Highlights from ASH 2021: Practice-changing developments

Tuesday, March 1, 2022 | 17:00–18:30 (CET)

Welcome and introductions

Chair: Professor Véronique Leblond

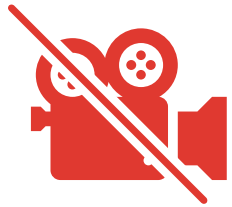
Disclosures

- **Speakers bureau:** Roche, Gilead, Janssen, AbbVie, BeiGene, GSK
- **Board:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, AstraZeneca, AbbVie
- **Honoraria:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, Lilly, Amgen, AstraZeneca, BeiGene

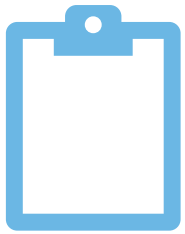
Disclaimers

- The information contained herein is intended for healthcare professionals only and is given for educational purposes only. This document is not intended for professional counseling or advice.
- The views expressed in the presentations are those of the speakers and may not necessarily reflect the opinion of BeiGene. BeiGene does not guarantee the accuracy or reliability of the information provided herein and expressly disclaims liability for any errors or omissions in this information.
- Prescribing information (PI) may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local materials such as the PI and/or the summary of product characteristics (SPC).
- Zanubrutinib is not approved for the treatment of CLL/SLL and is not approved for MCL in Europe.

Housekeeping



Please note that personal recording of this meeting is not permitted
(a recording will be available to watch soon after the meeting)



A post-meeting survey will be shared at the end of the webinar;
we would greatly appreciate your feedback

Introducing the speakers

Véronique Leblond
Pitié-Salpêtrière Hospital and Sorbonne University, France

Christian Buske
University Hospital of Ulm, Germany

Paolo Ghia
Vita-Salute San Raffaele University and IRCCS San Raffaele Hospital, Italy

Wojciech Jurczak
Maria Skłodowska-Curie National Research Institute of Oncology, Poland

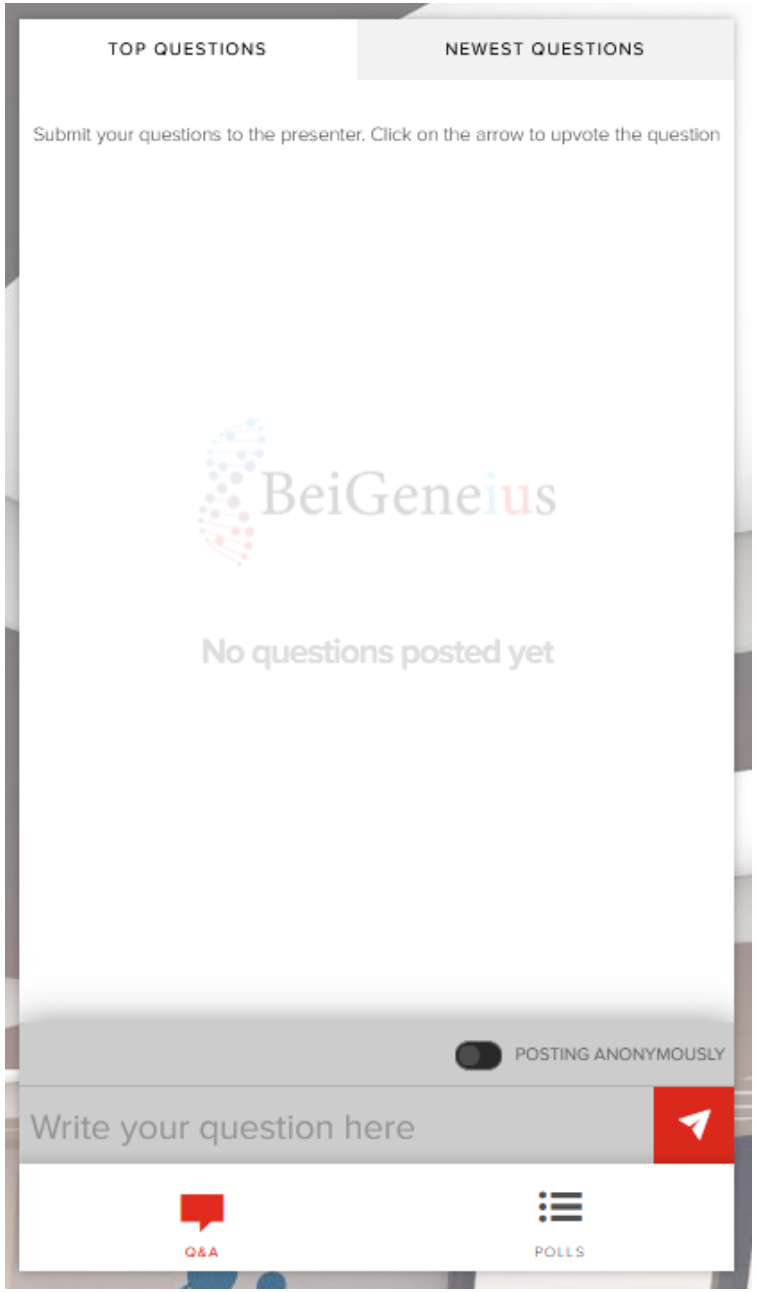
Agenda

17:00	**Welcome and introductions**	Véronique Leblond
17:05	**ASH 2021 highlights: Mantle cell lymphoma**	Christian Buske
17:20	**ASH 2021 highlights: Aggressive lymphomas**	Wojciech Jurczak
17:35	**ASH 2021 highlights: CLL/SLL**	Paolo Ghia
17:50	**ASH 2021 highlights: Indolent lymphomas**	Véronique Leblond
18:05	**Discussion and audience Q&A**	**Panel:** All faculty
18:25	**Summary and meeting close**	Véronique Leblond

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

Audience questions

- Please exit full-screen view and enter your question in the submission box for the panel to answer during the Q&A session
  - You can vote for the questions you would most like the panel to answer



63rd ASH Annual Meeting

- December 11–14, 2021
- Live at the Georgia World Congress Center (Atlanta, GA) – and virtually

ASH 2021 highlights: Mantle cell lymphoma

Professor Christian Buske
University Hospital of Ulm, Germany

February 2022 | 0222-BGB-3111-MRC-063

Disclosures

- **Honoraria:** Roche, Janssen, BeiGene, Celltrion, Pfizer, AbbVie, Novartis, Gilead
- **Research funding:** Roche, Janssen, Celltrion, AbbVie, Bayer, MSD

MCL

Rituximab maintenance – still standard?

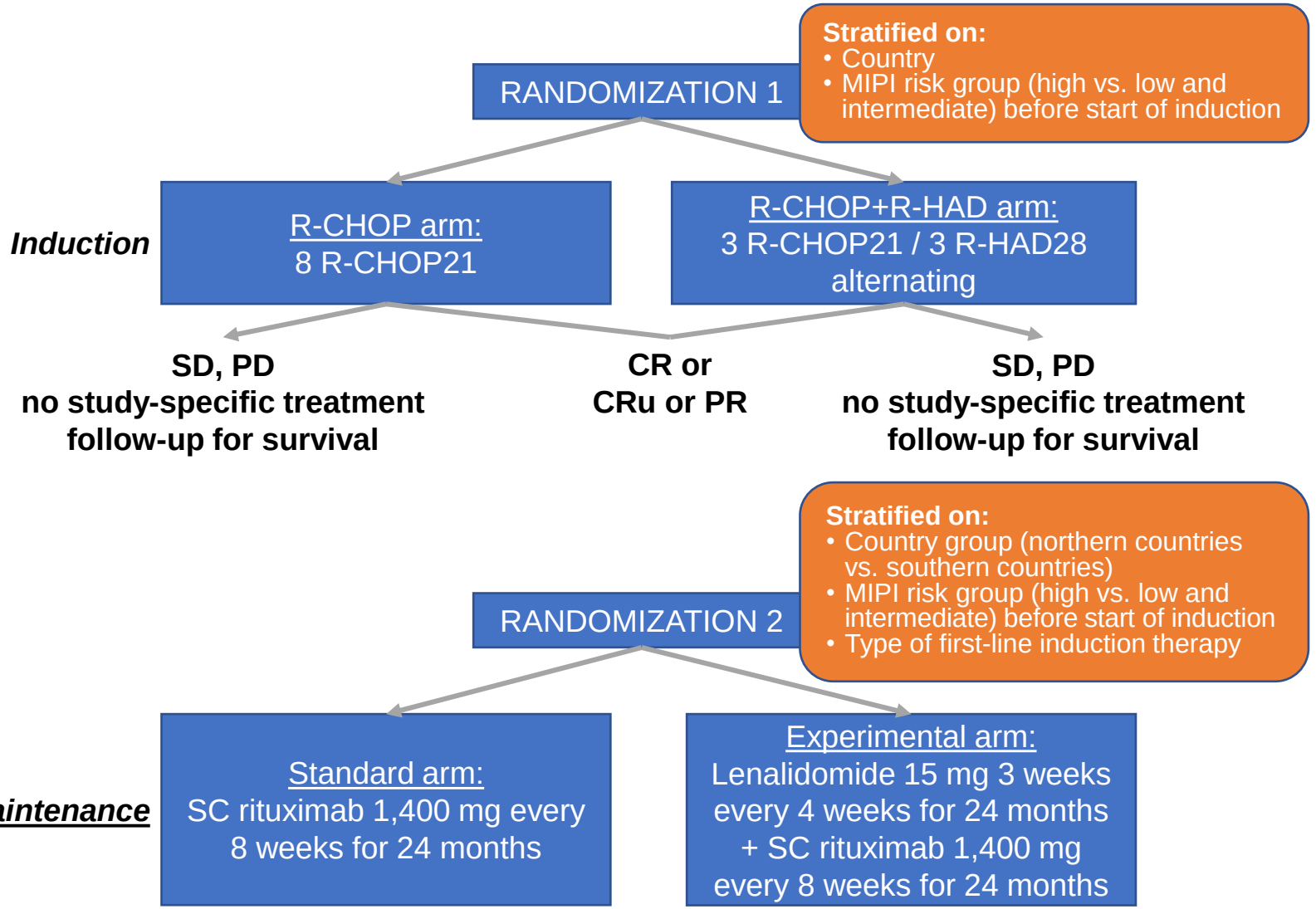
R2…?

MCL, mantle cell lymphoma; R2, rituximab + lenalidomide.

Rituximab + lenalidomide (R2) vs. rituximab (R) maintenance

MCL R2 Elderly clinical trial

- MCL according to WHO classification, with cyclin D1 overexpression or t(11;14)(q13;q32)
- ≥60 years of age and ineligible for autologous transplant
- Ann Arbor Stage II–IV
- Previously untreated
- ECOG PS ≤2



CR, complete response; CRu, unconfirmed complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HAD, rituximab, cytarabine, and dexamethasone; SC, subcutaneous; SD, stable disease; WHO, World Health Organization. Ribrag V *et al*. Abstract 379. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R2 vs. R maintenance

Patient characteristics

Patient characteristics at inclusion

	Induction arm		Induction ITT set (n=620)
	R-CHOP (n=312)	R-CHOP/ R-HAD (n=308)	
Age, years			
Median	71.0	71.0	71.0
Sex, n (%)			
Male	221 (70.8)	222 (72.1)	443 (71.5)
Ann Arbor stage, n (%)			
III	15 (4.8)	16 (5.2)	31 (5.0)
IV	284 (91.3)	275 (89.3)	559 (90.3)
LDH >upper limit, n (%)			
Yes	127 (41.2)	131 (43.0)	258 (42.1)
MIPI risk group at baseline, n (%)			
Low risk (<5.7)	21 (6.8)	18 (5.9)	39 (6.4)
Intermediate risk (≥5.7–<6.2)	137 (44.6)	134 (43.9)	271 (44.3)
High risk (≥6.2)	149 (48.5)	153 (50.2)	302 (49.3)

Patient characteristics at maintenance

	Maintenance actual arm		Maintenance mITT set (n=447)
	R (n=227)	R2 (n=220)	
Age, years			
Median	71.0	71.0	71.0
Sex, n (%)			
Male	161 (70.9)	154 (70.0)	315 (70.5)
Ann Arbor stage, n (%)			
III	12 (5.3)	13 (5.9)	25 (5.6)
IV	201 (88.5)	199 (90.5)	400 (89.5)
LDH >upper limit, n (%)	89 (39.6)	79 (36.4)	168 (38.0)
Complete response (CR/CRu), n (%)	110 (49.1)	93 (42.9)	203 (46.0)
Overall response, n (%)	223 (99.6)	216 (99.5)	439 (99.5)

CR, complete response; CRu, unconfirmed complete response; ITT, intention-to-treat; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; mITT, modified intention-to-treat; R, rituximab; R2, rituximab + lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HAD, rituximab, cytarabine, and dexamethasone.

Ribrag V *et al*. Abstract 379. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R2 vs. R maintenance
Safety

AEs during maintenance phase

AEs	R (N=250)	R2 (N=238)
Blood and lymphatic system disorders	68 (117 events)	140 (471 events)
Neutropenia, Grade ≥3	47 (64 events)	119 (315 events)
Anemia, Grade ≥3	1 (1 event)	7 (7 events)
Infections and infestations	6 (7 events)	26 (33 events)
SPM	26 (32 events)	32 (59 events)

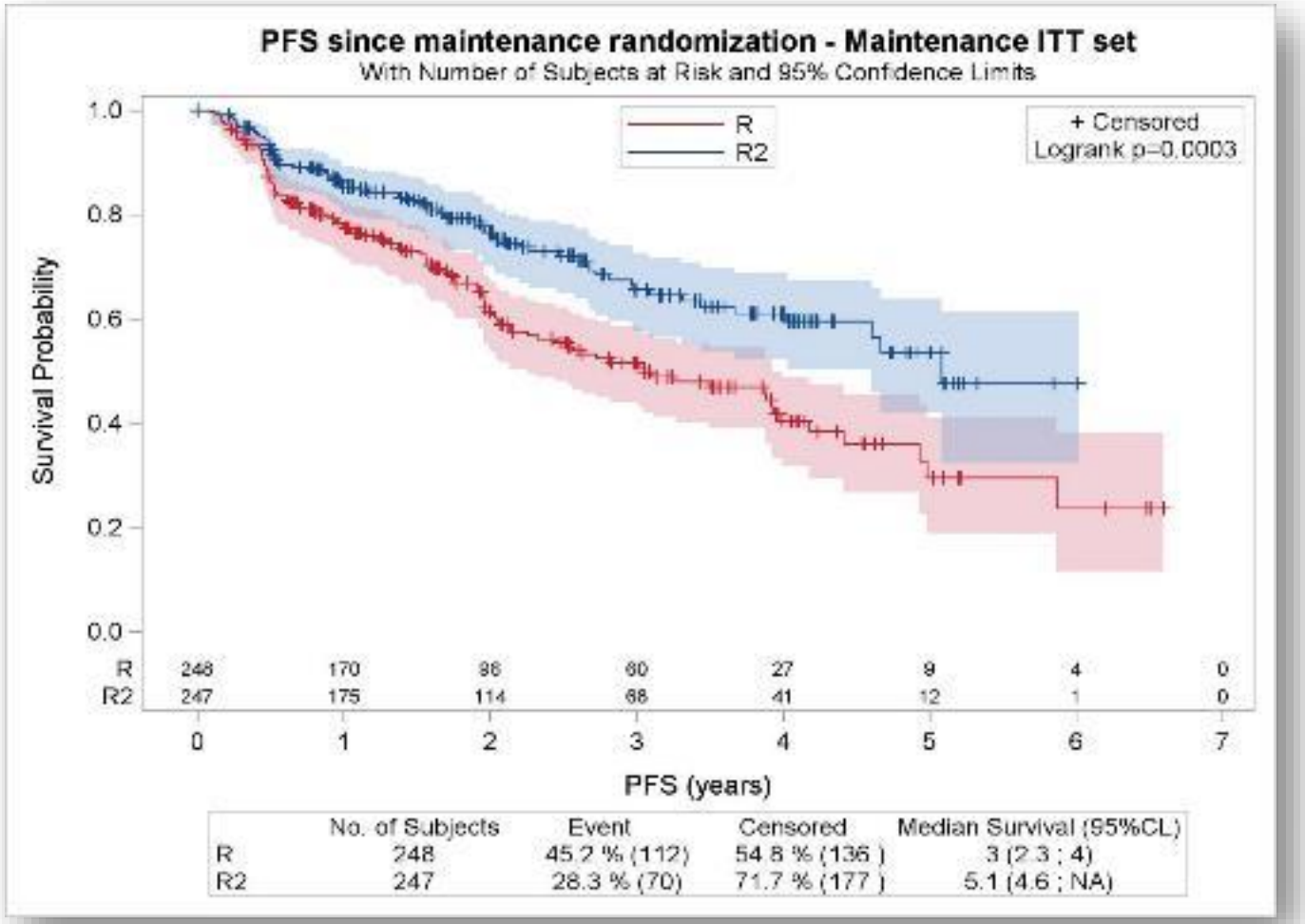
Deaths during maintenance phase

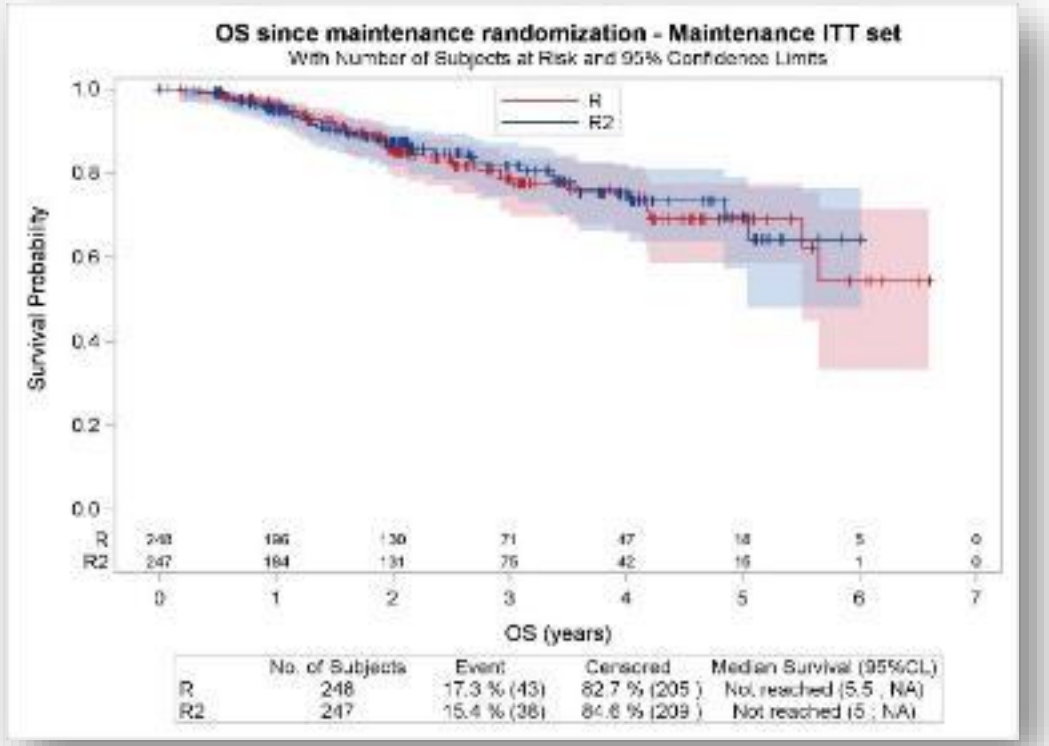
Cause of death	R (N=250)	R2 (N=238)
Lymphoma	31	29
Toxicity of study treatment	0	1
Other	3	1
Total	**47**	**43**

AE, adverse event; R, rituximab; R2, rituximab + lenalidomide; SPM, second primary malignancy.
Ribrag V *et al*. Abstract 379. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R2 vs. R maintenance

Survival analysis





ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; R, rituximab; R2, rituximab + lenalidomide.

Ribrag V *et al*. Abstract 379. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R2 vs. R maintenance

Conclusions

- Addition of lenalidomide significantly improved PFS
  - RR: 0.579 (95% CI: 0.429–0.781; *P*=0.003)

- So far, no difference in:
  - OS since induction randomization (median follow-up: 32.4 months)
  - OS since maintenance randomization (median follow-up: 25.2 months)

- More hematologic events in the R2 arm than the R arm

- One death due to toxicity of study treatment in the R2 arm

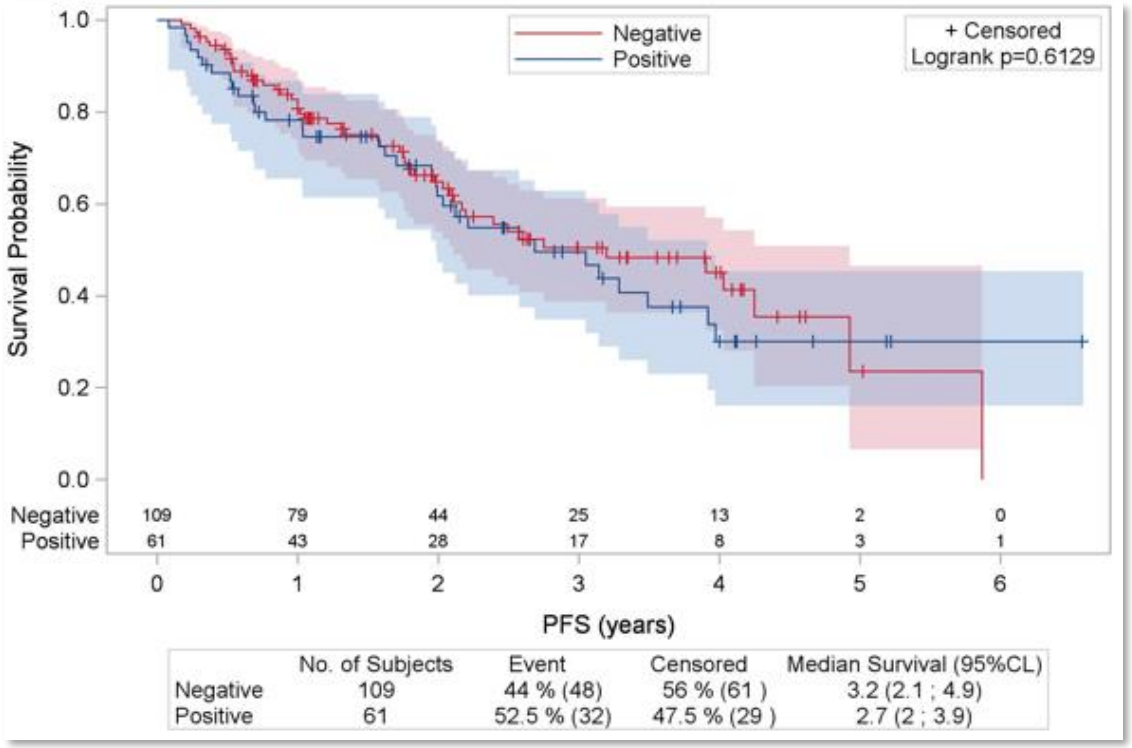
SHINE?

CI, confidence interval; OS, overall survival; PFS, progression-free survival; R, rituximab; R2, rituximab + lenalidomide; RR, risk ratio.
Ribrag V *et al*. Abstract 379. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

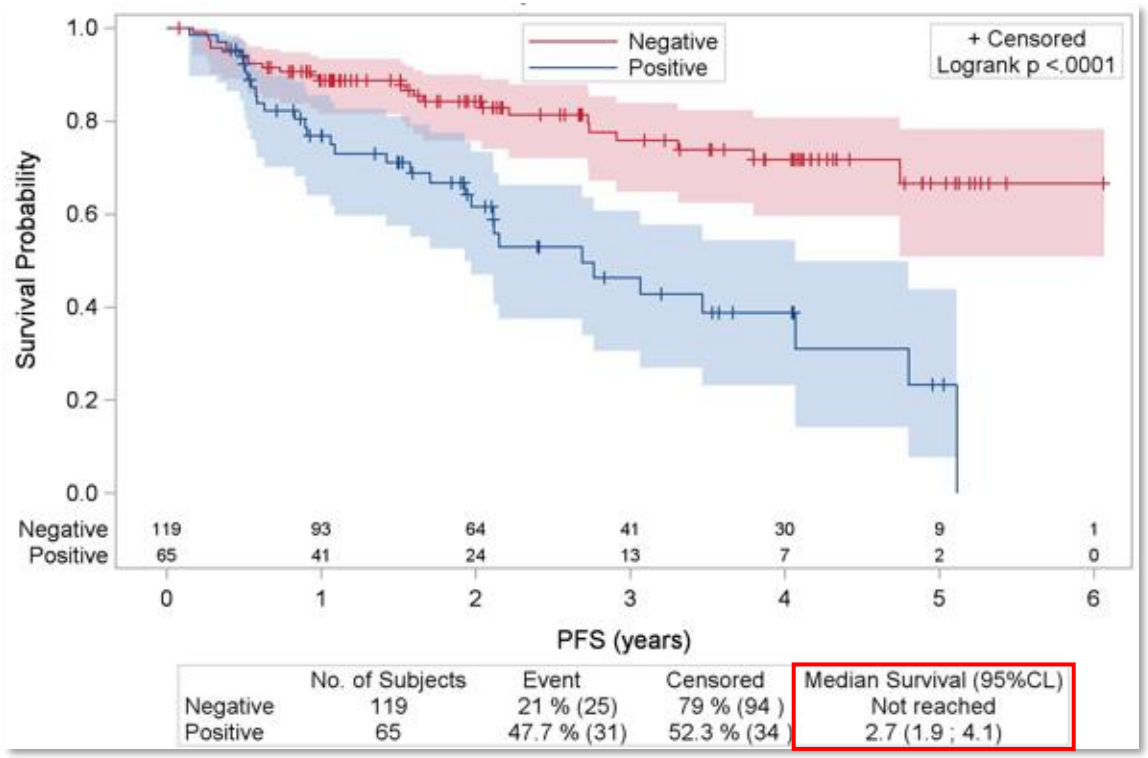
PFS depending on MRD

Status at end of induction

Rituximab maintenance



Rituximab + lenalidomide (R2) maintenance



Label	Modality	Hazard ratio	95% Hazard ratio Confidence limits		Global test
			Lower	Upper	*P* value
MIPI (calculated)		1.989	1.172	3.378	0.0109
MRD EOI	Positive	3.034	1.779	5.174	<0.0001
Induction treatment	R-CHOP	0.944	0.556	1.604	0.8322

EOI, end of induction; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, minimal residual disease; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Delfau M-H *et al*. Abstract 40. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

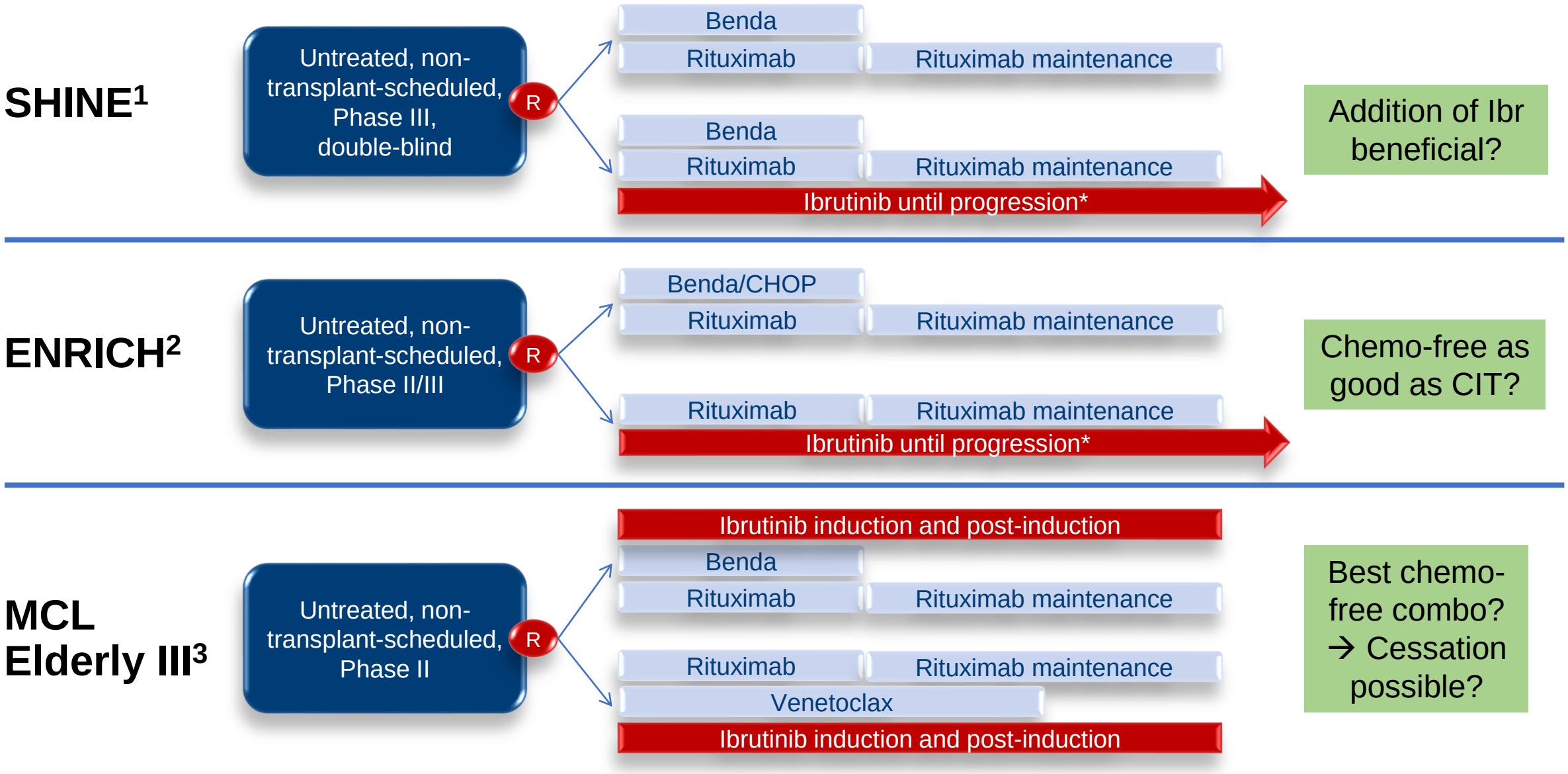
Conclusions

- After induction, in patients randomized for maintenance:
  - Patients with MRD (+) have a median PFS of 2.7 years regardless of maintenance
  - Patients with MRD (−)
    - R maintenance: No difference with MRD (+) patients
    - R2: Longer PFS observed (median not reached)

- Results suggest:
  - There is an MRD below the detection threshold of the currently used technique
  - R2 maintenance, unlike R maintenance alone, is able to control the re-emergence of this low MRD

MRD, minimal residual disease; PFS, progression-free survival; R, rituximab; R2, rituximab + lenalidomide.

Delfau M-H *et al*. Abstract 40. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.



*Or unacceptable toxicity, or study end.
Benda, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CIT, chemoimmunotherapy; Ibr, ibrutinib; MCL, mantle cell lymphoma; R, randomization.
1. ClinicalTrials.gov NCT01776840. Available at: https://clinicaltrials.gov/ct2/show/NCT01776840. 2. ISRCTN registry. ISRCTN11038174. Available at: https://www.isrctn.com/ISRCTN11038174. 3. German Lymphoma Alliance. ABC trial. Available at: https://www.german-lymphoma-alliance.de/media/public/69A8E32D-BB68-14F9-C371-EDCDEA135A6E/Synopse_ABC-trial-version-4.1-002.pdf?ts=1592906029. All accessed February 2022.

MCL

Bortezomib in relapsed patients?

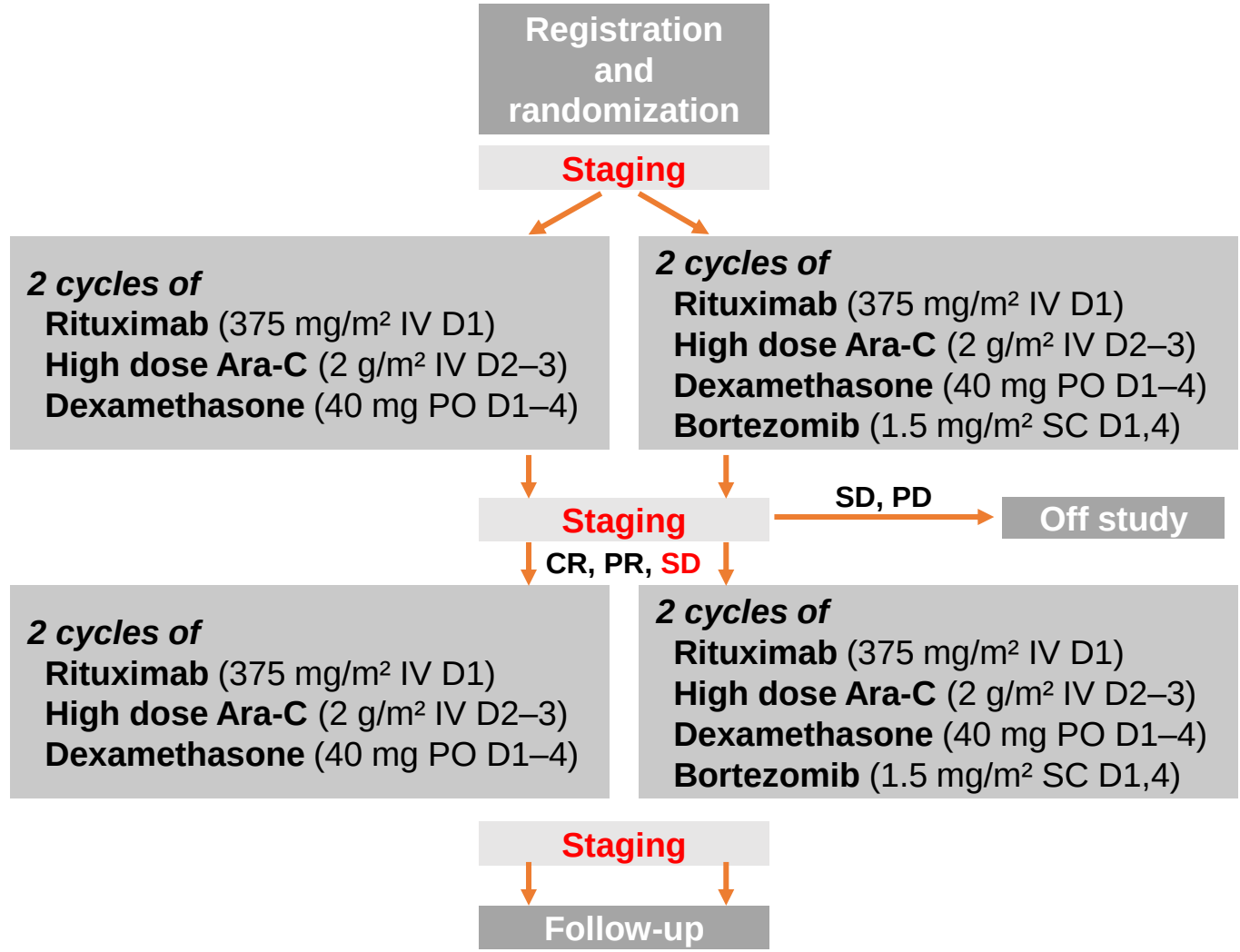
Still any major role in the future?

MCL, mantle cell lymphoma.

R-HAD plus bortezomib in R/R MCL

Phase III European MCL Network trial

- Randomized Phase III trial
- Patients:
  - MCL, relapse, or progression following 1–3 prior lines of anti-neoplastic standard therapy
- Primary endpoint:
  - Time to treatment failure
- Sample size:
  - 275 patients (78 events) needed to detect a hazard ratio of 0.55 with 95% power
  - Maximum 160 events among 275 patients



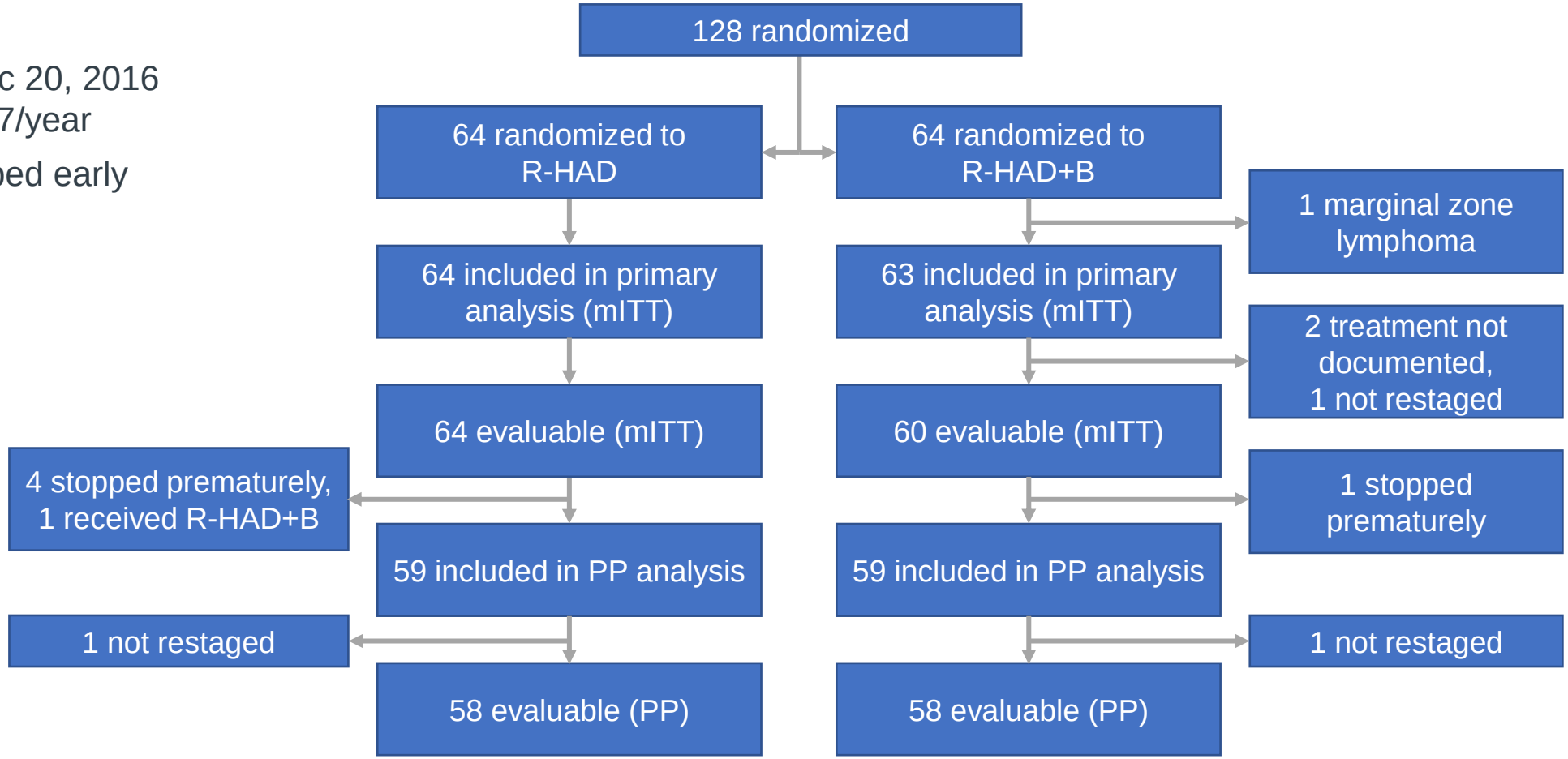
CR, complete response; D, Day; IV, intravenous; MCL, mantle cell lymphoma; PD, progressive disease; PO, by mouth; PR, partial response; R-HAD, rituximab, cytarabine, and dexamethasone; R/R, relapsed/refractory; SC, subcutaneous; SD, stable disease.

Dreyling M *et al*. Abstract 383. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R-HAD plus bortezomib in R/R MCL

Consort flow

- Randomization:
  - May 5, 2012 – Dec 20, 2016 recruitment rate 27/year
  - Recruitment stopped early



B, bortezomib; mITT, modified intention-to-treat; R-HAD, rituximab, cytarabine, and dexamethasone; PP, per-protocol.

Dreyling M *et al*. Abstract 383. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

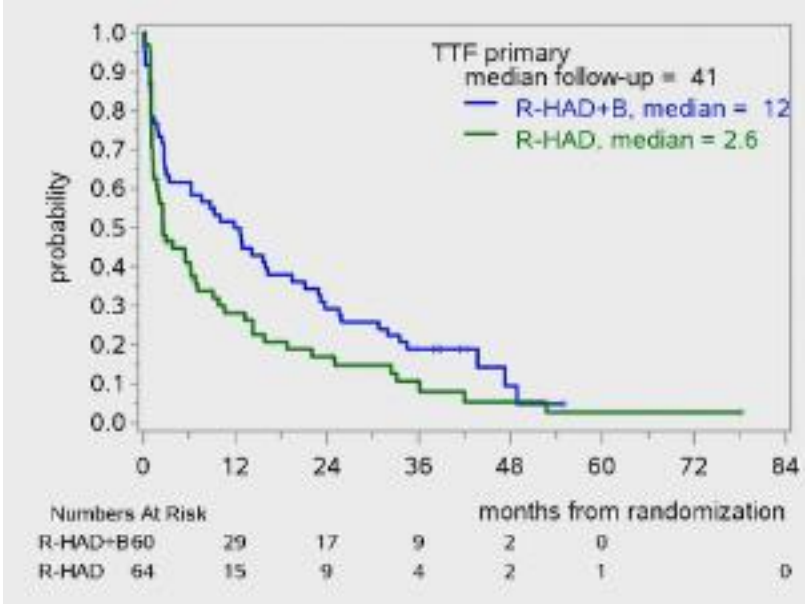
R-HAD plus bortezomib in R/R MCL

Outcomes

- Median follow-up: 41.3 months
- Median time to treatment failure
  - R-HAD: 2.6 months
  - R-HAD+B: 12.0 months
- Based on 107 events, a power of 87% is achieved to detect the prespecified hazard ratio of 0.55
- Underrunning analysis corrected for sequential design
  - Hazard ratio: 0.68; *P*=0.045
  - Statistical power 51.3%

	R-HAD (n=64)	R-HAD+B (n=60)	*P*-value
Complete remission (CR), n (%)	8 (12)	17 (28)	0.043
Complete remission (CR + CRu), n (%)	12 (19)	25 (42)	0.0062
Overall response (CR, CRu, PR), n (%)	29 (45)	38 (63)	0.049

Time to treatment failure (ITT)



B, bortezomib; CR, complete response; CRu, unconfirmed complete response; ITT, intention-to-treat; MCL, mantle cell lymphoma; PR, partial response; R-HAD, rituximab, cytarabine, and dexamethasone; R/R, relapsed/refractory.

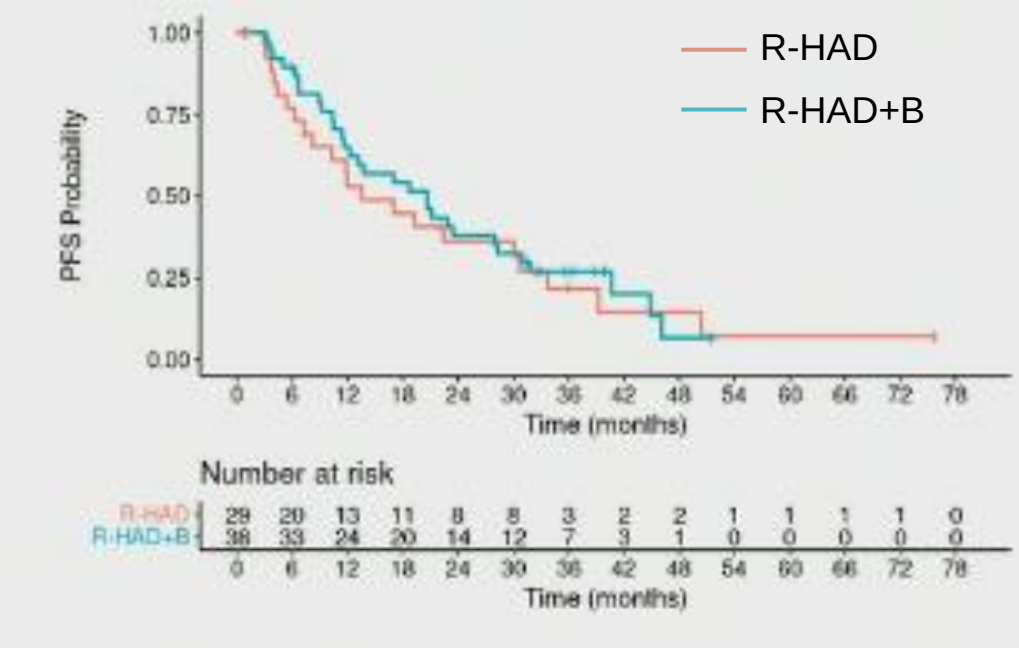
Dreyling M *et al*. Abstract 383. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R-HAD plus bortezomib in R/R MCL

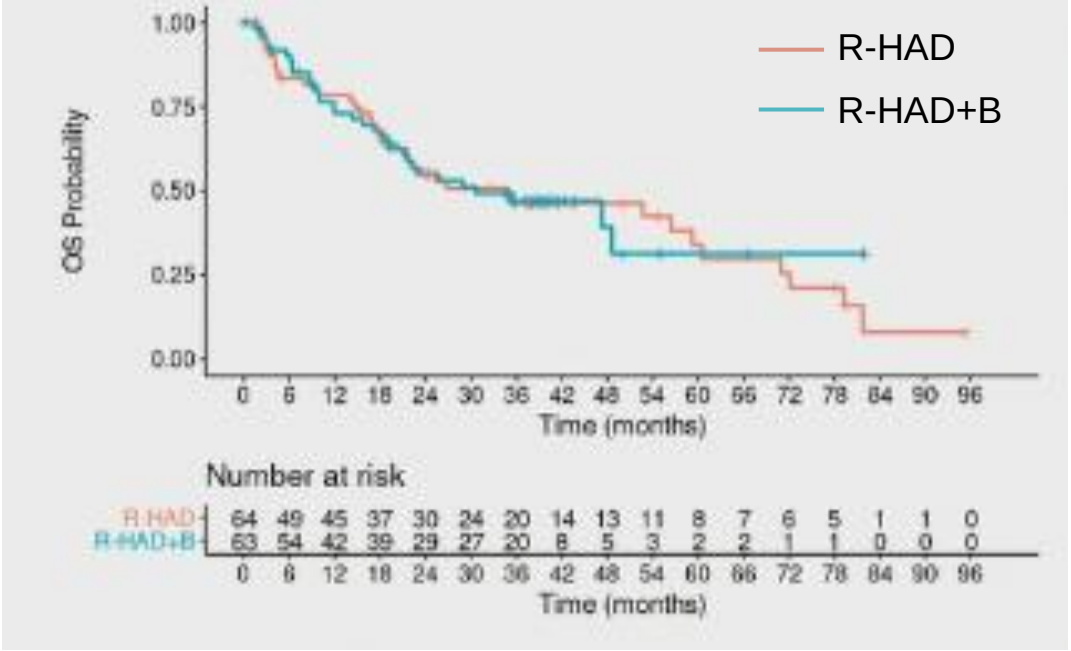
Response duration and OS

- No difference in median response duration (*P*=0.62) or median OS (*P*=0.93)

Response duration



Overall survival



B, bortezomib; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; R-HAD, rituximab, cytarabine, and dexamethasone; R/R, relapsed/refractory.

Dreyling M *et al*. Abstract 383. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

MCL

BTK inhibitors

BTK, Bruton’s tyrosine kinase; MCL, mantle cell lymphoma.

In brief: BTKis in TN and R/R MCL

Abstract, first author	Presentation title	Key findings
182, Di M[1]	Survival of mantle cell lymphoma in the era of Bruton tyrosine kinase inhibitors: A population-based analysis	• Increased survival in the BTKi era for patients aged 60–79 years • Benefits greatest in the 70–79 age group
2416, Wang M[2]	Safety and efficacy of acalabrutinib plus venetoclax and rituximab in patients with treatment-naïve (TN) mantle cell lymphoma (MCL)	Initial safety and efficacy results • Triple combination is well tolerated and provides a 100% clinical response rate • High rates of complete molecular responses

BTKi, Bruton's tyrosine kinase inhibitor; R/R, relapsed/refractory.

1. Di M *et al*. Abstract 182. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.
2. Wang M *et al*. Abstract 2416. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Zanubrutinib, obinutuzumab, and venetoclax in untreated *TP53* mutant MCL

Phase II, single-arm study – preliminary data

- 12 patients (of planned 25); median of 4 months' follow-up
  - 11 patients remain on study in continued response; 1 patient with PD
- BOVen was well tolerated
  - No dose reductions or modifications required
  - Grade 3 treatment-related AEs: infusion-related reaction (17%), neutropenia (8%), and elevation of transaminases (8%)
- Promising efficacy
  - Disease restaging by Lugano criteria at Cycle 3 post-BO
    - PET-CR = 8/10 patients (2 patients maintained PET-CR at Cycle 7)
    - PD = 1/10 patients; SD = 1/10 patients

Study details

Eligibility

- Untreated MCL with *TP53* mutation (any variant allele frequency allowed)
- ECOG PS ≤2
- ANC >1×10^9/L
- PLT >75×10^9/L
- Hgb ≥9 g/dL (unless if due to MCL)

↓

Treatment

- Zanubrutinib 160 mg BID starting on Day 1 of Cycle 1
- Obinutuzumab 1,000 mg on Days 1 (or split between Days 1 and 2), 8, and 15 of Cycle 1, and Day 1 of Cycles 2–8
- Venetoclax ramp-up initiated on Day 1 of Cycle 3 (target 400 mg)

↓

Primary endpoint

- PFS at 2 years

AE, adverse event; ANC, absolute neutrophil count; BID, twice a day; BOVen, zanubrutinib, obinutuzumab, and venetoclax; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Hgb, hemoglobin; MCL, mantle cell lymphoma; PET-CR, positron emission tomography–assessed complete response; PD, progressive disease; PFS, progression-free survival; PLT, platelet count; SD, stable disease.

Kumar A *et al*. Abstract 3540. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Zanubrutinib + rituximab vs. BR in untreated MCL*

Phase III Mangrove study

- **Primary endpoint:** PFS by IRC using the 2014 Lugano classification for NHL
- **Key secondary endpoints:** PFS by IA, ORR, DoR, OS, CR (or complete metabolic response), TTR by IRC and IA, PROs, safety

Key eligibility criteria

- Previously untreated
- Ineligible for stem cell transplant (**≥70 years old or 65–69 years old with comorbidities**)
- Measurable disease by CT/MRI
- ECOG PS 0–2

Stratification factors

- Age: <70 vs. ≥70 years
- Region: Asia Pacific vs. North America / Europe
- MCL IPI score: Low vs. intermediate/high

R 1:1

Treatment†

Zanubrutinib 160 mg PO BID + rituximab 375 mg/m² IV D1 × 6 cycles (n=250) → Zanubrutinib 160 mg PO BID

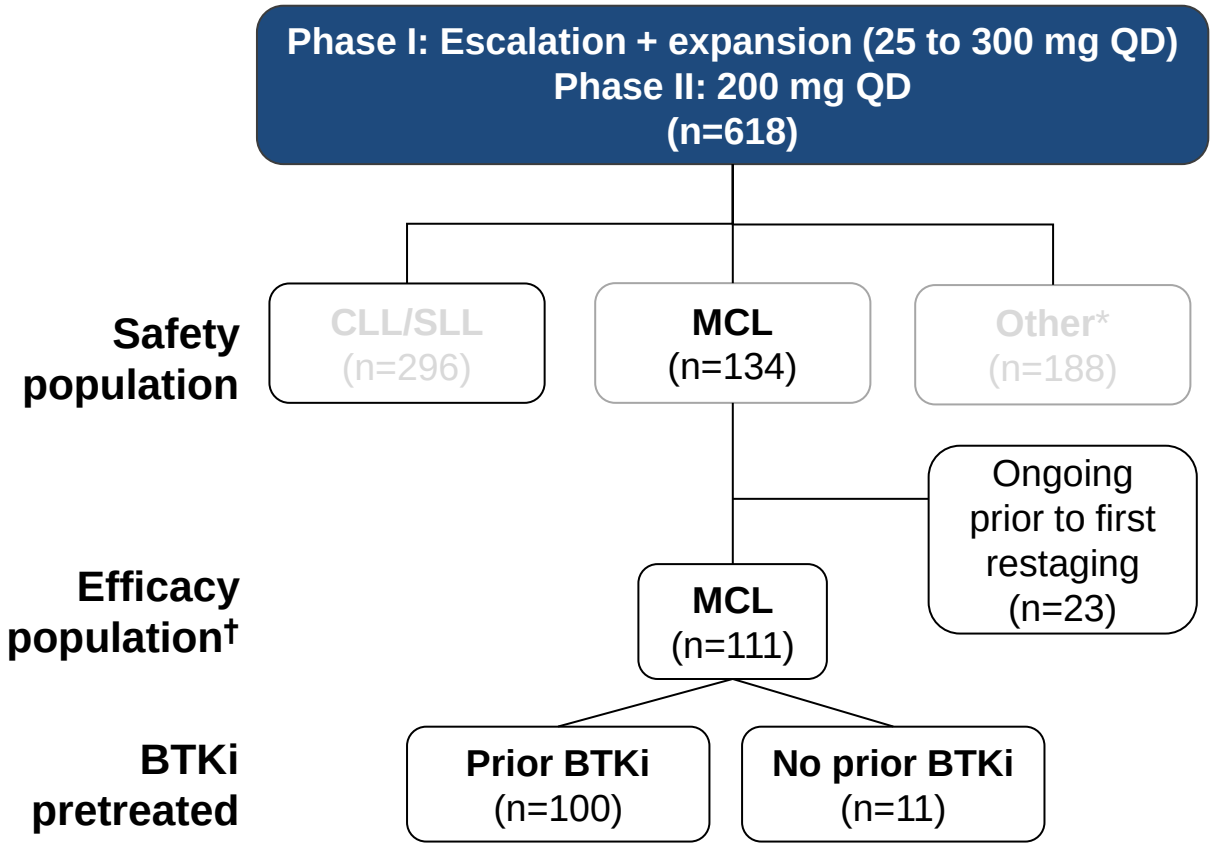
Bendamustine 90 mg/m² IV D1 and D2 + rituximab 375 mg/m² IV D1 × 6 cycles (n=250) → Observation

- Response assessed by imaging every 3 months for 2 years, then every 6 months
- Study duration estimated to be 7 years

*Patients ineligible for stem cell therapy. †Until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination.
BID, twice a day; BR, bendamustine and rituximab; CR, complete response; CT, computed tomography; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IA, investigator assessment; IPI, International Prognostic Index; IRC, independent review committee; IV, intravenous; MCL, mantle cell lymphoma; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; R, randomization; TTR, time to response.
Dreyling M *et al*. *Future Oncol* 2021; 17 (3): 255–262. This study is registered at ClinicalTrials.gov (NCT04002297).

Pirtobrutinib, a non-covalent BTKi

Phase I/II BRUIN study



Phase I 3+3 design

- 28-day cycles
- Intrapatient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18 years
- ECOG PS 0–2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase II dose
- Pharmacokinetics
- Efficacy according to ORR and DoR based on disease criteria (iwCLL, IWWM, Lugano)

Data cut-off: July 16, 2021. *'Other' includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, hairy cell leukemia, PCNSL, and other transformation. †Efficacy-evaluable patients are those who had at least one post-baseline response assessment or who had discontinued treatment prior to the first post-baseline response assessment. B-PLL, B-cell prolymphocytic leukemia; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IWWM, International Workshop on Waldenstrom's Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PCNSL, primary central nervous system lymphoma; QD, every day; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia. Wang M *et al*. Abstract 381. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Pirtobrutinib, a non-covalent BTKi

Patient characteristics

Characteristics	MCL (n=134)
Median age (range), years	70 (46–88)
Female / Male (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)

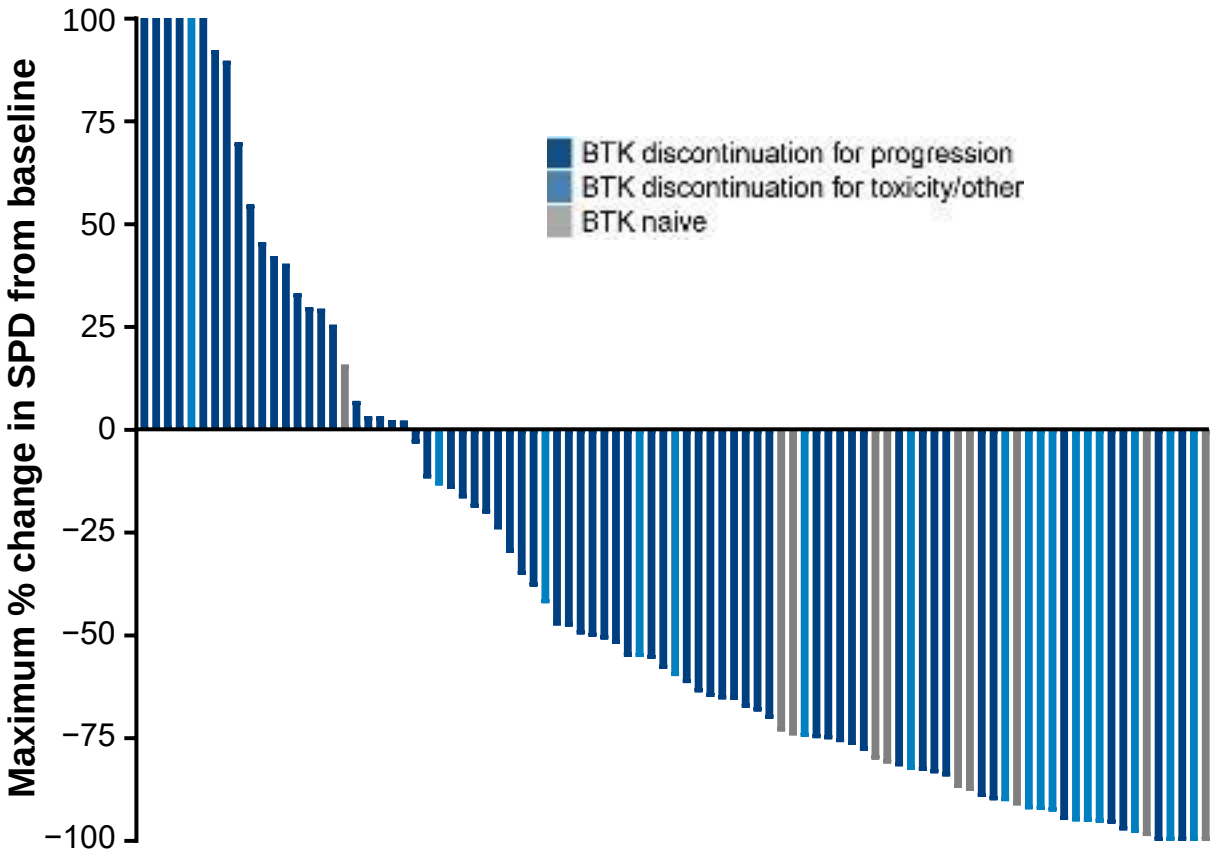
Characteristics	MCL (n=134)
Median prior lines of therapy, n (range)	3 (1–9)
Prior therapy	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant	30 (22)
IMiD	23 (17)
Bcl-2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTK inhibitor	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD, immunomodulatory drug; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase.

Wang M *et al*. Abstract 381. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Pirtobrutinib, a non-covalent BTKi

Responses



BTK-pretreated patients with MCL	n=100
Overall response rate, % (95% CI)	**51 (41–61)**
Best response, n (%)	
CR	25 (25)
PR	26 (26)
SD	16 (16)

BTK TN patients with MCL	n=11
Overall response rate, % (95% CI)	**82 (48–98)**
Best response, n (%)	
CR	2 (18)
PR	7 (64)
SD	1 (9)

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma; PR, partial response; SD, stable disease; SPD, sum of the product of the diameters; TN, treatment-naïve.

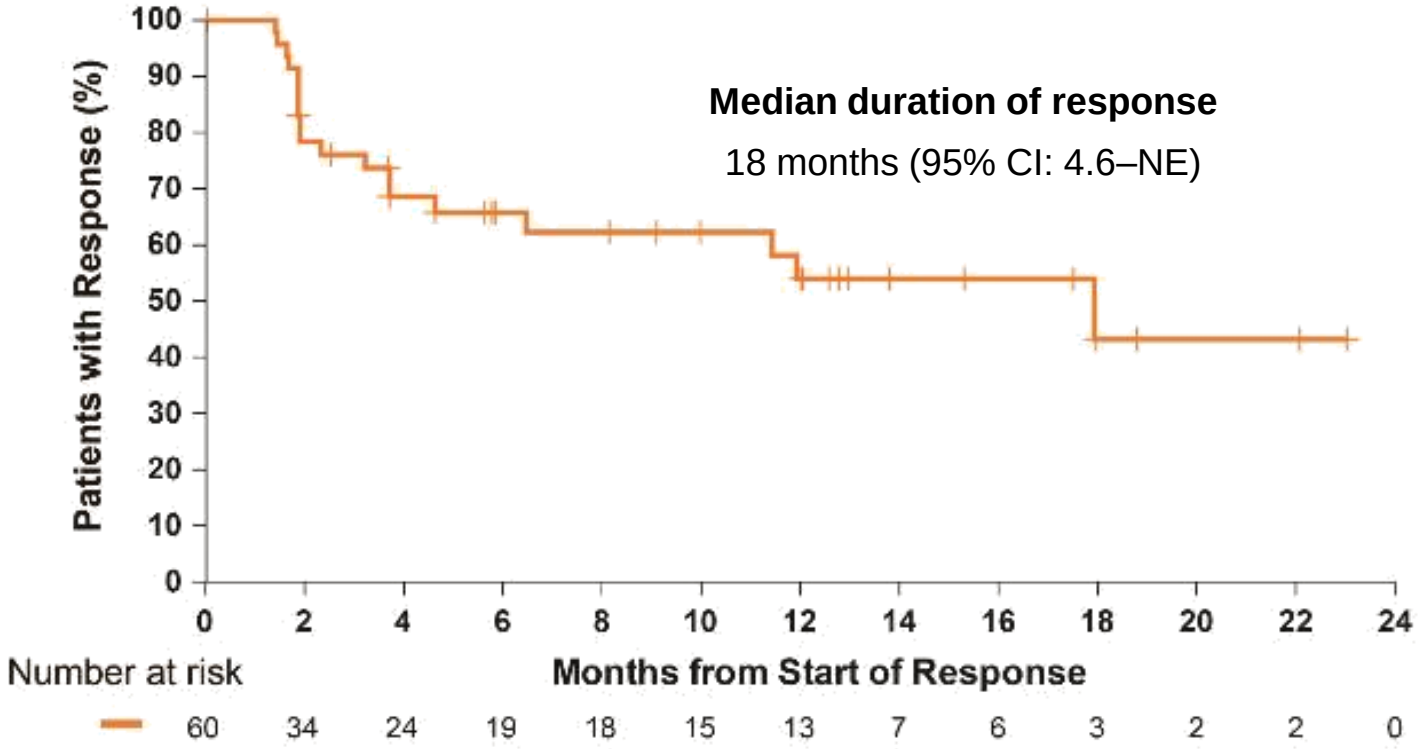
Wang M *et al*. Abstract 381. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Pirtobrutinib, a non-covalent BTKi

Duration of response in MCL

- Median follow-up of 8.2 months (range: 1.0–27.9 months) for responding patients

- 60% of responses (36 of 60) are ongoing



Data cut-off: July 16, 2021. Response status per Lugano 2014 criteria based on investigator assessment.
CI, confidence interval; MCL, mantle cell lymphoma; NE, not estimable.
Wang M *et al*. Abstract 381. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Pirtobrutinib, a non-covalent BTKi

Safety

- No DLTs reported and MTD not reached
- 96% of patients received ≥1 pirtobrutinib dose at or above the RP2D of 200 mg daily
- 1% of patients (n=6) permanently discontinued because of treatment-related AEs

	All doses and patients (n=618)						
	Treatment-emergent AEs (≥15%)					Treatment-related AEs	
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grades 3/4	Any grade
AE							
Fatigue	13%	8%	1%	–	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	–	–	17%	–	12%
AEs of special interest							
Bruising	20%	2%	–	–	22%	–	15%
Rash	9%	2%	<1%	–	11%	<1%	5%
Arthralgia	8%	3%	<1%	–	11%	–	3%
Hemorrhage	5%	2%	1%	–	8%	<1%	2%
Hypertension	1%	4%	2%	–	7%	<1%	2%
Atrial fibrillation/flutter	–	1%	<1%	<1%	2%	–	<1%

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended Phase II dose.

Wang M *et al*. Abstract 381. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

MCL

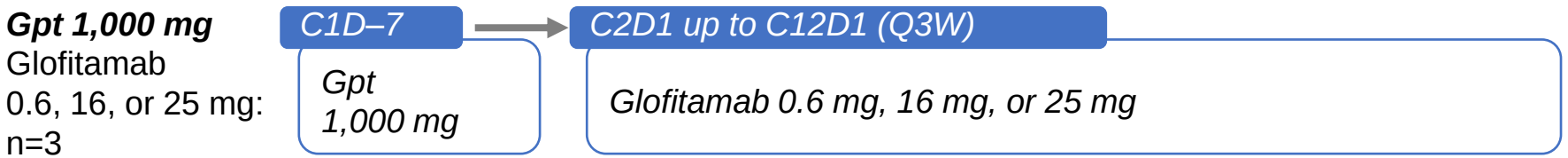
What about bispecific antibodies in MCL?

MCL, mantle cell lymphoma.

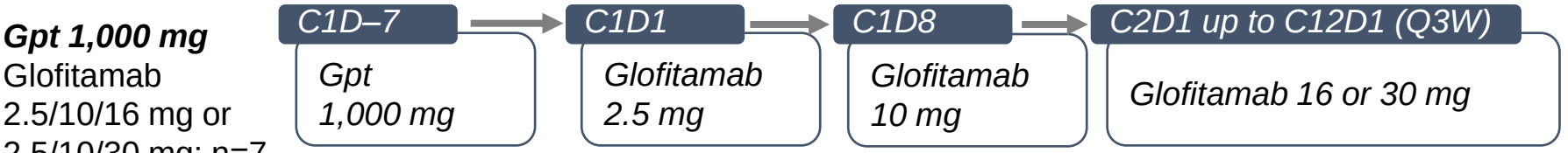
Glofitamab

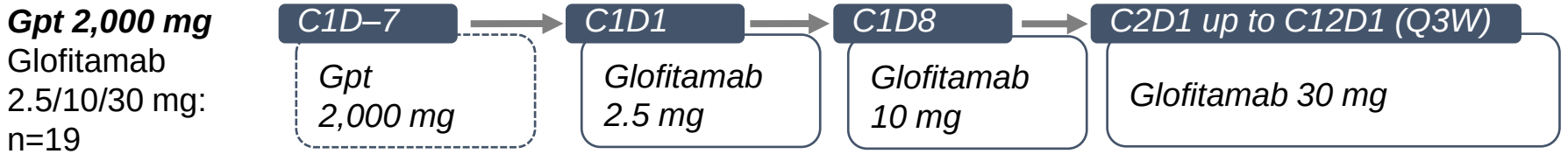
Dose escalation (Phase I)

Glofitamab fixed dosing



Glofitamab SUD





Population characteristics:

- *Age ≥18 years*
- *≥1 prior systemic therapy*
- *ECOG PS ≤1*

C, Cycle; D, Day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gpt, Glofitamab with obinutuzumab pretreatment; MCL, mantle cell lymphoma; Q3W, every 3 weeks; SUD, step-up doses.

Phillips T *et al*. Abstract 130. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Glofitamab

Patient characteristics

n (%) of patients unless stated		Glofitamab fixed dosing + Gpt 1,000 mg (n=3)	Glofitamab SUD + Gpt 1,000 mg (n=7)	Glofitamab SUD + Gpt 2,000 mg (n=19)	All patients (N=29)
Median age, years (range)		81.0 (66–84)	69.0 (64–75)	66.0 (41–84)	69.0 (41–84)
Male		2 (66.7)	6 (85.7)	12 (63.2)	20 (69.0)
Ann Arbor Stage III–IV at study entry		2 (66.7)	6 (85.7)	16 (84.2)	24 (82.8)
MCL IPI score ≥6 at study entry		3 (100)	3 (42.9)	12 (63.2)	18 (62.1)
Prior therapy	Median time since last therapy, months (range)	1.1 (1.0–8.5)	3.4 (1.2–53.2)	1.6 (0.1–107.5)	1.7 (0.1–107.5)
	Prior lines of therapy, median (range)	3 (2–5)	4 (3–5)	3 (1–6)	3 (1–6)
	BTKi	3 (100)	6 (85.7)	11 (57.9)	20 (69.0)
	Lenalidomide	0	1 (14.3)	3 (15.8)	4 (13.8)
	Chemotherapy	3 (100)	7 (100)	18 (94.7)	28 (96.6)
	Alkylator	0	6 (85.7)	7 (36.8)	13 (44.8)
	Anti-CD20 monoclonal antibody	3 (100)	6 (85.7)	14 (73.7)	23 (79.3)
Refractory status	Refractory to any prior therapy	3 (100)	7 (100)	16 (84.2)	26 (89.7)
	Refractory to prior anti-CD20 therapy	2 (66.7)	3 (42.9)	10 (52.6)	15 (51.7)
	Refractory to first-line therapy	2 (66.7)	2 (28.6)	11 (57.9)	15 (51.7)
	Refractory to last prior therapy	2 (66.7)	5 (71.4)	13 (68.4)	20 (69.0)

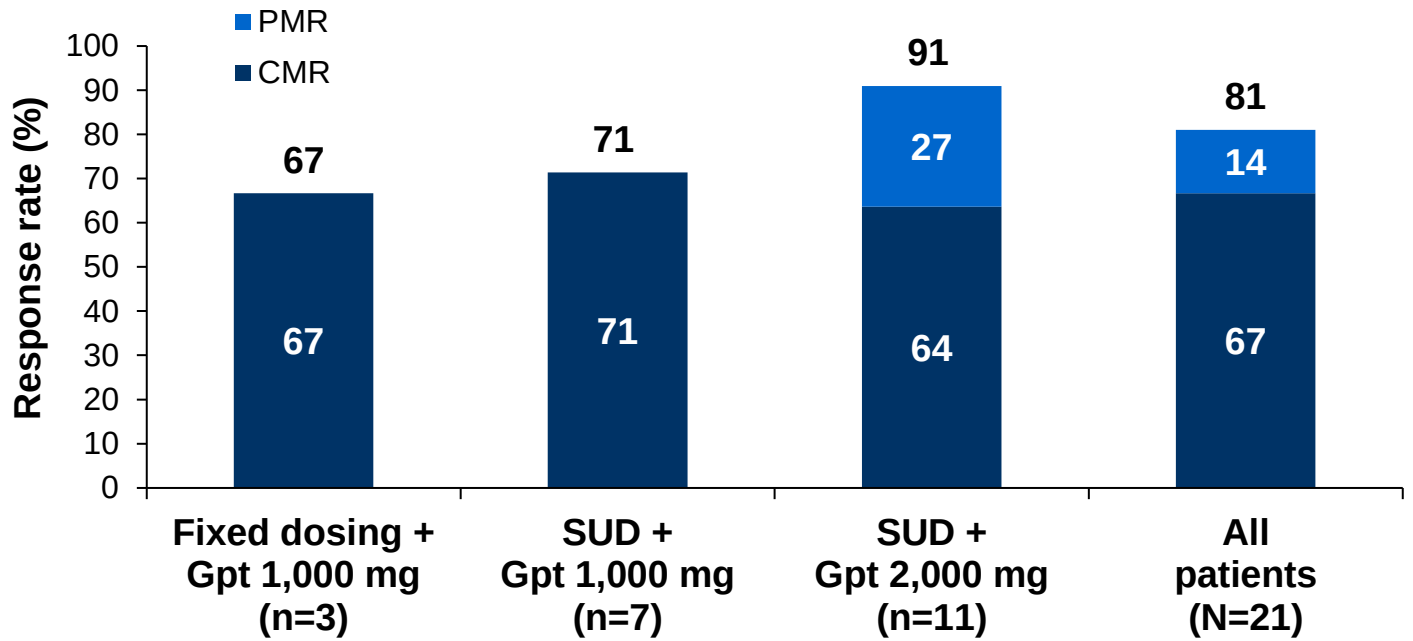
BTKi, Bruton's tyrosine kinase inhibitor; CD, cluster of differentiation; Gpt, Glofitamab with obinutuzumab pretreatment; IPI, International Prognostic Index; MCL, mantle cell lymphoma; SUD, step-up doses.

Phillips T *et al*. Abstract 130. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

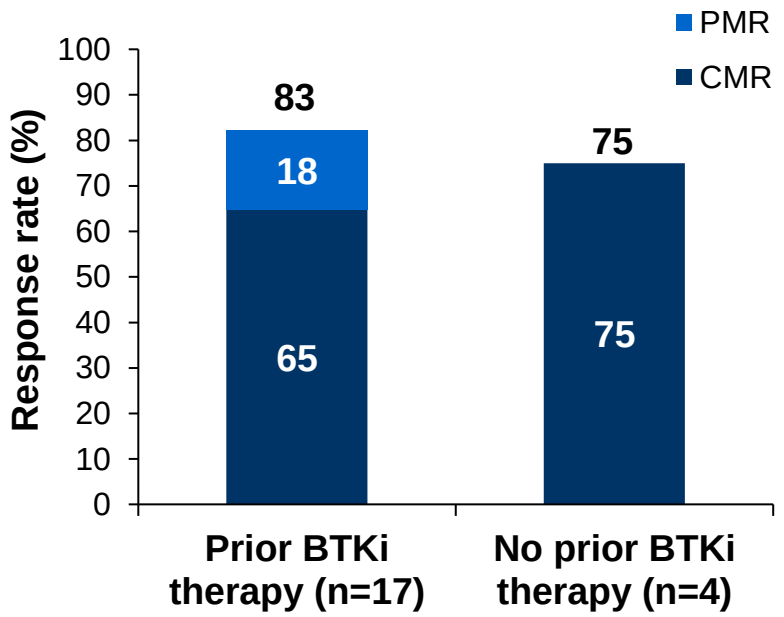
Glofitamab

Response rates

Response rates by glofitamab regimen



Response rates by prior BTKi therapy



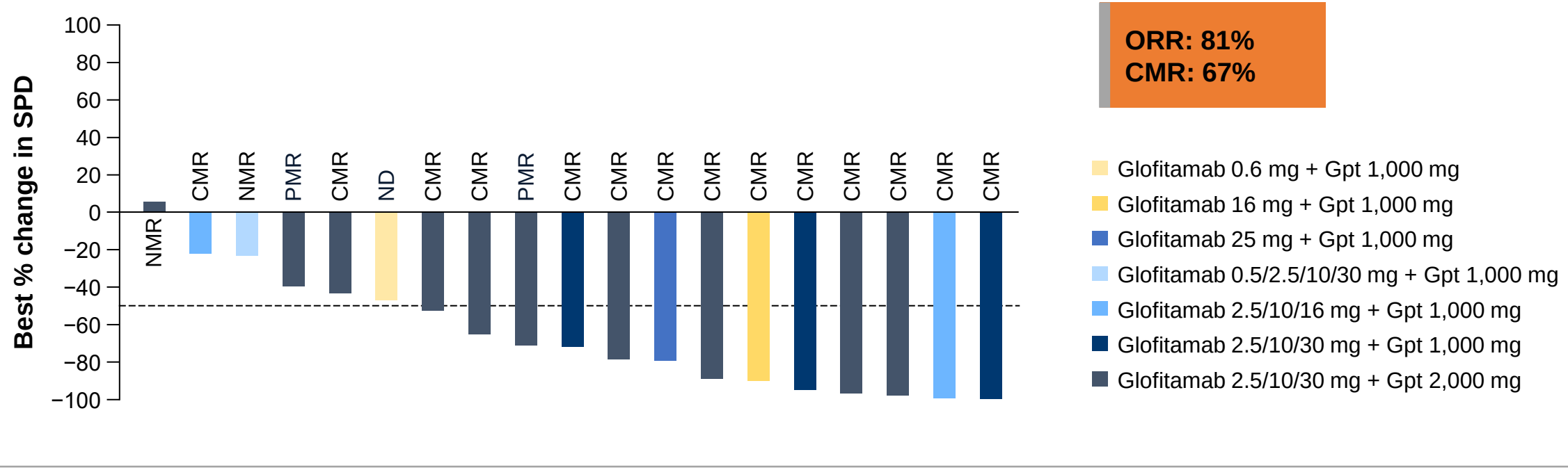
BTKi, Bruton's tyrosine kinase inhibitor; CMR, complete metabolic response; PMR, partial metabolic response; SUD, step-up doses.

Phillips T *et al*. Abstract 130. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Glofitamab

Antitumor activity

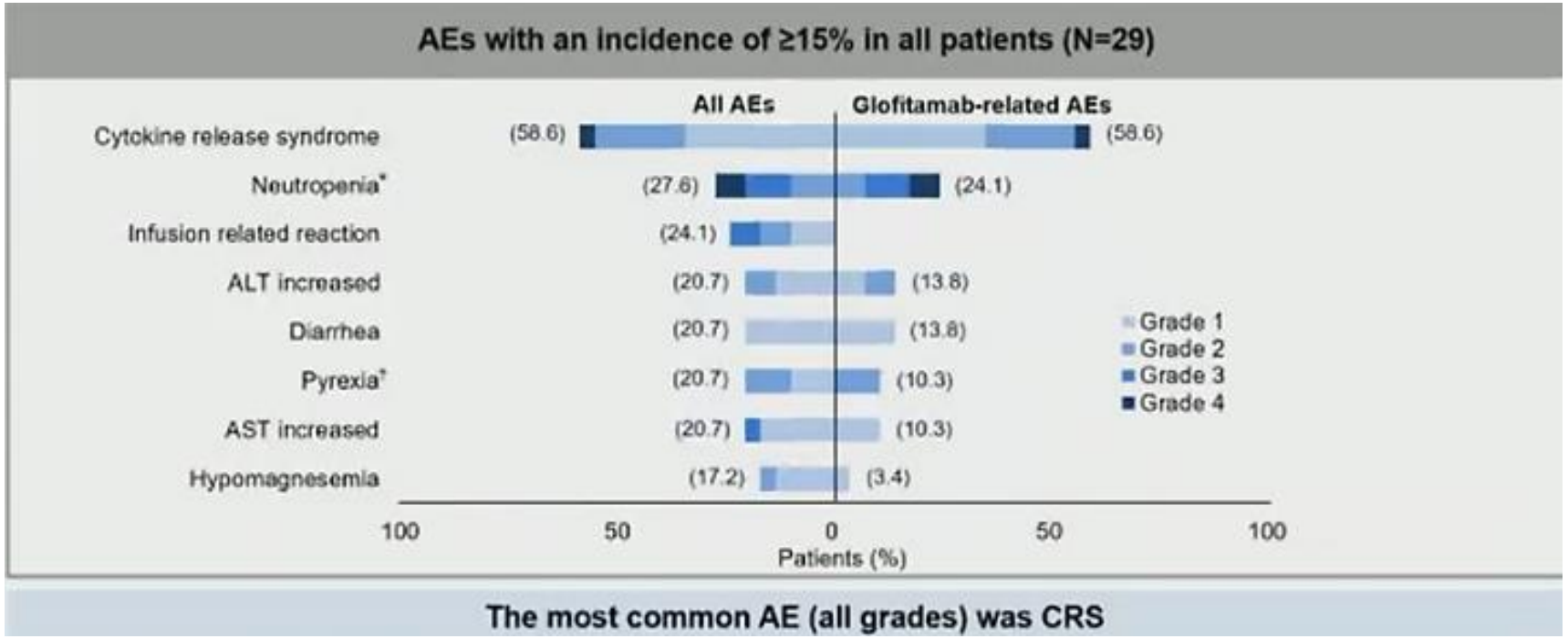
Best percentage change from baseline SPD



CMR, complete metabolic response; ND, not determined; NMR, no metabolic response; ORR, overall response rate; PMR, partial metabolic response; SPD, sum of the product of the diameters.

Phillips T *et al*. Abstract 130. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Glofitamab
Adverse events



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome.

Phillips T *et al*. Abstract 130. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.


ASH 2022
New Orleans
Many thanks!

ASH 2021 highlights: Aggressive lymphomas

Professor Wojciech Jurczak
National Research Institute of Oncology, Poland

February 2022 | 0222-BGB-3111-MRC-024

Disclosures

- **Honoraria:** AstraZeneca, BeiGene, Janssen
- **Advisory board:** BeiGene, Janssen

First-line DLBCL treatment

Preventing CNS relapse

- **Early integration** (intercalation) of high-dose methotrexate with R-CHOP or R-CHOP-like therapy **vs. end-of-treatment delivery** in CNS relapse
  - Multicentre international analysis of 1,384 patients with DLBCL

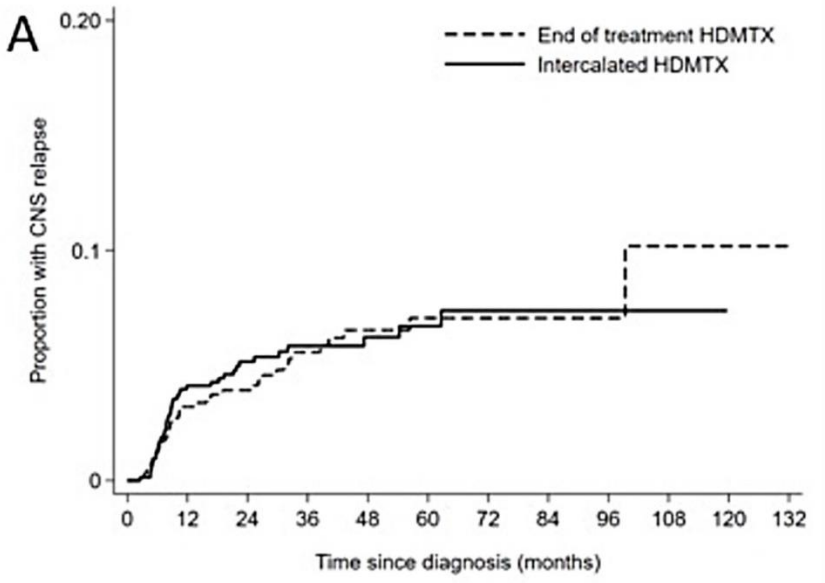
	All N=1384	Intercalated N=750	End of treatment N=634	p-value
Age*	62.5 (17 - 88)	62.0 (17 - 88)	63.0 (18 - 86)	0.073
Male sex (%)*	842 (60.8)	450 (60.0)	392 (61.8)	0.49
Advanced stage, N (%)*	1156 (83.5)	647 (86.3)	509 (80.3)	0.0028
Raised LDH baseline, N (%)*	943 (70.0)	534 (71.6)	409 (67.9)	0.15
ECOG ≥2, N (%)*	358 (25.9)	200 (26.7)	158 (25.0)	0.49
2+ Extra-nodal sites, N (%)*	798 (57.7)	445 (59.3)	353 (55.7)	0.17
Renal or adrenal, N (%)*	240 (17.3)	138 (18.4)	102 (16.1)	0.26
Testicular, N (%)	175 (12.7)	81 (10.8)	94 (14.9)	0.023
Double or triple hit, N (%)	66 (6.1)	34 (5.7)	32 (6.7)	0.46
High CNS IPI (4-6), N (%)	600 (44.2)	337 (45.1)	263 (43.1)	0.087
IT prophylaxis, N (%)*	636 (46.1)	285 (38.1)	351 (55.6)	<0.0001
≥2 cycles HD-MTX given, N (%)*	1199 (86.6)	557 (87.9)	642 (85.6)	0.22

*Factors analyzed in multivariable analysis for risk of CNS relapse. CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HD-MTX, high-dose methotrexate; IPI, International Prognostic Index; IT, intrathecal; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

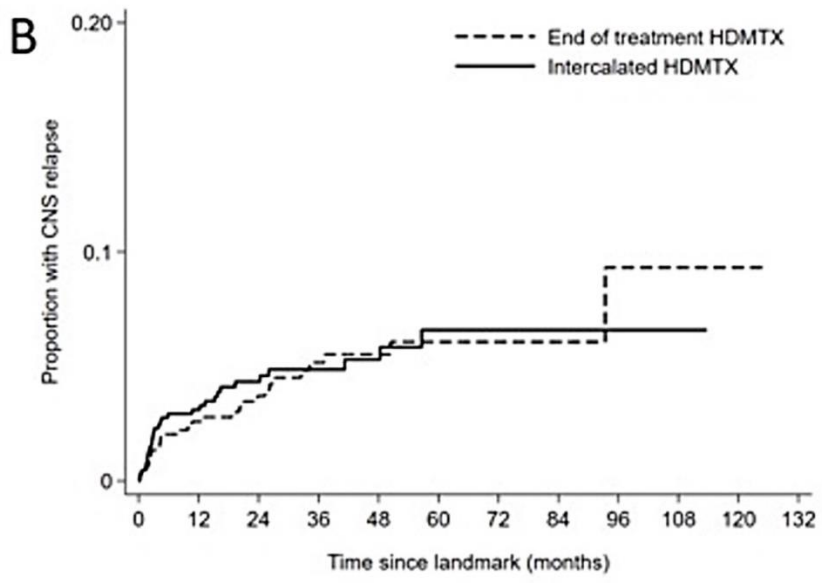
Wilson MR *et al*. Abstract 452. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Early integration of high-dose methotrexate does not have an impact on CNS relapse compared with end-of-treatment delivery

Cumulative incidence of CNS relapse in whole cohort (N=1,384)



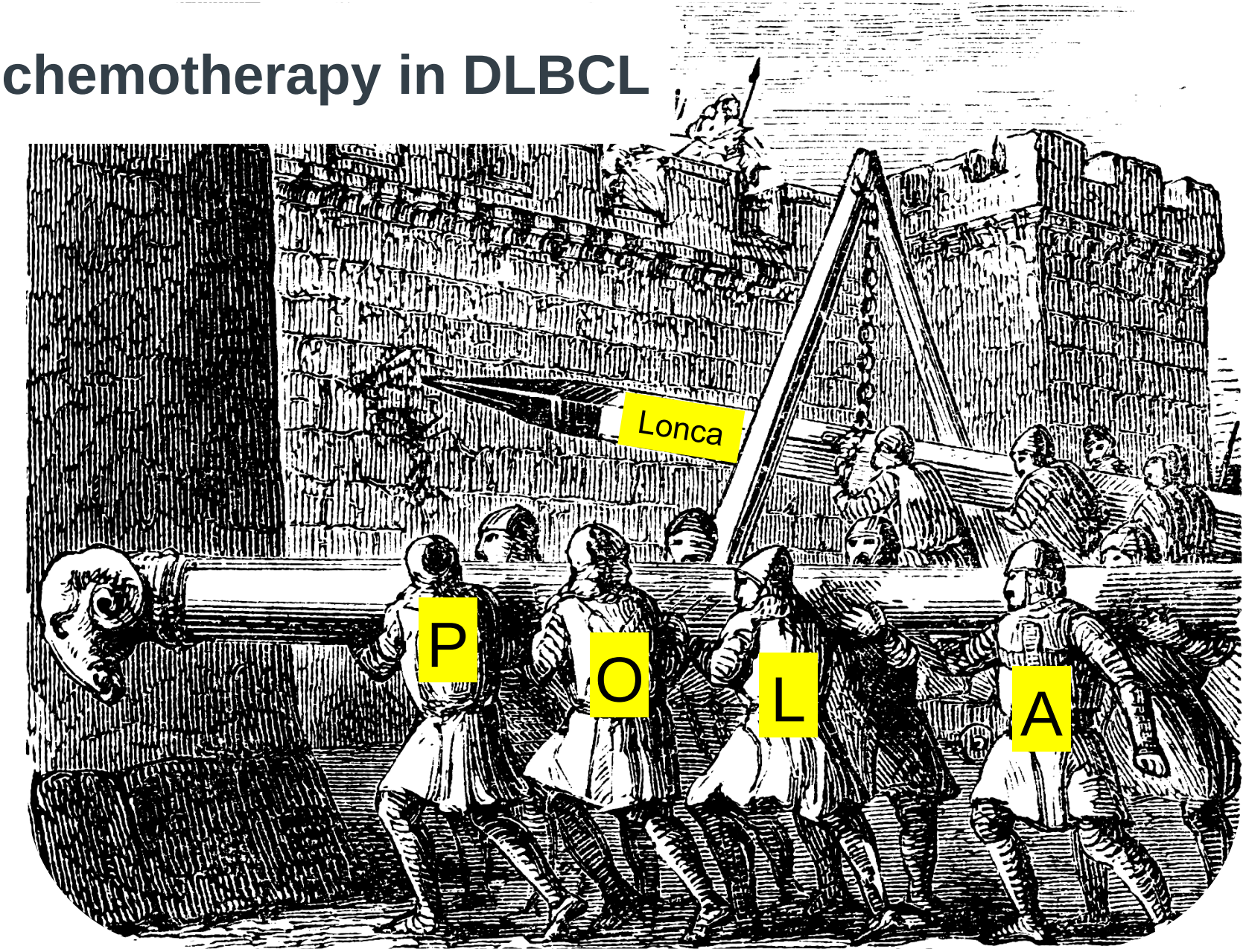
Cumulative incidence of CNS relapse in landmark cohort (n=1,259)*



- **Whole cohort survival outcomes**
  - 3-year PFS for i-HDMTX vs. EOT: **70.7% vs. 76.7% (p=0.098)**
  - 3-year OS for i-HDMTX vs. EOT: **79.9% vs 87.0% (p=0.0016)**

*The landmark cohort included only patients who were alive and free from progression at Month 6.
CNS, central nervous system; EOT, end-of-treatment; HDMTX, high-dose methotrexate; i-HDMTX; intercalated high-dose methotrexate; OS, overall survival; PFS, progression-free survival.
Wilson MR *et al*. Abstract 452. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Targeted chemotherapy in DLBCL



DLBCL, diffuse large B-cell lymphoma.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

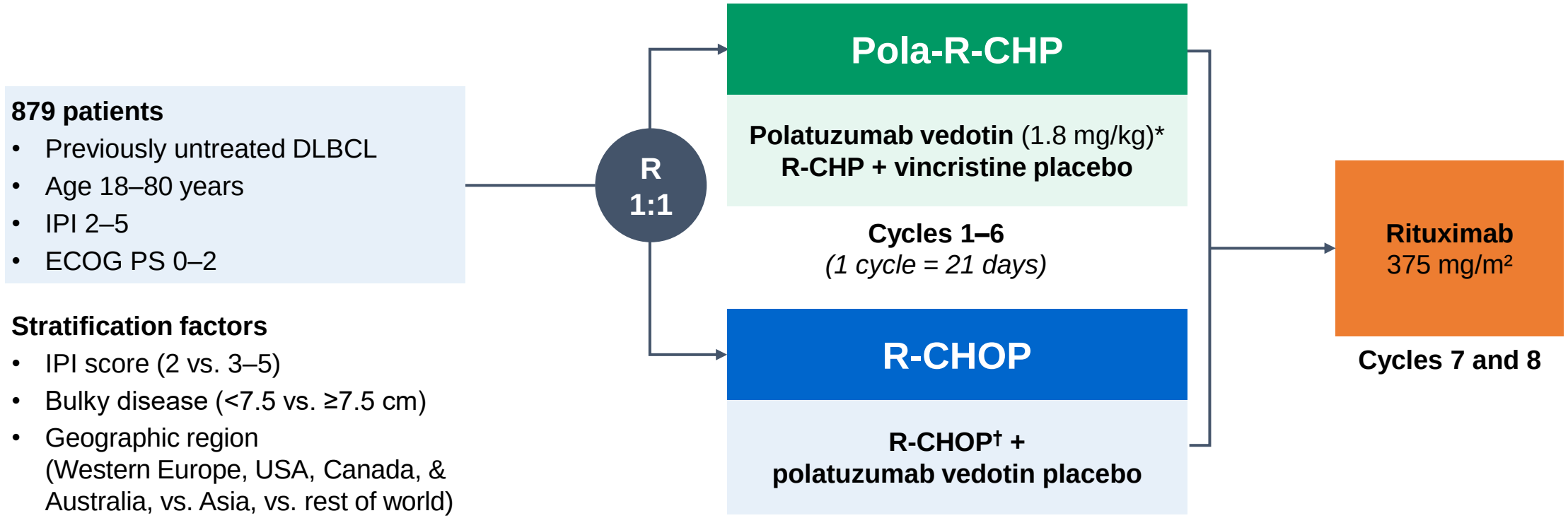
H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

Untreated DLBCL

POLARIX study

- Double-blind, placebo-controlled, international, Phase III trial of two regimens containing the CD79b-targeting ADC polatuzumab vedotin



*Intravenous on Day 1 of each cycle. †R-CHOP: intravenous rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (max. 2 mg) on Day 1, plus oral prednisone 100 mg once daily on Days 1–5.

ADC, antibody–drug conjugate; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R, randomization; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Tilly H *et al*. Abstract LBA-1. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

Untreated DLBCL

POLARIX study

- Double-blind, placebo-controlled, international, Phase III trial of two regimens containing the CD79b-targeting ADC polatuzumab vedotin

879 patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors
- IPI score (2 vs. 3–5)
- Bulky disease (<7.5 vs. ≥7.5 cm)
- Geographic region (Western Europe, USA, Canada, & Australia, vs. Asia, vs. rest of world)

Key endpoints	
Primary endpoint	Progression-free survival (investigator-assessed)
Secondary endpoints	• Event-free survival • Complete response rate • Disease-free survival • Overall survival
Safety endpoints	Incidence, nature, and severity of adverse events

- Median follow-up at the primary analysis was 28.2 months

*Intravenous on Day 1 of each cycle. †R-CHOP: intravenous rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (max. 2 mg) on Day 1, plus oral prednisone 100 mg once daily on Days 1–5.
ADC, antibody–drug conjugate; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R, randomization; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
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Baseline characteristics

POLARIX study

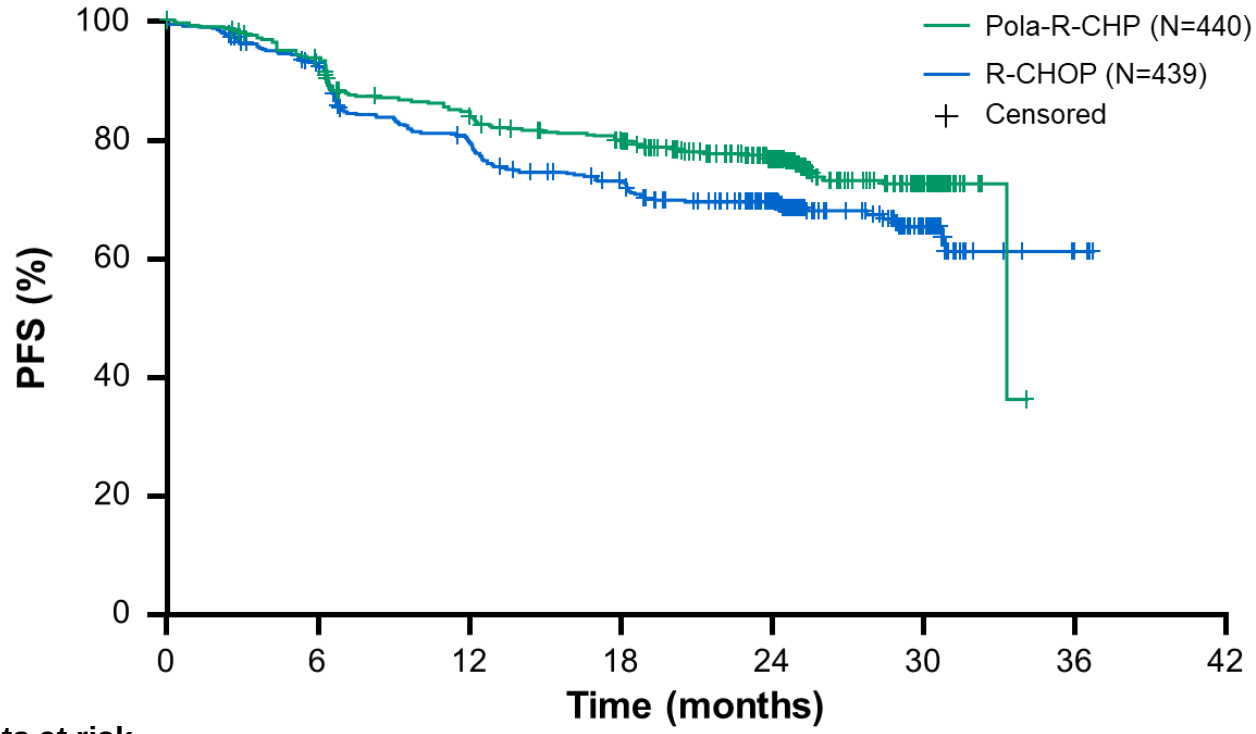
ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1 2	374 (85) 66 (15)	363 (83) 75 (17)
Bulky disease (≥7.5 cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	2 3–5	167 (38) 273 (62)	167 (38) 272 (62)
Cell-of-origin, n (%)	Activated B-cell–like subtype Germinal center B-cell–like subtype Unclassified	102/330 (31) 184/330 (56) 44/330 (13)	119/338 (35) 168/338 (50) 51/338 (15)
MYC/BCL2 expression, n (%)	Double expression	139/362 (38)	151/366 (41)
MYC/BCL2/BCL6 rearrangement, n (%)	Double-/triple-hit	26/331 (8)	19/334 (6)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; ITT, intention-to-treat; LDH, lactate dehydrogenase; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Tilly H *et al*. Abstract LBA-1. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

PFS significantly improved with Pola-R-CHP vs. R-CHOP

POLARIX study



Patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR: 0.73 (*P*<0.02)

95% CI: 0.57–0.95

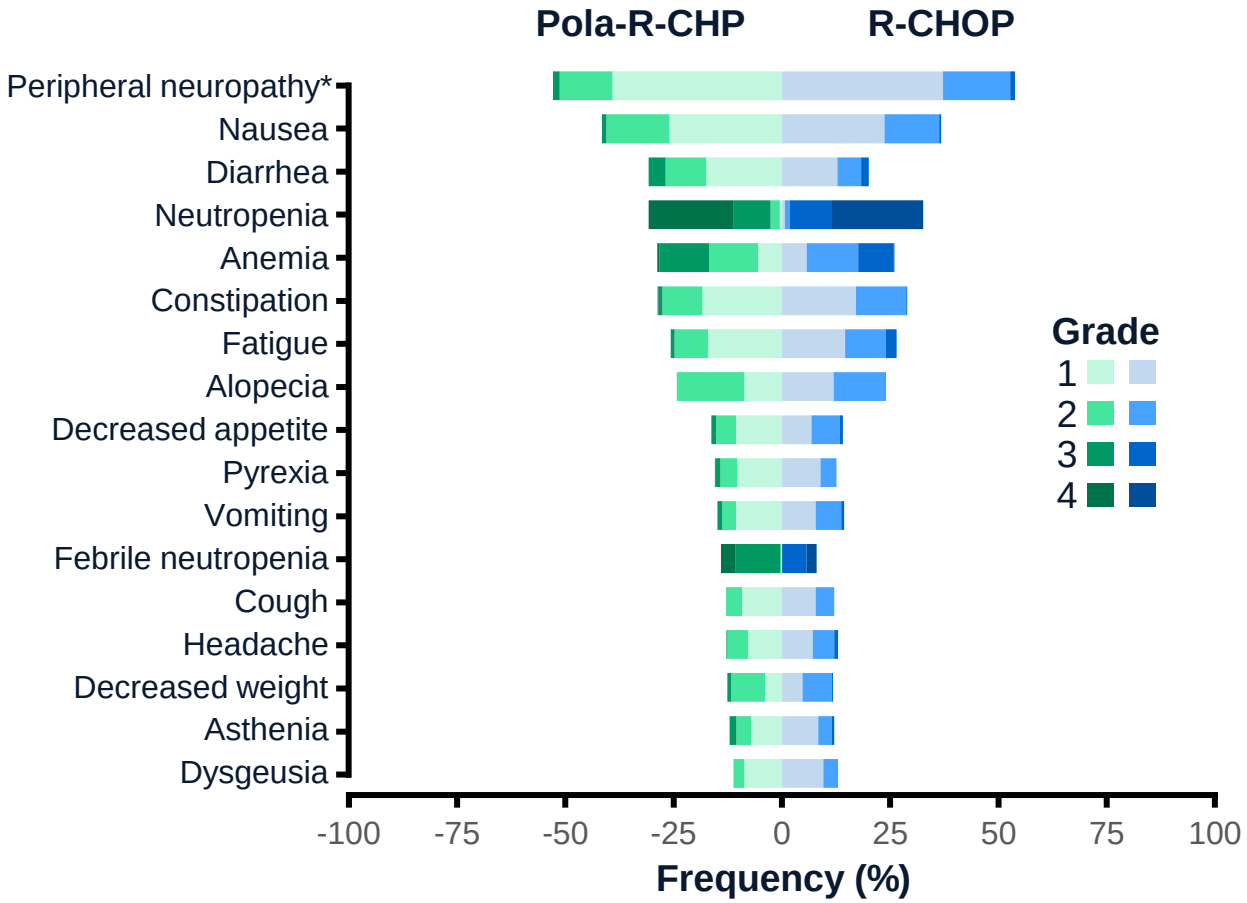
- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** vs. R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP vs. 70.2% with R-CHOP (Δ**=6.5%**)

CI, confidence interval; HR, hazard ratio; NE, not evaluable; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Tilly H *et al*. Abstract LBA-1. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

Common adverse events

POLARIX study



AEs, n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation	27 (6.2)	29 (6.6)
Dose reduction	40 (9.2)	57 (13.0)

*Peripheral neuropathy includes the following preferred terms from the system organ class of peripheral neuropathy: peripheral neuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, ear paresthesia, peroneal nerve palsy, and skin burning sensation.
AE, adverse event; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

Conclusions

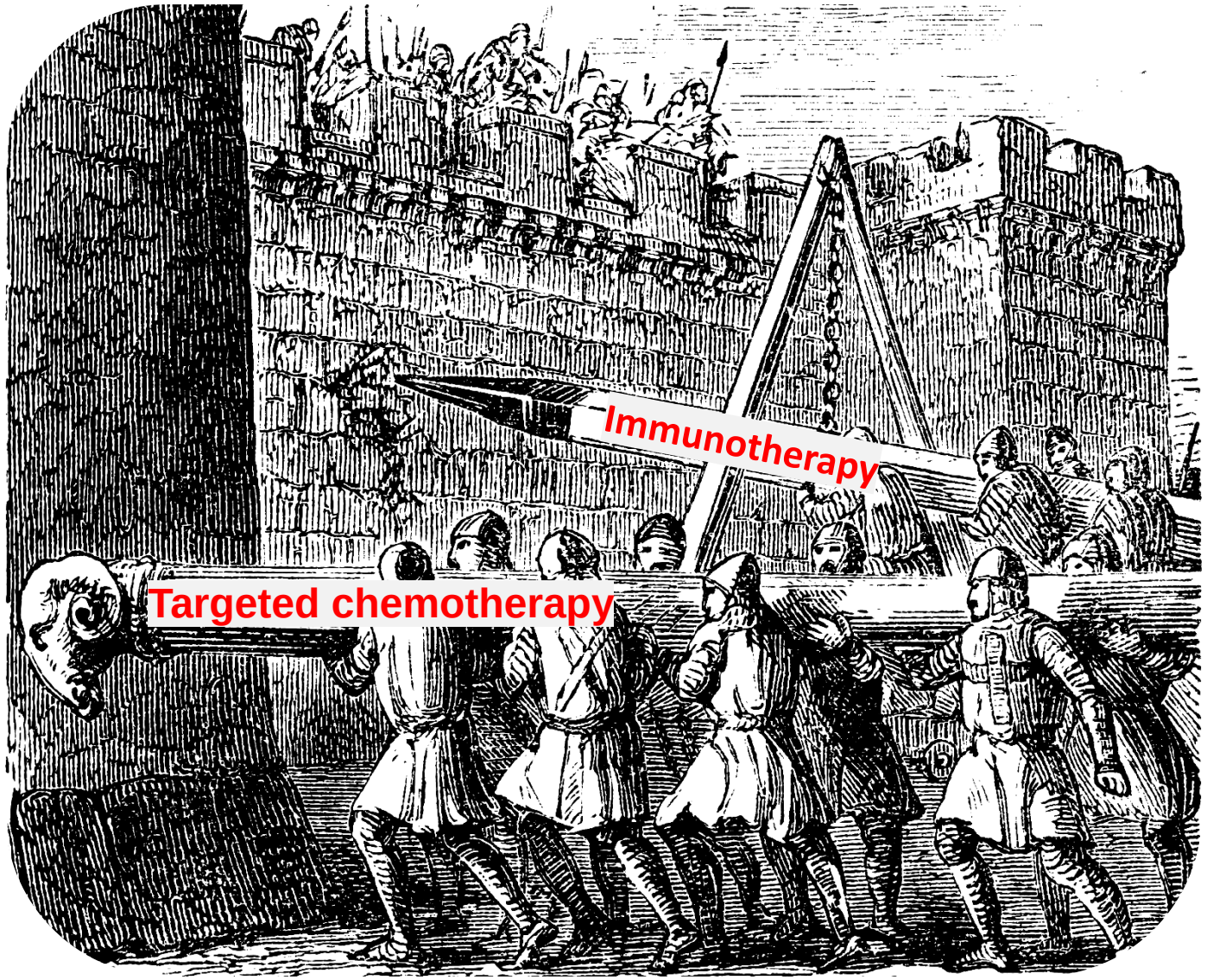
POLARIX study

- **Pola-R-CHP significantly prolongs PFS** compared with R-CHOP (HR: 0.73) in patients with intermediate- and high-risk previously untreated DLBCL
- The **safety profiles** of Pola-R-CHP and R-CHOP were **comparable**
- **Exploratory analyses** are ongoing with regard to various subgroups and other prognostic classification systems
- These results **support the use of Pola-R-CHP** in the initial management of patients with DLBCL

DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Tilly H *et al*. Abstract LBA-1. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Tilly H *et al. N Engl J Med* 2022; 386 (4): 351–363.

R/R DLBCL



DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory.

Polatuzumab vedotin plus mosunetuzumab in R/R aggressive B-cell NHL

Updated results from a Phase Ib/II study

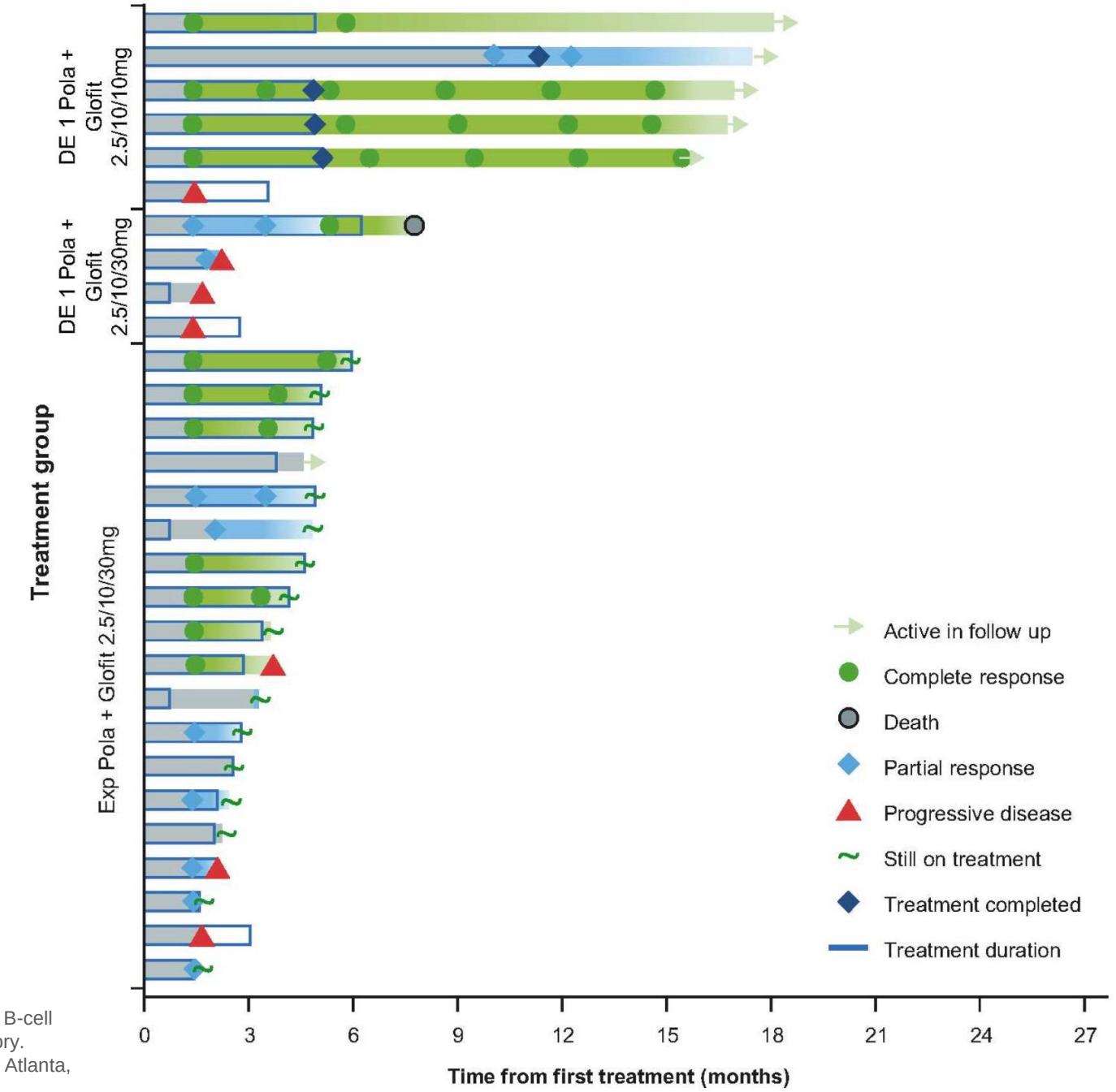
Response, n (%)	Dose escalation and dose expansion cohorts: Patients with R/R B-cell NHL only		Dose expansion cohort*	
	All (n=60)	Post-CAR-T therapy (n=24)	All (n=41)	Post-CAR-T therapy (n=17)
ORR	39 (65.0)	15 (62.5)	27 (65.9)	11 (64.7)
CR	29 (48.3)	10 (41.7)	20 (48.8)	8 (47.1)

*Only patients with R/R aggressive B-cell NHL were enrolled.
CAR-T, chimeric antigen receptor T-cell; CR, complete response; NHL, non-Hodgkin lymphoma; ORR, objective response rate; R/R, relapsed/refractory.
Budde LE *et al*. Abstract 533. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

R/R DLBCL

Polatuzumab + glofitamab

- Tolerable safety and encouraging preliminary efficacy
- Safety profile was consistent with that of the individual drugs
- CRS and neurologic AEs were limited to Grade 1 or 2; no new safety signals were detected



AE, adverse event; CRS, cytokine release syndrome; DE, dose escalation; DLBCL, diffuse large B-cell lymphoma; Exp, expansion; Glofit, glofitamab; Pola, polatuzumab vedotin; R/R, relapsed/refractory.

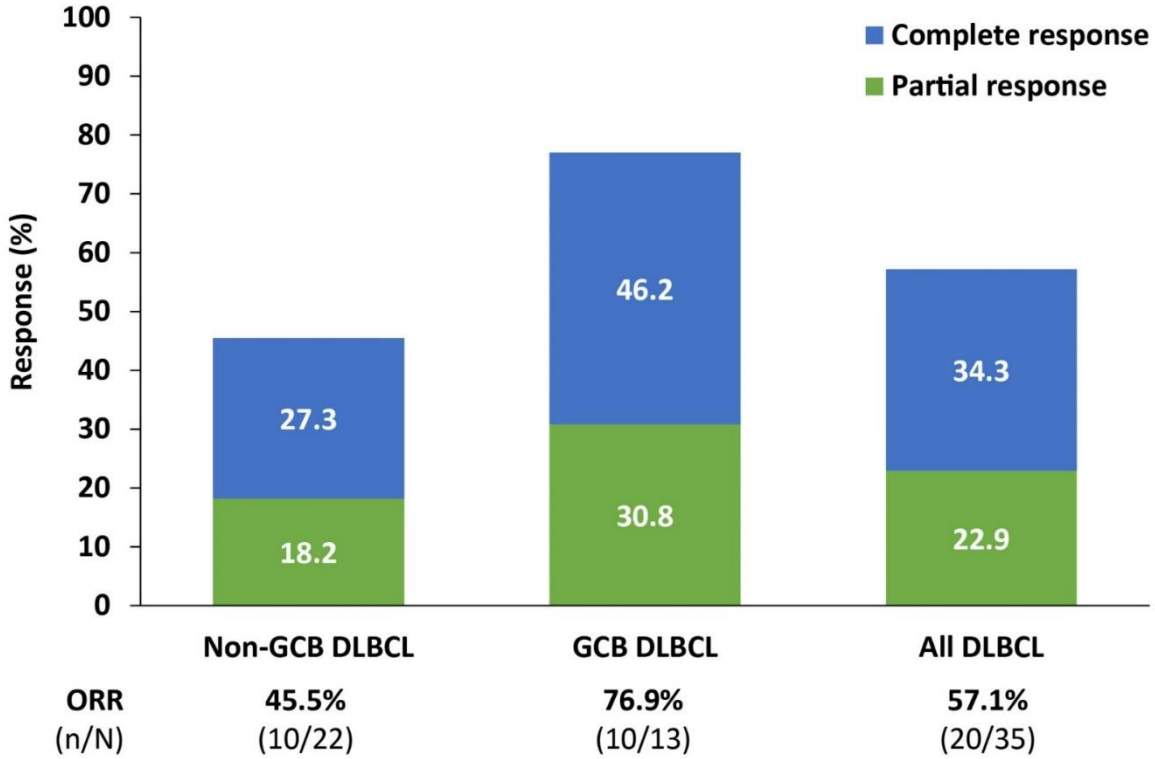
Hutchings M *et al*. Abstract 525. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Loncastuximab plus ibrutinib in patients with advanced DLBCL

Interim analysis of a Phase II study (LOTIS-3)

- Total patients with R/R DLBCL, N=35
  - R/R non-GCB DLBCL, n=22
  - R/R GCB DLBCL, n=13
- Median age of 72 years (range: 19–82)
- Median of 3 prior therapies (range: 1–6), including stem cell transplant
- Median of 2 (range: 1–6) cycles of loncastuximab and 4 (range: 1–10) cycles of ibrutinib

Response in patients receiving loncastuximab 60 µg/kg and ibrutinib 560 mg



DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell–like; ORR, overall response rate; R/R, relapsed/refractory.

Carlo-Stella C *et al*. Abstract 54. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Other highlights in brief

Abstract, first author	Presentation title	Key findings
3564, Bartlett NL[1]	Brentuximab vedotin in combination with lenalidomide and rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (ECHELON-3, trial in progress)	CRs were observed in both CD30-positive and CD30-negative patients
526, Levy MY[2]	Safety and efficacy of CD37-targeting naratuximab emtansine PLUS rituximab in diffuse large B-cell lymphoma and other NON-Hodgkin's B-cell lymphomas – a phase 2 study	The combination of naratuximab emtansine + rituximab resulted in good OR and CR rates, durable responses, a manageable safety profile, and full CD37 target engagement
2, Locke FL[3]	Primary analysis of ZUMA-7: A phase 3 randomized trial of axicabtagene ciloleucel (axi-cel) versus standard-of-care therapy in patients with relapsed/refractory large B-cell lymphoma	There was a statistically significant and clinically meaningful improvement in EFS with axi-cel vs. second-line SoC in R/R large B-cell lymphomas

CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; OR, overall response; R/R, relapsed/refractory; SoC, standard of care.

1. Bartlett NL *et al*. Abstract 3564. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 2. Levy MY *et al*. Abstract 526. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 3. Locke FL *et al*. Abstract 2. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Take-home messages

- Immunotherapy (immunomodulatory agents, bispecific monoclonal antibodies, CAR-T therapies) and targeted chemotherapy are becoming more and more important in DLBCL therapy
  - They may replace the present standard of care

- Escalating chemotherapy doses is no longer regarded as the most efficient salvage in DLBCL

CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma.


COLLEGE FOOTBALL
HALL OF FAME

ASH 2021 highlights: CLL/SLL

Professor Paolo Ghia
Vita-Salute San Raffaele University and
IRCCS San Raffaele Hospital, Italy

February 2022 | 0222-BGB-3111-MRC-062

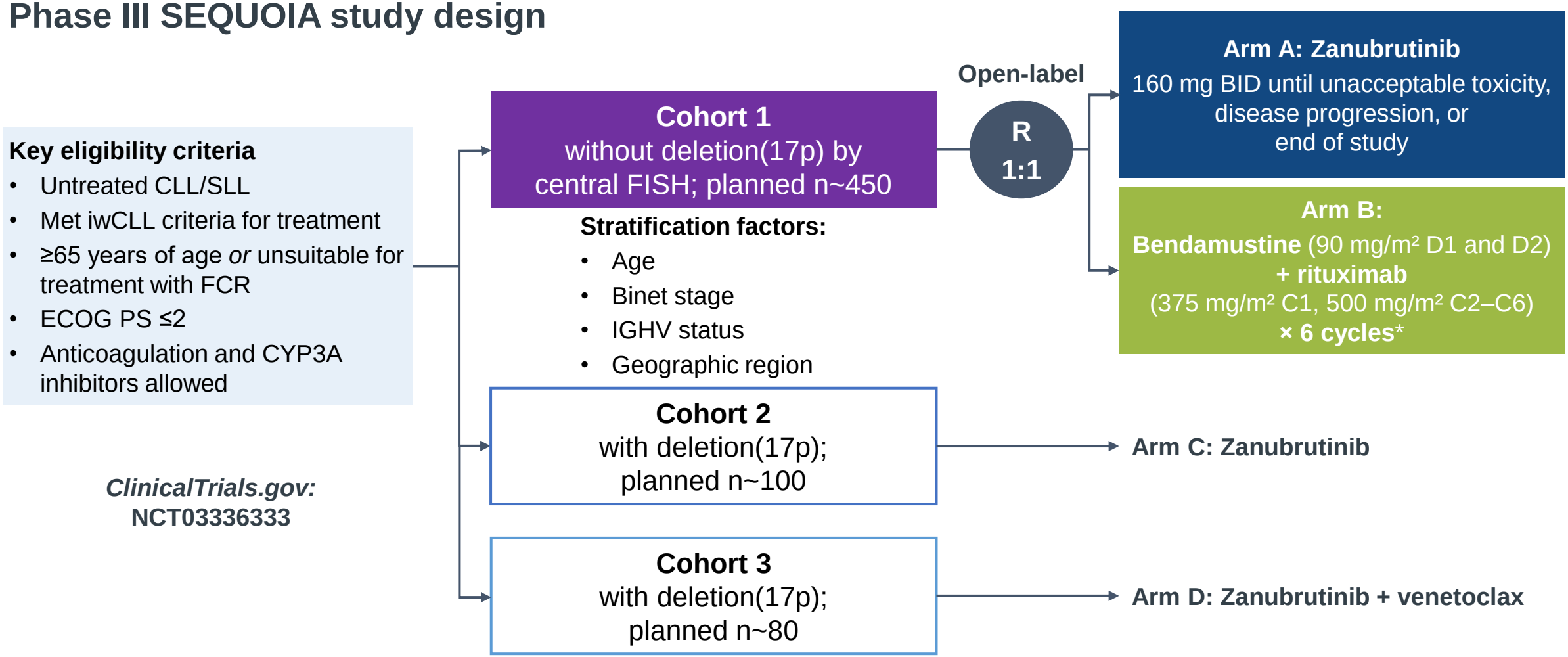
Disclosures

Research support / P.I.	AbbVie, AstraZeneca, BMS, Janssen
Employee	NA
Consultant	AbbVie, AstraZeneca, ArQule/MSD, BeiGene, BMS, Janssen, Loxo/Lilly, Roche
Major stockholder	NA
Speakers bureau	NA
Honoraria	AbbVie, AstraZeneca, ArQule/MSD, BeiGene, BMS, Janssen, Loxo/Lilly, Sanofi, Roche
Scientific advisory board	AbbVie, AstraZeneca, ArQule/MSD, BeiGene, BMS, Janssen, Loxo/Lilly, Roche

BMS, Bristol Myers Squibb; MSD, Merck Sharp & Dohme Corp.; NA, not applicable; P.I., principal investigator.

Zanubrutinib vs. bendamustine plus rituximab

Phase III SEQUOIA study design



*1 cycle = 28 days.

BID, twice a day; C, Cycle; CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P450 3A; D, Day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; R, randomization; SLL, small lymphocytic lymphoma.

Tam CS *et al*. Abstract 396. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Zanubrutinib vs. bendamustine plus rituximab

Baseline patient and disease characteristics

Characteristic	Arm A: Zanubrutinib (n=241)	Arm B: Bendamustine + rituximab (n=238)
Median age, years (IQR)	70 (66–75)	70 (66–74)
Age ≥65 years, n (%)	196 (81.3)	192 (80.7)
Male, n (%)	154 (63.9)	144 (60.5)
ECOG PS 2, n (%)	15 (6.2)	20 (8.4)
Geographic region, n (%) North America Europe Asia/Pacific	 34 (14.1) 174 (72.2) 33 (13.7)	 28 (11.8) 172 (72.3) 38 (16.0)
Binet stage C,* n (%)	70 (29.0)	70 (29.4)
Bulky disease ≥5 cm, n (%)	69 (28.6)	73 (30.7)
Cytopenia at baseline,† n (%)	102 (42.3)	109 (45.8)
Unmutated *IGHV* gene, n/N (%)	125/234 (53.4)	121/231 (52.4)
Deletion(11q), n (%)	43 (17.8)	46 (19.3)
***TP53* mutation, n/N (%)**	15/232 (6.5)	13/223 (5.8)

*Patients with SLL had Binet stage calculated as if they had CLL. †Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100 × 10^9/L) or neutropenia (absolute neutrophil count ≤1.5 × 10^9/L).
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; SLL, small lymphocytic lymphoma.
Tam CS *et al*. Abstract 396. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Zanubrutinib vs. bendamustine plus rituximab

AEs

Common AEs (≥12% of patients in any arm)

AE, n (%)	Arm A: Zanubrutinib (n=240*)		Arm B: Bendamustine + rituximab (n=227)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
URTI	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia	37 (15.4)	27 (11.3)	129 (56.8)	116 (51.1)
Diarrhea	33 (13.8)	0 (0.0)	30 (13.2)	4 (1.8)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Fatigue	28 (11.7)	3 (1.3)	36 (15.9)	2 (0.9)
Rash	26 (10.8)	0 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0 (0.0)	33 (14.5)	3 (1.3)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)
Infusion-related reaction†	1 (0.4)	0 (0.0)	43 (18.9)	6 (2.6)

AEs of interest

AE, n (%)	Arm A: Zanubrutinib (n=240)		Arm B: Bendamustine + rituximab (n=227)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic other cancers	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

Median follow-up: 26.2 months.

*Safety was assessed in patients who received ≥1 dose of treatment; I patient in arm A and 11 patients in arm B did not receive treatment. †Due to amphotericin B infusion.

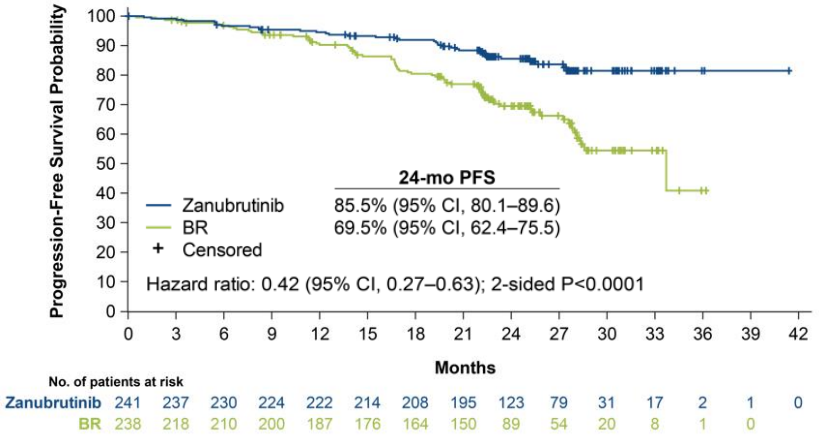
AE, adverse event; URTI, upper respiratory tract infection.

Tam CS *et al*. Abstract 396. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

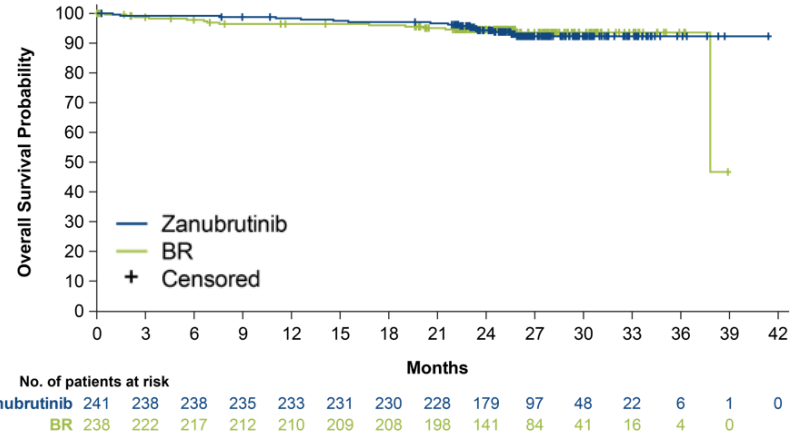
Zanubrutinib vs. bendamustine plus rituximab

Outcomes

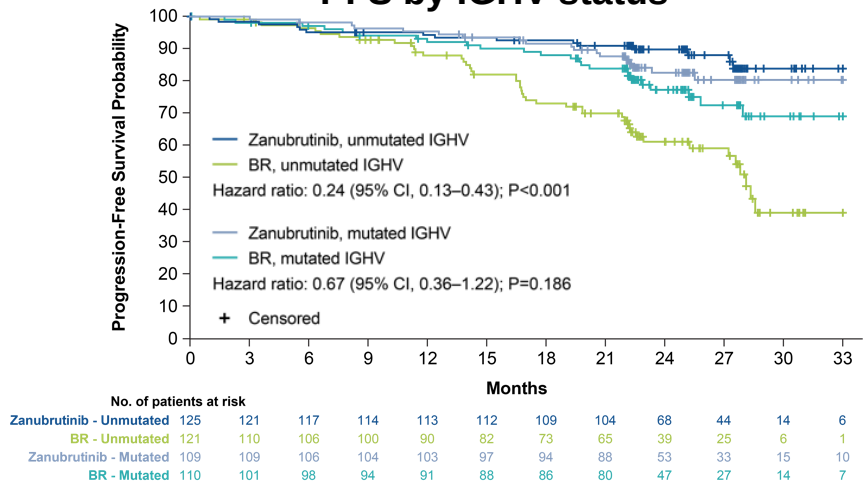
PFS



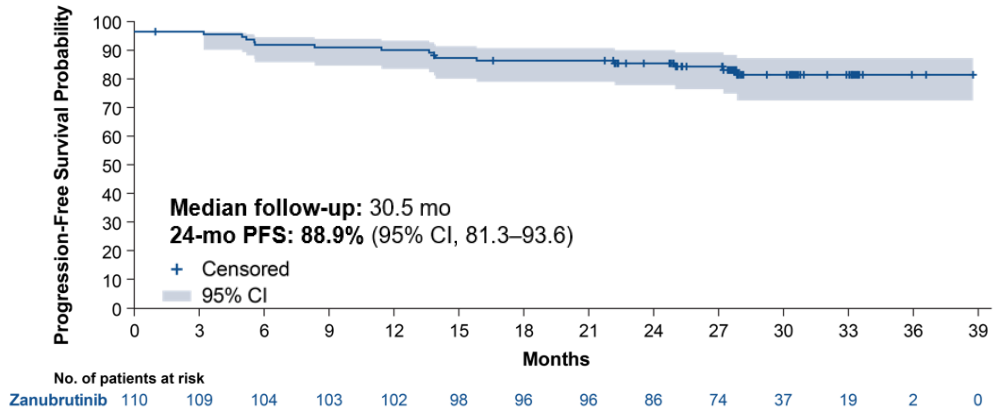
OS



PFS by IGHV status



Cohort 2: PFS in Patients With Del(17p)

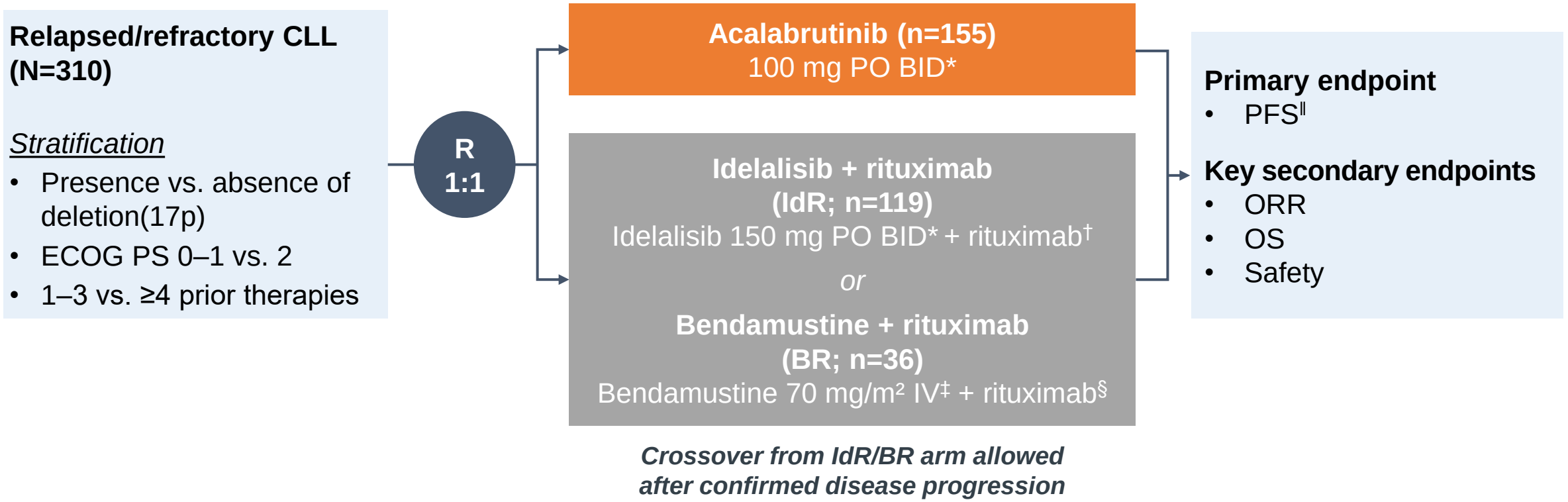


Median follow-up: 26.2 months. BR, bendamustine and rituximab; CI, confidence interval; IGHV, immunoglobulin heavy chain variable; OS, overall survival; PFS, progression-free survival.

Tam CS *et al*. Abstract 396. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Acalabrutinib vs. idelalisib plus rituximab or bendamustine plus rituximab

Phase III ASCEND study design



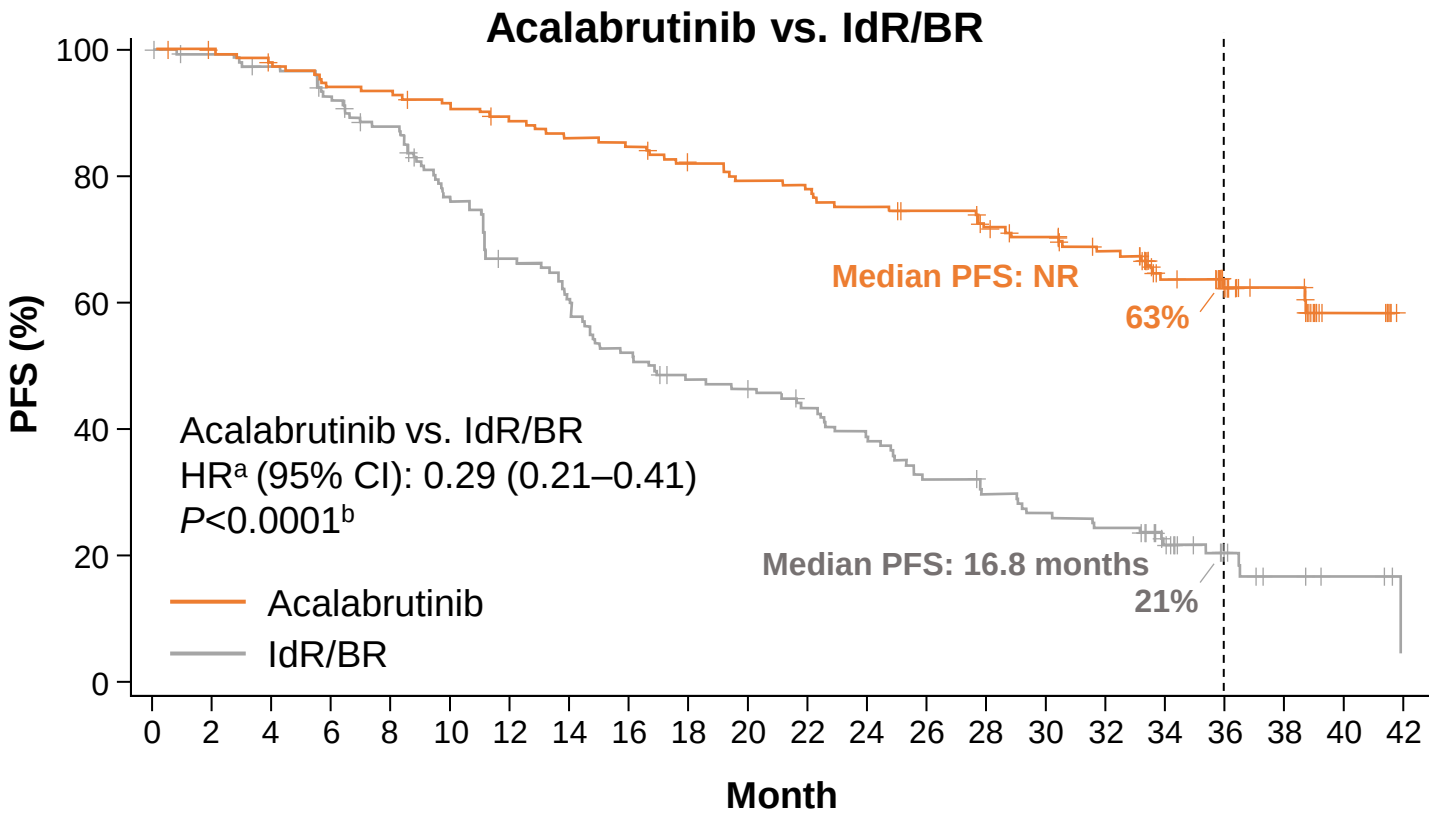
*Until progression or unacceptable toxicity. †375 mg/m² IV on Day 1 of the first cycle, then subsequent doses at 500 mg/m² every 2 weeks for four infusions followed by every 4 weeks for three infusions. ‡On Day 1 and Day 2 of Cycles 1–6. §375 mg/m² IV on Day 1 of the first cycle, then subsequent doses at 500 mg/m² on Day 1 of Cycles 2–6. ‖PFS was based only on investigator assessment after the interim analysis, when the primary endpoint of independent review committee–assessed PFS was met.

BID, twice a day; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization.

Ghia P *et al*. *J Clin Oncol* 2020; 38 (25): 2849–2861.

Acalabrutinib vs. idelalisib plus rituximab or bendamustine plus rituximab
Investigator-assessed PFS

- Median time on study: 36.0 months (acalabrutinib) and 35.2 months (IdR/BR)



Acalabrutinib vs. IdR vs. BR

Acalabrutinib vs. IdR
HR[c] (95% CI): 0.31 (0.22–0.43); *P*<0.0001[d]

Acalabrutinib vs. BR
HR[c] (95% CI): 0.25 (0.16–0.40); *P*<0.0001[d]

[a]Hazard ratio was based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in an interactive voice/web response system. [b]P-value was based on stratified log-rank test, stratified by randomization stratification factors as recorded in an interactive voice/web response system. [c]Hazard ratios were based on unstratified Cox proportional hazards model. [d]P-values were based on unstratified log-rank test. BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; IdR, idelalisib and rituximab; NR, not reached; PFS, progression-free survival.
Jurczak W *et al*. Abstract 393. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Acalabrutinib vs. idelalisib plus rituximab or bendamustine plus rituximab

AEs in ≥15% (any grade) or ≥5% (Grade ≥3) of patients in any cohort

Most common AEs, n (%)	Acalabrutinib (n=154)		IdR (n=118)		BR (n=35)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Headache	36 (23)	1 (1)	7 (6)	0	0	0
Neutropenia	36 (23)	29 (19)	55 (47)	47 (40)	12 (34)	11 (31)
Diarrhea	33 (21)	3 (2)	62 (53)	29 (25)	5 (14)	0
URTI	31 (20)	3 (2)	20 (17)	4 (3)	4 (11)	1 (3)
Pneumonia	28 (18)	14 (9)	16 (14)	11 (9)	2 (6)	1 (3)
Cough	27 (18)	0	18 (15)	1 (1)	2 (6)	0
Anemia	26 (17)	20 (13)	13 (11)	9 (8)	4 (11)	3 (9)
Pyrexia	24 (16)	3 (2)	23 (20)	8 (7)	6 (17)	1 (3)
Thrombocytopenia	19 (12)	6 (4)	19 (16)	10 (9)	5 (14)	1 (3)
Fatigue	19 (12)	2 (1)	10 (9)	1 (1)	8 (23)	1 (3)
Nausea	13 (8)	0	17 (14)	1 (1)	7 (20)	0
ALT increased	4 (3)	3 (2)	14 (12)	10 (9)	3 (9)	1 (3)
AST increased	4 (3)	2 (1)	11 (9)	6 (5)	2 (6)	1 (3)
Neutrophil count decreased	3 (2)	2 (1)	9 (8)	9 (8)	1 (3)	1 (3)
Infusion-related reaction	0	0	9 (8)	2 (2)	8 (23)	1 (3)
Transaminases increased	0	0	9 (8)	7 (6)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BR, bendamustine and rituximab; IdR, idelalisib and rituximab; URTI, upper respiratory tract infection.

Jurczak W *et al*. Abstract 393. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Acalabrutinib vs. idelalisib plus rituximab or bendamustine plus rituximab

AEs of clinical interest

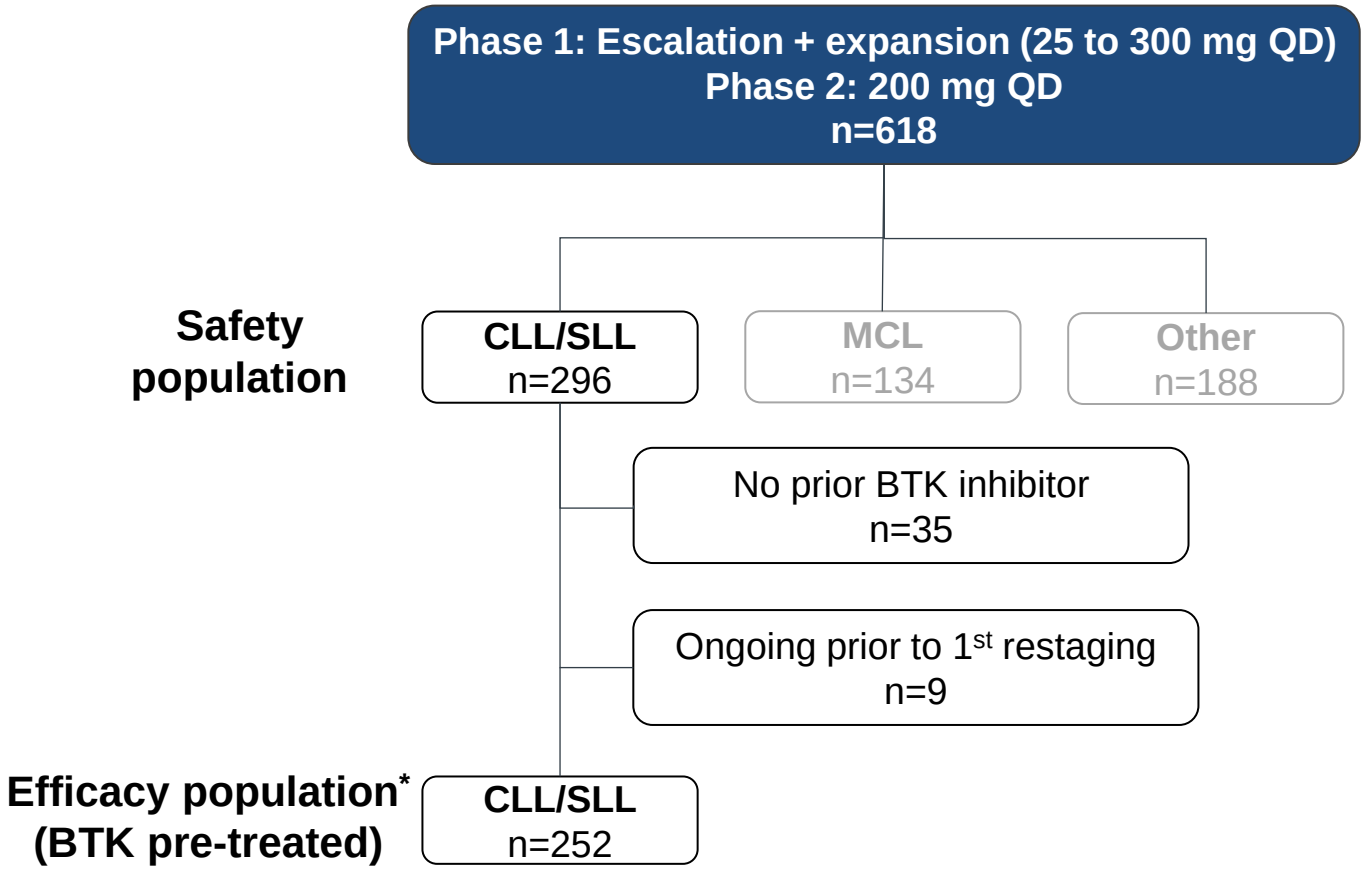
AE of clinical interest, n (%)	Acalabrutinib (n=154)		IdR (n=118)		BR (n=35)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Atrial fibrillation	10 (7)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Hemorrhage Major hemorrhage	46 (30) 5 (3)	4 (3) 4 (3)	10 (9) 3 (3)	3 (3) 3 (3)	2 (6) 1 (3)	1 (3) 1 (3)
Hypertension	11 (7)	7 (5)	6 (5)	1 (1)	0	0
Infections	100 (65)	38 (25)	83 (70)	37 (31)	17 (49)	4 (11)
Second primary malignancies excluding NMSC	11 (7)	8 (5)	2 (2)	1 (1)	2 (6)	2 (6)
Tumor lysis syndrome	1 (1)	1 (1)	1 (1)	1 (1)	0	0

AE, adverse event; BR, bendamustine and rituximab; IdR, idelalisib and rituximab; NMSC, non-melanoma skin cancer.

Jurczak W *et al*. Abstract 393. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

Pirtobrutinib, a non-covalent BTK inhibitor

Phase 1/2 BRUIN study



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18 years
- ECOG PS 0–2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

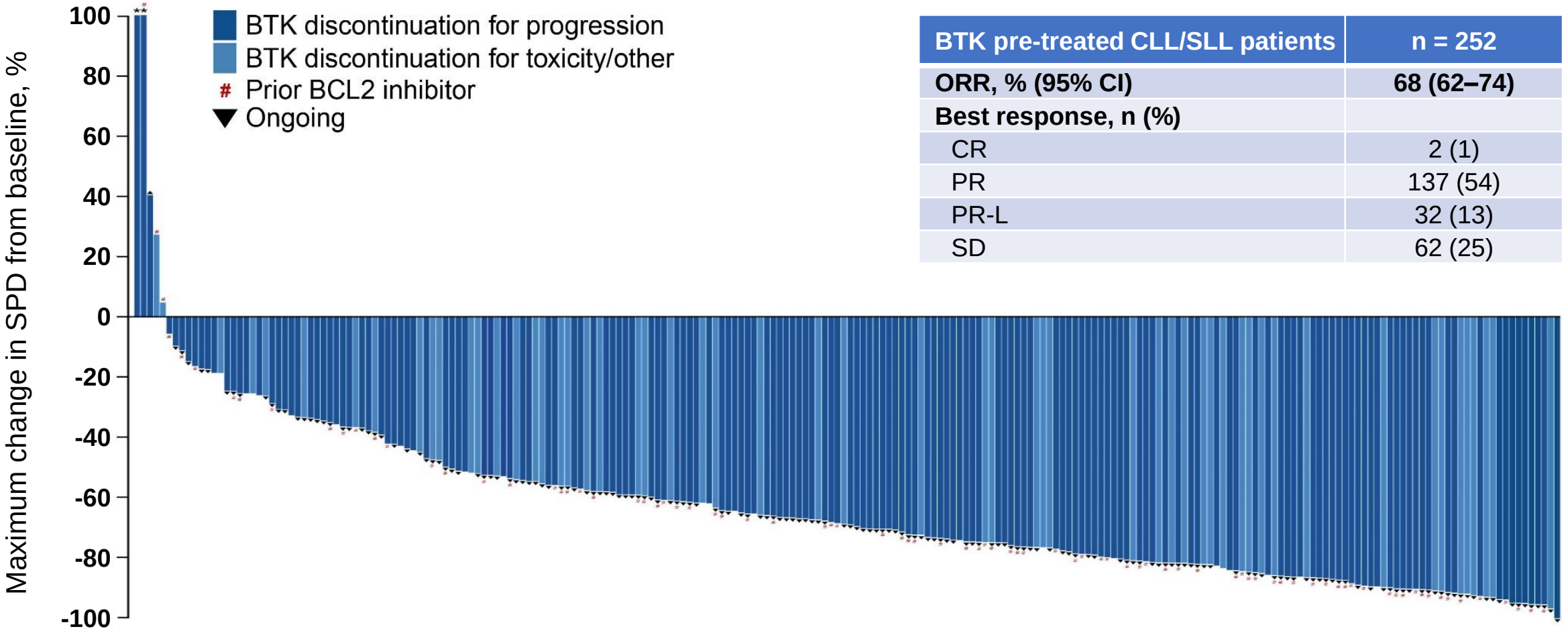
Key endpoints

- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (iwCLL)

Data cutoff: 16 July 2021. *Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment.
CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MTD, maximum tolerated dose; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; SLL, small lymphocytic lymphoma.
Mato AR *et al*. Abstract 391. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

Pirtobrutinib, a non-covalent BTK inhibitor

Responses in patients with CLL/SLL



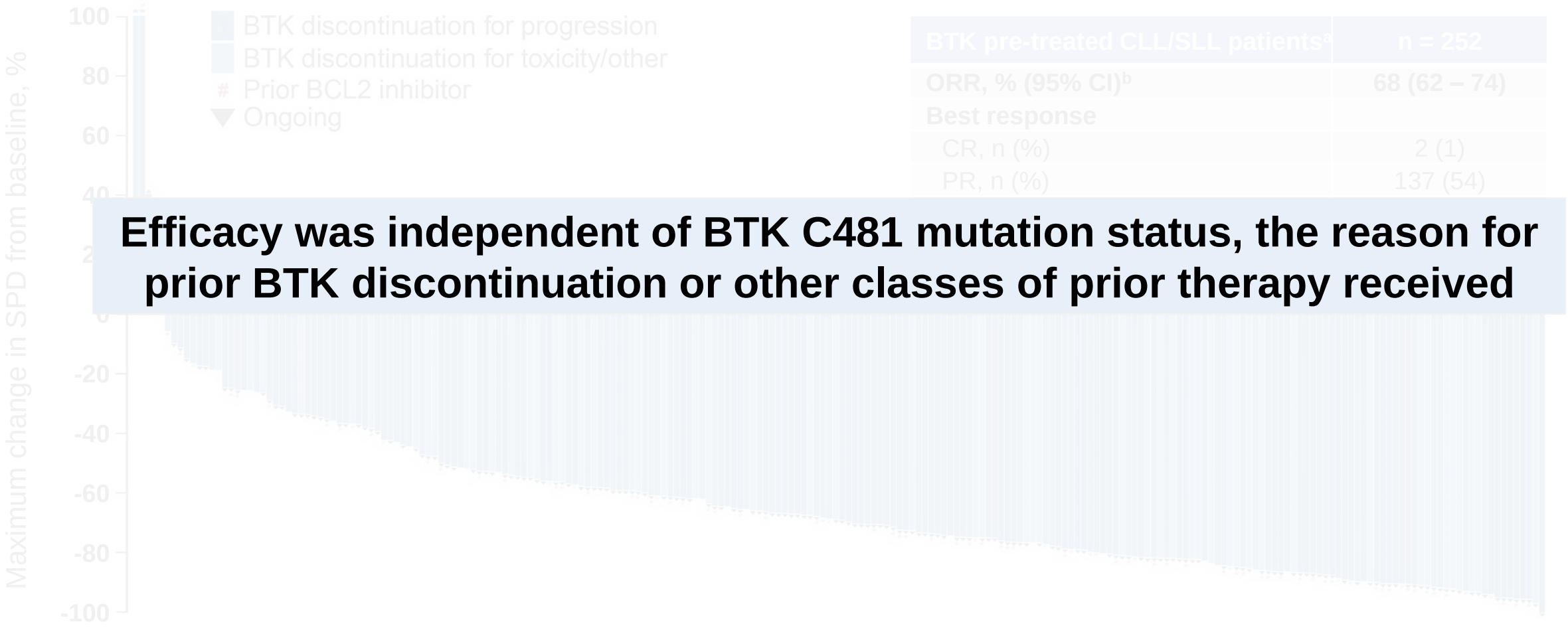
BTK pre-treated CLL/SLL patients	n = 252
ORR, % (95% CI)	**68 (62–74)**
Best response, n (%)	
CR	2 (1)
PR	137 (54)
PR-L	32 (13)
SD	62 (25)

CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the products of diameters.

Mato AR *et al*. Abstract 391. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Pirtobrutinib, a non-covalent BTK inhibitor

Responses in patients with CLL/SLL



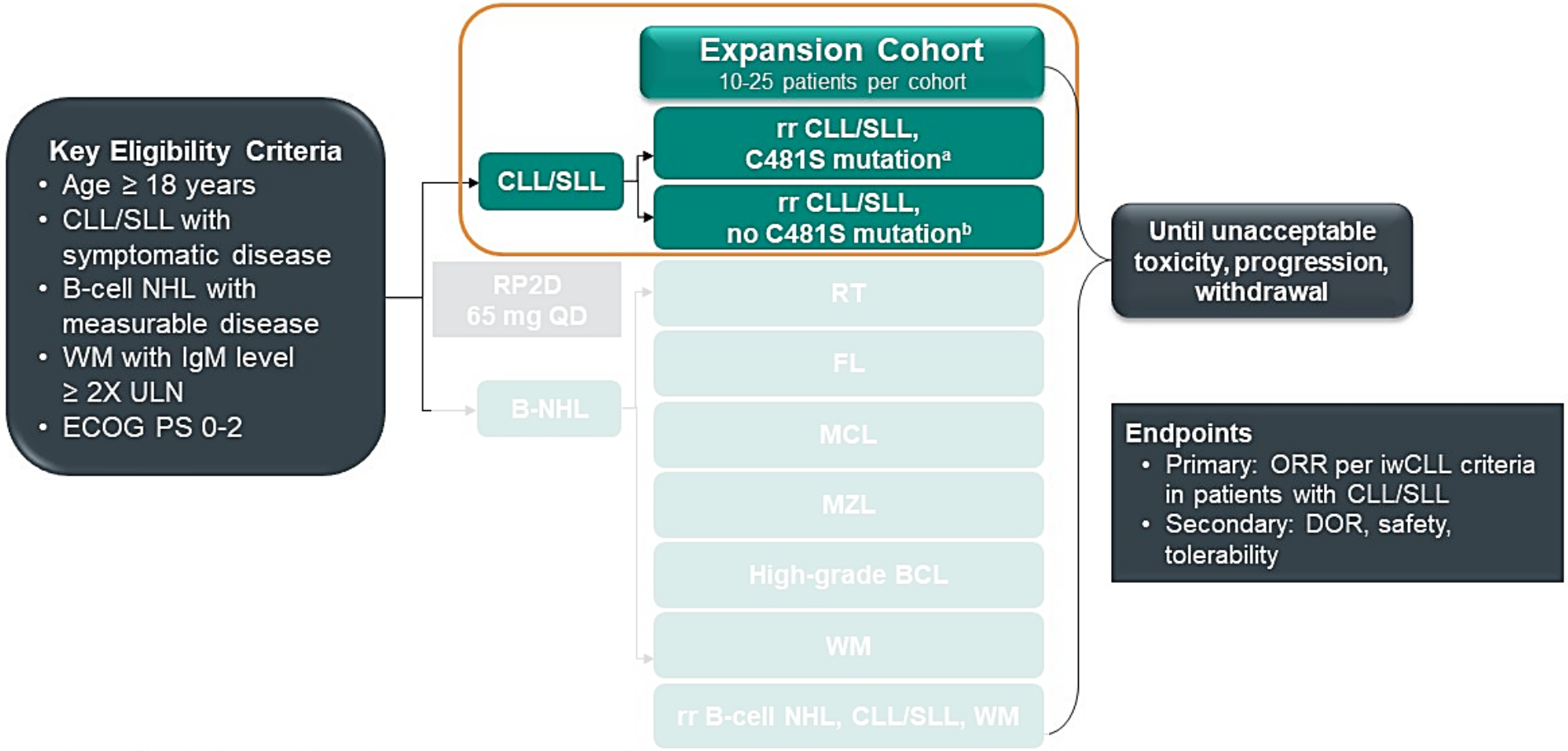
BTK pre-treated CLL/SLL patients[a]	n = 252
ORR, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)

Efficacy was independent of BTK C481 mutation status, the reason for prior BTK discontinuation or other classes of prior therapy received

Mato AR *et al*. Abstract 391. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

MK-1026, a non-covalent inhibitor of WT and C481S mutated BTK

Phase 2 dose expansion study



[a]Cohort A: patients with R/R CLL/SLL with ≥2 prior therapies including covalent BTKi, with C481S mutation. [b]Cohort B: patients with R/R CLL/SLL with ≥2 prior therapies who were intolerant to or progressed on a BTKi , with no C481S.

CLL, chronic lymphocytic leukemia; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; rr, relapsed/refractory; SLL, small lymphocytic lymphoma; ULN, upper limit of normal; WM, Waldenström's macroglobulinaemia.

Woyach JA *et al*. Abstract 392. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

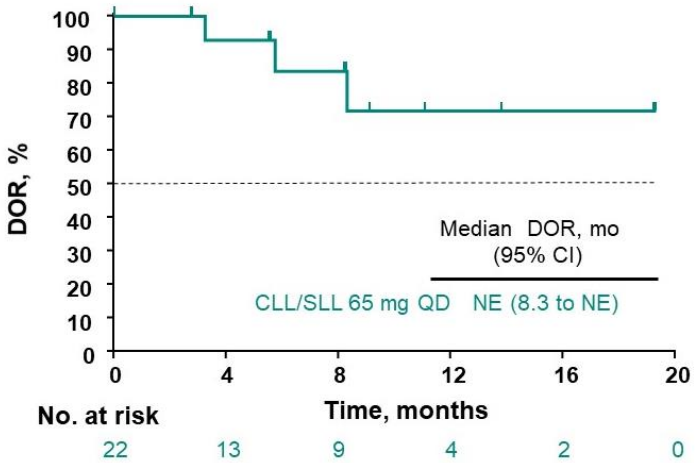
MK-1026, a non-covalent inhibitor of WT and C481S mutated BTK

Patient characteristics and outcomes

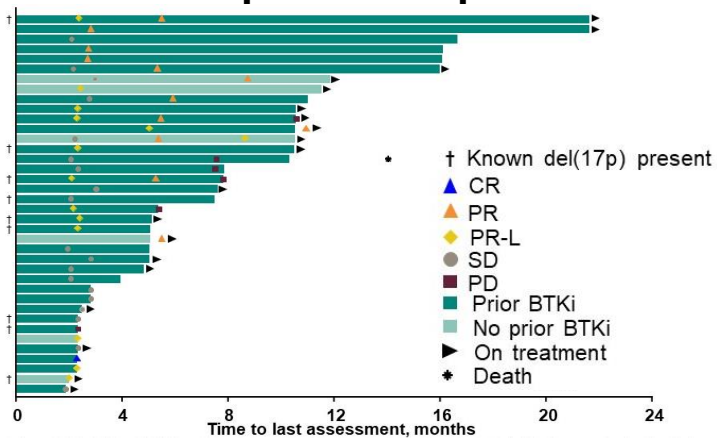
Characteristic, n (%)	CLL/SLL 65 mg QD N = 51
Prior lines, median (range)	4 (1-18)
Prior BTK inhibitor therapy	43 (84.3)
ECOG PS 0	14 (27.5)
1	32 (62.7)
2	5 (9.8)
IGHV Unmutated	30 (58.8)
Mutated	2 (3.9)
Unknown	19 (37.3)
Del (17p) Present	12 (23.5)
Absent	33 (64.7)
Missing	6 (11.8)
BTK C481S Present	32 (62.7)
Absent	12 (23.5)
Unknown/Missing	7 (13.7)

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38
ORR	**22 (57.9%)**
	[40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]

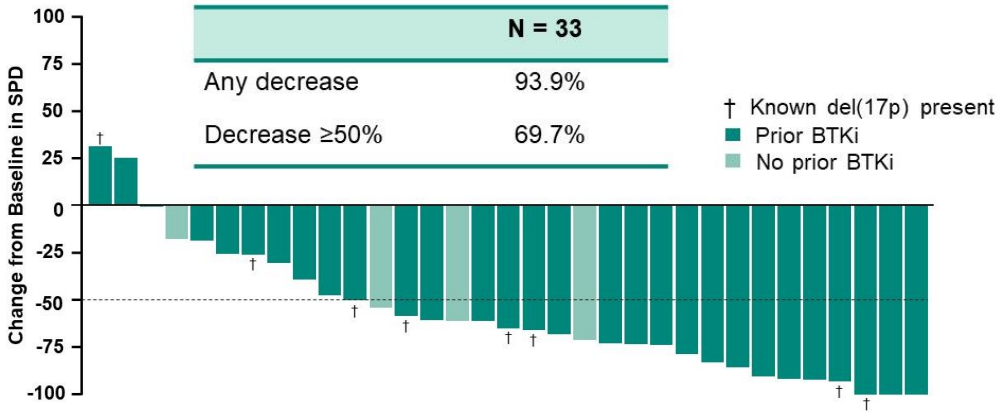
DOR



Individual patient responses



Percent SPD change from baseline

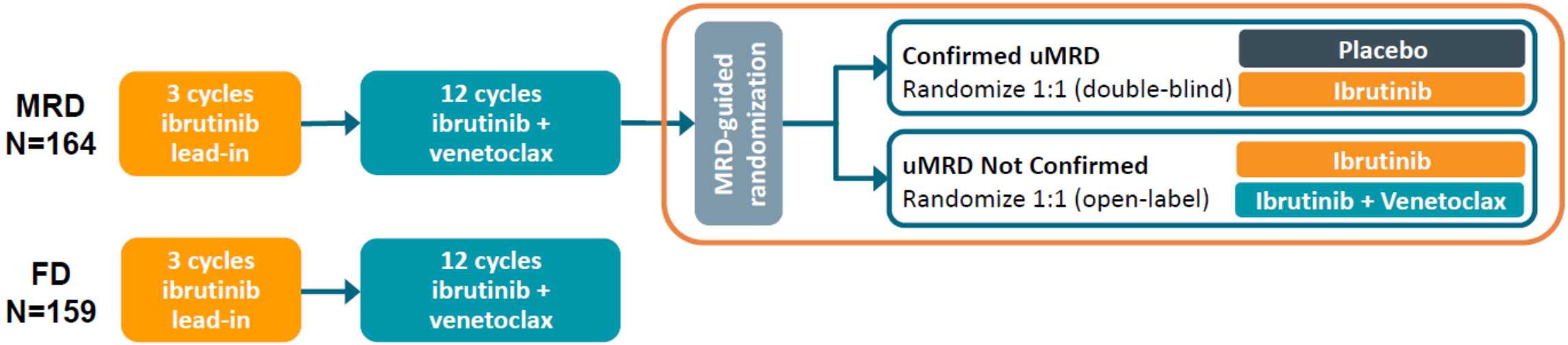


CLL, chronic lymphocytic leukemia; CI, confidence interval; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; QD, once a day; SD, stable disease; SLL, small lymphocytic lymphoma.

Woyach JA *et al*. Abstract 392. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

First-line treatment with ibrutinib plus venetoclax

Phase II CAPTIVATE study design



uMRD rates with 12 cycles of ibrutinib + venetoclax

	Peripheral blood (n=163)	Bone marrow (n=155)
Best response of uMRD in evaluable patients, % (95% CI)	75 (69–82)	72 (65–79)

CI, confidence interval; FD, fixed-duration; MRD, minimal residual disease; uMRD, undetectable minimal residual disease.

Ghia P *et al*. Abstract 68. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

First-line treatment with ibrutinib plus venetoclax

MRD cohort patient and disease characteristics

Characteristic	All Treated Population N=164	Confirmed uMRD (n=86)		uMRD Not Confirmed (n=63)	
		Placebo n=43	Ibrutinib n=43	Ibrutinib n=31	Ibrutinib + Venetoclax n=32
Median age (range), year	58 (28–69)	61 (43–69)	56 (34–69)	58 (28–69)	56 (37–69)
Rai stage III/IV disease, n (%)	53 (32)	15 (35)	8 (19)	14 (45)	11 (34)
High-risk features, n (%)					
del(17p)/*TP53* mutation	32 (20)	2 (5)	13 (30)	5 (16)	8 (25)
del(11q)[a]	28 (17)	8 (19)	10 (23)	3 (10)	2 (6)
Complex karyotype[b]	31 (19)	4 (9)	13 (30)	5 (16)	4 (13)
Unmutated IGHV	99 (60)	30 (70)	30 (70)	14 (45)	15 (47)
Any cytopenia, n (%)	59 (36)	19 (44)	6 (14)	13 (42)	14 (44)
ANC ≤1.5 × 10^9/L	14 (9)	5 (12)	0	2 (6)	4 (13)
Hemoglobin ≤11 g/dL	35 (21)	14 (33)	2 (5)	9 (29)	7 (22)
Platelets ≤100 × 10^9/L	30 (18)	4 (9)	4 (9)	9 (29)	9 (28)
Lymph node diameter, n (%)					
≥5 cm	53 (32)	18 (42)	10 (23)	7 (23)	11 (34)
Median ALC × 10^9/L (range)	56 (1–419)	53 (1–235)	56 (2–256)	85 (1–342)	87 (3–419)
ALC ≥25 × 10^9/L, n (%)	125 (76)	32 (74)	34 (79)	25 (81)	24 (75)

[a]Without del(17p) per Dohner hierarchy. [b]Defined as ≥3 abnormalities by CpG-stimulated cytogenetics.
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; IGHV, immunoglobulin heavy chain variable region; uMRD, undetectable minimal residual disease.
Ghia P *et al*. Abstract 68. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

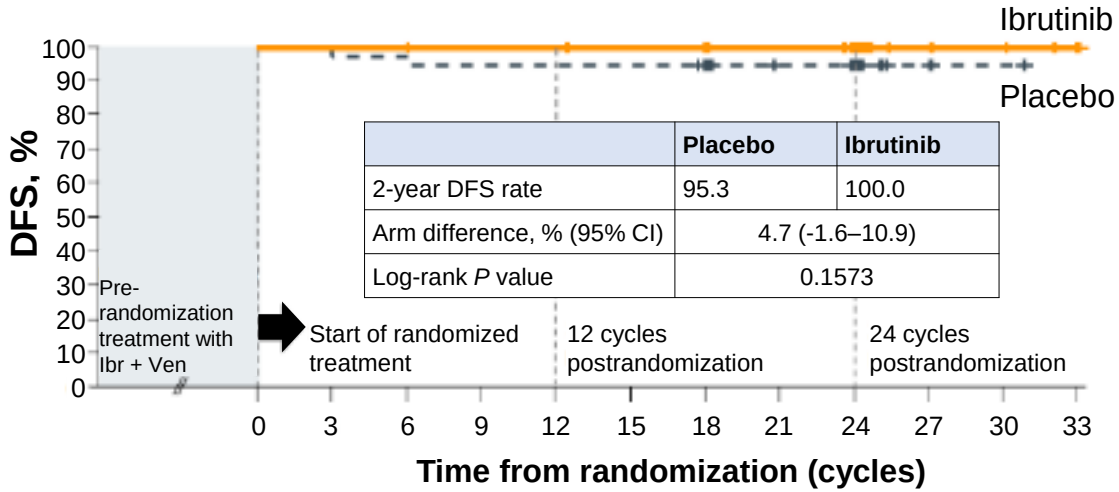
First-line treatment with ibrutinib plus venetoclax

MRD cohort outcomes

- 3-year PFS rates were ≥95% in all study arms
  - Confirmed uMRD
    - Placebo vs. Ibr: 95.3% vs. 100%
  - Not confirmed uMRD
    - Ibr vs. Ibr + Ven: 96.7% vs. 96.7%

- Not confirmed uMRD (Ibr vs. Ibr + Ven)
  - Best uMRD rates improved with further treatment
  - AEs were consistent with safety profiles of single-agent Ibr and Ven at 38-months median follow-up
  - No new safety signals emerged

DFS in patients with confirmed uMRD



	Placebo	Ibrutinib
2-year DFS rate	95.3	100.0
Arm difference, % (95% CI)	4.7 (-1.6–10.9)	
Log-rank *P* value	0.1573	

Patients at Risk

Ibrutinib	43	43	43	42	42	41	41	34	31	5	4	1
Placebo	43	43	42	41	41	40	36	28	22	2	1	0

Median follow-up: 24 months post-randomization

AE, adverse event; BM, bone marrow; DFS, disease-free survival; Ibr, ibrutinib; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable minimal residual disease; Ven, venetoclax.

Ghia P *et al*. Abstract 68. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. Speaker's personal files.

Summary

- Continuous BTKi use provides sustained responses[1,2]
- Second-generation BTKis appear to be well tolerated, with few cardiovascular toxicities reported in clinical trials[1,2]
- Third-generation BTKis appear to provide a well-tolerated option to rescue patients failing previous-generation molecules[3,4]
- The future will see the use of combinations of BTK and Bcl-2 inhibitors in a time-limited manner[5]

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor.

1. Tam CS *et al*. Abstract 396. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 2. Jurczak W *et al*. Abstract 393. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 3. Mato AR *et al*. Abstract 391. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 4. Woyach JA *et al*. Abstract 392. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 5. Ghia P *et al*. Abstract 68. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

ASH 2021 highlights: Indolent lymphomas

Professor Véronique Leblond
Pitié-Salpêtrière Hospital and Sorbonne University, France

February 2022 | 0222-BGB-3111-MRC-034

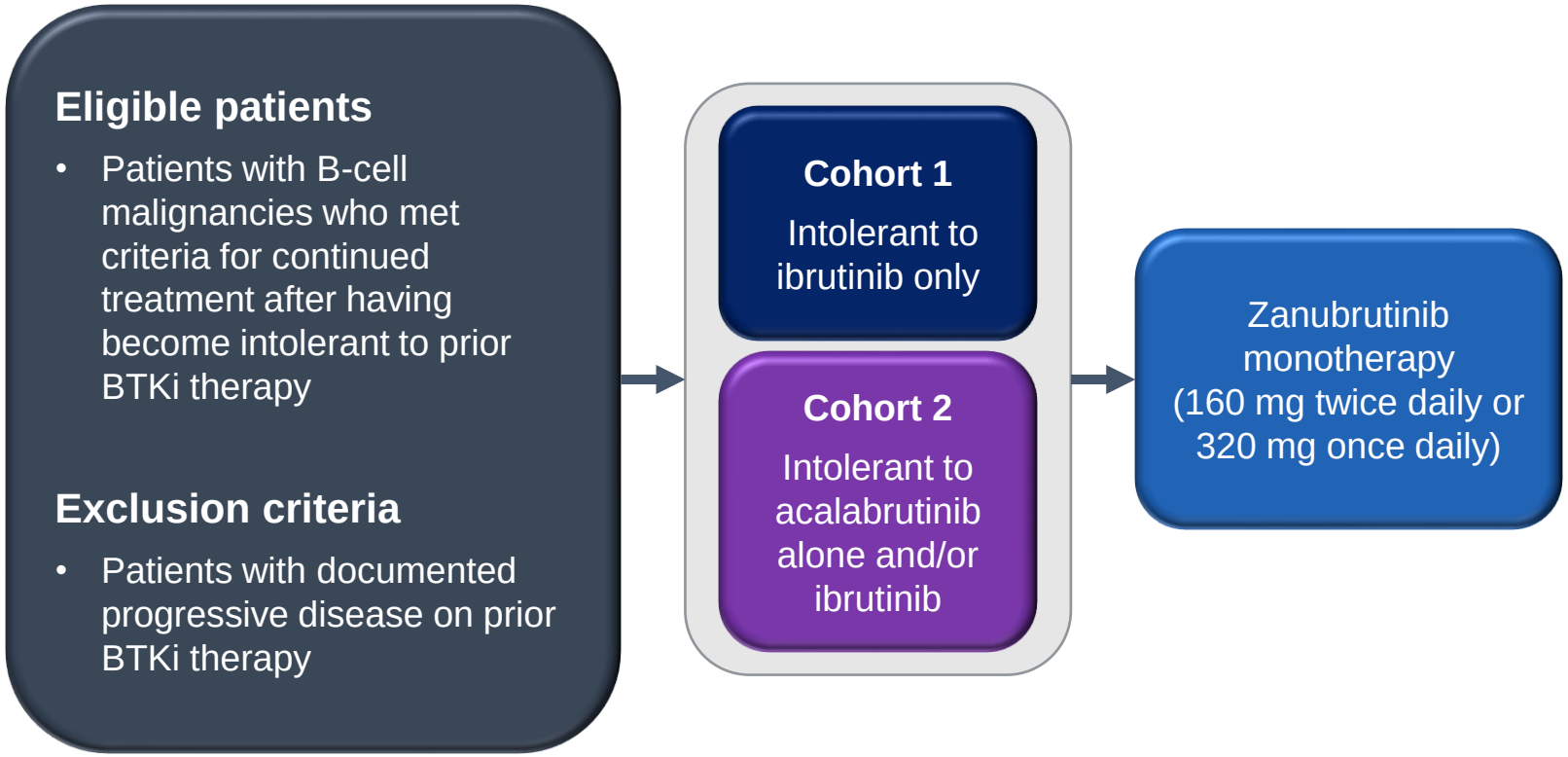
Disclosures

- **Speakers bureau:** Roche, Gilead, Janssen, AbbVie, BeiGene, GSK
- **Board:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, AstraZeneca, AbbVie
- **Honoraria:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, Lilly, Amgen, AstraZeneca, BeiGene

R/R B-cell malignancies

Zanubrutinib in BTK inhibitor–intolerant patients

- Phase II, US-based, multicenter, single-arm, open-label study



Primary outcome measure

- Recurrence and change in severity of treatment-emergent adverse events

Secondary outcome measures

- ORR*
- PFS*
- EQ-5D scores†
- EORTC scores†

*Determined by investigator at 24 months. †Patient-reported outcome at 24 months.
BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol 5-dimension questionnaire; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.
ClinicalTrials.gov NCT04116437. Available at: https://clinicaltrials.gov/ct2/show/NCT04116437. Accessed February 2022.

Zanubrutinib in BTK inhibitor–intolerant patients

Patient characteristics

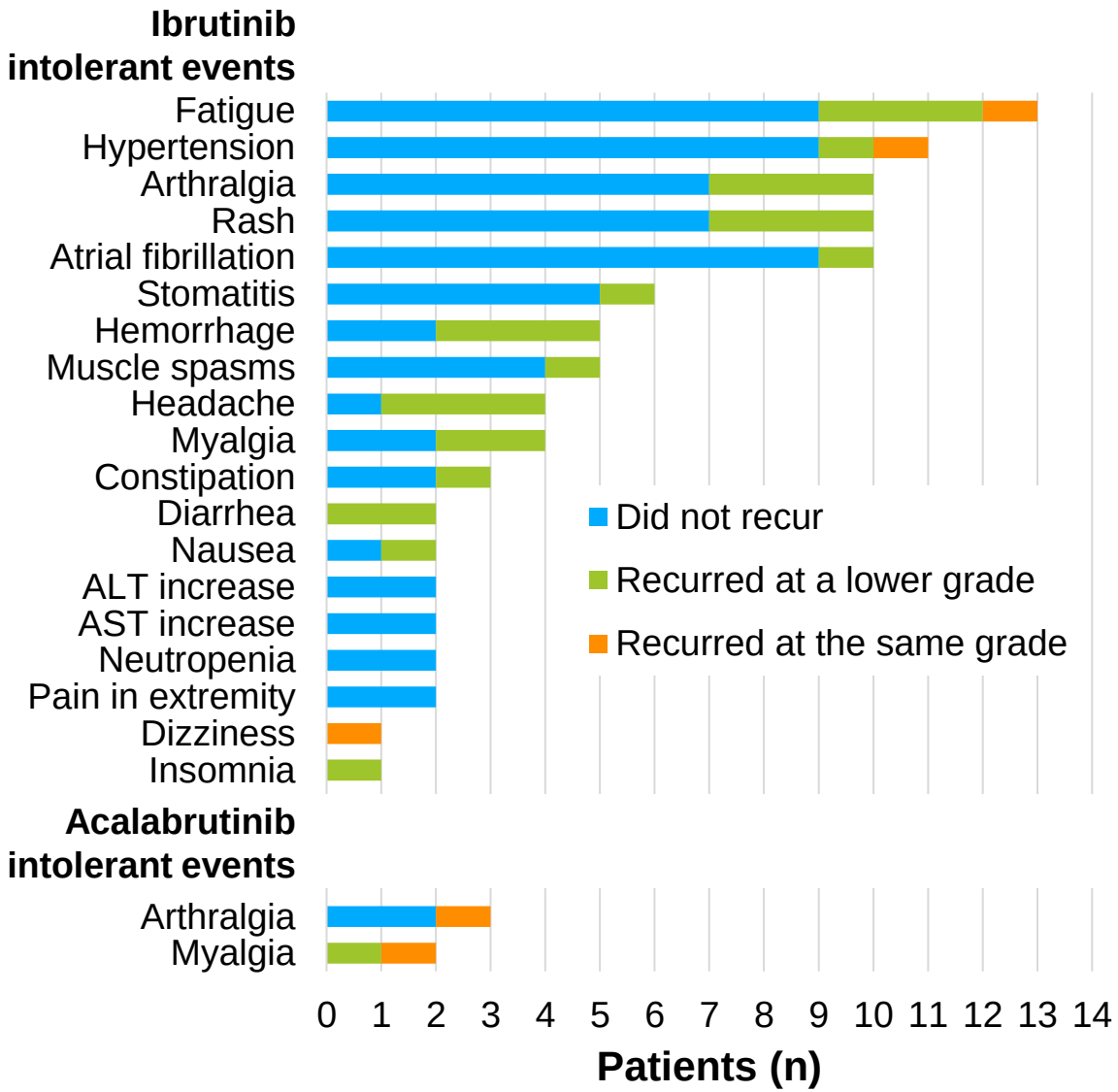
	Cohort 1*	Cohort 2†
All patients, n	57	7
CLL/SLL	44	4
WM	**9**	**1**
MCL	2	1
MZL	**2**	**1**
Median age, years (range)	71 (49–91)	71 (65–76)
Median duration of treatment, months (range)	8.7 (0.6–17.9)	8.2 (6.4–11.4)
Median prior regimens, n (range)	1 (1–12)	3 (2–5)
Median intolerant events per patient, n (range)	2 (1–5)	2 (1–5)

*Intolerant to ibrutinib only. †Intolerant to acalabrutinib alone and/or ibrutinib.
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.
Shadman M *et al*. Abstract 1410. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Efficacy and safety

- Patient responses to zanubrutinib:
  - 41% maintained and 53% improved on their reported best overall response on prior BTKis
  - Total disease control rate: 94%
  - **In WM: 30% PRs and 20% VGPRs**
- 73% of patients did not experience recurrence of their ibrutinib or acalabrutinib intolerant events
- 79% of recurrent events recurred at a lower severity
- **No patients experienced recurrence of an intolerant event at a higher severity**

Recurrence of ibrutinib and acalabrutinib intolerant events on zanubrutinib*



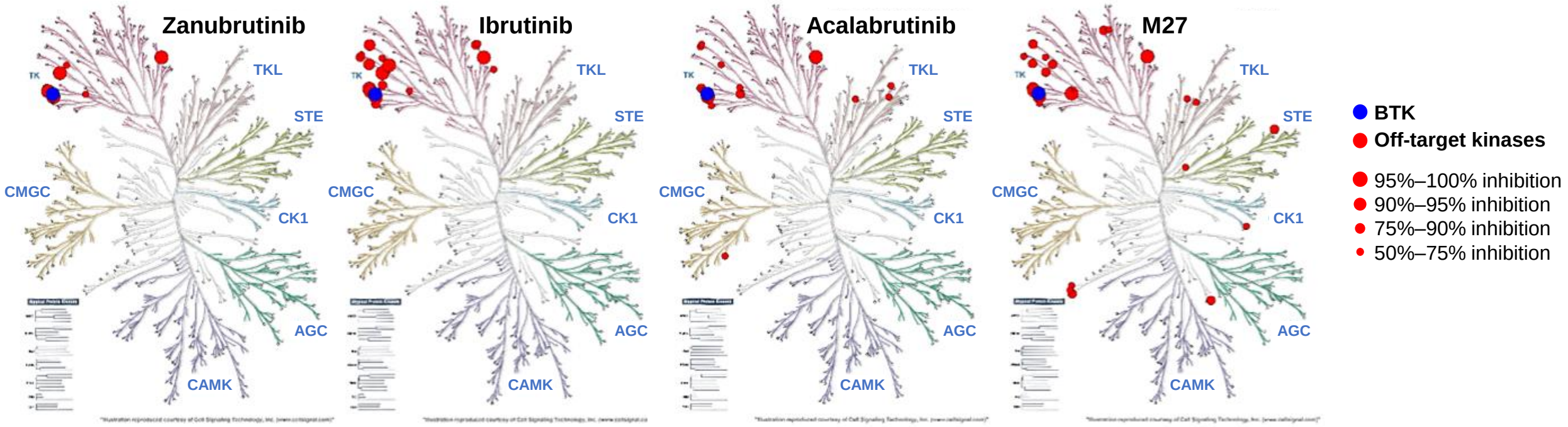
*Intolerant events occurring in ≥2 patients or recurring in ≥1 patient.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTKi, Bruton's tyrosine kinase inhibitor; PR, partial response; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

Shadman M *et al*. Abstract 1410. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Conclusion: Zanubrutinib is a potent and selective BTK inhibitor

- Kinase profiling supported the clinical findings, indicating favorable selectivity of zanubrutinib vs. ibrutinib and acalabrutinib plus its major metabolite (M27)



Assayed by Reaction Biology Corp. at 100X of IC_{50} (against BTK) concentration with IC_{50} (BTK) of 0.71 ± 0.09, 0.32 ± 0.09, 24 ± 9.2, and 63 ± 28 nM (n=3) for zanubrutinib, ibrutinib, acalabrutinib, and M27, respectively.
BTK, Bruton's tyrosine kinase; IC_{50}, half maximal inhibitory concentration.
Shadman M *et al*. Abstract 1410. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Bispecific antibodies in R/R follicular lymphoma

	Mosunetuzumab (N=92)[1]	Mosunetuzumab + lenalidomide (N=29)[2]	Glofitamab regimens (N=72)[3]	
			Monotherapy (obi pretreatment) (n=53)	Glofitamab + obinutuzumab (n=19)
Antibody target/s	CD20 and CD3 (1:1)	CD20 and CD3 (1:1)	Glofitamab: CD20 and CD3 (2:1) Obinutuzumab: CD20	Glofitamab: CD20 and CD3 (2:1) Obinutuzumab: CD20
Treatment regimen	• IV M step-up dosing to 17 cycles • C1D1 (1 mg) • C1D8 (2 mg) • C1D15 + C2D1 (60 mg) • D1D3+ (30 mg)	• IV M step-up dosing to 12 cycles (C1: 21 days; C1–12: 28 days) • C1D1 (1 mg) • C1D8 (2 mg) • Target dose on C1D15 (30 mg) and C2–12D1 • PO Len 20 mg C2–12D1–21	• Obinutuzumab 1,000 mg on D-7 • IV glofitamab SUD on C1D1+8 • At target dose on C2 *or* • SUD on C1D1+8, C2D1 • Target dose on C3D1	• Obinutuzumab 1,000 mg on D-7 • Glofitamab SUD on C1D1+8 • At target dose plus obinutuzumab 1,000 mg from C2D1 and onwards (every 21 days for up to 12 cycles)
ORR, % CRR, %	80 60	90 66	81 70	100 74
Response duration	57% at 18 months	86.2% at 5.4 months	Median: 10 months	NA
Safety, % Neutropenia G3–4 CRS G1–2 / G3–4 ICANS G1–2 / G3–4	 27 42 / 2 4 / 0	 24 28 / 0 3 / 0	 21 57 / 4 0 / 0	 41 79 / 0 0 / 0

C, Cycle; CRR, complete response rate; CRS, cytokine release syndrome; D, Day; G, Grade; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous; Len, lenalidomide; M, mosunetuzumab; NA, not available; ORR, overall response rate; PO, orally; R/R, relapsed/refractory; SUD, step-up doses.

1. Budde LE *et al*. Abstract 127. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.
2. Morschhauser F *et al*. Abstract 129. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.
3. Morschhauser F *et al*. Abstract 128. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

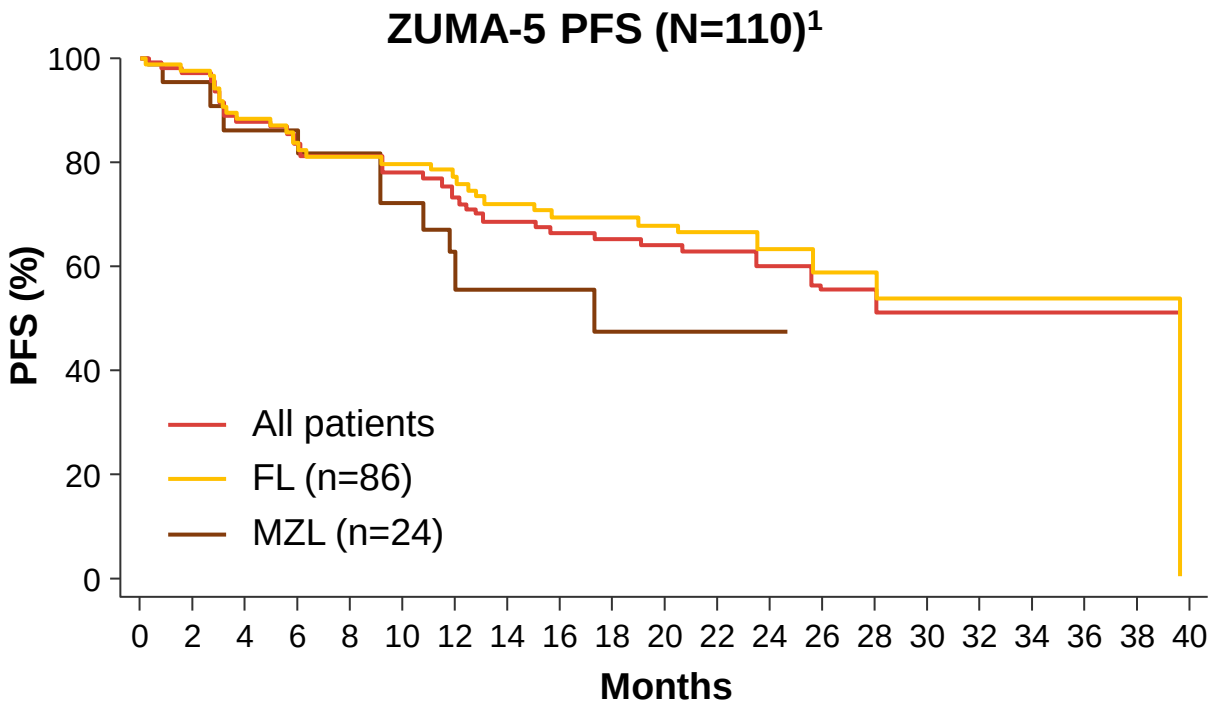
CAR-T in indolent B-cell lymphomas

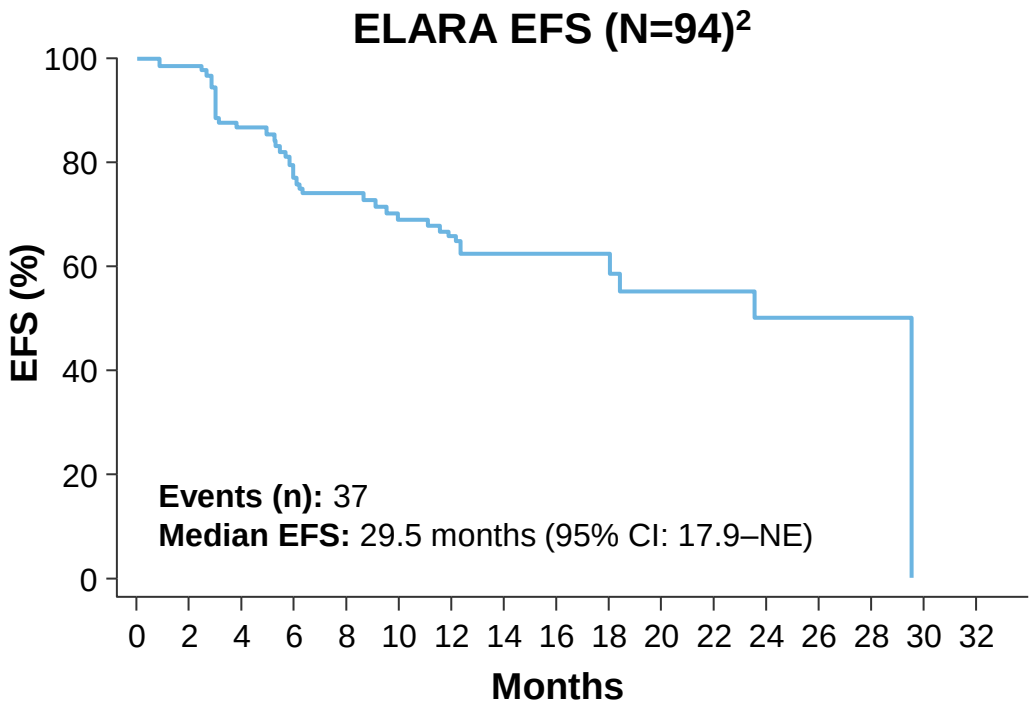
	ZUMA-5[1]	ELARA[2]
CAR-T	Axi-Cel	Tisa-Cel
Target	CD19	CD19
N	149 (FL: 124 / MZL: 25)	FL: 97
Median age, years (range)	61 (34–79)	57 (29–73)
Median follow-up, months	FL: 31 / MZL: 24	17
Bridge, %	0	43
Flu/Cy	500/30 × 3D	250/25 × 3D (or Benda 90 × 2D)
CAR-T dose	2×10^6/kg	0.6–6 × 10^8/kg
ORR, % CRR, %	92 75	86 69
PFS	60% at 24 months	67% at 12 months
OS	79% at 24 months	NR
CRS (all grades), % CRS Grade ≥3	82 7	48 0
ICANS (all grades), % ICANS Grade ≥3	60 19	4 1

Benda, bendamustine; CAR-T, chimeric antigen receptor T-cell therapy; CRR, complete response rate; CRS, cytokine release syndrome; Cy, cyclophosphamide; D, day; FL, follicular lymphoma; Flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; MZL, marginal zone lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Neelapu S *et al*. Abstract 93. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.
2. Thieblemont C *et al*. Abstract 131. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

CAR-T in indolent B-cell lymphomas





	All patients	FL	MZL
Median (95% CI), mo	40 (24–NE)	40 (26–NE)	17 (9–NE)
24-mo PFS (95% CI), mo	60 (49–69)	63 (52–73)	47 (23–68)

CAR-T, chimeric antigen receptor T-cell therapy; CI, confidence interval; EFS, event-free survival; FL, follicular lymphoma; mo, months; MZL, marginal zone lymphoma; NE, not evaluable; PFS, progression-free survival.

1. Neelapu S *et al*. Abstract 93. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.
2. Thieblemont C *et al*. Abstract 131. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Other highlights in brief

Abstract, first author	Presentation title	Key findings
3536, Zheng Z[1]	A phase II, multicenter, single-arm, open-label study of parsaclisib, a PI3Kδ inhibitor, in relapsed or refractory follicular lymphoma in China	• Parsaclisib showed promising efficacy and was generally well tolerated • It has potential for the treatment of patients with follicular lymphoma in third line and beyond
45, Chavez JC[2]	The combination of umbralisib plus ublituximab is active in patients with relapsed or refractory marginal zone lymphoma (MZL): Results from the phase 2 global Unity-NHL trial	• U2 was highly active in patients with R/R MZL, with improved efficacy when compared with a prior cohort of patients with MZL treated in this study with umbralisib monotherapy[3] • The safety profile of U2 was manageable
462, Moreno DF[4]	Prognostic impact of *MYD88* L265P mutation by droplet digital PCR in IgM MGUS and smoldering Waldenström macroglobulinemia	• Quantification of *MYD88* L265P by ddPCR has higher precision and sensitivity compared with AS-PCR • The risk of progression was higher in patients with an increased *MYD88* L265P burden

AS-PCR, allele-specific polymerase chain reaction; ddPCR, droplet digital polymerase chain reaction; IgM MGUS, immunoglobulin M monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin lymphoma; PCR, polymerase chain reaction; PI3K, phosphoinositide 3-kinase; R/R, relapsed/refractory; U2, umbralisib plus ublituximab.

1. Zheng Z *et al*. Abstract 3536. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 2. Chavez JC *et al*. Abstract 45. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 3. Fowler NH *et al*. *J Clin Oncol* 2021; 39 (15): 1609–1618. 4. Moreno DF *et al*. Abstract 462. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Summary

- Trial data indicate that zanubrutinib may be an effective and well-tolerated salvage treatment for patients with WM and MZL who have become intolerant to ibrutinib or acalabrutinib[1]

- Bispecific antibodies that engage B cells and T cells are a promising emerging treatment for patients with R/R FL
  - Deep and durable remissions in patients with third-line+ R/R FL with mosunetuzumab[2]
  - High response rates in patients with heavily pretreated R/R FL with glofitamab +/− obinutuzumab[3]
  - Longer follow-up needed

- CAR-T cell therapy may soon be an effective treatment option for patients with R/R FL who have a poor prognosis with other therapies, with durable responses in high-risk patients with R/R FL[4,5]

- The question in the future will be: ‘How do you choose between immunotherapies?’

CAR, chimeric antigen receptor; FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; WM, Waldenström’s macroglobulinemia.

1. Shadman M *et al*. Abstract 1410. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 2. Budde LE *et al*. Abstract 127. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 3. Morschhauser F *et al*. Abstract 128. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 4. Thieblemont C *et al*. Abstract 131. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021. 5. Neelapu S *et al*. Abstract 93. Oral presentation at the 63rd ASH Annual Meeting & Exposition; Atlanta, Georgia, USA, December 11–14, 2021.

Discussion and audience Q&A

Chair: Professor Véronique Leblond

Summary

Chair: Professor Véronique Leblond

Summary of speaker presentations

Immunotherapy and targeted therapies are becoming increasingly important, challenging traditional chemotherapy regimens as standard of care

New generation BTK inhibitors as monotherapy or in novel, chemo-free combinations have shown efficacy across a range of B-cell malignancies

Antibody-drug conjugates and bispecific antibodies that act against novel targets have also shown promise

CAR T-cell therapy may be considered in earlier lines of therapy in several malignancies

We would appreciate your feedback!
Please complete the post-meeting survey.

Thank you for your attention

BeiGeneius