KML Symposium DGHO 2019
Speed-Report: aggressive NHL

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Offenlegung Interessenskonflikte

1. **Anstellungsverhältnis oder Führungsposition:** keine

2. **Beratungs- bzw. Gutachtertätigkeit:** Roche, Celgene, Gilead, Janssen, Novartis, Riemser, MSD, Jazz

3. **Besitz von Geschäftsanteilen, Aktien oder Fonds:** keine

4. **Patent, Urheberrecht, Verkaufslizenz:** keine

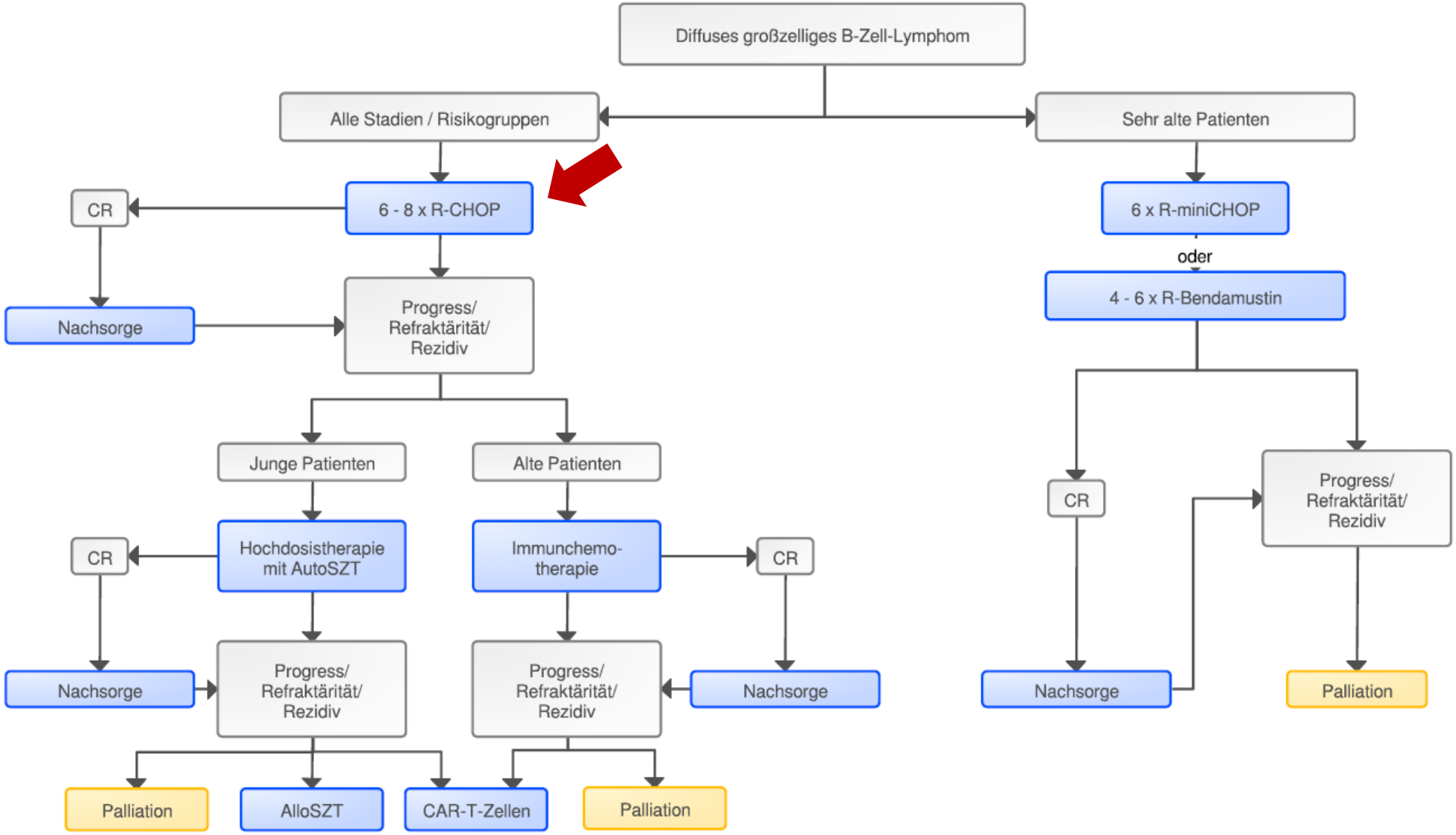
5. **Honorare:** Roche, Celgene, Riemser, Janssen, MSD, Jazz

6. **Finanzierung wissenschaftlicher Untersuchungen:** Roche, Celgene, Amgen

7. **Andere finanzielle Beziehungen:** keine

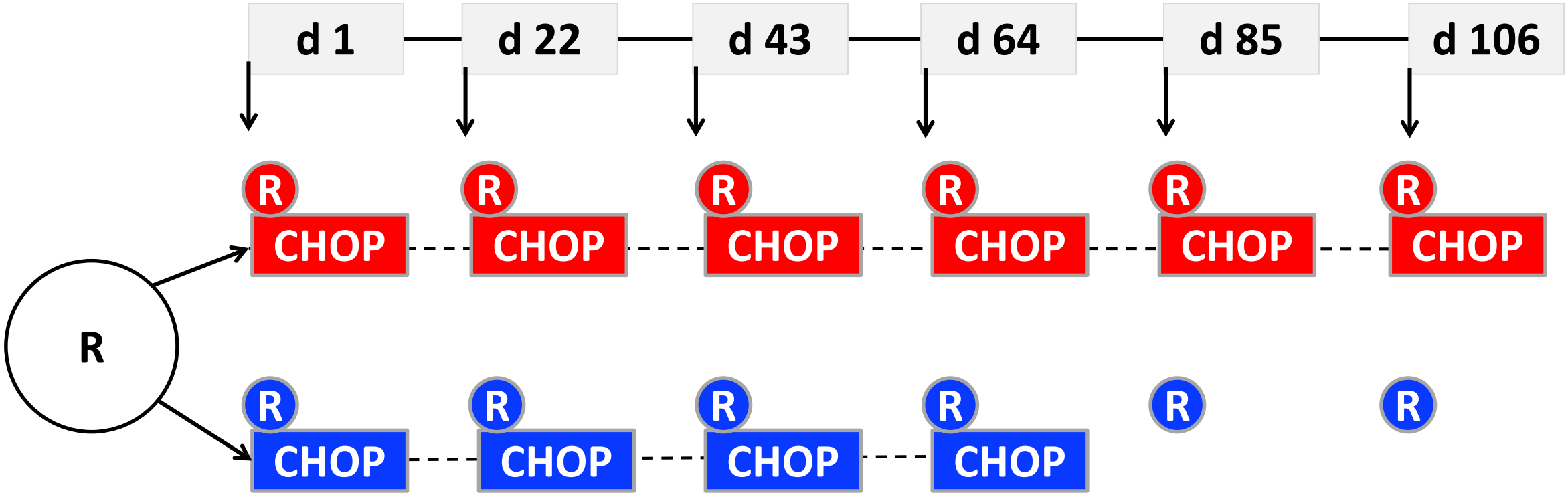
8. **Immaterielle Interessenkonflikte:** keine

Aggressive B-NHL
DGHO Guidline 2019 – current developments and open questions

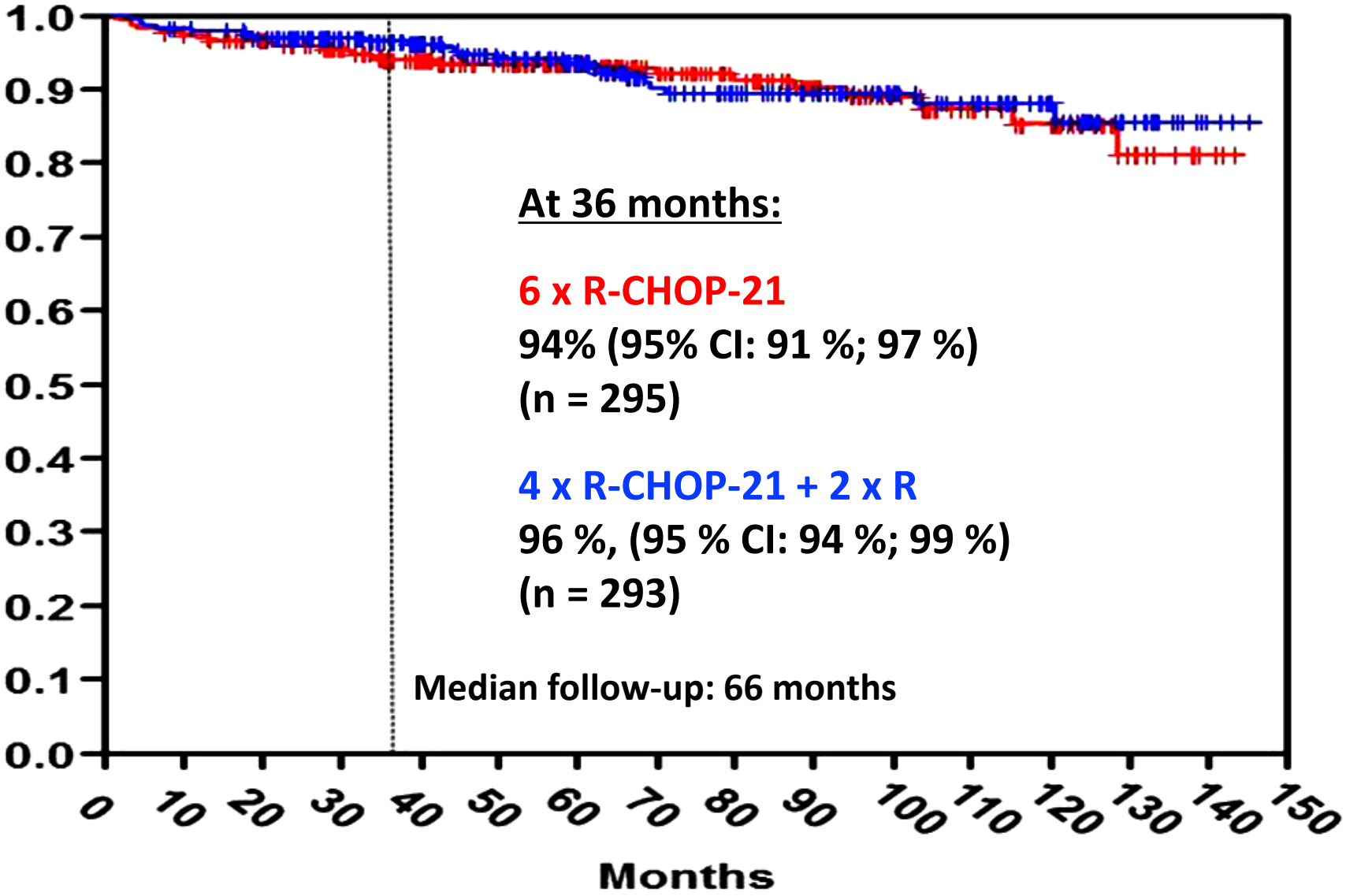


FLYER: Study Design

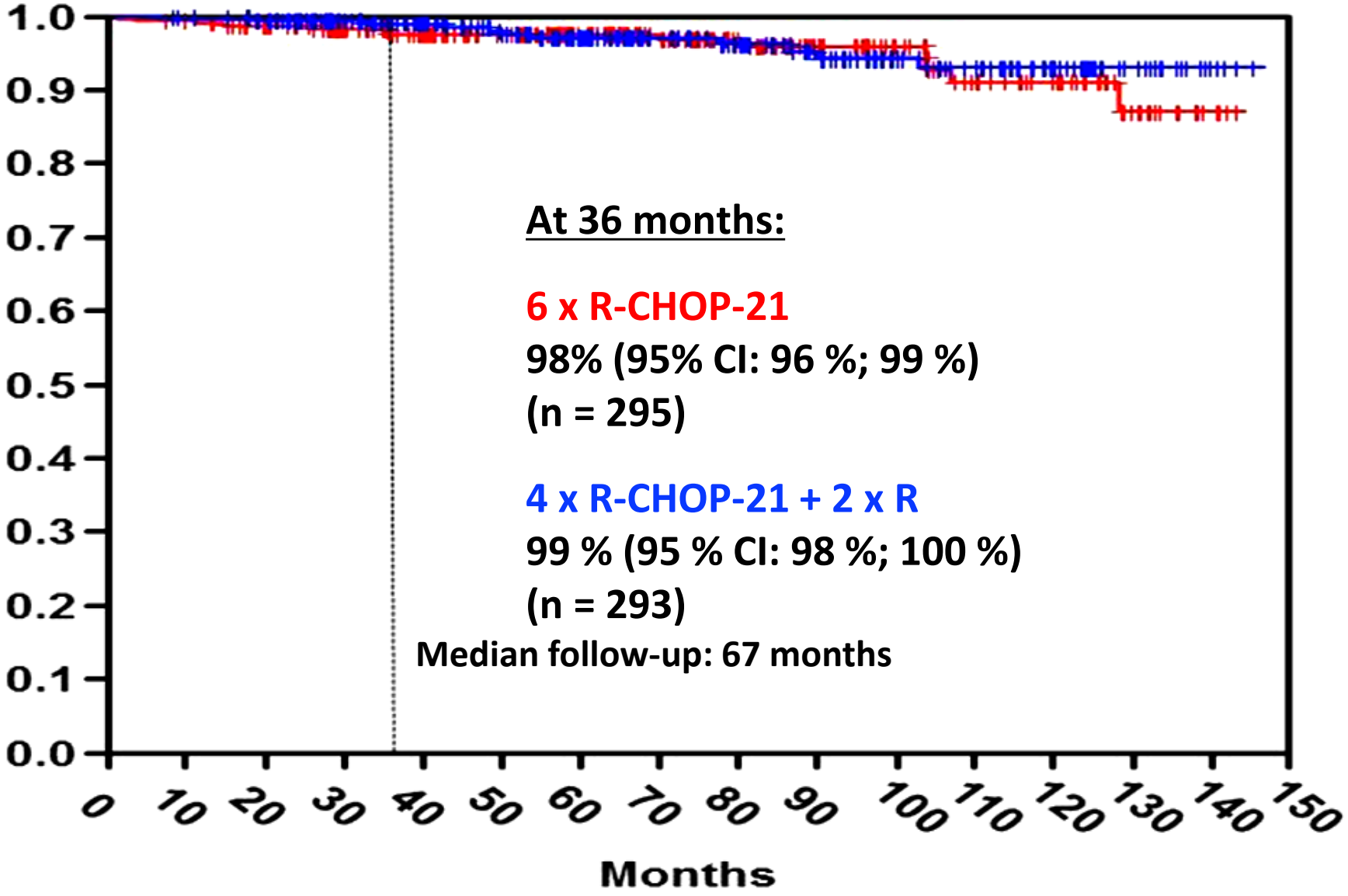
- **Front-line treatment of aggressive B-cell lymphoma**
- **18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)**



Primary Endpoint: PFS



Overall Survival (OS)



At 36 months:

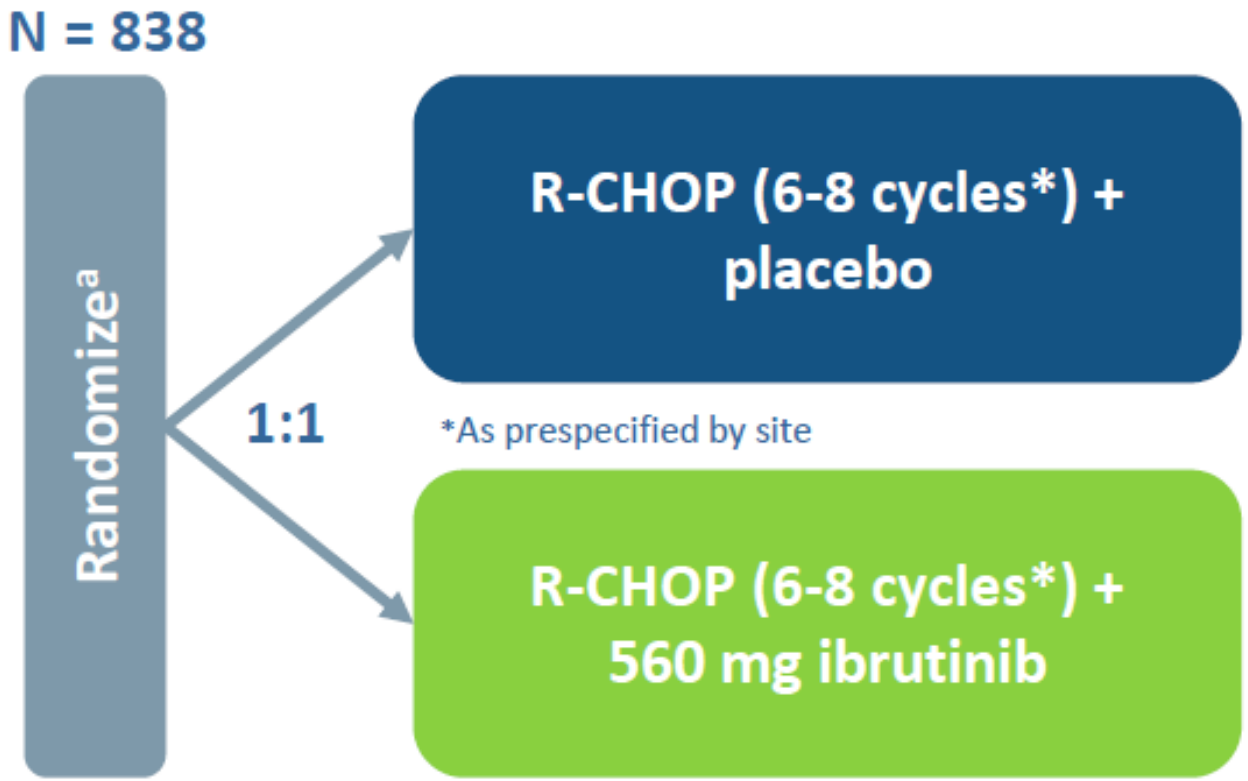
6 x R-CHOP-21
98% (95% CI: 96 %; 99 %)
(n = 295)

4 x R-CHOP-21 + 2 x R
99 % (95 % CI: 98 %; 100 %)
(n = 293)

Median follow-up: 67 months

Study Design: Double-Blind, Placebo-Controlled Study

PHOENIX PCI-32765DBL3001



[a]Stratified by R-IPI, region, and number of prespecified treatment cycles (6 vs 8 cycles).
- Prophylactic antibiotics and G-CSF were not mandated but were permitted at the investigator's discretion per local or other standard guidelines

[†]EFS: time from randomization to PD, relapse from CR, initiation of subsequent disease-specific therapy for PET-positive or biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death.

Key eligibility criteria

- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analyzed for ABC subtype using GEP
- Stage II to IV measureable disease
- R-IPI ≥ 1
- ECOG performance status ≤ 2

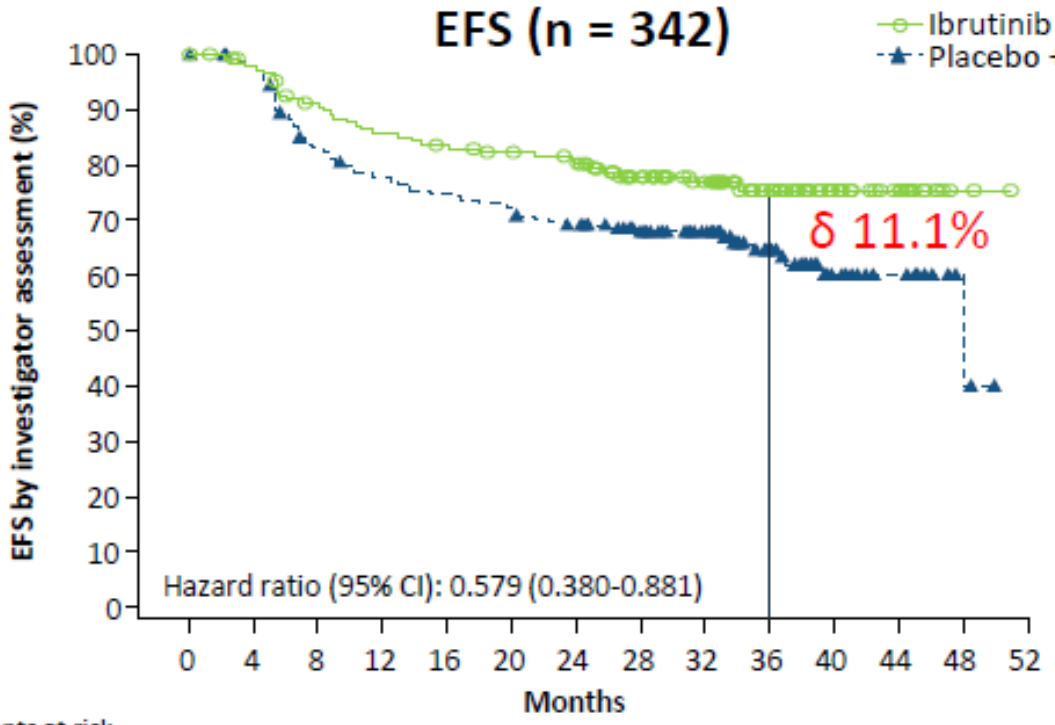
End points

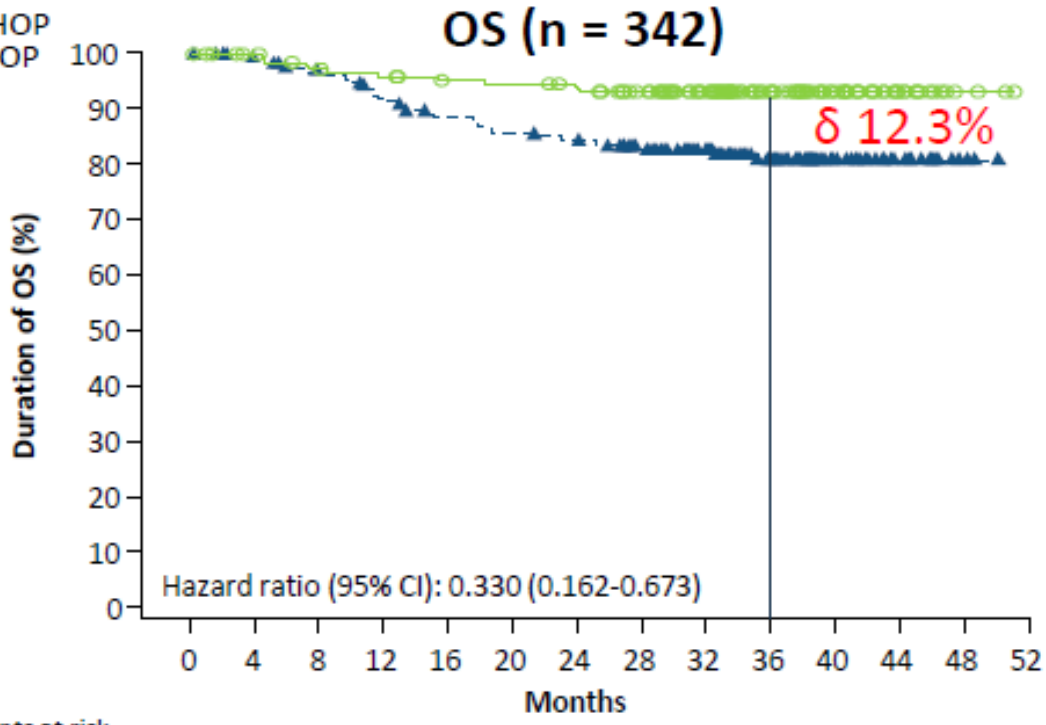
- Primary end point: EFS[†] in ITT (non-GCB) and ABC subgroup
- Secondary end points: PFS, CR rate, OS, safety
  - Response assessed per Revised Response Criteria for Malignant Lymphoma[1]

1. Cheson BD, et al. *J Clin Oncol*. 2007;25:579-586.

EFS and OS in Patients < 60 Years

PHOENIX
PCI-32765DBL3001





Patients at risk

Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0

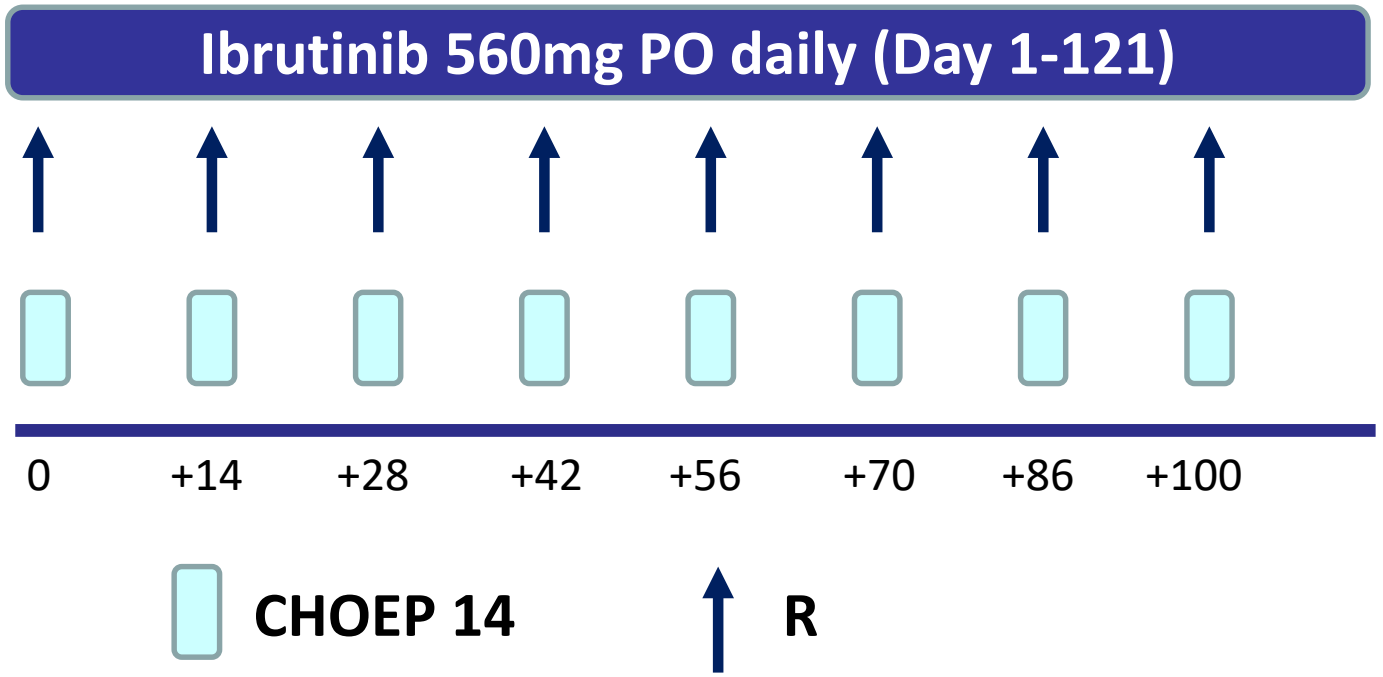
Patients at risk

Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

- **Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age**
- **Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors**
- **A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS)**
- **More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (25.2% vs 33.5%)**

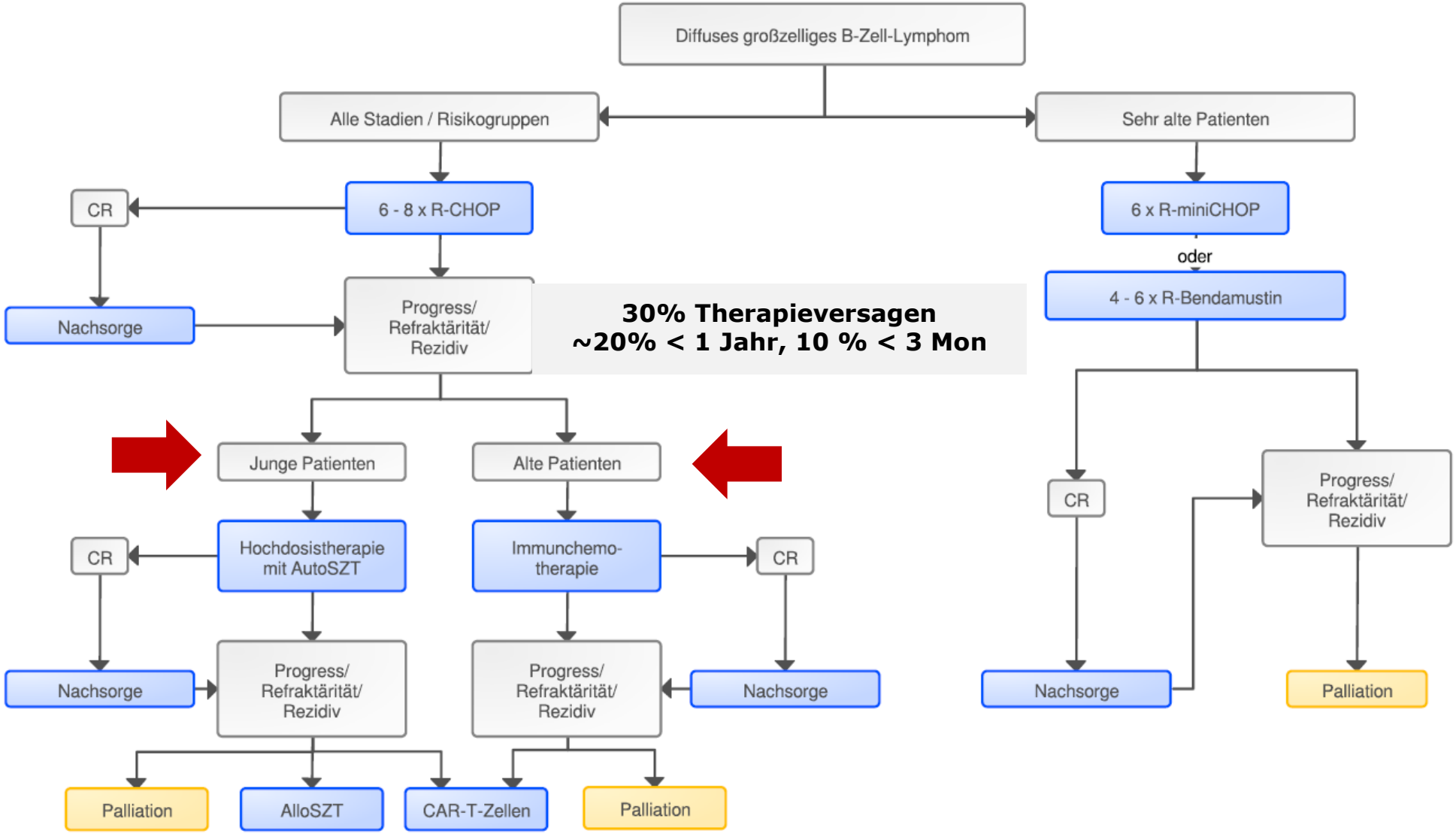
Trotz negativem Ausgang der PHOENIX-Studie: Projekt wird weiter verfolgt (Hinweis auf Subgruppen relevant)

- DLBCL (all molecular subtypes)
- No PMBL
- aaIPI= 2-3
- Age 18-60 yrs

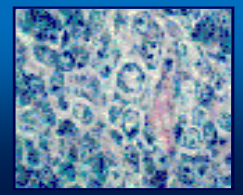


CYC 750 mg/m² d1
DOX 50 mg/m² d1
VCR 1.4 mg/m² d1
ETO 100 mg/m² d1-3
PRD 100 mg/m² d1-5

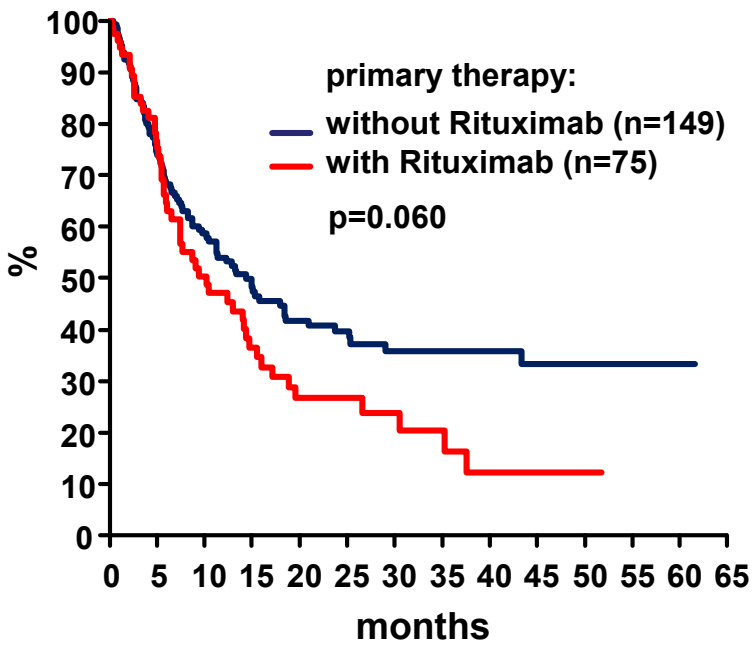
Diffuse Large B Cell Lymphoma: DGHO Leitlinie 2019



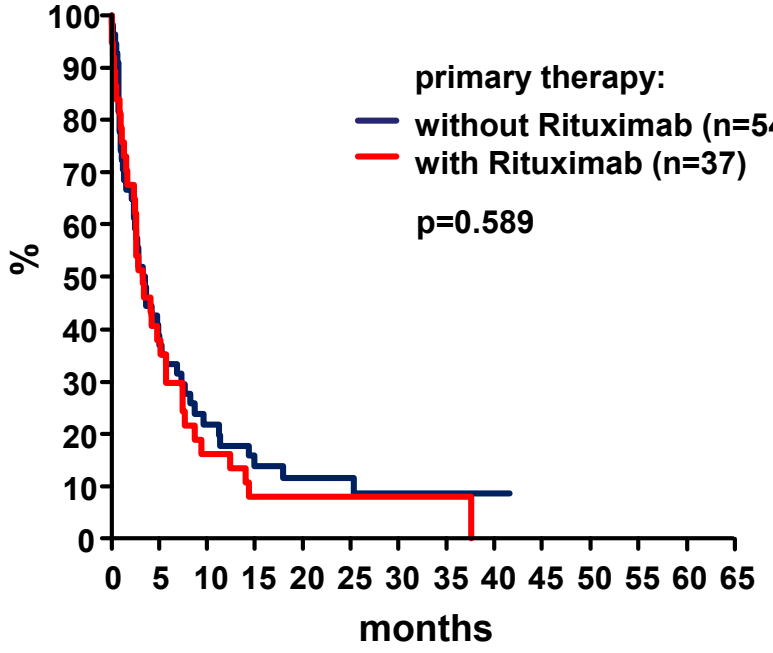
Second line treatment in elderly patients
Secondary OS after failure of standard therapy
RICOVER-60 study



relapsed disease



primary refractory



Randomised Phase II study of pola-BR versus BR (GO29365): study design

Patients
- R/R DLBCL
- R/R FL

Safety run-in phase → **Pola 1.8mg/kg + BR (n=6/histology)** OR **Pola 1.8mg/kg + BG (n=6/histology)**

Phase II expansion → **Pola 1.8mg/kg + BG (n=20/histology)**

Phase II randomisation → R 1:1 → **Pola 1.8mg/kg + BR (n=40/histology)**; **BR (n=40/histology)**

Primary endpoint (Phase II): PET-CR rate according to modified Lugano criteria

BG, bendamustine and obinutuzumab; BR, bendamustine and rituximab; FL, follicular lymphoma; PET-CR, positron electron tomography–complete response; pola, polatuzumab vedotin; R, randomisation; R/R, relapsed/refractory

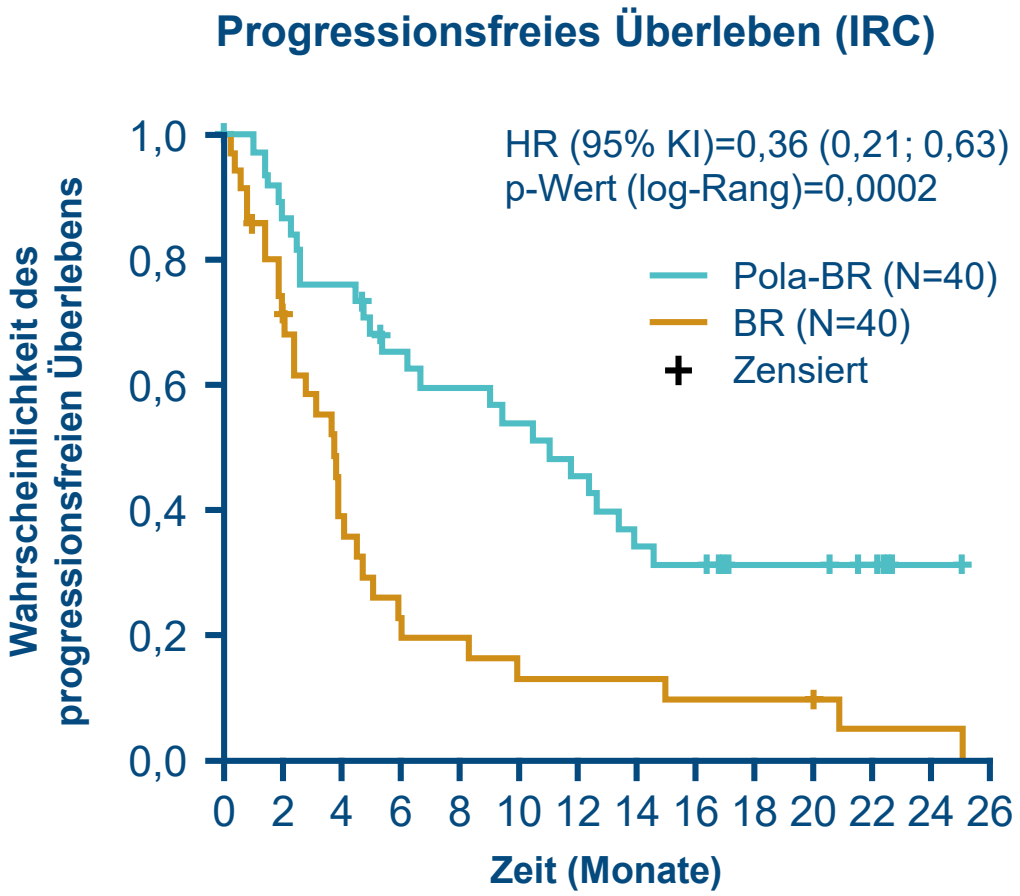
Sehn L, et al. Abstract #1683, ASH 2018

Ergebnisse: Baseline-Charakteristika

Hauptcharakteristika	Phase-Ib	Phase-Ib/II	Phase-II randomisiert	
	Pola-BR (N=6)	Pola-BG (N=27)	Pola-BR (N=40)	BR (N=40)
Mittleres Alter, Jahre (Range)	65 (58-79)	66 (26-86)	67 (33-86)	71 (30-84)
ECOG PS Score ≥2, n (%)	0	4 (14,8)	7 (17,5)	9 (22,5)
IPI Score 3-5 bei Registrierung, n (%)	2 (33,3)	20 (74,1)	22 (55,0)	29 (72,5)
Vorherige Therapielinien, n (%)				
1 Linie	2 (33,3)	6 (22,2)	11 (27,5)	12 (30)
≥2 Linien	4 (66,7)	21 (77,8)	29 (72,5)	28 (70)
Refraktär gegenüber der vorherigen Therapie, n (%)*	5 (83,3)	23 (85,2)	30 (75,0)	34 (85,0)
Vorherige Stammzelltransplantation, n (%)	0	2 (7,4)	10 (250)	6 (15,0)

*Kein Ansprechen oder PD innerhalb 6 Monate nach der letzten Therapiedosis
IPI: Internationaler Prognostischer Index

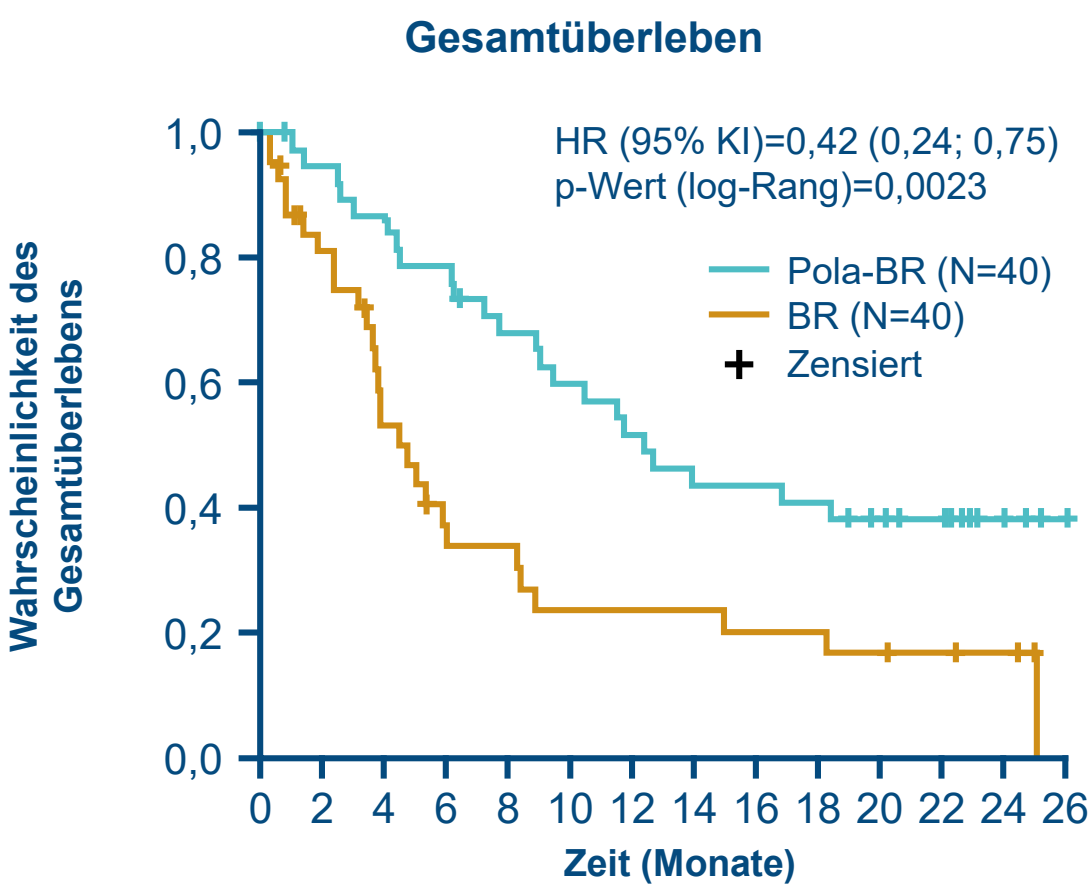
Ergebnisse: Wirksamkeit



Anzahl Patienten

Pola-BR(Ph II) 40383329292523212121191816141211118 7 7 7 6 5 1 1

BR(Ph II) 4030241812 9 7 6 6 5 4 4 4 4 4 3 3 3 3 3 2 1 1 1 1 1



Anzahl Patienten

Pola-BR(Ph II) 40383634333030272524222119171616161515131 2 9 9 5 3 2 1

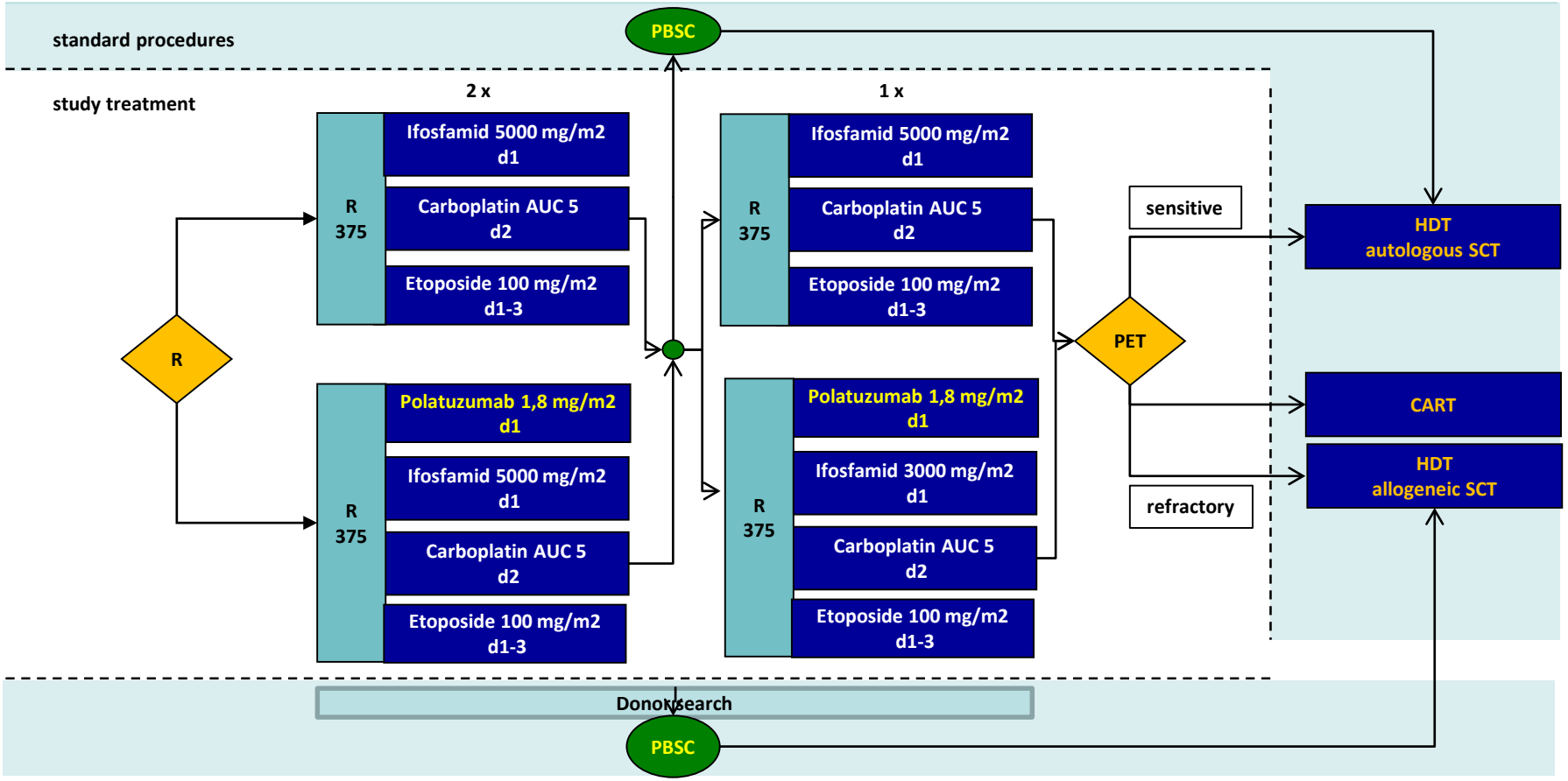
BR(Ph II) 403327251715111010 7 7 7 7 7 7 6 6 6 6 5 5 4 4 3 3 1

2. Linentherapie DLBCL: Resultate der Salvagetherapie und autologen SZT in 3 prospektiv-randomisierten klinischen Studien

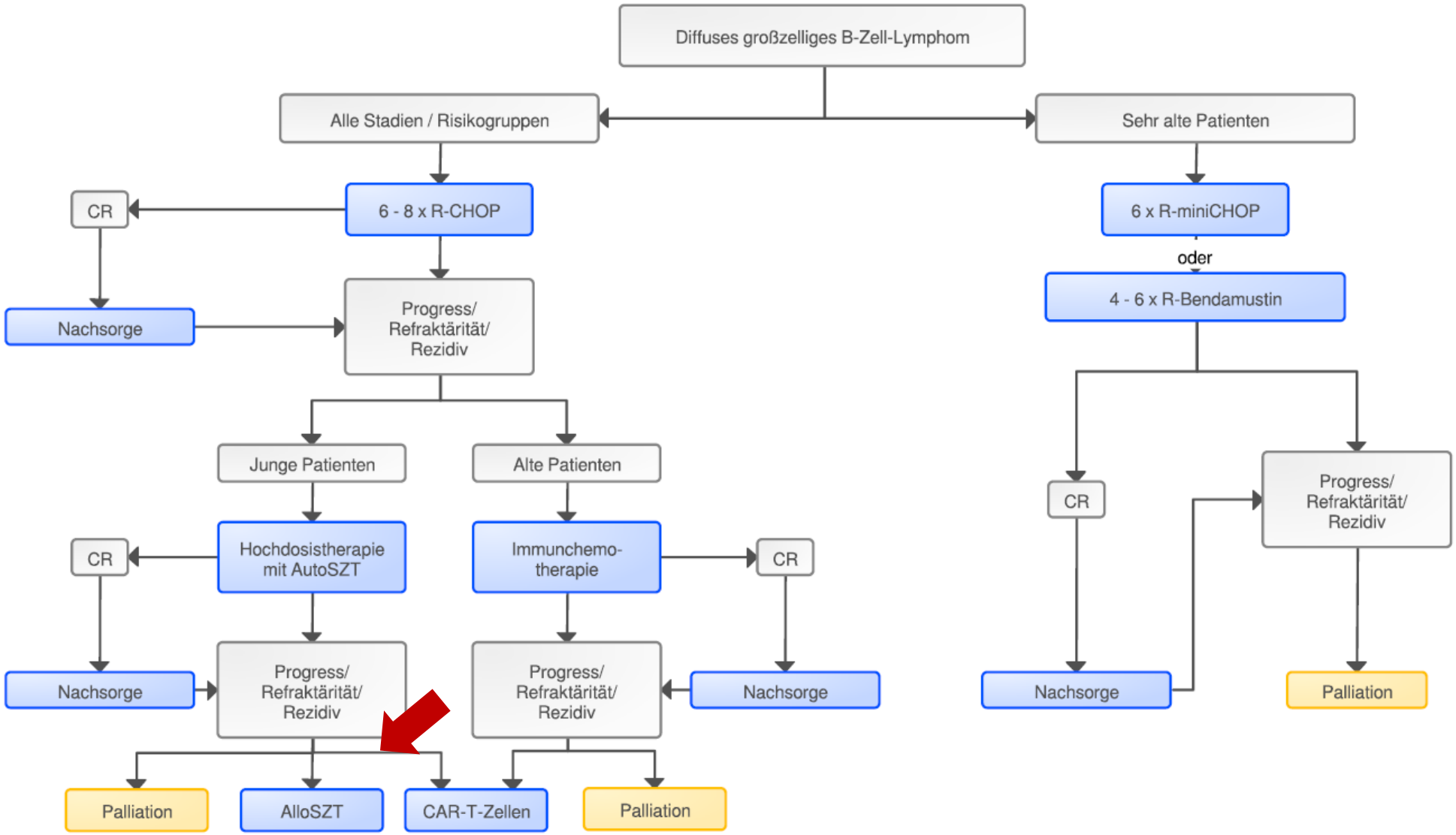
Study	Salvage regimen	ORR		PFS /EFS		OS		OT	Referenz
CORAL	R-DHAP	62,8 %	51% *	42%	21%* EFS	51%	40%*	3 y	Gisselbrecht JCO 2010
	R-ICE	63,5%		31%		47%			
NCIC-CTG LY.12**	R-DHAP	44,1 %		26% EFS		39%		4y	Crump JCO 2014
	R-GDP	45,1%		26% EFS		39%			
ORCHARD	R-DHAP	42%		26%		38%		2y	Van Imhoff JCO 2017
	O-DHAP	38%		24%		41%			

R-DHAP: Rituximab, Cytarabin, Cisplatin; R-ICE: Rituximab, Ifosfamid, Etoposid; R-GDP: Rituximab, Gemcitabin, Dexamethason, Cisplatin; O-DHAP: Ofatumomab, Cytarabin, Cisplatin ; ORR: overall response rate ; PFS: progression free survival; OS: overall survival; OT: (median) observation time

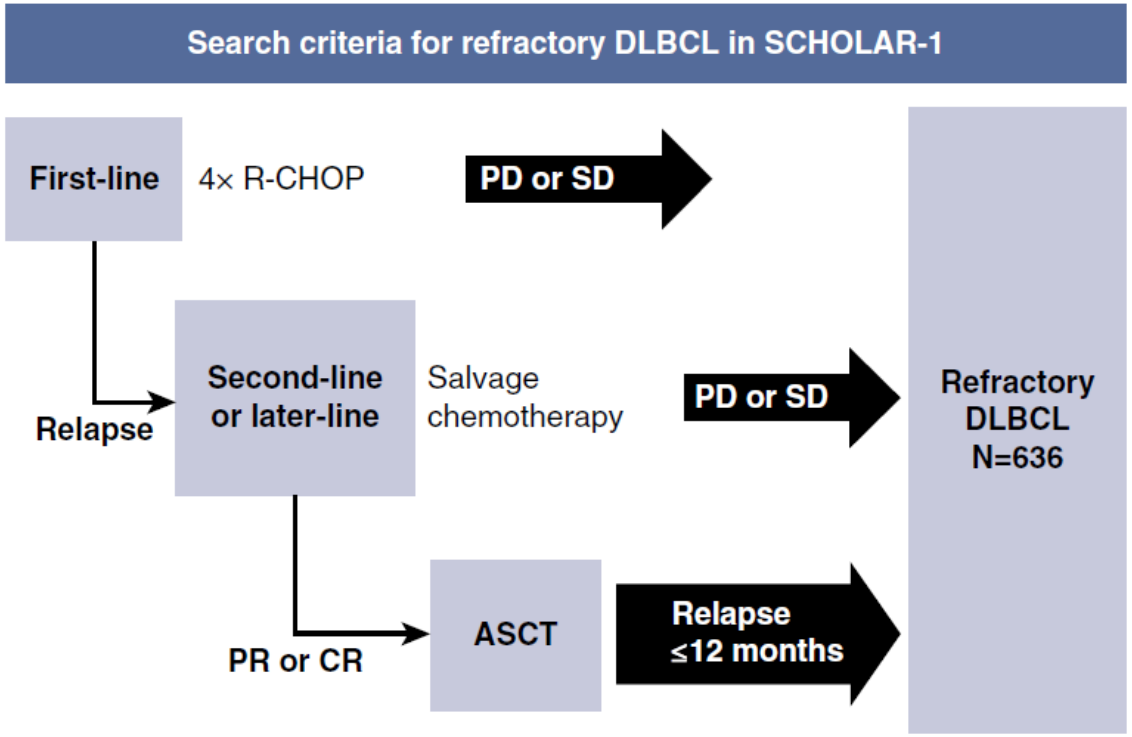
PolaRICE Phase III clinical trial: PolaR-ICE vs R-ICE in r/r DLBCL

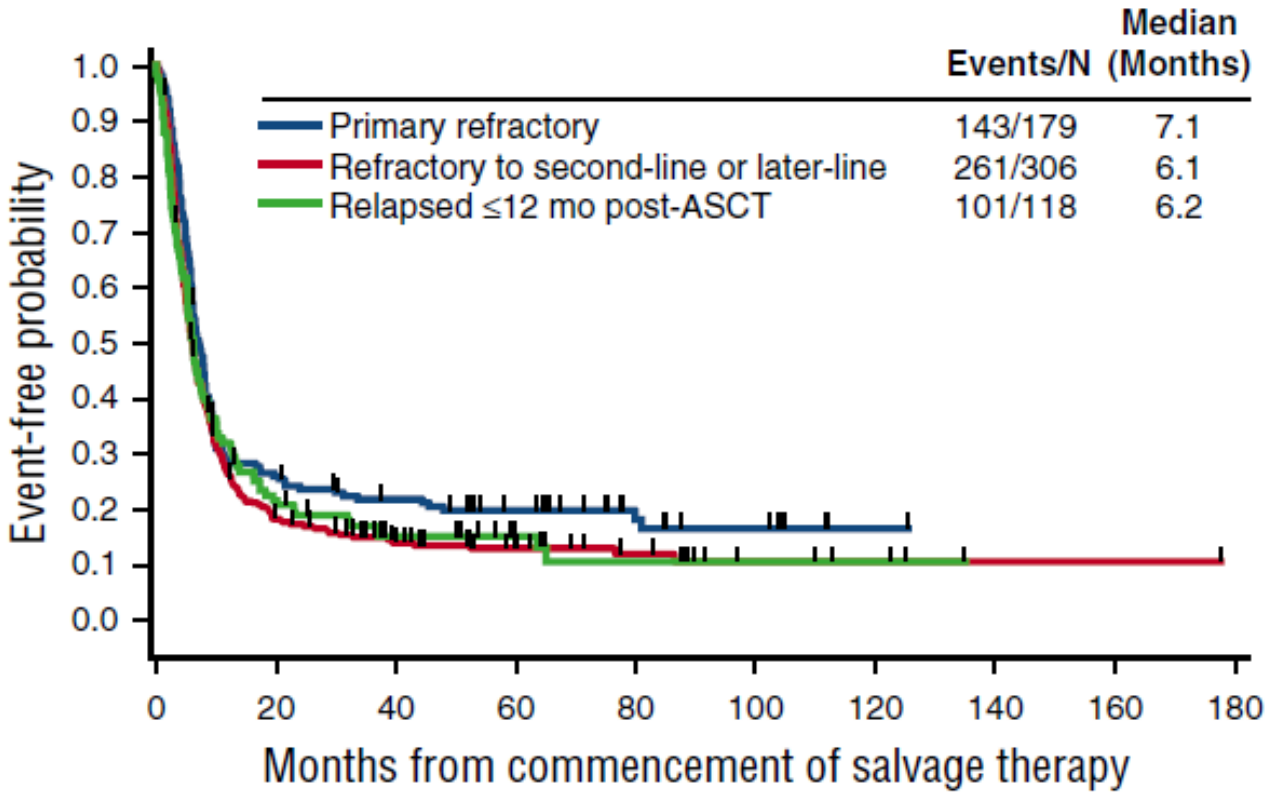


Aggressive B-NHL
DGHO Guidline 2019 – current developments and open questions



Ereignisfreies Überleben von Patienten mit refraktärem DLBCL

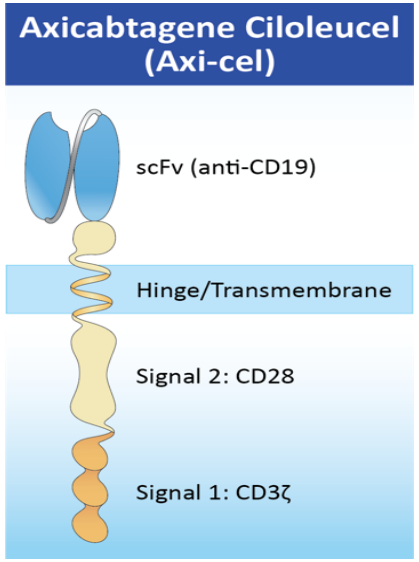


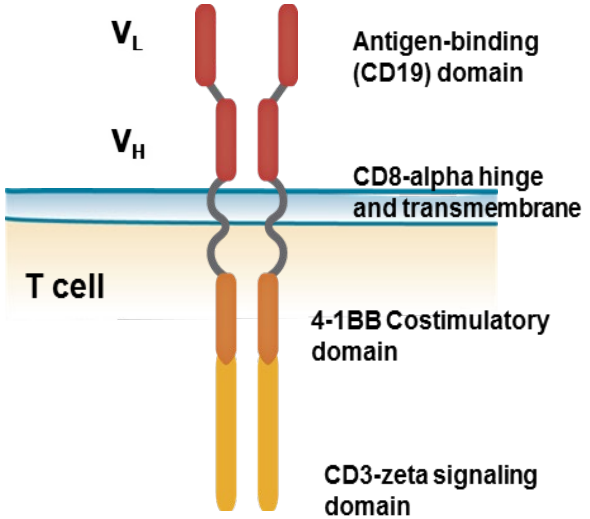


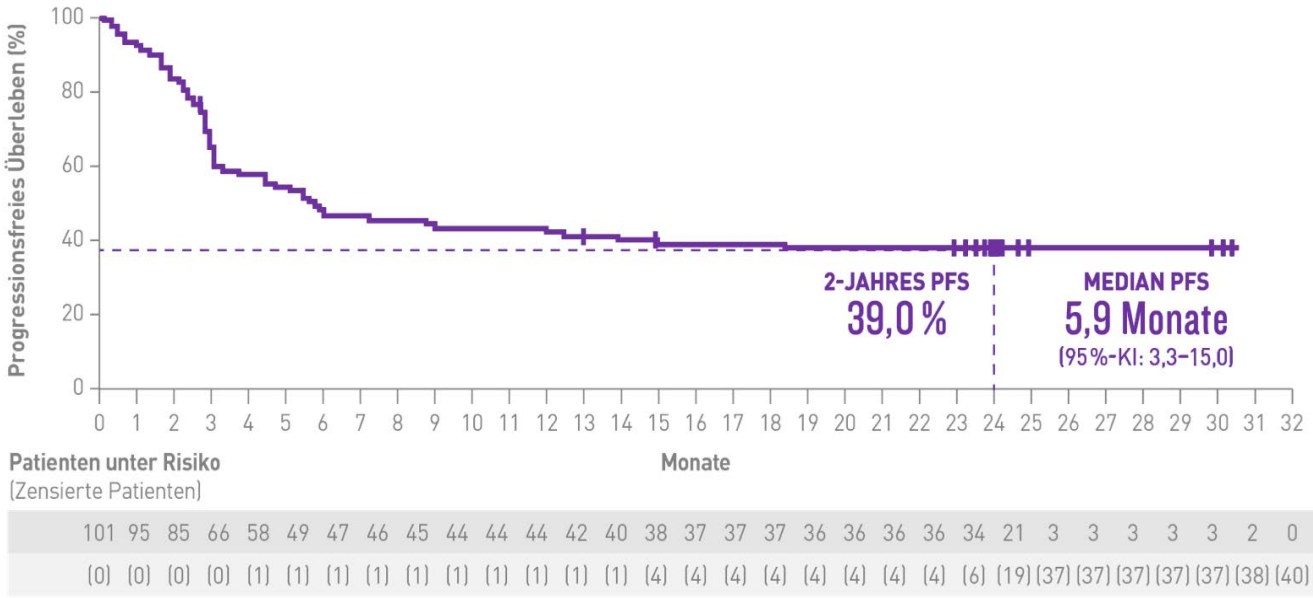
Crump-Blood-2017-130-1800-08

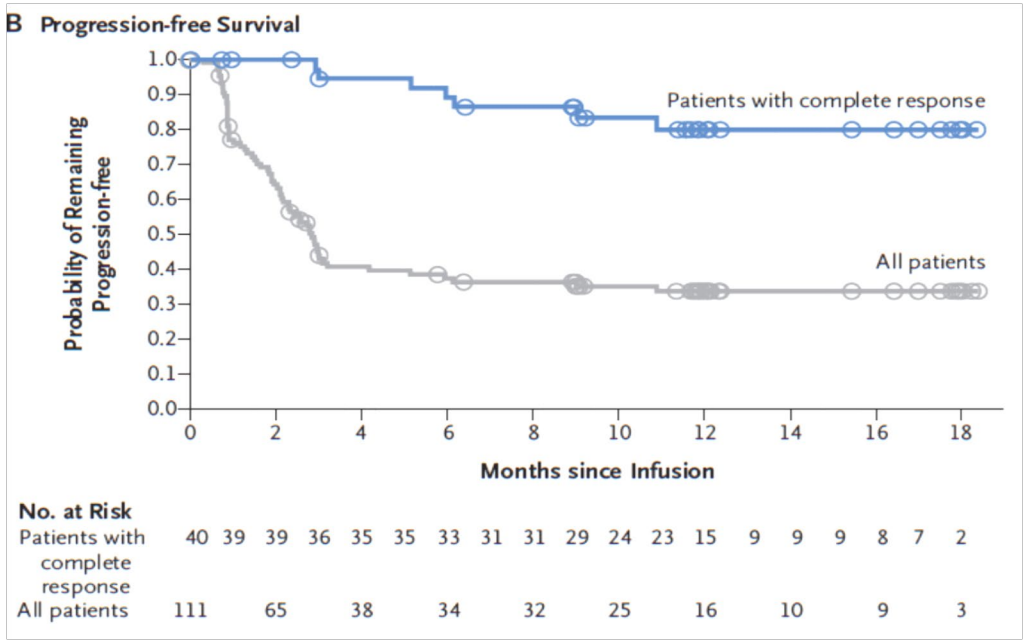
Ca. 400- 500 Patienten / Jahr in Deutschland

Axicabtagene ciloleucel, Tisagenlecleucel: Chimeric Antigen Receptor T cell gegen CD19+ NHL

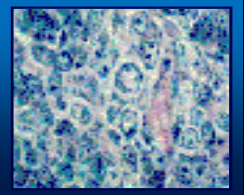




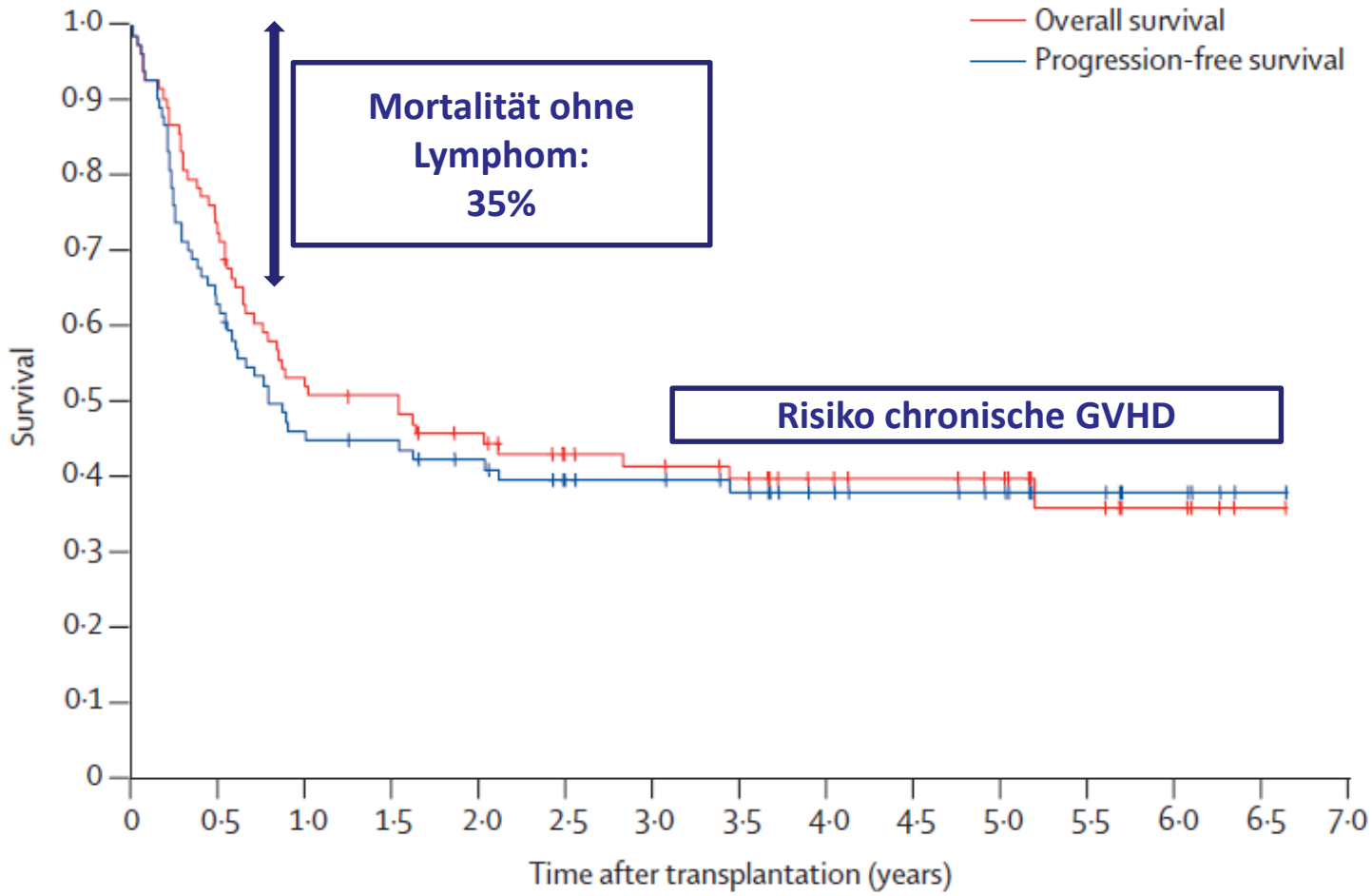




OS and PFS for all patients (n=84)



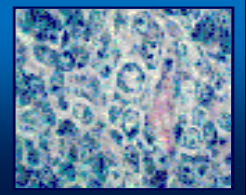
Nur jüngere Patienten ohne schwere Begleiterkrankung

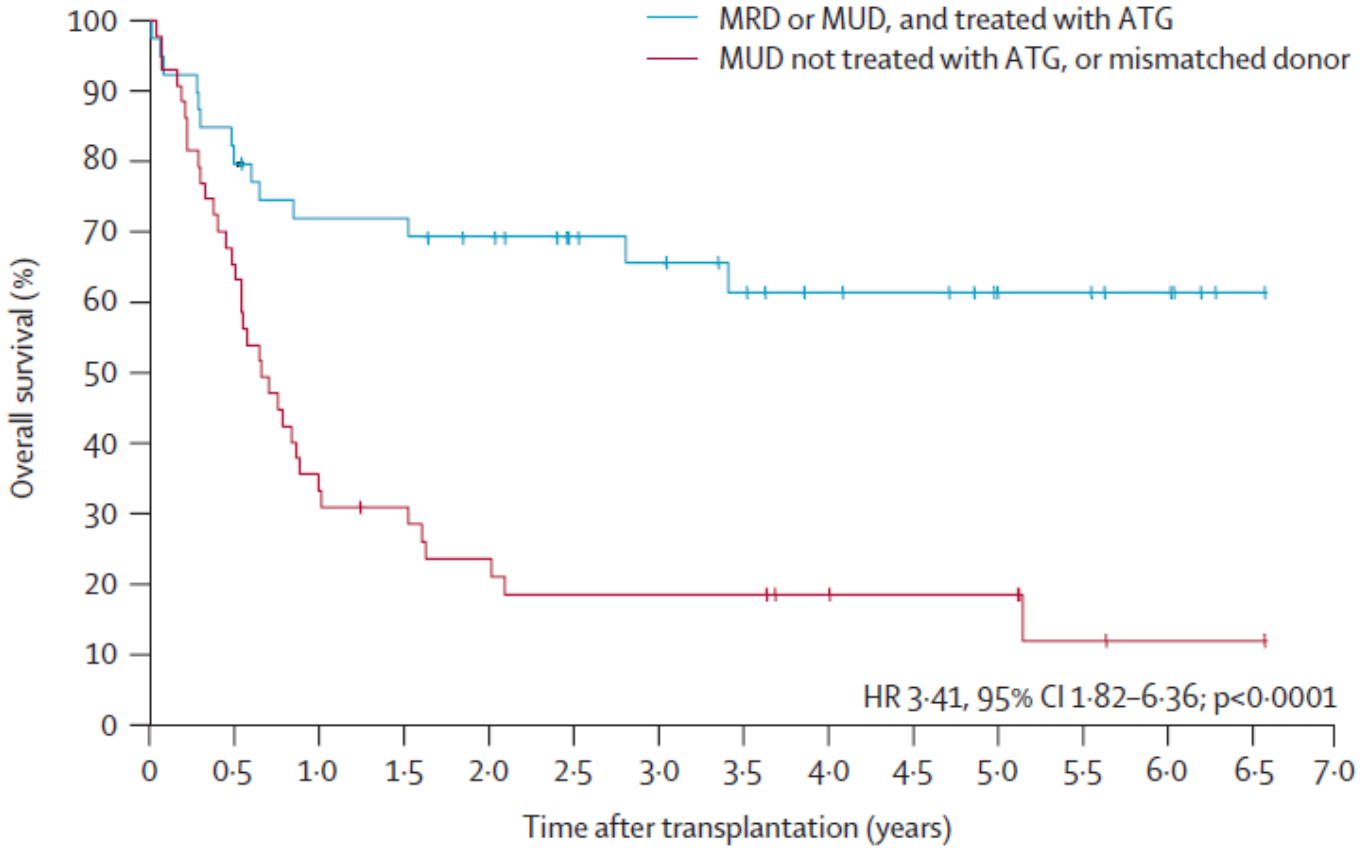


Number at risk															
Overall survival	84	62	43	41	35	28	26	23	18	16	14	9	6	2	0
Progression-free survival	84	52	37	36	32	26	25	22	17	15	13	9	6	2	0

Glass et al, Lancet Oncology 2014 15: 757-66

DSHNHL R3
Outcome due to donor match and ATG

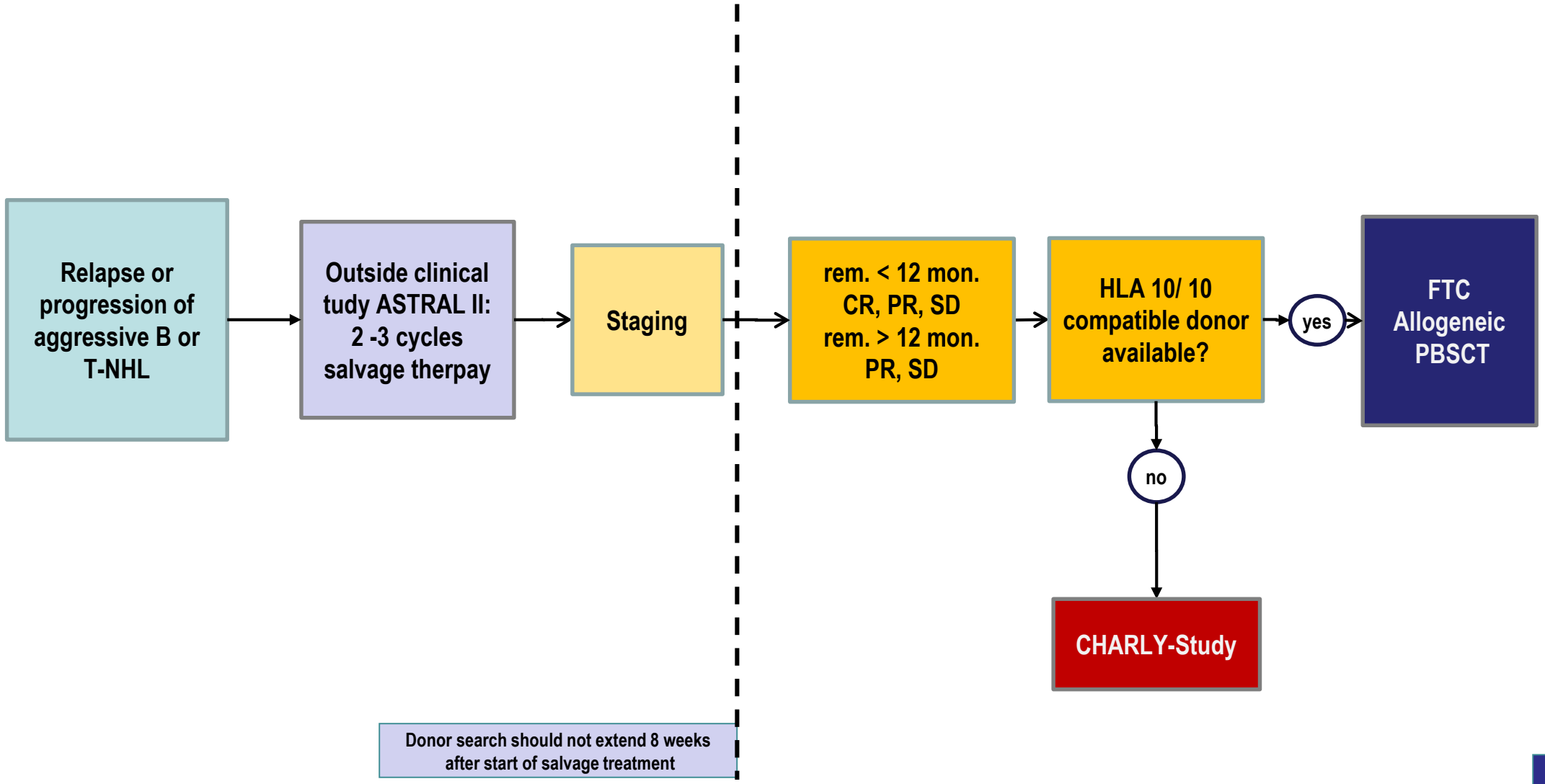




Number at risk															
MRD or MUD and ATG	40	33	28	28	25	20	15	12	11	9	7	5	4	1	0
MUD not treated with ATG, or mismatched donor	44	29	15	13	10	8	8	6	5	5	2	1	1	1	0

Glass et al, Lancet Oncology 2014 15: 757-66

DSHNHL-R7 ASTRAL II
Allogeneic SCT in Relapsed Aggressive NHL
Flowchart



Bertram.Glass@helios-gesundheit.de

CHARLY flow sheet

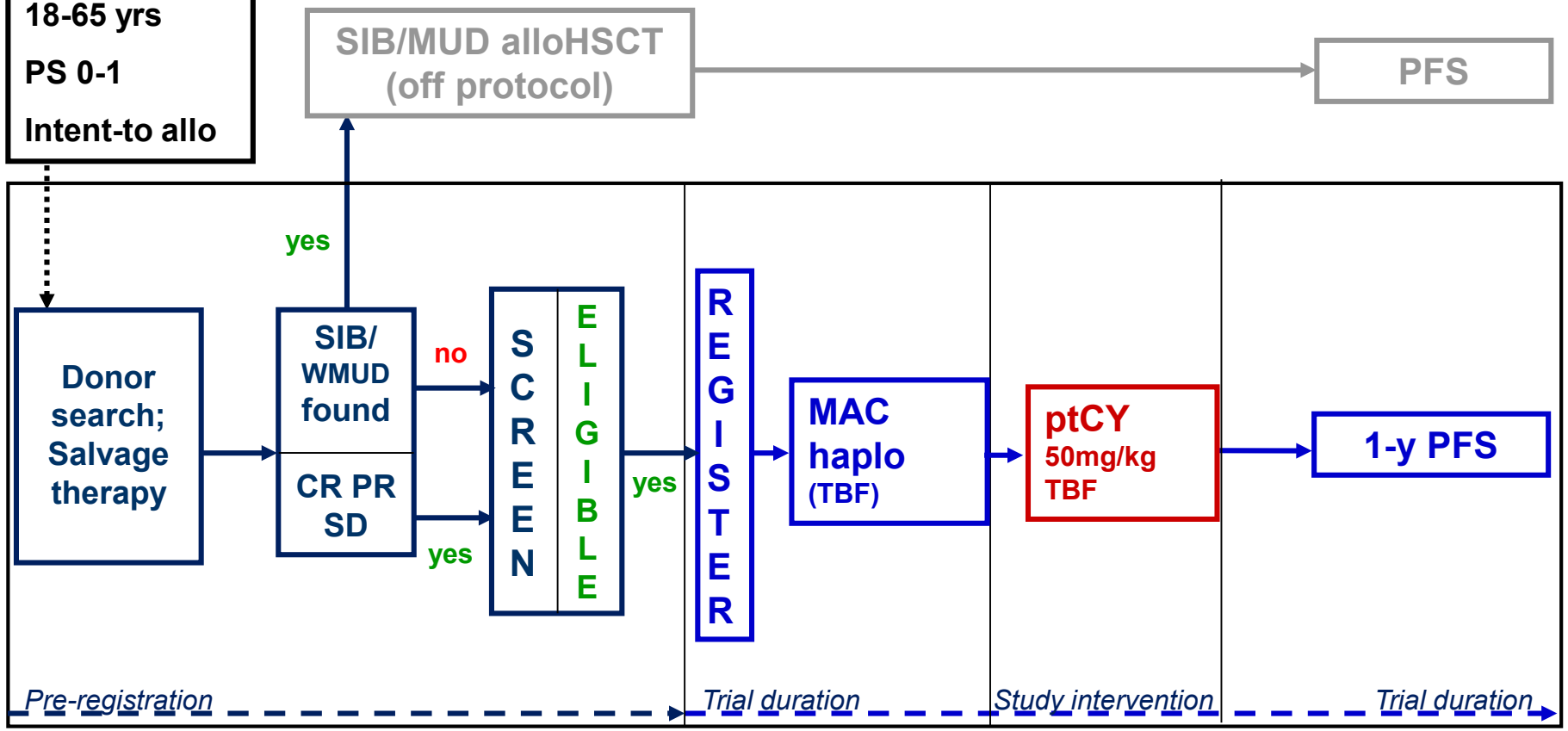
DLBCL, MCL, FL, PTCL, Richter

Failed auto or double refractory

18-65 yrs

PS 0-1

Intent-to allo



Sascha.Dietrich@med.uni-heidelberg.de

Speed-Report: aggressive NHL
Zusammenfassung

De-Esklation der Chemotherapie bei (jungen) Patienten mit niedrigem Risiko (IPI =, no bulk) möglich.

Ibrutinib + R-CHOP in Phase 3 Studie gescheitert, aber gute Ergebnisse bei jüngeren Patienten. Phase II Studie Ibrutinib + R-CHOEP weiter offen

ADC Polatuzumab Vedotin mit guten Ergebnissen in der Drittlininen-Therapie der nicht-transplantationsfähigen Patienten vor der Zulassung. Zukünftig Einsatz zum Bridging in der 2. und 3. Therapielinie vor Konsolidierung (SZT, CART) ?

CART im Routineeinsatz mit ca 30-40 % PFS für die Patienten, die die Infusion erhalten; allo SZT als Option bei CART-Versagen (für jüngere Patienten)