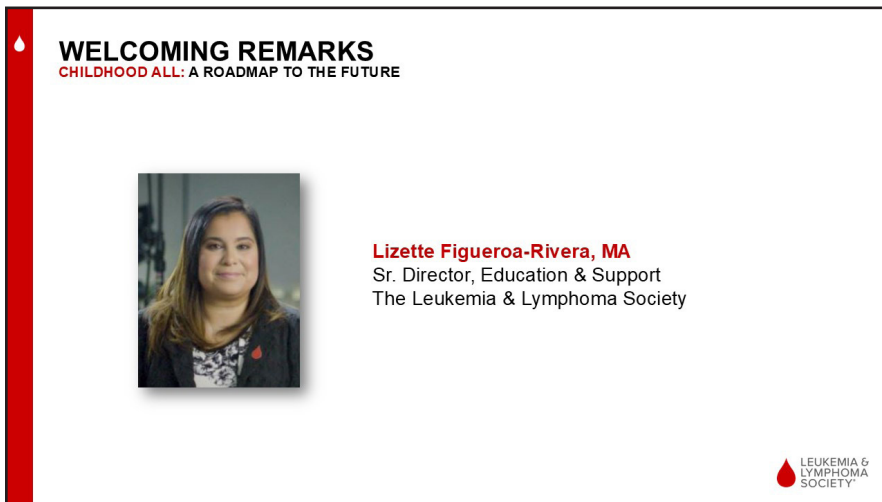


**Slide 1: THE FUTURE OF CML TREATMENT: WHAT'S NEXT?**

**Operator:**

Greetings. Welcome to the telephone and web education program, *The Future of CML Treatment: What's Next?*



**Slide 2: WELCOMING REMARKS**

It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you Lizette, please begin.

**Lizette Figueroa-Rivera:**

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I would like to welcome all of you. World CML Day is celebrated on September 22nd every year. The theme for World CML Day 2024 is Building Bridges, Leave No Patient Behind. This theme reflects the need for collaboration across borders, healthcare systems, and communities.

The goal of World CML Day aligns with LLS's goals when serving our patients and caregivers. The day's goals include, increasing awareness of CML (chronic myeloid leukemia), supporting patients and their families, celebrating the achievements in CML treatment, recognizing the challenges faced by those affected by CML, renewing efforts to find a cure, and encouraging collaboration between patients, caregivers, healthcare professionals, government, industry, and the wider community.

LLS funds life-saving blood cancer research around the world, provides free information and support services, and is the voice for all blood cancer patients seeking access to quality, affordable, and coordinated care. Let us be here for you and your family and please continue to tell us how we may assist you. Thank you for sharing your time with us.

Support for this program is provided by Novartis Pharmaceuticals Corporation. You may also view and print the slides from our website at [LLS.org/Programs](https://lls.org/Programs). Following the presentation, we will take questions from the audience.

It's now my pleasure to introduce Dr. Vivian Oehler, who is an Associate Professor in the Division of Translational Science Therapeutics at Fred Hutchinson Cancer Center and Division of Hematology and Oncology at the University of Washington in Seattle, Washington. Dr. Oehler, I'm privileged to turn the program over to you.



**FACULTY**  
THE FUTURE OF CML TREATMENT: **WHAT'S NEXT?**



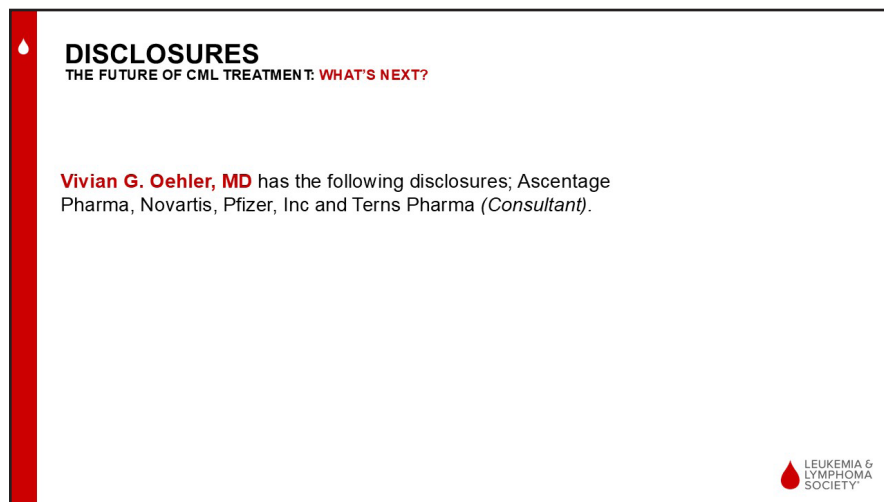
**Vivian G. Oehler, MD**  
Associate Professor, Division of Translational  
Science and Therapeutics  
Fred Hutchinson Cancer Center  
Division of Hematology/Oncology  
University of Washington  
Seattle, WA



### Slide 3: FACULTY


#### Dr. Vivian Oehler:

It's really a great pleasure to be here to talk to you about CML today.



**DISCLOSURES**  
THE FUTURE OF CML TREATMENT: **WHAT'S NEXT?**

**Vivian G. Oehler, MD** has the following disclosures; Ascentage  
Pharma, Novartis, Pfizer, Inc and Terns Pharma (*Consultant*).



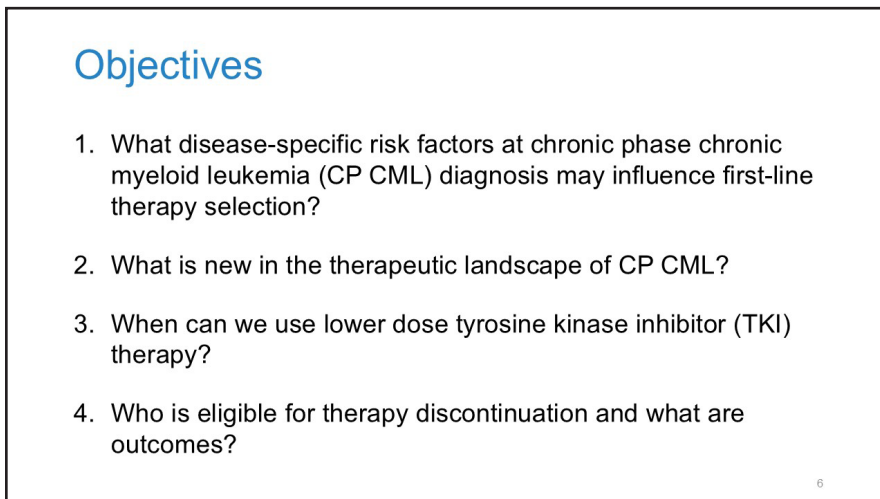
### Slide 4: DISCLOSURES

These are my disclosures.



## Slide 5: The Future of CP CML Treatment: What's Next?

I have a few objectives for my short talk today.



## Slide 6: Objectives

I think it's going to be important for you all to recognize what might be some disease-specific risk factors at chronic phase CML diagnosis that might influence how we select frontline therapy. I know really importantly for all of you is to discuss some of the new drugs in the therapeutic landscape for chronic phase CML, in particular asciminib (Scemblix®). I'm also going to discuss when lower dose TKI (tyrosine kinase inhibitor) therapy might be indicated because I think this is an important way for us to minimize adverse events and improve quality of life. Lastly, I'll talk about who's eligible to stop therapy and what might be the outcomes from this.

### Epidemiology

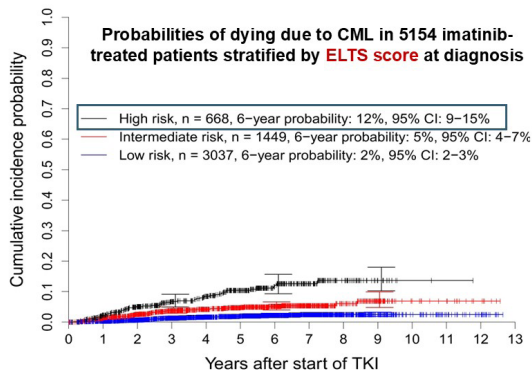
- ~8,930 people in the US will be diagnosed with CML in 2024
- ~15% of new cases of leukemia
- 5-year relative survival is 70.6% (2013-2019)
- Median age at diagnosis N. America and Europe: 65 to 74 years

NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). <https://seer.cancer.gov/statfacts/html/cmly.html>. Accessed January 18, 2024. Deminger et al. Blood (2000) 96 (10): 3343-3356

### Slide 7: Epidemiology

About 8,930 people in the United States were diagnosed with CML in 2024. In the United States, Canada, and North America, we see that the average age is typically between 65 to 74 years of age. I will say in other countries and on other continents, such as Africa, Asia, and South America, the age is actually younger – in the 40s.

### Clinical risk at diagnosis: EUTOS Long-Term Survival Score



Recommended by ELN

1. Better at identifying patients at risk of dying of CML
2. Classifies fewer patients as high-risk
3. Newer model recently proposed also includes genetic features

Variables: age, spleen size (cm) below the costal margin, peripheral blood blasts, and platelet count

Pfirschmann M, et al. Leukemia. 2020;34:2138-2149; Zhang XS, et al. Leukemia. 36, 482-491 (2022). Zhang X et al. Blood. 2024. published online 29 July 2024. <https://doi.org/10.1182/blood.2024024761>

### Slide 8: Clinical risk at diagnosis: EUTOS Long-Term Survival Score

At diagnosis, you probably sat down with your clinical team and talked about some risk factors and how to stratify you and what might be the best therapy. For many years, we have in the field of CML used clinical risk scores, such as Hasford and Sokal Score to identify that rare group of patients who might be more likely to have poor outcomes.

I will say, in 2024, these clinical risk scores are still meaningful, but we generally recommend now the use of something called the EUTOs (European Treatment and Outcome Study) Long-Term Survival Score, which is recommended by the European LeukemiaNet, also endorsed by the NCCN (National Comprehensive Cancer Network). It's a clinical risk factor that we calculate at diagnosis. The variables are actually similar to what the Sokal Score was that we used for many years, includes your age, includes how big your spleen is below your rib cage, how high those peripheral blasts are, and what your platelet count might be.

The reason we like this score a little bit better is it's better at identifying that small group of patients who may be at



risk for dying from CML. It also classifies fewer patients at high risk. Hot off the presses in a publication just out in Blood last month, there's a newer model that's starting to take into account features that I think are really important, such as genetic and molecular features.

### What defines higher risk at CP CML at diagnosis: molecular features

Prognostic	Likely Not Prognostic
<ul style="list-style-type: none"> <li>Higher clinical risk scores are associated with poorer OS</li> <li>Additional clonal chromosomal abnormalities (~3-7% of patients)</li> <li>p190-associated transcript e1a2</li> <li>p210-associated transcript e13a2 vs e14a2?                             <ul style="list-style-type: none"> <li>e13a2 lower rates of deep molecular response on imatinib and nilotinib</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Deletion derivative 9 chromosome</li> <li>Most variant translocations (e.g., 3-way)</li> <li>Other transcript variants?                             <ul style="list-style-type: none"> <li>No dedicated QPCR monitoring assays</li> </ul> </li> </ul>

Jain P, et al. *Blood* 2016;127:1269-1275; Genthon A, et al. *Oncotarget* 2020;11(26):2560-2570; Quintas-Cardama A, et al. *Cancer* 2011;117:5085-5093; Castagnetti F, et al. *J Clin Oncol* 2010; 28(16):2748-Testoni N, et al. *Blood* 2011;117:6793-6800; Verma D, et al. *Blood* 2009;114:2232-2235; Laurent E, et al. *Cancer Res* 2001;61:2343-2355.

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**Slide 9: What defines higher risk at CP CML at diagnosis: molecular features**

What are the features that might define a higher-risk chronic phase CML diagnosis? Well, we just talked about risk scores being important and these are still associated with overall survival. There are a small group of patients, a diagnosis who may have additional genetic abnormalities, pretty rare, between 3% to 7% of patients. This would be above and beyond the Philadelphia chromosome, which is the hallmark of CML patients who have the transcript that happens to be called p190, which we see more often in acute lymphoblastic leukemia (ALL). This is less than 2% of patients, can have poorer outcomes. What's not prognostic at this point is likely the deletion of the derivative chromosome 9.

Some patients may have a variant translocation where you can see 3-way translocations and others. I think, retrospectively, most of our data tell us that these patients share the same outcomes as patients with our garden variety chronic phase CML rearrangement.

Some of you may fall into that very rare group of having other transcript variants. We do think that our drugs are effective in patients who have these, although we don't have that super sensitive PCR (polymerase chain reaction) assay to monitor response. In these situations, we use something called fluorescence *in situ* hybridization or FISH for BCR-ABL to monitor.

### 2024 Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1 <sup>st</sup> generation	•		
Dasatinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Nilotinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Bosutinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Ponatinib	ATP-competitive 3 <sup>rd</sup> generation		•* (T315)	•
Asciminib	ABL Myristoyl Pocket STAMP inhibitor		•† (T315)	•
<del>Ompoxine</del>	<del>Protein synthesis inhibitor</del>	<del>•</del>	<del>•</del>	<del>•</del>

\*Approved in US for a patients after ≥ 2 TKIs or for patients with T315 CP-CML in any line. †Only available in the US. Hochhaus A, et al. *Leukemia* 2020, 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

### Slide 10: 2024 Treatment Options in CP-CML

What are your treatment options in 2024? Well, frontline, we've got imatinib (Gleevec®), our first-generation TKI. We have our second-generation TKIs, dasatinib (SPRYCEL®), nilotinib (Tasigna®), and bosutinib (Bosulif®). Our potent third-generation therapeutics, the TKI ponatinib (Iclusig®) or the myristoyl pocket inhibitor or asciminib are approved for T315 mutated CML and are also used in chronic phase CML in the third-line and beyond.

### Future Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1 <sup>st</sup> generation	•		
Dasatinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Nilotinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Bosutinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Ponatinib	ATP-competitive 3 <sup>rd</sup> generation		•* (T315)	•
Asciminib	ABL Myristoyl Pocket STAMP inhibitor	•	•† (T315)	•
<del>Ompoxine</del>	<del>Protein synthesis inhibitor</del>	<del>•</del>	<del>•</del>	<del>•</del>

\*Approved in US for a patients after ≥ 2 TKIs or for patients with T315 CP-CML in any line. †Only available in the US. Hochhaus A, et al. *Leukemia* 2020, 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

### Slide 11: Future Treatment Options in CP-CML

The future is changing in front of us and so I put this slide in today because I'm going to share some of this data with you a little bit later in this talk. We may be seeing asciminib moving to earlier lines of therapy and I'm going to share some of that data with you today.

### CML Treatment Goals: Talk to your team!

1. Life expectancy not impacted by CML	→	Recognize higher risk CML at diagnosis: risk score, molecular features Are treatment goals associated with normal life expectancy achieved?
2. Limit impact of TKI therapy on comorbidity outcomes	→	Medical history matters: history of cardiovascular or pulmonary disease?
3. Quality of life and minimizing adverse events	→	Medical history matters: history of IBS, pancreatitis, other? Emerging side effects on therapy – is dose reduction an option?
4. Treatment-free remission	→	What responses are needed for how long before stopping?
5. Limiting costs	→	Managing out of pocket costs: Generics (imatinib, dasatinib) vs other 2G and 3G therapies?
6. Family planning	→	2G and 3G therapies for patients who can give birth?

**Slide 12: CML Treatment Goals: Talk to your team!**

I think it's really important at the time of diagnosis and as you're taking therapy or switching therapies that you are sure to talk to your team. I think these are some of the important points that I like to talk about with my patients. One, I think it's really important that we have life expectancy that's not impacted by CML. That really means that we recognize who might be that rare, higher-risk patient at diagnosis, whether by risk score or molecular features.

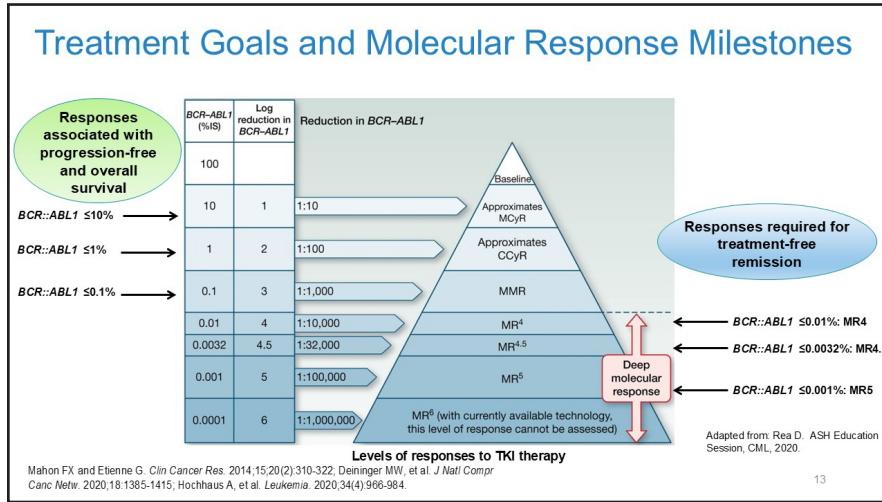
Are you achieving the treatment goals associated with normal life expectancy? It's really important to limit the impact of your therapy on other medical issues that you might have. It's really important for us, as your team, to know if you have a history of cardiovascular or pulmonary disease. That may influence how we select your therapy.

We also know really importantly, that quality of life and minimizing adverse events over time on treatment are really important. For example, if you have a history of irritable bowel syndrome or pancreatitis, this is important for us to know and can influence how we select therapy. Additionally, please share with us any emerging side effects that you have on therapy because we can be aggressive about managing them. For some patients, dose reduction is definitely an option that won't compromise outcomes.

I think an important topic for everyone is, "Am I eligible for treatment for remission? How soon can that happen? How long do I have to be on therapy? How successful are we at that?" We're going to talk about that a little bit today.

I also think managing out-of-pocket costs is really important. We have some really exciting drugs. The allosteric inhibitor and myristoyl pocket inhibitor, asciminib, but we also have drugs that are going generic. Dasatinib, for example, is going generic this month and so the cost of these drugs, out-of-pocket costs for you could be lower with these drugs. How do we balance this and ensure the best outcomes that we can?

I think for my younger patients who can give birth, family planning is really important. I may choose to use potent therapeutics, such as second-generation or third-generation drugs, to get to deep responses so that we can proceed with family planning.



**Slide 13: Treatment Goals and Molecular Response Milestones**

What are our treatment goals and what do they mean? What I show here on the left-hand of the slide, are the important treatment goals that are associated with a normal lifespan. Generally, we've learned over the last 25 years that a BCR-ABL of less than 1% is generally associated with the long-term survival benefit.

The deeper you go, the less likely you are to lose response. For many of us, we're aiming here for a major molecular response, which is a BCR-ABL of less than 0.1%. On the other side of the slide, on the right-hand side, you can see the deeper responses. It's important to note that these responses are not associated with improved survival but are absolutely the milestones you need to reach durably in order to be eligible for TKI discontinuation.

These include BCR-ABL of less than 0.01%, which you're going to hear me call MR4, and BCR-ABL of less than 0.003% or MR4.5. I will point out that's probably how sensitive the standard qPCR (quantitative polymerase chain reaction) assay is. Results below that are typically undetectable.

### NCCN Guidelines Version 2.2024: Early Treatment Response Milestones

Assess for mutations in ABL

BCR::ABL1	3 months	6 months	12 months
>10%	NCCN Possible TKI Resistance	NCCN TKI-resistant	NCCN TKI-resistant
>1% - 10%	NCCN TKI sensitive	NCCN TKI sensitive	NCCN Possible TKI Resistance
>0.1 - 1%	NCCN TKI sensitive	NCCN TKI sensitive	NCCN TKI sensitive*
≤ 0.1%	NCCN TKI sensitive	NCCN TKI sensitive	NCCN TKI sensitive

COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	<ul style="list-style-type: none"> <li>Evaluate patient adherence and drug interactions</li> <li>Consider BCR::ABL1 kinase domain mutational analysis</li> <li>Consider bone marrow cytogenetic analysis to assess for additional chromosomal abnormalities</li> </ul>	Switch to alternate TKI (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	<ul style="list-style-type: none"> <li>Evaluate patient adherence and drug interactions</li> <li>Consider BCR::ABL1 kinase domain mutational analysis</li> <li>Consider bone marrow cytogenetic analysis to assess for MCyR at 3 months or CCyR at 12 months</li> </ul>	Switch to alternate TKI or Continue same TKI and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	<ul style="list-style-type: none"> <li>Evaluate patient adherence and drug interactions</li> <li>If treatment goal is long-term survival: ≤1% optimal</li> <li>If treatment goal is treatment-free remission: ≤0.1% optimal</li> </ul>	<ul style="list-style-type: none"> <li>If optimal: continue same TKI</li> <li>If not optimal: shared decision-making with patient</li> </ul>
GREEN	TKI-sensitive disease	<ul style="list-style-type: none"> <li>Monitor response</li> <li>Evaluate patient adherence and drug interactions</li> </ul>	Continue same TKI

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024. 14

**Slide 14: NCCN Guidelines Version 2.2024: Early Treatment Response Milestones**

The NCCN as well as the European LeukemiaNet provide some guidance to your team on what kind of responses we're looking for early in your treatment course. We like to see a BCR-ABL of less than 10% at 3 months, less than 1% by 6 months, less than 0.1% by 12 months. These basically are the optimal responses.

I will say, achieving a BCR-ABL of less than 1% by 12 months is very reasonable. Not achieving 0.1% at 12 months is okay. You can see we now highlight, this is light green in the NCCN guidelines, and I'll just point over to it because we know that less than 1% is associated with long-term survival benefit. On the other hand, if you're someone who really would like to get to the deeper responses we call optimal is less than 0.1%.

What's shown here in red or what we define as resistance. If your BCR-ABL is greater than 10% at 6 months or greater than 1% at 12 months, we definitely want to pay attention. I'm going to make a recommendation to look for mutations in ABL, which are a common mechanism of acquired resistance.

### First-Line Therapy: NCCN 2.2024

Risk stratify: Sokal, Hasford, and EUTOS long-term survival (ELTS) scores

Chronic phase CML

→

**Low-risk score**

Imatinib or generic imatinib 400 mg QD or  
Bosutinib 400 mg QD or  
Dasatinib 100 mg QD or  
Nilotinib 300 mg BID

**Intermediate or high-risk score**

Preferred regimens \*  
Bosutinib 400 mg QD or  
Dasatinib 100 mg QD or  
Nilotinib 300 mg BID

Other recommended regimen \*\*  
Imatinib or generic imatinib 400 mg QD

\*\*Based on follow-up data from the BFORE, DASISION, and ENESTnd trials, 2G TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate or high-risk score. 2G TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefits/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.

\* Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease

Clinical trial, if available can be considered for all patients  
NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024. 15

**Slide 15: First-Line Therapy: NCCN 2.2024**

Frontline, we'll often select therapy based on your risk score. For a low-risk patient, I think imatinib, or a second-generation TKI, are always reasonable choices. For somebody who has a high-risk CML, I tend to prefer a second-generation TKI. This is also highlighted in the NCCN.

### First-Line 2<sup>nd</sup> Generation (2G) TKI: fewer progressions to AP or BP

ENESTnd 5-year results	Nilotinib 300 mg twice daily (n=282)	Nilotinib 400 mg twice daily (n=281)	Imatinib 400 mg once daily (n=283)
Progression to AP/BP on study, n	10	6	21
Estimated 5-year freedom from progression to AP/BP on study, % (95% CI)	96.3 (94.1-98.6)	97.8 (96.0-99.5)	92.1 (88.8-95.3)
HR vs imatinib (95% CI)	0.4636 (0.2183-0.9845)	0.2753 (0.1111-0.6821)	
P vs imatinib	0.0403	0.0028	

On study: on treatment or in follow-up after discontinuation of study treatment

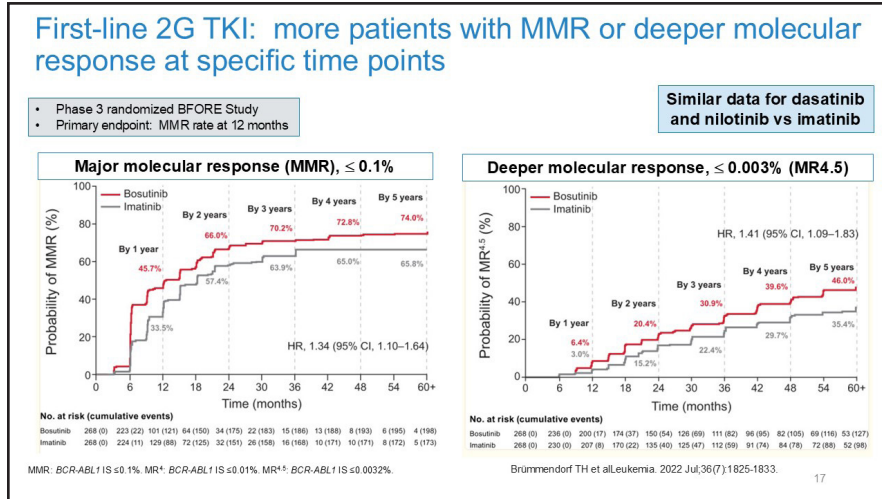
Hochhaus A, et al. Leukemia. 2016;30:1044-1054. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024. 16

**Slide 16: First-Line 2nd Generation (2G) TKI: fewer progressions to AP or BP**

You may say, "What's the data that might support that? If I have a higher high-risk Sokal score or ELTS (EUTOS long-term survival) score, for example, that may be a second-gen TKI is better." I'll say probably the strongest data that might support choosing a second-generation drug comes from the ENESTnd Study. This was the study that resulted in



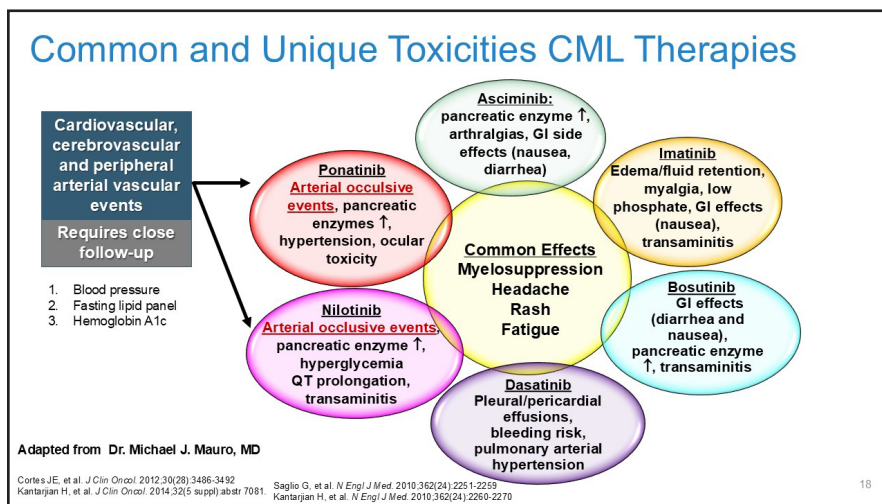
nilotinib becoming FDA approved frontline and patients were randomized to imatinib and 2 different doses of nilotinib. If you look very specifically at the number of patients, albeit low numbers of patients who had disease progression to accelerated phase or blast phase, you can see that the numbers were slightly higher in the imatinib-treated patients versus the nilotinib-treated patients.



Slide 17: First-line 2G TKI: more patients with MMR or deeper molecular response at specific time points

Additionally, if you start on a second-generation drug frontline, you're more likely to achieve a major molecular response or a deeper molecular response earlier in the treatment course and bispecific time points. For these data, I show you results of the BFORE Study, which randomized patients to imatinib versus bosutinib frontline.

You can see in red by 5 years on the left side that 74% of patients on bosutinib achieved MMR versus 65.8% who received imatinib. Then if we're focusing on the deeper molecular responses, again, more bosutinib-treated patients at 46% versus 35% of imatinib-treated patients by 5 years had achieved that particular response milestone.



Slide 18: Common and Unique Toxicities CML Therapies

We know that all of our therapies have common and unique toxicities. Some of the common side effects that we see on our therapy are something that we call myelosuppression. We see this early in the treatment course, which is lower platelets, some anemia, possibly low white blood cell count. Headaches, rash, and fatigue are also common across all of our therapies.



For imatinib, we see a lot more fluid retention, which we call edema, whether it's around your eyes or around your ankles. Muscle aches and pains are more common on imatinib. GI (gastrointestinal) side effects, in particular, nausea are common with imatinib and that's why it's really important to take that imatinib with food. Liver function test abnormalities can also be seen.

For bosutinib, up to 80% of patients can have GI side effects, more often diarrhea than nausea. This has led to recommendations that we start most patients, if we can, on a lower dose of bosutinib of 200 to 300 milligrams because that can minimize some of these side effects. We can also see abnormalities in pancreatic enzymes and liver function tests.

Dasatinib is known to be associated with a risk for pleural effusion, which is when you accumulate fluid between the lung and the lung lining. In our frontline study of imatinib versus dasatinib, 28% of patients who received dasatinib versus 0.8% of patients received imatinib had pleural effusion. We know that it's related to how old you are and how high your dasatinib does is. The higher your dose and the older you are, the more likely you're going to get a pleural effusion. Rarely do we see fluid around the heart sac (pericardial effusion) or pulmonary arterial hypertension. There is a mild aspirin-like effect associated with dasatinib as well.

One of the important things that we've learned about nilotinib over the years is that it is associated with an increased risk for heart attack, stroke, and peripheral vascular disease. Looking back across studies, up to 20% of patients may have had an event on this medication. We can also see elevations in pancreatic enzymes and liver function test abnormalities.

Our very potent third-generation TKI, ponatinib, is also associated with an increase in what we term arterial occlusive events. Again, this is heart attack, stroke and peripheral vascular disease. Also, if you start ponatinib, your blood pressure is very likely to increase within the first few weeks of starting this drug. It's really important to monitor blood pressure after you start this drug. I believe if you control the blood pressure, this can really help minimize the risks associated with this drug. There are also some toxicities associated. You can see for ponatinib and nilotinib, it's really important to follow blood pressure. We also will follow blood cholesterol levels, as well as glucose.

**2<sup>nd</sup> (and 3<sup>rd</sup>) Generation Therapy Selection Based on Co-Morbidities and Risks**

History with prior TKI or co-morbidity	Preferred	Less preferred
Diabetes	Dasatinib, Bosutinib, <i>Asciminib</i>	Nilotinib
Pulmonary disease/PAH	Bosutinib, Nilotinib, <i>Asciminib</i>	Dasatinib
GI Issues	Nilotinib, Dasatinib, <i>Asciminib</i>	Bosutinib
Cardiovascular	Bosutinib	Nilotinib, (?? <i>Asciminib</i> ??)
Peripheral arterial	Bosutinib ( <i>Dasatinib</i> ?)	Nilotinib
Liver	Dasatinib	Bosutinib
Renal	Nilotinib, Dasatinib, <i>Asciminib</i>	Bosutinib

Modified from Cortes J. Blood. 2020 Nov 26;136(22):2507-2512. 19

**Slide 19: 2nd (and 3rd) Generation Therapy Selection Based on Co-Morbidities and Risks**

We do have some recommendations and I borrowed this from Dr. Cortes in a paper that he wrote a few years ago. If we're selecting second- and third-generation drugs, you know what might be preferred or less preferred in specific scenarios. Sometimes we have to choose a drug because that's the best drug to treat your CML. When we have a choice, we can absolutely use these things to guide us.

We know that nilotinib can be associated with more difficult to control diabetes and consequently would be less preferred. For patients who have pulmonary disease, lung disease, dasatinib is less preferred. If you're somebody

who struggles with GI issues, diarrhea, nausea, probably bosutinib is not going to be an optimal choice for you.

For cardiovascular disease, nilotinib is not a good choice. For asciminib, I put a lot of question marks there because we just need longer-term follow-up. I don't think it has a strong signal, but we do need some time for that data to mature further. For peripheral arterial disease, nilotinib is also not a good choice and if you're somebody who has liver or renal dysfunction, bosutinib might be less optimal.

### What data support consideration for lower dose TKI use upfront?

TKI	Study	Patient Characteristics	TKI Dose	Study Findings
Dasatinib	Single center Pilot Study <sup>249</sup>	81 evaluable patients (majority of patients had low-risk (n = 55; 66%) or intermediate-risk (n = 21; 25%) disease by Sokol score Minimum follow up: 12 months	50 mg/day	The cumulative rates for MMR, MR4, and MR4.5 at 12 months were achieved in 81%, 55%, and 49% of patients respectively.
	DAVLEC (Phase II study) <sup>252</sup>	52 patients; aged >70 years; Median follow-up of 366 days	20 mg/day	MMR at 12 months was achieved in 60% of patients.

1. Lower dose dasatinib first-line in low/ intermediate risk or older CP CML patients
2. Retrospective data of dose modifications with durable response in the setting of intolerance

NCCN Guidelines. Chronic Myeloid Leukemia. V2.2024.

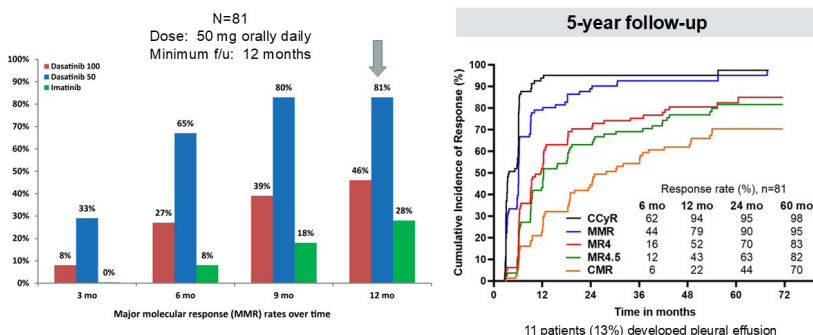
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### Slide 20: What data support consideration for lower dose TKI use upfront?

I think dosing of TKIs is a really important topic, and it's probably one that we haven't really shared as much with the community as we can. I will say that the NCCN very recently has incorporated some guidance on when it might be appropriate to adjust dose. I think this is important because lower-dose TKI can be associated with fewer adverse events and could be associated with better quality of life.

We have data on when we can start lower-dose therapy for dasatinib, for example, which I'll share shortly. We also have data which I'll share with you on when it's appropriate to reduce dose and still maintain that response and stay on track for TKI discontinuation.

### Mitigating treatment related side effects: starting lower dose dasatinib first-line



Naqvi K et al. Cancer. 2020 Jan 1;126(1):67-75.  
Gener-Ricos. Clin Lymphoma Myeloma Leuk. 2023 May 23:S2152-2650(23)00167-2.

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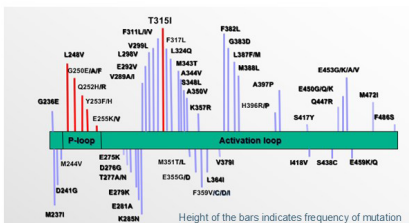
### Slide 21: Mitigating treatment related side effects: starting lower dose dasatinib first-line

Probably, the strongest data that supports starting a lower dose of therapy is for dasatinib frontline. I'm going to say that these were patients who had lower intermediate-risk disease, not high-risk disease for the most part. This data now has more than 5 years of follow-up. The investigators at MD Anderson enrolled 81 patients who all started on dasatinib, and then they compared their outcomes at specific time points to people who got imatinib or people who got full-dose dasatinib historically. As you can see here with my big gray arrow, the patients who got 50 milligrams actually did very well. Major molecular response rate at 12 months was 81% and certainly was not worse than the red and the green bars there. If anything, a little bit better, although it's hard to say that directly. If we look with longer-term follow-up here at right, you can see by 5 years patients who had received 50 milligrams of dasatinib rather than 100, 95% had MMR and more than 80% had deeper molecular responses.

Also, and I think this is important, fewer patients develop pleural effusion. Instead of that 28% at 5 years that we saw in the DASISION Study of 100 milligrams of dasatinib, it was only 13% in this study.

### BCR::ABL1 kinase domain mutations

THERAPY	CONTRAINDICATED MUTATIONS <sup>2</sup>
Asciminib	A337T, P465S, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L <sup>5a</sup>
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/I/C/I
Ponatinib, Omacetaxine, bb or allogeneic HCT (CML-6)	None <sup>6c</sup>



1. Acquired resistance
2. Primary resistance

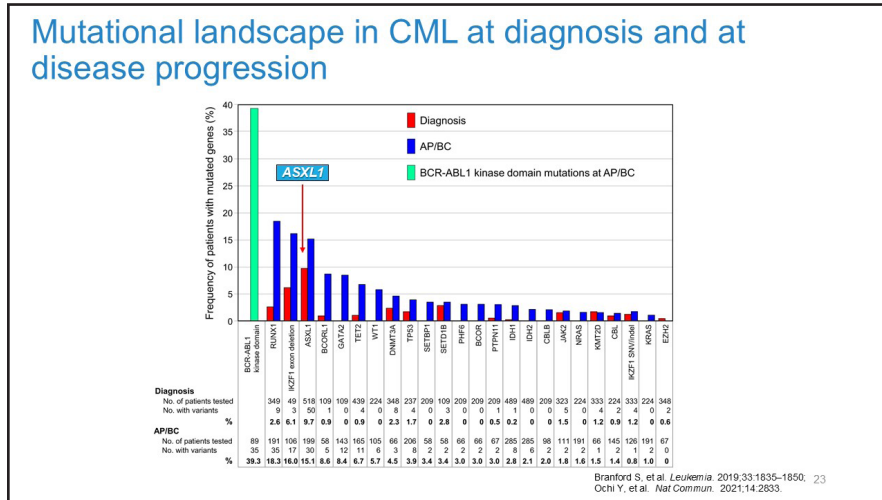
- <sup>5a</sup>Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.
- <sup>6c</sup>There are 6 compound mutations (defined as harboring ≥2 mutations in the same BCR::ABL1 allele that can cause resistance to ponatinib, but these are uncommon after 2<sup>nd</sup> generation TKI use

NCCN Guidelines. Chronic Myeloid Leukemia. V1.2025. 22

Slide 22: BCR:ABL1 kinase domain mutations

Moving on to what if you are not responding and what to do next? There are 2 types of resistance that we talk about. One is acquired resistance. You responded to therapy and then unexpectedly lost response, even though you're taking your pills. The other one is primary resistance, where you're just not meeting the milestones that we talked about a little bit earlier.

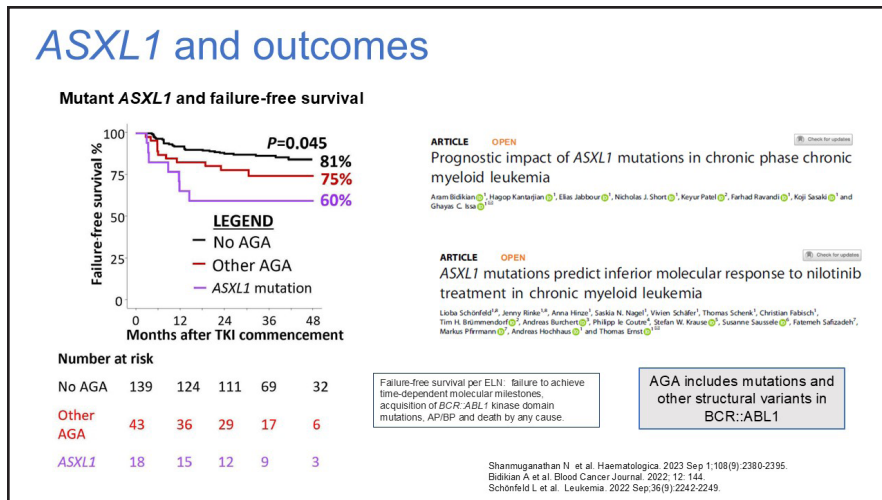
I will say for acquired resistance that a very common mechanism of resistance is acquiring mutations in the BCR-ABL kinase domain that prevent the drug from binding and acting. The NCCN and others provide helpful advice to providers on what drugs to avoid in the setting of specific mutations. I will say it's good to know that the T315I mutation is one that only the potent third-generation drugs ponatinib or asciminib can treat.



Slide 23: Mutational landscape in CML at diagnosis and at disease progression

Some of you may be wondering about, “Well, I’ve heard about other mutations and other blood cancers that are associated with prognosis. Is this really true for CML as well?” I will say that we have been acquiring data over a number of years, and I’m showing here a survey from Dr. Branford and colleagues, a few years old but still very true, where we found that other mutations were pretty rare in chronic phase CML.

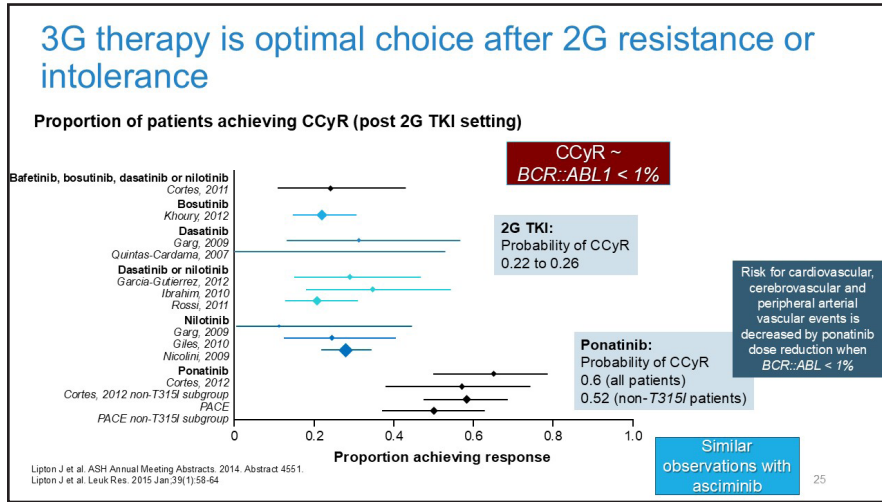
If we did find something, it was most often what we call an *ASXL1* mutation. On the other hand, if disease is transforming or progressing to accelerated phase or blast phase, we would be more likely to see additional mutations. Some of these could be ones important in disease-like *RUNX1* (runt-related transcription factor 1), for example.



Slide 24: *ASXL1* and outcomes

There have been a couple of papers in the last few years that are emerging that support that having one of these mutations at diagnosis may mean that you are less likely to respond to your TKI therapy. I’m going to say that I do have patients, I’ve been looking at these mutations across my panel for many years at this point.

I do have patients who have *ASXL1* mutations who have gone on to have excellent responses. On the other hand, there are patients who have this mutation, perhaps some other features who are less likely to respond. I do recommend we pay close attention to this, but it isn’t necessarily going to mean you won’t respond to your therapy.



**Slide 25: 3G therapy is optimal choice after 2G resistance or intolerance**

What happens if you’ve had second-generation drug like dasatinib, nilotinib, or bosutinib, and you’re either intolerant or resistant of this drug? What’s the best next step? What I show here is a retrospective review that’s now actually almost 10 years old, where the authors looked backwards to see whether it was better to get another second-generation drug after failing a second-generation drug or to go onto the potent third-generation drug, ponatinib.

What we found in this retrospective review is that you are more likely to have a BCR-ABL of less than 1%. Again, an important treatment milestone, if you switch to ponatinib, the potent third-generation drug, rather than switching to another second-generation drug. That was 60% of patients achieving it versus only about 25% on the second-generation drug. We also have similar observations for asciminib-treated patients.

### Asciminib, a BCR::ABL1 inhibitor with a distinct allosteric mechanism of action

1. Very high selectivity with narrow target profile
2. Active against many BCR::ABL1 mutations that confer resistance to TKIs, including T315I
3. FDA approved 2021 ≥ 3-line in intolerant and resistant CP CML based on ASCEMBL study

Asciminib has been designated as the first-in-class STAMP (Specifically Targeting the ABL1 Myristoyl Pocket) inhibitor

Hughes TP, et al. ASH Annual Meeting Abstracts. 2016, abstract 625. Hughes TP et al. N Engl J Med 2019;381:2315-26

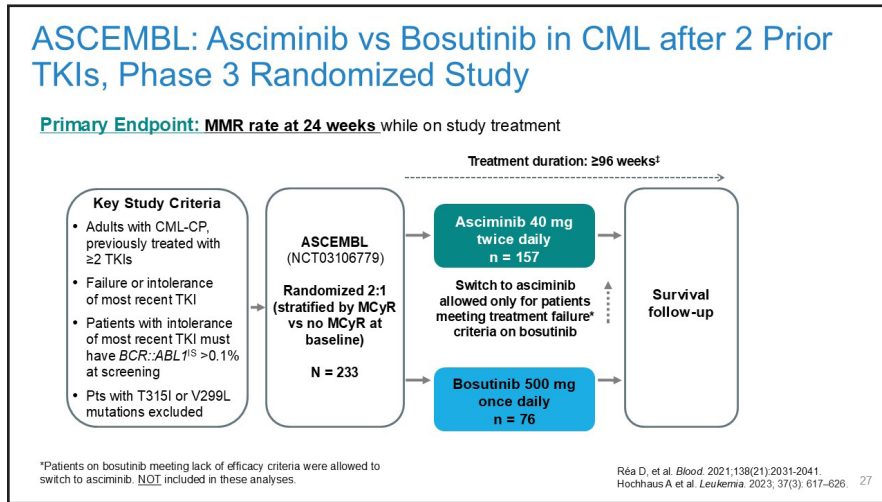
**Slide 26: Asciminib, a BCR:ABL1 inhibitor with a distinct allosteric mechanism of action**

Now, I’m going to start talking a little bit about asciminib because I know many of you have questions about this new drug and how we’re going to use this in our practice. Asciminib is actually a different drug design versus the TKIs that I’ve been talking about so far. Here you can see ponatinib in purple, as well as all the other TKIs, binds to what we call the ATP site on BCR-ABL.

It turns out in the human body, there are a lot of kinases, not just this ABL kinase. Although they’re all unique and different, they do share some features in common. It may be that some of the side effects that we see on TKI therapy



are driven by on-target, but off-cancer binding to these. Several pharmaceutical companies, including Novartis, went back to the drawing board, and they found another site on the BCR-ABL protein that was just more unique. This was the myristoyl pocket. They developed inhibitors of this pocket, and the very first one now FDA-approved is asciminib. This drug has a very high selectivity and a very narrow target profile, and this is why we think that it has fewer side effects. It's also very effective at treating a number of different mutations, including the T315I. This drug has been FDA-approved since 2021 in the third-line and beyond and for T315I-mutated CML.



**Slide 27: ASCEMBL: Asciminib vs Bosutinib in CML after 2 Prior TKIs, Phase 3 Randomized Study**

The reason it was approved by the FDA was based on the data from the Phase III ASCEMBL Study. This was a study of heavily pretreated patients in the third-line and beyond with chronic phase CML.

Patients were randomized 2:1 to either asciminib at 40 milligrams twice daily versus bosutinib at 500 milligrams daily. Essentially the primary endpoint, which is one that we use a lot in CML, is major molecular response by a specific time point. This happened to be 24 weeks.

### Demographics and Baseline Characteristics

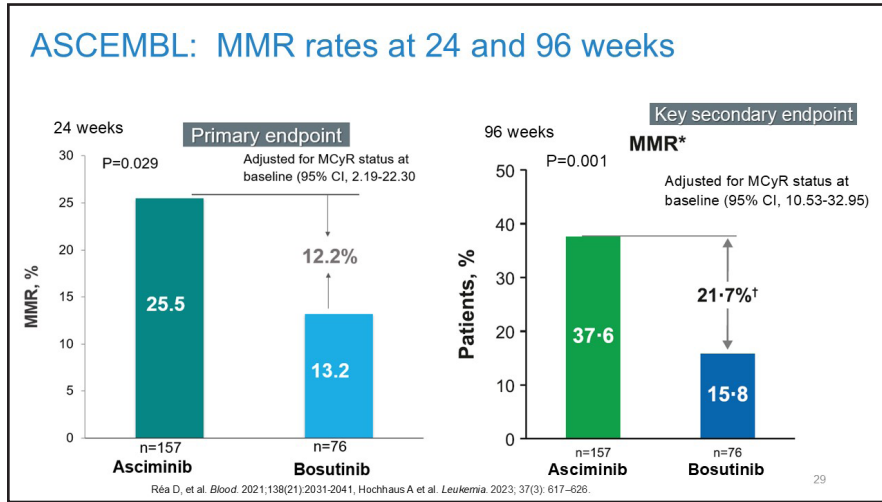
Variable	Asciminib 40 mg Twice Daily (n=157)	Bosutinib 500 mg Once Daily (n=76)	All Patients (N=233)
Median age, years (range)	52.0 (24-83)	52.0 (19-77)	52.0 (19-83)
Female sex, n (%)	75 (47.8)	45 (59.2)	120 (51.5)
MCyR, n (%)	46 (29.3)	22 (28.9)	68 (29.3)
Reason for discontinuation of last TKI, n (%)			
Lack of efficacy	95 (60.5)	54 (71.1)	149 (63.9)
Lack of tolerability	59 (37.6)	22 (28.9)	81 (34.8)
Other*	3 (1.9)	0	3 (1.3)
Number of lines of prior TKI therapy, n (%)			
2	82 (52.2)	30 (39.5)	112 (48.1)
$\geq 3$	75 (47.8)	46 (60.5)	121 (51.9)
BCR::ABL <sup>IS</sup> at baseline, n (%)			
$> 0.1\%$ to $\leq 1\%$ <sup>†</sup>	15 (9.6)	4 (5.3)	NA
$> 1\%$ to $\leq 10\%$	45 (28.7)	23 (30.3)	NA
$> 10\%$	97 (61.8)	49 (64.5)	NA
Patients with any BCR::ABL1 mutation, n (%)	20 (12.7)	13 (17.1)	33 (14.2)
Patients with multiple BCR::ABL1 mutations, n (%)	3 (1.9)	1 (1.3)	4 (1.7)

NA, not applicable. \* Includes improper assignment of study medication, lack of efficacy and tolerability, and optimal response not reached after 5 years of treatment.  
<sup>†</sup> All patients with BCR::ABL<sup>IS</sup>  $\leq 1\%$  at baseline were intolerant to the last TKI, except 1 in the asciminib arm (who deviated from the protocol).

R  a D, et al. *Blood*. 2021;138(21):2031-2041. 28

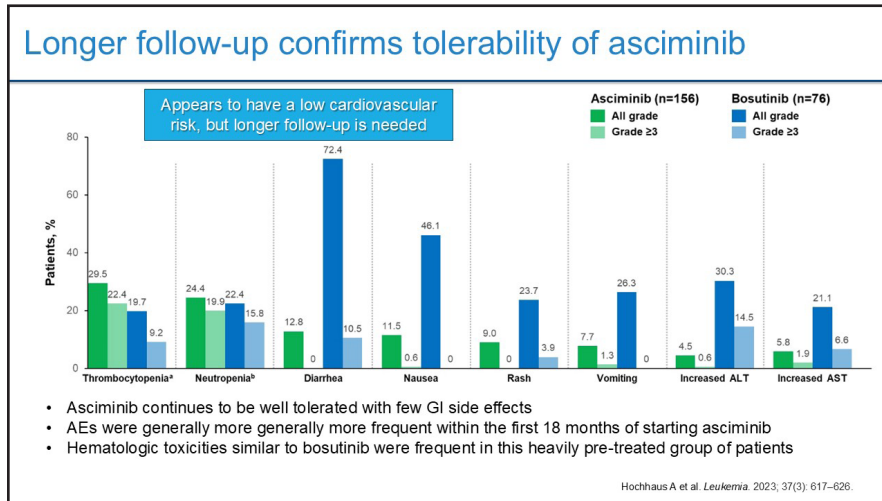
**Slide 28: Demographics and Baseline Characteristics**





**Slide 29: ASCEMBL: MMR rates at 24 and 96 weeks**

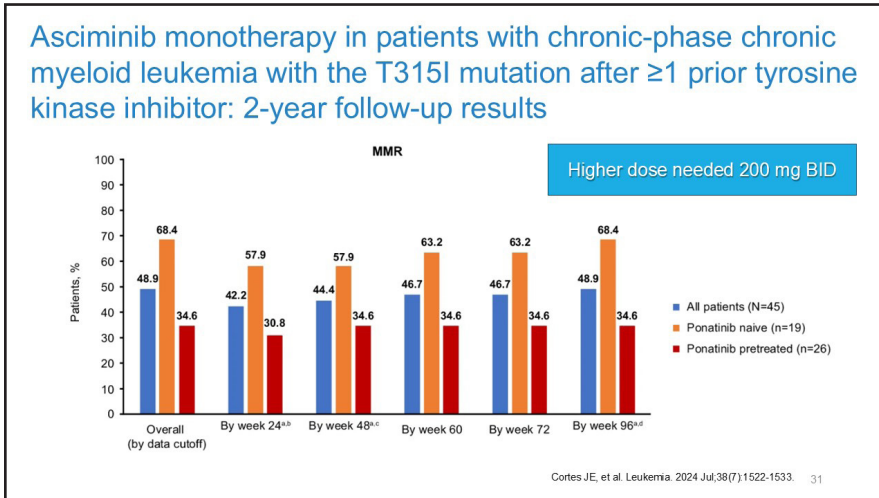
Patients were pretty well balanced, so I won't spend too much time on this slide, but what we found was that twice as many patients who received asciminib versus bosutinib had the primary endpoint, 25.5% versus 13.2% at 24 weeks. There was also a secondary endpoint later on, 96 weeks. You can see this difference between the 2 groups actually grew to 37.6% versus 15.8%.



**Slide 30: Longer follow-up confirms tolerability of asciminib**

What we also learned with longer-term follow-up is that asciminib is very well-tolerated. Asciminib is shown here in light green and dark green, and bosutinib in light blue and dark blue. As you can see, there was certainly less diarrhea, less nausea, less rash, less vomiting, less LF, liver function test abnormalities.

What was different in hematologic toxicity, either low platelets or low white blood cell. What about cardiovascular risk? We know longer-term that this is really important to know. I would say so far it appears to have low risk, but I do think we do need a little bit longer follow-up on this.



**Slide 31: Asciminib monotherapy in patients with chronic-phase chronic myeloid leukemia with the T315I mutation after ≥1 prior tyrosine kinase inhibitor: 2-year follow-up results**

What about patients who have T315I mutation who come on this drug? Well, we see really good responses as well. Need to point out you need 5 times as much drugs and not 40 twice a day or 80 daily. You need 200 milligrams twice daily, still very well tolerated even at these high doses. What we found in all patients with T315I, that 48%, 49% achieved major molecular response.

For patients who had actually been pretreated with ponatinib, we saw responses too. Not surprisingly, if you hadn't received the potent third-generation drug ponatinib beforehand, you were more likely to achieve a major molecular response.

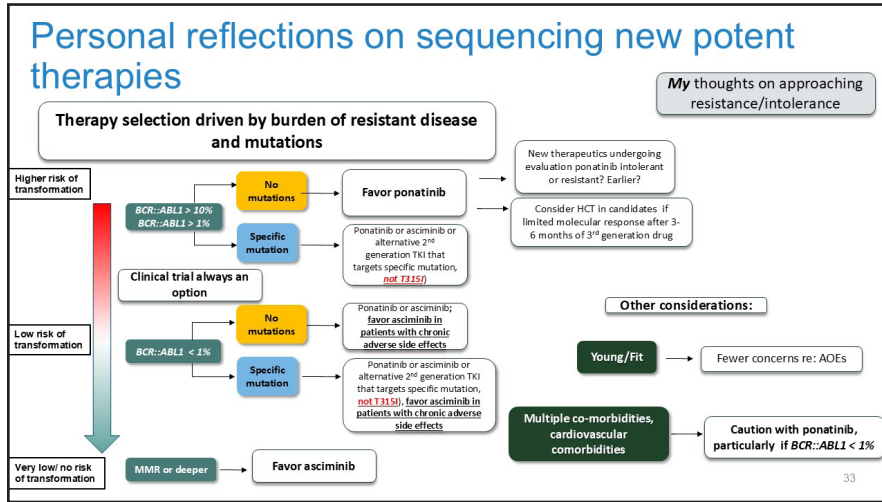
ASCEMBL study caveats:

- Was bosutinib the best comparator arm in patients failing prior 2G-TKI?
  - Ponatinib?
- High discontinuation rate in ASCEMBL vs other bosutinib studies

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**Slide 32: ASCEMBL study caveats**

Were there any caveats to this study? Well, as I pointed out earlier, we know that third-generation drugs are probably better choices when you're sequencing after a second-generation drug, but nonetheless, at that time, the indication for ponatinib was to have it later after this, and so bosutinib was a reasonable comparator at the time that this study was designed.



Slide 33: Personal reflections on sequencing new potent therapies

What about my personal reflections? For those of you, and I know that's fewer patients who might have a high burden of disease and are on third-line of therapy, I still favor ponatinib, and the reasoning for that is that ponatinib's very potent. It's not a very clean drug.

There's been some data that's emerged over the years that ponatinib may target other pathways that's important in CML that's resistant. For patients who don't have cardiovascular issues or have a high BCR-ABL burden, I do tend to favor ponatinib. On the other hand, if you have a low burden of disease, BCR-ABL of less than 1%, have a lot of tolerance issues, I really think asciminib is an excellent choice in these situations.

### Future Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1 <sup>st</sup> generation	•		
Dasatinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Nilotinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Bosutinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Ponatinib	ATP-competitive 3 <sup>rd</sup> generation	•	•* (T315I)	•
Asciminib	ABL Myristoyl Pocket STAMP inhibitor	•	•† (T315I)	•
<del>Ompoxine</del>	<del>Protein synthesis inhibitor</del>	<del>•</del>	<del>•</del>	<del>•</del>

\*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. \*Only available in the US.  
Hochhaus A, et al. Leukemia 2020; 34: 968-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

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Slide 34: Future Treatment Options in CP-CML

As I mentioned, we're seeing the landscape changing and asciminib moving up to earlier lines of therapy here.

### ASC4FIRST, a head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed patients with CML

NCT04971226

**Key inclusion criteria**

- Newly diagnosed Ph+ CML-CP with **no** prior TKIs<sup>a</sup>
- Age ≥18 years

**Prerandomization TKI selection**

- The TKI a patient will take if randomized to the investigator-selected (IS-TKI) arm
- Selected by the physician in consultation with the patient

**Stratification by:**

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category (high, intermediate, low)

**Study Arms (R 1:1, N=405)**

**Asciminib (ASC) 80 mg QD**

Imatinib stratum: ASC<sup>IMA</sup>

2G TKI stratum: ASC<sup>2G</sup>

**All IS-TKIs at label doses**

Imatinib stratum: IS-TKI<sup>IMA</sup>

2G TKI stratum: IS-TKI<sup>2G</sup>

Data cutoff: Nov. 28, 2023

End of study: LPFT + 5 years<sup>b</sup>

---

**Primary endpoints:**

- MMR at week 48 for asciminib vs all investigator-selected TKIs
- MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum

ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; LPFT, last person first treatment; Ph, Philadelphia chromosome; QD, once daily; R, randomized

<sup>a</sup> Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.

<sup>b</sup> Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

Hochhaus A, et al. N Engl J Med. 2024 May 31. doi: 10.1056/NEJMoa2400858. Epub ahead of print. PMID: 38820078. 35

Oral presentation at 2024 ASCO Annual Meeting, May 31-June 4, 2024, Chicago, Illinois, and virtual.

**Slide 35: ASC4FIRST, a head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed patients with CML**

Why is that? Well, hot off the presses, we have the *New England Journal of Medicine* paper at the end of May of this year where the Europeans and Australians published the results of the ASC4FIRST Study of frontline asciminib.

This was a head-to-head study of asciminib versus imatinib or a second-generation TKI. I will say it was a very good design. Patients would sit down with their providers and select, “Well, I think you’re a better candidate for imatinib or you’re a better candidate for a second-generation TKI.” You would pre-select what you would use, and then patients came on study and got randomized. That way we would have a fairer comparison of asciminib versus patients who were destined for imatinib and patients who received asciminib or were destined to get a second-generation TKI. Again, we were looking at major molecular response rates at 48 weeks here for all the TKIs or specifically versus imatinib.

### Baseline characteristics were well balanced between asciminib and all IS-TKIs

Variable	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Median age (range), years	52.0 (18.0-79.0)	56.0 (21.0-79.0)	43.0 (18.0-76.0)	50.5 (19.0-86.0)	54.5 (20.0-86.0)	43.0 (19.0-83.0)
<b>Age group, %</b>						
18 to <65 years	77.1	68.3	86.0	76.0	68.6	83.3
65 to <75 years	17.9	23.8	12.0	16.7	21.6	11.8
≥75 years	5.0	7.9	2.0	7.4	9.8	4.9
<b>Male, %</b>	65.2	61.4	69.0	61.3	63.7	58.8
<b>Framingham CV risk score, %<sup>a</sup></b>						
Low risk (<10%)	54.2	40.6	68.0	54.9	39.2	70.6
Intermediate risk (10%-20%)	15.9	20.8	11.0	21.6	28.4	14.7
High risk (≥20%)	29.9	38.6	21.0	23.5	32.4	14.7
<b>ELTS, %<sup>b</sup></b>						
Low	60.7	61.4	60.0	61.3	62.7	59.8
Intermediate	27.9	29.7	26.0	27.9	29.4	26.5
High	11.4	8.9	14.0	10.8	7.8	13.7

<sup>a</sup> Framingham estimated 10-year cardiovascular disease risk categories.

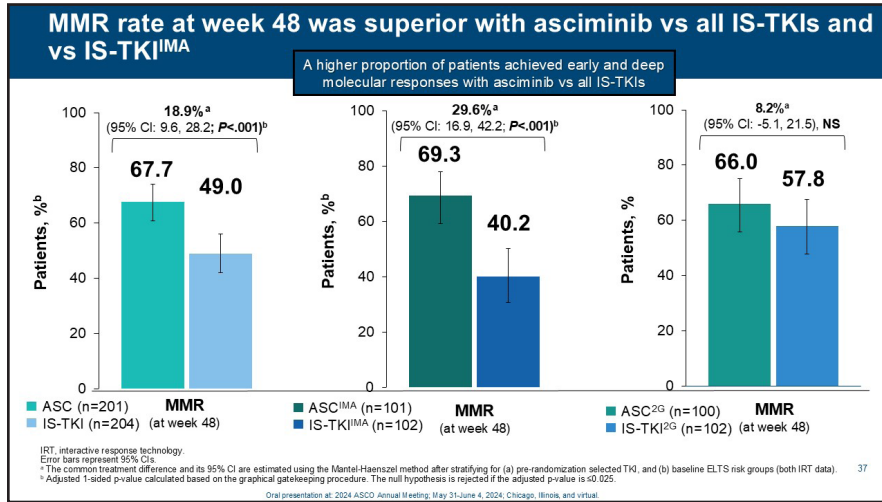
<sup>b</sup> Based on randomization data.

Hochhaus A, et al. N Engl J Med. 2024 May 31. doi: 10.1056/NEJMoa2400858. Epub ahead of print. PMID: 38820078. 36

Oral presentation at 2024 ASCO Annual Meeting, May 31-June 4, 2024, Chicago, Illinois, and virtual.

**Slide 36: Baseline characteristics were well balanced between asciminib and all IS-TKIs**

Again, patients were pretty well-balanced for this study.

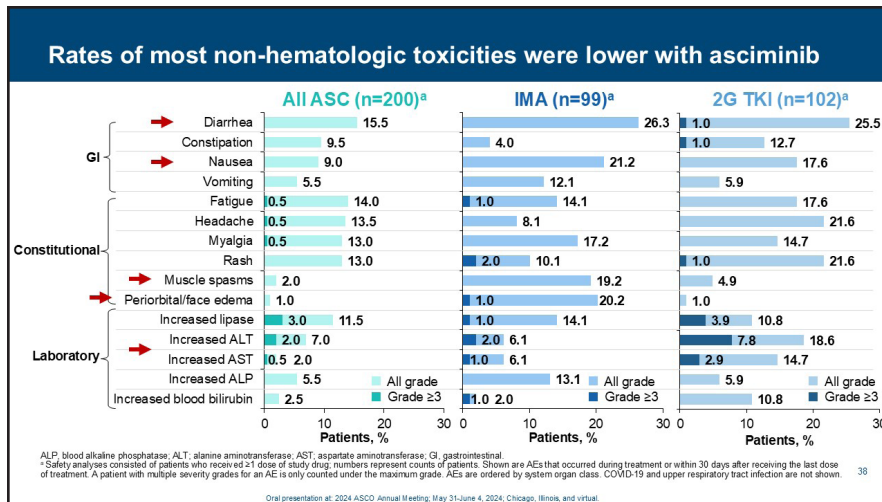


**Slide 37: MMR rate at week 48 was superior with asciminib vs all IS-TKIs and vs IS-TKI<sup>IMA</sup>**

What did we find? Well, it met its primary endpoint. We did see more patients achieving major molecular response by 48 weeks than the asciminib-treated patients versus patients who received TKI, 68% versus 49%.

Not surprisingly, it was a bigger difference for patients receiving the potent third-generation drug versus imatinib.

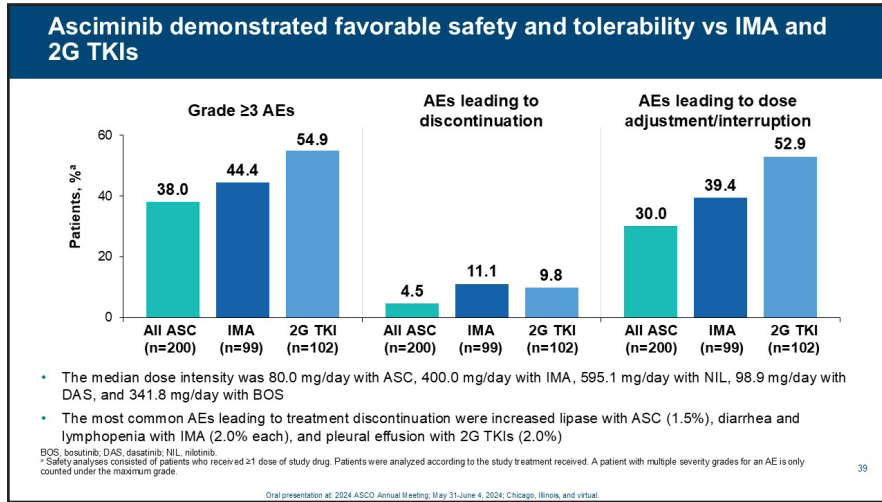
We also saw a trend for more patients who received asciminib achieving major molecular response versus 2G TKIs (second-generation TKIs), although I will say that this was not statistically significant. Additionally, more patients who received asciminib went on to achieve deeper molecular responses.



**Slide 38: Rates of most non-hematologic toxicities were lower with asciminib**

Importantly, we saw lower rates of non-hematologic toxicities for asciminib, but I've put some red arrows on this slide to highlight some important side effects where there were fewer side effects for asciminib. Less diarrhea, less nausea, less muscle spasm for asciminib versus imatinib, less periorbital and facial edema with asciminib versus imatinib, and less liver function test abnormality for asciminib versus either imatinib or second-generation TKIs.





**Slide 39: Asciminib demonstrated favorable safety and tolerability vs IMA and 2G TKIs**

Additionally, on the study, fewer patients had serious or high-grade adverse events on asciminib versus the TKIs. Fewer patients who received asciminib had to stop therapy because of side effects. Lastly, all the way at the right, fewer patients on asciminib had adverse events or side effects that led to dose adjustment or treatment interruption.

### Possible Future Treatment Options in CP-CML

Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1 <sup>st</sup> generation	•		
Dasatinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Nilotinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Bosutinib	ATP-competitive 2 <sup>nd</sup> generation	•	•	•
Ponatinib	ATP-competitive 3 <sup>rd</sup> generation	•	•* (T315)	• Clinical trials: 1. Olverembatinib
Asciminib	ABL Myristoyl Pocket STAMP inhibitor	•	•† (T315)	• 1. Tgrx-678 2. TERN-701
Omavene	Protein synthesis inhibitor			

\*Approved in US for a patients after ≥ 2 TKIs or for patients with T315 CP-CML in any line †Approved for a patients after ≥ 2 TKIs or for patients with T315 CP-CML in any line. \*Only available in the US.  
 Hochhaus A, et al. *Leukemia* 2020, 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

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**Slide 40: Possible Future Treatment Options in CP-CML**

Our possible future. Stay tuned in the next few months, we'll see if asciminib will be moving to earlier lines of therapy. Do we have anything new on the horizon? Absolutely. Currently, including here at the Fred Hutch, we have ongoing clinical trials of 2 other drugs of similar design to asciminib, allosteric inhibitors. This would be TERN-701 and Tgrx-678. Additionally, there are potent third-generation TKIs in clinical trial, including olverembatinib entering a Phase III study.



### When to consider allogeneic hematopoietic cell transplantation

- CP patients** → • ≥ 3<sup>rd</sup> line therapy
  - Typing at failure or intolerance of 2<sup>nd</sup>-line therapy, consider in some when initiating 2<sup>nd</sup> line therapy (failure of 1<sup>st</sup> line 2<sup>nd</sup> gen TKI without mutations)
- Progression to AP or BP** → • HCT using alternate TKI (+/- induction chemotherapy in BP) to bridge
- de novo AP patients** → • Type patient and siblings; use first-line TKI therapy with close monitoring for optimal response as some *de novo* AP patients without high-risk ACA do well. HCT in patients with high-risk ACA; *for others HCT when optimal milestones are not met.*
- BP patients** → • HCT after TKI therapy +/- induction chemotherapy. I favor induction chemotherapy + TKI in most HCT candidates.

Median survival is ~7-12 months with TKI-based therapy

Ohanian et al. Clin Lymphoma Myeloma Leuk. 2014 Apr;14(2):155-162

Slide 41: When to consider allogeneic hematopoietic cell transplantation

### TKI Discontinuation

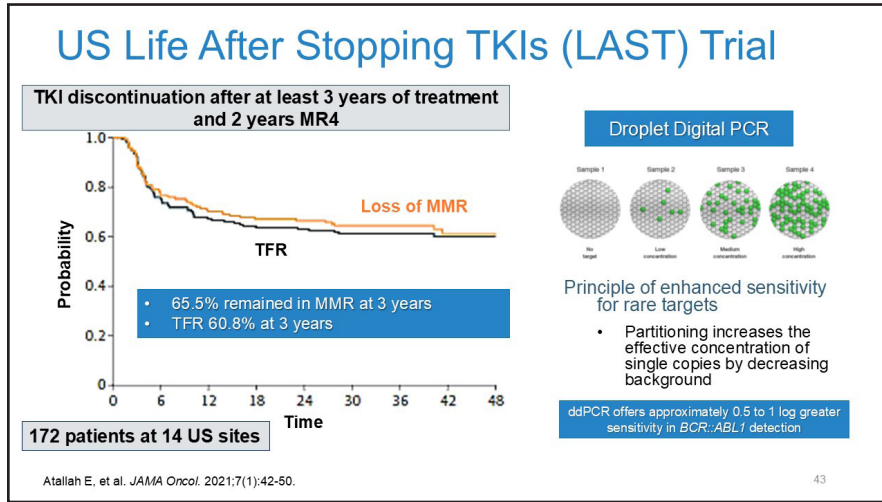
- Imatinib discontinuation: STIM1, STIM2, TWISTER
  - TFR rate at ~40%-50%
- 2<sup>nd</sup> Generation TKI discontinuation: similar results
  - ENESTfreedom and ENESTop (nilotinib)
  - DASFREE (dasatinib)
  - STOP 2G-TKI (dasatinib and nilotinib)
  - US LAST Study (imatinib, dasatinib, nilotinib, bosutinib)
- Success rates of TFR attempts in clinical trials range between 40 and 65%
  - Quite consistent even with varying entry criteria (e.g., duration of TKI use and molecular response and depth of response)

Rea D et al. Blood. 2017; 129(7): 846-854  
 Rousselet P et al. Blood Adv (2020) 4 (13): 3034-3040  
 Ross DM et al. Blood. 2013; 122(4): 515-533  
 Radich JP et al. Leukemia. 2021; 35(5): 1344-1355  
 Hughes TP et al. Leukemia. 2021; 35(9): 1831-1842  
 Shah NP et al. Leuk Lymphoma. 2020; 61(3): 650-659  
 Attallah E et al. JAMA Oncol. 2021; 7(1):42-50

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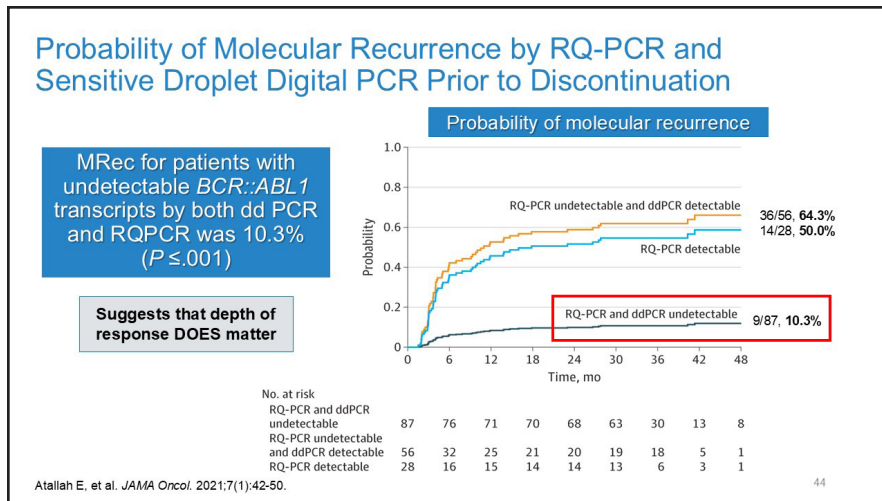
Slide 42: TKI Discontinuation

TKI discontinuation. I know this is an important topic for many. I will say, across all the different studies over the years, the success rates of attempts to stop therapy in our clinical trials have ranged between 40% to 65%.



**Slide 43: US Life After Stopping TKIs (LAST) Trial**

I'm going to share with you today the results of the US study, which we call the Life After Stopping TKI Study or the LAST Trial. This was a study of 172 patients at 14 US sites. Pretty much in keeping with the previously published data, treatment-free remission or the proportion of patients who remained off of therapy remaining in major molecular response at 3 years was 60.8%. We were also really interested in looking at whether maybe the depth of response at the time that you quit therapy actually mattered. In order to answer this question, we actually had a research PCR assay that is Droplet Digital PCR. It's about 3 to 5 times more sensitive than our standard PCR.



**Slide 44: Probability of Molecular Recurrence by RQ-PCR and Sensitive Droplet Digital PCR Prior to Discontinuation**

We did find that depth likely matters in this study and that patients who came onto study who had no BCR-ABL evident by our standard assay, or had no BCR-ABL evident by this research study, were much less likely to have molecular recurrence. Granted, small numbers, but there in the red box you can see patients who were negative by both assays, only 10.3% of them had molecular recurrence.

### TKI Discontinuation Criteria: NCCN and ELN

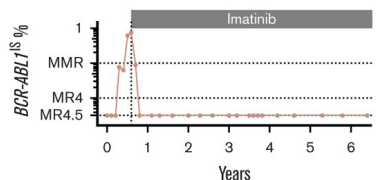
<p><b>TKI discontinuation may be considered (NCCN/ELN) if:</b></p> <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px; background-color: #e0f2f1;"> <p style="text-align: center; margin: 0;"><b>At least 3 years of TKI treatment</b></p> </div> <p style="text-align: center; margin: 0;">and</p> <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px; background-color: #e0f2f1;"> <p style="text-align: center; margin: 0;"><b>At least 2 years MR4</b></p> </div>	<p><b>Optimal TKI discontinuation Conditions (ELN) if:</b></p> <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px; background-color: #e0f2f1;"> <p style="text-align: center; margin: 0;"><b>At least 4-5 years of TKI treatment</b></p> </div> <p style="text-align: center; margin: 0;">and</p> <div style="border: 1px solid #ccc; padding: 5px; margin-bottom: 10px; background-color: #e0f2f1;"> <p style="text-align: center; margin: 0;"><b>&gt; 3 years of MR4 or &gt; 2 years of MR4.5</b></p> </div>
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Rea D. Blood Adv (2020) 4 (21): 5589-5594.  
 Hochhaus A, et al. Leukemia 2020;34(4):906-904.  
 NCCN Guidelines: Chronic Myeloid Leukemia, V3.2022.

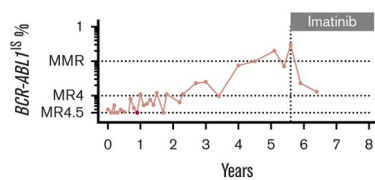
**Slide 45: TKI Discontinuation Criteria: NCCN and ELN**

It's consequently data, such as these as well as other data, that suggests that the longer you stay on therapy with a deep molecular response, the more likely you are to succeed at stop when you quit therapy. I use the optimal TKI discontinuation criteria endorsed by ELN (European LeukemiaNet). At least 4 to 5 years of therapy, at least 3 years of MR4, or at least 2 years of MR4.5, which is undetectable in BCR-ABL.

### Molecular Recurrence (Loss of MMR) After TKI Discontinuation: Long-term STIM1 follow-up



- 65 of 128 (51%) patients in STIM1 had molecular recurrence while off therapy
- Most within the first 6-12 months after discontinuation
- Most regain prior deep molecular response after restarting



- 9 of 65 (14%) patients with late molecular recurrence
- At 2.3, 2.5, 3, 3.5, 3.6, 5.4, 5.5, 5.7, and 6.4 years (median time to LMRRec, 3.6 years)

NCCN: Monitoring 1-2 months for the first 6 months, then every 2 months for months 7-12, then every 3 months if MMR is maintained indefinitely

Rousselot P et al. Blood Adv (2020) 4 (13): 3034-3040.

**Slide 46: Molecular Recurrence (Loss of MMR) After TKI Discontinuation: Long-term STIM1 follow-up**

We recommend a little bit accelerated monitoring in the first year because among the 50% of patients who fail stopping, 85% will fail within the first year, and usually actually within the first 6 months. We recommend monitoring at 2-month intervals. We know from the oldest study of its kind, STIM1, which stopped their first patient in approximately 2005, that there is also late molecular recurrence.

About 15% of the 50% who had molecular recurrence did so as late as 6.4 years after stopping therapy. Consequently, we recommend monitoring at 3-month intervals lifelong. We don't have a lot of data about what happens to patients after 10 years of therapy or longer, but we have no reason to think that we're going to see an uptick in molecular recurrence late.

### Risks of TKI discontinuation?

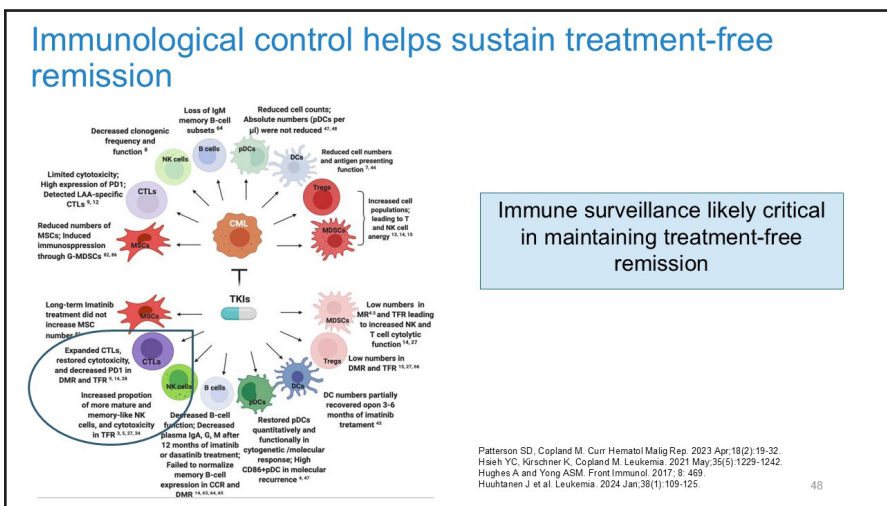
- **Loss of TKI sensitivity upon TFR failure:**
  - Exceptionally reported. Usually, MMR and DMR regained within 3 to 6 months after TKI re-introduction
- **CML progression:**
  - Exceptionally rare cases of “sudden blast phase” either during the treatment-free phase or soon after TKI reintroduction have been reported; mostly lymphoid blast crisis.
- **TKI withdrawal syndrome**

Alfayez M, et al. Br J Haematol 2019; 187: 543-545.  
 Richter J, et al. J Clin Oncol 2014; 32: 2821-2823.  
 Rea D, et al. Cancer 2018; 124: 2956-2963.  
 Rea D. Blood Adv (2020) 4 (21): 5589-5594.  
<https://doi.org/10.1182/bloodadvances.2020.025338>

**Slide 47: Risks of TKI discontinuation?**

Are there any risks associated with stopping therapy? I would say the risks are exceptionally low. You’re unlikely to lose sensitivity to your prior drug if you have to restart it at the time of recurrence. Exceptionally rare cases of CML progression have been reported, again, very rare. TKI withdrawal syndrome is not uncommon. The longer you’ve been on drug before you stop, the more likely to have it.

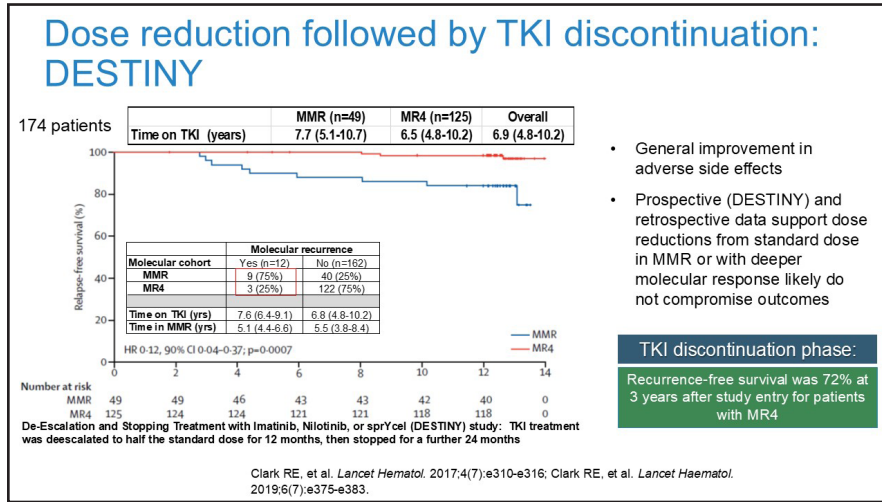
Patients who have been on therapy for more than 8 years, for example, are more likely to have pain in the shoulders, pain in the joints, some back pain. Usually last weeks, possibly a couple of months for rare patients, it can last quite a bit longer. Nonsteroidal anti-inflammatories are one way to treat this.



**Slide 48: Immunological control helps sustain treatment-free remission**

You might be wondering, how is it possible that patients who might have a little bit detectable CML can actually stay off of therapy? There have been several studies, but a very interesting paper, actually, that came out of a lab in Finland earlier this year by Dr. Mustjoki and colleagues that suggests it’s actually in our immune system.

Patients who succeed at treatment-free remission likely have an immune system that’s primed to surveil and keep disease under control. How to turn that into strategies to make treatment-free remission attainable by all is still a work in progress, though.



**Slide 49: Dose reduction followed by TKI discontinuation: DESTINY**

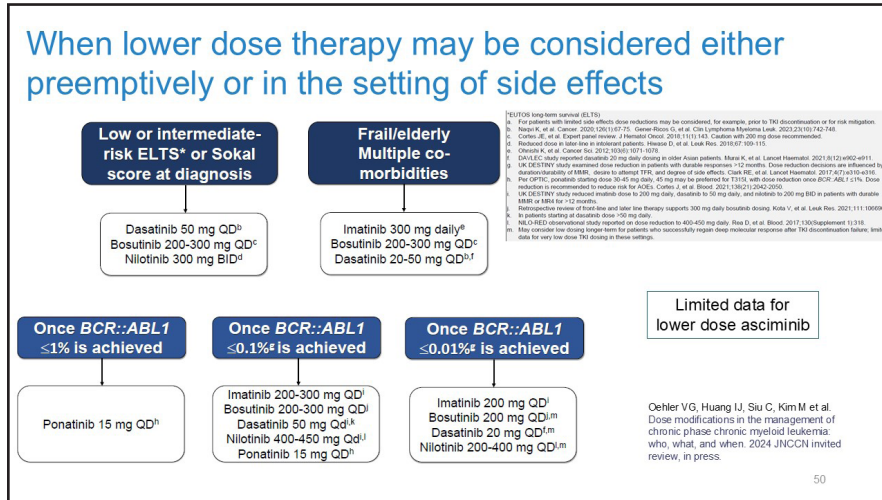
Dose reductions, we talked a little bit about starting lower-dose dasatinib frontline and a little bit about starting lower-dose bosutinib frontline. We also have data that support that if you have a durable major molecular response of at least 12 months or deeper molecular responses, that making a dose adjustment to half your dose is not likely going to impact your current response.

Where we learned this actually was from the prospective UK DESTINY Study, which enrolled 174 patients who were in durable major molecular response or deeper response. I'll say most of these patients were treated with imatinib. If you had a response, either MMR or deeper response for 12 months, you got to cut your dose in half, so imatinib at 200, dasatinib at 50.

Among that group of patients, only 19% actually lost major molecular response within the major molecular response group. If you're one of the patients who had a deep molecular response, only 2% lost that response. Overall, side effects improved in almost all patients who made these adjustments.

Importantly, there was a second part to this study. If you were a patient who had a durable deep molecular response after a year of dose reduction, you then were eligible to come off of therapy and 72% of those patients after 3 years after enrolling in this study actually remained off of therapy. Within my own practice, this is a strategy that I follow where I do a dose reduction followed by TKI discontinuation in eligible patients.





**Slide 50: When lower dose therapy may be considered either preemptively or in the setting of side effects**

This is summarized a little bit here in a paper that we have coming out from the NCCN about when we can advise doctors and their teams and patients on when we can think about making dose adjustments. Again, durable major molecular responses are deeper. It's unlikely you're going to lose that response if you make that adjustment.

### Conclusions

**Goals:**

1. Life expectancy not impacted by CML: high-risk CML
2. Limit impact of TKI therapy on comorbidity outcomes
3. Quality of life and minimizing adverse events
4. Treatment-free remission
5. Limiting costs
6. Family planning

**Therapy:**

1. 2<sup>nd</sup> generation TKI or asciminib vs imatinib
2. Imatinib vs 2<sup>nd</sup> generation TKI or asciminib
3. Asciminib vs TKI (role for lower dosing)
4. 2<sup>nd</sup> generation TKI or asciminib, imatinib
5. Generics (imatinib, dasatinib) vs others
6. 2<sup>nd</sup> generation TKI or asciminib vs imatinib

1. Patient-oriented and care provider-directed framework to guide therapy selection in CP CML based on current evidence

Oehler VG. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):228-236.

**Slide 51: Conclusions**

In conclusion, I do think it's really a team approach between your providers and you to select the best therapeutic strategy for your frontline and to select next-line therapies for patients with higher risk. I generally favor second-generation therapies or asciminib in earlier lines when it's available. I think for quality of life and minimizing adverse events, we know asciminib is really good at this, but I also think dose reduction of TKI in appropriate scenarios can help.

For treatment-free remission, getting there faster is definitely achieved with second- and third-generation drugs, although the success rate after you stop is not different between these 2. Limiting costs, I think we definitely have to think about how we're going to balance generics against the others. For family planning, again, for our patients who can give birth a second-generation or third-generation drug can get you to a deeper response faster.



## Conclusions

2. TFR is an important goal for many patients, but not all achieve durable deep molecular response and 40-50% fail therapy discontinuation. **Long-term quality of life on therapy is important.**
3. For patients resistant to 2G TKI, 3G therapeutics are more likely to result in  $BCR-ABL1 < 1\%$  or MMR
  - Additional potent 3G TKI and allosteric inhibitors are under evaluation in clinical trials BUT don't forget stem cell transplant for eligible resistant CP CML patients in >3<sup>rd</sup> line with high burden of CML or persistent severe hematologic toxicities which limit the ability to treat effectively.

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### Slide 52: Conclusions

I know that TFR (treatment-free remission) is a really important goal for everyone, but not everyone can get there. As I talked about, patients fail. I think really focusing on long-term quality of life is really important. I think for patients who are resistant to second-generation TKI, third-generation therapeutics are really more likely to result in the responses you need for normal lifespan.

I didn't talk about transplant today. For that rare patient who is very resistant or has intolerances that make it impossible to use our therapeutics, transplant still remains an important part of the treatment arsenal, and I still do a few a year, although incredibly rarely. With that, I'd like to thank you for your attention today, and I'm happy to take any questions.



### Slide 53: Thank you

**Lizette:**

Thank you so much for such great information, Dr. Oehler.



**ASK A QUESTION**  
**THE FUTURE OF CML: WHAT'S NEXT?**

Ask a question by **phone**:  
Press star (\*) then the number 1 on your keypad.

Ask a question by **web**:  
Click "Ask a question"  
Type your question  
Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.



## Slide 54: ASK A QUESTION

It is now time for our question-and-answer portion of our program.

We'll take the first question from our web audience. Doctor, Barbara asks: If in remission, why do you still have to take the SPRYCEL®?

### Dr. Oehler:

All right, so I'm going to qualify that a little bit. If you have a, let's say you hit 0, for example. First of all, I will say that we don't know that it's a true 0, because our assay can't detect every last leukemia cell in the body. We know that if you have 1 zero value undetectable or another undetectable value, that if you stop therapy at that point, 100% of patients are actually going to have molecular recurrence for the most part in that setting. It actually caught us really by surprise that treatment-free remission was actually going to be something.

You need to have that durably, multiple values that are undetectable. I will say that there is some information from Australia where they use very sensitive testing, where they actually were able to show that patients who stayed in treatment-free remission still had detectable disease. This is where it comes to this part where probably an individual patient's immune system is what's going to control disease. Some are lucky and some aren't. Having a deep molecular response for at least 2 to 3 years before you stop, still only half are going to succeed.

Unfortunately, there are either you still harbor one of these mother cells that makes CML that then wakes up and makes more CML, escapes the surveillance of the immune system, or your immune system is just not one of those that's really, really primed to hold the disease under control. That's why for most patients we have to be really cautious about stopping. Hopefully, I've addressed that question.

### Lizette:

Thank you so much. Operator, we'll take the next question from our telephone audience, please.

### Operator:

Our next question comes from Robert. Robert, your line is open.

### Robert:

I was diagnosed with CML 3 weeks ago. I'm just wondering, I've had ITP (immune thrombocytopenic purpura – low platelet count), kidney disease, for quite some time prior to this diagnosis. Am I considered super high risk?

### Dr. Oehler:

I'm going to say that, yes, we can treat your CML, but we're going to have to be really careful treating your CML. I will say, in terms of therapy that are the easiest on the kidney, generally, dasatinib is one of those that's good. On the other hand, patients who take dasatinib sometimes can have lower platelets or more of a bleeding tendency. It may be in that situation that we have to pay a little bit more close attention to it. Imatinib and dasatinib can be a little bit hard on the kidneys.

This might be one of those cases for you where if you're not, it sounds like you might actually be on therapy already. We're trying to get an early approval of asciminib, which would be less of an issue with bleeding tendencies or kidney might be a good way to go. I will point out when you start CML therapy when these drugs are not perfect, they can have some impact on normal blood cells. There is this rare group of patients who have a larger decline in platelets or white cells or red cells, which can sometimes lead to a management issue.

I'll be honest, whether it's asciminib or any of our TKIs, equal incidence. Thankfully, it's rare. I do have some strategies to manage those hard patients because it turns out that a diagnosis, your bone marrow is full of these CML cells, there's not really a lot of real estate for the normal hematopoiesis (development of blood cells in the bone marrow). Those leukemia cells might actually poison those normal cells from growing a little bit. Sometimes the secret to getting out of a low blood count situation is actually to treat to a good response, and then those normal blood counts have a better environment in which to grow in.

With you, just because you have lower platelets from ITP, it doesn't mean that this is going to happen, but you're going to be somebody we're going to have to watch really closely with your platelet count to ensure that we get to the outcomes that we need.

**Lizette:**

Our next question comes from Robert. Robert is asking: What can I do for muscle aches?

**Dr. Oehler:**

I'm guessing that you might actually be on imatinib, right? I'm going to say if it's early in the treatment course and you really need the full dose, it becomes a little bit more difficult. You want to make sure that your phosphate levels are normal, that's really important. Some of my patients say that magnesium has helped them with muscle cramps a little bit, but mainly it's just to make sure if you're somebody with low phosphate from imatinib, that's corrected.

I will also say that this kind of stuff is linked to your dosing too. If it's early on and you have to take a higher dose to get to treatment responses, symptomatic management, like we talked about, is good. If you're somebody who's further along in treatment and have a major molecular response, you can actually dose-reduce your drug, and that will help with some of the muscle spasms and the charley horses.

**Lizette:**

We'll take the next question from the phone audience, please.

**Operator:**

Our next question comes from Judith. Judith, your line is now open.

**Judith:**

I'm just curious as to whether new cases of CML have remained stable or have increased or decreased?

**Dr. Oehler:**

It's a great question. I know for some cancers, we've seen actually an uptick over the years. For others, a decrease. I would say for CML, the incidence is about the same as it's been over the year. I don't think we see more of it. I will say that there are regional differences. I will say that the incidence of CML in India, for example, is higher than what we see in the US. For example, and I don't know that we fully understand that, because we are so good at managing CML now, of course, the prevalence or the number of people living with the disease is increasing rapidly. Even though it's a really rare leukemia, we're going to have more people living with CML than some of our other blood cancers shortly.

**Lizette:**

Rebecca is asking about neuropathy or numbness in lower legs and feet. She's saying that many female patients online complain of the same thing. Is this a side effect of the TKIs or is this a symptom of the CML?

**Dr. Oehler:**

Thankfully within my own practice, neuropathy is fairly rare and I think it's actually drug-related rather than related to CML diagnosis. Honestly, sometimes it's hard to separate out nerve pain from muscle pain and bone pain. I mean, I know when your marrow is packed full of CML at diagnosis, that can be really uncomfortable, especially when we begin to treat, sort of diffuse bone aches and muscle pain, etc. can definitely be present. That generally gets better with each passing month.

On the other hand, true neuropathy, burning sensations, other things like that. I've had a few patients over the years who have had that. I've tried lower doses in appropriate circumstances. I've sometimes switched between drugs, but there is a very rare group of patients where it may travel from one drug to the next. Probably in that situation, in a true neuropathy where dose adjustment isn't present, I've also done more of a workup. I want to make sure I'm not blaming my drug. Sometimes I find my primary care physicians would like to blame everything that a patient has on my drug, and sometimes it's true and sometimes it's not.

I think you got to check your thyroid, you got to check your (vitamin) B12. I've even sent people to have EMG studies (electromyography tests the health of muscles and nerve cells) or workup by a neurologist just to make sure we understand what the neuropathy is. Then switching maybe from a TKI to asciminib might be a reasonable thing in that scenario as well, but I do think it's important to make sure that we fully understand that it's not something else contributing to the neuropathic pain.

**Lizette:**

The next question is from Carolyn. Should I take ibuprofen or Tylenol® (acetaminophen) with Gleevec?

**Dr. Oehler:**

We said no Tylenol with Gleevec in the very, very early days. I will say we've probably backed off from that a little bit, but you do wish to be a little bit cautious with it. We know if you've got low platelets for example, we try to avoid NSAIDs (nonsteroidal anti-inflammatory drugs), but I would say I use more NSAIDs in patients on imatinib, but on the other hand, we know that NSAIDs if you take non-steroidal anti-inflammatories and, Aleve®, ibuprofen long term, that can be damaging to the kidney. Also, you got to make sure to take it with food because it can be really irritating to the stomach. Tylenol in those situations can be better. It really depends on how much of a specific drug you're taking. If you're taking 1 or 2 tablets a day, it's probably fine of Tylenol.

**Lizette:**

**Jeanette is asking:** Are doses for seniors usually lower than for younger patients?

**Dr. Oehler:**

Yes. Great question. As it stands right now there are no differences in dosing, but I would say there are studies from Asia that certainly support lower dosing in older patients, whether it's imatinib at 300 or dasatinib at 50. There's even a study of patients over the age of 70. I think the average age in the study was about 75 where patients were receiving 20 of dasatinib frontline. I will say generally, outcomes for patients in Asia on lower doses are quite good. Whether that's true in the US, we don't quite have that data, but I will start 300 of imatinib in older patients and if you're over the age of 70, I might use 300 for dasatinib.

Unless you're a high-risk patient or a young patient, I'll often be using 50 of dasatinib based on the MD Anderson (research study). That's just my own practice and mainly because the risk of pleural effusion is tied to age. Over the

age of 50, I'm quite reluctant to use dasatinib at 100 milligrams daily. For bosutinib even if you're a younger patient because of the GI side effects I like to start at a lower dose of 200 to 300 milligrams too, but I do think in patients over the age of 70 lower doses of imatinib and dasatinib and bosutinib are certainly something to think about.

**Lizette:**

We'll take the next question from our telephone audience, please.

**Operator:**

Our next question comes from Stephanie. Stephanie, your line is open.

**Stephanie:**

Can you define intolerance? What does that mean and what should doctors be looking for?

**Dr. Oehler:**

Yes. I'm going to turn this around a little bit. I'm going to say when you meet with your team, you should just tell them how you feel. Let them put that into perspective. Intolerance is just this term that we use to describe, "I've got nausea, I've got loose stools, I've got diarrhea, I've got fluid around my ankles. My weight's gone up because I have fluid retention, I've got fluid around my eyes." Now, the things that doctors look at, lab abnormalities, intolerance, "My blood counts are low, my liver function tests are abnormal, I've developed pancreatitis."

I think that any symptom that you think is persistent or durable is something that you should sit down and talk with your team about. I tend to be as aggressive as I can in managing stuff, so antiemetics for nausea, antidiarrheals for diarrhea, got to be wary of constipation, steroid creams for skin rash. Hopefully, these things will make those side effects get better quickly.

**Lizette:**

Eileen would like to know: If there is a time limit on how long a person can stay on dasatinib?

**Dr. Oehler:**

Do you mean, do we know of anything that would be dangerous about dasatinib long-term that would want us to get off that drug?

That's a great question. One reason I do like imatinib is that we have 25 years where we know there's nothing really about imatinib that's not reversible in terms of the side effect, it doesn't really appear to increase the risk of cardiovascular disease. For the other drugs, we do have quite a bit of follow-up, so as it stands right now if you had to stay on dasatinib lifelong, I don't think we have any firm data that's going to result in an increased risk of cancer.

If we looked at long-term follow-up for dasatinib versus imatinib, maybe there was a smidge more cardiovascular disease, but I don't know how different that is from the baseline population matched for age. The biggest thing with dasatinib is that risk for pleural effusion. It can happen at any time. It could happen 8 years after you started the drug or early on. Some get it, some don't. Unfortunately, we're bad as doctors at predicting who's going to really get something, which is why I tend to use lower doses of dasatinib.

I think for many of my patients we want to try to attempt to get to treatment-free remission, and so I do that once you have a durable deeper response we're going to cut your dose in half for 12 months. I mimic the DESTINY Study a little bit, then we either dose-reduce further, which is a little bit of made-up medicine or do TKI discontinuation. Then, if you're going to restart again because you failed, a lot of my patients will be maintained longer term on lower doses, like 20 to 40 milligrams of dasatinib. Again, I'm trying to get away from that risk for pleural effusion if I can, but for other things, we don't really have any firm data.



I will say across studies, it always seems like CML patients have some hypertension – whether that's driven by age or what contribution by drugs – should pay attention to that as well too.

**Lizette:**

Our last question today. Jorge is asking: Is it possible to be cured even if you're still positive Philadelphia chromosome, but you've been in remission for so many years?

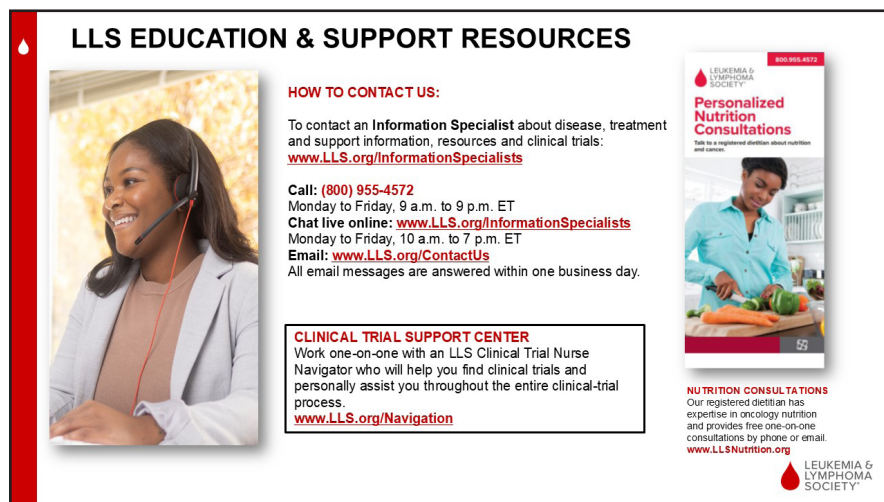
**Dr. Oehler:**

Yes. I think we learned this actually from Dr. Atallah at the Wisconsin Medical Center who actually asked this question. We learned from patients that the definition for cure for many was to be in remission, but also to be off therapy. As long as nobody did a very super-sensitive test on you to find out that you had one last CML cell, that definition of cure would be no detectable CML and off therapy. On the other hand, there are patients who can't, who have deep responses who have normal life expectancy, but have to continue therapy.

Whether we call that a cure or a functional cure or just a remission, I don't know. It depends I think on the individual patient, but I do think a great goal for everyone would be if we could make treatment-free remission accessible to all.

**Lizette:**

Thank you so much, doctor. Thank you for your question, Jorge, which was our last question today. Special thank you to Dr. Oehler for volunteering her time and expertise with us today.



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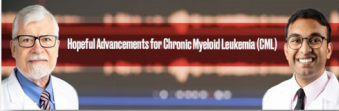
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Slide 56: LLS EDUCATION & SUPPORT RESOURCES

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877.557.2672

**Help With Finances**

The Leukemia & Lymphoma Society (LLS) offers financial assistance\* to help individuals with blood cancer.

The LLS Patient Aid Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a \$100 stipend. Visit [www.LLS.org/PatientAid](http://www.LLS.org/PatientAid)


The Urgent Need Program, established in partnership with Mopple's Love, helps pediatric and young adult blood cancer patients or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a \$500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit [www.LLS.org/UrgentNeed](http://www.LLS.org/UrgentNeed)

The Susan Long Pay-It-Forward Patient Travel Assistance Program provides blood cancer patients a \$500 grant to assist with transportation and lodging-related expenses. Visit [www.LLS.org/Travel](http://www.LLS.org/Travel)

The Co-Pay Assistance Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit [www.LLS.org/CoPay](http://www.LLS.org/CoPay)

\*Eligibility for LLS Co-Pay Assistance Program is restricted to governmental, non-profit, and non-commercial entities. Governmental entities are not eligible.

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: [www.LLS.org/Finances](http://www.LLS.org/Finances)



To order free materials: [www.LLS.org/Booklets](http://www.LLS.org/Booklets)



Slide 57: LLS EDUCATION & SUPPORT RESOURCES

Support for this program is provided by Novartis Pharmaceuticals Corporation. Thank you so much for your support.



**Slide 58: LLS EDUCATION & SUPPORT RESOURCES**

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us today for this program.

Again, Dr. Oehler, thank you for volunteering your time with us.

Goodbye, and we wish you well.