# Chronic Lymphocytic Leukemia

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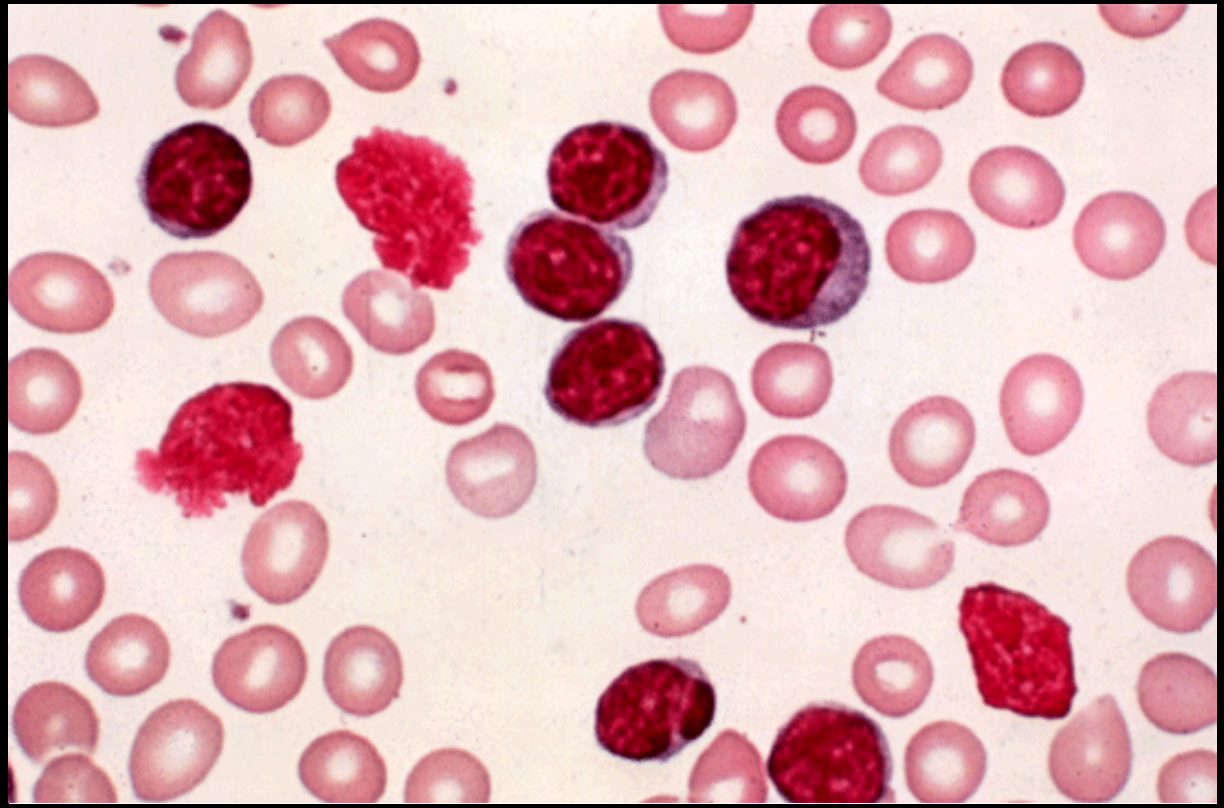
# Chronic Lymphocytic Leukemia



# Chronic Lymphocytic Leukemia

- Most common adult leukemia (~ 15,000 cases/yr)
  - 30% of adult leukemias
- Median age at diagnosis 72 years
- Median overall survival > 9 yrs (unknown with small molecule inhibitors)
- Survival increased over last 2 decades, continues to improving
- Advanced CLL has increased morbidity and mortality related to infections & other cancers

# CLL Diagnosis

- ALC: >5,000 /μL – mature monoclonal B cells
  - PLL = > 55% prolymphocytes or > 15,000 /μL
- Immunophenotype:
  - $CD5^+$ / $CD19^+$ / $CD23^+$ / surface Ig light chain restricted (κ or λ) - monoclonal
- BM Bx: not required for diagnosis
  - > 30% lymphocytes on aspirate
- Additional testing for prognosis:
  - FISH, IGHV mutation status, stimulated karyotype, CD38, ZAP70, serum B2M

# Clinical Course of CLL

- Diagnosis often incidental
- Asymptomatic at diagnosis and for prolonged periods
- Initial symptoms: lymph nodes ↑ , fatigue
- Progression: bone marrow impairment (anemia, thrombocytopenia)
- Increased susceptibility to infection
- Progressive hypogammaglobulinemia
- Long-term complications: autoimmune, Richter's transformation, 2$^{nd}$ cancers, infections

# Autoimmune Complications of CLL

- Autoimmune hemolytic anemia
  - Coombs variable
  - Clinical hemolysis
- Pure red cell aplasia
- Immune-mediated thrombocytopenia
- Granulocytopenia
- Other autoimmune diseases uncommon

# Rai System: Clinical Staging of CLL

| Stage | Simplified 3-Stage System | Clinical Features | Median Survival (y) |
|---|---|---|---|
| 0 | Low risk | Lymphocytosis in blood and marrow only | >10 |
| I | Intermediate risk | Lymphadenopathy | 7 |
| II | | Splenomegaly ± hepatomegaly | |
| III | High risk | Anemia (HGB 11g/dl) | 1.5 - 4 |
| IV | | Thrombopenia (PLT 100K) | |

*Rai et al. Blood. 1975;46:219*

# IWCLL-NCI: Indications to Initiate Treatment for CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months
- **NO EARLY TREATMENT, EVEN FOR HIGH-RISK**

Hallek et al Blood 2008;111:5446-5456

# Evolution of First-line Treatments for CLL

**1960s 1970s**

**Alkylating agents**
- Chlorambucil
- Cyclophosphamide

**1980s**

**Purine nucleosides**
- Fludarabine
- Pentostatin
- Cladribine

**1990s**

**Combination chemotherapy**
- FC
- PC

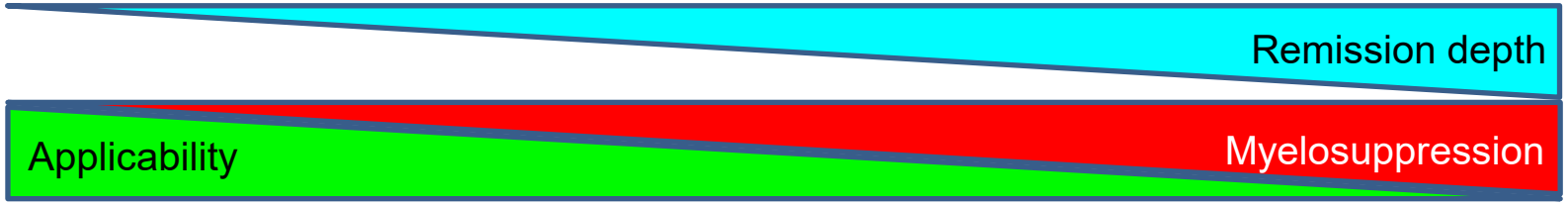
**2000s**

**Monoclonal antibodies**
- CD20 mAbs
- Alemtuzumab

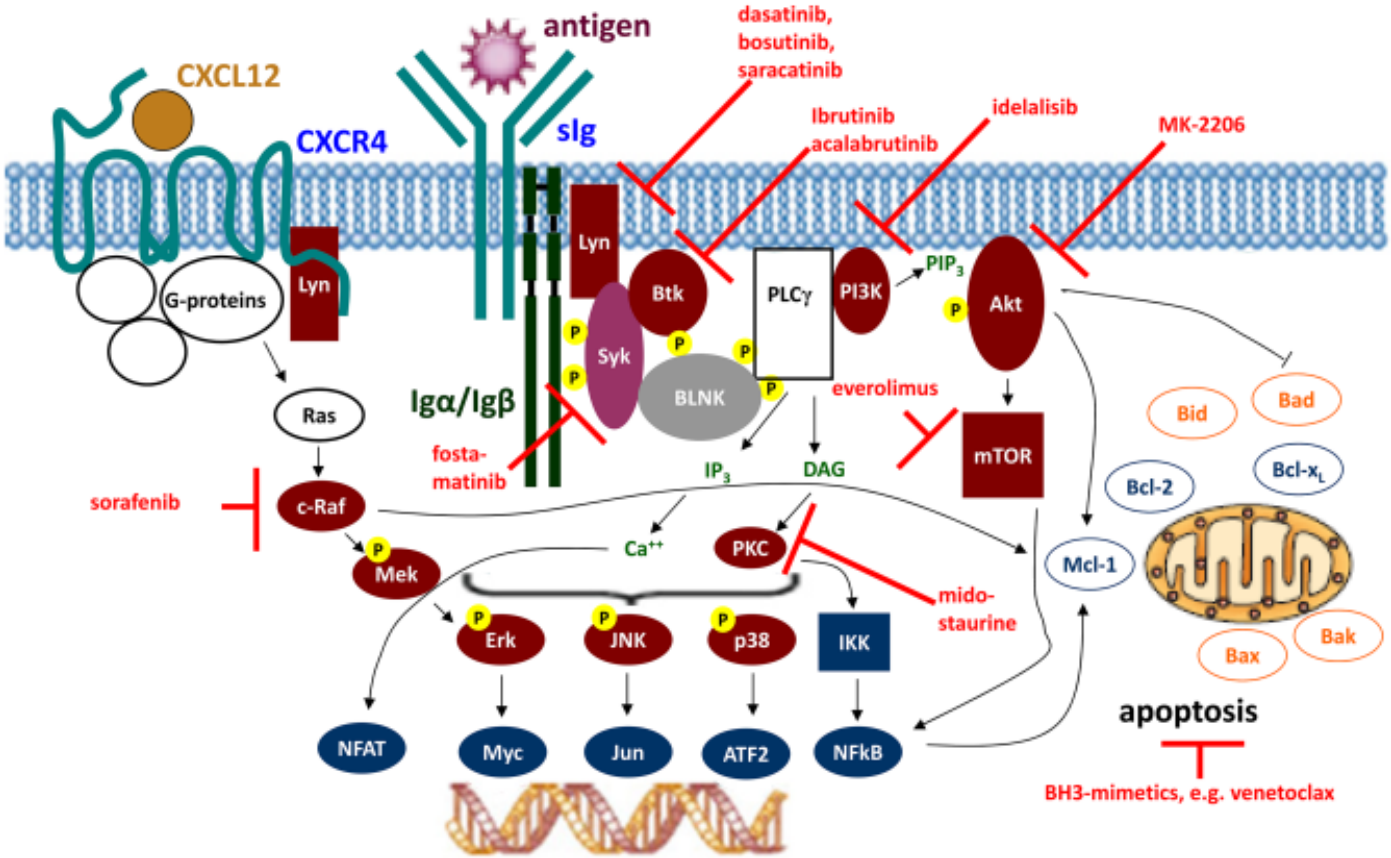
**Chemoimmunotherapy**
- FCR, PCR
- BR

**2010s**

**Targeted therapy - small molecule inhibitors**
- BCR pathway
- BCL-2



# Survival signaling in CLL: targets of novel agents




Hallek, M., Am J Hem. 92:946, 2017

# Therapeutic Agents for CLL

| Chemotherapy | CD20 Antibody | BTKi | PI3Ki | BCL-2i | Others |
|---|---|---|---|---|---|
| Chlorambucil | Rituximab | Ibrutinib | Idelalisib | Venetoclax | Lenalidomide |
| Fludarabine | Obinutuzumab | Acalabrutinib | Duvelisib | | CAR-T cells |
| Cyclophosphamide | ~~Ofatumumab~~ | Zanubrutinib | ~~Umbralisib~~ | | |
| Bendamustine | | Pirtobrutinib | | | |
| | | Nemtabrutinib | | | |
| | | Tirabrutinib | | | |
| | | CG-806 (Aptose) | | | |
| | | ~~Vecabrutinib~~ | | | |

FDA-approved for 1L treatment of CLL in US; FDA-approved for >1L treatment of CLL in US;
Not FDA-approved in US

# Generalizations about Treatments for CLL

- Treatment for indication, no early treatment - first-line & relapse CLL
- Most patients are >70 yrs, have comorbidities and more toxicities
- Del(17p)/*TP53*-M; complex = high-risk, even with continuous treatment
- Shorter PFS with finite-duration treatment for: IGHV-UM; del(17p); del(11q)
- Deeper response = longer remission with finite-duration therapy for both treatment-naïve and relapsed/refractory
- Relapsed disease is not necessarily refractory to finite-duration targeted treatment – retreatment is option, remission duration important
- Progression while on targeted therapy is resistance

# Important for Selecting Treatment in CLL

- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]
- IGHV mutation status (for first line): **does not change**[1]
- Age and comorbidities are considerations
- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

# BTKi- *vs.* BCL-2i-based Treatment

## BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

## BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

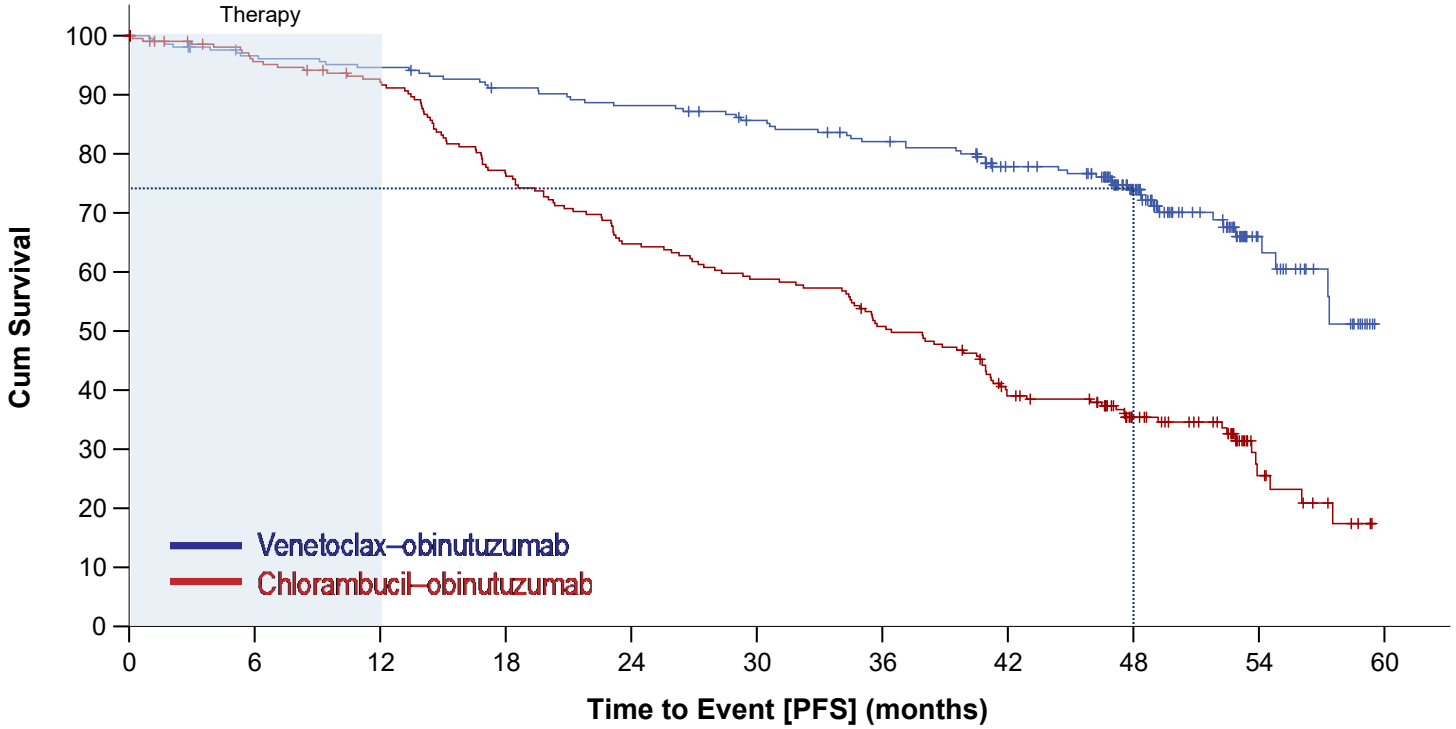
1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

# First-line Phase III Randomized Trials

- **CLL14** (CIRS >6; CrCl <70 mL/min)
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **GLOW** (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Venetoclax** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **CLL13 / GAIA** [CIRS ≤ 6; non-del(17p)]
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Venetoclax + Ibruitnib + Obinutuzumab** *vs.*
  - **Venetoclax + Rituximab** *vs.*
  - **FCR / BR**
- **RESONATE-2**
  - **Ibrutinib** *vs.*
  - **Chlorambucil**
- **iLLUMINATE** (PCYC-1130) (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **ECOG E1912** [<70yo; non-del(17p)]
  - **Ibrutinib + Rituximab** *vs.*
  - **FCR**
- **Alliance** (A041202) (>65yo)
  - **Ibrutinib** *vs.*
  - **Ibrutinib + Rituximab** *vs.*
  - **BR**
- **ELEVATE-TN** (>65yo or younger with CIRS score >6, or CrCl <70 mL/min)
  - **Acalabrutinib** *vs.*
  - **Acalabrutinib + Obinutuzumab**
  - **Chlorambucil + Obinutuzumab**
- **SEQUOIA** [≥65 yo OR unsuitable for FCR; non-del(17p)]
  - **Zanubrutinib** *vs.*
  - **BR**

# Progression-free Survival

Median observation time 52.4 months




**Median PFS**

Ven-Obi: not reached

Clb-Obi: 36.4 months

**4-year PFS rate**

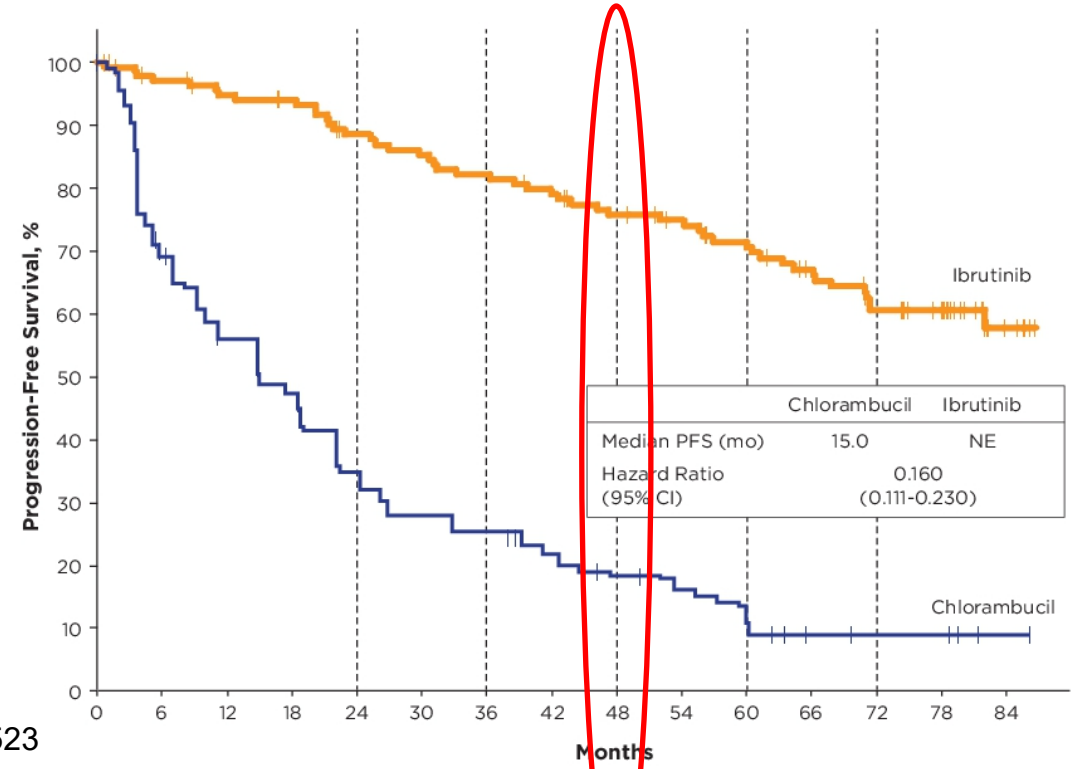
Ven-Obi: 74.0%

Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Al-Sawaf et al. EHA 2021, Abstract S146

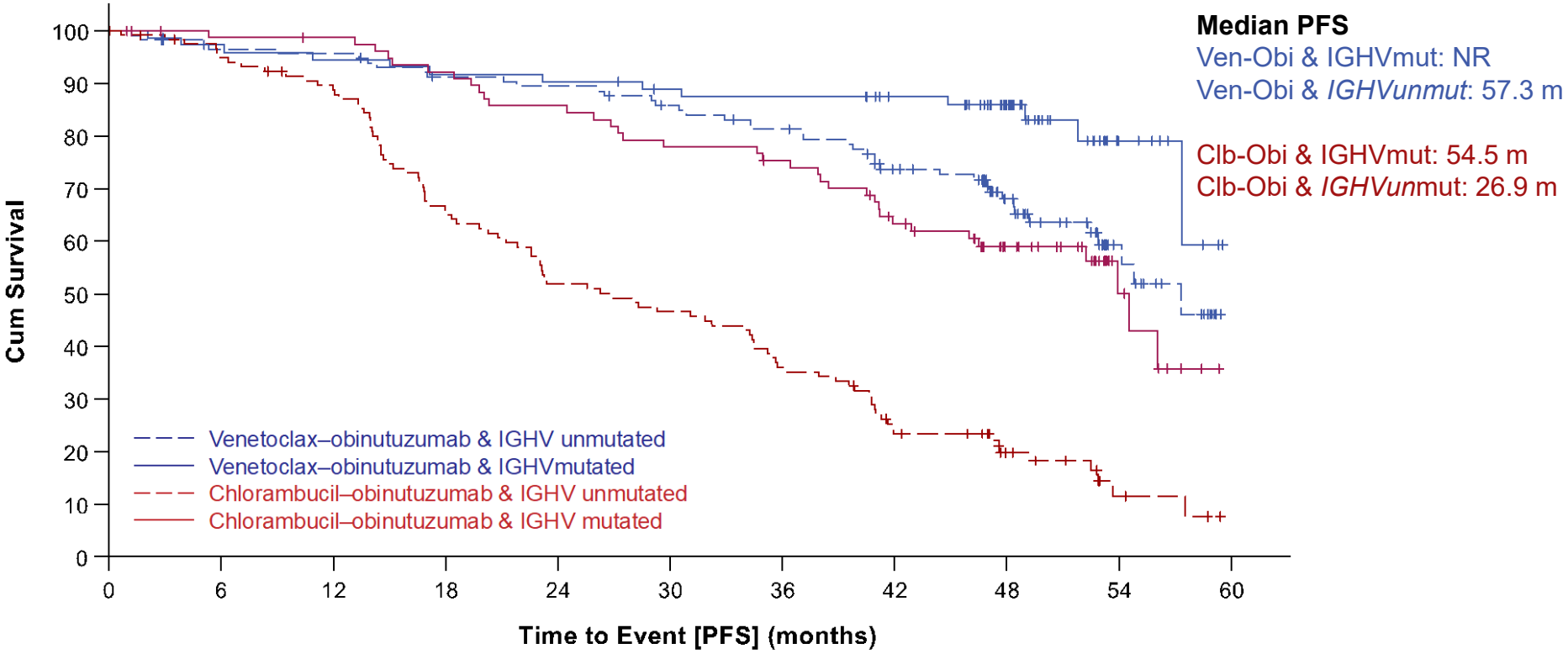
# RESONATE-2: First-line, Age >65yrs
# Ibrutinib Prolonged PFS Over Chlorambucil




Barr et al. ASCO 2021, Poster 7523

# Progression-free Survival – IGHV Status

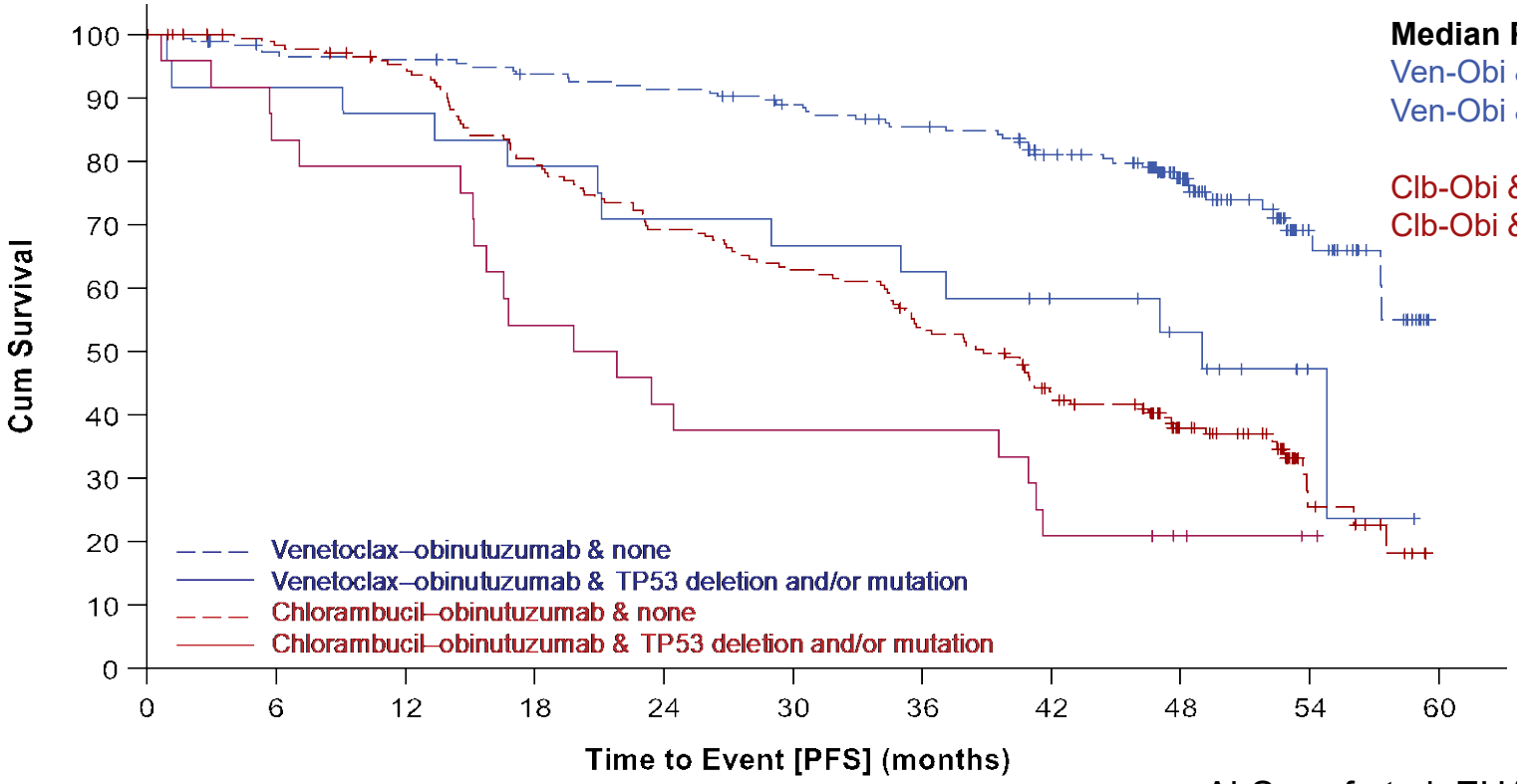
Median observation time 52.4 months




Al-Sawaf et al. EHA 2021, Abstract S146

# Progression-free Survival – *TP53* Status

Median observation time 52.4 months




**Median PFS**

Ven-Obi & no *TP53*del/mut: NR

Ven-Obi & *TP53*del/mut: 49.0 m

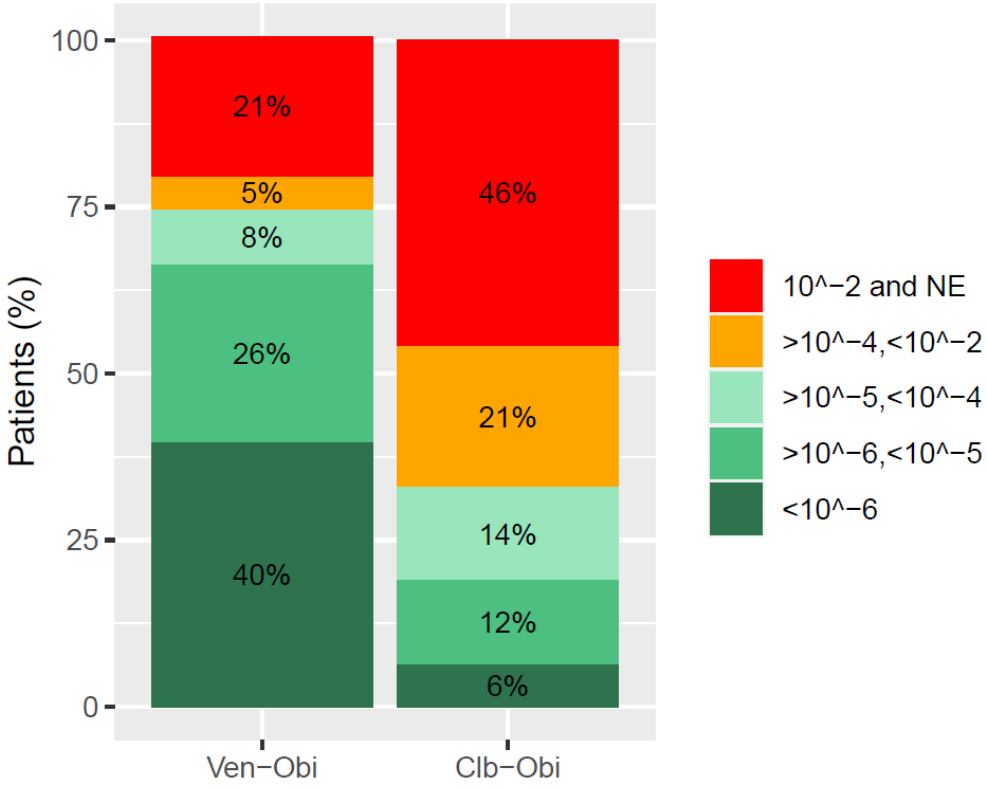
Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

Al-Sawaf et al. EHA 2021, Abstract S146

# CLL14 MRD Results

## MRD by NGS at EoT




### uMRD rate at EoT

- **Ven-Obin: 74%**
- **Clb-Obin: 32%**

**What happens *after* treatment completion?**

Fischer et al, N Engl J Med, 2019
Al-Sawaf et al, Lancet Oncol, 2020

# CLL14: Most Common ≥ Grade 3 Adverse Events

| | Venetoclax-obinutuzumab (N=212) | | Chlorambucil-obinutuzumab (N=214) | |
|---|---|---|---|---|
| | During Treatment | After Treatment | During Treatment | After Treatment |
| Neutropenia | 51.9% | 4.0% | 47.2% | 1.9% |
| Thrombocytopenia | 13.7% | 0.5% | 15.0% | 0.0% |
| Anemia | 7.5% | 1.5% | 6.1% | 0.5% |
| Febrile neutropenia | 4.2% | 1.0% | 3.3% | 0.5% |
| Leukopenia | 2.4% | 0.0% | 4.7% | 0.0% |
| Pneunomia | 3.3% | 3.0% | 2.8% | 1.4% |
| Infusion-related reaction | 9.0% | 0.0% | 9.8% | 0.5% |
| Tumour lysis syndrome | 1.4% | 0.0% | 3.3% | 0.0% |

# CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

Fit patients with untreated CLL:
CIRS ≤ 6 & normal CrCl

No *TP53* mutation or del(17p) in central screening

**CIT:**
**FCR/BR***
**6 cycles,n=230**

**RVe**
**12 cycles, n=230**

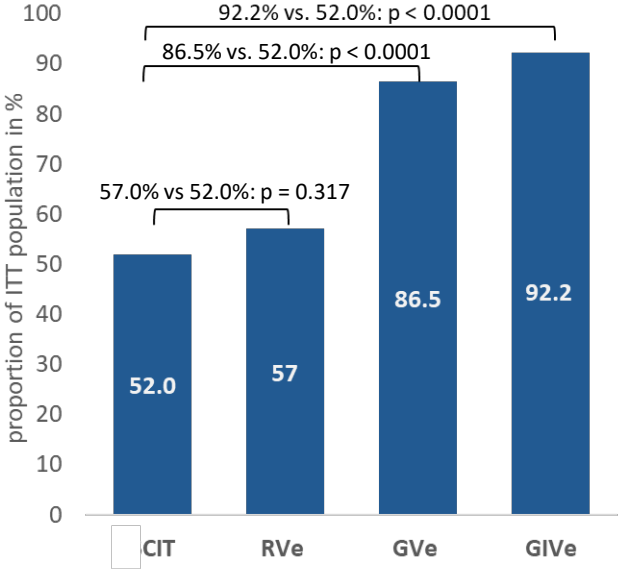
**GVe**
**12 cycles, n=230**

**GIVe**
**15# cycles, n=230**

* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR]
# continuation of ibrutinib up to cycle 36 if MRD detectable

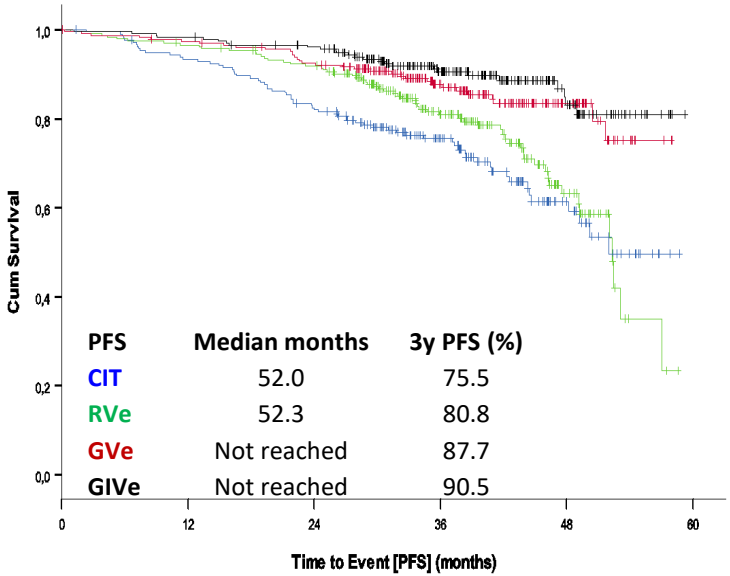
## uMRD (< $10^{-4}$)

at month 15 in PB by 4-colour-flow




## PFS

at median FU of 38.8 months




| PFS | Median months | 3y PFS (%) |
|---|---|---|
| CIT | 52.0 | 75.5 |
| RVe | 52.3 | 80.8 |
| GVe | Not reached | 87.7 |
| GIVe | Not reached | 90.5 |



Eichhorst et al, ASH2021 and EHA2022

# GAIA/CLL13: Multivariate analysis for CIT and RVe/GVe/GIVe

**Full trial analysis for PFS**

| | HR | 95%CI | p |
|---|---|---|---|
| GVe vs. CIT | 0.42 | 0.27-0.65 | <0.001 |
| GIVe vs. CIT | 0.33 | 0.21-0.52 | <0.001 |
| U-IGHV | 2.43 | 1.70-3.47 | <0.001 |
| CKT | 1.98 | 1.42-2.77 | <0.001 |
| Binet B/C vs. A | 1.55 | 1.06-2.27 | 0.03 |
| NOTCH1mut | 1.46 | 1.05-2.05 | 0.03 |

U-IGHV, CKT and *NOTCH1* mutations were independent prognostic factors for CIT and RVe/GVe/GIVe.

RAS/RAF mutations were only prognostic with venetoclax therapy.

**CIT for PFS**

| | HR | 95%CI | p |
|---|---|---|---|
| U-IGHV | 3.08 | 1.55-6.12 | 0.001 |
| >65 years | 2.26 | 1.34-3.83 | 0.002 |
| NOTCH1mut | 2.12 | 1.16-3.88 | 0.01 |
| del(11q) | 1.89 | 1.06-3.36 | 0.03 |
| CKT | 1.87 | 1.06-3.27 | 0.03 |

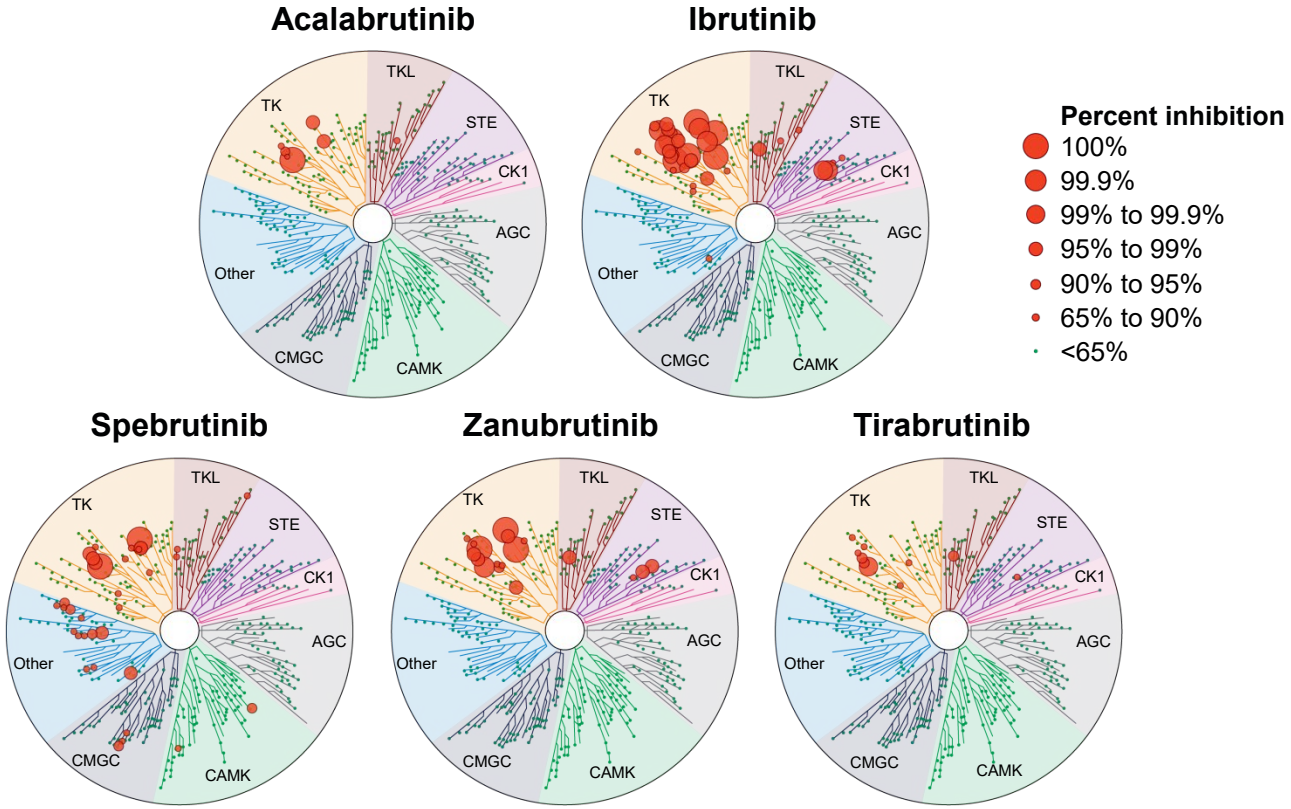
**RVe/GVe/GIVe for PFS**

| | HR | 95%CI | p |
|---|---|---|---|
| U-IGHV | 1.85 | 1.20-2.84 | 0.005 |
| RAS/RAFmut | 1.87 | 1.14-3.06 | 0.01 |
| CKT | 1.66 | 1.07-2.56 | 0.02 |
| b2MG>3.5mg/L | 1.56 | 1.03-2.36 | 0.04 |
| NOTCH1mut | 1.54 | 1.02-2.33 | 0.04 |



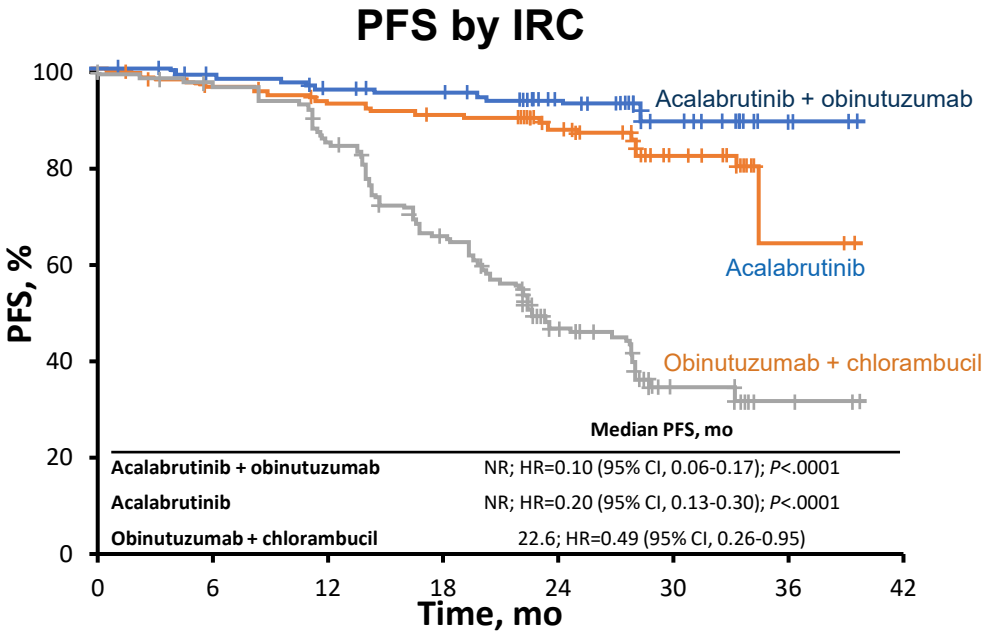
Tausch et al. ASH 2022, Abstract #345

# Differences in Overall Kinase Selectivity Among BTKi[1]




1. Kaptein A et al. 60th American Society of Hematology Annual Meeting & Exposition (ASH 2018). Abstract 1871.

# ELEVATE-TN: PFS (Primary Endpoint)




**Estimated PFS at 24 months**

- 93% with acalabrutinib + obinutuzumab (95% CI, 87%-96%)
- 87% with acalabrutinib monotherapy (95% CI, 81%-92%)
- 47% with obinutuzumab + chlorambucil (95% CI, 39%-55%)

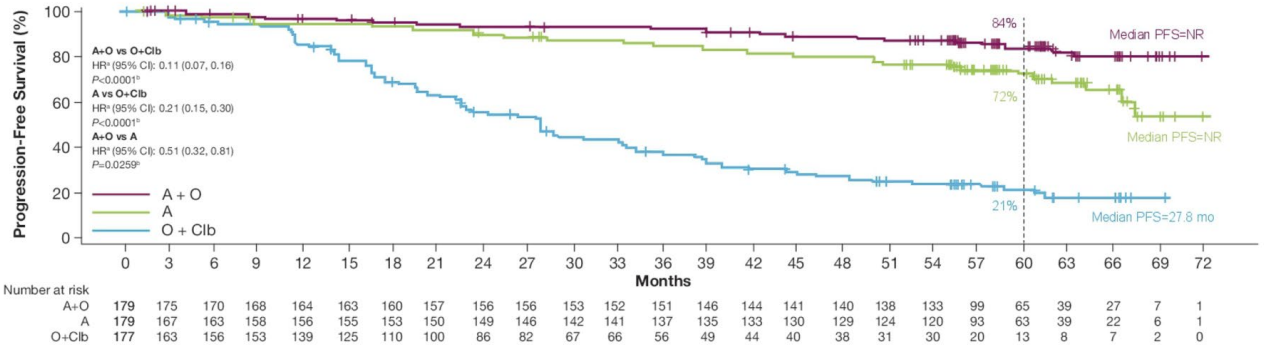
**Post-hoc analysis:** HR for PFS between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI, 0.26-0.95)

**IRC = independent review committee.**

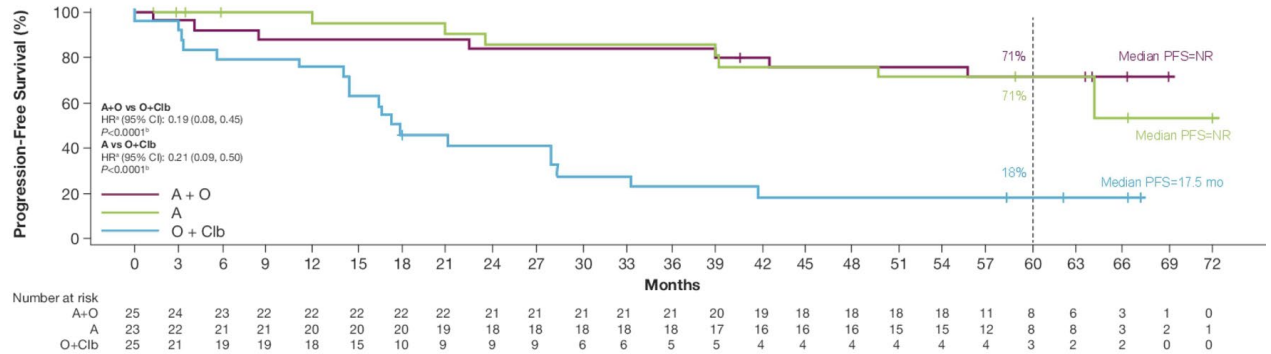
**Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.**

# ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

## INV-Assessed PFS




## INV-Assessed PFS in Patients With del(17p) and/or Mutated *TP53*

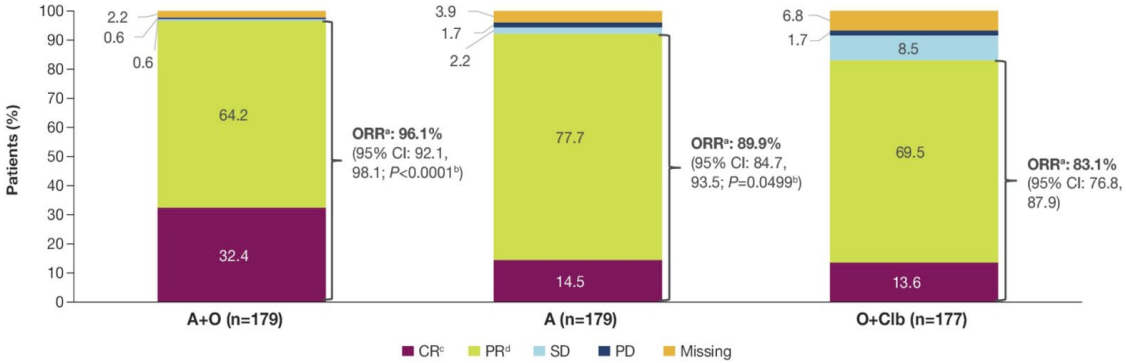



Median follow-up:
58.2 months
(range, 0.0-72.0)

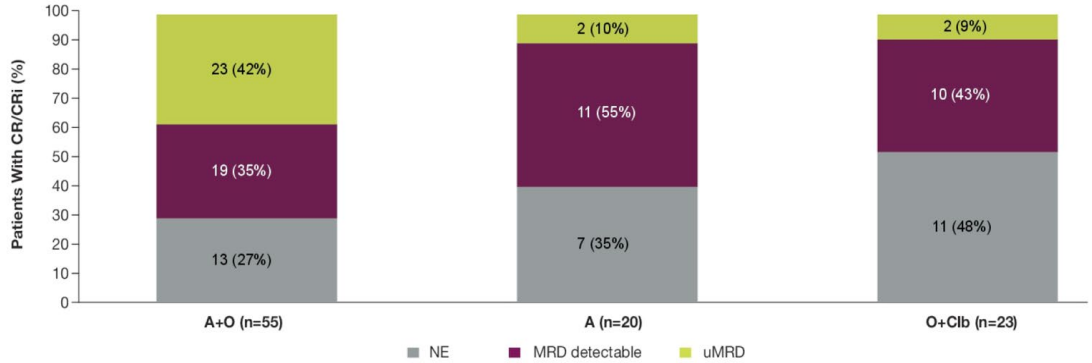
Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

# ELEVATE-TN Phase 3 Study: 5-Year Follow-Up ORR and CR

## INV-Assessed ORR




## MRD Status in Patients With CR/CRi




Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

# ELEVATE-TN Phase 3 Study: 5-Year Follow-Up AEs of Clinical Interest

| AEs of Clinical Interest, n (%) | A+O (n=178) | | A (n=179) | | O+Clb (n=169) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Cardiac events | 43 (24.2) | 17 (9.6) | 39 (21.8) | 18 (10.1) | 13 (7.7) | 3 (1.8) |
| AFib | 11 (6.2) | 2 (1.1) | 13 (7.3) | 2 (1.1) | 1 (0.6) | 0 |
| Bleeding | 88 (49.4) | 8 (4.5) | 78 (43.6) | 6 (3.4) | 20 (11.8) | 0 |
| Major bleeding | 12 (6.7) | 8 (4.5) | 8 (4.5) | 6 (3.4) | 2 (1.2) | 0 |
| Hypertension | 17 (9.6) | 8 (4.5) | 16 (8.9) | 7 (3.9) | 6 (3.6) | 5 (3.0) |
| Infections | 140 (78.7) | 50 (28.1) | 135 (75.4) | 35 (19.6) | 75 (44.4) | 14 (8.3) |
| SPMs | 31 (17.4) | 14 (7.9) | 27 (15.1) | 7 (3.9) | 7 (4.1) | 3 (1.8) |
| Excluding non-melanoma skin | 17 (9.6) | 12 (6.7) | 13 (7.3) | 5 (2.8) | 3 (1.8) | 2 (1.2) |

## Patient Disposition

- Treatment still ongoing: A+O 64.8% and A 59.8%
- Discontinuation rates: A+O 35.2%, A 40.2%, O+Clb 22.6%
  - Due to AEs: 17.3%, 15.6%, 14.1%
  - Due to PD: 5.6%, 10.1%, 1.7%

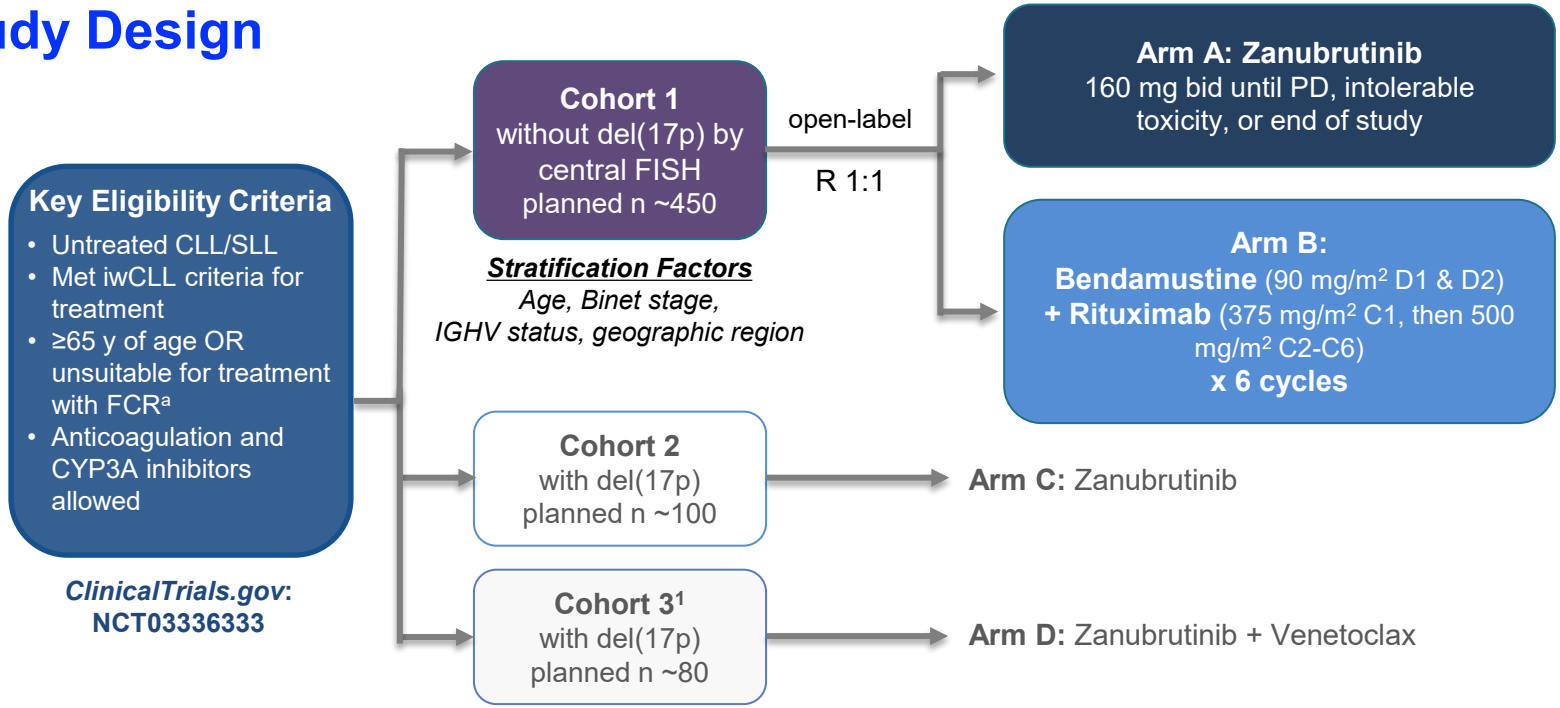
## Safety

- Most common AEs were similar to prior analyses
- AEs that occurred more frequently in A+O and A vs O+Clb included headache, diarrhea, and arthralgia
- AEs that occurred more frequently with O+Clb included neutropenia, nausea, and IRR

Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

# SEQUOIA (BGB-3111-304)

## Study Design

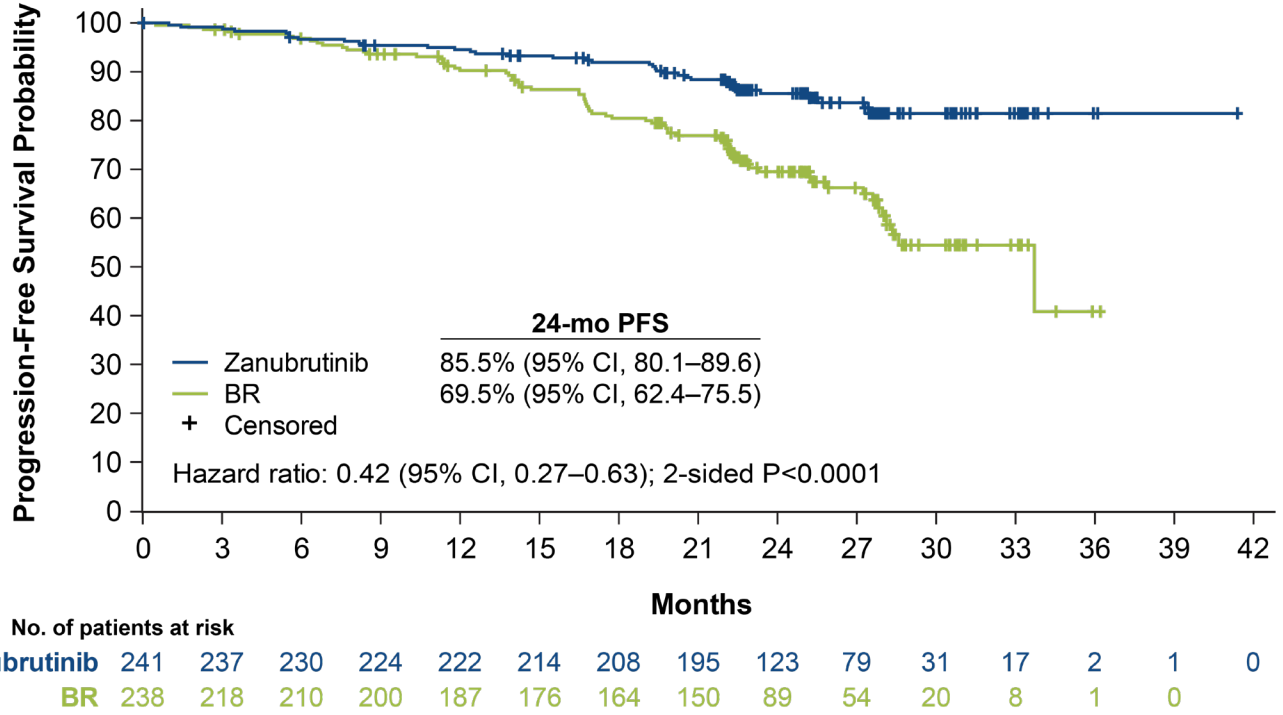



[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years.

C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.

1. Tedeschi A, et al. ASH 2021. Abstract 67.

# SEQUOIA: Progression-Free Survival Per IRC Assessment




BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

# SEQUOIA: Adverse Events of Interest

| AE, n (%) | Arm A Zanubrutinib (n=240[a]) | | Arm B Bendamustine + Rituximab (n=227[a]) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Anemia** | 11 (4.6) | 1 (0.4) | 44 (19.4) | 4 (1.8) |
| **Neutropenia[b]** | 38 (15.8) | 28 (11.7) | 129 (56.8) | 116 (51.1) |
| **Thrombocytopenia[c]** | 11 (4.6) | 5 (2.1) | 40 (17.6) | 18 (7.9) |
| **Arthralgia** | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| **Atrial fibrillation** | 8 (3.3) | 1 (0.4) | 6 (2.6) | 3 (1.3) |
| **Bleeding[d]** | 108 (45.0) | 9 (3.8) | 25 (11.0) | 4 (1.8) |
| Major bleeding[e] | 12 (5.0) | 9 (3.8) | 4 (1.8) | 4 (1.8) |
| **Diarrhea** | 33 (13.8) | 2 (0.8) | 31 (13.7) | 5 (2.2) |
| **Hypertension[f]** | 34 (14.2) | 15 (6.3) | 24 (10.6) | 11 (4.8) |
| **Infections[g]** | 149 (62.1) | 39 (16.3) | 127 (55.9) | 43 (18.9) |
| **Myalgia** | 9 (3.8) | 0 (0.0) | 3 (1.3) | 0 (0.0) |
| **Other cancers** | 31 (12.9) | 17 (7.1) | 20 (8.8) | 7 (3.1) |
| Dermatologic other cancers | 16 (6.7) | 2 (0.8) | 10 (4.4) | 2 (0.9) |

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.
AE, adverse event.



Tam, et al. ASH 2021, Abstract #396

# Select Ongoing First-line Phase III Clinical Trials

| Trial | Subgroup | N | Status* | MRD | Treatment Arms | | | |
|---|---|---|---|---|---|---|---|---|
| GAIA/CLL13 (NCT02950051) | Fit pts | 926 | Enrolled | Co-Primary | IbrVenOb | VenOb | VenR | FCR/BR |
| EA9161 (NCT03701282) | Fit, 18-69 yo | 720 | Enrolled | Secondary | IbrVenOb | IbrOb | | |
| A041702 (NCT03737981) | ≥70 yo | 454 | Enrolled | Secondary | IbrVenOb | IbrOb | | |
| ACE-CL-311 (NCT03836261) | All pts | 780 | Enrolling | Secondary | AcaVenOb | AcaVen | | FCR/BR |
| CRISTALLO (NCT04285567) | Fit pts [no del(17p)] | 165 | Enrolling | Primary | VenOb | | | FCR/BR |
| CLL17 (NCT04608318) | All pts | 897 | Enrolling | Secondary | IbrVen | VenOb | Ibr | |
| GCLLSG (NCT05197192) | High-risk | 650 | Enrolling | Secondary | AcaVenOb | VenOb | | |
| MAJIC (NCT05057494) | All | 600 | Enrolling | Secondary | AcaVen | VenOb | | |

*Status as of September 2022

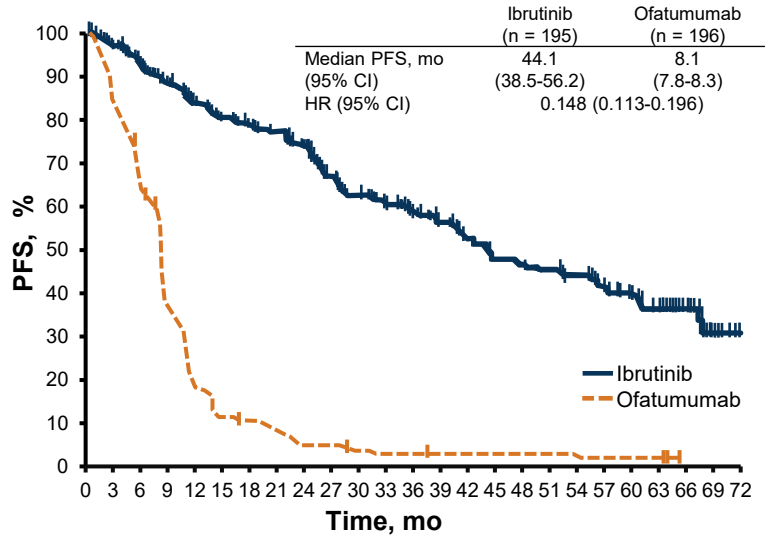
# Standard Treatments for Rel / Ref CLL by Disease Characteristics

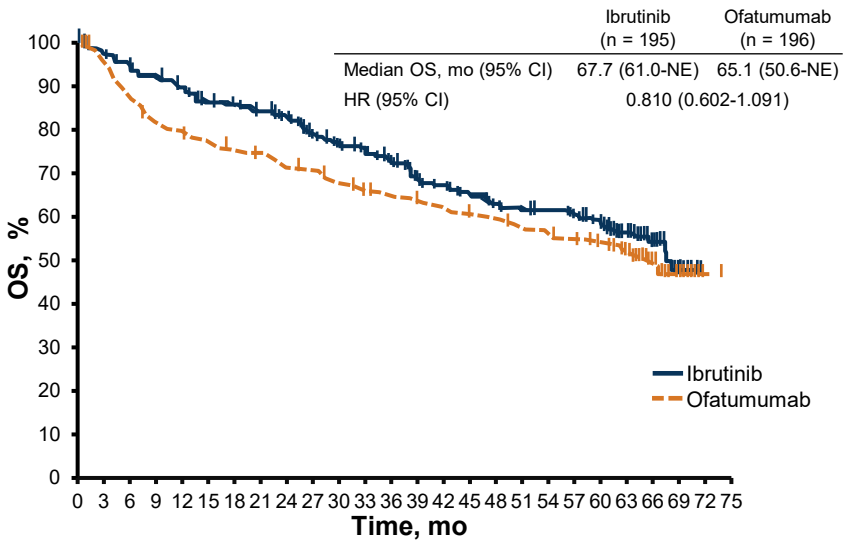
- **Relapsed / Refractory CLL - Durable disease control**
  - Del(17p) / m-*TP53*
  - Age / comorbidities
  - Prior CIT
  - Prior BTK-inhibitor ± CIT
  - Fludarabine-refractory (CIT)
  - Ibrutinib-refractory
  - Idelalisib-refractory

**Treatment Options:**

- BTK-inhibitor
- BCL-2-inhibitor ± rituximab
- PI3K-inhibitor + rituximab
- Lenalidomide ± CD20 mAb
- ~~CIT~~
- Allo-SCT
- Clinical Trial

# Phase 3 RESONATE Study in Relapsed CLL: Ibrutinib vs Ofatumumab—Outcomes[1-3]



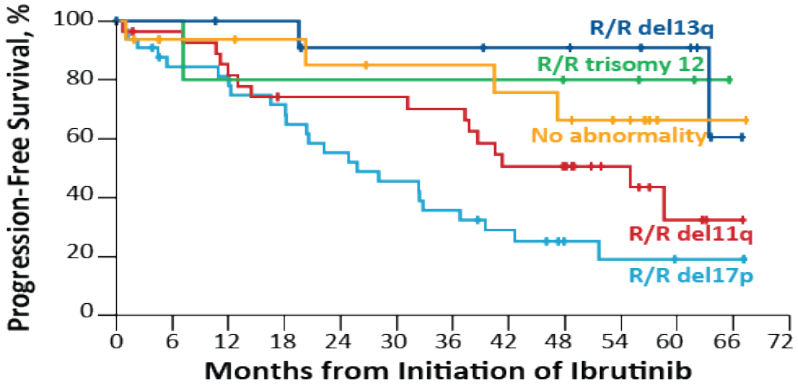

**Final RESONATE findings: ibrutinib safety profile remained consistent with prior reports**

- Cumulatively, all-grade (grade ≥3) hypertension and atrial fibrillation occurred in 21% (9%) and 12% (6%) of patients, respectively
- 16% discontinued ibrutinib because of AEs
- **Peripheral neuropathy:** all grade = 13%, grade ≥3 = 0.5%
- **CHF:** all grade = 5%, grade ≥3 = 3%
- **Ventricular arrhythmia:** all grade: 1%, no grade ≥3 events

1. Byrd JC et al. *N Engl J Med*. 2014;371:213-223. 2. Byrd JC et al. *J Clin Oncol*. 2017;35:7510. 3. Munir T et al. *Am J Hematol*. 2019;94:1353-1363.

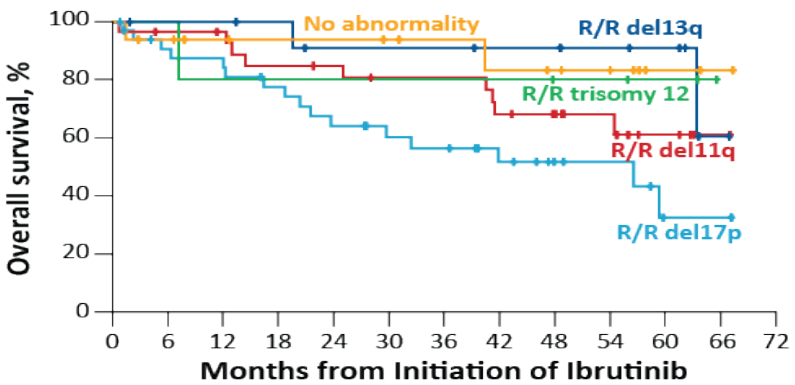
# 5-Year Experience With Ibrutinib Monotherapy Survival by FISH in R/R Patients*

## Progression-Free Survival




| | Median PFS | 5-year PFS |
|---|---|---|
| Del17p (n=34) | 26 mo | 19% |
| Del11q (n=28) | 55 mo | 33% |
| Trisomy 12 (n=5) | NR | 80% |
| Del13q (n=13) | NR | 91% |
| No abnormality** (n=16) | NR | 66% |

## Overall Survival



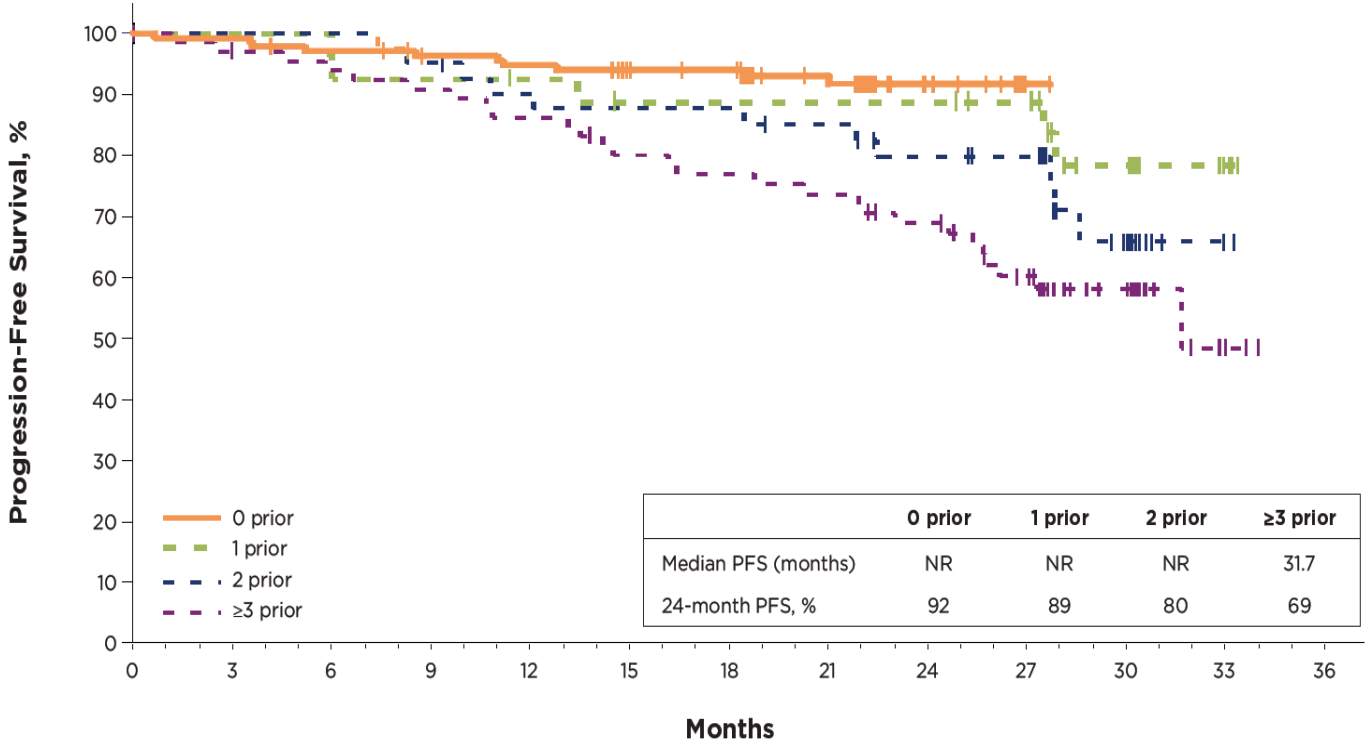

| | Median OS | 5-year OS |
|---|---|---|
| Del17p (n=34) | 57 mo | 32% |
| Del11q (n=28) | NR | 61% |
| Trisomy 12 (n=5) | NR | 80% |
| Del13q (n=13) | NR | 91% |
| No abnormality** (n=16) | NR | 83% |

*Only 2 patients in the TN group showed PD or death. Subgroup analyses, therefore, focused on the R/R population.

**No del17p, del11q, del13q, or trisomy 12; in hierarchical order for del17p, and then del11q.

O'Brien et al. ASH 2016, Abstract 233

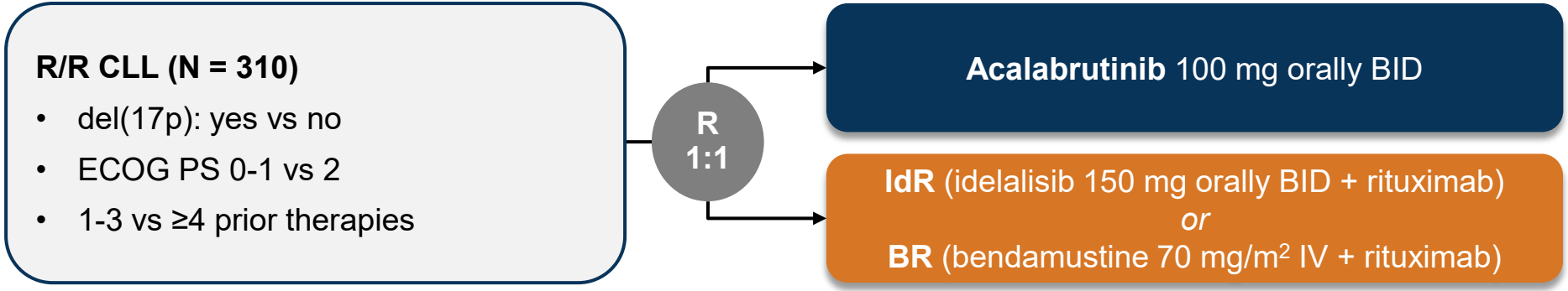
# PFS by Prior Lines of Therapy: RESONATE and RESONATE-2




| | 0 prior | 1 prior | 2 prior | ≥3 prior |
|---|---|---|---|---|
| Median PFS (months) | NR | NR | NR | 31.7 |
| 24-month PFS, % | 92 | 89 | 80 | 69 |

O'Brien et al ASCO 2016

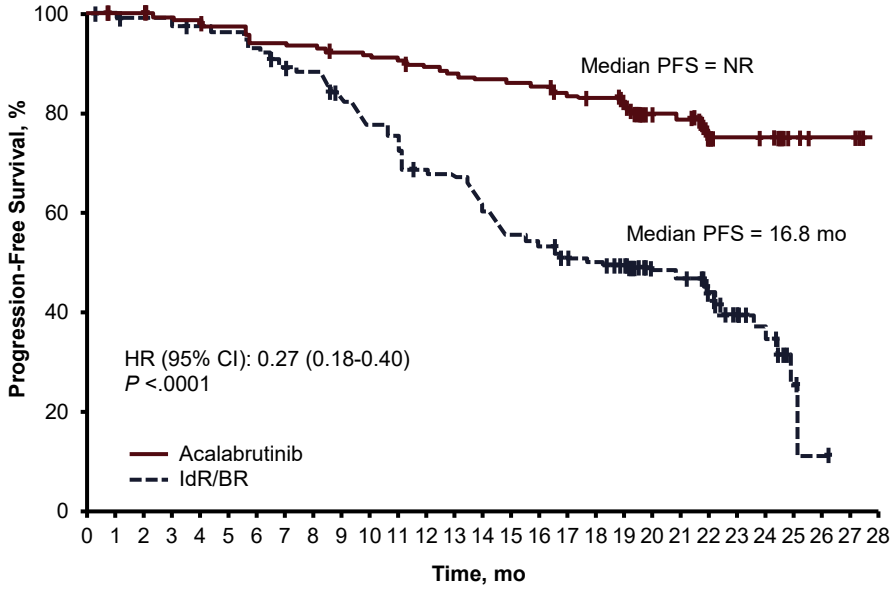
# Phase 3 ACE-CL-309/ASCEND: Acalabrutinib vs IdR or BR in R/R CLL[1]



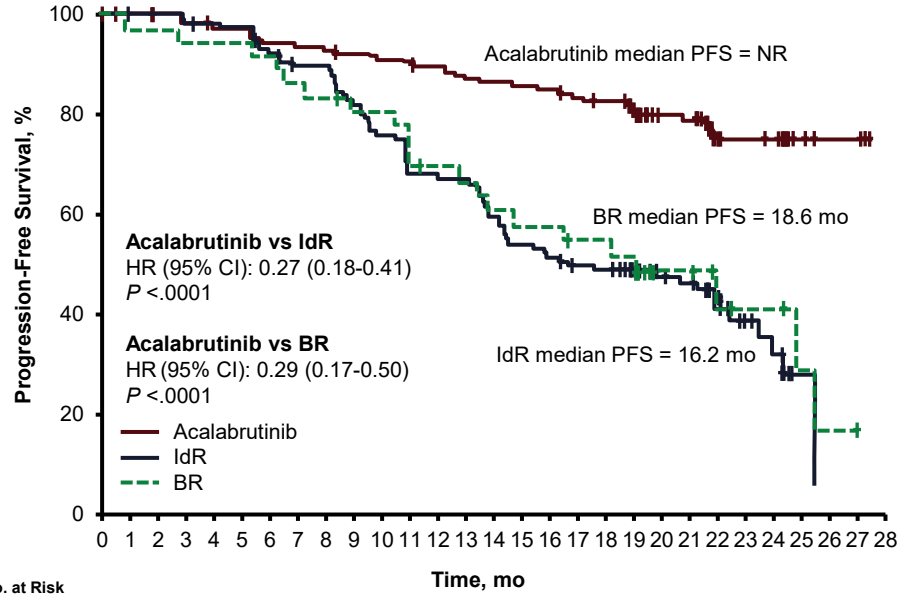

- Crossover from IdR/BR arm allowed after confirmed disease progression
- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)
- **Primary endpoint:** PFS (assessed by IRC)
- **Key secondary endpoints:** ORR (assessed by IRC and investigator), duration of response, PFS (assessed by investigator), OS

1. Ghia P et al. 24th European Hematology Association Congress (EHA 2019). Abstract LB2606.

# Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Improves PFS in R/R CLL[1]



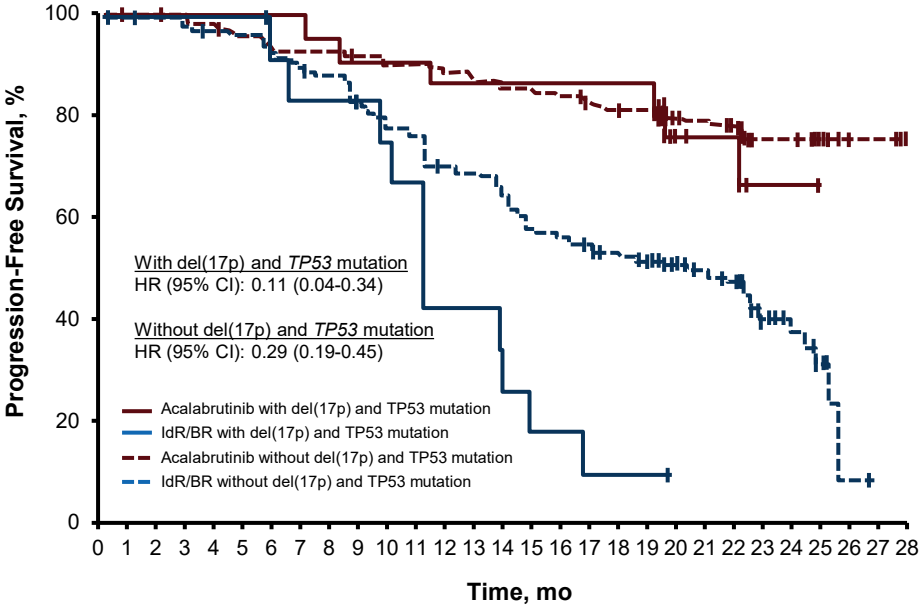

| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acalabrutinib | 155 | 154 | 153 | 151 | 148 | 147 | 143 | 142 | 142 | 139 | 138 | 137 | 133 | 131 | 129 | 128 | 127 | 122 | 119 | 119 | 79 | 77 | 73 | 34 | 34 | 16 | 5 | 5 | 0 |
| IdR/BR | 155 | 150 | 150 | 147 | 146 | 145 | 138 | 129 | 128 | 118 | 109 | 107 | 95 | 94 | 86 | 76 | 74 | 67 | 65 | 62 | 47 | 42 | 38 | 18 | 13 | 6 | 1 | 0 | |

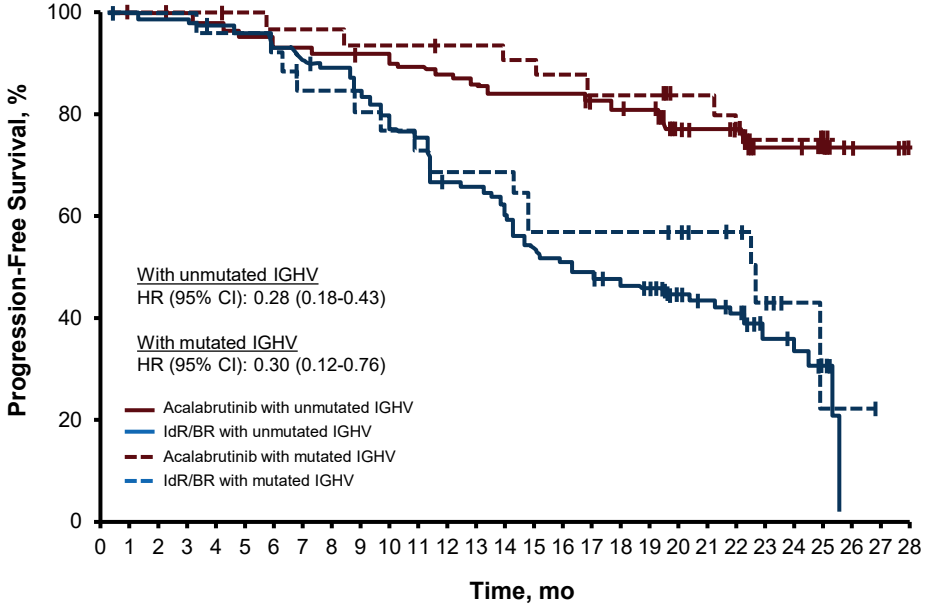



| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acalabrutinib | 155 | 154 | 153 | 151 | 148 | 147 | 143 | 142 | 142 | 139 | 138 | 137 | 133 | 131 | 129 | 128 | 127 | 122 | 119 | 119 | 79 | 77 | 73 | 34 | 34 | 16 | 5 | 5 | 0 |
| IdR | 119 | 116 | 116 | 114 | 113 | 112 | 106 | 99 | 99 | 90 | 82 | 81 | 73 | 72 | 66 | 57 | 56 | 51 | 49 | 47 | 37 | 33 | 30 | 14 | 9 | 3 | 0 | | |
| BR | 36 | 34 | 34 | 33 | 33 | 33 | 32 | 30 | 29 | 28 | 27 | 26 | 22 | 22 | 20 | 19 | 18 | 16 | 16 | 15 | 10 | 9 | 8 | 4 | 4 | 3 | 1 | 0 | |

1. Ghia P et al. ASCO 2020. Abstract 8015.

# Phase 3 ACE-CL-309/ASCEND: PFS in Del(17p) and IGHV Subgroups[1]

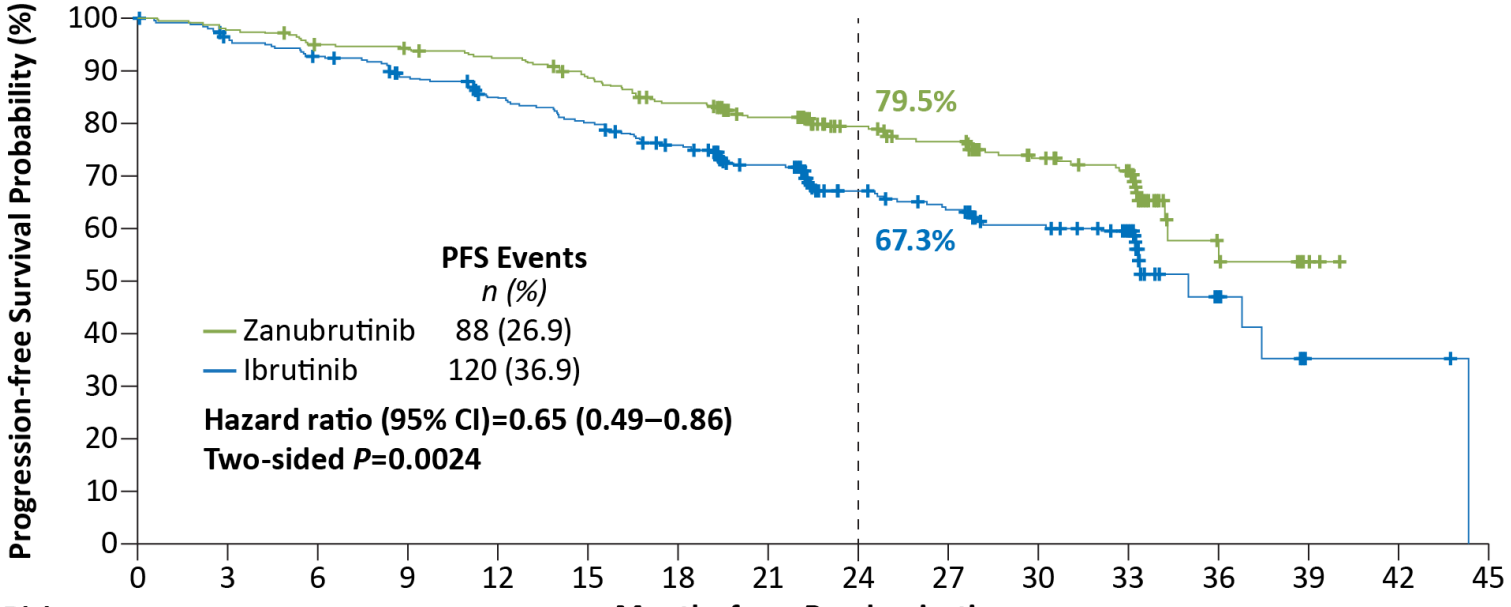



1. Ghia P et al. ASCO 2020. Abstract 8015.

# ALPINE: Zanubrutinib PFS by IRC Superior to Ibrutinib

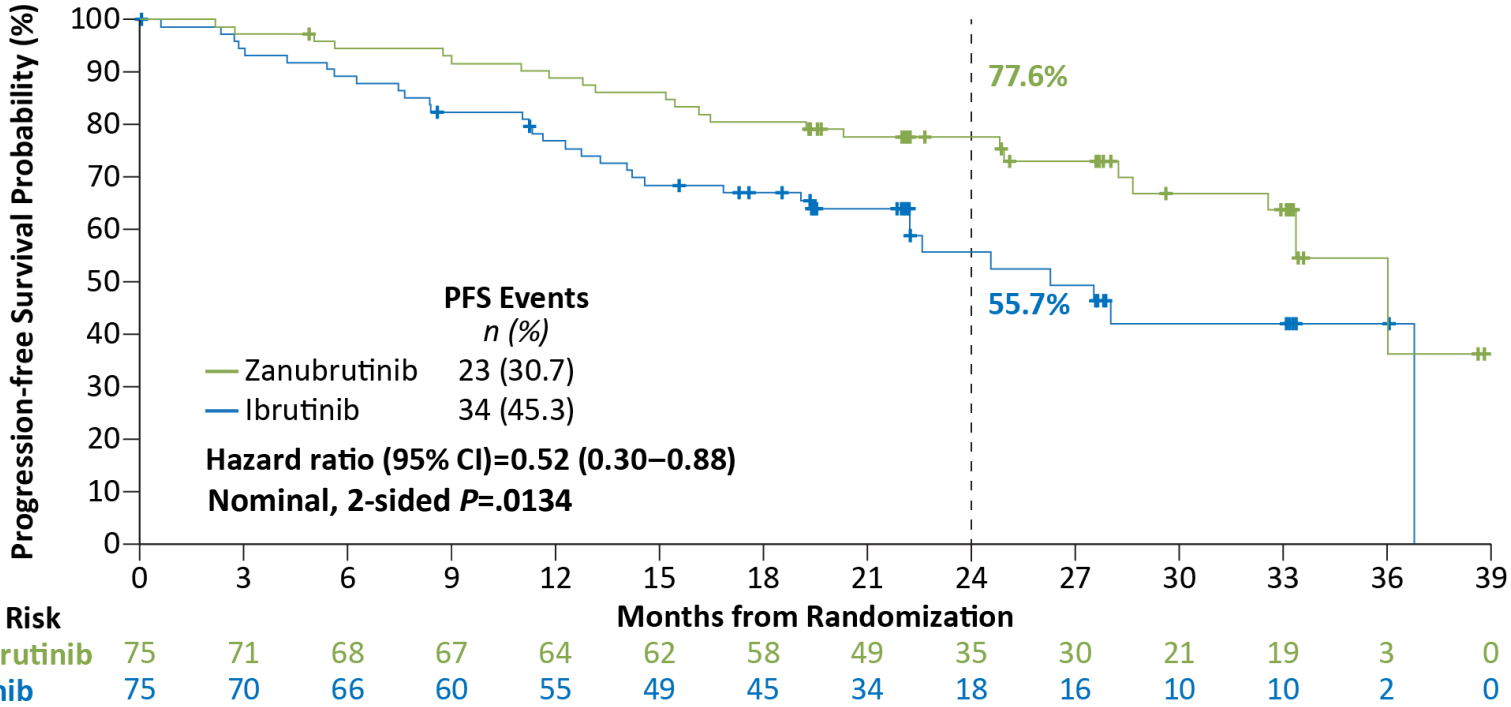
## Median study follow-up of 29.6 months




| No. at Risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanubrutinib | 327 | 315 | 304 | 301 | 294 | 280 | 263 | 226 | 172 | 161 | 125 | 113 | 14 | 2 | 0 | |
| Ibrutinib | 325 | 305 | 293 | 277 | 260 | 246 | 228 | 191 | 133 | 123 | 98 | 87 | 9 | 2 | 2 | 0 |

Data cutoff: 8 Aug 2022

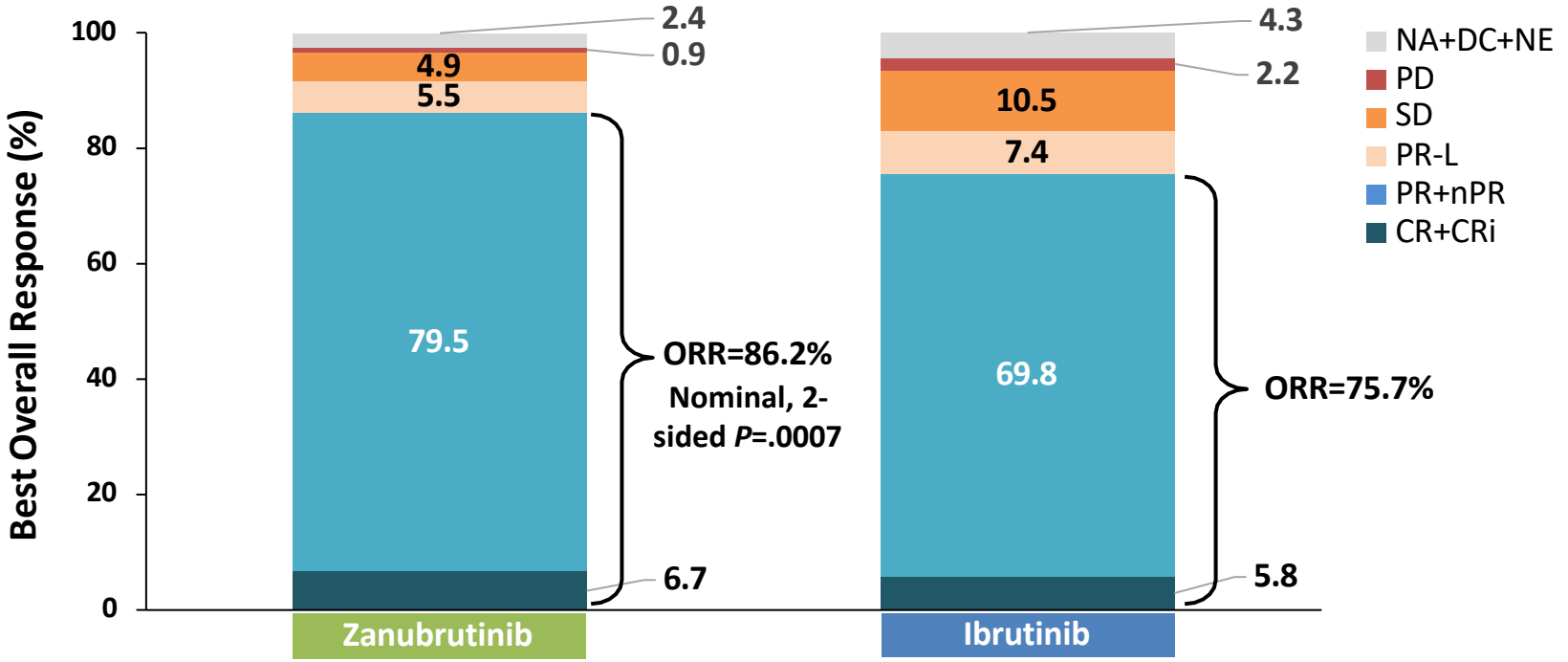
# ALPINE: Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*$^{mut}$




PFS data assessed by IRC

Data cutoff: 8 Aug 2022

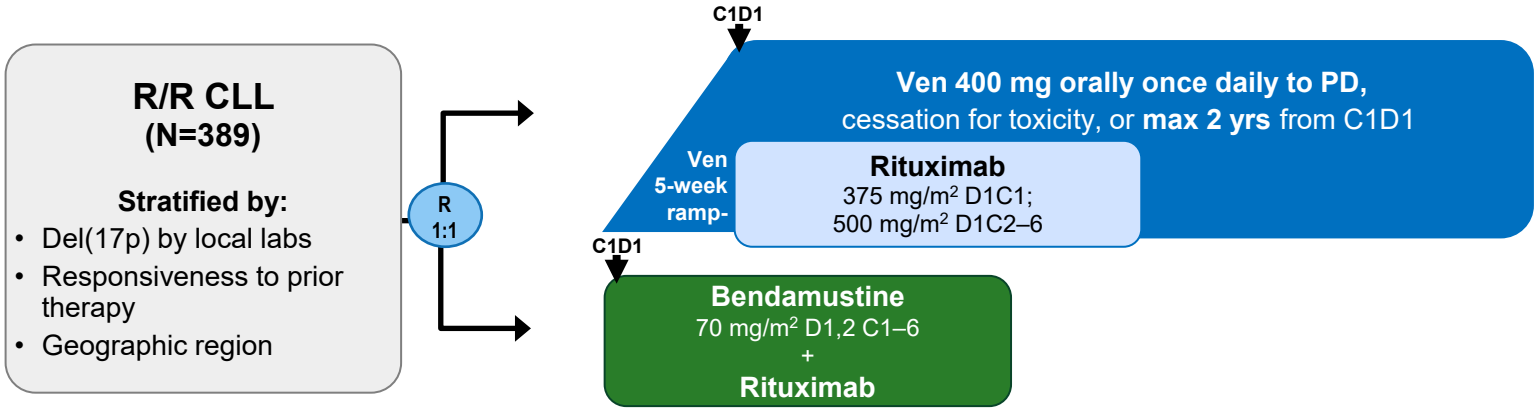
# ALPINE: Zanubrutinib Showed Higher ORR Assessed by IRC




CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

# MURANO study design




- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)
- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed every 3 months for 3 yrs, then every 6 months thereafter, or until PD
- Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 yr later

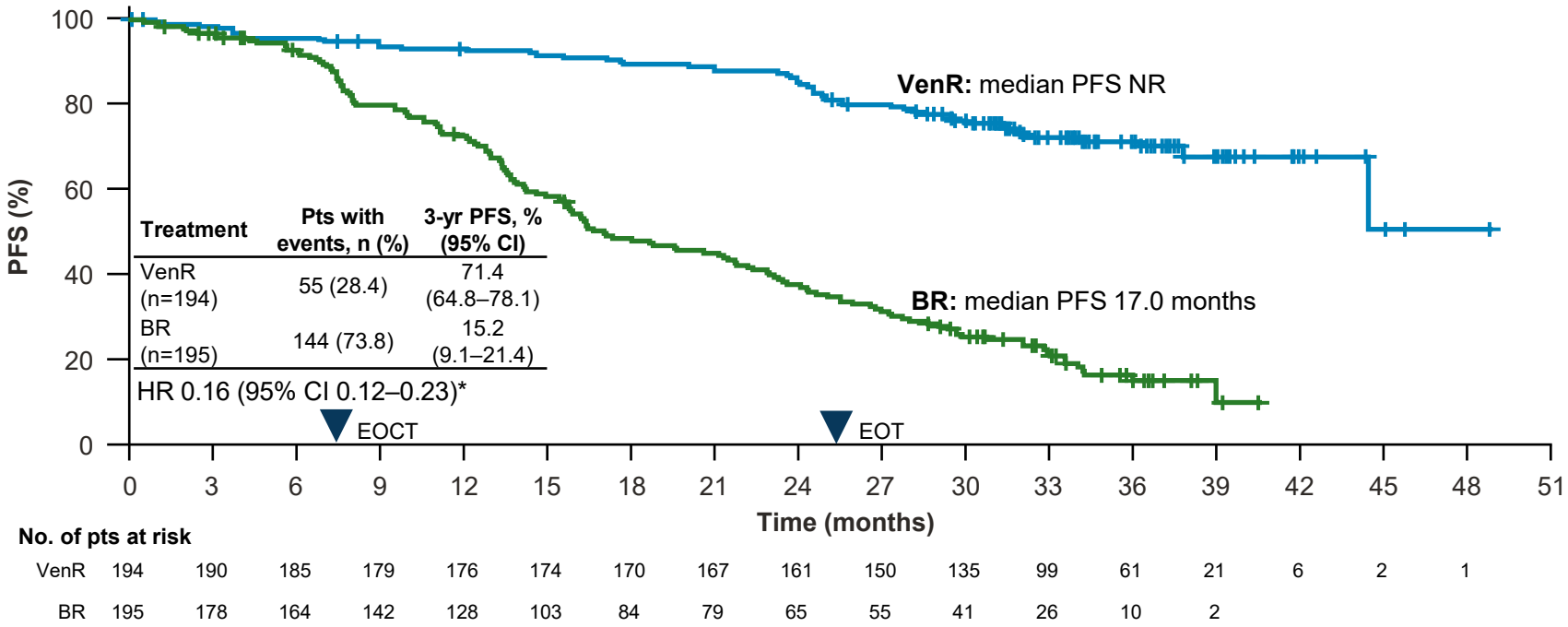
BM, bone marrow; C, cycle; D, day; PB, peripheral blood; PD, progressive disease; R, randomized

Seymour JF, et al. N Engl J Med 2018;378:1107–20

Seymour et al; ASH2018, Abstract 184

# MURANO: Superior PFS with VenR vs BR maintained with 1 additional year of follow-up: update

***Investigator-assessed PFS***



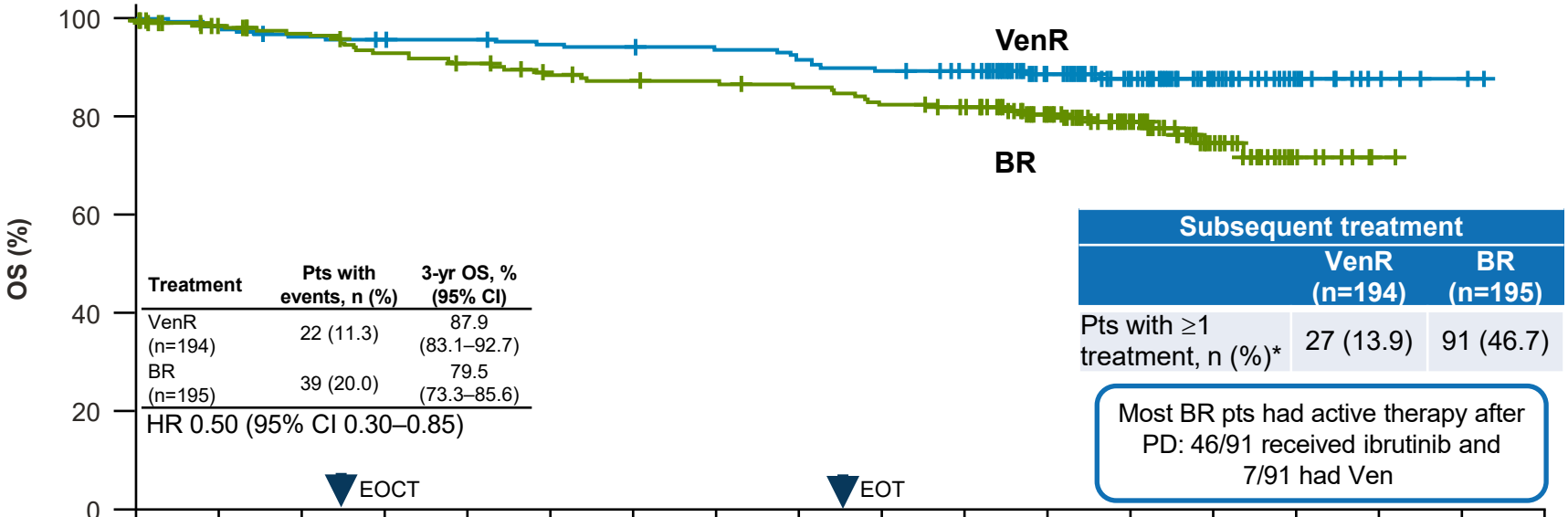

- Median follow-up 36.0 months (range 0.0–48.6); VenR 36.1 months, BR 35.9 months

*Stratified HR

Seymour et al; ASH2018, Abstract 184

Data cut-off date: May 8, 2018

# Clinically meaningful improvement in OS with VenR vs BR maintained after 3 years




| Treatment | Pts with events, n (%) | 3-yr OS, % (95% CI) |
|---|---|---|
| VenR (n=194) | 22 (11.3) | 87.9 (83.1–92.7) |
| BR (n=195) | 39 (20.0) | 79.5 (73.3–85.6) |

HR 0.50 (95% CI 0.30–0.85)

| Subsequent treatment | VenR (n=194) | BR (n=195) |
|---|---|---|
| Pts with ≥1 treatment, n (%)* | 27 (13.9) | 91 (46.7) |

Most BR pts had active therapy after PD: 46/91 received ibrutinib and 7/91 had Ven

**No. of pts at risk**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VenR | 194 | 190 | 185 | 183 | 182 | 179 | 178 | 176 | 173 | 168 | 163 | 128 | 87 | 39 | 13 | 4 | 2 |
| BR | 195 | 181 | 175 | 167 | 162 | 155 | 152 | 150 | 147 | 141 | 136 | 111 | 76 | 34 | 9 | 1 | |

*Unstratified HR 0.51 (95% CI 0.30–0.86)

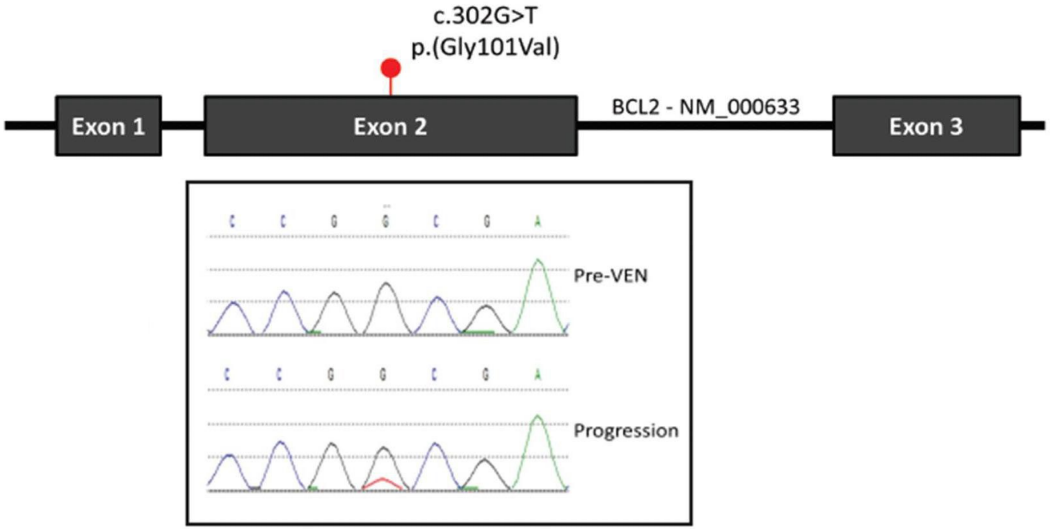
Median follow-up: 36.0 months (range 0.0–48.6). Median per arm: VenR 36.1 months; BR 35.9 months

Seymour et al; ASH2018, Abstract 184

Data cut-off date: May 8, 2018

# BCL2 coding mutation detected in four patients with CLL-type progression on venetoclax

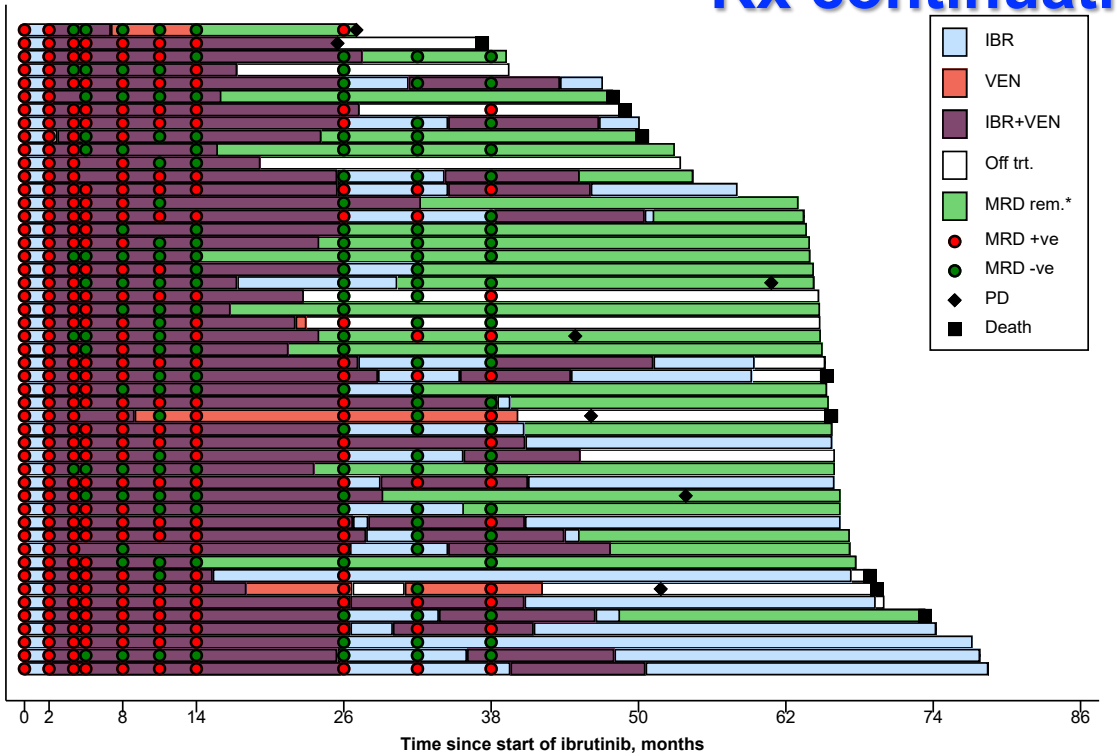
- *BCL2* c.302G>T, p.(Gly101Val) detected in samples from **7/15 patients** sequenced at CLL-type progression on venetoclax




Blombery et al; ASH2018, Abstract LBA-7

# IBR + VEN for R/R CLL

## Change in MRD after Rx discontinuation and Rx continuation




* Stopped treatment due to MRD negative remission

- 9 patients continued on ibrutinib after 60 months
- 11 disease progression
- 9 Deaths
- 17 patients continue in uMRD ($<10^{-4}$) after discontinuation at any time point

Date of data lock: 6-Nov-2020

Munir et al. ASH 2022, Abstract #91

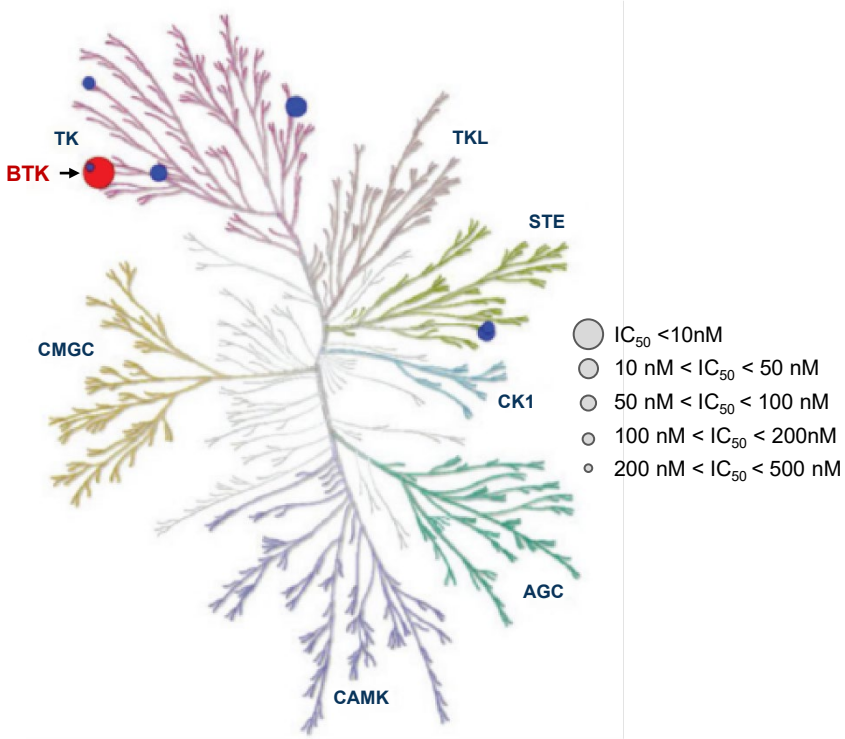
Date of data lock: 01-Nov-2022

# Differentiated Kinase Inhibition Profile

| | TEC Family Kinases | | | | | Inhibition of Other Kinases |
|---|---|---|---|---|---|---|
| | $IC_{50}$ (nM) | BTK | ITK | Tec# | TXK* | BMX* | Notable Target Kinases |
| *Irreversible (covalent)* | Ibrutinib[2] | 0.5 | 10.7 | 78 | 2.0[3] | 0.8 | >10 more: EGFR family |
| | Acalabrutinib[3] | 5.1 | >1000 | 93 | 368 | 46 | Selective |
| | Zanubrutinib[4] | 0.22 | 30 | 1.9 | n/a | n/a | N/A (not published) |
| *Reversible (non-covalent)* | Vecabrutinib[1] | 3 | 14 | 14 | 474 | 224 | Selective -4 non-Tec family kinases: SRC family, NEK11 |
| | ARQ 531[5] | 4.23 | >10000 | 5.8 | 36.4 | 5.23 | >20 more: SRC & TRK families, RAF1, MEK1 |
| | LOXO-305[6] | 3.15 | >5000 | 1234 | 209 | 1155 | Very Selective |
| | CG-806[7] (Aptose) | 8.4 | 4.3 | >1000 | n/a | 14.5 | 18 w/ $IC_{50}$ <10 nM: FLT3 (wt, ITD) c-MET, TRK family & Aurora kinases |

n/a=not available
* Determined with vecabrutinib free base (also relevant for SRC and EGFR)
# Activated (also relevant for LCK)
[1] Neuman et al., ASH 2016
[2] Honigberg et al., PNAS 2010
[3] Byrd et al., NEJM 2016
[4] Tam et al., ASH 2016
[5] Eathiraj et al., Pan Pacific Lymphoma Conference 2016
[6] Brandhuber et al. , SOHO 2018
[7] Zhang et al, EHA 2018

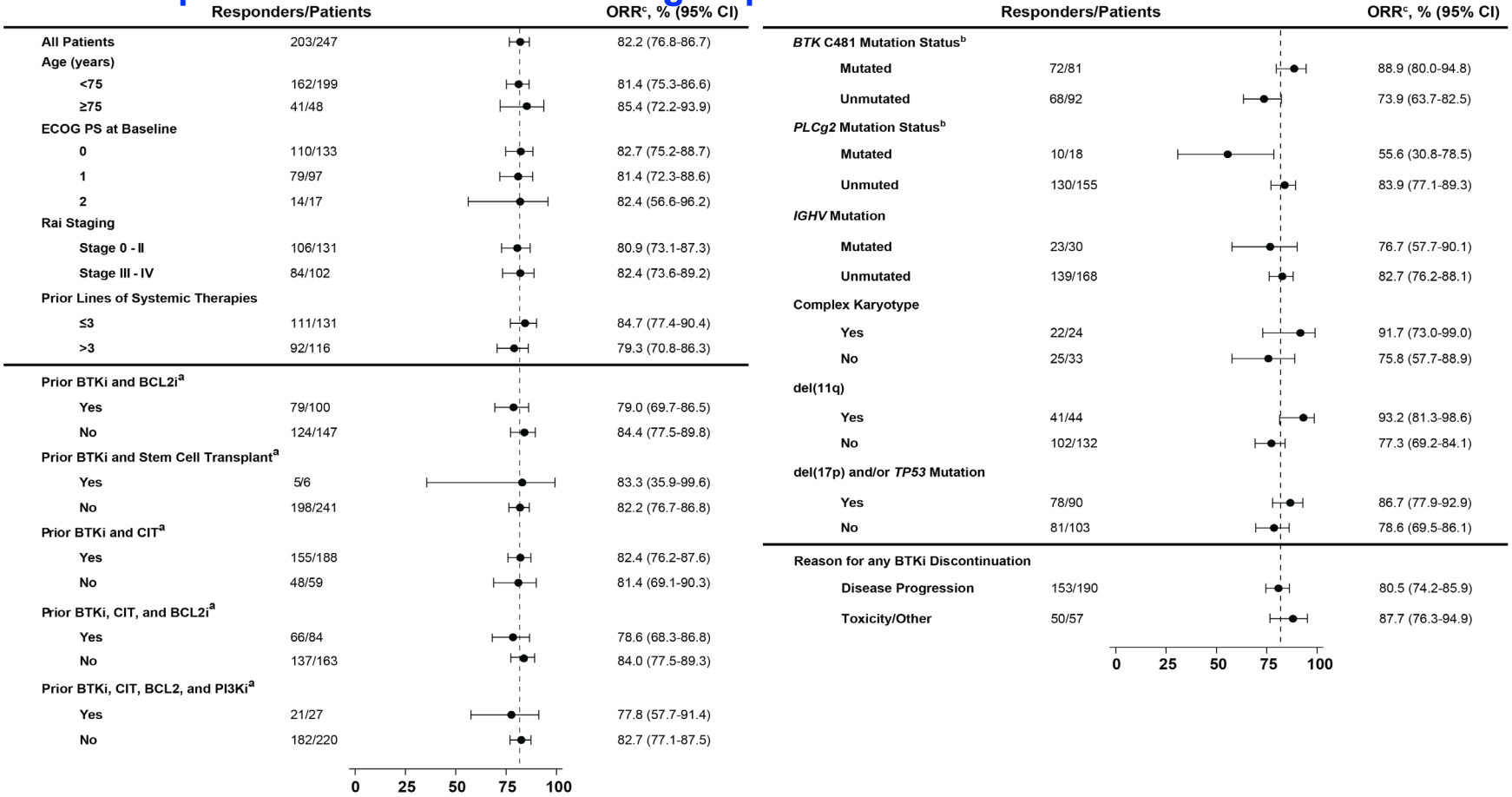
# LOXO-305 Potently and Selectively Inhibits BTK and *BTK* C481S Kinase Activity[1]




| Kinase | Percent of Control at 1 μM LOXO-305, [ATP] = $K_M$, % | $IC_{50}$ [ATP] = $K_M$, nM | Fold Selectivity Over BTK |
|---|---|---|---|
| BTK C481S | ND | 1.42 | 0.5 |
| BTK | 1.8 | 3.15 | 1.0 |
| ERBB4 | 2.6 | 13.3 | 4.2 |
| BRK | 10.3 | 54.3 | 17 |
| MEK2 | 7.6 | 82.7 | 26 |
| MEK1 | 12.2 | 147 | 47 |
| YES1 | 38.6 | 157 | 50 |
| TXK | 19.6 | 209 | 66 |
| BMX | 70.2 | 1,155 | 367 |
| TEC | 64.6 | 1,234 | 392 |
| BLK | 72.8 | 4,100 | 1,302 |
| EGFR | 60.6 | >1,000 | >317 |
| ITK | 103 | >5,000 | >1,587 |
| SRC | 90.5 | >5,000 | >1,587 |
| JAK1 | 96.4 | >30,000 | >9,524 |
| JAK2 | 94.5 | ND | ND |
| JAK3 | 97 | ND | ND |

1. Brandhuber B et al. Society of Hematologic Oncology Sixth Annual Meeting (SOHO 2018). Abstract CLL-200.

# Pirtobrutinib:
# Overall Response Rate in CLL/SLL Subgroups

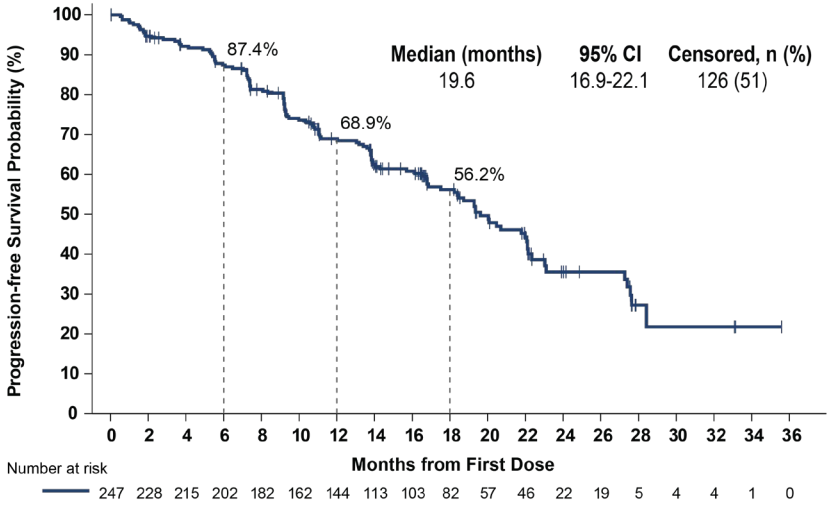



Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.

Mato et al. ASH 2022, Abstract

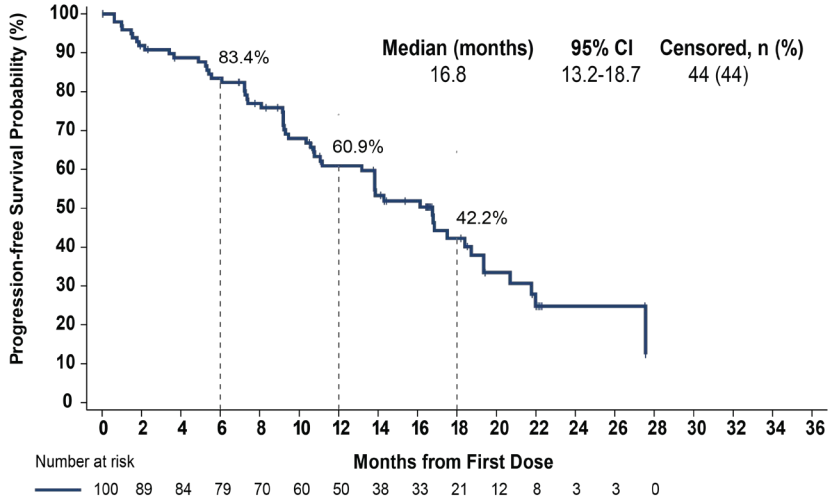
# Pirtobrutinib:
# Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

**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**



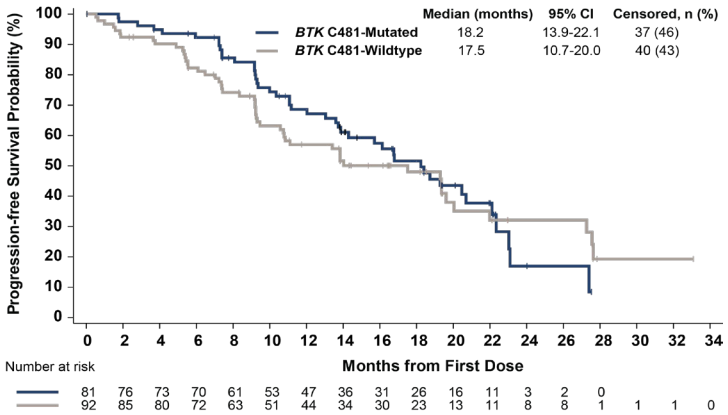

- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

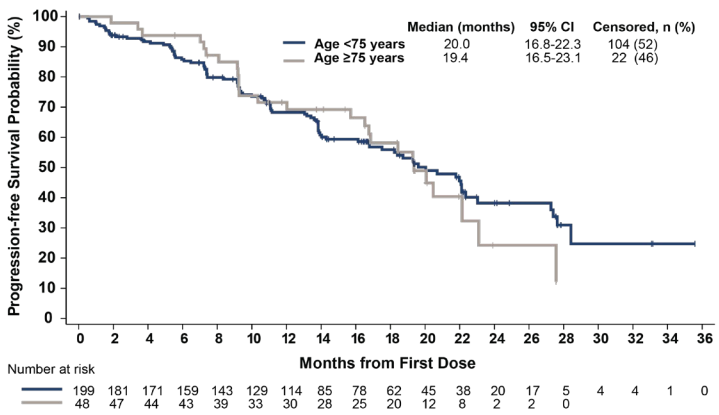
Mato et al. ASH 2022, Abstract

# Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

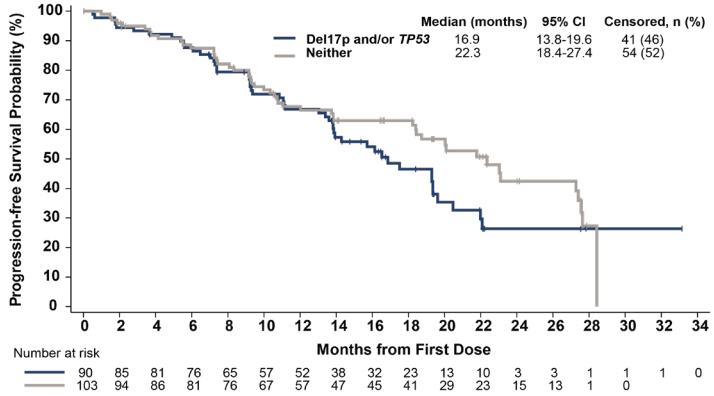
## *BTK* C481 mutation status[a,b]



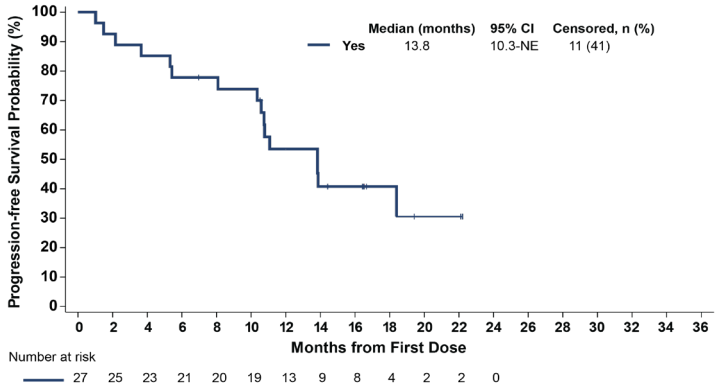

## Age




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




## Prior BTKi, CIT, BCL2i, and PI3Ki therapy




Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

Mato et al. ASH 2022, Abstract

# Idelalisib

- FDA approved for relapsed CLL appropriate for rituximab monotherapy
- Twice daily dosing, continuous + rituximab
- Toxicities: elevated LFTs, GI / diarrhea; less common colitis and pulmonary
- Most responses are partial, residual disease
- Median PFS was 19.4 months
- Efficacy in relapsed CLL with del(17p) & del(11q)
- Improved OS *vs*. rituximab + placebo
- Infection concerns in first-line

# THANK YOU!

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