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Phase 2 Study of Zanubrutinib in BTK Inhibitor-Intolerant Patients With Relapsed/Refractory B-cell Malignancies

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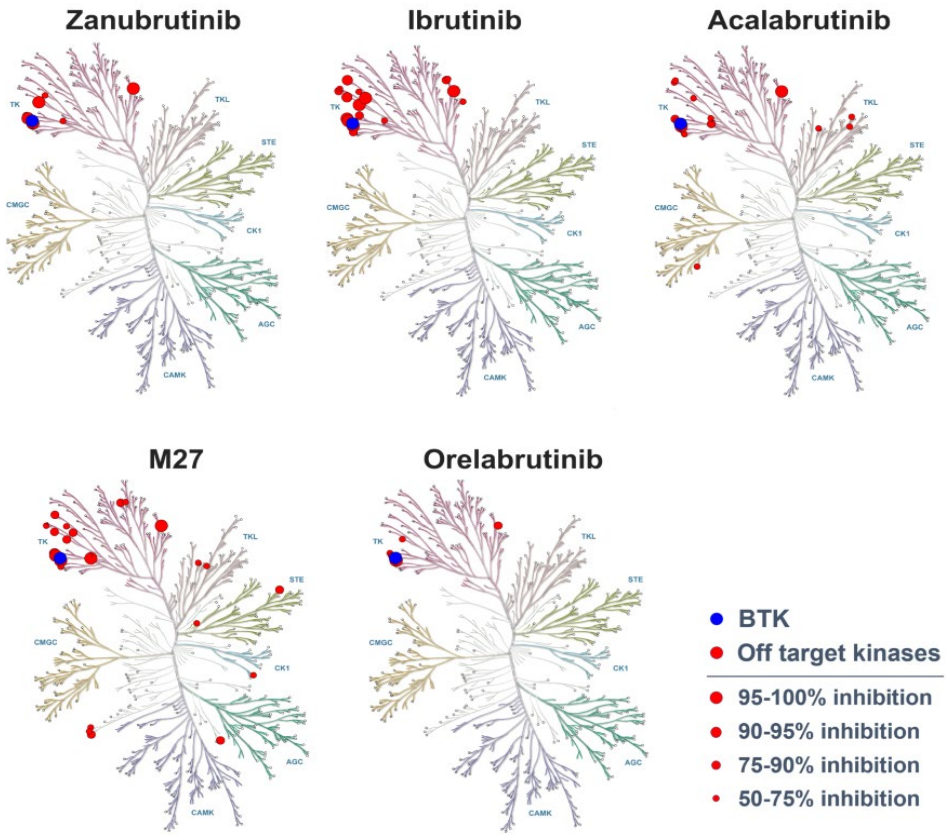
December 11, 2021
626. Session: Aggressive Lymphomas: Prospective Therapeutic Trials: Poster I

INTRODUCTION

- Bruton tyrosine kinase inhibitors (BTKi) provide effective treatment to several B-cell malignancies; however, duration of treatment is limited by AEs leading to treatment discontinuation, which occur early[1-3]
- BTKi-associated AEs are believed to be due to off-target effects of BTK inhibitors
- Two phase 3 head-to-head studies against ibrutinib demonstrated patients taking zanubrutinib[4,5] had
  - **lower rates of AEs** leading to treatment discontinuation and death
  - **lower rates of atrial fibrillation** at a median follow-up of 15-19 months

Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, M27, and Orelabrutinib



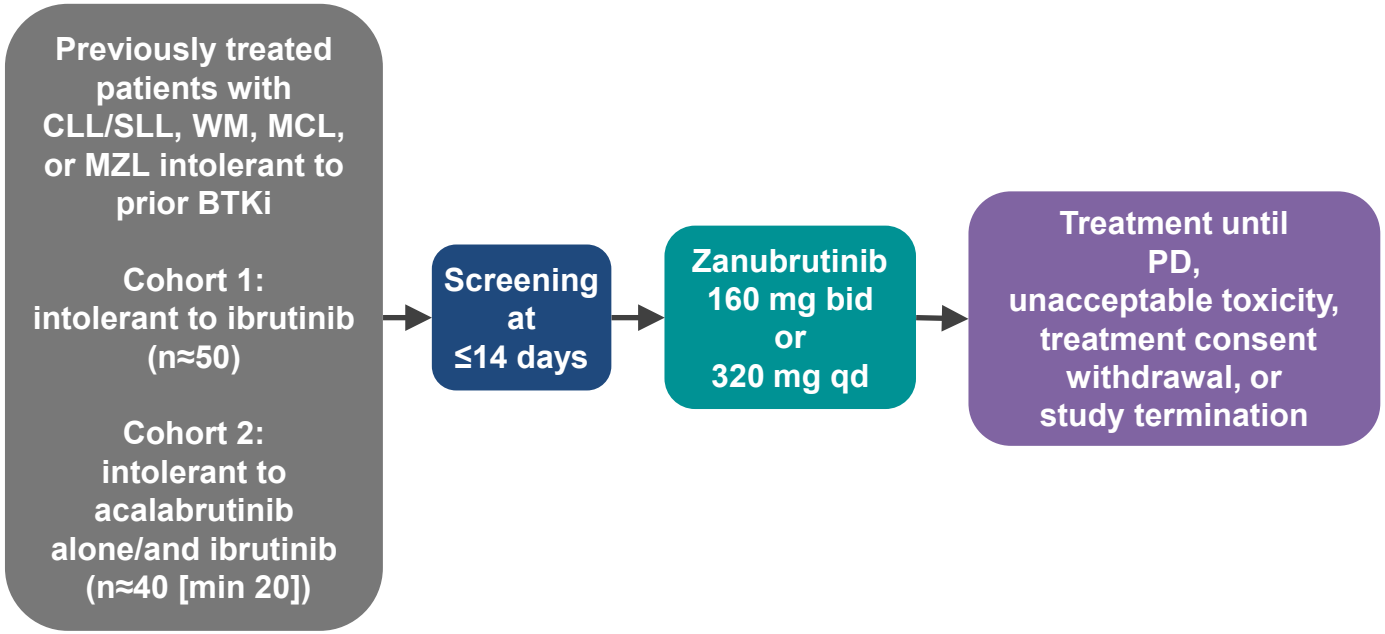
Assayed by Reaction Biology Corp. at 100X of IC_{50} (against BTK) concentration with IC_{50} (BTK)s of 0.71±0.09, 0.32±0.09, 24±9.2, 63±28 and 15±5.5 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib, M27, and orelabrutinib, respectively.

Zanubrutinib, a BTKi approved for treatment of MCL, MZL, and WM, was designed to optimize selectivity and maximize BTK occupancy

1. Mato AR, et al. *Haematologica.* 2018;103(5):874-879. 2. Yazdy MS, et al. *Blood.* 2019;134(suppl 1):4311.
3. Tam CS, et al. EHA 2019. Abstract PS1159. 4. Dimopoulos M, et al. EHA 2020. Abstract S225.
5. Hillmen P, et al. EHA 2021. Abstract LB1900.

AE, adverse event; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.

Study Design



Primary objective: To evaluate the safety of zanubrutinib in patients intolerant to ibrutinib and/or acalabrutinib treatment compared with their ibrutinib and/or acalabrutinib intolerance as assessed by the recurrence and the change in severity of AEs

Key Inclusion Criteria

- Ibrutinib and acalabrutinib intolerance
  - Grade ≥2 nonhematologic toxicity for >7 days
  - Grade ≥3 nonhematologic toxicity for any duration
  - Grade 3 neutropenia with infection or fever
  - Grade 4 hematologic toxicity that persists until BTKi therapy is discontinued due to toxicity
  - Resolution of BTKi toxicities to grade ≤1 or baseline prior to initiating zanubrutinib treatment
- Additional acalabrutinib intolerance criteria:
  - Grade ≥1 nonhematologic toxicity for >7 days
  - Grade ≥1 nonhematologic toxicity of any duration with ≥3 recurrent episodes
  - Inability to use acid-reducing agents or anticoagulants due to current BTKi use
- Resolution of grade 1 BTKi toxicities to grade 0 or baseline prior to initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTKi treatment

bid, twice daily; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; qd, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

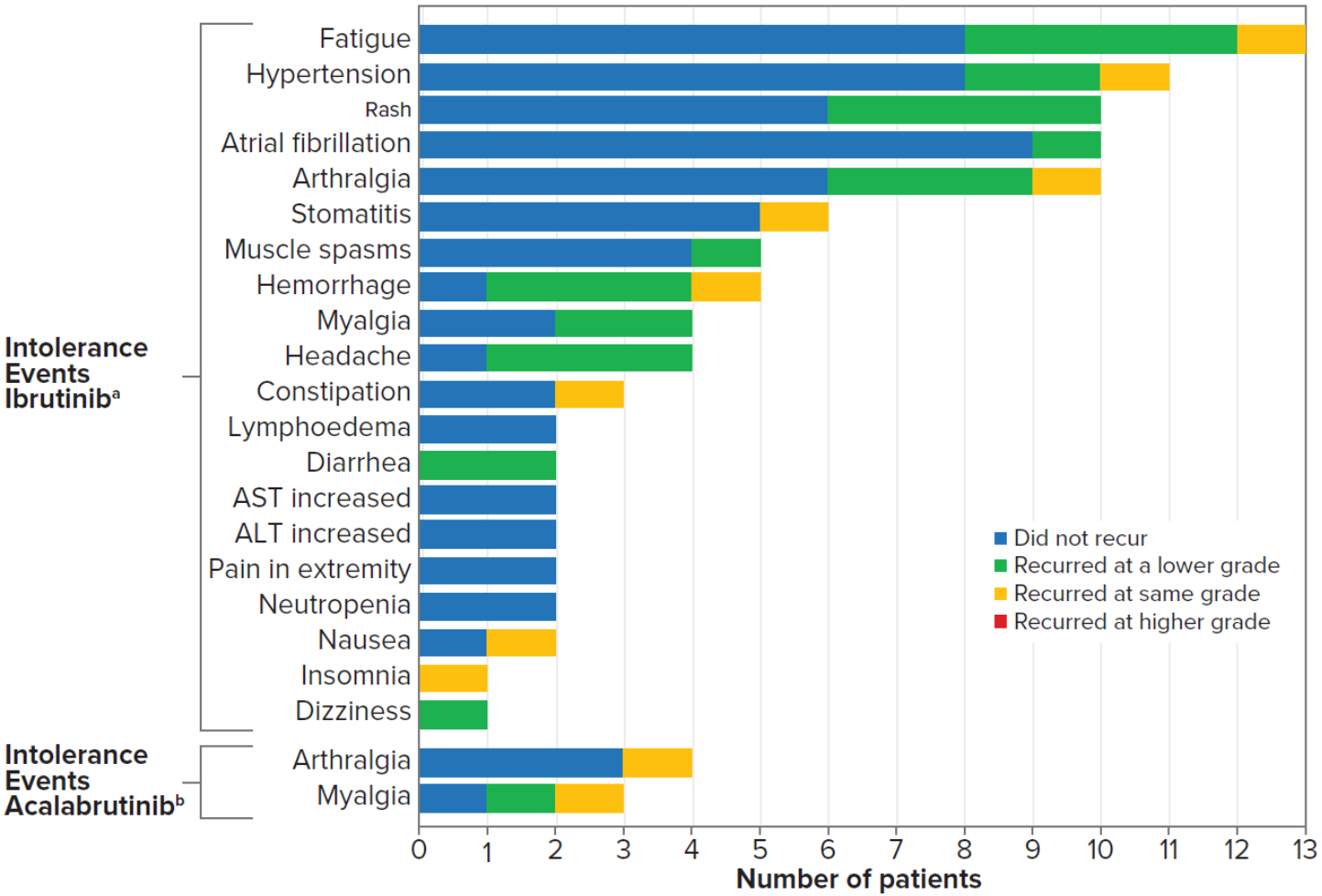
Patient Baseline Characteristics and Disposition

Characteristics	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Indication, n (%)			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0)	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
Age, median (range), year	71.0 (49-91)	73.5 (65-83)	71.0 (49-91)
Male, n (%)	30 (52.6)	6 (60.0)	36 (53.7)
ECOG PS 0, n (%)	33 (57.9)	4 (40.0)	37 (55.2)
No. of prior therapy regimens, median (range)	1.0 (1-12)	2.5 (1-5)	1.0 (1-12)
Time on prior BTKi,[a] median (range), months	10.61 (1.1-73.7)	3.33 (0.5-26.9)	—
Patients remaining on treatment, n (%)	48 (84.2)	8 (80.0)	56 (83.6)
Patients remaining on study, n (%)	54 (94.7)	10 (100)	64 (95.5)
Patients discontinued from treatment due to AE, n (%)	4 (7.0)[b]	1 (10.0)[c]	5 (7.5)
Death	1 (1.8)[d]	0	1 (1.5)
Zanubrutinib exposure, median (range), months	11.6 (0.6-20.3)	9.8 (0.5-12.0)	11.1 (0.5-20.3)
Follow-up, median (range), months	12.3 (1.0-22.8)	10.4 (0.5-15.0)	12.0 (0.5-22.8)

Data cutoff: 8 September 2021

[a]Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2. [b]Penile bleed, COVID-19 pneumonia (fatal), increased alanine aminotransferase/aspartate transaminase, and autoimmune hemolytic anemia. [c]Myalgia. [d]COVID-19 pneumonia.
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic leukemia; WM, Waldenström macroglobulinemia.

Recurrence of Ibrutinib and Acalabrutinib Intolerance Events on Zanubrutinib



- 34/57 (59.6%) of patients who took ibrutinib and 7/10 (70.0%) of patients who took acalabrutinib did not have recurrence of any intolerance event
- No ibrutinib or acalabrutinib intolerance events recurred at a higher severity
- 81/115 (70.4%) ibrutinib intolerance events and 15/18 (83.3%) acalabrutinib intolerance events did not recur
- 25/38 (65.8%) grade 3 ibrutinib intolerance events and 3/4 (75.0%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
- All grade 4 intolerance events (neutropenia [n=2], ALT increase [n=1], AST increase [n=1]) did not recur on zanubrutinib
- 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia; acalabrutinib)

[a]18 ibrutinib intolerance events (arthritis, bone pain, bronchitis, embolism, heart rate irregular, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, transaminases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in 1 patient and did not recur on zanubrutinib. [b]11 acalabrutinib intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (not shown here).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Most Common Adverse Events Occurring in ≥7.5% of Patients

AE, n (%)	All Grades (N=67)	Grades ≥3 (N=67)
Contusion/bruising	15 (22.4)	0
Fatigue	14 (20.9)	0
Myalgia	10 (14.9)	0
Arthralgia	9 (13.4)	0
Diarrhea	9 (13.4)	1 (1.5)
Hypertension	8 (11.9)	1 (1.5)
Dizziness	7 (10.4)	0
Nausea	7 (10.4)	0
Pain in extremity	6 (9.0)	0
Cough	5 (7.5)	0
Epistaxis	5 (7.5)	0
Insomnia	5 (7.5)	0
Muscle spasms	5 (7.5)	0
Neutropenia	5 (7.5)	5 (7.5)
Neutrophil count decreased	5 (7.5)	3 (4.5)
Petechiae	5 (7.5)	0
Rash	5 (7.5)	0
Urinary tract infection	5 (7.5)	0

AE, adverse event; SAE, serious adverse event.

- Most patients (95.5%) experienced ≥1 AEs
- 29.9% of patients experienced ≥1 grade 3 AE
- The most common grade ≥3 AEs:
  - Neutropenia/neutrophil count decrease: 8 (12.0%)
  - Syncope: 2 (3.0%)
- 11.9% of patients experienced ≥1 SAE
- 7.5% of patients discontinue treatment due to AE
- Bleeding events occurred in 25 (37.3%; grade 1: 19 [28.4%], grade 2: 6 [9.0%]) patients
- Atrial fibrillation occurred in 3 patients (4.5%; all grade 2)
- Infections occurred in 26 (38.8%; grade 1: 3 [4.5%], grade 2: 18 [26.9%], grade 3: 6 [6.0%]; grade 5: 1 [COVID-19; 1.5%]) patients
- Anemia occurred in 3 patients (3.1%; grade 1: 1 [1.5%], grade 2: 2 [3.0%])
- Thrombocytopenia/platelet count decrease occurred in 3 patients (4.5%; all grade 1)

Efficacy by Investigator Assessment in Patients With >90-Day Study Duration

Response	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=7)	Total (n=64)
Disease control rate [SD or better], n (%)	54 (94.7)	6 (85.7)	60 (93.8)
Overall response rate [better than SD], n (%)	36 (63.2)	5 (71.4)	41 (64.1)
BOR Rate, n (%)			
PR or better[a]	36 (63.2)	5 (71.4)	41 (64.1)
SD	18 (31.6)	1 (14.3)	19 (29.7)
PD	1 (1.8)	1 (14.3)	2 (3.1)
Not done	2 (3.5)[b]	0	2 (3.1)
Time to BOR, median (range), months	5.5 (2.6-11.3)	7.9 (2.9-11.1)	5.6 (2.6-11.3)
Time to first overall response, median (range), months	2.92 (2.6-11.1)	3.02 (2.7-11.1)	2.96 (2.6-11.1)

- **Disease parameters performed at study entry, in most cases after recent BTKi therapy, were used as baseline for response assessment**
- Three of 5 patients who progressed had *BTK*/*PLCG2* mutations associated with BTKi resistance at/after progression

[a]PR or better includes nodular partial response and very good partial response. [b]One patient withdrew from study before first assessment timepoint due to syncope; 1 patient died from COVID-19 pneumonia before first response assessment.
BOR, best overall response; BTKi, Bruton tyrosine kinase inhibitor; PD, progressive disease; PLCG2, phospholipase C gamma 2 gene; PR, partial response; SD, stable disease.

CONCLUSIONS

- Intolerable AEs experienced on ibrutinib and/or acalabrutinib were unlikely to recur while on zanubrutinib
  - With a median follow-up of 12 months, 70.4% of ibrutinib intolerance events and 83.3% of acalabrutinib intolerance events did not recur while on zanubrutinib
  - Of the intolerance events that recurred, 76.4% of ibrutinib and 33.3% of acalabrutinib intolerance events recurred at a lower severity; 23.5% of ibrutinib and 66.6% of acalabrutinib intolerance events occurred at the same severity
  - No events recurred at a higher severity
  - Only 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerance event (acalabrutinib)
- Zanubrutinib was tolerable, with 83.6% of patients remaining on zanubrutinib, and 7.5% of patients discontinued zanubrutinib due to AEs at the time of data cutoff
- Zanubrutinib was effective in at least maintaining response in 93.8% or improving response from baseline in 64.1% of patients
- Exploratory biomarkers analysis results indicated that progression on zanubrutinib was associated with BTKi-resistance mutations
- Zanubrutinib demonstrated favorable BTKi selectivity profiles over ibrutinib and acalabrutinib to support clinical finding
- These data suggest that zanubrutinib may provide a therapeutic option in patients intolerant to other BTKi across hematologic malignancies

AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor.

DISCLOSURES

MS served as a consultant for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, MorphoSys, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Atara Biotherapeutics, and Adpatimmune Therapeutics, received research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, and GenMab.
IF served as a consultant for AbbVie, AstraZeneca, BeiGene, Century Therapeutics, Genentech, Gilead Sciences, Great Point Partners, Hutchison MediPharma, Iksuda Therapeutics, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Novartis, Nurix Therapeutics, Pharmacyclics, Roche, Seagen, Seattle Genetics, Servier Pharmaceuticals, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, Vincerx Pharama, and Yingli Pharmaceuticals, and received research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, Loxo, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, SeaGen, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp, Unum Therapeutics, and Verastem.
MYL served as a consultant for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BeiGene, Gilead Sciences, Janssen, Jazz, Karyopharm, MorphoSys, Seattle Genetics, Takeda, TG Therapeutics, Dova, Epizyme, GSK, and Novartis; received honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BeiGene, Gilead Sciences, Janssen, Jazz, Karyopharm, MorphoSys, Seattle Genetics, Takeda, and TG Therapeutics; is on the speaker's bureaus for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BeiGene, Gilead Sciences, Janssen, Jazz, Karyopharm, MorphoSys, Seattle Genetics, and Takeda; served as a promotional speaker for AbbVie, Amgen, Bristol Myers Squibb, Janssen, Karyopharm, MosphoSys, Seattle Genetics, Takeda, Dova, Epizyme, GSK, and Novartis.
JMB served as a consultant for AstraZeneca, MorphoSys, Verastem, Adaptive Biotechnologies, Genentech/Roche, Kura Oncology, Epizyme, AbbVie, BeiGene, Kymera, Bristol Myers Squibb, X4 Pharmaceuticals, and SeaGen and served on the speakers' bureaus for BeiGene and SeaGen.
JLC has received research funding from BeiGene.
EK has current employment at Comprehensive Cancer Centers of Nevada.
HAY has current employment at Texas Oncology; is on the speakers' bureaus for Janssen, AstraZeneca, BeiGene, Karyopharm, GSK, Sanofi, Amgen and Pharmacyclics; and holds stock in Karyopharm.
ACh has current employment at Medical Oncology Associates and holds stocks in Novartis.
PKT has current employment at Texas Oncology.
MDG has received honoraria from GSK, Karyopharm, and TG Therapeutics.
SM received honoraria from MorphoSys and hold stock in GenMab.
DYC, KB, YL have current employment and equity ownership with BeiGene.
AC has current employment, equity ownership, and received travel expenses from BeiGene.
LX has current employment at BeiGene and previous employment with AstraZeneca.
JPS served as a consultant for AbbVie, AstraZeneca, BeiGene, BMS, Lilly, Pharmacyclics, TG Therapeutics, and Centessa; honoraria from AbbVie, AstraZeneca, BeiGene, Lilly, Pharmacyclics, TG Therapeutics, ADC Therapeutics, and Genentech; holds stock and serves on the advisory board of Centessa.
RP, SFZ, JM, BF, SSR, THG have nothing to disclose.

ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study

This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene

We also extend our thanks to Adam Idoine, PhD, Xiaoping Zhang, MD, and Ravi Vijayakumar for their contribution in developing the poster