Ritrattamento e Sequencing

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DIPARTIMENTO
DI MEDICINA E CHIRURGIA

Treatment sequencing selection depends on several factors

- What frontline therapy?
- Efficacy and long-term disease control
- Age and comorbidities (eg, fitness, cardiac issues, renal insufficiency)
- Current disease status (eg, repeat cytogenetics/FISH, imaging, BM test if necessary to elucidate immune cytopenias)
- Patient preference
- The unspoken: impact of social support, ease of administration (eg, Is hospitalization required? Multiple visits, COVID-19), finances

1L and 2L

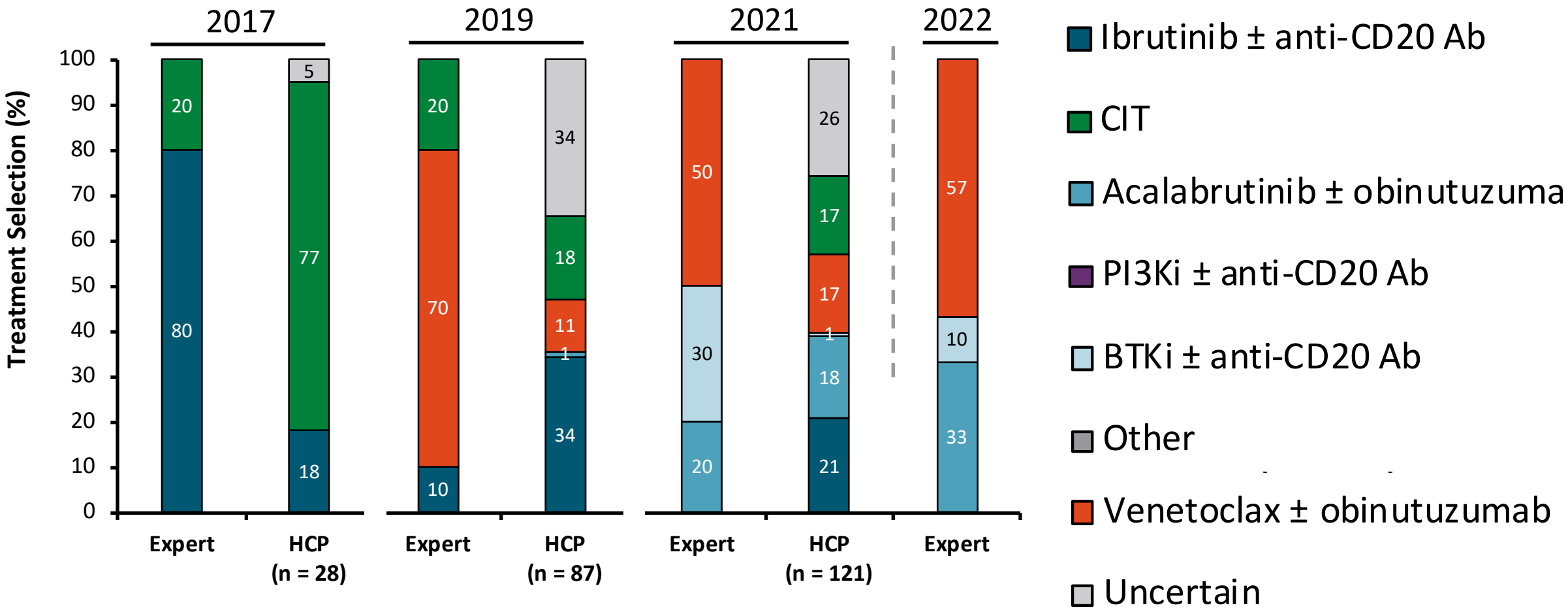
Which therapy is the “best initial therapy” in CLL?

There is no single best initial target therapy

Targeted Therapies	PFS Outcomes
Phase III E1912: ibrutinib + rituximab[1]	78% at 5 yr
ELEVATE-TN: acalabrutinib[2]	72% at 5 yr
ELEVATE-TN: acalabrutinib + obinutuzumab[2]	84% at 5 yr
CLL14: venetoclax + obinutuzumab[3]	74% at 5 yr
SEQUOIA: zanubrutinib[4]	~ >80% at 4 yr

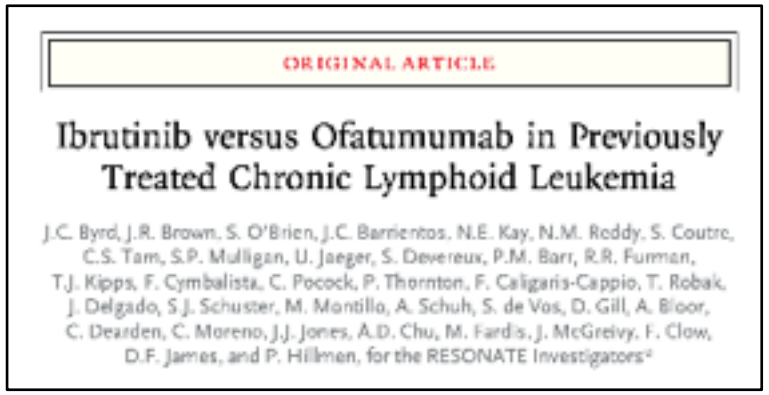
1. Shanafelt. Blood. 2022;140:112. 2. Sharman. ASCO 2022. Abstr 7539. 3. Al-Sawaf. EHA 2021. Abstr S146.
4. Tam. Lancet Oncol. 2022;23:1031

First-line treatment: CLL *without* del(17p), *TP53* mutation, or *IGHV* Mutation



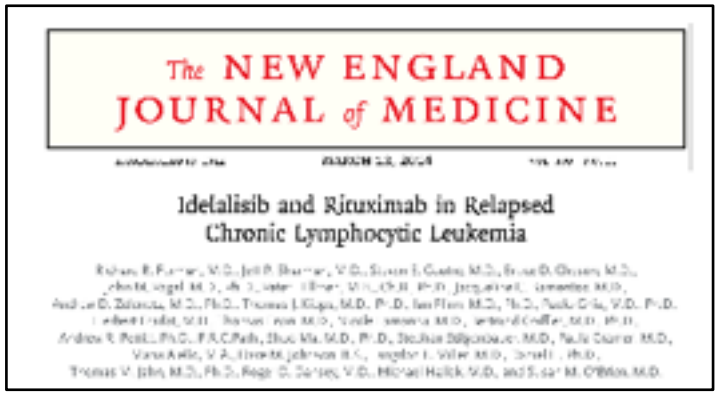
Additional variables (yes or no): 2017, age ≥65 yr and renal impairment; 2018, age ≥65 yr and fitness; 2019, age ≥65 yr and fitness and cardiac/bleeding concerns; 2020-2022, cardiac/bleeding concerns, bulky disease, or renal impairment. Analysis of younger, fit patients through 2019, then all patients included (no option to differentiate for these variables).

As CLL approaches expand, sequencing questions arise


ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

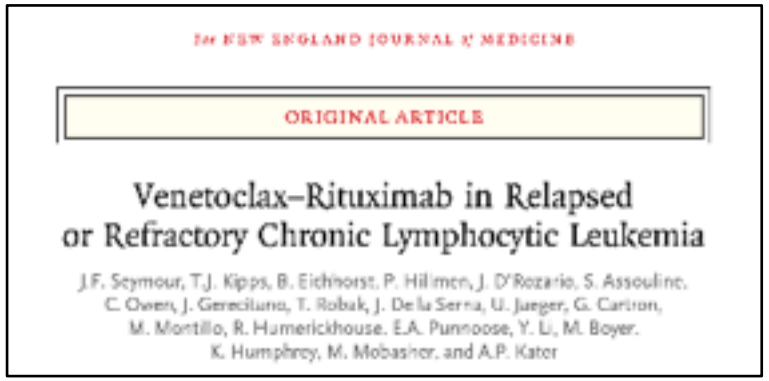
J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Jones, A.D. Chu, M. Fardis, J. McGreivy, F. Clow, D.F. James, and P. Hillmen, for the RESONATE Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia


original reports

ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

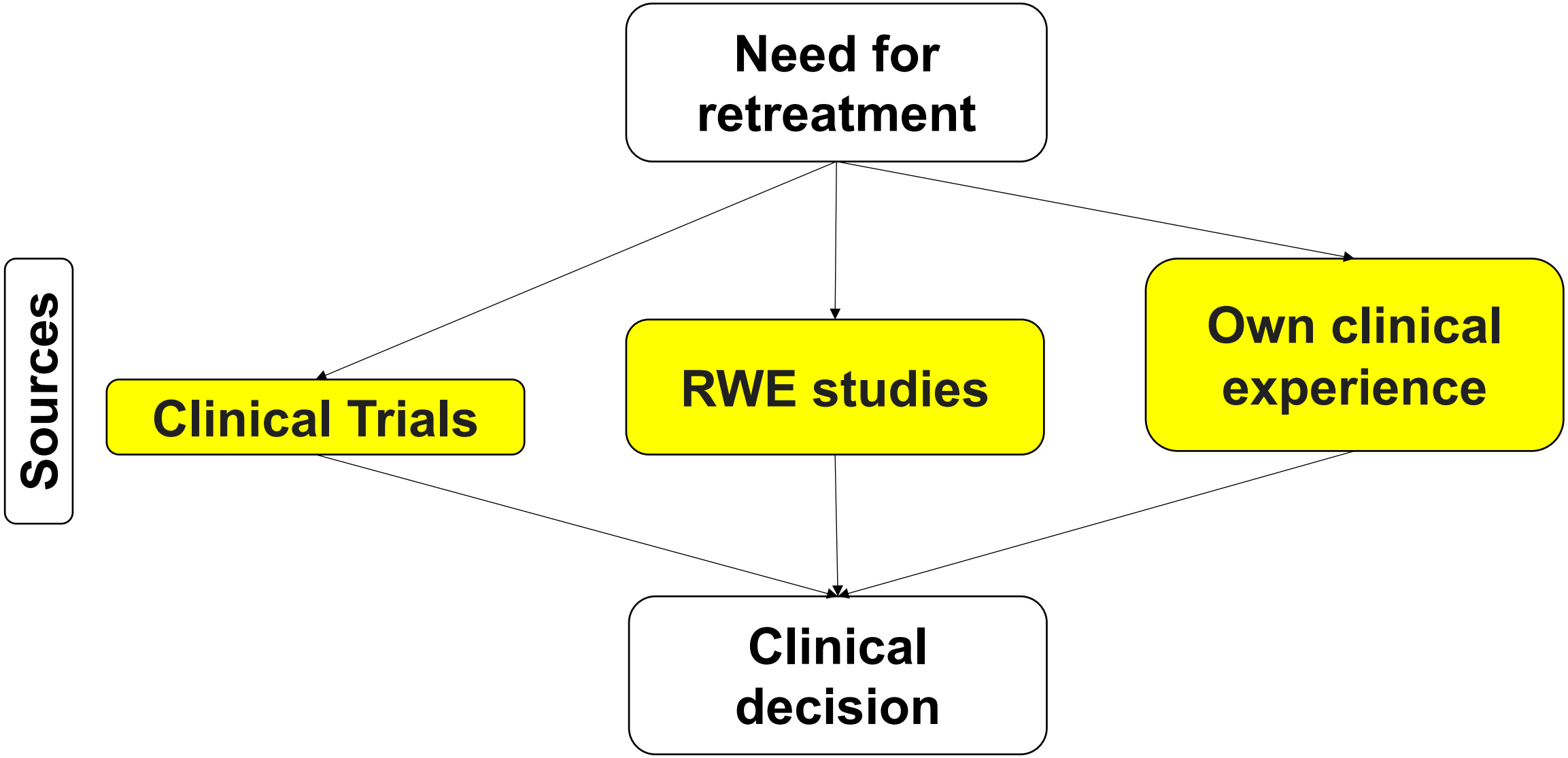
Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

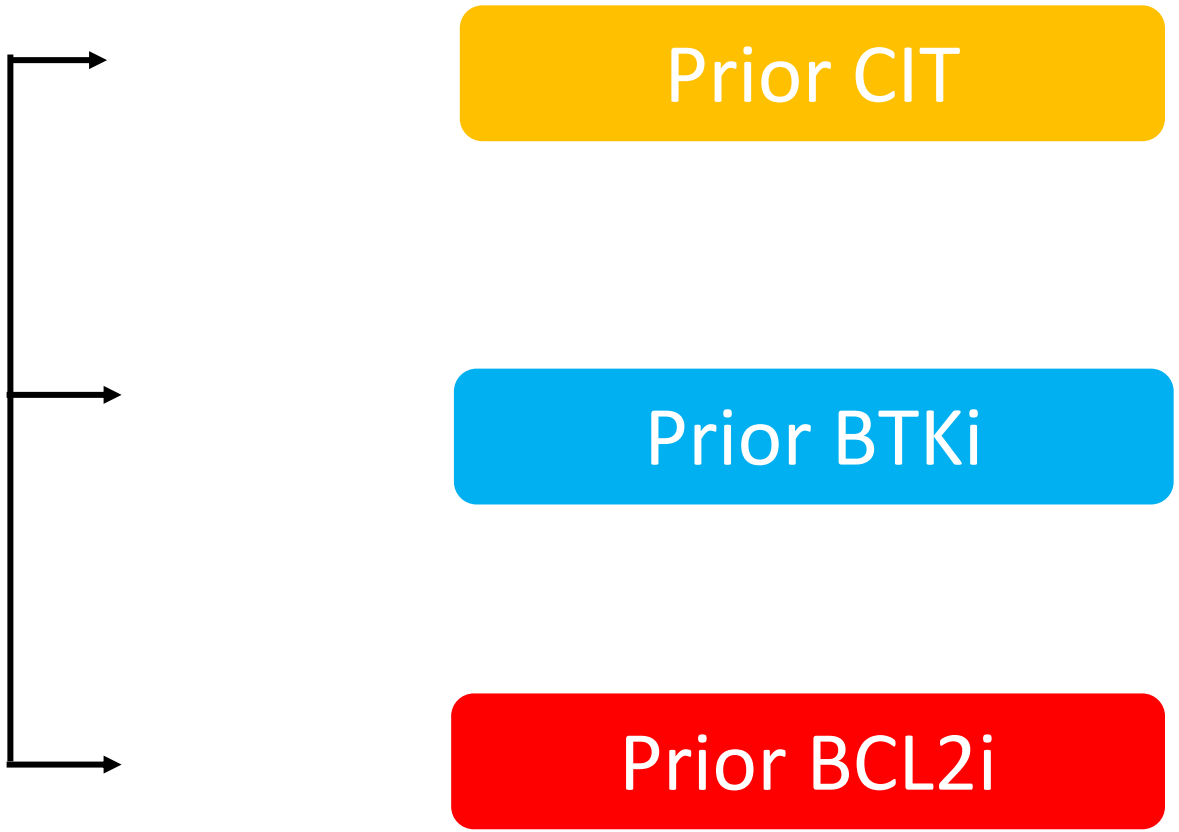
J.F. Seymour, T.J. Kipps, B. Eichhorst, P. Hillmen, J. D'Rozario, S. Assouline, C. Owen, J. Gerecitano, T. Robak, J. De la Serna, U. Jaeger, G. Carlton, M. Montillo, R. Humerickhouse, E.A. Punnoose, Y. Li, M. Boyer, K. Humphrey, M. Mobasher, and A.P. Kater

4 agents = 4 potential sequences in the R/R setting = 96 sequences
Who come first?

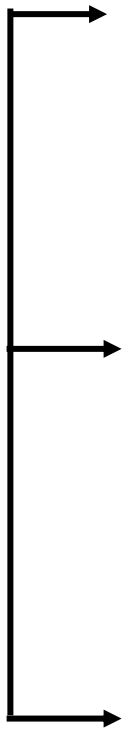

Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study

Byrd. NEJM. 2014;371:213. Furman. NEJM. 2014;370:997. Ghia. JCO. 2020;38:2849. Seymour. NEJM. 2018;378:1107. Flinn. Blood. 2018;132:2446. Stilgenbauer. Lancet Oncol. 2016;17:768.


Need for retreatment
Sources
Clinical Trials
RWE studies
Own clinical experience
Clinical decision


Prior CIT
Prior BTKi
Prior BCL2i

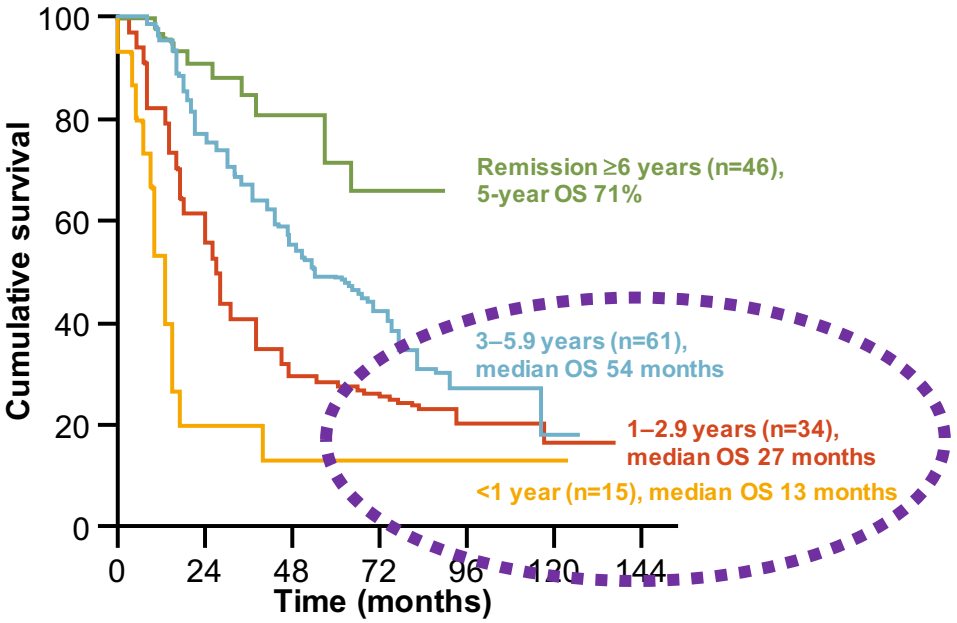
Prior CIT

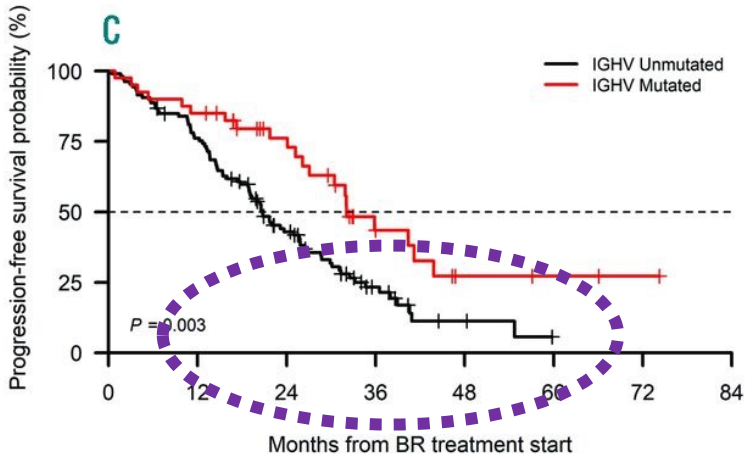


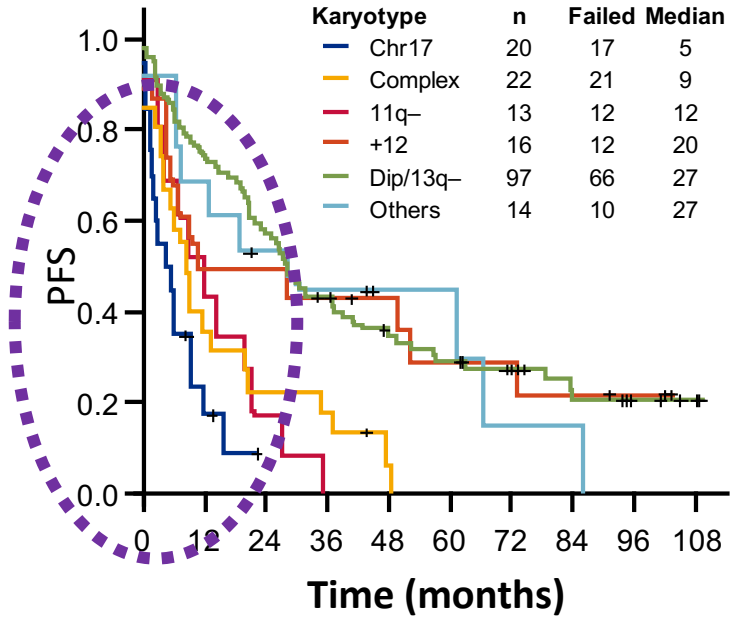
No role for second-line chemoimmunotherapy in CLL

Poor results in

- **PFS < 24-36 months**
- **unmutated IGHV**
- **TP53 aberrations**





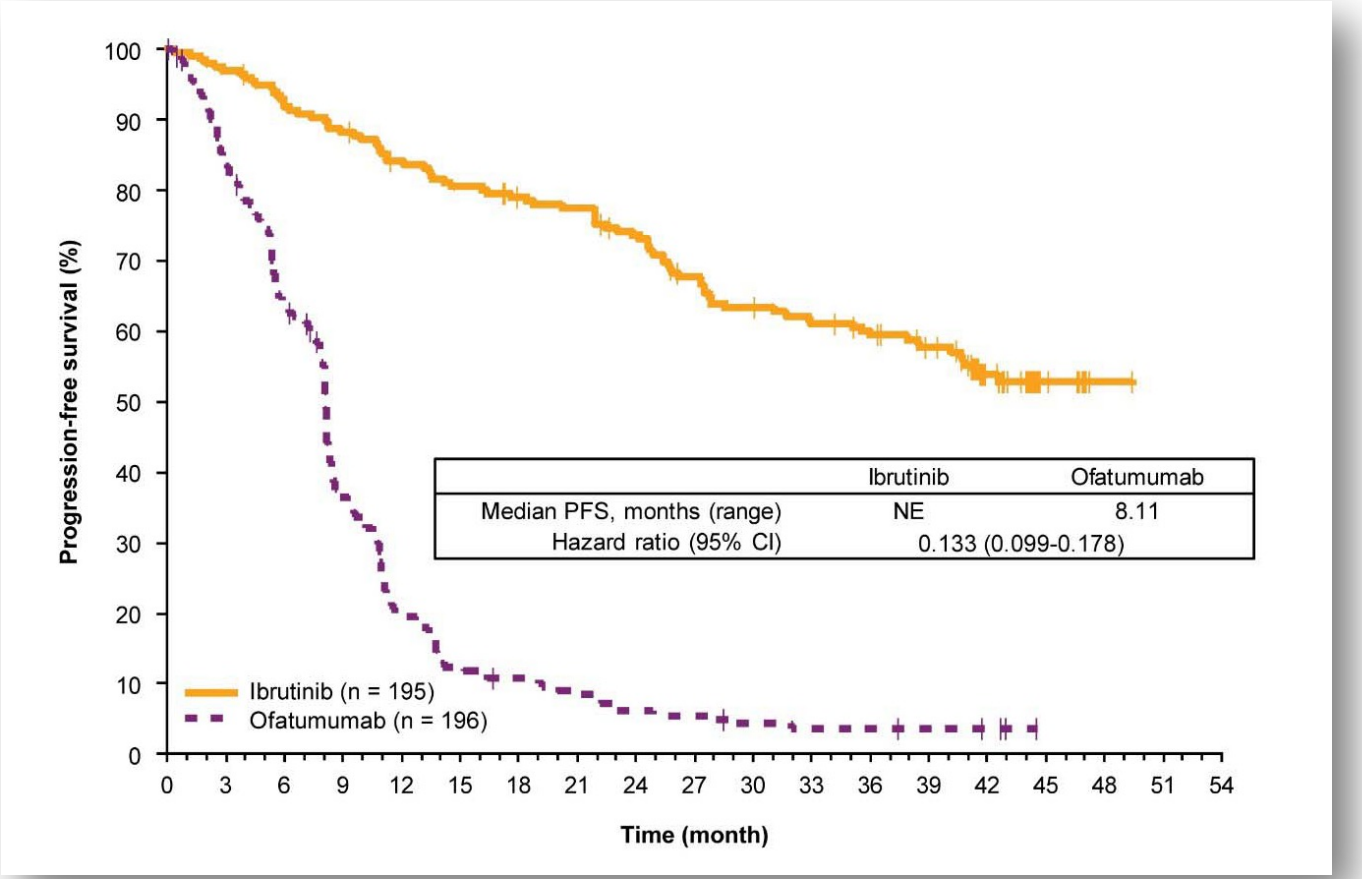


Tam CS, *et al. Blood* 2014; 124:3059–3064.

Cuneo A, *et al. Hematologica* 2018; 103:1209–1217

Badoux XC, *et al. Blood* 2011; 117:3016–3024.

Rationale for using Ibrutinib in R/R CLL: PFS Updated after 44 months of follow-up



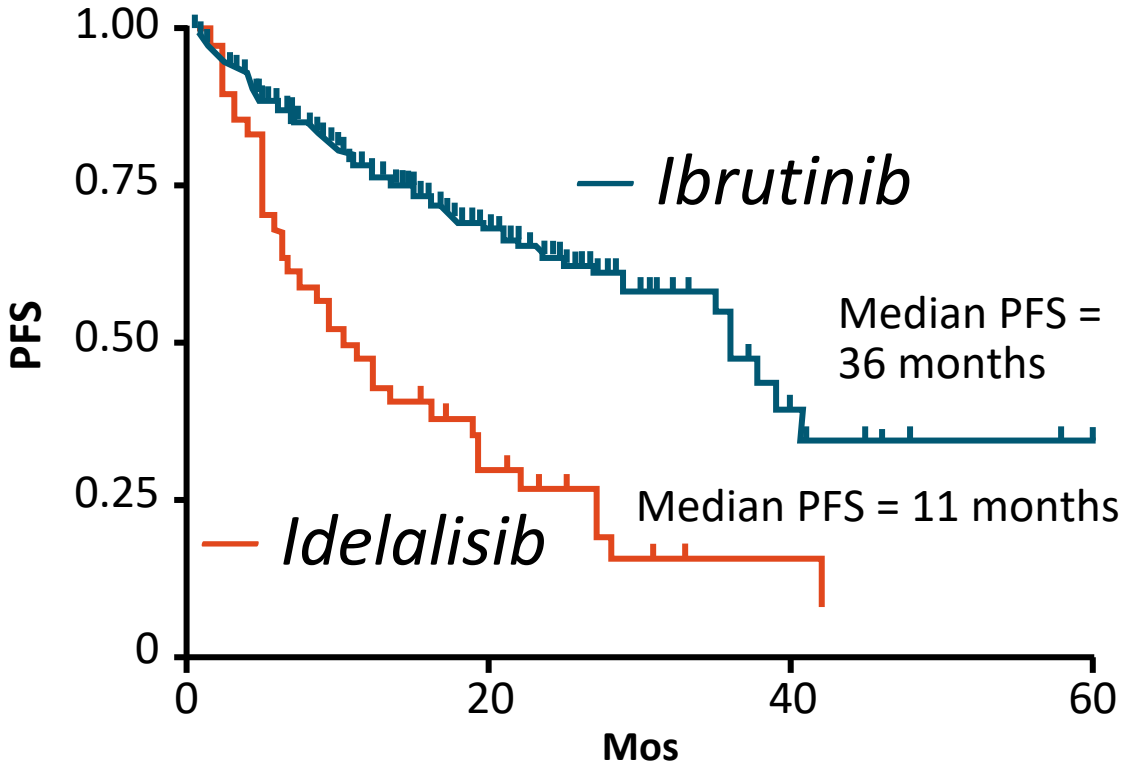
PFS mediana non raggiunta nel braccio Ibrutinib vs 8.11 mesi nel braccio Ofatumumab
HR 0.133

Durata mediana della terapia:
41 mesi
Il 46% dei pazienti è ancora in trattamento

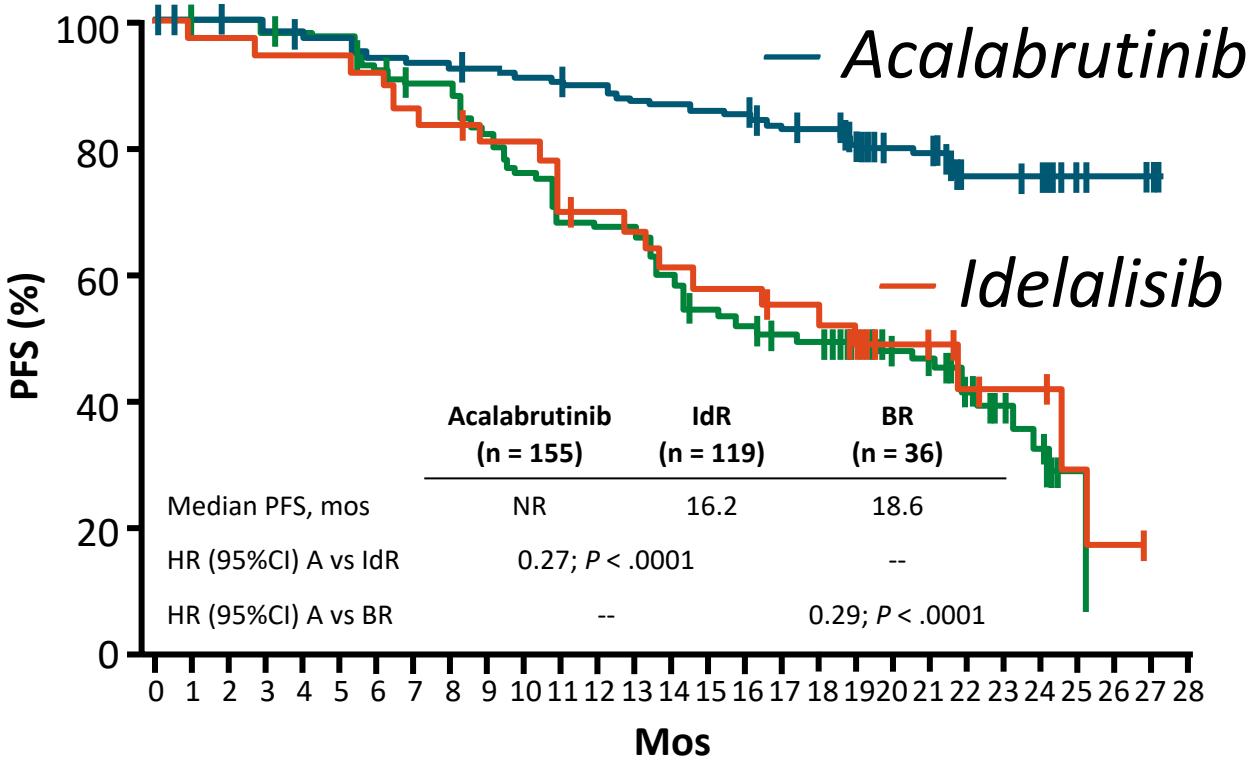
Byrd JC et al. Blood 2019

BTKi vs Idelalisib in R/R CLL (RWE and RCT Data)

RWE (2017): Multicenter Retrospective Analysis – PFS by First Kinase Inhibitor in R/R CLL[1]



RCT (2020): Phase III ASCEND Trial of Acalabrutinib vs Bendamustine-R or Idelalisib-R in R/R CLL[2]



BTKi vs Idelalisib: Superior PFS and, with acalabrutinib, fewer discontinuations due to AEs in real-world setting and RCT[1,2]

1. Mato. Ann Oncol. 2017;28:1050. 2. Ghia. JCO. 2020;38:2849.

Acalabrutinib vs Ibrutinib in Patients With High-Risk Relapsed/Refractory CLL (ELEVATE-RR)

Adults with previously treated CLL requiring treatment per iwCLL 2008; presence of del(17p) or del(11q); no significant CV disease; no prior tx w/BTK, PI3K, Syk, or BCL2 inhibitors; ECOG PS 0-2 (N = 533)

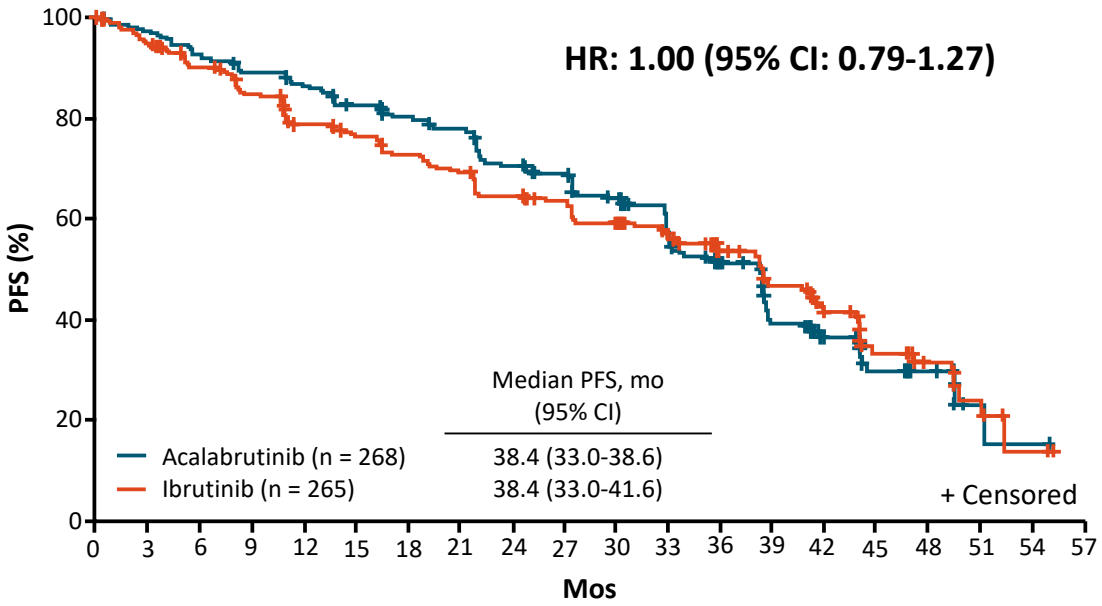
1:1

Acalabrutinib 100 mg PO BID (n = 268)

Ibrutinib 420 mg PO QD (n = 265)

→ *Continued until PD or unacceptable toxicity*

- Primary endpoint: noninferiority of IRC-assessed PFS (upper bound of 2-sided 95% CI for HR <1.429)
- Secondary endpoints: any-grade atrial fibrillation/flutter, grade ≥3 infection, Richter transformation, OS



Elevate R/R trial: Most common AE's (any grade ≥ 15%) in either arm

PROS

Any grade diarrhea, arthralgia, hypertensio, contusion, and atrial fibrillation occurred less frequently with acalabrutinib vs ibrutinib

	Any grade		Grade ≥3	
Events, n (%)	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Diarrhea[a,b]	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough[a]	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia[a]	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension[a,b]	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue[b]	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	47 (17.7)	49 (18.6)	0	1 (0.4)
Contusion[a]	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation[a]	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

CONS

Headache, cough and fatigue occurred more frequently with acalabrutinib vs ibrutinib

Higher incidence in **bold** for terms with statistical differences.
[a]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for any grade events. [b]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for grade ≥3 events.
AE = adverse event; URTI = upper respiratory tract infection.

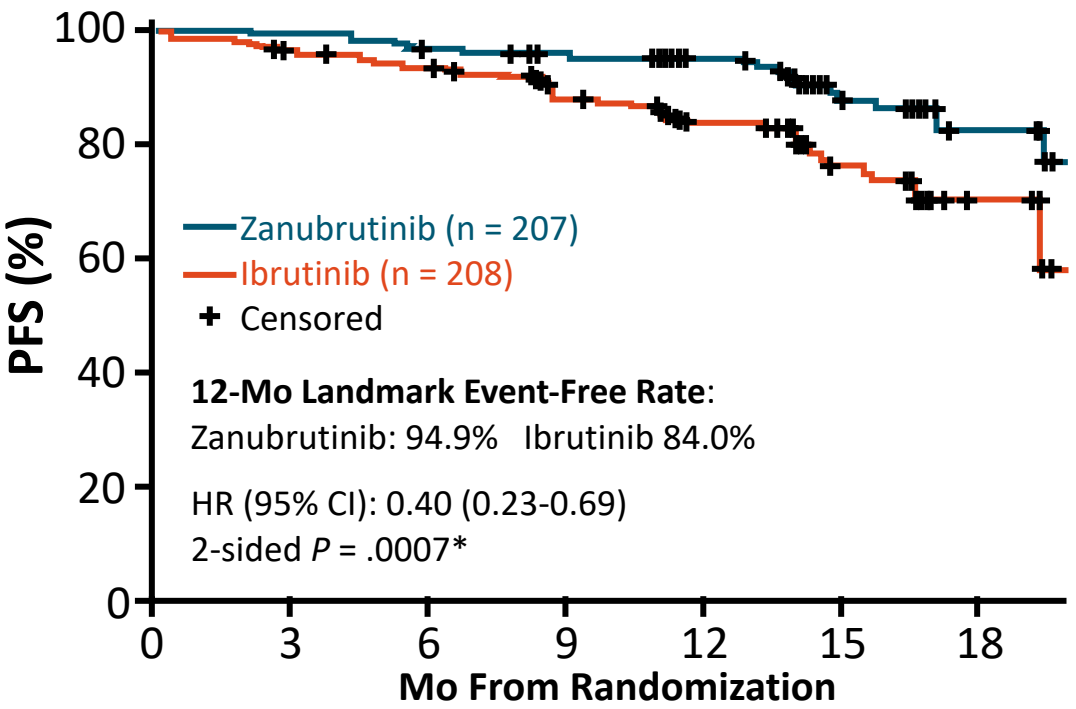
Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Zanubrutinib vs Ibrutinib in R/R CLL/SLL (ALPINE trial)

Open-label, randomized phase III trial of Zanubrutinib vs Ibrutinib for Patients with R/R CLL/SLL; ≥1 prior systemic tx for CLL/SLL; (N = 652; interim analysis: n = 415)

- Zanubrutinib significantly improved ORR vs ibrutinib (superiority 2-sided *P* = .0006; prespecified α = 0.0099)

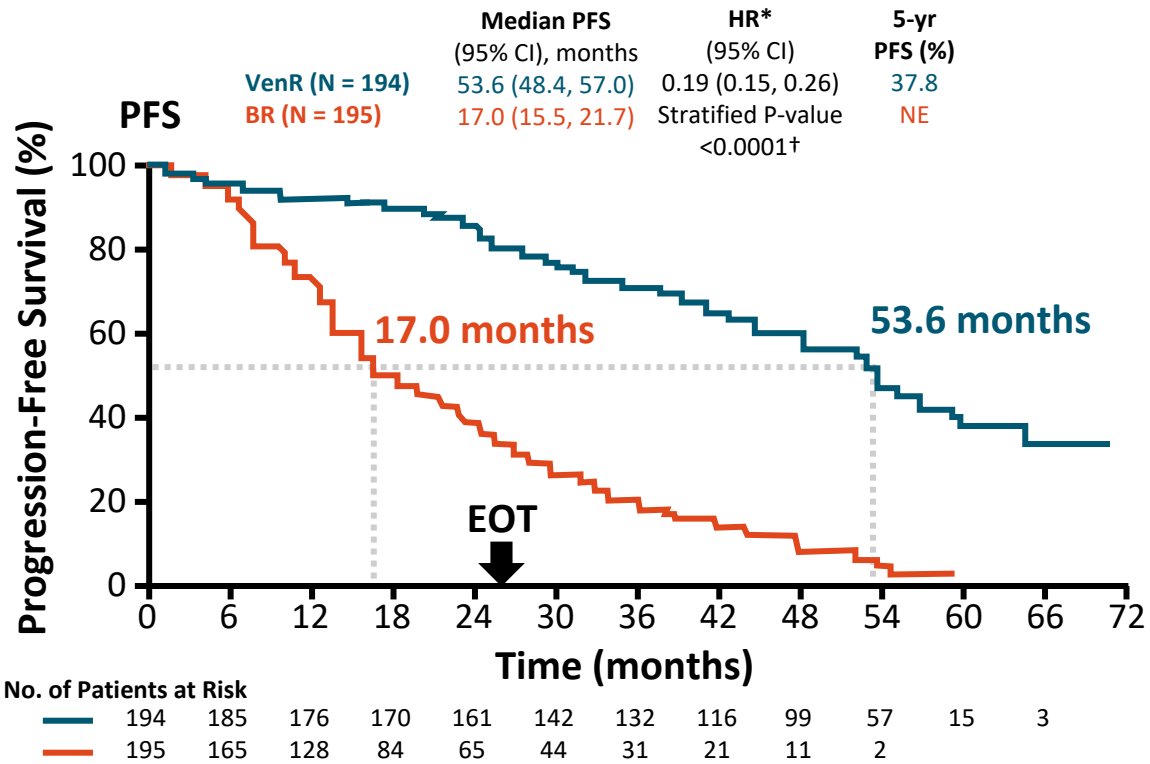
ORR, n/N (%)	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
All patients	162/207 (78.3)	130/208 (62.5)
Patients with del(17p)	20/24 (83.3)	14/26 (53.8)

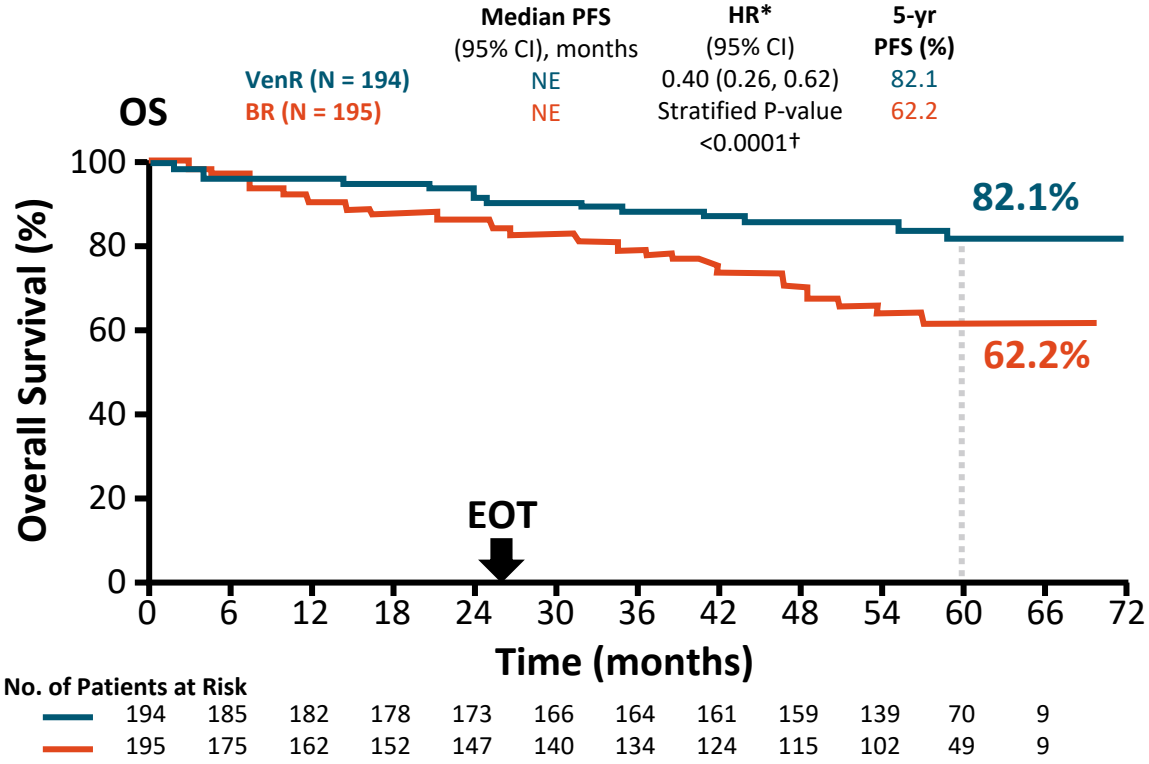


AE of Special Interest, n (%)	Zanubrutinib (n = 204)		Ibrutinib (n = 207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter	5 (2.5)*	2 (1.0)	21 (10.1)*	4 (1.9)
Hemorrhage ▪ Major hemorrhage	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 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	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies ▪ Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

Hillmen. EHA 2021. Abstr LB1900. NCT03734016.

5-Yr Analysis of the MURANO Study: PFS and OS

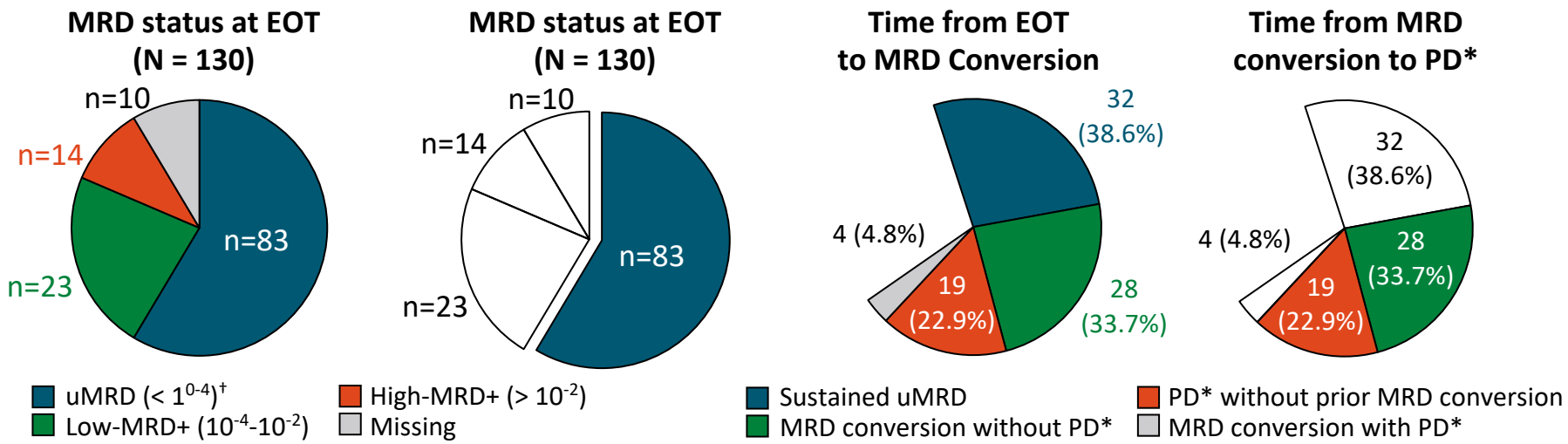


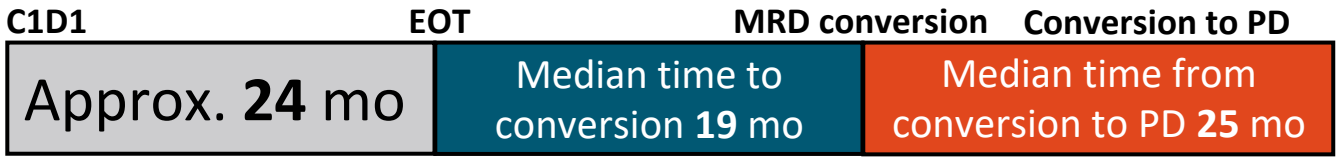


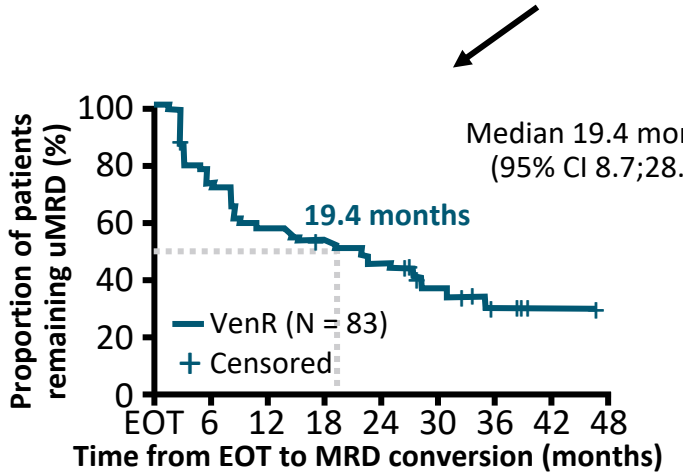
- This report included:
  - Outcomes with a median follow-up of 59 mos (range: 0-71.5)
  - Outcomes of patients off-therapy based on MRD status at EOT
  - MRD kinetics and MRD status of patients who received VenR retreatment

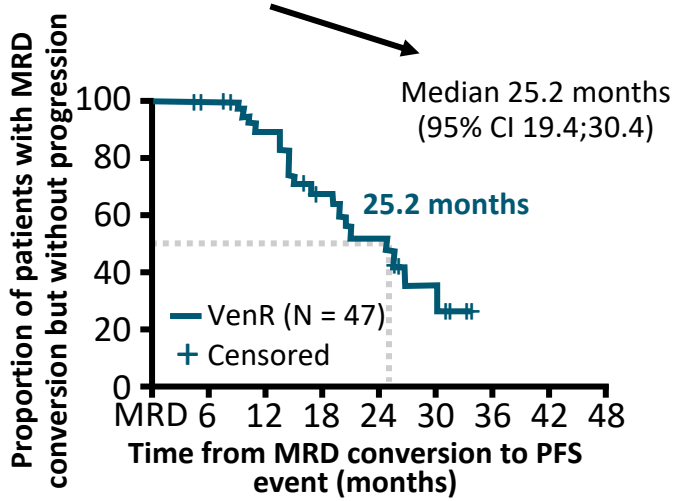
Kater. ASH 2020. Abstr 125.

5-Yr Analysis of uMRD From the MURANO Study









uMRD:<1 CLL cell/10,000 leukocytes.

Kater. ASH 2020. Abstr 125.

Relapsed/Refractory Setting in Novel Agent–Naive Patients: BTKi vs PI3Ki vs Venetoclax as Novel Agent?

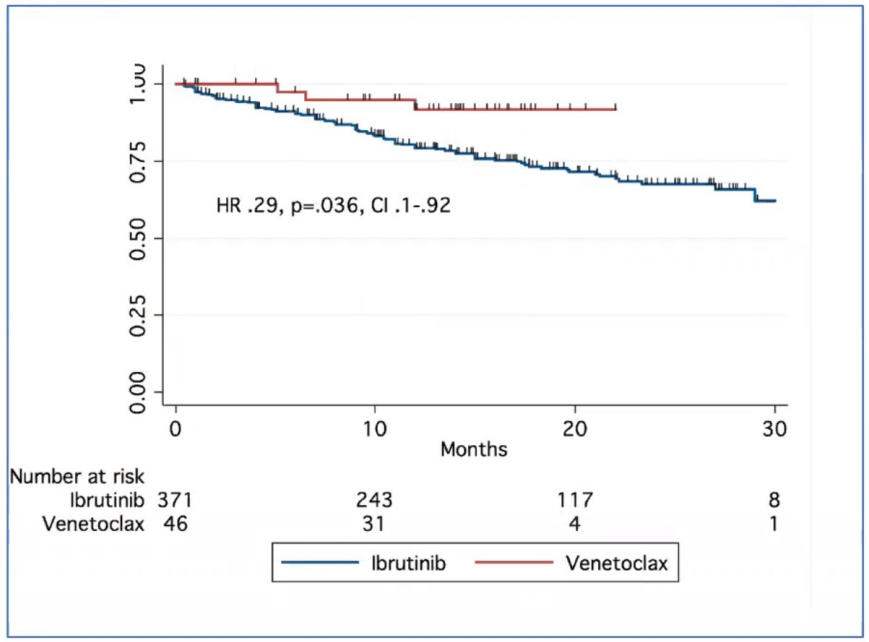
In all circumstances, when clinically acceptable, the data support BTKi or Ven before approved PI3Ki

No definitive comparative data to support Ven vs BTKi as first novel agent in novel agent–naive R/R CLL, but limited RWE data are intriguing

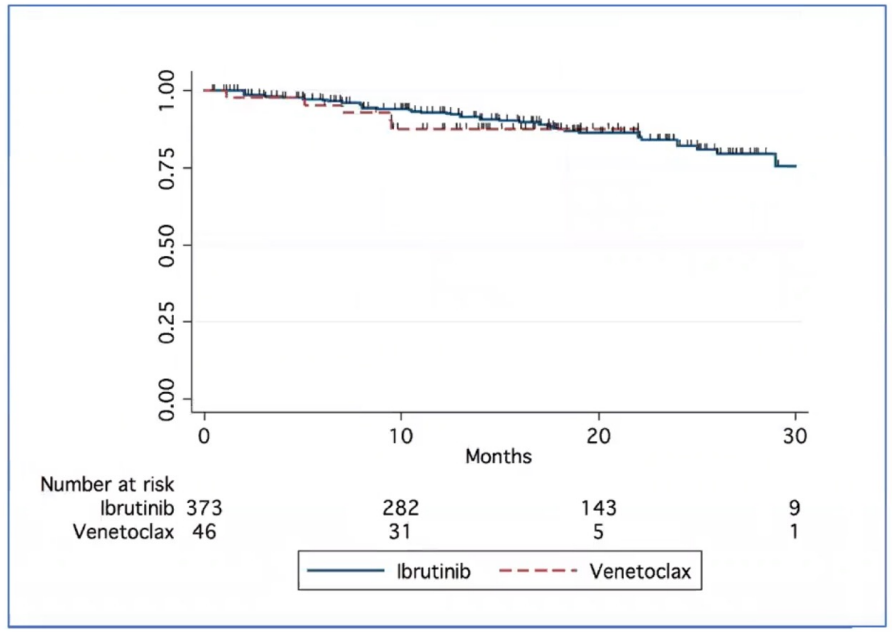
Table 1: Baseline characteristics of each novel therapy cohort

Baseline characteristics		Novel Agent		
First novel therapy	N	Ibrutinib	N	Venetoclax +/- anti-CD20
Median age at treatment (years; range)	382	69 (27-95)	48	65 (39-87)
Median number of prior therapies (number; range)	385	2 (1-4)	48	2 (1-4)
Del(17p)	255	24%	47	34%
Complex karyotype	157	32%	17	24%
Elevated LDH	189	45%	20	45%

Well Balanced

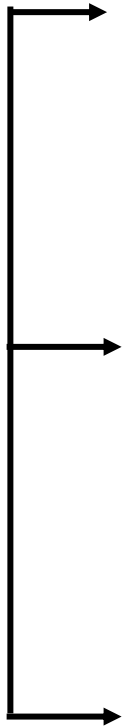


PFS



OS

Mato. Ann Oncol. 2017;28:1050. 2. Ghia. JCO. 2020;38:2849.
Eyre et al. Haematologica 2021 Jan 1;106(1):284-287. doi: 10.3324/haematol.2019.241539.



Prior BTKi

Prior BCL2i

How to best organize CLL treatment sequencing after front-line CT-free approach?

Consideration 1

Available options

*"Sequences are partially a consequence of the order in which they were **approved** rather than intrinsic tumor biology."*

Consideration 2

Reasons for discontinuation

- Completion of planned therapy (Ven-G only) with subsequent PD
- PD (known or unknown resistance mechanisms)
- Intolerance/AEs

Consideration 3

Levels of evidence

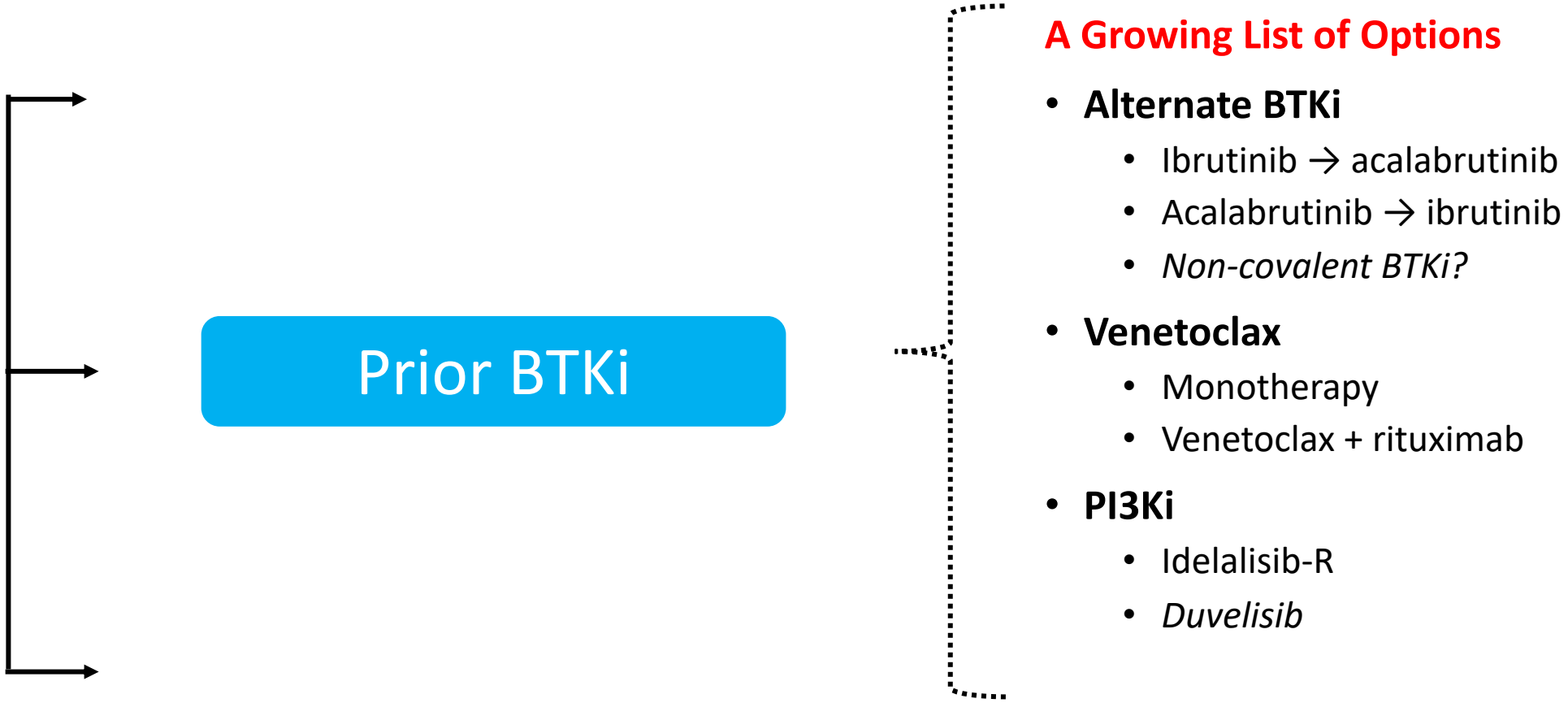
- Prospective data/interventional study (randomized data, single arm)
- Prospective registry data
- Retrospective "real-world" data

*"How readily data from **CIT** exposed patients can be **extrapolated** to the chemotherapy free pathway remains to be seen due to AE differences and resistance mechanisms"*

The majority of CLL patients on landmark R/R studies were not treated with prior novel agents

Agent	Study Name (Control Arm)	Number treated	Median (range) prior therapies	Percent on modern chemotherapy free pathways	Percent treated with ≥ 1 BTK, Ven or PI3K-i
Ibrutinib	Resonate (ofatumumab)	195	3 (1 - 12)	0%	0%
Acalabrutinib	ASCEND (investigator's choice: BR or idela-ritux)	155	1 (1 - 8)	0%	0%
Venetoclax monotherapy	Del 17p study (single arm)	107	2 (0 - 10)	Unknown <3.7%	3.7% (n=4)
Venetoclax-rituximab	Murano (BR)	194	1 (1 - >3)	Unknown <2.6%	2.6% (n=5)
Idelalisib-rituximab	STUDY 116 (placebo-ritux)	110	3 (1 – 12)	0%	0%
Duvelisib	DUO (ofatumumab)	160	2 (1 – 10)	0%	0%

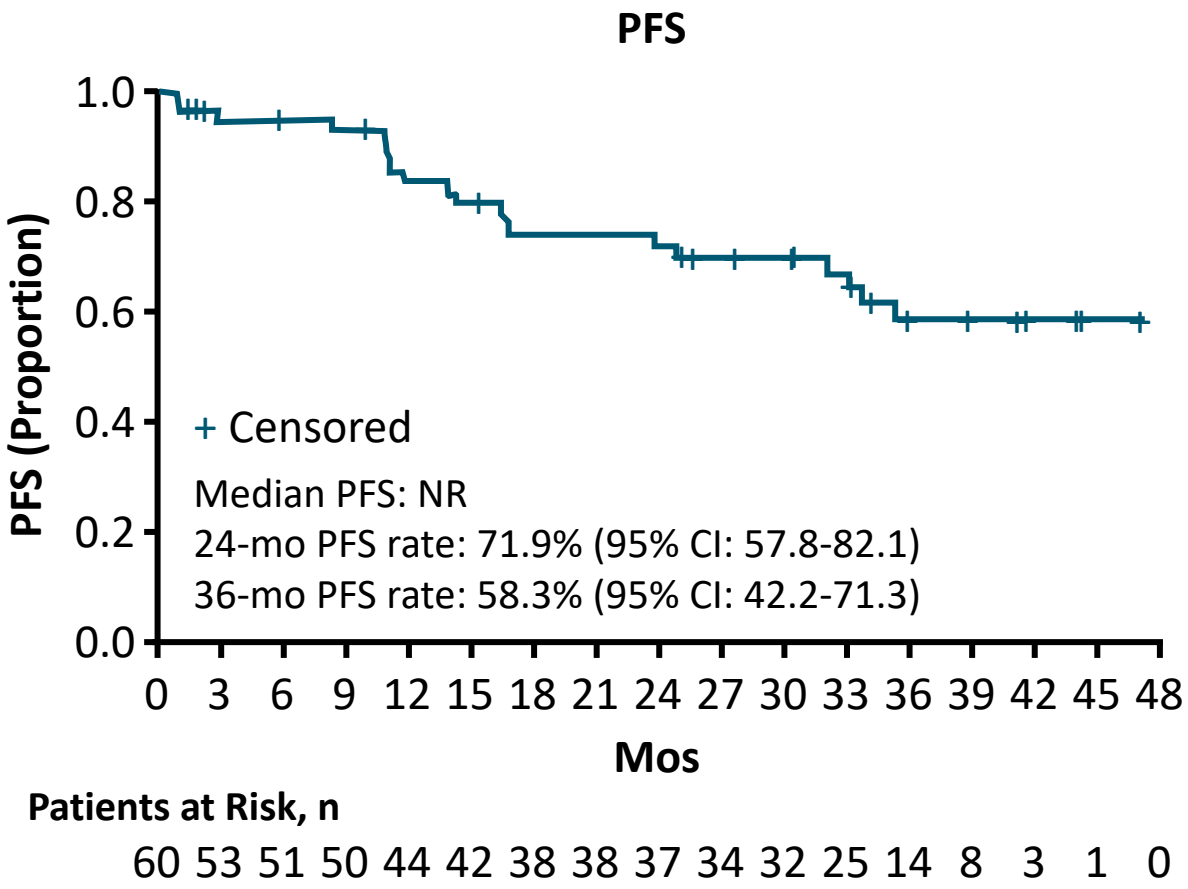
Only 9 of 921 patients (.001%) from 6 landmark studies were previously treated with at least one BTKi, Pi3Ki or venetoclax and likely none on a truly modern chemotherapy free pathway



All BTK inhibitor options are continuous therapies; treat until disease progression, transformation, or AE

Prospective Sequencing Data: Ibrutinib Intolerance → Acalabrutinib

- Phase II trial of acalabrutinib in patients with R/R CLL, ibrutinib intolerance, and disease activity



Parameter, n (%)	Patients (N = 60)
Median follow-up, mo (range)	34.6 (1.1-47.4)
On acalabrutinib	29 (48)
Discontinued acalabrutinib	31 (52)
▪ PD	14 (23)
▪ AE	10 (17)
▪ Patient withdrawal	3 (5)
▪ Physician decision	3 (5)
▪ Death	1 (2)*
▪ Other	1 (2)†
Death on study	11 (18)

*Due to AE leading to discontinuation (pneumonia). †Comorbid anorexia.

- At median follow-up of 34.6 mo, 48% of patients remain on acalabrutinib

Rogers. Haematologica. 2021;[Epub].

ACE-CL-208: Sequential Use of Acalabrutinib in Patients With Ibrutinib Intolerance is Safe and Effective

- ORR with acalabrutinib: 73% (CR/CRi: 8%)

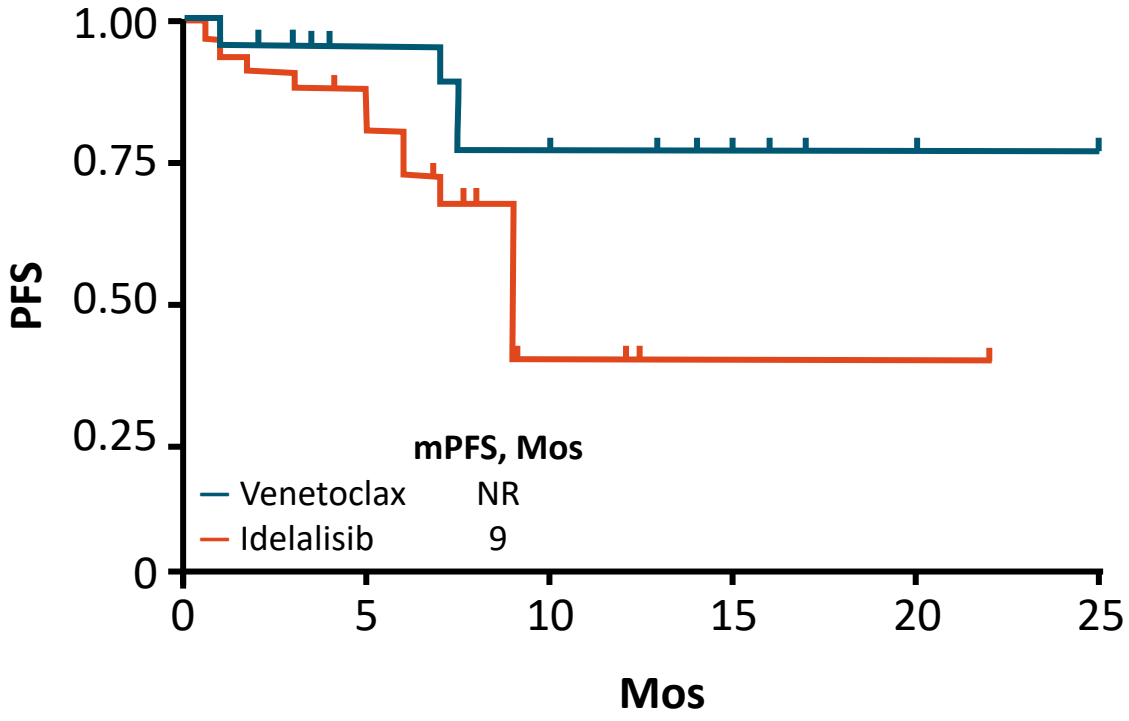
Events Resulting in Ibrutinib Intolerance*	No. of Patients	Acalabrutinib Experience for Same Patient, n			
		Overall	Lower Grade	Same Grade	Higher Grade
Atrial fibrillation	16†	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding‡¶	6	5	3	2	0
Arthralgia	7§	2	1	1	0

*41 of 60 patients meeting the study enrollment criteria had a medical history of ≥1 (43 events in total) of the following categories of ibrutinib intolerance events: atrial fibrillation, diarrhea, rash, bleeding, arthralgia. †Includes patients with atrial flutter (n = 2). ‡Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. ¶All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. §Includes 1 patient with arthritis.

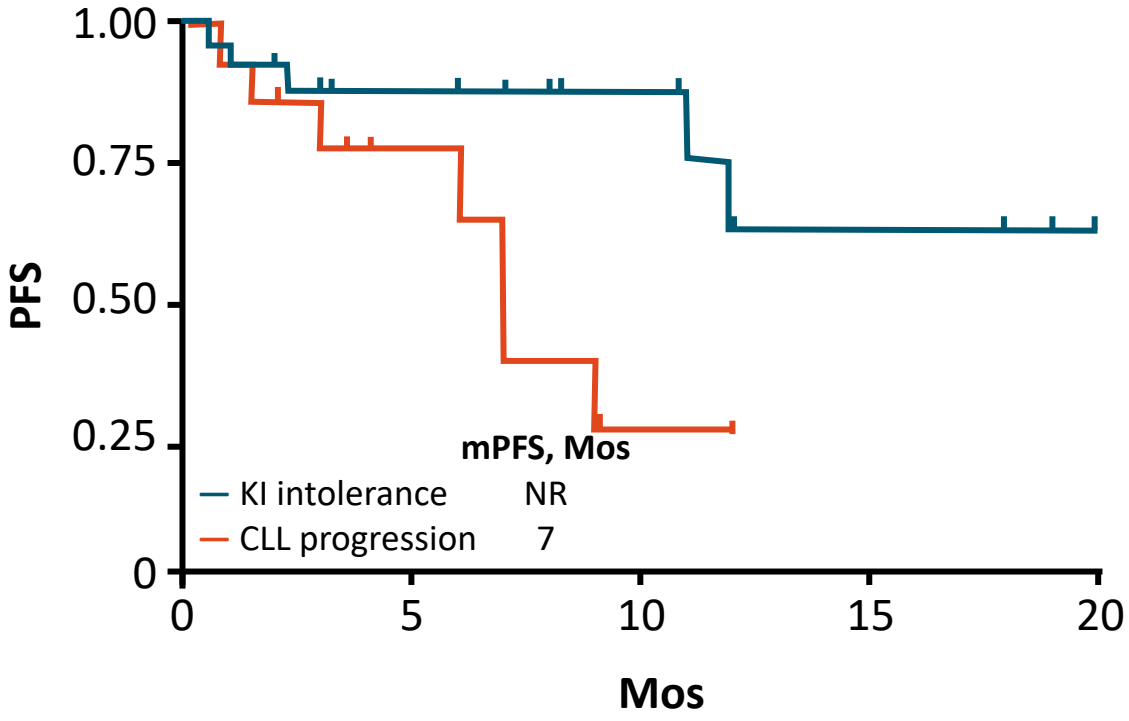
Rogers. Haematologica. 2021;106:2364.

Real-World Outcomes Following Ibrutinib in Patients Who Discontinued for Failure or Intolerance

RWE (2017): Multicenter Retrospective Analysis – PFS by Second Novel Agent After Ibrutinib Failure[1]

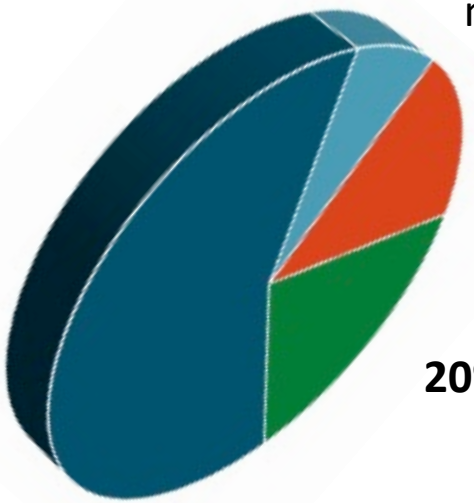


RWE (2016): Multicenter Retrospective Analysis – PFS by Discontinuation Reason (Treated With Alternate Kinase Inhibitor)[2]



1. Mato. Ann Oncol. 2017;28:1050. 2. Mato. Blood. 2016;128:2199.

Why Planning for Sequential Therapy Is Important?
Resistance to Covalent BTK Inhibitors

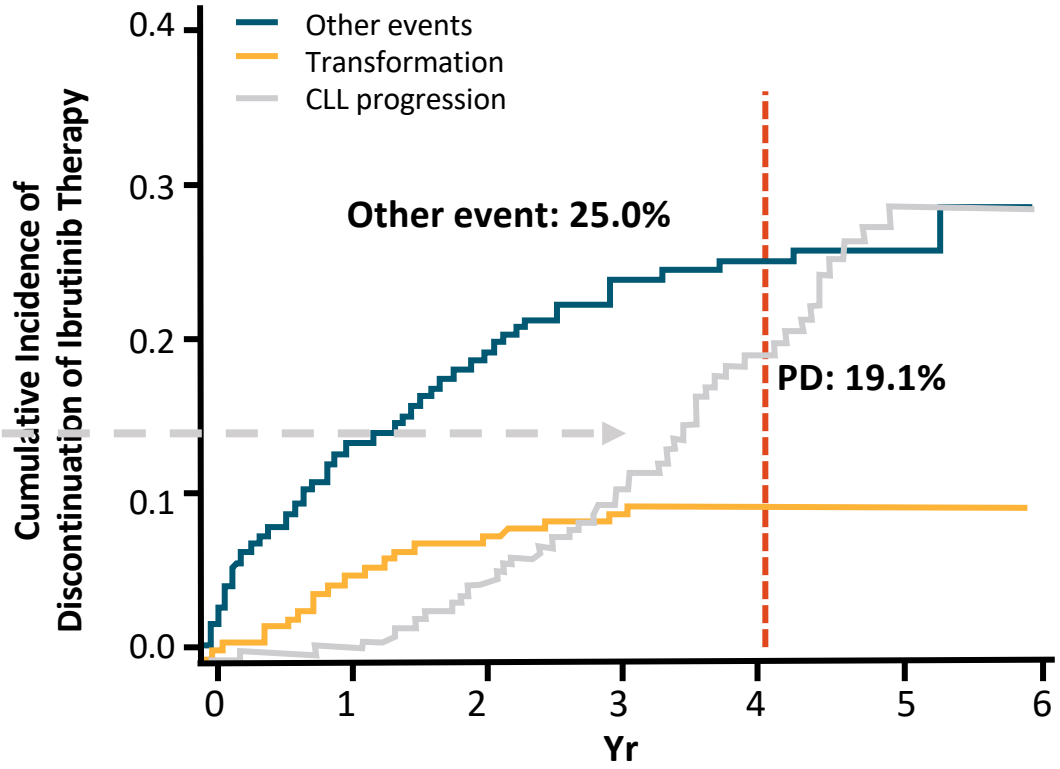


8% PLCγ2 mutants

16% BTK and PLCγ2 mutants

20% BTK and PLCγ2 not identified

56% BTK mutants



Ibrutinib Discontinuation Across 4 Clinical Trials

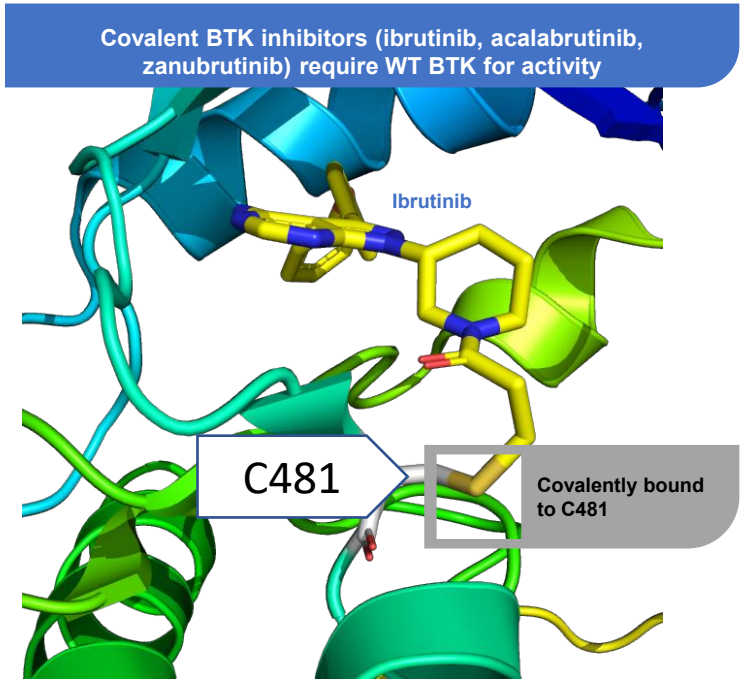
(Front line, 41%; R/R, 54% at 5 yrs FU)

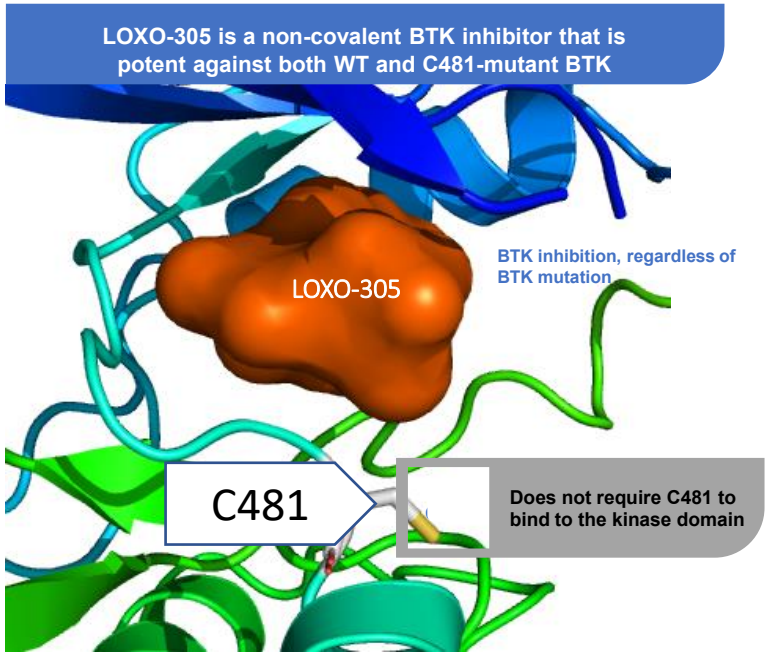
- BTK-activating mutations cause BTK inhibition by ibrutinib to be reversible and significantly decrease ibrutinib and BTK affinity (~50×)
- PLCγ2-activating mutations lead to autonomous activation of the B-cell receptor signal transduction pathway and are insensitive to BTK inhibition by ibrutinib

1. Woyach. JCO. 2017;35:1437. 2. Lampson. Expert Rev Hematol. 2018;11:185. 3. Mato. ASH 2019. Abstr 501. 4. Burger. Leukemia. 2020;34:787.

Classes of BTK Inhibitors

COVALENT	NON-COVALENT
IRREVERSIBLE	REVERSIBLE
Ibrutinib Acalabrutinib Zanubrutinib	Pirtobrutinib (LOXO-305) Nemtabrutinib (ARQ531)

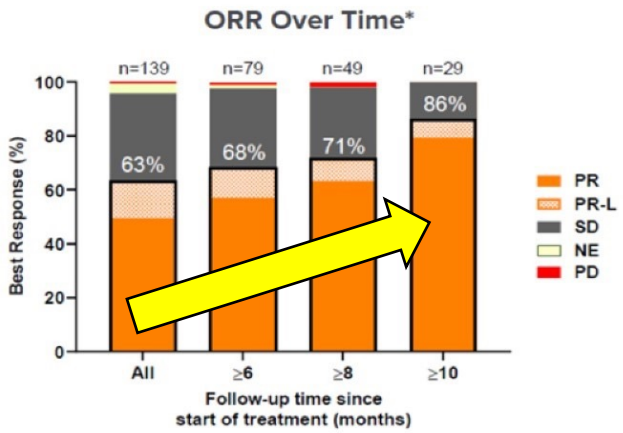


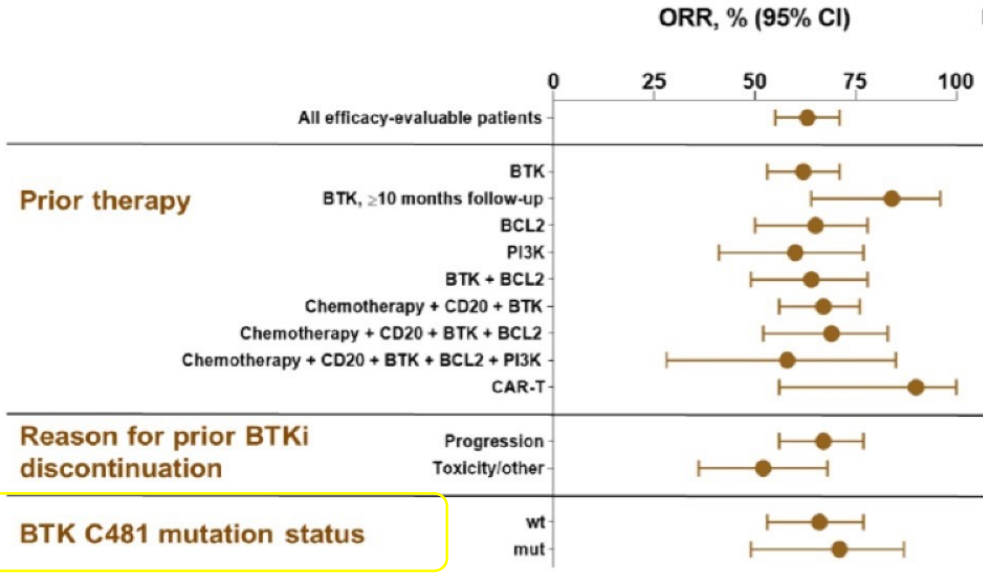


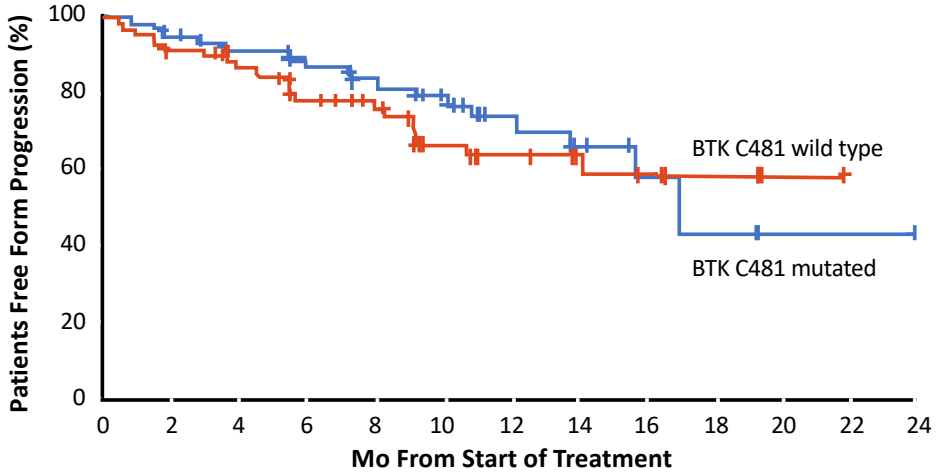
Pirtobrutinib efficacy regardless of BTK experience, C481 mutations and other prior therapy

Overall Response Rate in all CLL/SLL patients and BTK pre-treated subgroup

Response	Efficacy Evaluable (n = 139)	BTK-Pretreated Efficacy Evaluable (n = 121)
ORR, % (95% CI)	63 (55-71)	62 (53-71)
Best response, n (%)		
CR	0	0
PR	69 (50)	57 (47)
PR-L	19 (14)	18 (15)
SD	45 (32)	41 (34)







Mato et al., Lancet 2021; 397: 892–901
Roeker L et al EHA 2021 Abs EP633

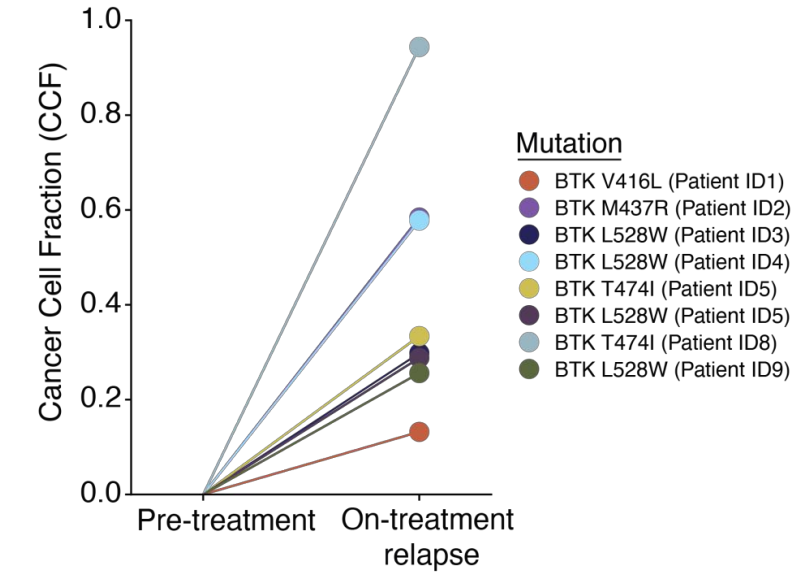
Pirtobrutinib Safety Profile

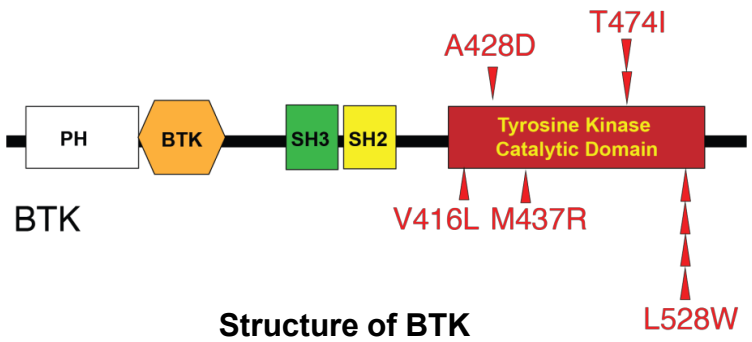
Adverse Event	All doses and patients (n=323) Treatment-emergent AEs, (≥10%), n (%)					Treatment-related AEs, n (%)	
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs of special interest							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter (<1%)	-	2	-	-	2 (<1%)	-	-

No DLTs reported and MTD not reached
5 of 323 patients (1.5%) discontinued due to treatment-related AEs
200mg QD selected as recommended Phase 2 dose

Mato et al., Lancet 2021; 397: 892–901

Acquired BTK mutations on Pirtobrutinib





Structure of BTK

We identified novel acquired mutations in BTK at the time of disease progression including:

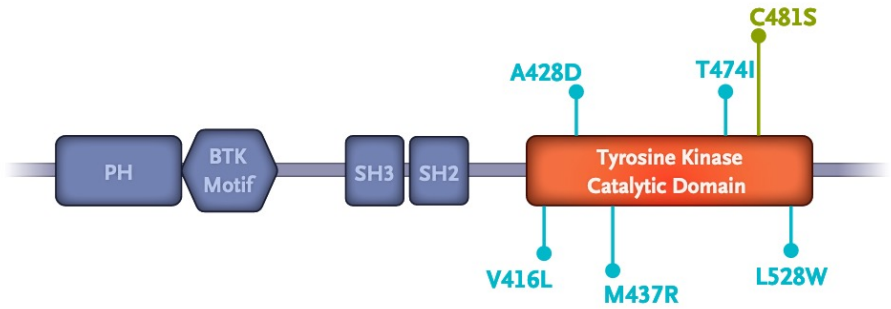
- ***BTK* L528W**
- ***BTK* V416L**
- ***BTK* M437R**
- ***BTK* T474I**
- ***BTK* A428D**

These mutations cluster around the tyrosine kinase catalytic domain of BTK.

Additionally, several patients with progressive disease had pre-existing PLCG2 mutations.

Wang et at. NEJM 2022

Mutations Conferring Resistance to BTK Inhibitors

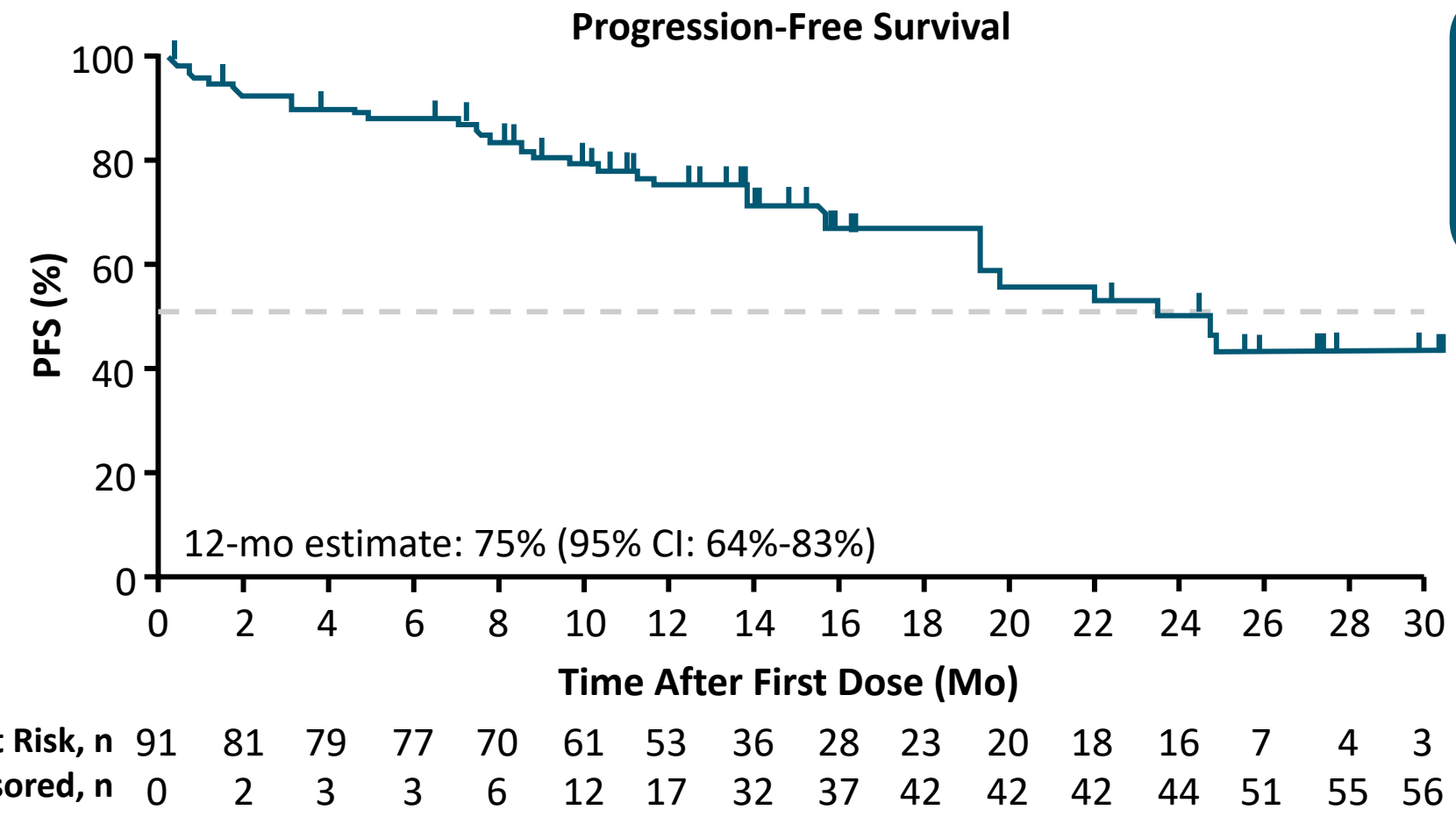


Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

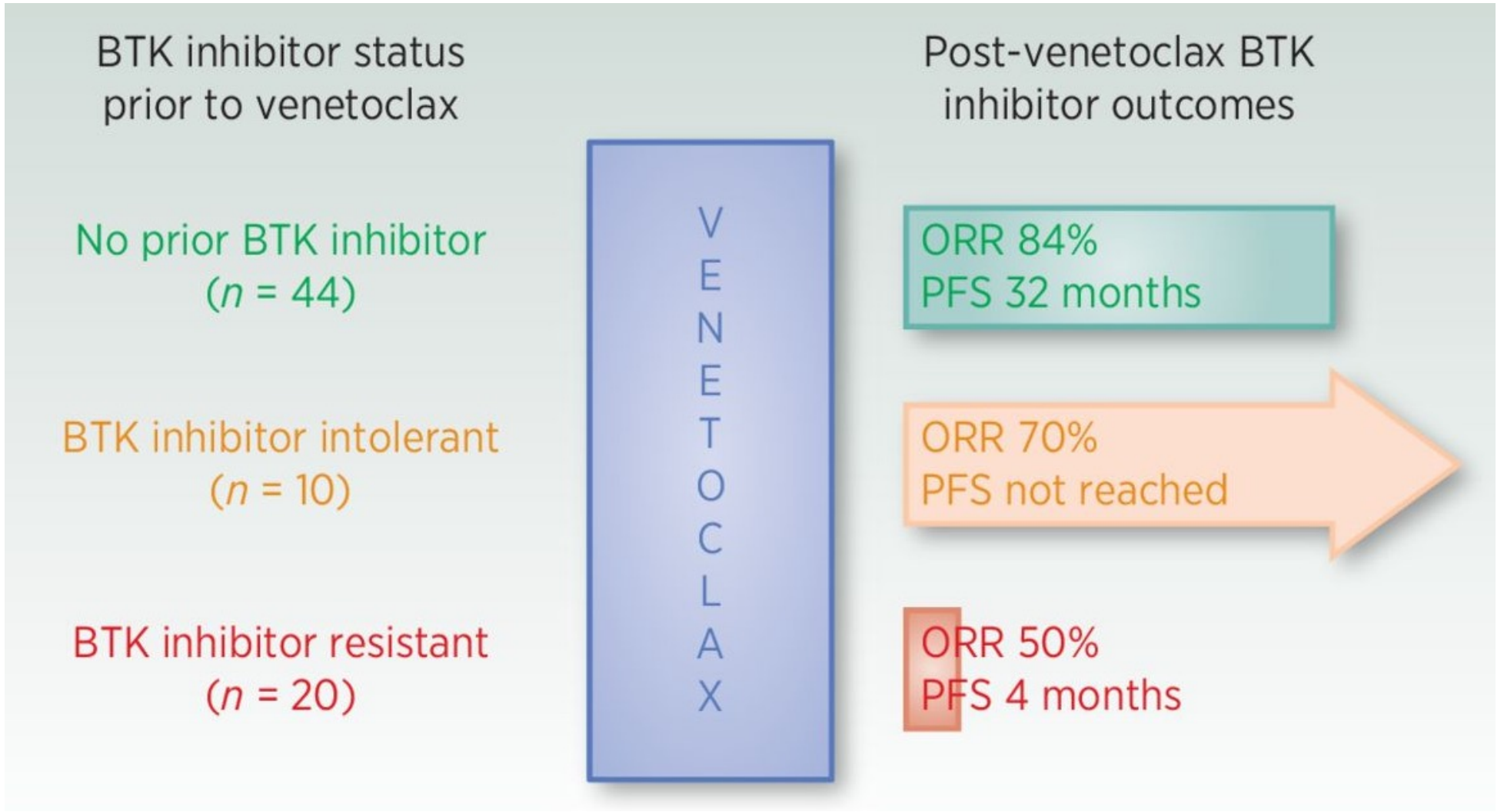
Wang et at. NEJM 2022

Venetoclax is an Active Option in Ibrutinib-Refractory/Ibrutinib-Intolerant CLL



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

Jones. Lancet Oncol. 2018;19:65.



Rogers K. Clin Cancer Res. 2020
Mato A et al. Clin Cancer Res. 2020

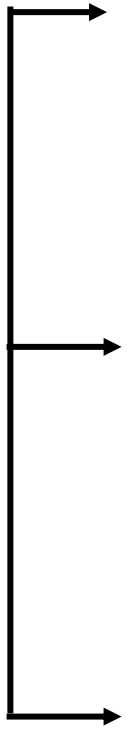
Next Options Determined by Reason for BTK Inhibitor Discontinuation

BTK Inhibitor Intolerance

- Alternative BTK inhibitor
- Venetoclax-based therapy
- PI3K inhibitor

BTK Inhibitor Resistance

- Venetoclax-based therapy
- PI3K inhibitor (untested prospectively/limited data to show)
- *Alternative:* noncovalent BTK inhibitor on a clinical study



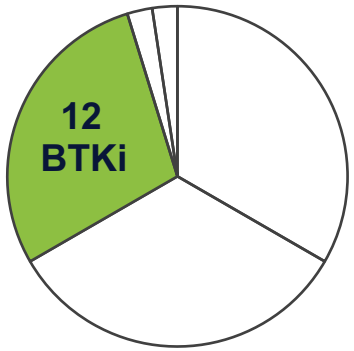
Prior BCL2i

A Growing List of Options/Less Data

- **Venetoclax-based therapy in retreatment**
  - Ven-G
  - Ven-R
  - Ven monotherapy
- **BTKi**
  - Covalent
  - *Non-covalent*
- **PI3Ki**
  - idelalisib-R
  - *duvelisib*

Time limited for 12 mo; treat to completion of therapy, CLL progression, transformation, or AE

Retreatment With Venetoclax Following Time-Limited Venetoclax-Based Regimens: *Response to Ibrutinib*



- 9/12 patients completed MURANO therapy regimen
- 2/12 discontinued treatment early due to AE, but had meaningful treatment-free intervals of 857 and 874 days
- 1/12 progressed on active venetoclax therapy and appeared to be Ven refractory

VenR → Ibrutinib

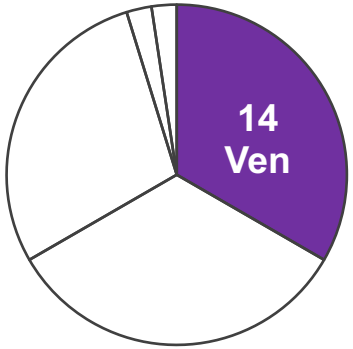
Time on Ibr	Best response to Ibr
190*	PR
215	PR
250	Not available
359*	PR
364*	PR
374*	PR
431*	PR
458	PR
470*	PR
665*	PR
683*	Not available
1304	PR

- 8/12 patients have ongoing Ibr treatment.
- 3/12 patients have progressed (one death due to PD).
- 1/12 patients did not progress but has started new therapy

Response rate: 10/10 (100%)

Seymour JF, et al. ASH 2019 Abstract #355

Retreatment With Venetoclax Following Time-Limited Venetoclax-Based Regimens: *Response to Venetoclax*



- 13/14 patients completed MURANO therapy regimen
- 1/14 discontinued treatment early
- 4/14 achieved CR as best response on MURANO

VenR → Venetoclax

	Time on Ven-based regimen	Best response to Ven-based regimen
Ven	20	Not available
	281*	Not available
	504	PR
Ven R	221*	PR
	59	PR
Ven + Ibr	867*	PR?
VenR (MURANO regimen)	49	PD
	160*	Not available
	175*	Not available
	243	PD
	252*	PR
	259*	PR
	261*	SD
	270*	SD

- 9/14 patients have ongoing treatment with Ven-based regimen.
- 2/14 achieved stable disease status – both of which are participants in the substudy and both patients continue therapy.
- 3/14 had PD (one death).

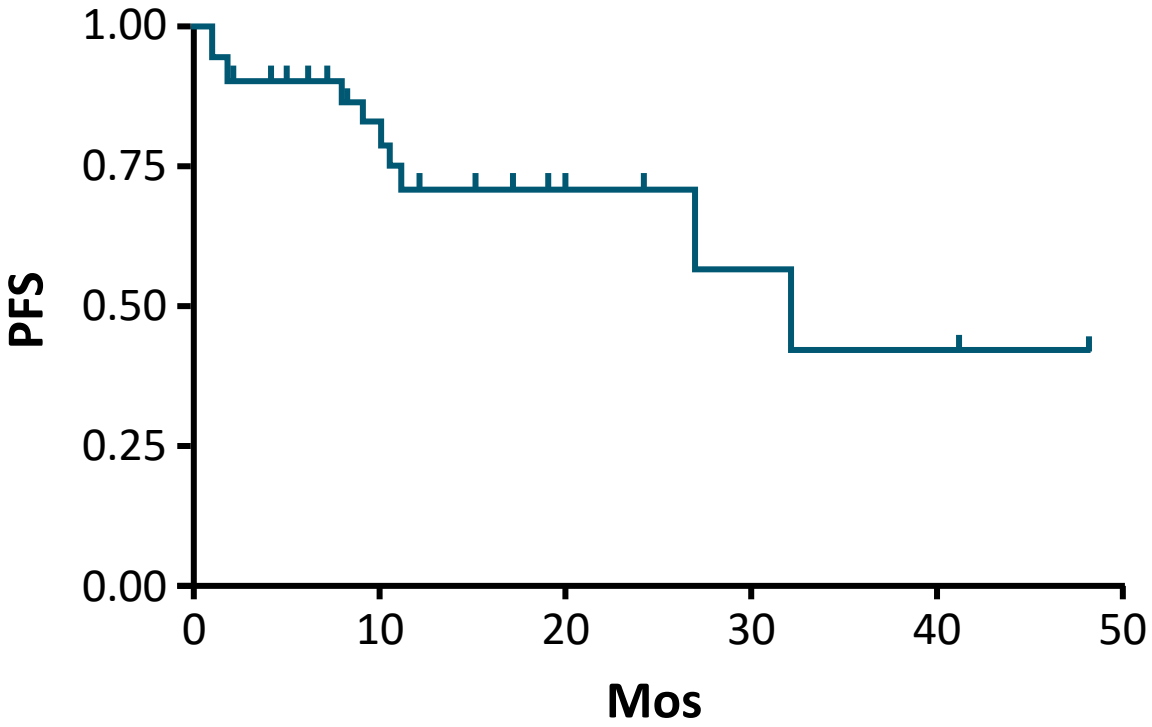
Clinical response rates for patients who received salvage therapy with venetoclax or ibrutinib support early use of venetoclax

Response rate: 6/10 (60.0%)

Seymour JF, et al. ASH 2019 Abstract #355

Efficacy of Therapies After Venetoclax Discontinuation: *BTKi in BTKi-Naive Patients*

Venetoclax → BTKi produces high ORR and durable remissions in BTKi-naive patients



PFS for BTKi in BTKi-Naive Patients Post Venetoclax (n = 42)

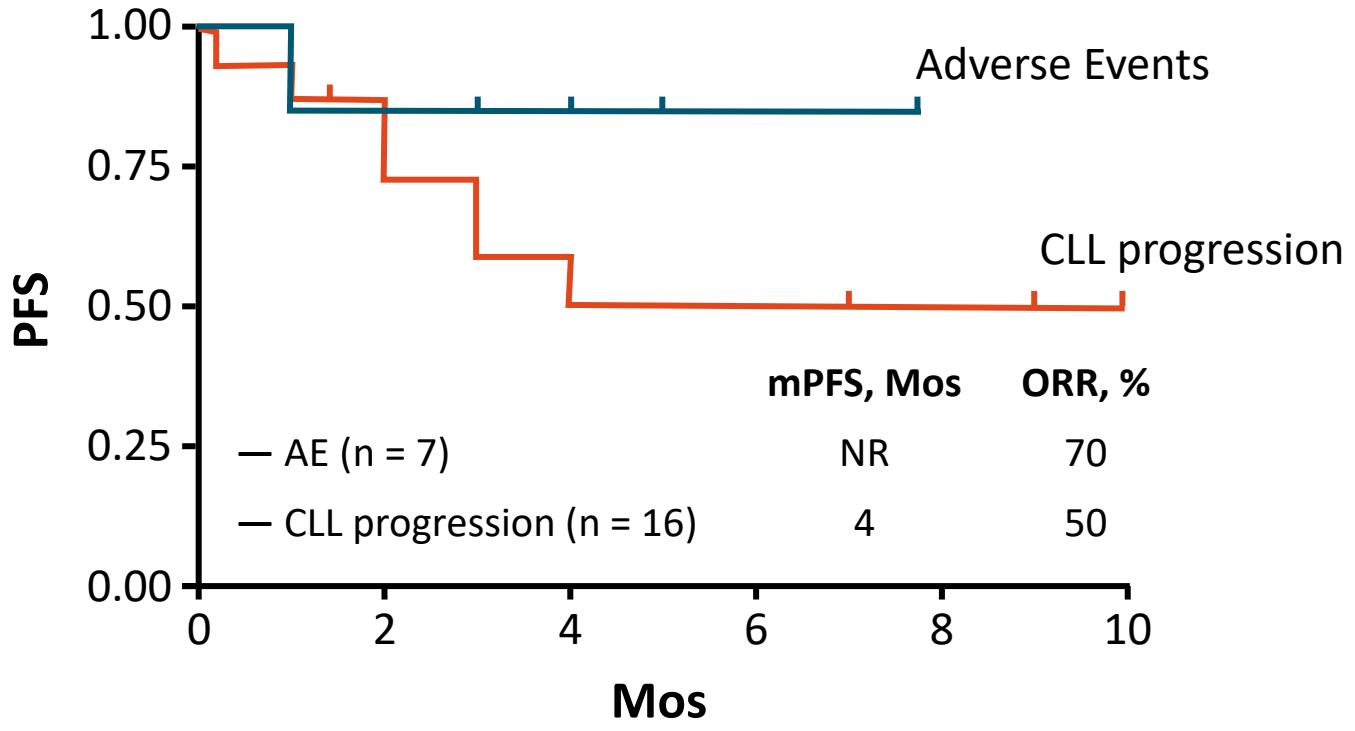
N = 44 BTKi-naive patients:

- ORR: 83.9%
- Median PFS: 32 mo
- Median follow-up: 10.5 mo

Mato. Clin Cancer Res. 2020;26:3589.

Efficacy of Therapies After Venetoclax Discontinuation: *BTKi in BTKi-Exposed Patients*

Venetoclax → Response to BTKi in BTKi-exposed patients depends on reason for discontinuation

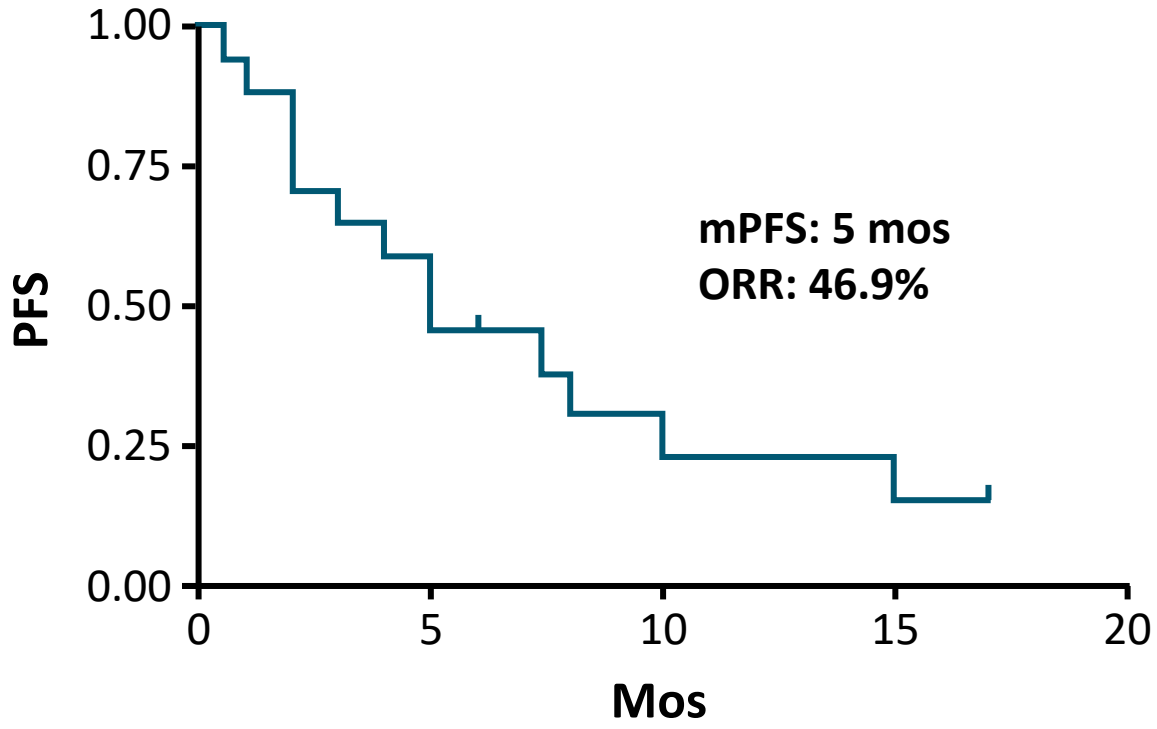


PFS for BTKi in BTKi-Exposed Patients Post Venetoclax

Mato. Clin Cancer Res. 2020;26:3589.

Efficacy of Therapies After Venetoclax Discontinuation: *PI3Ki in PI3Ki-Naive, BTKi-Exposed Patients*

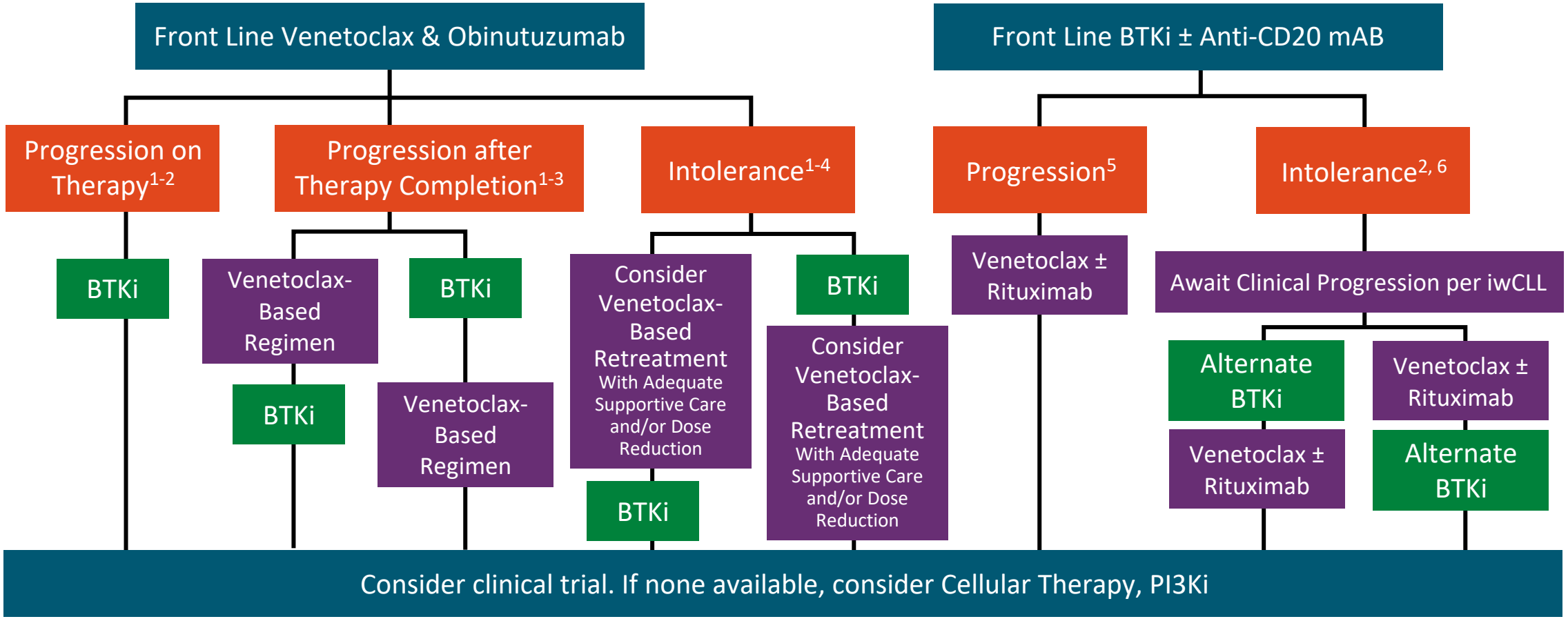
BTKi → Venetoclax → PI3Ki did not result in durable remissions



PFS for PI3Ki in PI3Ki-Naive, BTKi-Exposed Patients Post Venetoclax (n = 17)

Mato. Clin Cancer Res. 2020;26:3589.

Treatment Algorithm: CT-Free Management of CLL



1. Harrup. ASH 2020. Abstr 3139. 2. Mato. Clin Cancer Res. 2020;26:3589. 3. Thompson. ASH 2020. Abstr 3136.
4. Kater. ASH 2020. Abstr 125. 5. Jones. Lancet Oncol. 2018;19:65. 6. Rogers. Haematologica. 2021;[Epub].