Next-generation BTK inhibitors for relapsed/refractory B-cell malignancies: What are the options and how do they compare?

Monday, September 27, 2021 | 17:30–19:00 (CEST)

Welcome and introductions

Chair: Professor Wojciech Jurczak

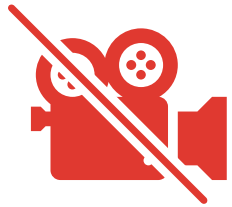
Disclosures

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

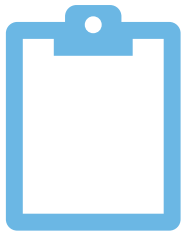
Disclaimers

- 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.
- Any case studies included in presentations refer to clinical cases and images from the clinical practice of the speaker. They have been interpreted and evaluated by the speaker based on his/her knowledge and experience.
- 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 Waldenström’s macroglobulinemia outside of the US and Canada.

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

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

Paolo Ghia
The Vita-Salute San Raffaele University, Italy

Federico Pea
University of Bologna, Italy

Alessandra Tedeschi
Niguarda Cancer Center, Italy

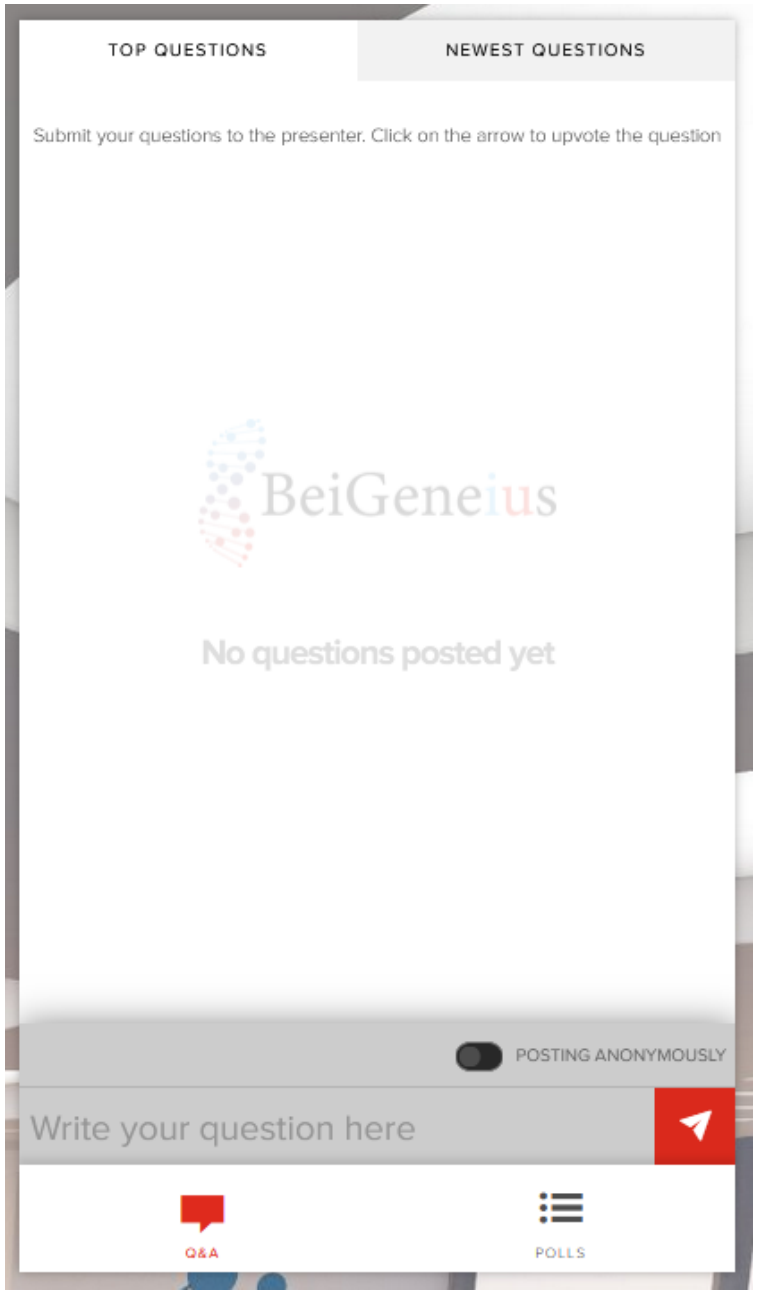
Agenda

17:30	Welcome and introductions	Wojciech Jurczak
17:35	What are the clinical implications of the different pharmacologic properties of BTK inhibitors?	Federico Pea
17:55	Next-generation BTK inhibitor monotherapy versus ibrutinib in the treatment of relapsed/refractory CLL/SLL	Paolo Ghia
18:20	Next-generation BTK inhibitor monotherapy in the treatment of relapsed/refractory B-cell lymphomas	Alessandra Tedeschi
18:35	Discussion and audience Q&A	**Panel:** All
18:55	Summary and meeting close	Wojciech Jurczak

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

Audience questions

- Please exit full-screen 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 during the Q&A session
- Please note that it may not be possible for the panel to answer all of the questions that are submitted



BTK inhibitors

Current EMA and FDA approval status

	Zanubrutinib[1,2]	Acalabrutinib[3,4]	Ibrutinib[5,6]
EMA	Not approved in any indication • *Sept 2021: CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the treatment of WM*	Indicated for treatment of adult patients with: • TN CLL (monotherapy and with obinutuzumab) • R/R CLL (monotherapy)	Indicated for treatment of adult patients with: • R/R MCL (monotherapy) • TN WM patients unsuitable for immunochemotherapy (monotherapy and with rituximab) • R/R WM (monotherapy and with rituximab) • TN CLL (monotherapy and with rituximab or obinutuzumab) • R/R CLL (monotherapy and +BR)
FDA	Indicated for treatment of adult patients with: • R/R MCL • WM • R/R MZL patients who have received ≥1 prior anti-CD20-based therapy	Indicated for treatment of adult patients with: • R/R MCL • CLL/SLL	Indicated for treatment of adult patients with: • R/R MCL • CLL (+/- 17p deletion) • WM • MZL patients who require systemic therapy and have received ≥1 prior anti-CD20-based therapy • cGVHD after failure of ≥1 lines of systemic therapy

BR, bendamustine and rituximab; BTK, Bruton's tyrosine kinase; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PI, Prescribing Information; R/R, relapsed/refractory (≥1 prior therapy); SmPC, Summary of Product Characteristics; WM, Waldenström's macroglobulinemia.

1. EMA: Brukinsa. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/brukinsa. 2. FDA: Brukinsa PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213217s005lbl.pdf. 3. EMA: Calquence SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_en.pdf. 4. FDA: Calquence PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf. 5. EMA: Imbruvica SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf. 6. FDA: Imbruvica PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf. All accessed September 2021.

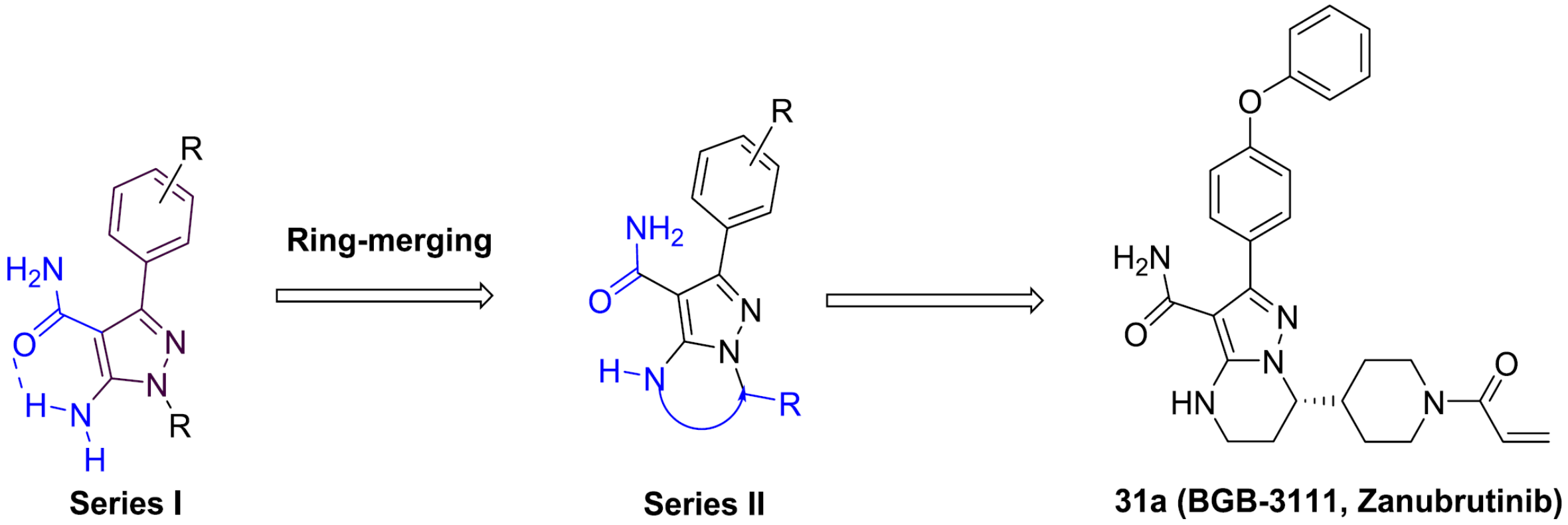
What are the clinical implications of the different pharmacologic properties of BTK inhibitors?

Professor Federico Pea
Department of Surgical and Medical Sciences, Alma Mater Studiorum, University of Bologna, Italy
University Hospital IRCCS Policlinico Sant'Orsola, Bologna, Italy

Disclosures

- **Speakers bureau**: Angelini, Basilea Pharmaceutica, BeiGene, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, Sun Pharma
- **Consultant**: Angelini, Basilea Pharmaceutica, BeiGene, Gilead, Hikma, MSD, Novartis, Pfizer, Sanofi-Aventis, Shionogi, Thermo Fisher

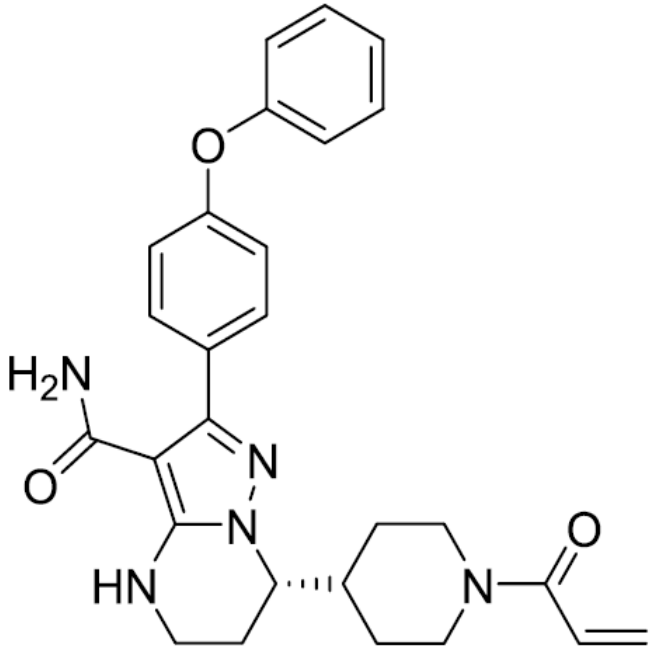
Discovery of zanubrutinib (BGB-3111)



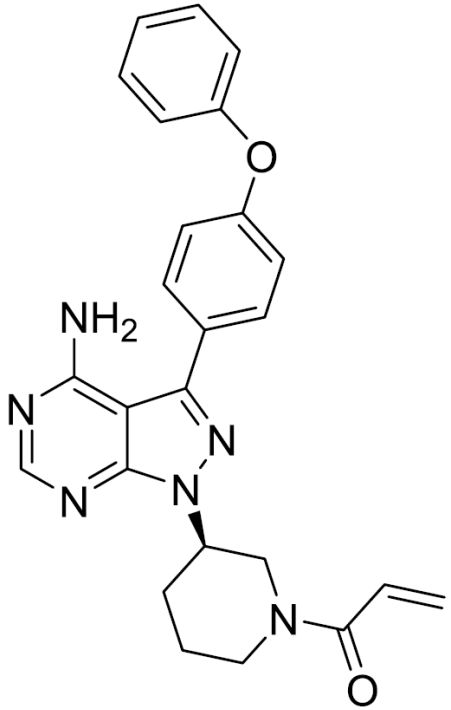
Series I **Series II** **31a (BGB-3111, Zanubrutinib)**

BTK, Bruton's tyrosine kinase.
Guo Y *et al. J Med Chem* 2019; 62: 7923−7940.

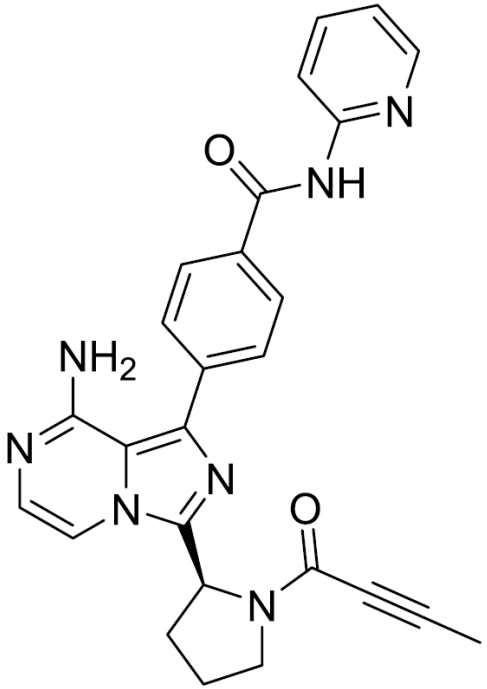
First- and second-generation BTK inhibitors



31a (BGB-3111, Zanubrutinib)



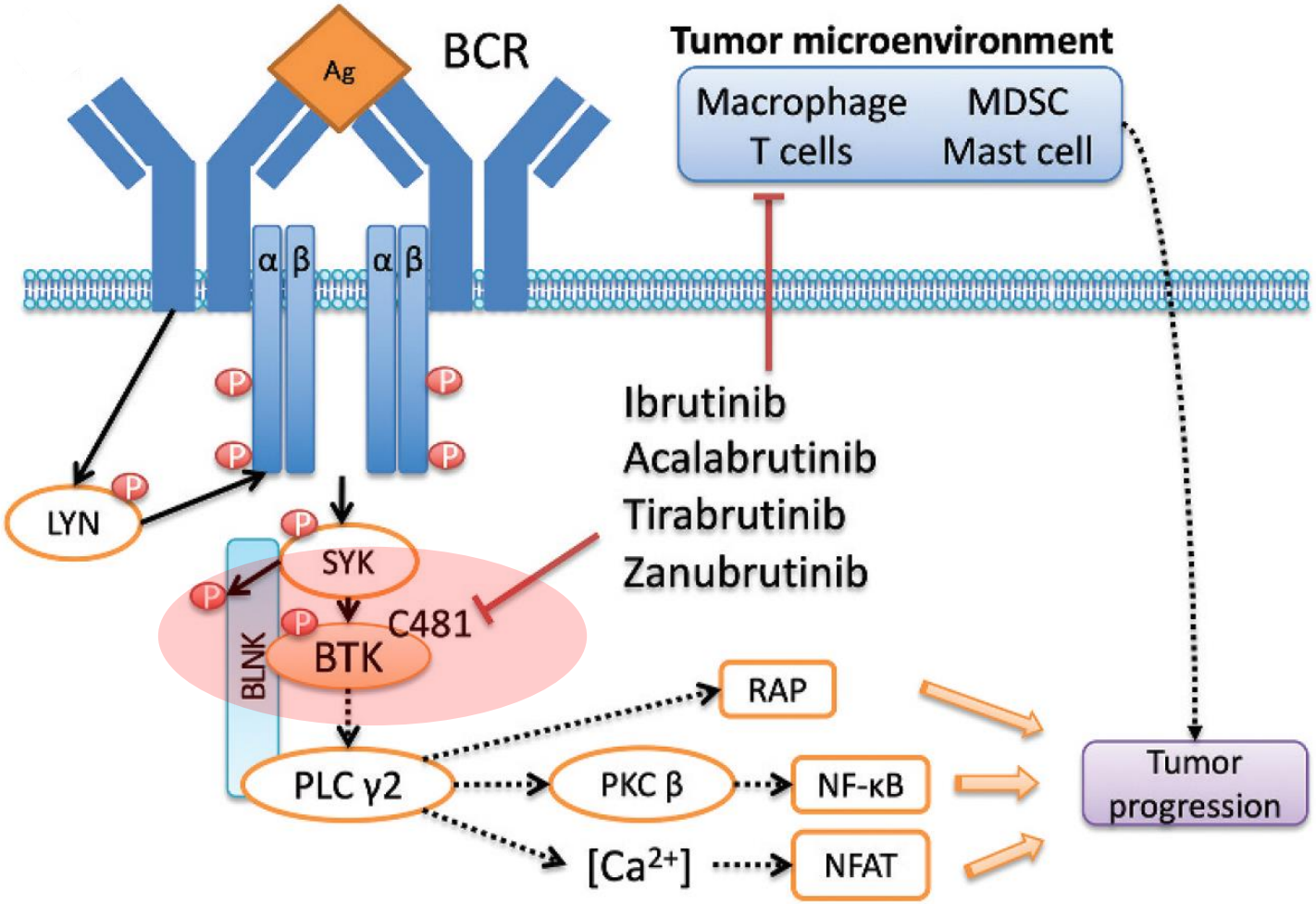
1a. Ibrutinib



1b. Acalabrutinib (ACP-196)

BTK, Bruton's tyrosine kinase.
Guo Y *et al. J Med Chem* 2019; 62: 7923−7940.

Mechanism of action of BTK inhibitors on B cells



Ag, antigen; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; MDSC, myeloid-derived suppressor cell.
Makita S *et al*. *Expert Opin Drug Saf* 2020; 19 (9): 1105–1120.

Molecular targets of the various BTK inhibitors

Variable	Inhibitor			
	Ibrutinib	**Acalabrutinib**	**Zanubrutinib**	**Tirabrutinib**
Target	BTK	BTK	BTK	BTK
Major off-targets	ITK EGFR TEC BMX	Minimal	ITK (weak)	TEC (weak)
Anti-platelet activity	Yes	No	No	No

BTK, Bruton's tyrosine kinase.
Owen C *et al. Curr Oncol* 2019; 26 (2): e233–e240.

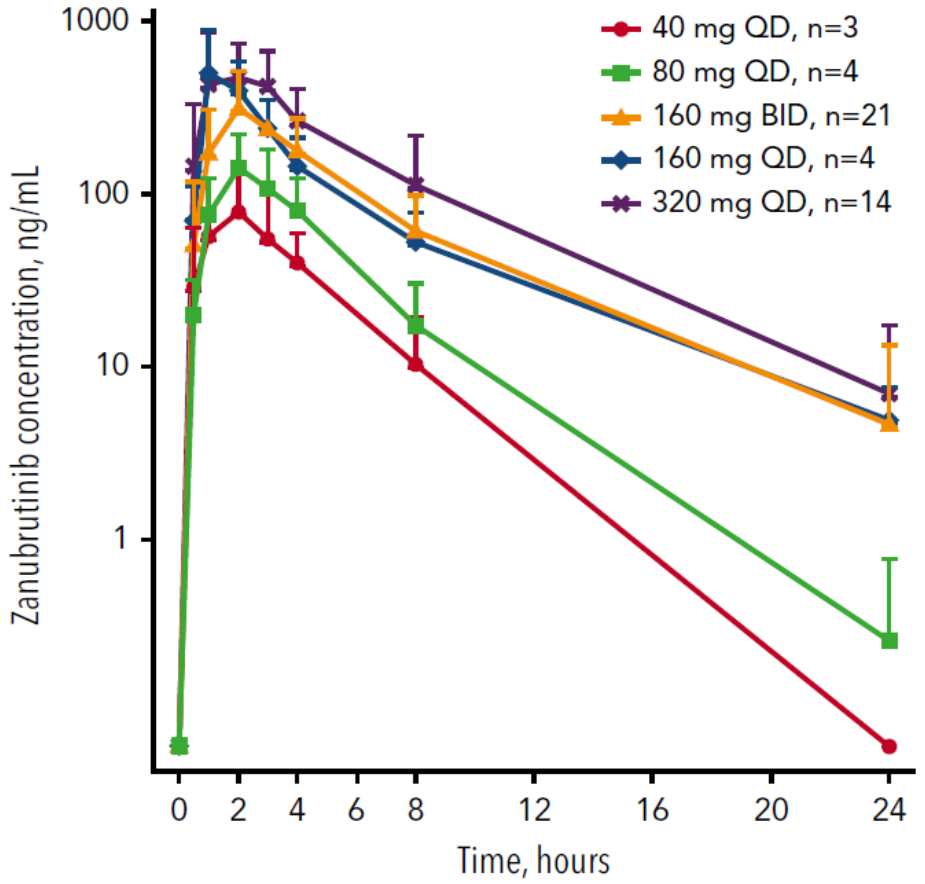
Biochemical kinase selectivity of 31a (zanubrutinib) and ibrutinib

enzyme	IC_{50} (nM) of **31a**	IC_{50} (nM) of Ibrutinib	selectivity of **31a**	selectivity of Ibrutinib
BTK[c]	0.30 ± 0.06[b]	0.18 ± 0.04[b]		
ITK[c]	56 ± 12[b]	3.0 ± 0.7[b]	187	17
TEC[c]	2.0 ± 0.8[b]	0.57 ± 0.18[b]	6.7	3.2
JAK3[c]	580 ± 21[b]	10 ± 2[b]	1933	56
EGFR[c]	2.6 ± 1.0	0.75 ± 0.14	8.7	4.2
HER2[c]	530 ± 273[b]	19 ± 7[b]	1800	106
BLK[d]	1.13	0.23	1.2	0.5
BMX[d]	0.62	0.5	0.7	1.1
BRK[d]	33	18	36	39
HER4[d]	1.58	0.25	1.7	0.5
FGR[d]	155	1.82	168	4.0
FRK/PTK5[d]	379	79	412	172
LCK[d]	187	2.85	203	6.2
TXK[d]	2.95	2.89	3.2	6.3

[a]n: number of determinations. [b]n=3; where unspecified n=1. [c]Note: IC_{50} values of compounds were measured at K_m of ATP for the kinases and with 1hr preincubation at BeiGene by using a TR-FRET assay. [d]Data were generated at Reaction Biology Corp. using 33P-TAP and filter-binding assay. IC_{50} values of compounds were measured at 1 μM ATP and with 1hr preincubation. Selectivity for these kinases was calculated based on IC_{50} of BTK generated in Reaction Biology Corp. for **31a** (0.92 nM) and ibrutinib (0.46 nM).
BTK, Bruton's tyrosine kinase, IC_{50}, half-maximal inhibitory concentration; TR-FRET, time-resolved Förster resonance energy transfer.
Guo Y *et al. J Med Chem* 2019; 62: 7923−7940.

Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies, and safety and efficacy evaluation in CLL

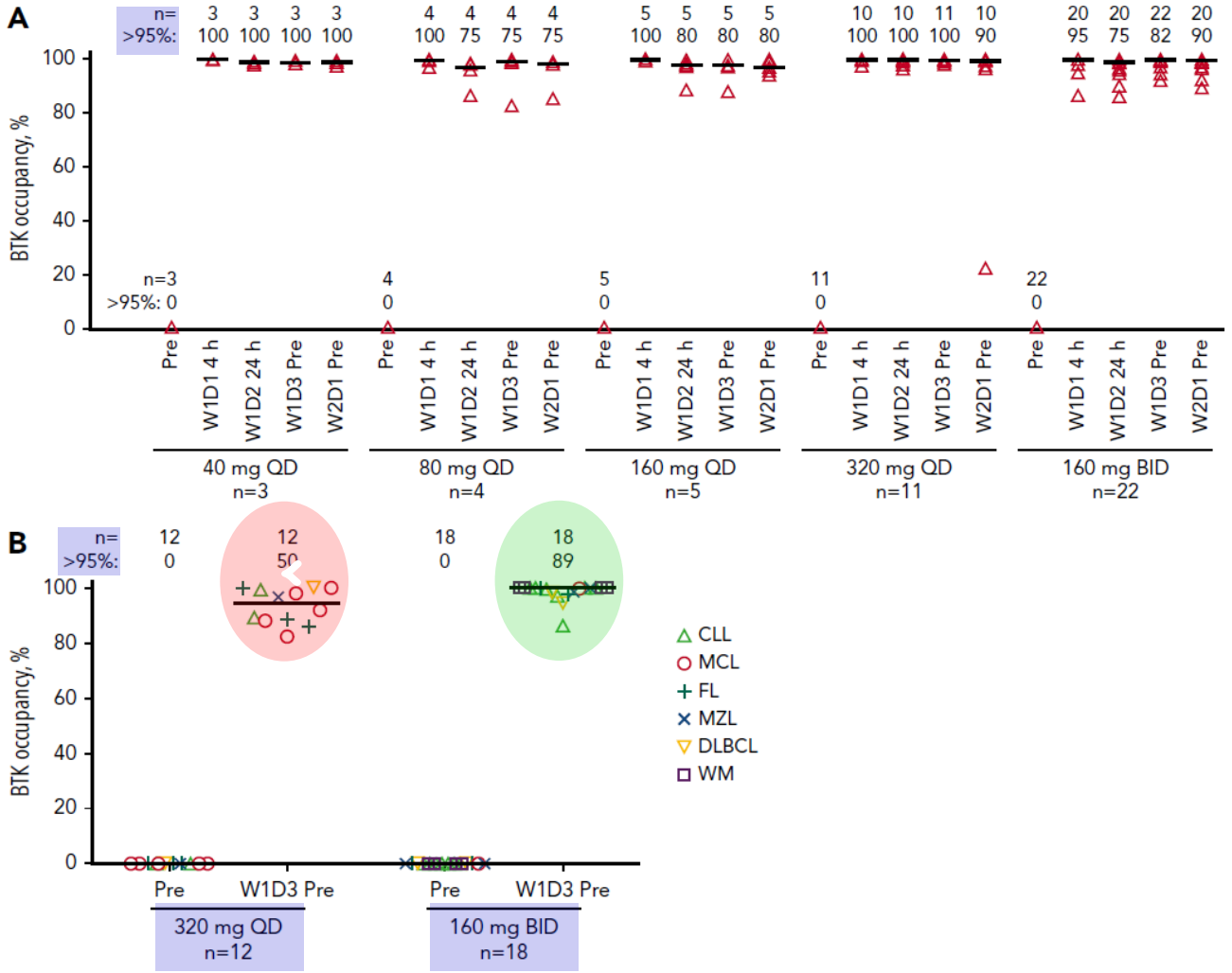
Plasma concentration-time profile of zanubrutinib after initial doses



BID, twice a day; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; QD, once a day.
Tam CS *et al. Blood* 2019; 134 (11): 851–859.

Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies, and safety and efficacy evaluation in CLL

BTK occupancy in (A) PBMCs and (B) nodal tissue



BID, twice a day; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once a day; PBMC, peripheral blood mononuclear cell; WM, Waldenström's macroglobulinemia. Tam CS *et al. Blood* 2019; 134 (11): 851–859.

Features and properties of zanubrutinib

Alternative names	BGB-3111, zanubrutinib
Class	Amides, Actineoplastics, Phenyl ethers, Piperidines, Pyrazoles, Pyrimidines, Small molecules
Mechanism of action	Bruton’s tyrosine kinase inhibitor
Route of Administration	Oral
Pharmacodynamics	Highly selective for BTK; inhibits BTK with potency similar to ibrutinib; less off-target kinase inhibition than ibrutinib; associated with near complete and sustained BTK occupancy in PBMCs as well as lymph nodes

BTK, Bruton’s tyrosine kinase; C_{max}, maximum observed concentration; h, hours; PBMC, peripheral blood mononuclear cell.
Syed YY. *Drugs* 2020; 80 (1): 91–97.

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BTK, Bruton's tyrosine kinase; C_{max}, maximum observed concentration; h, hours; L, litres; PBMC, peripheral blood mononuclear cell.
Syed YY. *Drugs* 2020; 80 (1): 91–97.

Population pharmacokinetic analysis of the BTK inhibitor zanubrutinib in healthy volunteers and patients with B-cell malignancies

Summary of studies included in the population PK analysis

Study no.	Dose regimen	*N*	Study description	PK sampling design
BGB-3111-AU-003 (NCT02343120)	40 mg, 80 mg, 160 mg, and 320 mg q.d. 160 mg b.i.d.	337	A phase I, open-label, multiple-dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of the BTK inhibitor BGB-3111 in patients with B-cell lymphoid malignancies	Part 1: W1D1: Predose, 0.5, 2, 3, 4, 8, 24 hours W2D1: Predose, 0.5, 2, 3, 4, 7, 8 hours W5D1 and W9D1: Predose Part 2: W1D1 and W2D1: Predose, 2 hours
BGB-3111-1002 (NCT03189524)	320 mg q.d. 160 mg b.i.d.	44	A phase I clinical study to investigate the safety, tolerability, and PKs/pharmacodynamics of the BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma	Part 1: W1D1: Predose, 0.5, 1, 2, 3, 4, 8, 12, 24 hours (W1D2 predose) W2D1: Predose, 0.5, 1, 2, 3, 4, 8 hours W5D1 and W9D1: Predose Part 2: W1D1: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours (W1D2 predose) W2D1: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 hours W5D1 and W9D1: Predose
BGB-3111-205 (NCT03206918)	160 mg b.i.d.	13	A single-arm, open-label, multicenter phase II study to evaluate safety and efficacy of BGB-3111, a BTK inhibitor in relapsed or refractory CLL/SLL	C1D1: Predose, 2, 4–6 hours C2D1: Predose, 2, 4–6 hours
BGB-3111-206 (NCT03206970)	160 mg b.i.d.	20	A single-arm, open-label, multicenter phase II study to evaluate the efficacy and safety of BGB-3111, a BTK inhibitor, in patients with relapsed or refractory MCL	C1D1: Predose, 2, 4–6 hours C2D1: Predose, 2, 4–6 hours
BGB-3111-103 (NCT04163523)	320 mg q.d.	18	A single-center, phase I, open-label, randomized, crossover study to evaluate the effect of food on the PKs of a single dose of 320 mg BGB-3111 given orally to healthy adult subjects	Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours (under each of high-fat, low-fat, and fasted conditions)
BGB-3111-104 (NCT03301181)	20 mg q.d. 320 mg q.d.	38	A phase I, open-label, parallel-group, fixed-sequence study to investigate the effect of the CYP3A inducer rifampin and the CYP3A inhibitor itraconazole on the PKs of BGB-3111 in healthy subjects	Part A: D1 and D10: Predose, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 hours Part B: D1 and D6: Predose, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 hours
BGB-3111-105 (NCT04163783)	320 mg q.d.	6	A phase I study to investigate the absorption, metabolism, and excretion of [14C] BGB-3111 following a single oral administration in healthy male subjects	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 hours
BGB-3111-106 (NCT03432884)	160 mg q.d. 480 mg q.d.	28	A two-part study consisting of a randomized, placebo-controlled, single dose safety and tolerability study (part A) evaluating a supratherapeutic dose of zanubrutinib followed by a randomized, placebo and positive-controlled, crossover study (part B) to evaluate the effect of zanubrutinib on cardiac repolarization in HVs	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48 hours
BGB-3111-302 (NCT03053440)	160 mg b.i.d.	128	A study comparing BGB-3111 and ibrutinib in subjects with WM	C1D1: Predose 2, 3–6 hours C2D1: Predose 2, 3–6 hours

BID, twice a day; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; PK, pharmacokinetic; QD, once a day; SLL, small lymphocytic leukemia; WM, Waldenström's macroglobulinemia.

Ou YC *et al. Clin Transl Sci* 2021; 14 (2): 764–772.

Population pharmacokinetic analysis of the BTK inhibitor zanubrutinib in healthy volunteers and patients with B-cell malignancies

- No statistically significant differences in the PK of zanubrutinib were observed based on age, sex, race (Asian, Caucasian, and other), body weight, mild or moderate renal impairment (creatinine clearance ≥30 mL/min as estimated by Cockcroft-Gault), baseline aspartate aminotransferase, bilirubin, tumor type, or use of acid-reducing agents (including proton pump inhibitors)

BTK, Bruton's tyrosine kinase; PK, pharmacokinetic.
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- These results support that no dose adjustment is considered necessary based on the aforementioned factors

BTK, Bruton's tyrosine kinase; PK, pharmacokinetic.
Ou YC *et al. Clin Transl Sci* 2021; 14 (2): 764–772.

Features and properties of zanubrutinib

Alternative names	BGB-3111, zanubrutinib
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Pharmacokinetics	Median time to C_{max} ≈2 h; minimal accumulation; volume of distribution at steady state 881 L; mean half-life ≈2–4 h; primarily metabolized by CYP3A

BTK, Bruton's tyrosine kinase; C_{max}, maximum observed concentration; h, hours; L, litres; PBMC, peripheral blood mononuclear cell.
Syed YY. *Drugs* 2020; 80 (1): 91–97.

Drug interactions with BTK inhibitors

Clinical implications and management

- All three BTK inhibitors have potential drug–drug interactions with agents that are metabolized via the CYP3A pathway

BTK, Bruton's tyrosine kinase.

Fancher KM *et al. Cancer Chemother Pharmacol* 2020; 86 (4): 507–515.

Drug interactions with BTK inhibitors

Clinical implications and management

- All three BTK inhibitors have potential drug–drug interactions with agents that are metabolized via the CYP3A pathway
- Co-administration of strong inducers of CYP3A and any of the BTK inhibitors should be avoided, but should the combination be necessary, the labeling of acalabrutinb makes recommendations for dosage adjustment, while the labeling of ibrutinib and zanubrutinib do not

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- Recommendations for co-administration with inhibitors of CYP3A vary among the agents; most notably, co-administration of ibrutinib and zanubrutinib with azole antifungals warrants dosage adjustment, while acalabrutinib does not

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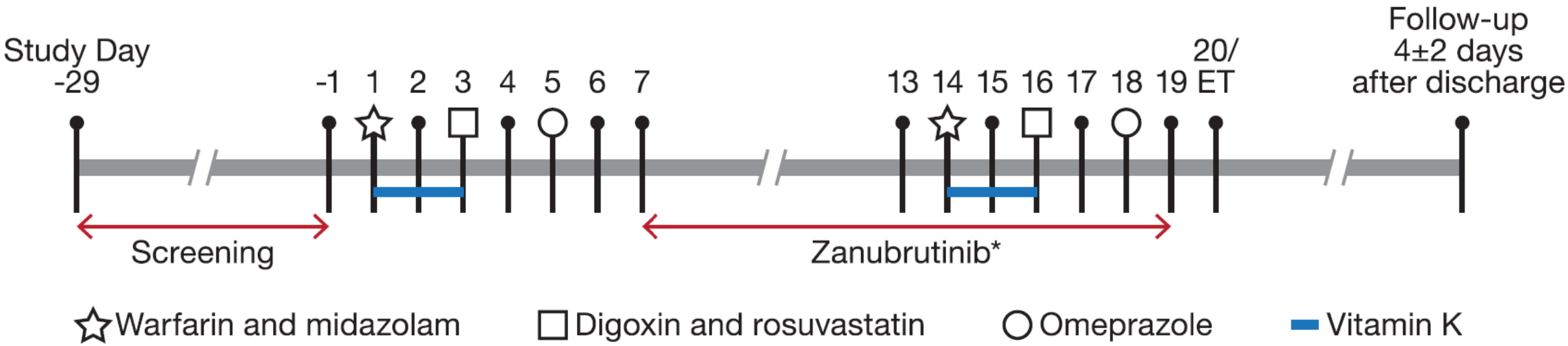
- Recommendations for co-administration with inhibitors of CYP3A vary among the agents; most notably, co-administration of ibrutinib and zanubrutinib with azole antifungals warrants dosage adjustment, while acalabrutinib does not
- Conversely, concomitant use of acalabrutinib with gastric acid-reducing agents may present challenges in clinical practice, especially when the widespread use and availability of such products are considered

BTK, Bruton's tyrosine kinase.

Fancher KM *et al. Cancer Chemother Pharmacol* 2020; 86 (4): 507–515.

Evaluation of drug interaction potential of zanubrutinib with cocktail probes representative of CYP3A4, CYP2C9, CYP2C19, P-GP AND BCRP

Study design



*PK samples for zanubrutinib were collected on Day 13 and Day 18.
BCRP, breast cancer resistance protein; CYP, cytochrome P450; ET, end of study; P-GP, P-glycoprotein.
Ou YC *et al. Br J Clin Pharmacol* 2021; 87 (7): 2926–2936.

Evaluation of drug interaction potential of zanubrutinib with cocktail probes representative of CYP3A4, CYP2C9, CYP2C19, P-GP AND BCRP

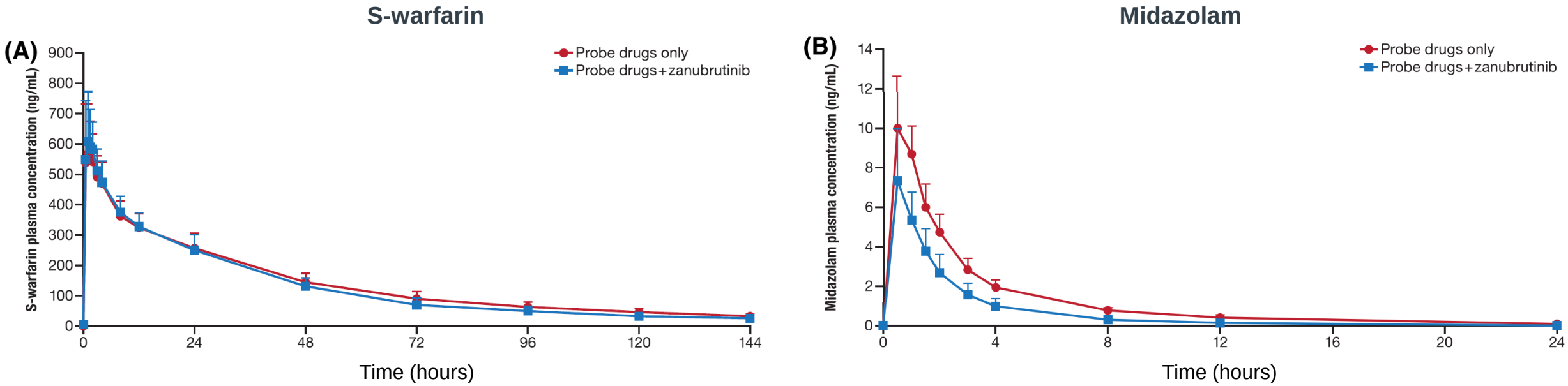
Investigational product administration and blood sampling times

Investigational product	Dose	CYPs/transporters of interest	Blood sampling time
Zanubrutinib	320 mg daily (160 mg b.i.d.)	Not applicable	Predose and 0.5, 1, 2, 3, 4, 6, 8, and 12 h postdose (Day 13 and Day 18)
Midazolam	2 mg	CYP3A	Predose and 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h postdose (Days 1–2, Days 14–15)
Warfarin	10 mg	CYP2C9 (for S-warfarin)	Predose and 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, and 144 h postdose (Days 1–7, Days 14–20)
Vitamin K	10 mg	Not applicable	NA
Omeprazole	20 mg	CYP2C19	Predose and 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h postdose (Days 5–6, Days 18–19)
Digoxin	0.25 mg	P-gp	Predose and 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h postdose (Days 3–4, Days 16–17)
Rosuvastatin	10 mg	OATP1B1, OATP1B3, BCRP	Predose and 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 h postdose (Days 3–4, Days 16–17)

BCRP, breast cancer resistance protein; BID, twice a day; CYP, cytochrome P450; NA, not applicable; OATP, organic anion-transporting polypeptide; P-GP, P-glycoprotein; PK, pharmacokinetic.
Ou YC *et al. Br J Clin Pharmacol* 2021; 87 (7): 2926–2936.

Evaluation of drug interaction potential of zanubrutinib with cocktail probes representative of CYP3A4, CYP2C9, CYP2C19, P-GP AND BCRP

Pharmacokinetic profile of probe drugs administered alone and with zanubrutinib 160 mg B.I.D.



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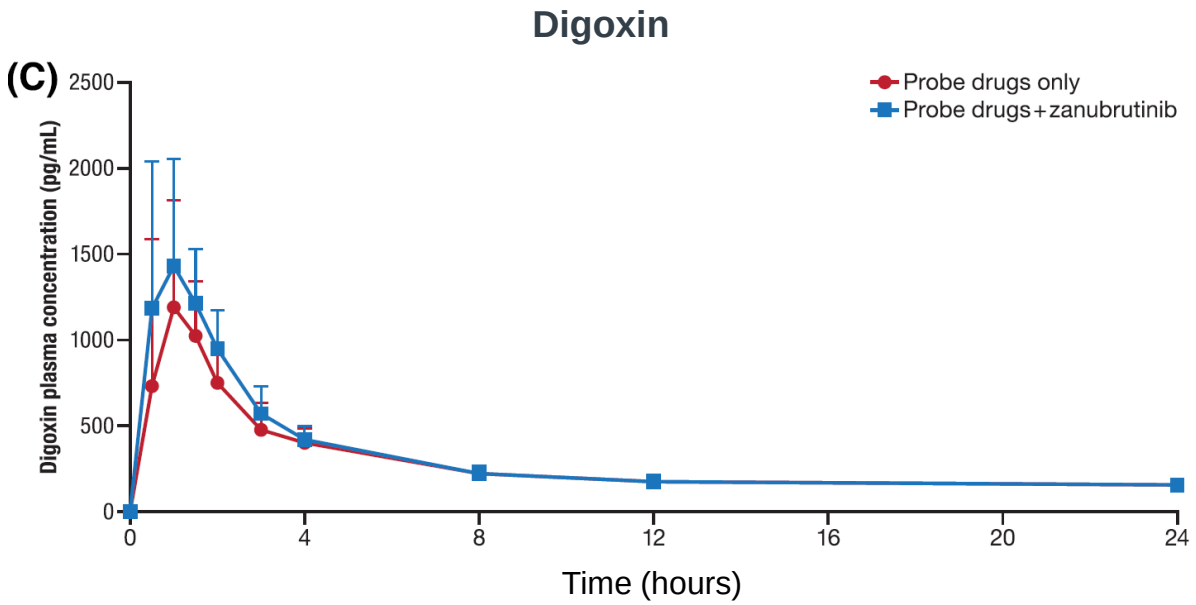

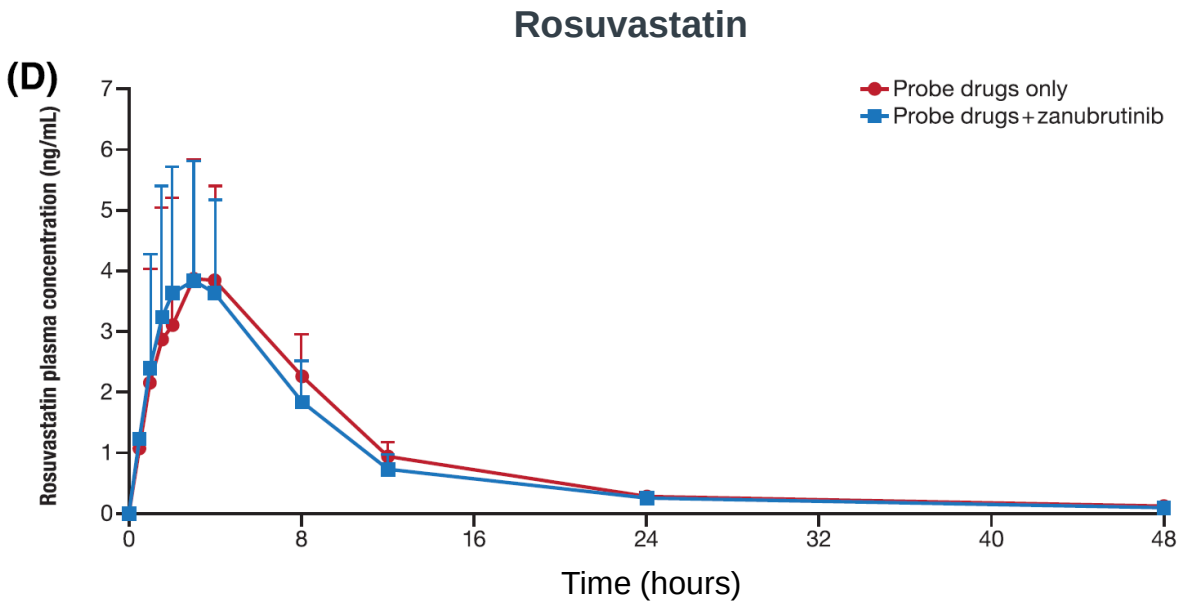

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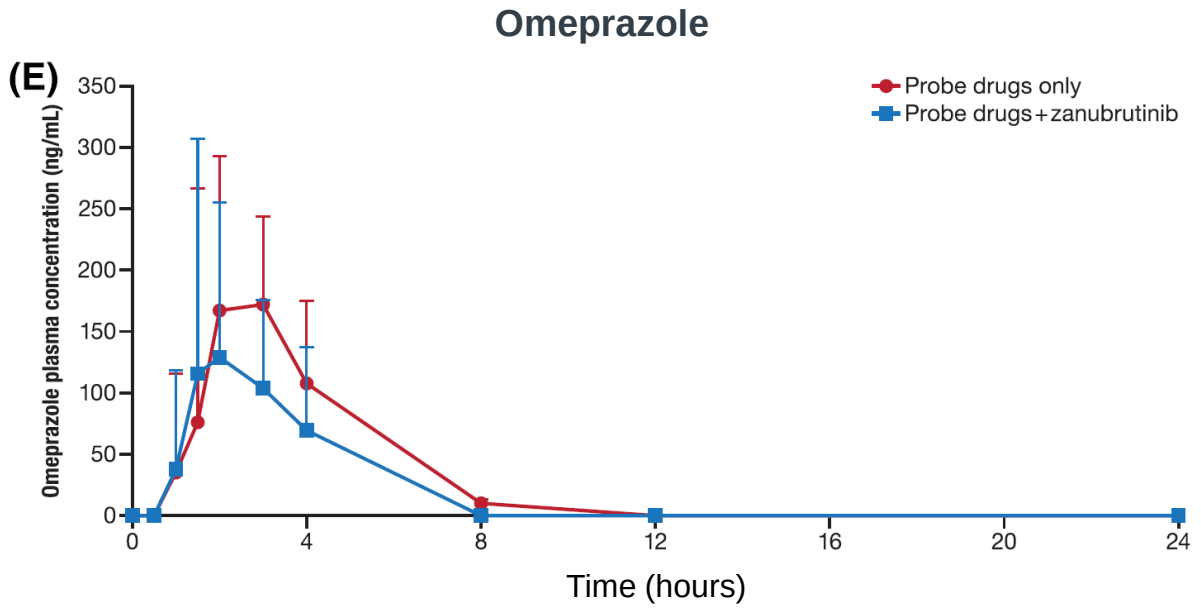

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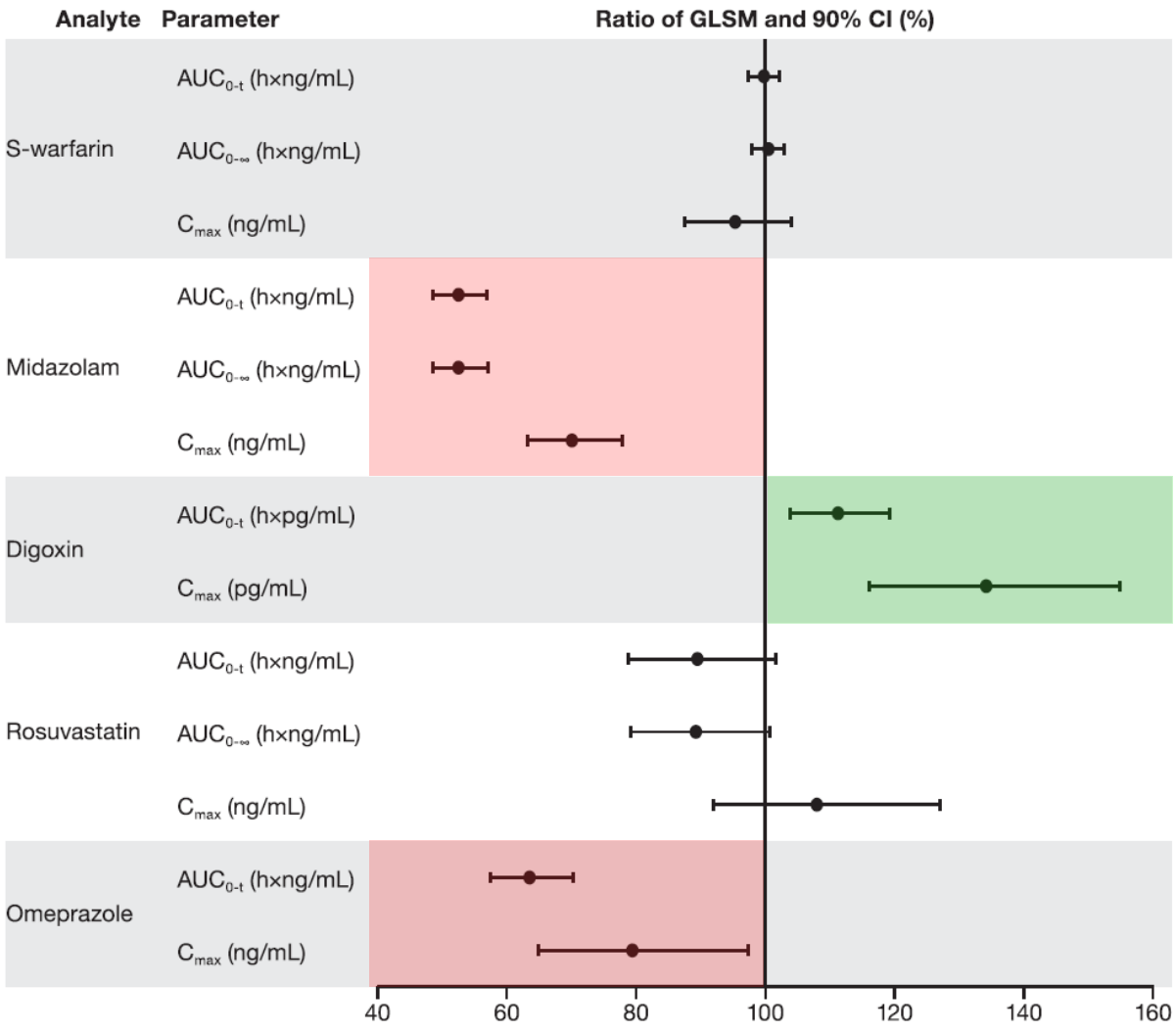
Evaluation of drug interaction potential of zanubrutinib with cocktail probes representative of CYP3A4, CYP2C9, CYP2C19, P-GP AND BCRP

Summary plot of the effect of zanubrutinib on the pharmacokinetic parameters of probe drugs



AUC_{0-t}, area under the concentration–time curve from time zero to the last quantifiable concentration; BCRP, breast cancer resistance protein; BID, twice a day; CI, confidence interval; C_{max}, maximum observed concentration; CYP, cytochrome P450; GLSM, geometric least squares mean; P-GP, P-glycoprotein.

Ou YC *et al. Br J Clin Pharmacol* 2021; 87 (7): 2926–2936.

Evaluation of drug interaction potential of zanubrutinib with cocktail probes representative of CYP3A4, CYP2C9, CYP2C19, P-GP AND BCRP

- At clinically relevant concentrations, zanubrutinib did not impact the activity of CYP2C9 and BCRP, but it had a weak induction effect on CYP3A and CYP2C19.

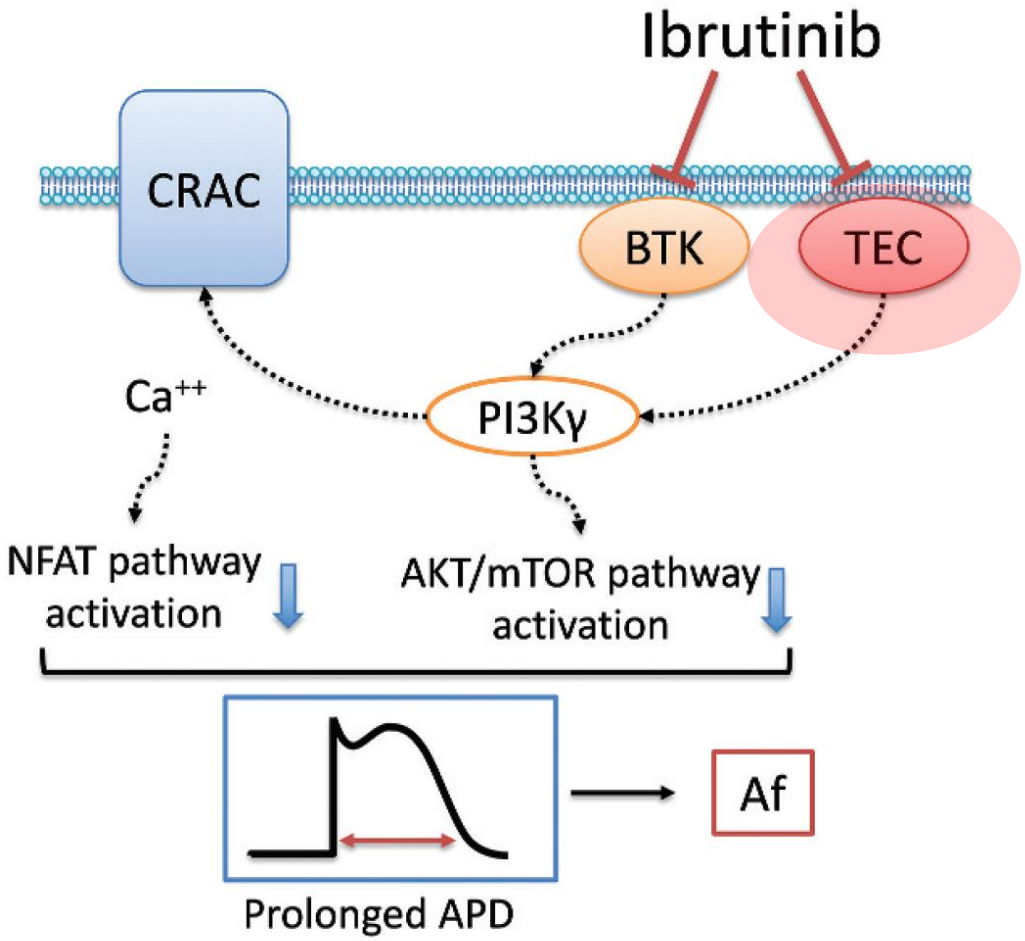
BCRP, breast cancer resistance protein; CYP, cytochrome P450; P-GP, P-glycoprotein.
Ou YC *et al. Br J Clin Pharmacol* 2021; 87 (7): 2926–2936.

Rates of serious adverse events

	Grade ≥ 3			All Grades	
	AU003	ASPEN		ASPEN	
	Zanubrutinib	Zanubrutinib	Ibrutinib	Zanubrutinib	Ibrutinib
Atrial Fibrillation/Flutter	1%	0%	4%	2%	15%
Diarrhea	3%	3%	1%	21%	31%
Hemorrhage	4%	6%	8%	49%	58%
Hypertension	4%	6%	12%	11%	17%
Infection	27%	18%	19%	67%	66%
Neutropenia	16%	20%	8%	30%	13%
Secondary Malignancy		2%	1%	12%	11%

AU003 median follow-up: 36.0 months / ASPEN median follow-up: 32.7 months
Lim KJC *et al. Expert Rev Hematol* 2020; 13 (12): 1303–1310.

Possible mechanism of potential ibrutinib-associated atrial fibrillation



APD, atrial action potential durations; Af, atrial fibrillation; BTK, Bruton's tyrosine kinase.
Makita S *et al. Expert Opin Drug Saf* 2020; 19 (9): 1105–1120.

No QTc prolongation with zanubrutinib

Results of concentration-QTc analysis from a thorough QT study in healthy subjects

Summary of zanubrutinib PK parameters in healthy TQT study participants

	Zanubrutinib dose		
	Part A	Part B	
Parameter	480 mg (*n* = 6)	160 mg (*n* = 28)	480 mg (*n* = 30)
T_{max}, median (min, max), hour	2.8 (1.0, 3.5)	1.5 (1.0, 6.0)	2.0 (0.5, 6.0)
C_{max}, mean (CV%), ng/mL	353 (33.5)	216 (24.2)	406 (30.7)
AUC_{0-t}, mean (CV%), hour × ng/mL	2,570 (36.2)	1,160 (25.1)	2,770 (28.9)
$AUC_{0-\infty}$, mean (CV%), hour × ng/mL	2,670 (39.1)	1,230 (23.5)	3,060 (25.9)
$t_{½}$, mean (CV%), hour	11 (50)	5.3 (47)	8.1 (68)
CL/F, mean (CV%), L/hour	180 (39.2)	126 (29.0)	140 (38.8)
V_z/F, mean (CV%), L	2,840 (41.0)	966 (36.7)	1,630 (55.8)

AUC_{0-t}, area under the concentration-time curve from time zero to the last quantifiable concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time zero extrapolated to infinity; CL/F, apparent systemic clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time maximum observed concentration; TQT, thorough QT; V_2/F, apparent volume of distribution during the terminal elimination phase.

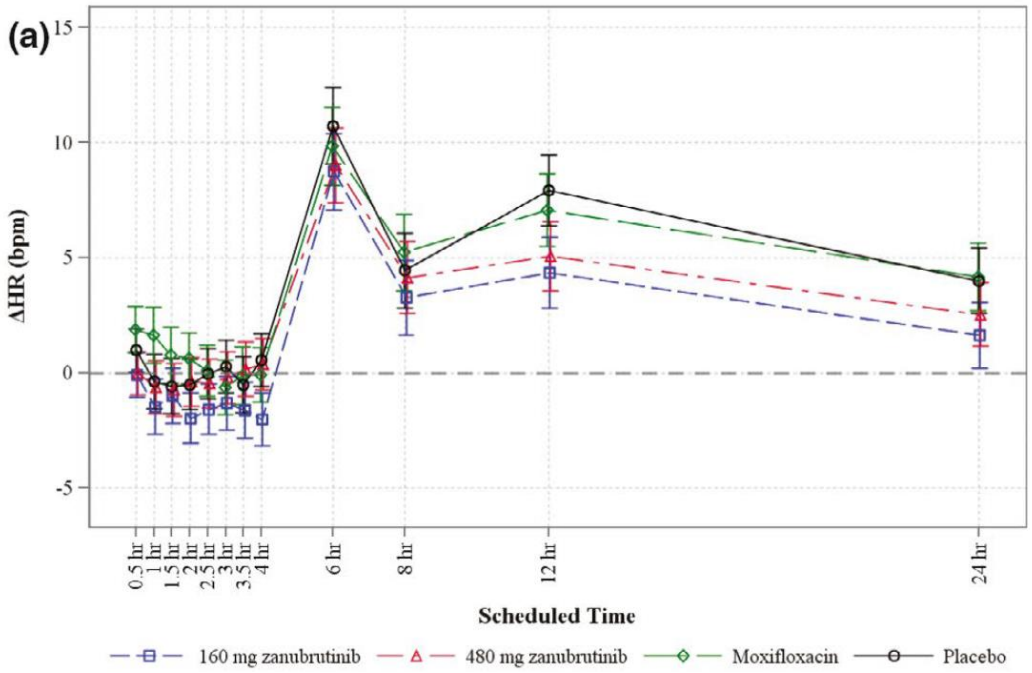
Mu S *et al. Clin Transl Sci* 20 20; 13 (5): 923–931.

No QTc prolongation with zanubrutinib

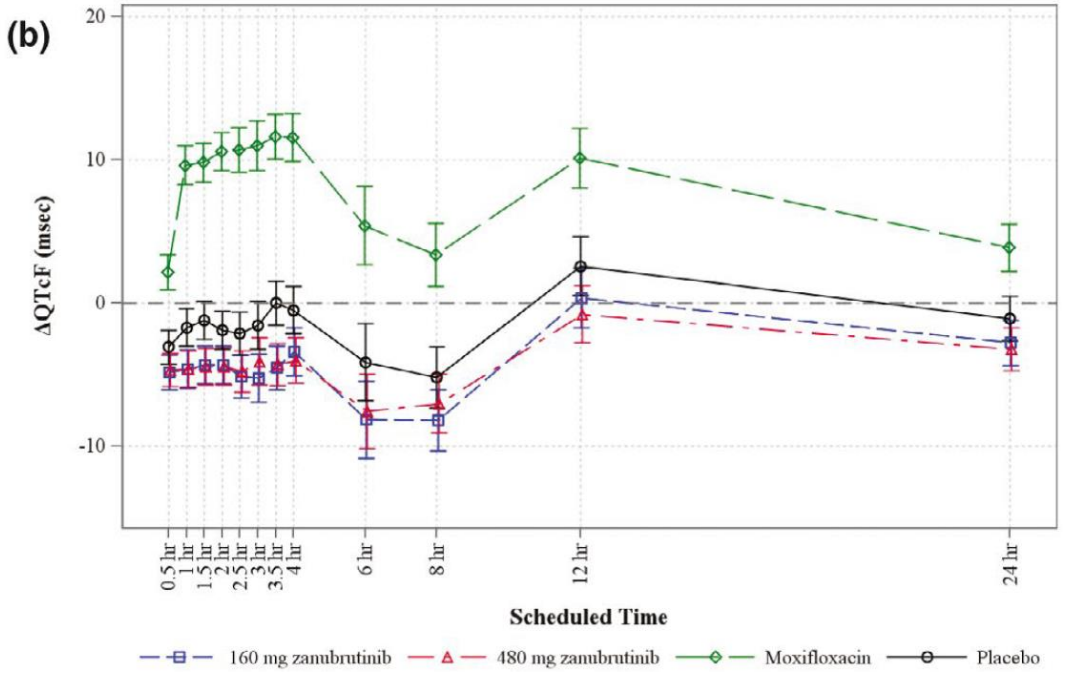
Results of concentration-QTc analysis from a thorough QT study in healthy subjects

Effects of zanubrutinib on ECG parameters

Change-from-baseline heart rate (δHR) across timepoints



Mean change from baseline in QTcF interval over time using Fridericia's formula (δQTcF)



ECG, electrocardiogram; HR, heart rate; QTcF, corrected QT interval by Fridericia.

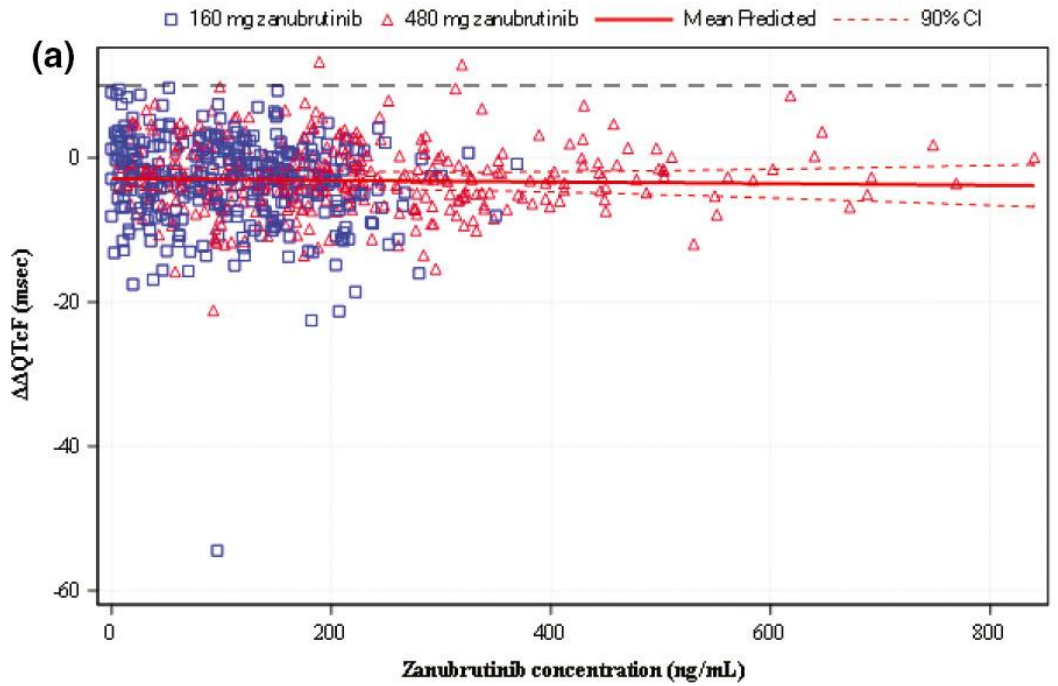
Mu S *et al. Clin Transl Sci* 2020; 13 (5): 923–931.

No QTc prolongation with zanubrutinib

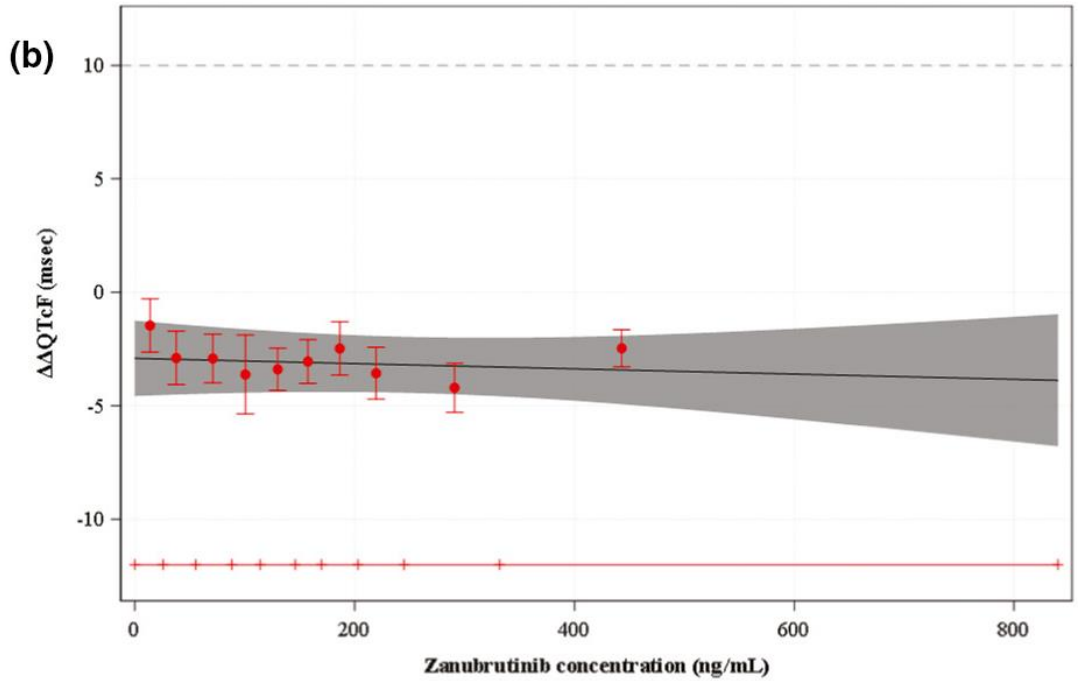
Results of concentration-QTc analysis from a thorough QT study in healthy subjects

Zanubrutinib concentration-QTc analysis

Scatter plot of observed zanubrutinib plasma concentrations and mean change from baseline in QTcF interval over time using Fridericia's formula (ΔΔQTcF)



Mean (90% confidence interval (CI)) model-predicted and observed ΔΔQTcF across deciles of zanubrutinib plasma concentrations)*



*The red dots with vertical bars denote the observed mean (90% CI) ΔΔQTcF at the median zanubrutinib plasma concentration within each decile. The solid black line within the gray shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF. The horizontal red line with notches shows the range of concentrations divided into deciles for zanubrutinib. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the second 10%, and so on.

QTcF, corrected QT interval by Fridericia. Mu S *et al. Clin Transl Sci* 2020; 13 (5): 923–931.

Rates of serious adverse events

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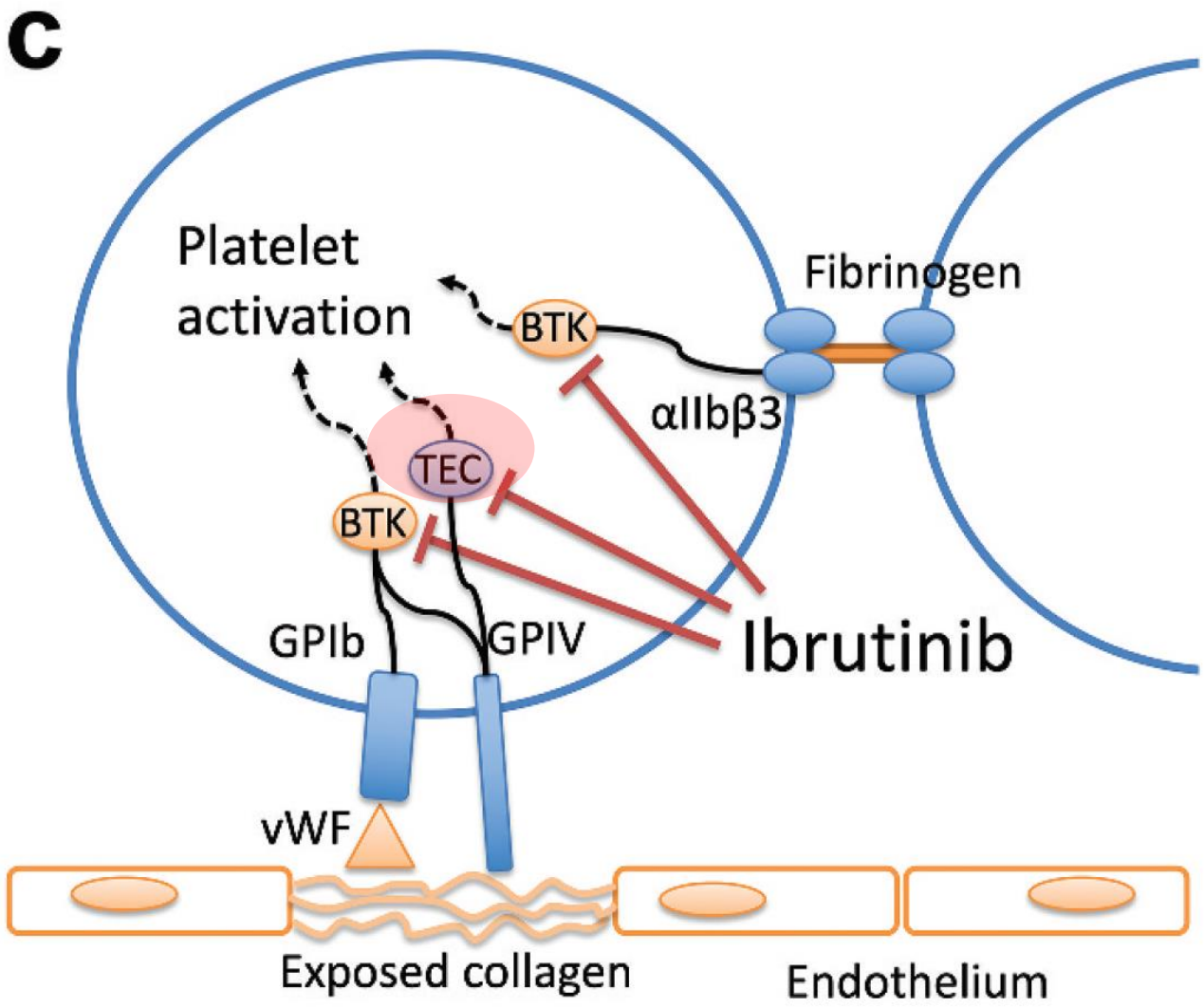
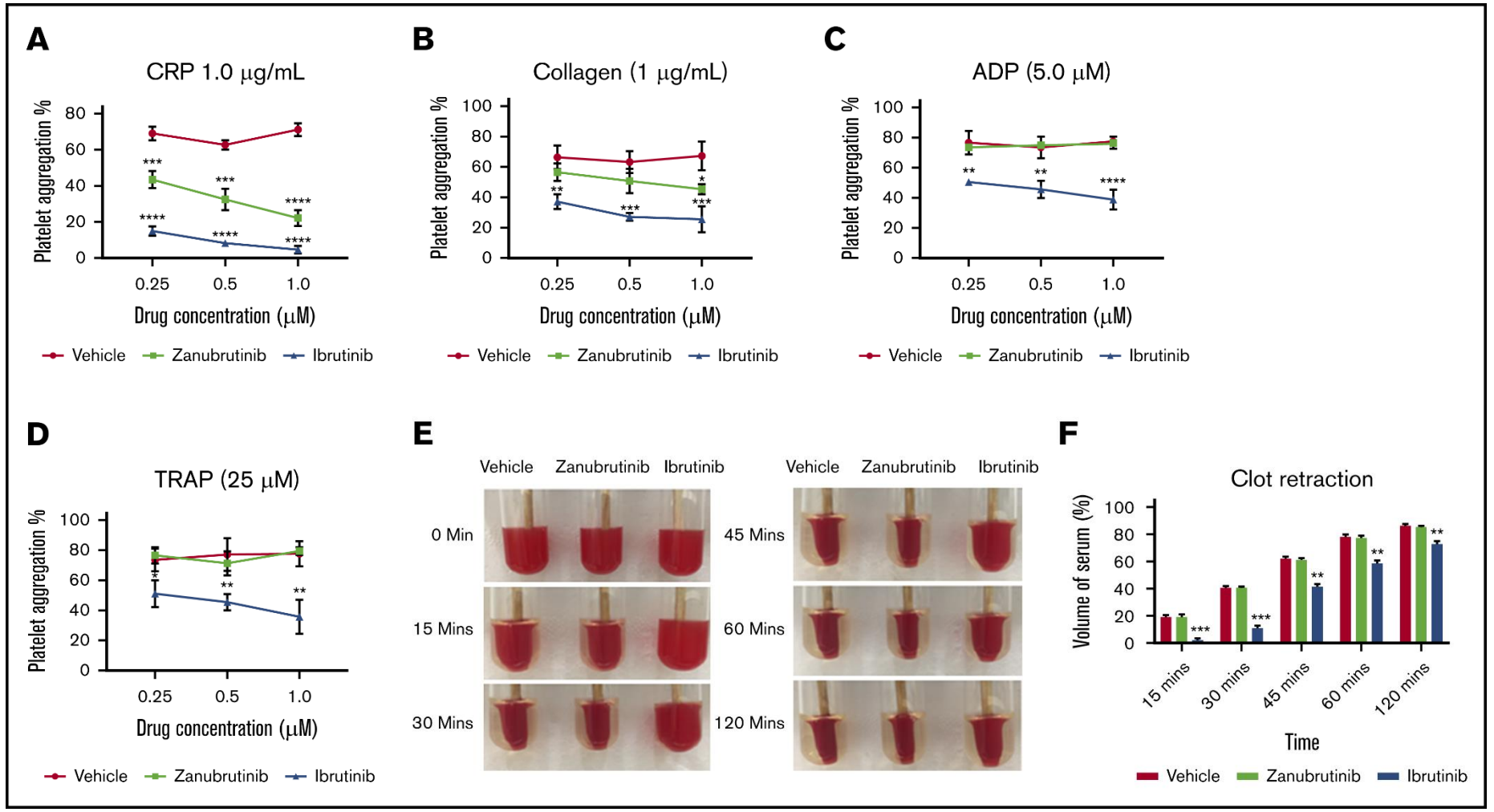


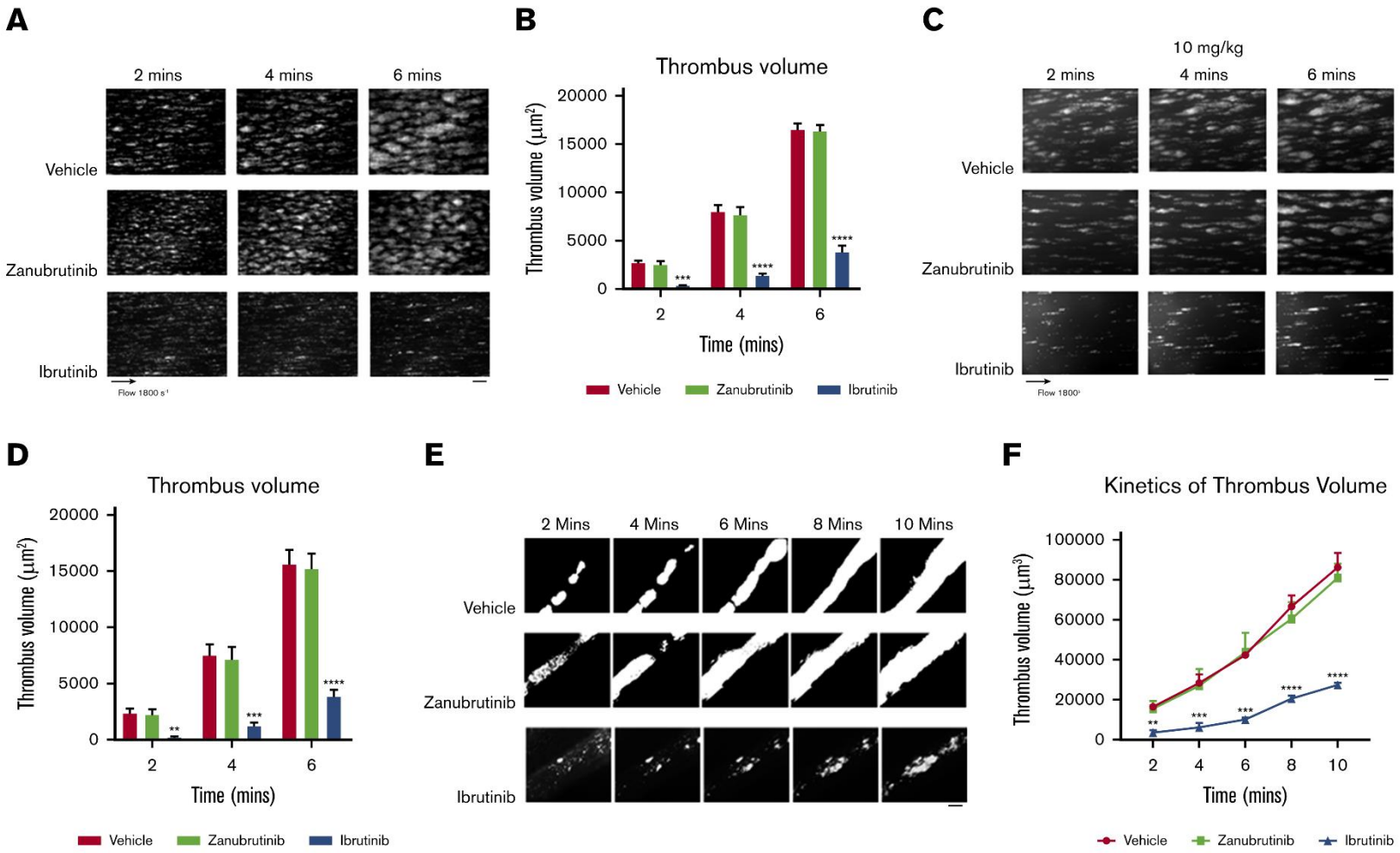
BTK, Bruton's tyrosine kinase.
Makita S *et al. Expert Opin Drug Saf* 2020; 19 (9): 1105–1120.

The effect of BTK inhibitors on agonist-induced platelet aggregation and clot retraction *in vitro*



ADP, Adenosine diphosphate, BTK, Bruton's tyrosine kinase; CRP, C-reactive protein; TRAP, thrombin receptor activating peptide.
Dobie G *et al. Blood Adv* 2019; 3 (24): 4298–4311.

The effect of ibrutinib and zanubrutinib on *in vitro*, *ex vivo*, and *in vivo* thrombus formation and tail bleeding time



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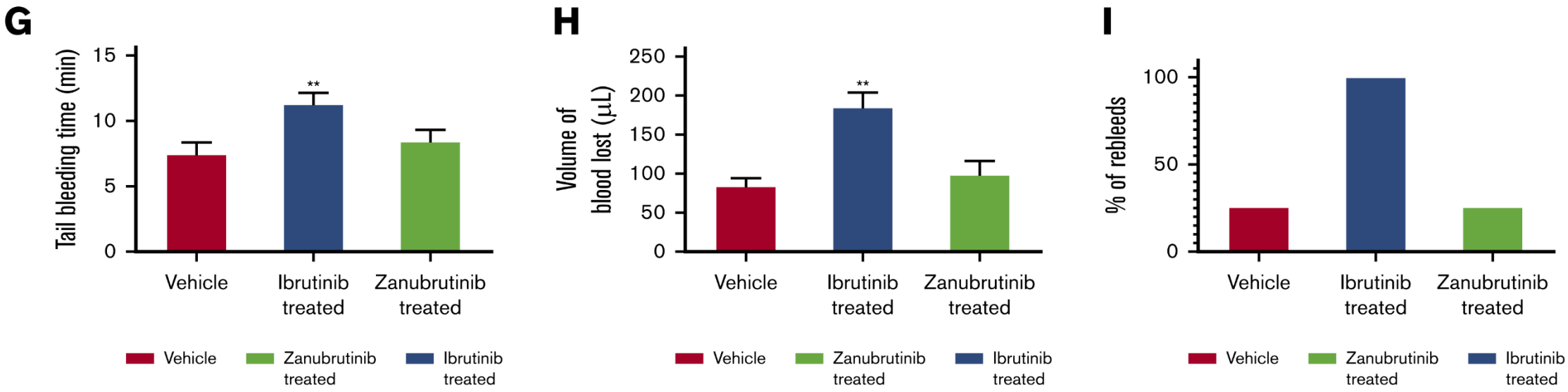

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Conclusions

Makita S *et al*. *Expert Opin Drug Saf* 2020

BTK, Bruton’s tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

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- The BTK inhibitor is an important game-changer in B-cell lymphoma management, especially in B-CLL/SLL

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Makita S *et al. Expert Opin Drug Saf* 2020

- The BTK inhibitor is an important game-changer in B-cell lymphoma management, especially in B-CLL/SLL
- Although ibrutinib, the first-in-class BTK inhibitor, is generally well tolerated compared with conventional cytotoxic chemotherapies, several toxicities including atrial fibrillation, bleeding, and infection were reported

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- And these toxicities may be overcome with more specific second-generation BTK inhibitors
- We currently prefer to utilize second-generation BTK inhibitors among patients with comorbidities such as histories of heart disease and/or concomitant use of anticoagulants

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Makita S et al. Expert Opin Drug Saf 2020; 19 (9): 1105–1120.

Next-generation BTK inhibitor monotherapy vs. ibrutinib in the treatment of relapsed/refractory CLL/SLL

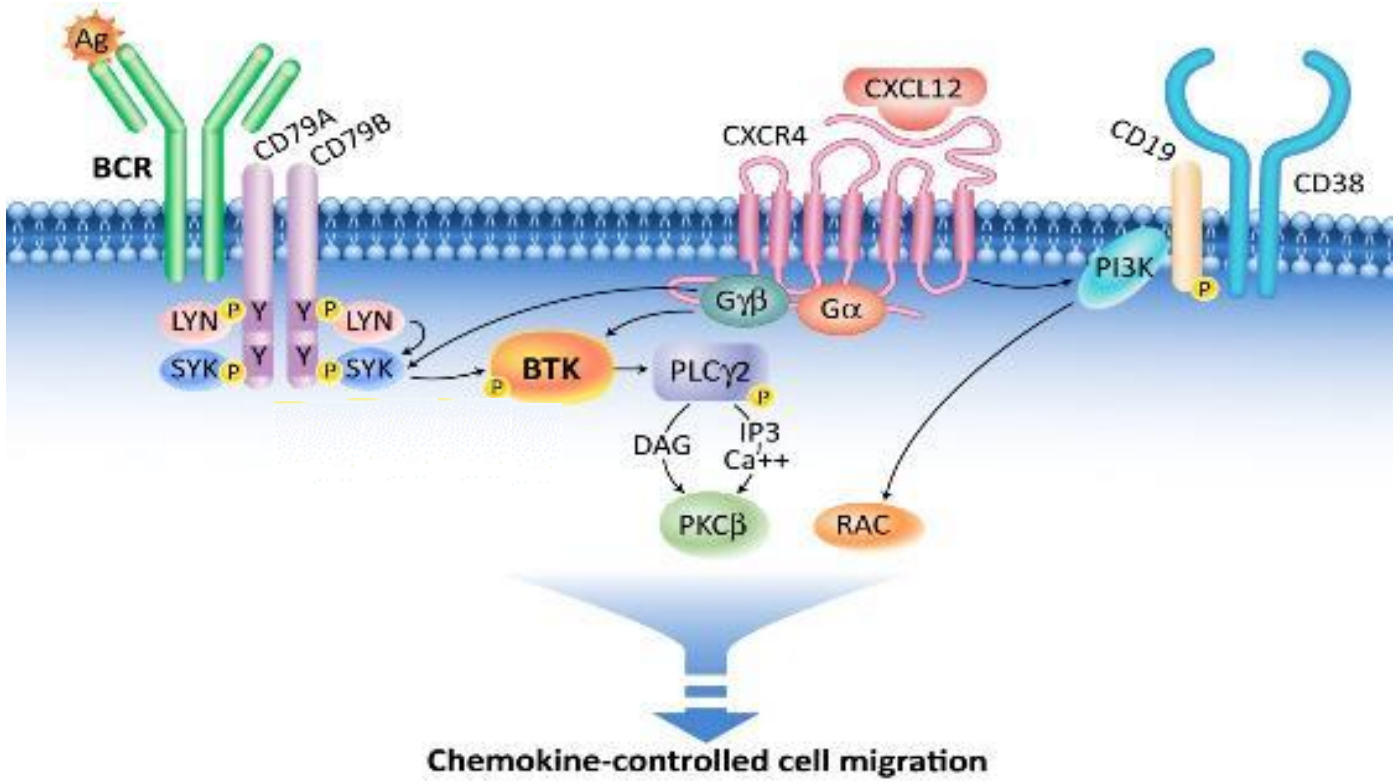
Professor Paolo Ghia
Vita-Salute San Raffaele University and
IRCCS San Raffaele Hospital, Italy

Disclosures

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

Chemotherapy-free treatments for B-cell malignancies

- BTK is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- BTK also acts downstream of certain chemokine receptors, impacting integrin molecules that help in promoting egression from the lymph node environment

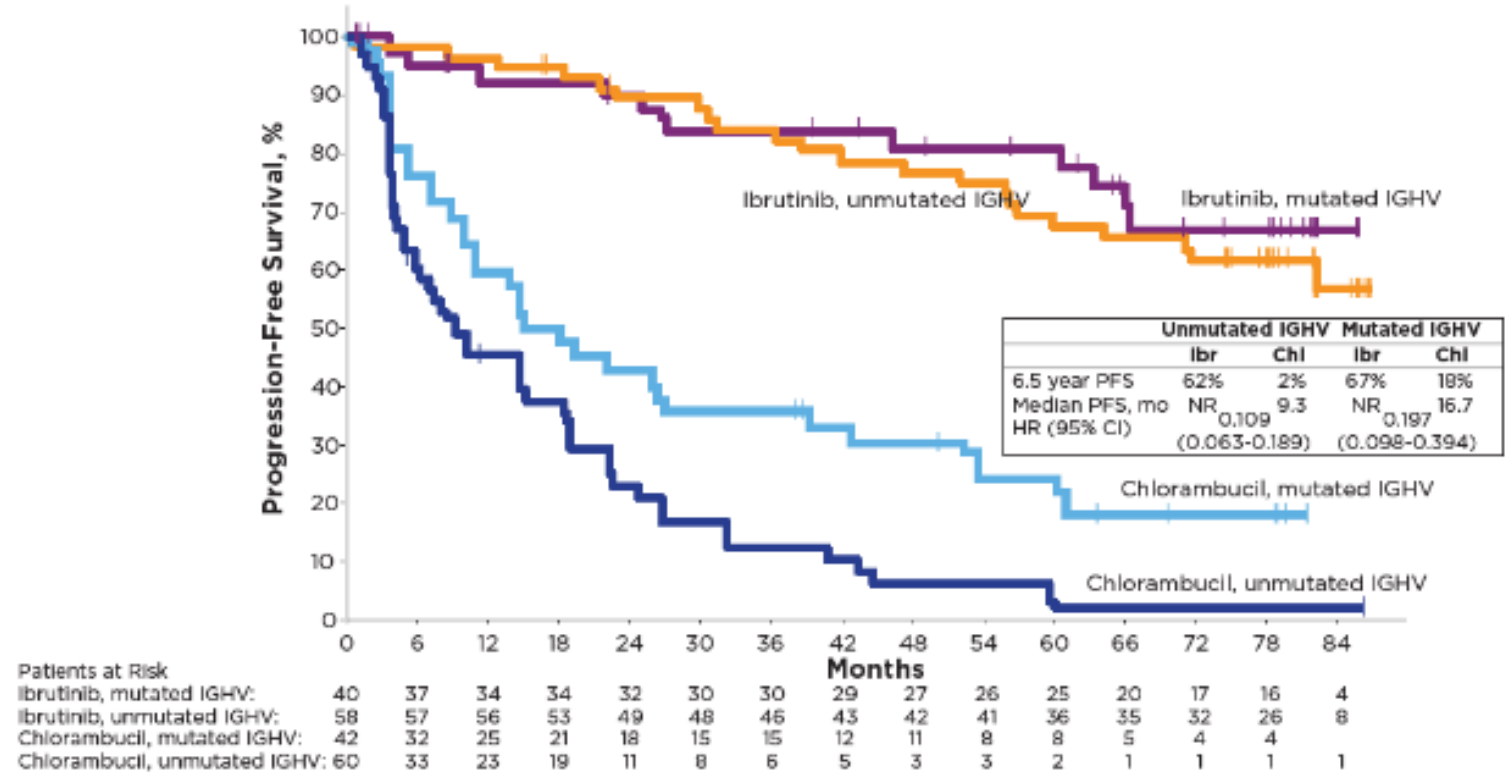


BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; PI3K, phosphatidylinositol 3-kinase.
Niiro H *et al*. *Nat Rev Immunol* 2002; 2 (12): 945–956. Aalipour A *et al*. *Ther Adv Hematol* 2014; 5 (4): 121–133.

Phase III study RESONATE-2: First-line ibrutinib vs. chlorambucil
Up to 7 years follow-up

- PFS and OS benefits across all patient subgroups with ibrutinib
  - Overall PFS: 61%
  - Overall OS: 78%
- Sustained and deepening responses
  - CR/CRi: 34%
  - Only 16 patients (12%) progressed while receiving ibrutinib
- ~50% of patients remained on therapy; dose adjustments managed most AEs
  - Specific AEs of concern with ibrutinib
    - Atrial fibrillation
    - Hypertension
    - Hemorrhage

PFS: Ibrutinib vs. chlorambucil by IGHV status



AE, adverse event; CR, complete response; CRi, complete response with incomplete bone marrow recovery; OS, overall survival; PFS, progression-free survival.
Ghia *et al*. 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

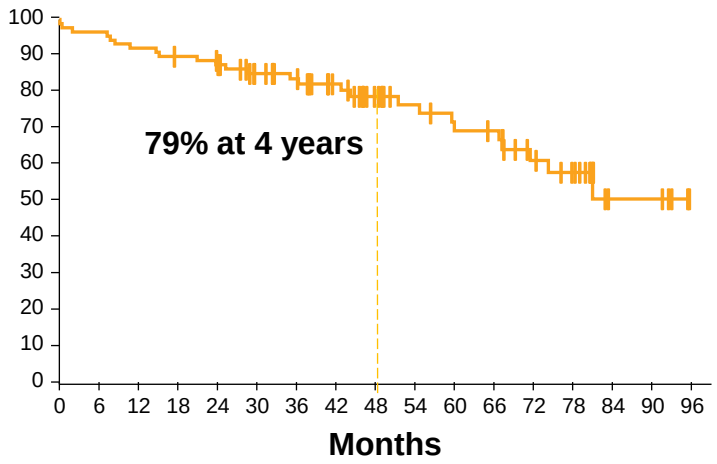
Long-term efficacy of first-line ibrutinib

CLL with *TP53* aberrations

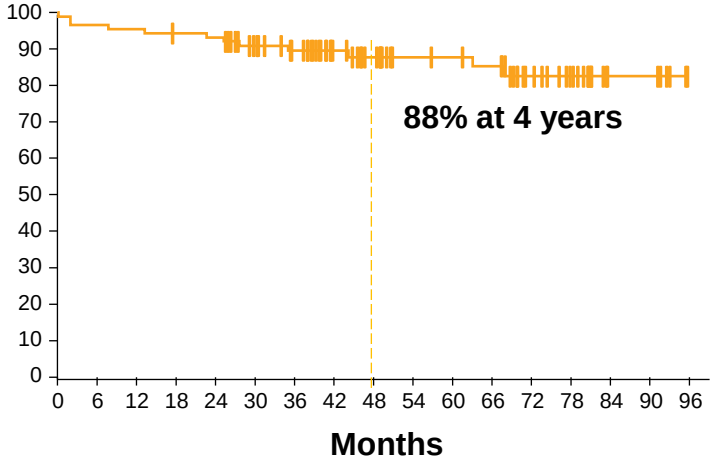
Pooled analysis: 4-year follow-up[1]

	PCYC-1122e (NIH study)	RESONATE-2	iLLUMINATE	ECOG1912
N	34	11	18	26
Regimen	Ibrutinib	Ibrutinib	Ibrutinib + obinutuzumab	Ibrutinib + rituximab
Patients	del(17p)/ *TP53*^{Mut}	*TP53*^{Mut}	del(17p)/ *TP53*^{Mut}	*TP53*^{Mut}

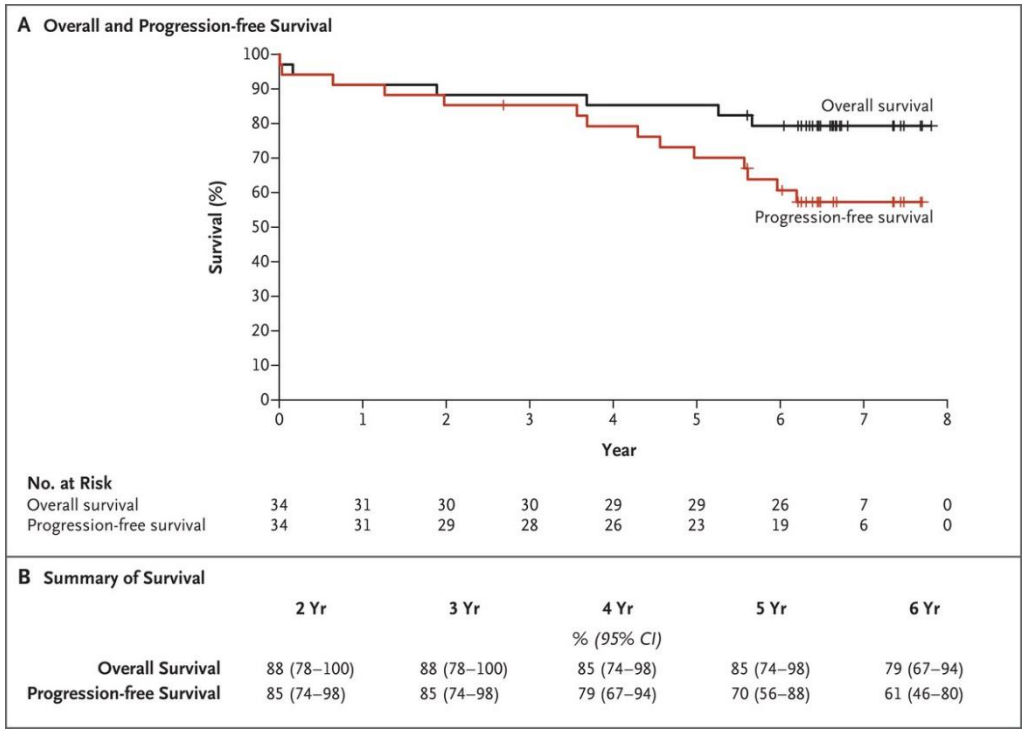
PFS[1]



OS[1]



6-year follow-up of the NIH phase 2 study[2]



CI, confidence interval; CLL, chronic lymphocytic leukemia; Mut, mutated; NIH, National Institutes of Health; OS, overall survival; PFS, progression-free survival; Yr, year.

1. Allan JN *et al*. Abstract 2219 presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020. 2. Ahn IE *et al. N Engl J Med* 2020; 383 (5): 498–500.

Phase III study ELEVATE-RR

Acalabrutinib vs. ibrutinib in high-risk R/R CLL

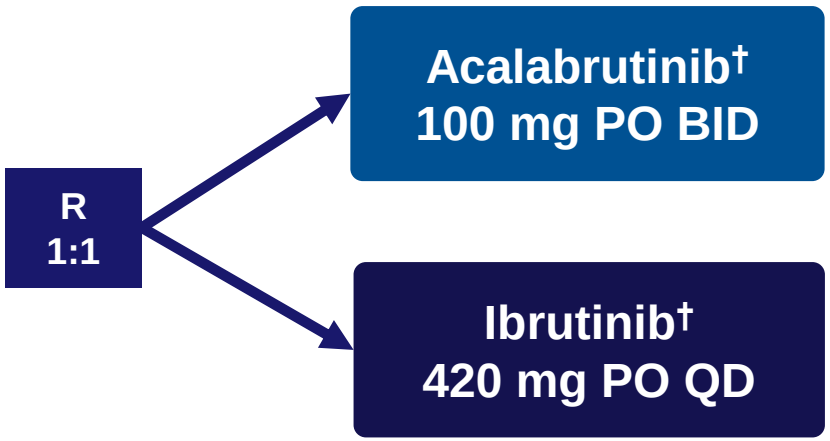
Patients (N=533)

Key inclusion criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria)
- Presence of del(17p) or del(11q)*
- ECOG PS ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs. ≤1)
- Number of prior therapies (1–3 vs. ≥4)



Primary endpoint

- Non-inferiority on IRC-assessed PFS‡

Secondary endpoints (hierarchical order):

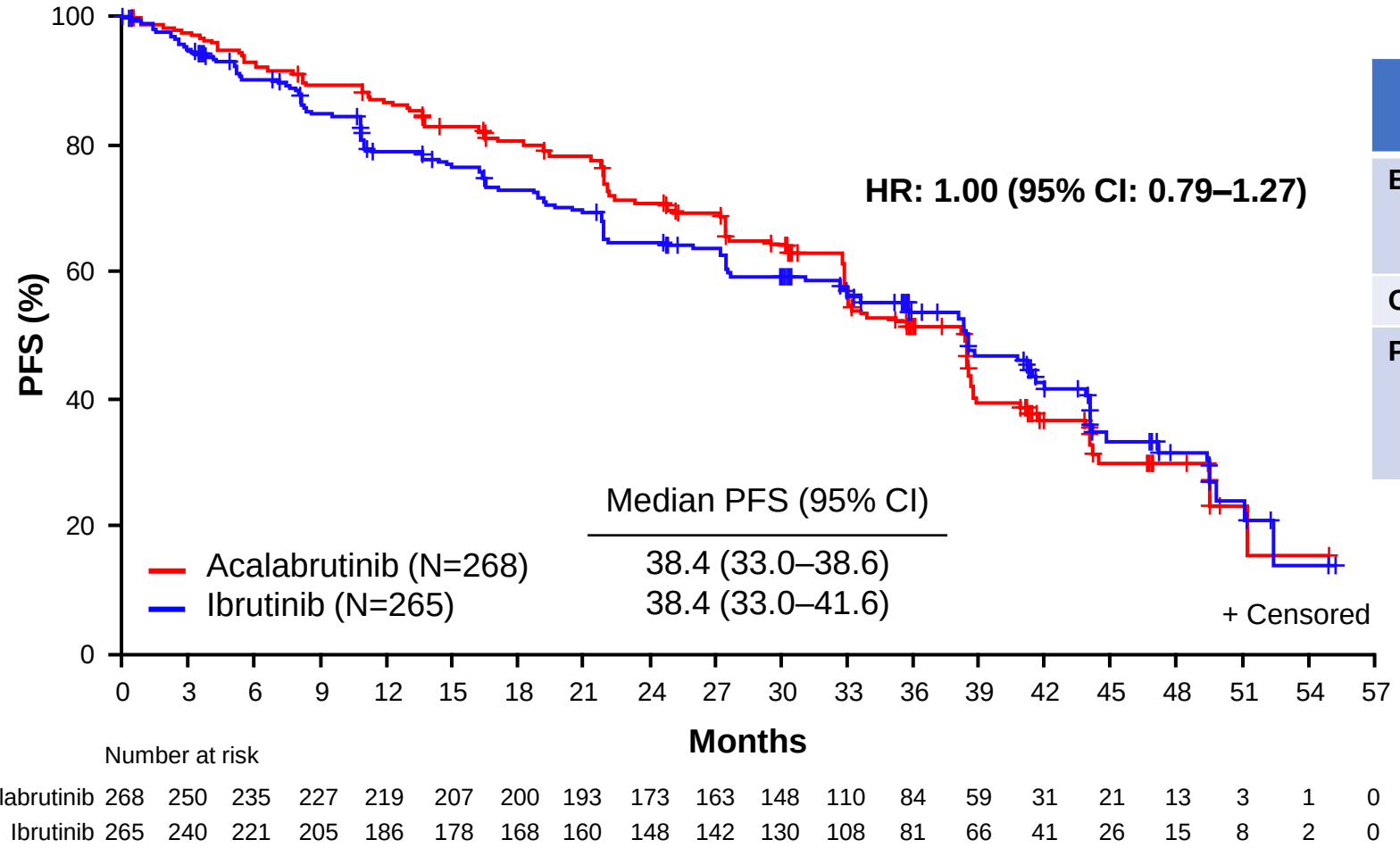
- Incidence of any grade atrial fibrillation/flutter
- Incidence of Grade ≥3 infection
- Incidence of Richter transformation
- OS

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (e.g. BTK, PI3K, or Syk inhibitors), or a BCL-2 inhibitor (e.g. venetoclax)

*By central laboratory testing. †Continued until disease progression or unacceptable toxicity. ‡Conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
BCL, B-cell lymphoma; BCR, B-cell receptor; BID, twice a day; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, by mouth; Syk, spleen tyrosine kinase; QD, once a day; R, randomization; R/R, relapsed/refractory.
ClinicalTrials.gov NCT02477696. Available at: https://clinicaltrials.gov/ct2/show/NCT02477696. Accessed September 2021. Byrd JC *et al. J Clin Oncol* 2021; Epub ahead of print (DOI: 10.1200/JCO.21.01210).

ELEVATE-RR: Acalabrutinib vs. ibrutinib in high-risk R/R CLL

IRC-assessed PFS



Median follow-up: 41 months

	Acalabrutinib (N=268)	Ibrutinib (N=265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS, % (95% CI)		
12 months	86.7 (81.8–90.3)	78.8 (73.1–83.4)
24 months	70.9 (64.8–76.1)	64.5 (58.1–70.2)
36 months	51.4 (44.7–57.8)	53.8 (47.0–60.1)

Non-inferiority achieved if the upper bound of the 95% CI of the HR was less than the prespecified margin of 1.429

CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; IRC, independent review committee; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory.

Byrd JC *et al. J Clin Oncol* 2021; Epub ahead of print (DOI: 10.1200/JCO.21.01210). Byrd JC *et al. J Clin Oncol* 2021; 39 (15): 7500–7500.

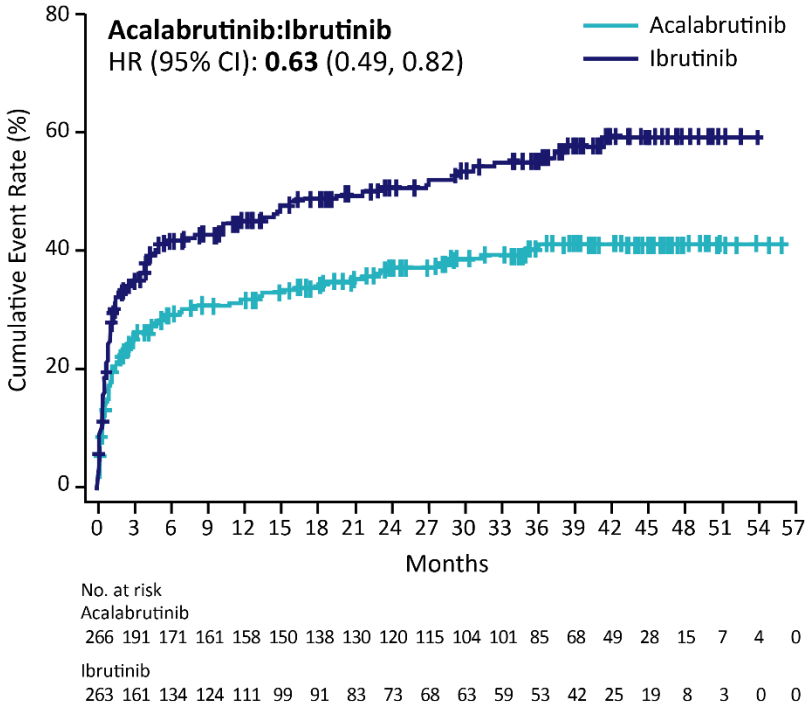
Events of clinical interest

Event, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

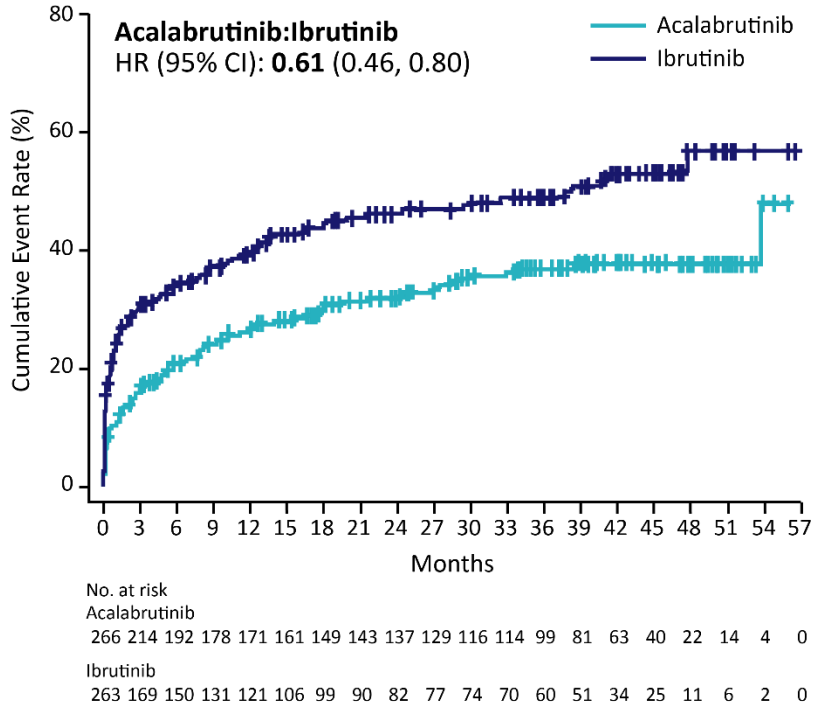
Higher incidence indicated in bold red for terms with statistical differences.
*Two-sided *P*-value for event comparisons <0.05 without multiplicity adjustment. [a]Includes events with preferred terms: atrial fibrillation and atrial flutter. [b]Includes events with preferred terms: torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia. [c]Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade). [d]Included events with the preferred terms: hypertension, blood pressure increased, and blood pressure systolic increased. [e]Most common Grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs. 2.7%, respectively), and UTI (1.1% vs. 2.3%, respectively).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPM, second primary malignancy; UTI, urinary tract infection.
Ghia P *et al.* Oral presentation JSH 2021.

Lower cumulative incidences of bleeding events, diarrhea, and arthralgia of any grade with acalabrutinib

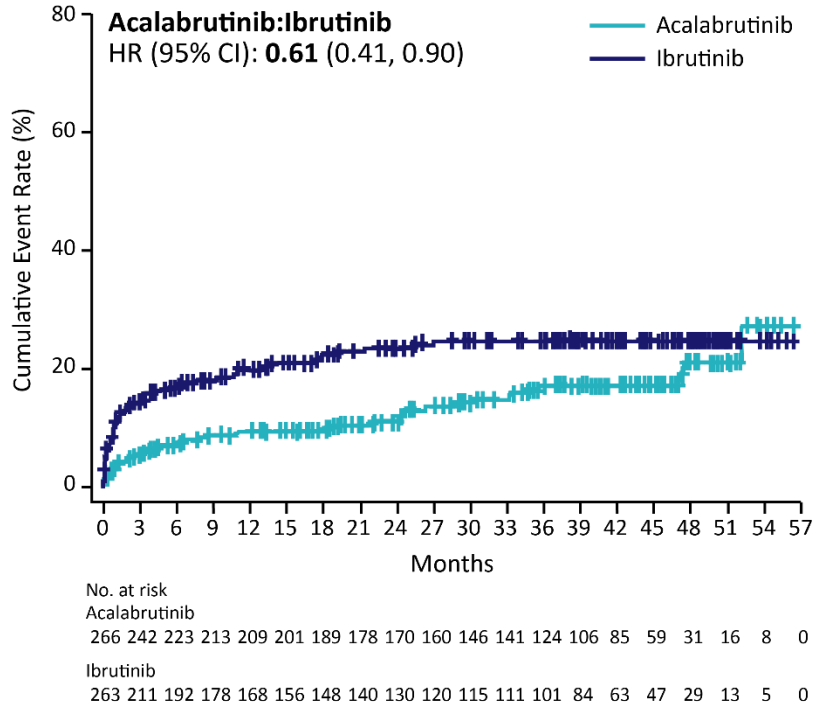
Bleeding events



Diarrhea

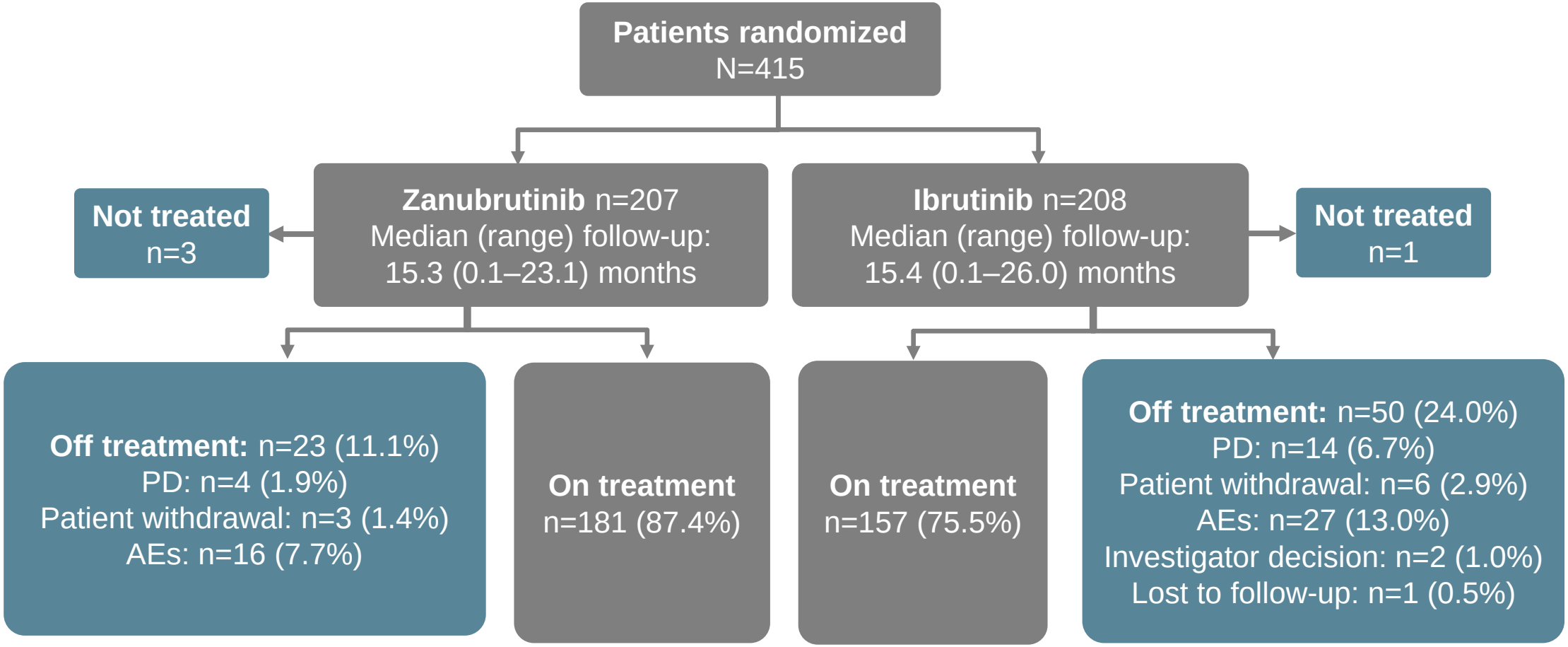


Arthralgia



CI, confidence interval; HR, hazard ratio.
Ghia P *et al.* Oral presentation JSH 2021.

Phase III study ALPINE: Ibrutinib vs. zanubrutinib in R/R CLL



AE, adverse event; CLL, chronic lymphocytic leukemia; PD, progressive disease; R/R, relapsed/refractory.

Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

ORR by investigator assessment

Pre-specified interim analysis

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR + CR)	162 (**78.3**) 95% CI: 72.0–83.7	130 (**62.5**) 95% CI: 55.5–69.1
	Superiority two-sided *P*=0.0006 compared with prespecified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)

CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

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CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to first assessment	6 (2.9)	9 (4.3)

CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

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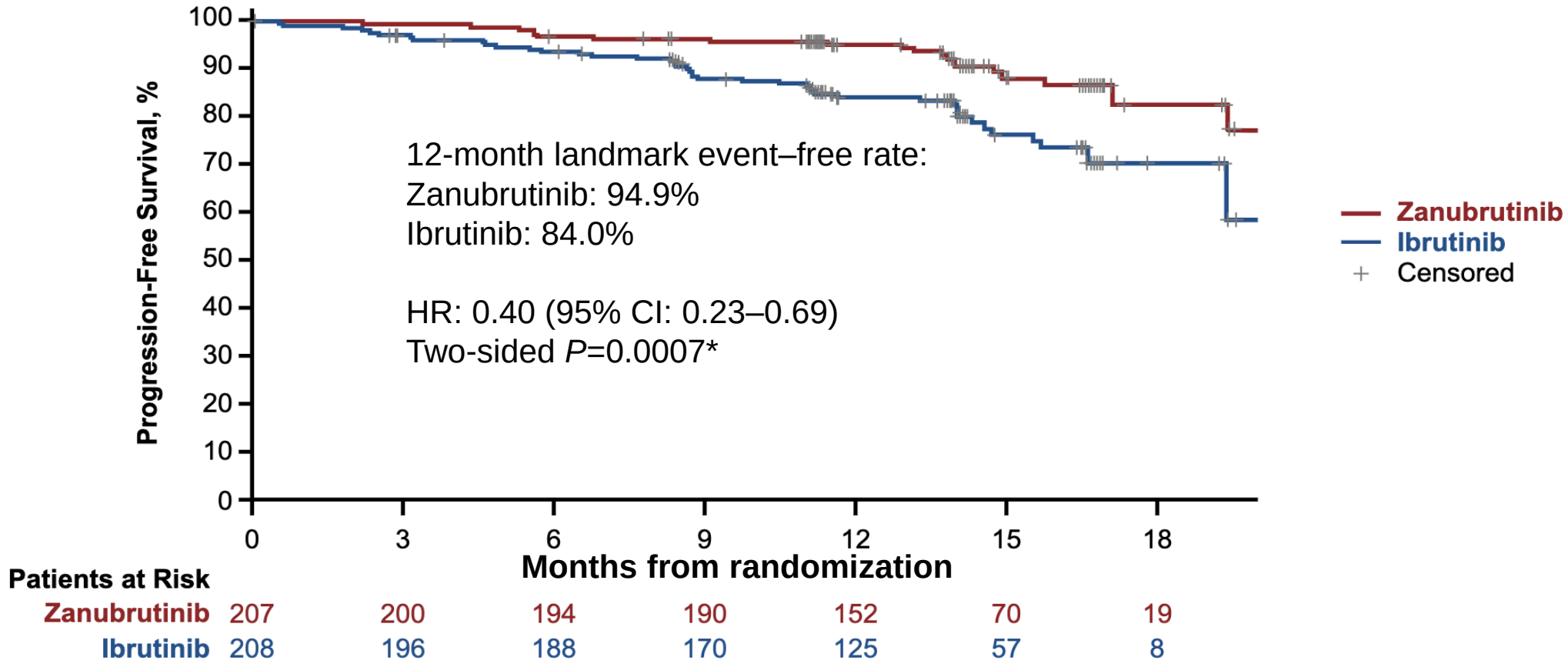
Discontinued or new therapy prior to first assessment	6 (2.9)	9 (4.3)

	del(17p) (n=24), n (%)	del(17p) (n=26), n (%)
ORR (PR + CR)	20 (83.3)	14 (53.8)

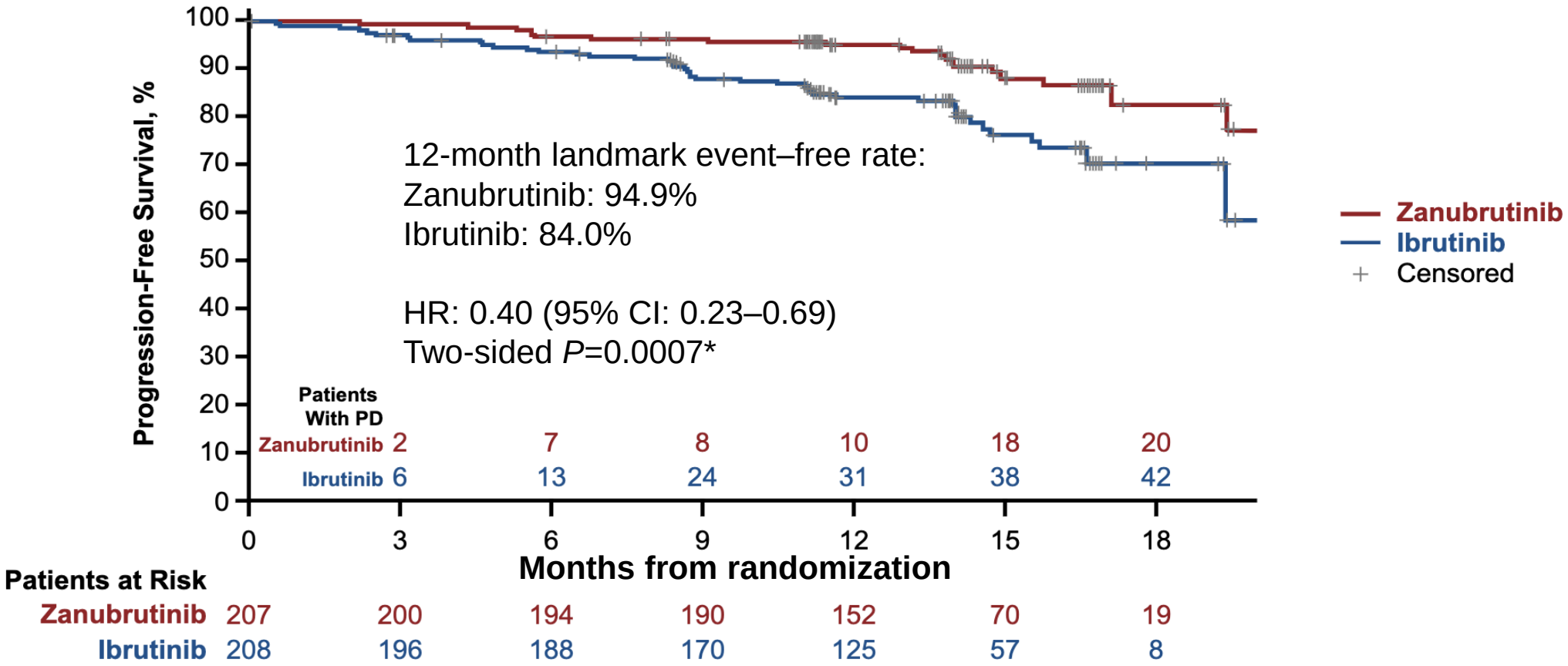
CI, confidence interval; CR, complete response; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

PFS by investigator assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PD, progressive disease; PFS, progression-free survival.
Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

PFS by investigator assessment



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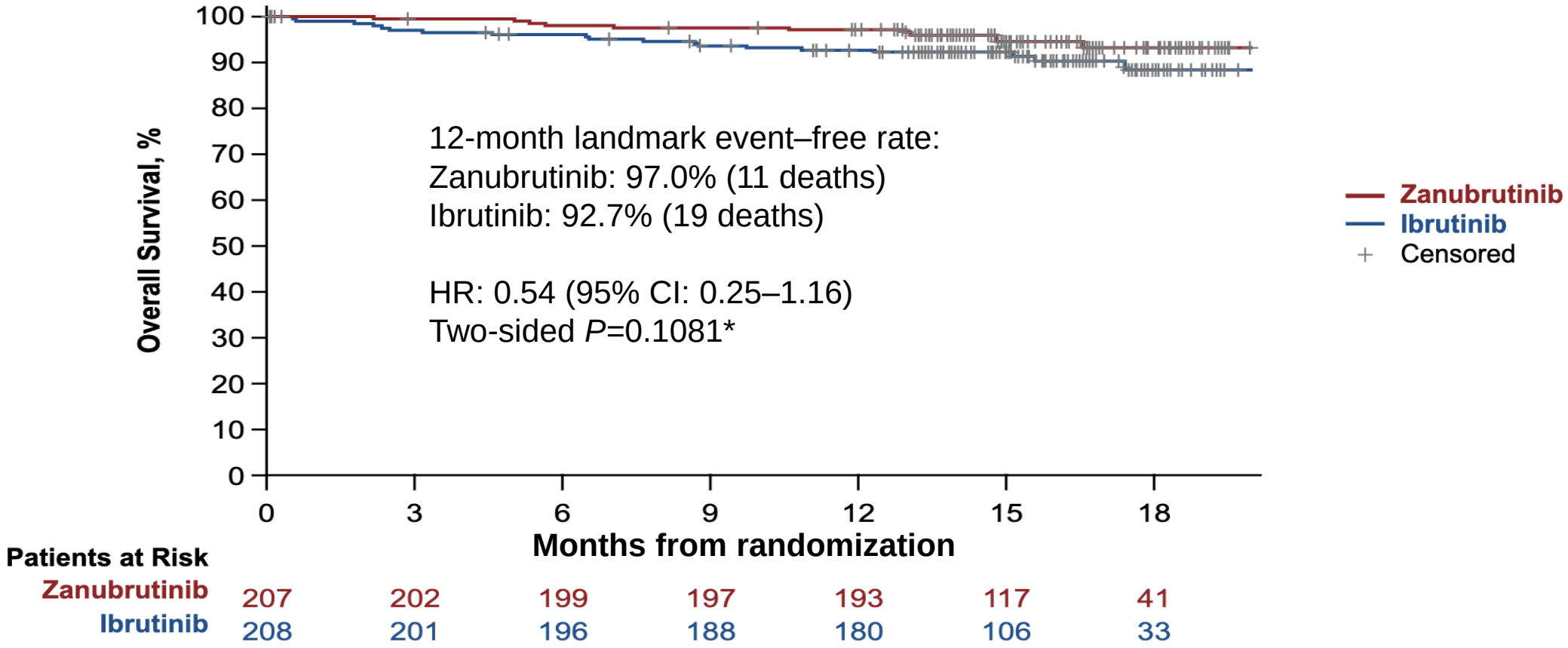
Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

Overall survival



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CI, confidence interval; HR, hazard ratio.
Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

Additional AEs of special interest

Safety analysis population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key secondary endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

Median follow-up: 15 months. All events are of any grade unless otherwise specified. [a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 patients (3.4%). [b]Includes hemorrhages that were serious or Grade ≥3, or CNS hemorrhages of all grades. [c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.
AE, adverse event; CNS, central nervous system.
Hillmen P *et al*. Abstract LB1900 presented at the 26th Annual Congress of the European Hematology Association (EHA) 2021 (virtual); June 10–13, 2021.

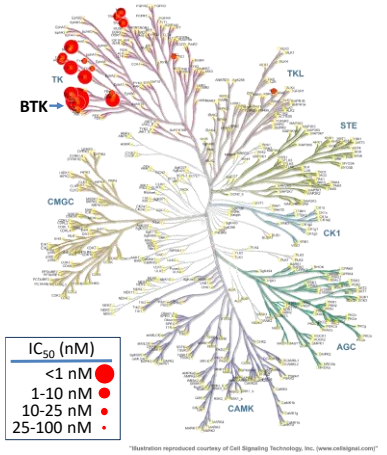
Third-generation BTK inhibitors

MK-1026 (ARQ 531)[1] | **LOXO-305[2] (pirtobrutinib)** | **Vecabrutinib**

– They bind **REVERSIBLY** to BTK

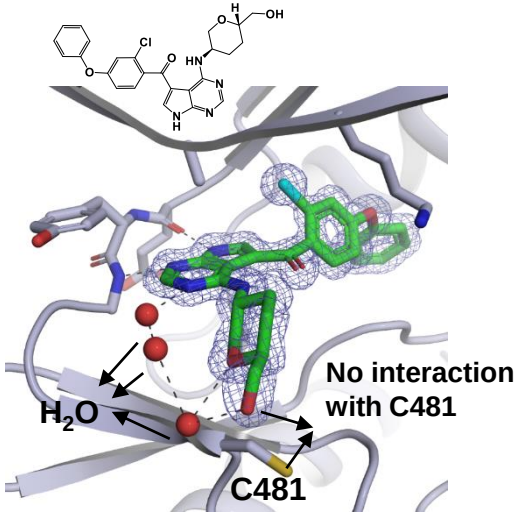
– They are **DUAL INHIBITORS** of both wild-type and C481S mutated BTK

ARQ 531 exhibits distinct kinase selectivity



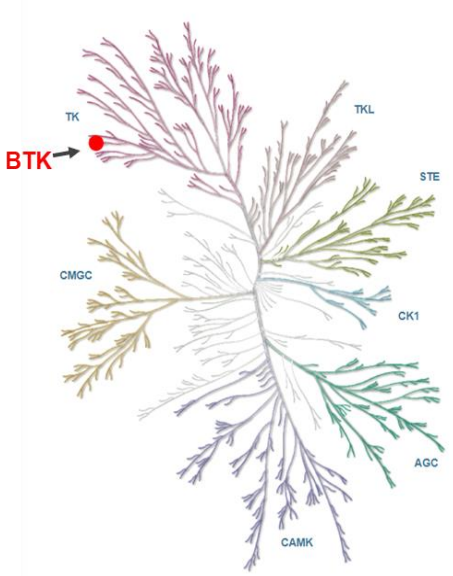
In addition to BTK, ARQ 531 inhibits TEC, TRK, and SRC family kinases

ARQ 531 is a non-covalent reversible inhibitor of BTK



Crystal structure of BTK / ARQ 531 complex at 1.1 Å resolution

LOXO-305 is highly selective for BTK



BTK, Bruton's tyrosine kinase; IC_{50}, half maximal inhibitory concentration.

1. Reiff SD *et al. Cancer Discov* 2018; 8 (10): 1300–1315. 2. Mato AR *et al*. Abstract 542; Oral presentation at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

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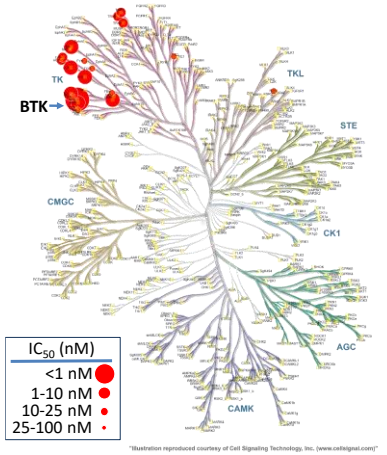

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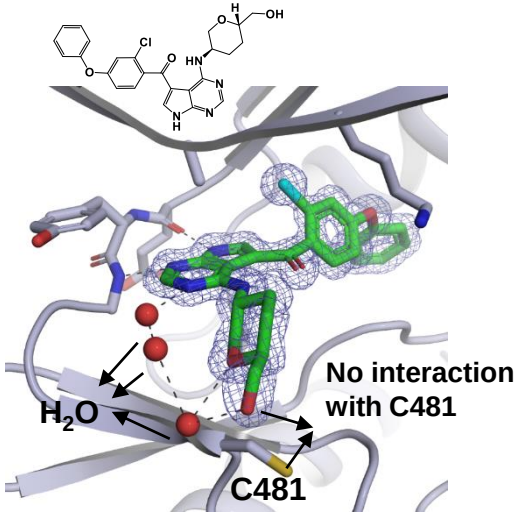

Crystal structure of BTK / ARQ 531 complex at 1.1 Å resolution

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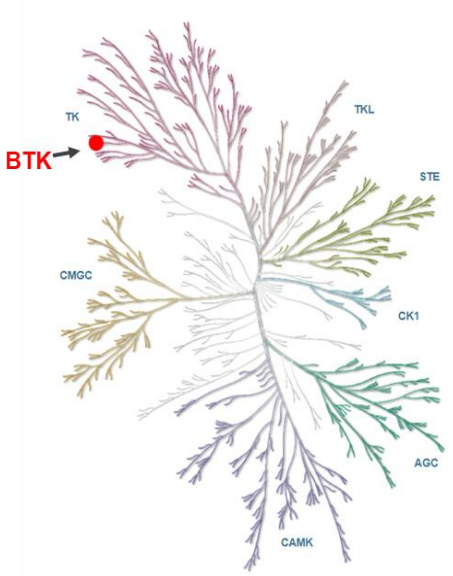

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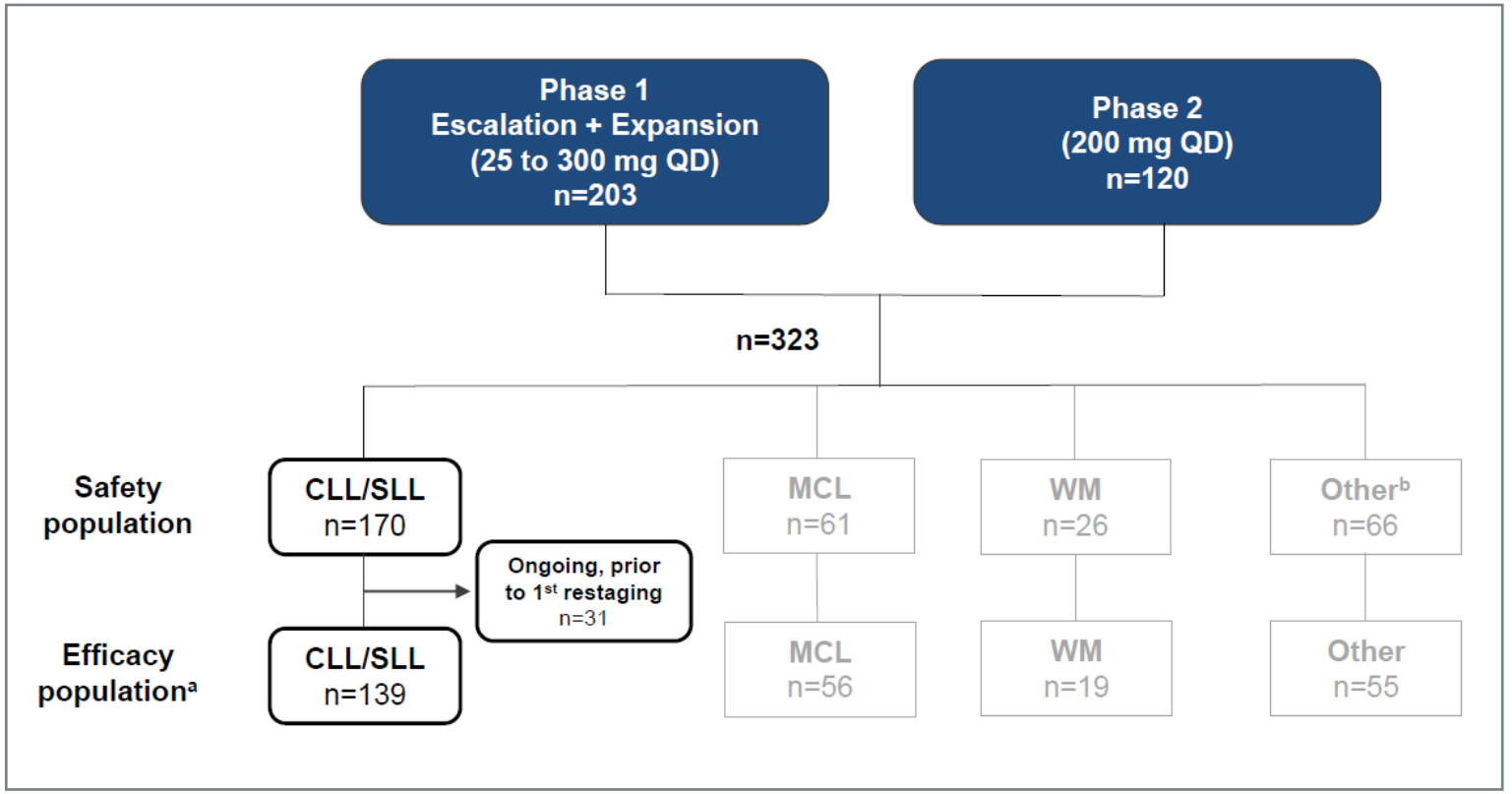
LOXO-305 in previously treated CLL/SLL

Phase I/II BRUIN Study



Characteristics	n=170
Median age, years (range)	69 (36–88)
Female, n (%)	61 (36)
Male, n (%)	109 (64)
ECOG PS, n (%)	
0	87 (51)
1	69 (41)
2	13 (8)
Median prior lines of systemic therapy (range)	3 (1–11)
BTK pre-treated	4 (1–11)
Prior therapy, n (%)	
BTK inhibitor	146 (86)
Chemotherapy	140 (82)
Anti-CD20 antibody	153 (90)
BCL2 inhibitor	57 (34)
PI3K inhibitor	36 (21)
Lenalidomide	14 (8)
Autologous stem cell transplant	0
Allogeneic stem cell transplant	3 (2)
CAR-T	10 (6)
Reason discontinued any prior BTKi, n (%)	
Progressive disease	98 (67)
Toxicity/other	48 (33)

Baseline molecular characteristics	
Mutation status, n (%)	
BTK C481-mutant	25 (27)
BTK wild-type	66 (73)
PLCG2-mutant	4 (4)
High-risk molecular findings, n (%)	
17p deletion	20 (25)
TP53 mutation	27 (30)
17p13 deletion + TP53 mutant	18 (22)
IGHV unmutated	71 (88)
11q deletion	15 (19)

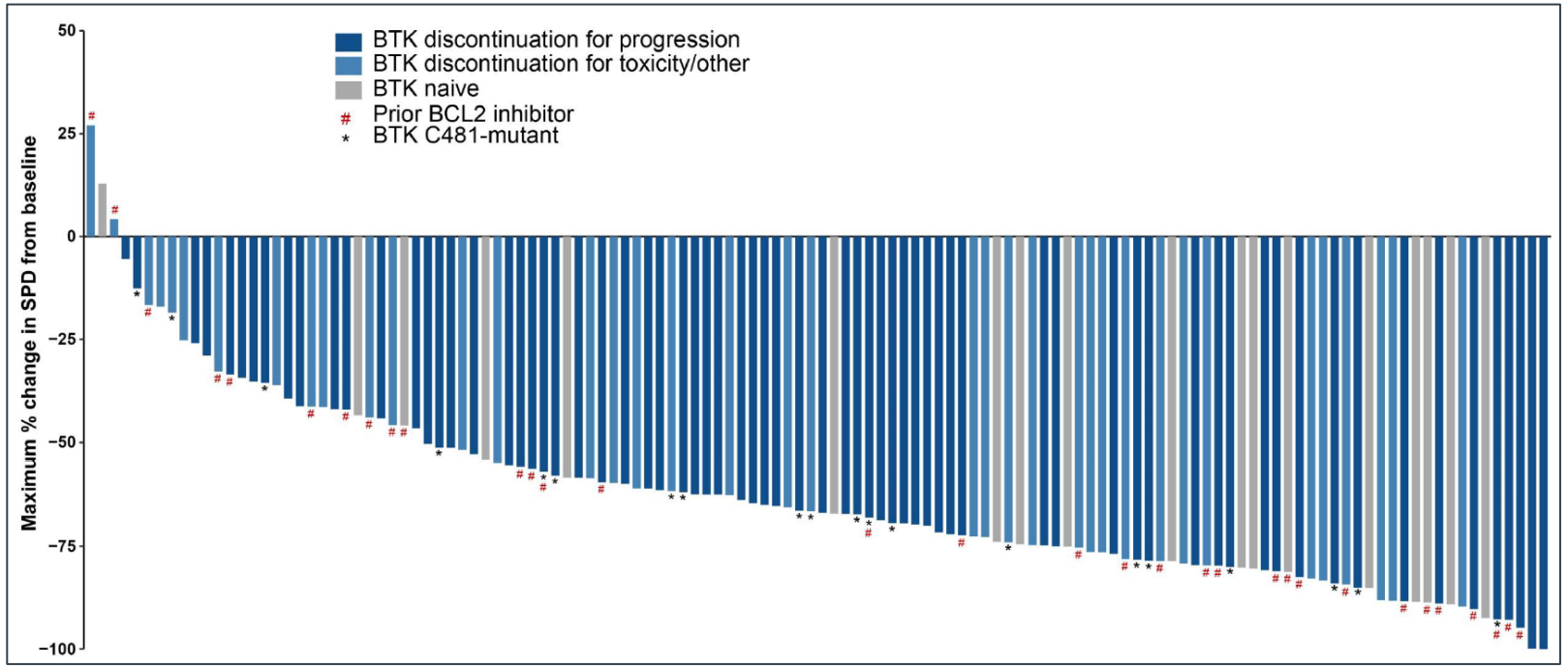
BCL, B-cell lymphoma; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase; QD, once a day; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Mato AR *et al*. Abstract 542; Oral presentation at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

BRUIN study

Safety profile and efficacy

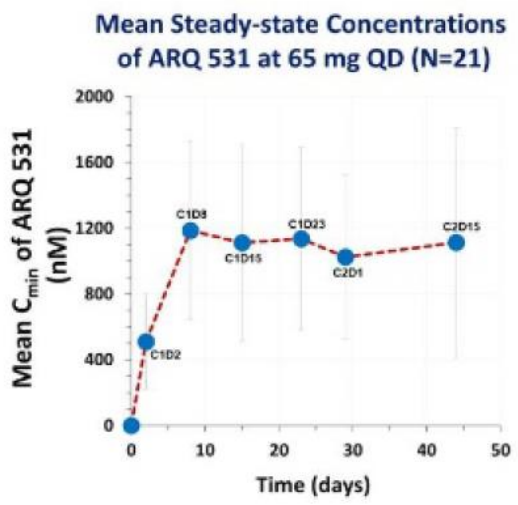
All doses and patients (n=323)							
Adverse event	Treatment-emergent AEs, (≥10%), n (%)					Treatment-related AEs, n (%)	
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grades 3/4	Any grade
Fatigue	40 (12)	22 (7)	3 (1)	–	65 (20)	2 (<1)	27 (8)
Diarrhea	45 (14)	10 (3)	–	–	55 (17)	–	28 (9)
Contusion	37 (12)	5 (2)	–	–	42 (13)	–	29 (9)
AEs of special interest							
Bruising	48 (15)	5 (2)	–	–	53 (16)	–	37 (12)
Rash	30 (9)	5 (2)	–	–	35 (11)	–	18 (6)
Arthralgia	13 (4)	3 (1)	–	–	16 (5)	–	5 (2)
Hemorrhage	10 (3)	4 (1)	1 (<1)	–	15 (5)	–	5 (2)
Hypertension	2 (<1)	9 (3)	4 (1)	–	15 (5)	–	4 (1)
AF/flutter	–	2 (<1)	–	–	2 (<1)	–	–

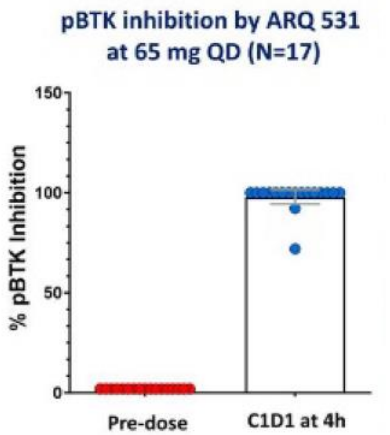


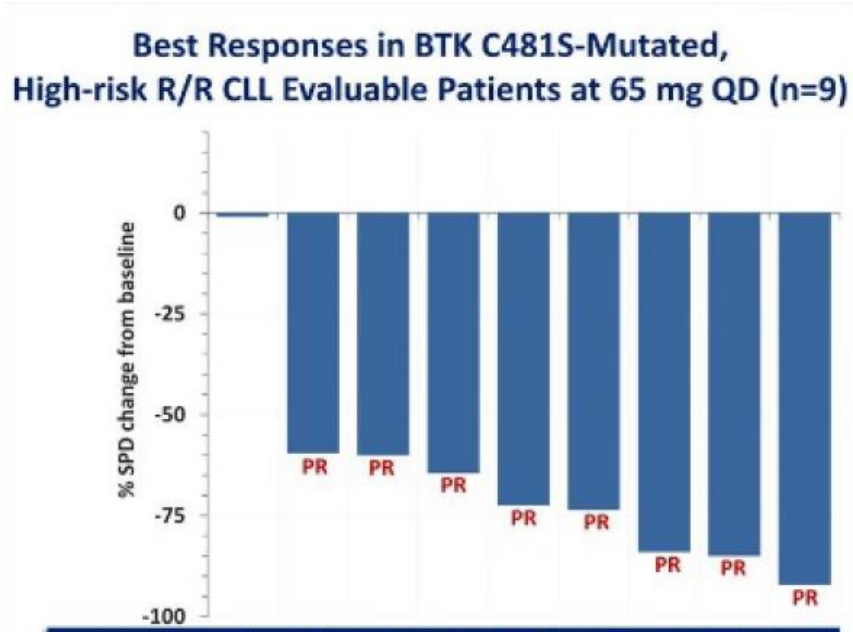
AE, adverse event; AF, atrial fibrillation; BCL, B-cell lymphoma; BTK, Bruton's tyrosine kinase; SPD, sum of the products of the diameters.

Mato AR *et al*. Abstract 542; Oral presentation at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

Phase I dose escalation study of MK-1026 (ARQ 531)



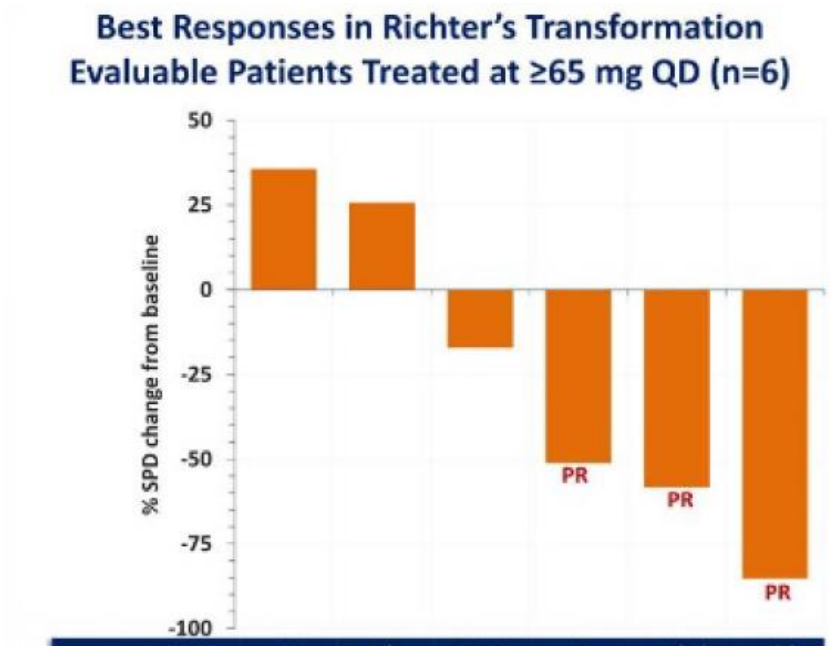




Pt #	36[b]	30[a]	48	33	40[a]	32	35	43[c]	27
Weeks on therapy	12	42	9	39	27	40	38	20	54
IGHV unmutated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complex karyotype	Yes	Yes	No	Yes	Yes	No	No	No	Yes

[a] BTK mutation unknown
[b] Positive to del17p
[c] Positive to del11q

Preliminary unmonitored data as of 6 Nov 2019



Pt #	41	45[b,c]	122-36[c]	42	34[a,b,c,d]	47[a,d]
Weeks on therapy	10	13	12	19	26	12
IGHV unmutated	Yes	Yes	Yes	Yes	No	Yes

[a] MYC(+)/BCL6(+) positive
[b] Positive to del17p
[c] Positive to del11q
[d] positive to complex karyotype

Preliminary unmonitored data as of 6 Nov 2019

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{min}, minimum concentration; pBTK, Bruton's tyrosine kinase phosphorylation; QD, once a day; Pt, patient; R/R, relapsed/refractory; SPD, sum of the products of the diameters.

Woyach J *et al*. Abstract 4298 (poster) from the 61st American Society of Hematology (ASH) Annual Meeting and Exposition 2019; Orlando, FL, USA, December 7–10, 2019.

Summary: BTK inhibitors in CLL/SLL

- The RESONATE-2 study demonstrated the long-term clinical benefits of first-line ibrutinib monotherapy to patients with CLL, including those with high-risk prognostic features
  - TEAEs are usually manageable
  - Specific TEAEs of concern are atrial fibrillation, hypertension, and bleeding

- Next-generation BTK inhibitors have the potential to offer non-inferior or superior efficacy with improved safety profiles compared with ibrutinib in patients with R/R CLL
  - ELEVATE-RR trial demonstrated the non-inferiority of acalabrutinb vs. ibrutinib and a reduced incidence of cardiovascular side effects and bleeding
  - ALPINE trial demonstrated a superior ORR of zanubrutinib vs. ibrutinib and reduced incidence of cardiovascular AEs

- Non-covalent BTK inhibitors may become a valuable option for patients with CLL who are resistant to covalent BTK inhibitors targeting C481

AE, adverse event; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; ORR, overall response rate; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.

Clinical case study

Medical history

- **69-year-old man, retired, active life**

Comorbidities

- Tuberculosis (–50 years from CLL diagnosis)
- Partial gastrectomy with Billroth 2 resection due to peptic ulcer (–47 years)

CLL history

- **Year 0: CLL diagnosis, Rai Stage IV**
- **WBC: 10.6 × 10^9/L, Hgb: 5.8 g/dL, PLT: 91 × 10^9/L**
- Negative Coombs test, no vitamin and/or iron deficiency, consumed haptoglobin
  - Steroid treatment started but achieved only mild and short-lasting benefit
- Due to consumed haptoglobin, steroid treatment was started but achieved only mild and short-lasting benefit

Staging procedures

- CT scan: Multiple lymph nodes up to 3×3 cm, splenomegaly 24 cm
- Bone marrow biopsy: 80%–90% infiltration by CLL cells

Biomarker assessment

- FISH on PB: Normal
- *TP53* mutation status: Wild-type
- IGHV mutation analysis: Borderline (identity 97.96%)

CLL, chronic lymphocytic leukemia; CT, computed tomography; FISH, fluorescence *in situ* hybridization; Hgb, hemoglobin; PB, peripheral blood, PLT, platelets; WBC, white blood cells.

Treatment history

+5–10 months after CLL diagnosis

- Randomized to chlorambucil + ofatumumab (COMPLEMENT 1 – OMB110911)
- Response assessment: PR (residual mild splenomegaly: 15 cm)

CLL, chronic lymphocytic leukemia; CT, computed tomography; EGD, esophagogastroduodenoscopy; QD, once a day; PR, partial response; WBC, white blood cell.

Treatment history

+5–10 months after CLL diagnosis

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- Response assessment: PR (residual mild splenomegaly: 15 cm)

Follow-up

- **+1 year, 4 months**: Right hip replacements due to coxarthrosis
- **+6 years, 5 months**: Right ear squamous cell carcinoma surgically treated

CLL, chronic lymphocytic leukemia; CT, computed tomography; EGD, esophagogastroduodenoscopy; QD, once a day; PR, partial response; WBC, white blood cell.

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Follow-up

- **+1 year, 4 months**: Right hip replacements due to coxarthrosis
- **+6 years, 5 months**: Right ear squamous cell carcinoma surgically treated

CLL progression (+6.5 years – 75 years of age)

- WBC: 4.0 × 10^9/L (neutrophils: 1.6 × 10^9/L; lymphocytes: 2.3 × 10^9/L); hemoglobin: 9.0 g/dL; platelets: 81 × 10^9/L
- EGD: No abnormal findings in gastric resection
- Bone marrow biopsy: 90% CLL infiltration
- CT scan: Cervical lymph nodes up to 2.5 × 2.2 mm, axillary lymph nodes 3 × 2 cm, confluent abdominal lymph nodes, splenomegaly (bipolar diameter: 22 cm)

CLL, chronic lymphocytic leukemia; CT, computed tomography; EGD, esophagogastroduodenoscopy; QD, once a day; PR, partial response; WBC, white blood cell.

Treatment history

+5–10 months after CLL diagnosis

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- CT scan: Cervical lymph nodes up to 2.5 × 2.2 mm, axillary lymph nodes 3 × 2 cm, confluent abdominal lymph nodes, splenomegaly (bipolar diameter: 22 cm)

CLL treatment (+7 years)

- Started **ibrutinib** 420 mg QD → PR, anemia recovered

CLL, chronic lymphocytic leukemia; CT, computed tomography; EGD, esophagogastroduodenoscopy; QD, once a day; PR, partial response; WBC, white blood cell.

Treatment history: AEs

Date	AE
+7 years	G2 diarrhea
+7 years	G3 diarrhea

AE, adverse event; ER, emergency room; G, Grade; QD, once a day.

Treatment history: AEs

Date	AE
+7 years	G2 diarrhea
+7 years	G3 diarrhea
+7 years, 9 months	Iron deficiency with **fecal occult blood test positive (three samples)**
+7 years, 10 months	ER access due to left arm hyposthenia → clopidogrel prescribed
+7 years, 10 months	ER access due to fever: **right pneumonia** (first ibrutinib temporary interruption)
+8 years	ER access due to fever: **left pneumonia** (second ibrutinib temporary interruption) → Ibrutinib restarted at 280 mg QD

AE, adverse event; ER, emergency room; G, Grade; QD, once a day.

Treatment history: AEs

Date	AE
+7 years	G2 diarrhea
+7 years	G3 diarrhea
+7 years, 9 months	Iron deficiency with **fecal occult blood test positive (three samples)**
+7 years, 10 months	ER access due to left arm hyposthenia → clopidogrel prescribed
+7 years, 10 months	ER access due to fever: **right pneumonia** (first ibrutinib temporary interruption)
+8 years	ER access due to fever: **left pneumonia** (second ibrutinib temporary interruption) → Ibrutinib restarted at 280 mg QD
+8 years, 5 months	Hospitalization due to bleeding from type IIb gastric ulcer with anemia requiring transfusion support; ibrutinib stopped (third ibrutinib temporary interruption) and restarted at 280 mg QD; clopidogrel discontinued
+8 years, 6 months	Hospitalization (4 days) due to bleeding from gastrojejunal ulcer with anemia requiring transfusion support; ibrutinib stopped (fourth ibrutinib temporary interruption) and restarted at 280 mg QD
+8 years, 8 months	Gastrointestinal bleeding → **ibrutinib discontinuation**

AE, adverse event; ER, emergency room; G, Grade; QD, once a day.

Personalized treatment in CLL

CLL, chronic lymphocytic leukemia.

Next-generation BTK inhibitor monotherapy in the treatment of relapsed/refractory B-cell lymphomas

Dr. Alessandra Tedeschi
Niguarda Cancer Center, Italy

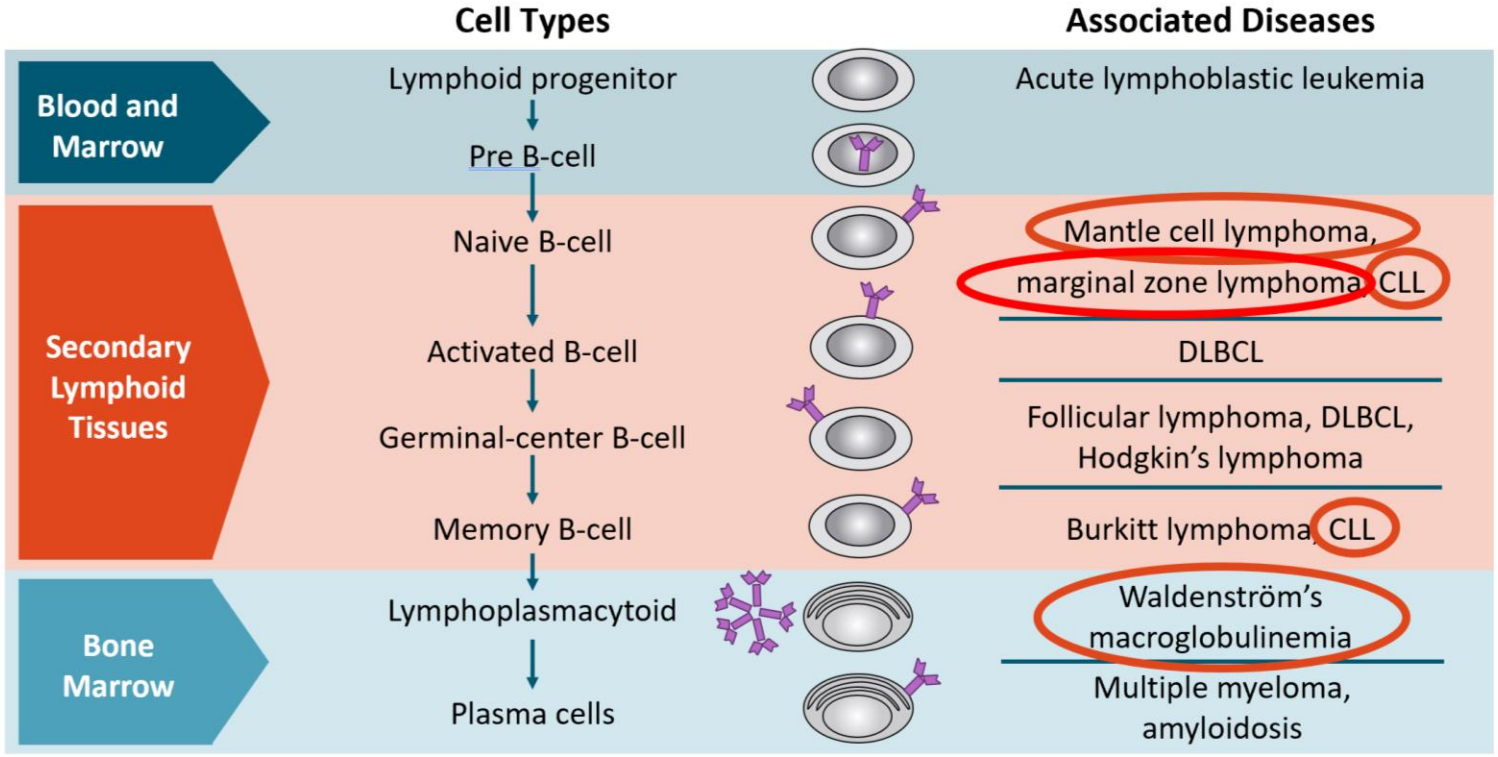
Disclosures

- Consulting services for AbbVie, AstraZeneca, BeiGene, and Janssen-Cilag S.P.A.

B-cell malignancies / B-cell receptor signaling

- Survival of resting mature B-cells depends on BCR signaling
- Some B-cell malignancies depend on tonic BCR signaling for tumor expansion and proliferation
  - Constitutive BCR activation
  - Antigen-driven BCR activation

B-cell development and associated diseases



BCR, B-cell receptor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma.
Valla K *et al. Expert Opin Investig Drugs* 2018; 27 (6): 513–522.

Approved covalent BTK inhibitors in WM, MZL, and MCL

Ibrutinib

- First-in-class BTK inhibitor
- Irreversible inhibition
- Approved:
  - FDA
    - MCL, MZL, WM
  - EMA
    - MCL, WM
- Once-daily dosing:
  - 420 mg PO daily for WM
  - 560 mg PO daily for MCL/MZL

Acalabrutinib

- Next-generation BTK inhibitor
- Irreversible inhibition
- Highly selective
- Approved:
  - FDA
    - MCL
- Twice-daily dosing:
  - 100 mg PO every 12 hours for MCL

Zanubrutinib

- Next-generation BTK inhibitor
- Irreversible inhibition
- Highly selective
- Approved:
  - FDA
    - MCL, MZL, WM
  - EMA
    - CHMP positive opinion for WM
- 160 mg twice daily or 320 mg once daily for MCL/WM/MZL

BTK, Bruton's tyrosine kinase; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PO, by mouth; WM, Waldenström's macroglobulinemia.

1. EMA: Brukinsa. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/brukinsa. 2. FDA: Brukinsa PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213217s005lbl.pdf. 3. EMA: Calquence SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_en.pdf. 4. FDA: Calquence PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf. 5. EMA: Imbruvica SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf. 6. FDA: Imbruvica PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf. All accessed September 2021.

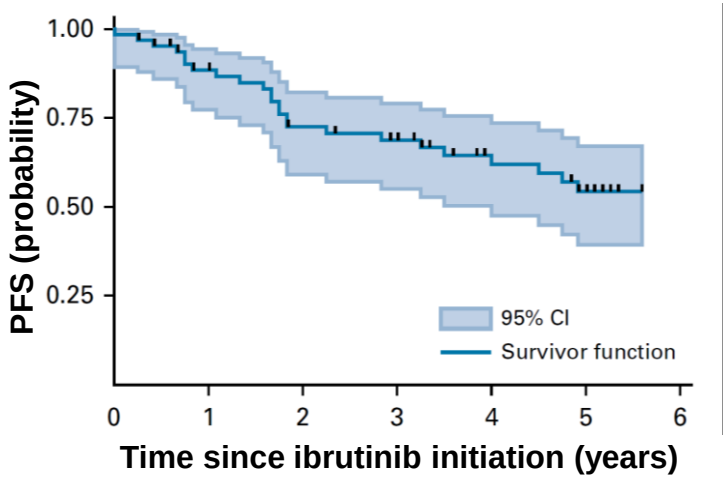
Waldenström's macroglobulinemia

Ibrutinib monotherapy in symptomatic pretreated patients with WM

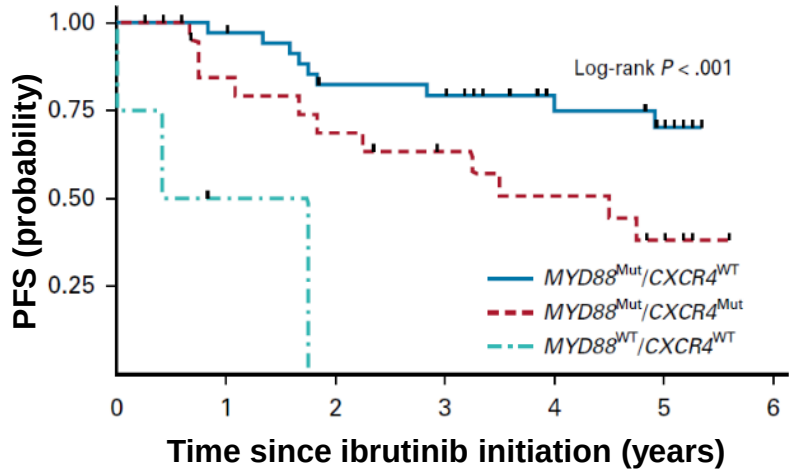
Response rates and kinetics of responses of pretreated patients with WM who received ibrutinib monotherapy

Variable	All	*MYD88*^{Mut} *CXCR4*^{WT}	*MYD88*^{Mut} *CXCR4*^{Mut}	*MYD88*^{WT} *CXCR4*^{WT}	*P*
No. of patients	63	36	22	4	
Overall response rate	57 (90.5)	36 (100.0)	19 (86.4)	2 (50.0)	< .0100
Major response rate	50 (79.4)	35 (97.2)	15 (68.2)	0 (0.0)	< .0001
Categorical responses					
No response	6 (9.5)	0 (0.0)	3 (13.6)	2 (50.0)	< .0001
Minor response	7 (11.1)	1 (2.8)	4 (18.2)	2 (50.0)	
Partial response	31 (49.2)	18 (50.0)	13 (59.1)	0 (0.0)	
Very good partial response	19 (30.2)	17 (47.2)	2 (9.1)	0 (0.0)	

PFS in patients with R/R WM (N=63)



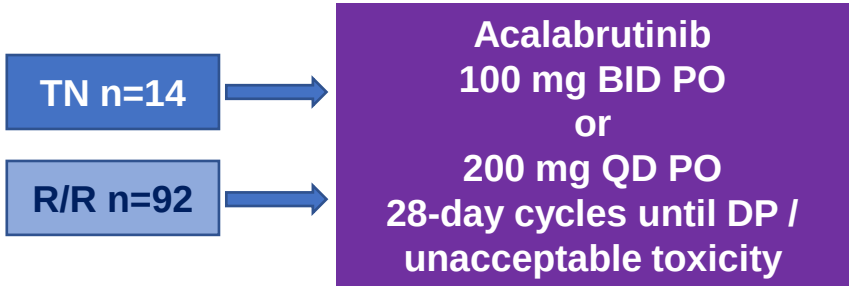
PFS by genotype (N=62)



12.7% atrial arrhythmia

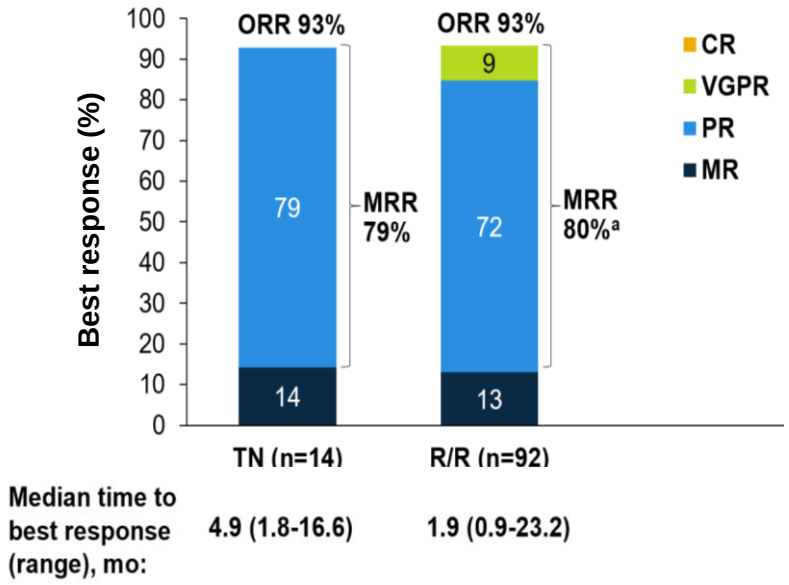
CI, confidence interval; Mut, mutated; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia; WT, wild-type.
Treon SP *et al. J Clin Oncol* 2021; 39 (6): 565–575.

Acalabrutinib monotherapy in patients with WM: A Phase II study

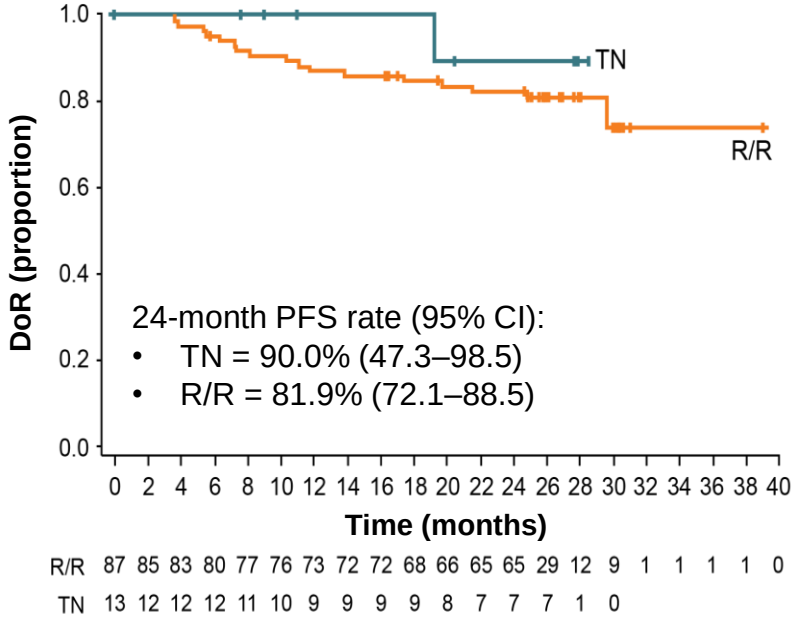


Characteristic	TN (n=14)	R/R (n=92)
Median (range) age, years	73 (48–86)	69 (39–90)
Median (range) number of prior treatments	–	2 (1–7)
≥3 previous treatments, n (%)	–	41 (45)
Refractory disease, n (%)	–	33 (36)

Best responses by treatment status



DoR by treatment status



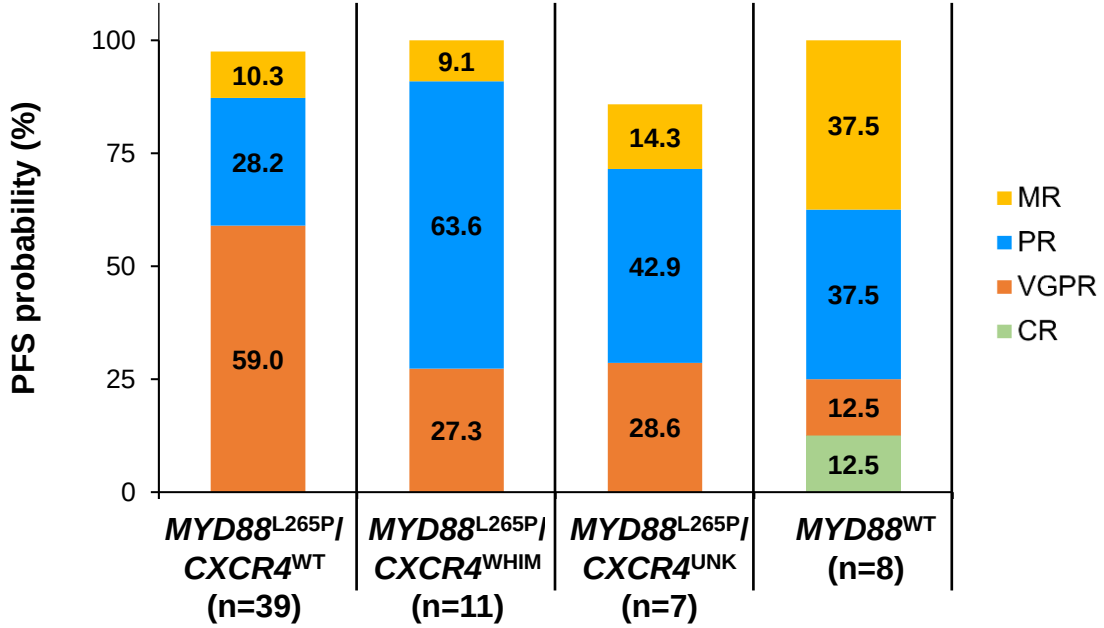
BID, twice a day; CI, confidence interval; CR, complete response; DoR, duration of response; DP, disease progression; MR, minor response; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; PO, by mouth; PR, partial response; QD, once a day; R/R, relapsed/refractory; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

Owen RG *et al. Lancet Haematol* 2020; 7 (2): e112–e121.

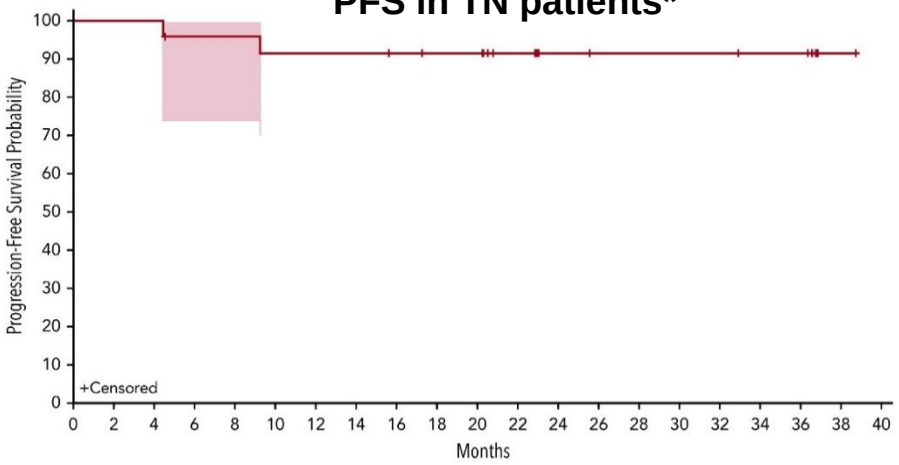
Phase I/II of study BGB-3111-AU-003: WM cohort

Best overall response by *MYD88*/*CXCR4* genotype

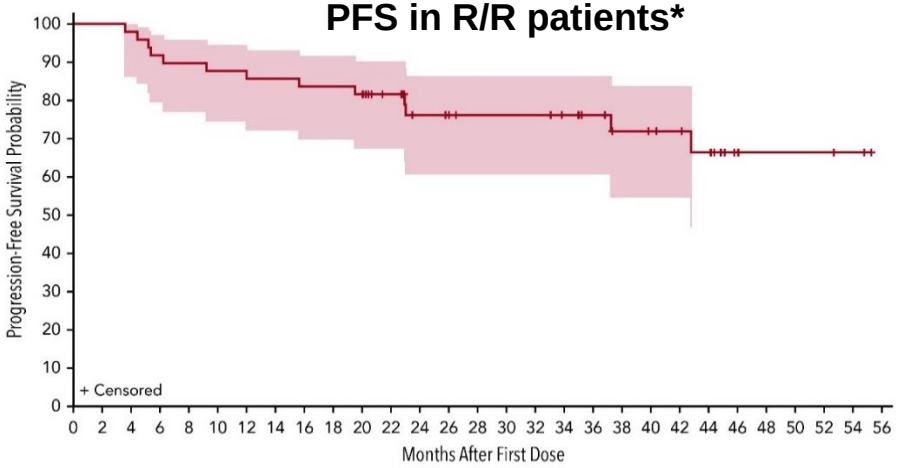
ORR, n (%)	38 (97)	11 (100)	6 (86)	8 (100)
MRR, n (%)	34 (87)	10 (91)	5 (71)	5 (63)
VGPR/CR, n (%)	23 (59)	3 (27)	2 (29)	2 (25)



PFS in TN patients*

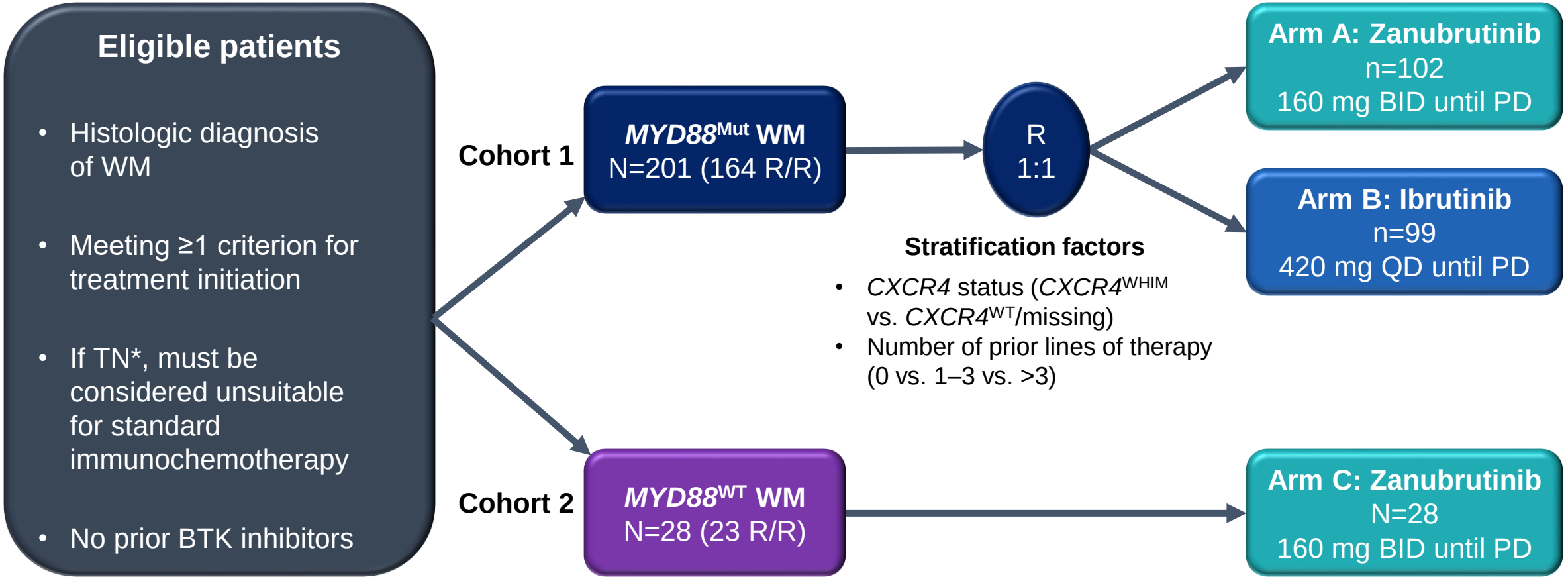


PFS in R/R patients*



*Shaded areas indicate 95% confidence intervals.
CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; TN, treatment-naive; UNK, unknown; VGPR, very good partial response; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.
Trotman J *et al. Blood* 2020; 136 (18): 2027–2037.

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{Mut} WM

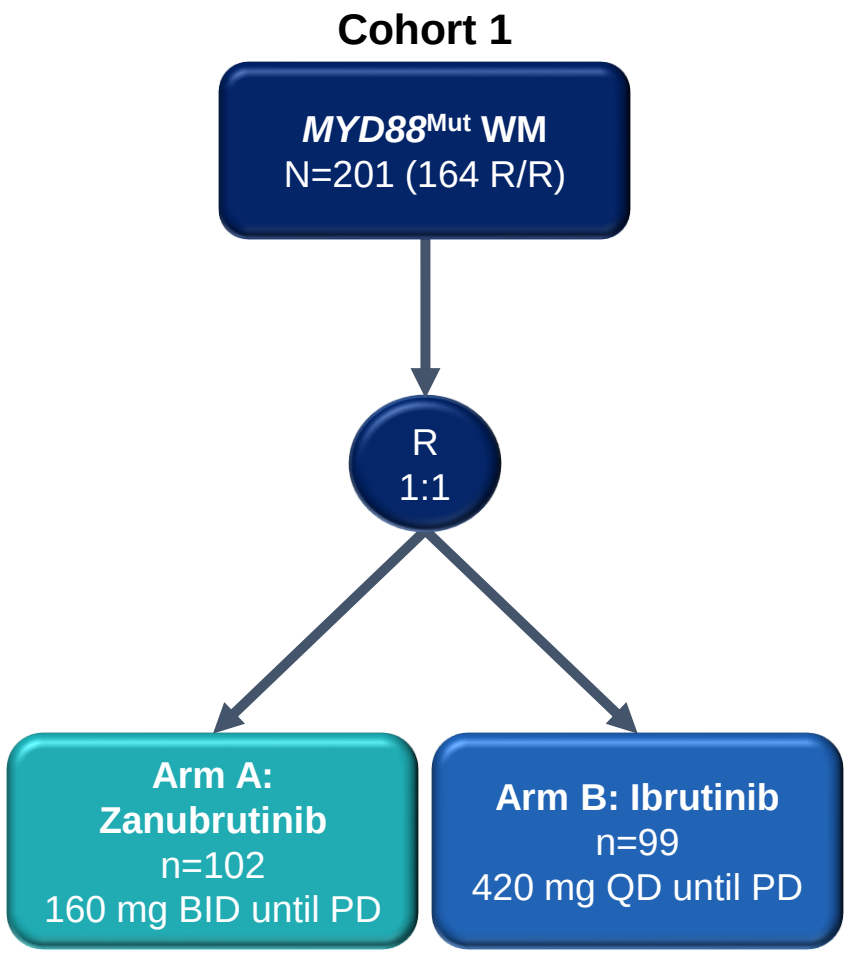


*Up to 20% of the overall population.

BID, twice a day; BTK, Bruton's tyrosine kinase; Mut, mutated; PD, progressive disease; QD, once a day; R, randomization; R/R, relapsed/refractory; TN, treatment-naive; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

1. Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020. 2. Dimopoulos MA *et al. Blood* 2014; 124 (9): 1404–1411.

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{Mut} WM



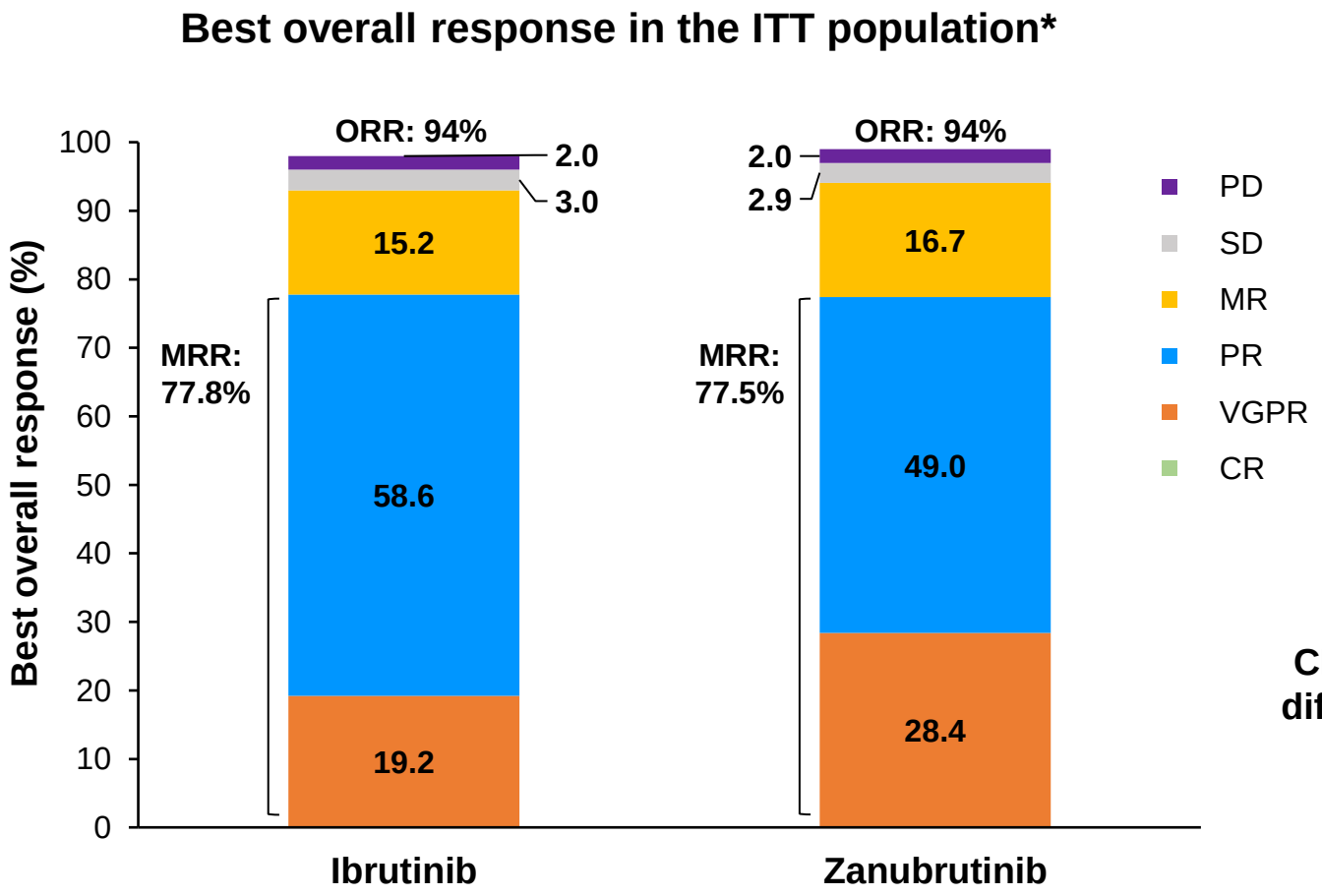
Characteristics	Overall ITT	
	Zanubrutinib (n=102)	Ibrutinib (n=99)
Median (range) age, years	70.0 (45, 87)	70.0 (38, 90)
>75 years	34 (33)	22 (22)
Gender: Male/female, n (%)	69 (68) / 33 (32)	65 (66) / 34 (34)
Prior lines of therapy, n (%)		
0	19 (19)	18 (18)
1–3	76 (75)	74 (75)
>3	7 (7)	7 (7)
Genotype by central lab*, n (%)		
MYD88^{L265P}/*CXCR4*^{WT}	91 (89)	90 (91)
MYD88^{L265P}/*CXCR4*^{WHIM}	11 (11)	8 (8)
IPSSWM (derived), n (%)		
Low	17 (17)	13 (13)
Intermediate	38 (37)	42 (42)
High	47 (46)	44 (44)
Hemoglobin ≤110 g/L, n (%)	**67 (66)**	53 (54)

*Up to 20% of the overall population.

BID, twice a day; Mut, mutated; PD, progressive disease; QD, once a day; PD, progressive disease; R, randomization; R/R, relapsed/refractory; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type. Tam CS *et al. Blood* 2020; 136 (18): 2038–2050.

ASPEN study: IRC-assessed efficacy

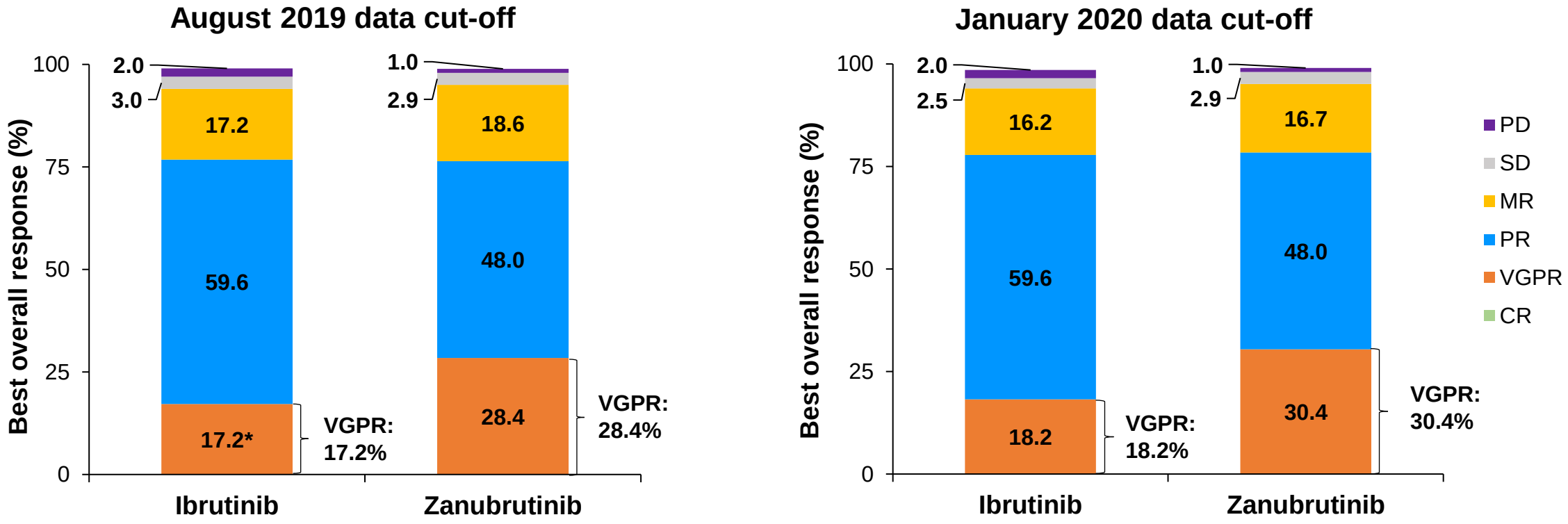
- Superiority in CR + VGPR rate for zanubrutinib compared with ibrutinib in the R/R population (primary study hypothesis) was not significant



CR + VGPR rate difference = 10.2‡ (–1.5, 22.0)
***P*=0.0921**

Overall concordance between IRC and investigators = 94%. *Data cut-off: August 31, 2019. ‡Adjusted for stratification factors and age group.
CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease, PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good partial response.
Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

ASPEN study: Investigator-assessed efficacy

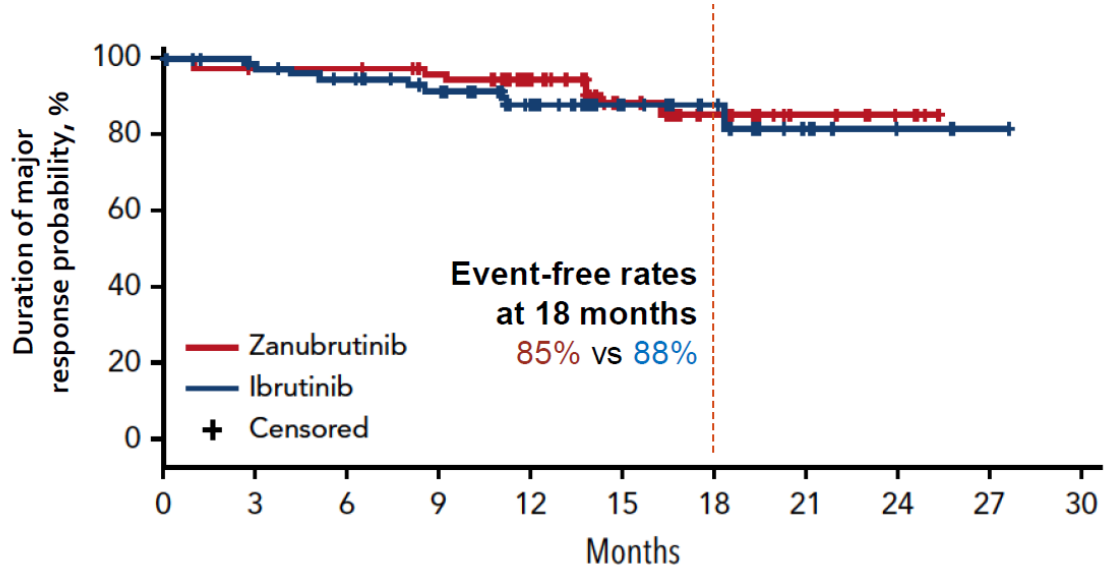


IgM reduction: AUC for IgM reduction over time was significantly greater for zanubrutinib vs. ibrutinib (*P*=0.037)

*Excluded 2 patients with VGPR by IRC: MR (extramedullary disease present) and PR (immunoglobulin M assessment by local serum protein electrophoresis M-protein test).
AUC, area under the curve; CR, complete response; IgM, immunoglobulin M; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

Duration of major response and CR/VGPR

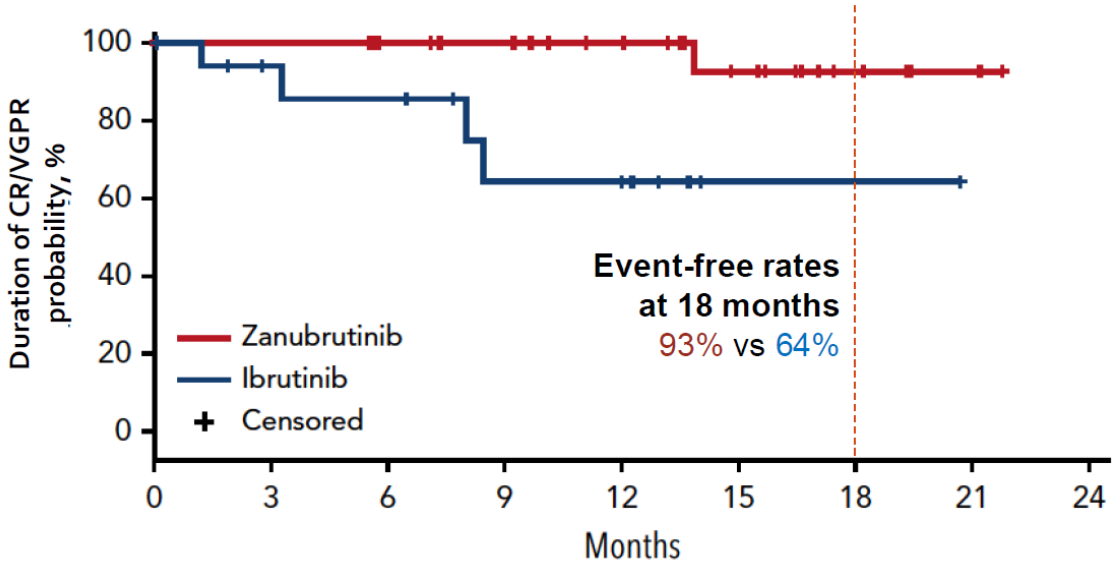
Duration of major response



No. of Patients at Risk

Zanubrutinib	79	72	71	66	52	32	21	10	6	0
Ibrutinib	77	72	67	59	44	29	15	7	3	1	0

Duration of CR/VGPR



29	27	24	22	18	12	5	2	0
19	11	10	6	5	1	1	0	

CR, complete response; VGPR, very good partial response.

Tam CS *et al. Blood* 2020; 136 (18): 2038–2050.

Patient disposition, PFS, and OS in the ITT population

Median study follow-up: 19.4 months

Zanubrutinib
Enrolled 102; treated 101

Off study treatment: 20 patients
- 15 R/R, 5 TN

Reason for treatment change
- 7 PD, 4 AE, 5 patient decision, 2 investigator decision, 2 other

On study treatment:
81 patients (79.4%)

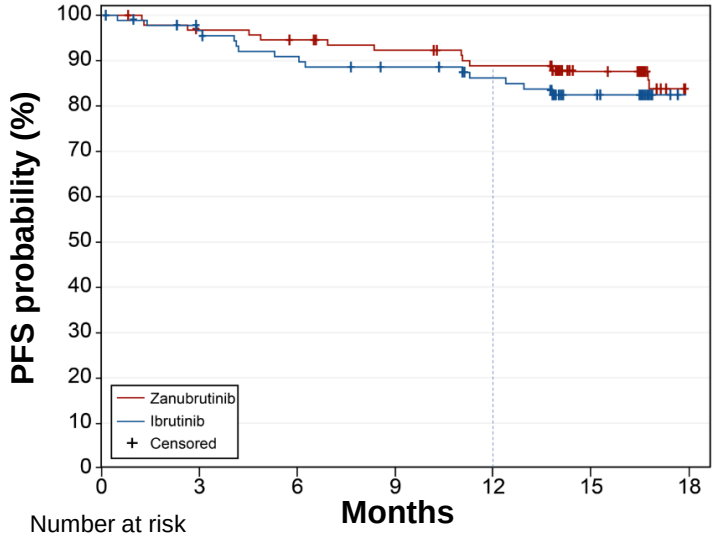
Ibrutinib
Enrolled 99; treated 98

Off study treatment: 21 patients
- 17 R/R, 4 TN

Reason for treatment change
- 5 PD, 9 AE, 4 investigator decision, 3 other

On study treatment:
77 patients (77.8%)

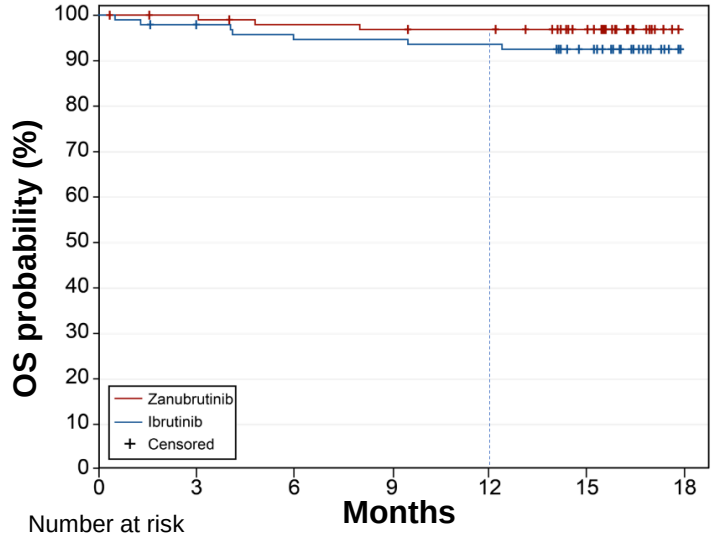
PFS



Number at risk

Zanubrutinib	102	96	93	89	84	63	43
Ibrutinib	99	92	86	82	77	62	42

OS



Number at risk

Zanubrutinib	102	100	97	96	95	86	62
Ibrutinib	99	96	93	92	91	83	61

AE, adverse event; ITT, intention-to-treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive.

Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

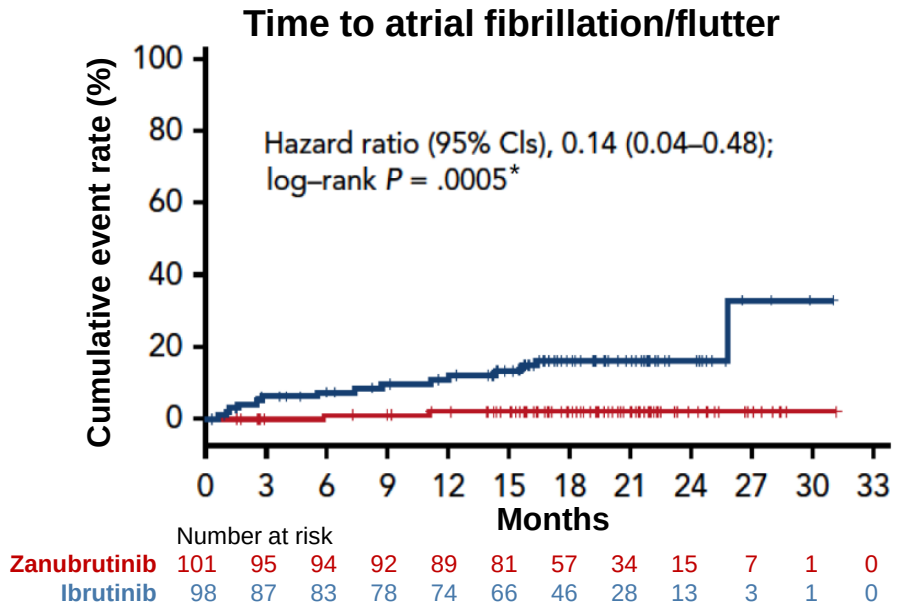
Safety and tolerability

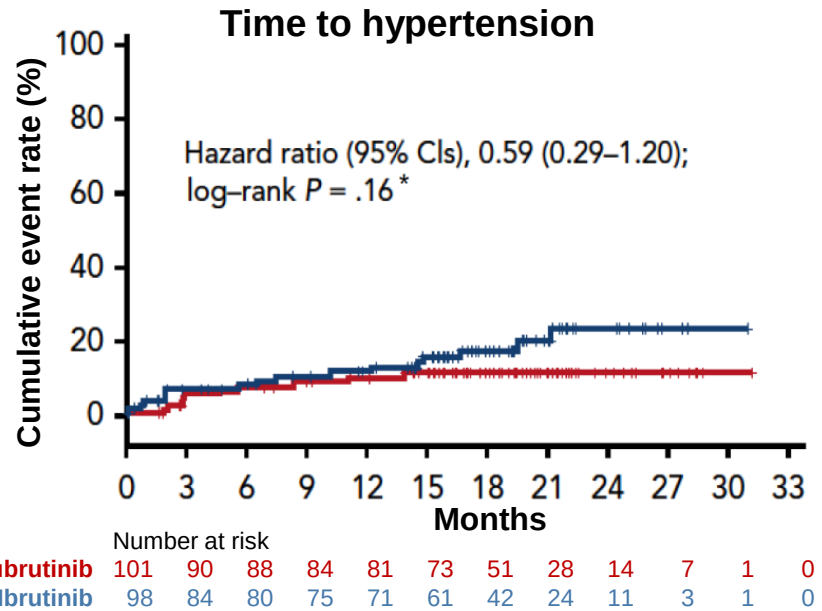
Category, n (%)	Zanubrutinib (n=101)	Ibrutinib (n=98)
Patients with ≥1 AE	98 (97.0)	97 (99.0)
Grade ≥3	59 (58.4)	62 (63.3)
Serious	40 (39.6)	40 (40.8)
Fatal AEs	1 (1.0)*	4 (4.1)‡
AEs leading to treatment discontinuation	4 (4.0)†	9 (9.2)§
AEs leading to dose reduction	14 (13.9)	23 (23.5)
AEs leading to dose held	47 (46.5)	55 (56.1)
Patients with ≥1 treatment-related AE	80 (79.2)	84 (85.7)
Patients with ≥1 AE of interest	86 (85.1)	81 (82.7)

*Cardiac arrest after plasmapheresis. †G5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage; G2 plasma cell myeloma. ‡Cardiac failure acute; sepsis (n=2); unexplained death. §G5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis; G3 pneumonia; G2 drug-induced liver injury; G2 pneumonitis; G1 pneumonitis.
AE, adverse event.
Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

BTK inhibitor class AE categories of interest

Event preferred term, n (%)	All grades (≥20%)		Grade ≥3 (≥5%)	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/Flutter	**18 (18.4)**	3 (3.0)	7 (7.1)	0 (0.0)
Diarrhea (PT)	**32 (32.7)**	22 (21.8)	2 (1.0)	3 (3.0)
Hemorrhage	**59 (60.2)**	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	**15 (15.3)**	8 (7.9)





AE, adverse event; CI, confidence interval; PT, preferred term.

Tam CS *et al. Blood* 2020; 136 (18): 2038–2050. Tam CS *et al*. Abstract 8007 presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting (virtual); May 29–31, 2020.

ASPEN study: Zanubrutinib in *MYD88*^{WT} WM

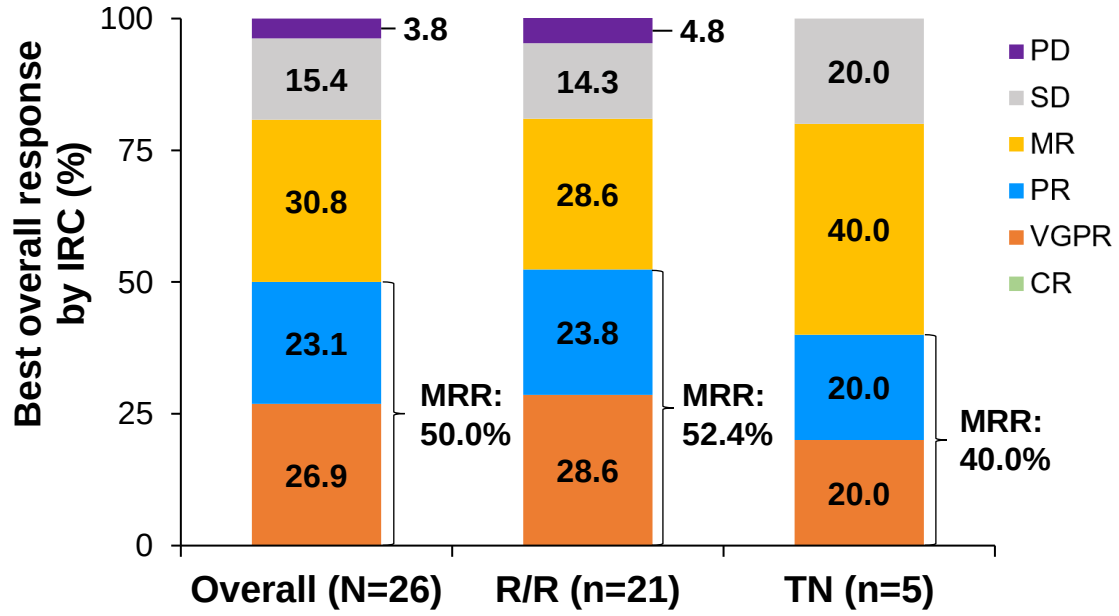
***MYD88*^{WT} WM**
(N=28: 26 WT, 2 unknown)

→

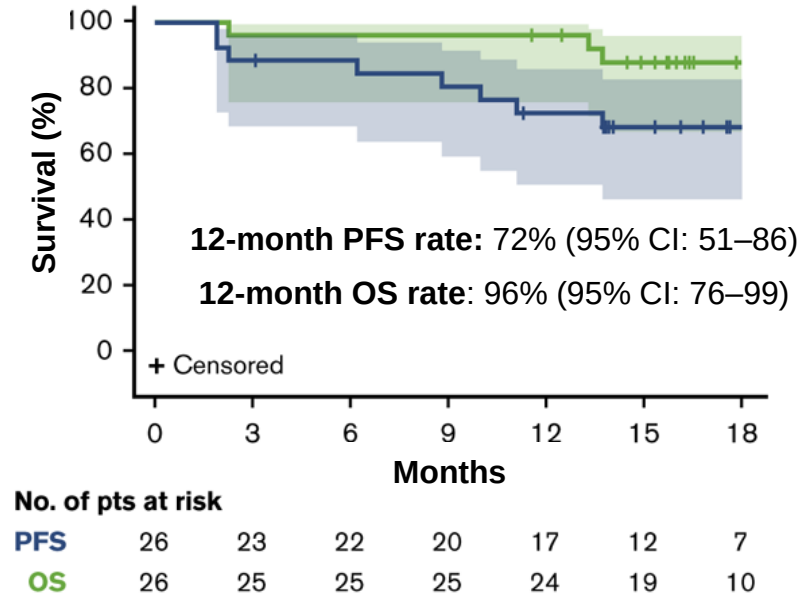
Arm C
Zanubrutinib
160 mg BID until PD / unacceptable toxicity

Patient and disease characteristics	Total (N=28)
Median (range) age, years	70.1 (39–87)
TN, n (%)	5 (17.9)
R/R, n (%)	23 (82.1)
Median (range) number of prior treatments	1 (1–5)
***MYD88*^{WT}/*CXCR4*^{WT}, n (%)**	23 (82.1)

Best overall response in R/R or TN WM



Survival in R/R or TN† WM



BID, twice a day; CI, confidence interval; CR, complete response; IRC, independent review committee; MR, minimal response; MRR, major response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild-type. Dimopoulos M *et al*. Abstract 2022 presented at the 25th Annual Congress of the European Hematology Association (EHA) 2020 (virtual); June 11–21, 2020.

Summary: BTK inhibitors in WM

- Ibrutinib based on a Phase II study is the first-in-class BTK inhibitor approved in WM
- Zanubrutinib treatment compared with ibrutinib is associated with:
  - Better quality of responses
  - Greater and sustained IgM reduction over time
  - High percentage of responses and rapid IgM decrease even in *MYD88*^{WT} patients
- Zanubrutinib demonstrated clinically meaningful advantages in safety and tolerability
  - A reduction in the risk of atrial fibrillation/flutter
  - Lower rates of major bleeding
  - Fewer AEs leading to death or treatment discontinuation

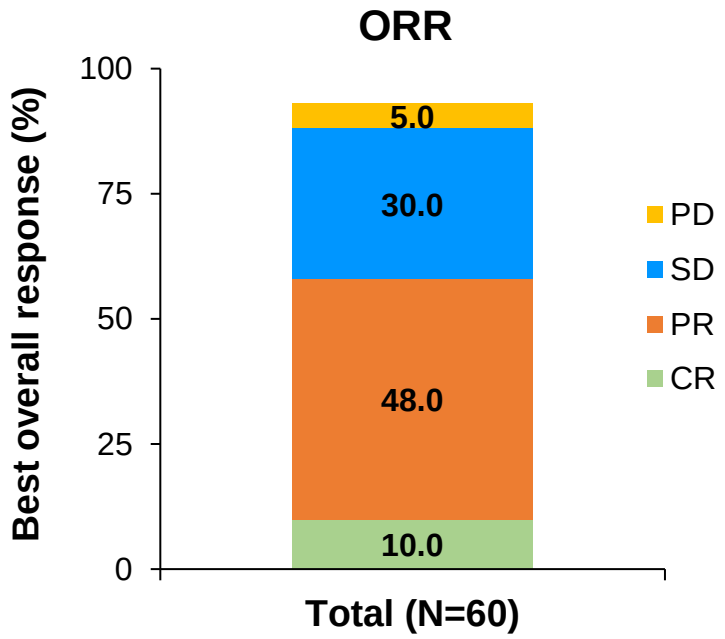
AE, adverse event; BTK, Bruton's tyrosine kinase; IgM, immunoglobulin M; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström's macroglobulinemia; WT, wild-type.

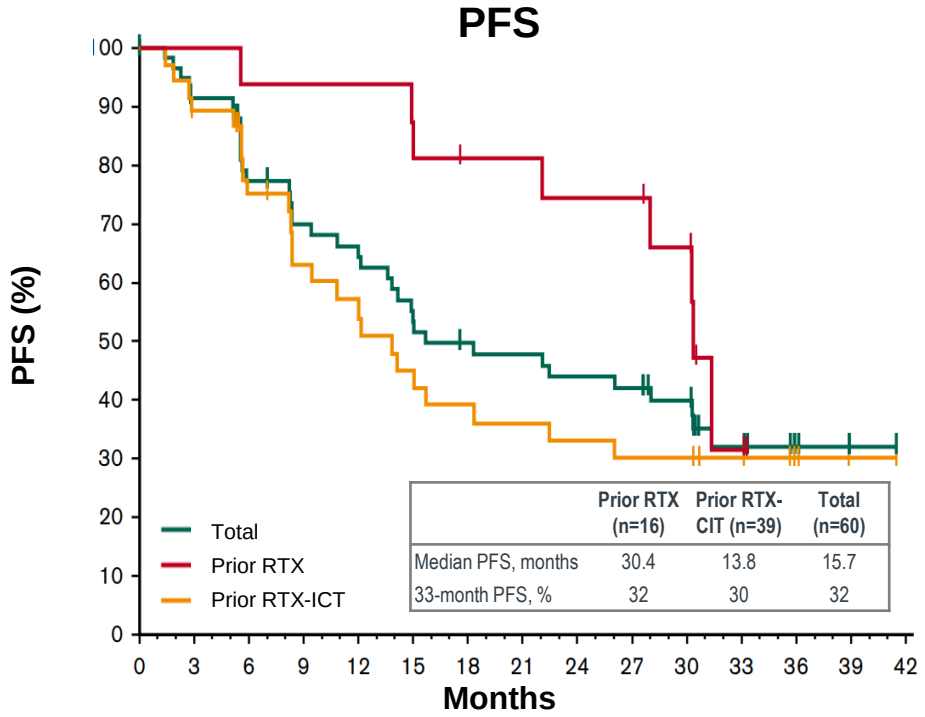
Marginal zone lymphoma

Ibrutinib in R/R MZL

- N=60, median (range) age: 66 years (30–92 years)
- Median (range) number of prior therapies: 2 (1–9)
- ≥3 prior therapies: 35%
- Median follow-up: 33.1 months

Safety	
Treatment discontinuations due to AEs, %	19
TEAEs, %	
Atrial fibrillation (all grades)	8
Bleeding events	68
Major hemorrhage	3
Grade ≥3 TEAEs, %	
Anemia	16
Infections	22





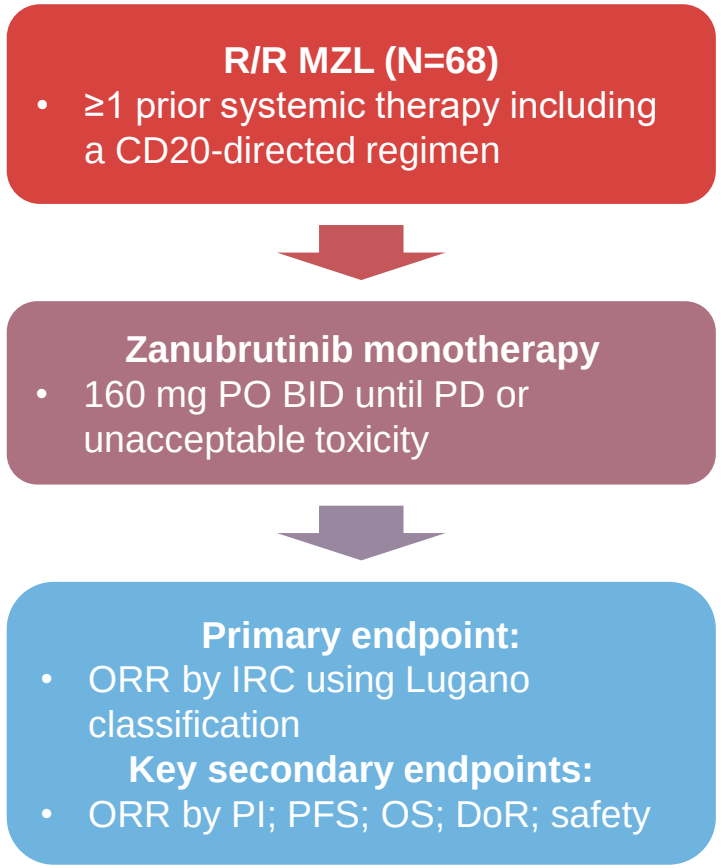
AE, adverse event; ICT, immunochemotherapy; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; RTX, rituximab; SD, stable disease; TEAE, treatment-emergent adverse event.

Noy A *et al. Blood Adv* 2020; 4 (22): 5773–5784.

Phase II study MAGNOLIA: Zanubrutinib in R/R MZL

- Tumor response by investigator assessment
  - Response is based on the Lugano classification for non-Hodgkin lymphoma
  - Blinded response assessment by IRC is ongoing
- 68 patients enrolled
- 66 patients evaluable
  - Relapsed: n=44 (66.7%) / refractory: n=22 (33.3%)
  - MZL subtypes:
    - Extranodal: n=26 (38.2%)
    - Nodal: n=26 (38.2%)
    - Splenic: n=12 (17.6%)
    - Unknown: n=4 (5.9%)

MAGNOLIA study design: Zanubrutinib in R/R MZL



BID, twice a day; DoR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PI, principal investigator; PFS, progression-free survival; PO, by mouth; R/R, relapsed/refractory.

Opat S *et al*. Abstract 339 presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

MAGNOLIA: Best overall response

Investigator assessment by MZL subtypes (N=66)

- Discontinued prior to first assessment / missing: n=2 (3%)

Best response	Total (N=66)	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (n=4)
ORR (CR or PR), n (%) [95% CI]†	49 (74.2) [61.99–84.22]	17 (68.0) [46.50–85.05]	21 (84.0) [63.92–95.46]	9 (75.0) [42.81–94.51]	2 (50.0) [6.76–93.24]
CR, n (%)	16 (24.2)	10 (40.0)	4 (16.0)	1 (8.3)	1 (25.0)
PR, n (%)	33 (50.0)	7 (28.0)	17 (68.0)	8 (66.7)	1 (25.0)
SD, n (%)	10 (15.2)	5 (20.0)	2 (8.0)	1 (8.3)	2 (50.0)
PD, n (%)	5 (7.6)	2 (8.0)	2 (8.0)	1 (8.3)	0

Median (range) time to response, months:	2.8 (1.7–11.1)
Median (range) study follow-up, months:	10.7 (1.6–16.7)

CI, confidence interval; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

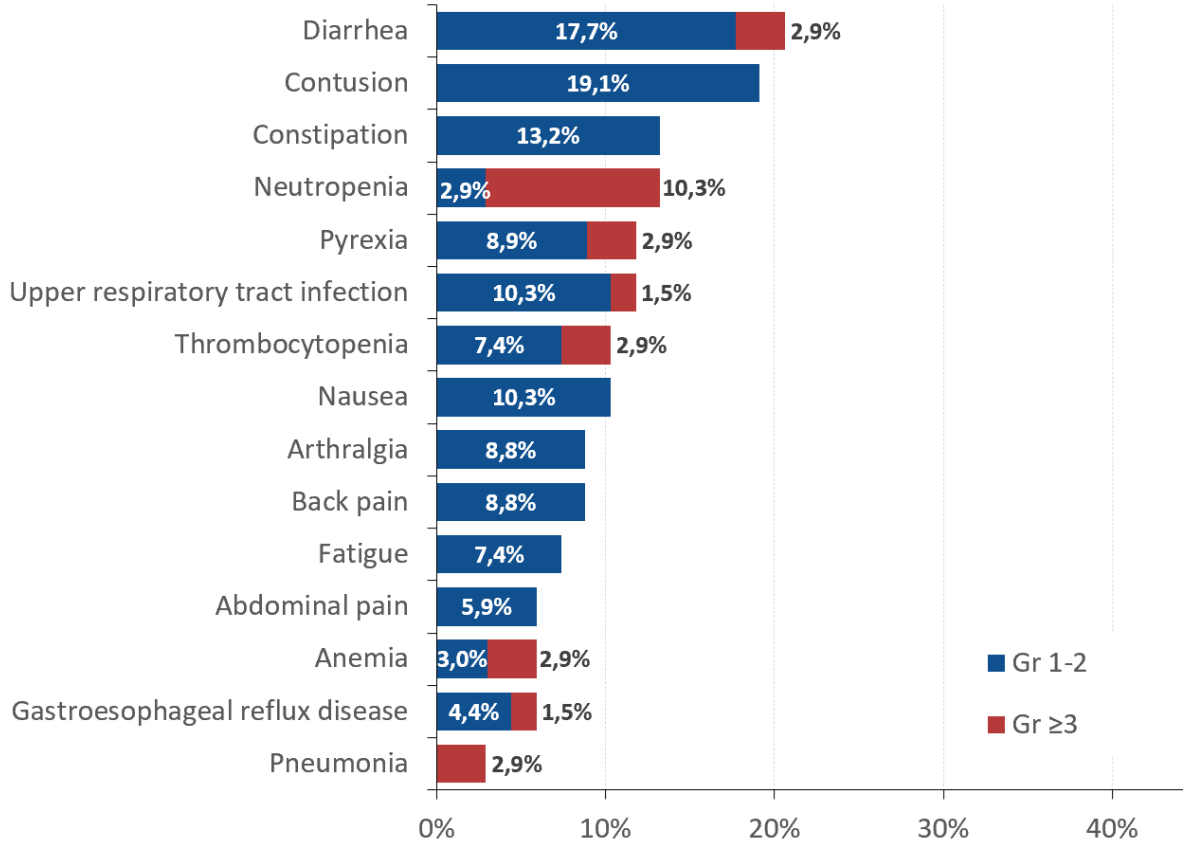
Opat S *et al*. Abstract 339 presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

MAGNOLIA: TEAEs

Summary of TEAEs

TEAEs (N=68)	n (%)
Patients with at least 1 TEAE	65 (95.6)
Grade ≥3 TEAEs	26 (38.2)
Serious TEAEs	22 (32.4)
TEAEs leading to dose interruption	16 (23.5)
TEAEs leading to study drug discontinuation	2 (2.9)*
TEAEs leading to death	1 (1.5)†
TEAEs leading to dose reduction	0
Atrial fibrillation/flutter (all grades)	2 (2.9)‡
Hypertension	0
Major hemorrhage	0

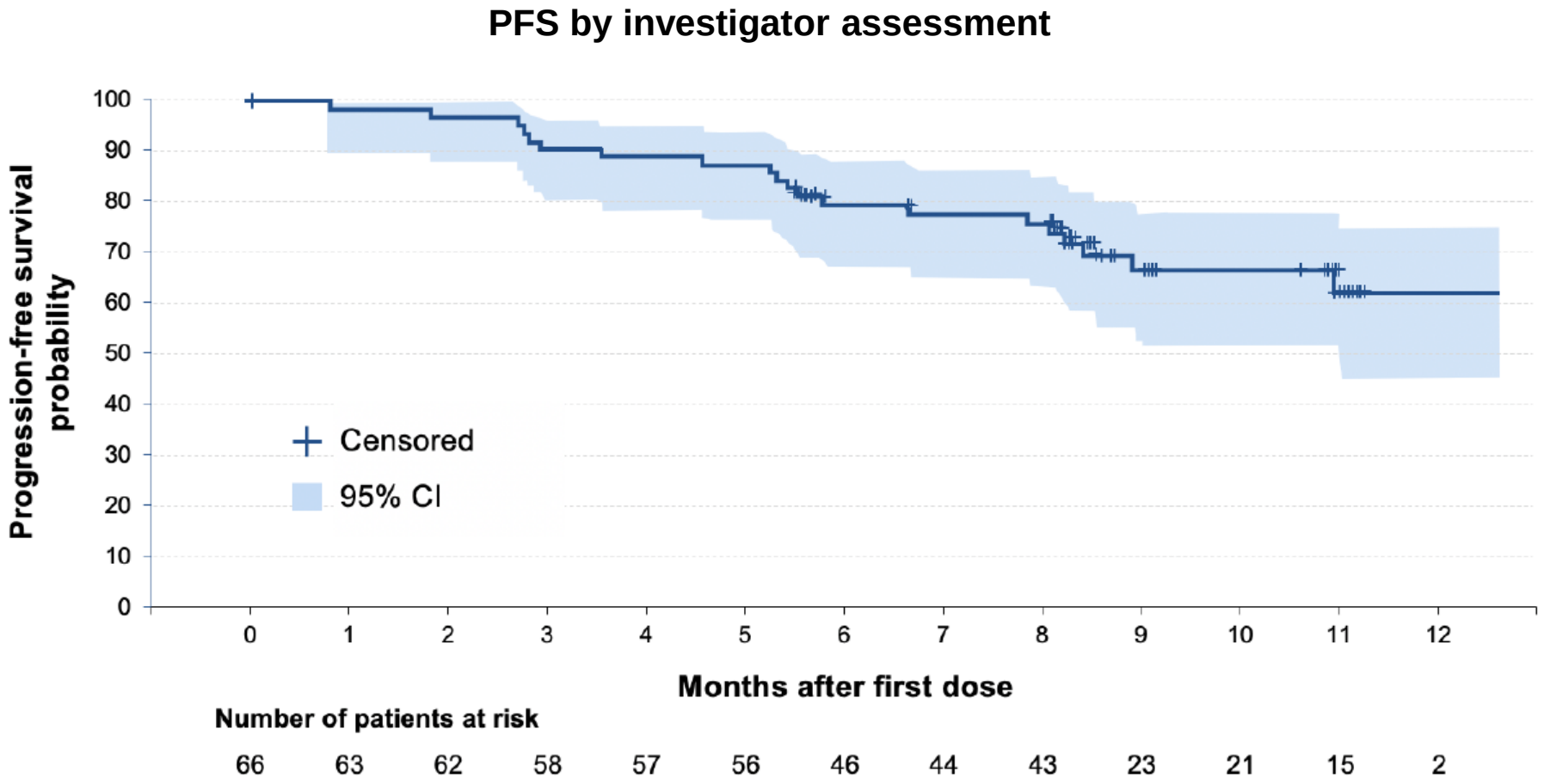
TEAEs in ≥5% of patients or Grade ≥3 TEAEs in ≥2 patients regardless of causality §



*One patient discontinued because of pyrexia (later attributed to disease progression); one patient died from myocardial infarction. †One patient with pre-existing cardiovascular disease died from myocardial infection. ‡Atrial fibrillation occurred in a patient with pre-existing atrial fibrillation (21 days after end of treatment due to disease progression). §Neutropenia includes neutropenia and neutrophil count decreased; thrombocytopenia includes thrombocytopenia and platelet count decreased.
Gr, grade; TEAE, treatment-emergent adverse event.
Opat S *et al*. Abstract 339 presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

MAGNOLIA: PFS by investigator assessment

- PFS median (range) follow-up of 9.13 (0.03–16.46) months
- Patients on study treatment (n=44; 64.7%)
- Event-free rate
  - 80% (6 months)
  - 67% (9 months)



CI, confidence interval; PFS, progression-free survival.
Opat S *et al*. Abstract 339 presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition 2020 (virtual); December 5–8, 2020.

Summary: BTK inhibitors in MZL

- Chemotherapy-free treatment may become an effective option in R/R MZL
- Based on efficacy and tolerability, BTK inhibitors may become the treatment of choice in patients with advanced disease
- Ibrutinib is the first-in-class BTK inhibitor approved by the FDA
- The next-generation BTK inhibitor zanubrutinib showed:
  - High activity with clinical benefit observed in 89% of patients
  - Responses consistent across subgroups including high-risk patients
  - Good tolerability resulting in high treatment adherence (99.6% median relative dose intensity)

BTK, Bruton’s tyrosine kinase; EMA, European Medicines Agency; FDA, Food and Drug Administration; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

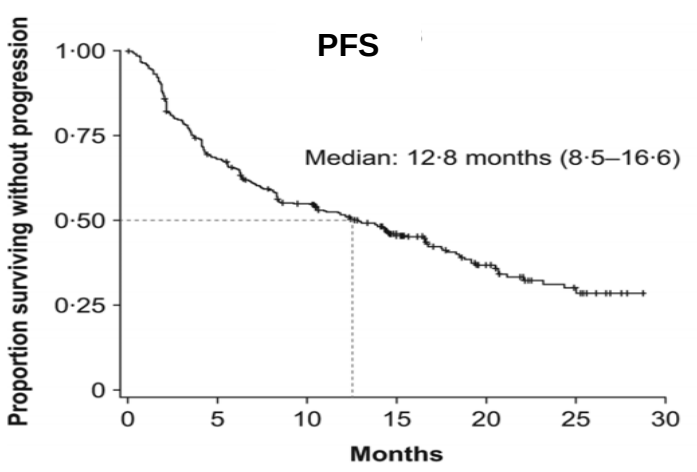
Mantle cell lymphoma

BTK inhibitors in R/R MCL

Ibrutinib

Pooled analysis from three studies:[1] PCYC-1104, SPARK, RAY

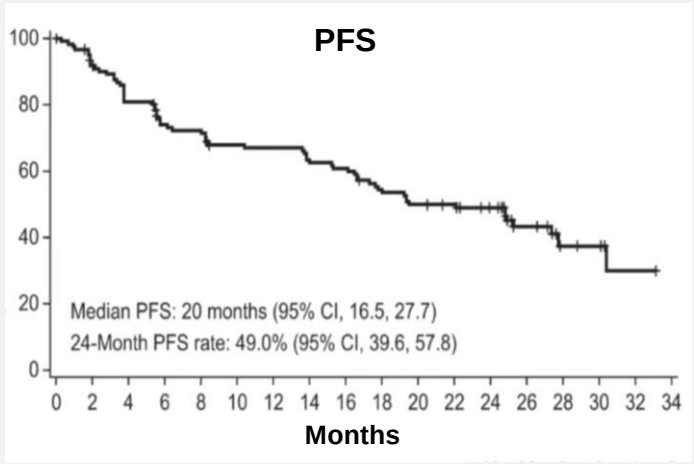
- 370 patients (median prior number of treatments: 2)
  - ORR: 66%
  - CR: 20%
  - PR: 46%



Acalabrutinib

ACE-LY-0045[2]

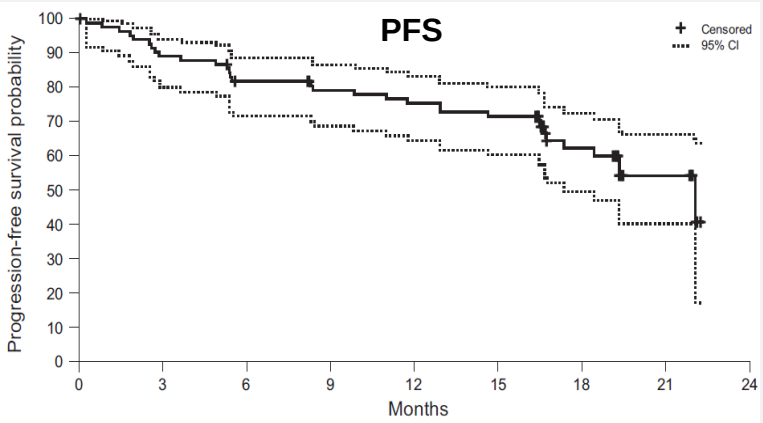
- 124 patients (median prior number of treatments: 2)
  - ORR: 82%
  - CR: 43%
  - PR: 38%



Zanubrutinib

BGB-3111-206[3]

- 86 patients (median prior number of treatments: 2)
  - ORR: 84%
  - CR: 69%
  - PR: 15%



BTK, Bruton's tyrosine kinase; CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory.

1. Rule S *et al. Br J Haematol* 2017; 179 (3): 430–438. 2. Wang M *et al. Lancet* 2018; 391 (10121): 659–667. 3. Song Y *et al. Clin Cancer Res* 2020; 26 (16): 4216–4224.

Summary: BTK inhibitors in MCL

- BTK inhibitors changed the treatment paradigm in salvage therapy of MCL and are now considered to be the standard of care
- Data from clinical trials (non-randomized) suggest that next-generation BTK inhibitors may offer greater selectivity and more tolerable side effect profiles than ibrutinib
- Zanubrutinib achieves high quality responses, which translate into long PFS durations

BTK, Bruton’s tyrosine kinase; MCL, mantle cell lymphoma; PFS, progression-free survival.

The BTK inhibitor story is not over…

BTK, Bruton’s tyrosine kinase.

The BTK inhibitor story is not over…

May the non-covalent BTK inhibitor overcome resistance?

BRUIN study: LOXO-305 (pirtobrutinib) Phase I/II study

- MCL: 56 patients (median prior number of treatments: 3; 93% received a prior BTK inhibitor)
  - ORR: 52%
  - CR: 25%
  - PR: 27%

- WM: 19 patients (median prior number of treatments: 3; 68% received a prior BTK inhibitor)
  - ORR: 68%
  - CR: 0%
  - PR: 47%
  - Minor response: 21%

BTK, Bruton's tyrosine kinase; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.
Mato AR *et al*. *Lancet* 2021; 397 (10277): 892–901.

Discussion and audience Q&A

Moderator: Professor Wojciech Jurczak

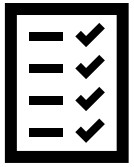
Summary

Chair: Professor Wojciech Jurczak

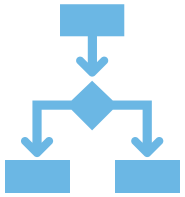
Summary of speaker presentations

BTK inhibition with ibrutinib is effective and generally well-tolerated for patients with CLL, WM or MCL, but treatment may be limited by adverse events, such as atrial fibrillation, bleeding, or infection

The next-generation BTK inhibitors, such as zanubrutinib and acalabrutinib, are more selective for BTK compared with ibrutinib, which may reduce off-target inhibition and improve safety and efficacy outcomes



Large-scale, head-to-head trials in R/R CLL or WM consistently show improved safety outcomes with next-generation BTK inhibitors over ibrutinib. Zanubrutinib has also shown superior efficacy to ibrutinib in a phase III trial of patients with R/R CLL



Next-generation BTK inhibitors may be especially relevant to patients with cardiovascular comorbidities and/or patients requiring anticoagulants

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

We would appreciate your feedback!

Please complete the post-meeting survey.

Thank you for your attention

BeiGeneius