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

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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:

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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
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
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


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

Patients with AML or AML secondary to MDS (n = 271) (included FLT3-ITD[+] and [-] patients with a 10% allelic ratio cutoff by a central laboratory)

Cohort 1 (n = 133)
≥60 years, 1st relapse within 1 year or refractory to 1st-line treatment

FLT3-ITD(+) (n = 90)
FLT3-ITD(-) (n = 42)

Cohort 2 (n = 138)
≥18 years, relapsed after or refractory to 2nd-line treatment or HSCT

FLT-ITD(+) (n = 100)
FLT3-ITD(-) (n = 38)

- 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)


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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.

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(-)


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

Confirmatory Cohort 1: OS by Response

Pts with FLT3-ITD(+) AML

Median Survival (Weeks)
- CRc+PR: 31.1
- No CRc+PR: 12.9

Pts with FLT3-ITD(-) AML

Median Survival (Weeks)
- CRc+PR: 29.4
- No CRc+PR: 11.4


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

Median Survival (Weeks)
- HSCT: 32.2
- No HSCT: 24.9

Confirmatory Cohort 1: Select Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Grade</th>
<th>FLT3-ITD(+) (n = 90)</th>
<th>FLT3-ITD(-) (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Any AE</td>
<td>100%</td>
<td>89%</td>
</tr>
<tr>
<td>Nausea</td>
<td>56%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41%</td>
<td>3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>QT prolongation*</td>
<td>30%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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


Confirmatory Cohort 1: Disposition of Patients

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

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

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


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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).


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Phase II Trial Design

Patients with AML or AML secondary to MDS (n = 271) (included FLT3-ITD[+] and [-] patients with a 10% allelic ratio cutoff by a central laboratory)

- Cohort 1 (n = 133)  
  ≥60 years, 1st relapse within 1 year or refractory to 1st-line treatment

  - FLT3-ITD(+) (n = 90)
  - FLT3-ITD(-) (n = 42)

- Cohort 2 (n = 138)  
  ≥18 years, relapsed after or refractory to 2nd-line treatment or HSCT

  - FLT-ITD(+) (n = 100)
  - FLT3-ITD(-) (n = 38)

- 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)

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.*

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Cohort 2: OS by FLT3-ITD Status

- Censored
- FLT3-ITD Status
  - Positive
  - Negative

With permission from Levis MJ et al. *Proc ASH 2012;Abstract 673.*
Cohort 2: OS in Patients Bridged to HSCT vs No HSCT

Pts with FLT3-ITD(+) AML

Median OS: 33.3 weeks; 1 yr survival: 38% with HSCT
Median OS: 17.7 weeks; 1 yr survival: 14% No HSCT

Pts with FLT3-ITD(-) AML

Median OS: NR; 1 yr survival: 64% with HSCT
Median OS: 20.8 weeks; 1 yr survival 4% 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%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>FLT3-ITD(+) (n = 100)</th>
<th>FLT3-ITD(-) (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Any AE</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td>Nausea</td>
<td>55%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41%</td>
<td>3%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td>Anemia</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Thrombocytopenia/↓ platelet count</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>QT prolongation*</td>
<td>25%</td>
<td>8%</td>
</tr>
</tbody>
</table>

* No Grade 4 QT interval prolongation

## Cohort 2: Disposition of Patients

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

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


## 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

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*