Supplemental Appendix

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Supplemental methods

Assay methodology for *MYD88* and *CXCR4* mutation analysis

MYD88 mutational status was analyzed on baseline bone marrow aspirates without CD-19+ cell selection using a proprietary, PCR-based assay that employs locked oligonucleotides to block amplification of *MYD88* wild-type (WT) DNA during PCR followed by bidirectional Sanger sequencing of the amplicon.[1] This approach captures all mutations from amino acids 260 to 278 in the Toll/IL-1R (TIR) binding domain of MYD88 with a 0.2%–0.5% limit of detection. Assay for the presence of non-L265P mutations in *MYD88* was performed using a next-generation sequencing method with a 0.5% limit of detection. Three patients (all zanubrutinib-treated and all TN) had 2nd missense mutations detected within the TIR binding domain: M232T, V217F, and P182L. Additional mutations were identified in non-TIR binding domains in 4 patients: D165del (R/R zanubrutinib patient); W91ter, G93ter (R/R ibrutinib patient); L72M (R/R zanubrutinib patient); and T107S, fs24ter (TN, zanubrutinib patient).

Mutations in *CXCR4* were detected using PCR, followed by bidirectional Sanger sequencing of the amplicon in non-CD19+ selected bone marrow aspirates. The lower limit of assay sensitivity allows detection of 10%–15% mutant alleles in a background of wild-type allele, and detects nonsense, frameshift, and other mutations from T318 to S341, which includes almost the full range of *CXCR4*^{WHIM} mutations previously reported. The table below summarizes the individual mutations identified (those in **bold** type have been previously described). CXCR4 mutation analysis was conducted at Neogenomics, Inc., Aliso Viejo, CA, USA.

CXCR4 mutations were also detected using PredicineCARE™, a next-generation sequencing assay (Predicine, Inc., Hayward CA) targeting a panel of 152 genes including full exonic regions

of CXCR4. Genomic DNA from bone marrow samples was extracted, enzymatically fragmented and purified. Up to 30ng fragmented DNA were used for library preparation, capture, sequencing and data analysis, as described previously.[2,3] Data were analyzed using a proprietary bioinformatics pipeline (Predicine, Inc, Hayward, CA) and CXCR4 mutations with allelic frequencies ≥ 0.25% were reported.

1. Albitar A, Ma W, DeDios I, Estella J, Agersborg S, Albitar M. Positive selection and high sensitivity test for MYD88 mutations using locked nucleic acid. *Int J Lab Hematol*. 2016;38(2):133-140
2. Kohli et al. Clinical and Genomic Insights Into Circulating Tumor DNA-based Alterations Across the Spectrum of Metastatic Hormone-Sensitive and Castrate-Resistant Prostate Cancer. EBioMedicine. 2020 Apr;54:102728.
3. Fettke et al. Combined Cell-free DNA and RNA Profiling of the Androgen Receptor: Clinical Utility of a Novel Multianalyte Liquid Biopsy Assay for Metastatic Prostate Cance. Eur Urol. 2020 May 30;S0302-2838(20)30219-0

The table below summarizes the individual mutations identified either by the Next Generation Sequencing Method, Sanger Sequencing Method or both (those in **bold** type have been previously described):

Mutation type:	Nucleotide change:	Amino acid change:	No. (treatment assignment) of patients with mutation detected by NGS:	No. (treatment assignment) of patients with mutation detected by Sanger Sequencing:
FS	952_956del	**Thr318Cysfs**	2 (zanubrutinib)	Not Detected
FS	952dup	**Thr318Asnfs**	1 (zanubrutinib); 2 (ibrutinib)	1 (ibrutinib)
FS	954del	**Ser319Leufs**	1 (zanubrutinib)	Not Detected
FS	956_957del	**Ser319Cysfs**	1 (zanubrutinib)	1 (zanubrutinib)
FS	963dup	**Arg322Glnfs**	1 (zanubrutinib)	Not Detected
FS	965dup, 1012_1015del	Gly323Argfs, Ser338Leufs	1 (ibrutinib, 2 mutations)	Not Detected
FS	976dup	**Leu326Profs**	1 (ibrutinib)	1 (ibrutinib)
FS	988_989del	Ser330Glnfs	1 (zanubrutinib)	1 (zanubrutinib)
NS	1000C>T	**Arg334***	2 (zanubrutinib)	1 (zanubrutinib)
NS	1003_1025del	Gly335*	1 (zanubrutinib)	Not Detected
FS	1007_1013del	**Gly336Aspfs**	1 (zanubrutinib)	Not Detected
FS	1007dup	His337Thrfs	1 (zanubrutinib)	1 (zanubrutinib)
FS	1009_1010insCTCCA	His337Profs	1 (zanubrutinib)	Not Detected
FS	1010_1011del	His337Leufs	1 (zanubrutinib)	Not Detected
FS	1012dup	**Ser338Phefs**	2 (zanubrutinib)	Not Detected
FS	1013_1020del	**Ser338Phefs**	1 (ibrutinib)	Not Detected

NS	1013C>A	**Ser338***	9 (5 zanubrutinib; 4 ibrutinib)	4 (2 zanubrutinib; 2 ibrutinib)
NS	1013C>G	**Ser338***	14 (5 zanubrutinib; 9 ibrutinib)	4 (3 zanubrutinib; 1 ibrutinib)
FS	1014_1018del	**Ser339Phefs**	1 (zanubrutinib)	Not Detected
FS	1017dup	Val340Cysfs	1 (zanubrutinib)	1 (zanubrutinib)
FS	1018_1022del	Val340Hisfs	1 (zanubrutinib)	1 (zanubrutinib)
FS	1021_1022del	**Ser341Hisfs**	1 (zanubrutinib)	Not Detected
FS	1021del	**Ser341Profs**	2 (1 zanubrutinib; 1 ibrutinib)	Not Detected
FS	1021dup	**Ser341Phefs**	2 (1 zanubrutinib; 1 ibrutinib)	1 (ibrutinib)
NS	1032dup	**Glu345***	1 (zanubrutinib)	Not Detected
FS	1012_1013insT	**S338Ffs**	quality control failure	1 (ibrutinib)
Deletion		S338_S352 deletion	Not Detected	1 (ibrutinib)

Abbreviations: FS, frameshift; NS, nonsense; ins, insertion; del deletion; NGS, next generation sequencing.

Supplemental Tables

Supplemental Table 1. Zanubrutinib treatment-modification guidelines for toxicity.

Toxicity	Modification
Hematologic toxicities	Zanubrutinib was interrupted for hematologic toxicity suspected to be study drug–related under any of the following conditions: • Grade 4 neutropenia (lasting >10 days despite the use of growth factors) or grade ≥3 febrile neutropenia • Grade 4 thrombocytopenia (lasting >10 days) or grade ≥3 thrombocytopenia associated with significant bleeding After a first occurrence, zanubrutinib may have been restarted at full dose upon recovery of the toxicity to grade ≤1 or baseline. If the same event recurred, patients restarted at 1 dose level lower (80 g BID) upon recovery of the toxicity to grade ≤1 or baseline. If the event recurred at 80 mg BID, zanubrutinib was once again interrupted until recovery to grade ≤1 or baseline and restarted at 80 mg QD. A maximum of 2 dose reductions was allowed.
Non-hematologic Toxicities	For grade ≥3 non-hematologic toxicities (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events [laboratory events indicating liver or renal dysfunction were not considered asymptomatic laboratory events]) suspected to be study drug–related, zanubrutinib was interrupted until recovery to grade ≤1 or baseline, then restarted at the original dose level. • If the event recurred at grade ≥3, zanubrutinib was interrupted until recovery to grade ≤1 or baseline and restarted at 80 mg BID • If the event recurred at grade ≥3, zanubrutinib was once again interrupted until recovery to grade ≤1 or baseline and restarted at 80 mg QD. If the event recurred at grade ≥3 at 80 mg QD, zanubrutinib treatment was discontinued. For patients experiencing atrial fibrillation that was symptomatic and/or incompletely controlled, zanubrutinib may have been restarted at either the original dose or 80 mg BID, per the investigator's discretion, after the atrial fibrillation was adequately controlled. • Zanubrutinib was interrupted for any grade 3≥ bleeding • The drug was permanently discontinued for any treatment-related grade ≥3 hemorrhage with the exception of those where the underlying condition could be fully treated (eg, gastric ulcer resulting in gastrointestinal bleed) and the risk of a rebleed was deemed acceptable. For any intracranial hemorrhage, regardless of grade or relationship to the study drug, the study drug was held and the risk of rebleeding was assessed. If the risk of rebleeding was deemed unacceptable, zanubrutinib was permanently discontinued. Zanubrutinib was not resumed unless event resolution was demonstrated by computed tomography (CT) scan or MRI, the risk of rebleeding was deemed low, and the patient did not have a need for concurrent anti-thrombotic medications (except low-dose aspirin or low–molecular-weight heparin used to prevent venous thromboembolism). Study drug resumption only occurred after a discussion and approval by the study medical monitor.

Supplemental Table 2. Reasons for unsuitability for standard immunochemotherapy among treatment-naive patients enrolled in the ASPEN study.

Reason(s)*	Ibrutinib (n=18) n (%)	Zanubrutinib (n=19) n (%)	Total (N=37) n (%)
Age	13 (72)	14 (74)	27 (73)
Co-morbidity:			
Cardiac	3 (17)	5 (26)	8 (22)
Renal	2 (11)	2 (11)	4 (11)
Infection	1 (6)	1 (5)	2 (5)
Other	5 (28)	2 (11)	7 (19)

* Patients may have multiple reasons for unsuitability.

Supplemental Table 3:. Response assessment criteria.*

Response category	Definition
Complete response (CR)	Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline)[a,b]
Very good partial response (VGPR)	Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline[a] or normal serum IgM values • Improvement in lymphadenopathy/splenomegaly if present at baseline[a,b] • No new signs or symptoms of active disease
Partial response (PR)	• ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline)[a,b]
Minor response (MR)	At least 25% but <50% reduction of serum IgM from baseline
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	At least one of the following: • Confirmed, ≥25% increase in serum IgM and total on-treatment increase of ≥500 mg/dL from nadir[c] • New lymph node(s) >1.5 cm, or ≥50% increase from nadir in the sum of the product of diameter (SPD) of >1 node, or ≥50% increase in longest diameter of a previously identified node • New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease New or recurrent involvement in bone marrow New symptomatic disease

*Adapted from criteria established at the Sixth International Workshop on Waldenström's Macroglobulinemia as reported by Owen et al 2013.[23] Sequential changes in IgM levels (separated by at least 4 weeks) assessed nephelometrically were employed for the quantitative serum immunoglobulin level measurements, unless due to assay limitations, this was not possible, in which case the M-paraprotein level by serum protein electrophoresis was used.

[a] For response assessments that occur in cycles that do not require imaging studies, results from prior scans performed up to 12 weeks during the first 48 weeks of study and up to 24 weeks thereafter can be carried forward in subjects with extramedullary disease at baseline.

[b] If only physical examination (PE) findings of extramedullary disease are assessable and indicative of unequivocal improvement from baseline (enlarged spleen and/or palpable lymph nodes have regressed), reduction in extramedullary disease can be assessed by PE alone.

[c] An assessment of IgM flare will be assigned instead of PD after study drug has been held at least 7 consecutive days and there is a rapid rise in serum IgM level (or an increase in known extramedullary disease for response assessments that include extramedullary disease evaluation) that might otherwise lead to an "apparent" response of PD. The period that this is applicable begins on the day of the first missed dose and ends when the patient has IgM levels or extramedullary disease that no longer qualify as apparent PD (eg, there is a drop in IgM level below 25% and <500 mg/dL from nadir) or the subject has a confirmed response of PD, whichever comes first.

Supplemental Table 4. Adverse events of interest categories

Adverse events of interest were identified in accordance with predefined MedDRA (Version 22.0) search criteria (see below) and categorized into the following categories of BTK-associated toxicities:

Adverse event of interest category	Search criteria
Hemorrhage	Hemorrhage terms (excluding laboratory terms) (SMQ) narrow
Major hemorrhage - Defined as serious or grade ≥3 bleeding at any site, or central nervous system bleeding of any grade	Major hemorrhage: • Subdural hematoma PT, subdural hemorrhage PT • All hemorrhage PTs if adverse event SOC is "Nervous system disorders" or • Serious or ≥ grade 3 hemorrhage PT if adverse event SOC is not "Nervous system disorders"
Atrial fibrillation and/or flutter	Atrial fibrillation PT, atrial flutter PT
Hypertension	Hypertension (SMQ) narrow
Second primary malignancies Skin cancers	Malignant tumors (SMQ) narrow Subcategory - skin malignant tumors (SMQ) narrow
Tumor lysis syndrome	Tumor lysis syndrome (SMQ) narrow
Infection Opportunistic infections	Infections: infections and infestations SOC Subcategory - opportunistic infections: opportunistic infections (CMQ)
Neutropenia	Neutropenia PT, neutrophil count decreased PT, febrile neutropenia PT, agranulocytosis PT, neutropenic infection PT, neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, platelet count decreased PT
Anemia	Anemia PT, hemoglobin decreased PT

Abbreviations: PT, preferred term; SMQ, standard MedDRA query; CMQ, company MedDRA query.

Supplemental Table 5. Reasons for initiation of study therapy

	Relapsed/Refractory		Treatment-naive		Overall		Total (N=201)
	Ibrutinib (n=81)	Zanubrutinib (n=83)	Ibrutinib (n= 8)	Zanubrutinib (n=19)	Ibrutinib (n=99)	Zanubrutinib (n=102)	
Clinical indications, n (%)							
Fatigue	47 (58)	44 (53)	10 (56)	14 (74)	57 (58)	58 (57)	115 (57)
B-symptoms [a]	22 (27)	29 (35)	4 (22)	6 (32)	26 (26)	35 (34)	61 (30)
Hyperviscosity	19 (24)	20 (24)	8 (44)	7 (32)	27 (27)	27 (27)	54 (27)
Peripheral neuropathy due to WM	17 (21)	18 (22)	4 (22)	6 (32)	21 (21)	24 (24)	45 (22)
Symptomatic or bulky lymphadenopathy [b]	7 (9)	10 (12)	1 (6)	0	8 (8)	10 (10)	18 (9)
Symptomatic hepatomegaly and/or splenomegaly	4 (5)	2 (2)	2 (11)	0	6 (6)	2 (2)	8 (4)
Symptomatic organomegaly and/or organ or tissue infiltration	2 (3)	0	0	0	2 (2)	0	2 (1)
Laboratory indications, n (%)							
Hemoglobin ≤10 g/dL	30 (37)	36 (43)	10 (56)	12 (63)	40 (40)	48 (47)	88 (44)
Platelet count <100 x 10^9/L	12 (15)	11 (13)	0	1 (5)	12 (12)	12 (12)	24 (12)
Amyloidosis related to WM	6 (7)	9 (11)	3 (17)	3 (16)	9 (9)	12 (12)	21 (10)
Immune hemolytic anemia and/or thrombocytopenia	2 (3)	2 (2)	0	1 (5)	2 (2)	3 (3)	5 (3)
Symptomatic cryoglobulinemia	1 (1)	1 (1)	0	1 (5)	1 (1)	2 (2)	3 (2)
Neuropathy related to WM	2 (3)	0	1 (6)	1 (5)	3 (3)	1 (1)	4 (2)
Cold agglutinin anemia	0	0	0	1 (5)	0	1 (1)	1 (1)

[a] Includes recurrent fever, night sweats, and weight loss.
[b] Bulky is defined as ≥5 cm in maximal diameter.

Supplemental Table 6. Summary of prior systemic therapies for relapsed/refractory WM patients

Prior therapy, n (%)	Ibrutinib (n=81)	Zanubrutinib (n=83)
Number of prior systemic regimens		
1	46 (57)	47 (57)
2	15 (19)	15 (18)
3	13 (16)	14 (17)
4	2 (2)	4 (5)
5	3 (4)	0
≥6	2 (3)	3 (4)
Anti-CD20 (rituximab, ofatumumab)	74 (91)	75 (90)
Alkylating agents (cyclophosphamide, chlorambucil, bendamustine, ifosamide, lomustine, melphalan, cisplatin)	66 (82)	73 (88)
Glucocorticoids (dexamethasone, prednisone, prednisolone, methylprednisone, methylprednisolone, hydrocortisone)	50 (62)	60 (72)
Nucleoside analogues (fludarabine, cladribine, cytarabine, gemcitabine,)	18 (22)	20 (24)
Vinca alkaloids (vincristine, vinblastine, vinorelbine)	18 (22)	23 (28)
Proteasome inhibitors (bortezomib, ixazomib)	10 (12)	10 (12)
Anthracyclines (doxorubicin, epirubicin)	9 (11)	9 (11)
Kinase inhibitors (idelalisib, everolimus)	3 (4)	2 (2)
Immunomodulators (lenalidomide, thalidomide)	1 (1)	1 (1)
Topoisomerase inhibitors (etoposide)	1 (1)	2 (2)
Multi-agent regimens, including anti-CD20	0	1 (1)
Others (interferon, bleomycin, belimumab, methotrexate)	0	4 (5)

Abbreviations: BTK, Bruton tyrosine kinase; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.
* Categories of systemic therapies listed are not mutually exclusive (patients may have received agents from multiple different categories). Percentages may total more or less than 100 due to rounding.

Supplemental Table 7. Changes from baseline in log-transformed IgM levels for relapsed/refractory WM patients and overall

	Relapsed/Refractory		Overall	
Parameter	**Ibrutinib (n=81)**	**Zanubrutinib (n=83)**	**Ibrutinib (n=99)**	**Zanubrutinib (n=101)**
Slope over time (in months)	-0.06687	-0.07493	-0.06106	-0.06812
P value (2-sided) [a]	0.0358		0.0314	
AUC				
Top 25% percentile	851	1086	849	1030
Median	528	623	551	621
P value (2-sided) [b]	0.0243		0.0370	

[a] From repeated measures, mixed effect model with time as continuous variable and treatment arm and time as fixed effects. *P* value is for the interaction between treatment arm and time effects.
[b] From Mantel-Haenszel test.
Abbreviation: AUC, area under the $\log_{10}$ serum IgM concentration x time curve.

Supplemental Table 8. Serious AEs reported in >1 patient in either treatment arm and deaths due to adverse events

Event term, n (%)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Pneumonia	9 (9)	1 (1)
Sepsis	3 (3)	2 (2)
Pyrexia	3 (3)	2 (2)
Atrial fibrillation/flutter	3 (3)	0 (0)
Cholecystitis	2 (2)	0 (0)
Loss of consciousness	2 (2)	0 (0)
Myocardial infarction	2 (2)	0 (0)
Pericarditis	2 (2)	0 (0)
Urinary tract infection	2 (2)	0 (0)
Influenza	1 (1)	3 (3)
Pleural effusion	1 (1)	2 (2)
Neutropenia	0 (0)	3 (3)
Febrile neutropenia	0 (0)	3 (3)
Anemia	0 (0)	2 (2)
Lower respiratory tract infection	0 (0)	2 (2)
Thrombocytopenia	0 (0)	2 (2)
Basal cell carcinoma	0 (0)	2 (2)

Deaths due to adverse events

Diagnosis sex/age (y)	Study treatment	MedDRA-preferred term (verbatim AE term)	Date of death <30 days of last dose	Comments
R/R WM M/85	Ibrutinib	Bacterial sepsis (Gram negative septicemia)	Yes	Death preceded by pneumonia, septic shock; history of hypertension, myocardial ischemia, atrial fibrillation
R/R WM M/84	Zanubrutinib	Cardiomegaly (Cardiomegaly)	Yes	History of hypertension, valvular and ischemic heart disease. Patient collapsed and died from complications of sudden cardiac arrest after an elective plasmapheresis performed in the setting of progressive disease.
R/R WM F/79	Ibrutinib	Sepsis (Sepsis)	Yes	Death preceded by pneumonia, urinary tract infection; history of hypertension, cardiac murmur.

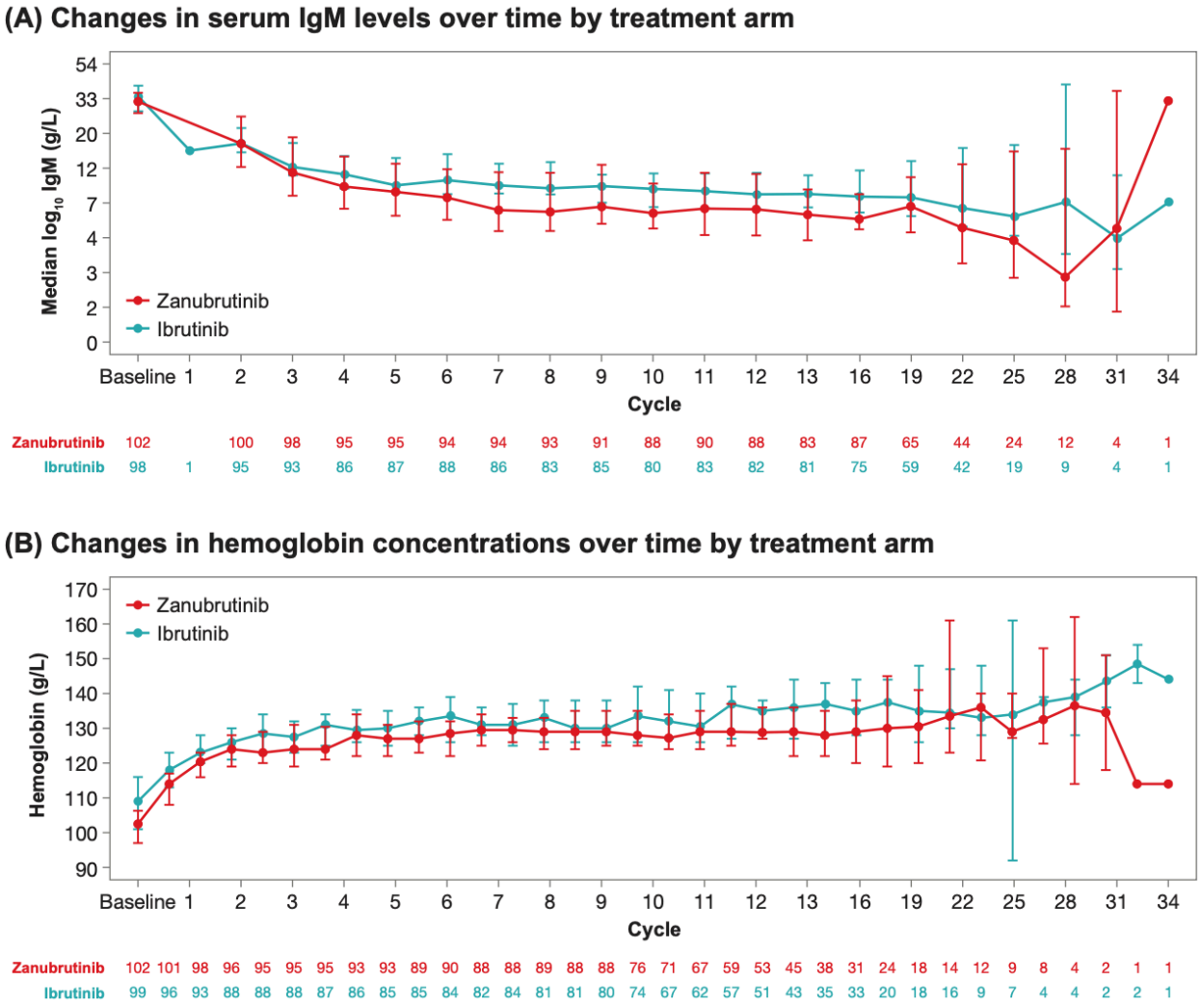
Supplemental Table 9. Post-hoc Analysis of CR/VGPR and Major Response Rates Based on Next Generation Sequencing for Detection of *CXCR4*^{WHIM} Mutations [a]

Patients with NGS results for CXCR4 mutation detection [b]	Ibrutinib N=92	Zanubrutinb N= 98
CXCR4^{WHIM} , n (%)	20 (22)	33 (34)
VGPR, n (%)	**2 (10)**	**6 (18)**
Median time to VGPR, months	10.6	10.3
Major response, n (%)	13 (65)	23 (70)
Median time to major response, months	6.5	3.0
CXCR4^{WT}, n (%)	72 (78)	65 (66)
VGPR, n (%)	**17 (24)**	**22 (34)**
Median Time to VGPR, months	7.4	4.7
Major response, n (%)	59 (82)	53 (82)
Median time to major response, months	2.8	2.8
Overall		
VGPR, n (%)	**19 (21)**	**28 (29)**
Major response, n (%)	72 (78)	76 (78)

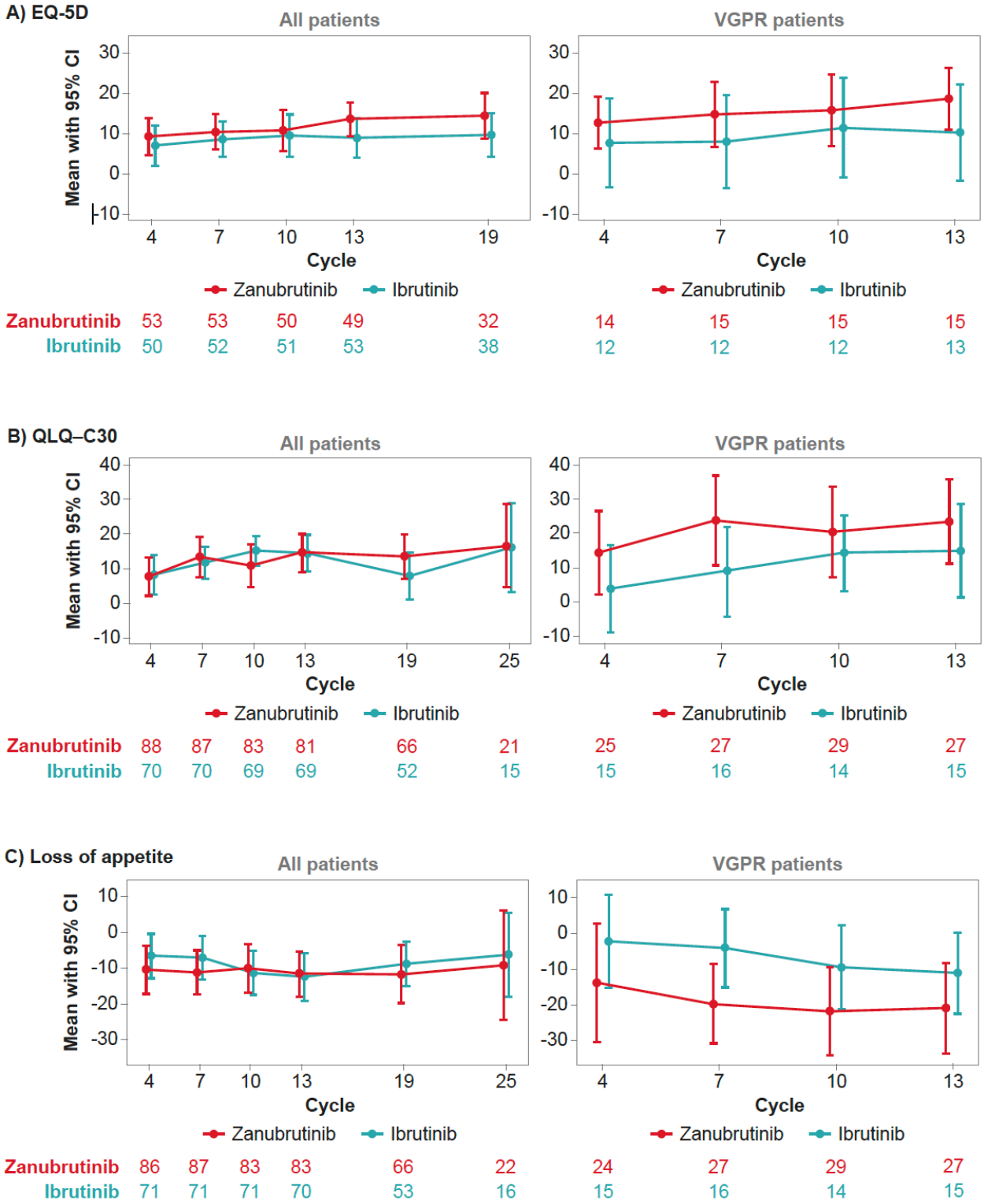
[a] Denominators represent the number of patients with CXCR4 NGS results in each treatment arm/subgroup.
[b] Seven ibrutinib- and 4 zanubrutinib-treated patients did not undergo re-assay for CXCR4 mutation detection by NGS. Of these, 6 ibrutinib patients achieved a best response of PR and 2 zanubrutinib patients achieved a best response of VGPR and PR.
Abbreviations: VGPR, very good partial response; NGS, next generation sequencing; CXCR4, chemokine receptor 4

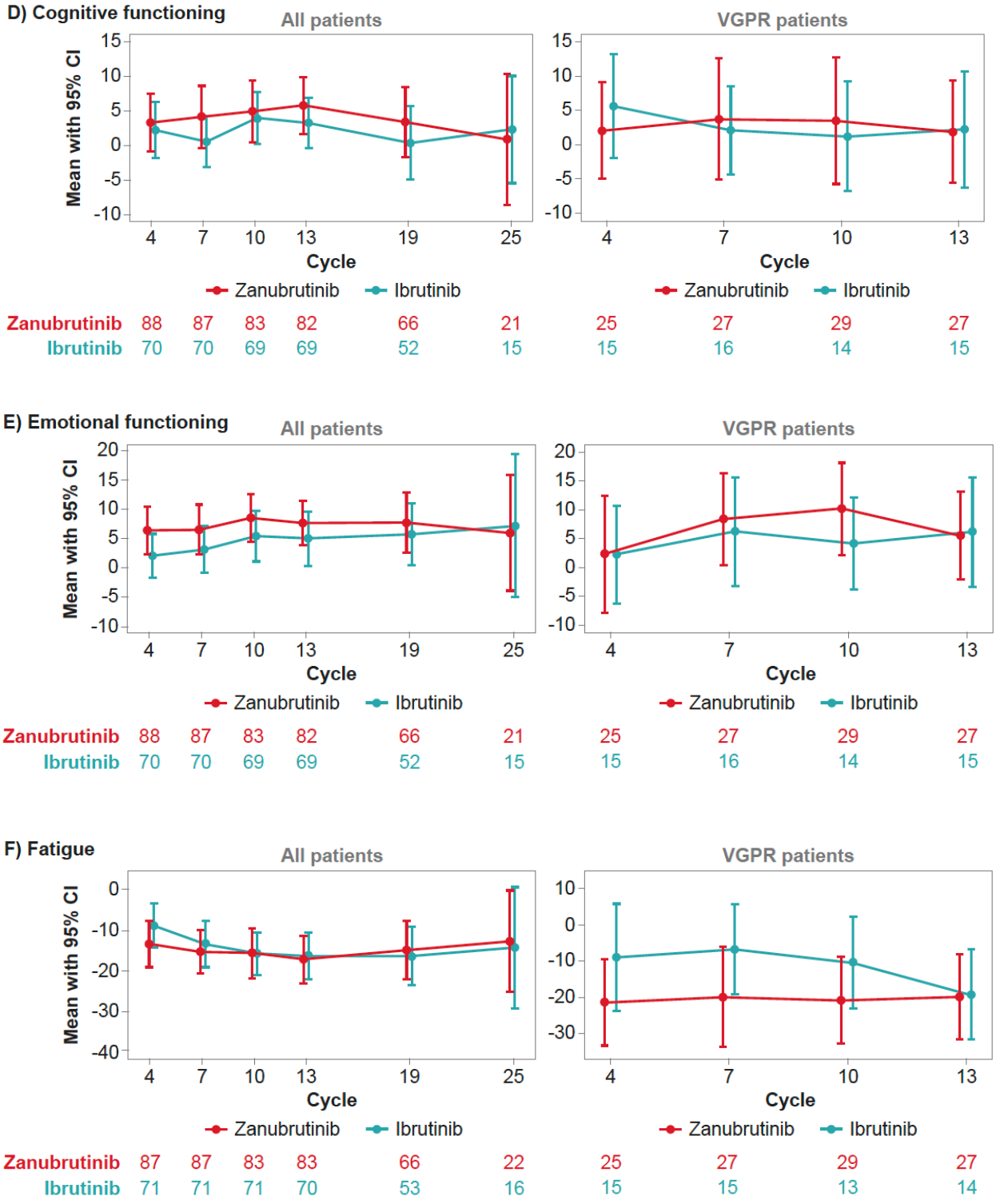
Supplemental Figures

Supplemental Figure 1. Changes in (A) IgM and (B) hemoglobin concentrations

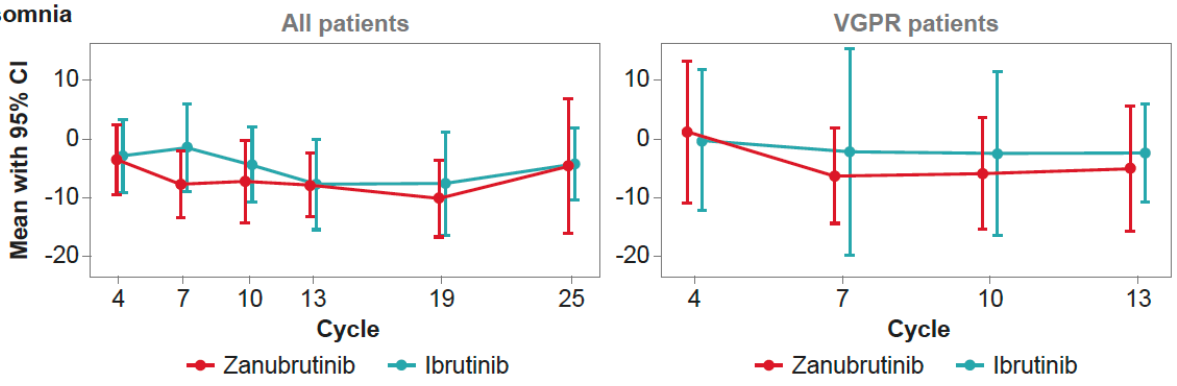


Supplemental Figure 2. Quality-of-life measures over time



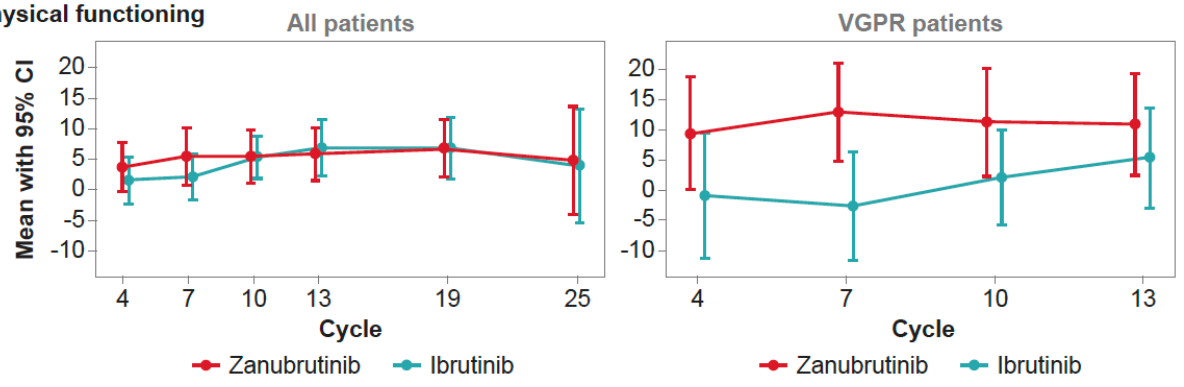

D) Cognitive functioning
All patients
VGPR patients
Mean with 95% CI
Cycle
Zanubrutinib
Ibrutinib
Zanubrutinib 88 87 83 82 66 21 25 27 29 27
Ibrutinib 70 70 69 69 52 15 15 16 14 15
E) Emotional functioning
All patients
VGPR patients
Mean with 95% CI
Cycle
Zanubrutinib
Ibrutinib
Zanubrutinib 88 87 83 82 66 21 25 27 29 27
Ibrutinib 70 70 69 69 52 15 15 16 14 15
F) Fatigue
All patients
VGPR patients
Mean with 95% CI
Cycle
Zanubrutinib
Ibrutinib
Zanubrutinib 87 87 83 83 66 22 25 27 29 27
Ibrutinib 71 71 71 70 53 16 15 15 13 14

G) Insomnia



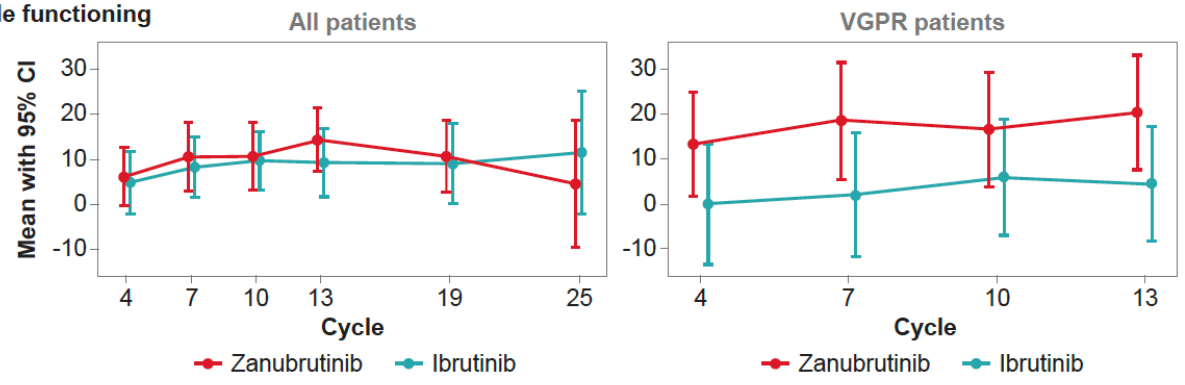
Zanubrutinib	87	87	83	82	66	22	25	27	29	27
Ibrutinib	69	70	70	69	53	16	15	16	14	15

H) Physical functioning



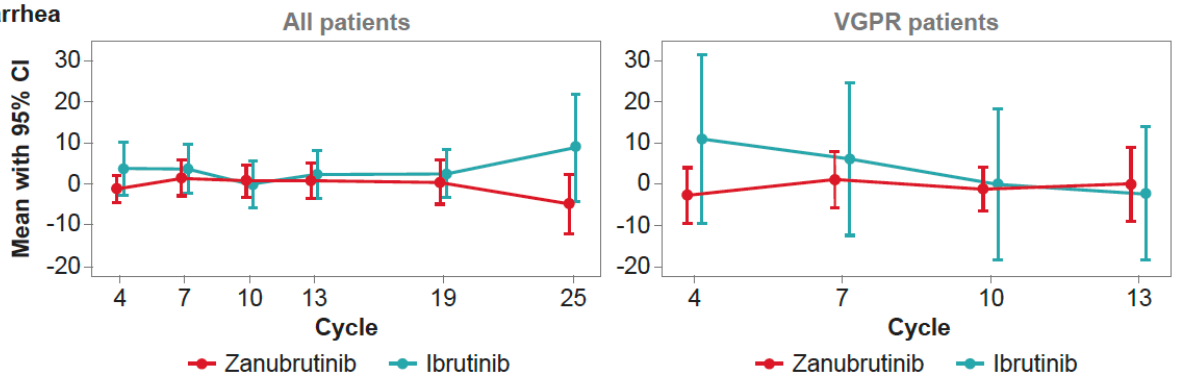
Zanubrutinib	87	87	83	83	66	22	25	27	29	27
Ibrutinib	70	70	69	70	54	15	14	15	13	15

I) Role functioning



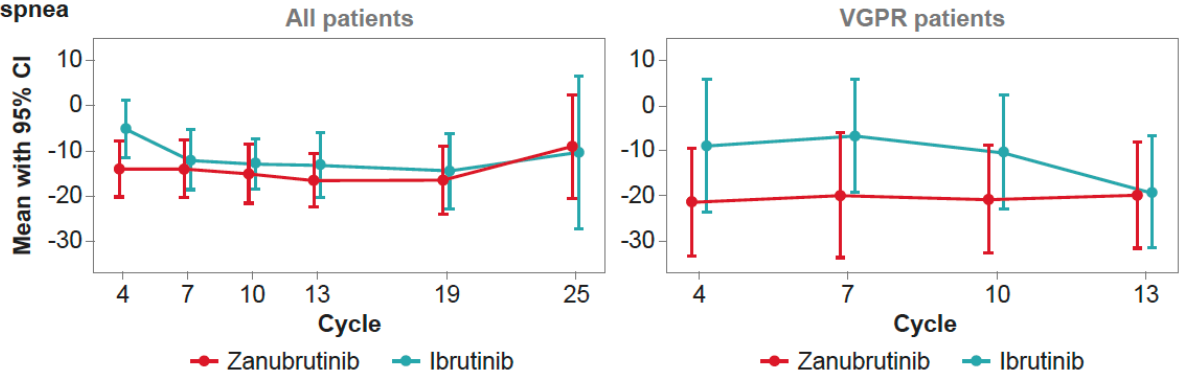
Zanubrutinib	87	87	83	83	66	22	25	27	29	27
Ibrutinib	70	71	71	70	54	16	15	16	14	15

J) Diarrhea



Zanubrutinib	88	87	83	82	66	21	25	27	29	27
Ibrutinib	70	70	68	69	52	15	15	16	13	15

K) Dyspnea



Zanubrutinib	86	86	82	83	65	22	25	27	29	27
Ibrutinib	71	70	70	69	53	16	15	15	13	14