5 Minute JournalClub

POST-ASH Issue 2, 2014

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CME Information

LEARNING OBJECTIVES

- Evaluate the impact of early molecular response or dose interruption of tyrosine kinase inhibitors (TKIs) on the prognosis of patients with CML.
- Compare and contrast the benefits and risks of nilotinib versus imatinib therapy in patients with newly diagnosed chronic-phase CML.
- Appraise recent clinical data on the effect of switching to nilotinib in patients with a suboptimal response to imatinib therapy versus continuation of imatinib at a higher dose.
- Analyze the outcomes of the STIM1 and STIM2 studies of discontinuation of imatinib in patients with a deep molecular response, and consider these results in the management of CML.
- Assess the efficacy and safety of ponatinib as initial therapy and in patients with TKI-resistant CML.

CME Information (Continued)

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FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

CME Information (Continued)

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No real or apparent conflicts of interest to disclose.

5 MinuteJournalClub

POST-ASH Issue 2, 2014

Sometimes I have to pinch myself to see if this is a dream or if I really have a job listening to and learning from the great minds in our chosen field. Last week was a perfect reminder of just how cool "work" can be when within the space of a few days my calendar included extensive interviews with Drs Jorge Cortes and then Hagop Kantarjian. As deputy chair and chair of MD Anderson's Department of Leukemia, respectively, these 2 investigators lead a unique clinical and research powerhouse that has contributed perhaps as much to the care of patients with these and other related hematologic disorders as any other institution in the world.

Jorge E Cortes, MD

Hagop M Kantarjian, MD

To get a sense of just how prolific they are, peruse the 2013 ASH abstracts and you will find that Drs Cortes and Kantarjian helped author 103 oral presentations and posters, including 30 on chronic myelogenous leukemia (CML) alone. As such, and not surprisingly, each of these conversations focused heavily on that disease — which has

become the poster child for targeted oncologic treatment — and below find the bottom line on their thoughts about how the data sets from New Orleans helped address the following important questions in CML.

1. What are the key early markers of response, and when should consideration be given to switching to another tyrosine kinase inhibitor (TKI)?

Another MD Anderson leukemia maven and chair of the NCCN CML guidelines committee, Dr Susan O'Brien frequently reinforces the important concept that although there are many reasons to seek deep molecular responses (DMR), the classic and most important endpoint is complete cytogenetic response (CCyR) — a milestone that is achieved faster and more frequently with the second-generation agents, nilotinib and dasatinib. The question of whether suboptimal molecular response should trigger a switch to another TKI ties directly into the issue of selection of up-front therapy and whether long-term outcomes are compromised when residual disease is present.

Equally relevant and looming in the background is a fascinating question of "quality" and cost associated with oncology care. Specifically, imatinib is due to go off patent in January 2015, and it is expected that this will dramatically lower the annual tab (about $90,000 with imatinib, and with nilotinib and dasatinib closer to $100,000). With a current prevalence of about 100,000 CML cases in the United States alone — a number that will likely double in the next 3 decades before plateauing — researchers, clinicians and policy makers will almost

certainly continue the debate about the value of starting with imatinib (the soon-to-be less costly and perhaps slightly less effective agent) and reserving second-generation treatment for patients with higher-risk disease and those with suboptimal initial responses to imatinib. How these potential resource savings stack up against others in oncology related to, for example, futile care and unnecessary imaging will be discussed extensively, and more globally Dr Kantarjian has taken a leadership role in organizing a group of "CML experts" (including Dr Cortes) who have been on a dedicated and major offensive attacking the current CML cost structure.

At ASH we witnessed a number of related papers that tie in to the issue of imatinib versus the rest, including the **36-month update** of the ENESTcmr study. This landmark Phase III effort demonstrated that among patients in CCyR but with detectable BCR-ABL transcripts, those randomly assigned to switch to nilotinib achieved more DMRs compared to those continuing on imatinib (47% with nilotinib versus 33% with imatinib at 36 months). This benefit came with greater toxicity, which may in part be attributable to the trial design in that patients who transitioned to nilotinib were already tolerating imatinib well.

On a similar note, an ASH data set presented by Dr Cortes from the Phase III **LASOR trial** revealed that switching to nilotinib versus escalating the dose of imatinib in patients who experienced suboptimal response resulted in a better rate of CCyR at 6 months (49% versus 42%, respectively), although the findings were not statistically significant (p = 0.3844).

Finally, a **retrospective analysis** of 3- and 6-month responses in early trials of imatinib demonstrated that some patients who achieve an optimal response by 6 instead of 3 months have long-term outcomes comparable to those who achieved an optimal response at 3 months, suggesting that waiting a few additional months before considering a change in treatment is a rational approach.

Proponents of using imatinib as initial treatment in standard-risk situations often point out that so far, no survival benefit has been demonstrated using the second-generation agents — possibly because these drugs also effectively rescue patients experiencing disease progression on imatinib. Thus, although DMR is an intuitively appealing goal, until further research identifies more accurately who can cease TKI treatment (now there's a cost saving!), there will be debate and controversy about what to start with and when and if to make a switch. This is particularly true as more follow-up occurs with the landmark second-generation trials, some of which are documenting more long-term complications, such as the 5-year update of the **ENESTnd trial** presented at ASH that now shows not only deeper molecular responses with nilotinib but also an increasing number of cardiovascular events.

2. Are there situations in which it is safe to discontinue TKI treatment?

At ASH we saw more data from **2 French studies** (STIM 1 and 2) attempting to define the outcomes of patients with prolonged (more than 2 years) DMRs who discontinued treatment. These studies and others have documented that when

taken off therapy more than half the patients experience relapse — usually quickly — and the remainder fare well off treatment. Importantly, although most patients experiencing relapse can be effectively salvaged with the same or a different TKI, at this point there is no way to pick who will do well without treatment and therefore neither professor employs this approach outside a trial setting, although Dr Kantarjian notes that if ongoing research shows how to identify these patients, both long-term toxicity and financial costs can be avoided.

Interestingly, Dr Cortes commented on one situation in which a variation of this stopping strategy is often a consideration — specifically, in women with CML who wish to become pregnant — and so far he has managed about 2 dozen carefully selected patients, most of whom have not required retreatment until after childbirth.

Another fascinating and somewhat **related ASH report** documented that in a major Phase III trial of dasatinib versus imatinib patients starting treatment who missed doses due to toxicities like cytopenias had significantly worse 3-month outcomes. Importantly, this effect appears to occur when missing even 1 dose (in the case of imatinib) and increases with the number of doses missed.

3. What is the current role of ponatinib?

In December 2012 this pan-BCR-ABL "super TKI" was approved by the FDA, but last October it was pulled off the market due to toxicity concerns, mainly

arteriothrombotic events. By December ponatinib was once again available, accompanied by a new black box warning and a Risk Evaluation and Mitigation Strategy program designed to help clinicians more effectively evaluate the risks and benefits of using the agent.

In discussing ponatinib, Dr Kantarjian noted that the approved daily dose of 45 mg not uncommonly leads to toxicities such as hypertension, vasospastic reactions, pancreatitis and skin rashes that are not acceptable in the up-front setting, where safer effective choices exist. In this regard an MD Anderson single-arm **pilot study** of 51 patients presented at ASH was amended to include a starting dose of 30 mg daily. Regardless, accrual was suspended in October, as in another major Phase III up-front study comparing ponatinib to imatinib.

However, in discussing the updated ASH results from the pivotal **PACE trial** in relapsed disease, Dr Kantarjian reiterated that ponatinib, when used in that indicated setting, can be a life-altering therapy, particularly for those with BCR-ABL T315I mutations. He also pointed out that the vaso-occlusive reactions that have been observed with this drug occur infrequently with the other TKIs.

Next on this series, we provide an update on ASH reports in lymphoma, including encouraging data sets on the nonchemotherapy combination of lenalidomide and rituximab, the antibody-drug conjugate brentuximab vedotin and a fascinating paper on crizotinib in ALK-positive lymphoma.

Neil Love, MD
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Achievement and Maintenance of Deeper Molecular Response by Switching to Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) with Residual Disease on Long-Term Imatinib: ENESTcmr 36-Month Follow-Up

Leber B et al.

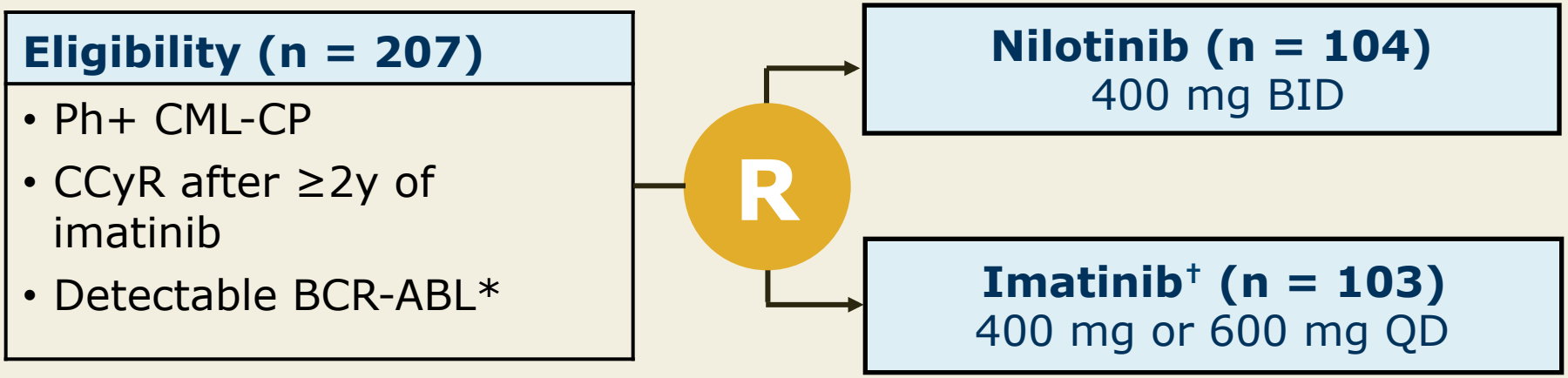
Proc ASH 2013;Abstract 94.

Background

- Sustained deep molecular response is the main eligibility requirement for most treatment-free remission studies.
- The ENESTnd study demonstrated that patients with CML who received nilotinib were more likely to attain deep molecular responses compared to those who received imatinib (*Leukemia* 2012;26:2197).
- The 24-month results of the Evaluating Nilotinib Efficacy and Safety in clinical Trials — complete molecular response (ENESTcmr) trial reported that patients with CML-CP with minimal residual disease after ≥2 years of imatinib achieved deeper molecular responses after switching to nilotinib (*Proc ASCO* 2013;Abstract 7053).
- **Study objective:** To report updated results for ENESTcmr comparing nilotinib to imatinib with a follow-up of 36 months.

Leber B et al. *Proc ASH* 2013;Abstract 94.

ENESTcmr Trial Design



* By real-time quantitative PCR (RQ-PCR) with sensitivity of ≥4.5 log; † Same dose of imatinib continued

CCyR = complete cytogenetic response

- Crossover from nilotinib to imatinib for detectable BCR-ABL at 2 y or treatment failure
- Rates of major molecular response (MMR; BCR-ABL ≤0.1% by International Scale [IS]) and $MR^{4.5}$ ($BCR\text{-}ABL^{IS}$ ≤0.0032%) evaluated by RQ-PCR.

Leber B et al. *Proc ASH* 2013;Abstract 94.

Cumulative Incidence of $MR^{4.5}$ in Patients without $MR^{4.5}$ at Baseline (ITT)

Response	Nilotinib (n = 104)	Imatinib (n = 103)	*p*-value
At 12 mo	33%	14%	0.002
At 24 mo	43%	21%	0.0006
At 36 mo	47%	33%*	0.0453

* 9% of these patients had crossed over to nilotinib

- In a subgroup analysis when only responses to crossover were counted, 47% vs 24% of patients in the nilotinib and imatinib arms, respectively, achieved $MR^{4.5}$ ($p = 0.0003$)
- Median time to $MR^{4.5}$ was accelerated by more than 1 y in the nilotinib arm (24 mo vs not reached in the imatinib arm, $p = 0.0011$)

Leber B et al. *Proc ASH* 2013;Abstract 94.

Achievement of Undetectable BCR-ABL in Patients Who Had Detectable BCR-ABL at 24 Months

Detectable BCR-ABL at 24 mo	Undetectable BCR-ABL by 36 mo
Imatinib (n = 78)	
Crossed over to nilotinib (n = 43)*	26%
Continued imatinib (n = 35)†	0%
Nilotinib (n = 52)	
Continued nilotinib (n = 52)	8%

* 3 patients crossed over to nilotinib with undetectable BCR-ABL

† Patients who were eligible for crossover but did not cross over

Leber B et al. *Proc ASH* 2013;Abstract 94.

Safety 1 Year After Randomization or After Crossover

Adverse event (AE)	Nilotinib, 1 y (n = 101)	Crossover to nilotinib (n = 46)
Any AE	88%	74%
Grade 3/4 AE	29%	28%
AEs leading to discontinuation	9%	15%
Serious AE	4%	9%
Deaths	1%	0%

Cardiovascular events at 36 mo — Nilotinib arm: 12/101; imatinib arm: 2/103; crossover to nilotinib: 2/46

Leber B et al. *Proc ASH* 2013;Abstract 94.

Author Conclusions

- Switching to nilotinib resulted in significantly deeper molecular responses in patients with detectable disease on imatinib.
- Responses to nilotinib were achieved faster than those to imatinib, with a median time to $MR^{4.5}$ more than a year shorter.
- No patient who remained on imatinib with detectable BCR-ABL at 2 years achieved undetectable BCR-ABL by 3 years (n = 35).
- Numerically, more cardiovascular events were reported in the nilotinib arm than in the imatinib arm.
- An additional 12 months of follow-up support the strategy of switching to nilotinib in patients seeking to attain deep molecular responses.

Leber B et al. *Proc ASH* 2013;Abstract 94.

Investigator Commentary: ENESTcmr 36-Month Follow-up — Deep Molecular Responses by Switching to Nilotinib in CML-CP

The results of the ENESTcmr trial indicate that more patients achieved a deep molecular response after switching to nilotinib compared to those who continued on imatinib.

However, more patients also developed adverse events and discontinued therapy because of side effects in the nilotinib arm compared to the imatinib arm. This is slightly counterintuitive because nilotinib is thought to be better tolerated and is administered to patients who are intolerant to imatinib. I believe part of the reason for this is that patients were used to the side effects with imatinib. It was not that they were intolerant to nilotinib, but when they were switched to nilotinib the side effects they experienced were different. We have to consider whether the tradeoff of benefits versus potential side effects in achieving a complete molecular response is worth it.

Treatment discontinuation can be considered after achieving a complete molecular response, which is beneficial. However, that's not something that we should be recommending to every patient.

Interview with Jorge E Cortes, MD, January 24, 2014

Switching to Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase with Suboptimal Cytogenetic Response on Imatinib: Results from the LASOR Trial

Cortes JE et al.

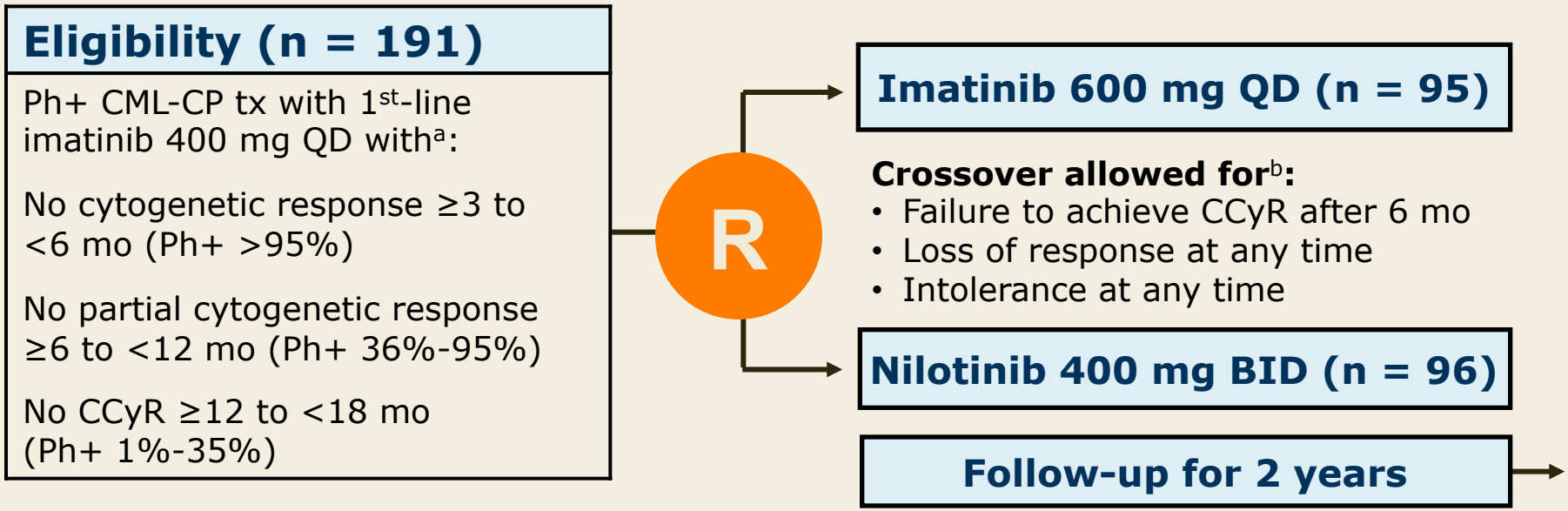
Proc ASH 2013;Abstract 95.

Background

- The availability of more potent TKIs in the front-line setting has led to expectations of earlier, deeper responses in consensus recommendations (*Blood* 2013;122:872; *J Natl Compr Canc Netw* 2013;11:1327).
- Inferior long-term outcomes and poor prognosis are associated with suboptimal response to front-line tyrosine kinase inhibitor (TKI) therapy by today's standards in chronic myeloid leukemia (CML) (*Cancer* 2009;115:3709; *Blood* 2008;112:4437).
- The best approach for patients with suboptimal response is not established.
- **Study objective:** To compare the effects of imatinib dose escalation to those of switching to nilotinib in patients with Philadelphia chromosome-positive (Ph+) CML in chronic phase (CML-CP) who have experienced suboptimal response to front-line imatinib.

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

LASOR: Phase III Study Design



- **Primary endpoint:** Complete cytogenetic response (CCyR) at 6 months
- **Key secondary endpoint:** Major molecular response (MMR) at 12 months
- **Other secondary endpoints:** Event-free survival (EFS), progression-free survival (PFS), overall survival (OS) at 24 months

[a] All patients had complete hematologic response (CHR) at study entry.
[b] Crossover could also be allowed for other reasons, as approved by the study management committee.

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Primary Endpoint: CCyR at 6 Months (ITT)

Treatment	CCyR 6 mo	*p*-value
Nilotinib 400 mg BID (n = 96)*	49%	$p = 0.3844$
Imatinib 600 mg QD (n = 95)†	42%	

* In the nilotinib arm, 6 patients crossed over to imatinib and 10 patients were nonevaluable.

† In the imatinib arm, 15 patients crossed over to nilotinib and 7 patients were nonevaluable.

- By 6 months after randomization: 0 of 6 patients who received nilotinib and crossed over to imatinib vs 6 of 15 patients who crossed over to nilotinib achieved CCyR after crossover.
- Median time to crossover among 6 responders who crossed over from the imatinib arm: 2.75 months.

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Key Secondary Endpoint: MMR at 12 Months (ITT)

Treatment	MMR 12 mo	*p*-value
Nilotinib 400 mg BID (n = 96) Crossover to imatinib*	35% 1%	*p* = NR
Imatinib 600 mg QD (n = 95) Crossover to nilotinib†	16% 9%	

* In the nilotinib arm, 7 patients crossed over to imatinib and 26 patients were nonevaluable.

† In the imatinib arm, 35 patients crossed over to nilotinib and 26 patients were nonevaluable.

- At 12 mo after randomization: 1 of the 7 nilotinib patients who crossed over to imatinib vs 9 of the 35 imatinib patients who crossed over to nilotinib achieved MMR
- Median time to crossover: 4.8 mo and 6.9 mo in the 1 and 9 responders who crossed over from the nilotinib and imatinib arms, respectively

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Select Any-Grade Adverse Events — Nonhematologic

	Before crossover		After crossover	
	N 400 mg BID (n = 96)	I 600 mg QD (n = 93)	N → I (n = 13)	I → N (n = 56)
Rash	23%	4%	8%	16%
Headache	15%	6%	31%	13%
Arthralgia	9%	3%	8%	4%
Fatigue	6%	3%	—	—
Myalgia	8%	1%	—	—
Pruritus	8%	—	—	5%
Diarrhea	6%	15%	8%	2%
Nausea	5%	15%	15%	5%
Vomiting	4%	11%	23%	7%
Eyelid edema	1%	11%	—	—

N = nilotinib; I = imatinib

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Select Grade 3/4 Adverse Events — Hematologic/Laboratory Abnormalities

	Before crossover		After crossover	
	N 400 mg BID (n = 96)	I 600 mg QD (n = 93)	N → I (n = 13)	I → N (n = 56)
Newly occurring or worsening hematologic abnormalities				
Thrombo-cytopenia	15%	10%	15%	16%
Leukopenia	5%	6%	8%	9%
Anemia	5%	1%	8%	5%
Newly occurring or worsening biochemical abnormalities				
Phosphate	9%	8%	31%	2%
Magnesium	5%	2%	—	—
Bilirubin (total)	4%	—	—	7%
Potassium	1%	5%	—	2%

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Author Conclusions

- LASOR is the only randomized trial to have examined the potential benefit of switching to nilotinib versus imatinib dose escalation in patients with Ph+ CML-CP with suboptimal responses.
- The primary endpoint of LASOR was not met (CCyR at 6 mo = 49.0% vs 42.1%; $p = 0.3844$).
- Nilotinib was associated with higher MMR rates at 12 months.
- Accounting for crossover, higher rates of CCyR at 6 months (data not shown) and MMR at 12 months were reported with nilotinib versus dose-escalated imatinib.
- The suboptimal responses in this trial would now be considered "failure" according to updated 2013 European LeukemiaNet recommendations.
- In accordance with 2013 European LeukemiaNet recommendations, patients with "failure" responses should switch therapy.

Cortes JE et al. *Proc ASH* 2013;Abstract 95.

Investigator Commentary: The LASOR Trial — Switching to Nilotinib for Patients with CML-CP and Suboptimal Response to Imatinib

The LASOR study was developed with the intent of evaluating suboptimal response, a term that is typically used to refer to patients who are clearly not in treatment failure but whose response at 6 or 12 months is not what we would like it to be. Patients who had experienced suboptimal response to front-line imatinib were randomly assigned to either an increased dose of imatinib or a switch to nilotinib. The CCyR at 6 months after intervention was better for patients who received nilotinib, although the values were not statistically significant. This was the first look at the data, but they do suggest that changing to nilotinib may be appropriate for these patients to obtain a better response rate.

Interview with Jorge E Cortes, MD, January 24, 2014

This study can be interpreted in different ways, and my opinion is that we have not yet proven that early switching to a second-generation TKI before a cytogenetic relapse on imatinib improves the survival of patients. A similar study by Hughes and colleagues (ASH 2012, Abstract 694) showed that by changing to the second TKI you improve on the incidence of molecular responses but you do not improve survival, which is an important point.

Interview with Hagop M Kantarjian, MD, January 24, 2014

Any BCR-ABL Reduction Below 10% at 6 Months of Therapy Significantly Improves Outcome for CML Patients with a Poor Response at 3 Months

Branford S et al.

Proc ASH 2013;Abstract 254.

Background

- The molecular response at 3 months after commencement of tyrosine kinase inhibitor (TKI) therapy for patients with CML has prognostic significance.
- Analyses by Neelakantan et al suggest that additional measurement of BCR-ABL1 transcript levels at 6 months adds little prognostic value to the 3-month result (*Blood* 2013;121:2739).
- However, another recent study based on cytogenetic response concluded that for patients with poor response at 3 months, assessing the response at 6 months may provide a better predictor of long-term outcome (*Haematologica* 2013;98:1686).
- **Study objective:** To evaluate the prognostic importance of assessing both the 3- and 6-month molecular response for patients with chronic-phase CML (CML-CP).

Branford S et al. *Proc ASH* 2013;Abstract 254.

Study Design

- The study included patients with CML-CP enrolled in consecutive clinical trials of first-line imatinib from 2000 to 2011 (n = 528).
  - Many patients were treated before alternative TKIs were available, but 89 switched therapy.*
- The utility of BCR-ABL as a predictor of death (overall survival), progression (AP/BC: progression-free survival), treatment failure (failure-free survival) and major molecular response (MMR) was assessed.
- Patients were divided according to the 2013 European LeukemiaNet (ELN) definitions of 3- and 6-month molecular response:
  - 3 mo, optimal ≤10% or warning >10%
  - 6 mo, optimal <1%, warning 1-10% or failure >10%

* Study was not powered to assess the effect of treatment intervention

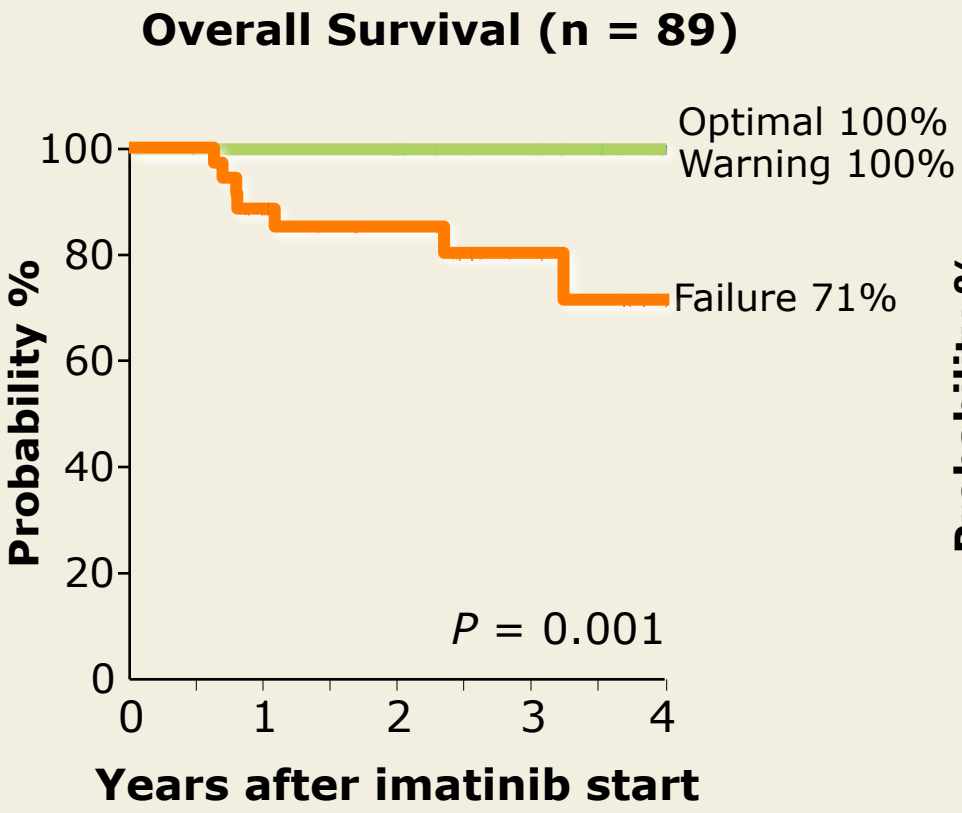
Branford S et al. *Proc ASH* 2013;Abstract 254.

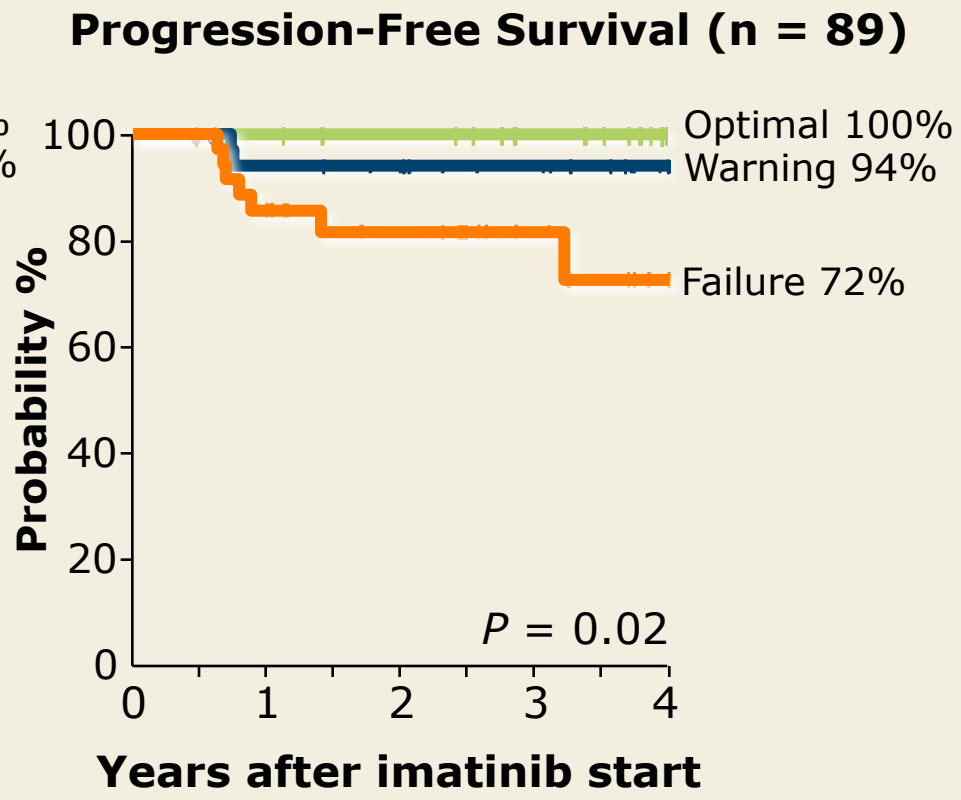
Outcomes at 4 Years for Patients in the Optimal (≤10%) versus Warning (>10%) Category at 3 Months

Outcome at 4 y	Optimal (n = 406)	Warning (n = 100)	*p*-value
Overall survival	97%	89%	0.0003
Progression-free survival	99%	86%	<0.0001
Failure-free survival	83%	46%	<0.0001
MMR	89%	42%	<0.0001

Branford S et al. *Proc ASH* 2013;Abstract 254.

Survival of Patients in the 3-Month Warning Category Grouped by Category at 6 Months





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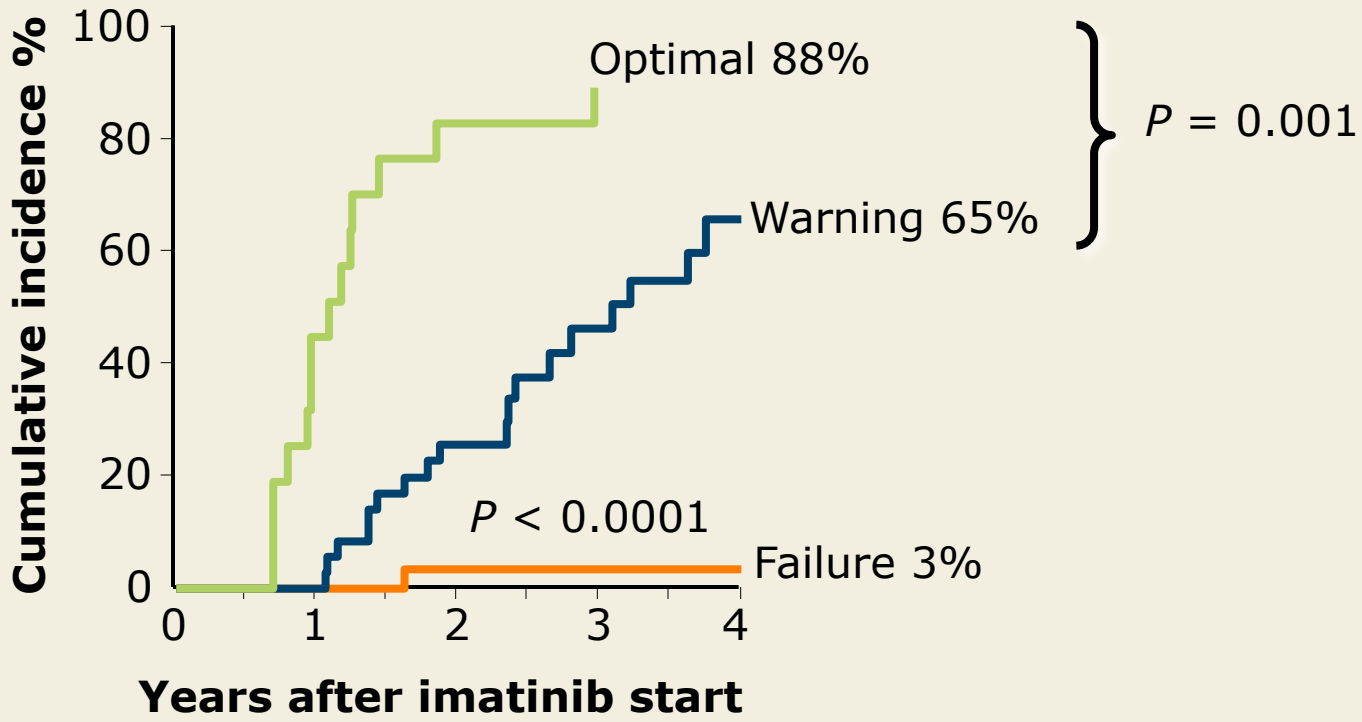
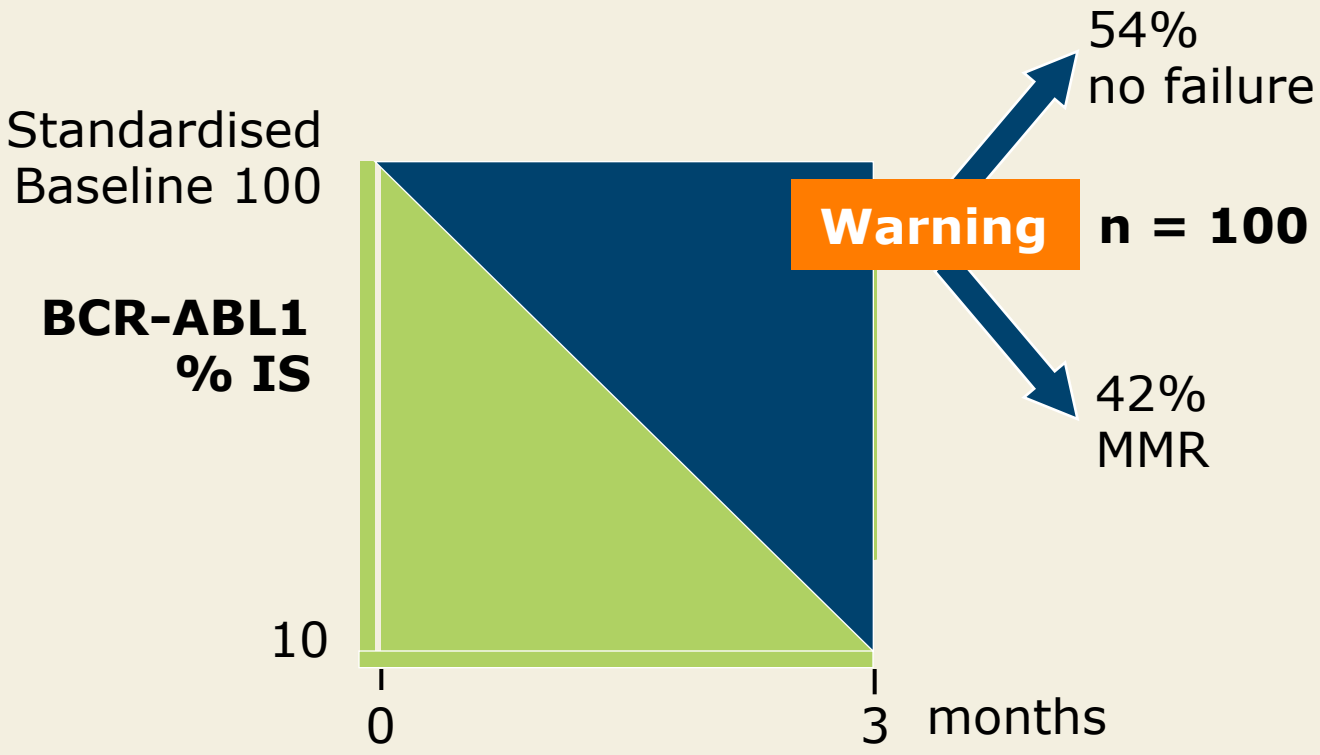
MMR for Patients in the 3-Month Warning Category Grouped by Category at 6 Months



- Patients in the warning category at 3 months who have BCR-ABL1 <10% at 6 months have improved outcomes
- No significant difference in any outcome assessment after 6 months between those who were in the optimal category at 3 months and 6 months versus those in the warning category at 3 months who moved to the optimal category at 6 months

With permission from Branford S et al. *Proc ASH* 2013;Abstract 254.

Patients at High Ongoing Risk of Poor Response



Change of BCR-ABL1 level from baseline to 3 months was important for outcome

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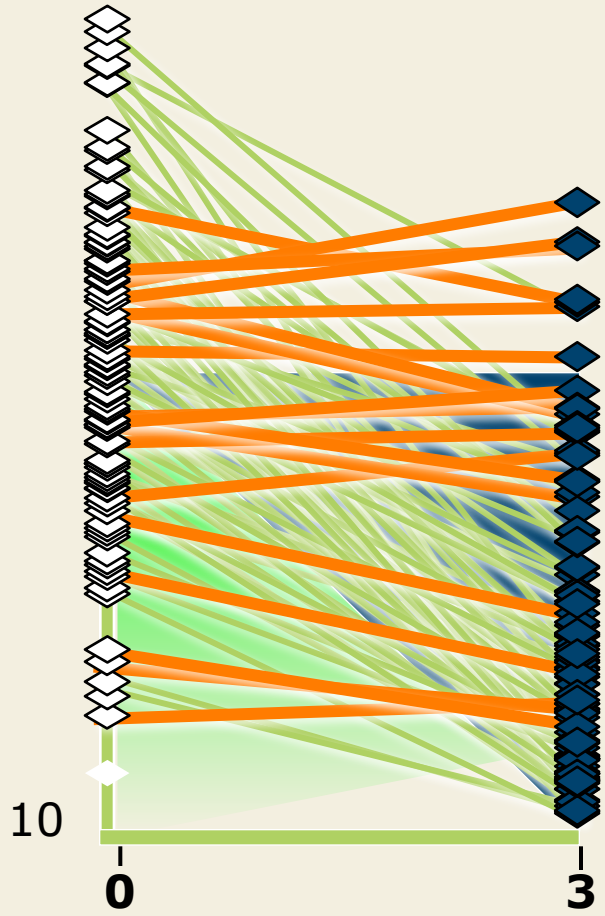
Use of Halving Time to Predict Outcome for Patients at High Ongoing Risk of Poor Response

n = 79
Halving Time
≤90 days

median 32 days
(range 16-90)



n = 19
Halving Time
>90 days

Rate of reduction was measured by the number of days over which BCR-ABL1 halved:
Halving Time

When BCR-ABL1 was measured as a continuous covariate, patients with the same value at 3 months had better outcomes if their baseline value was higher.

With permission from Branford S et al. *Proc ASH* 2013;Abstract 254.

Outcomes for Patients in the Warning Category at 3 Months by Halving Time Responses

Outcome at 4 y	Overall (n = 100)	Halving time response		
		≤90 d (n = 79)	>90 d (n = 19)	*p*-value
Overall survival	89%	93%	69%	0.0008
Progression-free survival	86%	90%	69%	0.017
Failure-free survival	46%	56%	7%	<0.0001
MMR	42%	53%	5%	0.017

The halving time at 3 months may also be predictive of overall and progression-free survival for the 35 patients who subsequently met the ELN failure criteria at 6 months.

Branford S et al. *Proc ASH* 2013;Abstract 254.

Author Conclusions

- BCR-ABL1 >10% at 3 months is a poor risk category.
- Not all patients with a BCR-ABL1 value >10% at 3 months have a high ongoing risk of treatment failure.
  - Any reduction below 10% by 6 months may improve outcome.
  - The rate of reduction over the first 3 months is an important factor for outcome and could be considered when making therapeutic decisions.

Branford S et al. *Proc ASH* 2013;Abstract 254.

Investigator Commentary: BCR-ABL Levels <10% at 6 Months Significantly Improve Outcome for Patients with CML-CP with a Poor Response at 3 Months

This study showed that some patients who do not have a good molecular response at 3 months may be able to catch up at 6 months, whereas others continue to have a poor response. The patients who catch up at 6 months have the same good prognosis as those who achieve the response at 3 months. Those who do not catch up even by 6 months will have a poor outcome. This has important implications for how we care for patients who have BCR-ABL levels >10% at 3 months.

My recommendation is not to change treatment for any patient at 3 months but to ensure that the patients are monitored at 6 months. I would consider changing the treatment for those who continue to respond poorly.

With imatinib, about a third of patients don't achieve a good response at 3 months and about half of these patients will continue to fare poorly at 6 months. However, with dasatinib or nilotinib, only 10% to 15% of patients will not have a good response at 3 months and half of those will continue to respond poorly at 6 months. That is a rationale for using dasatinib or nilotinib as up-front therapy.

Interview with Jorge E Cortes, MD, January 24, 2014

ENESTnd Update: Nilotinib (NIL) vs Imatinib (IM) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) and the Impact of Early Molecular Response (EMR) and Sokal Risk at Diagnosis on Long-Term Outcomes

Saglio G et al.

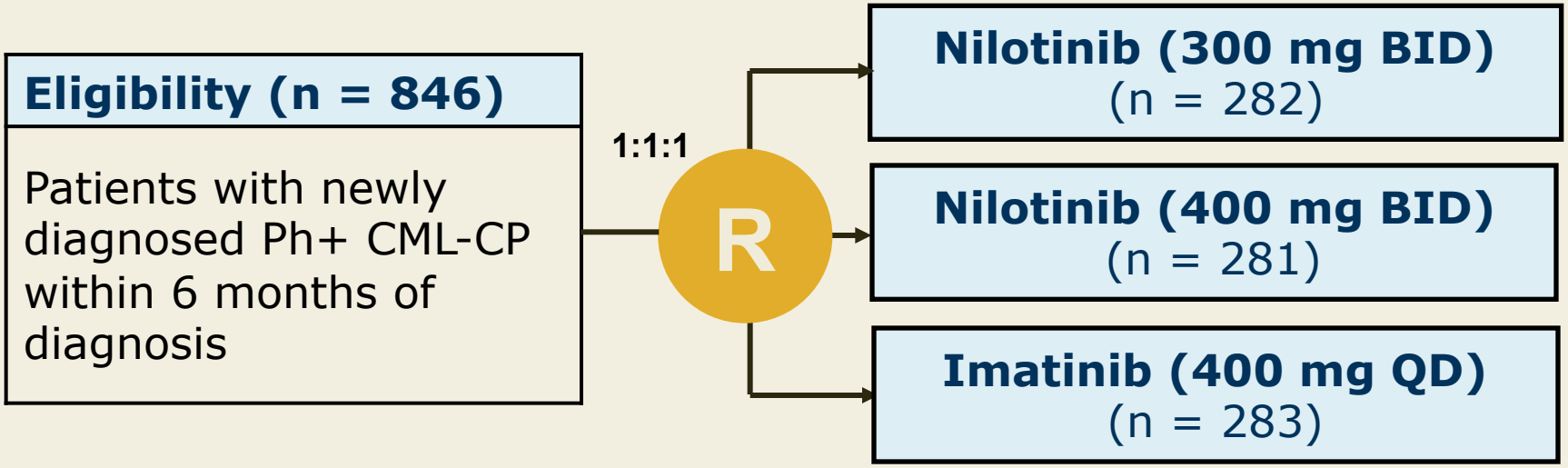
Proc ASH 2013;Abstract 92.

Background

- Previously, the ENESTnd trial for patients with Philadelphia chromosome-positive (Ph+) CML-CP demonstrated that front-line nilotinib (NIL) continues to show benefit over imatinib (IM) (*Lancet Oncol* 2011;12(9):841):
  - Higher rates of major molecular response (MMR): BCR-ABL on the International Scale (BCR-ABL^{IS}) ≤0.1%
  - Higher rates of deep molecular response (MR$^{4.5}$): BCR-ABL^{IS} ≤0.0032%
  - Lower rates of progression to accelerated phase (AP)/blast crisis (BC)
- **Study objective:** To report updated results from the ENESTnd trial for patients with newly diagnosed CML-CP after a long-term follow-up of 4 years based on a 5-year follow-up study.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Phase III ENESTnd Trial Design



- **Primary endpoint:** MMR at 12 months, defined as BCR-ABL^{IS} ≤0.1% by quantitative real-time PCR in peripheral blood
- Disease progression and overall survival (OS) events were collected prospectively during follow-up, including after discontinuation of study treatment.
- Efficacy in the NIL at 300 mg BID and IM arms was evaluated based on achievement of EMR (BCR-ABL^{IS} ≤10% at 3 months).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Patient Outcomes at 5 Years

	NIL 300 mg (n = 282)	NIL 400 mg (n = 281)	IM 400 mg (n = 283)
Still on study	86%	88%	83%
Still on core treatment	62%	65%	51%
Response at 5 y (*p*-value versus IM)			
MMR	77% (<0.0001)	77% (<0.0001)	60%
$MR^{4.5}$	54% (<0.0001)	52% (<0.0001)	31%
5-y freedom from progression to AP/BC (*p*-value versus IM)			
On core treatment	99.3% (0.0059)	98.9% (0.0185)	95.8%
On study	96.5% (0.0588)	97.9% (0.0047)	92.9%
5-y OS (*p*-value versus IM)			
On study	93.6% (0.58)	96.0% (0.04)	91.6%

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Landmark Efficacy Analysis by BCR-ABL Levels at 3 Months: NIL (300 mg BID) vs IM (400 mg QD)

Outcome	NIL (300 mg BID) (n = 258)*		IM (400 mg QD) (n = 264)*	
	≤10%	>10%	≤10%	>10%
No. of patients	91%	9%	67%	33%
5-year PFS	95%	78%	97%	80%
p-value	0.001		<0.0001	
5-year OS	97%	82%	97%	80%
p-value	0.0007		<0.0001	

PFS = progression-free survival

* Patients with evaluable BCR-ABL at 3 months

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Landmark Analysis of Rates of BCR-ABL^{IS} ≤10% at 3 Months by Sokal Risk Score

Outcome	BCR-ABL ≤10% at 3 months	
Sokal risk score	**NIL 300 mg**	**IM 400 mg**
Low (n = 97, 102)	93%	79%
Intermediate (n = 91, 92)	92%	70%
High (n = 70, 70)	86%	44%

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Proportion of Patients with $MR^{4.5}$ by BCR-ABL Levels at 3 Months

	Patients with $MR^{4.5}$	
BCR-ABL at 3 mo	**NIL 300 mg BID**	**IM 400 mg QD**
≤1% (n = 144,43)	56%	16%
>1% to ≤10% (n = 89, 133)	35%	50%
>10% (n = 24, 88)	9%	33%

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Summary of Efficacy Results

- Patients with EMR failure (BCR-ABL >10% at 3 months) have significantly worse 5-year PFS and OS:
  - Rates of EMR failure are lower with NIL 300 mg BID than with IM.
- Rates of $BCR\text{-}ABL^{IS}$ ≤10% at 3 months were improved with NIL regardless of Sokal risk score:
  - IM 400 mg QD = 67%
  - NIL 300 mg BID = 91%
- Patients with BCR-ABL ≤1% at 3 months have significantly higher rates of $MR^{4.5}$ by 5 years in the NIL 300 mg BID arm than in the IM arm (56% vs 16%):
  - Patients with EMR had significantly higher rates of PFS and OS at 5 y than those with BCR-ABL >10% at 3 months.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Summary of Efficacy Results (Continued)

- In patients with intermediate or high Sokal risk scores, PFS and OS at 5 years were higher in both NIL arms than in the IM arm (data not shown).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Select Adverse Events (AEs) by 5 Years (All Cause, All Grades)

By year 5, n (%)	NIL 300 mg (n = 279)	NIL 400 mg (n = 277)	IM 400 mg (n = 280)
Peripheral arterial disease (PAD)	4 (1.4%)	6 (2.1%)	0 (0%)
Ischemic heart disease (IHD)	11 (3.9%)	21 (7.6%)	5 (1.8%)
Ischemic cerebrovascular event (ICVE)	4 (1.4%)	8 (2.9%)	1 (0.4%)

- Due to the discontinuation rate, more patients were exposed to NIL than IM.
- Approximately 85% of patients with a cardiovascular event had at least 1 risk factor and were suboptimally treated.
- Events reported in year 5 included 9 new cases of IHD (IM n = 2; NIL 400 mg BID, n = 7), 4 new ICVEs (NIL 300 mg BID, n = 1; NIL 400 mg BID, n = 3) and 1 new PAD event (NIL 400 mg BID).

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Author Conclusions

- NIL demonstrated higher rates of early molecular response and deeper molecular response, including $MR^{4.5}$, and a reduced risk of progression.
- By 5 years, more than half of patients who received NIL had achieved $MR^{4.5}$, a key eligibility criterion for many treatment-free remission studies.
- More cardiovascular events were reported in both NIL arms than in the IM arm, but they occurred most frequently in the NIL 400 mg BID arm.
- At 5 years of follow-up, there is a trend toward higher event-free and progression-free survival in patients who received NIL than in those who received IM.
- These long-term data confirm NIL 300 mg BID as a standard treatment for patients with newly diagnosed CML-CP.
- NIL continues to show good tolerability with long-term follow-up.
- Although selected cardiac and vascular events (including PAD) are slightly more frequent with NIL than with IM, no increase in annual incidence of these events over time has been observed.

Saglio G et al. *Proc ASH* 2013;Abstract 92.

Updated Results of the Phase III ENESTnd Trial for Patients with Newly Diagnosed Ph+ CML-CP

These data show the long-term follow-up results of the ENESTnd trial, and nilotinib continues to show improvement in the overall clinical outcome. An important point is that, to date, we have seen little, if any, difference in event-free survival and overall survival. The investigators now have results from 5 years of follow-up. Perhaps with more time we will start seeing a bit of an improvement in survival. However, that's not significant at this point. The benefit of nilotinib is mostly in terms of the deeper responses observed. From the early days of this trial, we learned that nilotinib elicited a decreased rate of transformation to accelerated and blast phase. Essentially, those results are holding up.

An interesting observation is that more patients appear to develop cardiovascular toxicities, ischemic heart disease, peripheral arterial occlusive disease and cerebrovascular events with nilotinib than with imatinib and to a lesser extent with dasatinib than with imatinib. We are learning that we will see these adverse events with the use of these drugs. We need to be mindful of these adverse events so that we can monitor our patients well.

Interview with Jorge E Cortes, MD, January 24, 2014

Long Term Follow-Up After Imatinib Cessation for Patients in Deep Molecular Response: The Update Results of the STIM1 Study[1]

Preliminary Report of the STIM2 Study: A Multicenter Stop Imatinib Trial for Chronic Phase Chronic Myeloid Leukemia De Novo Patients on Imatinib[2]

[1] **Mahon FX et al.**
Proc ASH 2013;Abstract 255.

[2] **Mahon FX et al.**
Proc ASH 2013;Abstract 654.

Long Term Follow-Up After Imatinib Cessation for Patients in Deep Molecular Response: The Update Results of the STIM1 Study

Mahon FX et al.

Proc ASH 2013;Abstract 255.

Background

- Imatinib treatment significantly improves survival in patients with chronic myeloid leukemia (CML) (*J Clin Oncol* 2011;29:2514).
- The STIM study previously demonstrated that imatinib can be safely discontinued in patients with a deep molecular response (DMR), ie, with undetectable minimal residual disease (UMRD) for at least 2 years (*Lancet Oncol* 2010;11:1029).
- Around 40% of patients with CML with stable DMR on imatinib for at least 2 years are likely to remain in a prolonged treatment-free remission after treatment is stopped.
  - This rate was safely confirmed by the recent TWISTER study (*Blood* 2013;122:515).
- **Study objective:** To assess the risk of molecular relapse after imatinib discontinuation after a median follow-up of 50 months.

Mahon FX et al. *Proc ASH* 2013;Abstract 255.

STIM1 Study Methods

- Eligibility (N = 100):
  - Patients with CML who had discontinued imatinib (>2 years duration)
  - Sustained DMR for at least 2 years
  - Patients who had received immunomodulatory treatment (other than IFN-α), treatment for other malignancies or allogeneic hematopoietic stem cell transplantation were excluded
- Rate of relapse was assessed by quantitative RT-PCR:
  - Molecular relapse was defined as positivity of BCR-ABL transcript levels, confirmed by a second analysis point indicating the increase of 1 log in relation to the first analysis point, at 2 successive assessments or loss of major molecular response at 1 point.

Mahon FX et al. *Proc ASH* 2013;Abstract 255; *Lancet Oncol* 2010;11(11):1029-35.

STIM1 Study Methods (Continued)

- Quantitative RT-PCR analysis using peripheral blood samples was performed every month for the first year, every 2 months for the second year and every 3 months thereafter.
- Beyond 2 years, the treating physician was recommended to reintroduce therapy with a tyrosine kinase inhibitor (TKI) in case of molecular relapse.

Mahon FX et al. *Proc ASH* 2013;Abstract 255; *Lancet Oncol* 2010;11(11):1029-35.

Response After Imatinib Discontinuation and Rechallenge

- Molecular relapse: 61 patients
  - 58 relapses during first 7 months
  - 3 relapses at 19, 20 and 22 months
- Cumulative incidence of molecular relapse: 60%
- All 58 surviving patients were sensitive to TKI rechallenge and underwent re-treatment with
  - Imatinib (n = 48), nilotinib (n = 5), dasatinib (n = 5)
  - 1 patient had to discontinue therapy because of side effects
- Second attempt of TKI discontinuation was proposed for 15 patients in sustained DMR, and 5 cases of molecular relapse were reported at the last update after this second attempt at TKI cessation

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

Deaths Due to Adverse Events

- Extrahematologic deaths observed (n = 4)
  - 1 case in DMR after 9 months of imatinib cessation
    - Due to myocardial infarction
  - 3 cases in the group of patients with molecular relapse
    - Due to stroke, mesothelioma and gastric carcinoma

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

Author Conclusions

- Imatinib can be safely discontinued in patients with a DMR of at least 2 years duration.
- Discontinuation should be proposed only in clinical trials with close molecular monitoring.
- Although no other molecular relapses beyond 2 years were observed, a long-term follow-up of the different cessation studies will be necessary to affirm cure.
- Because the life expectancy of patients with de novo CML is now close to that of the healthy population, long-term medical costs and quality of life have become important and depend on the possibility of safely ceasing TKI therapy in the long term.

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

Preliminary Report of the STIM2 Study: A Multicenter Stop Imatinib Trial for Chronic Phase Chronic Myeloid Leukemia De Novo Patients on Imatinib

Mahon FX et al.

Proc ASH 2013;Abstract 654.

Background

- The STIM1 trial previously demonstrated that imatinib could be safely discontinued in patients with a sustained deep molecular response (DMR) (undetectable BCR-ABL transcripts [UMRD] for at least 2 years) (*Lancet Oncol* 2010;11:1029).
- These results were recently confirmed by the TWISTER study using criteria for imatinib cessation similar to those used in the STIM1 study (*Blood* 2013;122:515).
- However, in both of these studies, half of the patients had previously received IFN, leading to a nonhomogenous cohort of patients.
- **Study objective:** To conduct a prospective second trial in which cessation of imatinib treatment was proposed for patients in sustained DMR who had received only imatinib.

Mahon FX et al. *Proc ASH* 2013;Abstract 654.

STIM2 Study Methods

- Eligibility (N = 124):
  - Same criteria as those reported previously for the STIM1 trial:
    - Patients with CML who had discontinued imatinib (>2 years duration)
    - Sustained DMR for at least 2 years
- Rate of relapse was assessed by quantitative RT-PCR:
  - Same definition of molecular relapse as in the STIM1 trial
- Quantitative RT-PCR analysis using peripheral blood samples was performed every month for the first year, every 2 months for the second year and every 3 months thereafter.

Mahon FX et al. *Proc ASH* 2013;Abstract 654; www.clinicaltrials.gov, accessed February 2014.

Response After Imatinib Discontinuation and Rechallenge

- Molecular relapse: 48 patients
  - 45 relapses during first 6 months
  - 3 relapses between 6 and 12 months
- Patients free of treatment at the last update with DMR (n = 76)
  - 41 experienced a BCR-ABL quantitative RT-PCR fluctuation without clear molecular relapse
  - BCR-ABL reappearance does not automatically mean clinical relapse
- All patients in molecular relapse were sensitive to TKI rechallenge and underwent re-treatment with:
  - Imatinib (n = 33), nilotinib (n = 5), dasatinib (n = 3)
- Median time to achieve a DMR again from the molecular relapse was 7 months (range 4-16 months) and median time from reinitiation of TKI was 4 months (range 2-14)

Mahon FX et al. *Proc ASH* 2013;Abstract 654 (abstract only).

Author Conclusions

- STIM2 confirms that imatinib can be safely and prospectively discontinued in patients with DMR of at least 2 years duration who received only imatinib.
- The complete eradication of residual leukemic stem cells may not be required to discontinue treatment because positive fluctuation PCR results do not lead to CML relapse or progression.
- These intriguing results, even for patients who received imatinib only since disease onset (already observed after IFN therapy), are comparable to those reported with the more sensitive PCR on DNA in the TWISTER study and are currently under investigation.

Mahon FX et al. *Proc ASH* 2013;Abstract 654 (abstract only).

Investigator Commentary: Discontinuation of Imatinib Therapy in Patients with CML

These are important studies because everyone is concerned not only about the long-term cost of TKIs but also about the potential long-term toxicities at 5 or 10 years into treatment. STIM1 and STIM2 investigators stopped the TKI in patients who had complete molecular responses for more than 2 years and reported that about 40% to 50% of those patients continue to be in a complete molecular response, suggesting that perhaps these patients may never require TKI therapy in the future.

Although we found in these studies that most of the molecular responses occurred in the first 12 months, I'm concerned that patients might experience a sudden transformation at 8 or 10 years, after we've discontinued therapy and become more relaxed about follow-up. These are important studies, however, in terms of trying to limit the cost and potential long-term side effects of TKIs, but discontinuation should not be routine in everyday practice. These patients should be entered on clinical trials so that they can be monitored over the long run.

Interview with Hagop M Kantarjian, MD, January 29, 2014

Dose Interruption/Reduction of Tyrosine Kinase Inhibitors in the First 3 Months of Treatment of CML Is Associated with Inferior Early Molecular Responses and Predicts for an Increased Likelihood of Discontinuation of the 1st Line Agent

Apperley JF et al.

Proc ASH 2013;Abstract 93.

Background

- In chronic myeloid leukemia (CML), rapid reductions in tumor load, defined by ≤65% Philadelphia chromosome negativity and/or BCR-ABL^{IS} <10% at 3 months, are associated with an improved probability of complete cytogenetic response (CCyR) and better progression-free survival (PFS) and overall survival (OS).
- However, about 15% to 20% of patients experience cytopenias shortly after starting tyrosine kinase inhibitor (TKI) treatment and receive drug interruptions and/or dose reduction.
- It is unclear whether these early periods of altered treatment should be considered in the interpretation of the results of BCR-ABL^{IS} <10% at 3 months.
- **Study objective:** To investigate the effects of therapy interruptions and dose reduction during the first 3 months of therapy on the achievement of BCR-ABL^{IS} <10% at 3 months, CCyR rate at 12 months and ability to remain on study.

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

Study Methods

- This was a randomized Phase III trial of imatinib (IM) versus dasatinib (DA) for patients with newly diagnosed CML.
- Quantitative real-time PCR (qRT-PCR) results of BCR-ABL^{IS} levels at 3 months were available for 585 of 632 patients who completed 3 months of therapy:
  - IM (n = 292)
  - DA (n = 293)
- Patients were divided according to the agent assigned on randomization and the amount missed:
  - Patients who did not miss Tx (IM0, DA0): IM0 (n = 243); DA0 (n = 211)
  - Patients who missed 1-14 days of Tx (IM1-14, DA1-14): IM1-14 (n = 38); DA1-14 (n = 37)
  - Patients who missed >14 days of Tx (IM>14, DA>14): IM>14 (n = 11); DA>14 (n = 45)

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

Achievement of BCR-ABL^{IS} <10% at 3 Months

Outcome	IM0	IM1-14	IM>14
BCR-ABL^{IS} <10%	78.6%	63.2%	63.5%
p-value	0.033		
	DA0	**DA1-14**	**DA>14**
BCR-ABL^{IS} <10%	93.8%	91.9%	77.8%
p-value	0.001		

- More patients who received DA missed days of dosing (28%) than patients who received IM (17%); $p = 0.008$:
  - Median number of missed days for DA = 16 (range 1-62)
  - Median number of missed days for IM = 12.5 (range 1-42)
- Predictably, the likelihood of a qRT-PCR level of BCR-ABL^{IS} <10% at 3 months is higher with DA than with IM, but DA is less well tolerated in the early months.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

Summary of BCR-ABL^{IS} <10% Results at 3 Months

- Of patients who received >95% of the standard doses, BCR-ABL^{IS} <10% at 3 months occurred in 78.7% (IM) versus 93.8% (DA).
- In contrast, of patients who missed >20% of the prescribed doses, BCR-ABL^{IS} <10% at 3 months occurred in 60% (IM) versus 84% (DA).
- Thus, drug interruptions and dose reductions are associated with a reduced probability of achieving BCR-ABL^{IS} <10% at 3 months.
  - This effect is not observed among patients missing <14 days of DA.
  - It is less marked for reduced average dosing of DA.
  - These results suggest that the higher potency of DA compensates for dose reduction or a few missed days of therapy.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

BCR-ABL^{IS} <1% (MR2) as a Surrogate for CCyR

Outcome	IM0	IM1-14	IM>14
12-month MR2 rate	78%	78%	90%
p-value	0.5		
	DA0	**DA1-14**	**DA>14**
12-month MR2 rate	96%	88.6%	79.5%
p-value	0.026		

- 107/632 (17%) of patients had discontinued the study by 12 months, and qRT-PCR results were available for all remaining patients.
- These results confirm the superiority of DA over IM for MR2 and the potential impact of missing early doses of DA.
- However, it is not yet clear whether these results are related to inadequate dosing or whether failure to tolerate the recommended dose is indicative of higher-risk disease.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

Treatment Continuation and Discontinuation Rates

Proportion of patients	IM0/DA0	IM1-14/ DA1-14	IM>14/ DA>14
Able to receive Tx consistently through months 3-12	91%	71%	57%
	IM0	**IM1-14**	**IM>14**
Who discontinued Tx	12.5%	38.1%	35.7%
	DA0	**DA1-14**	**DA>14**
Who discontinued Tx	4.4%	12.8%	18.8%

- Thus, tolerance of the daily drug in the first 3 months predicts future tolerability and efficacy during the subsequent 9 months and long-term compliance with the first-line therapy.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

BCR-ABL^{IS} <0.1% (MR3) Rates with Respect to Average Dosing During the First 3 Months

Treatment	Prescribed dose completed		
	>95%	80%-95%	<80%
IM	50%	52.8%	54.9%
p-value	0.17		
DA	68.1%	59.4%	53.1%
p-value	0.038		

- Because long-term qRT-PCR monitoring was provided for all patients entered into the study irrespective of their continuation in the study, it was possible to study the achievement of MR3 at 12 months in an intention-to-treat analysis with all patients.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

Author Conclusions

- Similar results were obtained using the number of days of missed drug (data not shown), suggesting that early failure to tolerate IM as first-line therapy does not affect subsequent responses because effective alternative therapy is available for the majority of patients.
- In contrast, failure to tolerate DA is associated with a reduced chance of MR3 at 12 months.
- Patients who experience cessation or reduction of either agent in the first 3 months are less likely to achieve BCR-ABL^{IS} <10% at 3 months and are more likely to require a change of drug in the longer term.
  - Therefore, these patients require close observation during the first year.

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

Investigator Commentary: Interruption or Reduction of TKIs in the First 3 Months After Diagnosis of CML

In this study, the investigators examined the important question of treatment continuation during the first 3 months after CML diagnosis and evaluated how this affects the probability of getting the best response at 3 months. They found that patients who undergo any treatment interruption, even for only a day, already have a diminished probability of a good response at 3 months. The more treatment the patient misses, the higher the probability that the patient's disease will progress or undergo transformation.

Interview with Jorge E Cortes, MD, January 24, 2014

Different reasons exist for dose interruptions, and each of them probably carries a different implication for long-term prognosis. If the interruption is due to nonmyelosuppressive toxicity, then the dose can be reduced or changed to a different TKI, and I believe the prognosis will be unchanged. Noncompliance and myelosuppression carry a different meaning because you expect these patients in the long run to have a lower incidence of CCyR or major molecular response and probably more adverse events such as transformation.

Interview with Hagop M Kantarjian, MD, January 29, 2014

Ponatinib as Initial Therapy for Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

Cortes JE et al.

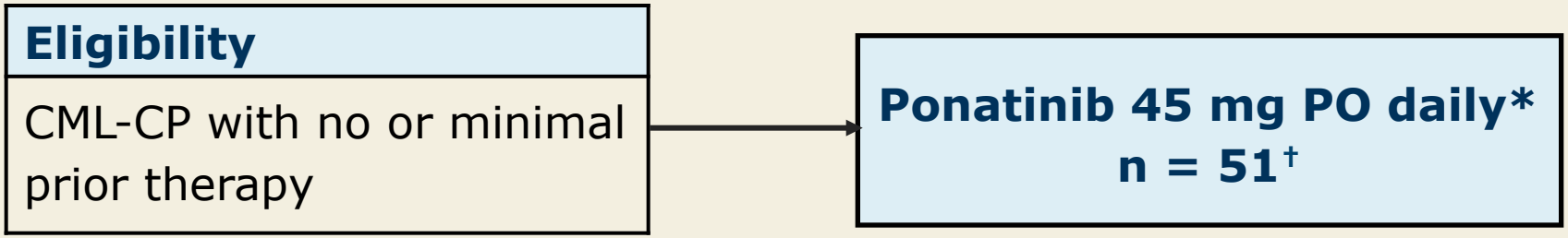
Proc ASH 2013;Abstract 1483.

Background

- Ponatinib is an oral, pan-BCR-ABL tyrosine kinase inhibitor (TKI) approved for patients with CML that is resistant or intolerant to previous TKI therapy.
- In vitro, ponatinib at clinically relevant concentrations (40 nM) is able to prevent the emergence of drug-resistant CML clones (*Cancer Cell* 2009;16:401).
- Use of ponatinib as front-line therapy may therefore result in high rates of early responses and prevent drug resistance in patients with CML.
- **Study objective**: To assess the efficacy and safety of single-agent ponatinib as initial therapy for patients with CML-CP.

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Phase II Trial Design



* Trial amendment changed starting dose from 45 mg daily to 30 mg daily (July 2013): 43 patients enrolled at 45 mg daily and 8 enrolled at 30 mg daily starting doses

† Accrual suspended in October 2013 because of increased cumulative incidence of serious arteriothrombotic events

Primary endpoint: Complete cytogenetic response (CCyR) rate at 6 months

- Patients were followed with cytogenetic analysis and PCR every 3 months for the first 12 months, then every 6 months (data cutoff October 1, 2013).

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Overall Response

Response parameter	n (%)
Complete hematologic response (CHR)*	43/48 (90%)
CCyR†	41/42 (98%)
Major molecular response (MMR)	34/42 (81%)
Complete molecular response	11/42 (26%)

* Only patients not in CHR at start of treatment

† Patients with at least 3 months follow-up and evaluable karyotype

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Cytogenetic Response Over Time

Patient group	3 months	6 months	9 months	12 months	Best response
Inevaluable	0	0	0	1	0
No cytogenetic response	1	1	0	0	0
Partial cytogenetic response	3	1	2	1	1
CCyR	38	32	25	17	41

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Select Grade 3/4 Treatment-Emergent Adverse Events

Hematologic	**n**
Neutropenia	6
Thrombocytopenia	5
Anemia	2
Nonhematologic	**n (%)**
Elevated serum lipase	23 (45%)
Pancreatitis*	10 (20%)
Abdominal pain	4 (8%)
Elevated amylase level	4 (8%)

* 10/23 patients had symptomatic Grade 3 pancreatitis, and of these 9/10 had CT/ultrasound findings of pancreatitis; 13/23 had chemical pancreatitis; 2/23 had a repeated episode of pancreatitis.

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Cardiac and Vascular Adverse Events

Adverse events	Any grade n (%)	Grade 3/4 n (%)
Hypertension*	11 (22%)	4 (8%)
Chest pain†	7 (14%)	0
Acute coronary syndrome	1 (2%)	1 (2%)
Raynaud syndrome	2 (4%)	0
Transient ischemic attack	1 (2%)	0
Peripheral vascular disease	1 (2%)	0
Palpitations	1 (2%)	0
Prolonged QTc interval	1 (2%)	0
Pericarditis	1 (2%)	0

* 3 patients had new onset hypertension (HTN) and 8 had preexisting HTN (5 had worsening of HTN, 3 stable HTN); 2 patients with Grade 3 HTN were receiving 45 mg and 2 were receiving 30 mg

† 1 due to Grade 2 pericarditis and 6 patients had negative EKG and cardiac enzymes

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Author Conclusions

- Ponatinib induces a high rate of early CCyR and MMR in patients with newly diagnosed CML-CP.
- With a dose of 45 mg daily most patients require dose reductions, most frequently because of elevation of lipase with or without pancreatitis.
- Hypertension occurs frequently in patients who receive ponatinib in this setting.
- Possible arteriovascular thrombotic events occur in nearly 20% of patients.
- Because of safety concerns related to increased cumulative incidence of arteriovascular thrombotic events in Phase I and Phase II studies for patients previously treated with other agents, enrollment to this study has ended.

Cortes JE et al. *Proc ASH* 2013;Abstract 1483.

Single-Agent Ponatinib as Initial Therapy for CML-CP

This was a single-arm, single-institution study with about 50 patients, and we reported that response rates with ponatinib at 3 months are excellent. At 3 months, more than 80% of patients have a complete cytogenetic response and we observe a high rate of major molecular response. The patients respond well to ponatinib and respond quickly.

We did have a number of patients for whom we had to lower the dose of ponatinib. This was mainly due to the presence of elevated lipase levels, which was frequently asymptomatic. We also observed pancreatitis, but only occasionally was it regarded as true pancreatitis. Although most patients began the study at a dose of 45 mg, the median dose of ponatinib in the study was 30 mg daily.

We did not have a control arm in this study. We do, however, have historical data with imatinib, and the results we observed with ponatinib look better than what we would expect with imatinib.

Interview with Jorge E Cortes, MD, January 24, 2014

Ponatinib in Patients (pts) with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 2-Year Follow-Up of the PACE Trial

Cortes JE et al.

Proc ASH 2013;Abstract 650.

Background

- Ponatinib — a potent, oral, pan-BCR-ABL inhibitor with activity against native and mutant forms of BCR-ABL, including the tyrosine kinase inhibitor (TKI)-resistant T315I mutant — was approved in December 2012 by the FDA and July 2013 by the EMA.
- Because of an accumulation of vascular events over time, ponatinib was temporarily suspended from commercial distribution in the United States in October 2013 and became available only under a single-patient investigational new drug application or expanded access registry program.
  - In November 2013, the EMA retained the authorized indication with measures to reduce risk.
- **Study objective:** To provide 2-year follow-up data from the PACE trial.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

PACE: Phase II Trial Design

Eligibility (n = 449)

- CML-CP, CML-AP, CML-BP or Ph+ ALL
- BCR-ABL T315I mutation **or** resistant or intolerant (R/I) to dasatinib or nilotinib

→ **Ponatinib**
45 mg orally once daily

CML-CP = chronic-phase CML; CML-AP = accelerated-phase CML; CML-BP = blast-phase CML

Primary endpoints

- Major cytogenetic response (MCyR) at any time within 12 months for CML-CP
- Major hematologic response (MaHR) at any time within 6 months for advanced CML or Ph+ ALL

Cortes JE et al. *Proc ASH* 2012;Abstract 163.

Responses at Any Time

	CML-CP			CML-AP	CML-BP	Ph+ ALL
	MCyR	CCyR	MMR	MaHR*	MaHR	MaHR
R/I to dasatinib or nilotinib	56%	48%	31%	62%	32%	50%
T315I mutation	72%	70%	58%	61%	29%	36%
Total†	60%	54%	38%	61%	31%	41%

CCyR = complete cytogenetic response; MMR = major molecular response

* 14 patients with CML-AP with baseline MaHR and 1 patient with CML-AP with no baseline MaHR assessment were counted as nonresponders

† Total comprises all eligible patients who received ponatinib. It excludes 5 patients (3 CML-CP, 2 CML-AP) who were not cohort assigned (postimatinib, non-T315I) but received treatment; all 5 achieved MCyR.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Response Characteristics and Survival: CML-CP

Median time to response	
MCyR	2.8 months
CCyR	2.9 months
MMR	5.5 months
Clinical outcomes	
MCyR at 2 years (n = 149)	89%
PFS (n = 267) Median PFS PFS at 2 years	 29 months 67%
OS (n = 267) Median OS OS at 2 years	 Not yet reached 86%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Response Characteristics and Survival: CML-AP, CML-BP and Ph+ ALL

CML-AP	
Median time to response	
MaHR	0.7 months
Clinical outcomes	
MaHR at 2 years	21%
PFS (n = 83) Median PFS PFS at 2 years	 15 months 37%
OS (n = 83) Median OS OS at 2 years	 Not yet reached 72%

OS	
CML-BP (n = 62) Median OS OS at 2 years	 7 months 18%
Ph+ ALL (n = 32) Median OS OS at 2 years	 8 months 21%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Select Treatment-Emergent Adverse Events (AEs)

	CMP-CP (n = 270)		Total population (n = 449)	
Nonhematologic	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Rash	44%	4%	40%	4%
Abdominal pain	43%	9%	40%	9%
Headache	41%	3%	36%	2%
Dry skin	41%	3%	36%	2%
Constipation	39%	3%	36%	2%
Hypertension	27%	10%	24%	9%
Hematologic	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Thrombocytopenia	44%	35%	43%	35%
Neutropenia	19%	16%	25%	22%
Anemia	16%	9%	22%	15%

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Hypertension

Baseline BP (mm Hg), NCI CTCAE	Increase in BP on study (single measurement)*		
	Grade 1	Grade 2	Grade 3
Normal (<120/<80), N = 70	36%	30%	23%
Grade 1 (120-139)/(80-89), N = 167	—	53%	34%
Grade 2 (140-159)/(90-99), N = 157	—	—	60%
Grade 3 (≥160/≥100), N = 55	—	—	—

- 379/449 (84%) patients had elevated BP at baseline (≥140/90, 47%)
- 301/449 (67%) patients experienced any increase in BP* on study
- AEs of hypertension were reported in 109/449 (24%) patients (serious AEs in 8/449 [2%])

* Any shift to higher grade (NCI CTCAE v.4.0), based on single BP measurements

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Incidence of Vascular Occlusive Events Over Time

	N = 449 N (%)			
Data as of	**23 July 2012 (USPI)**		**03 Sep 2013**	
Median follow-up (exposure)	**12 months (340 patient years)**		**24 months (578 patient years)**	
Category	**SAE**	**AE**	**SAE**	**AE**
Cardiovascular	21 (5)	29 (6)	28 (6)	41 (9)
Cerebrovascular	8 (2)	13 (3)	18 (4)	25 (6)
Peripheral vascular	7 (2)	17 (4)	16 (4)	28 (6)
Total arterial thrombosis	34 (8)	51 (11)	53 (12)	77 (17)
Venous thromboembolism	10 (2)	15 (3)	13 (3)	23 (5)
Vascular occlusion*				
Method 1†	41 (9)	62 (14)	62 (14)	91 (20)
Method 2‡	47 (10)	81 (18)	67 (15)	109 (24)

* Combined incidence of cardiovascular, cerebrovascular, peripheral vascular, venous thromboembolism events;
† EMA press release Nov 22, 2013; ‡ FDA drug safety communication, Oct 31, 2013

USPI = US package insert; SAE = AE reported as serious by the investigator, per standard criteria

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Multivariate Analysis of Arterial Thrombotic AEs

- Risk factors significantly associated with arterial thrombotic AEs:
  - Older age ($p < 0.0001$)
  - History of diabetes ($p = 0.0003$)
  - Higher dose intensity to time of first event ($p = 0.0009$)
  - History of ischemia ($p = 0.0087$)
  - Longer time since diagnosis ($p = 0.0228$)
  - Higher baseline neutrophil count ($p = 0.0276$)
  - Higher baseline platelet count ($p = 0.0466$)
- Each 15 mg/day reduction in dose intensity results in a predicted reduction of ~40% in the risk of an arterial thrombotic event.

Data are similar for vascular occlusive events.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Author Conclusions: 2-Year Follow-Up Summary

- This study confirmed substantial clinical activity in patients with heavily pretreated Ph+ leukemias.
- Early, deep and durable responses were observed:
  - 89% maintained MCyR for at least 2 years in CML-CP.
- Arterial thrombotic events occurred; higher dose intensity, older age and presence of other risk factors at baseline were associated with a higher likelihood of events.
- Overall survival was not reduced for patients experiencing arterial thrombotic events.
- Ponatinib is an important treatment for patients in whom the need and potential benefit outweigh the risks.

Cortes JE et al. *Proc ASH* 2013;Abstract 650.

Investigator Commentary: 2-Year Follow-Up of PACE — A Pivotal Phase II Trial of Ponatinib in Refractory CML and Ph+ ALL

With 2 years of follow-up, the PACE trial continues to show outstanding results with regard to major cytogenetic responses in patients with chronic-phase CML for whom more than 2 TKIs have failed. We reported 60% of patients with a major cytogenetic response, and about two thirds of the patients enrolled had experienced disease progression on 3 or more TKIs. We also reported on the risk of cardiovascular events and hypertension, which is common. We need to monitor carefully those patients with cardiovascular risk factors and care for them proactively to minimize complications.

Interview with Jorge E Cortes, MD, January 24, 2014

At our institution we've administered ponatinib to more than 100 patients and have observed the same toxicities that were described at the ASH meeting. Our concerns are mostly with some less common but serious problems such as pancreatitis and vaso-occlusive disorders. We are also concerned about less serious events that in the long run could cause organ damage, such as hypertension, which was a risk in the case of ponatinib at the dose of 45 mg a day. In my opinion using a lower dose of ponatinib, perhaps 30 mg per day, will alleviate most of the associated side effects such as hypertension, pancreatitis and skin rash.

Interview with Hagop M Kantarjian, MD, January 29, 2014