Recent Breakthroughs and Other Promising Approaches in the Treatment of Diffuse Large B-Cell Lymphoma (DLBCL)

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Disclosures

Consulting Agreements	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Amgen Inc, Apobiologix, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Genentech, Gilead Sciences Inc, Janssen Biotech Inc, Karyopharm Therapeutics, Kite Pharma Inc, Lundbeck, Merck, MorphoSys, Roche Laboratories Inc, Seattle Genetics, Takeda Oncology, Teva Oncology, TG Therapeutics Inc
Contracted Research	Genentech, Roche Laboratories Inc

Case Presentation: Dr Brenner

84-year-old woman

- Presents with extensive lymphadenopathy and bone involvement
  - Very high LDH
- Diagnosis: DLBCL
- R-mini-CHOP, with complete resolution of symptoms
  - Relapse 4 months later, with PS 2

Case Presentation: Dr Morganstein

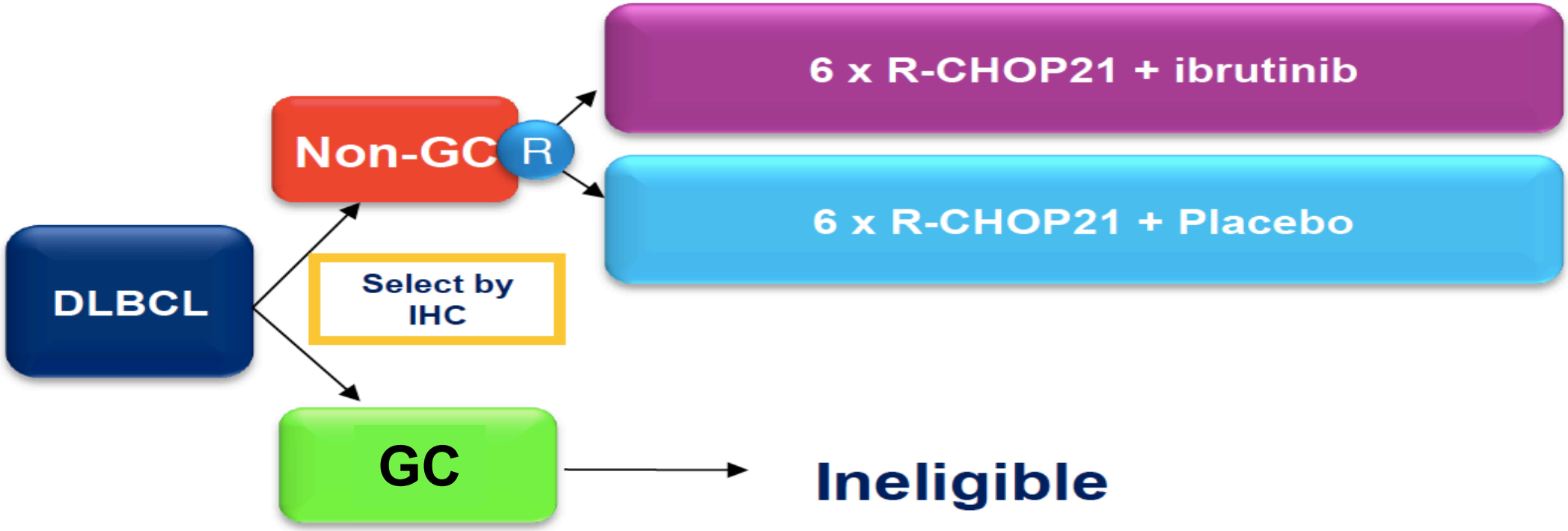
62-year-old man

- Presents with rapidly enlarging cervical lymph nodes, night sweats and extreme weight loss
- Diagnosis: Triple-hit DLBCL
  - LDH very elevated
  - GI involvement
- Dose-adjusted R-EPOCH

Novel Agents in Untreated DLBCL

Author	Therapy	Better than R-CHOP
Crump, JCO 2016	**R-CHOP + Enzastaurin MTN**	**No**
Leonard, JCO 2017	**R-CHOP- Bortezomib**	**No**
Davies, Lancet 2019	**R-CHOP- Bortezomib**	**No**
Vitolo, JCO 2017	**Obinutuzumab-CHOP**	**No**
Thieblemont, JCO 2017	**R-CHOP + Lenalidomide MTN**	**PFS only**
Witzig, Ann Oncol 2018	**R-CHOP + Everolimus MTN**	**No**
Younes, JCO 2019	**R-CHOP-Ibrutinib**	**No (?)**
Vitolo, ICML 2019	**R-CHOP-lenalidomide**	**No**
Nowakowski, ICML 2019	**R-CHOP-lenalidomide**	**Yes (?)**

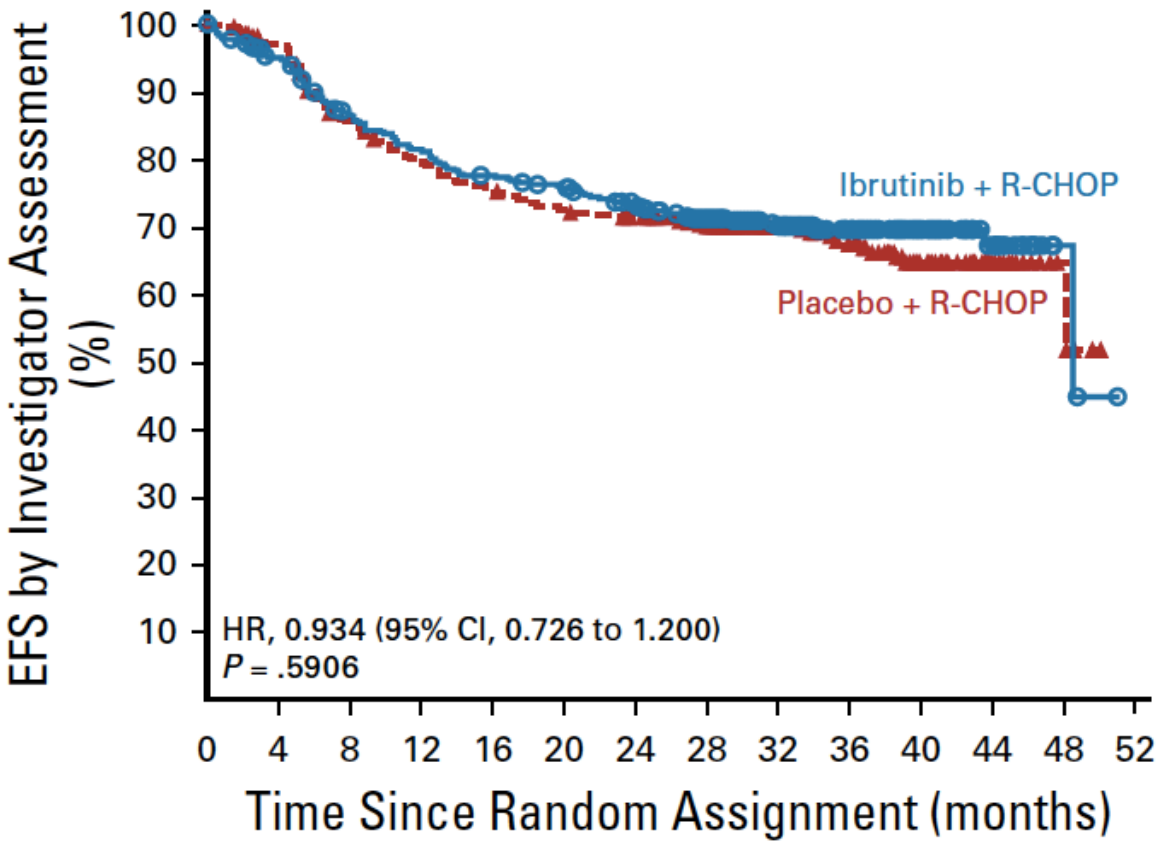
PHOENIX Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



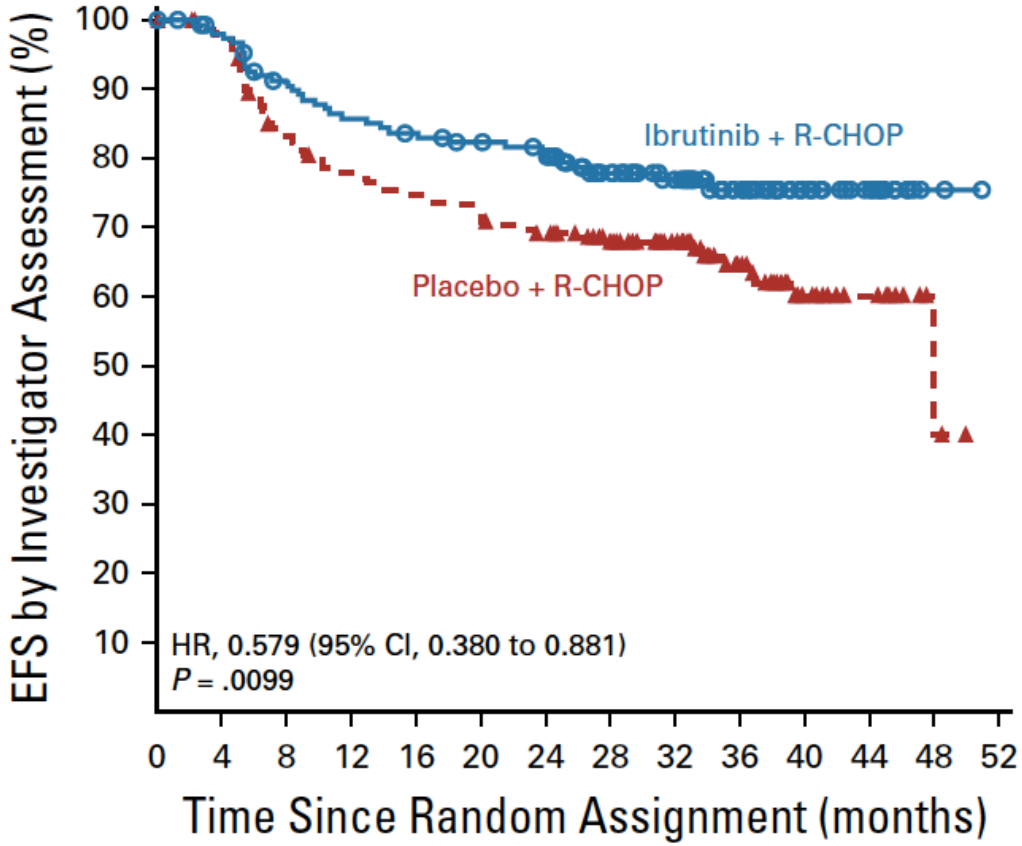
- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = EFS
- N = 800

*** Ibrutinib 560 mg daily x 6 cycles or placebo**

PHOENIX Study: R-CHOP +/- Ibrutinib in Newly Diagnosed non-GCB DLBCL



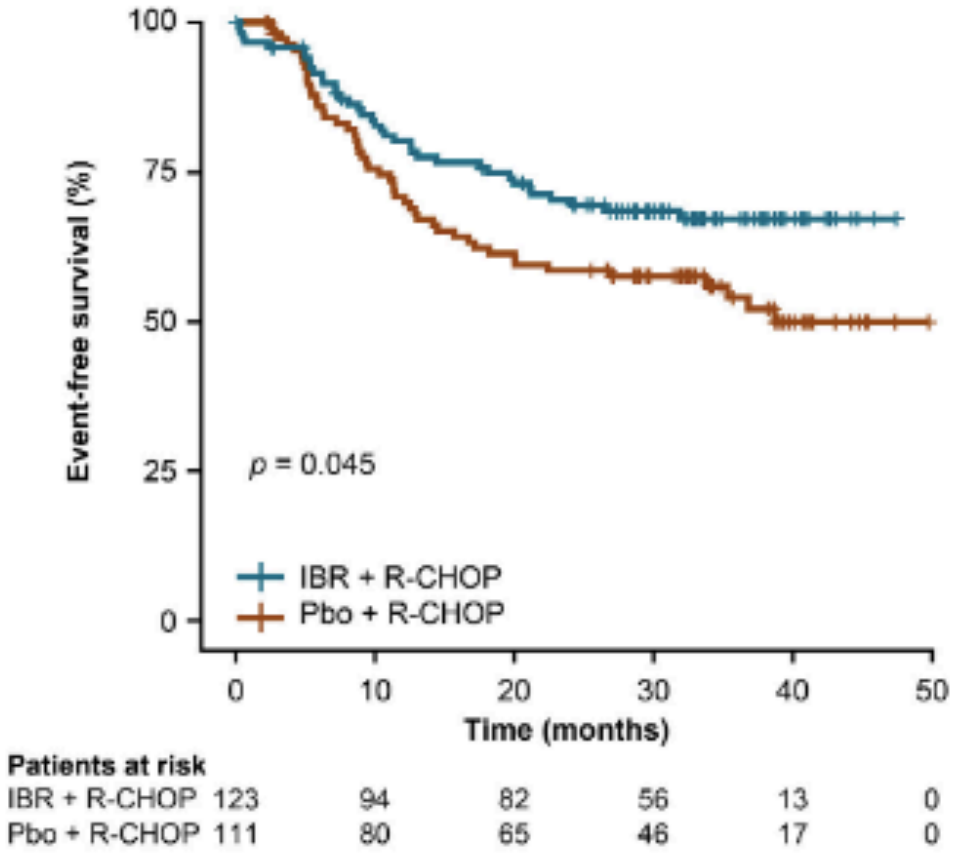
ITT Population



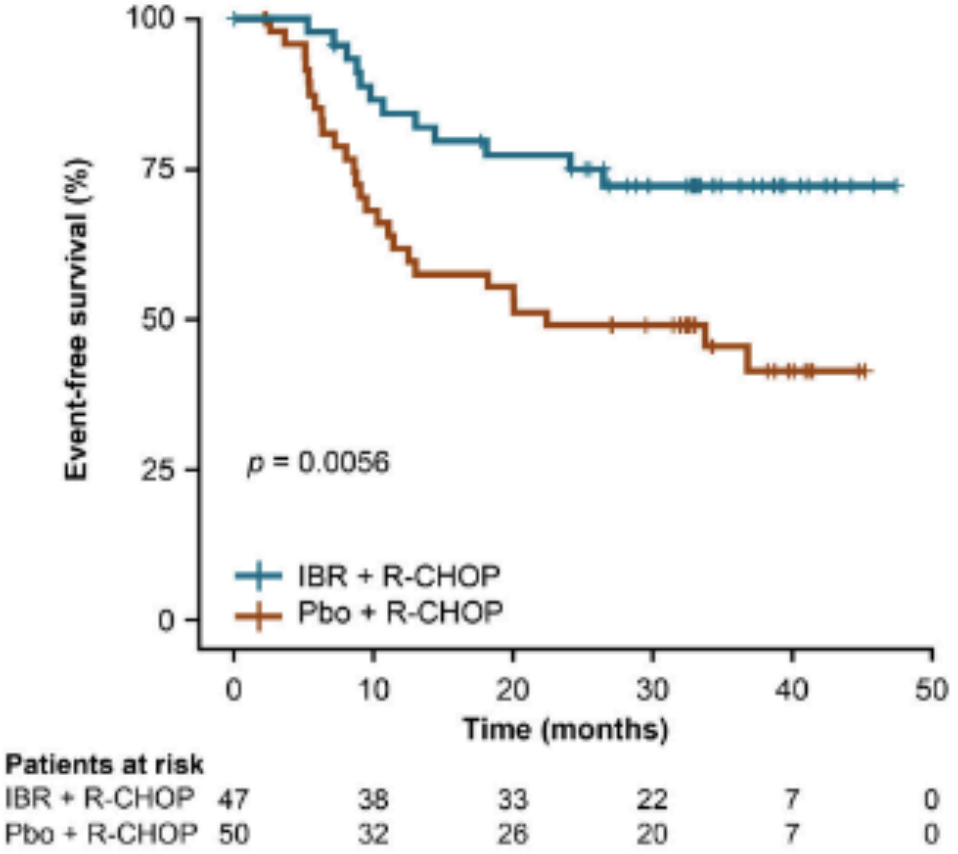
Age <60 years

Younes, A et al, JCO 2019

PHOENIX Study: Impact of Ibrutinib + R-CHOP in Patients Co-Expressing *BCL2* and *MYC*



ITT Population

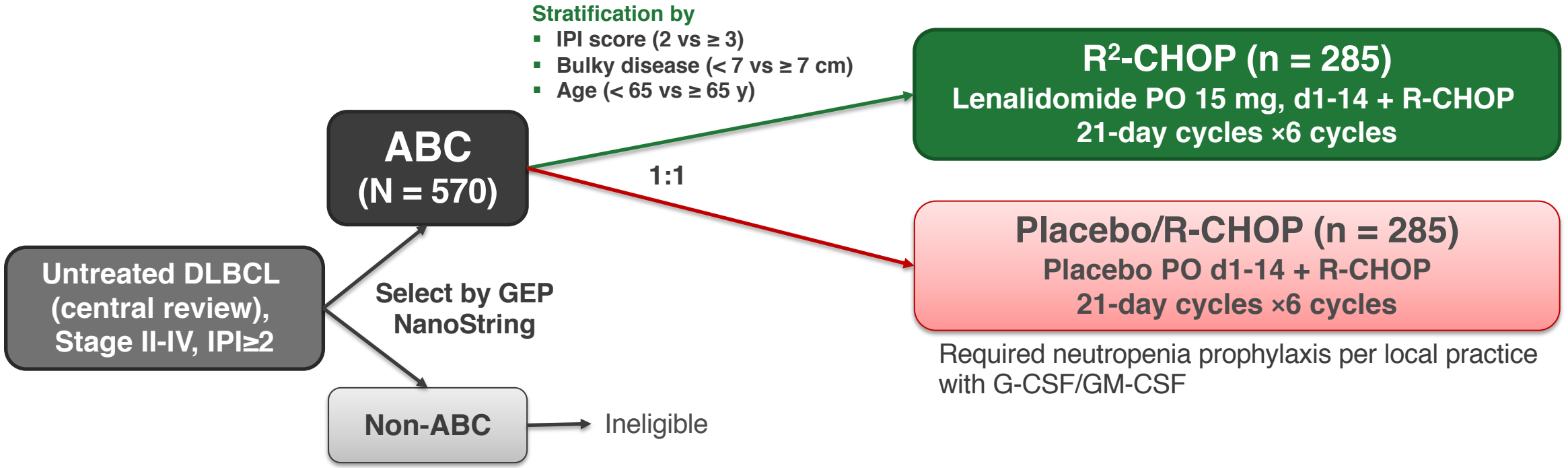


Age <60 years

Johnson, P et al, ASH 2019 abstract 354

ROBUST Phase III Study Design

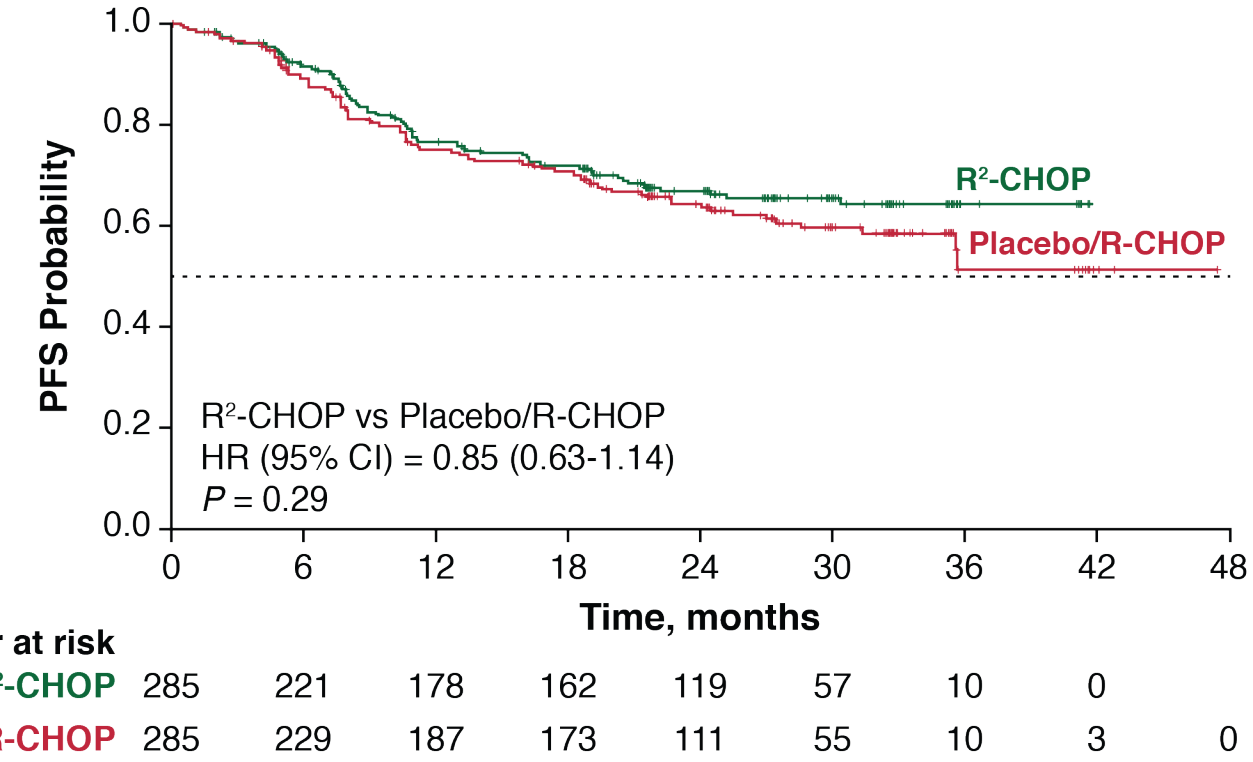
- Multicenter, international, randomized, double-blind, **placebo-controlled**, Phase III study
- **Primary endpoint: PFS by central review** (per 2014 IWG)[1]
- Secondary endpoints: EFS (key secondary), OS, ORR, CR rate, DOR, and safety



NCT02285062; EudraCT 2013-004054-21. 1. Cheson et al. *J Clin Oncol.* 2014;32:3059-3068.

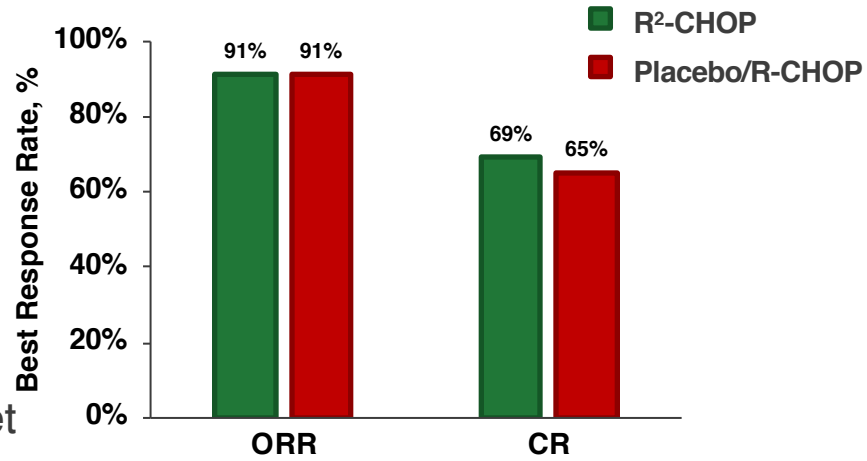
Vitolo U et al, ICML 2019

ROBUST Primary Endpoint: Progression-Free Survival (ITT, IRAC)



Number at risk									
R²-CHOP	285	221	178	162	119	57	10	0	
Placebo/R-CHOP	285	229	187	173	111	55	10	3	0

PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%



- Median follow-up 27.1 mo (range, 0-47): primary endpoint of PFS was not met
- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

Data cut-off 15Mar2019.
Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson et al. *J Clin Oncol.* 2014;32:3059-3068).

Vitolo U et al, ICML 2019

E1412: US Multicenter Randomized Phase 2 of R2CHOP vs RCHOP

ECOG
SWOG
Alliance

Untreated DLBCL
Bulky stage 2, or 3-4
IPI≥2

DLBCL → R **1:1**

→ **R-CHOP x 6**

→ **R2-CHOP x 6**

Stratification
- Age (< 60 vs. ≥60)
- IPI 2/3 vs. 4/5

Tissue ↓

Pathology review and COO tissue analysis:
- GEP – NanoString – Predefined Analysis in ABC DLBCL
- IHC - Hans algorithm

R2CHOP:
Len 25 mg/day day 1-10
with R-CHOP21
Mandatory G-CSF

Primary endpoint:
- PFS in all comers DLBCL, and within ABC DLBCL (co-primary)

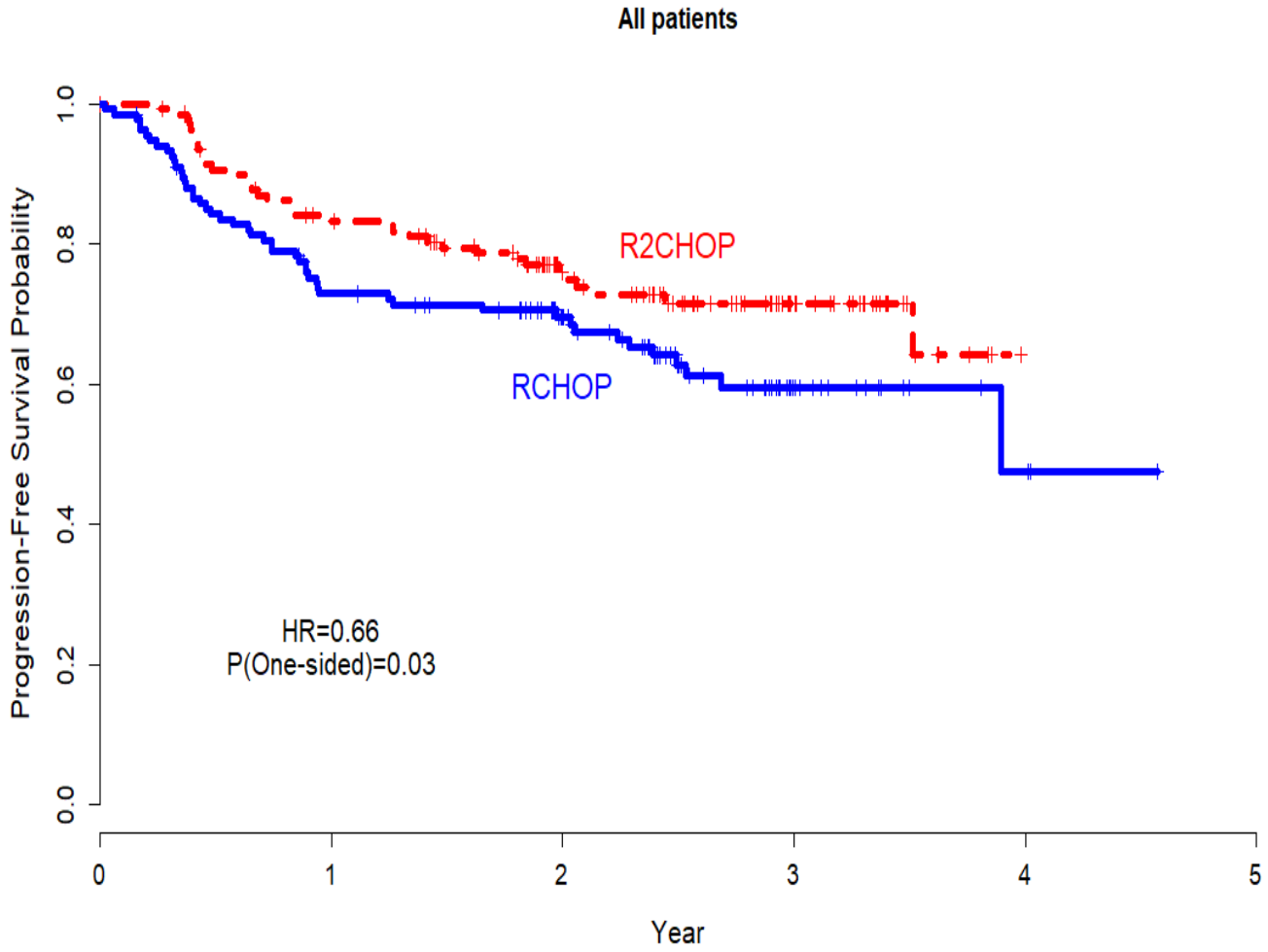
Secondary endpoints:
- ORR, PET CR, EFS and OS,
- PFS in ABC DLBCL

Statistical assumptions:
- 282 eligible patients , 89% power, one-sided alfa 0.1 for HR - 0.59 for **all comers**
- 102 eligible **ABC DLBCL**, 81% power, one-sided alfa 0.125, HR- 0.52

ClinicalTrials.gov Identifier: NCT01856192.

Nowakowski G et al, ICML 2019

E1412: Primary Endpoint: PFS All Patients (n=280)



R2CHOP was associated with 34% reduction in risk of progression or death

Median follow up 2.5 years

	All patients (n=280)	
	R2CHOP (n=145)	RCHOP (n=135)
1yr PFS	0.83	0.73
2yr PFS	0.76	0.70
Stratified HR (80% CI)	0.66 (0.50, 0.88)	
Stratified one-sided P	0.03	

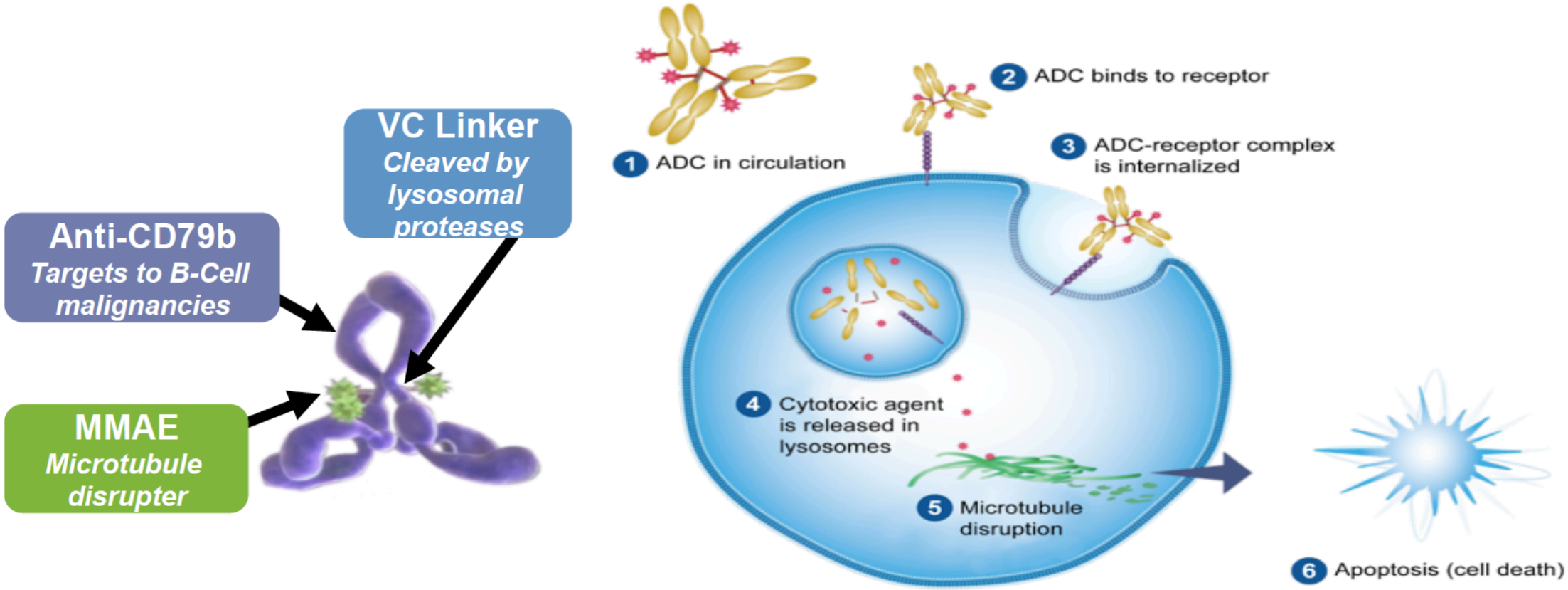
- **Median time from diagnosis to treatment 21 days**

ECOG-ACRIN cancer research group | Reshaping the future of patient care

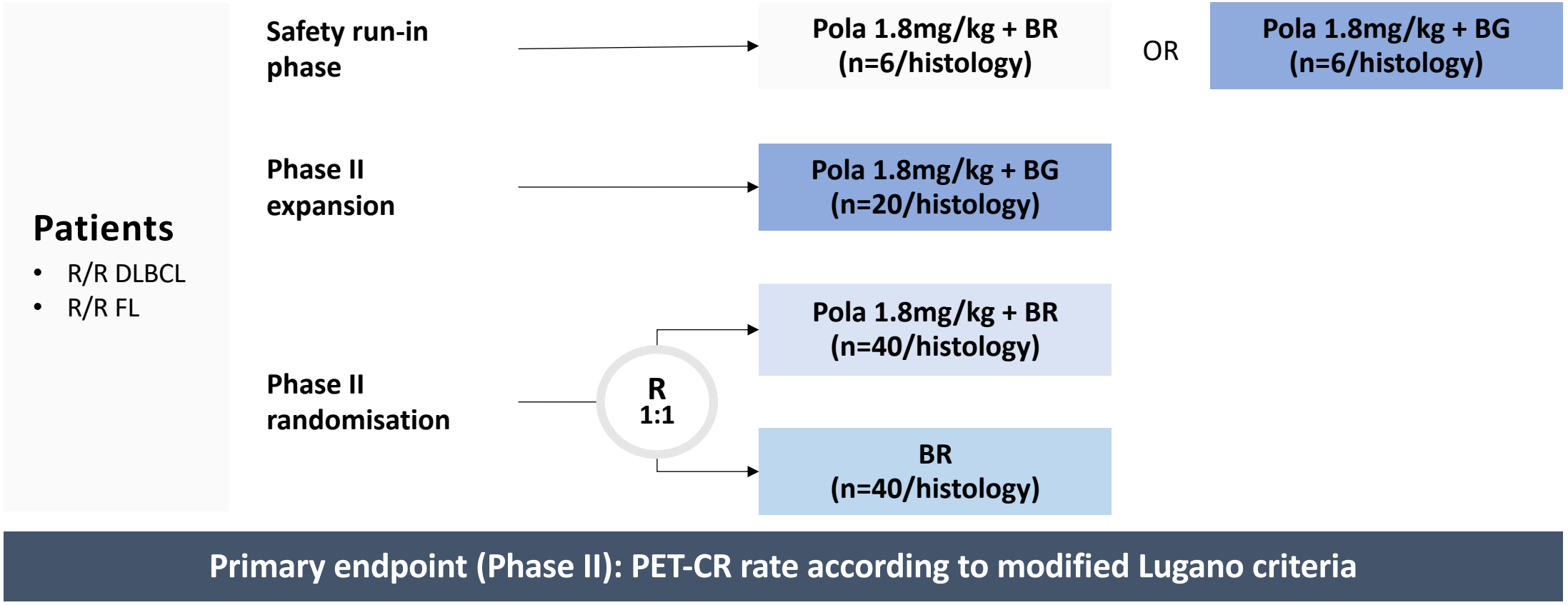
Nowakowski G et al, ICML 2019

Polatuzumab Vedotin: Anti-CD79b Drug Conjugate

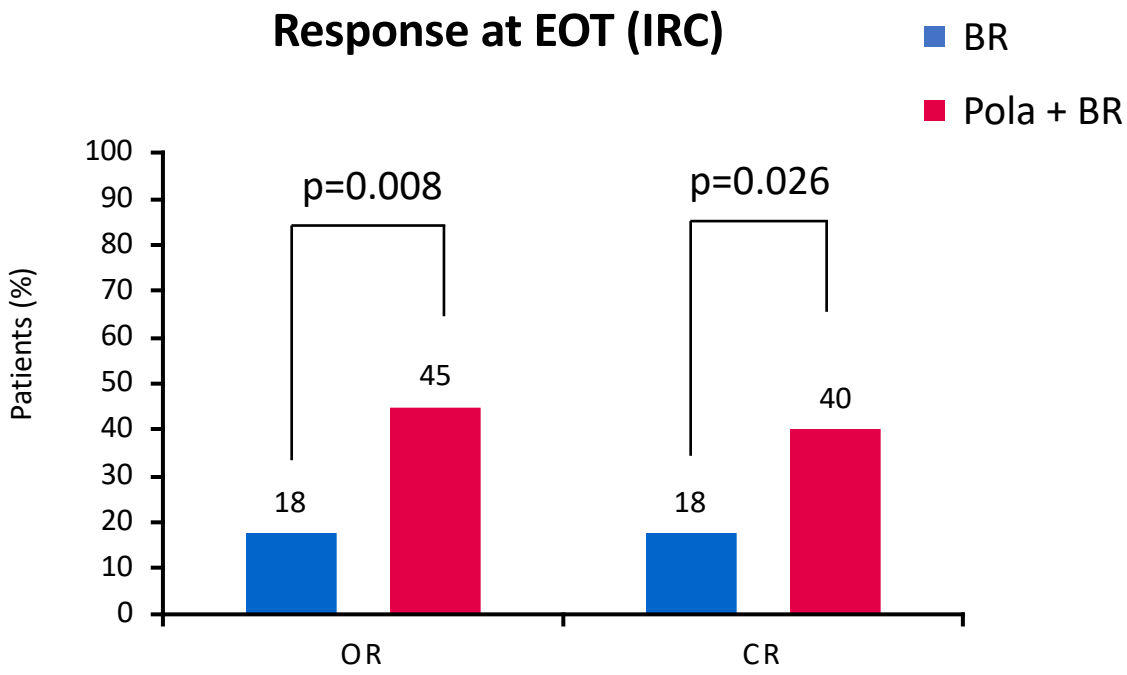
- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker

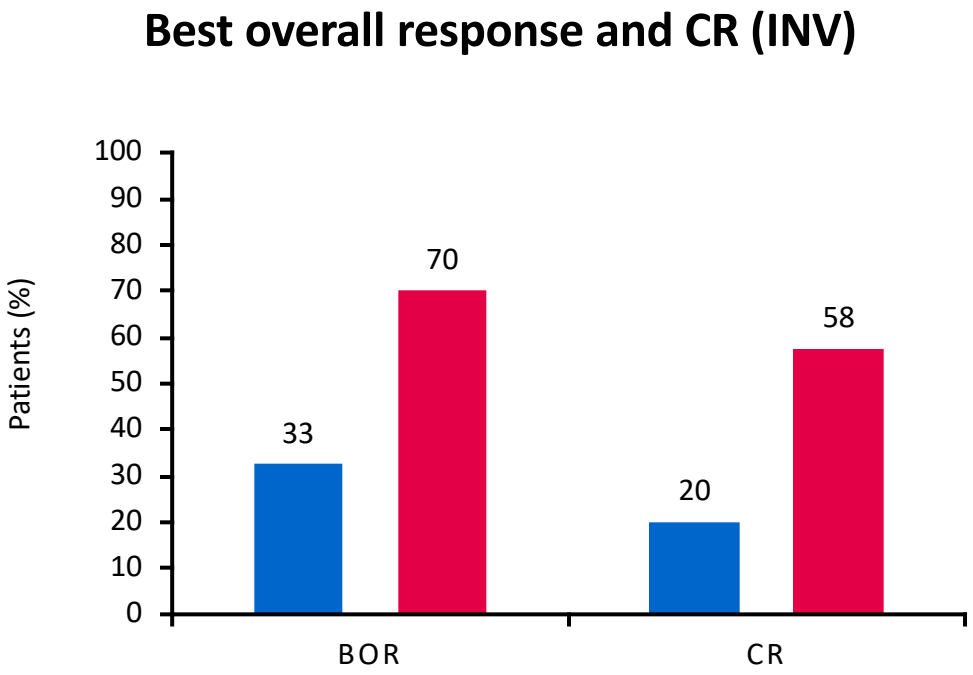


GO29365 Study: Polatuzumab + Bendamustine-Rituximab or Bendamustine-Obinutuzumab



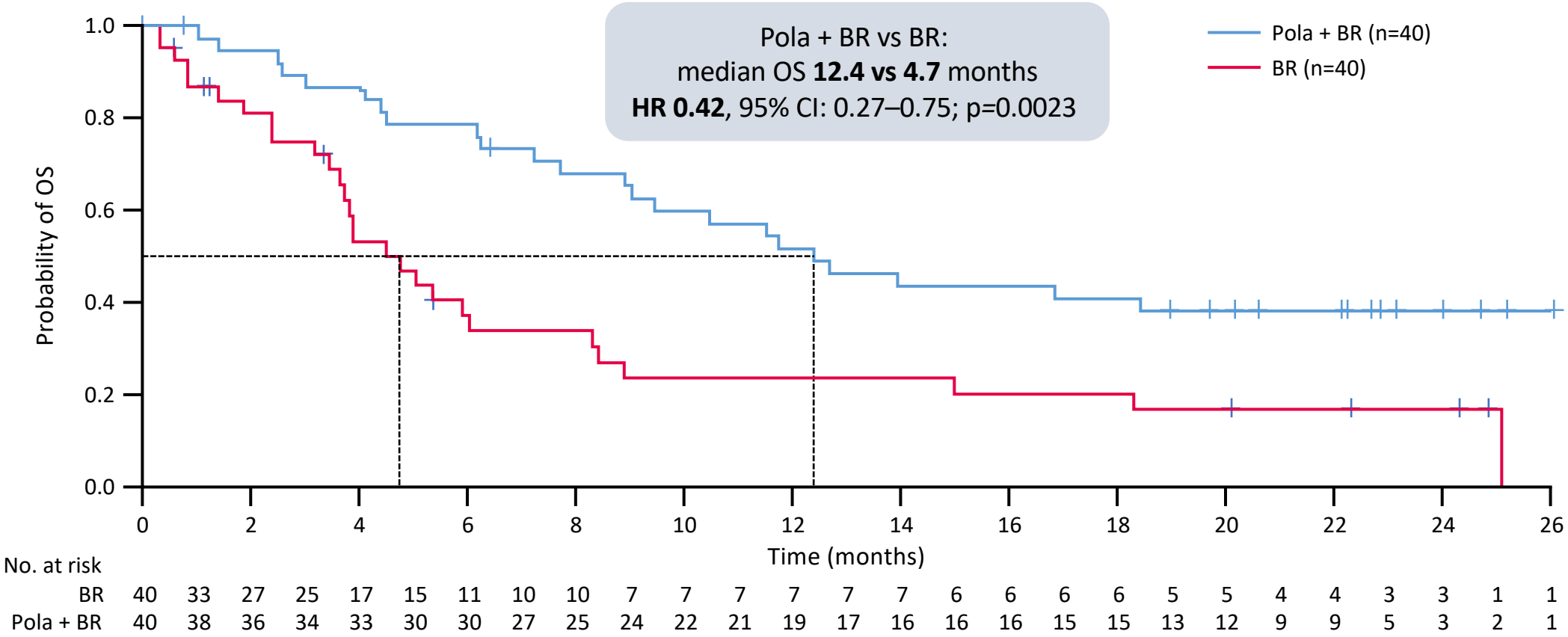
Primary Endpoint: PET CR Rate at End of Treatment





Sehn et al, JCO 2019

Overall Survival Significantly Longer with Pola-BR versus BR

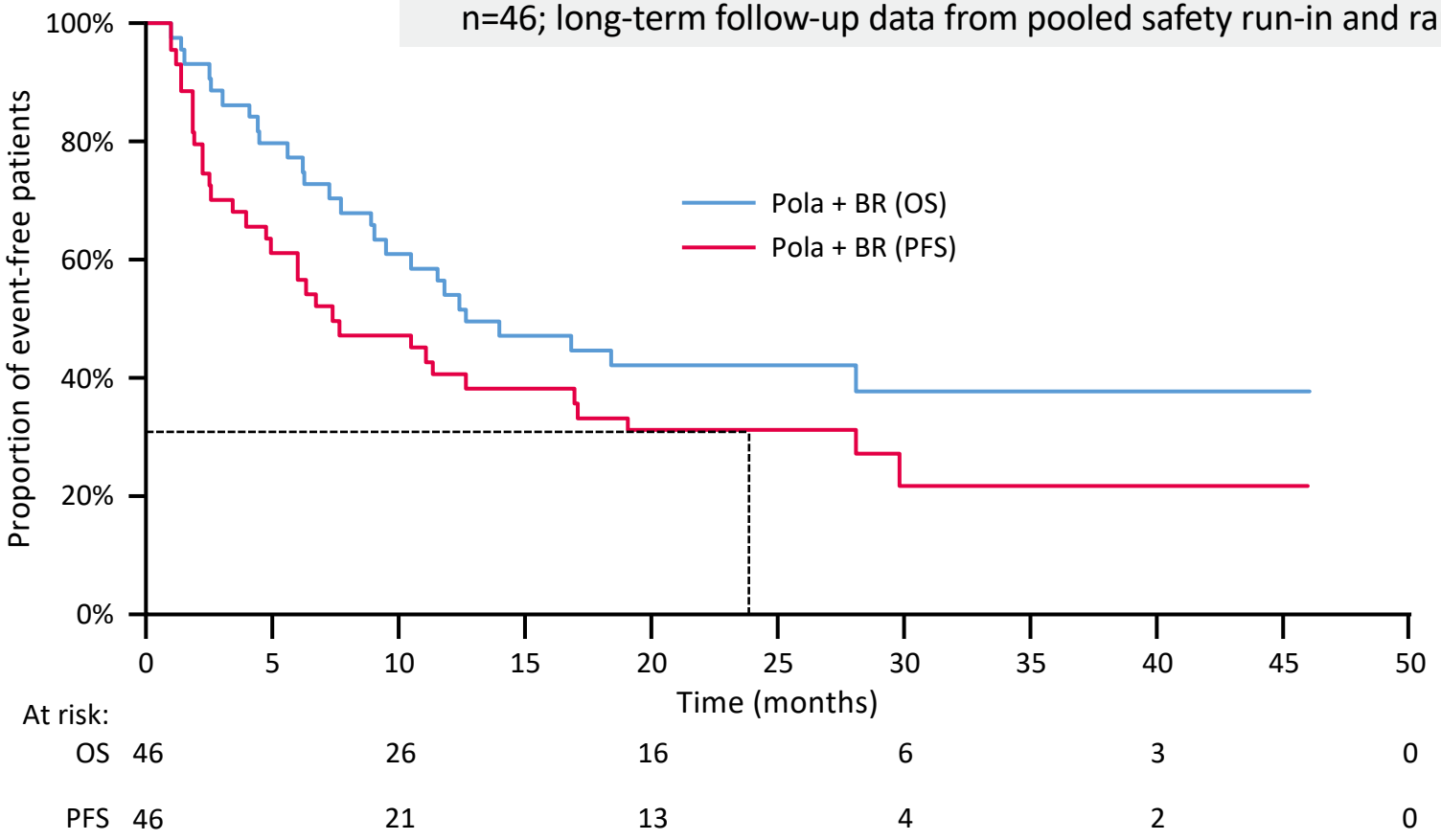


Median follow-up: 22.3 months

Sehn et al, JCO 2019

Combined Phase I and II Experience with Pola-BR

n=46; long-term follow-up data from pooled safety run-in and randomized patients



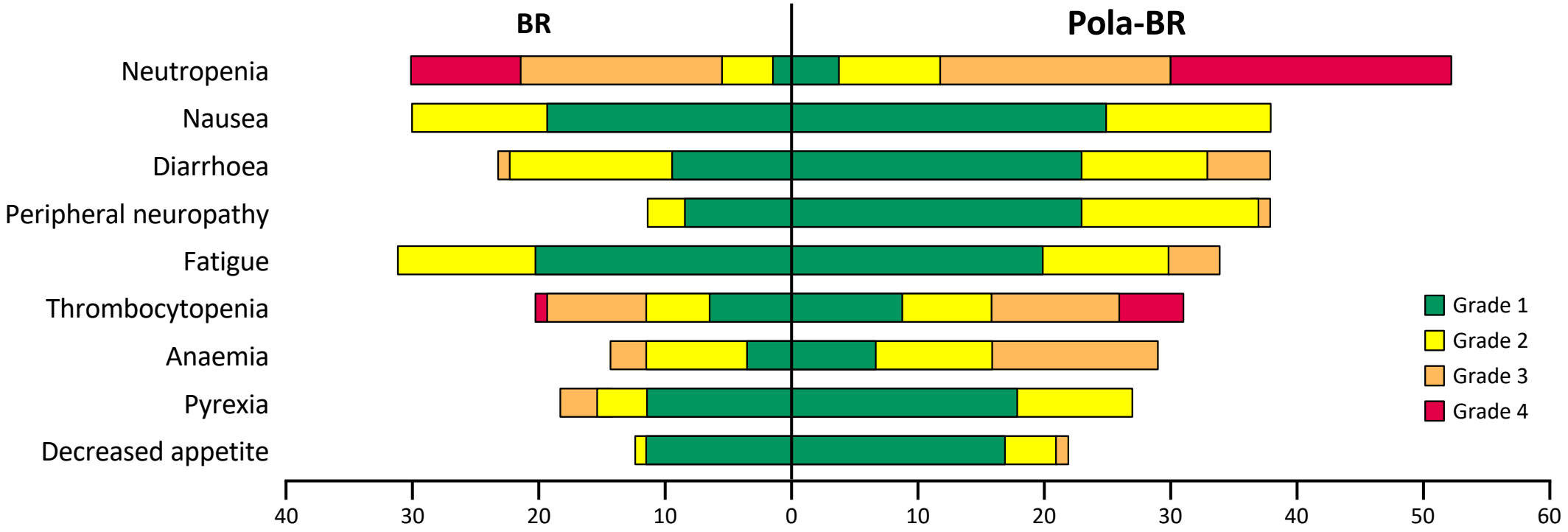
2-year PFS of 31.4%

22% of pola + BR patients remain in complete remission at last follow-up (ongoing DoR of >20 months)

Maximum follow-up: 45.9 months; median follow-up: 27.6 months

Sehn et al, ICML 2019

GO29365: All-grade AEs in ≥20% Patients

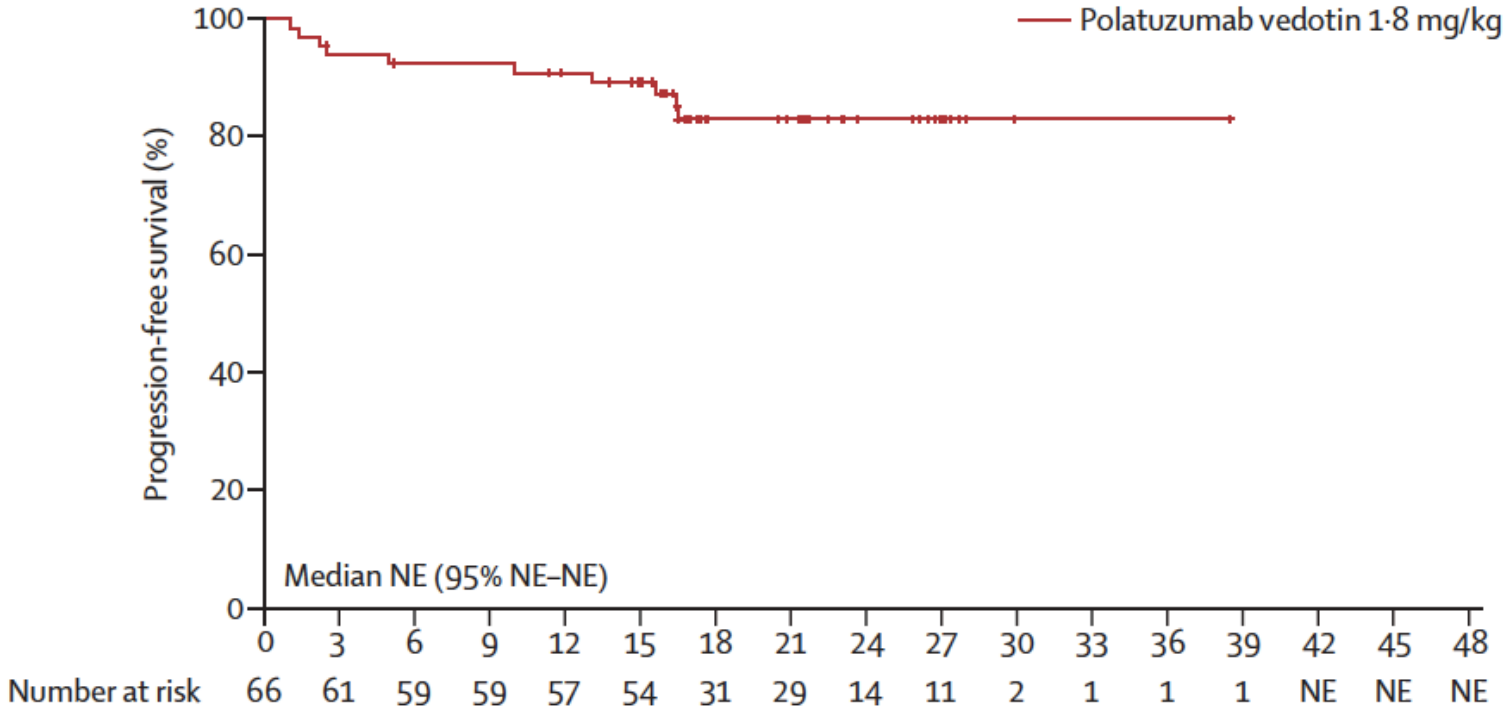


Median number of completed cycles: 3 (range, 1–6) with BR; 5 (range, 1–6) with pola + BR

Sehn et al, JCO 2019

Phase Ib/II Trial of Polatuzumab Vedotin + R-CHP or G-CHP in Patients with Untreated DLBCL

DLBCL Patients treated with Pola 1.8 mg/kg + R-CHP/G-CHP



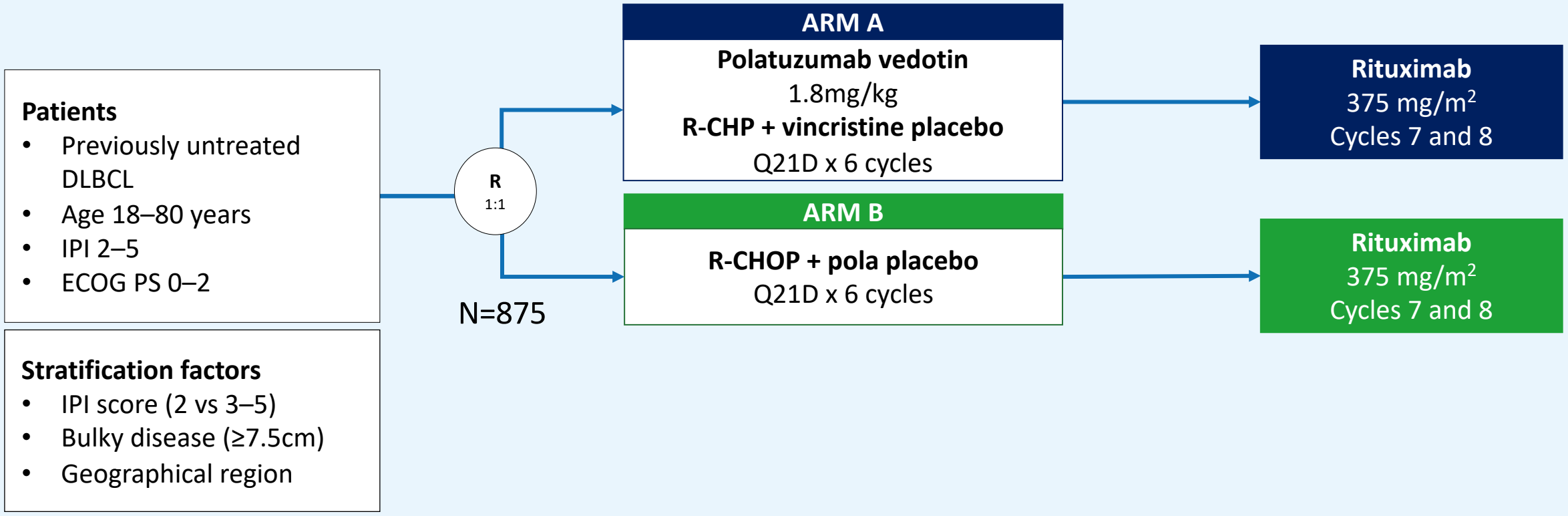
Pola-R-CHP in DLBCL	N=45 n (%)
Overall Response	40 (89)
CR	34 (76)
PR	6 (13)
Progressive Disease	3 (7)
Missing	2 (4)

Median follow-up: 21.5 m

Tilly et al, Lancet Oncology 2019

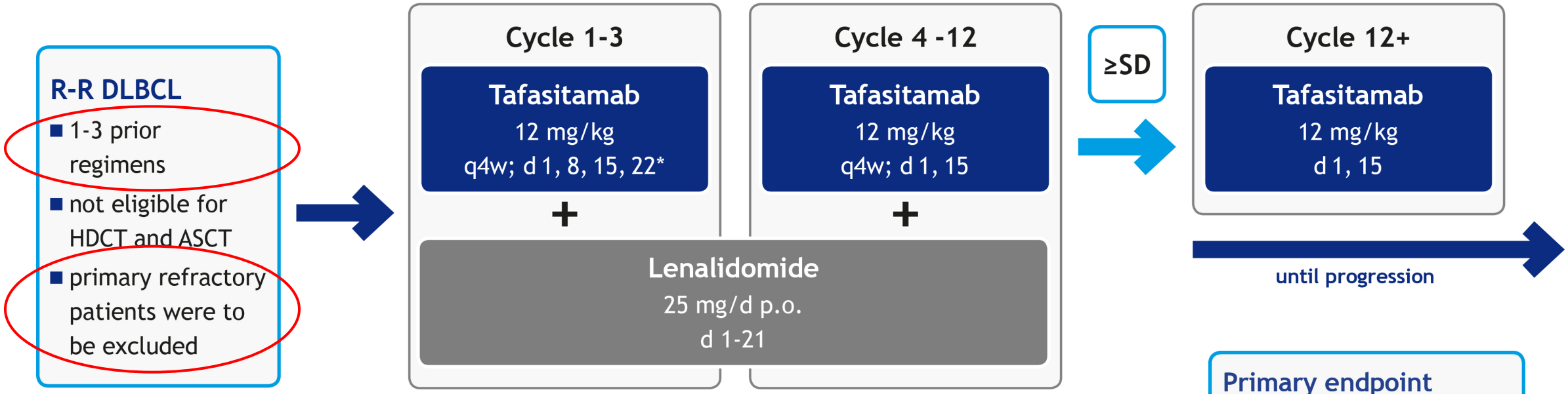
POLARIX: Phase III Trial of Pola-R-CHP versus R-CHOP In Previously Untreated DLBCL

A double-blind, phase 3, placebo-controlled trial



MOR208 (Tafasitamab) and Lenalidomide: L-MIND Study

Phase 2, single-arm, open-label, multicenter study (NCT02399085)



* a loading dose of MOR208 was administered on day 4 of cycle 1

- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

Primary endpoint
- ORR (Central read)

Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

-Primary refractory DLBCL was defined as no response to or progression/relapse during or within 6 months of frontline therapy.
-Response assessment (Cheson 2007 Criteria) was after cycles 2, 4, 6, 9 and 12, thereafter every 3 cycles.
-ASCT, autologous stem cell transplant; HDCT, high-dose chemotherapy; SD, stable disease, p.o., per os.

Salles G et al, ICML 2019

L-MIND: Efficacy (n=80)

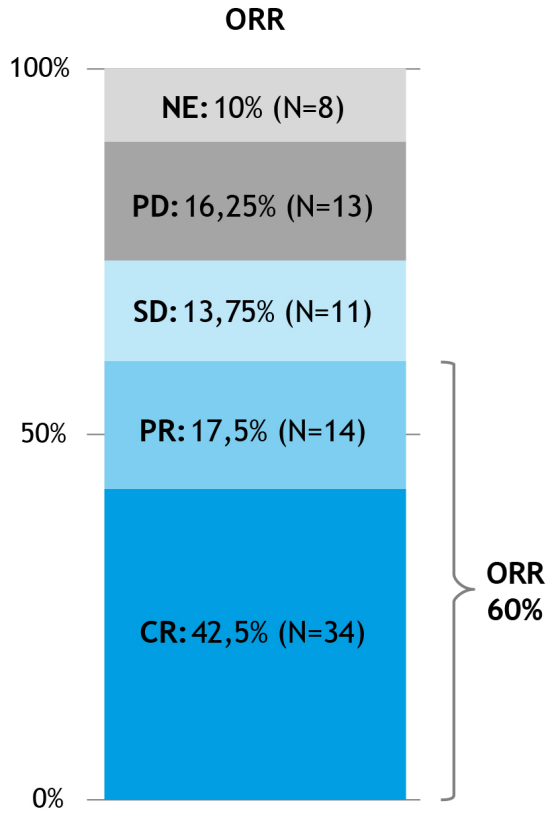
ORR 60%, CR rate 42.5% by IRC

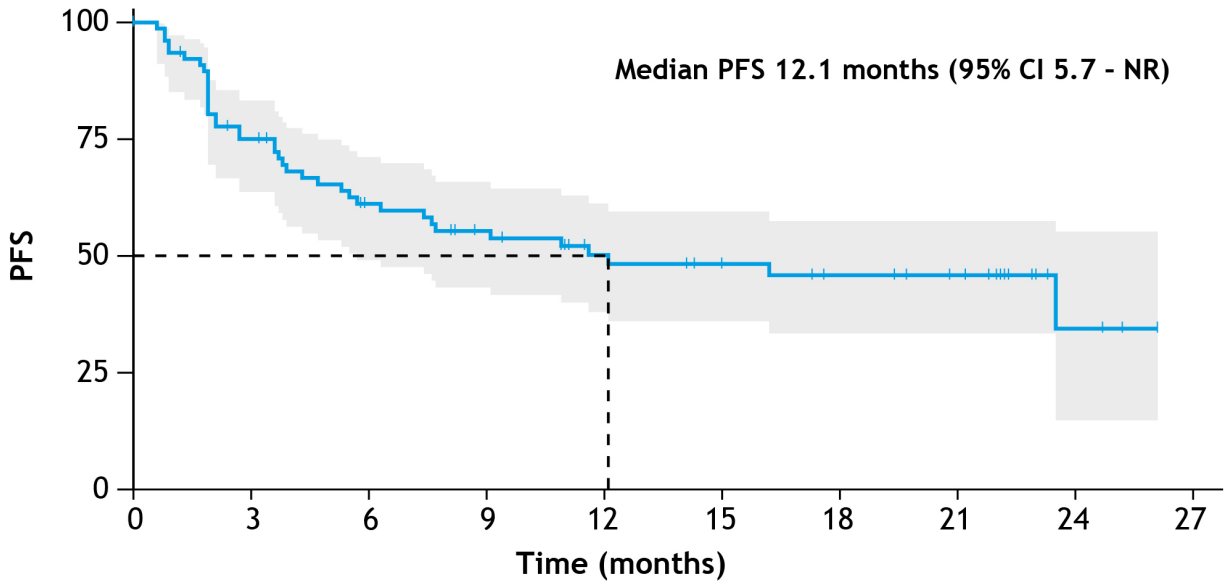
82% CRs were PET/CT-confirmed

➔ Median follow-up 17.3 months

➔ Median PFS: 12.1 mos (95% CI: 5.7 mos - NR)

➔ 28 patients still ongoing with study treatment





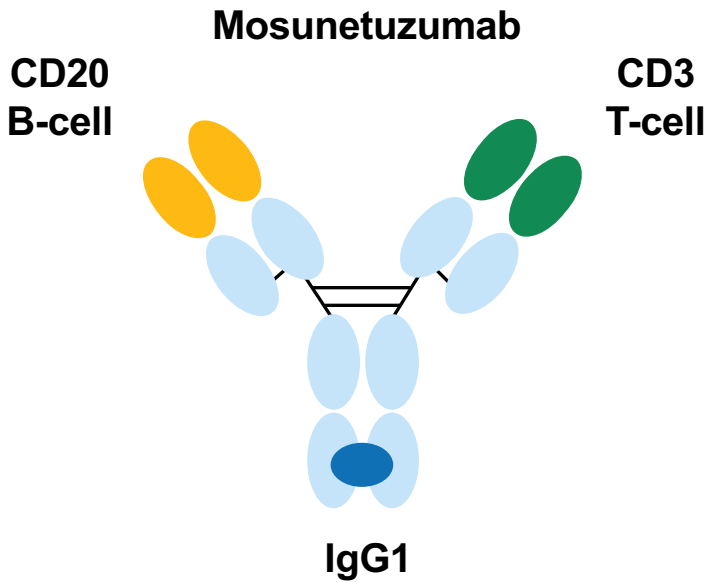
Number of patients at risk

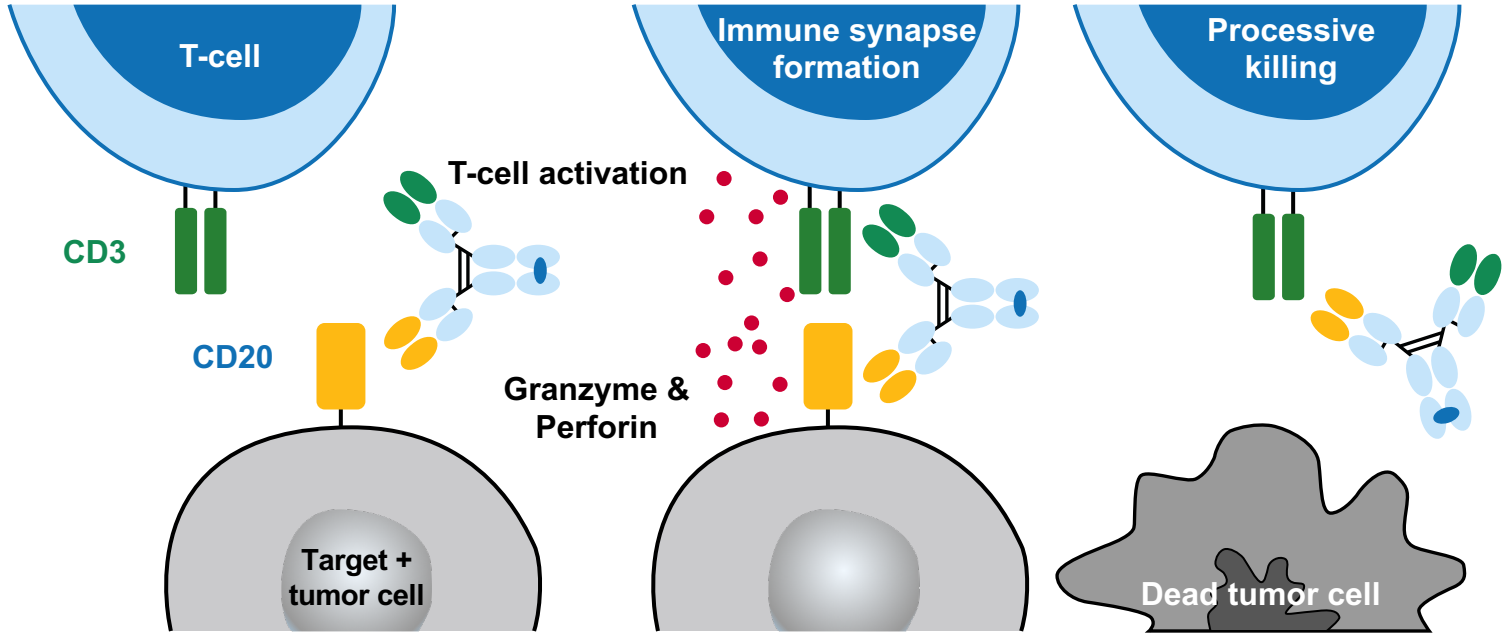
Overall	80	56	42	35	26	22	17	13	3	0

Salles G et al, ICML 2019

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drugs
  - PK properties enable once weekly to q3w dosing
- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells





ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

Phase I/Ib Study Design and Baseline Characteristics

Patients aged ≥18 years with previously treated R/R B-cell NHL,
ECOG PS 0–1

→

Group A (fixed dosing)
Mosunetuzumab 0.05mg to 2.8mg IV on D1 of every 21-day cycle

Group B (step-up dosing)
Mosunetuzumab 0.4/1.0/2.8mg to 1.0/2.0/60.0mg IV on D1/D8/D15 of C1 and a fixed dose on D1 of C2–8

→

Initially 8 cycles; up to 17 cycles in patients with PR or SD. Patients who relapse after CR can be retreated

GO29781 (NCT02500407) is an ongoing open-label, multicenter, phase I/Ib study

Objective: *safety and efficacy*

Outcome measures: *MTD, tolerability, pharmacokinetics, and best objective response (Cheson 2007 criteria)*

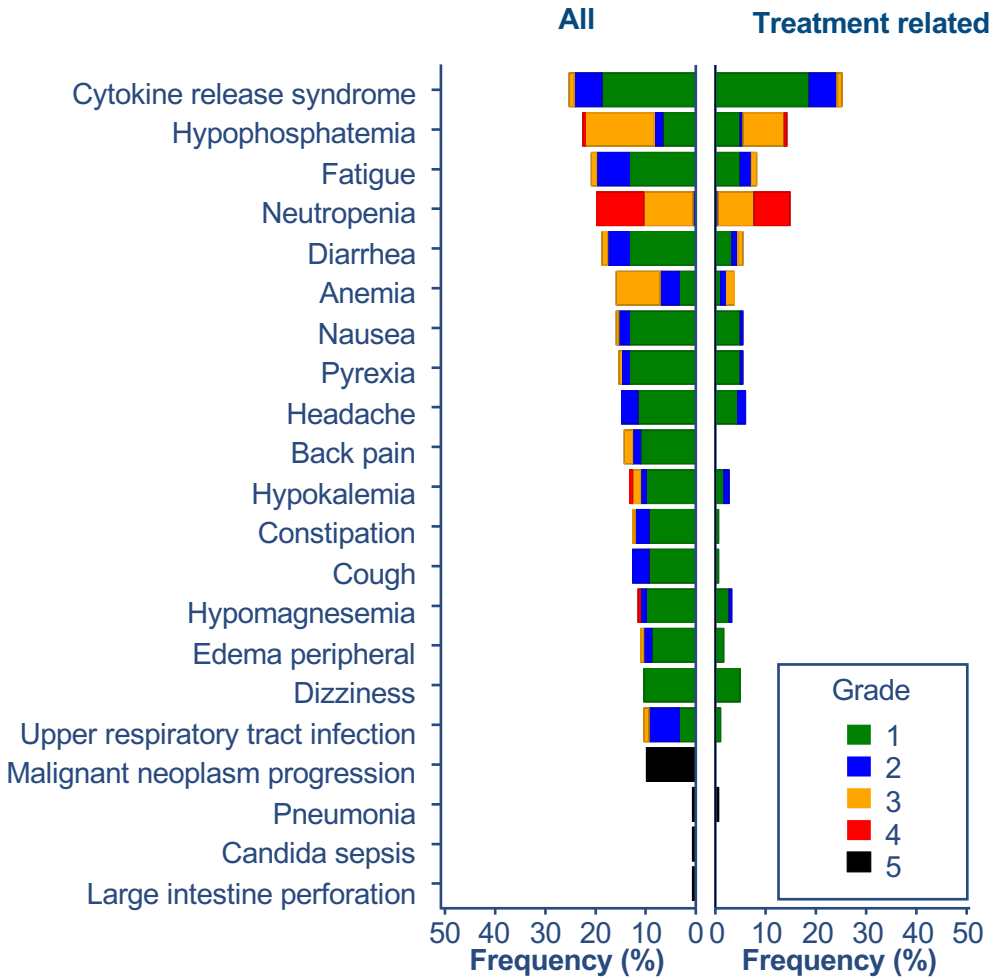
Baseline demographics	Group A (n=33)	Group B (n=182)
Median age, years (range)	64 (30–84)	62 (19–91)
DLBCL / trFL, n (%)	**14 (42.4) / 5 (15.2)**	**68 (37.4) / 25 (13.7)**
MCL, n (%)	**2 (6.1)**	**13 (7.1)**
FL, n (%)	**9 (27.3)**	**64 (35.1)**
Other, n (%)	3 (9.1)	12 (7.0)
Median prior systemic therapies, n (range)	**3 (1–9)**	**3 (1–14)**
Prior stem cell transplant, n (%)	9 (27.3)	50 (27.5)
Prior CAR-T, n (%)	0	17 (9.3)
Refractory to last prior therapy,* n (%)	21 (63.6)	120 (65.9)
Refractory to any prior anti-CD20,* n (%)	20 (60.6)	125 (68.7)

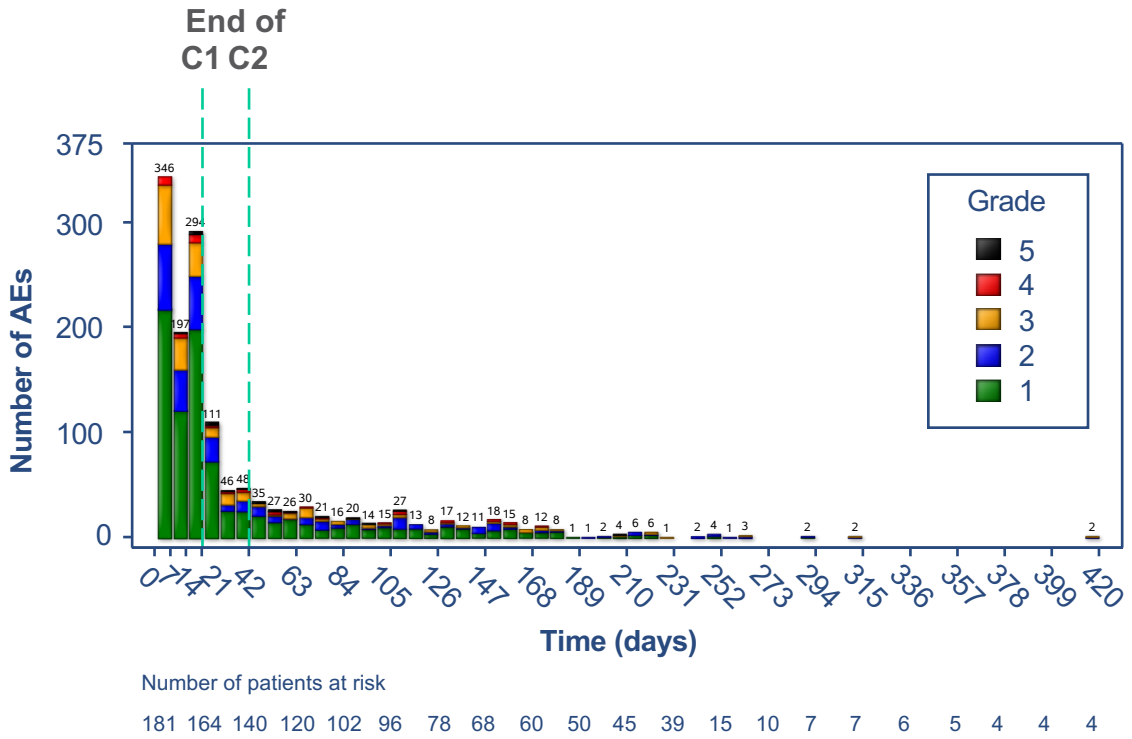
Heavily pre-treated R/R NHL population
MTD not reached, step-up dosing mitigated CRS

Bartlett, et al. ASCO 2019

Safety: Most AEs were Grade 1/2 and Occurred During Cycle 1

AE frequency (≥10% incidence and Grade 5) and time to onset of AEs in Group B (n=182)



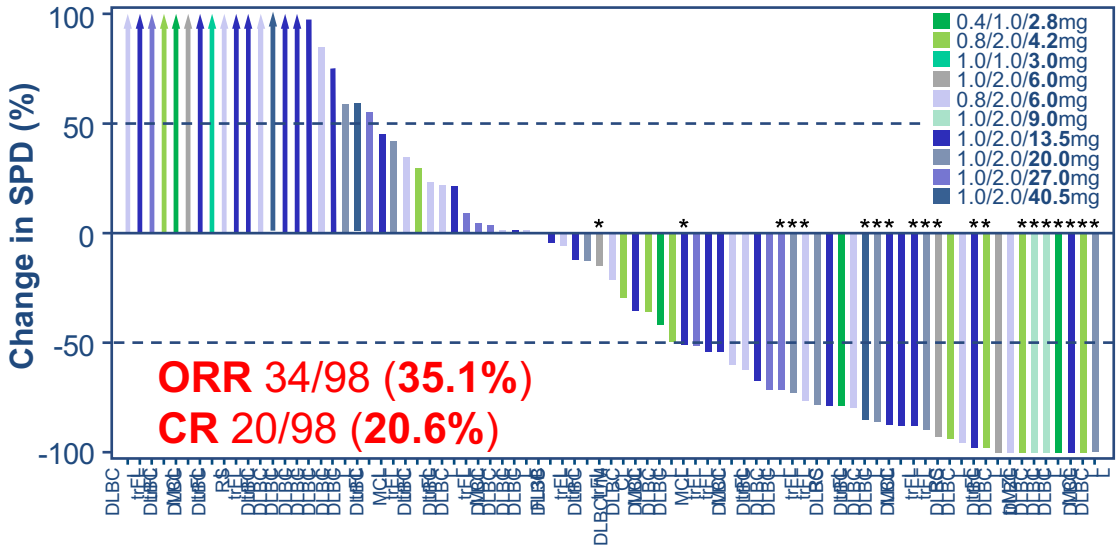


Bartlett, et al. ASCO 2019

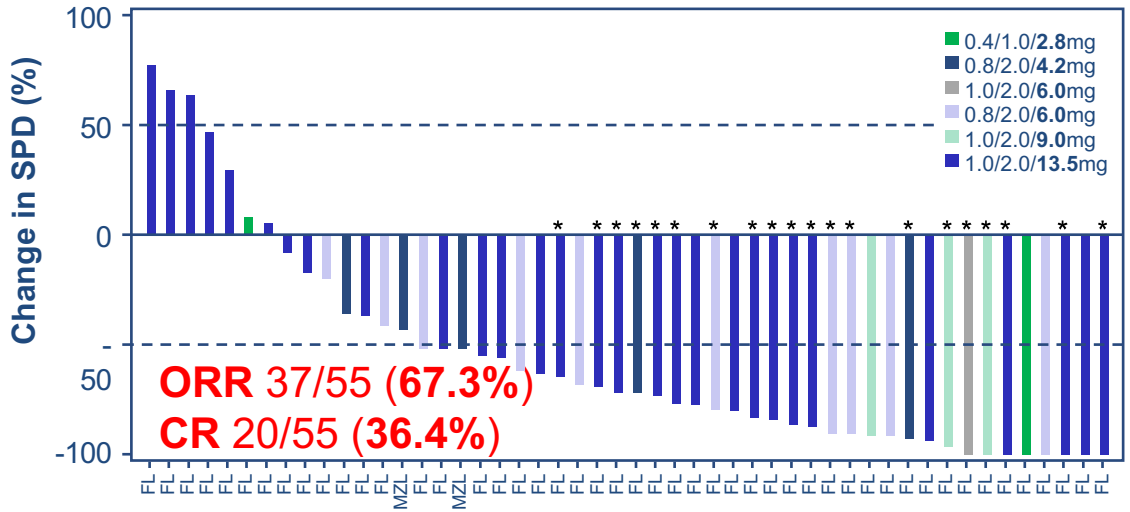
Efficacy: Responses Observed Across Multiple Dose Levels and NHL Subtypes

Change in tumor burden by NHL type and dose cohort in Group B

R/R aggressive NHL



R/R indolent NHL

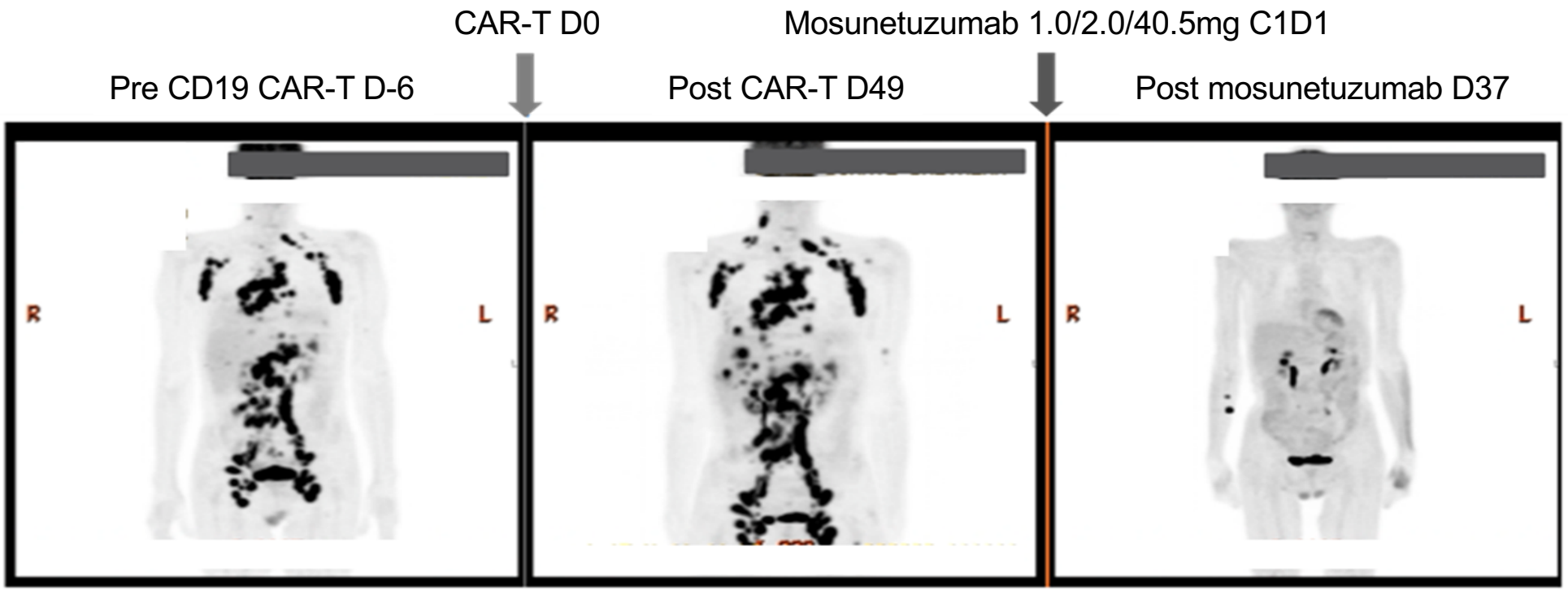


Most patients in CR remain in remission;
15/20 pts with aggressive NHL and 19/20 pts with iNHL,
median follow-up 4 months (range: 0–19) and 6 months (range: 0–24)

Bartlett, et al. ASCO 2019

Complete Responses Observed After Prior CAR-T Therapy

PET complete response in a heavily pretreated elderly patient with DLBCL after prior anti-CD19 CAR-T therapy



A 69-year-old, fifth-line DLBCL patient, who was refractory to prior anti-CD19 CAR-T therapy, achieved a complete response after receiving mosunetuzumab

Schuster, et al. ASH 2019, Abstract #6, Plenary Presentation