5 Minute JournalClub

POST-ASH Issue 3, 2013

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the long-term efficacy and safety of ruxolitinib for patients with myelofibrosis, and apply this information to clinical practice.
- Evaluate the efficacy and dose-finding studies of ruxolitinib in patients with myelofibrosis who have low platelet counts.
- Compare and contrast the benefits and risks of homoharringtonine-based induction regimens for patients with de novo acute myeloid leukemia.
- Evaluate the efficacy and safety of quizartinib for patients with FLT3-ITD-positive or negative acute myeloid leukemia.

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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:

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5 MinuteJournalClub

POST-ASH Issue 3, 2013

Does the JAK1/2 inhibitor ruxolitinib benefit patients with myelofibrosis without JAK2 mutations?...and more

Medical oncologists love to see clinical trial results that are so impressive that the effectiveness of a therapy can be immediately understood simply by viewing a single graphic. Because of this, the relatively recent innovation of waterfall plots — especially those in which the majority of the bars point down — has increasingly been used to provide poignant and memorable snapshots of antitumor efficacy.

In this regard, a unique series of waterfall plots presented at the June 2011 ASCO meeting caused an immediate stir and are still being talked about today. These startling graphics did not plot tumor size but disease-related symptoms and spleen size in the seminal Phase III COMFORT-I and II trials evaluating the JAK1/2 small molecule inhibitor ruxolitinib (Rux) in patients with myelofibrosis (MF). In addition to the rapid and profound impact in the treated group, another fascinating aspect of the waterfall plots was what was going on in the control patients, and there the bars were moving north fast, suggesting that these trials

were intervening in patients who were very ill and getting worse quickly. These data paved the way for the almost immediate FDA approval of this agent for patients with intermediate-2 and high-risk MF.

In Atlanta we saw an additional year of follow-up from these studies, including my favorite graphic from the entire ASH meeting (see below), showing side by side the survival benefit seen in COMFORT-I for patients with and without JAK2 mutations.

There is considerable debate about the mechanisms that produce the often-profound symptomatic benefit with Rux, and some have postulated it's related to the suppression of release of cytokines implicated in the pathogenesis of MF clinical progression. Regardless, the clear practical message is that this is not BRAF-positive melanoma or EML4-ALK-positive non-small cell lung cancer and symptomatic patients with MF should be considered for therapy with Rux regardless of JAK2 mutation status.

In this issue of our post-ASH series we review the COMFORT updates and two related MF papers along with data sets in acute myelogenous leukemia (AML), where several intriguing agents are showing promising results.

1. COMFORT trial updates

Perhaps the MF investigators chose the COMFORT trial acronym to symbolize the profound palliative effect of Rux that had been observed even in early Phase I-II studies. The initial published Phase III data were derived with a median of

about a year of follow-up, and now that another year has passed the results keep getting better. Perhaps the most important and “comforting” message is that most patients have maintained responses and are continuing to enjoy significant symptom palliation. In addition, an important effect on overall survival has been demonstrated in both trials in spite of the fact that crossover after progression on the control arm was allowed and occurred in more than two thirds of patients. The two ASH COMFORT updates are loaded with practical clinical information, which is summarized in the attached slide set, and it’s clear that this disease has entered a new era.

2. Use of Rux in patients with platelet counts (PC) of 50,000-100,000

MF can be associated with decreased PC through a variety of mechanisms, and Rux itself causes reversible declines in PC and hemoglobin levels, although these are rarely treatment limiting. The COMFORT trials required a minimum PC of 100,000, but the lack of an effective palliative alternative pushed investigators to determine if this agent could be safely and beneficially used in patients falling below this threshold. Two separate ASH papers evaluated a cautious stepwise approach in patients with PC between 50,000 and 100,000. In **the North American trial** led by Dr Moshe Talpaz patients started at 5 mg BID and escalated up, usually targeting a 10-mg BID dose. Interestingly, although patients in the COMFORT trials received 15 or 20 mg BID, those treated in these two new studies at reduced doses seemed to experience similar treatment benefit.

Unfortunately, there are currently no data to guide management of patients with PC under 50,000, and as such this situation probably warrants consideration of referral to a tertiary center, where many studies are being conducted with a plethora of promising agents in MF.

3. AML update: Homoharringtonine (HHT, otherwise known as omacetaxine)

On one of our upcoming audio programs Dr Hagop Kantarjian spins a fascinating tale of herbal drug development in China under Mao Zedong, and one of the positive outcomes (in addition to ATRA and arsenic) was this plant alkaloid that has significant activity in AML (and was recently approved in CML). In a prominent ASH report of a Phase III AML trial done in China, cytarabine (C) and an anthracycline (A) combined with HHT resulted in more CRs and better survival but also more deaths during induction than CA alone. These findings have led to both optimism and caution as this fascinating agent is further developed.

4. More on AML: Quizartinib, a potent FLT3 receptor inhibitor

FMS-like tyrosine kinase 3 (FLT3) internal tandem duplications can be found in up to a third of patients with AML and are associated with high blast counts, increased rates of relapse and reduced survival. In an effort to potentially exploit this target, quizartinib was evaluated in a Phase II trial with 2 cohorts reported separately at ASH and revealed impressive responses in patients both without and, more commonly, with FLT3 mutations, and the drug, which was well

tolerated other than prolonged QT intervals, stabilized a number of patients, enabling transplant. Enthusiasm from these findings has led to Phase III trials in FLT3-mutant AML, including efforts to combine quizartinib with the classic 3 + 7 regimen up front.

Next on this ASH highlights series we consider Hodgkin and T-cell lymphoma, where more good news on the CD30 antibody-drug conjugate brentuximab vedotin was unveiled in Atlanta.

Neil Love, MD
Research To Practice
Miami, Florida

Long-Term Outcome of Ruxolitinib Treatment in Patients with Myelofibrosis: Durable Reductions in Spleen Volume, Improvements in Quality of Life, and Overall Survival Advantage in COMFORT-I[1]

Long-Term Safety, Efficacy, and Survival Findings from COMFORT-II, a Phase 3 Study Comparing Ruxolitinib with Best Available Therapy (BAT) for the Treatment of Myelofibrosis (MF)[2]

[1] **Verstovsek S et al.**

Proc ASH 2012;Abstract 800.

[2] **Cervantes F et al.**

Proc ASH 2012;Abstract 801.

Long-Term Outcome of Ruxolitinib Treatment in Patients with Myelofibrosis: Durable Reductions in Spleen Volume, Improvements in Quality of Life, and Overall Survival Advantage in COMFORT-I

Verstovsek S et al.

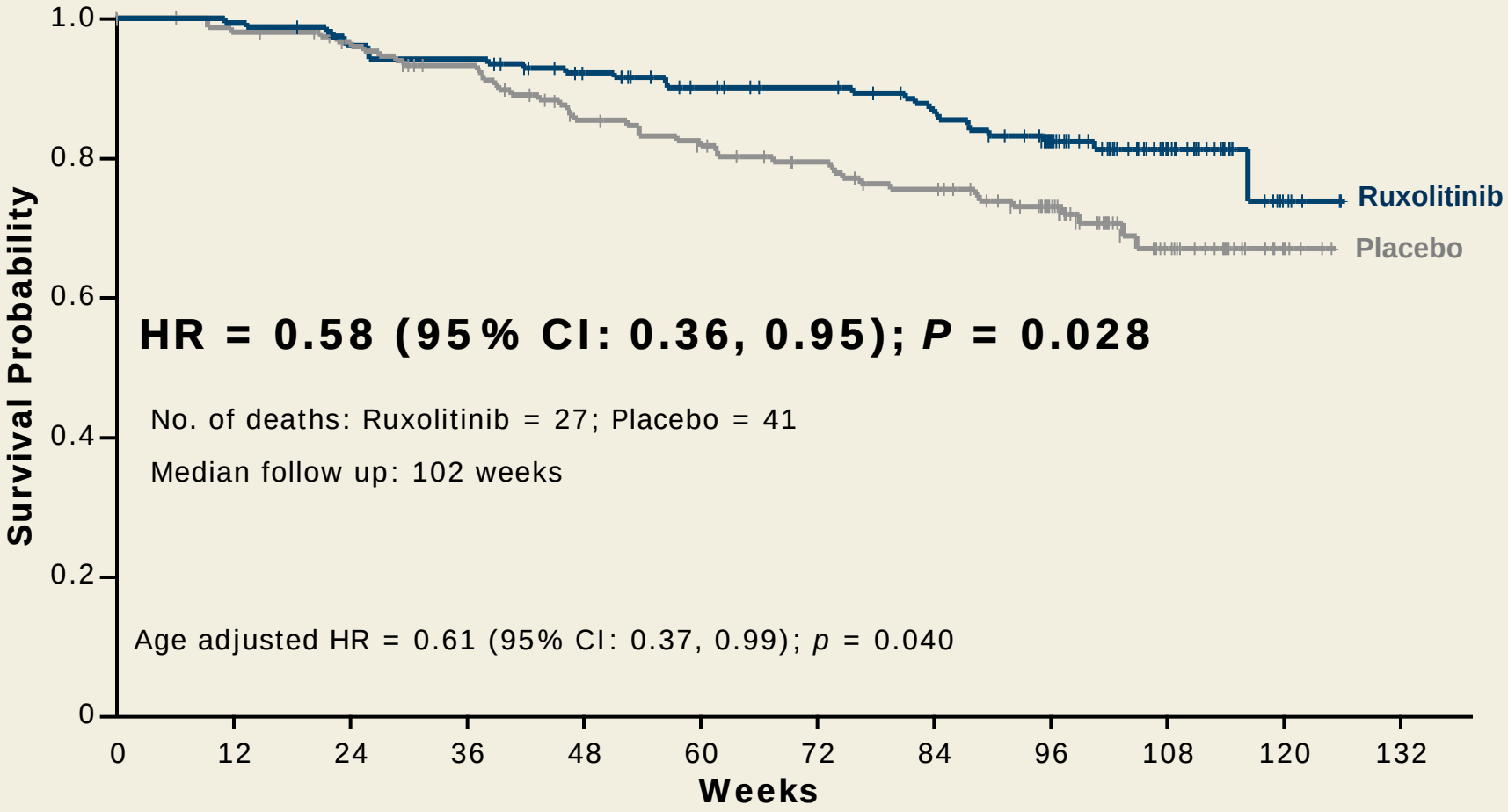
Proc ASH 2012;Abstract 800.

Background

- Ruxolitinib is a potent JAK1/JAK2 inhibitor that has shown superiority over placebo or conventional therapies for the treatment of myelofibrosis (MF).
- In the Phase III COMFORT-I and COMFORT-II studies, ruxolitinib demonstrated reductions in splenomegaly and an improvement in MF-related symptoms, quality of life (QoL) and overall survival (*N Engl J Med* 2012;366(9): 799; *N Engl J Med* 2012;366(9):787).
- **Study objective:** To describe the long-term efficacy and safety of ruxolitinib on the COMFORT-I study with 1 year of additional follow-up beyond previously published data (median follow-up ~24 months).

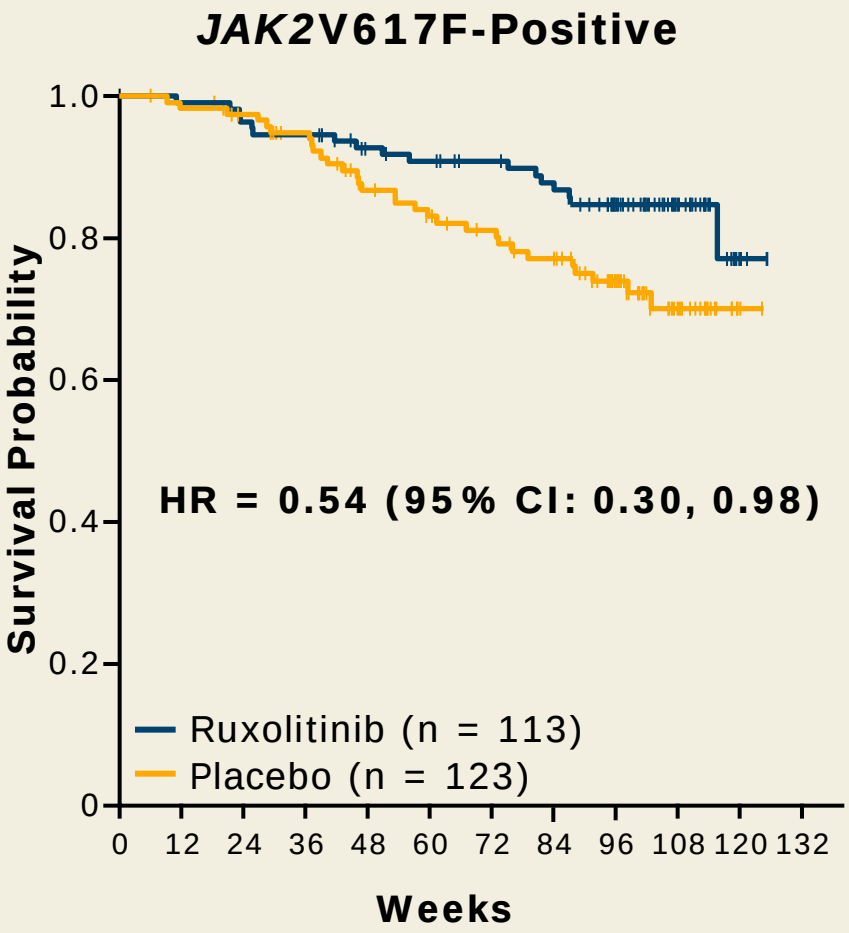
Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

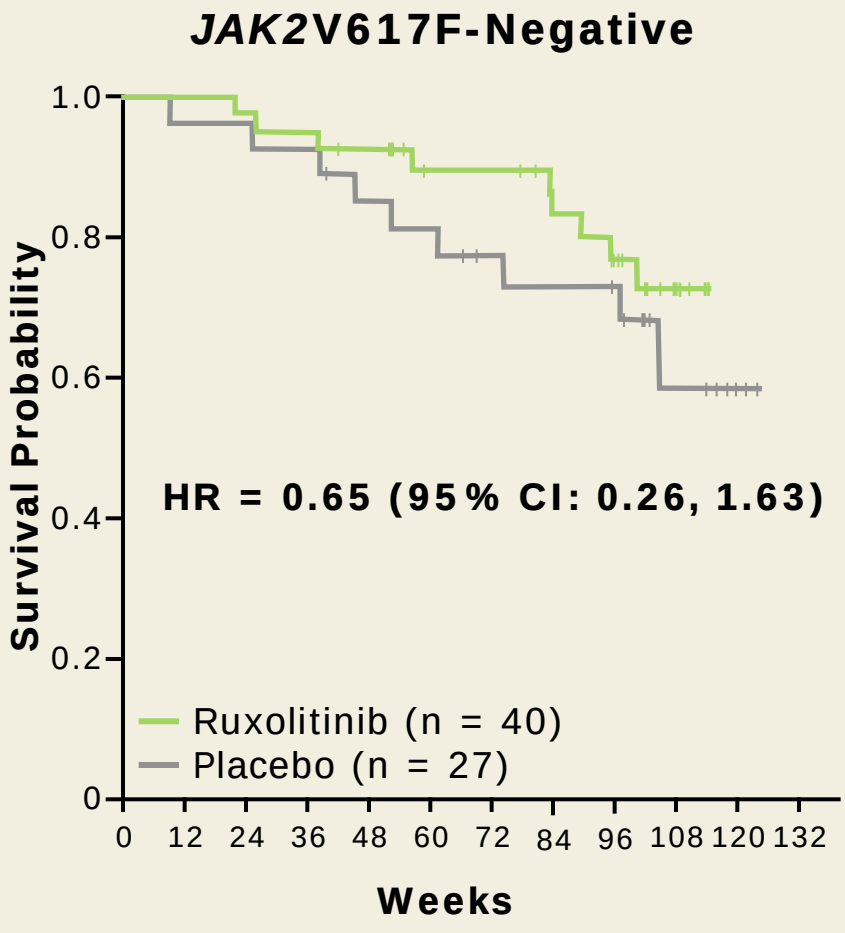
COMFORT-I: Updated Overall Survival Analysis — ITT Population



With permission from Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

COMFORT-I: Updated Overall Survival Analysis by *JAK2*V617F Mutation Status





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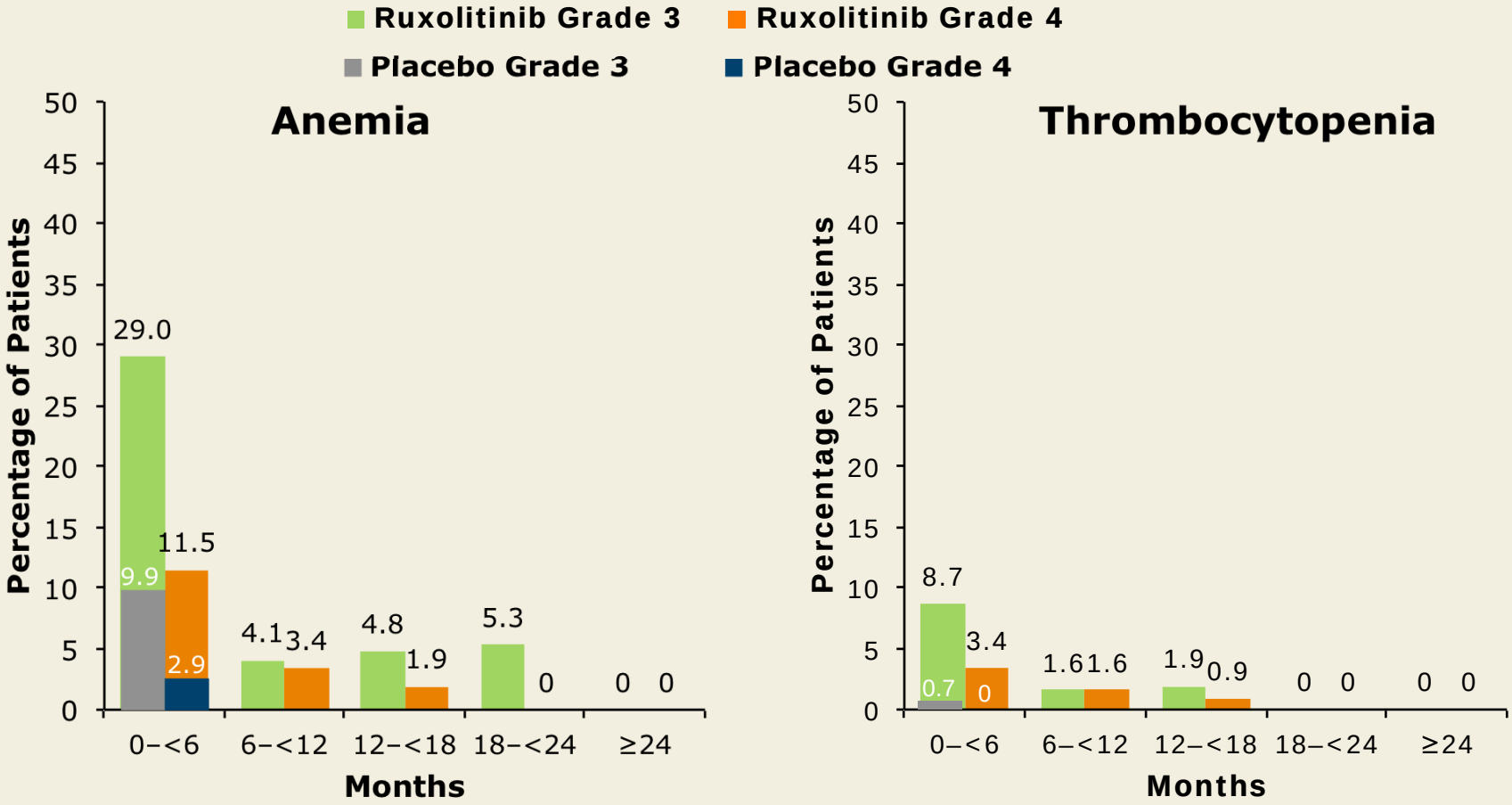
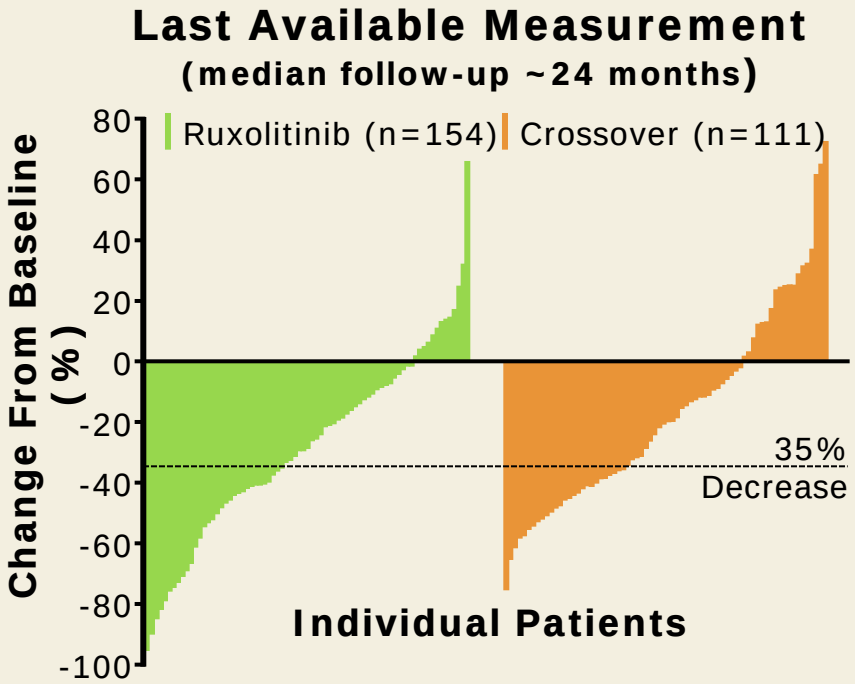
COMFORT-I: Incidence of New-Onset Grade 3 or 4 Anemia and Thrombocytopenia Over Time



- All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, data for patients receiving placebo is shown for 0–<6 months only

With permission from Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

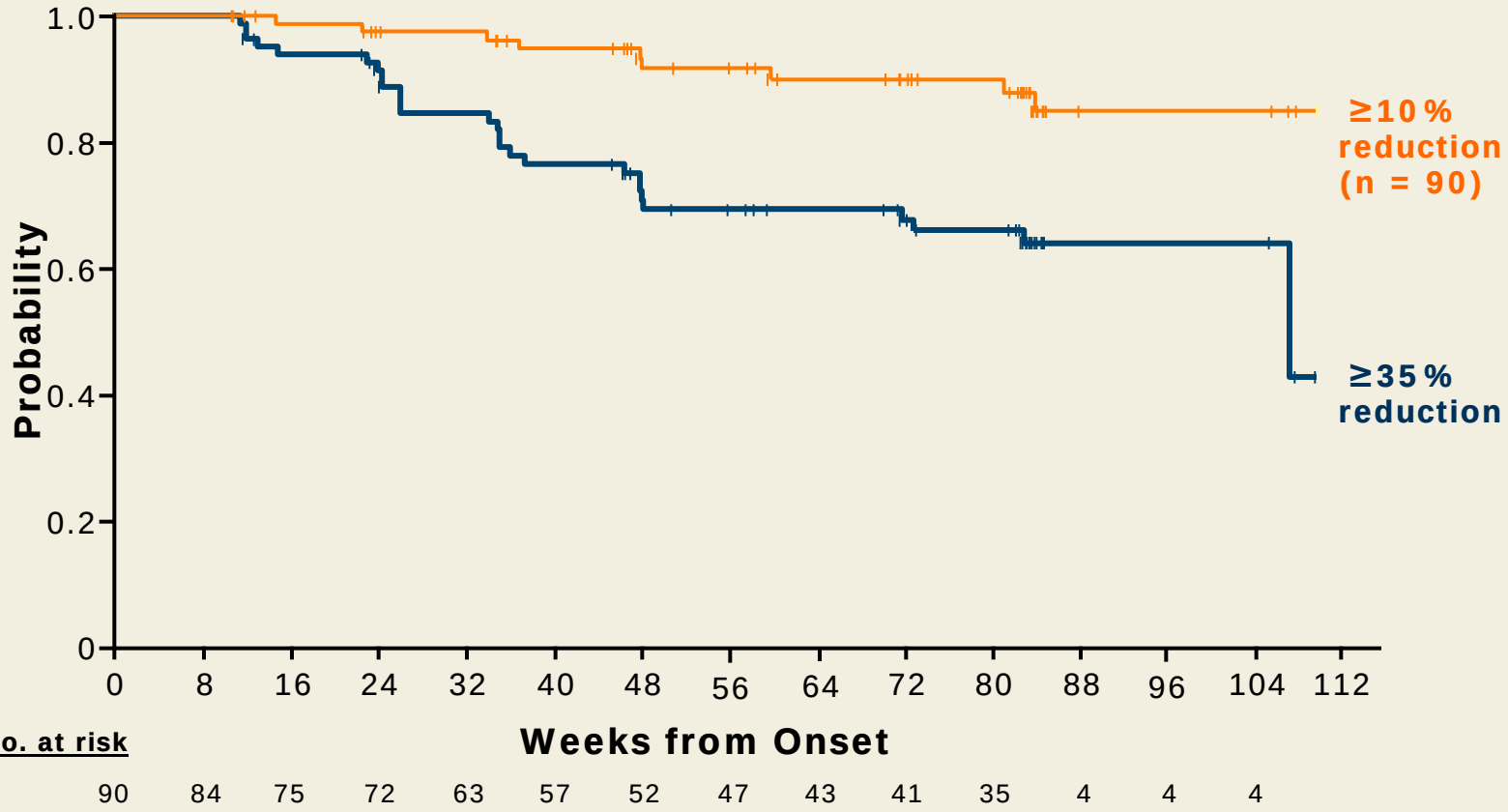
COMFORT-I: Spleen Volume Reduction



- The majority of ruxolitinib-treated patients maintained a spleen volume reduction.
- The majority of crossover patients experienced spleen volume reduction relative to baseline.

With permission from Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

COMFORT-I: Durability of Spleen Volume Reduction



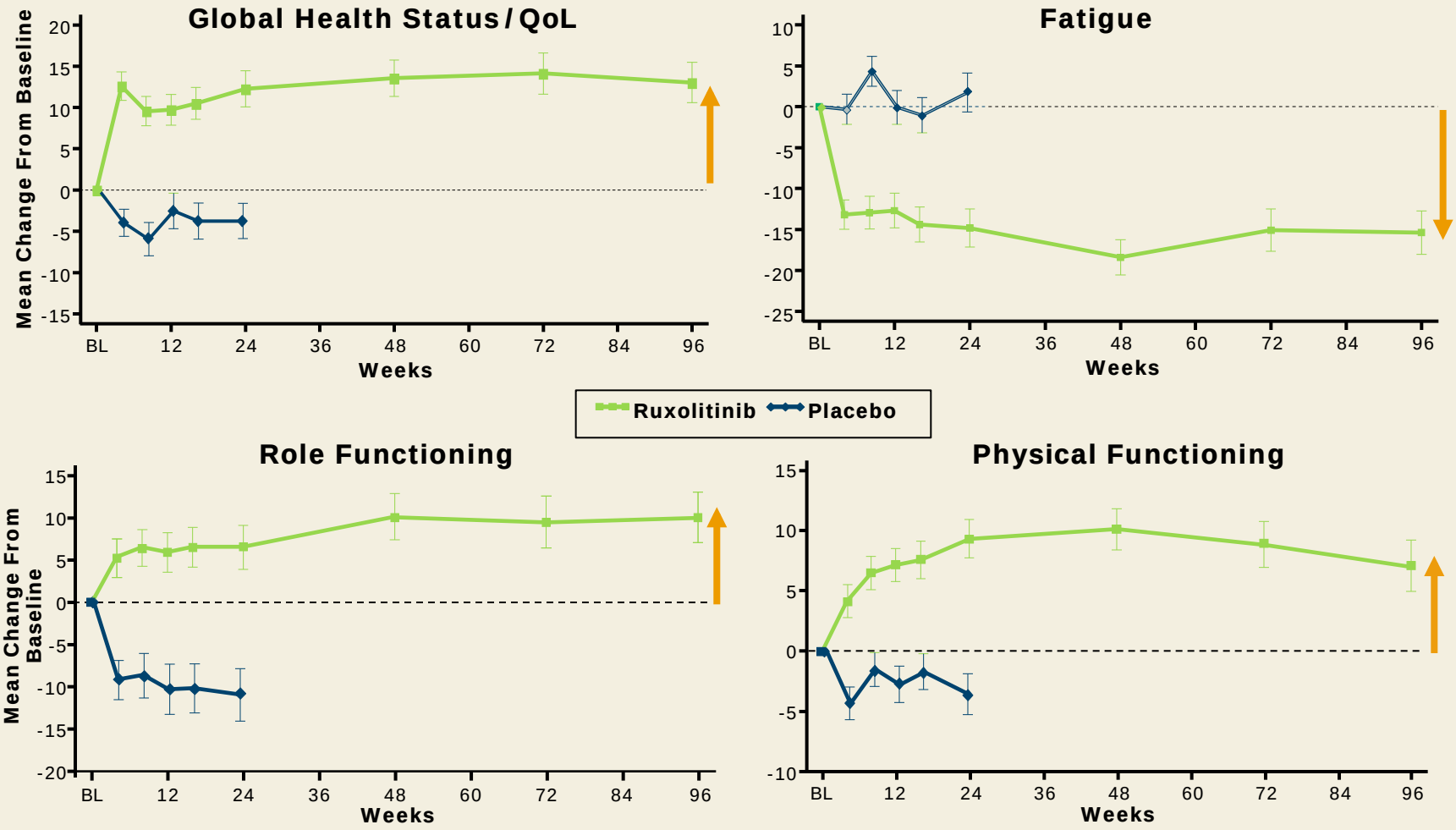
- 90/155 (58%) had a 35% reduction at any time point during the study
- 64% maintained a ≥35% reduction for at least 2 years

≥35% reduction: Time from first 35% reduction to <35% reduction and 25% increase from nadir.

≥10% reduction: Time from first 35% reduction to <10% reduction from baseline.

With permission from Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

COMFORT-I: Updated QoL Over Time (Assessed by EORTC QLQ-C30)



Arrows indicate improvement.

With permission from Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

Author Conclusions

- Ruxolitinib continues to be associated with a survival advantage relative to placebo in the COMFORT-I study.
- Reductions in spleen volume and improvements in symptoms and QoL were sustained.
- Incidence of new-onset Grade 3 or 4 anemia and thrombocytopenia decreased with longer-term therapy:
  - Proportion of patients receiving RBC transfusions decreased over time to rates similar to placebo (data not shown).
- After initiating ruxolitinib at 15 or 20 mg BID, patients titrated to a mean dose of ~10 to 15 mg BID with longer-term treatment (data not shown).
- These data reinforce the durable efficacy and longer-term safety of ruxolitinib in patients with myelofibrosis regardless of *JAK2*V617F mutation status.

Verstovsek S et al. *Proc ASH* 2012;Abstract 800.

Long-Term Safety, Efficacy, and Survival Findings from COMFORT-II, a Phase 3 Study Comparing Ruxolitinib with Best Available Therapy (BAT) for the Treatment of Myelofibrosis (MF)

Cervantes F et al.

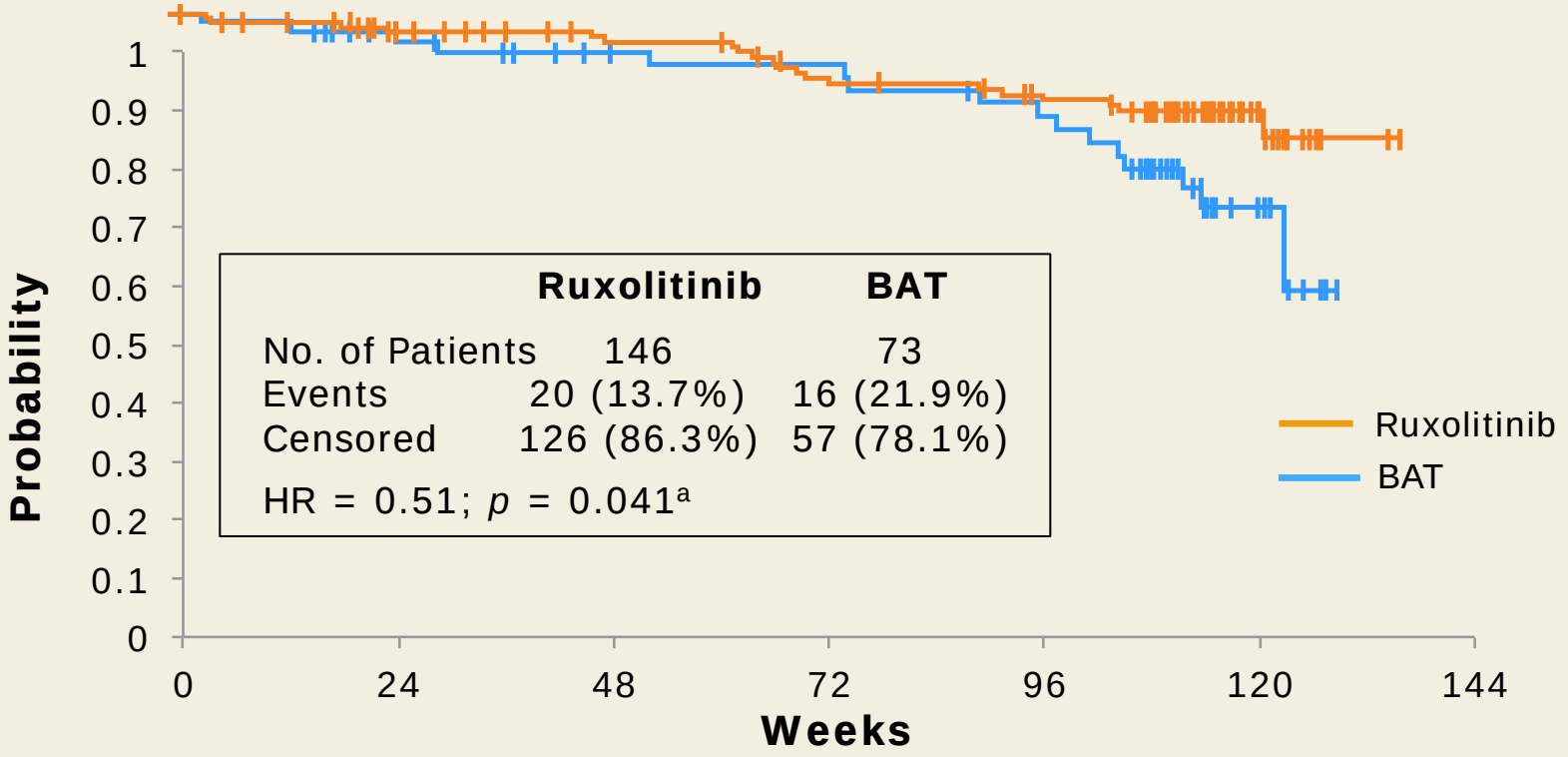
Proc ASH 2012;Abstract 801.

Background

- The primary and key secondary endpoints of the COMFORT-II trial were both met (*N Engl J Med* 2012;366:787).
  - The proportion of patients achieving a response (defined as a ≥35% reduction in spleen volume) at week 24 was 32% and 0% ($p < 0.001$) with ruxolitinib and best available therapy (BAT), respectively.
  - The proportion of patients achieving a response at 48 weeks was 28% and 0% ($p < 0.001$), respectively.
- **Study objective:** To update the efficacy and safety findings of COMFORT-II with longer follow-up (median 28 months; cutoff March 1, 2012)

Cervantes F et al. *Proc ASH* 2012;Abstract 801.

COMFORT-II: Updated Overall Survival Analysis



[a] *P* value for log-rank test is provided for descriptive purposes and was not adjusted for multiple comparisons.

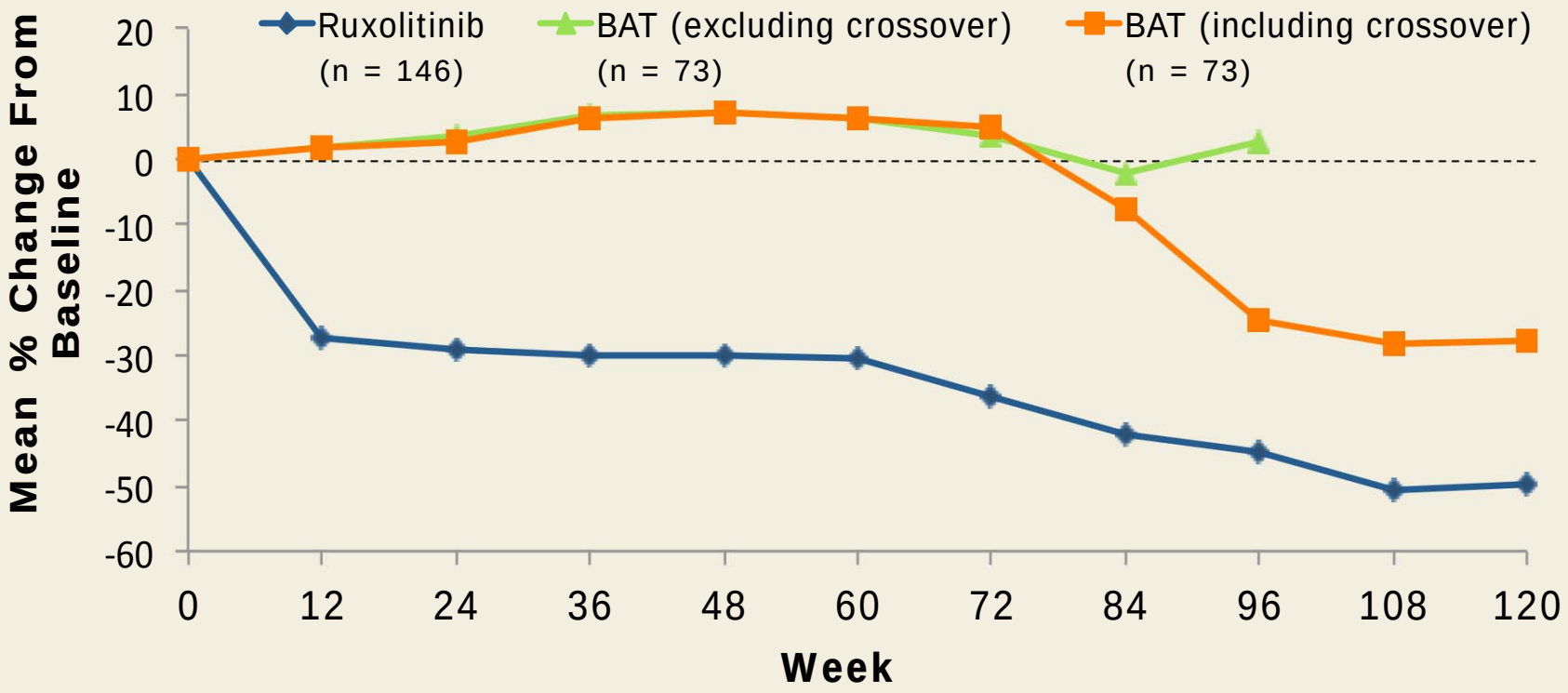
With permission from Cervantes F et al. *Proc ASH* 2012;Abstract 801.

COMFORT-II: Summary of Overall Survival Analysis

- Median survival time not yet reached for both arms:
  - OS is an exploratory endpoint in this trial. At this cutoff, there are <30% events in both arms
- Many early censored observations:
  - Lost to follow-up: BAT, 27% vs ruxolitinib, 14%
  - Survival follow-up was initially not collected (addressed later by an amendment)
  - Efforts to collect survival information ongoing
- Despite the above limitations and the switch of a majority of BAT patients to ruxolitinib, there is an apparent survival benefit favoring ruxolitinib in an ITT analysis:
  - HR = 0.51 (95% CI, 0.26-0.99), p = 0.041

Cervantes F et al. *Proc ASH* 2012;Abstract 801.

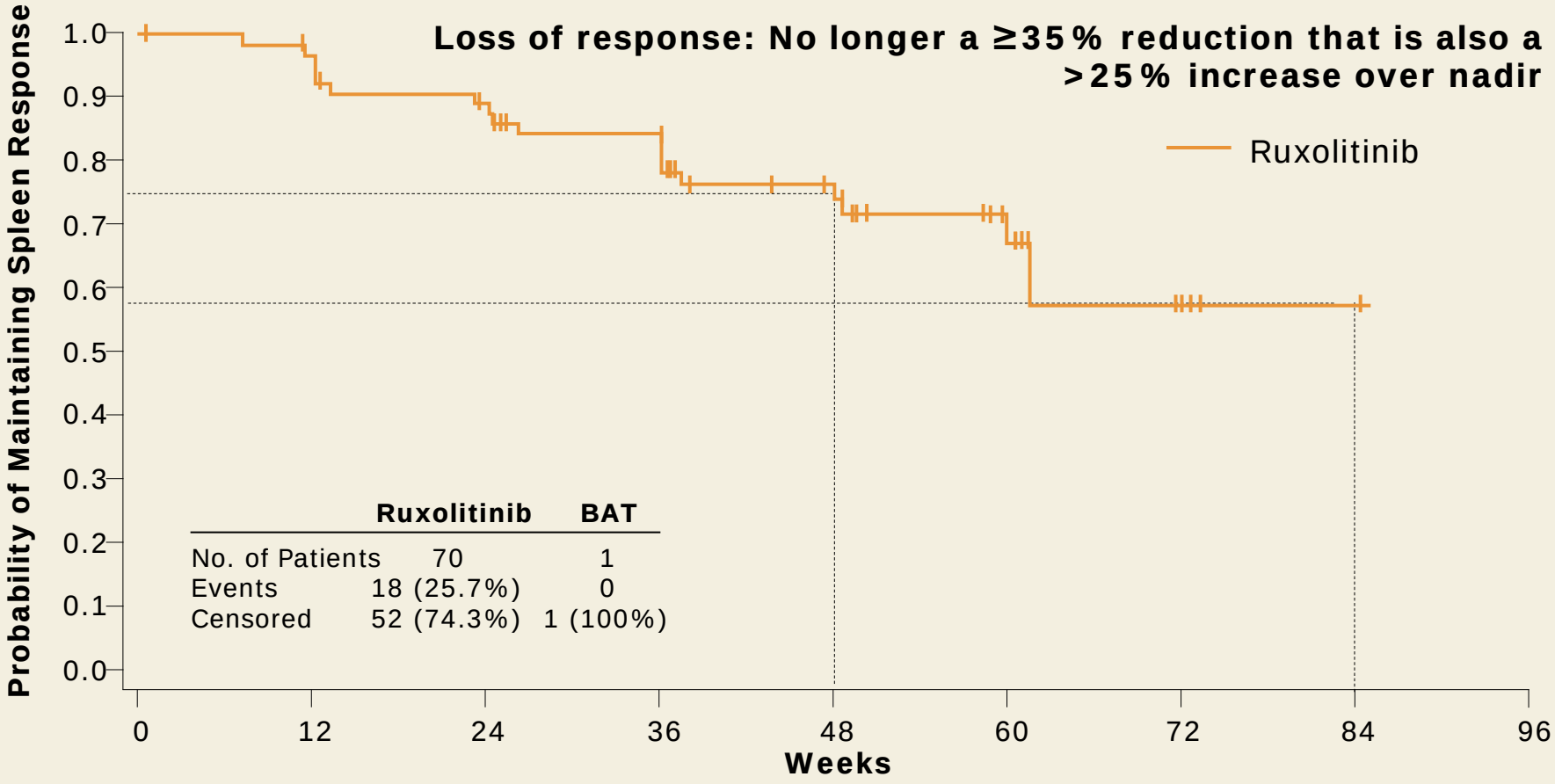
COMFORT-II: Updated Percent Change in Spleen Volume



- BAT patients who crossed over to ruxolitinib had reductions in spleen volume after crossover.

With permission from Cervantes F et al. *Proc ASH* 2012;Abstract 801.

COMFORT-II: Duration of Spleen Response



- Patients have a 58% probability of maintaining their response for 84 weeks.
- The median duration of spleen response has not yet been reached.

With permission from Cervantes F et al. *Proc ASH* 2012;Abstract 801.

Author Conclusions

- Ruxolitinib provided rapid and durable reductions in splenomegaly that were sustained over 2 years of treatment in the majority of patients on the COMFORT-II trial.
- Ruxolitinib was well tolerated, with the majority of patients remaining on study after more than 2 years of therapy (data not shown):
  - No adverse events after ruxolitinib discontinuation were observed with longer follow-up.
- Longer follow-up suggests a relative reduction in the risk of death with ruxolitinib compared to BAT:
  - This finding is consistent with the survival advantage observed in COMFORT-I (*Proc ASH* 2012;Abstract 800) and with the comparison of patients in a Phase I/II study with matched historical controls (*Blood* 2012;120(6):1202).

Cervantes F et al. *Proc ASH* 2012;Abstract 801.

Investigator Commentary: COMFORT-I and II — Updated Phase III Trial Results with the JAK1/JAK2 Inhibitor Ruxolitinib for MF

One of the most important findings of the updated results of the COMFORT-I study is the sustained splenic response, especially among patients who experienced ≥35% reduction in spleen volume. Even though some regression of response was observed, the durability of spleen volume reduction of ≥10% was maintained and ongoing beyond 2 years in the majority of the patients. Stable and ongoing improvements in symptoms are also impressive, and the modest survival advantage is confirmed in patients who received ruxolitinib compared to placebo.

The updated results of the COMFORT-II study of ruxolitinib versus best available therapy demonstrated survival benefits that should also be interpreted with caution. Spleen volume reductions were sustained, particularly in the group of patients with the deepest response. The development of anemia remains an issue with JAK2 inhibitors. However, at a ruxolitinib dose of 10 mg BID, it was limited to a few months and then tended to return to baseline levels. It is important to emphasize the lack of impact of JAK2 mutations. Responses and survival benefits were seen equally among patients with or without JAK2 mutations.

Interview with Moshe Talpaz, MD, February 19, 2013

EXPAND: A Phase 1b, Open-Label, Dose-Finding Study of Ruxolitinib in Patients with Myelofibrosis and Baseline Platelet Counts between 50 x 10^9/L and 99 x 10^9/L

Harrison CN et al.

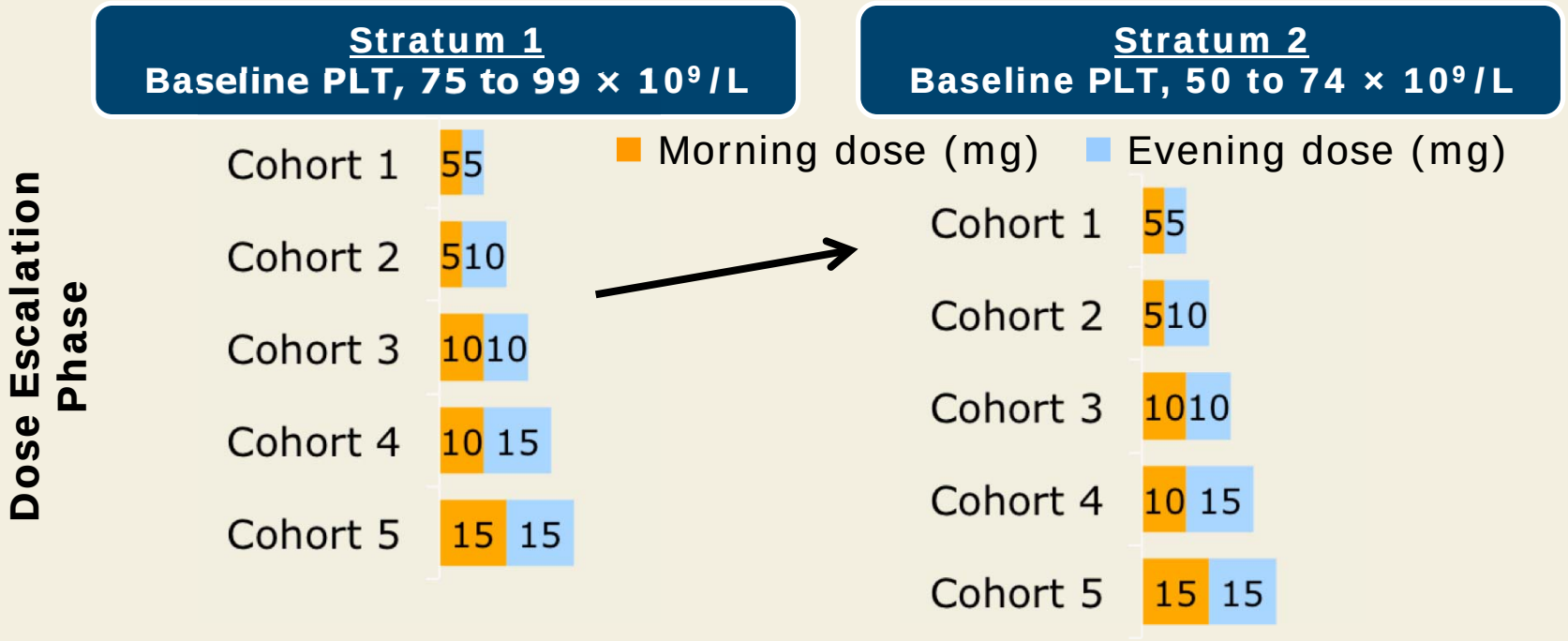
Proc ASH 2012;Abstract 177.

Background

- Ruxolitinib, a JAK1/JAK2 inhibitor, has demonstrated rapid, durable reductions in splenomegaly and improved myelofibrosis (MF)-associated symptoms and quality of life in the Phase III COMFORT-I and -II studies (*N Engl J Med* 2012;366(9):799; *N Engl J Med* 2012;366(9):787).
- To date, there has been limited experience with patients who have baseline thrombocytopenia with platelet (PLT) counts <100 × 10^9/L as this patient population was excluded from the COMFORT studies.
- **Study objective:** To evaluate the safety of ruxolitinib and to establish the maximum safe starting dose (MSSD) in patients with MF who have baseline platelet counts 50 × 10^9/L to 99 × 10^9/L.

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

EXPAND: Dose-Escalation Phase Schema



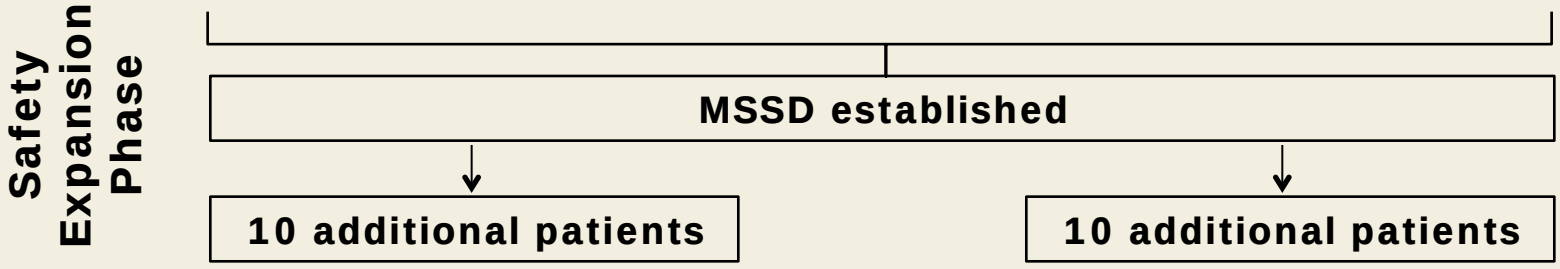
- Patients will receive increasing doses until the MSSD is determined.
  - Escalation from a given dose level to the following one will occur only if both that dose level and the previous one are deemed safe.
  - Each dose level in stratum 2 will be open to patients only if both that dose level and the following one have been deemed safe in stratum 1.
  - A minimum of 9 patients from each stratum must be treated at the dose declared to be the MSSD.

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

EXPAND: Safety Expansion Phase Schema

Stratum 1	Stratum 2
Baseline PLT, 75 to 99 × 10^9/L	Baseline PLT, 50 to 74 × 10^9/L

- In the safety expansion phase, the safety and tolerability of the MSSD will be further evaluated to establish that it is suitable for use in the low-platelet population.
- 20 patients (10 from each stratum) additional to those treated at the MSSD during dose escalation will be treated at the respective MSSD for their stratum.



Harrison CN et al. *Proc ASH* 2012;Abstract 177.

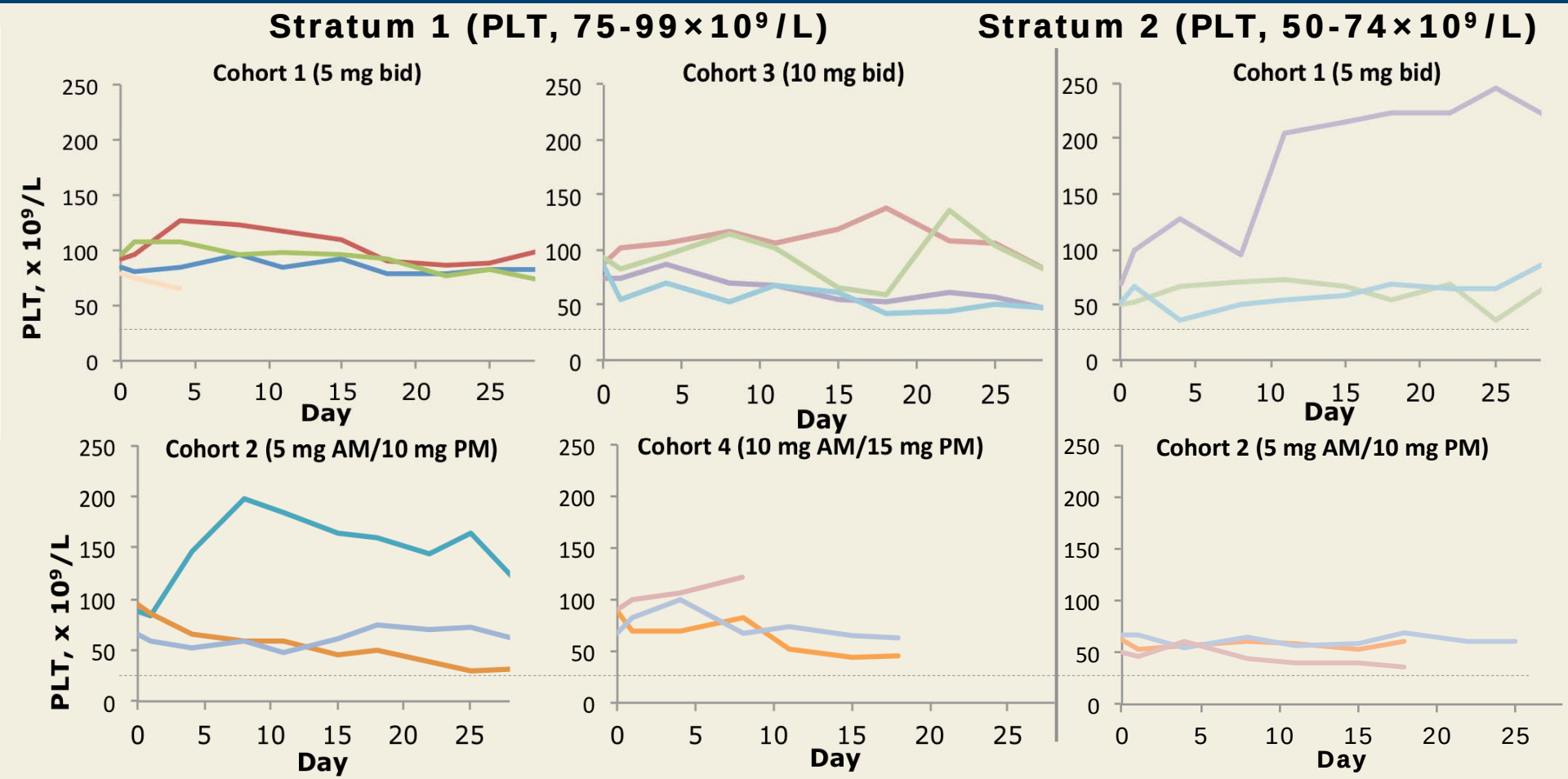
Patient Disposition

Stratum 1 (PLT, 75 to 99 × 10^9/L)					
n	Cohort 1 5 mg/5 mg	Cohort 2 5 mg/10 mg	Cohort 3 10 mg/10 mg	Cohort 4 10 mg/15 mg	Cohort 5 15 mg/15 mg
Enrolled	4	3	4	3	Enrolling
Evaluable	3	3	3	2	
Ongoing	2	2	3	3	
Stratum 2 (PLT, 50 to 74 × 10^9/L)					
n	**Cohort 1** **5 mg/5 mg**	**Cohort 2** **5 mg/10 mg**	**Cohort 3** **10 mg/10 mg**	**Cohort 4** **10 mg/15 mg**	**Cohort 5** **15 mg/15 mg**
Enrolled	3	3	Ongoing	Not open	
Evaluable	3	3			
Ongoing	3	3			

- The median duration of exposure to ruxolitinib was 65.5 days (range, 1-256 days)

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

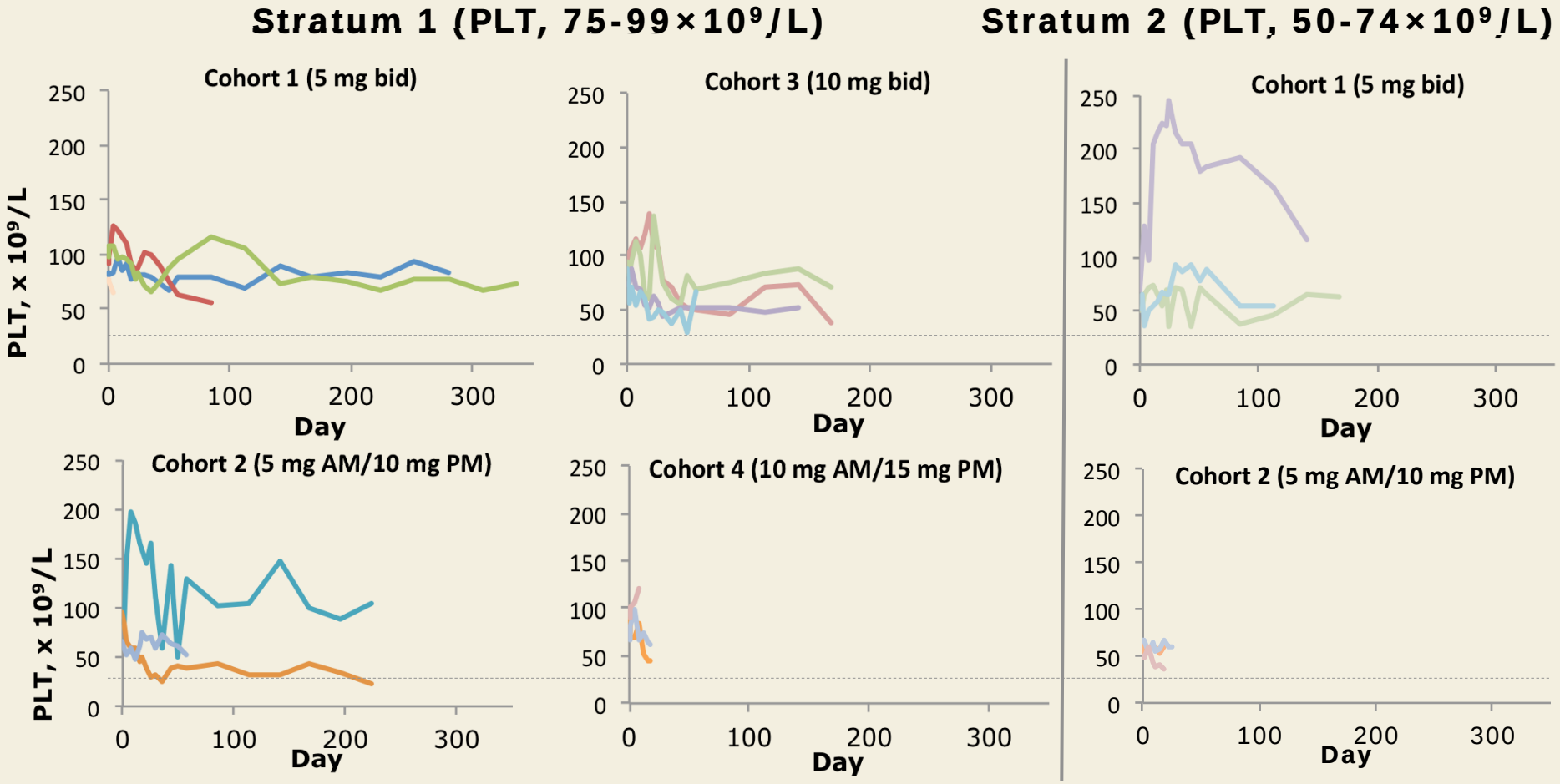
Platelet Counts During the First 28 Days (DLT Period)



- Dose changes within the first 28 days were not allowed
- PLT counts of $<25 \times 10^9$/L constitute a DLT

With permission from Harrison CN et al. *Proc ASH* 2012;Abstract 177.

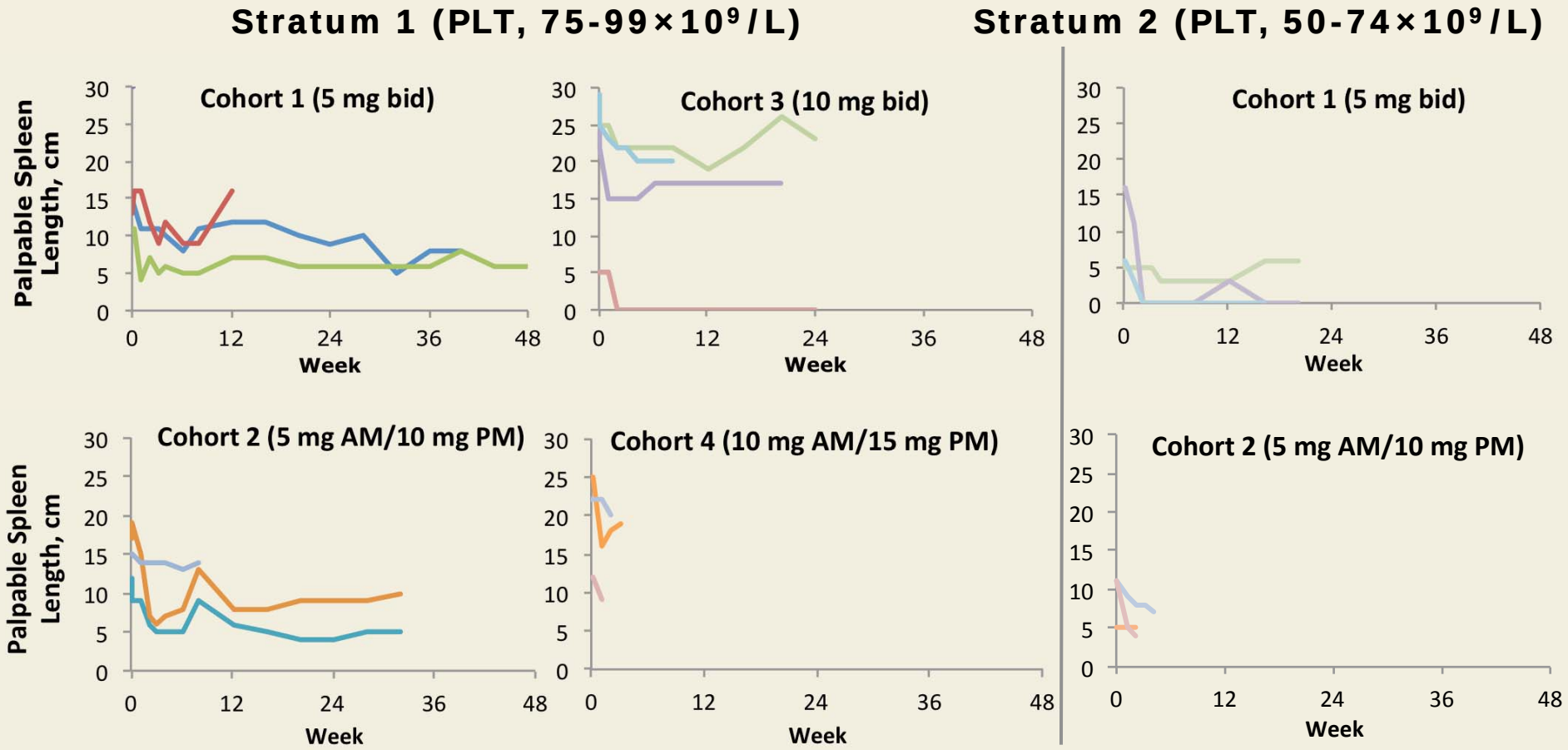
Platelet Counts up to Data Cutoff



- No patient dropped below PLT 20 × 10^9/L
- The lowest PLT count on study was 22 × 10^9/L

With permission from Harrison CN et al. *Proc ASH* 2012;Abstract 177.

Efficacy: Spleen Length Over Time



- 3 of 18 evaluable patients (17%) achieved a 100% reduction in palpable spleen length in at least 1 postbaseline assessment

With permission from Harrison CN et al. *Proc ASH* 2012;Abstract 177.

DLTs and Serious Adverse Events (SAEs)

Dose-limiting toxicity

- No DLTs were reported for 17 evaluable patients during the first 28 days of treatment

Serious adverse events

- 7 patients experienced SAEs
  - 2 related to study drug (anemia, gastrointestinal hemorrhage)

Discontinuations due to adverse events

- 3 patients discontinued because of AEs; none related to study drug
  - 1 patient had general health deterioration
  - 1 patient had blood bilirubin increased (secondary to gallstones)
  - 1 patient had third-nerve paralysis and granulocytic sarcoma

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

Author Conclusions

- No DLTs have occurred to date, and this study is ongoing.
  - Stratum 1 (PLTs 75-99 × 10^9/L) is ongoing at 15 mg bid
  - Stratum 2 (PLTs 50-74 × 10^9/L) is ongoing at 10 mg bid
- Toxicities were similar to those reported in previous studies of ruxolitinib, and no patient has discontinued due to thrombocytopenia.
  - No patient dropped below PLT 20 × 10^9/L
  - No Grade 3-4 hemorrhagic events were reported (data not shown)
- Treatment with ruxolitinib led to spleen length reductions from baseline in 17 of 20 patients.
  - 3 patients experienced complete resolution of palpable splenomegaly as best response on study
  - Spleen length reductions were similar to those observed in the COMFORT studies

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

Investigator Commentary: Phase Ib EXPAND Trial of Ruxolitinib for Patients with MF and Low Baseline Platelet Counts

The COMFORT-I and COMFORT-II studies, which evaluated the efficacy and safety of ruxolitinib for patients with MF, only enrolled patients who had platelet counts of 100 x 10^9/L or more. This study investigated whether ruxolitinib could be administered to patients with mild to moderate thrombocytopenia.

This is a classical Phase I study including small cohorts of patients for whom the ruxolitinib dose was gradually escalated. Patients with platelet counts between 50 and 99 x 10^9/L were included in the study. A small number of patients experienced an increase in platelets counts as a consequence of therapy. This is probably because thrombocytopenia was secondary to platelet sequestration by the spleen rather than poor production in the bone marrow.

This study is still ongoing and without definitive data.

Interview with Moshe Talpaz, MD, February 19, 2013

Efficacy, Hematologic Effects and Dose of Ruxolitinib in Myelofibrosis Patients with Low Platelet Starting Counts (50-100 x 10^9/L): A Comparison to Patients with Normal or High Starting Platelet Counts

Talpaz M et al.

Proc ASH 2012;Abstract 176.

Background

- The Phase III COMFORT-I trial demonstrated clinical benefit with ruxolitinib (RUX) for patients with myelofibrosis (MF) with or without the JAK2V617F mutation at starting doses of 15 or 20 mg PO BID (*NEJM* 2012;366(9):799-807).
- Reversible declines in platelet counts and hemoglobin (Hgb) can occur with RUX but are rarely treatment-limiting factors.
- Given the potential risk of bleeding complications, patients with MF with low platelet counts represent an important subset.
- **Study objective:** To assess an alternative strategy starting with a lower RUX dose with subsequent dose escalations in the treatment of MF in patients with low platelet counts.

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

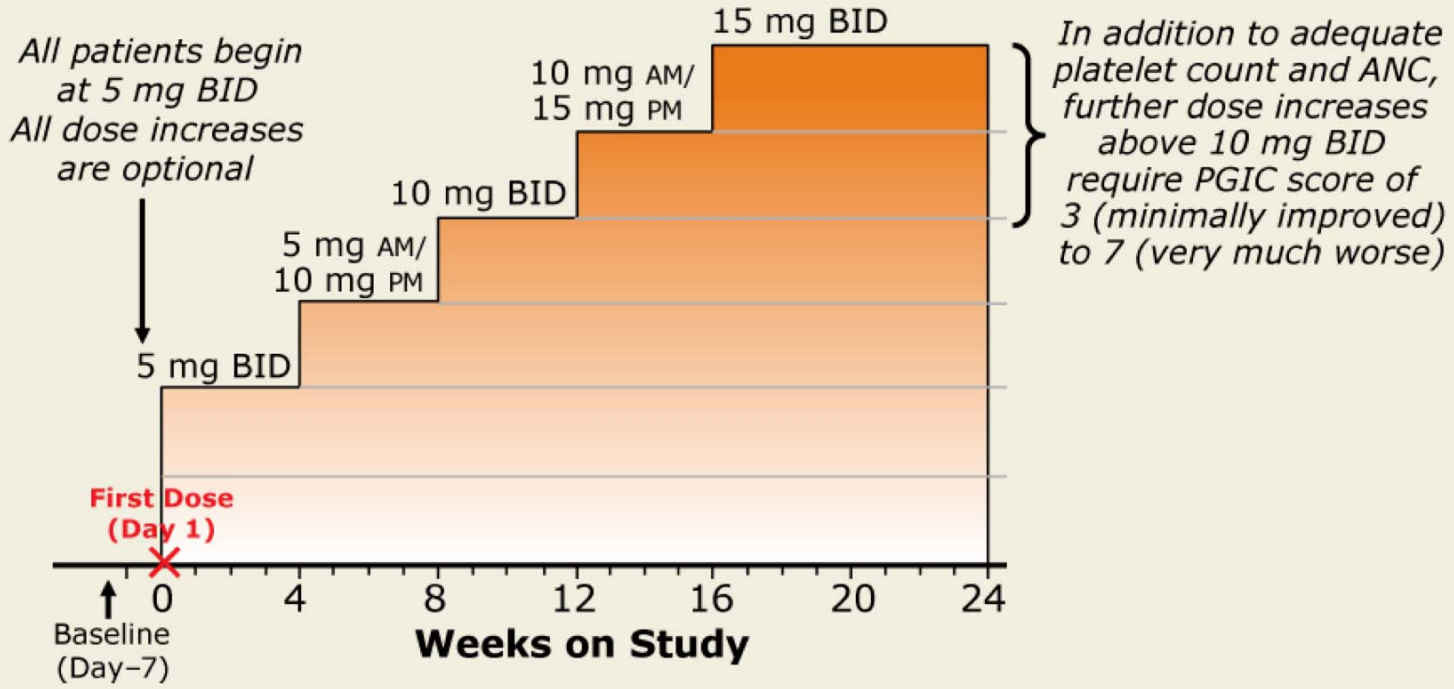
Phase II INCB018424-258 Study Design

- Eligibility:
  - Primary, postpolycythemia vera or postessential thrombocytopenia MF with symptoms
  - Platelet counts of 50-100 x 10^9/L
  - Intermediate-1, intermediate-2 or high-risk MF
- Assessments:
  - Spleen volume by MRI or CT: Baseline, week 24
  - Spleen palpation: Each study visit
  - Modified MF symptom assessment form v2.0*: Daily
  - Patient Global Impression of Change (PGIC): Every study visit starting at week 4
  - EORTC QLQ-C30: Baseline, weeks 4, 12, 24

* Total Symptom Score: Average of the daily sum of individual symptom scores over time (baseline: 7 d; week 24: 28 d) except inactivity

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Dosing Schedule



- Dose reductions required for platelet count ≥25 x 10^9/L to 35 x 10^9/L
- Dose interruptions required for platelet count <25 x 10^9/L, absolute neutrophil count <0.5 x 10^9/L or Grade ≥2 active hemorrhage
- Dosing could be restarted or re-escalated when platelet count was ≥35 x 10^9/L

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

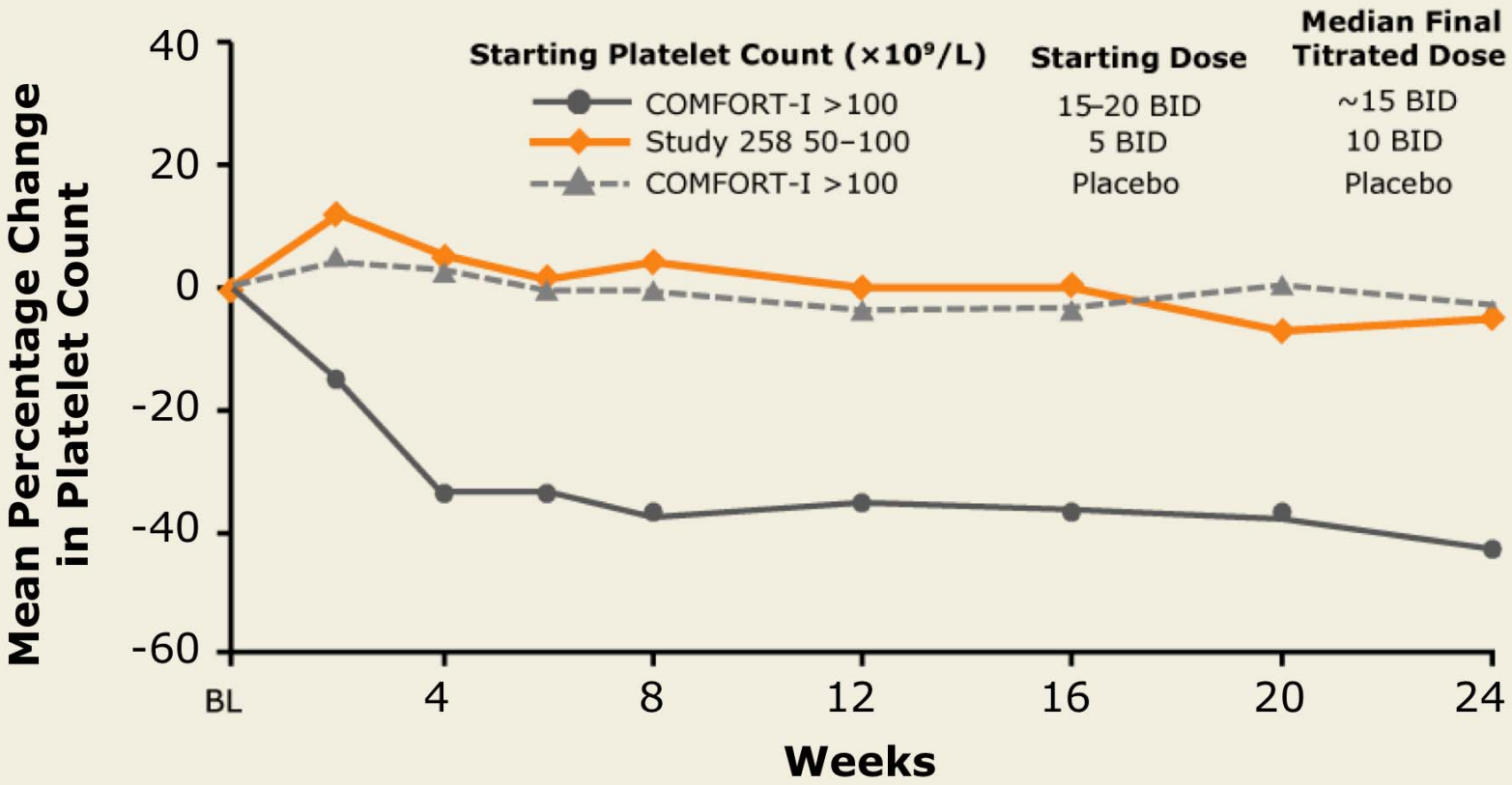
Efficacy at Week 24: Study 258 versus COMFORT-I

Efficacy parameter	Study 258 (n = 22*)	COMFORT-I	
		RUX (n = 155)	Placebo (n = 154)
≥50% reduction in TSS	36.4%	45.9%	5.3%
≥35% reduction in spleen volume	33.3%	41.9%	0.7%
Much/very much improvement on PGIC	59.1%	60.0%	7.8%
Mean change from baseline			
QLQ-C30 fatigue subscale†	-23.4	-14.8	1.8
QLQ-C30 global health/QoL‡	16.2	12.3	-3.4

* Maximum number of evaluable patients; † Negative changes indicate improvement; ‡ Positive changes indicate improvement

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Changes in Platelet Counts During Study 258 and COMFORT-I



Mean percentage change in platelet counts were comparable in RUX-treated patients in Study 258 and placebo-treated patients in COMFORT-I.

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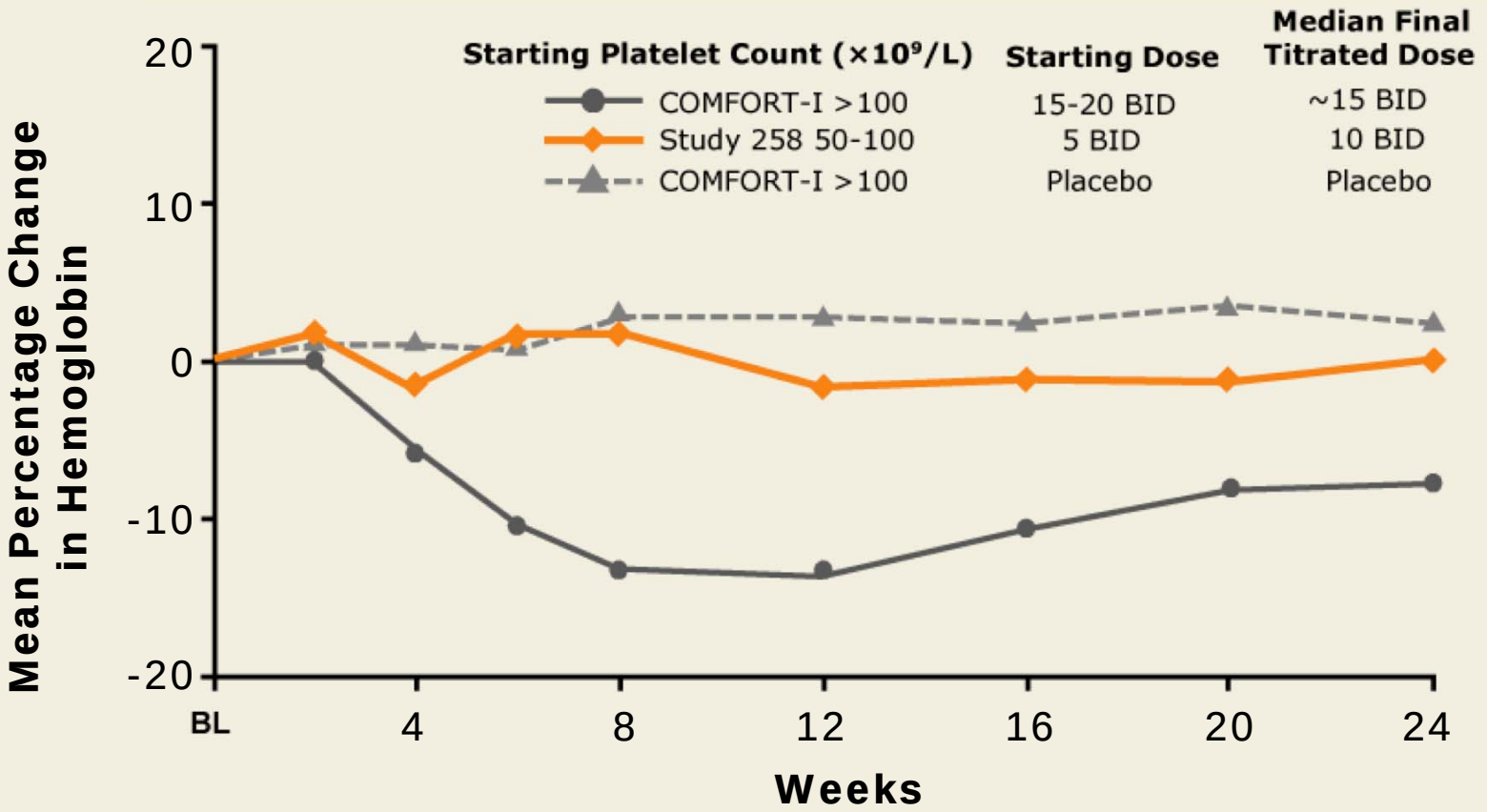
Changes in Hgb in Patients without Transfusions During Study 258 and COMFORT-I



Decreases in Hgb levels in Study 258 were of lesser magnitude compared to patients receiving RUX and similar to patients receiving placebo in COMFORT-I.

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Study 258 Select Adverse Events (Regardless of Causality)

Adverse event (n = 41)	Overall	Grade 3/4
Nonhematologic adverse events		
- Diarrhea	13 (31.7%)	2 (4.9%)
- Fatigue	9 (22.0%)	2 (4.9%)
- Nausea	9 (22.0%)	2 (4.9%)
Bleeding events		
- Subdural hematoma (secondary to fall)	1 (2.4 %)	0
- Hematochezia	1 (2.4 %)	0
- Hemorrhoidal hemorrhage	1 (2.4 %)	0
- Epistaxis	1 (2.4 %)	0

Dose reduction for adverse event: 6 (14.6%) patients
Adverse event leading to death: 2 (4.9%) patients, COPD (n = 1), unknown (n = 1)

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Author Conclusions

- For patients with baseline platelet counts of 50–100 × 10^9/L, starting at a RUX dose of 5 mg BID and titrating to 10 mg BID or greater resulted in spleen volume reductions and improvements in symptoms and QoL that were consistent with COMFORT-I.
- Decreases in mean Hgb were of lesser magnitude compared to RUX-treated patients in COMFORT-I.
- Changes in mean platelet count were similar to patients receiving placebo in COMFORT-I.
- These findings suggest that titration to 10 mg BID may be an effective and well-tolerated approach for patients with MF starting with or developing low Hgb or platelet count, while higher doses are beneficial for patients with higher Hgb and platelet count and those with inadequate response to 10 mg BID.

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Investigator Commentary: Efficacy, Safety and Dose of Ruxolitinib for Patients with MF with Low Starting Platelet Counts

This study determined whether ruxolitinib should be administered to patients with mild to moderate thrombocytopenia. The take-home message was that the vast majority of patients can be treated if they have a platelet count from 50 to 100 x 10^9/L. Most of these patients will end up receiving ruxolitinib therapy at 15 to 20 mg/d. In addition, the responses observed were slightly lower than was observed in the COMFORT-I and II trials, with about 35% of patients experiencing a reduction in spleen volume to a level of partial response. About 40% of the patients experienced ≥50% reduction in symptoms. Anemia was much less pronounced, probably due to the gradual dose escalation. This strategy is likely to be adopted by physicians. An interesting finding was the identification of a small group of 5 patients, or about 11% of the total study population, who experienced an increase in platelet counts after therapy as opposed to a decrease. This was most likely because thrombocytopenia was secondary to platelet sequestration by the spleen rather than poor bone marrow production. These patients were diagnosed early and had a better prognosis. The other patients had a predictable drop in platelets.

Interview with Moshe Talpaz, MD, February 19, 2013

Homoharringtonine-Based Induction Regimens for Patients with De Novo Acute Myeloid Leukemia: A Multicenter Randomized Controlled Phase 3 Trial

Jin J et al.

Proc ASH 2012;Abstract 45.

Background

- Homoharringtonine is a plant alkaloid that inhibits protein synthesis and has considerable activity in patients with acute myeloid leukemia (AML).
- Homoharringtonine-based induction regimens have been widely used in China for patients with AML and have been shown to improve the rate of complete remission (CR) and overall survival (*Leukemia* 2006;20:1361).
- **Study objective:** To further evaluate the efficacy and safety of homoharringtonine-based induction regimens for patients with de novo AML.

Jin J et al. *Proc ASH* 2012;Abstract 45.

Phase III Study Methods

- This Phase III study evaluated patients between the ages of 14 and 59 with untreated AML in 17 institutions in China.
- Patients were randomly assigned to receive as induction:
  - HAA (homoharringtonine/cytarabine/aclarubicin)
  - HAD (homoharringtonine/cytarabine/daunorubicin)
  - DA (daunorubicin/cytarabine)
- Patients who achieved partial remission or had a decrease of blast >60% could receive a second induction course of the same regimen.
- All patients who achieved a complete remission (CR) were offered the same regimen as consolidation chemotherapy according to cytogenetic risk.
- **Primary endpoints:**
  - CR and event-free survival (EFS)

Jin J et al. *Proc ASH* 2012;Abstract 45.

Complete Remission Rate with First Course of Induction Therapy (Abstract Only)

Induction regimen	Complete remission rate
HAA	67.5%
HAD	64.9%
DA	54.0%
HAA vs DA, p = 0.005; HAD vs DA, p = 0.026	

- The overall CR rate remained significantly higher in the HAA arm than in the DA arm (75.0% vs 61.9%, p = 0.005).

Jin J et al. *Proc ASH* 2012;Abstract 45.

Median EFS for All Patients (Abstract Only)

Induction regimen	n	Events	Censored	Median EFS
HAA	206	127	79	11.7 mo
HAD	198	130	68	8.6 mo
DA	205	154	51	6.9 mo

- Three-year EFS was greatly improved in the HAA arm versus the DA arm (35.4 ± 3.5% vs 23.1 ± 3.1%, p = 0.002).
- Three-year EFS was not significantly improved in the HAD arm versus the DA arm (32.7 ± 3.5% vs 23.1 ± 3.1%, p = 0.078).
- Patients in the HAD arm with NPM1 but not FLT3 ITD mutations had an improved EFS versus those in the DA arm (p = 0.038).

Jin J et al. *Proc ASH* 2012;Abstract 45.

Median Overall Survival (OS) for Patients with Favorable or Intermediate Cytogenetic Profiles (Abstract Only)

Induction regimen	n	Deaths	Censored	Median OS
HAA	149	66	83	Not reached
HAD	139	73	66	20.6 mo
DA	147	88	59	18.4 mo
HAA vs DA, p = 0.014; HAD vs DA, p = not significant				

- In patients with favorable or intermediate cytogenetic profiles, an OS advantage of the HAA arm over the DA arm was observed.
- In the overall patient population, OS did not differ significantly in the HAA or HAD arms versus the DA arm.

Jin J et al. *Proc ASH* 2012;Abstract 45.

Median Relapse-Free Survival (RFS) for Patients with Favorable or Intermediate Cytogenetic Profiles (Abstract Only)

Induction regimen	n	Relapse / deaths	Censored	Median RFS
HAA	119	50	69	Not reached
HAD	94	48	46	17.8 mo
DA	93	55	38	15.9 mo
HAA vs DA, p = 0.022; HAD vs DA, p = not significant				

- In patients with favorable or intermediate cytogenetic profiles, an RFS advantage of the HAA arm over the DA arm was observed.
- Patients with intermediate cytogenetic profile and mutant CEBPA had prolonged RFS in the HAA arm versus the DA arm (p = 0.045).
- In the overall population, RFS did not differ significantly in the HAA or HAD arms versus the DA arm.

Jin J et al. *Proc ASH* 2012;Abstract 45.

Adverse Events (Abstract Only)

- The HAA and HAD regimens had similar rates of adverse events as compared to the DA regimen.
- **Significant increase in risk of induction death:**
  - HAA vs DA (5.8% vs 1.0%, $p = 0.007$)
  - HAD vs DA (6.6% vs 1.0%, $p = 0.003$)

Jin J et al. *Proc ASH* 2012;Abstract 45.

Author Conclusions

- Homoharringtonine-based induction regimens are associated with higher rates of complete remission and improved survival compared to the DA regimen for patients with de novo AML and favorable or intermediate cytogenetic profiles.
- Toxicities were mild with the exception of a higher rate of induction death:
  - HAA versus DA (5.8% vs 1.0%, $p = 0.007$)
  - HAD versus DA (6.6% vs 1.0%, $p = 0.003$)

Jin J et al. *Proc ASH* 2012;Abstract 45.

Investigator Commentary: A Phase III Trial of Homoharringtonine-Based Induction Regimens for Patients with De Novo Acute Myeloid Leukemia

Homoharringtonine (HHT) is an old drug, also known as omacetaxine. It was recently approved as a treatment for chronic myeloid leukemia. This intriguing study included a large number of patients treated in 3 different arms. The induction included an anthracycline/cytarabine with or without HHT. The 2 arms including HHT demonstrated about a 10% better response rate with an improved survival advantage compared to the arm without HHT. However, there was a higher risk of death among the patients who received HHT. Further analysis of prognostic features showed that patients with AML harboring NPM1 mutations or CEBPA mutations, who are considered to be at low risk, tend to respond better to combination therapy including HHT. The difference was more pronounced in this particular group.

Although I am unable to attest to how carefully this study was conducted, these data need to be verified and should not be ignored. HHT is a protein synthesis inhibitor, and perhaps because its mechanism of action is different from anthracyclines and nucleoside analogs, it is synergistic with those drugs.

Interview with Moshe Talpaz, MD, February 19, 2013

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients ≥60 Years of Age with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia[1]

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia After Second-Line Chemotherapy or Hematopoietic Stem Cell Transplant[2]

[1]**Cortes JE et al.**

Proc ASH 2012;Abstract 48.

[2]**Levis MJ et al.**

Proc ASH 2012;Abstract 673.

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients ≥60 Years of Age with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia

Cortes JE et al.

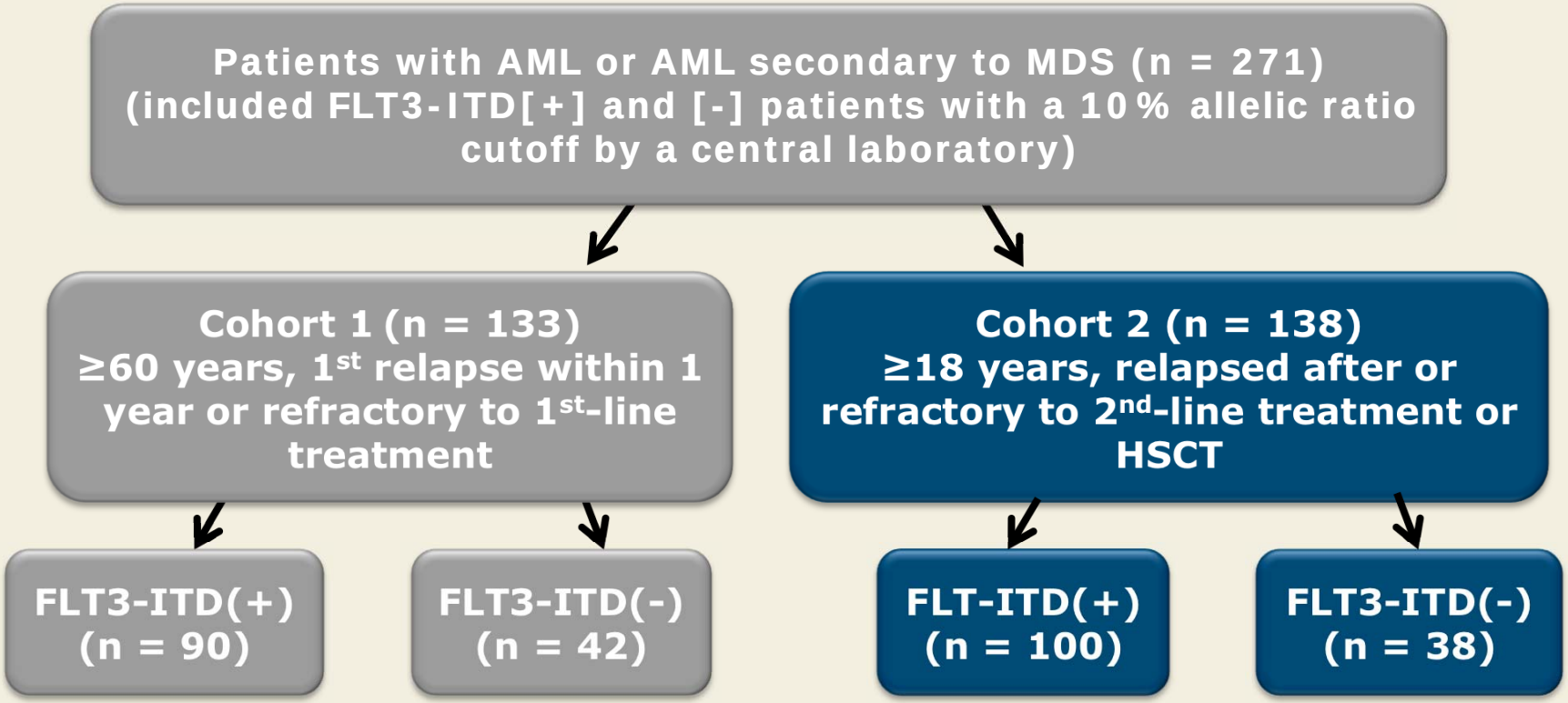
Proc ASH 2012;Abstract 48.

Background

- FMS-like tyrosine kinase 3 internal tandem duplications (FLT3-ITD) occur in 34% of patients with acute myeloid leukemia (AML) and are associated with a poor prognosis (*Blood* 2002;100:1532).
- Quizartinib (AC220) is an oral FLT3 receptor tyrosine kinase inhibitor that is active against both ITD-mutant and wild-type FLT3 and has shown promising activity in a Phase I study of patients (pts) with AML.
- **Study objective:** To assess the efficacy and safety of quizartinib monotherapy in cohort 1 of a 2-cohort study of patients with FLT3-ITD-positive and negative relapsed/ refractory AML.

Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Phase II Trial Design



- 333 patients enrolled in Phase II (first 62 in an exploratory phase)
- **Primary endpoint:** Composite complete remission (CRc)
- **Secondary endpoints:** Complete remission (CR), duration of response, bridge to hematopoietic stem cell transplantation (HSCT) and overall survival (OS)

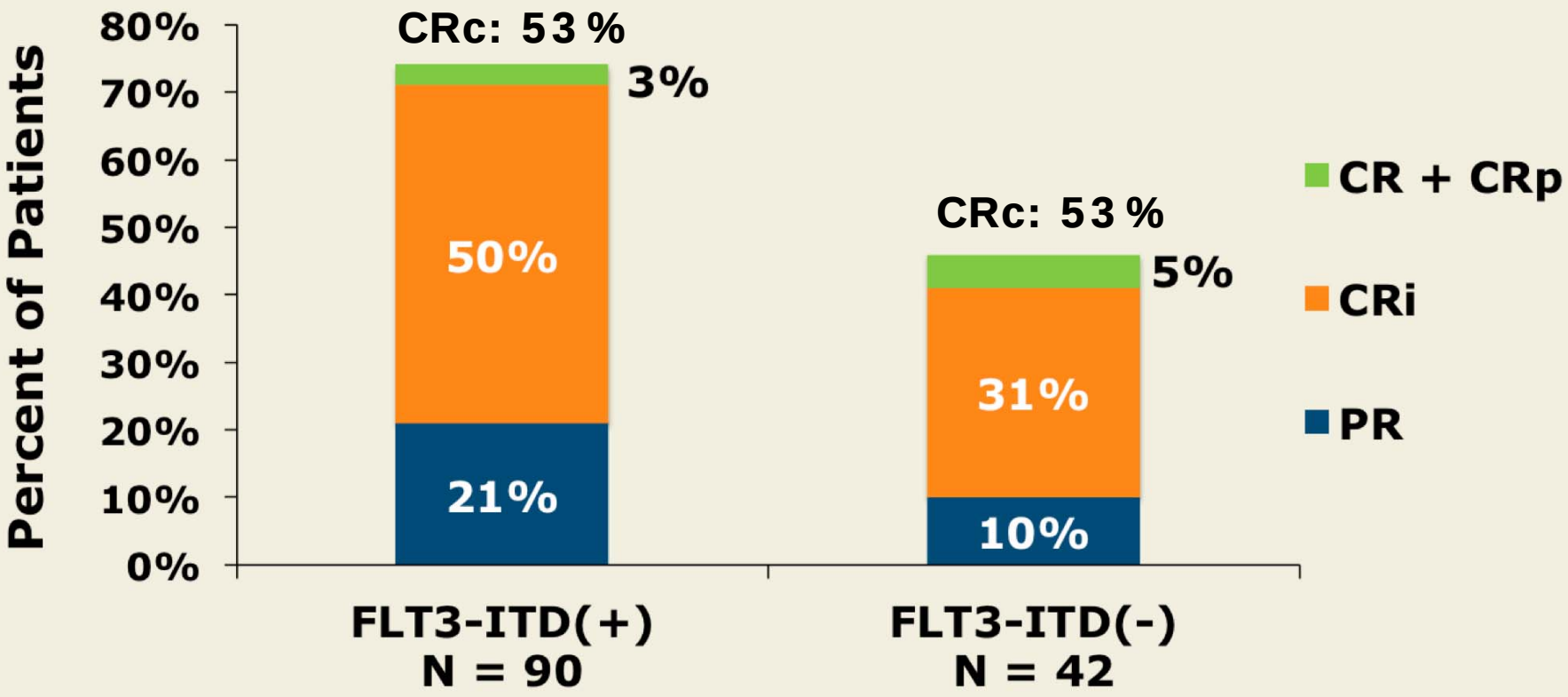
Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Exploratory Phase: Summary of Results

- 24 patients were enrolled in Cohort 1 and 38 patients in Cohort 2 at 200 mg/d of quizartinib in the exploratory phase of the trial.
- The CRc rate and overall survival (OS) were determined (CRc = CR + CR with incomplete platelet recovery [CRp] + CR with incomplete hematologic recovery [CRi]).
- CRc = 67% and 42%, respectively, in Cohort 1 and Cohort 2
- Median duration of CRc = 14.3 wk (cohort 1) and 10.4 wk (cohort 2)
- Median OS = 26.3 wk (cohort 1) and 24.6 wk (cohort 2)
- Starting dose for subsequent analysis of patients in confirmatory Cohort 1 and 2 was established at 135 mg/d (males) and 90 mg/d (females).
- Dose was reduced from initial starting dose due to Grade 3 QT prolongation.

Cortes JE et al. *Proc ASH* 2012;Abstract 48.

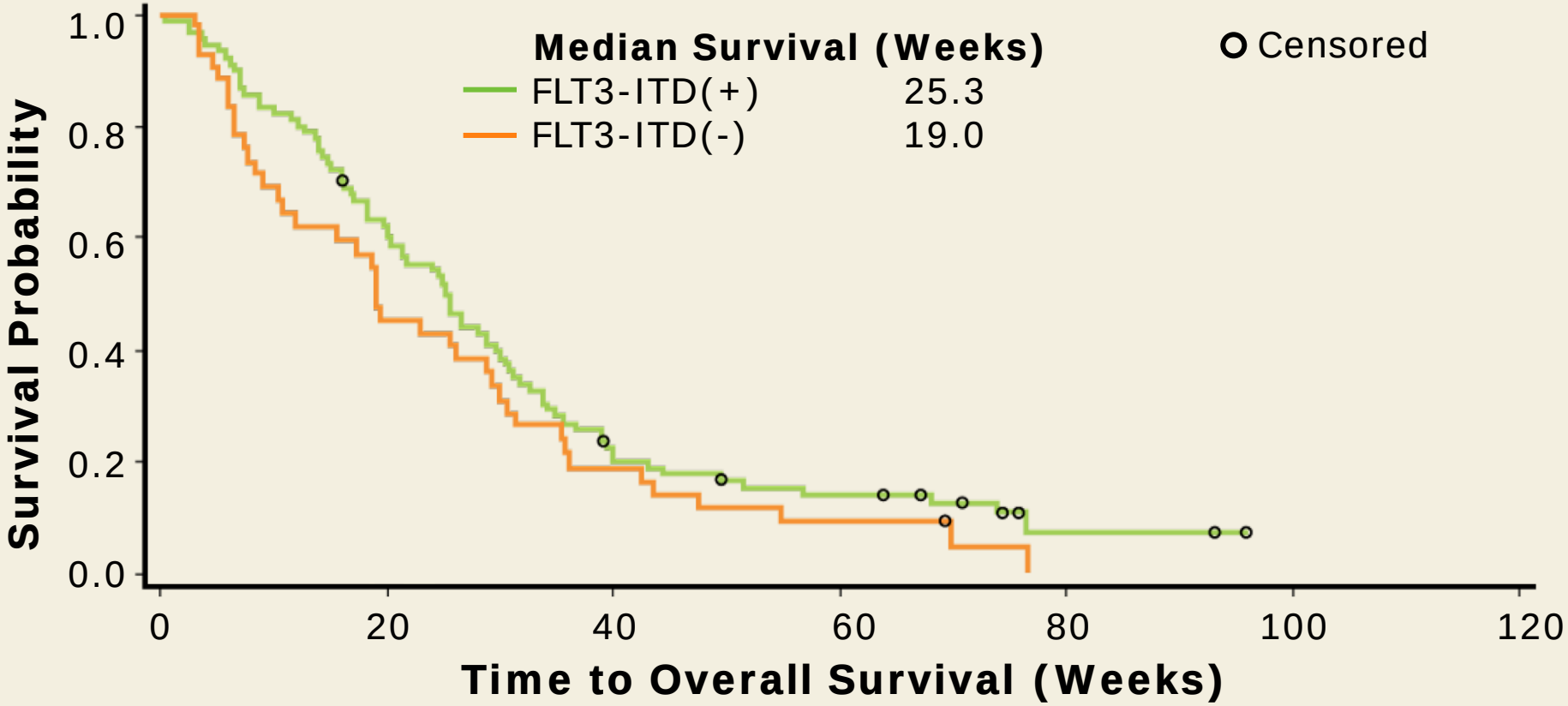
Confirmatory Cohort 1: Response to Quizartinib



- 70% of patients with FLT3-ITD(+) and 55% with FLT3-ITD(-) AML refractory to last prior therapy achieved at least a PR
- Median CRc duration: 10.4 wk for FLT3-ITD(+), 9.3 wk for FLT3-ITD(-)

With permission from Cortes JE et al. *Proc ASH* 2012;Abstract 48.

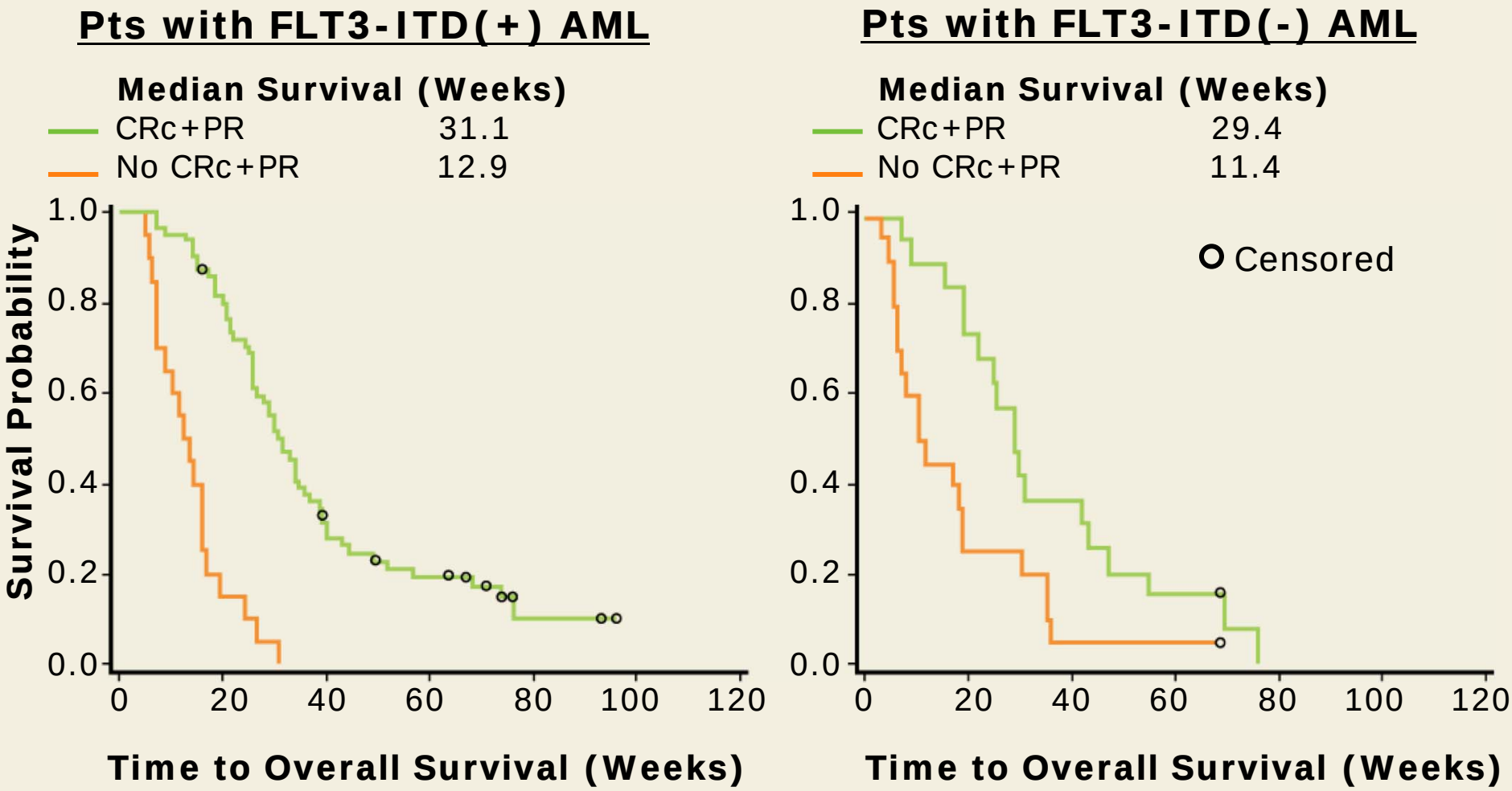
Confirmatory Cohort 1: OS by FLT3-ITD Status



- 12/90 (13%) patients with FLT3-ITD(+) and 5/42 (12%) with FLT3-ITD(-) AML survived 12+ months
- 2 patients with FLT3-ITD(+) AML survived 18+ months

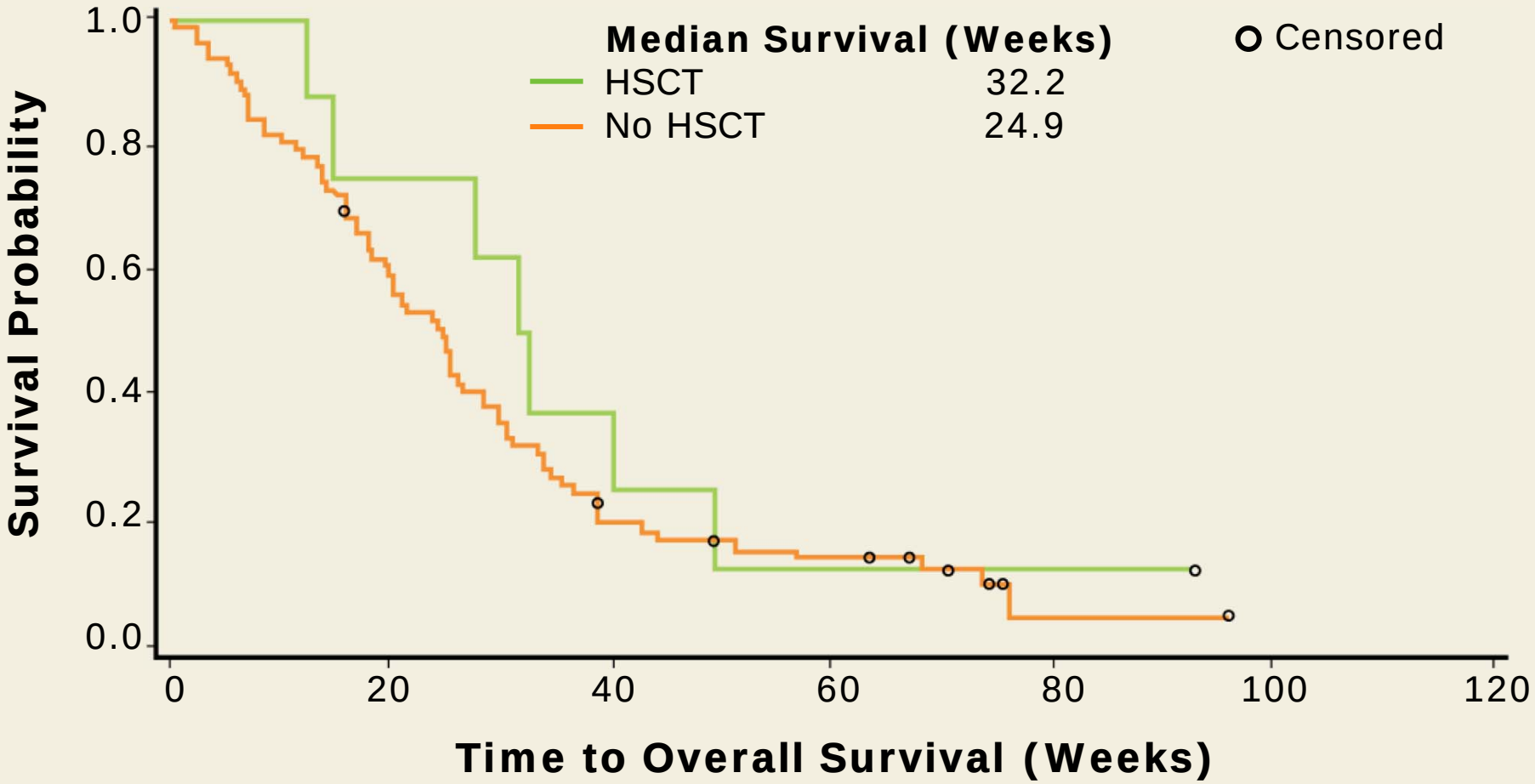
With permission from Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Confirmatory Cohort 1: OS by Response



With permission from Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Confirmatory Cohort 1: OS for Patients with FLT3-ITD(+) AML by HSCT



With permission from Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Confirmatory Cohort 1: Select Adverse Events (AEs)

Grade	FLT3-ITD(+) (n = 90)		FLT3-ITD(-) (n = 42)	
	All	3 or 4	All	3 or 4
Any AE	100%	89%	100%	88%
Nausea	56%	1%	48%	5%
Diarrhea	41%	3%	43%	7%
Anemia	34%	33%	24%	20%
Febrile neutropenia	33%	33%	48%	48%
Thrombocytopenia	32%	29%	21%	19%
QT prolongation*	30%	10%	21%	12%

*All were Grade 3 except for 1 Grade 4 (torsade de pointes)

Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Confirmatory Cohort 1: Disposition of Patients

Patient, n (%)	FLT3-ITD(+) (n = 90)	FLT3-ITD(-) (n = 42)	Total* (n = 133)
Active treatment	2 (2%)	0	2 (1%)
Discontinued treatment	88 (98%)	42 (100%)	131 (99%)
Relapse	35 (39%)	10 (24%)	45 (34%)
Adverse event(s)	23 (26%)	12 (29%)	35 (27%)
Death	5 (6%)	4 (10%)	9 (7%)
HSCT	8 (9%)	1 (2%)	10 (8%)
Lack of response	15 (17%)	13 (31%)	28 (21%)
Other reason	2 (2%)	2 (5%)	4 (3%)

*1 patient with unknown FLT3-ITD status discontinued for HSCT

Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Author Conclusions

- Quizartinib produced high response rates in relapsed/refractory FLT3-ITD-positive AML.
- The responses are clinically meaningful with some patients successfully bridged to transplant.
- 17 patients (13%) survived >1 y of therapy and 10 (8%) were alive at the last follow-up.
- Quizartinib is well tolerated with manageable toxicities:
  - GI toxicities, reversible QT prolongation and myelosuppression, possibly related to KIT inhibition
- Future directions include:
  - A randomized 2-dose (30 vs 60 mg) study in relapsed/refractory FLT3-ITD-positive AML — currently accruing
  - Combination studies
  - A randomized Phase III study is planned for the end of 2013

Cortes JE et al. *Proc ASH* 2012;Abstract 48.

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia After Second-Line Chemotherapy or Hematopoietic Stem Cell Transplant

Levis MJ et al.

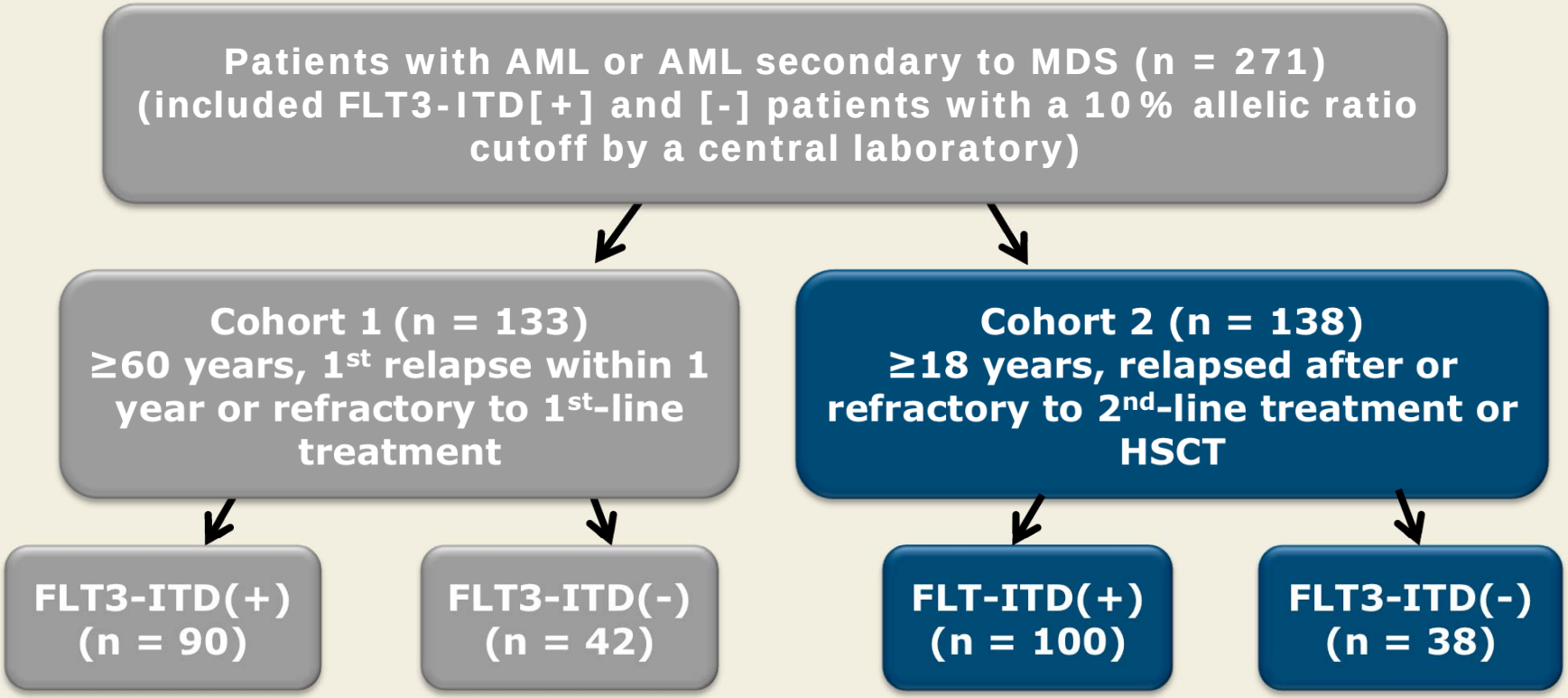
Proc ASH 2012;Abstract 673.

Background

- In acute myeloid leukemia (AML), the FLT3-ITD mutation occurs in 34% of patients and constitutively activates FLT3 (*Blood* 2002;100(5):1532-42).
- FLT3-ITD mutation is associated with high blast counts, increased rate of relapse, more rapid relapse and reduced overall survival.
- Quizartinib (AC220) is a potent and selective inhibitor of the FLT3 receptor tyrosine kinase (*J Medicinal Chemistry* 2009;52 (23):7808).
- **Study objective:** To assess the efficacy and safety of quizartinib monotherapy in cohort 2 of a 2-cohort study of patients with FLT3-ITD-positive and negative AML, relapsed or refractory to second-line salvage chemotherapy or relapsed after hematopoietic stem cell transplantation (HSCT).

Levis MJ et al. *Proc ASH* 2012;Abstract 673.

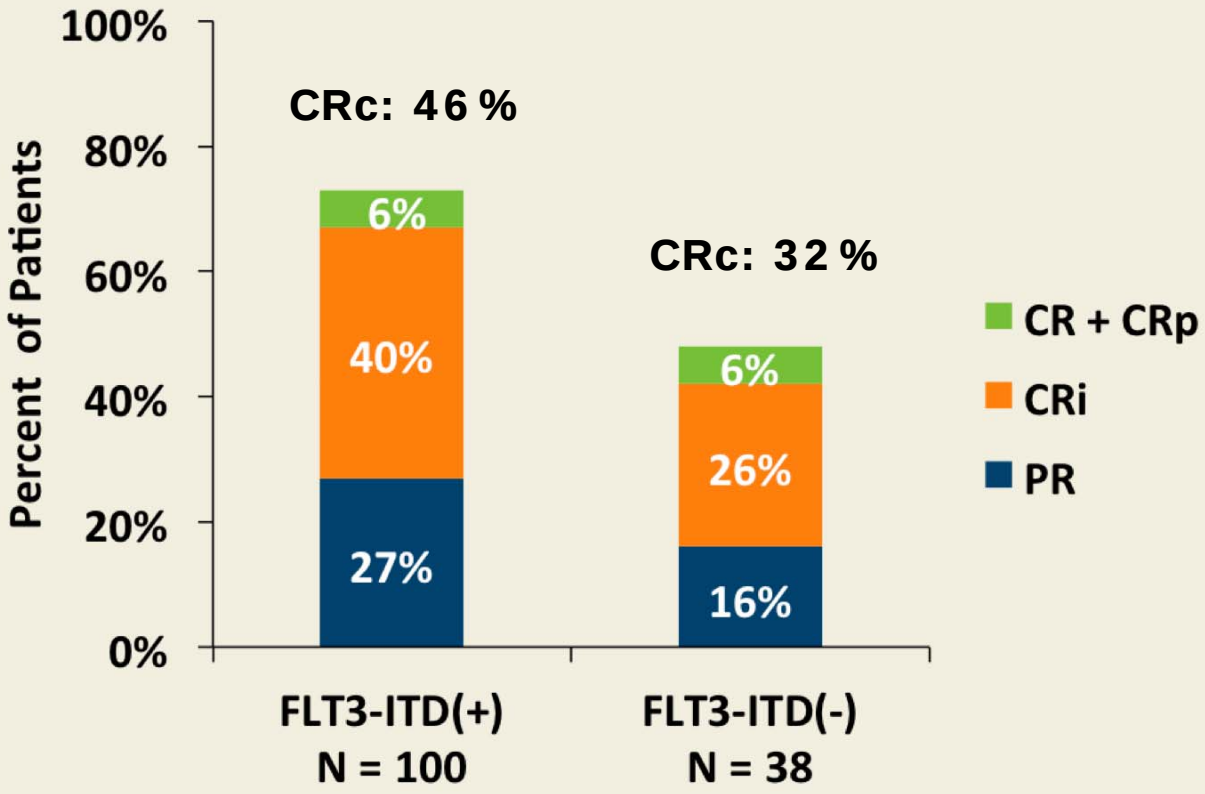
Phase II Trial Design



- 333 patients enrolled in Phase II (first 62 in an exploratory phase)
- **Primary endpoint:** Composite complete remission (CRc)
- **Secondary endpoints:** Complete remission (CR), duration of response, bridge to hematopoietic stem cell transplantation (HSCT) and overall survival (OS)

Levis MJ et al. *Proc ASH* 2012;Abstract 673.

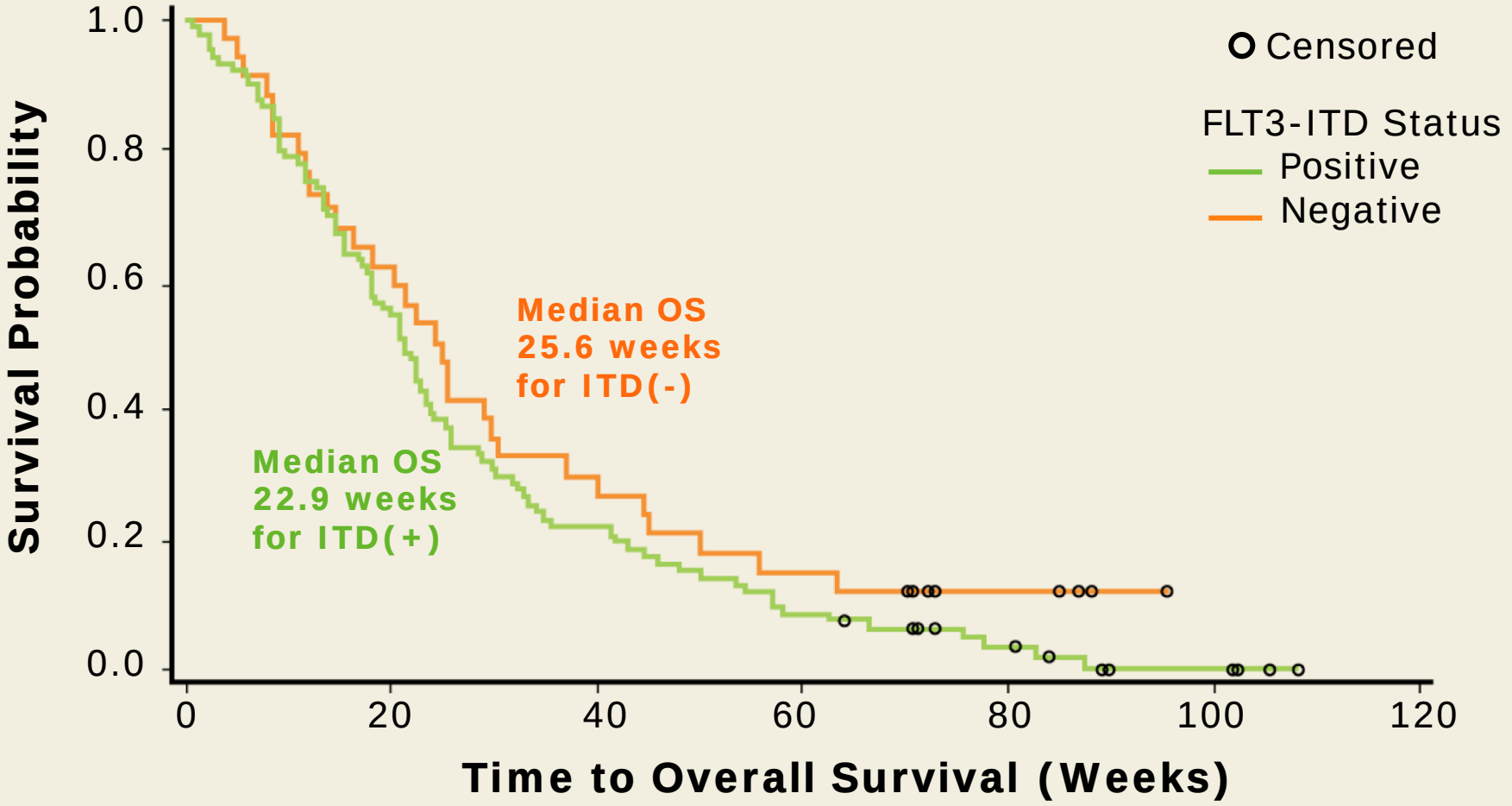
Cohort 2: Response Rates



- Median duration of response: 12.1 weeks FLT3-ITD(+), 7.0 weeks FLT3-ITD(-)
- 75% of patients with FLT3-ITD(+) and 48% of FLT3-ITD(-) AML refractory to their last prior therapy achieved at least a PR to quizartinib.

With permission from Levis MJ et al. *Proc ASH* 2012;Abstract 673.

Cohort 2: OS by FLT3-ITD Status



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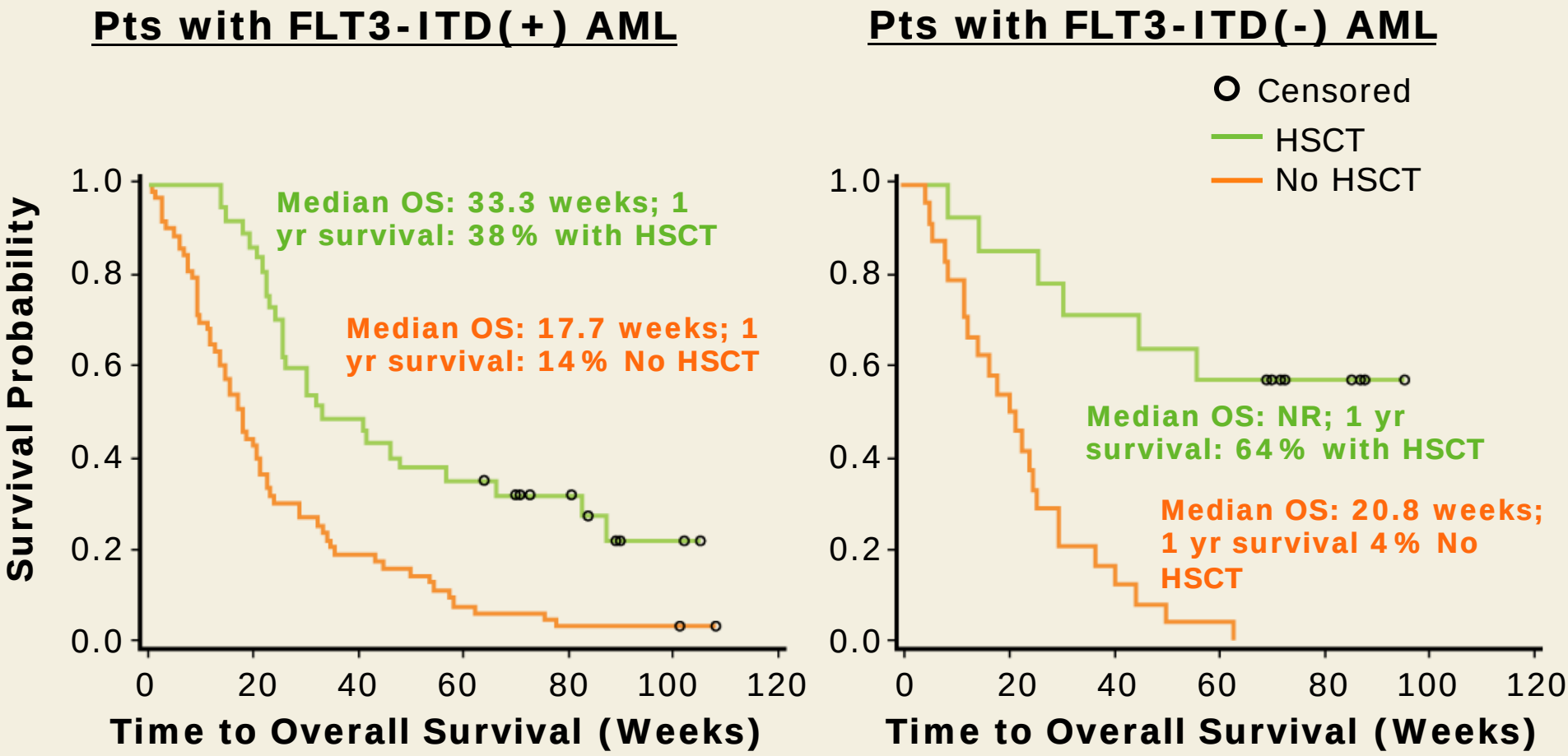
Cohort 2: OS in Patients Bridged to HSCT vs No HSCT



- NR = not reached

With permission from Levis MJ et al. *Proc ASH* 2012;Abstract 673.

Cohort 2: Select Adverse Events (AEs) (Incidence ≥20%)

Grade	FLT3-ITD(+) (n = 100)		FLT3-ITD(-) (n = 38)	
	All	3 or 4	All	3 or 4
Any AE	100%	84%	100%	76%
Nausea	55%	3%	47%	3%
Diarrhea	41%	3%	26%	5%
Febrile neutropenia	41%	40%	29%	29%
Anemia	31%	26%	42%	39%
Thrombocytopenia/ ↓ platelet count	27%	26%	21%	21%
QT prolongation*	25%	8%	32%	3%

* No Grade 4 QT interval prolongation

Levis MJ et al. *Proc ASH* 2012;Abstract 673.

Cohort 2: Disposition of Patients

Patient, n (%)	FLT3-ITD(+) (n = 100)	FLT3-ITD(-) (n = 38)	Total* (n = 138)
Active treatment	2 (2%)	0	2 (1%)
Discontinued treatment	98 (98%)	38 (100%)	136 (99%)
Relapse	20 (20%)	2 (5%)	22 (16%)
Adverse event(s)	21 (21%)	4 (11%)	25 (18%)
Death	5 (5%)	2 (5%)	7 (5%)
HSCT	37 (37%)	14 (37%)	51 (37%)
Lack of response	11 (11%)	13 (34%)	24 (17%)
Other reason	4 (4%)	3 (8%)	7 (5%)

- Median time on treatment for patients who went on HSCT:
  - FLT3-ITD(+): 9.2 weeks
  - FLT3-ITD(-): 7.5 weeks

Levis MJ et al. *Proc ASH* 2012;Abstract 673.

Author Conclusions

- Quizartinib produced a high response rate (46% CRc) in patients with relapsed/refractory FLT3-ITD(+) AML.
- Responses are clinically meaningful with a high percentage (37%) bridged to HSCT.
- 33 (24%) patients survived >1 y of therapy, and 12 patients with FLT3-ITD(+) AML remain alive at last follow-up.
- An additional 12 (12%) patients with FLT3-ITD(+) AML had a durable disease control rate for 5+ months with quizartinib.
- Quizartinib was well tolerated with manageable toxicity:
  - GI toxicities, reversible QT prolongation and myelosuppression possibly related to KIT inhibition

Levis MJ et al. *Proc ASH* 2012;Abstract 673.

Investigator Commentary: Final Results of a Phase II Study of Quizartinib Monotherapy for Patients with FLT3-ITD(+) or FLT3-ITD(-) Relapsed/Refractory (R/R) AML

Quizartinib is the most potent inhibitor of FLT3 in development. These studies demonstrated a high response rate to quizartinib in FLT3-ITD(+) RR AML. The study by Cortes and colleagues demonstrated responses in about 70% of patients with FLT3-ITD(+) RR AML. Of these, 50% experienced CRi. About a third of patients without FLT3-ITD mutations experienced a CRi. This is remarkable. The responses lasted for a few months and the impact on survival was modest. However, a more pronounced survival benefit was noted with responders when compared to nonresponders. Both studies demonstrated quizartinib to be well tolerated. Diarrhea and nausea were the most frequent toxicities but were mostly Grade 1/2 in intensity. Because myelosuppression is expected, I don't consider it a side effect in the treatment of leukemia. Another important side effect that was observed was QT prolongation, which led to dose reductions in a significant proportion of patients. Overall, quizartinib is another kinase inhibitor of interest for this group of patients. In the future, I believe quizartinib will be investigated in Phase III studies in combination with the classic 3+7 regimen for AML in patients with FLT3-ITD mutations.

Interview with Moshe Talpaz, MD, February 19, 2013