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Aggressive Lymphome

Peter Neumeister, MD

Klinische Abteilung für Hämatologie

Research Unit: Lymphoid Malignancies

www.medunigraz.at/lymphomforschung/

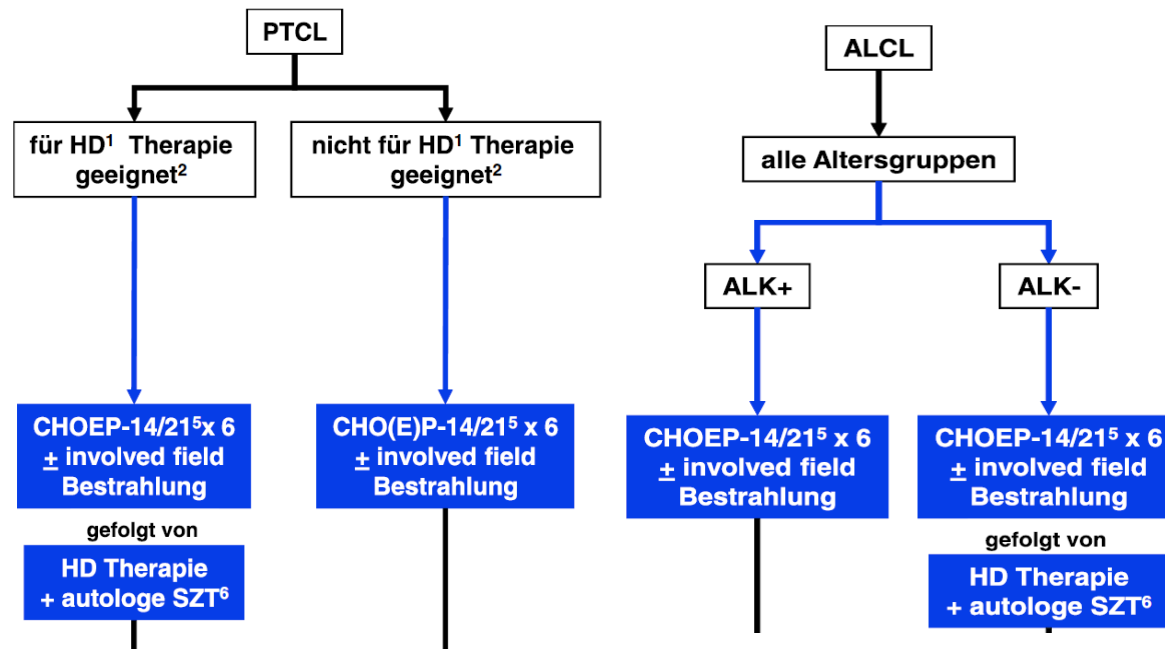
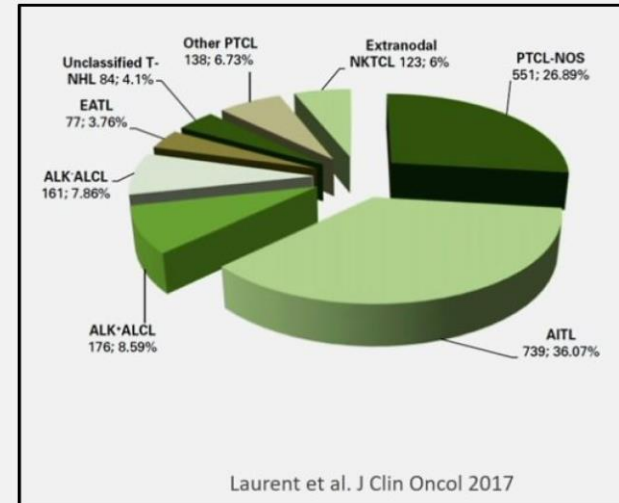
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Periphere T-Zell Lymphome



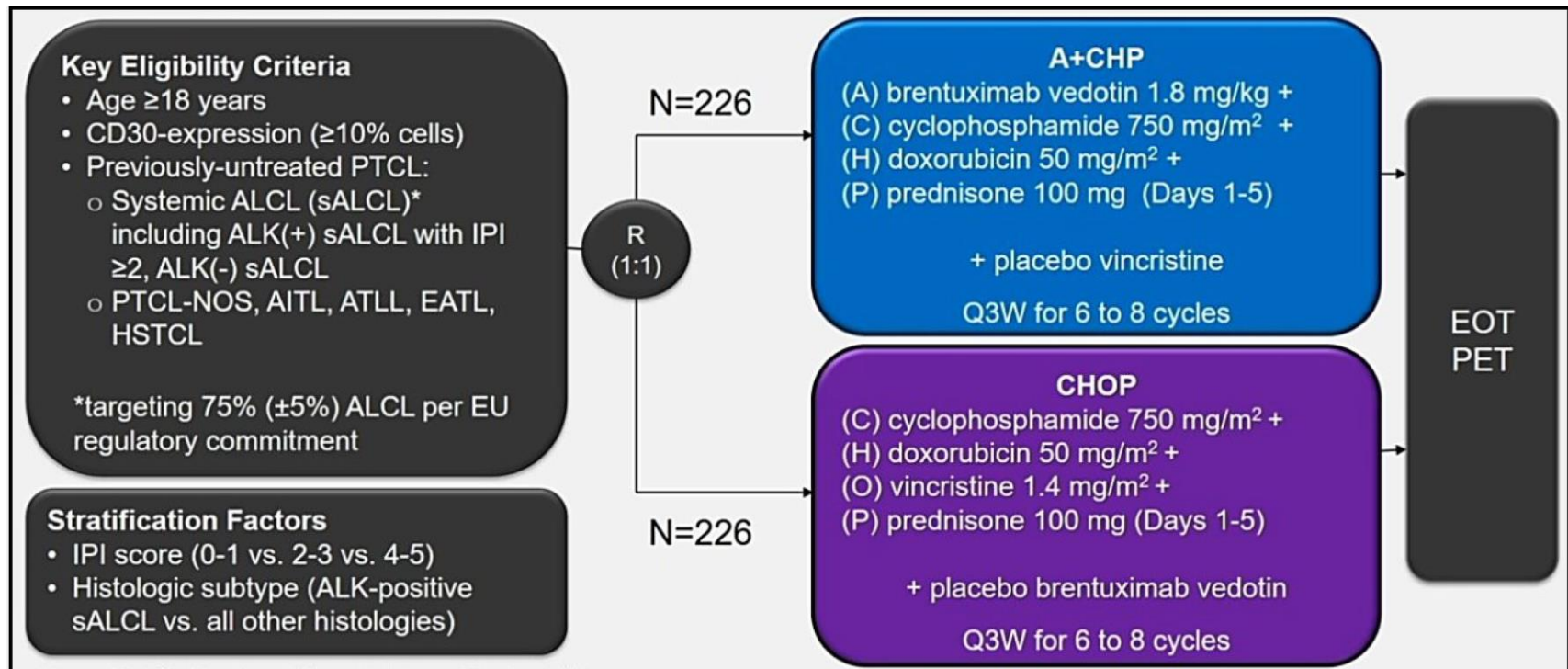
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- Periphere T-Zell-Lymphome (PTCL): heterogene Gruppe
- CHOP/CHOP-ähnliche Therapien sind der aktuelle Standard
 - ALK+ systemisches anaplastisches großzelliges Lymphom (sALCL): gute Prognose
 - andere PTCL: schlechte Prognose
- Ca. 50% der PTCL exprimieren CD30 (sALCL: 100%)
- Brentuximab-Vedotin (BV) ist für R/R sALCL zugelassen



*ALCL ALK+ with a high-risk profile (e.g. IPI >2) should be considered for autoSCT consolidation

Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial





ECHELON-2: Remission, SAE

response rates

	A+CHP group (n=226)	CHOP group (n=226)	Response rate difference (95% CI), p value
Proportion of patients who achieved an objective response [95% CI]	188 (83% [77.7–87.8])	163 (72% [65.8–77.9])	11.1 (3.4–18.7), 0.0032
Complete remission rate	153 (68% [61.2–73.7])	126 (56% [49.0–62.3])	11.9 (3.1–20.8), 0.0066
Response*			
Complete remission	153 (68%)	126 (56%)	..
Partial remission	35 (15%)	37 (16%)	..
Stable disease	5 (2%)	11 (5%)	..
Progressive disease	15 (7%)	31 (14%)	..
Not evaluable†	18 (8%)	21 (9%)	..

adverse events

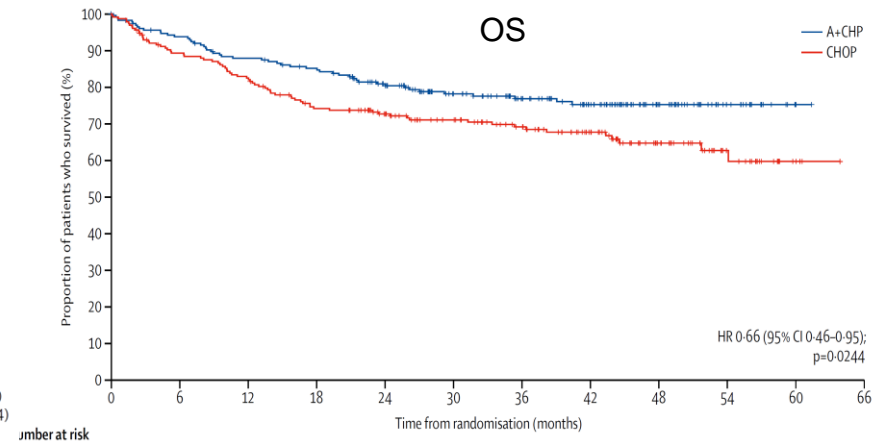
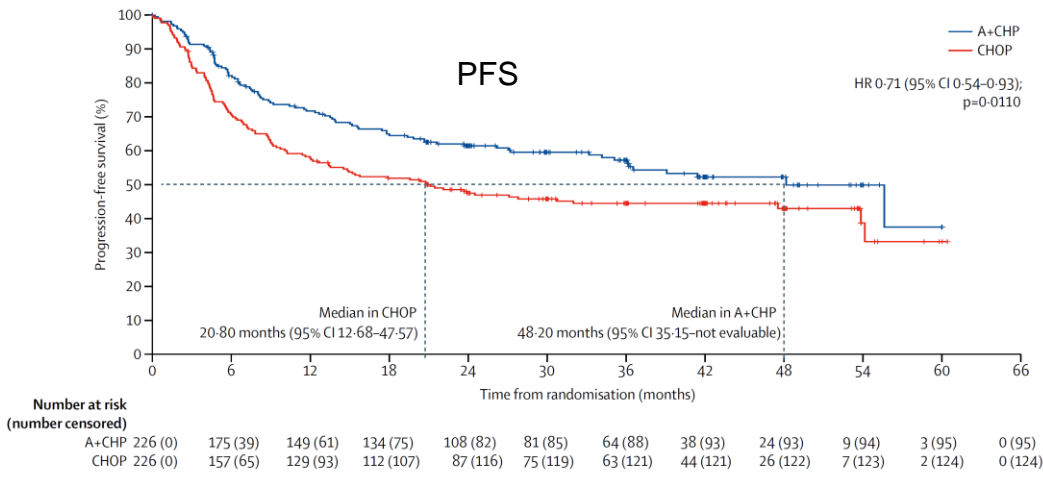
	A+CHP group (n=223)		CHOP group (n=226)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	103 (46%)	5 (2%)	87 (38%)	4 (2%)
Peripheral sensory neuropathy	100 (45%)	8 (4%)	92 (41%)	6 (3%)
Neutropenia	85 (38%)	77 (35%)	85 (38%)	76 (34%)
Diarrhoea	85 (38%)	13 (6%)	46 (20%)	2 (1%)
Constipation	64 (29%)	2 (1%)	67 (30%)	3 (1%)
Alopecia	58 (26%)	0	56 (25%)	3 (1%)
Pyrexia	58 (26%)	4 (2%)	42 (19%)	0
Vomiting	57 (26%)	2 (1%)	39 (17%)	4 (2%)
Fatigue	54 (24%)	2 (1%)	46 (20%)	4 (2%)
Anaemia	46 (21%)	30 (13%)	36 (16%)	23 (10%)

ECHELON-2: PFS, OS

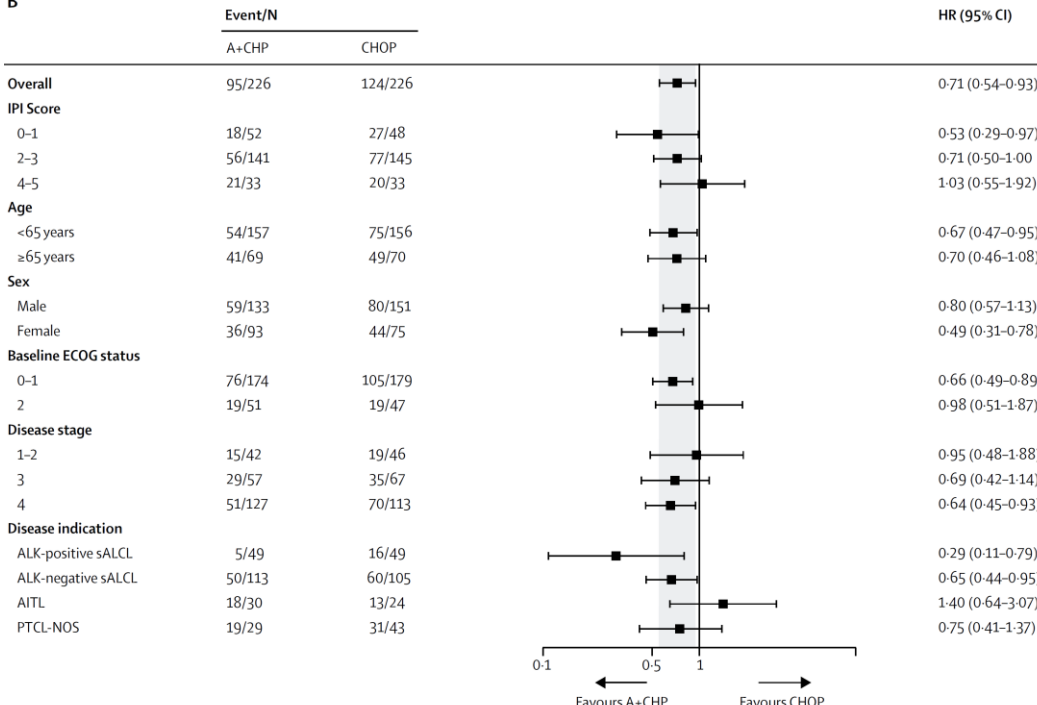


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A



B



Summary

- Front-line treatment with A+CHP is superior to CHOP for patients with CD30-positive T NHL
- PFS (3yPFS 57% vs 44%) and OS with a manageable safety profile
- Approved for aALCL and other CD30 pos PTCL
- **NCCN 2019:**
- in ALCL: preferred regimen
- other CD30 pos. histologies: together with CHOP, CHOEP, DA EPOCH

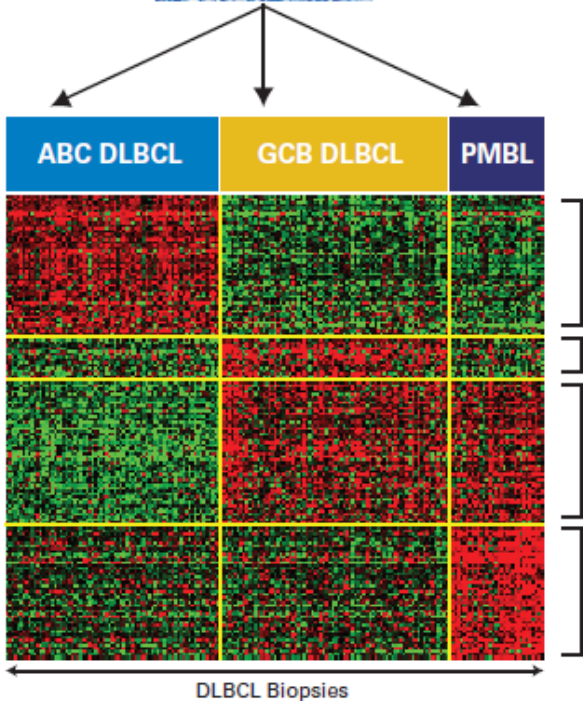
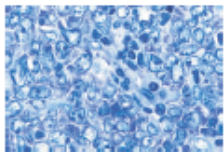
Diffuse large B cell lymphoma (DLBCL)

Gene expression profiling



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Histologic diagnosis
of DLBCL



Genes highly
expressed in
ABC DLBCL

Genes highly
expressed in
GCB DLBCL

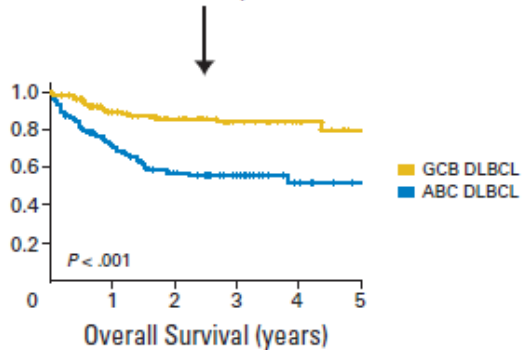
Genes highly
expressed in
GCB DLBCL/PMBL

Genes highly
expressed in
PMBL

Table 2 | PFS and overall survival for each DLBCL molecular subtype

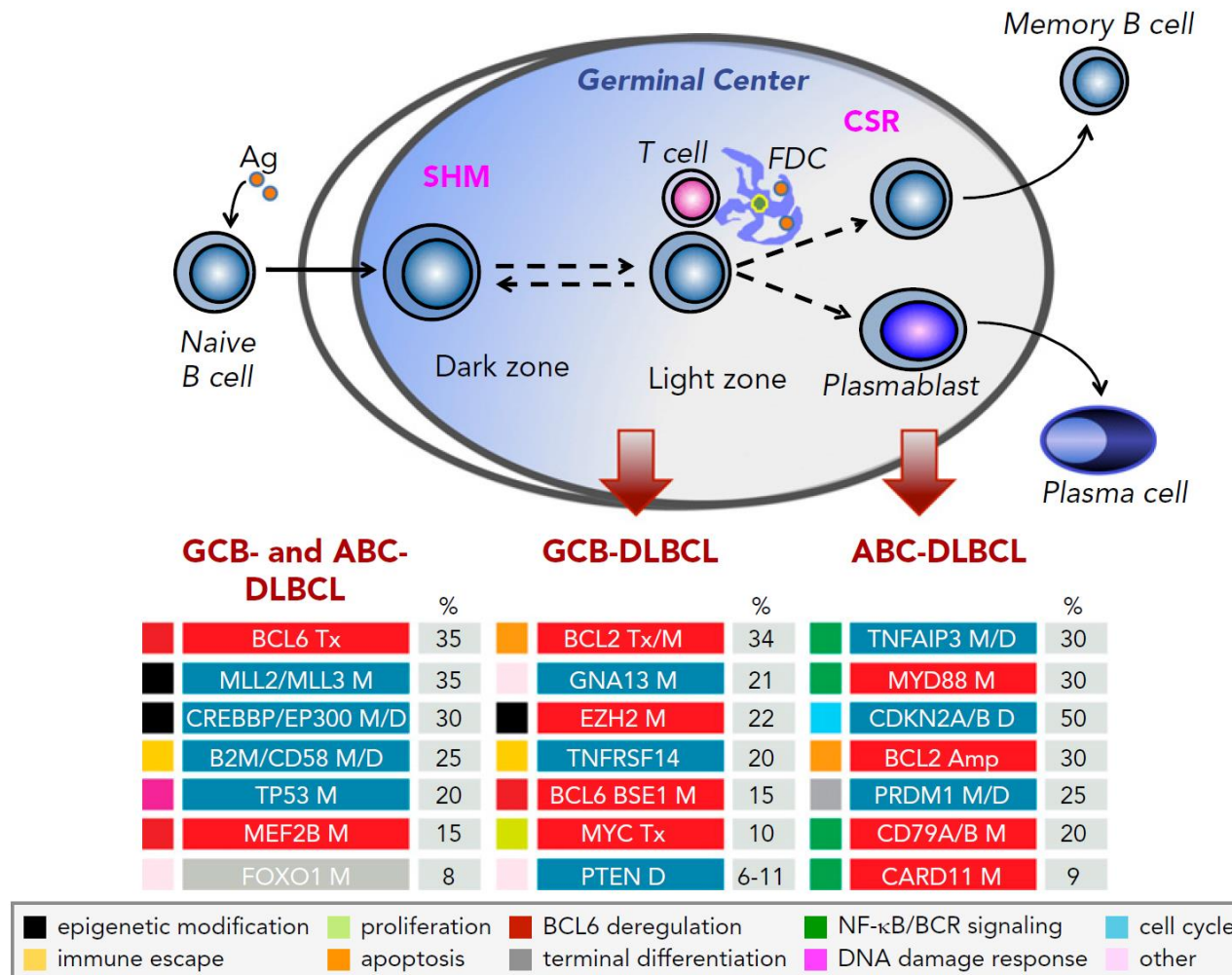
Molecular subtype	Regimen	3-year PFS rate	3-year overall survival rate	Reference
ABC DLBCL	R-CHOP	40%	Approximately 45%	Lenz <i>et al.</i> (2008) ²⁹
GCB DLBCL	R-CHOP	74%	Approximately 80%	Lenz <i>et al.</i> (2008) ²⁹
PMBL	DA-EPOCH-R	100%*	97%*	Dunleavy <i>et al.</i> (2013) ¹⁶

Clinical
implications

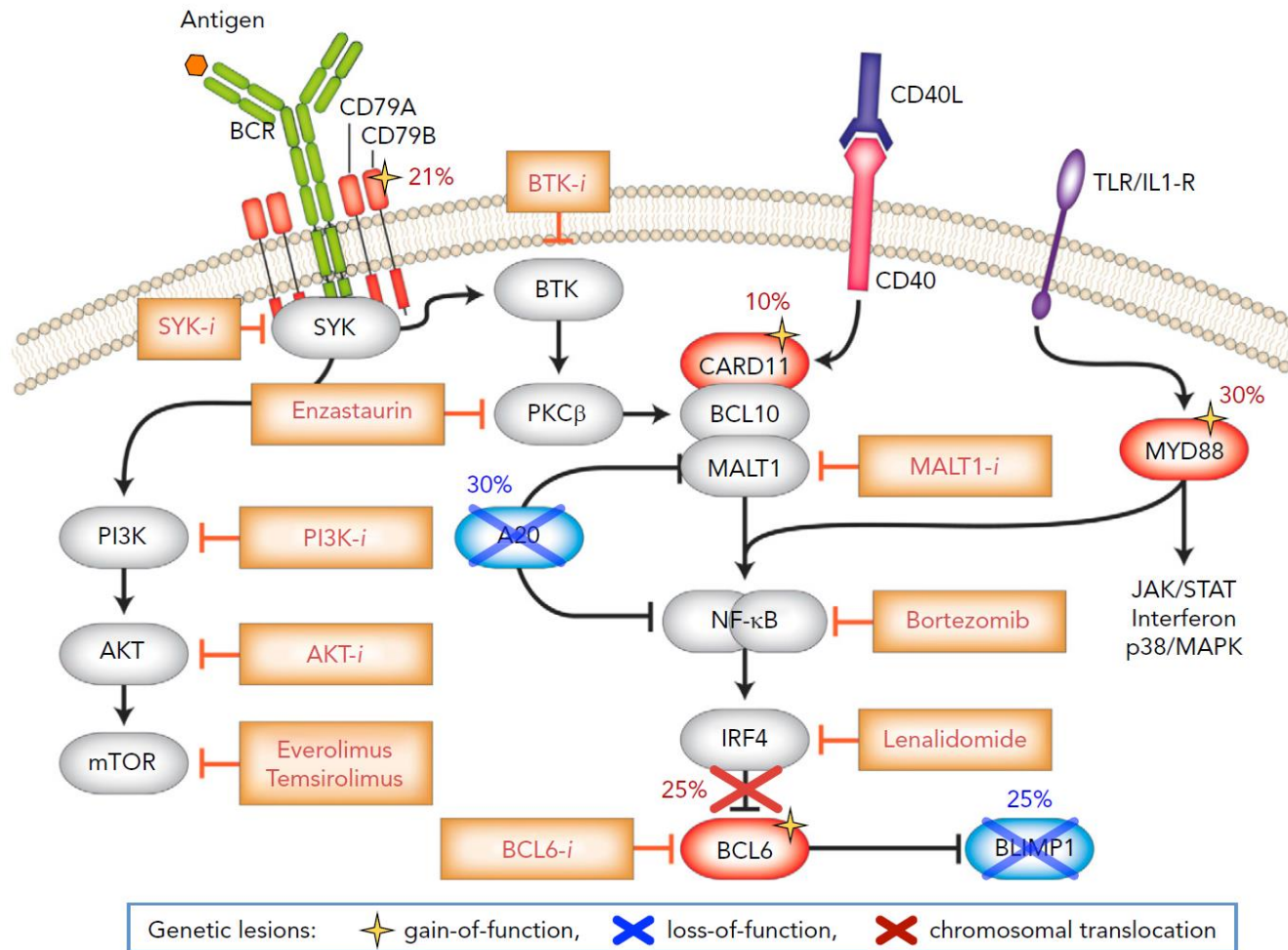


Genetics of diffuse large B-cell lymphoma

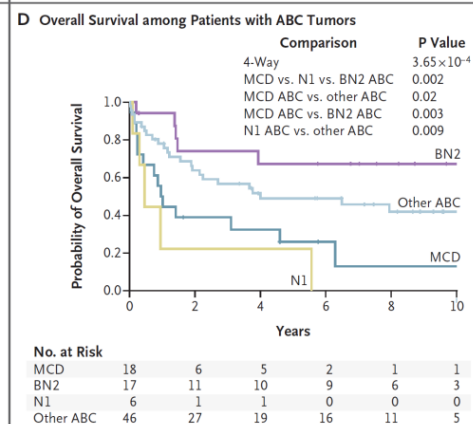
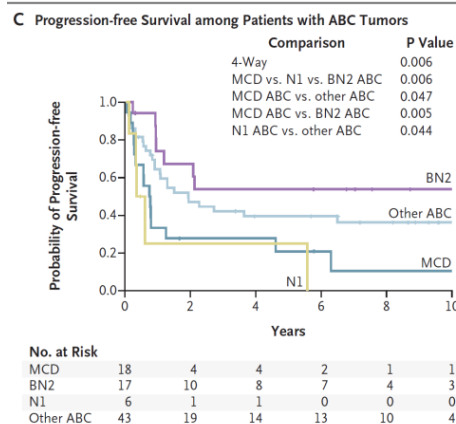
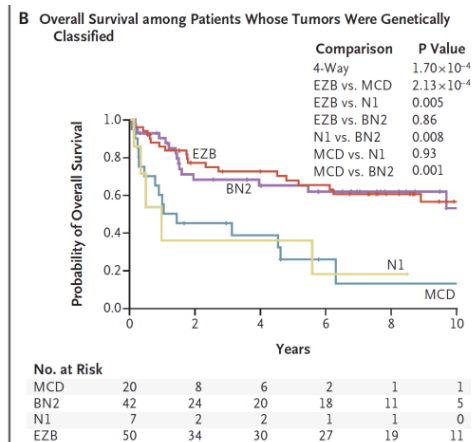
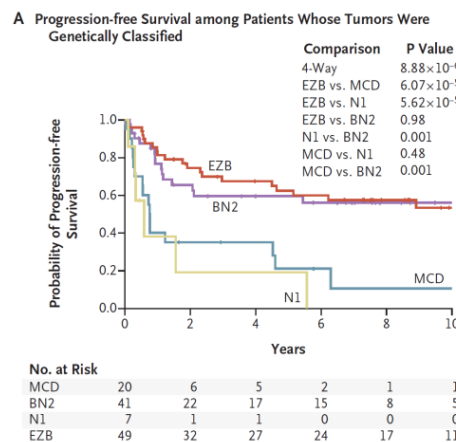
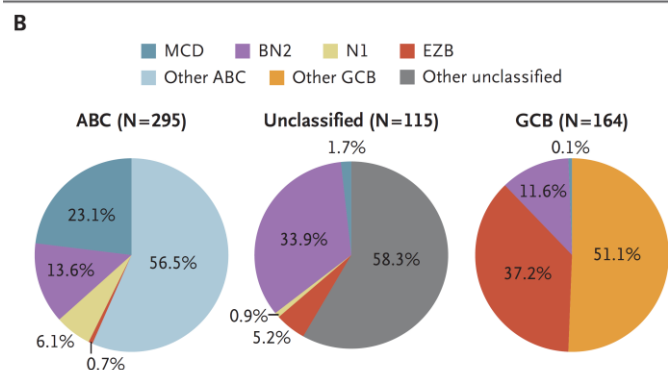
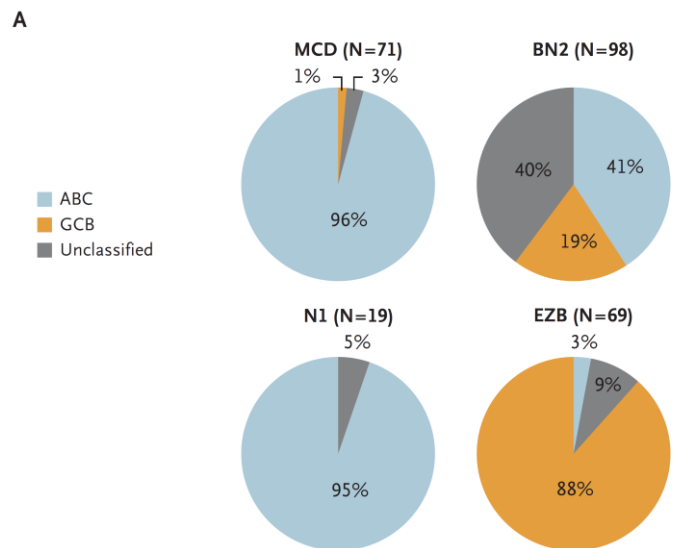
Cellular origin and genetic lesions associated with distinct DLBCL subtypes



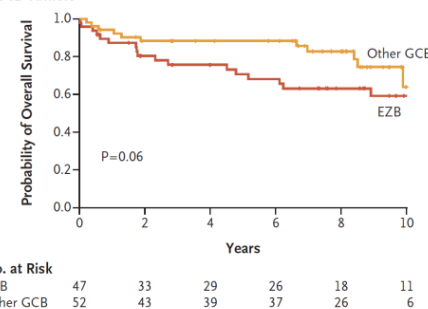
Disrupted signaling pathways in ABC-DLBCL



Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma



E Overall Survival among Patients with GCB Tumors



4 genetic subtypes of DLBCL with distinct genotypic, epigenetic, and clinical characteristics, providing a potential for precision-medicine strategies



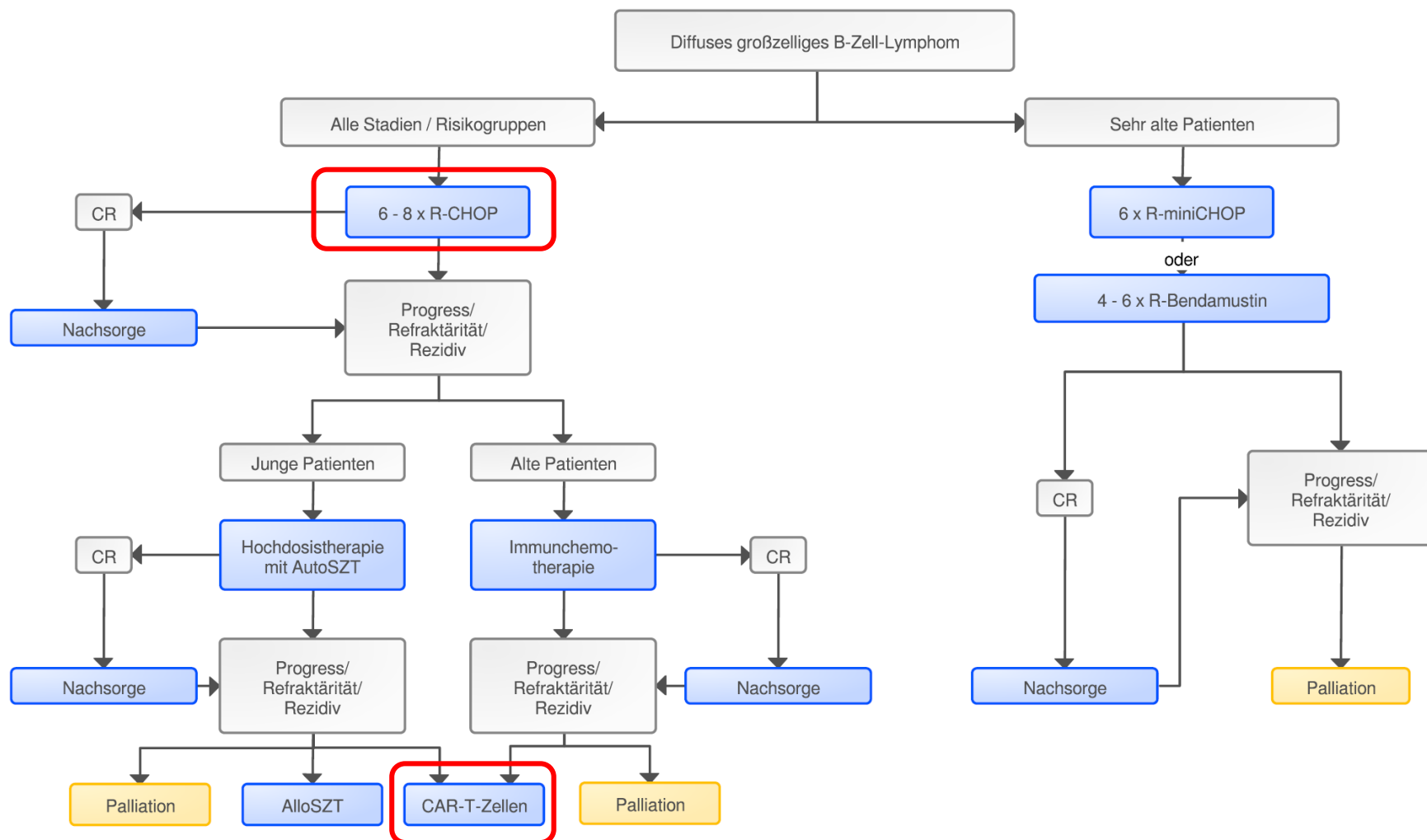
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DLBCL 1.LINE

DLBCL Onkopedia 2018



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ESMO 2015 : first line therapy

Patients ≤60 years

IPI low risk (aaIPI = 0) and no bulk	IPI low risk (aaIPI = 0) with bulk or IPI low-intermediate risk (aaIPI = 1)	IPI intermediate-high risk or IPI high risk (aaIPI = 2, 3)
R-CHOP21 × 6 3y PFS 90% 3y OS 95%	R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk 3y PFS 75% 3y OS 90%	R-CHOP21 × 6–8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens in selected patients: R-CHOEP14 × 6 or R-CHOP or R-ACVBP plus HDCT with ASCT

No current standard !
PFS~ 50% with R-CHOP

Consider CNS prophylaxis in patients at risk for CNS progression

Elderly >60 years

Fit, 60–80 years	>80 years without cardiac dysfunction	Unfit or frail or >60 years with cardiac dysfunction
R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R	Attenuated regimens: R-miniCHOP21 × 6	Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care

Consider CNS prophylaxis in patients at risk

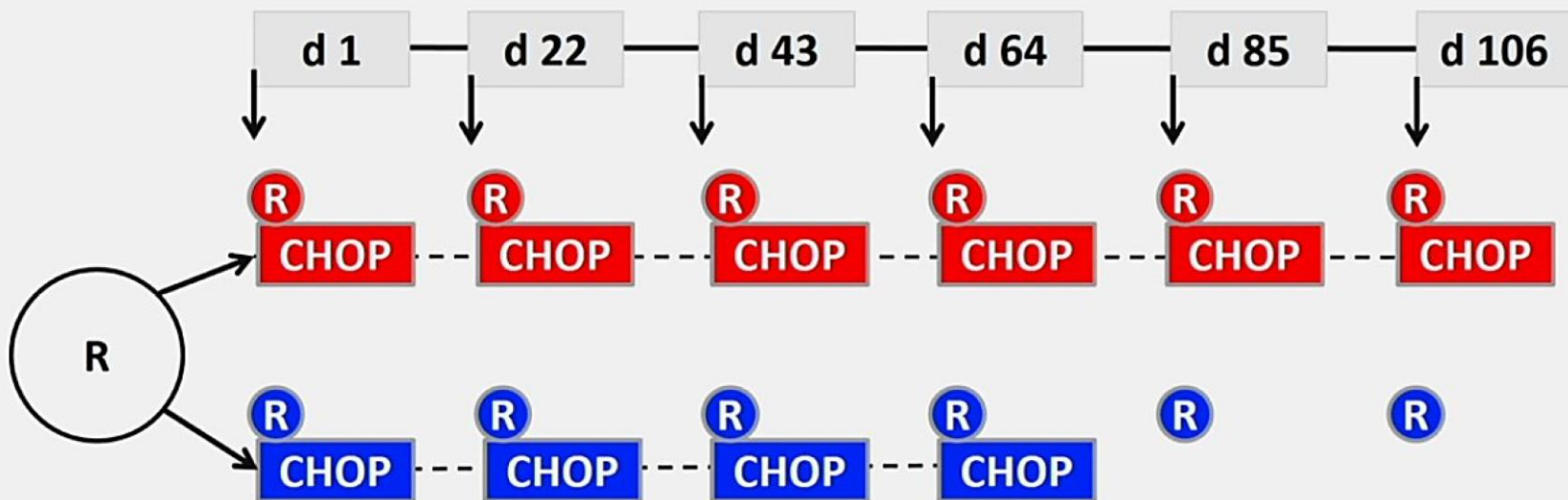
Excellent Outcome of Young Patients (18-60 years) with Favourable-Prognosis DLBCL Treated with 4 Cycles CHOP Plus 6 Applications of Rituximab: Results of the 592 Patients of the Flyer Trial of the Dshnhl



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- MInT-Trial (Pfreundschuh et al 2006):
R-CHOP, aalPI = 0, kein Bulk → 36-Monate PFS 95%
- aalPI = 0:
Alter ≤ 60 Jahre, LDH normal, CS \leq II, ECOG ≤ 1
- Ziel des FLYER-Trials:
Reduzierung der Toxizität durch Reduktion der CHOP-Zyklen

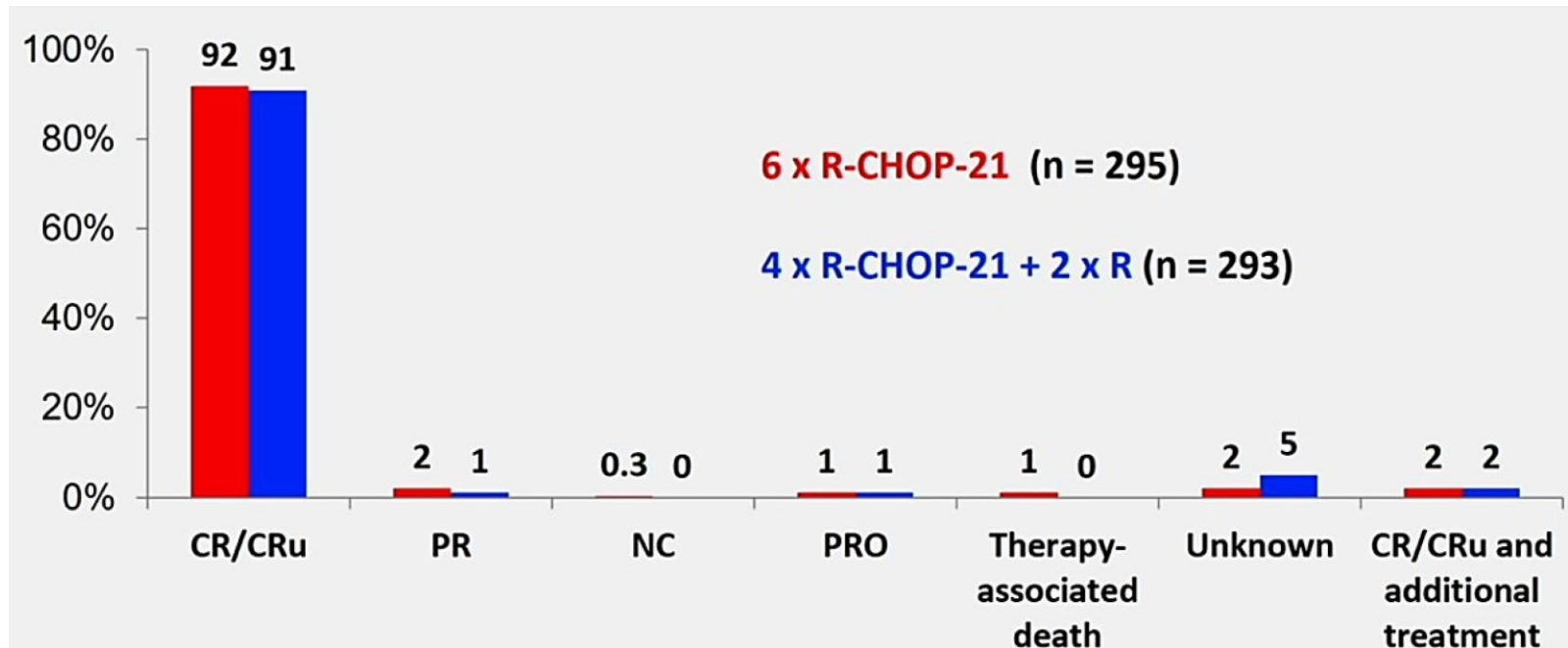
- Front-line treatment of aggressive B-cell lymphoma
- 18-60 years, stage I/II, aalPI = 0, no bulk (max. diameter < 7.5 cm)



Flyer Trial: response rate



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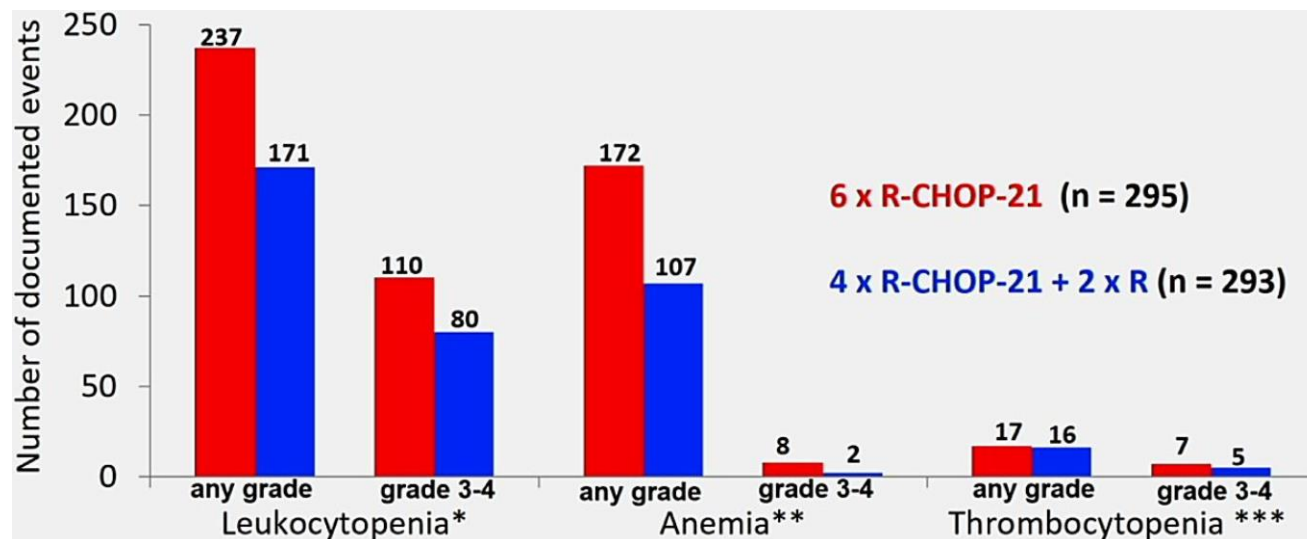


Flyer Trial: Toxicity



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Hematological toxicity



Non-hematological toxicity

	6x R-CHOP-21 (n=295)		4 x R-CHOP-21 + 2 x R (n = 293)	
	any grade	grade 3-4	any grade	grade 3-4
All	1295	70	835	46
Paresthesia	370	14	227	12
Nausea	319	12	195	6
Infection	156	23	98	20
Vomiting	117	7	56	1
Mucositis	105	3	68	1

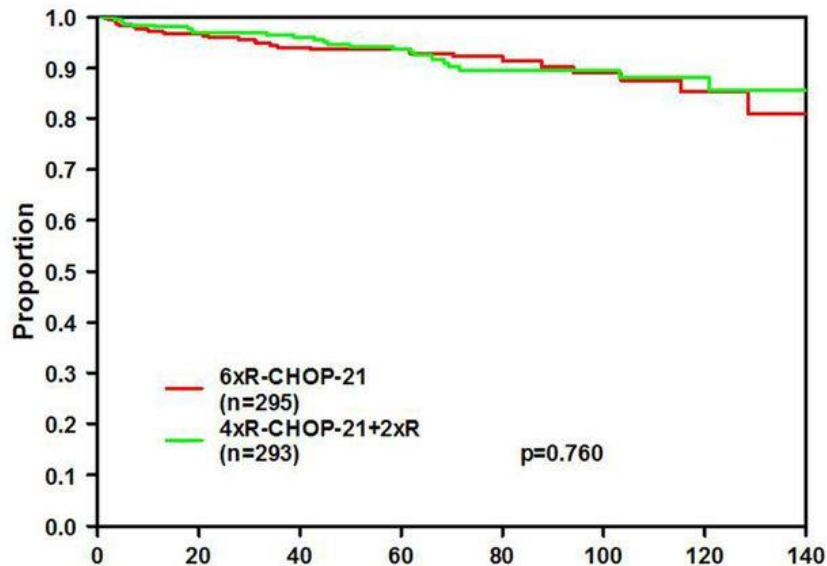
Flyer Trial: PFS and OS



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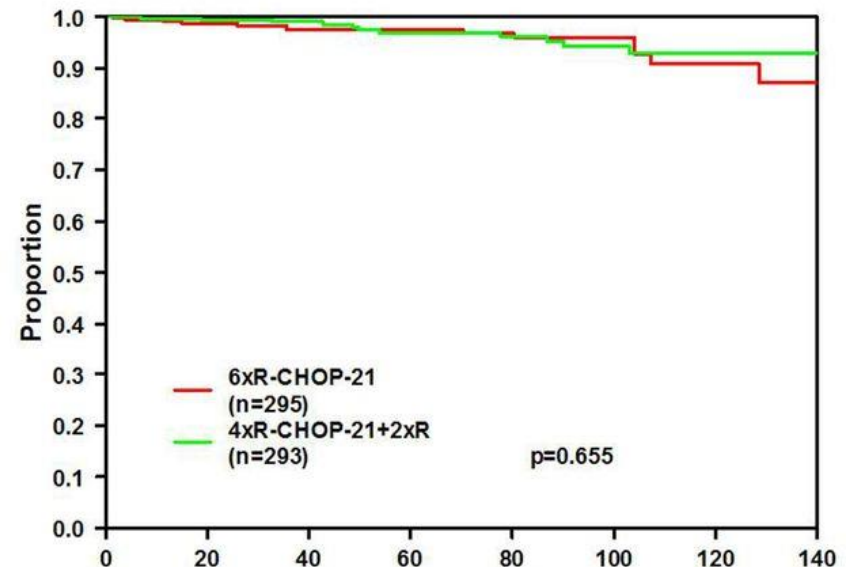
FLYER study (phase III)

Patients 18 - 60 years, aalPI 0, non bulk, ITT (n=588)
PFS according to treatment arm



FLYER study (phase III)

Patients 18 - 60 years, aalPI 0, non bulk, ITT (n=588)
OS according to treatment arm



DSHNHL 18.06.18

FLYER: Zusammenfassung

- 4x R-CHOP + 2x R gleichwertig zu 6x R-CHOP (PFS, EFS, OS)
bei jungen Pat. mit aalPI = 0 und fehlendem Bulk
- Ca. 30% weniger Nebenwirkungen im 4x R-CHOP + 2x R -Arm



No Added Benefit of Eight Versus Six Cycles of Rituximab-CHOP in Previously Untreated DLBCL: Results from the International Phase III GOYA Study

- Standard: 8x R-CHOP-21
- RICOVER-60 Studie (Pfreundschuh M, et al. Lancet Oncology 2008):
6x R-CHOP-14 \equiv 8x R-CHOP-14 ✓
- Cunningham D et al. Lancet 2013:
6x R-CHOP-14 + 2x R \equiv 8x R-CHOP-21 ✓
- 6x R-CHOP-21 + 2x R \equiv 8x R-CHOP-21 ?

International, open-label, randomized Phase 3 study in first-line DLBCL patients

Previously untreated DLBCL (N=1418)*

- Age ≥ 18 years
- IPI ≥ 2 or IPI 1 not due to age alone or IPI 0 with bulky disease (one lesion ≥ 7.5 cm)
- Adequate hematologic function
- ≥ 1 bi-dimensionally measurable lesion
- ECOG PS ≤ 2

Randomized
1:1

G-CHOP arm (N=706)

G 1000mg C1 D1/8/15 and C2–8 D1
CHOP 6 or 8 cycles every 21 days

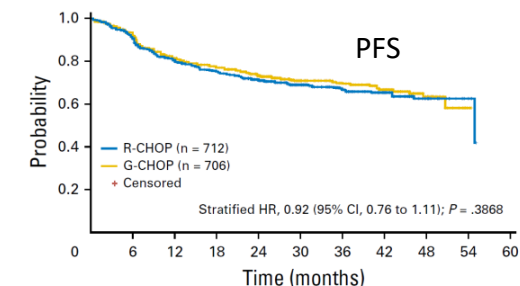
R-CHOP arm (N=712)

R 375mg/m² C1–8 D1
CHOP 6 or 8 cycles every 21 days

- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region
- **Number of CHOP cycles pre-selected at each site prior to trial opening**

Obinutuzumab or Rituximab Plus CHOP in Previously Untreated DLBCL, the GOYA Study

A

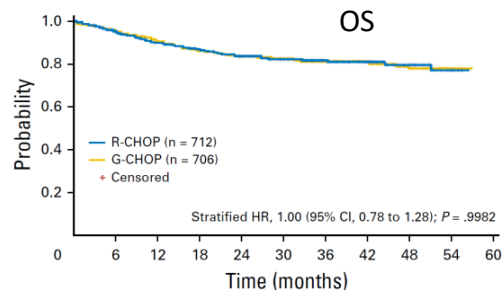


No. at risk:

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

1,418 patients 8x21-day cycles of G or R plus **six or eight cycles** of CHOP

B

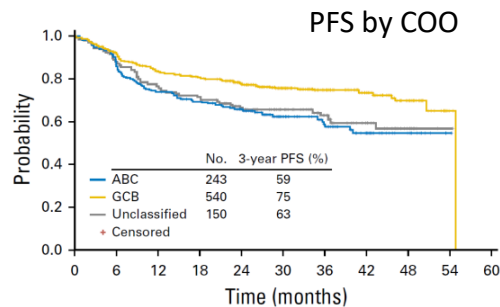


No. at risk:

R-CHOP	712	663	617	586	540	319	190	138	71	9
G-CHOP	706	659	616	582	552	316	201	138	67	8

G-CHOP did not improve PFS compared with R-CHOP in pts previously untreated DLBCL

C



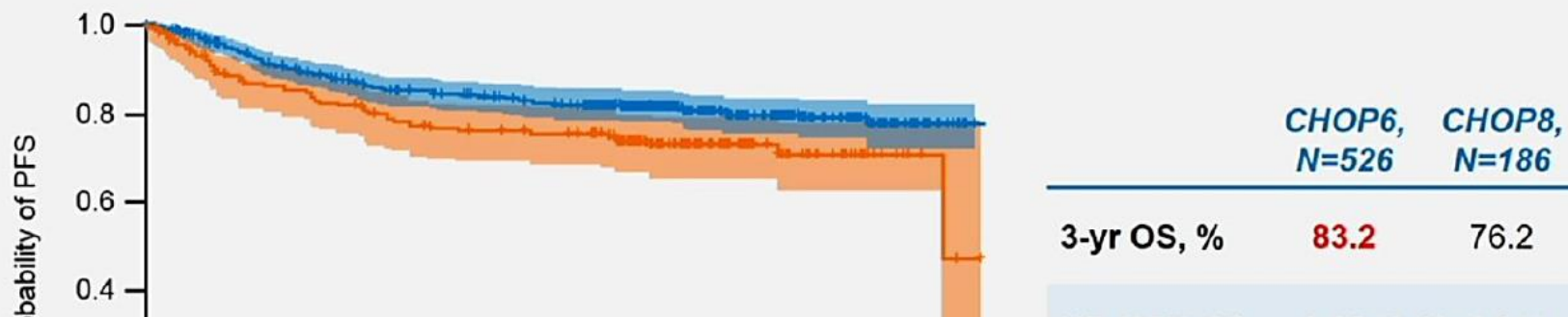
No. at risk:

ABC	243	209	174	161	144	78	52	32	13	2
GCB	540	480	417	398	344	207	139	96	41	3
Unclassified	150	128	111	103	86	64	42	25	9	1

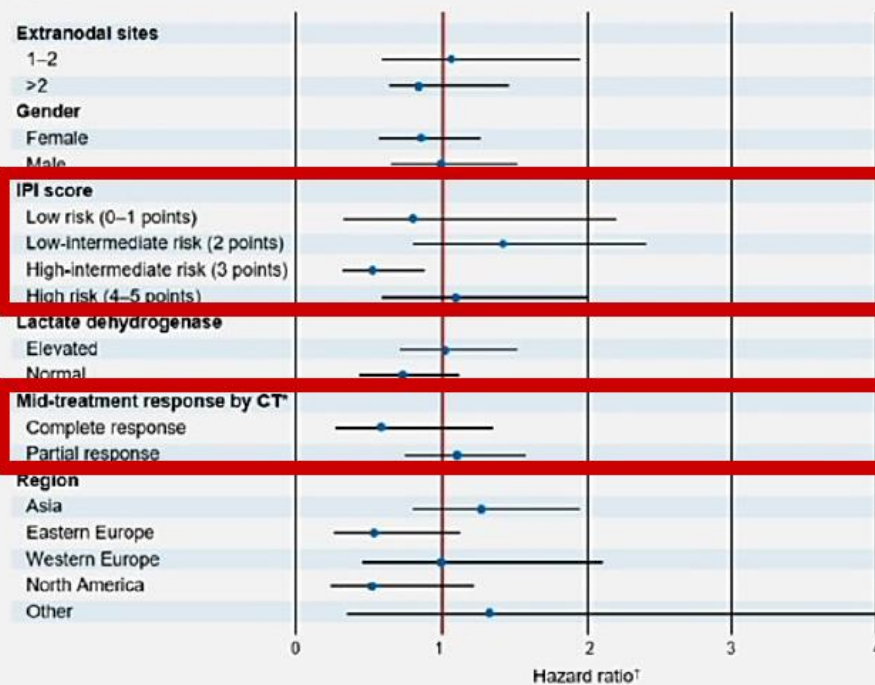
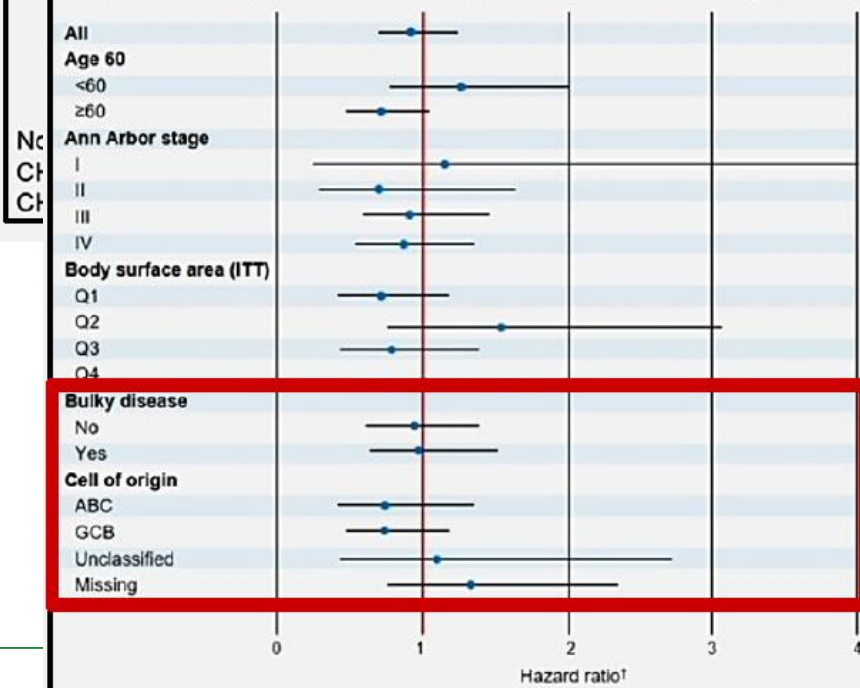
GOYA Study: PFS and OS



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- Model-based subgroup analysis of PFS according to baseline patient characteristics
- HR>1 indicates a benefit of 8 versus 6 cycles of CHOP



GOYA Study: SAE and summary



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<i>Treatment-emergent AE, N (%) of patients reporting ≥1 event</i>	<i>CHOP6, N=461</i>	<i>CHOP8, N=144</i>
Total AEs	197 (42.7)	94 (65.3)
Grade 3–5 toxicity	82 (17.8)	56 (38.9)
Grade 4 toxicity	21 (4.6)	25 (17.4)
Grade 5 toxicity	7 (1.5)	4 (2.8)
Cardiac AEs	11 (2.4)	9 (6.3)
Grade 3–5 toxicity	6 (1.3)	5 (3.5)
Infections (all grades)	49 (10.6)	34 (23.6)
Grade 3–5 infections	22 (4.8)	9 (6.3)
Total SAEs	56 (12.2)	29 (20.1)
Cardiac SAEs	8 (1.7)	5 (3.5)
Second malignancies (SMQ)	19 (4.1)	3 (2.1)

- Kein Vorteil durch 8 Zyklen vs. 6 Zyklen CHOP in Kombination mit R
- SAEs bei CHOP8 häufiger
- Gleiche Ergebnisse bei G-CHOP!
- **Neuer Standard: 6x R-CHOP-21 + 2x R ?**

(R)-CHOP PLUS

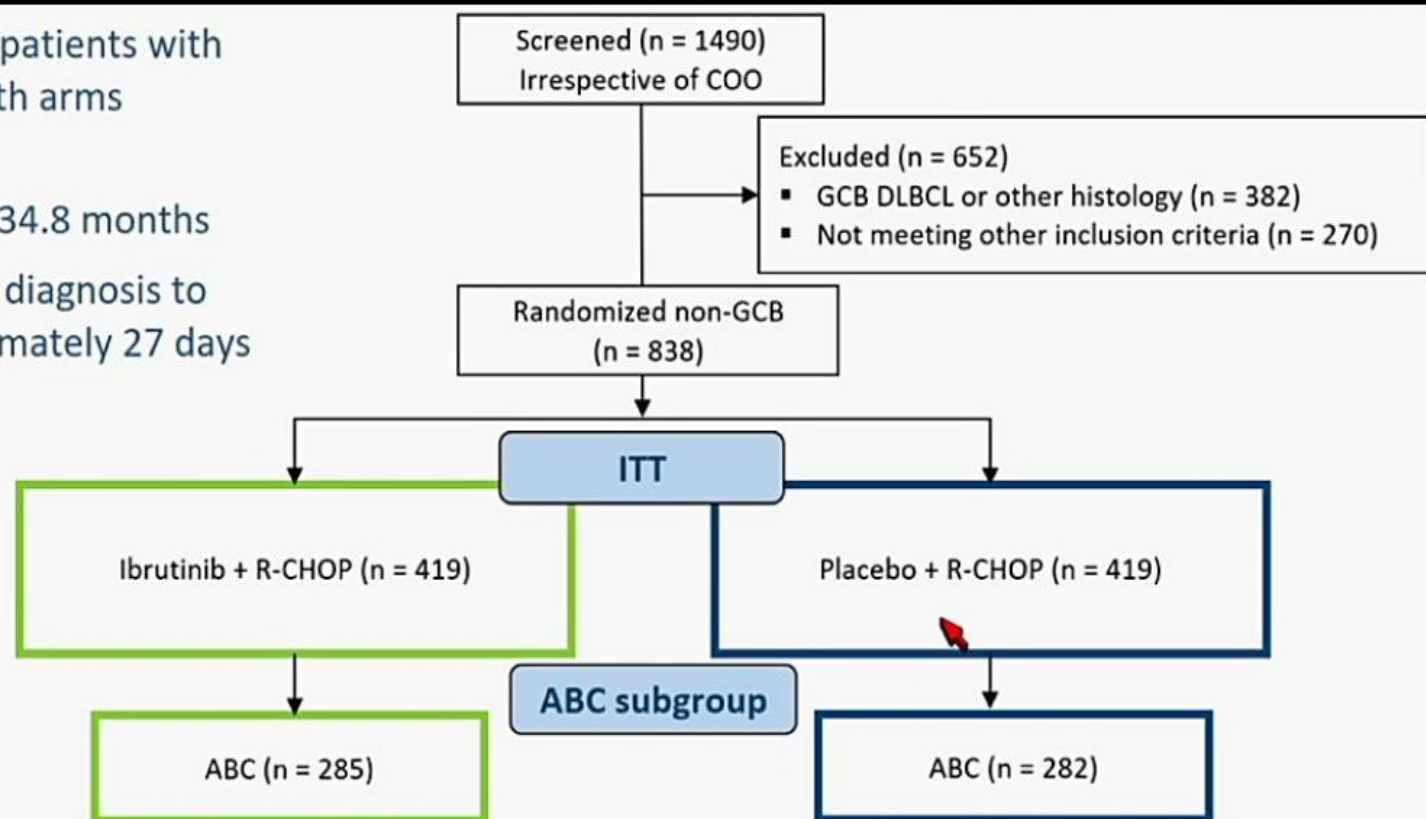
- Novel anti-CD20 antibodies: Ob~~X~~ituzumab (GOYA)
 - Optimising Rituximab
 - BCL 2 Inhibitoren- Venetoclax (CAVALLI)
 - Brentuximab vedotin
 - Ibrutinib (PHOENIX)
 - Lenal~~X~~omid (ROBUST)
 - Borte~~X~~mib (REMoDL)
- } preferential ABC type

A Randomized, Placebo-Controlled Phase 3 Study of Ibrutinib Plus R-CHOP in Patients with Previously Untreated Non-Germinal Center B-Cell-like (GCB) DLBCL



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- Similar number of patients with ABC subtype in both arms (77.0% vs 74.8%)
- Median follow-up 34.8 months
- Median time from diagnosis to treatment approximately 27 days



^aStratified 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

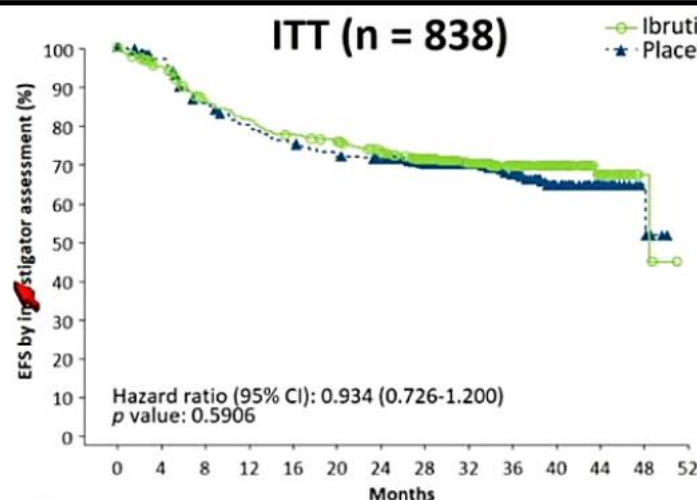
— Secondary end points: PFS, CR rate, OS, safety

- Response assessed per Revised Response Criteria for Malignant Lymphoma¹

Ibrutinib Plus R-CHOP vs Placebo R-CHOP in Patients with Previously Untreated Non-GCB DLBCL: EFS

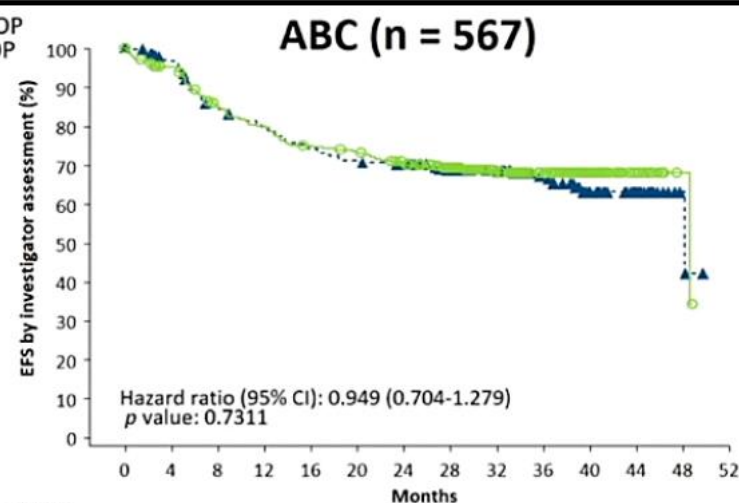


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Patients at risk

Ibrutinib + R-CHOP	419	374	336	316	300	291	276	233	179	120	63	25	3	0
Placebo + R-CHOP	419	390	341	316	297	286	277	244	184	118	60	33	5	0

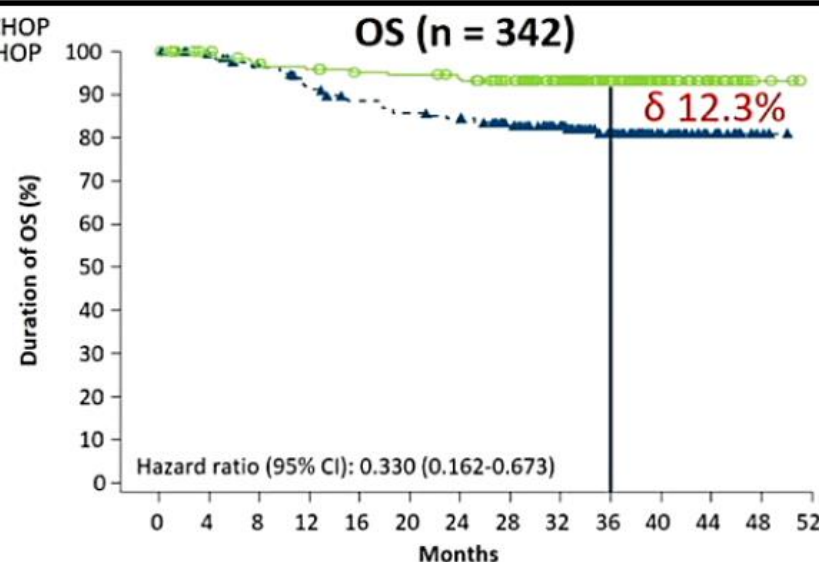
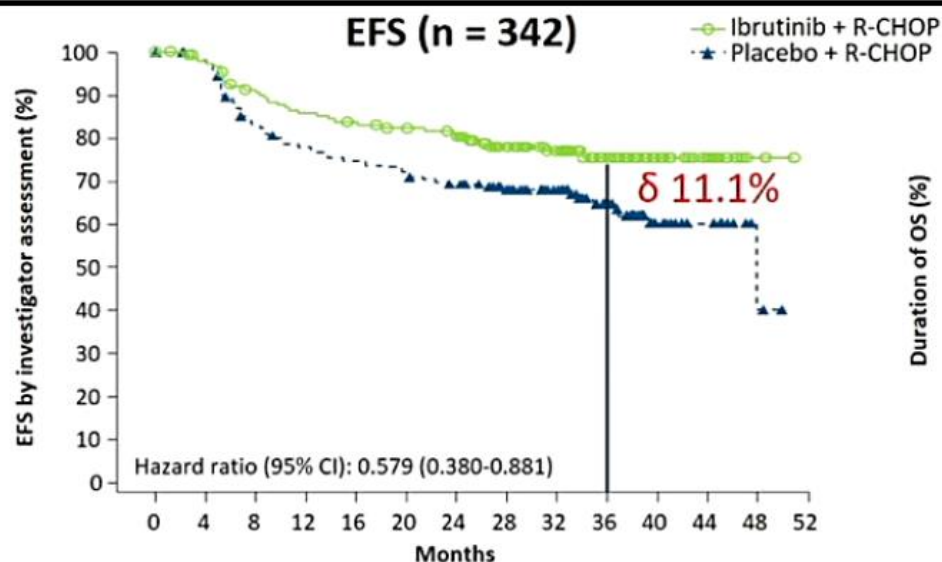


Patients at risk

Ibrutinib + R-CHOP	285	256	225	211	197	191	181	149	111	77	39	15	2	0
Placebo + R-CHOP	282	260	225	212	196	188	183	160	125	78	41	25	3	0

- Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population
- CNS progression was observed: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

Ibr+R-CHOP vs. R-CHOP: EFS (Subgruppe: Alter <60 Jahre)



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	52	24	16	3	0	0

Patients at risk

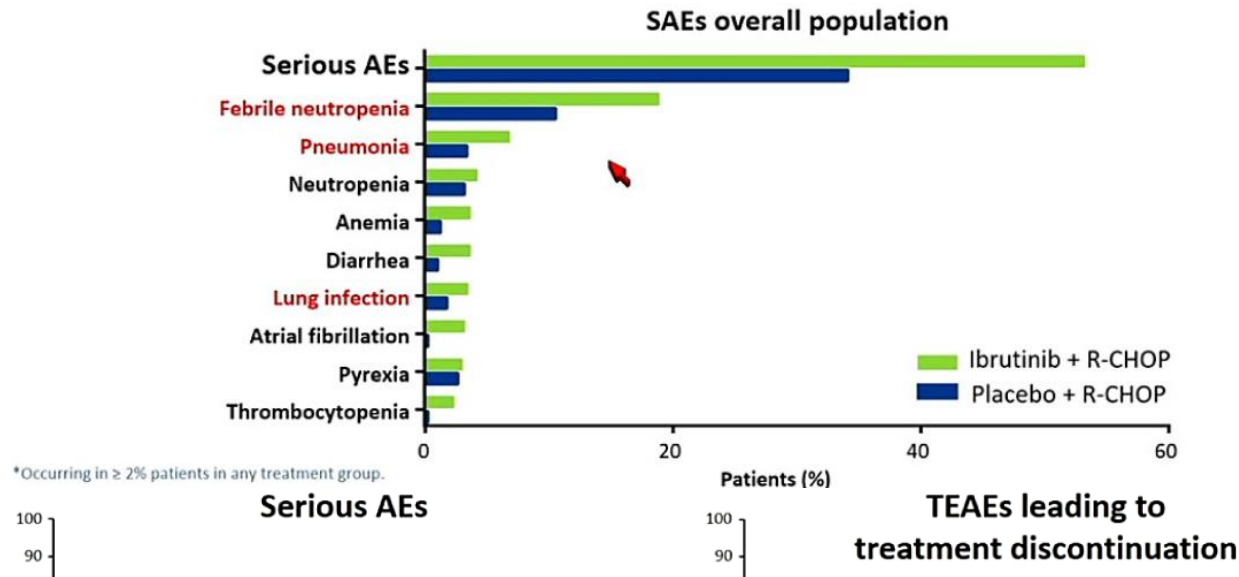
Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

- 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%)

Ibrutinib Plus R-CHOP vs Placebo R-CHOP: safety and summary



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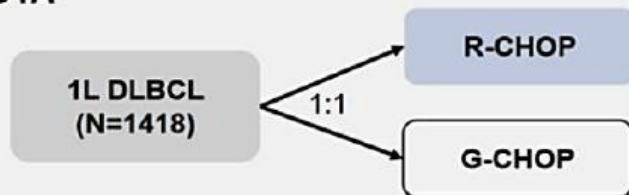
- **ITT-Population: Kein Vorteil durch Zugabe von Ibrutinib zu R-CHOP**
- Deutliche Zunahme von SAE ab einem Alter von 60 Jahren durch Ibrutinib
- Ibrutinib in der Erstlinie bei unter 60 jährigen Patienten: Weitere prospektive Konfirmationsstudie notwendig!

Ibrutinib + R-CHOP Placebo + R-CHOP

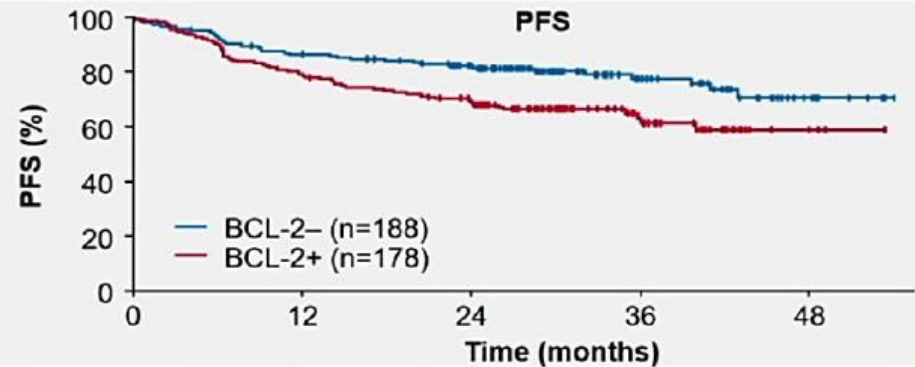
- AE rates were analyzed in cumulative age groups from < 53 to < 89 years
- Higher rates of SAEs and AEs leading to discontinuations were seen in older patients treated with ibrutinib + R-CHOP

Venetoclax Plus R-CHOP Improves Outcomes in BCL2-Positive First-Line DLBCL: First Safety, Efficacy and Biomarker Analyses from the Phase II CAVALLI Study

GOYA



No significant PFS or OS difference between arms; therefore, arms were combined for analysis



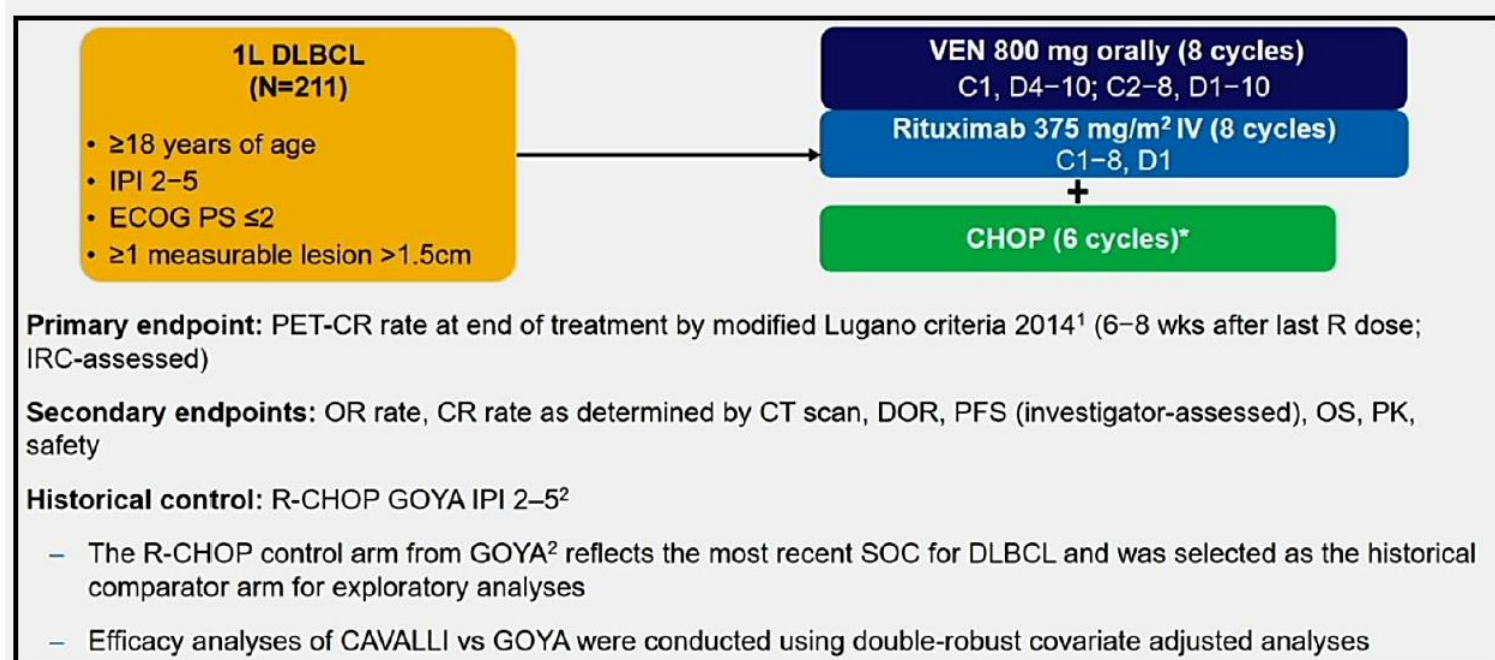
Study	BCL-2 IHC status* n (%)	3-year PFS % (95% CI)	Multivariate HR (95% CI)	Multivariate model
GOYA (combined arms) ¹	BCL-2+, 178 (49) BCL-2-, 188 (51)	63 (55, 71) 78 (70, 84)	1.72 (1.05, 2.82)	Adjusted for treatment, IPI and COO
MAIN (combined arms) ²	BCL-2+, 88 (48) BCL-2-, 96 (52)	61 (48, 71) 71 (58, 80)	1.66 (0.81, 3.4)	Adjusted for treatment, IPI and COO
British Columbia Cancer Agency (BCCA) ^{2†}	BCL-2+, 180 (58) BCL-2-, 130 (42)	62 (54, 68) 76 (67, 82)	1.89 (1.29, 2.78)	Adjusted for IPI and COO

1. Sehn L, et al. ICML 2017
2. Punnoose E, et al. ASH 2017

CAVALLI Study: design



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Biomarker analyses:

IHC: BCL2 (cutoff 50%), MYC (cutoff 40%)

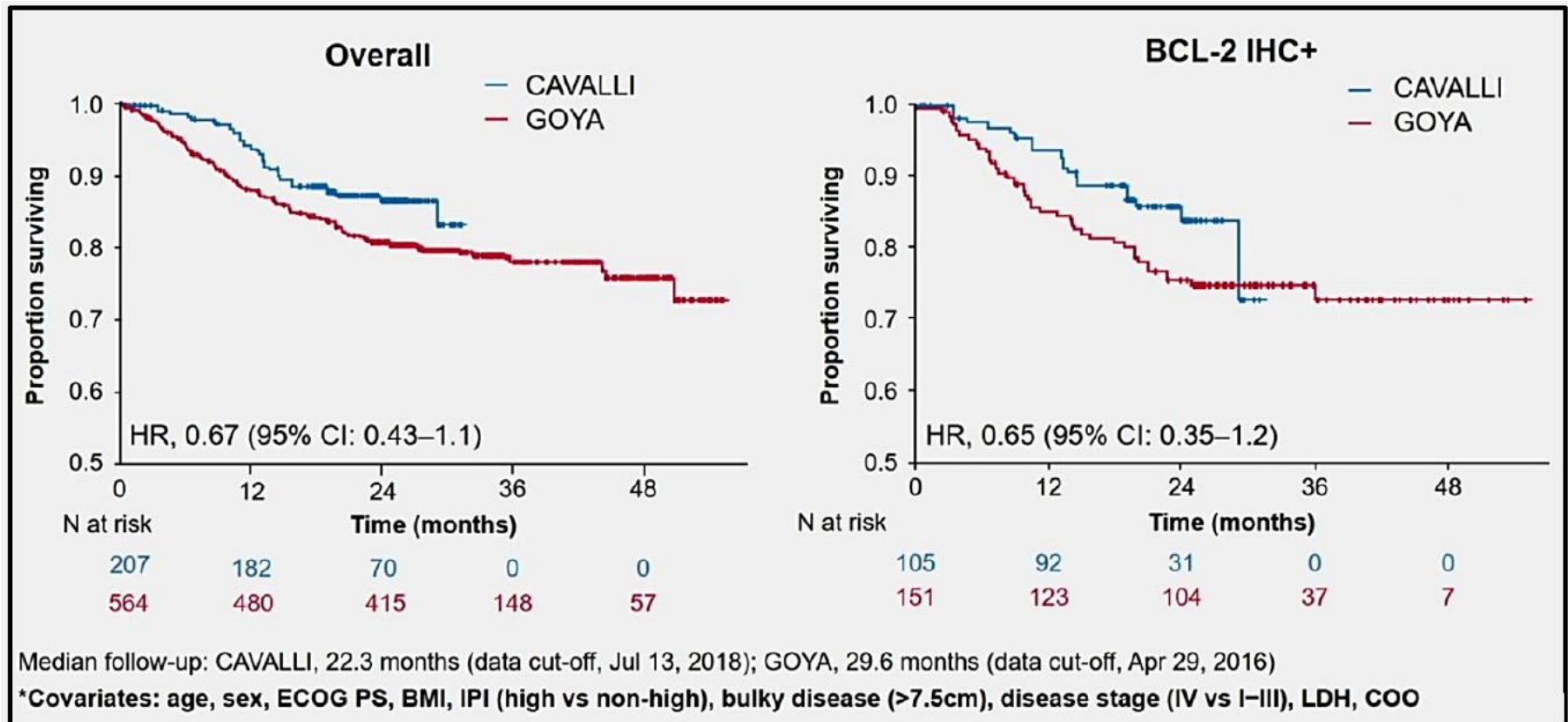
iFISH: BCL2 and MYC

COO: (ABC vs GCB): GEP (nanosttring)

CAVALLI Study: OS and summary



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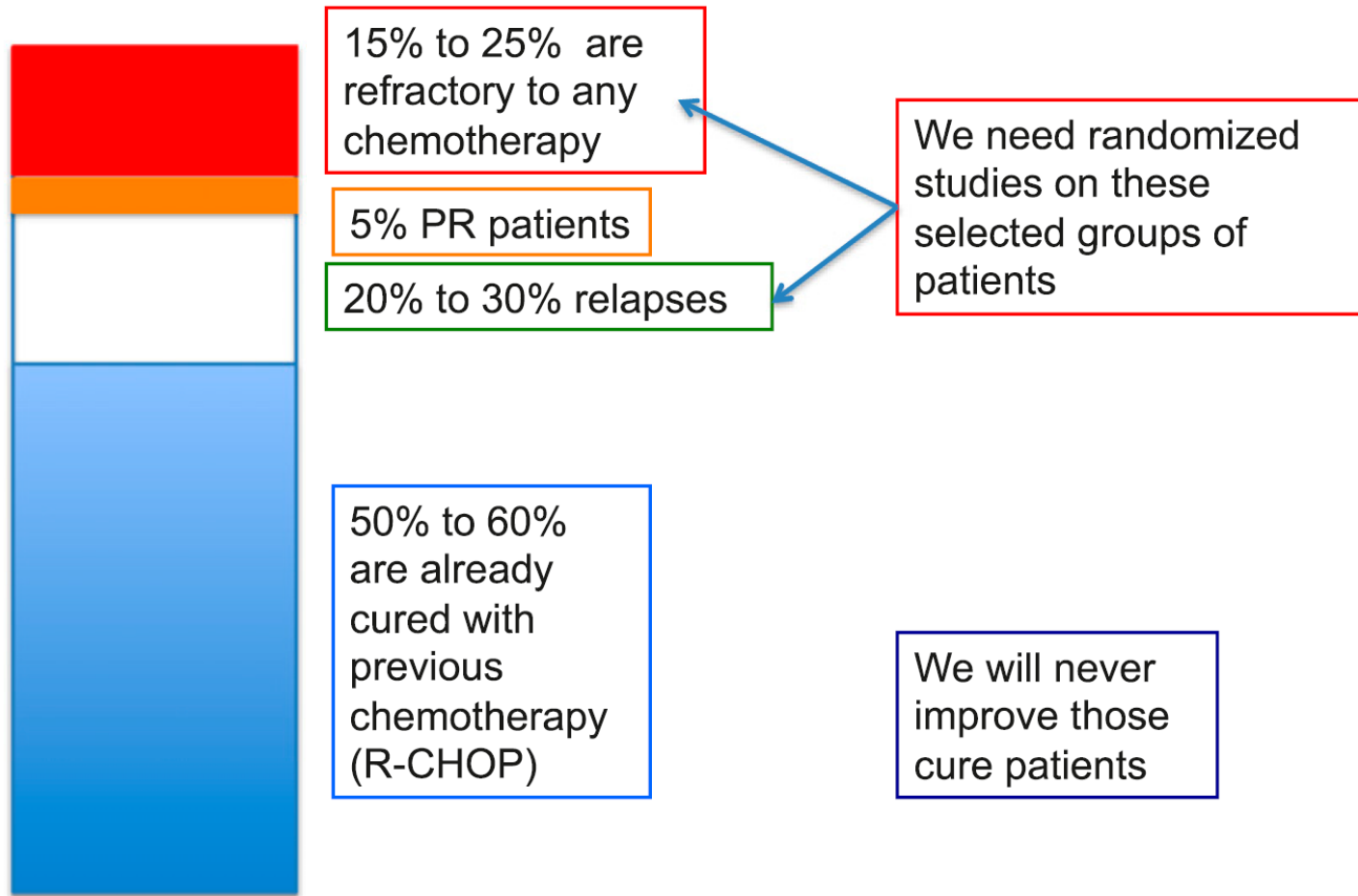
- Verbessertes **PFS** und **OS** im historischen Vergleich durch VEN+R-CHOP beim neudiagnostizierten **BCL-2 pos.** DLBCL
- Höhere Rate an Nebenwirkungen



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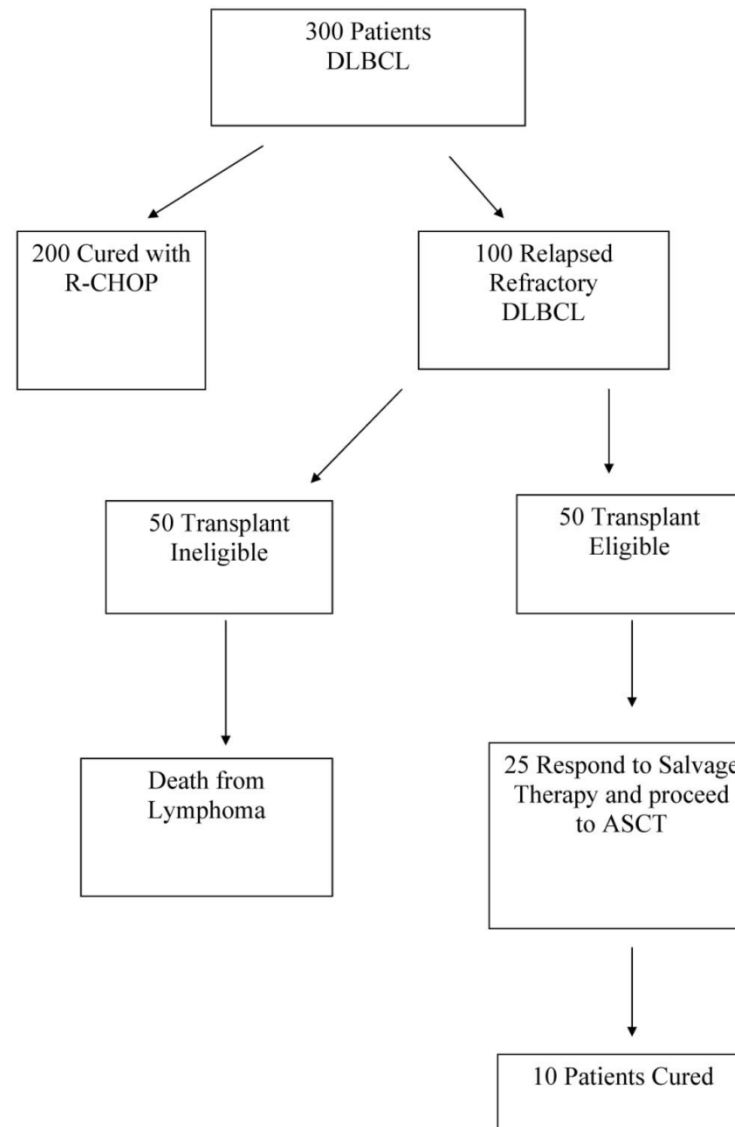
Relapsed refractory DLBCL

Outcome of patients with DLBCL after R-CHOP chemotherapy



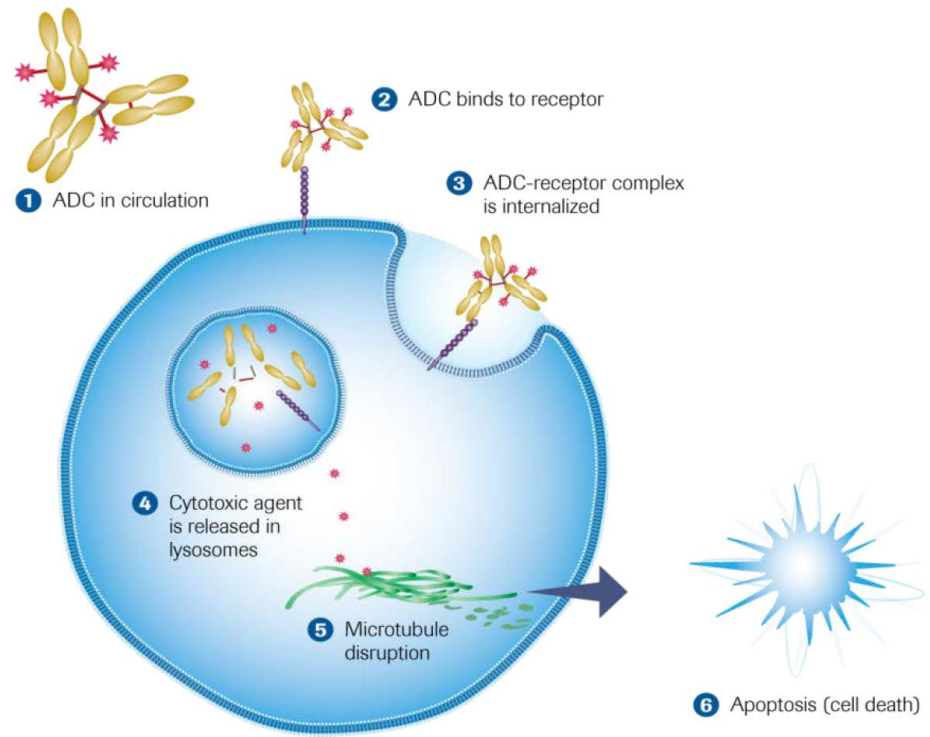
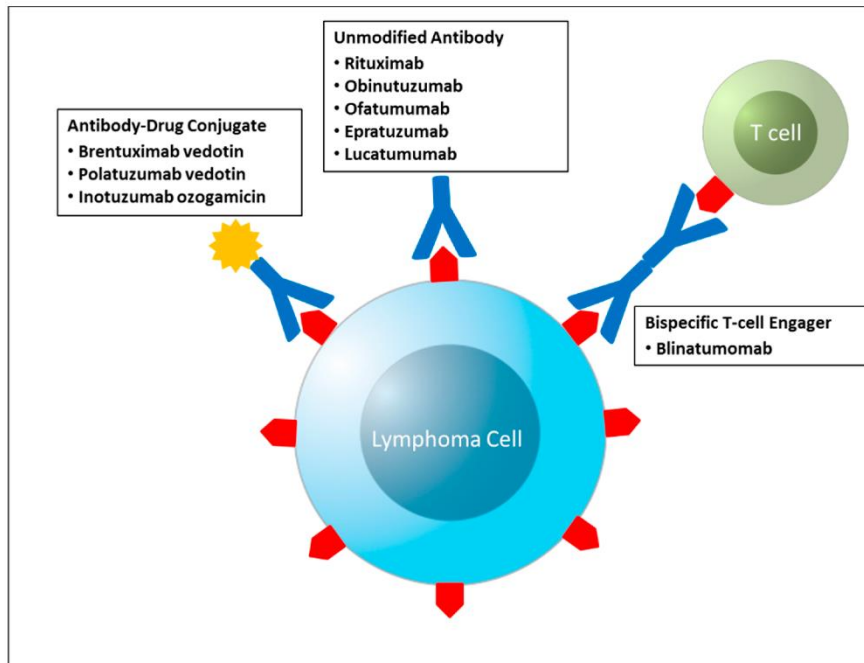
Rebiopsy ! 17% indolent lymphoma in late relapses

Limited benefit of ASCT for relapsed DLBCL



Adding Polatuzumab vedotin (Pola) to Rituximab Bendamustin (BR) improves survival in relapsed /refractory DLBCL

Polatuzumab vedotin (pola) is an antibody-drug conjugate (ADC) targeting CD79b expressed in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL)

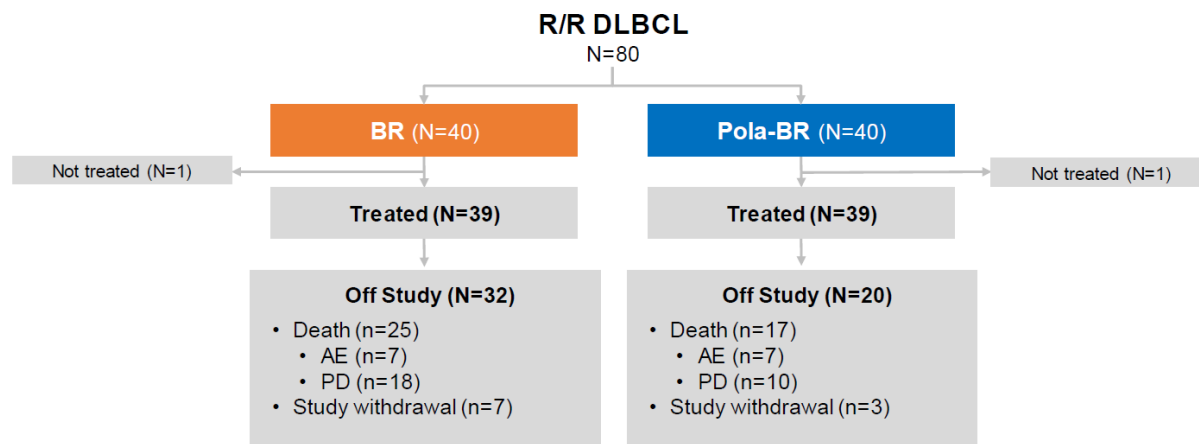


MMA (monomethyl auristatin) : binds to tubulin and inhibits its polymerization

Pola BR vs BR in relapsed /refractory DLBCL: design and patient characteristics

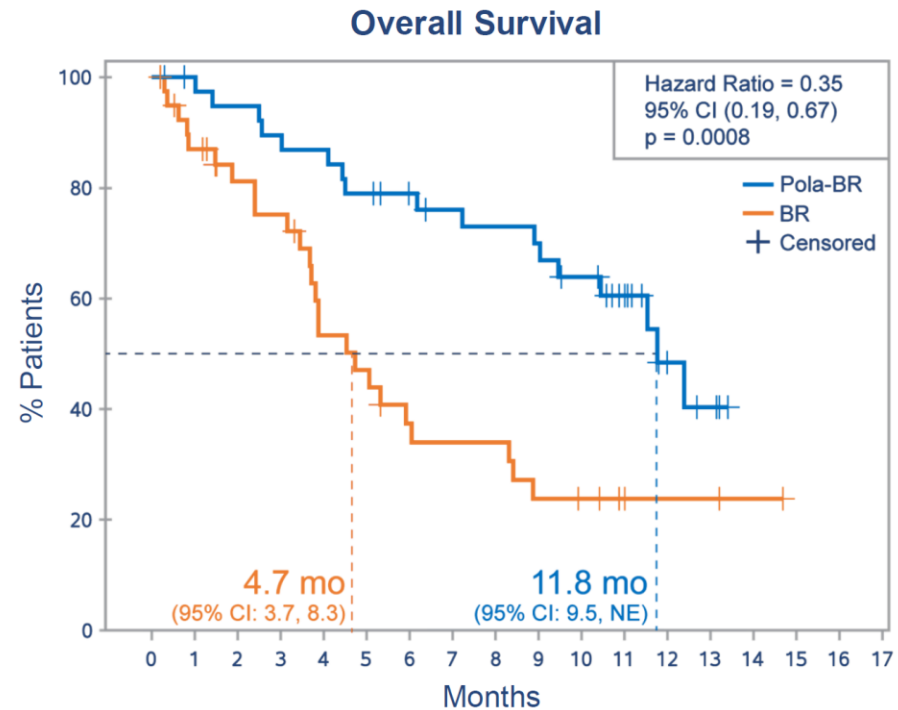
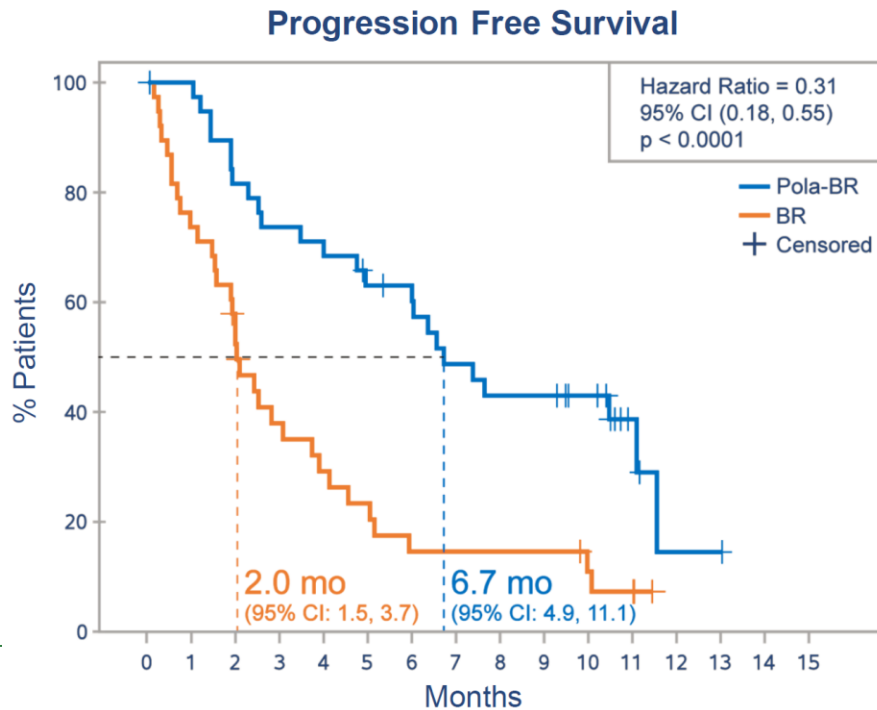
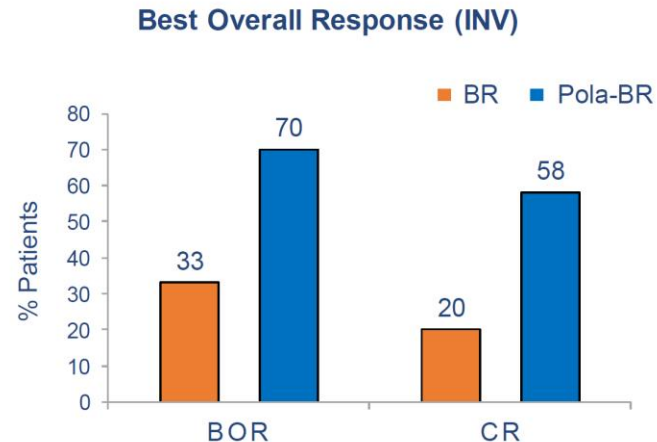
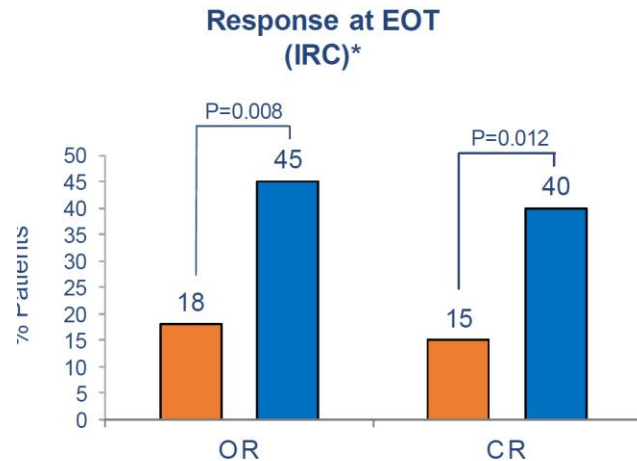


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	BR (N=40)	Pola-BR (N=40)
Median age, years (range)	71 (30-84)	67 (33-86)
Male, n (%)	25 (63)	28 (70)
Baseline ECOG PS, n (%)		
0-1	31 (78)	33 (83)
2	8 (20)	6 (15)
Stage III/IV disease, n (%)	36 (90)	34 (85)
IPI ≥3 at enrollment, n (%)	29 (73)	22 (55)
Has bulky disease (≥7.5 cm), n (%)	15 (38)	10 (25)
Has extranodal disease, n (%)	29 (73)	27 (68)
Stratification factor, n (%)		
DOR of last treatment ≤12 months	33 (83)	32 (80)
Prior anti-CD20 agent, n (%)	39 (98)	39 (98)
Refractory, n (%)		
Last prior therapy*	33 (83)	30 (75)
Primary refractory	28 (70)	20 (50)

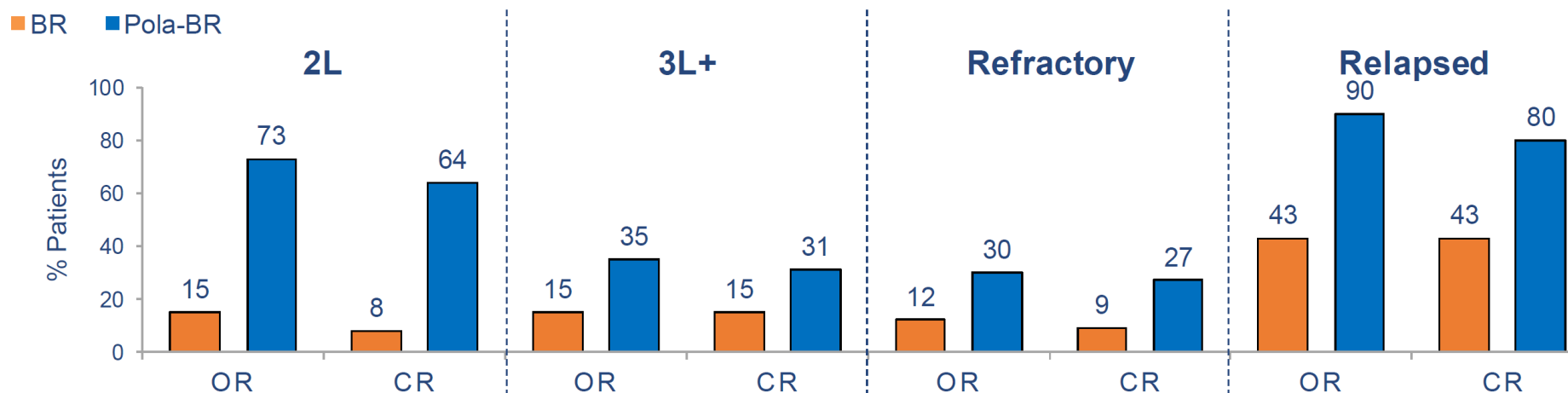
Pola BR vs BR in relapsed /refractory DLBCL: Response and survival



Pola BR vs BR in relapsed /refractory DLBCL



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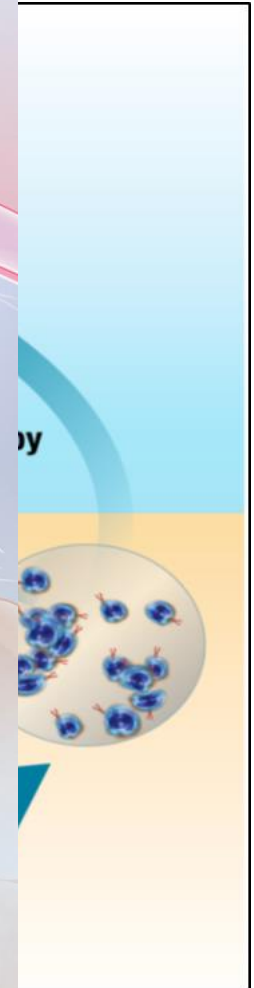
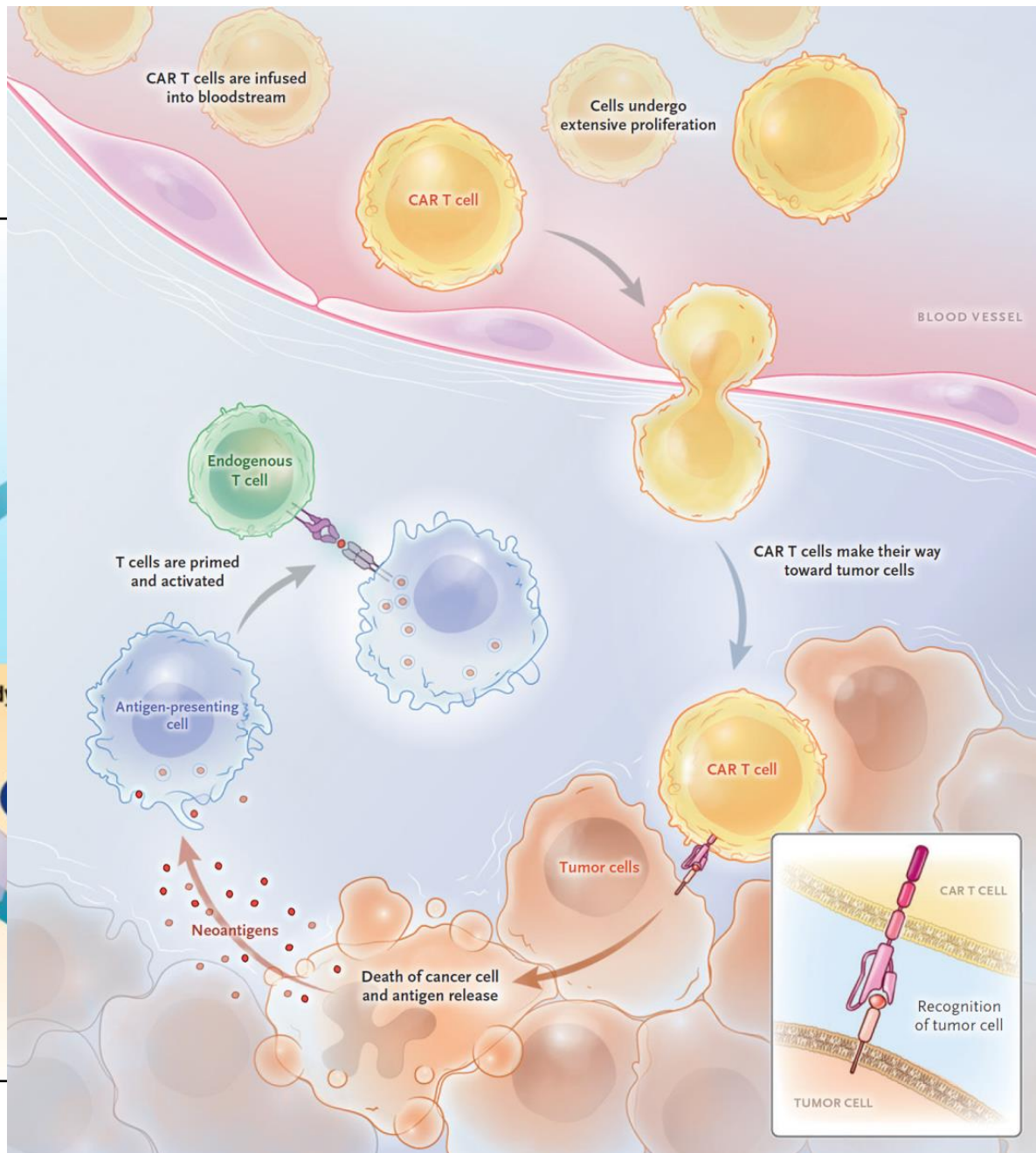
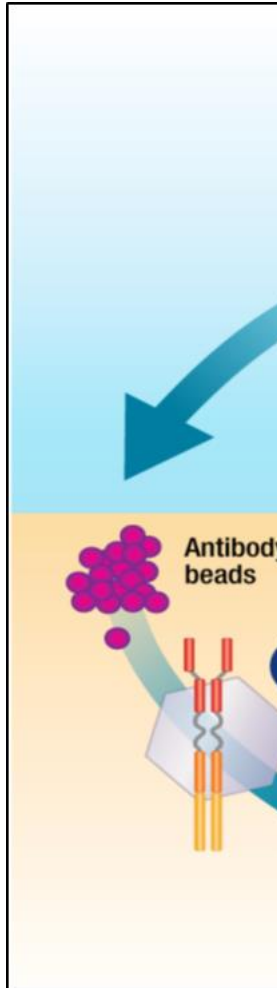
IRC (EOT)	2L		3L+		Refractory		Relapsed	
	BR (N=13)	Pola-BR (N=11)	BR (N=27)	Pola-BR (N=29)	BR (N=33)	Pola-BR (N=30)	BR (N=7)	Pola-BR (N=10)
Median PFS, mo (95% CI)	3.7 (1.5, 5.1)	11.1 (10.4, NE)	2.0 (1.5, 2.8)	6.0 (4.0, 7.6)	1.9 (1.1, 2.8)	6.0 (3.5, 7.4)	5.1 (2.5, 10.0)	11.1 (10.4, NE)
Median OS, mo (95% CI)	5.9 (3.9, 8.4)	NR (10.5, NE)	3.8 (3.2, 8.9)	11.5 (8.9, NE)	3.8 (3.2, 5.3)	11.5 (7.2, 12.4)	NR (NE, NE)	NR (6.0, NE)

- Adding Polatuzumab to BR significantly improves response rates, PFS and OS
- Polatuzumab received breakthrough designation by FDA and EMA for rr DLBCL



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CAR T cells in relapsed /refractory DLBCL



Tisagenlecleucel (Kymriah®) in Adult Relapsed or Refractory DLBCL (JULIETstudy)

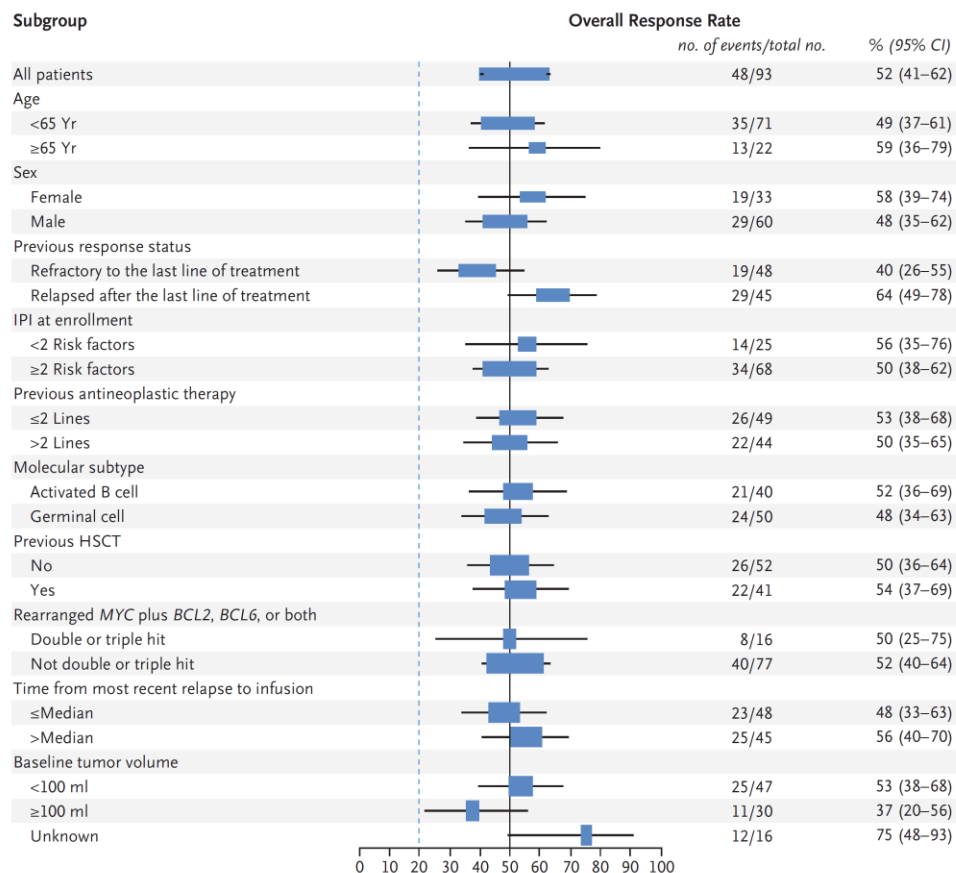
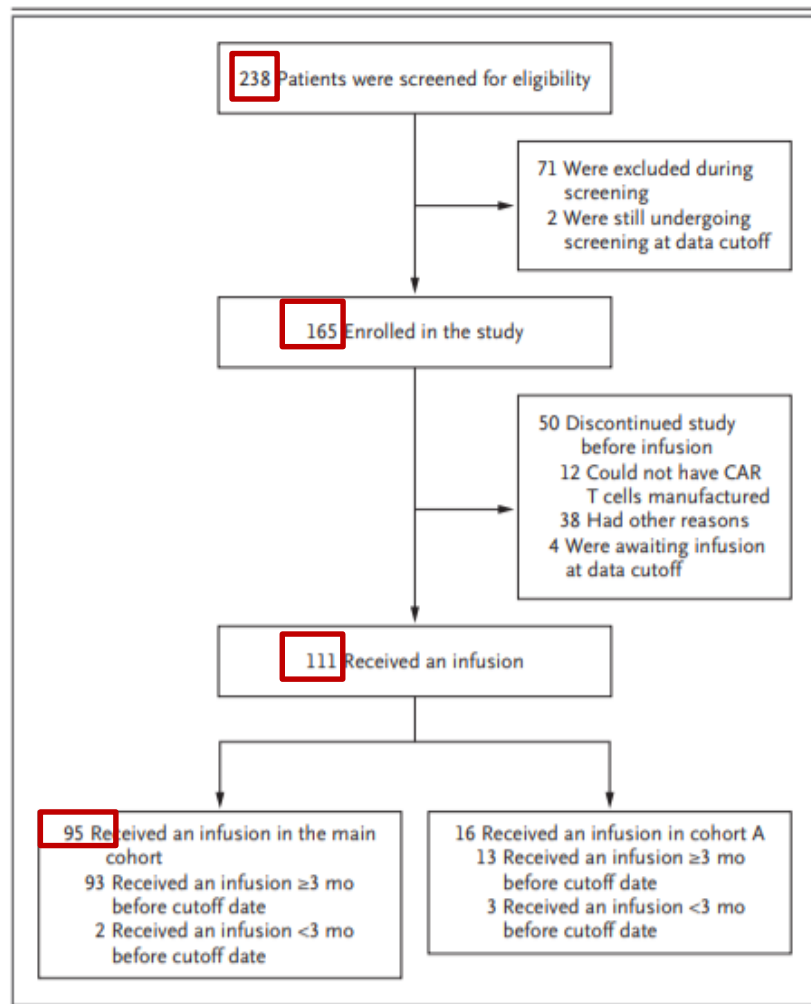


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Best ORR 52%, 40% CR; no differences across prognostic subgroups.

At 3 mo: 38% ORR, 32% CR

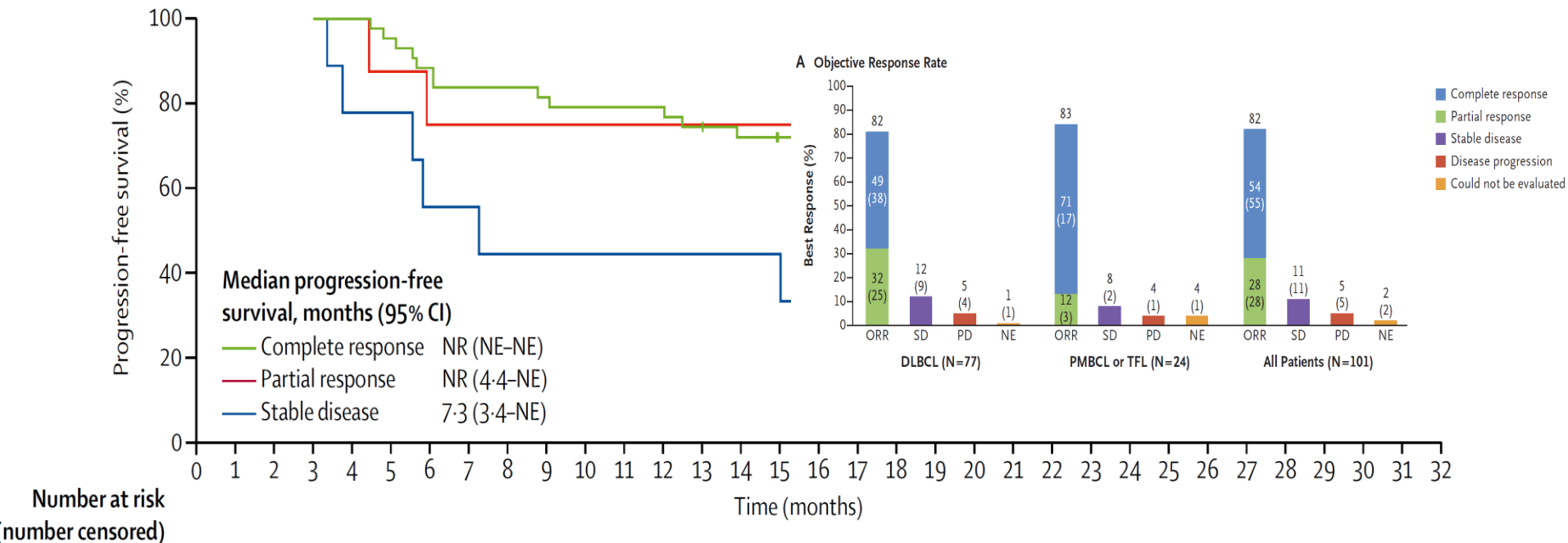
At 6 mo: 33% ORR, 29% CR



Long-term safety and activity of axicabtagene ciloleucel (YESCARTA®) in refractory large B-cell lymphoma : ZUMA-1



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- 108 pts (DLBCL, PMBCL, tFL) lymphoma—refractory or relapsed after ASCT
- followup of 27.1 months
- 83% had an objective response, and 58% had a complete response
- median PFS 5.9 months
- These 2-year FU data from ZUMA-1 suggest that axicel can induce durable responses and a median overall survival of greater than 2 years

“Real world” data with Axi-cel from US sites



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	ZUMA-I ²⁷	17 sites ⁴⁴	6 sites ⁴⁵	Houston ⁴⁶ Elderly*	Houston ⁴⁶ Younger*	Stanford ⁴⁷
Patient leukapheresed	111	294	117	n.a.	n.a.	25
Patient treated	101	274	104	20	52	22
Age (years)	58 (23–76)	60 (21–82)	64 (21–84)	68 (65–83)	42 (23–64)	n.a.
Fullfilling inclusion criteria of ZUMA I	100%	57%	52%	n.a.	n.a.	64%
	78%	32%	57%	20%	40%	n.a.
Bridging	0%	55%	31%	n.a.	n.a.	n.a.
Time from leukapheresis to reinfusion	17 days	27 days	n.a.	n.a.	n.a.	22 days
Best OR/best CR	82%/58%	81%/57%	71%/44%	94%/71%	78%/50%	86%/45%
Grade 3–5 CRS	13%	7%	16%	10%	15%	0%
Grade 3–5 CRES	28%	33%	39%	45%	58%	27%
Tocilizumab use	43%	63%	67%	75%	64%	77%
Fatal events	3/101	7/274	7/104	n.a.	n.a.	n.a.

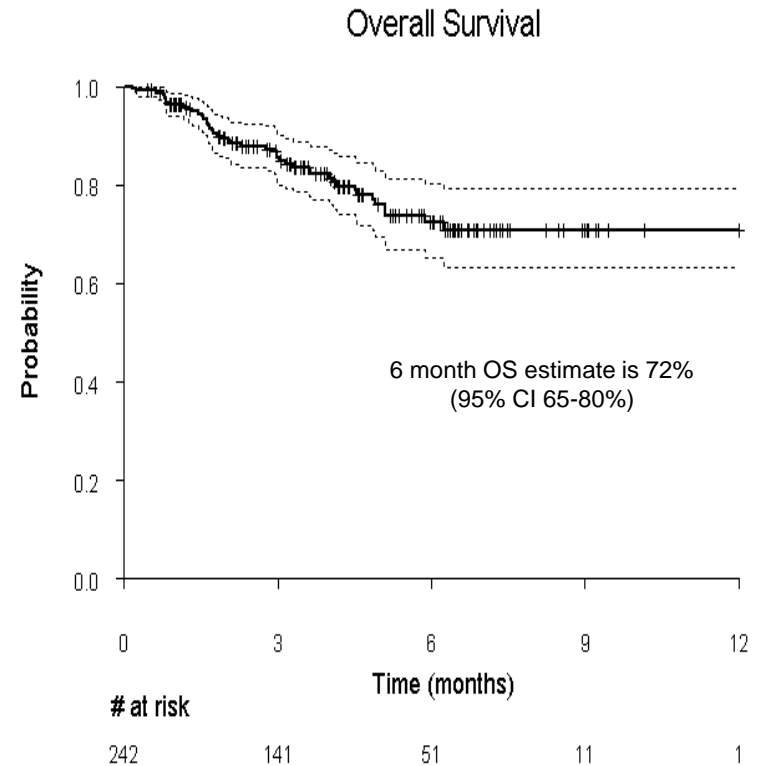
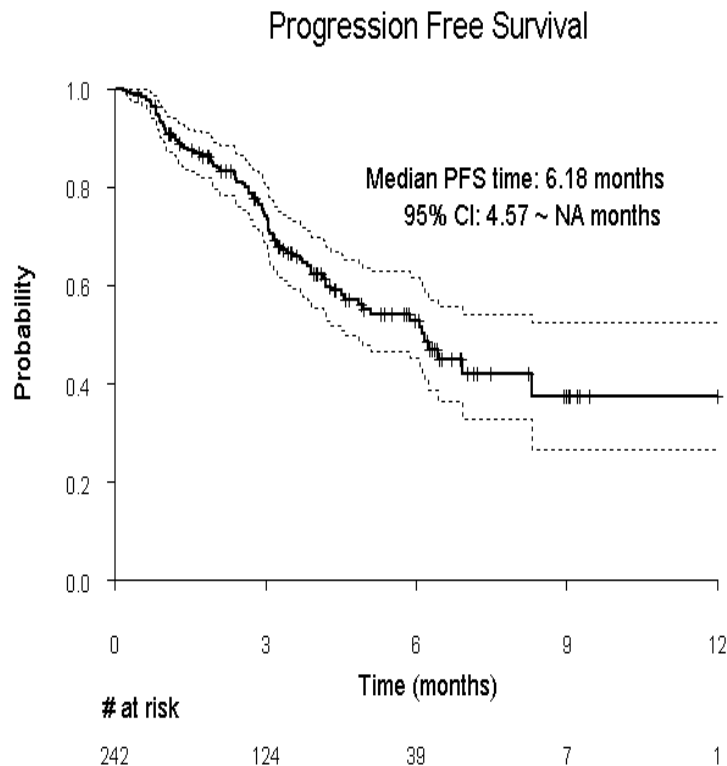
Risk factors for Response:

- ECOG 0-1 vs. ≥ 2 , relapsed vs. primary refractory/refractory, non-bulky vs. bulky ($\geq 10\text{cm}$)
- Met eligibility for ZUMA-1 vs. not

Axi-Cel in the Real World: PFS and OS



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Safety and 30 day response in the real world setting are comparable to the best response in ZUMA-1 although nearly half the pts failing to meet ZUMA-1 eligibility criteria

Comparison of commercially developed anti-CD19 CAR T-cells



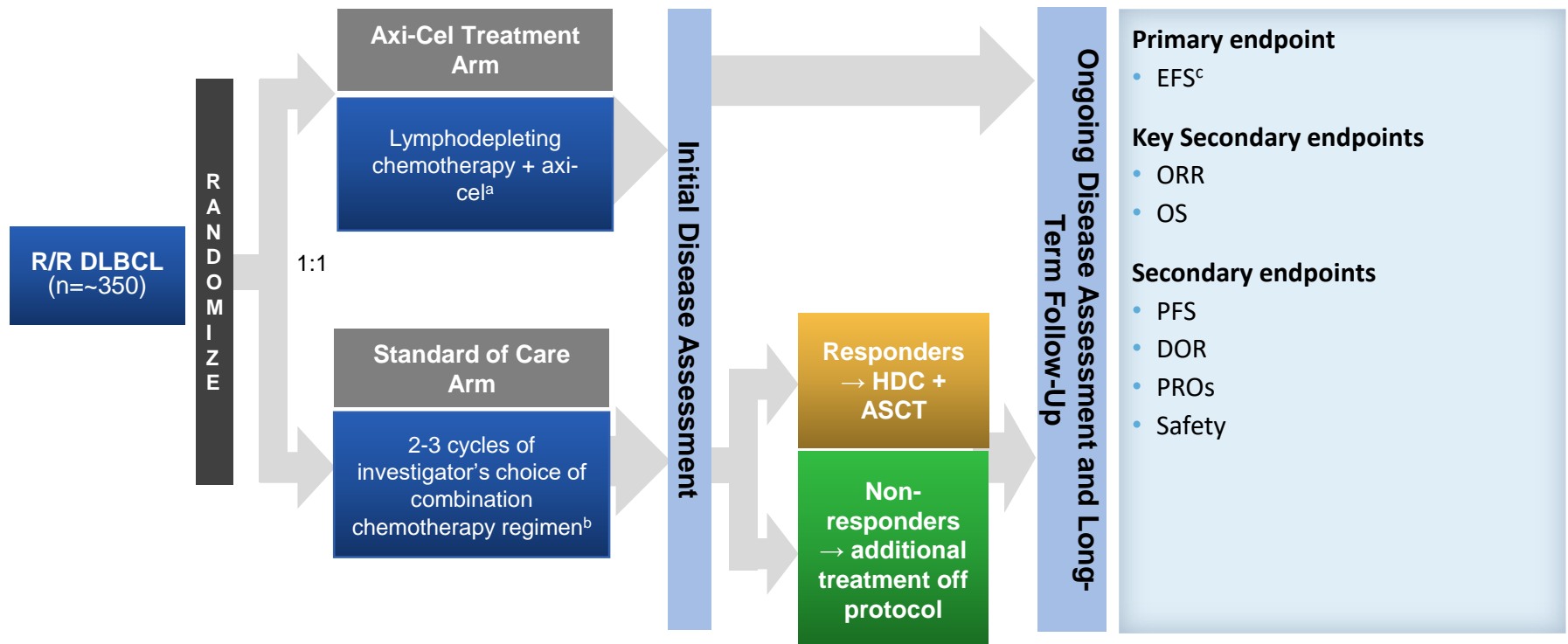
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	Axicabtagene ciloleucel (KTE019)	Tisagenlecleucel (CTL019)	Lisocabtagene Maraleucel (JCAR017)
Structure			
Anti-CD19 domain	FCM63	FCM63	FCM63
Costimulatory domain	CD28	4-1BB	4-1BB
Viral transfection	Gamma-retrovirus	Lentivirus	Lentivirus
Target Cells	PMBCs	PMBCs	CD4:CD8 ratio = 1
Phase-II clinical trial	ZUMA-I ²⁷	JULIET ⁴²	TRANSCEND ⁴³
Patient characteristics			
Indication	DLBCL, tFL, PMBCL Refractory disease: (1) PD or SD to most recent chemotherapy (2) PD or relapse within 12 months after ASCT	DLBCL, tFL (1) after at least two lines of therapy (2) either relapsed after or ineligible for ASCT	DLBCL, tFL, PMBCL, FL3b (1) after two lines of treatment (2) MCL after one line of treatment
Refractory to last treatment	74%	55%	67%
Patients included	111	165	134
Patients infused	101	111	114
Time from leuka-pheresis /enrolment to reinfusion	17 days	54 days	n.a.
Efficacy			
Best OR/best CR	OR 82% CR 54%	OR 52% CR 40%	OR 75% CR 55%
CR after 6 months	40%	29%	34%
Toxicity			
CRS grade 3–5	13%	22%	1%
Tocilizumab usage	43%	14%	12%
CRES grade 3–5	28%	12%	12%
Duration of response	11 months (3.9 months; NR) ³⁶	NR (181; 527 days)	NR (5 months; NR)

ZUMA-7: Second-Line R/R DLBCL Study Design



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Inclusion criteria: **Relapsed or refractory disease after 1L chemoimmunotherapy**

Refractory disease defined as no CR to 1L therapy

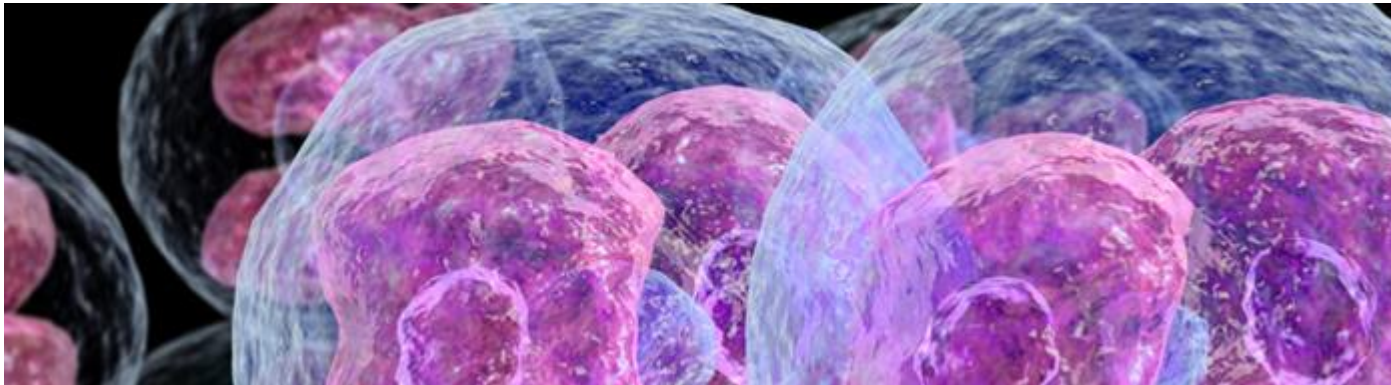
PD as best response to 1L therapy

SD as best response after ≥4 cycles of 1L therapy

PR as best response after ≥6 cycles and biopsy-proven residual disease or PD <12 mo from initiation of therapy

Relapsed disease defined as CR to 1L therapy followed by

DANKE FÜR DIE AUFMERKSAMKEIT



ZUMA-7: Second-Line R/R DLBCL

Key Eligibility Criteria



Key Inclusion Criteria

- Histologically proven DLBCL, including transformation from FL
- **Relapsed or refractory disease after 1L chemoimmunotherapy**
 - Refractory disease defined as no CR to 1L therapy
 - PD as best response to 1L therapy
 - SD as best response after ≥ 4 cycles of 1L therapy
 - PR as best response after ≥ 6 cycles and biopsy-proven residual disease or PD < 12 mo from initiation of therapy
 - Relapsed disease defined as CR to 1L therapy followed by biopsy-proven disease relapse ≤ 12 mo of initiation of 1L therapy
- Adequate 1L therapy
 - Anti-CD20 monoclonal antibody, unless tumor CD20 negative
 - An anthracycline containing chemotherapy regimen
- Intent to proceed to HDT and ASCT
- Age ≥ 18 years at the time of informed consent
- ECOG PS 0-1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function



Key Exclusion Criteria

- More than one line of therapy for DLBCL
- Prior CD19-targeted therapy
- Prior CAR or other genetically modified T cell therapy
- History of ASCT or allogeneic SCT
- Clinically significant infection or cardiopulmonary disease
- Indwelling lines or drains (dedicated central venous access catheters allowed)
- History or presence of nonmalignant CNS disorder or CSF malignant cells or brain metastases
- History of autoimmune disease
- History of DVT or PE within 6 mo of enrollment



Conclusions CAR-T cells

CAR-T cells are promising in relapsed/refractory DLBCL

Further technical improvements

- Improved patient selection
- Criteria for qualification of applying centers
- Costs

Updated Analysis of Tisagenlecleucel in Relapsed/Refractory ALL



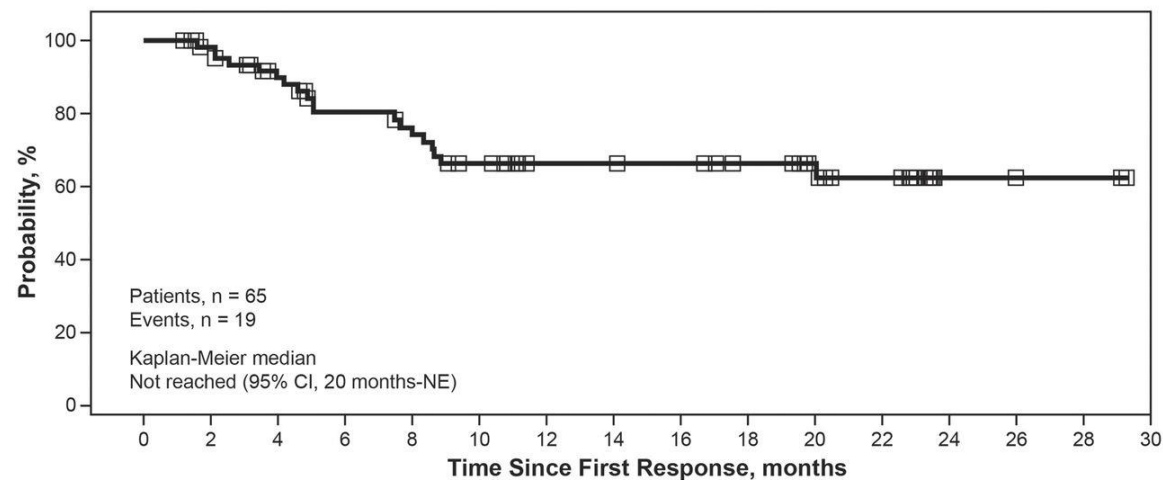
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Efficacy Results

	Patients (N = 79)	
	n (%)	95% CI, %
ORR	65 (82)	72-90
CR	49 (62)	
CRi	16 (20)	
Probability of relapse-free survival, % ^a		
12 Months	66	52-77
18 Months	66	52-77
Probability of overall survival, %		
12 Months	76	65-85
18 Months	70	58-79

^a Among responding patients (n = 65).

Kaplan-Meier Plot of Duration of Remission Censoring SCT (by IRC assessment; full analysis set)



Patients, n = 65 60 49 41 37 31 25 25 24 21 17 13 3 2 2 0

Grupp SA et al. Blood 2018;
132(Suppl 1):895

Table 1. PET-CR at end of therapy across biomarker subgroups in the CAVALLI and GOYA efficacy populations (pts who received any study drug)

% (N)	PET-CR		
	CAVALLI Ven + R-CHOP (IRC)	GOYA IPI 2-5 R-CHOP (IRC)	DeltaCR, % (95% CI)
All	69.2% (N=208)	62.8% (N=564)	6.6% (0–17.6)
BCL2 IHC-positive	64.8% (n=105)	60.3% (n=151)	4.5% (0–14.1)
DE	66.7% (n=81)	60.5% (n=124)	6.2% (0–17.7)
GCB, IHC pos	51.1% (n=47)	55.4% (n=65)	–4.3% (NA)
GCB, IHC neg	80.9% (n=47)	74.2% (n=93)	6.7% (NA)
ABC, IHC pos	75.0% (n=44)	59.0% (n=61)	16% (NA)
DH	71.4% (n=7)	25.0% (n=8)	46.4 (37.2–55.6)
BCL2 FISH-positive	70.0% (n=40)	47.5% (n=59)	22.5 (6.6–38.5)

CR, complete response; DE, double-expressor; DH, double-hit; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; IPI, International Prognostic Index score; IRC, independent review committee; NA, not available; PET, positron emission tomography; pts, patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; Ven, venetoclax



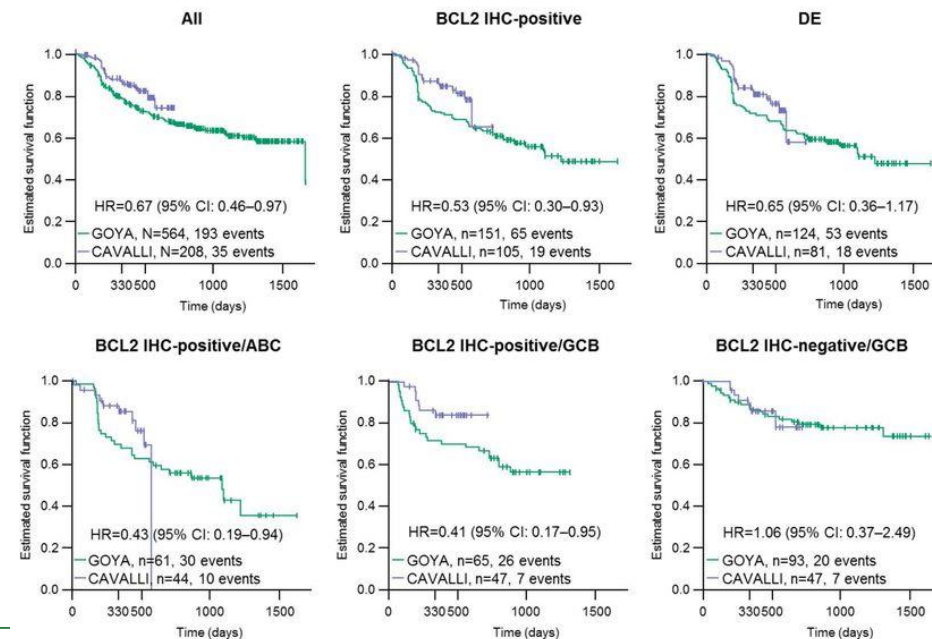
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Table 2. Grade 3–4 AEs in ≥10% of CAVALLI pts

AE, %	CAVALLI Ven + R-CHOP (N=208)	GOYA IPI 2-5 R-CHOP (N=564)
Neutropenia	64.9%	38.8%
Febrile neutropenia	33.2%	16.3%
Anemia	22.1%	8.9%
Thrombocytopenia	23.6%	1.6%
Infections	22.6%	16.0%
Sepsis	3.4%	1.1%
Pneumonia	3.4%	5.0%
Leukopenia	10.6%	9.6%

AE, adverse event; IPI, International Prognostic Index score; pts, patients; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; Ven, venetoclax

Figure 1. PFS in CAVALLI (Ven + R-CHOP) and GOYA IPI 2–5 (R-CHOP) in biomarker-defined and COO subgroups. Median follow-up: 20 months CAVALLI, 29.5 months GOYA



KM curves based on unadjusted HRs; HR presented in the graphs are adjusted for baseline covariates (age, sex, Eastern Cooperative Oncology Group performance status, body mass index, stage, lactic acid dehydrogenase, COO, IPI, bulky disease) by Cox methodology



AE	CAVALLI (N=208)		GOYA IPI 2-5 (N=564)	
	%	N	%	N
Any AE	99	206	94	528
AE with fatal outcome (Grade 5)	2	4*	5	30
Serious AE	56	116	41	230
Grade 3-4 AE	86	179	66	373
AE leading to withdrawal from any treatment	24	50	10	56
AE leading to withdrawal from VEN treatment	20	41	NA	NA
Median follow-up: CAVALLI, 22.3 months (data cut-off, Jul 13, 2018); GOYA, 29.6 months (data cut-off, Apr 29, 2016)				

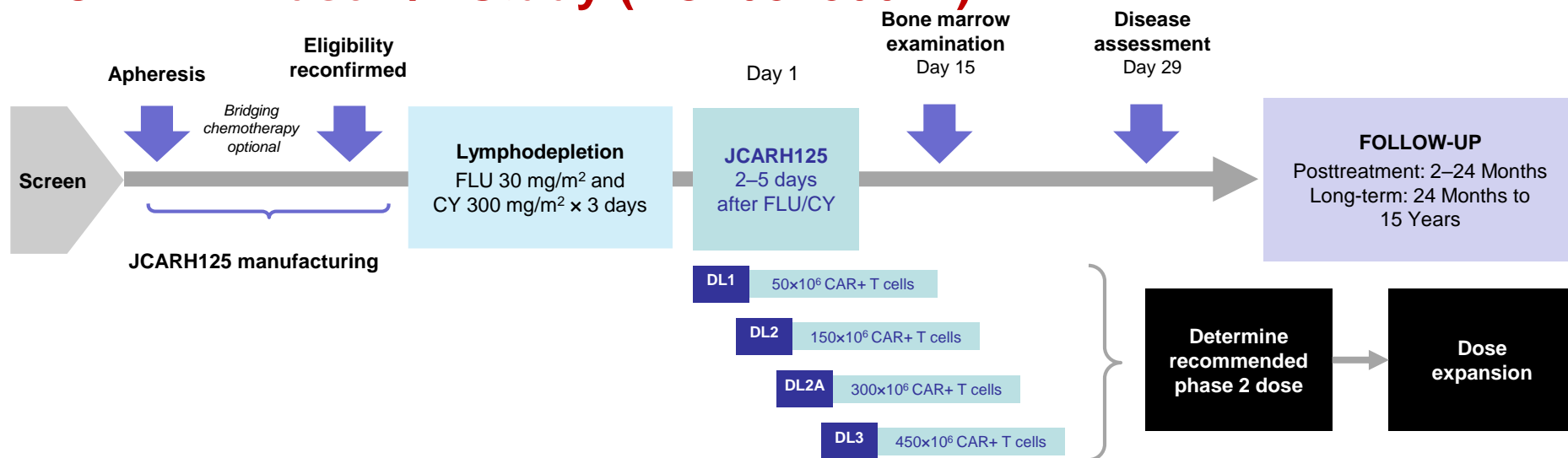
CAVALLI Study: Patient characteristics

	CAVALLI (N=208)	GOYA IPI 2–5 (N=564)
Median age, n (min–max)	65 (18–85)	62 (18–83)
Female, n (%)	94 (45)	267 (47)
ECOG PS, n (%)		
0–1	174 (84)	476 (85)
2	34 (16)	87 (15)
Stage, n (%)		
III–IV	177 (85)	478 (85)
IPI, n (%)		
2–3	155 (75)	455 (81)
4–5	51 (25)	109 (19)

JCARH125, Anti-BCMA CAR T-Cell Therapy for Relapsed/Refractory Multiple Myeloma: EVOLVE: Phase 1/2 Study (NCT03430011)



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Key Eligibility

- Relapsed/refractory multiple myeloma
- Failed at least 3 prior therapies
 - Autologous stem cell transplantation
 - IMiD, proteasome inhibitor
 - Anti-CD38 (combination or monotherapy)
- Refractory to last line of therapy
- ECOG performance status 0–1
- No selection based on BCMA expression

Study Objectives (Phase 1)

Primary

- To evaluate safety and tolerability (DLTs, adverse events)
- To determine a recommended phase 2 dose

Secondary

- To determine JCARH125 pharmacokinetics (C_{max} , T_{max} , AUC)
- To evaluate preliminary antitumor activity
- To evaluate MRD

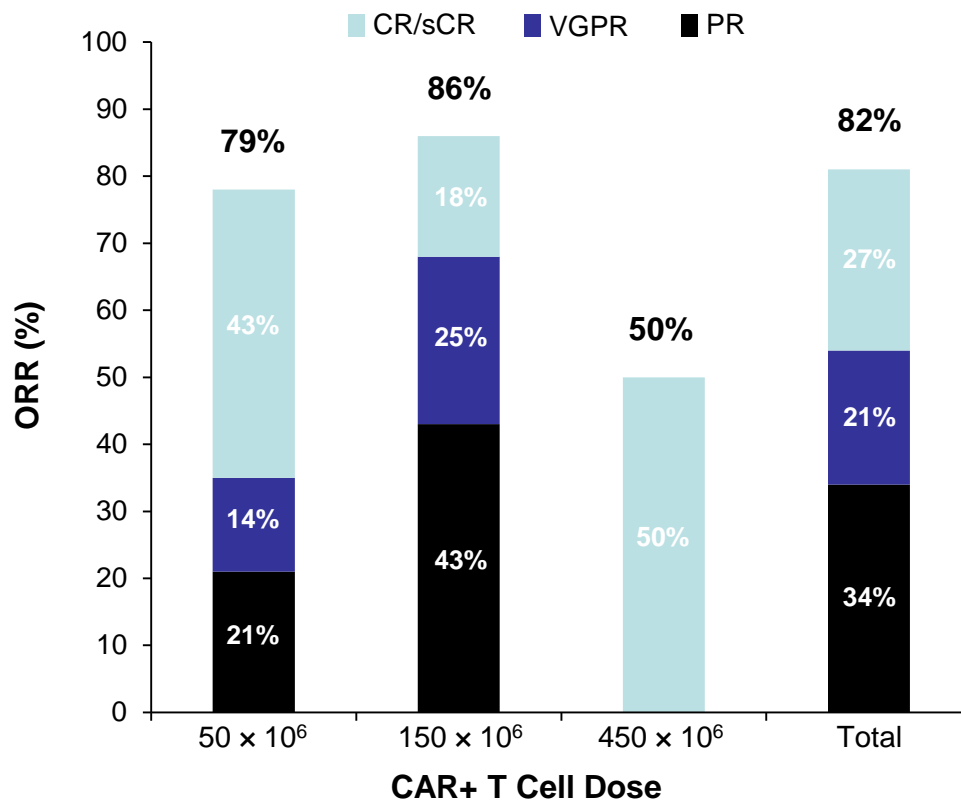
JCARH125 CAR: fully human binder, low affinity for sBCMA, optimized manufacturing process that enriches for central memory T cell phenotype.

JCARH125, Anti-BCMA CAR T-Cell Therapy for Relapsed/Refractory MM



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Best Overall Response



**ORR 82%,
with 48% ≥VGPR**

Mailankody S et al. Blood 2018;
132(Suppl 1):957

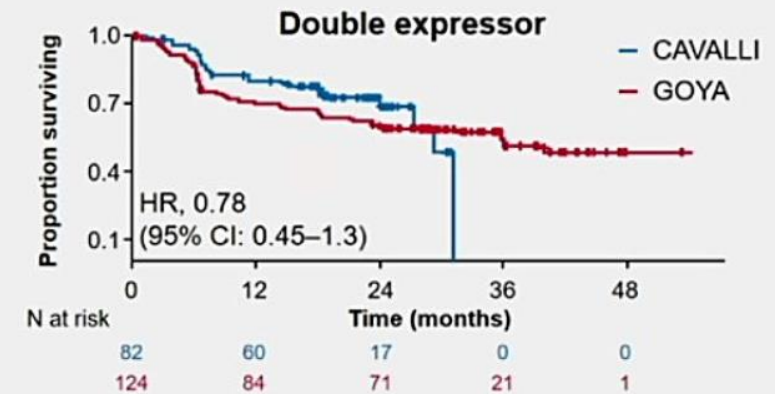
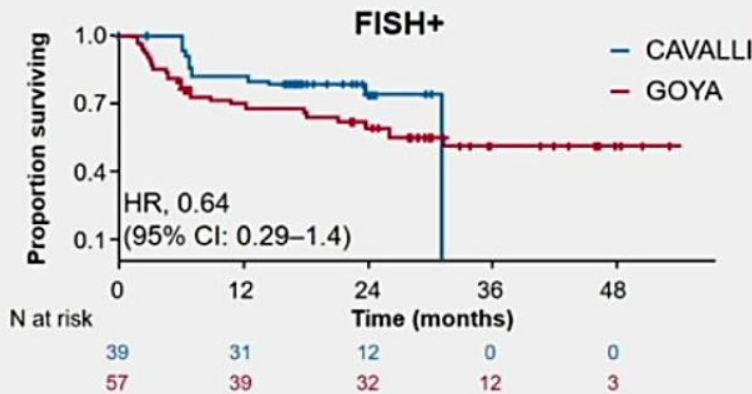
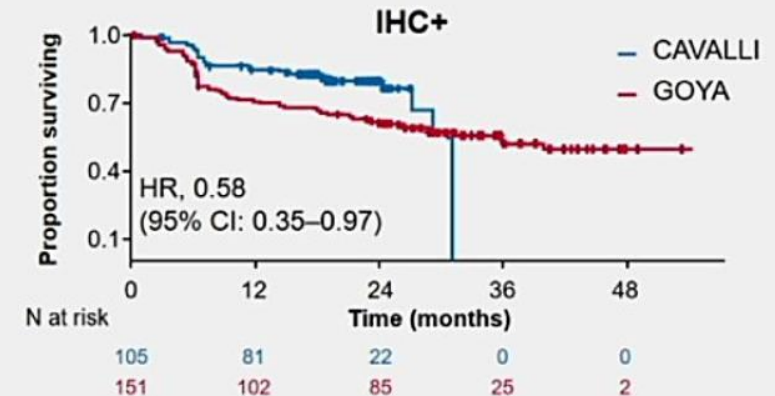
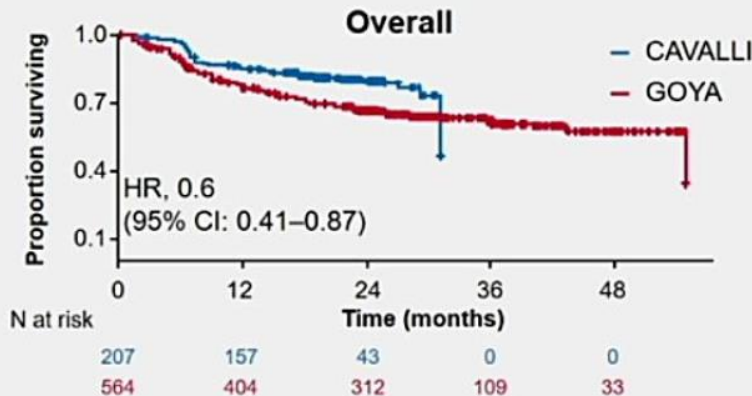
Patients, n:	14	28	2 ^a	44
Median follow-up, weeks:	17	9	7	11

Median of 7 (3-23) prior therapies, 77% high risk cytogenetics. Median FU 11 weeks.
CRS 80%, neurologic tox 25%, ICU admission 3 (7%), cytopenias grade 3-4 >29 days in 67%.
JCARH125 was active in patients with **high baseline levels of sBCMA**.

CAVALLI Study: OS according to subgroups



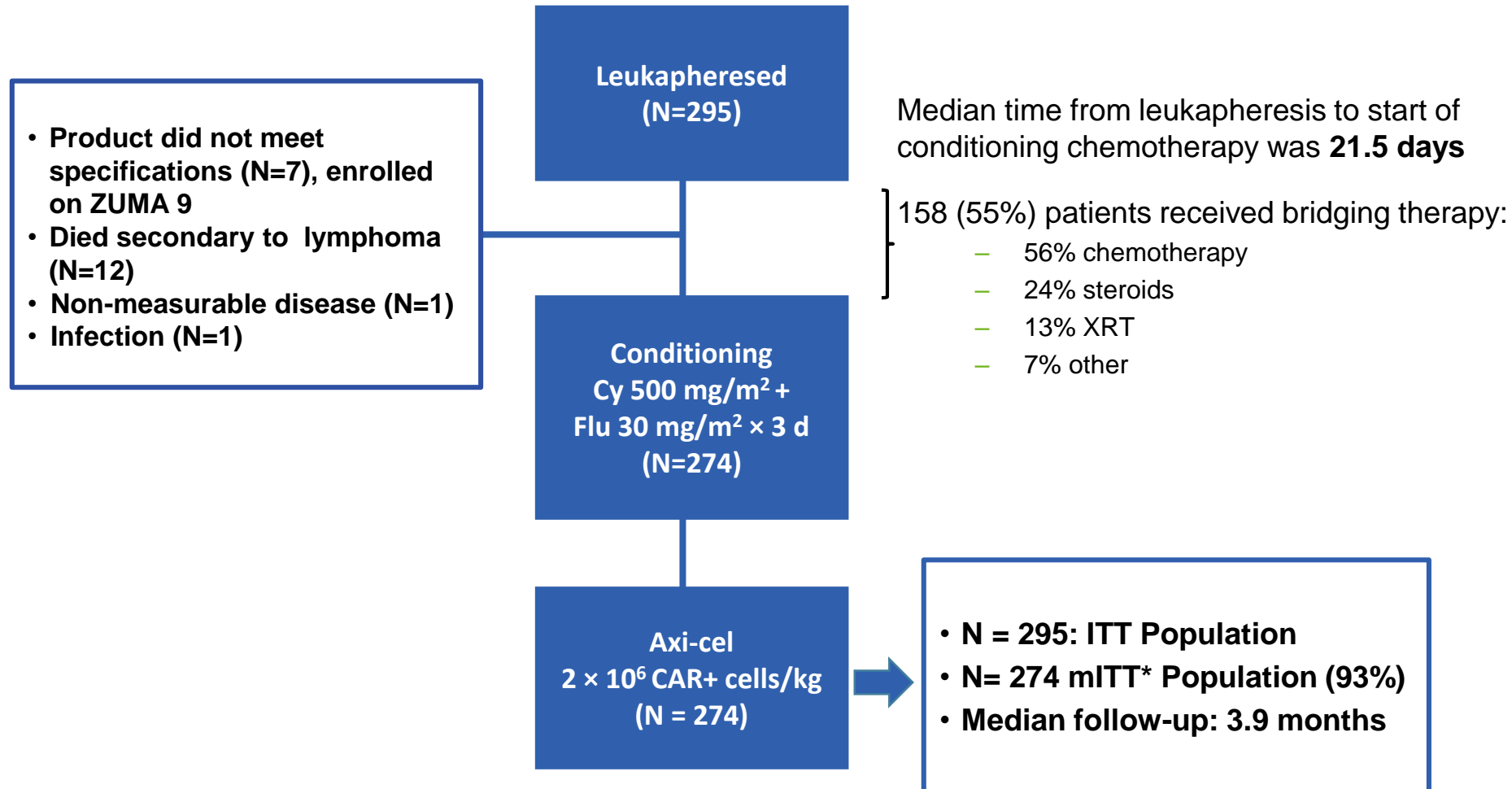
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Median follow-up: CAVALLI, 22.3 months (data cut-off, Jul 13, 2018); GOYA, 29.6 months (data cut-off, Apr 29, 2016)

*Covariates: age, sex, ECOG PS, BMI, IPI (high vs non-high), bulky disease (>7.5cm), disease stage (IV vs I–III), LDH, COO

Axicabtagene Ciloleucel (Axi-cel, Yescarta®) CD19 CAR T-Cells for Relapsed/Refractory DLBCL: Real World Experience



*includes 3 patients treated on ZUMA9 with product that was out of spec

Median age 60 (21-83) years, **prim. refract. 35%**, refract. relapse 42%, relapse after ASCT 33%. ABC like 40%, DE 38%. **43% did not meet criteria of ZUMA-1 at leukapheresis**



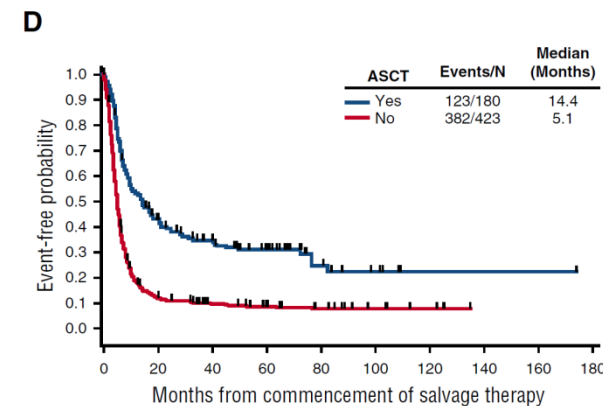
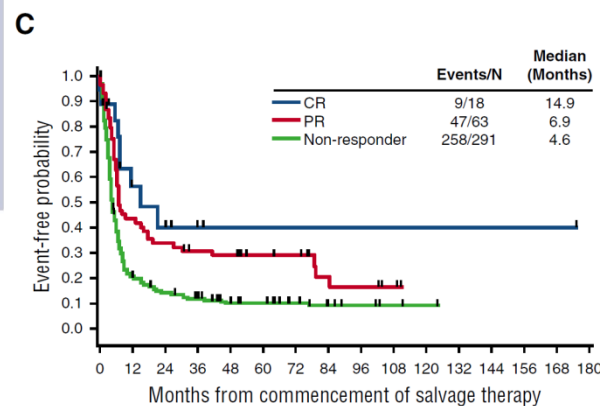
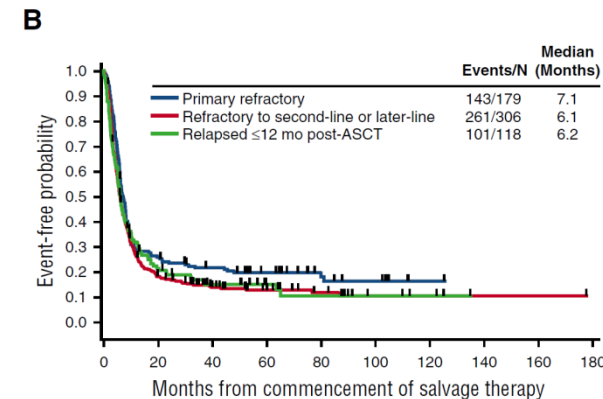
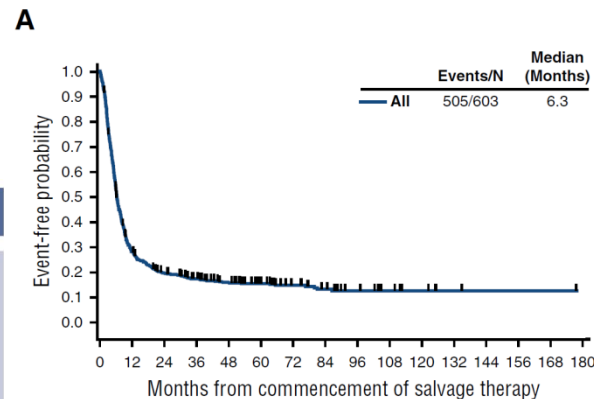
ECHELON-2: Patient characteristics

	A+CHP (N=226)	CHOP (N=226)		A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)	Disease diagnosis, n (%)		
Age in years, median (range)	58 (18-85)	58 (18-83)	sALCL	162 (72)	154 (68)
IPI score, n (%)			ALK+	49 (22)	49 (22)
0-1	53 (23)	48 (21)	ALK-	113 (50)	105 (46)
2-3	140 (62)	144 (64)	PTCL-NOS	29 (13)	43 (19)
4-5	33 (15)	34 (15)	AITL	30 (13)	24 (11)
Stage III/IV, n (%)	184 (81)	180 (80)	ATLL	4 (2)	3 (1)
			EATL	1 (0)	2 (1)

	A+CHP (N=226)	CHOP (N=226)
Exposure to study drug, n	223	226
Number of subjects treated by cycle, n (%)		
6 cycles	156 (70)	140 (62)
8 cycles	40 (18)	44 (19)
Completed treatment cycles as planned, %	88	81
Median relative dose intensity (brentuximab vedotin or vincristine), %	99	99
Subsequent therapy, n	226	226
Systemic therapy for residual or progressive disease, n (%)	59 (26)	94 (42)
Palliative radiation, n (%)	10 (4)	8(4)



Outcomes in **refractory** diffuse large B-cell lymphoma: results from the international **SCHOLAR-1** study



- In Pts with refractory DLBCL the objective response rate was 26% (CR 7%) to the next line of therapy
- median overall survival was 6.3 months
- 20% of patients were alive at 2 years

CAVALLI Study: PET CR Response and toxicity



Medizinische Universität Graz

% (N)	PET-CR		
	CAVALLI Ven + R-CHOP (IRC)	GOYA IPI 2-5 R-CHOP (IRC)	DeltaCR, % (95% CI)
All	69.2% (N=208)	62.8% (N=564)	6.6% (0–17.6)
BCL2 IHC-positive	64.8% (n=105)	60.3% (n=151)	4.5% (0–14.1)
DE	66.7% (n=81)	60.5% (n=124)	6.2% (0–17.7)
GCB, IHC pos	51.1% (n=47)	55.4% (n=65)	–4.3% (NA)
GCB, IHC neg	80.9% (n=47)	74.2% (n=93)	6.7% (NA)
ABC, IHC pos	75.0% (n=44)	59.0% (n=61)	16% (NA)
DH	71.4% (n=7)	25.0% (n=8)	46.4 (37.2–55.6)
BCL2 FISH-positive	70.0% (n=40)	47.5% (n=59)	22.5 (6.6–38.5)

AE, %	CAVALLI Ven + R-CHOP (N=208)	GOYA IPI 2-5 R-CHOP (N=564)
Neutropenia	64.9%	38.8%
Febrile neutropenia	33.2%	16.3%
Anemia	22.1%	8.9%
Thrombocytopenia	23.6%	1.6%
Infections	22.6%	16.0%
Sepsis	3.4%	1.1%
Pneumonia	3.4%	5.0%



GOYA Study: Patient characteristics

	<i>CHOP6, N=526</i>	<i>CHOP8, N=186</i>
Age, median (IQR)	62 (54–70)	60 (47–67)
Male, n (%)	291 (55)	91 (49)
Ann Arbor stage, n (%)		
I	37 (7)	11 (5.9)
II	85 (16)	38 (20)
III	181 (34)	74 (40)
IV	223 (42)	62 (33)
Extranodal sites, n (%)		
1–2	202 (38)	63 (34)
>2	323 (61)	122 (66)
IPI category, n (%)		
Low risk (0-1 points)	103 (20)	37 (20)
Low-intermediate (2 points)	204 (39)	64 (34)
Intermediate-high (3 points)	140 (27)	52 (28)
High risk (4-5 points)	79 (15)	32 (17)
Bulky disease (≥ 7.5cm), n (%)	189 (36)	73 (39)
LDH (elevated), n (%)	224 (43)	81 (44)

	<i>CHOP6, N=526</i>	<i>CHOP8, N=186</i>
Cell of origin (COO), n (%)		
ABC	86 (16)	32 (17)
GCB	192 (37)	77 (41)
Missing	191 (36)	59 (32)
BSA quartiles (ITT), n (%)		
Q1	118 (22)	54 (29)
Q2	126 (24)	42 (23)
Q3	136 (26)	41 (22)
Q4	140 (27)	47 (25)
Mid-term CT response, n (%)		
CR	106 (20)	38 (20)
PR	338 (64)	117 (63)
Geographic region, n (%)		
Asia	166 (32)	92 (50)
Eastern Europe	54 (10)	45 (24)
Western Europe	190 (36)	25 (13)
North America	93 (18)	14 (7.5)
Other	23 (4.4)	10 (5.4)

Suggested algorithm for therapy in patients for whom R-CHOP therapy failed

