

# Chronic Lymphocytic Leukemia

## Highlights & Updates

## Practice-Changing Data

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# Disclosures

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**Consultant:** AbbVie, AstraZeneca, BeOne, Genentech, Lilly, Johnson & Johnson, Pfizer, Pharmacyclics

**Research Funding to Institution:** AbbVie, BeOne, Genentech

# Agenda: Questions

1

Continuous vs Time Limited Frontline Targeted CLL Treatment?

2

Frontline BTK inhibitor + BCL2 inhibitor?

3

Pirtobrutinib in Frontline CLL?

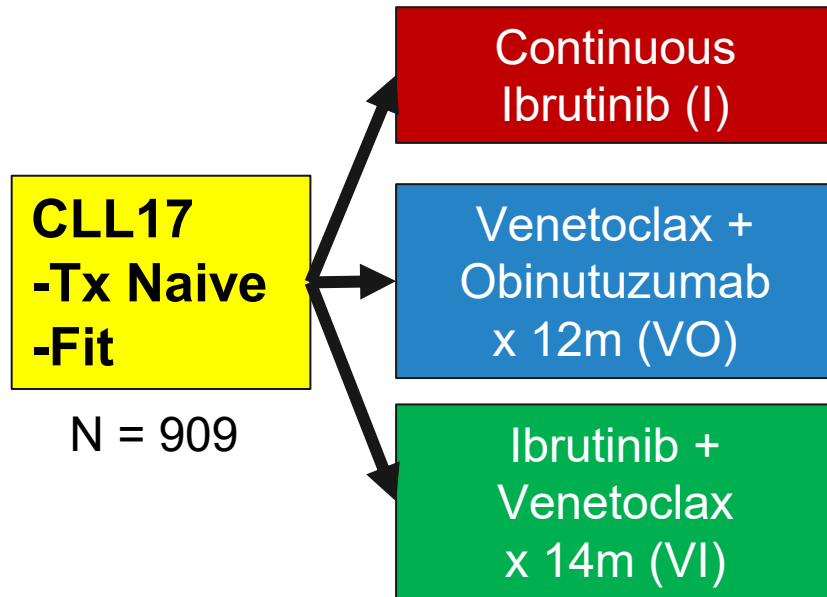
4

Pirtobrutinib Combination in RR CLL?

# 1

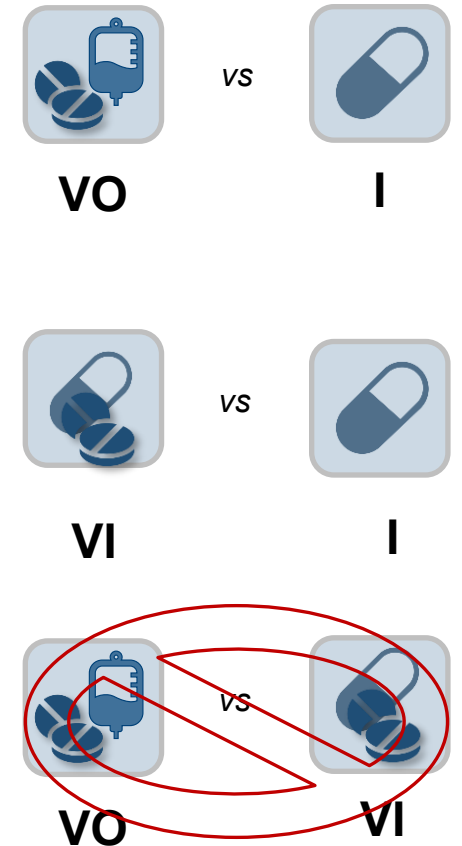
Continuous vs Time-Limited Frontline  
Targeted Therapy? – CLL17 Trial

# Time Limited vs Continuous- CLL17



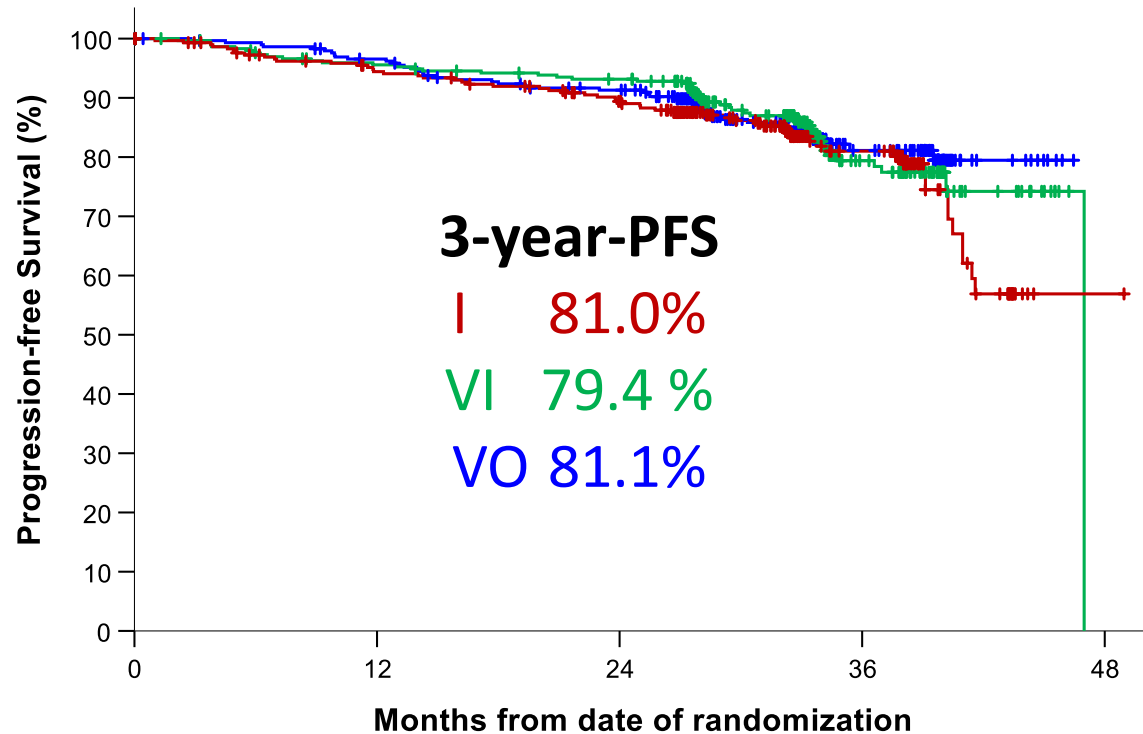
## Study Design:

- PFS Non-inferiority of VO vs I
- PFS Non-inferiority of VI vs I
- <8% reduction in 3-yr PFS is considered Non-inferior
- Not powered to detect difference in VO vs VI



# Time Limited vs Continuous- CLL17

Median follow-up 34.2 mos



Were VO and VI non-inferior to I?

- Yes for 3-yr PFS
- Note: ibrutinib is continuous

Was VO non-inferior to VI? Not powered

What about higher risk groups?

- uIGHV – similar
- Del17p/mTP53 – shorter with VI/VO
- CIRS >6 – shorter with I

# Time Limited vs Continuous- CLL17

| Toxicity, (%)*         | VO (n=295)                                                                              | VI (n=303) | I (n=298)                                                                              |
|------------------------|-----------------------------------------------------------------------------------------|------------|----------------------------------------------------------------------------------------|
| Atrial Fibrillation    | 4                                                                                       | 13         | 17  |
| Hypertension           | 12                                                                                      | 17         | 24  |
| Neutropenia            | 53                                                                                      | 36         | 16                                                                                     |
| Febrile Neutropenia    | 5     | 2          | 0                                                                                      |
| Infections             | 76                                                                                      | 80         | 80                                                                                     |
| Grade 3-5 <sup>#</sup> | 35   | 25         | 25                                                                                     |
| COVID-19               | 16  | 9          | 7                                                                                      |

\*All Grade Unless Noted

## Toxicity

- Ibrutinib-associated toxicity → I
- Neutropenia and severe infections → VO

# CLL17 – Questions and Take-home Points

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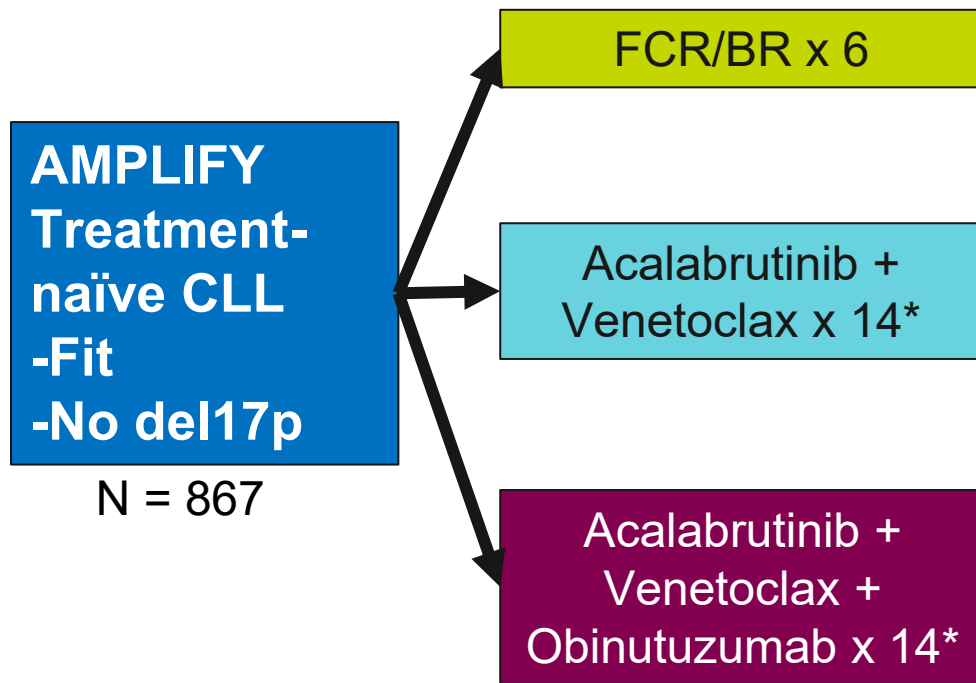
- Are the results already outdated given lack of current use of ibrutinib?
- Would results be better with acalabrutinib or zanubrutinib?
- Will longer follow-up change the results?
- Overall, many good choices for frontline CLL treatment
- Treatment selection can be tailored to individual patients



# 2

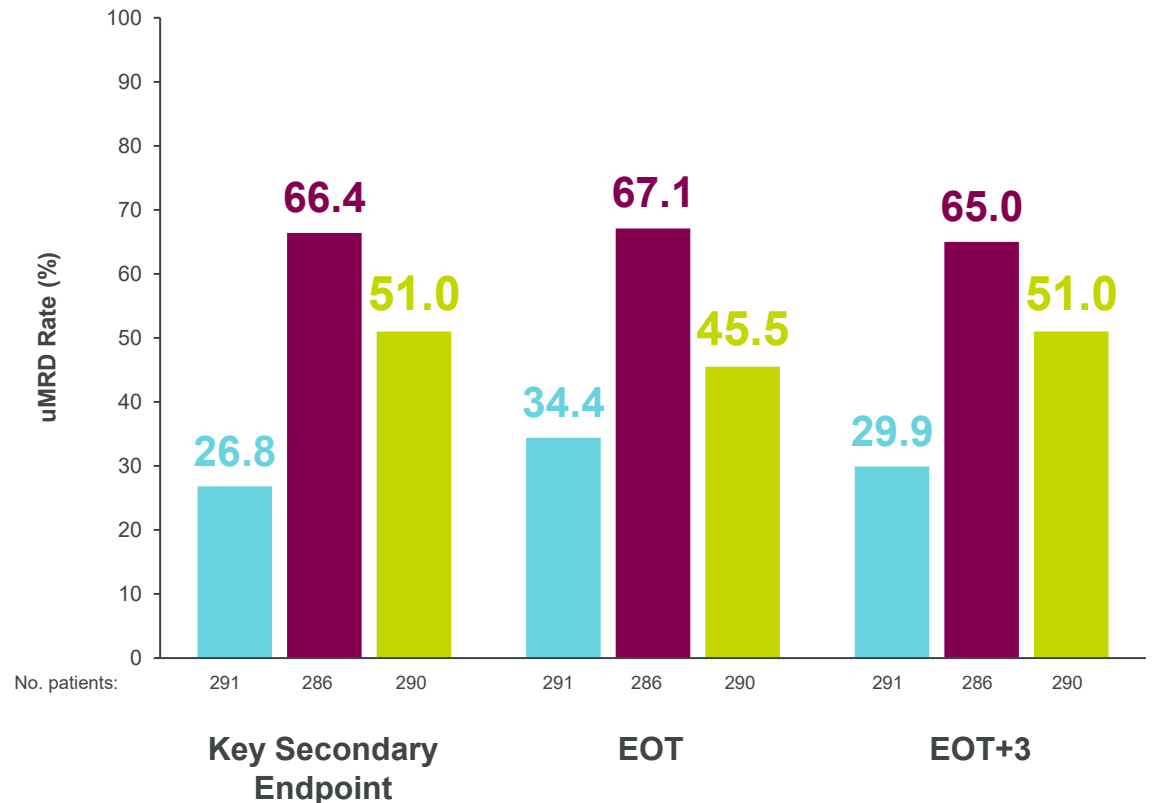
Frontline BTK inhibitor + BCL2 inhibitor?—  
AMPLIFY Trial

# AMPLIFY

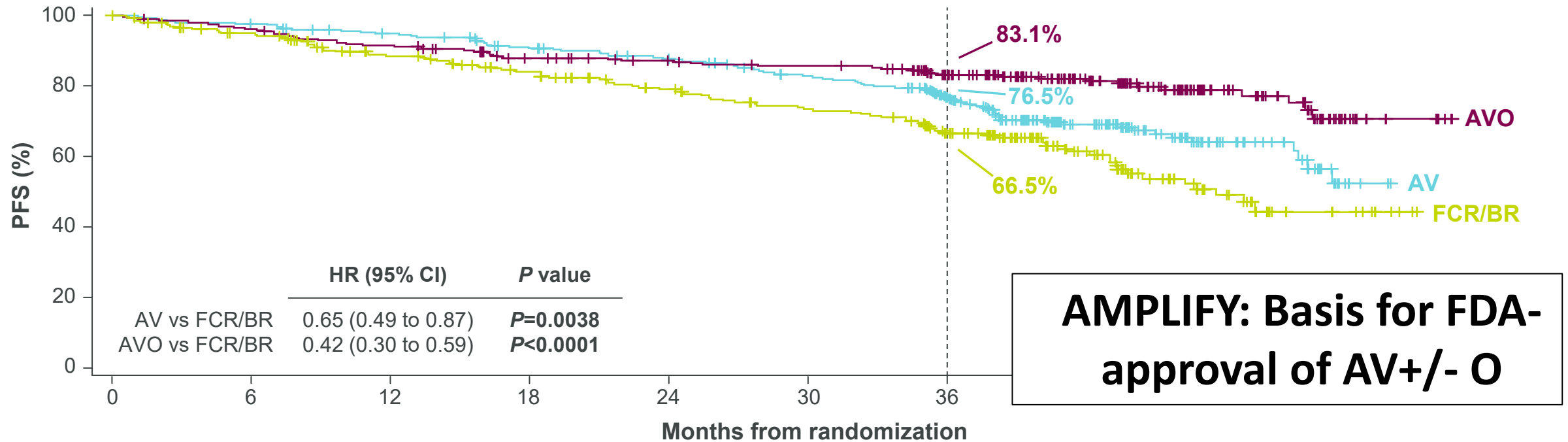


\*A+/-O Initiated prior to Venetoclax  
Resulted in Reduced Risk of TLS

## uMRD by Flow in ITT Population\*



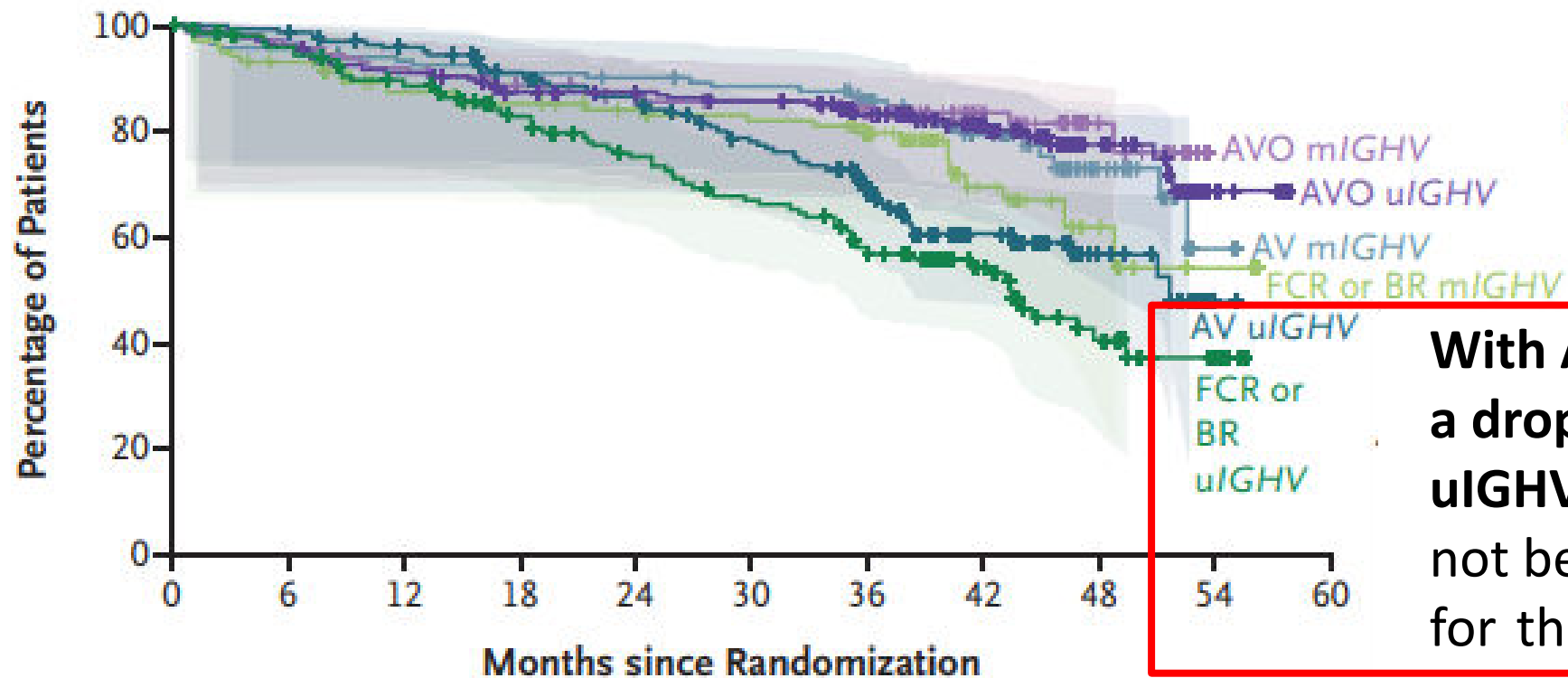
# AMPLIFY



More COVID-19 Deaths in AVO (25) and CIT (21) Arms than AV (10) Arm

When COVID-19 deaths were censored, there was a bigger improvement in PFS of AVO arm

# AMPLIFY



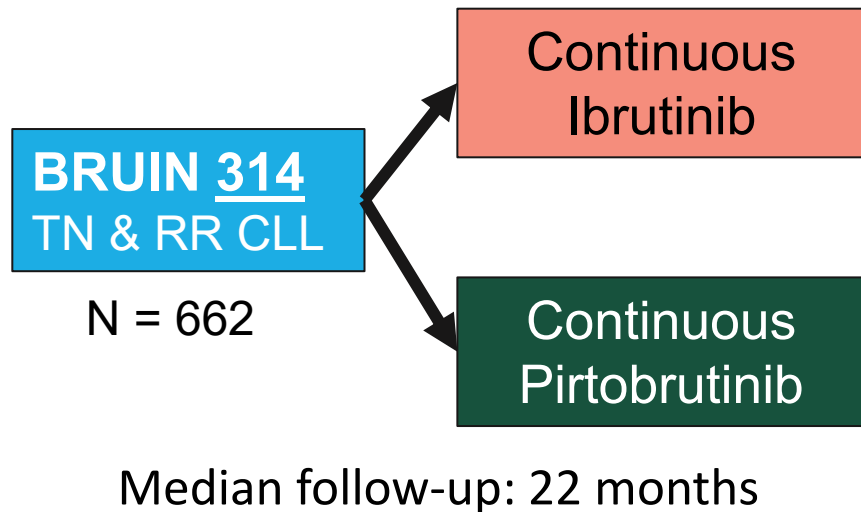
**With AV and CIT there was a drop in PFS for the pts w uIGHV - indicating this may not be the best strategy for these patients**

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Pirtobrutinib in Frontline CLL? –  
BRUIN 314

# Frontline Pirtobrutinib

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## Study Design:

- ORR Non-inferiority of **P** vs **I** in all patients
- **Not powered specifically for TN population**

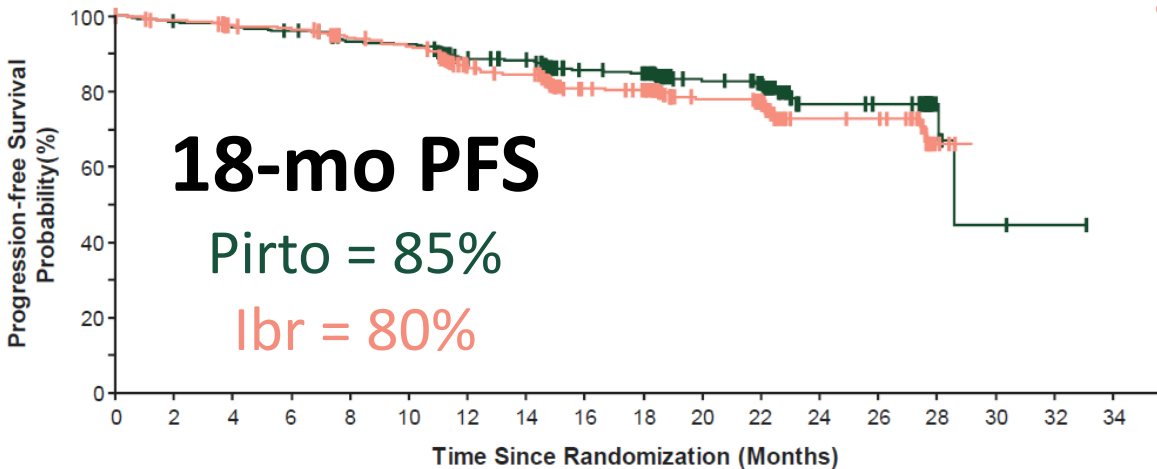
## Efficacy- ORR:

- **P (87%)** non-inferior to **I (79%)**
- Del(17p)/TP53m (30% of pts): No difference

## Does ORR matter in CLL?

# Case: Older, Less Fit, High Risk

## PFS (All Pts) – BRUIN 314



Median follow-up: 22 months

**Safety:** Not as different as you might guess

- **Ibrutinib = More:**
  - Atrial fibrillation (14% v 2%)
  - HTN (15% v 11%)
  - Diarrhea (19% v 13%)
  - Arthralgia (13% v 8%)
  - ↓Plt (18% v 12%)
- **Pirto = More neutropenia (31% vs 23%)**
- **Same = Infection (70%), Bleeding (35%), Rates of Discontinuation (10%)**

# BRUIN 314 – Take Home Points

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- No details provided about progression (mutation types/response to next treatment)
- Will this matter for older patients?
- NCCN- Pirtobrutinib useful in “certain circumstances” in frontline setting
- Consideration for older, higher comorbidity patients

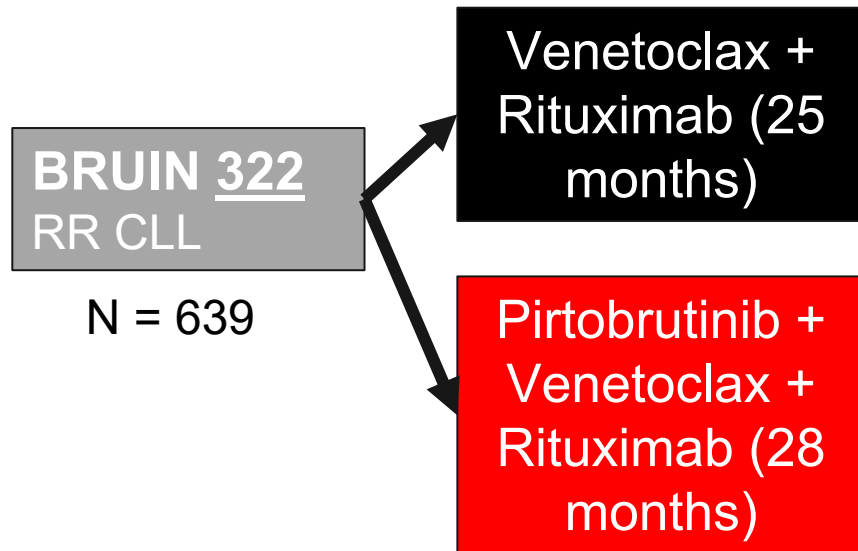
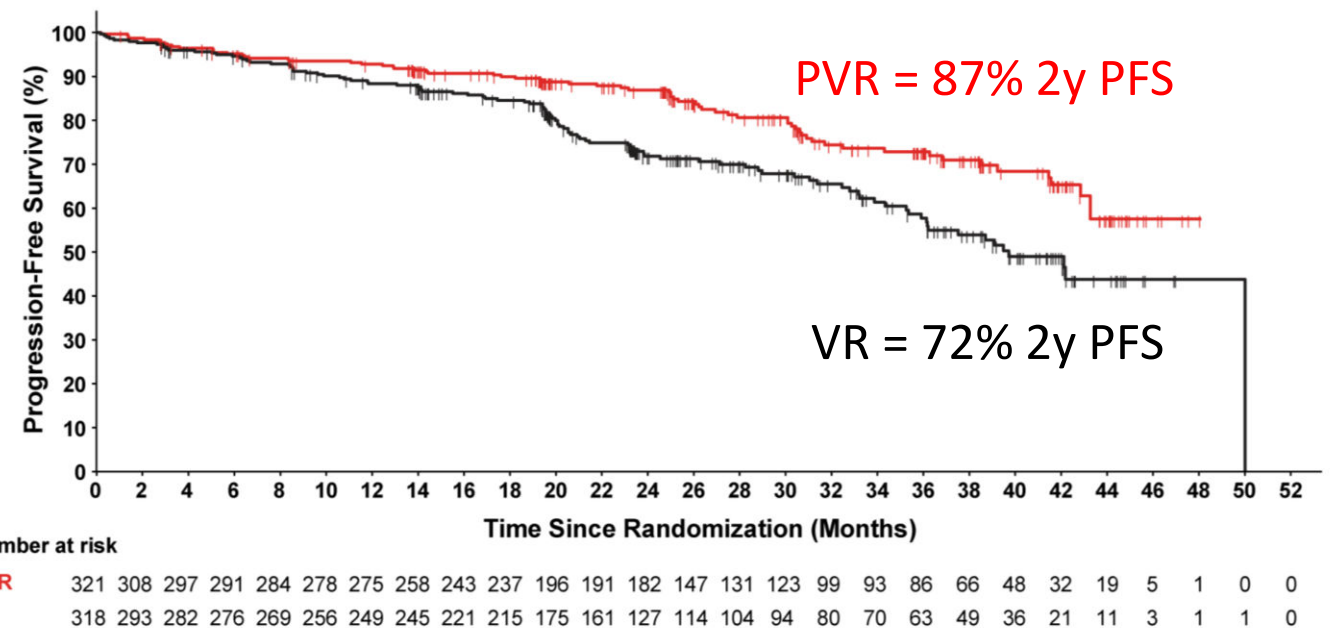
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Pirtobrutinib Combination in Secondline CLL—  
BRUIN 322

# BRUIN 322

## Study Design:

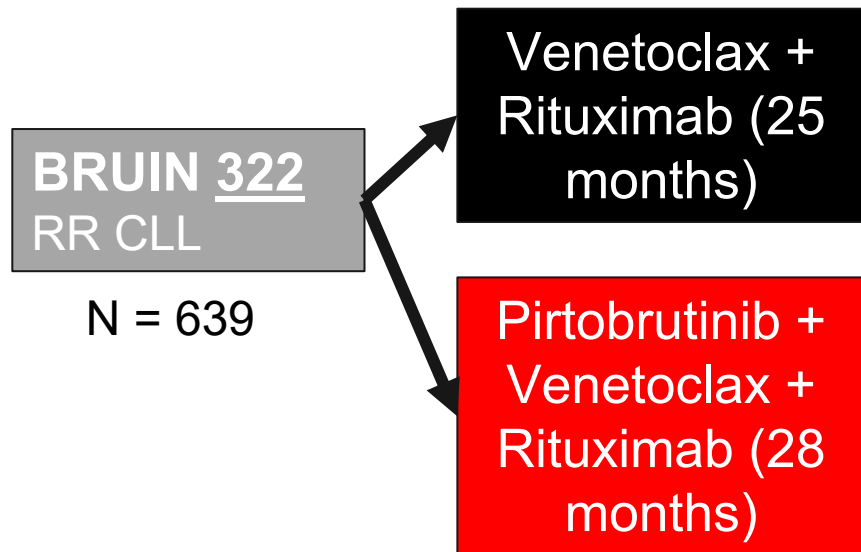
- PFS Superiority of **PVR** vs **VR** in all patients



Median follow-up: 27 months

# BRUIN 322

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Median follow-up: 27 months

## Subgroup analyses:

- Almost all favored **PVR**
  - *IGHV* unmutated
  - *TP53* mutated and/or del(17p)
  - Prior covalent BTK inhibitor
  - Prior cBTKi discontinued for progressive disease

## Safety:

- Grade 3+ adverse events = very similar

# BRUIN 322 – Take Home Points

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- PVR prolonged PFS compared to VR in RR CLL without adding significant toxicity
- High-risk subgroups had longer PFS with PVR vs VR
- Not yet in NCCN, likely basis for approval submission
- How does PVR compare with venetoclax + obinutuzumab?  
Or PV + obinutuzumab?
- Resistance mutations at relapse?
- Consideration for patients with prior cBTKi (especially in setting of progressive disease), *TP53m/del17p*, *IGHV* unmutated

# Summary: Questions Answered

1

CLL17: Continuous or Time Limited Treatments Have Similar Efficacy

2

AMPLIFY: Acalabrutinib + Venetoclax +/- Obinutuzumab – FDA Approved

3

BRUIN 314: Pirtobrutinib in Frontline CLL in Select Patients

4

BRUIN 322: PVR prolonged PFS over VR with Similar Toxicity Profile