4463 A First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase (BTK) Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B Cell Malignancies

Program: Oral and Poster Abstracts

Session: 626. Aggressive Lymphomas: Prospective Therapeutic Trials: Poster III

Hematology Disease Topics & Pathways:

Therapies

Monday, December 11, 2023, 6:00 PM-8:00 PM

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Introduction: Although BTK inhibitors (BTKi) are effective therapeutics in the treatment of B cell malignancies, emerging BTK resistance mutations in chronic lymphocytic leukemia (CLL), as well as potential growth-promoting kinase-independent scaffolding function of BTK, present a need for improved or new approaches. Additionally, preclinical and clinical data in non-Hodgkin’s lymphoma (NHL) suggest that drugs modulating cereblon may synergize with BTKi to provide a therapeutic effect. NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines BTK degradation with the immunomodulatory activity of an

Ikaros and Aiolos degrader. Preliminary safety of NX-2127 in patients across B cell malignancies and efficacy in patients with CLL have been presented previously [Mato et al. 2022; Danilov et al. 2023]. Here we report further safety and efficacy follow-up in patients with CLL and efficacy data in patients with NHL enrolled to date.

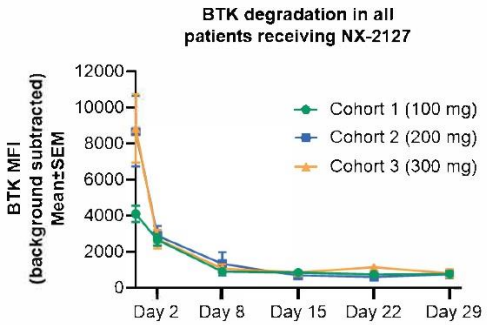
Methods: NX-2127-001 (NCT04830137) is a first-in-human, multicenter, open-label, dose-escalation (Phase 1a) and cohort-expansion (Phase 1b) trial evaluating the safety and preliminary efficacy of NX-2127 in adults with relapsed/refractory B cell malignancies, including CLL, diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenstrom's macroglobulinemia (WM). NX-2127 is administered orally once daily in 28-day cycles.

Results: As of 9 June 2023, 47 patients were enrolled and treated with NX-2127 at once-daily doses of 100 mg (n=28), 200 mg (n=10), and 300 mg (n=9). Patients were predominantly male (66%), with a median age of 74 (range 50–92) years. Twenty-nine patients were treated for CLL/small lymphocytic lymphoma, 5 DLBCL (2 GCB [Germinal-center B-cell-like], 3 non-GCB), 5 MCL, 3 MZL, 3 WM, and 2 FL. Patients enrolled were heavily pretreated with median prior lines of therapy of 4 (range 2–10) in NHL and 5 (range 2–11) in CLL. Prior treatments in patients with CLL comprised: BTKi 100% (including covalent [cBTKi] and non-covalent [ncBTKi] inhibitors); BCL2 inhibitor 76%, with a large proportion of CLL patients exhibiting BTKi resistance mutations at baseline. Prior treatments in patients with NHL included: BTKi 72% (cBTKi and ncBTKi); bispecific antibody 1/18; bispecific antibody and CAR-T 1/18. There were two reported dose-limiting toxicities: one previously reported cognitive disturbance in a patient with CLL treated at 300 mg; and neutropenia in a patient with MZL treated at 300 mg. The most common any grade treatment-emergent adverse events (TEAEs) were fatigue (48.9%), neutropenia (42.6%) and hypertension (36.2%, see Table). The most common grade ≥3 TEAEs were neutropenia (38.3%), hypertension (14.9%) and anemia (12.8%). Contusion was reported in 27.7% of patients (all below grade 3), atrial fibrillation in 12.8% of patients (6.4% grade ≥3). Most common reasons for treatment discontinuation were progressive disease (PD, 25.5%) and AE (21.3%). Median follow-up for the study was 9.5 (range 0.1–24.3) months. NX-2127 exhibited dose-dependent pharmacokinetics (PK) with a mean half-life of 2–4 days across cohorts. Rapid, robust and sustained BTK degradation was observed in all patients, regardless of their absolute BTK starting level, tumor type, or dose level of NX-2127 (Figure). In addition, degradation of the cereblon neo-substrate Ikaros was observed. Among the efficacy evaluable patients with CLL, there were 9 PRs/PR with rebound lymphocytosis; additionally, 11 patients had SD at the time of data cut-off and 4 had PD. Two patients with WM were treated and efficacy evaluable (1 SD, 1 PD). Among the efficacy evaluable patients with NHL, there were 2 CRs and 1 PR; additionally, 3 patients had SD, and 5 had PD. Two CRs are ongoing with 9.2 and 11.8 months of duration.

Conclusion: This first-in-human study of NX-2127 is actively enrolling and dose-expansion cohorts in DLBCL and MCL have been initiated at the 300 mg daily dose. Findings include dose-dependent PK accompanied by degradation of BTK and Ikaros. Encouraging and persistent responses were observed in heavily pretreated patients with relapsed/refractory CLL and NHL with a manageable safety profile. These data support the

treatment concept of combining immunomodulatory activity and BTK degradation in a single molecule and support further development of NX-2127 in B cell malignancies.

Figure. BTK expression in all patients receiving NX-2127



Dose (mg)	Number of patients per day				
100	27	23	22	21	19
200	9	8	9	7	6
300	7	5	6	4*	3

*1 out of 4 patients had dose modification from Day 19 onwards

Table. Frequency of any grade TEAEs in ≥20% of patients or grade ≥3 TEAEs in >1 patient (N=47)

Adverse events, n (%)	TEAEs Any grade	TEAE grade ≥3
Fatigue	23 (48.9)	–
Neutropenia[a]	20 (42.6)	18 (38.3)
Hypertension	17 (36.2)	7 (14.9)
Diarrhea	14 (29.8)	–
Contusion[b]	13 (27.7)	–
Anemia	12 (25.5)	6 (12.8)
Thrombocytopenia[c]	12 (25.5)	3 (6.4)
Constipation	11 (23.4)	–
Dyspnea	10 (21.3)	1 (2.1)
Pruritis	10 (21.3)	1 (2.1)
Pneumonia	6 (12.8)	3 (6.4)
COVID	6 (12.8)	3 (6.4)
Atrial fibrillation	6 (12.8)	3 (6.4)
Leukocytosis	3 (6.4)	3 (6.4)
Lymphocyte count increased	2 (4.3)	2 (4.3)
Sepsis	2 (4.3)	2 (4.3)

[a]Aggregate of 'neutropenia' and 'neutrophil count decreased'; [b]Contusion includes episodes of bruising and other similar terms; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'.

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OffLabel Disclosure: NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines BTK degradation with the immunomodulatory activity of an Ikaros and Aiolos degrader.

3276 Clinical Outcomes with Venetoclax-Based Treatment Regimens in Patients with Chronic Lymphocytic Leukemia (CLL)

Program: Oral and Poster Abstracts

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster II

Hematology Disease Topics & Pathways:

Research, Lymphoid Leukemias, adult, CLL, Clinical Research, Diseases, real-world evidence, Therapies, Lymphoid Malignancies, Study Population, Human

Sunday, December 10, 2023, 6:00 PM-8:00 PM

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INTRODUCTION

We aim to identify factors that impact outcomes of venetoclax for patients with CLL treated in routine practice at a tertiary center. We report on the use of venetoclax in the most frequently encountered disease scenarios: first-line, relapsed/Bruton tyrosine kinase inhibitor (BTKi)-naïve, and relapsed/BTKi-exposed.

METHODS

We identified patients who received venetoclax therapy for CLL (between 4/2012–4/2023) from the Mayo Clinic CLL Database. Undetectable measurable residual disease (uMRD) was defined as <1 CLL cell per 10,000 leukocytes using 8-color flow cytometry on peripheral blood (PB) or bone marrow (BM). Overall survival (OS) was defined as the time from venetoclax start until date of death or last known to be alive. Treatment-free survival (TFS) after venetoclax was defined as the time from venetoclax start until the earliest of date of next

treatment, or death. Kaplan–Meier was used to display OS and TFS. Multivariable Cox proportional hazards regression models were used to estimate associations of factors with time-to-event outcomes.

RESULTS

A total of 155 patients received venetoclax: firstline therapy (in combination with obinutuzumab, n=55) and relapsed CLL (n=100; 17 had relapsed/BTKi-naïve CLL, and 83 had previously received BTKi [55 with progression after BTKi], relapsed/BTKi-exposed). The median follow-up for the cohorts of first-line therapy, relapsed/BTKi-naïve, and relapsed/BTKi-exposed was 12.9 months, 37.0 months, and 27.6 months, respectively. Baseline characteristics at the time of venetoclax initiation for all patients are shown in *Table 1*. The median TFS for the overall cohort was 39.0 months. The median OS was 54.6 months.

Among patients treated with venetoclax as first-line therapy (n=55), the 2-year TFS (*Figure 1*) and 2-year OS rates were both 91%. MRD testing was performed in 28 patients and was uMRD in 23 (82%) patients (only PB assessed, n=7; only BM assessed, n=2; PB and BM assessed, n=14). Detectable MRD was identified in 3 patients, and 2 patients had discordant results (PB uMRD and BM detectable disease).

Among patients treated with venetoclax in the relapsed/BTKi-naïve setting (n=17), the 2-year TFS rate was 73% (*Figure 1*) and the 2-year OS rate was 100%. MRD testing was performed in 7 patients and was uMRD in all 7 (100%) (only PB assessed, n=3; only BM assessed, n=2; PB and BM assessed, n=2). The median time to first uMRD result was 14.1 months.

Among relapsed/BTKi-exposed venetoclax-treated patients (n=83), the median TFS was 26.9 months (*Figure 1*), and the median OS was 39.4 months. In this subgroup, the median TFS for patients with (n=55) and without (n=28) prior disease progression on prior BTKi were 22.3 and 42.3 months, respectively. Median TFS with venetoclax monotherapy (n=30) was 24.0 months, venetoclax in combination with rituximab (n=37) was 26.9 months, and venetoclax in combination with obinutuzumab (n=16) was 39.0 months. BTKi-exposed patients that were chemotherapy-naïve (n=27) and chemotherapy-exposed (n=56) had median TFS of 29.1 and 24.0 months, respectively. MRD testing was performed in 28 patients and was uMRD in 16 (57%) patients (only PB assessed, n=9; only BM assessed, n=2; PB and BM assessed, n=5). Detectable MRD was identified in 11 patients, and 1 had discordant results (PB uMRD and BM detectable disease). The median time to first uMRD result was 11.5 months.

TP53 disruption, unmutated *IGHV* genes, older age, complex karyotype (CK; defined as more than 3 chromosomal aberrations on CpG stimulated karyotype), and disease progression on prior BTKi were associated with shorter TFS in the overall cohort on univariate analysis. *TP53* disruption, older age, CK, and disease progression on prior BTKi were associated with shorter OS in the overall cohort on univariate analysis. Multivariable analysis was performed by including only those patients where all variables significant in univariable analysis were available (OS model n=65, TFS model n=53). In these models, only CK was significantly associated with shorter TFS (HR 8.5; 95%CI 2.5-29.1; P<0.001) and shorter OS (HR 4.1; 95%CI 1.2-14; P=0.03).

CONCLUSIONS

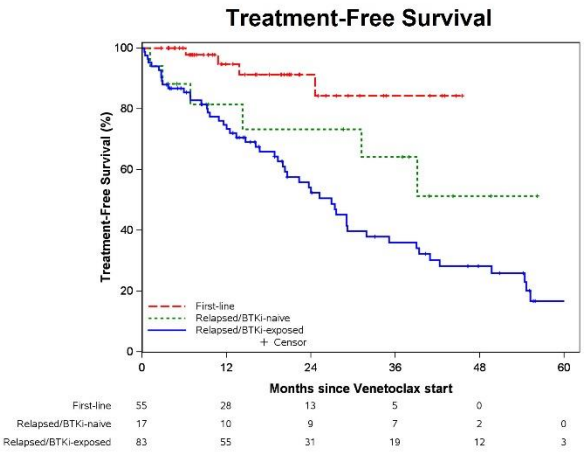
Patients with BTKi-exposed CLL, particularly those with prior disease progression on BTKi, had worse outcomes. Our study identified CK as one of the most important baseline predictors of adverse TFS and OS in the overall cohort of patients, supporting karyotype assessment for prognostication prior to venetoclax treatment.

Table 1: Baseline characteristics at the time of venetoclax start

Parameter		Number (%) or Median [range]			
		All patients	Firstline	Relapsed/ BTKi-naïve	Relapsed/BTKi-exposed
N		**155**	**55**	**17**	**83**
Age, years		66 [41-93]	65 [41-84]	67 [51-83]	68 [43-93]
Males		108 (70)	36 (66)	12 (71)	60 (72)
Prior lines of therapy		1 [0-11]	0	1 [1-6]	3 [1-11]
Combination with anti-CD20mAb	Rituximab	45 (29)	0 (0)	8 (47)	37 (45)
	Obinutuzumab	80 (52)	55 (100)	9 (53)	16 (19)
	Monotherapy	30 (19)	0 (0)	0 (0)	30 (36)
Rai stage, n=148	0	20 (14)	2 (4)	2 (13)	16 (20)
	I-II	62 (42)	30 (58)	5 (31)	27 (34)
	III-IV	66 (45)	20 (39)	9 (56)	37 (46)
Absolute Lymphocyte Count (x 10^9/L)*, n=150		22.4 [0-539]	80.7 [0-539]	16.2 [4-108]	13.0 [0.3-533]
IGHV mutation status*, n=129	Unmutated	93 (72)	20 (39)	8 (57)	8 (13)
FISH*, n=134	None detected	20 (15)	11 (21)	4 (27)	5 (8)
	Other	5 (4)	0 (0)	0 (0)	5 (8)
	13q-	34 (25)	16 (30)	4 (27)	14 (21)
	Trisomy 12	23 (17)	11 (21)	2 (13)	10 (15)
	11q-	28 (21)	13 (25)	4 (27)	11 (17)
	17p-	24 (18)	2 (4)	1 (7)	21 (32)
Complex karyotype*, n=69	Complex (≥3 abnormalities)	27 (39)	3 (12)	3 (38)	21 (58)
TP53 Disruption (either del17p or *TP53* mutation)*, n=136	Present (Abnormal)	32 (24)	2 (4)	2 (13)	28 (41)

*not available for all patients

Figure 1: Treatment-free survival from the start of venetoclax for patients grouped by disease scenario



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108 Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter's Transformation: An International Multicenter Retrospective Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Cellular Therapy for B Cell Lymphomas: Prospective Clinical Trials and Real World Data

Hematology Disease Topics & Pathways:

Lymphoid Leukemias, Biological therapies, CLL, Lymphomas, non-Hodgkin lymphoma, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, aggressive lymphoma, Therapies, Lymphoid Malignancies

Saturday, December 9, 2023: 10:45 AM

Adam S Kittai, MD[1], *David A. Bond, MD, BS*[2], *Ying Huang, MS, MA*[3], *Seema A Bhat, MD*[1], *Emily Blyth, MD, PhD*[4], *John C. Byrd, MD*[5], *Julio C Chavez, MD*[6], *Matthew S. Davids, MD, MMSc*[7], *Jamie P Dela Cruz*[7*], *Mark R Dowling, MBBS, PhD*[8*], *Caitlyn Duffy*[7*], *Carrie I Ho, MD*[9], *Caron A Jacobson, MD, MMSc*[10], *Samantha M. Jaglowski, MD, MPH*[1], *Nitin Jain, MD*[11], *Kevin H Lin, MD*[12*], *Christine McCarthy, BS*[13*], *Erin M Parry, MD, PhD*[7], *Manoj Rai, MD*[14*], *Kerry A Rogers, MD*[3], *Aditi Saha, MBBS*[6], *Levanto Schachter, DO, MS*[15], *Hamish Scott, MD*[8*], *Jayastu Senapati, MD, MBBS, DM*[11], *Mazyar Shadman, MD, MPH*[9], *Tanya Siddiqi, MD*[16], *Deborah M. Stephens, DO*[17], *Vinay Vanguru, MBBS, FRACP, FRCPA*[18*], *William G. Wierda, MD, PhD*[19], *Omer Zulfa, MD*[5*], *Jennifer A. Woyach, MD*[3] *and Philip A. Thompson, MBBS*[20*]

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Background:

Aggressive lymphoma, most commonly large B-cell lymphoma (LBCL), arising in the setting of chronic lymphocytic leukemia (CLL) is known as Richter's transformation (RT), and is associated with poor outcomes. CD19 CART has revolutionized the treatment (tx) of LBCL, with durable responses for patients (pts) with relapsed/refractory disease. Pts with RT have been excluded from most major CD19 CART trials. Therefore, there is limited data describing outcomes of pts with RT receiving CD19 CART

Methods:

We conducted an international multicenter retrospective study of pts with RT who received CD19 CART approved for hematologic malignancies at 9 academic centers. RT was defined as pts with LBCL with preceding or concurrently diagnosed CLL. We collected pt, disease, and tx characteristics. Progression-free survival (PFS) and overall survival (OS) were measured from date of CD19 CART infusion and estimated using the Kaplan-Meier method. Cox regression model was used to associate prognostic factors with PFS and OS. Response was assessed by Lugano criteria.

Results:

62 pts were included. Median age at CD19 CART infusion was 65 (range: 27-80). Median prior lines of therapy for CLL or RT were both 2 (CLL range: 0-10, RT range: 0-7). 52 (84%) pts previously received a Bruton tyrosine kinase inhibitor (BTKi) or BCL2 inhibitor (BCL2i) for CLL or RT. Median Ki-67 on pathology sample was 80% (range: 40-100), median SUV on brightest lymph node (LN) on PET-CT was 15.0 (range: 3-50.6), median size of largest LN was 3.8cm (range: 0-16), and median LDH prior to CD19 CART was 244 (range: 96-2878, ULN range: 190-271). Median time from apheresis to CD19 CART infusion was 33 days (range: 24-100), and 52 (84%) pts received bridging therapy. 40 (65%), 14 (23%), 7 (11%), and 1 (2%) pts received axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), and brexucabtagene autoleucel (brexu-cel), respectively.

Overall response rate was 65%, with 29 (47%) and 11 (18%) pts attaining complete response (CR) and partial response (PR), respectively. After a median follow up of 24.1 months (mos) from CD19 CART infusion, the median PFS was 4.7 mos (95% CI: 2.3-6.9), and median OS was 8.5 mos (95% CI: 5.1-32.5) (Figure). Median duration of response was 14.5 mos (95% CI: 4.0-NR), with a median not reached (NR) (95% CI: 13.1-NR) for pts

who achieved a CR, and a median of 2.3 mos (95% CI: 1.0-3.3) for pts who achieved a PR. Among 39 pts who died, 28 (72%) died due to progression of disease (PD), and 11 (28%) died for other reasons including 8 infections (4 COVID), 1 septic shock, 1 stroke, and 1 respiratory failure. The cumulative incidence of non-relapse mortality at 12 mos was 13% (95% CI: 6.2-23.4). 3 pts in a CR underwent allogeneic stem cell transplantation, 2 were alive at last known follow up (3.9 and 24.2 mos post-transplant), and 1 pt died from PD 21 mos post-transplant. 55 (89%) pts had CRS, with 9 (15%) grade ≥3 events. 43 (69%) pts had ICANS, with 23 (38%) grade ≥3 events.

On univariable analysis, increasing Ki-67 and LDH were found to be associated with worse PFS and OS, and attaining a CR with CD19 CART was found to be associated with improved PFS and OS. On multivariable analysis, increasing Ki-67 and LDH, and greater number of prior lines of therapy for RT were independent prognostic variables for worse PFS and OS, and attaining a CR was associated with improved OS. All other variables, including type of CD19 CART product received, were not correlated with PFS or OS (Table).

Conclusions:

We report findings from the largest cohort of pts with RT who received CD19 CART. Of note, 84% of pts were exposed to either BTKi or BCL2i for the tx of CLL or RT. RT remains a disease of unmet need, as the median OS was 8.5 mos in this study. However, there is some progress made as historically the median OS for patients with RT previously treated with BTKi is 4 mos (Kittai et al AJH 2023). Given higher number of prior therapies is associated with worse OS, earlier use of CD19 CART in the RT disease course may be warranted. Our data support the use of CD19 CART for pts with RT, with durable disease control in a subset of pts, however there is clear room to improve and develop better therapies. Given observed high response rate to CD19 CART, along with most pts experiencing early relapse, allogeneic stem cell transplantation at response should be

considered. Prospective clinical trials evaluating CD19 CART with novel agents for RT are currently ongoing.

Figure. PFS and OS of patients receiving CD19 CART for RT.

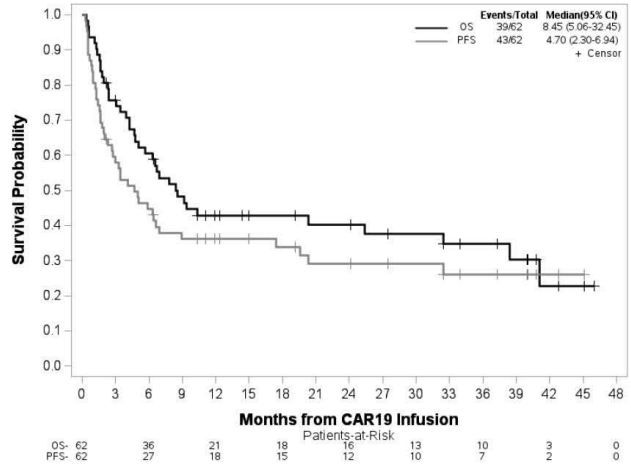

Table. Univariable and Multivariable Cox Model for OS

	Univariable Models		Multivariable Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at CD19 CART infusion, 5-years older	1.00 (0.86-1.16)	0.98	-	-
# prior lines of therapy for CLL prior to RT	1.11 (0.92-1.32)	0.27	-	-
# prior lines of therapy for RT prior to CART	1.31 (1.02-1.68)	0.04	1.68 (1.29-2.20)	0.0001
Total prior lines of therapy	1.17 (1.02-1.35)	0.03	-	-
Presence of del17p or TP53 in preceding CLL	0.99 (0.49-2.04)	0.99		
Ever received prior BTKi or Ven for CLL or RT, vs No				
Received BTKi or BCL2i for CLL but not RT	2.66 (0.69-10.18)	0.15	-	-
Received BTKi or BCL2i for RT but not CLL	2.12 (0.69-6.48)	0.19	-	-
Received BTKi or BCL2i for both CLL and RT	1.19 (0.44-3.18)	0.73	-	-
Ki-67, 10% higher	1.44 (1.12-1.84)	0.0045	1.43 (1.10-1.86)	0.0083
LDH, 2-fold increase	1.95 (1.40-2.71)	<.0001	1.56 (1.03-2.37)	0.04
SUV, 1-unit increase	1.01 (0.99-1.04)	0.29	-	-
Size of LN, 1-cm increase	1.01 (0.92-1.10)	0.87	-	-
Received BTKi concurrently with CART*	0.73 (0.39-1.37)	0.32	-	-
Days from apheresis to CD19 CART, 5 more days	1.05 (0.93-1.19)	0.46	-	-
Received bridging therapy	1.25 (0.49-3.21)	0.64	-	-
Achieving CR vs. not achieving CR**	0.19 (0.08-0.46)	0.0003	0.17 (0.05-0.59)	0.0052
Types of CD19 CART therapy, vs Brexu-cel or Liso-cel				
Axi-cel	0.78 (0.30-2.06)	0.62	-	-
Tisa-cel	0.63 (0.21-1.89)	0.41	-	-

* Received BTKi as part of the most recent therapy prior to apheresis, or as part of the bridging tx or concurrently with CD19 CART.

** Entered model as a time dependent variable.

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1737 Pirtobrutinib in Richter Transformation: Updated Efficacy and Safety Results with 18-Month Median Survival Follow-up from the Phase 1/2 BRUIN Study

Program: Oral and Poster Abstracts

Session: 626. Aggressive Lymphomas: Prospective Therapeutic Trials: Poster I

Hematology Disease Topics & Pathways:

Research, clinical trials, Lymphoid Leukemias, CLL, Lymphomas, Non-Biological therapies, Clinical Research, B Cell lymphoma, drug development, Diseases, Therapies, Lymphoid Malignancies

Saturday, December 9, 2023, 5:30 PM-7:30 PM

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Background: Richter transformation (RT) occurs in up to 10% of patients with chronic lymphocytic leukemia (CLL), typically presents as an aggressive diffuse large B-cell lymphoma (DLBCL) and is associated with poor survival. RT has no approved standard therapy; and clinical trial enrollment is the preferred first line of therapy. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, that inhibits both wildtype and C481-mutant BTK with equal low nM potency, has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval. Pirtobrutinib demonstrated durable overall response rates (ORR) and was well tolerated in patients (pts) with poor-prognosis B-cell malignancies regardless of prior therapy. Here we provide updated safety and efficacy of pirtobrutinib in RT pts from the phase 1/2 BRUIN trial (NCT03740529).

Methods: Pts with previously treated, histologically confirmed RT were eligible in the global, multicenter, phase 1/2 BRUIN study. Pts with untreated RT became eligible after Amendment 10. All but one patient received the recommended phase 2 dose of 200 mg daily. Key endpoints included investigator-assessed ORR, DoR per Lugano 2014 criteria, OS, and safety. A data cut of 05 May 2023 was utilized. To assess clonal relationship, IGH rearrangement studies were done on tissue biopsies with RT involvement, and baseline blood or bone marrow (BM) samples with CLL involvement.

Results: Among all pts with RT (N=82) the median age was 67 (range, 26-95) and the median total number of lines of prior systemic therapy was 4 (range, 0-13). Pts with prior treatment had a median of 2 CLL-directed therapies and 2 RT-directed therapies. Eight pts did not have a previous line of RT-directed therapy, and 1 patient received neither RT- nor CLL-directed therapy. Common prior RT- and CLL-directed therapies (RT, CLL) included: chemotherapy (76%, 52%), cBTKi (34%, 62%), anti-CD20 antibody (78%, 66%), BCL2i (38%, 49%), stem cell transplant (SCT; 6%, 7%), and CAR-T (11%, 4%). Of 29 pts with bone marrow screening, 41.4% had CLL alone present in BM, 13.8% had DLBCL present and 24.1% had both CLL and DLBCL present. For 39 pts with available PET data, the median SUVmax was 19.1 (range, 2.6-41.2).

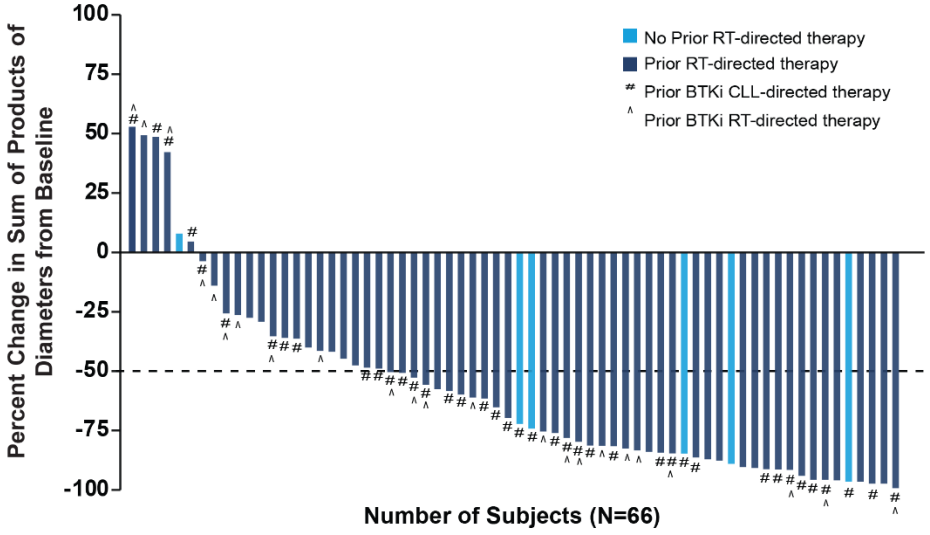
For all 82 pts, the ORR was 50.0% (95% CI, 38.7-61.3) including complete (13.4%, n=11) and partial (36.6%, n=30) responses. For 61 pts who received prior cBTKi therapy, the ORR was 45.9% (95% CI 33.1-59.2). Among

28 pts with an RT-directed cBTKi and 51 pts with prior CLL-directed cBTKi, the ORR was 42.9% (95% CI, 24.5-62.8) and 43.1% (95% CI, 29.3-57.8), respectively. In 50 pts who discontinued prior cBTKi due to disease progression, the ORR was 42.0% (95% CI, 28.2-56.8). At median follow-up time of 9.7 months, the median DoR for all 82 RT pts was 7.4 months (95% CI, 3.1-19.1) and the estimated rate at 12 months was 45.9% (95% CI, 28.3-61.8). The median time on treatment for the 41 pts who responded to treatment was 8.3 months. Eight pts stopped pirtobrutinib to pursue curative-intent allogeneic SCT and DoR was censored at the last preceding disease assessment. At a median survival follow-up of 18.3 months, the median OS for the entire RT cohort was 12.5 months (95% CI, 6.9-20.5). At 18 months, the OS rate was 44.3% (95% CI, 32.5-55.4).

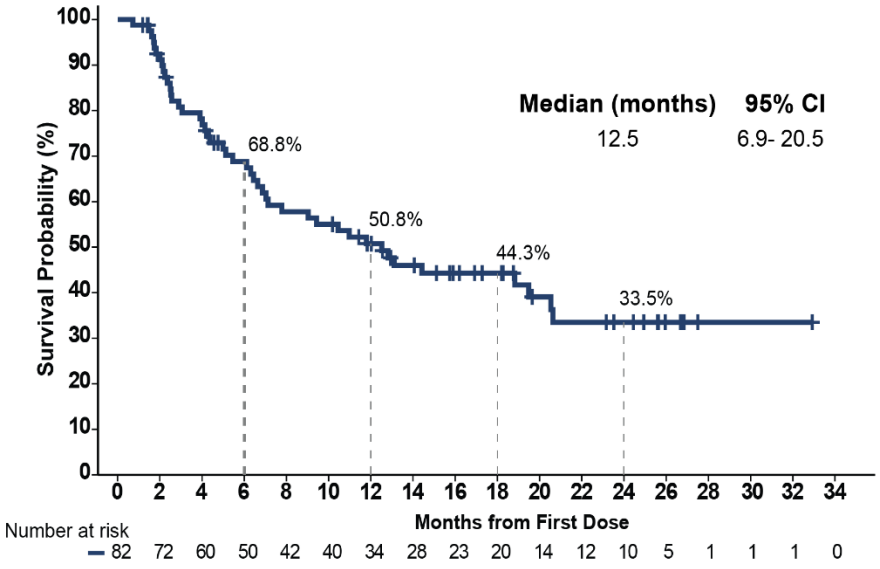
Frequent treatment-emergent adverse events (TEAE) in the RT cohort (n=82) were neutropenia/decreased neutrophil count (29.3%, n=24), fatigue (24.4%, n=20) and diarrhea, dyspnea, thrombocytopenia, and pyrexia (18.3% each, n=15). Common grade ≥3 TEAEs were neutropenia/decreased neutrophil count (23.2%, n=19), thrombocytopenia (11.0%, n=9), plus anemia and sepsis (9.8% each, n=8). Any grade hypertension (3.7%, n=3) or atrial fibrillation (1.2%, n=1) were infrequent. Three pts (3.7%) had treatment-related AEs leading to dose reductions, but no pt had a treatment-related AE leading to pirtobrutinib discontinuation. Analyses of clonality will be presented.

Conclusions: Continued follow-up from BRUIN demonstrates encouraging response and OS in pts with RT. Pirtobrutinib remains well-tolerated with low rates of discontinuation and manageable safety profile. While RT remains a challenging diagnosis, pirtobrutinib represents a potential treatment option that warrants further investigation.

A. Efficacy in pre-treated RT patients with prior therapy indicated.



B. Overall survival in pre-treated patients with RT.



Disclosures: Wierda: *Numab THerapeutics:* Research Funding; *Loxo Oncology, Inc./Lilly:* Research Funding; *Janssens Biotech Inc*: Research Funding; *NIH P30 CA016672/MDACC Cancer Center Support Grant:* Research Funding; *GlaxoSmithKline:* Research Funding; *AbbVie:* Consultancy, Research Funding; *Cyclacel:* Consultancy, Research Funding; *Nurix THerapeutics:* Research Funding; *Juno Therapeutics:* Research Funding; *National Comprehensive Cancer Network:* Other: Nonrelevant Financial Relationship/Chair, CLL). Supported by the NIH/NCI under award number P30 CA016672 and used MDACC Cancer Center Support Grant (CCSG) shared resources; *Miragen:* Research Funding; *Oncternal Therapeutics, Inc.*: Research Funding; *Janssens Biotech:* Research Funding; *Accutar Biotechnology:* Research Funding; *Sunesis:* Research Funding; *KITE Pharma:* Research Funding; *Bristol Myers Squibb (Juno & Celgene):* Consultancy, Research Funding; *Gilead Sciences:* Research Funding; *AstraZeneca/Acerta Pharma:* Consultancy, Research Funding; *Genentech:* Research Funding; *Pharmacyclics LLC:* Research Funding; *GSK/Novartis:* Research Funding. **Shah:** *Umoja:* Consultancy; *Janssen:* Consultancy; *BMS/Juno:* Consultancy; *Tundra Therapeutics:* Current holder of *stock options* in a privately-held company; *LOXO-Lilly:* Consultancy, Other: Travel support; *Epizyme:* Consultancy; *TG therapeutic:* Consultancy; *Novartis:* Consultancy; *Seattle Genetics:* Consultancy; *Gilead/Kite:* Consultancy; *Incyte:* Consultancy; *Abbvie:* Consultancy; *Lilly Oncology:* Consultancy, Research Funding; *Miltenyi Biotec:* Consultancy, Other: Travel support, Research Funding. **Cheah:** *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: TRAVEL, ACCOMMODATIONS, EXPENSES, Research Funding; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *MSD:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Gilead:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Ascentage Pharma:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *AstraZenecca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Lilly:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *TG therapeutics:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AbbVie:* Research Funding; *Menarini:* Consultancy, Honoraria; *Genmab:* Consultancy, Honoraria; *Daizai:* Consultancy, Honoraria. **Lewis:** *Kite:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Roche:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Lilly:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory

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202 Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Analysis and Treatment of High Risk and Treatment of Relapsed CLL or Richter Transformation

Hematology Disease Topics & Pathways:

Lymphoid Leukemias, CLL, Diseases, Lymphoid Malignancies

Saturday, December 9, 2023: 2:45 PM

Jennifer R. Brown, MD, PhD[1], *Barbara F. Eichhorst, MD*[2], *Nicole Lamanna, MD*[3], *Susan M. O'Brien*[4], *Constantine S. Tam, MD, MBBS*[5], *Luqui Qiu*[6], *Maciej Kaźmierczak, MD*[7*], *Wojciech Jurczak, MD, PhD*[8], *Keshu Zhou, MD*[9*], *Martin Simkovic, MD*[10*], *Jiri Mayer, MD*[11], *Amanda L. Gillespie-Twardy, MD*[12], *Alessandra Ferrajoli, MD*[13], *Peter S. Ganly, PhD*[14], *Robert Weinkove, MBBS, PhD, FRACP, FRCPA*[15*], *Sebastian Grosicki, MD, PhD*[16*], *Andrzej Mital*[17*], *Tadeusz Robak*[18*], *Anders Osterborg, MD, PhD*[19*], *Habte A. Yimer, MD*[20], *Megan (Der Yu) Wang*[21*], *Tommi Salmi, MD*[22*], *Liping Wang*[23*], *Jessica Li, MSc*[21*], *Kenneth Wu*[21*], *Aileen Cleary Cohen, MD, PhD*[21] *and Mazyar Shadman, MD, MPH*[24]

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Introduction: ALPINE, a randomized, multinational phase 3 study (NCT03734016) in patients with R/R CLL/SLL, established the statistical and clinically meaningful superiority of zanubrutinib over ibrutinib on progression-free survival (PFS) and overall response rate (ORR) and confirmed the favorable safety/tolerability profile of zanubrutinib (Brown et al. *NEJM*; 2022). Now, with 3 years of overall study follow-up, we report the results of an extended follow-up analysis.

Methods: As previously published, patients with R/R CLL/SLL who had received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive zanubrutinib or ibrutinib. Efficacy assessments, including PFS and ORR, were evaluated by the investigator based on 2008 iwCLL criteria; sensitivity analyses to confirm PFS results were also conducted. Updated safety analyses were performed. All reported *P*-values are descriptive.

Results: Overall, 652 patients were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325). As of 15 May 2023, 63.3% (n=207/327) of patients remain on zanubrutinib and 52.3% (n=170/325) remain on ibrutinib. At a median study follow-up of 36.3 months, benefit of zanubrutinib over ibrutinib was sustained (HR: 0.67 [95% CI, 0.52-0.86]; 2-sided *P*=.002; **Fig 1**). At 36 months, the PFS rates were 65.8% with zanubrutinib and 54.3% with ibrutinib. Benefits in PFS with zanubrutinib were also observed across major subgroups, including in patients with del(17p)/*TP53* mutations (HR: 0.52 [95% CI, 0.32-0.83] 2-sided *P*=.005) where 36-month PFS rates were 60.1% and 43.6%, respectively. Additionally, the zanubrutinib PFS benefit was confirmed in a sensitivity analysis that included only progression and death events that occurred on active treatment (HR: 0.69 [95% CI, 0.49-0.97]; 2-sided *P*=.031). ORR remained higher with zanubrutinib compared with ibrutinib (85.0% vs 74.8%; 2-

sided *P*=.001). Responses deepened in both arms with CR/CRi rates of 10.1% (zanubrutinib) and 7.4% (ibrutinib); the rate of PR-L or better was 90.2% vs 82.8%, respectively. Fifty-nine (18.0%) patients treated with zanubrutinib and 71 (21.8%) treated with ibrutinib had died (OS HR: 0.76 [95% CI, 0.54-1.08]); 36-month OS rates were 82.6% (zanubrutinib) and 79.7% (ibrutinib).

In this extended follow-up, median treatment duration was 34.7 months (zanubrutinib) and 31.5 months (ibrutinib). Across both arms, the most common reasons for treatment discontinuation were AEs (20.2%, zanubrutinib; 24.9%, ibrutinib) and progressive disease (12.2%, zanubrutinib; 16.3%, ibrutinib). Dose interruption and dose reduction due to AEs were 59.6% vs 61.1% and 14.2% vs 17.6% with zanubrutinib vs ibrutinib, respectively.

The most common AEs of any grade with zanubrutinib and ibrutinib were COVID-19 (37.3% vs 25.6%), diarrhea (17.9% vs 25.6%), and upper respiratory tract infection (25.9% vs 17.3%). Rates of any grade ≥3 AEs and serious AEs were 72.2% vs 75.6% and 49.7% vs 57.4% with zanubrutinib vs ibrutinib, respectively. Most commonly reported grade ≥3 AEs were neutropenia (17.3% vs 16.4%) and hypertension (15.1% vs 12.0%). Rates of serious infections were 30.6% in each treatment arm. Discontinuation rates due to cardiac disorders were lower with zanubrutinib (0.6% [n=2]) vs ibrutinib (4.6% [n=15]). Overall cardiac events remain lower with zanubrutinib, including atrial fibrillation/flutter (6.2% vs 16.0%; 2-sided *P*<.0001). Across this study, no grade 5 AEs due to cardiac disorders were observed with zanubrutinib but were reported in 6 patients (1.9%) with ibrutinib (**Table 1**).

Conclusions: ALPINE was the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors. At a median follow-up of 3 years, the study showed sustained PFS benefits of zanubrutinib over ibrutinib. The durable PFS benefits with zanubrutinib were observed across major subgroups, including multiple sensitivity analyses. The overall safety/tolerability profiles were consistent with previous reports for both treatments. The cardiac safety profile remained favorable for zanubrutinib compared with ibrutinib, with no new safety signals emerging with longer follow-up. With over 3 years of treatment, zanubrutinib continues to be a more efficacious and better tolerated treatment than ibrutinib for patients with R/R CLL/SLL. At time of presentation, data with further follow-up will be presented.

Figure 1. Investigator-Assessed Progression-Free Survival (ITT Population)

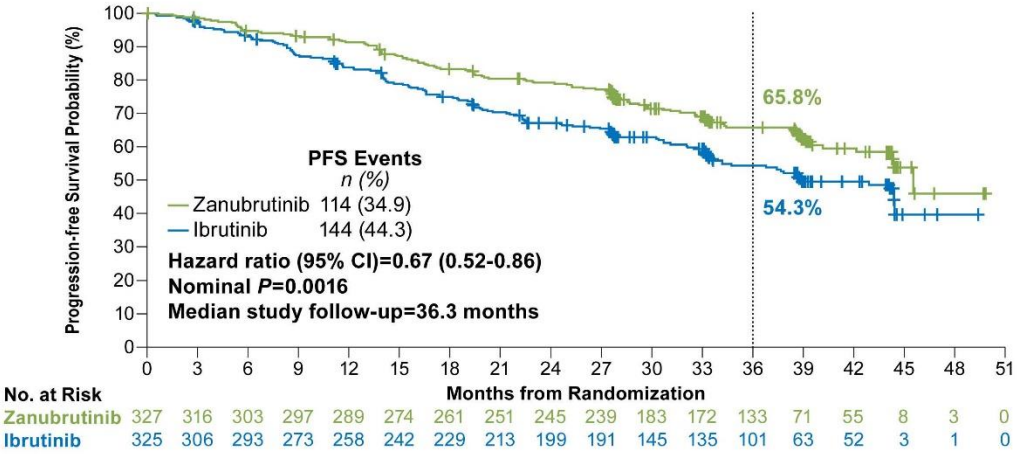

Table 1. Summary of Cardiovascular Adverse Events in Extended Analyses

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac AEs (any grade)	**76 (23.5%)**	**107 (33.0%)**
Cardiac AEs (grade ≥3)	**23 (7.1%)**	**36 (11.1%)**
Serious cardiac AEs	**10 (3.1%)**	**31 (9.6%)**
Cardiac deaths	**0**	**6 (1.9%)**
Atrial fibrillation/flutter*	**20 (6.2)**	**52 (16.0)**
Cardiac AEs leading to treatment discontinuation	**2 (0.6)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	1 (0.3)	5 (1.5)
Cardiac arrest	0	2 (0.6)[a]
Atrial flutter	0	1 (0.3)
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)[a]
Dilated cardiomyopathy	0	1 (0.3)[a]
Myocardial infarction	0	1 (0.3)[a]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

*2-sided *P*<.0001.

[a]Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

AE, adverse event.

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325 Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: New Inhibitors and Cellular Therapies for Treatment of Relapsed CLL

Hematology Disease Topics & Pathways:

Research, clinical trials, Lymphoid Leukemias, CLL, Clinical Research, Diseases, Lymphoid Malignancies

Saturday, December 9, 2023: 4:00 PM

Jennifer A. Woyach, MD[1*], *Jennifer R. Brown, MD, PhD*[2], *Paolo Ghia, MD, PhD*[3], *Lindsey E. Roeker, MD*[4], *Krish Patel, MD*[5], *Toby A. Eyre*[6*], *Talha Munir, MBBS, MRCP, FRCPath, PhD*[7*], *Ewa Lech-Maranda, MD, PhD*[8*], *Nicole Lamanna, MD*[9], *Constantine S. Tam, MD, MBBS*[10*], *John F. Seymour, MBBS, PhD, FRACP*[11], *Benoit Tessoulin*[12*], *Nirav N. Shah, MD*[13], *Chaitra S Ujjani, MD*[14], *Bita Fakhri, MD, MPH*[15], *Catherine C. Coombs, MD*[16], *Ian W. Flinn, MD, PhD*[17], *Manish Patel, MD*[18*], *Sunita D. Nasta, MD*[19], *Jonathon B. Cohen, MD, MS*[20], *Alvaro J. Alencar, MD*[21], *Chan Y. Cheah, MD, DMSc*[22], *Shuo Ma, MD, PhD*[23], *Joanna M. Rhodes, MD, MSCE*[24*], *Deepa Jagadeesh, MD*[25], *Pier Luigi Zinzani, MD, PhD*[26], *Anders Osterborg, MD, PhD*[27*], *Koji Izutsu, MD, PhD*[28], *Donald E. Tsai, MD, PhD*[29*], *Paolo Abada, MD*[29], *Minna Balbas, PhD*[29*], *Jian Li, MS*[29*], *Amy S. Ruppert, PhD*[30*], *Wojciech Jurczak, MD, PhD*[31] *and William G. Wierda, MD, PhD*[32]

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Background: The treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has benefited from covalent (c) Bruton tyrosine kinase inhibitors (BTKi), however, therapy can fail due to progression or intolerance. Sequential treatment with B-cell lymphoma 2 protein inhibitor (BCL2i) venetoclax, either as monotherapy or combined with an anti-CD20 monoclonal antibody, has been the primary treatment option for CLL/SLL patients (pts) whose disease has progressed on cBTKi. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that demonstrated promising efficacy in patients with relapsed or refractory CLL/SLL (Mato *et al*, NEJM, 2023). Here, we report on the efficacy of pirtobrutinib treatment in CLL/SLL in the post-cBTKi setting, including subgroups with or without prior BCL2i, using data from the BRUIN study (NCT03740529) with more than 2 years follow-up.

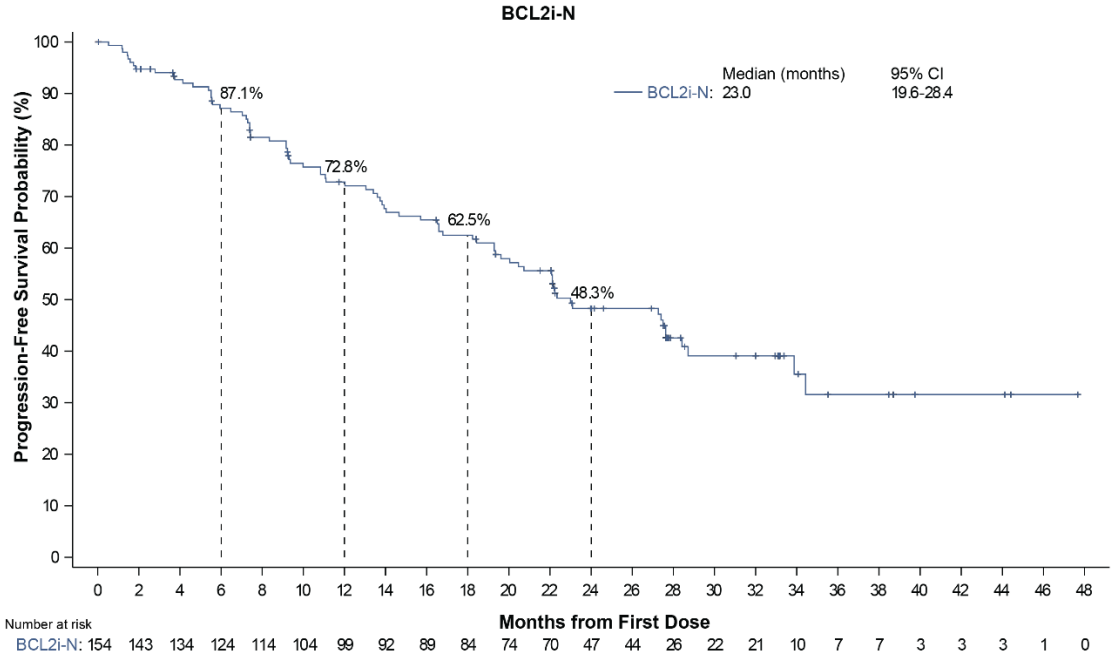
Methods: Pts with previously treated CLL/SLL were eligible for treatment with pirtobrutinib in the multicenter Phase 1/2 BRUIN study. Key endpoints included ORR (including partial response with lymphocytosis; PR-L) as assessed by an independent review committee per 2018 iwCLL response criteria, DoR, PFS, OS, and safety. A data cut of 05MAY2023 was utilized.

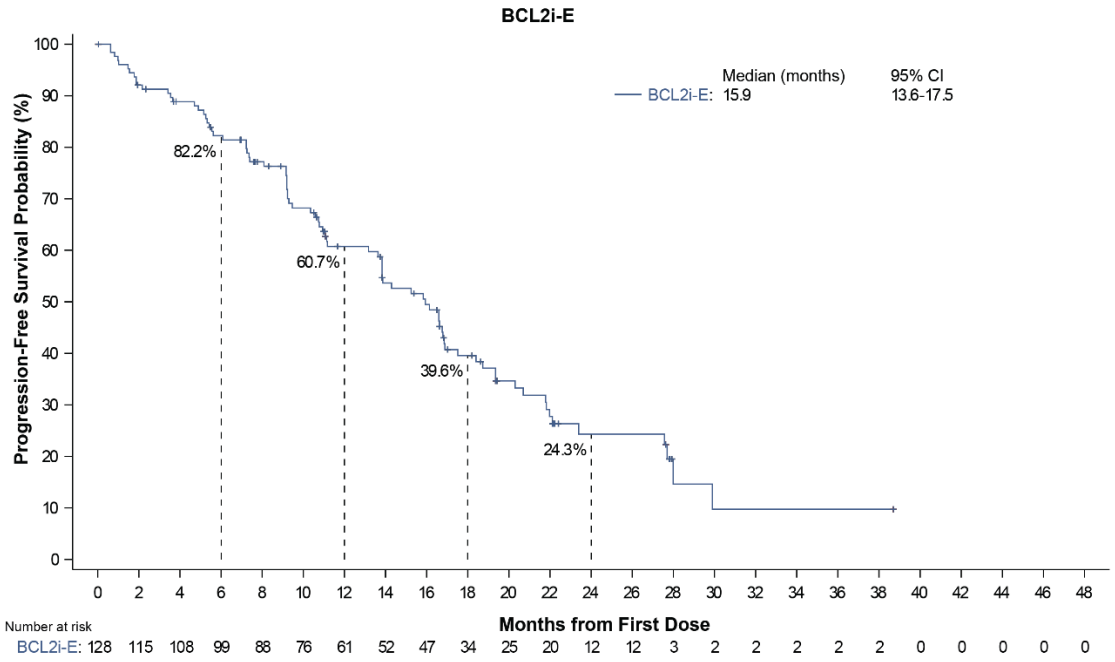
Results: In total, 282 pts with CLL/SLL who received prior cBTKi were included in this analysis. Median age was 69 years (range, 36-88), 68% were male, and median number of prior therapies was 4 (range, 1-11). Of 282 pts, 154 (55%) had not received prior-BCL2i therapy (Naïve; BCL2i-N) and 128 (45%) had (Exposed; BCL2i-E). BCL2i-N pts were exposed to fewer prior therapies than BCL2i-E pts (median prior therapies 3 and 5, respectively), including anti-CD20 antibody (83% and 97%), chemotherapy (74% and 89%), PI3K inhibitor (11% and 42%), CAR-T cell therapy (1% and 12%), and hematopoietic cell transplantation (1% and 6%). The ORR for all post-cBTKi pts was 72% (95% CI, 66.4-77.1), and ORR including PR-L was 82% (95% CI, 76.5-85.9). Post-cBTKi pts included

a subgroup of 19 pts with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had ORR including PR-L of 89.5% (CI 95%, 66.9-98.7). The ORR including PR-L was 83.1% (95% CI, 76.2-88.7) for BCL2i-N pts, and 79.7% (95% CI, 71.7-86.3) for BCL2i-E pts. Median DoR was 18.4 months (95% CI, 15.3-20.4) for all cBTKi pre-treated pts, 24.9 months (95% CI, 18.4-32.0) for BCL2i-N, and 14.8 months (95% CI, 12.0-17.4) for BCL2i-E. With a median follow up of 27.5 months, the median PFS was 19.4 months (95% CI, 16.6-22.1) among all cBTKi pre-treated pts, 23.0 months (95% CI, 19.6-28.4) for BCL2i-N, and 15.9 months (95% CI, 13.6-17.5) for BCL2i-E (Figure). With a median follow up of 29.3 months, the median OS was not estimable for all cBTKi pre-treated pts, BCL2i-N, and BCL2i-E; the 24-month OS rates were 73.2% (95% CI, 67.4-78.2), 83.1% (95% CI,75.9-88.2), 60.6% (50.9-68.9), respectively.

In the CLL/SLL cohort (N=282), the most frequent treatment-emergent adverse events (TEAE), regardless of attribution, were fatigue (36.9%), diarrhea (28.4%), cough (27.3%) and contusion (26.2%). The most frequent Grade ≥3 TEAE was neutropenia/neutrophil count decreased (28.4%). Grade ≥3 TEAEs of hypertension (4.3%) and atrial fibrillation/flutter (1.8%) were infrequent. The AE profile of BCL2i-N and BCL2i-E pts was overall similar. Though Grade ≥3 neutropenia/neutrophil count decreased was higher in BCL2i-E pts (36.7% and 21.4%), this may have been attributed to the higher frequency of baseline neutropenia in BCL2i-E pts (27.3% and 11.0%). In total, 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) pts had treatment-related AE leading to pirtobrutinib discontinuation.

Conclusion: Pirtobrutinib continues to demonstrate promising and durable efficacy in pts with post-cBTKi heavily pretreated CLL/SLL. ORR was high regardless of prior BCL2i status. Longer PFS was observed in BCL2i-N pts than BCL2i-E pts, likely due to the more heavily pretreated status of the BCL2i-E population which can be associated with poorer prognosis. Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BTKi-N and BTKi-E pts. These results suggest that continuation of BTK pathway inhibition following a cBTKi may be an important sequencing approach to consider in the treatment of CLL/SLL.


BCL2i-N
Median (months)
95% CI
BCL2i-N: 23.0
19.6-28.4
87.1%
72.8%
62.5%
48.3%
Progression-Free Survival Probability (%)
Months from First Dose
Number at risk
BCL2i-N: 154 143 134 124 114 104 99 92 89 84 74 70 47 44 26 22 21 10 7 7 3 3 3 1 0


BCL2i-E
Median (months)
95% CI
BCL2i-E: 15.9
13.6-17.5
82.2%
60.7%
39.6%
24.3%
Progression-Free Survival Probability (%)
Months from First Dose
Number at risk
BCL2i-E: 128 115 108 99 88 76 61 52 47 34 25 20 12 12 3 2 2 2 2 2 0 0 0 0 0

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631 Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Frontline Treatment With Targeted Agents in Patients With Chronic Lymphocytic Leukemia

Hematology Disease Topics & Pathways:

Lymphoid Leukemias, CLL, Combination therapy, Diseases, Therapies, Adverse Events, Lymphoid Malignancies, Minimal Residual Disease

Sunday, December 10, 2023: 4:30 PM

Peter Hillmen, MB ChB, PhD[1], *David Allan Cairns, PhD*[2*], *Adrian John Clifton Bloor, PhD, FRCPath, FRCP*[3*], *David Allsup, MD*[4*], *Kate Cwynarski, MBBS, PhD, FRCP, FRCPath*[5*], *Andrew Pettitt*[6*], *Shankaranarayana Paneesha, MD*[7], *Christopher P. Fox, MD, PhD*[8], *Toby A. Eyre*[9*], *Francesco Forconi, MD, PhD, DM, FRCPath*[10*], *Nagah Elmusharaf*[11*], *Ben Kennedy*[12*], *John G. Gribben, MD, DSc*[13], *Nicholas Pemberton*[14*], *Oonagh Sheehy*[15*], *Gavin Preston, PhD, MBBS, FRCP, FRCPath*[16*], *Anna Schuh, MD, PhD, FRCP, FRCPath*[17], *Dena Howard*[18*], *Anna Hockaday*[18*], *Sharon Jackson*[18*], *Natasha Greatorex*[18*], *Sean Girvan*[18*], *Sue Bell*[18*], *Julia Brown*[19*], *Nichola Webster*[20,21*], *Surita Dalal, PhD*[20,21*], *Ruth M de Tute, MSc, PhD, FRCPath*[20*], *Andrew Rawstron, PhD*[22*], *Piers EM Patten, FRCP, FRCPath, PhD*[23,24] *and Talha Munir, MBBS, MRCP, FRCPath, PhD*[25*]

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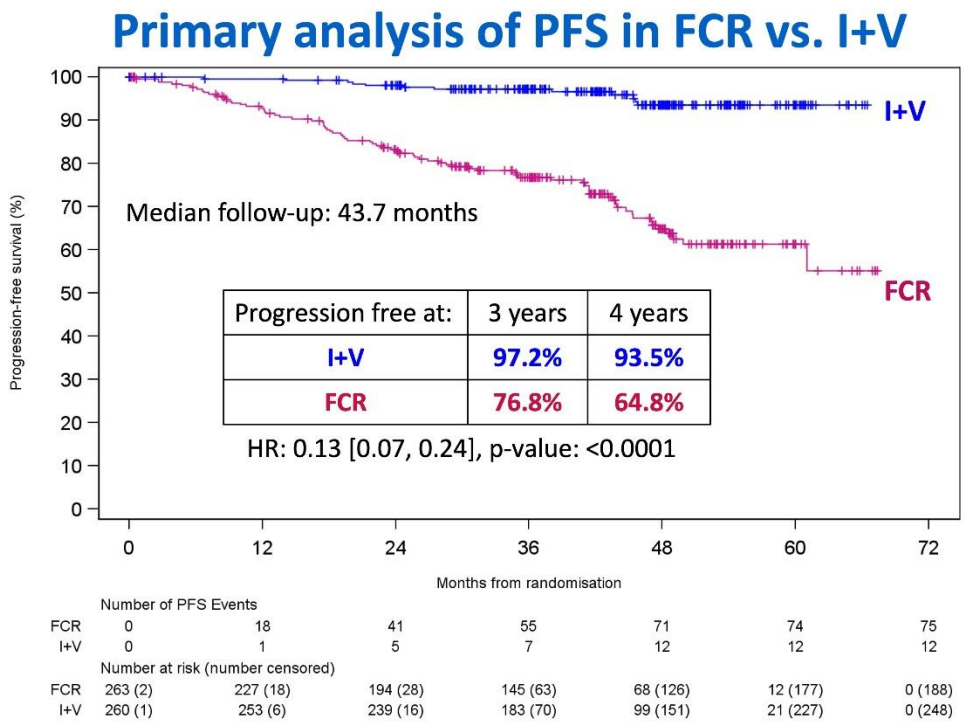
Introduction: Ibrutinib (I), an irreversible Btk inhibitor, and venetoclax (V), a Bcl-2 inhibitor, improve CLL outcomes in trials compared to chemoimmunotherapy. I and V target two key pathophysiological pathways in CLL and should be synergistic. This is supported both by *in vitro* studies and Phase II trials in which I+V results in high proportions of measurable residual disease (MRD) negativity. A Phase III trial comparing I+V (15 months [mo]) with chlorambucil-obinutuzumab led to the approval of I+V. However, mathematical disease modelling and Phase II studies favor defining duration of I+V according to individual patient sensitivity. We hypothesized that I+V is more effective than FCR in CLL and that treatment duration personalised using MRD response would optimize outcome.

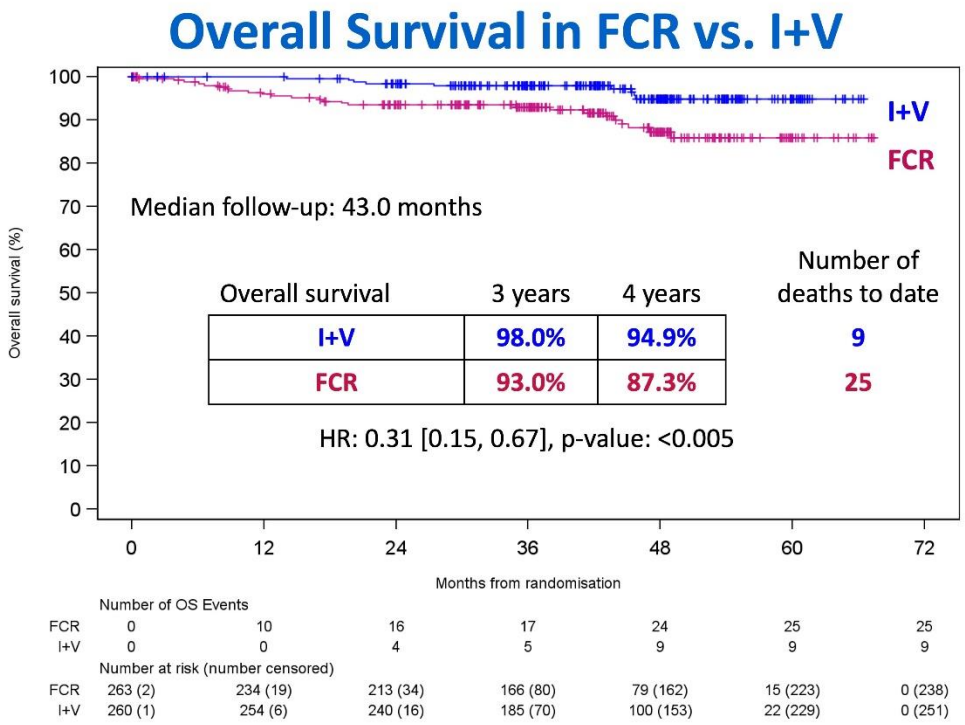
Methods: FLAIR (ISRCTN01844152) is a phase III, multicentre, randomised, controlled, open, parallel group trial for untreated CLL. Patients (pts) with >20% 17p deleted cells were excluded. FLAIR was adapted in 2017 to add 2 arms, I alone and I+V compared to FCR. Here we report the planned analysis of I+V vs FCR. In I+V after 2 mo I, V was added with a 4-week dose escalation to 400mg/day and then I+V for up to 6 years with duration of I+V defined by MRD (<1 CLL cell in 10,000 [flow cytometry]). PB MRD was assessed at 12 mo and then 6 monthly and if negative, was repeated at 3 mo and 6 mo in PB and BM. If all were MRD neg, then the duration of I+V was double the time between start of I+V and the initial MRD neg PB (I+V duration: 2 to 6 years). The primary endpoint for I+V vs FCR was investigator-assessed PFS. Key secondary endpoints presented were OS, IWCLL response, MRD and safety. Appropriate endpoints were analysed by CLL prognostic sub-groups.

Results: 523 pts were randomised to FCR (n=263) and I+V (n=260) at 96 UK Centers from 07/20/2017 to 03/24/2021. Data-lock on 05/23/2023. 71.3% male, median age 62 yrs (31.2% >65yo) and 40.9 % Binet Stage C. IGHV unmutated (≥98% homology to germline) in 56.9%, 37.6% IGHV mutated and 5.5% Subset 2. Hierarchical FISH: 20.6% 11q del, 20.1% trisomy 12, 27.8% normal and 31.4% 13q del. At 2 yrs 111/260 (42.7%)

and 3 yrs 135/232 (58.1%) pts stopped I+V according to the MRD stopping rules. At a median 43.7 months there were 87 progressions - 75 FCR and 12 I+V. The hazard ratio (HR) for PFS for I+V vs FCR is 0.13 (95% CI: [0.07, 0.24]; p<0.0001; Fig). This result was consistent for gender, age or stage. At 3 yrs 2.8% had progressed on I+V compared to 23.2% on FCR. There have been 34 deaths (25 FCR and 9 I+V) resulting in improved overall survival for I+V vs FCR: HR 0.31 (95% CI: [0.15, 0.67]; p=0.0029; Fig). At 3 years 2.0% of I+V pts had died compared to 7.0% for FCR. At 9 months (3 mo post-FCR) 48.3% FCR pts became MRD neg in BM compared to 41.5% for I+V. However, with continued I+V more pts became MRD neg: the odds of MRD negativity at any time for I+V vs FCR were 2.03 (95% CI: [1.43, 2.89]; P<0.001) in BM and 3.91 (95% CI: [2.55, 6.00]; P<0.001) in PB. 90.6% pts achieved PB MRD negativity at up to 5 yrs I+V and 88% of these were BM MRD negative 6 mo after their first PB MRD neg result. At 9 months a higher proportion achieved CR and overall response for I+V; CR – FCR 49.0% (95% CI: [42.9%, 55.3%]), I+V 59.2% (53%, 65.3%); ORR - FCR 76.4% (70.8%, 81.4%); I+V 86.5% (81.8%, 90.4%). This difference was greater for best response at any time: ORR 83.7% (78.6%, 87.9%) for FCR vs 95.4% (92.1%, 97.6%) for I+V; CR 71.5% (65.6%, 76.9%) for FCR vs 92.3% (88.4%, 95.2%) for I+V. The odds ratios estimate to achieve CR with I+V vs FCR is 1.51 (95% CI: [1.07, 2.14]; p<0.05). Responses and outcomes by FISH and IGHV will be presented. SAEs were reported in 252 (51.3%) pts (129 FCR vs 123 I+V). Notable SAEs by organ class for FCR vs I+V were: infections 18.8% of FCR pts vs 22.2% for I+V; blood and lymphatic 31% vs 5%; and cardiac in 0.4% vs 10.7%. 4 pts had sudden or cardiac deaths – 2 FCR and 2 I+V. 69 other cancers were diagnosed (45 in FCR, 24 in I+V) in 51 pts (34 FCR, 17 I+V). The incidence of other cancers per 100 pt-years was greater for FCR than I+V; 5.4 (95% CI: [5.11, 5.68]) vs. 2.6 (2.40, 2.79). There were 7 cases of MDS/AML with FCR and 1 with I+V.

Conclusion: Ibrutinib plus venetoclax significantly improved progression-free and overall survival compared to FCR in untreated CLL. Using MRD to direct the duration of I+V maximizes outcome with 97.2% progression free survival at 3 years The efficacy seen in FLAIR is superior to previous Phase III CLL trials indicating that I+V with duration guided by MRD is a new gold standard for CLL treatment.





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