Selection and Sequencing of Available Therapies for Relapsed/Refractory (R/R) CLL

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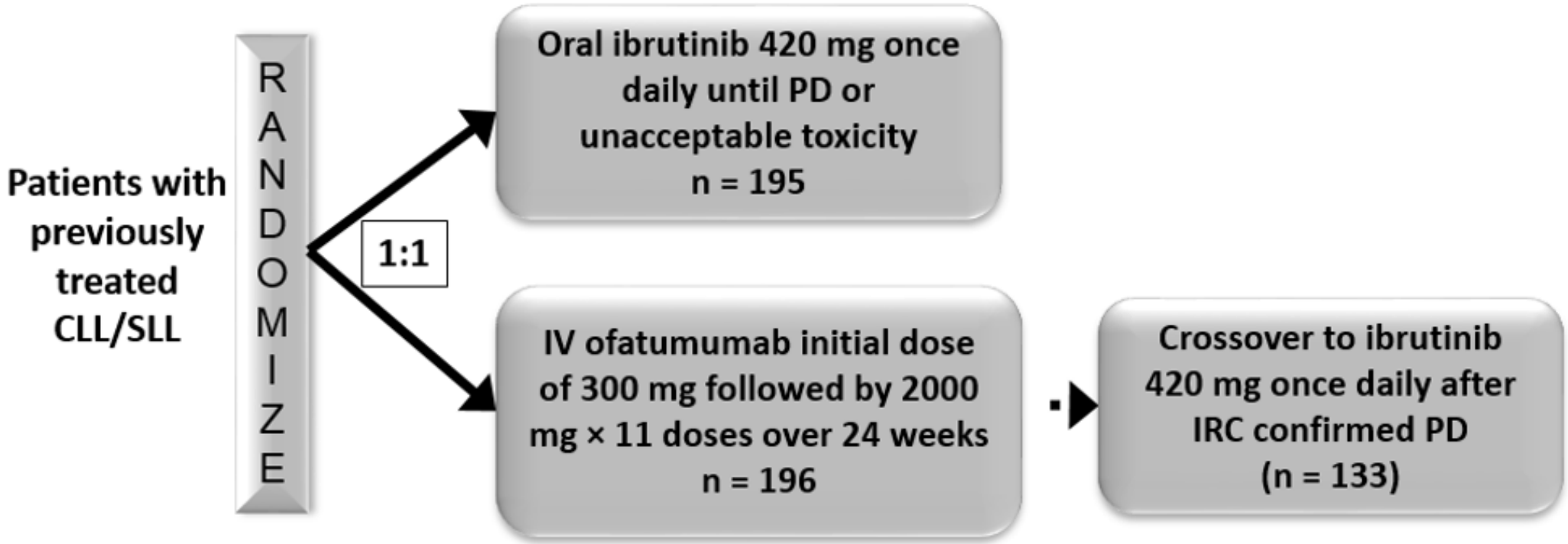
Topics

- Long-term follow-up data from phase III studies in R/R CLL.
- How I think about sequencing therapies.
- Role for PI3K inhibitors in CLL.
- Novel approaches to CLL and RS.

RESONATE Phase III Study Design

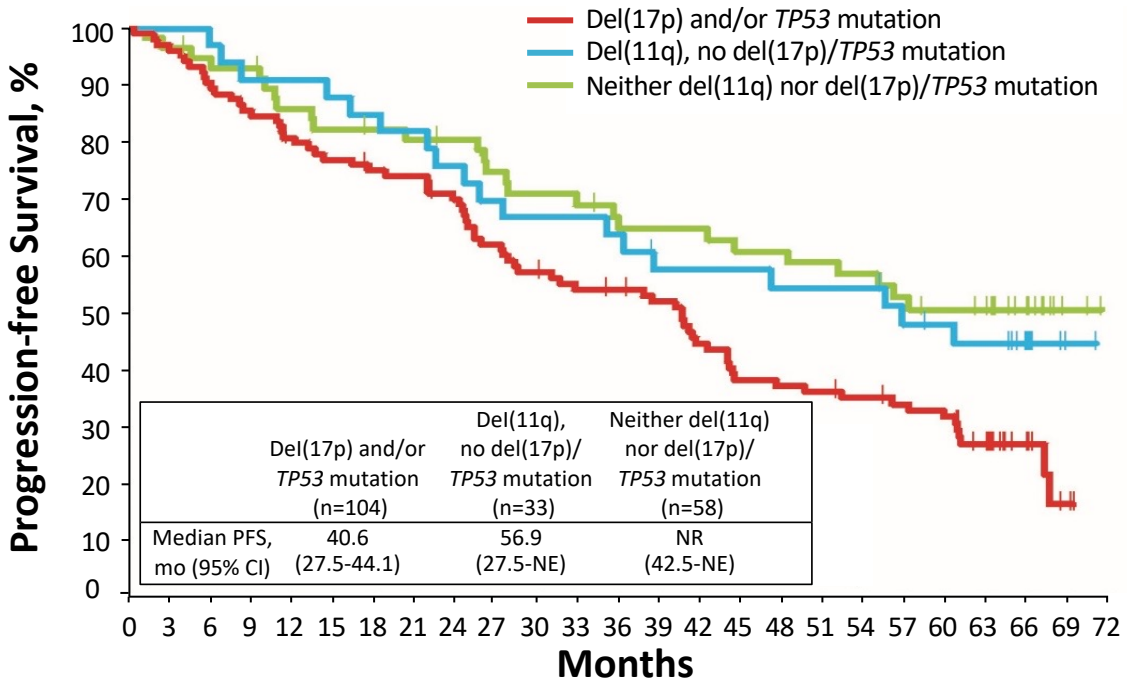


- Primary endpoint: PFS
- Median # therapies in ibrutinib arm = 3.
- In ibrutinib arm, 32% had del(17p) and 32% del(11q).

Byrd J et al. N Engl J Med. 2014;371(3):213-23

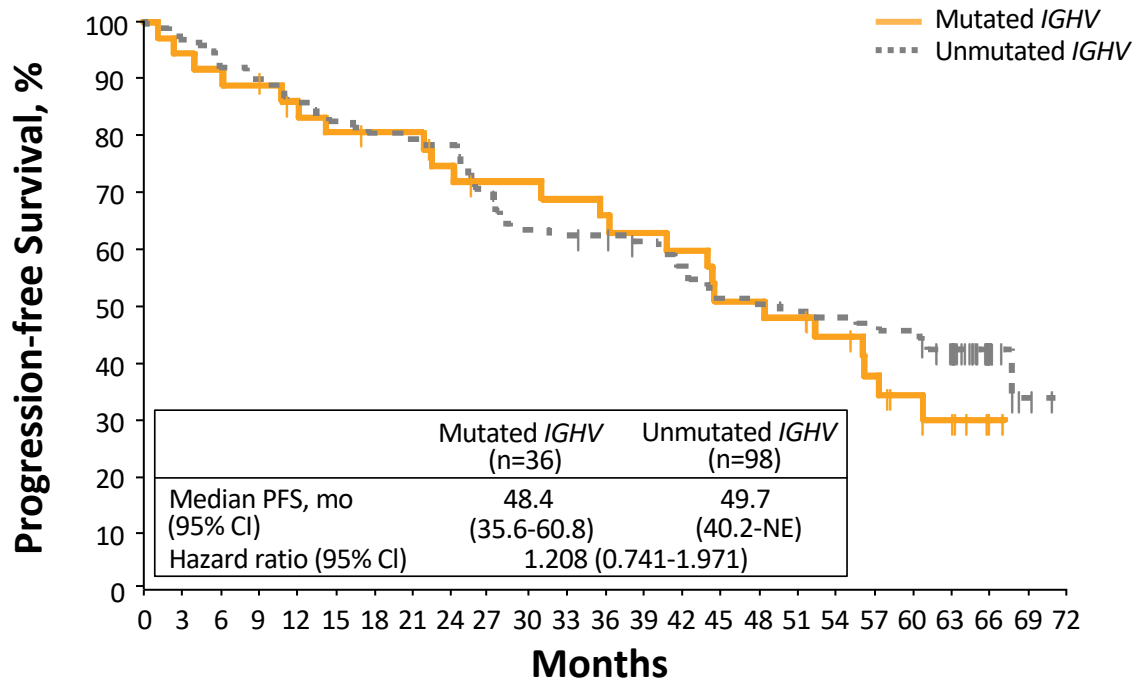
RESONATE: Long-term PFS Benefit With Ibrutinib Across Subgroups by Del(17p)/*TP53* Mutation, Del(11q), and *IGHV* Mutation Status

By Del(17p)/*TP53* Mutation and Del(11q)[a]



	Del(17p) and/or *TP53* mutation (n=104)	Del(11q), no del(17p)/ *TP53* mutation (n=33)	Neither del(11q) nor del(17p)/ *TP53* mutation (n=58)
Median PFS, mo (95% CI)	40.6 (27.5-44.1)	56.9 (27.5-NE)	NR (42.5-NE)

By *IGHV* Mutation



	Mutated *IGHV* (n=36)	Unmutated *IGHV* (n=98)
Median PFS, mo (95% CI)	48.4 (35.6-60.8)	49.7 (40.2-NE)
Hazard ratio (95% CI)	1.208 (0.741-1.971)	

- In ibrutinib-treated patients, median PFS was shorter for patients with del(17p) and/or *TP53* mutation (41 months) than in patients with del(11q) (57 months) or those without any of these abnormalities (not reached)
- PFS with ibrutinib was similar irrespective of *IGHV* mutation status

NE, not estimable; NR, not reached.

[a]Genomic abnormalities by fluorescence in situ hybridization cytogenetics were categorized according to Döhner hierarchical classification.

Blood 2019, RESONATE PCYC-1112; Mulligan et al.

ELEVATE-RR:
Phase 3 Randomized Non-inferiority Open-Label Trial

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

- **Acalabrutinib[b] 100 mg PO BID**
- **Ibrutinib[b] 420 mg PO QD**

Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK , PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).

[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.

Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.

1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS

Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Events of Clinical 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)

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

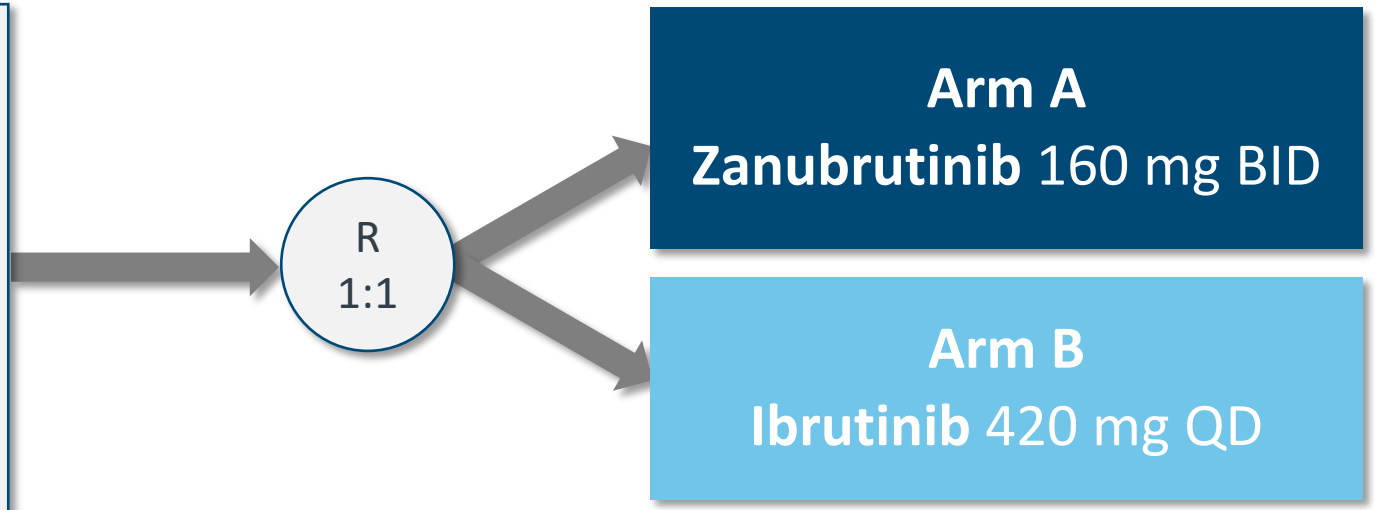
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



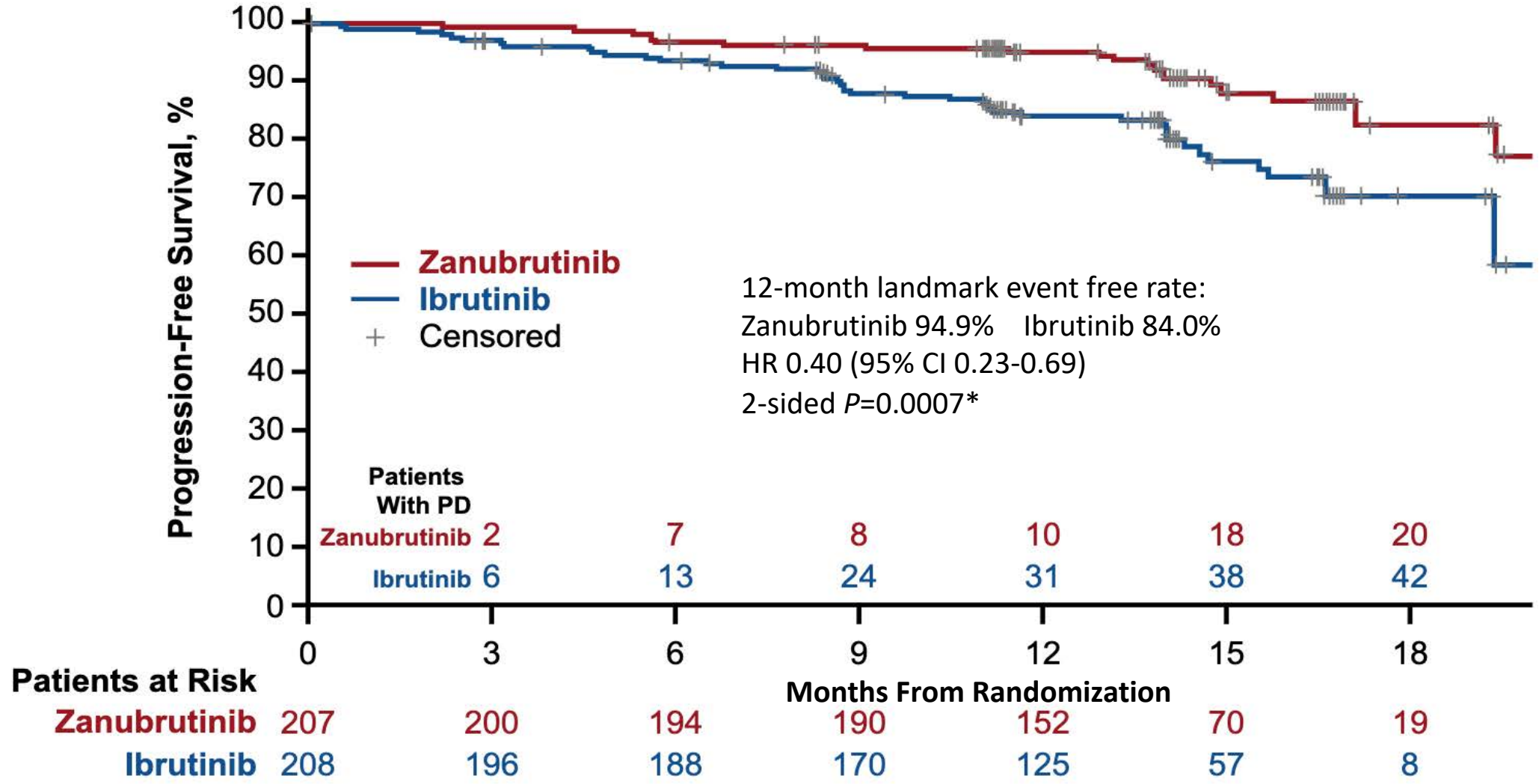
Stratification Factors

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Hillmen et al, EHA 2021

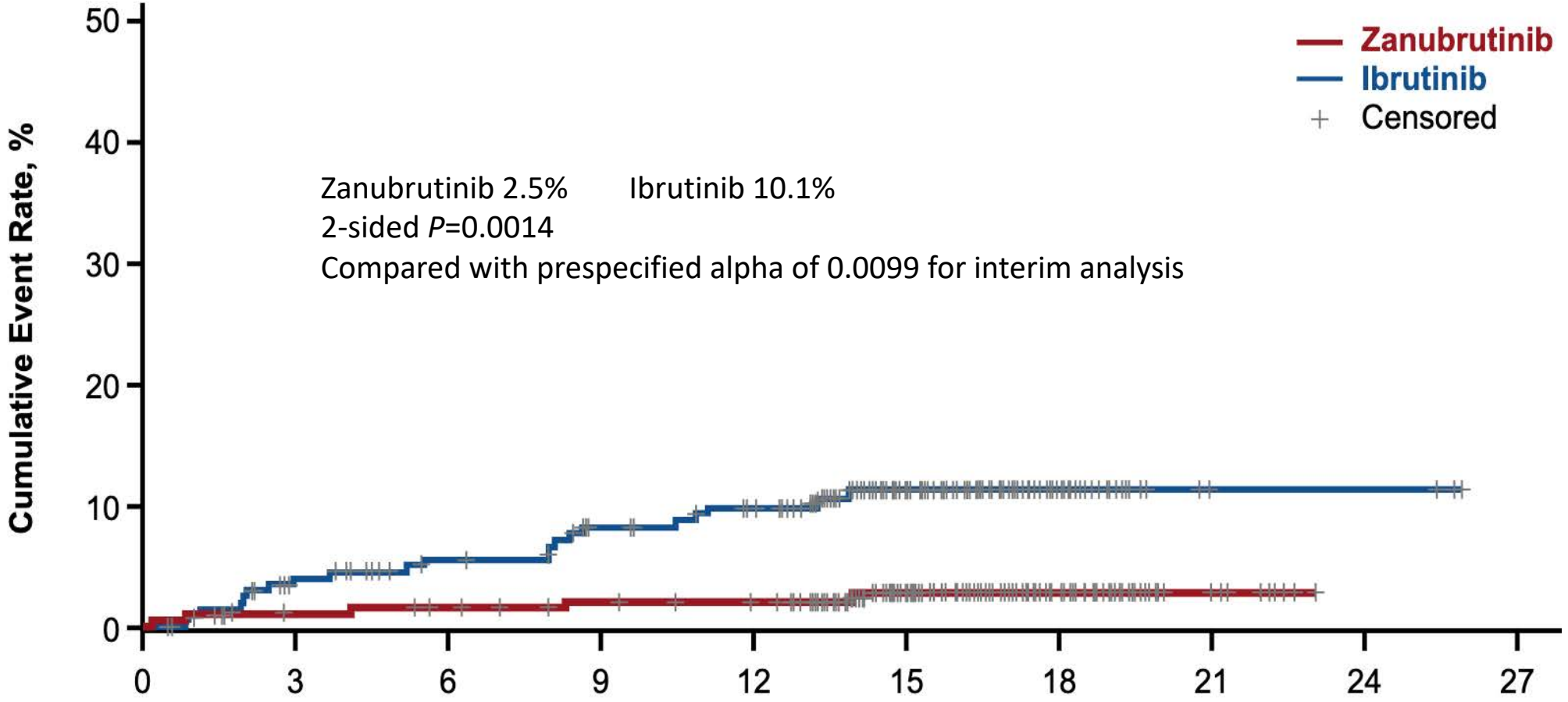
BID, twice daily; BTK, Bruton tyrosine kinase' CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
PFS, progression-free survival.

Atrial Fibrillation/Flutter



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

2nd Generation BTKi after ibrutinib intolerance

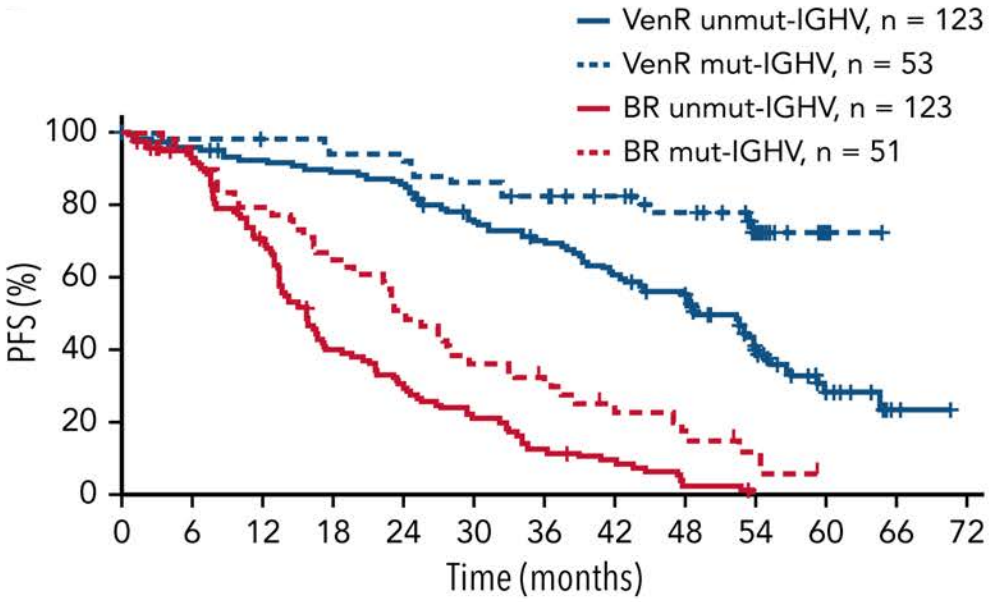
- 83% of patients treated with acalabrutinib after ibrutinib intolerance tolerate acalabrutinib, with 2y PFS of 72%.[1]
- 60% of patients treated with zanubrutinib after ibrutinib intolerance did not have recurrence of the intolerance event and recurrent AEs were of similar or lesser severity, leading to no discontinuations for intolerance.[2]

[1]Rogers et al. *Haematologica* 2021 Vol. 106 No. 9 (2021): September, 2021;
[2]Shadman et al. *Lancet Haematology* 2022

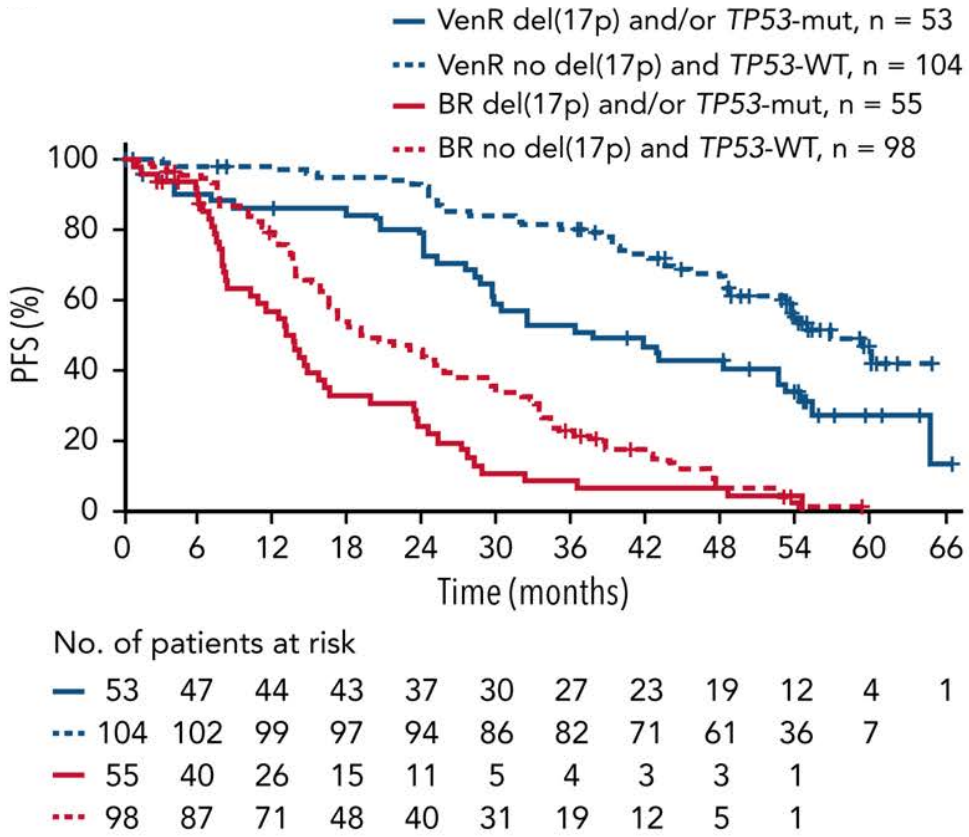
Summary

- BTK inhibitors are efficacious in R/R CLL.
- Overcome negative prognostic impact of del(11q) and unmutated *IGHV.* Del(17p) remains a high risk feature.
- 2nd generation covalent BTK inhibitors (acalabrutinib and zanubrutinib) have at least equivalent efficacy with more favorable AE profile.

MURANO: Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab



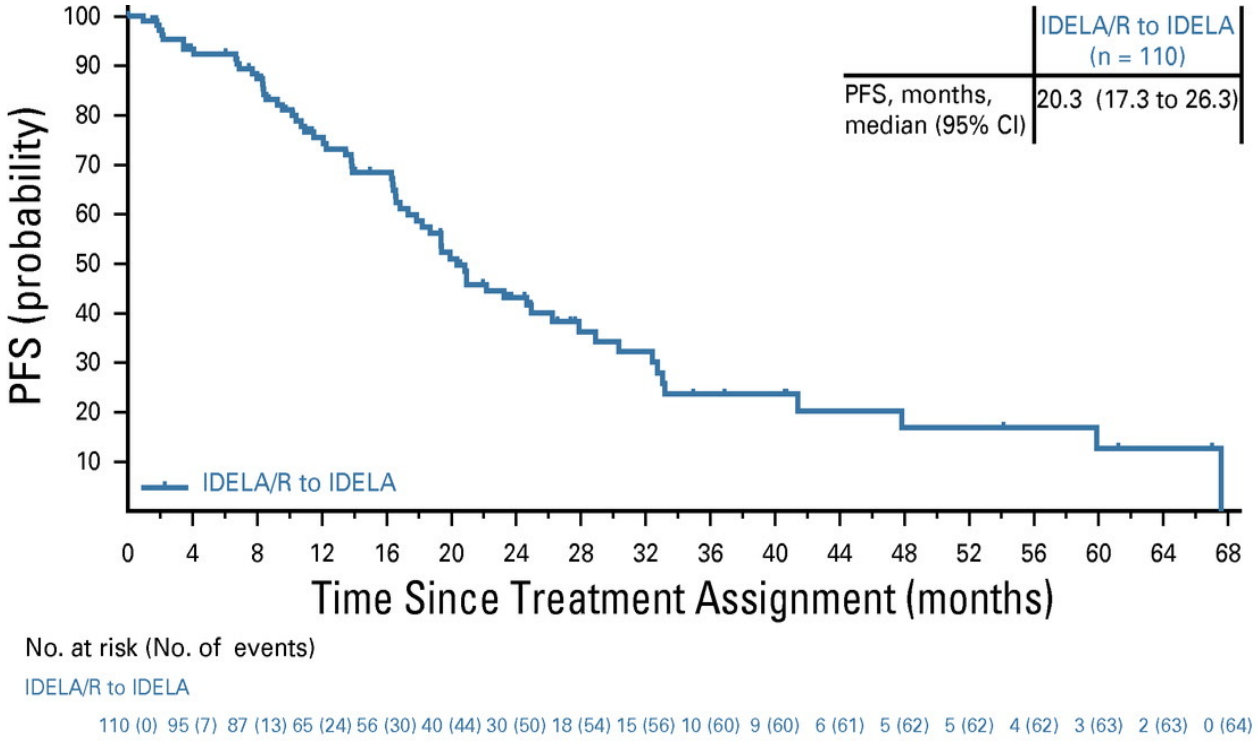
Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE

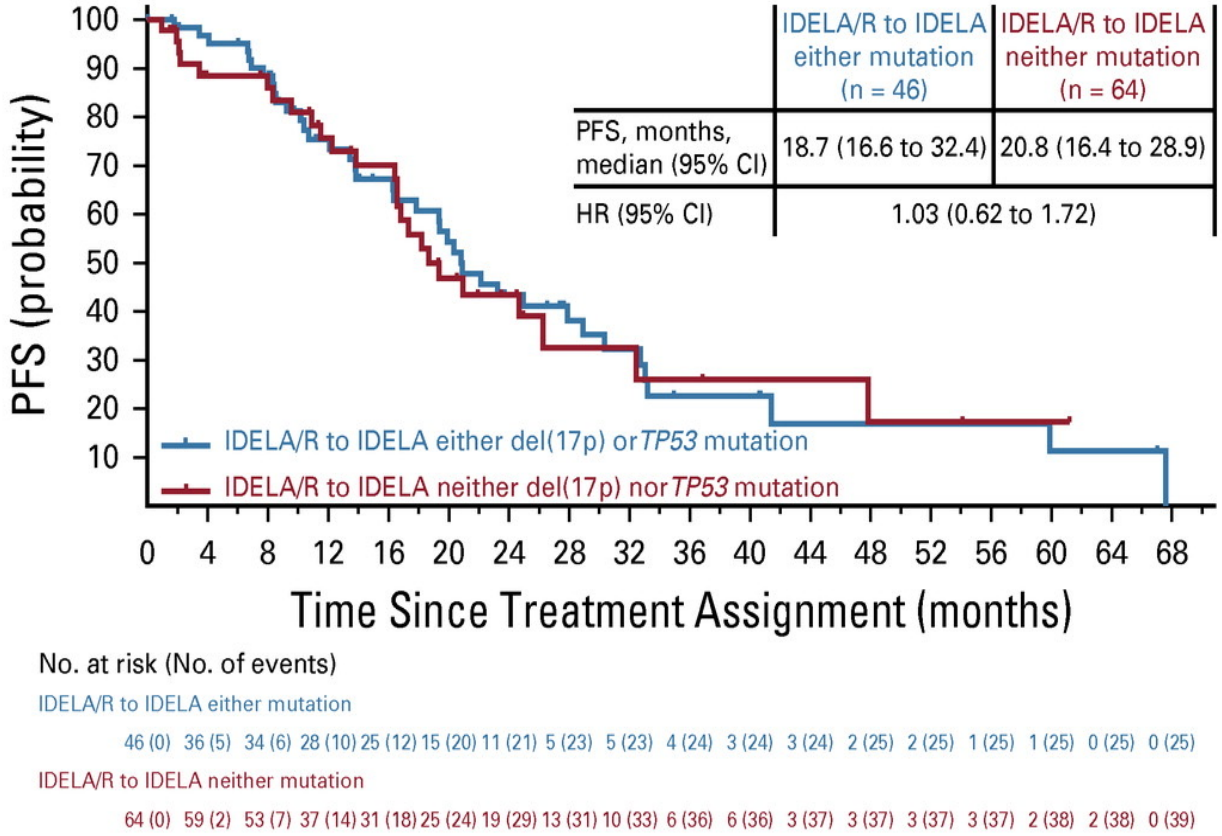


Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and *TP53*-WT	19.6 (16.4, 25.4)	.0059	NE

Seymour et al. Blood 2022

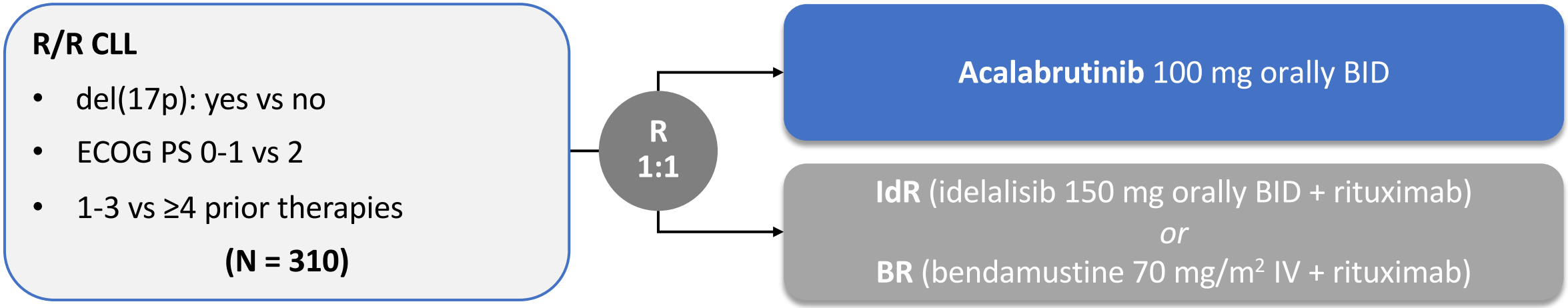
Idelalisib + Rituximab PFS





Sharman et al. *Journal of Clinical Oncology* 37, no. 16 (June 01, 2019) 1391-1402.

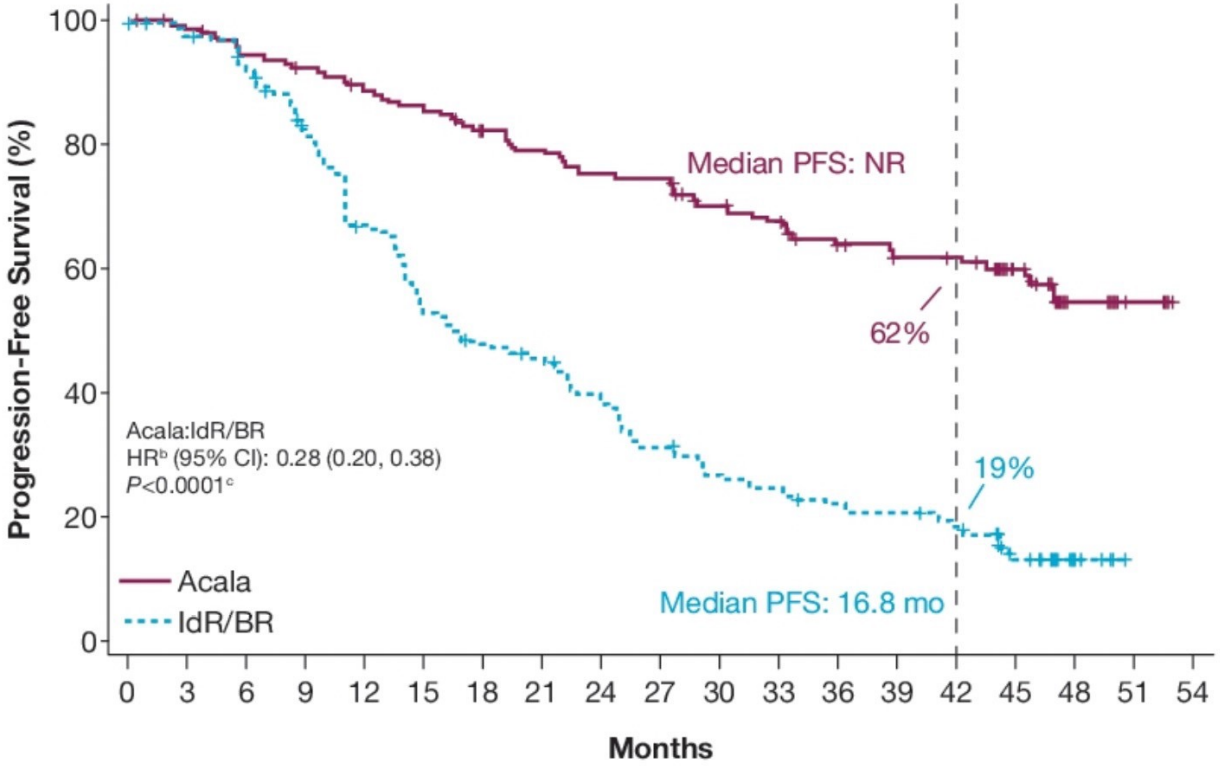
Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Versus IdR or BR in R/R CLL[1]

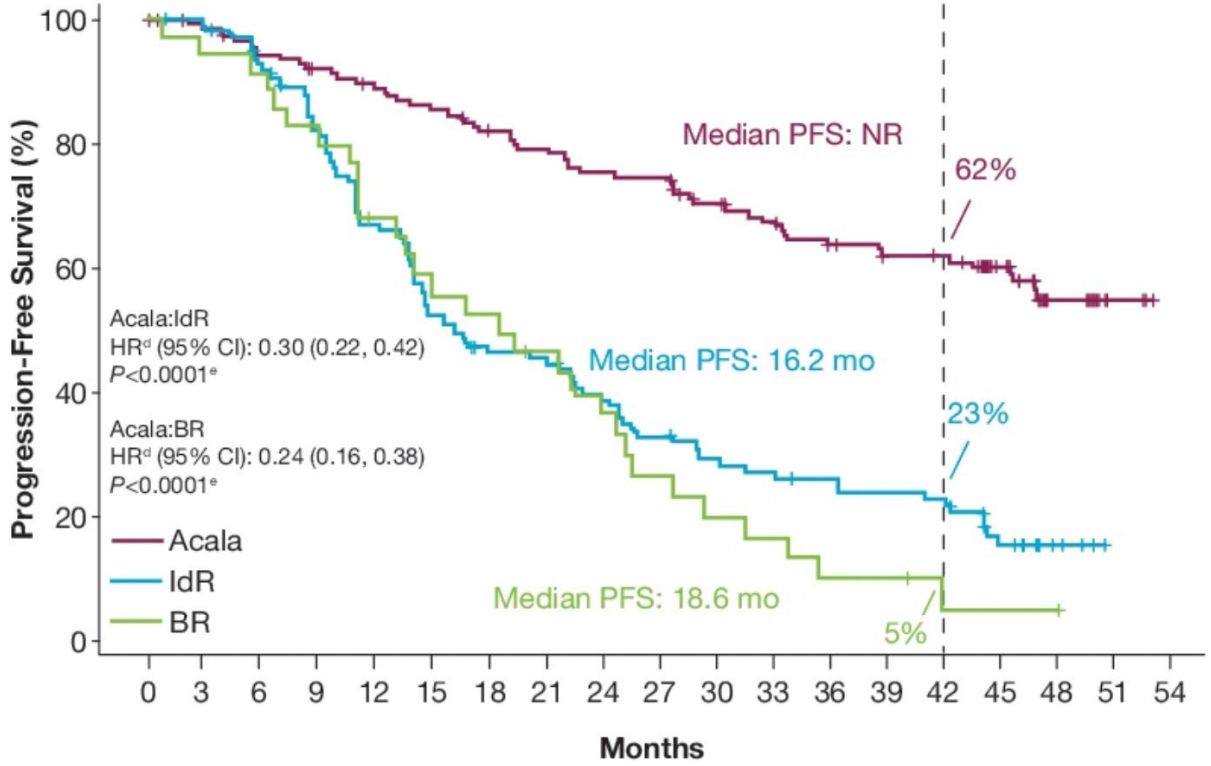


- Crossover from IdR/BR arm allowed after confirmed disease progression
- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)
- **Primary endpoint:** PFS (assessed by IRC)
- **Key secondary endpoints:** ORR (assessed by IRC and investigator), duration of response,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

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

ASCEND: Superior PFS for acalabrutinib





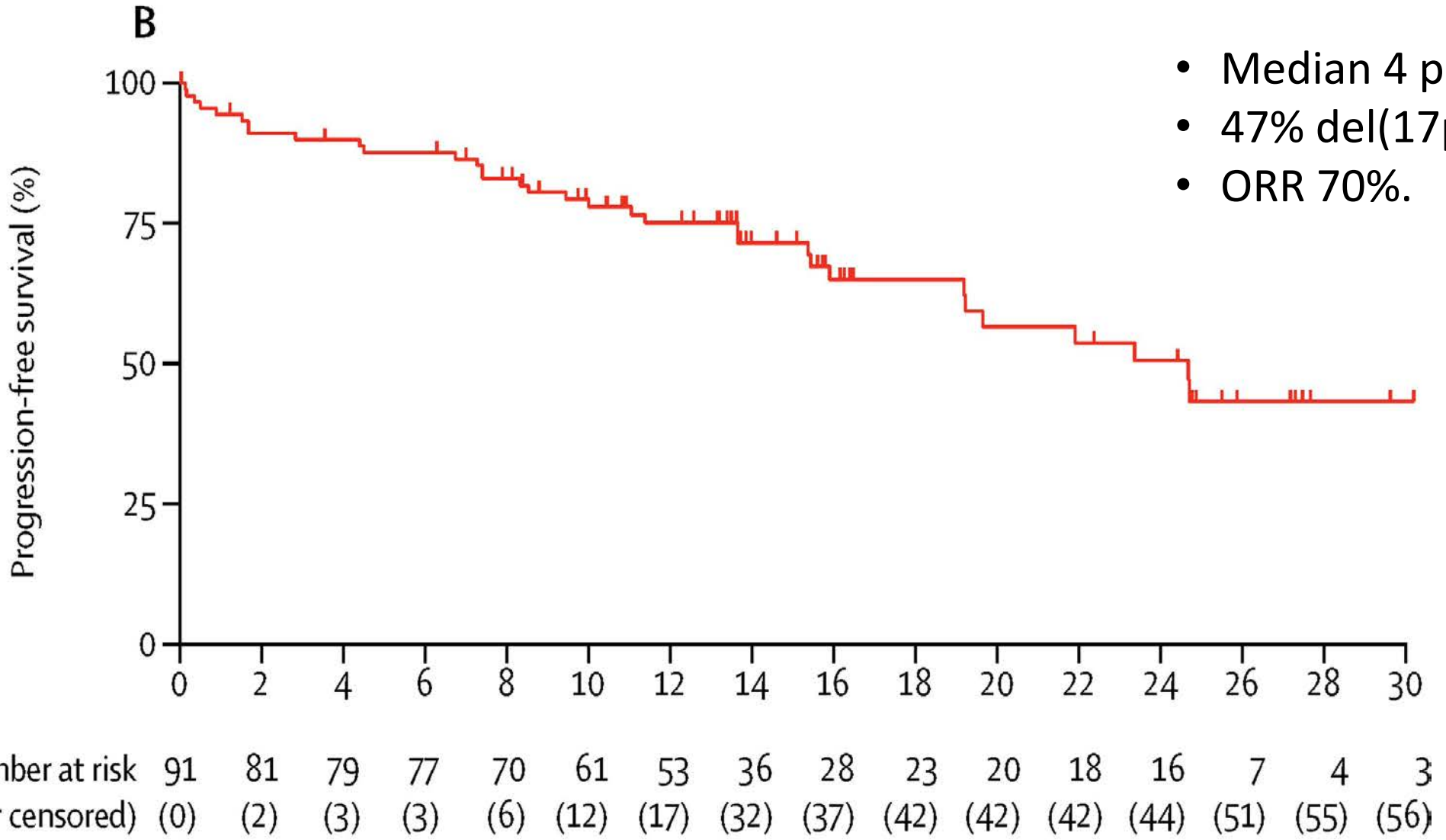
Jurczak W et al. ASCO 2022;Abstract 7538.

Summary – PI3K-delta inhibitors

- Idelalisib 150mg BID + rituximab remains approved for R/R CLL.
- Duvelisib withdrawn, umbralisib + ublituximab application for approval withdrawn.
- Tricky to use – close monitoring for immune transaminitis, colitis, opportunistic infections (PJP, CMV).
- Inferior PFS compared to acalabrutinib in head-to-head data.
- May have a role after failure/unavailability of both BTKi + ven, but extremely limited data for efficacy in this setting (and prefer clinical trials for such patients).

Treatment after failure of a targeted agent

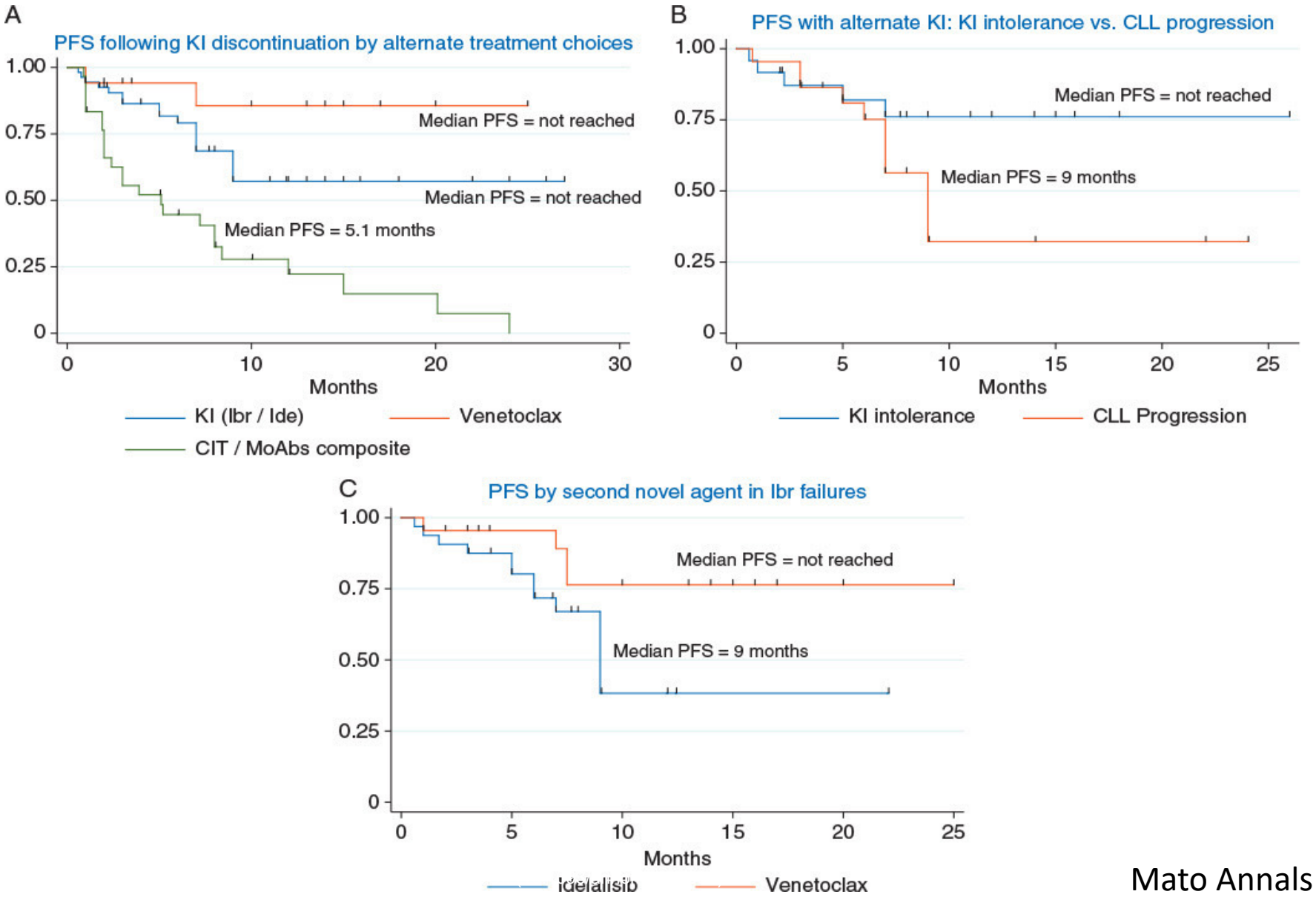
Venetoclax in ibrutinib refractoriness/intolerance



- Median 4 prior therapies.
- 47% del(17p)
- ORR 70%.

Jones et al. *Lancet Oncol* 2018

Treatment after kinase inhibitor failure – Real World data



Mato Annals of Oncology 2017

Treatment after time-limited venetoclax

- Venetoclax + Rituximab:

1. 72% ORR in 32 patients (5.6% CR) with venetoclax re-treatment.
2. Reasonable option, especially if U-MRD with first venetoclax therapy and long duration of off-treatment remission.

- Ibrutinib treatment after ven-R (n=18) showed 100% ORR.
- After ibrutinib + venetoclax:

1. 9 patients on CAPTIVATE Fixed duration cohort re-treated with ibrutinib monotherapy. 7 responded, 2 too early.[2]

[1]Seymour et al. *Blood* 2022 [2] Tam *Blood* (2022) 139 (22): 3278–3289)

Selecting 2nd line therapy

- No data based on long term efficacy to decide between BTKi/ven
- Key determinants: what 1L therapy was received; comorbidities and AE profile; desire for time-limited therapy:

1. Chemoimmunotherapy 1L → BTKi or venetoclax.
2. Venetoclax + Obinutuzumab 1L → BTKi or venetoclax if prolonged remission and deep initial response (ideally on clinical trial).
3. BTKi 1L →:
   - Intolerance → trial of alternative BTKi or venetoclax +/- rituximab.
   - Resistance → venetoclax +/- rituximab.

Double-refractory CLL

- Non-covalent BTKi – pirtobrutinib, nemtabrutinib.
- CAR-T – lisocabtagene ciloleucel. Others.
- Bi-specific antibodies – studies of epcoritamab in CLL/RS and mosunetuzumab

Efficacy of Pirtobrutinib, a Highly Selective, Non- Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results from the Phase 1/2 BRUIN Study

- 57 patients, 50 evaluable.
- Heavily pre-treated. Median 2 prior therapies for RT. Most had had prior covalent BTKi.
- 50 evaluable, 54% ORR (10% CR).
- Median DOR 8.6mo.

Wierda WG et al. ASH 2022; Abstract 347.

Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase Ib/2 Trial

- CD3x20 bi-specific antibody.
- Phase I study in CLL R/R CLL.
- 10 patients with Richter's Syndrome (1L therapy for RS in 6/10).
- Manageable toxicity (low-grade CRS in 90%).
- ORR 60%. 50% CR.

Kater AP et al. ASH 2022. Abstract 348