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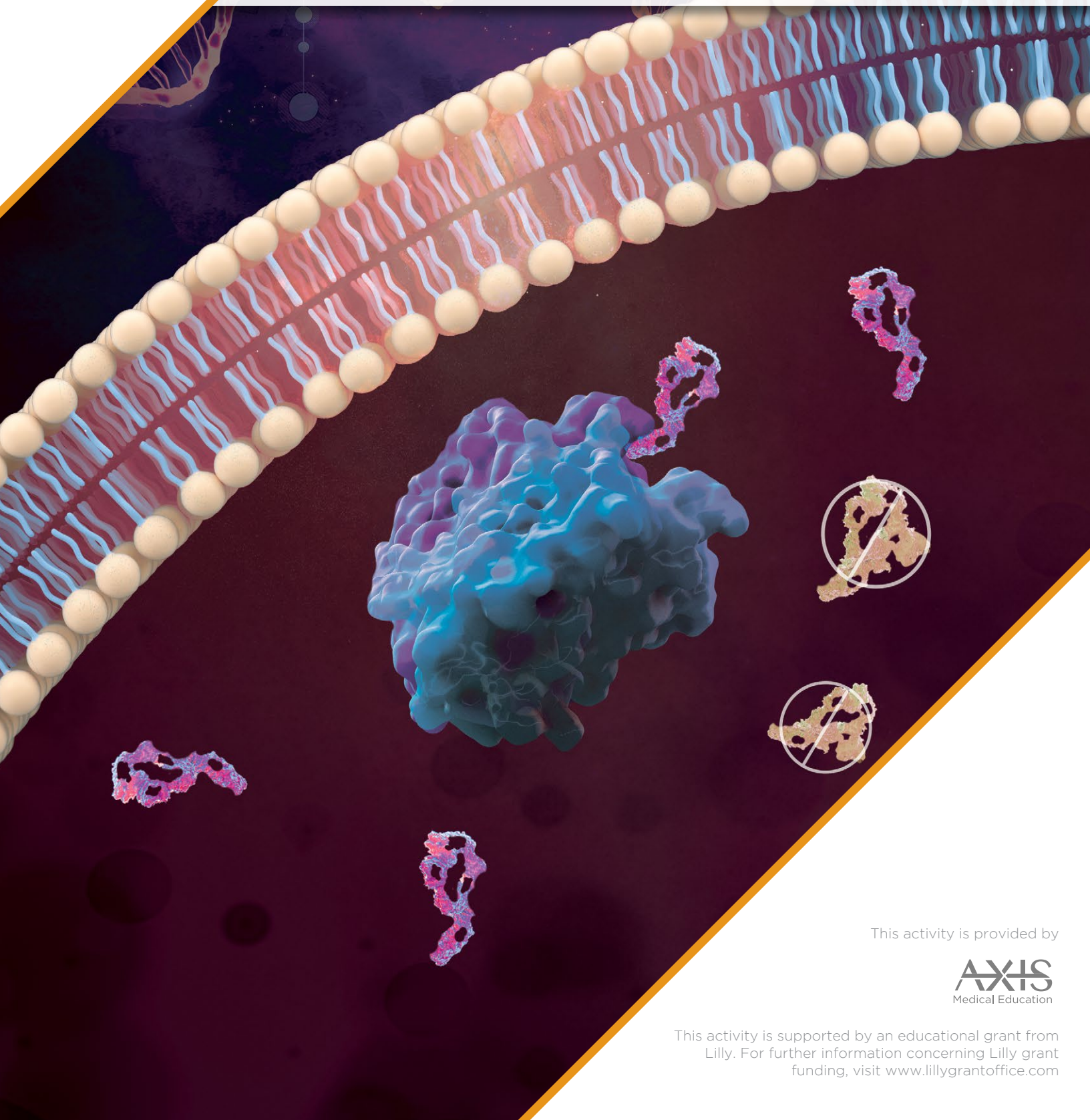
Advancing Global Care with Emerging BTK Inhibitors in Relapsed/Refractory CLL:

Connecting Hematology Leaders to Worldwide Learners

This transcript has been edited for style and clarity and includes all slides from the presentation.



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Advancing Global Care with Emerging BTK Inhibitors in Relapsed/ Refractory CLL: Connecting Hematology Leaders to Worldwide Learners

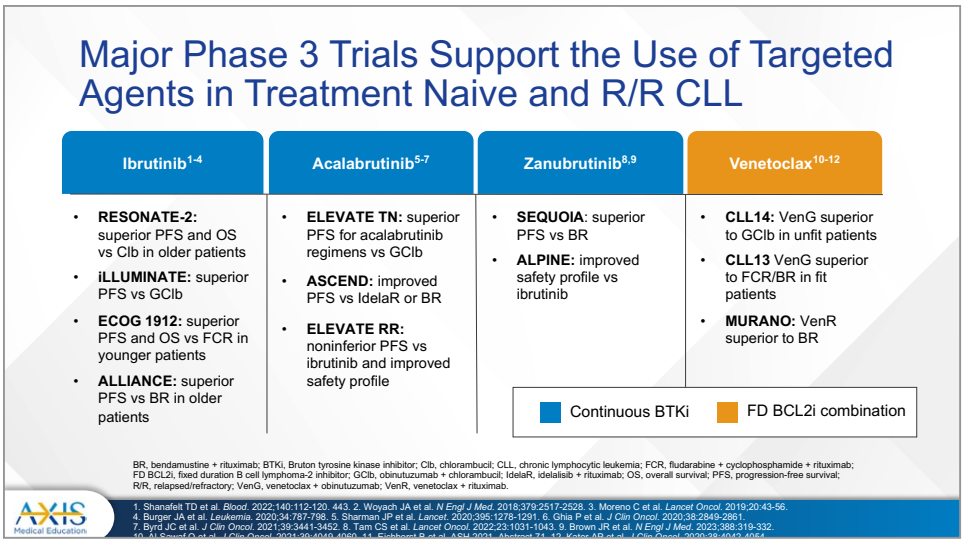
Anthony Mato, MD, MSCE; Toby A Eyre, MD, MBChB and Talha Munir, PhD

Anthony Mato, MD, MSCE: Hello, and welcome to this CME activity entitled: *Advancing Global Care with Emerging BTK Inhibitors in Relapsed/Refractory CLL, Connecting Hematology Leaders to Worldwide Learners.*

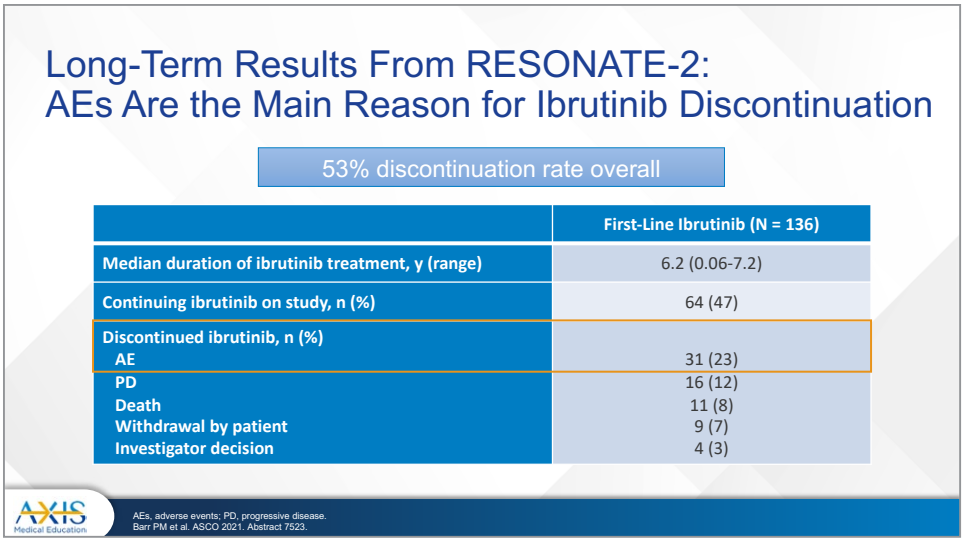
My name is Dr. Anthony Mato. I'm your moderator for today. And I'm pleased to be joined by two international colleagues, Dr. Toby Eyre from Oxford, and Dr. Talha Munir from Leeds — two colleagues from the UK who are representing expert opinions from Europe.

Today I'll be discussing the most recent clinical data and providing our insights on current and emerging evidence supporting the clinical utility of Bruton's tyrosine kinase (BTK) inhibitors in relapsed and refractory chronic lymphocytic leukemia (CLL). Let's begin.

First, I'll briefly review the key BTK inhibitor trials in relapsed/ refractory CLL.



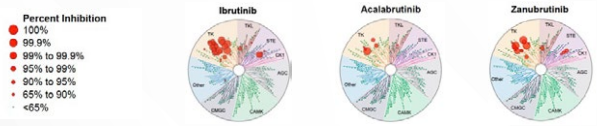
I want to start by just reminding everyone where we are with BTK inhibitors. The first BTK inhibitor approved both in the frontline and in the relapsed/refractory settings was ibrutinib.



But now we have long-term follow-up from the frontline setting. And we know that the discontinuation rate for ibrutinib is about 53%, with more than half of the discontinuations being due to intolerance, with the second most common reason being due to clinical resistance.

Therefore, by studying ibrutinib in the long-term setting, we're identifying the major reasons for discontinuation — either adverse events or progression of disease due to resistance to this particular molecule — highlighting some of the limitations for the first-in-class BTK inhibitor.

Selectivity of BTK Inhibitors (Average IC_{50} nmol/L)



TEC Kinases	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
BMX	0.8	46	1.4
TXK	2.0	368	2.2
ERBB2/HER2	6.4	~1000	88
EGFR	5.3	>1000	21
ITK	4.9	>1000	50
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X; BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; ERBB2/HER2, erb-b2 receptor tyrosine kinase/human epidermal growth factor receptor 2; IC, inhibitory concentration; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T and X cell expressed kinase.

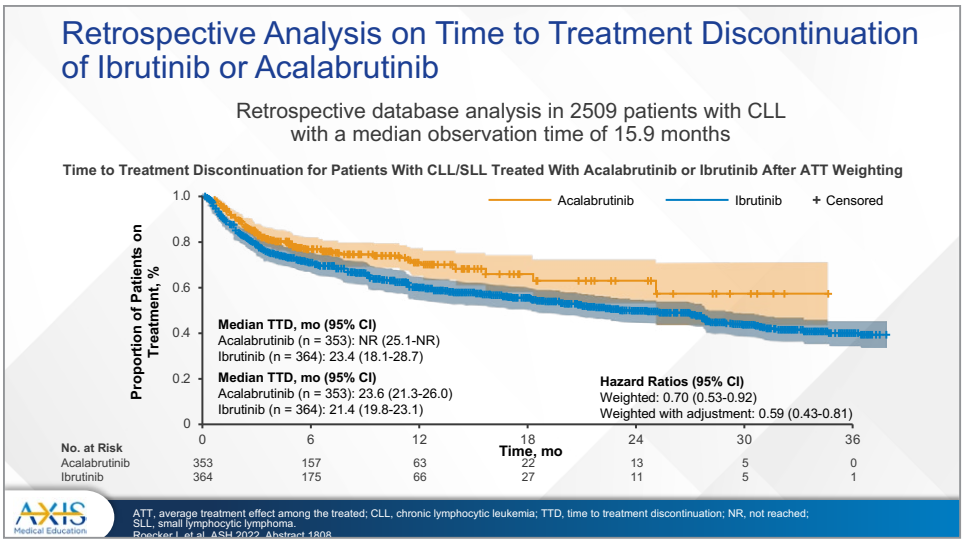
- I want to start by highlighting the adverse events associated with BTK inhibitors — the covalent inhibitors — particularly looking at ibrutinib versus acalabrutinib versus zanubrutinib. And the three BTK inhibitors are covalent inhibitors, but they have differences in their selectivity for off targets, with acalabrutinib being the most specific BTK inhibitor and ibrutinib and zanubrutinib having similar specificity or selectivity for other targets.

Adverse Event Profiles of Different BTK Inhibitors

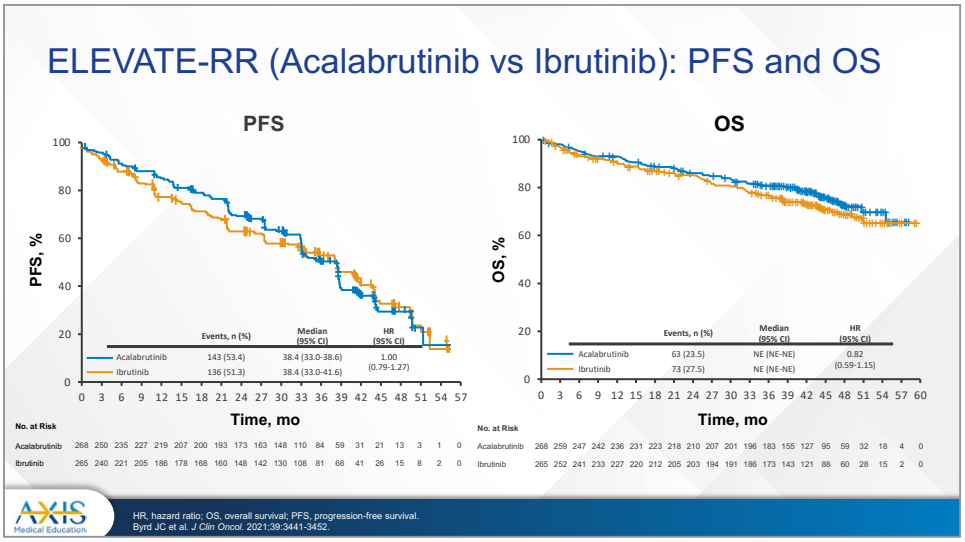
AE ≥ CTC Grade 3	Ibrutinib			Acalabrutinib	Zanubrutinib
	E1912 (Ibrutinib + Rituximab)[1]	RESONATE-2[2]	ALLIANCE[3]	ELEVATE-TN[4]	SEQUOIA[5]
Median observation time, months	**70**	**60**	**38**	**47**	**24**
Hypertension, %	11.4	8	29	2.8	6.3
Cardiac, %	7.7	N/A	N/A	8.4	N/A
AF, %	4.5	5	9	1.1	0.4
Neutropenia, %	28.4	13	15	11.2	11.3
Infection, %	11.4	12[a]	19	16.2	16.3

AE, adverse events; AF, atrial fibrillation; CTC, Common Terminology Criteria. [a] Pneumonia only.
1. Shanafelt TD et al. *Blood.* 2022;140:112-120. 2. Barr PM et al. *Blood Adv.* 2022;6:3440-3450. 3. Woyach JA et al. *N Engl J Med.* 2018;379:2517-2528. 4. Sharman JP et al. *Lancet.* 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396.

- We also have new data available, looking across trials and directly comparing the BTK inhibitors. Particularly, here, I'm highlighting data for ibrutinib, acalabrutinib, and zanubrutinib from the frontline trials: the ECOG trial, the ALLIANCE trial, RESONATE-2, acalabrutinib in the ELEVATE trial, and zanubrutinib in the SEQUOIA trial, where you can see the amount of follow-up and then the degree of specific adverse events (AEs) like hypertension, cardiac events, atrial fibrillation, neutropenia, and infection. Of course, we sometimes get ourselves into trouble by doing cross-trial comparisons. But it does look like the AEs associated with ibrutinib, particularly cardiovascular adverse events, seem to be more frequently observed as compared to acalabrutinib and zanubrutinib.

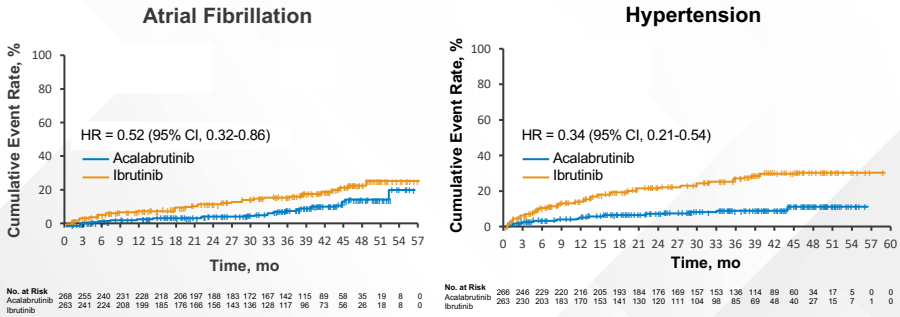


- Here, I'm highlighting some retrospective data published by Dr. Lindsey Roeker, showing differences in the time-to-treatment discontinuation between ibrutinib and acalabrutinib, favoring acalabrutinib. Again, retrospective data, but a snippet of information suggesting that there may be differences between these molecules, both in terms of their tolerability as well as in terms of development of clinical resistance while patients are on these inhibitors continuously.



- Of course, now we have the head-to-head comparisons, and those are probably the most relevant. The first I'll mention is ELEVATE-RR, a head-to-head comparison of acalabrutinib versus ibrutinib in the relapsed/refractory setting in a select patient population. This was a noninferiority trial. The trial was positive in that acalabrutinib was noninferior to ibrutinib, both from the perspective of the primary endpoint progression-free survival (PFS) and overall survival.

ELEVATE-RR (Acalabrutinib vs Ibrutinib): Cardiac AEs of Interest



AEs, adverse events; HR, hazard ratio.
Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

- What was more exciting about this data was a window into the differences in terms of adverse events. And here you can see atrial fibrillation was less common with acalabrutinib. Hypertension was significantly less common with acalabrutinib as compared to ibrutinib.

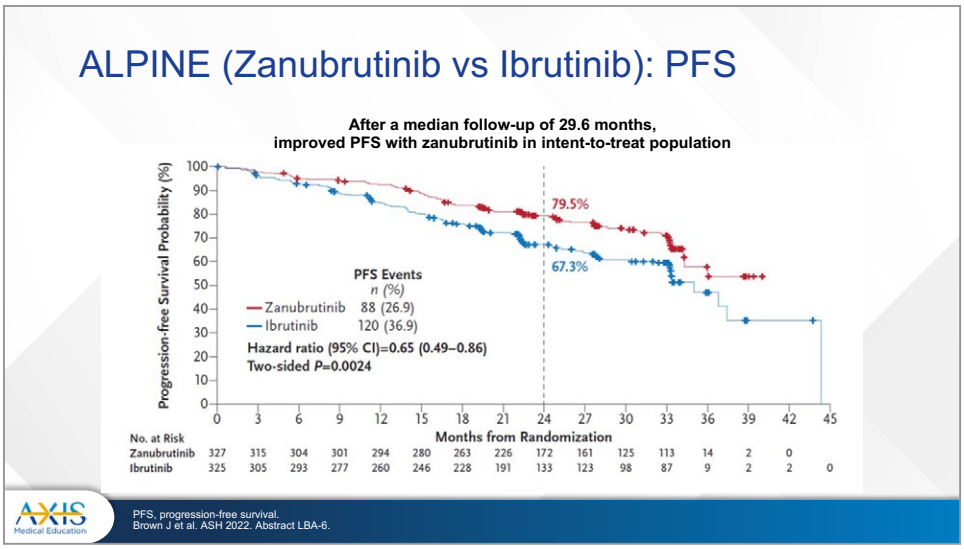
ELEVATE-RR (Acalabrutinib vs Ibrutinib): AE Burden Score
Defined by Duration and Weighted Severity of the AE

TEAE	Patients With Event, n (%)		Grades 1-4		Grades 1-5	
			AE Burden Score, Mean (SD)		AE Burden Score, Mean (SD)	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
Atrial fibrillation/flutter	25 (9)	42 **(16)**	0.03 (0.187)	**0.08 (0.316)**	0.03 (0.187)	**0.08 (0.316)**
Cardiac events	64 (24)	79 (30)	0.11 (0.355)	0.26 (1.059)	0.11 (0.354)	0.26 (1.053)
Hypertension	25 (9)	61 **(23)**	0.07 (0.336)	**0.24 (0.682)**	0.07 (0.336)	**0.24 (0.682)**
Hemorrhage	101 (38)	135 **(51)**	0.15 (0.377)	**0.26 (0.568)**	0.18 (0.667)	**0.26 (0.568)**
Major hemorrhage	12 (5)	14 (5)	0.02 (0.143)	0.01 (0.153)	0.05 (0.576)	0.01 (0.153)
Infections	208 (78)	214 (81)	0.37 (1.056)	0.36 (0.797)	0.46 (1.513)	0.41 (0.904)
Fatigue	54 (20)	44 (17)	0.088 (0.2683)	0.095 (0.4005)	0.088 (0.2683)	0.095 (0.4005)
Diarrhea	92 (35)	121 **(46)**	**0.112 (0.5370)**	0.108 (0.3245)	**0.112 (0.5370)**	0.108 (0.3245)
Headache	92 **(35)**	53 (20)	**0.084 (0.2960)**	0.076 (0.4396)	**0.084 (0.2960)**	0.076 (0.4396)
Musculoskeletal events	79 (30)	98 (37)	0.142 (0.3727)	**0.346 (1.1026)**	0.142 (0.3727)	**0.346 (1.1026)**

AE, adverse event; HR, hazard ratio; SD, standard deviation; TEAE, treatment emergent AE.
Seymour J et al. ASH 2022. Abstract 3133.

- And then we have longer-term follow-up associated with this study. And we can sort of delve into the different adverse events. But the general picture is that for the adverse events that really matter to us: the cardiovascular events and bleeding to a certain extent including hypertension, atrial fibrillation (a-fib), et cetera — they seem to be better with acalabrutinib as compared to ibrutinib.

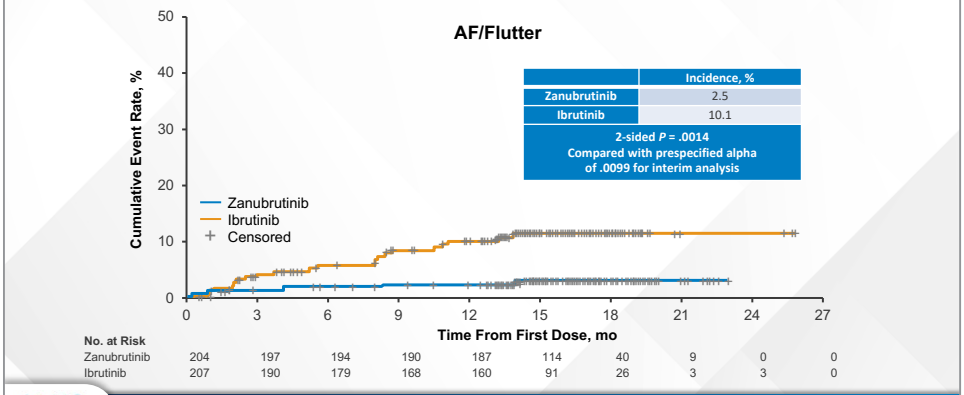
ALPINE (Zanubrutinib vs Ibrutinib): PFS



PFS, progression-free survival.
Brown J et al. ASH 2022. Abstract LBA-6.

- Now, we also had data presented most recently at the American Society of Hematology (ASH) meeting and then presented in *New England Journal of Medicine* for the ALPINE trial, looking at the comparison of zanubrutinib versus ibrutinib. Again, a head-to-head comparison in the relapsed setting, different primary endpoint, different patient population, but the overall response rate greatly favored zanubrutinib versus ibrutinib. And with a median of 29.6 months follow-up, there was also an improvement in progression-free survival.

ALPINE (Zanubrutinib vs Ibrutinib): Safety Analysis



AF, atrial fibrillation.
Hillmen P et al. EHA 2021. Abstract LB1900.

- But a similar theme in terms of cardiovascular events, particularly a-fib favored zanubrutinib over ibrutinib, although interestingly hypertension here was similar between the two molecules.

ALPINE (Zanubrutinib vs Ibrutinib): AEs of Special Interest*

AESI, n (%) Safety Population; N=648	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	294 (90.7)	300 (92.6)	186 (57.4)	184 (56.8)
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (14.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

*Specific related MedDRA preferred terms were pooled for each AESI category and summarized.
†Febrile neutropenia was reported in 4(1.2%) vs 3(0.9%) patients treated with zanubrutinib and ibrutinib, respectively.
AESI, adverse events of special interest.

PANEL DISCUSSION

Dr. Mato: So that gets me to our panel discussion. And I want to kind of throw this out to both of our faculty panelists. First, it would be great if you could highlight, in your opinion, the differences in European practices regarding the covalent inhibitors I've just reviewed. I want to hear from your country's perspective, and Europe in general, how does one pick and choose between these different BTK inhibitors? Toby, do you want to start?

Dr. Eyre: Yeah, great. Thank you, Anthony. Thanks for that overview. Well, I think the first thing to say is it's great to have options now. We're moving into an era where there are several BTK inhibitors that we potentially can use. Ibrutinib and acalabrutinib have been licensed and approved for quite a while in the frontline and relapse setting. And recently, we've seen approval for zanubrutinib, again, in the frontline and relapsed setting. Now of course, availability of these agents is dependent on reimbursement and in individual countries. And now, we have quite broad approval for acalabrutinib in the UK: frontline and relapsed as monotherapy and relapsed for ibrutinib.

I think in answer to your question about how to choose between the BTK inhibitors, clearly the second-generation BTK inhibitors look more selective and have an improved toxicity profile compared with ibrutinib. And so, it's certainly my opinion that one should be choosing a second-generation BTK inhibitor over ibrutinib. Now, I think we're moving into that era, and I think there are relatively few patients where ibrutinib would be the primary agent of choice.

Between acalabrutinib and zanubrutinib, there are obviously several nuances in terms of particular toxicity profile, and slight differences in, as you mentioned Anthony, hypertension, atrial fibrillation rates, general off-target toxicity. And of course, the differences in the ALPINE study and the ELEVATE-RR study also can be discussed in detail, but essentially are different studies with different primary endpoints with different follow-up in different patient populations. And so, I think it's a little bit difficult to cross compare across them.

So, my view basically is acalabrutinib and zanubrutinib represent two standard-of-care options now in most patients.

Dr. Mato: Tal, do you do basically agree? Anything to add?

Dr. Munir: No, I think Toby has covered this very nicely. And I think the European practice as well as the UK practice is pretty much reflecting that we're using the second generation BTK inhibitors. I think it will be interesting to see as zanubrutinib gets approval, what the uptick is from that perspective, because it is the first trial that has shown superiority over ibrutinib, which is obviously a very nice debate to have. But I think a cross-trial comparison is not justified at this moment in time, in my opinion. But I think, well, the most important thing is we have got options now as Toby quite rightly said.

Dr. Mato: And then just briefly, Tal, just to follow up this will definitely be an education for me. In the US, many practitioners are using the National Comprehensive Cancer Network (NCCN) guidelines, I'm guessing in Europe more practitioners use the European Society for Medical Oncology (ESMO) guidelines. Can you maybe just highlight some differences or similarity between these two and how the ESMO guidelines are guiding practice in the UK and Europe?

Dr. Munir: So, I think ESMO guidelines usually are lagging behind the NCCN guidelines really. The issue really is that as the practice is changing very quickly, our guideline procedure is a bit slower. We get the European Medicines Agency (EMA) approval, but the guidelines change over time. And then it is very much dependent on the reimbursement of the molecule in individual countries. For example, in UK, we can still not use ibrutinib in the frontline setting because it was never funded by the National Health Service (NHS) apart from the TP53-deleted cohort. So, I think we are in that process of getting access to zanubrutinib. And it is very much country dependent how these molecules are incorporated into the practice.

If you look at the ESMO guideline, still now from 2021, we still have venetoclax/obinutuzumab approval for unfit patients. Whereas in UK, we can use that combination in the frontline setting.

Just highlighting the fact that the guidelines do lag a little bit behind, and it is very much dependent on each country, how the reimbursement process happens, and how long would it take.

Targeted Therapy: Approvals and Current Status in CLL

Agent	Target		US Status in CLL/SLL
Ibrutinib[1]	BTK	covalent	FDA Approved
Acalabrutinib[2]			FDA Approved
Zanubrutinib[3]			FDA Approved
Pirtobrutinib	BTK	noncovalent	Phase 3 BRUIN CLL-321 Phase 3 BRUIN CLL-322 Phase 3 BRUIN CLL-313 Phase 3 BRUIN CLL-314
Nemtabrutinib			Phase 2 BELLWAVE-001 Phase 3 BELLWAVE-008
Venetoclax[4]	BCL-2		FDA Approved
Idelalisib[5]	PI3K		FDA Approved
Duvelisib[6]			FDA Approved

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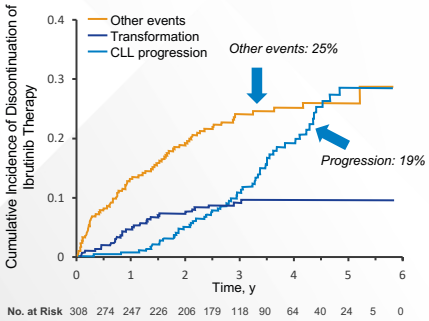
BCL-2, B cell lymphoma; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FDA, US Food and Drug Administration; SLL, small lymphocytic lymphoma; PI3K, phosphoinositide-3-kinase.
1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information.

Dr. Mato: Thanks so much. That's a great overview in terms of some similarities and differences between what options we have. In the US, we have ibrutinib, acalabrutinib, and zanubrutinib approved, and I think many of us are excited about the next-generation noncovalent BTK inhibitors: pirtobrutinib and nemtabrutinib in particular, which we'll talk more about in the upcoming sections.

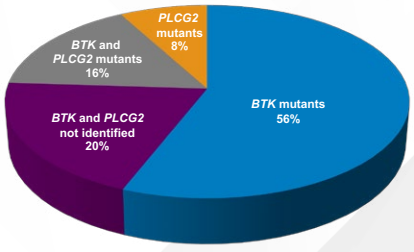
Now I want to delve into the topic of sequential management after a covalent BTK inhibitor. Here we're really thinking again about the major reasons for discontinuation: resistance and intolerance. When those events happen, what do we do next? And I think this is an important topic in a world where none of the therapies are curative, and we need to sequence from therapy to therapy to help patients to do well in the long term.

Resistance and Intolerance Limit Outcomes With Covalent BTK Inhibitors in CLL

Ibrutinib Discontinuation Over Four Prospective Studies[1]



Ibrutinib-Acquired Resistance in Patients With Progressive CLL[2]



- *BTK* C481 mutations are the dominant reasons for progressive CLL after covalent BTK inhibitors[1-8]
- *BTK* C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

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BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.
1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11:185-194. 3. Burger JA et al. *Leukemia*. 2020;34:787-798. 4. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 5. Hershkovitz-Rokah O et al. *Br J Haematol*. 2018;181:306-319. 6. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294.

Here, I'm highlighting a slide that's been presented many times in the past, again, highlighting those differences between resistance and intolerance, limiting covalent BTK inhibitors. And I think every one of us faces the situation in the clinic every day where we see patients who just can't tolerate ibrutinib for example, or acalabrutinib for example, or they're on a drug for 4 years and suddenly develop a resistance mutation in BTK or PLC gamma-2.

Sequential Use of Acalabrutinib in Patients With Ibrutinib Intolerance Is an Effective and Safe Option

AE	No. of Patients With Ibrutinib Intolerance[a]	Acalabrutinib Experience for Same Patients, n			
		Total	Lower Grade	Same Grade	Higher Grade
AF	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0
Total	41	24	18	6	1

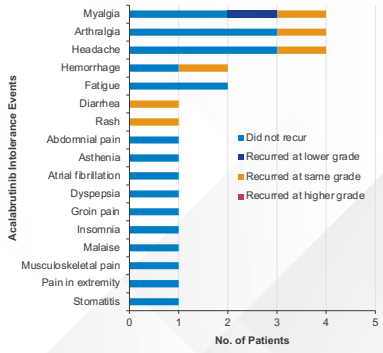
AE, adverse event; AF, atrial fibrillation.
[a] Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of ≥1 (43 events in total) of the following categories of ibrutinib-intolerance events: AF, diarrhea, rash, bleeding, or arthralgia. [b] Includes patients with atrial flutter (n = 2). [c] Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. [d] All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e] Includes 1 patient with arthritis.
Rogers KA et al. *Haematologica*. 2021;106:2364-2373.

Similarly, Zanubrutinib Is Effective in the Setting of BTK Inhibitor Intolerance

- Prior evidence has shown that zanubrutinib was effective in B-cell cancer patients intolerant of ibrutinib or acalabrutinib[1]
- For example, of 87 ibrutinib-intolerant events, 72 intolerant events (83%) did not recur

ASH 2022: zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies[2]

- Disease was controlled in 13 (93%) of 14 efficacy-evaluable patients treated with zanubrutinib, and 11 (65%) did not experience any recurrence of prior intolerance events



ASH, American Society of Hematology; BTK, Bruton's tyrosine kinase
[a] No intolerance AEs recurred at a higher grade.
1. Shadman M et al. ASCO 2021. Abstract e19506. 2. Shadman M et al. ASH 2022. Abstract 1587.

So, what are the options for these patients? Here I want to highlight two studies without getting into the specifics, but just when talking about the intolerance question, the data presented by Kerry Rogers and Mazyar Shadman, looking at switching from ibrutinib or acalabrutinib, or ibrutinib or acalabrutinib to zanubrutinib, really, I think highlight the difference between the first- and second-generation molecules. And the take-home for the acalabrutinib sequencing study was that, for the large part, you could switch from ibrutinib to acalabrutinib safely and the responses were durable. And the same is true for zanubrutinib just for example, highlighting the fact that 65% of patients did not experience recurrence of any of their prior intolerance events; very similar data with acalabrutinib. So that's the intolerance data.

PANEL DISCUSSION

Dr. Mato: I want to jump first to a question for both of you guys. And just, if you can give me your thoughts — we want to jump really to resistance more so than intolerance. What causes covalent BTK inhibitor resistance? And how is it identified in your practice, either clinically or molecularly?

Dr. Munir: I think the covalent BTK inhibitor resistance is primarily related to drug pressure; basically, the drug binds covalently to the cysteine 481 area; that's the ATP binding site. And over time, especially in the relapsed/refractory space, in patients with high-risk disease, the cysteine 481 undergoes a mutation, and because of that, the covalent BTK inhibitors start becoming ineffective because BTK undergoes autophosphorylation after that.

There are some differences in terms of when we see some resistance mutations, like with zanubrutinib, we could find some other mutations such as L528W as well. But the primary mechanism of resistance is the point mutation that we're seeing in the cysteine 481 area.

Dr. Mato: Thanks so much. Any other alternative mechanisms of resistance to highlight? I think it's largely that the BTK mutations and the downstream are the story, but Toby, anything to add?

Dr. Eyre: I think they're obviously the main mutations. Clearly as Tal mentioned, there are some alternative mutations that we've seen in small patient numbers with zanubrutinib, which may have implications for subsequent sequencing of therapy. And there's been a recent European analysis showing that the covalent binding site mutations do not occur in all patients — perhaps a third of patients don't have these. And I think it's a little bit unknown, the mechanisms of resistance in some of those patients. So, there's certainly more work to do in a proportion. But as mentioned, the dominant mutation is that seen in the Cys-481 covalent binding site.

Dr. Mato: And Toby, we're going to talk about the noncovalent inhibitors a lot in the next section, but just briefly, could you outline the differences between a covalent and noncovalent BTK inhibitor? How do they differ in your mind?

Dr. Eyre: Yeah, that's a great question. It's important to understand this when you're thinking about using a noncovalent BTK inhibitor. So, there are several key differences. But two key differences are the fact that the binding of a noncovalent BTK inhibitor is not reliant on the covalent binding site. It's kind of in the name really, but that's the key thing, that the BTK inhibitor can bind in the ATP pocket of BTK and inhibit BTK without requiring the covalent binding site. So, if you have a mutation in the covalent binding site, you can still inhibit BTK. So that's key. And that's sort of the unique nature of these agents. The other point is you've also got reversible binding, which may have implications for more proliferative disease as well. So those are the two key points.

Dr. Mato: And then, Tal and Toby, we're going to talk about the data for pirtobrutinib and nemtabrutinib, but in your opinion, what are the most compelling data to support the use of one or both agents in the relapsed/refractory setting? I know we could spend all day talking about how exciting the data are, but just a couple of the highlights; what's really grabbed you over the last couple of years from these datasets that have been presented? And what trial results are you excited to see coming up soon?

Dr. Munir: We've looked at the BRUIN data, evaluating pirtobrutinib monotherapy data for a very large set of patients, many of whom had double refractory disease, which means that they were resistant to a covalent BTK inhibitor as well as a BCL2 inhibitor. And there is data to support that these patients' outcomes were very poor. And even in those patients, it was mind blowing how these drugs were effective in controlling the CLL and prolonging the lives of the patients. So, I think that was exciting to see.

Now the next step really is how these molecules are going to be developed in the earlier lines of therapy, what combination therapies are we going to see, and whether we're going to get these patients into deeper remissions with combination therapy more effectively than with the covalent BTK inhibitors?

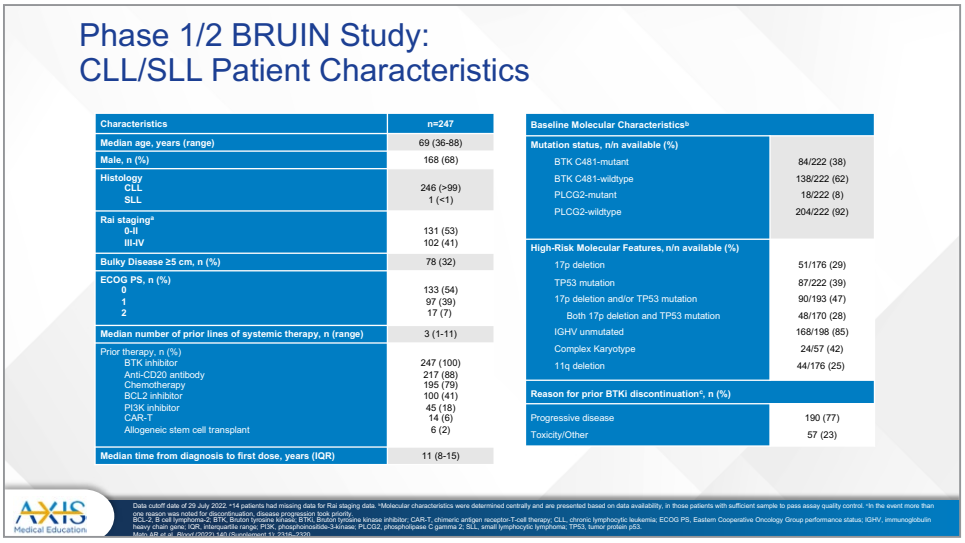
So, I think that future outcomes with multiple other trials, like the BRUIN CLL-321 trial, as well as the other trials looking at the combination of pirtobrutinib with venetoclax/rituximab versus venetoclax/rituximab. It's very exciting to

see how these molecules will be developed in near future.

Dr. Mato: Toby?

Dr. Eyre: Yeah, I'd agree with those points. I think from the BRUIN study, we've got very clear efficacy for pirtobrutinib in the post-covalent BTK inhibitor setting. It works very well in some of those high-risk groups that Tal mentioned as well as those that have been exposed to nearly every drug you can use in CLL up until now, but also gratifying that the activity looks equally promising in those with p53 mutations and those with Cys-481 mutations. So really a clinical proof of principle that this agent is active in patients who've been previously resistant to covalent BTK inhibitors.

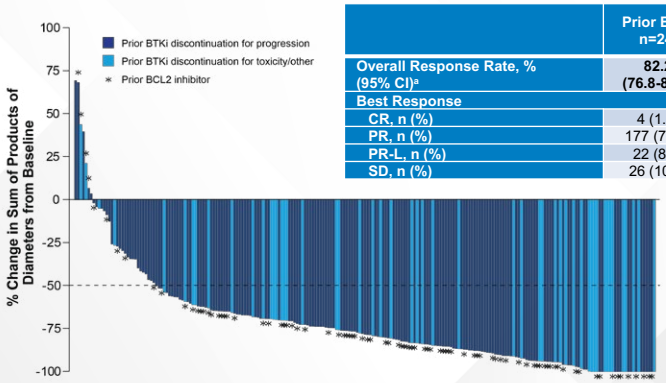
I think moving forward, the ongoing CLL-321 trial and others will hopefully help establish its role in the post-covalent BTK setting, but there are other clinical studies as mentioned, so the CLL-322 trial evaluating pirtobrutinib in combination with venetoclax/rituximab versus venetoclax/rituximab alone may well help bring the agent further forward in the treatment pathway.



Dr. Mato: Great points, guys. And I think just for the audience, I will summarize some of the key data from the BRUIN study and the BELLWAVE study, just highlighting some of the most recent data associated with pirtobrutinib and nemtabrutinib.

So, for the BRUIN trial, it's probably the largest phase 1/2 trial I've seen in quite a while for CLL. Data were presented at the most recent ASH meeting on 247 patients with CLL. A heavily pretreated patient population with a lot of high-risk features, including about 40% having a mutation in BTK. Most patients who discontinued a prior covalent BTK inhibitor — which is one of these hot topics that we mentioned earlier — did so in the setting of disease progression, about three-quarters, and about one-quarter discontinued in the setting of adverse events.

Phase 1/2 BRUIN Study: Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment



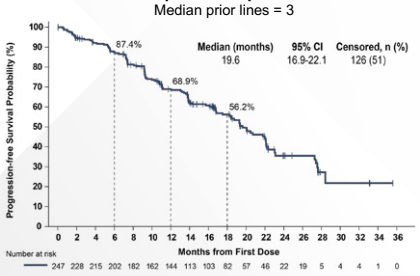
	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.
BCL-2, B cell lymphoma-2; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; PR-L, partial response with rebound lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.

- So just to get to the highlight. The most interesting data, I think here are the response rate data. Overall response rate is up to 82.2%. Nearly every patient benefited in terms of a reduction in lymphadenopathy, including patients who had received prior venetoclax, so-called double-exposed patients, and patients who had the BTK mutations also regardless of the reason for discontinuation.

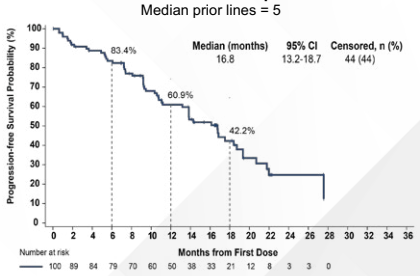
Phase 1/2 BRUIN Study: Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

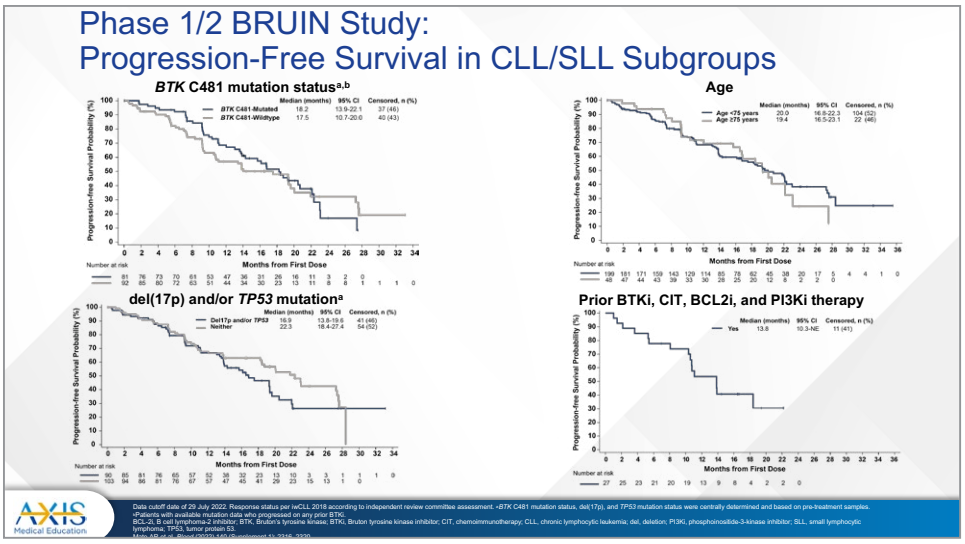
Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.
BCL-2, B cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

- We saw median progression-free survival presented for the study now at 19.6 months, with now a median follow-up of 19.4 months, and even a median for the heavily pretreated patient population who had had five prior lines of therapy, including the double-exposed component to all those patients where the median was impressive at 16.8 months.



- We also got to look at some subgroups across the study. PFS looked very similar regardless of the BTK mutation status and patient age. Older patients did quite well with this molecule. Patients who had a 17p deletion or p53 mutation had a very similar PFS. And then of course for those pentavalent failure patients, those who had a BTK inhibitor, chemo, inhibitors to CD20, BCL2, PI3K, who essentially exhausted everything, they had excellent progression-free survival.

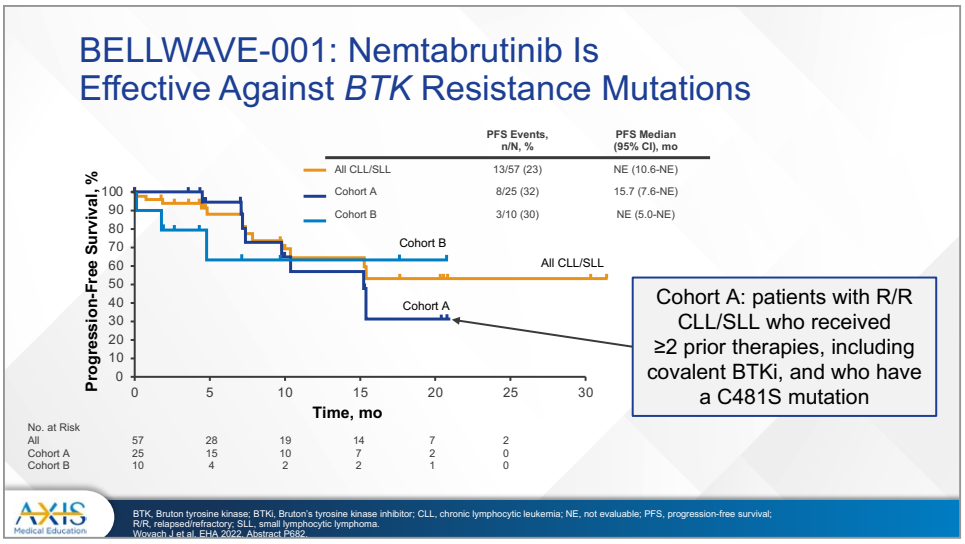
Phase 1/2 BRUIN Study: Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

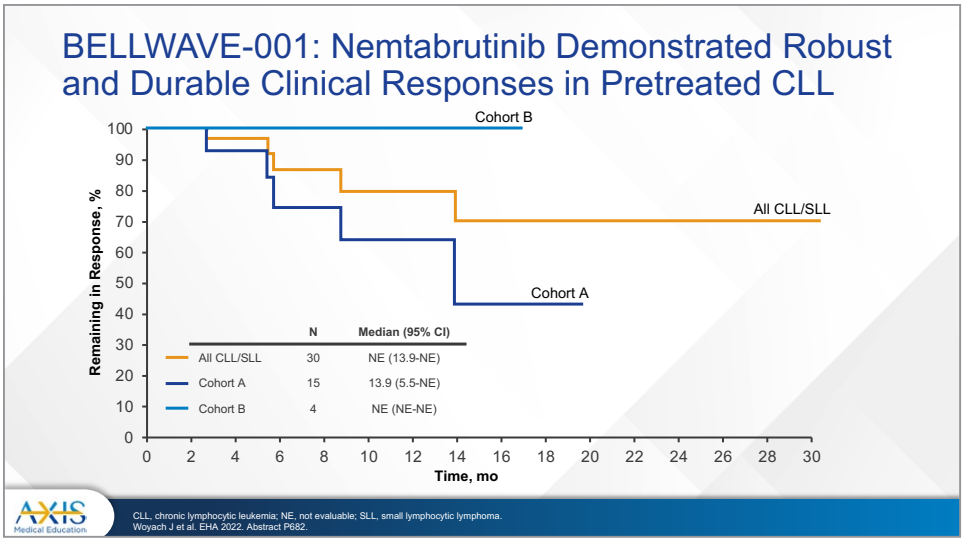
- Median time on treatment for the overall safety population was 9.6 months
- Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
- Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
- Overall and CLL/SLL safety profiles are consistent[h]

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]CLL/SLL safety population data can be found via QR code.
AEs, adverse events; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

- Of course, when you have a continuous therapy — we've talked about adverse events — you want to make sure it's well tolerated. The AE table speaks for itself in terms of the proportion of patients who've had high-grade AEs — the proportion was low. The proportion of patients who had a cardiovascular event — like any grade a-fib or flutter — was 2.8%. And then the discontinuation rate due to an adverse event was still low, 2.6%, at almost 20 months of follow-up.



- BELLWAVE is a trial that neither Toby nor Tal has mentioned so far. But this study evaluates another noncovalent BTK inhibitor, a little bit of a less BTK-specific inhibitor, called nemtabrutinib. This activity of this drug has now been evaluated several times, in CLL, Richter's, and non-Hodgkin lymphoma. And we've included some of the most recent data, looking at progression-free survival and duration of response, demonstrating that responses to this molecule can be quite durable.



Updated Findings Continue to Show Efficacy of Nemtabrutinib in Pretreated CLL/SLL

Patients With CLL/SLL Treated With Nemtabrutinib 65 mg Once Daily (N = 57)

	CLL/SLL With Prior BTK and BCL-2 Inhibitors	C481S-Mutated BTK	del(17p)	IGHV Unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%) CR PR PR with residual lymphocytosis	14 (58) 0 6 (25) 8 (33)	21 (58) 1 (3) 11 (31) 9 (25)	10 (53) 1 (5) 2 (11) 7 (37)	15 (50) 0 8 (27) 7 (23)
Median DOR, mo 95% CI	8.5 2.7-NE	24.4 8.8-NE	11.2 5.7-NE	24.4 8.5-NE
Median PFS, mo 95% CI	10.1 7.4-15.9	26.3 10.1-NE	10.1 4.6-NE	15.9 7.4-NE

Nemtabrutinib 65 mg continued to show promising and durable anti-tumor activity with a manageable safety profile in a highly R/R population who had prior therapy with novel agents

BCL-2, B cell lymphoma-2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; del, deletion; DOR, duration of response; IGHV, immunoglobulin heavy chain gene; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Woyach J et al. ASH 2022. Abstract 3114.

- And then across subgroups, I think most importantly, you see double-exposed BTK-mutated patients, del17-positive patients, and IGHV unmutated patients, with very similar overall response rates, ranging from 50% to 58%.

Pirtobrutinib Ongoing Trials

BRUIN CLL-321 (NCT04666038)

- Phase 3 global, randomized, open-label study
- Comparing pirtobrutinib (LOXO-305; Arm A) to investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab (Arm B)
- In CLL/SLL patients who have been treated with at least a covalent BTKi
- Patients may have discontinued the prior covalent BTKi due to disease progression or intolerance
- Patients who have received venetoclax are eligible for the study
- Eligible patients will be randomized in 1:1 to Arm A and Arm B

BRUIN CLL-322 (NCT04965493)

- Phase 3 open-label, randomized study
- Fixed-duration pirtobrutinib (LOXO-305) plus venetoclax and rituximab (Arm A) versus venetoclax and rituximab (Arm B)
- In CLL/SLL patients who have been previously treated with at least one prior line of therapy
- Eligible patients will be randomized 1:1 into Arm A and Arm B

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
NCT04666038; NCT04965493.

- The ongoing trial, already mentioned by Toby, that is exciting to us is the BRUIN CLL-321 trial. This is the phase 3 randomized trial in the relapsed/refractory setting looking at pirtobrutinib and versus investigator's choice, idelalisib/rituximab or bendamustine/rituximab, an important registrational trial for patients. I think, you know, many people who are involved in the CLL community are participating in this trial, and hopefully these results will lead to an approval for this molecule.

  Then there's the BRUIN CLL-322 trial which is also a relapsed/refractory trial. But here, instead of using pirtobrutinib alone as a continuous therapy, this is a time-limited triplet versus doublet venetoclax/rituximab, which is a standard of care as per the MURANO trial, plus or minus pirtobrutinib with a PFS endpoint and important data collected on MRD.

  So, two trials that we're very excited about.

Nemtabrutinib Ongoing Trial

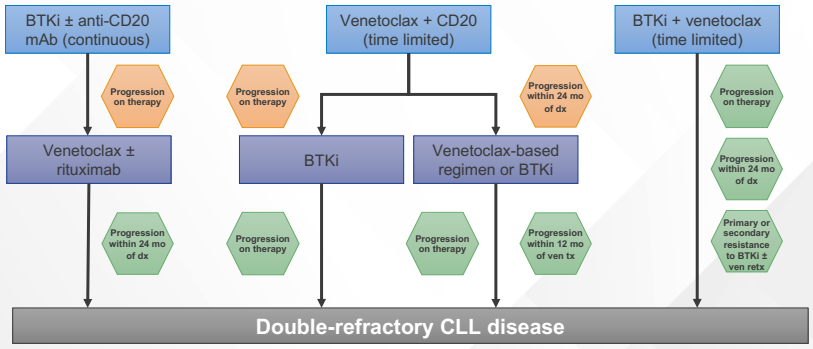
Phase 3 BELLWAVE-008 (NCT05624554)

- Phase 3, randomized study
- Comparing the efficacy and safety of nemtabrutinib versus chemoimmunotherapy (investigator's choice of fludarabine plus cyclophosphamide plus rituximab [FCR] or bendamustine plus rituximab [BR])
- In previously untreated CLL/SLL without *TP53* aberrations

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; TP53, tumor protein 53.
NCT05624554.

- Nemtabrutinib is also being studied in a phase 3 trial. Here you have a frontline trial of nemtabrutinib versus investigator's choice of BR Or FCR in a non p53-aberrant patient population.

Defining Double-Refractory Disease



Dx, diagnosis; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; mAB, monoclonal antibody; retx, retreatment; tx, treatment; ven, venetoclax.
Aronson JH et al. *Am J Hematol*. 2022;97(suppl 2):S19-S25.

- Now we'll delve into a little bit more of a discussion about the double refractory patient. This is a patient who has exhausted the exciting possibilities of the covalent BTK inhibitors and venetoclax. And here's an algorithm that I put together a while ago, defining what a double refractory patient is. By no means is this the final definition. But when you start to have different ways of giving covalent inhibitors and venetoclax, either sequentially or together, time limited or continuous, we're going to really need to define what it means to be exposed to both agents, and then what it means to be refractory to both agents.

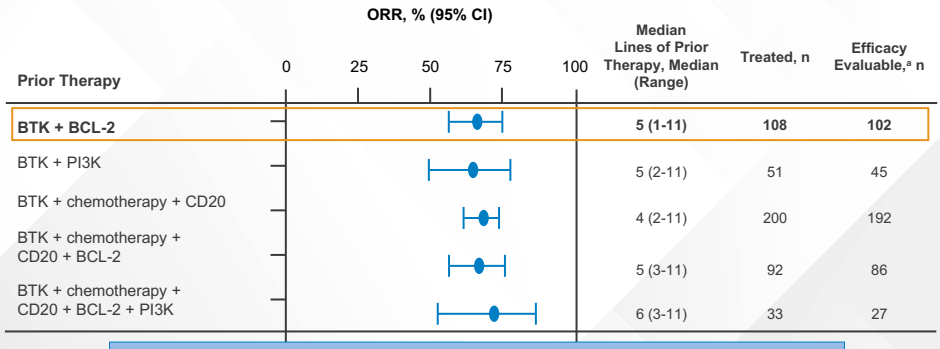
Where Do We Stand With Treatment for Double-Refractory Disease?

- There are few good options; median time to discontinuation of the immediate subsequent LOT (post–BTKi/BCL-2i therapy) or death was 5.5 months[1]
- Novel BCL-2 mutations have been described in venetoclax-resistant, ibrutinib-resistant CLL patients with BTK/PLCG2 mutations[2]
- What is being explored?
  - Venetoclax retreatment
  - Noncovalent BTKi
  - CAR-T therapy

BCL-2, B cell lymphoma-2; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T-cell therapy; CLL, chronic lymphocytic leukemia; LOT, line of treatment; PLCG2, phospholipase C gamma 2.
1. Mato A et al. ASH 2021. Abstract 3743. 2. Lucas F et al. *Blood*. 2020;135: 2192-2195.

And in terms of standard of care for these patients, probably in terms of approved agents, none of us would argue passionately for any molecule, including the PI3K inhibitors. But some options to think about, particularly if you're still sensitive to it, include venetoclax retreatment, the noncovalent BTK inhibitors on a clinical trial, CAR T cell therapy, and then I would throw in there what people think about now, use of chemotherapy in non-chemo exposed patients as an option, PI3K inhibitors, and stem cell transplantation.

BRUIN: Pirtobrutinib Is Active in CLL/SLL Patients Progressing After BTKi Therapy and Venetoclax[1]

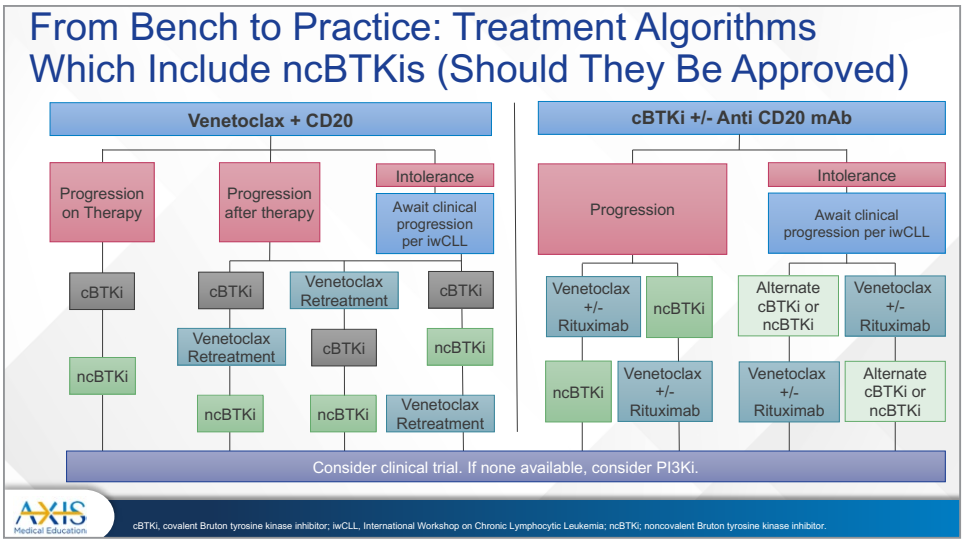


Prior Therapy	Median Lines of Prior Therapy, Median (Range)	Treated, n	Efficacy Evaluable,[a] n
BTK + BCL-2	**5 (1-11)**	**108**	**102**
BTK + PI3K	5 (2-11)	51	45
BTK + chemotherapy + CD20	4 (2-11)	200	192
BTK + chemotherapy + CD20 + BCL-2	5 (3-11)	92	86
BTK + chemotherapy + CD20 + BCL-2 + PI3K	6 (3-11)	33	27

ASH 2022: with longer follow-up, ORR of 74% in patients failing prior cBTKi and venetoclax[2]

[a] Efficacy-evaluable patients are those who had ≥1 evaluable postbaseline assessment or had discontinued treatment prior to first postbaseline assessment.
ASH, American Society of Hematology; BCL-2, B cell lymphoma-2; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PI3K, phosphoinositide-3-kinase; SLL, small lymphocytic lymphoma.

We already highlighted so I won't go into this in detail, but one nice thing about the BRUIN trial and the BELLWAVE study was that we did see double-exposed patients experiencing durable responses to the noncovalent BTK inhibitors; by far and away the largest series was in the BRUIN study. And there you have many patients who have previously been treated with venetoclax and a covalent BTK inhibitor having a durable response.



- And so of course what Toby does, and Tal does, and I do, and others in the field, we are thinking about how we are going to incorporate these new and exciting molecules into our clinical algorithms. And of course, this is a little bit forward thinking, this is an algorithm that I put together a while back, just imagining if the noncovalents were approved, how would I incorporate them into my sequencing strategy for patients in the relapsed and refractory setting?

PANEL DISCUSSION

Dr. Mato: So, I'll ask Dr. Munir and Dr. Eyre, are there any notable differences between the potential treatment and algorithm that I discussed and your current practices? What do you imagine your practice will be once these molecules are approved?

Dr. Eyre: No, I think you raise some very important points here. I think clearly we have highly active agents. Venetoclax-based therapy generally is fixed duration; now we have continuous covalent BTK inhibition; and in the future, we'll have covalent BTK inhibition in combination with venetoclax as fixed duration. So, one of the key things will be to define whether the patient is resistant or exposed to both those agents as you mentioned.

I think at least initially, until we have evidence to the contrary, the noncovalent BTK inhibitors generally will generally take their place after a covalent BTK inhibitor. And you could debate whether they should come ahead of venetoclax-based therapy if you use a covalent BTK inhibitor in the frontline setting. I think probably both sequencing paradigms are very reasonable. But in essence, we're going to have three highly active classes of therapy, which patients will be able to sequence through over potentially many, many decades.

The question of where cellular therapies fit in, in that algorithm in younger high-risk patients, remains to be seen, but we'll have an increasing number of options in the future.

Dr. Mato: Dr. Munir?

Dr. Munir: Yeah. So, I think that we've got two classes of drugs: the BTK inhibitors and the venetoclax-based therapy, which really will serve a lot of our CLL patients quite well. I think these double-refractory patients will come through, and essentially, we now have a class of drug by which we are going to be salvaging those patients. And if you look at the cellular therapy data, it doesn't look any better than the noncovalent BTK inhibitors where maybe you can argue that the tolerability is so much better compared with many cellular therapies.

So, I think the focus really is to try to extend the life of a BTK inhibitor therapy if you're going to go for a continuous therapy. And that is something I really want to stress. Because if we stop the treatment early on, then we lose the class effect very quickly. And that's where the second-generation BTK inhibitors, the covalent BTK inhibitors are important.

I think I completely agree with Toby. I think in terms of the noncovalent BTK inhibitors now, they are going to be following the path of covalent BTK inhibitor- and venetoclax-based therapy. But you never know what we might see when we combine the noncovalent BTK inhibitor with venetoclax-based therapy, whether we get deeper responses, I don't know. But that's what's exciting about the new trials, the upcoming phase 3 trials, which hopefully will be able to answer some of these burning questions.

CASE LEARNING LAB DISCUSSION

Dr. Mato: Now we're going to delve into our next section, which is the practical application, Case Learning Lab; we want to talk about cases. So, I'm going to highlight three cases, and we'd love for you guys to give some feedback on management. Of course, we're not going to go into the detail here, but just take kind of a snapshot in terms of what you think the standard of care would be for a patient like this. What are you excited about? And what data are there to support it?

So, the first case is a 75-year-old patient with IGHV-mutated, trisomy 12-positive CLL, who's had two lines of therapy; the first was BR in 2016. Unfortunately, the patient progressed and received ibrutinib 3 years later in 2019 and discontinued in the setting of rash and arthralgias. Do either of you want to take this case on and tell me how you'd manage this patient in the setting of intolerance? Are you thinking about an alternate covalent inhibitor? Would you put them on a noncovalent trial? Would you use a PI3K inhibitor? How would you manage a patient like this?

Dr. Eyre: The first thing to say is biologically this is a fairly low risk patient. So, I think you need to think about that when you're going to sequence therapy over time. And I think you'd be fairly confident that you'd be able to control this disease for some time. I think clearly you've highlighted, Anthony, that there's data for acalabrutinib and zanubrutinib, when used after ibrutinib intolerance, so I think either of those would be very reasonable options. Of course, in the future, we may well have the availability to use pirtobrutinib here, and there's clear efficacy data and tolerability data suggesting that pirtobrutinib is active following ibrutinib discontinuation as well. So that may be an option in the future.

I think personally I would probably stay in class and switch to a covalent BTK inhibitor, either zanubrutinib or acalabrutinib. The other option would be to give, I suppose, a break from a BTK inhibitor and switch to venetoclax-based therapy, which is not a wrong thing to do by any means. But I think I would probably switch to a second-generation covalent BTK.

Dr. Mato: Tal, we're going to jump to the next case and give this one to you. So, this is a similar story, a similar patient anyway. The patient is a 75-year-old with IGHV mutated, trisomy 12 CLL; they get BR and progress and then go on to ibrutinib 3 years later, but this time, they progress in the setting of a BTK C-481 mutation and acquire a deletion 17p. So how would you manage this patient?

Dr. Munir: In this patient, there's no point in going back to a covalent BTK inhibitor because the patient has acquired a cysteine 481 mutation, so you really are limited to either changing the class of the drugs, which is venetoclax with rituximab — the alternative option would be a noncovalent BTK inhibitor if there is a clinical trial where the patient can be enrolled and essentially can get the benefit of the noncovalent BTK inhibitor, which would be entirely reasonable. We know that the patient has acquired a TP53 mutation. So, if you look at the MURANO data, the data would suggest that these patients would have inferior outcomes. So, putting a patient on a trial where they can use a noncovalent BTK inhibitor would be an entirely reasonable option in my opinion as well.

Dr. Mato: Final case, I want Toby to briefly weigh in on management. So this is a 75-year-old patient with IGHV mutated, trisomy 12 CLL; they get BR and ibrutinib, but this time, let's say they discontinued ibrutinib in the setting of grade 3 or grade 4 atrial fibrillation. They go on to get venetoclax/rituximab, MURANO style, and then progress. So now you have some options, you could take a chance and go with a covalent inhibitor, though the prior event was life threatening. You could do venetoclax retreatment; you could use a noncovalent BTK inhibitor. So, I'm just curious how you would tackle this sequencing question? And then this patient at age 75, would you do something different than if they were 45?

Dr. Eyre: Yeah, great questions. So, the first thing I'd do is try to find out a little bit more about how severe their atrial fibrillation was, whether they were genuinely very decompensated, whether there was a substantial clinical concern around that time; clearly the patient stopped therapy.

I think if I were going to use a BTK inhibitor, again, I'd probably feel comfortable using zanubrutinib. I think that's probably the BTK inhibitor — if you look across trials — probably the BTK inhibitor with the lowest atrial fibrillation rates. And so, I think that remains an option.

The data that we have with pirtobrutinib so far — the atrial

fibrillation rates — are very low, down at 2%. So, I think that also is potentially an option in a 75-year-old. You may get years of disease control with that. And although they have progressed relatively soon after venetoclax/rituximab, they did have a reasonably durable remission. I also think retreating with venetoclax monotherapy is an option. I think all three of those options have potential, sequentially. I think, given that they were only on ibrutinib for 2 years, they're probably unlikely to be resistant to covalent BTK inhibitor. I think I'd probably test for Cys-481 mutation status because I think that might help. And if then, if that is intact, then I think I would probably use zanubrutinib subsequently. I probably would — assuming they got on well with venetoclax-based therapy — I'd probably use that first: venetoclax-based therapy, because you may well not need any further therapy after, say, venetoclax monotherapy.

But I think you've got options here. I'd use the agent that I thought would cause the least problems first.

And if they were 45. Yes, I think all those three options would remain. And I have no reason to expect that they'd be resistant to all of them immediately. I think I would consider allogeneic transplant or CAR T cell therapy if available further down the track. But I think I would probably exhaust the covalent BTK inhibitor and BCL2-based therapy first and then use a noncovalent BTK inhibitor to either bridge to an allotransplant or use sequentially prior to CAR T cell therapy. So, I think that's how I would go about ordering therapy in a young, high-risk patient.

Dr. Mato: Great discussion. I want to thank my colleagues, Dr. Toby Eyre from Oxford and Dr. Tal Munir from Leeds. Loved having a conversation with you on this topic. And then most importantly, I want to thank all of you for participating in this activity. Thank you so much.

REFERENCES

Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. *J Clin Oncol.* 2021;39(36):4049-4060.

Aronson JH, Skånland SS, Roeker LE, Thompson MC, Mato AR. Approach to a patient with "double refractory" chronic lymphocytic leukemia: "Double, double toil and trouble" (Shakespeare). *Am J Hematol.* 2022;97 Suppl 2:S19-S25.

Barr PM, Owen C, Robak T, et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *J Clin Oncol.* 2021;39 (15)(suppl):7523.

Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv.* 2022;6(11):3440-3450.

Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): Results from final analysis of ALPINE randomized phase 3 study. Abstract presented at: Annual Meeting of the American Society of Hematology; December 13, 2022; New Orleans, LA. Abstract LBA-6. https://ash.confex.com/ash/2022/webprogram/Paper171538.html

Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388(4):319-332.

Brukinsa. Prescribing information. BeiGene; 2023 Accessed February 23, 2023. https://www.brukinsa.com/prescribing-information.pdf

Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia.* 2020;34(3):787-798.

Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374(4):323-332.

Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol.* 2021;39(31):3441-3452.

Calquence. Prescribing information. AstraZeneca; 2022. Accessed February 23, 2023. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/e2a005a7-65a0-4388-a671-dc887815a938/e2a005a7-65a0-4388-a671-dc887815a938_viewable_rendition__v.pdf

Copiktra. Prescribing information. Secura Bio, Inc.; 2021. Accessed February 23, 2023. https://copiktra.com/pdf/COPIKTRA-PI-USCPR2007403.pdf

Eichhorst B, Niemann C, Kater AP, et al. A randomized phase III study of venetoclax-based time-limited combination treatments (RVe, GVe, GIVe) vs standard chemoimmunotherapy (CIT: FCR/BR) in frontline chronic lymphocytic leukemia (CLL) of fit patients: first co-primary endpoint analysis of the international intergroup GAIA (CLL13) Trial. *Blood.* 2021;138(1)(suppl):71.

Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2020;38(25):2849-2861.

Hershkovitz-Rokah O, Pulver D, Lenz G, Shpilberg O. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. *Br J Haematol.* 2018;181(3):306-319.

Hillmen P, et al. First interim analysis of ALINE Study: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Abstract presented at: Annual Meeting of the European Hematology Association; June 11, 2021. Abstract LB1900. https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/330170/peter.hillmen.first.interim.analysis.of.alpine.study.results.of.a.phase.3.html

Imbruvica. Prescribing information. AbbVie; 2022. Accessed February 23, 2023. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. Potency and Selectivity of BTK Inhibitors in Clinical Development for B-Cell Malignancies. *Blood.* 2018;132(1)(suppl):1871.

Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-Year Results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol.* 2020;38(34):4042-4054.

Lampson BL, Brown JR. Are BTK and PLCG2 mutations necessary and sufficient for ibrutinib resistance in chronic lymphocytic leukemia?. *Expert Rev Hematol.* 2018;11(3):185-194.

Lucas F, Larkin K, Gregory CT, et al. Novel BCL2 mutations in venetoclax-resistant, ibrutinib-resistant CLL patients with BTK/PLCG2 mutations. *Blood.* 2020;135(24):2192-2195.

Mato AR, Pagel JM, Coombs CC, et al. Pirtobrutinib, A next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: Updated results from the phase 1/2 BRUIN study. *Blood.* 2021;138 (1)(suppl):391. doi:10.1182/blood-2021-147599

Mato AR, Woyach JA, Brown JR, et al. Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed / refractory CLL/SLL: Additional patients and extended follow-up from the phase 1/2 BRUIN study. Annual Meeting of the American Society of Hematology; December 12, 2022; New Orleans, LA. Abstract 961. https://ash.confex.com/ash/2022/webprogram/Paper159497.html

Mato AR, Woyach JA, Brown JR, et al. Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed / refractory CLL/SLL: Additional patients and extended follow-up from the phase 1/2 BRUIN study. *Blood.* 2022;140 (1)(suppl):2316-2320.

Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, obinutuzumab, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(1):43-56.

Roeker L, DerSarkissian M, Ryan KJ, et al. Comparing acalabrutinib and ibrutinib in the real world: A study of 2,509 patients with chronic lymphocytic leukemia. Abstract presented at: Annual Meeting of the American Society of Hematology; December 10, 2022; New Orleans, LA. Abstract 1808. https://ash.confex.com/ash/2022/webprogram/Paper167213.html

Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. *Haematologica.* 2021;106(9):2364-2373.

Seymour JF, Byrd JC, Munir T, et al. Assessing the burden of adverse events in a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia (CLL). Abstract presented at: Annual Meeting of the American Society of Hematology; December 12, 2022; New Orleans, LA. Abstract 3133. https://ash.confex.com/ash/2022/webprogram/Paper157060.html

Shadman M, Sharman JP, Levy MY, et al. Preliminary results of the phase 2 study of zanubrutinib in patients with previously treated B-cell malignancies intolerant to ibrutinib and/or acalabrutinib. *J Clin Oncol.* 2021;39(15)(suppl): e19506.

Shadman M, Flinn IW, Kingsley EC, et al. Zanubrutinib in acalabrutinib-intolerant patients (pts) with B-cell malignancies. Abstract presented at: Annual Meeting of the American

REFERENCES

Society of Hematology; December 10, 2022; New Orleans, LA. Abstract 1587. https://ash.confex.com/ash/2022/webprogram/Paper159726.html

Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood.* 2022;140(2):112-120.

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.

Tam CS, Giannopoulos K, Jurczak W, et al. SEQUOIA: results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma. *Blood.* 2021;138(1)(suppl):396.

Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2022;23(8):1031-1043.

Venclexta. Prescribing information. AbbVie; 2022. Accessed February 23, 2023. https://www.rxabbvie.com/pdf/venclexta.pdf

Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med.* 2014;370(24):2286-2294.

Woyach JA, Ruppert AS, Guinn D, et al. BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol.* 2017;35(13):1437-1443.

Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med.* 2018;379(26):2517-2528.

Woyach JA, Huang Y, Rogers K, et al. Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations. *Blood.* 2019;134(1)(suppl):504.

Woyach J, et al. Nemtabrutinib (MK-1026), A non-covalent inhibitor of wild-type and C481S mutated Bruton tyrosine kinase for B-cell malignancies: efficacy and safety of the phase 2 dose-expansion BELLWAVE-001 study. Abstract presented at: Annual Meeting of the European Hematology Association; June 10, 2022. Abstract P682. https://library.ehaweb.org/eha/2022/eha2022-congress/357544/jennifer.woyach.nemtabrutinib.28mk-102629.a.non-covalent.inhibitor.of.wild-type.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1

Woyach JA, Flinn IW, Awan FT, et al. Efficacy and safety of nemtabrutinib, a wild-type and C481S-mutated Bruton tyrosine kinase inhibitor for B-cell malignancies: Updated analysis of the open-label phase 1/2 dose-expansion Bellwave-001 Study. Abstract presented at: Annual Meeting of the American Society of Hematology; December 11, 2022; New Orleans, LA. Abstract 3114. https://ash.confex.com/ash/2022/webprogram/Paper163596.html

Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. *Blood.* 2017;129(18):2519-2525.

Zydelig. Prescribing information. Gilead; 2022. Accessed February 23, 2023. https://www.gilead.com/-/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf

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