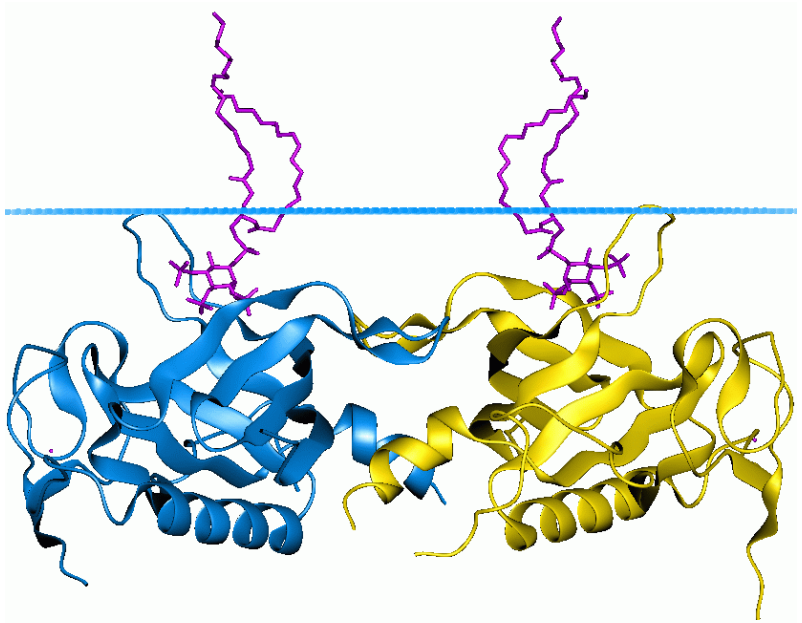
Year in Review

Chronic Lymphocytic Leukemia

BTK Inhibitors



Matthew S. Davids, MD, MMSc

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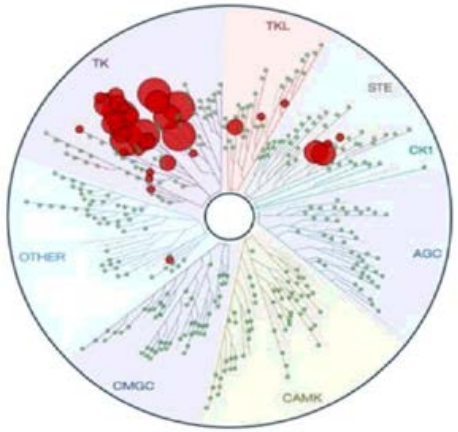
Director of Clinical Research | Division of Lymphoma |Dana-Farber Cancer Institute

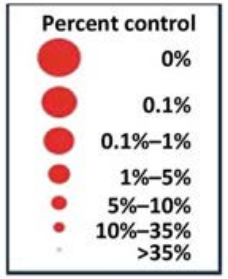
January 2021

The BTKi floodgates have opened…

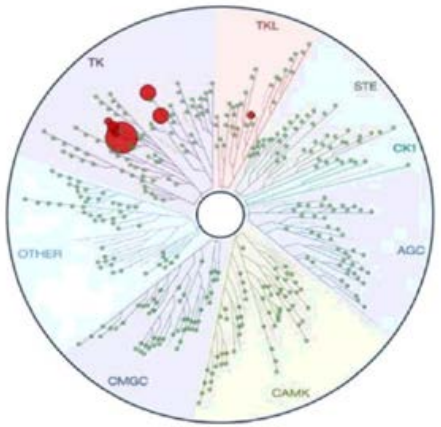
Irreversible

Ibrutinib

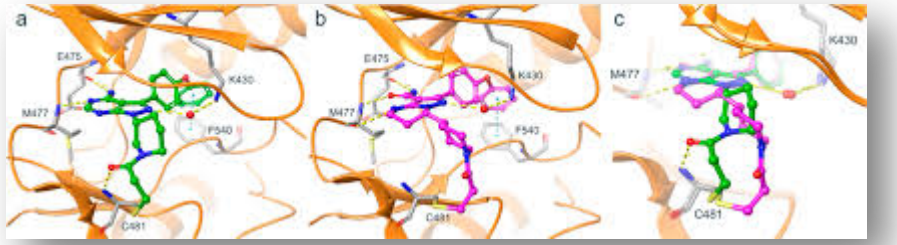




Acalabrutinib

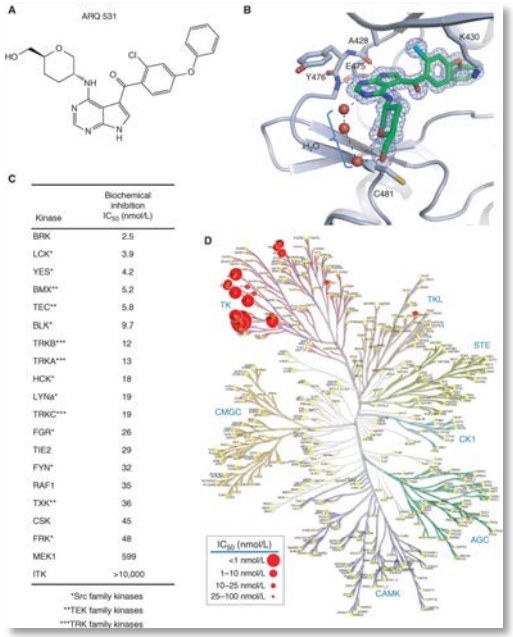


Zanubrutinib

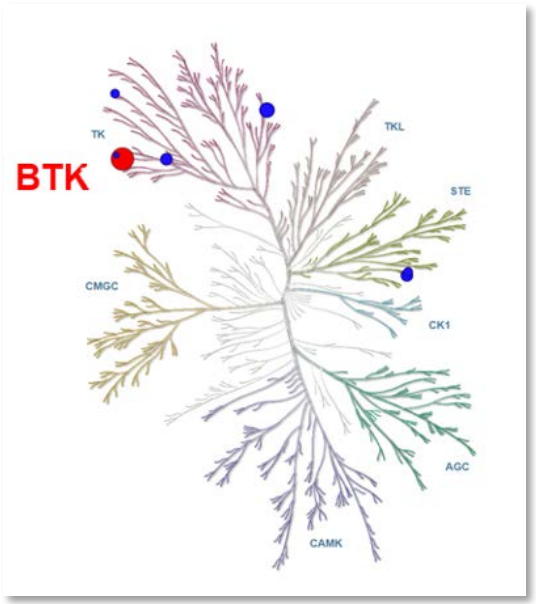


Reversible

ARQ-531 (MK-1026)



LOXO-305



Courtesy of Matthew S Davids, MD, MMSc

Phase 3 E1912: IR vs FCR
IR Effective as Initial Treatment for CLL

Previously Untreated CLL (N = 529)
- Age ≤ 70
- ECOG 0-2
- CrCl>40
- Able to tolerate FCR
- **No deletion 17p by FISH**

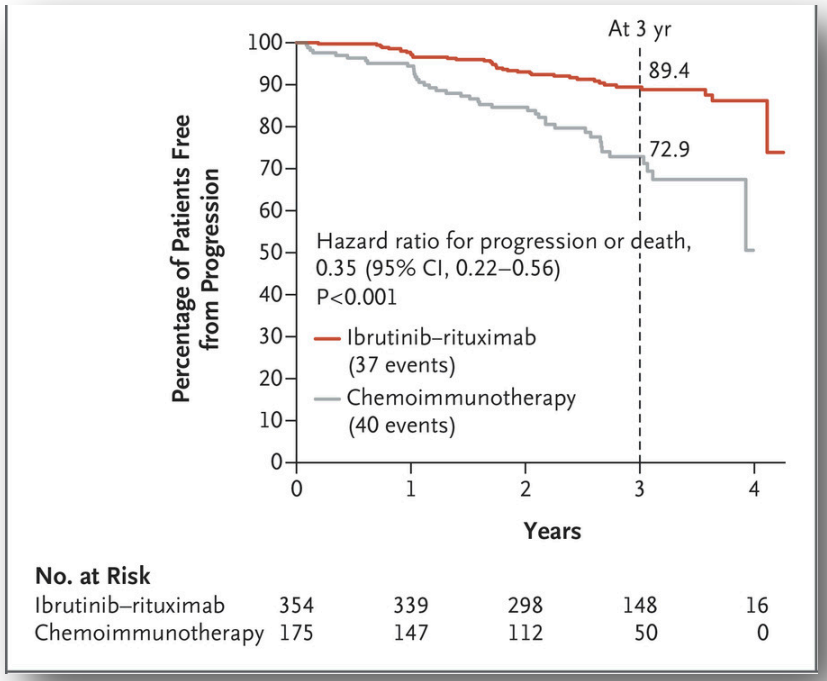
Randomized 2:1

- **Ibrutinib + Rituximab (IR)** → **Ibrutinib until PD**
- **FCR**

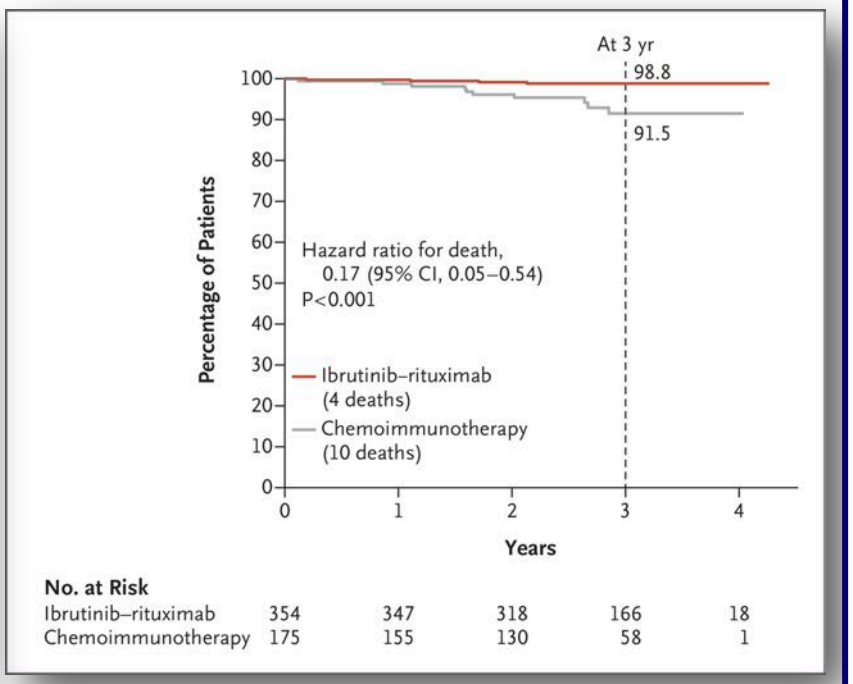
Primary Endpoint

PFS

PFS-All Patients



OS



- IR was superior to FCR for *IGHV* unmutated patients
- AEs grade ≥ 3
  - IR, 80.1%
  - FCR, 79.7%
- Infectious complications of grade ≥ 3
  - IR, 10.5%
  - FCR, 20.3%
- **April 21, 2020: FDA expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with CLL/SLL**

Shanafelt T, et al. *N Engl J Med*. 2019;381:432-443. doi: 10.1056/NEJMoa1817073

Courtesy of Matthew S Davids, MD, MMSc

Phase 3 RESONATE-2 Trial: 5-Year Update

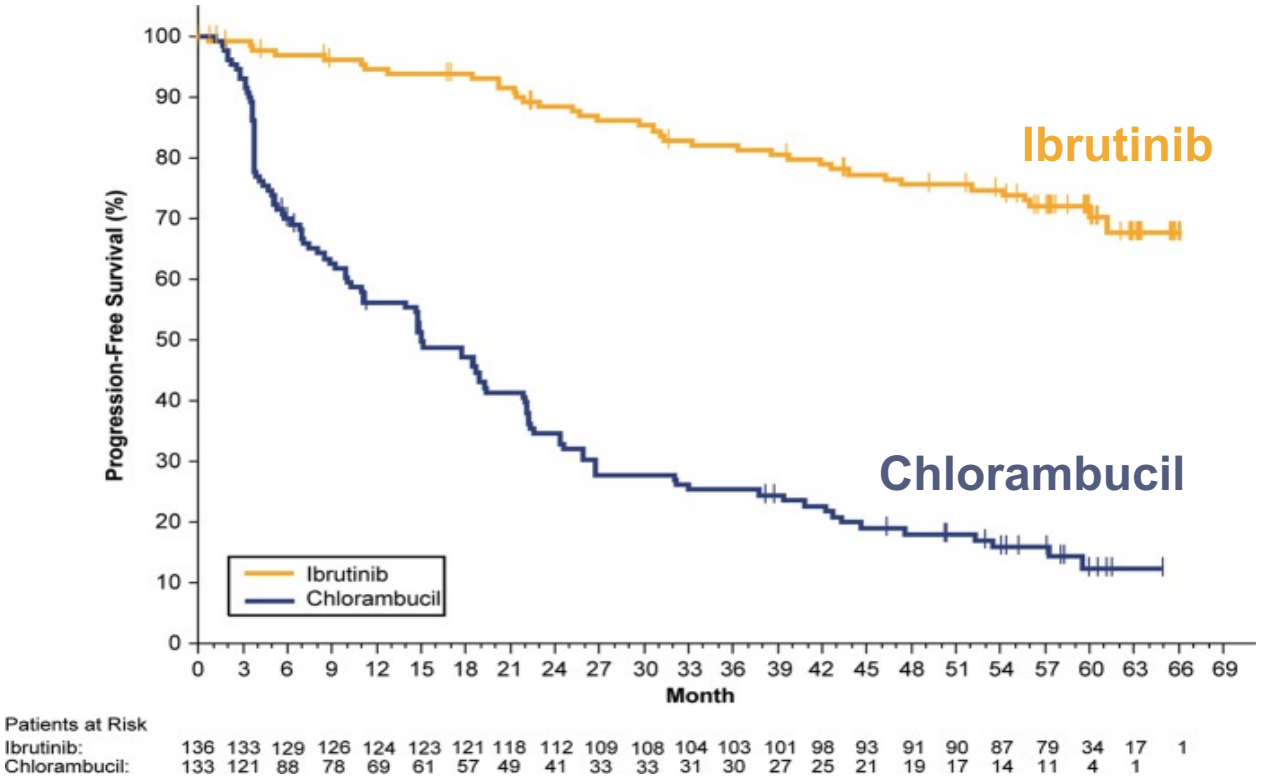
Ibrutinib Provides Durable Response as Initial Therapy in Frail Pts

Efficacy

- Ibrutinib benefit was also consistent in patients with high prognostic risk (*TP53* mutation, 11q deletion, and/or unmutated *IGHV*)

Safety

- Discontinuation due to AEs decreased over time, with 58% of ibrutinib pts continuing daily treatment



	Median PFS, mo	HR (95% CI)
Ibrutinib	NE	0.146 (0.098-0.218)
Chlorambucil	15.0	

Burger JA, et al. *Leukemia.* 2020;34(3):787-798. doi: 10.1038/s41375-019-0602-x.

Courtesy of Matthew S Davids, MD, MMSc

Conclusions

Impact on Patient Care and Treatment Algorithm

- Ibrutinib-based therapy is superior to FCR for young, fit patients with unmutated IGHV
- Ibrutinib provides long term benefit with reasonable tolerability for older patients
- Discontinuations due to toxicity do continue over time, esp. in older patients

Implications for Future Research

- Longer term follow-up needed to understand how to approach mutated-IGHV patients
- Ongoing studies are looking at ibrutinib + CIT (iFCR, iFCG, etc.)
- Ibrutinib will be a key comparator in the CLL17 study (I vs IV vs VO) and in combination with obin in the US cooperative group studies (vs IVO)

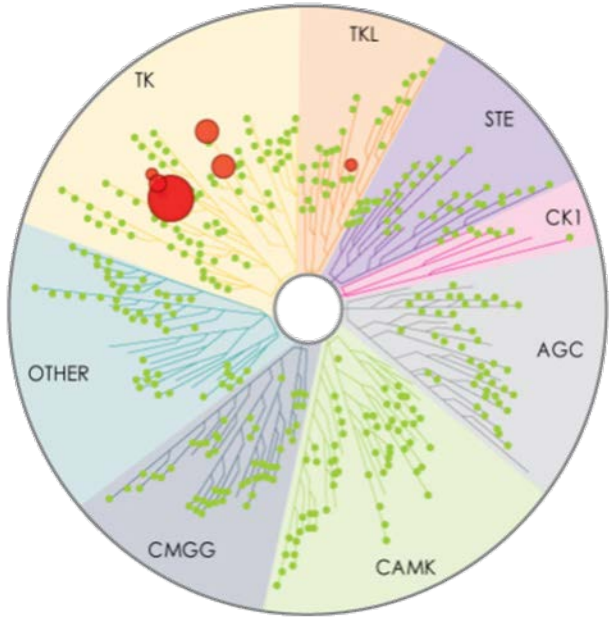
Courtesy of Matthew S Davids, MD, MMSc

Second Generation BTKi: Acalabrutinib: Agent Overview

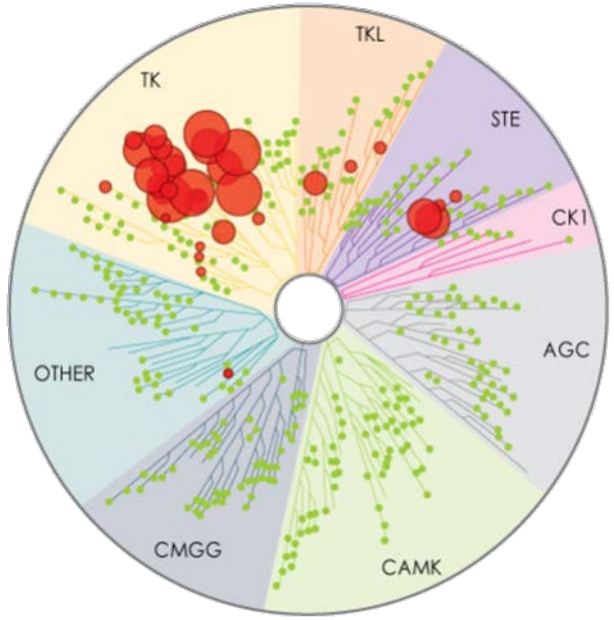
- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling
- Dosing is 100 mg PO bid

Kinase selectivity profiling at 1 μM

Acalabrutinib



Ibrutinib



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Barf T, et al. *J Pharmacol Exp Ther.* 2017.

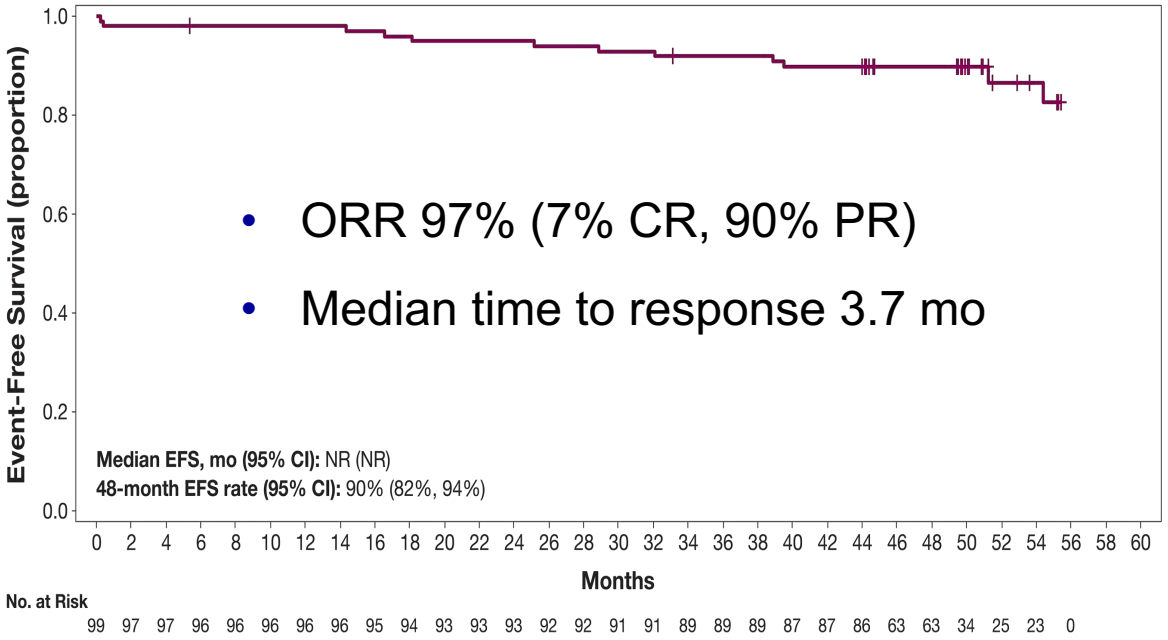
Courtesy of Matthew S Davids, MD, MMSc

Acalabrutinib is Highly Effective in Front-Line CLL

Phase 1/2 ACE-CL-001 Study in patients with previously untreated CLL requiring tx (N = 99)

→

Acalabrutinib
200 mg once daily
or
100 mg twice daily



- ORR 97% (7% CR, 90% PR)
- Median time to response 3.7 mo

ASCO/EHA 2020 Update: Acalabrutinib monotherapy demonstrated durable remissions and long-term tolerability (median follow-up of 53 months)

- 86% of patients remain on treatment
- Median DOR was not reached
  48-month DOR rate: 97% (95% CI, 90%–99%)
- Median EFS was not reached 48-month EFS rate: 90% (95% CI, 82%–94%)

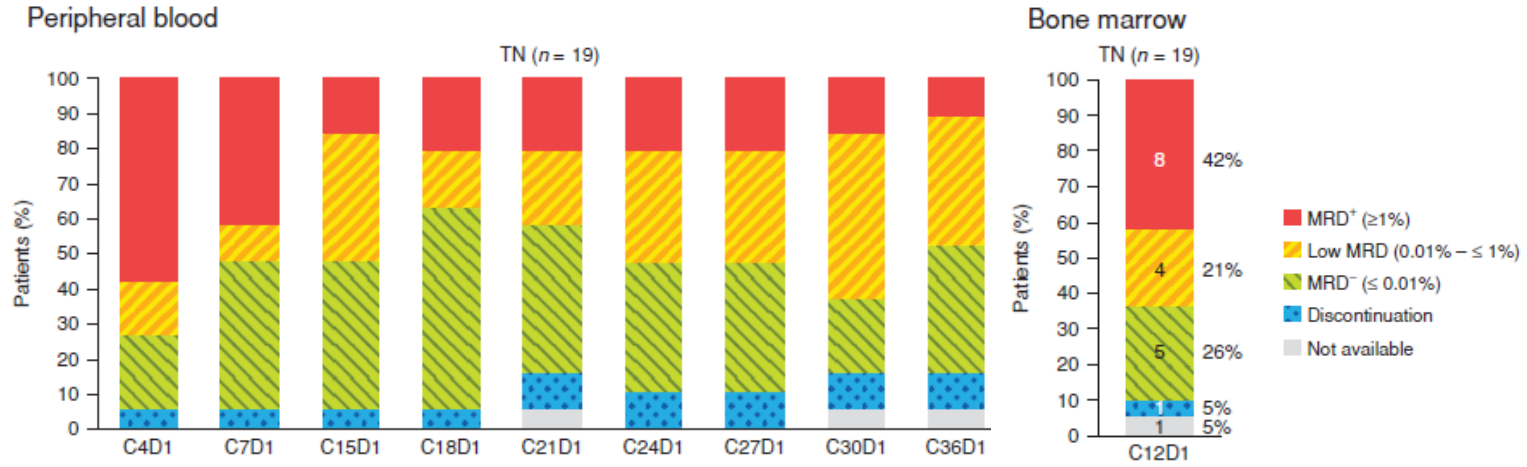
Courtesy of Matthew S Davids, MD, MMSc

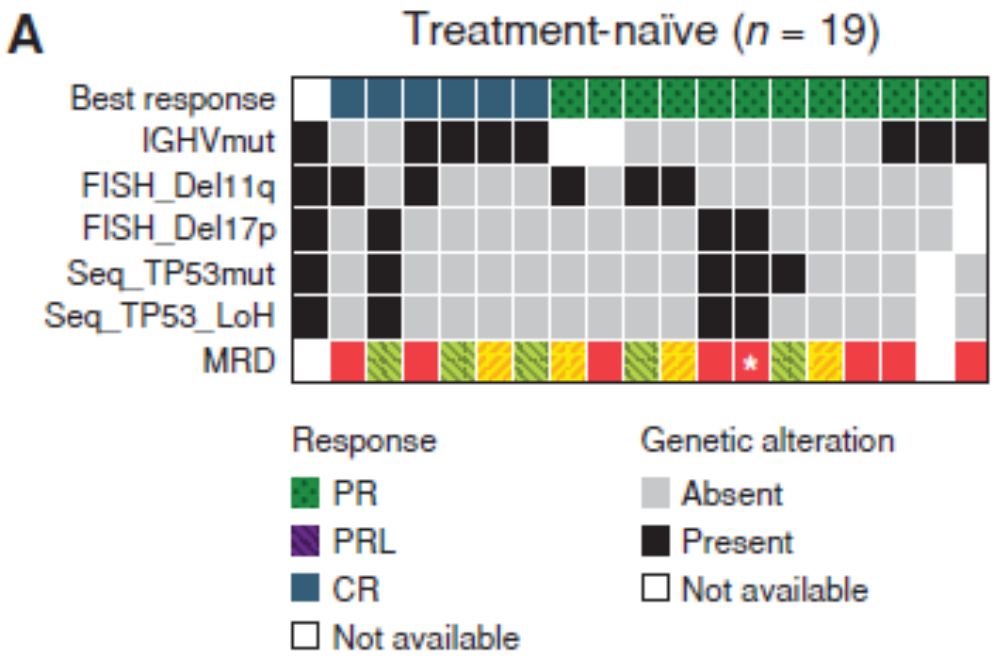
Byrd, et al. *Blood*. 2018; 132 (Supplement 1): 692. doi.org/10.1182/blood-2018-99-110451. Byrd, et al. *J Clin Oncol. 2020;*38, no. 15_suppl:8024-8024.. doi.org/10.1200/JCO.2020.38.15_suppl.8024.

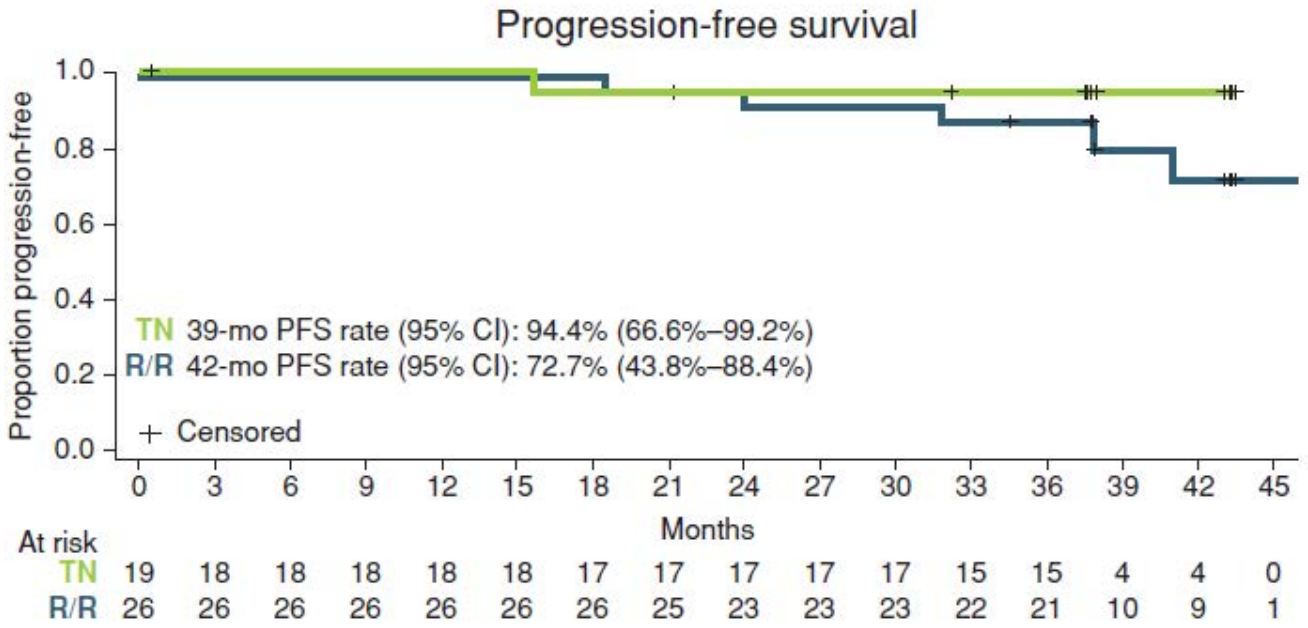
RESEARCH ARTICLE

Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia

Jennifer A. Woyach[1], James S. Blachly[1], Kerry A. Rogers[1], Seema A. Bhat[1], Mojgan Jianfar[1], Gerard Lozanski[1], David M. Weiss[1], Barbara L. Andersen[1], Michael Gulrajani[2], Melanie M. Frigault[2], Ahmed Hamdy[2], Raquel Izumi[2], Veerendra Munugalavadla[2], Cheng Quah[2], Min-Hui Wang[2], and John C. Byrd[1]







Woyach et al, Cancer Discovery, 2020

Courtesy of Matthew S Davids, MD, MMSc

Phase 3 ELEVATE-CLL TN: Acalabrutinib is Superior to Obinutuzumab + Chlorambucil for Treatment-Naïve CLL

Treatment-naive CLL (N=535)

Age ≥65 or <65 years with coexisting conditions:

- CIRS score >6, or
- creatinine clearance <70 mL/min

Stratification

- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

RANDOMIZE

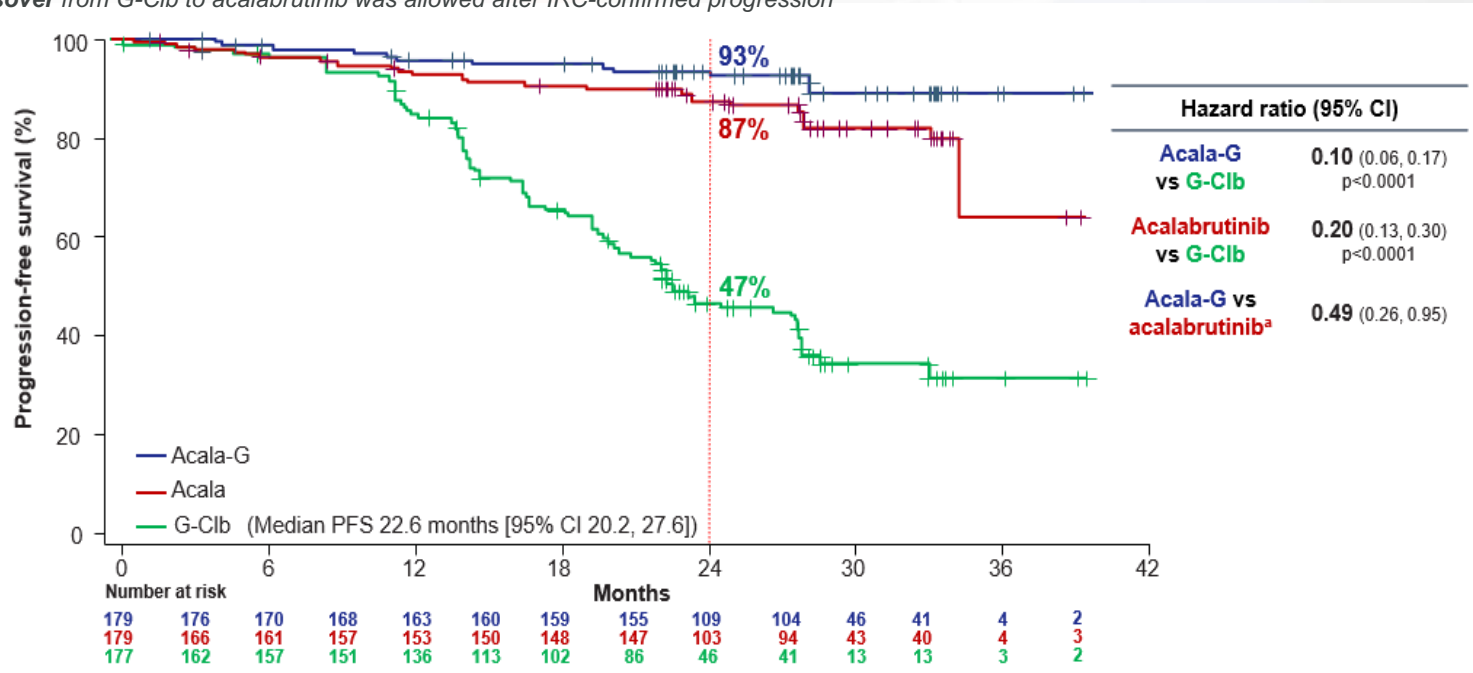
- **Acalabrutinib + Obinutuzumab (G)**
- **Acalabrutinib**
- **Obinutuzumab (G) + Chlorambucil (Clb)**

Primary endpoint

- PFS (assessed by IRC) Acala-G vs G-Clb

Crossover *from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

- Median follow-up: 28.3 months
- 90% reduction in disease progression or death with acalabrutinib + obinutuzumab
- On November 21, 2019, the FDA approved acalabrutinib monotherapy for the treatment of adult patients with chronic CLL based on analyses from the ELEVATE-TN and ASCEND phase III trials.



Sharman, et al. *Lancet.* 2020;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2.

Courtesy of Matthew S Davids, MD, MMSc

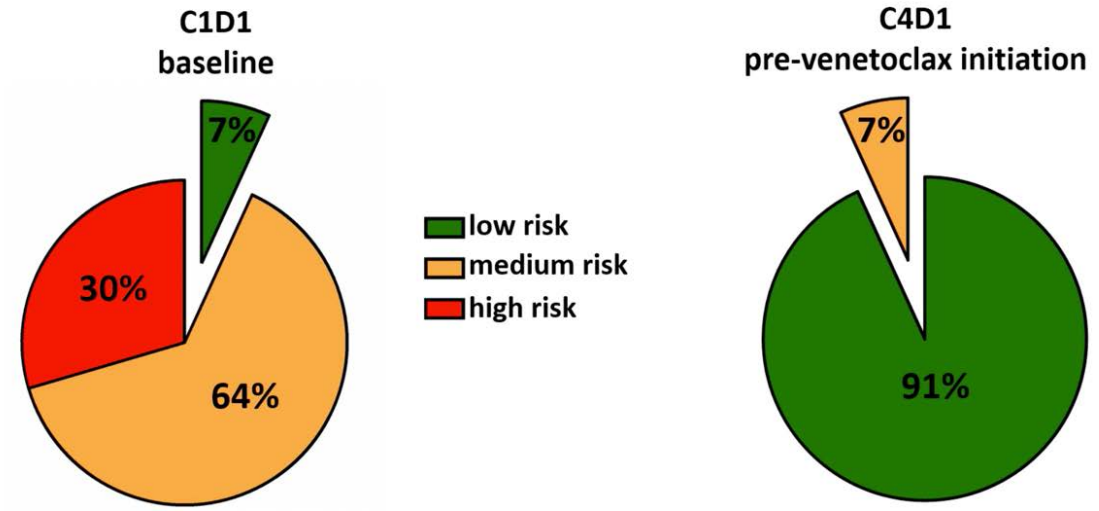
A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Safety

AEs (N=44), %		All Grades	Grade ≥3
Most frequent hematologic	Neutropenia	77	34
	Thrombocytopenia	70	22
	Anemia	52	5
Non-hematologic (≥20%)	Headache	80	2
	Fatigue	77	2
	Bruising	57	0
	Nausea	45	0
	Hypocalcemia	34	2
	Rash	32	0
	Diarrhea	27	0
	GERD	25	0
	IRR	25	2
	Elevated creatinine	23	0

SAEs

- Grade 4 neutropenia (n=4), grade 4 hyperkalemia (n=1; in the setting of AKI just prior to C4D1 without TLS), grade 3 cardiac troponin I elevated (n=1; in the setting of O IRR), grade 3 lung infection (n=1)

3 cycle lead-in with acalabrutinib and obinutuzumab reduces TLS risk at the time of ven initiation (n=44)



AEs of special interest

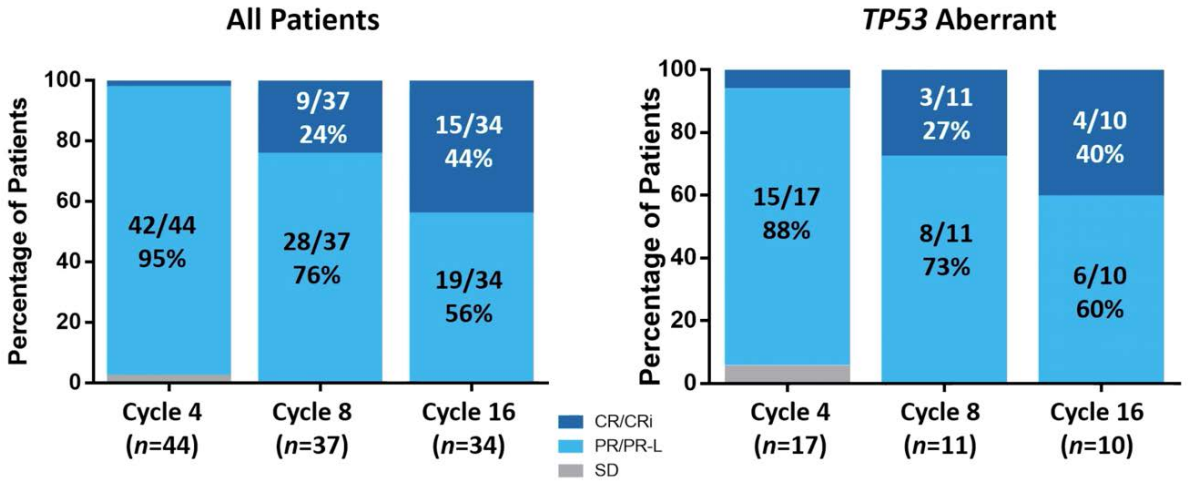
- Grade ≥3 infections: 1 (2.3%, grade 3 lung infection)
- IRRs: 11 (25%, including 23% grade 1/2, 2% grade 3)
- Hypertension: 5 (11%; no grade ≥3)
- Afib: 1 grade 3
- Lab TLS: 2 grade 3 (both after O and prior to V)

Davids MS, et al. ASH 2020. Abstract 2216.

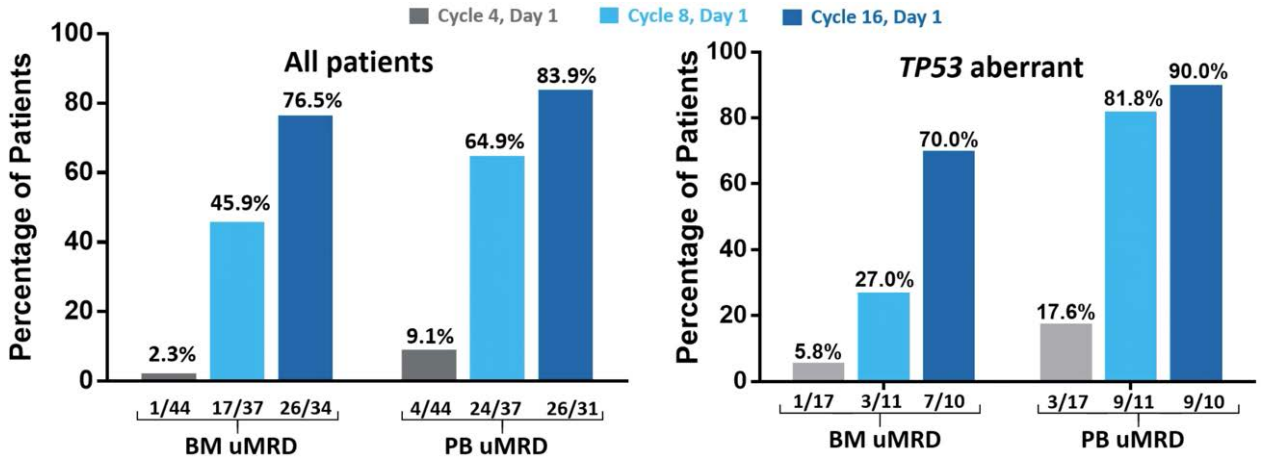
Courtesy of Matthew S Davids, MD, MMSc

A Phase 2 Study of Acalabrutinib, Venetoclax and Obinutuzumab (AVO) for 1L CLL: Efficacy and Summary

iwCLL Response



MRD by ITT



- 11 pts in BM-uMRD CR discontinued after 15 cycles, as per protocol
  - Median time off therapy: 4 months (range: 1-10)
- Median follow-up: 19 cycles (range, 6-26)
- No patients had progressed or had recurrent MRD to date

Summary

- AVO demonstrated efficacy and a favorable safety profile in patients with high-risk, TN CLL
- No TLS due to Ven was observed using a 4-week Ven ramp-up
- Accrual to a TP53-aberrant cohort is ongoing

Davids MS, et al. ASH 2020. Abstract 2216.

Courtesy of Matthew S Davids, MD, MMSc

Phase 3 ASCEND: Acalabrutinib Monotherapy Significantly Improves PFS in R/R CLL

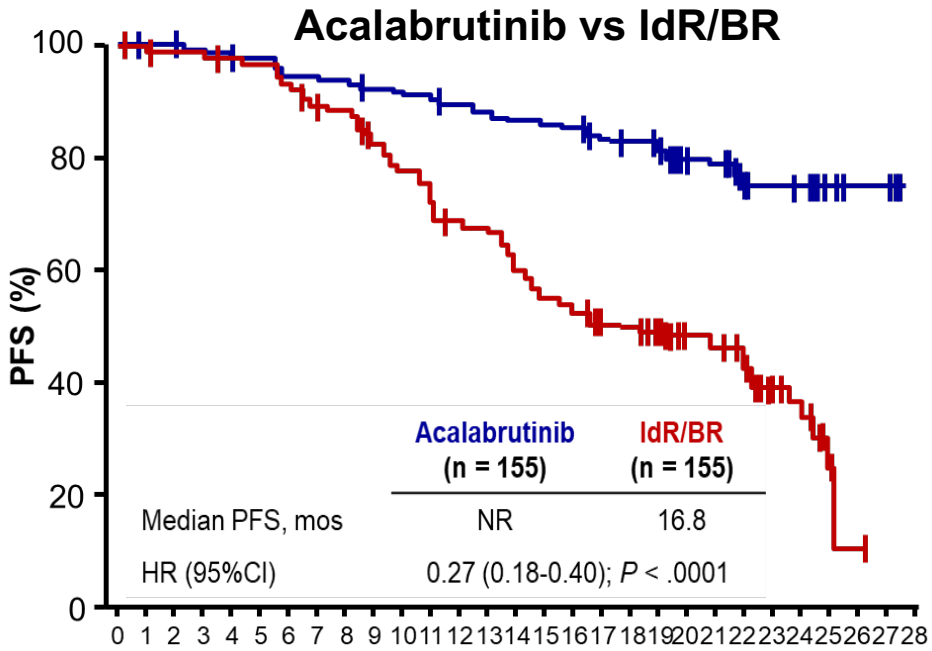
Adult patients with R/R CLL
N = 310

- ≥ 1 prior systemic therapies (no prior exposure to a BCL-2 inhibitor or BCR-signalling inhibitor)
- ECOG PS 0-2
- **Stratified by** Del(17p), ECOG PS 0-1 vs 2, 1-3 vs ≥ 4 prior tx

Randomization

- **Idelalisib + Rituximab or Bendamustine + Rituximab**
- **Acalabrutinib**

Primary endpoint: IRC-assessed PFS



- Median follow-up of 22.0 months
- Estimated 18-month PFS was 82% for acalabrutinib vs 48% for investigator's choice
- Estimated 18-month OS was 88% for both treatment regimens
- ORR was 80% for acalabrutinib vs 84% for investigator's choice

Courtesy of Matthew S Davids, MD, MMSc

Ghia. EHA 2019. Abstr LB2606. NCT02970318. Ghia, et al. *J Clin Oncol*. 2020 May 27;JCO1903355. doi: 10.1200/JCO.19.03355; Ghia P et al. EHA 2020;Abstract S159

Conclusions

Impact on Patient Care and Treatment Algorithm

- Acalabrutinib is a well-tolerated BTKi with evolving long term efficacy data
- Safety profile of acala makes it a good option, especially for older patients
- Combining acala with obin can deepen response, ?improve PFS

Implications for Future Research

- Ongoing study is examining AVO vs AV vs CIT (CL-311 study)
- Future studies needed to compare AV-based therapy to VO

Courtesy of Matthew S Davids, MD, MMSc

MAIC: Acalabrutinib ± Obinutuzumab (G) Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

AEs With Statistically Significant Differences After Matching

Acalabrutinib vs Ibrutinib

AE rate, %	Acala ESS=79	Ibr n=136	Rate difference % (95% CI)	*P*-value
Grade 3/4 AEs				
Infections	12.4	24.0	−11.6 (−21.9,−1.0)	<0.05
Atrial fibrillation	0	4.0	−4.0 (−7.3 ,0.0)	<0.05
Grade 1-4 AEs				
Peripheral edema	7.5	21.0	−13.5 (−21.7,−5.0)	<0.001
Pyrexia	6.2	20.0	−13.8 (−21.6,−6.0)	<0.001
Hypertension	6.4	18.0	−11.6 (−19.9,−3.0)	<0.01
Major hemorrhage	1.8	7.0	−5.2 (−10.2,0.0)	<0.05

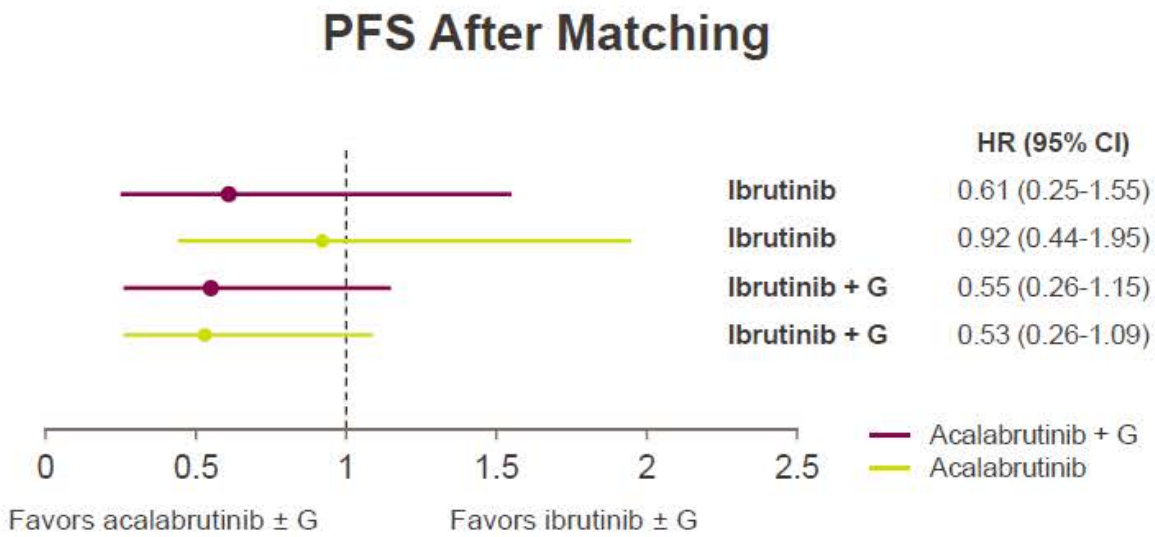
Acalabrutinib + G vs Ibrutinib + G

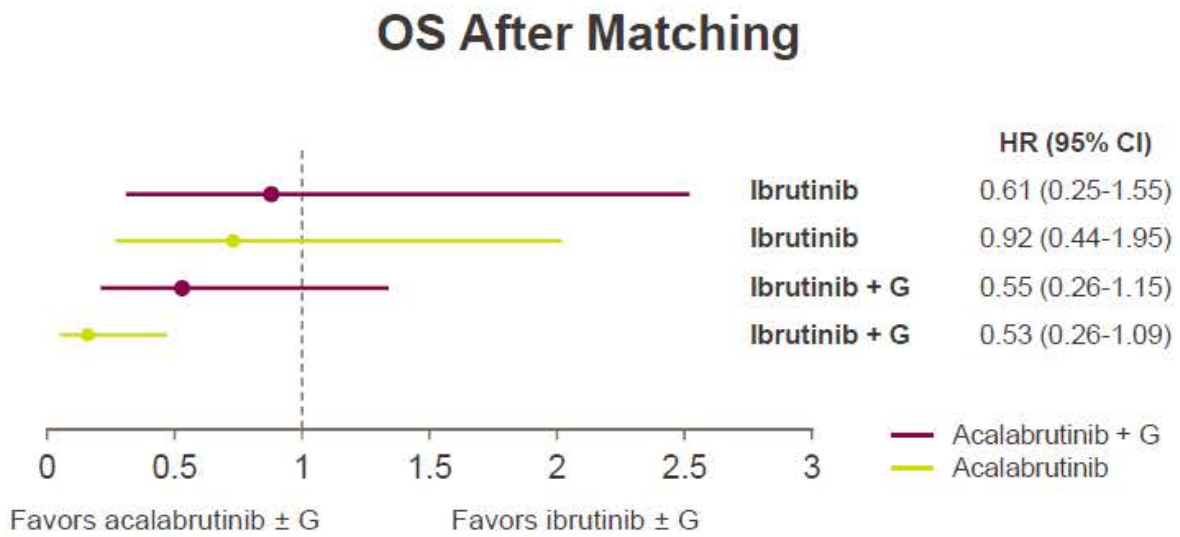
AE rate, %	Acala + G ESS=97	Ibr + G n=113	Rate difference % (95% CI)	*P*−value
Grade 3/4 AEs				
Peripheral edema	0.6	12.0	−11.4 (−17.5,−5.3)	<0.001
Febrile neutropenia	0.5	5.0	−4.5 (−8.6,−0.4)	<0.05
Grade 1-4 AEs				
Headache	32.1	8.0	+24.1 (+14.6,+33.6)	<0.001
Thrombocytopenia	20.7	36.0	−15.3 (−26.8,−3.9)	<0.01
Atrial fibrillation	3.4	12.0	−8.6 (−15.6,−1.7)	<0.05

Davids MS et al, EP724, Presented at 25th Annual congress of EHA. June 11-21, 2020

Courtesy of Matthew S Davids, MD, MMSc

MAIC: Acalabrutinib ± G Demonstrated a Trend Towards Improved PFS and OS vs Ibrutinib ± G in TN CLL





Acalabrutinib monotherapy significantly reduced risk of death compared with ibrutinib + G by 84% (*P*<0.001) after matching

Davids MS et al, EP724, Presented at 25th Annual congress of EHA. June 11-21, 2020

Courtesy of Matthew S Davids, MD, MMSc

Conclusions

Impact on Patient Care and Treatment Algorithm

- The MAIC found that acalabrutinib (with or without obin) had lower rates of several AEs than ibrutinib (with or without obin) in treatment-naïve patients with CLL, without compromising efficacy
- Although not definitive, this study provides some initial insights into differences between these drugs

Implications for Future Research

- ELEVATE R/R will help define the differences between acala and ibrutinib

Courtesy of Matthew S Davids, MD, MMSc

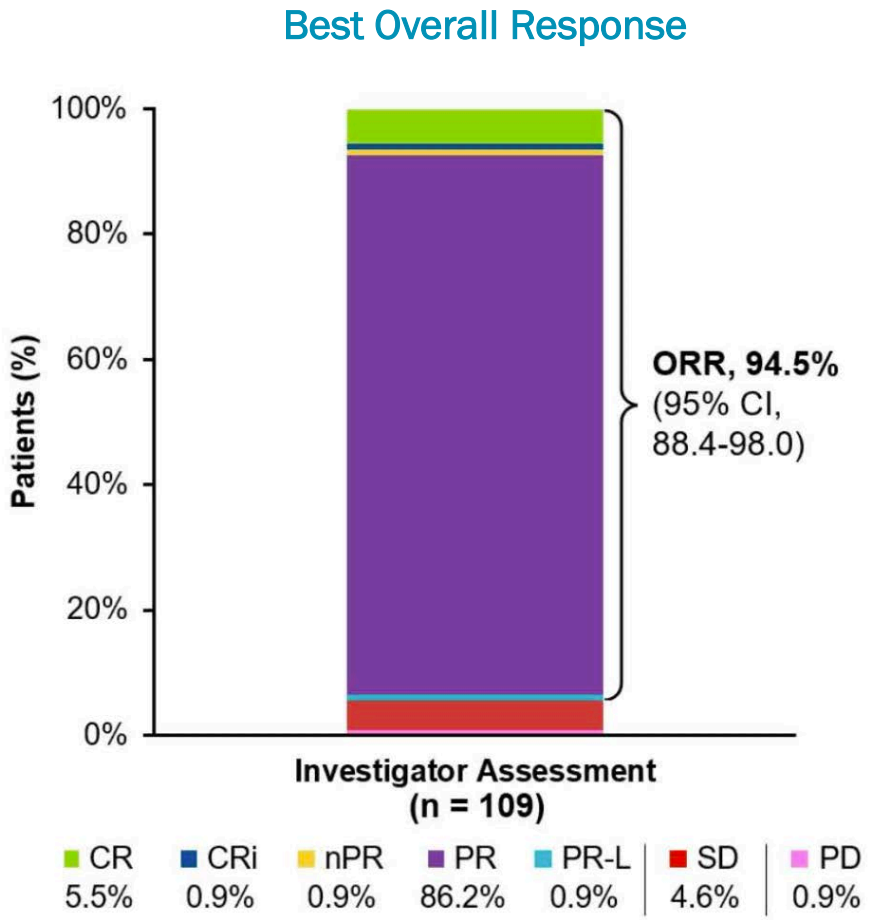
Zanubrutinib (BGB-3111): High BTK Selectivity

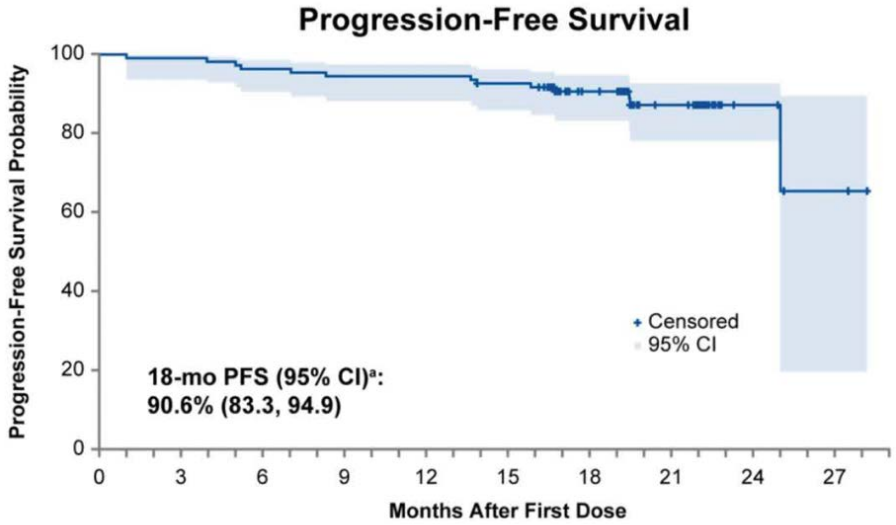
Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

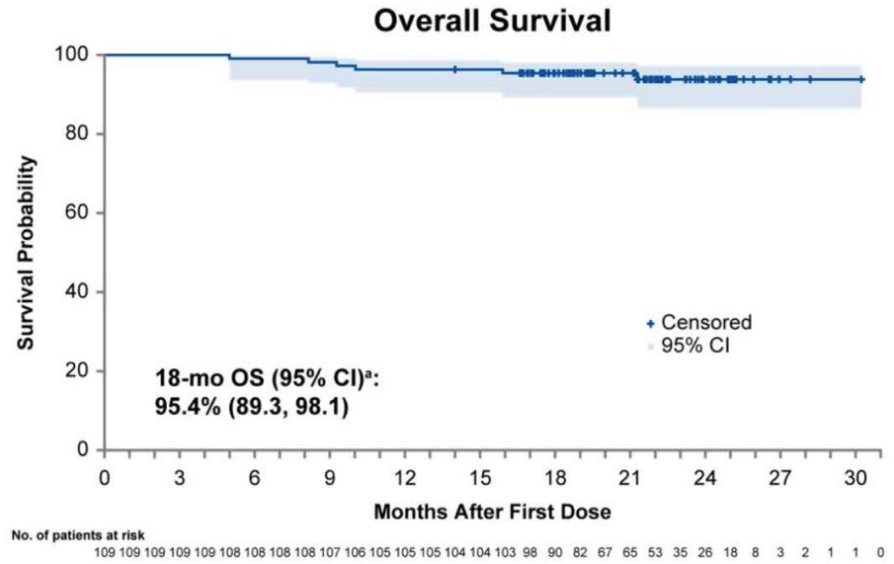
Brown JR, et al. ASH 2020. Abstract 1306.

Courtesy of Matthew S Davids, MD, MMSc

Results From Arm C of the Phase 3 SEQUOIA Trial of Zanubrutinib for Patients With TN del(17p) CLL/SLL: Efficacy







[a]Data cutoff for 2019 ASH presentation: August 7, 2019.
Brown JR, et al. ASH 2020. Abstract 1306.

Courtesy of Matthew S Davids, MD, MMSc

Median follow-up: 21.9 months (range, 5.0-30.2)

Conclusions

Impact on Patient Care and Treatment Algorithm

- Zanubrutinib is efficacious in patients with high risk TN CLL
- The toxicity profile looks more similar to acala than to ibrutinib
- Possible advantages of zanubrutinib include potential for daily dosing and no drug-drug interaction with PPIs

Implications for Future Research

- Awaiting registrational arm of the SEQUOIA study for zanubrutinib approval in CLL
- Other promising combinations with zanu under evaluation (e.g. BOVen)

Courtesy of Matthew S Davids, MD, MMSc

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Assessment of the Efficacy of Therapies Following Venetoclax Discontinuation in CLL Reveals BTK Inhibition as an Effective Strategy

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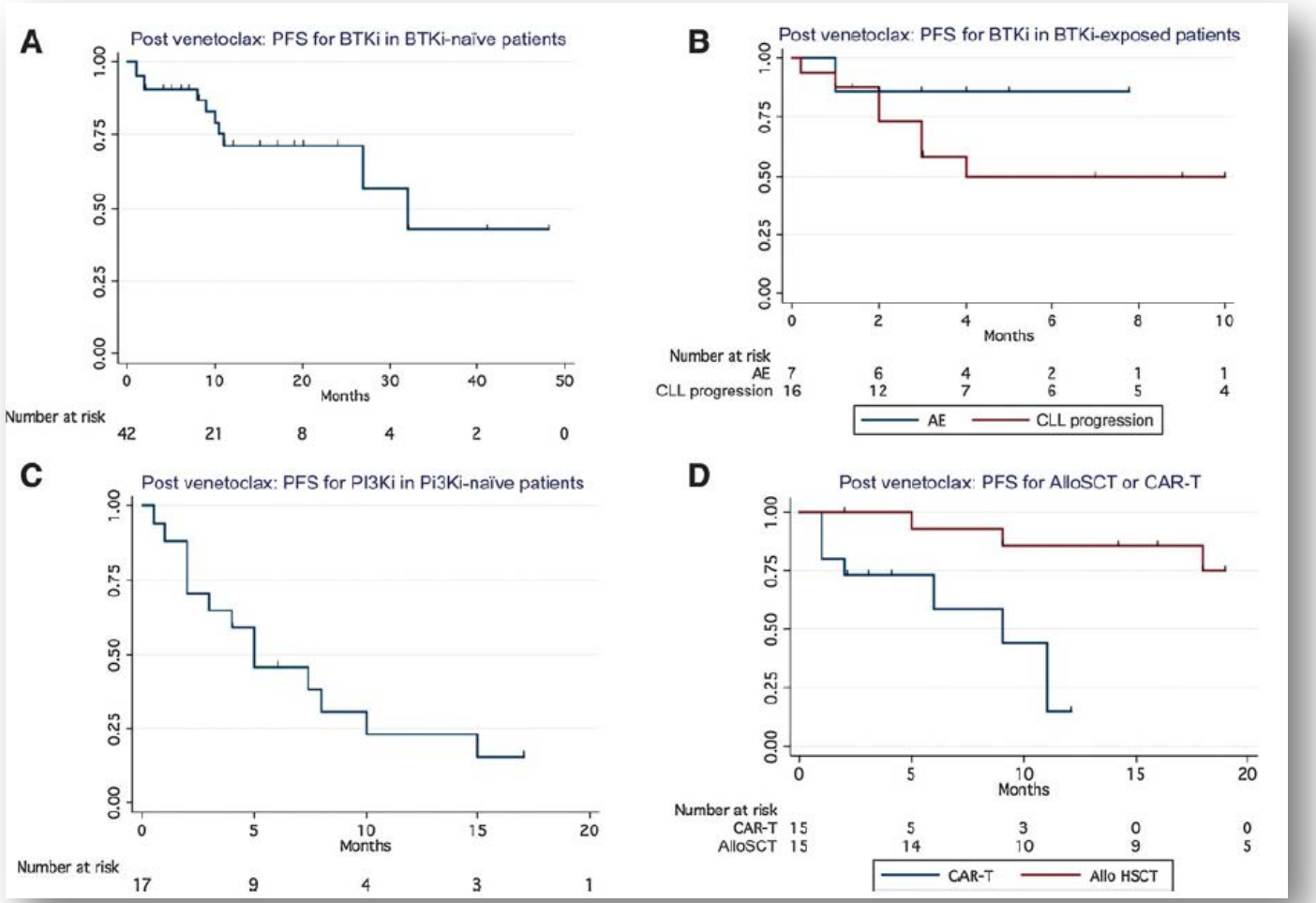


Overall response rates to BTKi:

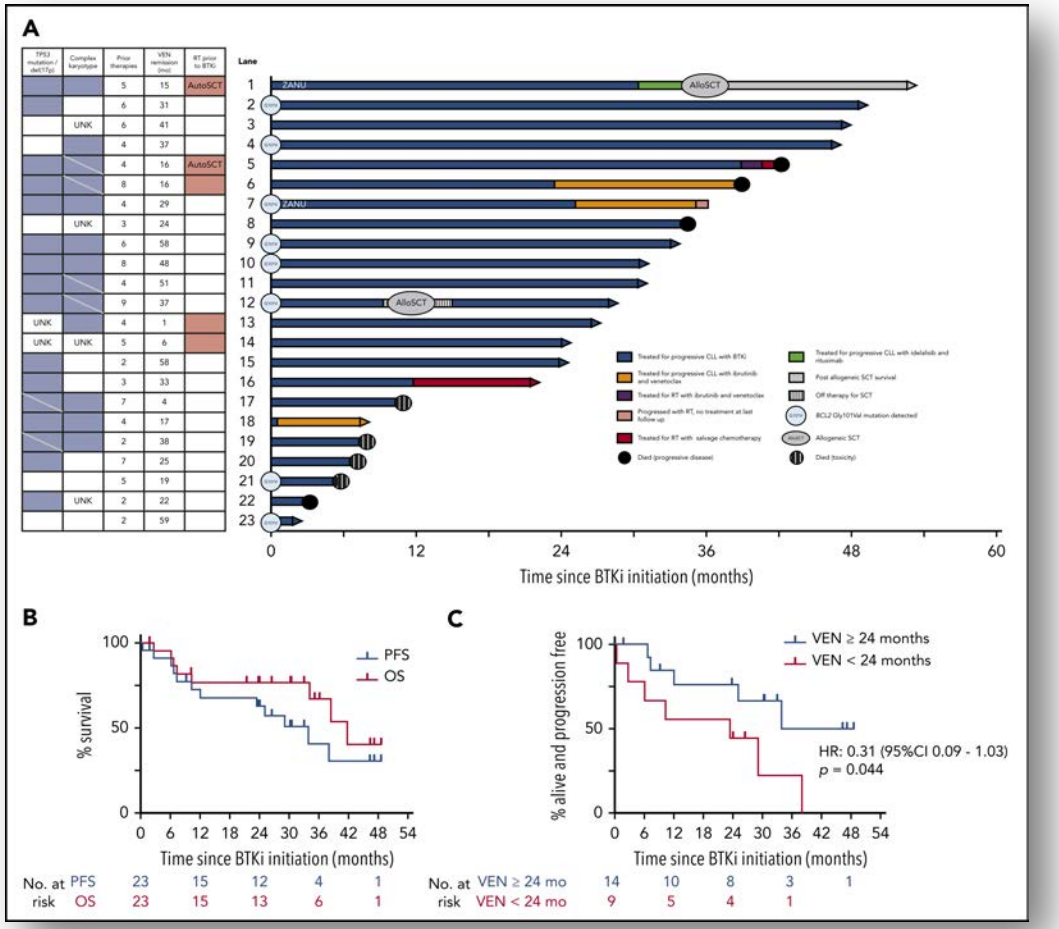
- **BTKi naïve (n=44): 84%**
- **BTKi exposed (n=30): 53%**
- **PI3Ki (n=17): 47%**
- **CAR-T (n=18): 67%**

Mato et al., *Clin Cancer Res*, 2020

Courtesy of Matthew S Davids, MD, MMSc

BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax

ORR: 91%, CR: 18%



Lin VS et al., *Blood,* 2020

LYMPHOID NEOPLASIA

Comment on Lin et al, page 2266

Inverting the BTK-BCL2 order

Jennifer R. Brown | Dana-Farber Cancer Institute

In this issue of *Blood*, Lin et al report the first long-term follow-up data showing that Bruton tyrosine kinase inhibitors (BTKi's) are effective in chronic lymphocytic leukemia (CLL) after previous progression on venetoclax.[1]

Courtesy of Matthew S Davids, MD, MMSc

Conclusions

Impact on Patient Care and Treatment Algorithm

- Several retrospective datasets have emerged suggesting that BTKis are active post-venetoclax
- For patients with prior BTKi progression, re-treatment with a BTKi is unlikely to be helpful
- PI3Kis are an option for patients who progress on both BTKi and BCL-2i, but initial data suggest responses are unlikely to be durable

Implications for Future Research

- Awaiting prospective data on this sequence (MURANO will provide some)
- Sequencing questions are important but it is challenging to incorporate the next line of therapy into a clinical trial
- Prospective registry-based studies are one way to capture this information

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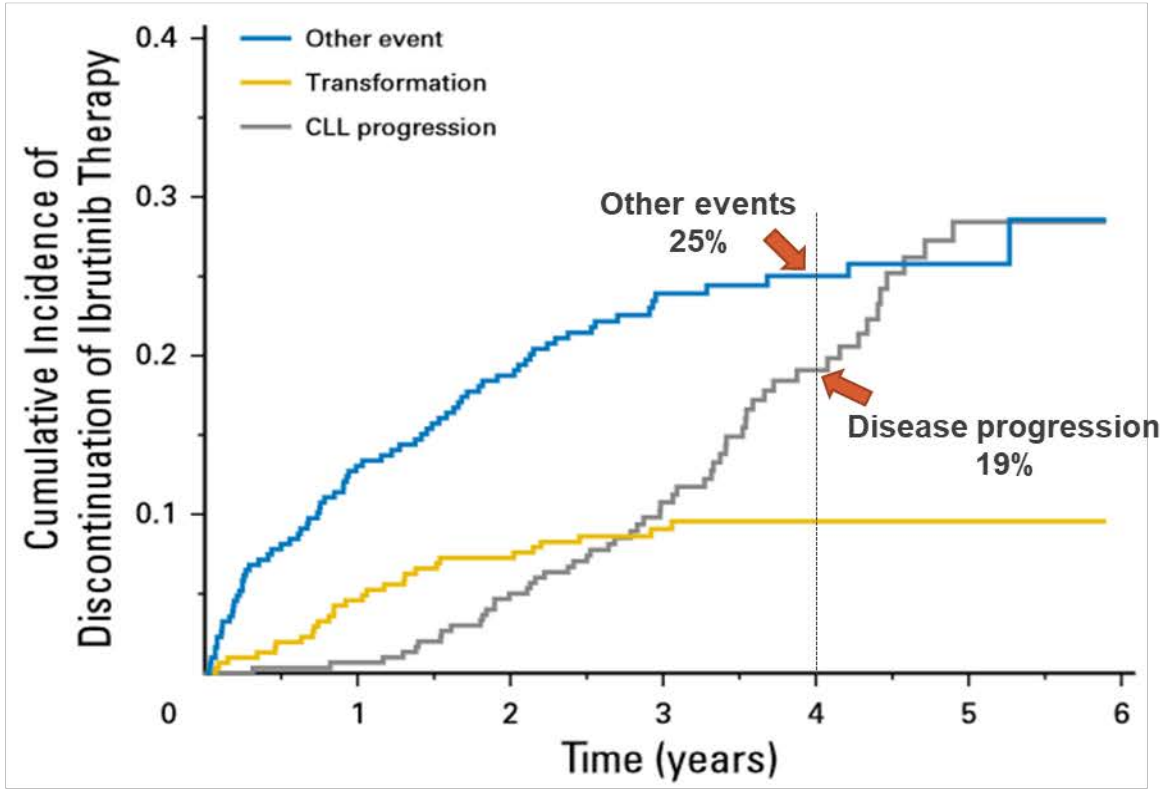
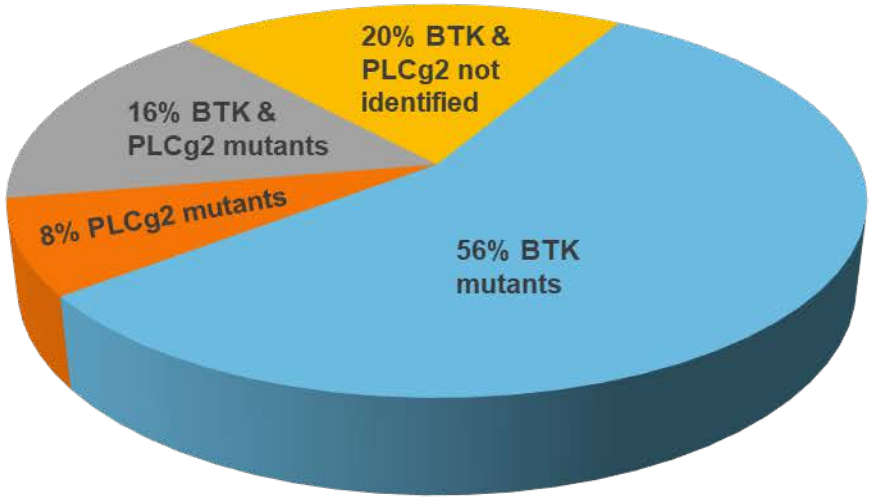
Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 sequential studies[1]



Ibrutinib acquired resistance in patients with progressive CLL[2]



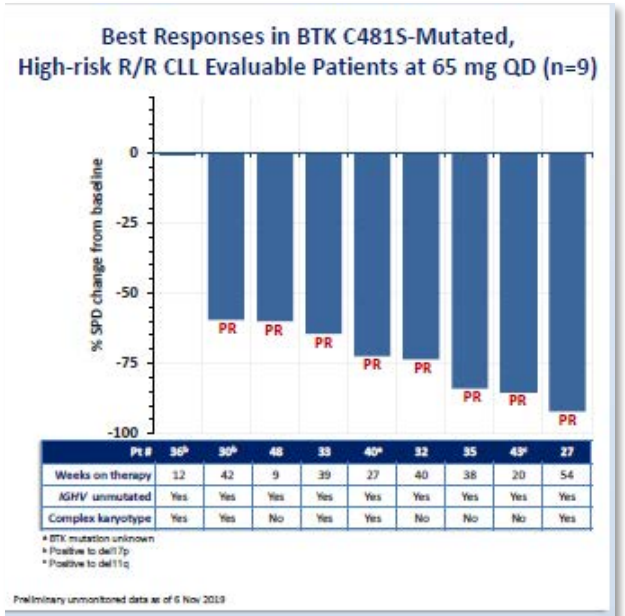
- Front line: Ibrutinib discontinuation rate at 5 years = 41%[1]
- Relapsed/refractory: Predicted ibrutinib discontinuation rate at 5 years = 53.7% (4 sequential studies) [7]
- The appearance of BTK C481 mutations is the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

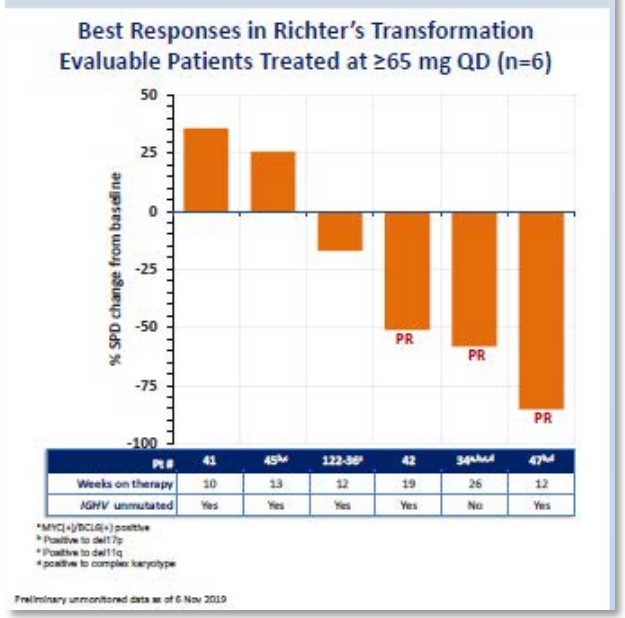
References: 1. Woyach et al. *J Clin Oncol*. 2017; 35:1437–43. 2. Lampson et al. *Expert Rev Hematol*. 2018 Mar;11(3):185-94. 3. Woyach et al. *N Engl J Med*. 2014; 370:2286–94. 4. Byrd et al. *N Engl J Med*. 2016; 374:323–32. 5. Xu et al. *Blood*. 2017; 129:2519–25. 6. Hershkovitz-Rokah et al. *Br J Haematol*. 2018; 181:306–19. 7. Burger. *Leukemia*. 2019;[Epub]. 8. Woyach et al. ASH2019.

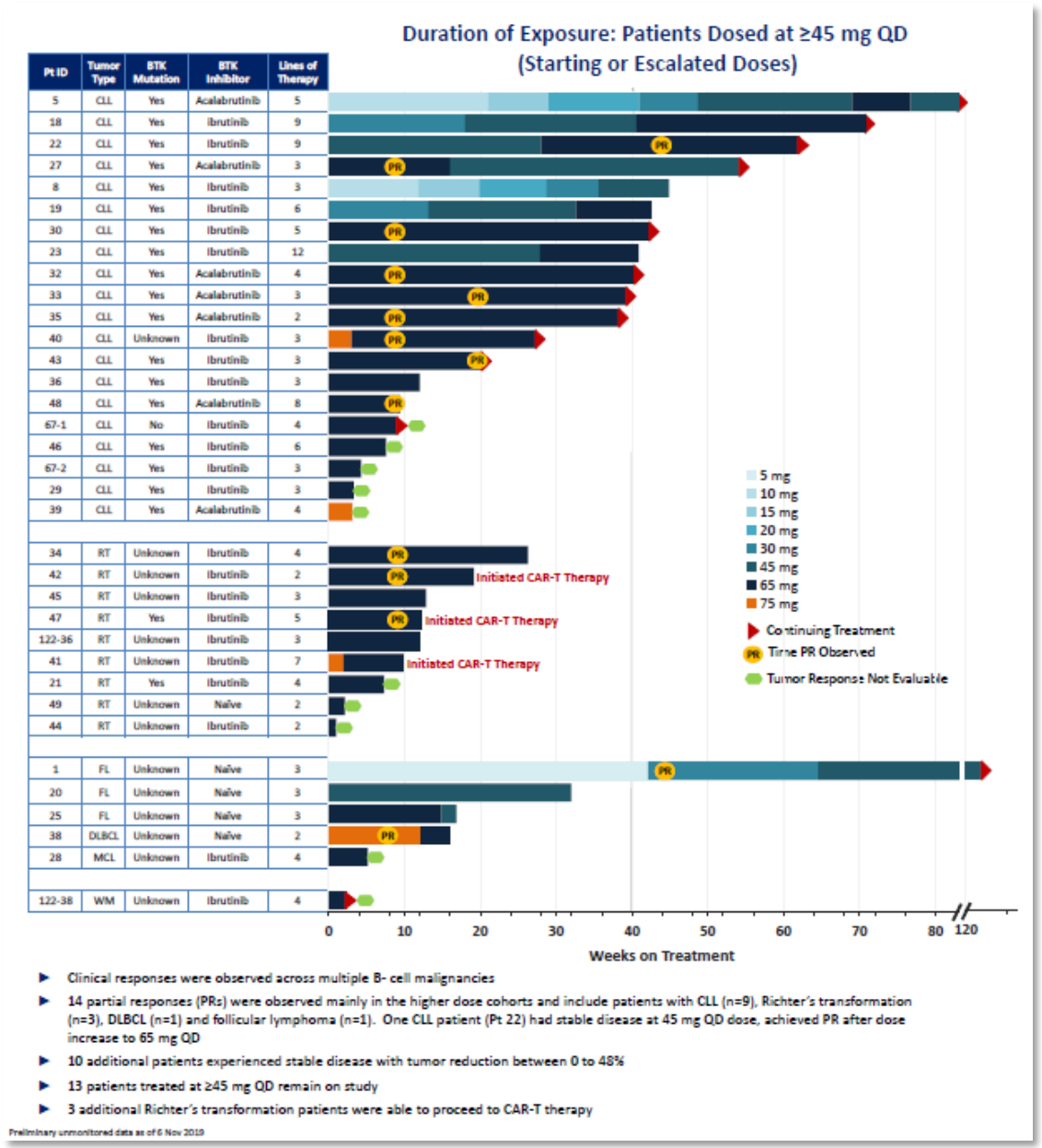
Courtesy of Matthew S Davids, MD, MMSc

(Courtesy of A. Mato)

ARQ-531 (MK-1026) is active in high risk CLL patients including C481S *BTK* mut







Woyach et al., ASH, 2019

Courtesy of Matthew S Davids, MD, MMSc

Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Safety

Adverse Events, at All Doses and Patients (N=323), n (%)		Treatment-Emergent AEs, (≥10%)[a]				Treatment-Related AEs	
		Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 3/4
Fatigue		65 (20)	40 (12)	22 (7)	3 (1)	27 (8)	2 (<1)
Diarrhea		55 (17)	45 (14)	10 (3)	-	28 (9)	-
Contusion		42 (13)	37 (12)	5 (2)	-	29 (9)	-
AEs of special interest, [b,c]	Bruising	53 (16)	48 (15)	5 (2)	-	37 (12)	-
	Rash	35 (11)	30 (9)	5 (2)	-	18 (6)	-
	Arthralgia	16 (5)	13 (4)	3 (1)	-	5 (2)	-
	Hemorrhage	15 (5)	10 (3)	4 (1)	1 (<1)[d]	5 (2)	-
	Hypertension	15 (5)	2 (<1)	9 (3)	4 (1)	4 (1)	-
	AFib/Flutter	2 (<1)	-	2 (<1)[e]	-	-	-

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

Data cutoff date of 27 September 2020.[a]TheAEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. [b]AEs of special interest are those that were previously associated with covalent BTKi. [c]Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular. [d]Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. [e]Both events considered by investigators as unrelated to LOXO-305 due to a history of prior atrial fibrillation in each.

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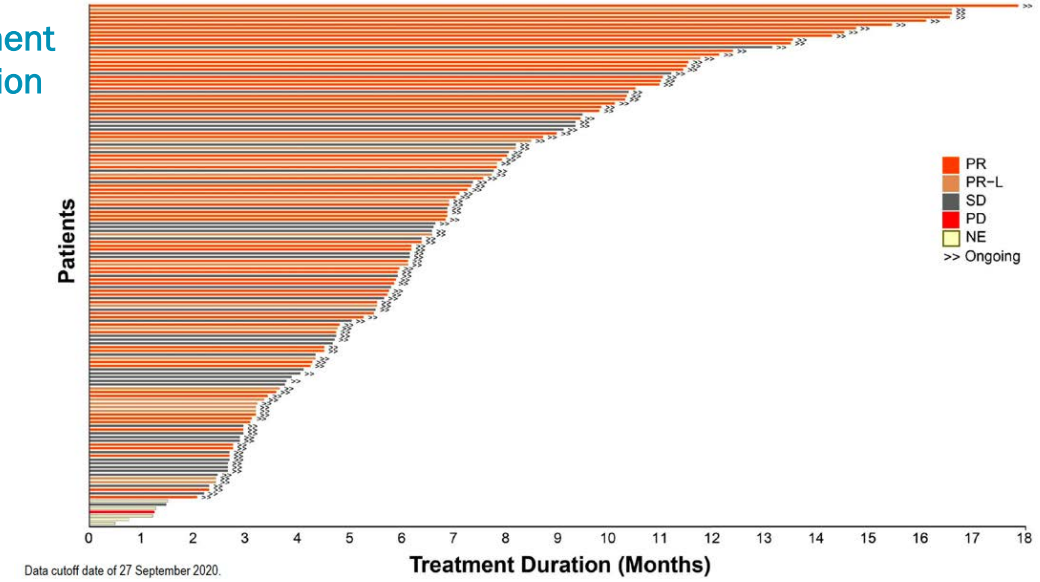
Phase 1/2 BRUIN Study of LOXO-305 in Patients With R/R CLL/SLL: Efficacy

Response Rates		All Patients[a] (N=139)	BTK Pre-Treated Patients[a] (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)

- ORR increased over time: PR/PR-L 63% to 86% from start of treatment to ≥10 months follow-up
- Median follow-up: 6 months (0.6-17.8+) for efficacy-evaluable[a] pts
- 83 (94%) of responding patients with CLL/SLL are ongoing/in response
  - 5 responders discontinued: 4 for PD, 1 in PR electively underwent transplantation

Treatment Duration



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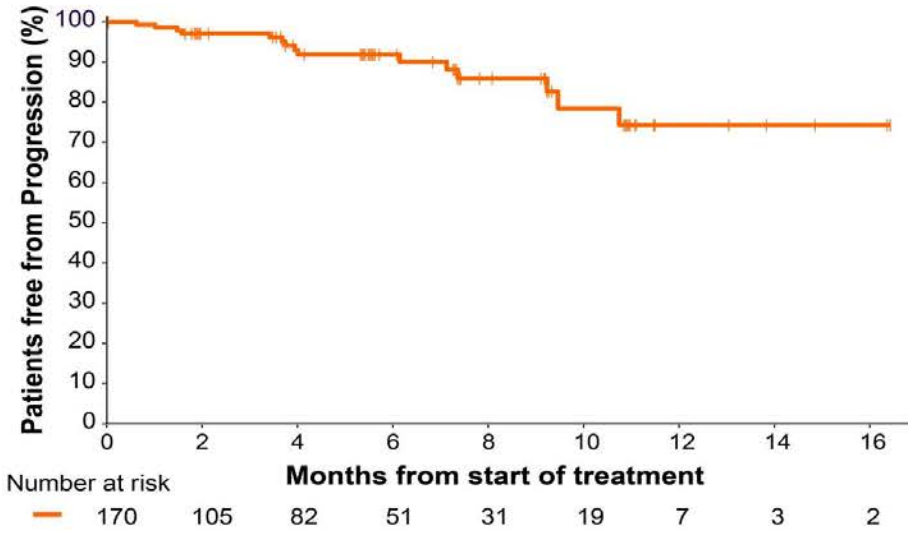

[a]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment.

Mato AR, et al. ASH 2020. Abstract 542.

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Conclusions

Impact on Patient Care and Treatment Algorithm

- Reversible, non-covalent BTKi appear to be active in both *BTK* wildtype and mutant patients
- Though early, the toxicity profile of these new drugs also appears to be favorable
- Once approved, these drugs will initially have a role in BTKi progressors

Implications for Future Research

- Studies are in development to compare the new BTKis to R/R SOC
- Frontline study of new BTKis vs. ibrutinib will also likely be pursued
- These drugs have the potential for broader use if these studies are positive

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