CME

How I Think, How I Treat: BTK Inhibitors as a Clinical Strategy in CLL, MCL, and Beyond—Therapeutic Selection, Sequencing, and Next Steps

PeerView

Chair

Andre H. Goy, MD
John Theurer Cancer Center
Regional Cancer Care Associates
Georgetown University
Seton Hall
Hackensack Meridian School of Medicine
Hackensack, New Jersey

Faculty

Richard R. Furman, MD
Weill Cornell Medicine
New York, New York

Faculty

Krish Patel, MD
Swedish Cancer Institute
Center for Blood Disorders and Stem Cell Transplantation
Seattle, Washington

Faculty

Deborah M. Stephens, DO
University of Utah/Huntsman Cancer Institute
Salt Lake City, Utah

What's Inside

MLI
Medical Learning Institute, Inc.

This CME activity is jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

Participate in interactive questions, download activity slides, and obtain your instant CME credit online.

PeerView.com/FKM900

Activity Information

Media: Enduring Material
Accredited Activity Release Date: December 30, 2019
Accredited Activity Expiration Date: December 29, 2020
Time to Complete Activity: 120 minutes

Activity Description
First- and second-generation Bruton tyrosine kinase (BTK) inhibitors have transformed the therapeutic landscape of several lymphoid cancers, including chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL). The present and future management of these diseases will increasingly be defined by the integration of BTK inhibitors—along with other novel therapeutics—into management protocols that have previously been characterized by the use of immunochemotherapy-focused options. Several important practical issues arising from the use of BTK inhibitors, ranging from the initial therapy selection to therapeutic sequencing and use of active combinations, will continue to be a part of patient management for years to come.

This PeerView Live "How I Think, How I Treat" on-demand activity, based on a satellite symposium preceding the 61st ASH Annual Meeting and Exposition, exposes learners to the personal insights of several experts in the field and includes in-depth analyses of the cutting-edge science on the present and future role of BTK inhibitors in CLL, MCL, and other lymphoid cancers. Key topics include BTK inhibitor sequencing, selecting patients for treatment, differentiating among first- and second-generation compounds, and safety management. Ultimately, this event provides a "virtual mentorship" experience on the use of BTK inhibitors in several different diseases.

Target Audience
The activity has been designed to meet the educational needs of hematologists, hematologist-oncologists, and other clinicians involved in the management of patients with B-cell malignancies.

Educational Objectives
Upon completion of this activity, participants should be better able to:
- Describe updated evidence regarding the use of first- and second-generation BTK inhibitors in the management of B-cell NHL, including agent potency/selectivity, response data, survival outcomes, and activity in BTK inhibitor–intolerant or –resistant disease
- Recommend personalized therapy with BTK inhibitors for patients across the spectrum of B-cell malignancies, including chronic lymphocytic leukemia and mantle cell lymphoma, among others
- Manage unique safety considerations associated with BTK inhibitor therapy in patients with B-cell NHL

Providership, Credit, and Support
This CME activity is jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

This activity is supported by an independent educational grant from AstraZeneca.

Physician Continuing Medical Education
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education. The Medical Learning Institute, Inc. is accredited by the ACCME to provide continuing medical education for physicians.

The Medical Learning Institute, Inc. designates this enduring material for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Faculty Disclosures
Chair
Andre H. Goy, MD
Chairman & Executive Director
Lymphoma Division Chief – John Theurer Cancer Center
Chief Science Officer – Regional Cancer Care Associates
Lydia T. Pfund Chair for Lymphoma
Professor of Medicine – Georgetown University
Professor and Chair, Dept. of Oncology, Seton Hall
Hackensack Meridian School of Medicine
Hackensack, New Jersey

Andre H. Goy, MD, has a financial interest/relationship or affiliation in the form of:
Consultant and/or Advisor for Acerta Pharma; Celgene Corporation; Janssen Pharmaceuticals, Inc.; and Kite Pharma, Inc./Gilead.
Grant/Research Support from Acerta Pharma; AstraZeneca; Bayer; CALGB (Cancer and Leukemia Group B); Celgene Corporation; Genentech, Inc.; Janssen Pharmaceuticals, Inc.; Kite Pharma, Inc.; MD Anderson; MorphoSys; and Pharmacyclics LLC.
Other financial interest/relationship Board Member and shareholder for COTA.

Faculty
Richard R. Furman, MD
Morton Coleman, M.D. Distinguished Professor of Medicine
Weill Cornell Medicine
New York, New York

Richard R. Furman, MD, has a financial interest/relationship or affiliation in the form of:
Consultant and/or Advisor for AbbVie; Acerta Pharma; AstraZeneca; BeiGene; Genentech, Inc.; Janssen Pharmaceuticals, Inc.; Loxo Oncology; Oncotracker; Pharmacyclics LLC; Sunesis Pharmaceuticals.; TG Therapeutics, Inc.; and Verastem.
Grant/Research Support from Acerta Pharma; AstraZeneca; Janssen Pharmaceuticals, Inc.; and TG Therapeutics, Inc.
Data Safety Monitoring Board for Incyte Corporation.
Other financial interest/relationship Speaker fee from AbbVie and Janssen Pharmaceuticals, Inc.

Krish Patel, MD
Director, Lymphoma Program
Swedish Cancer Institute
Center for Blood Disorders and Stem Cell Transplantation
Seattle, Washington

Krish Patel, MD, has a financial interest/relationship or affiliation in the form of:
Consultant and/or Advisor for AstraZeneca; Celgene Corporation; Genentech; Pharmacyclics/Janssen; and Sunesis Pharmaceuticals.
Grant/Research Support from AstraZeneca.
Speakers Bureau participant with AstraZeneca; Celgene Corporation; Genentech; and Pharmacyclics/Janssen.

Deborah M. Stephens, DO
Assistant Professor
Division of Hematology and Hematologic Malignancies
University of Utah/Huntsman Cancer Institute
Salt Lake City, Utah

Deborah M. Stephens, DO, has a financial interest/relationship or affiliation in the form of:
Grant/Research Support from Acerta Pharma; Gilead; and Karyopharm.

Planning Committee Disclosures
The planners from Medical Learning Institute, Inc., the accredited provider, and PeerView Institute for Medical Education, the joint provider, do not have any financial relationships with an ACCME-defined commercial interest related to the content of this accredited activity during the past 12 months unless listed below.

Content/Peer Reviewer Disclosures
The following Content/Peer Reviewer has nothing to disclose:
Natalie I. Vokes, MD

Disclosure of Unlabeled Use
This educational activity may contain discussions of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Method of Participation
There are no fees for participating in or receiving credit for this accredited activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and will be emailed to you upon completion. You will receive your certificate from email@email.peerviewpress.com. If you have questions regarding the receipt of your emailed certificate, please contact via email at info@PeerView.com.

About This CME Activity
PVI, PeerView Institute for Medical Education, and Medical Learning Institute, Inc. are responsible for the selection of this activity's topics, the preparation of editorial content, and the distribution of this activity. Our activities may contain references to unapproved products or uses of these products in certain jurisdictions. The preparation of PeerView activities is supported by educational grants subject to written agreements that clearly stipulate and enforce the editorial independence of PVI and Medical Learning Institute, Inc.

The materials presented here are used with the permission of the authors and/or other sources. These materials do not necessarily reflect the views of PeerView or any of its partners, providers, and/or supporters.

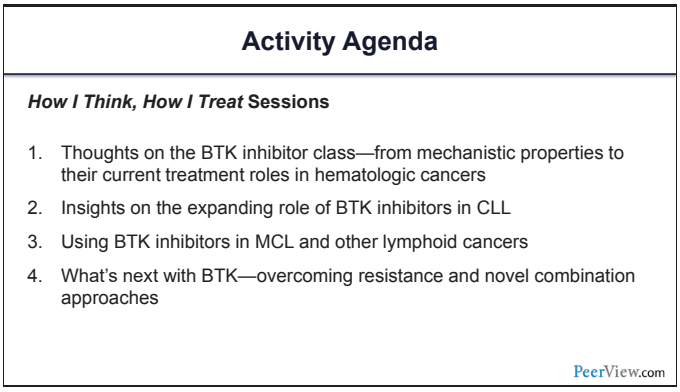
Welcome and Introduction

Andre H. Goy, MD

Dr. Goy: Good morning. My name is Andre Goy. I'm the Chairman of Oncology at Hackensack Meridian Health, and I want to welcome you to this symposium.

I want to thank my colleagues and speakers who will share with us this morning some of the most rapid changes in the field of hematology/oncology. And we are very fortunate to be practicing oncology nowadays. I'm totally convinced that the field is going to continue to accelerate. And just to give you an idea, in medicine, it is estimated that we have over 10,000 new drugs in the pipeline; two-thirds are in oncology. So there's a lot of work ahead of us.

We're going to focus this morning on BTK inhibitors as a clinical strategy in a variety of lymphoid malignancies—CLL, MCL, and beyond—and try to see how these rapid changes are impacting the way we practice.



So, today's agenda: the "How I Think, How I Treat" sessions. Again, we'll try to be very practical. We're going to start with an overview of the thoughts on the BTK inhibitor class—from their mechanistic properties to their current treatment roles in hematological cancers.

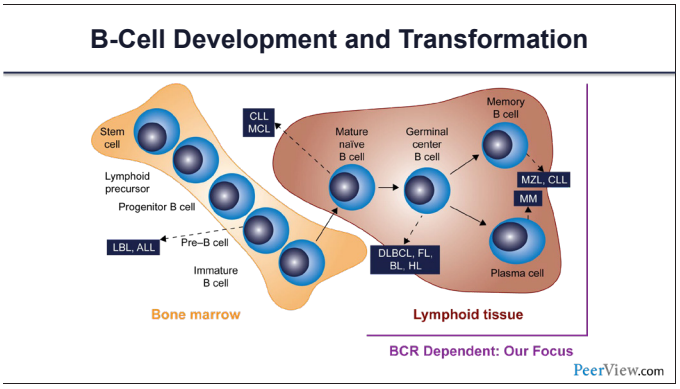
Then we'll go on to discuss insights on the expanding role of BTK inhibitors in CLL, where they have had a dramatic impact, as we'll hear. And then we'll go over the use of BTK in MCL and other lymphoid malignancies. Also, we'll look at what's next in BTK, particularly overcoming resistance and novel combination approaches.

Targeting the BCR Pathway: My Take on the Emergence of BTK Inhibitors as Potent Targeted Options in B-Cell Cancer

Krish Patel, MD

Dr. Goy: So, it is my pleasure to start by introducing Dr. Krish Patel, who is the Director of the Lymphoma Program at the Swedish Cancer Institute. Krish has a lot of interest in novel therapies in lymphoma, so he's going to tell us about how BTK became such an important field, focusing on the BCR pathway. Krish, thank you.

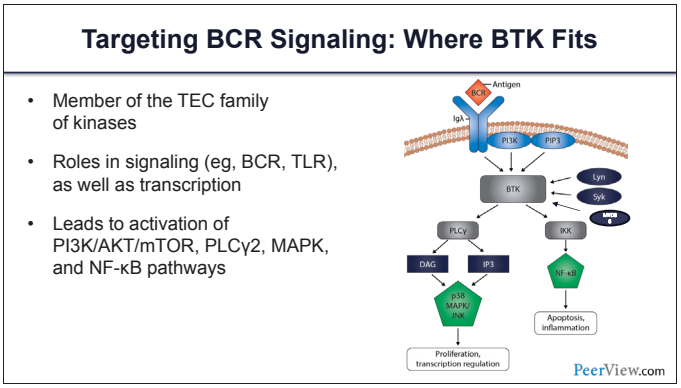
Dr. Patel: Thank you Dr. Goy. And thank you all. So, my job is really to set the stage for you.



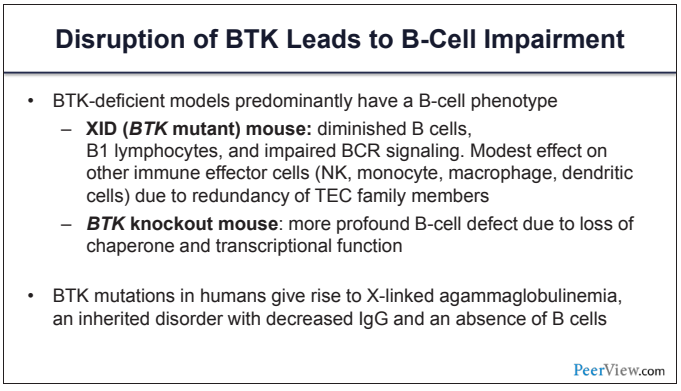
So, I'm going to start by providing an overview of the BCR pathway. And, just to remind you all, when we're thinking about mature B-cell malignancies, remember that these are diseases that originate at different time points in B-cell maturation. But primarily, what we're thinking about are diseases that arise in lymphoid tissue—so, recognizing that the normal B cell goes through a maturation process in secondary lymphoid organs. This is really where the B cells acquire their affinity for target antigens, and, as such, there's a lot of important biology that involves the B cell receptor pathway that can become dysregulated and lead to lymphomagenesis.

And so, thinking about the BCR pathway, I remember that a normal B cell has an extracellular receptor that is responsible for binding a cognate antigen, and that receptor is coupled through a number of adaptor proteins and kinase inhibitors to ultimately control proliferation and a number of transcriptional programs once that B cell encounters its antigen.

This pathway can become quite disordered and dysregulated in a number of mature lymphoid malignancies, and it makes sense that we might be able to target some of the moieties that are associated with the BCR.

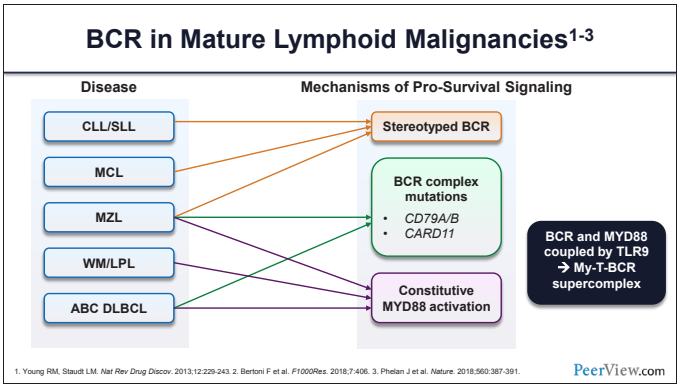


In particular, BTK, or Bruton's tyrosine kinase, is a member of the TEC family of kinases, and BTK seems to have a central role in the B-cell receptor pathway, as well as in interfacing with other pathways through toll-like receptors and other adaptor proteins.



So, it makes sense that if we have this central moiety in the B-cell receptor pathway, that perhaps we can target this therapeutically. We know that disruption of BTK in normal B cells has a profound impact on B-cell phenotype. So, for example, if we were to knock out BTK, or to create mutant forms of BTK in animal models, we see that we achieve diminished B-cell numbers and impaired BCR signaling, and there tends to be a modest effect on other immune effector cells. So this seems to be more important in B cells than in other immune cells. And, of course, we know that there are some

diseases of germline mutations in BTK that give rise to human diseases, for example, X-linked agammaglobulinemia—and this was the disorder in which BTK was first actually discovered by Ogden Bruton, for which BTK is named: Bruton's tyrosine kinase.



So, disruption of BTK leads to changes in B-cell phenotype, and, as I mentioned, there are a number of mature lymphoid diseases in which the B-cell receptor is disordered. In particular, there are a number of ways in which B-cell receptor signaling can be disordered in mature lymphoid diseases.

Many of these mechanisms lead to tonic signaling through the BCR, which then leads to pro-survival signals or pro-proliferation signals. And across different diseases, there are a number of different mechanisms by which this might happen.

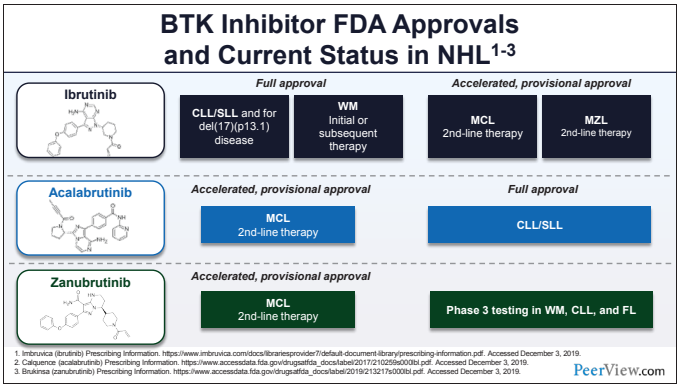
One is stereotyping of the B-cell receptor, which may suggest perhaps that there are autoantigens that can drive lymphomagenesis. The other may be gain-of-function mutations in proteins associated with a B-cell receptor complex, such as *CD79A/B* or *CARD11*.

And then, as well, there are adaptor proteins that will link the B-cell receptor signaling cascade to other cascades—an adaptor protein such as MYD88, which links the BCR complex to a toll-like receptor—the so-called My-T-BCR supercomplex.

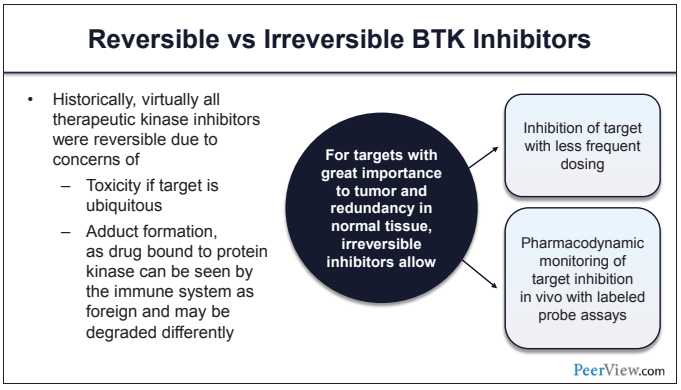
And what we see is, across different lymphoid diseases, we may have one or more of these types of mechanisms that lead to tonic B-cell receptor signaling. So, in these diseases in particular, it may make sense to target BTK, which plays a central role in B-cell receptor signaling.

Current-Generation BTK Inhibitors

So, that sort of sets the stage for why this might be an important approach. What do we know about this strategy?



So, we have now three BTK inhibitors approved for clinical use. Ibrutinib was the first and has full approval in CLL, Waldenström's, mantle cell lymphoma, and marginal zone lymphoma. Acalabrutinib is now approved for mantle cell lymphoma and CLL. And zanubrutinib is approved for second-line therapy in mantle cell lymphoma, and in ongoing studies in Waldenström's, CLL, and follicular lymphoma.



So, I'll tell you a little bit about each of these agents and how they might be different. But before I do that, I just want to bring up an important historical note. So, really, until the development of BTK inhibitors for clinical use, almost all therapeutic kinase inhibitors

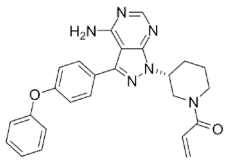
that were used were reversible, and that's due to a couple concerns.

So, previously, it was felt that perhaps irreversible inhibitors may be more toxic if the target that they inhibit is ubiquitous. As well, if we're forming covalent bonds with kinases, perhaps that increases immunogenicity. And so for a long time most of the kinase inhibitors that we use in oncology are of the reversible kind.

However, if we think about the fact that there are some targets where the kinase that we wish to inhibit is much, much more important in the tumor and then there's a redundancy in normal tissues, perhaps irreversible inhibitors in that setting may be beneficial. They might allow us to have less frequent dosing. They may allow us different ways to actually monitor target inhibition. And this is the setting in which BTK inhibitors have been developed.

Ibrutinib: First BTK Inhibitor Approved for Use in Hematologic Cancers[1]

A Potent *Irreversible* BTK Inhibitor



- Forms a specific and irreversible bond with cysteine-481 in BTK
- Potent and **irreversible** BTK inhibition with IC_{50} = 0.5 nM
- Blocks BCR signaling; active in canine model of spontaneous lymphoma
- Orally bioavailable with short half-life
- Alternative irreversible targets could include EGFR, ERBB4, BMX, ITK, TEC, BLK, and JAK3; many reversible targets

1. Honigberg LA et al. *Proc Natl Acad Sci USA*. 2010;107:13075-13080.

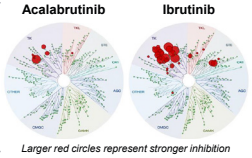
PeerView.com

So ibrutinib, as you all know, is the first irreversible BTK inhibitor available for clinical use. It forms a covalent bond with the cysteine-481 residue in BTK. It's a potent and irreversible inhibitor, so it inhibits at nanomolar concentrations. And we know that ibrutinib impairs B-cell receptor signaling through preclinical studies. It's orally bioavailable and has a short half-life, and in addition to binding and inhibiting BTK, it does have some other irreversible targets, including EGFR, other TEC kinases, and many reversible targets. So it's selective for BTK, but does also have some off-target kinase effects.

Acalabrutinib: Next-Generation BTK Inhibitor Approved in MCL and CLL[1]

Acalabrutinib is more selective for BTK compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 µM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126	10
ITK	>1,000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1,000	5.3
ERBB2	~1,000	6.4
ERBB4	16	3.4
BLK	>1,000	0.1
JAK3	>1,000	32

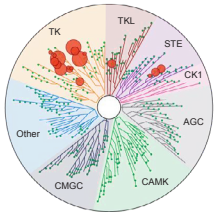
1. Byrd JC et al. *N Engl J Med*. 2016;374:323-332.

PeerView.com

What about acalabrutinib? How does this differ? Acalabrutinib is generally more selective for BTK compared to ibrutinib. So, if we look at this kinome scan here, you see that, generally, acalabrutinib is largely hitting TEC family kinases, and not much outside of the TEC family. And even within the TEC family of kinases, we see that acalabrutinib has selectivity for BTK over other TEC kinases, such as TEC or ITK.

Zanubrutinib: Next-Generation BTK Inhibitor Approved in MCL, Being Assessed in CLL[1]

Zanubrutinib



- Zanubrutinib (BGB-3111) is an investigational second-generation irreversible BTK inhibitor
- Lower off-target inhibitory activity on other kinases, including ITK, JAK3, and EGFR[1]
- Recent FDA accelerated approval for the treatment of patients with MCL who have previously received ≥1 prior therapy

1. Hillmen P et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract TPS7572

PeerView.com

What about zanubrutinib? So it has a different selectivity profile than ibrutinib and, again, is an irreversible BTK inhibitor.

Potency of BTK Inhibitors (Based on Biochemical Binding Kinetics)[1]

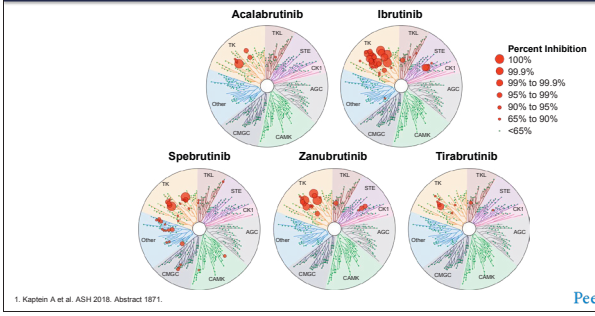
BTK Parameter	Acalabrutinib	Ibrutinib	Zanubrutinib
K_I (nM)	181 ± 13.6	54.2 ± 48.6	126 ± 58.5

1. Kaptein A et al. 60th American Society of Hematology Annual Meeting & Exposition (ASH 2018). Abstract 1871.

PeerView.com

And so we see that we now have three kinase inhibitors that irreversibly inhibit BTK at nanomolar concentrations.

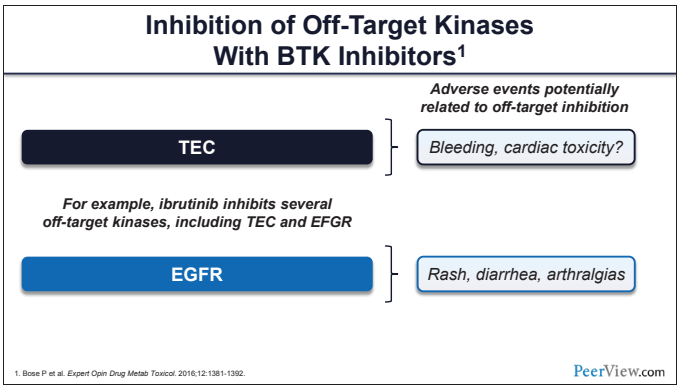
Differences in Overall Kinase Selectivity Among BTK inhibitors[1]



1. Kaptein A et al. ASH 2018. Abstract 1871.

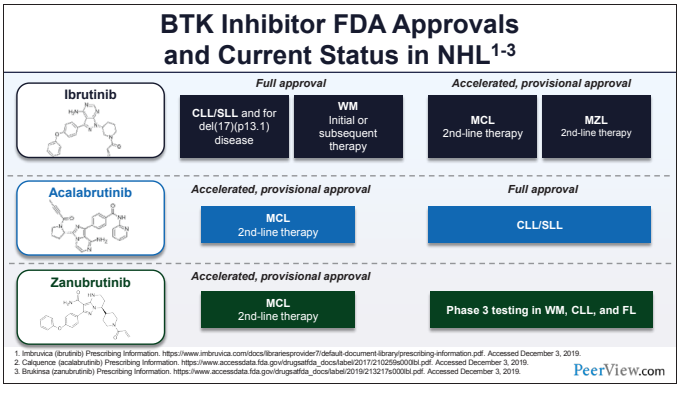
PeerView.com

And I like this slide here because you can see visually that, while we are therapeutically targeting BTK, the selectivity of the kinase inhibitors is quite different across the board. So we go from the most selective, which is acalabrutinib, to the least selective, which is ibrutinib.



And why might that selectivity matter? Well, we know from clinical studies—and my colleagues will review some of these—that there are adverse events associated with BTK inhibitors, and some of these adverse events may be driven by off-target kinase inhibition. In particular, we know that BTK inhibitors are associated with bleeding risk and cardiac toxicity. While it's not completely clear what drives that, it may be, in part, mediated by TEC kinase inhibition.

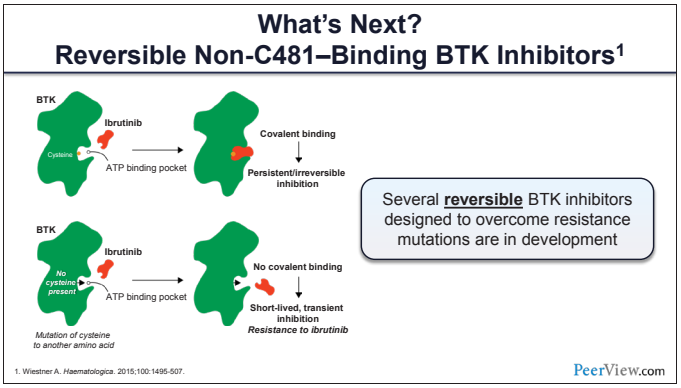
And we have another host of adverse events that are commonly reported in clinical trials that affect patient quality of life, and some of these toxicities may be driven by off-target inhibition of EGFR.



So this selectivity may be important as we're thinking about toxicity profiles. And as we'll hear shortly, all of these agents have been studied in CLL and mantle cell lymphoma.

Next-Generation BTK Strategies

What about the next generation of BTK strategies?

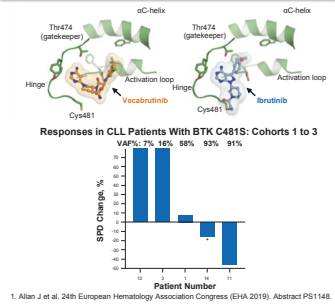


Well, all of the drugs that I mentioned to you previously are irreversible inhibitors. They all have the same binding site, so they all irreversibly bind C481 and BTK.

And one potential challenge of irreversible inhibitors is that, if the BTK molecule is mutated—so, for example, there is no cysteine present in the binding space—that renders these agents relatively ineffective at inhibiting BTK. So they go from being irreversible inhibitors to transient reversible inhibitors. And this is one of the mechanisms of resistance that occurs in CLL, and may occur in other lymphoid malignancies as well.

And so, there are now a host of reversible BTK inhibitors that have different binding sites, or different mechanisms of action, that are being designed to overcome resistance.

Vecabrutinib Selectively Inhibits BTK, With Potential Activity in *BTK* C481S CLL/SLL Patients[1]



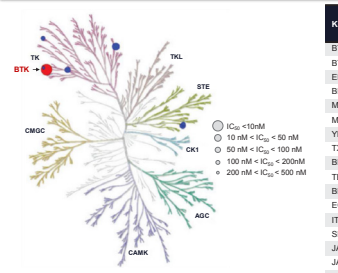
	Vecabrutinib IC_{50}, nM	Ibrutinib IC_{50}, nM
TEC family kinases		
BTK	3	0.5
ITK	14	10.7
TEC	14	78
TXK	474	2
BMX	224	0.8
Other kinases		
LCK	8	33.2
c-SRC	84	171
BLK	23	0.5
NEK11	90	NR
EGFR	>1,000 (6,644)	5.6
ERBB2	450	9.4
ERBB4	317	3.4
CSK	>1,000	2.3
FGR	>1,000	2.3
BRK	>1,000	3.3
HCK	276	3.7
YES	402	6.5
JAK3	>1,000	16.1
FRK	>1,000	29.2
RET	>1,000	36.5
FLT3	>1,000	73
ABL	>1,000	86
FYN	651	96

1. Allan J et al. 24th European Hematology Association Congress (EHA 2019). Abstract PS1148.

PeerView.com

So, for example, on the right here, you see that vecabrutinib selectivity for TEC-family kinases is quite selective, with relatively little off-target inhibition of other major kinase families. Very, very early data suggests potential for clinical activity in CLL patients who have C481 mutations.

LOXO-305 Potently and Selectively Inhibits BTK and *BTK* C481S Kinase Activity[1]



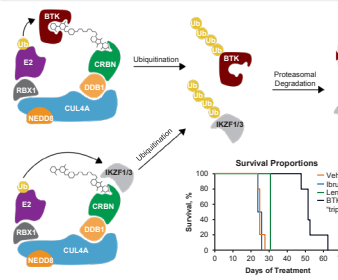
Kinase	Percent of Control at 1 μM LOXO-305, [ATP] = K_m, %	IC_{50} [ATP] = K_m, nM	Fold Selectivity Over BTK
BTK C481S	ND	1.42	0.5
BTK	1.8	3.15	1.0
ERBB4	2.6	13.3	4.2
BRK	10.3	54.3	17
MEK2	7.6	82.7	26
MEK1	12.2	147	47
YES1	38.6	157	50
TXK	19.6	209	66
BMX	70.2	1,155	367
TEC	64.6	1,234	392
BLK	72.8	4,100	1,302
EGFR	60.6	>1,000	>317
ITK	103	>5,000	>1,587
SRC	90.5	>5,000	>1,587
JAK1	96.4	>30,000	>9,524
JAK2	94.5	ND	ND
JAK3	97	ND	ND

1. Brandhuber B et al. Society of Hematologic Oncology Sixth Annual Meeting (SOHO 2018). Abstract CLL-200.

PeerView.com

The LOXO compound is also quite selective. And here you can see that it has greater selectivity for C481S-mutant BTK than even the native BTK. And so, these agents may provide a useful tool in patients who have developed resistance to our existing class of irreversible inhibitors.

BTK Degraders[1]



- E3 ligase ligand binds BTK through linked BTK ligand
- Promotes BTK ubiquitination and subsequent proteasomal degradation
- In vitro, it can overcome *BTK* C481S resistance

1. Dobrovolsky E et al. *Blood*. 2019;133:952-961.

PeerView.com

What about beyond that? Well, in preclinical studies, we now have different examples of what are so-called BTK degraders. So rather than inhibit the kinase with a small molecule, we may be actually able to degrade the BTK.

And this is an example from a preclinical study that demonstrates that by using small molecules that bind to E3 ubiquitin ligase complexes on one end, and then BTK on the other, we can actually target BTK for ubiquitination and then subsequent proteasomal degradation. And this may also prove to be a strategy in the future that could overcome C481S resistance.

How I Think, How I Treat

And then, as a final part of my talk, I was asked to think a little bit about how I use these agents in my own practice. And, as you'll hear from my colleagues today, there's a lot of data to inform us about how these agents may be used.

How I Think, How I Treat
Placing BTK Inhibitors in CLL and MCL Care

CLL/SLL

TN
BTKi is my preferred first-line option for ***most*** patients

R/R
There are several choices, but BTK-directed strategies continue to be attractive

MCL

BTKi is my preferred second-line therapy given a paradigm shift away from chemo in R/R MCL management (eg, CAR T, venetoclax)

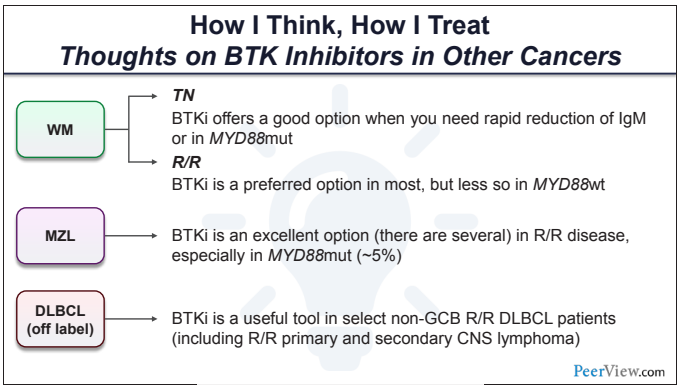
PeerView.com

But in my own practice, when I think about patients with CLL—treatment-naïve patients—so, as we'll hear later on, I think for many, BTK inhibitors may be an appropriate first-line therapy. So in CLL, the field has really shifted away from chemoimmunotherapy or genotoxic drugs to targeted therapies. We do now have choices among targeted therapies for frontline use, but in most of my patients I use BTK inhibitors.

In the relapsed/refractory setting, we really have seen a significant paradigm change to small molecule inhibitors. And so, in patients who have previously not had small molecule inhibitors, like BTK inhibitors, that remains a very attractive strategy.

And mantle cell lymphoma in the second-line, I think—as we have seen in CLL over the past few years—there really seems to be a shift away from chemoimmunotherapy-based strategies in second-line therapy and beyond. And so, BTK agents really are my

preferred second-line options there. We'll learn at this meeting more about other exciting strategies in mantle cell lymphoma.



And then when I think about less common lymphoid diseases and Waldenström's, in treatment-naïve patients we have several different options. But in particular in patients who may need rapid reduction of their IgM proteins, BTK inhibitors offer a good option. They don't usually cause IgM flares, which can be seen in rituximab-containing regimens. In particular, BTK agents seem to work best in patients who have *MYD88* mutations.

And in the relapsed/refractory setting, they can be used really across the board, but are perhaps less preferred in those who have wild-type *MYD88*.

In marginal zone lymphoma, we have a number of different choices in the relapsed setting, but it is recognized that a small proportion of patients will have *MYD88* mutations and those patients do seem to respond quite well—although patients [with marginal zone lymphoma] don't need that mutation to respond to BTK inhibitors.

And then, as a thought about off-label use, diffuse large B-cell lymphoma, which is a disease for which none of the BTK inhibitors are FDA-approved, there are some particularly useful scenarios in which these agents can be used.

So this is a disease in which, often, now even into the third-line setting, we have therapies that may be potentially providing cures. But sometimes to get to those therapies we need bridging therapies or therapies that can control the disease for short time periods.

In patients with non-germinal center B-cell lymphomas, I find BTK inhibitors can be quite useful. And recalling that BTK inhibitors do actually cross the blood-brain barrier, they can be quite helpful in the setting of primary or secondary CNS lymphoma as well.

Summary

- The B-cell receptor pathway is central to survival in CLL and various NHL histologies
- BTK plays a critical role in the B-cell receptor pathway
- Irreversible BTK inhibitors are clinically efficacious
- Differences in the off-target kinase specificity of the current BTK inhibitors ***may*** yield different toxicity profiles
- Reversible BTK inhibitors are being investigated in trials to address resistance
- BTK degradation (preclinical) may be a future strategy to further exploit BTK in CLL and NHL

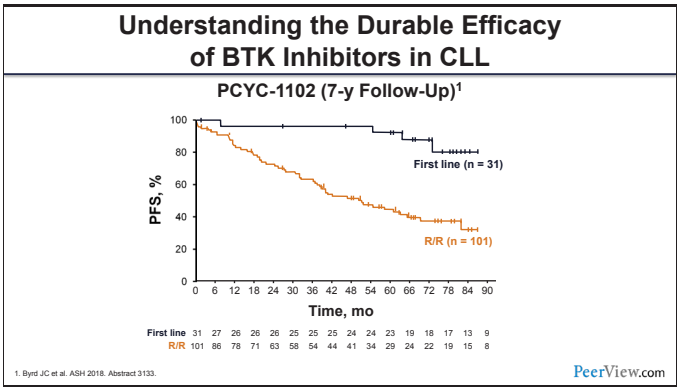
PeerView.com

All right, so to summarize, the B-cell receptor pathway plays a central role in survival in a number of mature B-cell malignancies. BTK has a central role in the B-cell receptor pathway. Our current-generation BTK inhibitors are irreversible and have proven clinical efficacy, but there are some specific differences in off-target kinase specificity that may ultimately lead to different toxicity profiles.

And as a strategy for next-generation BTK inhibition, reversible inhibitors are being investigated, as well as, potentially in the future, a very novel mechanism of BTK degraders. Thank you.

How I Use BTK Inhibitors in CLL: Thoughts on Present Applications and Future Directions

Richard R. Furman, MD



Dr. Goy: So our next speaker is Dr. Richard Furman. Richard is an authority in the field of CLL, and he will share with us his perspective on how the field is changing with the impact on BTK. And he has been involved in the development of most, if not all, novel therapy in CLL. And he has the great honor to actually carry the Chair for Mort Coleman, who is, himself, a figure in the field of lymphoma and leukemia. So, Richard, thank you.

Dr. Furman: Thank you. And thank you all for joining us.

What I hope to do with this talk is really discuss the clinical application and the clinical data that we have for these agents. Now, it's important to keep in mind that BTK inhibitors actually don't work in vitro.

And so, whereas we heard that the original idea for targeting BTK may have come from X-linked agammaglobulinemia (XLA) patients, the degradation of BTK or the absence of BTK as a protein—which is what we see in XLA—really results in a very different phenotype. And the kids with X-linked agammaglobulinemia really do have a lot of issues with infections.

And one of the important take-home messages from my discussion today will be the tolerability, and how over the long term we really see that the efficacy and the tolerability of these agents really enable our patients to enjoy what we hope will be a normal life and a normal life expectancy.

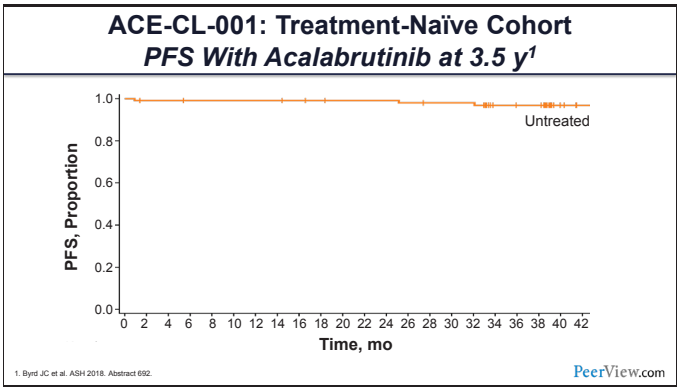
And so, with that in mind, I'd like to first just point out that, in my practice and in my view, BTK inhibitor therapy is the frontline or first-choice therapy for all my patients with CLL. I think we now have great data that shows durable responses.

And so, in essence, what I'm showing you here is the first phase 2 data looking at ibrutinib in CLL patients, and it was two populations: frontline and relapsed/refractory. And I'll speak more to the data in a moment. But I really want everyone to sort of take a look at these two curves and see that they really represent what I consider to be the current standard of care.

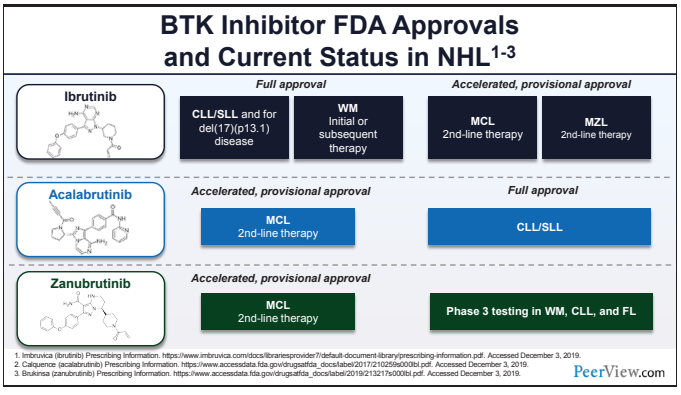
Now we have a lot of options that enable us to tailor our therapies to our patients, and I really do think that's a very important idea to keep in mind.

I also want to point out on these two curves, really, the differences between upfront and relapsed/refractory disease. So clearly, we've always known that treating relapsed disease is more difficult, and we have a tremendous amount of data in chemoimmunotherapy showing that. We do have data now in BTK inhibitor therapies that also show that.

And so it's important to remember that we talk about the efficacy. It does change when it's post-chemotherapy, in my opinion, due to a lot of the secondary changes that chemotherapy induces in the DNA.



In order just to make sure we cover the whole group of agents, I'm also showing you the acalabrutinib data here, which is certainly not as long; but you can see it certainly looks as impressive as the ibrutinib data.



So we just recently heard about the three agents and their approval pathways. I'm going to discuss the data and I want everyone to really, not so much focus on the data, as much as, sort of, the important take-home points, which are really about how these agents, I think, can be most used with our patients.

NCCN Guidelines for Treatment-Naïve CLL (2020)[1]

Patient Characteristics	Preferred Regimens	Other Recommended Regimens
Frail patients with significant comorbidities (not able to tolerate purine analogs) *Or* Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	• **Ibrutinib (category 1)** • **Acalabrutinib ± obinutuzumab** • Venetoclax + obinutuzumab	• Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) + anti-CD20 monoclonal antibody (not recommended for frail patients) • Chlorambucil + obinutuzumab • HDMP + rituximab (category 2B) • Ibrutinib + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients aged <65 y without significant comorbidities	• **Ibrutinib (category 1)** • **Acalabrutinib ± obinutuzumab** • Venetoclax + obinutuzumab	• Bendamustine + anti-CD20 monoclonal antibody • FCR (preferred for patients with *IGHV*-mutated CLL) • FR • HDMP + rituximab (category 2B) • Ibrutinib + rituximab (category 2B) • PCR (category 3)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 3.2020. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed December 3, 2019.

PeerView.com

So here are the NCCN guidelines. I'm not a big fan of guidelines. I think that looking at the patient and deciding what you think is best for the patient is really going to be the most important thing.

So, with that being said, I'd like to highlight right now, for the treatment-naïve CLL guidelines and the relapsed/refractory guidelines—for the first time now—our preferred regimens are all nonchemotherapeutic. And I think that's really a tremendous step forward. So, nonchemotherapeutic regimens: preferred regimens.

And the other thing I'd really like to emphasize is that, all of a sudden, frail or elderly versus young—there's no difference. These regimens are, sort of, recommended for both those patients who are young and old.

And it really just shows you how excellent these regimens are, and how being heavy-handed, or being most aggressive doesn't necessarily result in better outcomes. I will show some data later on looking at one issue, namely, atrial fibrillation with BTK inhibitors and the impact of age on that risk.

Updated NCCN Guidelines for R/R CLL (2020)[1]

Patient Characteristics	Preferred Regimens	Other Recommended Regimens	
Frail patients with significant comorbidities *Or* Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	• **Acalabrutinib (category 1)** • **Ibrutinib (category 1)** • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab	• Alemtuzumab ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab	• Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax • Dose-dense rituximab (category 2B) • BR ± ibrutinib, or idelalisib (not recommended for frail patients) (category 2B for BR and BR + rituximab; category 3 for BR + idelalisib)
Patients aged <65 y without significant comorbidities	• **Acalabrutinib (category 1)** • **Ibrutinib (category 1)** • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab	• Alemtuzumab ± rituximab • BR • FC + ofatumumab • FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab	• Obinutuzumab • Ofatumumab • PCR • Venetoclax • BR + ibrutinib (category 2B) • BR + idelalisib (category 2B)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 3.2020. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed December 3, 2019.

PeerView.com

And here you can see the NCCN guidelines for relapsed/refractory CLL, with duvelisib added on as an additional agent, and idelalisib for preferred regimens in relapsed/refractory CLL.

Updates on Frontline BTK Inhibition

So, a couple of updates on upfront therapy.

Summary of Major Studies With Ibrutinib in Treatment-Naïve CLL

Phase 1b/2 PCYC-1102[1]
(both TN and R/R patients)
Single-arm study
- After 7 years follow-up, durable responses with stable or improved CR rates, and sustained PFS and OS rates

RESONATE-2[2]
Randomized phase 3 (older patients)
- Improvement in PFS vs chlorambucil

Treatment-Naïve Patients

A0412021[3]
Randomized phase 3
- Ibrutinib regimens improved PFS vs BR in older patients

E1912[4]
Randomized phase 3
- Ibrutinib + rituximab improved PFS vs FCR in younger patients

1. Byrd JC et al. ASH 2018. Abstract 3133. 2. Burger JA et al. EHA 2018. Abstract PF343. 3. Woyach J et al. *N Engl J Med*. 2018;379:2517-2528. 4. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443.

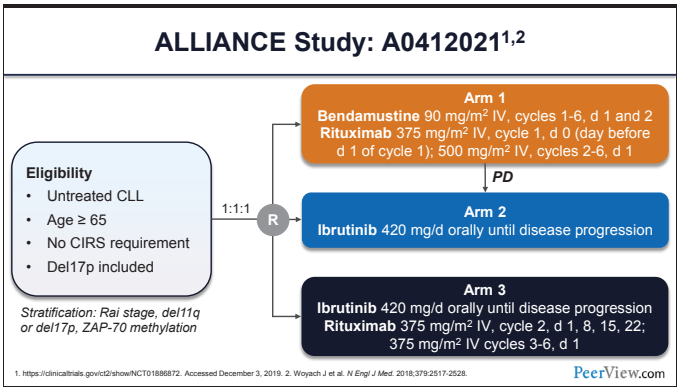
PeerView.com

Here are four studies that we have looking at treatment-naïve patients. The original study was the 1102 study, which I remarked on already, for which we have 7-year follow-up data, and which really shows durable responses with stable or improved complete response rates. And remember, these agents do work slowly so that the number of PRs with lymphocytosis is going down. And the PR rate went up initially, and now the PR rate is going down and the CR rate is going up.

And that's why I think it's always important to not look at MRD and not to look at complete remission rate, but to really focus on PFS because that's really what's most important for our patients.

The second trial is RESONATE-2, which led to the full approval of ibrutinib in treatment-naïve CLL. And that [study], of course, compared ibrutinib to chlorambucil in elderly patients.

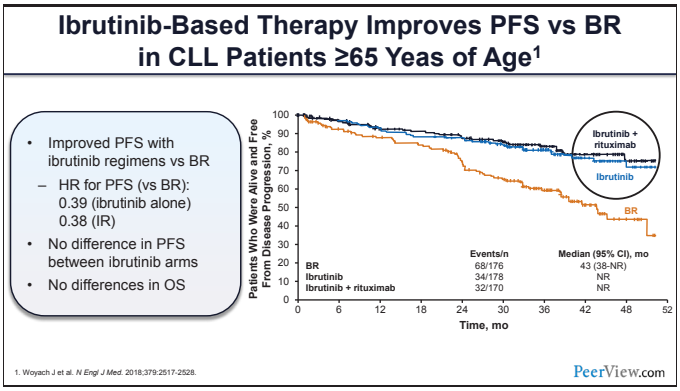
And then we have two randomized phase 3 studies that were done by the cooperative groups—the ALLIANCE and the ECOG studies—which looked at ibrutinib and ibrutinib-rituximab against chemoimmunotherapy, either bendamustine-rituximab or fludarabine-cyclophosphamide-rituximab, in patients that were either young or old. I'll go through this data in more detail.



So here you can see the ALLIANCE study. And what I really want people to remember from this study are the doses. So bendamustine was administered at 90 mg/m^2. We have a lot of different regimens out there, but this is, sort of, what was settled on as, sort of, the standard of care and, so, representing what really is a good comparator for patients who are over the age of 65.

Ibrutinib was administered at 420 mg daily, and when it was used in combination with rituximab, it was also administered at 420 mg daily.

The eligibility for this study was treatment-naïve CLL patients over the age of 65. There was no requirement for comorbidities, and importantly, del17p was included in this study.

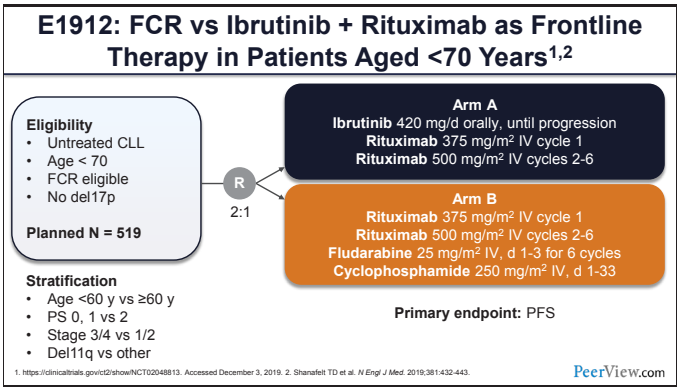


And what you can see here is really an improved progression-free survival for both ibrutinib regimens compared to bendamustine. And it's important to recognize the way the study was powered. So we have a hazard ratio for ibrutinib and ibrutinib-rituximab against bendamustine-rituximab of 0.39 and 0.38, respectively, for those two regimens.

Now, there was no difference in PFS between both ibrutinib arms, and there was no difference in overall survival in all three arms. That, of course, is going to be important to keep in mind and follow, because we did see differences in overall survival when we looked at the RESONATE-2 data. So, even though there was a crossover, there was a difference in overall survival.

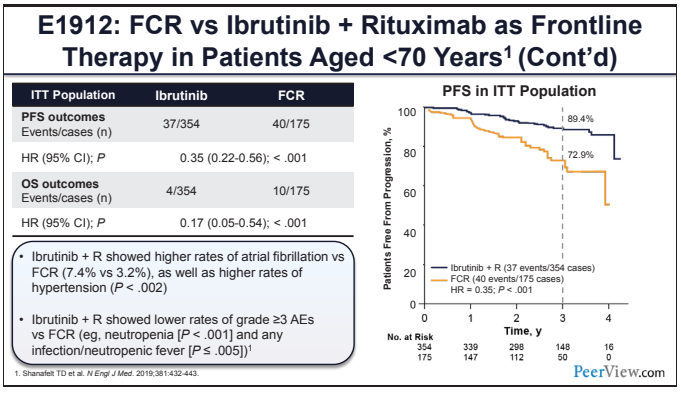
So, best foot forward first—giving our best agent first, really did, based on the RESONATE data, result in better outcomes for our patients.

And you can see here, the median PFS is 43 months for bendamustine-rituximab versus not reached for both ibrutinib regimens.



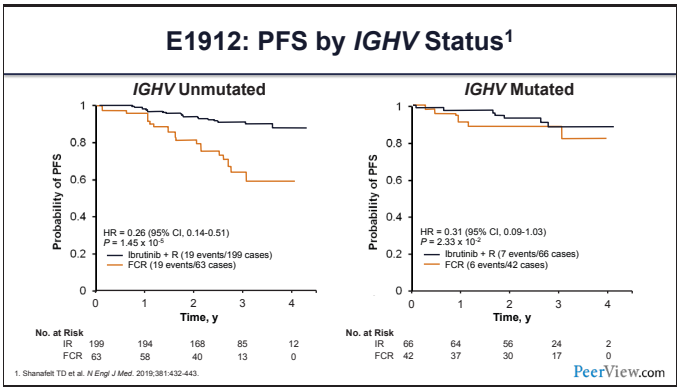
Looking at the ECOG study—and so there was a little bit of overlap here. They used age less than 70 years to define young, and this was once again, in untreated CLL patients who would be considered eligible for FCR. So while there really wasn't a requirement for fitness, it certainly does have that bias in there.

And 17p-deleted patients were excluded from this study—so that's a very important difference here. And they looked really at ibrutinib-rituximab or FCR using standard dosing. Patients here were stratified for ages younger or older than 60, performance status, Rai stage, and del11q versus other abnormalities.



So when we look at the outcomes for these data, what you see here actually is an improvement in PFS for ibrutinib-rituximab as compared to FCR. And this also resulted in an improvement in the overall survival. And you can see it here, with a PFS of 3 years of 89.4% versus 72.9% for the ibrutinib versus bendamustine regimens, respectively.

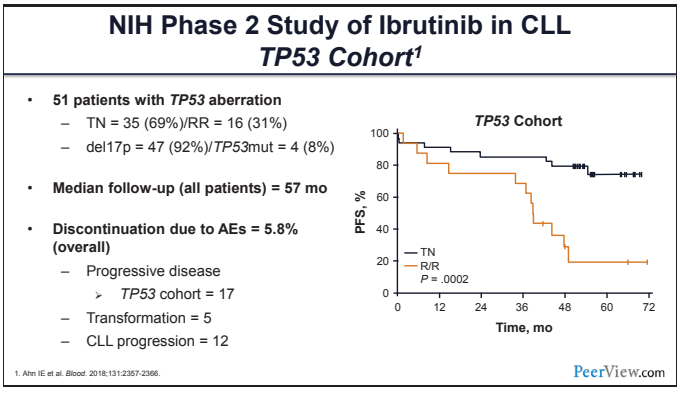
The ibrutinib-rituximab arm did show higher rates of atrial fibrillation versus FCR, and that was 7.4% versus 3.2%, as well as higher rates of hypertension. Ibrutinib plus rituximab also showed lower rates of grades 3 and greater adverse events, including neutropenia—as would be expected—as well as infections and neutropenic fevers.



The ECOG data actually does show—and I do want to highlight this, because these are data that a lot of people are going to be talking about—where there was a clear benefit in the population overall, and there was a clear benefit in the IgG unmutated patients.

The benefit was not seen with the mutated patients. And while that could still be used to justify using chemoimmunotherapy in the mutated immunoglobulin patients, it's important to recognize that it's not really a difference of how ibrutinib's impacting on the mutated CLL cases, but really more about how the mutated patients are very sensitive to FCR.

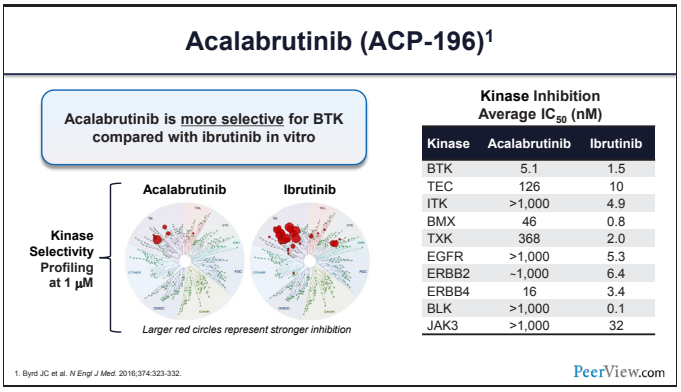
It is important to keep in mind, though, that the toxicity profile of FCR is going to be agnostic with regard to the mutational status, and so we are taking some very good prognostic patients who will do well with almost any regimen and really exposing them to very aggressive therapy. So I do add that as a word of caution.



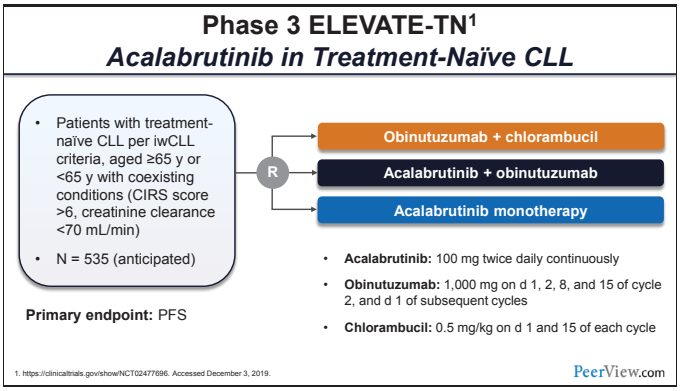
I also want to point out a very important issue that we see less frequently than we once were. So 17p deletion— *TP53*-dysfunctional CLL—representing maybe about 3% to 7% of the patients at diagnosis, but actually climbing to about 35% to 45% when you look at the RESONATE and the idelalisib pivotal studies, really is still a difficult endeavor for us to treat.

So at the NIH, there's been a study looking at 17p deletion, both in relapsed/refractory and treatment-naïve patients. And what I wanted to show you here is that the 35 treatment-naïve patients, with a median follow-up of 57 months, were really doing quite well with a very low discontinuation rate of 5.8%.

And remember that because these patients are 17p-deleted, they're certainly going to be very motivated to stay on therapy. But we're talking about a PFS that's really approaching about 78%, and so it really does suggest that the 17p-deleted patients, who we do know do worse on BTK inhibitor therapy, can still have good outcomes on the therapies when given to them up front.



Speaking about acalabrutinib now; we've heard a lot about the differences in selectivity. I just want to show you the data that we have regarding the phase 3 studies that led to some of the approvals that we now have.

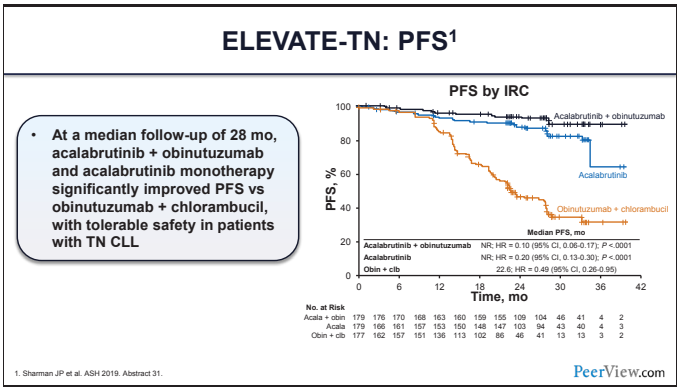


So, the first one was the ELEVATE-TN. It's always important to remember that the ELEVATE comes in two flavors, ELEVATE and ELEVATE-TN, and the TN, of course, is treatment naïve.

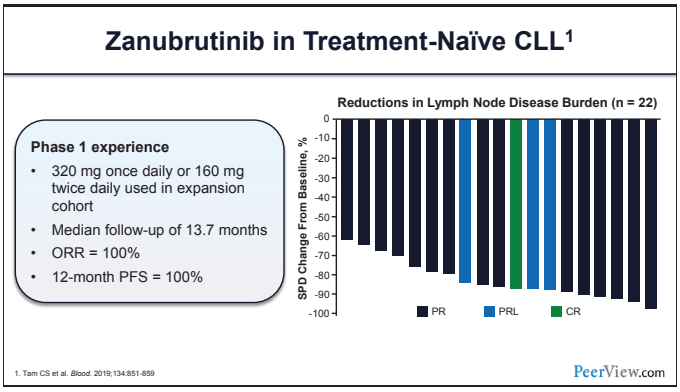
And in this study, patients with treatment-naïve CLL who required treatment and were over age 65 years—or they could be younger than 65 years with comorbidities—were actually randomized to

obinutuzumab-chlorambucil, acalabrutinib-obinutuzumab, or acalabrutinib monotherapy.

And you can see here the dosing for the three agents. Chlorambucil, obviously, the one that has the greatest variability, was dosed at 0.5 mg/kg on days 1 and 15 of each cycle.



Here you can see the results with the median follow-up of 28 months. Acalabrutinib and obinutuzumab, and acalabrutinib monotherapy significantly improved the progression-free survival compared with obinutuzumab plus chlorambucil, with an excellent tolerability and safety panel.



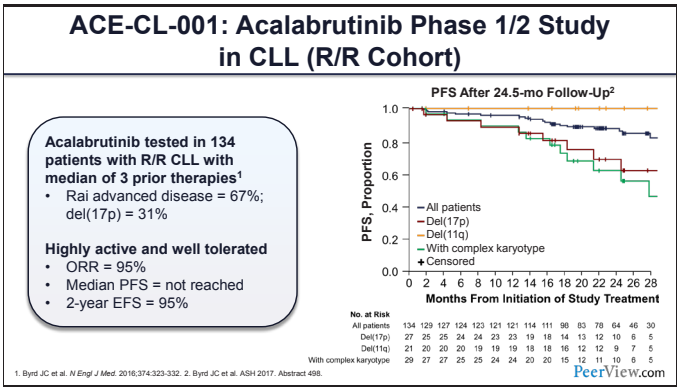
And then, of course, zanubrutinib, which actually has recently been approved for treatment of mantle cell lymphoma, does have data that's emerging for CLL. And what I'm showing you right now is the phase 1 experience.

Interestingly, for zanubrutinib, we actually have two doses that have been approved by the FDA—so 320 mg once a day or 160 mg twice a day. It's unclear to me whether or not there really is a clinical difference between the two of them. I mean, we do see some differences, biologically, but whether or not those biological differences translate into a different clinical outcome is going to be important to understand.

You can see here, with a median follow-up of 13.7 months, an overall response rate of 100% and a 12-month progression-free survival of 100%—so very impressive data. And here you can see the waterfall plot for the reductions in lymph node disease.

BTK Inhibition in R/R CLL

So I want to move on to the relapsed/refractory discussion.



So, looking at first at acalabrutinib in relapsed/refractory disease, we have once again a large phase 1 study. This is the ACE-CL-001 study, which actually had a median of three prior therapies. The acalabrutinib was very active and very well tolerated, with an overall response rate of 95%, a median PFS that was not reached, and a 2-year event-free survival of 95%.

So we have, actually, the curves up here, and the way this looks is a little difficult. But here we have our total population of patients. Here we have the 17p-deleted patients and the complex karyotype. And then up here we have the 11q-deleted patients.

Certainly not implying that the 11q-deleted patients are particularly sensitive, but we do actually, here, have confirmatory data of the role of 17p, and complex karyotype, with its demonstration of genomic instability, does predict the ability to actually progress or develop resistance to both acalabrutinib as well as ibrutinib.

ACE-CL-001: Acalabrutinib Phase 1/2 Study in CLL (R/R Cohort)

42.5-mo follow-up[1]

- ORR (PR with lymphocytosis or above) was 94%
- Median values had yet to be reached for DOR, EFS, and PFS in the 134-patient cohort; estimated 45-mo EFS and PFS were 58% and 62%, respectively
- Patients with high-risk characteristics also obtained long-term benefits: del(17p), median PFS of 36 mo; complex karyotypes, 33 mo; del(11)(q22.3), not yet reached
- Reported AEs indicate a tolerable and consistent safety profile, with a low rate of major bleeding events

1. Furman RR et al. ASH 2019. Abstract 3039.

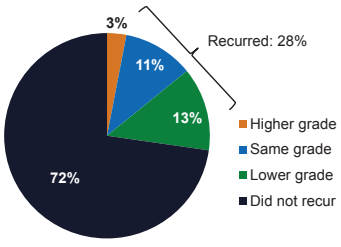
PeerView.com

So, as mentioned, the overall response rate with 42.5-month follow-up was 94%. Median duration of response, PFS, and event-free survival [were] not reached, with a 42-month duration of response estimated to be 61%. Very tolerable, once again, with a consistent safety profile with a low rate of major bleeding events.

Narrator: In addition to the efficacy findings noted by Dr. Furman, the updated estimated 45-month EFS and PFS were 58% and 62%, respectively.

ACE-CL-208: Acalabrutinib for Ibrutinib-Intolerant CLL Patients (N = 33)[1]

Recurrence of Ibrutinib-Related AEs During Acalabrutinib Treatment



1. Awan FT et al. *Blood Adv.* 2019;3:1553-1562.

PeerView.com

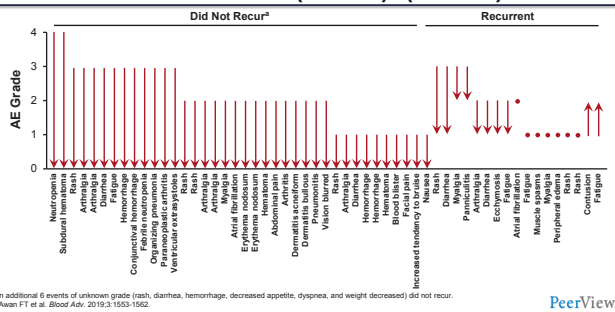
So the other question, of course, is what do we do about all these different agents? And is there anything that we can glean regarding, sort of, tailoring the selection of these agents for our patients?

So we do have one study called the ACE-CL-208 study that looked at acalabrutinib in ibrutinib-intolerant patients. And these patients had to have, sort of, a defined course. They needed to come off of ibrutinib and then actually go on acalabrutinib. And you can see here that they could come off ibrutinib for any reason.

And just looking at everything overall, we see that 72% of the patients who had come off for an adverse event didn't have that adverse event recur when they were on acalabrutinib. Twenty-eight percent did have recurrence: 3% had a higher grade, 11% had the same grade, and 13% had a lower grade.

So this really, actually, does suggest that there's really a difference in the AE profile, and that, certainly, trying one after the other is certainly a viable option—moving from ibrutinib to acalabrutinib.

ACE-CL-208: Acalabrutinib for Ibrutinib-Intolerant CLL Patients (N = 33)[1] (Cont'd)



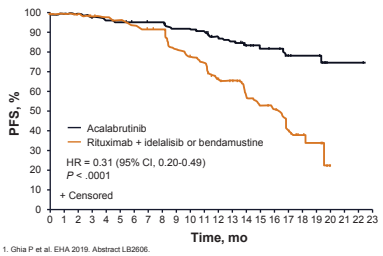
[a]An additional 6 events of unknown grade (rash, diarrhea, hemorrhage, decreased appetite, dyspnea, and weight decreased) did not recur.
1. Awan FT et al. *Blood Adv.* 2019;3:1553-1562.

PeerView.com

And I like this demonstration, graphically, because it really shows you the drop in adverse events. And you can see the various adverse events listed there, with the reductions and the quantity of the reductions—really, some of these patients are going from grade 4 all the way down to grade 0.

Update From Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Improves PFS in R/R CLL[1]

- Acalabrutinib vs rituximab + idelalisib or bendamustine (investigator's choice); N = 306
- ECOG PS 0-2; patients received ≥1 prior systemic therapy for CLL



In ASCEND, acalabrutinib improved PFS compared with investigator's choice

- 12-mo PFS: 88% with acalabrutinib vs 68% with rituximab + idelalisib or bendamustine
- 12-mo OS: 94% with acalabrutinib and 91% with rituximab + idelalisib or bendamustine

1. Ghia P et al. EHA 2019. Abstract LB2606.

PeerView.com

So, looking at the relapsed/refractory ASCEND data—and this was acalabrutinib versus rituximab plus idelalisib or bendamustine, and it was investigator's choice. This was part of what led to the approval of acalabrutinib in relapsed/refractory CLL.

So you can see here, in the ASCEND trial, acalabrutinib improved the progression-free survival compared with investigator's choice, with a 12-month PFS of 88% with acalabrutinib versus 68% with rituximab and idelalisib or bendamustine. The 12-month overall survival was 94% with acalabrutinib and 91% with the comparator arms. And you can see the curves here, demonstrating the split really starting at about 9 months.

Other Phase 3 Studies With Acalabrutinib in CLL

ELEVATE CLL R/R (ACE-CL-006)[1]

- N = 533
- Patients with previously treated high-risk CLL (del17p or del11q)
- ECOG PS 0-2
- ≥ 1 prior therapies for CLL.

R → Acalabrutinib; Ibrutinib

Primary endpoint: PFS

1. https://clinicaltrials.gov/ct2/show/NCT02477696. Accessed December 3, 2019.

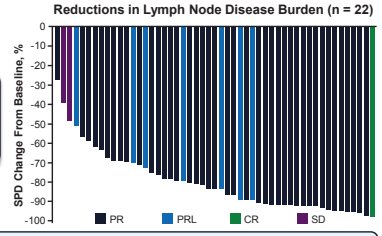
PeerView.com

Other phase 3 studies with acalabrutinib that will be reading out in the near future include the ELEVATE-RR. So this will be the second part of the ELEVATE study—the ELEVATE-TN study that we already discussed—looking at acalabrutinib versus ibrutinib in relapsed/refractory patients who are at high risk of progression, namely with 17p or 11q deletion.

Zanubrutinib in R/R CLL[1]

Phase 1 experience

- Median follow-up of 13.7 mo
- ORR = 94.6%
- 12-month PFS = 100%



Phase 3 ALPINE trial (NCT03734016) of zanubrutinib vs ibrutinib in patients with R/R CLL is ongoing (N = 400); endpoints include ORR, PFS, safety, DOR, and OS[2]

1. Tam CS et al. *Blood*. 2019;134:851-859. 2. https://clinicaltrials.gov/ct2/show/NCT03734016. Accessed December 3, 2019.

PeerView.com

So, looking at zanubrutinib in relapsed/refractory CLL, you can see these data here that we've already discussed in brief really showing a very nice reduction in lymphadenopathy, with an excellent PFS of 100% at 12 months. The data, of course, need to mature some more, but, from my perspective, we really don't see differences in efficacy between the three BTK inhibitors.

And there is the phase 3 ALPINE trial that's actually looking at zanubrutinib versus ibrutinib specifically in relapsed/refractory CLL.

How I Think, How I Treat

So, how do I treat? How do I approach my patients when it comes to BTK inhibitor therapy?

My Approach to the CLL Patient
Key Concepts

1. **Overall survival and QoL are the most important to patients**
   - PFS surrogate for OS
   - ORR and depth of response are not important
2. **Patients die from CLL, complications of CLL, or complications of chemotherapy, including risk of MDS/AML**
   - Risk of MDS/AML will likely rise as population lives

PeerView.com

The first thing that I believe is that overall survival and quality of life, basically, are the most important things to the patients. Obviously, overall survival is a very hard endpoint in a disease like CLL, and so we've adopted PFS as a surrogate endpoint, and so I'm going to use the PFS data to demonstrate that.

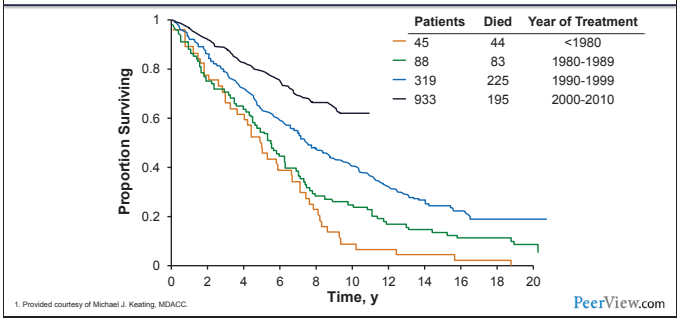
But there is an important caveat, which is, when we're talking about chemoimmunotherapy, progression is only one bad event. The risk of secondary MDS and AML, and the risks of secondary cancers, really are devastating events for our patients.

And so, looking at these agents, it's important to keep in mind that once a patient develops MDS and AML, the game is over. And so I do look very cautiously at the long-term complications.

And a lot of what we don't know is that the incidence of MDS and AML might be 5% to 8% in patients at about 7 years after FCR. But when you take a 50-year-old who now potentially could live until they're 80—and there's a background incidence of MDS and AML in 80-year-olds anyway—the question is, is there going to be a marked increase in that number of MDS and AML cases? And that risk is what really does drive, at the current time, my interest in avoiding chemoimmunotherapy completely for my patients.

Now, so patients die from CLL, the complications of CLL, and the complications of chemotherapy, and so trying to do whatever we can to avoid those is important. And I do recognize that BTK inhibitors come with their own complications, and that's why it's important to try to identify who are the best candidates for what.

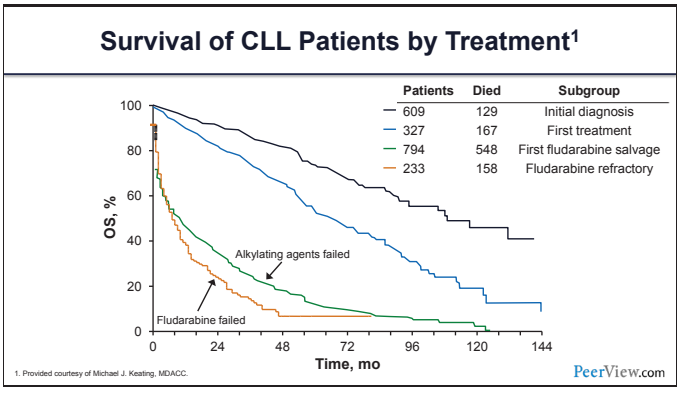
Survival of CLL Patients by Decade[1]



So when we look at CLL by survival by decades—looking at these data, it really suggests that we are doing better with each subsequent decade. And what I really want you all to take home from this slide, though, is that we're not. So the last decade looked at here was the decade ending in 2010. And, really, lead-time bias explains all of the improvement that we see in these curves.

So each subsequent decade, patients were being diagnosed earlier and earlier, such that the Rai stage 0 diagnosis was made in only 23% of the patients in the 1970s, and that number increased to 72% in the 1990s. So that just gives you an example of how much lead-time bias there is in these survival curves.

Survival of CLL Patients by Treatment[1]



Now, 2010 is when these data end, and I do believe 2010, which, when we first started the phase 1 studies with idelalisib, ibrutinib, and venetoclax, really represent entities that will change our outcomes for our patients. So, of course, these survival curves will look very different, hopefully, in the long term.

And along those same lines as patients get treated with chemoimmunotherapy and relapse, they have worse responses to each subsequent treatment course, such that they really develop—when they're fludarabine-refractory—a very, very short median survival. And you can see here that the median survival really is in the order of about 9 months.

One of the advantages of our novel agents is, by not being genotoxic, we really can avoid all these damaging events that probably really add to the cells becoming so resistant. It's absolutely unclear to me whether or not we're selecting for cells that might already be damaged, or whether or not we're really inducing the damage.

But what we do know from looking at this is that we really do see a decline in the responsiveness with each subsequent line of therapy. And while the data is still not very mature, it does not look like this happens with our novel agents.

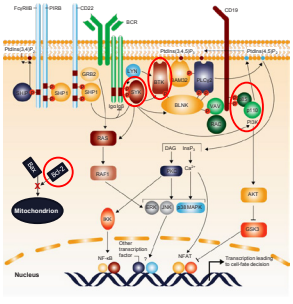
My Approach to the CLL Patient
Key Concepts

1. **Overall survival and QoL are the most important to patients**
   - PFS surrogate for OS
   - ORR and depth of response are not important
2. **Patients die from CLL, complications of CLL, or complications of chemotherapy, including risk of MDS/AML**
   - Risk of MDS/AML will likely rise as population lives

PeerView.com

So, once again, overall survival—most important—and avoiding the complications that we see with chemoimmunotherapy.

Novel Agents:
BCR-Associated Kinase and BCL-2 Inhibitors



Syk (spleen tyrosine kinase)
1. Fostamatinib (R935788)
2. Entospletinib (GS-9973)

BTK (Bruton's tyrosine kinase)
1. Ibrutinib (PCI-32765)
2. Acalabrutinib (ACP-196)
3. Tirabrutinib (GS-4059)

PI3K (phosphatidylinositol 3-kinase)
1. Idelalisib (GS-1101)
2. Duvelisib (IPI-145)
3. Umbralisib (TG-1202)

BCL-2
1. Venetoclax (ABT-199)

PeerView.com

So how do we do that with our current novel agents? So we have our B-cell receptor–associated kinase and BCL-2 inhibitors.

So, the first ones that we had were actually directed at Syk, and fostamatinib, which was a plenary session at ASH in 2008, was recently approved for ITP. We have BTK inhibitors, and you can see here acalabrutinib, ibrutinib, and tirabrutinib—just a very small selection. Then, of course, our PI3 kinase inhibitors and our BCL-2 inhibitors.

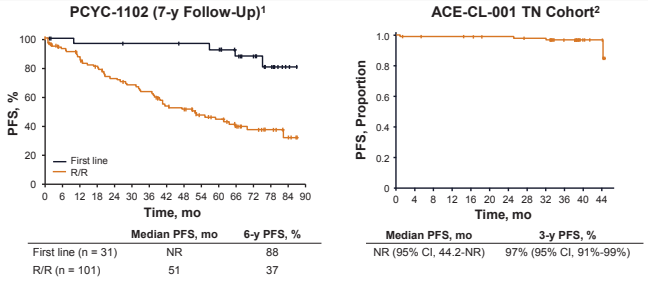
My Approach to the CLL Patient
Key Concepts (Cont'd)

- No longer genotoxic or immunosuppressive
- Select agent based on patient's risks and preferences
- BTK inhibitor therapy currently has the longest duration and highest efficacy of all novel agents
- **How good are BTK Inhibitors?**

PeerView.com

So, overall, just to emphasize, these novel agents are not genotoxic. They're also not immunosuppressive. I do believe in selecting agents that are going to be based on patients' risks and preferences. And I do believe BTK inhibitor therapy is the current preference based upon the durability and the duration of the data that we currently have. So, once again, how good are the BTK inhibitors?

Durable Efficacy of BTK Inhibitors in CLL



	Median PFS, mo	6-y PFS, %
First line (n = 31)	NR	88
R/R (n = 101)	51	37

Median PFS, mo	3-y PFS, %
NR (95% CI, 44.2-NR)	97% (95% CI, 91%-99%)

1. Byrd J et al. ASH 2018. Abstract 3133. 2. 1. Byrd J et al. ASH 2018. Abstract 692.

PeerView.com

Here are the curves. Obviously, the data are the data, and the real-world data may be very different from the clinical trials data. But these data are very good, in my opinion.

Who Is High Risk in 2019?

- Those patients that will not have long-term disease control with BTK inhibition due to progression
- Causes of treatment failure for BTK inhibitor therapy
  1. Adverse events
  2. Progression of CLL
  3. Richter's transformation
  4. Secondary cancers (AML/MDS)
- Can we identify these patients ahead of time and change their outcome?

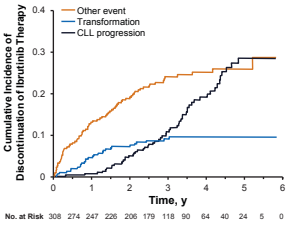
PeerView.com

So, who are the patients that aren't going to have or enjoy long-term disease-free survival? Basically, who is high risk in 2019? So most of our prognostic markers indicate who are the patients that are going to be at risk of progressive disease and needing treatment?

I think we need to rethink that. The way I look at high risk is: Who are those patients that aren't going to be on the BTK inhibitor at year 7 still enjoying progression-free survival? And so, I like to break down the cause of treatment failure of BTK inhibitor therapy into either adverse events, CLL progression, or Richter's transformation.

So these are the three ways that BTK inhibitors fail our patients. And then, of course, secondary cancers—MDS and AML—that really is just because of the CLL background itself and prior chemoimmunotherapy.

Cumulative Incidence of Discontinuation of Ibrutinib by Cause[1]



Cumulative Incidence Estimate (95% CI)	At 2 y	At 3 y	At 4 y
CLL progression	5.0% (2.5%-7.5%)	10.8% (7.1%-14.4%)	19.1% (13.9%-24.3%)
Transformation	7.3% (4.3%-10.2%)	9.1% (5.8%-12.4%)	9.6% (6.2%-13.0%)
Other event	18.7% (14.3%-23.1%)	23.9% (19.0%-28.8%)	25.0% (20.0%-30.1%)

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

So these are data from OSU looking at the causes of discontinuation. So we have our three curves. This curve here is the curve for adverse events. What I want to emphasize here: this is the curve for Richter's transformation. And I really think it's important to understand that this plateau here—at around 2 years—really shows that the Richter's transformation itself is really about the biology.

We know from other data that patients who develop Richter's, actually, half of them will transform even before they have an iwCLL indication for treatment. But in theory, once you're beyond that 2-year point, you can look at the patient and say that they've proven themselves to not have the biology that puts them at risk. But here we have the CLL progression, and you can see that this curve really starts to increase beyond year 2.

Now, we have some interesting data suggesting that the mutations that give rise to this progression actually predate the initiation of BTK inhibitor therapy. And so, the time that we take to get to that relapse is really based upon that one cell growing out, and I'll show you how that plays into potential ways we can have of avoiding these issues subsequently.

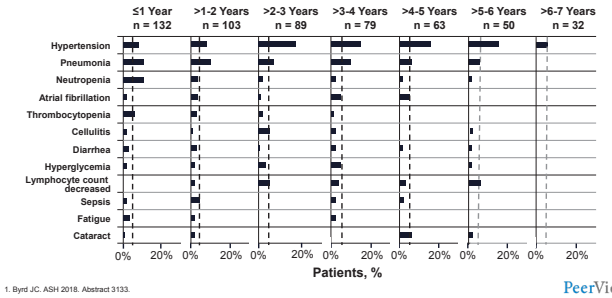
Other Questions With BTK Inhibitors in CLL

1. **BTK inhibitors are well tolerated, but not by everyone**
2. **What insights can we learn to prevent progressions?**

PeerView.com

So, we know that BTK inhibitors are well tolerated, and I want to actually just focus right now on the adverse events. And you can see here, as we talk about longevity, of course understanding the impact of BTK inhibitors over time becomes very important.

Decrease in Grade ≥3 AEs Over Time With Ibrutinib[1]

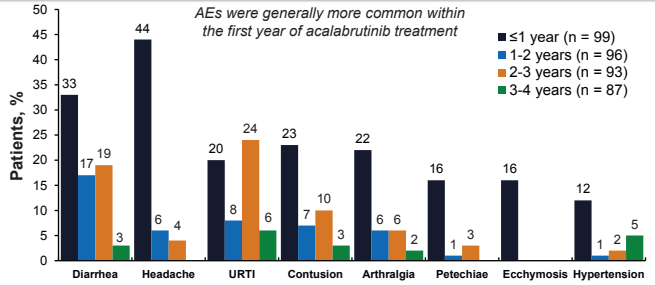


1. Byrd JC. ASH 2018. Abstract 3133.

PeerView.com

So you can see here, we actually—with the exception of hypertension—have decreased incidences of adverse events with ibrutinib.

Incidence of AEs on Acalabrutinib by Year[1]



1. Byrd JC et al. ASH 2018. Abstract 692.

PeerView.com

And then you can see the same thing here with acalabrutinib. It's interesting to note the hypertension again, because we really don't understand the mechanism of the hypertension for BTK inhibitors. But whether or not we see it with both ibrutinib and acalabrutinib versus one of the others will play an important part in helping formulate some hypotheses.

BTK Inhibitor–Associated Toxicities[1-4]

1. **Diarrhea**
   - Possibly due to EGFR inhibition in GI tract
   - RESONATE: ibrutinib = 48% vs ofatumumab = 18%
   - HELIOS: ibrutinib = 35% vs placebo = 21%
   - RESONATE2: ibrutinib = 42% vs chlorambucil = 22%
   - Acalabrutinib: all grades = 39%; grade ≥3 = 1%
2. **Bleeding**
   - Possibly due to inhibition of BTK and TEC in platelets
   - RESONATE: ibrutinib = 44% vs ofatumumab = 12%
   - HELIOS: ibrutinib = 31% vs placebo = 15%
   - Acalabrutinib: all grades = 34%; grade ≥3 = 0%

1. Brown JR et al. *Leukemia*. 2018;32:83-91. 2. Chanan-Khan A et al. *Lancet Oncol*. 2016;17:200-211. 3. Burger JA et al. *N Engl J Med*. 2015;373:2425-2437. 4. Byrd JC et al. ASH 2018. Abstract 692.

PeerView.com

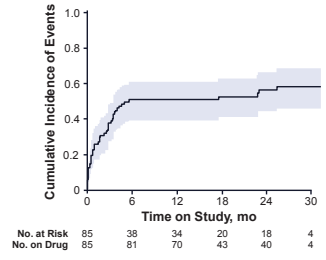
So, how do I look at the BTK inhibitor therapies? And how do I actually use these with my patients?

So, the first one that's most common is diarrhea, possibly due to EGFR inhibition in the GI tract. You can see the rates there for the RESONATE, HELIOS, RESONATE2, and acalabrutinib studies.

So what do I do? I believe that inhibiting EGFR and then having food in the GI tract is the problem. So dosing ibrutinib at bedtime and basically not having any food in the GI tract afterwards will allow regeneration of EGFR activity and really avoid diarrhea. So the incidence of diarrhea really falls from about 35% to 40%, down to less than 5%. And that's obviously an important way to keep patients on therapy.

Bleeding: This looks like it's due to inhibition of both BTK and TEC kinase in platelets. It's important to remember that the kids with X-linked agammaglobulinemia don't have any bleeding diathesis because the TEC kinase is able to compensate for BTK. Ibrutinib and acalabrutinib—both by inhibiting BTK and TEC—do actually have an impact of basically damaging the platelet reactivity.

Cumulative Incidence of Ibrutinib-Related Bleeding AEs[1]



1. Provided courtesy of Weistner A. NHLBI 12-H-0035.

PeerView.com

You can see the incidence, here, of bleeding, but most importantly, these are all grades 1 and 2—so a lot of bruising; nothing more significant than that.

But what I also find very interesting is, when you look at the ibrutinib adverse events, the bleeding really seems to plateau at 6 months. And what I think we start seeing is, due to a platelet half-

life that's shortened—probably by BTK and TEC as well—we end up with a marrow that actually looks like an ITP marrow.

So patients will have some thrombocytopenia that's usually mild—typically in the 100 to 110 range. But these are giant platelets, and so, the platelet mass is preserved. And so, the 6 months it takes for the marrow to sort of clear out enough that you can have the hypertrophy, or the hyperplasia rather, or the megakaryocytes, will allow the platelet mass to increase and really help preserve the bleeding risk.

BTK Inhibitor–Associated Toxicities[1-4] (Cont'd)

3. **Thrombocytopenia**
   - Possibly due to shortened platelet lifespan due to inhibition of BTK and TEC in platelets
   - RESONATE: ibrutinib = 17% vs ofatumumab = 12%
   - Acalabrutinib = <2%

4. **Atrial fibrillation**
   - Possibly due to ibrutinib metabolism
   - Ibrutinib = 5% vs ofatumumab = 1%
   - HELIOS: ibrutinib + BR = 7.7% vs placebo + BR = 2.4%
   - RESONATE2: ibrutinib = 7.4% vs chlorambucil = 1%
   - Acalabrutinib = 6%

1. Brown JR et al. *Leukemia*. 2018;32:83-91. 2. Chanan-Khan A et al. *Lancet Oncol*. 2016;17:200-211. 3. Burger JA et al. *N Engl J Med*. 2015;373:2425-2437. 4. Byrd J et al. ASH 2018. Abstract 692.

PeerView.com

I already mentioned the thrombocytopenia. And then the atrial fibrillation, which—this is really, I think, the most important adverse event when we start discussing reasons for discontinuing therapy. We don't really know what causes it. It is possibly due to a metabolite of ibrutinib. We do see it with both ibrutinib and acalabrutinib, as you can see here, and so it probably is a direct effect of BTK inhibition.

Some people believe that it might be the impact of BTK inhibition on macrophages in the myocardium, or impacting the myocardium conductivity. But this is what I really do see as a big issue, and fortunately in 2019, with our other agents to choose from, we have a lot of other choices that we can quickly go to.

BTK Inhibitor–Associated Toxicities[1-4] (Cont'd)

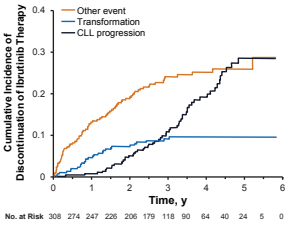
5. **Hypertension**
   - HELIOS: ibrutinib = 10% vs placebo = 5%
   - RESONATE2: ibrutinib = 14% vs chlorambucil = 0%
   - Acalabrutinib = 17%

1. Brown JR et al. *Leukemia*. 2018;32:83-91. 2. Chanan-Khan A et al. *Lancet Oncol*. 2016;17:200-211. 3. Burger JA et al. *N Engl J Med*. 2015;373:2425-2437. 4. Byrd J et al. ASH 2018. Abstract 692.

PeerView.com

And then hypertension—you can see here the incidences for ibrutinib and acalabrutinib. Interestingly, so we don't have data yet for zanubrutinib in this regard, because this is really a late effect. And it's important to recognize that, over time, this number keeps increasing, so that the 7-year data you saw really had a hypertensive adverse event profile of about 25%. So it's always important when looking across the different agents that you keep that in mind.

Cumulative Incidence of Discontinuation of Ibrutinib by Cause[1]



Cumulative Incidence Estimate (95% CI)	At 2 y	At 3 y	At 4 y
CLL progression	5.0% (2.5%-7.5%)	10.8% (7.1%-14.4%)	19.1% (13.9%-24.3%)
Transformation	7.3% (4.3%-10.2%)	9.1% (5.8%-12.4%)	9.6% (6.2%-13.0%)
Other event	18.7% (14.3%-23.1%)	23.9% (19.0%-28.8%)	25.0% (20.0%-30.1%)

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

And in the final minute, I just want to talk about what we can possibly do for these patients who are progressing on BTK inhibitor therapy. And so I'm only talking about the patients who have CLL progression, or the patients who have Richter's transformation.

Variables Associated With Ibrutinib Discontinuation[1]

Variable	CLL	Transformation	Other Event
Complex karyotype	2.81 (1.34-5.88) *P* = .006	5.00 (1.51-16.52) *P* = .008	–
***MYC* abnormalities**	–	2.15 (1.00-4.65) *P* = .051	–
Del17p	2.14 (1.15-3.96) *P* = .016	–	–
Age (≥65)	0.49 (0.27-0.91) *P* = .023	–	2.02 (1.25-3.28) *P* =.004
>3 therapies	–	–	1.99 (1.23-3.23) *P* = .005

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

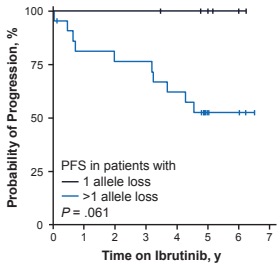
PeerView.com

So, from the same study at OSU, they looked at risk factors for progression. And for a lot of reasons, this is not a complete list, but it certainly highlights what they found statistically.

So, progression for CLL includes complex karyotype, 17p deletion, and age younger than 65, and a risk for Richter's transformation was seen with complex karyotype and *MYC* abnormalities.

And I really have to emphasize that I believe 17p deletion and complex karyotype, going forward, are really going to be the most important predictors for what patients are going to do long term, because we really see the ability of the DNA to mutate and really come up with these mutations that will lead to bypassed pathways, including the C481S mutation and the *PLCγ2* mutations. They probably require that ability for the cells to mutate. And so that's why I think that these are the important surrogates for these patients progressing on BTK inhibitors.

Impact of *TP53* Allele Loss on Outcomes With Ibrutinib[1]



- Detection limit: VAF 0.2%
- TN = 21; R/R = 8
- Median follow up: 5 y

1. Brieghel C et al. ASH 2018. Abstract 3111.

PeerView.com

One important study, which actually came out recently, looked at the patients who were 17p-deleted. Now, when we typically do 17p-deleted by interphase FISH, we only look at one allele, right? Most of us haven't seen 17p biallelic deletion. The question, of course, is: What's going on in the other allele?

So when we do next-generation sequencing commercially, we are typically looking at a variant allele frequency, or we're looking for a mutation prevalence of about above 5% to 10%. And the question, of course, is if you have one cell that has both alleles knocked out, is that one cell going to then grow back and behave with a biallelic loss of TP53 function?

So, in this study, they looked at NGS profiling with an allele frequency that went down to 0.2%. And what they were able to show is that, if you had absolutely both alleles knocked out, you did not do well, but if you had at least one allele preserved, you actually had no progression on ibrutinib.

So these are data that I think are very important moving forward because it's really going to help us identify the patient who can be on ibrutinib and have nothing else to worry about and not need additional therapy.

Risk of CLL Progression at 4 Years[1]

- **Risk of CLL progression at 4 years:**
  - For patients ≥65 y of age, without complex karyotype, and no del17p = 1.9%
  - For patients >65 y of age, with complex karyotype, and del17p = 44%

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

And from Jennifer Woyach's paper, as well, we basically have that, if you're over the age of 65 and you don't have a complex karyotype or 17p deletion, your risk of progression at 4 years is 1.9%. If you do have age younger than 65, complex karyotype, and 17p deletion, your risk of progression is going to be 44%. So we're beginning to identify these risk factors. And of course the question is now, what do we do for that?

Risk Factors for Richter's Transformation[1,2]

1. ***NOTCH1* mutation**	7. Unmutated *IGHV*
2. Complex karyotype	8. Advanced Rai stage
3. iFISH risk category	9. β_2 microglobulin
4. Stereotyped BCR	10. ZAP-70 expression
5. CD49d expression	11. CD38 expression
6. c-Myc abnormalities	12. Purine analog + alkylating agent

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 2. Parikh SA et al. *Br J Haematol*. 2013;162:774-782.

PeerView.com

And then I just want to show you really quickly, for the Richter's transformation, what we have is, sort of, risk factors. And I really want to highlight the *NOTCH* mutation, the interphase FISH risk category, and the stereotyped B-cell receptor as really being very impactful on overall outcomes, with patients who are NOTCH-mutated or stereotyped B-cell receptors, having frequencies of a Richter's transformation as high as 50% at 5 years.

How Might We Avoid BTK Inhibitor Treatment Failures in the Future

For "high-risk" CLL

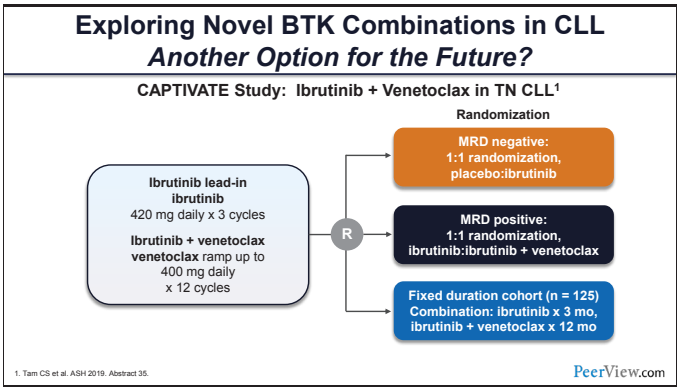
1. **Early treatment: initiation at diagnosis**
   - (Watch and wait revisited)
   - Prevent development of resistant subclones (C481S) and transformed cells
   - Requires therapies that do not induce genomic instability (genotoxic)
2. **Combination Therapy: BCR antagonist + venetoclax**
3. **Reversible BTK inhibitors: ARQ-531, SNS-062, and LOXO-305**
4. **Novel agents**

PeerView.com

So what I recommend for how we might avoid these BTK inhibitor failures in the future, since the mutation happens before the initiation of therapy in these patients who have genomic instability, maybe we should revisit "watch and wait" and start BTK inhibitor therapy earlier in these patients. And by shutting down proliferation, maybe we can prevent ongoing mutation that will lead to the ability of these cells to have the resistant mutation develop.

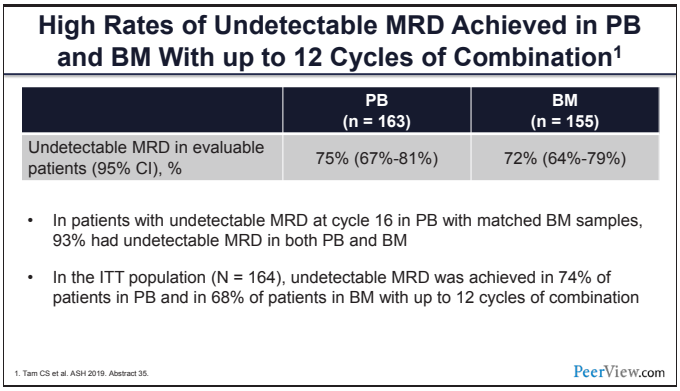
The other option, of course, is combination therapies. And we have data now emerging on BCR antagonists plus venetoclax—and this is ibrutinib-venetoclax, acalabrutinib-venetoclax, duvelisib-venetoclax, umbralisib-venetoclax—the list goes on and on and on. And so there's definite synergy. And you also just have two agents, so resistance to both agents is certainly going to be far less likely than the resistance to one.

We also have the reversible BTK inhibitors that you're going to hear about next. And then, of course, there are other novel agents to be named later.



And then I just want to show you the CAPTIVATE study—looking at the schema for the patients who were actually getting the combination of ibrutinib plus venetoclax. So patients had 3 months of ibrutinib followed by ibrutinib plus venetoclax for 12 cycles.

Now, there are actually two cohorts: an MRD cohort, where the patients were randomized—if they were negative—to either ibrutinib or placebo, and then a MRD-positive cohort, where patients were randomized to either ibrutinib or ibrutinib plus venetoclax. The second cohort was fixed-duration, and these patients actually stopped treatment after 12 months, regardless of their MRD status.



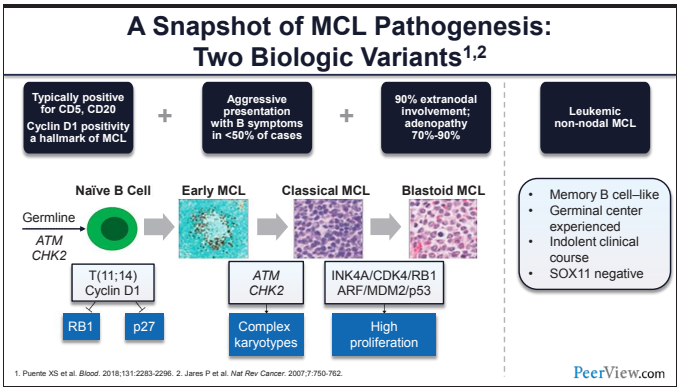
Narrator: In the recently presented update to the CAPTIVATE trial, 75% of patients receiving the ibrutinib-venetoclax combination achieved undetectable MRD with up to 12 cycles of therapy.

So this study is actually very important because it's really going to tell us a lot about what to do when these patients do progress with discontinuation of therapy. And that, I think, is still a very important question. And this abstract is going to be updated on Saturday during the CLL session.

All right, so with that, I conclude, and I'd like to turn the mic back to Dr. Goy.

What I Think About BTK Inhibition as a Strategy in MCL and Other Lymphoid Cancers

Andre H. Goy, MD

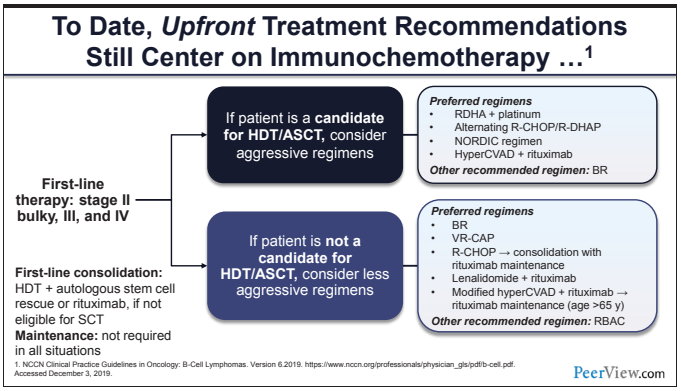


Dr. Goy: Thank you very much. So we're going to go through mantle cell lymphoma and other lymphoid malignancies.

So first, on mantle cell lymphoma—this is a rare disease, as you know—CD5/CD20-positive, cyclin D1-positive. Less than half the patients have aggressive presentation and B symptoms, but all patients have advanced disease with extranodal involvement—bone marrow and GI tract particularly.

Molecularly speaking, we have really had an increasing awareness of the biological diversity of mantle cell lymphoma. So there are two types. One is the leukemic non-nodal mantle cell lymphoma—so no lymphadenopathy, large spleen, and high white count. They look like a CLL, but they have a t11;14 and they are somatically mutated. This is a different disease, different biology. A small subset of those can become p53 abnormal over time; they become more aggressive, but, otherwise, it can be managed very conservatively.

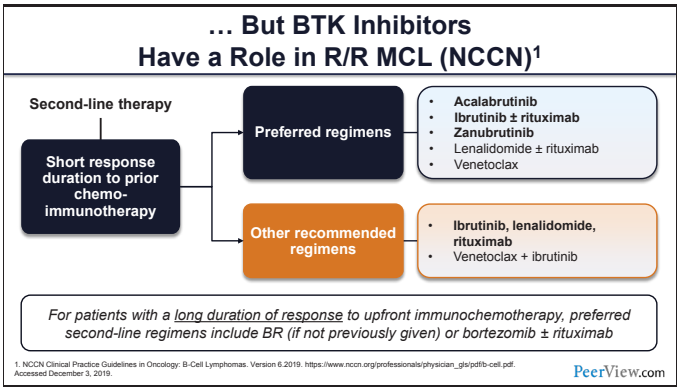
The others are just a spectrum of disease—and I'm not going to go into the detail for the sake of time—showing that you have an early mantle cell lymphoma in situ that continues to progress over time and becomes more accelerated with, typically, the acquisition of additional secondary genetic abnormalities over time that make their cells more blastoid variant, p53 mutated, and so on.



The treatment recommendations are typically based on age and [if the patient is a] candidate for high dose intensive therapy, with or without transplant. So, a number of regimens that you're familiar with: high-dose cytarabine, typically, R-CHOP and high-dose cytarabine, NORDIC regimen, hyperCVAD and rituximab.

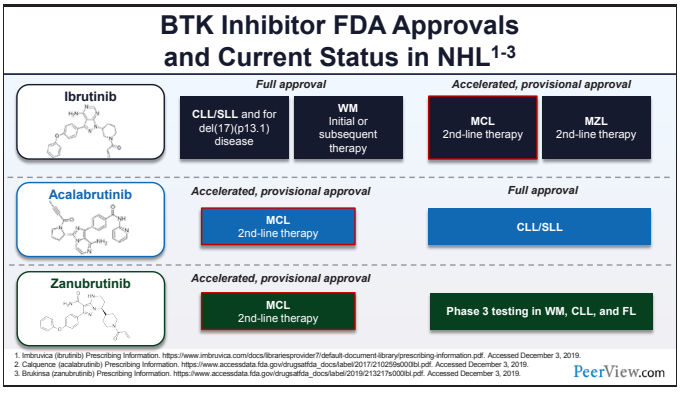
And the consolidation is, typically, when you have a less intensive regimen, you get a consolidation with high-dose therapy and transplant, and the maintenance is now more and more a part of the armamentarium—even after high-dose therapy—because of an increased improvement in PFS and, of course, survival, as per the European data.

If the patient is not a candidate for high-dose therapy, there are a number of combinations: BR, VR-CAP, R-CHOP with maintenance R^2, and modified hyperCVAD. RBAC is also, actually, a very interesting regimen; we'll go a little bit more into the details in a moment.

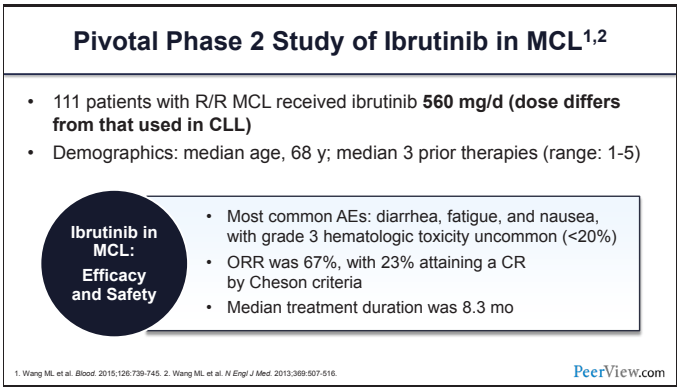


But the BTK inhibitors have had a growing role in the field of mantle cell lymphoma relapse, because a patient—when they relapse—they can relapse several years later after induction, but they typically relapse earlier, and preferred regimens are acalabrutinib, rituximab, or zanubrutinib—the three approved options. R^2 works as well, and venetoclax—although it's not approved yet.

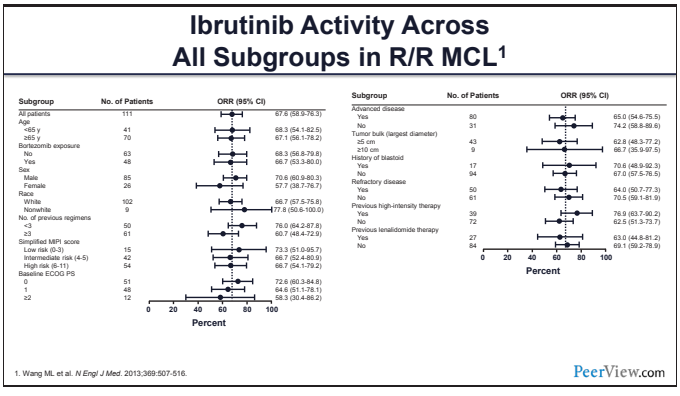
Other recommended regimens: ibrutinib, again, lenalidomide, rituximab, and ibrutinib-venetoclax. We'll go a little more into all the results of these novel therapies.



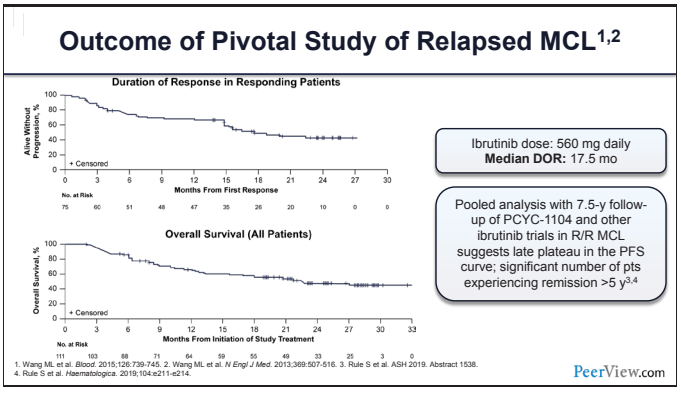
But in terms of approval by the FDA of BTK inhibitors in mantle cell, we now have three BTK inhibitors approved in mantle cell—again, ibrutinib, acalabrutinib, and zanubrutinib.



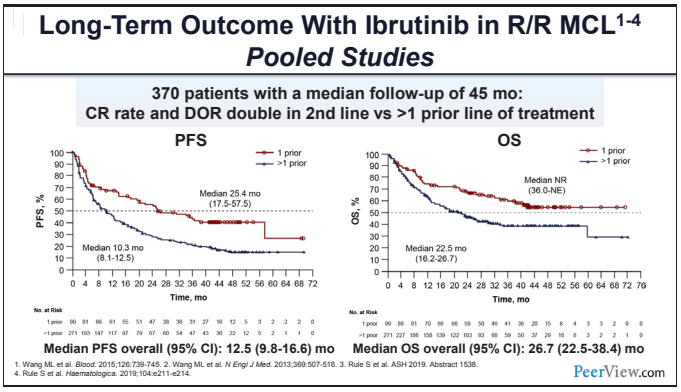
So the original approval of ibrutinib in mantle cell was based on a pivotal trial—560 mg/d—so a different dosing than CLL; and the median age was 68 years; a median of three prior therapies, range 1-5. And you heard about the toxicity profile. But the overall response rate was 67%, with 23% achieving a CR. So this became a game-changing treatment. The median treatment duration was 8.3 months, and the median duration of response was 17.5 months.



What was interesting—and we have heard this also in CLL—but we see activity across the different [subgroups]. This is the forest plot, looking at activity across all the characteristics of mantle cell lymphoma patients, including failing high-dose therapy, multiple lines of therapy, bulky tumors, etc. So typically, patients respond very well to these agents.



This is the long-term outcome—median duration of response, as I mentioned, 17.5 months. And the overall survival is shown here. There seems to be, sort of, a plateau over time. And there will be an update at ASH [2019] on the long-term follow-up, which is very impressive, and some patients that have very persistent response on this treatment.



Three hundred and seventy patients from the pooled study looking at the outcome, where the number of prior therapies actually impacts the PFS and the overall survival. And we heard this from Richard: that probably bringing these BTK inhibitors earlier would be important.

Ibrutinib Combinations in R/R MCL

Combination Regimen	Notes
Ibrutinib + rituximab[1] R/R MCL, median of 3 prior therapies, (range 1–6), N = 50	• High response rate; long-term benefit in low proliferative rate disease[1] • CR of 58%
Ibrutinib + rituximab + lenalidomide[2] **(R^2) (PHILEMON Trial)** R/R MCL, N = 42	• High response rate in relapsed MCL, justifying phase 3 trial • ORR of 76%, CR of 56%
R^2-Ib (JTCC)[3]	• 25 pts ORR 85% CR 70% even in p53 mut pts • Durable +++
Ibrutinib + venetoclax vs ibrutinib + placebo (SYMPATICO)[4]	• Ongoing

1. Jain P et al. *Br J Haematol*. 2018;182:404-411. 2. Jerkeman M et al. *Lancet Haematol*. 2018;5:e109-e116.
3. https://clinicaltrials.gov/ct2/show/NCT01776840. Accessed December 3, 2019. 4. Goy A et al. ASH 2017. Abstract 623.

PeerView.com

So, here are combinations in the relapsed/refractory setting. With ibrutinib-rituximab, the CR rate goes up to 58%, particularly in a patient with not very high-risk disease—Ki-67 or blastoid variant, obviously.

The PHILEMON trial was with R^2-ibrutinib, and we had a similar study at our institution. Basically, the take-home message for the response rate is 76% to 85%. The CR rate was 56% to 70%, even in p53-mutated patients.

What is our experience with R^2-ibrutinib in relapsed/refractory mantle cell lymphoma? It is highly durable. We have patients who have been 4 years on response. And ibrutinib-venetoclax versus ibrutinib-placebo, the SYMPATICO trial is ongoing.

Ibrutinib Combinations in Frontline MCL

Combination Regimen	Notes
Ibrutinib + BR[1] **Newly diagnosed MCL**	• Can be safely combined • Multicenter phase 3 SHINE completed enrollment • IR vs BR (UK) ongoing
TRIANGLE study EU[2]	• 6 R-CHOP/R-DHAP → ASCT • vs 6 RCHOP + ibrutinib/R-DHAP → ASCT + maintenance (2 y Ib) • vs 6 RCHOP + ibrutinib/RHAP and 2 years MI
Ibrutinib + rituximab → PR or CR → 4 R-HyperCVAD (MDACC/WINDOW trial)[3]	• 50 pts (ICML) ORR 100% all CR; 91% MRD- • 3 y PFS: 88% • **Might be beneficial in pts with molecular high-risk features (p53) +++**
Non-chemo options +++	• Ib-R in elderly or iMCL: CR: 65%-75%; MRD- +++ • Ib-VTX-obin • R^2-Ib

1. Jain P et al. 15th International Conference on Malignant Lymphoma (ICML 2019). Abstract 011. 2. https://clinicaltrials.gov/ct2/show/NCT02858258.
3. Wang ML et al. ICML 2017. Abstract 133.

PeerView.com

Now ibrutinib has been brought into the frontline setting—so BR plus/minus ibrutinib—as a large randomized phase 3 trial, the SHINE trial, that is completed, and the results are pending. IR versus BR in the UK, that is ongoing. The TRIANGLE study in Europe is looking at integrating in their model, which is 6 R-CHOP/RDHAP and transplant, and combining this with or without ibrutinib, and then on the second randomization, going with a transplant with maintenance ibrutinib versus no transplant and just maintenance ibrutinib.

And finally, I think what is going to be even more interesting in mantle cell—and we'll touch more on in a minute—is the ability to develop non-chemotherapy options. I'm a strong believer that if you cannot give intensive therapy or something that will bring a deep, early—hopefully—molecular CR in mantle cell lymphoma, it is probably better to not use chemotherapy upfront, particularly in a patient with high risk p53 mutation, etc.

So ibrutinib-rituximab in the elderly: it gives a very high CR rate, 65%. This is going to be updated at ASH. This was presented in Lugano. Ibrutinib-venetoclax-obinutuzumab will be presented at ASH as well, and R^2-ibrutinib, among a number of other trials that are ongoing in the frontline setting.

Venetoclax + Ibrutinib in R/R MCL[1,2]

Response at 16 wk, %	Without PET (n = 24)	With PET (n = 24)
CR	42	62
CRu	17	–
PR	17	8
SD	8	4
MRD negative	67 (12/18 pts) (with flow cytometry)	15 (2/13 pts) (with ASO-PCR)

- Best CR: 67% without PET; 71% with PET
- Best MRD negative: 16/19 pts (84%) without PET; 9/16 pts (56%) with PET

Longer-term follow-up: median PFS of 29 months; treatment interruption was feasible for patients in MRD-negative complete remissions

1. Tam CS et al. *N Engl J Med*. 2018;378:1211-1223. 2. Handunnetti SM et al. ASH 2019. Abstract 756.

PeerView.com

An ibrutinib-venetoclax study was published a few years ago in *The New England Journal of Medicine*. This was a small number of patients. What was very impressive—this was a relapsed/refractory setting—is that the CR rate was very high, and the MRD negativity, also very high.

But what was really more impressive—and we'll hear it at this ASH [2019]—is that some of these patients stopped therapy for a number of reasons, and some of them have remained in response for up to 18 months, which is unheard of in relapsed/refractory mantle cell lymphoma.

Phase 3 Study of Ibrutinib in Combination With Venetoclax in MCL (SYMPATICO)[1]

Safety run-in period: Participants are enrolled into the open-label safety run-in period to evaluate the occurrence of TLS and DLTs with the concurrent administration of ibrutinib and venetoclax

Patients with pathologically confirmed MCL and:

- ✓ ≥1 measurable site of disease on cross-sectional imaging (CT/PET)
- ✓ ≥1 but ≤5 prior treatment regimens for MCL
- ✓ Failure to achieve at least PR with, or documented PD after, the most recent treatment regimen

Estimated N = 287

→ **Ibrutinib + venetoclax**

→ **Ibrutinib + placebo**

- **Primary endpoints:** occurrence of TLS and DLT (run-in phase); PFS

1. https://clinicaltrials.gov/ct2/show/NCT03112174. Accessed December 3, 2019.

PeerView.com

The SYMPATICO trial is ongoing: ibrutinib-venetoclax versus ibrutinib plus placebo, 287 patients, and the primary endpoint is PFS.

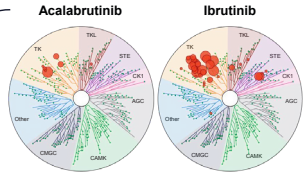
Background on Acalabrutinib in MCL[1]

Acalabrutinib is more selective for BTK, with less off-target kinase inhibition compared with ibrutinib in vitro

The phase 1/2 ACE-CL-001 trial in CLL provided evidence for activity in B-cell malignancies

- Led to the phase 2 ACE-LY-004 trial in R/R MCL
- Tested 100 mg twice daily dose until PD or toxicity

Kinase Selectivity Profiling at 1 µM



Larger red circles represent stronger inhibition

1. Byrd JC et al. *N Engl J Med*. 2016;374:323-332.

PeerView.com

Acalabrutinib is a second BTK. We heard that this is more selective—as from the profile shown here—and so it potentially has fewer off-target effects.

And this led to the phase 2 trial, based on the very impressive CLL data initially. That was the ACE-LY-004 trial, where patients received acalabrutinib BID until progression or toxicity.

Acalabrutinib in R/R MCL[1]

- Phase 2 study of 124 patients with R/R disease treated with acalabrutinib 100 mg twice daily until progression: ACE-LY-004
- Demographics: median age, 68 y; 2 prior therapies (range 1-5)

Acalabrutinib in R/R MCL: Efficacy and Safety

- **ORR was 81%, with 40% attaining a CR**
- Median duration of treatment was 13.8 mo, with 31% discontinuation for PD and 6% discontinuation for AEs
- Common AEs included headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%)
- Common grade ≥3 AEs included neutropenia (10%), anemia (9%), and pneumonia (5%), with no cases of atrial fibrillation

1. Wang M et al. *Lancet*. 2018;391:659-667.

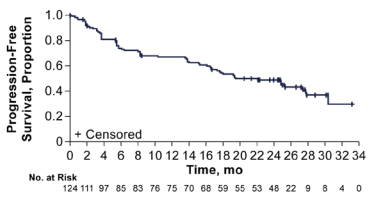
PeerView.com

The results are shown here. The overall response rate was 81%, with 40% achieving a CR. The median duration of treatment was 14 months, with one-third of the discontinuation for progression, and 6% for AEs.

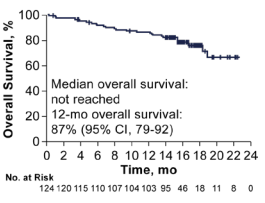
The toxicity profile we heard from Richard, and this was very typical. These were typically grade 1/2 BTK-related AEs, and no case of atrial fibrillation in that study.

Acalabrutinib in R/R MCL: ACE-LY-004 PFS and OS[1,2]

Median PFS: 19.5 mo



Estimated 24-Month OS Rate: 72%



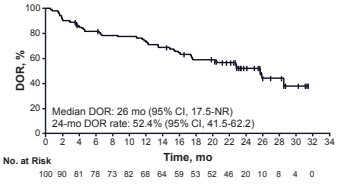
1. Wang M et al. ASH 2018. Abstract 2876. 2. Wang M et al. *Lancet*. 2018;391:659-667.

PeerView.com

This is the median PFS and the 24-month overall survival—very impressive in a population with relapsed/refractory mantle cell lymphoma.

Durable Remissions With Acalabrutinib in R/R MCL *Median 26-Month Follow-Up*[1]

	N = 124
ORR (CR + PR), n (%) [95% CI]	100 (80.6) [72.6-87.2]
Best response, n (%) [95% CI]	
CR	53 (42.7) [33.9-51.9]
PR	47 (37.9) [29.3-47.1]
Stable disease	11 (8.9) [4.5-15.3]
Median time to best response (range), mo	2.0 (1.6-25.7)
Median DOR	26 mo (17.5-NR)
Median time to CR (range), mo	3.7 (1.7-25.7)

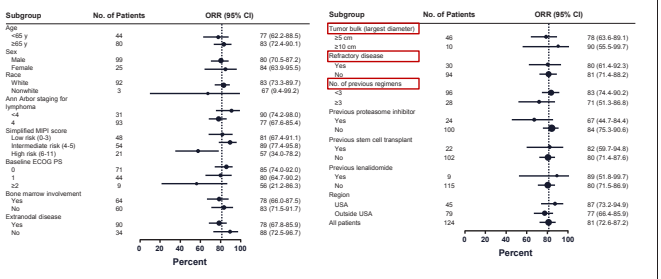


1. Wang M et al. *Leukemia*. 2019;33:2762-2766.

PeerView.com

And what was also impressive is the durable response with a recent update of a median 26-month follow-up, where you see the CR rate, again, at 53%, and a 26-month median duration of response; so that's very impressive, again, in that setting.

Activity of Acalabrutinib Across All Subgroups in R/R MCL[1]



1. Wang M et al. *Lancet*. 2018;391:659-667.

PeerView.com

As I mentioned, as with ibrutinib, here, again, is the forest plot showing activity across the board in a number of different typical clinical parameters that matter for the prognosis of MCL, including bulky disease, refractory disease, high-dose therapy, and a number of prior regimens. So this is obviously very significant because these patients with heavily pretreated MCL do not respond to standard therapy, even high-dose therapy and transplant.

ACE-LY-004: Incidence of Select Adverse Events by 6-Month Intervals[1]

AE, n (%)	1-6 mo (n = 124)	7-12 mo (n = 99)	13-18 mo (n = 74)	19-24 mo (n = 65)	>24 mo (n = 55)
Headache, any grade	42 (34)	2 (2)	0	0	0
Grade ≥3	2 (2)	0	0	0	0
SAE	1 (1)	0	0	0	0
Diarrhea, any grade	31 (25)	8 (8)	3 (7)	5 (8)	5 (9)
Grade ≥3	3 (2)	1 (1)	0	0	0
SAE	0	0	1 (1)	0	0
Infection, any grade	51 (41)	20 (20)	17 (23)	11 (17)	6 (11)
Grade ≥3	11 (9)	4 (4)	2 (3)	2 (3)	1 (2)
SAE	8 (6)	4 (4)	2 (3)	2 (3)	1 (2)
Bleeding events, any grade	31 (2)	14 (14)	5 (7)	4 (6)	0
Major hemorrhage	1 (1)	0	0	2 (3)	0
Atrial fibrillation, any grade	0	0	0	0	0
Rash, any grade	10 (8)	5 (5)	2 (3)	1 (2)	0
Grade ≥3	1 (1)	0	1 (1)	1 (2)	0
SAE	0	0	0	0	0

1. Wang M et al. *Leukemia*. 2019;33:2762-2766.

PeerView.com

The side effect profiling we heard from Richard very nicely. This is typically very much grade 1/2. There seems to be less cardiac toxicity, particularly atrial fibrillation. Hypertension is probably similar. The rest of it is pretty much a similar toxicity profile, maybe less bleeding, but still some contusion and ecchymosis.

Phase 3 ACE-LY-308 Study: Acalabrutinib + BR in Newly Diagnosed MCL[1]

- Patients with newly diagnosed MCL
- Aged ≥65 y
- Pathologically confirmed MCL requiring treatment; no prior systemic therapies
- ECOG PS ≤2
- Estimated N = 546[a]

R

Acalabrutinib administered twice daily orally **+ bendamustine** on d 1 and 2 and **rituximab** on d 1 cycles are repeated every 28 d

Placebo + bendamustine on d 1 and 2 and **rituximab** on d 1 cycles are repeated every 28 d

- **Primary endpoint:** PFS per the Lugano classification for NHL in arm 1 vs arm 2

[a]Agreement to use highly effective forms of contraception during the study and 90 days after the last dose of acalabrutinib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longest.
1. https://clinicaltrials.gov/ct2/show/NCT02972840. Accessed December 3, 2019.

PeerView.com

Similar to the SHINE trial, the BR plus/minus acalabrutinib trial is currently ongoing in elderly patients with MCL. Elderly is a relative term as we go on in life.

Phase 2 Studies of Zanubrutinib in R/R MCL[1,2]

- Zanubrutinib assessed in phase 2 (BGB-3111-206), phase 1/2 trial (BGB-3111-AU-003)
- Dose: 160 mg twice daily until disease progression or unacceptable toxicity (320 mg orally once daily also tested)
- Median number of prior treatments: 2 (range: 1 to 4)
- Primary efficacy endpoint: ORR

	BGB-3111-206 (N = 86)	BGB-3111-AU-003 (N = 32)
ORR (95% CI), % CR, % PR, %	84 (74-91) 59 24	84 (67-95) 22 62
Median DOR (95% CI), mo	19.5 (16.6-NE)	18.5 (12.6-NE)

2019: accelerated FDA approval of zanubrutinib for adult patients with MCL who have received at least one prior therapy

1. Song Y et al. ASH 2018. Abstract 148. 2. Tam CS et al. ASH 2018. Abstract 1592.

PeerView.com

The next wave of BTK inhibitors is zanubrutinib. And this is the phase 2 data showing an overall response rate of 84%—very impressive—and a CR rate of 59%. And this led to the accelerated approval for patients who have failed one prior line of therapy in mantle cell lymphoma.

Zanubrutinib Safety Summary From the Early-Phase Experience[1]

Most common (≥15%) TEAEs, %	
Decreased neutrophil count	41.9
Rash	33.7
Upper respiratory tract infection	33.7
Decreased WBC count	26.7
Decreased platelet count	25.6
Hypokalemia	16.3
Diarrhea	15.1

26 patients discontinued treatment
- 16 due to PD
- 10 due to TEAEs

1. Tam CS et al. ICML 2019. Abstract 191.

PeerView.com

The toxicity profile, again, is not different from what I had just mentioned for BTK. Twenty-six patients discontinued treatment: 16 due to progression, 10 due to AEs.

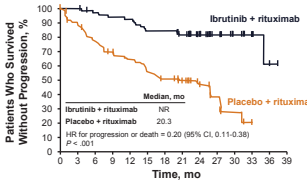
Selected Evidence on BTK Inhibitors in Other Lymphoid Cancers

What about other lymphoid cancers?

BTK Inhibitors in Other Settings: Waldenström's Macroglobulinemia

- Ibrutinib active in phase 2 setting[1] → ORR of 90%; 2-y PFS 70% in R/R WM
- Phase 3 iNNOVATE trial in WM[2]

Phase 3 study of ibrutinib + rituximab vs rituximab in newly diagnosed WM:[3] significant improvement in PFS



1. Treon SP et al. *N Engl J Med*. 2015;372:1430-1440. 2. Dimopoulos MA et al. *Lancet Oncol*. 2017;18:241-250.
3. Dimopoulos MA et al. *N Engl J Med*. 2018; 378:2399-2410.

PeerView.com

What about other lymphoid cancers? In Waldenström's macroglobulinemia, the early data in phase 2 showed an overall response rate of 90%, with a 2-year PFS of 70% in relapsed/refractory Waldenström's; so this was very appealing.

This led to the phase 3 iNNOVATE trial that's shown here: ibrutinib-rituximab versus placebo-rituximab. The data speaks for itself. This was a very impressive improvement of PFS.

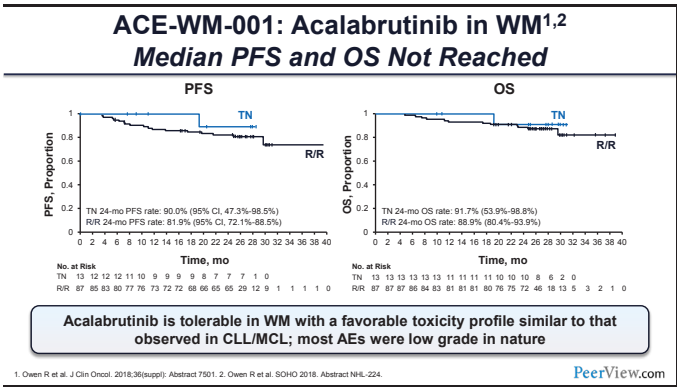
ACE-WM-001: Acalabrutinib in WM[1-3]

Characteristic	6th IWWM Criteria[1]		Modified 3rd IWWM Criteria[2]	
	TN (n = 14)	R/R (n = 92)	TN (n = 14)	R/R (n = 92)
ORR (≥MR), n (%) 95% CI	13 (93) 66-100	86 (93) 86-98	13 (93) 66-100	86 (93) 86-98
MRR (≥PR), n (%) 95% CI	11 (79) 49-95	74 (80) 71-88	11 (79) 49-95	72 (78) 68-86
Best response, n (%)				
CR	0	0	0	0
VGPR	0	8 (9)	1 (7)	30 (33)
PR	11 (79)	66 (72)	10 (71)	42 (46)
MR	2 (14)	12 (13)	2 (14)	14 (15)
SD	1 (7)	6 (7)	1 (7)	4 (4)
Median DOR not reached in either cohort				

1. Owen R et al. *J Clin Oncol*. 2018;36(suppl): Abstract 7501. 2. Kimby E et al. *Clin Lymphoma Myeloma*. 2006;6:380-383.
3. Owen R et al. SOHO 2018. Abstract NHL-224.

PeerView.com

The responses were two different criteria from the Third and the Sixth International Workshop on Waldenström Macroglobulinemia. But, basically, the take-home message is that the response rate is very high, in the mid-90%, and the major response rate is 79% to 80% across the board.



This is the duration of response in treatment-naïve and relapsed/refractory patients. And again, it's very impressive for a population that is typically elderly. And it's well tolerated.

Summary of Ibrutinib in Other Lymphomas

Regimen / Setting	Notes
Single-agent ibrutinib until progression or intolerance[1] R/R MZL (≥1 treatment including rituximab)	• N = 63 • Median age of 66 years; median of 2 prior treatments • ORR 48% with 23% attaining CR
Ibrutinib-lenalidomide-rituximab[2] R/R non-GCB DLBCL pts ineligible for SCT	• N = 55 • ORR of 55% (CR of 30%) • Median DOR was 9 mo • ORR of 47%; CR of 28% (Abstract 761)[3]
Ibrutinib + R-CHOP vs R-CHOP (phase 3 randomized study)[4] **PHOENIX study** previously untreated non-GCB DLBCL	• N = 838 • Addition ibrutinib to R-CHOP did not improve efficacy in the ITT population • In pts <65 y, addition of ibrutinib showed clinically meaningful improvement in EFS, PFS, and OS

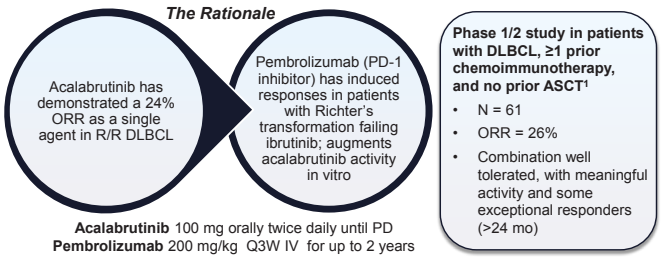
1. Noy A et al. *Blood*. 2017;129:2224-2232. 2. Ramachandren R et al. ASH 2018. Abstract 402. 3. Ramachandren R et al. ASH 2019. Abstract 761. 4. Younes A, et al. ASH 2018. Abstract 784.
PeerView.com

So, in the summary of ibrutinib in other lymphomas, for example, with single-agent ibrutinib until progression in marginal zone lymphoma—we heard from Krish earlier—in 63 patients with a median of two prior therapies, the overall response rate was 48%, with a number of patients attaining a CR, so 23%.

With ibrutinib-lenalidomide-rituximab in non-GCB large cell lymphoma [patients] not eligible for stem cell transplant, the response rate was 55%, with a CR of 30%. We actually have a presentation at ASH—an update on that—showing an activity that is very impressive in a population that is not eligible for transplant, including some patients who had a response up to 4 years.

Ibrutinib plus R-CHOP versus R-CHOP—this was the PHOENIX study that was presented previously showing that ibrutinib plus R-CHOP did not improve the efficacy in the intent-to-treat population. However, in patients younger than 65, the addition of ibrutinib improved the EFS, PFS, and overall survival.

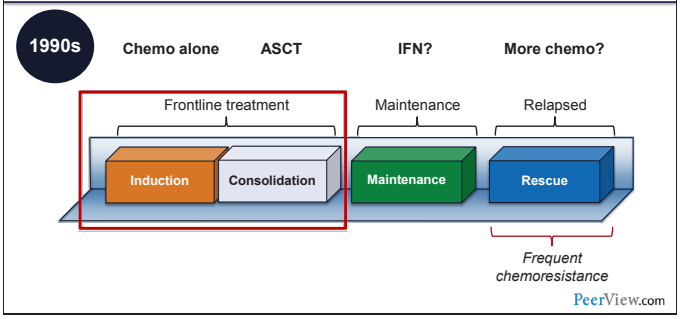
BTK Inhibitor + Immunotherapy in DLBCL



BTK plus immunotherapy in large cell lymphoma—there was an interesting study presented by Tom Witzig from the Mayo Clinic, where the rationale is taking the immunomodulatory activity of BTK inhibition in addition to checkpoint inhibitors for patients who had large cell lymphoma, were relapsed/refractory after R-chemo, and had no prior high-dose therapy and transplant.

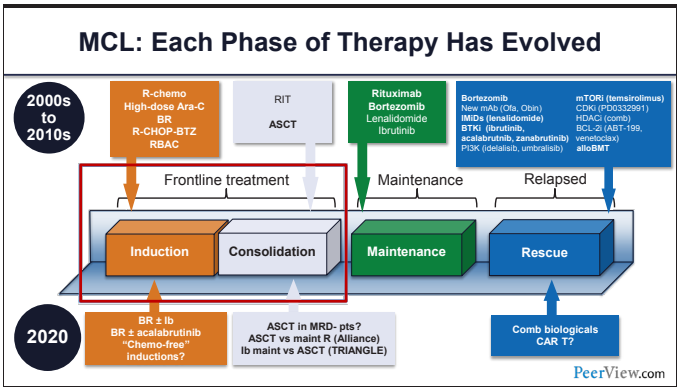
The response rate was 26%. But what was interesting in that study—where typically you don't see a great response with checkpoint inhibitors, single-agent, in large cell lymphoma—there were some responders for more than 24 months. So it's early and a small number of patients, but an interesting concept.

Treatment of MCL: Historical Foundation



So if we put things into perspective in mantle cell lymphoma, the original backbone of treatment for mantle cell lymphoma—because chemotherapy alone was so bad—so chemotherapy became chemo plus consolidation. And then we had some studies, particularly in Europe, looking at interferon maintenance.

And when patients relapsed—because most patients relapsed—they very typically developed chemoresistance. And only a very small subset of patients seen in academic institutions who could get an allotransplant could have a long-term benefit. Otherwise, the median survival was very poor.



In the 2000s—the first decades, actually—we have demonstrated that the field changed across the board. Each phase of therapy, induction, consolidation, maintenance, and relapse, has changed. So clearly now, the backbone has to contain cytarabine induction if you use an intensive regimen

If you don't use an intensive regimen: BR or R-CHOP-bortezomib. VR-CAP is very interesting. RBAC data is very impressive in a relapsed setting and—there's data at ASH [2019]—even in patients who are failing ibrutinib, we have some very durable responses. My experience with RBAC was for a study that was published from Italy—again, not a large number of patients, but 50 patients in the frontline setting. It was very impressive and with very sustained response, and a lot of MRD negativity—more than 80%.

So this is very appealing—and I know this is somewhat toxic, the original RBAC. So the RBAC with the cytarabine 500 mg/m^2 is better tolerated, and I've been able to manage a lot of patients just with four cycles of RBAC and they do really well.

The consolidation—there was a look at radioimmunotherapy, but it was not really convincing. The consolidation with high-dose therapy and transplant, particularly if you did not have an intensive therapy, definitely improved the outcome.

And then the maintenance was explored with rituximab, initially in the elderly after FCR or R-CHOP. It improved the PFS and the survival, and, obviously, reduced the risk of relapse. Maintenance bortezomib also was better than historical control. Maintenance lenalidomide data, the trials are ongoing. And maintenance ibrutinib, the trials are also ongoing.

In a relapsed setting, the box is getting bigger. There are a number of novel agents that are being looked at, obviously. We talked about BTK, but there's also the BCL-2 inhibitors, venetoclax, CDK inhibitors, PI3K, new monoclonal antibodies, and lenalidomide, a second-generation IMiD, that were very appealing and helped build up the field, and making it almost difficult to recruit patients with relapsed/refractory mantle cell lymphoma.

So where we are, and where are we going? This is in 2020. So for the frontline, we are eagerly waiting for the BR plus/minus ibrutinib or plus/minus acalabrutinib. Very likely, this is going to show significant benefit. What I think is going to be even most impressive and interesting is to build up on the chemo-free induction, or less chemotherapy.

And there are a number of studies that are ongoing looking at taking advantage of ibrutinib-rituximab in elderly patients, where the CR rate is very impressive—65%— and a lot of patients are also MRD negative, and it is maintained and well tolerated. And there are triplets, also, that are being brought to the frontline setting that we'll hear at about ASH [2019] as well.

The role of consolidation of high-dose therapy and transplant is being addressed in the Alliance trial, where you get induction, and then if you're MRD-negative, you get randomized for high-dose therapy and transplant versus maintenance therapy.

The TRIANGLE study in Europe, as I just mentioned, is trying to see if ibrutinib after induction could replace a transplant just by doing ibrutinib maintenance. So I am not convinced that high-dose therapy and transplant is something that is here to stay, particularly if patients achieve MRD negativity.

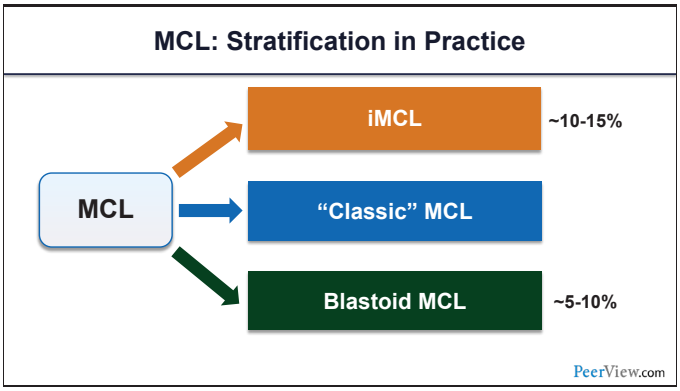
What matters in mantle cell lymphoma is achieving early MRD negativity. And again, if you get a less optimal induction, high-dose therapy and auto-transplantation are probably more beneficial. But, if you get a deep induction and MRD negative early, probably the high-dose therapy and auto-transplantation doesn't bring as much.

The maintenance therapy, as I mentioned, is being looked at with a number [of options], including R^2 and other small molecules, and again, ibrutinib.

And finally, in a relapsed setting, what is also changing in the field now, besides the small molecules that I mentioned particularly—again, BTK, but also venetoclax and a number of other novel therapies in the population of mantle cell lymphoma—is the combination of biologicals. It's a small number of patients, but a proof of concept, taking the combination of venetoclax and ibrutinib—and I know there are studies ongoing with acalabrutinib and other BCL-2 inhibitors—showing that you can achieve such a deep response that you might be able to stop therapy in a relapsed/refractory setting with having a sustained response. This is not routine, obviously, as it's based on a very small number of patients, but I think a very appealing concept where a combination of biologicals could actually really shift the paradigm in a relapsed/refractory setting.

What is really changing the field is the treatment of patients who are chemo resistant. And, typically, when patients become, over time, more and more accelerated, blastoid variant, p53-mutated/-deleted, and very complex, genetically speaking, these patients are very resistant to even high-dose therapy, as I mentioned.

So CAR T therapy—we have a presentation at ASH [2019] looking at the ZUMA-2, which is axi-cel in relapsed/refractory mantle cell lymphoma. This is very impressive early data, but I think this is really something that's going to be very critical in this population where there's a true unmet need.



So how do we stratify patients? How do we decide in practice? And how do we integrate those small molecules? Very simply put, there are three different types of mantle cell lymphomas. The indolent mantle cell lymphoma makes up 10% to 15% of all MCL. As a reminder: high white count, splenomegaly, very few have a lymphadenopathy. They are somatically mutated. They are not complex genetically speaking. They can be monitored for a very long time.

They can, over time, sometimes acquire deletion 17p, and, obviously, the disease then becomes more aggressive. That's a small number of patients, and these patients should not even be put in clinical trials the same way. They have a different genetic expression profile. It's a different subset of mantle cell.

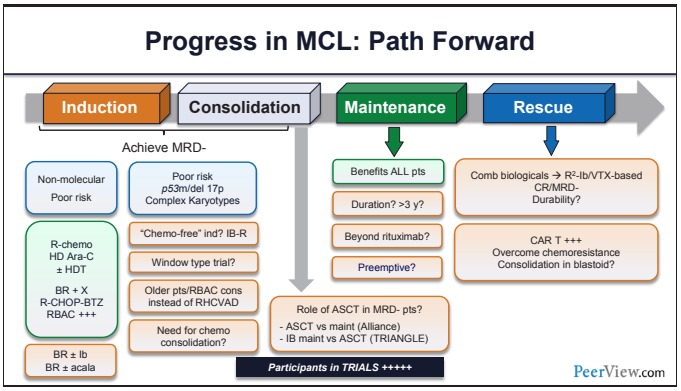
You have the blastoid variant presentation, which makes up 5% to 10% of patients. They can be blastoid, morphologically. They can be pleomorphic. They typically have a p53-mutation. And I think this is a take-home message that is very important, particularly in the context of BTK inhibition today—is that, when we look at p53 abnormalities in mantle cell lymphoma, although patients have a leukemic phase, it's not as much as in CLL.

And we don't do cytogenetic assessment enough routinely, or FISH at baseline. The deletion 17p is not very commonly [detected] at baseline. But, if you do NGS or IHC for p53 abnormalities at baseline in mantle cell lymphoma, it's up to 20% to 23% of patients that have a de novo abnormal p53 mutation, even if they don't have the blastoid variant—so put them into the molecular high risk.

And then you have the classic mantle cell lymphoma. It is, as I mentioned, a spectrum of disease. There's still a subset of patients—maybe one-third of those—that can be watch-and-wait: low tumor burden, no aggressive features, low Ki67. And these patients can be monitored.

Typically, the median to stop therapy is roughly a year—a year and a half, and these patients can therefore be monitored initially. And then you have all the other subsets of mantle cell lymphoma that, depending on the age and if they're fit for high-dose therapy, we talked about the way to approach those patients.

So that becomes a little more complex when mantle cell lymphoma—a rare disease to start with—becomes, already, three or four different subsets of patients.



So we try to look at the path forward. With induction therapy, the goal is to achieve a negative MRD as early as possible. So with the non-molecular, poor-risk, the patient can tolerate intensive therapy: high-dose Ara-C-containing regimens with or without high-dose therapy and transplant, BR plus X, ibrutinib, or acalabrutinib—the data are pending, as I mentioned—R-CHOP-bortezomib and RBAC if you cannot tolerate intensive therapy. My preference outside of a study is actually to use RBAC. I think the duration is much better, and, again, we're waiting for the impact of the BTK inhibitors added to the BR backbone.

In patients who have poor risk, molecularly-speaking, so *p53*-mutation, or deletion 17p—and, again, the p53, I want to insist, this is largely underestimated at baseline—and patients, also, who have complex karyotype at baseline, so for these patients, I agree with the approach that Michael had described [when discussing] the WINDOW trial, where you actually can give ibrutinib-rituximab, for example, where a very high number of patients end up achieving a CR, and even MRD negativity. So they get on this trial, they get ibrutinib-rituximab until they achieve a CR or PR, and then they get a shorter consolidation of four hyperCVAD instead of six.

This trial is ongoing, but I have been using this even in older patients when they have p53 abnormalities, and then consolidate it with a short [course] of RBAC.

The question of the need of chemotherapy consolidation, as I mentioned, or cell therapy consolidation, in these very high-risk patients is still not answered. We still don't really know. I mean, this is a very impressive result.

I have patients who had blastoid variant, leukemic phase, who came to see us *de novo*, had ibrutinib-rituximab, and went into MRD negativity. We gave them a short consolidation of hyperCVAD. Do we still need the chemotherapy afterwards? The rationale is that you kill the bad clones—because this is a clonal heterogeneity, obviously—you kill the bad clones with ibrutinib-rituximab and potentially complete the consolidation with chemotherapy.

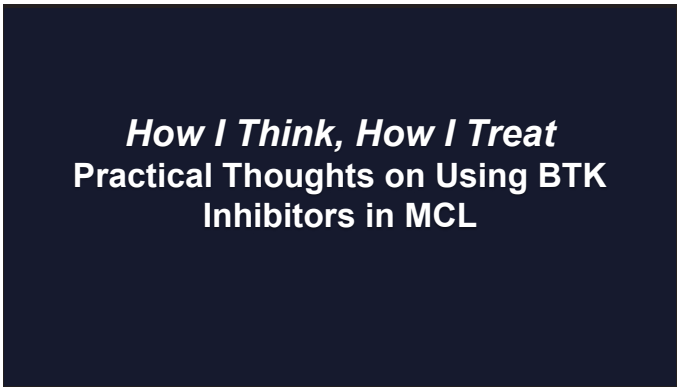
The role of transplant in MRD-negative patients, as I mentioned, is something that is still being evaluated. I am not convinced that if you use the proper induction, you need a transplant. But we're waiting for the results of the ALLIANCE trial, and then, also, the results of the TRIANGLE study in Europe, where ibrutinib maintenance might replace the transplant after induction.

The maintenance therapy benefits all patients as we speak now. Again, it was established in elderly patients. It is very well established that it benefits all patients—elderly and younger patients—even after high-dose therapy, typically, up to 3 years. I don't know. There's no clearly optimal duration. Beyond rituximab maintenance, R^2, the trials are ongoing.

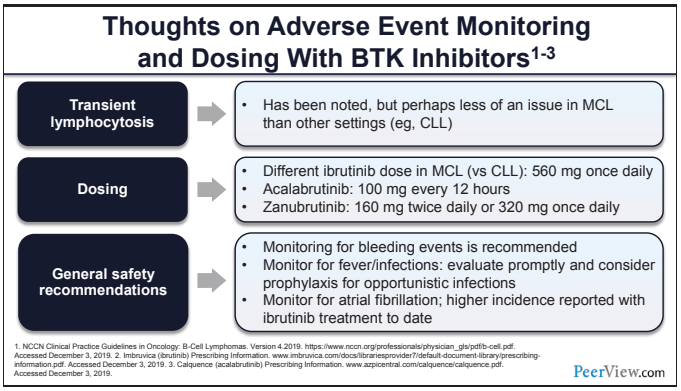
I think what is more appealing, and we have started to adopt—and we heard it from Richard, as well—is the impact of MRD in CLL. In mantle cell lymphoma, this is something that we do routinely. And I actually base my maintenance on MRD and do a preemptive maintenance instead of doing a scheduled maintenance.

And finally, in a relapsed/refractory setting, this is the combination of biologicals—as I mentioned, R^2-ibrutinib or venetoclax-based combinations—where you might be able to obtain very durable response, even after treatment. And the CAR T, that is definitely a novel strategy that will be very helpful in a population that does very poorly.

And again, the only way to salvage these patients when they have failed multiple lines of therapy is cell therapy with allotransplant, which is obviously not feasible all the time. The median age at diagnosis is in the mid-60s, roughly, so by the time they get into the relapsed setting for an allotransplant, it's sometimes difficult to do because of comorbidities, finding a donor—obviously—and then more than half of the patients have chronic GVHD—and definitely this is an issue to take into consideration. So I think the CAR T is going to be very helpful in that setting.



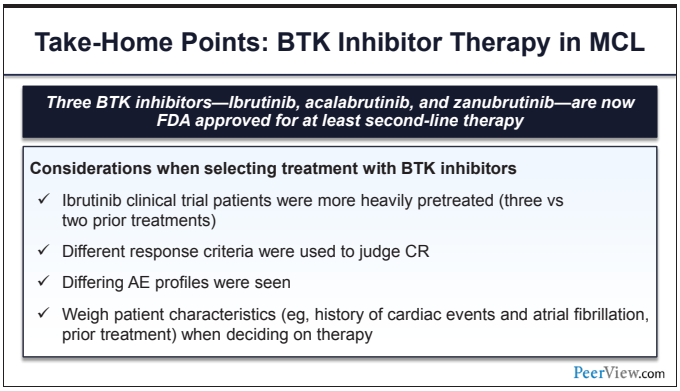
So, some practical thoughts now.



Transient lymphocytosis—we know that in CLL, this is something important that has affected the design and interpretation of the responses, initially. This has been seen in mantle cell lymphoma in patients who have a lot of bone marrow involvement. This [occurs] much later, is not as significant, and really doesn't have a lot of impact, particularly no tumor lysis syndrome.

The dosing is different. Ibrutinib is 560 mg once daily, acalabrutinib is 100 mg BID, and zanubrutinib is 160 mg BID or 320 mg once daily.

The safety recommendation is, obviously, to monitor these patients carefully—particularly at the beginning—for bleeding events, counts, and infection, [and consider] prophylaxis, if needed, and to monitor for A-fib. A higher incidence [of A-fib] has been reported so far with ibrutinib, but we have also seen some in the acalabrutinib setting, and it's possible, over time, that we will see a little bit more in that setting as well.



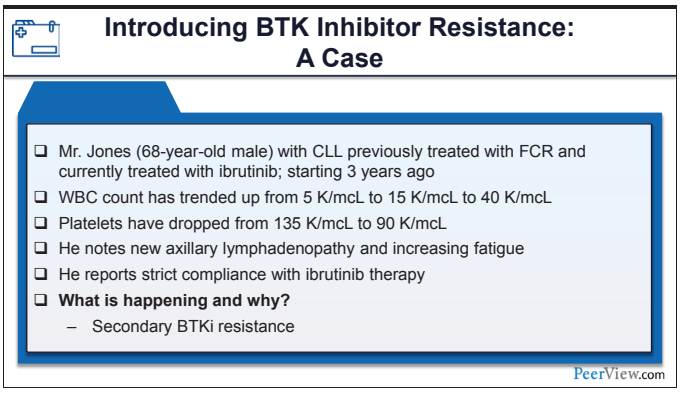
So, the take-home message, in summary, is that the three BTK inhibitors—ibrutinib, acalabrutinib, and zanubrutinib—are all approved for second-line therapy in mantle cell lymphoma. In the ibrutinib clinical trials, patients were more heavily pretreated—three versus two prior therapies. Remember, the CR rate was 20% versus 40%, so that might explain some of it, as well as the duration of response. The different response criteria to judge the CRs might also be a factor.

Differing AE profiles were seen—definitely an easier toxicity profile with acalabrutinib and zanubrutinib. And weigh the patient characteristics—the setting, history of cardiac events, the context, A-fib, prior treatment—to decide on therapy, given the fact that we now have all these options.

So this is really exciting, because in the field of mantle cell lymphoma we have had a lot of novel agents approved, and we can see now that this is allowing us to change the paradigm on how we manage patients with mantle cell lymphoma.

Perspectives on New Science With BTK Inhibitors: Overcoming Resistance and Beyond

Deborah M. Stephens, DO



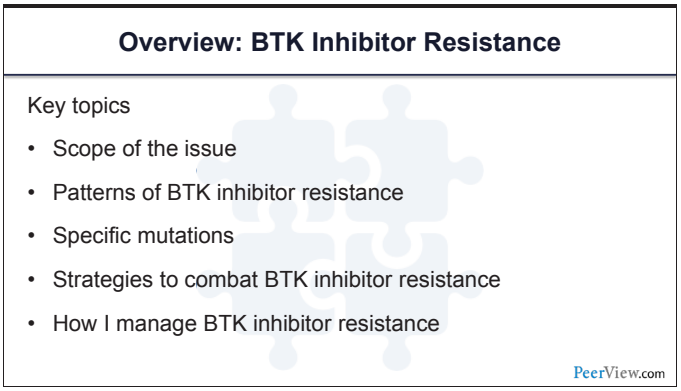
Dr. Goy: So it is my pleasure now to introduce Dr. Deborah Stephens from the Huntsman Cancer Institute. She's going to share with us how we move on from BTK resistance. Deborah, thank you.

Dr. Stephens: Well, thank you very much for the other speakers that have really nicely introduced how much these BTK inhibitors have really helped our patients with B-cell malignancies. And so, I think today my job is really to talk a little about what we think of as a bit of the Achilles' heel of these BTK inhibitors, and that is resistance. And what do we do about the patients that become resistant? And how could we potentially prevent resistance?

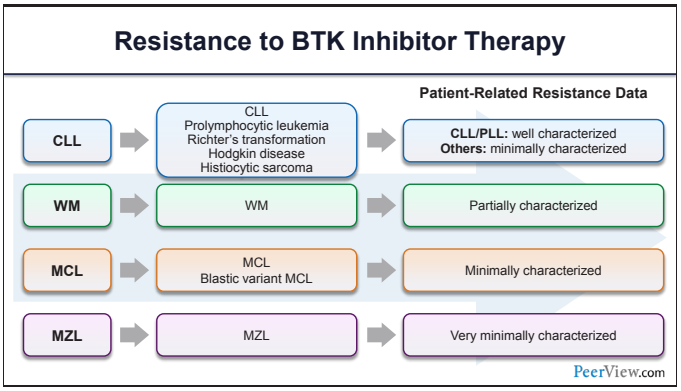
So, to introduce my topic a little, I'd like to give you a classic case presentation of BTK inhibitor resistance. So, Mr. Jones is a 68-year-old man with CLL, who was previously treated with FCR, but is now currently being treated with ibrutinib, starting about 3 years ago.

Over the last few visits, his white blood cell count has trended up from 5,000/mcL to 15,000/mcL, to now 40,000/mcL. His platelets have dropped from 135,000/mcL at baseline to 90,000/mcL now. And he notes some new axillary lymphadenopathy and increasing fatigue. He does report strict compliance with ibrutinib therapy, which is important to assess in these patients.

So, really, what is happening in this patient and why? And that's what I'd like to cover today. This patient has a classic case presentation of secondary BTK resistance.



So, key topics I'd like to cover in my portion of the talk are, really: the scope of this issue, patterns of BTK inhibitor resistance, specific mutations that you need to be aware of, strategies to combat these resistant cases, and, lastly, I'll end with how I manage these BTK inhibitor-resistant patients.



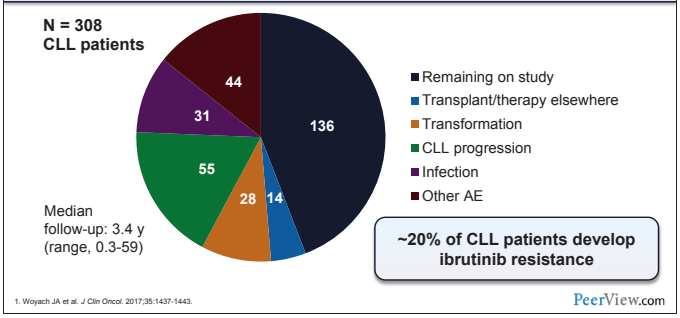
So we know a lot about BTK inhibitor resistance, but there is still a lot to learn. And I wanted to highlight, with the different diseases for which BTK inhibitors are approved, the knowledge that we have available to us at the current time.

We know the most about resistance in CLL, and I've shown here in the diagram that when CLL patients develop resistance, you can see the progression of CLL, but you can also see its transformation into prolymphocytic leukemia, diffuse large B-cell lymphoma, Hodgkin disease, or even histiocytic sarcoma.

The resistance to CLL and PLL is pretty well characterized, but the others are minimally characterized at this time.

With Waldenström's, mantle cell, and marginal zone lymphoma, resistance is a little less characterized, but I'll share with you the data that we have available.

Scope of the Ibrutinib Resistance Issue in CLL?[1]



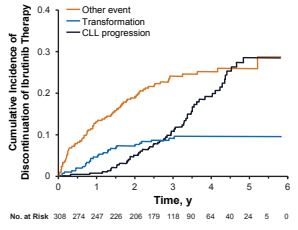
1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

Next, I'd like to focus on what's the scope of the issue. And again, I had mentioned that we know the most about this in CLL. This is a study that's already been discussed earlier today. It's about patients who were treated with ibrutinib who had CLL, on clinical trials and otherwise, at Ohio State University. This included 308 CLL patients, and it was published after a median follow-up of about three and a half years.

The majority of patients were still on ibrutinib at this time point—about 45%. But I'd like to focus on the green and the orange pieces of this pie. The green piece shows those patients who have CLL progression, and the orange represents those who have had transformation of disease. And really, I'd like to highlight that in CLL at least, it looks like approximately 20% of patients will develop ibrutinib resistance over time.

When Is Ibrutinib Resistance Likely To Occur?[1]



Cumulative Incidence Estimate (95% CI)	At 2 y	At 3 y	At 4 y
CLL progression	5.0% (2.5%-7.5%)	10.8% (7.1%-14.4%)	19.1% (13.9%-24.3%)
Transformation	7.3% (4.3%-10.2%)	9.1% (5.8%-12.4%)	9.6% (6.2%-13.0%)
Other event	18.7% (14.3%-23.1%)	23.9% (19.0%-28.8%)	25.0% (20.0%-30.1%)

Increasing incidence of ibrutinib resistance after 2 years

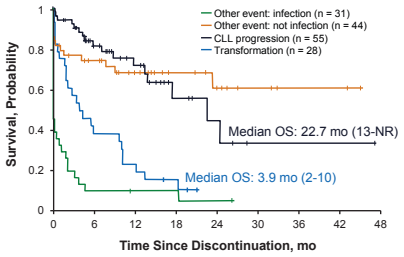
1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

Again, you've already seen a little bit of this data earlier, but I really want to focus now on the black curve, and that is CLL progression. This really depicts when patients discontinue ibrutinib and why. And you can see that this black curve starts to peak up after about a year and continually rises over time. So it shows us that, over time, patients do develop progression of CLL.

And this really is something that you want to look at starting at about 2 years. So if a patient comes to you and they've only been on ibrutinib therapy for 3 or 4 months, it's pretty unlikely that they would have developed resistance in that time period.

How Does Ibrutinib Resistance Impact Survival?[1]



1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443.

PeerView.com

So this is really important, of course, for our patients because it really does impact survival. And these are curves—again, from the same study from Ohio Stat—that show patient survival after discontinuation of ibrutinib. I'd like to highlight the black curve, which represents patients with progressive CLL, and their median overall survival is only about 2 years. And this is a really low number in patients with CLL.

Even lower is the blue curve, which [represents] patients that have had transformed disease, and their median overall survival is only about 4 months. So these patients are really in need of research to figure out how we can overcome this resistance of BTK inhibitors.

Patterns of Resistance to BTK Inhibitor Therapy

	Initial Treatment	Salvage Treatment
CLL	Primary resistance: nonexistent Secondary resistance: very rare	Primary resistance: very rare Secondary resistance: common
WM	Not well characterized	Primary resistance: occurs Secondary resistance: common
MCL	Not well characterized	Primary resistance: common Secondary resistance: very common
MZL	Unknown	Primary resistance: common Secondary resistance: very common

PeerView.com

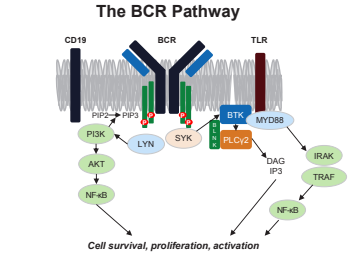
Again, this is highlighting what we know in different diseases, and really looking at it as far as what line of therapy patients are receiving. And so, for example, in patients who are initially receiving a BTK inhibitor as frontline therapy, primary resistance is really nonexistent. And so, again, if you see a patient who has only been on ibrutinib therapy for a couple of months, it is most likely that resistance is not the reason why they're progressing.

Secondary resistance is pretty rare, as you've seen with the survival curves that Dr. Furman showed when using ibrutinib in frontline therapy. However, when using ibrutinib or other BTK inhibitors in salvage treatment, primary resistance, again, is quite rare; however, secondary resistance is common.

When you look at other disease groups, such as Waldenström's, mantle cell, and marginal zone [lymphoma], resistance to the initial

treatment is really not well characterized at this time. And as far as salvage therapy goes, primary resistance does occur in these diseases, and is actually even common in mantle cell and marginal zone lymphoma, and secondary resistance is still more common in these groups of patients.

Relapse-Related Discontinuation: Mechanisms of Resistance to Ibrutinib[1]



- *BTK* and *PLCγ2* mutations are associated with **acquired resistance**
- Aberrant activation of PI3K/AKT and NF-κB pathways, and *MYD88* mutations are associated with **primary resistance**

1. Zhang SQ et al. *Br J Haematol*. 2015;170:445-456.

PeerView.com

We've touched on this a little. I wanted to get into a few more details about why patients discontinue BTK inhibitors and how resistance develops. And as you likely know, the most important and key mutations that happen are mutations in *BTK* and *PLCγ2*, and these are really associated highly with acquired resistance.

As far as primary resistance, aberrant activation of other parts of the B-cell receptor signaling pathway, such as PI3K/AKT and NF-κB pathways, and *MYD88* mutations.

Ibrutinib Resistance in CLL (What We Know)

- **Acquired resistance to ibrutinib:**[1-5]
  - Mutations in *BTK* gene at C481 binding site
    - Changes to reversible inhibitor
    - ↓ binding efficiency
    - ↑ BTK enzymatic activity
  - Mutations in *PLCγ2* at multiple hotspots (R665, L845, and S707)
    - Promote gain of function and BCR activation[6]
  - Rare mutations: *BRAF, CARD11*, etc.[5]

1. Woyach J et al. *N Engl J Med*. 2014;70:2286-2294. 2. Ahn IE et al. *Blood*. 2017;129:1469-1479. 3. Sharma S et al. *Oncotarget*. 2016;7:68833-68841. 4. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 5. Kanagal-Shamanna R et al. *Cancer*. 2019;125:559-574. 6. Liu TM et al. *Blood*. 2015;126:61-68.

PeerView.com

In CLL, we know quite a bit, again, about ibrutinib resistance. And I want to highlight some key features that research has developed.

The most important mutations are mutations in the *BTK* gene at the C481 binding site. As you have heard, ibrutinib is designed to be an irreversible inhibitor. However, this mutation does change ibrutinib to a reversible inhibitor. It decreases binding efficacy and it increases the BTK enzymatic activity.

And so, therefore, if you've seen these patients like I just described in the initial case report, ibrutinib is still binding to BTK, however, it is not a solid bond. And so, these patients will typically show slow progression, at which time you discontinue the ibrutinib, and then you will see a rapid progression of disease—unless you've started the patient on another therapy.

Other than *BTK* mutations, of course, mutations in the downstream component of the B-cell receptor signaling pathway, *PLCγ2*, at multiple hotspots have been detected. These promote gain-of-function and BCR activation. Of course, the rarest mutations—*BRAF, CARD11*, etc.—have been described.

Acalabrutinib Resistance in CLL

Acquired resistance to acalabrutinib[1]

- 105 CLL patients with a median follow-up of 47.5 mo
- 16 patients with progressive CLL, 1 with Richter's (17%)
- 69% (11/16) had *BTK* C481 (S = 10, R and Y = 1)
  - *BTK* T474I gatekeeper mutation
  - 2 with co-existing *PLCγ2* mutations
- Monitoring for *BTK* mutations every 3-6 mo
  - Median time to development of mutation = 30-40 mo
  - Median time from mutation to clinical relapse = 12 mo

1. Woyach JA et al. ASH 2019. Abstract 509.

PeerView.com

We have some new knowledge to learn about acalabrutinib resistance in CLL, and Dr. Woyach studied 105 CLL patients treated with acalabrutinib with a median follow-up of about 4 years. In this series, 16 patients developed progressive CLL, and one patient had Richter's transformation, with a total of about 17% of patients developing resistant disease—so quite similar to the numbers seen with ibrutinib.

And specifically, in those patients who developed progressive CLL, 11 of the 16 had a *BTK* mutation at the C481 binding site. Other notable mutations and mutations that we've seen in ibrutinib resistance: A *BTK* T474I gatekeeper mutation was found in one of these patients. And that mutation basically prevents ibrutinib from entering the BTK binding pocket; that's why it's called a gatekeeper mutation.

She also found that two other patients had co-existing *PLCγ2* mutations. So the resistance patterns are quite similar to what we see in ibrutinib therapy.

In this study, patients were monitored for *BTK* mutations every 3 to 6 months. And she found that the median time to development of *BTK* mutation was about 30 to 40 months after initiation of acalabrutinib therapy, and the median time from mutation detection to clinical relapse was 12 months. And so clearly, in these diseases, we can see these small mutations pop up before clinical relapse.

Ibrutinib in Waldenström's Macroglobulinemia[1]

- Phase 2 study treated 63 pts with ibrutinib (420 mg/d) until progression or intolerance

Genomic Feature	ORR, %	Major Response, %
All Groups	90	73
MYD88^{L256P}/*CXCR4*^{WT}	100	91
MYD88^{L256P}/*CXCR4*^{WHIM}	85	61
MYD88^{WT}/*CXCR4*^{WT}	71	28

- Estimated 2-year PFS was 69% and OS was 95%

1. Treon SP et al. *N Engl J Med*. 2015;372:1430-1440.

PeerView.com

Resistance to Ibrutinib in MCL

Primary/secondary resistance is more common in MCL

- Primary resistance associated with cell cycle, *ERB4*, *PIM*, *SMARCA2*, *SMARCA4*, *TRAF2*, *BIRC2*, and other mutations that activate NF-κB[1-3]
- Secondary resistance to ibrutinib is complicated, but includes uncommon mutations in C481S, *PLCγ2* mutations, *CARD11*, *SMARCA4*, and others[1-3]

Driving mechanisms may represent signal reprogramming

- PI3K, Akt, mTOR signaling[4,5]
- CXCR4/α4β1 integrin activation (via BAFF signaling)[4]

1. Agarwal R et al. *Nature Med*. 2019;25:119-129. 2. Jain P. *Br J Haematol*. 2019;183:578-587. 3. Mohanty A et al. *Oncotarget*. 2018;7:73558-73572. 4. Zhao X et al. *Nat Commun*. 2017;8:14920. 5. Chiron D et al. *Cancer Discov*. 2014;4:1022-1035.

PeerView.com

So, how about BTK inhibitor resistance in Waldenström's macroglobulinemia? What do we know at this time? I wanted to highlight a pivotal phase 2 study that treated 63 patients with ibrutinib that had Waldenström's.

Interestingly, we saw a clear distinction of response based upon patients' genomic feature. Patients with a *MYD88* mutation and a wild-type *CXCR4* mutation had a very impressive overall response rate of 100%, with 91% major response rates.

In those patients that had the *MYD88* mutation, but a mutated CXCR4, we saw a slightly lower overall response rate of 85%. And patients who had a wild type of both genes had an even lower overall response rate.

How about mantle cell lymphoma, and what do we know here? Again, we know a little bit less, but there are lots of emerging data in this area. Primary resistance to ibrutinib in mantle cell lymphoma patients is associated with cell cycle. So *ERB4*, *PIM*, *SMARCA2* and *-4*, *TRAF2*, *BIRC2* and other mutations that activate NF-kB have been implicated.

Secondary resistance to ibrutinib is a little more complicated, but it includes uncommon mutations in C481S, *PLCγ2* mutations, *CARD11*, *SMARCA4*, and others.

Driving mechanisms may represent signal reprogramming with PI3K, Akt, and mTOR signaling, and CXCR4/α4β1 integrin activation via BAFF signaling.

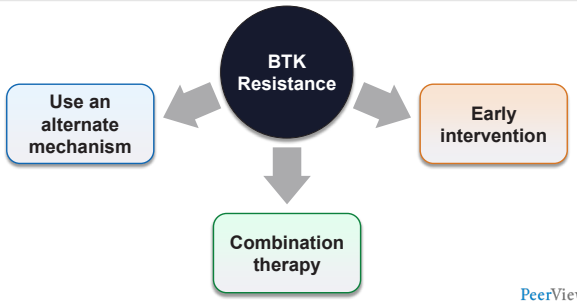
Resistance in Waldenström's

- C481S *BTK* mutations are common and subclonal as in CLL with secondary *CARD11* and *PLCγ2* mutations noted[1]
- C481S *BTK* mutations can be identified in asymptomatic patients prior to clinical relapse[1]
- Majority of patients with C481 *BTK* mutations had baseline *CXCR4* mutations[1]
- *BTK* mutations have increased *ERK1* signaling and downstream paracrine-mediated resistance to surrounding cells via IL-6 and IL-10, explaining potentially how small C481S clones mediate resistance[2]

1. Xu L et al. *Blood*. 2017;129:2519-2525. 2. Chen JG et al. *Blood*. 2018;131:2047-2059.

PeerView.com

Strategies to Combat BTK Inhibitor Resistance



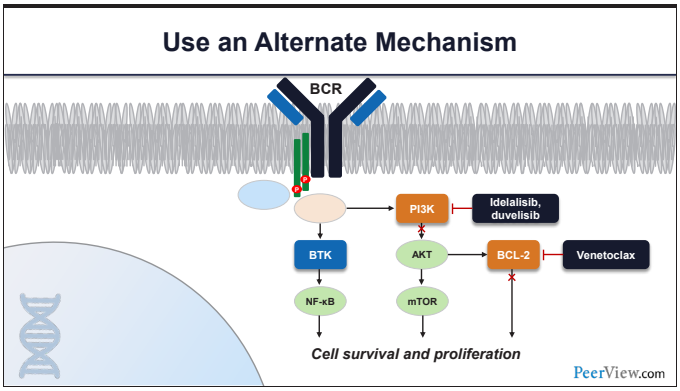
PeerView.com

In Waldenström's, C481S *BTK* mutations are also common and, similar to what we have seen in CLL, they are subclonal. And we do see secondary *CARD11* and *PLCγ2* mutations as well.

Similar to what we have seen in CLL, the C481S *BTK* mutations can be identified in asymptomatic patients prior to clinical relapse. The majority of the patients with these mutations have baseline *CXCR4* mutations.

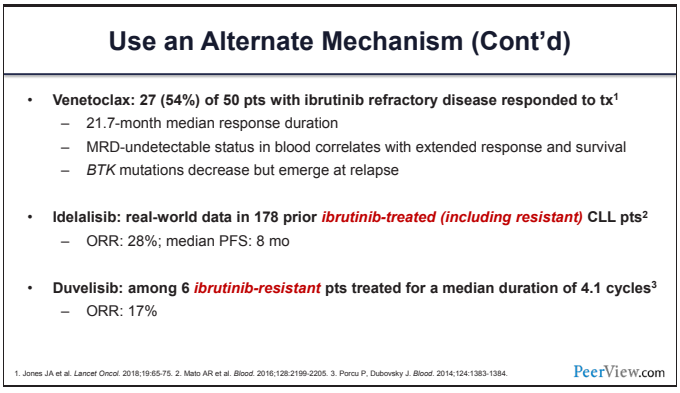
BTK mutations have increased ERK signaling and downstream paracrine-mediated resistance to surrounding cells via IL-6 and IL-10, explaining potentially how small C481S clones can mediate resistance.

So, of course, now that we know what the mutations are, how do we combat these resistant patients? And really, I wanted to highlight three main strategies that I think of in my practice. And the first one is, really, just using an alternate mechanism of action in these patients. And I wanted to highlight on here the B-cell receptor signaling pathway and different ways that we can actually attack resistant cells.



So once patients have progressed on a BTK inhibitor, of course we think about venetoclax therapy, as this is another great targeted inhibitor in CLL cells. This targets something called BCL-2, which is an anti-apoptotic protein, and it has shown efficacy in this space.

Additionally, other inhibitors that are approved in this space are idelalisib and duvelisib, which inhibit PI3K. So basically, finding a different way to attack the B-cell receptor signaling pathway.

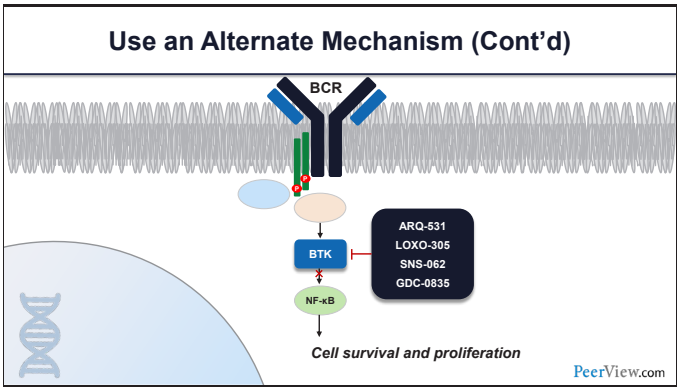


I wanted to highlight a couple of studies that have shown data in this specific space of ibrutinib-resistant patients. With venetoclax, 50 patients were treated who had ibrutinib refractory disease.

They had around a 22-month median response duration and a 54% overall response rate. MRD-undetectable status in the blood, obviously, can correlate with extended response and survival in this space. And an interesting finding is that *BTK* mutations decrease in prevalence, but they do emerge at relapse.

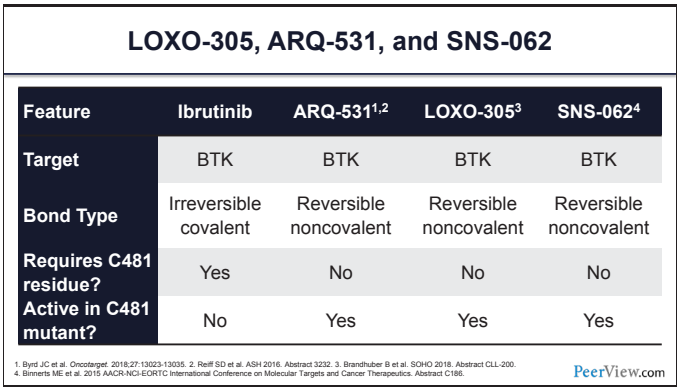
As far as idelalisib, the approved PI3K inhibitor, this was studied in 178 real-world patients who were previously treated with ibrutinib, including resistant patients. The overall response rate here was only 28%, with a median progression-free survival of 8 months.

Duvelisib, another PI3K inhibitor, was studied in six ibrutinib-resistant patients treated for a median of 4 cycles. The overall response rate here was only 17%. And this highlights if you're going to switch treatments after ibrutinib resistance—when I'm choosing a therapy, I will first look to venetoclax therapy, just based on these data.



Other novel studies look at using an alternate mechanism. However, just when you think BTK inhibitors have found their Achilles' heel, this next generation of BTK inhibitors has emerged. And these drugs, I think, are very exciting drugs.

There are four of these reversible ibrutinib tyrosine kinase inhibitors, ARQ-531, LOXO-305, SNS-062—which is also vecabrutinib—and GDC-0835. And I'm really going to focus on the first three, as the last one has not really been clinically developed at this time.



I wanted to just very briefly highlight some of the data from these, and highlight the really key portions of these interesting reversible inhibitors, and really highlight that all of these drugs are BTK inhibitors.

However, the major difference is that these new drugs are reversible and noncovalent inhibitors. They do not require the C481 residue in order to bind, and, therefore, are highly active pre-clinically. And we're starting to see with the initial data in the BTK-resistant patients that they are active in these patients.

Other Alternate Mechanisms

- Kinase inhibitors
  - PKC-β inhibition: MS-553
  - CDK9 inhibitors
- Immunotherapies
  - CAR T cell trials
  - ROR1 antibodies
  - CD20–CD3 bispecific Ab
  - CC-122

PeerView.com

So, of course, there is a multitude of ways that we can approach this. I really wanted to just briefly tell you about some really interesting compounds that are coming through clinical trials right now that I think have great promise for the future.

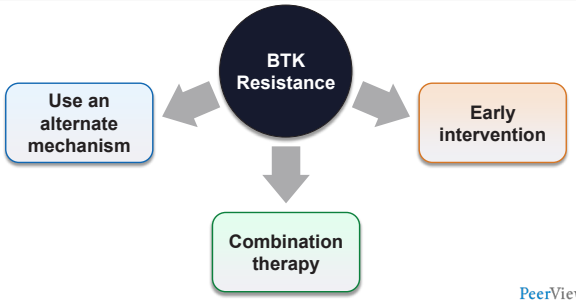
Using other kinase inhibitors, such as other inhibitors of B-cell receptor pathway targets, such as PKC-β—I'm participating in a phase 1 study with a drug called MS553 that looks very interesting pre-clinically, and we're starting to see some exciting clinical data at this time. There are also drugs called cyclin-dependent kinase 9 inhibitors that are showing good promise.

Other potential mechanisms are looking at immunotherapy, such as CAR T cell trials, with BTK inhibitors, either combined or on their own, ROR1 antibodies, CD20–CD3 bispecific antibodies, and CC-122, which is an immunomodulatory agent.

So, again, all of these are a little bit early in development, but they're all very exciting and potential strategies that we can use to combat these BTK-resistant mutations.

Earlier, Dr. Patel mentioned some BTK-degrading compounds. And I didn't mention them here. I think that they are very interesting, and it's a very novel way to approach it. The drug so far has had some issues with oral bioavailability, and so that still needs to be sorted before we can see any real clinical efficacy in these patients.

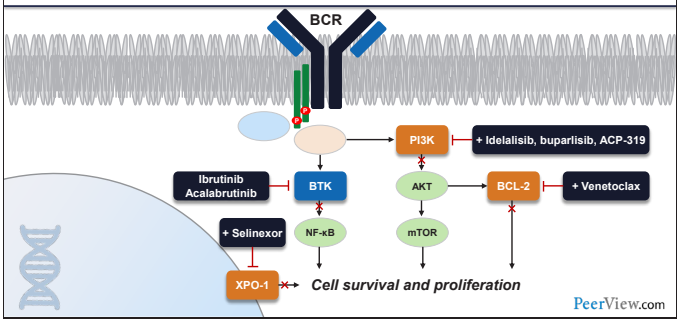
Strategies to Combat BTK Inhibitor Resistance



PeerView.com

So, other than using an alternative mechanism, another thing to consider is combination therapy. And so when you're already blocking BTK, what are some other rational ways to block this pathway?

Use Combination Therapy



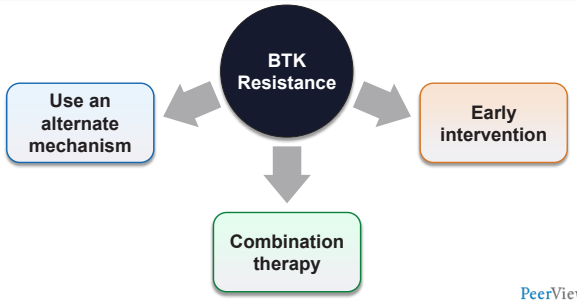
PeerView.com

Of course, you've heard a lot of data already about combination with venetoclax therapy. And one reason why this really does make sense preclinically is that, as you know, ibrutinib and acalabrutinib—other BTK inhibitors—really help to mobilize cells out of the bone marrow into the peripheral blood. And, at least, we've seen in CLL cells that these cells that are floating around in the peripheral blood are more dependent upon BCL-2 for survival, and so it makes very good rational sense to help block that with venetoclax therapy. There are multiple studies ongoing, and there are multiple presentations at ASH [2019] about these combination therapies.

Another potential way is to block the B-cell receptor signaling pathway in an alternate fashion using both PI3K inhibitors and BTK inhibitors. Of course, there have been some issues previously with toxicity in combining these drugs, and so, I'm really waiting for more mature data to see if this is a good strategy.

One area that I'm personally very interested in is using the XPO-1 inhibitor called selinexor—not necessarily because of this mechanism of action, but because it also actually down-modulates BTK, and so it's really trying to do dual inhibition of BTK with combination therapy. And I'm presenting a poster abstract on this on Monday evening [ASH 2019].

Strategies to Combat BTK Inhibitor Resistance



PeerView.com

So, we've talked about using alternate mechanisms and combination therapy. One other area that I think is crucial is thinking about early intervention. I mentioned—at least in CLL

patients and Waldenström's patients—that we can see early emergence of these clones before we see clinical relapse.

Early Intervention

- Monitor for resistant clones
- Add another agent to ibrutinib prior to clinical relapse
  - Venetoclax (BCL-2 inhibitor): NCT03513562
  - VAY 736 (BAFF inhibitor): NCT03400176
  - Ublituximab (anti-CD20) + umbralisib (PI3K inhibitor): NCT04016805

PeerView.com

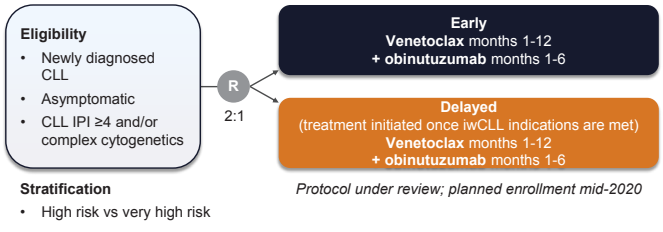
And so, really, the concept of early intervention would be monitoring for these resistant clones and adding another agent to ibrutinib prior to clinical relapse.

There are some interesting concepts here. I think Ohio State is leading a trial that we're participating in, where patients are monitored for BTK resistance and then, at a time of resistance and cells emerge, [we are] adding venetoclax therapy.

Another drug that I think is particularly interesting is a drug made by Novartis that's called VAY 736. This is a BAFF inhibitor. BAFF is another survival signal, so, basically, blocking multiple survival signals is the concept here.

There's another ongoing clinical trial that combines ibrutinib with ublituximab and umbralisib, which I think is very interesting as well.

Early Intervention: S1925 EVOLVE CLL[1]



1. Provided courtesy of Deborah M. Stephens, DO.

PeerView.com

Another thing that's personally very interesting to me is even earlier intervention. And so you've seen in other presentations that early intervention with targeted therapies seems less likely to lead to the development of resistant disease.

And so, along with the SWOG group, I'm leading a trial, which should be opening mid-next year that, that will be called the EVOLVE study. And this is really only for newly-diagnosed, asymptomatic CLL patients who have high-risk disease—so a CLL IPI of 4 or higher and/or complex cytogenetics.

So in order to have a CLL IPI score of 4 or higher—deletion 17p or TP53 gets you 4 points already. And so any newly diagnosed patient with the disease should be considered.

These patients will be randomized to either receive early venetoclax and obinutuzumab therapy versus delayed venetoclax and obinutuzumab therapy. And it really is a test of patients, because we are looking at overall survival in these patients, and that is really the only thing that I think is going to move the bar in this group.

Right now, the protocol is under review at CTEP, but we're planning and hopeful for enrollment to start in mid-2020, and it will be open to the cooperative group sites.

Case: Mr. Jones

- ❑ Mr. Jones (68-year-old male) with CLL previously treated with FCR and currently treated with ibrutinib; starting 3 years ago
- ❑ WBC count has trended up from 5 K/mcL to 15 K/mcL to 40 K/mcL
- ❑ Platelets have dropped from 135 K/mcL to 90 K/mcL
- ❑ He notes new axillary lymphadenopathy and increasing fatigue
- ❑ **How do I monitor for BTK inhibitor resistance?**
- ❑ **What is my treatment approach for patients with BTK inhibitor resistance?**

PeerView.com

So I really want to tie this back into our original case and talk about what I would do with a patient similar to this. So, again, Mr. Jones is a CLL patient. He's been on ibrutinib for 3 years—so a classic time period when you might expect ibrutinib resistance. White count is going up. Platelets are dropping. There are new lymph nodes and symptoms.

And so, how do I monitor for BTK inhibitor resistance? And what is my treatment approach for patients with resistance?

How I Monitor for BTK Inhibitor Resistance in CLL

When to Monitor for Resistance

- Not standard of care
- Evaluate at time of clinical progression
- If previously intolerant to BTKi, evaluate for resistance prior to recommendation of alternate BTKi
- Clinical trial: add venetoclax to ibrutinib; NCT03513562)

How to Monitor for Resistance

- No CLIA-approved test
- Next-generation sequencing panels available
- Whole exome sequencing

PeerView.com

So, how I monitor for ibrutinib resistance—and I will say that this is

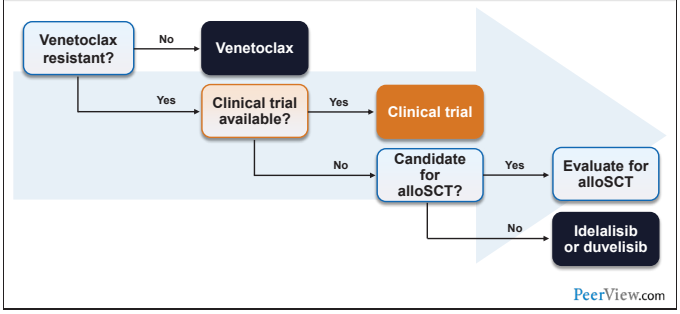
not currently the standard of care. There are no approved assays, but in my own practice, what I do at the time for a patient who is presenting like Mr. Jones and I suspect clinical progression, I will evaluate for BTK inhibitor resistance with sequencing. And this is in order to help to guide my next therapy.

I think that's especially important in patients who are previously intolerant to BTK inhibitor. For example, a patient was on ibrutinib for a certain amount of time, and they had to come off of therapy because they were resistant. I like to assess them at that time point because I want to know: Do they have a C481S mutation? Because those are not patients who I would then put on acalabrutinib, because the same resistance patterns are seen in both drugs.

Again, in my clinical practice, I'm participating in a clinical trial where we add venetoclax to ibrutinib in these resistant patients, and so that would be a time point that I would monitor for resistance.

So, how do you monitor for resistance, other than just clinical tests? There's no specific CLIA-approved test for this right now, but multiple next-generation sequencing panels are available and they specifically look at these mutations. Obviously, whole exome sequencing is available as well.

How I Treat BTK Inhibitor Resistance in CLL



PeerView.com

So, coming back to a patient like Mr. Jones, the first questions I would ask: Have they already been on venetoclax? And are they resistant to venetoclax? If they are not, I would use venetoclax. And, typically, how I use it is how it's designed to be used in the MURANO study, along with rituximab therapy.

If they have already progressed through venetoclax, I consider whether a clinical trial is available, and if there is, I will put them on that clinical trial, because I think this is a really important area to research.

If they are not, I will consider: Are they a candidate for an allogeneic stem cell transplant? And I will say that the majority of patients with CLL are not candidates for allogeneic stem cell transplant, secondary to age or comorbidities. But these are the patients who I might consider for it. And if not, I would consider using therapy with a PI3K inhibitor, such as idelalisib or duvelisib.

BTK Inhibitor Resistance: Summary

Key topics

- Scope of the issue
- Patterns of BTK inhibitor resistance
  - Primary versus secondary
- Specific mutations
  - Vary by B-cell malignancy
- Strategies to combat BTK inhibitor resistance
  - Use alternate mechanism, combination therapy, and early intervention
- How I manage BTK inhibitor resistance

PeerView.com

And that concludes my presentation, but I hope that you learned a little bit about the scope of the issue, the patterns of resistance, specific mutations that are important, and some strategies to combat this resistance.

Q&A and Concluding Remarks

Andre H. Goy, MD
Richard R. Furman, MD
Krish Patel, MD
Deborah M. Stephens, DO

Audience Question 1

Are there some CLL patients that benefit from FCR?

PeerView.com

Dr. Goy: So, without further ado, actually, we have some really great questions, and we're going to try to organize them by sequence—managing a patient with CLL, for example—and then I'm going to ask you the first question. I want each member of the panel to respond sort of briefly because we have a lot of questions. So, now, are there some patients that can see a benefit from FCR. Deborah?

Dr. Stephens: I do think that there is a small, select group of patients that can benefit from FCR, and those are the younger patients that have deletion 13q and mutated *IGHV*, but I really have a very long conversation with those patients about long-term toxicities and the potential of MDS. But some patients still really prefer to do a short course of therapy as well.

Dr. Goy: Richard?

Dr. Furman: So, I'm really not a fan of chemoimmunotherapy. And my concern, of course, is—even in these patients who have indolent disease—we really might be setting them up for a lot of complications long term. So I really do avoid FCR chemotherapy.

Dr. Goy: Krish?

Dr. Patel: And I would agree with what's been said before. I have those conversations like Dr. Stephens mentioned. It's very rare that any of my patients then choose to go that route. And I agree with Dr. Furman completely, that there are a lot of toxicities that we have to be wary of with that approach.

Audience Question 2

How do you choose a BTK inhibitor for a patient with CLL?
How do comorbidities and other factors inform your decision?

PeerView.com

Dr. Goy: So if we consider using a BTK, there are several questions. How do you pick a BTK? How do comorbidities and the context help you decide on which BTK you're going to use in managing the CLL? Richard?

Dr. Furman: So, that's a question that's often going to be determined by insurance and what's available. If we do discuss sort of a general situation where we have everything available, the data are early. But I do believe that acalabrutinib does demonstrate better tolerability. And that would be sort of my first choice overall.

One of the big drawbacks to acalabrutinib is the need to avoid proton pump inhibitors, which a large portion of patients are already on. And so for patients that are on PPIs, I typically then would just go straight to ibrutinib.

Dr. Goy: Deborah, a question on the mutation: If you actually have the ability to look at baseline to see if there are some existing mutations, would that help you to try to decide on which BTK you're going to use?

Dr. Stephens: I think it potentially could. However, as I mentioned, primary resistance to these BTK inhibitors, in CLL specifically, is very rare. We really don't see it. And so I don't think that it would really guide my therapy, and I don't routinely check it upfront.

Dr. Goy: Would a patient with a *p53* mutation or deletion at baseline—whether the result is worse than the non-mutated or deleted—have more benefit from looking at mutation at baseline?

Dr. Stephens: I still don't think that it makes sense to look at these mutations because almost every single patient is going to respond to the B-cell receptor inhibitors.

Dr. Furman: So I'd like to just add there two things to keep in mind. I mean, when we talk about next-generation sequencing panels, it's important to remember the sensitivity is only about 5 to 10%. So if you're thinking about this mutation really being in, really, one cell and growing out, it really is going to take a lot of very special testing to identify it.

The best data we have are data from Jan Berger, which really do suggest that the mutation probably does predate the initiation of the ibrutinib, and that a 3- to 5-year period is typically just the time for that cell to grow out.

So it's really, from our perspective, more important to try to identify what might be the risk factors for having that mutation develop. And overall, I really think the genomic instability is sort of the best way to make that prediction—so, complex karyotyping and 17p deletion.

Audience Question 3

How beneficial are reversible BTK inhibitors in the setting of resistance to irreversible BTK inhibitors?

PeerView.com

Dr. Goy: There are two or three members in our audience that actually had a question—somewhat interesting and provocative—on the fact that we now are looking at reversible inhibitors, where initially they didn't really work; and then when you look at patients who have the mutation that makes classic BTK become reversible because it can bind, how beneficial will these reversible inhibitors be in that setting?

Dr. Patel: So we don't yet know. Right? The data is very early. But these inhibitors all actually do have, probably, activity in wild-type *BTK*, as well as mutated *BTK*. And so, if they show, I think, clear activity, then the advantage of going back to a reversible inhibitor—recognizing what was just said—is that these subclones of C481 mutants exist predating our existing BTK therapy. You can imagine that these reversible inhibitors may be advantageous as a frontline therapy if they not only inhibit wild-type BTK, but they also have activity in mutants. And so it's too early, and we really don't have very high volumes of clinical data, but I think it's an exciting, sort of, potential for those agents.

Dr. Stephens: Yes, and I would agree, because we, at my center, have the ARQ-531 drug, and it's interesting because it's a different side effect profile than ibrutinib.

And other interesting features are that it doesn't inhibit CYP3A4, so that kind of eliminates some of the adverse effects or the drug interactions that you see with ibrutinib. And so I think we need to learn a lot more about these reversible inhibitors, but they certainly look very promising with initial data.

Audience Question 4

What is the role of anti-CD20 therapy in combination with BTK inhibitors?

PeerView.com

Dr. Goy: And the next question is that, if you use a BTK inhibitor, obviously, there's the question of adding an anti-CD20, rituximab or obinutuzumab, and we know the data was not showing a significant difference in the ibrutinib setting with rituximab. But Richard, what do you think of the role of anti-CD20 in combination with BTK inhibitors?

Dr. Furman: So, I really believe the BTK inhibitor's doing the heavy lifting, and so, until we really have data confirming an advantage to adding the anti-CD20, I do not.

There will be some data coming out shortly—which has been shown in abstract form—looking at ublituximab, which is a next-generation anti-CD20, and, which—because it might be a little bit more efficacious—may be able to sort of add something to ibrutinib—at least in a relapsed population. So until those data are actually out and published and confirmed, I do not use an anti-CD20.

Audience Question 5

Is it difficult to confirm secondary resistance in the CLL salvage setting, particularly for heavily pretreated patients?

PeerView.com

Dr. Goy: In your experience, is it difficult to confirm secondary resistance in the CLL salvage setting, particularly for heavily pretreated patients?

I think it's a little bit of an unusual question. I think the way I would look at it, is that, when patients progress on BTK inhibitors, what is the outcome?

Typically, in mantle cell lymphoma, the outcome is actually bad, because these patients have been very heavily pretreated, with a

median survival only of a few months. Can you comment, in the CLL setting, on what's the picture when patients become BTK resistant—heavily pretreated?

Dr. Stephens: Yes. And, I mean, I showed the data from the Ohio State Study, which showed that, in that group, the overall survival was about 22 months. And I think that this will change over time as we develop these new drugs. But it's pretty poor. Those are pretty bad numbers for CLL patients.

Audience Question 6

When would you use venetoclax to overcome BTK inhibitor resistance? Should venetoclax be used in the frontline or relapsed/refractory setting?

PeerView.com

Dr. Goy: To overcome resistance, when would you use venetoclax? In the primary line or in the relapsed/refractory setting?

Dr. Furman: So one of the things I think that's very interesting and worth looking at is the data from OSU and the 1102 data of the ibrutinib phase 2 trial, which really suggests that if you're genomically stable, you're going to do excellently with ibrutinib long term, as long as you don't have tolerability issues.

So for the vast majority of patients, if we just treat them with ibrutinib when they meet iwCLL indications for treatment, they're going to do just fine. It really is the 20% that are going to develop resistance, and they're the ones that we need to identify ahead of time.

I do think we're getting better at identifying those patients, and those are the patients who would benefit from an ibrutinib-venetoclax combination at diagnosis. Of course, if we never have sufficient faith in our ability to make that distinction between those who may or may not progress on ibrutinib, treating everyone with the combination would sort of resolve that issue as well.

So I sort of see that as the way the future is going. And, of course, now looking at fixed-duration therapy with ibrutinib plus venetoclax, it really could sort of change how we approach our patients.

Audience Question 7

What would you recommend as a next step for a patient with Richter's transformation who achieved a CR after R-CHOP therapy but presents with relapsed CLL?

PeerView.com

Dr. Goy: Dr. Furman, what do you recommend for a patient who is in CR after R-CHOP for Richter's, and now has relapsed CLL?

Dr. Furman: So actually, theoretically thinking I believe a lot of the secondary changes that led to the Richter's are probably due to ongoing changes in the DNA that might be actually prevented by BTK inhibitors.

So I actually will—if patients have evidence of CLL at the completion of their R-CHOP or at the first sign of it coming back—start BTK inhibitor therapy; really just sort of have an early prevention of, basically, a recurrence or a second Richter's transformation.

And that's something that we have seen quite a bit anecdotally, but in *NOTCH* patients, who will have one Richter's, and then have a second Richter's, and the two of them are probably distinct subclones. But it's just because the propensity for a *NOTCH1*-mutated patient to transform is going to be there even after you've fixed the first Richter's.

Audience Question 8

How do you treat a patient who has Richter's transformation and progresses on ibrutinib?

PeerView.com

Dr. Goy: Originally, particularly in a relapsed/refractory setting, there were some patients who relapsed. And you mentioned this, that some are biologically related, not necessarily ibrutinib-related. But, biologically speaking, even if they're not transformed morphologically speaking, how do you treat those patients? Obviously, we have venetoclax now, but how do you treat a true Richter's in that setting? How do you treat a true Richter's in a patient who progressed on ibrutinib?

Dr. Furman: How do I treat a Richter's patient who's progressed on ibrutinib? So, you know, Richter's patients are notoriously difficult to treat—and when I say Richter's, I really mean those that are actually clonally related. And I think that that's really the only important distinction we have right now.

I mean, right now, the treatment's going to be the initiation of chemoimmunotherapy. I usually use ibrutinib plus R-EPOCH. We've tried some venetoclax-R-EPOCH, but we've run into some issues with cytopenias.

We have a trial also looking at polatuzumab plus R-EPOCH—really trying to build on some of the other novel regimens. My goal is, of course, to dramatically improve upon R-EPOCH, which really isn't very efficacious in the vast majority of patients who develop Richter's.

Dr. Stephens: And I do think that any patients who develop Richter's should be enrolled on a clinical trial, if at all possible, because I think there is a lot to learn about these patients, and I don't think we really have a true standard of care at this point.

Audience Question 9

How do you manage issues with adherence to treatment with these novel agents?

PeerView.com

Dr. Goy: The last question for the panel for each of you: What about issues with compliance and adherence to treatment with these novel agents?

Dr. Patel: So the question's about compliance, and now we have agents that also have different dosing schedules: once a day versus twice a day. I think most patients who are on medications at all have at least some that are twice a day. So I'm not so worried about compliance and the different schedules.

I do think that compliance is an important issue early on, right? So, early on we know that a high percentage of BTK occupancy is really important for patients. Later on, I think you find that, if you really ask patients, the compliance is actually quite poor. So we did a study of oral TKI therapies, not just CLL and lymphoid malignancies, but across thousands of patients.

And what you find is that, probably about a year or more after you start therapy, less than half the patients are taking their medicines on a reliable schedule based on prescription refills. So that should be pretty reliable. If they're taking their medicines, they refill them.

And so I think compliance is really important. I think it's also probably quite different in terms of early versus late, because there is this different sink of BTK much later on. And while we used to be, I think, a bit more afraid of dose reductions, or patients who were less compliant later on, I mean, I think that's probably less of an issue. And we understand a bit more about that, biologically, now than we did. But regardless, I think the compliance is important, especially early on in therapy.

In other lymphoid diseases, like mantle cell, it's particularly important, because there, of course, as you know, we have a very high proportion of patients that still progress, and so those patients still have measurable disease. But in CLL, I think later on patients generally don't take their meds as much, but they seem to do as well.

Dr. Goy: Richard, compliance?

Dr. Furman: So, compliance is always going to be an issue that we're going to confront as physicians. I think that the most important thing that we can do is actually educate our patients and really try to work through with them on any of the adverse events that they might be experiencing. Obviously, if we could help them avoid the adverse events, then that's one way to improve compliance. And other than that, it's really just educating them on the dangers of not remaining compliant.

Dr. Goy: Deborah, final words on compliance?

Dr. Stephens: Yes. And I would absolutely echo what Dr. Furman said. I think that the biggest portion of your education should go in before the patient starts on ibrutinib, because you can see—we didn't really highlight it much—but the first 6 months are really that key period of time when patients are going to have side effects.

And if they don't know that these side effects will get better over time, they're more likely to discontinue the therapy. So I think educating patients, educating your nurses or your nurse practitioners, or whoever is on the frontline, so that whenever the patient calls in with these side effects, that they know how to manage these. And just make sure that the patient knows that what we're worried about is resistance. And so the more you're taking the medication, the more you're inhibiting the BTK, and the less likely that the resistant cells have time to grow.

And so I think really, heavy patient education and support—because I always plan to see my patients after I start them on ibrutinib or acalabrutinib, at least within a week or 2 after starting the drug, just so that we can talk about side effects and make sure that they are being compliant with the drug and there's no

issues, and to continually remind them when they come in about compliance.

Dr. Goy: I want to thank all my colleagues for all their perspectives on a very exciting field. I hope you enjoyed the program. Thank you.

Narrator: This activity has been jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

CME

How I Think, How I Treat: BTK Inhibitors as a Clinical Strategy in CLL, MCL, and Beyond—Therapeutic Selection, Sequencing, and Next Steps

PeerView

This CME activity is jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

This activity is supported by an independent educational grant from AstraZeneca.

MLI
Medical Learning Institute, Inc.