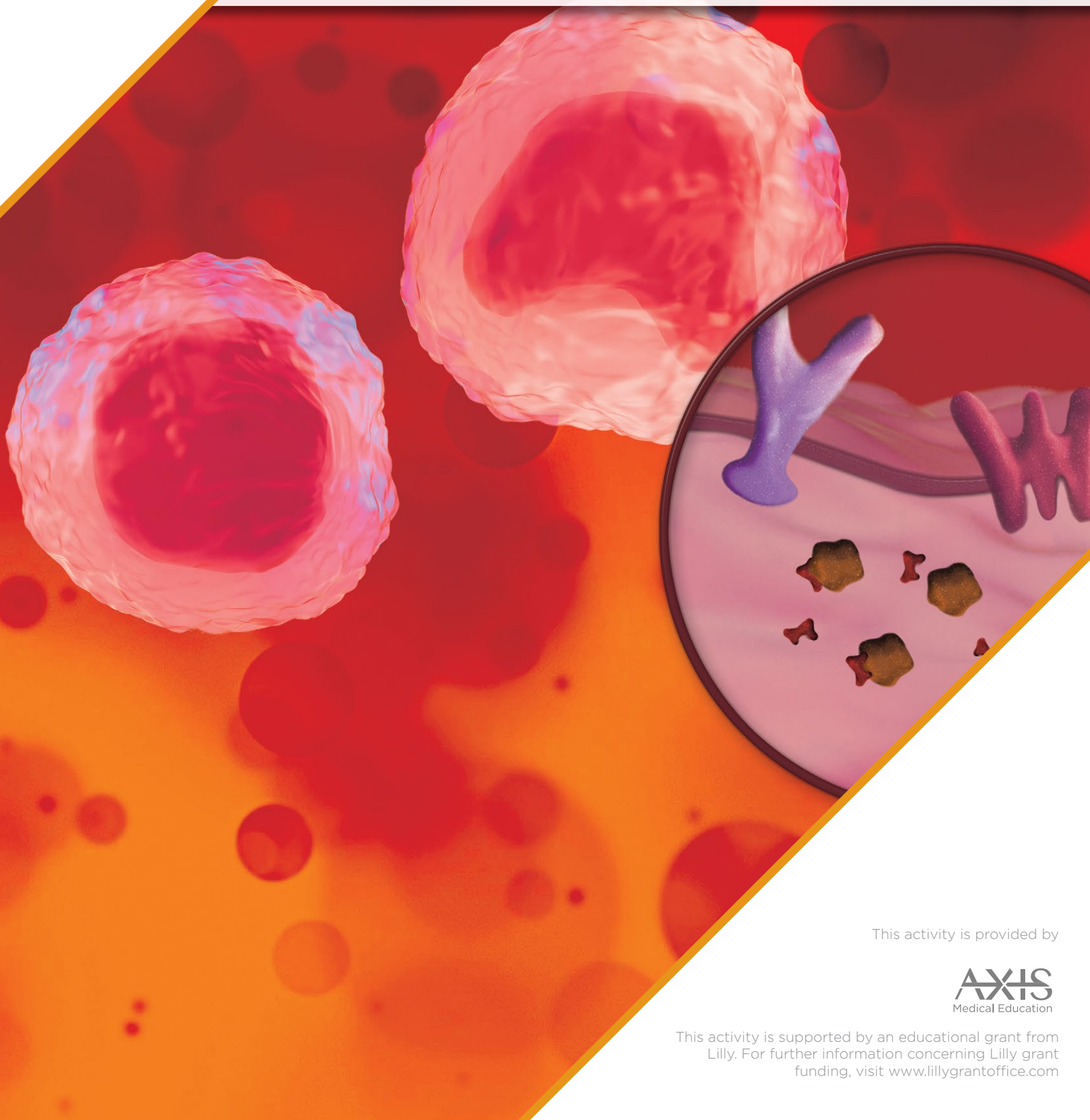
AXIS Medical Education

Non-Covalent BTK Inhibitors for B-Cell Malignancies (MCL/CLL):

Setting the Stage for Future Use

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



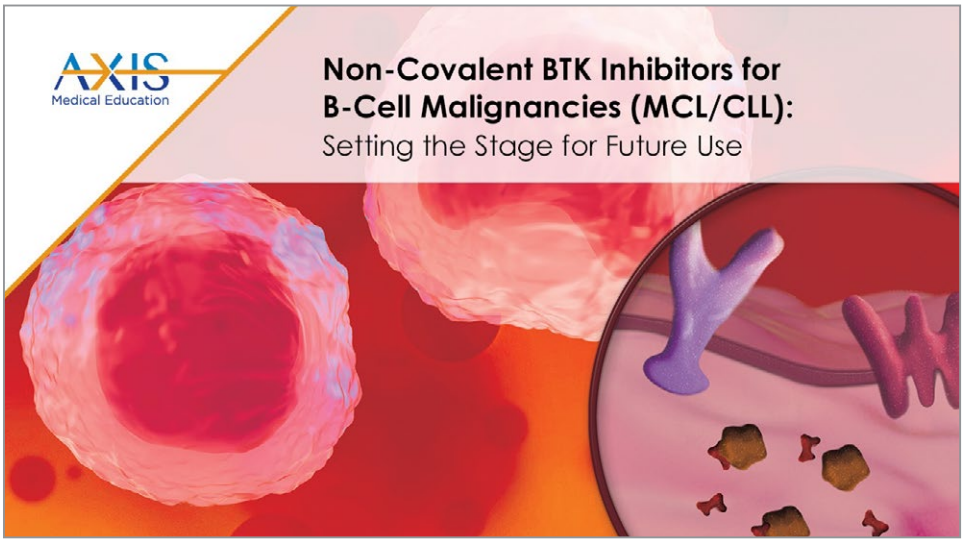
This activity is provided by

AXIS Medical Education

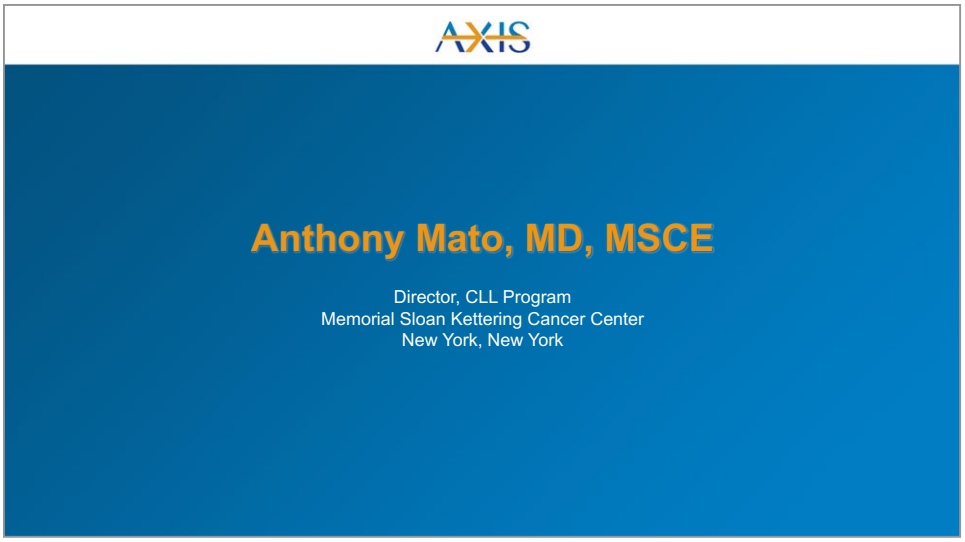
This activity is supported by an educational grant from Lilly. For further information concerning Lilly grant funding, visit www.lillygrantoffice.com

Non-Covalent BTK Inhibitors for B-Cell Malignancies (MCL/CLL): Setting the Stage for Future Use

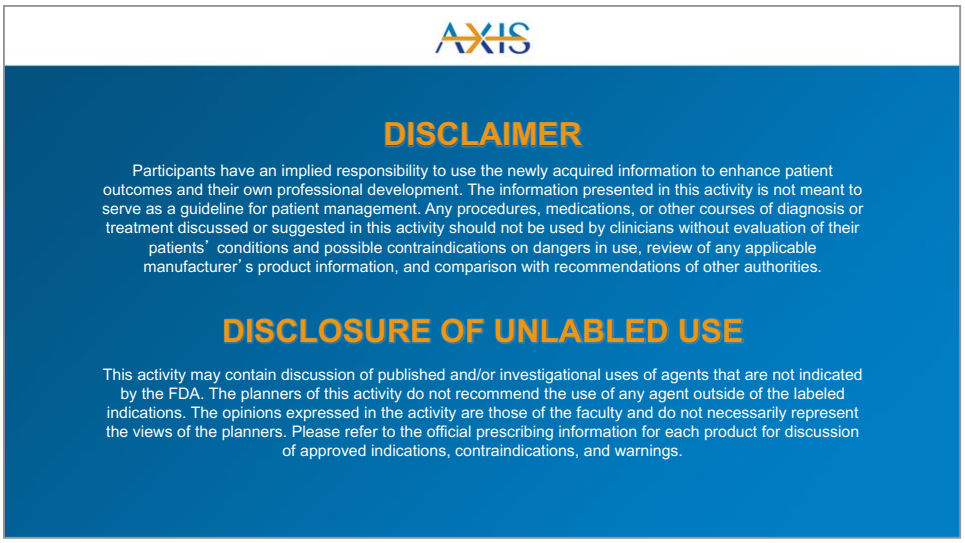
Anthony Mato, MD, MSCE



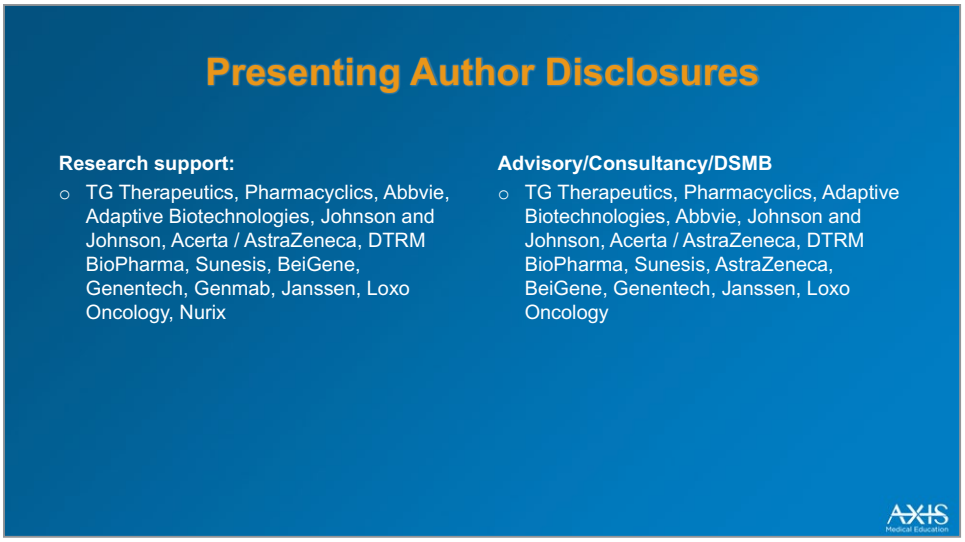
Anthony Mato, MD, MSCE: Hello, and welcome to this educational activity entitled *Non-Covalent BTK Inhibitors for B-Cell Malignancies (MCL/CLL): Setting the Stage for Future Use*.



I'm Anthony Mato, Director of the CLL Program at Memorial Sloan Kettering Cancer Center in New York.



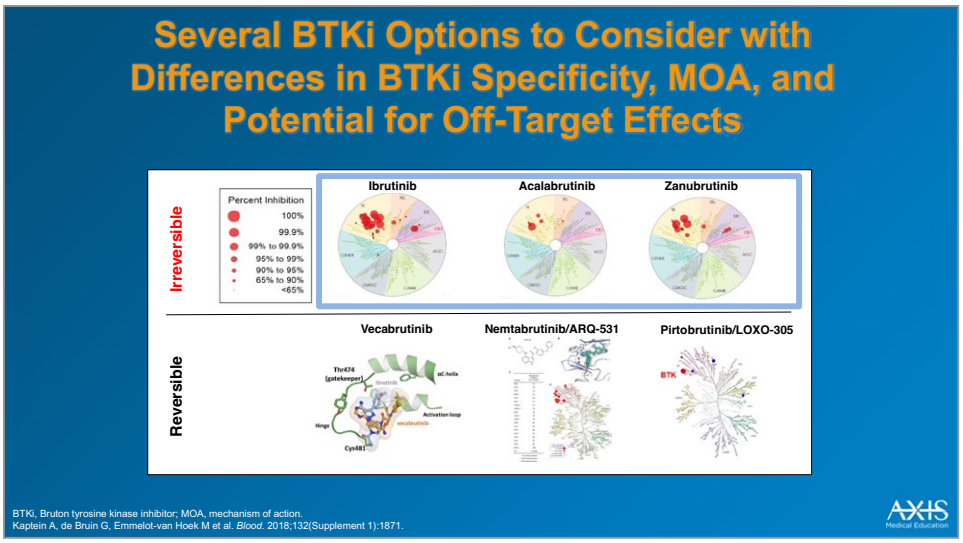
- First, a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.



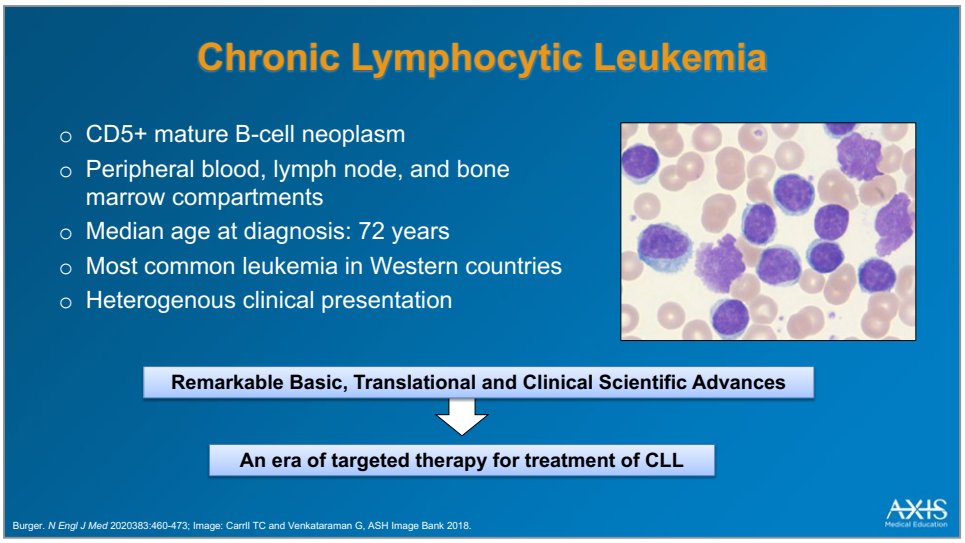
- Here are my financial disclosures.

- During this activity, we will review the latest evidence for noncovalent BTK inhibitors for the treatment of CLL and mantle cell lymphoma. Let's get started.

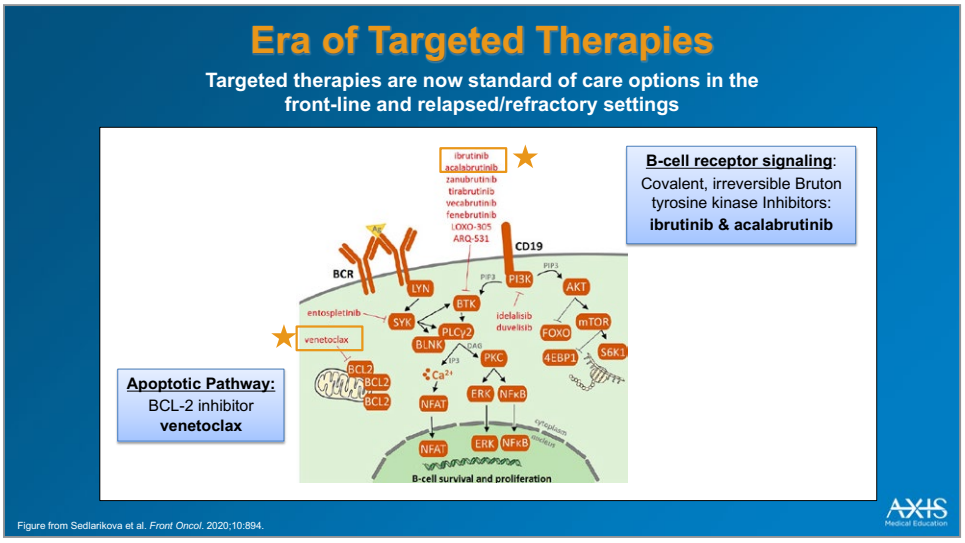
  For the first section of the presentation, I'd like to begin by discussing where we are in 2022, highlighting the limitations of covalent BTK inhibitors, and also identify patients who are at most risk and have the most important unmet medical needs with CLL.



- There are several BTK inhibitor options that we can consider—irreversible or covalent BTK inhibitors, and reversible or noncovalent BTK inhibitors. For the irreversible inhibitors, we have ibrutinib and acalabrutinib, which have been approved. We also have zanubrutinib, which is in development. For the reversible inhibitors, we have vecabrutinib, nemtabrutinib, and pirtobrutinib. For the purposes of today's presentation, I will highlight the data for nemtabrutinib and pirtobrutinib.



- Chronic lymphocytic leukemia is a CD-5 positive mature B cell neoplasm. There are several presentations, including peripheral blood involvement, lymph node involvement, and bone marrow involvement. It's generally a disease of older patients with a median age of 72 years. It's the most common leukemia in Western countries, and there's a heterogeneous clinical presentation, where some patients may never warrant therapy, some are treated immediately, and some are treated on average 5 to 7 years after diagnosis.



- Over the past several years, there have been remarkable basic translational and clinical scientific advances that have led to a dawning of the era of targeted therapies for the treatment of patients with CLL.

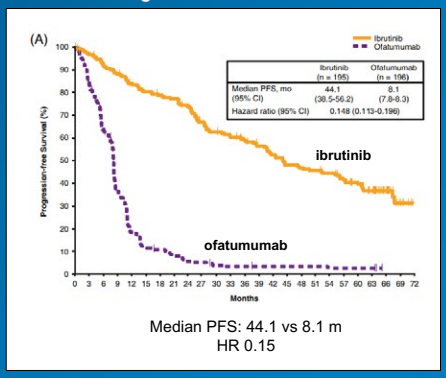
  Here I have a schematic of important cell signaling pathways that are relevant to modern therapies for treating patients with CLL. Targeted therapies are now the standard of care options in the frontline and the relapsed/refractory setting. You won't hear me discussing the use of chemotherapy or chemoimmunotherapy at all for patients today.

  The two most important pathways are the B cell receptor signaling pathway where we have covalent irreversible BTK inhibitors approved including ibrutinib and acalabrutinib. The PI3K inhibitors are also involved in this pathway as well as the apoptotic pathway where we have the B cell BCL-2 inhibitor, venetoclax, approved.

Covalent BTK Inhibitors

- **Ibrutinib & acalabrutinib**: bind irreversibly to BTK protein
- Oral, **continuous therapies**
- Improved PFS compared to CIT controls
  - R/R ibrutinib: RESONATE (ofatumumab)
  - F/L ibrutinib: RESONATE -2 (chlorambucil)
  - F/L acalabrutinib: ELEVATE-TN (obinutuzumab + chlorambucil)

Progression-free Survival



Median PFS: 44.1 vs 8.1 m
HR 0.15

CIT, chemoimmunotherapy; F/L, first-line; PFS, progression-free survival; R/R, relapsed/refractory.
Munir et al. Am J *Hematol* 2019;94:1353-1363 Barr et al. *J Clin Oncol*. 2021;39:7523; Sharman et al. *J Clin Oncol*. 2021;39:7509.

AXIS Medical Education

In terms of the covalent BTK inhibitors, again, we have ibrutinib and acalabrutinib. They bind irreversibly to the BTK protein, they're oral continuous therapies, and there are several trials that I have highlighted here, and I could have included more, where we've demonstrated not only improved progression-free survival as compared to controls, but also, in some instances related to ibrutinib, an improvement in overall survival.

Just as one example, this is the RESONATE trial, which compared ibrutinib to the CD20 antibody, ofatumumab, demonstrating an improvement in both progression-free and overall survival. The median progression-free survival in a heavily pretreated patient population for ibrutinib was 44.1 months.

Ibrutinib Discontinuation for Intolerance

Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: A Real-World Analysis

- **41% of patients discontinued ibrutinib** at a median follow-up of 17 months
- Toxicity accounted for the **majority** of discontinuations (over half) in both first-line and relapsed/refractory CLL
- Most common toxicities in relapsed/refractory CLL:
  - Atrial fibrillation 12.3%
  - Infection 10.7%
  - Pneumonitis 9.9%
  - Bleeding 9%
  - Diarrhea 6.6%

Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n = 10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

This study identified covalent BTK inhibitor **intolerance** as a major emerging issue in the field of CLL

BTK, Bruton tyrosine kinase; CAR T-cell, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; RT DLBCL, Richter transformation to diffuse large B-cell lymphoma; RT, Richter transformation.
Mato et al. *Haematologica* 2018;103:874-879.

AXIS Medical Education

I also wanted to highlight some limitations for the class of the covalent inhibitors. These include the major reasons for discontinuation, which are intolerance and resistance. This is a real-world data set that our group published looking at 616 patients treated with ibrutinib, both in the frontline and relapsed/refractory setting. I want to highlight that 41% of patients discontinued ibrutinib with a median follow-up of 17 months. Toxicity accounted for the majority of discontinuations, both in the frontline and relapsed/refractory populations, with the most common toxicities leading to discontinuation including a-fib, infection, pneumonitis, bleeding, and diarrhea. This is just one example of many studies that have identified covalent BTK inhibitor intolerance as an emerging issue in the field of CLL.

Acquired Resistance to Covalent BTKi

- Majority of patients have identified mutations in *BTKC481* at the time of disease progression on ibrutinib; ~53-87% of patients
- **Catalytically activating** mutations
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTKC481* mutations are also main mechanism of resistance for acalabrutinib; 69% of patients

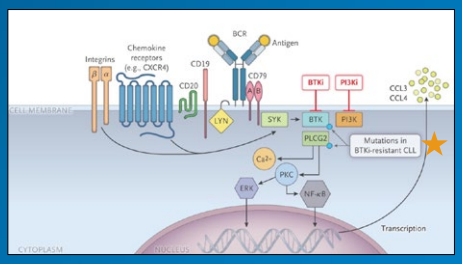


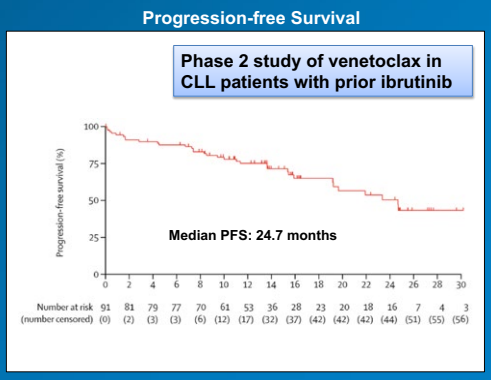
Figure from Burger. *N Engl J Med*. 2020;383:460-473.
BTKi, Bruton tyrosine kinase inhibitor.
Burger et al. *Nat Commun* 2016;7:11589. Woyach et al. *N Engl J Med*. 2014;370:2286-2294; *J Clin Oncol*. 2017;35:1437-1443; *Blood* 2019;134(suppl 1):504.
Scarfò et al. EHA 2020;4:34-35. Ahn et al. *Blood* 2017;129:1469-1479.

AXIS Medical Education

I also wanted to highlight the second most common reason for discontinuing a covalent BTK inhibitor, and that's acquired resistance. A majority of patients have identified mutations in *BTK* C481 at the time of disease progression on ibrutinib, and the range is between 53% and 87% of patients. We also see downstream activating mutations in PLC G2 as a second most common identified reason for discontinuation due to resistance. This is not only limited to ibrutinib, but also seen in patients treated with acalabrutinib, for example, where 69% of patients with progression also had a C481 mutation. So again, highlighting that intolerance and resistance are major issues that we need to address for patients treated with covalent inhibitors.

Treatment of CLL After Covalent BTKi

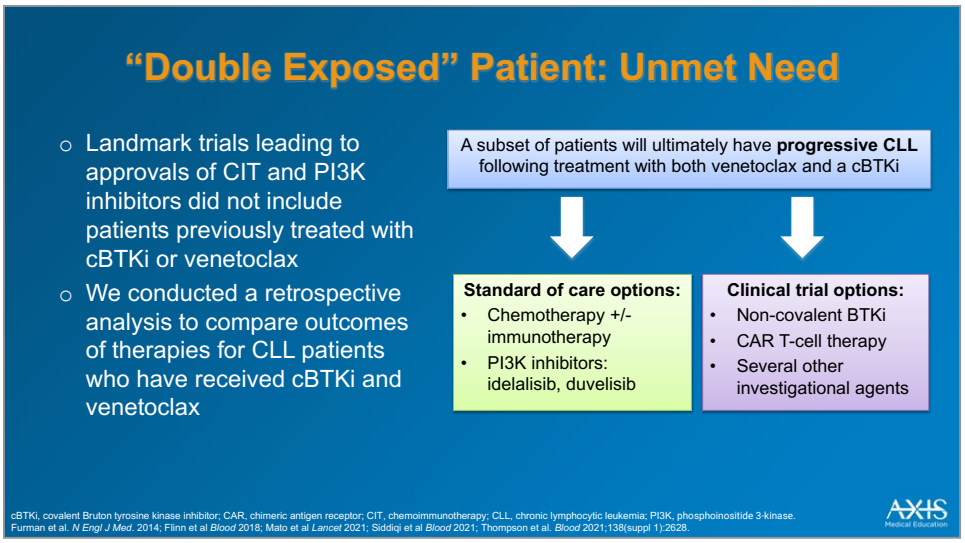
- **Venetoclax:** oral BCL-2 inhibitor
- First-line setting and relapsed setting including after cBTKi
- Approved as **fixed-duration** therapy (24 months in R/R setting)



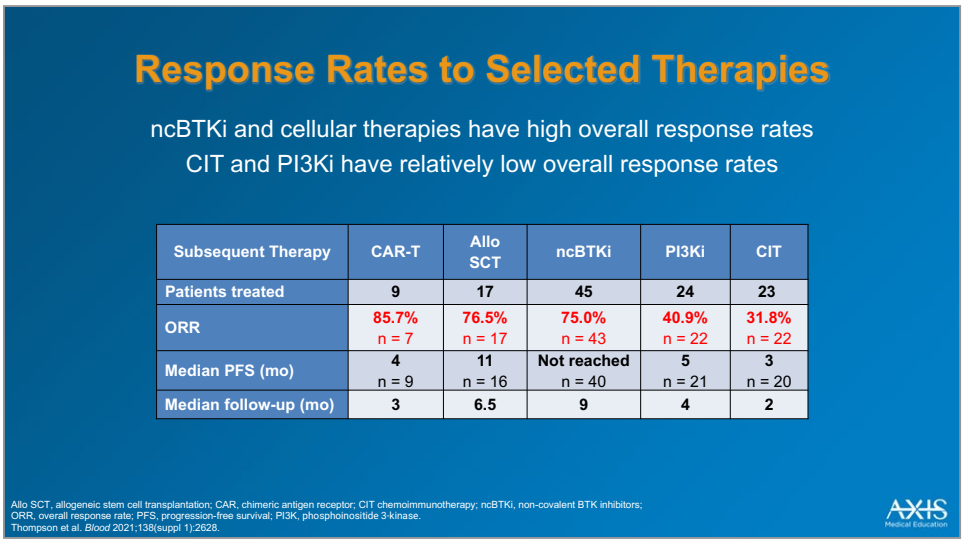
cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory.
Figure from Jones et al. *Lancet Oncol*. 2018;19:65-75.

AXIS Medical Education

What agents are available to patients? Well, from the perspective of having prospective data, you can see that venetoclax has been tested in patients who were previously treated with ibrutinib that was discontinued either for intolerance or progression of disease. Venetoclax is approved as a fixed duration or as a continuous therapy in the relapsed/refractory setting. Here you can see venetoclax is a continuous monotherapy and resulted in a median progression-free survival of 24.7 months following ibrutinib.



I also want to highlight the double-exposed patient population, which still represents a major unmet need. These are a subset of patients who have been treated with a covalent BTK inhibitor and venetoclax. We call them double exposed if they have both been treated with, and double refractory if they're actually resistant to both classes. In terms of standard-of-care options, they're quite limited to chemotherapy or PI3K inhibitors. I'll just highlight that those agents or those classes have not really been tested prospectively in this group of patients. And then of course, clinical trial options include noncovalent BTK inhibitors, CAR T, and other classes. And I'll highlight today the data for the noncovalent BTK inhibitors.

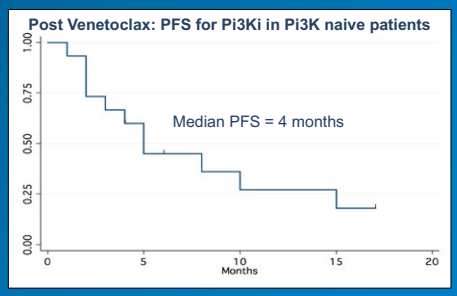


Subsequent Therapy	CAR-T	Allo SCT	ncBTKi	PI3Ki	CIT
Patients treated	9	17	45	24	23
ORR	85.7% n = 7	76.5% n = 17	75.0% n = 43	40.9% n = 22	31.8% n = 22
Median PFS (mo)	4 n = 9	11 n = 16	Not reached n = 40	5 n = 21	3 n = 20
Median follow-up (mo)	3	6.5	9	4	2

Here we have a real-world data set presented at the most recent ASH meeting, looking at several classes of agents tested retrospectively in patients who were exposed to a covalent BTK inhibitor and venetoclax. Let's highlight two different classes here just for comparison. For PI3K inhibitors, the median progression-free survival was only 5 months. For the noncovalent BTK inhibitors, as a class, we saw a response rate of 75% with a median progression-free survival that was not reached. These retrospective real-world data really do indicate that this class is quite promising.

Post Venetoclax

- After BTKi and/or venetoclax: PI3Ki did not result in durable remissions and therefore is not an acceptable standard of care in the third-line setting in modern era



BTKi, BTK inhibitor; PI3K, phosphoinositide 3-kinase inhibitor.
Mato et al. *Clin Cancer Res.* 2020;26(14):3589-3596.

AXIS Medical Education

- I have one more data set that we've looked at retrospectively for PI3K inhibitors following BTK inhibitors and venetoclax. We found a median progression-free survival of 4 months for the class of PI3K, we did not see durable remissions, and therefore, this is probably not an acceptable standard of care in the third-line setting in the modern era.

Summary: Alternate Covalent BTK Inhibitors

Intolerance

- Intolerance remains the most common reason for ibrutinib discontinuation
- Direct comparison suggest next-generation covalent BTK inhibitors lead to lower discontinuation rates due to adverse events; early data suggest fewer adverse events lead to better progression-free survival

Resistance

- *C481* mutations are the most common cause of resistance to ibrutinib
- Limited data from more selective covalent BTK inhibitors suggest similar mechanisms of resistance

AXIS Medical Education

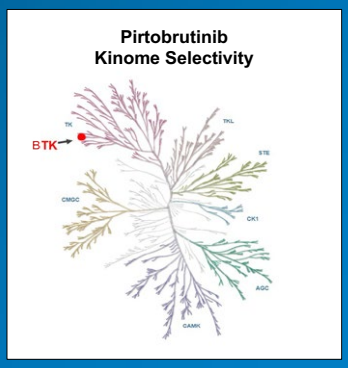
- In summary for the covalent BTK inhibitors, intolerance remains the most common reason for discontinuation. We do have head-to-head data for ibrutinib versus either zanubrutinib or acalabrutinib. The next-generation agents do appear to be more promising from the perspective of adverse events. In terms of resistance, C481 mutations are the most common cause of resistance to ibrutinib, and emerging data suggest the same for patients treated with other covalent BTK inhibitors. Therefore, switching from ibrutinib to acalabrutinib, for example, in the setting of resistance, won't result in a durable remission.

Non-Covalent BTK Inhibitors

- Now we'll delve into the noncovalent BTK inhibitors. I'll highlight today data for two agents, nemtabrutinib, or formerly ARQ 531, and pirtobrutinib, LOXO-305.

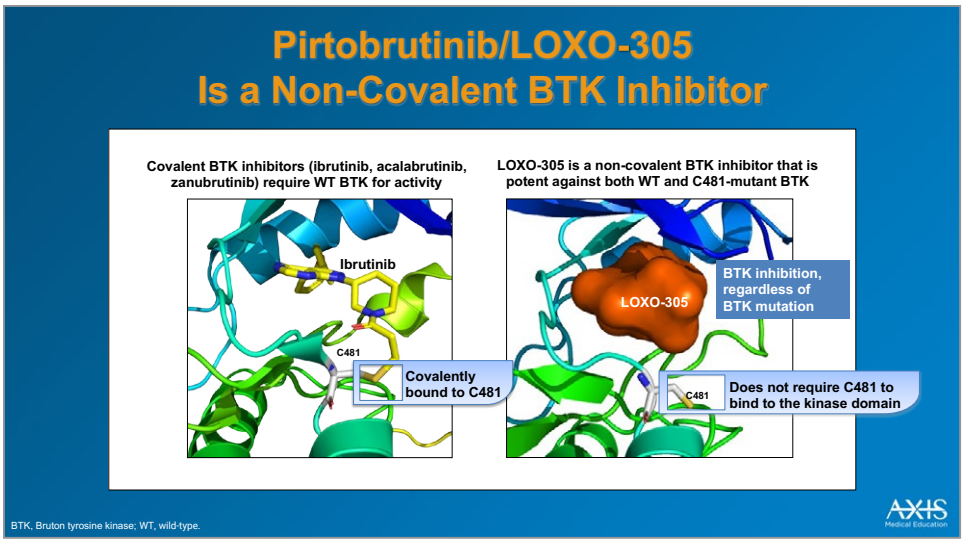
Non-Covalent BTK Inhibitors

- **Reversible** binding to BTK
- Several agents in clinical development
  - Nemtabrutinib (ARQ-531/MK-1026)[1]
  - Pirtobrutinib (LOXO-305)[2]
    - Highly selective: minimal activity against non-BTK kinases
    - Longer half-life and increased BTK occupancy compared to covalent BTK inhibitors

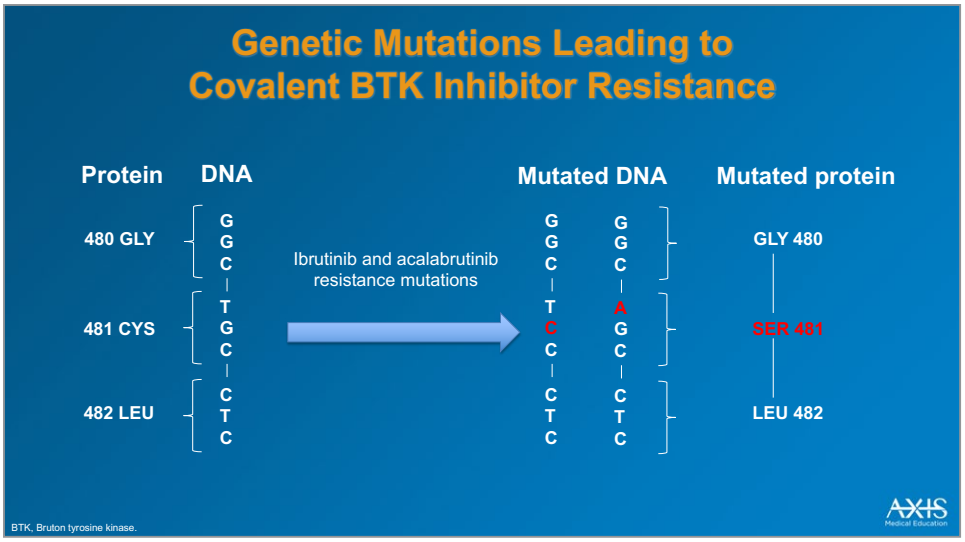


1. Reiff et al. *Cancer Discov*. 2018;8:1300-1315. 2. Mato et al *Lancet* 2021;397:892-901.
BTK, Bruton tyrosine kinase.

- Pirtobrutinib is a highly selective agent with minimal activity against non-BTK kinases. You can see that highlighted here in this kinome map. It has a longer half-life and increased BTK occupancy. The drug is designed to be very specific for BTK; therefore, it has minimal off-target effects. But because of its binding mode, it can overcome resistance due to C481mutations and should be active in patients with resistant disease.



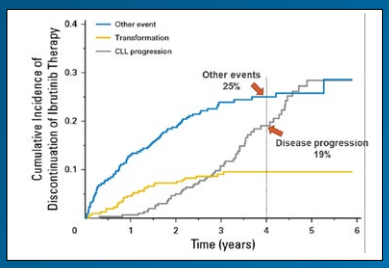
- Here's an image looking at LOXO-305 versus ibrutinib. Clearly, you need to have C481 to covalently bind BTK. When you have mutated disease where you have a serine in that place, ibrutinib can't bind, but LOXO-305, due to its different position, is able to bind.



- Here we have a schematic of the C481 mutation from cysteine to serine.

Resistance and Intolerance Limit Covalent BTK Inhibitor Efficacy

Ibrutinib Discontinuation (4 prospective studies)[1]



- Ibrutinib discontinuation rates at 5 years
  - Front-line = 41%[1]
  - Relapsed/refractory = 54%[2]

- Available options following covalent BTK inhibitor treatment are limited:
  - **Covalent BTK inhibitor retreatment:** Only effective in the context of covalent BTK intolerance, not progression
  - **Venetoclax:** Efficacious, but complicated administration and not appropriate for all patients
  - **PI3K inhibitors:** Limited benefit in this population and induces significant toxicity burden
  - **Chemoimmunotherapy:** Limited benefit in this population because most patients have already been exposed to these drugs

[1]Woyach et al. *J Clin Oncol.* 2017;35:1437-1443. [2]Burger. *Leukemia* 2020;34:787-7898.
BTK, Bruton tyrosine kinase; PI3K, phosphoinositide 3 kinase.

AXIS Medical Education

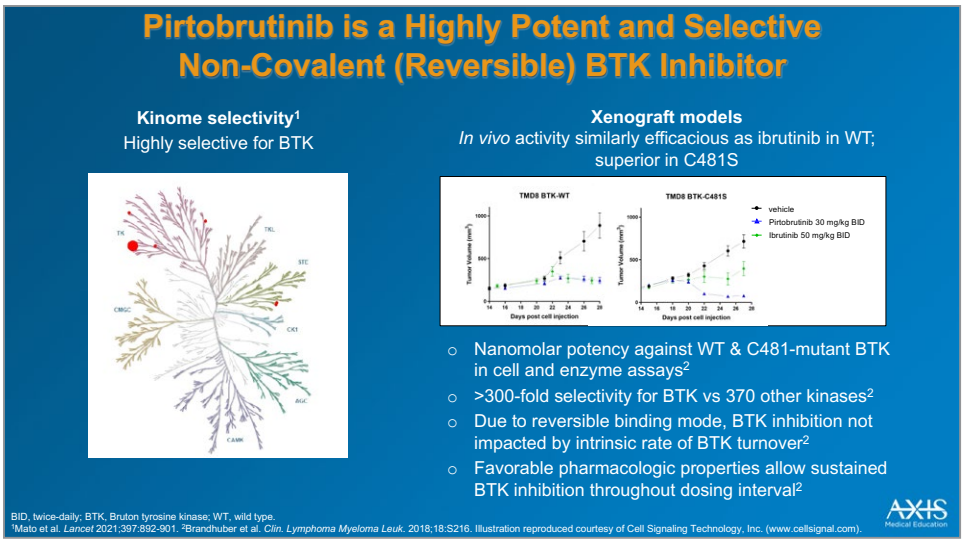
- These are again the most common reasons for discontinuation, both resistance and intolerance to the noncovalent inhibitors. And when you think about alternatives, as I presented earlier, the covalent inhibitors aren't a great choice in the setting of resistance, but maybe can be used in the setting of intolerance. Venetoclax is active but complicated due to its administration route. It may not be appropriate for all patients. And then while prospective data are lacking on PI3K inhibitors, the retrospective data are not promising at all.

AXIS

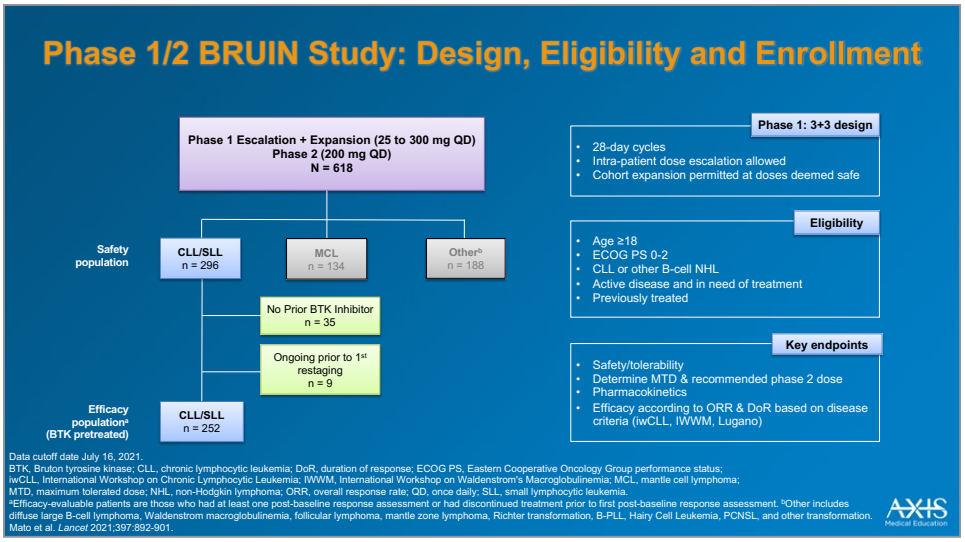
Non-Covalent BTK Inhibitors: Promising New Agents in CLL

Pirtobrutinib
Nemtabrutinib

- Now we'll go into the clinical data.

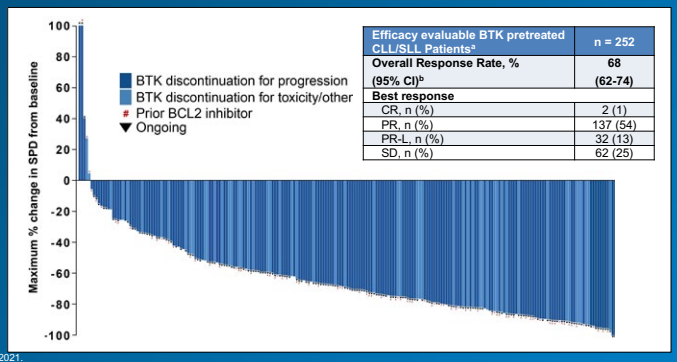


- Here again, you see that same kinome of map that I highlighted earlier. And the preclinical data that I've included on this slide really emphasizes the fact that this molecule is quite active against both wild-type and C481 mutant *BTK*, it's highly selective for BTK. And due to its binding mode, the BTK inhibition is not impacted by the intrinsic rate of BTK turnover. Therefore, the properties of this molecule would allow for sustained BTK inhibition throughout the dosing interval.



- The BRUIN trial is a phase 1/2 study assessing pirtobrutinib in patients with CLL and other B-cell malignancies. We've now treated 252 patients with pirtobrutinib who have previously received a covalent BTK inhibitor. So those are the patients I'm going to highlight in the later part of this presentation. Again, just as a reminder, the BRUIN trial is a phase 1/2 trial 3 by 3 design initially to get to the go-forward dose of 200 milligrams daily. Patients had relapsed refractory CLL or B cell malignancies. The primary endpoints were safety, tolerability, determination of the MTD, pharmacokinetic data, and then efficacy results, including overall response rate, duration of response and progression-free survival.

Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients



Efficacy evaluable BTK pretreated CLL/SLL Patients[a]	n = 252
Overall Response Rate, %	**68**
(95% CI)[b]	**(62-74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

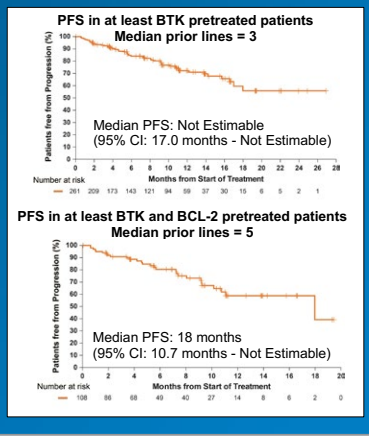
Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; PR-L, partial responses with ongoing lymphocytosis; SD, stable disease; SLL, small lymphocytic leukemia.
[a]Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.
Mato et al. *Blood* 2021;138:391.

AXIS Medical Education

- Here we see the waterfall plot indicating that nearly every patient had a significant reduction in their lymph node volume when treated with pirtobrutinib. All patients here at received a prior BTK inhibitor. Dark blue indicates patients who had discontinued due to progression. Light blue indicates patients who had discontinued due to toxicity, hashmarks indicate prior venetoclax exposure. And with all that being said, the overall response rate across the 252 patients was 68%.

Pirtobrutinib: Progression-free Survival in BTK Pretreated CLL/SLL Patients

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3-27.4) for all BTK pretreated patients

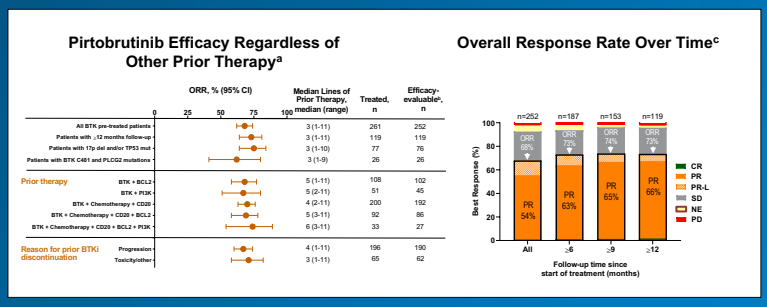


Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; SLL, small lymphocytic leukemia.
Response status per iwCLL 2018 according to investigator assessment.
Mato et al. *Blood* 2021;138:391.

AXIS Medical Education

- In terms of progression-free survival, for the entire population with a median number of 3 prior therapies, the median progression-free survival was not reached. For the double-exposed patients with a median prior therapies of 5, the median progression free survival was 18 months; 74% of BTK inhibitor pretreated patients remain on pirtobrutinib. And then median follow-up here is 9.4 months.

Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients



Data cutoff date July 16, 2021.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR rate with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.
Total % may be different than the sum of the individual components due to rounding. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment. [c]Includes the BTK pre-treated efficacy-evaluable CLL/SLL patients at the time of data cutoff. Data at each timepoint includes the BTK pre-treated efficacy-evaluable CLL/SLL patients who had the opportunity to be followed for at least the indicated amount of time.
Mato et al. *Blood* 2021;138:391.

- Across many subgroups, we can see the response was maintained. This includes all BTK pretreated patients, patients with a deletion 17p, patients with a C481 mutation and a PLC G2 mutation. Heavily pretreated patients including those who were pentavalent failures, who had received BTKs, chemotherapy, CD20, PCL-2 inhibitor, and a PI3K inhibitor, and then as well as no difference regardless of the reason for discontinuation. And with ongoing follow-up in the subset of patients who have had 12 or more cycles of therapy, the overall response rate has deepened to 73%.

Pirtobrutinib: Safety Profile

	All Doses and Patients (N = 618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

- No DLTs reported and MTD not reached
- 96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
- 1% (n = 6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date July 16, 2021.
AEs, adverse events; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.
Total % may be different than the sum of the individual components due to rounding. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.
Mato et al. *Blood* 2021;138:391.

- Here are data on the safety profile for pirtobrutinib. You can see overall this molecule is well tolerated. There are only four adverse events that are seen in greater than or equal to 15% of patients: fatigue, diarrhea, neutropenia, and contusion. BTK inhibitor–associated adverse events like afib are quite low at 2%. No dose-limiting toxicities were reported. The maximum tolerated dose was not reached. And the discontinuation rate due to adverse events was only 1%.

Pirtobrutinib CLL Conclusions

- Pirtobrutinib demonstrates promising efficacy in CLL/SLL patients previously treated with BTK inhibitors
  - Efficacy was independent of *BTK* C481 mutation status, the reason for prior BTKi discontinuation (ie, progression vs intolerance), or other classes of prior therapy received (including covalent BTK inhibitors, BCL-2 inhibitors, and PI3K-delta inhibitors)
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent reversible BTK inhibitor
- Randomized, global, phase 3 trials evaluating pirtobrutinib in CLL/SLL ongoing:
  - **BRUIN CLL-321:** Pirtobrutinib vs investigator's choice of IdelaR or BendaR, requires prior BTK treatment (NCT04666038)
  - **BRUIN CLL-322:** Pirtobrutinib + VenR vs VenR, permits prior BTK treatment (NCT04965493)
  - **BRUIN CLL-313:** Pirtobrutinib vs BendaR in treatment-naïve patients (NCT05023980)

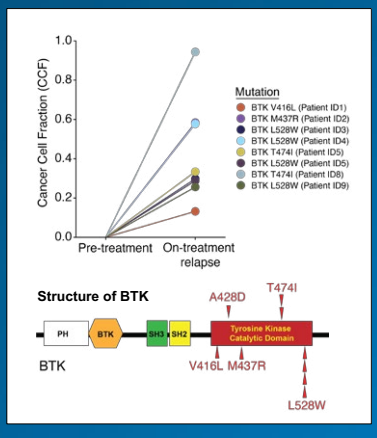
BendaR, bendamustine and rituximab; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; IdelaR, idelalisib and rituximab; SLL, small lymphocytic leukemia; VenR, venetoclax and rituximab.

AXIS Medical Education

In conclusion, pirtobrutinib demonstrated promising efficacy in CLL patients previously treated with BTK inhibitors, as well as several other modern therapies. We saw a favorable safety and tolerability consistent with the design of pirtobrutinib as a selective and noncovalent reversible BTK inhibitor.

And I'll just highlight there are several ongoing clinical trials of importance. The CLL-321 trial randomizes pirtobrutinib versus investigators choice, idelalisib/rituximab or bendamustine/rituximab, in the relapsed/refractory setting, CLL-322 randomizes pirtobrutinib rather venetoclax/rituximab, plus or minus pirtobrutinib as a time-limited therapy in the relapsed/refractory setting, and the CLL-313 trial randomizes pirtobrutinib versus bendamustine/rituximab in treatment-naive patients.

Acquired *BTK* Mutations on Pirtobrutinib

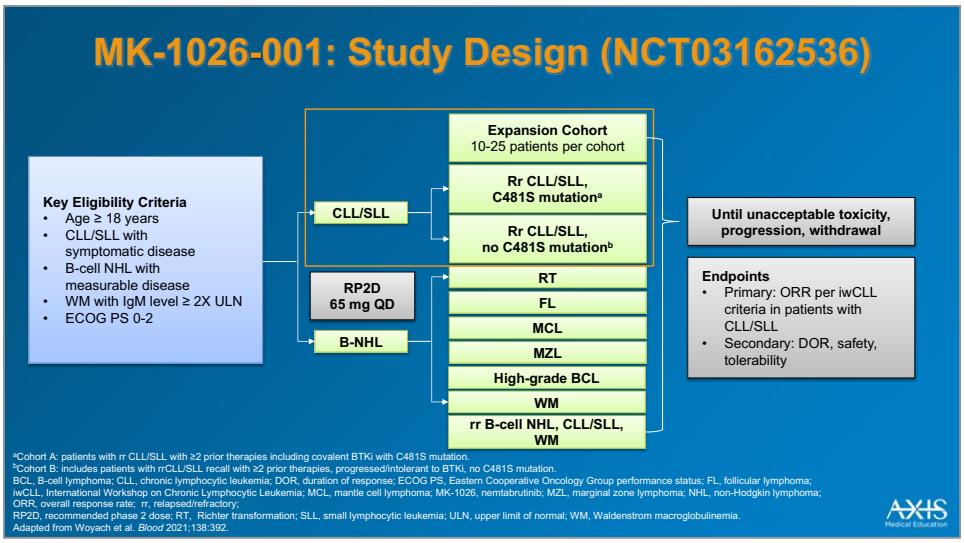


- We identified novel acquired mutations in *BTK* at the time of disease progression including:
  - *BTK* L528W
  - *BTK* V416L
  - *BTK* M437R
  - *BTK* T474I
  - *BTK* A428D
- These mutations cluster around the tyrosine kinase catalytic domain of *BTK*
- Additionally, several patients with progressive disease had pre-existing PLCG2 mutations

Wang et al. In press 2022.

AXIS Medical Education

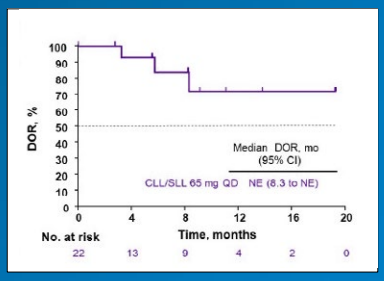
Of course, there are patients who do progress on pirtobrutinib with CLL. These are the progressors from the MSKCC cohort. I'll highlight a recent paper published by our group in *The New England Journal of Medicine* looking at mechanisms of resistance to noncovalent BTK inhibitors on pirtobrutinib, and just highlight that we identified novel acquired mutations in *BTK* at the time of disease progression, but preliminary, this is quite interesting. And if interested in this data set, I would highlight you to review the paper in more detail.



- I also want to highlight data on other molecules that are noncovalent inhibitors. Here we have data on MK-1026, or nemtabrutinib, which is also a noncovalent inhibitor studied in CLL and other B-cell malignancies. I'll focus today on the data for nemtabrutinib, specifically in CLL.

MK-1026/Nemtabrutinib: Summary of Response (CLL/SLL), Efficacy Evaluable Population

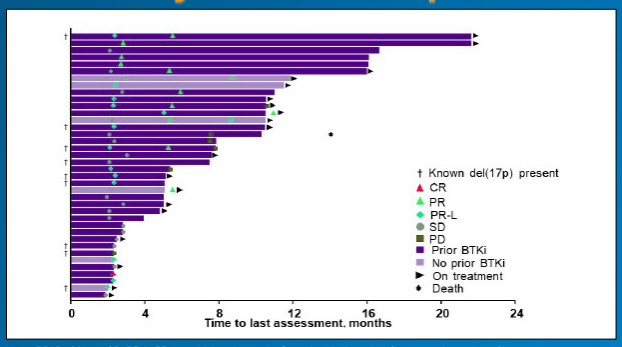
N (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%) [40.8-73.6]**
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]



[a]Efficacy evaluable patients with CLL/SLL who received at least one cycle of MK-1026 at preliminary RP2D of 65 mg QD and had ≥1 post-baseline assessment; Response assessed per iwCLL criteria Data cut-off: April 7, 2021.
CLL, chronic lymphocytic leukemia; CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR rate with lymphocytosis; QD, once daily; SD, stable disease; SLL, small lymphocytic leukemia.
Adapted from Woyach et al. Blood 2021;138:392.

- Here we can see the overall response rate was 57.9%.

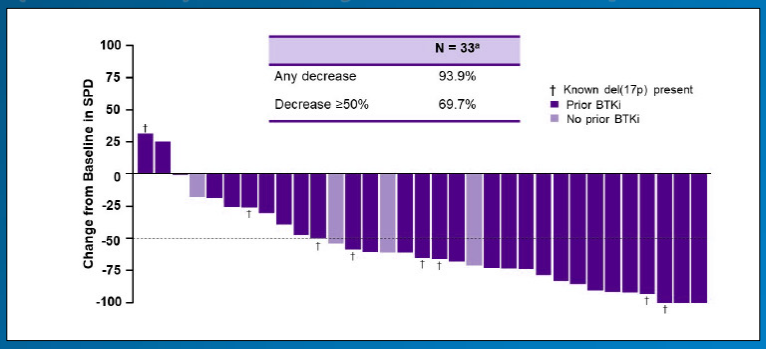
MK-1026/Nemtabrutinib: Treatment Duration Response (CLL/SLL), Efficacy Evaluable Population



Patietns with CLL/SLL treated at preliminary RP2D of 65 mg QD; PR-L, PR rate with lymphocytosis; Green bars indicate time from screening to date of last assessment; Patients not on treatment had discontinued due to progression, adverse event, patient or physician decision, or other reason. Data cut-off: April 7, 2021.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; SLL, small lymphocytic leukemia.
Adapted from Woyach et al. *Blood* 2021;138:392.

- And the median duration of response for responders was not reached. This is not progression-free survival.

MK-1026/Nemtabrutinib: Percent Change from Baseline in SPD (CLL/SLL), Efficacy Evaluable Population



A33 of 38 patients with ≥1 assessment post-baseline were evaluable for change from baseline in sum of product of diameters (SPD); Data cut-off: April 7, 2021.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; SPD, sum of the products of lymph node diameters.
Adapted from Woyach et al. *Blood* 2021;138:392.

- You can see that 94% of patients had any decrease in their lymph nodes, while 69.7% had a greater than or equal to 50% decrease.

MK-1026/Nemtabrutinib: Treatment-Emergent AEs

Events, n (%)		All Patients, N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Grade ≥3 related TEAEs[b]		31 (26.3)
Related TEAEs leading to discontinuation		9 (7.6)
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	24.6%	0
Nausea	24.6%	0.8%
Pyrexia	24.6%	0
Dizziness	22.9%	0
Hypertension	22.9%	9.3%
Peripheral edema	22.0%	0
Diarrhea	21.2%	0.8%
Arthralgia	20.3%	0

Data cut-off: April 7, 2021.
[a]8 patients had grade 5 TEAEs including death after PD (n=3), sepsis (n=1), and respiratory failure (n=2).
[b]No grade 5 drug related TEAEs were reported.
TEAEs, treatment-emergent adverse events.
Adapted from Woyach et al. *Blood* 2021;138:392.

AXIS Medical Education

- Here we can see the adverse event profile. Grade 3 or higher treatment-emergent adverse events occurred in 68% of patients. Treatment-emergent adverse events leading to discontinuation was 7.6%. Treatment-emergent adverse events that occurred in 20% or more of patients were, in descending order, fatigue, constipation, dysgeusia, cough, and nausea as the five most common.

AXIS

Non-Covalent BTK Inhibitors in Mantle Cell Lymphoma

- Now I'll delve into mantle cell lymphoma, specifically looking at pirtobrutinib.

Outcomes in MCL Are Extremely Poor Following Covalent BTK Inhibitor Progression

- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
- *BTK* C481-mutations are uncommon; bypass alterations and epigenetic changes implicated in some patients[7]
- Overall survival following covalent BTK inhibitor therapy is poor[3,4,11]

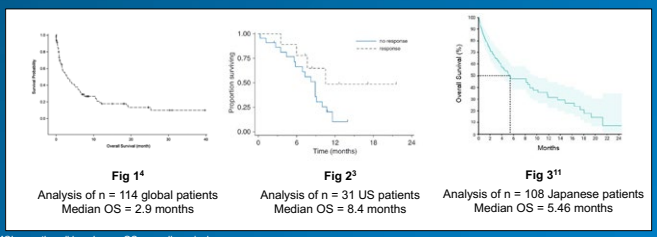


Fig 1[4]
Analysis of n = 114 global patients
Median OS = 2.9 months

Fig 2[3]
Analysis of n = 31 US patients
Median OS = 8.4 months

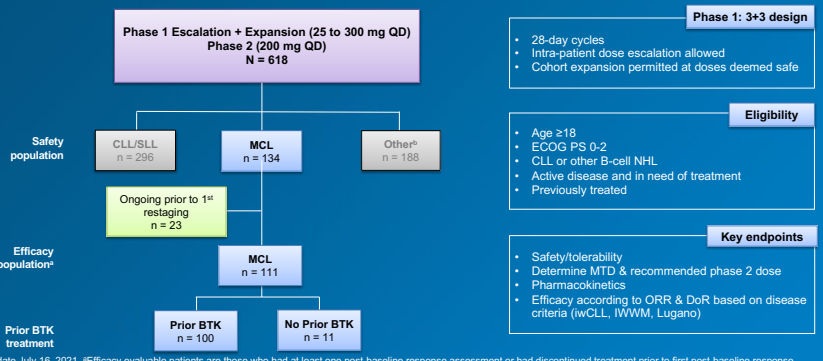
Fig 3[11]
Analysis of n = 108 Japanese patients
Median OS = 5.46 months

BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; OS, overall survival.
[1]Hershkovitz-Rokah et al. *Br J Haematol.* 2018;181:306-19. [2]Wang et al. *N Engl J Med.* 2013;369:507-16. [3]Cheah et al. *Ann Oncol.* 2015;26:1175-79. [4]Martin et al. *Blood* 2016;127:1559-63. [5]Dreyling et al. *Lancet* 2016;387:770-8. [6]Epperla et al. *Hematol Oncol.* 2017;35:528-35. [7]Ondrisova L and Mraz M, *Front Oncol.* 2020;10. [8]O'Brien et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:648-57. [9]Byrd et al. *Blood* 2019;130(Suppl 1):4326. [10]Tam et al. *Blood* 2020;136:2038-50. [11]Rai et al. *Clin Lymphoma Myeloma Leuk.* 2021; 21(Suppl 1):S407-S408.

AXIS Medical Education

- Mantle cell lymphoma is a disease where patients have fewer options than patients with CLL. Covalent BTK inhibitor resistance in mantle cell lymphoma and other lymphomas is not completely understood. C481 mutations are uncommon, and bypass alterations and epigenetic changes are likely the more common mechanisms of resistance. And survival data following covalent BTK inhibitor is poor. And here you see several datasets presented. Median overall survival 2.9 months, 8.4 months, 5.46 months— this is a patient population with an extremely poor prognosis.

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

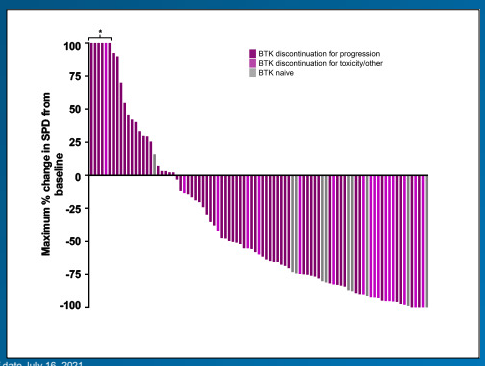


Data cutoff date July 16, 2021. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]Other includes diffuse large B-cell lymphoma, Waldenstrom macroglobulinemia, follicular lymphoma, marginal zone lymphoma, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IWWM, International Workshop on Waldenstrom's Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; ORR, overall response rate; QD, once daily; SLL, small lymphocytic leukemia.
Wang et al. *Blood* 2021;138:381.

AXIS Medical Education

- The BRUIN trial treated 134 patients with mantle cell lymphoma with pirtobrutinib for an efficacy evaluable population, there are 111 patients of whom 100 had a prior BTK inhibitor.

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



BTK Pre-Treated MCL Patients[a]	n = 100
Overall Response Rate[b], % (95% CI)	51% (41-61)
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	n = 11
Overall Response Rate[b], % (95% CI)	82% (48-98)
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

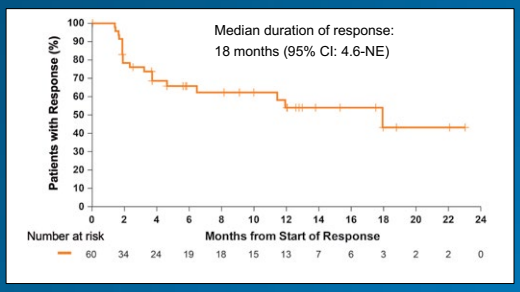
- Efficacy also seen in patients with prior:
  - Stem cell transplant (n = 28):
    - ORR 64% (95% CI 44-81)
  - CAR-T therapy (n = 6):
    - ORR 50% (95% CI 12-88)

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CAR, chimeric antigen therapy; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease; SPD, sum of the products of diameters.
Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.
Adapted from Wang et al. *Blood* 2021;138:381.

AXIS Medical Education

- Here you see the waterfall plot where nearly every patient had a significant reduction in their lymph node volume. The overall response rate in the BTK inhibitor–pretreated population was 51%, and was 82% in the smaller subset that was BTK inhibitor naive.

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma

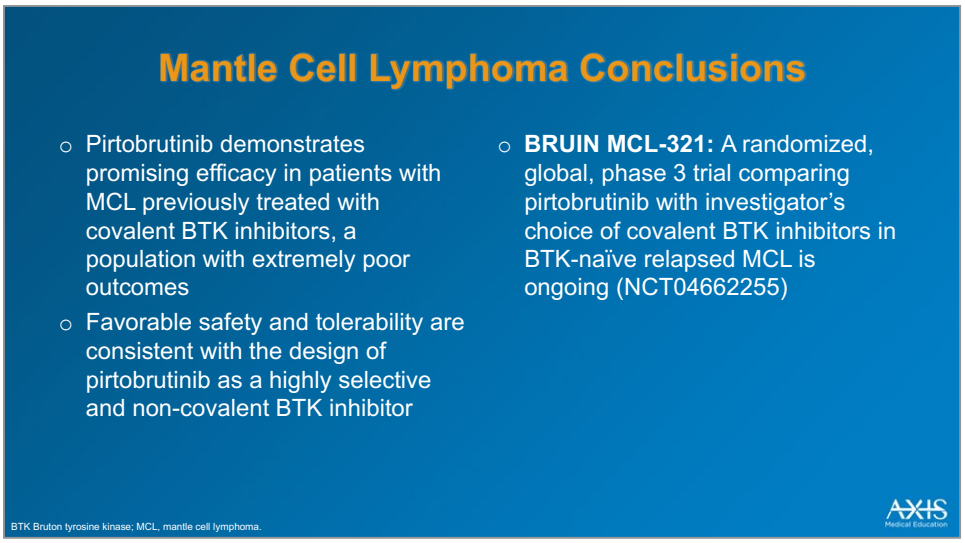


- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

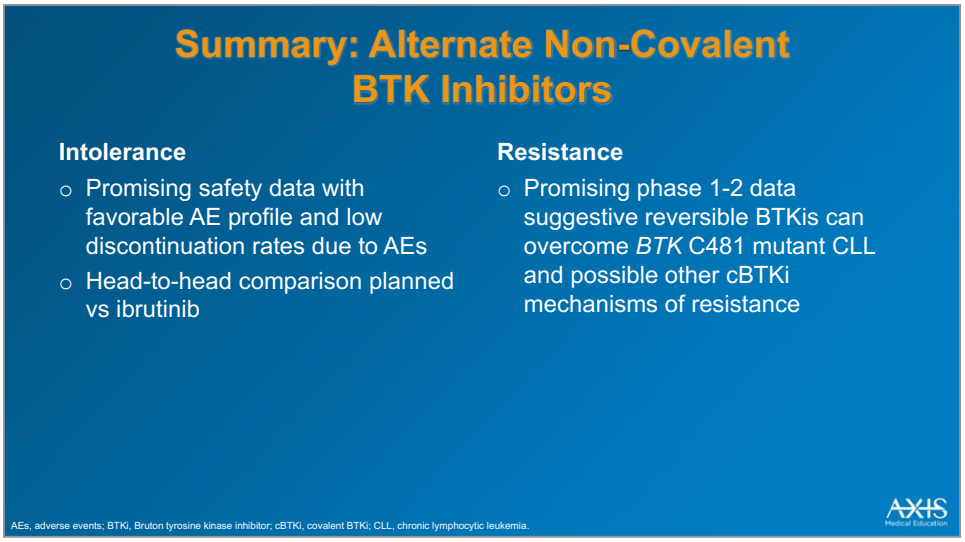
Data cutoff date July 16, 2021. Response status per Lugano 2014 criteria based on investigator assessment.
NE, not estimable.
Wang et al. *Blood* 2021;138:381.

AXIS Medical Education

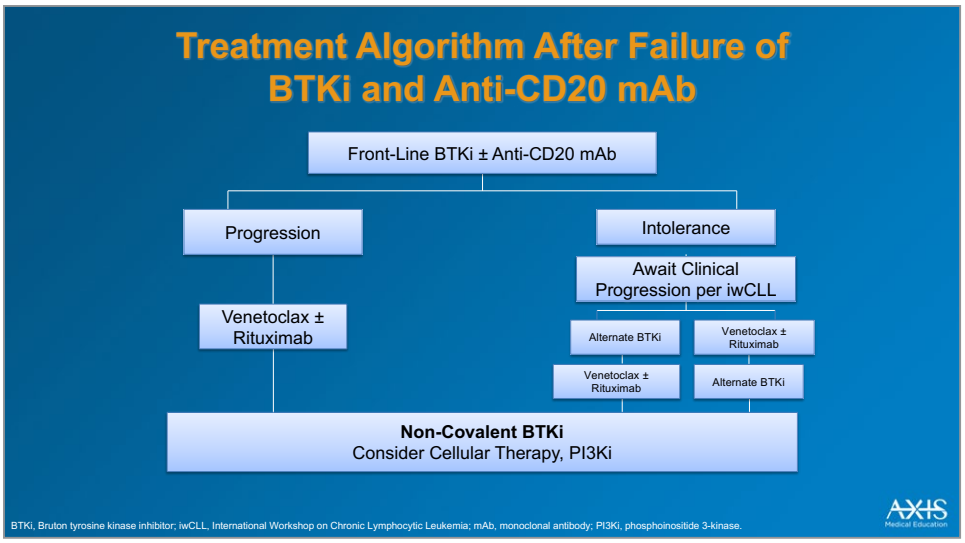
- The median duration of response was reached at 18 months for responders with 60% of responses ongoing.



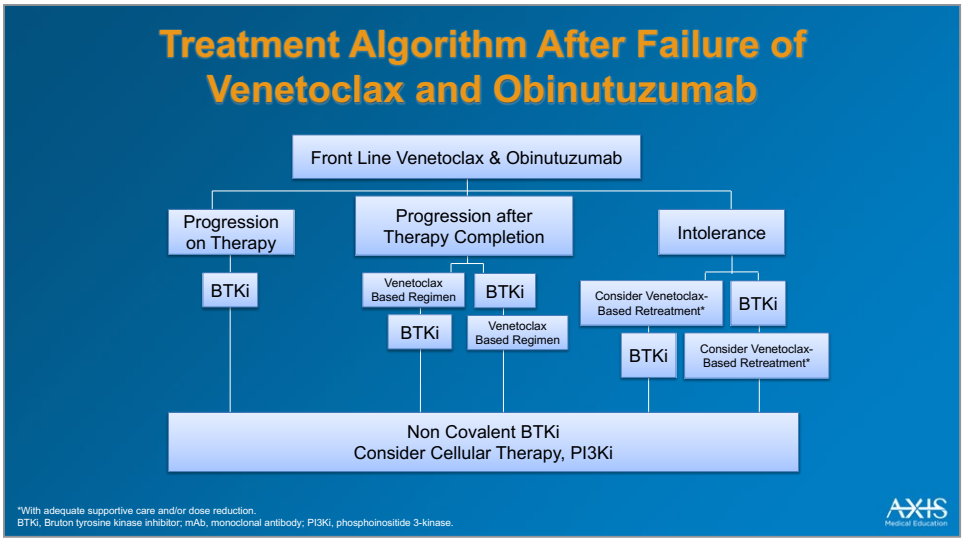
- In conclusion for mantle cell lymphoma, pirtobrutinib demonstrates promising efficacy in patients previously treated with BTK inhibitors, a population with an extremely poor prognosis. Favorable safety and tolerability are consistent with the design of pirtobrutinib as I already highlighted in the CLL section. There's a randomized global phase 3 trial comparing pirtobrutinib with investigators choice of covalent BTK inhibitors, and BTK inhibitor–naive relapsed mantle cell lymphoma—so essentially pirtobrutinib versus ibrutinib, acalabrutinib, or zanubrutinib.



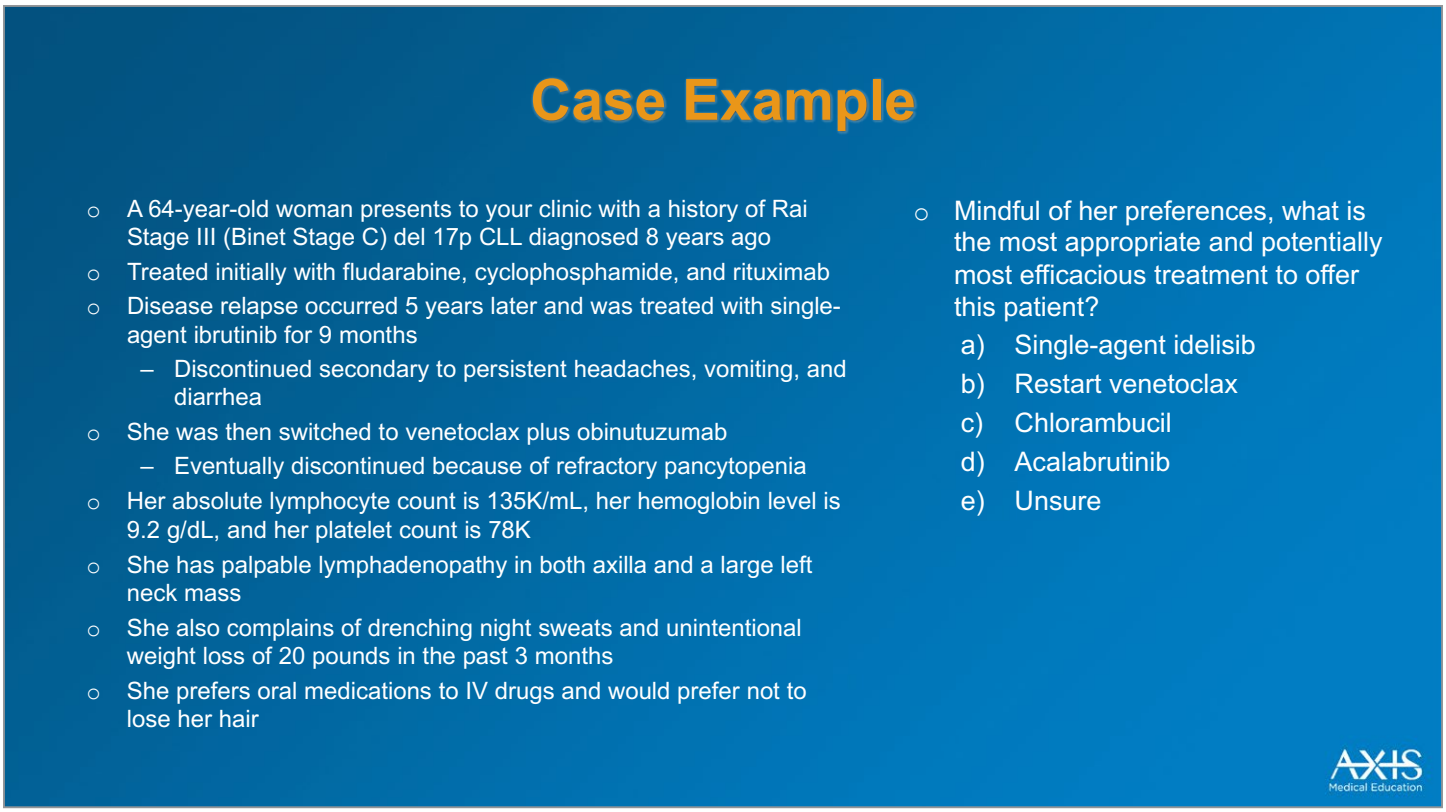
- Here are the summary data for the non-covalent BTK inhibitors. In terms of intolerance, we have promising safety data with favorable adverse event profile and low discontinuation rate due to adverse events. This is particularly true of pirtobrutinib with a head-to-head comparison planned versus ibrutinib. In terms of resistance, we have promising phase 1/2 data suggesting reversible BTK inhibitors can overcome C481 mutant CLL and possibly other mechanisms of resistance.



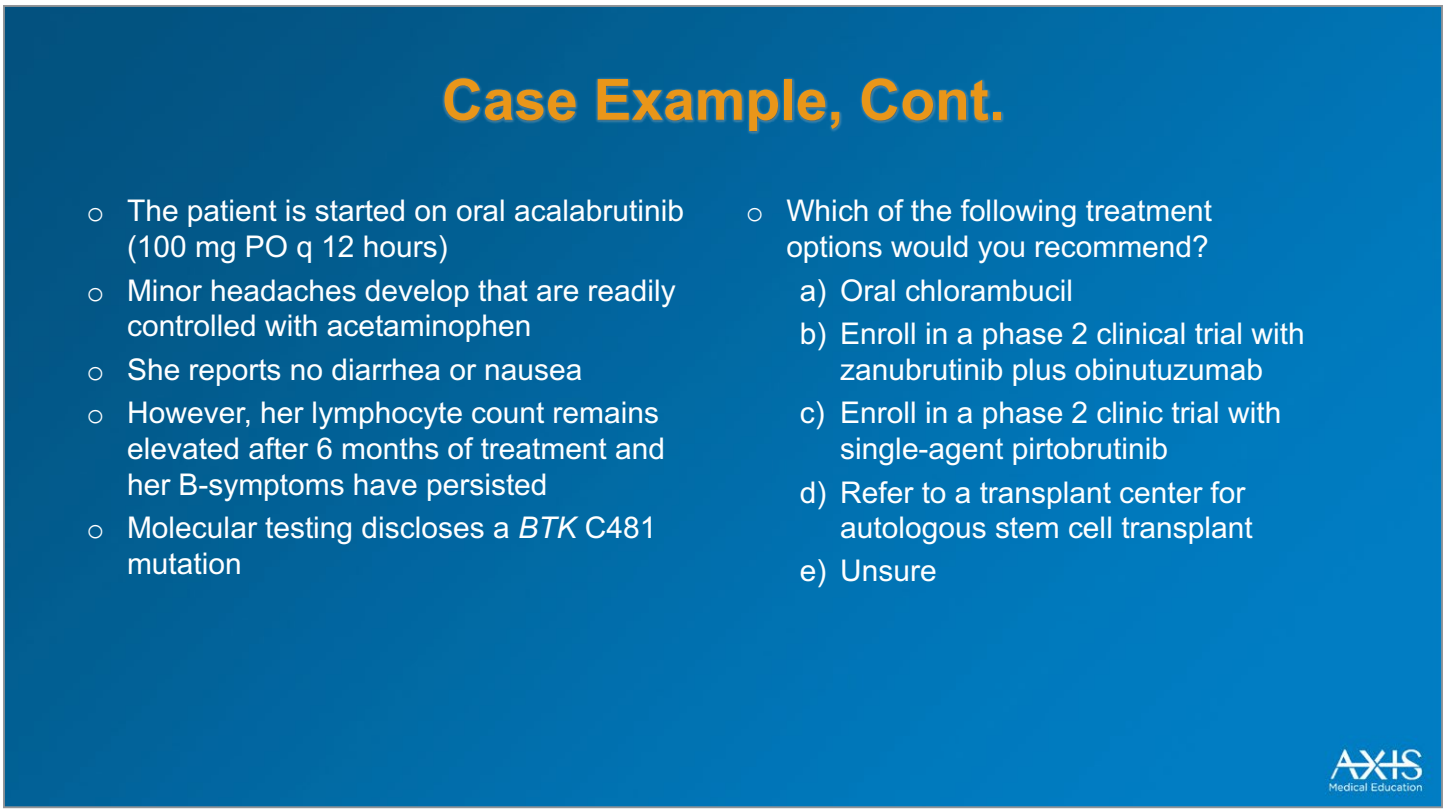
- Here is a sequencing algorithm for patients who start with a covalent BTK inhibitor and then may discontinue either due to progression or intolerance. Right now, I've included non-covalent BTK inhibitors on the algorithm where they approved, but certainly the trials that I've highlighted provide opportunity to move this class of agents up to even higher levels in the relapsed/refractory or frontline settings.



- Here is a sequencing algorithm that includes venetoclax and obinutuzumab, focusing on the reasons for discontinuation and incorporation of current therapies, where you can see non-covalent BTK inhibitors can easily fit into the third-line setting with more modern trials potentially moving this up to earlier lines of therapy.



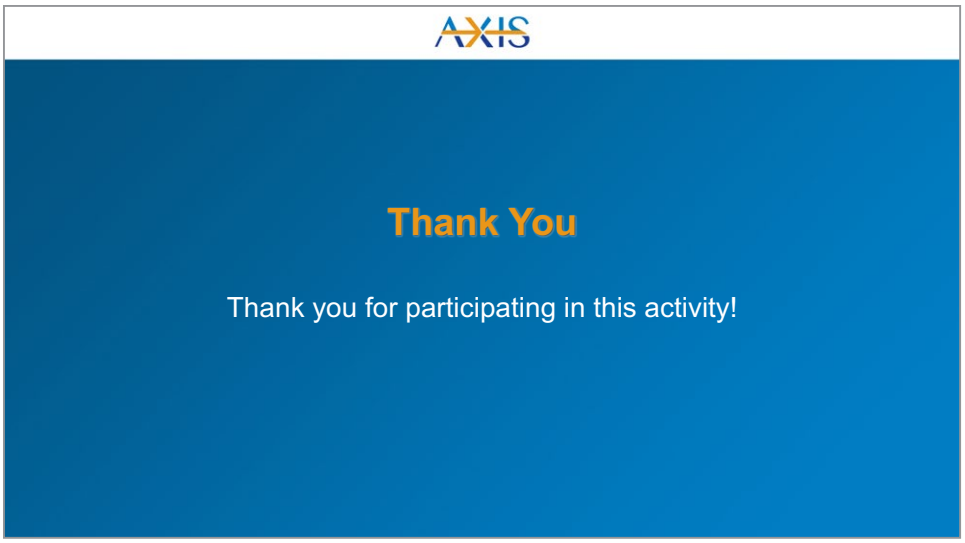
I also want to discuss a case today. This is a 64-year-old woman who presents to your clinic with a history of stage 3 CLL deletion 17p. CLL was diagnosed 8 years ago and treated initially with fludarabine, cyclophosphamide, and rituximab. She experienced disease relapse 5 years later and then was treated with ibrutinib for 9 months; however, ibrutinib was discontinued in the setting of adverse events, specifically headaches, vomiting, and diarrhea. She was then switched to venetoclax plus obinutuzumab, but this was discontinued also due to pancytopenia. Now disease is progressing following discontinuation. She has a high white blood cell count, decreased hemoglobin and platelet count, palpable lymphadenopathy at several locations, and drenching night sweats. She's also lost 20 pounds in the previous 3 months. After you've ruled out Richter transformation, you decide she needs CLL-directed therapy. She's only interested in oral medications, not IV, and so you are mindful of her preferences, and consider the following choices: single-agent idelalisib, rechallenge with venetoclax, chlorambucil, or acalabrutinib.



In this setting, the patient chooses acalabrutinib, which is a completely reasonable option given that it is all oral and that she discontinued ibrutinib in the setting of intolerance. She has minor headaches on acalabrutinib but gets over that with acetominophen. She has no nausea or diarrhea. However, 15 months later, progressive lymphadenopathy and B symptoms develop, and molecular testing reveals a C481 mutation.

So now we have some other options to explore. Oral chlorambucil, enrollment on a trial looking at zanubrutinib plus obinutuzumab, enrollment on a trial looking at pirtobrutinib, referral for transplantation. I'll just go through these choices and give you my opinion.

Oral chlorambucil is not a standard of care in this setting. Chemotherapy in general has not been tested in these patients who have been receiving prior targeted therapies. Chlorambucil is a medicine whose time has passed. It was introduced in the mid-1950s. This would not be a viable option. Zanubrutinib also would not be an option here particularly because of the C481 mutation. This really renders the class of covalent inhibitors to be ineffective. Pirtobrutinib would be an excellent option here. This patient is similar to the patient population studied in the BRUIN trial, and therefore we would expect to see the same results or similar results to what I presented. Transplantation particularly allogeneic transplant, could be considered in a young, fit patient, but the disease needs to be controlled initially anyway, so you need an agent like pirtobrutinib to do so. And then you could consider that, but I wouldn't consider that the treatment option at this time.



- Thank you so much for participating in this activity.

REFERENCES

Ahn IE, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. *Blood* 2017;129:1469-1479.

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

Binnerts ME, Otipoby KL, Hopkins BT. SNS-062 is a potent noncovalent BTK inhibitor with comparable activity against wild type BTK and BTK with an acquired resistance mutation. *Mol Cancer Ther.* 2015;14:C186.

Brandhubrt B, Gomez E, Smith S, et al. LOXO-305, A next generation reversible BTK inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216.

Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med*. 2020;383:460-473.

Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia* 2020;34:787-7898.

Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. *Nat Commun.* 2016;7:11589.

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

Byrd JC, Smith S, Wagner-Johnston N, et al. First-in-human phase 1 study of the BTK inhibitor GDC-0853 in relapsed or refractory B-cell NHL and CLL. *Oncotarget* 2018;9:13023-13035.

Byrd JC, Owen RG, O'Brien SM, et al. Pooled analysis of safety data from clinical trials evaluating acalabrutinib monotherapy in hematologic malignancies [abstract]. *Blood* 2017;130(suppl 1):4326.

Cheah CY, Chihara D, Romaguera JE, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. *Ann Oncol.* 2015;26:1175-1179.

Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016;387:770-778.

Epperla N, Hamadani M, Cashen AF, et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-a "real world" study. *Hematol Oncol*. 2017;35:528-535.

Flinn IW, O'Brien S, Kahl B, et al Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood* 2018;131(8):877-887.

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2014;370:997-1007.

Herman SEM, Montraveta A, Niemann CU, et al. The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib demonstrates potent on-target effects and efficacy in two mouse models of chronic lymphocytic leukemia. *Clin Cancer Res*. 2017;23(11):2831-2841.

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

Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2018;19:65-75.

Kaptein A, de Bruin G, Emmelot-van Hoek, et al. Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies. *Blood* 2018;132(suppl 1):1871.

Martin P, Maddocks K, Leonard JP, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. *Blood* 2016;127:1559-1563.

Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica* 2018;103:874-879.

Mato AR, Pagel JM, Coombs CC, et al. Pirtobrutinib, a next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: updated results from the phase 1/2 BRUIN study. *Blood* 2021;138:391.

Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet* 2021;397:892-901.

Mato AR, Roeket LE, Jacobs R, et al. Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clin Cancer Res.* 2020;26:3589-3596.

Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94:1353-1363.

O'Brien S, Hillmen P, Coutre S, et al. Safety Analysis of four randomized controlled studies of ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma or mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk.* 2018;18:648-657.

Ondrisova L, Mraz M. Genetic and non-genetic mechanisms of resistance to BCR signaling inhibitors in B cell malignancies. *Front Oncol*. 2020;10. doi.org/10.3389/fonc.2020.591577.

Rai S, Tanizawa Y, Cai Z, et al. MCL-041: outcomes for recurrent mantle cell lymphoma post-BTK inhibitor therapy in Japan: an administrative database study. *Clin Lymphoma Myeloma Leuk.* 2021;21(suppl 1):S407-S408.

Reiff SD, Mantel R, Smith LL, et al. The BTK inhibitor ARQ 531 targets ibrutinib-resistant CLL and Richter transformation. *Cancer Discov*. 2018;8:1300-1315.

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

Sedlarikova L, Petrackova A, Papajik T, et al. Resistance-associated mutations in chronic lymphocytic leukemia patients treated with novel agents. *Front Oncol.* 2020;10:894.

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib 3 obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Elevate-TN four-year follow up. *J Clin Oncol.* 2021;39:7509.

Siddiqi T, Aoumerai JD, Dorritie KA, et al Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. *Blood* 2021 Oct 26;blood.2021011895.

Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood* 2020;136:2038-2050.

Thompson MC, Roeker LE, Coombs CC, et al. Addressing a new challenge in chronic lymphocytic leukemia: outcomes of therapies after exposure to both a covalent Bruton's tyrosine kinase inhibitor and venetoclax. *Blood* 2021;138(suppl 1):2628.

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369:507-516.

REFERENCES

Wang M, Shah NN, Alencar AJ, et al. Pirtobrutinib, A next generation, highly selective, non-covalent BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study. *Blood* 2021;138:381.

Woyach JA, Flinn IW, Awan FT, et al. Preliminary efficacy and safety of MK-1026, a non-covalent inhibitor of wild-type and C481S mutated Bruton tyrosine kinase, in B-cell malignancies: a phase 2 dose expansion study. *Blood* 2021;138:392.

Woyach JA, Furman RR, Liu T-M, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med.* 2014;370:2286-2294.

Woyach J, Huang Y, Rogers K, Bhat SA, Grever MR, Lozanski A, et al. Resistance to acalabrutinib in CLL Is mediated primarily by BTK mutations. *Blood* 2019;134(suppl. 1):504.

Woyach JA, Ruppert AS, Guinn D, et al. BTK C481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol.* 2017;35:1437-1443.

About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

AXIS
Medical Education