Selection and Sequencing of Therapies for R/R CLL

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Swedish Cancer Institute
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A 75-year-old man with CLL and a history of Barrett's esophagus

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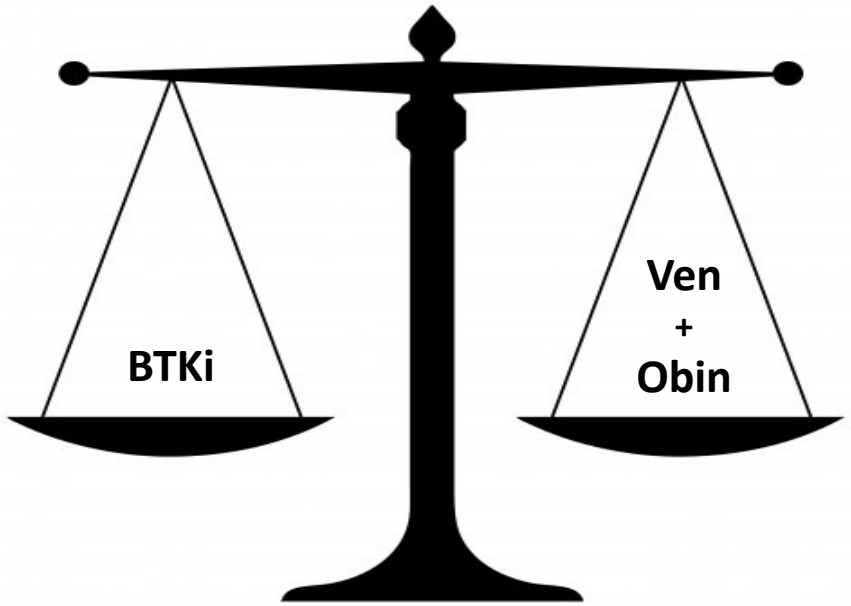
Where Do We Use Novel Inhibitors for CLL in 2021?

So, in retrospect, in 2016, not a single person got the answer right to: "Where do you see yourself 5 years from now?"

The CLL Scale of Justice

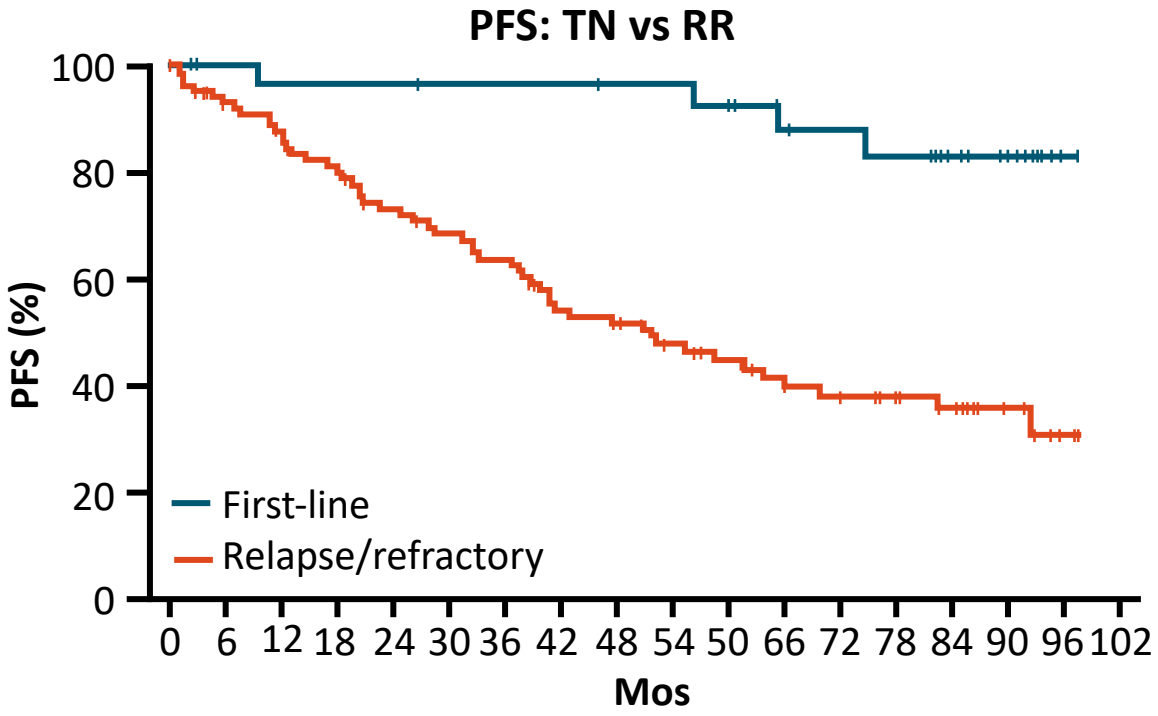


- Excellent PFS and OS with indefinite therapy
  - Mostly PR with limited uMRD
  - More potential discontinuations
- More concern for long-term adherence
- More expense over the long-term

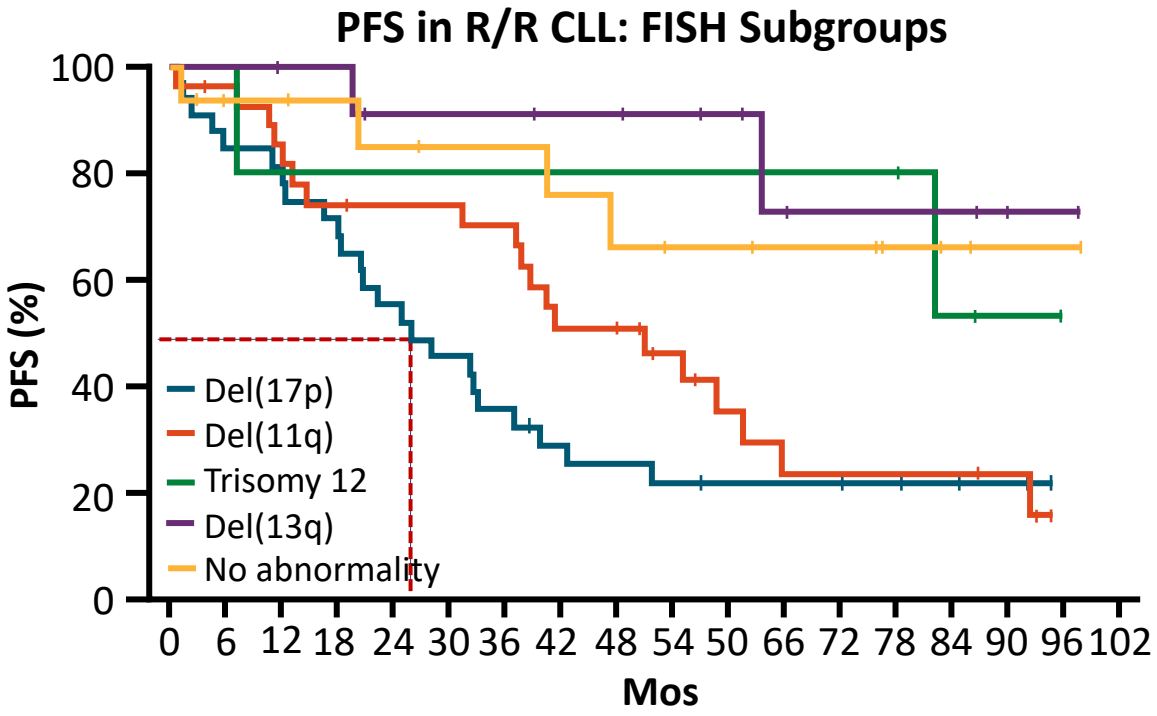
- Excellent PFS and OS with finite therapy
  - High CR and significant uMRD
  - Low level discontinuations
- Less concern for long-term adherence
- Potential for cost-savings

How do we Sequence Therapy?

7-Yr PFS Outcomes With Ibrutinib in R/R CLL



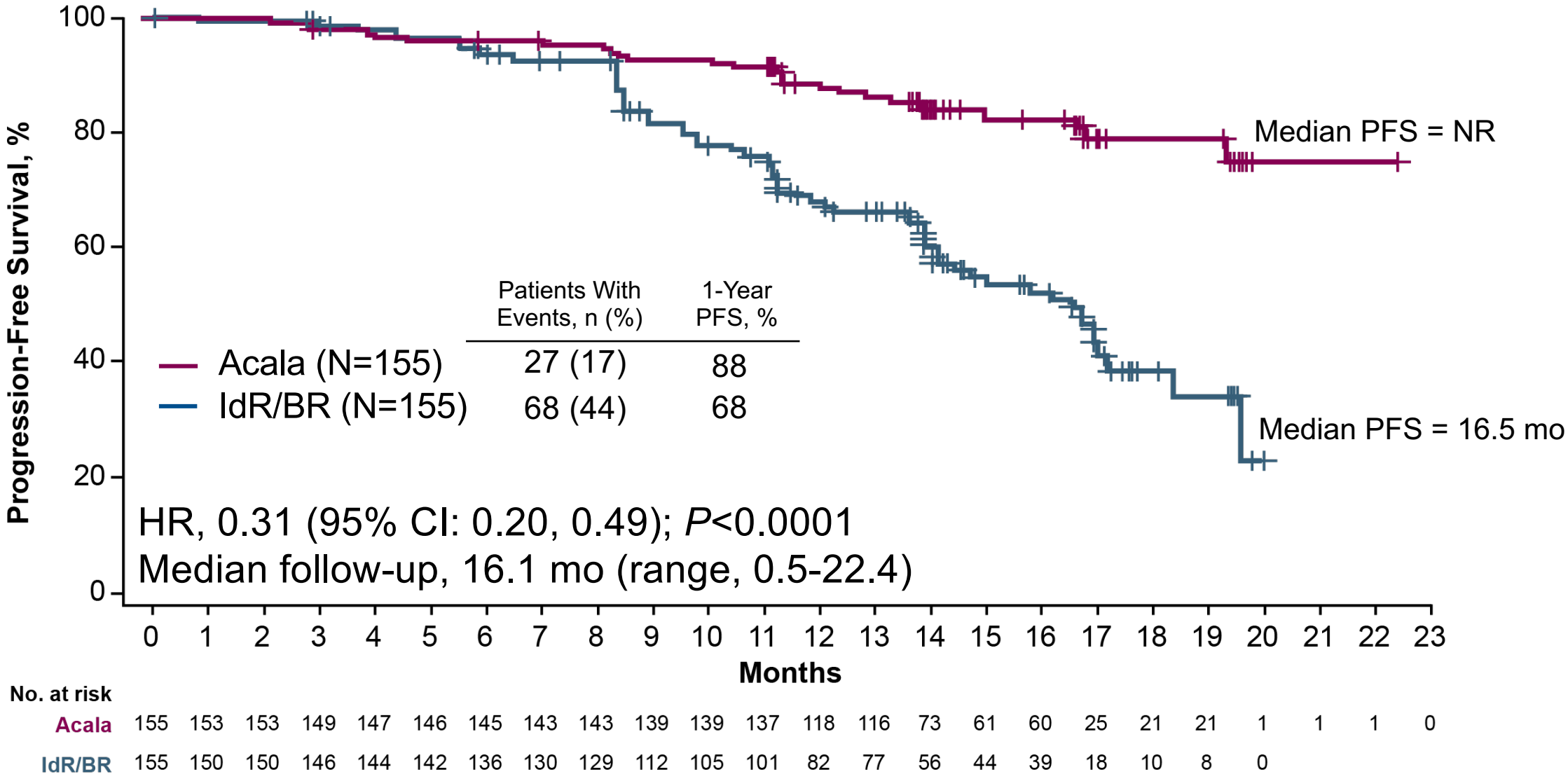
	Median PFS, Mos	7-Yr PFS, %
TN (n = 31)	NR	83
R/R (n = 101)	52	34



	Median PFS, Mos	7-Yr PFS, %
del17p (n = 34)	26	17
del 11q (n = 28)	51	23
Trisomy 12 (n = 5)	NR	53
del 13q (n = 13)	NR	73
No abnormality	88	66

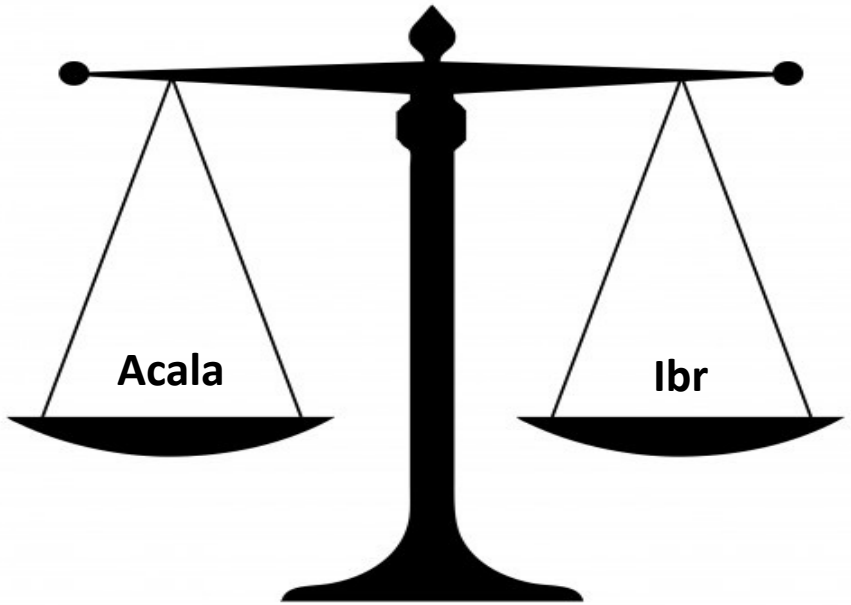
Byrd. Clin Cancer Res. 2020;26:3918.

IRC-Assessed PFS Superior for Acalabrutinib vs IdR/BR



Ghia et al. JCO 020 Sep 1;38(25):2849-2861.

Acalabrutinib vs. Ibrutinib: *The CLL Scale of Justice*

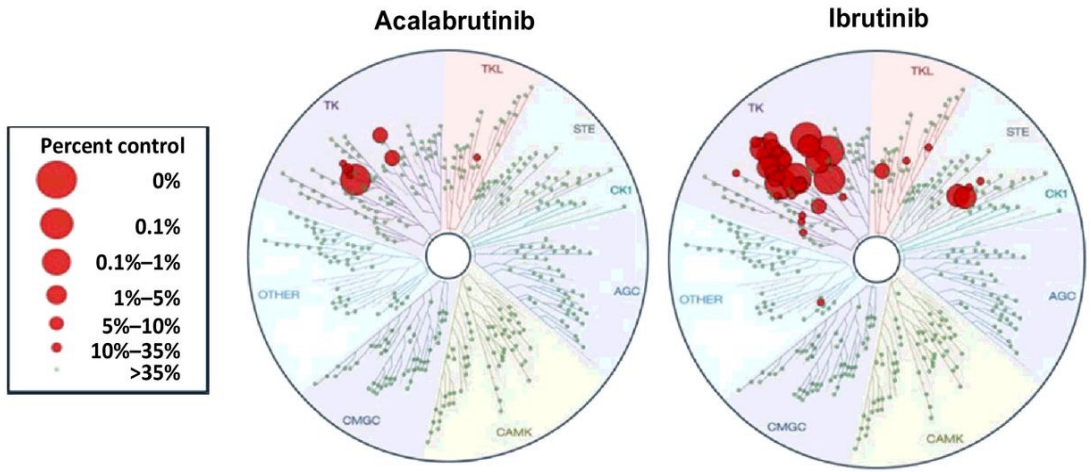


- Better tolerated
- Low rates of adverse events of significance
  - Fewer discontinuations
- Can “rescue” after Ibrutinib discontinuation due to adverse event

- More patients treated with longer follow up
- More adverse events of significance
  - More discontinuations

Acalabrutinib versus Ibrutinib

- Selective, covalent 2nd-generation BTK inhibitor approved in Canada in August 2019
- Indicated for R/R MCL and frontline and R/R CLL*
- Associated with limited off-target effects in preclinical studies

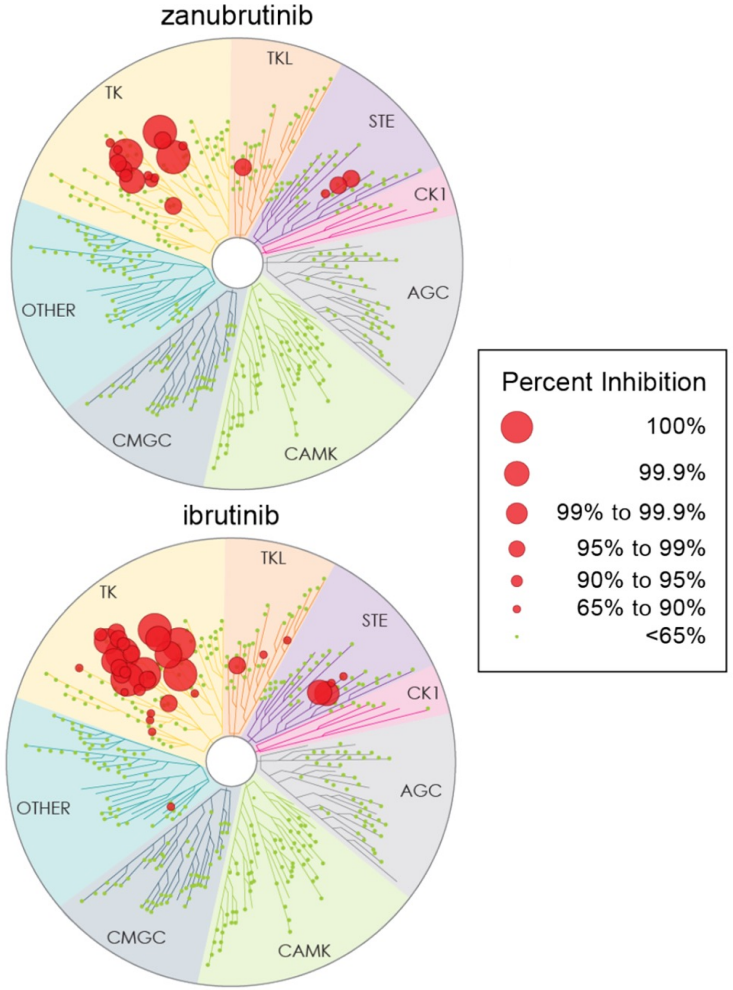


Kinase Inhibition (Average IC_{50}, nM)		
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	> 1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	> 1000	5.3
ERBB2	~ 1000	6.4
ERBB4	16	3.4
BLK	> 1000	0.1
JAK3	> 1000	32

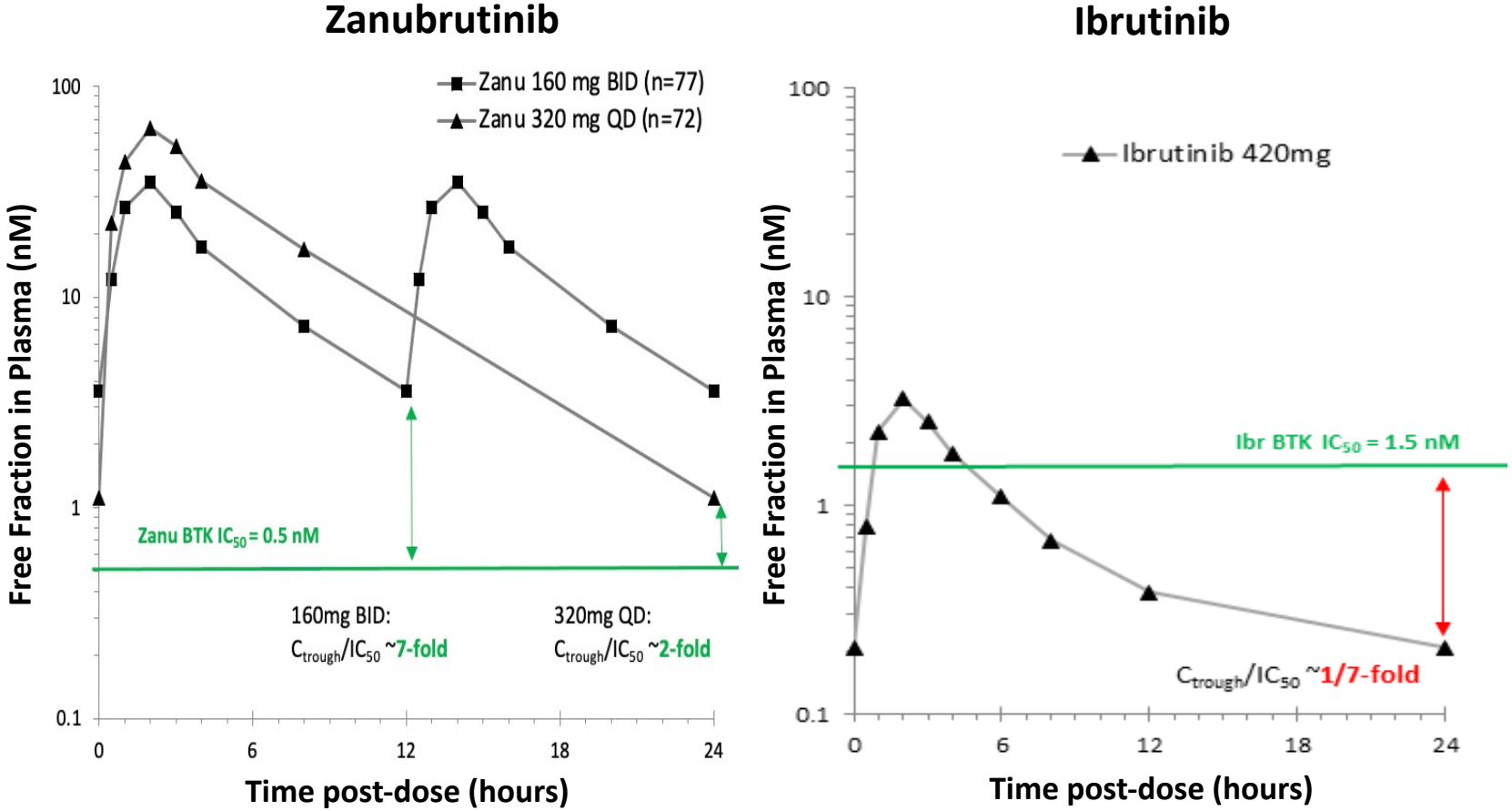
Figure from Herman et al. *Clin Cancer Res* 2017;23:2831-2841.
Byrd JC, et al. *N Engl J Med*. 2016;374:323-332.
Barf T, et al. *J Pharmacol Exp Ther*. 2017;363:240-252.

Pharmacokinetics and Selectivity of Zanubrutinib and Ibrutinib

Whole Kinase Panel Selectivity Profiles



Free Drug Concentration Time Profiles Relative to IC_{50}



Adapted from: 1. Kaptein, et al. *Blood.* 2018;132:1871. 2. Ou, et al. *Leuk Lymphoma.* In press. 3. Marostica, et al. *Cancer Chemother Pharmacol*. 2015;75:111-121.

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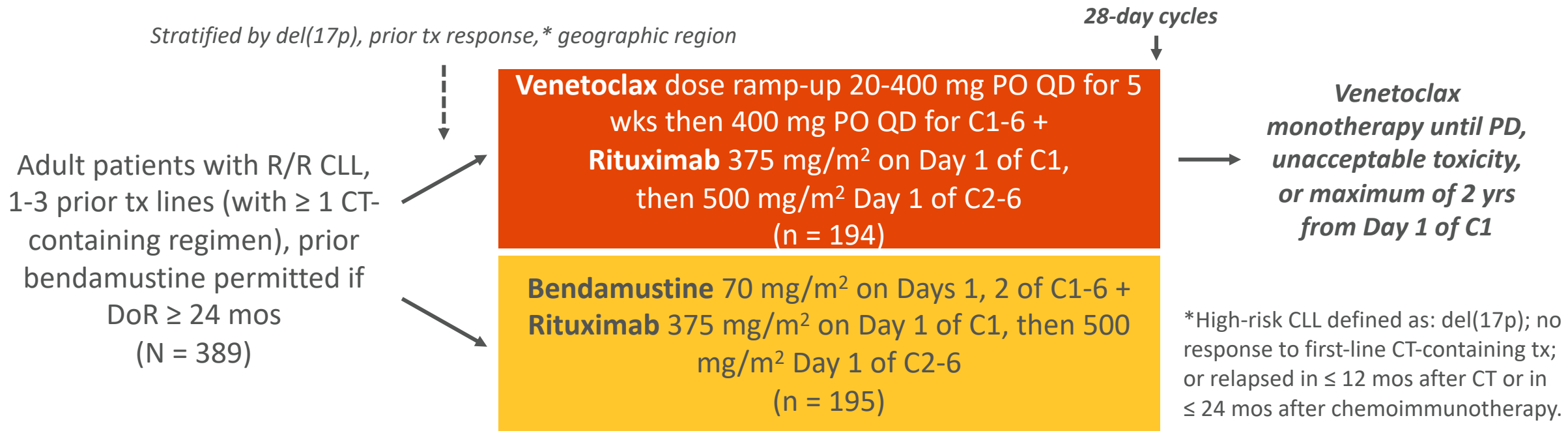
MURANO: Venetoclax + Rituximab vs BR in Previously Treated CLL/SLL

Multicenter, randomized, open-label phase III trial



- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS, safety

Seymour. NEJM. 2018;378:1107. Kater. JCO. 2020;[Epub]. NCT02005471.

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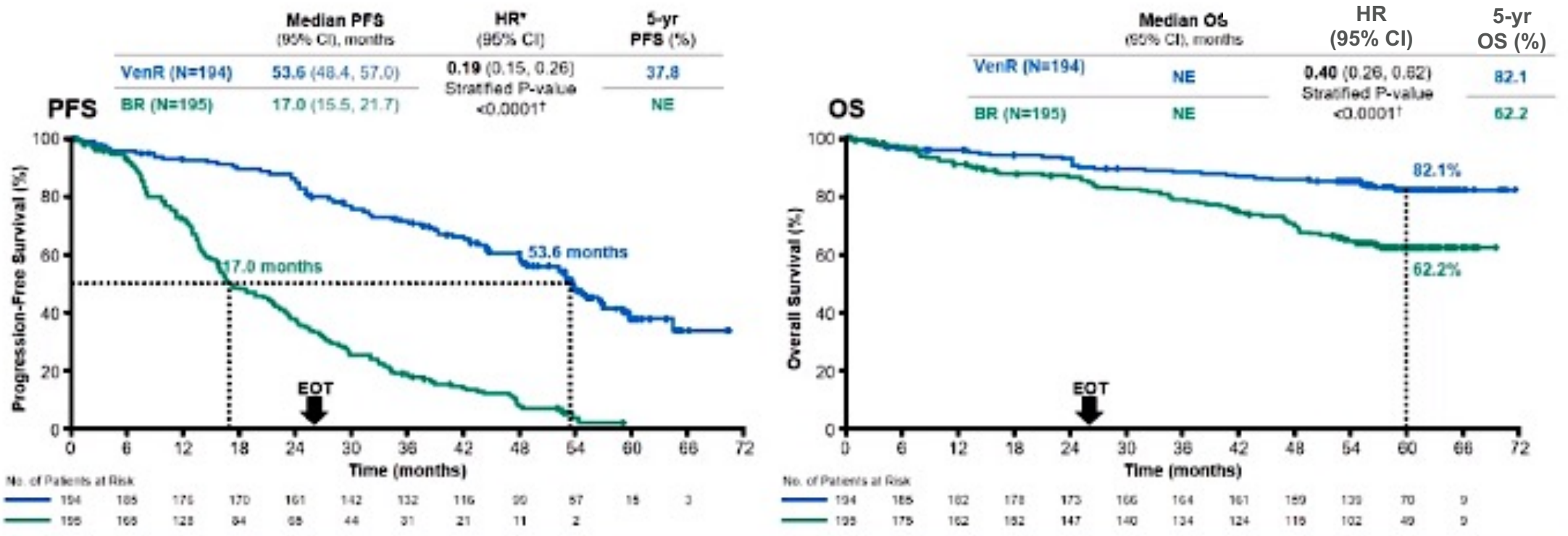
PFS and OS Benefit with VenR over BR Sustained 3 Years after EOT



- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

Seymour. NEJM. 2018;378:1107. Kater. JCO. 2020;[Epub]. NCT02005471.

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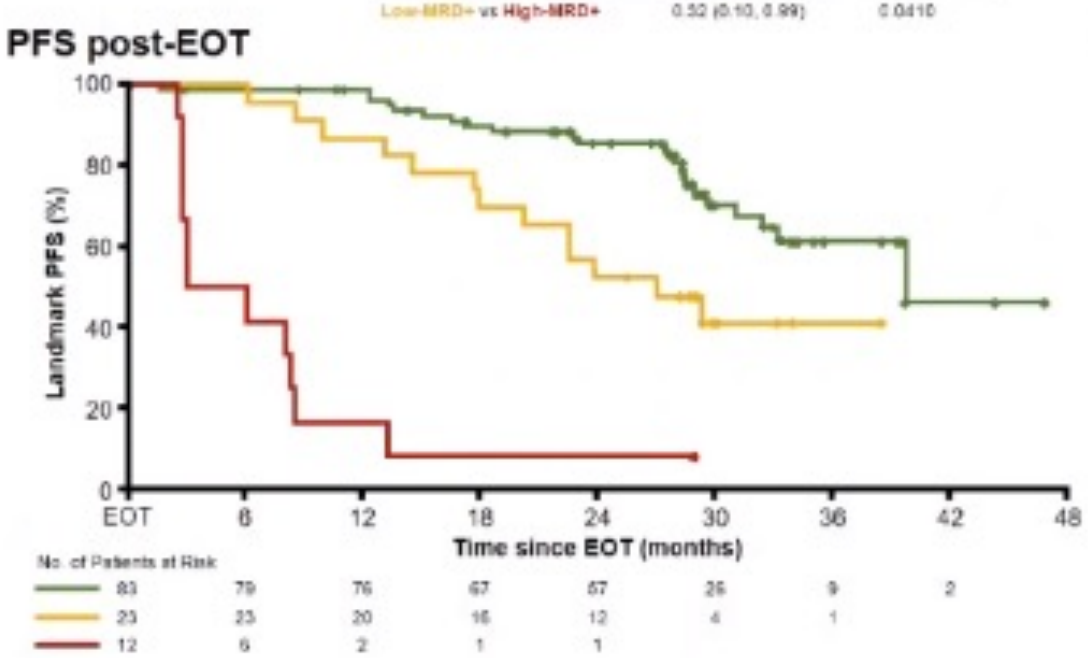
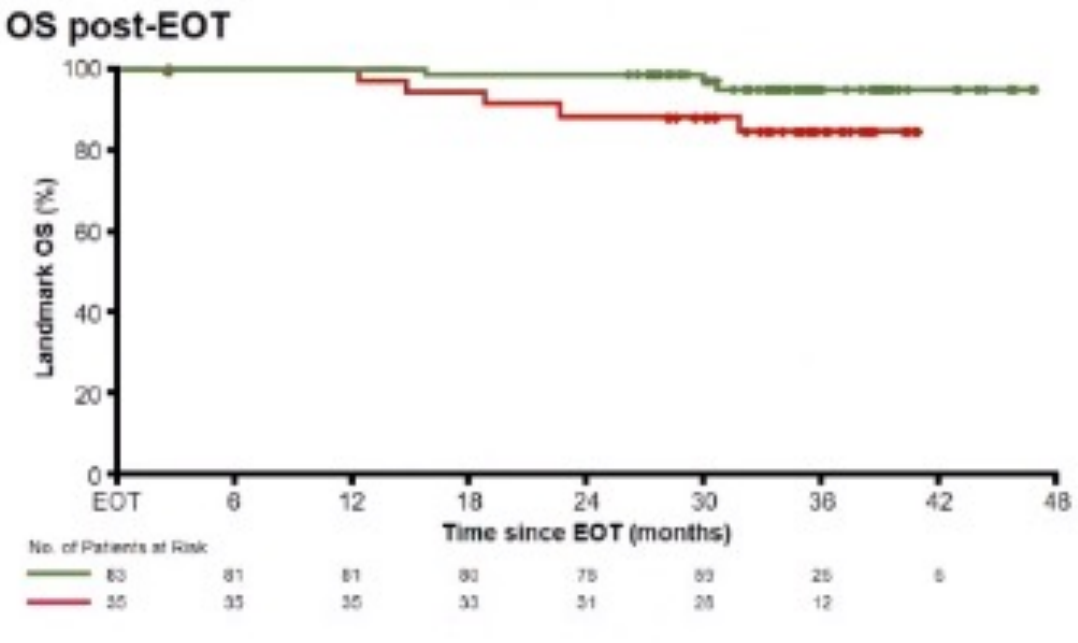
uMRD at EOT is Associated with Improved Outcomes in VenR Patients

Category	24 month	36 month
uMRD (<10⁻⁴)* (N=83)	85.4% (77.4, 93.4)	81.3% (47.3, 75.2)
Low-MRD+ (10⁻⁴–10⁻²) (N=23)	52.2% (31.8, 72.6)	40.7% (19.2, 62.2)
High-MRD+ (>10⁻²) (N=12)	8.3% (0.0, 24.0)	NE
	HR (95% CI)	P-value
uMRD vs Low-MRD+	0.40 (0.18, 0.91)	0.0246
uMRD vs High-MRD+	0.02 (<0.01, 0.16)	<0.0001
Low-MRD+ vs High-MRD+	0.32 (0.10, 0.99)	0.0410

Category	24 month	36 month
uMRD (<10⁻⁴)* (N=83)	95.8% (90.4, 100.0)	95.3% (90.0, 100.0)
MRD (≥10⁻⁴) (N=35)	88.6% (78.0, 99.1)	80.0% (72.8, 97.2)
	HR (95% CI)	P-value
uMRD vs MRD	NS	NS





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ASH Annual Meeting 2020 **Abstract Publication Number 3136**

Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia Patients after a Previous Venetoclax-based Regimen

Meghan C. Thompson, MD[1], John N. Allan, MD[2], Kavita Sail, PhD[3], Beenish S. Manzoor, PhD, MPH[4], Jeffrey J. Pu, MD, PhD[5], Paul M. Barr, MD[6], Callie C. Coombs, MD[7], Stephen J. Schuster, MD[8], Alan Skarbnik, MD[9], Joanna M Rhodes, MD[10], Jacqueline C. Barrientos, MD[10], Lindsey E Roeker, MD[1], Lori A. Leslie, MD[11], Manali Kamdar, MD[12], Michael Y. Choi, MD[13], Martin Simkovic, MD, PhD[14], Frederick Lansigan, MD[15], Brittany Jane Hale, MD[15], Andrew D Zelenetz, MD, PhD[16], Alison J. Moskowitz, MD[1], Kurt S. Bantilan, MPH[1], Celina J. Komari, BS[1], Andre H. Goy, MD[1], Tatyana A. Feldman, MD[11], Richard R. Furman, MD[2] and Anthony R. Mato, MD[1]

Study Design and Endpoints

- Multicenter, retrospective study
- 13 centers and the CLL Collaborative Study of Real-World Evidence (CORE) database
- Eligibility:
  - CLL patients treated with Ven-based regimen (any line of therapy, Ven1)
  - Then re-treated with second Ven-based regimen (Ven2) in a later line of therapy
- Data collected by investigators at individual sites
  - Demographics, prognostic disease characteristics, tumor lysis syndrome risk and incidence, clinical response and reasons for treatment discontinuation

- Primary endpoint:
  - Investigator-assessed ORR
  - CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease, iwCLL 2018
- PFS estimated by Kaplan-Maier method
- All other analyses descriptive

Memorial Sloan Kettering Cancer Center
Weill Cornell Medicine
UPSTATE CANCER CENTER
UC San Diego Health
University of Colorado
UR MEDICINE
UNC
Penn
Hackensack Meridian John Theurer Cancer Center
NOVANT HEALTH
Northwell Health
Dartmouth-Hitchcock NORRIS COTTON CANCER CENTER
Fakultní nemocnice Hradec Králové

Thompson MC et al. ASH 2020;Abstract 3136.

Conclusions

- **ORR:** High ORR of 72.2% for Ven re-treatment
- **Heavily pretreated population:** Cohort studied had median 2 prior therapies, majority R/R (88%), BTKi exposed (60%)
- **Safety:** TLS rare event and majority were able to tolerate 400 mg daily
- **Improved outcomes with time:** Patients with CR to Ven re-treatment had a longer median follow-up than PR or SD patients
  - Potential for better responses with longer time on therapy?
- **Next steps:** Longer follow-up and prospective validation of Ven re-treatment → potential role of Ven re-treatment in sequencing algorithms

Thompson MC et al. ASH 2020;Abstract 3136.

It may seem obvious but . . .
Do we know if a BTKi is appropriate after venetoclax?

Does sequencing matter?

Two studies examined efficacy of BTKi post venetoclax

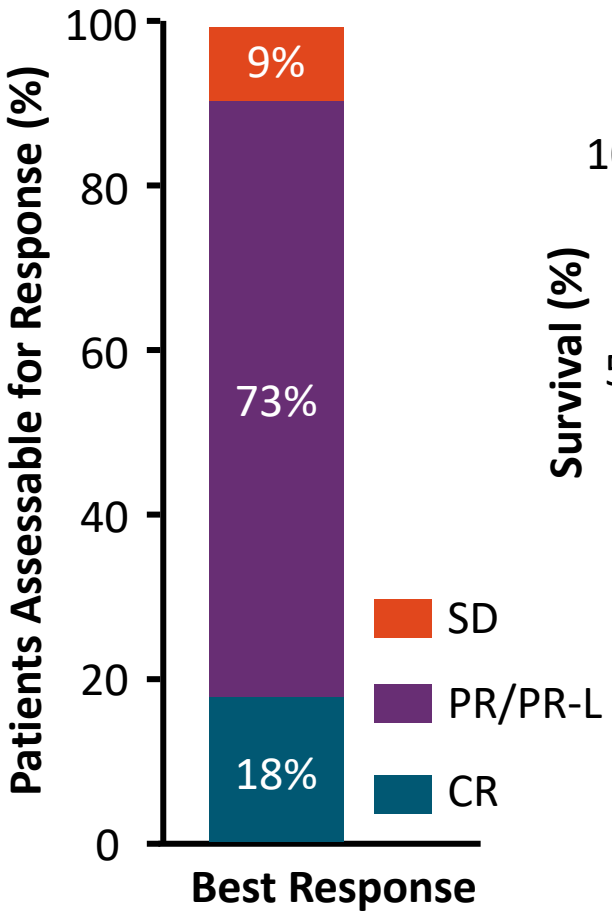
Lin et al *Blood* 2020: 23 pts with r/r CLL who received BTKi following ven

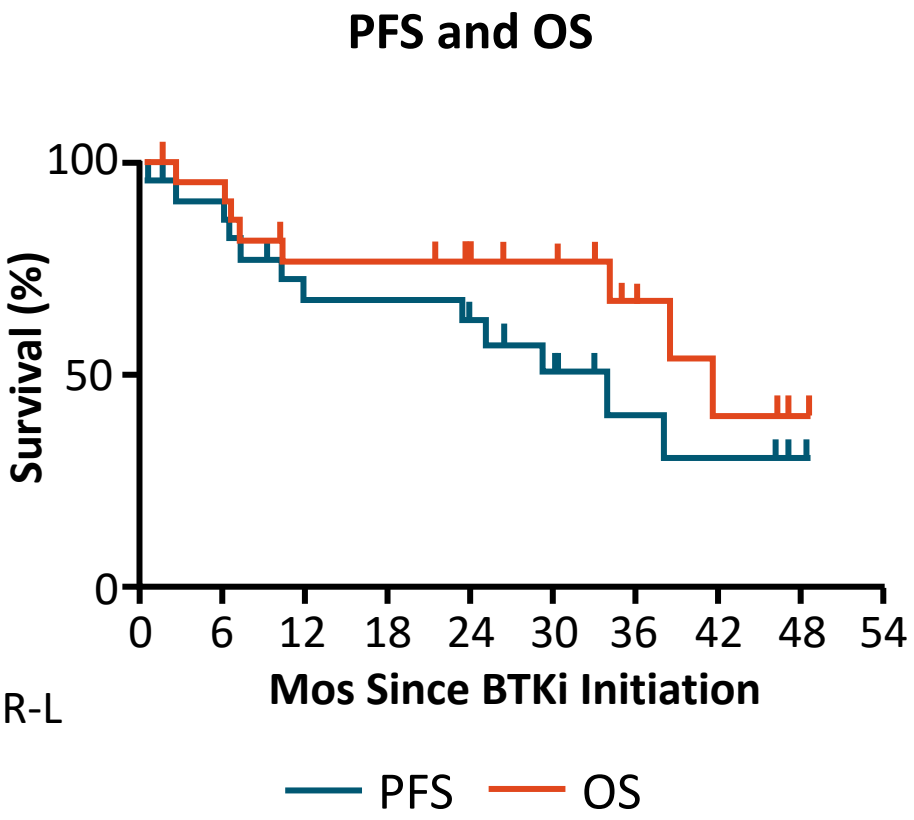
- PFS 34 months and OS 42 months

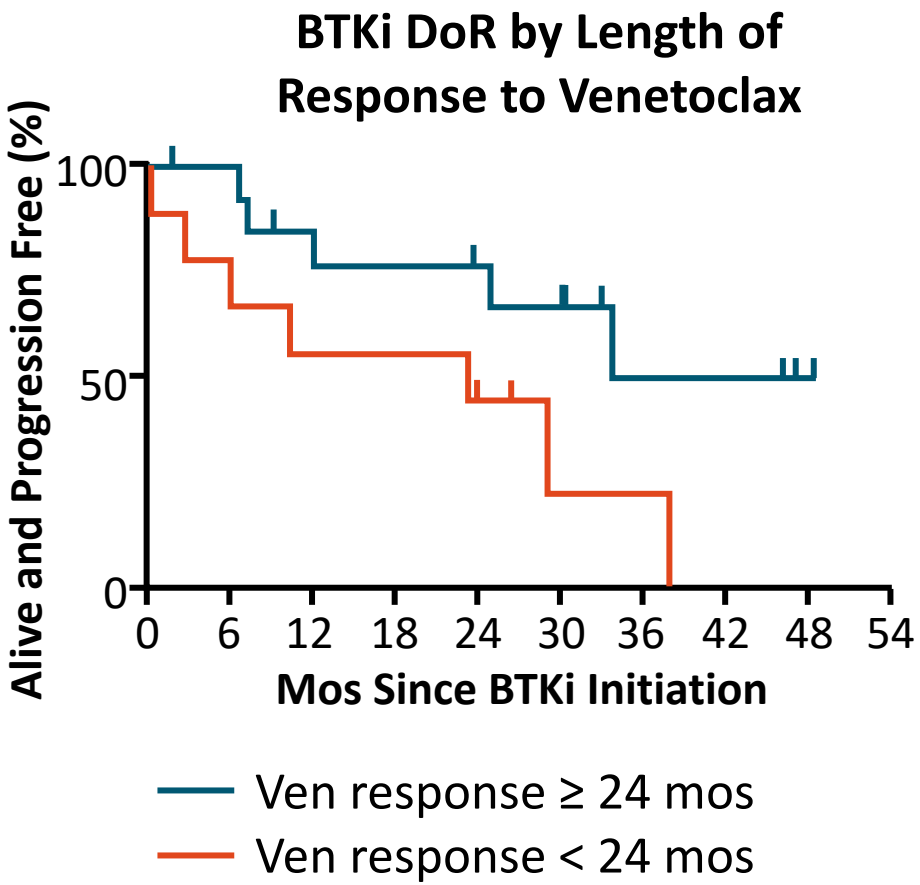
Mato et al *CCR* 2020: 74 pts with r/r CLL who received BTKi following venetoclax

- 44 were BTKi naïve and 30 were previously BTKi exposed (33% intolerant, 66% resistant)
- ORR in BTKi naïve pts was 84% with median PFS 32 months
  - Response rate lower for pts receiving BTKi post-ven who had already had a BTKi in past - ORR 54% (median PFS not reached in BTKi intolerant, but 4 months in BTKi resistant)

BTK inhibitor Therapy Is Effective in Patients With CLL Resistant to Venetoclax (Retrospective Analysis, N = 23)







Lin. Blood. 2020;135:2266.

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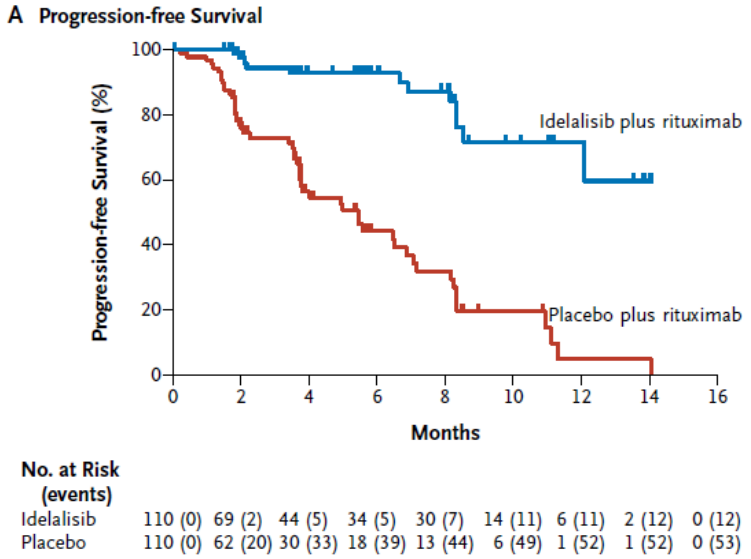
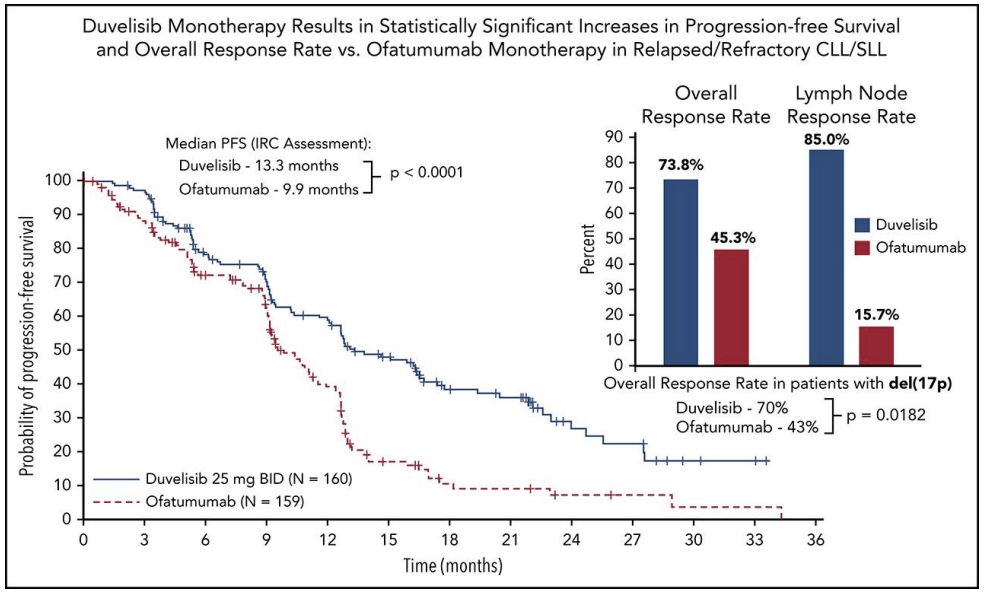
Role for PI3K inhibitors

Toxicity of PI3Ki limit their use especially in earlier lines of therapy

Prior BTKi were excluded for pts who participated on the phase 3 trials leading to approval of idelalisib-rituximab and duvelisib so efficacy for these agents post-BTKi is limited



Furman et al *NEJM* 2014



Flinn et al *Blood* 2018

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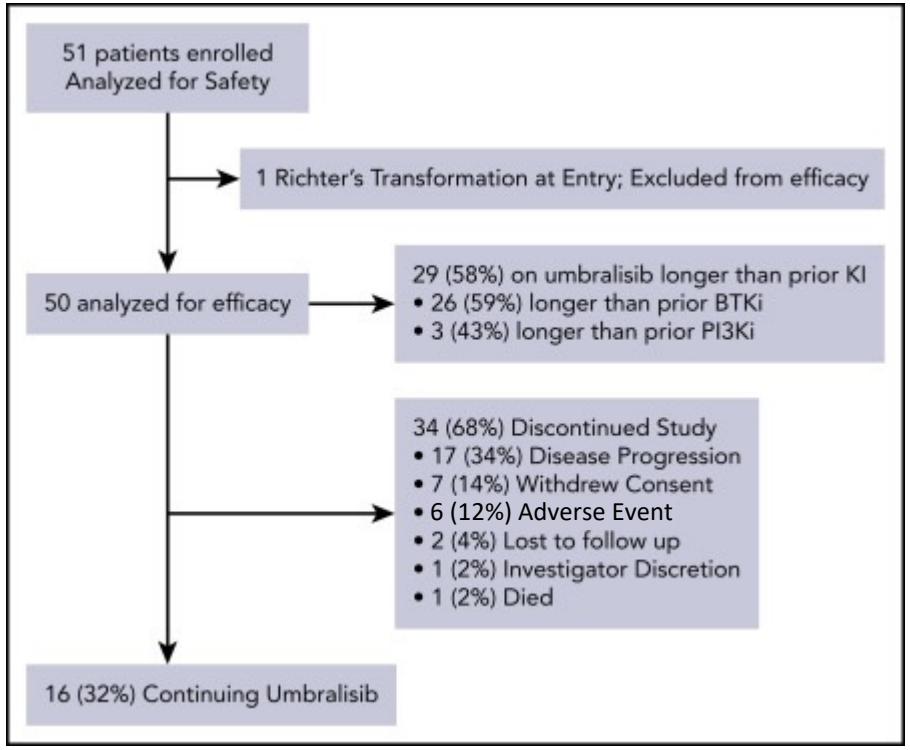
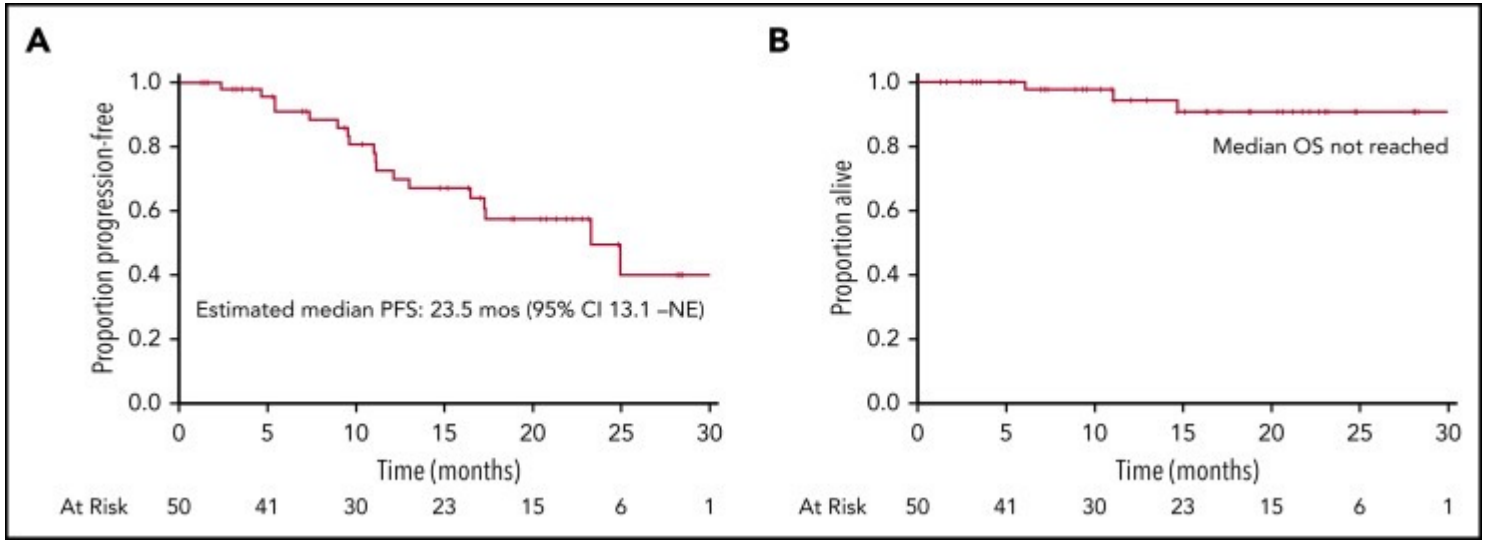
Umbralisib in pts with BTKi intolerance

Mato et al. *Blood* 2021: phase 2 of umbralisib in pts with BTKi / PI3Ki intolerance (86% of pts had prior BTKi)





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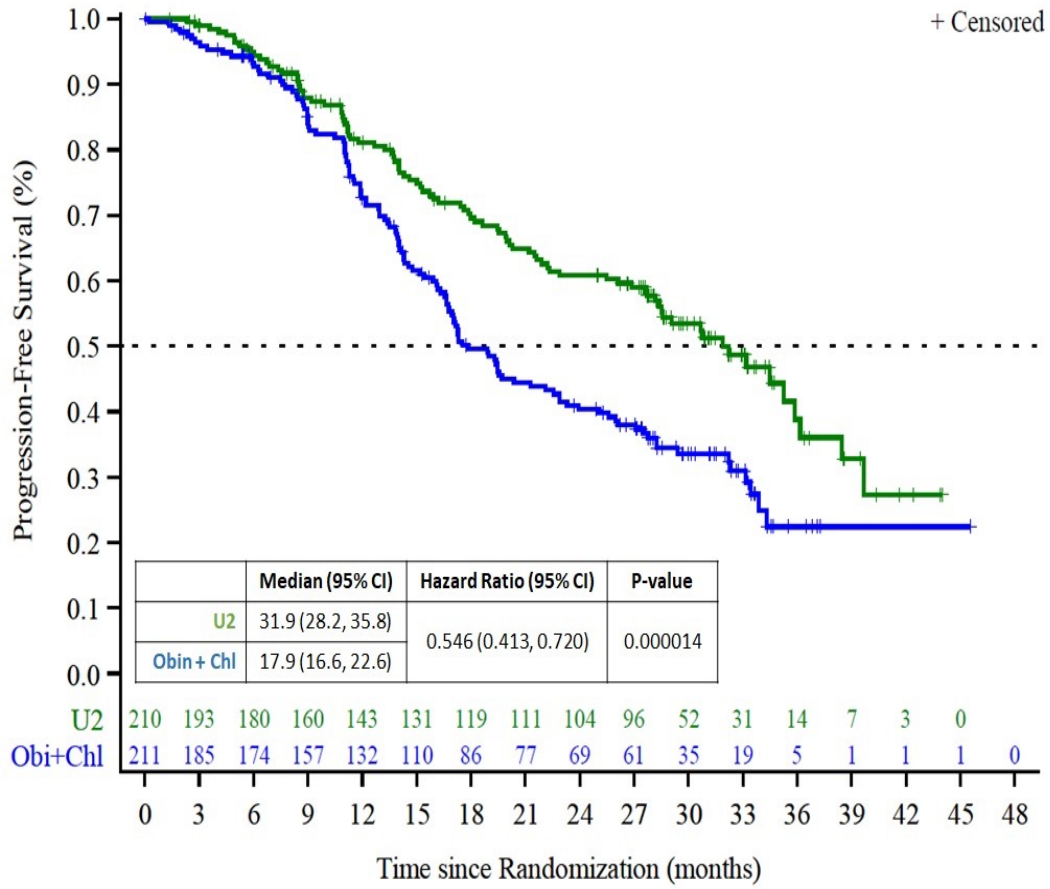
Umbralisib + ublituximab (U2)

- Phase 3 UNITY study of U2 regimen vs chlor-obi
- Both frontline and r/r CLL included
- Included pts with prior BTKi (n=26 of 181 r/r CLL pts enrolled, 14 on the U2 arm)
- - 40% (2/5 pts) on the phase 1/1b trial of U2 with prior ibrut responded



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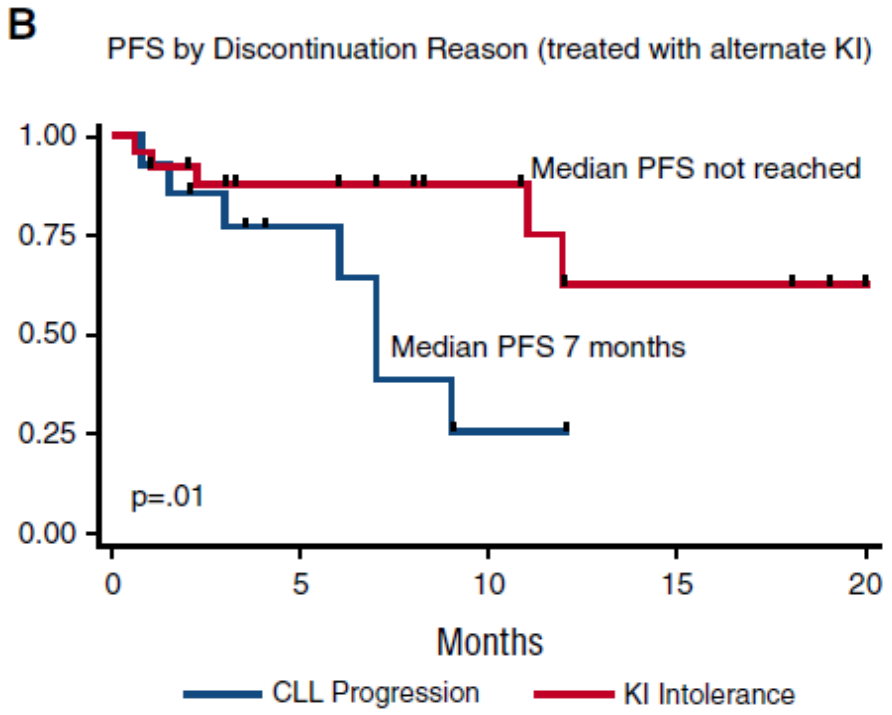
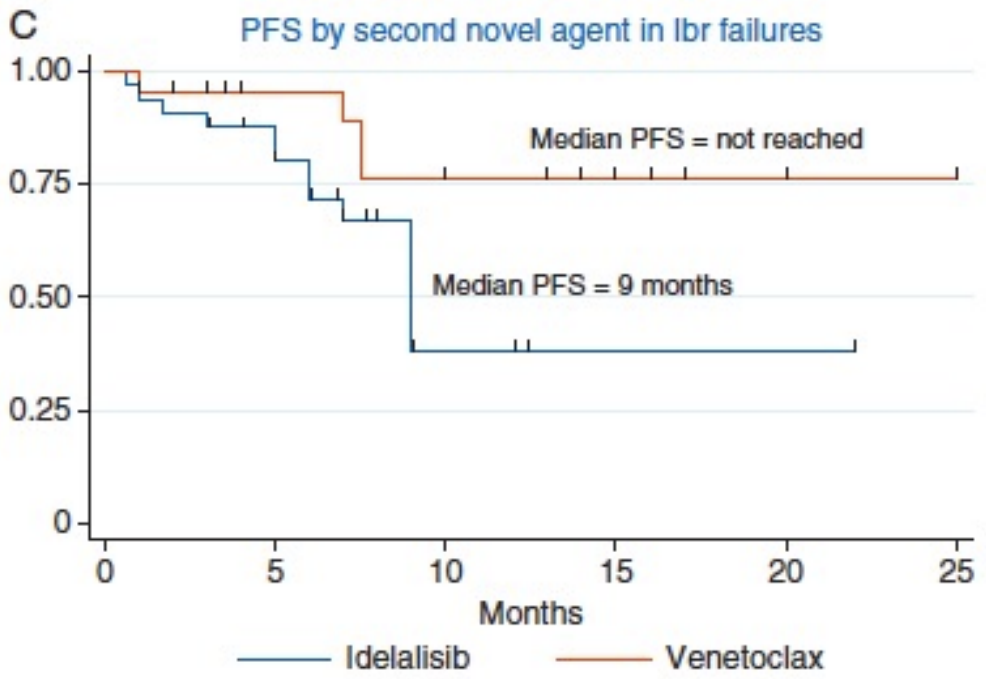
Data are limited on PI3Ki effectiveness after progression on covalent BTKi

Mato et al. *Blood* 2016



Mato et al. *Ann Oncol* 2017



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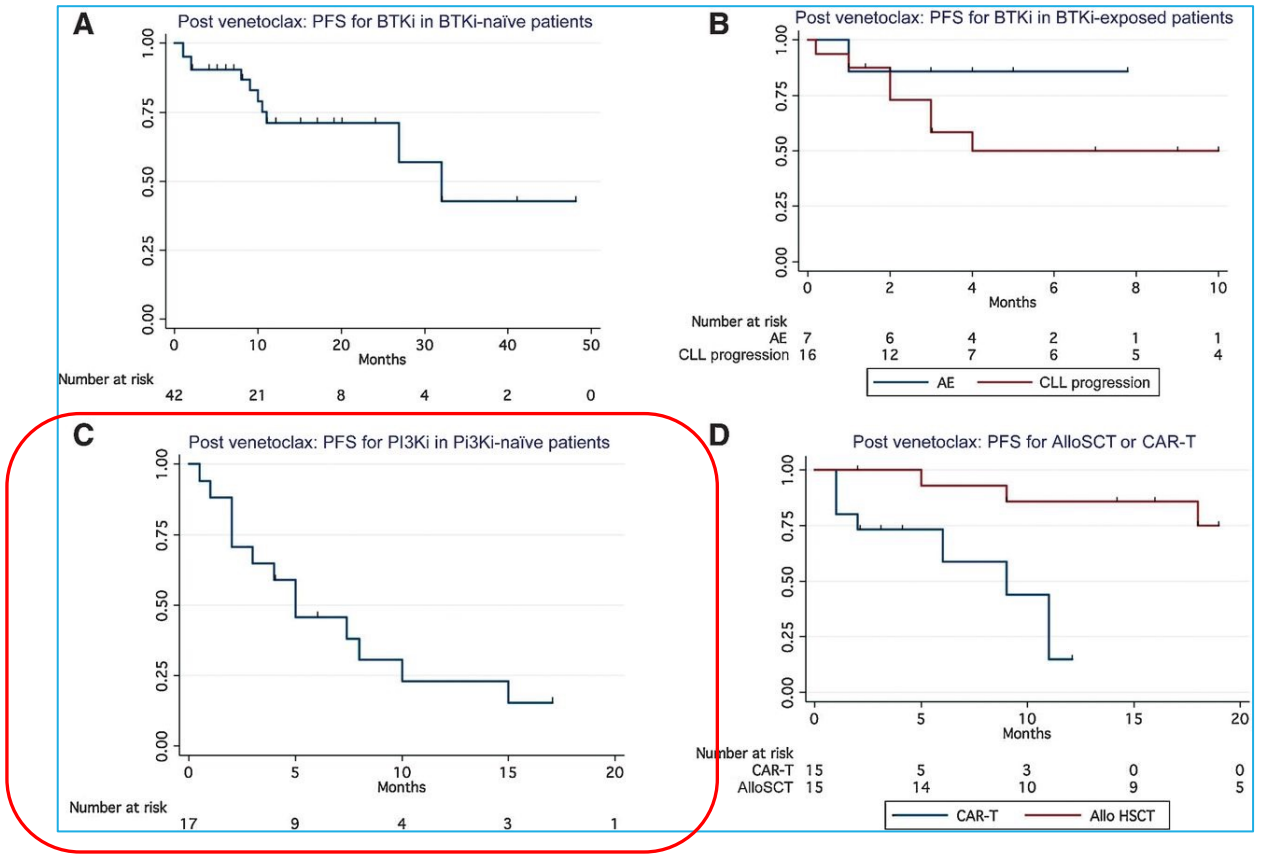
PI3Ki After Venetoclax

- Mato et al. *Clin Cancer Res* 2020: 5 month median PFS for pts receiving PI3Ki following venetoclax



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Summary: Treatment Sequence for Patients With R/R CLL

- BTK inhibitor (ibrutinib or acalabrutinib)
- **If BTK inhibitor intolerant**: alternative BTK inhibitor, PI3Ki, venetoclax (± CD20 Ab)
- **If BTK inhibitor resistant**: venetoclax (± CD20 Ab), PI3Ki, reversible non-covalent BTKi, CAR T-cell therapy
- **If del(17p) and BTK inhibitor resistant or intolerant**: venetoclax (± CD20 mAb), PI3Ki, CAR T-cell therapy, allogeneic HCT
- Clinical trials whenever possible
  - Emerging agents including bispecific Ab among others

Thank You

"FREE HAMMOCKS, all over town. It's like a miracle!"