INCONTRO DI AGGIORNAMENTO SUI

DISORDINI LINFOPROLIFERATIVI

E SUI PROTOCOLLI DELLA

FONDAZIONE ITALIANA LINFOMI

Linfomi marginali nodali ed extranodali

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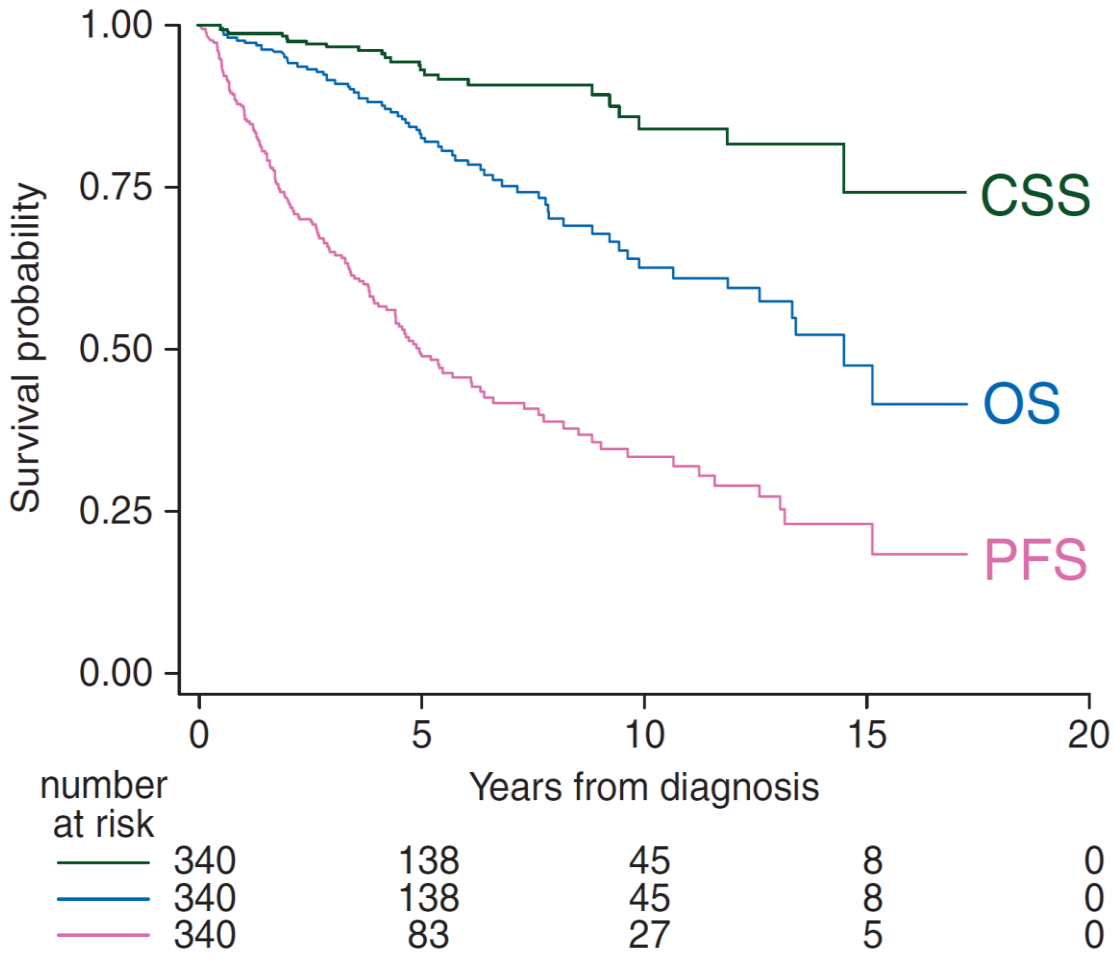
2019

MZL, 3 distinct subtypes

NOT THE SAME	% of all lymphomas in SEER registries
▪ Splenic MZL	**0.7%**
▪ Nodal MZL	**2.4%**
▪ Extranodal MZL of Mucosa-Associated Lymphoid-Tissue (MALT Lymphoma)	**5%**

Olszewski AJ and Castillo JJ. *Cancer* 2013

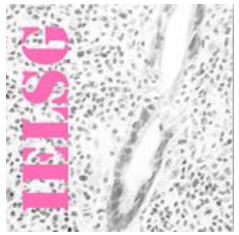
Marginal zone lymphomas: outcome



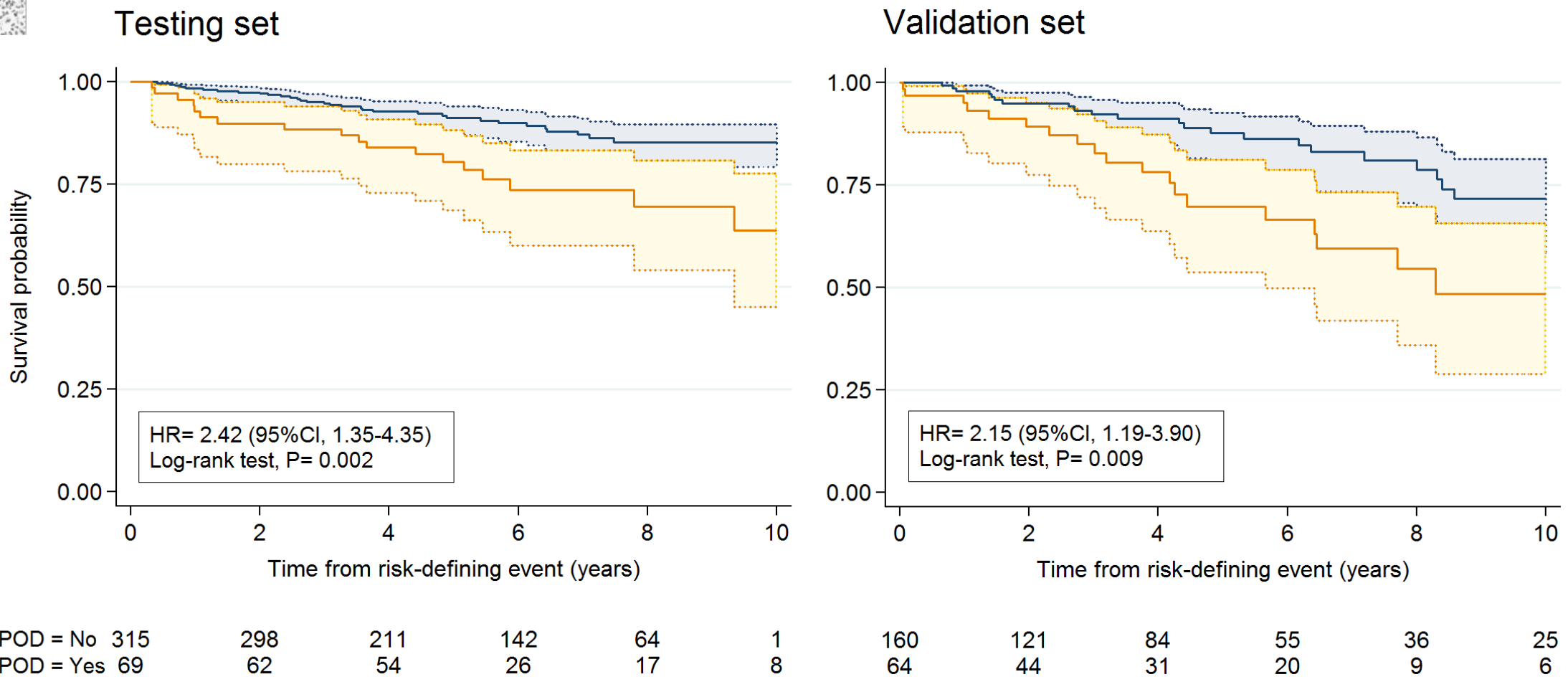
MALT lymphoma, 157
Splenic MZL, 85
Nodal MZLs, 37
CBL-MZL, 61

A. Conconi et al. *Annals of Oncology* 26: 2329–2335, 2015

EMZL: Prognosis



Impact of POD24 on survival in MALT Lymphoma patients

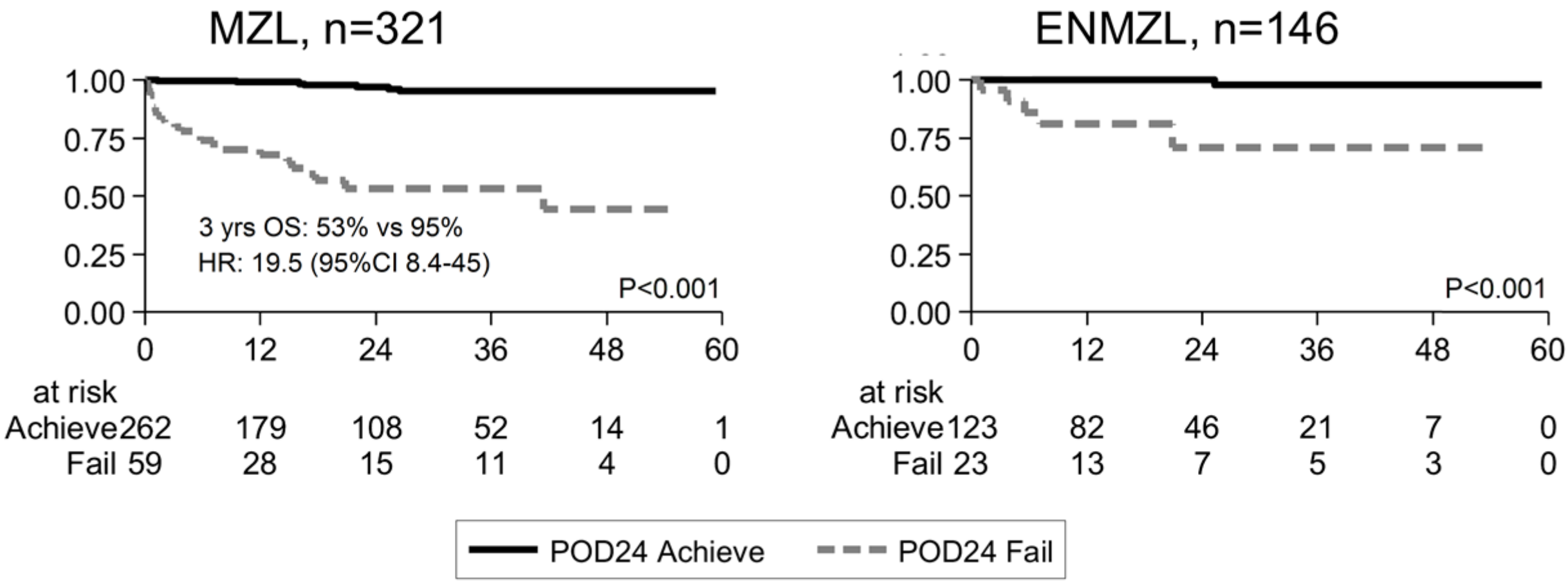


Conconi A. et al. Haematologica in press

FONDAZIONE ITALIANA LINFOMI

Overall survival by POD24

MZL subtypes analysis from the FIL-NF10 study



Luminari et al. *Blood* 2019

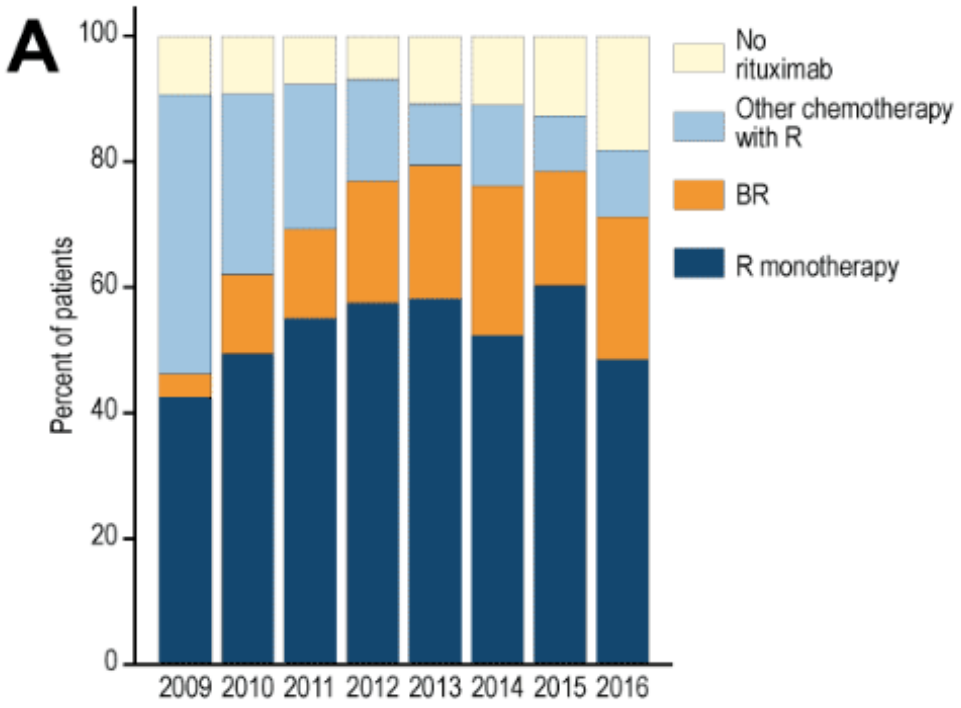
Extranodal marginal zone lymphoma

- Most frequent entity in the group
- Antigen-driven growth
- Molecular features
- Prospective phase II-III trials
- Prognostic models

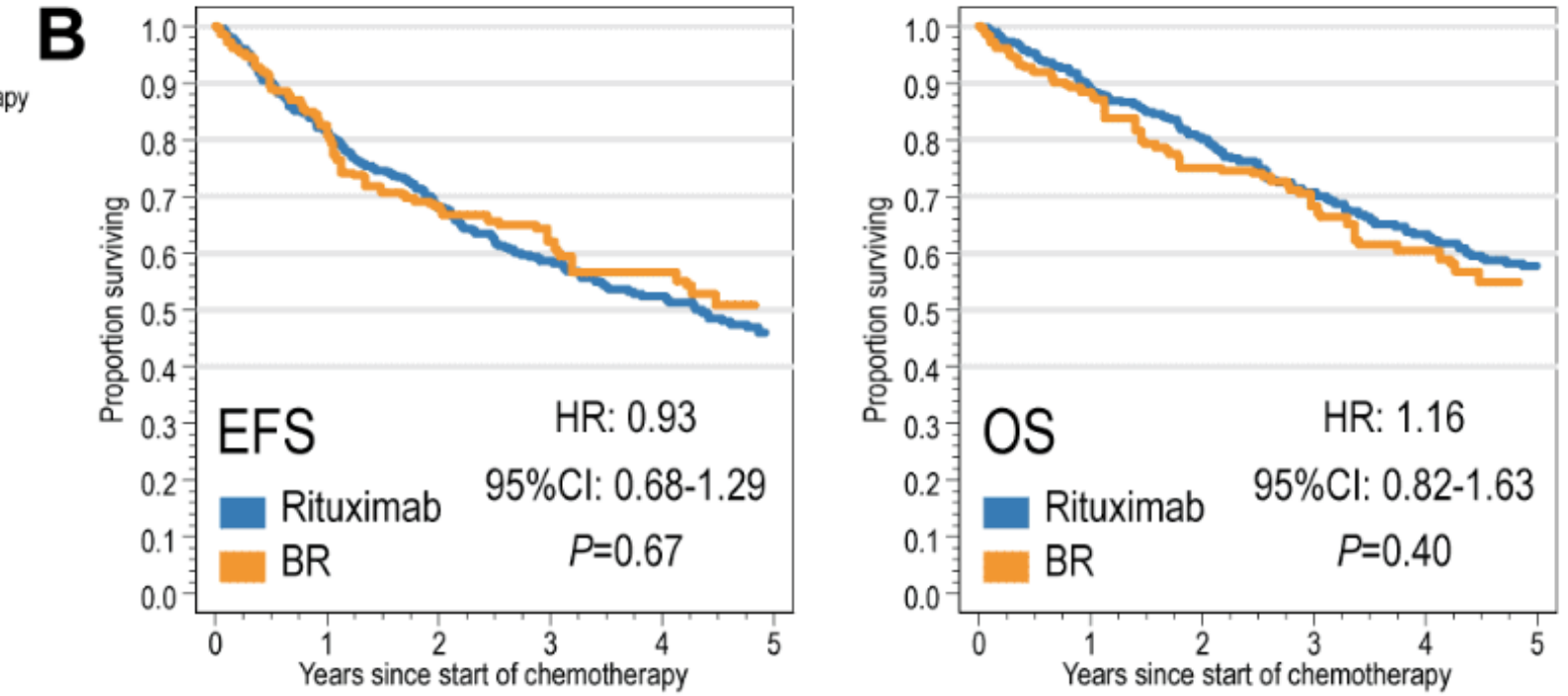
- Non-extranodal/non-splenic MZL
- No (or very few) investigations specifically addressing biological and clinical features

Nodal marginal zone lymphoma

Bendamustine-Rituximab Does Not Improve Survival over Rituximab Monotherapy for Older Patients with Nodal or Splenic MZL (A SEER-Medicare analysis)



A. Proportion of NMZL/SMZL treated with various first-line regimens, by year



B. EFS and OS in the propensity score-weighted cohort with NMZL

901 NMZL, median age 78 years
median follow-up 3.8 years
median EFS was 4.3 years
median OS was 5.2 years

Olszewski AJ et al, ASH 2019

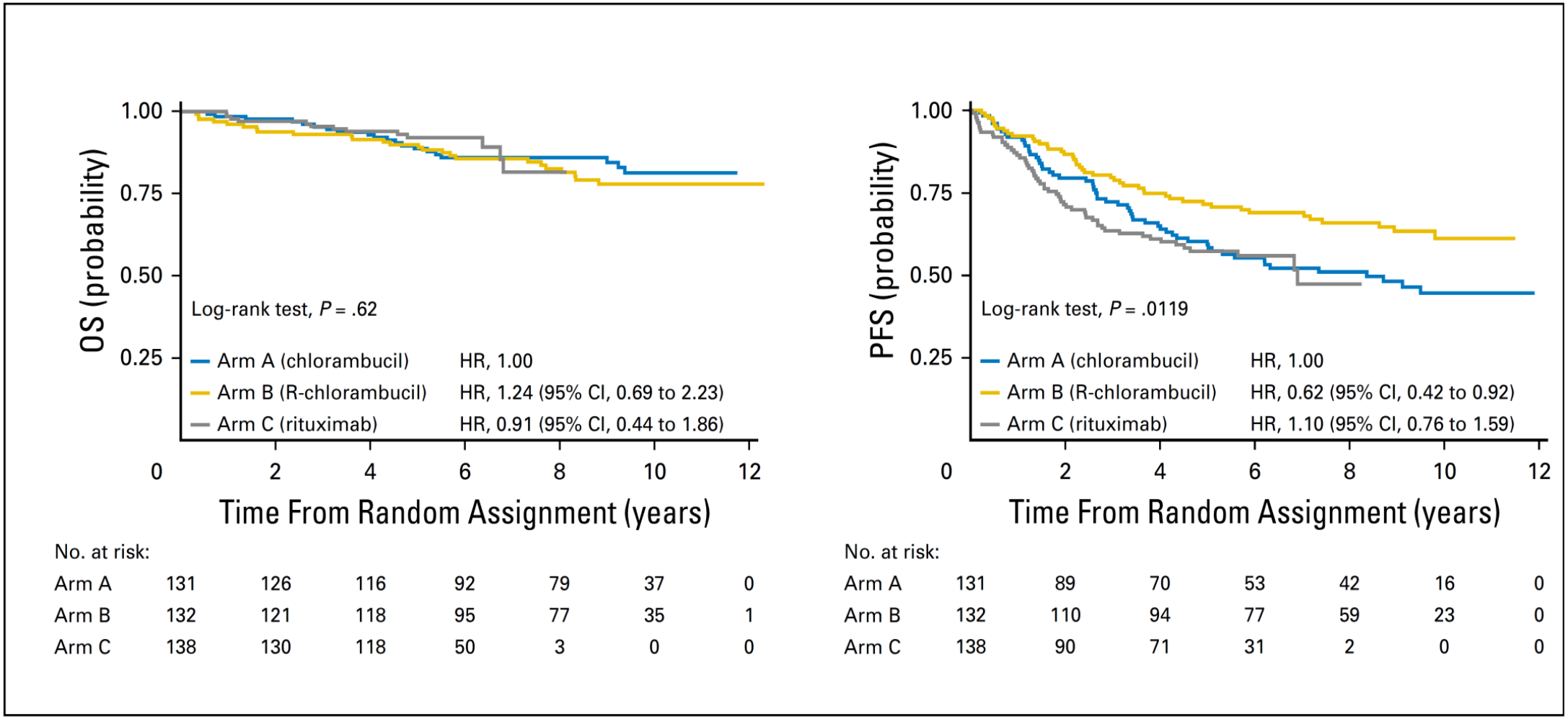
Novel compounds in MZL

Results from single agents clinical trials and new combinations

- New MoAbs
- New small molecules
- Trials to start with new compounds in MZL

IELSG 19

IELSG-19 Randomized Study
Final Results



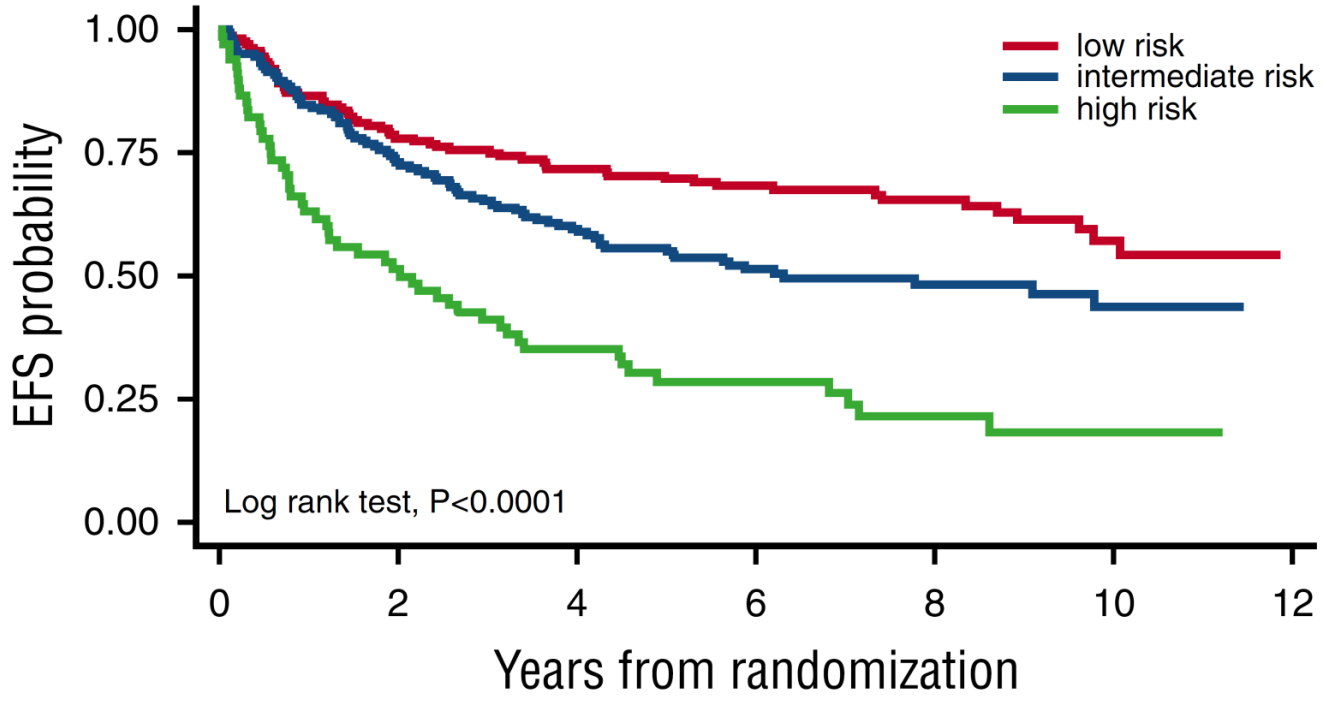
Zucca E, et al. JCO 2017; 35:1905-12

EMZL risk definition – the MALT-IPI model

Prognostic Group	No. of Factors	No. of IELSG-19 Pts (N=400)
Low risk	0	167 (42%)
Intermed. risk	1	165 (41%)
High risk	>1	68 (17%)

Risk Factors
Stage III-IV
Age>70 years
LDH >UNL

EFS Multivariate Analysis
(Stepwise Cox regression with backward selection using a p<0.005 cut-off)
N=400 (failures = 195)
P (Wald test) <0.0001



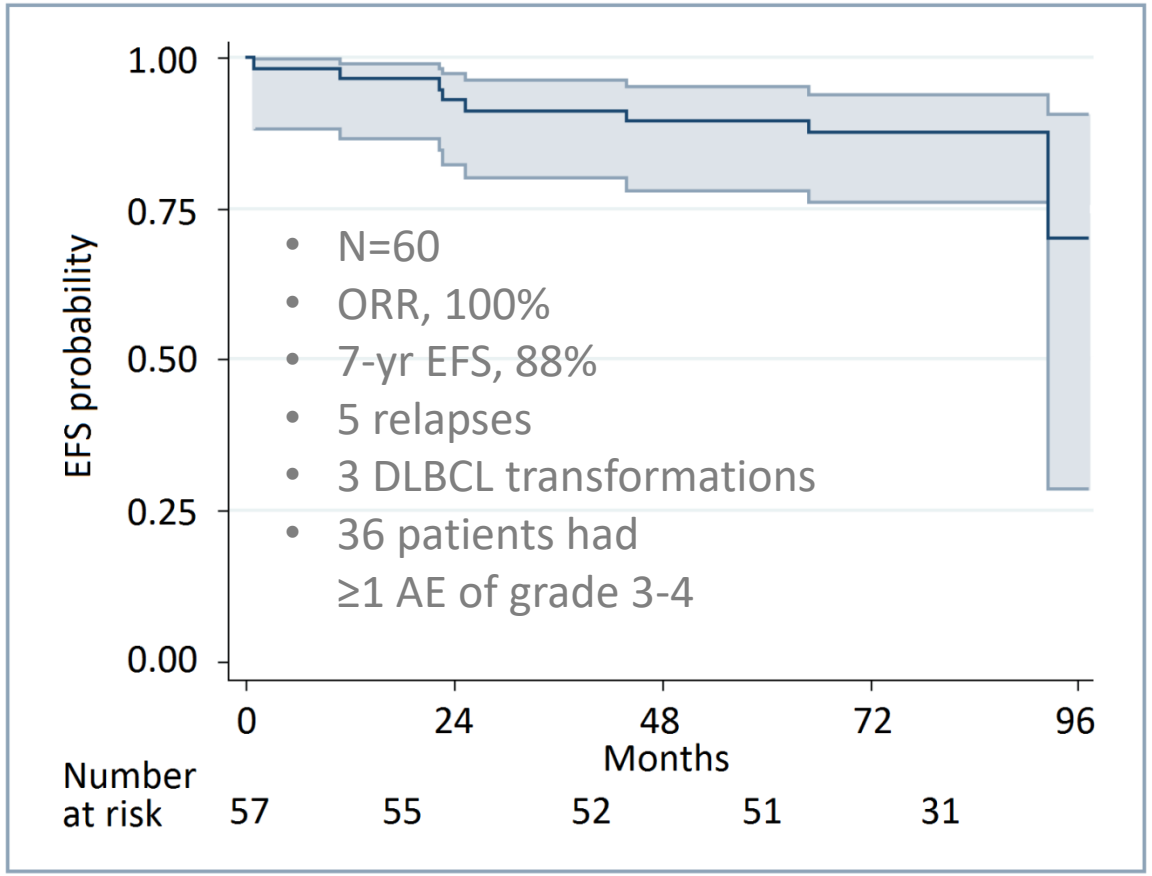
Number at risk

low risk	167	126	112	84	57	22	0
intermediate risk	165	120	94	61	37	16	0
high risk	68	35	24	14	7	1	0

Thieblemont C, et al. Blood 2017;130:1409-17

MALT-2008-01 GELTAMO phase-2 study

R-Bendamustine as 1st-line response-adapted therapy (4 to 6 cycles)

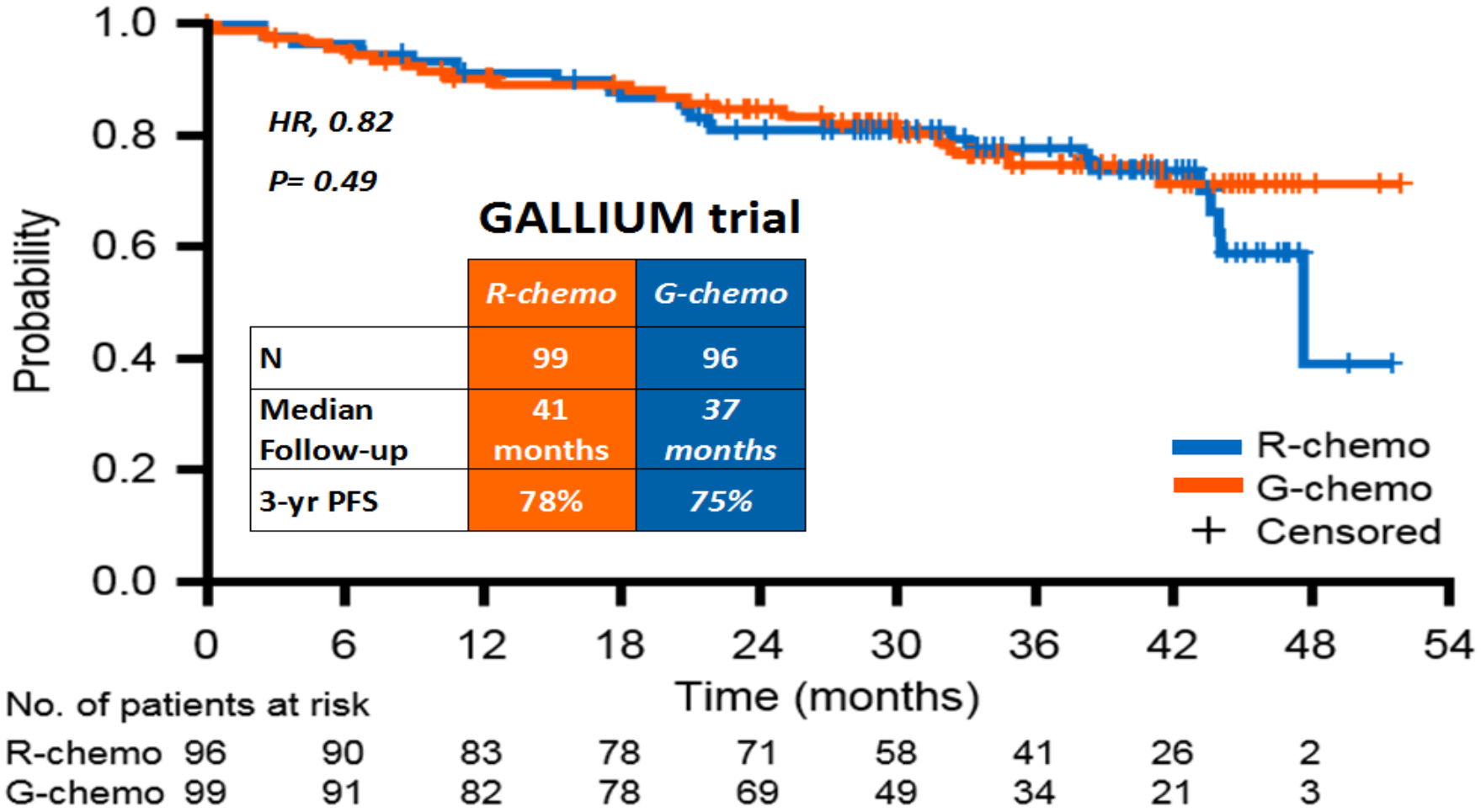


After 3 cycles:

- patients in CR received 1 additional cycle
- those in PR received 3 additional cycles

Salar A, et al. Lancet Haematol. 2014 and Blood 2017

Immunochemotherapy with Bendamustine or CHOP plus Obinutuzumab or Rituximab in patients with untreated MZL



Herold et al. Hematol Oncol 2017;35 (S2):146-7

Gallium Study: Adverse events in MZL patients

n (%) of pts with ≥1 one event	R-chemo, n=93	G-chemo, n=101
Any AE	93 (100)	101 (100)
Grade 3–5 AEs	72 (77)	83 (82)
SAE	48 (52)	65 (64)
Infections†	62 (67)	84 (83)
Second neoplasms‡	8 (9)	7 (7)
AE leading to treatment discontinuation	19 (20)	27 (27)
Grade 5 (fatal) AE	6 (6)	12 (12)

Herold et al. Hematol Oncol 2017; 35 (S2):146-7

MZL: A future of targeted treatments?

Phase II studies in r/r MALT lymphoma

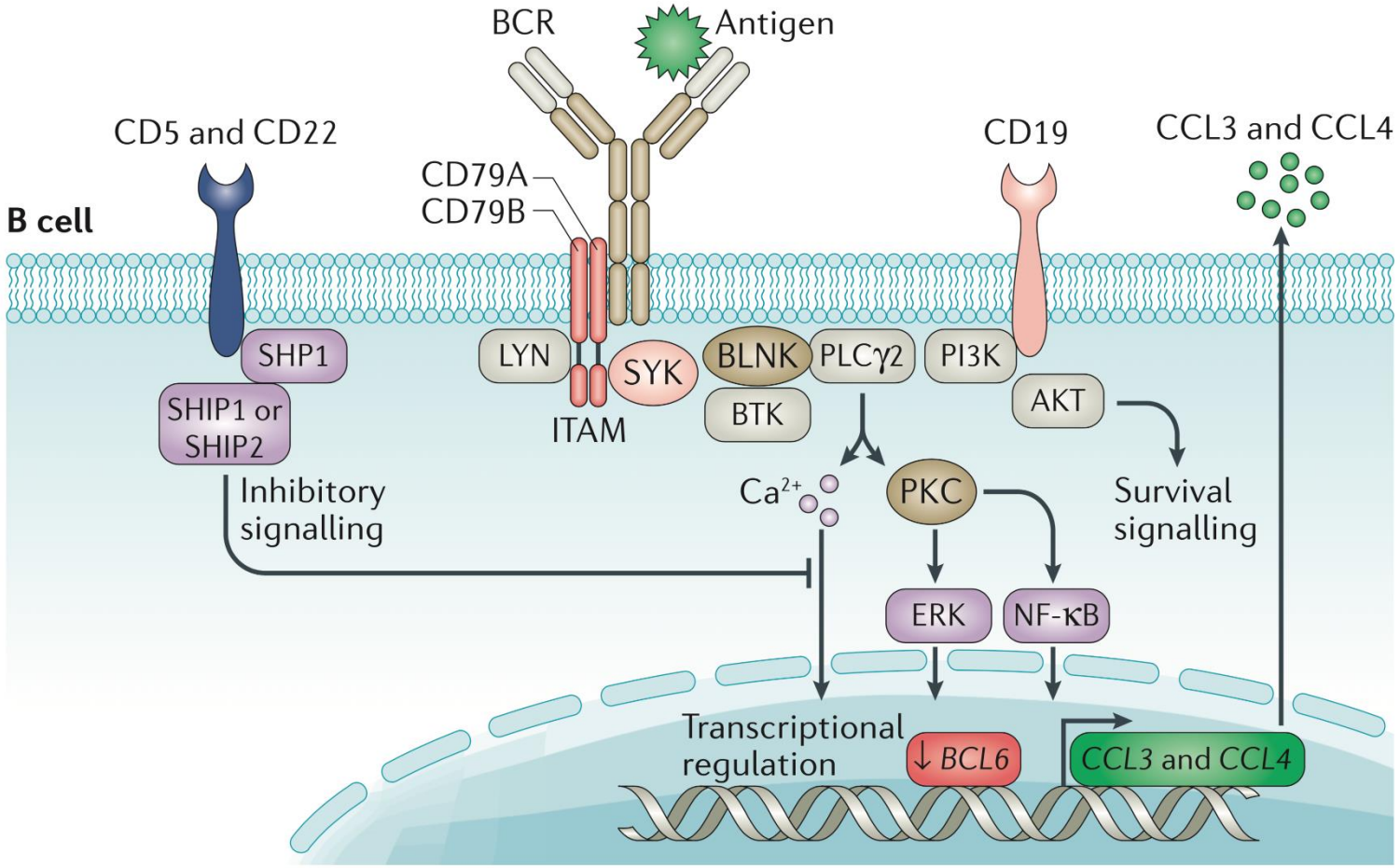
	ORR	Study	
Rituximab	45%	IELSG	Conconi et al, Blood 2003
Rituximab	44%	AUGMENT (Celgene)	Leonard et al, J Clin Oncol 2019
Bortezomib	48%	IELSG	Conconi et al, Ann Oncol 2011
Everolimus	20%	IELSG	Conconi et al, Br J Haematol 2014
Copanlisib	78%	Bayer	Dreyling M et al. ASH 2019
Lenalidomide	61%	Vienna	Kiesewetter et al, Haematologica 2013
R-lenalidomide	85%	Vienna	Kiesewetter et al, Blood 2017
R-Lenalidomide	65%	AUGMENT (Celgene)	Leonard et al, J Clin Oncol 2019
Idelalisib	47%	Gilead	Gopal et al, N Engl J Med 2014
Ibrutinib	51%	Pharmacyclics	Noy et al, Blood 2017
Umbralisib	57%	TG Therapeutics	Zinzani et al. 15-ICML 2019

NEW Drugs in lymphoma

- Small molecules FDA approved for lymphoma since 2015

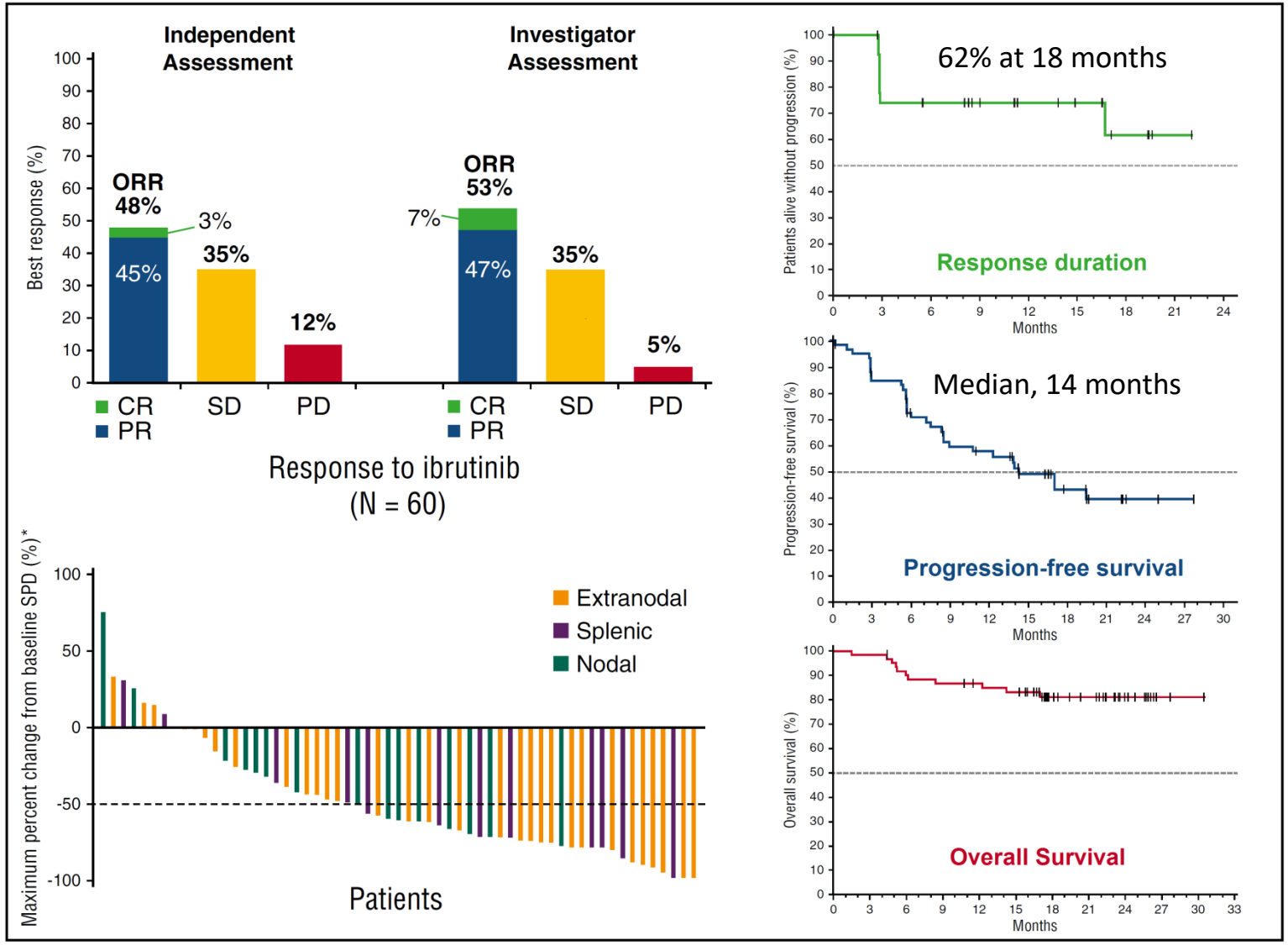
Year	Drug	Indication	Endpoint	N pts
2019	Zanubrutinib	MCL	ORR	86
2019	Acalabrutinib	SLL/CLL	PFS	535+310
2019	Lenalidomide (+R)	FL/MZL	PFS	295/63
2018	Duvelisib	FL	ORR	83
2018	Ibrutinib	WM (+R)	PFS	150
2017	Acalabrutinib	MCL	ORR	124
2017	Copanlisib	FL	ORR	142
2017	Ibrutinib	MZL	ORR	63
2015	Ibrutinib	WM	ORR	63

PREFERRED TARGETS IN MZL



Burger & Wiestner, Nat Rev Cancer 2018

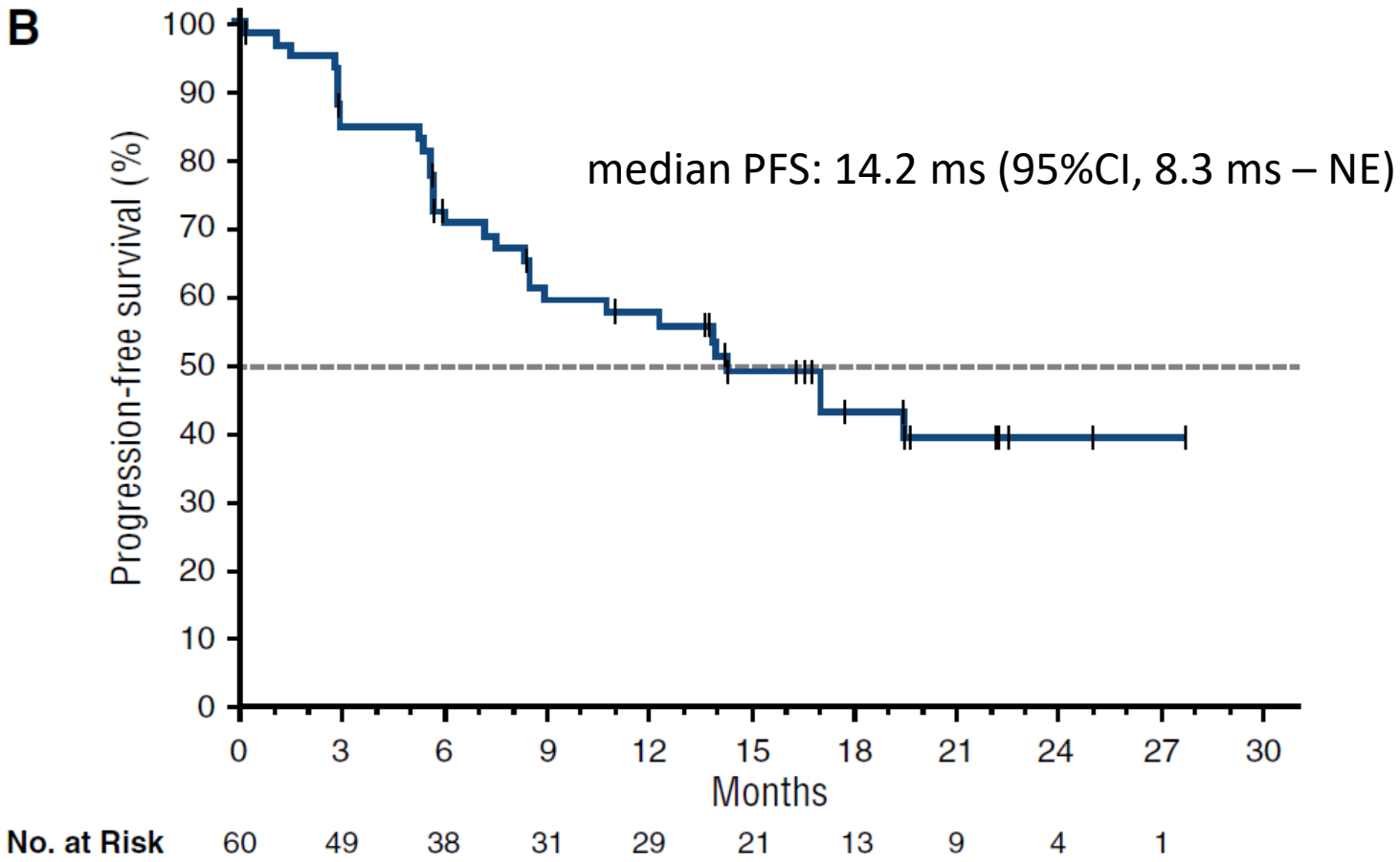
Targeting BTK with ibrutinib in r/r MZL



Noy A, et al. Blood 2017

IBRUTINIB IN R/R MZL

PFS



median PFS: 14.2 ms (95%CI, 8.3 ms – NE)

Noy A, et al. Blood 2017

IBRUTINIB IN R/R MZL

Adverse events

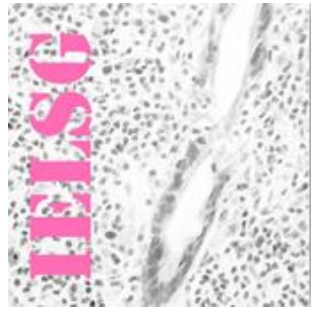
AEs grade ≥3†	
Anemia	9 (14)
Pneumonia	5 (8)
Fatigue	4 (6)
Cellulitis	3 (5)
Diarrhea	3 (5)
Hypertension	3 (5)
Lymphocyte count decreased	3 (5)
Neutropenia	3 (5)
Asthenia	2 (3)
Autoimmune hemolytic anemia	2 (3)
Blood bilirubin increased	2 (3)
Muscle spasms	2 (3)
Multiple organ dysfunction	2 (3)
Neutrophil count decreased	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)
Serious AEs‡	
Pneumonia	5 (8)
Cellulitis	2 (3)
Autoimmune hemolytic anemia	2 (3)
Pneumothorax	2 (3)
Sepsis	2 (3)

- TEAE ≥gr 3 in 67% of pts
- Anemia in 14%
- Pneumonia in 8%
- Fatigue 6%

Noy A, et al. Blood 2017

IBRUTINIB IN 1ST LINE?

The IELSG-47 (Malibu) Trial



IELSG 47/MALIBU

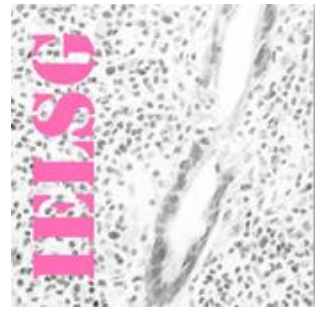
Phase II study of ibrutinib plus rituximab in untreated MZL

FONDAZIONE ITALIANA LINFOMI

Lysa
THE LYMPHOMA STUDY ASSOCIATION

SAKK

Malibu trial - Inclusion criteria



1/ Previously untreated and symptomatic patients with histologically proven diagnosis of CD20-positive marginal zone B-cell lymphoma (MZL) not eligible for local therapy, including :

EMZL	SMZL	NMZL
1. MALT-IPI 1 -3 in need of treatment 2. Either de novo, or relapsed following local therapy (RT, surgery or ATB) 2. Measurable disease 3. Any stage (Ann Arbor I-IV)	- either de novo or relapsed following local therapy (surgery and anti- HCV) - symptomatic disease - cytopenias : Hb < 10 g/dL, or Platelets < 80 000/µL, or neutrophil count < 1000/µL	- de Novo - Disseminated

- Measurable or evaluable disease.
- Ann Arbor II-IV Stage I disease may be eligible only if not candidate to local therapy (surgery or radiotherapy)
- ECOG Performance status 0-2

n= 130 **n=15** **n=15**

MALIBU trial - Primary endpoints

1/ Complete Response (CR) rate at 12 months

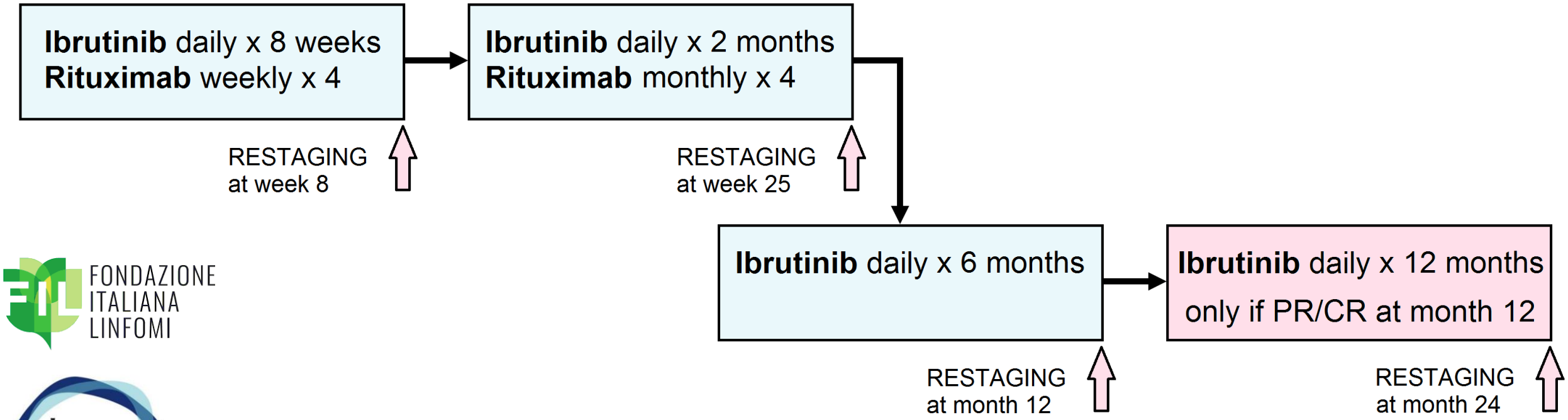
2/ PFS at 5 years

assessed by the investigators,

according to revised response criteria for malignant lymphomas,

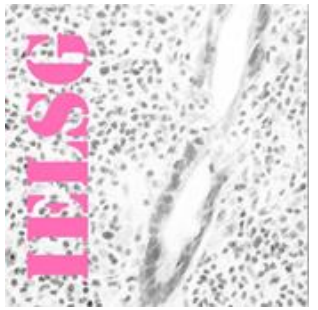
from study entry to death from any cause or PD

IELSG 47/MALIBU Study design



BTK TARGETING + ANTI-CD19 IN R/R MZL

IELSG 49 new phase II trial: Acalabrutinib + MOR208

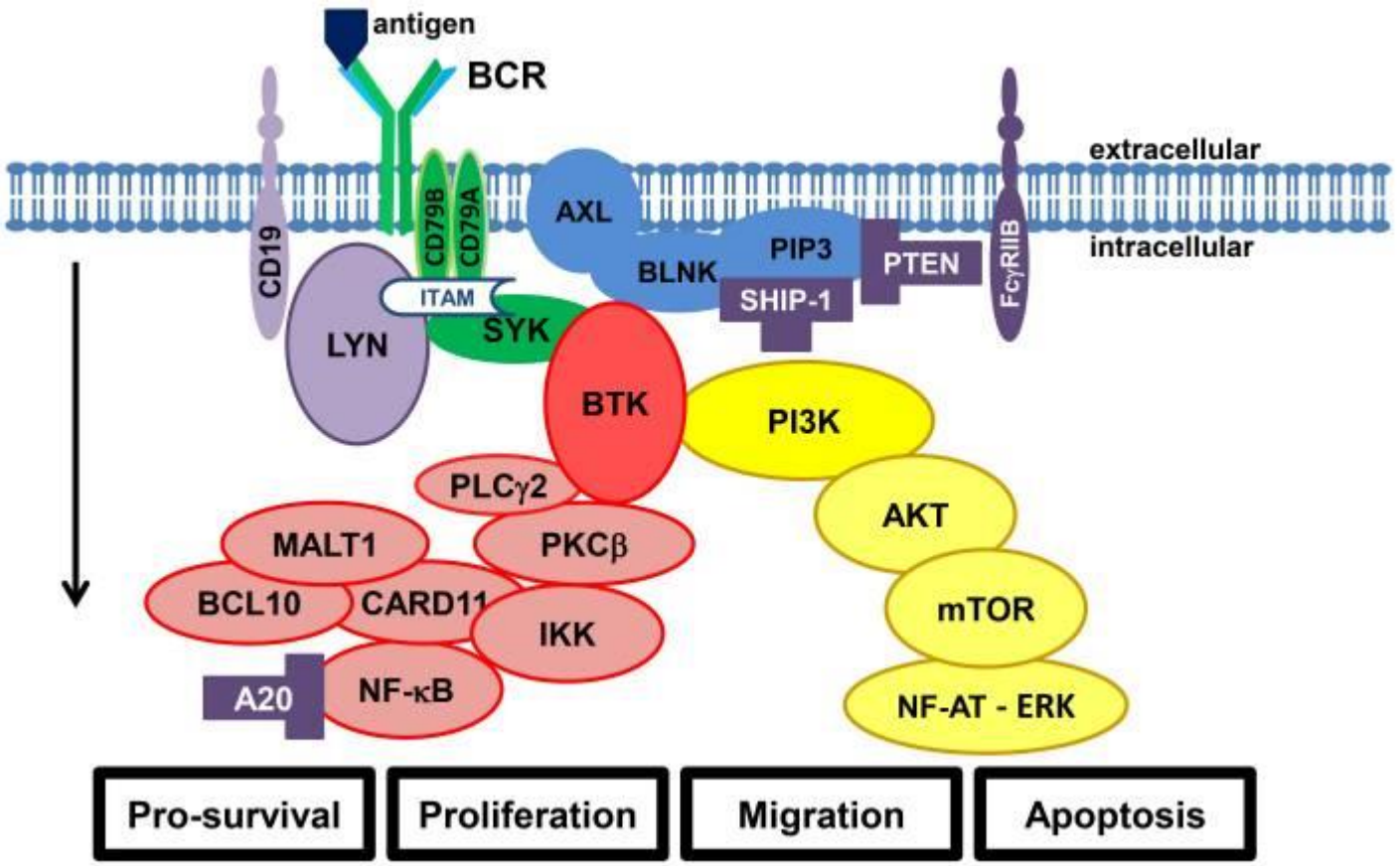


- CD19 is broadly and homogeneously expressed in MZLs
- MOR208 is an Fc-engineered, humanized, anti-CD19 monoclonal antibody active in iNHL
- Acalabrutinib more selective BTK inhibitor than ibrutinib (less effects on ITK/TEK)
- Spares NK-cell and macrophage functions preserving ADCC and phagocytosis

PI3K Signaling in Marginal Zone Lymphoma

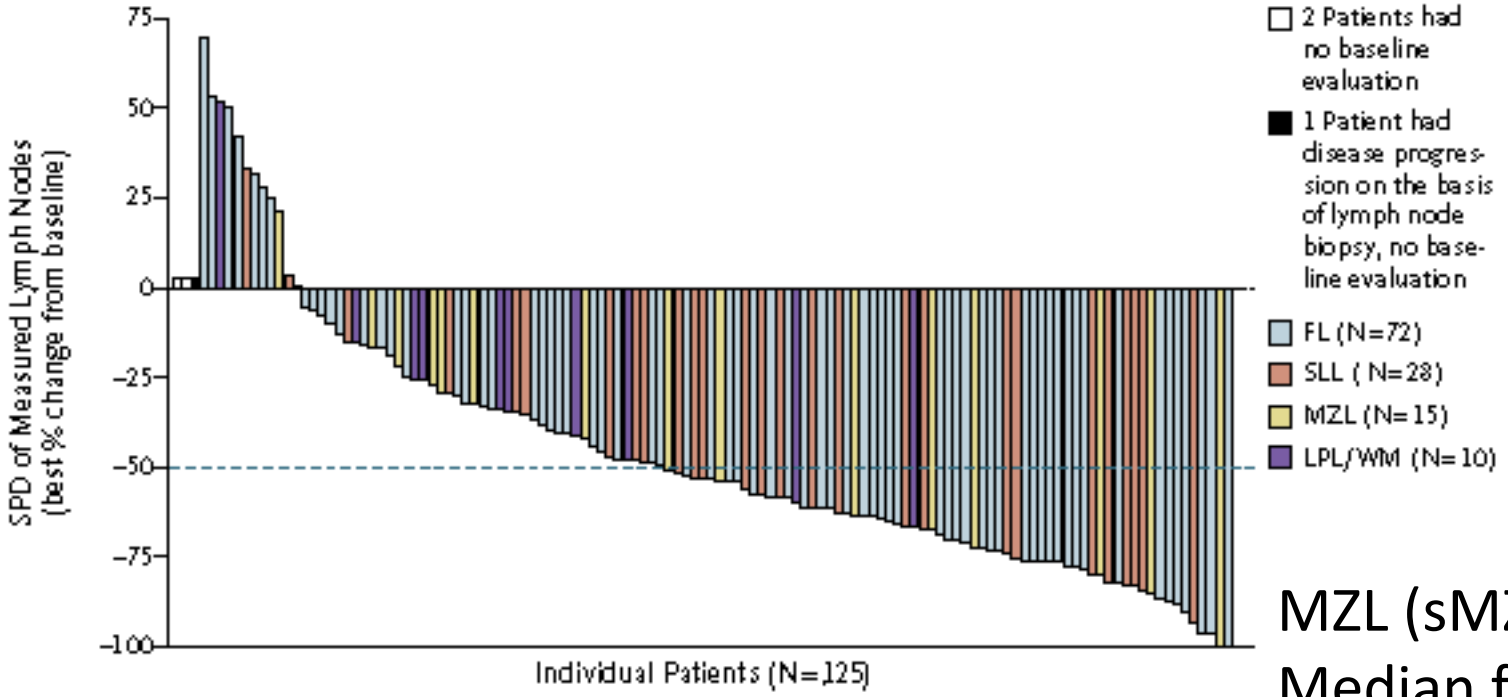
- B cell receptor (BCR) signaling is critical to the development of normal B cells and has been implicated in lymphomagenesis
- PI3K is a downstream intermediary in the BCR pathway essential for BCR-dependent B cell survival
- Recent evidence suggests the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL[2]

The B cell Receptor (BCR) and its Downstream Pathways[1]



[1]Niemann et al., Semin Cancer Biol. 2014. [2]Sindel et al., Blood. 2018

IDELALISIB IN r/r MZL



Gopal et al. N Engl J Med, 2014

MZL (sMZL, n = 1; NMZL, n = 5; EMZL, n = 9)
Median follow-up: 6.4 months (range: 1.8-37)

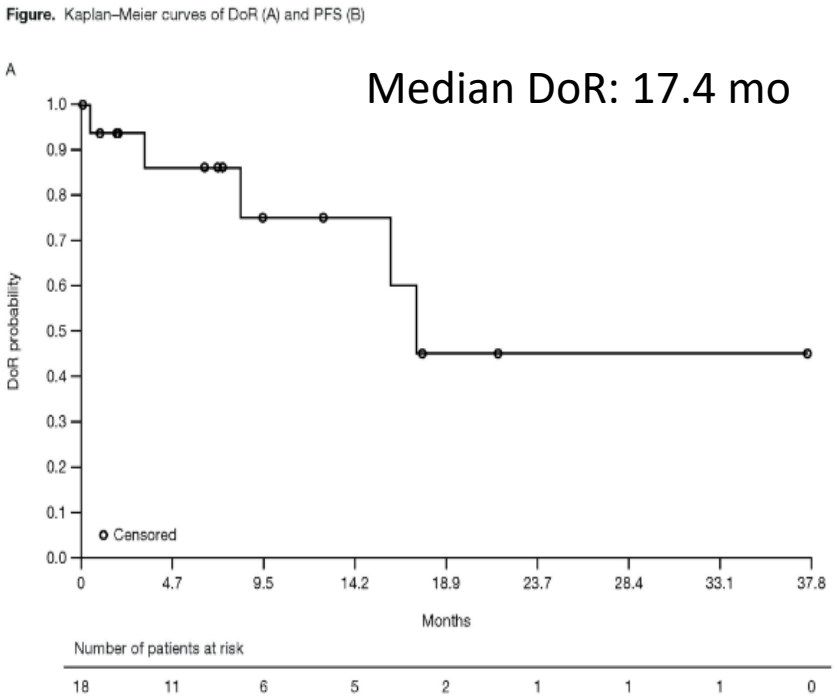
	MZL (N = 15)
ORR, % (95% CI)[a]	47 (21, 73)
DOR, median (95% CI), months[a]	18 (3.6, 18)
TTR, median (95% CI), months[a]	3.5 (1.9, 4.6)
PFS, median (95% CI), months[a]	6.6 (3.5, 22)
OS, median (95% CI), months[b]	NE (6.4, NE)

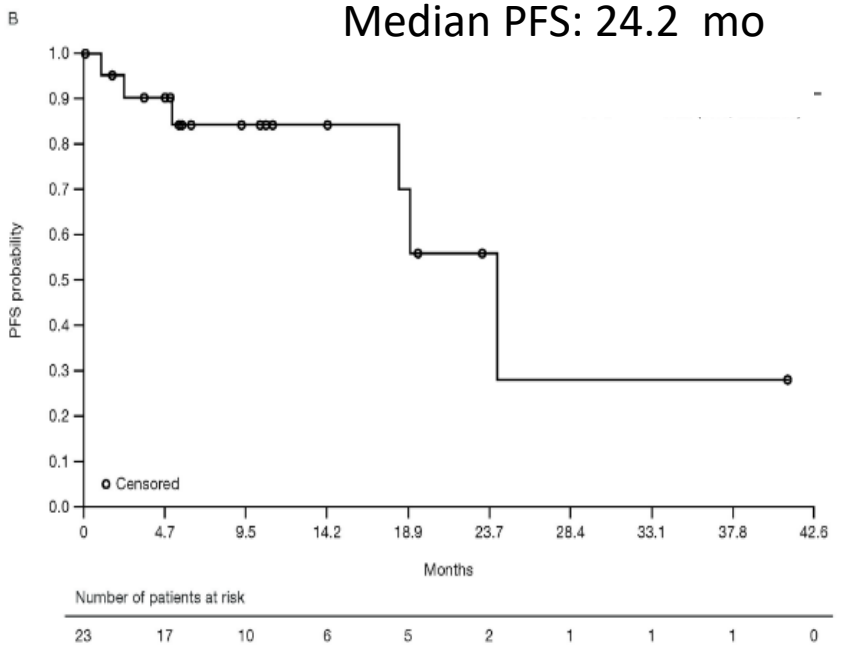
Wagner-Johnston ND, ASH 2019

Copanlisib in multiple relapsed/refractory MZL

18-months follow-up of CHRONOS-1

Best response, *n* (%)	MZL (*n*=23)	SMZL (*n*=4)	NMZL (*n*=15)	EMZL (*N*=4)
CR	3 (13)	3	0	0
PR	15 (65)	0	13	2
SD	2 (9)			
PD	0	0	0	0
NE/NA	3 (13)			
ORR, n (%)	18 (78)	3 (75)	13 (87)	2 (50)





Dreyling M et al. ASH 2019 poster #1531

ADVERSE EVENTS PI3K INHIBITORS

Copanlisib in r/r iNHL: CHRONOS-1 trial

Common treatment-related AEs, *n* (%)	Total (*N*=142)		
Grade	**All**	**3**	**4**
Any treatment-related AE	126 (88.7%)	71 (50.0%)	30 (21.1%)
Hyperglycemia	69 (48.6%)	47 (33.1%)	10 (7.0%)
Hypertension	41 (28.9%)	32 (22.5%)	0
Decreased neutrophil count	35 (24.6%)	9 (6.3%)	18 (12.7%)
Diarrhea	26 (18.3%)	6 (4.2%)	0
Nausea	22 (15.5%)	1 (0.7%)	0
Lung infection	20 (14.1%)	13 (9.2%)	2 (1.4%)
Decreased platelet count	19 (13.4%)	5 (3.5%)	1 (0.7%)
Oral mucositis	17 (12.0%)	4 (2.8%)	0
Fatigue	17 (12.0%)	2 (1.4%)	0
Laboratory toxicities			
Increased aspartate aminotransferase	39 (27.7%)	1 (0.7%)	1 (0.7%)
Increased alanine aminotransferase	32 (22.7%)	1 (0.7%)	1 (0.7%)
Treatment-related AEs of special interest			
Pneumonitis (non-infectious)	10 (7.0%)	2 (1.4%)	0
Colitis[b]	1 (0.7%)	0	1 (0.7%)

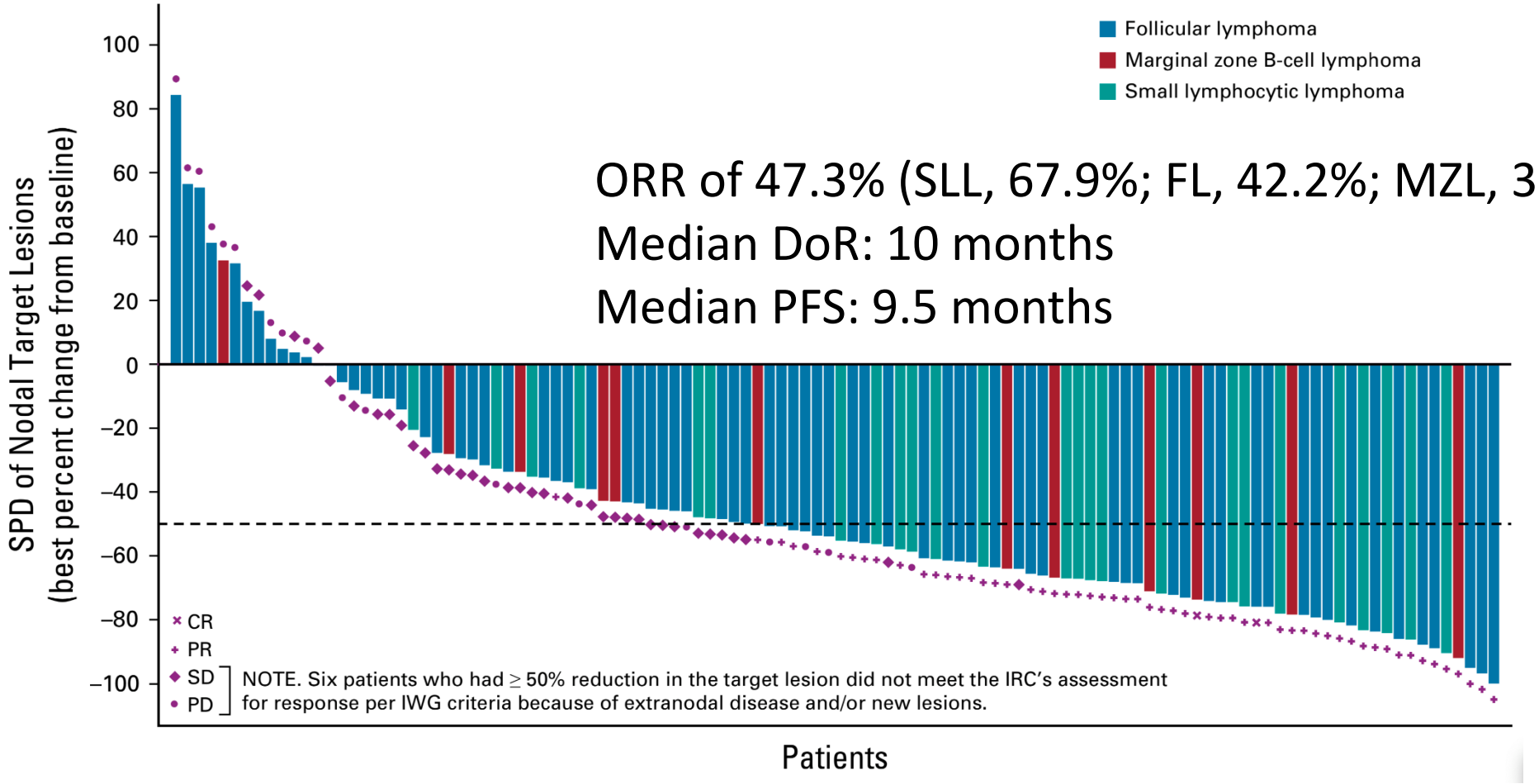
2 patients (1.4%) had grade 3 pneumonitis and 1 patient (0.7%) had grade 4 colitis

3 deaths (2.1%) were drug-related: lung infection, respiratory failure, and a thromboembolic event (0.7%)

Dreyling M et al, ICML 2017

DUVELISIB CLINICAL ACTIVITY IN MZL

Dynamo Trial



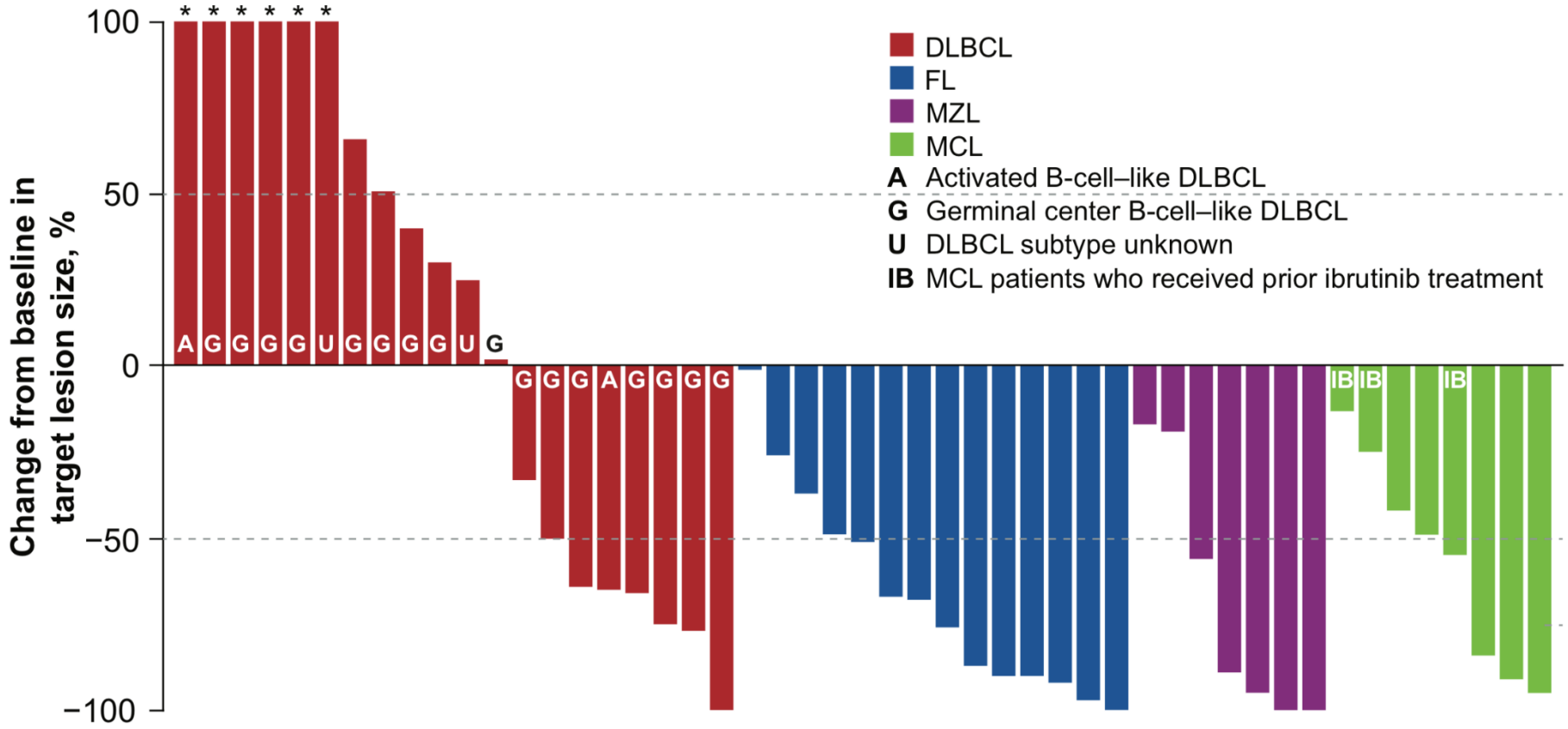
ORR of 47.3% (SLL, 67.9%; FL, 42.2%; MZL, 38.9%)
Median DoR: 10 months
Median PFS: 9.5 months

duvelisib 25 mg orally twice daily in 28-day cycles until progression
129 patients (median age, 65 years; median of 3 prior lines of therapy)
18 MZL (9 EMZL, 5 SMZL, 4 NMZL)

Flinn et al, J Clin Oncol 2019

PARSACLISIB IN MZL

Novel PI3Kδ inhibitor

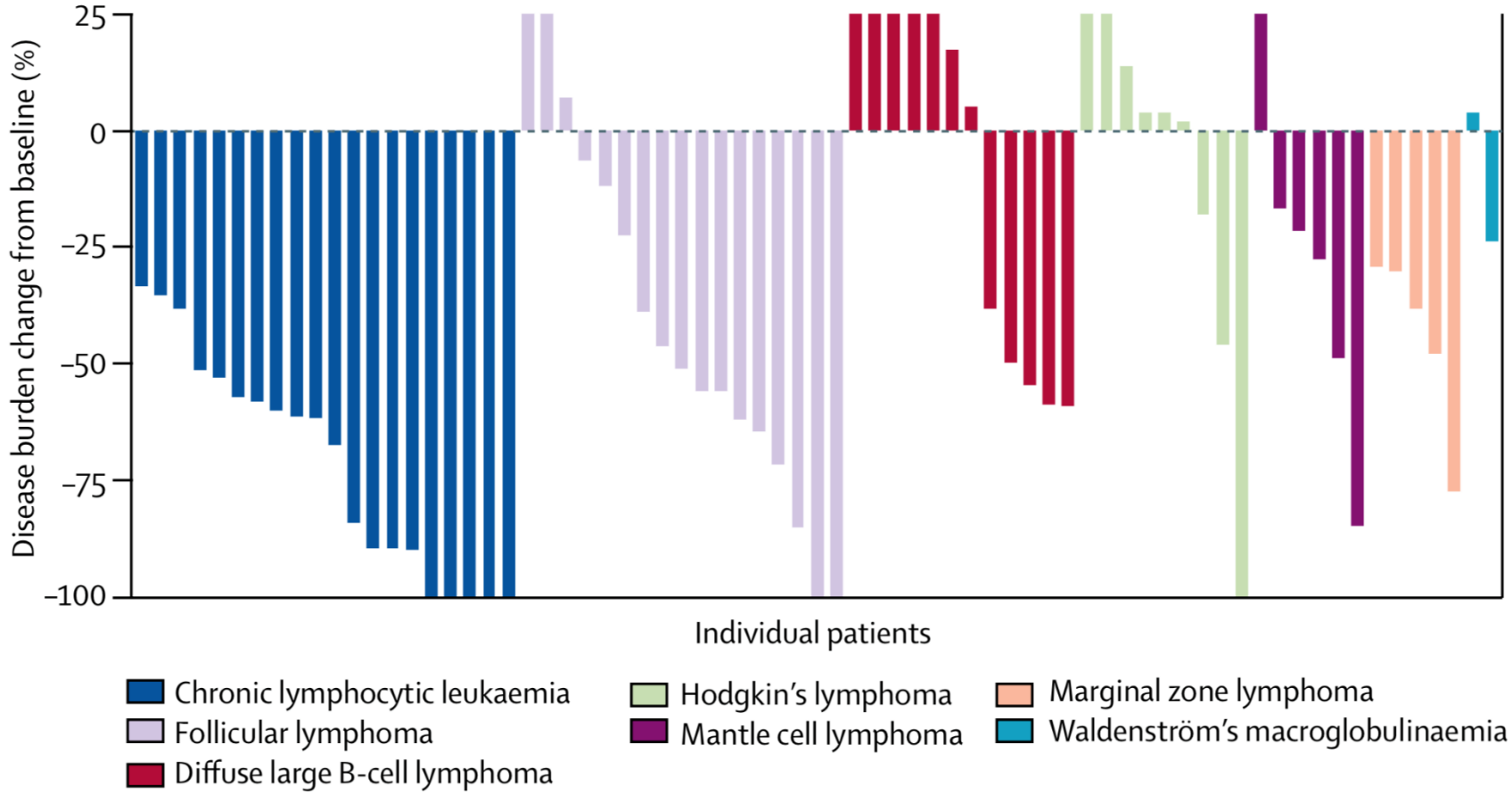


MZL (9): EMZL(2), NMZL (4), SMZL (2), unkMZL subtype (1).

ORR FL:71%,
MZL:78% median DoR:4.4 months
MCL:67%
DLBCL:30%

UMBRALISIB IN MZL

dual PI3Kδ/casein kinase-1ε inhibitor

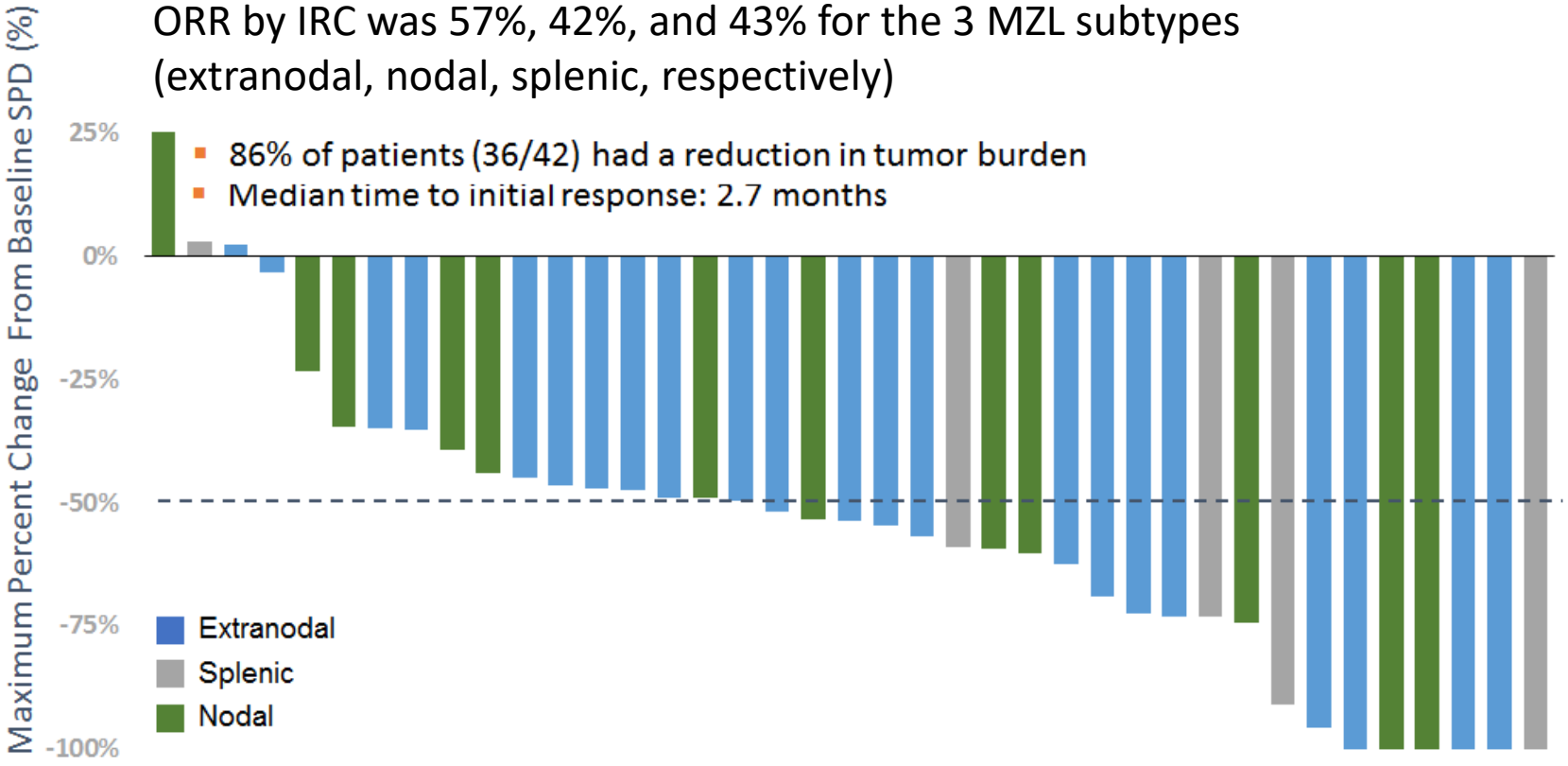


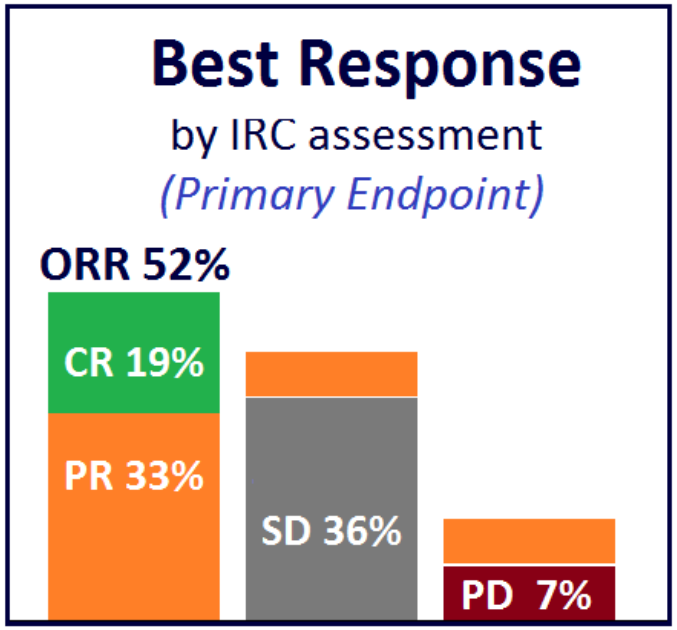
Burris III et al, Lancet Oncol 2018

Umbralisib activity in r/r MZL

Interim Efficacy Population (N=42)

ORR by IRC was 57%, 42%, and 43% for the 3 MZL subtypes (extranodal, nodal, splenic, respectively)

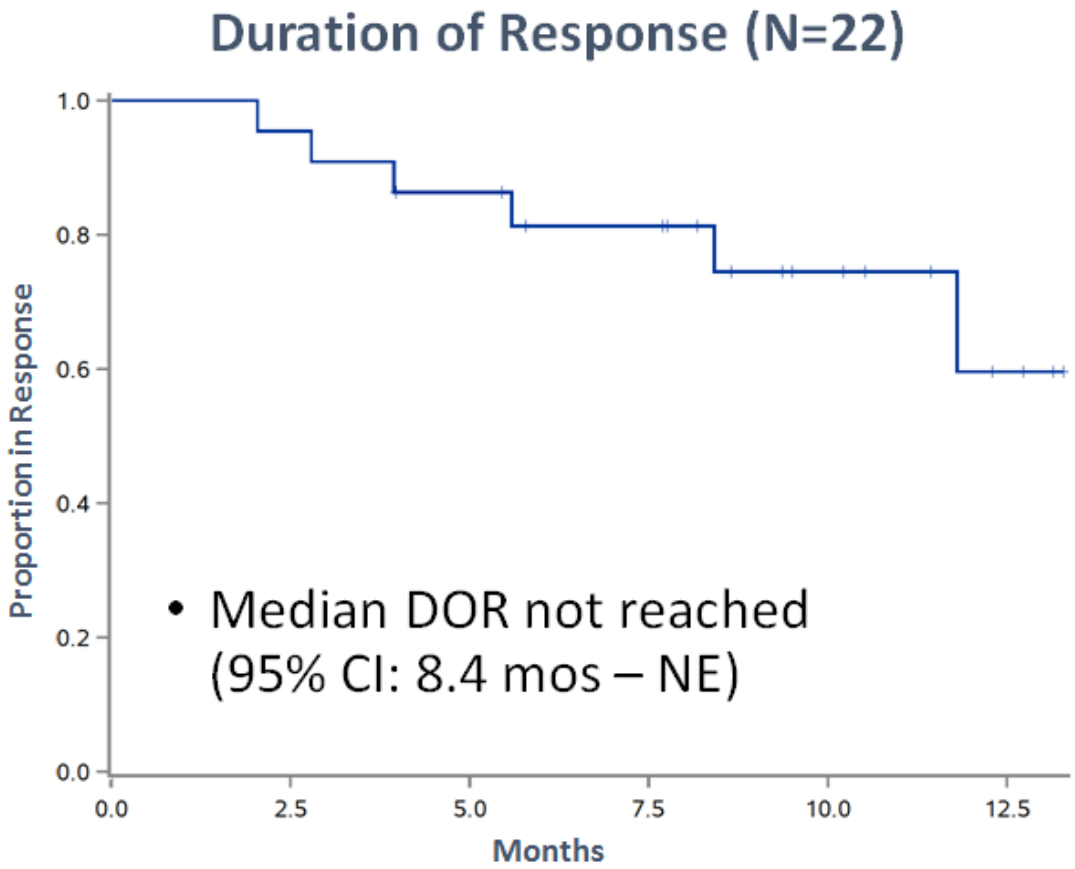


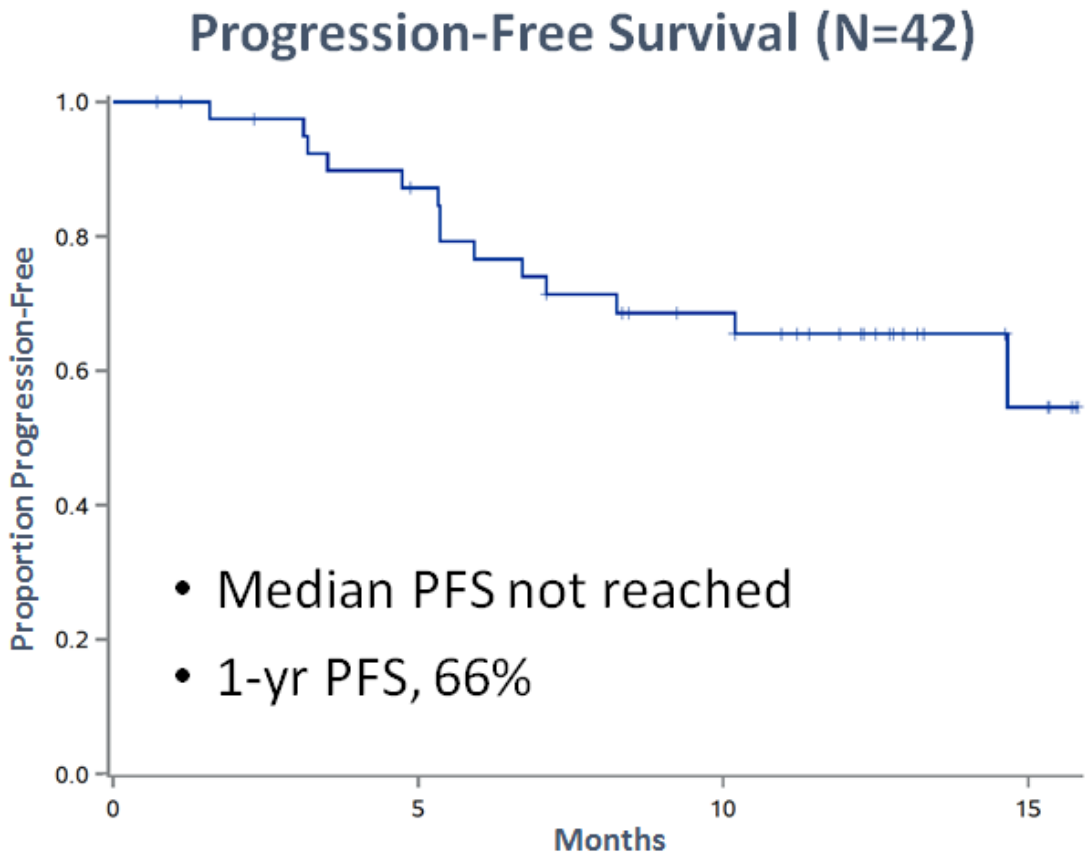


P. Zinzani et al. 2019; 15-ICML Abstract 133

Umbralisib activity in r/r MZL

Interim Efficacy Population (N=42)





P. Zinzani et al. 2019; 15-ICML Abstract 133

Umbralisib in r/r MZL
Safety summary

- No colitis reported
- AE's leading to dose reduction occurred in 6 subjects (9%)
- 10 subjects (14%) discontinued umbralisib due to an AE considered at least possibly related to treatment
- The median duration of exposure to umbralisib was 6.9 months as of data cutoff date
- No deaths occurred on study
- Grade 3 infections were limited, occurring in 3 patients (bronchitis, pneumonia, and influenza)

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	33%	19%	10%	-
Nausea	17%	14%	-	-
Fatigue	19%	9%	3%	-
AST increased	17%	3%	9%	-
ALT increased	6%	9%	9%	1%
Headache	16%	6%	3%	-
Cough	17%	4%	-	-
Decreased appetite	14%	7%	1%	-
Vomiting	12%	9%	-	-
Rash	12%	3%	3%	
Dysgeusia	14%	3%	-	-
Edema peripheral	12%	4%	-	-
Dizziness	7%	7%	-	-
Neutropenia	1%	-	7%	6%
Insomnia	9%	4%	-	-
Upper respiratory tract infection	1%	12%	-	-
Back pain	6%	3%	3%	-
Hyperuricemia	10%	-	-	-
Pyrexia	6%	4%	-	-

P. Zinzani et al. 2019; 15-ICML Abstract 133

Synergism of copanlisib with venetoclax

Combination with copanlisib	% of cell lines in which combination was beneficial*	95% Conf. Interval	Mechanism of action of combination partner
Venetoclax	**94% (16/17)**	**71.3 - 99.9**	**BCL2 inhibition**
MI2	88% (15/17)	63.5 - 98.5	MALT1 inhibition
Palbociclib	82% (14/17)	56.2 - 96.2	CDK4/6 inhibition
Ibrutinib	82% (14/17)	56.2 - 96.2	BTK inhibition
Panobinostat	76% (13/17)	50.1 - 93.2	HDAC inhibition
BAY 1125976	76% (13/17)	50.1 - 93.2	AKT1/2 inhibition
Lenalidomide	71% (12/17)	44.0 - 89.7	immunomdulation
BAY 1238097	71% (12/17)	44.0 - 89.7	BET inhibition
Rituximab	65% (11/17)	38.3 - 85.8	Anti CD20 moAb
Romidepsin	59% (10/17)	32.3 - 81.6	HDAC inhibition
Roniciclib	53% (9/17)	27.8 - 77.0	CDK inhibition
Bortezomib	47% (8/17)	23.0 - 72.2	Proteasome inhibition
BAY 1143572	35% (7/17)	18.4 - 67.1	PTEFb/CDK9 inhibition
Bendamustine	35% (6/17)	14.2 - 61.7	chemotherapy
Ruxolitinib	12% (2/17)	1.5 - 36.4	JAK1/2 inhibition

Gaudio E et al, AACR 2017

NEW PHASE I TRIAL- SAKK 6618

Combination of copanlisib and venetoclax with expansion cohort in MZL

Part A – Dose Escalation (3+3 Scheme)

Dose Level	Dose	Schedule
	Venetoclax	
1 - 3	• Target dose: ➢ MZL: 1200 mg ➢ FL: 800 mg • Dose level 1: 400 mg • Dose level 2: 800 mg • Dose level 3: 1200 mg If rump-up is necessary will be discussed with AbbVie*	• Every day p.o., in a 28-day cycle • Patients continue with the target dose for subsequent cycles, once-daily, continuously
	Copanlisib	
-2	30 mg (optional)	• i.v. infusion (over 1 hour) • Days 1, 8 and 15 • 28-day cycle
-1	45 mg (optional)	
1	60 mg (approved dose)	

→

Up to 12 cycles (1 yr)

Extension of treatment permitted in patients who benefited

Stop treatment if:
- Progressive disease
- Symptomatic deterioration
- Unacceptable toxicity
- Patient refusal
- Withdrawal by HCP
- etc

* Suggested ramp-up and target dose of Venetoclax to be discussed with Abbvie.
TLS prophylaxis and monitoring based on AbbVie safety language.

Part B – Dose Expansion

MZL cohort	FL cohort
N = up to 12 pts	N = up to 12 pts
Up to 1 year of treatment	Up to 1 year of treatment

MZL: Perspectives on therapy

- Selection of patients to be offered to treatments directed against infectious agent
- Investigation on strategies to spare toxicity related to radiotherapy
- Selection of patients to be offered to immunochemotherapy
- Investigations on new drugs
- Identification of biomarkers predicting the response to biologic agents

Grazie per l’attenzione