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Spectrum, Frequency, Severity and Management of Toxicities Associated with Novel Agents and Regimens

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Four buckets of agents (for now)

BTKi

- Ibrutinib
- Acalabrutinib
- Zanubrutinib*
- (Pirtobrutinib*)

BCL2i

- venetoclax

PI3Ki

- Idelalisib
- Duvelisib
- Umbralisib*

Anti-CD20

- Rituximab
- Obinutuzumab

Key factors impacting treatment selection:
--age
--comorbidities
--*TP53* status (mutation or del(17p))
--IGHV mutation status
--TN vs. RR setting (and prior treatment)
--?other

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*not approved for CLL/SLL

Combinations are seemingly endless!

BTKi	BCL2i	PI3Ki	Anti-CD20
▪ Ibrutinib	▪ venetoclax	▪ Idelalisib	▪ Rituximab
▪ Acalabrutinib		▪ Duvelisib	▪ Obinutuzumab
▪ Zanubrutinib*		▪ Umbralisib*	
▪ (Pirtobrutinib*)			

Ibrutinib/rituximab
Ibrutinib/obinutuzumab
Ibrutinib/venetoclax
Acalabrutinib/obinutuzumab

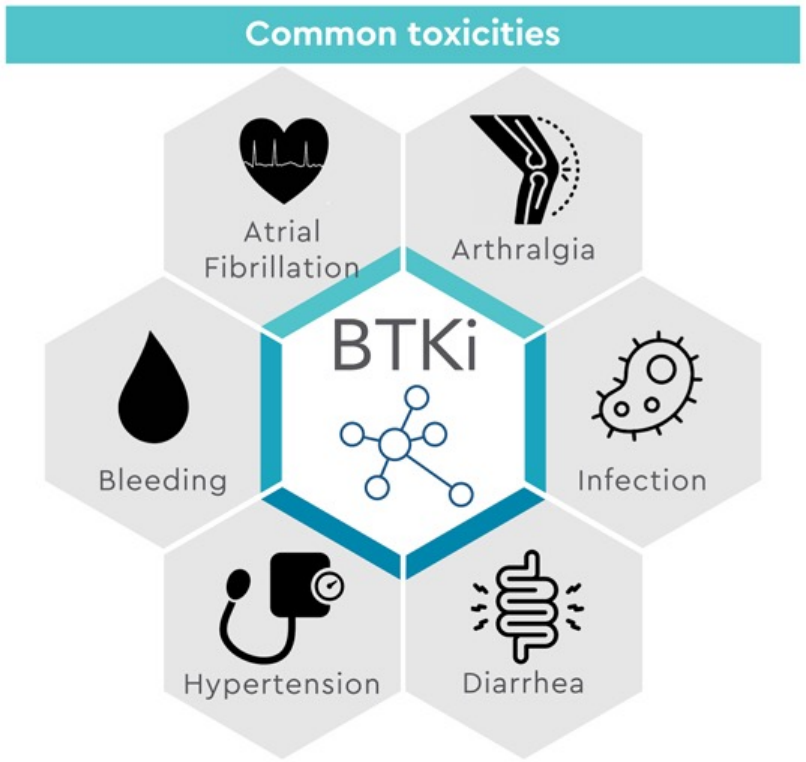
Venetoclax/obinutuzumab
Idelalisib/rituximab
Umbralisib/ublituximab
Zanubrutinib/obinutuzumab

And the triplets are coming:

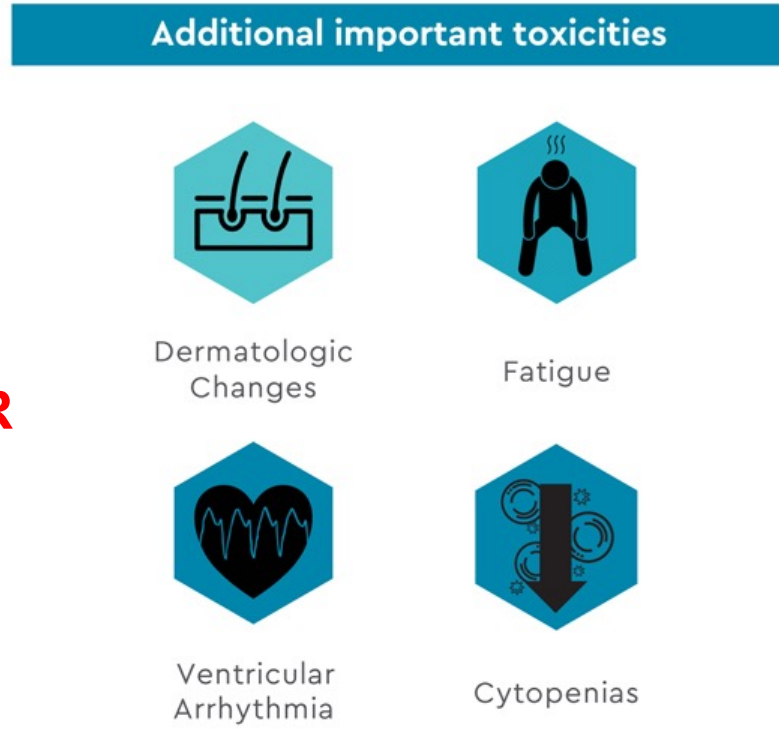
Alliance A041702: RP3 of IO vs. IVO in untreated older patients (≥ 70 Years)

BOVen (NCT03824483) Ph I/II trial of zanubrutinib/Obinutuzumab/venetoclax

Common BTKi adverse effects are likely related to spectrum of off-target kinase inhibition



TEC
ITK
EGFR
CSK



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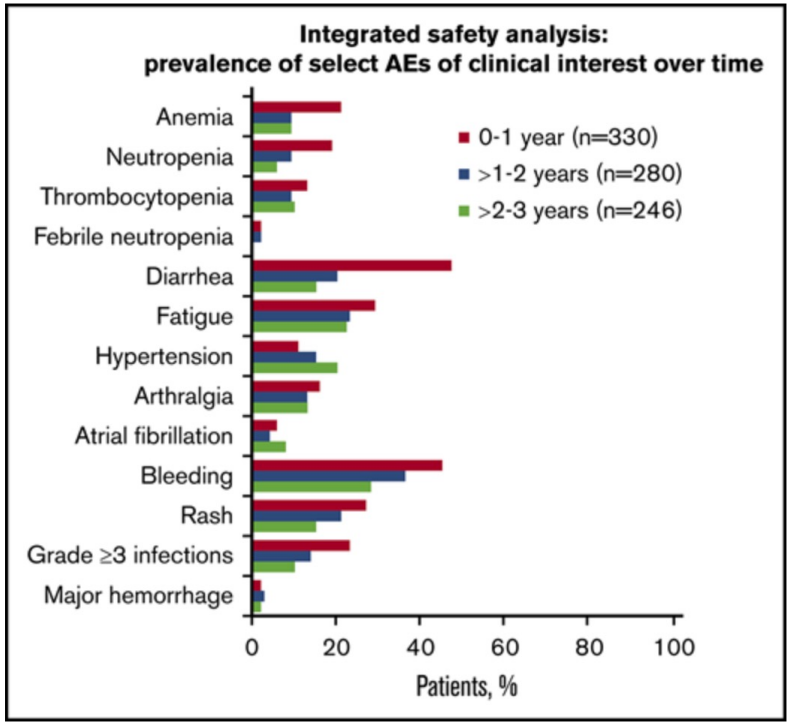
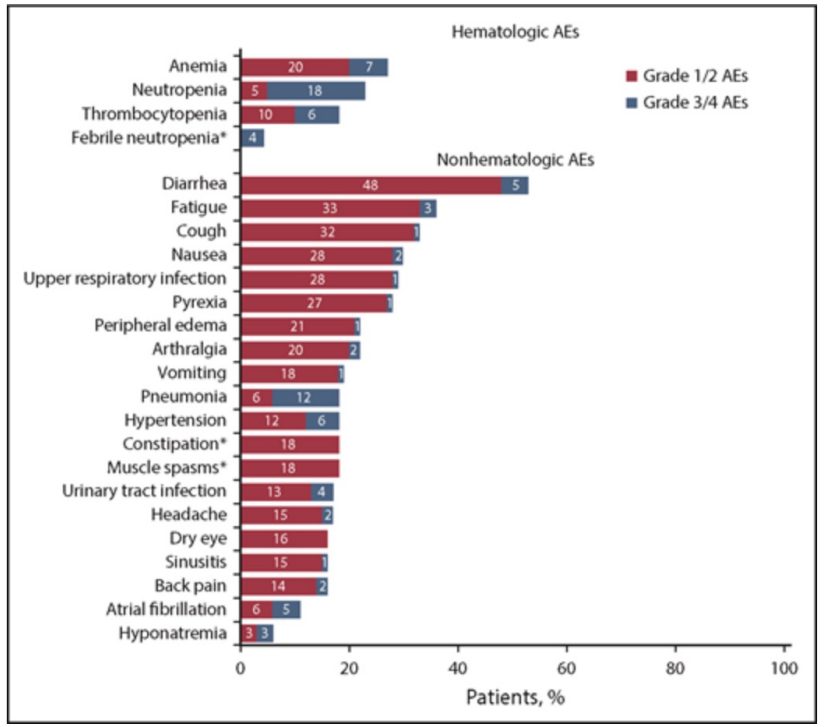
Andrew Lipsky,Nicole Lamanna, Managing toxicities of Bruton tyrosine kinase inhibitors, Hematology Am Soc Hematol Educ Program, 2020; Xiao Circulation. 2020 Dec 22;142(25):2443-2455

What do discontinuation rates tell us?

IBRUTINIB	Discontinuation due to AEs
RESONATE	16%
Pooled analysis of prospective trials	12% (decreases annually)
RWE ibrutinib	42%





RWE = Real World Experience

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Munir Am J Hematol 2019 Dec;94(12):1353-1363; Coutre Blood Adv 2019 Jun 25;3(12):1799-1807;
Mato Haematologica 2018 May;103(5):874-879

Pooled analysis of acalabrutinib toxicity

	All patients ($N = 1040$)					
AE preferred term, *n* (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Headache	393 (37.8)	286 (27.5)	96 (9.2)	11 (1.1)	0	0
Diarrhea	382 (36.7)	247 (23.8)	108 (10.4)	27 (2.6)	0	0
URTI	229 (22.0)	56 (5.4)	165 (15.9)	8 (0.8)	0	0
Contusion	226 (21.7)	202 (19.4)	24 (2.3)	0	0	0
Nausea	226 (21.7)	162 (15.6)	52 (5.0)	12 (1.2)	0	0
Fatigue	222 (21.3)	133 (12.8)	70 (6.7)	18 (1.7)	0	0
Cough	218 (21.0)	152 (14.6)	65 (6.3)	1 (0.1)	0	0
Arthralgia	199 (19.1)	127 (12.2)	65 (6.3)	7 (0.7)	0	0
Constipation	151 (14.5)	127 (12.2)	23 (2.2)	1 (0.1)	0	0
Pyrexia	149 (14.3)	102 (9.8)	37 (3.6)	10 (1.0)	0	0
Dizziness	139 (13.4)	124 (11.9)	13 (1.3)	2 (0.2)	0	0
Anemia	138 (13.3)	18 (1.7)	39 (3.8)	75 (7.2)	6 (0.6)	0
Vomiting	138 (13.3)	96 (9.2)	33 (3.2)	9 (0.9)	0	0
Neutropenia	128 (12.3)	2 (0.2)	10 (1.0)	49 (4.7)	67 (6.4)	0
Rash	126 (12.1)	94 (9.0)	28 (2.7)	4 (0.4)	0	0
Back pain	123 (11.8)	69 (6.6)	46 (4.4)	8 (0.8)	0	0
Myalgia	113 (10.9)	88 (8.5)	23 (2.2)	2 (0.2)	0	0
Dyspnea	111 (10.7)	65 (6.3)	28 (2.7)	13 (1.3)	5 (0.5)	0
Edema peripheral	111 (10.7)	87 (8.4)	20 (1.9)	4 (0.4)	0	0
Petechiae	111 (10.7)	104 (10.0)	7 (0.7)	0	0	0
Sinusitis	111 (10.7)	19 (1.8)	89 (8.6)	3 (0.3)	0	0

Table 5 Grade ≥3 AEs reported in ≥2% of patients.

	All patients ($N = 1040$)			
AE preferred term, *n* (%)	All grade ≥3	Grade 3	Grade 4	Grade 5
Neutropenia	116 (11.2)	49 (4.7)	67 (6.4)	0
Anemia	81 (7.8)	75 (7.2)	6 (0.6)	0
Pneumonia	53 (5.1)	40 (3.8)	5 (0.5)	8 (0.8)
Thrombocytopenia	37 (3.6)	14 (1.3)	23 (2.2)	0
Hypertension	33 (3.2)	33 (3.2)	0	0
Diarrhea	27 (2.6)	27 (2.6)	0	0
Syncope	21 (2.0)	20 (1.9)	1 (0.1)	0

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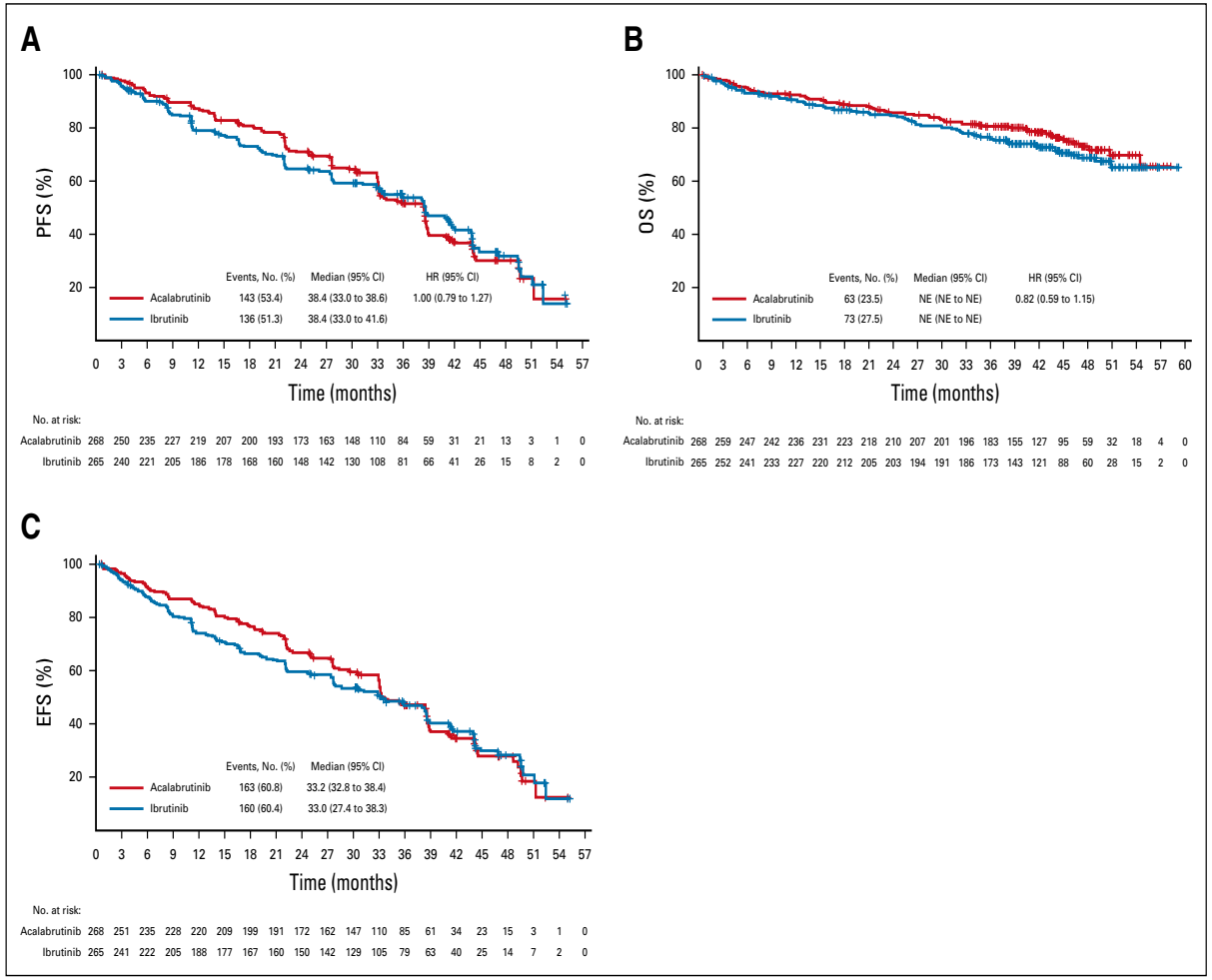
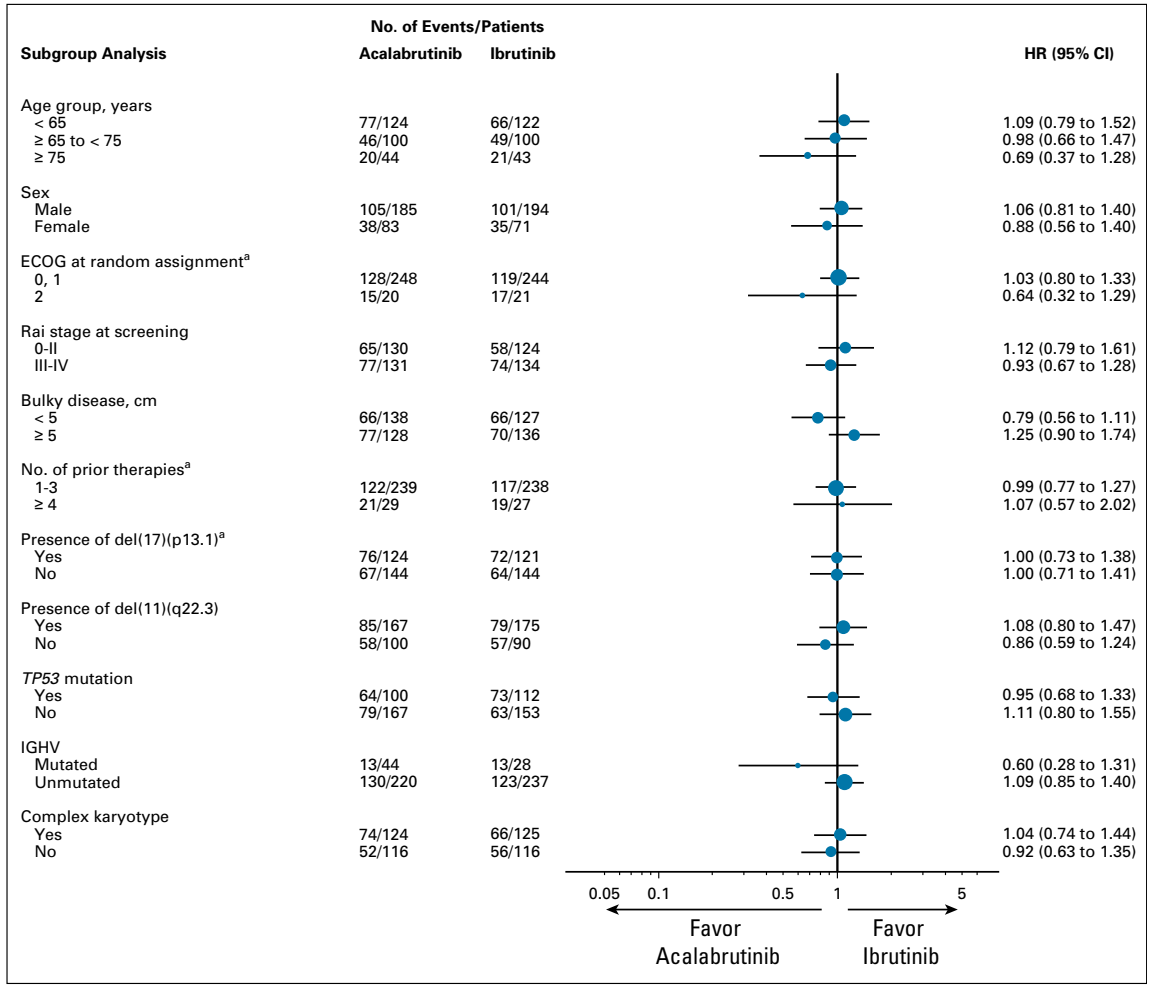
Furman Leukemia 2021 Apr 27.
doi: 10.1038/s41375-021-01252-y

Acalabrutinib vs. Ibrutinib: no difference in efficacy





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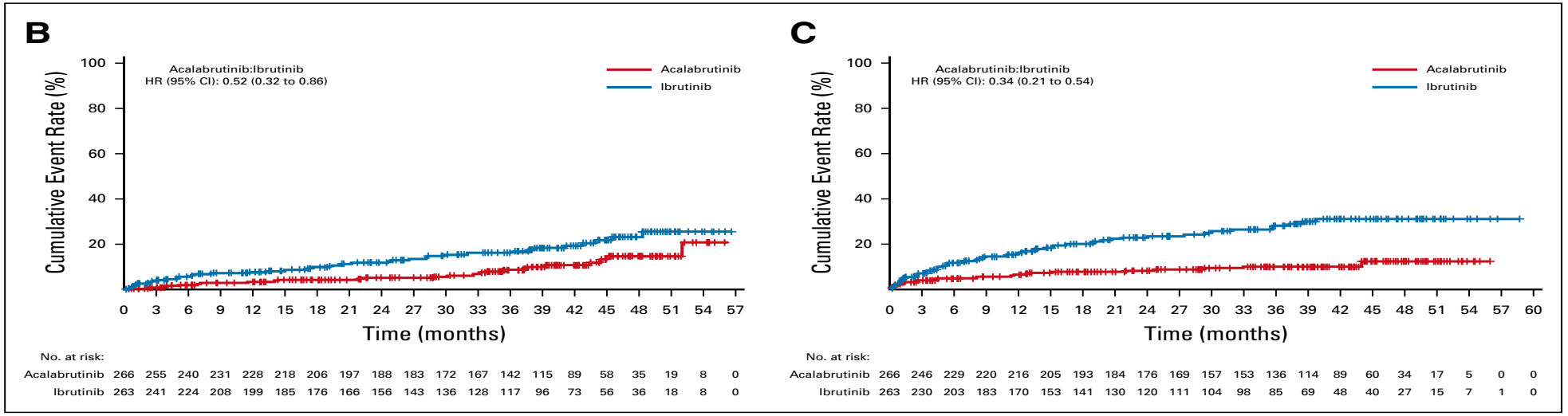
Byrd J Clin Oncol 2021 Jul 26;JCO2101210

Acalabrutinib vs. Ibrutinib: rates of Atrial fib and HTN



	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Events	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension events[a]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of hypertension	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)
Atrial fibrillation or flutter incidence in patient subgroups				
Age 75 years or older	8 of 44 (18.2)	6 of 44 (13.6)	11 of 42 (26.2)	4 of 42 (9.5)
Without previous history of atrial fibrillation or flutter	15 of 243 (6.2)	7 of 243 (2.9)	37 of 249 (14.9)	8 of 249 (3.2)
Without risk factors[d]	2 of 99 (2.0)	1 of 99 (1.0)	10 of 99 (10.1)	2 of 99 (2.0)
Time to atrial fibrillation onset, median (range), months	28.8 (0.4-52.0)	22.3 (0.4-45.1)	16.0 (0.5-48.3)	4.8 (0.5-28.2)

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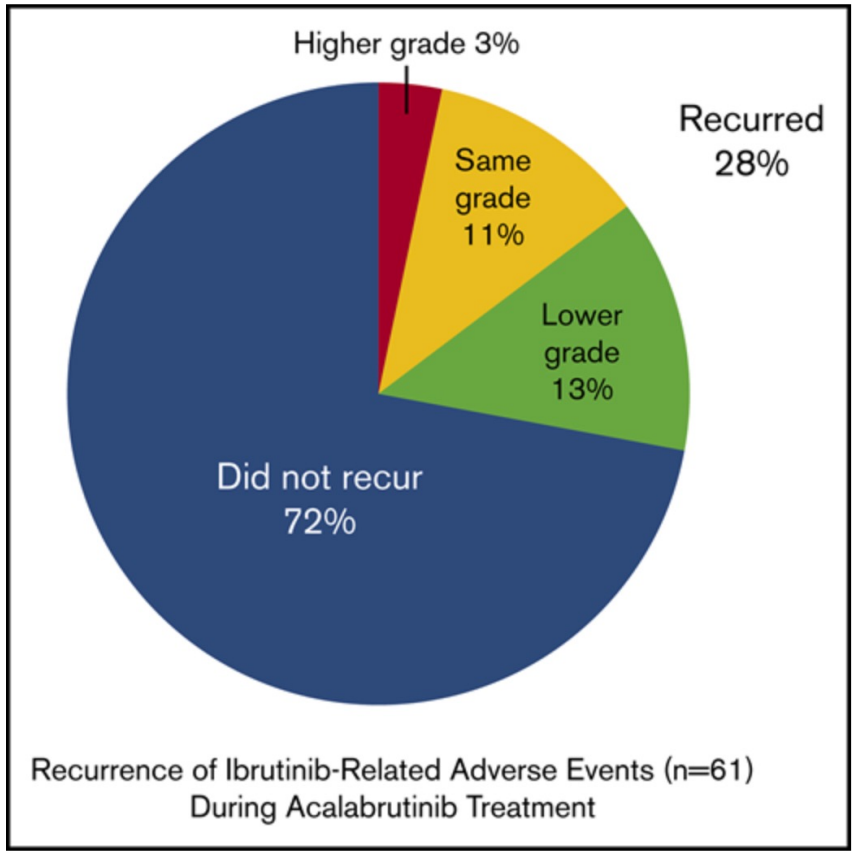
Byrd J Clin Oncol 2021 Jul 26;JCO2101210

What to do for my patient on longstanding ibrutinib needing discontinuation for AEs?

- ***Does the patient need ongoing treatment?***

- Change to alternative irreversible BTKi
  - Acalabrutinib
  - Zanubrutinib? (not approved)

- Change to reversible BTKi
  - Pirtobrutinib? (not approved)



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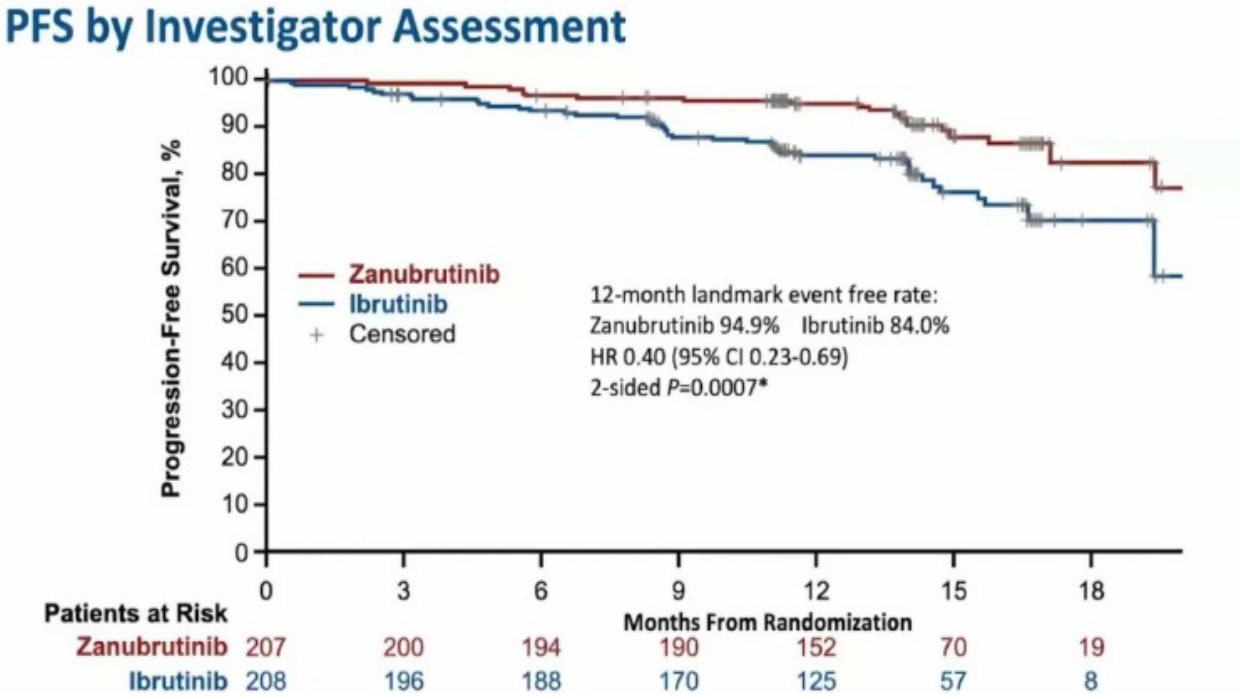
Awan Blood Adv 2019 May 14;3(9):1553-1562; Rogers Haematologica. 2021 Mar 18. doi: 10.3324/haematol.2020.272500

Zanubrutinib:

- Currently approved for RR MCL
- Listed in NCCN as option for ibrutinib intolerance
- Favorable safety profile:
  - Most AEs were of grade 1 or 2 severity
  - Grade 3/4 AEs were uncommon (neutropenia, anemia, pneumonia, disseminated zoster)
  - 1 pt with atrial fibrillation
  - 1 pt with major hemorrhage

First Interim Analysis of the Phase III ALPINE Study of Zanubrutinib versus Ibrutinib In Patients with Relapsed or Refractory CLL/SLL – Results reported at EHA 2021 (Hillmen P et al. EHA 2021;Abstract LB1900)

ALPINE



Comparative trials in Waldenstroms reported!

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Tam Blood 2019 Sep 12;134(11):851-859

Management of AEs of Interest: AFib, bleeding risk

Adverse event	Management recommendations
Atrial fibrillation	• Obtain a baseline clinical risk assessment of cardiovascular risk factors before initiating therapy. • New AF: Interdisciplinary risk–benefit assessment. CHA2DS2-VASc 0-1, most clinicians favor continuing BTKi therapy; ≥2, consider temporary drug hold until AF control or discontinuation. • Consider beta-blockade, often preferred as the first choice over CYP3A4 inhibitors (eg, verapamil and diltiazem) or P-glycoprotein substrates (amiodarone), which interact with BTKis. • Anticoagulation strategies include either low-dose apixaban (2.5 mg twice daily given CYP3A4 interaction) or enoxaparin (at regular doses in patients with a platelet count >50,000/μL). Where possible, avoid combination with vitamin K antagonists.
Bleeding risk	• Commonly encountered bruising seen with BTKis does not confer an increased risk of major hemorrhage and does not necessitate cessation of therapy. • When possible, send patients for necessary procedures before starting therapy. • Hold BTKis for either 3 days (minor procedure) or 7 days (major procedure) both before and after invasive procedures because of increased periprocedural bleeding risk. • For minor bleeding, holding BTKi results in the resolution of bleeding tendency in 2-3 days. For severe bleeds, transfuse platelets as appropriate to overcome clinical bleeding, regardless of platelet count. • Encourage patients with bleeding to abstain from over-the-counter supplements that may exacerbate bleeding risk, such as vitamin E or fish oil. • Consider treatment options other than BTKi when dual antiplatelet therapy is indicated.

KEY POINTS:

--use CHA2DS2-VASc score to determine drug hold until AF control vs. discontinuation

--**avoid** vitamin K antagonists for anticoagulation

--avoid BTKi when dual antiplatelet therapy is needed

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Lipsky and Lamanna Hematology Am Soc Hematol Educ Program (2020) 2020 (1): 336–345

Management of AEs of special interest: HTN, diarrhea, headache

Hypertension	• Optimize pharmacotherapy for control of baseline hypertension before treatment initiation. • Routinely monitor and begin appropriate medical therapy for incident hypertension in conjunction with the patient's primary care provider.
Diarrhea	• Most BTKi-related diarrhea can be managed with supportive care, antimotility agents, and evening dosing of ibrutinib to mitigate symptoms. • Consider temporary drug holds in the case of grade ≥3 diarrhea.
Headache	• Acalabrutinib-associated headache resolves with extended treatment and is often responsive to caffeine.

KEY POINTS:

--ensure good BP control prior to starting BTKi

--evening dose of BTKi may mitigate diarrhea

--acetaminophen or caffeine for headaches

Lipsky and Lamanna Hematology Am Soc Hematol Educ Program (2020)
2020 (1): 336–345

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Targeting BCL2 in CLL: Focus on toxicity

CLL14, MURANO: Venetoclax plus anti-CD20 antibody offers fixed duration treatment with manageable toxicity

CLL14 (TN CLL):

- Fixed duration treatment for 12 cycles
  - Obinutuzumab weekly x 4, then D1 of C2-6
  - Venetoclax started on D22 of C1 with ramp up
- Major toxicities:
  - NO tumor lysis related to venetoclax
- Grade 3 or 4 events:
  - Febrile neutropenia 5.2%
  - Infections 17.5%

MURANO (RR CLL):

- Fixed duration treatment for 24 cycles
  - Venetoclax 5-week ramp up, *then*
  - Rituximab 500 mg/m^2 C1, 375 mg/m^2 C2-6
- Major toxicities:
  - 1 tumor lysis related to venetoclax
- Grade 3 or 4 events:
  - Neutropenia 58%

Fischer N Engl J Med 2019 Jun 6;380(23):2225-2236; Seymour N Engl J Med. 2018 Mar 22;378(12):1107-1120

Venetoclax: TLS mitigation and management

Assessments before treatment	TLS risk category	Risk parameters	Mitigation measures		
			Prophylactic medication	Hydration	Hospitalization
Tumor burden assessment CT scan Lymphocyte count	Low	All lymph nodes <5 cm AND ALC <25 × 10^9/L	2-3 d before venetoclax intake: allopurinol In cases of elevated uric acid: rasburicase	Oral hydration (1.5-2 L/d), starting 2 d before dose ramp up.	Outpatient, check TLS parameters and creatinine clearance at least 6 to 8 h and 24 h after each ramp up step
Blood chemistry Potassium Phosphate Calcium Uric acid	Medium	Any lymph node 5-10 cm OR ALC ≥ 25 × 10^9/L		Oral hydration or consider IV hydration	Outpatient, check TLS parameters and creatinine clearance at least 6 to 8 h and 24 h after each ramp up step OR inpatient, in case of preexisting abnormalities or relevant coexisting conditions (creatinine clearance <80 mL/min)
Renal function Creatinine clearance	High	Any lymph node ≥10 cm OR Any lymph node ≥ 5 cm AND ALC ≥ 25 × 10^9/L		Oral hydration AND intravenous hydration	Admission to an inpatient or day hospital to ensure sufficient IV hydration and TLS monitoring

Approach:
--assess TLS risk category
--institute uric acid management (allopurinol vs. rasburicase)
--Hydration strategy (oral vs. IV)
--Determine treatment setting (inpatient vs. outpatient)

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Fischer Hematology Am Soc Hematol Educ Program2020 Dec 4;2020(1):357-362

RWE: Venetoclax toxicity is slightly higher

TLS risk category n=134	TLS prophylaxis Allopurinol	Rasburicase	Normal saline	Total	TLS events Laboratory	Clinical
Low 44.8% (n=60)	93.1% (n=54/58)	17.2% (n=10/58)	82.1% (n=46/56)	5	3	2
Intermediate 35.8% (n=48)	87.5% (n=42/48)	31.3% (n=15/48)	91.7% (n=44/48)	4	3	1
High 19.4% (n=26)	100.0% (n=26/26)	46.2% (n=11/26)	100.0% (n=25/25)	9	6	3

NOTABLE TOXICITIES:

- 21% discontinuation rate
- TLS 13.4%
- Neutropenic fevers 11.6%
- Grade 2 diarrhea 7.3%
- Opportunistic infection 8%

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Mato Haematologica Vol. 103 No. 9 (2018): September, 2018

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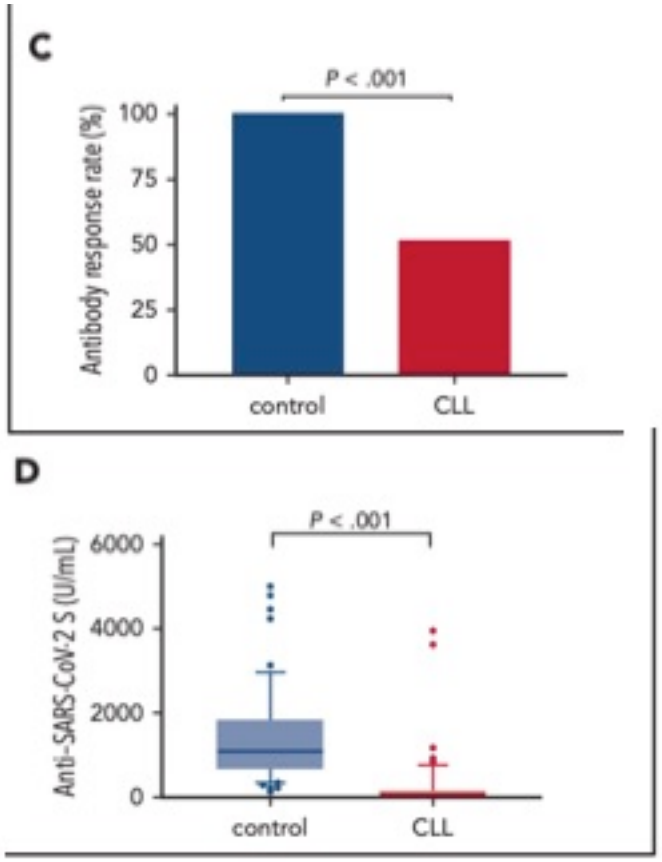
COVID-19 and CLL Treatment

Patients with CLL are less likely to respond to vaccination against SARS-CoV-2

Parameter	Patients with CLL (N = 167)
Age, median (IQR), y	71.0 (63.0-76.0)
Age ≤65 y, N (%)	50 (29.9)
Male sex, N (%)	112 (67.1)
Disease/treatment status, N (%)	
Treatment-naive	58 (34.7)
On-therapy	75 (44.9)
Off-therapy in remission	24 (14.4)
Off-therapy in relapse	10 (6.0)
BTKis	50 (66.7)
Venetoclax ± anti-CD20 antibody	22 (29.3)
Others	3 (4.0)
Time from last anti-CD20 antibody to vaccination, N (%)	
<12 mo	22 (28.6)
≥12 mo	55 (71.4)



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Herishanu Blood 2021 Jun 10;137(23):3165-3173

Impact of treatment status and treatment on response to vaccine

Variable	Serologic response , N (%)		Total	P
	Pos	Neg		
Treatment Status				
Untreated	58%	41%	92	<0.001
Treated	16%	84%	75	
Treatment protocol				
BTKi	16%	84%	50	NS
Ven +/- anti-CD20 Ab	14%	86%	22	
Anti-CD20 Ab (last treatment)				
At least 12m later	46%	55%	55	<0.001
within <12m	0	100%	22	

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Modified from Herishanu Blood 2021 Jun 10;137(23):3165-3173

Treating CLL during the COVID-19 pandemic

28% case fatality rate from COVID-19 for CLL pts in GAIA/CLL13 trial (venetoclax-based)

Furstineau Leukemia 2020 Aug;34(8):2225-2229

The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients.

Treon.Blood. 2020 May 21;135(21):1912-1915

Ibrutinib interferes with innate immunity in chronic lymphocytic leukemia patients during COVID-19 infection

Fiorcari Haematologica 2021 Mar 11. doi: 10.3324/haematol.2020.277392

Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukemia and COVID-19.

Thibaud Br J Haematol. 2020 Jul;190(2):e73-e76.. Epub 2020 Jun 4.

ERIC analysis: (1) COVID-19 severity increases with age; (2) antileukemic treatment (particularly BTK inhibitors) appears to exert a protective effect; (3) age and comorbidities did not impact on mortality, alluding to a relevant role of CLL and immunodeficiency.

Scarfo Leukemia 2020 Sep;34(9):2354-2363

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Image from https://www.presentermedia.com/powerpoint-clipart/cost-benefit-risk-red-dice-pid-2631

Summary

- Monotherapy and combination targeted therapy in CLL are here
- Managing toxicities in acute and chronic settings is critical
- BTKi: toxicity/AEs may prompt change to another BTKi or change to another class of agents
- BCL2 inhibitors: baseline assessment is key to preventing TLS
- COVID-19 pandemic is an added wrinkle
- **NOT ADDRESSED**: financial toxicity

Case 1: 56 yo man with CLL and severe GERD

- 56 yo man with CLL/SLL, mutated IGHV, no adverse cytogenetic features
- PMHx notable for severe GERD on chronic PPI, smokes 2ppd
- He opts for BR and has stable disease with persistent fatigue and mild dysphagia
- Starts acalabrutinib 100mg BID. Given the interaction with proton pump inhibitors, he stops his PPI.
- Over the next several days, he develops severe heartburn, myalgias, and right knee pain. He stays on treatment for approximately one month without any improvement.
- Treatment is changed to zanubrutinib, he resumes his PPI, and all symptoms have resolved.