Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

ASH 2020 VIRTUAL
5. – 8. Dezember 2020

KML-Experten berichten vom ASH 2020 VIRTUAL

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Indolente Lymphome (iNHL)

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

Offenlegung potentieller Interessenskonflikte

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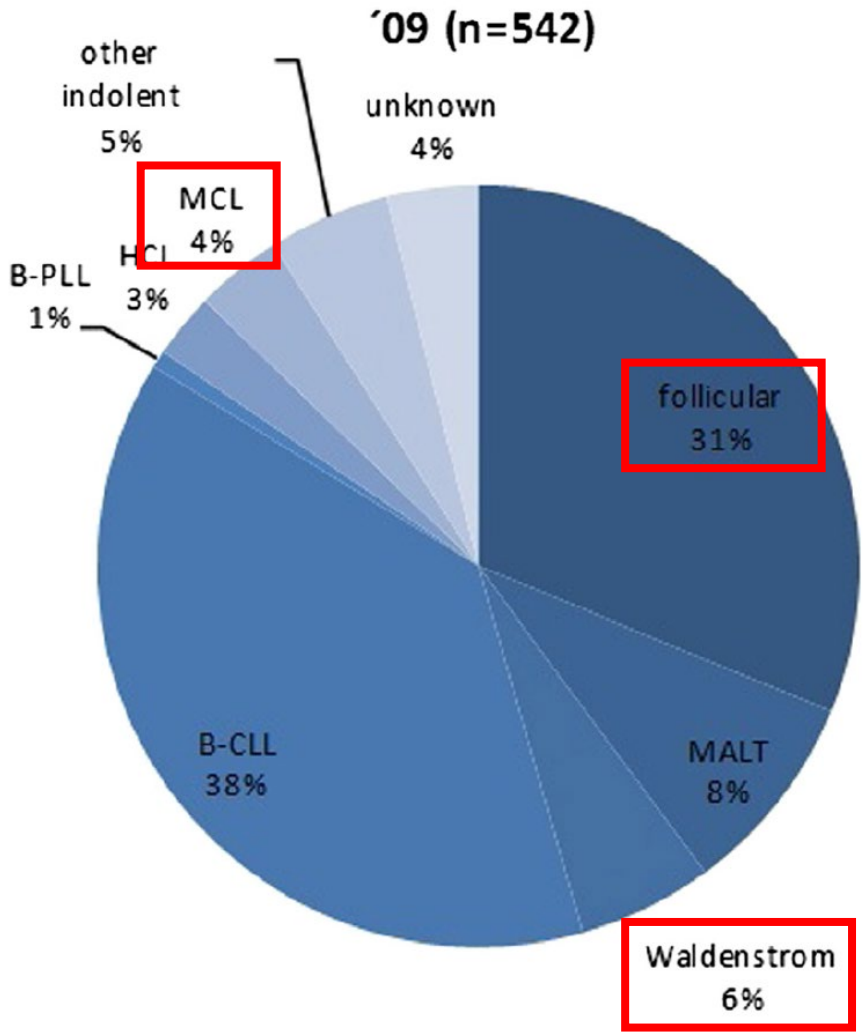
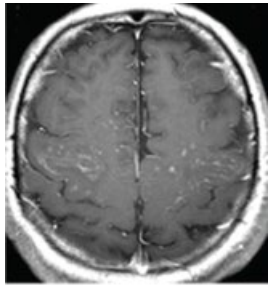
Indolent Lymphoma
Frequency of subtypes



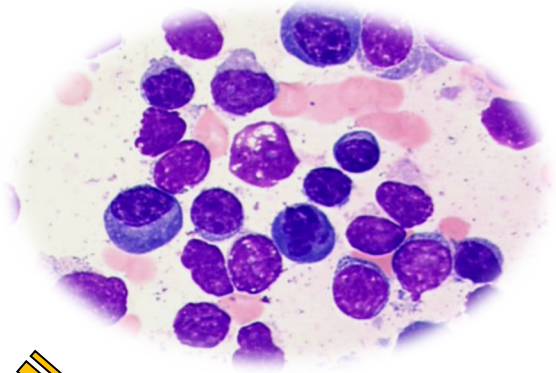
Schmidt, Leuk Lymph 2014

Morbus Waldenstroem
Clinical characteristics

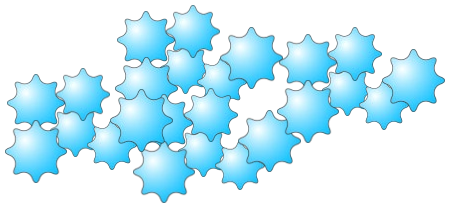
↓Hb>>> ↓PLT> ↓WBC



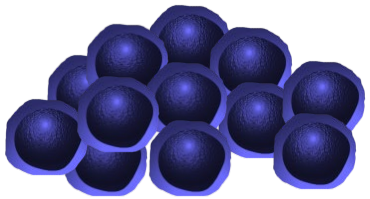
Bing-Neel



BM

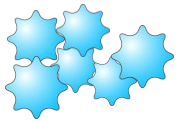


Symptomatic
Hyperviscosity
IgM >5,0g/l
Viscosity > 4,0 cp



Lymphadenopathy
Splenomegaly
≤20% firstline
50-60% Relapse

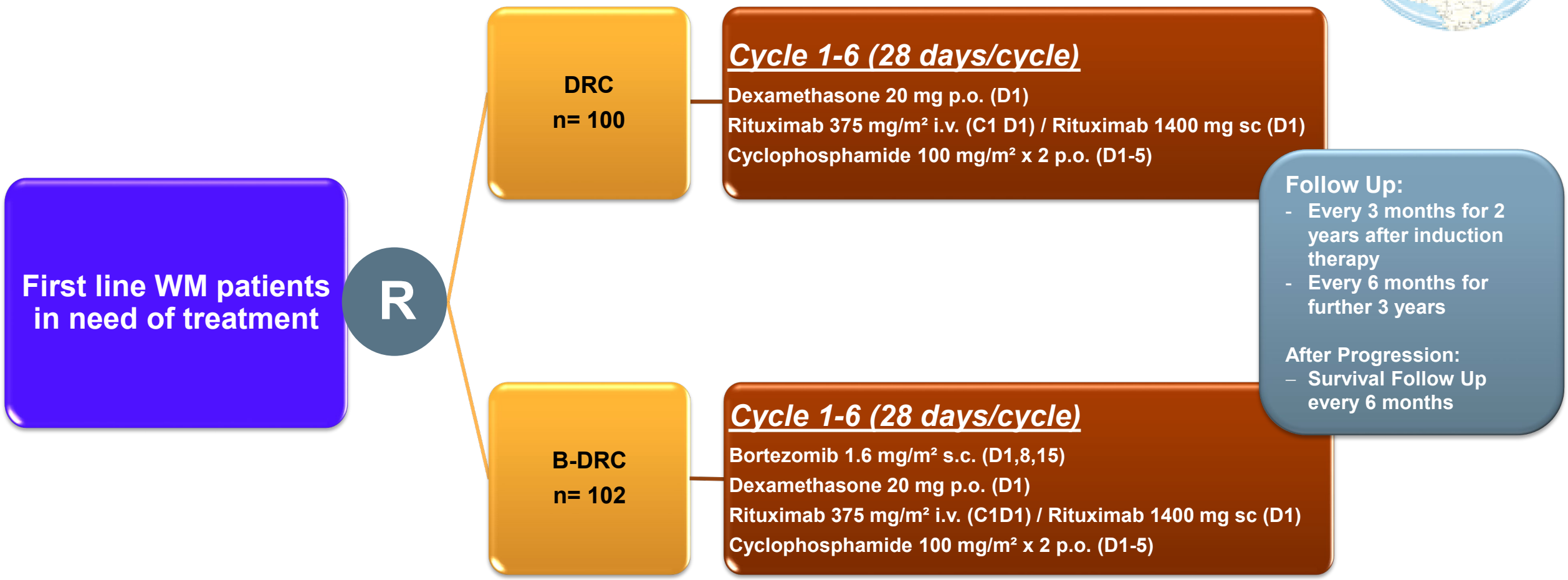
Hepcidin
↓ IDA



IgM Neuropathy (22%)
Cryoglobulinaemia (10%)
Cold agglutinimaemia(5%)

Treon, Hematol Oncol 2013

ECWM-1 Study Design



Randomized Phase II

Endpoints: PFS, response rates, OS, safety

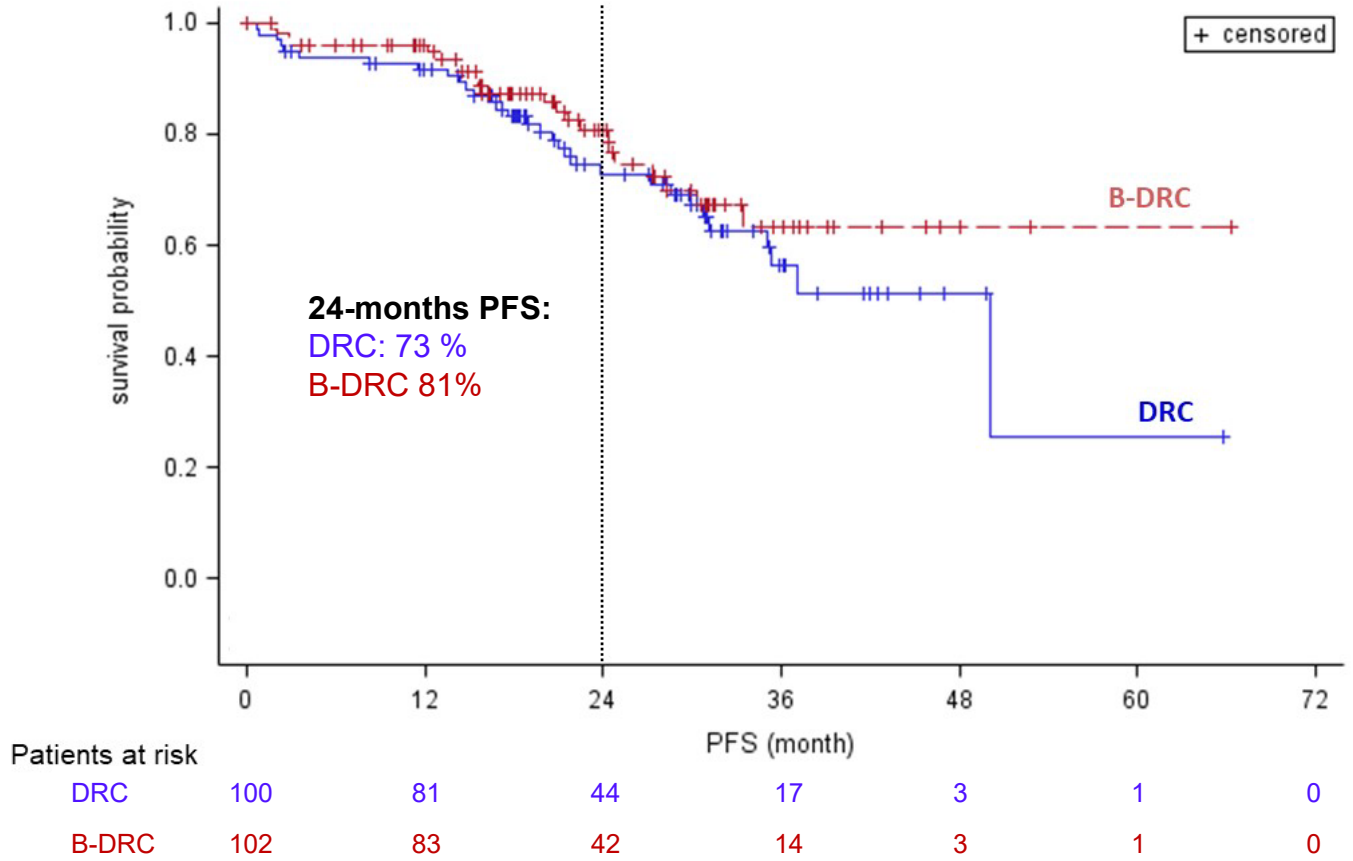
Buske, ASH 2020

Safety Profile

Event Prefered Term n (%)	Total (n=202)	DRC (n=100)	B-DRC (n=102)
Infections (all grades)			
Upper respiratory infection	6 (3.0%)	1 (1%)	5 (4.9%)
Lung infection	1 (0.5%)	-	1 (0.9%)
Bronchial infection	10 (5.0%)	1 (1%)	9 (8.8%)
Infections (≥ 3 grade)			
Upper respiratory infection	1 (0.5%)	-	1 (0.9%)
Lung infection	1 (0.5%)	-	1 (0.9%)
Bronchial infection	1 (0.5%)	-	1 (0.9%)
Peripheral sensory neuropathy			
Grade 1-2	21 (10.4%)	3 (3%)	18 (17.6%)
Grade 3	2 (1%)	-	2 (2.0%)

Buske, ASH 2020

Progression-Free Survival

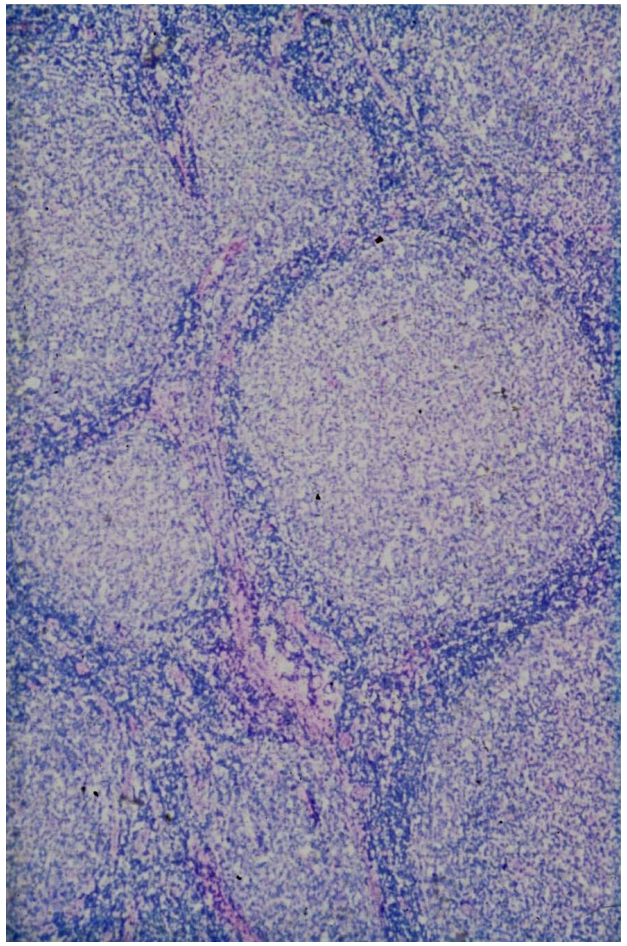


Median follow-up was 27.5 months at the time of the data cut.

	DRC	B-DRC
Median PFS, months (95% CI)	50.1 (31.2-n.a.)	n.a. (33.5-n.a.)
HR (95% CI)	0.759 (95% CI: 0.439; 1.311)	
Logrank p-value	P=0.32	

Buske, ASH 2020

Follicular lymphoma
Clinical characteristics



- about 25% of lyymphoma
- Median age 60-65 years
- 85% advanced stage III/IV
- Indolent clinical course (median survival 15-20 years)
- In relapse still sensitive to therapy

Follicular lymphoma
Clinical course

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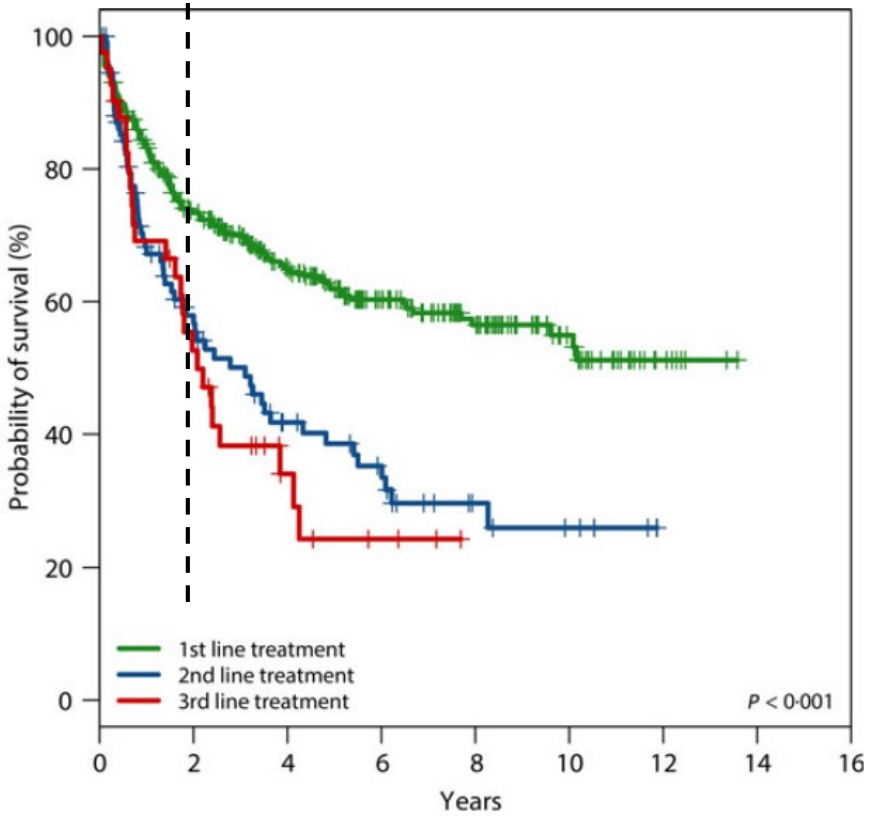
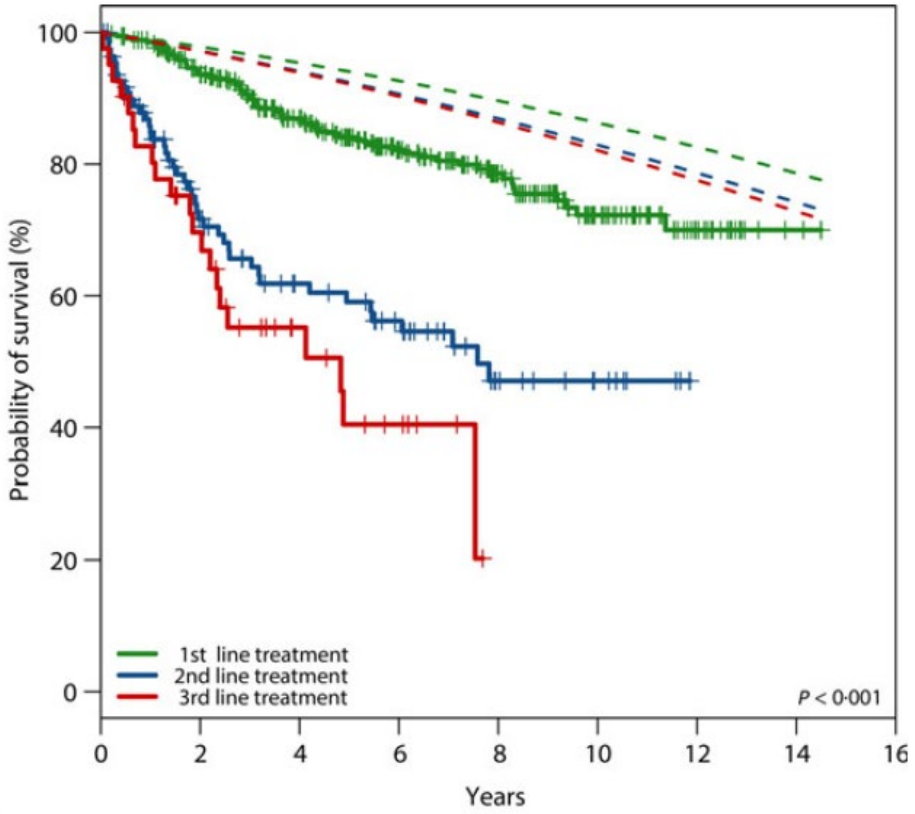
Response duration



Overall survival



Rivas-Delgado, Br J Haematol. 2019

Follicular lymphoma
Immunotherapy

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- **Car T-lymphocytes**

  (Chimeric antigen-receptor)

- **bispecific antibodies**

- **checkpoint inhibitors**

Cytokine Release Syndrome

Parameter	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
CRS, n (%)[a]			
Any grade	97 (78)	22 (100)	119 (82)
Grade ≥ 3	8 (6)	2 (9)	10 (7)
Most common symptoms of any grade, n/n (%)			
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)
AE management, n (%)			
Tocilizumab	56 (45)	15 (68)	71 (49)
Corticosteroids	19 (15)	6 (27)	25 (17)
Median time to onset (range), days	4 (1 – 15)	4 (1 – 9)	4 (1 – 15)
Median duration of events (range), days	6 (1 – 27)	6 (2 – 14)	6 (1 – 27)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]

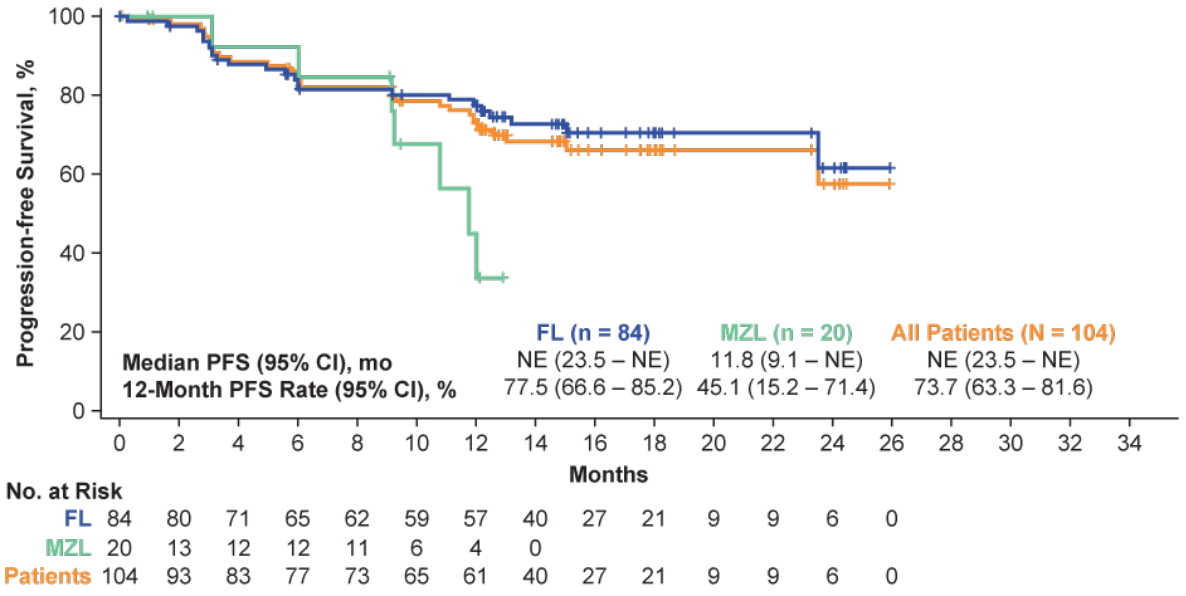
- Grade 4 and Grade 5 CRS occurred in 1 patient each
- No patients had ongoing CRS as of the cutoff date[b]

Placeholder for video recording

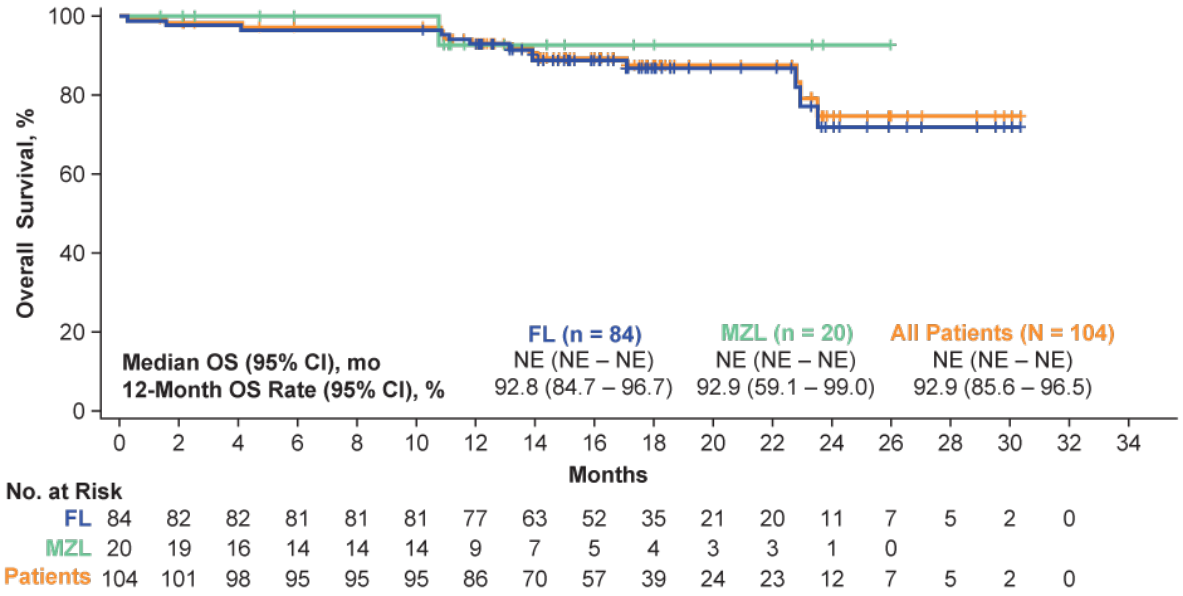
[a] CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. [b] One patient with FL died of multisystem organ failure in the context of CRS (Day 7) prior to the resolution of CRS.
AE, adverse event; CRS, cytokine release syndrome; FL, follicular lymphoma; MZL, marginal zone lymphoma.

Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival



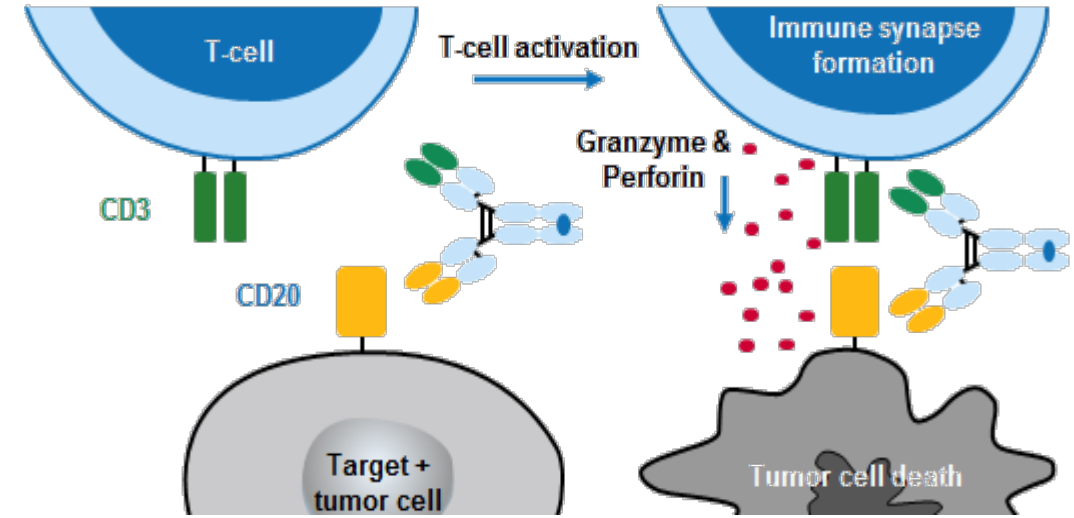
- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients

Placeholder for video recording

Introduction

- Follicular lymphoma (FL) remains an incurable disease despite available therapies
- Patients with FL having received ≥2 prior systemic therapies typically have a poor prognosis[1]
- High-risk subgroups include patients who:
  - Have progression of disease within 24 months of frontline treatment (POD24)[2]
  - Are refractory to both a prior anti-CD20 antibody and an alkylating agent (double refractory)
- Mosunetuzumab is a full-length, fully humanized immunoglobulin G1 CD20xCD3 bispecific antibody that redirects T cells to engage and eliminate malignant B cells

Mosunetuzumab mechanism of action

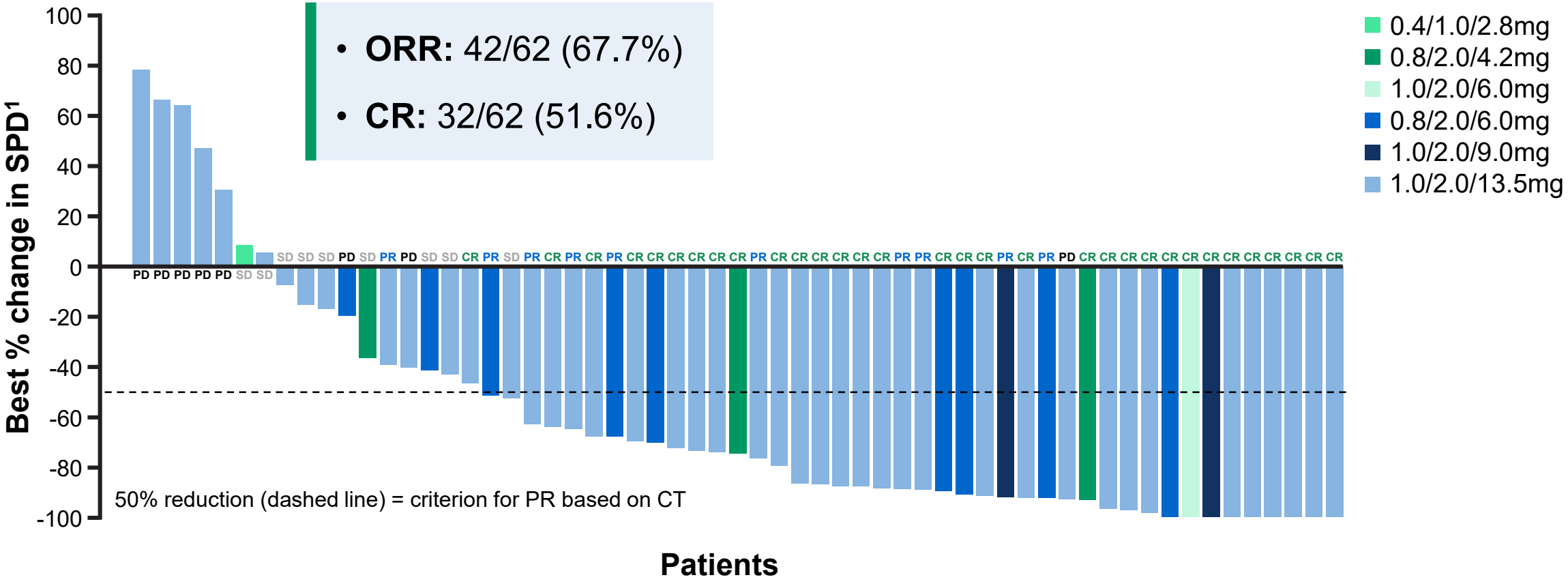


Here, we present updated clinical data from 62 patients with relapsed/refractory (R/R) FL treated with mosunetuzumab after ≥2 prior systemic therapies

(NCT02500407; Clinical cut-off date: August 07, 2020)

1. Batlevi CL, et al. Blood Cancer Journal 2020;10(7):74; 2.Casulo C, et al. Blood 2017;133(14):1540–47.

Mosunetuzumab antitumor activity in patients with R/R FL across dose levels



Assouline, ASH 2020

1. Cheson BD, et al. J Clin Oncol 2007; 25(5):579–86.

Follicular lymphoma
Bispecific antibodies: Toxicity

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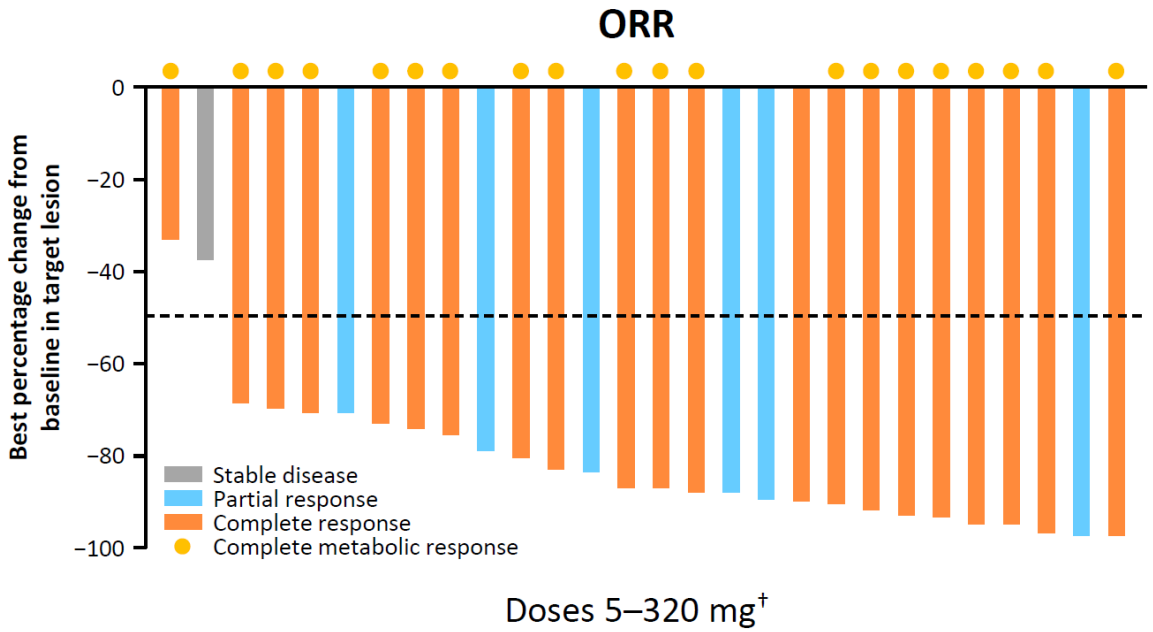
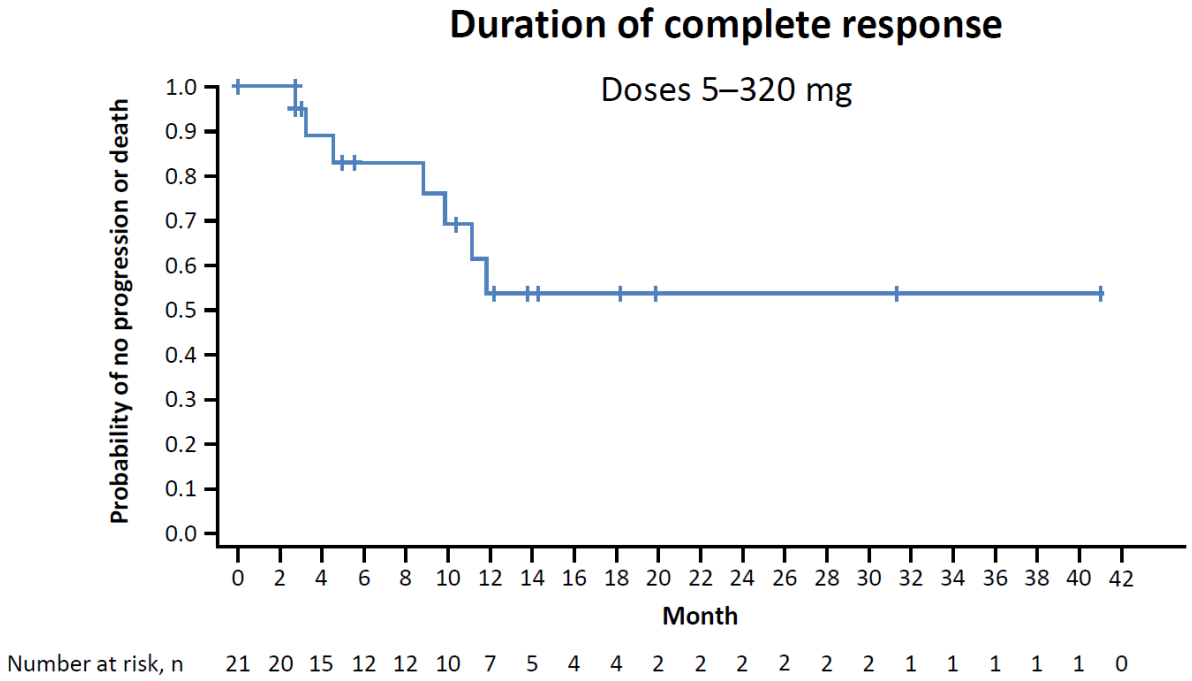
TEAE of special interest, n (%)		DLBCL (N=78)		FL Gr 1–3a (N=38)		Other B-NHL (N=20)		Total (N=136)	
		Initial/ int. dose	Full dose	Initial/ int. dose	Full dose	Initial/ int. dose	Full dose	Initial/ int. dose	Full dose
CRS	Gr 3	4 (5.1)	0 (0)	0 (0)	1 (2.6)	4 (20.0)	0 (0)	8 (5.9)	1 (0.7)
	Gr 4	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.0)	0 (0)	1 (0.7)	0 (0)
ICANS-like	Gr 3	2 (2.6)	1 (1.3)	0 (0)	0 (0)	1 (5.0)	1 (5.0)	3 (2.2)	2 (1.5)
	Gr 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TLS	Gr 3	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.0)	0 (0)	1 (0.7)	0 (0)
	Gr 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Gr 5	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.0)	0 (0)	1 (0.7)	0 (0)

Bannerji, ASH 2020

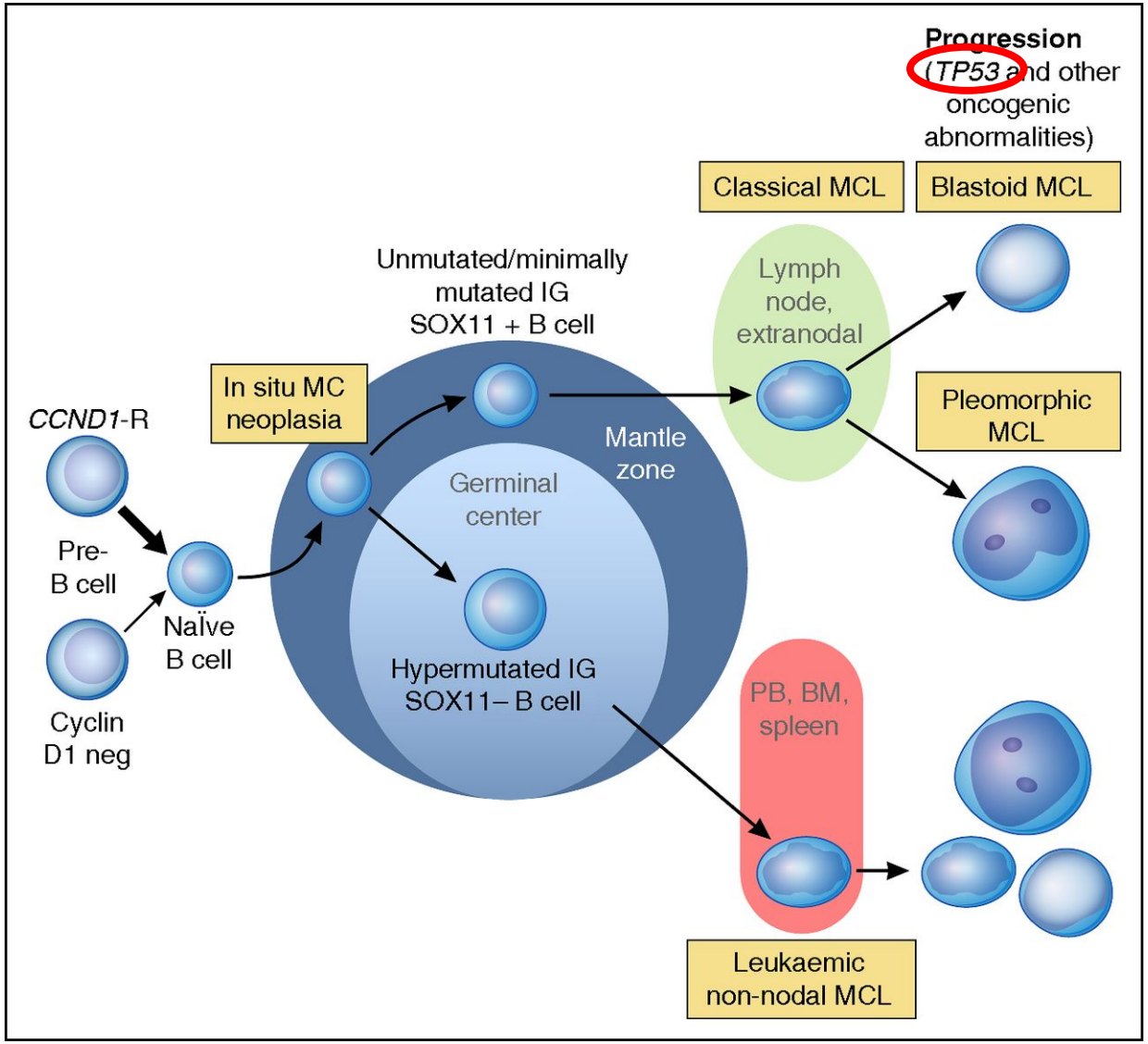
Follicular lymphoma
Bispecific antibodies: Efficacy





Bannerji, ASH 2020

Mantle cell lymphoma
Spectrum of disease



Dreyling, ESMO CR 2017

Mantle cell lymphoma
Therapeutic algorithm

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young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR, R-BAC) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (R-BAC, BR) or targeted approaches ↓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ↓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

Dreyling, ESMO CR MCL 2017 (updated)

LOXO-305 Safety Profile

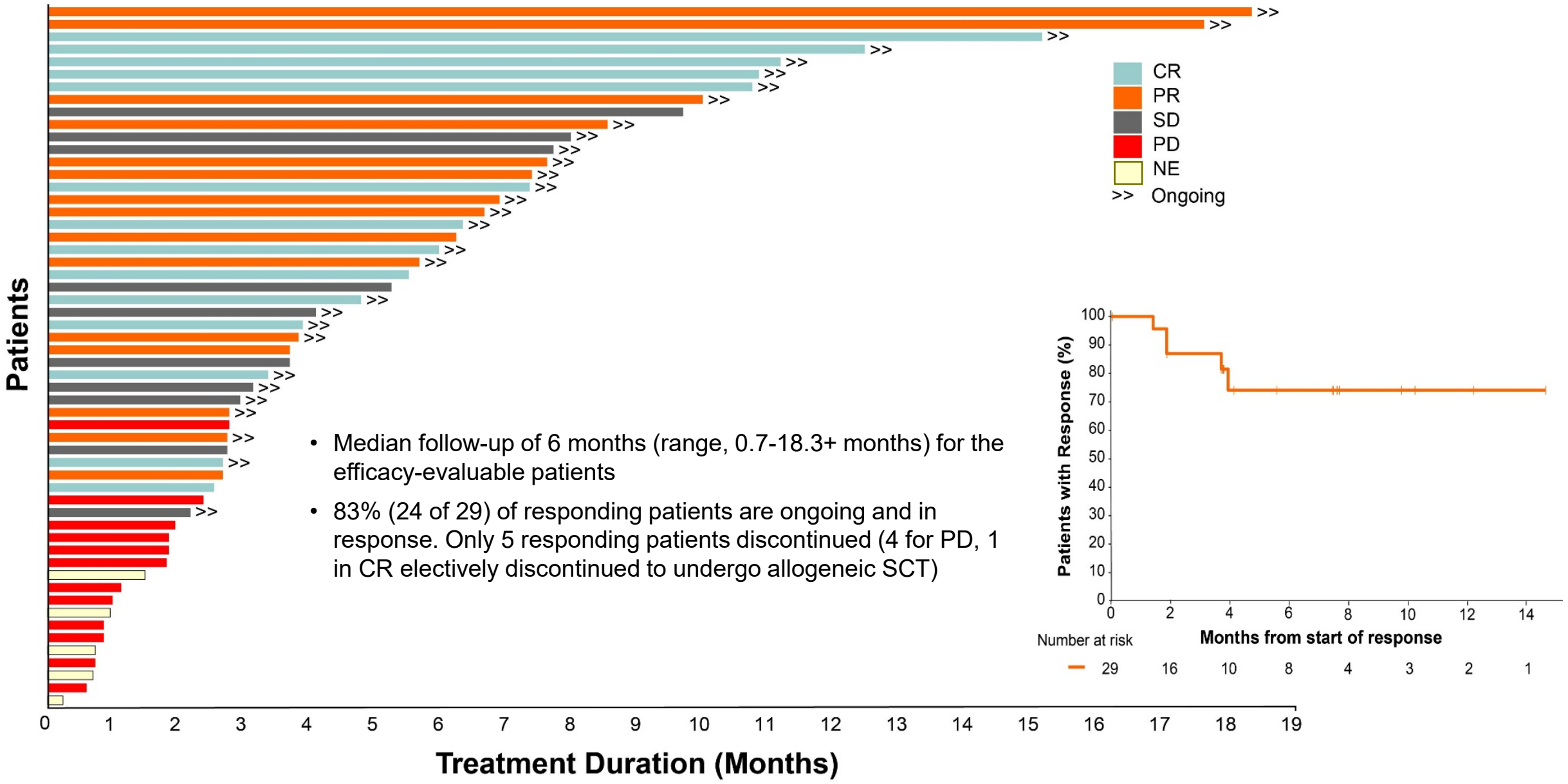
All doses and patients (n=323)							
	Treatment-emergent AEs, (≥10%), n (%)[a]					Treatment-related AEs, n (%)	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs of special interest[b,c]							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)[d]	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter	-	2 (<1%)[e]	-	-	2 (<1%)	-	-

No DLTs reported and MTD not reached
5 of 323 patients (1.5%) discontinued due to treatment-related AEs
200mg QD selected as recommended Phase 2 dose

Data cutoff date of 27 September 2020. Total % may be different than the sum of the individual components due to rounding. [a]The AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular. [d]Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. [e]Both events considered by investigators as unrelated to LOXO-305 due to a history of prior atrial fibrillation in each.

Wang, ASH 2020

LOXO-305 Treatment Duration in Mantle Cell Lymphoma

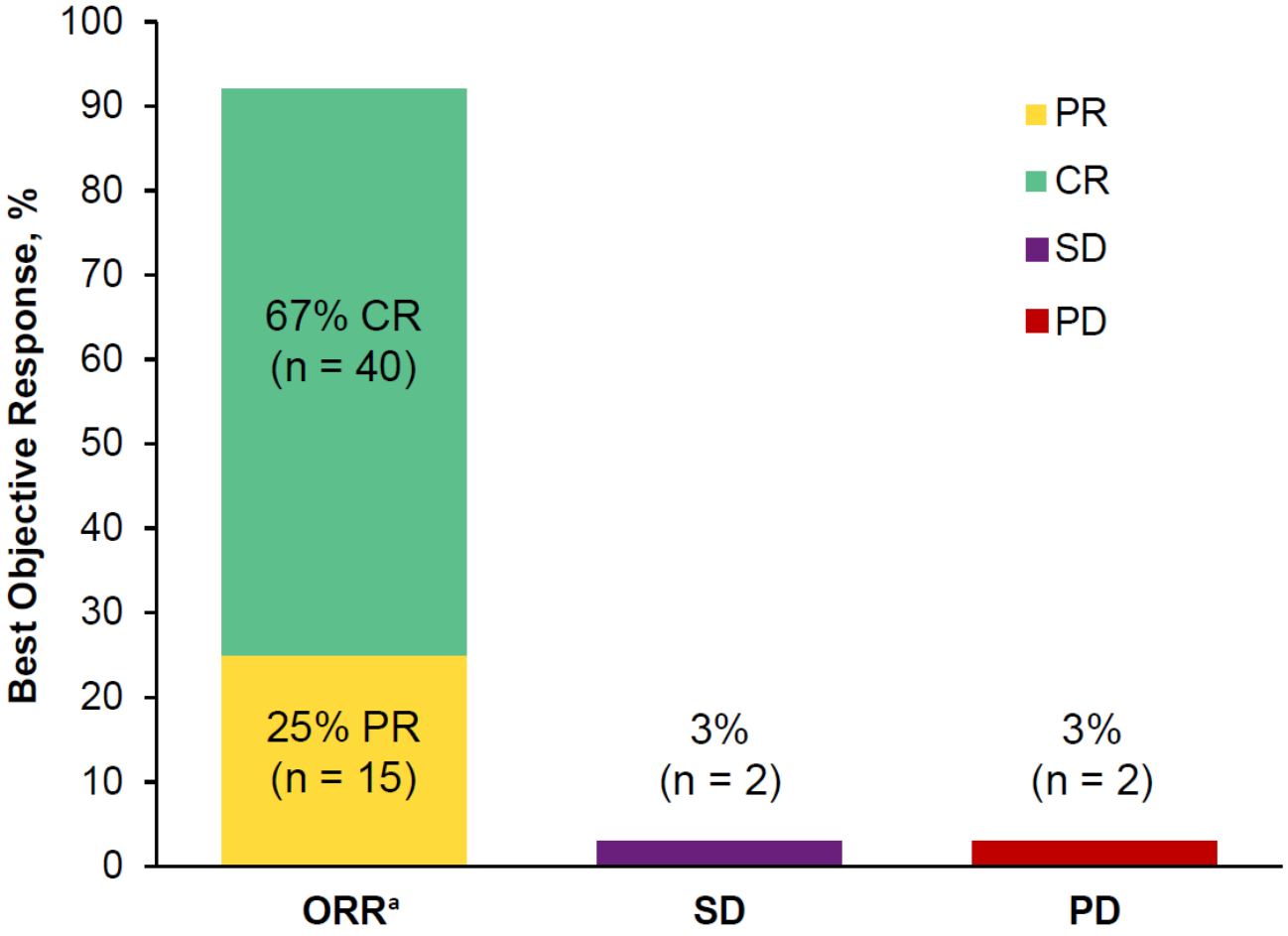


- Median follow-up of 6 months (range, 0.7-18.3+ months) for the efficacy-evaluable patients
- 83% (24 of 29) of responding patients are ongoing and in response. Only 5 responding patients discontinued (4 for PD, 1 in CR electively discontinued to undergo allogeneic SCT)

Data cutoff date of 27 September 2020.

Wang, ASH 2020

CAR T-Zellen im MCL
Ansprechraten



Wang, ASH 2020

- At a median follow-up of 17.5 months (range, 12.3 – 37.6), 29 of 60 evaluable patients (48%) remain in ongoing responses
  - 28 of 40 patients who achieved CR (70%) remain in response
- The first 28 patients treated had a median follow-up of 32.3 months (range, 30.6 – 37.6)
  - 39% of patients remain in continued remission with no further therapy
- In all enrolled patients (N = 74), ORR was 84% (59% CR rate)

CAR T-Zellen im MCL
Überlebensraten

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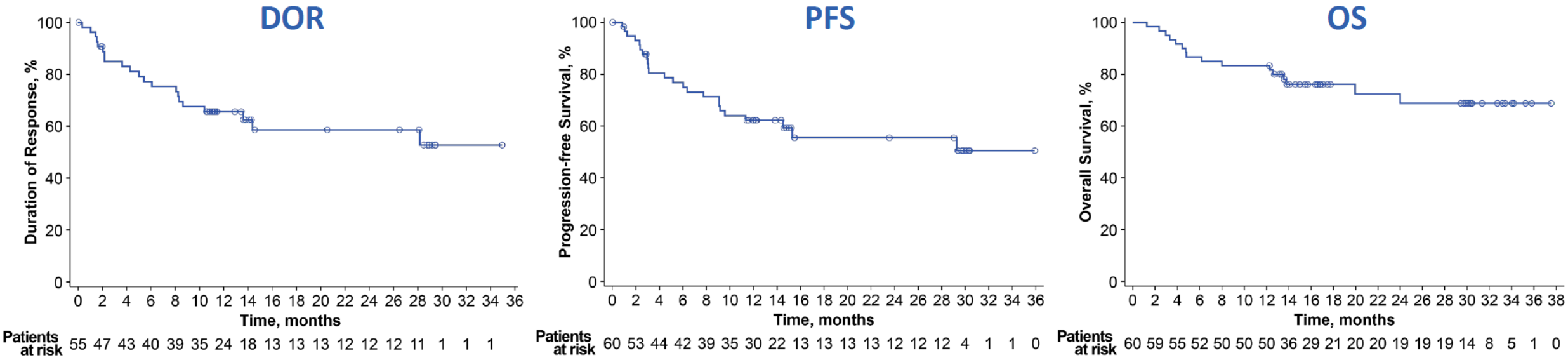
- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months



Wang, ASH 2020

European MCL Network
Study generation 2020/21

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< 65 years	> 60 years	> 65 years	
MCL younger: R-CHOP/DHAP =>ASCT R-CHOP+I/DHAP =>ASCT => I R-CHOP+I/DHAP => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	BR +/- Ibrutinib ⇒ Rituximab M +/- Ibrutinib	*MCL elderly 3:* BR (+ Ibrutinib) vs R-Ibrutinib/Venetoclax

Relapse

Ibrutinib/ Bortezomib	R-HAD +/- Bortezomib	Ibrutinib +/- ABT-199

Indolente Lymphome
Take home messages 2020/21

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- **Waldenstroem:**
  - R-Chemo weiterhin Standard in der Firstline,
    (Ibrutinib-(R) im Frührezidiv)

- **Follikuläres Lymphom:**
  - in Hochrisikopatienten: bispezifische AK, CAR T-Zellen

- **Mantelzell-Lymphom:**
  - LOXO-305 : hohe Wirksamkeit in BTK-Versagern
  - CAR T-Zellen: Zulassung 2021 in BTK-Versagern ?

European MCL Network
Acknowledgements

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Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2020

Für den Inhalt verantwortlich:

Prof. Dr. med. Martin Dreyling

Medizinische Klinik III • Klinikum der Universität München

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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5. – 8. Dezember 2020

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