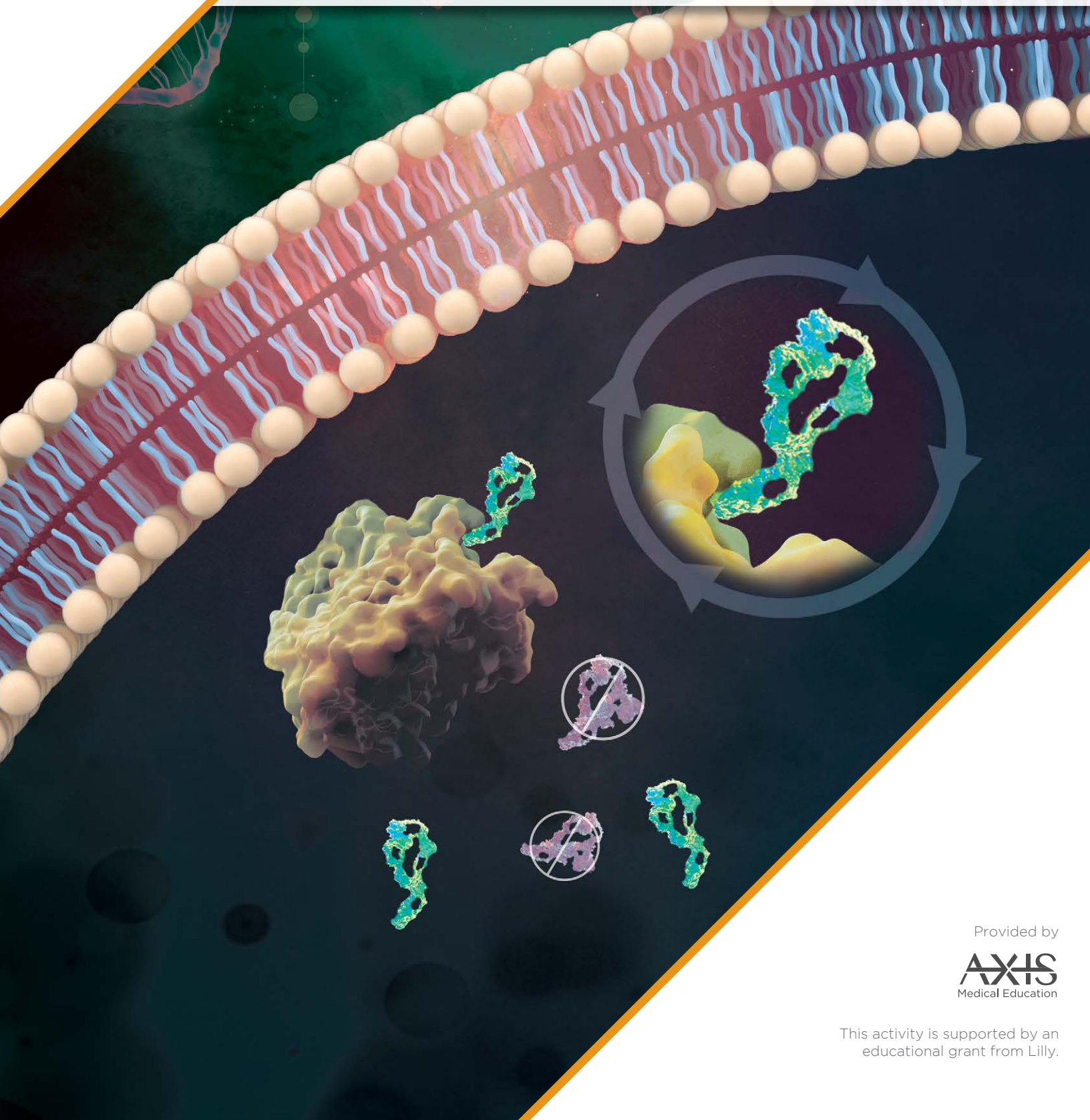
AXIS Medical Education

Practice-Changing Strategies in Community Care Settings for Patients with CLL/SLL and MCL

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



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AXIS Medical Education

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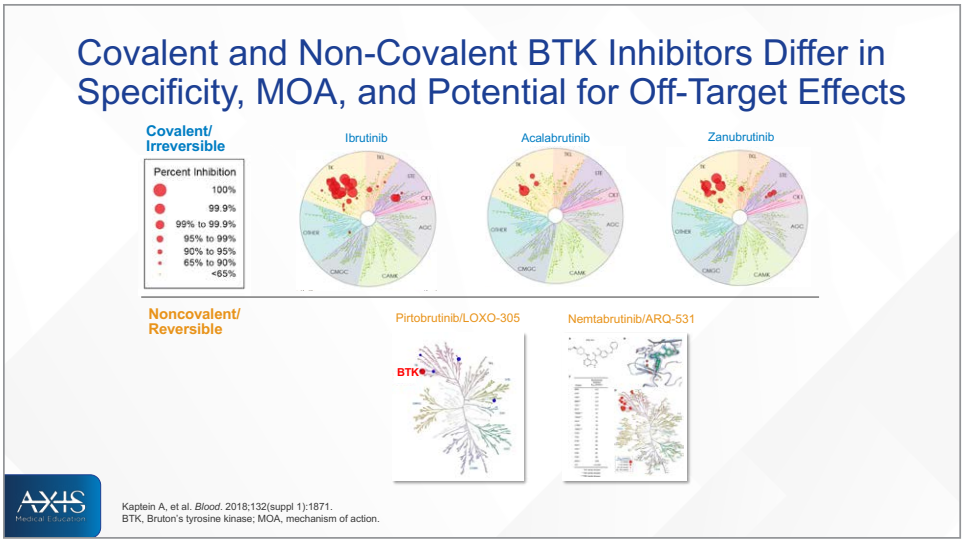
Practice-Changing Strategies in Community Care Settings for Patients with CLL/SLL and MCL

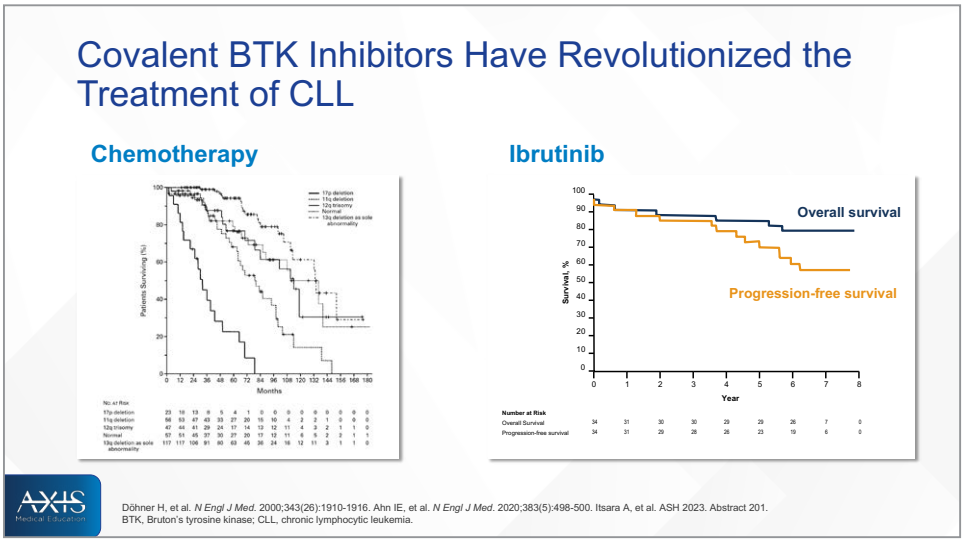
Matthew S. Davids, MD, MMSc

Dr. Davids: Hello and welcome to this educational activity.

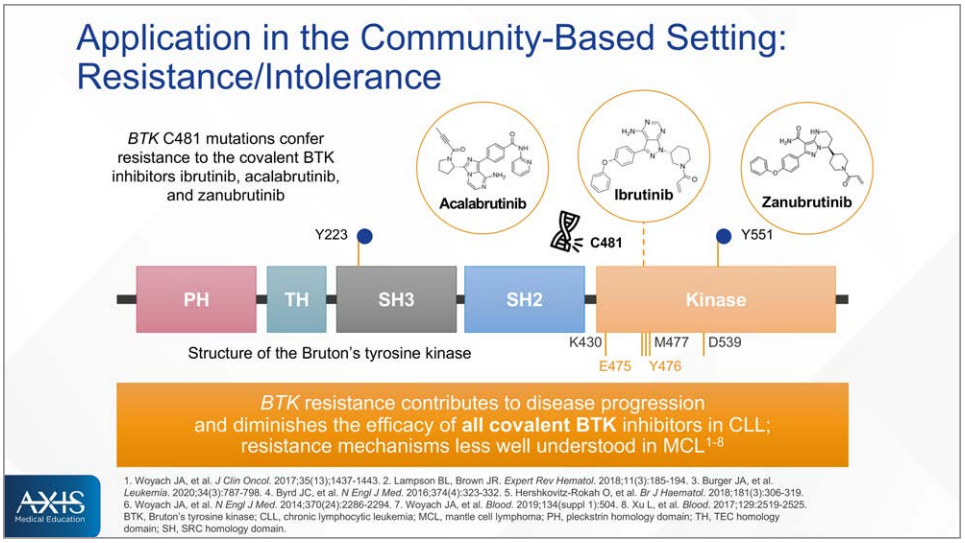
I'm Dr. Matthew Davids, Associate Professor of Medicine at Harvard Medical School, leader of the Lymphoma Program in the Dana-Farber Harvard Cancer Center, and Clinical Research Director in the Division of Lymphoma at Dana-Farber Cancer Institute in Boston. Today we'll be reviewing BTK inhibitors for the treatment of CLL, SLL and MCL. So, let's begin.



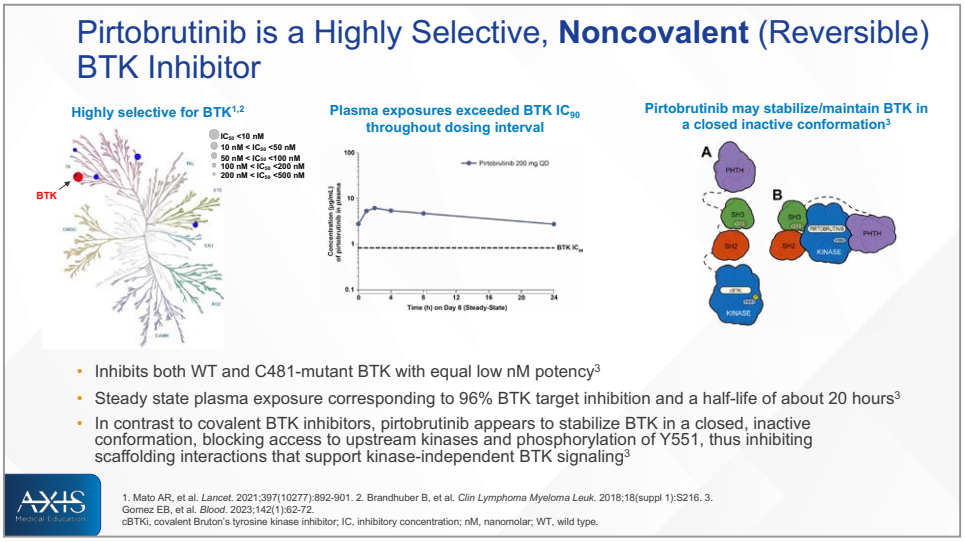
So, to start, I want to review the mechanisms and advantages that we see with BTK inhibitors. First, we're fortunate now to have a variety of covalent and noncovalent BTK inhibitors, and these kinome plots differ in terms of their specificity, mechanism of action and potential for off-target effects. The three approved covalent or irreversible BTK inhibitors, including ibrutinib, acalabrutinib and zanubrutinib. Ibrutinib has the most off-target effects, whereas acalabrutinib and zanubrutinib are more selective for BTK. There's also a new class of noncovalent, or reversible, BTK inhibitors, including pirtobrutinib and nemtabrutinib. Pirtobrutinib is particularly selective for BTK, and nemtabrutinib also is fairly selective, although it does have a few off-target effects.



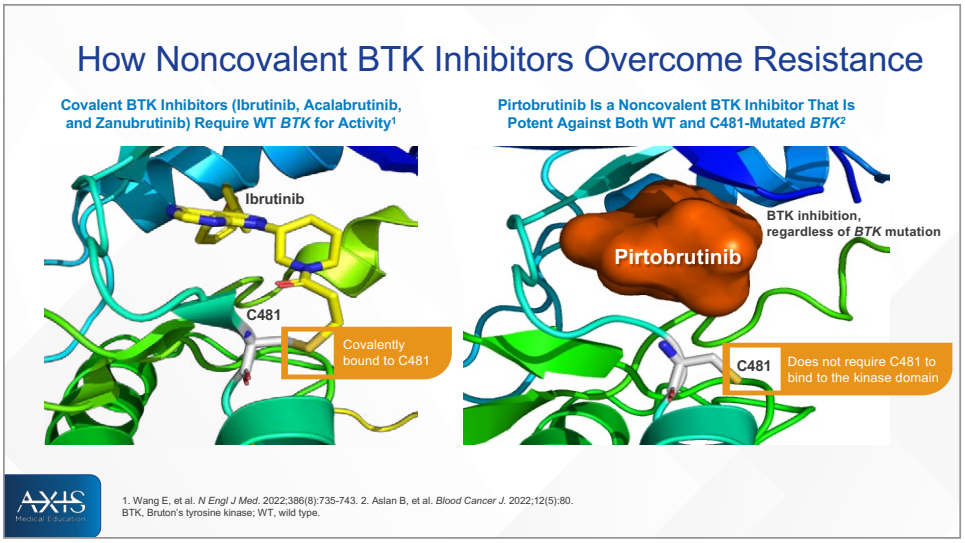
So, I think it's really important to understand that covalent BTK innovators really have revolutionized the treatment of CLL. One example of this is for patients with high-risk disease, defined by deletion 17p. On the left, you can see the historical results for those patients who are treated in an era of chemotherapy. And that dark line represents patients with deletion 17p where there was a median overall survival only in the range of about a year and a half to two years. On the right you can see longer term follow up from a single agent study of ibrutinib in patients with deletion 17p CLL, and the overall survival is still in the range of 80% with 6 years of follow up. So, really a dramatic improvement in the outcome for these high-risk patients, but also for patients even with lower genetic risk CLL.



Now, in the community setting, we've been using these drugs for several years now, particularly ibrutinib. And we've noticed that patients eventually will develop resistance in many cases. And most commonly, a mutation can arise in the BTK gene itself at the cysteine 481 (C481) position. When that mutation arises, it confers resistance to all three of these covalent BTK inhibitors. And we do think that these mutations contribute to disease progression and diminish the efficacy of all of these covalent BTK inhibitors in CLL. A variety of other mutations that have been described, primarily in the kinase domain. I'll note that the resistance mechanisms in mantle cell lymphoma are less well understood, currently.



So, a little bit more about pirtobrutinib. This is a highly selective, noncovalent or reversible BTK inhibitor. As I mentioned before, it's highly selective for BTK. The plasma exposures of pirtobrutinib have exceeded the IC_{90} for BTK inhibition throughout the dosing interval, and that's with daily dosing at 200 mg. Pirtobrutinib actually acts to stabilize or maintain BTK in a closed or inactive confirmation, allowing it to potentially overcome the C481 mutations. So, from a biochemical standpoint, pirtobrutinib can inhibit the wild-type and C481-mutant BTK at equal low nanomolar potency. The steady state plasma exposure corresponds to about 96% BTK target inhibition with a half-life of about 20 hours.



So, these are some of the unique features of pirtobrutinib, which allow it to be active even in the presence of resistance mutations to covalent inhibitors. Ibrutinib requires the C481 to covalently bind to BTK. Pirtobrutinib can inhibit BTK regardless of what's there at C481, it does not require this domain binding in order to inhibit the enzyme.

BTK Inhibitors Overview

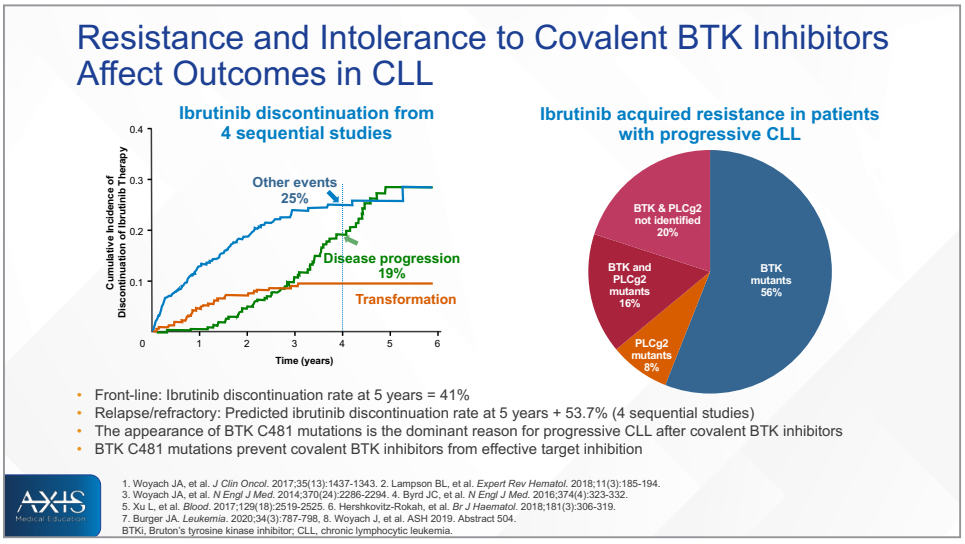
BTK Inhibitor	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib	Nemtabrutinib
Generation	First	Second	Second	Third	Third
FDA approval (Earliest FDA approval)	(2014) CLL/SLL, WM, cGVHD	(2018) CLL/SLL, R/R MCL	(2019) CLL/SLL, R/R MCL, WM, R/R MZL	(2023) R/R MCL after 2+ lines of tx including BTKi (2023) CLL/SLL after 2+ lines of tx including BTKi and BCL-2i	In clinical trials
Mechanism of action	Covalent	Covalent	Covalent	Noncovalent	Noncovalent
Dosing	420 mg daily	100 mg twice daily	160 mg twice daily or 320 mg daily	200 mg daily	65 mg daily (Phase II dosing)

IMBRUVICA® (ibrutinib). Prescribing information. Janssen Biotech; 2022. CALQUENCE® (acalabrutinib). Prescribing information. AstraZeneca Pharmaceuticals; 2022. BRUKINSA® (zanubrutinib). Prescribing information. BeiGene USA; 2023. JAYPIRCA (pirtobrutinib). Prescribing information. Eli Lilly; 2023. Montoya S, Thompson MC. *Cancers (Basel)*. 2023;15(14):3648. FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic
BCL-2, B-cell leukemia/lymphoma 2 protein; BTKi, Bruton's tyrosine kinase inhibitor; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; tx, treatment; WM, Waldenström's macroglobulinemia.

So, here's an overview of all five of the BTK inhibitors we've been discussing. So, the three covalent inhibitors, and then the two noncovalent inhibitors. They've been roughly, kind of, termed in terms of first generation with ibrutinib, second generation with acalabrutinib and zanubrutinib, and now third generation with pirtobrutinib and nemtabrutinib. The approvals of these drugs across different indications with ibrutinib going back all the way to 2014 with the initial indications in CLL/SLL, Waldenström's, and eventually, chronic graft versus host disease. Acalabrutinib, with indications in CLL and mantle cell lymphoma. And zanubrutinib, the most recent of the covalent inhibitors, with indications in CLL/SLL, mantle cell, Waldenström's, and relapsed/refractory marginal cell lymphoma. With pirtobrutinib the indications are much more recent. So, 2023 is the most recent, of these BTK inhibitors. An initial approval in relapsed/refractory mantle cell, and more recently, in terms of relapsed/refractory CLL. Nemtabrutinib is not yet approved but is currently in clinical trials. The dosing dose differ between these different drugs, and, in general, these drugs are given either once daily or twice daily, depending on their pharmacokinetic profiles.

Chairperson Perspectives

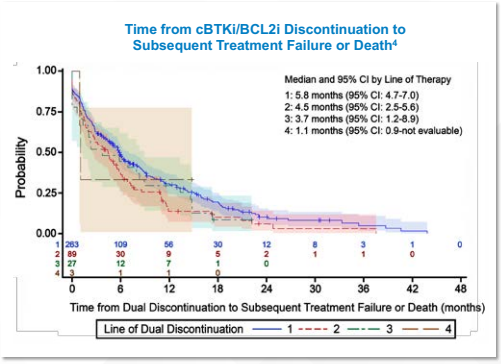
So, overall, in terms of my perspectives, very helpful to have all these different choices for BTK inhibitors that we can use in clinical practice, but I can see how it could also be a bit overwhelming, if you're seeing patients with many different types of cancer, to keep track of all these different BTK inhibitors. There are pros and cons to each. I would say probably most helpful to consider the class of covalent inhibitors, kind of separately from the noncovalent inhibitors. And as we'll see in the next section, there's clearly differences between these BTK inhibitors, and so, I think once you see some of the nuanced data, hopefully you'll understand a little bit more about how to implement these BTK inhibitors into your practice, and really to individualize them for your particular patients.



But let's dive a little bit more deeply now into the clinical efficacy and safety profiles of BTK inhibitors. First, in the early studies of ibrutinib, the most common reasons for discontinuation initially were other events including infection and atrial fibrillation and other adverse events. But as patients stayed on ibrutinib for longer, we see that disease progression and Richter's transformation can arise. And so, when we look in the frontline setting by 5 years, about 40% of patients will have discontinued ibrutinib. On the right, you can see the different acquired resistance mutations in patients progressing on ibrutinib, and the most common reason would be BTK mutations. But there's also mutations that can occur downstream of BTK in PLC gamma, which can provide further resistance to this therapy. In the relapsed/refractory setting, the discontinuation rates are even higher, closer to 54% of patients by 5 years. And again, the dominant reason for progression is the BTK C481 mutations.

Limited Therapeutic Options and Poor Outcomes After Covalent BTK Inhibitor Treatment Represent a Major Unmet Medical Need in CLL/SLL

- The vast majority of patients discontinue cBTKi for either progression or intolerance[1-3]
- Limited prospective data and treatment options in the post-cBTKi setting currently exist
- Venetoclax (BCL2i) based regimens have often been a next treatment option after cBTKi for patients with CLL/SLL
- An increasing number of patients who have discontinued cBTKi have also discontinued venetoclax
  - Outcomes are poor and there is a need for additional treatment options[4]

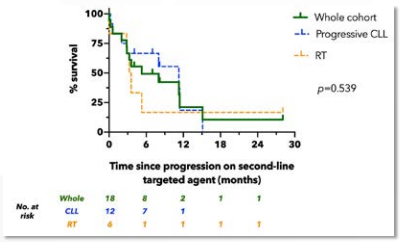


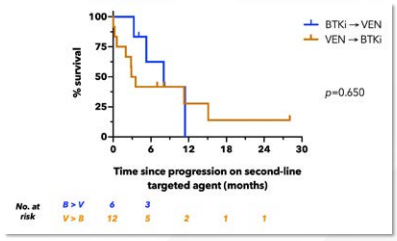
1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. 2. Barr PM, et al. *Blood Adv*. 2022;6(11):3440-3450.
3. Byrd JC, et al. ASH 2022. Abstract 4431. 4. Mato AR, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23(1):57-67.
BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

So, from the real-world setting, there are also some data to help us understand the outcomes for patients who progress after covalent BTK inhibitors. This really has become a growing unmet need in CLL or SLL. And we see that patients, who discontinue often have, a short progression-free survival, regardless of line of therapy from which they progressed. So, we also have a growing number of patients who have discontinued after both the covalent BTK inhibitors and venetoclax. And the outcomes for those patients are particularly poor, so-called double-refractory patients.

Outcomes for "Double Class Resistant" CLL Are Poor

2011 to 2020: 165 pts treated with Ven or BTKi → 42 double exposed → 18 double refractory

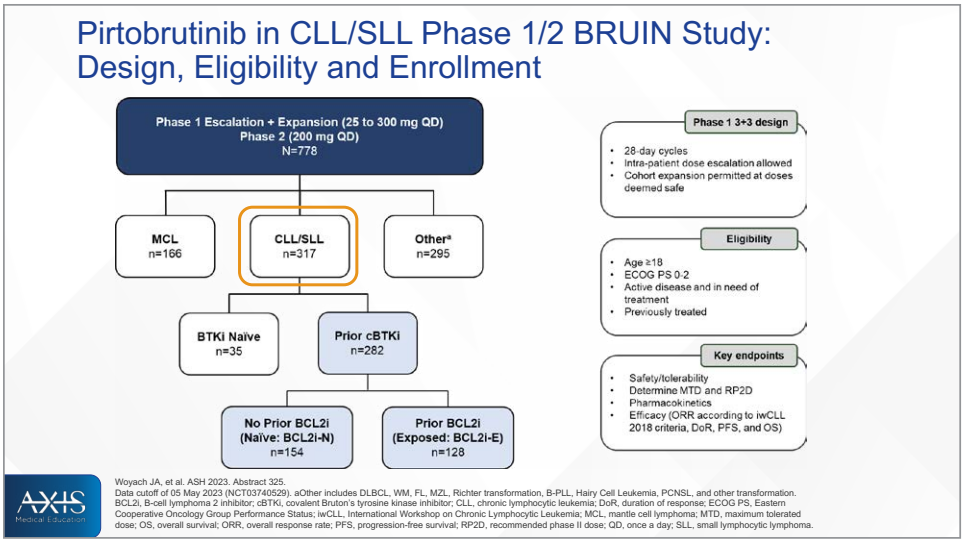




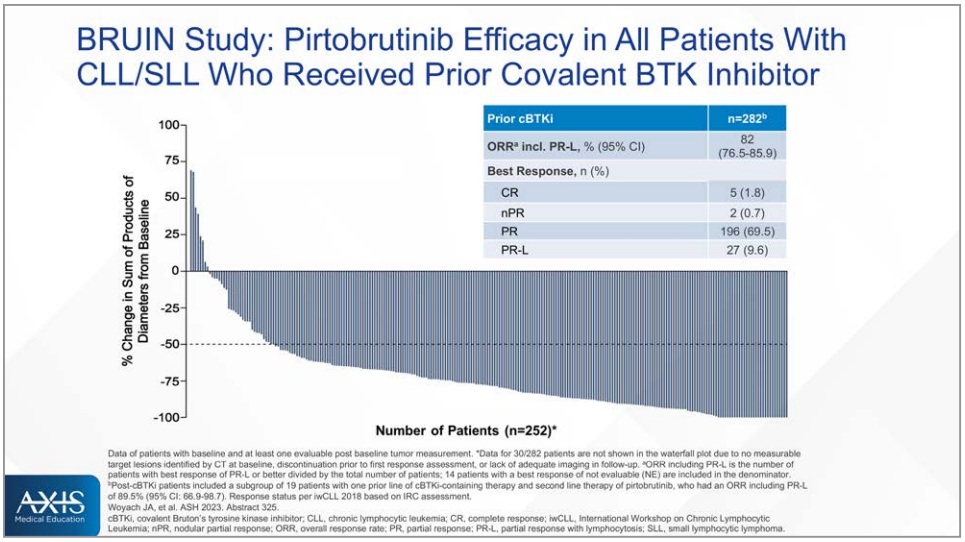
- Whole cohort median OS: 5.3 months
- No difference in OS between progressive CLL (11.3 months) and RT (3.4 months)
- No difference in OS between BTKi → VEN (8 months) and VEN → BTKi (3.2 months)

Lew TE, et al. *Blood Adv*. 2021;5(20):4054-4058.
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; OS, overall survival; RT, Richter transformation; VEN, venetoclax.

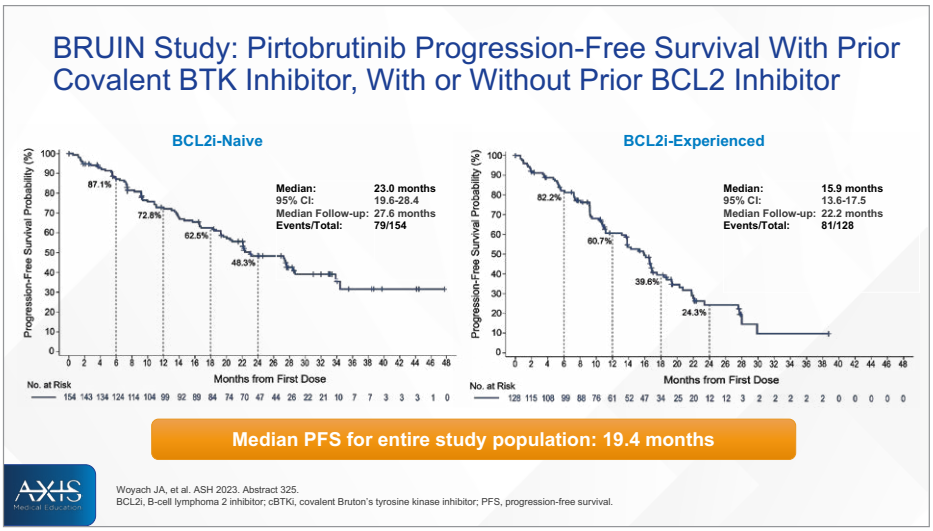
This is a study from the group in Australia looking over the past decade or so at their patients treated with venetoclax, or covalent BTK inhibitor. Forty-two of them were exposed to both drugs, and 18 patients were considered truly double-refractory to both mechanisms. So, for the whole cohort of these patients, the median overall survival was only just over 5 months and there was no difference between whether patients progressed with CLL or Richter's transformation. It didn't matter whether patients had gone from a BTK inhibitor to venetoclax or vice versa. In both scenarios the survival subsequently was quite short.



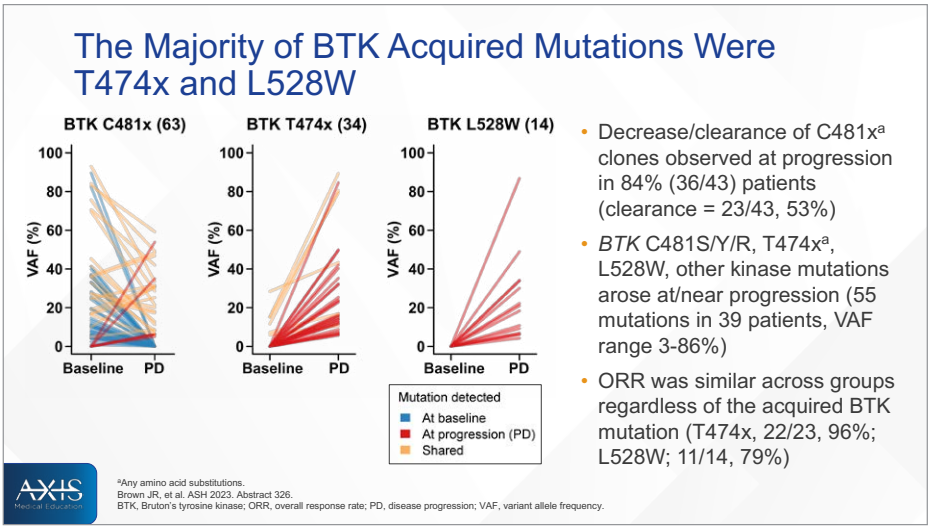
- So, this is really where pirtobrutinib has made the biggest difference from the Phase 1/2 BRUIN study. We can see the 317 patients with CLL and SLL, and of those, about 282 had prior treatment with a covalent BTK inhibitor.



- In the updated data set that was presented at the ASH meeting in 2023, the waterfall plot for lymph node decrease was quite impressive. So, most patients had a significant reduction in their lymphadenopathy, and the overall response rate was 82% for single-agent pirtobrutinib in this relapsed setting.



- The durability was particularly good for patients who had not previously had a BCL2 inhibitor, so-called BCL2i-naïve, where the median PFS was just under 2 years. In BCL2i-experienced patients, it was a bit shorter of a PFS at about 16 months. And the median PFS for the entire study population was about 19 months.



- One of the interesting aspects of this BRUIN study is that they were able to track the resistance mutations in real time in these patients on the study. And one of the things that was predicted with pirtobrutinib, and now has borne out in terms of the data, is that from baseline to time of progressive disease, a decrease in the fraction of mutations in the BTK C481. So, this is what we would have predicted because we know that pirtobrutinib is active in the setting of that mutation. However, comparing baseline to time of progression on pirtobrutinib, we see rising of the T474 and L528W mutations. So, these are actually mutations that seem to confer resistance to pirtobrutinib and are now posing a new challenge that we must face in terms of figuring out ways to overcome that.

Pirtobrutinib FDA Approval in CLL/SLL

- December 2023: the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor
- BRUIN Trial (NCT03740529)
  - ORR: 72%
  - Median DoR: 12.2 months
- ASH 2023 updated data:
  - Prior BTK inhibitor (n=282)
    - > ORR: 81.6%
    - > mPFS: 19.4 months
  - Prior covalent BTK inhibitor and BCL-2 inhibitor (n=128)
    - > ORR: 79.7%
    - > mPFS: 15.9 months

FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic. Woyach JA, et al. ASH 2023. Abstract 325.
BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; mPFS, median progression-free survival; ORR, overall response rate; SLL, small lymphocytic lymphoma.

So, with regard to pirtobrutinib's approval in CLL and SLL, this is pretty recent, just December of 2023. The label is for patients who have had at least 2 prior lines of therapy, including a covalent BTK inhibitor and a BCL2 inhibitor. And again, this was based largely on the BRUIN trial that we just reviewed, where the updated data suggested close to 82% of patients responding with a median of about a year and a half or a little bit longer in terms of progression-free survival.

BELLWAVE-001: Nemtabrutinib Demonstrated Robust and Durable Clinical Responses in Pretreated CLL[1,2]

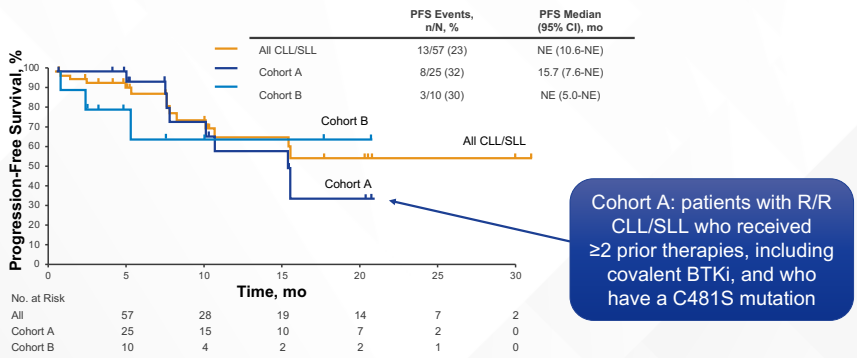
Nemtabrutinib: Noncovalent, Reversible Inhibitor of Both WT and Ibrutinib-Resistant C481S-Mutated *BTK*

n (%) [95% CI]	CLL/SLL 65 mg QD n = 57	CLL/SLL Cohort A[a] n = 25	CLL/SLL Cohort B[b] n = 10
ORR	**30 (53) [39-66]**	**15 (60) [39-79]**	**4 (40) [12-74]**
CR	2 (4) [0.4-12]	0 (0) [0-14]	1 (10) [0.3-45]
PR	15 (25) [15-40]	5 (20) [7-41]	2 (20) [3-56]
PR-L	13 (23) [13-36]	10 (40) [21-61]	1 (10) [0.3-45]
SD	17 (30) [18-43]	8 (32) [15-54]	3 (30) [7-65]
PD	2 (4) [0.4-12]	0 (0) [0-14]	2 (20) [3-56]
No assessment	8 (14) [6-26]	2 (8) [1-26]	1 (10) [0.3-45]

[a]Cohort A comprises patients with mCLL/SLL who received ≥2 prior therapies, including covalent BTKi and who have C481S mutation.
[b]Cohort B comprises patients with mCLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and who have no C481S mutation.
1. Woyach J, et al. EHA 2022. Abstract P682. 2. ClinicalTrials.gov identifier: NCT03162536.
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; PD, disease progression; QD, once daily; SLL, small lymphocytic lymphoma; WT, wild type.

So, pirtobrutinib is not the only noncovalent BTK inhibitor being explored in CLL and SLL. The other is nemtabrutinib. And this was explored in the BELLWAVE-001 trial, which really did demonstrate robust and durable clinical responses in patients with relapsed/refractory CLL. With about 57 patients treated at the recommended Phase 2 dose of 65 milligrams, the overall response rate is in the range of about 53%, including in patients who had, mutation in C481S, as well as patients who did not.

BELLWAVE-001: Nemtabrutinib Is Effective Against *BTK* Resistance Mutations[1]



No. at Risk

All	57	28	19	14	7	2
Cohort A	25	15	10	7	2	0
Cohort B	10	4	2	2	1	0

Cohort A: patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have a C481S mutation

1. Woyach J, et al. EHA 2022. Abstract P682.
BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; NE, not evaluable; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

- The progression-free survival for nemtabrutinib in these different cohorts. Cohort A is patients who had a covalent, BTK inhibitor and who have a C481S resistance mutation. Cohort B, these patients did not have a resistance mutation. The PFS looks similar between these two groups. With the median PFS actually not reached yet at the time of this evaluation.

Ongoing Phase 3 Trials With Noncovalent BTK Inhibitors in CLL

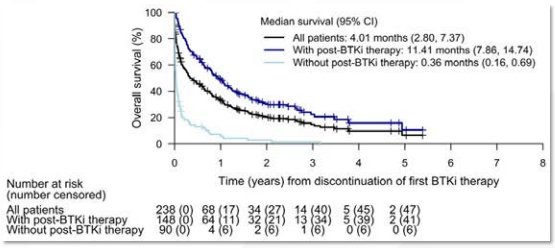
Noncovalent BTKi	Phase 3 Trial	Study Arms	Population
Pirtobrutinib	BRUIN CLL-321 (NCT04666038)	pirtobrutinib vs idelalisib + R or BR	Prior BTKi required
	BRUIN CLL-322 (NCT04965493)	pirtobrutinib + venetoclax + R vs venetoclax + R	Prior BTKi allowed
	BRUIN CLL-313 (NCT05023980)	pirtobrutinib vs BR	Treatment-naive patients
	BRUIN CLL-314 (NCT05254743)	pirtobrutinib vs ibrutinib	BTKi-naive patients
Nemtabrutinib	BELLWAVE-008 (NCT05624554)	nemtabrutinib vs FCR or BR	Previously untreated CLL; no TP53 mutation/del(17p)
	BELLWAVE-010 (NCT05947851)	nemtabrutinib + venetoclax vs venetoclax + R	Following at least 1 prior therapy

BR, bendamustine, rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, rituximab; R, rituximab.

- So, there's a number of ongoing Phase 3 trials with these noncovalent BTK inhibitors in CLL. Several with pirtobrutinib, including relapsed/refractory studies, where pirtobrutinib is being compared to a PI3-kinase inhibitor, idelalisib, with rituximab or bendamustine and rituximab, a separate study where pirtobrutinib was being combined with venetoclax and rituximab and being compared to venetoclax and rituximab alone. Then, frontline studies of pirtobrutinib versus bendamustine and rituximab and pirtobrutinib versus ibrutinib. With nemtabrutinib, there's also a frontline study comparing to chemoimmunotherapy, and then there's a relapsed/refractory study of nemtabrutinib with venetoclax compared to rituximab with venetoclax.

Covalent BTK Inhibitor Resistance is Common and Not Well Understood in MCL

- Most patients will ultimately experience disease progression
- Post-progression outcomes historically poor (OS <1 year)
- Mechanisms less well understood compared to CLL
- Options:
  - Noncovalent BTKi
  - CAR T
  - Trials



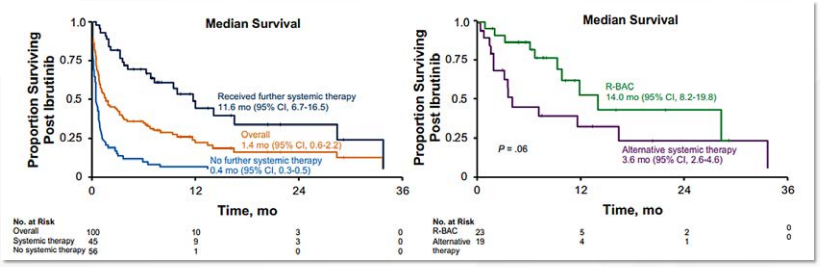
Hess, G et al. *Br J Haematol.* 2023;202(4):749-759.
CAR T, chimeric antigen receptor T-cell therapy; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; OS, overall survival.

So, as I mentioned before, covalent BTK inhibitor resistance is common, but also not very well understood in mantle cell lymphoma. The majority of patients with mantle cell lymphoma will progress on their covalent BTK inhibitor, and usually within a much shorter time-frame than what we were just describing for patients with CLL. On the right, you can see that time-frame reflected, in terms of a short overall survival for all patients who progress after BTK inhibitors, and particularly in mantle cell, I think the options are much more limited for these patients as compared to CLL. We do have the noncovalent BTK inhibitor, pirtobrutinib, that we'll see data for. Also, CAR T-cells or clinical trials.

In MCL, Real-World Data Confirm That Outcomes Are Poor After Progression on Covalent BTK Inhibitor Therapy

- Post-ibrutinib OS for patients progressing on ibrutinib and receiving additional treatment versus no further treatment

- Progression on BTKi likely involves therapeutic resistance
- **Overall post-ibrutinib OS was 1.4 months**
- 0.4 months for patients receiving no further therapy

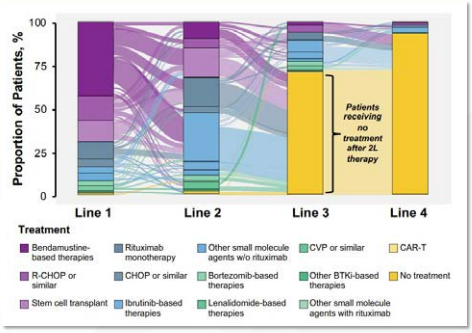


McCulloch R, et al. *Br J Haematol.* 2021;193:290-298.
BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma; OS, overall survival; R-BAC, rituximab, bendamustine, cytarabine.

So, these are some real-world data in mantle cell lymphoma suggesting, again, that outcomes are poor after progression on covalent BTK inhibitor. Patients who received additional therapy did do better. The median survival there was closer to a year, whereas patients who were not able to even receive additional therapy had a very short survival of just 0.4 months. Overall, in the post-pirtobrutinib setting, the survival in this real-world series was just 1.4 months, and patients who were able to move on to R-BAC chemotherapy did have a longer survival. But again, this is retrospective real-world data. So, it's more likely that the fitter patients were able to get chemoimmunotherapy, and so that, I think, is one of the confounding aspects of this analysis.

Although BTK Inhibitors Are a Step Forward in MCL, More Needs to Be Done in Later-Line Care

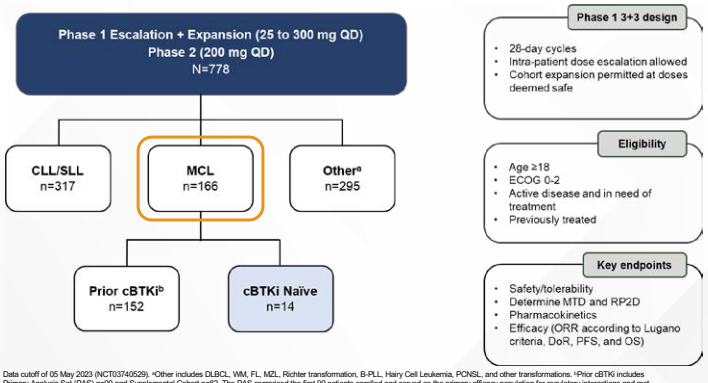
- Based on retrospective claims data from the United States between 2015 and 2021 (N = 696)
- Majority of patients received no treatment in the 3L setting
- Data demonstrate clear unmet needs for 3L care in MCL



Garg M, et al. ASH 2022. Abstract 3534.
2L, second-line; 3L, third-line; BTK, Bruton's tyrosine kinase; CVP, cyclophosphamide, vincristine, prednisone; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CAR-T, chimeric antigen receptor T-cell therapy.

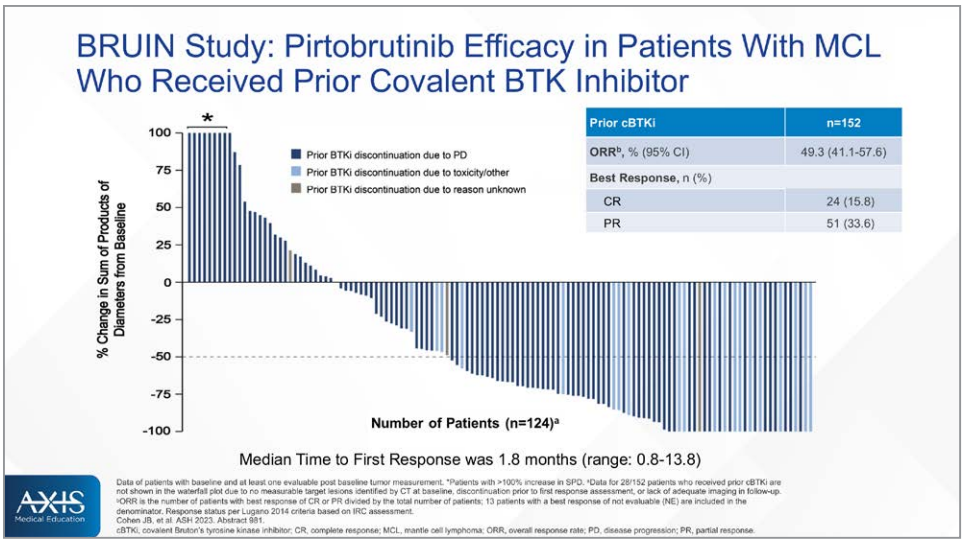
So, in mantle cell lymphoma, I would say, although the BTK inhibitors are a step forward, we certainly need more options in later lines of care. Some more retrospective claims data from the US from 2015 to 2021 shows in these, about, 700 patients or so that the majority of mantle cell patients actually did not receive any treatment in the third-line setting, and that's often because they were so sick. After second-line setting, many of these patients moved on to hospice, for example. Where in the frontline setting majority patients are getting bendamustine-based chemotherapy. In the second-line setting, small-molecule agents like BTK inhibitors become more commonly used. And then patients not getting any additional therapy. So, it really does speak to the need for better therapies in the later lines of therapy for mantle cell lymphoma.

Pirtobrutinib in MCL Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment

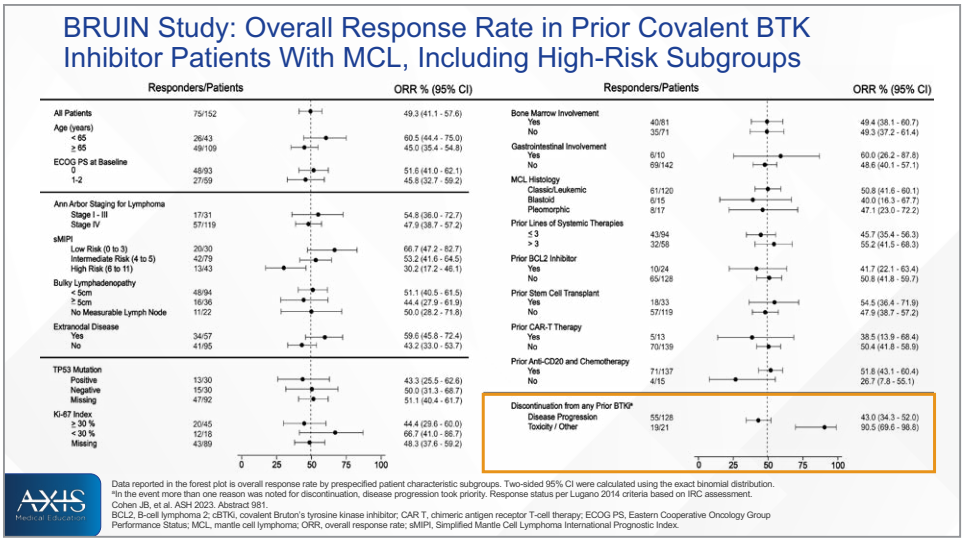


Data cutoff of 05 May 2023 (NCT03740529). [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformations. [b]Prior cBTKi includes Primary Analysis Set (PAS) n=80 and Supplemental Cohort n=62. The PAS comprised the first 90 patients enrolled and served as the primary efficacy population for regulatory interactions and met the following criteria:; had measurable disease, had received a prior cBTKi containing regimen, had no known central nervous system involvement. Updated data from the PAS90 population can be found in supplemental via QR code.
Cohen JB, et al. ASH 2023. Abstract 981.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once a day; RP2D, recommended phase II dose; SLL, small lymphocytic lymphoma.

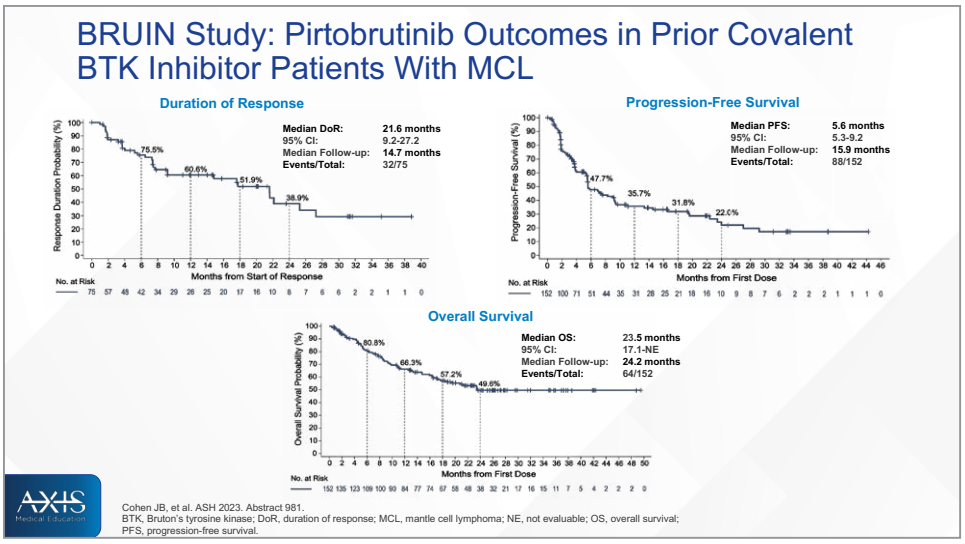
So, the BRUIN study of pirtobrutinib also included a cohort of 166 patients with relapsed/refractory mantle cell lymphoma, and we'll review those data now.



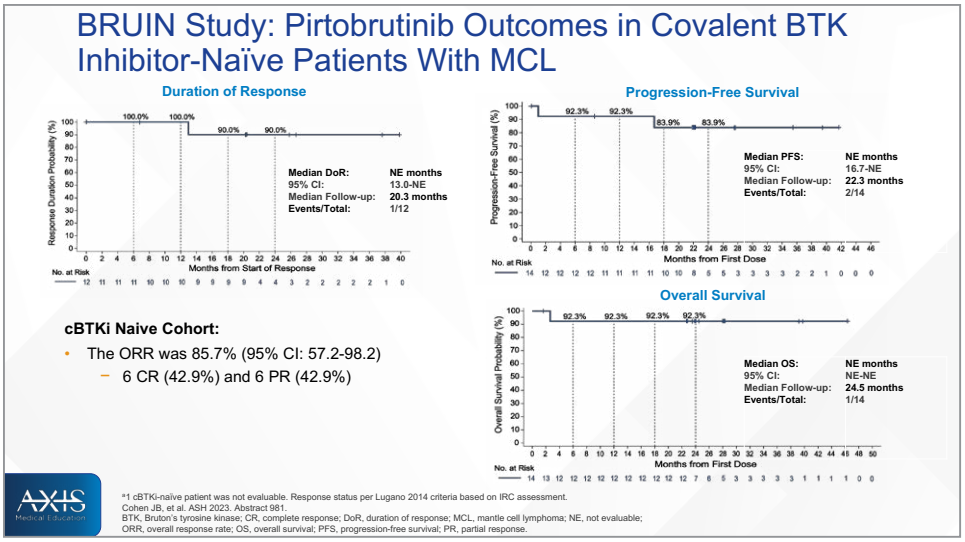
- The waterfall plot looking at lymph node decrease with the different colors here representing patients who discontinued their prior BTK inhibitor due to progressive disease, versus patients who discontinued the prior BTK inhibitor due to toxicity. And regardless of reason for discontinuation, the majority of patients did have a decrease in lymph node size, and the overall response rate was close to 50% in this very difficult-to-treat population.



- Here, you can see in these forest plots the different factors that may have influenced overall response rate in mantle cell lymphoma. Whether looking at various genetic subgroups, clinical characteristics, or histology, in general, there wasn't one particular group that benefited more than another. Really pirtobrutinib was quite active across all the different groups. The one factor I think that did seem to have significance, patients who had previously discontinued a BTK inhibitor due to toxicity, seemed to have an even higher overall response rate at close to 90% compared to those patients who had progressed on their prior covalent BTK inhibitor, where the response rate was more in the range of 43%.



- With regard to durability, if patients do respond, these responses can be durable. And so, you see the duration of response median is about 21.6 months. However, many patients don't respond and as such, the median progression-free survival is a relatively short 5.6 months. That being said, I think the overall survival is promising with a median of about 2 years. It suggests that patients who do respond probably can be bridged to other types of therapy, for example, cellular therapies like CAR T-cells or even allogeneic transplantation.



- There was a smaller group of patients in the BRUIN study with mantle cell lymphoma who were covalent BTK inhibitor-naive. And you can see the results look much better for this group. The overall response rate is about 86%, including 43% complete remissions, and duration of response, progression-free survival, and overall survival are all quite high, suggesting that this is a drug that could be potentially moved up into an earlier line of therapy, maybe even before covalent BTK inhibitors, in mantle cell lymphoma.

Pirtobrutinib FDA Approval in MCL

- January 2023: the Food and Drug Administration granted accelerated approval to pirtobrutinib for relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor
- BRUIN Trial (NCT03740529)
  - ORR: 50%
    - > CR: 13%
  - DOR: 8.3 months
- ASH 2023 updated data:
  - Prior covalent BTK inhibitor (n=152)
  - ORR of 49.3%
    - > CR: 15.8%
    - > PR: 33.6%
  - Median DoR: 21.6 months
  - Median PFS: 5.6 months
  - Median OS: 23.5 months

FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma. Cohen JB, et al. ASH 2023. Abstract 981.
ASH, American Society of Hematology; BTK, Bruton's tyrosine kinase; CR, complete response; DoR, duration of response; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

So, the original approval for pirtobrutinib was in mantle cell lymphoma back in January of 2023. This is, a label that's an accelerated approval for relapsed or refractory mantle cell after at least 2 lines of systemic therapy, including a BTK inhibitor.

Ongoing Phase 3 Trials With Noncovalent BTK Inhibitors in MCL

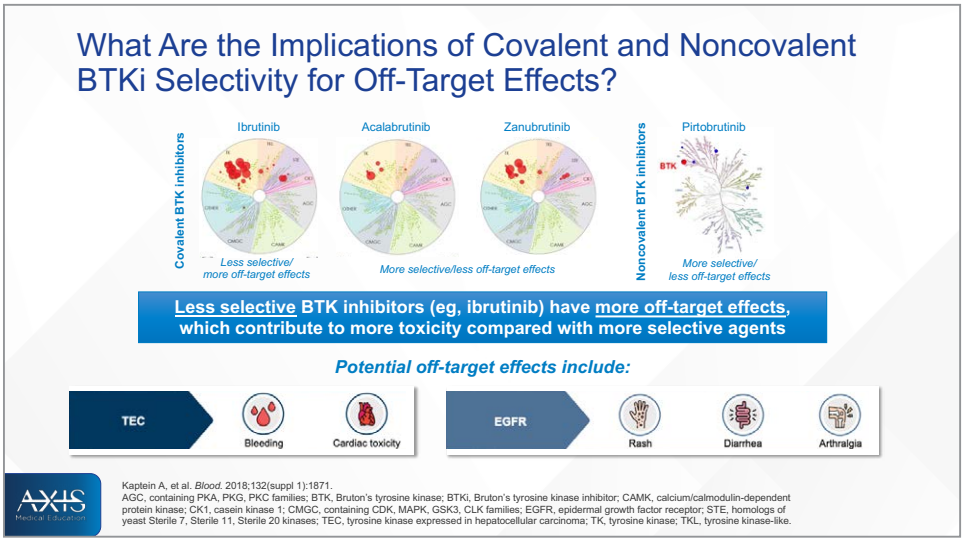
Noncovalent BTKi	Phase 3 Trial	Study Arms	Population
Pirtobrutinib	BRUIN MCL-321 (NCT04662255)	pirtobrutinib vs investigator's choice of BTKi (ibrutinib, acalabrutinib, or zanubrutinib)	Previously treated and BTKi-naïve

Wang M, et al. *J Clin Oncol.* 2023;41(16_suppl):TPS7587.
BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma.

So, with regard to ongoing Phase 3 trials with the noncovalent BTK inhibitors in mantle cell, right now, it's mainly this one trial, which is the BRUIN MCL-321 trial. This is pirtobrutinib versus investigator's choice of other covalent BTK inhibitor, and it could be ibrutinib, acalabrutinib, or zanubrutinib. And this is looking primarily at a previously treated population, but does also include BTK inhibitor-naive patients.

Chairperson Perspectives

So, kind of summarizing my perspectives from that section, I would say that it's definitely been a major advance to have pirtobrutinib approved now for CLL and mantle cell lymphoma. Certainly, something I'm using commonly in my own clinical practice. The data right now for using pirtobrutinib in early lines of therapy is pretty sparse, so I certainly am not using pirtobrutinib as a frontline treatment in either of these diseases. I would use it in patients who have progressed on a covalent BTK inhibitor. I think an interesting question is whether to use pirtobrutinib or venetoclax in that post covalent BTK inhibitor population. Technically, pirtobrutinib is only approved in CLL, for example, in the double-exposed population. So, if you want to follow the FDA label, you give covalent BTK inhibitor and then venetoclax, and then pirtobrutinib. But that being said, actually, in the NCCN guidelines now, pirtobrutinib does appear as an option for second-line therapy. And there is also some appeal for patients, maybe, who like the idea of being on a continuous treatment and have tolerated it well. If they start to progress on their covalent BTK inhibitor, rather than switching to venetoclax, to switch to a different BTK inhibitor with pirtobrutinib, and potentially extend that response for longer.



All right. So, let's talk now in a little more detail about management strategies for adverse events on BTK inhibitors. When we see these kinome plots, really one of the things that comes to mind is whether the off-target effects may be related to some of the different toxicities that are observed. In theory, because ibrutinib has a number of different off-target effects, we would say that it is more likely to have effects on, other kinases that could lead to different toxicities, compared to the more selective agents, where if we're only targeting BTK and not targeting other kinases as much, maybe we'll see less toxicities. And so, some of these theoretical risks, which we've seen now, bear out in practice include, targeting TEC kinase, which we think is related to the leading risks of BTK inhibitors, as well as possibly the cardiovascular toxicities we observe. One of the off-target effects of ibrutinib is actually to target EGFR. We think this may be related to the increased incidence of rash, diarrhea, and arthralgia that we see with this drug.

BRUIN Trial: Pirtobrutinib Safety Profile of CLL Patients Who Received Prior Covalent BTK Inhibitor

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥25%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation
Safety profiles of BCL2i-N and BCL2i-E subgroups were similar

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3. [c]Aggregate of neutropenia and neutrophil count decreased. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.
Woyach JA, et al. ASH 2023. Abstract 325.
AE, adverse event; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; N, naive; E, experienced.

- So, in the BRUIN trial, they looked in detail at the safety profile of pirtobrutinib in CLL patients, and these were the patients, again, who had received prior covalent BTK inhibitors, and then came on this study of pirtobrutinib. In general, this drug is very well-tolerated. Very few grade 3 or higher events, just some neutropenia in about 15% of patients, primarily, and some infections, but the rates of other issues that we see with BTK inhibitors, like bleeding risks, AFib/flutter, hypertension, are quite low with pirtobrutinib. And this was with a reasonable amount of time on therapy. Median time on treatment here was about 18 months, and so overall the safety profile looks quite favorable for this drug.

BRUIN Trial: Pirtobrutinib Safety Profile in R/R MCL Patients

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Thrombocytopenia	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

Median time on treatment was 5.5 months for the MCL cohort
Discontinuations due to TRAEs occurred in 3% (n=5) of patients with MCL
Dose reductions due to TRAEs occurred in 5% (n=8) of patients with MCL

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of all preferred terms including infection and COVID-19. [c]Aggregate of contusion, bone contusion, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hemorrhage or hematoma. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, treatment-related AEs leading to discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).
Cohen JB, et al. ASH 2023. Abstract 981.
AE, adverse event; MCL, mantle cell lymphoma; R/R, relapsed/refractory; TRAE, treatment-related adverse event.

- Similarly, in mantle cell lymphoma, we again see very low rates of treatment-related grade 3 or higher AEs. You do see some lower-grade diarrhea in about 13% of patients. You see infections and bruising in about 11% of patients. Median time on treatment here was a lot shorter in the mantle cell cohort, about 5 1/2 months, but that's mostly because patients were discontinuing due to disease progression rather than discontinuing due to AEs.

Pirtobrutinib Adverse Event Summary

Infections	Monitor for signs and symptoms of infection, evaluate promptly, and treat appropriately
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
	Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections
Hemorrhage	Monitor for bleeding and manage appropriately
	Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue
Cytopenias	Monitor complete blood counts during treatment
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
Cardiac Arrhythmias	Monitor for symptoms of arrhythmias (eg, palpitations, dizziness, syncope, dyspnea) and manage appropriately
	Based on severity, reduce dose, temporarily withhold, or permanently discontinue
Second Primary Malignancies	Monitor and advise patients to use sun protection
Embryo-Fetal Toxicity	Advise females of potential risk to a fetus and recommend use of effective contraception
Most common adverse reactions (≥20%)	Fatigue, musculoskeletal pain, diarrhea, COVID-19, bruising, and cough
Grade 3 or 4 laboratory abnormalities (≥10%)	Neutropenia, thrombocytopenia, anemia, and lymphopenia

AXIS Medical Education

JAYPIRCA (pirtobrutinib). Prescribing information. Eli Lilly and Company; 2023.

So, kind of summarizing the adverse events for pirtobrutinib, certainly in any of these B cell malignancies like CLL or mantle cell lymphoma, we worry about infections. We have to monitor closely for these and consider prophylaxis, including vaccinations and antimicrobial prophylaxis, for patients that increase risk. Hemorrhage is not common with pirtobrutinib, but minor bleeding issues like bruising can be seen. We do sometimes see cytopenias that require us to more closely monitor the CBC and occasionally provide growth factor support. We have not commonly seen cardiac arrhythmias on pirtobrutinib, but given that it is a BTK inhibitor it is something that we watch for. Our patients, particularly with CLL are at a higher risk of secondary primary malignancies. So, we need to be mindful of that, particularly sun protection is important in these patients. There is some potential for embryo fetal toxicity, so certainly patients need to be on effective contraception if they're using these drugs. And then you see in terms of the most common adverse reactions, fatigue, very common in this population, musculoskeletal pain, diarrhea, COVID infections, bruising and cough. In terms of grade 3 or 4 lab abnormalities, the most common is actually probably neutropenia, but you can see thrombocytopenia or anemia.

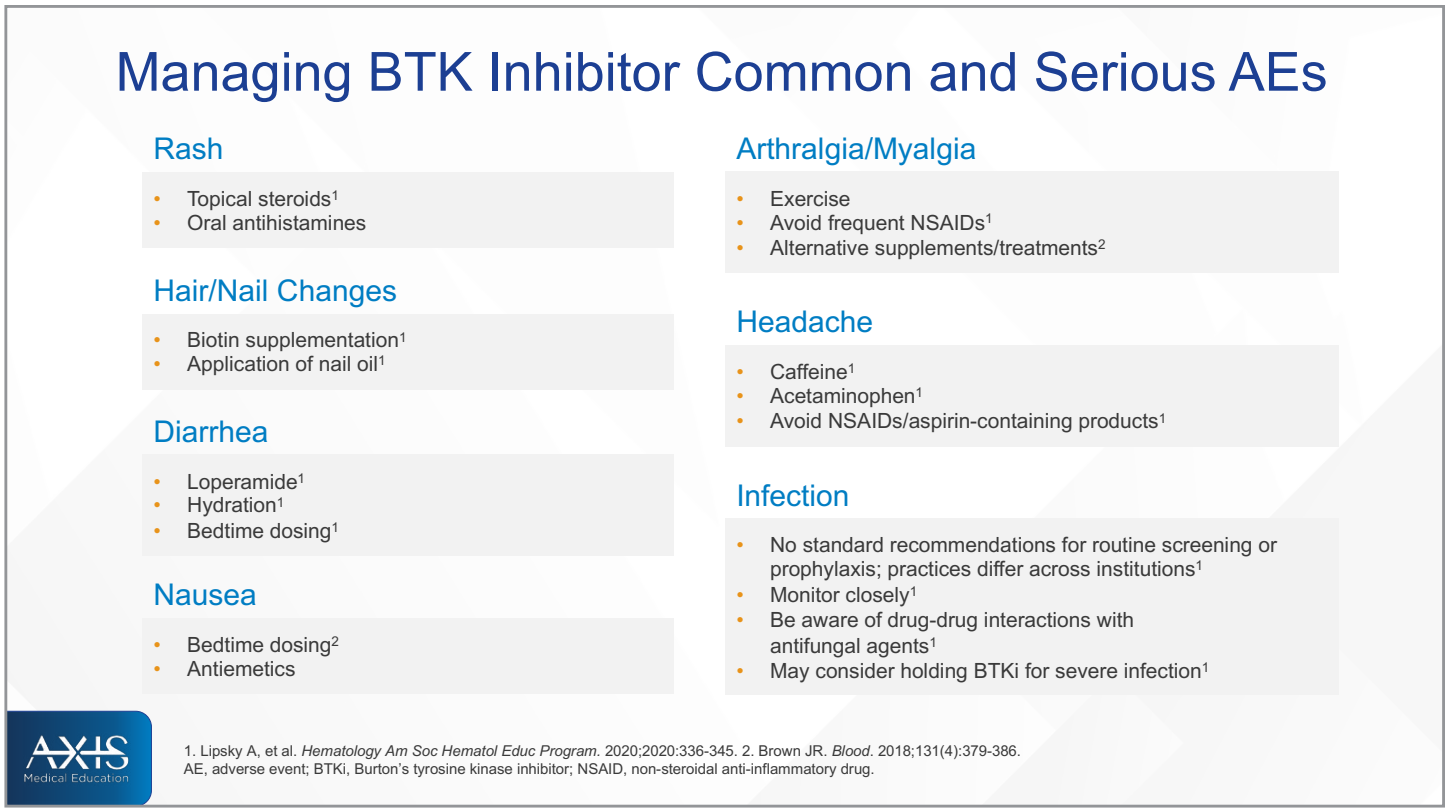
BELLWAVE-001 Trial: Nemtabrutinib Safety Profile

Treatment-related Adverse Events, n (%)	All Patients at 65 mg QD N=112	
	All	Grade ≥3
Any treatment-related AEs	82 (73)	45 (40)
Treatment-related AEs ≥ 5%		
Dysgeusia	23 (21)	0 (0)
Neutropenia	22 (20)	19 (17)
Fatigue	14 (13)	2 (2)
Thrombocytopenia	13 (12)	5 (4)
Nausea	13 (12)	0 (0)
Hypertension	11 (10)	4 (4)
Diarrhea	11 (10)	2 (2)

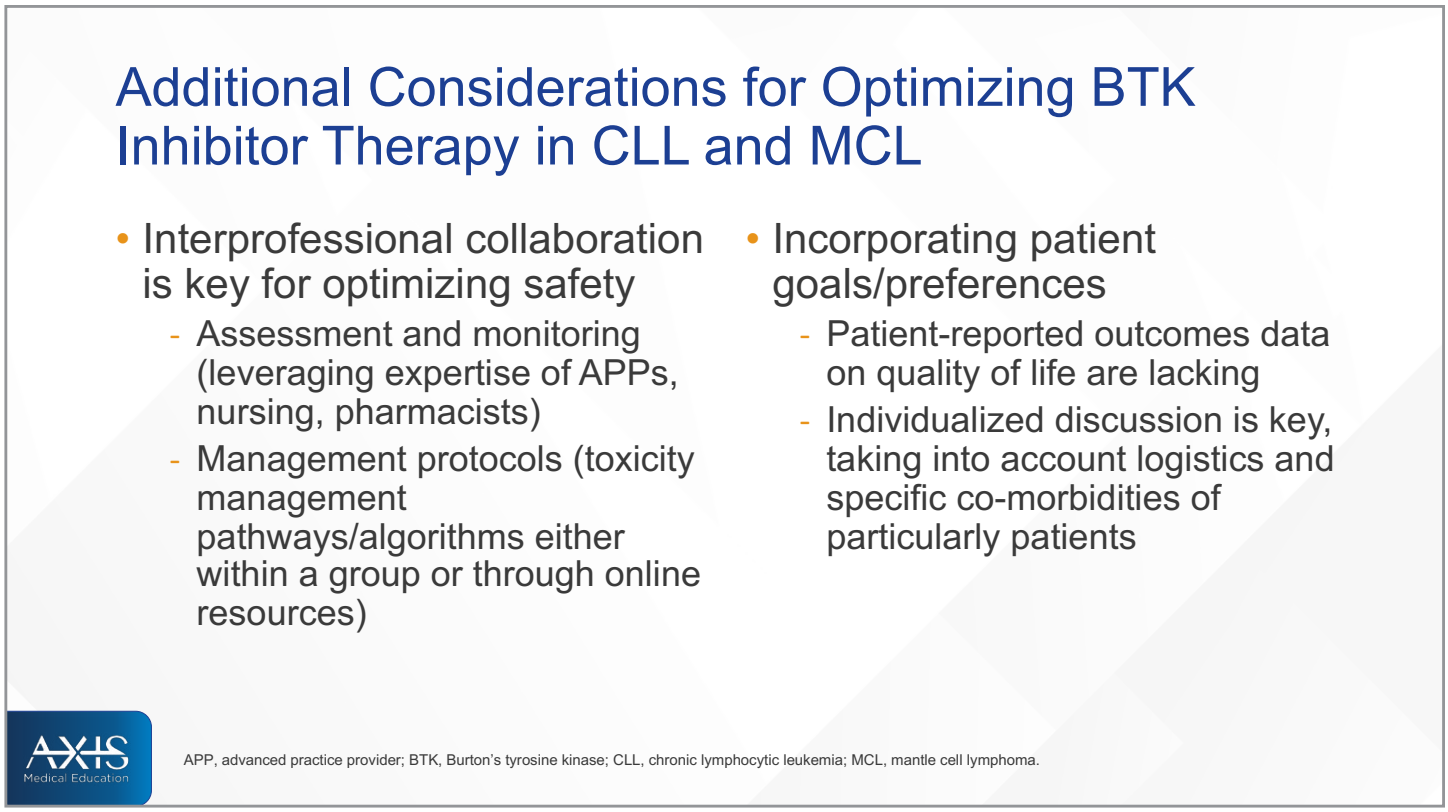
AXIS Medical Education

Woyach J, et al. ASH 2022. Abstract 3114.
AE, adverse event; QD, once daily.

- With nemtabrutinib, the safety profile, this is in 112 patients treated at the recommended phase 2 dose of 65 milligrams daily. Certainly any treatment related AE's or common, but grade 3 or higher events are less common. Neutropenia being the most common one again seen in terms of grade 3 or higher toxicities in about 19% of patients. One of the unique toxicities seen with nemtabrutinib is dysgeusia, which can occur in a little over 20% of patients. This does tend to be mild and transient, fortunately. And then again, you do see some of the other issues around hypertension and diarrhea that we see with other BTK inhibitors.



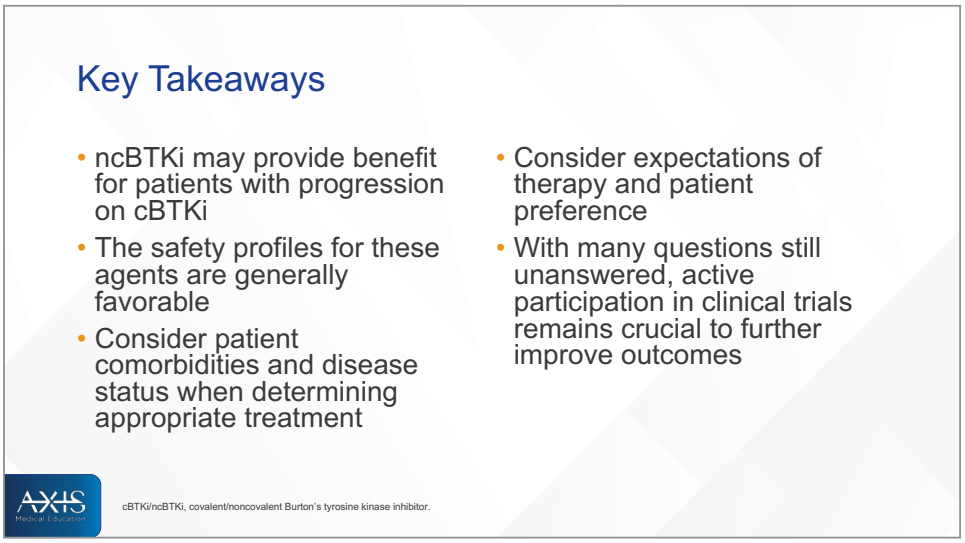
So, what are some tips and tricks in terms of managing BTK inhibitor toxicities? You know, mostly kind of common things that you'd expect with rash, they do tend to be responsive to topical steroids and oral antihistamine. We do also see hair and nail changes sometimes on BTK inhibitors and particularly those nail changes can be helped by biotin supplementation or application of nail oil. We manage diarrhea, symptomatically, sometimes even altering the dosing of the timing of dosing, doing it at bedtime instead of in the morning, for example, can be helpful. Similarly, with nausea, we can adjust the dosing timing that can sometimes be helpful. Arthralgias and myalgias are common with BTK inhibitors. I find that when my patients are regularly exercising, that can actually be helpful there. Some selective NSAID use is OK, but we try to avoid more frequent NSAID use and there are some alternative supplements and treatments that various patients have found to be helpful. Headache is not that common with BTK inhibitors, with the exception of acalabrutinib where it is seen a little bit more commonly when patients are first starting the drug. I do recommend patients increase their caffeine intake and use acetaminophen. And that usually takes care of it. And that headache usually goes away within a couple of weeks of starting acalabrutinib. For infection, there's no standard recommendation in terms of routine screening or prophylaxis. There is a lot of variation across different institutions in terms of what to do here. Certainly, we monitor patients closely for infection. We need to stay aware of drug, drug interactions if we need to use particular antimicrobials, especially antifungal agents. And generally, my practice is for patients who develop a severe infection when they're on BTK inhibitors, I will usually hold the BTK inhibitor until the infection is clearly resolving.



So, additional thoughts here. I think that interprofessional collaboration is really one of the keys to optimize safety. We really want to leverage the expertise of our whole team. So, if we work with AP's, nurses and pharmacists, they all have different expertise that can be complementary to our own as the MD's and so utilizing all those folks to help manage the toxicities can be quite helpful. It's often also helpful if there's management protocols. We've also done this in our practice. We've developed toxicity management pathways and algorithms with BTK inhibitors. You can do this within your own group or there's online resources to help with. And as we think about utilizing these treatments in CLL and mantle cell lymphoma, incorporating patient goals and preferences really is also crucial. We don't have that much data in terms of patient reported outcomes or quality of life in these trials. So, I think in general, the individualized discussion is one of the keys often there's certain logistical considerations of starting these different treatments. We want to think about specific comorbidities of particular patients. And these all factor into our recommendations about which BTK inhibitor to use and which kind of order of covalent, noncovalent, and other therapies that we have available.

Chairperson Perspectives

So, from this final section here, I think that, again, we're so fortunate to have all these different options with BTK inhibitors. It can be a bit overwhelming. I encourage you to really think about using, one or two of these BTK inhibitors more consistently, whichever one you choose. We're using less ibrutinib these days because of some of the head-to-head data showing an improved safety profile of acalabrutinib and zanubrutinib compared to ibrutinib. So, I think covalent BTK inhibitors, either of those two would be my preferred treatment to start with. In the noncovalent space, because nemtabrutinib is not approved at this point really pirtobrutinib is the main option and so I think getting some comfort with pirtobrutinib would be helpful as well. If you have patients who are eligible candidates for it. And I think once you have more comfort with these different BTK inhibitors, you'll be able to really think about how to optimize therapy for particular patients, how to do different dose adjustments if needed. And how to sequence these therapies with the other very effective therapies we have available for our patients with CLL.



So, in terms of the key takeaways here, I would say that the noncovalent BTK inhibitors may provide benefit for patients with progression on covalent BTK inhibitors. In general, the safety profiles for these drugs are good, but we do need to be mindful of the common toxicities and manage them as needed. As we're helping patients to decide on which therapies to embark on, we do want to consider what their specific comorbidities are as well as what their disease status is. That will help us to optimize the therapy for patients. Often patients have particular expectations or preferences around which therapies they choose, and so we want to take that into account. And although we have a lot of new data in this area, there's still many questions that are unanswered and so I would encourage you if you have patients who are interested in clinical trials, to actively encourage them to participate in these trials. I think the trials really are the way that we'll be able to further improve outcomes for patients in the future.

Thank you very much for your attention. And with that, we will conclude today's activity. I really want to thank you for participating in this activity.

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