LBA-6 Zanubrutinib Demonstrates Superior Progression-Free Survival (PFS) Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Results from Final Analysis of ALPINE Randomized Phase 3 Study

Program: General Sessions

Session: Late-Breaking Abstracts Session

Hematology Disease Topics & Pathways:

Research, clinical trials, Lymphoid Leukemias, CLL, Clinical Research, Plasma Cell Disorders, Diseases, Therapies, Lymphoid Malignancies

Tuesday, December 13, 2022, 9:00 AM-10:30 AM

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Introduction: CLL/SLL is usually characterized by consecutive relapses and response to therapy ultimately dictates survival. While ibrutinib, a first-generation Bruton tyrosine kinase inhibitor (BTKi), has become standard therapy, it has well-described off-target effects that can limit use. Compared with ibrutinib, zanubrutinib, a next-generation BTKi, provides improved BTK occupancy across disease-relevant tissues with greater kinase selectivity. In a randomized phase 3 study (ALPINE; NCT03734016), zanubrutinib was compared head-to-head with ibrutinib as treatment for R/R CLL/SLL. At predefined response analyses, zanubrutinib demonstrated superior overall response rate (ORR); data from the predefined final PFS analysis are reported here.
Methods: Patients (pts) with R/R CLL/SLL who had received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive zanubrutinib or ibrutinib until disease progression or unacceptable toxicity. Stratification was based on age, refractory status, geographical region, and del(17p)/*TP53* mutation status. As the primary endpoint of ORR was superior with zanubrutinib, the key secondary efficacy endpoint of PFS was tested for noninferiority under hierarchical testing when 205 PFS events were observed. If PFS noninferiority between zanubrutinib and ibrutinib was demonstrated, superiority of zanubrutinib vs ibrutinib could be tested and claimed if the 2-sided *P*-value was <.04996. Other endpoints included overall survival (OS), ORR including PR with lymphocytosis (PR-L) or better, and safety parameters including atrial fibrillation/flutter.
Results: Pts (N=652) from 15 countries were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325). Demographic and disease characteristics were balanced between zanubrutinib and ibrutinib arms (age ≥65 yrs [61.5 vs 61.5%]; male [65.1 vs 71.4%]; unmutated IGHV [73.1 vs 73.5%]; del(17p) [13.8 vs 15.4%]; *TP53* mutated without del(17p) [9.2 vs 7.7%]). Across the study population, median age was 67 and 68 yrs, respectively; in both arms, median prior lines of therapy was 1.

With a median follow-up of 29.6 mo (data cutoff, 8 Aug 2022), zanubrutinib PFS, assessed by independent review committee (PFS_{IRC}), was superior to ibrutinib in the ITT population (HR: 0.65 [95% CI, 0.49-0.86]; 2-sided *P*=.0024 [**Fig 1**]); identical statistical values were reported when assessed by investigator (INV). Median PFS_{IRC} was 35.0 mo (95% CI, 33.2-44.3) for ibrutinib-treated pts but not reached for zanubrutinib-treated pts. In a predefined subgroup of pts with del(17p)/*TP53* mutation, longer PFS_{IRC} was demonstrated with zanubrutinib than ibrutinib (**Fig 2**). PFS, regardless of IRC or INV assessment, consistently favored zanubrutinib across other major predefined subgroups, including IGHV status. Compared with ibrutinib, zanubrutinib had a higher ORR_{IRC} (86.2 vs 75.7%, nominal 2-sided *P*=.0007), with a rate of PR-L or better of 91.7% vs 83.1% (nominal 2-sided *P*=.001).

Treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%) with most due to AEs (16.2 vs 22.8%) or progressive disease (7.3 vs 12.9%); discontinuation rates due to cardiac disorders were 0.3% vs 4.3%. Rates of grade ≥3 AEs (67.3 vs 70.4%), serious AEs (42.0% vs 50.0%), dose interruption (50.0% vs 56.8%), and dose reduction (12.3 vs 17.0%) were also lower with zanubrutinib vs ibrutinib. Rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%); rates of other AEs of special interest were similar between treatments. There were no grade 5 AEs due to cardiac disorders with zanubrutinib vs 6 (1.9%) with ibrutinib. Overall, 48 (14.7%) pts treated with zanubrutinib and 60 (18.5%) treated with ibrutinib had died (OS HR: 0.76 [95% CI, 0.51-1.11]).

Conclusions: As ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors, zanubrutinib has now proven superiority to ibrutinib in both ORR and PFS in pts with R/R CLL/SLL. Efficacy benefits with zanubrutinib were observed across all major subgroups, including high-risk pts. Zanubrutinib had a favorable safety profile compared with ibrutinib, with a lower rate of treatment discontinuation and fewer cardiac disorder events, including fewer cardiac events leading to death. These data

suggest zanubrutinib is more efficacious and better tolerated than ibrutinib as treatment for R/R CLL/SLL.

Figure 1: IRC-Assessed Progression-Free Survival (ITT Population)

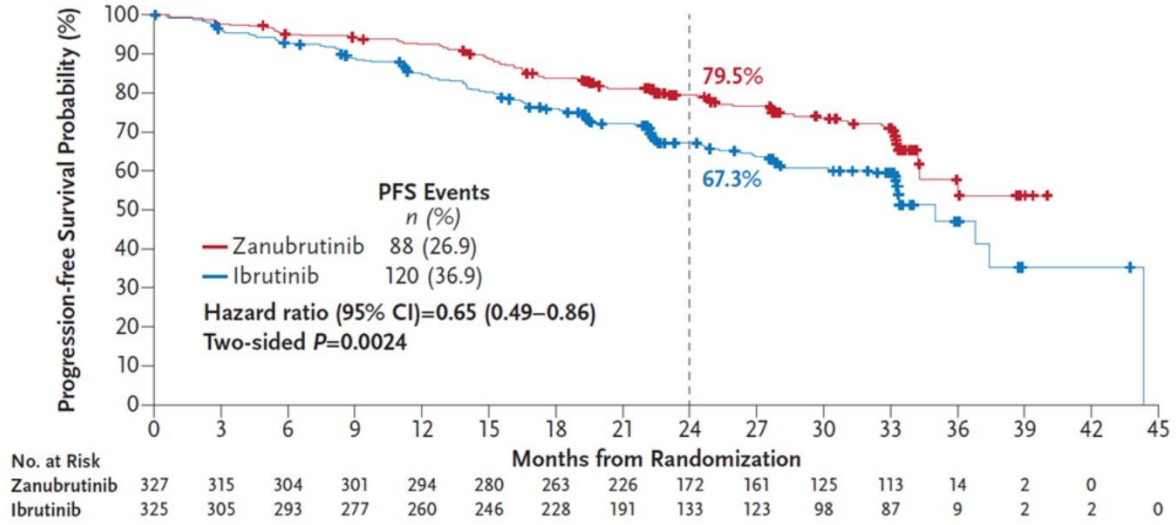
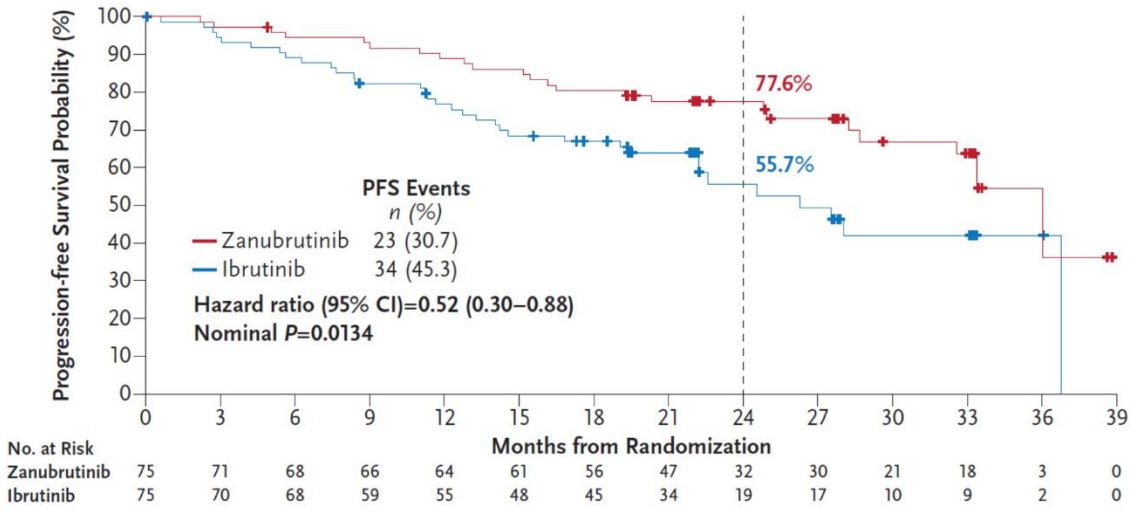


Figure 2: IRC-Assessed Progression-Free Survival in Patients with del(17p)/TP53 mutation



Disclosures: Brown: *Abbvie:* Consultancy; *Acerta/Astra-Zeneca:* Consultancy; *Beigene:* Consultancy, Research Funding; *Bristol-Myers Squibb/Juno/Celgene:* Consultancy; *Catapult:* Consultancy; *Genentech/Roche:* Consultancy; *Janssen:* Consultancy; *MEI Pharma:* Consultancy, Research Funding; *Morphosys AG:* Consultancy; *Novartis:* Consultancy; *Pfizer:* Consultancy; *Rigel:* Consultancy; *Gilead:* Research Funding; *Loxo/Lilly:* Research Funding; *Verastem/SecuraBio:* Research Funding; *Sun:* Research Funding; *TG Therapeutics:* Research Funding; *Invectys:* Other: served on the data safety monitoring committee; *Grifols Worldwide Operations:* Consultancy; *Hutchmed:* Consultancy; *iOnctura:* Consultancy, Research

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OffLabel Disclosure: Zanubrutinib is not yet approved for CLL/SLL treatment

1815 Contribution of Obinutuzumab to Acalabrutinib Therapy in Patients with Treatment-Naive Chronic Lymphocytic Leukemia: Analysis of Survival Outcomes By Genomic Features

Program: Oral and Poster Abstracts

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

Hematology Disease Topics & Pathways:

adult, Biological therapies, Lymphoid Leukemias, Research, clinical trials, Non-Biological therapies, CLL, Clinical Research, Diseases, Therapies, Lymphoid Malignancies, Human, Study Population

Saturday, December 10, 2022, 5:30 PM-7:30 PM

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Background: Treatment with the highly selective Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib (A), administered with or without obinutuzumab (O), has demonstrated significant progression-free survival (PFS) benefits compared with chemoimmunotherapy in patients (pts) with treatment-naive (TN) chronic lymphocytic leukemia (CLL), including those with higher-risk genomic characteristics (ELEVATE-TN; Sharman et al. Leukemia. 2022;36:1171-5); significantly better PFS and numerically better overall survival (OS) outcomes were also seen with A+O vs A monotherapy, albeit with some additional toxicity observed. However, a better understanding of the impact of adding O to A in pts with TN CLL is needed, particularly because adding rituximab to ibrutinib did not improve outcomes in the Alliance A041202 trial (Woyach et al. N Engl J Med. 2018;379:2517-28). To assess the contributory effects of adding O to A in first-line CLL, we performed a pooled analysis of 2 clinical studies (ELEVATE-TN and CL-003) to compare PFS and OS for A+O vs A monotherapy in pts with TN CLL by prognostic factors within each genomic characteristic.

Methods: In this retrospective analysis, PFS and OS outcomes were compared between the A+O and A arms by prognostic factors (age, bulky disease, CLL International Prognostic Index [CLL-IPI] score and beta-2 microglobulin (B2M) levels at baseline) in pts with and without the selected genomic characteristics. Del(17p) and/or *TP53* mutation [del(17p)/*TP53*m], unmutated IGHV (uIGHV), and complex karyotype (CK, ≥3 chromosomal abnormalities) were considered higher-risk genomic features in this analysis and analyzed

separately. Lower-risk genomic features (absence of del(17p)/*TP53*m, mutated IGHV, and absence of CK) also were analyzed separately. The impact of co-mutation was not assessed.

Results: The pooled analysis included 376 pts (A+O, n=197; A monotherapy, n=179). Overall, 28 (14%) A+O and 24 (13%) A pts had del(17p)/*TP53*m, 112 (57%) and 118 (66%) had uIGHV, and 35 (18%) and 32 (18%) had CK.

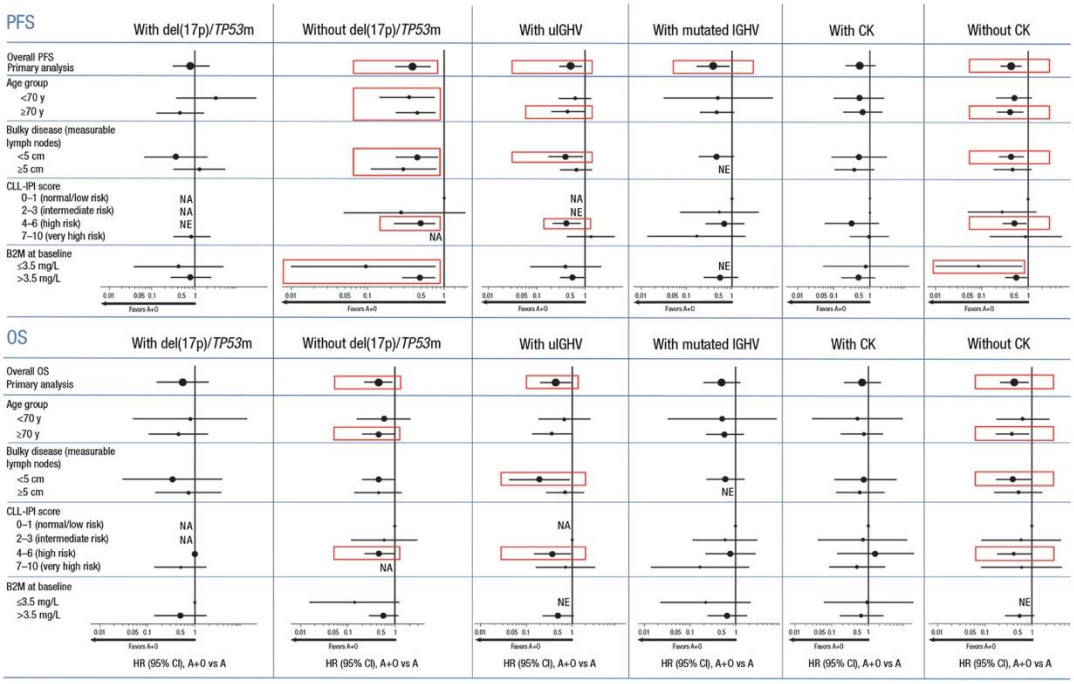
PFS improved with A+O vs A in pts with uIGHV (hazard ratio [HR] 0.51; 95% confidence interval [CI] 0.29–0.89). The HRs for the PFS comparisons between the A+O and A arms were 0.82 (95% CI 0.31–2.18) and 0.56 (95% CI 0.21–1.52) for pts with del(17p)/*TP53*m and CK, respectively. PFS improved with A+O vs A in pts without del(17p)/*TP53*m (HR 0.38; 95% CI 0.23–0.65), pts with mutated IGHV (HR 0.39; 95% CI 0.17–0.89), and pts with no CK abnormality (HR 0.43; 95% CI 0.25–0.72). PFS benefits of A+O vs A by subgroup are shown in **Figure 1**.

OS was improved with A+O vs A in pts with uIGHV (HR 0.44; 95% CI 0.20–0.97). No significant improvement was noted in pts with del(17p)/*TP53*m (HR 0.55; 95% CI 0.16–1.95) (**Figures 1, 2**) or in pts with CK (HR 0.69; 95% CI 0.21–2.27). OS was improved in pts without del(17p)/*TP53*m (HR 0.44; 95% CI 0.23–0.87) and in pts with no CK abnormality (HR 0.41; 95% CI 0.21–0.82); the HR for the OS comparison between the A+O and A arms in pts with mutated IGHV was 0.49 (95% CI 0.20–1.22). OS benefits of A+O vs A by subgroup are shown in **Figure 1**.

Conclusions: This retrospective pooled analysis of clinical trial data in 376 pts demonstrated the benefit of adding O to A monotherapy across genomic subgroups, particularly in pts with uIGHV or without del(17p)/*TP53*m or CK abnormalities. The benefit of adding O was not as evident in pts with del(17p)/*TP53m* or CK; however, the sample size was limited in these subgroups. Thus, it is unclear whether the addition of O imparts additional benefit beyond that of a BTKi alone to change the natural course of disease in *TP53*-aberrant pt populations. Overall, this analysis sheds light on the CLL pt populations most likely to benefit from the addition of O to A across various genomic and clinical prognostic subgroups. Novel combination strategies

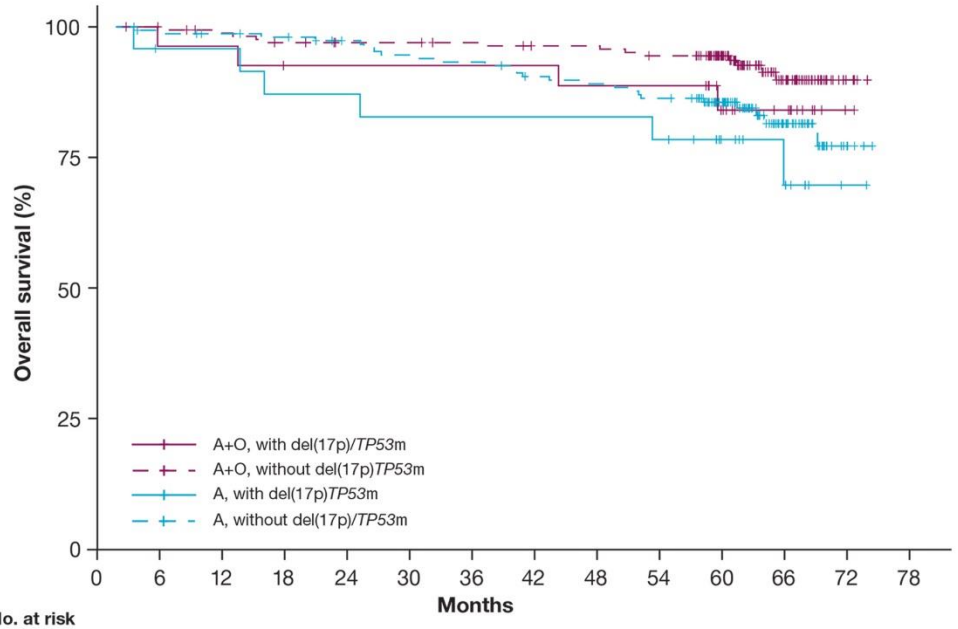
might still be needed to further improve outcomes in pts with del(17p)/*TP53*m.

Figure 1. PFS and OS analysis by selected genomic features and prognostic factors for A+O vs A



CK defined as ≥3 chromosomal abnormalities. Red boxes indicate statistical significance (95% CI <1.00). A, acalabrutinib; B2M; beta-2 microglobulin; CI, confidence interval; CK, complex karyotype; CLL-IPI, chronic lymphocytic leukemia International Prognostic Index; HR, hazard ratio; NA, not applicable; NE, not estimable; O, obinutuzumab; OS, overall survival; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 2. Kaplan-Meier curve of OS by del(17p)/TP53m status



No. at risk														
A+O, with del(17p)/*TP53*m	28	26	25	24	24	24	24	24	23	23	12	6	0	0
A+O, without del(17p)*TP53*m	169	167	163	160	157	156	154	152	151	148	89	31	2	0
A, with del(17p)*TP53*m	24	22	21	20	19	19	19	19	19	17	10	5	1	0
A, without del(17p)/*TP53*m	155	151	148	146	140	137	135	129	127	123	73	25	1	0

A, acalabrutinib; O, obinutuzumab; OS, overall survival.

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348 Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1)

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Targeted Triplet Combinations and Richter's Transformation

Hematology Disease Topics & Pathways:

Research, clinical trials, Lymphoid Leukemias, Biological therapies, CLL, Bispecific Antibody Therapy, Clinical Research, Diseases, Therapies, Lymphoid Malignancies

Saturday, December 10, 2022: 5:15 PM

Arnon P. Kater, MD, PhD[1], *J Christine Ye, MD, MSc*[2], *Jose Sandoval-Sus, MD*[3], *Mar Bellido, MD, PhD*[4*], *Jacob Haaber Christensen, MD, PhD*[5*], *Anthony R. Mato, MD, MSCE*[6], *Ann Janssens, MD, PhD*[7*], *Toshihiko Oki, MD, PhD*[8*], *Daniela Hoehn, MD, PhD*[9], *Marcia Rios, MBA*[9*], *Alexandra Kuznetsova, PhD*[10*], *Rebecca Valentin, MD, PhD*[10*] *and Herbert Eradat, MD*[11]

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[10]*Genmab, Copenhagen, Denmark*

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Background: Prognosis of relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) is particularly poor upon relapse after treatment with targeted agents and, in particular, following transformation to Richter's syndrome (RS). RS is characterized by transformation of CLL to an aggressive lymphoma, most commonly CD20+ large B-cell lymphoma (LBCL). Because no established standard of care exists, a major unmet medical need remains for patients with RS. Epcoritamab is a novel, subcutaneously administered (SC) CD3xCD20 bispecific antibody that has shown substantial clinical efficacy in R/R LBCL (Thieblemont et al, EHA 2022, abstract LB2364). Encouraging early results were also observed in patients with R/R CLL from the dose-escalation phase of the EPCORE CLL-1 trial, which is currently assessing the safety and efficacy of

epcoritamab in multiple expansion cohorts. Here we present initial data from the RS-LBCL cohort in the ongoing phase 1b/2 EPCORE CLL-1 trial (NCT04623541).

Methods: Eligible adults had biopsy-proven transformation to CD20+ RS-LBCL with a clinical history of CLL or small lymphocytic lymphoma (SLL) disease (PET and/or CT/MRI) and no more than 1 prior line of therapy for RS. SC epcoritamab was administered QW in cycles 1–3, Q2W in cycles 4–9, and Q4W in cycles ≥10 (28 d/cycle) until disease progression or unacceptable toxicity. In cycle 1, step-up dosing and corticosteroid prophylaxis were required to mitigate CRS. Response assessment was performed according to Lugano 2014 criteria using PET-CT.

Results: As of the data cutoff on July 15, 2022, 10 patients with RS (median age, 70.5 y; range, 53–80) had received epcoritamab 48 mg with a follow-up of ≥12 wk. The median time from RS diagnosis to first dose of epcoritamab was 2 mo (range, 0.5–11). Prior therapies for RS included rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP), and 6 patients received epcoritamab as first-line therapy for RS. Median treatment duration was 2.5 mo (range, 0.5–6.5), with 5 (50%) patients receiving ongoing treatment. The most common related treatment-emergent AEs (TEAEs) of any grade were CRS (90%; 40% grade 1, 50% grade 2), anemia (40%), diarrhea (40%), hypophosphatemia (30%), injection-site reaction (30%), and thrombocytopenia (30%). Notable grade 3–4 TEAEs included neutropenia (n=4; 2 patients grade 3, 2 patients grade 4), anemia (n=2), and COVID-19 (n=2). Most CRS events were associated with the first full dose of epcoritamab. All CRS events resolved (median time to resolution, 3 d), no patients discontinued treatment due to CRS, and 6 patients received tocilizumab. No cases of ICANS were observed. Clinical tumor lysis syndrome (grade 2) occurred in 1 patient and resolved within 3 d. No patients discontinued treatment due to AEs. Two patients died due to disease progression. Antitumor activity was observed early (majority of responses seen at the first [wk 6] assessment), with an overall response rate of 60% and a complete response rate of 50%.

Conclusions: In patients with RS, SC epcoritamab demonstrated a manageable safety profile with only low-grade CRS events, mostly associated with the first full dose and all of which resolved. This safety profile was consistent with previous reports of epcoritamab monotherapy, and no new safety signals were reported. Preliminary efficacy findings show that SC epcoritamab has encouraging single-agent activity in RS-LBCL, with high overall and complete response rates observed and the majority of responses seen at the first (wk 6) assessment. This is the first report of epcoritamab in patients with RS-LBCL. The study is ongoing, and updated data with longer-term follow-up and additional treated patients will be presented.

Disclosures: Kater: *Abbvie, Astra Zeneca, BMS, Janssen, Roche/Genentech:* Research Funding; *Abbvie, Astra Zeneca, Janssen:* Other: Speakers fee; *Janssen, LAVA:* Patents & Royalties: Pending; *Astra Zeneca, BMS, Roche/Gennetech, Janssen, Abbvie, LAVA:* Membership on an entity's Board of Directors or advisory committees; *Amsterdam UMC, University of Amsterdam:* Current
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92 Treatment Outcomes after Undetectable MRD with First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed Duration Treatment (Placebo) Versus Continued Ibr with up to 5 Years Median Follow-up in the CAPTIVATE Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Targeted Doublet Combinations

Hematology Disease Topics & Pathways:

Biological therapies, Lymphoid Leukemias, CLL, Combination therapy, Diseases, Therapies, Lymphoid Malignancies

Saturday, December 10, 2022: 9:45 AM

John N. Allan[1], *Tanya Siddiqi, MD*[2*], *Thomas J. Kipps, MD, PhD*[3], *Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA*[4*], *Xavier C. Badoux, MBBS, FRACP, FRCPA*[5], *Jacqueline C. Barrientos, MD, MS*[6*], *Alessandra Tedeschi*[7*], *Stephen Opat, FRACP, FRCPA, MBBS*[8*], *Ian W. Flinn, MD PhD*[9], *Eva Gonzalez Barca, MD, PhD*[10*], *Ryan Jacobs, MD*[11*], *Edith Szafer-Glusman, PhD*[12*], *Cathy Zhou, MS*[12*], *Anita Szoke, MD*[12*], *William G. Wierda, MD, PhD*[13*], *Paolo Ghia, MD, PhD*[14] *and Constantine S. Tam*[15*]

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Background*:* Ibr and Ven are oral inhibitors of BTK and BCL-2, respectively, approved as single agents or in combination with obinutuzumab for CLL treatment (tx). With distinct and complementary mechanisms of action, Ibr and Ven work synergistically to mobilize CLL cells from lymph nodes and lymphoid niches, enhance cell

killing, and eliminate distinct CLL cell populations. CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line Ibr + Ven in patients (pts) with CLL/SLL who have indication for tx. In this MRD cohort, after completion of Ibr + Ven, pts with Confirmed undetectable minimal residual disease (uMRD) were randomly assigned to placebo (PBO) (ie, a fixed-duration regimen), or continued Ibr. At primary analysis, disease-free survival (DFS) rates were similar in pts from these 2 arms (95% and 100%, respectively), 2 y after randomization (Ghia et al. ASH 2021). Here we present efficacy and safety results with median 56 mo (range, 25–68) follow-up (median 41 mo post randomization).

***Methods**:* Pts aged ≤70 y with previously untreated CLL received 3 cycles of Ibr lead-in then 13 cycles of combined Ibr + Ven (oral Ibr 420 mg/d; oral Ven ramp-up to 400 mg/d). Pts achieving Confirmed uMRD (uMRD serially over at least 3 cycles, in both peripheral blood and bone marrow) with Ibr + Ven were then randomly assigned 1:1 to double-blinded tx with PBO or single-agent Ibr. Endpoints included investigator-assessed best response per iwCLL, rates of uMRD ($<10^{-4}$ by 8-color flow cytometry), DFS rate (time from randomization to MRD relapse [for a confirmed uMRD pt, $\geq 10^{-2}$ CLL cells/leukocytes confirmed on 2 serial visits], PD per investigator assessment, or death, whichever occurs first), PFS, OS, and AEs.

***Results**:* 164 pts were enrolled to receive combined Ibr + Ven tx; after completion, 86 pts with Confirmed uMRD were randomly assigned to PBO or single-agent Ibr (n=43 each). Baseline characteristics were previously reported (Wierda et al. *J Clin Oncol.* 2021;39:3853). For pts with Confirmed uMRD, median time on study was 56 mo (Ibr arm range, 25–68 mo; PBO arm range, 40–65 mo); median post-randomization follow-up was 41.2 mo and 41.5 mo in the PBO and Ibr arms, respectively. In the PBO arm, 63% of pts have now achieved a best response of CR (increased from 60% at 2 y); among pts who continued Ibr, 81% achieved a best response of CR (increased from 72% at 2 y). Rates of uMRD remained stable from y 2 to y 3 post randomization (PBO, 56% [n=24] and 58% [n=25]; Ibr 60% [n=26] and 63% [n=27], respectively). The 3-y DFS rate was 85% (95% CI, 69–93) with PBO and 93% (95% CI, 80–98) among pts who continued Ibr (p=0.1621). The 4-y PFS was 88% (95% CI, 74–95) with PBO and 95% (95% CI, 82–99) with continued Ibr; 4-y OS was 100% (n=0 deaths) and 98% (95% CI, 84–100), respectively. Notably, efficacy outcomes in high-risk subgroups were consistent with the total population although low sample size in the PBO arm limits interpretation (**Table**). Prevalence of AEs during the post-randomization period was generally stable in each arm (**Table)**. New occurrences of hypertension in post randomization ys 1–3 were generally lower with PBO vs Ibr (y 1, n=1/43 vs n=3/43; y 2, n=1/41 vs n=4/41; y 3, n=3/38 vs n=2/41, respectively). No new atrial fibrillation or grade ≥3 hemorrhage events occurred in the PBO arm during the 3-y post randomization period; 1 pt in the Ibr arm had atrial fibrillation in 2nd y post randomization. In the 3rd y post randomization, no pts had dose reduction or discontinuation due to an AE as expected in the PBO arm; 1/41 pts had a dose reduction and 2/41 discontinued Ibr due to an AE. In total, 7 and 2 pts have experienced progressive disease in the PBO and Ibr arms, respectively; 4/7 pts in the PBO arm have initiated subsequent therapy (3 with Ibr, 1 with other agent/s; 0 pts in the Ibr arm have initiated subsequent tx).

Conclusions*:* First-line Ibr + Ven is an all-oral, once-daily, chemotherapy-free regimen that continues to provide deep, durable clinical responses in pts with CLL. With an additional y of follow-up in pts with Confirmed uMRD after Ibr + Ven, 4-y OS rates were ≥98% and 4-y PFS rates were ≥88% in pts randomly assigned to PBO (representing fixed duration) or continued Ibr. The durability of uMRD and the 3-y DFS rate of 85% without ongoing tx are encouraging and support the promising potential for tx-free remission. Together with the

safety data, these results demonstrate a favorable benefit-risk profile with fixed duration Ibr + Ven.

Table. Efficacy Outcomes and Prevalence of AEs Over Time

Efficacy outcomes, % (95% CI)	All treated PBO (N=43)	All treated Ibr (N=43)			High-risk[a] PBO (N=6)	High-risk[a] Ibr (N=20)		
DFS (3-y)	85 (69–93)	93 (80–98)			100 (100–100)	95 (70–99)		
PFS (4-y)	88 (74–95)	95 (82–99)			100 (100–100)	95 (70–99)		
OS (4-y)	100 (100–100)	98 (84–100)			100 (100–100)	100 (100–100)		
Prevalence of AEs of clinical interest, n (%)	I+V → PBO Pre-randomization	PBO Time from randomization, mo			I+V → Ibr Pre-randomization	Ibr Time from randomization, mo		
	1st 16 cycles N=43	1–12 N=43	13–24 N=41	25–36 N=38	1st 16 cycles N=43	1–12 N=43	13–24 N=41	25–36 N=41
Arthralgia (any grade)	13 (30)	9 (21)	11 (27)	9 (24)	12 (28)	12 (28)	10 (24)	12 (29)
Hypertension (any grade)	6 (14)	4 (9)	5 (12)	6 (16)	9 (21)	9 (21)	10 (24)	11 (27)
Neutropenia (any grade)	15 (35)	3 (7)	2 (5)	2 (5)	24 (56)	8 (19)	1 (2)	2 (5)
Atrial fibrillation (any grade)	4 (9)	2 (5)	2 (5)	2 (5)	3 (7)	2 (5)	3 (7)	2 (5)
Diarrhea (grade ≥2)	12 (28)	1 (2)	1 (2)	2 (5)	15 (35)	3 (7)	2 (5)	0
Infections/ infestations (grade ≥3)[b]	2 (5)	1 (2)	1 (2)	2 (5)	2 (5)	3 (7)	4 (10)	3 (7)
Hemorrhage (grade ≥3)	0	0	0	0	1 (2)	0	0	0
Grade ≥3 AEs (≥5% incidence overall), n (%)								
Neutropenia	11 (26)	1 (2)	0	0	21 (49)	2 (5)	0	0
Hypertension	5 (12)	2 (5)	2 (5)	1 (3)	4 (9)	3 (7)	2 (5)	2 (5)

[a]High-risk includes pts with del(17p), *TP53*, or complex karyotype. In Ibr arm, 20 high-risk: 13 del(17p)/*TP53* + 7 CK without del(17p)/*TP53*.

[b]Of these, 1 and 2 COVID-19 infections were reported in the PBO and Ibr arms, respectively, at 25–36 mo.

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Therapeutics: Consultancy; *Ascentage:* Consultancy; *Celgene:* Research Funding; *Janssen:* Honoraria, Research Funding, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Speakers Bureau. **Siddiqi:** *Beigene:* Consultancy, Research Funding, Speakers Bureau; *Astrazeneca:* Consultancy, Research Funding, Speakers Bureau; *Ascentage Pharm:* Research Funding; *Oncternal:* Research Funding; *TG Therapeutics:* Research Funding; *Kite Pharma:* Consultancy, Research Funding; *BMS:* Consultancy; *Celgene:* Consultancy; *Juno Therapeutics:* Consultancy, Research Funding; *Jannsen:* Speakers Bureau; *Pharmacyclics:* Research Funding, Speakers Bureau. **Kipps:** *Pharmacyclics, LLC an AbbVie Company:* Consultancy, Research Funding; *AbbVie:* Consultancy, Research Funding; *Genentech-Roch:* Consultancy, Research Funding; *Oncternal:* Research Funding; *Gilead:* Consultancy; *Celgene:* Consultancy. **Kuss:** *Mundipharma:* Consultancy, Honoraria; *Roche Pharmaceuticals:* Consultancy, Honoraria, Speakers Bureau; *Commonwealth Serum Laboratories:* Current equity holder in private company, Current holder of *stock options* in a privately-held company; *AbbVie:* Consultancy, Honoraria, Other: expert textinomy, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Merck:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Kyowa Kirin:* Consultancy, Honoraria. **Badoux:** *AbbVie:* Honoraria, Other: travel, accomodations, expenses; *Janssen:* Honoraria. **Barrientos:** *Janssen:* Honoraria; *Beigene:* Consultancy; *AbbVie:* Consultancy; *AstraZeneca:* Consultancy; *MEI:* Consultancy; *Oncternal:* Research Funding; *Velosbio:* Research Funding; *Pharmacyclics, LLC an AbbVie Company:* Research Funding. **Tedeschi:** *Beigene:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Speakers Bureau. **Opat:** *Pharmacyclics, LLC an AbbVie Company:* Research Funding; *Antegene:* Consultancy, Honoraria, Research Funding; *CSL:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Gilead:* Consultancy, Honoraria, Research Funding; *Merck:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *Belgene:* Research Funding. **Flinn:** *Fate Therapeutics:* Research Funding; *Biopath:* Research Funding; *Hutchison MediPharma:* Consultancy; *Forty Seven:* Research Funding; *Forma Therapeutics:* Research Funding; *Curis:* Research Funding; *Constellation Pharmaceuticals:* Research Funding; *Celgene:* Research Funding; *Incyte:* Research Funding; *IGM Biosciences:* Research Funding; *Merck:* Research Funding; *Loxo@Lilly:* Research Funding; *Infinity Pharmaceuticals:* Research Funding; *2seventy bio:* Research Funding; *Triphase Research & Development*

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Funding; *Janssen:* Research Funding; *Xencor:* Research Funding; *Genentech:* Research Funding. **Ghia:** *Lilly/Loxo:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria, Research Funding. **Tam:** *Beigene:* Honoraria, Research Funding; *AstraZeneca:* Honoraria; *LOXO:* Honoraria; *Janssen:* Honoraria, Research Funding; *AbbVie:* Honoraria, Research Funding.

OffLabel Disclosure: Ibrutinib in combination with venetoclax is not approved in any indication.

965 NX-2127-001, a First-in-Human Trial of NX-2127, a Bruton's Tyrosine Kinase-Targeted Protein Degrader, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia and B-Cell Malignancies

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Drugs in Development and COVID-19

Hematology Disease Topics & Pathways:

Biological therapies, Therapies

Monday, December 12, 2022: 5:30 PM

Anthony R. Mato, MD, MSCE[1], *William G. Wierda, MD, PhD*[2], *Weiyun Z. Ai, MD, PhD*[3], *Ian W. Flinn, MD PhD*[4], *Michael Tees, MD, MPH*[5], *Manish R. Patel, MD*[6], *Krish Patel, MD*[7], *Susan M. O'Brien*[8], *David A. Bond, MD, BS*[9], *Lindsey Roeker, MD*[1], *Tanya Siddiqi, MD*[10*], *Michael L. Wang, MD*[11], *Clare Sun, MD*[12], *Omar Abdel-Wahab, MD*[13], *Amanda Schwab*[14*], *May Tan, BSc*[15*], *Erin Meredith*[14*], *Melissa A. Gessner, PhD*[14*], *Su Young Kim, MD*[14], *Adrian Wiestner, MD*[12] *and Alexey V Danilov, MD*[10]

[1]*Memorial Sloan Kettering Cancer Center, New York*

[2]*MD Anderson Cancer Center, Houston*

[3]*University of California San Francisco Medical Center, San Francisco*

[4]*Tennessee Oncology, Nashville*

[5]*Colorado Blood Cancer Institute, Denver*

[6]*Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL*

[7]*Swedish Cancer Institute, Center for Blood Disorders and Cellular Therapy, Seattle*

[8]*Chao Family Comprehensive Cancer Center, University of California, Irvine*

[9]*The James Cancer Hospital at The Ohio State University, Columbus*

[10]*City of Hope National Medical Center, Duarte*

[11]*MD Anderson Cancer Center, Houston, TX*

[12]*National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda*

[13]*Memorial Sloan Kettering Cancer Center, New York, NY*

[14]*Nurix Therapeutics, Inc., San Francisco*

[15]*Nurix Therapeutics, Inc., San Francisco, CA*

Introduction: Bruton's tyrosine kinase (BTK) is a key component of the B-cell receptor (BCR) signaling pathway. Targeting this pathway has proven highly effective in patients with chronic lymphocytic leukemia (CLL) and other B-cell malignancies. However, mutations in BTK develop with both covalent (cBTKi) and non-covalent inhibitors (ncBTKi) resulting in treatment resistance and disease progression. In addition, increased

expression of the transcription factor IKZF3 may contribute to resistance to cBTKi/ncBTKi. Thus, novel therapeutic mechanisms are needed that target BCR signaling, particularly in patients whose disease has relapsed or is refractory (R/R) to existing BTK targeting therapies. NX-2127 is a novel small molecule that drives targeted BTK and IKZF3 degradation through ubiquitination and proteasomal degradation. This BTK degradation and immunomodulatory activity represents a novel mechanism of action and may overcome resistance to currently available novel agents including cBTKi and ncBTKi, addressing the unmet medical needs of patients whose disease is R/R to any BTKi (including ncBTKi) and a BCL2 inhibitor.

Methods: NX-2127-001 is a first-in-human, multicenter, US-based, open-label, Phase 1 dose-escalation (Phase 1a) and cohort-expansion (Phase 1b) trial, evaluating the safety, tolerability, and preliminary efficacy of NX-2127 in adult patients with R/R CLL and B-cell malignancies. Patients receive NX-2127 orally once daily in 28-day cycles starting at 100 mg. We report the initial findings from the Phase 1a portion of the trial and the rationale for initiating the Phase 1b portion at 100 mg for patients with CLL.

Results: As of 16 June 2022, 28 patients (17 CLL/SLL) were enrolled at dose levels 100, 200 and 300 mg. Patients were predominantly male (64.3%) with a median age of 76 (range 61–92) years. The most common adverse events in all patients are summarized in Table 1. One dose-limiting toxicity (DLT) of cognitive impairment was observed in a patient with CLL at 300 mg. No DLTs were observed in non-CLL indications. As of 16 June 2022, 17 patients with CLL were enrolled having received a median of 6 prior therapies (range 2–12). All have previously received a BTKi and 76.5% had also received venetoclax. Poor prognostic factors include unmutated *IGHV* (23.5%), mutations/deletions in *TP53* (17.6%). Of the 14 CLL patient samples tested, mutations included *BTK* [C481 (29%), L528 (29%), T474 (14%), V416 (7%)] and *BCL2* (14%). Mutations C481, V416 and L528 result in loss of BTK kinase function.

A mean BTK degradation of 86% was observed in all patients by Cycle 1 Day 22 with a mean degradation of 83% in patients with CLL, resulting in decreased BCR signaling as measured by reduction of plasma CCL4. Immunomodulatory activity, as evidenced by Ikaros (IKZF1) degradation, was observed at all dose levels and in all indications. 10 patients with CLL continue on study (Figure 1). There were 12 response-evaluable patients with CLL. The best overall response rate (ORR) was 33% with evidence that ORR increases with longer follow up (ORR: 16.7% at 2 mos, 42.9% at 4 mos, 50% at 6 mos). Importantly, responses were noted in BTKi/BCL2 double-refractory patients and those who progressed on a ncBTKi.

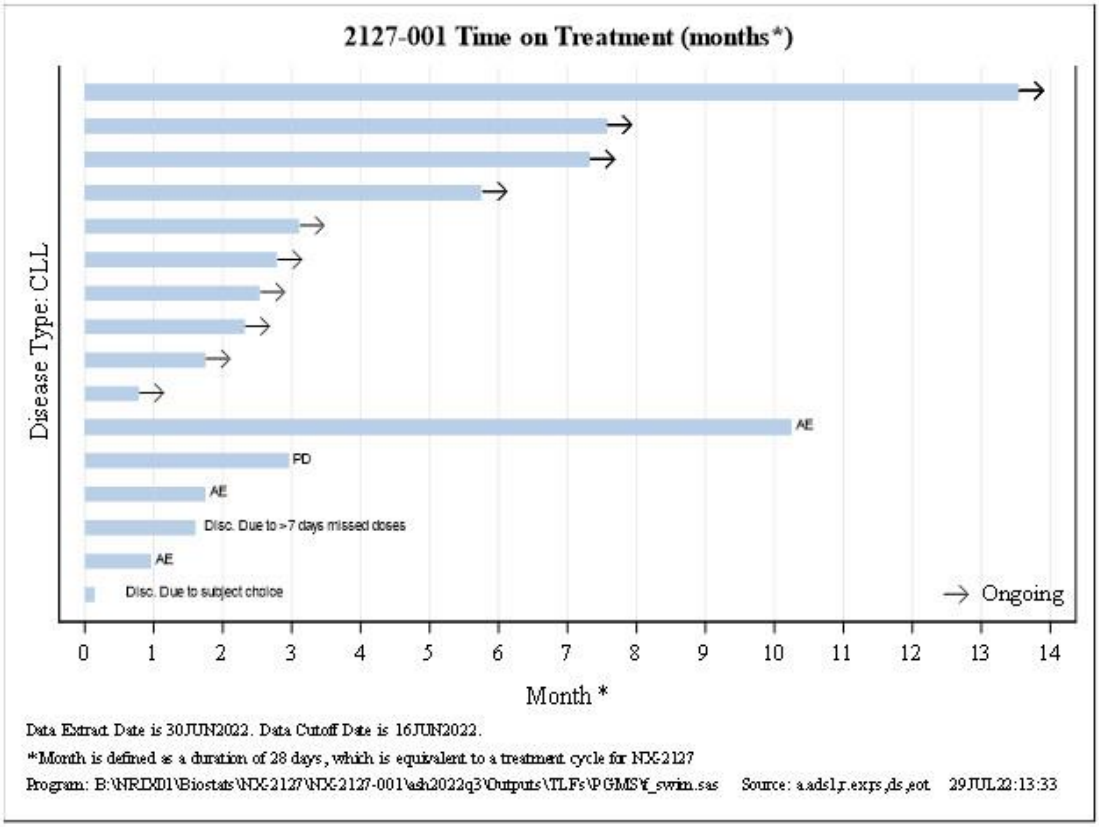
Conclusions: Double- and emerging triple-refractory CLL (patients who progressed on cBTKi, ncBTKi, and a BCL2 inhibitor) represents a major unmet medical need with no approved therapeutic options and poor survival. These patients may thus benefit from the interruption of BTK kinase-independent scaffolding signaling. In this first-in-human, first-in-class study of a BTK degrader, clinical responses and benefit were observed in heavily pretreated (median 6 prior therapies) patients with CLL who have poor prognostic factors, including those with *BTK* mutations resistant to cBTKi and ncBTKi, *BCL2* mutations and those who were previously treated with both BTKi and BCL2 inhibitors. These data support further clinical development of NX-2127 in CLL,

including expansion at the 100 mg dose level, and continued dose exploration for other B-cell malignancies. (NCT04830137).

Table 1. Summary of treatment-emergent adverse events (TEAEs) occurring in >15% of all patients (including patients with CLL and NHL)

Preferred Term	All Grades (N=26)	Grade ≥ 3 (N=26)	Grade ≥ 3 Related (N=26)
Any AE	25 (96%)	15 (58%)	12 (46%)
Fatigue	16 (62%)	0 (0%)	0 (0%)
Neutrophil Count Decrease	10 (39%)	9 (35%)	9 (35%)
Anemia	7 (27%)	4 (15%)	2 (8%)
Contusion	7 (27%)	0 (0%)	0 (0%)
Hypertension	7 (27%)	1 (4%)	1 (4%)
Dyspnoea	5 (19%)	1 (4%)	0 (0%)
Pruritis	5 (19%)	0 (0%)	0 (0%)
Rash maculo-papular	5 (19%)	0 (0%)	0 (0%)
Blood creatinine increased	4 (15%)	0 (0%)	0 (0%)
COVID-19	4 (15%)	1 (4%)	0 (0%)
Diarrhea	4 (15%)	0 (0%)	0 (0%)
Petechiae	4 (15%)	0 (0%)	0 (0%)
Platelet count decreased	4 (15%)	1 (4%)	0 (0%)

Figure 1. CLL patient disposition



1 patient with CLL did not have dosing data entered at time of the data cut and thus was not included in this figure.

Disclosures: Mato: *Curio:* Honoraria; *AbbVie:* Honoraria, Research Funding; *Johnson & Johnson:* Honoraria, Research Funding; *Medscape:* Honoraria; *AstraZeneca:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding; *Genentech:* Honoraria, Research Funding; *Genmab:* Honoraria, Research Funding; *DTRM Biopharma:* Honoraria, Research Funding; *Octopharma:* Honoraria, Research Funding; *LOXO:* Honoraria, Research Funding; *BeiGene:* Honoraria, Research Funding; *Dava:* Honoraria; *Pharmacyclics, LLC:* Honoraria, Research Funding; *Pfizer:* Research Funding; *TG Therapeutics, Inc:* Honoraria, Research Funding; *Nurix:* Research Funding; *Acerta:* Research Funding; *PER:* Honoraria; *BMS:* Honoraria; *Adaptive Biotechnologies:* Honoraria; *PerView:* Honoraria. **Wierda:** *Sanofi:* Consultancy; *Karyopharm:* Research Funding; *Miragen:* Research Funding; *Genzyme:* Consultancy; *Cyclacel:* Research Funding; *Bristol Meyers Squibb (Juno and Celgene):* Research Funding; *Genentech:* Research Funding; *Juno:* Research Funding; *Janssen:* Research Funding; *Kite, a Gilead Company:* Research Funding; *Oncternal Therapeutics, Inc.:* Research Funding; *Gilead Sciences:* Research Funding; *Xencor:* Research Funding; *Sunesis:* Research Funding; *Pharmacyclics LLC:* Research Funding; *Loxo Oncology, Inc./Lilly:* Research Funding; *GSK/Novartis:* Research Funding; *AstraZeneca/Acerta Pharma. Inc.:* Research Funding; *AbbVie:* Research Funding. **Ai:** *Secura Bio:* Consultancy; *More Health:* Consultancy; *Kymera:* Consultancy; *Kite:* Consultancy; *AC therapeutics:* Consultancy; *Acrotech:* Consultancy; *BeiGene:* Consultancy; *Walking Fish:* Consultancy. **Flinn:** *AstraZeneca:* Consultancy, Research Funding; *City of Hope National Medical Center:* Research Funding; *CTI Biopharma:* Research Funding; *BeiGene:* Consultancy, Research Funding; *Triphase Research & Development Corp:* Research Funding; *2seventy bio:* Research Funding; *Epizyme:* Research Funding; *Fate Therapeutics:* Research Funding; *Millenium Pharmaceuticals:* Research Funding; *Tessa Therapeutics:* Research Funding; *TCR2 Therapeutics:* Research Funding; *Kite Pharma:* Consultancy, Research Funding; *Acerta Pharma:* Research Funding; *Forty Seven:* Research Funding; *ArQule:* Research Funding; *Agios:* Research Funding; *Vincerx Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Verastem:* Consultancy, Research Funding; *Unum Therapeutics:* Research Funding; *TG Therapeutics:* Consultancy, Research Funding; *Takeda:* Consultancy; *Curis:* Research Funding; *Celgene:* Research Funding; *Constellation Pharmaceuticals:* Research Funding; *Servier Pharmaceuticals:* Consultancy; *Seattle Genetics:* Research Funding; *MorphoSys:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Nurix Therapeutics:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding; *Roche:* Consultancy, Research Funding; *CALIBR:* Research Funding; *Bristol Myers Squibb:* Research Funding; *Secura Bio:* Consultancy; *Myeloid Therapeutics:* Research Funding; *Trillium Therapeutics:* Research Funding; *Rhizen Pharmaceuticals:* Research Funding; *Portola Pharmaceuticals:* Research Funding; *Pfizer:* Research Funding; *Merck:* Research Funding; *Loxo@Lilly:* Research Funding; *Incyte:* Research Funding; *Infinity*

Pharmaceuticals: Research Funding; *CALGB:* Research Funding; *Century Therapeutics:* Consultancy; *Genmab:* Consultancy; *Genentech:* Consultancy, Research Funding; *Gilead Sciences:* Research Funding; *Iksuda Therapeutics:* Consultancy; *InnoCare Pharma:* Consultancy, Research Funding; *Janssen:* Consultancy, Research Funding; *Forma Therapeutics:* Research Funding; *Biopath:* Research Funding; *Xencor:* Consultancy; *Hutchison MediPharma:* Consultancy; *IGM Biosciences:* Research Funding; *AbbVie:* Consultancy, Research Funding. **Patel:** *Exelixis:* Speakers Bureau; *ION Pharma:* Other: Leadership; *Adaptive Biotechnologies:* Honoraria; *Bayer:* Honoraria; *Pharmacyclics:* Honoraria; *Blueprint Pharmaceuticals:* Research Funding; *Immunogen:* Research Funding; *Compugen:* Research Funding; *Accutar Biotech:* Research Funding; *Astellas:* Research Funding; *Adagene:* Research Funding; *Olema:* Research Funding; *Zymeworks:* Research Funding; *TeneoBio:* Research Funding; *Silicon Therapeutics:* Research Funding; *Samumed:* Research Funding; *Relay Therapeutics:* Research Funding; *Nurix:* Research Funding; *Novartis:* Research Funding; *NGM Biopharmaceuticals:* Research Funding; *Black Diamond Therapeutics:* Research Funding; *BioTheryX:* Research Funding; *Puretech:* Research Funding; *IgM Biosciences:* Research Funding; *MabSpace:* Research Funding; *Treadwell:* Research Funding; *Artios:* Research Funding; *ORIC:* Research Funding; *Vigeo:* Research Funding; *TopAlliance BioSciences Inc:* Research Funding; *Tesaro:* Research Funding; *Takeda:* Research Funding; *Taiho Pharmaceutical:* Research Funding, Speakers Bureau; *Syndax:* Research Funding; *Seven and Eight Biopharmaceuticals:* Research Funding; *Ribon Therapeutics:* Research Funding; *Prelude Therapeutics:* Research Funding; *Portola Pharmaceuticals:* Research Funding; *Placon:* Research Funding; *Pfizer:* Honoraria, Research Funding; *Moderna Therapeutics:* Research Funding; *Mirati Therapeutics:* Research Funding; *Millennium:* Research Funding; *Merck:* Research Funding; *Macrogenics:* Research Funding; *Lycera:* Research Funding; *LSK Biopartners:* Research Funding; *Loxo:* Research Funding; *Kymab:* Research Funding; *Klus Pharma:* Research Funding; *Janssen:* Honoraria, Research Funding; *Jacobio:* Research Funding; *Incyte:* Research Funding; *Ignyta:* Research Funding; *Hutchison MediPharma:* Research Funding; *Hengrui Therapeutics:* Research Funding; *H3 Biomedicine:* Research Funding; *GlaxoSmithKline:* Research Funding; *Gilead Sciences:* Research Funding; *Genentech/Roche:* Honoraria, Research Funding, Speakers Bureau; *FORMA Therapeutics:* Research Funding; *Evelo Therapeutics:* Research Funding; *EMD Serono:* Research Funding; *Eli Lilly and Company:* Research Funding; *Daiichi Sankyo:* Research Funding; *Cyteir Therapeutics:* Research Funding; *Clovis Oncology:* Research Funding; *CicloMed:* Research Funding; *Checkpoint Therapeutics:* Research Funding; *Celgene:* Research Funding, Speakers Bureau; *Boehringer Ingelheim:* Research Funding; *BioNTech AG:* Research Funding; *AstraZeneca:* Research Funding; *Aileron Therapeutics:* Research Funding; *Agenus:* Research Funding; *ADC Therapeutics:* Research Funding; *Acerta Pharma:* Research Funding; *Pfizer/EMD Serono:* Consultancy; *Pharmacyclics/Janssen:* Consultancy. **Patel:** *Trillium*

Therapuetics/Pfizer: Consultancy, Research Funding; *Fate Therapeutics:* Research Funding; *AstraZeneca:* Consultancy, Research Funding, Speakers Bureau; *CRISPR Therapeutics:* Research Funding; *TG Therapeutics:* Consultancy, Speakers Bureau; *MEI Pharma:* Consultancy, Research Funding; *Morphosys:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding, Speakers Bureau; *Epizyme:* Consultancy, Research Funding; *Caribou Biosciences:* Consultancy; *Curis, Inc:* Research Funding; *Celgene:* Consultancy, Research Funding, Speakers Bureau; *BeiGene:* Consultancy; *Genetech/Roche:* Consultancy, Research Funding, Speakers Bureau; *Sunesis Pharmaceuticals:* Research Funding; *Nurix:* Research Funding; *Pharmacyclics/Janssen:* Consultancy, Research Funding, Speakers Bureau; *Kite pharma:* Consultancy, Research Funding, Speakers Bureau; *Loxo Oncology:* Consultancy, Research Funding; *Xencor:* Consultancy, Research Funding; *Aptevo Therapeutics:* Research Funding; *ADC Therapeutics:* Consultancy; *Abbvie:* Consultancy; *Adaptive Biotechnologies:* Research Funding; *Velos Bio:* Research Funding. **O'Brien:** *AbbVie, Alexion, Amgen, Aptose Biosciences, Astellas, AstraZeneca, Autolus, Bristol Myers Squibb, Celgene, DynaMed, Eli Lilly and Company, Gilead, GlaxoSmithKline, Janssen Oncology, Johnson and Johnson, Juno Therapeutics, MEI Pharma Inc, Merck:* Consultancy; *Acerta, Alliance, Beigene Ltd, Caribou Biosciences Inc, Gilead, Kite, Loxo Oncology, Mustang, Nurix Therapeutics Inc, Pfizer, Pharmacyclics, Regeneron, Sunesis, and TG Therapeutics.:* Research Funding; *Nova Research Company, Pfizer, Pharmacyclics, TG Therapeutics, Vaniam Group LLC, Verastem, Vida Ventures:* Consultancy. **Bond:** *Novartis:* Research Funding; *Nurix:* Research Funding; *Kite/Gilead:* Consultancy, Honoraria; *SeaGen:* Consultancy, Honoraria. **Roeker:** *AbbVie:* Consultancy , Divested equity in a private or publicly-traded company in the past 24 months; *AstraZeneca:* Consultancy; *Beigene:* Consultancy; *Janssen:* Consultancy; *Loxo Oncology:* Consultancy, Other: Travel support, Research Funding; *Pharmacyclics:* Consultancy; *Pfizer:* Consultancy, Research Funding; *TG Therapeutics:* Consultancy; *Abbott Laboratories:* Current equity holder in publicly-traded company; *Aptose Biosciences:* Research Funding; *Ascentage:* Consultancy; *Qilu Puget Sound Biotherapeutics:* Research Funding. **Siddiqi:** *Astrazeneca:* Consultancy, Research Funding, Speakers Bureau; *Beigene:* Consultancy, Research Funding, Speakers Bureau; *Pharmacyclics:* Research Funding, Speakers Bureau; *Jannsen:* Speakers Bureau; *Juno Therapeutics:* Consultancy, Research Funding; *Celgene:* Consultancy; *BMS:* Consultancy; *Kite Pharma:* Consultancy, Research Funding; *TG Therapeutics:* Research Funding; *Oncternal:* Research Funding; *Ascentage Pharm:* Research Funding. **Wang:** *OncLive:* Honoraria; *Studio ER Congressi:* Honoraria; *Pharmacyclics:* Consultancy, Honoraria, Research Funding; *VelosBio:* Consultancy, Research Funding; *Celgene:* Research Funding; *Genmab:* Research Funding; *Genentech:* Consultancy, Research Funding; *InnoCare:* Consultancy, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Kite*

Pharma: Consultancy, Honoraria, Research Funding; *Leukemia & Lymphoma Society:* Consultancy, Honoraria; *Lilly:* Consultancy, Research Funding; *Juno Therapeutics:* Consultancy, Research Funding; *Loxo Oncology:* Research Funding; *Molecular Templates:* Research Funding; *Vinverx:* Research Funding; *Dava Oncology:* Honoraria; *MJH Life Sciences:* Honoraria; *IDEOlogy Health:* Honoraria; *Eastern Virginia Medical School:* Honoraria; *Moffit Cancer Center:* Honoraria; *Practice Point Communications (PPC):* Honoraria; *Physicians Education Resources (PER):* Honoraria; *Pepromene Bio:* Consultancy; *Oncternal:* Consultancy, Research Funding; *Milken Institute:* Consultancy; *Merck:* Honoraria; *LLC TS Oncology:* Honoraria; *Meeting Minds Experts:* Honoraria; *Medscape:* Honoraria; *Oncology Specialty Group:* Honoraria; *Deciphera:* Consultancy; *BioInvent:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *Acerta Pharma:* Honoraria, Research Funding; *AbbVie:* Consultancy. **Sun:** *Genmab:* Research Funding. **Abdel-Wahab:** *H3B Biomedicine, LOXO Oncology, and Nurix Therapeutics:* Research Funding; *Envisagenics Inc., AIChemy, Harmonic Discovery Inc., and Pfizer Boulder:* Membership on an entity's Board of Directors or advisory committees; *H3B Biomedicine, Foundation Medicine Inc, Merck, Prelude Therapeutics, and Janssen:* Consultancy. **Schwab:** *Nurix Therapeutics, Inc.:* Current Employment. **Tan:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Meredith:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Gessner:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Kim:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Wiestner:** *Nurix:* Research Funding; *Merck:* Research Funding; *Abbvie company:* Research Funding; *Pharmacyclics:* Research Funding; *GenMab:* Research Funding; *Acerta Pharma:* Research Funding; *Verastem:* Research Funding. **Danilov:** *Incyte:* Consultancy; *Genentech:* Consultancy; *Morphosys:* Consultancy; *MEI:* Consultancy, Research Funding; *Takeda Oncology:* Research Funding; *Astra Zeneca:* Consultancy, Research Funding; *Beigene:* Consultancy; *Bristol-Meyers-Squibb:* Consultancy, Research Funding; *Bayer Oncology:* Research Funding; *Abbvie:* Consultancy, Research Funding; *Nurix:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy; *Cyclacel:* Research Funding; *GSK:* Consultancy.

OffLabel Disclosure: NX-2127 is a novel small molecule that drives targeted BTK and IKZF3 degradation through ubiquitination and proteasomal degradation.

961 Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

Program: Oral and Poster Abstracts

Type: Oral

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Drugs in Development and COVID-19

Hematology Disease Topics & Pathways:

Research, clinical trials, Lymphoid Leukemias, CLL, Clinical Research, B Cell lymphoma, Diseases, Lymphoid Malignancies

Monday, December 12, 2022: 4:30 PM

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Background: Covalent Bruton tyrosine kinase inhibitors (BTKi) have transformed the treatment landscape of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Despite the efficacy of covalent BTKi, treatment failure often occurs through development of resistance or intolerance. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover. Pirtobrutinib is well tolerated and has demonstrated promising efficacy in patients (pts) with poor-prognosis B-cell malignancies following prior therapy, including prior covalent BTKi (Mato et al. Lancet, 2021). Here, we report updated CLL/SLL results from the BRUIN study (NCT03740529).

Methods: Pts with previously treated B-cell malignancies, including CLL/SLL, were eligible for treatment with pirtobrutinib monotherapy in either the dose escalation or expansion portion of the multicenter BRUIN study. Key endpoints included overall response rate (ORR) per 2018 iwCLL response criteria, progression-free survival (PFS), and safety. The response evaluable cohort consisted of all CLL/SLL pts enrolled to either phase 1 or 2 who had received a prior covalent BTKi containing regimen and had undergone their first response assessment or discontinued therapy. The safety cohort consisted of all pts with B-cell malignancies who received at least one dose of pirtobrutinib monotherapy (n=725). A data cut of 31 January 2022 was utilized.

Results: Among the 276 pts with CLL/SLL who had received a prior BTKi, median age was 69 (range 36-88) years and the median number of prior therapies was 3 (range 1-11). Additional prior therapies included anti-CD20 antibody (89%), chemotherapy (80%), BCL2 inhibitor (44%), PI3K inhibitor (24%), CAR-T cell therapy

(6%), and stem cell transplantation (2%). High-risk features were frequent: del(17p) in 29% (58/197), mutated *TP53* in 40% (91/230), and unmutated IGHV in 85% (188/220). The majority of pts (n=206, 75%) discontinued prior BTKi therapy due to disease progression. Overall, 84% (n=232) received the recommended phase 2 dose of 200 mg once daily as starting dose. In this group of heavily pretreated relapsed/refractory CLL/SLL patients, including all with prior BTKi use, the ORR by investigator assessment was 74% (95% CI, 68-79) (Table) including 3 complete responses (1%), 174 partial responses (PR; 64%), 23 PRs with lymphocytosis (PR-L; 8%), and 1 nodular PR (<1%). At a median follow up time of 13.9 months, the median PFS was 19.4 months (95% CI, 16.6-22.3) (Figure). The 12-month and 18-month estimated PFS rates were 68% (95% CI, 62-74) and 54% (95% CI, 46-61), respectively. The ORR and PFS across various patient subgroups are depicted in the Table. In the safety cohort of all pirtobrutinib treated pts with B-cell malignancies (n=725), the most common TEAEs, regardless of attribution, were fatigue (26%, n=191), diarrhea (22%, n=160), and contusion (19%, n=138). The most frequent Grade ≥3 TEAE was neutropenia (20%, n=143). Low rates of Grade ≥3 TEAEs of hypertension (3%, n=20), hemorrhage (2%, n=16), and atrial fibrillation/flutter (1%, n=7) were observed. Overall, 15 (2%) pts discontinued due to a treatment-related AE.

Conclusion: In this updated analysis with additional pts and extended follow-up, pirtobrutinib continues to demonstrate promising and durable efficacy in heavily pre-treated R/R CLL/SLL pts who have been treated with a prior covalent BTKi, regardless of prior therapy, reason for prior BTKi discontinuation, age, high-risk *TP53* mutations, C481 mutational status, and/or del(17p). Pirtobrutinib was well-tolerated with low-rates of

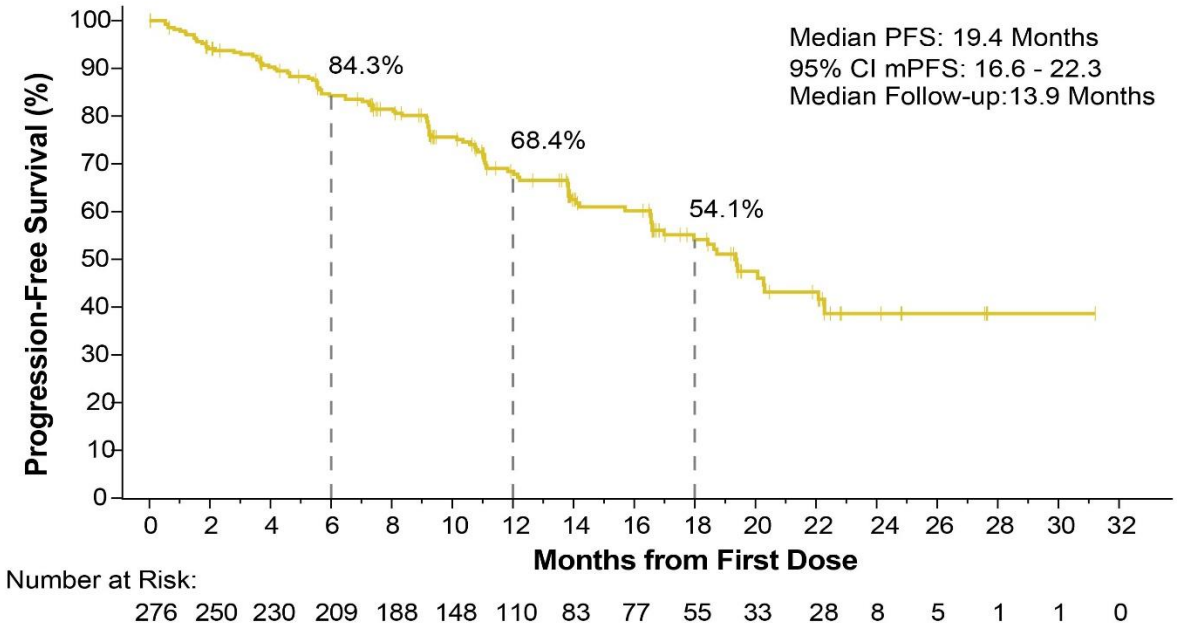
discontinuation due to drug-related toxicity.

Table. ORR including PR-L and progression-free survival in all BTKi pre-treated CLL/SLL patients and select patient subgroups

		BTKi pre-treated CLL/SLL, n	Response Evaluable Cohort, n	ORR, % (95% CI)	Median PFS, months (95% CI)	Estimated 12-month PFS rate, % (95% CI)	Estimated 18-month PFS rate, % (95% CI)
Overall		276	273	74 (68-79)	19.4 (16.6-22.3)	68 (62-74)	54 (46-61)
Age	**≥75**	57	56	71 (58-83)	20.1 (15.7- NE)	78 (63-87)	62 (44-75)
	<75	219	217	74 (68-80)	18.7 (16.6- NE)	66 (58-73)	52 (43-60)
At least prior BTKi and BCL2i	**Yes**	122	119	73 (64-81)	14.1 (11.1-18.7)	58 (47-68)	42 (29-55)
	No	154	154	74 (66-81)	22.1 (18.4-NE)	75 (67-82)	62 (52-70)
Del(17p) and/or *TP53* mutation	**Yes**	99	98	80 (70-87)	16.6 (13.8-22.1)	69 (58-78)	47 (33-59)
	No	107	107	67 (58-76)	19.4 (14.1-NE)	66 (55-75)	58 (46-68)
BTK C481 status*	**Mutated**	85	85	81 (71-89)	17.0 (13.8-20.3)	69 (57-79)	49 (35-61)
	Unmutated	91	91	65 (54-75)	20.3 (13.8-NE)	63 (52-73)	54 (40-65)
Reason for Prior BTKi discontinuation	**Disease progression**	206	205	73 (66-79)	18.6 (13.9-20.3)	66 (58-73)	50 (41-59)
	Intolerance & Other	68	66	76 (64-85)	NE (18.4-NE)	77 (64-86)	67 (51-79)

*Pts with available mutation data who progressed on any prior covalent BTKi, excluding those who were covalent BTKi intolerant.
Del(17p)- deletion 17p; PFS- median progression-free survival; DOR- median duration of response; CI- confidence interval; ORR- overall response rate; N- number of patients; n- number of response evaluable patients in sample; NE- not evaluable

Figure. Progression-free survival in covalent BTKi pre-treated CLL/SLL



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OffLabel Disclosure: We will be presenting data from the BRUIN trial. Pirtobrutinib is not approved yet.

3114 Efficacy and Safety of Nemtabrutinib, a Wild-Type and C481S-Mutated Bruton Tyrosine Kinase Inhibitor for B-Cell Malignancies: Updated Analysis of the Open-Label Phase 1/2 Dose-Expansion Bellwave-001 Study

Program: Oral and Poster Abstracts

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

Hematology Disease Topics & Pathways:

Research, Clinical Research, Diseases, Lymphoid Malignancies, Human, Study Population

Sunday, December 11, 2022, 6:00 PM-8:00 PM

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Background: Bruton tyrosine kinase inhibitors (BTKis) have transformed the treatment landscapes of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and certain B-cell neoplasms. However, the most common mechanism of resistance is due to mutations to BTK at the cysteine binding site (C481). Nemtabrutinib (MK-1026, formerly ARQ-531) is a noncovalent, potent inhibitor of both wild-type and ibrutinib-resistant C481S-mutated BTK. Initial results from the phase 1/2 BELLWAVE-001 study (NCT03162536) showed nemtabrutinib had a manageable safety profile and promising antitumor activity in heavily pretreated patients (pts) with relapsed or refractory (R/R) CLL/SLL, including pts whose disease progressed after prior covalent BTKis (Woyach et al. *Blood*. 2021;138:392). We present updated efficacy for all pts with CLL/SLL treated with nemtabrutinib 65 mg and safety for all pts with hematological malignancies who were treated with nemtabrutinib at the 65-mg dose.

Methods: In this open-label, single-arm, phase 1/2 study, 9 expansion cohorts were initiated after determination of the preliminary nemtabrutinib recommended phase 2 dose (RP2D). Eligible pts with CLL/SLL

were enrolled in cohort A (R/R CLL/SLL, with ≥2 prior therapies, including covalent BTKis, with documented C481 mutation), cohort B (R/R CLL/SLL with ≥2 prior therapies, intolerant to a BTKi, without C481 mutation), a dose-expansion group, or cohort I (food effect). Primary end points were ORR (per 2018 IWCLL criteria, by investigator), safety, and RP2D for pts with CLL/SLL. Secondary end points were DOR (including partial response [PR] with lymphocytosis), PFS, and safety. Efficacy analysis included CLL/SLL pts treated with nemtabrutinib 65-mg once-daily dose and safety included all pts with hematological malignancies who were treated with the nemtabrutinib 65-mg dose.

Results: A total of 112 pts were enrolled and were treated with nemtabrutinib 65 mg once daily: 57 had CLL/SLL, 46 had B-cell non-Hodgkin lymphoma (NHL), 6 had Waldenstrom's macroglobulinemia, and 3 had a diagnosis of "other." Among the 57 pts with CLL/SLL enrolled and treated with nemtabrutinib 65 mg (cohort A, n = 25; cohort B, n = 10; dose escalation, n = 13; cohort I, n = 9); median age was 66.0 years; 16 pts (28%) were female, and 50 (88%) had ECOG PS ≤1. Median (range) number of prior therapies was 4 (1-18); 54 pts (95%) had prior BTKi therapy; 24 (42%) had prior BTKi and BCL2i therapy. In addition, 36 pts (63%) had C481S-mutated BTK; 18 (32%) had *TP53* mutation; 19 (33%) had del(17p); and 30 (53%) had unmutated *IGHV*. Of pts with CLL/SLL, 39 (68%) discontinued, most commonly because of clinical disease progression [PD] and "other" causes (10 [18%] each); 8 (14%) discontinued owing to adverse events (AEs). Among the 24 pts with CLL/SLL who received prior BTKis and BCL-2is, 19 (33%) discontinued, most commonly because of clinical PD and other causes (6 [11%] each) and AEs (4 [7%]).

At data cutoff (April 08, 2022), median (range) follow-up for pts with CLL/SLL was 8.1 months (0.1-38.8); 32 pts had objective response (ORR, 56% [95% CI, 42-69]; complete response, 2; PR, 15; PR with residual lymphocytosis, 15). Among the 32 pts who responded, median DOR was 24.4 months (95% CI, 13.9-not evaluable [NE]); median PFS was 26.3 months (95% CI, 10.1-NE). Efficacy by key subgroups is presented in the table. Among all pts with B-cell malignancies treated with nemtabrutinib at the 65-mg dose (N = 112) included in the safety analysis, 82 (73%) had any-grade treatment-related AEs (TRAEs), most common (≥10%) were dysgeusia (21%); decreased neutrophils (20%); fatigue (13%); nausea and decreased platelets (12%, each); and diarrhea and hypertension (10%, each). Grade 3 or 4 TRAEs occurred in 45 pts (40%); most common (≥5%) were decreased neutrophils (17%) and decreased platelets and lymphocytosis (5%, each). Treatment-related discontinuations occurred in 15 pts (13%). No deaths were attributed to treatment.

Conclusion: Nemtabrutinib 65 mg continued to show promising and durable antitumor activity with a manageable safety profile in a highly relapsed/refractory population who had prior therapy with novel agents.

Pts with CLL/SLL treated with nemtabrutinib 65 mg once daily N = 57				
	CLL/SLL with prior BTK and BCL2 inhibitors	C481S-mutated BTK	del(17p)	*IGHV*-unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95%, CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%)	14 (58)	21 (58)	10 (53)	15 (50)
CR	0	1 (3)	1 (5)	0
PR	6 (25)	11 (31)	2 (11)	8 (27)
PR with residual lymphocytosis	8 (33)	9 (25)	7 (37)	7 (23)
Median duration of response, months	8.5	24.4	11.2	24.4
95% CI	2.7-NE	8.8-NE	5.7-NE	8.5-NE
Median PFS, months	10.1	26.3	10.1	15.9
95% CI	7.4-15.9	10.1-NE	4.6-NE	7.4-NE

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