Genomic Characterization of Patients in a Phase 2 Study of Zanubrutinib in BTK Inhibitor–Intolerant Patients With Relapsed/Refractory B-Cell Malignancies

Abstract 4176

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INTRODUCTION

- Targeting BTK to inhibit B-cell receptor signaling is an effective way to treat B-cell malignancies. Some patients, however, have experienced toxicities to the BTK inhibitors ibrutinib and acalabrutinib, leading to dose reduction or treatment discontinuation[1-3]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor[4,5]
- BGB-3111-215 (NCT04116437) is an ongoing, phase 2 study of the safety and efficacy of zanubrutinib monotherapy in patients with CLL, SLL, WM, MCL, or MZL who discontinued ibrutinib, acalabrutinib, or acalabrutinib and ibrutinib because of intolerance[6]
- The mutational profile of patients who were intolerant to BTK inhibitors has not been extensively studied
- Here, we evaluated blood samples collected from patients in the BGB-3111-215 study by NGS in order to understand the mutational landscape of patients who were intolerant to BTK inhibitors

OBJECTIVES

- Profile the genetic alterations of patients who are intolerant to ibrutinib or acalabrutinib
- Explore the association between gene mutations and response to zanubrutinib in patients who are intolerant to ibrutinib or acalabrutinib

METHODS

- Eligible patients with CLL/SLL, WM, MCL, or MZL who met protocol-defined criteria for intolerance to ibrutinib and/or acalabrutinib where enrolled in the BGB-3111-215 study and received zanubrutinib 160 mg twice daily or 320 mg once daily
  - Patients who progressed on prior BTK inhibitor therapy were excluded
- Peripheral blood samples from patients were collected at baseline and at and/or after the time of disease progression
- Biomarker analysis
  - Genomic DNA was isolated from peripheral blood mononuclear cells or plasma
  - Gene mutations were examined using the 106-gene NGS panel PredicineHEME™ (Predicine Inc.)
  - Samples were sequenced to a median depth of >20,000 reads, with a validated sensitivity of 0.1-0.25% mutant allele frequency for all genomic regions

RESULTS

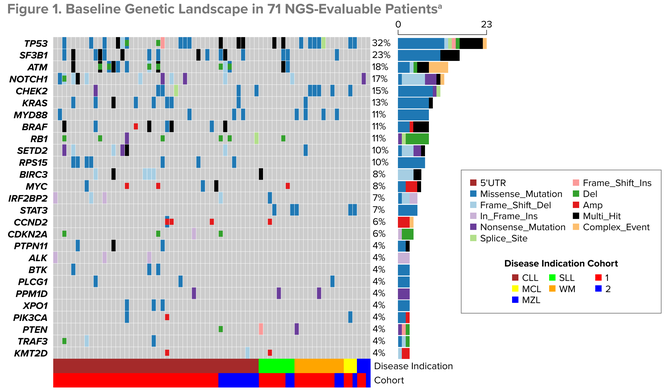
Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 ibrutinib-intolerant (n=56)	Cohort 2 Acalabrutinib or acalabrutinib and ibrutinib-intolerant (n=15)	Total (N=71)[a]
Indication, n (%)			
CLL	37 (66.1)	9 (60.0)	46 (64.8)
WM	9 (16.1)	2 (13.3)	11 (15.5)
SLL	6 (10.7)	2 (10.0)	8 (11.3)
MCL	2 (3.6)	1 (6.7)	3 (10.3)
MZL	2 (3.6)	1 (6.7)	3 (10.3)
Median age (range), years	71 (49-91)	73 (51-87)	71 (49-91)
Male, n (%)	30 (53.6)	9 (60.0)	39 (54.9)
ECOG PS 0, n (%)	33 (58.9)	8 (53.3)	41 (57.7)
Median no. of prior therapy regimens (range)	1 (1-12)	2 (1-6)	1 (1-12)
Prior BTK inhibitor, n (%)	56 (100)	15 (100)	71 (100)
Ibrutinib monotherapy	47 (83.9)	7 (46.7)[b]	54 (76.1)
Ibrutinib combination therapy	9 (16.1)[c]	0	9 (12.7)
Acalabrutinib monotherapy	0	8 (53.3)	7 (9.9)
Median time on prior BTK inhibitor[d] (range), month	10.61 (1.1-73.7)	3.33 (0.5-26.9)	NA

Data cutoff: 6 June 2022.
[a]Nine patients had disease progression and 7/9 had PD samples for NGS analysis. [b]Seven patients had both prior ibrutinib and acalabrutinib therapies. [c]One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. [d]Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2.

- The top mutated genes were *TP53* (32%), *SF3B1* (23%), *ATM* (18%), *NOTCH1* (17%), and *CHEK2* (15%) (**Figure 1**)
- Three patients had *BTK* mutations at baseline. Two of these patients progressed, and 1 died due to COVID-19 before any assessments were completed
- One patient (with CLL) who progressed had mutations in both *BTK* and *PLCG2* genes at baseline (**Table 2**)
- Commonly mutated genes per disease were (**Figure 1**)
  - CLL/SLL: *TP53* (16/54, 30%), *SF3B1* (15/54, 28%), *ATM* (13/54, 24%), *NOTCH1* (11/54, 20%), *KRAS* (8/54, 15%), *BIRC3* (6/54, 11%), and *MYD88* (4/54, 7.4%)
  - WM: *TP53* (5/11, 45%), *MYD88* (4/11, 36%), and *CXCR4* (1/11, 9.1%)

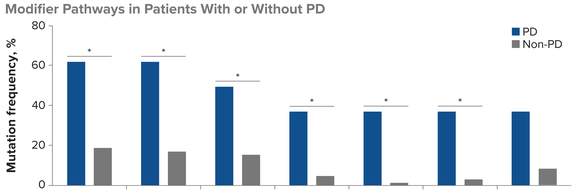
Figure 1. Baseline Genetic Landscape in 71 NGS-Evaluable Patients[a]



[a]Results shown include only genes affecting at least 3 patients.

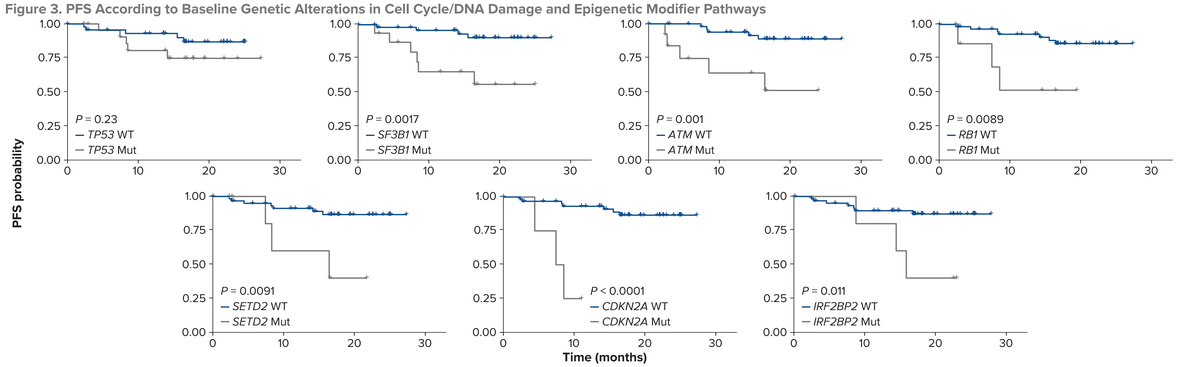
- Baseline genetic alterations in cell cycle/DNA damage and epigenetic modifier pathways are associated with inferior response (**Figure 2**) and inferior PFS in this patient population (**Figure 3**)

Figure 2. Baseline Genetic Alterations in Cell Cycle/DNA Damage and Epigenetic Modifier Pathways in Patients With or Without PD



*P < 0.05 Fisher's exact test.

Figure 3. PFS According to Baseline Genetic Alterations in Cell Cycle/DNA Damage and Epigenetic Modifier Pathways



- Mutational status of *BTK* and *PLCG2* was assessed in patients with PD, both at baseline and at and/or after disease progression (**Table 2**)
  - In this subset of patients, more mutations in these genes were detected at and/or after progression compared with baseline
  - In addition, in those patients with detectable mutations of *BTK* or *PLCG2* at baseline, the VAF of the original mutation was higher at and/or after progression than at baseline
- Patients with CLL who progressed and did not have *BTK* or *PLCG2* mutations (Patients 4, 6, 7 and 8 in **Table 1**) all had mutations associated with poor prognosis (**Table 3**)

Table 3. Mutations Associated With Poor Prognosis in Patients With PD and Without Any *BTK/PLCG2* Mutations Detected

Patient	Indication	Gene mutations associated with PD
4	CLL	*ATM, FBXW7*
6	CLL	*MCL1, TP53*
7	CLL	*TP53, SF3B1, FBXW7*
8	CLL	*TP53, NOTCH1, BRAF, SF3B1, MAPK14*

Table 2. *BTK* and *PLCG2* Mutational Status of PD Patients at Baseline and at and/or After Relapse

			***BTK* mutational status**				***PLCG2* mutational status**			
Patient	Indication	Days on zanubrutinib	Baseline	VAF (%)	At and/or after progression	VAF (%)	Baseline	VAF (%)	At and/or after progression	VAF (%)
1	CLL	280	Not detected[a]	N/A	Cys481Ser, 1442G>C	19.21	Not detected	N/A	Leu845Phe, 2535A>C	0.99
					Cys481Ser, 1442T>A	1.13			Asn750Asp, 2248A>G	0.79
									Arg665Trp, 1993C>T	0.34
2	SLL	545	Not detected	N/A	Cys481Ser, 1442G>C	0.32	Not detected	N/A	Ser707Phe, 2120C>T	5.77
					Cys481Ser, 1442T>A	3.77			Leu845Val, 2533T>G	1.74
					Cys481Tyr, 1442G>C	14.03			Glu1139del, 3417_3419del	4.7
									Met1141Lys, 3422T>A	0.89
3	CLL	140	Cys481Ser, 1442G>C	60.86	Cys481Ser, 1442G>C	69.06	Not detected	N/A	Not detected	N/A
4	CLL	408	Not detected	N/A	Not detected	N/A	Not detected	N/A	Not detected	N/A
5[b]	MCL	264	Not detected[c]	N/A	Not detected	N/A	Not detected[c]	N/A	Not detected	N/A
6	CLL	388	Not detected	N/A	No sample available	N/A	Not detected	N/A	No sample available	N/A
7	CLL	234	Not detected	N/A	Not detected	N/A	Not detected	N/A	Not detected	N/A
8	CLL	167	Not detected	N/A	No sample available	N/A	Not detected	N/A	No sample available	N/A
9	CLL	537	Cys481Ser, 1442G>C	0.89	Cys481Ser, 1442G>C	20.38	Asn868Lys, 2604C>A	48.08	Asn868Lys, 2604C>A	50.09
									Leu845Phe, 2535A>C	0.41
									Asp993His, 2977G>C	0.60

[a]Initial sample collected on study day 141. [b]Initial sample collected on study day 87. [c]MCL patient with *CCND1-IGH* fusion at both baseline and relapse, which was reported to contribute to ibrutinib resistance in MCL.

CONCLUSIONS

- This exploratory analysis suggests that cell cycle, DNA damage, and NOTCH1 pathway genes were frequently mutated in patients with B-cell malignancies who were intolerant to ibrutinib and/or acalabrutinib
- Patients who progressed on zanubrutinib were more likely to have *BTK* mutations that convey resistance to BTK inhibitors or other mutations associated with poor prognosis

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ABBREVIATIONS

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; del, deletion; ins, insertion; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; Mut, mutant; MZL, marginal zone lymphoma; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic lymphoma; UTR, untranslated region; VAF, variant allele frequency; WM, Waldenström macroglobulinemia; WT, wild type.

DISCLOSURES

LX: employment with BeiGene; previous employment with AstraZeneca

MS: consulting for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, TG Therapeutics, Innate Pharma, Kite, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune Therapeutics, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, Atara Biotherapeutics; research funding from AbbVie, BMS, Celgene, Pharmacyclics, Gilead, Genentech, Mustang Bio, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, MorphoSys/Incyte

AP, AiCo, VR: employment with BeiGene

IWF: consulting for AbbVie, AstraZeneca, BeiGene, Century Therapeutics, Genentech, Genmab, Hutchison MediPharma, Ikouda Therapeutics, InnoCare, Janssen, Kite, MorphoSys/Incyte, Myeloid Therapeutics, Novartis, Nurix Therapeutics, Pharmacyclics, Roche, Secura Bio, Servier Pharmaceuticals, Takeda, TG Therapeutics, Verastem, Vincerx Pharma, Xencor; research funding from AbbVie, Acerta, Agios, ArQule, AstraZeneca, BeiGene, Brupath, BMS, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI Biopharma, Epizyme, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead, InnoCare, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite, Lowo Oncology, Merck, Millennium Pharmaceuticals, MorphoSys/Incyte, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola, Rhizen Pharmaceuticals, Roche, Seagen, Tessa Therapeutics, TCR2 Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp, Curis, Verastem, Zeaventy bio; advisory board for Vincerx

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SFZ: honoraria from BMS, Epizyme, Immunoscience, AbbVie

DYC: employment with Treadwell Therapeutics; previous employment with BeiGene

JPS: consulting for AbbVie, AstraZeneca, BeiGene, BMS, Eli Lilly, Pharmacyclics, TG Therapeutics, Centessa; honoraria from AbbVie, AstraZeneca, BeiGene, Eli Lilly, Pharmacyclics, TG Therapeutics, ADC Therapeutics, Genentech; stock with Centessa; advisory board for Centessa

RP, JLC, JM, ECK, HAY, BF, ArCh, PKT, MDG, SM: nothing to disclose

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