Multidisciplinary Perspectives on BTK Inhibitors Adverse Events Management in CLL and MCL

Dr. Vose: Good morning and welcome to our *Multidisciplinary Perspectives on Bruton Tyrosine Kinase Inhibitors Adverse Events Management in Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma.* This is an educational symposium supported by educational grants from Pharmacyclics, Janssen Biotech in Beijing, and provided by MediCom Worldwide.

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I'm Julie Vose from the University of Nebraska Medical Center where I'm Chief of Hematology-Oncology. I'd like to welcome our other faculty today, Dr. Nicole Lamanna, Associate Professor and Director of the Chronic Lymphocytic Leukemia Program from Columbia University in New York; Peter Campbell, who's a PharmD, Clinical Manager and Hematology/Oncology Program Director from the Oncology Pharmacy Residency Program in New York-Presbyterian Hospital; and Jeremy Stone, who is an Assistant Professor here with me at the University of Nebraska. He is in cardiovascular medicine and does our cardio-oncology program.

Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Select a BTKi therapy for patients with CLL/SLL and MCL, considering safety data and associated patient selection factors
- Employ AE monitoring and management strategies for individual patients with CLL and MCL on BTKi therapies
- Collaborate with the multidisciplinary team, such as hematology/ oncology, cardiology and pharmacy clinicians, to effectively support AE monitoring and management strategies

Today, we're going to be looking at a number of different cases and trying to discuss some of these issues for Bruton's tyrosine kinase inhibitors and some of the toxicities that we see. For learning objectives, upon completion of this educational activity, participants should be able to select a Bruton tyrosine kinase inhibitor therapy for patients with CLL/SLL and mantle cell lymphoma while considering the safety data and associated patient selection factors. Also, to employ adverse event monitoring and management strategies for these patients that are on Bruton's tyrosine kinase inhibitors, and also to collaborate within a multidisciplinary team such as hematology/ oncologists, with cardiology, pharmacy clinicians, and other supportive care physicians to be able to help with adverse event monitoring and management strategies.

Overview of BTK

- BTK: non-receptor intracellular kinase that belongs to TEC family of tyrosine kinases
- Plays essential role in initiation, progression, and survival of lymphocytes in B-cell malignancies
- Critical effector molecule involved in all aspects of B-cell development
- Overexpression of BTK in CLL and MCL
  - Leads to cell survival and proliferation
  - Makes BTK inhibition attractive therapeutic target

Burger JA, Wiestner A. *Nat Rev Cancer*. 2018;18(3):148-167.; Singh SP, et al. *Mol Cancer*. 2018;17(1):1-23.; Aalipour A, Advani RH. *Ther Adv Hematol*. 2014;5(4):121-133.

Just a little bit of an overview of the Bruton's tyrosine kinase pathway and inhibitors. BTK is a non-receptor intracellular kinase that belongs to the TEC family of tyrosine kinases. It plays a very essential role in the initiation, progression, and survival of lymphocytes in B-cell malignancies, and is a very critical effector molecule involved in all aspects of B-cell development. We do see overexpression of BTK in CLL and mantle cell as well as a few other lymphomas. This leads to cell survival and proliferation. These concepts makes BTK inhibition a very attractive therapeutic target.

Evolving Role of BTKi Therapy

- Effective alone or in combination with other therapies for CLL/MCL
  - BTKi's have become the standard first-line therapy in CLL in select patients
  - Represent a new option for relapsed/refractory MCL
- Newer BTKi's have improved efficacy and specificity in targeting BTK
  - How will this translate into clinical practice?
- Resistance, toxicity remain problematic

There's an evolving role of BTK inhibitor therapy and it has been shown to be effective alone or in combination with other therapies for CLL as well as mantle cell lymphoma, and of course, is now FDA-approved for both of those. Bruton's tyrosine kinase inhibitors has become really standard of care for patients with CLL for the most part in selected patients and represents a new option for patients with relapsed/refractory mantle cell that's been quite successful. There are some newer Bruton's tyrosine kinase inhibitors that have some improved efficacy and/or the possibility of decreased toxicity. How will these translate into our clinical practice are some things we'll talk about today as well as looking at resistance and some toxicity which still remains a difficulty in some of these patients.

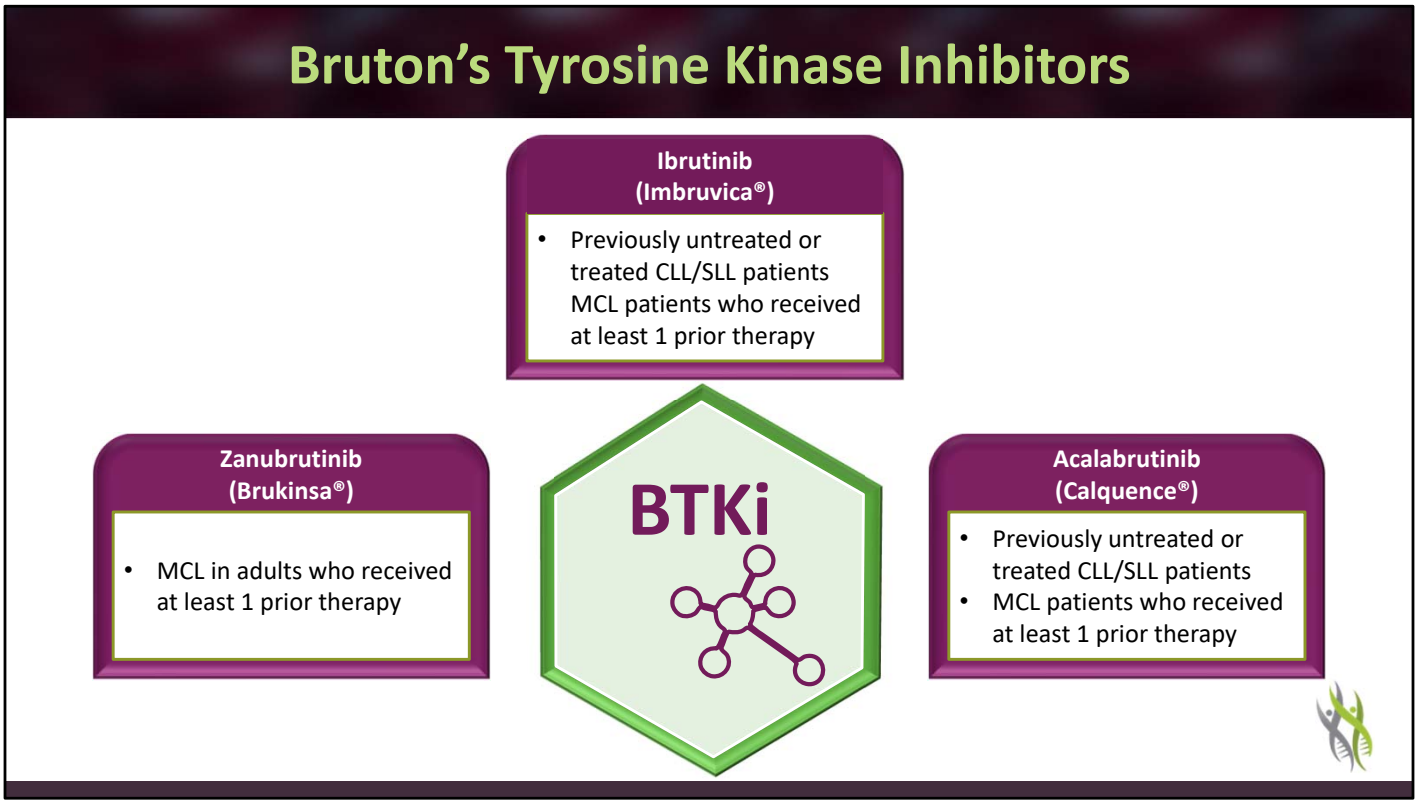
Ongoing Research

Ongoing Trials	
Acalabrutinib	• Acalabrutinib/bendamustine/rituximab vs. placebo/bendamustine/rituximab in treatment-naïve MCL • Acalabrutinib/venetoclax ± obinutuzumab vs. chemotherapy for treatment-naïve CLL • Acalabrutinib/venetoclax/obinutuzumab in CLL/SLL – phase 2 • Acalabrutinib/umbralisib/ublituximab in CLL/SLL – phase 2
Zanubrutinib	• SEQUOIA phase 3 - zanubrutinib vs. bendamustine plus rituximab in treatment-naïve CLL/SLL • ALPINE phase 3 - zanubrutinib vs. ibrutinib in relapsed/refractory CLL/SLL • Zanubrutinib induction/maintenance in treatment-naïve MCL – phase 2
Ibrutinib	• Ibrutinib plus obinutuzumab/venetoclax in relapsed or treatment-naïve MCL (phase 1/2) • Ibrutinib vs. ibrutinib/venetoclax in relapsed/refractory MCL (phase 3)
Investigational BTKis	
LOXO-305 (pirtobrutinib)	Phase 1/2 in treatment-naïve or previously treated CLL/NHL
Orelabrutinib	Phase 2 in Chinese patients with relapsed/refractory CLL/SLL
ARQ 351	Phase 1/2 in relapsed/refractory hematologic malignancies including CLL
TG-1701	Phase 1 in combination with ublituximab and umbralisib in CLL/NHL

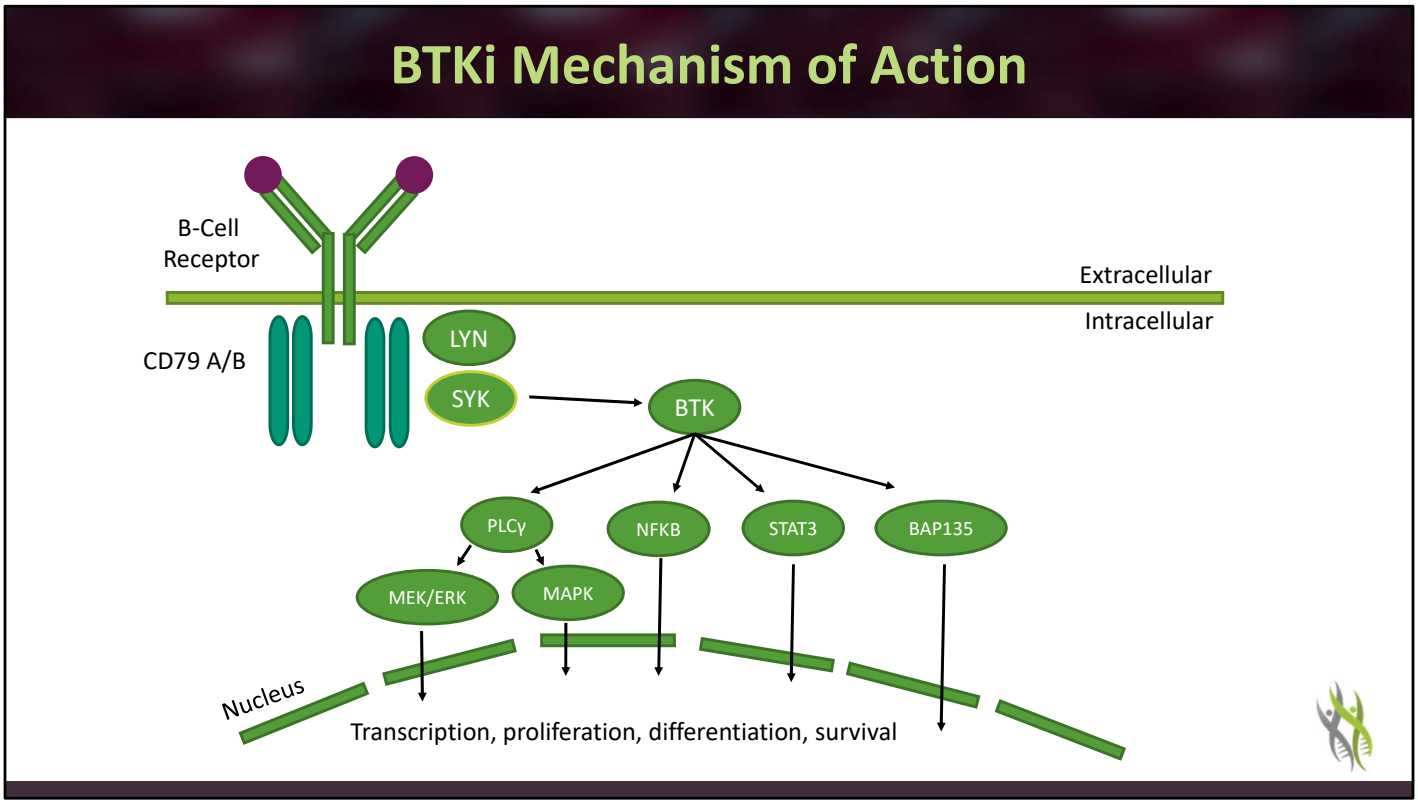
Patel K, Pagel JM. *J Hematol Oncol*. 20201;14(1):69.; Maddocks K. *Blood*. 2021;137(7):861-862. ClinicalTrials.gov.

There's ongoing research obviously with many of these inhibitors, looking at different combinations and different diseases with CLL and mantle cell and we have currently three FDA-approved BTK inhibitors for mantle cell and then two for CLL, possibly a third one coming along. There's also a number of investigational Bruton's tyrosine kinase inhibitors that try to overcome some of the resistance or have other mechanisms that may be important for our patients that we're treating with these agents.

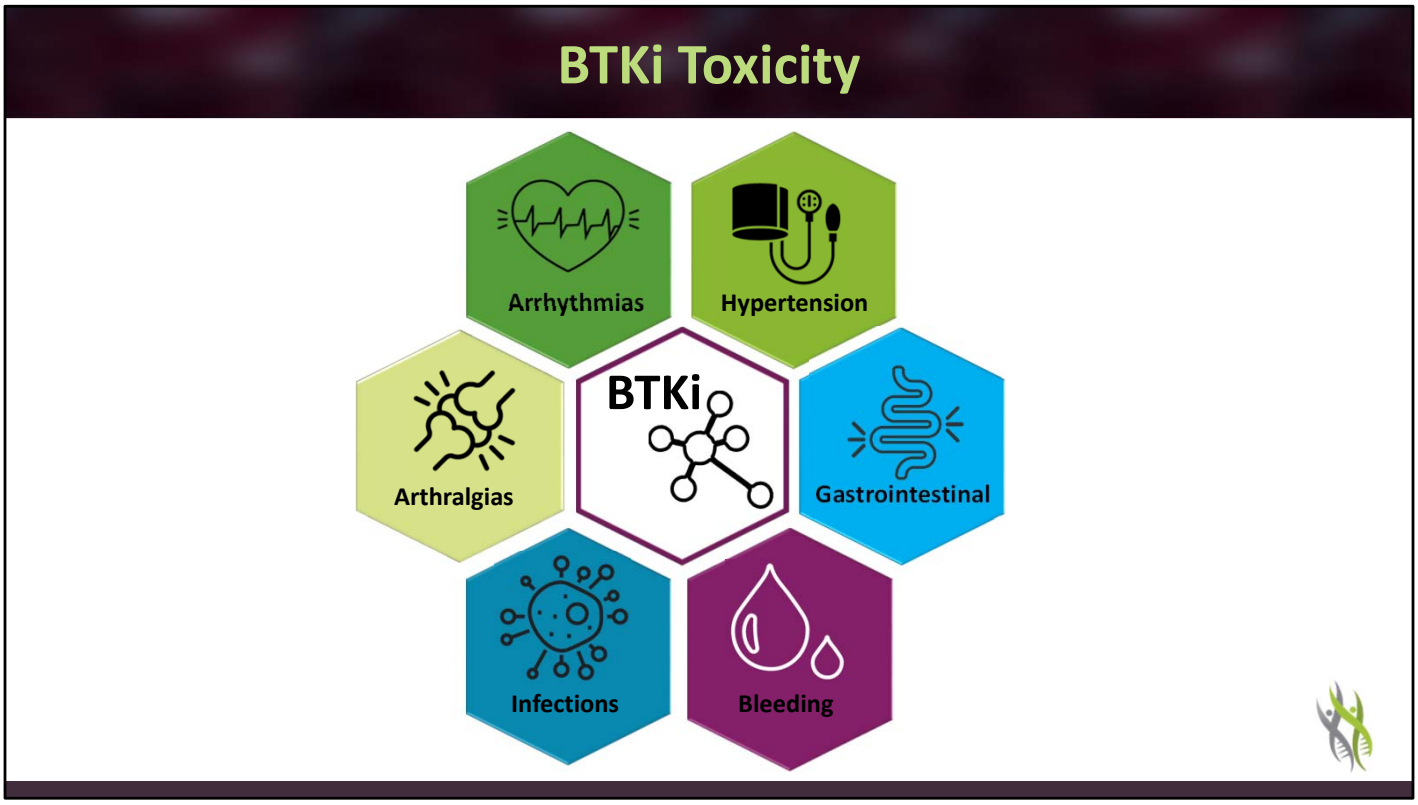
Today, we're going to talk about these Bruton's tyrosine kinase inhibitors, talk about what we currently have available, some of the data, how to overcome some of these issues, and look at toxicities. I'm going to turn it over to Dr. Lamanna to talk the next few slides.



Dr. Lamanna: As Dr. Vose alluded to, there are three currently FDA-approved BTK inhibitors. Two are approved, only three are approved in mantle cell lymphoma, two are approved in CLL. Ibrutinib was the first to market. This was approved in 2013. This is currently available for both untreated and treated CLL patients and for mantle cell patients who have received at least one prior therapy. Acalabrutinib was the next to market. Again, pre-approved in both frontline and relapsed CLL patients and again in mantle cell folks who have received at least one prior therapy. Then zanubrutinib, which we'll hear more about later, is the third that was approved in mantle cell lymphoma and awaiting approval in CLL.



Obviously, as Dr. Vose mentioned, the importance of BTK as a signaling molecule in the B-cell receptor pathway obviously has been a great target for us in the B-cell malignancies. It's really, the BTK is a cytoplasmic tyrosine kinase important to B-cell lymphocyte development, differentiation, and signaling. This is a driver of growth and proliferation.



Many of us are familiar with the BTK inhibitor toxicities and the most that we really frequently talk about are cardiac arrhythmias, such as atrial fibrillation, although you can have other arrhythmias as well. Hypertension, which we can see, which can be one of the toxicities that certainly doesn't necessarily go away with time. We can see an increased incidence with the BTK inhibitors. Gastrointestinal such as diarrhea, increased bruising, or bleeding. Thankfully, serious bleeding is not very common. Infectious complications, although this can be tricky because we also see infectious complications normally in our patients, particularly with CLL who are immunosuppressed and prior therapies may influence that as well. Then arthralgias, which can sometimes be difficult. This can be something that can impact quality of life, particularly for individuals if they're plagued with this for a period of time. These are the main toxicities, although there are others as well.

Summary of Significant AEs Occurring in Patients Treated With BTKi's

BTK Clinical Trial	Arthralgia (%)	Atrial Fibrillation (%)	Hematologic[a] (%)	Bleeding/ Hemorrhage (%)	Hypertension (%)	Infection (%)
RESONATE Ibrutinib (n=195)	17	3	17-23	44[b]	NR	NR
RESONATE-2 Ibrutinib (n=136)		6	–	4	14	–
iLLUMINATE Ibrutinib/obin (n=113)	22	12	17-44	NR	17	14[e]
ALLIANCE- A041202 Ibrutinib (n=180) Ibrutinib/rituximab (n=181)	1[c] 2[c]	17[b] 14[b]	41[c] 39[c]	2[c] 4[c]	29[c] 34[c]	20[c] 20[c]
ECOG-1912 Ibrutinib/rituximab (n=352)	4.8[c]	6.5[c]	34.7[c]	1.1[c]	18.8[c]	10.5[c]
ASCEND Acalabrutinib (n=155)	NR	5[b]	28[d]	2[c]	2[c]	15[c]
ELEVATE-TN Acalabrutinib (n=179) Acalabrutinib/obin (n=179)	15.6[b] (0.6) 21.9[b] (1.1)	4.0[b] 3.4[b]	9.5[c] 29.8[c]	15.1[b] (2) 23.6[b] (2)	2[c] 3[c]	14[c] 21[c]
BGB-3111-206/BGB-311-AU-003 Zanubrutinib (n=118)	14	2	25[c]	11	14	11[c]

NR, not reported. [a] Includes anemia, neutropenia, thrombocytopenia. [b] Any grade, most commonly petechiae including ecchymoses. [c] Grade 3 or higher. [d] Anemia and neutropenia, grade 3 or higher. [e] Upper respiratory tract.

Now, when we talk about some of the adverse events that we see in BTK inhibitors, Dr. Vose had alluded to the fact that the second-generation BTK inhibitors may have decreased frequency of some of these adverse events. These were the key adverse events that I showed you on the slide previously. There are some now emerging data from head-to-head trials that were recently just presented at ASCO and also EHA comparing acalabrutinib and ibrutinib, and zanubrutinib and ibrutinib. You can see actually from some of these studies that from the data, there seems to be decreased adverse events with the second generation, but for statistical significance, from both the head-to-head studies, atrial fibrillation was statistically significantly different with acalabrutinib and ibrutinib, and similarly in the zanubrutinib and ibrutinib studies also statistically significantly different. The efficacy of acalabrutinib versus ibrutinib was non-inferior. In the zanubrutinib versus ibrutinib trial, there was an increased overall response. We'll have to see if that translates into a difference in PFS between zanubrutinib and ibrutinib. That's the initial data that came out recently from these presentations. I think it's fair to say that they all have, unfortunately, they all share these adverse events, slightly decreased frequency with the second generation. Obviously, there's still adverse events that we need to deal with on our routine practice with our patients.

BTKi Toxicity: Off-Target to Blame?

- Second-generation BTKi have less off-target effects
  - Tyrosine protein kinase (TEC): bleeding, cardiotoxicity
  - Endothelial growth factor receptor (EGFR): rash, diarrhea
  - Interleukin-2-inducible T-cell kinase (ITK): infection, pneumonitis/inflammation

	IC50/EC50 (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5 ± 1.0	5.1 ± 1.0	0.5 ± 0.0
TEC	10 ± 12	126 ± 11	44 ± 19
EGFR	5.3 ± 1.3	>1000	21 ± 1
ITK	4.9 ± 1.2	>1000	50 ± 5

Kaptein Y, et al. *Blood*. 2018;132(Supplement 1):1871.

What is the explanation for some of these off-target effects? Clearly, the reason why we think that some of the second generations may have less of these is because they're a little bit more selective. When we think about some of the other kinase inhibitors or I should say kinases that they affect, you have TEC, EGFR and ITK. Certainly, this may explain some of the toxicities that we see with this class in general, and certainly, the second generations might be slightly more selective with a little bit less off-target effects than ibrutinib, which was the first to market.

Wait It Out, Dose Reduce, or Interrupt Therapy?

- Dose-reducing or interrupting therapy secondary to toxicities is an area of active research
  - Currently published literature presents conflicting data on outcomes
    - Analysis of RESONATE trial suggests interrupting therapy and dose intensity influences outcomes
      - Dose interruptions greater than one week reduced progression-free survival
- Drug discontinuation due to toxicity varies across agents and study →
  - 12%-16% ibrutinib
  - 9%-11% acalabrutinib
  - 5%-10% zanubrutinib
- "Real World" analysis shows higher BTKi discontinuation rates than studies:
  - US Experience (n=546): AEs contribute to half of an overall 42% discontinuation rate
  - Danish Experience (n=205): Also found 42% discontinuation rate, with 55% of discontinuations due to AEs
- Holding BTKi or dose-reducing can be appropriate in selected settings

Barr P, et al. *Blood*. 2017;129(19):2612-2615.; Mato A, et al. *Haematolgica.* 2018;103(5):874-879.; Aarup K, et al. *Eur J Haem.* 2020 ;105(5):646-654.

What do we do when we commonly encounter some of these adverse events? I think this is the, how do you manage your patients in practice? What do we do? Do we dose reduce? Do we interrupt their therapy? The initial data with regards to this was very conflicting. Now, remember, when we initially started studying ibrutinib, this was in heavily pretreated relapsed/refractory patients. Some of the data on some of the initial studies looked like dose interruption was not a good idea for patients. That obviously, this would obviously affect or reduce their progression-free survival and their outcomes. There's been some newer data of late that may suggest that this might be different or not as negative as we once thought, particularly in these heavily pretreated studies. The upfront data might be actually okay, given that this was their first-line therapy. I think we just need longer-term follow-up about whether or not this absolutely will impact long-term progression-free survival in these patients who might require dose reductions due to some of these toxicities. The real-world analysis is very different. Obviously, there's a higher BTKi discontinuation rate in some of these retrospective studies. There were two studies in particular. One was a US experience that was large, about 500 patients, where the adverse events contributed to about half of some of the discontinuation rates. In other words, there was just as many that were coming off due to adverse events than there was really due to progressive disease.

Then there was also a Danish experience report that also noted about 40% discontinuation rate. There clearly is adverse events that we need to deal with with the BTK inhibitors. Albeit some of it, the question is, is some of it due to the fact that these are adverse effects that we can't really get the patient through or whether or not because the patient--remember, BTK inhibitors currently are chronic, continuous daily therapy and with that in mind if you have a nagging, even if it's a grade 1/2 adverse event, the patient might just want to discontinue. Some of this could be more of a patient wanting to come off the drug rather than us trying to help our patients continue on these chronic daily medications. I think there's a little bit of selection bias and we need to keep that in mind when we're trying to keep our patients on therapy and on target. Certainly, we know there are adverse events that patients need to hold or appropriately dose reduce. We're going to go over some cases to highlight some of those.

Case 1: 65-year-old Male With MCL: Relapsed After Autologous PSCT

- Previously diagnosed with MCL 5 years ago – Stage IVA when he presented with diffuse lymphadenopathy and BM +. He was in good health at that time and received bendamustine/rituximab X 6 cycles and had a CR
- He then underwent BEAM/auto PSCT in CR1 but refused post-transplant rituximab
- He was well until 5 years after the transplant when he again developed diffuse lymphadenopathy and cytopenias with BM +. The patient also had developed atrial fibrillation one year prior and is on a beta-blocker and a DOAC
- Options for therapy at this point – BTK inhibitor, R2, bortezomib, R-CHOP, VR-CAP, and CAR-T cell therapy

Dr. Vose: We're going to go over a few cases here. The first case is a 65-year-old male, who was previously diagnosed with mantle cell lymphoma about five years ago. Stage 4A, as most of these patients are with diffuse lymphadenopathy, bone marrow involvement. He was in good health at the time, and he received bendamustine-rituximab for 6 cycles. Had a complete remission. He then underwent BEAM auto-transplant in first complete remission, but he refused post-transplant rituximab maintenance. He did well for about five years and then developed diffuse lymphadenopathy, again, cytopenias, bone marrow positivity. The patient also had developed about a year prior to that, atrial fibrillation and was on a beta-blocker and a direct oral anticoagulant. Options for therapy for this patient could include a BTK inhibitor, R2, bortezomib, R-CHOP, VR-CAP, or CAR T-cell therapy and there's probably many other options as well.

Case 1: Treatment

- He was started on acalabrutinib 100 mg BID
- He continued therapy for the atrial fibrillation with a beta-blocker and a DOAC
- No exacerbation of the atrial fibrillation occurred
- The patient had some easy bruising but no significant bleeding
- He continues on acalabrutinib 4 years later with good MCL control

Acalabrutinib 100 milligrams BID. That indeed was what this patient was started on. Acalabrutinib 100 milligrams BID. He continued therapy for his atrial fibrillation with a beta-blocker and a DOAC. He had no exacerbation of the atrial fibrillation that occurred and no modifications. He had some easy bruisability, but no significant bleeding and he continues to be on acalabrutinib four years later with good mantle cell control. This is a good example of how the BTK inhibitors have really helped this type of patient.

I think one thing we do want to discuss is a potential for some of these drug interactions in these medications we use for atrial fibrillation and also the issues regarding which medication to treat with respect to atrial fibrillation. Not only the medication for the heart rate but also for the anticoagulant. Dr. Stone is going to discuss some of these issues.

Drug Interactions Between Ibrutinib and Medications for Atrial Fibrillation

Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	**Major**	↑↑ ibrutinib level	CYP450 3A4 inhibition by diltiazem/verapamil
Digoxin	Moderate	↑ digoxin level	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	**Major**	↑↑ ibrutinib level	CYP450 3A4 inhibition amiodarone/dronedarone
Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	Moderate	↑ factor Xa inhibitor level	CYP450 3A4 inhibition and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor (dabigatran)	**Major**	↑ dabigatran level	P-glycoprotein inhibition by ibrutinib

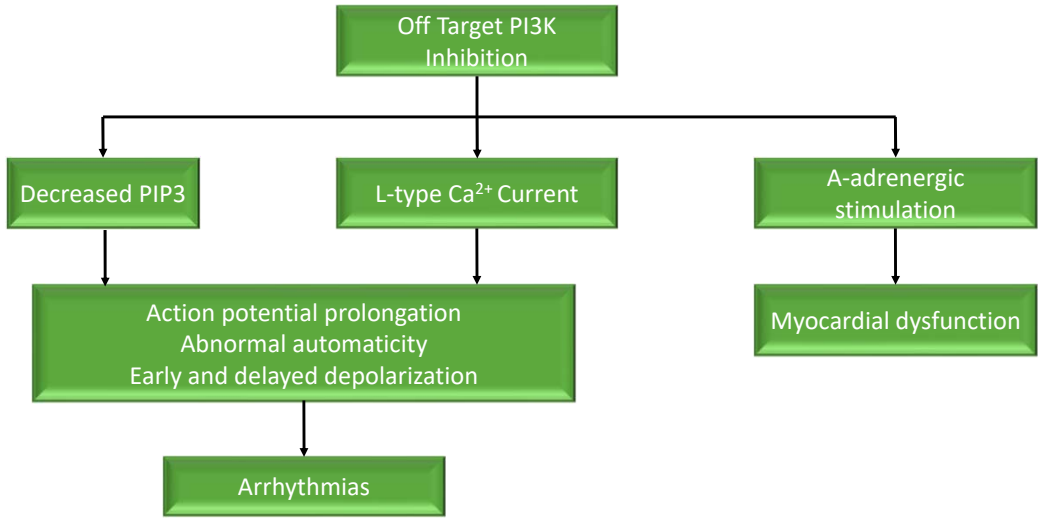
Table adapted from Ganatra S, et al. *JACC: Clinical Electrophysiology.* 2018; 4(12):1491-1500.

Dr. Stone: Sure. Thank you, Dr. Vose. This patient seemed to have a really good outcome. This patient had AFib before going on acalabrutinib and thankfully did not have an exacerbation. Was able to stay on the same meds for rate control and also for their blood thinner as well. One of our key components of control of atrial fibrillation is of course rate control because these patients tend to go into rapid AFib when they do have AFib but we're limited in some of the medication we would normally use. Beta-blockers are definitely okay and safe to use in this population and I just rely on those. A lot of these patients will be coming to you already on a calcium channel blocker like diltiazem or verapamil. These medications have a major level of interaction with ibrutinib and can lead to increased ibrutinib levels, so you have to be really careful about using these medicines. I would immediately switch them to a beta-blocker if possible. Digoxin is one that's less commonly used for rate control in AFib. This has a moderate level of interaction, and it leads to an increase in the digoxin level. If you're working closely with a cardiologist and you're really struggling with rate control you could potentially use digoxin over a calcium channel blocker for rate control, but you just have to monitor the digoxin level really closely. Sometimes we're unable to stick with the rate control strategy. We need to work on rhythm control and because we can't get the rates under control, they're really symptomatic from their AFib. You want to keep them on their BTK inhibitor therapy. Sometimes you want to reach for an antiarrhythmic with the help of a cardiologist. The best antiarrhythmic as far as rhythm control is definitely amiodarone, but we all know that these drugs have side effects. Thyroid, liver toxicity, lung toxicity as well. Beyond that, it has a major level of interaction with ibrutinib and can lead to a significantly increased level of ibrutinib. In general, just stay away from these antiarrhythmics.

The other aspect of AFib management, which we're all aware of, is stroke prevention. We do have our normal ways that we risk-stratify these patients to see who would benefit from being on a blood thinner for stroke prevention. That's our Chadsvasc score. There's also a risk stratification score called a HAS-BLED score to see which patients would be at high and prohibitive bleeding risk from being on a blood thinner. Unfortunately, these risk calculators do not take in consideration our cancer patients or that they might be on a BTK inhibitor as well. These decisions need to be individualized for each patient. Whether they have a history of stroke from AFib, if they're high-risk for having another stroke from AFib or if they are at high bleed risk. That needs to be individualized. In general, the blood thinners that you can use tend to be the factor of 10a inhibitors. While they do have a moderate level of interaction and the factor 10a inhibitor level is increased when you're also on a BTK inhibitor. With close monitoring and seeing how these patients tolerate this, they could perhaps stay on these medicines. The direct thrombin inhibitors like dabigatran I would just stay away from in general. I normally don't reach for that anyway as a first-line therapy for anticoagulation for AFib. That's because that increases the dabigatran level and can lead to significant bleeding risk. Warfarin, you should also stay away from. That's definitely not one of our major treatments that we use anyway for anticoagulation for AFib. That's a last resort. In the early trials with ibrutinib, there was an increased risk of intracerebral hemorrhage, so we tend to stay away from that one if possible.

BTKi Associated Cardiotoxicity

- Interfere with all Class I PI3K isoforms including PI3Kα, PI3Kα, PI3Kγ, and PI3Kδ



It's important also to understand why we have so many issues with cardiotoxicity with BTK inhibitors. To understand the mechanism of that, the mechanism is that there's off-target effects from the BTK inhibitors on the PI3K isoform pathway. By having this off-target inhibition, this pathway is normally protective during stress situations in the heart, but when that is inhibited leads to alterations in the calcium channel current. This can lead to action potential prolongation, early and delayed depolarization, and these things together can lead to arrhythmias like AFib or in extreme instances can lead to ventricular arrhythmias and cardiac arrest. That's more rare, but that is a consideration for sure. This off-target PI3K inhibition can also lead to alpha-adrenergic stimulation which could lead to myocardial dysfunction as well as hypertension. This normally protective pathway that we have in cardiac stress is inhibited by BTK inhibitors, so that's why we have so many issues. Hopefully, with the second-generation BTK inhibitors and further developments down the line, maybe this won't be so much of an issue in the future. I'll turn this back to Dr. Vose.

Case 2: 78-year-old Female With Relapse

- Originally presented 7 years ago with Stage IVA MCL. She was treated with VR-CAP at diagnosis and then relapsed 4 years later
- She then had pancytopenia and lymphadenopathy and was treated with rituximab as a single agent with resolution within 2 months. She continued on maintenance rituximab after induction
- Three years later she again had diffuse lymphadenopathy and periorbital infiltrates that were biopsy proven MCL

Dr. Vose: Thank you so much. Appreciate all your help on these patients. Going to go over another case. Case number two, a 78-year-old female, who seven years ago had a stage 4A mantle cell. Again, she was treated with VR-CAP at the diagnosis. She relapsed four years later. She then had pancytopenia and lymphadenopathy and was treated with rituximab as a single agent with resolution of her symptoms within a couple of months. She continued on rituximab maintenance every two months after induction. Unfortunately, three years later she did develop diffuse lymphadenopathy and periorbital infiltrates which revived serpiginous mantle cell. This is an unusual area where a mantle cell likes to be is in that periorbital area.

Case 2: Treatment

- Therapy was started with Ibrutinib 560 mg po daily. The sites of MCL involvement decreased over the first few weeks
- She developed severe arthralgias within a week of starting Ibrutinib that was not decreased by NSAIDs, narcotics, decreasing the dose of Ibrutinib
- She was switched to acalabrutinib 100 mg BID with continued improvement in lymphadenopathy and peri-orbital involvement
- She developed intermittent headaches while on acalabrutinib that was relieved by caffeine intake
- Her MCL remains in remission now 3 years later

This patient was started on ibrutinib 560 milligrams per day and the mantle cell involvement really responded to that with decrease over the next few weeks. However, she developed pretty severe arthralgias within a week of starting the ibrutinib that was not improved with NSAIDs, narcotics, or decreasing the dose ibrutinib, unfortunately. She was switched to acalabrutinib 100 milligrams BID and she did have continued improvement in her lymphadenopathy and periorbital involvement. She developed headaches while on the acalabrutinib, which is a known potential side effect, but this was relieved with caffeine intake and then eventually went away. Her mantle cell remains in remission now three years later and she remains on the ibrutinib.

BTKi-Induced Arthralgia/Myalgia

- Mechanism of BTKi-induced arthralgia/myalgia is unknown
  - Incidence:
    - Ranges widely from study to study, agent to agent
    - Can present in delayed fashion, some studies report median onset beyond one year
  - Risk factors:
    - Age <65, female gender, frontline therapy (ibrutinib), history of autoimmune disease
  - Management strategies:
    - Toxicities not affecting daily living: continue BTKi and monitor
      - Approximately 50% of patients will have spontaneous symptom resolution without intervention
    - Toxicities affecting daily living: consider dose reduction, or hold until symptom resolution

Rhodes J, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20(7):438-444.e1.

The issue regarding the mechanism of Burton's tyrosine kinase inhibitor arthralgias/myalgias is a little bit unknown as far as the mechanism. It ranges wildly from study to study. I would say in my experience, it happens pretty quickly when they start, although it can be delayed and can be an ongoing problem. Risk factors, definitely female gender. I personally have seen that it's in usually older patients, not younger patients, although it does say here less than 65, and with frontline ibrutinib, as opposed to patients who have relapsed, although certainly can again happen in those patients. Management strategies, obviously we want to try to continue to keep them on the drug if we can. Some patients have spontaneous resolution without much intervention, but otherwise, we do have to sometimes dose reduce, do some of those other interventions we talked about for management, but sometimes patients just, unfortunately, cannot withstand it and do have to be changed to other possibilities as this patient was. This is an interesting outcome for this patient, and she had some pretty significant myalgias with that.

Dr. Campbell, if you want to talk a little bit about what you see with this and interaction with any of the NSAIDs or other drugs that we might use for myalgias.

Dr. Campbell: Yes, sure. Certainly, patients have a propensity to self-medicate, especially for pain symptoms, and so we're typically okay with short duration NSAIDs as a trial to see if this can help alleviate symptoms, but any prolonged use of these agents certainly presents a concern, because we start to worry about things like the bleeding risk that is presented in these patients. Having an open line of communication with them, knowing when these symptoms start, whether or not they're persisting and if any of these over-the-counter strategies work, that way we know when do we need to pivot and start thinking about a dose reduction or just holding the drug altogether is important. Again, we'll touch on this again later, but having that narrative about all the meds that patients are taking is important because some of the over-the-counter treatment strategies for things like arthralgia, it's going to actually start to present a bit of a challenge when people are on BTK inhibitors.

Dr. Vose: I've also seen some of these older patients that are on a lot of NSAIDs, it really can cause some renal issues for sure so keep that in mind.

Case 3: 57-year-old Male Patient With Relapsed MCL

- Patient diagnosed 8 years ago with stage IIIA MCL
- He was treated with R-CHOP/alternation with R-DHAP X 6 cycles followed by auto PSCT
- He relapsed 8 years later in the same locations
- He then was placed on zanubrutinib 320 mg daily
- He developed hypertension with BP 190/100

We're going to move to case number three, which is a 57-year-old male. He was diagnosed eight years ago with Stage 3A mantle cell, was treated with R-CHOP alternating with R-DHAP, which was a common protocol that was used in Europe and some in the US. He received 6 cycles followed by an autotransplant. However, he relapsed eight years later in the same locations he had the original disease. At this time, he was placed on zanubrutinib 320 milligrams once per day, but developed hypertension with a blood pressure of 190/100.

Case 3: Treatment Outcome

- He was started on amlodipine 10 mg/day with BP improved to 150/90
- Metoprolol mg/day was added with BP now 130/80
- Patient continues on zanubrutinib 320 mg daily for at least 3 years at last follow up

This patient was actually started on amlodipine 10 milligrams per day, and his blood pressure did improve to 150/90, but was still a bit on the high side and so a second agent, metoprolol, was added with a blood pressure much better control 130/80. The patient was able to continue on the zanubrutinib, which was doing a good job for his disease and was still doing well three years later after follow-up.

Just a little bit of a discussion regarding the hypertension here, I'm going to turn again to Dr. Stone and critique what this patient was put on for hypertension and if you would have done something different.

Dr. Stone: Sure. Thanks, Dr. Vose. That was a tricky question. I think you guys were not incorrect by choosing a metoprolol necessarily because that, like I said before, metoprolol is very safe to use in patients already on a BTK inhibitor because of low level of interaction with the drug, but by general hypertension management, the guidelines do say that you should start with a dihydropyridine calcium channel blocker, like amlodipine, which unlike the non-dihydropyridine cousins of amlodipine like diltiazem, and verapamil, amlodipine does not have this interaction with BTK inhibitors. Amlodipine would be very safe here and definitely the most effective as a first-line treatment for hypertension of the choices that were given in the question. This patient had a great response and got the blood pressure down 150/90 but definitely was not to goal yet.

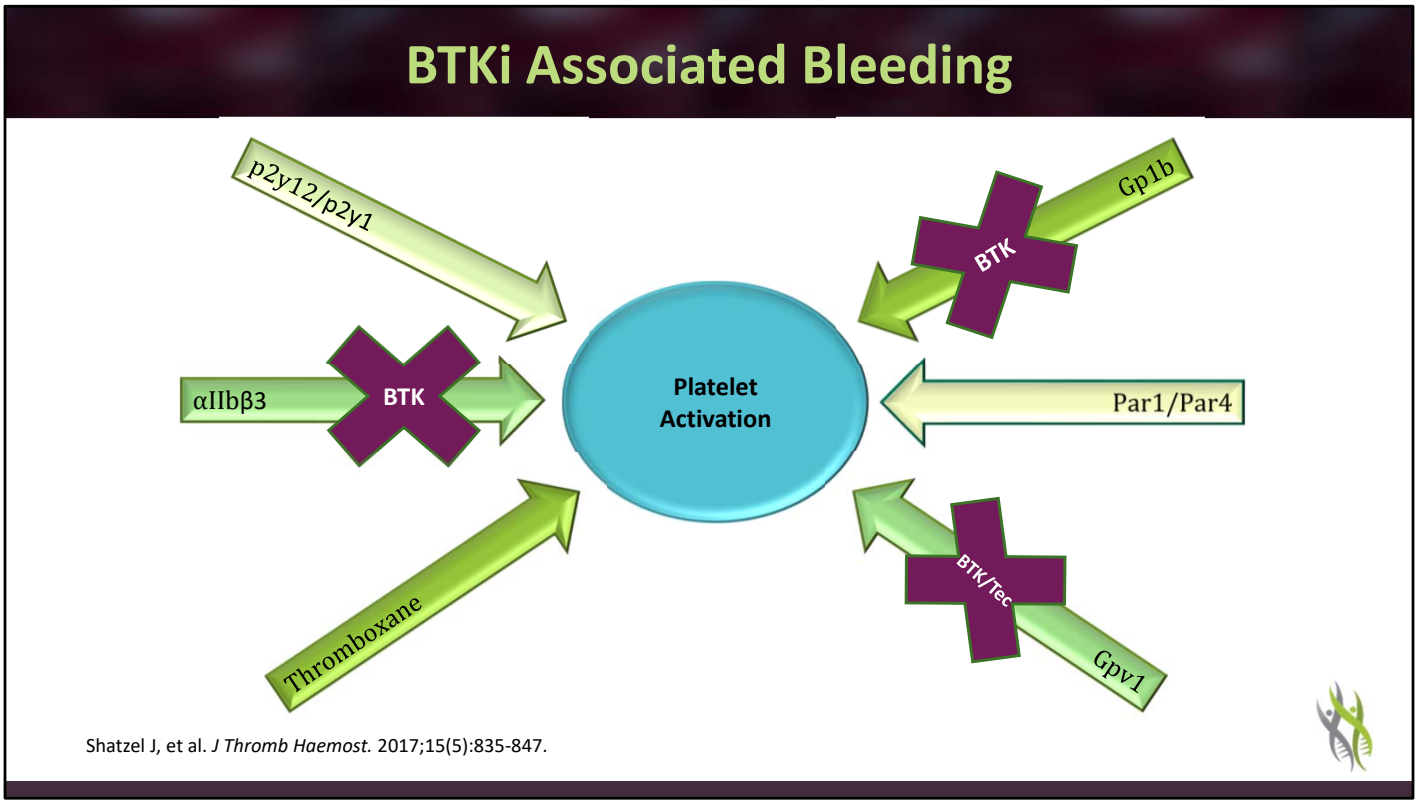
The next medication, metoprolol, that was chosen, was not a bad choice. The patient did get some benefit there, but by the International Hypertension Society guidelines, they recommend starting with high calcium channel blocker dihydropyridine, like amlodipine or with an ACE inhibitor, or an ARB like lisinopril, enalapril, or losartan. I would have used one of those as the second medication, but the patient that gets some benefit from metoprolol, no harm done, but if you were really insistent on using a beta-blocker, I would use another beta-blocker like carvedilol or labetalol which have alpha-1 blocking activity. You would actually get more blood pressure benefit than metoprolol with those medications. No harm done on this patient. The patient had a good outcome, but potentially some things that could have been not done a little better.

Dr. Vose: Yes. Those of us who are a bit older, we don't know a lot of those new medicines. We've got to keep up or have the patient come to see you. All right. I am going to turn over this over to Dr. Lamanna who's going to talk about some CLL cases.

Case 4: 70-year-old Female Diagnosed CLL With del(17p) and a TP53 Mutation

- Patient previously presented in 2018 with WBC 13 x 10^9/L, ANC 8 x 10^9/L, Hgb 13 g/dL, PLTs 160,000
- Flow cytometry: consistent with CLL
- She was observed for 3 years
- Now progressive weight loss, splenomegaly, bulky lymphadenopathy
- WBC 220 x 10^9/L, Hgb 9.4, platelet count 102,000
  - *IGHV* unmutated
  - *TP53* mutation
  - FISH: del(17p)
- She is initiated on ibrutinib and feels improved, but after 6 months develops bright red blood per rectum. Her ibrutinib is held and a GI evaluation is underway. She is placed on a PPI

Dr. Lamanna: Switching over, so here we're going to talk about a 70-year-old woman who has a CLL with deletion 17p and a TP53 mutation. She presented in 2018 with a white count of 13, hemoglobin 13, and platelets of 160. Her flow is consistent with CLL and she was monitored. She then developed progressive weight loss, splenomegaly, and bulky lymphadenopathy. Her white count is now 220, hemoglobin 9.4, platelet count 102. She has an IgHV that is unmutated, a TP53 mutation, and a deletion 17p, so high-risk features. She initiated on ibrutinib and felt improved, but after six months on ibrutinib, unfortunately, she developed bright red blood per rectum. Her ibrutinib was held and a GA evaluation began, and she was placed on a PPI.



If there's an adverse event as Dr. Vose presented earlier, you might switch to a second-generation BTK inhibitor as she did in one of her former patients with mantle cell and switched to zanubrutinib, or switched to a different BTK inhibitor for arthralgia to see if it improves. Here's a GI bleed. It's a little tricky. Acalabrutinib also has issues with drug-drug interactions with PPIs. I think that's interesting. Duvelisib is a PI3 kinase inhibitor, certainly that could be chosen but certainly that has other GI issues, with more likely immune-mediated inflammatory colitis. That's something to consider as well. Venetoclax and rituximab, of course, completely different mechanisms of BCL2 inhibitor, does not have GI bleeding associated with that. That certainly would be an acceptable option. It is very interesting, depending upon the duration of BTK inhibitor that a patient might have gone under, here she was only six months, but let's say it was longer. Let's say somebody developed an adverse event that the patient was on a BTK inhibitor much, much longer. You might be able to monitor them for a period of time and watch for progression. In this particular patient, because she had a 17p deletion, that is concerning, and I likely would not wait for her to actually progress before putting on therapy. These are folks that I would actually keep on indefinitely on chronic therapy. Even with venetoclax/ rituximab, I might even choose to continue on the venetoclax as monotherapy. There are other options for our patients, but I think you need to weigh that risk-benefit ratio. Remember, she's going to need to be on a PPI as well. You'll have to look at drug-drug interactions too.

BTKi Associated Bleeding

- Ibrutinib is associated with predominantly minor bleeding grade ≤2, ecchymoses and petechiae in two-thirds of patients[1]
- Major bleeding (grade ≥3, necessitating transfusion or hospitalization) occurs less frequently, in 2%-9% of patients[2]
- Less bleeding reported on acalabrutinib monotherapy trials, eg, 2% major, 37% minor bleeding[3]
- Mechanism is thought to involve inhibition of BTK and other related TEC family kinases which play an important role in platelet aggregation mediated via the collagen receptor glycoprotein VI

Lipsky A, Lamanna N, et al. *Hematology Am Soc Hematol Educ Program*. 2020;(1):336-345. 1. Lipsky A, et al. *Haematologica.* 2016;101(3):e124-125. 2. O'Brien S, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(10):648-657.e15. 3. Sharman J, et al. *Lancet.* 2020;395(10232):1278-1291.

What about the associated bleeding risks that we see with BTK inhibitors? Clearly, this is tricky because thankfully most of them are in the form of minor bleeding and bruising. When they're really sort of that grade 1/grade 2, some minor petechiae or bruising, we try to educate our patients to know that they should be aware that this can happen, but certainly this is not a reason to discontinue therapy. That's important to note. Both BTK and TEC play an important role in collagen-induced platelet adhesion, which is mediated through glycoprotein 6, and TEC is able to compensate for this loss of function of BTK in this setting. However, BTK is essential also for Von Willebrand factor-induced platelet aggregation and thrombus formation. The initial studies of the phase 1B/2 studies with ibrutinib noted a low frequency of subarachnoid hemorrhages as Dr. Stone noted earlier on. Warfarin, concomitant warfarin, was excluded from the initial studies with ibrutinib, and interesting to note that's where we tend to say, if you need to be on an anticoagulant, we're looking at a different anticoagulation agent and to try to not use warfarin. Back in the day, we didn't have as many options as Dr. Vose and I are probably well aware that in our multiply relapsed patients, when ibrutinib was first approved, there were many patients that we might've considered because of some of the medications that they're on, but this was the only available salvage therapy. Of course, what would we do? We'd co-manage with our colleagues from cardiology and others to maintain patients on these other agents if we knew we needed this for their efficacy of their disease. Now, there's lots of options of therapies, including anticoagulation. You have to educate your patients about the risks associated that can occur with BTK inhibitors, such as bleeding, and co-manage the other medical problems accordingly.

When we talk about the associated bleeding, as I said, most of this is minor bleeding. Even with ibrutinib, the majority is grade 1/grade 2 bruising and major bleeding is really infrequent. As I said, the initial head-to-head studies that were just recently presented at ASCO and EHA, there's a slightly even decreased frequency of bleeding with those second-generation agents, although not statistically significant. As I said, I just went over the mechanism with you, but obviously related to both BTK and TEC.

Management: Bleeding Risk

- Commonly encountered bruising seen with BTKi's 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 BTKi's for either 3 days (minor procedure) or 7 days (major procedure) both before and after invasive procedures
- 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

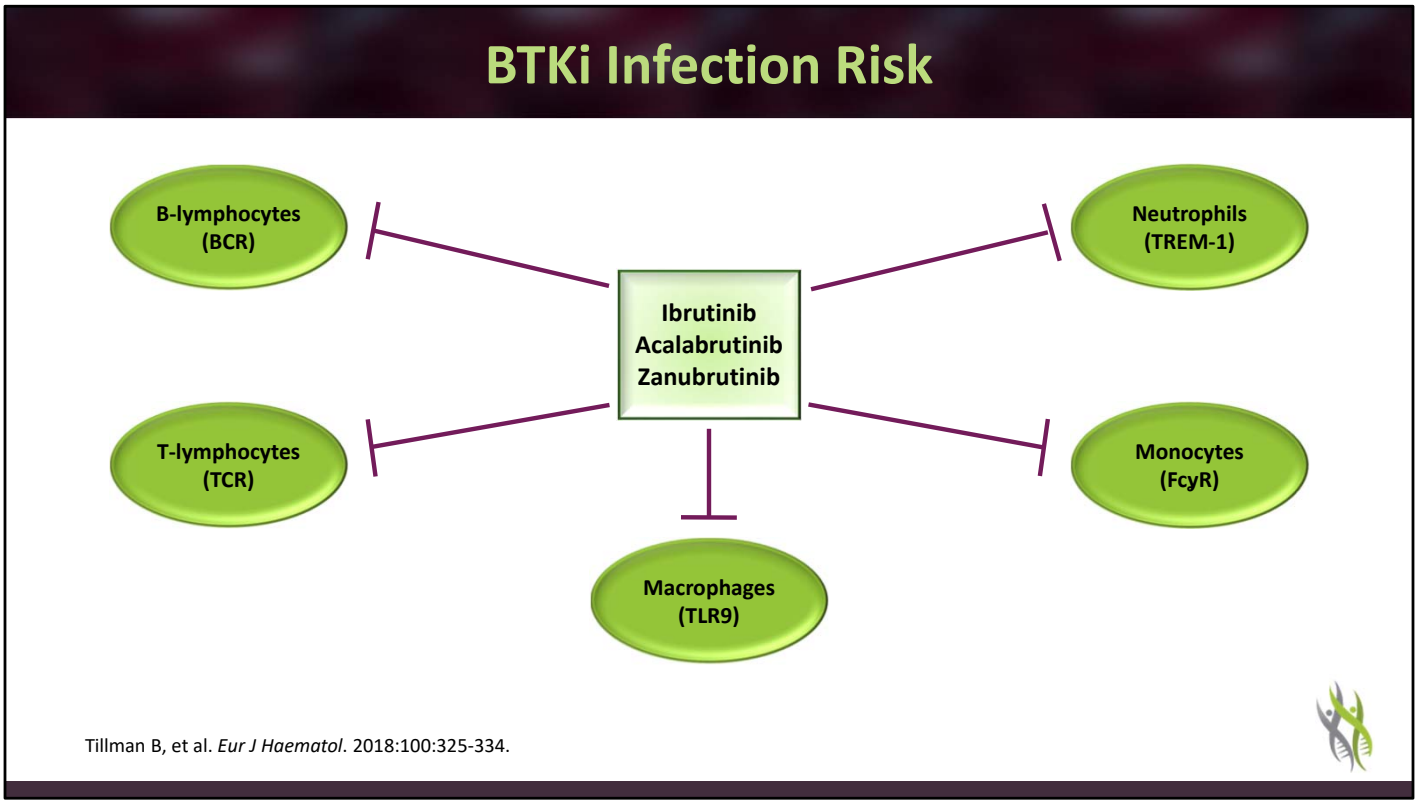
Lipsky A, Lamanna N, et al. *Hematology Am Soc Hematol Educ Program*. 2020;(1):336-345.

When we try to teach patients and educate them, I think it's really important to again, educate them that the minor bleeding is minor and so it shouldn't necessitate cessation of therapy. If they need a major procedure prior to starting treatment, if you know about it, you ask your patient is there anything that they need to undergo in the upcoming weeks to months because then you might want to say, why don't we do that first before starting your therapy, if possible. Certainly, as somebody may be on these medicines continuously near chronic right now currently, if they're going to have any kind of procedure, you're going to counsel them about how to hold their BTK inhibitor. If it's a minor procedure, about three days, if it's a major procedure, seven days accordingly. I think as long as the patients keep you in the loop about what procedures that they may have, whether it's a shoulder surgery versus something as minor as dental, you can accordingly tell them how long to hold their BTK inhibitor. Clearly, obviously for any minor bleeding that develops, you're going to tell them to hold their BTK a little bit longer, that usually resolves on its own. For severe bleeding, you might have to transfuse appropriately, depending upon the bleeding or the procedure that they had, or their platelet count if it happens to be low. I think you have to just be aware. Of course, I would be remiss, Dr. Campbell, if I didn't say that, obviously we're going to talk about their over-the-counter supplements, so that if there's anything that they're on that to exacerbate bleeding risks, such as vitamin E or fish oil. Sometimes patients just really aren't aware that some of the medicines that they may take for other medical problems, can interact with what they're on for their cancer therapy, and certainly can have drug-drug interactions and increase their risk of bleeding.

Case 5: 68-year-old Male CLL Patient With Trisomy 12 and IGHV Unmutated

- Diagnosed with CLL 10 years ago
- Previously treated with FCR achieving a CR
- After a multi-year period of observation, he now develops dyspnea on exertion
- PE: diffuse adenopathy (3-4 cm) and splenomegaly palpable 4cm below left costal margin
- Laboratory evaluation: white blood cell count 160,000/µL; 95% lymphocytes, hemoglobin 10 g/dL, platelets 95 k/µL; FISH: trisomy 12; IGHV: unmutated
- The need for therapy was discussed with the patient and he was placed on acalabrutinib
- He presents to clinic with fever, cough and physical exam notable for crackles and rhonchi of his right base and pulse Ox is 90% on room air
- Imaging reveals diffuse ground glass opacities; more predominant on right side. Cultures are performed.

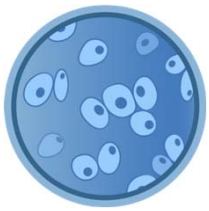
Let's move on to another gentleman. A 68-year-old gentleman who was previously diagnosed with CLL 10 years ago, and treated with chemo immunotherapy with FCR and achieved a complete response. After many years of being observed, he developed a dyspnea on exertion and some shortness of breath. He has some adenopathy and splenomegaly, his white count is 160. His hemoglobin is 10, and his platelets are 95. He has a trisomy 12 by FISH, and he has an unmutated IGHV. He was placed on acalabrutinib for therapy. He presented to clinic with fever, cough, and on physical exam notable for crackles and rhonchi of his right base, his pulse ox was 90% on room air. Imaging revealed diffuse ground-glass opacities, more predominantly on the right side, and cultures were performed.



One would be holding the acalabrutinib and the reason to do so the question is what if this patient needs a procedure such as the bronchoscopy? If they need a procedure, they're being admitted to the hospital, you can decrease any risk of bleeding. The other concern is, although it sounds like in this case it was predominantly on the right side, more telling of a pneumonia, an infectious complication, of course, you can always think of pneumonitis as a possibility with the BTK inhibitors, they're going to need antibiotics. His pulse-ox was low at 90%. I think hospitalization is totally appropriate for this individual as you're working them up for the infectious complications.

I'm going to turn this over to my colleague, Dr. Campbell, who rounds with me on the leukemia service. This is a common scenario that we run into all the time.

Infections

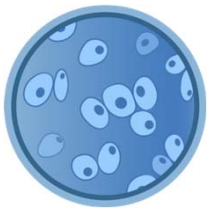


- Infection (of any grade) occurs in >50% of patients on BTKi's
- Pneumonia is the most common, observed in a landmark analysis in 12% of patients (grade ≥3)[1]
- Opportunistic infections, including *Aspergillus fumigatus* and *Pneumocystis jirovecii* are also reported[2-3]
- Counsel patients to promptly reports any signs/symptoms of an infection

1. Coutre S, et al, *Blood Adv.* 2019;3(12):1799-1807. 2. Rogers K, et al, *Leukemia.* 2019;33(10):2527-2530. 3. Ryan C, et al, *Blood Adv.* 2020;4(7):1458-1463.

Dr. Campbell: Yes. Thank you, Dr. Lamanna. Of course, when we talk about the BTK inhibitors, we have to talk about the infection risk that these patients face. Because of both the BTK activity as well as the TEC activity, you can see inhibition of neutrophils, monocytes, macrophages, your T-lymphocytes, and B-lymphocytes in some form or another. With some degree of inhibition of these different pathways that are used for infection-fighting, we tend to see patients at an increased risk for viral, bacterial, or sometimes even fungal infections, such as the previous case alluded to. Now, infections of any grade can occur in a majority of patients at some point when they're on BTK inhibitors and the data shows that this is about 50% of patients. Now, pneumonia is going to be the most common, with a landmark analysis showing about 12% of patients having grade 3 or greater with typically upper respiratory tract infections in general, or what you will most commonly see in patients that are on BTK inhibitors. You also have to keep a lookout for opportunistic infections. Now, while we mostly see some bacterial or viral infections, things like *Aspergillus* and *PJP* should also be on your radar as well. Because of the severity of some of these infections in certain patients, it's always important to counsel patients to know the signs and symptoms that they should look out for. That way they can promptly report it to the medical teams and that way we can help make the determination, especially for inpatient versus outpatient management.

Management: Infections



- Obtain a complete work-up with an appropriate index of suspicion for opportunistic infections such as *Aspergillus fumigatus* and *Pneumocystis jirovecii* (PJP)
- In the case of severe infection, hold BTKi until a definitive diagnosis is determined and restart after the start of clinical improvement
- Provide clinically indicated vaccinations (eg, against influenza and pneumococcus) of patients before treatment
- Consider PJP prophylaxis for patients deemed at high risk of infection (eg, R/R or heavily pretreated patients) or patients with a prior history of infection

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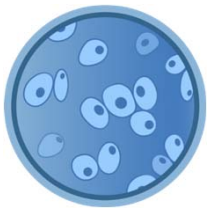
When we're managing these patients, clearly it will differ a little bit based on the severity of the infection and whether they're inpatient or outpatient, but you always want to do a complete workup, sending cultures, viral panels, and any imaging that's appropriate, especially if you were trying to rule out things like *Aspergillus* or *PJP* infections. Now as Dr. Lamanna had stated, in the case of a severe infection, you do want to hold your BTK inhibitor briefly, and then if the patient is starting to show signs of clinical improvement, that's the point in which you can restart it, but you want to make sure that patient is able to have procedures like a bronchoscopy within the window of when you need to hold it. Also, provide clinically indicated vaccinations, so things like having an annual influenza vaccine or the pneumococcus vaccine for certain patients when they're eligible prior to treatment. That way, you make sure that the patients are already vaccinated when starting. You also want to consider *PJP* prophylaxis for certain patients, and these would be the ones that we're thinking are high risk, so either relapsed/refractory or heavily pretreated patients, or especially those that have a prior history of infection. There is a meta-analysis that looks at the incidents of *PJP* infections in patients that are on BTK inhibitors. What it largely showed was that the patients that were susceptible were those that were heavily pretreated or relapsed/refractory, or those that were not on prophylaxis, and the incidence was only about 2.5%. Across the board, not all patients will necessarily need *PJP* prophylaxis, but this is a decision that needs to be individualized for each patient, taking their individual risk factors into consideration.

Infections Recommendations

- Vaccinations
  - Annual influenza vaccine
  - Pneumococcal vaccine every 5 years
  - COVID vaccine
  - Avoid live vaccines
  - Patient education: may have suboptimal response to influenza vaccine, recommend additional preventative measures, 'social distancing' and safe
- Herpes virus prophylaxis (eg, acyclovir/valacyclovir) and PJP prophylaxis (eg, sulfamethoxazole/trimethoprim)
  - Consider in patients receiving chemoimmunotherapy or PI3K inhibitors
- Consider HBV prophylaxis and monitoring
  - Anti-CD20 mAB containing regimens (rituximab, obinutuzumab, or ofatumumab), BTKi's, PI3Ki's
- Monitor for CMV viremia and prophylactic ganciclovir if viremia present



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Now touching a little bit on the vaccines again, we talked about the annual influenza vaccine, the pneumococcal vaccine, one thing that's important is to avoid live vaccines. Think of the intra-nasal flu vaccine, so for patients that will be getting the flu vaccine, just make sure that it is not a live vaccine. Then of course in this day and age, the COVID vaccine is certainly a recommendation for our patients. I'll ask Dr. Vose and Dr. Lamanna, what recommendations are you making for the COVID vaccine in your patients?

Dr. Vose: Yes, I'm giving it to all the patients. Unfortunately, some of them will not respond to that. Probably the ones, especially that are on therapy, especially anti-CD20 therapies, but I still think that it's important for all of them to receive it and then I also counsel them and all of their family or other close contacts to receive it as well.

Dr. Lamanna: Yes, obviously this is data that's emerging. There have been some publications about the inadequate response that our hematologic patients are experiencing with the vaccine. Obviously, this is an evolution and we're going to try to look at--there are some trials and things that we'll try to look at whether or not patients will require a third vaccine or a different vaccine or if there's any prophylaxis. Stay tuned. Obviously, I still recommend all our patients to receive the COVID vaccine regardless. Perhaps we'll have to figure out how our hematologic patients, whether or not--obviously the testing of whether or not they've mounted immune response may not be adequate and so certainly this is something that we're going to learn about over the course of the next year and figure out how maybe to best optimize the vaccine in our patients who have hematologic malignancies. It's tricky and I agree with Dr. Vose, we try to recommend that others get vaccinated to help our immune-suppressed patients do better with the virus going forward.

Dr. Campbell: Yes, so data is still forthcoming, but clearly at this point, we generally make the recommendation to get the shot, even if it's not as robust of a response. In the event that patients do have that suboptimal response, clearly recommended that we have patients take any preventative measures that they can such as social distancing and just maintaining safe behaviors. Here in New York City, we certainly have to talk about riding the subway, being in enclosed environments with a lot of other people, and so just good conversations to have with patients, especially if you think they're not having a robust vaccine response. Another prophylaxis to talk about, we talked about *PJP* prophylaxis, but also herpes virus prophylaxis with either acyclovir or valacyclovir could be considered in these patients as well as HPV prophylaxis and routine monitoring for patients on a number of these oral therapies. Then lastly, also consider monitoring for CMV and then starting prophylactic or preemptive therapy if necessary.

Case 6: 73-year-old With Occurrence of BTKi Drug-Drug Interaction

- DT is a male patient with a past medical history of hypertension, type II diabetes, atrial fibrillation, and Crohn's disease, diagnosed with CLL in 2015 with Rai Stage I
- Followed without treatment until 2020, at which time he was started on ibrutinib following progressive cytopenias
- Patient presents to the emergency room following one week of fevers, unproductive cough, and diarrhea 4-5x a day. The patient's home medication list is as follows:
  - Metformin 1000 mg once daily
  - Lisinopril 20 mg once daily
  - Hydrochlorothiazide 12.5 mg once daily
  - Diltiazem 120 mg ER once daily
  - Apixaban 5 mg twice daily
  - Sulfasalazine 2 g twice daily
- The team in the emergency room obtains a CT scan which shows bilateral ground glass opacities, with a right-sided 1 mm nodule. Concerned for a fungal infection, the team starts voriconazole and admits the patient to the oncology service

We'll go through one more case. This is a 73-year-old with an occurrence of BTK inhibitor drug-drug interaction and so this is a male patient with a past medical history of hypertension, Type 2 diabetes, AFib, and Crohn's disease who was diagnosed with CLL in 2015 with Rai Stage 1. Was filed without treatment until 2020 at which time he had started on Ibrutinib following some new progressive cytopenias. The patient presented to the emergency room after one week of fevers and a non-productive cough and diarrhea four to five times a day. His medication list includes metformin, lisinopril, hydrochlorothiazide, diltiazem, apixaban, and sulfasalazine The emergency room team did a CT scan, it shows bilateral ground-glass opacities, a right-sided 1 millimeter nodule, and a concern for a fungal infection for which they start voriconazole and admit the patient to the inpatient oncology service. When we look at this patient, the drug-drug interactions for all oral chemotherapy agents should be foremost on most people's minds because, unfortunately, they are prone to interact with at least one med on someone's medication profile. You can see, voriconazole as an interacting drug that's being started by the emergency department. However, if we look closely at this patient's list, as Dr. Stone alluded to earlier, he's already on a drug in diltiazem that interacts at home.

BTKi Drug-Drug Interactions

Ibrutinib	Acalabrutinib	Zanubrutinib
Substrate: CYP3A4 (major), CYP2D6 (minor)	**Substrate**: CYP3A4 (major), P-gp/ABCB1 (minor)	**Substrate**: CYP3A4 (major)
Induces: N/A	**Induces**: N/A	**Induces**: CYP2C19 (weak), CYP3A4 (weak)
Strong inhibitor: 70 mg QD	**Strong inhibitor**: Avoid use	**Strong inhibitor**: 80 mg QD
Moderate inhibitor: 280 mg QD	**Moderate inhibitor**: 100 mg QD	**Moderate inhibitor**: 80 mg BID
Strong CYP3A4 inhibitors: Clarithromycin, telithromycin, itraconazole, posaconazole, voriconazole, protease inhibitors*		
Moderate CYP3A4 inhibitors: Amiodarone, erythromycin, fluconazole, isavuconazole, amprenavir, fosamprenavir, diltiazem, verapamil		

*amprenavir & fosamprenavir are moderate CYP3A4 inhibitors

With that, we'll go into some drug-drug interaction talks here. Notice that all of the BTK inhibitors are substrates of 3A4. We always need to take this into consideration when they're on either strong or moderate inhibitors because you'll see that there are dose adjustments that are recommended here. Whenever someone's on a strong or moderate 3A4 inhibitor, we need to consider what is the effect that this is going to have on the ibrutinib and the acalabrutinib and the zanubrutinib, and do we need to dose adjust accordingly? Now because it gets really tricky to manage drug-drug interactions in patients that may be on a lot of different medications, one strategy that we take is to have them keep a list of all of their medications from all of their different specialists and to bring that list with them to every appointment. That way, even though they're seeing different providers or even maybe using different pharmacies, we can keep track and catch anything quick. Even if an offending med is started perhaps by a different provider, we'll be quick to catch it and can either dose-adjust or recommend changing some of the other supportive therapy that the patient is on. But important to note, that for all of the oral oncolytics, but particularly with the BTK inhibitors, always think about drug-drug interactions whenever starting or stopping therapy. I say stopping therapy as well, because if you dose-adjust the BTK inhibitor when starting a drug like for voriconazole, when they stop that agent, you have to remember also to dose-adjust back up to a proper dose as well. I'll pass it back over to Dr. Vose.

Selecting BTKi Therapy: Considerations

- Pharmacokinetics/pharmacodynamics
  - Zanubrutinib has a longer plasma half-life
- Toxicity
  - Zanubrutinib and acalabrutinib have fewer AEs vs. ibrutinib (final phase 3 comparison data pending)
    - Lower risk for bleeding and atrial fibrillation
    - Less GI and dermatologic toxicity
  - However, there is more long-term safety data on ibrutinib
- Drug interactions
  - Zanubrutinib appears to have fewer drug-drug interactions vs. ibrutinib
- Medication adherence
  - Twice-daily vs. once-daily dosing schedules

Dr. Vose: Thanks. When selecting BTK inhibitors, there's a lot of different considerations. We've talked about many of those today, but pharmacokinetics and pharmacodynamics, zanubrutinib does have a longer plasma half-life in that, of course, it is a once-a-day dosing now. Toxicity, there's obviously lots of different toxicities that we've talked about. There's these phase 3 studies with final data pending, but some early data showing that maybe the later-generation BTK inhibitors do have potentially lower bleeding and the most recent data to show lower atrial fibrillation and possibly less GI and dermatologic toxicity, although obviously, the results are pending on the long-term outcome here. We need long-term safety data for all of these and ibrutinib of course has been around the longest, but we really need to look at that long-term data. Drug interactions, obviously we just talked about those and there's lots of them, so we have to keep that in mind and work with our pharmacists to help us with that. Medication adherence, even though to us maybe twice-a-day versus once-a-day dosing isn't a big deal, it is to a lot of the patients and that's something to discuss because if we give the patients a twice-a-day regimen and they're not going to take it, then it doesn't really help and so then you may want to think about the once-a-day dosing, so less to think about in any individual patient.

Panel Discussion

- How do we optimize collaborations with the multidisciplinary team to address AEs with BTK inhibitors?
- What are we going to do for patients who develop resistance?
- What is the mechanism of resistance for BTK inhibitors?
- Is there a point where we can stop treatment?

How do we optimize these considerations? Obviously, it's very important to use multidisciplinary teams to address a lot of these and we've talked about some of the ways to do that today. I think we have to take into consideration that there's lots of moving parts in these types of patients and to use a multidisciplinary team is very helpful with respect to all the different areas. We didn't talk very much about resistance and I don't know, Dr. Lamanna or Dr. Campbell, do you want to talk a little bit about resistance development and how do we look for that or how do we test for that and what do we do when that happens?

Dr. Lamanna: Yes, so obviously this is emerging data that's been coming out last couple of years for patients who have been on ibrutinib and obviously now acalabrutinib and zanubrutinib, so clearly patients can develop resistant mutations that you can test for. In our institution right now, currently is a test we send out for-- you could look for a BTK C481S mutation or a PLC-gamma mutation. Some of the patients may have no mutations, but they are progressing, so it's definitely something you can test for, but be aware that there are patients who may not have either and are still progressing. Now there's obviously--so switching to a different class, so when we talked about patients who develop adverse events, certainly you can try a second-generation because if they're having efficacy from the BTK inhibitor, you might want to continue them on a BTK inhibitor. However, patients who are developing a resistant mutation, oftentimes we're going to switch altogether. You might actually-- one--we talk about what can you switch them to? In CLL, there are PI3 kinase inhibitors. Remember, that's still part of the B-cell receptor pathway.

They may not have as big a bang for the buck by switching to another B-cell receptor pathway agent. Normally, we would consider switching to venetoclax, a BCL-2 inhibitor, in that case. Then clearly, there are some other BTK inhibitors that are being developed that are non-covalent BTK inhibitors. The closest is LOXO-305 or pirtobrutinib, that now has a name, based on some data that got presented at ASH recently showing that for patients who develop resistant mutations, that they're able to salvage those individuals. Even though the data presented was about up to 12 months, now it's certainly more mature. The response rate looked very good in these highly multiple treated relapsed/refractory patients, about overall response 60%. The longer patients are on drug, the responses seem to improve over time. Very young data, but it has efficacy both in CLL as well as other B-cell malignancies. We look forward to more data with non-covalent BTK inhibitors as well because that might be yet another agent that can salvage patients who have resistance.

Dr. Vose: All the clinical trials that we talked about today had ongoing therapy. There wasn't necessarily any trials yet like they are in CML, where we actually stop therapy. Is there a point where you think it could be safe to stop therapy in these patients?

Dr. Lamanna: That's a good one. Obviously, and we might be a little bit further along in CLL than mantle cell, Dr. Vose can comment about that. Certainly, there are trials looking at time-limited therapies for patients with CLL. Venetoclax and rituximab is an example of that or venetoclax and obinutuzumab is an example of that. There were presentations, again, at the recent meetings looking at ibrutinib plus venetoclax. Two dual all-oral therapies at time-limited with very good efficacy in patients, and so those were studies like CAPTIVATE and GLOW, and there are others. We're going to look forward to seeing that. I think in our high-risk individuals such as with 17p or p53 mutation, we have to see whether stopping therapy in a high-risk individual is okay. For those individuals, I still favor actually chronic BTK inhibition even over venetoclax, or I'm going to continue the venetoclax. I think we just need longer-term data on some of our high-risk individuals to see if a time-limited approach is okay for high risk. You're going to see a lot more emerging data on BTK plus BCL-2 inhibition, certainly in CLL.

Dr. Vose: I think in CLL it's a little bit easier as you alluded to. Mantle cell, they often don't have a real deep response. You're controlling the disease, but not necessarily having it in a deep mission. I think it's going to be more difficult to see clinical trials where we stop it in that disease. We'll see what happens in the future.

Summary Points

- BTKi's will likely play an increasing role in CLL and MCL
  - Ongoing studies will provide further clarification
- Toxicity remains a barrier to use
  - Monitor for cardiotoxicity, infection, major bleeding
    - Ensure recommended vaccination occurs
  - Mild arthralgia/myalgia, bruising should not affect dosing
- Clarification needed on strategies to manage toxicities
  - Dose reduction and/or dose interruption
- Be mindful of potential drug-drug interactions

Basically, in summary today, the Bruton's tyrosine kinase inhibitors obviously play a very important role in CLL and mantle cell. Looking at more and more studies with combinations or time-limited therapy, I think we'll continue to see these as we go on over the next several years really will be very important. Toxicity does, unfortunately, remain a barrier to use for some of our patients, cardiotoxicity, infection, bleeding issues. We need to think about the other kind of day-to-day things like bruising, arthralgias that may be sort of a nuisance, but still have an issue with quality of life for the patients. Working together as a team is really helpful to manage some of these toxicities with either dose reductions or modifications, or just manipulation of some of their other agents that they're on. Always be mindful of drug-drug interactions. I think that's one of the biggest things that we learned is we have to have an updated medication list, including all the over-the-counter medications patients are on, which they don't often think of as medications, to make sure that we're looking for all these drug-drug interactions.