
# Leucemia linfatica cronica

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Starhotels Terminus

# Disclosures of FR MAURO

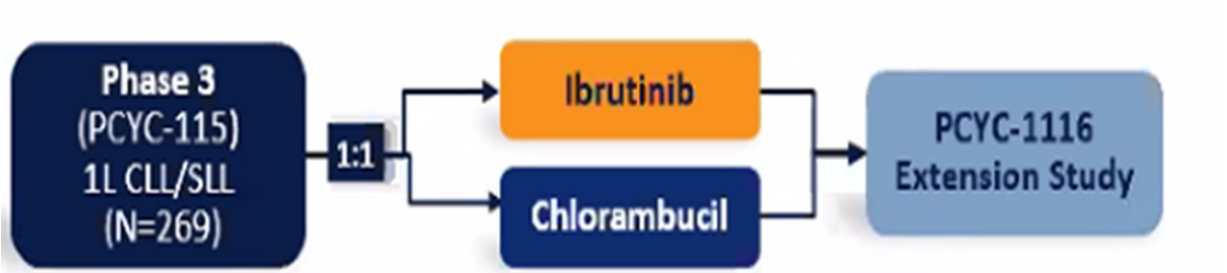
| | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Janssen | | | | | x | x | |
| AstraZeneca | | | | | x | x | |
| Abbvie | x | | | | x | x | |
| Beigene | | | | | | x | |
| Takeda | x | | | | x | x | |

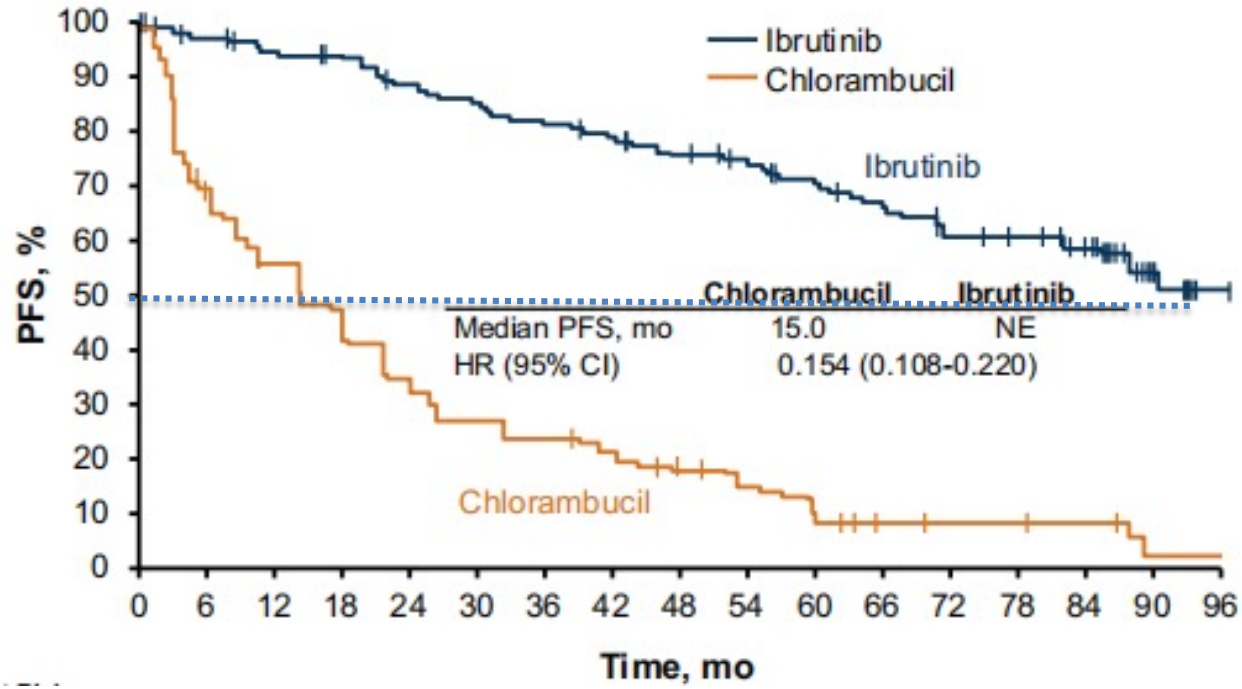
# Chronic Lymphocytic Leukemia

## HOT NEWS

| | |
|---|---|
| Ibrutinib | Resonate-2<br>ECOG E1912 |
| Acalabrutinib | ASCEND<br>ELEVATE TN<br>ELEVATE R/R |
| Zanubrutinib | SEQUOIA coohort 1- arm B<br>SEQUOIA coohort 2- arm C<br>ALPINE |
| Pirtobrutinib | BRUIN trial |
| Venetoclax-obinuruzumab | CLL14 |
| Venetoclax-ibrutinib | CAPTIVATE<br>GLOW<br>CLL13 ( Gaia)<br>FLAIR |

# RESONATE-2: 8-YEAR FOLLOW-UP OF FRONTLINE IBRUTINIB




**7 year-PFS:**

**Ibrutinib: 59%**
**Chlorambucil: 9%**

Barr et al. *Blood Adv.* 2022

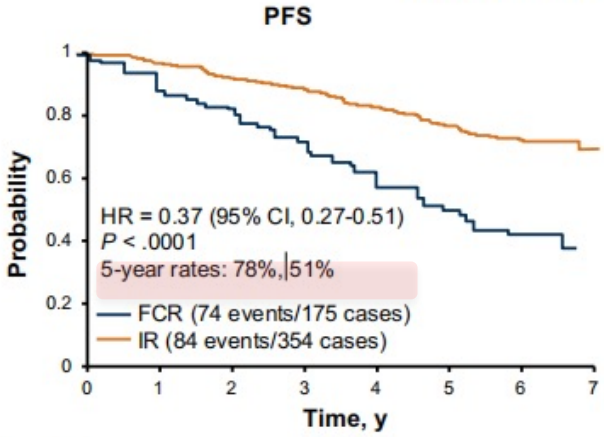
# ECOG E1912 TRIAL- IR VS. FCR: >5 YR-FU

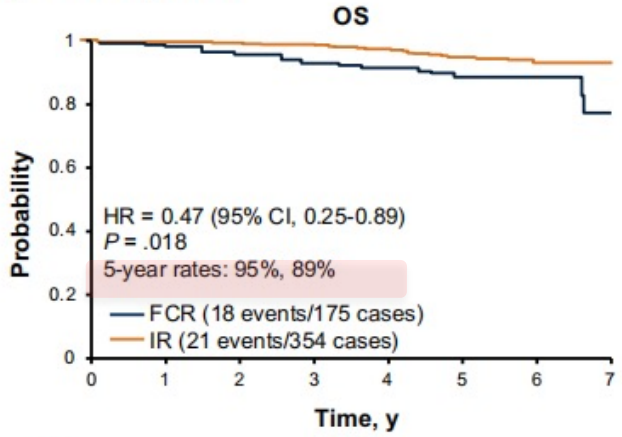
- Phase 3, randomized, open-label trial
- Treatment-naive CLL (N=529)
- ≤70 years of age
- ECOG PS 0-2
- CrCl >40 mL/min
- FCR eligible
- No del(17p) by FISH

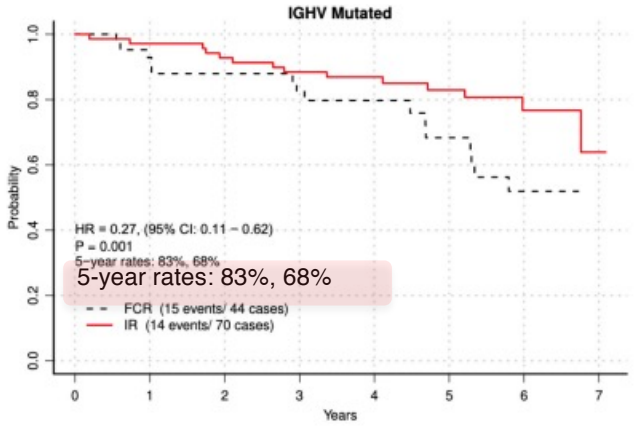
RANDOMIZED 2:1

- Ibrutinib + rituximab (n=354) → Ibrutinib maintenance until PD
- Fludarabine + cyclophosphamide + rituximab (n=175)

## Median Follow-Up of 5.8 years[1]



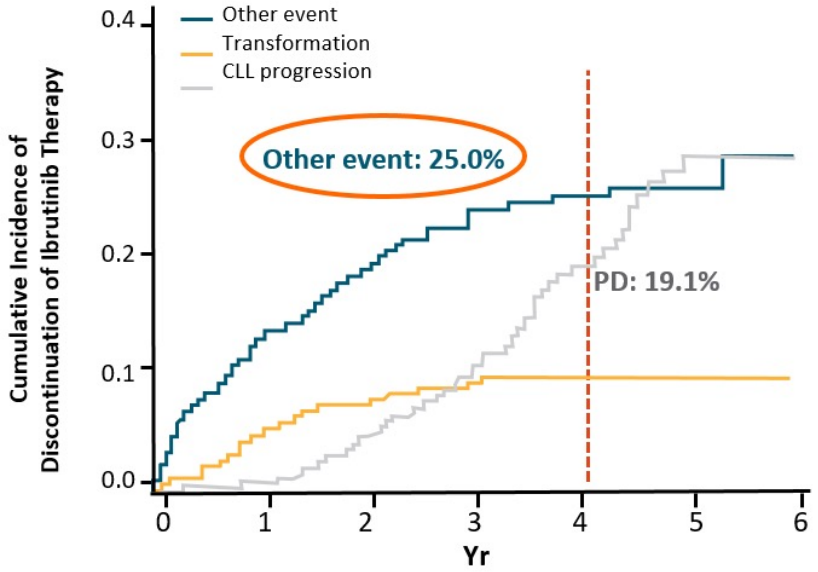




Patients on the IR arm also had superior PFS in both *IGHV* unmutated (HR = 0.27, $P < .001$) and *IGHV* mutated subgroups

Shanafelt TD, et al. Blood 2022

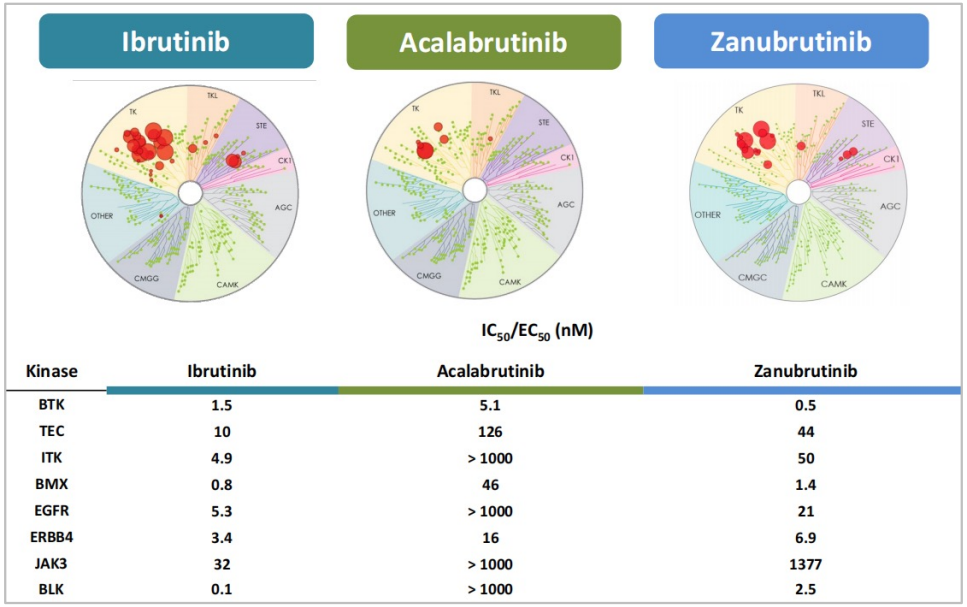
# SECOND GENERATION BTK INHIBITORS:EFFECTIVE WITH MORE FAVORABLE TOXICITY PROFILE

## Ibrutinib: treatment dicontinuations




Woyach et al. *J Clin Oncol*. 2017

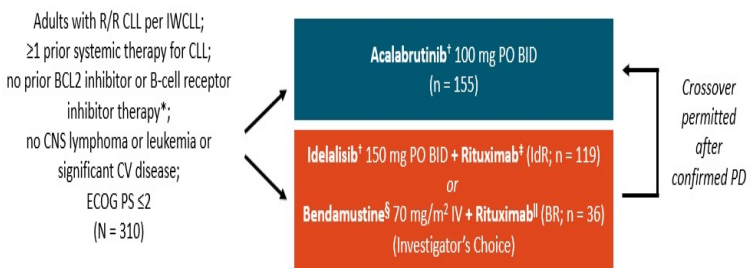
## Second generation BTK inhibitors



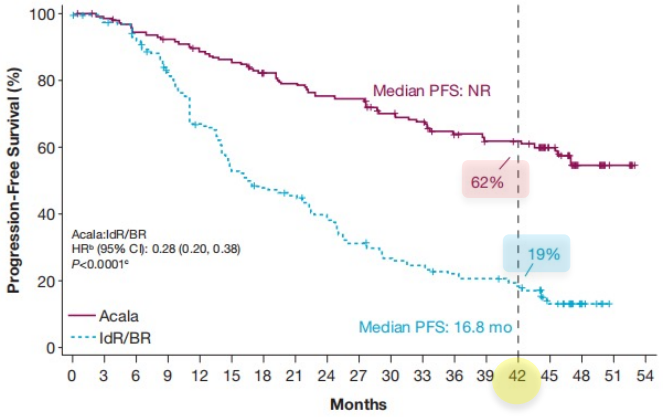

$IC_{50}/EC_{50}$ (nM)

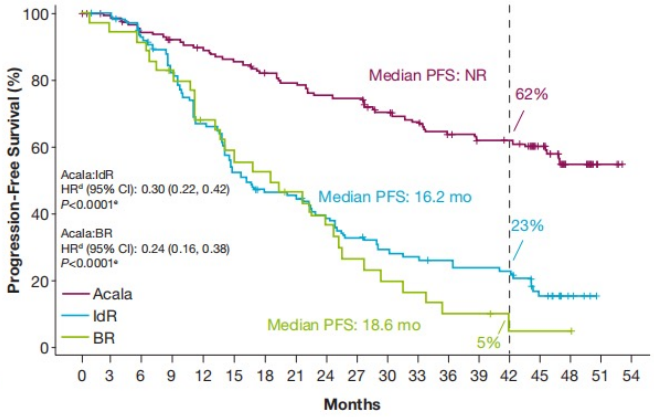
| Kinase | Ibrutinib | Acalabrutinib | Zanubrutinib |
|---|---|---|---|
| BTK | 1.5 | 5.1 | 0.5 |
| TEC | 10 | 126 | 44 |
| ITK | 4.9 | > 1000 | 50 |
| BMX | 0.8 | 46 | 1.4 |
| EGFR | 5.3 | > 1000 | 21 |
| ERBB4 | 3.4 | 16 | 6.9 |
| JAK3 | 32 | > 1000 | 1377 |
| BLK | 0.1 | > 1000 | 2.5 |

# ASCEND TRIAL: ACALABRUTINIB IN R/R PATIENTS WITH CLL: 4 YEAR UPDATED RESULTS

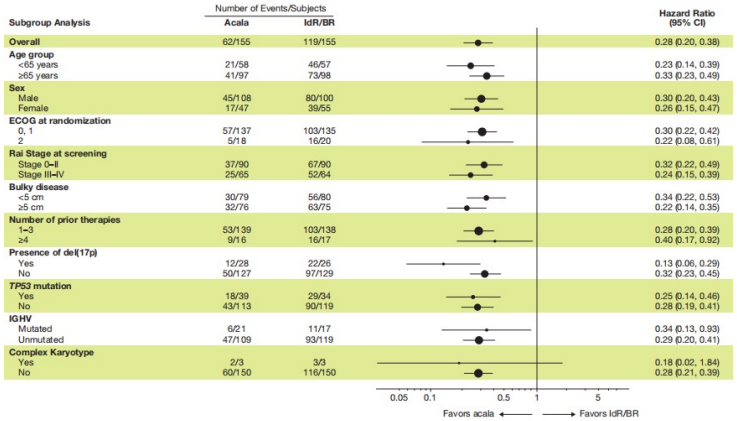



## Investigator-Assessed PFS



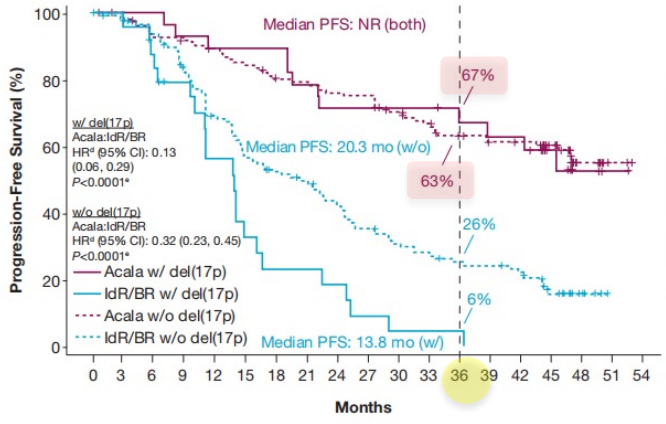

## Investigator-Assessed PFS in Patient Subgroups (Acala vs IdR/BR)



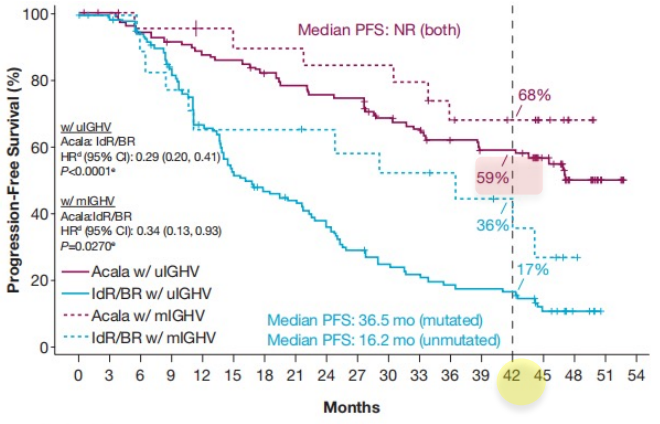
| Subgroup Analysis | Number of Events/Subjects Acala | IdR/BR | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Overall** | 62/155 | 119/155 | 0.28 (0.20, 0.38) |
| **Age group** | | | |
| <65 years | 21/58 | 46/57 | 0.23 (0.14, 0.39) |
| ≥65 years | 41/97 | 73/98 | 0.33 (0.23, 0.49) |
| **Sex** | | | |
| Male | 45/108 | 80/100 | 0.30 (0.20, 0.43) |
| Female | 17/47 | 39/55 | 0.26 (0.15, 0.47) |
| **ECOG at randomization** | | | |
| 0, 1 | 57/137 | 103/135 | 0.30 (0.22, 0.42) |
| 2 | 5/18 | 16/20 | 0.22 (0.08, 0.61) |
| **Rai Stage at screening** | | | |
| Stage 0–II | 37/90 | 67/90 | 0.32 (0.22, 0.49) |
| Stage III–IV | 25/65 | 52/64 | 0.24 (0.15, 0.39) |
| **Bulky disease** | | | |
| <5 cm | 30/79 | 56/80 | 0.34 (0.22, 0.53) |
| ≥5 cm | 32/76 | 63/75 | 0.22 (0.14, 0.35) |
| **Number of prior therapies** | | | |
| 1–3 | 53/139 | 103/138 | 0.28 (0.20, 0.39) |
| ≥4 | 9/16 | 16/17 | 0.40 (0.17, 0.92) |
| **Presence of del(17p)** | | | |
| Yes | 12/28 | 22/26 | 0.13 (0.06, 0.29) |
| No | 50/127 | 97/129 | 0.32 (0.23, 0.45) |
| ***TP53* mutation** | | | |
| Yes | 18/39 | 29/34 | 0.25 (0.14, 0.46) |
| No | 43/113 | 90/119 | 0.28 (0.19, 0.41) |
| **IGHV** | | | |
| Mutated | 6/21 | 11/17 | 0.34 (0.13, 0.93) |
| Unmutated | 47/109 | 93/119 | 0.29 (0.20, 0.41) |
| **Complex Karyotype** | | | |
| Yes | 2/3 | 3/3 | 0.18 (0.02, 1.84) |
| No | 60/150 | 116/150 | 0.28 (0.21, 0.39) |



## Investigator-Assessed PFS by del(17p)

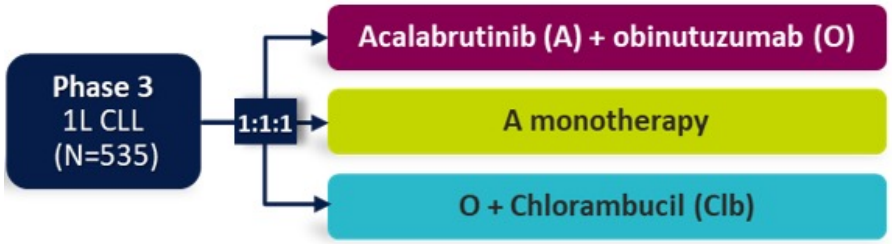



## Investigator-Assessed PFS by IGHV



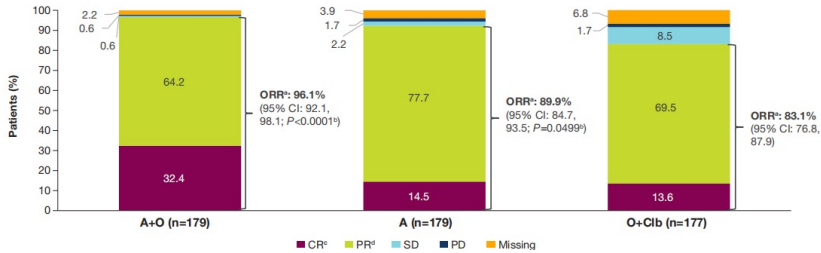

Jurczak et al. ASCO 2022

# ELEVATE TN trial: in TN Patients With CLL: 5-year updated results

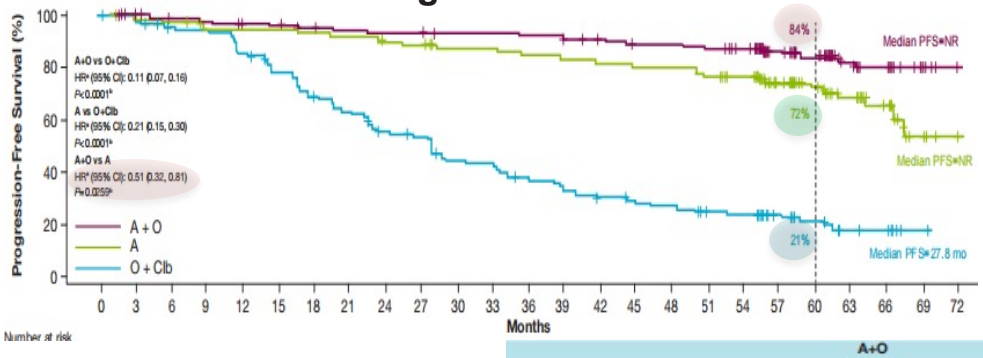



CR increase

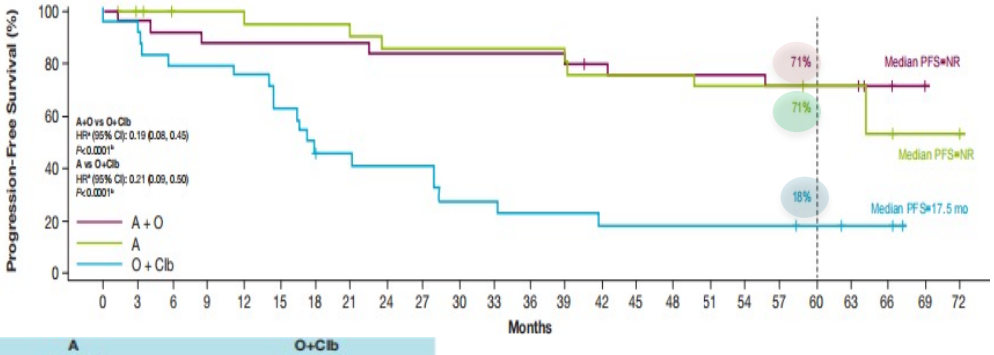
**A+O:** 24.0%7 , 30.7%8 , and 32.4%
**A:** 7.8%7 , 11.2%8 , and 14.5%




## Investigator-assessed PFS




## Investigator-assessed PFS: del(17p)/ mut*TP53*




## Adverse events of clinical interest

| | 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) |
| Atrial fibrillation | 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[a] | 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) |
| SPMs excluding non-melanoma skin | 17 (9.6) | 12 (6.7) | 13 (7.3) | 5 (2.8) | 3 (1.8) | 2 (1.2) |

Sharman et al., ASCO 2022

# ELEVATE R/R: ACALABRUTINIB VS. IBRITINIB IN R/R PATIENTS WITH CLL

Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria)

Presence of del(17p) or del(11q)

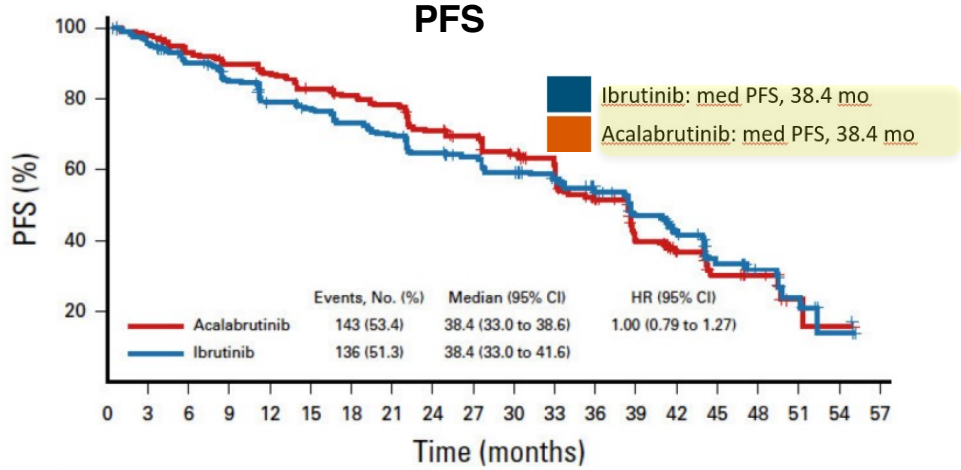
ECOG PS ≤ 2

→ Ibrutinib (n = 268)

→ Acalabrutinib (n = 265)

→ *Until PD or unacceptable AE*

## PFS

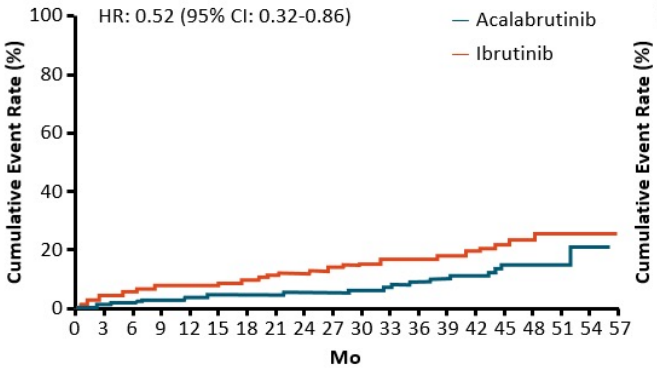



**Median follow-up: 41 months**

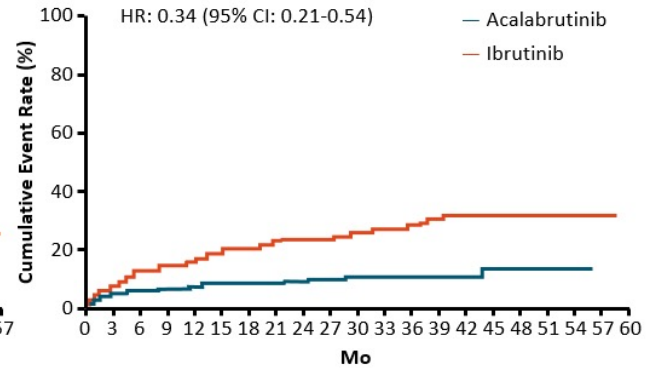
## AEs of special interest

| Events, n (%) | Any grade | | Grade ≥3 | |
|---|---|---|---|---|
| | Acalabrutinib (n=266) | Ibrutinib (n=263) | Acalabrutinib (n=266) | Ibrutinib (n=263) |
| Cardiac events | 64 (24.1) | 79 (30.0) | 23 (8.6) | 25 (9.5) |
| Atrial fibrillation[a]* | 25 (9.4) | 42 (16.0) | 13 (4.9) | 10 (3.8) |
| Ventricular arrhythmias[b] | 0 | 3 (1.1) | 0 | 1 (0.4) |
| Bleeding events* | 101 (38.0) | 135 (51.3) | 10 (3.8) | 12 (4.6) |
| Major bleeding events[c] | 12 (4.5) | 14 (5.3) | 10 (3.8) | 12 (4.6) |
| Hypertension[d]* | 25 (9.4) | 61 (23.2) | 11 (4.1) | 24 (9.1) |
| Infections[e] | 208 (78.2) | 214 (81.4) | 82 (30.8) | 79 (30.0) |
| ILD/pneumonitis* | 7 (2.6) | 17 (6.5) | 1 (0.4) | 2 (0.8) |
| SPMs excluding NMSC | 24 (9.0) | 20 (7.6) | 16 (6.0) | 14 (5.3) |

### Atrial Fibrillation



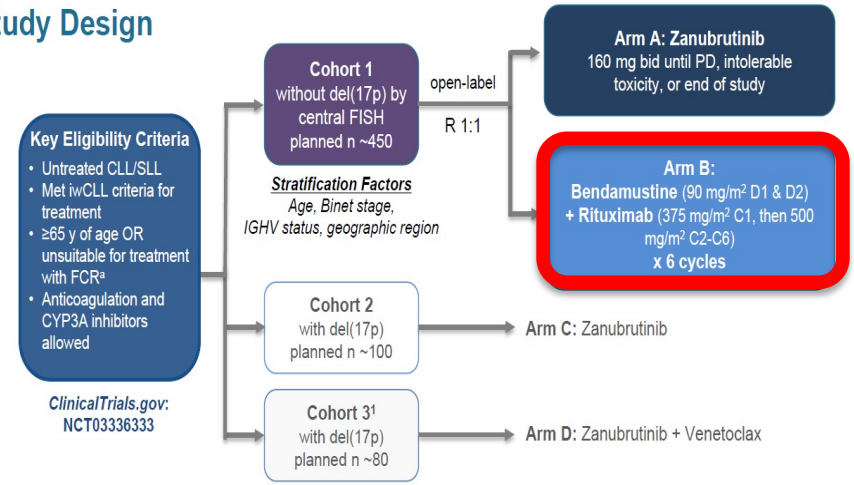

### Hypertension




Byrd, et al. JCO 2021

# SEQUOIA TRIAL: 1L Zanubrutinib vs BR (Cohort 1-Arm B)

## Study Design

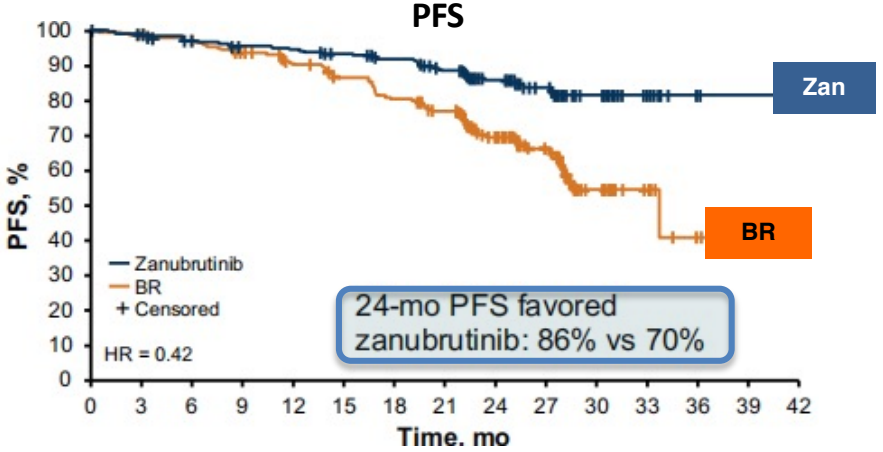



Median follow-up: 26.2 months

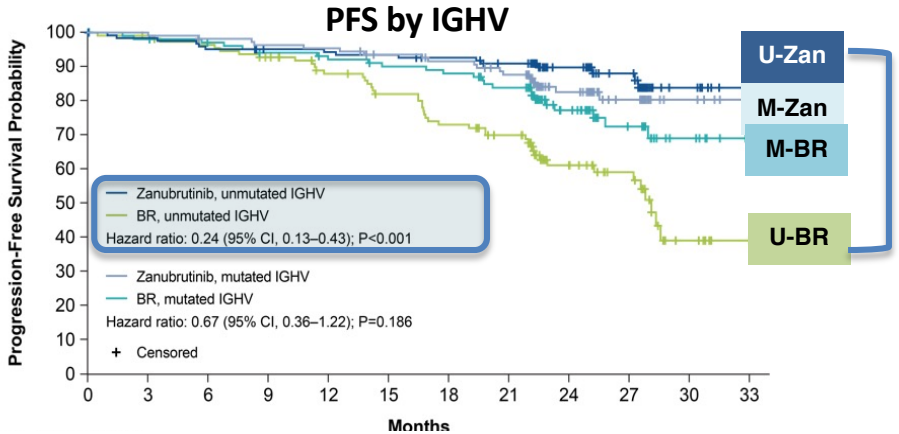
## Common Adverse Events
(≥12% of Patients in Any Arm)

| | Arm A Zanubrutinib (n=240[a]) | | Arm B Bendamustine + Rituximab (n=227[a]) | |
|---|---|---|---|---|
| AE, n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Contusion | 46 (19.2) | 0 (0.0) | 8 (3.5) | 0 (0.0) |
| Upper respiratory tract infection | 41 (17.1) | 2 (0.8) | 27 (11.9) | 2 (0.9) |
| Neutropenia[b] | 37 (15.4) | 27 (11.3) | 129 (56.8) | 116 (51.1) |
| Diarrhea | 33 (13.8) | 0 (0.0) | 30 (13.2) | 4 (1.8) |
| Arthralgia | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| Fatigue | 28 (11.7) | 3 (1.3) | 36 (15.9) | 2 (0.9) |
| Rash | 26 (10.8) | 0 (0.0) | 44 (19.4) | 6 (2.6) |
| Constipation | 24 (10.0) | 1 (0.4) | 43 (18.9) | 0 (0.0) |
| Nausea | 24 (10.0) | 0 (0.0) | 74 (32.6) | 3 (1.3) |
| Pyrexia | 17 (7.1) | 0 (0.0) | 60 (26.4) | 8 (3.5) |
| Vomiting | 17 (7.1) | 0 (0.0) | 33 (14.5) | 3 (1.3) |
| Anemia | 11 (4.6) | 1 (0.4) | 43 (18.9) | 4 (1.8) |
| Thrombocytopenia | 9 (3.8) | 4 (1.7) | 31 (13.7) | 16 (7.0) |
| Infusion-related reaction[c] | 1 (0.4) | 0 (0.0) | 43 (18.9) | 6 (2.6) |

## PFS

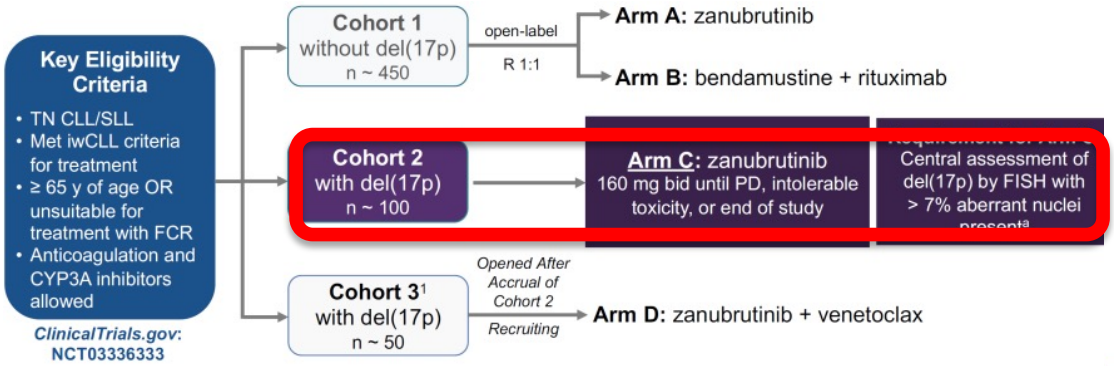



## PFS by IGHV

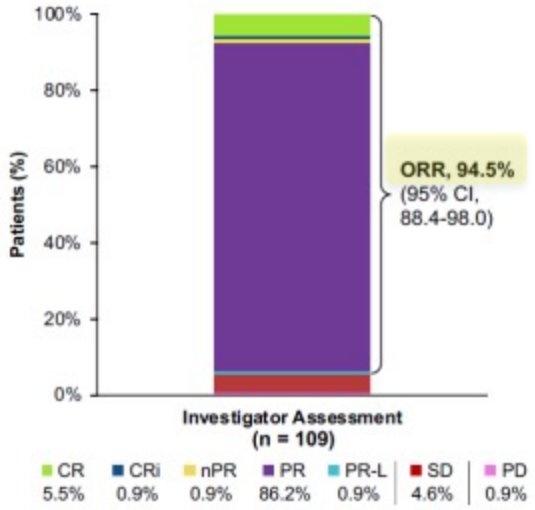


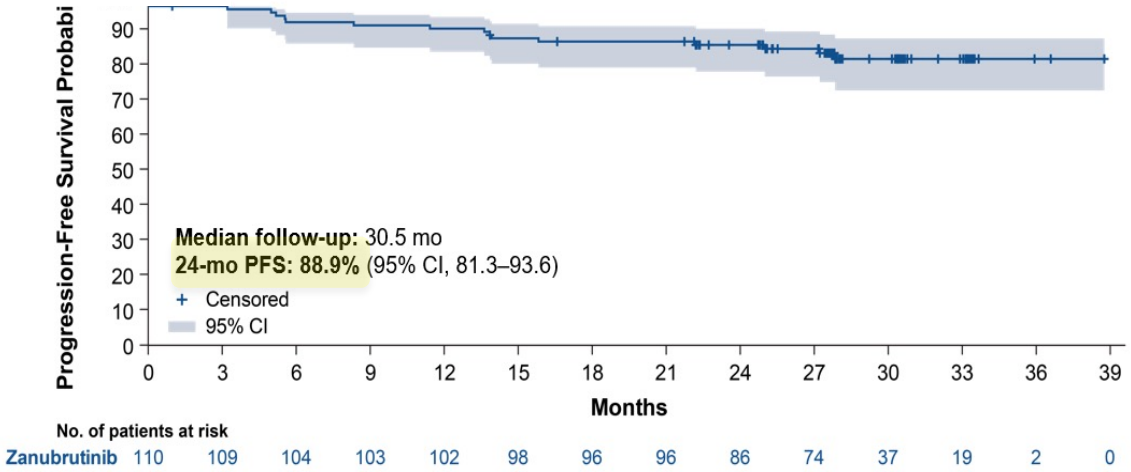

Tam et al., ASH 2021

# SEQUOIA TRIAL: 1L Zanubrutinib in patients with del (17p)



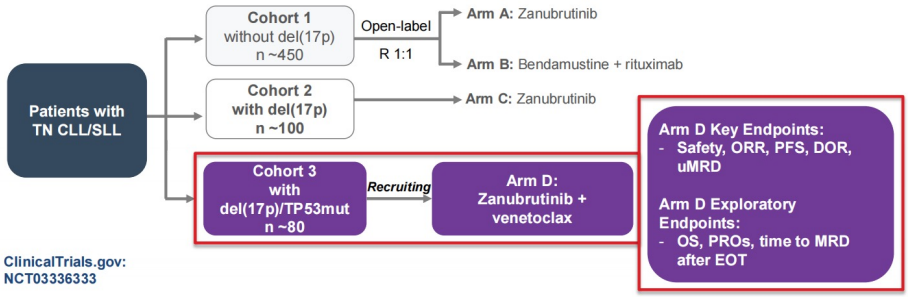

**109 TN patients with del(17p) CLL or SLL**

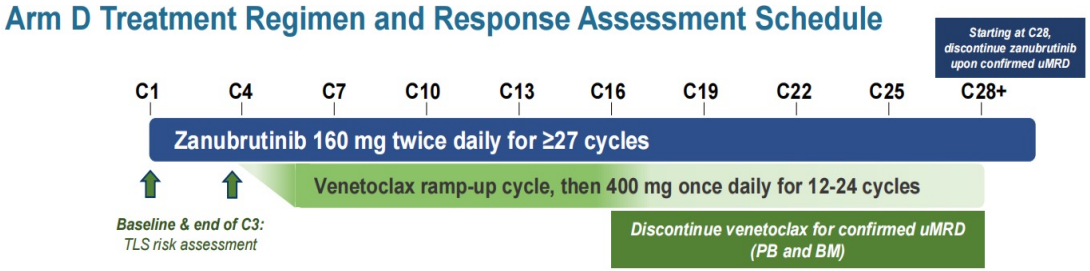



*Tam et al., ASH 2021; abstract 396*

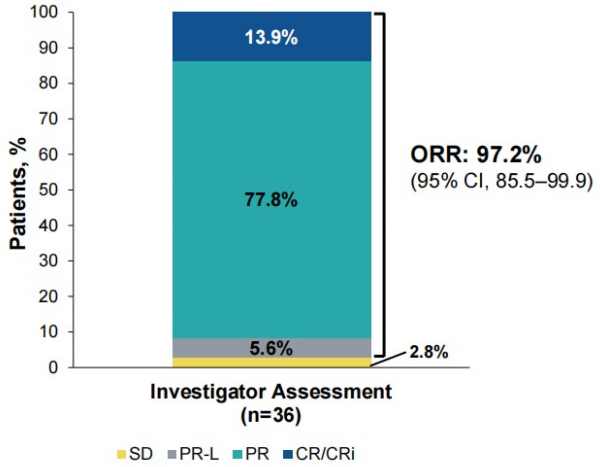
# SEQUOIA TRIAL: 1L Zanubrutinib+ Venetoclax in patients with del (17p)

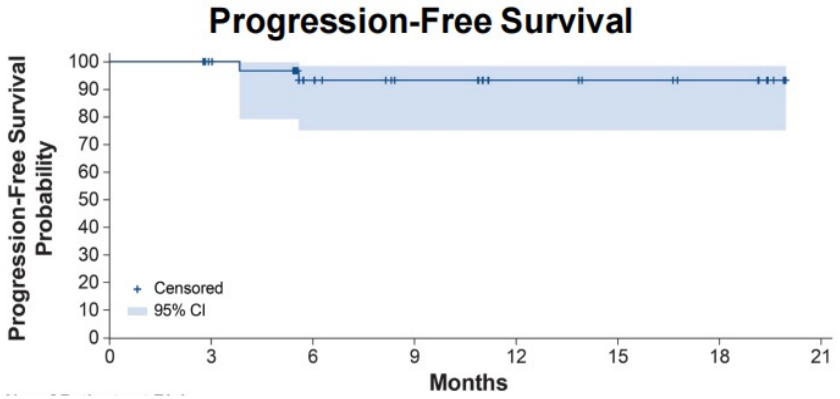



Median Follow-Up: 12.0 Months

| | n=49 |
|---|---|
| **Disease characteristics** | |
| del(17p) by central lab FISH, n (%) | |
| Positive | 46 (93.9) |
| Negative (eligible by local lab TP53 mutation) | 3 (6.1) |
| del(17p) percent of abnormal nuclei, median | 77.5 |
| del(13q), n (%) | 25 (51.0) |
| del(11q), n (%) | 1 (2.0) |
| Trisomy 12, n (%) | 11 (22.4) |
| Retrospective TP53 mutation,[a] n/N (%) | 34/37 (91.9) |
| IGHV mutational status, n (%) | |
| Unmutated | 43 (87.8) |
| Mutated | 6 (12.2) |
| Complex karyotype,[b] n/N (%) | |
| Non-complex (0–2 abnormalities) | 4/24 (16.7) |
| Complex (3 or more abnormalities) | 20/24 (83.3) |
| Complex (5 or more abnormalities) | 17/24 (70.8) |




*Tedeschi et al., ASH 2021*

# ALPINE TRIAL: Ibrutinib vs Zanubrutinib in Patients With R/R CLL

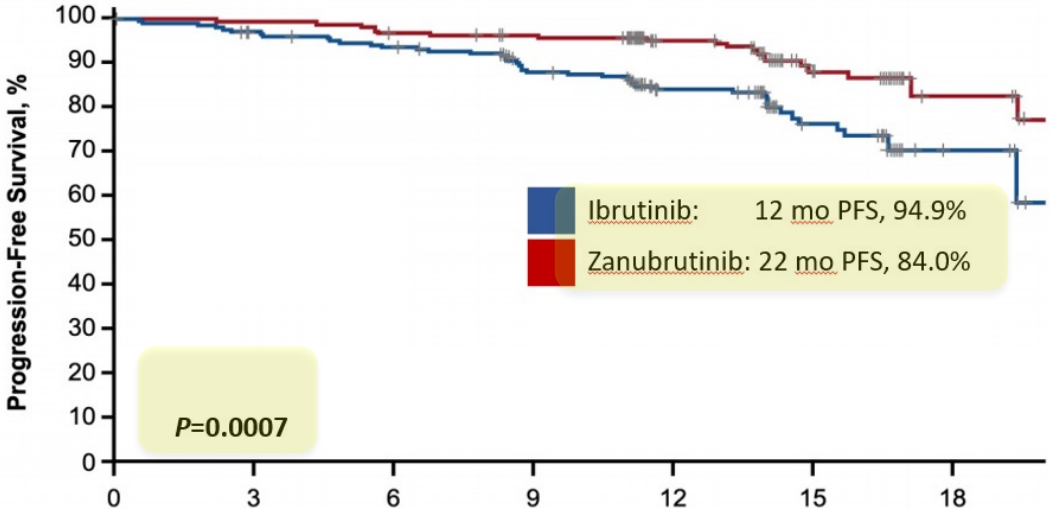
Ongoing randomized, multicenter phase III trial

Patients with CLL requiring treatment
R/R to ≥ 1 previous treatment
ECOG PS 0-2
Adequate organ function
No clinically significant cardiac disease
(planned N = 400)

**Ibrutinib** 420 mg PO QD

**Zanubrutinib** 160 mg PO BID

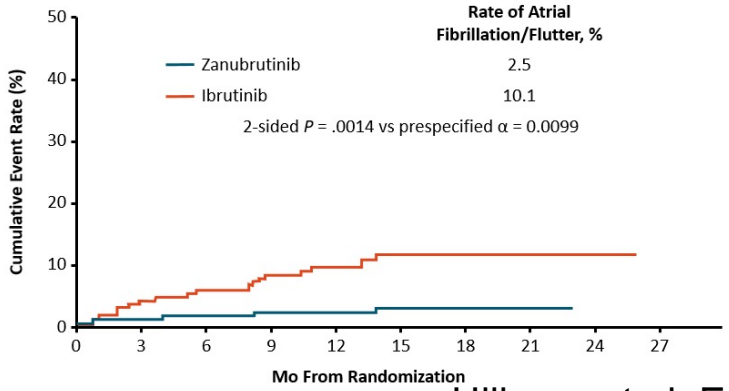
Until PD or unacceptable AE




## Response

| | Zanubrutinib (n=207), n (%) | Ibrutinib (n=208), n (%) |
|---|---|---|
| **Primary endpoint: ORR (PR+CR)** | 162 (**78.3**) | 130 (**62.5**) |
| | 95% CI: 72.0, 83.7 | 95% CI: 55.5, 69.1 |
| | Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099 | |

| 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) |




Hillmen et al. EHA 2021

HOT NEWS IN HEMATOLOGY
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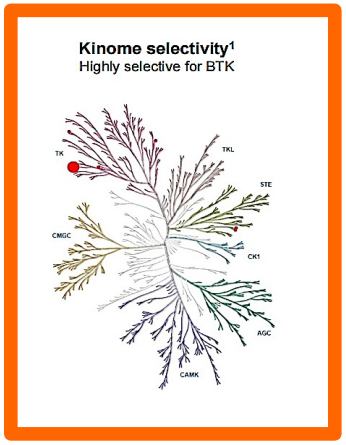
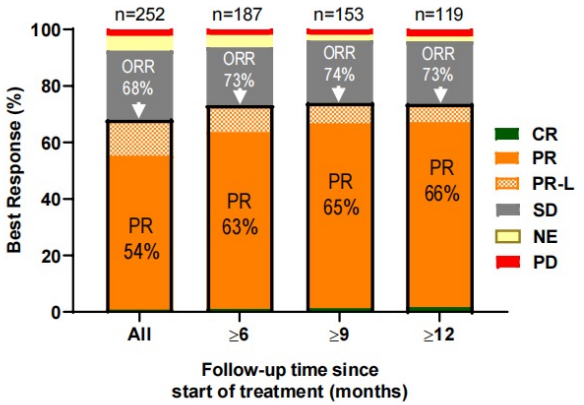
# PIRTOBRUTINIB IN R/R PATIENTS WITH CLL PREVIOUSLY TREATED WITH BTKI



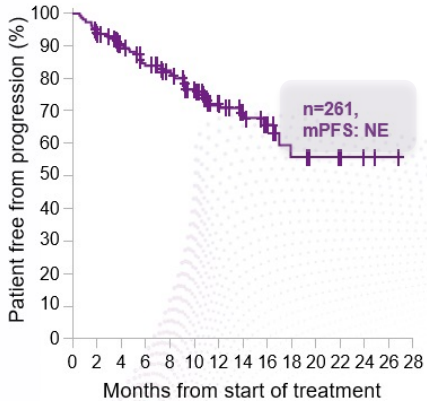

| Characteristics | N = 261 |
|---|---|
| Median age, years (range) | 69 (36-88) |
| Female, n (%) | 84 (32) |
| Male, n (%) | 177 (68) |
| ECOG PS[a], n (%) | |
| 0 | 138 (53) |
| 1 | 104 (40) |
| 2 | 19 (7) |
| Median number of prior lines of systemic therapy (range) | 3 (1-11) |
| Prior therapy, n (%) | |
| BTK inhibitor | 261 (100) |
| Anti-CD20 antibody | 230 (88) |
| Chemotherapy | 207 (79) |
| BCL2 inhibitor | 108 (41) |
| PI3K inhibitor | 51 (20) |
| CAR-T | 15 (6) |
| Stem cell transplant | 6 (2) |
| Allogeneic stem cell transplant | 5 (2) |
| Autologous stem cell transplant | 1 (<1) |
| Reason discontinued prior BTKi, n (%) | |
| Progressive disease | 196 (75) |
| Toxicity/Other | 65 (25) |

| Baseline Molecular Characteristics[a] | |
|---|---|
| Mutation status, n (%) | |
| BTK C481-mutant | 89 (43) |
| BTK C481-wildtype | 118 (57) |
| PLCG2-mutant | 33 (16) |
| High Risk Molecular Features, n (%) | |
| 17p deletion | 51 (28) |
| TP53 mutation | 64 (37) |
| 17p deletion or TP53 mutation | 77 (36) |
| Both 17p deletion and TP53 mutation | 38 (27) |
| IGHV unmutated | 168 (84) |
| 11q deletion | 45 (25) |

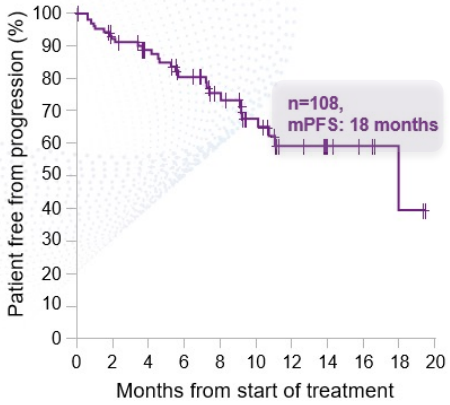
## Responses over time



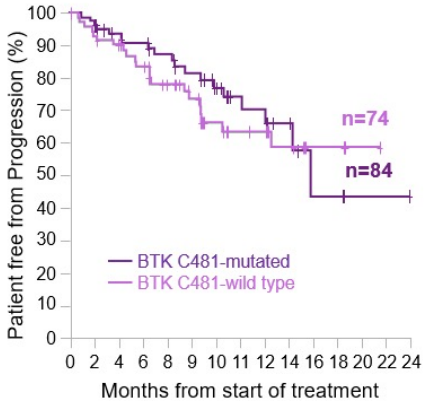

**PFS in BTKi pre-treated patients**
(median prior lines of therapy: 3)




**PFS in BTKi and BCL-2i pre-treated patients**
(median prior lines of therapy: 5)




**PFS by *BTK C481* mutation status* in patients with PD on a prior BTKi**




## Safety Profile

| | Treatment-emergent AEs, (≥15%), % | | | | |
|---|---|---|---|---|---|
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade |
| Fatigue | 13% | 8% | 1% | - | 23% |
| Diarrhea | 15% | 4% | <1% | <1% | 19% |
| Neutropenia[a] | 1% | 2% | 8% | 6% | 18% |
| Contusion | 15% | 2% | - | - | 17% |
| AEs of special interest[b] | | | | | |
| Bruising[c] | 20% | 2% | - | - | 22% |
| Rash[d] | 9% | 2% | <1% | - | 11% |
| Arthralgia | 8% | 3% | <1% | - | 11% |
| Hemorrhage[e] | 5% | 2% | 1%[g] | - | 8% |
| Hypertension | 1% | 4% | 2% | - | 7% |
| Atrial fibrillation/flutter[f] | - | 1% | <1% | <1% | 2%[h] |

Mato et al., EHA 2022

HOT NEWS IN HEMATOLOGY
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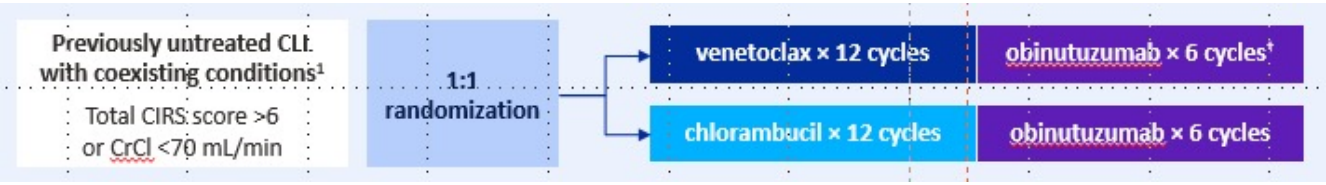
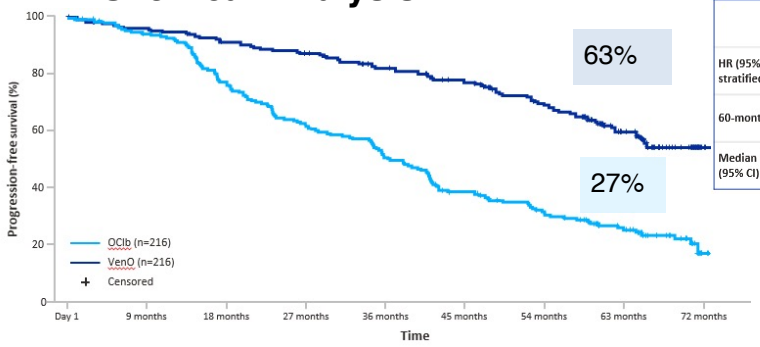
# VENETOCLAX+OBINUTUZUMAB IN TN PATIENTS WITH CLL ( CLL14 TRIAL): 5-YEAR FOLLOW-UP

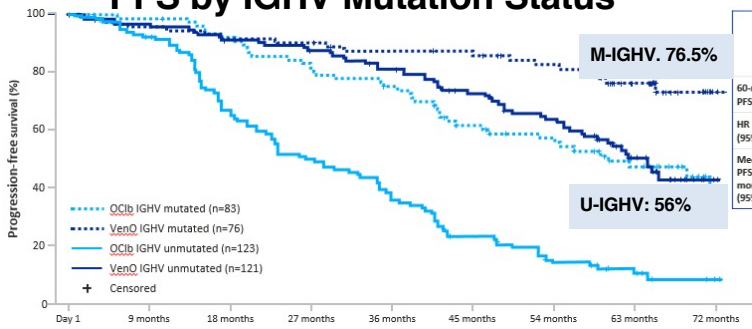



## PFS: 5-Year Analysis



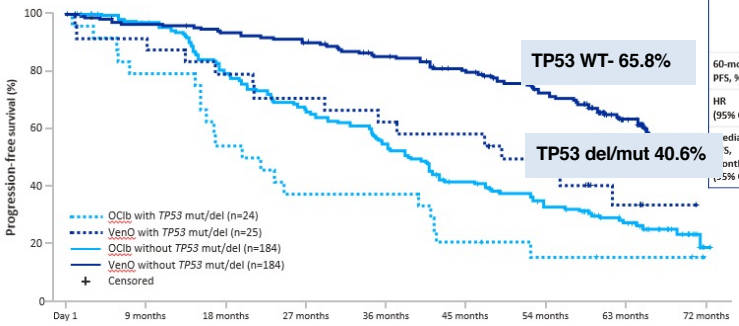

| | VenO (n=216) | OClb (n=216) |
|---|---|---|
| HR (95% CI), stratified p-value | 0.35 (0.26–0.46) p<0.0001 | |
| 60-month PFS, % | 63 | 27 |
| Median PFS, months (95% CI) | NR | 36.4 (34.1–41.0) |

## PFS by IGHV Mutation Status



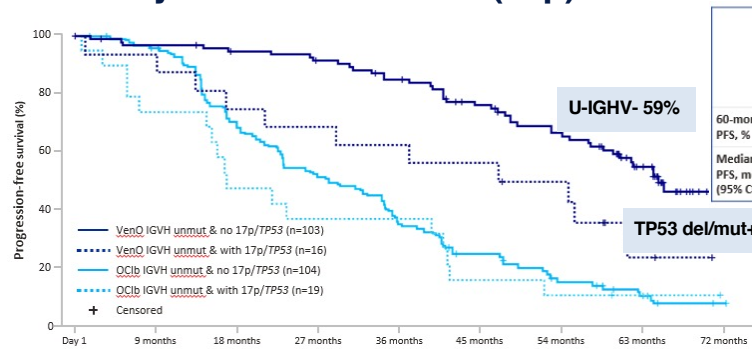

| | VenO IGHV mutated (n=76) | OClb IGHV mutated (n=83) | VenO IGHV unmutated (n=121) | OClb IGHV unmutated (n=123) |
|---|---|---|---|---|
| 60-month PFS, % | 76.5 | 49.7 | 55.8 | 12.5 |
| HR (95% CI) | 0.41 (0.23-0.73) | | HR 0.25 (0.17-0.36) | |
| Median PFS, months (95% CI) | NE (NE–NE) | 59.9 (46.0-NE) | 64.2 (57.0–NE) | 26.9 |

## PFS *TP53* Mutation Status




| | VenO TP53 mut/del (n=25) | OClb TP53 mut/del (n=24) | VenO no TP53 mut/del (n=184) | OClb no TP53 mut/del (n=184) |
|---|---|---|---|---|
| 60-month PFS, % | 40.6 | 15.6 | 65.8 | 49.0 |
| HR (95% CI) | 0.36 (0.14-0.88) | | HR 0.33 (0.24-0.45) | |
| Median PFS, months (95% CI) | 49.0 (29.0–NE) | 20.8 (15.2-40.9) | NR (65.4–NE) | 38.9 (34.7-42.0) |

## PFS by IGHV Unmut ± del(17p)/TP53 mut.




| | VenO IGHV unmutated & TP53 mut/del (n=16) | VenO IGHV unmutated no TP53 mut/del (n=103) | VenO (n=216) |
|---|---|---|---|
| 60-month PFS, % | 35.7 | 59.4 | 63 |
| Median PFS, months (95% CI) | 50.9 (21.1–61.4) | 64.8 (59.8–NE) | NR |

Al-Sawaf EHA 2022

# THE CLL13-GAIA TRIAL IN TN PATIENTS WITH CLL

**Fit patients with CLL N=926**

Select inclusion criteria:
CIRS ≤6 & normal CrCl*
Excludes:
del(17p)/*TP53*$^{mut}$

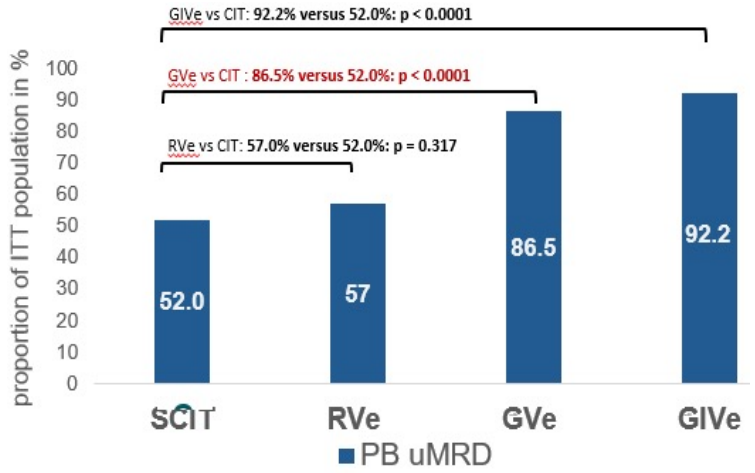
**Stratification factors:**
- Age
- Binet stage
- Country

**1:1:1:1 randomization**

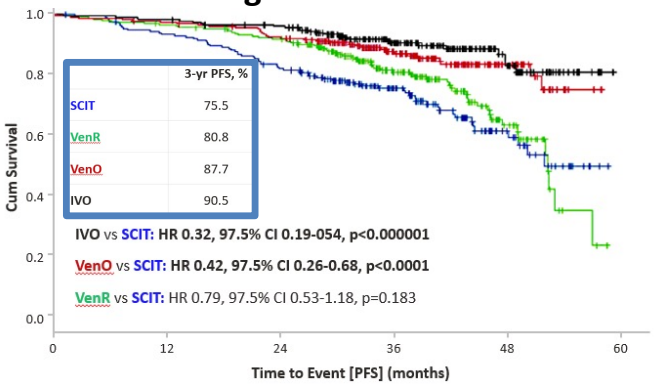
| | | |
|---|---|---|
| n=229 | CIT: FCR ≤65 yrs (n=150); BR >65 yrs (n=79) × 6 cycles | CIT |
| n=237 | Venetoclax 400 mg PO QD (ramp-up) × 12 cycles + Rituximab 375 (500) mg/m² IV × 6 cycles | R Ve |
| n=229 | Venetoclax 400 mg PO QD (ramp-up) × 12 cycles + Obinutuzumab 1,000 mg IV × 6 cycles | G Ve |
| n=231 | Venetoclax 400 mg PO QD (ramp-up) × 12 cycles + Ibrutinib 420 mg PO QD x 12 cycles up to cycle 36 if no uMRD + Obinutuzumab 1,000 mg IV × 6 cycles | GI Ve |

**Co-Primary Endpoints**
- uMRD (<10-4) in PB at month 15 (VenO vs CIT)
- PFS (IVO vs CIT)

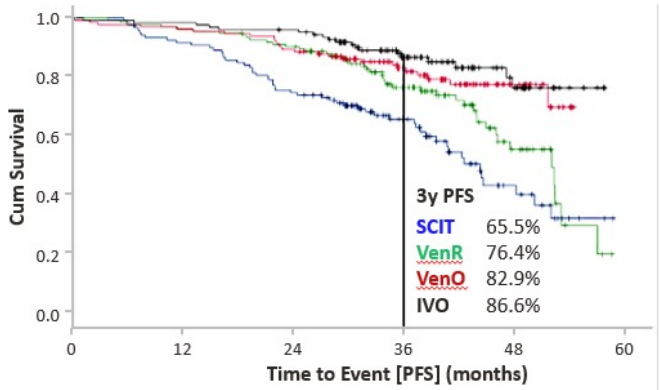
**Key Secondary Endpoints**
- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate
- OS



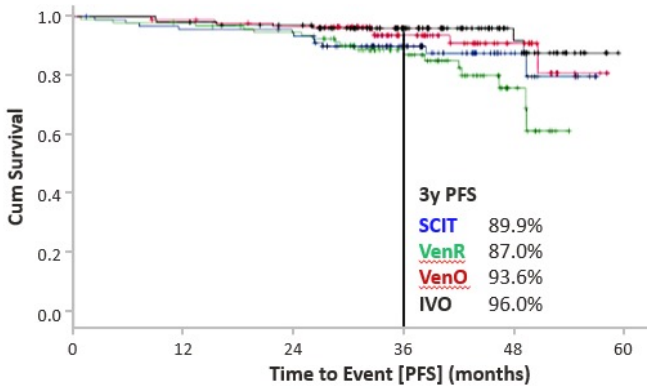

## PFS according to treatment arm




## Unmutated IGHV




## Mutated IGHV




SCIT — VenR — VenO — IVO

Eichhorst B, *et al.* EHA2022

# GLOW TRIAL: 1L Ibrutinib+Venetoclax vs Chlorambucil+Obinutuzumab

*Stratified by IGHV status, del(11q) presence*

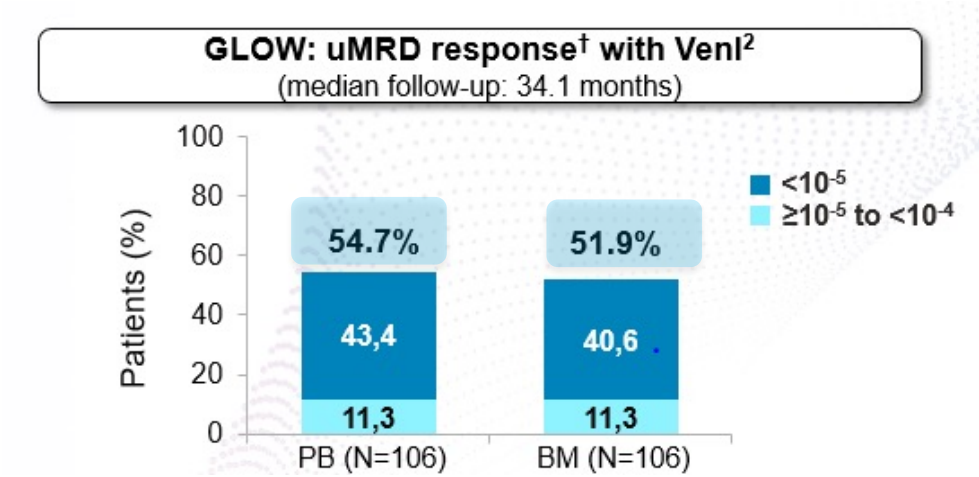
Patients with previously untreated CLL; aged ≥65 yr or <65 yr with CIRS >6 or CrCl <70 mL/min; no del(17p) or known *TP53* mutation; ECOG PS 0-2 (N = 211)

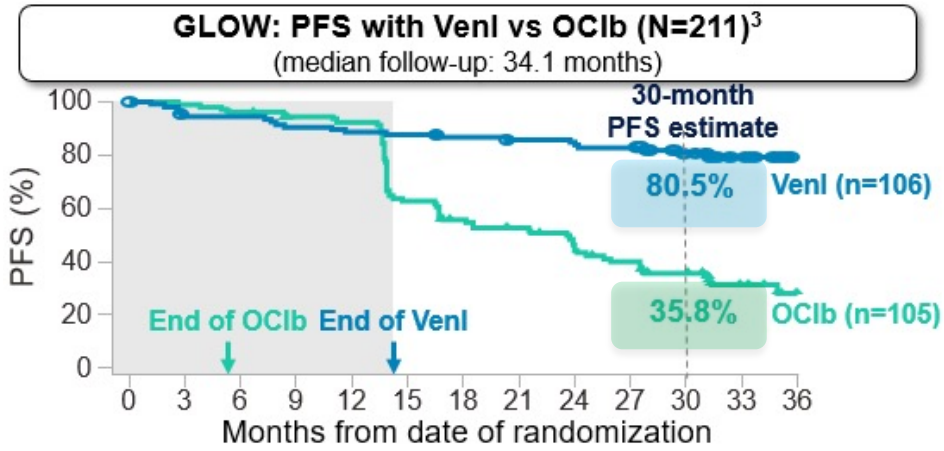
**Ibrutinib** 420 mg PO QD x 3 cycles followed by **Ibrutinib** + **Venetoclax*** 12 cycles (n = 106)

**Chlorambucil** 0.5 mg/kg on D1, 15 x 6 cycles + **Obinutuzumab** 1000 mg on D1-2, 8, 15 of cycle 1 and D1 of cycles 2-6 (n = 105)

*Ramp-up from 20 to 400 mg over 5 wks starting in cycle 4.

| Characteristic, % | Ibr + Ven | Clb + O | RR |
|---|---|---|---|
| Age, ≥65 yr | 52.2 | 17.0 | 3.07 |
| Rai stage III-IV | 50.9 | 15.1 | 3.37 |
| IGHV unmutated | 58.2 | 14.8 | 3.93 |
| del11q | 60.0 | 11.1 | 5.40 |

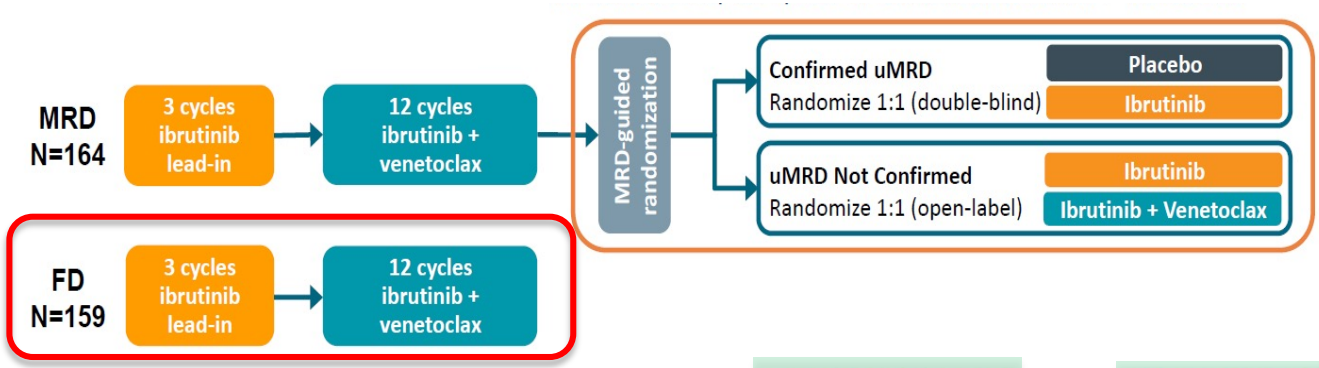


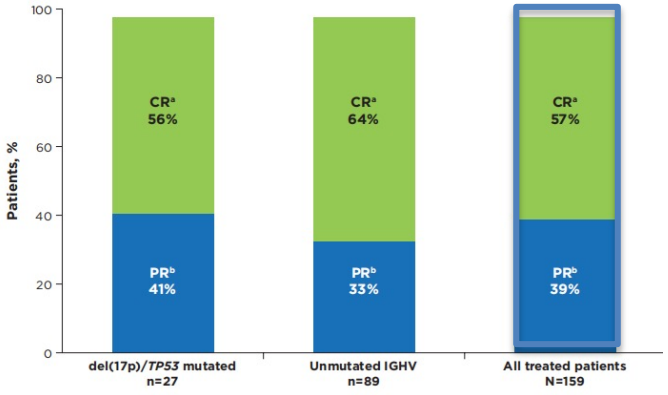

Deep responses observed in both BM and PB in patients with uIGHV

Munir. ASH 2021

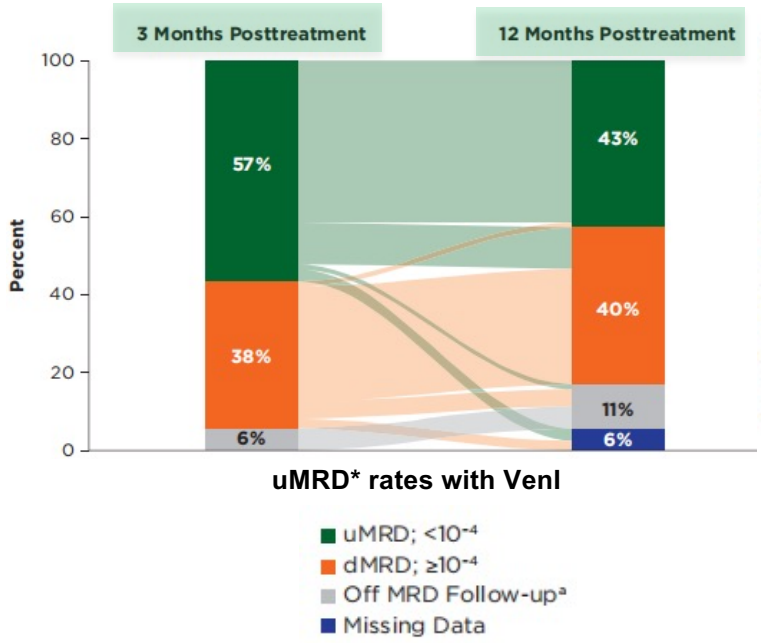
# CAPTIVATE TRIAL-: **1L** ibrutinib plus venetoclax- FD cohort, 3-year follow-up



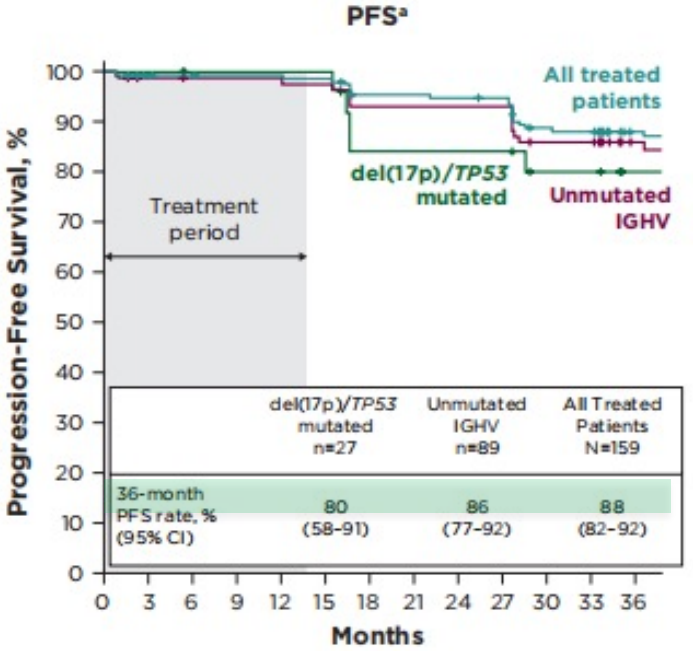

| Characteristic | All Treated Patients (n = 159) |
|---|---|
| Median age, yr (range) | 60 (33-71) |
| High-risk features, n (%) | |
| ▪ Unmutated *IGHV* | 89 (56) |
| ▪ del(17p)/*TP53* mutation | 27 (17) |
| ▪ del(17p) | 20 (13) |
| ▪ del(11q)* | 28 (18) |
| ▪ Complex karyotype† | 31 (19) |




**Response rates with Ven I**




**uMRD* rates with VenI**




Ghia. et al., ASCO 2021; Moreno et al., EHA 2022

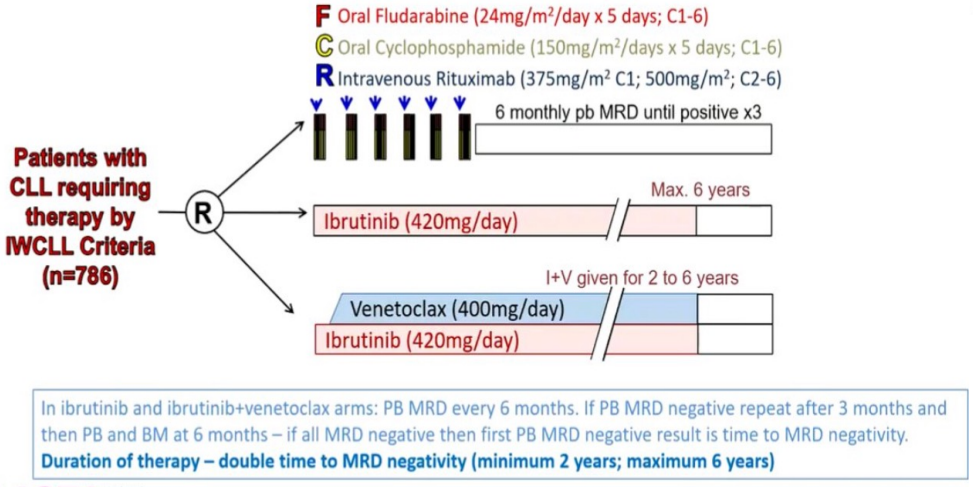
# 1L IBRUTINIB+ VENETOCLAX: INTERIM ANALYSIS OF THE PHASE III NCRI FLAIR TRIAL

FLAIR randomized trial ibrutinib vs. ibrutinib+venetoclax.

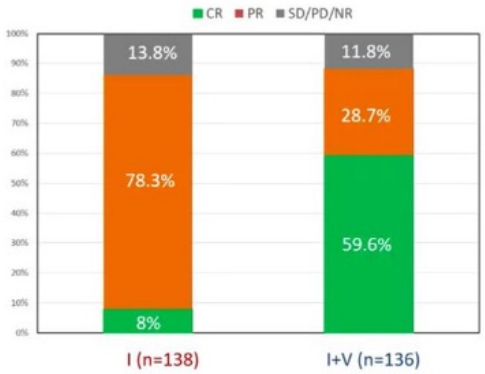
- Pts <75 yrs or with <20% 17p
- Duration of therapy defined by MRD with treatment for up to 6 years.
- The earliest therapy could stop was 2 years post-randomisation

MRD assessed centrally by FC in PB and BM

Interim analysis in the first 274 pts
(I [n=138] and I+V [n=136]) reaching 2 yrs post-randomisation.

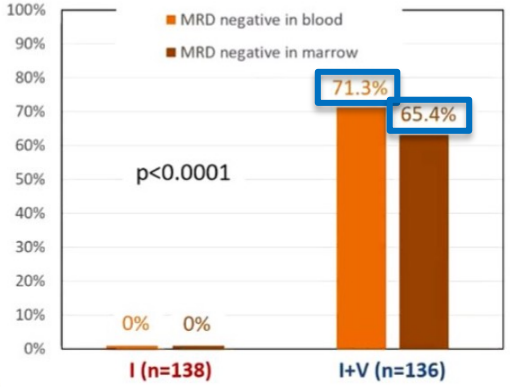



## iwCLL Response at 9 months




| | I (n=138) | I+V (n=136) |
|---|---|---|
| ORR | 119 (86.2%) | 120 (88.2%) |
| CR | 11 (8.0%) | 81 (59.6%) |

## Primary endpoint: uMRD at 2 years




| N (%), Exact 95% CI | I (n=138) | I+V (n=136) |
|---|---|---|
| MRD Negative in the marrow | 0 [0%, 2.64%] | 89 (65.4%) [56.81%, 73.38%] |
| MRD Negative in the blood | 0 [0%, 2.64%] | 97 (71.3%) [62.95%, 78.75%] |

- MRD assessed by 8-colour flow cytometry
- MRD negative defined by IWCLL criteria of <1 CLL cell in 10,000 leucocytes

Hillmen et al., EHA 2022

# CLL: HOT NEWS- SUMMARY

- Long term responses with ibrutinib single agent
- Second-generation and investigational BTKis offer higher selectivity with the improved safety profile and outcomes
- Pirtobrutinib improved outcomes and efficacy in patients with BTKi-resistant CLL
- Venetoclax and BTKi combinations produce deep responses further improves PFS outcomes