Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

16th ICML 2021 Virtual

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Prof. Dr. med. Martin Dreyling
Medizinische Klinik und Poliklinik III| Klinikum der Universität München

Indolente Lymphome

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ICML2021 wird in Kooperation mit vier unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

• **Research Support (institution)**	Abbvie, Bayer, Celgene, Janssen, Roche
• **Employee**	-
• **Major Stockholder**	-
• **Speakers Bureau**	-
• **Speakers Honoraria**	Amgen, Astra Zeneca, Bayer, Celgene, Gilead, Janssen, Roche
• **Scientific Advisory Board**	Astra Zeneca, Bayer, Beigene, Celgene, Genmab, Gilead, Incyte, Janssen, Novartis, Roche

Indolente Lymphome: Subtypen

- ***Follikuläres Lymphom/Marginalzonen-Lymphom:***

  - Erstlinie: +/- Rituximab-Erhaltung ?

  - Rezidiv: PI3K-Inhibitoren im 1. Rezidiv ?

  - Rezidiv: CAR T-Zellen? Bispezifische AK?

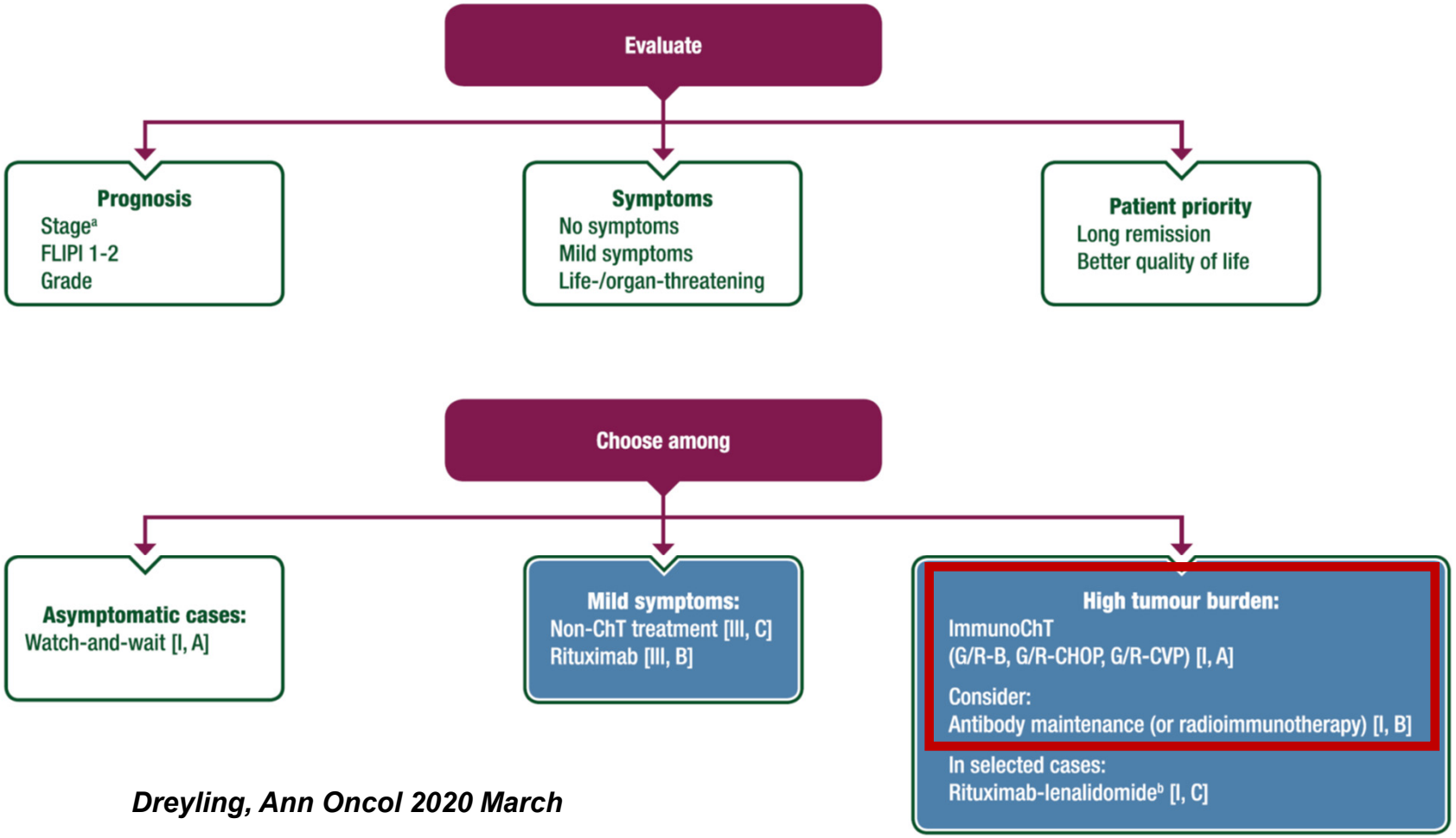
- ***Mantelzell-Lymphom***

  - Erstlinie: BR +/- Rituximab-Erhaltung

  - Ibrutinib + R/Bortezomib ?

  - Rezidiv: CAR T-Zellen in BTKi-Versagern

Follikuläres Lymphom: ESMO/EHA therapeutischer Algorithmus

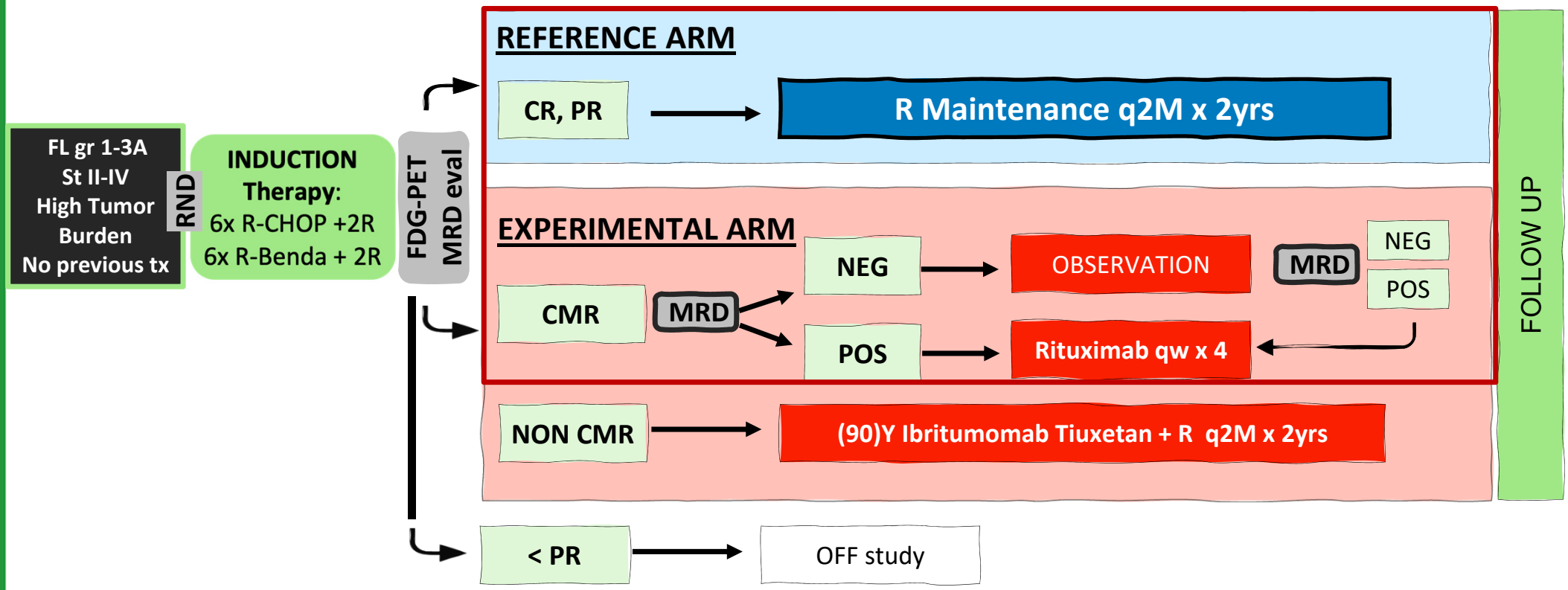


Dreyling, Ann Oncol 2020 March

FONDAZIONE ITALIANA LINFOMI

FOLL12 TRIAL DESIGN
RESPONSE ADAPTED POST INDUCTION MANAGEMENT
EUDRACT N° : 2012-003170-60

www.filinf.it



MRD: minimal residual disease assessed by PCR for t(14;18) on bone marrow and peripheral blood sample (central lab)
CMR: Complete Metabolic Response defined as c Deauville score 1-3 (central review)

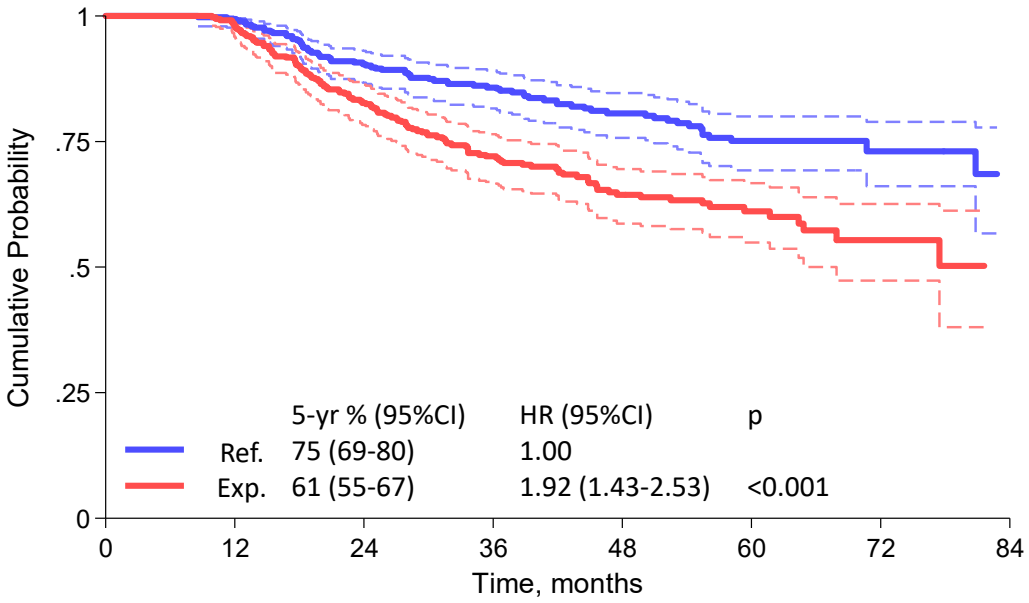
FONDAZIONE ITALIANA LINFOMI

Updated results of the FOLL12 trial

N=712, Med f-up 53m, 197 PFS events , 30 deaths

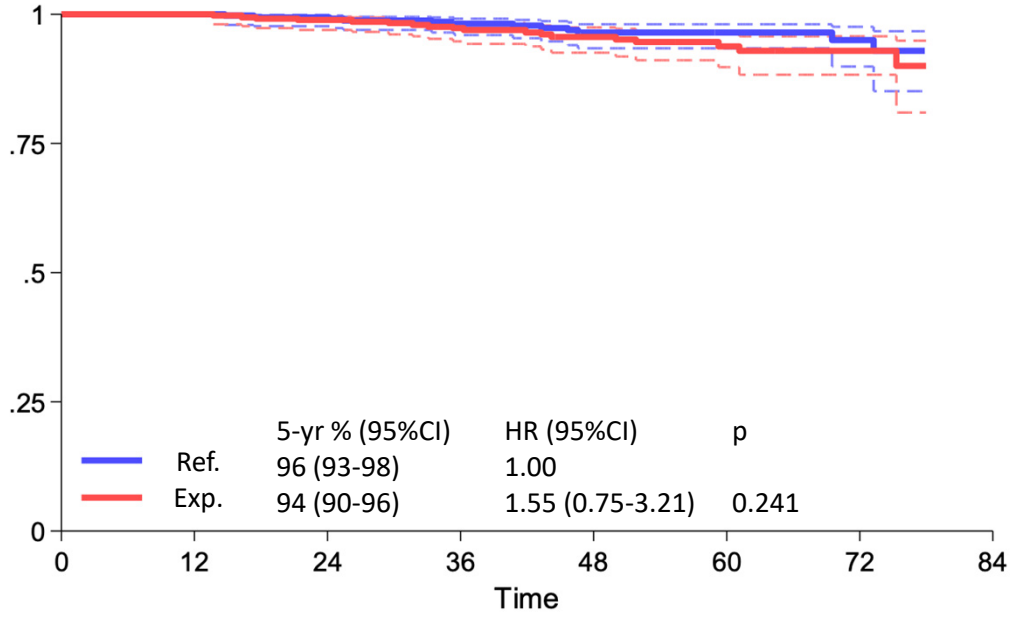
www.filinf.it

PFS



At risk								
Ref.	351	345	306	248	173	96	34	5
Exp.	361	344	283	217	135	65	19	4

OS



At risk								
Ref.	351	347	337	283	206	125	50	8
Exp.	361	351	337	285	202	111	45	9

FONDAZIONE ITALIANA LINFOMI

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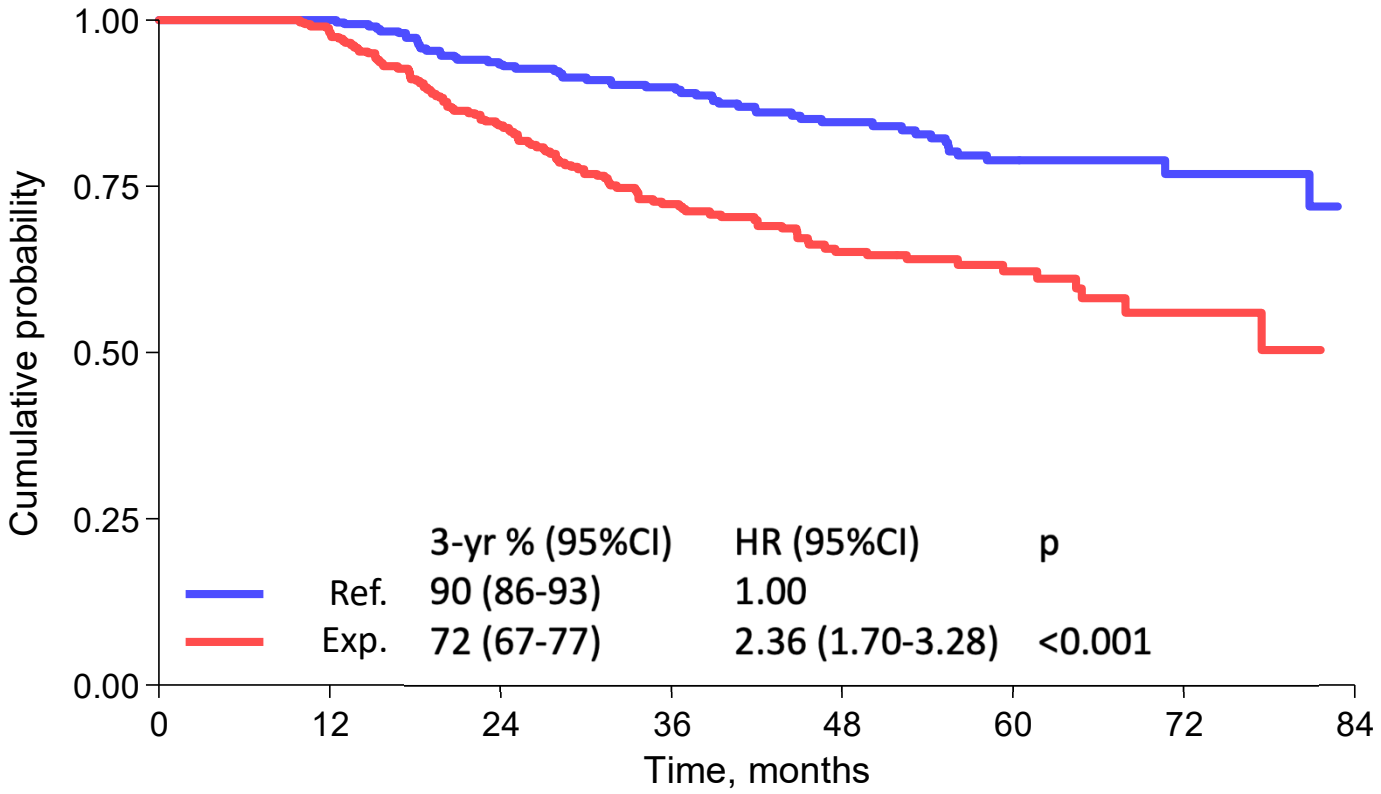
PFS: CMR patients by Arm (N=628)

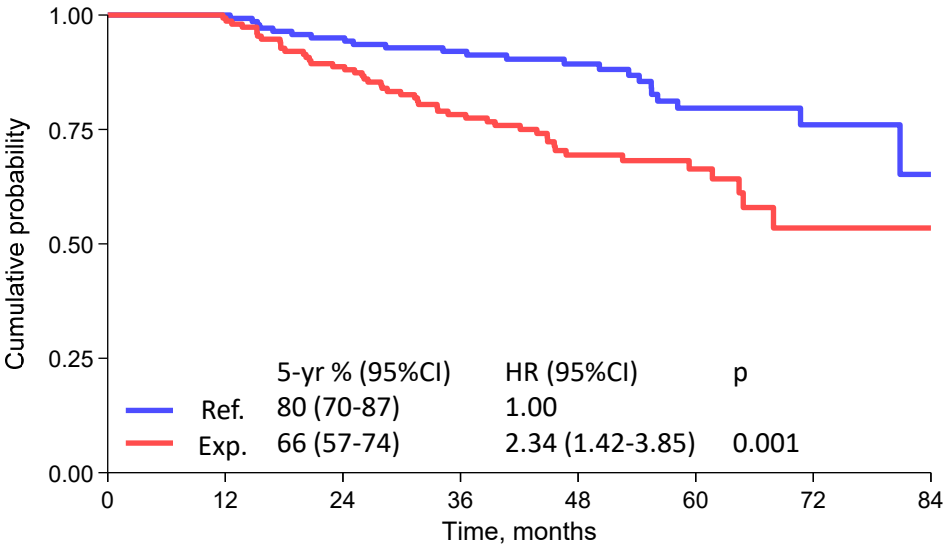


FONDAZIONE ITALIANA LINFOMI

PFS for CMR patients by MRD status

www.filinf.it

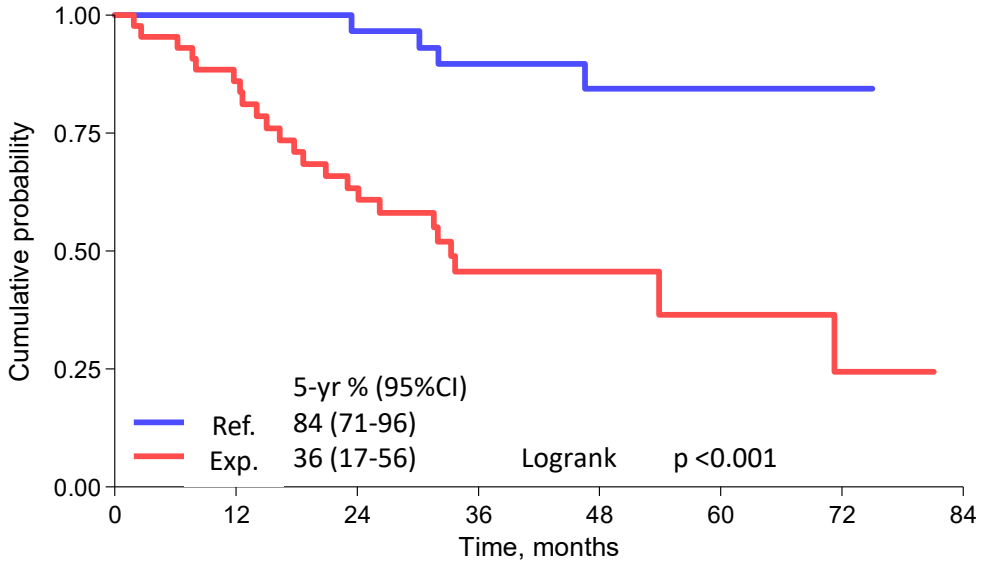
MRD negative EoT and CMR (N=299)



At risk

Ref.	143	141	132	113	81	44	19	3
Exp.	156	151	133	106	68	34	8	1

MRD CMR and MRD positive EoT or follow-up (N=76)

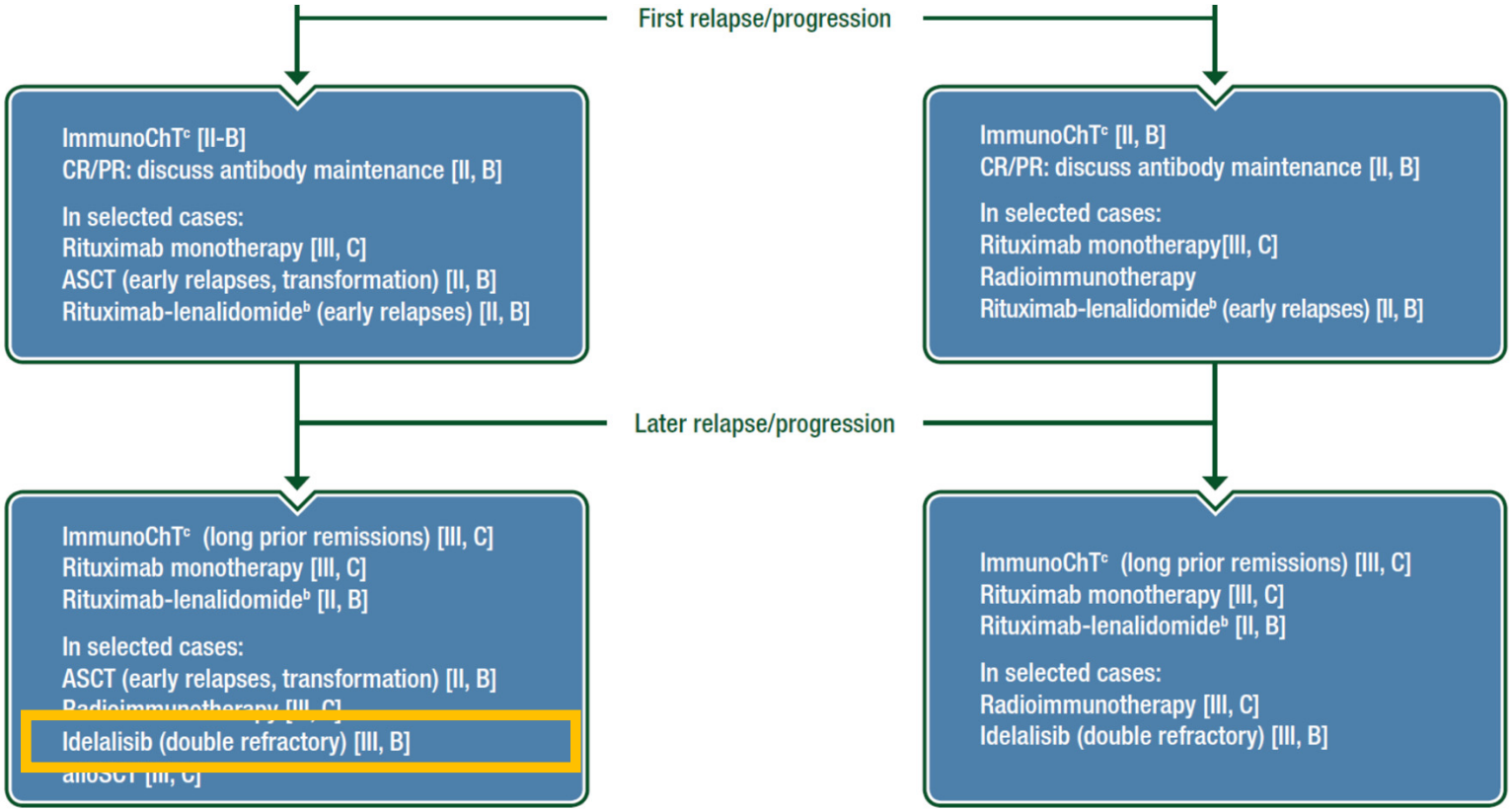


At risk

Ref.	32	30	28	25	16	8	1	0
Exp.	44	36	25	11	8	3	2	0

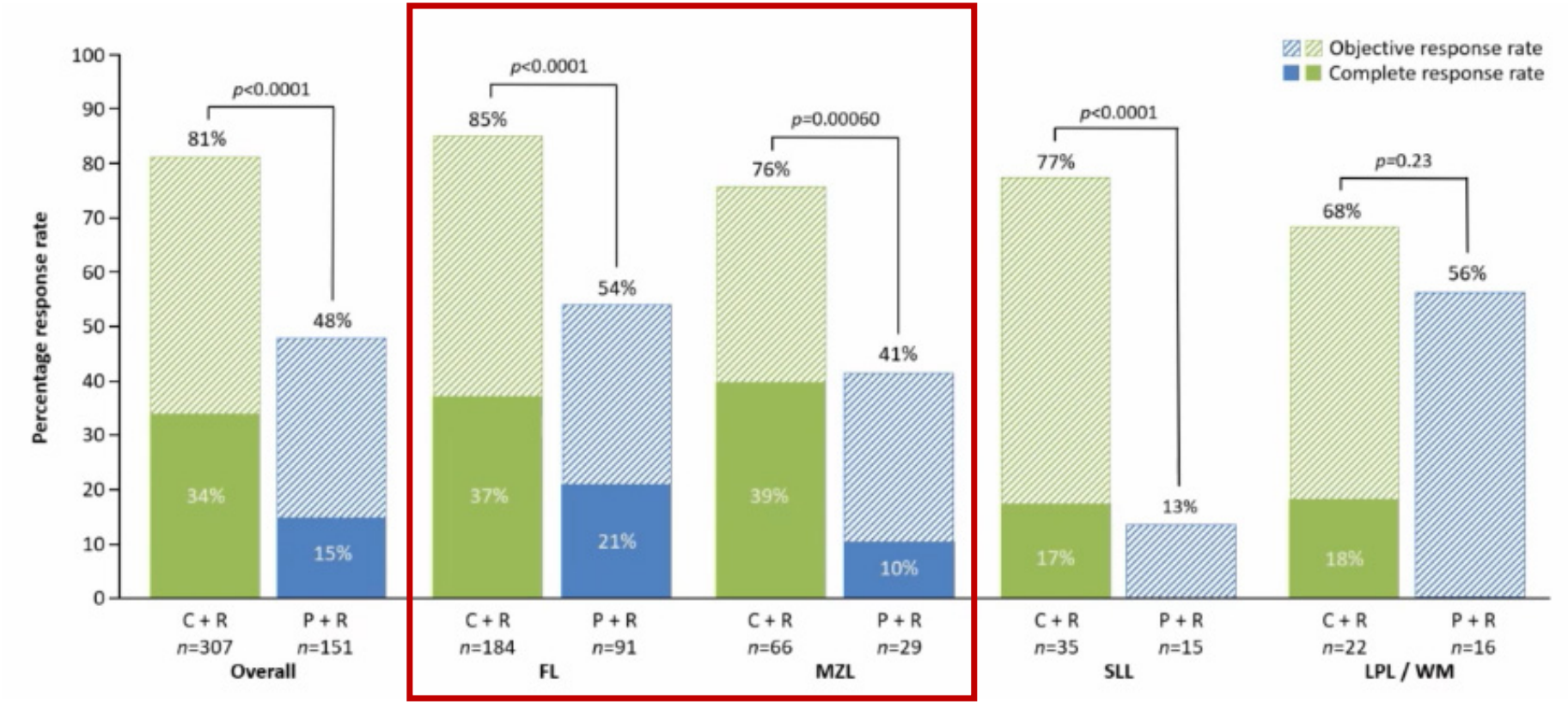
MRD: minimal residual disease assessed by PCR for t(14;18) on bone marrow and peripheral blood sample (central lab)
CMR: Complete Metabolic Response defined as c Deauville score 1-3 (central review)

Follikuläres Lymphom: ESMO/EHA therapeutischer Algorithmus



Dreyling, Ann Oncol 2021 March; Ladetto, Hemasphere 2021

CHRONOS-3: RANDOMIZED PHASE III STUDY OF COPANLISIB PLUS RITUXIMAB VS RITUXIMAB/PLACEBO IN RELAPSED INDOLENT NHL



Zinzani, P.L. et al., Bologna, Italien

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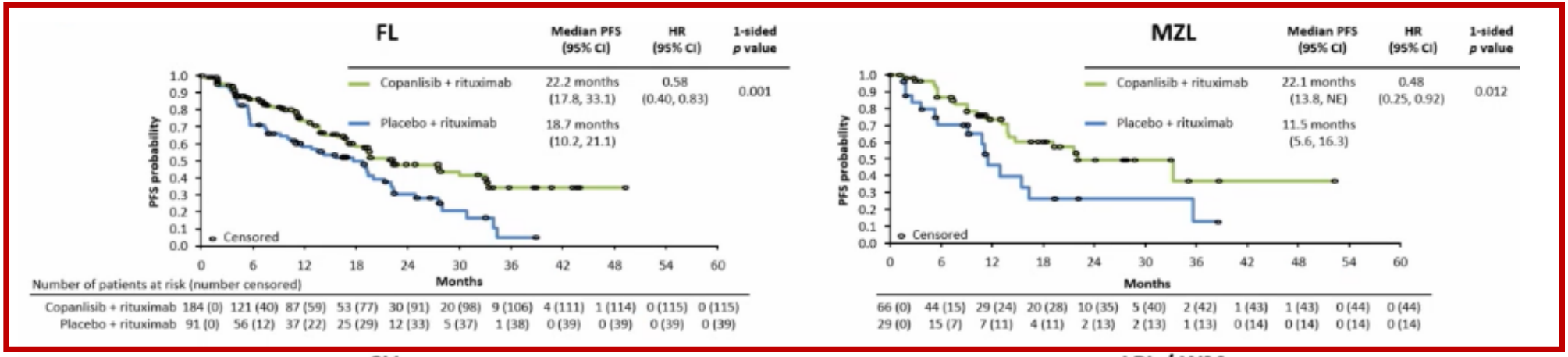
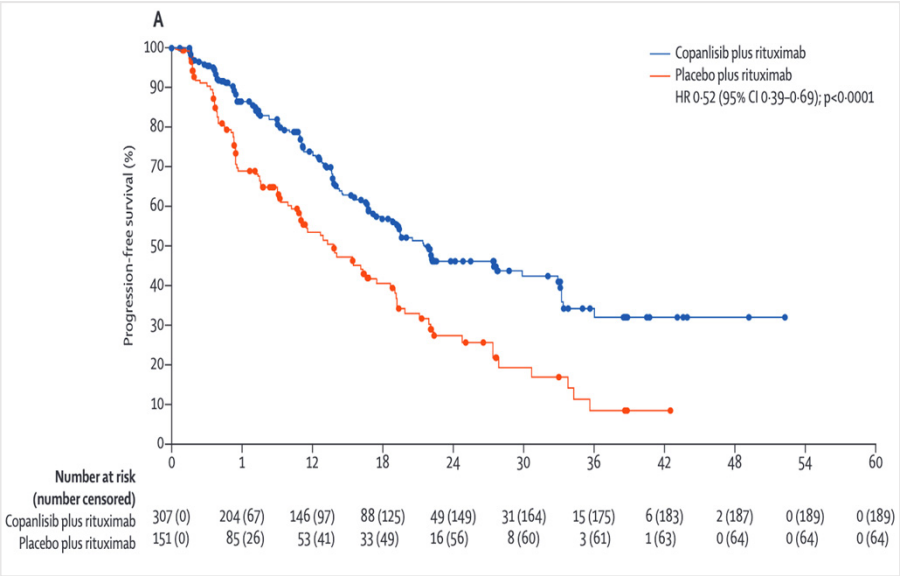


Zinzani, P.L. et al., Bologna, Italien

Indolentes Lymphom: R-Copanlisib vs. R-Lenalidomid

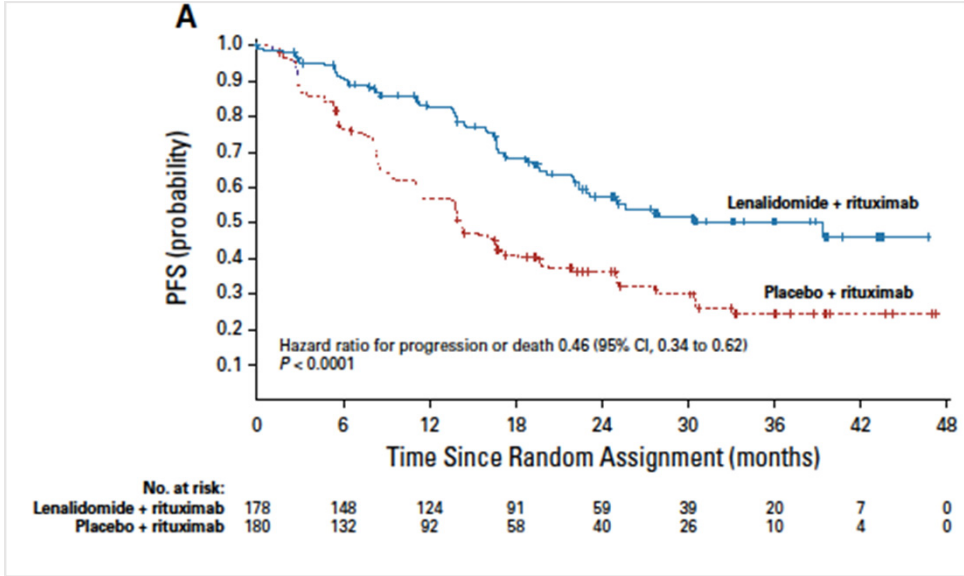
Copanlisib plus R



OR 81%, CR 34%
Median PFS 21,5 vs. 13.8 months
HR 0,52 [95% CI 0·39–0·69]; p<0·0001

Matasar Lancet Oncol 2021

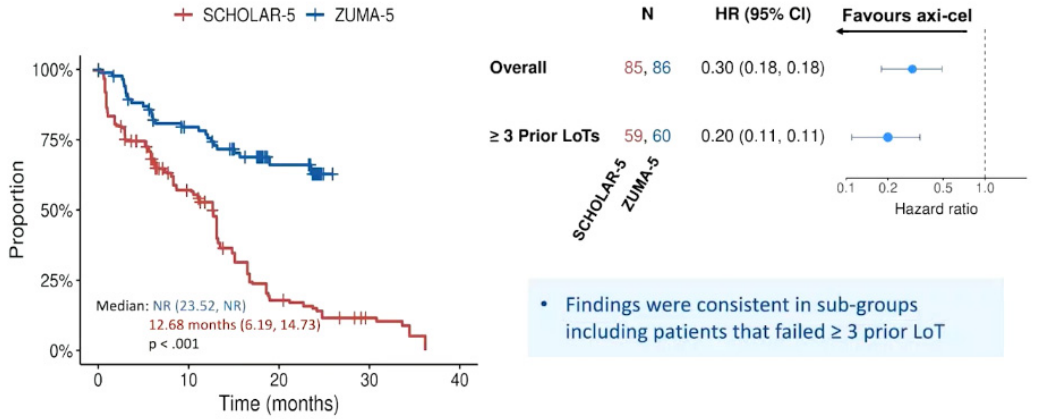
Lenalidomid plus R



OR 78%, CR 34%.
Median PFS 39 vs. 14 months
HR 0.46 (95% CI, 0.34 to 0.62; p= 0.001)

Leonhard JCO 2019

PFS was significantly longer in ZUMA-5 compared to SCHOLAR-5

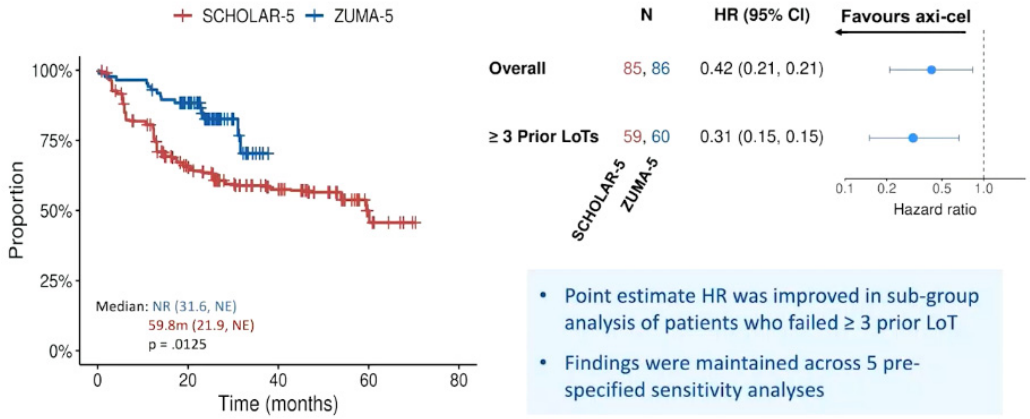


- Findings were consistent in sub-groups including patients that failed ≥ 3 prior LoT

NR = Not reached
Median follow-up time for ZUMA-5 was 23.3 months and for SCHOLAR-5 was 26.2 months

EHA2021 VIRTUAL

OS was significantly longer in ZUMA-5 compared to SCHOLAR-5



- Point estimate HR was improved in sub-group analysis of patients who failed ≥ 3 prior LoT
- Findings were maintained across 5 pre-specified sensitivity analyses

S-5= SCHOLAR-5, Z-5= ZUMA-5
Median follow-up time for ZUMA-5 was 23.3 months and for SCHOLAR-5 was 26.2 months
Sensitivity analyses included removal of DELTA trial data, use of matching rather than

EHA2021 VIRTUAL

Ghione et al., ICML 2021

Demographics and Baseline Disease Status

Infusion therapy details

- 18% of patients received tisagenlecleucel infusion in outpatient setting
- Bridging therapy was administered for stabilization in 44% of patients[a]
- Baseline imaging repeated prior to infusion for patients who received bridging therapy
- Median infused dose of tisagenlecleucel was 2.06×10^8 CAR+ viable T cells[b]

	All Patients (N=97)
Median age (range), y	57.0 (29-73)
≥65 y, n (%)	24 (24.7)
ECOG PS, n (%)	
0	56 (57.7)
1	37 (38.1)
2	4 (4.1)
Bulky disease at study entry,[c] n (%)	63 (64.9)
Stage at study entry III-IV, n (%)	82 (84.5)
FLIPI ≥3 at study entry, n (%)	58 (59.8)
Median no. of prior therapies (range)	4 (2-13)
≥5, n (%)	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy,[d] n (%)	58 (59.8)
Refractory to last line of therapy,[e] n (%)	76 (78.4)
Prior autologous HSCT, n (%)	35 (36.1)
Refractory to ≥2 regimens,[f] n (%)	74 (76.3)
Double refractory,[g] n (%)	67 (69.1)
Prior therapy	
Anti-CD20 mAb and alkylating agents,[h] n (%)	63 (64.9)
PI3K inhibitors, n (%)	20 (20.6)
Lenalidomide and rituximab, n (%)	16 (16.5)

Fowler et al., ICML 2021

Adverse Events of Special Interest

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	**All grades, %**	**Grade ≥3, %**
Cytokine release syndrome[a,1]	48.5	**0**
Neurological adverse reactions	9.3	**1.0**
Infections	18.6	5.2
Tumor lysis syndrome	1.0	1.0
Prolonged depletion of B cells and/or agammaglobulinemia[b]	10.3	0
Hematologic disorders including cytopenias		
Neutropenia[c,d]	30.9	27.8
Anemia[c]	24.7	13.4
Thrombocytopenia[c]	16.5	9.3

- Median onset of NEs was 8.5 (4-190[e]) days
  - Median time to resolution was 2 days
- Only 1 case of serious ICANS within the first 8 weeks
- CRS median onset was 4.0 (1-14) days and all cases were low grade
- 74.5% of the CRS events and 100% of ICANS occurred in patients with bulky disease

All neurological and CRS events resolved with appropriate management

Fowler et al., ICML 2021

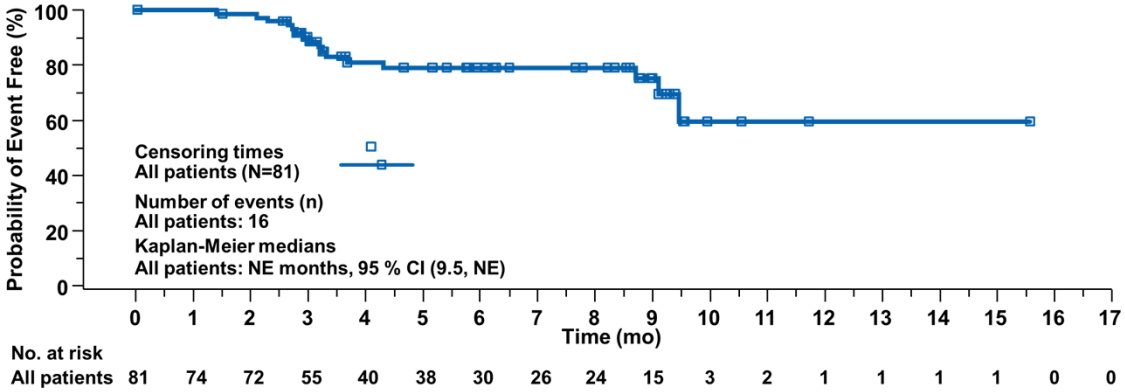
Primary Endpoint Complete Response Rate by IRC

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

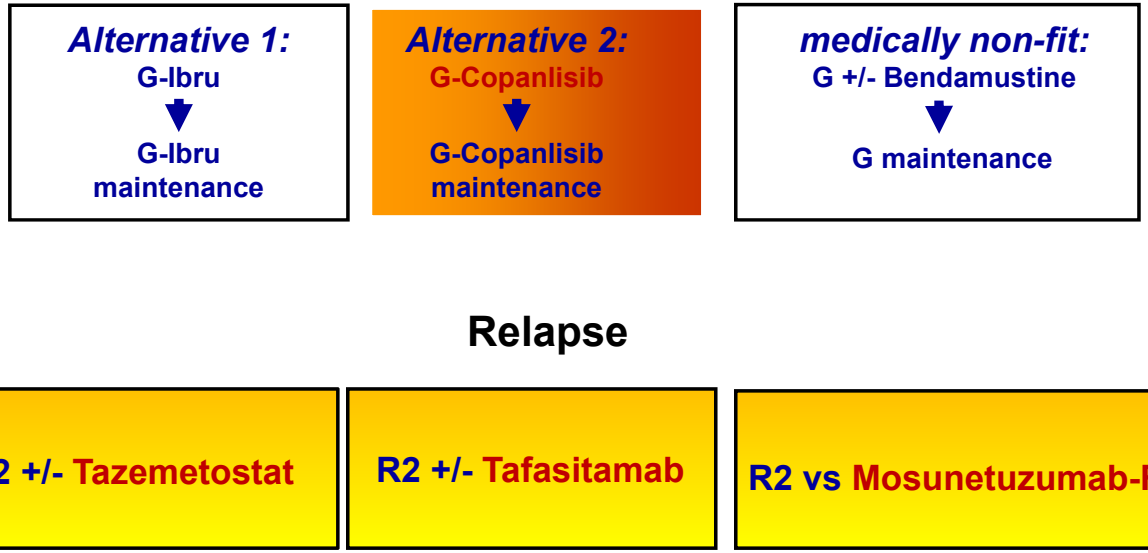
- Investigator-assessed CRR was 69.1%[c] (ORR 90.4%)
- CRRs/ORRs were comparable among key high-risk subgroups

Median DOR Was Not Reached at 11 Months Median Follow-Up

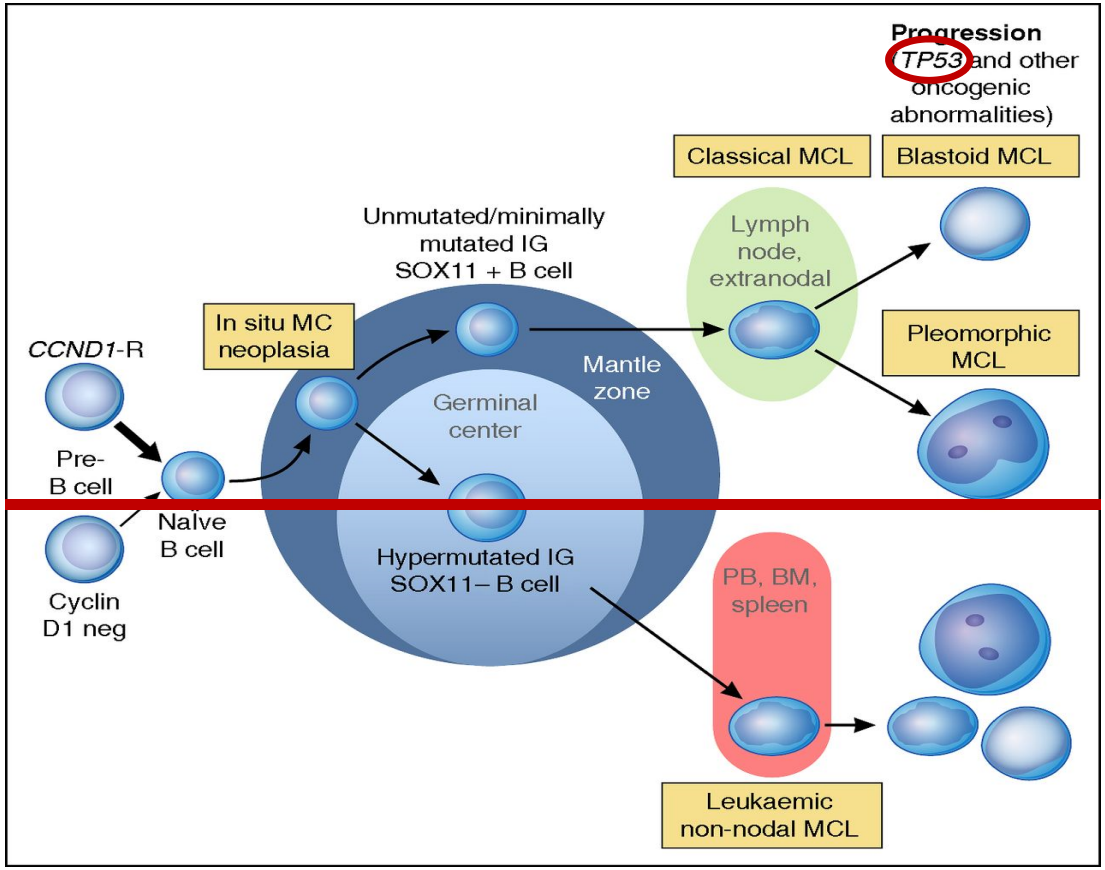


- Median follow-up for efficacy (n=94): 11 (4.3-19.7) months
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI, 66-87)
- 12 of 31 PRs (38.7%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached

Follikuläres Lymphom: GLA Studien 2021



Mantelzell-Lymphom: Spektrum der Erkrankung



Dreyling, Ann Oncol 2017

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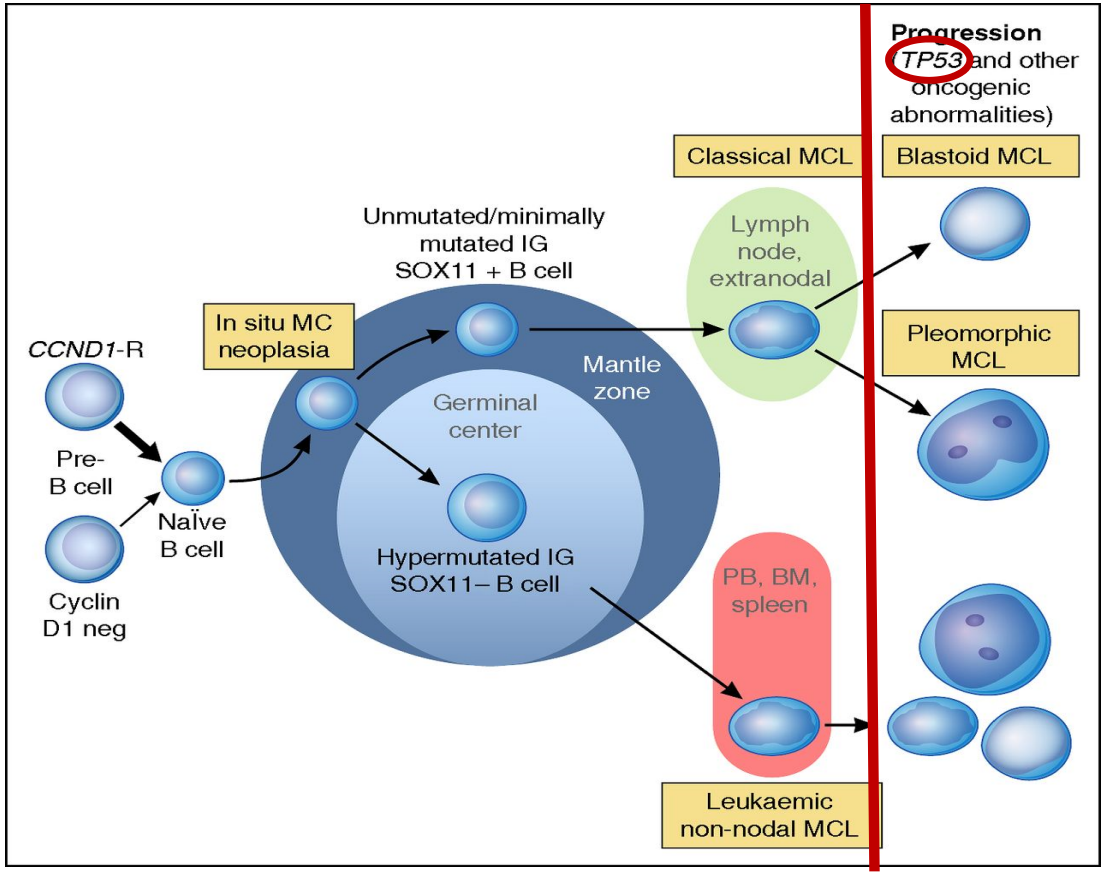


Dreyling, Ann Oncol 2017

Indolente Lymphome: Subtypen

- ***Follikuläres Lymphom/Marginalzonen-Lymphom:***

  - Erstlinie: +/- Rituximab-Erhaltung ?

  - Rezidiv: PI3K-Inhibitoren im 1. Rezidiv ?

  - Rezidiv: CAR T-Zellen? Bispezifische AK?

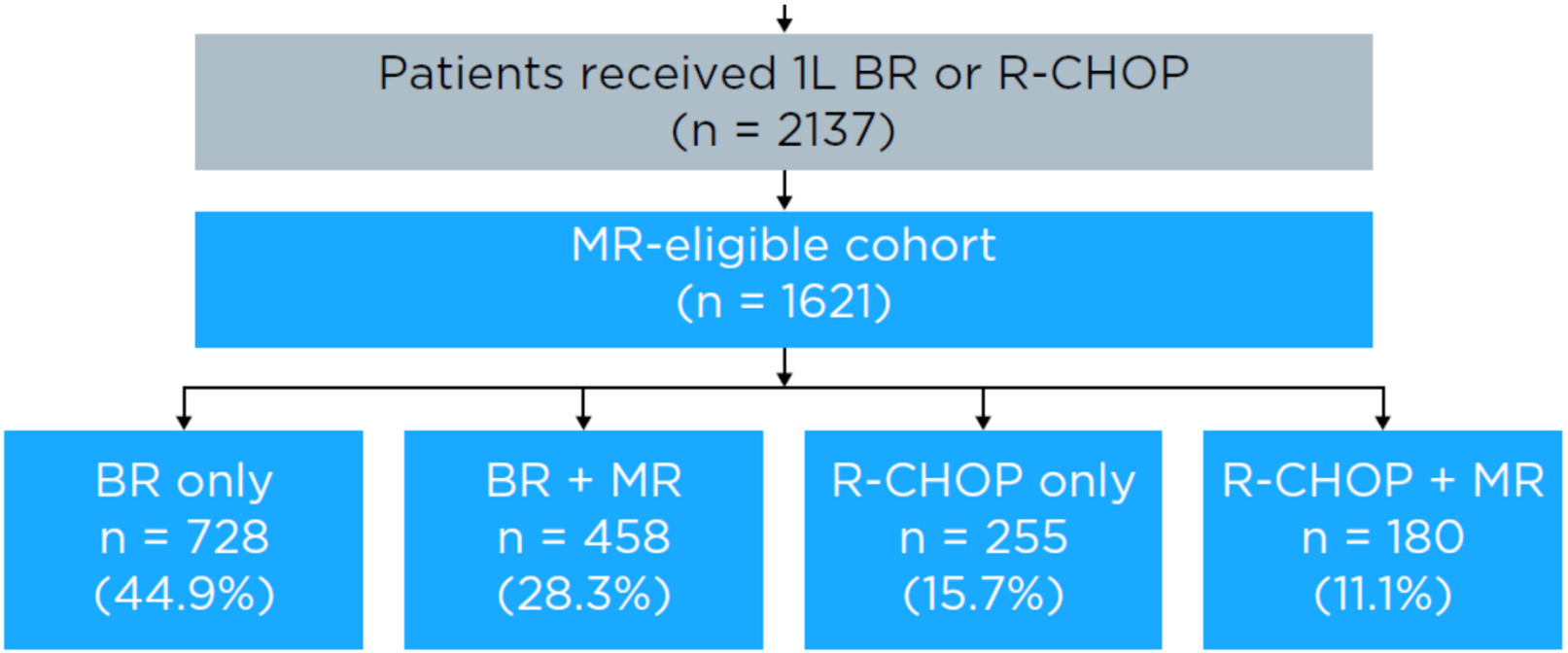
- ***Mantelzell-Lymphom***

  - Erstlinie: BR +/- Rituximab-Erhaltung

  - Ibrutinib + R/Bortezomib ?

  - Rezidiv: CAR T-Zellen in BTKi-Versagern

ROLE OF MAINTENANCE RITUXIMAB AFTER FIRST-LINE BR OR R-CHOP IN MCL PATIENTS FROM A LARGE US REAL-WORLD COHORT



Wang et al, ICML 2021

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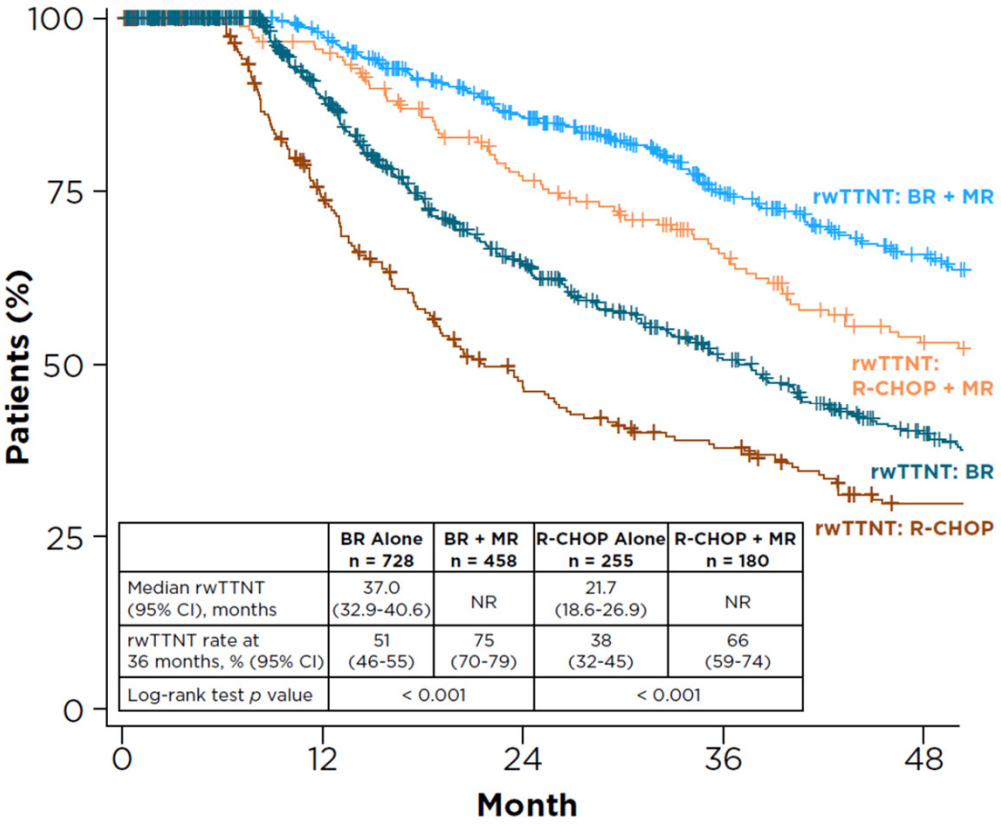
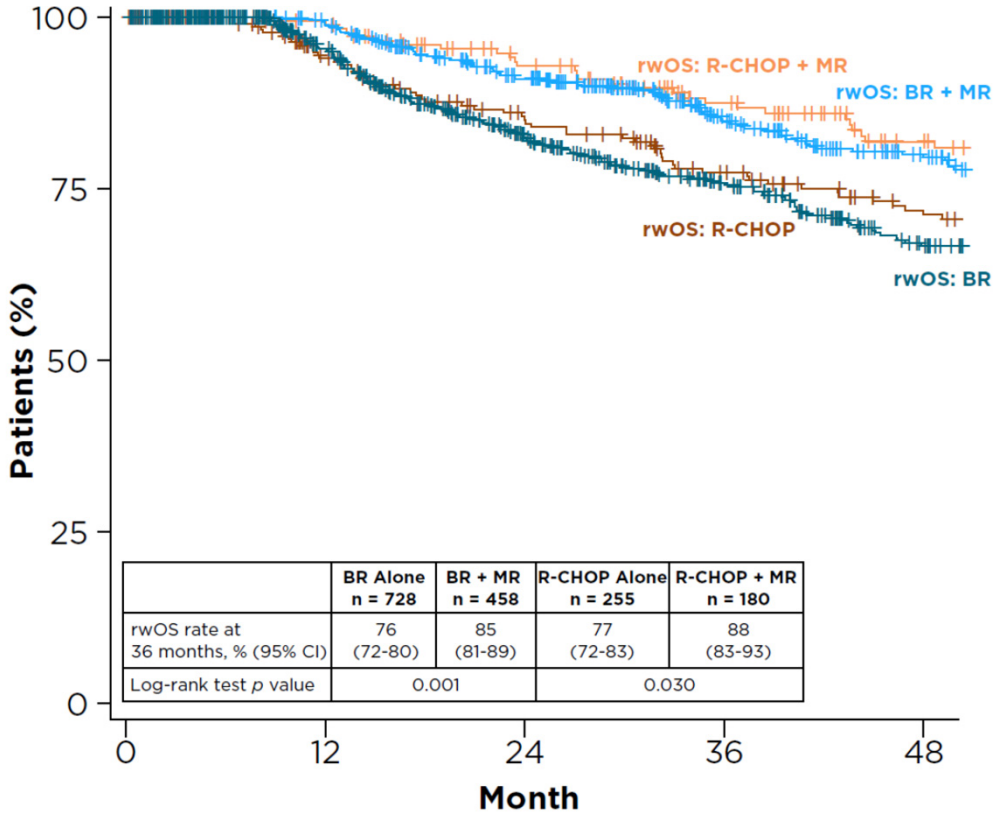


	BR Alone n = 728	BR + MR n = 458	R-CHOP Alone n = 255	R-CHOP + MR n = 180
Median rwTTNT (95% CI), months	37.0 (32.9-40.6)	NR	21.7 (18.6-26.9)	NR
rwTTNT rate at 36 months, % (95% CI)	51 (46-55)	75 (70-79)	38 (32-45)	66 (59-74)
Log-rank test *p* value	< 0.001		< 0.001	



	BR Alone n = 728	BR + MR n = 458	R-CHOP Alone n = 255	R-CHOP + MR n = 180
rwOS rate at 36 months, % (95% CI)	76 (72-80)	85 (81-89)	77 (72-83)	88 (83-93)
Log-rank test *p* value	0.001		0.030	

Wang et al, ICML 2021

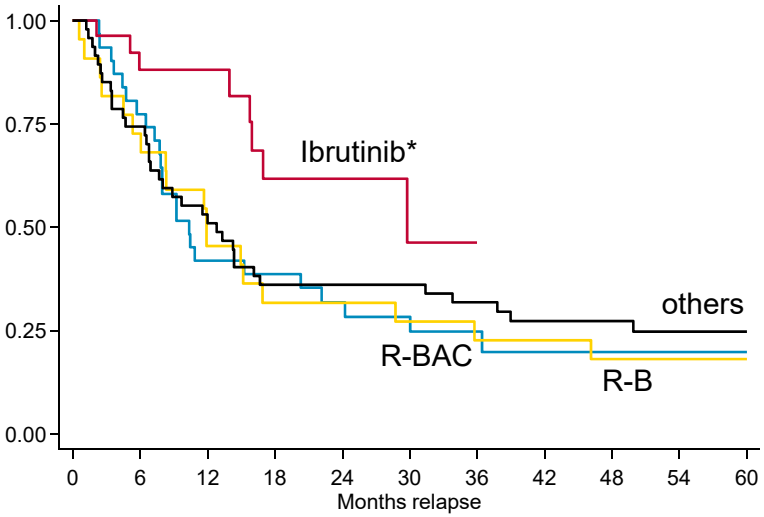
ROLE OF MAINTENANCE RITUXIMAB AFTER FIRST-LINE BR OR R-CHOP IN MCL PATIENTS FROM A LARGE US REAL-WORLD COHORT

Variables	MR-Eligible Cohort (N = 1621)					
	rwTTNT			rwOS		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
MR: No vs Yes	2.13	1.82-2.48	< 0.001	1.69	1.38-2.06	< 0.001
Age: ≥ 65 years	1.53	1.28-1.82	< 0.001	2.70	2.07-3.54	< 0.001
LDH/ULN: ≥ 1.00 vs < 1.00	1.36	1.06-1.75	0.017	1.51	1.11-2.06	0.008
Blastoid/pleomorphic MCL: Yes vs No	1.54	1.19-2.01	0.001	1.56	1.12-2.17	0.008
Bulky disease: Yes vs No	1.32	1.08-1.61	0.007	1.35	1.04-1.75	0.022
WBC: ≥ 10×10^9/L vs < 10×10^9/L	1.11	0.90-1.36	0.300	1.24	0.96-1.61	0.110
ECOG PS: ≥ 2 vs 0-1	0.95	0.63-1.43	0.800	1.57	0.98-2.52	0.061

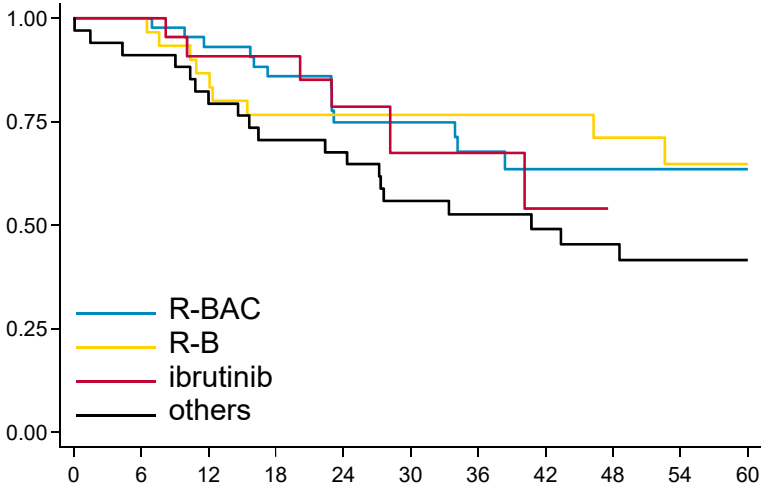
Wang et al, ICML 2021

Rezidiviertes Mantelzell-Lymphom: Gesamt-Überleben

Early POD



Late-POD



Visco, Leukemia 2020

IMCL-2015

Key Inclusion Criteria:

- MCL diagnosis (classical, small cell variants)
- Age ≥ 18 years
- No prior therapies
- Asymptomatic patients (to MCL) with ECOG 0-1
- Clinical presentation as leukemic non-nodal forms
- Other clinical presentations were allowed:

  Nodal forms with lymph nodes ≤ 3 cm (largest diameter) and Ki-67 < 30%

- Stable disease without clinical progression at the minimum period of 3 months

Key Exclusion Criteria:

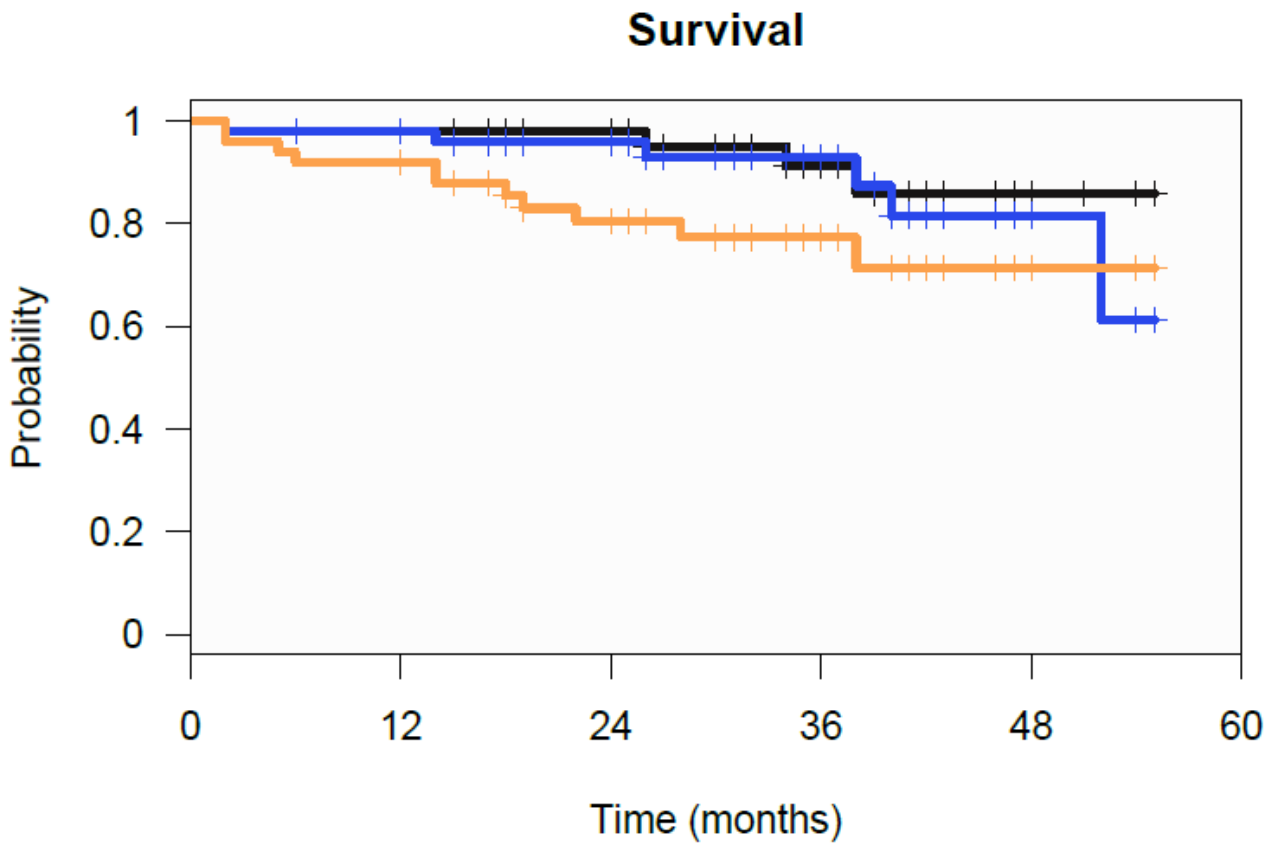
- MCL with blastic or pleomorphic variants
- Monoclonal B-cell lymphocytosis
- Lymph nodes > 3 cm (largest diameter) and/or Ki-67 ≥ 30%
- ECOG ≥2 and/or symptomatic patients requiring treatment initiation before 3 months
- Cytopenias attributable to MCL:

  Neutrophil count < 1 x10^9/L, Hemoglobin < 100 g/L and Platelet count < 100 x 10^9/L

- CNS infiltration

IMCL-2015: SURVIVAL

(Data cut-off 22 Jan 2021)



No. at risk:						
OS	50	48	37	21	7	0
PFS	50	48	36	21	6	0
EFS	50	46	31	17	4	0

3-yr OS: 91% (CI95%: 82-100)

3-yr PFS: 92% (CI 95%: 85-100)

3-yr EFS: 77% (CI95%: 65-91)

Median follow-up: 33 months

DESIGN

- ***Phase I***: 3+3 design
  (Sample size: 4-18)

Level	Bortezomib s.c. [1] days 1,4,8,11 q21d	Ibrutinib p.o continously
-1	*1.3 mg/m²*	*(280 mg/day)*
1	*1.3 mg/m²*	*420 mg/day*
2	*1.3 mg/m²*	*560 mg/day*

→ 6 cycles, followed by Ibrutinib maintenance *(until progression or unacceptable toxicity)*

- ***Phase II***

→ s.c. Bortezomib at labeled dose and Ibrutinib

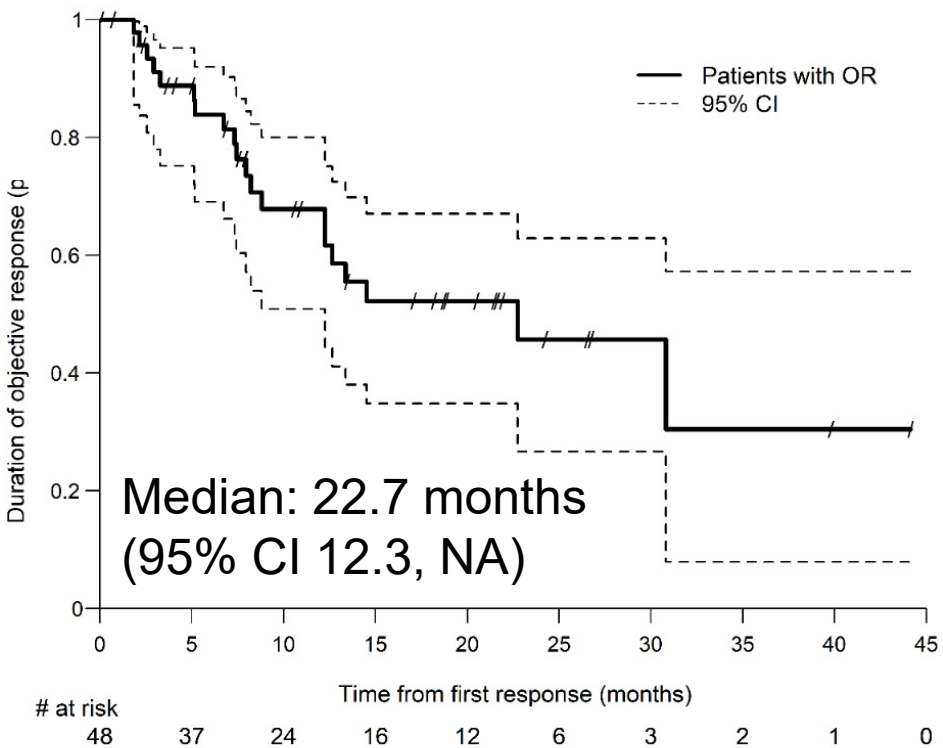
→ 6 cycles of this combination *(later amended to at least 4 cycles)*

followed by Ibrutinib maintenance *(until progression or unacceptable toxicity)*

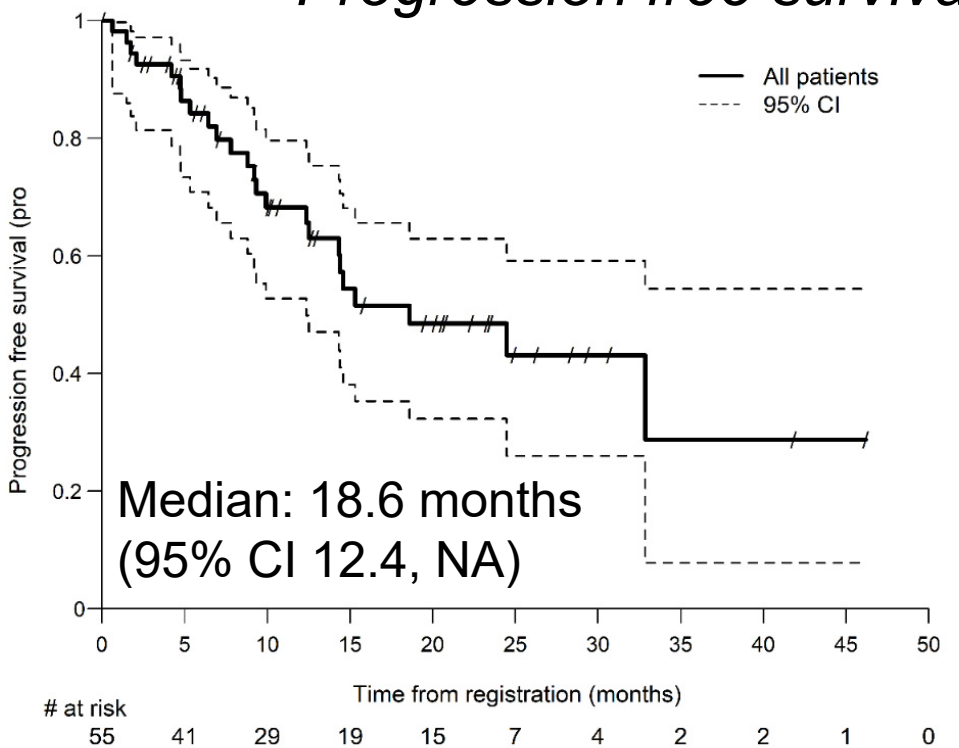
[1] Gerecitano, BJH 2009

SECONDARY ENDPOINTS

Duration of response



Progression free survival



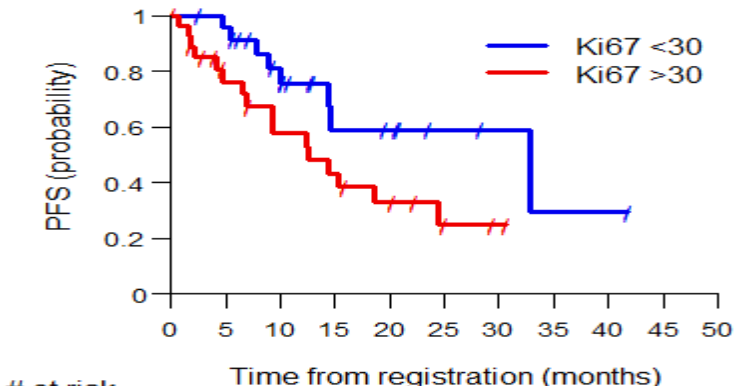
Median follow-up 24.4 months (95% CI 21.3, 30.5)

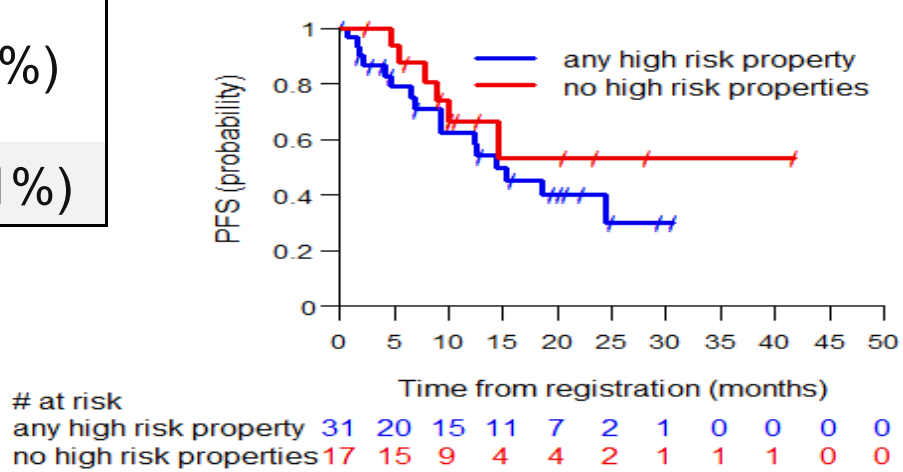
SAKK
WE BRING PROGRESS TO CANCER CARE

EFFICACY IN HIGH RISK PATIENTS

31/55 (56.4%) with ≥1 high risk feature [1]

	Low risk		High risk [1]	
Characteristic	**N**	**OR [2]**	**N**	**OR [2]**
Ki67 (<30 vs. >30)	24	23 (96%)	28	22 (79%)
p53 (<50 vs. >50)	35	32 (91%)	11	8 (73%)
blastoid (normal vs. blastoid/pleomorph)	46	42 (91%)	9	6 (67%)
any of the above	17	16 (94%)	31	25 (81%)





Overlapping time to best response *(data not show*

[1] Jain, JCO 2020; [2] during trial treatment

SAKK
WE BRING PROGRESS TO CANCER CARE

KTE-X19 versus Standard of Care for Relapsed/Refractory Mantle Cell Lymphoma Previously Treated with Bruton Tyrosine Kinase Inhibitors: Real-World Evidence from Europe

Georg Hess* [1], Martin Dreyling[2], Lucie Oberic[3], Eva Gine[4], Pier Luigi Zinzani[5], Kim Linton[6], Adam Vilmar[7], Mats Jerkeman [8], Jenny MH Chen[9], Anke Ohler[1], Stephan Stilgenbauer [10], Catherine Thieblemont[11], Jonathan Lambert[12], Vittorio Ruggero Zilioli[13], Juan Manuel Sancho[14], Ana Jimenez Ubieto[15], Luca Fischer[2], Sam Keeping[9], Julie E Park[9], Gregory A. Maglinte[16], Liliosa Nyamutswa[16], Rubina Siddiqi[16], John Reitan[17], Sally Wade[18], Gilles Salles[19]

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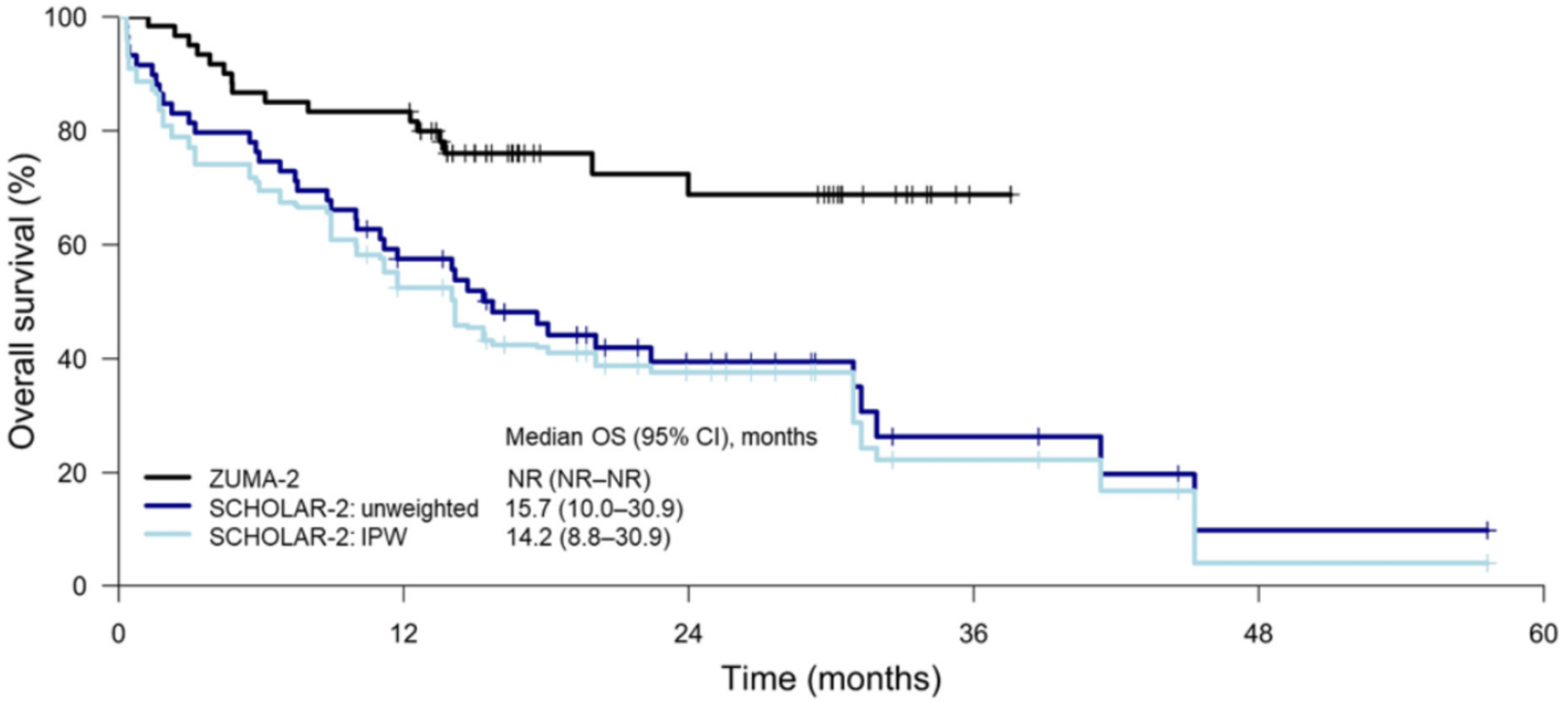
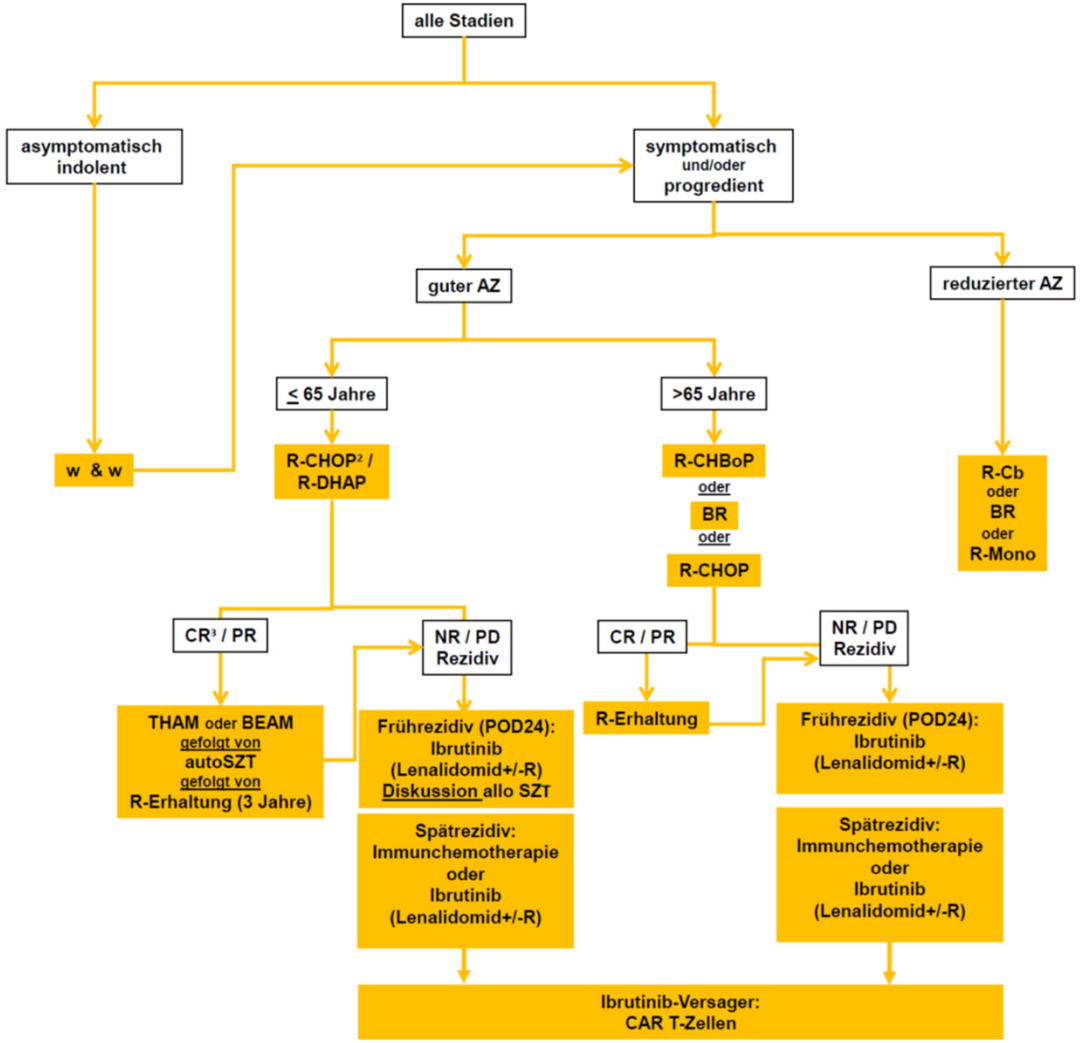


Number at risk (number censored)

ZUMA-2	60 (0)	50 (0)	19 (25)	1 (43)	0 (44)	0 (44)
SCHOLAR-2 (unweighted)	59 (0)	32 (2)	15 (10)	5 (17)	1 (19)	0 (20)
SCHOLAR-2 (IPW)	59 (0)	30 (1)	15 (8)	4 (16)	0 (18)	0 (19)

Mantelzell-Lymphom: Oncopedia 2021



Haben Sie Fragen zu diesem Thema?

Schreiben Sie uns!

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Die Kurzpräsentationen sind online unter

www.lymphome.de/icml2021

Für den Inhalt verantwortlich:

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