BGB-11417-101

Sonrotoclax Plus Zanubrutinib

TN CLL

BGB-11417-101 Trial Design

TN CLL

Phase 1

Study Identifier:
BGB-11417-101, NCT04277637

Primary Endpoints: Safety (TEAEs, SAEs, AEs leading to discontinuation, TLS), MTD, RP2D,
Secondary Endpoints: PK/PD, ORR by investigator

Eligibility criteria

Confirmed diagnosis of:

- R/R MZL: ≥2L, extranodal, splenic, or nodal
- R/R FL: ≥2L, grade 1-3a
- R/R DLBCL: ≥3L
- Transformed indolent B-cell NHL
- **CLL/SLL: TN** or R/R
- R/R MCL: ≥2L
- R/R WM
- ECOG PS 0-2
- No prior therapy ≥2 months with, or progression on, a BCL2 inhibitor

Monotherapy Cohorts

Part 1: Dose Escalation (Sonrotoclax Monotherapy)

Cohort	Population	Disease	N
1A	R/R	NHL (*FL, DLBCL, MZL, or transformed NHL*)	15-30
1B	R/R (*low TLS risk*)	CLL/SLL	15-30
1C	R/R (*high TLS risk*[a])	CLL/SLL	3-6
1D	R/R	MCL	3-6
1E	R/R	WM	3-6

RP2D

RP2D per disease type will be decided based on SMC review of available safety and activity data

Part 2: Expansion (Sonrotoclax Monotherapy)

Cohort	Population	Disease	N
2A	R/R (*Food effect*)	Indolent NHL (*FL, MZL*)	10
2B	R/R (*food effect*)	Aggressive NHL (DLBCL, transformed NHL)	10
2C	R/R (*low TLS risk*)	CLL/SLL	20
2D	R/R (*high TLS risk*[a])	CLL/SLL	10
2E	R/R (*prior ven*)	CLL/SLL	10
2F	R/R	MCL	20
2G	R/R	WM	20

Combination Cohorts

Part 3: Dose Finding (Sonrotoclax + Zanubrutinib Combination)

Cohort	Population	Disease	Planned N
3A	R/R	CLL/SLL	15-30
3B	R/R	MCL	3-6
3C	TN	CLL/SLL	

RP2D

RP2D per disease type will be decided based on SMC review of available safety and activity data

Part 4: Dose Expansion (Sonrotoclax + Zanubrutinib Combination)

Cohort	Population	Disease	Planned N
4A	R/R	CLL/SLL	30
4B	TN	CLL/SLL	20
4C	R/R	MCL	20

[a]High TLS risk defined as the presence of any lymph node ≥10 cm or the presence of any lymph node ≥5 cm with concurrent absolute lymphocyte count ≥25×109/L.
AE=adverse event, BCL2=B-cell lymphoma-2, CLL=chronic lymphocytic leukemia, CTCAE=Common Terminology Criteria for Adverse Events, DLBCL=diffuse large B-cell lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance status, FL=follicular lymphoma, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, MCL=mantle cell lymphoma, MTD=maximum tolerated dose, MZL=marginal zone lymphoma, NHL=Non-Hodgkin lymphoma, ORR=objective response rate, PD=pharmacodynamic, PK=pharmacokinetics, QD=once daily, RP2D=recommended phase 2 dose, R/R=relapsed/refractory, SAE=serious adverse event, SLL=small lymphocytic lymphoma, SMC=safety monitoring committee, TEAE=treatment-emergent adverse event, TLS=tumor lysis syndrome, TN=treatment naïve, WM=Waldenström macroglobulinemia.

1. Cheah C et al. Oral presentation presented at ASH 2022. Abstract 962 2. Opat et al. EHA Presentation. 2022. Abstract number: P687.

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Baseline Characteristics

TN CLL

Characteristics	Sonrotoclax 160 mg + Zanubrutinib (n=51)	Sonrotoclax 320 mg + Zanubrutinib (n=86)	All Patients (N=137)
Study follow up time, median (range), months	19.5 (12.6-33.3)	19.3 (0.4-29.7)	19.4 (0.4-33.3)
Age, median (range), years	63 (38-82)	61 (32-84)	62 (32-84)
≥65 years, n (%)	20 (39.2)	35 (40.7)	55 (40.1)
Male sex, n (%)	37 (72.5)	61 (70.9)	98 (71.5)
Disease type, n (%)			
CLL	48 (94.1)	82 (95.3)	130 (94.9)
SLL	3 (5.9)	4 (4.7)	7 (5.1)
Risk status, n/tested (%)[a]			
del(17p)	5/45 (11.1)	6/77 (7.8)	11/122 (9.0)
del(17p) and/or *TP53*^{mut}	11/47 (23.4)	13/62 (21.0)	24/109 (22.0)
del(11q)	10/45 (22.2)	11/77 (14.3)	21/122 (17.2)
IGHV status, n/tested (%)			
Unmutated	32/47 (68.1)	32/60 (53.3)	64/107 (59.8)
High tumor bulk[b] at baseline, n/tested (%)	22/51 (43.1)	17/82 (20.7)	39/133 (29.3)

Data cutoff: August 23, 2024.
[a]*TP53* mutations defined as >0.1% VAF. [b]Nodes ≥10 cm or nodes >5 cm and ALC >25×109/L.
ALC=absolute lymphocyte count, CLL=chronic lymphocytic leukemia, IGHV=immunoglobulin heavy chain variable region, SLL=small lymphocytic lymphoma, TN=treatment naïve, VAF=variant allele frequency.
Soumerai JD et al. Oral Presentation at ASH 2024;1012.

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Dose Modification and AE Summary

TN CLL

Sonrotoclax in combination with zanubrutinib is well tolerated, with low rates of treatment discontinuation. As of the data cutoff date, 19 patients in the 320-mg cohort remained in zanubrutinib lead-in

	Sonrotoclax 160 mg + Zanubrutinib (n=51)	Sonrotoclax 320 mg + Zanubrutinib (n=86)	All Patients (N=137)
Duration of exposure, median (range), months	18.7 (5.8-33.3)	19.3 (0.4-29.7)	19.2 (0.4-33.3)
Any TEAEs, n (%)	51 (100)	77 (89.5)	128 (93.4)
Grade ≥3	29 (56.9)	39 (45.3)	68 (49.6)
Serious TEAEs	13 (25.5)	20 (23.3)	33 (24.1)
Leading to death	0	0	0
Leading to discontinuation of zanubrutinib	1 (2)	4 (4.7)	5 (3.6)[a,b]
Treated with sonrotoclax, n (%)	51 (100)	67 (77.9)	118 (86.1)
Leading to discontinuation of sonrotoclax	1 (2)	2 (2.3)	3 (2.2)[a]
Relative dose intensity of sonrotoclax, median, %	98.9	99.0	99.0

Data cutoff: August 23, 2024.
[a]Three discontinuations of sonro + zanu (n=1 each): meningitis (sonro 160 mg on study day 177), CMML (sonro 320 mg on study day 742), recurrent sinusitis (sonro 320 mg on study day 533); [b]Two discontinuations of zanu only (n=1 each): intracranial hemorrhage (study day 318), intermittent diarrhea (grade 1 on study day 30).
CLL=chronic lymphocytic leukemia, TEAE=treatment-emergent adverse event, TN=treatment naïve.
Soumerai JD et al. Oral Presentation at ASH 2024;1012.

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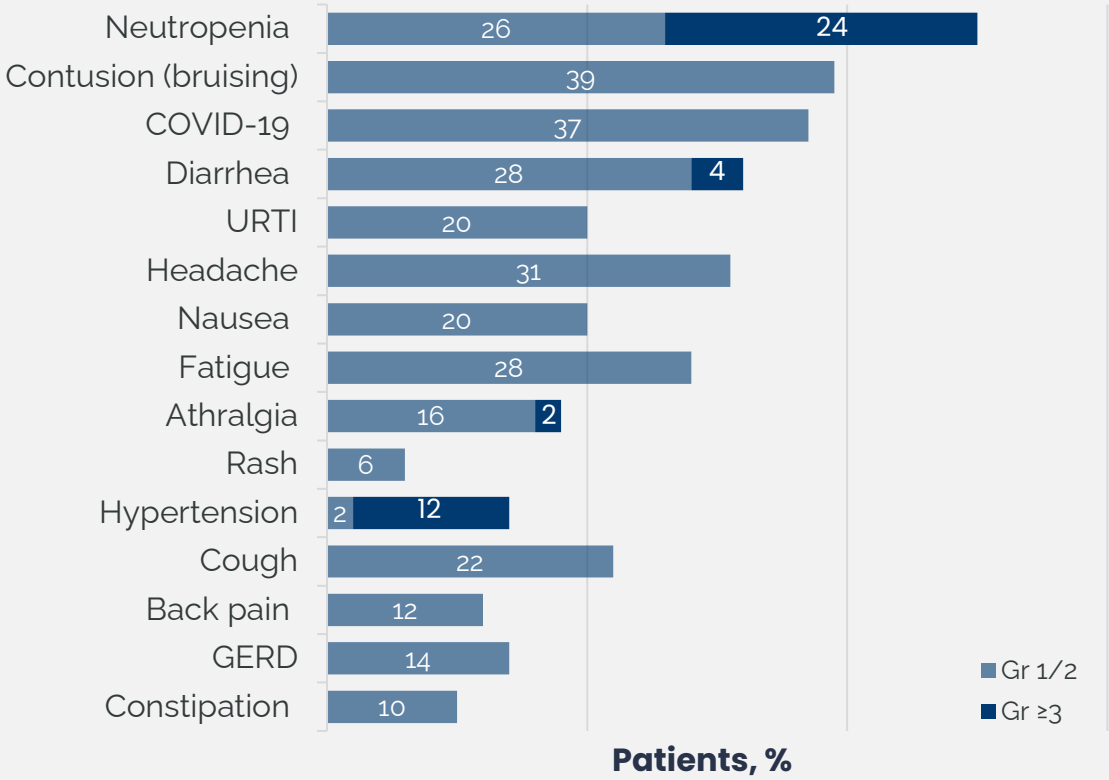
Most Frequent AEs (Incidence ≥10 Patients)

TN CLL

TEAEs observed with sonrotoclax and zanubrutinib were mostly low grade and transient. Neutropenia was transient and did not lead to higher rates of grade ≥3 infections

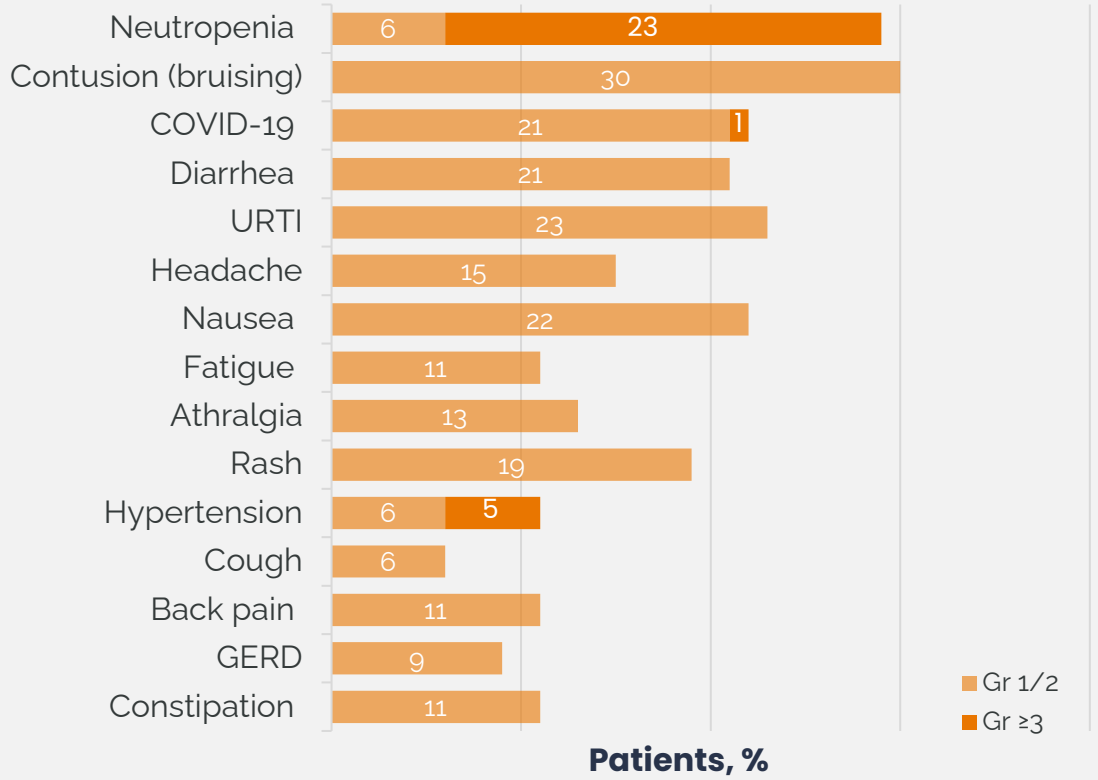
Sonrotoclax 160 mg + Zanubrutinib (n=51)

Median follow-up: 19.5 mo (range, 12.6-33.3 mo)



Sonrotoclax 320 mg + Zanubrutinib (n=86)

Median follow-up: 19.3 mo (range, 0.4-29.7 mo)



Data cutoff: August 23, 2024.
[a]Includes the combined preferred terms neutrophil count decreased and neutropenia.
AE=adverse event, CLL=chronic lymphocytic leukemia, GERD=gastroesophageal reflux disease, TEAE=treatment-emergent adverse event, TN=treatment naïve, URTI=upper respiratory tract infection.
Soumerai JD et al. Oral Presentation at ASH 2024;1012.

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ORR and MRD in Peripheral Blood

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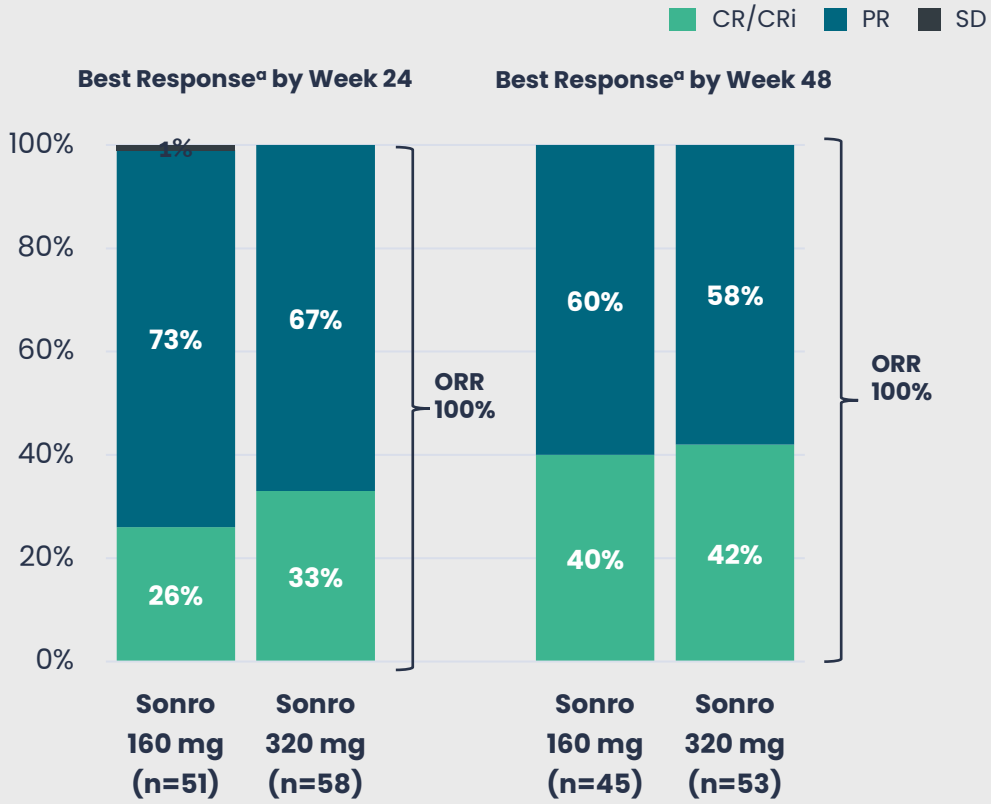
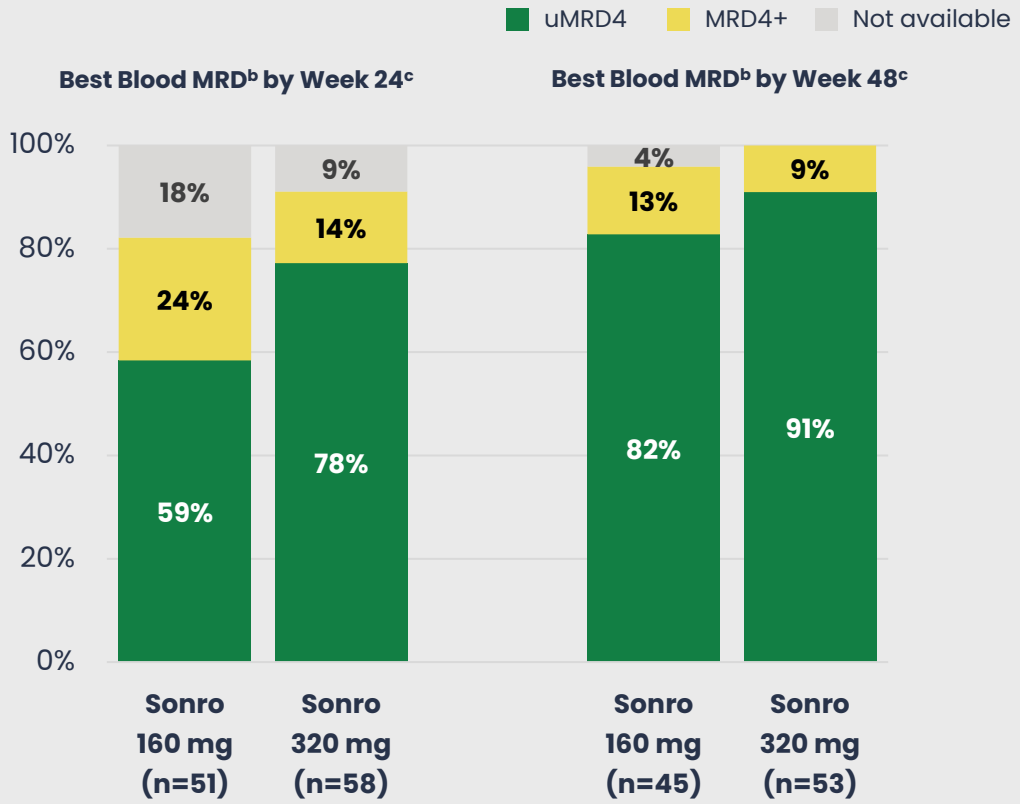


- Sonrotoclax + zanubrutinib demonstrates antitumor activity in TN CLL



- High blood uMRD4 rates occurred early
- As of the data cutoff date, no patients had switched from uMRD to MRD4+

Data cutoff: August 23, 2024.
[a]Percentages based on the number of patients who reached assessment at 24 or 48 weeks after completion of ramp-up, following zanu monotherapy and sonro ramp-up to target dose; [b]As measured by ERIC flow cytometry panel; uMRD4 is defined as less than one CLL cell per 10,000 leukocytes (<10-4). [c]Number of weeks at target dose, following zanu monotherapy and sonro ramp-up to target dose.
CLL=chronic lymphocytic leukemia, CR=complete response, CRi=complete response with incomplete count recovery, MRD=minimal residual disease, ORR=overall response rate, PR=partial response, SD=stable disease, TN=treatment-naïve, uMRD=undetectable minimal residual disease.
Soumerai JD et al. Oral Presentation at ASH 2024;1012.

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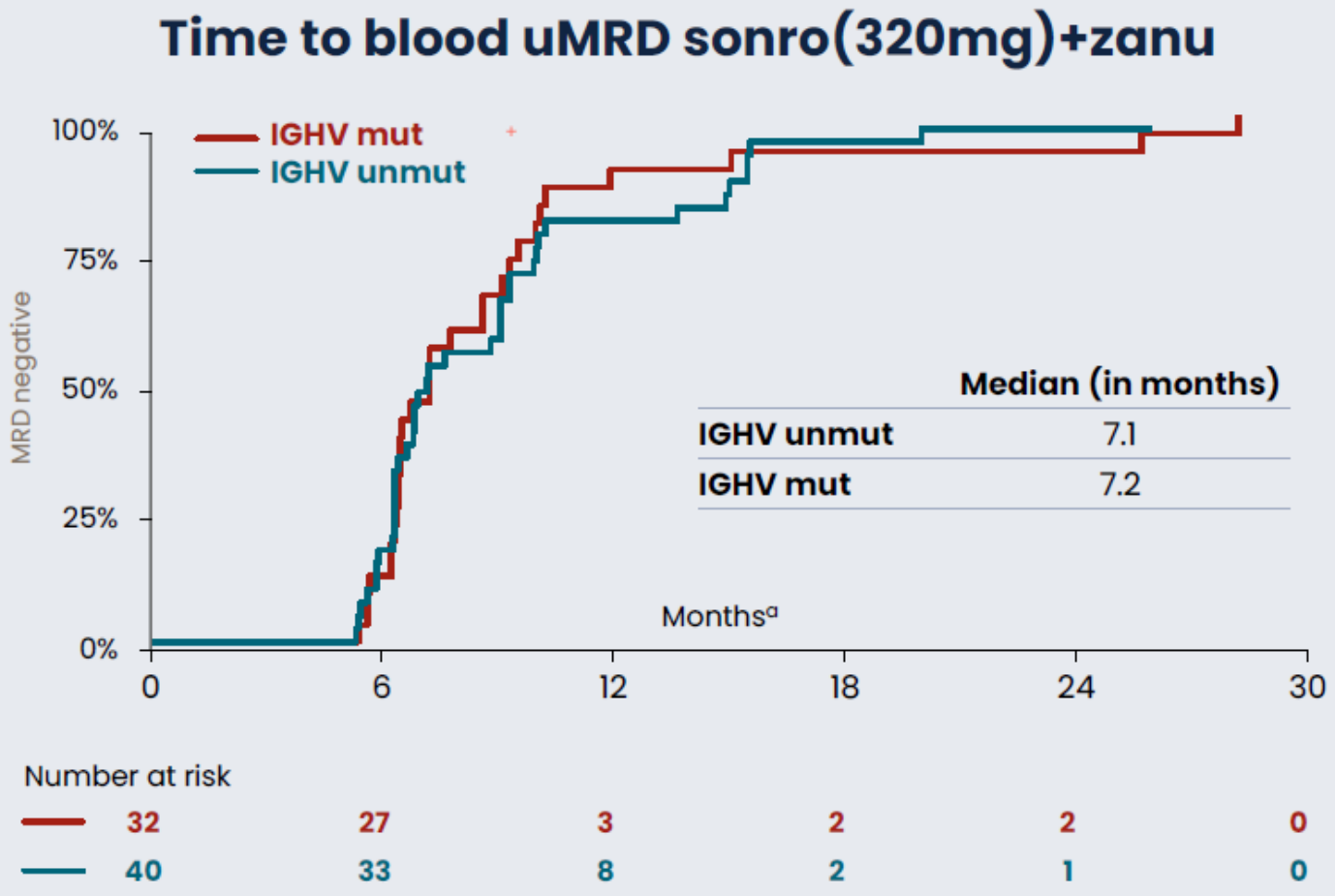
MRD Kinetics: Time to uMRD by IGHV Mutation Status

TN CLL



Data cutoff: March 1, 2025.
[a]From day 1 of zanubrutinib monotherapy treatment.
IGHV=immunoglobulin heavy chain variable region, MRD=minimal residual disease, sonro=sonrotoclax, uMRD=undetectable minimal residual disease, zanu=zanubrutinib.
Data on File.