POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

3° SESSIONE---Leucemia Linfatica Cronica

Novità dal Meeting della Società Americana di Ematologia

Terapie di salvataggio

Verona
Palazzo della Gran Guardia
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Disclosures of Luca Laurenti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x				x	x	
AstraZeneca					x	x	
Beigene					x	x	
Johnson & Johnson			x		x	x	

Extended follow-up: Alpine, BRUIN

Sequencing: Captivate, Murano

New molecules: Car-T, ROR-1, BTKi covalent non covalent LP-168

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)

R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R
1:1

Stratification factors:
Age, geographic region, refractoriness, del(17p)/*TP53*

Zanubrutinib 160 mg BID

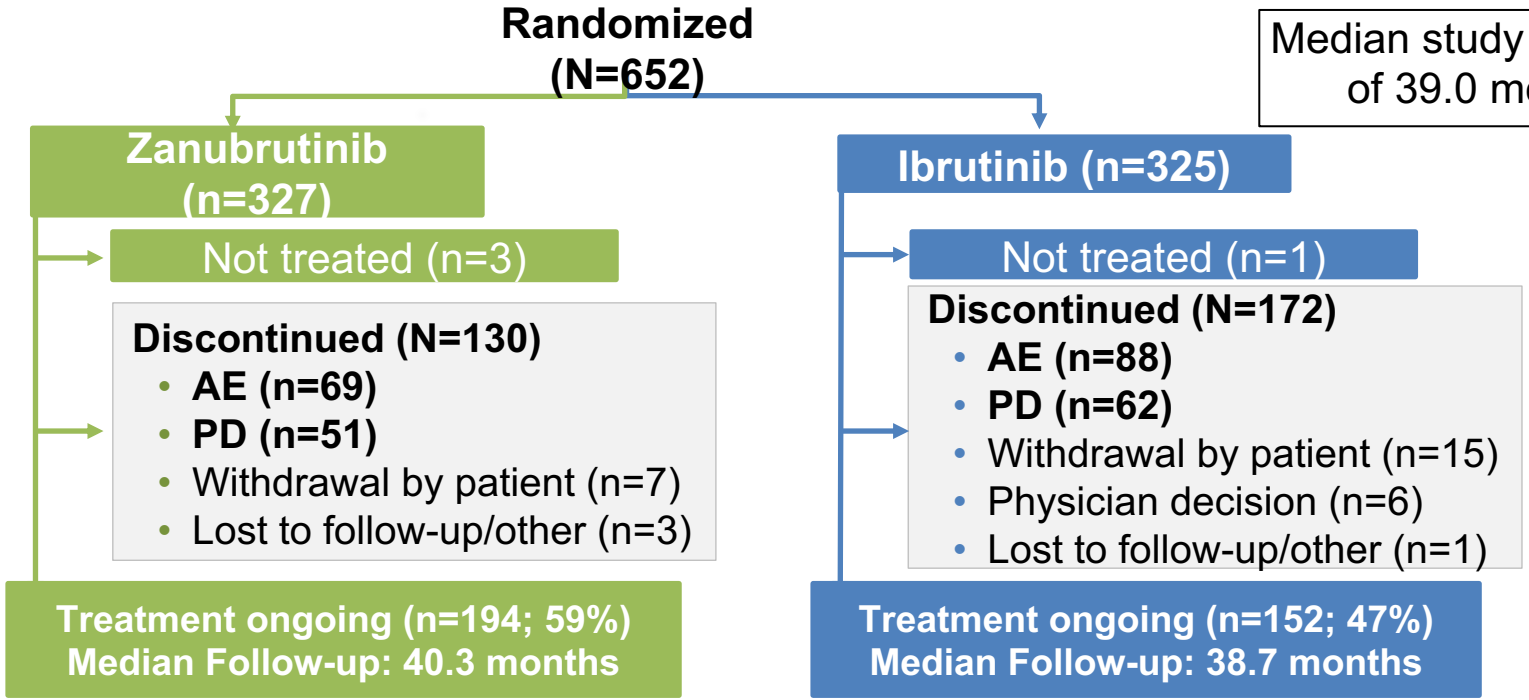
Ibrutinib 420 mg QD

Treatment until disease progression or unacceptable toxicity

Median study follow-up of 39.0 months

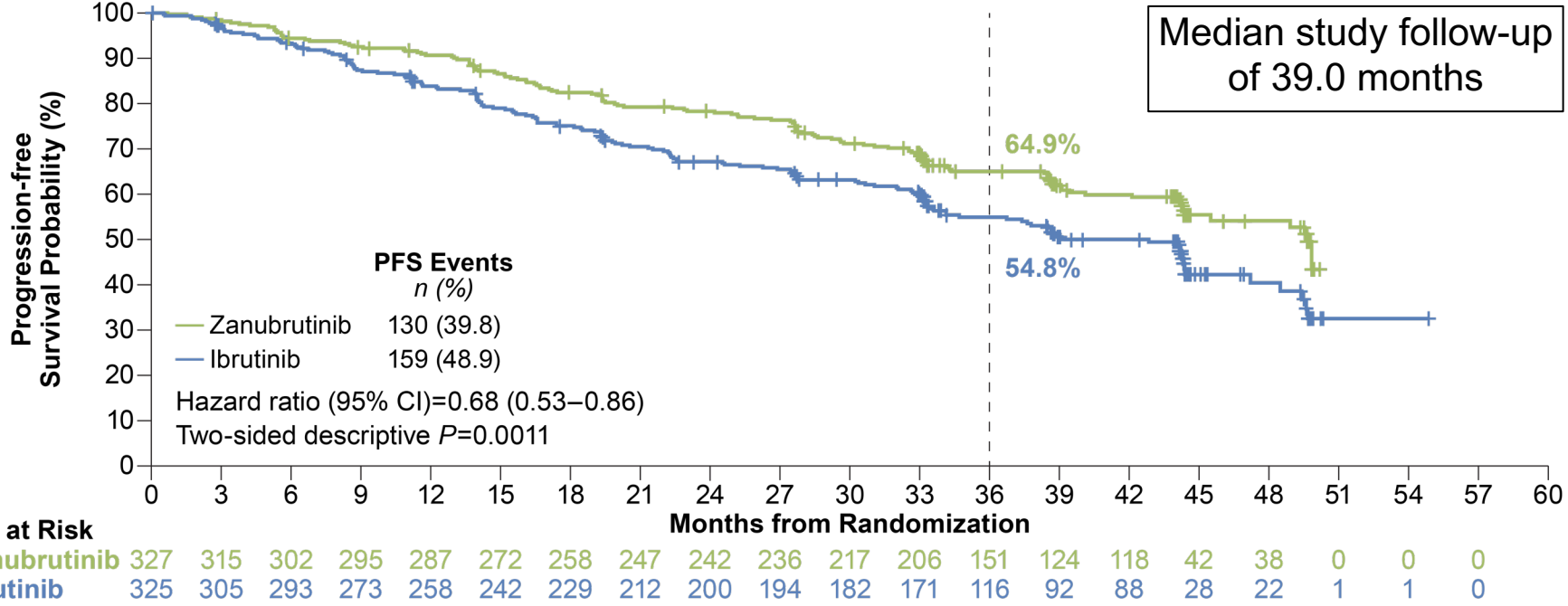
Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202

Patient Disposition At Extended Follow-Up



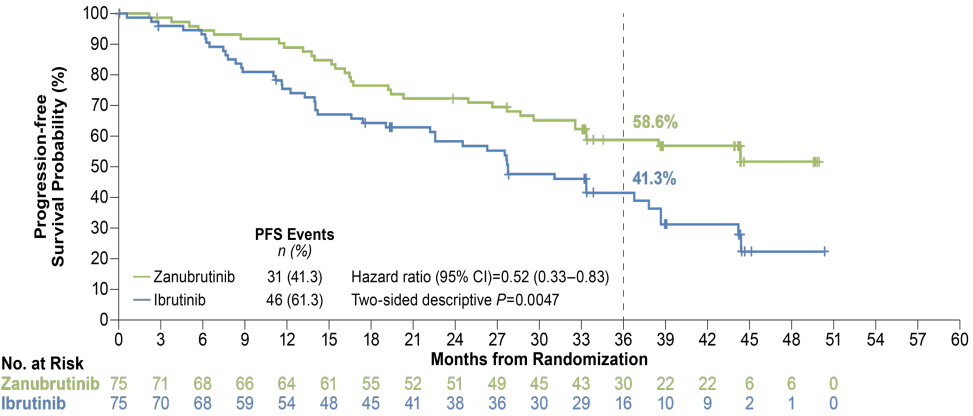
- Data cutoff: 15 Sep 2023. AE=adverse event, PD=progressive disease. Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

Zanubrutinib Sustains PFS Benefit Over Ibrutinib at Extended Follow-up

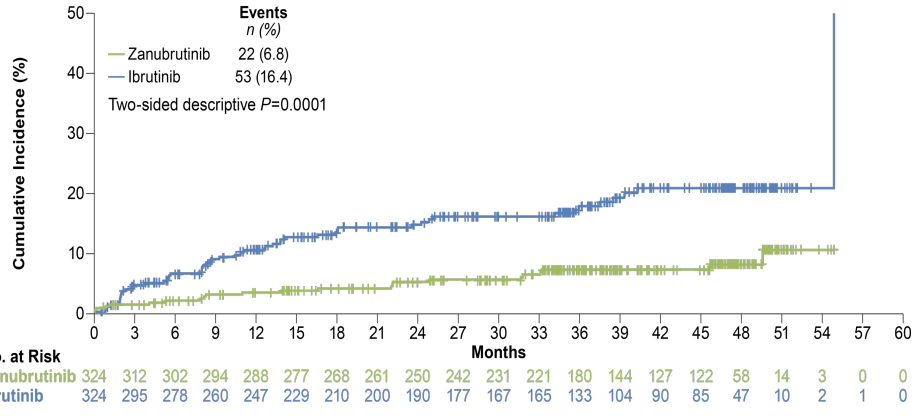


- Data cutoff: 15 Sep 2023. CI=confidence interval, PFS=progression-free survival. Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

Improved PFS with Zanubrutinib in Patients with del(17p)/*TP53*^{mut}



Significantly Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



- Data cutoff: 15 Sep 2023.
- CI=confidence interval, HR=hazard ratio, PFS=progression-free survival.
  Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

Author Conclusions

- ALPINE is the only study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors
- Zanubrutinib demonstrated sustained PFS benefit over ibrutinib in patients with R/R CLL/SLL with a median follow-up of 39 months
  - Durable PFS benefits seen across major subgroups, including the del(17p)/*TP53*^{mut} population
  - PFS benefit is consistent across multiple sensitivity analyses demonstrating that PFS advantage with zanubrutinib was primarily driven by efficacy and not tolerability
- While responses deepened over time in both arms, ORR was higher with zanubrutinib with increased rates of CR/CRi compared with ibrutinib
- Zanubrutinib continues to demonstrate a more favorable safety/tolerability profile compared with ibrutinib
  - Lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation, and dose reduction
  - Safer cardiac profile than ibrutinib with significantly lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and no fatal cardiac events
- **With over 3 years of follow-up, these data reconfirm zanubrutinib improved efficacy over ibrutinib and a more favorable safety profile in patients with R/R CLL/SLL**

- CLL=chronic lymphocytic leukemia, PFS=progression-free survival, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma.
Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study

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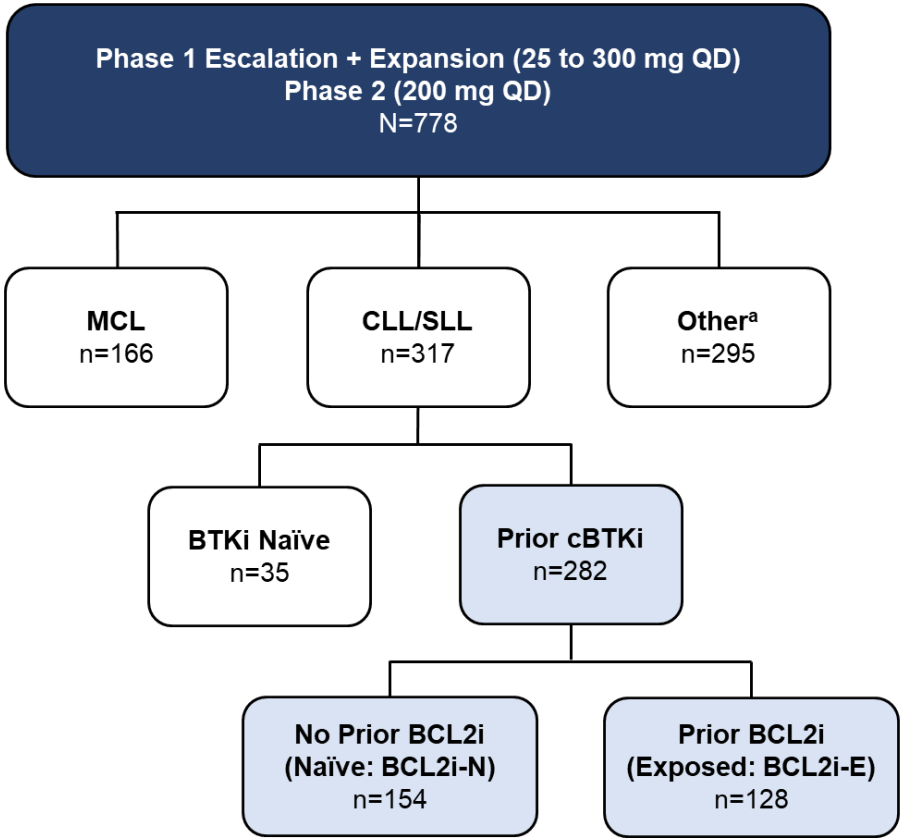
- [1]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [4]Memorial Sloan Kettering Cancer Center NY; [5]Swedish Cancer Institute, Seattle, WA; [6]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, UK; [7]Department of Haematology, St. James's University Hospital, Leeds, UK; [8]Institute of Hematology and Transfusion Medicine, Poland; [9]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [10]Alfred Health and Monash University, Melbourne, Victoria, Australia; [11]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia; [12]Haematology Department, University Hospital, Nantes, France; [13]Medical College of Wisconsin, Milwaukee, WI; [14]Fred Hutchinson Cancer Research Center, Seattle, WA; [15]Division of Hematology at Stanford University School of Medicine, Stanford, CA; [16]University of California Irvine, Irvine, CA; [17]Sarah Cannon Research Institute, Nashville, TN; [18]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [19]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [20]Winship Cancer Institute, Emory University, Atlanta, GA; [21]Sylvester Comprehensive Cancer, Miami, FL; [22]Linear Clinical Research and Sir Charles Gairdner Hospital, West Australia, Australia; [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [24]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [25]Cleveland Clinic, Cleveland, OH; [26]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [27]Karolinska Institute and Karolinska University Hospital, Stockholm, SE; [28]National Cancer Center Hospital, JP; [29]Loxo@Lilly, Indianapolis, IN; [30]Eli Lilly and Company, Indianapolis, IN; [31]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [32]MD Anderson Cancer Center, Houston, TX.



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Data cutoff of 05 May 2023 (NCT03740529); [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Woyach et al.; ASH 2023

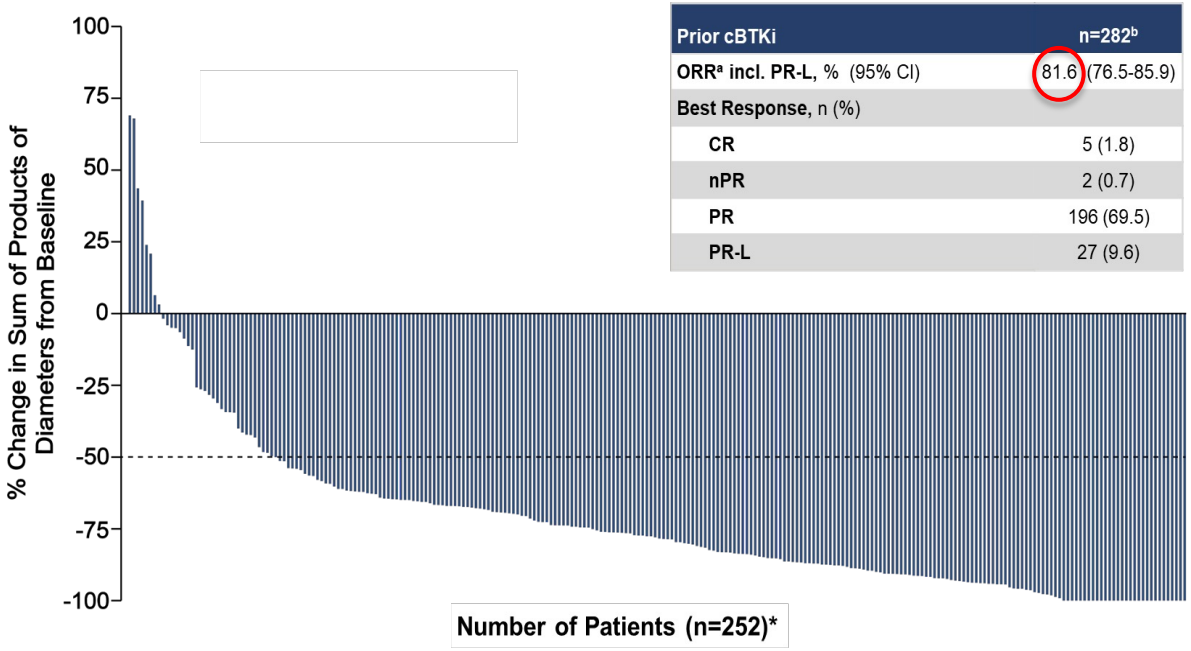
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	**4 (1-11)**	**3 (1-9)**	**5 (1-11)**
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	**17 (6)**	**2 (1)**	**15 (12)**
Allogeneic stem cell transplant	**7 (3)**	**1 (1)**	**6 (5)**

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	**57/123 (46)**	**47/94 (50)**
IGHV unmutated	193/225 (86)	**100/125 (80)**	**93/100 (93)**
Complex Karyotype	33/73 (45)	**17/41 (42)**	**16/32 (50)**
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.

Woyach et al.; ASH 2023



Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)

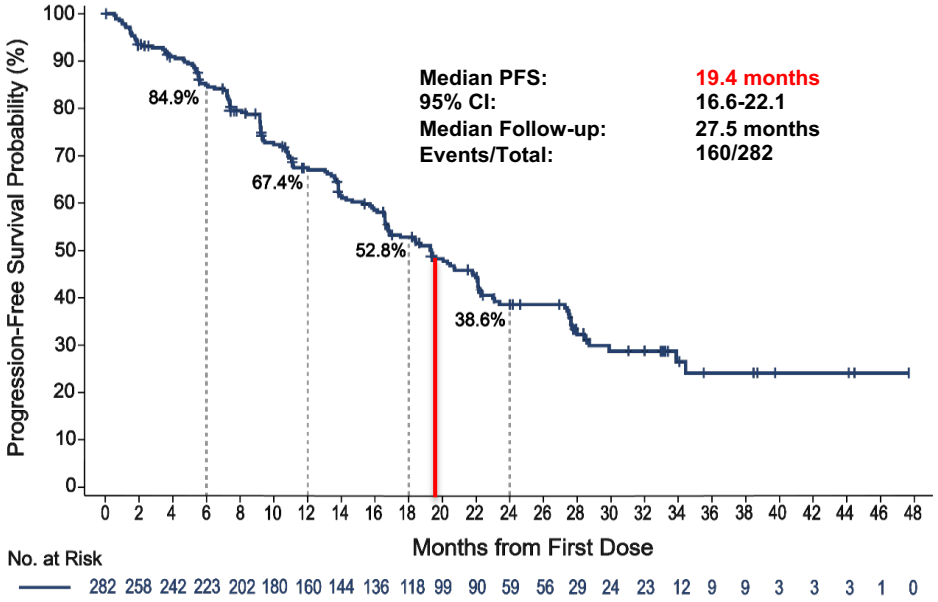
BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Woyach et al.; ASH 2023

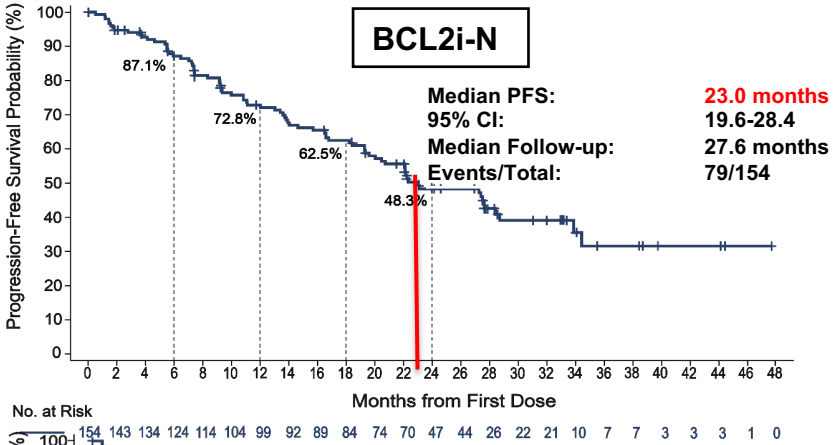
All Prior cBTKi



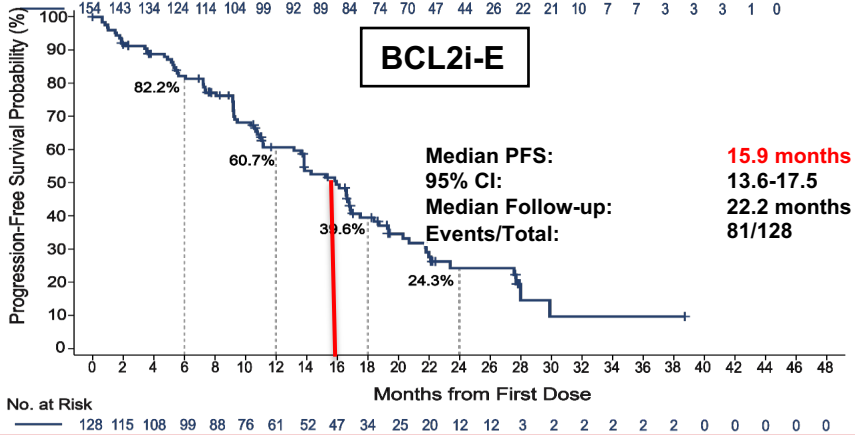
AEs grade>3: neutropenia 28,4%; Infections 30,9%
AF/Flutter 1,8%

Woyach et al.; ASH 2023

BCL2i-N



BCL2i-E



- **With median follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor**
  - **ORR** including PR-L was ~80% regardless of prior BCL2 inhibitor exposure
  - **Median PFS** was 19.4 months overall, with 23.0 months for BCL2i-N patients and 15.9 months for BCL2i-E patients
- Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BCL2i-N and BCL2i-E patients
- These results suggest that continuation of BTK pathway inhibition may be an important sequencing approach to consider in the treatment of CLL/SLL
- On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor

Woyach et al.; ASH 2023

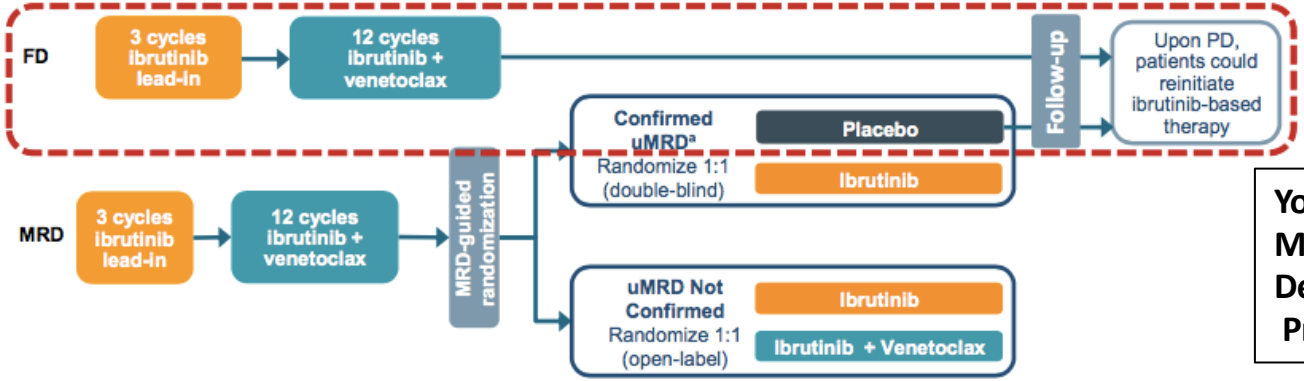
Extended follow-up: Alpine, BRUIN

Sequencing: Captivate, Murano

New molecules: Car-T, ROR-1, BTKi covalent non covalent LP-168

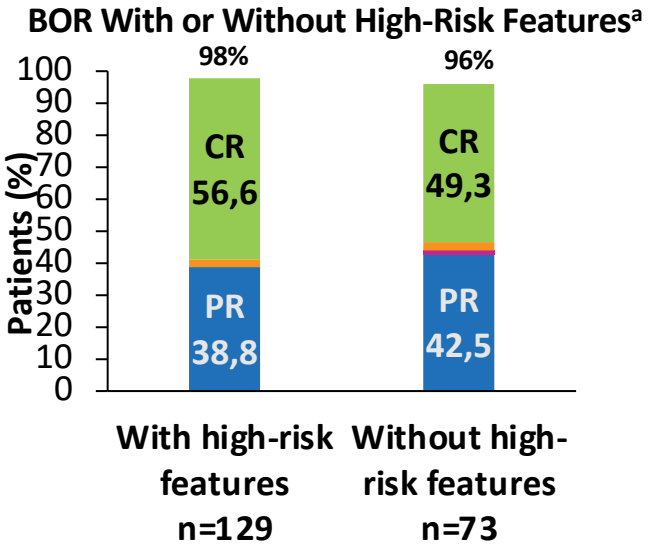
Relapse after First-line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of *BTK* Mutations in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With Up To 5 Years of Follow-Up in the Phase 2 CAPTIVATE Study

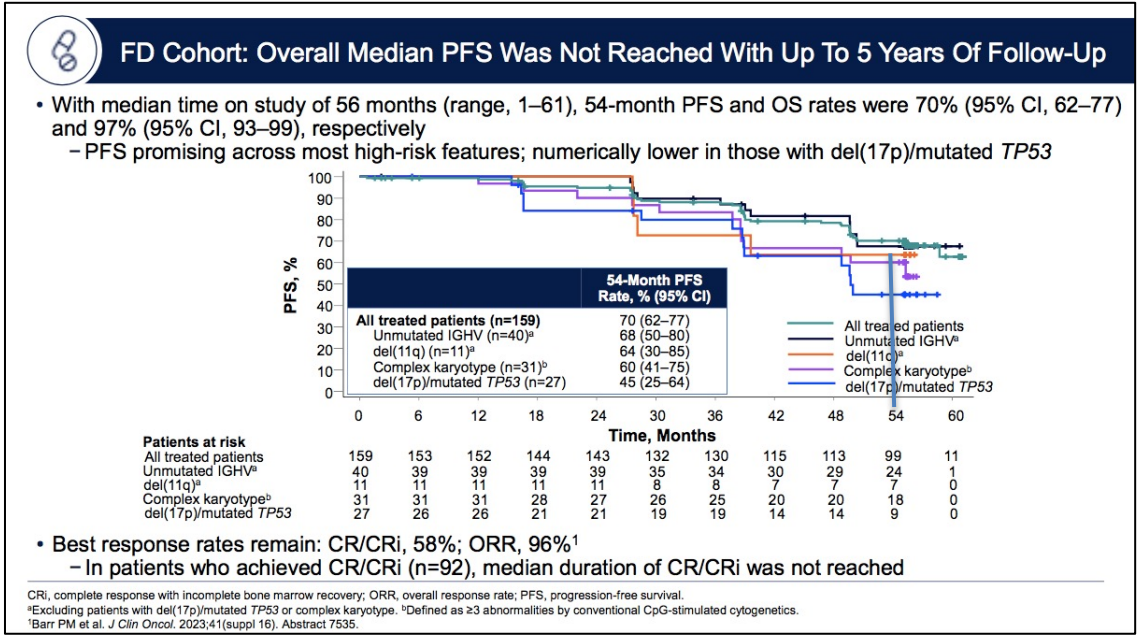
Paolo Ghia, MD, PhD[1]; William G. Wierda, MD, PhD,[2]; Paul M. Barr, MD[3]; Thomas J. Kipps, MD[4]; Tanya Siddiqi, MD[5]; John N. Allan, MD[6]; Zoë Hunter, PhD[7]; Cathy Zhou, MS[7]; Anita Szoke, MD[7]; James P. Dean, MD, PhD[7]; Constantine S. Tam, MBBS, MD[8]



FD, fixed duration; MRD, minimal residual disease; PD, progressive disease.
[a]Confirmed uMRD was defined as uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in both peripheral blood and bone marrow.
[1]Wierda, WG. *J Clin Oncol*. 2021;39:3853-3865. [2]Tam CS et al. *Blood*. 2022;139:3278-3289.

Young/FIT	
Median age	**60y**
Del17p/TP53	**17%**
Primary end-point	**CR**





AEs >Grade3: Neutropenia 33%, AF 1%

BOR, best overall response.
[a]Overall response was assessed at the end of Cycle 3, on Day 1 of Cycles 7, 10, 13, 19, 25, 28, and 31, and every 6 months thereafter.
[b]Unmutated IGHV without del(17p)TP53 mutation.

AACR 2022, PCYC-1142; Allan et al.

Baseline Characteristics of Patients With and Without PD

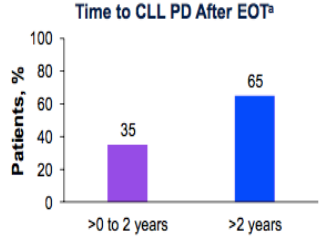
- Of 202 patients treated with fixed-duration ibrutinib + venetoclax in the FD cohort (n=159) or the MRD cohort placebo arm (n=43), 53 have had PD to date
  - 49 patients with progressive CLL and 4 patients with Richter transformation

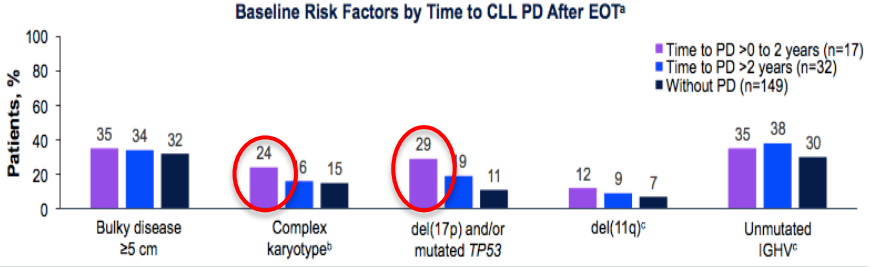
Characteristic	Patients With CLL PD[a] n=49	Patients Without PD n=149
Median age (range), years	61 (38–71)	60 (33–70)
Male, n (%)	34 (69)	94 (63)
Rai stage III/IV, n (%)	9 (18)	49 (33)
High-risk genomic features, n (%)		
Complex karyotype[b]	9 (18)	23 (15)
del(17p)/mutated *TP53*	11 (22)	17 (11)
del(11q)[c]	13 (27)	22 (15)
Unmutated IGHV	37 (76)	78 (52)
Any cytopenia, n (%)	13 (27)	59 (40)
ANC ≤1.5 × 10^9/L	2 (4)	16 (11)
Hemoglobin ≤11 g/dL	11 (22)	40 (27)
Platelet count ≤100 × 10^9/L	3 (6)	21 (14)
Bulky disease, n (%)		
≥5 cm	17 (35)	47 (32)
≥10 cm	1 (2)	4 (3)
Median ALC × 10^9/L (range)	76 (1–368)	56 (1–503)
ALC ≥25 × 10^9/L, n (%)	39 (80)	111 (74)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.
[a]Excluding 4 patients with Richter transformation. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 10/49 (20%) patients with PD and 20/149 (13%) patients without PD. [c]Without del(17p) per Döhner hierarchy.

PD Occurred >2 Years After Completion of Treatment in 65% of Patients

- Progression occurred >2 years after EOT in most patients with CLL PD (32/49 [65%])
- Prevalence of del(17p)/mutated *TP53* or complex karyotype (≥3 abnormalities) tended to be higher in patients with PD in the first 2 years after EOT





EOT, end of treatment.
[a]Excluding 4 patients with Richter transformation; [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; [c]Excluding patients with del(17p)/mutated *TP53* or complex karyotype.

Time to Next Treatment and Retreatment After Fixed-Duration Ibrutinib + Venetoclax

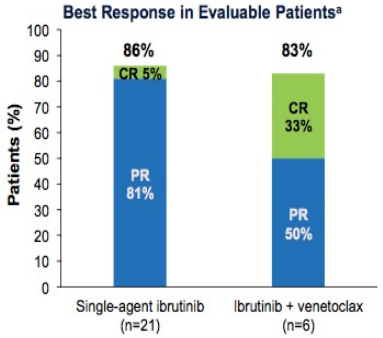
- 202 patients treated with fixed-duration ibrutinib + venetoclax
  - Median TTNT not reached
  - Estimated 4.5-year rate of freedom from next-line treatment was 82% (95% CI, 76–87)
- Of the 53 patients with PD
  - 18 have not yet initiated subsequent treatment
  - 28 have reinitiated ibrutinib-based therapy
    - Median time from EOT to PD for these patients was 2.1 years (range, 0.2–4.3)[a]
    - 22 reinitiated with single-agent ibrutinib
    - 6 reinitiated with ibrutinib + venetoclax
  - 7 have initiated other subsequent therapies[b]

Characteristic	Patients With PD Retreated with Ibrutinib-Based Therapy (n=28)
Median age (range), years	62 (39–71)
Male, n (%)	19 (68)
Rai stage III/IV, n (%)	5 (18)
High-risk genomic features, n (%)	
Complex karyotype[c]	10 (36)
del(17p)/mutated *TP53*	9 (32)
del(11q)[d]	7 (25)
Unmutated IGHV	22 (79)
Any cytopenia, n (%)	9 (32)
ANC ≤1.5 × 10^9/L	0
Hemoglobin ≤11 g/dL	7 (25)
Platelet count ≤100 × 10^9/L	2 (7)
Bulky disease, n (%)	
≥5 cm	9 (32)
≥10 cm	1 (4)
Median ALC × 10^9/L (range)	74 (1–297)
ALC ≥25 × 10^9/L, n (%)	22 (79)

TTNT, time to next treatment.
[a]Per protocol, only patients with PD >2 years after completion of treatment were eligible to reinitiate ibrutinib + venetoclax. [b]Subsequent therapies included acalabrutinib, pirtobrutinib, umbralisib + ublituximab + venetoclax, venetoclax + rituximab, and stem cell transplant. [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 5/28 (18%) patients. [d]Without del(17p) per Döhner hierarchy.

Responses and Safety With Reintroduction of Ibrutinib-Based Therapy

- Median time on retreatment:
  - 17 months (range, 0–45) for single-agent ibrutinib (n=22)
  - 14 months (range, 5–15) for ibrutinib + venetoclax (n=6)



AEs, n (%)	Single-agent ibrutinib (n=22)	Ibrutinib + venetoclax (n=6)
Any AE	18 (82)	6 (100)
Most frequent AEs[b]		
COVID-19[c]	6 (27)	2 (33)
Diarrhea	5 (23)	2 (33)
Hypertension	4 (18)	3 (50)
Pyrexia	3 (14)	0
Grade 3/4 AEs	5 (23)	2 (33)
Serious AEs	4 (18)	0
AEs leading to discontinuation	0	0
AEs leading to dose reduction	0	0

AE, adverse event; CR, complete response; PR, partial response.
[a]One patient who initiated single-agent ibrutinib retreatment had not yet undergone response assessment. [b]Occurring in ≥10% of patients with single-agent ibrutinib or ≥2 patients with ibrutinib + venetoclax. [c]All events were grade 1/2.

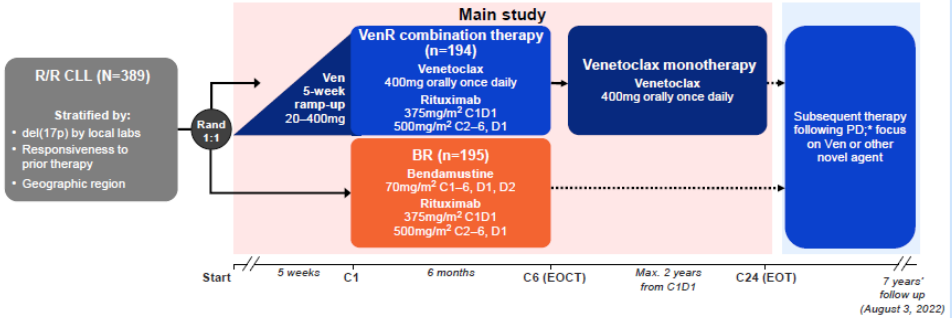
Conclusions

- Ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free fixed-duration regimen for first-line treatment of CLL/SLL
- With up to 5 years of follow-up, fixed-duration ibrutinib + venetoclax continues to provide deep remissions with clinically meaningful PFS, including in patients with high-risk genomic features
- The safety profile is manageable and unchanged from that previously reported
- First-line fixed-duration treatment with ibrutinib + venetoclax may mitigate development of resistance mechanisms associated with continuous single-agent targeted therapies; to date, only one mutation of uncertain clinical significance has been detected in *BCL-2*, and none in *BTK* or *PLCG2*
- Ibrutinib-based retreatment results show promising responses in patients needing subsequent therapy

Response to Subsequent Novel Therapies and Time to Second Progression-Free Survival Event in the MURANO Trial in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia Previously Treated with Fixed-Dose Venetoclax Plus Rituximab

Rosemary Harrup,[1] Arnon P. Kater,[2] Barbara Eichhorst,[3] Carolyn Owen,[4] Brenda Chyla,[5] Hyun Yong Jin,[6] Yanwen Jiang,[6] Yi Meng Chang,[7] Rosemary Millen,[7] Marcus Lefebure,[7] Maria Thadani-Mulero,[7] Michelle Boyer,[7] John F. Seymour[8]*

Figure 1. MURANO (NCT02005471) study design.



*Investigator-assessed PD according to iwCLL criteria. C, cycle; D, day; del(17p), deletion 17p; EOCT, end of combination treatment; EOT, end of treatment; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; max., maximum; Rand, randomization.

Methods: a global, open-label, randomized, Phase III trial

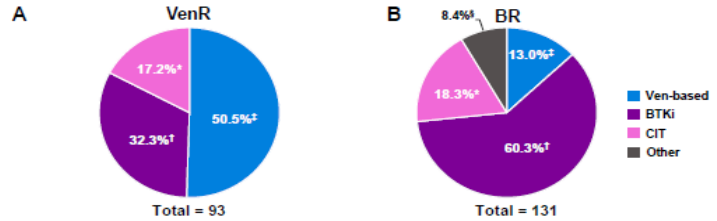
- Overall, 389 patients were randomized to VenR (2 years of Ven, with R for the first 6 months) or 6 months of BR (**Figure 1**).
- Patients in either arm with progressive disease (PD) were followed for disease response to any subsequent anti-CLL therapeutic regimens, PFS and OS.
- A sub-study, introduced in 2018, allowed patients who developed PD following treatment with VenR or BR to receive the MURANO VenR regimen.
- Patients who initiated new anti-CLL therapy without a response assessment reported by the investigator were considered unevaluable.

Poster1898

Results: Subsequent therapies

- The final data cutoff was August 3, 2022; the median follow-up of the main study was 85.7 months (range: 0–99.2)
  - PFS, time-to-next treatment or death, and OS benefits were maintained at the 7-year follow-up [3]
- Overall, 73/194 (37.6%) patients in the VenR arm had not received a next-line therapy at the final cutoff, and 26 patients had died without subsequent therapy.
- In the BR arm, 36/195 (18.5%) patients had not received a next-line therapy at the final cutoff, and 28 patients had died without subsequent therapy.
- Following PD, 95 patients randomized to VenR and 131 patients randomized to BR had received a subsequent therapy
  - Of the 95 VenR patients who received subsequent therapy, two patients received a non-CLL therapy for another malignancy so were excluded from the analysis
  - The distribution of subsequent anti-CLL therapies received by patients in the VenR arm (n=93) and the BR arm (n=131) are shown in **Figures 2A** and **2B**, respectively.

Figure 2. Subsequent anti-CLL therapies.

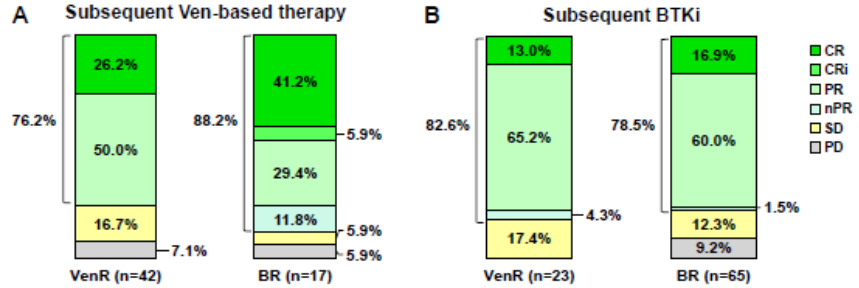


*VenR: n=16; BR: n=24. †VenR: ibrutinib (n=25), acalabrutinib (n=4), and zanubrutinib (n=1), with 18 patients ongoing at the time of the final cutoff; BR: ibrutinib (n=69), acalabrutinib (n=6), and zanubrutinib (n=4), with 20 patients ongoing at the time of the final cutoff. ‡VenR: sub-study (retreated with VenR; n=25), Ven-mono (n=9), Ven-combo (n=12), and Ven-based (no other information provided; n=1), with 12 patients ongoing at the time of the final cutoff; BR: sub-study (retreated with VenR; n=9), Ven-mono (n=7), and Ven-combo (n=1), with three patients ongoing at the time of the final cutoff. §n=11. CIT, chemoimmunotherapy; combo, combination; mono, monotherapy.

Results: best overall response (BOR) of subsequent therapies

- BORs (defined as complete remission [CR], CR with incomplete count recovery [CRi], partial remission [PR], and nodular PR [nPR]) are presented in **Figure 3**.
- Among evaluable patients previously treated with VenR and BR:
  - The BOR rate of subsequent Ven-based therapies was 76.2% (32/42) and 88.2% (15/17), respectively (**Figure 3A**)
  - The BOR rate of subsequent BTKi therapy was 82.6% (19/23) and 78.5% (51/65), respectively (**Figure 3B**).

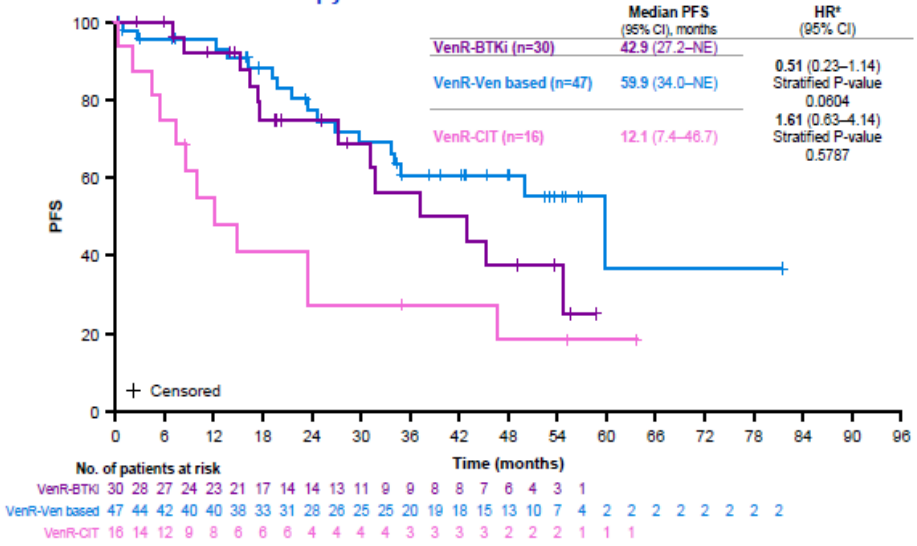
Figure 3. Response rates to subsequent VenR and BTKi therapies among evaluable patients.



SD, stable disease.

- PFS in patients treated with VenR who received a subsequent therapy is shown by treatment type in **Figure 5**.

Figure 5. Kaplan Meier plot of PFS for patients in the VenR arm who received a subsequent therapy by treatment type; landmark (time zero) taken at initiation of next-line therapy.



*Stratified HR is presented.

Conclusions

- Final data from MURANO demonstrate that, despite the majority of BR patients receiving novel therapies after relapse on MURANO, there was a significantly prolonged time to second PFS observed in favor of the VenR arm.
- Patients who had relapsed and received retreatment or crossed over to Ven-based regimens or subsequent BTKi therapy also demonstrated high response rates, as well as sustained PFS and OS.
- Time to second PFS event was similar for those treated with Ven-based regimens or BTKi therapy post-VenR, confirming re-treatment as a feasible option.
- These results indicate that early intervention with fixed-duration VenR in R/R CLL is an effective approach, with high response rates to subsequent therapies.

Extended follow-up: Alpine, BRUIN

Sequencing: Captivate, Murano

New molecules: Car-T, ROR-1, BTKi covalent non covalent LP-168

Lisocabtagene Maraleucel in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 24-Month Median Follow-up of TRANSCEND CLL 004

Tanya Siddiqi,[1] David G. Maloney,[2] Saad S. Kenderian,[3] Danielle M. Brander,[4] Kathleen Dorritie,[5] Jacob Soumerai,[6] Peter A. Riedell,[7] Nirav N. Shah,[8] Rajneesh Nath,[9] Bita Fakhri,[10] Deborah M. Stephens,[11] Shuo Ma,[12] Tatyana Feldman,[13] Scott R. Solomon,[14] Stephen J. Schuster,[15] Serena K. Perna,[16] Sherilyn A. Tuazon,[17] San-San Ou,[17] Neha Rane,[16] William G. Wierda[18]

Efficacy outcomes: DL2 only

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12–29]	10 (20) [10–34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49–71]	30 (60) [45–74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Time to first response, months, median (range)	1.3 (0.8–17.4)	1.1 (0.8–17.4)
Time to first CR/CRi, months, median (range)	5.5 (0.8–18.0)	2.1 (0.8–18.0)

- **uMRD was achieved in MRD-evaluable patients in the full population at DL2 by:**
  - **15/15 (100%) patients with CR/CRi in blood and 15[a]/16 (94%) in marrow**
  - 24/24 (100%) patients with PR/nPR in blood and 23/23 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines. SD, stable disease.

Siddiqi T, et al. ASH 2023 [Presentation #330]

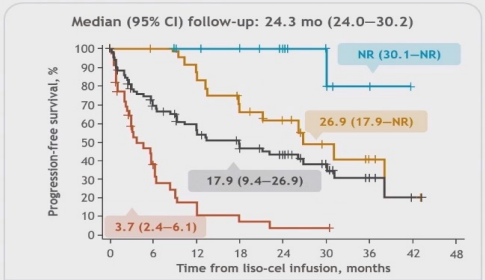
TRANSCEND CLL 004 uMRD
Poster 3263
Papp et al.
6:00–8:00 PM PST, Sunday, December 10, 2023

Safety Grade>3	
CRS	8%
Neutropenia	60%
Anemia	53%
PLTS	42%

ASH 2023: presentation 330

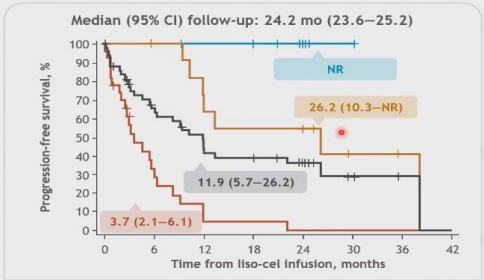
Progression-free survival by best overall response

(A) Full study population at DL2 (n = 88)



No. at risk									
CR/CRi	17	17	15	14	10	5	2	0	0
PR/nPR	25	24	21	15	11	6	3	1	0
Nonresponder	46	12	4	2	1	1	0	0	0
Total	88	53	40	31	22	12	5	1	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



No. at risk									
CR/CRi	10	10	9	9	5	1	0	0	
PR/nPR	12	11	8	6	5	2	1	0	
Nonresponder	28	7	2	1	0	0	0	0	
Total	50	28	19	16	10	3	1	0	

Data on KM curves are expressed as median (95% CI, if available).

Siddiqi T, et al. ASH 2023 [Presentation #330]

Summary

- A single administration of liso-cel demonstrated sustained, rapid, deep, and durable responses in patients with R/R CLL/SLL, at a median follow-up of 23.5 months
- The study met its primary endpoint; the current data cut demonstrated a CR/CRi rate of 20% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, which compares favorably with historical CR/CRi rates of 0%–5%[1]
- Safety data were consistent with previous reports, demonstrating that the safety profile was manageable, with low rates of grade ≥ 3 CRS and NEs, and no new safety signals
- Overall, these results support liso-cel as a potential new treatment option for R/R CLL/SLL

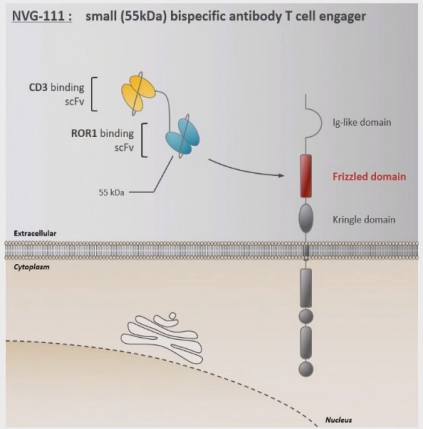
Time Limited Exposure to a ROR1 Targeting Bispecific T Cell Engager (NVG-111) Leads to Durable Responses in Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)

William Townsend[1*], Sarah Leong[1], Mittal Shah[2], Toby Batten[3], David Tucker[4], Bryson Pottinger[5], Shankara Paneesha[6], Dima El-Sharkawi[7], Toby A. Eyre[8], Ho Pui Jeff Lam[1], Jiexin Zheng[9], Sarah Cook[2], David Granger[2], David Ahern[10], Kieran O'Donovan[2], Amit C. Nathwani[2,9], **Parag Jasani**[1,9]

[1]National Institute for Health Research Clinical Research Facility, University College London Hospitals NHS Foundation Trust, London, United Kingdom; [2]NovalGen Ltd, London, United Kingdom; [3]Veramed, Twickenham, United Kingdom; [4]Royal Cornwall Hospital, Cornwall, United Kingdom; [5]Dep. of Haematology, Royal Cornwall, Hospital, Truro, United Kingdom; [6]Birmingham Heartlands Hospital, Birmingham, United Kingdom; [7]The Royal Marsden NHS Foundation Trust, Surrey, United Kingdom; [8]Department of Haematology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, United Kingdom; [9]Royal Free London NHS Foundation Trust, London, United Kingdom; [10]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom

*Funding and support from the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre

NVG-111: A First in Class ROR1 x CD3 T Cell Engager



- **NVG-111** is a bispecific humanized tandem scFv T cell engager (TCE) targeting **ROR1xCD3**
- NVG-111 mediates **potent killing of ROR1⁺ tumors**[1,2] by:
  - Binding to a **unique** membrane proximal Frizzled domain epitope
  - Possessing an optimized **geometry of binding** for efficient synapse formation
  - Redirecting T cells via the humanized CD3 binder, which is **optimized for efficient tumor killing** and **attenuated cytokine release**

References
1. Gohil *et al*, Oncoimmunol 2017, 6:e1326437
2. Gohil *et al*, Br J Haematol 2019, 186:380

- ROR1 is **highly expressed on hematological and solid tumors**[3,4,5,6]

CLL	MCL	Lymphomas	Solid Tumors
95%	95%	90%	54-90%

Adapted from Zhang et al [6]

- ROR1 is expressed on **most malignant B cells** but not normal B cells[2]

Participant Inclusion

Multicenter phase I adaptive trial design (NCT04763083)

Key Inclusion Eligibility

I. R/R CLL participants: ≥12 months BTKi or ≥6 months venetoclax ± anti-CD20 mAb
II. R/R MCL participants: ≥6 months BTKi
III. Tumor centrally assessed for ROR1 positivity at screening
IV. ≥2 prior lines of treatment
V. ECOG ≤2
VI. No active CNS disease
VII. Lymphocyte count <50x10^9/L and lymph nodes <10cm

Study Endpoints

I. Primary: Safety and tolerability
II. Secondary: Efficacy and durability of response

BTKi=Bruton's tyrosine kinase inhibitor; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; SOC=standard of care

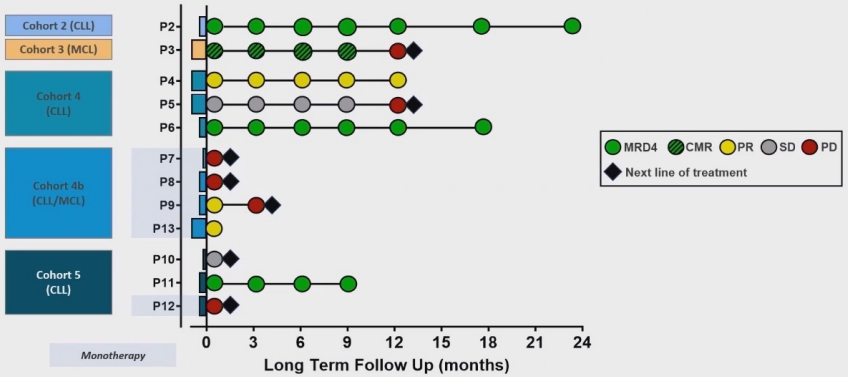
Demographics and Treatment Groups

Baseline characteristics	n (%)
Age	
Median Age Years (range)	60 (52-83)
Sex	
Male	11 (85%)
Female	2 (15%)
Ethnicity	
Caucasian	9 (69%)
Black or African American	4 (31%)
Cancer diagnosis	
Chronic Lymphocytic Leukemia	11 (85%)
Mantle Cell Lymphoma	2 (15%)

Participants (n=13)	% median baseline disease in bone marrow
Group 1: NVG-111 + ibrutinib (N=8)	6% (0.1-31%)
Group 2: NVG-111 monotherapy (N=5)	66% (11-74%)

Depth and Duration of Response

Responses durable despite time limited exposure (median: 3 cycles)



Restricted mean survival time for DoR is 14 months

Minimal residual disease (MRD4=1 in 10,000 CLL cells); CMR=complete metabolic response assessed by Lugano criteria
DoR=duration of response; PR=partial response; SD=stable disease; PD=progressive disease.

Data cut off November 1st, 2023

ORR 58%

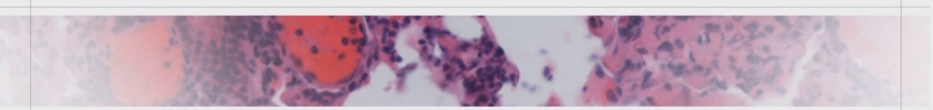
Conclusions

NVG-111 first in human clinical trial: encouraging safety and efficacy data

- **Safety**
  - Safety profile is **predictable and consistent with TCE mechanism of action** with **no evidence of on-target, off-tumor toxicity**
  - Majority of AEs were Grade 1 or 2, limited mainly to cycle 1, and **fully reversible with no long lasting or late-emerging toxicity**
  - Three Grade 3 DLTs observed, **all fully recovered** upon NVG-111 cessation
- **Efficacy**
  - Overall response rate **(ORR) of 58%**
  - NVG-111 combined with ibrutinib resulted in **MRD negative in peripheral blood** in three CLL participants and **CMR** in one MCL participant
  - NVG-111 monotherapy shows **clear objective clinical responses** in CLL and MCL participants

These data merit further evaluation

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



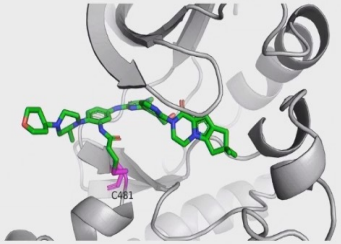
Initial Results of a Phase 1 Dose Escalation Study of LP-168, a Novel Covalent and Non-Covalent Next-Generation Inhibitor of Bruton's Tyrosine Kinase

Jennifer A Woyach MD, Deborah M Stephens DO, Danielle M Brander MD, Adam S Kittai MD, Boyu Hu MD, Andrea Sitlinger MD, Emily Curran MD, Fenlai Tan MD PhD, Yi Chen PhD, Stephen P Anthony DO, Yu Chen MD PhD, John C Byrd MD

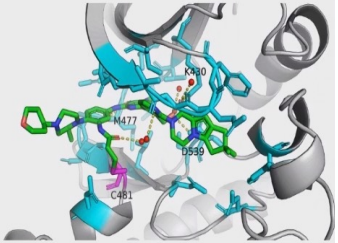
Background

- Covalent inhibitors of Bruton's Tyrosine Kinase (BTKi) have been transformative in the treatment of CLL and other B cell malignancies. Mutations in BTK that confer resistance have been effectively targeted with noncovalent BTKi, but additional mutations in BTK, including T474 mutations, can emerge
- LP-168 is an extremely selective, orally available inhibitor of BTK with a dual mechanism of action. LP-168 can bind BTK covalently in the presence of WT BTK, and non-covalently in the presence of C481 mutated BTK
- Here we present initial data from the Phase 1 dose escalation study of LP-168

Covalent Binding



Non-Covalent Interactions



Patient Characteristics (DLT-evaluable, n=45)

Characteristics	N=45
Median age, years (range)	70(41-85)
Gender, n(%)	
Female	8(18)
Male	37(82)
ECOG PS, n(%)	
0	17(38)
1	27(60)
2	1(2)
Median number prior lines of systemic therapy (range)	3(1-8)
Prior therapy, n(%)	
1 prior covalent BTK inhibitor	23(51)
2 prior covalent BTK inhibitors	12(27)
Prior covalent + reversible BTK inhibitors	6(13)
BTK inhibitor-naive	4(9)
Chemotherapy	34(76)
Anti-CD20 antibody	38(84)
BCL2 inhibitor	19(42)
BCL2 inhibitor + BTK inhibitor	17(38)
PI3K inhibitor	2(4)
Lenalidomide	5(11)
Allogeneic stem cell transplant	1(2)
CAR-T	3(7)

Characteristics	N=45
Reason discontinued any prior BTKi, n(%)	
Progressive disease	29(64)
Toxicity/other	17(38)
Disease type, n(%)	
R/R CLL	37(82)
R/R MCL	4(9)
R/R MZL	2(4)
R/R WM	2(4)

Known Molecular Characteristics of CLL Patients	N=37
Mutation status, n	
BTK C481S-mutant	21
BTK C481F/Y/R-mutant	6
BTK gatekeeper mutations (T474I/F/H)	9
BTK Wildtype	11
BTK mutation status unknown	1
PLCG2-mutant	5
High Risk Molecular Findings, n	
17p deletion	15
TP53 mutation	10
17p deletion, TP53 mutation, or both	20
17p13 deletion + TP53 mutant	5
IGHV unmutated	27
11q deletion	16
Complex karyotype	11

Response Rate in Select Patient Subsets (≥200mg QD)

Best Overall Response	All Patients	Only 1 Prior BTKi	BTKi + BCL2i	TP53 Alteration
N	19	11	8	10
ORR n(%)	14 (73.7%)	9 (81.8%)	6 (75.0%)	7 (70.0%)
CR n(%)	0	0	0	0
PR or PR-L n(%)	14 (73.7%)	9 (81.8%)	6 (75.0%)	7 (70.0%)
SD n(%)	5 (26.3%)	2 (18.2%)	2 (25.0%)	3 (30.0%)
PD n(%)	0	0	0	0

Efficacy in patients with T474 Mutation: 5/7 patients (71,4%)

Safety > Grade3
Infections 15,6%
Neutropenia 13%

Conclusions

- LP168 demonstrates safety and early efficacy in this phase 1 trial
- Efficacy and PK support a dose of 200 mg or 300 mg daily as RP2D
- Activity in patients with gatekeeper mutations and high risk features is encouraging and will be evaluated in larger numbers of patients
- Larger clinical studies and combinations are in development
- Preclinical Data: Sunday December 10, 9:45 am (Oral Abstract 416)
- Additional Clinical Data in NHL: Sunday and Monday poster sessions (Abstracts 3033 and 4400)

Take Home messages

Extended follow-up:

Alpine: Zanubrutinib demonstrated sustained PFS benefit over ibrutinib

BRUIN: With median follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor

Sequencing:

Captivate: Ibrutinib-based retreatment results show promising responces in patients needing subsequent therapy

Murano: Time to second PFS event was similar for those treated with Ven-based regimens or BTKi therapy post VenR confirming re-treatment as a feasible option.

New molecules:

Car-T: CR rate 20%, median F-UP 23,5 months, low rates of grade>3 CRS……CAR-T is a potential new treatment option

ROR-1: No evidence off–tumor toxicities, majority of AEs were grade 1 or 2, ORR 58%, combination with IBR= MRD-

BTKi covalent non covalent LP-168: Safe and efficacy at dose of 200-300mg, large clinical study and combination are ongoing