POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
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LEUCEMIA LINFATICA CRONICA

Terapie di salvataggio

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	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					x	x	
AstraZeneca					x	x	
Abbvie	x				x	x	
Beigene						x	
Takeda	x				x	x	

ALPINE: Final Analysis of Zanubrutinib vs Ibrutinib for Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Randomized, open-label phase III trial (median f/u: 29.6 mo)

R/R CLL/SLL
≥1 prior systemic tx
no prior BTKi
no warfarin
no vitamin K antagonists
(N = 652)

→ **Zanubrutinib** 160 mg PO BID
→ **Ibrutinib** 420 mg PO QD

Until PD or unacceptable toxicity

Primary Endpoint
- ORR (PR+CR) noninferiority and superiority (by investigator)

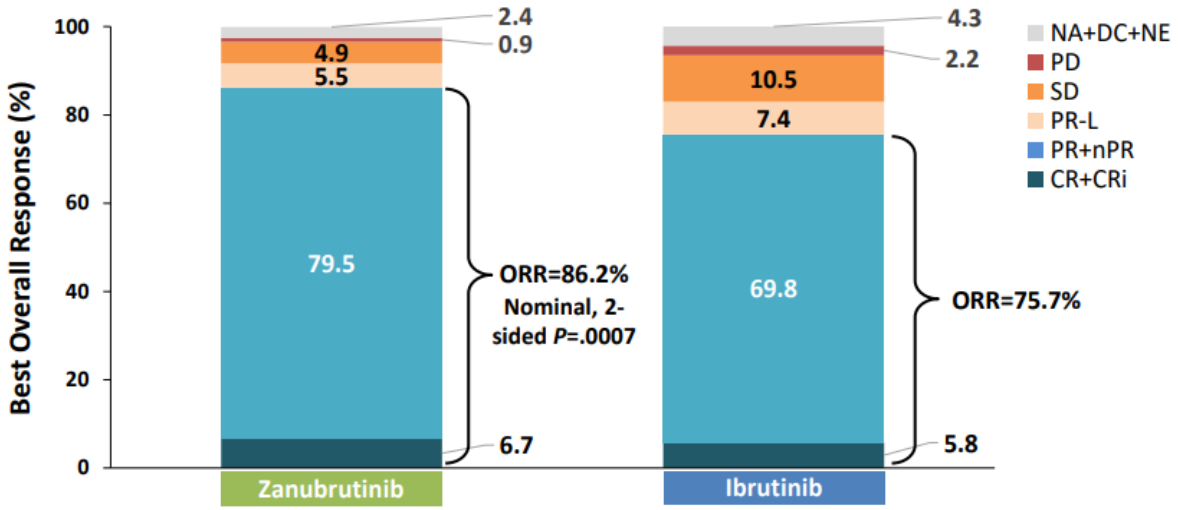
Key Secondary Endpoints
- PFS
- Incidence of atrial fibrillation

Other Secondary Endpoints
- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety

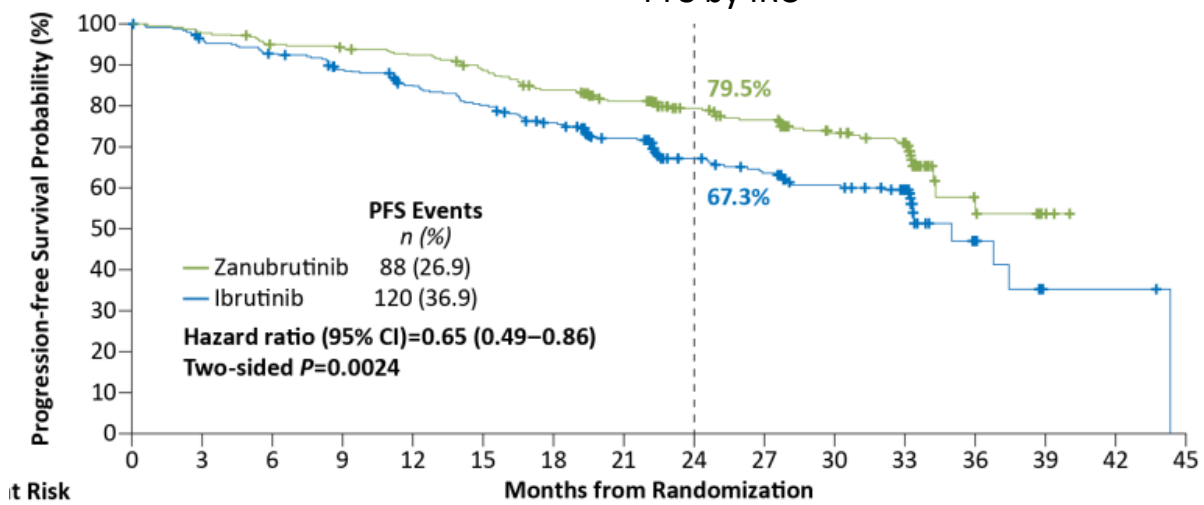
Baseline Characteristics

Characteristics	Zanubrutinib (n = 327)	Ibrutinib (n = 325)
Median age, yr (range)	67 (35-90)	68 (35-89)
Med. No prior Txs (range)	1 (1-6)	1 (1-12)
del(17p) and/or *TP53*^{mut}, n (%)	75 (22.9)	75 (23.1)
Unmutated IGHV, n (%)	239 (73.1)	239 (73.5)
Complex karyotype, n (%)*	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

Median study follow-up :
29.6 months



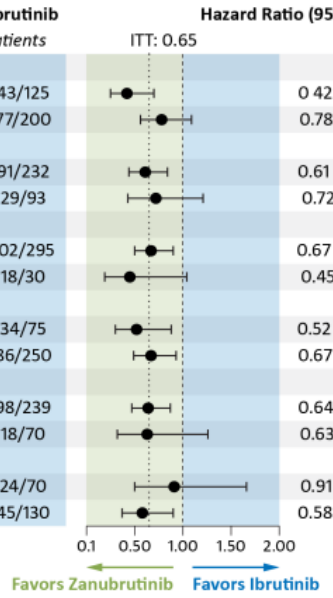
PFS by IRC



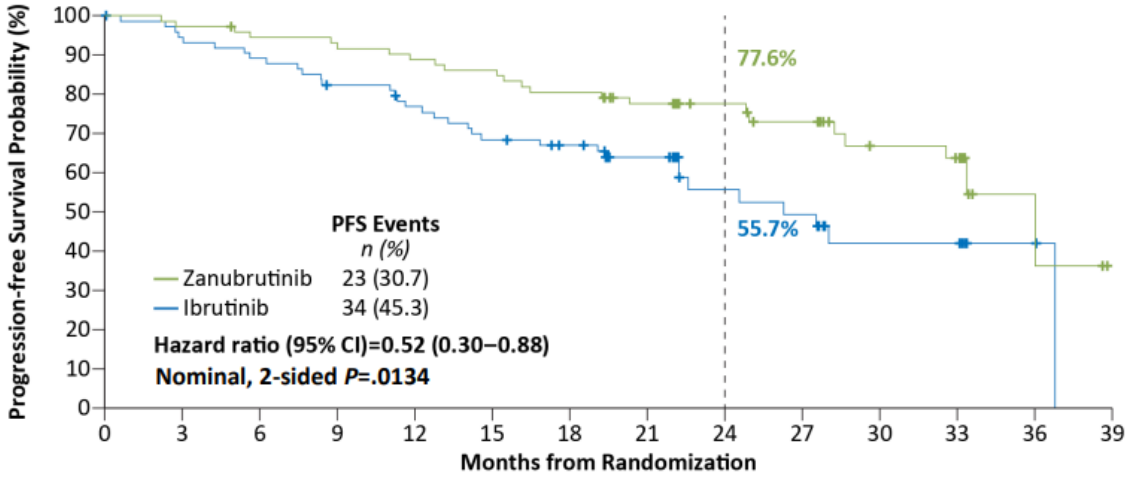
ALPINE: Final Analysis of Zanubrutinib vs Ibrutinib for Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

PFS Across Subgroups

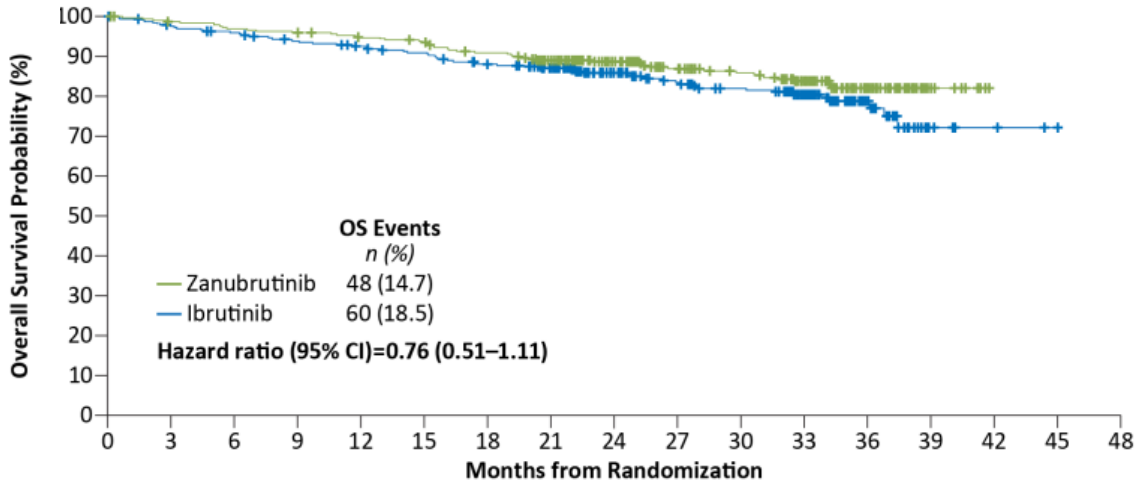
Subgroup	Zanubrutinib Response/Patients	Ibrutinib Response/Patients	Hazard Ratio (95% CI)[a]
Age group			
<65 years	23/126	43/125	0 42 (0.25, 0.70)
≥65 years	65/201	77/200	0.78 (0.56, 1.09)
Sex			
Male	59/213	91/232	0.61 (0.44, 0.84)
Female	29/114	29/93	0.72 (0.43, 1.21)
Prior lines of therapy			
1–3	80/303	102/295	0.67 (0.50, 0.90)
>3	8/24	18/30	0.45 (0.19, 1.04)
Baseline *del*(17p)/*TP53* mutation status			
Present	23/75	34/75	0.52 (0.30, 0.88)
Absent	65/251	86/250	0.67 (0.49, 0.93)
Baseline IGHV mutation status			
Unmutated	72/239	98/239	0.64 (0.47, 0.87)
Mutated	15/79	18/70	0.63 (0.32, 1.26)
Complex karyotype			
Yes	20/56	24/70	0.91 (0.50, 1.66)
No	37/153	45/130	0.58 (0.37, 0.90)



IRC-PFS del(17p)/TP53mut



OS-IRC

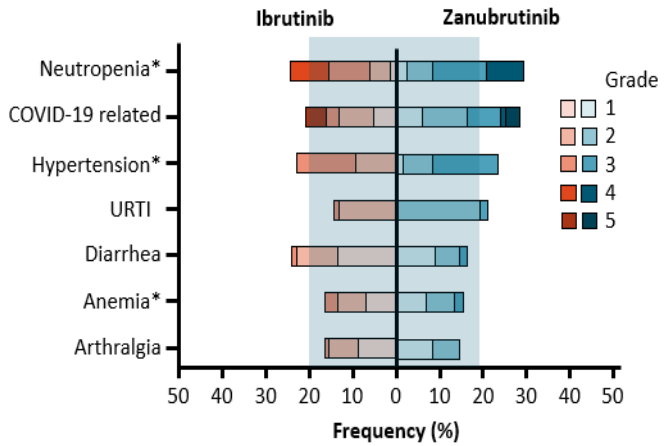


ALPINE: Final Analysis of Zanubrutinib vs Ibrutinib for Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Safety and Most Common AEs

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade adverse event	**318 (98.1)**	**321 (99.1)**
Grade 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious adverse event	**136 (42.0)**	**162 (50.0)**
Adverse events leading to		
Dose reduction	**40 (12.3)**	**55 (17.0)**
Dose interruption	**162 (50.0)**	**184 (56.8)**
Treatment discontinuation	**50 (15.4)**	**72 (22.2)**

Most Common AEs (Occurring in ≥15% of Patients)



Cardiac Events

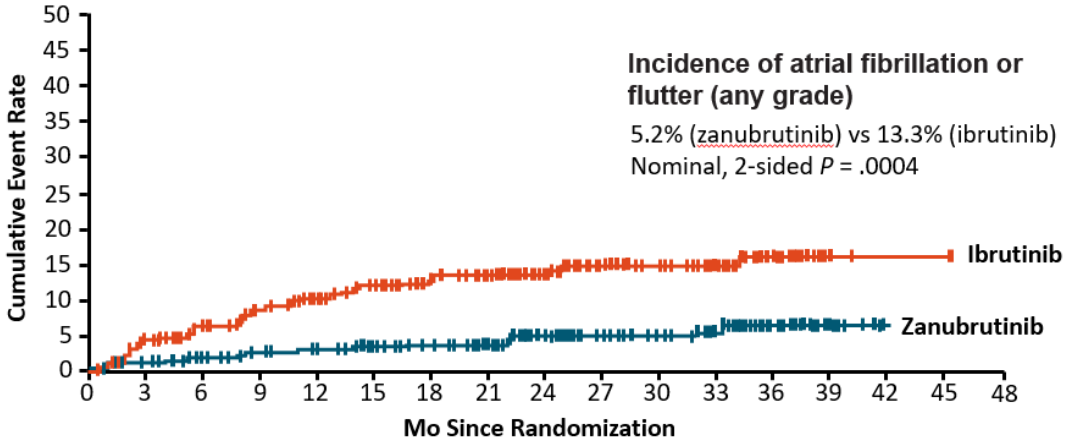
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**

Fatal cardiac events:

- **Zanubrutinib, n=0 (0%)**
- **Ibrutinib, n=6 (1.9%)**

Adverse Events of Special Interest

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	**Ibrutinib (n=324)**	**Zanubrutinib (n=324)**	**Ibrutinib (n=324)**
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)

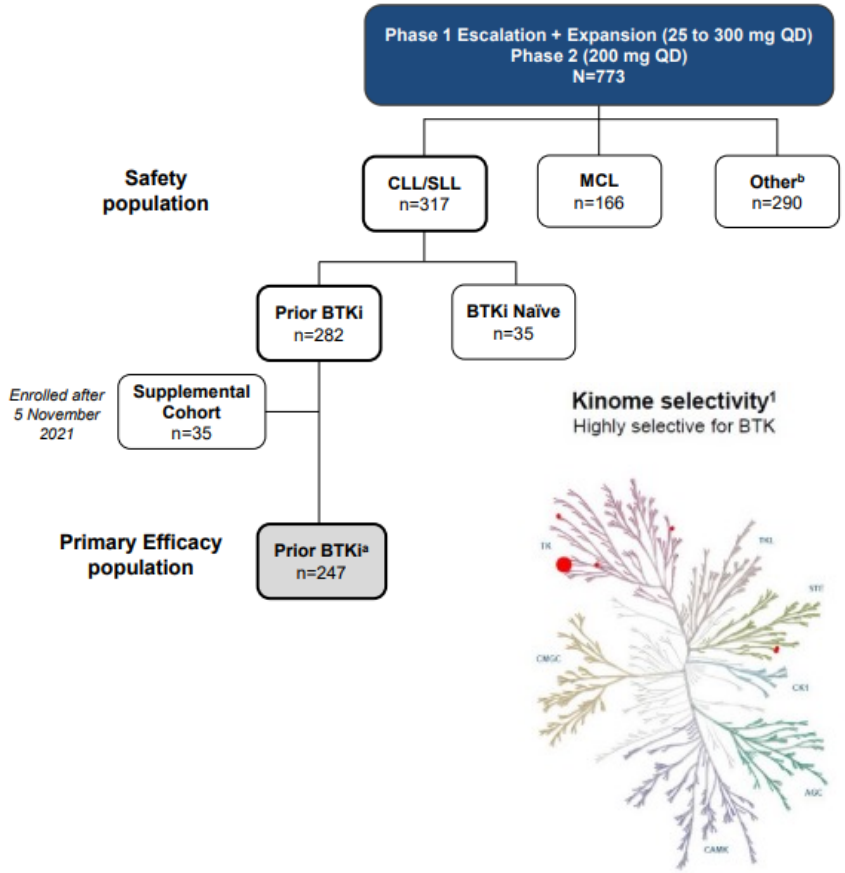


Incidence of atrial fibrillation or flutter (any grade)

5.2% (zanubrutinib) vs 13.3% (ibrutinib)
Nominal, 2-sided *P* = .0004

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

Phase 1 / 2 Study Design



Baseline Characteristics

Characteristics	n=247
Median age, years (range)	69 (36-88)
Male, n (%)	168 (68)
Histology	
CLL	246 (>99)
SLL	1 (<1)
Rai staging[a]	
0-II	131 (53)
III-IV	102 (41)
Bulky Disease ≥5 cm, n (%)	78 (32)
ECOG PS, n (%)	
0	133 (54)
1	97 (39)
2	17 (7)
Median number of prior lines of systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	247 (100)
Anti-CD20 antibody	217 (88)
Chemotherapy	195 (79)
BCL2 inhibitor	100 (41)
PI3K inhibitor	45 (18)
CAR-T	14 (6)
Allogeneic stem cell transplant	6 (2)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)

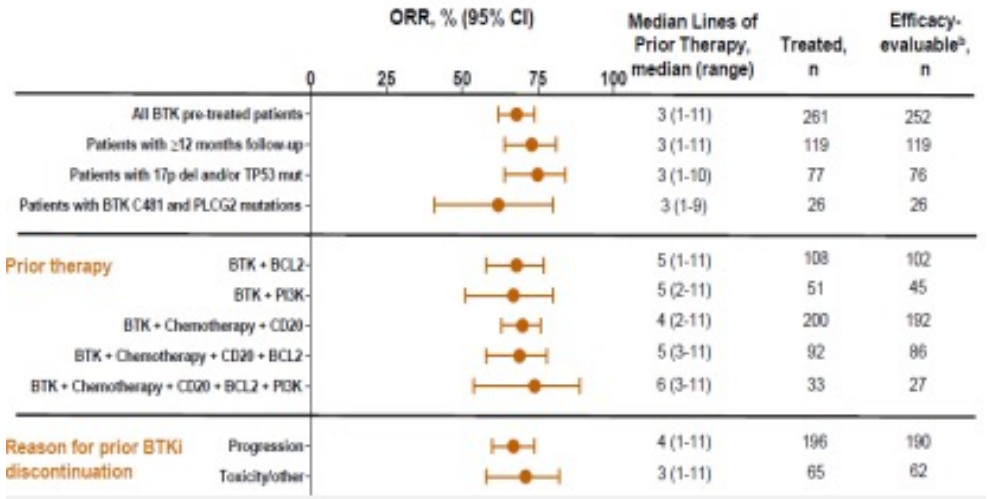
Baseline Molecular Characteristics[b]	
Mutation status, n/n available (%)	
BTK C481-mutant	84/222 (38)
BTK C481-wildtype	138/222 (62)
PLCG2-mutant	18/222 (8)
PLCG2-wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	
17p deletion	51/176 (29)
TP53 mutation	87/222 (39)
17p deletion and/or *TP53* mutation	90/193 (47)
Both 17p deletion and *TP53* mutation	48/170 (28)
IGHV unmutated	168/198 (85)
Complex Karyotype	24/57 (42)
11q deletion	44/176 (25)
Reason for prior BTKi discontinuation[c], n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

Overall, 84% (n=232) received the recommended phase 2 dose of 200 mg once daily as starting dose.

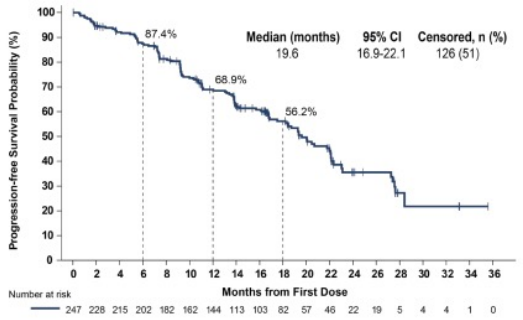
Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated R/R CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

Efficacy-Evaluable Patients With Pretreated CLL/SLL Pretreated	Prior BTKi (n = 247)	Prior BTKi + BCL2i (n = 100)
ORR, % (95% CI)	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
CR, n (%)	4 (1.6)	0
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]

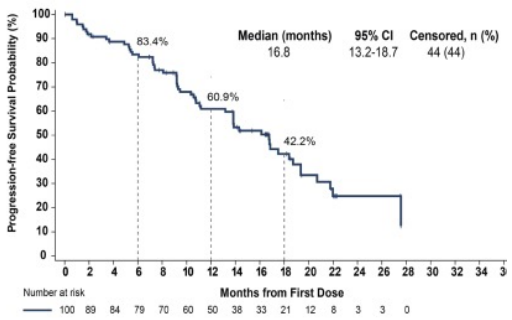


All prior BTKi patients
Median prior lines = 3



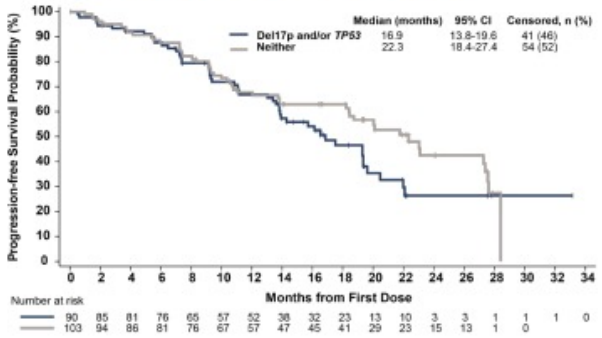
- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5

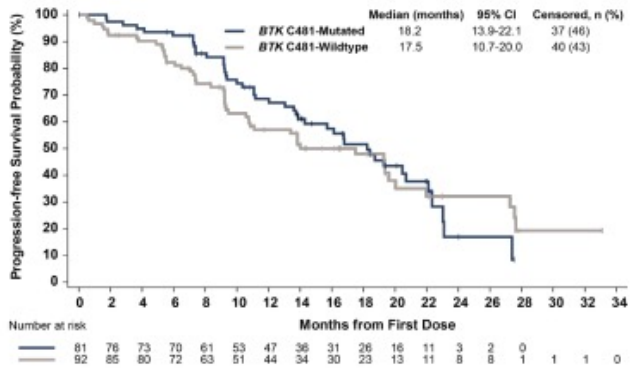


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

del(17p) and/or *TP53* mutation[a]



***BTK* C481 mutation status[a,b]**



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

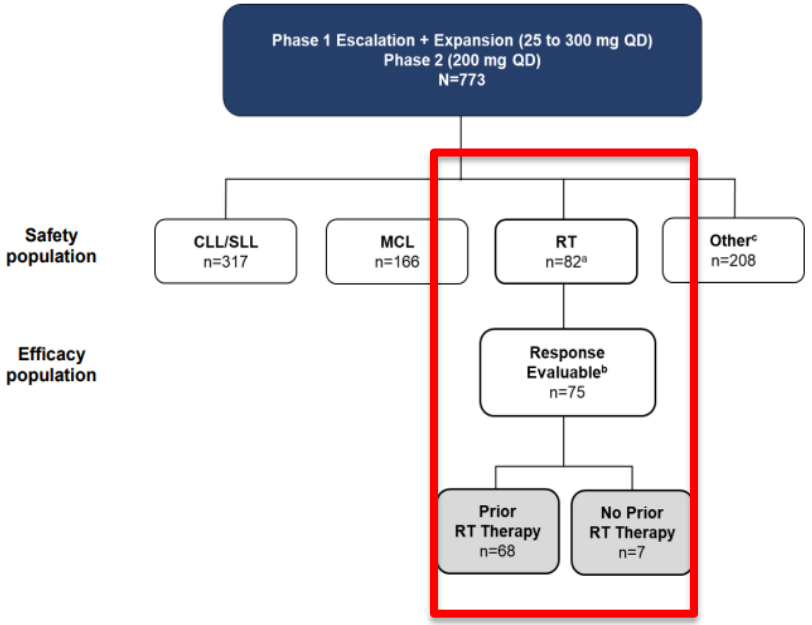
Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Pirtobrutinib Future Development: CLL

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results from the Phase 1/2 BRUIN Study

Study Design



Patient Characteristics

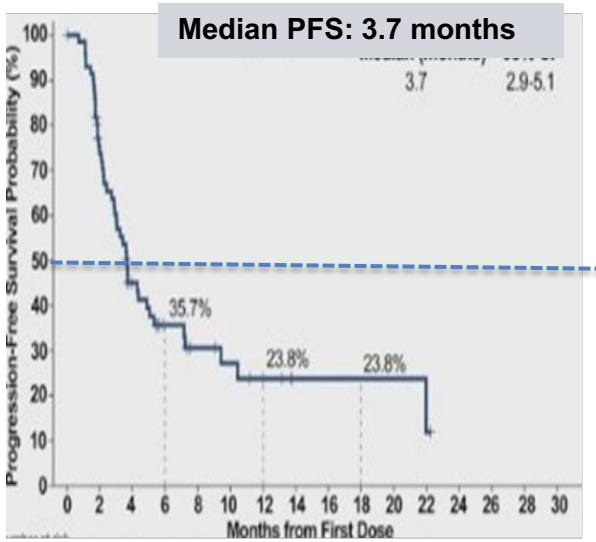
Characteristics	All n=82	Prior RT Therapy[a] n=68
Median age, years (range)	67 (26-95)	66 (26-95)
Male, n (%)	55 (67)	49 (72)
ECOG PS, n (%)		
0	32 (39)	29 (43)
1	38 (46)	29 (43)
2	12 (15)	10 (15)
Ann Arbor Stage		
Stage I-II	8 (10)	8 (12)
Stage III	15 (18)	13 (19)
Stage IV	42 (51)	35 (52)
Missing	17 (21)	12 (18)
Tumor bulk, cm, n (%)		
<5 cm	41 (50)	30 (44)
≥5 cm	31 (38)	31 (46)
Missing	10 (12)	7 (10)
Elevated LDH, n (%)		
Yes	66 (81)	54 (79)
No	16 (20)	14 (21)
Median time from initial CLL diagnosis to RT presentation (months, IQR)	60.8 (17.4-101.5)	67.5 (16.9-98.9)
Median time from transformation to first pirtobrutinib dose (months, IQR)	4.6 (1.8-13.1)	5.6 (2.2-15.3)

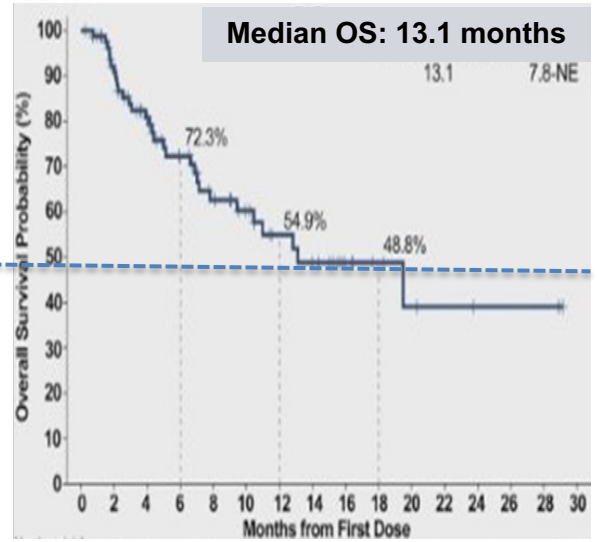
Characteristics	All n=82	Prior RT Therapy[a] n=68
Median number of prior lines of CLL therapy (range)[c]	2 (0-13)	2 (0-11)
Median number of prior lines of RT therapy (range)	2 (0-8)	2 (1-7)
Median number of prior lines of CLL and RT therapy (range)	4 (0-13)	4 (1-12)
Prior RT therapies, n(%)		
Anti-CD20 antibody	64 (78)	58 (85)
Chemotherapy	62 (76)	57 (84)
BCL2 inhibitor	31 (38)	26 (38)
BTK inhibitor	28 (34)	25 (37)
CAR-T cell therapy	9 (11)	9 (13)
PI3K inhibitor	8 (10)	8 (12)
Stem cell transplant	5 (6)	3 (4)
Allogenic	4 (5)	3 (4)
Autologous	1 (1)	0 (0)
Immunomodulator[b]	3 (4)	3 (4)
Other systemic therapy	25 (31)	23 (34)

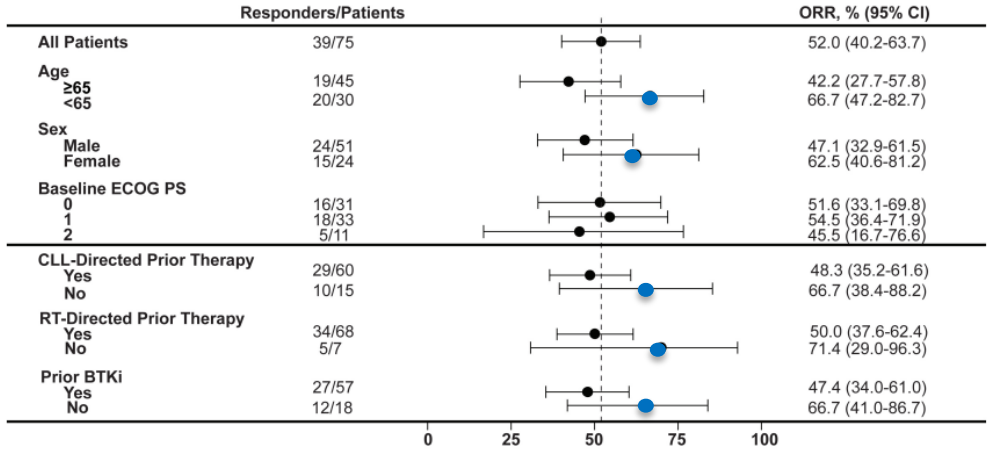
Overall, 98% of pts received the recommended phase 2 dose of 200 mg once daily as starting dose

Response

Response Evaluable RT Patients[a]	All n=75	Prior RT Therapy n=68
Overall Response Rate, % (95% CI)	**52.0 (40.2-63.7)**	**50.0 (37.6-62.4)**
Best Response		
CR, n (%)	10 (13.3)	9 (13.2)
PR, n (%)	29 (38.7)	25 (36.8)
SD, n (%)	10 (13.3)	10 (14.7)

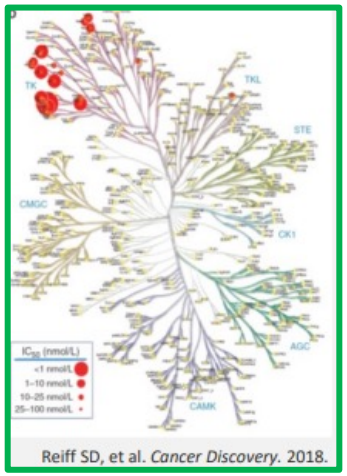






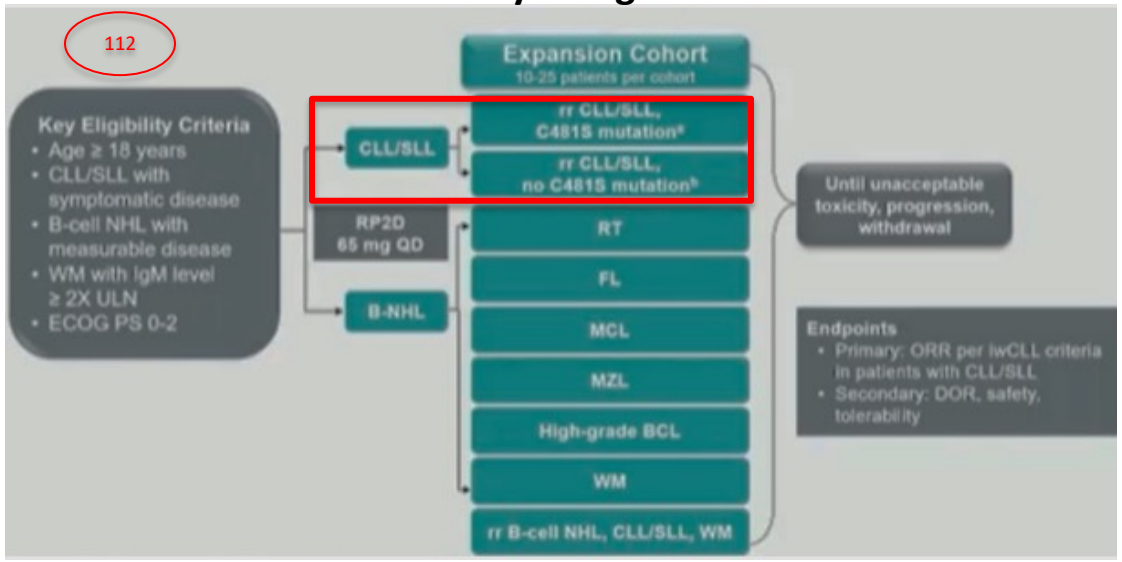
Six pts discontinued pirtobrutinib in ongoing response to pursue curative-intent therapy (allogeneic transplan)

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



Reiff SD, et al. *Cancer Discovery*. 2018.

Study Design



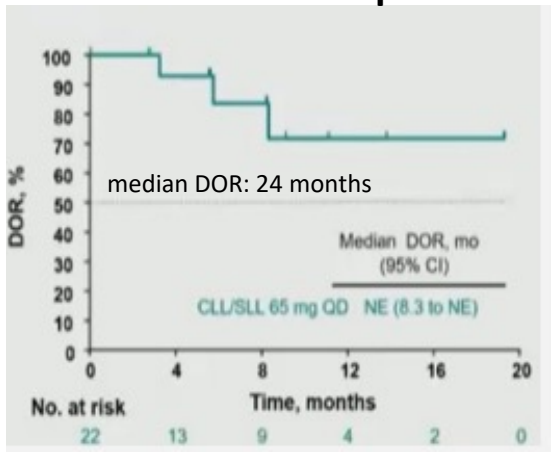
Baseline Characteristics

Characteristic, n (%)	CLL/SLL 65 m N = 51
Prior lines, median (range)	4 (1-18)
Prior BTK inhibitor therapy	43 (84.3)
ECOG PS 0	14 (27.5)
1	32 (62.7)
2	5 (9.8)
IGHV Unmutated	30 (58.8)
Mutated	2 (3.9)
Unknown	19 (37.3)
Del (17p) Present	12 (23.5)
Absent	33 (64.7)
Missing	6 (11.8)
BTK C481S Present	32 (62.7)
Absent	12 (23.5)
Unknown/Missing	7 (13.7)

Response

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	22 (57.9%) [40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]

Duration of Response

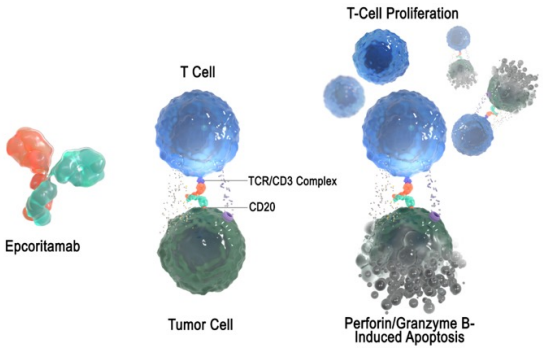


median PFS 26 months

Safety

Events, n (%)		All Patients N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Treatment-related discontinuations		13%
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	24.6%	0
Nausea	24.6%	0.8%
Pyrexia	24.6%	0
Dizziness	22.9%	0
Hypertension	22.9%	9.3%
Peripheral edema	22.0%	0
Diarrhea	21.2%	0.8%
Arthralgia	20.3%	0

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



Epcoritamab (DuoBody®-CD3xCD20)

CD3/CD20 bispecific monoclonal antibody
binds to CD3 on T cells and CD20 on B cells

Induces T-cell activation by binding to CD3 on T cells and CD20 on malignant B cells

Promotes immunological synapse between bound cells, resulting in T-cell–mediated killing of CD20+ malignant B cell

Binds to a distinct epitope on CD20, different from the epitopes of rituximab and obinutuzumab

Retains activity in the presence of CD20 mAbs

Dose escalation → **Median follow-up: 4.9 mo (range, 0.6–9.3)**

CLL[1]

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key RS inclusion criteria

- Ineligible for or voluntarily declined chemotherapy
- ≤1 prior line of therapy for RS-DLBCL
- Biopsy-proven transformation to CD20+ RS-DLBCL
- Prior clinical history of CLL or SLL
- ECOG PS 0–2
- Measurable disease by PET and/or CT/MRI

RS-DLBCL expansion, N=10

Step-up dosing[a]: Epcoritamab (SC) 48 mg — QW C1–3, Q2W C4–9, Q4W C10+ → Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter → Treatment until disease progression

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first 4 doses of epcoritamab
- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete metabolic response (CMR) rate, time to response (TTR), and safety/tolerability

CLL Characteristic, n (%)	Total N=10
IGHV unmutated[a]	8 (80)
TP53 mutation[b]	5 (50)
NOTCH1 mutation[c]	2 (20)
FISH	
Trisomy 12[d]	1 (10)
Del17p[e]	3 (30)
Del11q[f]	3 (30)
Del13q[g]	4 (40)

Data for CLL characteristics were obtained from local laboratories. [a]*IGHV* mutation status unknown for 2 patients. [b]*TP53* mutation status unmutated for 4 patients and unknown for 1 patient. [c]*NOTCH1* mutation status unmutated for 4 patients and unknown for 4 patients. [d]Trisomy 12 status negative for 8 patients and unknown for 1 patient. [e]Del17p status negative for 7 patients. [f]Del11q status negative for 7 patients. [g]Del13q status negative for 4 patients and unknown for 2 patients.

RS Characteristic	Total N=10
Median age, y (range)	70 (53–79)
Male, n (%)	7 (70)
Ann Arbor stage, n (%)	
IE	1 (10)
II	1 (10)
III	3 (30)
IV	5 (50)
Elevated lactate dehydrogenase, n (%)	8 (80)
Cell of origin, n (%)[a]	
Germinal center B-cell	1 (10)
Non–germinal center/Activated B-cell	6 (60)

Data cutoff: September 16, 2022. [a]Cell of origin was unknown for 3 patients.

Characteristic of Prior CLL Therapy	Total N=10
Median time from initial CLL diagnosis to first dose, y (range)	12 (2.6–24.0)
Median number of prior lines of therapy for CLL (range)	**3 (0–7)**
Prior CLL/SLL therapy, n (%)	7 (70)
Chemoimmunotherapies	7 (70)
Targeted agents	6 (60)
BCL2 inhibitor	5 (50)
BTK inhibitor	5 (50)
CAR T-cell therapy	1 (10)
Median time from last CLL treatment to first dose, mo (range)	12 (0.2–61.8)

Data cutoff: September 16, 2022.

Characteristic of Prior RS-DLBCL Therapy	Total N=10
1 prior line of RS-DLBCL therapy, n (%)	**5 (50)**
R-CHOP	3 (30)
No response	2 (20)
R-DHAP	1 (10)
No response	1 (10)
VR-EPOCH[a]	1 (10)
Median time from disease transformation to first dose, mo (range)	3.4 (0.5–21.4)
Median time from end of last line of RS-DLBCL therapy to first dose, mo (range)	2 (0.5–5.4)

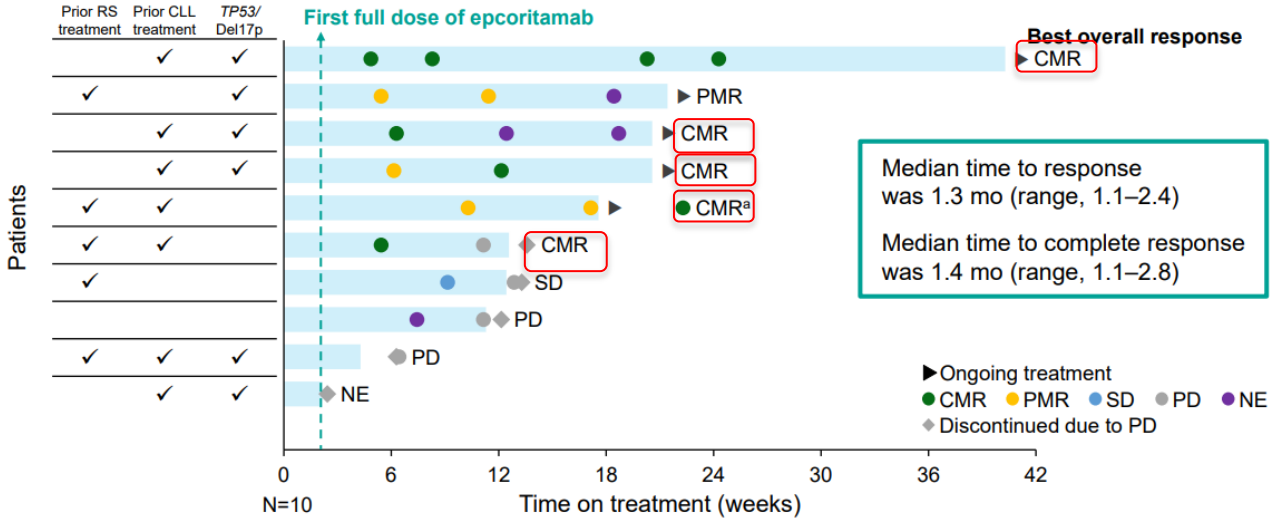
[a]Response to VR-EPOCH unknown.
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; VR-EPOCH, venetoclax plus dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

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

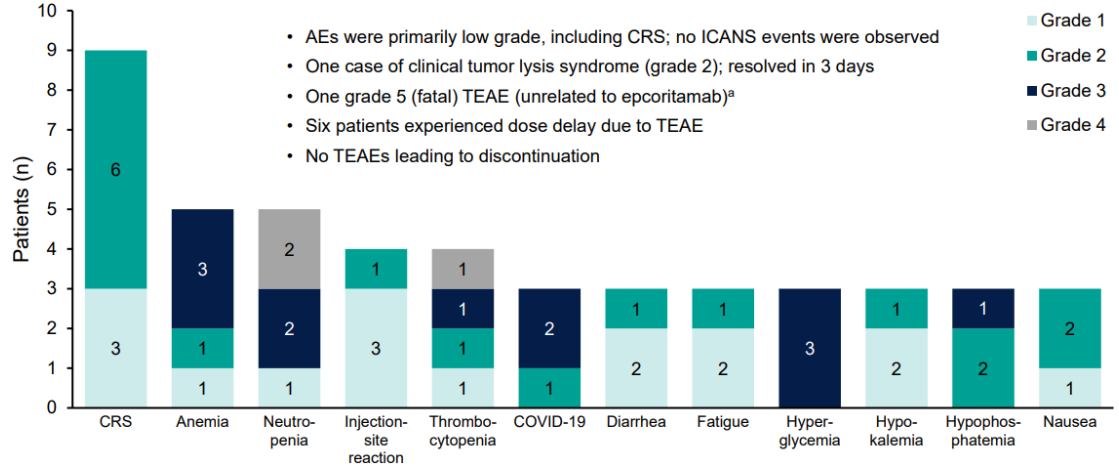
Responses

Response, n (%)[a]	Total Efficacy Evaluable N=10
Overall response[b]	**6 (60)**
Complete metabolic response (CMR)	5 (50)
Partial metabolic response (PMR)	1 (10)

Depth and Duration of responses

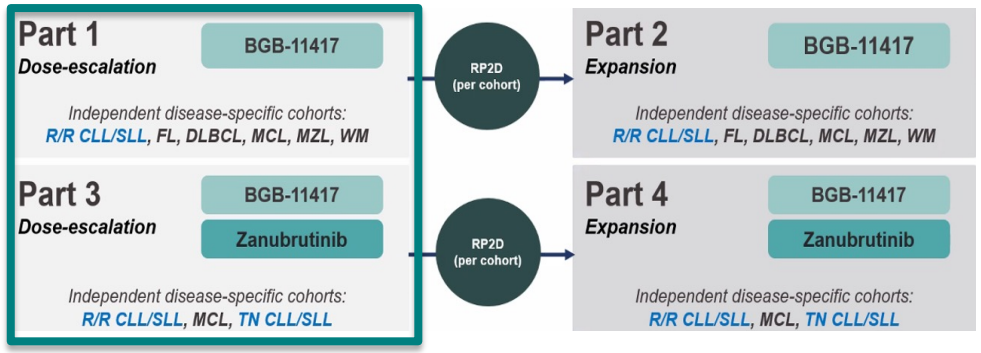


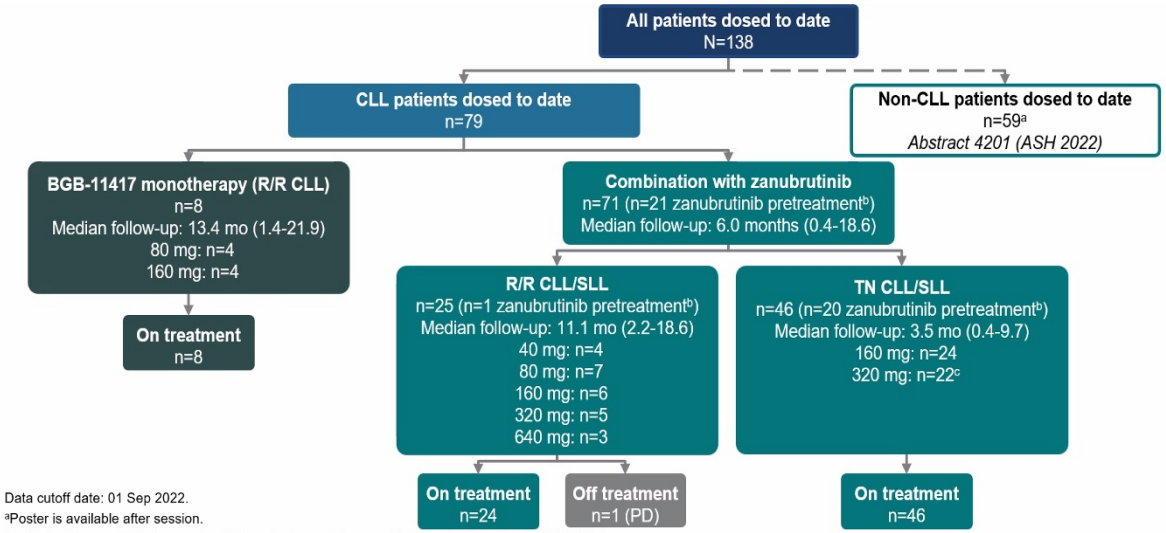
Treatment-emergent AEs ≥30%



	Total, N=10
CRS, n (%)[a]	9 (90)
Grade 1	3 (30)
Grade 2	6 (60)
CRS resolution, n/n (%)	**9/9 (100)**
Median time to onset after first full dose, h (range)	12.5 (8–394)
Median time to resolution, d (range)[b]	3 (2–9)
Treated with tocilizumab, n (%)	7 (70)
Leading to treatment discontinuation, n (%)	**0**

A Phase 1 Study with the Bcl-2 Inhibitor Bgb-11417 As Monotherapy or in Combination with Zanubrutinib (ZANU) in Patients (Pts) with CLL/SLL: Preliminary Data





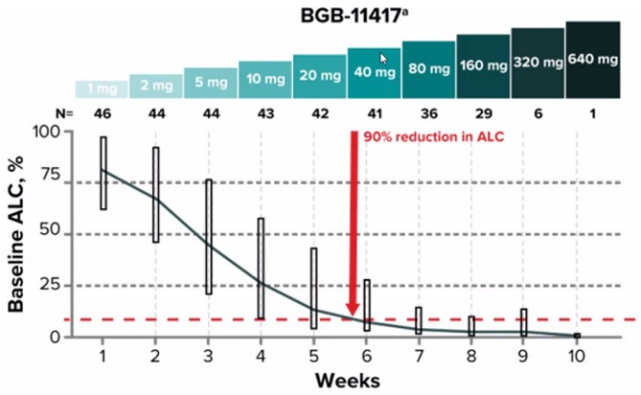
Data cutoff date: 01 Sep 2022.
[a]Poster is available after session.
[b]Patients who are still in the zanubrutinib pretreatment phase and have not yet received BGB-11417.
[c]All patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320mg dose level).

ZANU (320 mg QD or 160 mg twice daily) beginning 8-12 weeks before BGB-11417
MTD has not yet been reached for any CLL cohort

TEAE, n, %	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (N=71)	All patients with CLL (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Leading to death	0	0	0
Treated with BGB-11417	**8**	**50**	**58**
Leading to hold of BGB-11417	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of BGB-11417	0	1 (2)	1 (2)
Leading to discontinuation of BGB-11417	0	0	0

With combination, contusion, neutropenia, and low-grade gastrointestinal toxicity the most common No clinical TLS was reported.

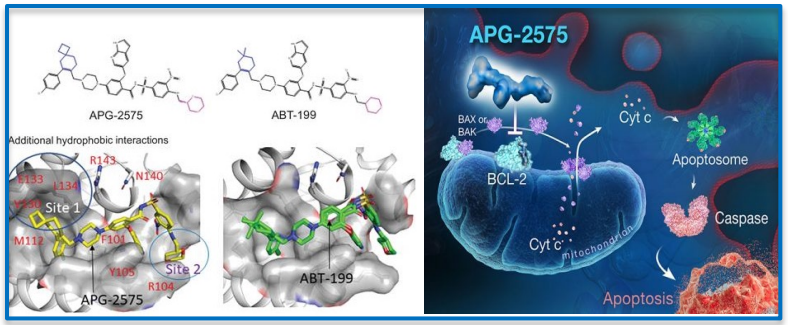
Response, n (%)	R/R BGB-11417 (n=8)	R/R BGB-11417 + zanubrutinib (n=25)	TN BGB-11417 + zanubrutinib (n=46)
Treated with BGB-11417	**8**	**24**	**26**
Efficacy evaluable	**6**	**20[a]**	**11[a]**
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]

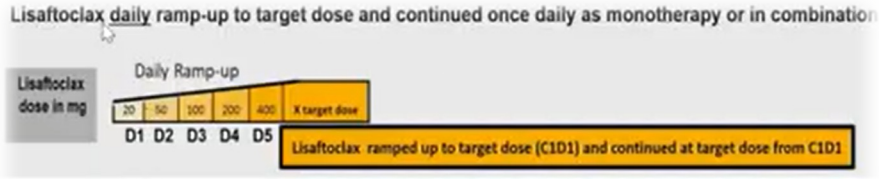


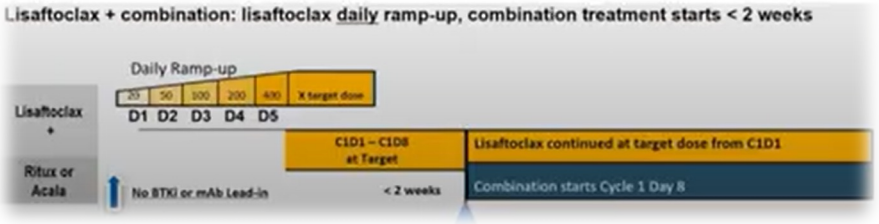
MRD data are early

Lisaftoclax With or Without Rituximab or Acalabrutinib Elicits Favorable Responses and Safety in CLL/SLL

Lisaftoclax a highly potent orally active BCL-2 inhibitor
Mulicenter study - **164 patients**





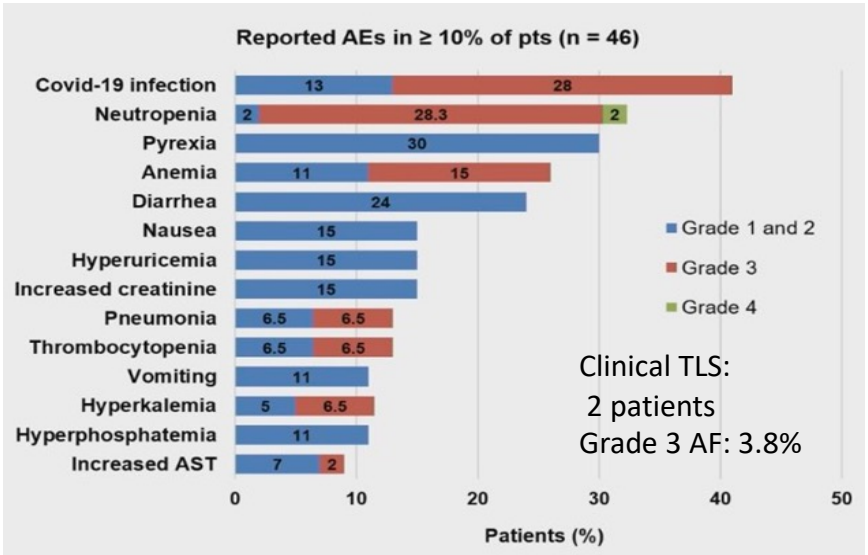


Daily ramp-up of lisaftoclax if no TLS
(20 mg, 50 mg, 100 mg, 200 mg 400 mg).
TLS labs: at 0, 6- 8 hours, at 24 hours
after each dose. Inpatient setting.

Combination cohorts: same daily ramp-up,
2 weeks later, rituximab or acalabrutinib added

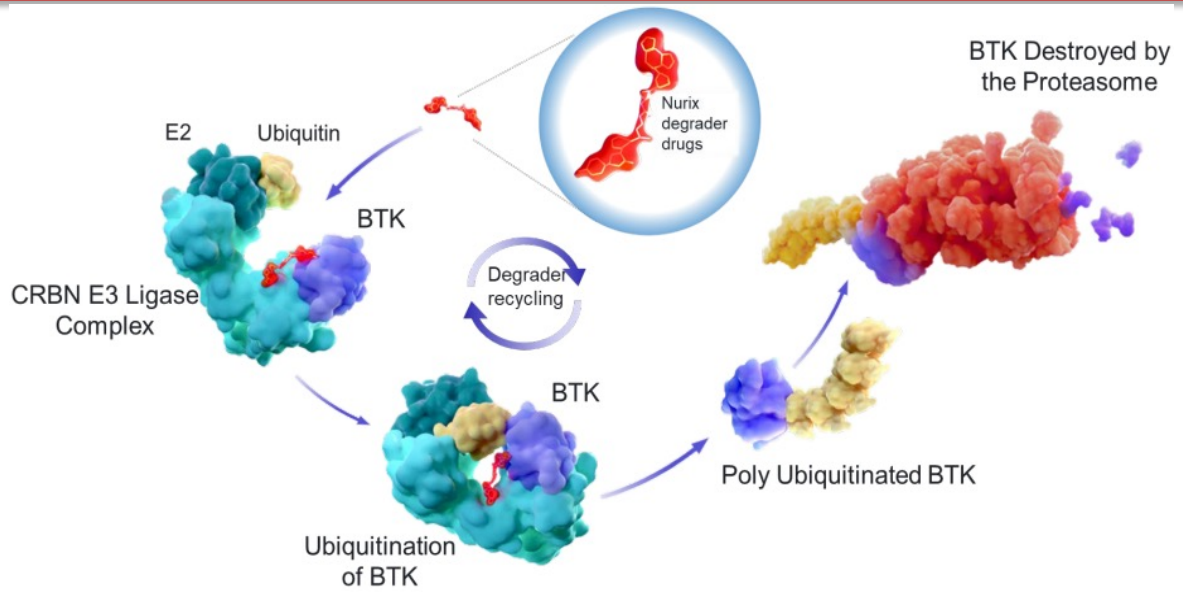
Response	Monotherapy	Combined + Rituximab	Combined + Acalabrutinib	
	R/R	R/R	R/R	TN
	N=43	N=34	N=57	N=16
ORR	67%	79%	98%	100%
Del(17p)/TP53mut	–	83%	92%	100%
Complex Karyotype (≥3 abn.)		100%	94%	100%
BTK resist./intol.	67%	0	88%	NA
High TLS risk	41%	33%	30%	
Discontinued therapy	65%	13%	14%	
Disease progression	39%	5%	3%	

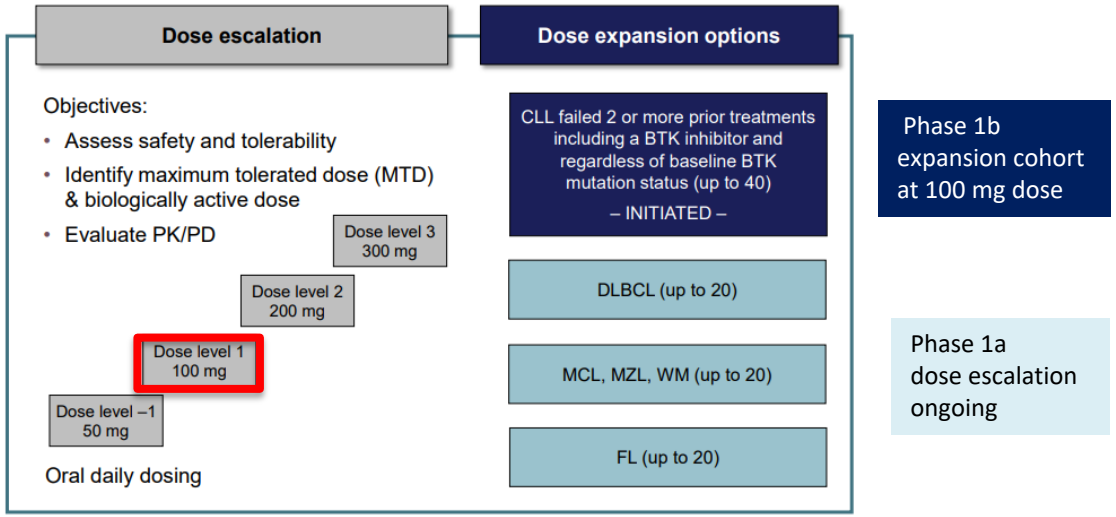
Data on CR and MRD rate not yet available



Clinical TLS:
2 patients
Grade 3 AF: 3.8%

NX-2127-001, a first-in-human trial of NX-2127, a BTK-targeted protein degrader, in patients with R/R chronic lymphocytic leukemia and B-cell malignancies

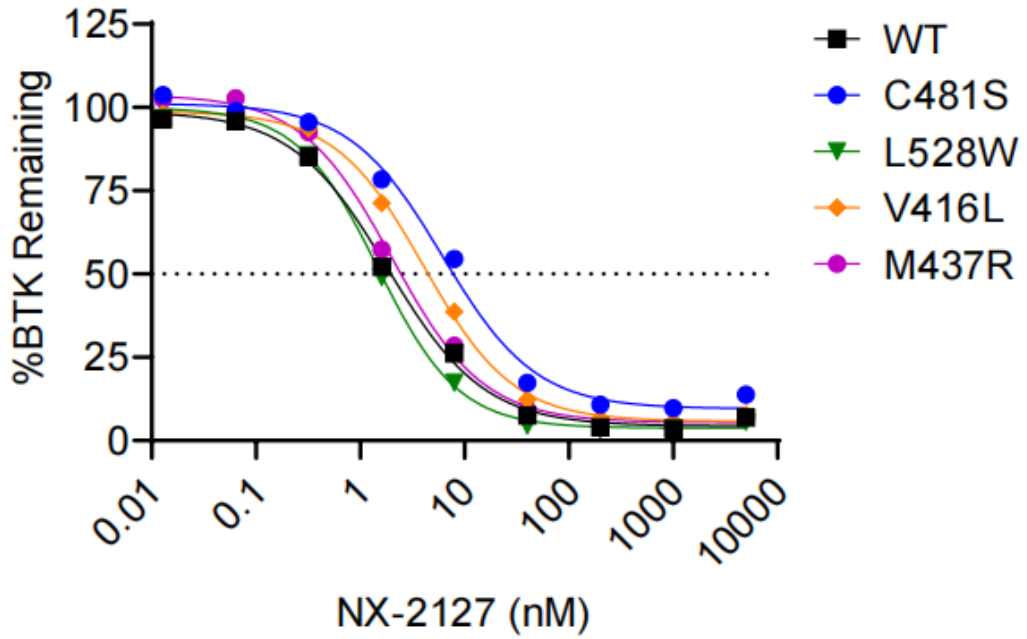




Phase 1b expansion cohort at 100 mg dose

Phase 1a dose escalation ongoing

NX-2127 degrades wild-type and mutant BTK, not only C481x, but also the novel BTK mutations post treatment with pirtobrutinib



Patients receive NX-2127 orally once daily in 28-day cycles starting at 100 mg.
Findings from the Phase 1a portion

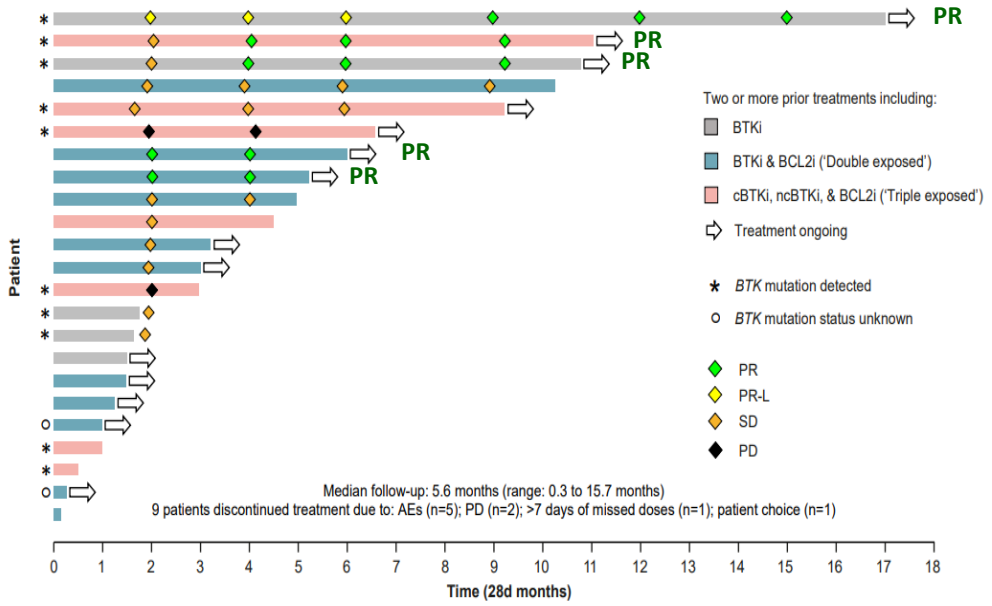
NX-2127-001, a first-in-human trial of NX-2127, a BTK-targeted protein degrader, in patients with R/R chronic lymphocytic leukemia and B-cell malignancies

Characteristics	CLL (n=23)
Median age, years (range)	75 (61–90)
Female, n (%)	9 (39.1)
Male, n (%)	14 (60.9)
Lines of prior therapy, median (range)	5 (2–11)
BTKi, n (%)	23 (100)
Pirtobrutinib, n (%)	8 (34.8)
BTKi and BCL2i, n (%)	18 (78.3)
cBTKi, ncBTKi, and BCL2i, n (%)	7 (30.4)
***BTK* mutation present**[a], n (%)	10 (48)
C481	5 (24)
L528W	4 (19)
T474	3 (14)
V416L	1 (5)
***BCL2* mutation present**[a], n (%)	4 (19)
***PLCG2* mutation present**[a], n (%)	0 (0)

median follow up of 5.6 months (range 0.3 to 15.7 months)

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)

Responses noted in BTKi/BCL2 double-refractory patients and those who progressed on a ncBTKi



AEs: all grades, n (%)	All doses (n=36)	100 mg* (n=22)
Fatigue	19 (53)	13 (59)
Neutropenia[a]	14 (39)	5 (23)
Contusion[b]	10 (28)	4 (18)
Thrombocytopenia[c]	9 (25)	5 (23)
Hypertension	9 (25)	5 (23)
Anemia	8 (22)	6 (27)
Constipation	7 (19)	7 (32)
Dyspnea	7 (19)	4 (18)
Pruritis	7 (19)	5 (23)
Atrial fibrillation/Atrial flutter[d]	6 (17)	3 (14)
Diarrhea	6 (17)	5 (23)
Petechiae	6 (17)	4 (18)
Rash	6 (17)	5 (23)

These data support further clinical development of NX-2127 in CLL, including expansion at the 100 mg dose level