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Das diffuse großzellige B-Zell-Lymphom (DLBCL): Aktuelle Therapiestrategien

Peter Borchmann

C-LWG

University Hospital Cologne

Disclosures

Advisory role or expert testimony:
Takeda Oncology, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Amgen

Honoraria:
Takeda Oncology, Novartis, Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Kite-Gilead, Incyte

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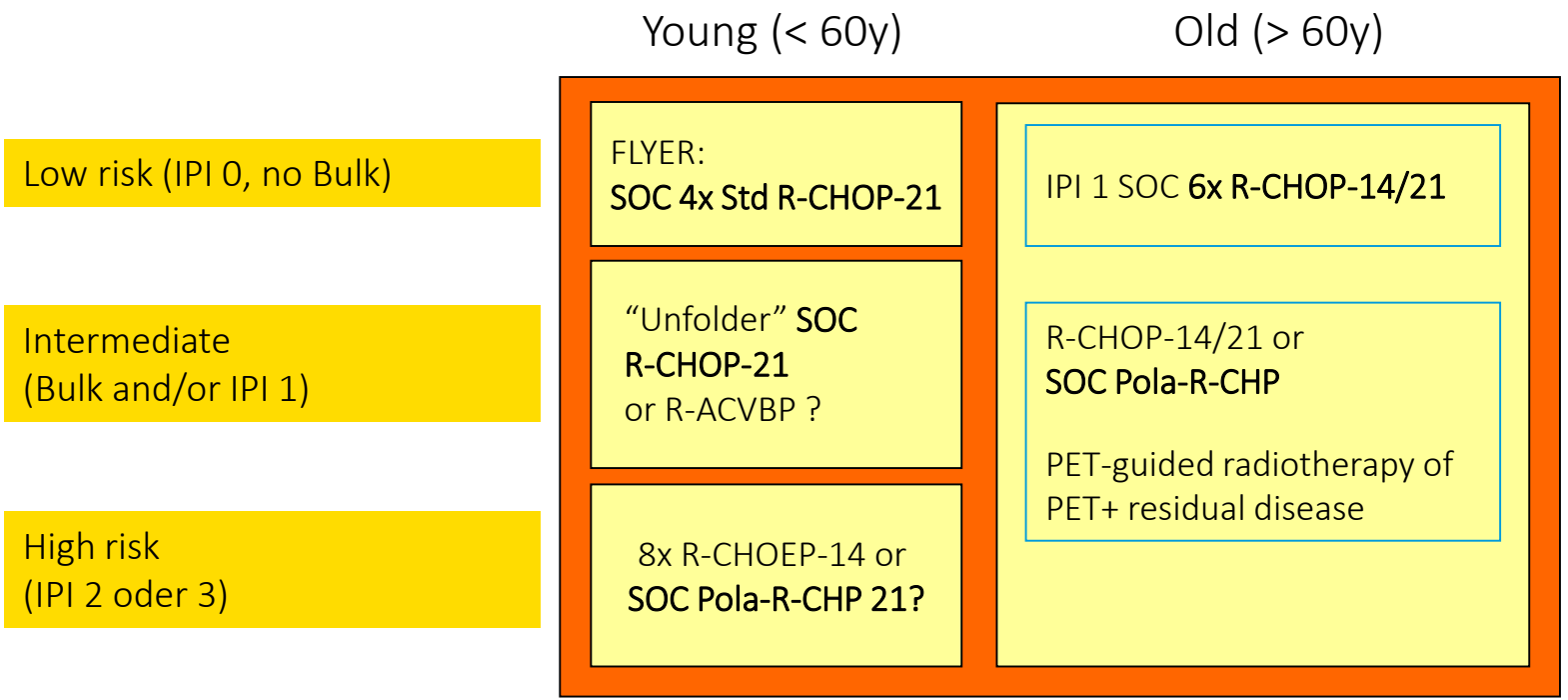
Takeda Oncology, MPI, Roche, Novartis, Merck Sharp & Dohme, Amgen

Das diffuse großzellige B-Zell-Lymphom (DLBCL): Aktuelle Therapiestrategien

1. Erstlinie
2. Zweitlinie
3. Nach der Zweitlinie
4. Perspektiven

Summary of the „German perspective“ (former DSHNHL, today GLA)



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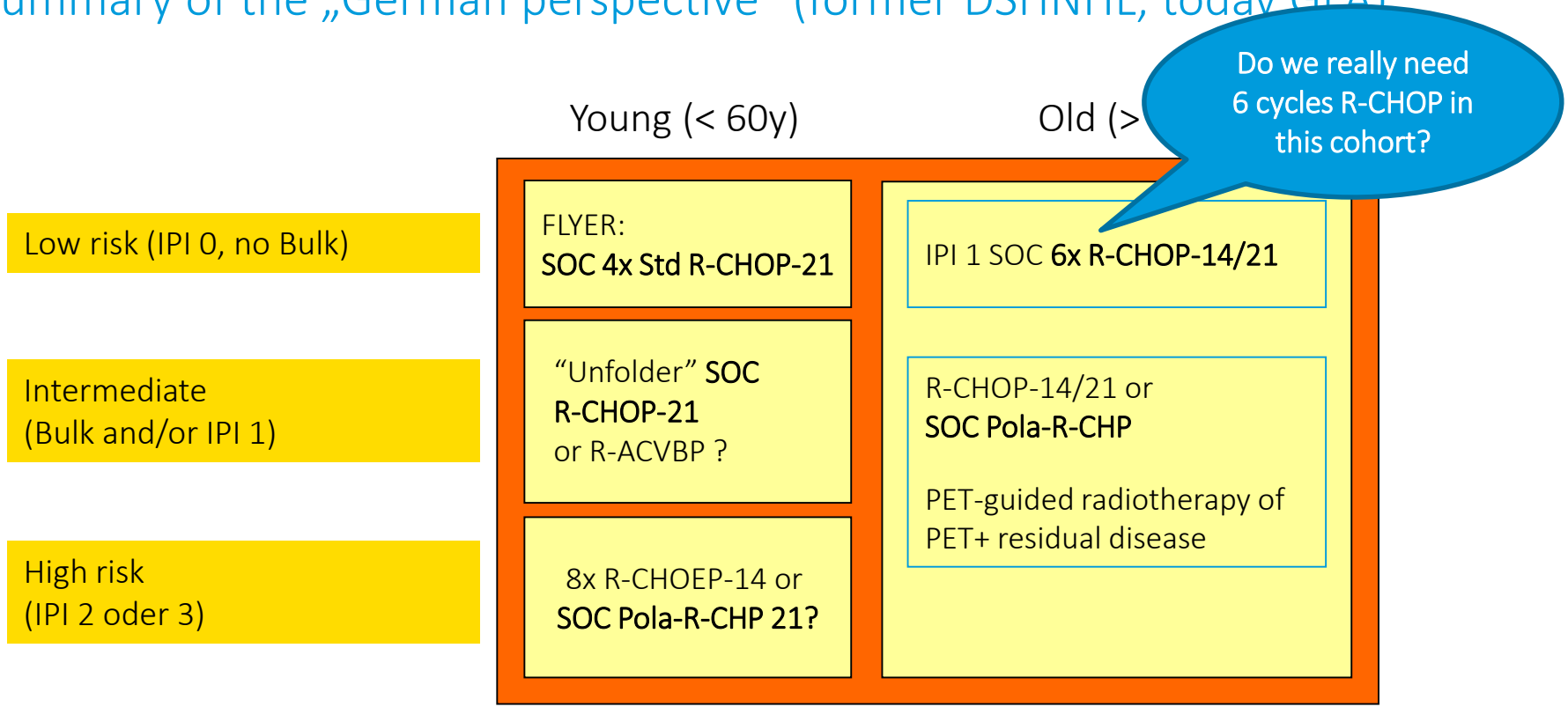
Summary of the „German perspective“ (former DSHNHL, today GLA)



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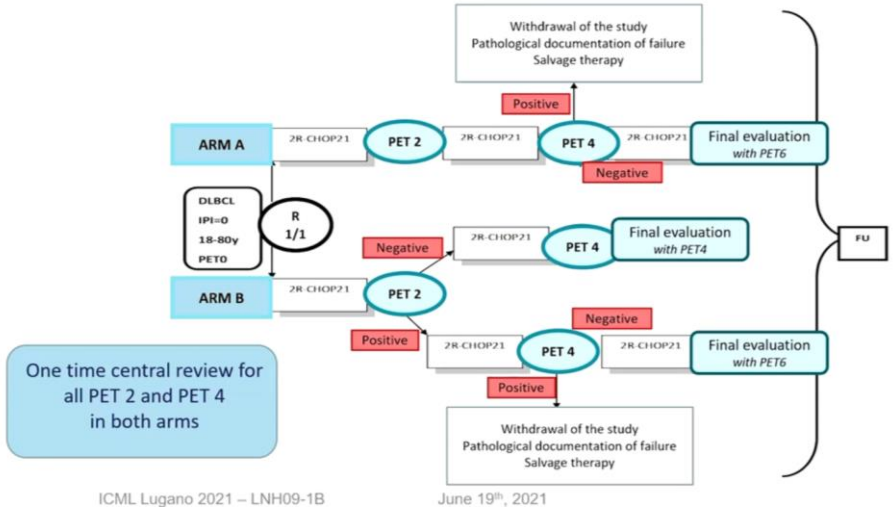
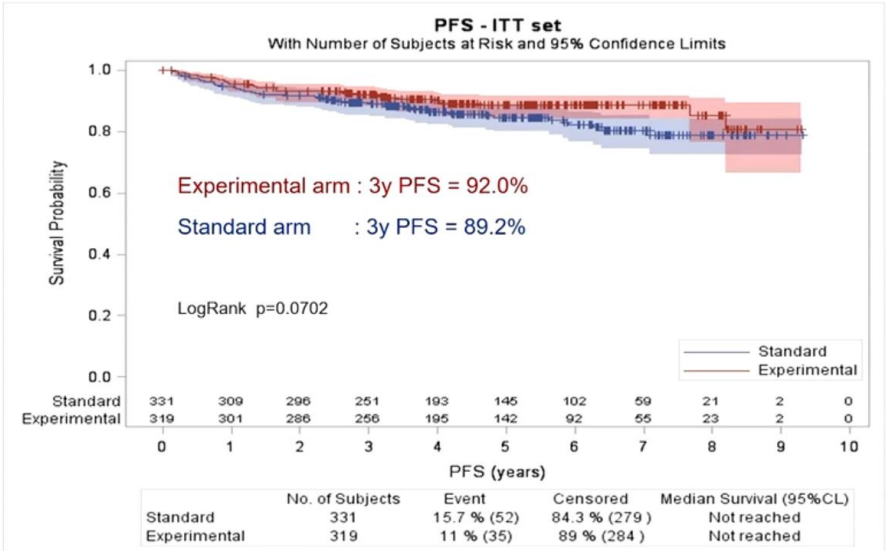
The Phase 3 LNH-09-1B Trial: PET-guided reduction of Tx cycles





Die Studie wird hoffentlich iPET beim DLBCL erlauben.

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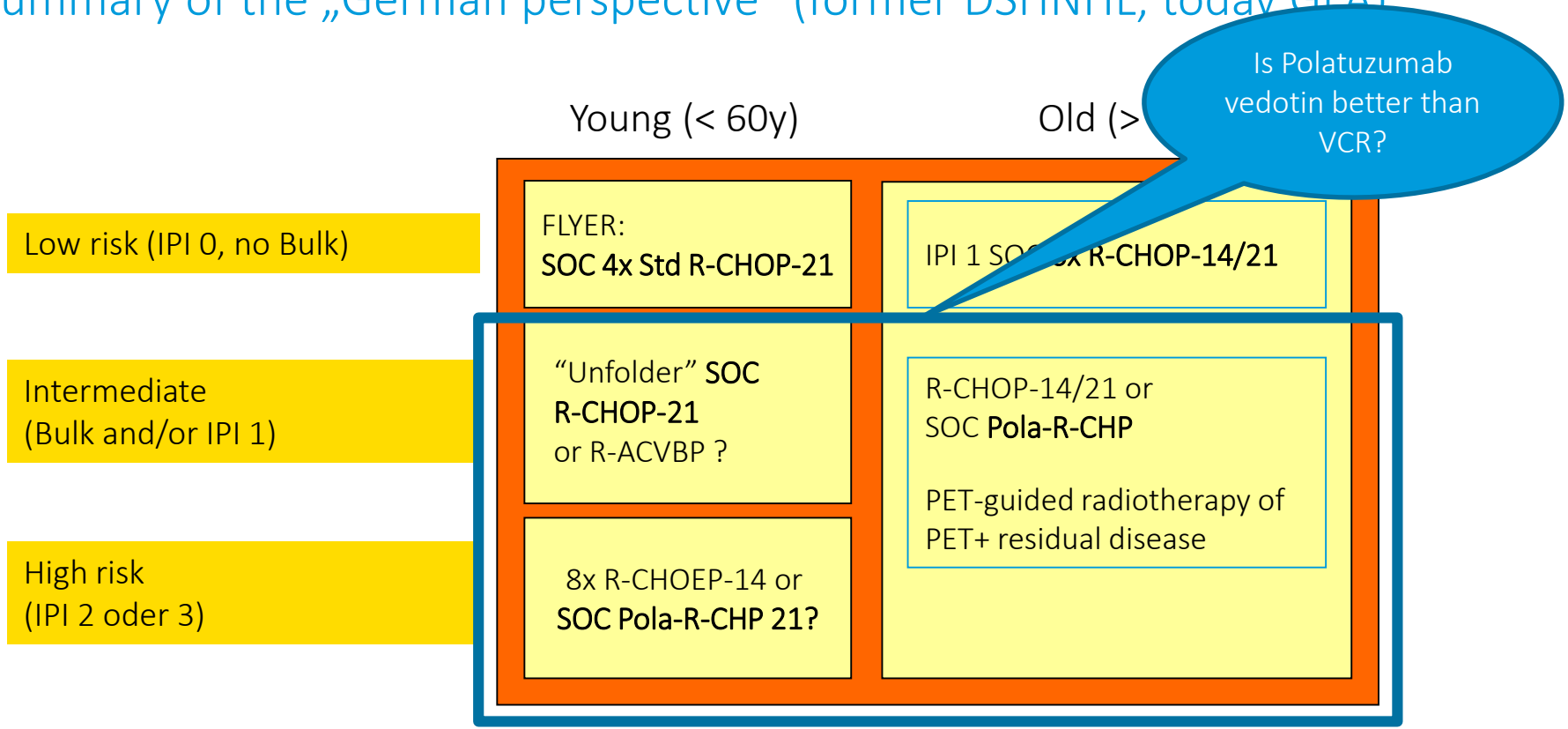
Summary of the „German perspective“ (former DSHNHL, today GLA)



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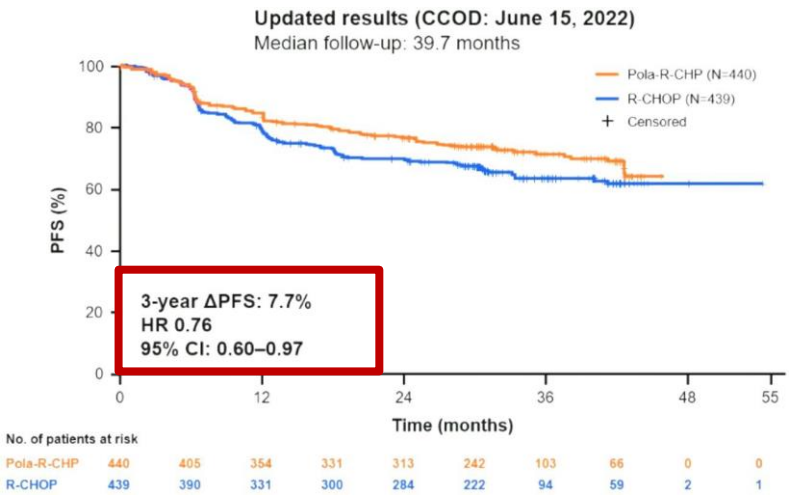
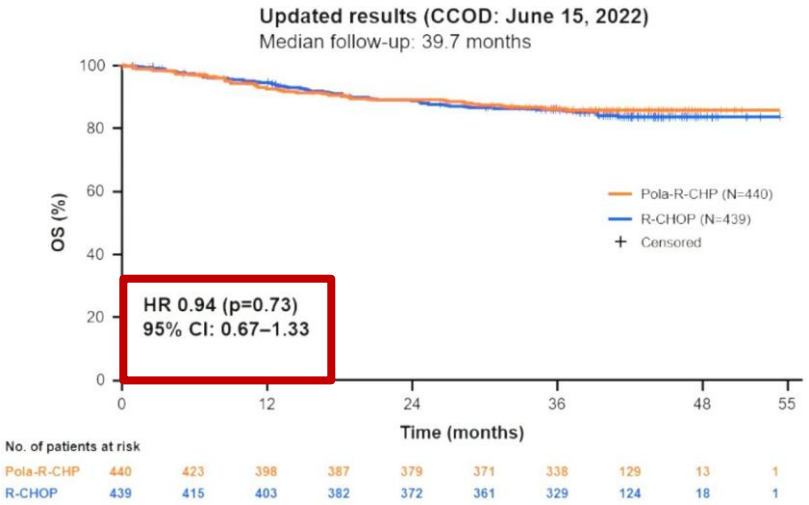
Die Polarix Studie – Pola-R-CHP vs. R-CHOP (IPI 2-5)

Progression free survival



Overall survival



Pola-R-CHP stellt gegenüber R-CHOP eine effizientere Therapie bei fast gleicher Toxizität dar und erweitert damit das Spektrum der zugelassenen R-CHOP-like Therapien in der Erstlinie

Tilly et al N Engl J Med. 2021 Herrera et al ASH 2022

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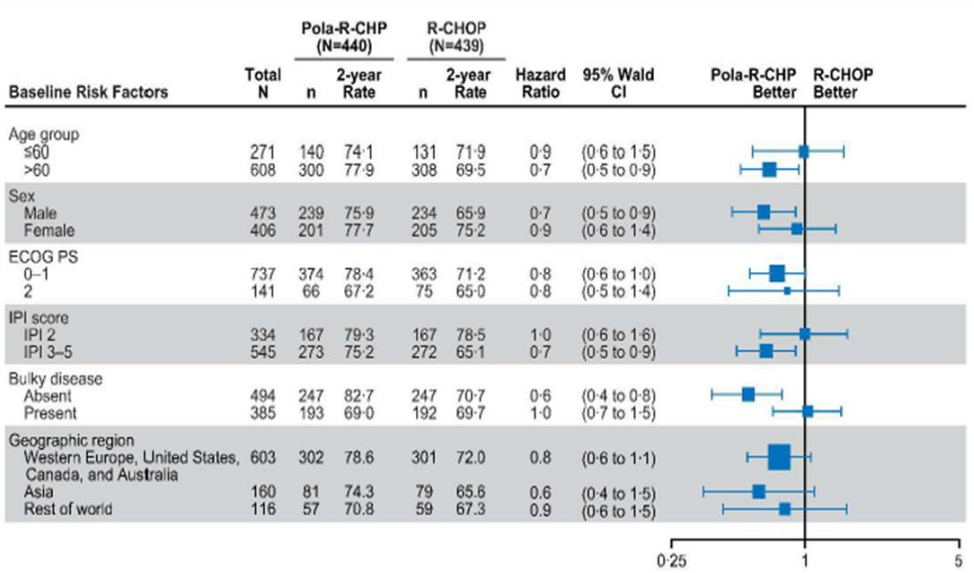
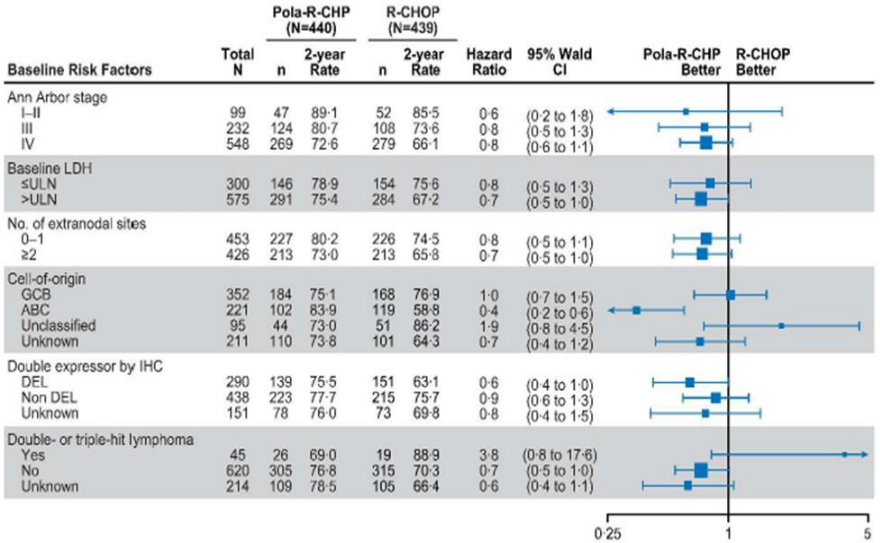
POLARIX: **EXPLORATORY** PFS subgroup analysis



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

Favours Pola-R-CHP:

- > 60 y, male gender
- IPI 3-5
- Absence of bulky disease

Favours Pola-R-CHP:
COO ABC

Tilly et al., N Engl J Med. 2022 Jan 27;386(4):351-363.

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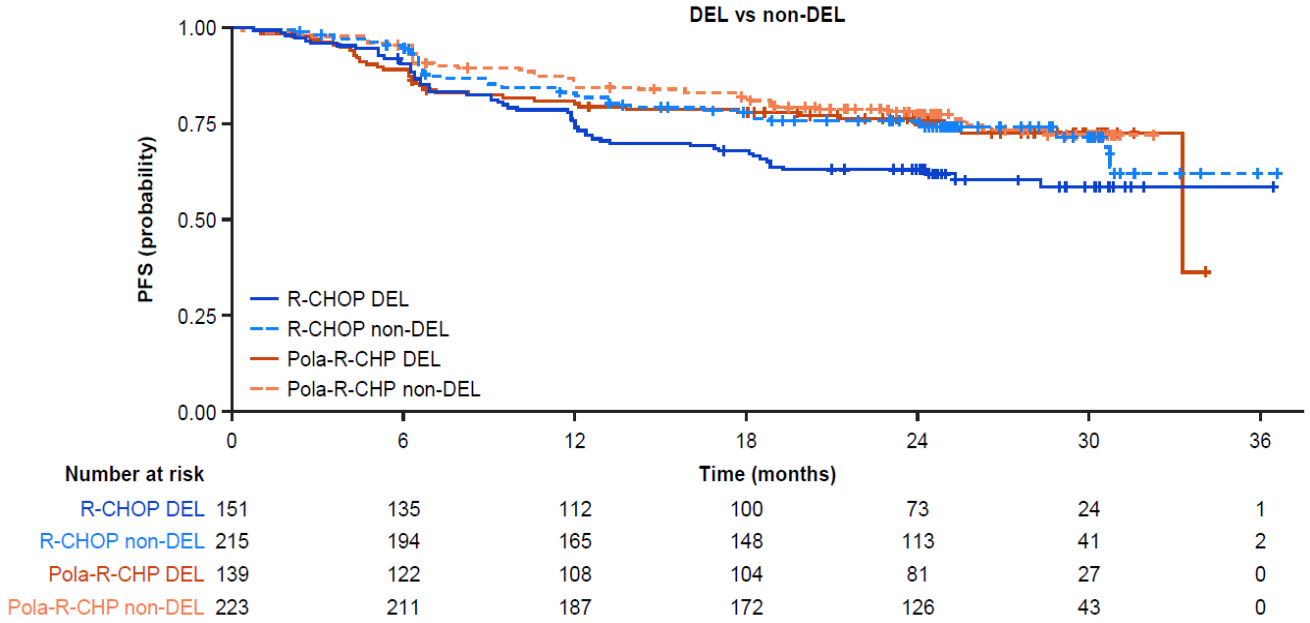
P7517: Outcomes by BCL2 and MYC expression and rearrangements in untreated diffuse large B-cell lymphoma (DLBCL) from the POLARIX trial: The prognostic impact of DEL vs non-DEL (Morschhauser et al.)



The prognostic impact of DEL vs non-DEL was more pronounced with R-CHOP (univariate HR (95% CI) 1.53; 1.06-2.21; multivariate HR 1.29; 0.88-1.91) vs Pola-R-CHP (univariate HR 1.10; 0.72-1.69; multivariate HR 1.42; 0.89-2.28).

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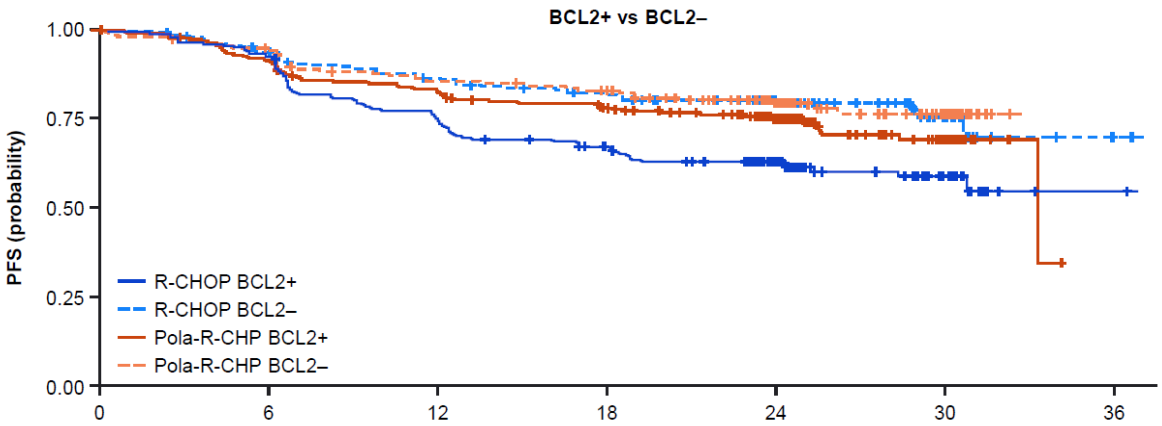
P7517: The prognostic impact of BCL2+ vs BCL2- was more pronounced with R-CHOP vs Pola-R-CHP



Number at risk							
R-CHOP BCL2+	202	184	148	129	94	36	1
R-CHOP BCL2–	163	144	129	120	93	30	2
Pola-R-CHP BCL2+	202	183	163	152	115	36	0
Pola-R-CHP BCL2–	157	147	129	122	89	33	0

Patients with BCL2+ lymphoma had inferior PFS vs patients with BCL2 in the R-CHOP arm, but no prognostic difference was detected in the Pola-R-CHP arm.

- In univariate analysis, the HR (95% CI) for R-CHOP was 1.96 (1.31-2.93) and the HR for Pola-R-CHP was 1.30 (0.85-2.01).
- In multivariate analysis, the HR for R-CHOP was 1.74 (1.14-2.66) and the HR for Pola-R-CHP was 1.56 (0.99-2.47).

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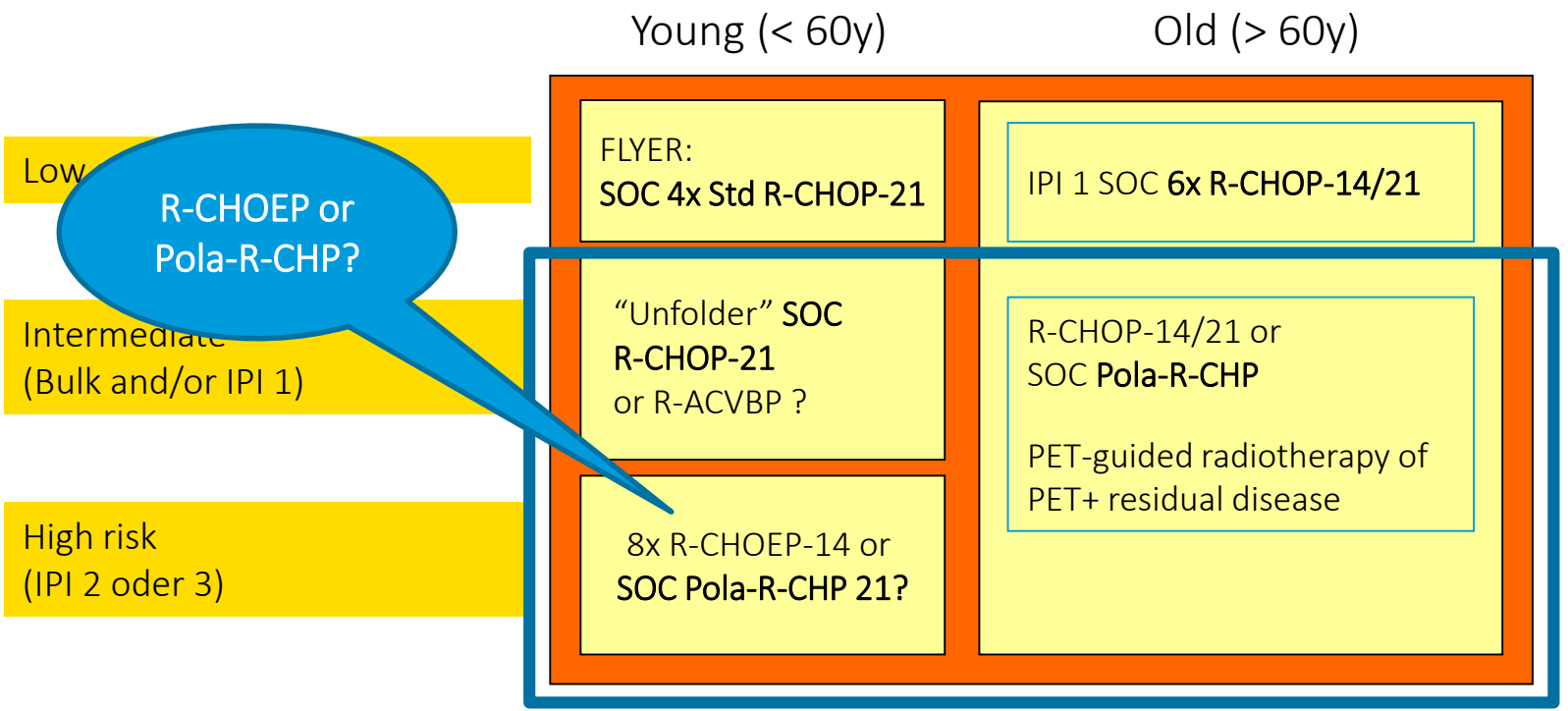
Summary of the „German perspective“ (former DSHNHL, today GLA)



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Pola-R-CHP versus R-CHOEP in young high-risk patients (Mega-CHOEP versus Polarix, indirect comparison)

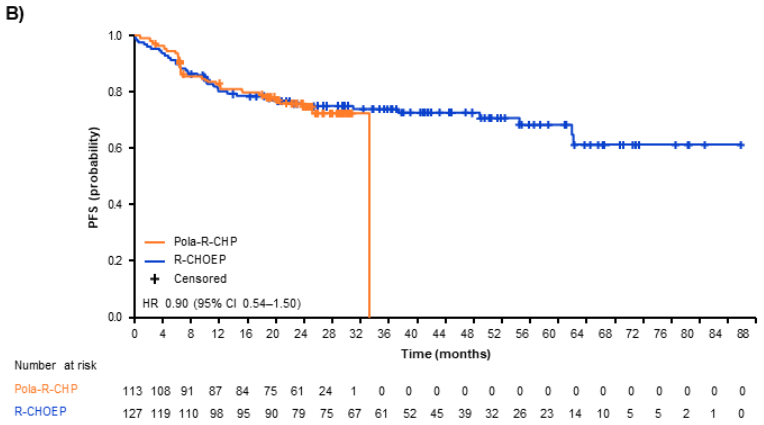
	Pola-R-CHP (n=113)	R-CHOEP (n=127)
Median age (range), years	52 (19–60)	50 (18–60)
Sex, n (%)		
Male	68 (60.2)	79 (62.2)
Female	45 (39.8)	48 (37.8)
aaIPI score, n (%)		
2	99 (87.6)	92 (72.4)
3	14 (12.4)	35 (27.6)
Elevated LDH level, n (%)	100 (88.5)	124 (97.6)
ECOG PS,* n (%)		
0–1	92 (81.4)	85 (66.9)
>1	21 (18.6)	42 (33.1)
Ann Arbor stage,* n (%)		
I–II	3 (2.6)	4 (3.1)
III–IV	110 (97.4)	123 (96.9)
Extranodal sites >1,* n (%)	61 (54.0)	55 (43.3)
Bone marrow involvement, n (%)	26 (23.0)	16 (12.6)
Bulky disease (≥7.5 cm), n (%)	60 (53.1)	75 (59.1)

	Pola-R-CHP (n=113)	R-CHOEP (n=127)
Tumor expression,† n (%)		
BCL2 positive	48/96 (50.0)	26/36 (72.2)
MYC positive	63/98 (64.3)	8/38 (21.1)
Tumor gene rearrangements, n (%)		
BCL2	17/95 (17.9)	9/52 (17.3)
BCL6	2/8 (25.0)	18/51 (35.3)
MYC	8/90 (8.9)	4/47 (8.5)
DEL status, n (%)		
DEL	37 (32.7)	5 (3.9)
non-DEL	61 (54.0)	32 (25.2)
Unknown	15 (13.3)	90 (70.9)
Double-/triple-hit lymphoma, n (%)		
Negative	86 (76.1)	43 (33.9)
Positive	4 (3.5)	4 (3.1)
Unknown	23 (20.4)	80 (63.0)

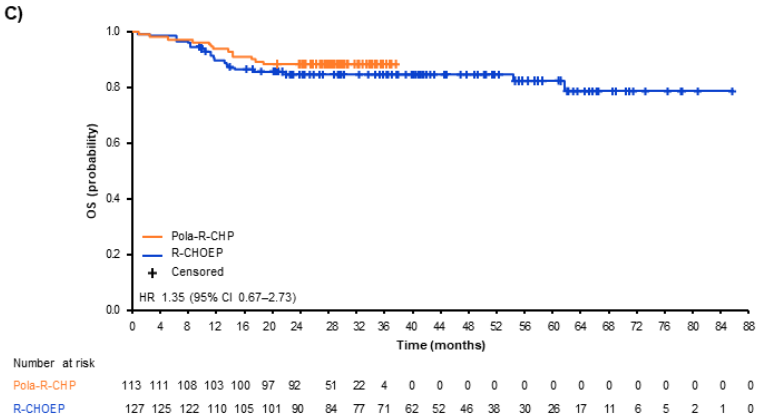
Lenz et al., ASH 2023, https://doi.org/10.1002/hon.3164_308

Pola-R-CHP versus R-CHOEP in young high-risk patients (Mega-CHOEP versus Polarix, indirect comparison)

PFS



OS



Overlapping efficacy results for aaIPI 2 and 3, but relevant differences in tolerability in favour of Pola-R-CHP

Lenz et al., ASH 2023, https://doi.org/10.1002/hon.3164_308

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Das diffuse großzellige B-Zell-Lymphom (DLBCL): Aktuelle Therapiestrategien

1. Erstlinie
2. Zweitlinie
3. Nach der Zweitlinie
4. Perspektiven

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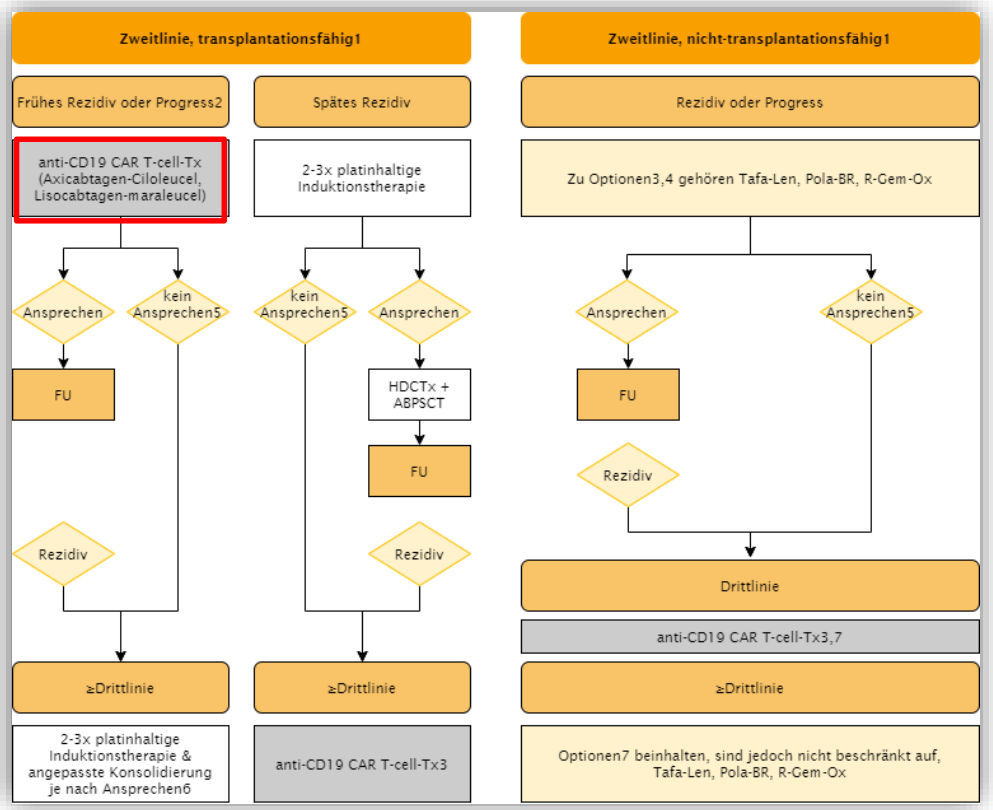
S3– Schlüsselempfehlungen zur Rezidivtherapie: Zweitlinie



CAVE:

1. „Sollte“-Empfehlung
2. „Hochdosis-Fähigkeit“ wird sehr gerne als Begriff verwendet, ist aber keineswegs definiert, ebenso wenig wie „CAR-T-Zellfähigkeit“ (Onkopedia)
3. *Ich **persönlich** richte mich eher nach dem Therapieziel: Soll die Therapie in kurativer Intention erfolgen? Dann CARs!*

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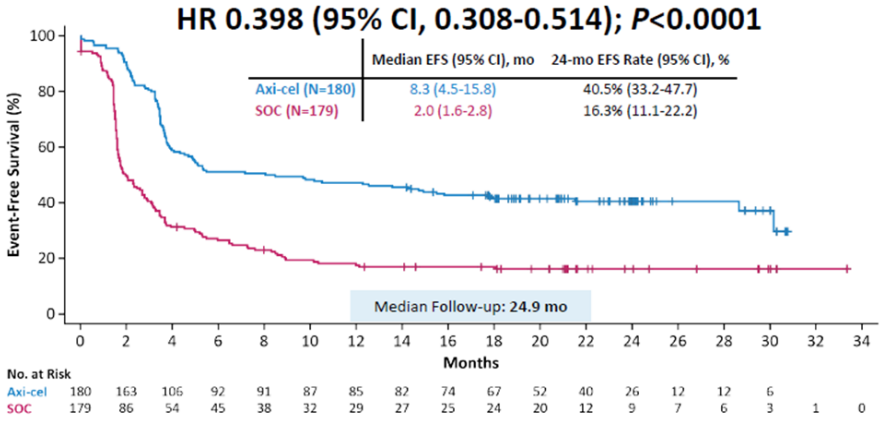
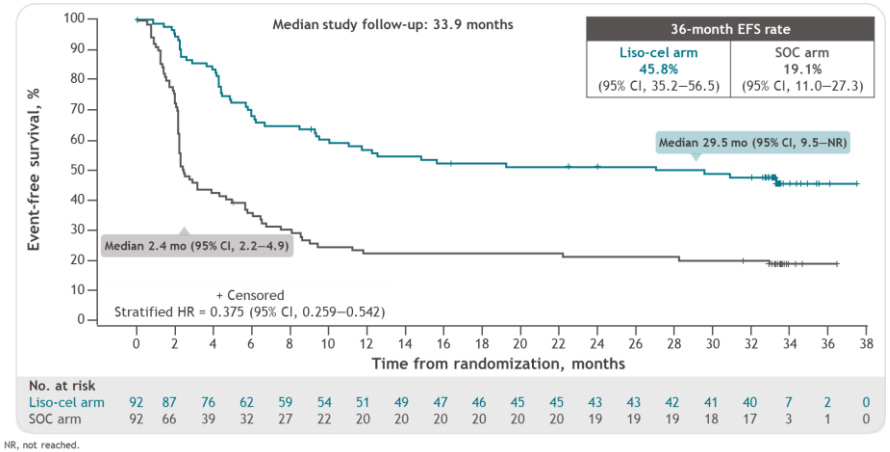
Axi-cel (ZUMA-7) und Liso-cel (TRANSFORM) in “transplant-eligible” patients: primary endpoint EFS

Axi-cel (ZUMA-7)



Locke et a., N Engl J Med. 2022 Feb 17;386(7):640-654

Liso-cel (TRANSFORM)



Kamdar et al., ASCO 2024 *Abstract number 7013*

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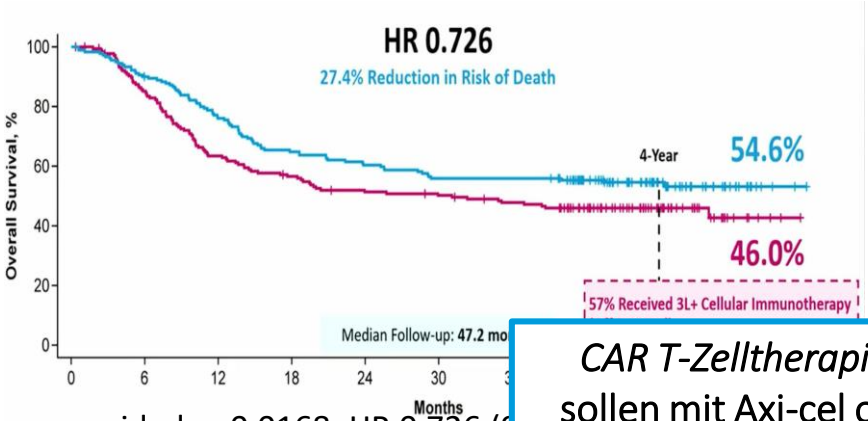
Axi-cel (ZUMA-7) und Liso-cel (TRANSFORM) in “transplant-eligible” patients: OS

Axi-cel (ZUMA-7)



one-sided p=0.0168; HR 0,726 (9

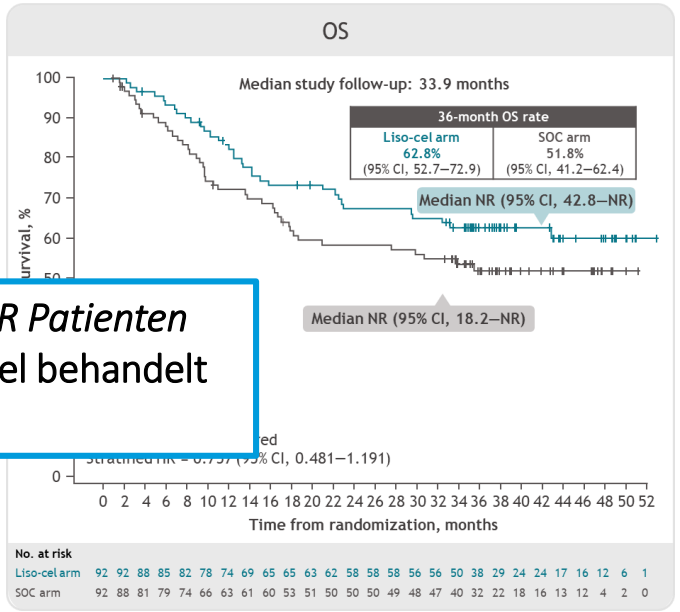
CAR T-Zelltherapie fähige HR Patienten sollen mit Axi-cel oder Liso-cel behandelt werden.

27.4% reduced risk of death compared to SOC, despite cross-over in 57% of out-of-study patients

- **1st study in 30 years to clearly show significant overall survival benefit in 2L DLBCL.**

Locke et a., N Engl J Med. 2022 Feb 17;386(7):640-654

Liso-cel (TRANSFORM)



› 57 (62%) patients in SOC arm crossed over to receive liso-cel

Kamdar et al., ASCO 2024
Abstract number 7013

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Abs 2 – Primary Analysis of ZUMA-7: safety aspects

	Axi-Cel		SOC	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any AE	175 (100)	155 (91)	168 (100)	140 (83)
Any serious AE	85 (50)	72 (42)	77 (46)	67 (40)
CRS	159 (92)	11 (6)		
NE (ICANS), n (%)	102 (60)	36 (21)	33 (30)	1 (1)
Tozi/Steroids, n (%)	111/40 (65, 24)			
Definitive TRM n/N(%)	**1/170 (1)**		**2/64 (3)**	
ICU (median duration)	25%, 5d		5%, 3d	
Hospitalization (med. duration)	16d		21d	

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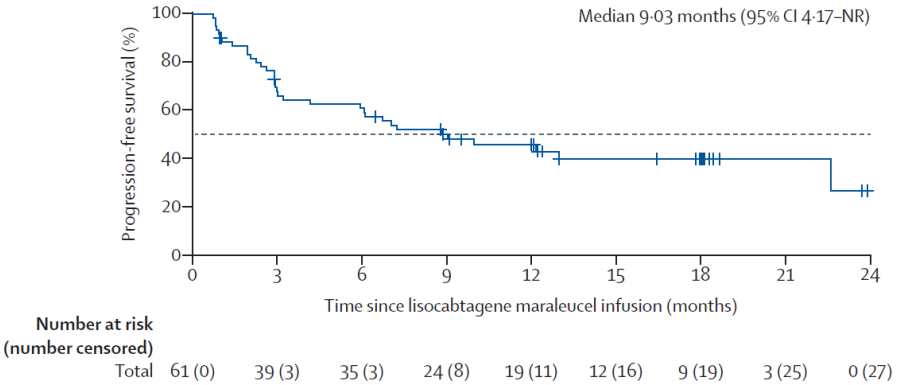
Zweitlinien-CAR-T-Therapie bei “nicht-hochdosisfähigen Patienten” mit DLBCL

Lisocabtagen maraleucel
(PILOT-Studie, 61 Patienten, PFS)



Medianes Follow-up 12,3 Monate

CRS Gr.3 2%

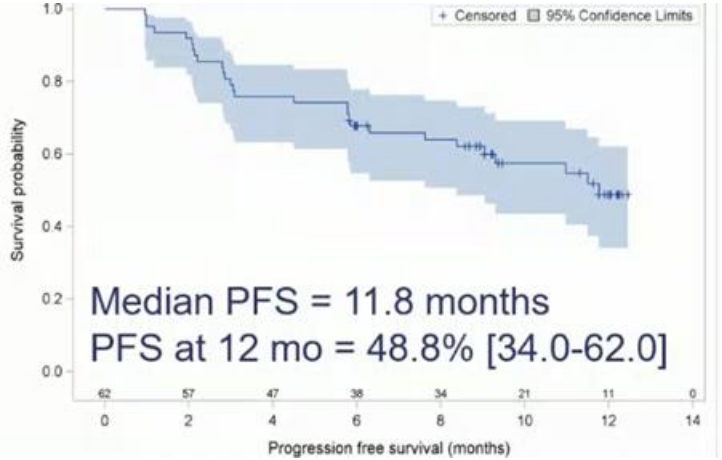
ICANS Gr.3 5%

Infektionen Gr.3-4 7%; Gr. 5 3,3%

Non-relapse mortality 3,3%

Final analysis Sehgal ASH 2023:
18-Monats PFS 43%; OS 59%

Axicabtagene ciloleucel
(Alycante-Studie, 62 Patienten, PFS)



Medianes Follow-up 12 Monate

CRS Gr.3-4 8,1%

ICANS Gr.3-4 14,5%

Infektionen Gr.3-4 29%; Gr. 5 9,7%

Non-relapse mortality 9,7%

Houot et al. EHA 2023; Sehgal Lancet Oncol et al. 2022

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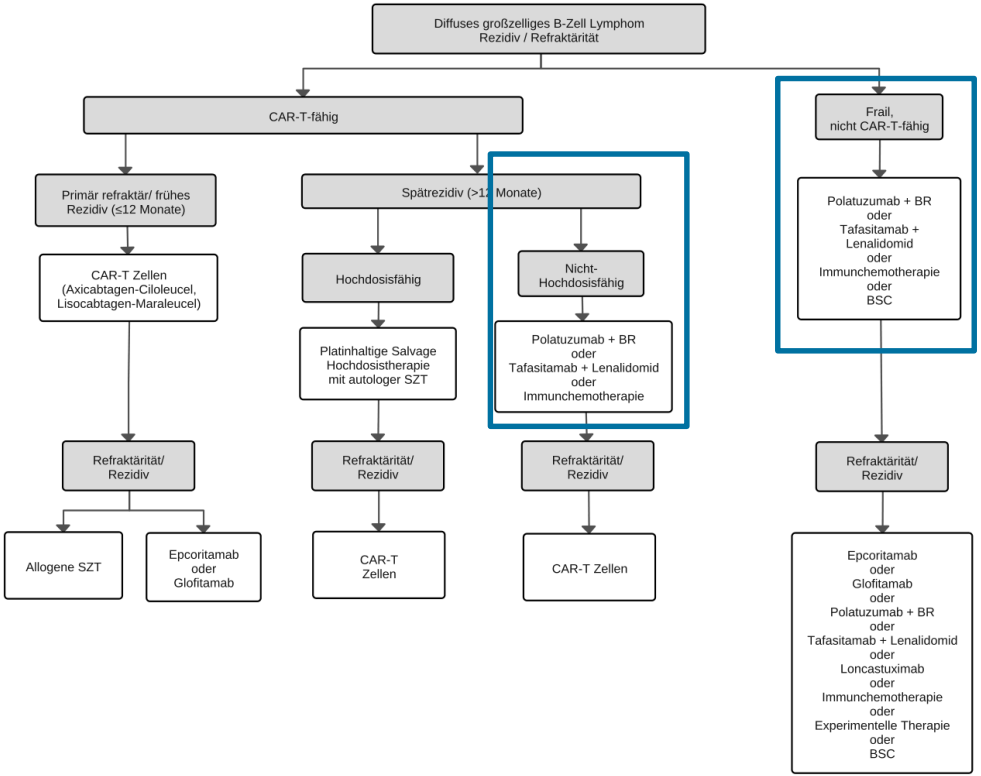
Rezidivtherapie bei diffusem großzelligem B-Zell-Lymphom (erstes und nachfolgende Rezidive)



Zweitlinie für Nicht-HDCTX fähige Patientinnen Rezidive war bisher ohne Phase III Studien-Ergebnisse.

- Welche der zahlreichen Optionen hier die beste Nutzen/Risiko Relation hat, ist unbekannt.

Legende:
BSC: best supportive care.
Die Beschreibung der Therapieprotokolle findet sich im zugehörigen Dokument „Medikamentöse Tumortherapie“

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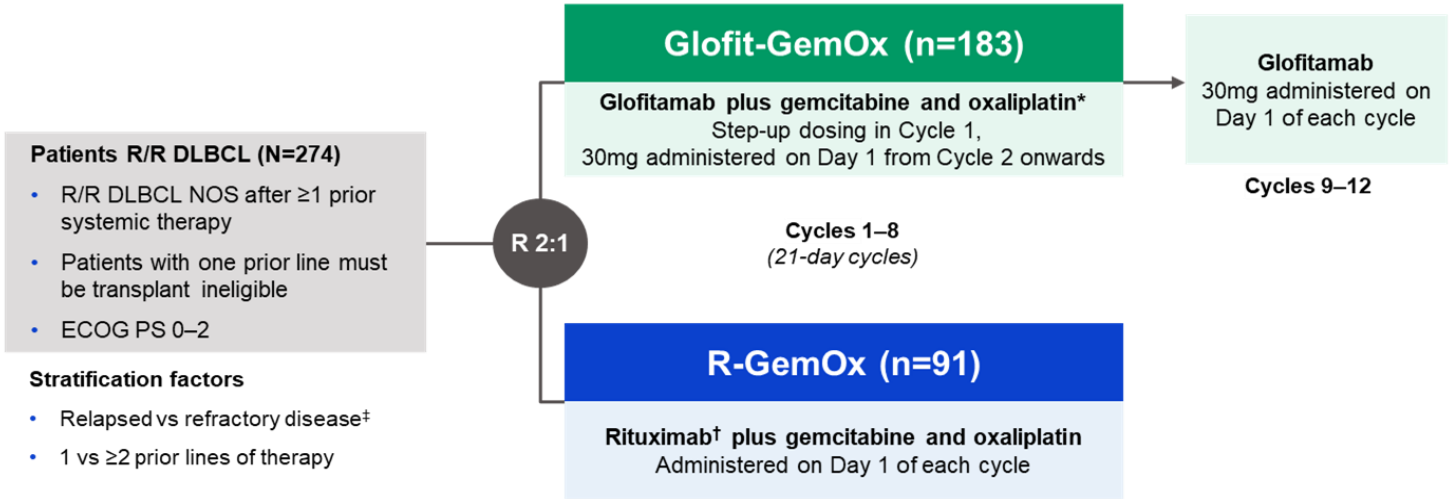
EHA LB3438: Glofitamab plus Gemcitabine and Oxaliplatin (Glofit-GemOx) for Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL): Results of a Global Randomized Phase III Trial (STARGLO). Abramson et al



*Gemcitabine 1000mg/m² and oxaliplatin 100mg/m². In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m². ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. ASCT, autologous stem cell transplant; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; NOS, not otherwise specified; R 2:1, patients randomized in a 2:1 ratio.

Abramson et al., Oral presentation #LB3438, EHA 2024

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EHA LB3438: Glofitamab plus Gemcitabine and Oxaliplatin (Glofit-GemOx, STARGLO). Baseline characteristics

n (%), unless otherwise stated		R-GemOx (n=91)	Glofit-GemOx (n=183)
Age, years	Median (range) ≥65 years	68.0 (20–84) 56 (61.5)	68.0 (22–88) 116 (63.4)
Sex	Male	53 (58.2)	105 (57.4)
Race	Asian Black or African American White Unknown	51 (56.0) 1 (1.1) 33 (36.3) 6 (6.6)	86 (47.0) 2 (1.1) 82 (44.8) 13 (7.1)
ECOG PS	0 1 2	44 (50.0) 36 (40.9) 8 (9.1)	72 (40.0) 89 (49.4) 19 (10.6)
Ann Arbor stage	I–II III–IV	20 (22.0) 70 (76.9)	60 (32.8) 123 (67.2)
Number of prior lines of therapy	1 ≥2	57 (62.6) 34 (37.4)	115 (62.8) 68 (37.2)
Primary refractory	Yes	47 (51.6)	106 (57.9)
R/R to last prior therapy	Relapsed / refractory	37 (40.7) / 54 (59.3)	71 (38.8) / 112 (61.2)
Bulky disease (≥10cm)	Present	14 (15.4)	23 (12.6)
Cell of origin at initial diagnosis	GCB Non-GCB (including ABC) Unknown	29 (31.9) 50 (54.9) 12 (13.2)	60 (32.8) 103 (56.3) 20 (10.9)
Prior CAR T-cell therapy	Received	8 (8.8)	13 (7.1)

ABC, activated B-cell-like; CAR, chimeric antigen receptor; GCB, germinal center B-cell-like.

Abramson et al., Oral presentation #LB3438, EHA 2024

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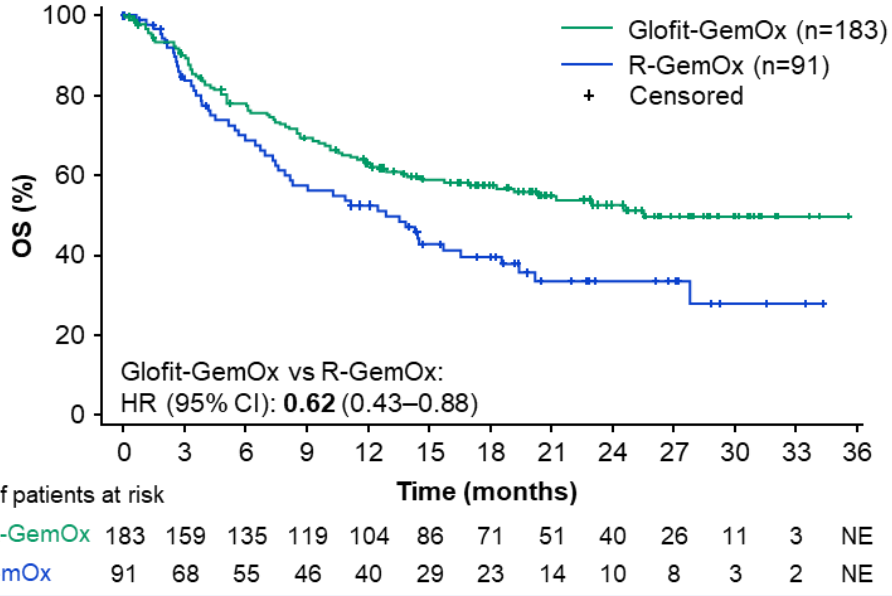
Primary endpoint: overall survival

Updated analysis



	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

Statistically significant and clinically meaningful **OS benefit for Glofit-GemOx** vs R-GemOx

24-month OS not reported at the primary analysis as data were not sufficiently mature.
*p-value is alpha-controlled at the primary analysis and descriptive at updated analysis. CI, confidence interval; HR, hazard ratio; NE, not evaluable.

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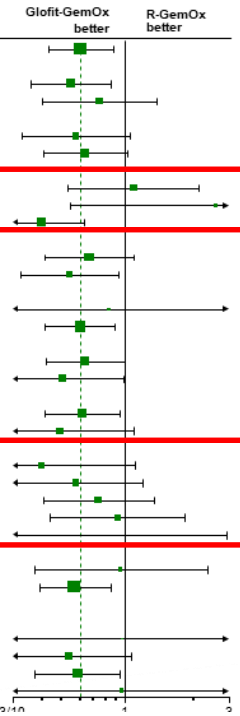
OS in pre-specified subgroups: exploratory analysis

Baseline Risk Factors	Total n	R-GemOx (n=91) n	R-GemOx (n=91) Events	R-GemOx (n=91) Median (Months)	Glofit-GemOx (n=183) n	Glofit-GemOx (n=183) Events	Glofit-GemOx (n=183) Median (Months)	HR	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Sex									
Male	158	53	36	10.3	105	51	20.4	0.56	(0.37, 0.86)
Female	116	38	16	20.2	78	29	NE	0.76	(0.41, 1.40)
Age group									
<65	102	35	19	9.0	67	29	NE	0.59	(0.33, 1.06)
≥65	172	56	33	14.3	116	51	22.9	0.65	(0.42, 1.01)
Enrollment by geographic region									
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Rest of the World	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
No. of previous lines of systemic therapy for DLBCL									
1	172	57	28	15.7	115	44	NE	0.68	(0.42, 1.09)
≥2	102	34	24	6.7	68	36	18.3	0.55	(0.33, 0.93)
Prior CAR T-cell therapy									
Yes	21	8	4	27.8	13	6	13.7	0.84	(0.23, 3.01)
No	253	83	48	12.9	170	74	NE	0.62	(0.43, 0.89)
Relapse or refractory to last line of therapy									
Refractory	166	54	36	7.5	112	61	11.9	0.65	(0.43, 0.99)
Relapsed	108	37	16	27.8	71	19	NE	0.51	(0.26, 0.98)
Refractory to first line of therapy									
Yes	153	47	34	7.3	106	59	10.2	0.60	(0.40, 0.92)
No	121	44	18	27.8	77	21	NE	0.54	(0.29, 1.01)
Total number of risk factors for IPI (Derived)									
Low (0–1)	61	13	6	NE	48	12	NE	0.41	(0.15, 1.10)
Low–intermediate (2)	70	28	14	18.5	42	16	NE	0.59	(0.28, 1.20)
High–intermediate (3)	79	30	20	14.3	49	26	21.2	0.75	(0.42, 1.35)
High (4–5)	55	17	11	8.3	38	24	8.5	0.92	(0.45, 1.88)
Unknown	9	3	1	0.6	6	2	NE	0.18	(0.01, 2.93)
Bulky disease ≥10cm									
Yes	37	14	7	11.1	23	13	12.0	0.95	(0.38, 2.40)
No	236	76	45	13.5	160	67	NE	0.58	(0.40, 0.85)
Unknown	1	1	0	NE	-	-	-	NE	NE
Cell of origin									
ABC	6	2	1	NE	4	2	NE	0.97	(0.09, 10.98)
GCB	89	29	15	11.1	60	25	NE	0.55	(0.29, 1.06)
Non-GCB (by IHC + non-GCB unclassified)	147	48	32	10.9	99	45	25.5	0.60	(0.38, 0.94)
Unknown	32	12	4	20.2	20	8	NE	0.96	(0.28, 3.21)



- Comparable results were observed in clinically relevant stratified subgroups: relapsed vs refractory and 2L vs 3L+
- Regional inconsistencies were observed, but interpretation was limited by wide CI and small patient numbers

Abramson et al., Oral presentation #LB3438, EHA 2024

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Safety profile summary

n (%), unless otherwise stated	R-GemOx (n=88)	Glofit-GemOx (n=180)
Number of cycles,* median (range)	4 (1–8)	11 (1–13)
Any grade AEs	84 (95.5)	180 (100)
Rituximab/glofitamab related	58 (65.9)	149 (82.8)
Serious AEs	15 (17.0)	98 (54.4)
Rituximab/glofitamab related	7 (8.0)	62 (34.4)
Grade 3–5 AEs	36 (40.9)	140 (77.8)
Rituximab/glofitamab related	20 (22.7)	85 (47.2)
Grade 5 (fatal) AEs	4 (4.5)	15 (8.3)
Rituximab/glofitamab related	1 (1.1)	5 (2.8)
AE leading to any treatment discontinuation	11 (12.5)	48 (26.7)

The safety profile of Glofit-GemOx is **consistent with the known risk of the individual study drugs**

Abramson et al., Oral presentation #LB3438, EHA 2024

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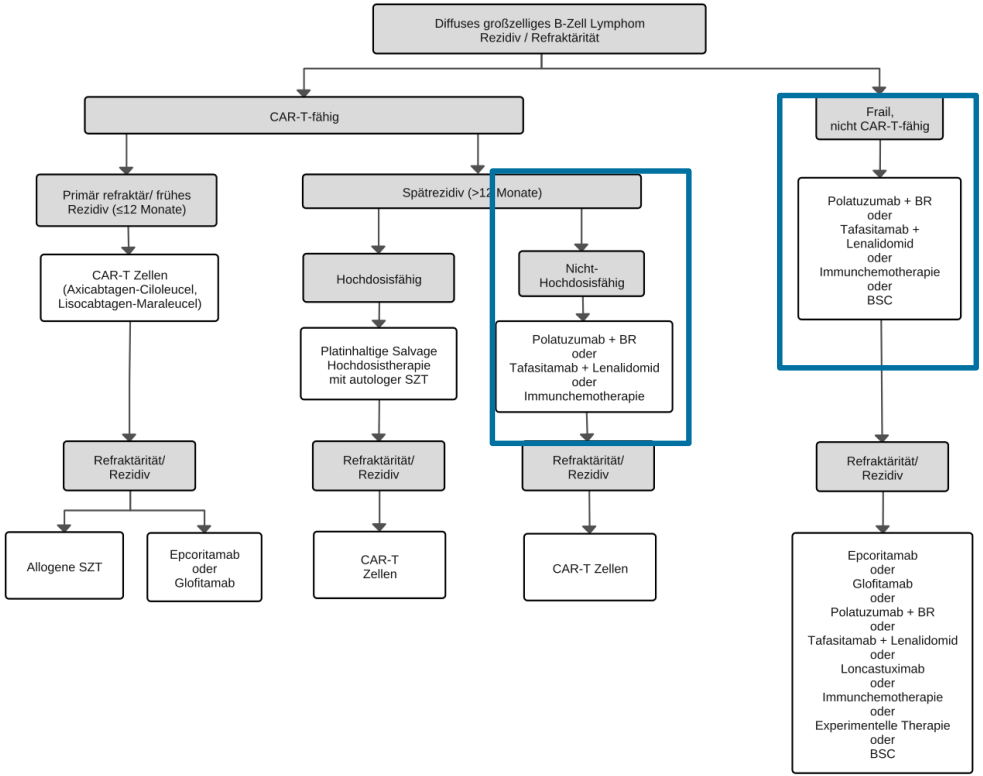
Rezidivtherapie bei diffusem großzelligem B-Zell-Lymphom (erstes und nachfolgende Rezidive)



Legende:
BSC: best supportive care.
Die Beschreibung der Therapieprotokolle findet sich im zugehörigen Dokument „Medikamentöse Tumortherapie“

Zweitlinie für Nicht-HDCTX fähige Patientinnen Rezidive war bisher ohne Phase III Studien-Ergebnisse.

- Welche der zahlreichen Optionen hier die beste Nutzen/Risiko Relation hat, ist unbekannt.

- **Und es wird in Kürze noch mehr Wissen in diesem Kollektiv geben!**

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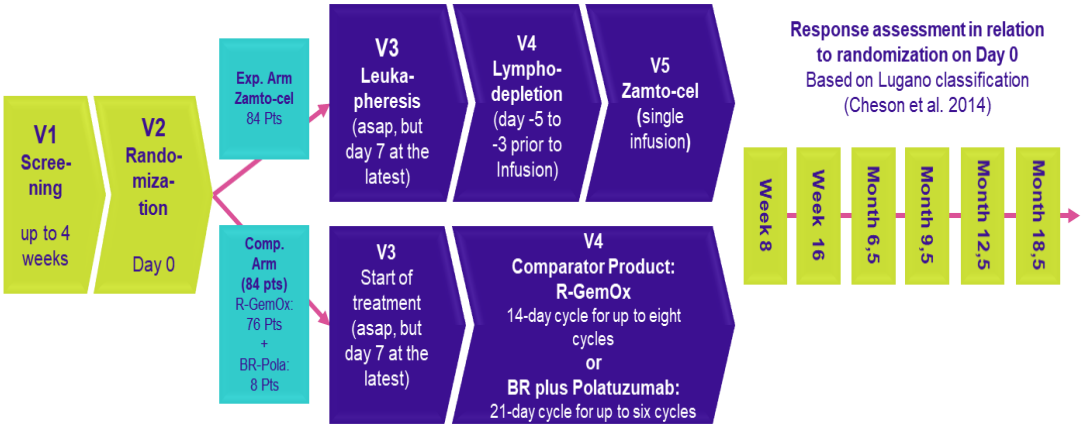
Development of CAR T-cell therapy for non-transplant eligible patients: the tandem CAR Zamtocabtagene autoleucel in the DALY 2-EU trial



- Studie ist im Moment voll rekrutiert.
- Ergebnisse sind Q1 2025 zu erwarten.
- Falls positiv, „POC production“ denkbar in voll automatisiertem System.

Primary objective: To determine the superiority of Zamtocabtagene autoleucel treatment *versus* SoC based on **PFS**

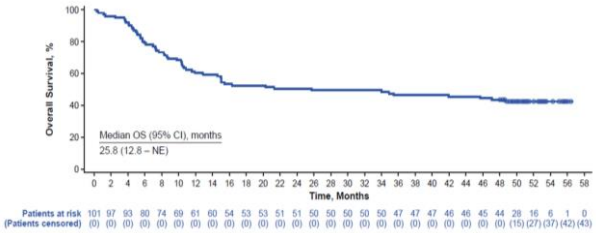
UNIKLINIK KÖLN

Das diffuse großzellige B-Zell-Lymphom (DLBCL): Aktuelle Therapiestrategien

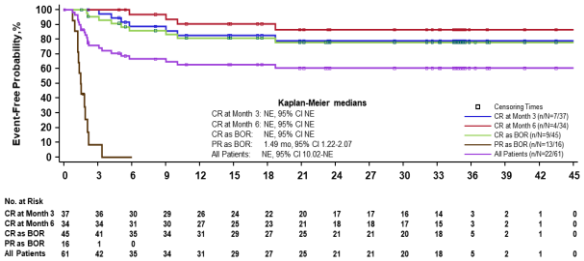
1. Erstlinie
2. Zweitlinie
3. Nach der Zweitlinie
4. Perspektiven

Die Prognose hat sich mit CAR-T-Zelltherapie in der Dritt(!)linie grundsätzlich gewandelt

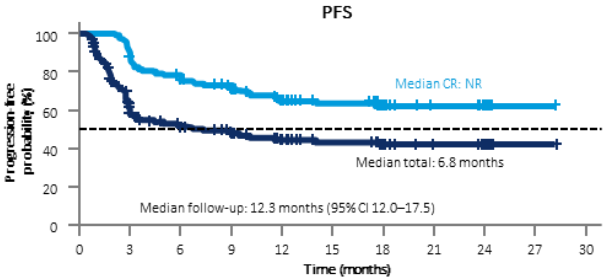
Axicabtagene Ciloleucel



Tisagenlecleucel



Lisocabtagene maraleucel



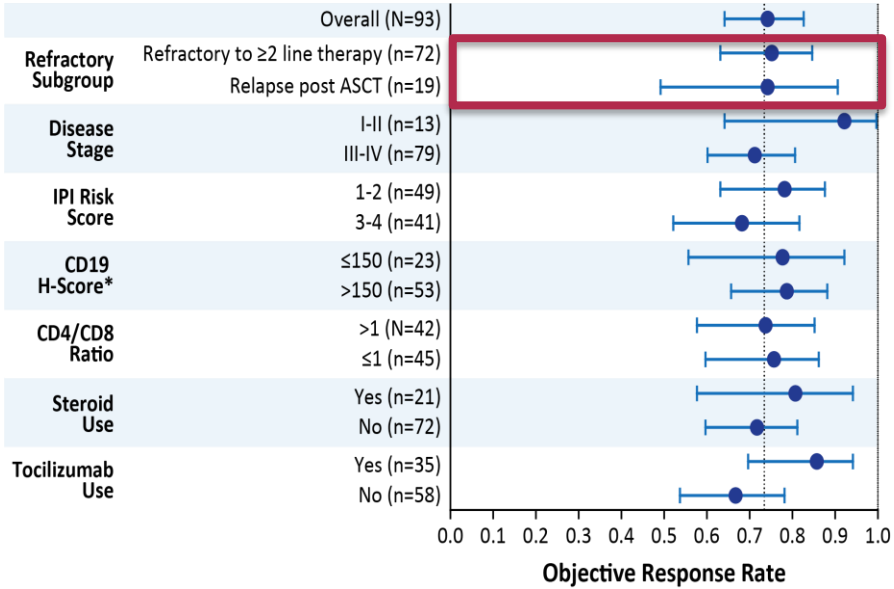
These charts are provided for ease of viewing information from multiple trials.

Direct comparison between trials is not intended and should not be inferred.

Jacobson C, et al. Presented at ASH 2020; abstract 1187. Jaeger U, et al. Presented at ASH 2020; abstract 1194.; Abramson JS, et al. Presented at EHA-EBMT 2020; abstract 290353.

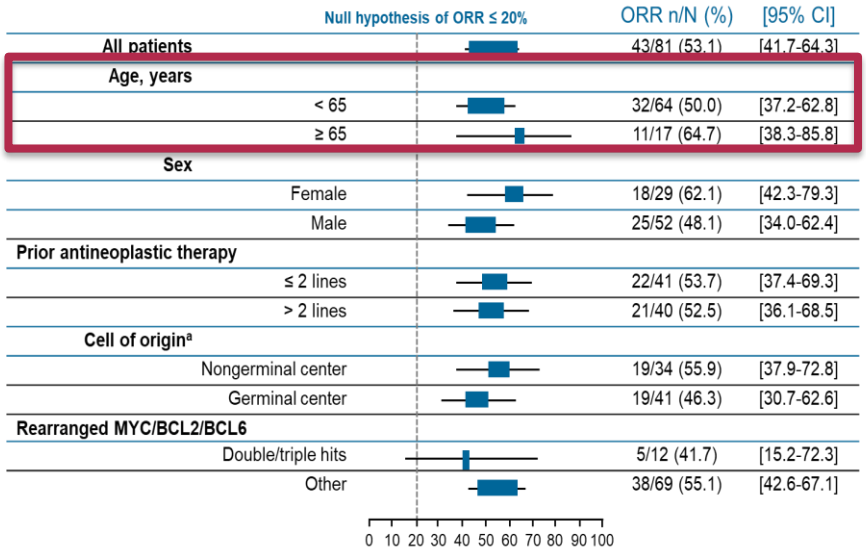
Mit CAR T-Zelltherapien verlieren Chemo-Refraktärität und Alter ihre prognostische Bedeutung beim r/r DLBCL praktisch vollständig

Axicabtagene Ciloleucel



Neelapu et al., N Engl J Med 2017;377:2531-44. Neelapu et al., LBA, ASH 2016

Tisagenlecleucel



Schuster et al., ASH abs 2017

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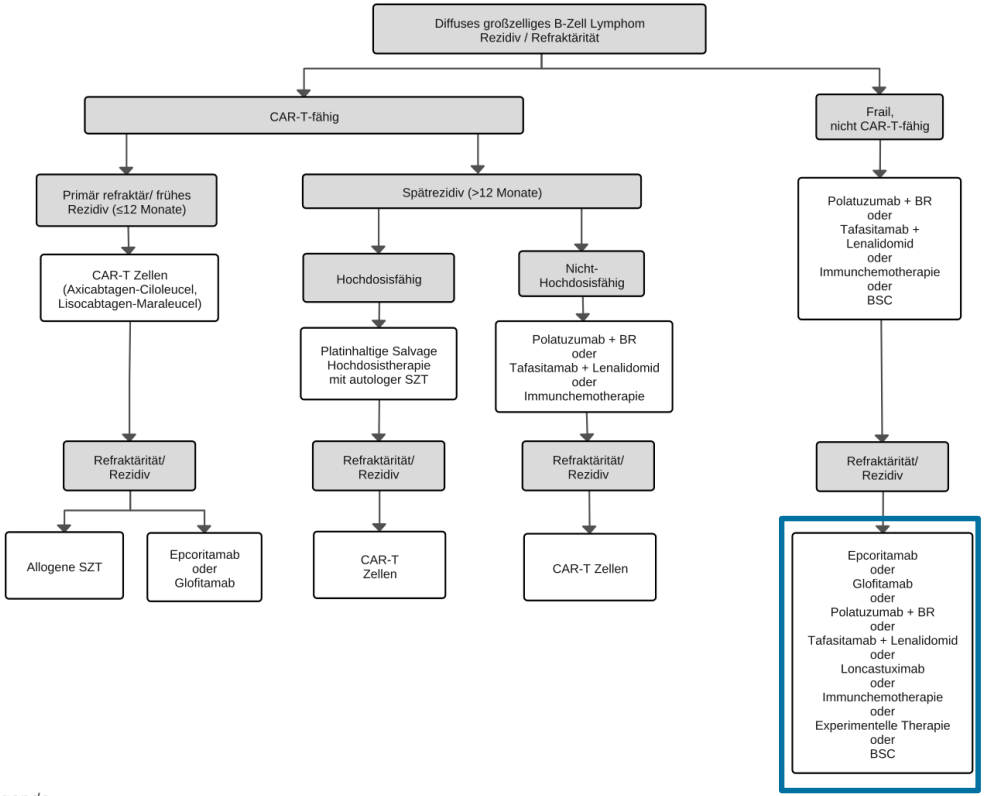
Rezidivtherapie bei diffusem großzelligem B-Zell-Lymphom (erstes und nachfolgende Rezidive)



➢ Hier gibt es sehr viele “Optionen”

Legende:
BSC: best supportive care.
Die Beschreibung der Therapieprotokolle findet sich im zugehörigen Dokument „Medikamentöse Tumortherapie“

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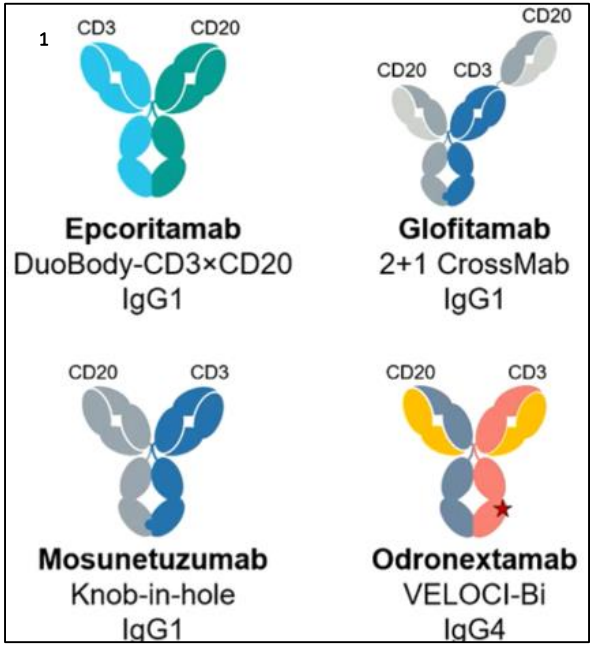
Selected CD3xCD20 bispecific Antibodies in development for B-NHL



Zugelassen oder in Zulassung

	Mosunetuzumab (RG7828)[2]	Odronextamab (REGN1979)[3]	Glofitamab (RG60269)[4]	Epcoritamab (GEN3019)[5]
Patients	98	35	154	157
ORR	38%	40%	51.6%	63%
CR	20%	31%	39.4%	39%
Median PFS [m]			4.9	4.4

Focus ***hier und heute*** Glofitamab (wegen der Zeit und ohne Wertung)

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Glofitamab in der Drittlline des DLBCL

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - anti-CD20 antibody
  - anthracycline

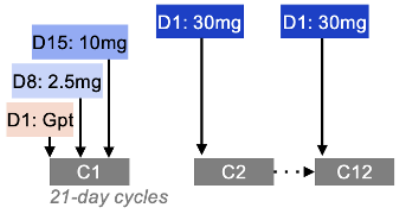
Glofitamab IV administration

Fixed-duration treatment

- **Max. 12 cycles (=8.3 months)**

CRS mitigation:

- Obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

Primary: CR (best response) rate by IRC*

Key secondary: ORR rate, DoR, DoCR, PFS, and OS

Adaptiert von D. Mougiakakos, Hämatologie Summit 2023, modifiziert nach Dickinson et al, ASCO 2023

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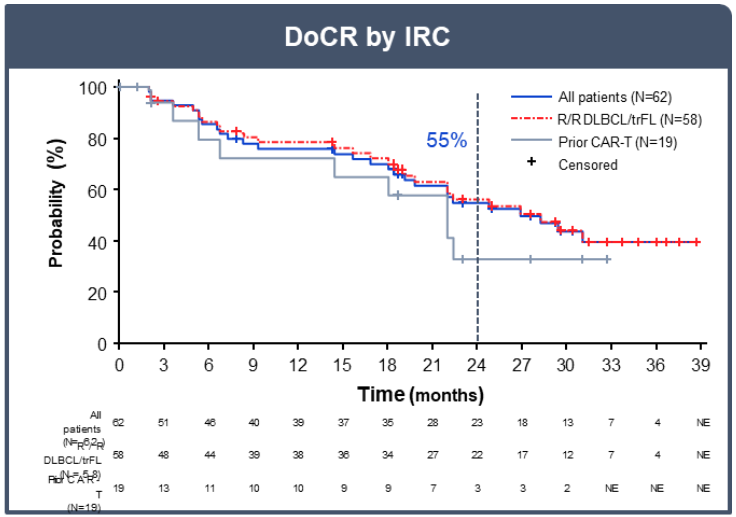
Glofitamab Monotherapy in Relapsed or Refractory Large B-Cell Lymphoma: Extended Follow-Up from a Pivotal Phase II Study and Subgroup Analyses in Patients with Prior Chimeric Antigen Receptor T-Cell Therapy and by Baseline Total Metabolic Tumor Volume

Martin Hutchings et al., Abs 433 ASH 2023

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1] †‡	Prior CAR-T (N=52) †
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% I)	26.9 (19.8–NR)	28.3 (19.8NR)	22.0 (6.7–NR)



Liso cel Transcend ORR, CR [%]	73 / 53
DoCR	**58.5% @ 24 m**

- Median time on study: 32.1 months (range: 0–43)

Abramson et al., 1 FEBRUARY 2024 | VOLUME 143, NUMBER 5

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EPCORE NHL-1 (GCT3013-01): Design

kontiuierliche subkutane (s.c.) Therapie

Dose expansion data cutoff: November 18, 2022
Median follow-up: 20.0 mo

Key inclusion criteria:

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

LBCL Cohort (N=157)
DLBCL, n=139; HGBCL, n=9; PMBCL, n=4; FL G3B, n=5

Step-up dosing

- Priming C1D1 0.16 mg
- Intermediate C1D8 0.8 mg
- First Full C1D15 48 mg
- Second Full C1D22 48 mg

Epcoritamab SC RP2D 48mg
QW C1–3,
Q2W C4–9,
Q4W C10+

Treatment until PD or unacceptable toxicity

Primary endpoint: ORR by independent review committee (IRC)

Key secondary endpoints: DOR, TTR, PFS, OS, CR rate, and safety/tolerability

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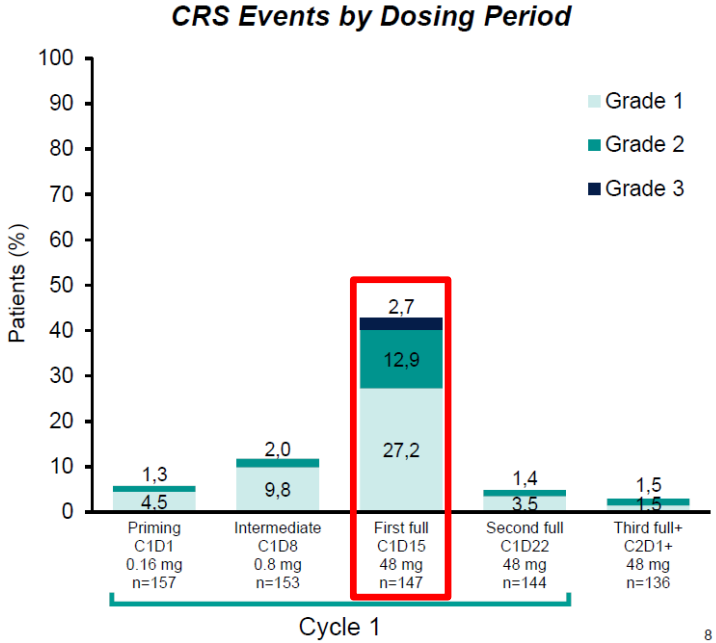
EPCORE NHL-1 (GCT3013-01): SC Aufsättigung und CRS-events

	LBCL N=157
CRS, n (%)[a]	80 (51)
Grade 1	50 (32)
Grade 2	25 (16)
Grade 3	5 (3)
Median time to onset after first full dose, h	20
Treated with anticytokine therapy, n (%)	23 (15)
Leading to treatment discontinuation, n (%)	1 (1)
CRS resolution, n/n (%)	79/80 (99)
Median time to resolution, d (range)[b]	2 (1–27)

[a]Graded by Lee et al 2019 criteria.[10] [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.



CRS was primarily low grade and predictable: most events occurred following the first full dose

Jurczak et al. EHA 2023, P1118 (left table)
Thieblemont et al. EHA 2022, LBA 2364 (right figure)

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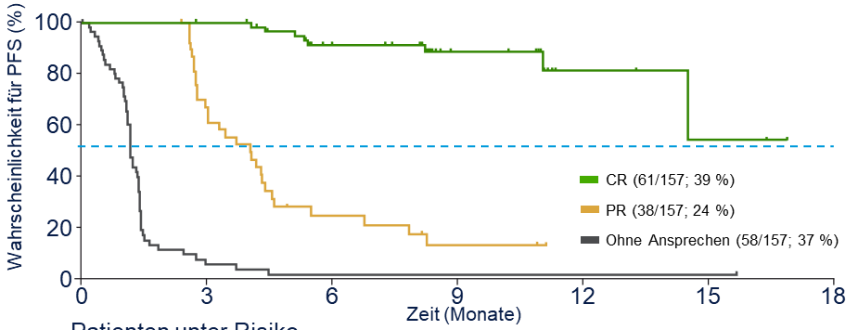
EPCORE NHL-1 (GCT3013-01): PFS and OS

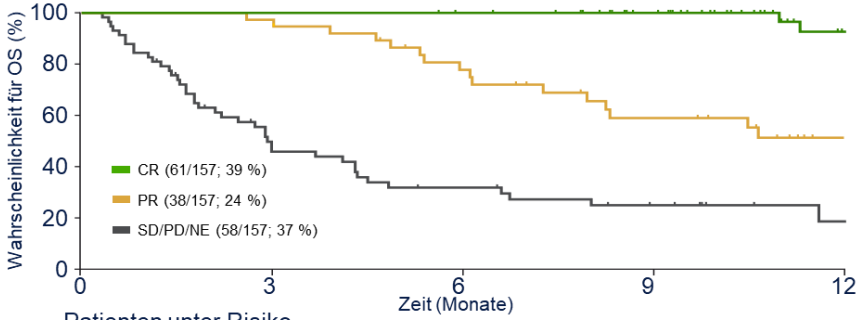
PFS correlates to quality of response



Patienten unter Risiko

61	60	43	24	4	2	0
38	23	7	3	0	0	0
58	3	1	1	1	1	0

OS correlates to quality of response



Patienten unter Risiko

61	61	59	47	21
38	37	27	18	7
58	24	15	9	3

Gesamtansprechen 63%, CRR 39%
mediane Dauer bis zum Erreichen einer CR 2.7 Monate
mediane Dauer des Therapienansprechens 15.5 Monate (bei CR 20.8 Monate)
medianes Gesamtüberleben 18.5 Monate (bei CR noch nicht erreicht)

Thieblemont et al. EHA 2022, LBA 2364

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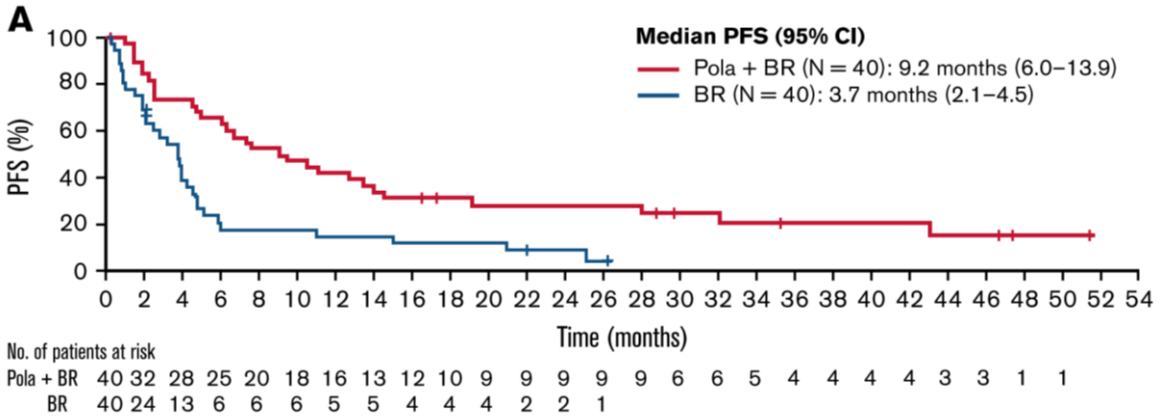
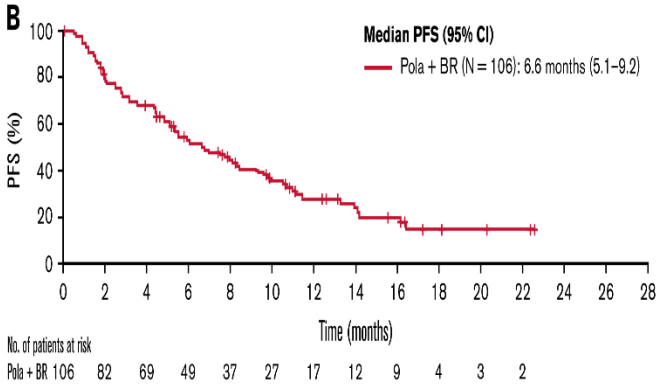
Polatuzumab vedotin bei r/r DLBCL





Polatuzumab vedotin plus Bendamustine with Rituximab in Relapsed/Refractory DLBCL (transplant –ineligible): Randomized Phase II follow-up and extension cohort

- Randomisierter Arm: medianes PFS: 9.2 vs 3.7 Monate Pola-BR vs BR
- Extensions-Kohorte: medianes PFS 6,6 Monate und medianes OS 12,5 Monate
- Gepoolte Pola-BR-Gruppe (151 Pat.): 31,1% Neuropathie (alle Grade); 2% Grad 3-4 Polyneuropathie

Sehn LH et al. Blood Adv 2022

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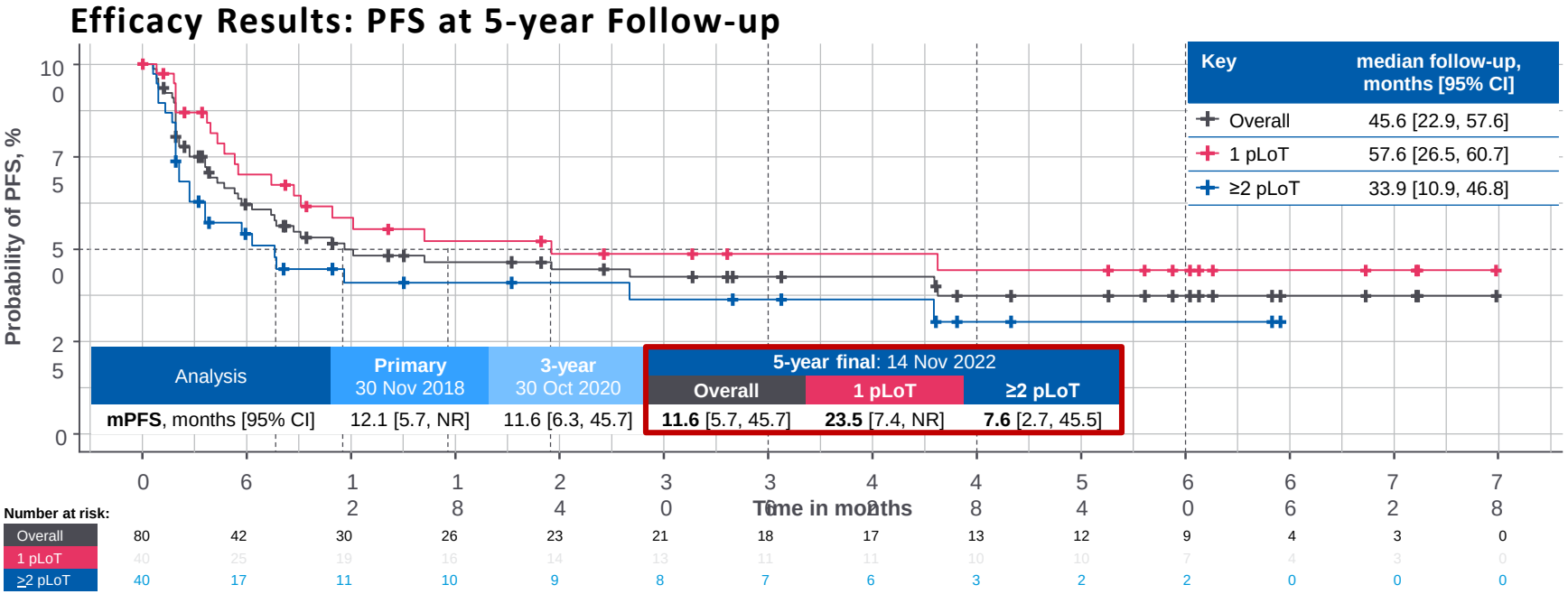
Tafasitamab bei rezidiviertem DLBCL



mPFS, median PFS; PFS, progression-free survival; pLoT, prior line of therapy; NR, not reached.
Modified from Duell J, et al., AACR annual meeting 2023, oral abstract #CT022. Data on file.

- L-MIND: Gute Ergebnisse & akzeptables Sicherheitsprofil bei ASCT-ungeeigneten Pat. mit rezidiviertem DLBCL
- Selektionierte Patientenkohorte (!) mit besonders guten Ergebnissen im ersten späten Rezidiv

Duell J et al. AACR 2023

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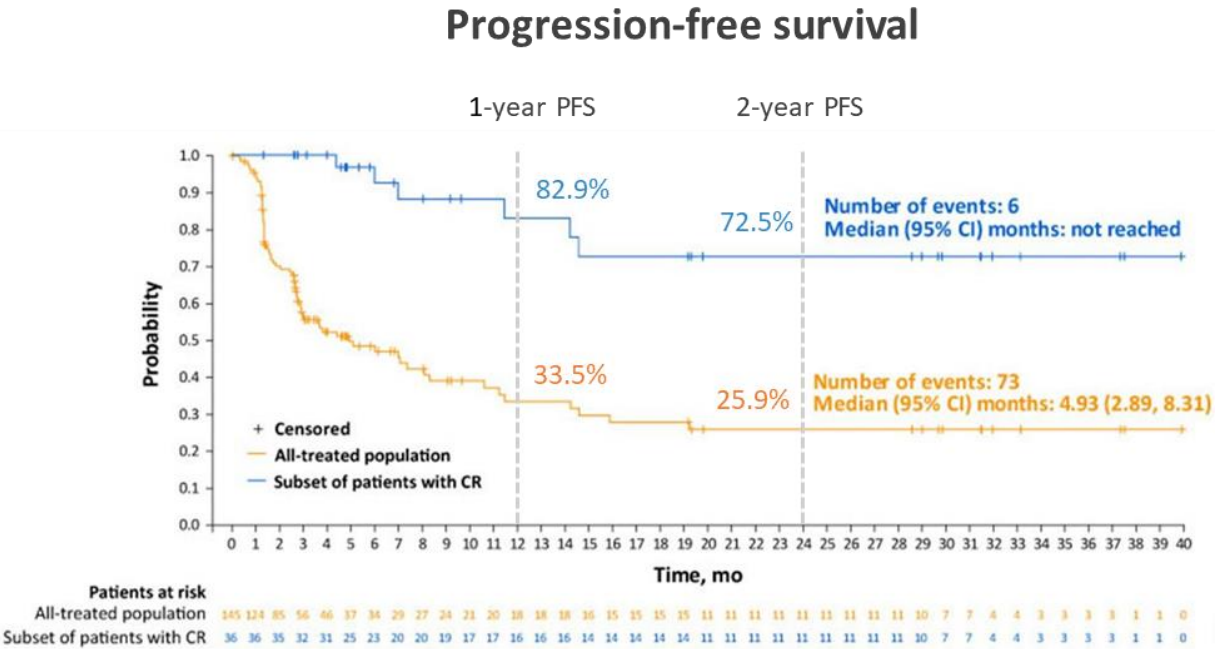
Loncastuximab tesirine bei r/r DLBCL: LOTIS-2 FU

- Phase II r/r DLBCL ≥2 Vortherapien
- i.v. Lonca 150 µg/kg Q3W) für 2 Zyklen, dann 75 µg/kg Q3W für bis zu 1 Jahr (bei Benefit länger möglich); Dexamethason-Prophylaxe
- 145 Patienten; medianes follow-up 7,8 Monate; 35 Monate für CR-Pat.
- Besondere Nebenwirkungen (alle Grade): Ödeme/Ergüsse (31%), Haut- und Nagelreaktionen (43,4%), Leberenzymveränderungen (52.4%)



- Primärer Endpunkt Overall response rate: 48.3% (24,8% CR und 23,4% PR)
- Medianes PFS 4,9 Monate, medianes OS 9,5 Monate; mediane Dauer des Ansprechens 13,4 Monate

Caimi et al. ICML 2023

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Das diffuse großzellige B-Zell-Lymphom (DLBCL): Aktuelle Therapiestrategien

1. Erstlinie
2. Zweitlinie
3. Nach der Zweitlinie
4. Perspektiven

Perspektive Erstlinie

Titel:	Tx groups	Popu-lation	n	% of all 1st D[1]
ZUMA-23 NCT05605899	R-CHOP / DA-R-EPOCH versus Axi-cel	IPI 4, 5	300	16
EPCORE™ DLBCL-2 NCT05578976	R-CHOP versus Epco-R-CHOP	IPI 3-5	900	38
FRONTMIND	Tafa-Len R-CHOP vs R-CHOP	IPI 3-5	899	38
SKYGLO NCT06047080	Pola-R-CHP versus Glofi-Pola-R-CHP	IPI 2-5	1130	65

[1] International Non-Hodgkin's Lymphoma Prognostic Factors Project, NEJM 1993

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Immun- oder Chemotherapie? Paradigmenwechsel beim rezidivierten DLBCL. Zusammenfassung

1. Chemotherapie bleibt Therapie der Wahl für PatientInnen mit niedrigem Risiko für Tod, also Erstlinie und LR-Zweitlinie

2. Aber: Paradigmenwechsel! Immuntherapie vor Chemotherapie, seien es CARs oder bispecs oder bispecs+Ctx

3. CARs sind dabei die bisher einzige Option mit nachgewiesenem relevanten Potential für Heilung

➢ Dran denken bei der Indikationsstellung und
Strukturen schaffen oder festigen, damit das komplexe PatientInnenmanagement möglichst reibungsarm funktionieren kann

Cologne Lymphoma Working Group

Study Physicians
Nadine Kutsch
Philipp Goedel
Jan-Michel Heger

Study Assistance
Hanna Birkholz
Armin Memic

Project Management
Lars Pester
Brigitta Becker

Laboratory
Ron Jachimowicz
Paul Bröckelmann
Ruth Fühmann
Sven Borchmann
Hyatt Balke-Want

Apheresis Unit
Udo Holtick
Christoph Scheid

ICU Physicians
Boris Böll
Matthias Kochanek

Thank you very much for your attention!

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EHA LB3438: Glofitamab plus Gemcitabine and Oxaliplatin (Glofit-GemOx) for Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL): Results of a Global Randomized Phase III Trial (STARGLO). Abramson et al

1. Pluspunkte
   - Primärer Endpunkt ist erreicht: Das OS von Glo-GemOx ist besser als von R-GemOx. PFS und ORR und CRR sind es auch. Es ist auf jeden Fall wirksamer als R-GemOx.
   - Das Tox Profil entspricht de Summer beider Interventionen. Es gibt relevante TRM, allerdings wurde die Studie zu COVID Zeiten durchgeführt und COVID hat dazu relevant beigetragen. Es ist auf jeden Fall machbar.
2. Offene Fragen
   - Fehlende Hochdosis-Fähigkeit ist ungewöhnlich bei einem medianen Alter von 68 Jahren, aber vor allem keine Kategorie mehr in der CAR-Ära.
   - Somit ist die Implementierung in den aktuellen Therapiealgorithmus schwierig. Vergleich zu CAR Daten? Heilung und Plateau?

Perspektive Erstlinie

Titel:	Tx groups	Popu-lation	n	% of all 1st D[1]
ZUMA-23 NCT05605899	R-CHOP / DA-R-EPOCH versus Axi-cel	IPI 4, 5	300	16
EPCORE™ DLBCL-2 NCT05578976	R-CHOP versus Epco-R-CHOP	IPI 3-5	900	38
FRONTMIND	Tafa-Len R-CHOP vs R-CHOP	IPI 3-5	899	38
SKYGLO NCT06047080	Pola-R-CHP versus Glofi-Pola-R-CHP	IPI 2-5	1130	65

[1] International Non-Hodgkin's Lymphoma Prognostic Factors Project, NEJM 1993

Update High-Grade NHL: Zusammenfassung

1. Erstlinie bleibt im Prinzip Chemotherapie-basiert (R-CHOP oder Pola-R-CHP)

2. Ab dann aber: Paradigmenwechsel! Immuntherapie vor Chemotherapie, seien es CARs oder bispecs oder bispecs+Ctx

➢ Dran denken bei der Indikationsstellung und
Strukturen schaffen oder festigen, damit das komplexe PatientInnenmanagement möglichst reibungsarm funktionieren kann

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