Phase 2 Study of Zanubrutinib in Patients With Previously Treated B-Cell Malignancies Intolerant to Ibrutinib/Acalabrutinib

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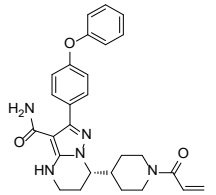
Introduction



- BTK inhibitors have been shown to improve outcomes in patients with CLL/SLL; however, AEs were the most common reason for ibrutinib or acalabrutinib discontinuation (median time ≤6 months)[1,2]
- Off-target effects of ibrutinib have been implicated in BTK inhibitor-related AEs
- Zanubrutinib, a BTK inhibitor approved for treatment of MCL and in development for other hematologic malignancies, was engineered to optimize selectivity and maximize BTK occupancy
- In the head-to-head ASPEN trial of zanubrutinib vs ibrutinib in patients with WM, zanubrutinib showed a lower rate of AEs leading to death (1% vs 4.1%), discontinuation (4% vs 9.2%), dose reduction (13.9% vs 56.1%), and dose holds (46.5% vs 56.1%); and a lower rate of atrial fibrillation (2% vs 14%)[3]

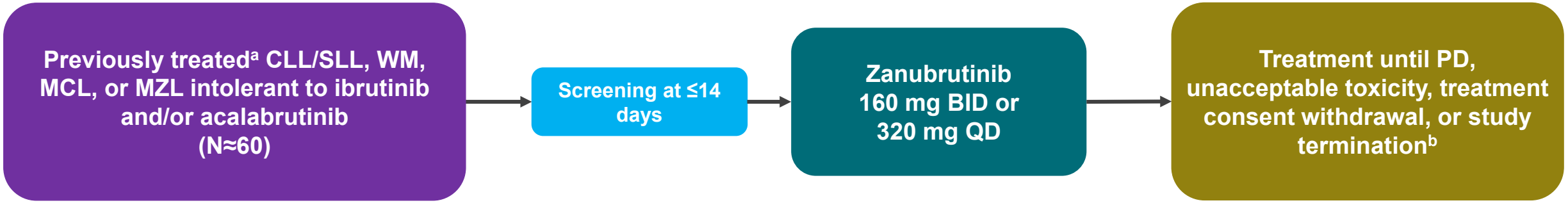
Objectives

- This is a phase 2, multicenter, US, single-arm, open-label study of the safety and efficacy of zanubrutinib in 60 ibrutinib and/or acalabrutinib–intolerant patients with previously treated B-cell malignancies (CLL/SLL, MCL, MZL, or WM)
  - Primary objectives: To evaluate the safety of zanubrutinib in patients with previously treated CLL/SLL, WM, MCL, or MZL intolerant to prior ibrutinib and/or acalabrutinib treatment as defined per protocol, compared with their ibrutinib and/or acalabrutinib intolerance AE profile as assessed by the recurrence and the change in severity of AEs
  - Secondary objectives: investigator-assessed ORR, investigator-assessed PFS, and patient-reported outcomes

AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

1. Mato et al. *Haematologica.* 2018;103:874. 2. Yazdy et al. *Blood.* 2019; Supplement1: 4311. 3. Dimopoulos et al. EHA 2020. Abstract S225.

Study Design



Key Inclusion Criteria

- Meets disease criteria for treatment in respective disease prior to initiation of ibrutinib or acalabrutinib
- Ibrutinib and/or acalabrutinib intolerance
  - ≥1 Grade ≥2 non-hematologic toxicity for >7 days
  - ≥1 Grade ≥3 non-hematologic toxicity for any duration
  - ≥1 Grade 3 neutropenia with infection or fever
  - Grade 4 hematologic toxicity that persists until ibrutinib therapy is discontinued due to toxicity NOT until progression
- Resolution of ibrutinib- and/or acalabrutinib-related toxicities to grade ≤1 or baseline prior to initiating treatment with zanubrutinib
- ECOG PS ≤2
- ANC ≥1000/mm^3 and platelet count ≥50,000/mm^3

Key Exclusion Criteria

- Documented disease progression during any BTKi treatment
- Current or past Richter transformation
- History of ischemic stroke 180 days before first zanubrutinib dose
- History of CNS hemorrhage
- Known infection with HIV
- Active HBV or HCV
- History of opportunistic infection while on ibrutinib and/or acalabrutinib
- Clinically significant cardiovascular disease
- Requires ongoing corticosteroid treatment >10 mg daily of prednisone or equivalent corticosteroid

ANC, absolute neutrophil count; BID, twice daily; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.
[a]There is a ≥7-day washout period for any anticancer therapy other than immunotherapy and a ≥4-week washout period for immunotherapy, taken alone or as part of a chemoimmunotherapy regimen. [b]Safety follow-up 30 days after end of treatment.

Patient Demographics and Baseline Characteristics

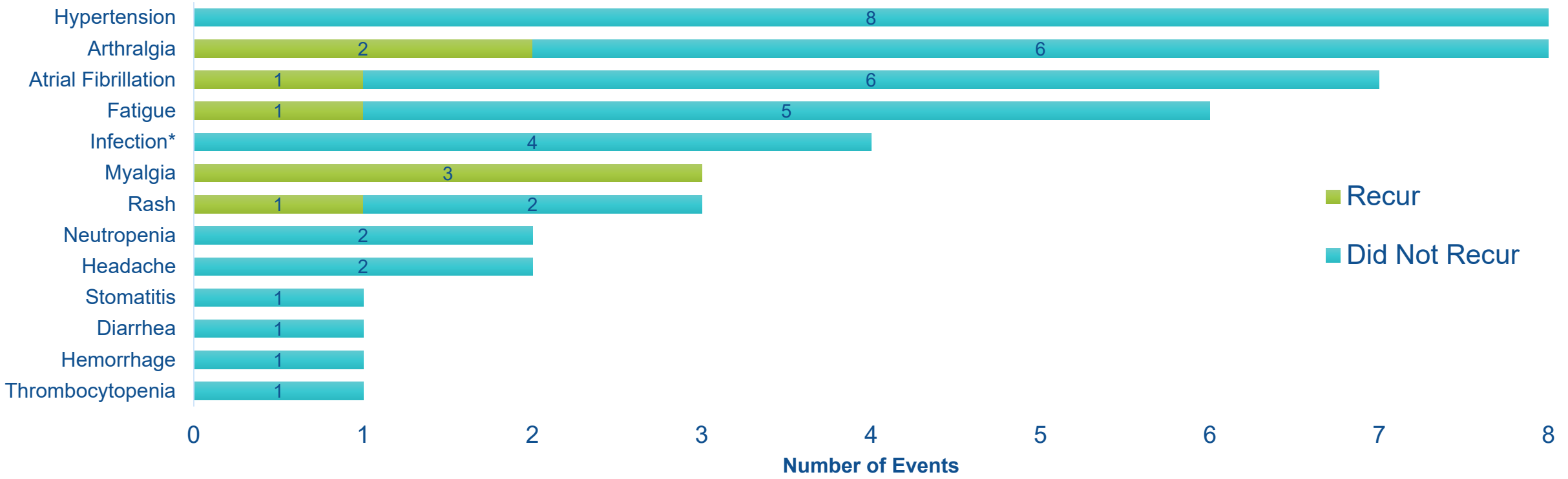
Data Cutoff: 28Aug2020

Characteristics	CLL (n=20)	SLL (n=5)	MCL (n=2)	WM (n=5)	Total (N=32)
Median age, y (range)	70.5 (49-87)	69.0 (53-91)	72.0 (65-79)	74.0 (58-80)	70.5 (49-91)
Male/Female, n (%)	12 (37.5)/8 (25)	2 (6.3)/3 (9.4)	2 (6.3)/0 (0)	3 (9.4)/2 (6.3)	19 (59.4)/13 (40.6)
ECOG PS 0/1, n (%)	14 (43.8)/6 (18.8)	4 (12.5)/1 (3.1)	2 (6.3)/0 (0)	3 (9.4)/2 (6.3)	23 (71.9)/9 (28.1)
CLL Binet stage at study entry, n (%)					
Stage A	8 (40)	NA	NA	NA	NA
Stage B	9 (45)	NA	NA	NA	NA
Stage C	3 (15)	NA	NA	NA	NA
Prior therapy regimens, median (range)	1.0 (1, 5)	2.0 (1, 3)	3.5 (3, 4)	2.0 (1, 12)	2.0 (1, 12)
Prior BTKi use, n (%)					
Ibrutinib monotherapy	18 (56.3)	5 (15.6)	2 (6.3)	3 (9.4)	28 (87.5)
Ibrutinib combination therapy	3 (9.4)	0 (0)	0 (0)	2 (6.3)	5 (15.6)[a]
Acalabrutinib monotherapy	1 (3.1)	0 (0)	0 (0)	1 (3.1)	2 (6.3)[b]
Median time on the most recent prior BTKi, months (range)	8.8 (1.1, 37)	10.32 (1.9, 16)	6.41 (6.4, 6.4)	12.91 (1.6, 33.6)	9.64 (1.1, 37)
On-study zanubrutinib dosing regimen					
160 mg BID	19 (59.4)	4 (12.5)	0 (0)	4 (12.5)	27 (84.4)
320 mg QD	1 (3.1)	1 (3.1)	2 (6.3)	1 (3.1)	5 (15.6)
Median study drug exposure, months (range)	4.42 (0.2, 7.0)	6.7 (2.7, 10.5)	1.71 (0.2, 3.3)	1.91 (1.1, 2.1)	3.5 (0.2, 10.5)

BID, twice daily; 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; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

[a]One patient received ibrutinib combination therapy followed by monotherapy. [b]All acalabrutinib patients also received ibrutinib.

Recurrence and Severity Change from Prior BTKi Exposure to Zanubrutinib Exposure



- Of the 66 ibrutinib intolerant events, 58 intolerant events (88%) did not recur
  - 8 ibrutinib intolerant events recurred, 7 (88%) recurred at a lower severity, and 1 (13%) recurred at the same severity
- Of the 4 acalabrutinib intolerant events, 2 intolerant events (both arthralgia) did not recur, 2 recurred (myalgia), one at lower grade and 1 at the same grade
- All grade 4 intolerant events (neutropenia [2], ALT increase [1], AST increase [1]) did not recur on zanubrutinib
- 23/25 grade 3 intolerant events did not recur while on zanubrutinib. 2/25 grade 3 intolerant events recurred on zanubrutinib

BTKi, Bruton tyrosine kinase inhibitor.
*Includes 1 event each of bronchitis, pneumonia, sinusitis, and subcutaneous abscess.

Safety (Summary)

Category, n (%)	CLL (N=20)	SLL (N=5)	MCL (N=2)	WM (N=5)	Total (N=32)
Patients with at least 1 AE	16 (80)	5 (100)	1 (50)	4 (80)	26 (81.3)
Grade ≥3	2 (10)[a]	1 (20)[b]	0 (0)	0 (0)	3 (9.4)
Serious AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AE leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AE leading to dose interruption	1 (5)[c]	0 (0)	0 (0)	0 (0)	1 (3.1)
AE leading to dose reduction	0 (0)	0 (0)	0 (0)	1 (20)[d]	1 (3.1)

- There were no SAEs and no treatment discontinuation due to AEs

AE, adverse event; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; QD, once daily; SAE, serious adverse event; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.
[a]Syncope and neutrophil count decrease. [b]Neutropenia. [c]Grade 2 dizziness. [d]Grade 2 myalgia, left calf.

Safety

- The most common grade ≥3 AEs:
  - Neutropenia/neutrophil count decrease (n=2 [6.2%])
  - Syncope (n=1 [3.1%]), all grade 3
- Bleeding events occurred in 8 (25%) patients:
  - 7 patients (21.9%), grade 1
  - 1 patient (3.1%), grade 2
- Atrial fibrillation and flutter occurred in 1 patient (grade 2; 3.1%); this is a recurrence of an intolerant event
- Infections occurred in 4 (12.5%) patients:
  - 1 patient (3.1%), grade 1
  - 3 patients (9.4%), grade 2
- Anemia occurred in 1 patient (3.1%, grade 1)
- Thrombocytopenia/platelet count decrease occurred in 2 patients (6.3%, grade 1)

Most Common AEs in ≥5% of Patients, n (%)	All Grades (N=32)	Grades ≥3 (N=32)
Myalgia	7 (21.9)	0
Contusion	6 (18.8)	0
Cough	5 (15.6)	0
Dizziness	5 (15.6)	0
Fatigue	4 (12.5)	0
Diarrhea	3 (9.4)	0
Skin laceration	3 (9.4)	0
Arthralgia	2 (6.3)	0
Constipation	2 (6.3)	0
Petechiae	2 (6.3)	0
Pruritis	2 (6.3)	0
Rash	2 (6.3)	0
Rhinorrhea	2 (6.3)	0

AE, adverse event.

Best Overall Response by Investigator Assessment in Patients With >90 Days of Follow-Up (First Assessment)

Response[a]	CLL (n=13)	SLL (n=4)	MCL (n=1)	Total (N=18)
Maintained or improved response on zanubrutinib	12 (92.3)	4 (100)	1 (100)	17 (94.4)
ORR, n (%) [Improved response on zanubrutinib]	5 (38.5)	4 (100)	0 (0)	9 (50)
PR	2 (15.4)	4 (100)	0 (0)	6 (33.3)
PR with lymphocytosis	3 (23.1)	NA	NA	3 (16.7)
SD [Maintained response on zanubrutinib]	7 (53.8)	0 (0)	1 (100)	8 (44.4)
Not done[b]	1 (7.7)	0 (0)	0 (0)	1 (5.6)
Median time to first response, weeks (range)	12.6 (12-13)	16.2 (12-24)	NA	12.6 (12-24)

- One patient (3.2%) with CLL developed syncope and withdrew from the study
- The 4 patients with WM were on study <90 days and have not reached first assessment
- No patients have developed disease progression

CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; NA, not applicable; ORR, overall response rate; PR, partial response; SD, stable disease; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

[a] Disease parameter (imaging and laboratory parameters) performed at study entry were used as the baseline for response assessment. [b]Patient withdrew from study due to syncope, prior to first assessment timepoint.

Conclusions

- Intolerable AEs experienced on ibrutinib and/or acalabrutinib were unlikely to recur while on zanubrutinib
  - 88% (58/66) of ibrutinib intolerant events and 50% (2/4) of acalabrutinib intolerant events did not recur while on zanubrutinib
  - Of the intolerant events that recurred, 88% (7/8) of ibrutinib intolerant events and 50% (1/2) of acalabrutinib intolerant events recurred at a lower severity
  - No recurrence of a prior intolerant event led to zanubrutinib discontinuation
- Zanubrutinib was tolerable and effective in patients who discontinued ibrutinib and/or acalabrutinib due to adverse events
  - At a median follow-up of 3.5 months, 31 (96.9%) patients remain on study
  - Zanubrutinib maintained (44.4%) or improved (50%) the response in a vast majority of patients compared with prior BTKi treatment
  - No patient discontinued zanubrutinib due to AEs
- The study was limited by a short follow-up period; as a result, data may change with longer follow-up
- These data suggest that zanubrutinib may provide a therapeutic option in patients intolerant to other BTK inhibitors

AE, adverse event; BTK, Bruton tyrosine kinase.

Disclosures

- **MS:** consultancy from AbbVie, Sound Biologics, Genentech, AstraZeneca, Bristol Myers Squibb, Verastem, ADC Therapeutics, Atara Biotherapeutics, Cellectar, Pharmacyclics, BeiGene, and MorphoSys, research funding from TG Therapeutics, MustangBio, Celgene, a Bristol Myers Squibb company, Sunesis, and Gilead, recently ended employment at Acerta Pharma
- **JPS:** research funding from BeiGene, consultancy and research funding from Genentech, AstraZeneca, Pharmacyclics, Pfizer, AbbVie, TG Therapeutics, Acerta, Roche, Celgene, a Bristol Myers Squibb company, Bristol Myers Squibb
- **MYL:** consultancy, research funding, and speakers' bureau from BeiGene, consultancy, honoraria, and research funding from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Karyopharm, Sanofi, Seagen, and Takeda
- **JM:** membership on a board of directors or advisory committee at Highmark Blue Cross
- **SFZ:** research funding from Sarah Cannon Research Institute, honoraria from Karyopharm, honoraria and travel expenses from AstraZeneca and Bristol Myers Squibb
- **BBF:** N/A
- **JMB:** speakers' bureau at Seagen, consultancy for Gilead, Bristol Myers Squibb, Roche, AbbVie, Bayer, AstraZeneca, Verastem, MorphoSys, Adaptive Biotechnologies, Epizyme, Kura, Celgene, a Bristol Myers Squibb company
- **JLC:** speakers' bureau for Celgene, a Bristol Myers Squibb company, Acrotech, Verastem
- **HAY:** consultancy for AstraZeneca, Amgen, Karyopharm, Epizyme, Celgene, a Bristol Myers Squibb company, and TG Therapeutics, board of directors or advisor for AstraZeneca, Amgen, Karyopharm, and Celgene, a Bristol Myers Squibb Company, speakers' bureau for AstraZeneca, Amgen, Karyopharm, BeiGene, Janssen, Takeda, and Sanofi, stock ownership at Karyopharm and Epizyme, research funding from BeiGene and Janssen, travel expenses from AstraZeneca, Amgen, Karyopharm, BeiGene, and Janssen
- **D-YC:** current employment and stock ownership at BeiGene
- **XZ:** current employment and stock ownership at BeiGene
- **AC:** current employment and stock ownership at BeiGene
- **SR:** stock ownership at Amgen and BeiGene, current employment at BeiGene
- **JH:** current employment, stock ownership, and travel expenses from BeiGene
- **IWF:** current employment at Sarah Cannon Research Institute, consultancy from AbbVie, AstraZeneca, BeiGene, Curio Science, Gilead Sciences, Great Point Partners, Iksuda Therapeutics, Janssen, Juno, a Bristol Myers Squibb company, Kite Pharma, MorphoSys, Nurix Therapeutics, Pharmacyclics, Roche, Seagen, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, Yingli Pharmaceutical (all payments to institute), equity in Johnson & Johnson, research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, a Bristol Myers Squibb Company, Constellation Pharmaceuticals, Curis, F. Hoffman-La Roche, 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, Roche, SeaGen, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem (all funding to Institute).

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