# CLL:Management After First-Line Therapy

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# Conflict$ of Intere$t

- Advisory boards/consulting – Morphosys, Karyopharm, Kite, Beigene, Tessa, Symbio, Lilly, Merck, Epizyme, TG Therapeutics, Roche-Genentech
- Speaking – Morphosys, Karyopharm, Beigene, TG Therapeutics, Epizyme

# Objectives

- Learn to manage kinase inhibitor intolerance
- Understand how to manage BTK refractory patients
- Recognize how to manage venetoclax refractory patients
- Be familiar with options for BTK and venetoclax refractory patients
- Develop an algorithm for the sequence of therapies in CLL

# Current and Future Front-Line Regimens in CLL

cBTKi +/- CD20

Ven+ cBTKi +/- CD20

Clb-G
FCR
BR

Ven-G

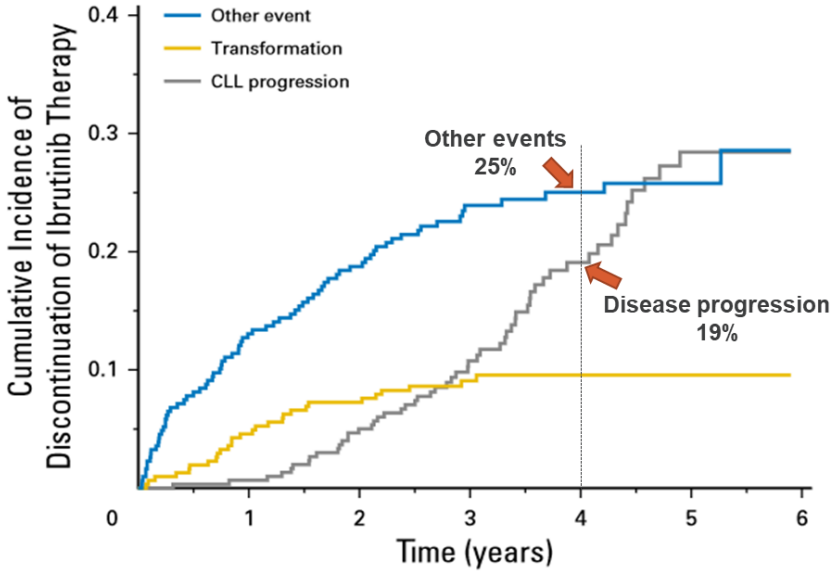
Management of second-line determined by

- Prior treatment, response to treatment
- Reason for treatment discontinuation
  - Intolerance
  - Relapse/refractory

cBTKI - Covalent Bruton tyrosine kinase inhibitor; V-venetoclax; G- obinutuzumab; clb – chlorambucil; FCR – Fludarabine, cyclophosphamide, rituximab

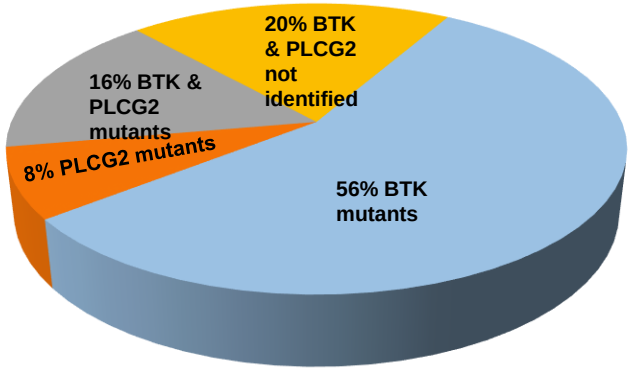
# Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

**Ibrutinib discontinuation from 4 prospective studies[1]**




- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[3]
  - Relapsed/refractory = 54%[1]

**Ibrutinib acquired resistance in patients with progressive CLL[2]**



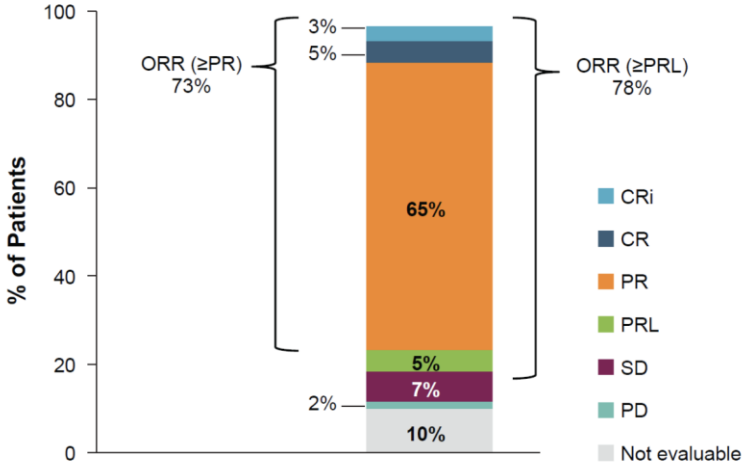

- BTK C481 mutations are the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

[1]Woyach et al. *J Clin Oncol*. 2017;35:1437-43. [2]Lampson et al. *Expert Rev Hematol.* 2018;11:185-94. [3]Burger et al. *Leukemia.* 2020;34:878-789. [4]Byrd et al. *N Engl J Med.* 2016;374:323-32. [5]Hershkovitz-Rokah et al. *Br J Haematol.* 2018;181:306-19. [6]Woyach et al. *N Engl J Med.* 2014;370:2286–94. [7]Woyach et al. *Blood*. 2019;134(Suppl 1):504. [8]Xu et al. *Blood.* 2017;129:2519–25.

# Acalabrutinib in Ibrutinib intolerant CLL

| Adverse Event | Number of Patients With Ibrutinib Intolerance[a] | Acalabrutinib Experience for Same Patients | | | |
|---|---|---|---|---|---|
| | | Total | Lower Grade | Same Grade | Higher Grade |
| Atrial fibrillation | 16[b] | 2 | 2 | 0 | 0 |
| Diarrhoea | 7 | 5 | 3 | 2 | 0 |
| Rash | 7 | 3 | 3 | 0 | 0 |
| Bleeding[c,d] | 6 | 5 | 3 | 2 | 0 |
| Arthralgia | 7[e] | 2 | 1 | 1 | 0 |
| Total | 41 | 24 | 18 | 6 | 1 |

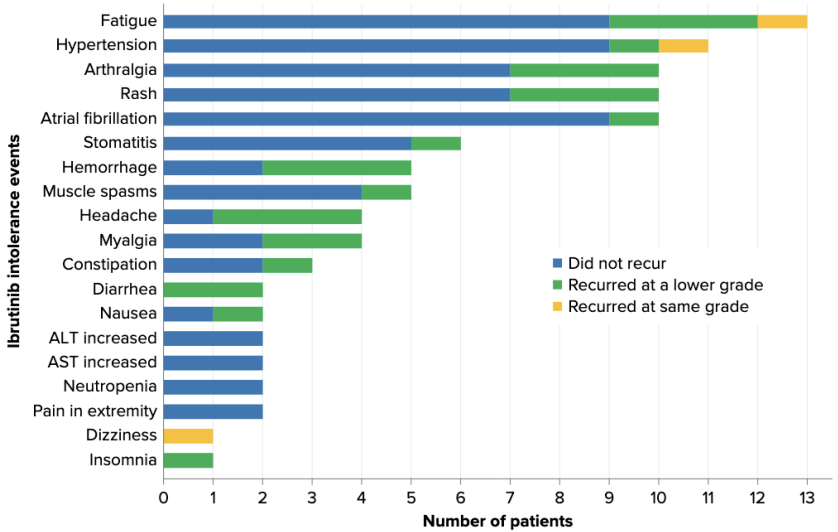
[a]Among 60 patients meeting the study enrolment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhoea, rash, bleeding, or arthralgia.
[b]Includes patients with atrial flutter (n=2).
[c]Events categorised as bleeding included ecchymosis, haemorrhage, epistaxis, contusion, haematuria, and subdural haematoma.
[d]All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment.
[e]Includes one patient with arthritis.




Rogers et al, Haematologica, in press

# Zanubrutinib in BTK Intolerant CLL

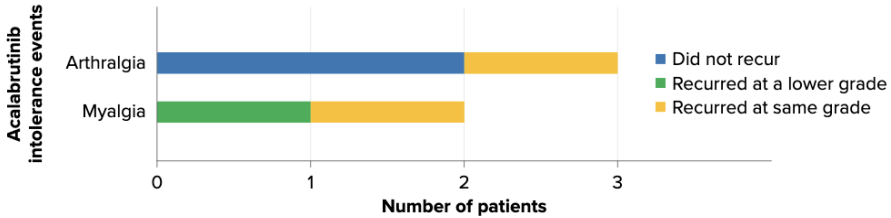
Ibrutinib Intolerant




Data cutoff: 01 Mar 21.
ALT, alanine aminotransferase; AST, aspartate transaminase.
[a] Intolerance events occurring in ≥2 patients or recurring in ≥1 patient shown here.

- 86/115 ibrutinib intolerance events (75%) did not recur (**Figure 2**)
  - Of the 29 recurrent ibrutinib intolerance events, 26 (90%) recurred at a lower severity, and 3 (10%) at the same severity

Acalabrutinib Intolerant




Data cutoff: 01 Mar 21.
[a] Intolerance events occurring in ≥2 patients shown here.

Shadman et al, Proc EHA, 2021

# Umbralisib in BTK-PI3k Intolerant CLL

## Safety of Umbralisib: All-causality AEs in ≥10% of Patients (N = 51)

| | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Diarrhea | 17 | 33% | 11 | 22% | 4 | 8% | - | - |
| Nausea | 20 | 39% | 7 | 14% | - | - | - | - |
| Fatigue | 4 | 8% | 9 | 18% | - | - | - | - |
| Insomnia | 11 | 22% | 2 | 4% | - | - | - | - |
| Thrombocytopenia | 4 | 8% | 3 | 6% | 4 | 8% | 2 | 4% |
| Headache | 9 | 18% | 3 | 6% | - | - | - | - |
| Neutropenia | 1 | 2% | 2 | 4% | 2 | 4% | 7 | 14% |
| Dizziness | 8 | 16% | 2 | 4% | - | - | - | - |
| Peripheral edema | 8 | 16% | 1 | 2% | - | - | - | - |
| Cough | 6 | 12% | 2 | 4% | - | - | - | - |
| Rash | 7 | 14% | 1 | 2% | - | - | - | - |
| Rash maculo-popular | 8 | 16% | - | - | - | - | - | - |
| Anemia | 1 | 2% | 4 | 8% | 2 | 4% | - | - |
| Arthralgia | 5 | 10% | 2 | 4% | - | - | - | - |
| Contusion | 7 | 14% | - | - | - | - | - | - |
| Decreased appetite | 5 | 10% | 2 | 4% | - | - | - | - |
| Leukocytosis | - | - | - | - | 7 | 14% | - | - |
| Myalgia | 5 | 10% | 2 | 4% | - | - | - | - |
| Pneumonia | - | - | 1 | 2% | 6 | 12% | - | - |
| Pyrexia | 4 | 8% | 2 | 4% | 1 | 2% | - | - |
| Upper respiratory tract Infection | 4 | 8% | 3 | 6% | - | - | - | - |
| Vomiting | 5 | 10% | 2 | 4% | - | - | - | - |
| AST/ALT increase | 2 | 4% | 2 | 4% | 3 | 6% | - | - |

[a]Bruising and diarrhea, diarrhea, rash, nausea and fatigue; all had prior ibrutinib

- Four patients (8%) had recurrence of an AE that led to prior KI intolerance[a]
  - In 3 patients, recurrent AEs were of lesser severity is most cases and did not require umbralisib dose modification or discontinuation
  - Umbralisib was discontinued in 1 patient due to recurrence of Gr3 drug-associated rash
  - No prior idelalisib treated patients (n = 7) had a recurrence of idelalisib-associated AEs while on umbralisib

## AEs of Interest (N = 51) During Umbralisib Treatment and Dose Reductions/ Discontinuations Due to AEs

**Adverse Events of Interest**

| | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Colitis | - | - | 1 | 2% | - | - | - | - |
| Pneumonitis | 1 | 2% | 1 | 2% | - | - | - | - |
| Transaminitis | 2 | 4% | 2 | 4% | 1 | 2% | - | - |

- 1 case of colitis was reported in a patient with del(17p) after 6 weeks on treatment
  - Colitis resolved following a 2-week treatment interruption and the patient remains on dose reduced umbralisib (600 mg daily) in complete remission (25 months on therapy)
- No fatal AEs were observed

**Dose Reductions and Discontinuations**

- Eight patients (16%) had dose reductions due to an AE[a] allowing them to continue umbralisib therapy
- Six patients (12%) discontinued umbralisib due to an AE[b]

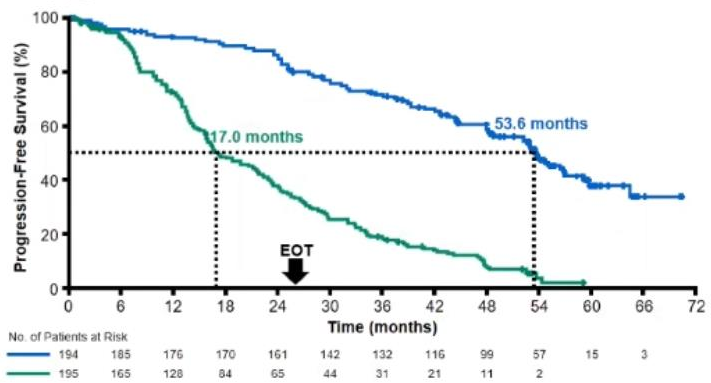
PI3k – phosphoinositide -3-kinase

Mato et al, Blood 137:2817, 2021

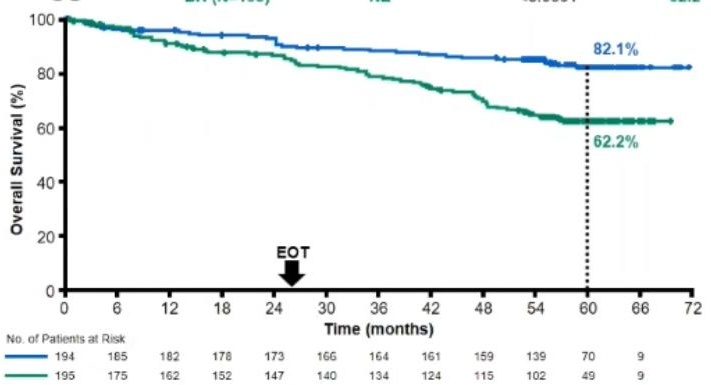
# MURANO Trial – 5-yr Analysis

## PFS and OS benefits with VenR over BR were sustained 3 years after EOT

| | Median PFS (95% CI), months | HR* (95% CI) | 5-yr PFS (%) |
|---|---|---|---|
| VenR (N=194) | 53.6 (48.4, 57.0) | 0.19 (0.15, 0.26) Stratified P-value <0.0001† | 37.8 |
| BR (N=195) | 17.0 (15.5, 21.7) | | NE |




| | Median OS (95% CI), months | HR‡ (95% CI) | 5-yr OS (%) |
|---|---|---|---|
| VenR (N=194) | NE | 0.40 (0.26, 0.62) Stratified P-value <0.0001† | 82.1 |
| BR (N=195) | NE | | 62.2 |




- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

*Unstratified HR=0.21;‡Unstratified HR=0.42; †P-values are descriptive only; +, censored

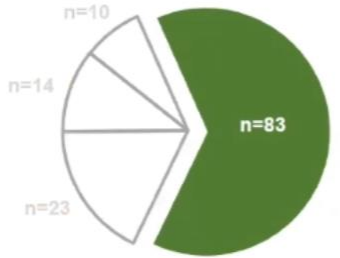
BR, bendamustine-rituximab; CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; VenR, venetoclax-rituximab; yr, year

Kater et al, ASH 2020

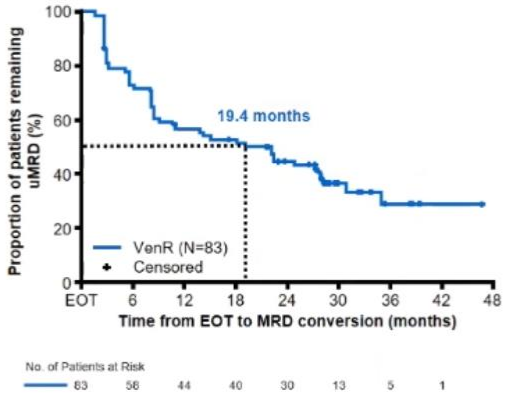
VenR-venetoclax/rituximab; BR – bendamustine/rituximab

# Long delay between MRD conversion and clinical PD observed

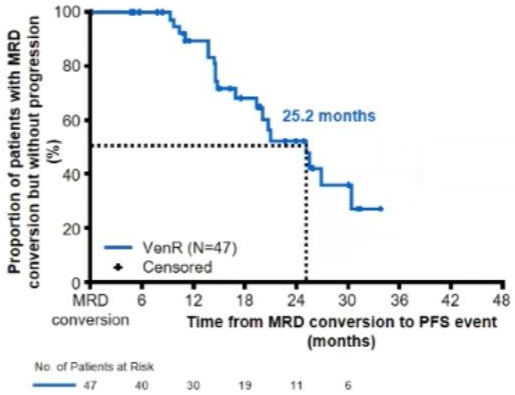
**MRD status at EOT (N=130)**




**Time from EOT to MRD Conversion**
**Median 19.4 months**
**(95% CI 8.7; 28.3)**




**Time from MRD conversion to PD***
**Median 25.2 months**
**(95% CI 19.4; 30.4)**





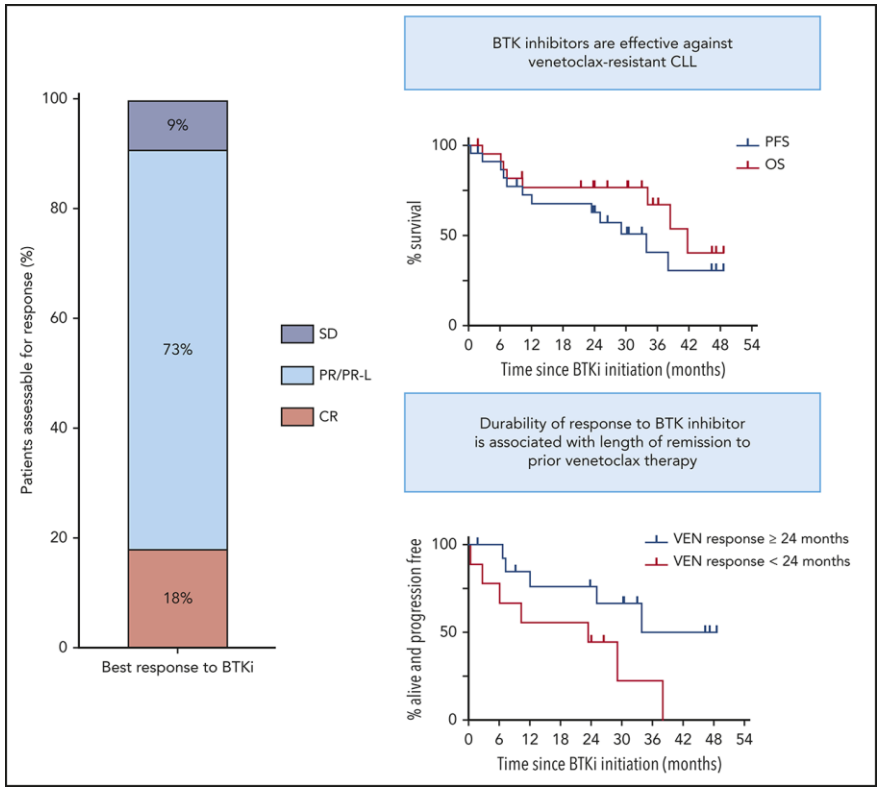
N=130; uMRD <1 CLL cell/10,000 leukocytes

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria

C, cycle; D, day; CLL, chronic lymphocytic leukemia; EOT, end of treatment; mo, months; PD, progressive disease; (u)MRD, (undetectable) minimal residual disease; Ven, venetoclax

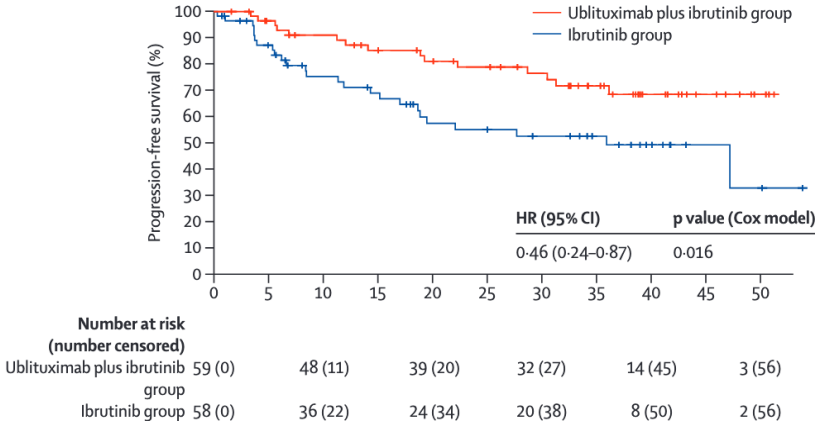
MRD – minimal residual disease

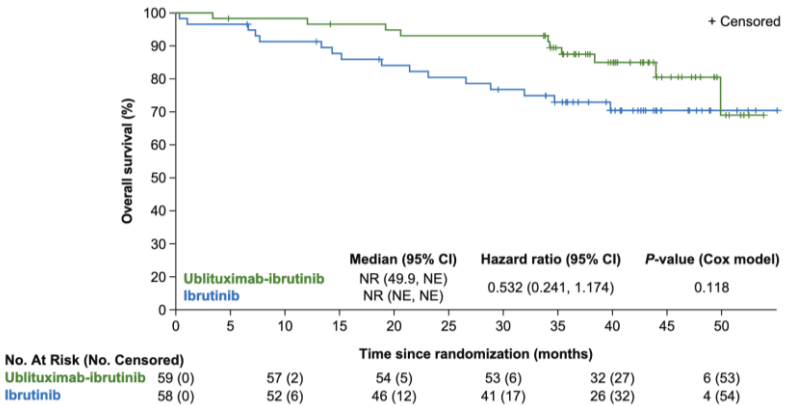
# Efficacy of BTK inhibitor therapy in CLL resistant to venetoclax




Lin, et al, Blood, 135:2266, 2020

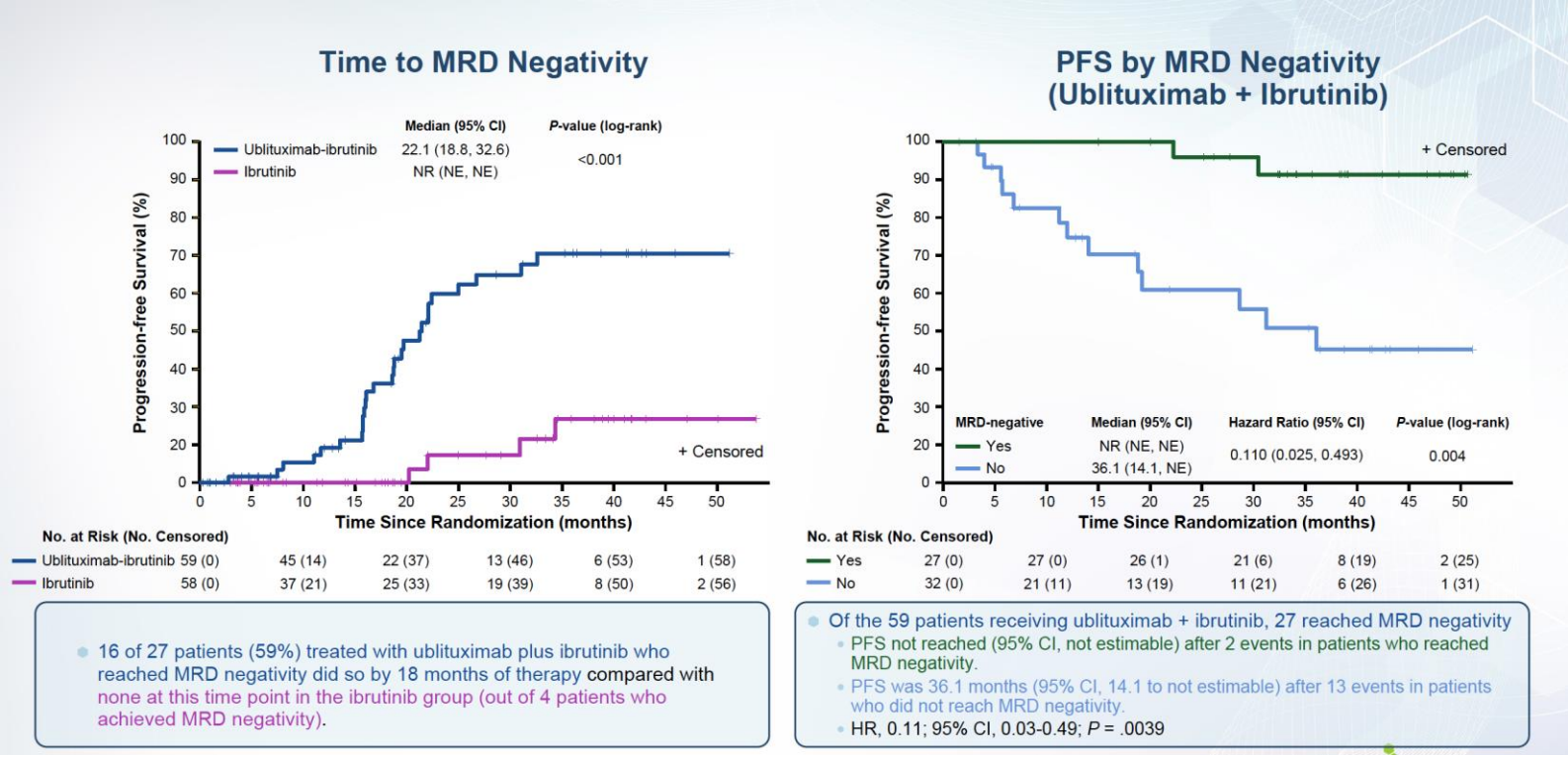
# Ibrutinib +/-Ublituximab:GENUINE




Sharman et al, Lancet Haematol 8:e254-e266, 2021

# GENUINE: MRD Status




Sharman et al, Lancet Haematol 8:e254-e266, 2021

# Pralsetinib (LOXO-305) CLL/SLL Patient Characteristics

| Characteristics | n=170 |
|---|---|
| Median age, years (range) | 69 (36-88) |
| Female, n (%) | 61 (36) |
| Male, n (%) | 109 (64) |
| ECOG PS[a], n (%) | |
| 0 | 87 (51) |
| 1 | 69 (41) |
| 2 | 13 (8) |
| Median number prior lines of systemic therapy (range) | 3 (1-11) |
| BTK pre-treated | 4 (1-11) |
| Prior therapy, n (%) | |
| BTK inhibitor | 146 (86) |
| Chemotherapy | 140 (82) |
| Anti-CD20 antibody | 153 (90) |
| BCL2 inhibitor | 57 (34) |
| PI3K inhibitor | 36 (21) |
| Lenalidomide | 14 (8) |
| Autologous stem cell transplant | 0 |
| Allogeneic stem cell transplant | 3 (2) |
| CAR-T | 10 (6) |
| Reason discontinued any prior BTKi, n (%)[b] | |
| Progressive disease | 98 (67) |
| Toxicity/other[c] | 48 (33) |

| Baseline Molecular Characteristics[d] | |
|---|---|
| Mutation status, n (%) | |
| BTK C481-mutant | 25 (27) |
| BTK Wildtype | 66 (73) |
| PLCG2-mutant | 4 (4) |
| High Risk Molecular Findings, n (%) | |
| 17p deletion | 20 (25) |
| TP53 mutation | 27 (30) |
| 17p13 deletion + TP53 mutant | 18 (22) |
| IGHV unmutated | 71 (88) |
| 11q deletion | 15 (19) |

Data cutoff date of 27 September 2020. Total % may be different than the sum of the individual components due to rounding. [a]Patients with missing ECOG PS status: n=1. [b]Calculated as percent of patients who received prior BTK inhibitor. [c]Other includes patients who completed treatment and those who discontinued voluntarily or due to physician's decision. [d]Molecular characteristics were determined centrally, in those patients with sufficient sample to pass assay quality control. 91 patients were tested for BTK and PLCG2, 81 patients for 17p13 deletion, 91 patients for TP53, 81 patients for 17p13 deletion + TP53, 81 patients for IGHV and 81 patients for 11q deletion.

Mato et al. ASH 2020

# Pralsetinib (LOXO-305) Safety Profile

| All doses and patients (n=323) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Treatment-emergent AEs, (≥10%), n (%)[a] | | | | | | Treatment-related AEs, n (%) | |
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | | Grades 3/4 | Any Grade |
| Fatigue | 40 (12%) | 22 (7%) | 3 (1%) | - | 65 (20%) | | 2 (<1%) | 27 (8%) |
| Diarrhea | 45 (14%) | 10 (3%) | - | - | 55 (17%) | | - | 28 (9%) |
| Contusion | 37 (12%) | 5 (2%) | - | - | 42 (13%) | | - | 29 (9%) |
| AEs of special interest[b,c] | | | | | | | | |
| Bruising | 48 (15%) | 5 (2%) | - | - | 53 (16%) | | - | 37 (12%) |
| Rash | 30 (9%) | 5 (2%) | - | - | 35 (11%) | | - | 18 (6%) |
| Arthralgia | 13 (4%) | 3 (1%) | - | - | 16 (5%) | | - | 5 (2%) |
| Hemorrhage | 10 (3%) | 4 (1%) | 1 (<1%)[d] | - | 15 (5%) | | - | 5 (2%) |
| Hypertension | 2 (<1%) | 9 (3%) | 4 (1%) | - | 15 (5%) | | - | 4 (1%) |
| Atrial fibrillation/flutter | - | 2 (<1%)[e] | - | - | 2 (<1%) | | - | - |

**No DLTs reported and MTD not reached**
**5 of 323 patients (1.5%) discontinued due to treatment-related AEs**
**200mg QD selected as recommended Phase 2 dose**

Data cutoff date of 27 September 2020. Total % may be different than the sum of the individual components due to rounding. [a]The AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular. [d]Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. [e]Both events considered by investigators as unrelated to LOXO-305 due to a history of prior atrial fibrillation in each.

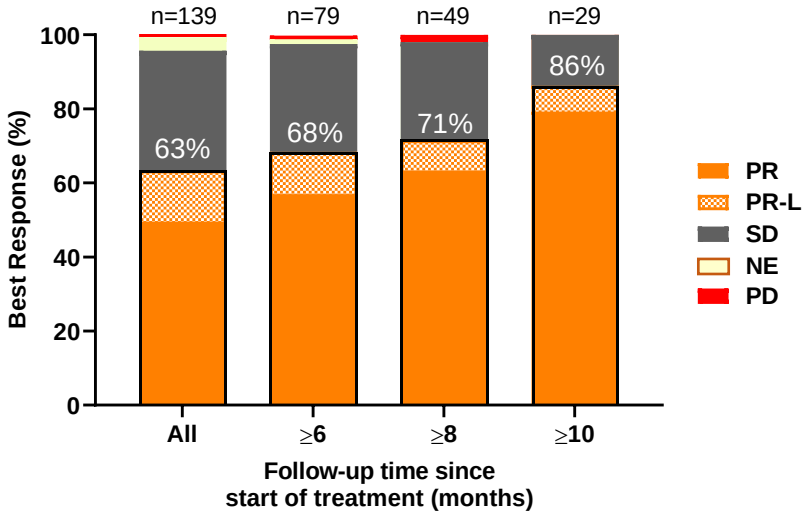
Mato et al, ASH 2020

# Efficacy of Pralsetinib (LOXO-305) in CLL/SLL

## Overall Response Rate in all CLL/SLL patients and BTK pre-treated subgroup

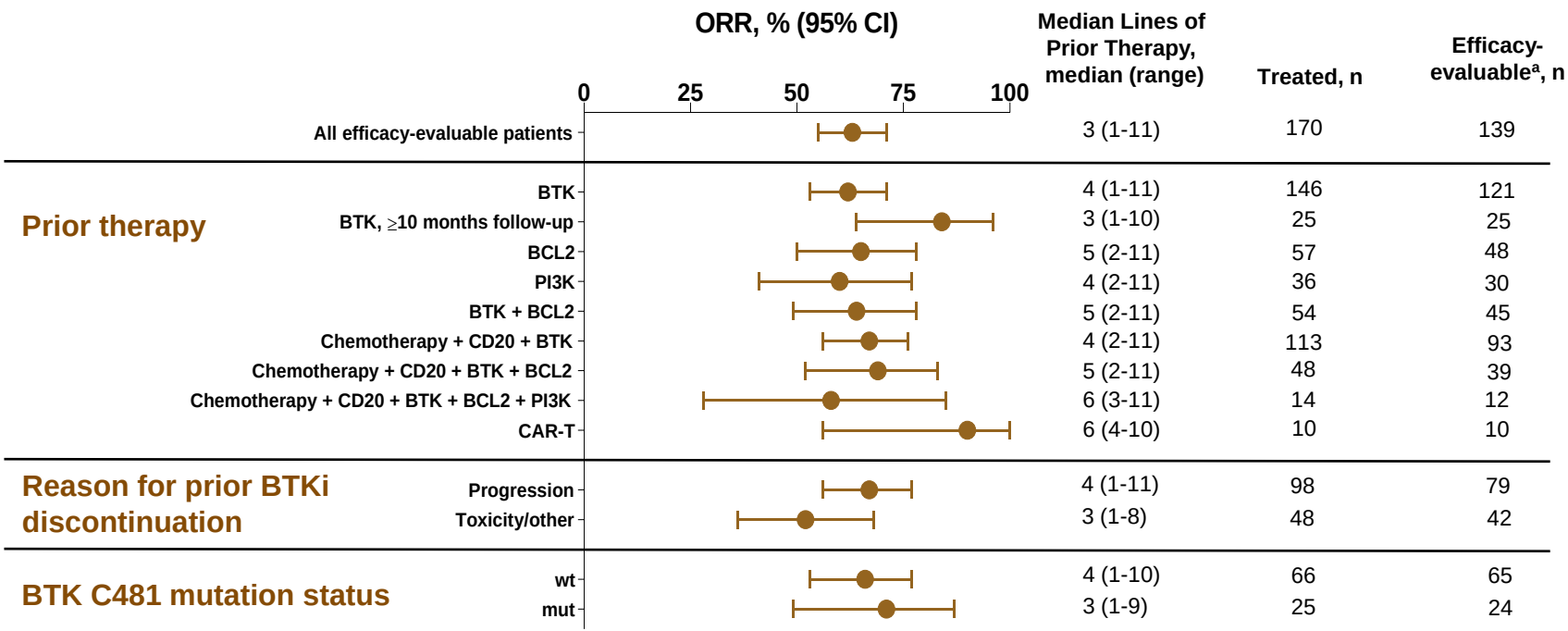
| All CLL/SLL Patients[a] | n=139 |
|---|---|
| Overall Response Rate[b], % (95% CI) | 63% (55 – 71%) |
| Best response | |
| CR, n (%) | 0 |
| PR, n (%) | 69 (50%) |
| PR-L, n (%) | 19 (14%) |
| SD, n (%) | 45 (32%) |
| **BTK Pre-Treated CLL/SLL Patients[a]** | **n=121** |
| Overall Response Rate[b], % (95% CI) | 62% (53 – 71%) |
| Best Response | |
| CR, n (%) | 0 |
| PR, n (%) | 57 (47%) |
| PR-L, n (%) | 18 (15%) |
| SD, n (%) | 41 (34%) |

## Overall Response Rate Increases Over Time[c]




Data cutoff date of 27 September 2020. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL. [c]Includes the efficacy-evaluable CLL/SLL patients at the time of data cutoff. Data at each timepoint includes the efficacy-evaluable CLL/SLL patients who had the opportunity to be followed for at least the indicated amount of time.

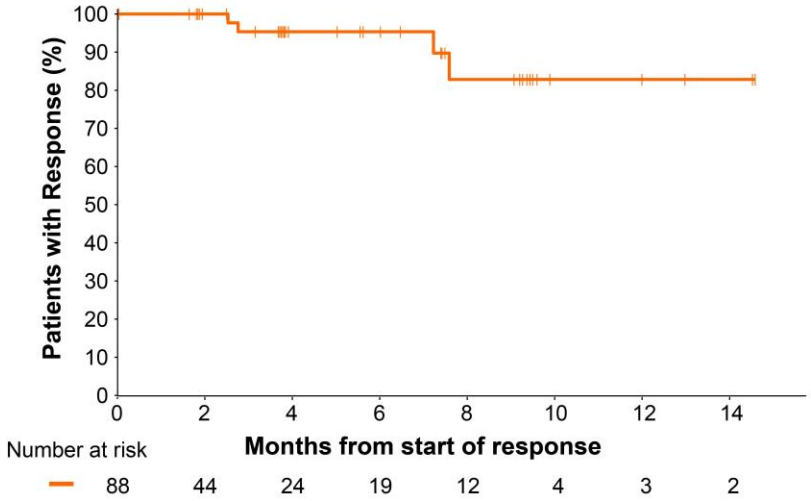
# Pralsetinib (LOXO-305) Efficacy By BTK Experience and Other Prior Therapy



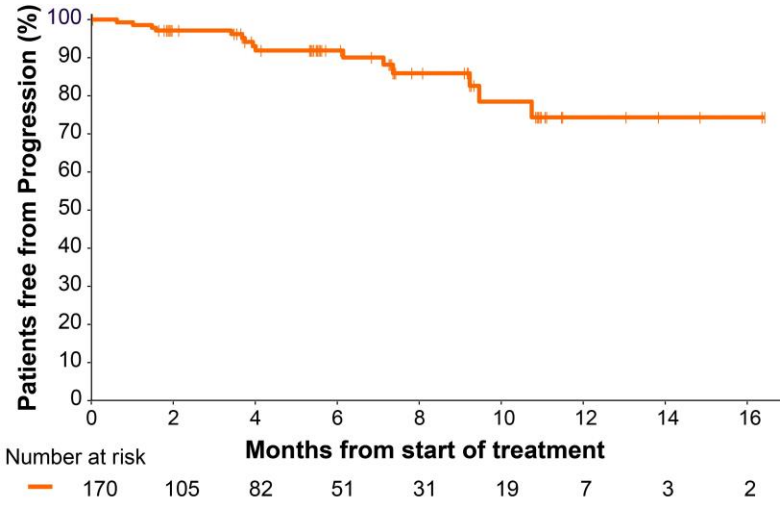

Data cutoff date of 27 September 2020. [a]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment.

# LOXO-305: Duration of Response and Progression-Free Survival in CLL/SLL

## Duration of Response

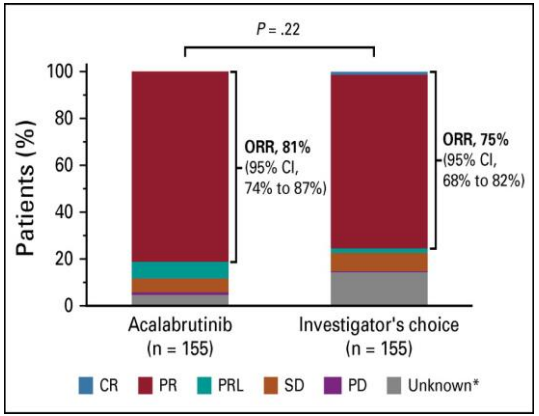


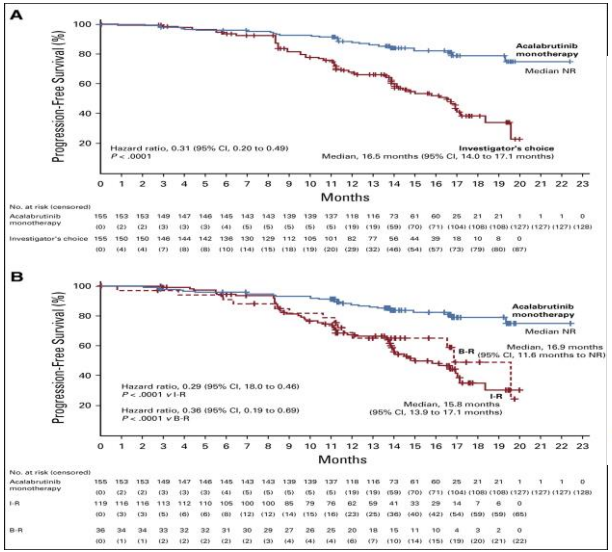

## Progression-Free Survival

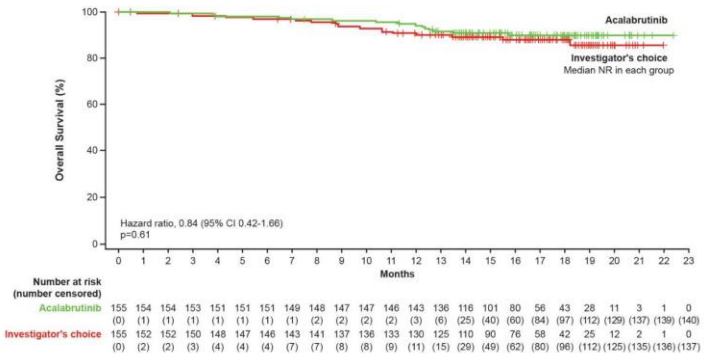



Data cutoff date of 27 September 2020.

# ASCEND Trial in R/R CLL




Ghia et al, JCO 38:2849, 2020

# ELEVATE R/R: Acalabrutinib vs Ibrutinib

- Randomized, non-inferiority trial of 533 pts
- High risk – 17p-, 11q-
- Met non-inferiority for PFS (med 38.4 mo both arms)
- OS comparable
- D/C for AEs – A - 14.7% vs I – 21.3%

Byrd et al, ASCO 2021, abstr #7500

Selected events of clinical interest.

| Events, n (%) | Acalabrutinib (n = 266) | | Ibrutinib (n = 263) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Cardiac events | 64 (24.1) | 23 (8.6) | 79 (30.0) | 25 (9.5) |
| Atrial fibrillation[a] | 25 (9.4) | 13 (4.9) | 42 (16.0) | 10 (3.8) |
| Ventricular tachyarrhythmias | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Hypertension[b] | 25 (9.4) | 11 (4.1) | 61 (23.2) | 24 (9.1) |
| Bleeding events | 101 (38.0) | 10 (3.8) | 135 (51.3) | 12 (4.6) |
| Major bleeding events[c] | 12 (4.5) | 10 (3.8) | 14 (5.3) | 12 (4.6) |
| Infections | 208 (78.2) | 82 (30.8) | 214 (81.4) | 79 (30.0) |
| Second primary malignancies excluding non-melanoma skin cancers | 24 (9.0) | 16 (6.0) | 20 (7.6) | 14 (5.3) |

Byrd, ASCO 2021

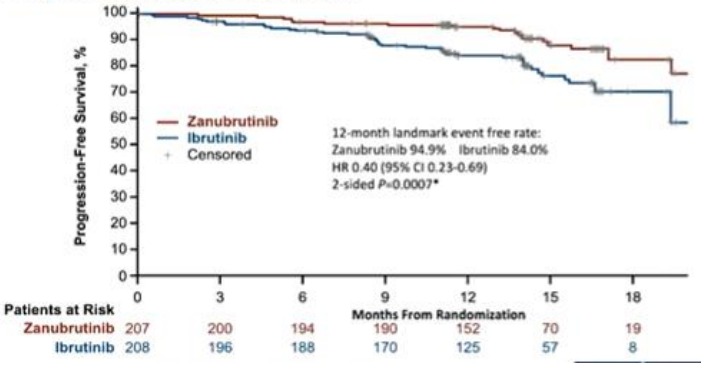
# ALPINE: Zanubrutinib vs Ibrutinib in R/R CLL

## ORR by Investigator Assessment

| | Zanubrutinib (n=207), n (%) | Ibrutinib (n=208), n (%) |
|---|---|---|
| **Primary endpoint: ORR (PR+CR)** | 162 (**78.3**)<br>95% CI: 72.0, 83.7<br>Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099 | 130 (**62.5**)<br>95% CI: 55.5, 69.1 |
| CR/CRi | 4 (1.9) | 3 (1.4) |
| nPR | 1 (0.5) | 0 |
| PR | 157 (75.8) | 127 (61.1) |
| *ORR (PR-L+PR+CR)* | *183 (88.4)* | *169 (81.3)* |
| PR-L | 21 (10.1) | 39 (18.8) |
| SD | 17 (8.2) | 28 (13.5) |
| PD | 1 (0.5) | 2 (1.0) |
| Discontinued or new therapy prior to 1st assessment | 6 (2.9) | 9 (4.3) |

| | del(17p) (n=24), n (%) | del(17p) (n=26), n (%) |
|---|---|---|
| ORR (PR+CR) | 20 (83.3) | 14 (53.8) |

## PFS by Investigator Assessment




Hillmen et al, EHA, 2021

# Additional AEs of Special Interest

| Safety Analysis Population | Zanubrutinib (n=204), n (%) | | Ibrutinib (n=207), n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Cardiac disorders[a] | 28 (13.7) | 5 (2.5) | 52 (25.1) | 14 (6.8) |
| **Atrial fibrillation and flutter (key 2º endpoint)** | **5 (2.5)** | **2 (1.0)** | **21 (10.1)** | **4 (1.9)** |
| Hemorrhage | 73 (35.8) | 6 (2.9) | 75 (36.2) | 6 (2.9) |
| Major hemorrhage[b] | 6 (2.9) | 6 (2.9) | 8 (3.9) | 6 (2.9) |
| Hypertension | 34 (16.7) | 22 (10.8) | 34 (16.4) | 22 (10.6) |
| Infections | 122 (59.8) | 26 (12.7) | 131 (63.3) | 37 (17.9) |
| Neutropenia[c] | 58 (28.4) | 38 (18.6) | 45 (21.7) | 31 (15.0) |
| Thrombocytopenia[c] | 19 (9.3) | 7 (3.4) | 26 (12.6) | 7 (3.4) |
| Secondary primary malignancies | 17 (8.3) | 10 (4.9) | 13 (6.3) | 4 (1.9) |
| Skin cancers | 7 (3.4) | 3 (1.5) | 10 (4.8) | 2 (1.0) |

AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

# UNITY-CLL Study Design (UTX-TGR-304)

*Presentation will focus on primary analysis:U2 vs O+Chl (n=421)*

**Patients (N=421)**
- Treatment-naïve or relapsed/refractory CLL
- Requiring treatment per iwCLL criteria
- Adequate organ function
- ECOG PS ≤2

**Stratification**
- del(17p): present vs absent
- Treatment status: treatment-naive vs previously treated

RANDOMIZE 1:1

**Umbralisib[a] + Ublituximab[b] (U2)**
[a]800 mg PO QD
[b]900 mg IV on D1/2, 8, 15 of Cycle 1, D1 of Cycles 2 – 6, D1 Q3 cycles

**Obinutuzumab[c] + Chlorambucil[d] (O+Chl)**
[c]1000 mg IV on D1/2, 8, 15 of Cycle 1, D1 of cycles 2 – 6
[d]0.5 mg/kg PO on D1 and D15 Cycles 1 – 6

**Primary endpoint**
- IRC-assessed PFS U2 vs O+Chl

**Secondary endpoints**
- IRC-assessed:
  - ORR, CR, DOR
- uMRD (central)
- Safety

- Interim analyses for PFS were performed at:
  - 50% IRC-assessed PFS events to assess futility only
  - 75% IRC-assessed PFS events to evaluate superiority of U2 vs O+Chl



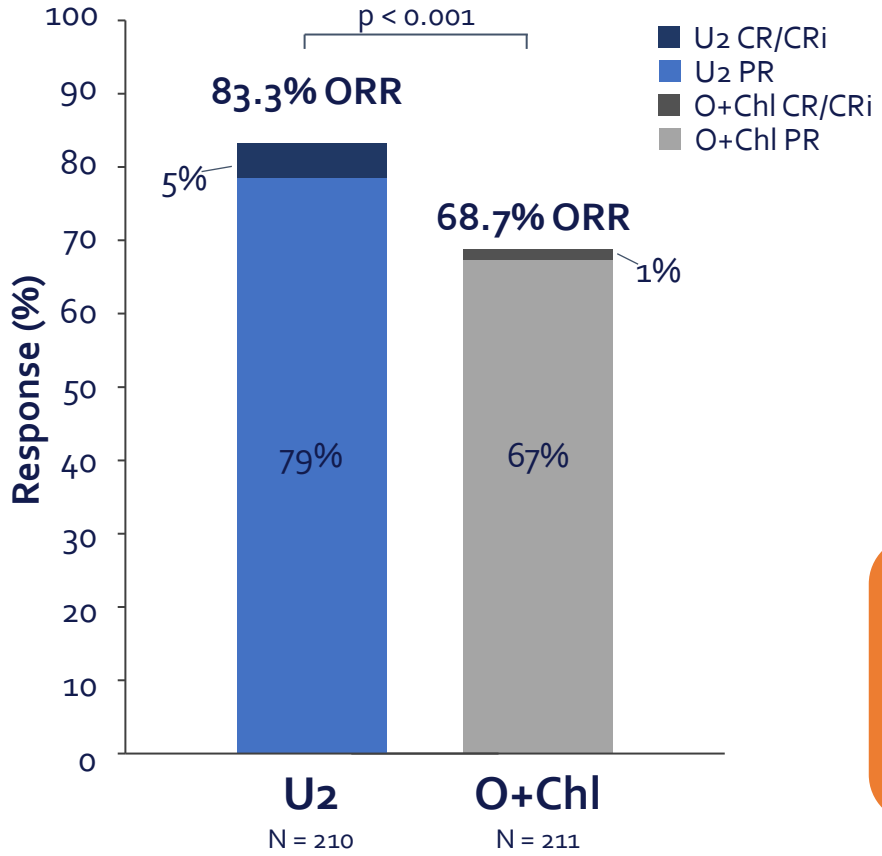
Gribben et al, ASH 2020

# Prior Therapies
# Previously Treated Population

| | U2 N=91 | O+Chl N=90 |
|---|---|---|
| **Prior Therapies, median (range)** | 2 (1 – 9) | 1 (1 – 8) |
| **Number of Prior Therapies, n (%)** | | |
| 1 | 44 (48) | 50 (56) |
| 2 | 25 (27) | 22 (24) |
| 3 | 10 (11) | 7 (8) |
| ≥4 | 12 (13) | 10 (11) |
| **Prior Therapy Type, n (%)** | | |
| Anti-CD20 Antibody | 83 (91) | 73 (81) |
| Chemoimmunotherapy | 81 (89) | 77 (86) |
| BTK Inhibitor | 14 (15) | 12 (13) |
| Venetoclax | 1 (1) | 0 |
| PI3K Inhibitor[a] | 1 (1) | 0 |

BTK: Bruton's tyrosine kinase; O+Chl: obinutuzumab + chlorambucil; PI3K: phosphatidylinositol-3-kinase-delta; U2: umbralisib + ublituximab. Trial excluded prior PI3K exposure; however, 1 patient with prior PI3K did enroll and was treated with U2.

# IRC-Assessed Response Rates

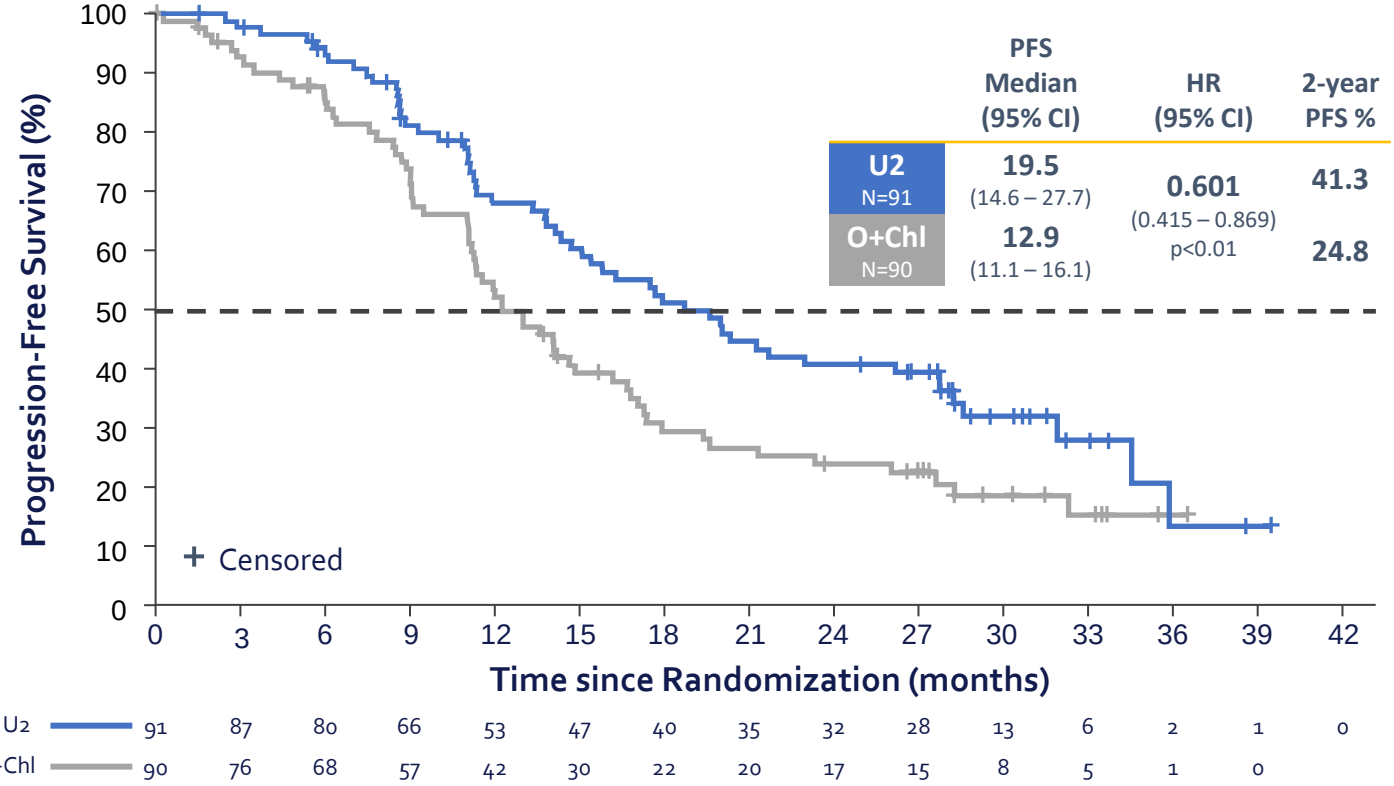



| ORR (%) | U2 | O+Chl |
|---|---|---|
| Treatment Naïve | 84% | 78% |
| Previously treated | 82% | 57% |
| Prior BTK inhibitor | 57% | 25% |

- U2 produced higher IRC – assessed response rates across subgroups
- U2 responses were durable with **62%** maintaining response at **2 years**
- **93%** disease control rate achieved by U2

CR: complete response; CRi: complete response with incomplete marrow recovery; Disease control rate = (CR+CRi+nPR+PR+PR-L+SD); IRC: independent review committee; ITT: intent to treat; nPR: nodular partial response; O+Chl: obinutuzumab + chlorambucil; ORR: overall response rate; PR: partial response; PR-L: partial response with lymphocytosis; SD: stable disease; U2: umbralisib + ublituximab

# IRC-Assessed Progression-Free Survival Previously Treated Population



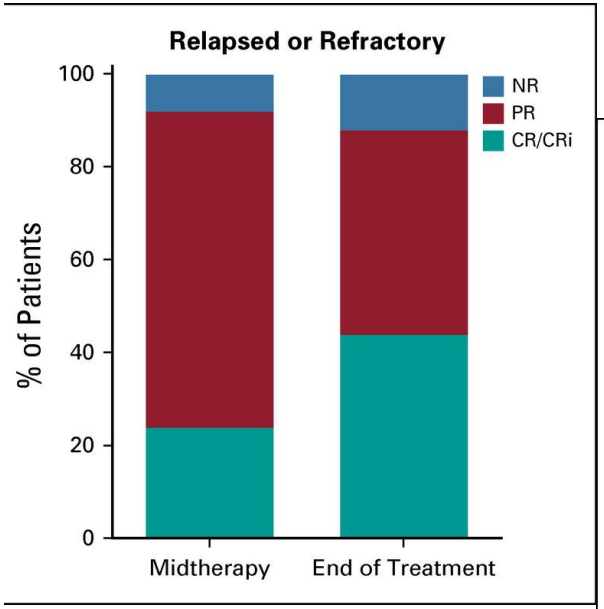

CI: confidence interval; HR: hazard ratio; IRC: independent review committee; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

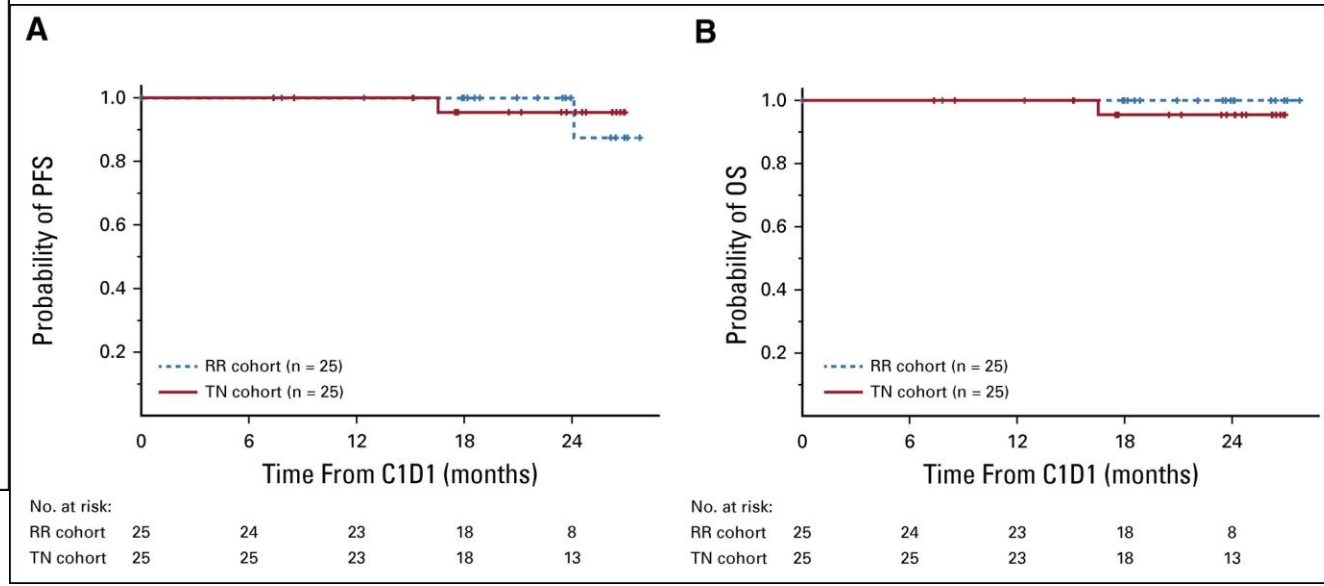
# Events of Clinical Interest – PI3K specific

| AEs, n (%) | U2 N=206 | | O+Chl N=200 | |
|---|---|---|---|---|
| | Any | Grade ≥3 | Any | Grade ≥3 |
| ALT elevation | 35 (17.0) | 17 (8.3) | 9 (4.5) | 2 (1.0) |
| AST elevation | 28 (13.6) | 11 (5.3) | 9 (4.5) | 4 (2.0) |
| Colitis (non-infectious)[a] | 10 (4.9) | 4 (1.9) | 0 | 0 |
| Colitis (infectious)[a] | 1 (0.5) | 1 (0.5) | 1 (0.5) | 1 (0.5) |
| Pneumonitis | 6 (2.9) | 1 (0.5) | 1 (0.5) | 0 |
| Rash[a] | 26 (12.6) | 5 (2.4) | 10 (5.0) | 1 (0.5) |
| Opportunistic Infections[a] | 29 (14.1) | 12 (5.8) | 11 (5.5) | 3 (1.5) |

[a]Group includes multiple MedDRA terms. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab.

# Phase 2 Study of Combination Obinutuzumab, Ibrutinib, and Venetoclax in Relapsed/Refractory CLL

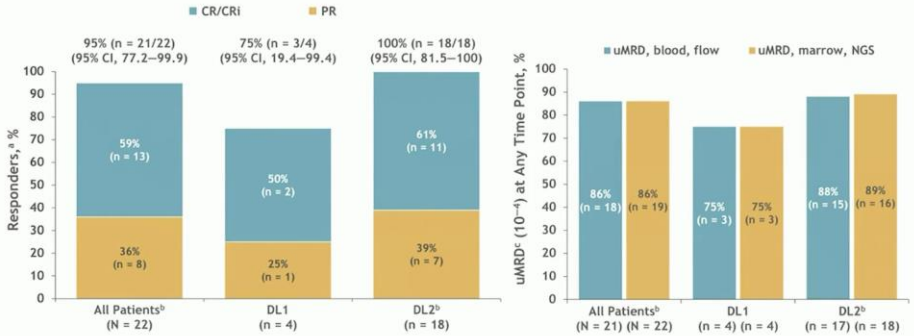



K.A. Rogers; et al *Journal of Clinical Oncology* 2020 383626-3637.

# TRANSEND: Liso-cell+Ibr in R/R CLL

## Best Objective Response by iwCLL and uMRD ($<10^{-4}$)





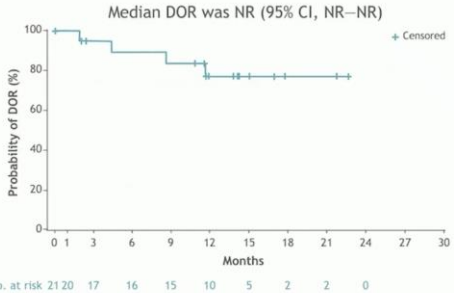


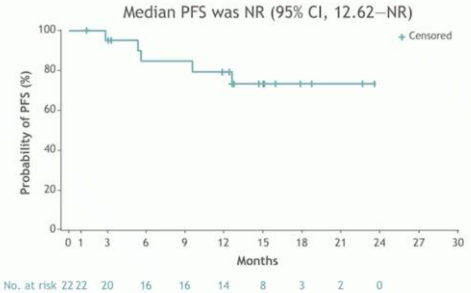
- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

[a]Evaluated according to iwCLL 2018 criteria; [b]At the time of this data cut, 1 patient had only 11 days of follow-up after liso-cel infusion and was not yet evaluable for response;
[c]Assessed in blood by flow cytometry and/or in bone marrow by NGS.
CRi, CR with incomplete blood count recovery; NGS, next-generation sequencing.

## Progression-Free Survival and Duration of Response

- The median follow-up for all patients was 17 months



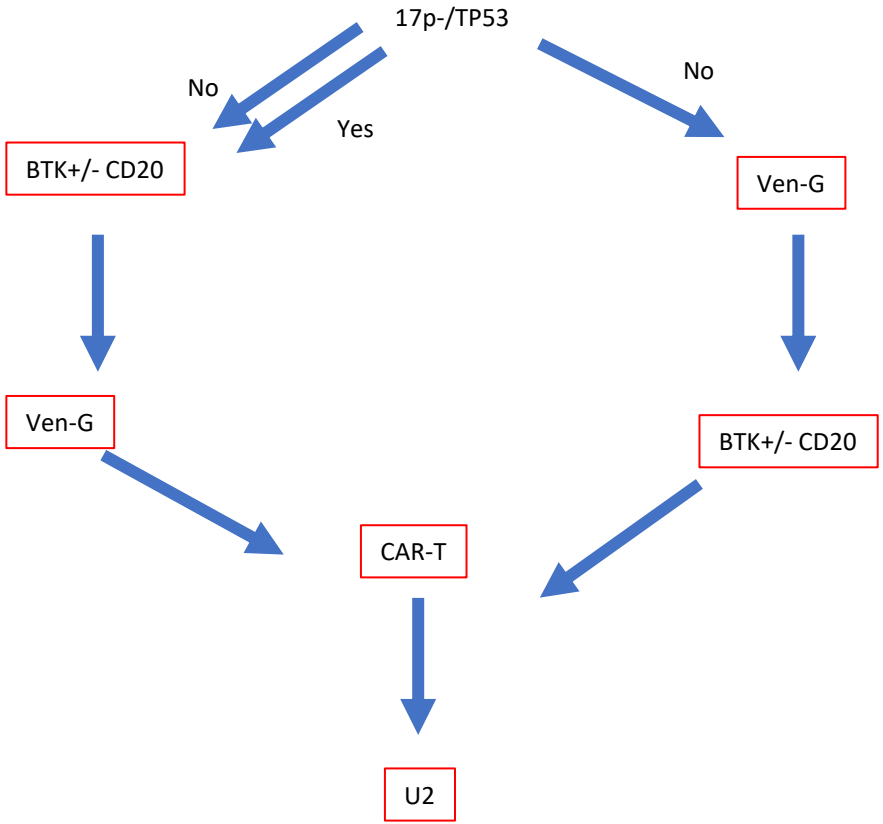




DOR, duration of response; NR, not reached; PFS, progression-free survival.

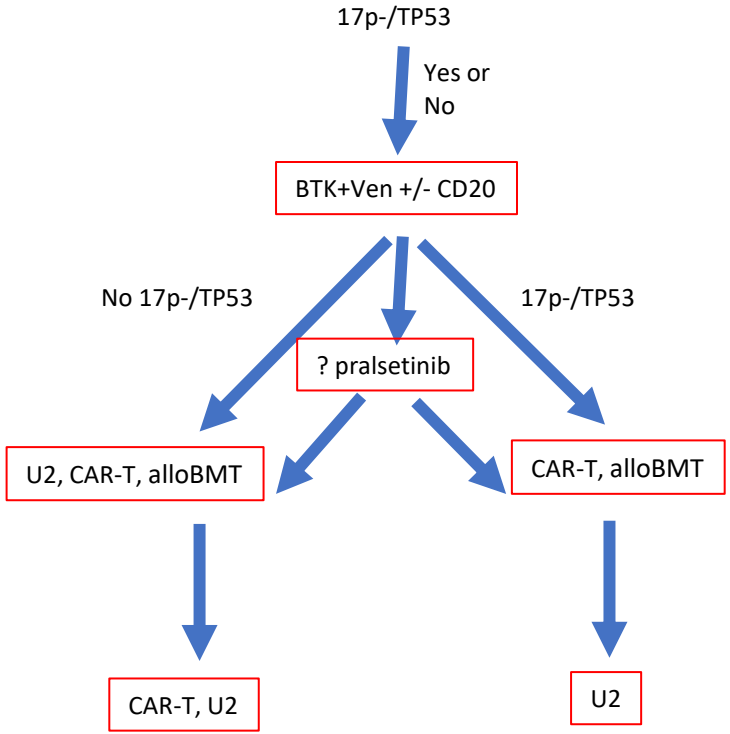


Wierda et al. Proc ICML, 2021

# CLL Treatment Algorithm



# CLL: Possible Future Treatment Algorithm



# Conclusions

- Chronic, incurable disorder that often require multiple lines of therapy
- No longer a role for chemotherapy in R/R CLL
- Numerous active therapies; combinations and sequence in dynamic flux
  - BTKs
  - BCL2i
  - PI3Ks
  - CAR-T
  - AlloBMT
- Proper treatment selection will further prolong survival of CLL patients