5 Minute JournalClub

POST-ASH Issue 3, 2013

Final Results of a Phase II Study of Quizartinib in Patients with FLT3 ITD-Positive or Negative Relapsed/Refractory AML

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2013/3/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — 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:

Moshe Talpaz, MD
Alexander J Trotman Professor of Leukemia Research
Associate Director of Translational Research, UM Comprehensive Cancer Center
Associate Chief, Division of Hematology/Oncology
Director, Hematologic Malignancies
University of Michigan Medical Center
Ann Arbor, Michigan

Advisory Committee: Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Abbott Laboratories, Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Sanofi; Speakers Bureau: Novartis Pharmaceuticals Corporation.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: March 2013
Expiration date: March 2014

5 MinuteJournalClub

POST-ASH Issue 3, 2013

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

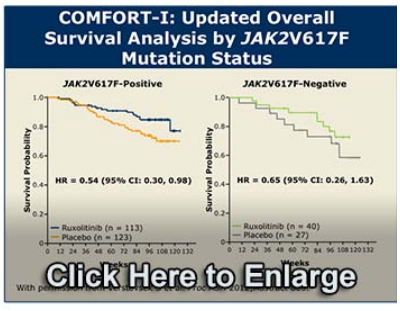
To go directly to slides and commentary for this issue, **click here**.

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

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/ Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

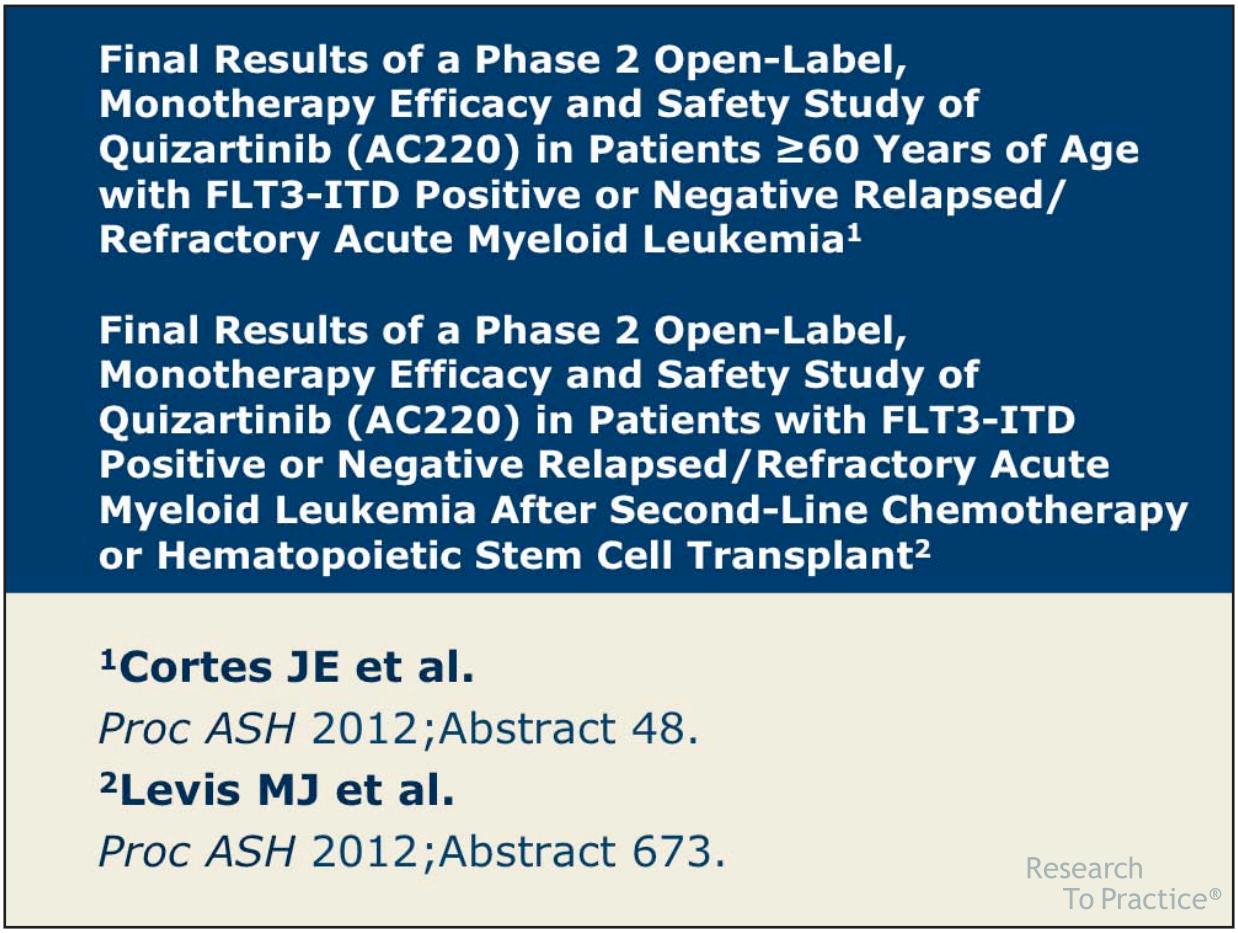
Final Results of a Phase II Study of Quizartinib in Patients with FLT3 ITD-Positive or Negative Relapsed/Refractory AML

Presentations discussed in this issue

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

Levis M et al. **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 transplantation.** *Proc ASH* 2012;**Abstract 673**.

Slides from presentations at ASH 2012 and transcribed comments from a recent interview with Moshe Talpaz, MD (2/19/13)



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

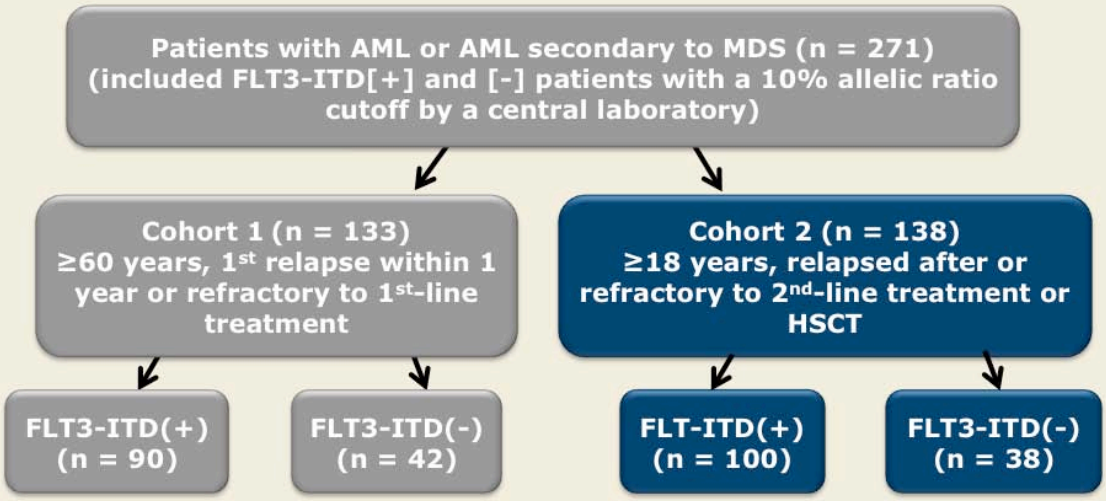
Cortes JE et al.

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.

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.

Research To Practice®

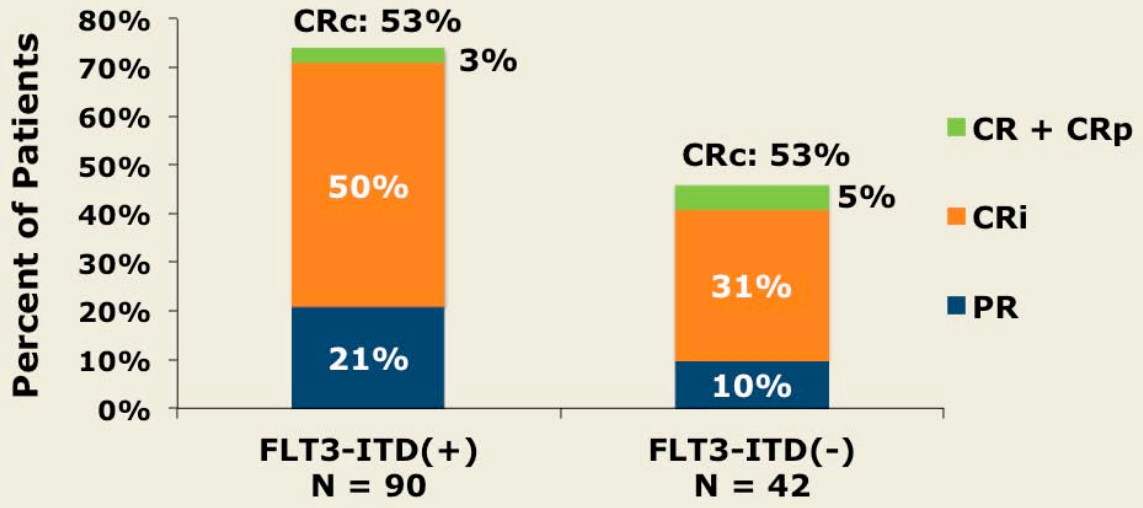
Exploratory Phase: Summary of Results

- 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.

Research To Practice®

Confirmatory Cohort 1: Response to Quizartinib

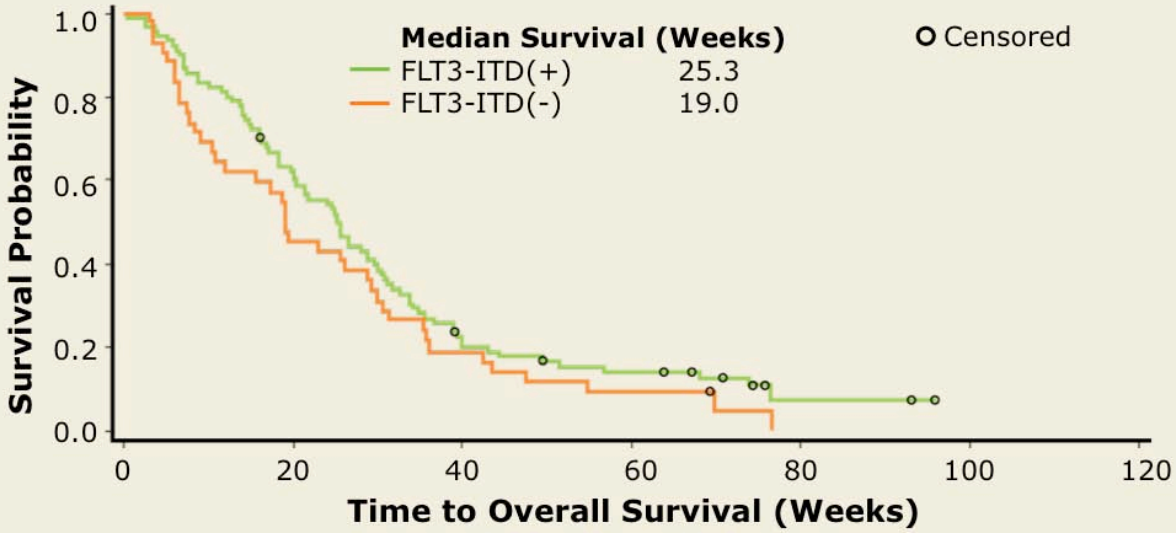


- 70% of patients with FLT3-ITD(+) and 55% with FLT3-ITD(-) AML refractory to last prior therapy achieved at least a PR
- Median CRc duration: 10.4 wk for FLT3-ITD(+), 9.3 wk for FLT3-ITD(-)

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

Research To Practice®

Confirmatory Cohort 1: OS by FLT3-ITD Status

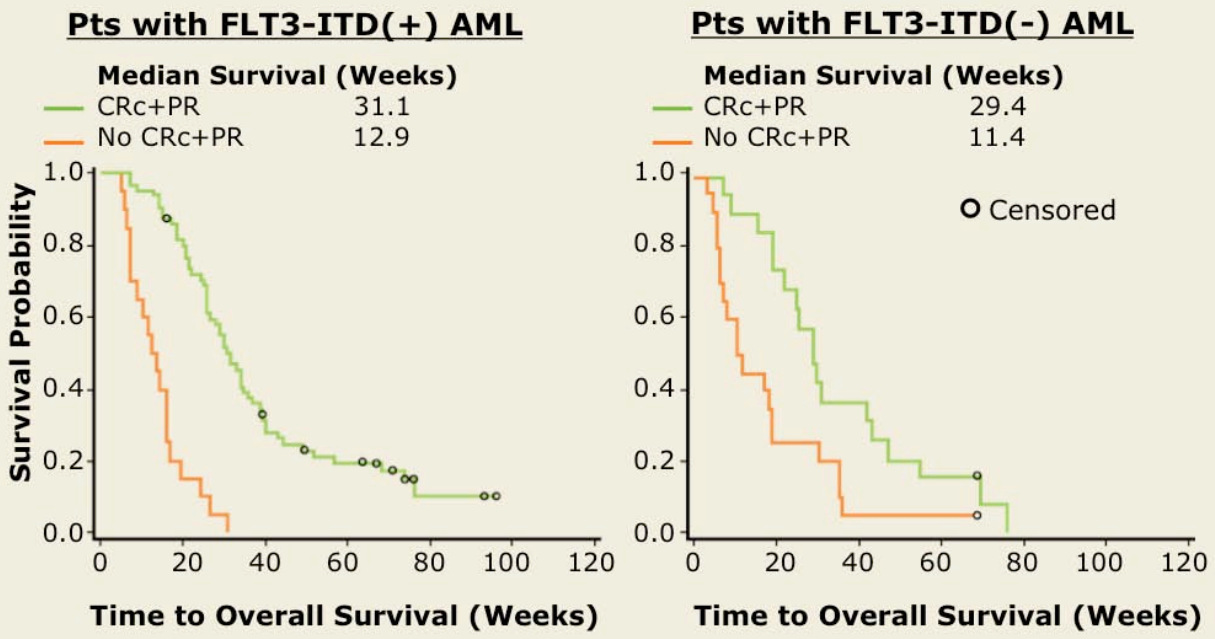


- 12/90 (13%) patients with FLT3-ITD(+) and 5/42 (12%) with FLT3-ITD(-) AML survived 12+ months
- 2 patients with FLT3-ITD(+) AML survived 18+ months

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

Research To Practice®

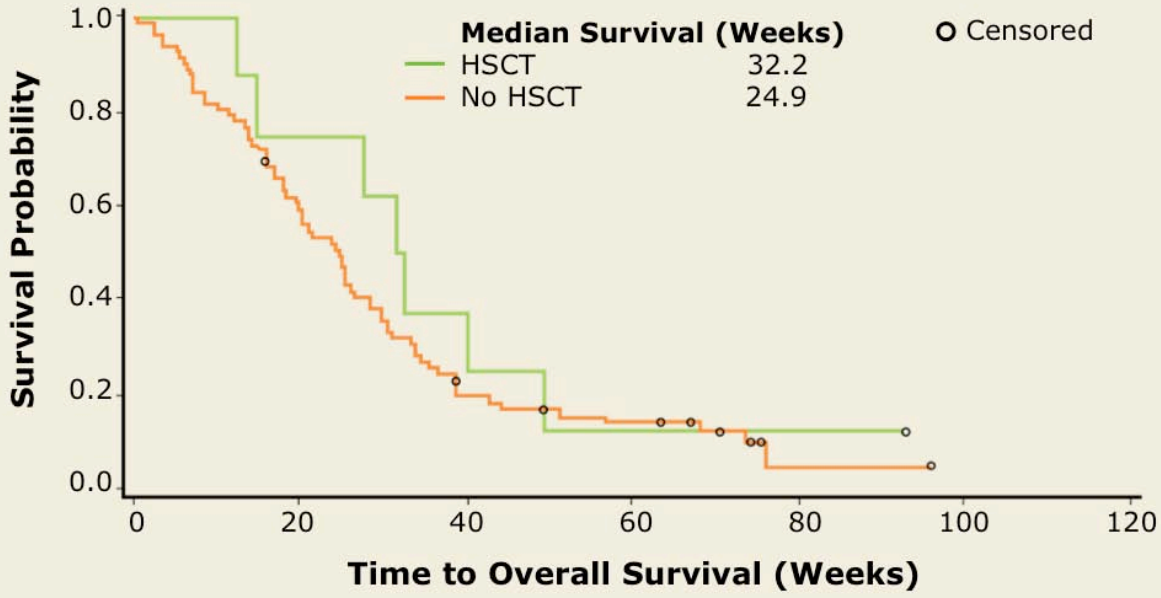
Confirmatory Cohort 1: OS by Response



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

Research To Practice®

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



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

Research To Practice®

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.

Research To Practice®

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.

Research To Practice®

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.

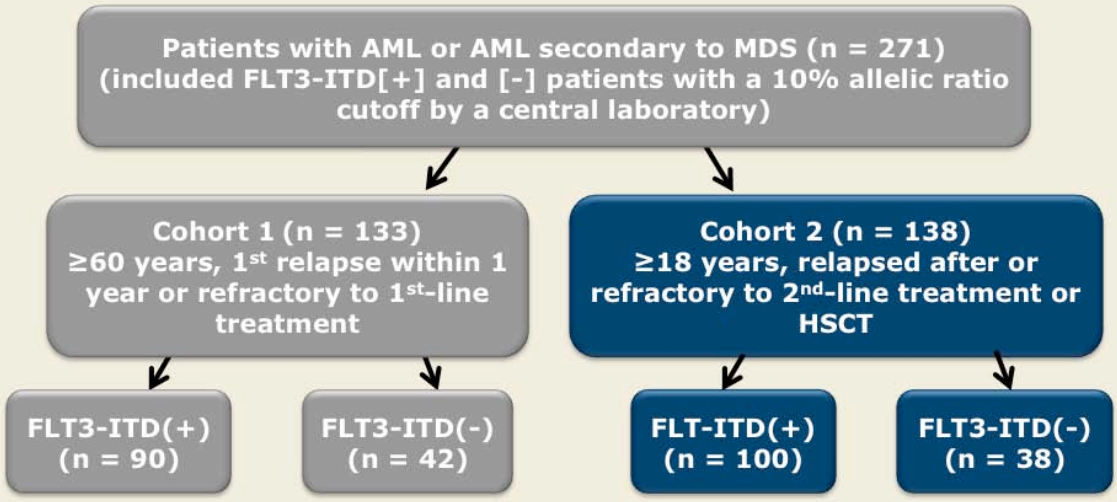
Background

- 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.

Research To Practice®

Phase II Trial Design

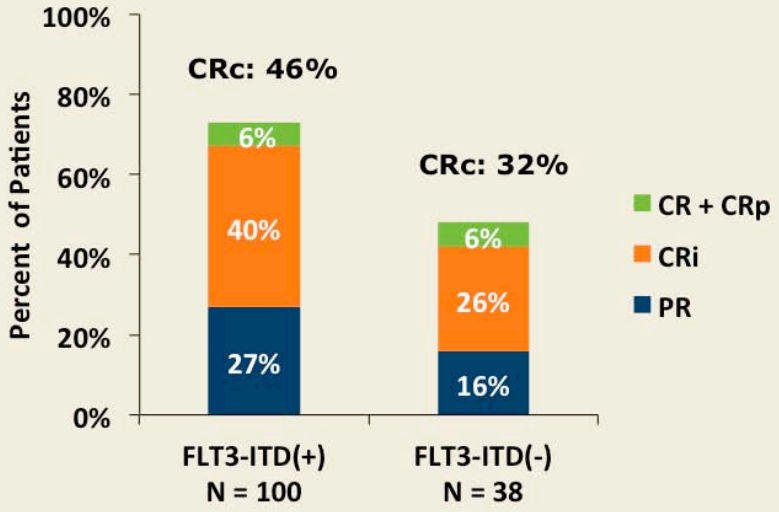


- 333 patients enrolled in Phase II (first 62 in an exploratory phase)
- **Primary endpoint:** Composite complete remission (CRc)
- **Secondary endpoints:** Complete remission (CR), duration of response, bridge to hematopoietic stem cell transplantation (HSCT) and overall survival (OS)

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

Research To Practice®

Cohort 2: Response Rates

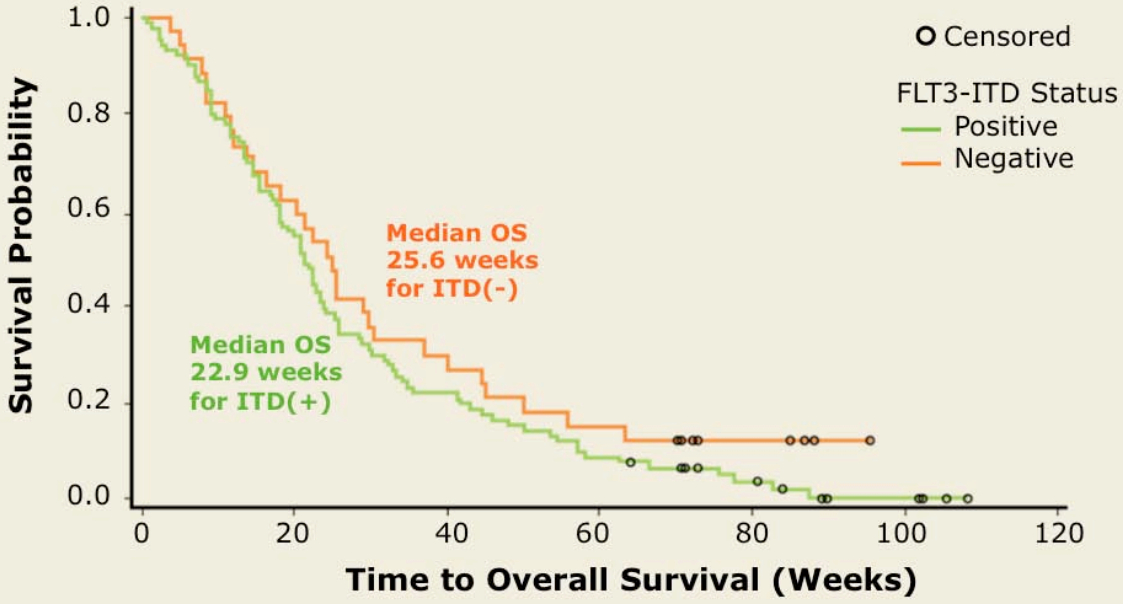


- Median duration of response: 12.1 weeks FLT3-ITD(+), 7.0 weeks FLT3-ITD(-)
- 75% of patients with FLT3-ITD(+) and 48% of FLT3-ITD(-) AML refractory to their last prior therapy achieved at least a PR to quizartinib.

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

Research To Practice®

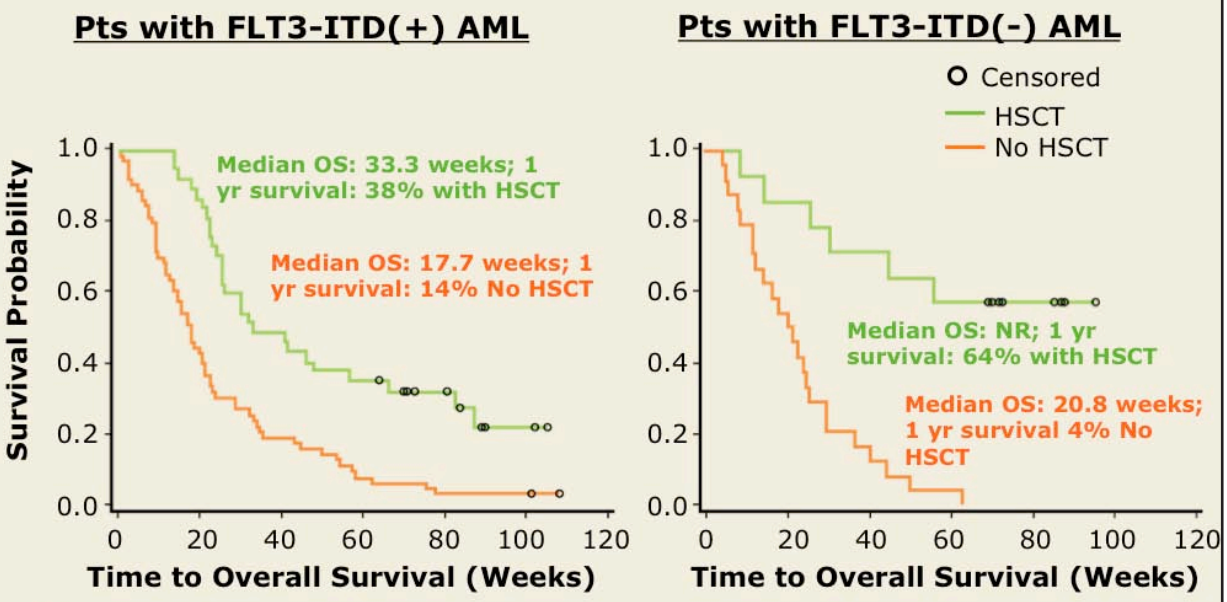
Cohort 2: OS by FLT3-ITD Status



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

Research To Practice®

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.

Research To Practice®

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

	FLT3-ITD(+) (n = 100)		FLT3-ITD(-) (n = 38)	
Grade	**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.

Research To Practice®

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.

Research To Practice®

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.

Research To Practice®

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

Research To Practice®