# Esistono criteri di come selezionare la strategia terapeutica paziente-specifico?

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*Milano*

LEUCEMIA LINFATICA CRONICA:
L'INNOVATIVITÀ TERAPEUTICA ED OLTRE...

28-29 MARZO 2023 BOLOGNA ROYAL HOTEL CARLTON

# BTK continuous Tx

**Ibrutinib, acalabrutinib, zanubrutinib**

# Fixed duration tx

**Venetoclax plus Obinutuzumab**

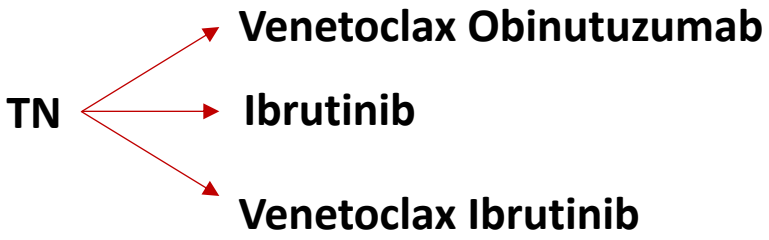
## No head to head comparison

***Approximately 75% 4 y PFS in RCT***

***Depends on***

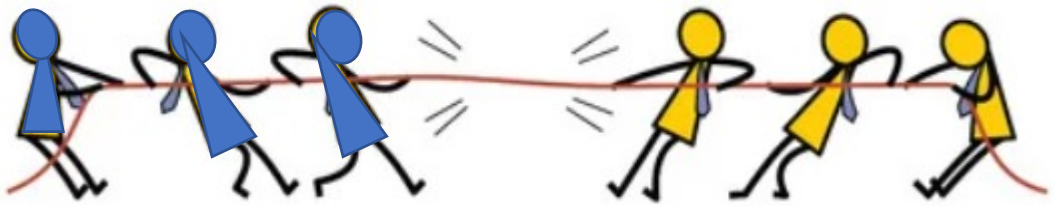
***Disease genetic charcateristics***

**CLL 17 DEFINITIVE RESPONSE**



# IN THE MEANWHILE?

BTK



Venetoclax
obinutuzumab

**ADVISORY BOARD: 12 Hematologists**

**IGHV MUTATED** → **Venetoclax Obinutuzumab (age independent): 9**

→ **BTKi in the very elderly/ Venetoclax Obinutuzumab in the younger: 3**

**IGHV UNMUTATED** → **BTKi (age independent): 6**

**BTKi in the very elderly /Venetoclax Obinutuzumab in the younger 6**

**Del 17 p** → **BTKi: 10**

→ **Venetoclax Obinutuzumab: 2**

## Patients

- Age

- Comorbidities
- Concomitant medications

- Logistics (care givers)

## Disease characteristics matters

Del17p/Tp53mu

IgHV mutational status

Bulky disease

## BTK continuous Tx

Ibrutinib, acalabrutinib, zanubrutinib

## Fixed duration tx

Venetoclax Obinutuzumab

*…….Patient's opinion……..?*

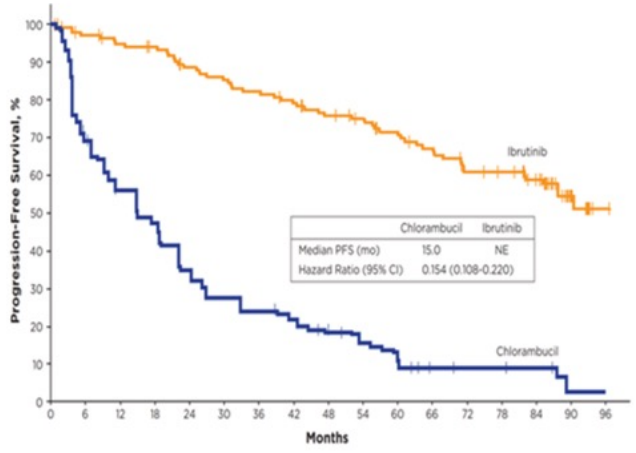
# BTK continuous Tx

**Ibrutinib, acalabrutinib, zanubrutinib**

## Efficacy

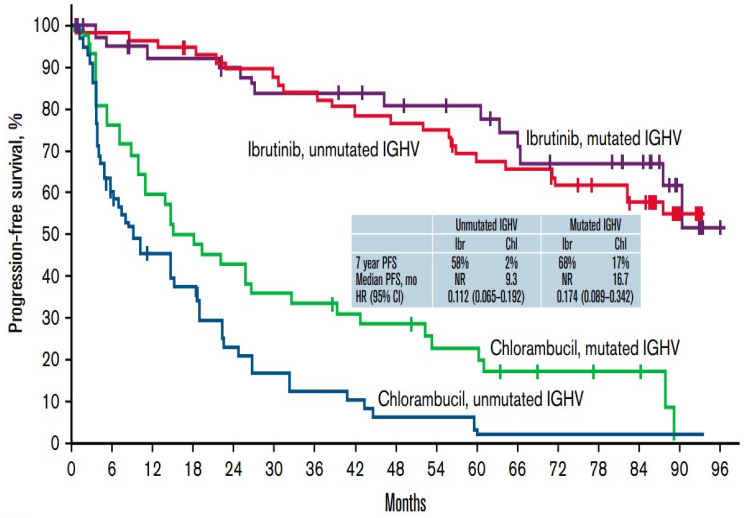
### Prolonged PFS

**Resonate 2 Ibrutinib vs Chl**



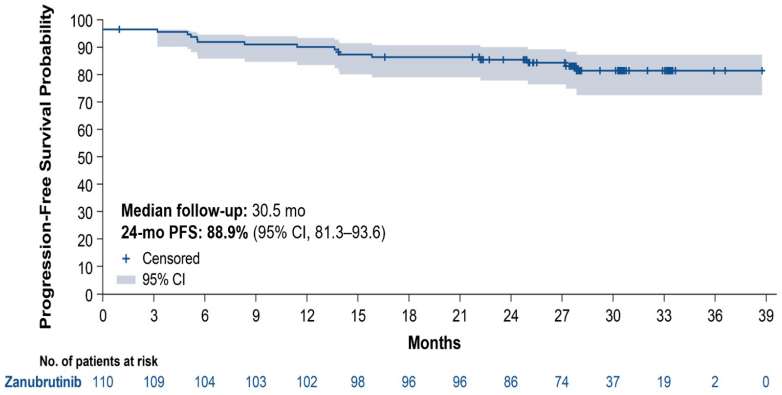

### PFS independent from IGHV status

**Resonate 2 Ibrutinib vs Chl**




### Prolonged PFS in del17p del

**SEQUOIA arm C: Zanubrutinib**




Barr et al, 2022
Tam et al, 2022

# BTK continuous Tx: Ibrutinib Clinical Trials

## Age impact

### *Indirect Comparison arm IR E1912 and Alliance*

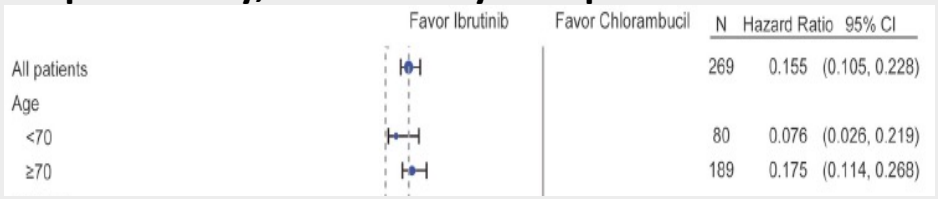
| Grade 3+ AE | IR Arm E1912[1] Median age 57 y | IR Alliance[2] Median age 71 y |
|---|---|---|
| Infection | 8% | 20% |
| Atrial fibrillation | 3% | 6% |
| Bleeding | 1% | 4% |
| Hypertension | 19% | 34% |
| Deaths during active treatment +30 days | 1% | 7% |

[1]Shanafelt et al 2019; [2]Woyach et al 2018

### RESONATE-2 Burger et al, NEJM 2015, Leukemia 2019

*Chlorambucil vs Ibrutinib*

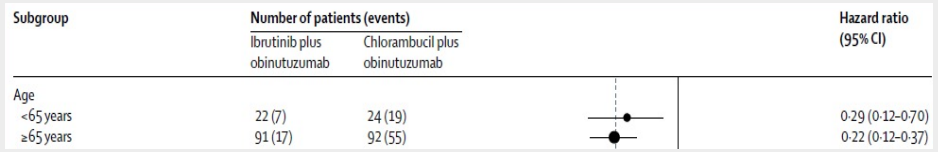
- Age ≥65 years
- For pts 65-70 y, comorbidity that preclude FCR




### Illuminate Moreno et al, Lancet 2019

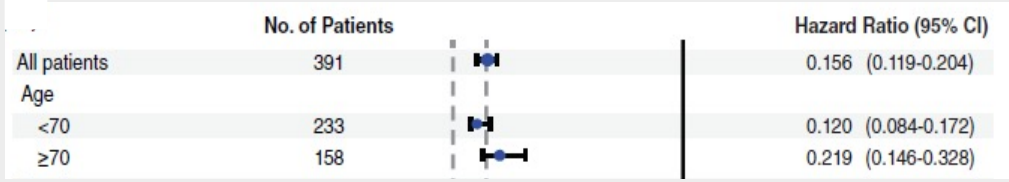
*Chlorambucil+Obin. vs Ibrutinib+Obin*

- Age ≥65 years
- Age < 65 if CIRS > 6 and/or CrCl< 70ml/min




### Resonate Munir et al, AJH 2019

*Ofatumumab vs ibrutinib*



# BTK continuous Tx: Ibrutinib Clinical Trials

## Comorbidities

### E1912 Ibrutinib + Rituximab vs FCR in Younger Patients With Previously Untreated CLL Update Median Follow-up 48 months

- 73% patients randomized to Ibrutinib + R remained on treatment (median: 43 mos)
- In 95 pts discontinuing Ibrutinib, median time on treatment was 20.3 mos
- Causes of Ibrutinib discontinuation:

  PD or death in 23 pts (7%), AEs in 48 pts (14%), other reasons in 24 pts (7%)

- 72 pts discontinuing Ibrutinib for reasons other than PD or death
  - Median PFS: 22.5 mos
  - Median time of therapy: 15.1 mos

➡ CIRS score predicted Ibrutinib discontinuation other than PD or death: (HR, 1.13 per each unit increase; 95% CI, 1.03-1.23; *P* = .009).

Shanafelt et al 2022

# BTK continuous Tx: Ibrutinib in common practice

## Age impact

Do age, fitness, and concomitant medications influence management and outcomes of patients with CLL treated with ibrutinib?

Alessandra Tedeschi,[1] Anna Maria Frustaci,[1] Francesca Romana Mauro,[2] Annalisa Chiarenza,[3] Marta Coscia,[4] Stefania Ciolli,[5] Gianluigi Reda,[6] Luca Laurenti,[7] Marzia Varettoni,[8] Roberta Murru,[9] Claudia Baratè,[10] Paolo Sportoletti,[11] Antonino Greco,[12] Chiara Borella,[13] Valentina Rossi,[14] Marina Deodato,[1] Annalisa Biagi,[15] Giulia Zamprogna,[1] Angelo Curto Pelle,[3] Gianfranco Lapietra,[2] Candida Vitale,[4] Francesca Morelli,[5] Ramona Cassin,[6] Alberto Fresa,[7] Chiara Cavalloni,[8] Massimiliano Postorino,[15] Claudia Ielo,[2] Roberto Cairoli,[1] Francesco Di Raimondo,[3] Marco Montillo,[1] and Giovanni Del Poeta[15]

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blood advances

Comorbidities did not independently influence Ibrutinib management

**Table 3. Cox proportional regression hazards model of factor on PFS, EFS, OS, Tox-DTD, and PDR**

| | PFS | | EFS | | OS | | Tox-DTD | | PDR | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age | 0.82 (0.57-1.18) | .296 | 0.83 (0.59-1.15) | .254 | 0.85 (0.54-1.35) | .496 | 0.91 (0.53-1.54) | .722 | 0.73 (0.45-1.18) | .201 |
| ECOG-PS | 2.43 (1.72-3.42) | <.001 | 2.63 (1.92-3.61) | <.001 | 3.90 (2.61-5.85) | <.001 | 3.30 (2.09-5.20) | <.001 | 1.52 (0.91-2.55) | .112 |
| CIRS6 | 1.48 (1.02-2.15) | .037 | 1.44 (1.03-2.00) | .033 | 1.01 (0.63-1.62) | .964 | 1.33 (0.80-2.21) | .270 | 1.12 (0.70-1.81) | .638 |
| CIRS3$^{+}$ | 0.79 (0.52-1.19) | .261 | 1.03 (0.71-1.48) | .894 | 0.95 (0.58-1.56) | .844 | 1.54 (0.94-2.51) | .084 | 1.72 (1.08-2.75) | .024 |
| CCI | 1.10 (0.71-1.72) | .662 | 1.19 (0.79-1.78) | .416 | 1.37 (0.75-2.52) | .306 | 1.53 (0.72-3.25) | .268 | 3.88 (1.50-10.06) | .005 |
| Neutropenia | 1.70 (1.09-2.67) | .020 | 1.51 (1.001-2.27) | .049 | 1.72 (1.01-2.91) | .044 | 1.83 (1.04-3.22) | .038 | 1.08 (0.57-2.02) | .814 |
| CYP3A4 | 1.07 (0.66-1.76) | .780 | 1.26 (0.82-1.94) | .285 | 1.09 (0.59-2.03) | .784 | 1.15 (0.59-2.25) | .670 | 2.05 (1.24-3.41) | .005 |
| del(17p) and/or *TP53*$^{mut}$ | 2.19 (1.57-3.04) | <.001 | 1.78 (1.32-2.40) | <.001 | 2.06 (1.35-3.15) | <.001 | 1.59 (0.98-2.57) | .059 | 0.94 (0.60-1.48) | .800 |
| Lines of previous Tx | 1.85 (1.17-2.95) | .009 | 1.65 (1.10-2.48) | .015 | 2.73 (1.33-5.60) | .006 | 1.80 (0.97-3.34) | .064 | 1.32 (0.79-2.22) | .289 |

# BTK continuous Tx: Ibrutinib

## PFS impact

Do age, fitness, and concomitant medications influence management and outcomes of patients with CLL treated with ibrutinib?

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blood advances

CIRS >6 was confirmed as a predictor of poorer PFS and EFS

Baseline ECOG-PS was the most accurate predictor of ibrutinib feasibility and outcomes

**Table 3. Cox proportional regression hazards model of factor on PFS, EFS, OS, Tox-DTD, and PDR**

| | PFS | | EFS | | OS | | Tox-DTD | | PDR | |
|---|---|---|---|---|---|---|---|---|---|---|
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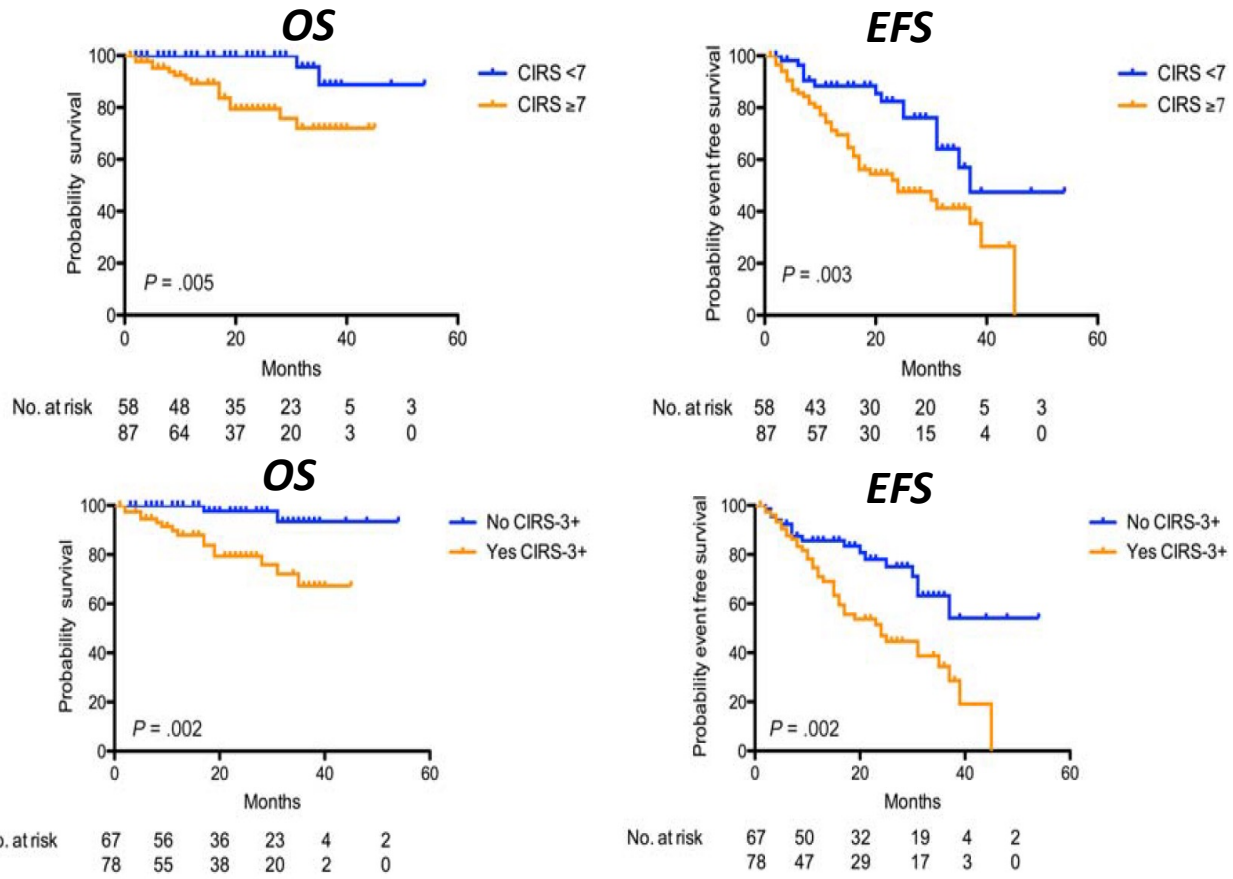
# BTK continuous Tx: Ibrutinib in common practice

## Comorbidities




| | Median EFS, % | *P* | Median OS, % | *P* |
|---|---|---|---|---|
| Age < 65 y | | | | |
| CIRS: ≥ 7 (n = 29) vs < 7 (n = 14) | 57 vs 83 | .08 | 63 vs 100 | .005 |
| CIRS-3+: yes (n = 26) vs no (n = 17) | 57 vs 91 | .01 | 70 vs 100 | .03 |
| Age ≥ 65 y | | | | |
| CIRS: ≥ 7 (n = 29) vs < 7 (n = 73) | 45 vs 75 | .11 | 83 vs 100 | .10 |
| CIRS-3+: yes (n = 41) vs no (n = 61) | 43 vs 68 | .10 | 82 vs 96 | .02 |

Gordon et et al, 2018

# Not all the comborbidities are the same!

## When BTKi should be avoided

BTKis **NOT** recommended for patients with:

- History of ventricular arrhythmia
  - Family history of sudden cardiac death
- Severe, uncontrolled HTN
- Severe or uncontrolled congestive heart failure (LVEF <30%)

Awan, Blood Adv 2022

# Ventricular arrhythmias and sudden death events following acalabrutinib initiation

Bhat et al Blood. 2022

***290 consecutive pts treated with acalabrutinib for B-cells malignancies (89% for CLL) between 2014 and 2020 Median age:***

***64 years***

***Over a median follow-up of around 42 months:***

***10 patients developed symptomatic ventricular tachyarrhythmias***

***including 1 sudden death/ ventricular fibrillation, and 1 recurrent sustained ventricular tachycardia.***

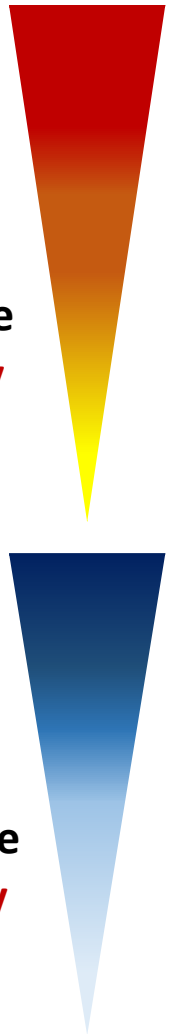
**Taken together, these initial data on second-generation BTK suggest a class effect also for ventricular tachyarrhythmias, to be confirmed by larger trials and real-world registries. As known, no trial has been powered for these events, and therefore, any conclusive consideration appears premature**

Boriani et al 2022

**In conclusion, it is vital that patients and caregivers be aware of the severe cardiotoxicity associated with ibrutinib and also with the second-generation BTKi acalabrutinib. Consideration of cardiovascular adverse effects is an important decision-making tool for selecting treatment for CLL, even in a regimen based on acalabrutinib.**

**Langerbeins P et al 2022**

# BTKi: concomitant use of interfering drugs

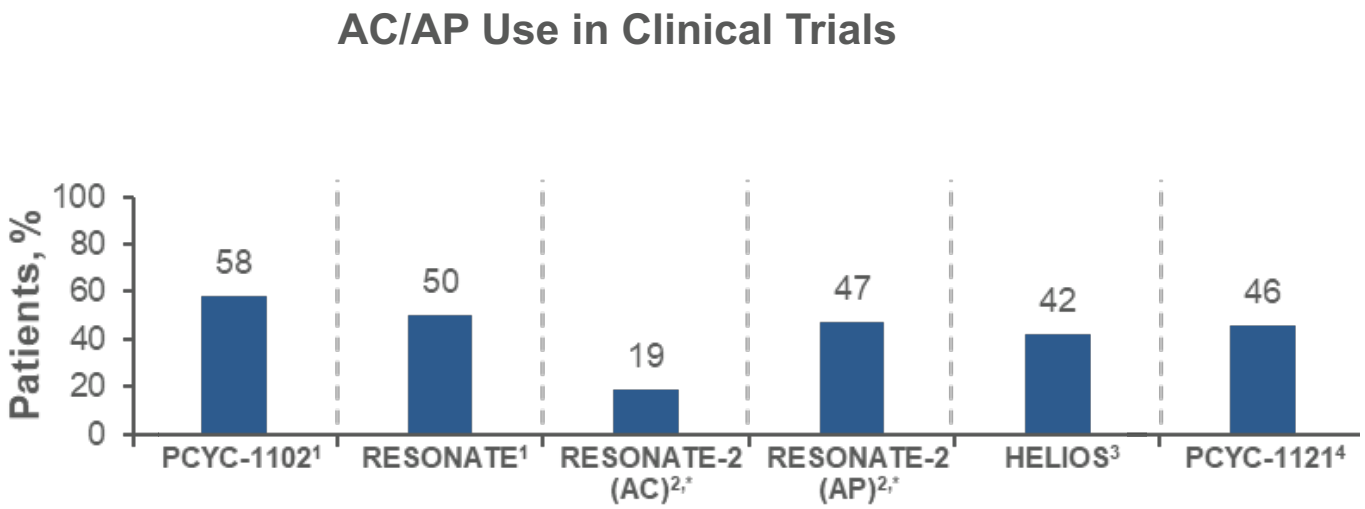



| | Ibrutinib[1] | Acalabrutinib[3] | Zanubrutinib[2] |
|---|---|---|---|
| **Strong CYP3A inhibitors** | Interrupt dose or temporary stop | Interrupt dose or temporary stop | May be ↓ 80 mg qd |
| **Moderate CYP3A inhibitors** | ↓ to 280 or 140 mg (low dose posa or voric) or 70 mg (high dose posa), qd | ↓ to 100 mg qd | ↓ 80 mg, bid |
| **Mild CYP3A inhibitors** | No changes | No changes | No changes |
| **Strong CYP3A inducers** | Avoid concomitant use | Increase dose to 200 mg approximately every 12 hrs | Avoid concomitant use |
| **Moderate and mild CYP3A inducers** | No indications, clinical judgment | No indications, clinical judgment | No indications, clinical judgment |

*[1]IMBRUVICA (ibrutinib) Prescribing Information 2013; [2]CALQUENCE (acalabrutinib). Prescribing Information, 2019; [3]BRUKINSA (zanubrutinib) Prescribing Information, 2021*

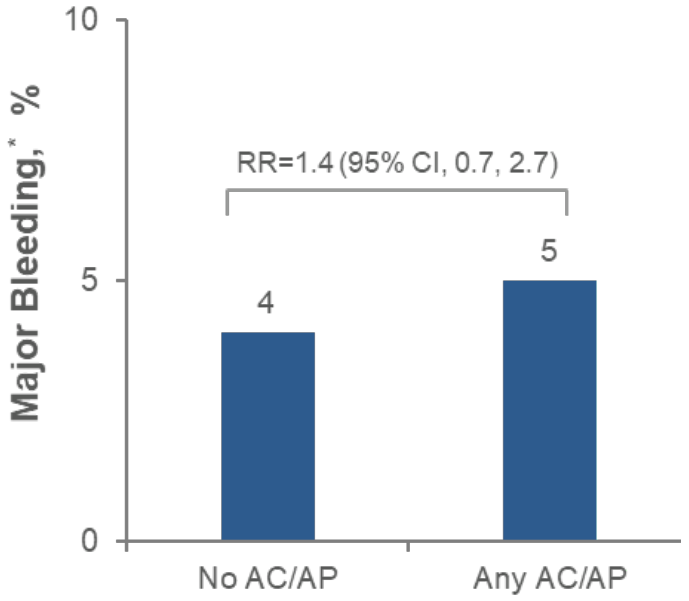
# Anticoagulant/Antiplatelet Use in Clinical Trials

## Concomitant use of ACs/APs was common in ibrutinib clinical studies




**Anticoagulants or antiplatelet agents were used in approximately 50% of patients in ibrutinib trials**

## Occurrence of Bleeding According to Antiplatelet/Anticoagulant Use




**AC/AP use did not significantly increase risk of major bleeding in the ibrutinib group**

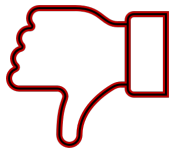
*Only for patients who received ibrutinib.

Abbreviations: AC, anticoagulant; AP, antiplatelet. 1. Jones JA et al. *Br J Haematol.* 2017;178(suppl):286-291. 2. Tedeschi A et al. ASH 2015 *[oral presentation]*. Abstract #495. 3. Cramer P et al. iwCLL/SLL 2015 *[oral presentation* 4. Noy A et al. *Blood.* 2017;129:2224-2232.

# BTK continuous Tx

**Ibrutinib, acalabrutinib, zanubrutinib**

- ✓ **EFFECTIVE**
  - **PFS independent from IGHV status**
  - **Prolonged PFS in del17p del**
- ✓ **FEASIBLE IN ALL AGES**
- ✓ **EASY TO DELIVER**
  **NO INTENSIVE EARLY MONITORING**
  **(TLS ONLY CASE REPORTS)**
  **EASY LOGISTICS**



- **SEVERE CARDIOLOGICAL COMORBIDITIES**

- **NEED OF CONCOMITANT:**
  - **POTENT CYP3A4 INDUCERS**
  - **POTENT CYP3A4 INHIBITORS**

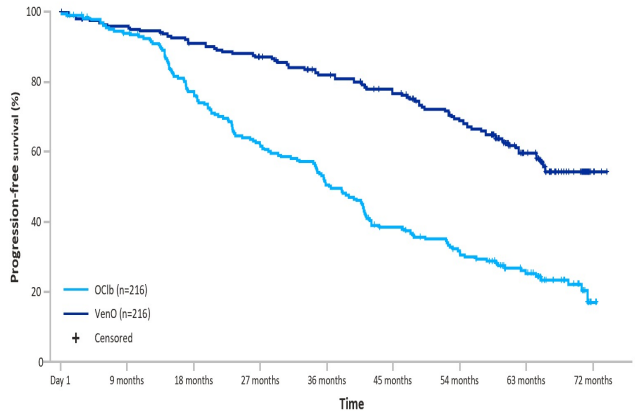
- ✓ **CIRS MAY HAVE AN IMPACT (SPECIFIC SCORE NEEDED, WHICH COMORBIDITIES?)**

# Fixed duration tx

## Efficacy

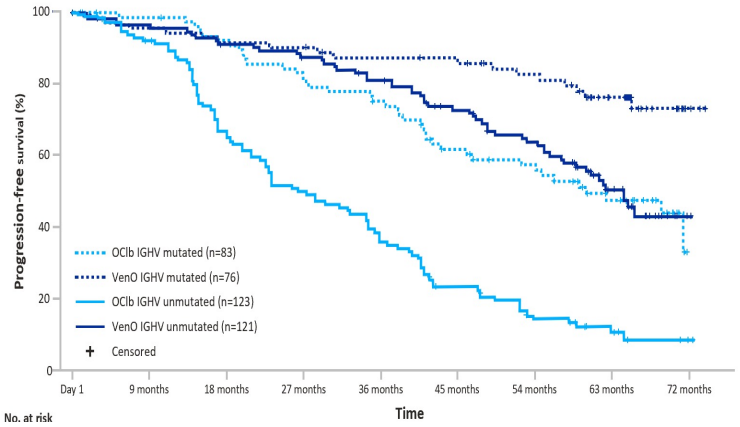
## CLL 14 Venetoclax Obinutuzumab vs Chlorambucil Obinutuzumab

### Prolonged PFS




| | VenO (n=216) | OClb (n=216) |
|---|---|---|
| Events, n (%) | 80 (37.0) | 150 (69.4) |
| 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 according to IGHV status



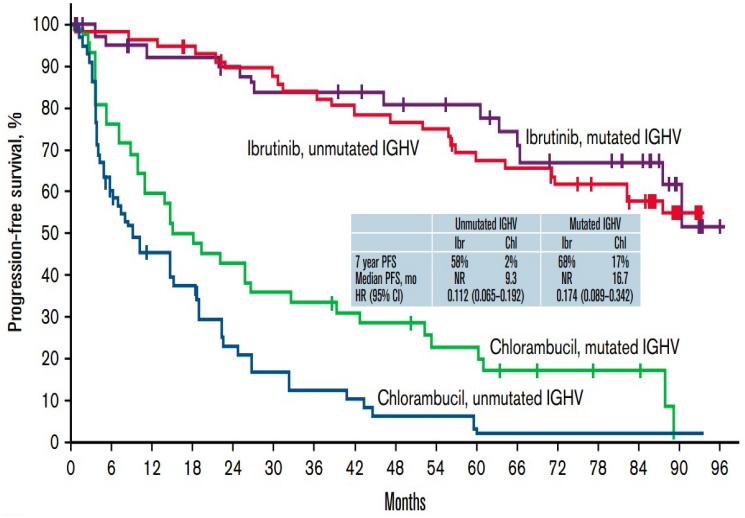

| | VenO IGHV mutated (n=76) | OClb IGHV mutated (n=83) | VenO IGHV unmutated (n=121) | OClb IGHV unmutated (n=123) |
|---|---|---|---|---|
| Events, n (%) | 17 (22.4) | 40 (48.2) | 55 (45.5) | 100 (81.3) |
| 60-month PFS, % | 76.5 | 49.7 | 55.8 | 12.5 |
| HR (95% CI) | 0.41 (0.23-0.73) | | HR 0.25 (0.17-0.36) | |
| Median PFS, months (95% CI) | NE (NE–NE) | 59.9 (46.0-NE) | 64.2 (57.0–NE) | 26.9 |

Al Sawaf et al 2022

# PFS in IGHV unmutated pts

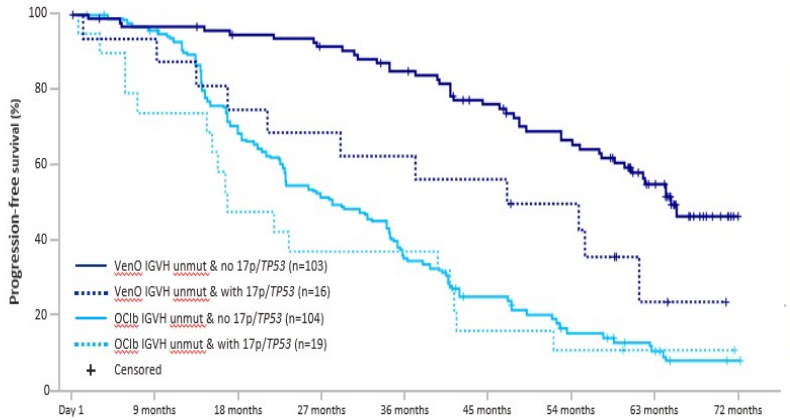
## PFS

### Resonate 2 Ibrutinib vs Chl



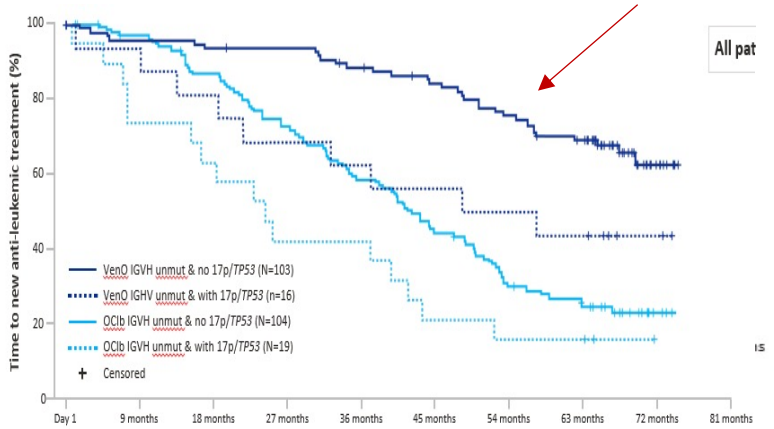

## CLL 14 Ven O vs Chl O

### PFS IGHV Unmut ± del(17p)/*TP53m*




| | VenO IGHV unmutated & *TP53* mut/del (n=16) | VenO IGHV unmutated no *TP53* mut/del (n=103) | VenO (n=216) |
|---|---|---|---|
| Events, n (%) | 11 (68.8) | 43 (41.7) | 80 (37.0) |
| 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 |

### TTNT IGHV Unmut ± del(17p)/*TP53m*



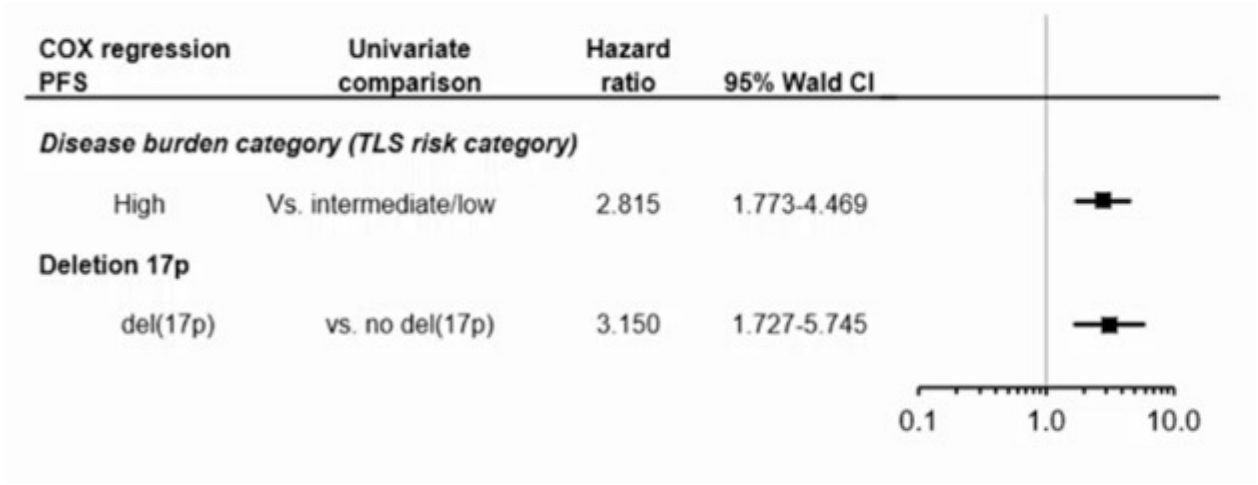

| | VenO IGHV unmutated & *TP53* mut/del (n=16) | VenO IGHV unmutated no *TP53* mut/del (n=103) | VenO (n=216) |
|---|---|---|---|
| Events, n (%) | 9 (56.3) | 32 (31.1) | 62 (28.7) |
| 60-month TTNT, % | 43.6 | **70.3** | **72.1** |
| Median PFS, months (95% CI) | 52.8 (15.2–41.7) | NE | NE |

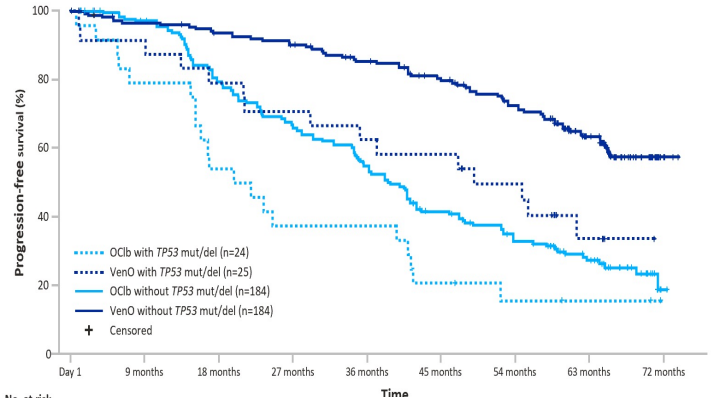
# Fixed duration tx

## Efficacy

## CLL 14 Venetoclax Obinutuzumab vs Chlorambucil Obinutuzumab

### Better PFS in non del17p




| | 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) |
|---|---|---|---|---|
| Events, n (%) | 15 (60) | 20 (83.3) | 63 (34.2) | 122 (66.3) |
| 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) |

In the context of Ven-Obi, **pre-treatment disease burden** (max. lymph node size >5 cm and absolute lymphocyte count > 25 G/l) and **deletion 17p** are independent prognostic factors for PFS.

# Venetoclax or Venetoclax Rituximab: clinical trials

## Age impact

**Data pooled from 4 phase 1 and 2 trials:**
**436 pts: 387 venetoclax mono**
**49 venetoclax plus rituximab**
**Median Age (range): 66 y (28-88)**
**≥70 y: 152 (35%)**

**≥70 yrs NO differences:**

- **response depth**
- **Response duration**
- **MRD negativity**

***Roberts et al, 2019***

**Data pooled from 4 phase 1 and 2 trials:**
**350 pts: 387 venetoclax monotherapy**
**49 venetoclax plus rituximab**
**Median Age (range): 66 y (28-88)**
**< 75 y /≥75 y: 65%/35%**

**<75 vs ≥75 yrs No differences:**

- **AE all/AE grade 3-4/SAE**
- **AEs leading to:-dose reductions**
  **-interruption**
  **-discontinuations**

***Davids et al., 2018***

# Venetoclax Monotherapy: common practice

## Age impact

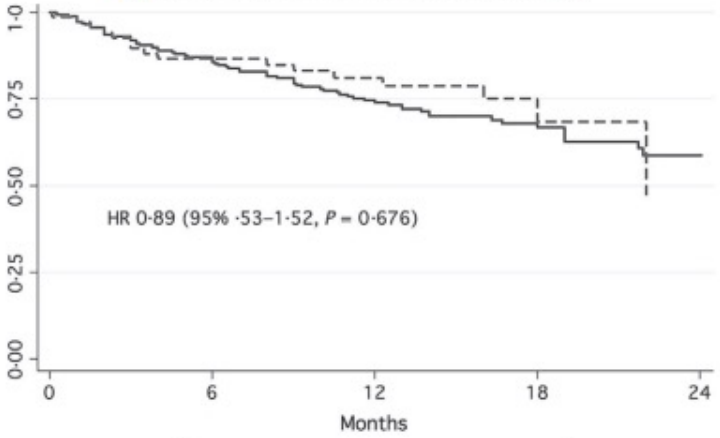
**M age: 66 yrs**
**M prior lines: 3**

**UK experience: 342 pts →Ven monotherapy (79%) or combo (21%)**

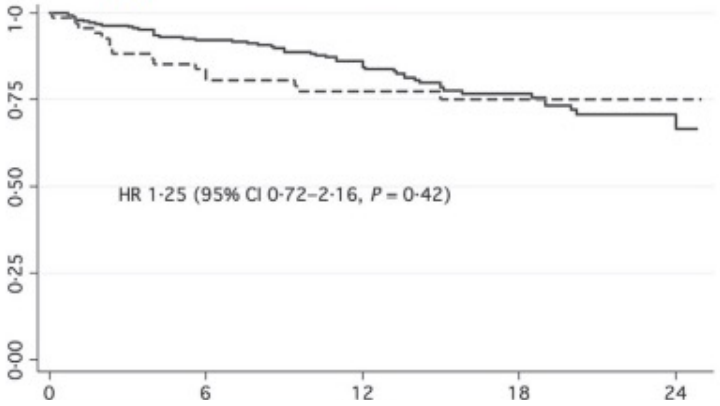
<75 yrs: 271

≥75 yrs: 71

**PFS**




**OS**




| | **<75 yrs *versus* ≥75 yrs *p*** |
|---|---|
| **M FU** | 11.5 mo vs 12.2 mo |
| **ORR(CR)** | 82%(32.6%) vs 81.6% (35.2%) |
| **Dose reductions** | .48 |
| **Ven discontinuations** | .95 |
| **TLS** | .78 |
| **G3 thrombocytopenia** | .13 |
| **G3 neutropenia** | .13 |
| **Neutropenic fever** | .51 |

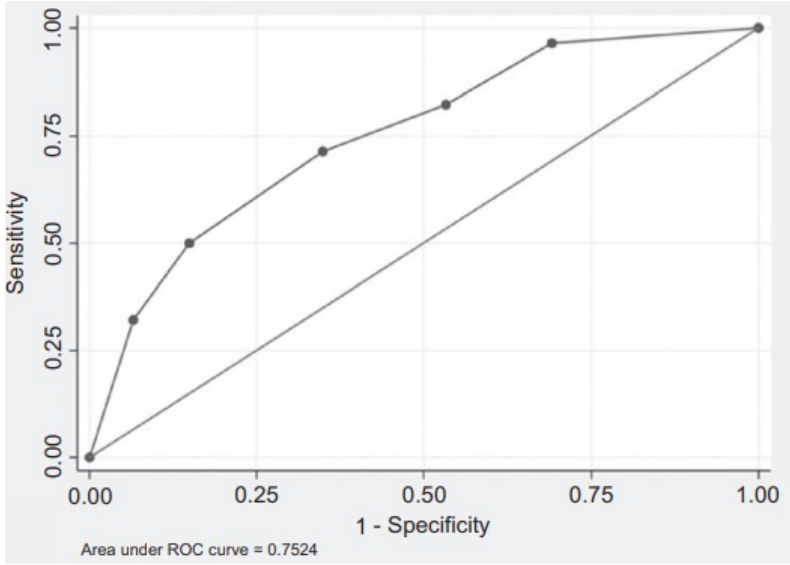
Eyre BJH 2019

# Venetoclax Monotherapy: common practice

## TLS risk

**TLS incidence (on 297 pts):**
clinical → 8 pts (2.7%)
lab → 17 pts (5.5%)

| Baseline Variable | Odds Ratio (95% Confidence Interval) | P value |
|---|---|---|
| Gender (female vs male) | 1.3 (0.55-3.1) | 0.55 |
| Age at venetoclax initiation (continuous) | 1.0 (1.0-1.1) | 0.11 |
| Number of prior therapies (continuous) | 1.0 (0.83-1.2) | 0.96 |
| Prior Ibrutinib (yes vs no) | 0.71 (0.27-1.9) | 0.49 |
| Deletion 17p (present vs absent) | 1.3 (0.54-2.9) | 0.59 |
| Complex karyotype (present vs absent) | 2.6 (0.96-7.1) | 0.061 |
| IGHV mutational status (unmutated vs mutated) | 0.95 (0.10-8.7) | 0.96 |
| Creatinine Clearance (<80 mL/min vs ≥80 mL/min) | 3.3 (1.1-9.5) | 0.031 |
| Administration strategy (monotherapy vs paired) | 2.9 (0.65-12.5) | 0.16 |
| TLS Risk Group (high vs low) | 3.0 (1.0-9.3) | 0.048 |
| TLS Risk Group (intermediate vs low) | 2.4 (0.77-7.3) | 0.13 |




On **297 pts** receiving venetoclax**, TLS risk group (low vs high) and CrCl (<80 vs ≥80 ml/min)** were the only factors influencing **TLS risk** at uni and multivariate analysis

Roeker CCR 2019

# Venetoclax Monotherapy: common practice

## Coexisting conditions and concomitant medications do not affect venetoclax management and survival in chronic lymphocytic leukemia

Anna Maria Frustaci, Giovanni Del Poeta*, Andrea Visentin, Paolo Sportoletti, Alberto Fresa, Candida Vitale, Roberta Murru, Annalisa Chiarenza, Alessandro Sanna, Francesca Romana Mauro, Gianluigi Reda, Massimo Gentile, Marzia Varettoni, Claudia Baratè, Chiara Borella, Antonino Greco, Marina Deodato, Giulia Zamprogna, Roberta Laureana, Alessandra Cipiciani, Andrea Galitzia, Angelo Curto Pelle, Francesca Morelli, Lucio Malvisi, Marta Coscia, Luca Laurenti, Livio Trentin, Marco Montillo, Roberto Cairoli and Alessandra Tedeschi

THERAPEUTIC ADVANCES in *Hematology* 2022, Vol. 13: 1–14

Tox-DTD and PDR were not influenced by age, fitness, number/type of concomitant medication, baseline neutropenia or impaired renal function

None of these factors were associated with TLS development

Age/CIRS had no influence on PFS, EFS and OS

**Table 4.** Cox proportional regression hazards model on PFS, EFS, OS, Tox-DTD, and PDR.

| | PFS | | EFS | | OS | | Tox-DTD | | PDR | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Age | 0.99 (0.55–1.81) | 0.984 | 0.79 (0.46–1.37) | 0.402 | 0.91 (0.45–1.83) | 0.783 | 1.08 (0.79–1.46) | 0.636 | 1.07 (0.78–1.48) | 0.664 |
| ECOG-PS | 1.67 (0.91–3.07) | 0.096 | 2.00 (1.17–3.42) | **0.011** | 3.41 (1.84–6.32) | **<0.0001** | 0.85 (0.58–1.25) | 0.421 | 0.97 (0.64–1.48) | 0.897 |
| CIRS3+ | 1.07 (0.60–1.91) | 0.815 | 1.36 (0.78–2.37) | 0.282 | 1.12 (0.58–2.18) | 0.741 | 0.89 (0.62–1.29) | 0.550 | 0.95 (0.64–1.40) | 0.777 |
| CIRS >6 | 0.90 (0.49–1.68) | 0.742 | 0.67 (0.37–1.21) | 0.179 | 0.89 (0.43–1.84) | 0.751 | 1.03 (0.72–1.47) | 0.887 | 0.98 (0.67–1.44) | 0.925 |
| Polypharmacy | 1.01 (0.49–2.07) | 0.978 | 1.03 (0.56–1.93) | 0.915 | 1.18 (0.53–2.64) | 0.685 | 1.09 (0.78–1.54) | 0.615 | 1.08 (0.76–1.52) | 0.678 |
| Neutropenia | 0.93 (0.47–1.83) | 0.838 | 1.09 (0.59–2.03) | 0.779 | 0.92 (0.43–1.97) | 0.824 | 1.14 (0.77–1.69) | 0.508 | 0.74 (0.49–1.11) | 0.143 |
| CrCl | 1.16 (0.63–2.14) | 0.639 | 1.11 (0.63–1.98) | 0.717 | 1.14 (0.56–2.29) | 0.721 | 1.02 (0.71–1.46) | 0.933 | 0.88 (0.59–1.31) | 0.529 |

Frustaci et al, 2022

# Venetoclax Obinutuzumab: CLL14 clinical trial

## Age/comorbidities

**Only pts with CrCl <30 ml/min *excluded***

| Characteristic | Venetoclax–Obinutuzumab (n=216) | Chlorambucil–Obinutuzumab (n=216) |
|---|---|---|
| Age | | |
| Median — yr (range) | 72 (43–89) | 71 (41–89) |
| ≥75 yr — n (%) | 72 (33.3) | 78 (36.1) |
| Male sex — n (%) | 146 (67.6) | 143 (66.2) |
| Median time from diagnosis — mo (range) | 31.2 (0.4–214.7) | 29.2 (0.3–244.8) |
| Binet stage — n (%) | | |
| A | 46 (21.3) | 44 (20.4) |
| B | 77 (35.6) | 80 (37.0) |
| C | 93 (43.1) | 92 (42.6) |
| B-symptoms present — n (%)† | 103 (47.7) | 112 (51.9) |
| TLS risk category — n (%) | | |
| Low | 29 (13.4) | 26 (12.0) |
| Intermediate | 139 (64.4) | 147 (68.1) |
| High | 48 (22.2) | 43 (19.9) |
| Total CIRS score | | |
| Median (range) | 9 (0–23) | 8 (1–28) |
| >6 — n (%) | 186 (86.1) | 177 (81.9) |
| Estimated creatinine clearance | | |
| Median — ml/min (range) | 65.2 (0.1–3670.0) | 67.5 (31.0–2217.6) |
| <70 ml/min — n (%) | 128/215 (59.5) | 118/213 (55.4) |

**Pts charcateristics:**

**High TLS risk: 22.2%**

**Renal Comorbidity: 30.1%**

**CrCl <70 ml/min 59.5%**

**TLS incidence (on 216 pts):**

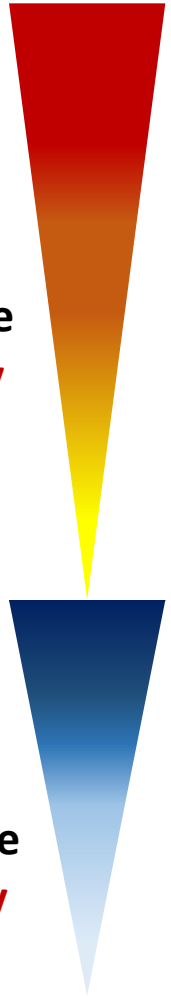
clinical → 0

lab → 3 pts (1.4%)

*All 3 occurring with obinu, before ven initiation*

Fischer Lancet Oncol 2019

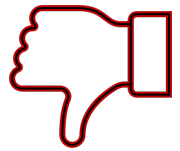
# Venetoclax: concomitant use of interfering drugs




| | Ramp-up phase | Treatment phase |
|---|---|---|
| **Strong CYP3A inhibitors** | Avoid concomitant use | Reduce at 75% |
| **PgP inhibitors** | Avoid concomitant use | Monitor carefully |
| **Moderate CYP3A inhibitors** | Avoid | Reduce 50% |
| **Mild CYP3A inhibitors** | No changes | No changes |
| **Strong CYP3A inducers** | Avoid concomitant use | Avoid concomitant use |
| **Moderate CYP3A inducers** | Avoid concomitant use | Avoid concomitant use |

# Venetoclax Obinutuzumab FD

- ✓ EFFECTIVE
- ✓ FEASIBLE IN ALL AGES
- ✓ NO COMORBIDITIES IMPACT



- ✓ ↓ PFS in del17p/*TP53 m*
- ✓ HIGH TUMOR BURDEN:
  - -TLS
  - -INTENSIVE MONITORING
- ✓ LOGISTICS (CARE GIVERS…

## PERSONAL CONSIDERATION (WHILE WAITING CLL17)

### PATIENTS FACTORS (1)

1 Severe Cardiocomorbidities → Venetoclax Obinutuzumab

2 Severe Renal Impairment Bulky disease → BTKi

3 Concomitant Medications → BTKi / Venetoclax/obinutuzumab

4 Elderly with difficulties to reach hospital Care givers Reduced compliace for iv tx → BTKi

### DISEASE FACTORS (2)

Consider pts factors

del 17p/*TP53*$^{m}$ → Preferred: BTKi

IGHV mutated → Preferred: Venetoclax Obinutuzumab

IGHV mutated → BTKi if n° 4 more true plus n° 2

IGHV unmutated → No preference

Consider:

- Patients factor
- Age matters: future program resistance