



**64th ASH Meeting 2022**  
**New Orleans & virtuell**

# Lymphom Kompetenz KOMPAKT



**KML KONGRESSE**

Expert:innen berichten zu  
Lymphomen & Leukämien



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Uniklinik Köln

# Follikuläre Lymphome (FL)

# Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2021 wird in Kooperation mit sechs unterstützenden Firmen durchgeführt.  
Meine persönlichen Disclosures betreffen:

<b>Anstellungsverhältnis, Führungsposition</b>	Oberarzt, Uniklinik Köln
<b>Beratungs-/ Gutachtertätigkeit</b>	Roche, BMS, Incyte, EUSA, AbbVie, Novartis, Gilead, Miltenyi Biotec
<b>Besitz von Geschäftsanteilen, Aktien oder Fonds</b>	entfällt
<b>Patent, Urheberrecht, Verkaufslizenz</b>	entfällt
<b>Honorare</b>	Roche, Incyte, EUSA, Sandoz, Novartis, BeiGene
<b>Finanzierung wissenschaftlicher Untersuchungen</b>	Roche, Gilead, Incyte, Sandoz
<b>Andere finanzielle Beziehungen</b>	entfällt
<b>Immaterielle Interessenkonflikte</b>	entfällt

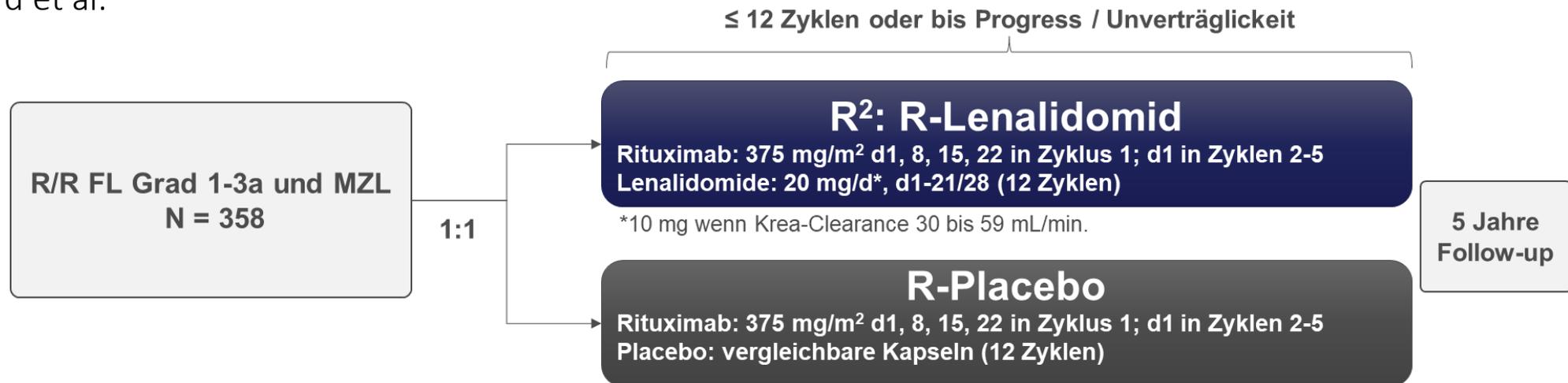
# Kapitel 1

Stellenwert von Rituximab und Lenalidomid („R<sup>2</sup>“) beim rezidierten follikulären Lymphom

# Five-Year Results and Overall Survival Update from the Phase 3 Randomized Study AUGMENT: Lenalidomide plus Rituximab (R<sup>2</sup>) vs Rituximab plus Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

## Abstract # 230

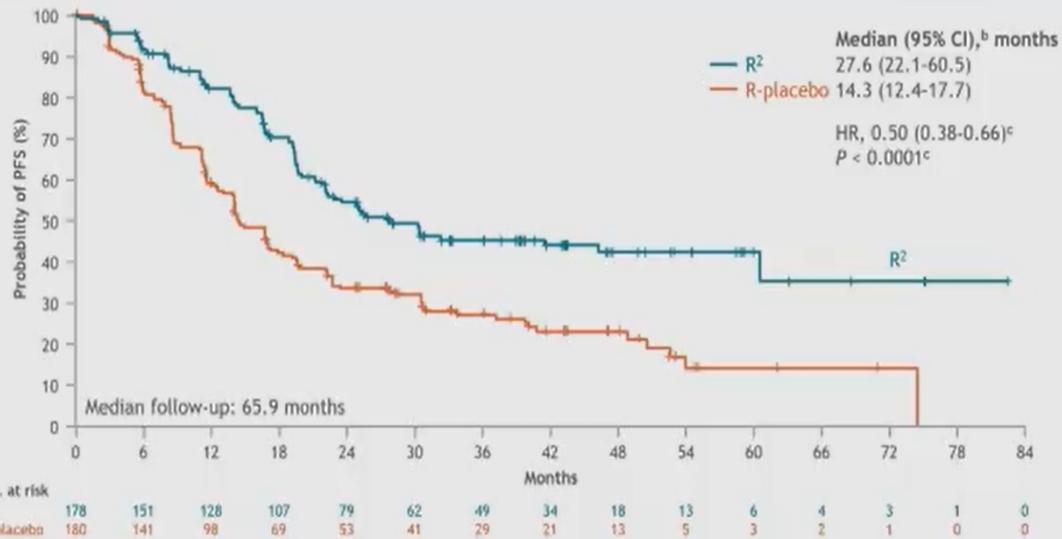
J.P. Leonard et al.



- **Primärer Endpunkt:** PFS (IRC)
- **Sekundäre Endpunkte:** ORR, CR, DOR, OS, EFS, TTNLT

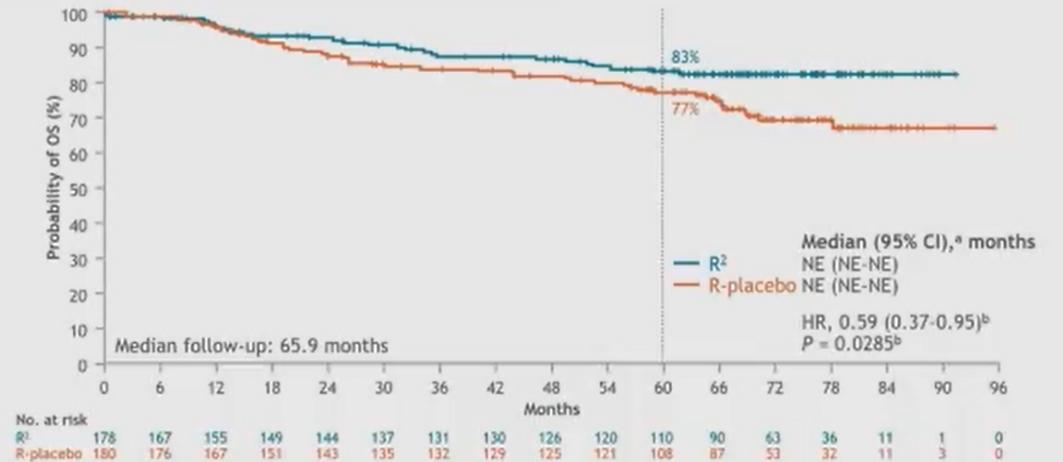
# AUGMENT: Überlebenskurven

## Progression-free survival<sup>a</sup> (ITT population)



- Median PFS was 27.6 months for R<sup>2</sup> versus 14.3 months for R-placebo (HR, 0.50; P < 0.0001)

## Overall survival (ITT population)



- Although median OS was not reached for either arm, there was an improvement in OS with R<sup>2</sup> compared with R-placebo (HR, 0.59; P = 0.0285)
  - 5-year OS rates for R<sup>2</sup> versus R-placebo were 83.2% and 77.3%, respectively

41% der Patienten mit R<sup>2</sup> und 61% der Patienten in der Kontrollgruppe erhielten mindestens eine nachfolgende Lymphomtherapie.

# AUGMENT: Nebenwirkungen

## Treatment-emergent adverse events (safety population)

Patients with TEAE, n (%)	R <sup>2</sup> (n = 176)	R-placebo (n = 180)
<b>Any-grade TEAE</b>	174 (99)	173 (96)
Any-grade TEAE related to lenalidomide or placebo	159 (90)	118 (66)
Any-grade TEAE related to rituximab	134 (76)	105 (58)
<b>Grade 3/4 TEAE<sup>a</sup></b>	121 (69)	58 (32)
Grade 3/4 TEAE related to lenalidomide or placebo	101 (57)	38 (21)
Grade 3/4 TEAE related to rituximab	57 (32)	20 (11)
<b>Grade 5 TEAE<sup>a,b</sup></b>	2 (1)	2 (1)
<b>Serious any-grade TEAE</b>	45 (26)	25 (14)
Any-grade TEAE related to lenalidomide or placebo	23 (13)	8 (4)
Any-grade TEAE related to rituximab	13 (7)	4 (2)

- Grade 3/4 TEAEs were more common in patients who received R<sup>2</sup> versus R-placebo (69% vs 32%); the most common was neutropenia (R<sup>2</sup>, 50%; R-placebo, 13%)
- The updated overall safety profile of both arms was consistent with the primary analysis, with no new safety signals detected<sup>1</sup>

# Kapitel 2

## Bispezifische Antikörper beim rezidierten folliculären Lymphom

# Subcutaneous Epcoritamab with Rituximab + Lenalidomide in Patients with Relapsed or Refractory Follicular Lymphoma: Phase 1/2 Trial Update

## Abstract # 609

L. Falchi et al.

### Key inclusion criteria

- R/R CD20<sup>+</sup> FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria<sup>1</sup>
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: September 16, 2022  
Median follow-up: 6.4 mo

Agent	Treatment Regimen Epcoritamab SC 48 mg + R <sup>2</sup>						
	C1	C2	C3	C4	C5	C6–C12	C13+
Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
Rituximab IV 375 mg/m <sup>2</sup>	QW	Q4W	Q4W	Q4W	Q4W		
Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

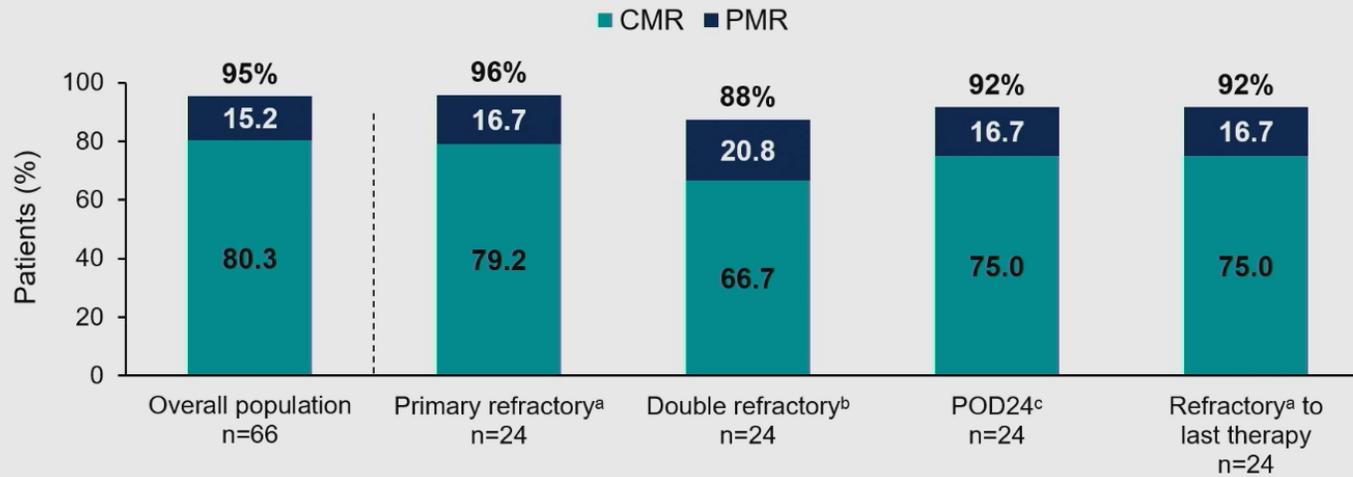
Primary objective: Safety and antitumor activity<sup>b</sup>

# EPCORE NHL-2 Arm2b: Patientencharakteristika

Demographics and Disease Characteristics	Total N=76	Treatment History	Total N=76
Median age, y (range)	64 (30–79)	Median time from diagnosis to first dose, mo (range)	59 (4–331)
Female, n (%)	37 (49)	Median time from end of last line of therapy to first dose, mo (range)	16 (0.2–198)
Ann Arbor stage, n (%)		Median number of prior lines of therapy (range)	1 (1–9)
II	12 (16)	1 prior line, n (%)	41 (54)
III	19 (25)	2 prior lines, n (%)	21 (28)
IV	45 (59)	≥3 prior lines, n (%)	14 (18)
Histologic grade, n (%) <sup>a</sup>		Primary refractory <sup>c</sup> disease, n (%)	29 (38)
1	6 (8)	Double refractory <sup>d</sup> disease, n (%)	30 (39)
2	37 (49)	POD24 <sup>e</sup> , n (%)	32 (42)
3A	24 (32)	Refractory <sup>c</sup> to last line of therapy, n (%)	29 (38)
FLIPI, n (%) <sup>b</sup>		Prior ASCT, n (%)	8 (11)
0–1	7 (9)	Prior CAR T, n (%)	2 (3)
2	24 (32)		
3–5	39 (51)		
ECOG PS, n (%)			
0	48 (63)		
1	25 (33)		
2	3 (4)		

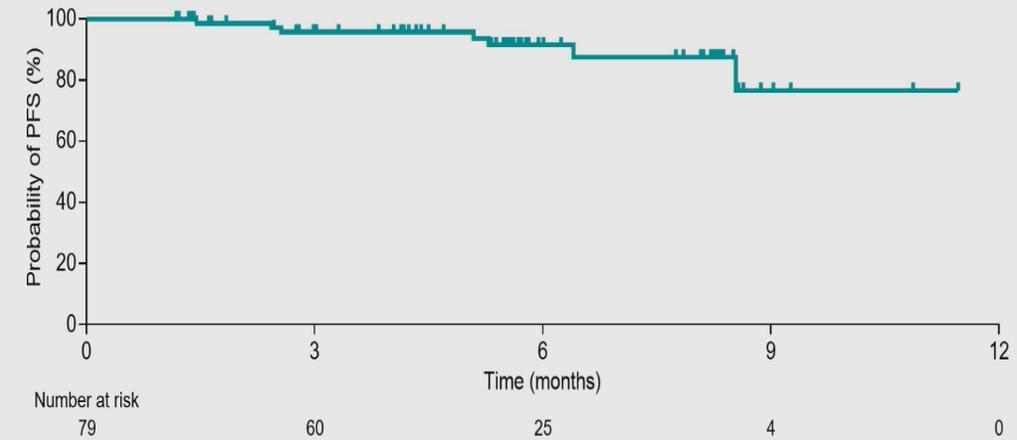
# EPCORE NHL-2 Arm2b: Ansprechen und PFS

## Responses Across High-risk Subgroups



Deep responses consistent across high-risk R/R FL subgroups

## Progression-Free Survival

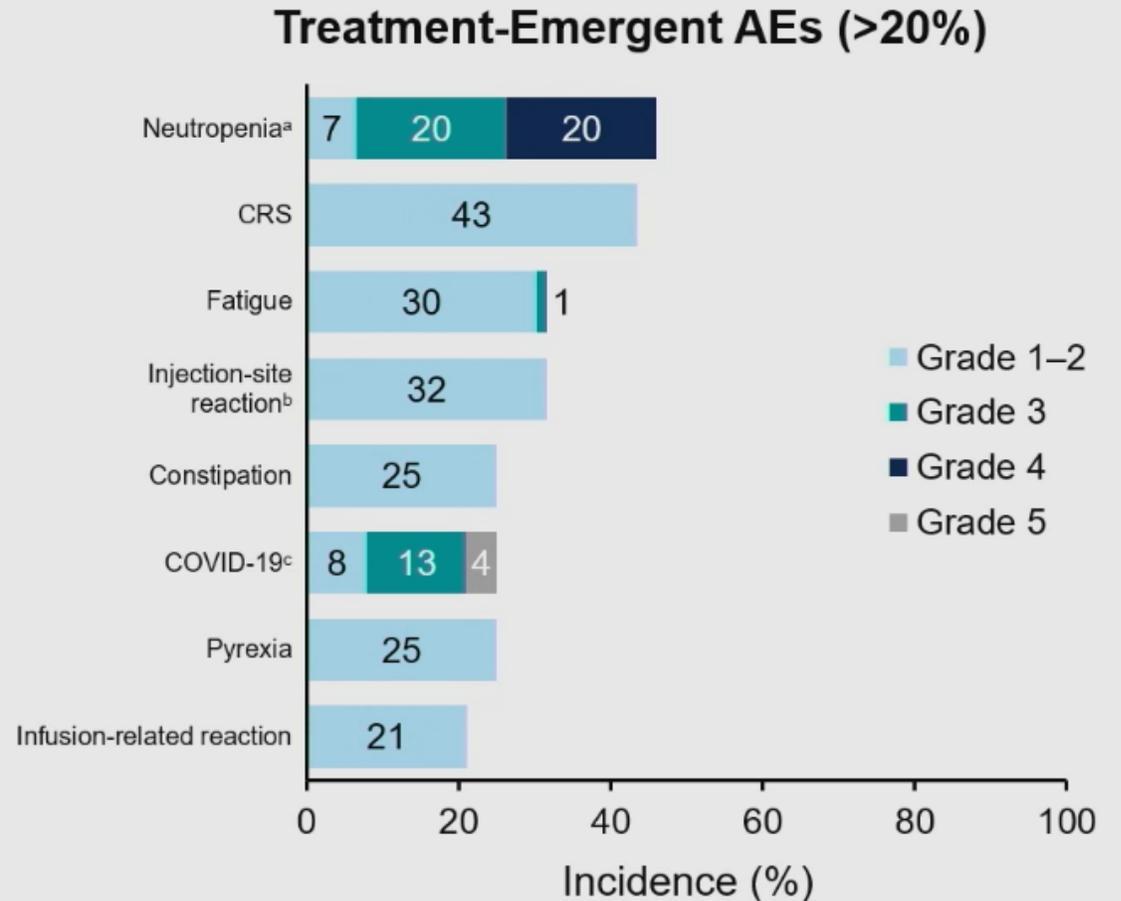


Median PFS not reached (95% CI, 8.5–not reached)

# EPCORE NHL-2 Arm2b: Nebenwirkungen

	Total N=76
Median number of epcoritamab cycles initiated (range)	6 (1–11)
Grade $\geq 3$ TEAE, n (%)	53 (70)
Related to epcoritamab	29 (38)
Fatal TEAE (all COVID-19), n (%)	3 (4)
Epcoritamab dose delay due to TEAE, n (%)	40 (53)
Related to epcoritamab	19 (25)
Epcoritamab discontinuation due to TEAE, n (%)	5 (7)
Related to epcoritamab	0

- No clinical tumor lysis syndrome was observed
- One patient experienced ICANS (grade 1), which resolved in 7 days



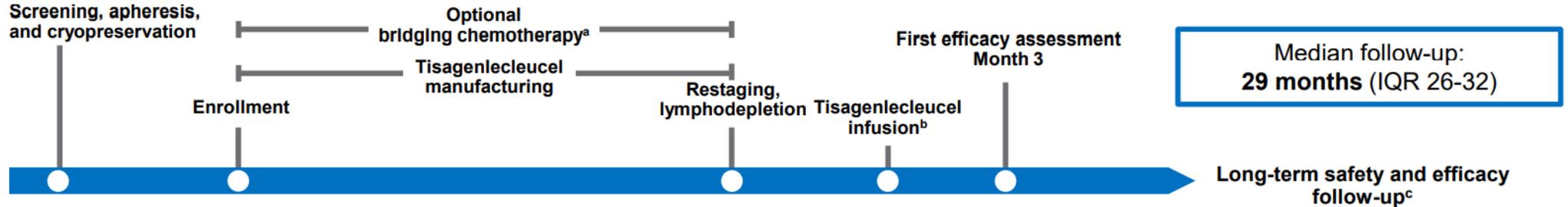
# Kapitel 3

## CAR-T-Zelltherapie beim rezidivierten folliculären Lymphom

# Long-Term Clinical Outcomes and Correlative Efficacy Analyses in Patients with Relapsed/Refractory Follicular Lymphoma Treated with Tisagenlecleucel in the ELARA Trial

## Abstract # 608

M. Dreyling et al.



Key eligibility criteria	Study treatment	End points
<ul style="list-style-type: none"> <li>• ≥18 years of age</li> <li>• FL grade 1, 2, or 3A</li> <li>• Relapsed/refractory disease<sup>d</sup></li> <li>• No evidence of histological transformation/FL3B</li> <li>• No prior anti-CD19 therapy or allogeneic HSCT</li> </ul>	<p>Tisagenlecleucel dose range (single IV infusion) was 0.6-6×10<sup>8</sup> CAR-positive viable T cells</p>	<p><b>Primary:</b> CRR by IRC</p> <p><b>Secondary:</b> ORR, DOR, PFS, OS, safety, cellular kinetics</p>

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- 18% (17/97) of patients received tisagenlecleucel in the outpatient setting

# ELARA: Therapieansprechen

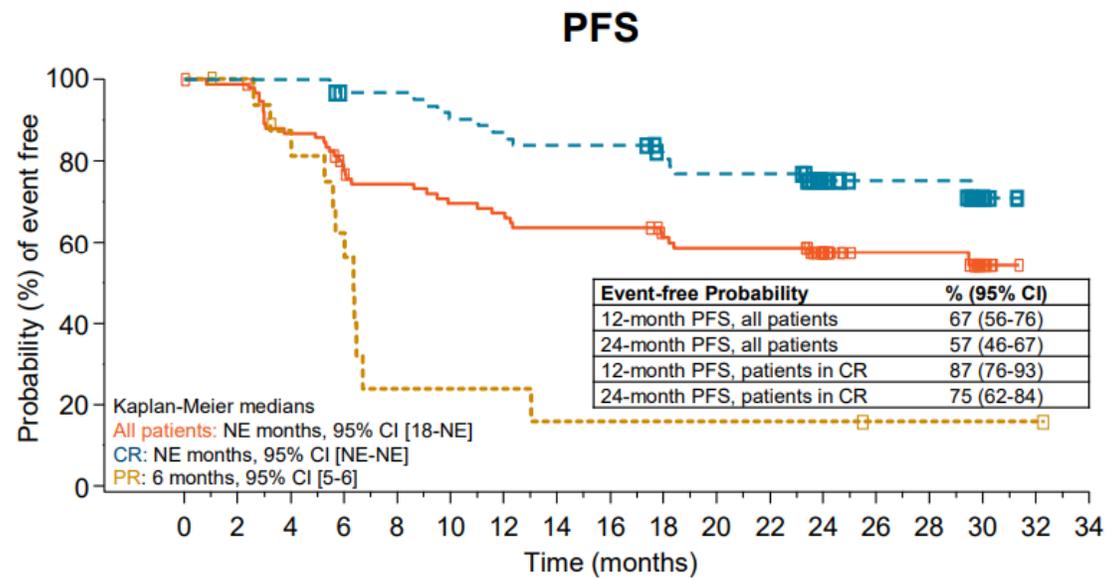
Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR <sup>a</sup>	68 (58-77) <sup>b</sup>
ORR <sup>c</sup>	86 (78-92) <sup>b</sup>

- High ORR (86%) and CRR (68%) are consistent with the primary analysis<sup>1</sup>

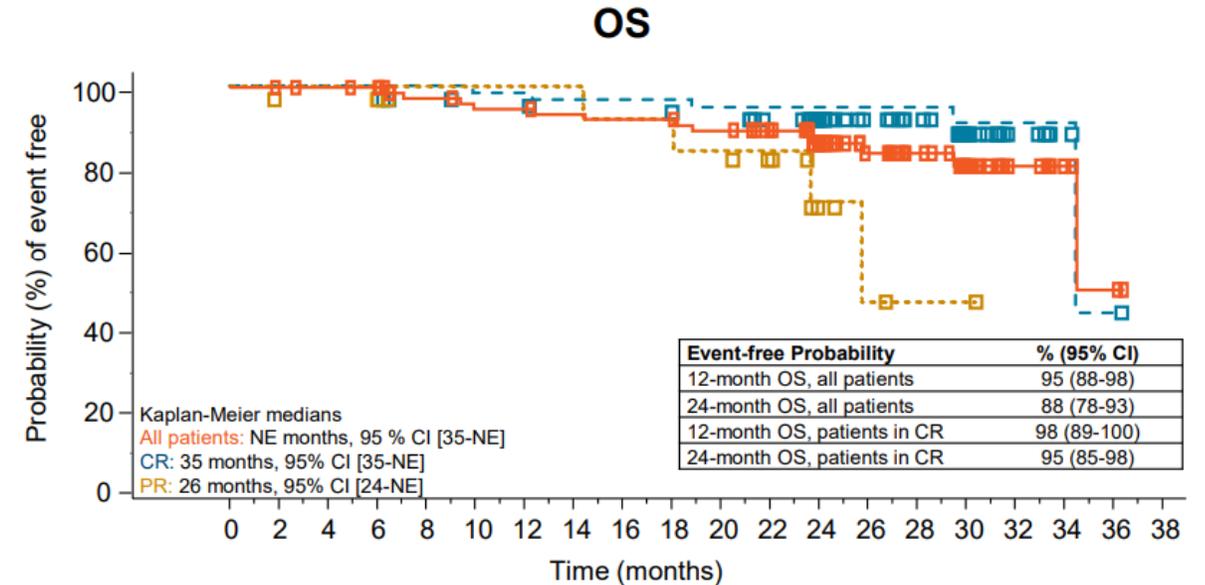
Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume <sup>d</sup>	20 (21)	40 (19-64)	75 (51-91)
Bulky disease <sup>e</sup>	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

- High rates of durable responses were observed in most patients in high-risk disease subgroups who have poor prognosis with current non-CAR-T cell therapies

# ELARA: Überlebenskurven



Number of patients still at risk	
All patients (N=94)	94 91 78 67 63 59 57 54 54 49 47 47 32 19 19 6 0 0
CR (N=64)	64 64 64 61 60 56 54 52 52 47 45 45 31 18 18 5 0 0
PR (N=17)	17 16 13 5 3 3 3 2 2 2 2 1 1 1 1 0 0



Number of patients still at risk	
All patients (N=94)	94 93 92 91 84 81 81 79 78 78 75 69 55 38 32 19 9 4 2 0
CR (N=64)	64 64 64 64 62 60 60 58 58 58 56 52 45 32 27 16 7 3 1 0
PR (N=17)	17 16 16 16 13 13 13 12 12 11 9 4 2 1 1 0 0 0 0

Das mediane PFS und OS wurde bisher nicht erreicht.

# ELARA: Nebenwirkungen

Selected Adverse Events Anytime Post Infusion	Safety Analysis Set <sup>a</sup> (N=97)	
	All Grade, n (%)	Grade ≥3, n (%)
Number of patients with at least 1 AE	73 (75)	45 (46)
CRS <sup>b,c</sup>	47 (49)	0
Hematological disorders including cytopenias	45 (46)	43 (44)
Neutropenia	23 (24)	23 (24)
Anemia	13 (13)	7 (7)
Thrombocytopenia	6 (6)	5 (5)
Infections	16 (17)	9 (9)
Hypogammaglobulinemia	11 (11)	1 (1)
Serious neurological adverse events	8 (8)	2 (2)
ICANS	4 (4)	1 (1)
Encephalopathy	3 (3)	1 (1)
Dyskinesia	1 (1)	0
Muscular weakness	1 (1)	0
Tremor	1 (1)	0
Deaths >30 days post infusion		13 (13) <sup>d</sup>
Deaths during the long-term follow-up		3 (3) <sup>e</sup>

- **No new safety signals** were reported in this long-term analysis
- One patient developed HLH >1 year after receiving tisagenlecleucel<sup>f</sup>
- Rate of all-grade neurological events was 12% and 3% were grade ≥3<sup>g</sup>
- The 17 (18%) patients who received tisagenlecleucel in the outpatient setting required no ICU care or hospitalization for AE management
- Twenty-two patients (23%) received ≥1 new antineoplastic medication after tisagenlecleucel, mostly due to stable disease or progressive disease

# ELARA: Correlative Efficacy Analyses

Mit einem ungünstigem PFS waren assoziiert:

- Hohes „tumor burden“ (TMTV  $\geq 510\text{cm}^3$ )
- POD24
- > 4 befallenen Lymphknotenstationen
- $\geq 3\%$  „LAG3+ exhausted“ T-Zellen im Microenvironment
- Hohe Serumspiegel von IL-10
- Hohe Serumspiegel von TNF- $\alpha$

# Kapitel 4

PI3-Kinaseinhibitoren und BTK-Inhibitoren beim rezidivierten follikulären Lymphom

# Safety and Efficacy of the PI3K $\delta$ Inhibitor Zandelisib in Combination with the BTK Inhibitor Zanubrutinib in Patients with Relapsed/Refractory Follicular Lymphoma or Mantle Cell Lymphoma

## Abstract # 78

J.D. Soumerai et al.

### Key Eligibility Criteria

- $\geq 18$  years
- FL Grade I-IIIa or MCL
- $\geq 1$  prior therapy
- Adequate organ function
- No cytopenias unless due to disease:
  - ANC  $\geq 1.0 \times 10^9/L$
  - Platelet count  $>75,000/mm^3$
  - Hemoglobin  $\geq 9.0$  g/dL
- No prior PI3Ki or BTKi

### ZANDELISIB Intermittent Dosing on RP2D 60 mg qd

**+ ZANUBRUTINIB 80 mg bid (half of approved dose)**

- Disease assessments after Cycles 2 and 6, then every 6 cycles thereafter
- Treatment continued until disease progression or intolerance

**Primary Objective:** Safety and tolerability  
**Efficacy Endpoints:** Investigator-assessed ORR (per Lugano criteria), DOR, and PFS

bid = twice daily; qd = once daily  
<sup>1</sup>Soumerai et al. EHA 2022. Abstr P1114

# Zandelisib/Zanubrutinib beim r/r FL: Patientencharakteristika

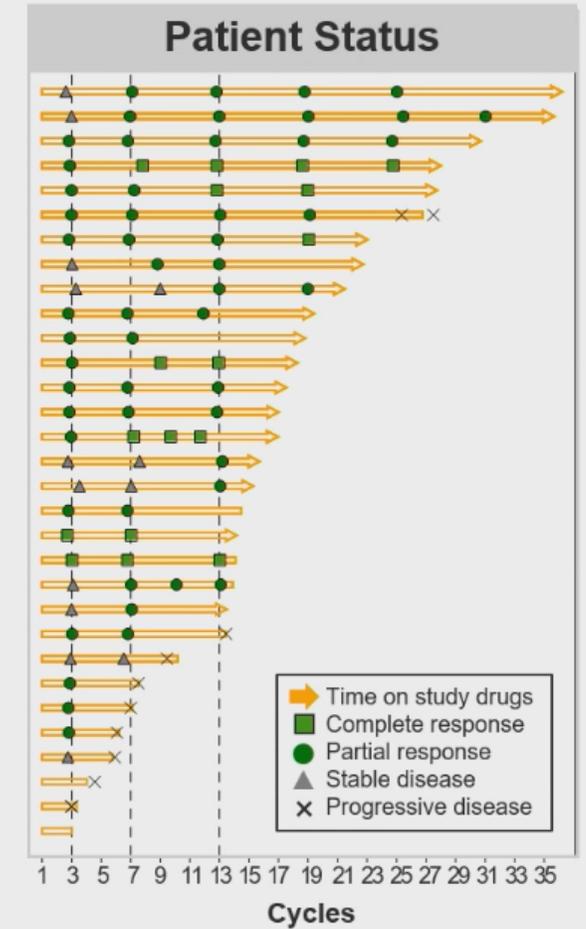
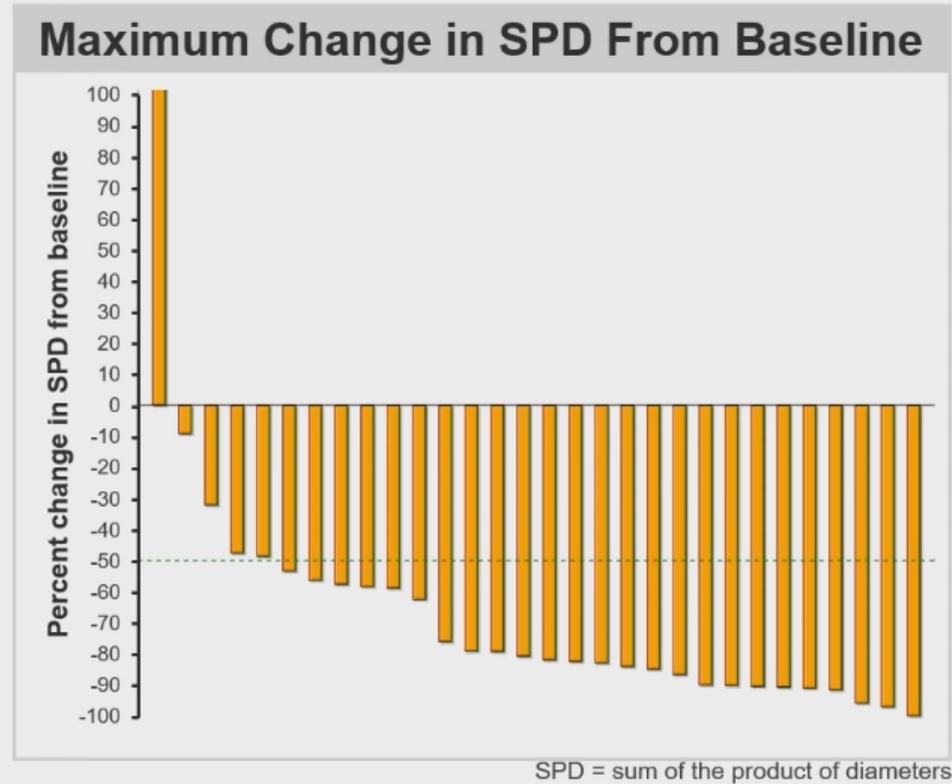
	<b>FL Patients (n=31)</b>	<b>MCL Patients (n=19)</b>
Age, median (range)	69 (40–83)	65 (52–78)
Male / female, %	54.8 / 45.2	73.7 / 26.3
Prior therapies, median (range)	2 (1–5)	1.5 (1–3)
Prior therapies, $\geq 2$ , n (%)	18 (58.1)	9 (47.4)
Refractory to last prior therapy, n (%)	6 (19.4)	9 (47.4)
Refractory to rituximab, n (%)	9 (29.0)	9 (47.4)
Prior ASCT, n (%)	1 (3.2)	2 (10.5)
<b>POD24</b>	<b>22 (71.0)</b>	<b>9 (47.4)</b>
Tumor bulk $\geq 50$ mm, n (%)	9 (29.0)	5 (26.3)

ASCT = autologous stem cell transplant; POD24, = progression of disease within 2 years of frontline chemoimmunotherapy

Data cutoff: 17 Oct 2022

# Zandelisib/Zanubrutinib beim r/r FL: Therapieansprechen

## Efficacy – Follicular Lymphoma

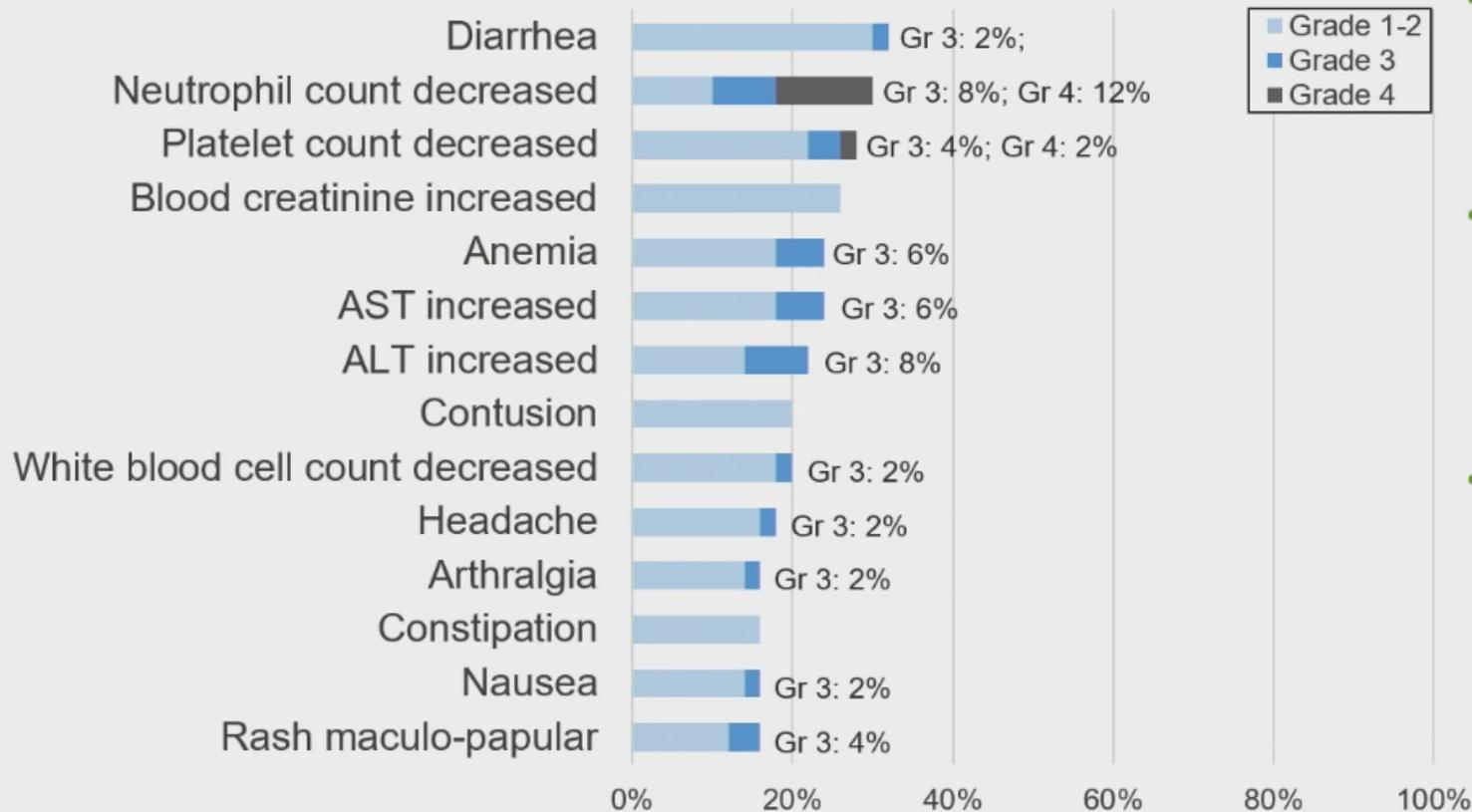


- Tumor reduction observed in 29 of 30 FL patients (97%) with post-baseline disease assessment

Data cutoff: 17 Oct 2022  
n=30 efficacy evaluable FL patients

# Zandelisib/Zanubrutinib beim r/r FL: Nebenwirkungen

## TEAEs in ≥15% of All Patients (N=50)



- Median follow-up time
  - 13.5 months (range, 1.8-32.4) for FL
  - 7.4 months (range, 1.9-20.9) for MCL
- 2 patients (4%) discontinued treatment due to treatment-related TEAEs
  - Neutrophil count decreased (n=1)
  - DRESS syndrome (n=1)
- 1 fatal Grade 5 TEAE due to COVID-19-related complications in 68-yo unvaccinated MCL patient who had one prior therapy (NORDIC)

Data cutoff: 17 Oct 2022

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRESS, Drug rash with eosinophilia and systemic symptoms

# Zusammenfassung | Take-Home-Messages

- Die 5-Jahres-Daten zu Lenalidomid plus Rituximab (R<sup>2</sup>) bestätigen den Stellenwert des Regimes als Standard in der Behandlung des rezidierten oder refraktären folliculären Lymphoms.
- Die Kombination eines bispezifischen Antikörpers mit R<sup>2</sup> ist gut verträglich und führt zu einer weiteren Verbesserung der Prognose.
- Im längeren Verlauf zeigt die CAR-T-Zelltherapie ein stabiles Ansprechen mit gutem Sicherheitsprofil. Auch Hochrisiko-Patienten profitieren von dem Therapieansatz.
- Zandelisib plus Zanubrutinib ist eine gut verträgliche und effektive Kombination beim rezidierten/refraktären folliculären Lymphom mit dem Potential, einen weiteren Therapieansatz zu definieren.

Die Kurzpräsentationen sind online unter

**[www.lymphome.de/ash2022](http://www.lymphome.de/ash2022)**

Für den Inhalt verantwortlich:

Prof. Dr. med. Kai Hübel

Uniklinik Köln

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