Disclosures

Prof. Wojciech Jurczak, M.D., Ph.D.

Advisory Boards :

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DLBCL na ASH 2018

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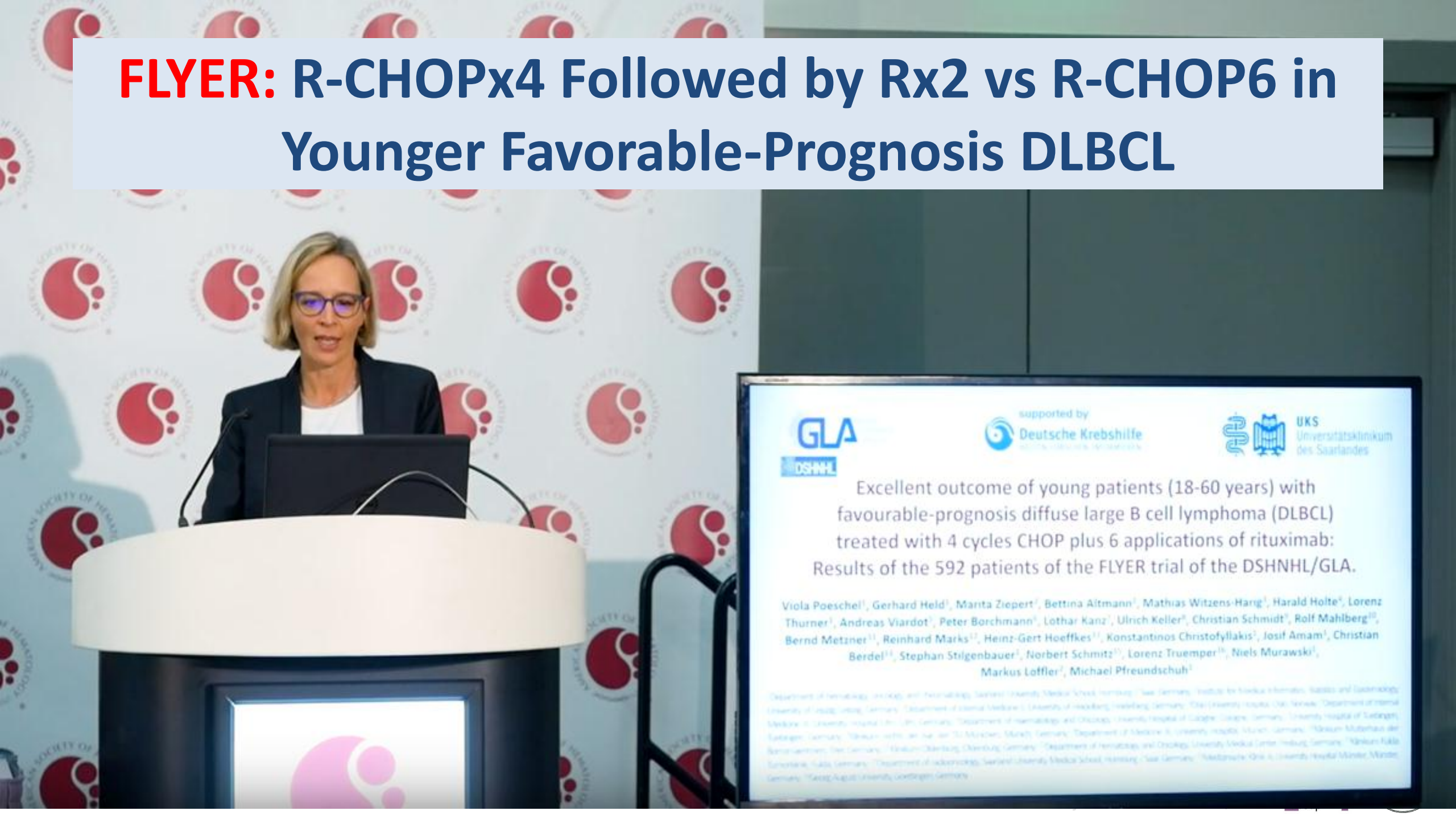
Polish Lymphoma Research Group

FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL



FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL – study design

untreated aggressive B-cell lymphoma, 18-60 yrs, **stage I/II disease, IPI = 0, no bulky disease (< 7.5 cm)** (N = 588)

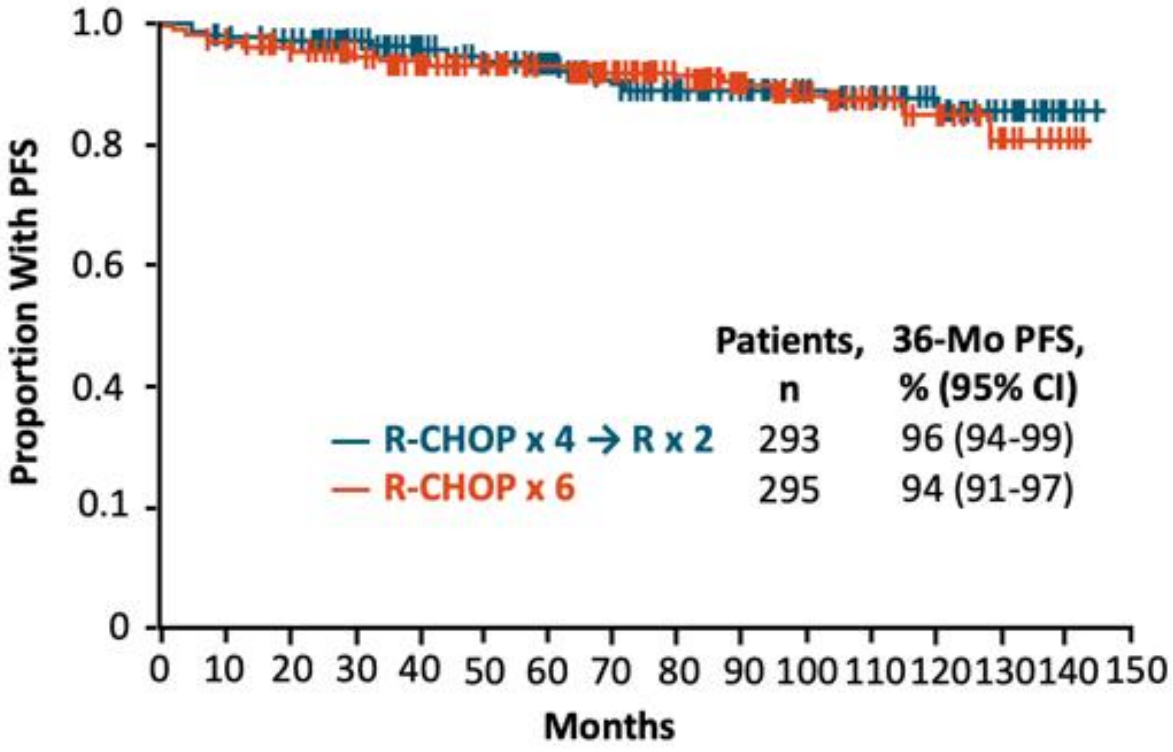
R-CHOP x 4 cycles followed by **Rituximab** x 2 cycles (n = 293)

R-CHOP x 6 cycles (n = 295)

- Primary endpoint: PFS, 3-yr PFS rate (non-inferiority study)
  - Assumed 3-yr PFS rate of 93% with R-CHOP x 6
  - Difference up to -5.5% allowed with R-CHOP x 4 → R x 2 while still proving noninferiority with 80% power and 1-sided $\alpha = 0.05$ (planned sample size: N = 592, assuming 10% loss yields final N = 532)
- Other endpoints: response, EFS, OS, safety

1. Pfreundschuh. Lancet Oncol. 2006;7:379. 2. Poeschel. ASH 2018. Abstr 781.

FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL - PFS (primary endpoint)



After median f/u of 66 mos, PFS noninferior with R-CHOP x 4 → R x 2 vs R-CHOP x 6

Poeschel. ASH 2018. Abstr 781.

FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL – Safety

- In younger patients with aggressive B-cell lymphoma and favorable prognosis, first-line treatment with **R-CHOP x 4 → R x 2 showed noninferior PFS, EFS, and OS** vs standard R-CHOP x 6
  - 36-mo PFS rate: 96% with R-CHOP x 4 → R x 2 vs 94% with R-CHOP x 6
- **Nonhematologic AEs were decreased by approximately one third** with R-CHOP x 4 → R x 2 vs R-CHOP x 6
  - Number of any-grade nonhematologic AEs (grade 3-4): R-CHOP x 4 → R x 2, n = 835 (46); R-CHOP x 6, n = 1295 (70)
- Both arms exhibited **comparable relapse patterns and rates**
  - Relapse rate was 4% with R-CHOP x 4 → R x 2 vs 5% with R-CHOP x 6

Poeschel. ASH 2018. Abstr 781.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - background

Anas Younes, Laurie H. Sehn, Peter Johnson, Pier Luigi Zinzani, Xiaonan Hong, Jun Zhu, Caterina Patti, David Belada, Olga Samoilova, Cheolwon Suh, Sirpa Leppä, Shinya Rai, Mehmet Turgut, Wojciech Jurczak, Matthew Cheung, Ronit Gurion, Su-Peng Yeh, Andres Lopez-Hernandez, Ulrich Dührsen, Catherine Thieblemont, Carlos Sergio Chiattone, Sriram Balasubramanian, Jodi Carey, Grace Liu, S. Martin Shreeve, Steven Sun, Sen Hong Zhuang, Jessica Vermeulen, Louis M Staudt,* and Wyndham Wilson,* for the PHOENIX investigators

Polish Lymphoma Research Group

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - study design

- International, randomized, double-blind phase III trial[1]

Stratified by R-IPI, region (US/Western Europe vs rest of world), no. prespecified R-CHOP cycles (6 vs 8)

6 or 8 x 21-d cycles

Patients with untreated non-GCB DLBCL determined centrally by Hans-based IHC; stage II-IV measurable disease; R-IPI ≥ 1; ECOG PS 0-2
(N = 838)

→ **Ibrutinib** 560 mg PO QD + **R-CHOP***
(n = 419)

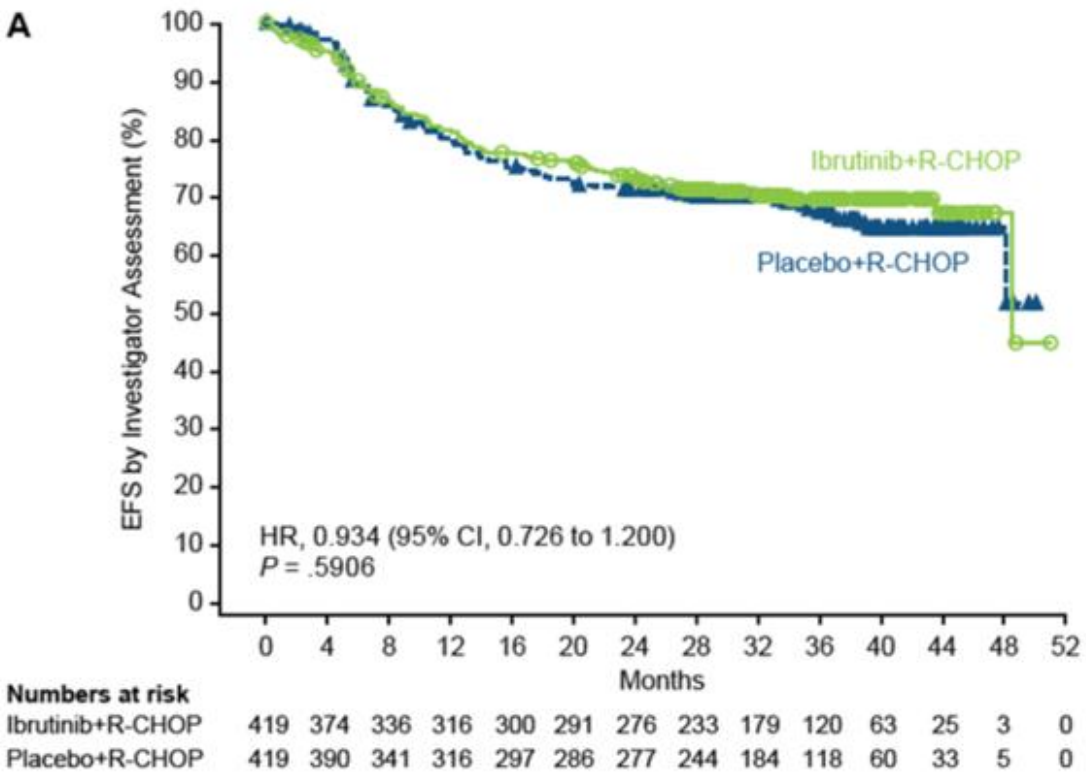
→ **Placebo** + **R-CHOP***
(n = 419)

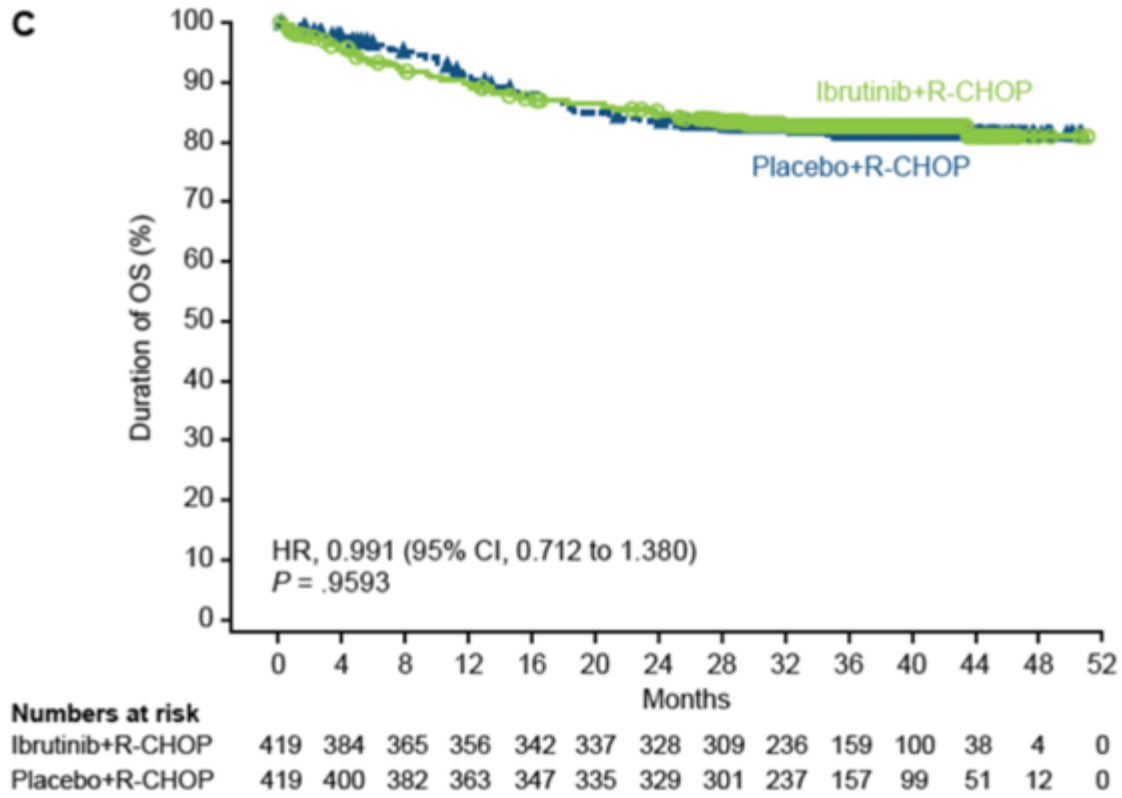
*Rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1, prednisone or equivalent 100 mg PO QD on Days 1-5. G-CSF and antibiotics permitted.[1,2]

- Primary endpoint: EFS in ITT population and ABC subgroup (determined retrospectively by gene expression profiling)
  - EFS events defined as PD, relapse from CR, starting subsequent disease-specific tx for PET-positive/biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death
- Secondary endpoints: CR rate, OS, PFS, safety
  - Response evaluated with Revised Response Criteria for Malignant Lymphoma[3]
- Exploratory stepwise analyses of potential interactions between treatment and prespecified BL characteristics for EFS and, if significant, PFS and OS

1. Younes. ASH 2018. Abstr 784. 2. NCT01855750. 3. Cheson. J Clin Oncol. 2007;25:579.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - EFS (Primary Endpoint)



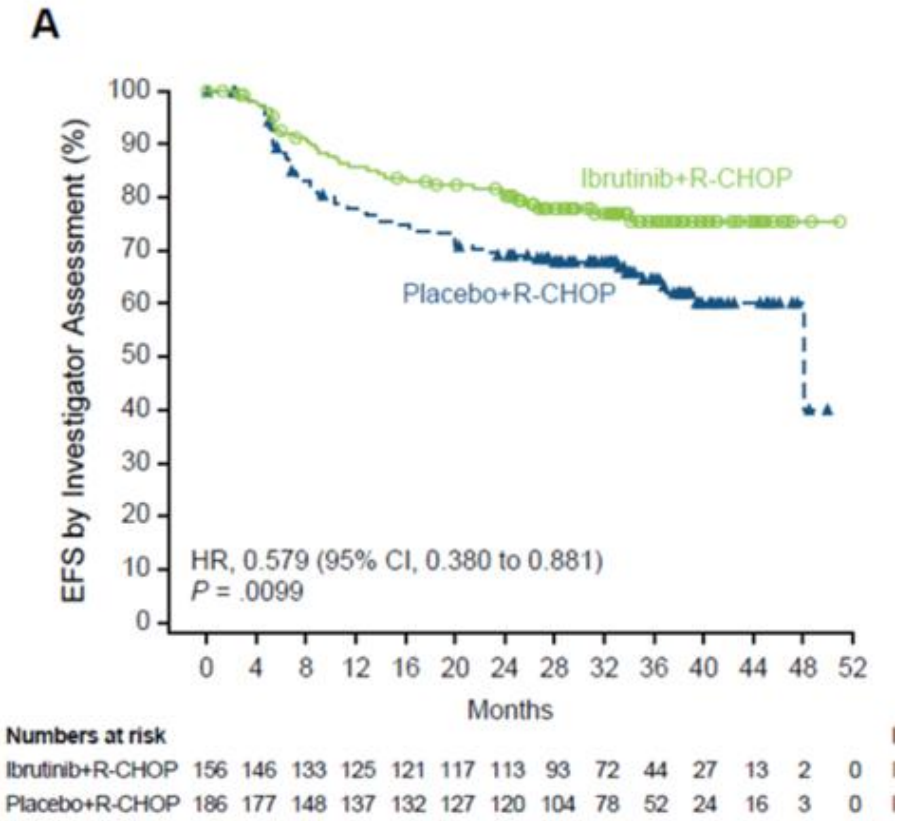


- **Addition of ibrutinib to R-CHOP did not significantly improve EFS in the ITT population or in those with ABC subtype**

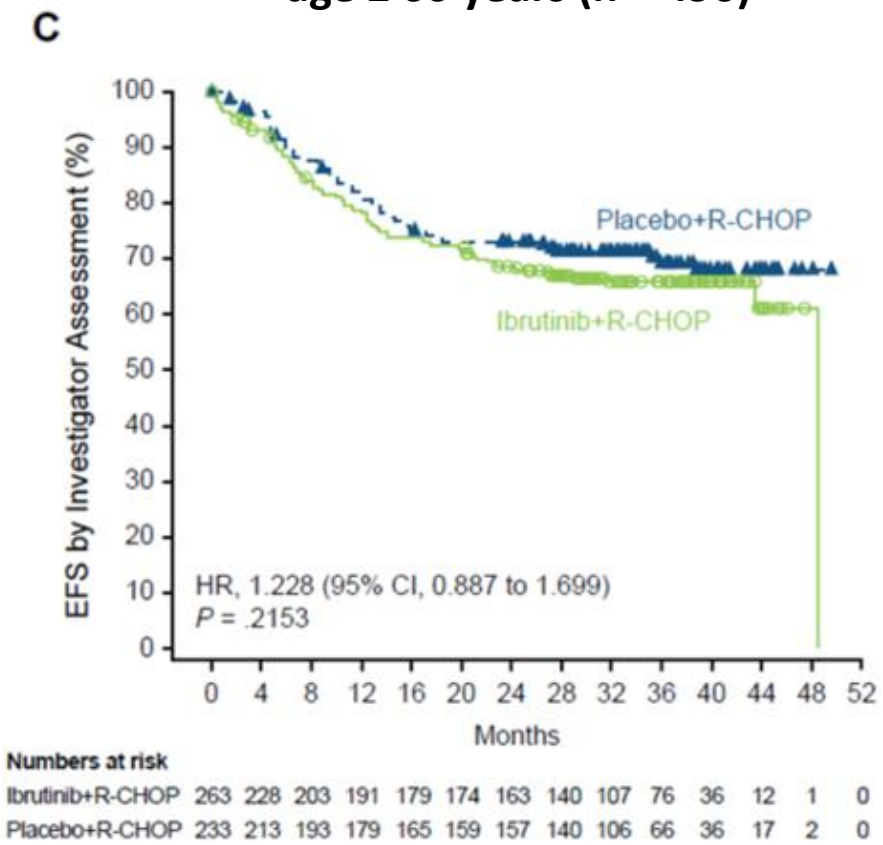
Younes. ASH 2018. Abstr 784.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - EFS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)



Younes. ASH 2018. Abstr 784.

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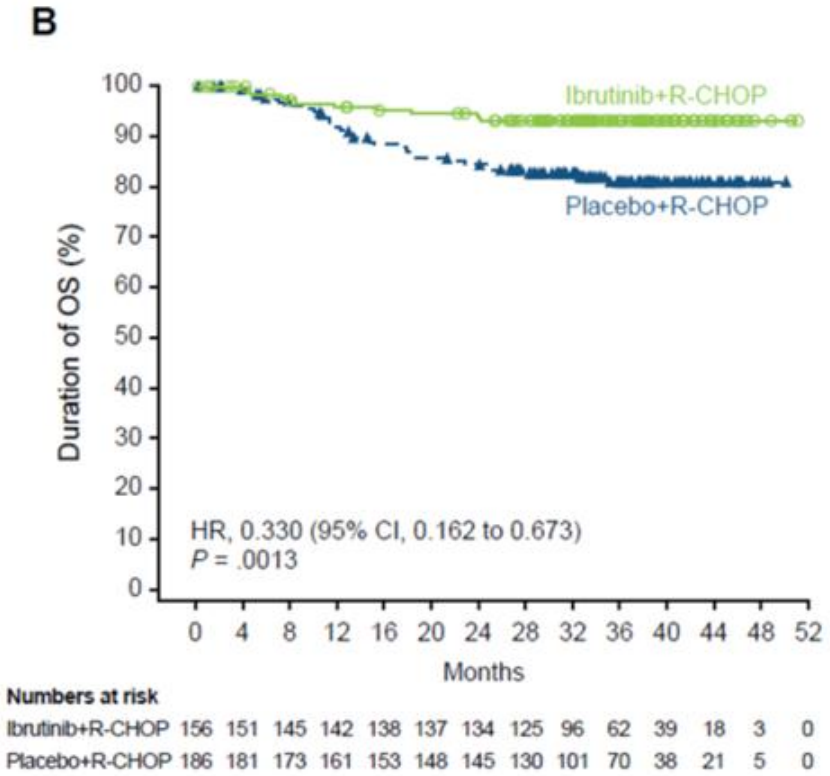
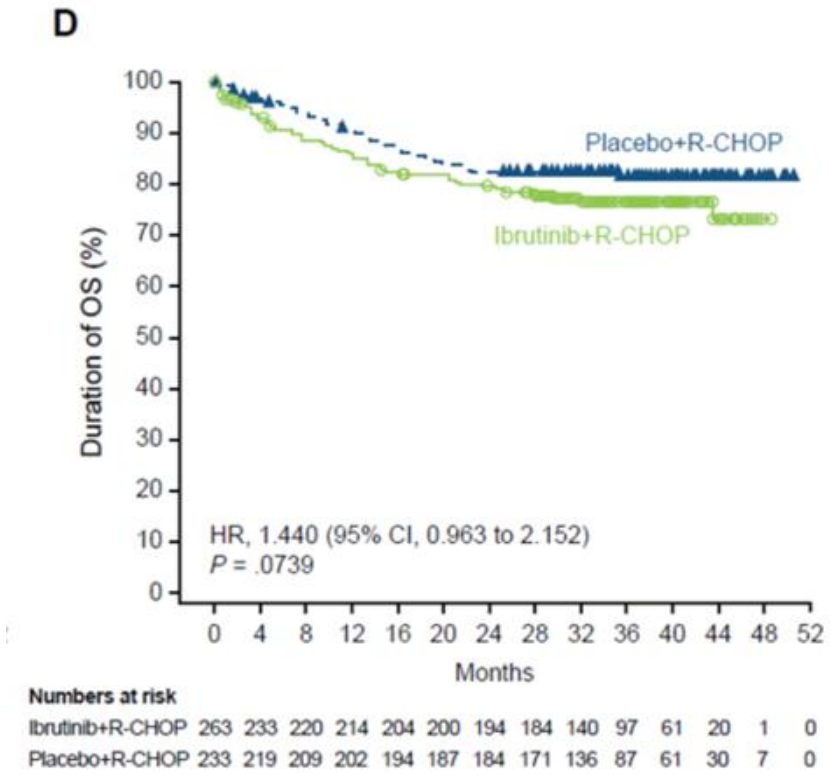
PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - OS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)



Younes. ASH 2018. Abstr 784.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - AEs and Treatment Exposure by Age

- Among patients aged < 60 yrs and ≥ 60 yrs, AEs were similar between treatment arms
- **Higher rates of both serious AEs and AEs leading to treatment discontinuation were observed in older patients receiving ibrutinib + R-CHOP vs placebo + R-CHOP**
  - Primary TEAEs leading to dose reduction/discontinuation were febrile neutropenia and peripheral neuropathy
- In the safety population, **drug exposure was lower** with ibrutinib + R-CHOP vs placebo + R-CHOP, **particularly among older patients**

Patients Receiving ≥ 6 Cycles of Treatment, n (%)	Age < 60 Yrs		Age ≥ 60 Yrs	
	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
R-CHOP exposure	143 (92.9)	172 (93.0)	193 (**73.7**)	207 (**88.8**)
Ibrutinib or placebo exposure	138 (89.6)	170 (91.9)	178 (**67.9**)	202 (**86.7**)

Younes. ASH 2018. Abstr 784.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - Conclusions

- In patients with non-GCB DLBCL, **first-line ibrutinib + R-CHOP did not prolong EFS** in the ITT population or in those with ABC DLBCL vs placebo + R-CHOP
  - HR for EFS: in ITT population, 0.93 (95% CI: 0.73-1.20); in ABC DLBCL, 0.94 (95% CI: 0.70-1.26)
- Ibrutinib + R-CHOP **benefit and safety profiles varied by age**
  - Among those aged < 60 yrs, ibrutinib + R-CHOP improved EFS, PFS, and OS vs placebo + R-CHOP
    - HR: for EFS, 0.579 (95% CI: 0.380-0.881); for OS, 0.330 (95% CI: 0.162-0.673)
  - Among those aged ≥ 60 yrs, ibrutinib + R-CHOP showed higher rates of serious AEs and AEs leading to discontinuation of R-CHOP, along with decreased drug exposure
    - Investigators suggested that higher rate of AE-related discontinuation and decreased drug exposure probably decreased treatment efficacy in this older population
- Investigators concluded that **risk outweighs benefit of adding ibrutinib to R-CHOP in older** patients; **observed benefit in younger patients requires confirmation in prospective trial**

Younes. ASH 2018. Abstr 784.

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2)

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): Study Design

- Multicenter, randomized, double-blind, active-controlled phase III trial (data cutoff: August 15, 2018)

Stratification for IPI score (0-1 vs 2-3 vs 4-5), histologic subtype (ALK+ sALCL vs other subtypes)

Adult patients with **previously untreated CD30+ (≥ 10% expression) PTCL*** (N = 452)

Brentuximab Vedotin† + **CHP**‡ Q3W for 6-8 cycles + **Placebo for Vincristine** (n = 226)

CHOP‡ Q3W for 6-8 cycles + **Placebo for Brentuximab Vedotin** (n = 226)

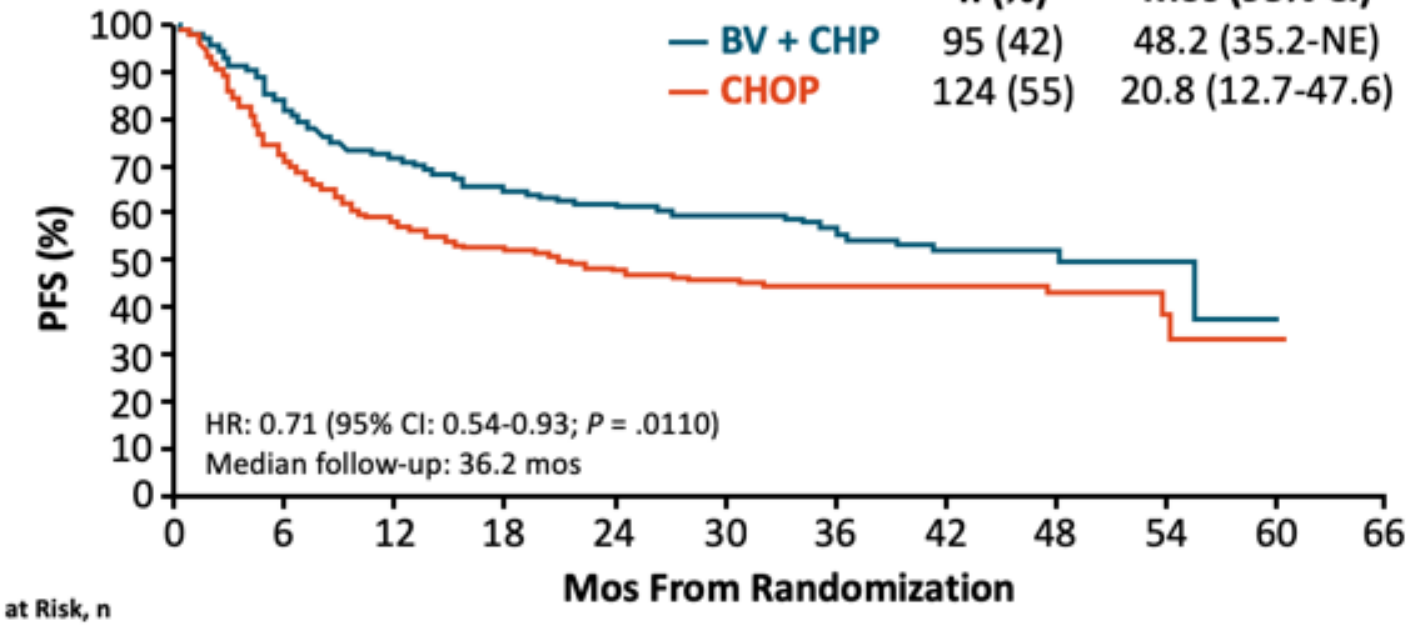
End-of-treatment PET

*PTCL includes sALCL (including ALK+ sALCL with IPI ≥ 2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin: 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): PFS (Primary Endpoint)

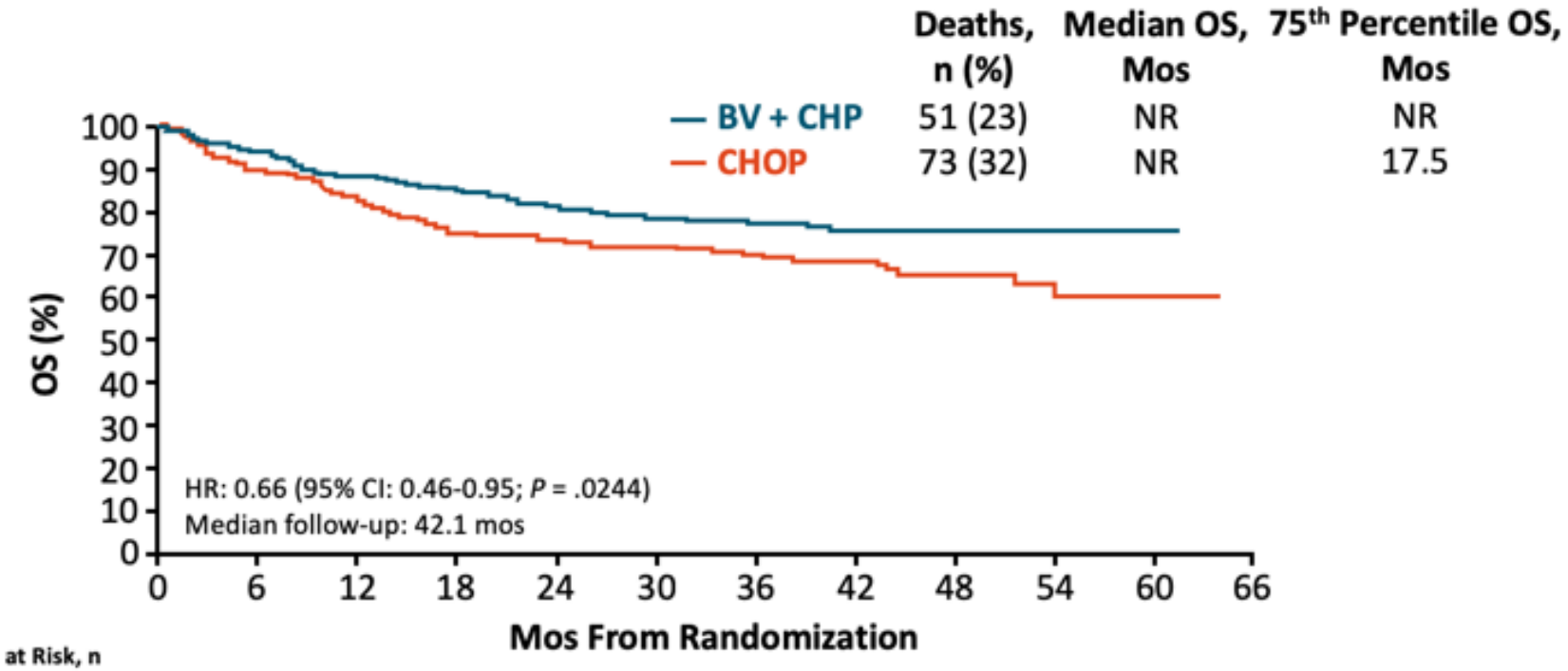


	Events, n (%)	Median PFS, Mos (95% CI)	3-Yr PFS, %
BV + CHP	95 (42)	48.2 (35.2-NE)	57.1
CHOP	124 (55)	20.8 (12.7-47.6)	44.4

Patients at Risk, n (Number Censored)												
BV + CHP	226 (0)	175 (39)	149 (61)	134 (75)	108 (82)	81 (85)	64 (88)	38 (93)	24 (93)	9 (94)	3 (95)	0 (95)
CHOP	226 (0)	157 (65)	129 (93)	112 (107)	87 (116)	75 (119)	63 (121)	44 (121)	26 (122)	7 (123)	2 (124)	0 (124)

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): OS (Secondary Endpoint)

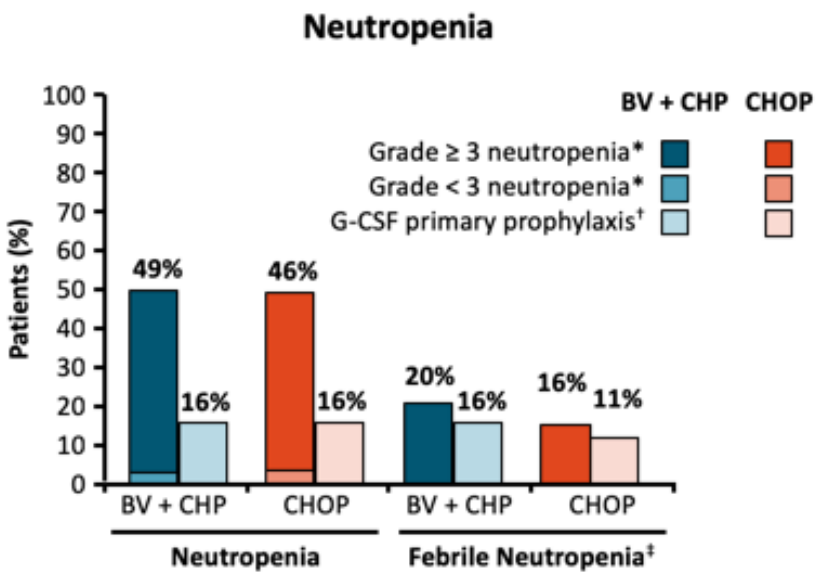


Patients at Risk, n (Number Censored)

BV + CHP	226 (0)	208 (14)	193 (27)	184 (33)	159 (42)	128 (47)	108 (49)	83 (51)	45 (51)	20 (51)	4 (51)	0 (51)
CHOP	226 (0)	196 (24)	181 (39)	158 (57)	140 (60)	121 (63)	103 (66)	79 (68)	46 (71)	22 (72)	4 (73)	0 (73)

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

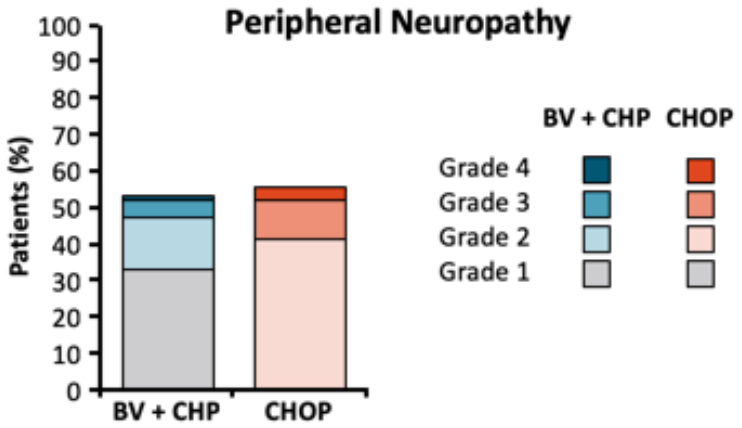
Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): EA of Special Interest



*Includes neutropenia, decreased ANC preferred terms.
†Permitted at investigator discretion. ‡Any grade.

- G-CSF primary prophylaxis recommended per BV FDA label

Horwitz. ASH 2018. Abstr 997.



Safety Outcome	BV + CHP (n = 223)	CHOP (n = 226)
Treatment-emergent PN, n	117	124
▪ All PN events resolved,* n (%)	58 (50)	79 (64)
▪ Ongoing PN at last visit, n (%)	61 (52)	45 (36)
• Grade 1	44 (72)	32 (71)
• Grade 2	15 (25)	12 (27)
• Grade 3	2 (1)	1 (1)

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): Conclusions

- In patients with untreated CD30+ PTCL, brentuximab vedotin + CHP **significantly improved survival vs standard CHOP**
  - Risk of progression event reduced by 29%
    - HR: 0.71 (95% CI: 0.54-0.93; *P* = .011)
  - Risk of death reduced by 34%
    - HR: 0.66 (95% CI: 0.46-0.95; *P* = .0244)
- Overall **safety similar between treatment arms**, including incidence of neutropenia and peripheral neuropathy
- Based on results of ECHELON-2, **FDA indication for brentuximab vedotin expanded to include previously untreated sALCL and other CD30+ PTCL (eg, AITL, PTCL-NOS) in combination with CHP**

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

KEYNOTE-170/KEYNOTE-013:
Pembrolizumab in R/R PMBCL

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL – study design

Phase Ib KEYNOTE-013

R/R PMBCL patients
≥ 18 yrs of age without ASCT*
(N = 21)

Pembrolizumab
10 mg/kg Q2W (patients 1-10)
or 200 mg Q3W (patients 11-21)

Treatment up to 2 yrs or until unacceptable toxicity, PD, or study withdrawal

Response assessment by PET/CT scan:

- KEYNOTE-013: Wk 12 then Q8W (10 mg/kg Q2W) or Wks 6, 12 then Q9W (200 mg Q3W), IWG 2007 criteria
- KEYNOTE-170: Wk 12 then Q12W, IWG 2007 criteria

Phase II KEYNOTE-170

R/R PMBCL patients
≥ 18 yrs of age without ASCT,* failed ≥ 2 prior regimens
(N = 53)

Pembrolizumab
200 mg Q3W

Treatment up to 2 yrs or until unacceptable toxicity, PD, or study withdrawal

Primary endpoints: ORR, safety (KEYNOTE-013 only)

Secondary endpoints: DoR, PFS, OS, safety (KEYNOTE-170)

*Failed, ineligible, or refused.

Armand. ASH 2018. Abstr 228. NCT02576990.

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL - efficacy

Characteristic, n (%)	KEYNOTE-013 (N = 21)	KEYNOTE-170† (N = 53)	KEYNOTE-170‡ (N = 53)
OR	**10 (48)**	**24 (45)**	**23 (43)**
▪ **CR**	**7 (33)**	**7 (13)**	**11 (21)**
▪ **PR**	**3 (14)**	**17 (32)**	**12 (22)**
SD	5 (24)	5 (9)	5 (9)
PD	4 (19)	12 (23)	13 (25)
Nonevaluable/ no assessment*	2 (10)	12 (23)	12 (23)

*Insufficient data for response assessment.
†Cheson criteria.
‡Lugano criteria.

Characteristic	KEYNOTE-013 (N = 21)	KEYNOTE-170 (N = 53)
Median duration of follow-up, mos	29.1	12.5
Median time to response, mos	2.7§	2.8‖
PFS		
▪ **12-mo, %**	**47**	**38**
▪ **Median, mos (range)**	**10.4 (3.4-NR)**	**5.5 (2.8-12.1)**
OS		
▪ 12-mo, %	65	58
▪ Median, mos (range)	31.4 (4.9-NR)	NR (7.3-NR)

§2 patients converted from PR to CR after 12 mos; 4 patients maintained CR after 2 yrs on treatment (2.3+, 2.5+, 3+, 3.5+ yrs).
‖No relapses in patients with CR reported at database lock.

Armand. ASH 2018. Abstr 228.

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL - safety

- Pembrolizumab results in **durable responses in R/R PMBCL**
  - Median DoR not yet reached with median follow-up of 29.1 mos (KEYNOTE-013), 12.5 mos (KEYNOTE-170)
  - 12-mo OS > 50%; durable CR in both studies
- **Manageable toxicity profile**
- Pembrolizumab **received accelerated FDA approval for R/R PMBCL in June 2018**

Armand. ASH 2018. Abstr 228.

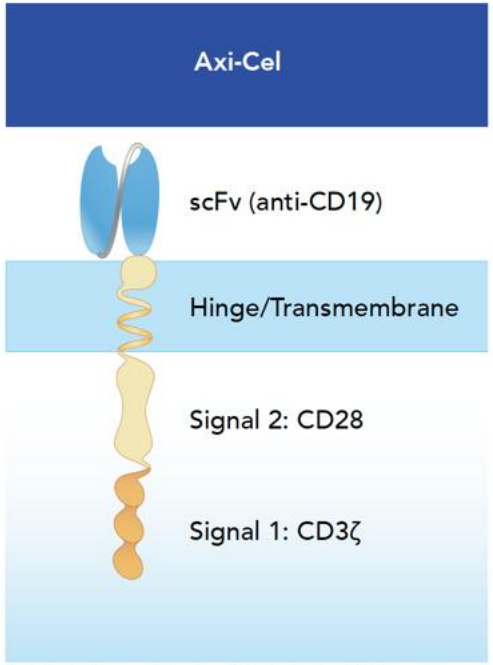
ZUMA-1: Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

BACKGROUND

- Outcomes in refractory large B cell lymphoma with traditional standard of care are extremely poor[1]
  - The SCHOLAR-1 analysis demonstrated an objective response rate (ORR) of 26%, a complete response (CR) rate of 7%, and a median overall survival (OS) of 6.3 months in this patient population
- Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, is approved in the United States and European Union for the treatment of patients with relapsed or refractory large B cell lymphoma with ≥ 2 prior systemic therapies based on the results of ZUMA-1[2,3]
- ZUMA-1 one-year analysis (N = 108; median follow-up, 15.4 months) demonstrated[4,5]:
  - ORR, 82%; CR rate, 58%
  - Ongoing response in 42% of patients
  - Adverse events (AEs) beyond 6 months were primarily manageable infections, and there were no late-onset axi-cel–related incidences of cytokine release syndrome (CRS) or neurologic events (NEs)

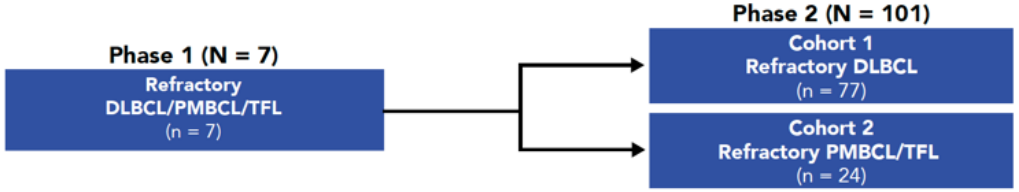
Figure 1. Structure of Axi-Cel



Axi-cel, axicabtagene ciloleucel; scFv, single-chain variable fragment.

METHODS

Figure 2. ZUMA-1 Study Design



Key eligibility criteria
- No response to last chemotherapy or relapse ≤ 12 months post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Conditioning regimen
- Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days

Axi-cel: 2 × 10^6 CAR T cells/kg
- 99% Enrolled were successfully manufactured
- 91% Enrolled were dosed

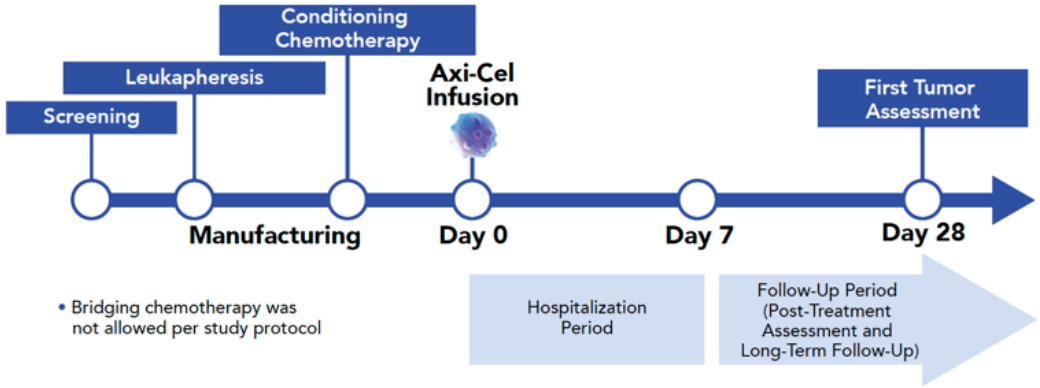
Data cutoff: August 11, 2018

Median follow-up for Phase 2: 27.1 months

Patient populations
- Safety: N = 108 (Phase 1 + 2)
- Efficacy: n = 101, assessed by investigator and central review

ASCT, autologous stem cell transplantation; DLBCL, diffuse large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

Figure 3. ZUMA-1 Treatment Schema



Sattva S. Neelapu et al. - Poset 2967 ASH 2018

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

Table 1. Baseline Characteristics

Characteristic	DE/HGBCL (n = 37)	Overall (N = 108)
Median age (range), y	60 (28 – 76)	58 (23 – 76)
≥ 65, n (%)	9 (24)	27 (25)
Male, n (%)	25 (68)	73 (68)
ECOG 1, n (%)	22 (59)	62 (57)
Disease stage III/IV, n (%)	29 (78)	90 (83)
IPI score 3 – 4, n (%)	15 (41)	48 (44)
≥ 3 Prior therapies, n (%)	28 (76)	76 (70)
Refractory Subgroup Before Enrollment	**(n = 37)**	**(N = 108)**
Refractory to second- or later-line therapy, n (%)	29 (78)	80 (74)
Best response as PD to last prior therapy	22 (59)	70 (65)
Relapse post-ASCT, n (%)	8 (22)	25 (23)

ASCT, autologous stem cell transplantation; DE/HBGCL, double-expressor or high-grade B cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PD, progressive disease.

- Overall, most patients had any-grade cytopenias according to baseline laboratory values: 93% had anemia, 34% had thrombocytopenia, and 15% had neutropenia
- Of the 47 patients with pretreatment tumor samples, 30 (64%) had DE and 7 (15%) had HGBCL, including 1 patient with triple-hit HGBCL, 4 with double-hit HGBCL, and 2 with HGBCL NOS

Table 2. Objective and Ongoing Response Rates

	Investigator-Assessed (n = 101)		Central Review (n = 101)	
	ORR	CR	ORR	CR
Best objective response, %	83	58	74	54
Ongoing, %[a]	39	37	36	35

[a]Three patients with ongoing response per investigator review were not ongoing responders per central review. Two of these patients underwent SCT prior to documented progression, which was considered a censor event per central review but not per investigator assessment. The third patient was deemed to have PD per central review after 10.9 months but was assessed to be in ongoing response at 23.4 mo per investigator.
CR, complete response; ORR, objective response rate; PD, progressive disease; SCT, stem cell transplantation.

- 93% of patients with ongoing response at 12 months remained in response at 24 months
- 81% concordance of ORR between investigator assessment and central review
- 91% ORR and 70% CR rate for the 33 Phase 2 patients with DE/HGBCL
  - 48% in ongoing response (all ongoing CR)
- Only 5% (2/39) ongoing responders underwent allogeneic stem cell transplant, and none received autologous stem cell transplant

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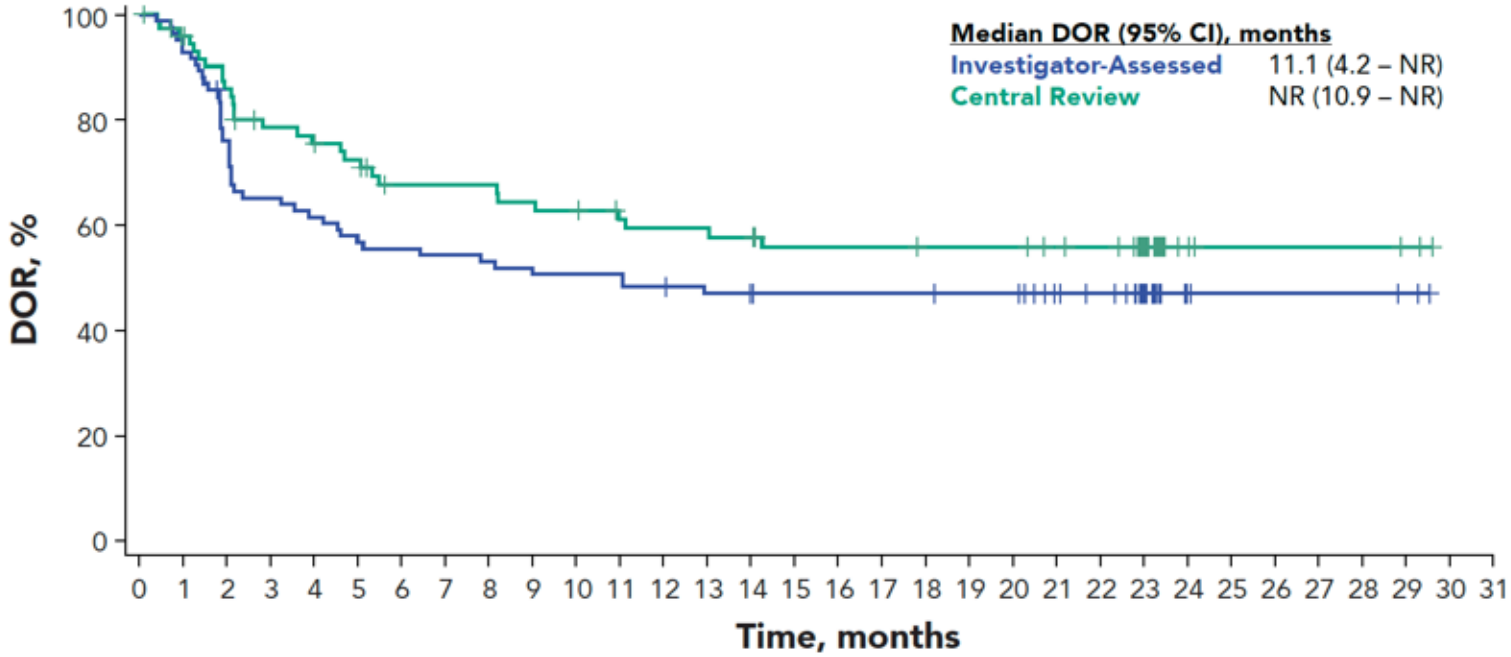
2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL



Median duration of response was NR (95% CI, 10.9 months – NR) by central review because of several patients with early progressive disease who were assessed as in response by central review and had to be censored for receiving next anticancer therapy.
DOR, duration of response; NR, not reached.

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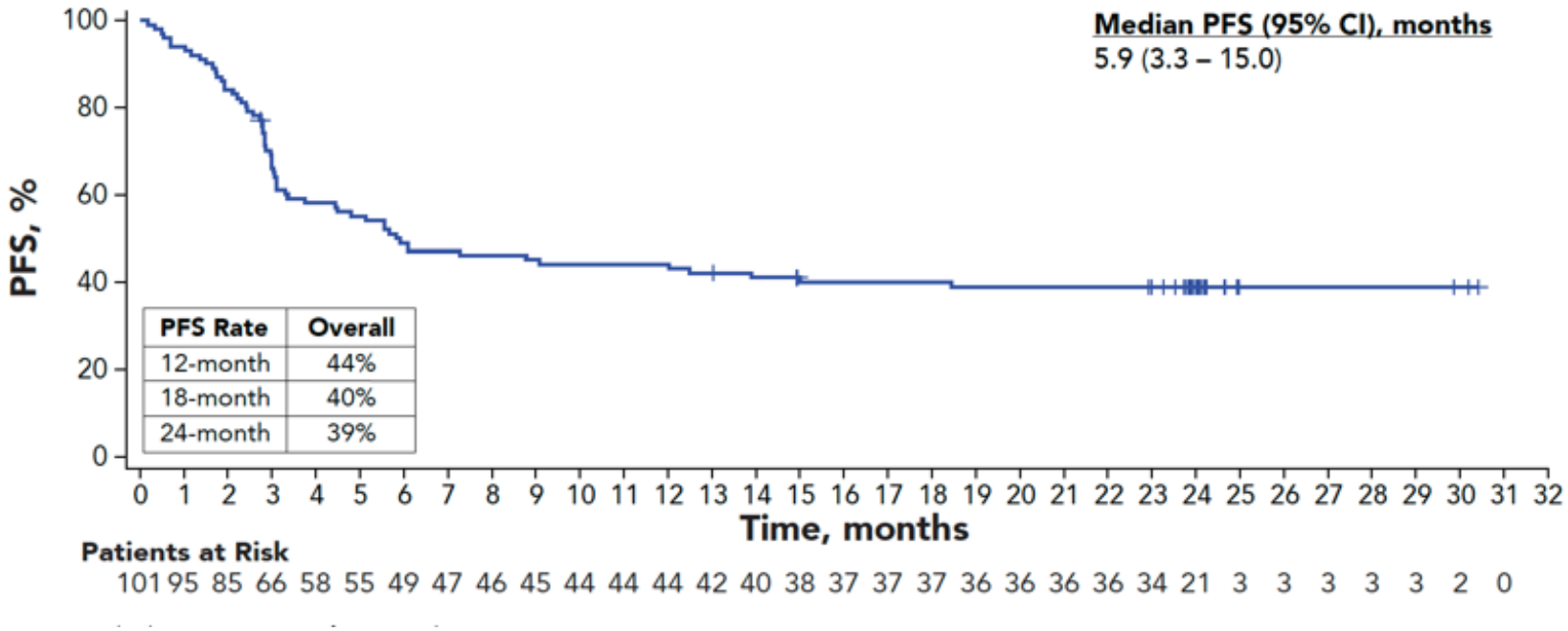
2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL



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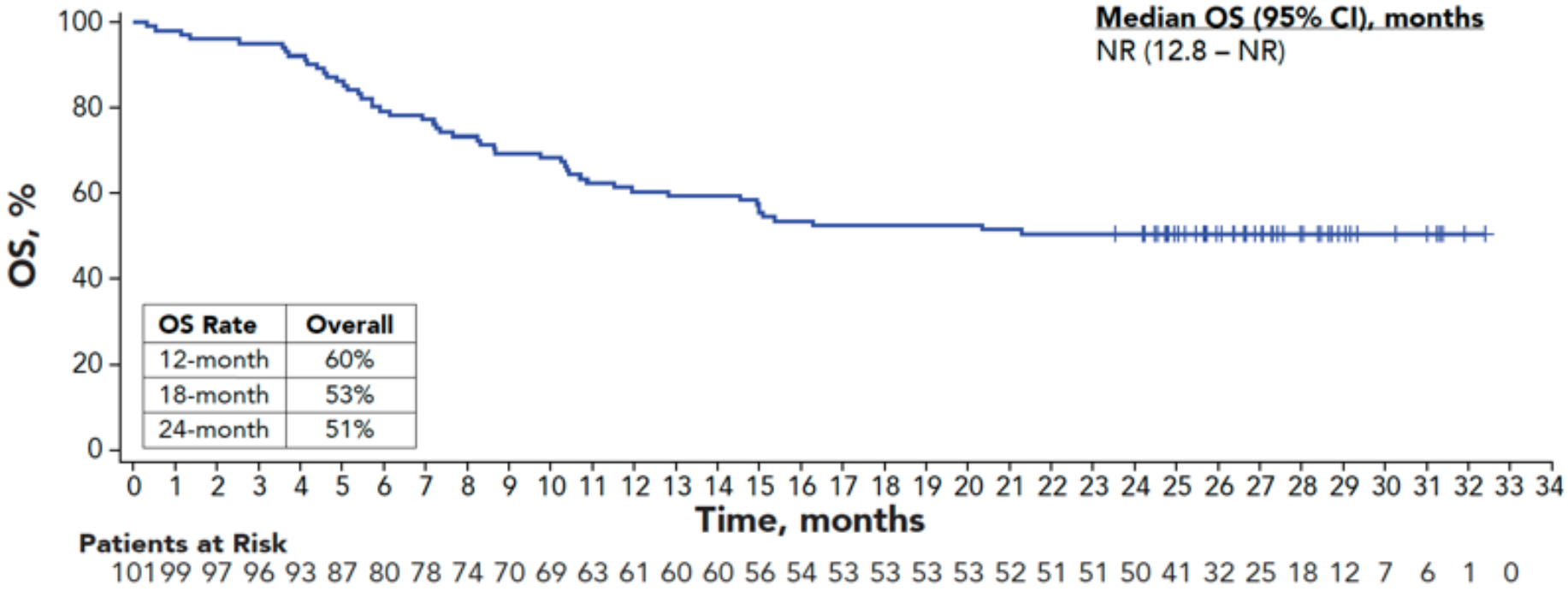
Polish Lymphoma Research Group

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL



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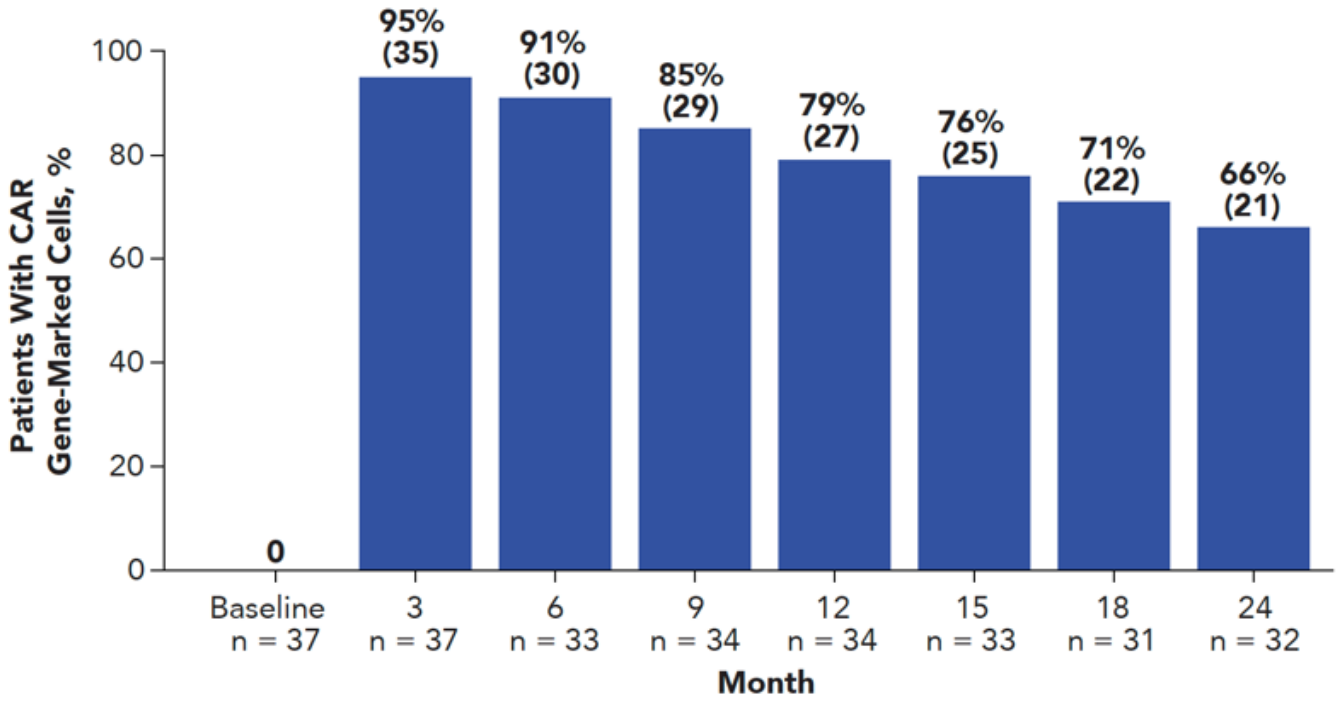
Polish Lymphoma Research Group

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

Figure 7. Proportion of Patients With Detectable CAR Gene-Marked T Cells in Blood Among Patients With Ongoing Response Over Time



Gene-marked CAR T cells were enumerated by quantitative PCR. The lower limit of quantification of the assay was 2 gene-marked CAR T cells per 100,000 PBMCs (0.002%). Values shown indicate the proportion (top) and number (in parenthesis) of patients with gene-marked CAR T cells in blood at a given time point. Number of patients evaluated at each time point are shown on x-axis. This analysis excludes 2 patients who received subsequent anticancer therapy while in response to axi-cel. CAR, chimeric antigen receptor; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction.

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2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

Treatment-Emergent Cytopenia, n (%)	Any Grade (N = 108)	Grade ≥ 3 (N = 108)
Any treatment-emergent cytopenia	100 (93)	93 (86)
Neutropenia	93 (86)	86 (80)
Thrombocytopenia	67 (62)	43 (40)
Anemia	73 (68)	49 (45)
Any cytopenia present on or after day 30	59 (55)	41 (38)
Neutropenia	39 (36)	28 (26)
Thrombocytopenia	44 (41)	26 (24)
Anemia	31 (29)	11 (10)
Any cytopenia present on or after month 3	37 (34)	18 (17)
Neutropenia	20 (19)	12 (11)
Thrombocytopenia	19 (18)	8 (7)
Anemia	19 (18)	3 (3)

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LYMRIT-37-01: A phase I/II study of ^{177}Lu-lilotomab satetraxetan antibody-radionuclide conjugate (ARC) for the treatment of relapsed non-Hodgkin's lymphoma (NHL): Analysis with 6 month follow-up

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BACKGROUND

- ^{177}Lu-satetraxetan-lilotomab (Betalutin®) is a novel beta-emitting anti-CD37 antibody-radionuclide conjugate (ARC) in a ready-to-use formulation for single-dose administration.
- Betalutin® has a Fast Track designation for follicular lymphoma (FL) patients who have received ≥2 prior therapies (US), and a Promising Innovative Medicine (PIM) designation in the UK for advanced relapsed/refractory FL.
- CD37 is a tetraspanin membrane protein that is highly expressed (>90%) on B cells, including B-cell NHL.
- This phase 1/2, open-label, multicenter study was conducted to assess the safety, PK and activity of Betalutin® in patients with relapsed iNHL.

STUDY DESIGN

Key Eligibility Criteria

- Histologically confirmed relapsed B-cell indolent NHL
- <25% bone marrow involvement
- Platelet count >150 x 10^9/L
- ANC ≥ 1.5 x 10^9/L
- No previous hematopoietic stem cell transplantation or RIT

Study Schema

The study was conducted in two parts: Four dose-escalation cohorts to determine the optimal cold antibody (lilotomab or rituximab, RTX) pre-dosing and Betalutin® regimen (phase 1), and dose expansion cohorts to confirm safety and evaluate efficacy (phase 2a). Three additional patients were enrolled in a separate arm (Arm 5) for additional PK data (60 mg/m² lilotomab + 20 MBq/kg Betalutin®).

The recommended dose for expansion (RDE) of Betalutin® in Arm 1 was 15 MBq/kg and 20 MBq/kg in Arm 4. Patients were subsequently enrolled into 2 phase 2 expansion cohorts (Fig 1).

All patients received pre-treatment with rituximab (RTX) (375 mg/m²) to deplete peripheral B cells and improve biodistribution of Betalutin®.

Fig 1: LYMRIT 37-01 study design

Assessments

- Dose-limiting toxicities (DLTs) were assessed during the first 12 weeks.
- Incidence and severity of adverse events (AEs) according to CTCAE v4.
- Response assessments: conducted at 3, 6 (FDG PET-CT), 9, 12, 18, 24, 36 and 48 months (CT) per the International Working Group (IWG) criteria for NHL (Cheson BD et al. *J Clin Oncol* 2007; 25: 579-586 & Cheson BD et al. *J Clin Oncol* 1999; 17: 1244-1253).

RESULTS

Data on 74 patients (data cut-off: 2 Nov 18) are reported in this analysis; the median follow-up time for all patients is 18.4 months (3.2-61.6 m).

Phase 1 (n=32)				Phase 2a (n=42)
Arm	Pre-dose	Betalutin® (MBq/kg)	N	N
1	40 mg lilotomab	10	3	
	40 mg lilotomab	**15**	**6**	**30**
	40 mg lilotomab	20	3	
2	None	10*	2	
	None	15	2	
3	RTX 375 mg/m²	15	3	
4	100 mg/m² lilotomab	15	3	
	100 mg/m² lilotomab	**20**	**7**	**12**
5	60 mg/m² lilotomab	20	3	

*Includes first patient enrolled in study.

Table 1: Baseline characteristics

	All Patients (n=74)	FL* (n=57)	Other** (n=17)
Median age, years (range)	68 (38-87)	69 (40-80)	68 (57-88)
≥65, n (%)	51 (69%)	36 (63%)	12 (70%)
Male	41 (55%)	32 (56%)	9 (53%)
Female	33 (45%)	25 (44%)	8 (47%)
Ann Arbor stage at diagnosis ***			
I/II	5 (12%)	5 (17%)	0 (0%)
III/IV	27 (64%)	18 (62%)	9 (69%)
Unknown	10 (24%)	6 (21%)	4 (31%)
Prior regimens, median (range)	3 (1-9)	3 (1-9)	3 (1-7)
≥2 prior regimens	48 (65%)	37 (65%)	11 (65%)
Prior alkylating agent	60 (81%)	44 (77%)	16 (94%)
Rituximab refractory	33 (44%)	30 (53%)	3 (18%)
Bulky disease ≥7 cm, n (%)	20 (27%)	15 (26%)	5 (29%)

*Follicular grades: I (n=16), II (n=32), IIIa (n=9).
**Mantle cell lymphoma (MCL; n=7), marginal zone lymphoma (MZL; n=9), small lymphocytic lymphoma (SLL; n=1).
***Information collected for phase 2 patients only (N=42).

SAFETY

- Overall, Betalutin® was well-tolerated. The most common grade 3/4 TEAEs were reversible neutropenia and thrombocytopenia (Table 2). G4 neutropenia/thrombocytopenia occurred in 19%/17% & 16%/10% of Arm 1 (40/15) and Arm 4 (100/20) pts respectively.
- SAEs occurred in 14 patients (19%). SAEs in ≥2 pts. were atrial fibrillation, thrombocytopenia, NHL progression and sepsis (all n=2).
- 5 patients received platelets (1 epistaxis, 1 hematuria; both G3), 3 for low platelet count; 1 RBC transfusion for anemia. 3 pts. received G-CSF.
- 18 m after subsequent treatment with bendamustine (24 m post- Betalutin®), MDS/AML was reported in 1 patient with prior alkylating agent exposure.
- There were no study drug-related deaths in the treatment period.

Table 2: Grade 3/4 TEAEs in ≥2 patients

Adverse Event	G3 n (%)	G4 n (%)
Neutropenia	26 (35%)	14 (19%)
Thrombocytopenia	21 (25%)	15 (20%)
Leukopenia	30 (40%)	4 (5%)
Lymphopenia	23 (31%)	2 (3%)
Infections	1 (1%)	2 (3%)
Urinary tract infection		
Sepsis/neutropenic sepsis	1 (1%)	
Pneumonia		
Bleeding	1 (1%)	
Epistaxis	1 (1%)	
Hematuria		
Hyperglycemia	2 (3%)	--
Lymphoma progression	4 (5%)	1 (1%)

EFFICACY

- Overall, objective responses (ORR = CR + PR) were observed in 45/74 (61%) of patients; 28% (n=21) obtained a CR.
- 90% of evaluable patients had a decrease in tumor size (Figure 3).
- For all patients with FL the ORR was 65% (CR 28%). The ORR for FL patients receiving the Arm 1 Betalutin® RDE of 15 MBq/kg was 64% (CR 32%). The ORR for FL patients receiving the Arm 4 Betalutin® RDE of 20 MBq/kg was 69% (CR 25%) (Table 3).
- For FL patients with ≥2 prior therapies (n=37), the ORR was 70% (CR 32%).
- 44% of patients were refractory to RTX: the ORR was 62% for RTX-refractory FL patients with 2 or more prior therapies (CR 19%).
- The median duration of response (DoR) for all patients (n=45) was 9.0 months; 25 pts (34%) remained free of disease progression for ≥12 m. For all patients with a CR (n=21), the median duration of response was 20.7 months (Figure 4).

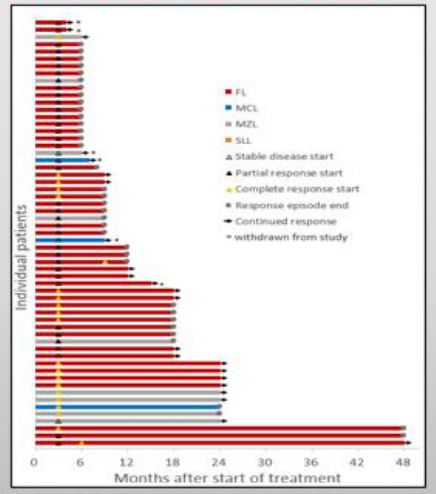
Table 3: Response rates: all patients

Subtype	ORR n (%)	CR n (%)	PR n (%)	SD n (%)	PD n (%)
FL (n=57)	37 (65%)	16 (28%)	21 (37%)	10 (18%)	10 (18%)
MZL (n=9)	7 (78%)	4 (44%)	3 (33%)	2 (22%)	--
MCL (n=7)	1 (14%)	1 (14%)	--	2 (28%)	4 (57%)
SLL (n=1)	--	--	--	--	1
Total	61%	28%	32%	19%	20%

Table 4: Response rates: FL patients

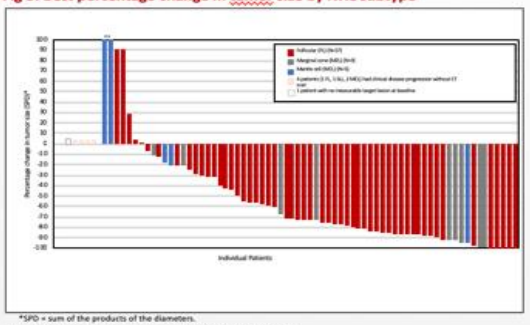
		ORR (CR + PR)	CR
All FL patients	(n=57)	65%	28%
Arm 1 (40/15)	(n=25)	64%	32%
Arm 4 (100/20)	(n=16)	69%	25%
FL with ≥2 prior therapies	(n=37)	70%	32%
RTX refractory FL, ≥2 prior therapies	(n=21)	62%	19%

Fig 2: Response duration for all patients by NHL subtype*



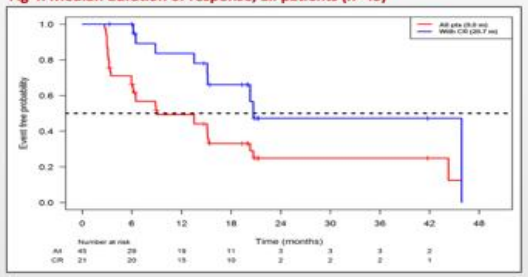
*Includes CR, PR and SD responses

Fig 3: Best percentage change in tumor size by NHL subtype



*SPD = sum of the products of the diameters.
**Change in size of target lesion is beyond the scale for this figure (n=2).

Fig 4: Median duration of response, all patients (n=45)



CONCLUSIONS

- Single-agent Betalutin® was effective and well-tolerated in this elderly heavily pre-treated population of patients with recurrent iNHL:
  - Overall response rate of 61% (CR 28%)
  - Highly active in FL patients with ≥2 prior therapies (ORR 70% CR 32%), and RTX-refractory FL (ORR 62% CR 19%)
  - Durable responses, especially for patients with a CR (20.7 months for all patients)
- Main grade 3/4 toxicities are reversible neutropenia and thrombocytopenia; low incidence of infections (5.4%).
- With its promising clinical profile, ready-to-use formulation and one-time administration, Betalutin® has the potential to be a novel, safe and effective therapy for recurrent B-cell lymphoma.
- The 2 RDEs are now being compared in a randomized phase 2b cohort ("PARADIGME") in relapsed, anti CD20-refractory FL patients who have received ≥2 prior therapies.

Poster No. 4161

A Phase I/II, First-in-Human Trial of the Bruton's Tyrosine Kinase Inhibitor M7583 in Patients with B-Cell Malignancies

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INTRODUCTION

- Bruton's tyrosine kinase (BTK) plays a key role in B-cell receptor-mediated pathways implicated in the pathogenesis of several B-cell malignancies, and its inhibition blocks several B-cell functions.[1]
- M7583 is a potent, highly selective BTK inhibitor (BTKi) that has shown *in vitro* and *in vivo* activity against several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL).[2]
- M7583 has been investigated in a Phase I/II trial (NCT02825836) in patients with refractory/resistant B-cell malignancies; final dose-escalation data are presented.

OBJECTIVES

- Primary objective: determine the recommended dose of single-agent M7583 for further investigation.
- Secondary objectives: included the evaluation of preliminary efficacy (best overall response, duration of response, progression-free survival) and safety/tolerability.

METHODS

Study Design

- Study conducted in patients with refractory/resistant B-cell malignancies who had failed 1–3 lines of prior therapy.
- M7583 given once daily (QD) in 28-day cycles in ascending dose cohorts until disease progression, withdrawal of consent, or early discontinuation from the study.
  - Starting dose was 80 mg QD for 3 days followed by 160 mg QD, then doses increased sequentially according to an adaptive Bayesian design up to 900 mg QD (n=3–6 patients per dosing cohort).

Key Eligibility Criteria

- Adults with pathologically confirmed DLBCL, CLL, small lymphocytic lymphoma, follicular lymphoma, MCL, or Waldenström's macroglobulinemia (WM) who had received 1–3 lines of prior therapy.
  - Other inclusion criteria included: life expectancy >4 months from first dose, Eastern Cooperative Oncology Group performance status ≤2, and adequate hematological, hepatic and renal function.
- Patients were excluded if they had had anticancer therapy within 28 days prior to trial drug treatment or any prior BTKi exposure, central nervous system lymphoma or leukemia, significant cardiac conduction abnormalities or a history of Richter's transformation, prolymphocytic leukemia or cardiovascular/cerebrovascular disease.

Assessments

- Dose-limiting toxicities (DLTs) were assessed during cycle 1 (primary endpoint) using NCI-CTCAE version 4.03 and defined as:
  - Treatment-related hepatocellular injury or treatment-related grade ≥3 non-hematological treatment-emergent adverse events (TEAEs) except: diarrhea or nausea/vomiting <3 days duration; asymptomatic grade 3 increase in liver function tests that resolve within 7 days; grade 3 skin toxicity that resolves to grade ≤2 within 7 days; grade 3 hyperglycemia (in patients with diabetes or decreased glucose tolerance) that resolves in <5 days; fatigue/headache of <7 days duration; or single laboratory values out of the normal range that resolve in <5 days.
  - Treatment-related grade 4 neutropenia of >5 days duration, grade ≥3 febrile neutropenia or grade 4 hemoglobin decrease, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, or any treatment-related TEAE causing the patient to miss ≥6 consecutive days of treatment in Cycle 1.
- Best overall response was assessed by investigators according to the revised International Working Group Criteria for Non-Hodgkin's lymphoma, and Owen criteria for WM.
- Incidence and severity of TEAEs were reported using NCI-CTCAE version 4.03.

RESULTS

Baseline Characteristics

- At the time of analysis (data cut-off, May 20, 2018), 25 patients had been screened and 18 had received M7583 treatment in five dose cohorts (**Table 1**).
  - Eleven patients were still on treatment; three patients had completed treatment and four had discontinued due to TEAEs (n=2), complete remission leading to stem cell transplant (n=1) and investigator's decision (n=1).
- Patients were white, predominantly male (aged 49 to 80 years).

Table 1. Baseline Demographics and Disease Characteristics

	M7583 dose					
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	Total (N=18)
Age, median years (range)	66 (57, 80)	66 (59, 74)	55 (49, 63)	63 (62, 73)	59 (43, 70)	63 (43, 80)
Male, n (%)	2 (66.7)	2 (66.7)	4 (80.0)	2 (66.7)	3 (75.0)	13 (72.2)
B cell malignancy, n (%)						
DLBCL	0 (0)	0 (0)	1 (20.0)	0 (0)	2 (50.0)	3 (16.7)
WM	1 (33.3)	2 (66.7)	1 (20.0)	0 (0)	0 (0)	4 (22.2)
MCL	1 (33.3)	0 (0)	3 (60.0)	2 (66.7)	2 (50.0)	8 (44.4)
SLL	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (5.6)
MZL	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)

BID, twice daily; QD, once daily; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Treatment Exposure

- Maximum treatment duration with M7583 was 20.1 months (**Table 2**).

Table 2. Duration of M7583 Treatment

	M7583 dose					
Treatment duration, months	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	Total (N=18)
n (%)						
≥0–6	0 (0)	0 (0)	2 (40.0)	0 (0)	3 (75.0)	5 (27.8)
>6–12	1 (33.3)	0 (0)	3 (60.0)	3 (100)	1 (25.0)	8 (44.4)
>12–18	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	3 (16.7)
>18–24	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)
Median (range)	19.5 (12.0, 20.1)	14.2 (14.0, 15.8)	6.2 (0.5, 11.9)	7.8 (7.7, 8.0)	2.8 (0.8, 6.6)	7.9 (0.5, 20.1)

BID, twice daily; QD, once daily.

Safety

- No DLTs were reported.
- Overall, 89% of patients reported ≥1 TEAE of any grade (**Table 3**).
- Ten (56%) patients reported grade ≥3 TEAEs, three (17%) had TEAEs considered to be related to treatment (**Table 3**), which were neutropenia, febrile neutropenia and pneumonia.
- Four (22%) patients had grade ≥4 TEAEs, considered to be treatment-related in one (6%) patient (neutropenia).
- Six patients (33%) had serious TEAEs, two (11%) patients had treatment-related serious TEAEs (**Table 3**), which were febrile neutropenia and pneumonia.
- Two deaths were due to TEAEs (disease progression), neither were related to treatment (**Table 3**).
- Most common TEAEs were diarrhea, fatigue and vomiting (**Table 4**).

Table 3. Summary of TEAEs

	M7583 dose					
Patients, n (%), with any	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	Total (N=18)
TEAE	3 (100)	3 (100)	4 (80.0)	2 (66.7)	4 (100)	16 (88.9)
M7583-related TEAE	3 (100)	2 (66.7)	3 (60.0)	2 (66.7)	4 (100)	14 (77.8)
Serious TEAE	0 (0)	0 (0)	2 (40.0)	0 (0)	4 (100)	6 (33.3)
Serious M7583-related TEAE	0 (0)	0 (0)	0 (0)	0 (0)	2 (50)	2 (11.1)
Grade ≥3 TEAE	3 (100)	0 (0)	3 (60.0)	0 (0)	4 (100)	10 (55.6)
Grade ≥3 M7583-related TEAE	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (50)	3 (16.7)
Grade ≥4 TEAE	1 (33.3)	0 (0)	1 (20.0)	0 (0)	2 (50)	4 (22.2)
Grade ≥4 M7583-related TEAE	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)
TEAE leading to death	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25)	2 (11.1)

BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.

Table 4. Most common TEAEs (Occurring in ≥2 Patients)

	M7583 dose					
Patients with TEAEs, n (%)	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	Total (N=18)
Diarrhea*	1 (33.3)	1 (33.3)	2 (40.0)	0 (0)	2 (50.0)	6 (33.3)
Fatigue	0 (0)	1 (33.3)	1 (20.0)	0 (0)	2 (50.0)	4 (22.2)
Vomiting*	0 (0)	0 (0)	2 (40.0)	0 (0)	1 (25.0)	3 (16.7)
Neutropenia*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Upper abdominal pain*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Gastro-esophageal reflux disease*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Nausea*	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Disease progression	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Peripheral edema	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Pyrexia	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Conjunctivitis	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)
Nasopharyngitis	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)
Dizziness	0 (0)	0 (0)	1 (20.0)	1 (33.3)	0 (0)	2 (11.1)
Rhinitis	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Dyspnea	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Dry skin	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)
Pruritus*	0 (0)	0 (0)	2 (40.0)	0 (0)	0 (0)	2 (11.1)

*TEAE was considered treatment-related in ≥2 patients.
BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.

Efficacy

- Objective response rate was 50% and disease control rate was 78% (**Table 5**).
- Two patients achieved complete response (**Table 5**).
  - One reached complete response after 4 months of treatment and complete remission after 6 months of treatment, and then went on to receive stem cell transplantation.
  - The second attained a complete response following 2 months of treatment.

Table 5. Best Overall Response to M7583

	M7583 dose					
Response, n (%)	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	Total (N=18)
Best overall response						
Complete response	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Partial response	1 (33.3)	2 (66.7)	2 (40.0)	2 (66.7)	0 (0)	7 (38.9)
Minor response	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (5.6)
Stable disease	2 (66.7)	0 (0)	0 (0)	1 (33.3)	1 (25.0)	4 (22.2)
Not evaluable	0 (0)	0 (0)	2 (40.0)	0 (0)	1 (25.0)	3 (16.7)
Objective response rate	1 (33.3)	2 (66.7)	3 (60.0)	2 (66.7)	1 (25.0)	9 (50.0)
Disease control rate	3 (100.0)	3 (100.0)	3 (60.0)	3 (100.0)	2 (50.0)	14 (77.8)

BID, twice daily; QD, once daily.

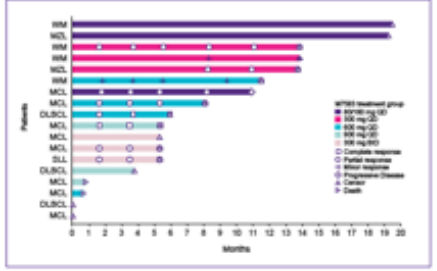
- Median time to the observed responses was 7.1 weeks (range, 7.1, 50.0 weeks).
- Decreases in tumor burden were observed across dose levels and tumor types: 10 patients had a decrease in tumor burden of ≥30% (**Figure 1**).

Figure 1. Change (%) in Tumor Burden* by Disease and Dose

*Maximum relative decrease in the sum of the products of the target tumor diameters (SPD) from baseline. Patients with WM are excluded along with patients who were not evaluable due to missing baseline or post-baseline assessments.
BID, twice daily; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; SLL, small lymphocytic lymphoma.

- At 12 months, 75% of patients were progression free (Kaplan–Meier estimate).
- The progression-free survival observed in individual patients is shown in **Figure 2**.

Figure 2. Progression-Free Survival in Patients by Disease Type



BID, twice daily; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

CONCLUSIONS

- **In this dose-escalation study, M7583 was well tolerated at all the doses investigated (80/160 mg QD, 300 mg QD, 600 mg QD, 300 mg BID, and 900 mg QD)**
  - **No DLTs were observed**
- **There was evidence of clinical benefit at all of the doses investigated and across the tumor types**
  - **Positive tumor response was observed at the lowest dose investigated (80/160mg QD)**
  - **Three quarters of patients were still progression free after 12 months of treatment; however, progression-free survival data are not yet mature**
- **M7583 appears, therefore, to have a favorable benefit:risk profile**
- **The recommended dose for further investigation is 300 mg BID, with 900 mg QD as a supporting daily dose**

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WT has received consultancy honoraria from Roche and Gilead.

DT declares no conflict of interest.

BS and **JS** are employees of Merck KGaA.

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Long-Term Follow-Up of Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma

Abstract 2876

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BACKGROUND

- Mantle cell lymphoma (MCL), an aggressive B-cell non-Hodgkin lymphoma, remains incurable with standard therapies
- Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor with minimal off-target activities in preclinical studies[1,2]
- Acalabrutinib was approved on October 31, 2017 by the US Food and Drug Administration for the treatment of relapsed/refractory (R/R) MCL based on clinical data showing a high rate of durable responses and a favorable safety profile[3,4]
- Here, we present median 26-month follow-up in these patients

METHODS

Study Design

- This Phase 2, multicenter, international, open-label study (ACE-LY-004; NCT02213926) evaluated acalabrutinib monotherapy in patients with R/R MCL
- Enrollment: March 12, 2015, through January 5, 2016, at 40 sites across 10 countries

BID = twice daily; MCL = mantle cell lymphoma; PD = progressive disease; PO = orally; R/R = relapsed/refractory.

Patients

- Key inclusion criteria:
  - Relapsed after or refractory to 1 to 5 prior treatments
  - Confirmed MCL with translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1
  - Measurable nodal disease (≥1 lymph node ≥2 cm in longest diameter)
  - Eastern Cooperative Oncology Group performance status ≤2
  - Age ≥18 years
- Key exclusion criteria:
  - Significant cardiovascular disease:
    - Uncontrolled or symptomatic arrhythmias
    - Congestive heart failure, or myocardial infarction within 6 months of screening
    - Any Class 3 or 4 cardiac disease, per New York Heart Association Functional Classification
    - Corrected QT interval >480 milliseconds
    - Patients with prior or concurrent atrial fibrillation were not excluded
  - Concomitant use of warfarin or equivalent vitamin K antagonists
  - Previous treatment with Bruton tyrosine kinase or BCL-2 inhibitors
- Investigators categorized the cytomorphologic variants of MCL for each patient as classical, aggressive (blastoid/pleomorphic), or other

Assessments

- The primary endpoint was investigator-assessed overall response rate based on the 2014 Lugano Classification[5]
  - Disease assessments were performed at the end of Cycles 2, 4, and 6 and every 3 cycles thereafter
- Secondary endpoints included:
  - Investigator-assessed duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
  - Safety
    - Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03
  - Pharmacokinetics and pharmacodynamics (previously reported)[3]
- Time to response was an exploratory endpoint
- Analysis of minimal residual disease (MRD) was conducted using the ClonoSEQ next-generation sequencing (10^{-6}) assay (Adaptive Biotechnologies) in consented patients with available paired archival tumor and whole blood sample after response

RESULTS

Patients

- 124 Patients with R/R MCL were enrolled and treated (**Table 1**)
- The median number of prior therapies was 2 (range, 1 to 5); 24% were refractory to the most recent prior treatment
- As of February 12, 2018, the median follow-up was 26 months (range, 0.3 to 35.1 months), with 40% (49/124) remaining on acalabrutinib (**Table 2**)
- For the 7 patients who discontinued due to progressive disease, the most common treatments received after progression were rituximab-based regimens (6 of 7 patients [86%])

Table 1. Demographic and baseline characteristics

Characteristic	N=124
Age, median (range), y	68 (42-90)
Male sex, n (%)	99 (80)
ECOG PS ≥1, n (%)	115 (93)
Simplified MIPI score, n (%)	
Low risk (0-3)	48 (39)
Intermediate risk (4-5)	54 (44)
High risk (6-11)	21 (17)
Ann Arbor Stage IV disease, n (%)	93 (75)
Tumor bulk, n (%)	
≥5 cm	46 (37)
≥10 cm	10 (8)
Extranodal disease, n (%)	89 (72)
Bone marrow	63 (51)
Gastrointestinal	13 (10)
Lung	12 (10)
Blastoid/pleomorphic MCL, n (%)	26 (21)
Ki-67 proliferation index, n (%)	
<50%	64 (52)
≥50%	32 (26)
Missing	28 (22)

ECOG PS = Eastern Cooperative Oncology Group performance status; MCL = mantle cell lymphoma; MIPI = Mantle Cell Lymphoma International Prognostic Index.

Table 2. Patient disposition

Characteristic	N=124
Follow-up, median (range), mo	26 (0.3-35.1)
On acalabrutinib, n (%)	49 (40)
On study, n (%)	76 (61)
Discontinued acalabrutinib, n (%)	75 (60)
Disease progression	54 (44)
Adverse event	10 (8)
Initiation of subsequent anticancer therapy	6 (5)
Death	2 (2)
Lost to follow-up	1 (1)
Withdrawal of consent	1 (1)
Other (patient decision to stop treatment)	1 (1)
Relative dose intensity, median (range), %	99 (27.1-100.0)

Efficacy

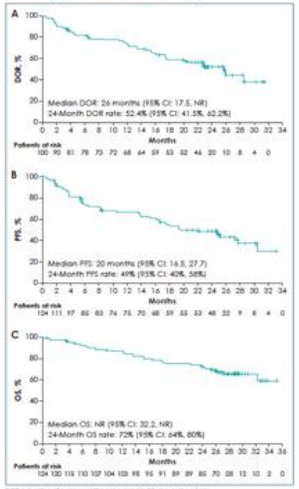
- Investigator-assessed overall response rate was 81%, with 43% achieving complete response (CR; **Table 3**)
  - The median time to best response was 2 months (range, 1.6 to 25.7 months)
- The median DOR was 26 months (**Figure 1A**), and the median PFS was 20 months (**Figure 1B**)
- The median OS was not reached (**Figure 1C**)
- Generally, prolonged DOR, PFS, and OS were observed in patients with low/intermediate (vs high) MIPI, classical (vs blastoid/pleomorphic) MCL, and Ki-67 index <50% (vs ≥50%)
- Of 89 patients (classic or aggressive variants) with Ki-67 data, the mean Ki-67 proliferation index for blastoid/pleomorphic patients (n=21) was 55.8% (SD: 22.3) vs 34.5% (SD: 22.6) in patients with classical MCL (n=68): 7 patients with Ki-67 data were in the other variant category
  - Patients with a Ki-67 index <50% (n=64): ORR, 89%; CR, 48%
  - Patients with a Ki-67 index ≥50% (n=32): ORR, 63%; CR, 41%

Table 3. Investigator-assessed response to acalabrutinib[a]

	N=124			
	Original Analysis (15-mo follow-up)[3]		Long-Term Analysis (26-mo follow-up)	
	n (%)	95% CI	n (%)	95% CI
ORR (CR + PR)	100 (81)	(73, 87)	100 (81)	(73, 87)
Best response				
CR	49 (40)	(31, 49)	53 (43)	(34, 52)
PR	51 (41)	(32, 50)	47 (38)	(29, 47)
SD	11 (9)	(5, 15)	11 (9)	(5, 15)
PD	10 (8)	(4, 14)	10 (8)	(4, 14)
Not evaluable	3 (2)	(1, 7)	3 (2)	(1, 7)

[a]Assessed using the 2014 Lugano Classification.[5]
CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Figure 1. Duration of response (A), progression-free survival (B), and overall survival (C)

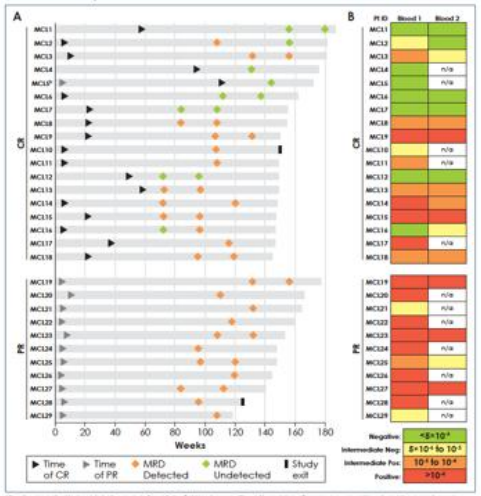


DOR = duration of response; NR = not reached; OS = overall survival; PFS = progression-free survival.

Minimal residual disease

- Of 124 patients, 29 (23%) had data available for MRD analysis. Undetectable MRD was achieved in 8 of these patients in at least 1 of the blood samples tested (28%; all are CRs; **Figure 2A**)
- Of 29 patients, 17 had a second blood sample collected and tested approximately 6 months after the first, including 5 of the 7 MRD-negative patients at first assessment after response (**Figure 2B**). Sustained MRD negativity (5×10^{-6}) was observed in 3 of those 5 patients; the fourth patient's MRD response deepened to MRD negative and the fifth patient showed a borderline switch to MRD positive
- Of 29 patients with MRD data, 2 are off study; therefore, correlation to PFS is unavailable at this time

Figure 2. Minimal residual disease in responding patients with evaluable samples[a]



[a]One line per patient is shown in both panels. In Panel B, the first blood sample (Blood 1) was taken after response was achieved, and the second sample (Blood 2) was taken approximately 6 months later, though the timing of both blood samples was variable.
[b]Response change from CR to PR.
CR = complete response; MCL = mantle cell lymphoma; MRD = minimal residual disease; n/a = not available; neg = negative; pos = positive; PR = partial response; pt = patient.

Safety

- Most AEs were Grade 1/2 (**Table 4**)
- Headache events were mostly Grade 1/2 and occurred primarily within the first month of treatment (**Table 5**)
- Most diarrhea events occurred in the first 6 months of treatment and were Grade 1/2 (**Table 5**)
- Serious AEs of any grade occurred in 54 patients (44%)
  - SAEs reported in ≥2 patients:
    - Pneumonia (n=6 [5%])
    - Anemia (n=5 [4%])
    - General physical health deterioration (n=3 [2%])
    - Sepsis (n=2 [2%])
    - Tumor lysis syndrome (n=2 [2%])
    - Vomiting (n=2 [2%])
    - Colitis (n=2 [2%])
    - Pyrexia (n=2 [2%])
- Events of clinical interest:
  - Cardiac AEs (n=16) occurred in 13 patients (10%): 4 events were Grade 3/4:
    - Grade 3 acute coronary syndrome (n=1, considered treatment-related by investigator)
    - Grade 3 acute myocardial infarction (n=1, not treatment-related)
    - Grade 4 cardiorespiratory arrest (n=1, not treatment-related)
    - Grade 3 coronary artery disease (n=1, not treatment-related)
  - There was 1 AE of atrial fibrillation (not treatment-related) in a patient with a history of paroxysmal atrial fibrillation
  - Four patients had hypertension events: 1 was Grade 3
  - Bleeding events occurred in 33% of patients, most frequently contusion (13%) and petechiae (9%); all but 3 were Grade 1/2 events
    - The three Grade 3 bleeding events were GI hemorrhage, hematuria, and hematoma
    - Any grade bleeding events decreased over time (**Table 5**)
  - Grade 3/4 infections occurred in 15% of patients, most commonly pneumonia (n=7 [6%])
    - There was 1 case of cytomegalovirus viremia and 1 case of *Pneumocystis jirovecii* pneumonia (both Grade 2)
    - There were no cases of *Aspergillus* infections
    - Frequency of any grade, Grade ≥3 and serious infections decreased over time (**Table 5**)

Table 4. AEs occurring in ≥10% of all patients (regardless of relationship to study therapy)

	N=124				
AE, n (%)[a]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Headache	47 (38)	30 (24)	15 (12)	2 (2)	0
Diarrhea	45 (36)	25 (20)	16 (13)	4 (3)	0
Fatigue	35 (28)	24 (19)	8 (6)	2 (2)	0
Cough	27 (22)	24 (19)	3 (2)	0	0
Myalgia	26 (21)	19 (15)	5 (4)	2 (2)	0
Nausea	24 (19)	12 (10)	10 (8)	2 (2)	0
Asthenia	21 (17)	14 (11)	5 (4)	2 (2)	0
Pyrexia	20 (16)	14 (11)	6 (5)	0	0
Constipation	19 (15)	15 (12)	4 (3)	0	0
Vomiting	18 (15)	9 (7)	6 (5)	3 (2)	0
Rash	17 (14)	9 (7)	6 (5)	2 (2)	0
Anemia	16 (13)	0	3 (2)	12 (10)	1 (1)
Confusion	16 (13)	14 (11)	2 (2)	0	0
Dizziness	15 (12)	12 (10)	3 (2)	0	0
Sinusitis	15 (12)	4 (3)	11 (9)	0	0
Dyspnea	13 (10)	8 (6)	2 (2)	2 (2)	1 (1)
Neutropenia	13 (10)	0	0	6 (5)	7 (6)
Upper respiratory tract infection	13 (10)	4 (3)	9 (7)	0	0

[a]No Grade 5 events were reported for these AEs.
AE = adverse event.

Table 5. Incidence of select AEs by 6-month intervals

AE, n (%)	1-6 mo (N=124)	7-12 mo (n=99)	13-18 mo (n=74)	19-24 mo (n=65)	>24 mo (n=55)
Headache, any grade	42 (34)[a]	2 (2)	0	0	0
Grade ≥3	2 (2)	0	0	0	0
SAE	1 (1)	0	0	0	0
Diarrhea, any grade	31 (25)	8 (8)	3 (4)	5 (8)	5 (9)
Grade ≥3	3 (2)	1 (1)	0	0	0
SAE	0	0	1 (1)	0	0
Infection, any grade	51 (41)	20 (20)	17 (23)	11 (17)	6 (11)
Grade ≥3	11 (9)	4 (4)	2 (3)	2 (3)	1 (2)
SAE	8 (6)	4 (4)	2 (3)	2 (3)	1 (2)
Bleeding events, any grade	31 (25)	14 (14)	5 (7)	4 (6)	0
Major hemorrhage[b]	1 (1)	0	0	2 (3)	0
Atrial fibrillation, any grade	0	0	0	0	0
Rash, any grade	10 (8)	5 (5)	2 (3)	1 (2)	0
Grade ≥3	1 (1)	0	1 (1)	1 (2)	0
SAE	0	0	0	0	0

[a]Thirty-eight patients (31%) experienced headache events in the first month of treatment, whereas 4 patients (4%) and 2 patients (3%) had headache events in the second and sixth months, respectively.
[b]Defined as Grade ≥3. SAE and/or any grade or seriousness of central nervous system hemorrhage.
AE = adverse event; SAE = serious adverse event.

- Ten patients (8%) discontinued due to AEs; all events occurred in 1 patient each
  - Aortic stenosis: B-cell lymphoma; blood blister and petechiae (both in 1 patient with Grade 3 acute coronary syndrome treated with clopidogrel); dyspnea and leukoklasis syndrome (both in 1 patient); noncardiac chest pain; pulmonary fibrosis; rash; thrombocytopenia; non-small cell lung cancer; pulmonary embolism
- There were 43 deaths (35%)
  - Twenty-nine patients (23%) died from progressive disease
  - Six patients (5%) died from AEs (none considered treatment related), which included bilateral pulmonary embolism, critical aortic stenosis, myelodysplastic syndrome, pneumonia, suicide, and non-small cell lung cancer
  - Two patients (2%) died of unknown causes ≥198 days after last dose
  - One patient (1%) died due to multiorgan failure 176 days after last dose
  - Five patients (4%) died of "other" causes (n=2 secondary acute AML both ≥277 days after last dose; n=1 intestinal obstruction; n=1 graft-versus-host disease 275 days after last dose; n=1 lung cancer 728 days after last dose)
- The primary cause of death was progressive disease

CONCLUSIONS

- Treatment with acalabrutinib monotherapy showed continued efficacy with durable responses in patients with R/R MCL after long-term follow-up
  - High response rates, including in refractory patients
  - Median DOR of 26 months
  - Median PFS of 20 months
  - Median OS has not yet been reached
- No new safety signals were observed in this long-term follow-up, including no new onset of atrial fibrillation
- A subset of CR patients (8/18 evaluable) achieved profound undetectable MRD beyond 5×10^{-6} level of detection with acalabrutinib monotherapy

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Safety and Efficacy of Acalabrutinib Plus Bendamustine and Rituximab in Patients With Treatment-Naive or Relapsed/Refractory Mantle Cell Lymphoma

Abstract 4144

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INTRODUCTION

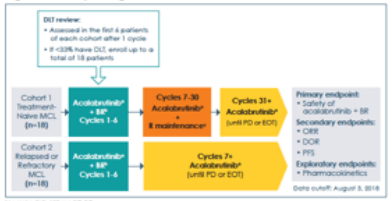
- Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma that remains largely incurable with conventional therapies; the combination of bendamustine and rituximab (BR) is standard first-line therapy[1]
- Acalabrutinib is a potent, highly selective, covalent Bruton tyrosine kinase (BTK) inhibitor with minimal off-target activity[2]
- Acalabrutinib was approved by the US Food and Drug Administration in October 2017 for the treatment of adult patients with MCL who have received at least 1 prior therapy
- This ongoing, multicenter, open-label Phase 1b study assessed the safety and efficacy of acalabrutinib + BR (ABR) in patients with treatment-naive (TN) or relapsed/refractory (R/R) MCL

METHODS

Study Design

- This is a multicenter, open-label Phase 1b study (NCT02717624; **Figure 1**)
- Patients were enrolled from May 2016 through March 2017 at 15 sites across 3 countries

Figure 1. Study design



*Acalabrutinib 100 mg BID PO.
#R: 375 mg/m² IV on Days 1 and 2 and 2 375 mg/m² IV on Day 1 in each 28-day cycle.
‡R: 375 mg/m² IV on Day 1 of every other (28-day) cycle for up to 12 doses starting on Cycle 8 for patients who achieve PR or CR.
BR = combination of bendamustine and rituximab; CR, complete response; DLT = dose-limiting toxicity; DOR = duration of response; EOT = end of treatment; IV = intravenous; MCL = mantle cell lymphoma; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; R = rituximab.

Patients

- Key inclusion criteria
  - Confirmed MCL with translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1 that requires treatment
    - R/R cohort: Disease that relapsed after or was refractory to ≥1 prior therapy; patients who discontinued prior MCL therapy for intolerance were also eligible
  - Eastern Cooperative Oncology Group performance status ≤2
- Key exclusion criteria
  - Prior BTK inhibitor or BCL-2 inhibitor therapy
  - Significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any NYHA Class III-IV cardiac disease, or corrected QT interval >480 milliseconds)
    - Patients with controlled, asymptomatic atrial fibrillation during screening were not excluded
  - Required systemic anticoagulation with warfarin or equivalent vitamin K antagonists

Assessments

- The primary endpoint was safety of acalabrutinib in combination with BR; adverse events (AEs) were graded using the NCI CTCAE v4.03
- Secondary endpoints were investigator-assessed efficacy of acalabrutinib in combination with BR
  - Overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS) were assessed using Lugano criteria[3]
  - Disease was assessed on Day 1 of Cycles 3, 5, and 8, then every 3 to 4 cycles thereafter
- Exploratory endpoints were pharmacokinetics (PK) of acalabrutinib and bendamustine
  - The concentrations of acalabrutinib (on Day 8 of Cycle 1 and Day 2 of Cycle 2) and bendamustine (Day 2 of Cycles 1 and 2) were measured in plasma
    - The first acalabrutinib dose was administered on the evening of Day 2 of Cycle 1
  - PK parameters were derived from concentration-time profiles of acalabrutinib and bendamustine, respectively
- Safety and efficacy analyses were performed on patients who received ≥1 dose of study drug

RESULTS

Patients

- A total of 38 patients were enrolled (**Table 1**)
- Most patients in the R/R cohort had received prior rituximab-containing therapy (**Table 2**)
- Most patients completed 6 cycles of acalabrutinib + BR (**Table 3**)

Table 1. Baseline demographic and disease characteristics

	TN (n=18)	R/R (n=20)
Age, median (min, max), y	66 (48, 86)	64.5 (47, 82)
≥65 y, n (%)	11 (61)	10 (50)
Men, n (%)	11 (61)	13 (65)
ECOG PS (0 or 1), n (%)	18 (100)	19[a] (95)
Bulky disease, n (%)		
<5 cm	14 (78)	14 (70)
5 to <10 cm	3 (17)	4 (20)
≥10 cm	1 (6)	2 (10)
Ann Arbor Stage IV, n (%)	16 (89)	19 (95)
Simplified MIPI score,[b] n (%)		
Low risk	7 (39)	4 (20)
Intermediate risk	8 (44)	12 (60)
High risk	2 (11)	3 (15)
Time from initial diagnosis to first dose, median (min, max), mo	2 (0.6, 50.5)	62 (8.1, 99.4)

[a]One patient had ECOG PS of 2.
[b]Defined using age, ECOG PS, lactate dehydrogenase level, and white cell count at baseline; 1 patient in each cohort had missing data.
ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = MCL International Prognostic Index; R/R = relapsed/refractory; TN, = treatment naïve.

Table 2. Prior therapies

	R/R (n=20)
No. of prior therapies, median (min, max)	2 (1, 4)
Refractory (< PR) to most recent prior therapy	9 (45)
Prior therapy, n (%)	
R-COP, R-CHOP, R-CHOP/R-ICE, R-CHOP/R-DHAP	14 (70)
Bendamustine (or chlorambucil) + rituximab	6 (30)
Cytarabine ± rituximab	4 (20)
DHAP or ESHAP	2 (10)
R-hyper-CVAD ± bortezomib	2 (10)
ASCT[a]	2 (10)
Rituximab (single agent)	2 (10)
Lenalidomide	1 (5)
Enzalutamide	1 (5)
ONC201	1 (5)

[a]A conditioning regimen preceded ASCT.
ASCT = autologous stem cell transplantation; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone; hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine; DHAP = dexamethasone, cytarabine, cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; ICE = ifosfamide, carboplatin, etoposide; PR = partial response; R = rituximab.

Table 3. Patient disposition

Patients, n (%)	TN (n=18)	R/R (n=20)
Time on study, median (min, max), mo	20.6 (0.6, 26.1)	16.9 (1.2, 26.6)
Completed 6 cycles of BR	14 (78)	10 (50)
Completed 6 cycles of acalabrutinib + BR	13 (72)	10 (50)
Discontinued all 3 study drugs	8 (44)	11 (55)
Continuing acalabrutinib	10 (56)	9 (45)
Discontinued from study	7 (39)	8 (40)
Death	3 (17)[a]	3 (15)[b]
AE/SAE[c]	2 (11)	1 (5)
Withdrawal of consent	0	1 (5)
Withdrawal by primary investigator	1 (6)	1 (5)
Disease progression	0	2 (10)
Other[d]	1 (6)	0

[a]Grade 5 pneumonitis (investigator assessed as related to acalabrutinib; 56 days after last dose) and unsuccessfulness cause and unknown cause (n=1 each).
[b]Grade 5 cerebrospinal meningitis (investigator assessed as unrelated to acalabrutinib; 123 days after last dose; n=1), unsuccessfulness cause (n=1), and progressive disease (n=1).
[c]Only events up to 30 days after the last dose of study drug were counted.
[d]Consent to survival follow-up only.
AE = adverse event; BR = combination of bendamustine and rituximab; R/R = relapsed/refractory; SAE = serious AE; TN = treatment naïve.

Safety Overview

- Across both cohorts, no DLTs were observed
- AEs occuring in ≥20% of patients overall are shown in **Table 4**
- Grade 3 or 4 AEs in ≥2 patients (≥5%) overall are shown in **Table 5**
- Eighteen patients (47%) had ≥1 serious AEs (SAEs)
  - SAEs in ≥2 patients
    - TN cohort (n=18): pneumonia (Grade 3, n=2 [11%]) and pyrexia (Grade 1, n=2 [11%])
    - R/R cohort (n=20): pneumonia (Grade 1, n=1 [5%]; Grade 3, n=2 [10%])
  - SAEs were Grade 3 in 12 (32%) and Grade 4 in 2 patients (5%)
- One patient (3%) had a Grade 5 AE of pneumonitis

Table 4. AEs in ≥20% of patients overall

	TN (n=18)			RR (n=20)			Total (N=38)		
Patients With AE, n (%)	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Preferred term									
Nausea	14 (78)	0	0	8 (40)	0	0	22 (58)	0	0
Fatigue	13 (72)	0	0	7 (35)	1 (5)	0	20 (53)	1 (3)	0
Neutropenia	7 (39)	4 (22)	3 (17)	11 (55)	5 (25)	5 (25)	18 (47)	9 (24)	8 (21)
Diarrhea	8 (44)	0	0	8 (40)	2 (10)	0	16 (42)	2 (5)	0
Vomiting	10 (56)	0	0	6 (30)	0	0	16 (42)	0	0
Cough	8 (44)	0	0	7 (35)	0	0	15 (39)	0	0
Upper respiratory tract infection	8 (44)	0	0	7 (35)	0	0	15 (39)	0	0
Constipation	9 (50)	0	0	5 (25)	0	0	14 (37)	0	0
Headache	9 (50)	0	0	4 (20)	0	0	13 (34)	0	0
Dizziness	7 (39)	0	0	4 (20)	1 (5)	0	11 (29)	1 (3)	0
Infusion-related reaction	4 (22)	0	0	6 (30)	1 (5)	0	10 (26)	1 (3)	0
Pyrexia	6 (33)	0	0	3 (15)	0	0	9 (24)	0	0

AE = adverse event; R/R = relapsed/refractory; TN = treatment naïve.

Table 5. Grade 3 or 4 AEs in ≥2 patients (≥5%) overall

	TN (n=18)		RR (n=20)		Total (N=38)	
Patients With AE, n (%)	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Preferred term						
Neutropenia	4 (22)	3 (17)	5 (25)	5 (25)	9 (24)	8 (21)
Decreased neutrophil count	0	1 (6)	2 (10)	1 (5)	2 (5)	2 (5)
Pneumonia	2 (11)	0	2 (10)	0	4 (11)	0
Thrombocytopenia	1 (6)	0	1 (5)	1 (5)	2 (5)	1 (3)
Abdominal pain	1 (6)	0	1 (5)	0	2 (5)	0
Acute kidney injury	1 (6)	0	1 (5)	0	2 (5)	0
Anemia	1 (6)	0	1 (5)	0	2 (5)	0
Decreased white blood cell count	0	0	2 (10)	0	2 (5)	0
Diarrhea	0	0	2 (10)	0	2 (5)	0
Hypertension	1 (6)	0	1 (5)	0	2 (5)	0
Hyperuricemia	0	1 (6)	1 (5)	0	1 (3)	1 (3)
Hypotension	1 (6)	0	1 (5)	0	2 (5)	0
Leukopenia	0	0	1 (5)	1 (5)	1 (3)	1 (3)

AE = adverse event; R/R = relapsed/refractory; TN = treatment naïve.

Additional Safety Results

- No patients had atrial fibrillation, cytomegalovirus infection, pneumocystis jiroveci pneumonia, or tumor lysis syndrome during the study
- Headache events occurred in 34% of patients and were all Grade 1 or 2 (**Table 4**)
- Grade 3 rash (includes all AE terms containing "rash") was observed in 2 patients (5%; both in the TN cohort); no rash events led to discontinuation of study treatment
- Major hemorrhage
  - TN cohort (n=1; 6%): Grade 4 pulmonary alveolar hemorrhage (investigator assessed as related to acalabrutinib) leading to discontinuation of study treatment (acalabrutinib + BR)
  - R/R cohort (n=3; 15%): all were Grade 3 events and considered unrelated to acalabrutinib by the investigator – subdural hematoma (after a traumatic fall; acalabrutinib was discontinued); large intestinal ulcer hemorrhage (on study Day 2; acalabrutinib dose was reduced); gastrointestinal hemorrhage (duodenal tumor found on endoscopy)

Efficacy

- ORRs were high in both TN and R/R cohorts (**Table 6**)
  - Most patients had a significant reduction in tumor burden (**Figure 2**)
- In both cohorts, median DOR and median PFS (**Figure 3**) were not reached

Table 6. Best response[a] to acalabrutinib + BR

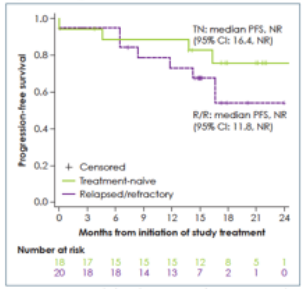
Best Response, n (%)	TN (n=18)	R/R (n=20)
ORR (complete response + partial response), n (%)	17 (94) 95% CI: 73, 100	17 (85) 95% CI: 62, 97
Complete response	13 (72)	13 (65)
Partial response	4 (22)	4 (20)
Stable disease	0	1 (5)
Progressive disease	0	0
Not evaluable[b]	1 (6)	2 (10)
Time to initial response, median (min, max), mo	1.9 (1.6, 2.8)	1.8 (1.6, 2.3)
Time to best response, median (min, max), mo	1.9 (1.6, 10.1)	2.0 (1.6, 14.8)

[a]Assessed using Lugano criteria.[3]
[b]Includes patients without adequate post-baseline response assessment.
BR = combination of bendamustine and rituximab; ORR = overall response rate; R/R = relapsed/refractory; TN = treatment naïve.

Figure 2. Maximum change from baseline in SPD[a]

[a]Three patients were not evaluable.
[b]Patient had bone marrow involvement at screening and achieved complete metabolic response by PET-CT after study treatment; however, patient refused postTreatment bone marrow biopsy to confirm CR.
CR = complete response; PET-CT = positron-emission tomography-computed tomography; SPD = sum of product diameters.

Figure 3. Progression-free survival by cohort

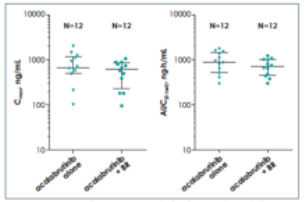


NR = not reached; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment naïve.

Pharmacokinetics

- Acalabrutinib exposure at steady state was similar with or without BR (**Figure 4**)
- Bendamustine exposure was similar when BR was administered with or without acalabrutinib (data not shown)

Figure 4. Steady-state acalabrutinib exposure



AUC = area under the curve from 0 to last; BR, combination of bendamustine and rituximab; C_{max}, maximum plasma concentration.

CONCLUSIONS

- Acalabrutinib in combination with BR showed an acceptable safety profile, consistent with expected safety profiles for acalabrutinib and BR
- ORR was 94% in TN and 85% in R/R patients, with high CR rates of 72% and 65%, respectively; median PFS was not reached in either cohort after a median of 21 and 17 months on study
- Acalabrutinib exposure at steady state was similar with or without BR
- The high response rates in both TN and R/R MCL further support an ongoing Phase 3 randomized, double-blind, placebo-controlled study of acalabrutinib + BR versus BR in TN MCL (NCT02972840)
- This study (LY-106) is currently enrolling patients with TN MCL into a newly added cohort evaluating the safety and efficacy of acalabrutinib in combination with venetoclax and rituximab (AVR)

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TC: equity ownership: AstraZeneca; employment: Acerta Pharma
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P4189 Results of a phase 3 randomized multicenter study comparing pixantrone + rituximab with gemcitabine + rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation

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CONCLUSIONS

- **This was the first study to investigate the efficacy of pixantrone + rituximab (PIX+R) versus gemcitabine + rituximab (GEM+R) as second-line or later therapy in patients with relapsed aggressive B-cell NHL non-eligible for SCT.**
- **PIX+R was associated with a numerically higher ORR and CR rate compared with GEM+R, but this did not translate into prolonged PFS or OS in the PIX+R group.**
- **Although the study did not meet its primary endpoint, the PFS observed in the two treatment groups was longer than previously reported values in similar patient populations.**

BACKGROUND

- There are limited treatment options for patients with relapsed aggressive B-cell non-Hodgkin lymphoma (NHL),[1] especially for those who are not candidates for high-dose therapy and stem cell transplantation (SCT).
- Reasons for ineligibility for intensive treatment include advanced age and overall condition, comorbidities, failure to respond to standard salvage treatment regimens, progressive disease following previous SCT, and presence of other adverse risk factors.[2]
- Pixantrone is an aza-anthracenedione agent derived from anthracyclines with proven reduced potential of cardiotoxicity and maintained antitumor activity.
- A previous phase 3 trial compared pixantrone with comparator chemotherapy (vinorelbine, oxaliplatin, ifosfamide, etoposide, gemcitabine, or mitoxantrone) in patients with aggressive NHL who had relapsed or were refractory to ≥2 previous lines of chemotherapy, and showed a significantly higher complete response (CR) rate and longer progression-free survival (PFS) in the pixantrone group.[3,4]
- This phase 3 study (PIX306) evaluated the efficacy of a combination of PIX+R versus GEM+R in the treatment of patients with relapsed aggressive B-cell NHL who progressed after ≥1 rituximab-containing multi-agent regimen and were not eligible for SCT.
- The primary results of the core analysis of the PIX306 trial are presented here.

RESULTS

Patients

- A total of 312 patients were randomized to treatment; the baseline characteristics of patients were well-balanced between the two treatment groups **(Table 1)**.

Table 1. Baseline characteristics of patients included in the study.

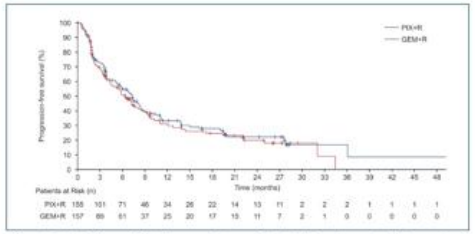
	PIX-R N=155	GEM-R N=157	Total N=312
Median age, years (range)	73.0 (30–91)	73.0 (26–90)	73.0 (30–91)
≥65 years	119 (76.8)	119 (75.8)	238 (76.3)
Male	69 (44.5)	67 (42.7)	136 (43.6)
Investigator-assessed histology			
DLBCL	122 (78.7)	120 (76.4)	242 (77.6)
DLBCL transformed from indolent lymphoma	22 (14.2)	21 (13.4)	43 (13.8)
FL Grade 3	11 (7.1)	16 (10.2)	27 (8.7)
Time since initial diagnosis (DLBCL/FL Grade 3), months	22.0	23.5	22.5
Ann Arbor stage of NHL			
I	11 (7.1)	9 (5.7)	20 (6.4)
II	32 (20.6)	30 (19.1)	62 (19.9)
III	38 (24.5)	37 (23.6)	75 (24.0)
IV	74 (47.7)	81 (51.6)	155 (49.7)
No. of extranodal sites			
0	57 (36.8)	60 (38.2)	117 (37.5)
1	49 (31.6)	38 (24.2)	87 (27.9)
>1	49 (31.6)	59 (37.6)	108 (34.6)
No. of prior lines of therapy for DLBCL or FL Grade 3			
0	9 (5.8)	5 (3.2)	14 (4.5)
1	93 (60.0)	100 (63.7)	193 (61.9)
2	35 (22.6)	33 (21.0)	68 (21.8)
3	18 (11.6)	18 (11.5)	36 (11.5)
International Prognostic Index (IPI) score			
0	2 (1.3)	0	2 (0.6)
1	24 (15.5)	17 (10.8)	41 (13.1)
2	47 (29.9)	53 (33.8)	100 (33.0)
≥3	82 (52.9)	86 (54.8)	168 (53.8)
Time between initiation of first-line therapy to first relapse			
<1 year	56 (36.1)	58 (36.9)	114 (36.5)
≥1 year	97 (62.6)	99 (63.1)	196 (62.8)
Prior stem cell transplantation			
Yes	17 (11.0)	16 (10.2)	33 (10.6)
No	138 (89.0)	141 (89.8)	279 (89.4)

Values presented as n (%) unless otherwise stated.
DLBCL, de novo diffuse large B-cell lymphoma; FL, follicular lymphoma.

Efficacy

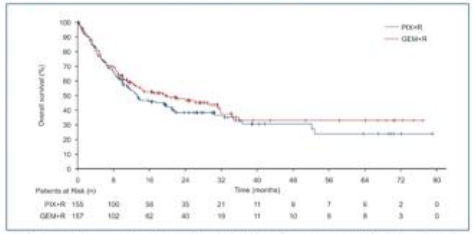
- The primary efficacy endpoint of the study was not met (P=0.28; HR=0.85; 95% CI: 0.64, 1.14; **Figure 1**). A total of 197 PFS events were reported (102 with PIX+R vs 95 with GEM+R).
- The median PFS (95% CI) was 7.3 months (5.2, 8.4) in the PIX+R group and 6.3 months (4.4, 8.1) in the GEM+R group.

Figure 1. Progression-free survival (PFS) in the intention-to-treat population during the study (N=312).



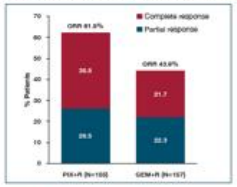
- According to the hierarchical testing procedure and given that the primary endpoint was not met, the secondary efficacy endpoints were not tested.
- The median OS (95% CI) in the PIX+R and the GEM+R groups was 13.3 (10.1, 19.8) versus 19.8 (12.4, 31.9) months, respectively (HR=1.13; 95% CI: 0.83, 1.53; **Figure 2**).

Figure 2. Overall survival (OS) in the intention-to-treat population during the study (N=312).



- ORR was 61.9% versus 43.9% in the PIX+R and GEM+R groups, respectively **(Figure 3)**, and CR was observed in 35.5% of patients in the PIX+R group compared with 21.7% in the GEM+R group.

Figure 3. Objective response rate (ORR) in the intention-to-treat population (N=312).



Safety

- Both treatment regimens were reasonably tolerated, and no new safety signals were reported **(Table 2)**.

Table 2. Summary of safety.

	PIX+R N=153	GEM+R N=157
Commonly reported AEs		
Neutropenia	106 (69.3)	88 (59.1)
Fatigue	45 (29.4)	35 (23.5)
Anemia	42 (27.5)	75 (50.3)
Nausea	38 (24.8)	24 (16.1)
Constipation	36 (23.5)	20 (13.4)
Alopecia	29 (19.0)	2 (1.3)
Anorexia	28 (18.3)	16 (10.7)
Thrombocytopenia	25 (16.3)	98 (65.8)
Diarrhea	24 (15.7)	21 (14.1)
Pyrexia	24 (15.7)	38 (25.5)
Grade 3/4 TEAEs		
Neutropenia	97 (63.4)	83 (55.7)
Anemia	26 (17.0)	56 (37.6)
Thrombocytopenia	17 (11.1)	55 (36.9)
Leukopenia	12 (7.8)	15 (10.1)
Lymphopenia	9 (5.9)	3 (2.0)
Infectious and infestations	24 (15.7)	30 (20.1)
Gastrointestinal disorders	17 (11.1)	9 (6.0)
Cardiac safety		
Patients with ≥1 Grade 3/4 cardiac TEAE	28 (18.3)	13 (8.1)
Atrial fibrillation	4 (2.6)	3 (2.0)
Cardiac failure	3 (2.0)	0
Cardiac failure congestive	1 (0.7)	2 (1.3)
Ejection fraction decreased	4 (2.6)	1 (0.7)
Deaths		
Deaths during the treatment period	12 (7.8)	16 (10.2)
Deaths due to AE	3 (2.0)	7 (4.7)
Deaths due to disease progression	7 (4.6)	7 (4.7)
Deaths due to other reasons	2 (1.3)*	2 (1.3)**

Safety is reported in all randomized patients who received at least one administration of the study drug. All values are presented as n (%). *Viral pneumonia and asthenia. **Acute renal failure and sepsis. AE, adverse event; GEM, gemcitabine; PIX, pixantrone; R, rituximab; TEAE, treatment-emergent adverse event.

METHODS

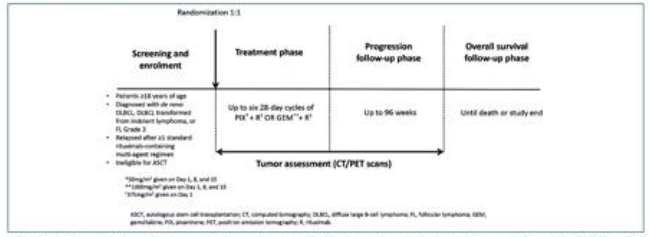
Patients

- This multicenter, randomized, open-label phase 3 study enrolled patients who were:
  - ≥18 years of age;
  - Diagnosed with de novo diffuse large B-cell lymphoma (DLBCL), DLBCL transformed from indolent lymphoma, or follicular lymphoma (FL) Grade 3 and received:
    - de novo DLBCL: 1–3 prior regimens for DLBCL
    - DLBCL transformed from indolent lymphoma: 1–4 prior regimens for NHL of any type
    - FL Grade 3: 1–3 prior regimens for FL of any grade;
  - Relapsed after ≥1 standard rituximab-containing multi-agent regimen;
  - Ineligible for autologous SCT for the following reasons: relapse after previous SCT, no response to a standard salvage regimen, unable to mobilize an adequate number of stem cells for SCT, unsuitable/unwilling to undergo SCT for any other reason.
- Patients with primary refractory de novo DLBCL and FL Grade 3 (defined as progression within 12 weeks of the last cycle of the first-line treatment regimen) were excluded; patients with DLBCL transformed from indolent lymphoma were required to have a complete or partial response to NHL therapy lasting ≥12 weeks.
- All patients were required to be free of any major cardiac pathology for <6 months before enrolment including New York Heart Association class III or IV heart disease and myocardial infarction.
  - Patients were required to have a left ventricular ejection fraction (LVEF) of ≥45% and serum troponin T in the normal range.
  - Patients previously treated with doxorubicin or equivalent were required to have a cumulative dose of <450 mg/m² at enrolment.
- Patients were selected by the investigator and their histological diagnosis was reviewed and confirmed by an independent Central Pathology Review Committee after randomization.

Randomization and treatment

- Patients were randomized 1:1 using an interactive web response system to receive PIX 50 mg/m² or GEM 1000 mg/m² on Days 1, 8, and 15 of a 28-day cycle, each in combination with R 375 mg/m² on Day 1, for up to six cycles **(Figure 4)**.
- Patients were followed for up to 96 weeks for disease progression.

Figure 4. Study design.



- Randomization was balanced and non-adaptive, and was stratified by the number of prior lines of therapy (0–2 vs ≥3) for DLBCL or FL Grade 3, the International Prognostic Index (IPI) score (0–2 vs ≥3), and the time until first relapse after initiation of first-line therapy for DLBCL or FL Grade 3 (<1 year vs ≥1 year).

Endpoints

- The primary endpoint was Independent Radiology Committee-assessed PFS, based on the modified International Working Group 2007 revised response criteria.[5]
- Secondary endpoints included:
  - Overall survival (OS)
  - Overall response rate (ORR)
  - CR rate
  - Safety.

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