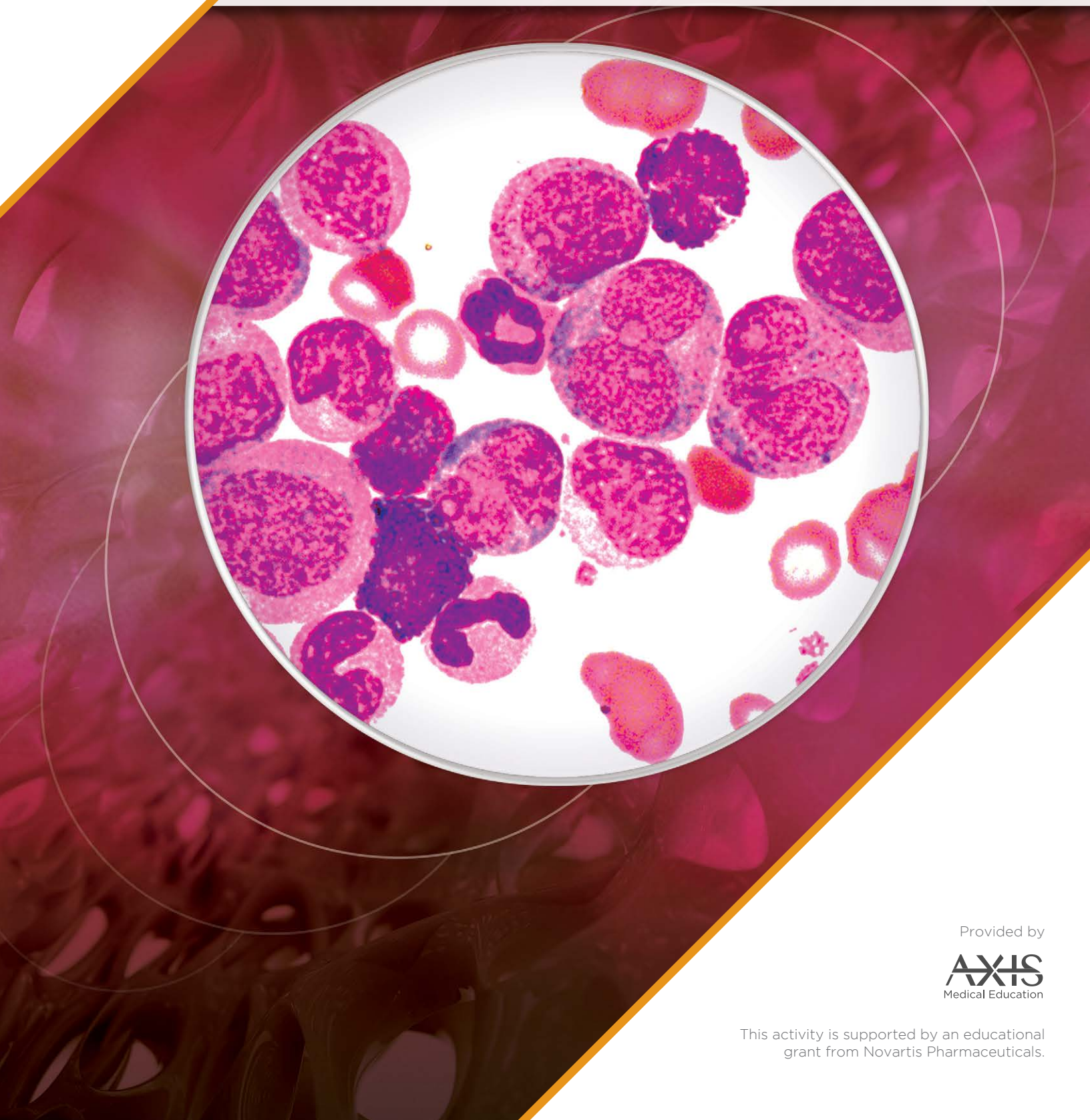
AXIS Medical Education

Novel Treatments for Newly Diagnosed Ph+ CML-CP:

Striking the Balance of Treatment with Patient Goals and QoL

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



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AXIS Medical Education

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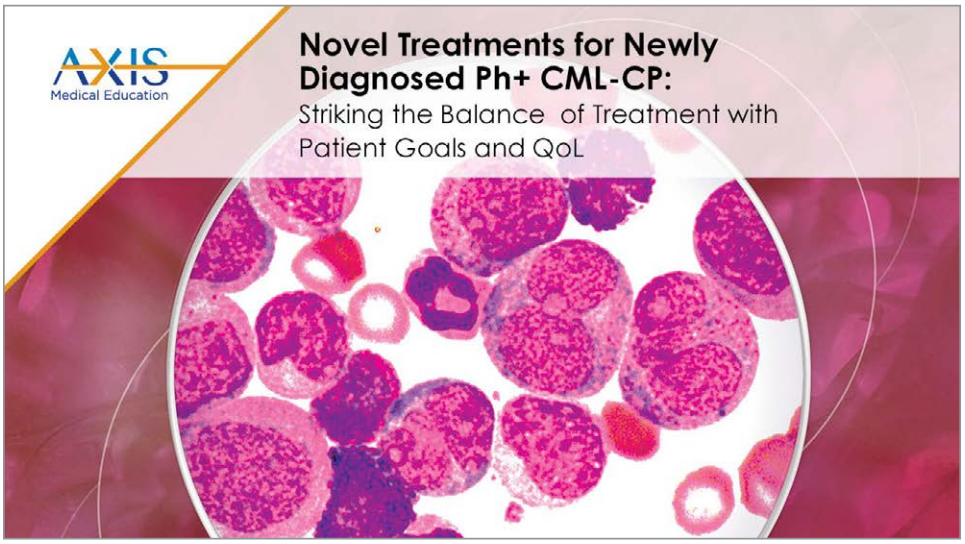
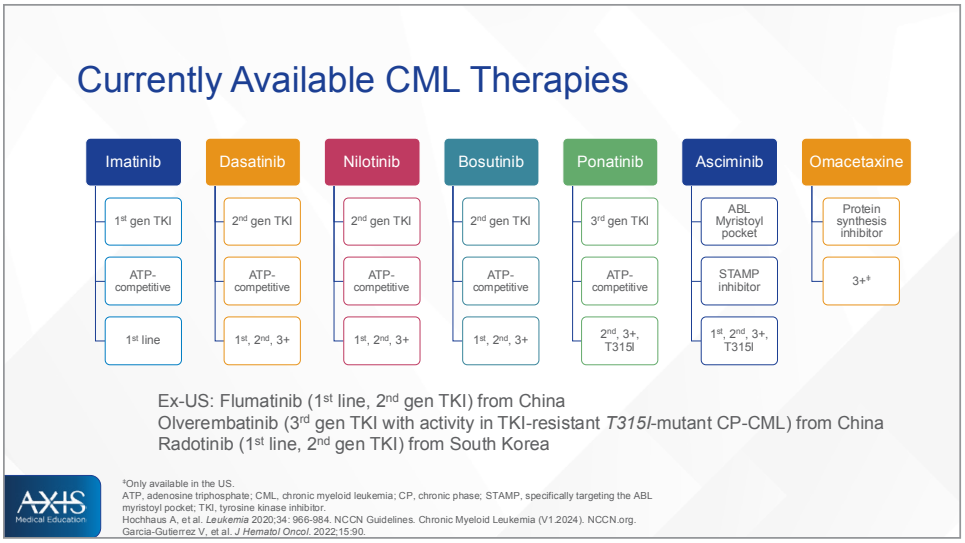
Novel Treatments for Newly Diagnosed Ph+ CML-CP: Striking the Balance of Treatment with Patient Goals and QoL

Jorge Cortes, MD

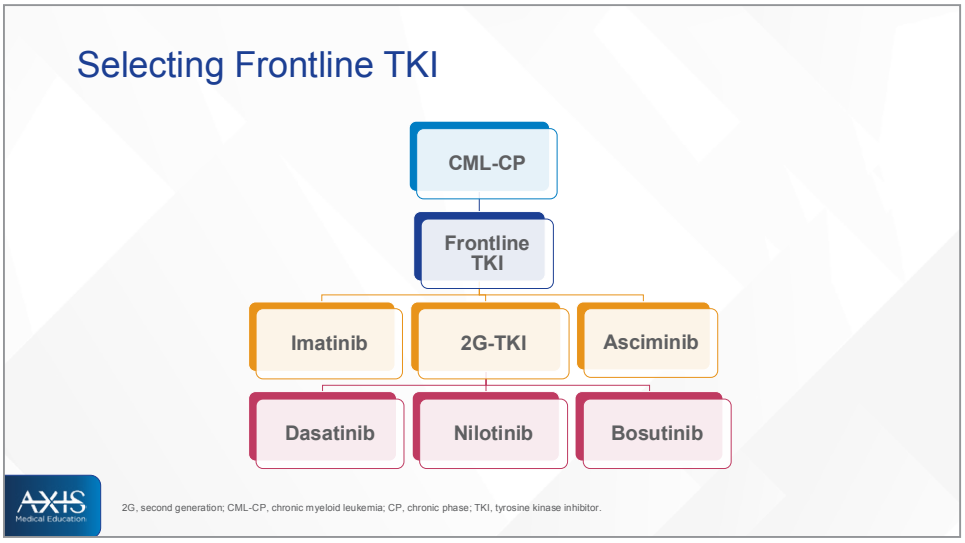


- **Dr. Cortes:** Hello. My name is Jorge Cortes, and I'm going to be talking today about some of the novel treatments for the newly diagnosed patients with chronic myeloid leukemia in the chronic phase, and how we balance the treatment goals and the quality of life in this process.

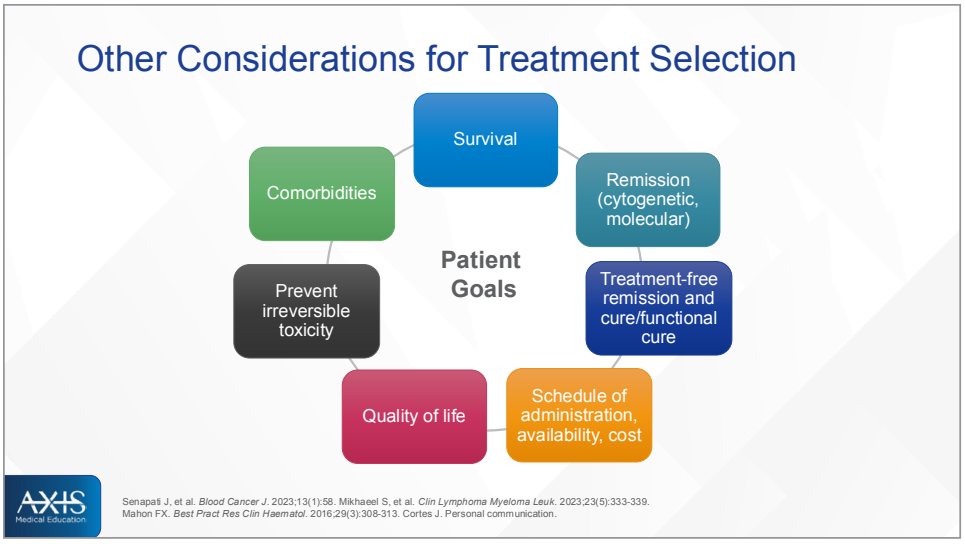
- Let's start first by an overview of the current treatments and the kind of interventions that we can do for the management of our patients.



- We today have seven different treatment options for patients with chronic myeloid leukemia. One of them, omacetaxine, is not a tyrosine kinase inhibitor; it's a drug that is intravenous, it's a protein synthesis inhibitor. We have six tyrosine kinase inhibitors. Of them, one, asciminib, is a STAMP inhibitor. That means it inhibits the myristoyl pocket of the ABL kinase. It is the only one that has this mechanism of action. All the other inhibitors are competitive ATP inhibitors. They have different properties. Some of them are indicated for different lines of therapy, imatinib only first line. The second generations, first, second, and third line and beyond, whereas ponatinib is only for second and third line and beyond. And asciminib, very recently got approval for all lines of therapy as well.



- When we have a new patient usually a mental algorithm that I follow is as follows: first I have to decide, am I going to give them imatinib, or am I going to give them a second-generation TKI? Now, with the very recent approval of asciminib, that even becomes a third choice that I need to decide. If I'm going to give a second-generation TKI, then I also have to decide which one of the three different drugs am I going to use.



- To kind of solve this puzzle, so usually what we want to see is the balance of the different elements that come into this decision. For example, what is the efficacy of the drug? What are the expected side effects of the drug? What are the comorbidities of my patients? What is the schedule of administration? What do I know about all of these drugs? The Sokal risk classification of my patient, and so on? With that, then we have to look very importantly at the patient goals. What is the goals that the patients are aiming for? Just having a longer survival? Having fewer side effects? Aiming for treatment-free remission? Frequently, it's a combination of these, and therefore we need to see what gives me the best balance to achieve those goals.

Outcome Across First-Line CML Studies

Parameter		DASISION		ENESTnd		BFORE	
		Dasatinib	Imatinib	Nilotinib	Imatinib	Bosutinib	Imatinib
Age	Median (range)	46 (18-84)	49 (18-78)	47 (18-85)	46 (18-80)	52 (18-84)	53 (19-84)
High risk[a]	%	19%	19%	28%	28%	20.7%	21.2%
EMR[b]	3 mo	84%	64%	91%	67%	80.6%	60.5%
MMR	12 mo	46%	28%	55%	27%	47.2%	36.9%
	24 mo	64%	46%	71%	44%	66%	57.4%
MR4	12 mo	NR	NR	20%	6%	20.7%	12.0%
	24 mo	NR	NR	39%	18%	26.6%	34.3%
MR4.5	12 mo	5%	3%	11%	1%	8.1%	3.3%
	18 mo	13%[c]	7%[c]	21%[c]	6%[c]		
	24 mo	17%	8%	25%	9%	20.4%	15.2%
Treatment change/ discontinued	1-3 yrs	23% (2 yrs)	25% (2 yrs)	25.5% (2 yrs)	32.5% (2 yrs)	18.3% (1 yr)	17.7% (1 yr)
	5 yrs	39%	37%	40.1%	50.2%	40.3%	41.9%

[a]Sokal in JALSG, ENESTnd and BFORE, Hasford in DASISION, and ELTS in ASC4FIRST. [b]*BCR::ABL1* ≤10%.
[c]Per trial design based on abstracts reporting median follow-up 18 mo.
CML, chronic myeloid leukemia; EMR, early molecular response; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale.
Veltmaat L, Cortes J. *Blood Adv*. 2024;8(20):5339-5341.

- We all know that all of these drugs are very good. All the ones that are available for frontline therapy are very good. Imatinib is a good drug. Second-generation tyrosine kinase inhibitors are also very good drugs. We know that in randomized studies, however, they provided some benefits over imatinib. They had better probability of achieving a response. The responses happened earlier. The responses were deeper, more deep molecular responses. There were fewer transformations to accelerated and blast phase. Now, still many patients ended up having this continuing therapy.

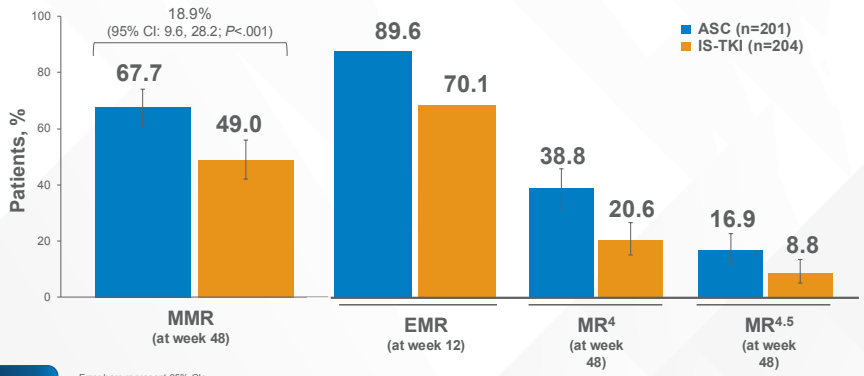
Persistent Challenges in CML

- ~40% change therapy by 5 yrs
- ~60% achieve MR4.5 by 10 yrs
- ~50% eligible for treatment discontinuation
- ~50% resume therapy after TFR
- Arterio-occlusive events with most TKIs
- Low-grade chronic AEs
- QoL

AE, adverse event; CML, chronic myeloid leukemia; MR4.5, molecular response by a 4.5 log reduction on the international scale; QoL, quality of life; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

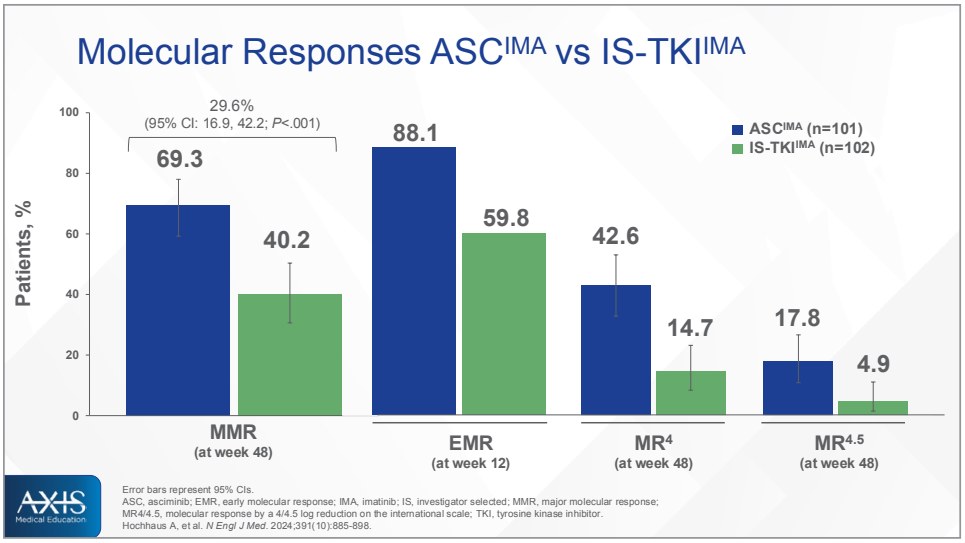
So as good as all these results have been with these studies, we know that there have been some challenges that still remain. About 40% of patients end up having to change therapy by 5 years. Only about 60% achieve deep molecular responses. And only about 50% are eligible for treatment discontinuation, and many of those who discontinue then have to resume therapy. There's also the risks. Arterial occlusive events are common to most of these drugs, particularly the second generation. There are a lot of low-grade but chronic adverse events that limit the quality of life of our patients. So better treatment options are therefore important.

Molecular Responses with Asciminib vs All IS-TKIs

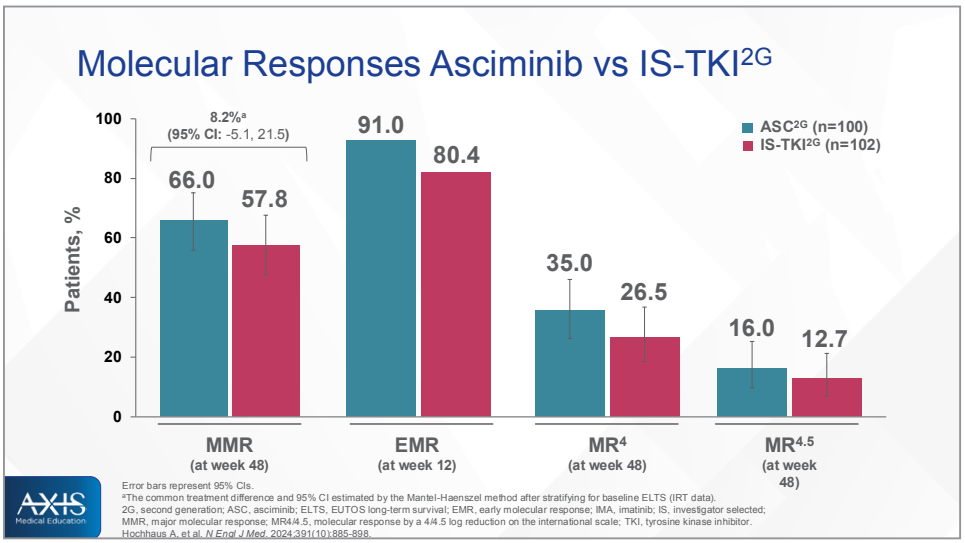


Error bars represent 95% CIs.
ASC, asciminib; EMR, early molecular response; IS, investigator selected; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

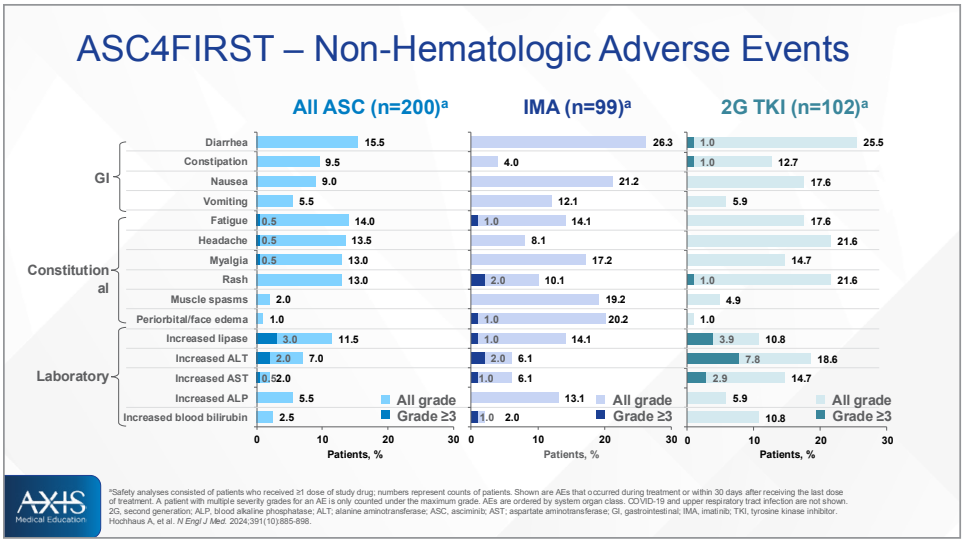
Well, recently, asciminib has shown in a randomized study that in terms of efficacy, it provides a better probability of response. The primary endpoint of this study was major molecule response at about 48 weeks. And compared to any of the tyrosine kinase inhibitors that is approved for frontline therapy, it showed a benefit and improved probability of response, and also for other responses, early molecular response, deep molecular responses.



- Another co-primary endpoint was the comparison versus specifically imatinib. And here we see an even larger benefit of asciminib compared to imatinib.

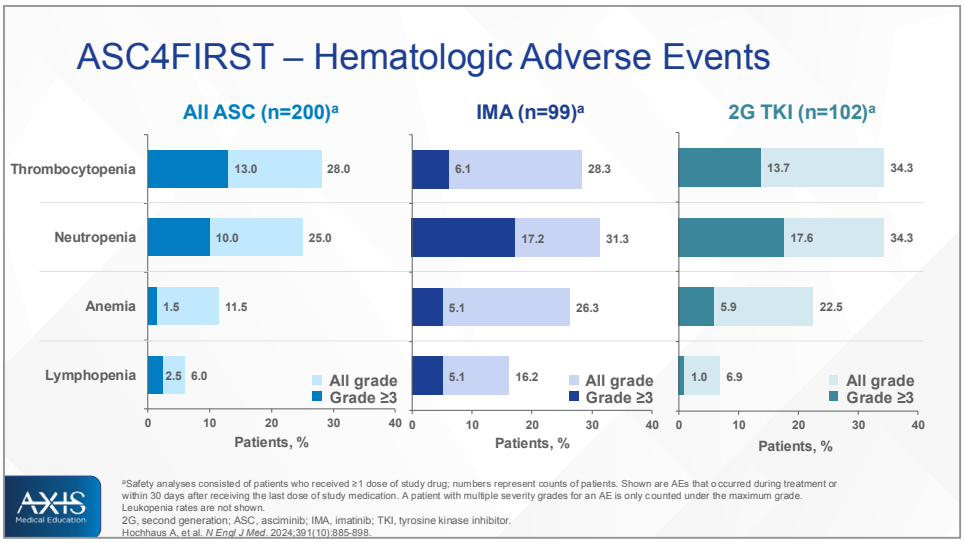


- And although not a primary endpoint and not powered for this outcome, it also showed a benefit compared to the second-generation TKIs, not only for major molecular response at 48 weeks, but also these other efficacy endpoints.



[a]Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of treatment. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs are ordered by system organ class. COVID-19 and upper respiratory tract infection are not shown. 2G, second generation; ALP, blood alkaline phosphatase; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IMA, imatinib; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

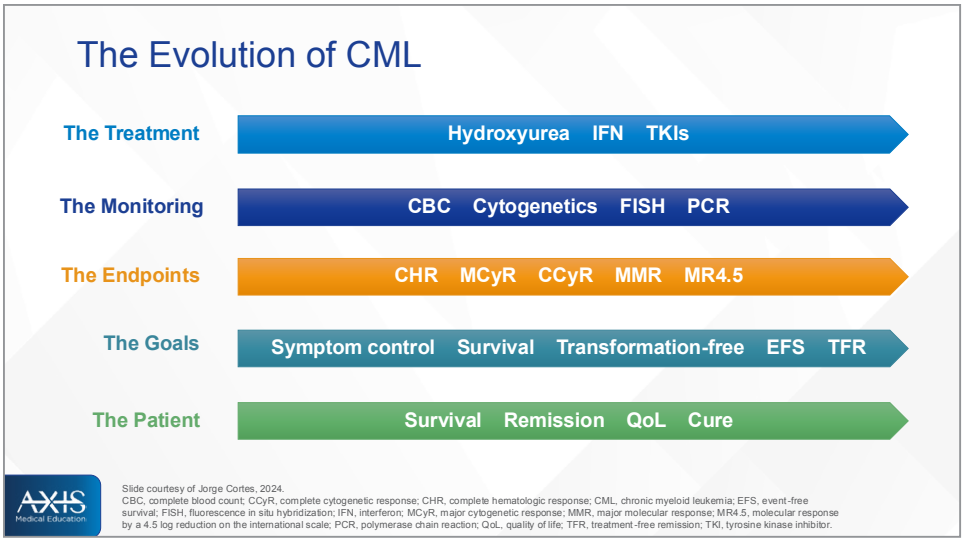
- Importantly, the toxicity profile seemed to be equal or actually better in most of these adverse events. Here you see all the non-hematologic adverse events that all occurred at the same frequency or less, with asciminib.



[a]Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of study medication. A patient with multiple severity grades for an AE is only counted under the maximum grade. Leukopenia rates are not shown.
2G, second generation; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898.

- And the hematologic toxicities that also occurred at the same frequency or less than what we see with second-generation TKIs, showing that asciminib is a very valuable addition to our frontline armamentarium.

- Let us talk now about the treatment goals in chronic phase CML.



- Well, as the treatment has evolved over the years from hydroxyurea to interferon and then to TKIs, and we have had better tools to assess the response of our patients, the goals of therapy have evolved from just symptomatic control, then survival, and more and more towards event-free survival and nowadays treatment-free remission. And for the patient from just wanting to live longer, they now want to live better, emphasizing the quality of life and eventually being cured.

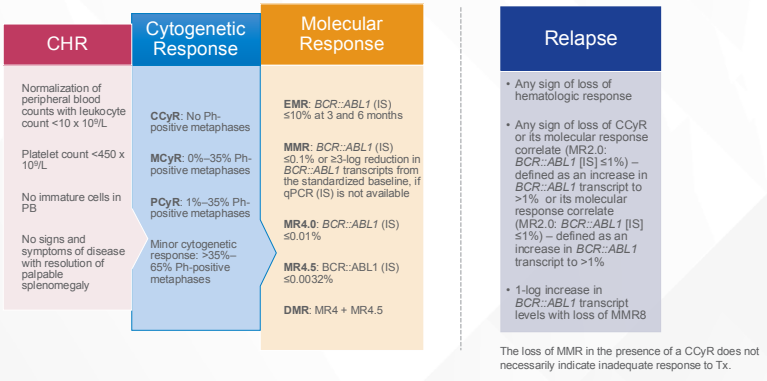
Monitoring Recommendations for CML According to the ELN and NCCN 2020

When	ELN	NCCN
At diagnosis	• CG (BM aspiration) • FISH (in case of Ph-) • PCR	• CG (BM aspiration) • FISH (in case of Ph-) • PCR
During treatment	• PCR (IS) every 3 mo • In patients with atypical translocations, rare or atypical BCR-ABL1 transcripts that cannot be measured by qPCR, treatment failure/resistance to exclude ACA, and with progression to AP or BP • FISH may be needed in patients with atypical transcripts	• Every 3 months after start of therapy • After BCR-ABL1 ≤1% IS, continue every 3 months for 2 years • Then every 3-6 months • Repeat in 1-3 months if in MMR and 1-log increase
Failure, progression	• PCR (IS), mutation analysis, cytogenetics • Immunophenotype for BP	PCR (IS), mutation analysis, cytogenetics
Warning	Repeat PCR in 1-3 months	

ACA, additional chromosomal abnormalities; AP, accelerated phase; BM, bone marrow; BP, blast phase; CG, cytogenetics; CML, chronic myeloid leukemia; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; IS, International Scale; MMR, major molecular response; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; qPCR, quantitative PCR.
Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

So to be able to follow this path, we want to do proper monitoring of our patients. And these are the recommendations by the ELN and the NCCN, very similar. At diagnosis, we want to do a bone marrow aspiration with cytogenetics, FISH, PCR. And very importantly to monitor the patients with PCR every 3 months. And once the patient achieves a stable molecular response, you can continue every 3 to every 6 months the monitoring. Very important to do this regularly to assess the response. If there is failure, we do a assessment of mutations to see if this can guide our further treatments.

Response Definitions



The loss of MMR in the presence of a CCyR does not necessarily indicate inadequate response to Tx.

CCyR, complete cytogenetic response; CHR, complete hematologic response; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; MR, molecular response; PB, peripheral blood; Ph, Philadelphia chromosome; PCyR, partial cytogenetic response; qPCR, quantitative polymerase chain reaction.
NCCN Guidelines. Chronic Myeloid Leukemia (Version 1.2024). NCCN.org.

The goals of response have evolved earlier with interferon. We focused on cytogenetic responses with the ultimate goal was to achieve a complete cytogenetic response. Now we aim for deeper responses, and we go for major molecular response. But importantly, for the deeper molecular responses defined as MR4, meaning BCR-ABL of 0.01% or less, or even better, MR4.5, 0.0032% or less. And those are the goals that we want to achieve over the course of therapy.

The Clinical Significance of Response to Therapy

Response	Translates into:
CCyR	Significantly improved **survival**
MMR	Improvement in **EFS**, possible longer duration CCyR
MR4.5	Possibility of considering **treatment discontinuation**

CCyR, complete cytogenetic response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale.

- What do we get with these responses? Well, complete cytogenetic response is very important because it correlates with improved survival. Major molecular response, once the patient achieves a complete cytogenetic response, correlates with a lower probability of a relapse, essentially a better probability of event-free survival. But deeper molecular responses are important because they provide the possibility of treatment discontinuation.

NCCN Response Milestones

BCR::ABL1 (IS)	3 mo	6 mo	12 mo
>10%	Possible TKI resistance	TKI-resistant disease	
>1% - 10%	TKI-sensitive disease		Possible TKI resistance
>0.1 - 1%	TKI-sensitive disease		TKI-sensitive disease
≤0.1%	TKI-sensitive disease		

Color	Concern	Clinical considerations*	Second-line treatment
Red	TKI-resistant disease	• Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for ACA	• Switch to alternate TKI (other than imatinib), evaluate for alloHSCT
Yellow	Possible TKI resistance	• Consider mutational analysis	• Switch to alternate TKI, or • Continue same TKI (other than imatinib)
Orange	Possible TKI resistance	• Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	• Consider switch to alternate TKI, or • Continue the same TKI if CCyR is achieved
Light Green	Possible TKI resistance	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with the patient
Green	TKI-sensitive disease	• Monitor response	• Continue same TKI

*In all instances evaluate patient adherence and drug interactions
ACA, additional chromosomal abnormalities; allo, allogeneic; CCyR, complete cytogenetic response; HSCT, hematopoietic stem cell transplantation; IS, International Scale; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.
NCCN Guidelines. Chronic Myeloid Leukemia (Version 1.2024). NCCN.org.

- But because of these, the NCCN has provided some guidelines as to what is optimal for the patient to achieve to have the signal that the patient is aiming for that deepest response, best possibility of treatment discontinuation. And it's based on the responses at 3 and 6 and 12 months. And they tell us what is optimal, what is green, what is intermediate, what's yellow or orange, and what is not good, which is the red.

European LeukemiaNet 2020 Recommendations

Time	ELN Optimal	ELN Warning	ELN Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 mo	≤10%	>10%	>10% if confirmed within 1-3 months
6 mo	≤1%	>1-10%	>10%
12 mo	≤0.1%	>0.1 - 1%	>1%
Any time	≤0.1%	>0.1 - 1%, loss of ≤0.1% (MMR)	>1%, resistance mutations, high-risk ACA

ACA, additional chromosomal abnormalities; ELN, European LeukemiaNet; ELTS, EUTOS long-term survival; MMR, mismatch repair.
Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

- The ELN has similar guidelines, probably a little bit more ambitious. They define optimal as a little bit deeper than the NCCN. But ultimately following the same kind of approach in both treatment recommendations.

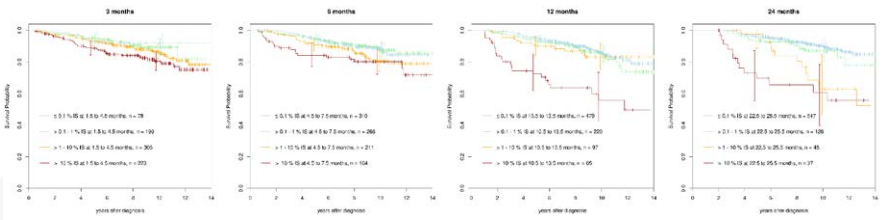
Recommendations for Management According to Response – ELN 2020

- Optimal: Continue
- Failure/resistance: Change
- Warning:
  - Carefully consider continuation or change, depending on patients' characteristics, comorbidities and tolerance
  - Additional qPCR testing may be indicated if the kinetics of the response are not clear, or if toxicity or intolerance cause dose interruptions or reductions

ELN, European LeukemiaNet; qPCR, quantitative polymerase chain reaction.
Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984.

- Now, there's this intermediate category that is important. The optimal, of course, we continue therapy. The failure, we recommend change of therapy when possible. But in that warning or suboptimal response or the yellow or orange, there are different possibilities. Usually, it just means that you need to monitor the patient closer. In some instances, you may want to consider change. In many others, you want to continue the same therapy, but with closer monitoring of the patients.

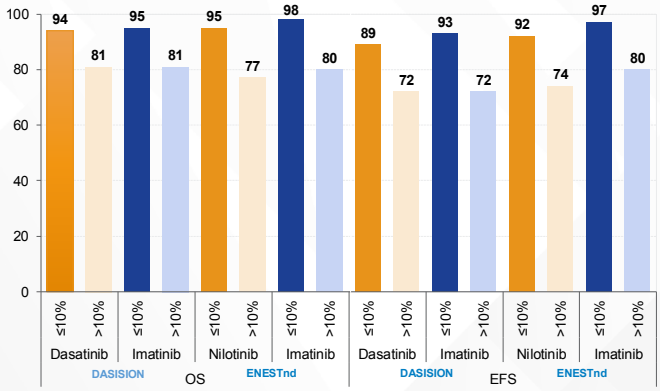
Benefit of TKI Treatment After Failing Milestones



TKI, tyrosine kinase inhibitor.
Lauseker M, et al. *Leukemia*. 2023;37(11):2231-2236.

- And this is emphasized by some recent data from Germany that has shown that patients that at least in the earlier timepoints, 3 and 6 months, that may have a suboptimal response, may still have a similar probability of survival. Therefore, no urgency on changing therapy. When you start getting to 12 months and 24 months, these higher transcript levels do correlate with a poorer outcome.

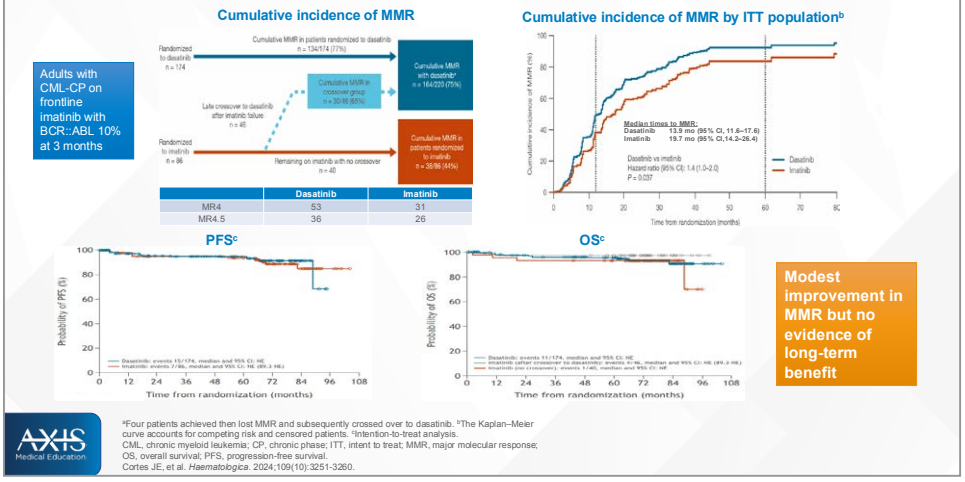
Decreased OS & EFS For Patients Without Early Molecular Response



EFS, event-free survival; OS, overall survival.
Jabbour E, et al. *Blood*. 2014;123(4):494-500. Hughes TP, et al. *Blood*. 2014;123(9):1353-1360.

- One category that has been somewhat controversial is these early molecular responses. We know that patients with more than 10% transcripts at 3 months have a lower probability of progression-free survival and a lower probability of overall survival.

Changing Therapy After Failure to Achieve DMR – The DASISION Study

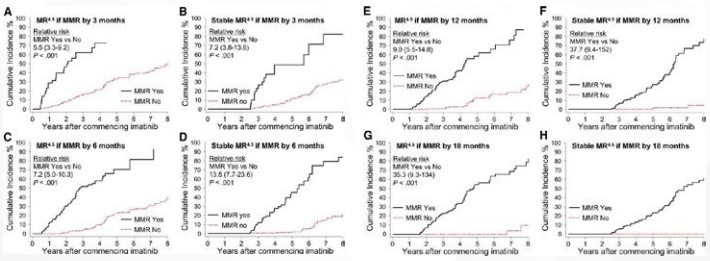


[a]Four patients achieved then lost MMR and subsequently crossed over to dasatinib. [b]The Kaplan–Meier curve accounts for competing risk and censored patients. [c]Intention-to-treat analysis.
CML, chronic myeloid leukemia; CP, chronic phase; ITT, intent to treat; MMR, major molecular response; OS, overall survival; PFS, progression-free survival.
Cortes JE, et al. *Haematologica*. 2024;109(10):3251-3260.

- However, interventions changing therapy, at least from imatinib to in this randomized study, dasatinib, has shown that although you can somewhat improve the probability of major molecular response, you really don't change the probability of progression-free survival and overall survival. So that intervention is not necessarily always indicated, and that's why that possibility of different options that is recommended for these suboptimal responses.

Early Molecular Response Predicts Long-Term DMR

- 423 patients treated with imatinib frontline
- Long-term outcome analyzed according to early hallmarks



DMR, deep molecular response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale.
Branford S, et al. *Blood*. 2013;121(19):3818-3824.

- Now, we have to remember that these 3-month responses are not only important for survival and progression-free survival, but these early responders are the ones that have the best probability of achieving a deep molecular response and eventually being eligible for treatment-free remission. That's why we emphasize that early responses, and the more patients that achieve early molecular responses, the better.

Requirements for TKI Discontinuation – ELN & NCCN 2020

ELN	NCCN
CML 1st **CP only** (Mand)	CP CML. **No history of AP or BP.**
TKI therapy >5 y (>4 y for 2GTKI) (Min)	On approved TKI ≥3 y
e13a2- or e14a2-BCR–ABL1 transcripts (Min)	Prior evidence of quantifiable BCR-ABL1 transcript.
Duration DMR **(MR^4 or better) >2 years** (Min)	**MR^4 for ≥2 years** (≥4 tests, performed ≥3 mo apart)
Access to high quality quantitative PCR using IS with **rapid turn-around for results** (Mand)	Access to a reliable qPCR test with sensitivity of at least MR4.5 IS and that provides **results within 2 wks.**
Patient's agreement to more frequent monitoring after stopping. **Monthly for the 1st 6 mo,** every 2 mo for mo 6-12, and every 3 mo thereafter. (Mand)	**Monthly molecular monitoring** for 6 m, then every 2 mo for the 6 m, and every 3 mo thereafter (indefinitely) is recommended.
Motivated patient with structured communication (Mand)	Age ≥18 years
1st-line therapy or 2nd-line if intolerance was the only reason for changing TKI (Min)	Prompt resumption of TKI within 4 wks of loss of MMR with monthly monitoring until MMR. If no MMR after 3 mo of resumption, order mutation testing and continue monthly molecular monitoring for another 6 mo.
No prior treatment failure (Min)	

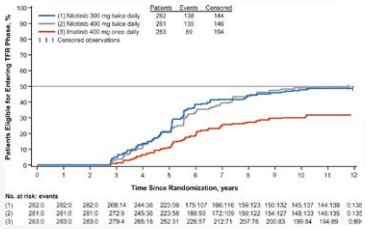
2G, second generation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; ELN, European LeukemiaNet; IS, International Scale; Mand; mandatory; Min, minimal; MMR, major molecular response; MR4/4.5, molecular response by a 4/4.5 log reduction on the international scale; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; qPCR, quantitative PCR; TKI, tyrosine kinase inhibitor.

Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984. NCCN Guidelines. Chronic Myeloid Leukemia (V1.2024). NCCN.org.

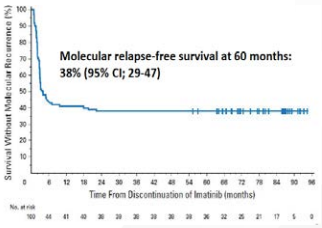
- So talking about treatment-free remission, we know that we want to achieve a sustained deep molecule response. That's a criteria for treatment discontinuation. And then when you stop therapy, you need to monitor the patients very close.

Challenges to Achieving Treatment-Free Remission

Eligibility
ENESTnd[1]



Recurrence
STIM[2]

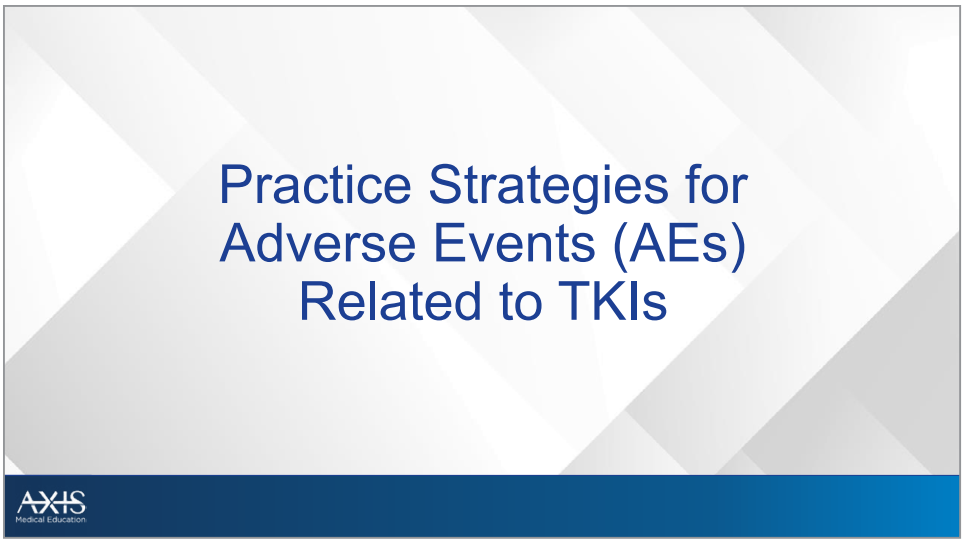


- Only a subset of patients is eligible for treatment discontinuation and many relapse
- TFR success with current strategies ~25-30%

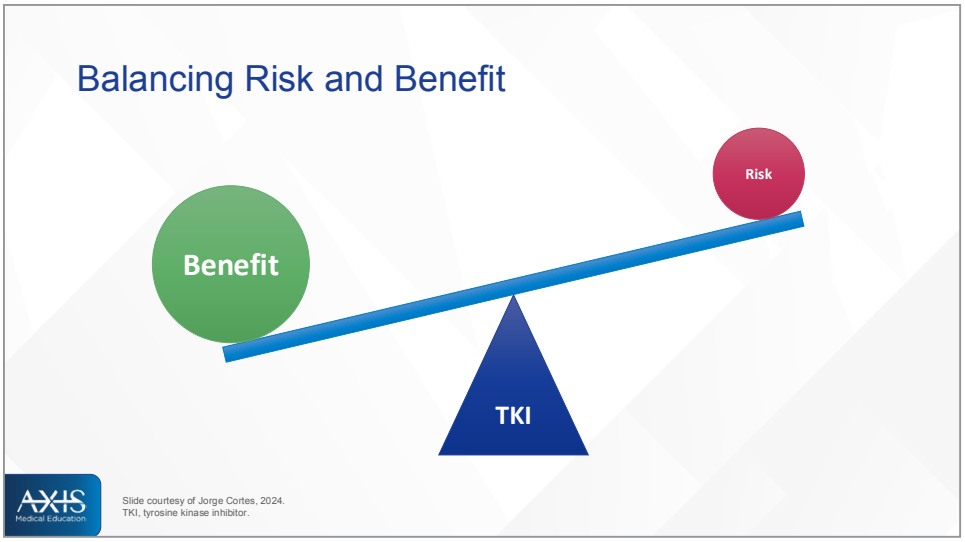
TFR, treatment-free remission.

Kantarjian HM, et al. *Leukemia*. 2021;35(2):440-453. Etienne G, et al. *J Clin Oncol*. 2017;35(3):298-305.

- However, the problem is that at best, 50% of the patients, even with a second-generation TKI, are eligible for treatment discontinuation. And of those who discontinued therapy, about half are going to relapse. Again, emphasizing that we still have room for improvement to improve the probability of treatment-free remission.



- Finally, let's talk about some strategies for the management of adverse events related to tyrosine kinase inhibitors.



- We need to remember these are very good drugs, but ultimately it is a balance between the risk and the benefit of the drugs. We want to obtain the outmost benefit with the drug that we use with the minimum risk for the patients, not only of the serious adverse event, but also of those low-grade toxicities that limit the quality of life of the patients.

Factors Affecting Adherence to TKIs – A Patient's Perspective

Characteristics associated with probability of high adherence (vs low adherence)

- 2546 questionnaires completed by CML patients from 63 countries
- Median age 51 years (range, 18–96); 52% male
- 61% imatinib, 22% nilotinib, 13% dasatinib, 4% other

Response: "high adherence"	Reference category or increment	OR	95% CI	p
Age	Per year	1.022	1.018–1.032	<0.0001
Sex	Female	1.302	1.093–1.558	0.0032
Living with someone	No	–	–	–
Chronic phase	No	–	–	–
Years since diagnosis	<2	0.592	0.475–0.739	<0.0001
Management of side effects	**Not well managed (vs none or well managed)**	**1.679**	**1.366–2.064**	**<0.0001**
Doses	>one	1.800	1.468–2.206	<0.0001
Other medications	No	–	–	–
Time on current medication	<6 months (vs 6 months to 3 years)	–	–	–
	<6 months (vs more than 3 years)	–	–	–
Personal payment obligations	<50 EUR	–	–	–
Use of reminding tools	No	0.740	0.604–0.907	0.036
Informed about risks	No	–	–	–
Satisfied with information on CML	4 stages from 'not at all' to 'very'	1.388	1.186–1.625	<0.0001

CML, chronic myeloid leukemia; EUR, Euros; TKI, tyrosine kinase inhibitor.
Geissler J, et al. *J Cancer Res Clin Oncol*. 2017;143(7):1167-1176.

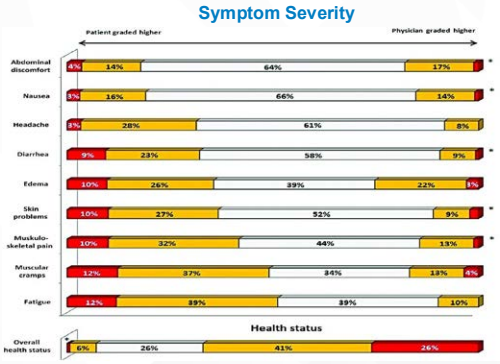
- And this is highlighted by a study that was done by patients for patients, where they asked them: What is your main motivation for stopping treatment? And one of the most important considerations for them is to manage the side effects. They are having side effects that they want to get rid of. We probably cannot call them intolerant, but they're definitely affecting their quality of life.

Patient vs Physician Reporting of Symptoms in CML

- Symptoms scored as "not at all", "a little", "quite a bit" & "very much".

Minor disagreement (difference = 1)

Major disagreement (difference ≥2)



CML, chronic myeloid leukemia.
Efficace F, et al. *Haematologica*. 2014;99(4):788-793.

- And also very important is that when we have assessed the severity of the adverse event as defined by a patient and as defined by a physician, the patients are telling us that we are underestimating the significance of the adverse events in their quality of life. So we should not forget this aspect.

Warnings and Precautions for TKIs – US Prescribing Information

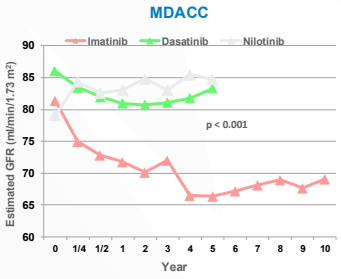
Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
No black-box warnings	No black-box warnings	Black-box warning: QT prolongation, sudden death. Avoid food 2-h prior and 1-h after	No black-box warnings	Black-box warning for arterio-occlusive events, heart failure, venous thromboembolism, hepatoxicity	No black-box warnings
• Fetal harm • Edema, severe fluid retention • Myelosuppression* • Severe congestive heart failure, LV dysfunction • Severe hepatotoxicity • Grade ¾ hemorrhage and GI perforations • Cardiogenic shock/LV dysfunction (conditions with eosinophilia) • Bullous dermatologic reactions • Hypothyroidism • Growth retardation • TLS • Renal toxicity • Motor-vehicle accidents	• Embryo-fetal toxicity • Myelosuppression* • Bleeding events • Fluid retention: pleural effusions • Cardiovascular toxicity • Pulmonary arterial hypertension • QT prolongation • Severe dermatologic reactions • TLS • Effects on growth and development (pediatric)	• Embryo-fetal toxicity • Myelosuppression* • Cardiac and arterial vascular occlusive events • Pancreatitis, elevated lipase • Hepatotoxicity • Electrolyte abnormalities • TLS • Hemorrhage • Fluid retention: pleural effusion, pericardial effusion, ascites, or pulmonary edema • Effects on growth and development (pediatric) • Treatment discontinuation	• Embryo-fetal toxicity • GI • Myelosuppression* • Hepatic • Cardiovascular: cardiac failure, left ventricular dysfunction, and cardiac ischemic events • Fluid retention: pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema • Renal: decline in GFR	• Embryo-fetal toxicity • Hypertension • Pancreatitis • Neuropathy: peripheral, cranial • Hemorrhage: cerebral, GI • Ocular toxicity • Fluid retention: peripheral edema, pleural effusion, pericardial effusion, & peripheral swelling • Cardiac arrhythmias • Myelosuppression* • TLS • Reversible posterior leukoencephalopathy syndrome • Compromised wound healing, GI perforation	• Embryo-fetal toxicity • Pancreatic toxicity • Myelosupression • Hypertension • Cardiovascular toxicity: ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions, cardiac failure • Hypersensitivity

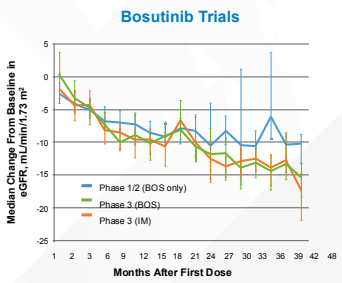
*Myelosuppression: anemia, thrombocytopenia, neutropenia.
CNS, central nervous system; GFR, glomerular filtration rate; GI, gastrointestinal; LV, left ventricular; TKI, tyrosine kinase inhibitor; TLS, tumor lysis syndrome.
GLEEVEC (imatinib mesylate). Prescribing information. Novartis; 2024. SPRYCEL (dasatinib). Prescribing information. Bristol Myers Squibb; 2024. TASIGNA (nilotinib). Prescribing information. Novartis; 2024. BOSULIF (bosutinib). Prescribing information. Pfizer; 2024. ICLUSIG (ponatinib). Prescribing information. Takeda; 2024. SCEMBLIX (asciminib). Prescribing information. Novartis; 2024.

- Well, we know that all of these drugs are generally safe. They're very similar. And there are different precautions that we need to monitor for all the drugs. They are in the label of each one of these drugs, some of them are common, like myelosuppression, some sort of fluid retention and so on. So it is important to familiarize yourself with what kind of expected adverse events you can see with each one of these drugs.

Renal Dysfunction with TKI

- 475 pts treated with imatinib (n=253), dasatinib (n=99), or nilotinib (n=116)
- ARF (↑ creatinine ≥0.3 mg/dl): IM 6%, dasatinib 1%, nilotinib 2%
- CRF (GFR ≤60 ml/min/1.73 m2 x ≥90 d): IM 22%, dasatinib 5%, nilotinib 4%
- No effect of ARF or CRF on outcome





ARF, acute renal failure; IM, imatinib; CRF, chronic renal failure; GFR, glomerular filtration rate; MDACC, MD Anderson Cancer Center; TKI, tyrosine kinase inhibitor.
Yilmaz M, et al. *Cancer.* 2015;121(21):3894-3904. Cortes JE, et al. *Clin Lymphoma Myeloma Leuk.* 2017;17(10):684-695.e6.

- There are some that are not common that we need to remember. For example, a decline in the renal function. With imatinib, we see that in a significant number of patients, a decline in the glomerular filtration rate. With bosutinib, we see that as well, similar to with imatinib. We don't see that as much with dasatinib or nilotinib.

Meta-Analysis of Cardiovascular Events With TKI

Source	Peto Odds Ratio (95% CI)	P value
Bosutinib		
NCT00574873-BELA	2.77 (0.39-19.77)	.31
Subtotal	2.77 (0.39-19.77)	.31
Dasatinib		
NCT00070499	7.39 (0.15-372.38)	.32
NCT00103844-START-R	4.46 (0.23-86.51)	.32
NCT00320190	0.09 (0.00-4.61)	.23
NCT00481247-DASISION	4.86 (1.30-18.12)	0.02
NCT00852566-NordCML006	8.09 (0.16-409.34)	.30
Subtotal	3.86 (1.33-11.18)	.01
Nilotinib		
NCT00471497-ENESTnd	3.31 (1.95-5.61)	<.001
NCT00760877-ENESTcmr	4.45 (0.99-20.02)	.052
Subtotal	3.42 (2.07-5.63)	<.001
Ponatinib		
NCT01650805-EPIC	3.47 (1.23-9.78)	.02
Subtotal	3.47 (1.23-9.78)	.02
Overall	**3.45 (2.30-5.18)**	**<.001**

TKI, tyrosine kinase inhibitor.
Douxfils J, et al. *JAMA Oncol.* 2016;2(5):625-632.

- Arterial occlusive events are also very important. There have been meta-analyses that have shown that compared to imatinib, ponatinib, nilotinib, and dasatinib, they all significantly increase the risk of arterial occlusive events. Bosutinib is perhaps the safest of all these second- generation TKIs, but it's still not quite as safe as imatinib. What we know so far with asciminib is that the risk is much lower than what we expect from ponatinib, probably closer to bosutinib, although maybe slightly higher than that.

TKI Selection Based on Co-Morbidities and Risk of Adverse Events

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

Suggestions should be considered in the whole clinical context of the patient and considering all available options

GI, gastrointestinal; PAH, pulmonary arterial hypertension; TKI, tyrosine kinase inhibitor.
Cortes J. *Blood.* 2020;136(22):2507-2512.

- Based on the known toxicity profile of these drugs, we can select what drug may be more beneficial for a patient, which drug is more likely to be well tolerated. For example, a patient with diabetes, I may not want to use nilotinib as my first choice. If a patient has GI issues, I may not want to use bosutinib. If a patient has lung problems, I may not want to use dasatinib.

  Now, fortunately, newer drugs like asciminib have a very good safety profile, as I showed you, and there are very few instances where I would think not to use asciminib as frontline.

Management of TKI-Associated Myelosuppression

- Monitor CBC weekly 2-3 mo, then every 6-8 wk
- Hold therapy if:
  - ANC <1x109/L
  - Platelets <50x109/L
- Holding for anemia as clinically indicated
- Monitor CBC at least weekly after holding
- Restart when ANC ≥1x109/L, platelets ≥50x109/L
  - If recover in <2 wk, start same dose
  - If recovery ≥2 wk, ⇓ dose (no <300mg/d)
- Use of growth factors, eltrombopag have been reported, not standard

ANC, absolute neutrophil count; CBC, complete blood count; TKI, tyrosine kinase inhibitor.
Quintas-Cardama A, et al. *Cancer*. 2004;100(12):2592-2597. Cortes J, et al. *Cancer*. 2004;100(11):2396-2402. Ault P, et al. *Leuk Res*. 2004;28(6):613-618.

I mentioned myelosuppression is a common feature for nearly all of these drugs. We have parameters that when the patients develop grade 3 toxicity, it's better to hold therapy and then resume when the patient has recovered. It's very important to monitor these.

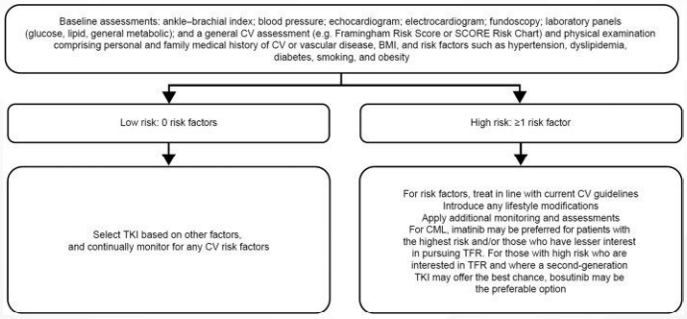
Management of Common Adverse Events With TKI

Toxicity	Management
Nausea, vomiting	Take with food (imatinib), antiemetics
Rash	Topical/systemic steroids
Diarrhea	Imodium, lomotil
Cramps	Tonic water, quinine, calcium gluconate
Fluid retention	Diuretics
Periorbital edema	Preparation H
Bone pain	NSAID
Weight gain	Diuretics, diet

NSAID, nonsteroidal anti-inflammatory drug; TKI, tyrosine kinase inhibitor.

And we have other toxicities that we always need to remember to manage properly to minimize the impact that these toxicities can have on the quality of life of our patients.

Suggested Guidelines and Monitoring for CV Risk Factors in Patients With CML



CML, chronic myeloid leukemia; CV, cardiovascular; SCORE, Systematic Coronary Risk Evaluation; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.
Lipton JH, et al. *Blood Rev.* 2022;56:100968.

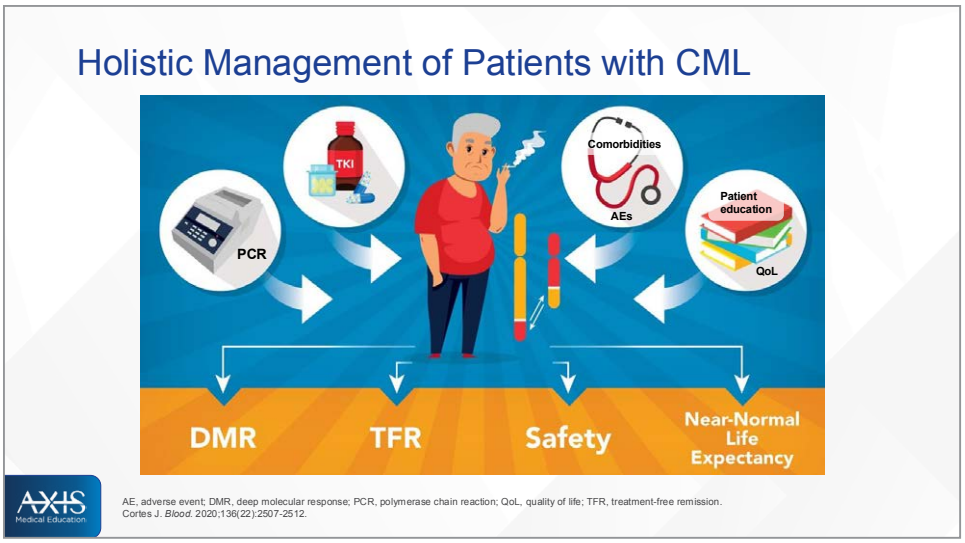
- There have been some guidelines for the management of the cardiovascular risk factors. Very important to assess comorbidities and manage aggressively comorbidities for the patients and use the drugs that may have the lowest risk of arterial occlusive events for patients at very high risk.

Cross-Intolerance Between TKI

- Many AEs occur with various TKI
- No significant cross-intolerance
- Re-occurrence of AEs relatively frequent; treatment discontinuation less frequent
- Cross-intolerance uncommon even for AEs common to 2nd TKI (eg, imatinib discontinuation for diarrhea → 20% bosutinib discontinuation for diarrhea)
- Some AEs occur more frequently with subsequent TKI if they occurred with previous (eg, pleural effusion)
- More cross-intolerance for hematologic AEs
- Some “AEs” likely to persist (eg, fatigue, memory issues)
- Arterio-thrombotic event cross-intolerance not explored

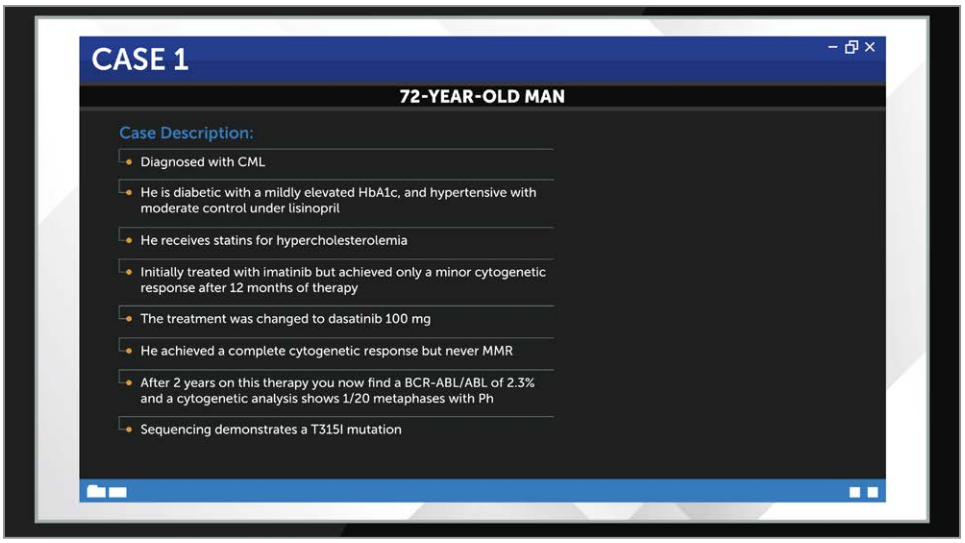
AE, adverse event; TKI, tyrosine kinase inhibitor.
Khoury HJ, et al. *Clin Lymphoma Myeloma Leuk.* 2016;16(6):341-349.e1.
Cortes JE, et al. *Blood.* 2011;117(21):5600-5606.

- And we should not forget that the patient, there may be some cross intolerance between TKI, some adverse events are common to all of them. Myelosuppression, I mentioned. Lipase elevation. So managing doses and trying to avoid those where we can expect more cross intolerance is important.



- Ultimately, we need to remember that the patient, we don't just have to treat them with a TKI and monitor the PCR, the patient is an individual that has comorbidities, that has goals, that has a quality of life that we need to preserve. And to do a holistic management of our patient, we need to integrate all of these so that we can do the best for our patients.

- Let us talk now about a patient.



- We have a 72-year-old gentleman diagnosed with CML. He has diabetes with a mildly elevated hemoglobin A1c. Has hypertension with some control on the lisinopril, though not perfect. He is taking statins for hypercholesterolemia. And was initially treated with imatinib. Only achieved a minor cytogenetic response after 12 months, and therefore the treatment was changed to dasatinib 100 mg daily.

  So he did achieve a complete cytogenetic response, but never a major molecular response. And then eventually he has an increase in the transcript levels. You do a mutation analysis, and you find that the patient has a mutation T315I.

Your recommendation now is:

a) Increase dasatinib to 140 mg
b) Change to imatinib 600 mg daily
c) Change to nilotinib 400 mg twice daily
d) Change to bosutinib 500 mg daily
e) Change to ponatinib 30 mg daily
f) Change to asciminib 200 mg twice daily
g) SCT

- So at this point, what would you recommend for the patient? To increase the dose of dasatinib? Change to imatinib 600 mg daily? Change to nivolumab 400 mg twice daily? Change to bosutinib 500 mg daily? Change to ponatinib 30 mg daily? Change to asciminib 200 mg twice daily? Or a stem cell transplant?

  Well, in my opinion, the optimal therapy for this patient is asciminib 200 mg twice daily.

Rationale

- Imatinib, dasatinib, nilotinib or bosutinib have no clinical benefit in patients with T315I
- Ponatinib is an adequate option, but the dose is important
- These patients in particular require a full dose of 45 mg daily to experience optimal benefit
- Because of the patient's co-morbidities, asciminib is a better option for this patient
- Although SCT can be considered, the age and co-morbidities may make this a higher risk proposition

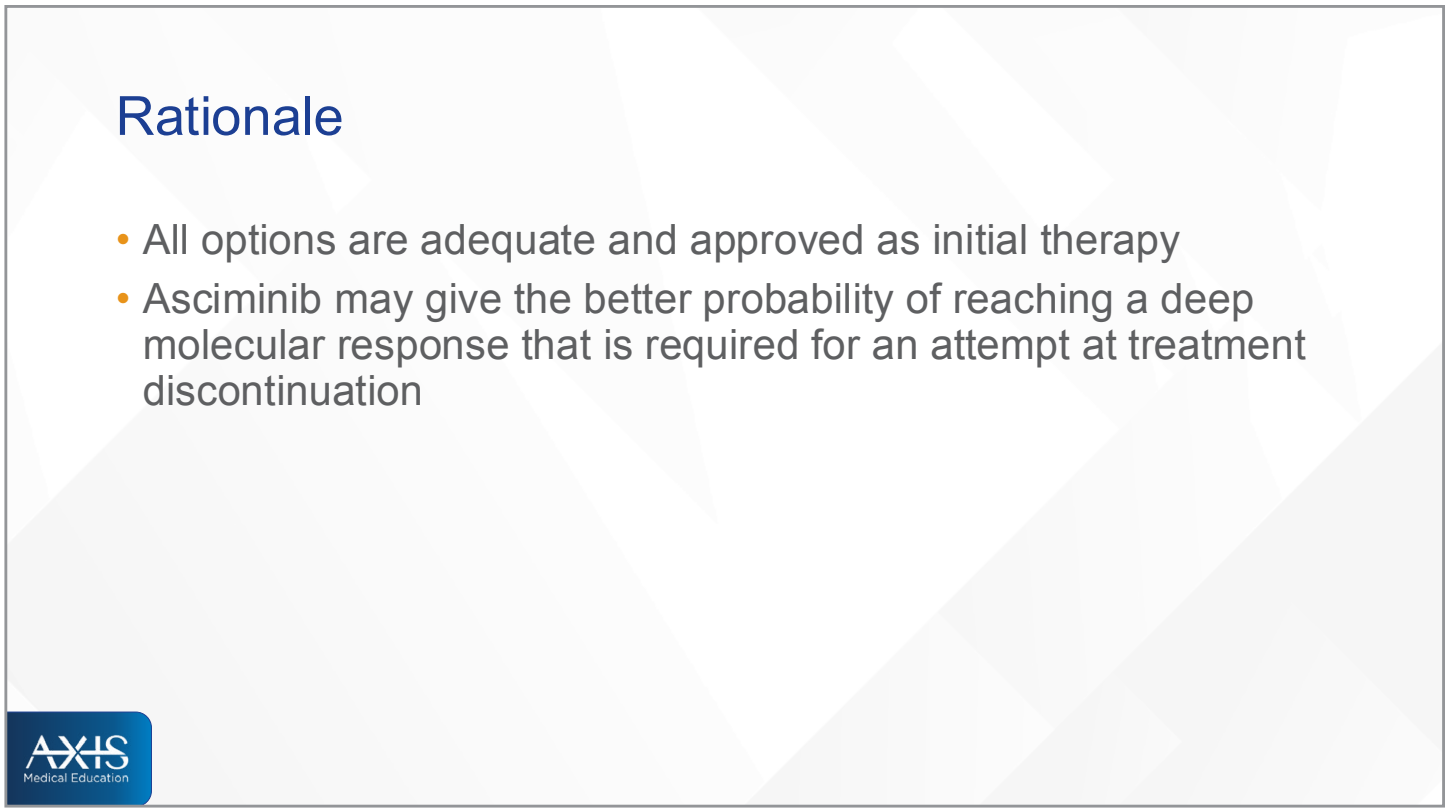
AXIS Medical Education

We know that imatinib, dasatinib, nilotinib, or bosutinib have no clinical benefit against the T315I so those are not good options. Ponatinib does have activity against T315I, but it is very it is very dose dependent. Clearly, those patients are the ones that mostly need a dose of 45 mg daily to achieve a response. The probability of response drops significantly when you use 30 mg daily. Now, this patient has comorbidities, so using 45 mg daily could be a problem. So the ponatinib could be a good choice. I think that asciminib with a better toxicity profile, it provides a greater probability of benefit. Now, transplant is definitely a consideration. But again, with the age and the comorbidities of the patient, I would at least give it a trial with asciminib to see if we can get a good response. And we know that about 60% of patients can get a major molecular response, so I think it is the best possibility for this patient.

- Let's review another patient now. A 35-year-old female patient is diagnosed with CML. Newly diagnosed. Comes to you. You do a confirmation with a bone marrow. She is in chronic phase, has no additional chromosomal abnormalities. The Sokal risk is low.

  Now, she tells you she's interested in eventually having a family, and therefore for her, the possibility of stopping therapy at some point, and the sooner the better, is very important.

- So with that in mind, what is your recommendation among the drugs that are approved as initial therapy for CML? You want to start on imatinib? Dasatinib? Nilotinib? Bosutinib? Or asciminib?



Well, all of these options are good, no question. Now, certainly we know that second-generation TKIs give a better probability of treatment-free remission than imatinib. However, based on the data from the ASC4FIRST study, we know that asciminib gives early responses, by 3 months and early molecular responses by 48 weeks, the major molecular response higher than all of the other tyrosine kinase inhibitors that are approved for frontline therapy. So with that in mind, I think it is likely that asciminib will give this patient the better probability of having a treatment discontinuation, and perhaps earlier than any of the other drugs. So that would be my first choice for this patient.

Thank you for your attention.

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

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

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

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

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

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