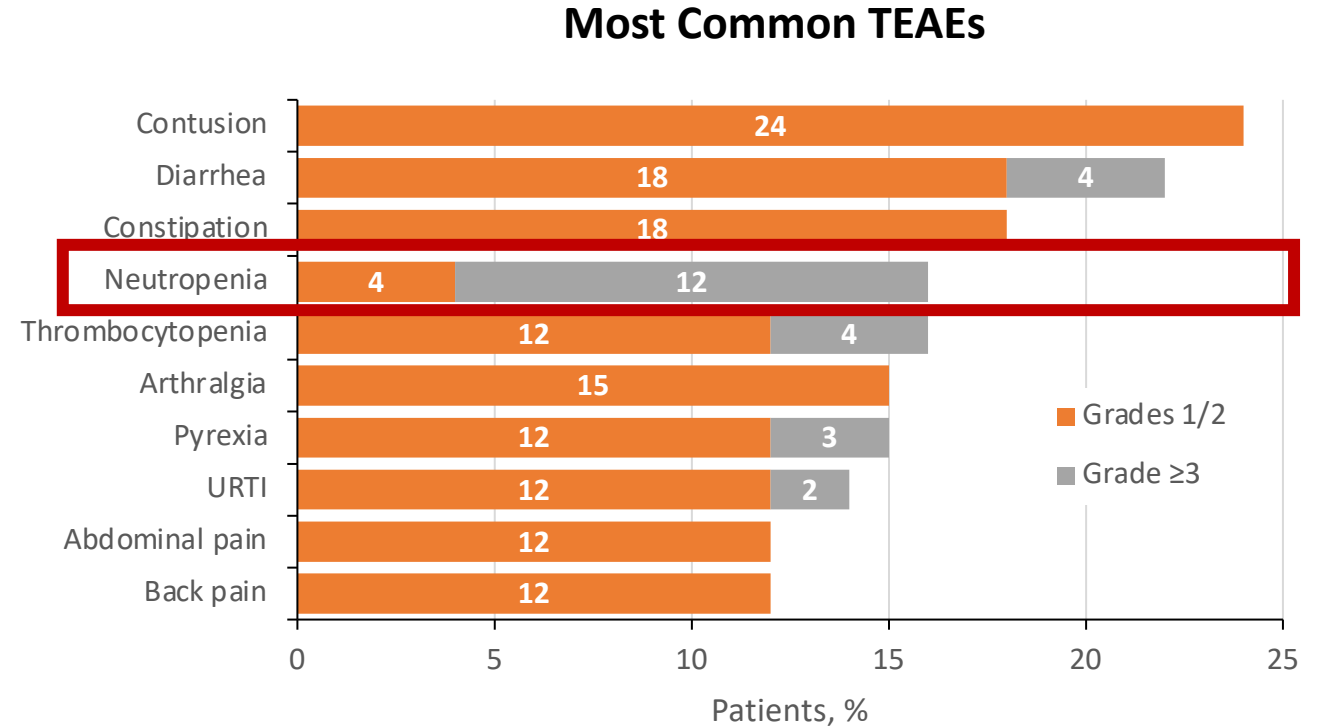
Zanubrutinib: MAGNOLIA Safety Profile



Safety Summary

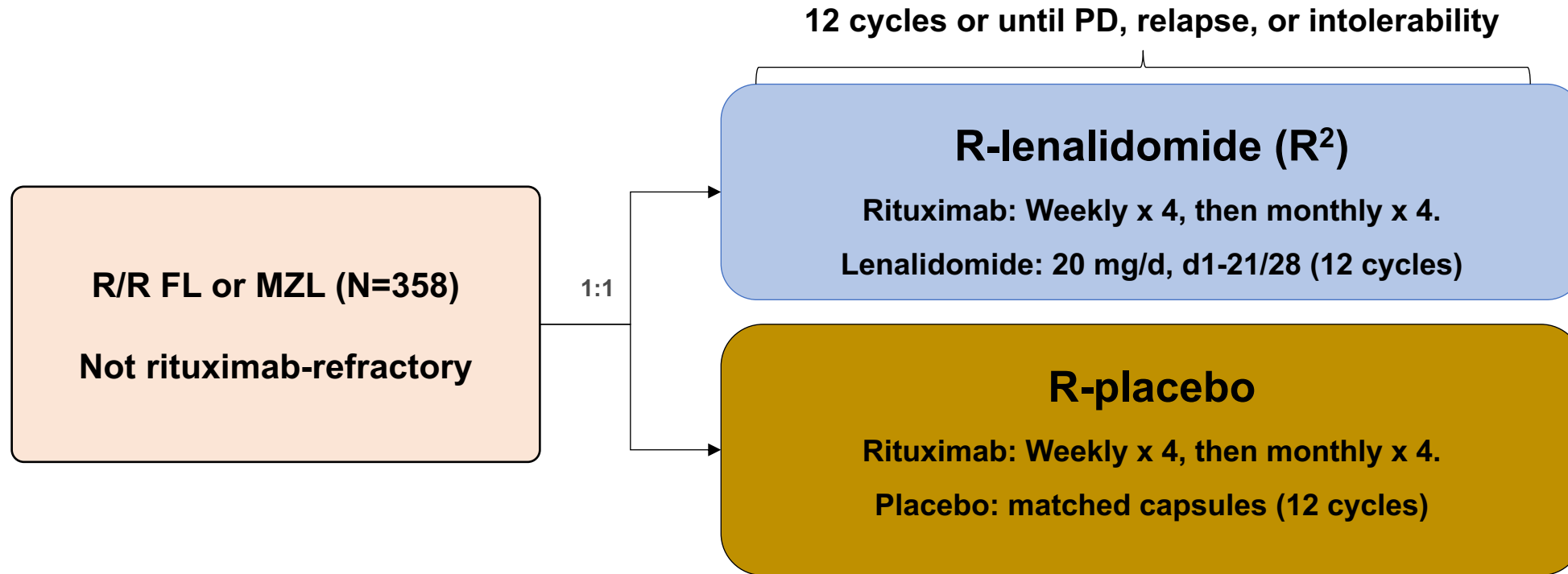
TEAEs, n (%)	N=68
Patients with ≥ 1 TEAE	68 (100)
Grade ≥ 3 TEAE	33 (48)
Serious TEAE	30 (44)
Leading to death	5 (7) ^a
Leading to dose interruption	25 (37) ^b
Leading to study drug discontinuation	5 (7) ^c
Leading to dose reduction	0

TEAEs of interest, n (%)	N=68	
	All grade	Grade ≥ 3
Infections	38 (56)	15 (22) ^a
Hemorrhage	28 (41)	1 (1.5) ^b
Cardiac		
Hypertension	3 (4) ^c	2 (3)
Atrial fibrillation/flutter	2 (3) ^d	1 (1.5)
Ventricular extrasystole	1 (1.5) ^e	0
Second primary malignancy	5 (7) ^f	3 (4)





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



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

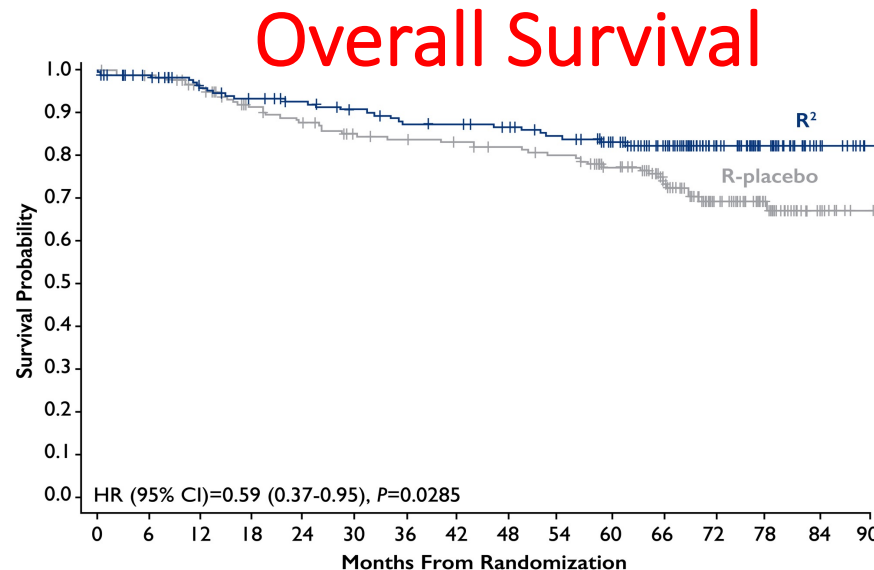
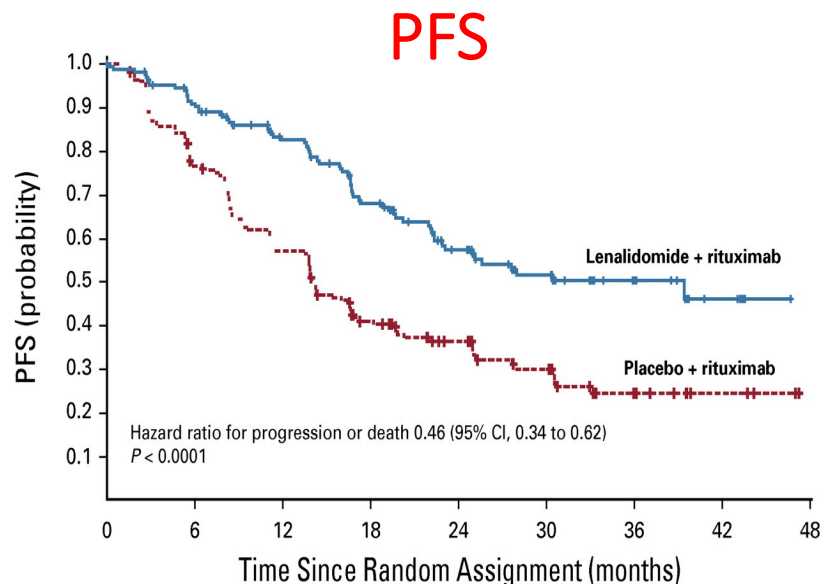


Baseline characteristics

Characteristic	R ² (n = 178)	R-placebo (n = 180)	Total (N = 358)
Median age (range), years	64 (26–86)	62 (35–88)	63 (26–88)
Male, n (%)	75 (42)	97 (54)	172 (48)
ECOG PS (0/1/2), %	65/34/1	71/28/1	68/31/1
Positive bone marrow involvement, n (%)	33 (19)	31 (17)	64 (18)
Biopsy not performed	72 (40)	69 (38)	141 (39)
Ann Arbor stage (I-II/III-IV), %	23/77	31/69	27/73
Bulky disease, n (%)	45 (25)	49 (27)	94 (26)
Histology (FL/MZL), %	83/ <u>17%</u>	82/ <u>18%</u>	82/ <u>18%</u>
MZL subtype (<u>n=63</u>)			
MALT	14	16	30
Splenic	9	6	15
Nodal	8	10	18

Augment study: 5.5 year Follow-up

Improved PFS and OS advantage with R2



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

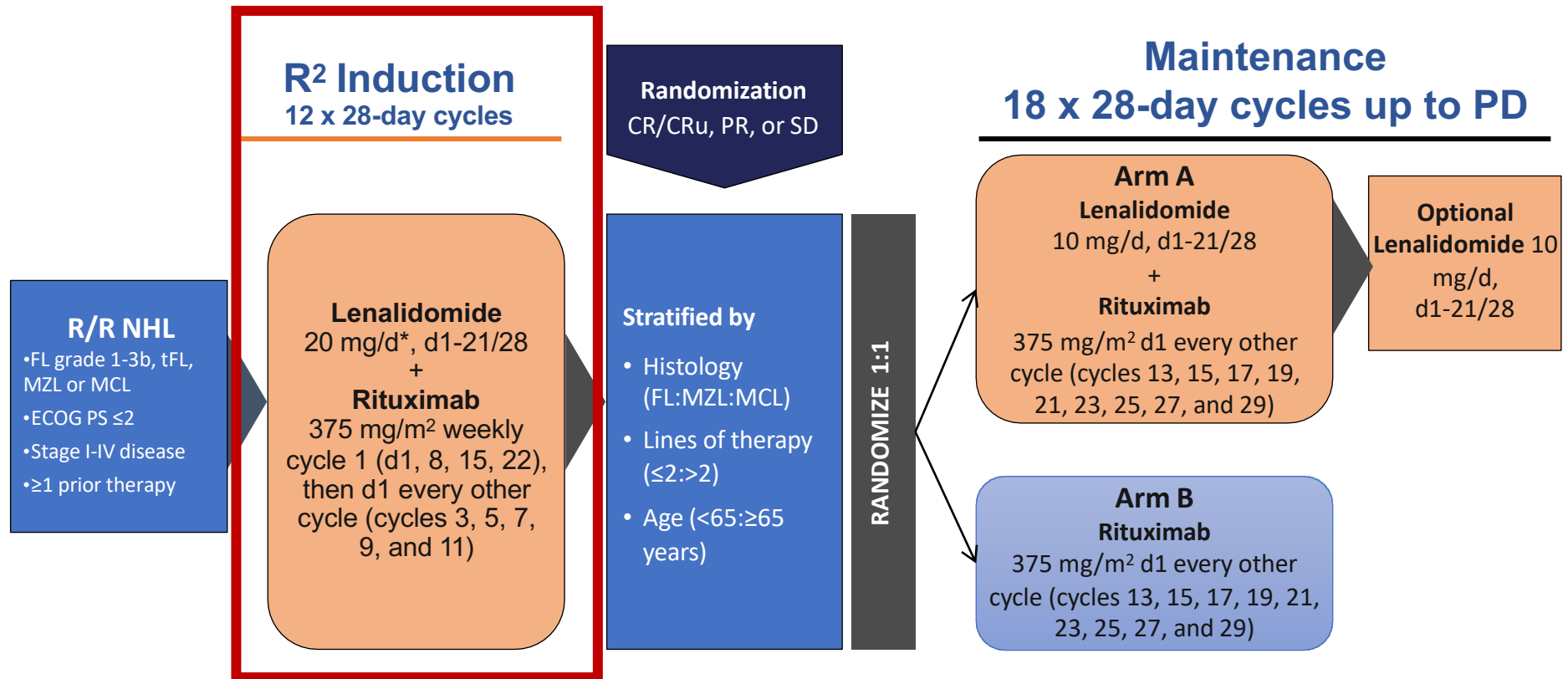
Not statistically significant for MZL

	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

- PFS and OS advantage for whole sample
- PFS and OS not different for MZL patients, but small sample size



MAGNIFY Trial: R/R Marginal Zone Lymphoma Subset Analysis



Primary endpoint: PFS (maintenance; 2-sided test $\alpha=0.05$ and HR=0.67)[†]

Secondary endpoints: OS, IOR, ORR, CR, DOR, DOCR, TTNT, TTHT, safety[†]

Exploratory: subgroup analysis of efficacy and safety by histology and QOL



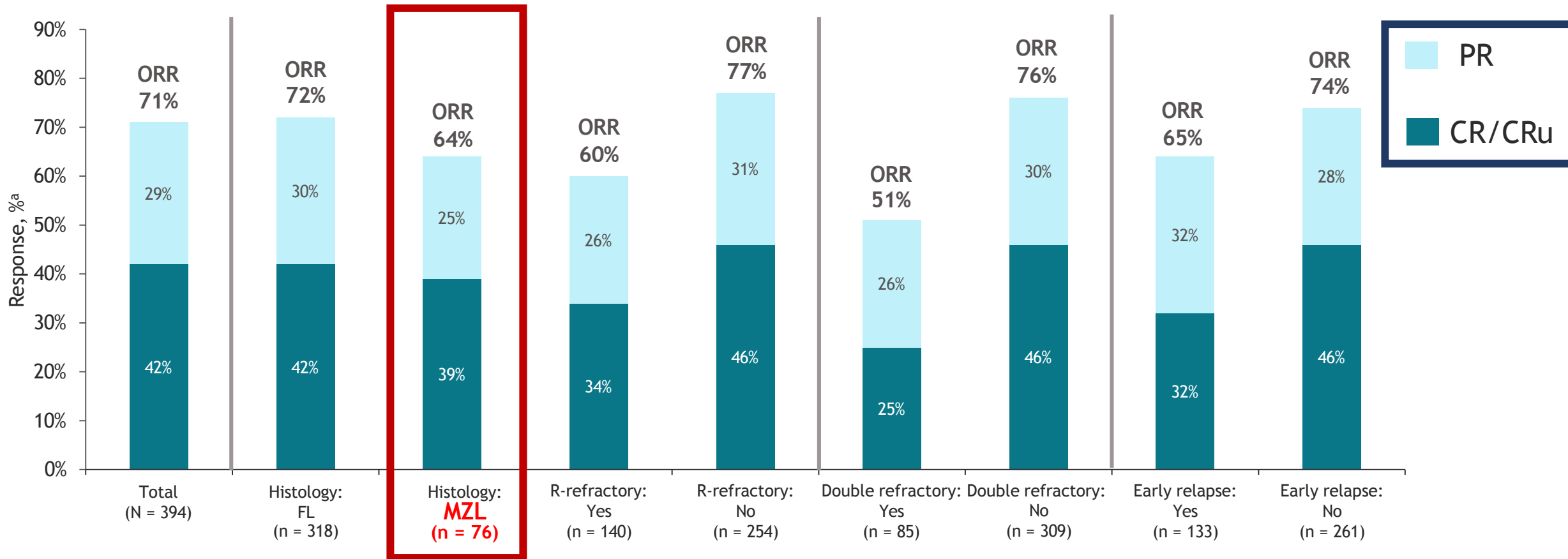
Baseline Characteristics and Treatment History

Characteristic, n (%)	Total (n = 394)
Age, median (range), y	66 (35-91)
≥ 65 y	221 (56)
Male	210 (53)
ECOG PS at enrolment	
0	193 (49)
1	192 (49)
2	9 (2)
Positive bone marrow involvement	123 (31)
Ann Arbor disease stage at enrollment	
I/II	66 (17)
III	99 (25)
IV	229 (58)
Bulky disease (> 7 cm or > 3 cm x 3)	161 (41)

Characteristic, n (%)	Total (n = 394)
FL	318 (81)
Grade 1	116 (29)
Grade 2	147 (37)
Grade 3a	55 (14)
MZL	76 (19)
MALT ^a	15 (4)
Nodal	44 (11)
Splenic	17 (4)
Prior lines of antilymphoma treatment, median (range)	2 (1-8)
Prior therapies	
Rituximab containing	372 (94)
Rituximab + chemotherapy	289 (73)
Rituximab monotherapy	159 (40)
Rituximab refractory ^b	140 (36)
Double refractory ^c	85 (22)
Early relapse ^d	133 (34)



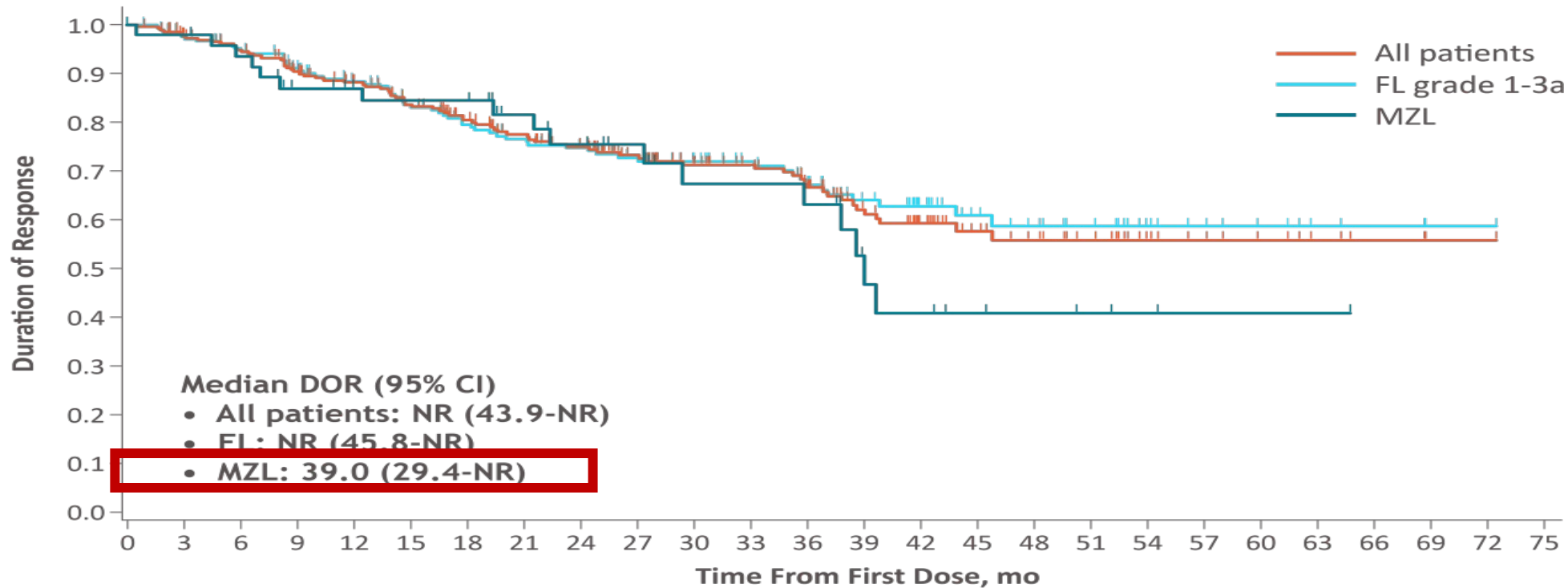
Best Overall Response in R2 Induction Treatment Phase



- R² showed clinical activity in patients with R/R iNHL, including those with FL or MZL histology and those refractory to rituximab, double refractory, or early relapse



Duration of Response



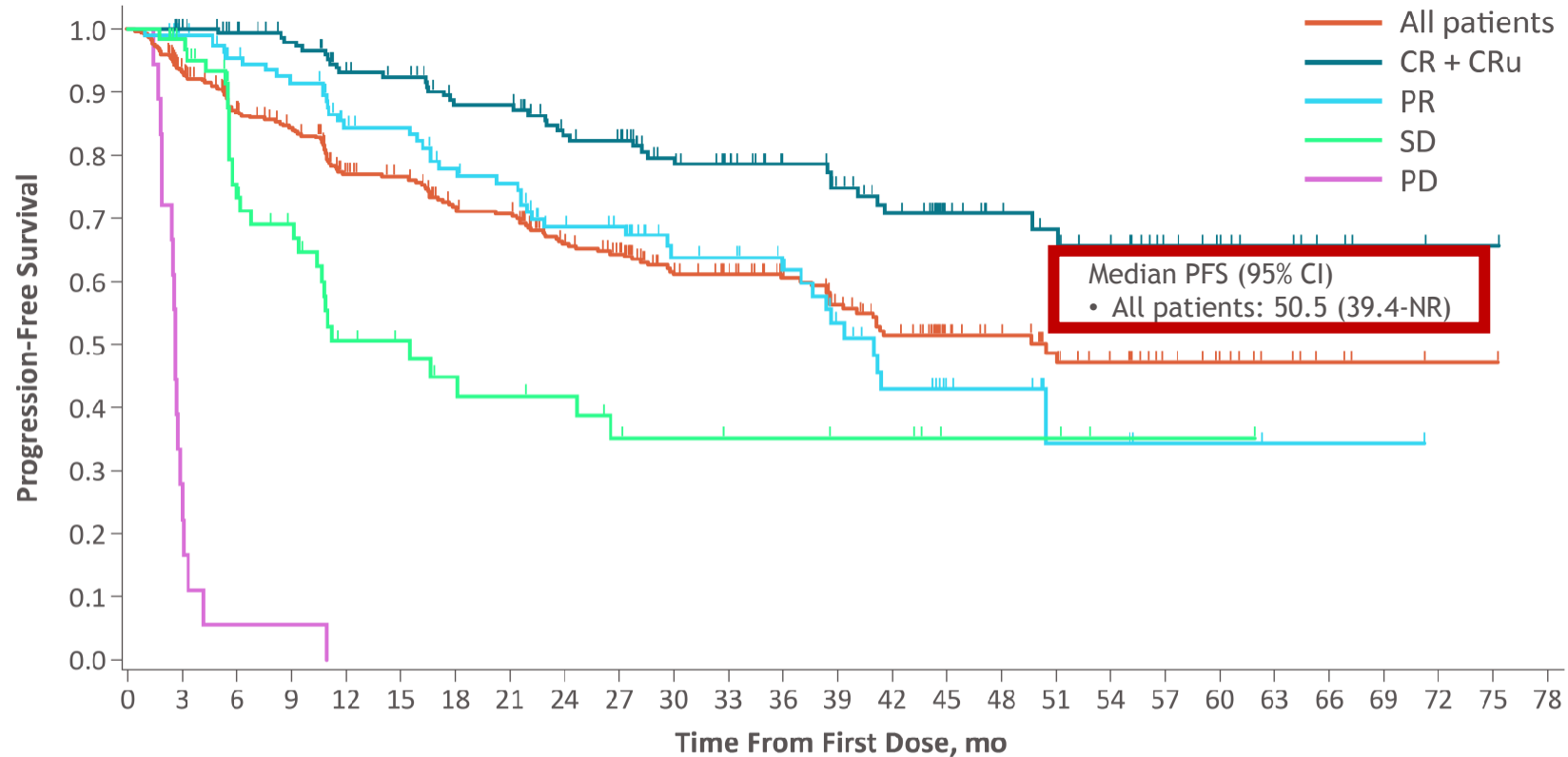
Patients at risk

All:	279	247	235	214	199	185	169	155	142	118	103	95	83	65	46	34	29	23	15	11	8	5	3	1	1	0
FL:	230	200	192	177	165	152	136	128	119	98	87	79	69	56	39	29	25	20	13	10	7	4	3	1	1	0
MZL:	49	47	43	37	34	33	33	27	23	20	16	16	14	9	7	5	4	3	2	1	1	1	0	0	0	0

- Median duration of follow-up: 40.6 months (range, 0.6-79.6)
- Median time to response in all patients was 2.8 mo (range, 0.5-17.2)

Lenalidomide + Rituximab: MAGNIFY Trial

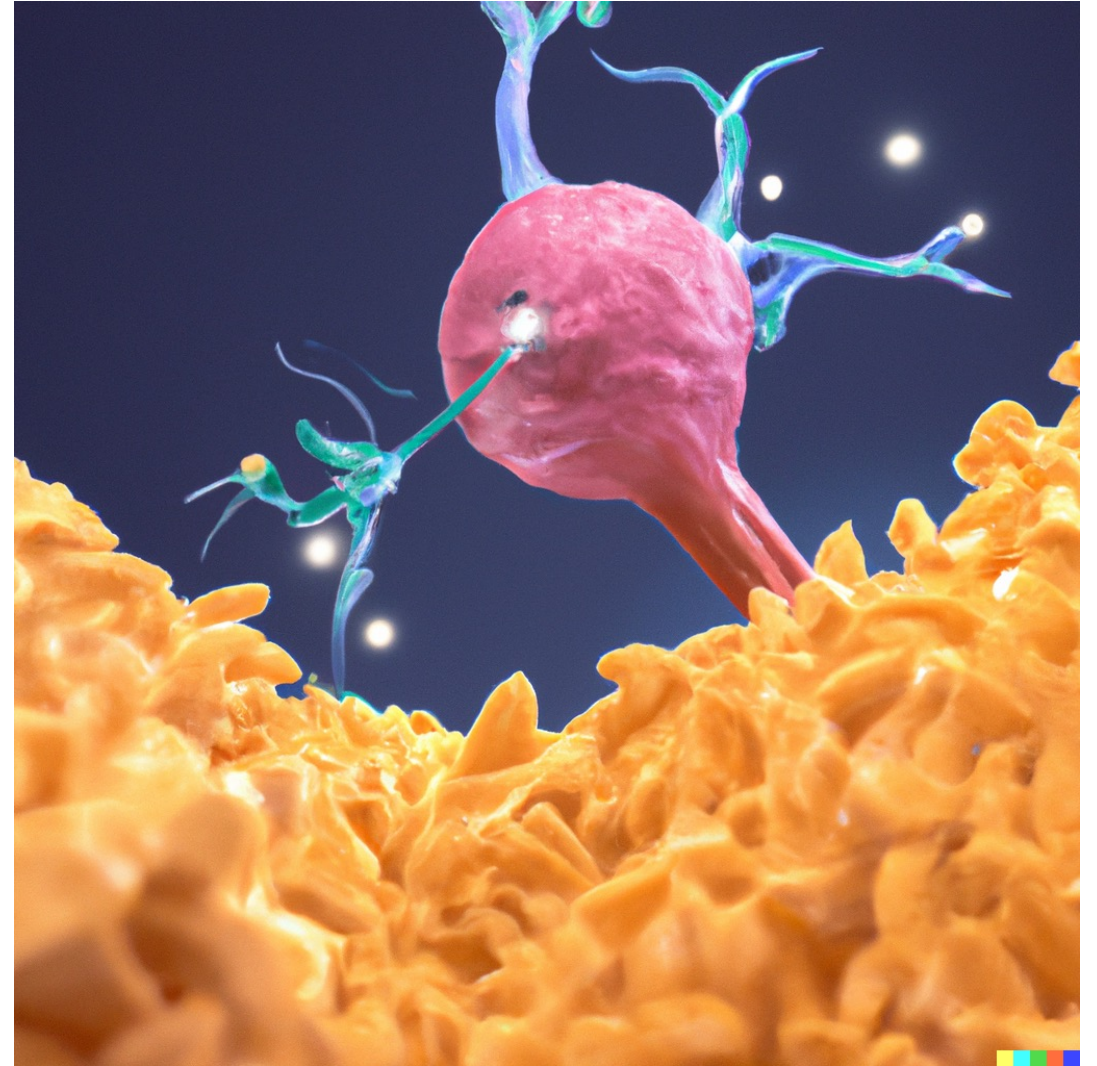
PFS by Best Overall Response



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78
All:	393	335	289	272	232	225	203	199	171	160	128	118	104	86	73	47	41	33	26	16	13	8	5	3	1	1	0
CR + CRu:	164	160	151	144	130	127	116	116	102	99	83	76	66	58	51	34	29	26	21	13	10	7	4	2	1	1	0
PR:	115	108	99	94	80	78	70	67	55	51	36	35	31	22	16	10	9	4	4	2	2	1	1	1	0	0	0
SD:	65	59	36	31	20	18	15	14	13	10	9	7	7	6	6	3	3	3	1	1	1	0	0	0	0	0	0
PD:	18	5	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

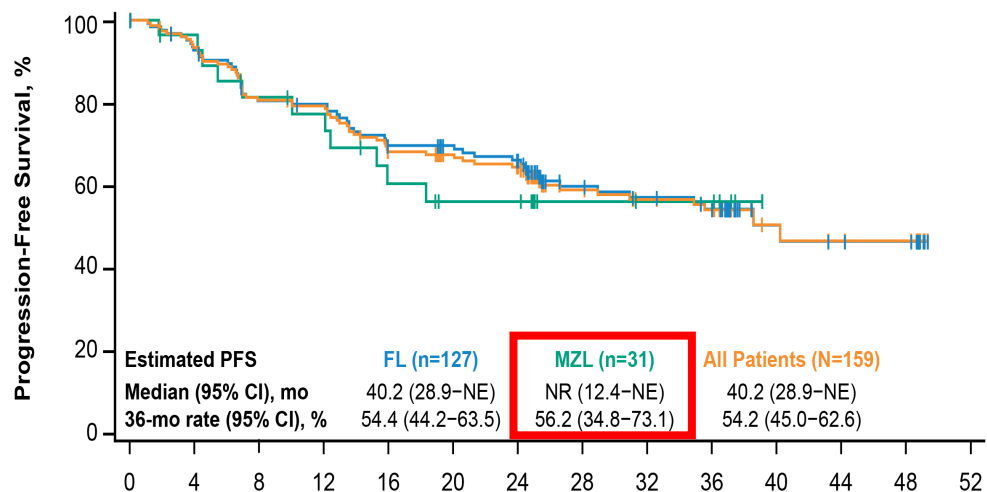
Chimeric antigen receptor T-cell updates



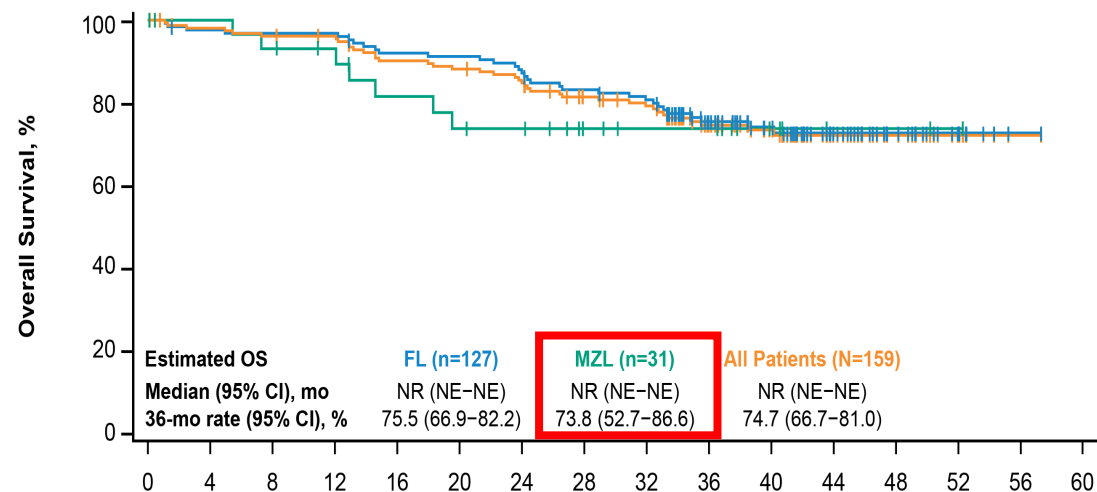
3-Year Follow-Up Analysis of ZUMA-5: A Phase 2 Study of Axi-Cel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma



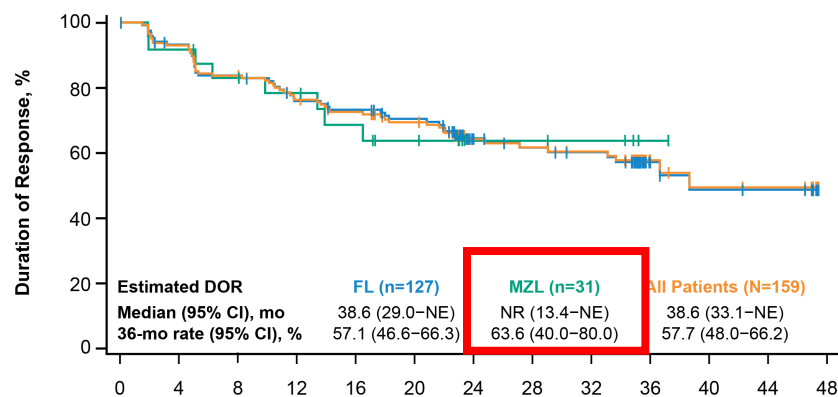
Progression-Free Survival



Overall Survival



Duration of Response



Median follow-up:
41.7 months for FL pts
31.8 months for MZL pts



Selected Trials in MZL

Population	Phase	Regimen	Status	Primary Endpoint(s)
Front-line MZL	3	Ibruinib + Rituximab Vs Rituximab	Recruiting	CR at 30 months
Front-line MZL or FL	2	Zanubrutinib + Rituximab	Planned	Overall Response
R/R NHL including MZL	1/2	Epcoritamab	Recruiting	Overall Response
R/R MZL or FL	3	Tafasitamab/ Rituximab/ lenalidomide	Recruiting	PFS
R/R MZL	2	Tafasitamab/ acalabrutinb	Recruiting	CRR



Thank you!!

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