Sequenza degli inibitori di BTK e BCL-2 nella LLC

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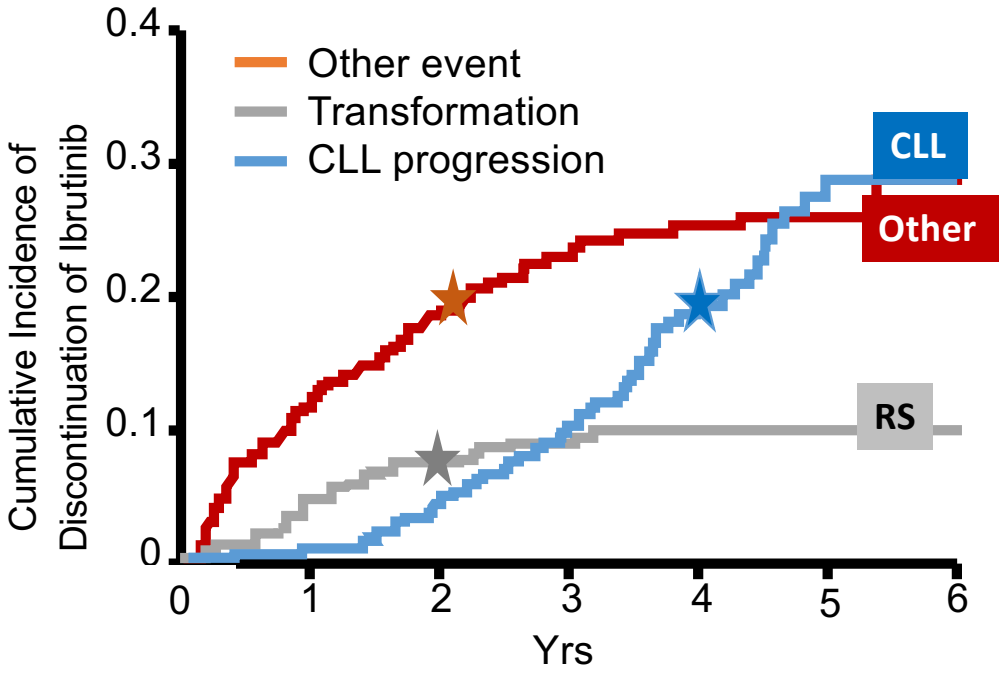
Outcome of 308 patients treated with ibrutinib at the Ohio State University

Cumulative Incidence Estimates, % (95% CI)	At 2 Yrs	At 3 Yrs	At 4 Yrs
CLL progression	5.0 (2.5-7.5)	10.8 (7.1-14.4)	19.1 (13.9-24.3)
Transformation	7.3 (4.3-10.2)	9.1 (5.8-12.4)	9.6 (6.2-13.0)
Other event	**18.7 (14.3-23.1)**	**23.9 (19.0-28.8)**	**25.0 (20.0-30.1)**

31%

54%

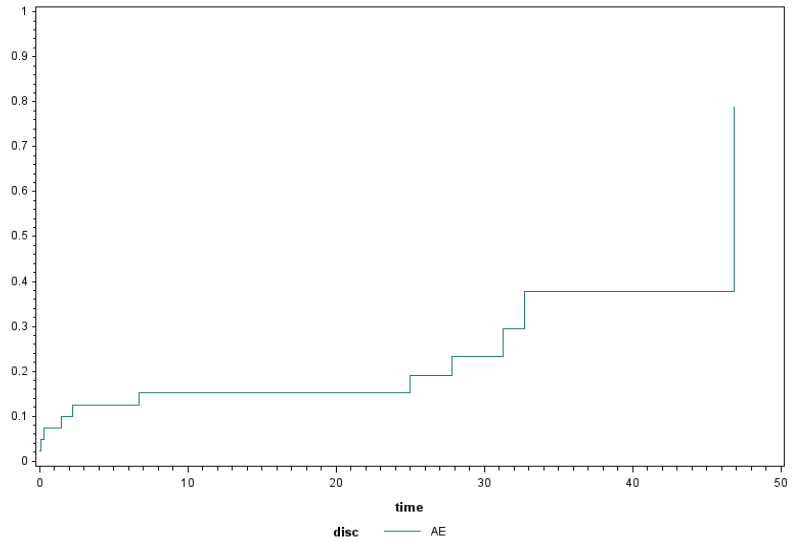
N = 158/308

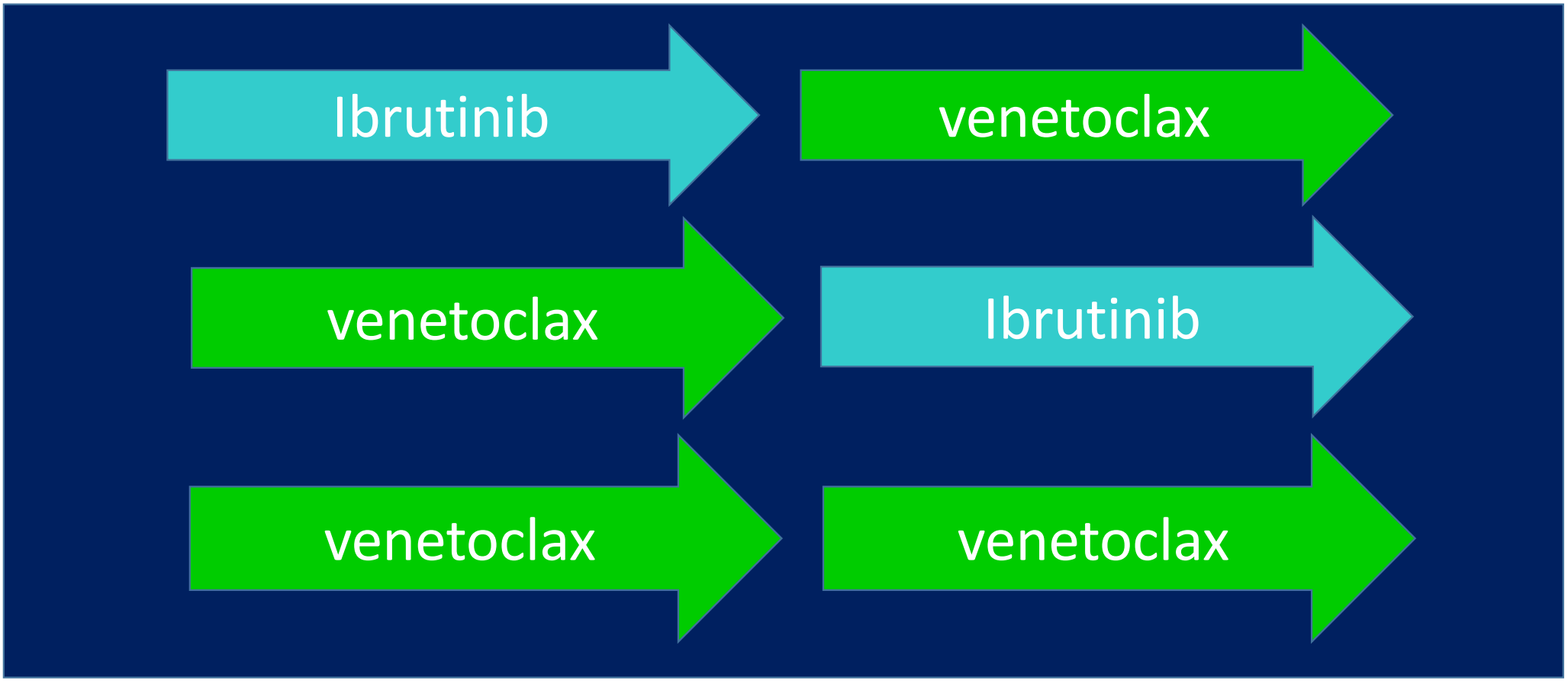


Woyach J, et al. J Clin Oncol. 2017

Events leading to discontinuation of front-line ibrutinib and rituximab combination in unfit patients with CLL: long-term results of the LLC 1114 GIMEMA study

Reason for treatment discontinuation	No patients	% patients	48-months cumulative incidence (95%IC)	Median age, years (range)
Disease progression	10	7%	5.6 (1.5-9.6)	76.2 (57.8-85.2)
Adverse events	44	30%	29.1 (21.5-36.6)	77.9 (56.8-90.2)
Second malignancies	9	6%	6 (1.9-10.1)	75.7 (56.1-81.2)




Ibrutinib
venetoclax
venetoclax
Ibrutinib
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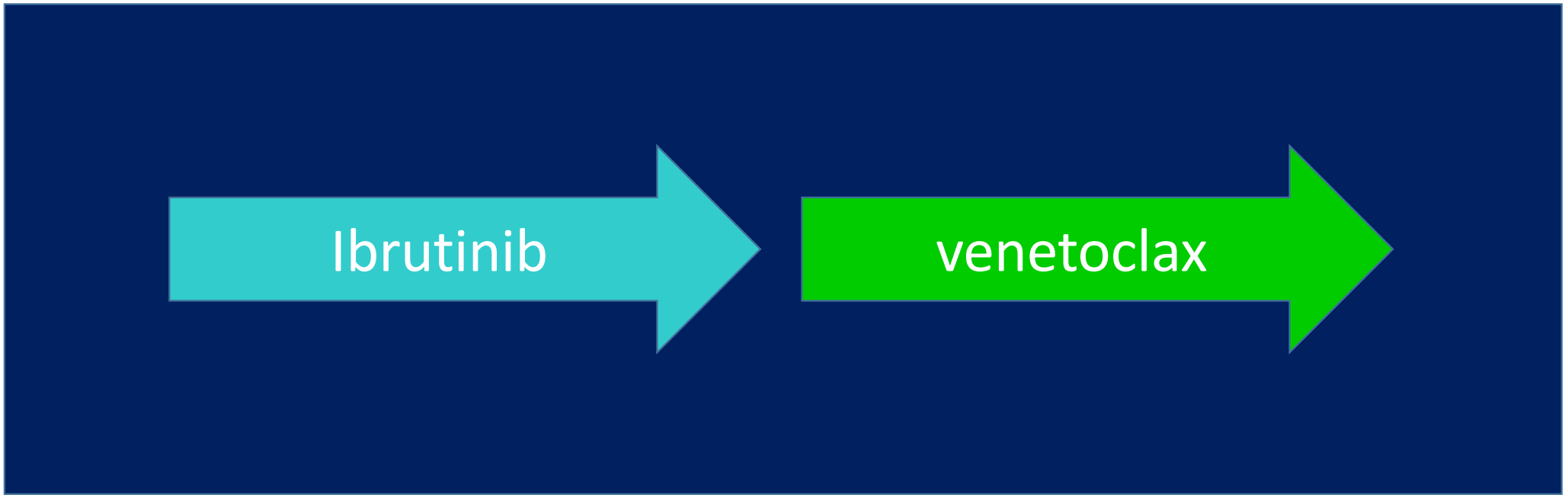
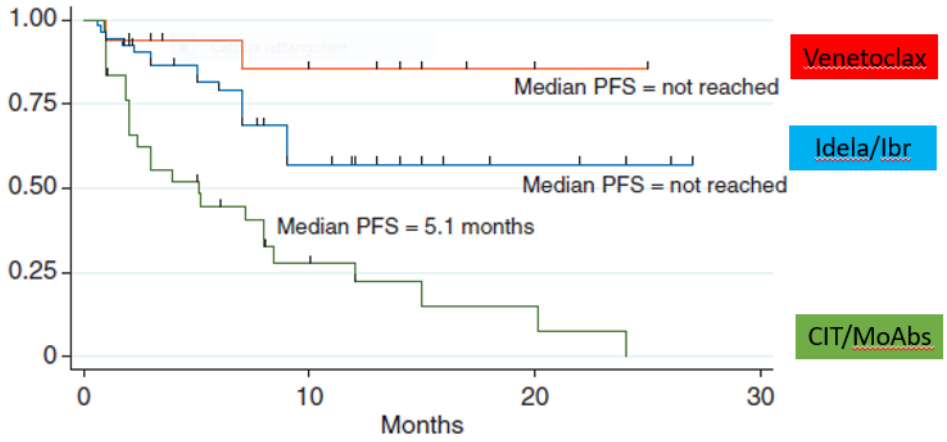


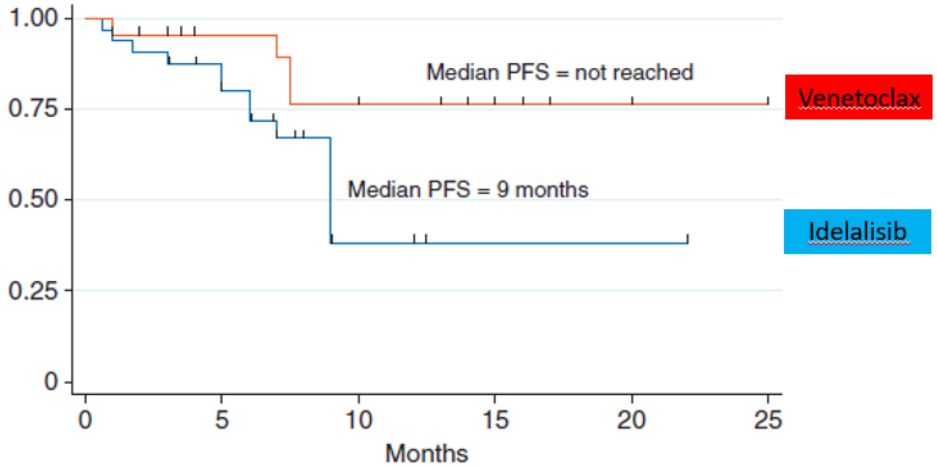
venetoclax naive

Response to subsequent therapy following first KI failure

Median time to next therapy after discontinuation: 1 month (0-28 months; N=167)

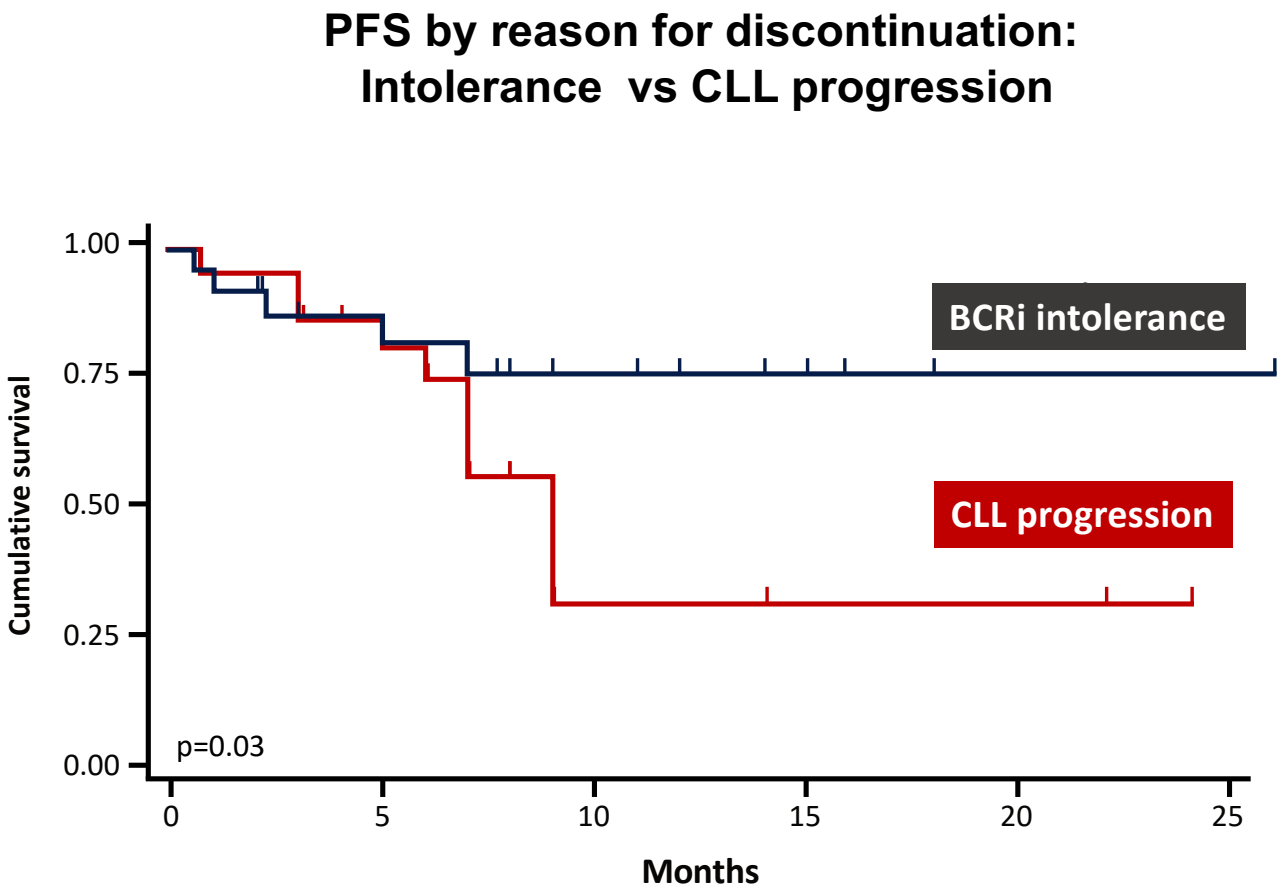
	KI treatment (N=72)	Venetoclax (N=26)	CIT (N=29)
ORR	59%	74%	50%
CR	4%	32%	2%





Mato et al. Ann Oncol. 2017

Outcome following first KI failure according to the reason of failure



Mato et al. Ann Oncol. 2017

Venetoclax post-BCRi in R/R

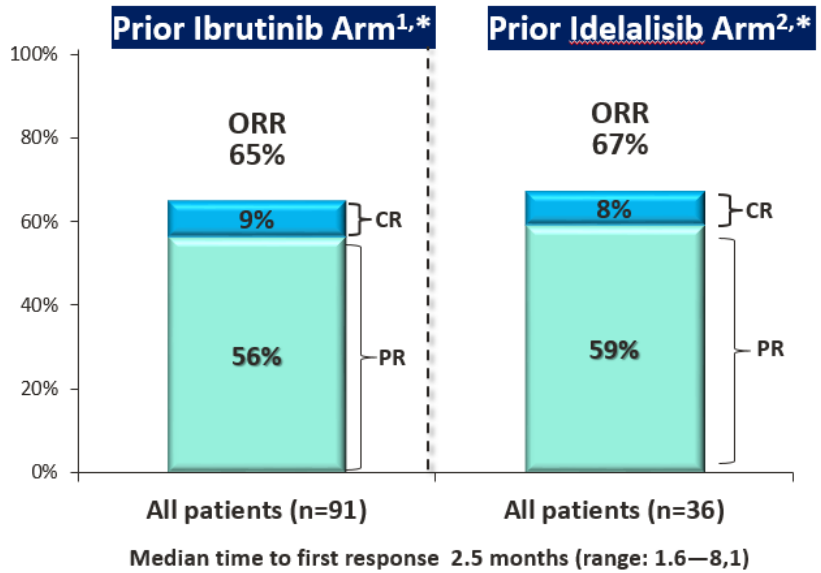
Venetoclax post-BCRi in R/R CLL (N=127)
Ibrutinib (N=91)
Idelalisib (N= 36)

→ Venetoclax until progression

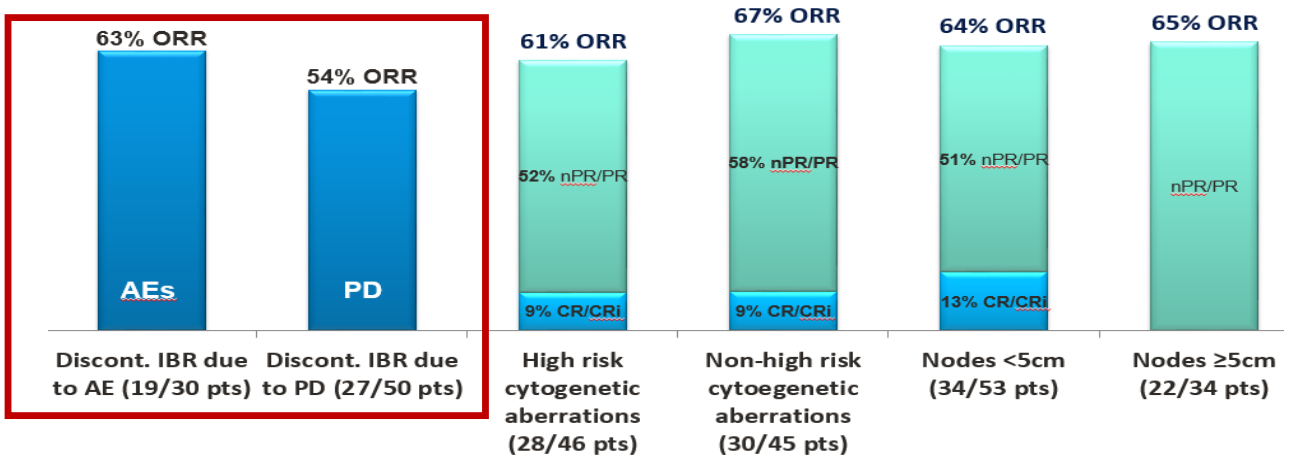
Characteristics		Prior Ibrutinib Arm (N=91)	Prior Idelalisib Arm (N=36)
Age, years		66 (28–81)	68 (56 – 85)
Bulky nodal disease	≥5 cm ≥10 cm	36 (40%) 9 (10%)	17 (47%) 5 (14%)
Prognostic factors, n/N (%)	Unmutated del(17p) del(11q) TP53 mut	50/67 (75%) 42/90 (47%) 30/91 (33%) 29/87 (33%)	22/25 (88%) 8/36 (22%) 13/36 (36%) 5/35 (14%)
Number of previous therapies		4 (1—15)	3 (1 – 11)

Jones et al. Lancet Oncol. 2017; Coutre et al. Blood. 2018

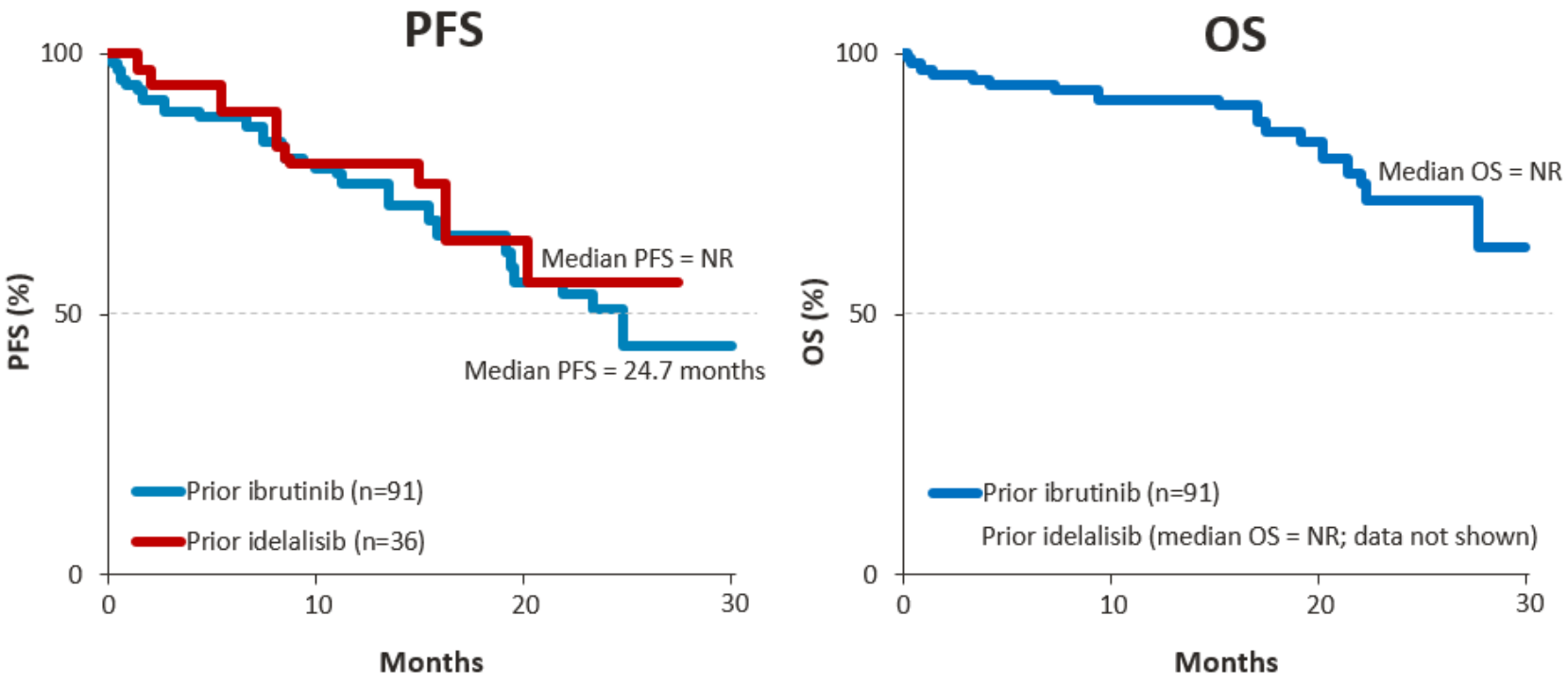
Venetoclax post-BCRi in R/R CLL



Response: 12/17 (**71%**) patients with *BTK* or *PLCG2* mutations



Venetoclax post-BCRi in R/R CLL (M14-032 trial)



12-month PFS and OS for the prior ibrutinib 75% and 91%

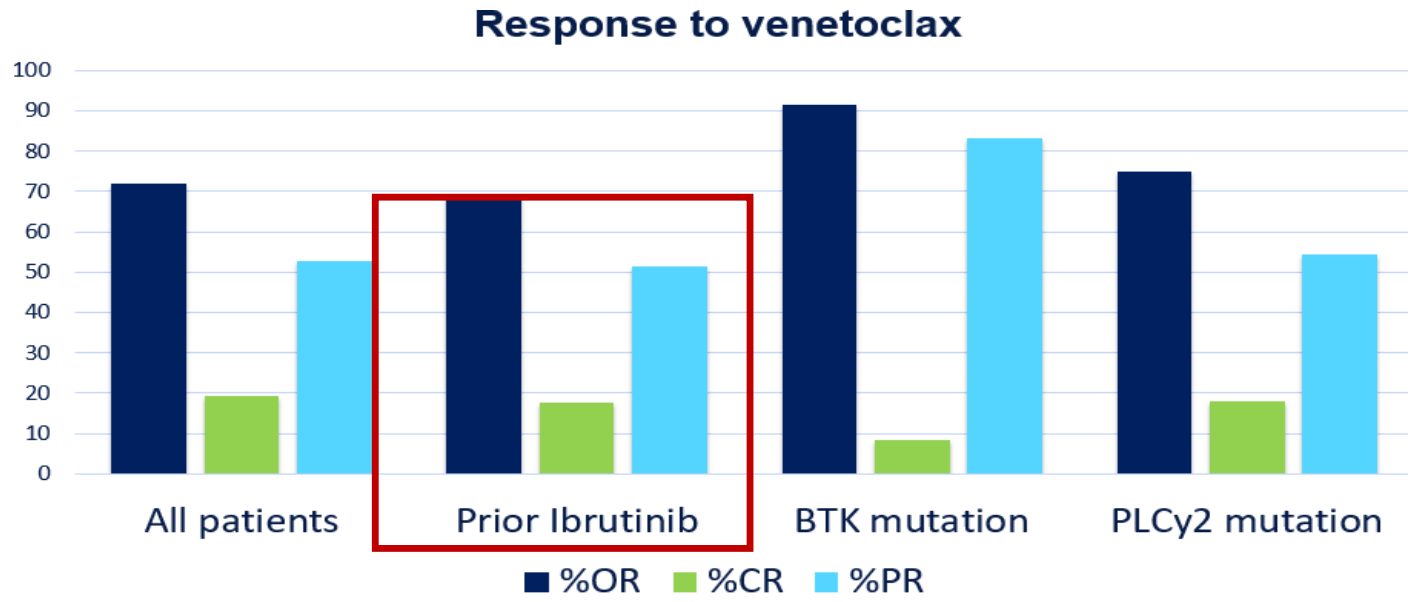
Jones JA, et al. Lancet Oncol. 2017; Coutre S, et al. Blood 2018

Real-world outcomes and management strategies for venetoclax-treated CLL patients in the US

141 patients treated at 19 US centers

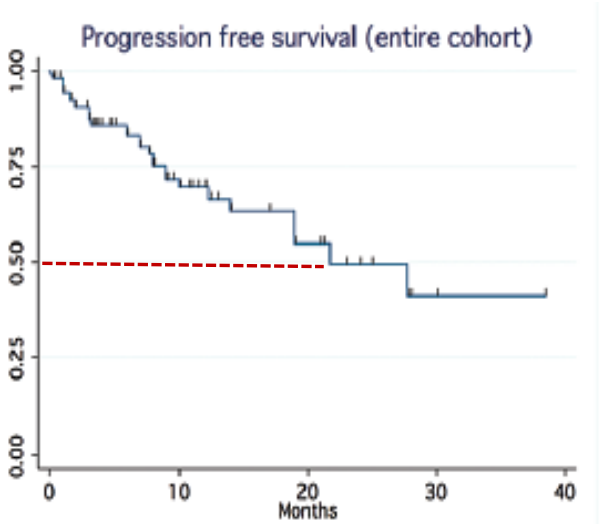
Patient characteristics	Median (range)
Median age at diagnosis, years	59 (30-88)
Median age at venetoclax start, years	67 (37-91)
Median prior lines of therapy	3 (0-11)
Follow up, months*	7 (0.1-38.4)
CLL characteristics	**Frequency (n with characteristic/ total n with available data)**
Relapsed/Refractory	98.6% (139/141)
Treatment naive	1.4% (2/141)
CLL genetics	
Del(17p)	44.9% (61/136)
Del(11q)	26.0% (34/131)
TP53 mutation	44.2% (42/95)
NOTCH1 mutation	26.8% (15/56)
Complex karyotype, ≥ 3 mutations	26.8% (52/130)
Unmutated *IGHV*	83.3% (60/72)
Prior ibrutinib exposure	81.6% (115/141)
Ibrutinib resistance mutations	
BTK mutation	35.3% (12/34)
PLCγ2 mutation	12.5% (4/32)
Venetoclax administered in combination	18.4% (26/141)
Venetoclax and ibrutinib	36% (9/26)
Venetoclax and obinutuzumab	32% (8/26)
Venetoclax and rituximab	24% (6/26)

*Median follow up calculated using overall survival.

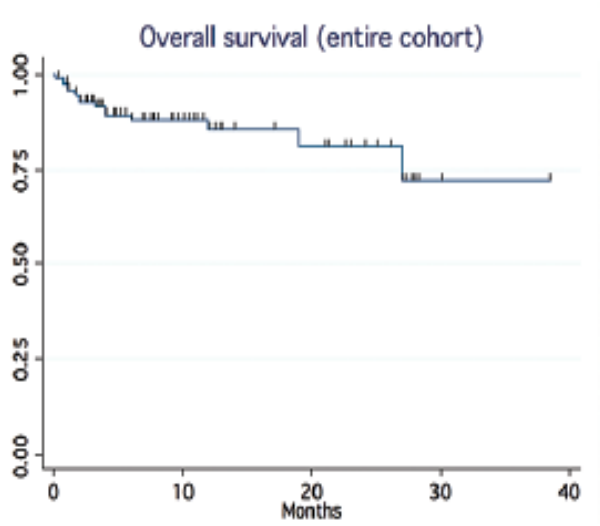


Mato et al. Haematologica 2018

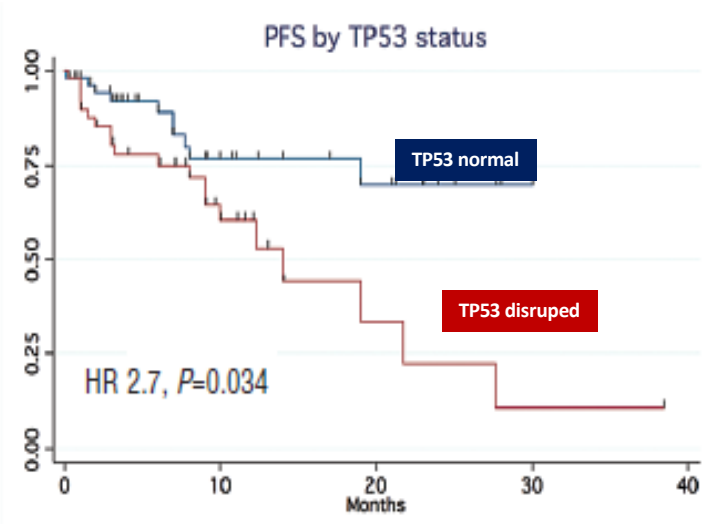
Real-world outcomes and management strategies for venetoclax-treated CLL patients in the US



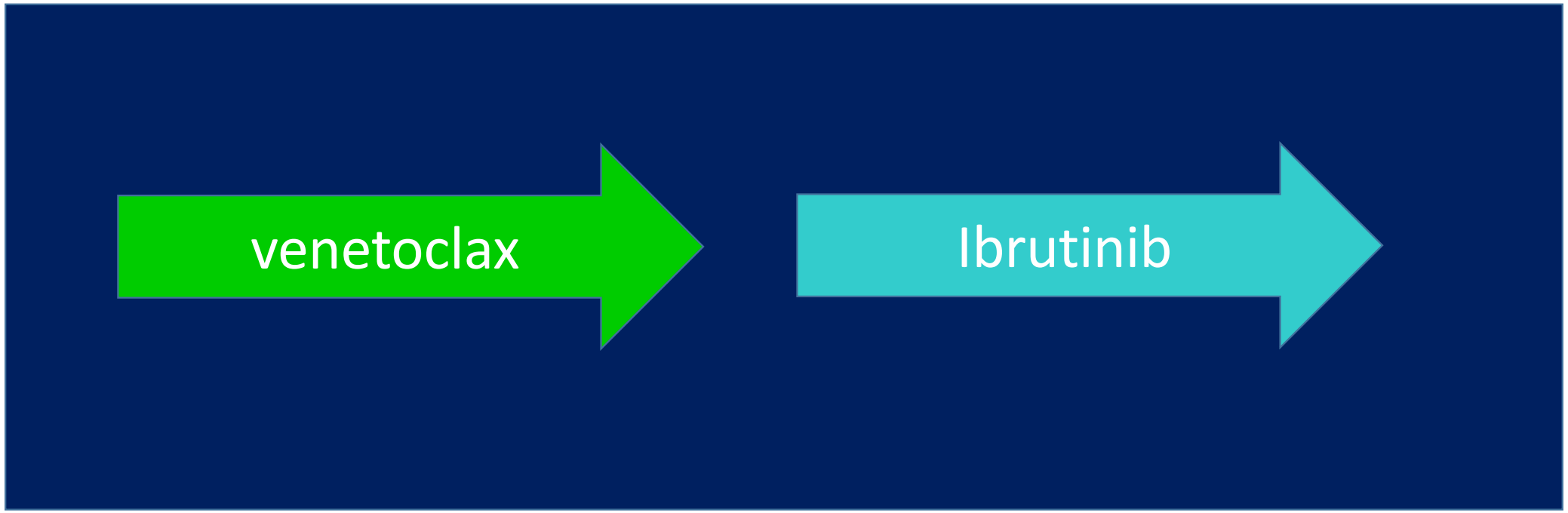
12-month PFS 68%



12-month OS 88%.



Mato et al. Haematologica 2018



Ibrutinib naive

Ibrutinib exposed

AEs-related DCs

DP-related DCs

Post venetoclax: baseline characteristics of patients

326 patients who discontinued venetoclax and have been subsequently treated in the front-line (4%) and relapsed/refractory settings (96%)

Thirty-one academic and community sites in the US, EU/UK, and South America

Characteristic	Result (range)
Median age at CLL diagnosis	58 years (32-88)
Median age at venetoclax start	66 years (38-91)
Median number therapies prior to venetoclax	3 (0-11)
Del(17p) positive	47%
TP53 mutation present	45%
TP53 disruption (del17p or TP53 mutation)	56 %
Del(11q) positive	27%
Complex karyotype present	39%
NOTCH1 mutation present	18%
IGHV unmutated	82%
Ibrutinib prior to venetoclax	60%
Any BTKi prior to venetoclax	61%
Idelalisib prior to venetoclax	19%

Mato et al. Clin Cancer Res 2020

Post venetoclax: baseline characteristics of patients

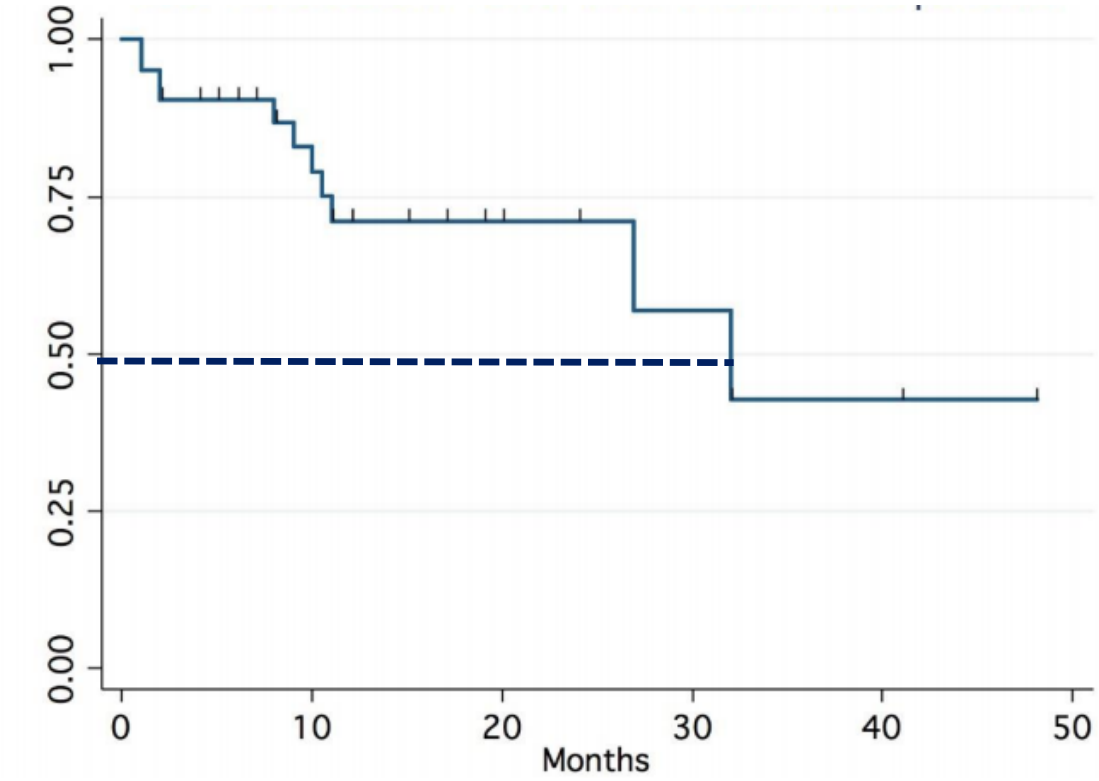
Subsequent Therapy	BTKi	BTKi
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi
Pre-Ven Exposure	BTKi-naïve	BTKi-exposed 33% BTKi-intolerant 66% BTKi-resistant
Patient Number	44	30
Lines of Therapy Pre-Ven, median (range)	2 (0-8)	4 (1-11)
ORR	83.9%	53.4%
CR	9.0%	10.0%

Subsequent Therapy	BTKi	BTKi
Median PFS (months)	32	12
Median Follow-up (months)	10.5	3.5
DC Rate	38%	38%
Reasons for DC (% discontinuations)		
CLL Progression	21.4%	66.6%
Adverse Event	14.3%	8.3%
Transformation	14.3%	-

For BTKi naïve patients, covalently binding BTKis results in high ORR and durable remissions.

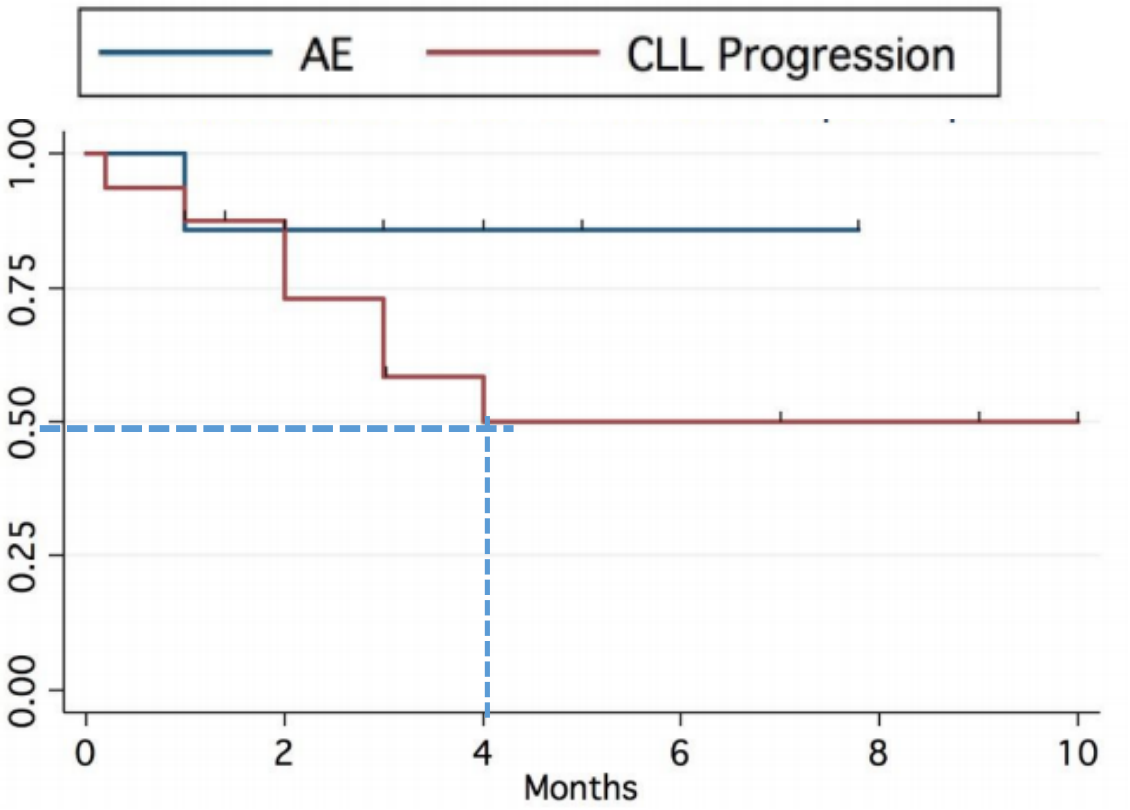
For BTKi exposed patients, covalent BTK inhibition is not effective in the setting of BTKi resistance, cellular therapies following venetoclax may be the most effective strategies.

Post venetoclax: PFS in BTKi naïve patients



Mato et al. Clin Cancer Res 2020

Post venetoclax: PFS in BTKi exposed patients



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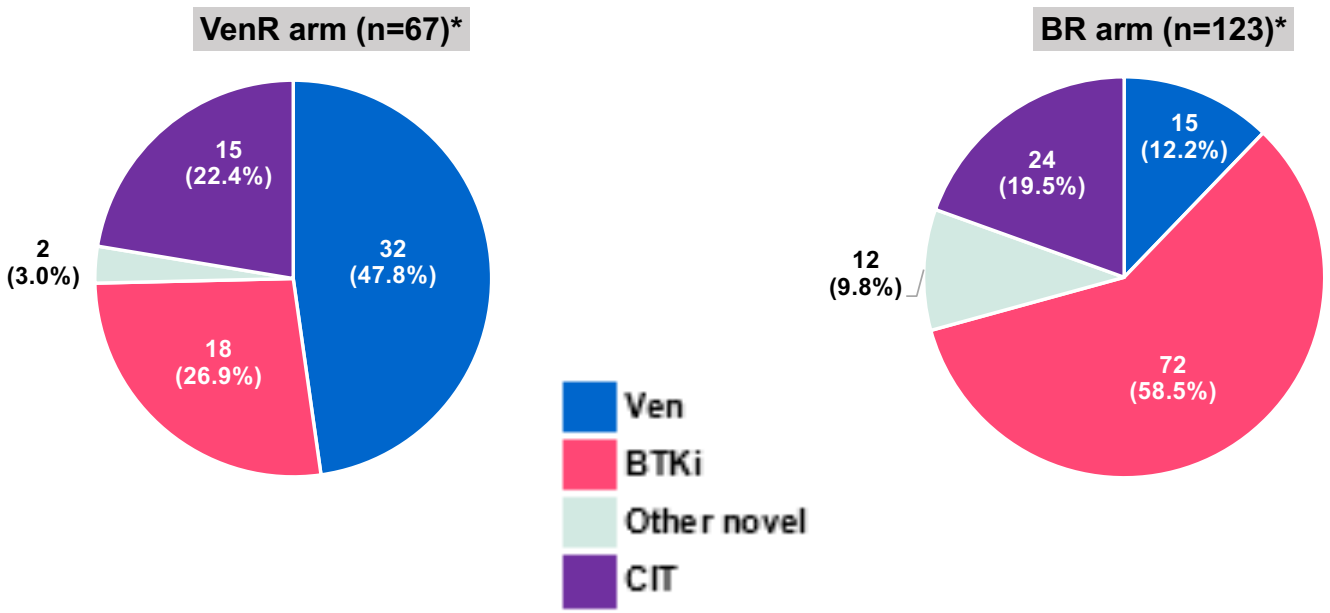
Mato et al. Clin Cancer Res 2020

Subsequent Targeted Therapies, in R/R CLL Previously Treated With VenR in the MURANO Study

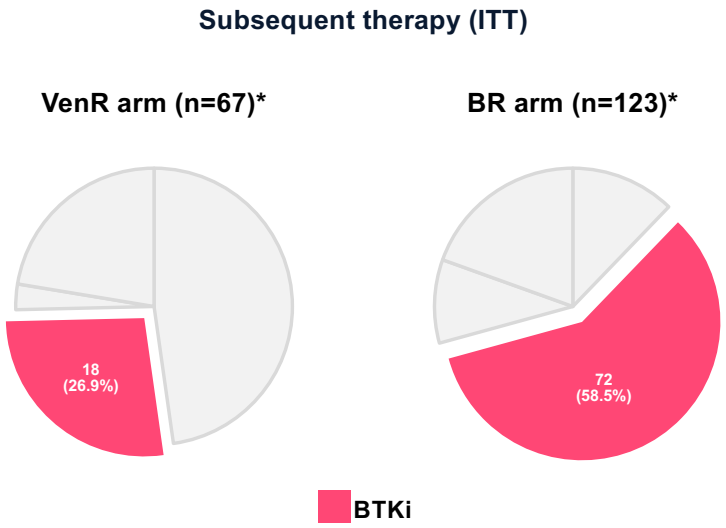
Subsequent therapy (ITT)

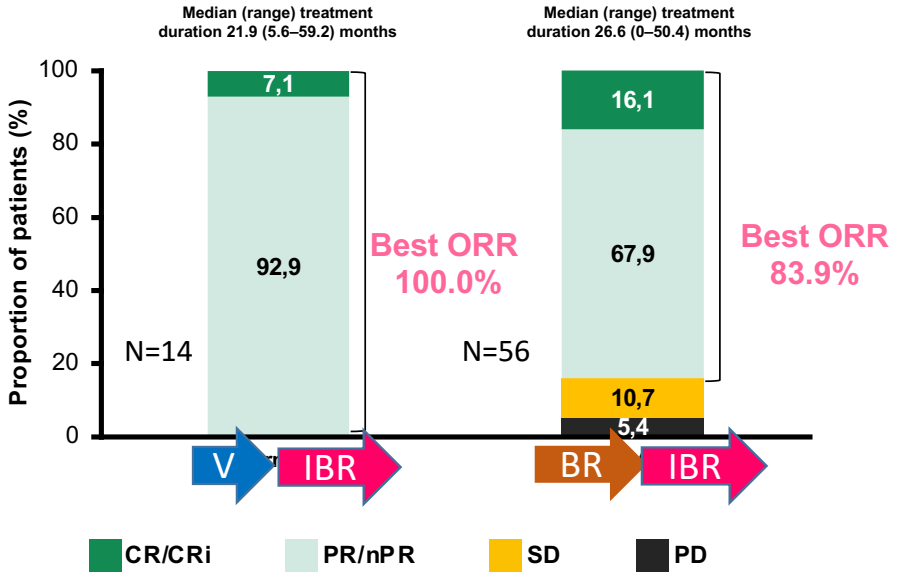


Harrup et al., ASH 2020

Subsequent Targeted Therapies, in R/R CLL Previously Treated With VenR in the MURANO Study

Subsequent therapy= BTKi-based*





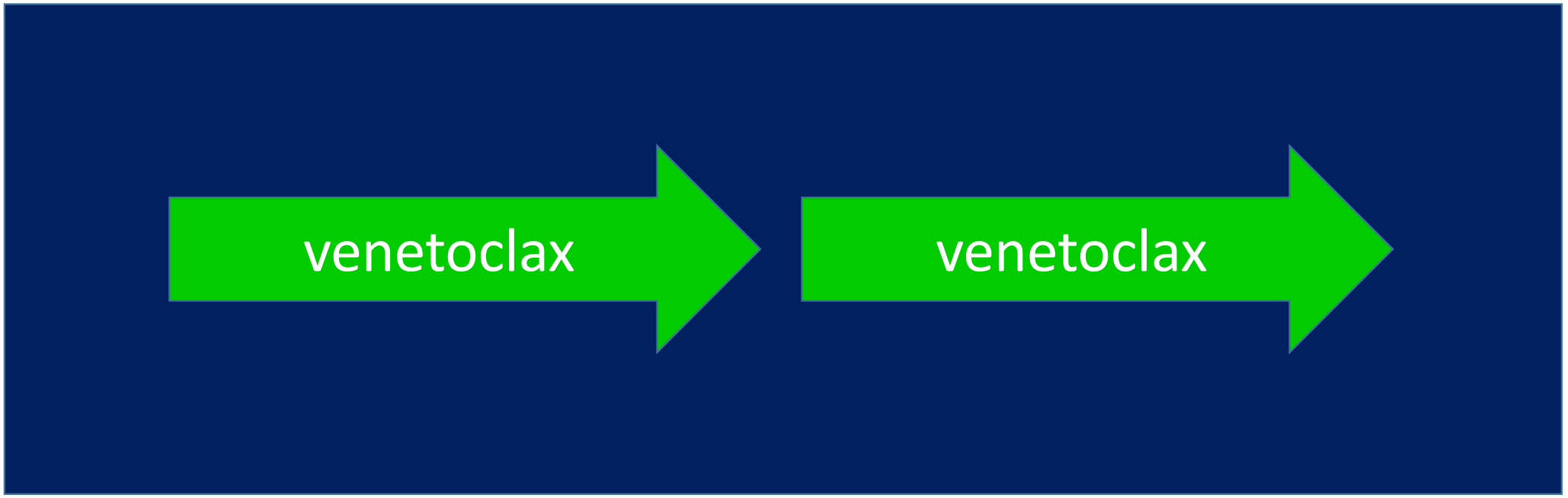
* Patients BTK naive

Real-World Data on Post-Venetoclax Ibrutinib/BCRi Treatment

Analyses of ibrutinib regimens post venetoclax regimen	Treatment	N	Prior BTKi	Response ORR	Response CR
Ibrutinib post Ven, in 4 US centers[1]	Ibrutinib post Ven (n=25)*	**25**	**0**	**14 (56%)**	1 (4%)
Ibrutinib post Ven regimen, in 19 US centers[2]	Ibrutinib-based regimen post Ven (n=5)	**5**	**3**	**1 (20%)**	0

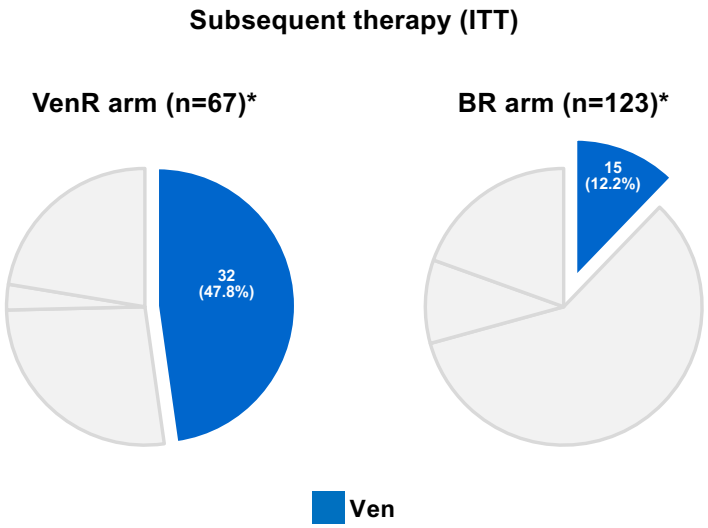
Analysis of BTKi/BCRi regimens post venetoclax regimen	Treatment			Response ORR	Response CR
BTKi post Ven/VenR, in 2 Australian centers[3]	Ibrutinib (n=21) or zanubrutinib (n=2) post Ven† All patients were BCRi-naïve	**23**	**0**	**91%**	18%
BCRi, CT/CIT, or other after Ven regimen (CORE Registry)[5]	Next regimen post Ven (n=23,¶ including n=9 ibrutinib and n=4 other BCRi)	**23**	**9**	**60.8% (Ibr: 5/9)**	21.7% (Ibr: 1/9)

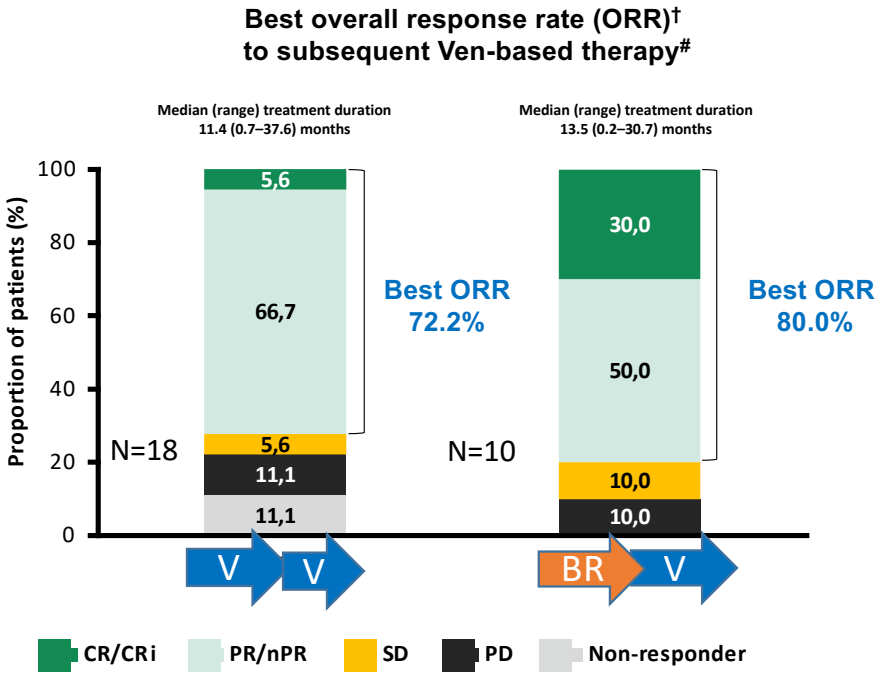
1. Brown J, *et al.* ASH 2019; poster 4320; 2. Mato AR, *et al. Haematologica* 2018; **103:**1511–1517; 3. Lin VS, *et al. Blood* 2020; **135**:2266–2270; 4. Mato AR, *et al. Clin Cancer Res* 2020; doi: 10.1158/1078-0432.CCR-19-381
5. Mato AR, *et al.* ASH 2019; Poster 1756;


venetoclax
venetoclax

Subsequent Targeted Therapies, in R/R CLL Previously Treated With VenR in the MURANO Study

Subsequent therapy= VEN-based



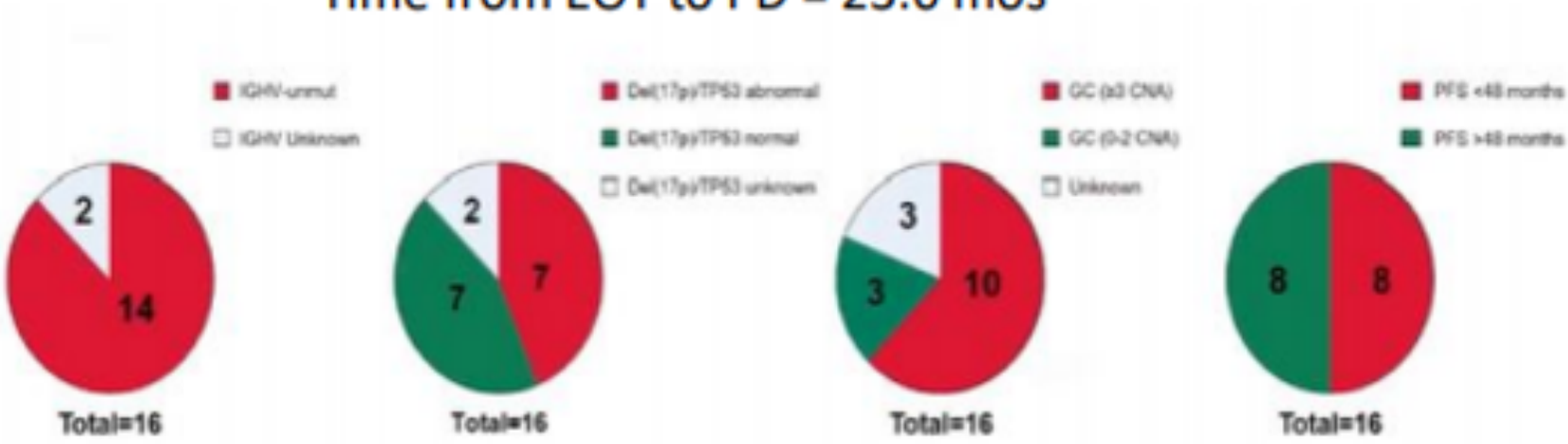


Harrup et al., ASH 2020

Subsequent Targeted Therapies, in R/R CLL Previously Treated With VenR in the MURANO Study

Re-treated Pts: Poor Risk Factors Over-represented

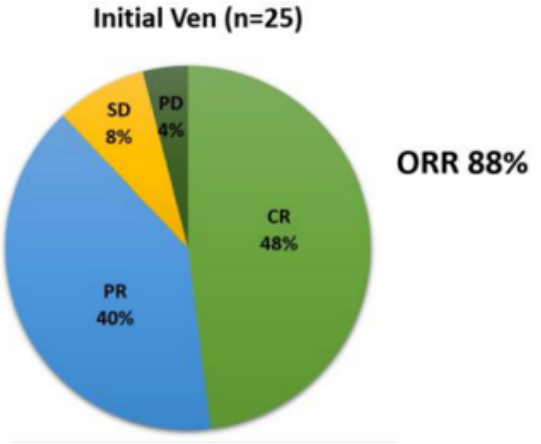
- 25 pts re-treated with VenR
- Among 16 re-treated pts with EOT assessments:
  - On MURANO study, median PFS 45.7 mos
  - Time from EOT to PD = 23.6 mos

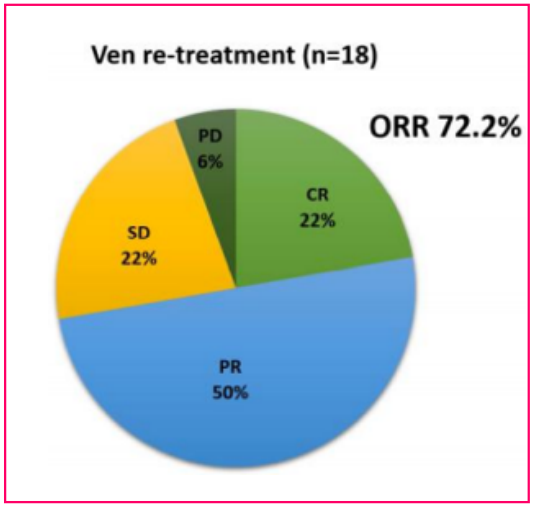


Kater et al., ASH 2020

Venetoclax re-treatment after previous venetoclax-based treatment

Baseline characteristics at initial Ven start	(n=patients with available data)
Median age at diagnosis in years (range)	57.7 (41-75) (n=25)
Median age at ven start in years (range)	66 (44-75) (n=25)
Sex	84.0% male, 16.0% female (n=25)
Race	59.0% white 22.7% black 18.1% other (n=22)
Initial ven administered as part of a clinical trial	24.0% (n=25)
Initial ven as monotherapy	56.0% (n=25)
Ven as first-line treatment	12.0% (n=25)
Median prior lines of therapy (range)	2 (0-10) (n=25)
Prior BTKi	60.0% (n=25)
Del(17p)	39.1% (n=23)
TP53 mutation	26.7% (n=15)
Del11q	39.1% (n=23)
Complex karyotype	30.0% (n=20)
IGHV unmutated	84.2% (n=19)
Rai stage	I: 36.3%; II: 18.1%; III: 13.6%; IV:





- Median 8.7 mos between Ven1 and Ven2
  - Re-treatment mainly due to clinical PD (88%) vs MRD+
  - 12% of pts had an intervening non-ven treatment
- Median follow-up for Ven2: 8 (0.2-29) mos
- Estimated 12-mo PFS with Ven2: 69.1%
- 7 (32%) pts discontinued, primarily due to PD (4 pts)

Thompson et al., ASH 2020

Sequencing of BTKi/BCL2i: Conclusions

- Relevant problem in the treatment management of CLL patients
- Limited data, short follow-up
- No prospective data for the use of ibrutinib after venetoclax
- Better responses in patients not previously exposed to the inhibitor
- Refractoriness to prior inhibitor associated to poor prognosis

Therapy selection following BTKi/BCL2i requires of consideration of

prior novel agent exposure

discontinuation reasons

biologic profile of CLL: TP53 aberrations, unmutated *IGVH* genes