5 Minute JournalClub

POST-ASH Issue 5, 2015

Phase II SORAML Trial of Sorafenib versus Placebo in Addition to Standard Therapy for Younger Patients with Newly Diagnosed AML

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia (APL) and myelodysplastic syndromes (MDS) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the results of the confirmatory Phase II BLAST study of blinatumomab in patients with relapsed/refractory ALL, and consider this information when developing treatment plans for these patients.
- Analyze the efficacy of a more intensive pediatric chemotherapy regimen for older adolescents and young adults with newly diagnosed B- or T-precursor ALL, and determine the feasibility of this approach for patients with ALL in this age group.
- Compare and contrast the benefits and risks reported in the Phase III APL0406 trial of all-trans retinoic acid (ATRA) with arsenic trioxide versus ATRA with chemotherapy, and consider the potential therapeutic benefit of a chemotherapy-free regimen for patients with newly diagnosed nonhigh-risk APL.
- Determine the clinical benefit seen with the addition of the multikinase inhibitor sorafenib to standard primary induction and consolidation therapy for younger patients with newly diagnosed AML.
- Assess the efficacy and tolerability profile of the novel agent vosaroxin combined with cytarabine from the Phase III VALOR trial in patients with relapsed or refractory AML.
- Examine the impact of lenalidomide therapy on the achievement of transfusion independence in red blood cell transfusion-dependent patients with lower-risk MDS without del(5q).

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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:

Mikkael A Sekeres, MD, MS
Professor of Medicine
Director, Leukemia Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Advisory Committee: Amgen Inc, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation.

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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: May 2015
Expiration date: May 2016

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POST-ASH Issue 5, 2015

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

Leukemias and Myelodysplastic Syndromes Think Tank Faculty
January 29, 2015

Jennifer R Brown, MD, PhD
Hagop M Kantarjian, MD
Charles A Schiffer, MD
B Douglas Smith, MD
David P Steensma, MD
Wendy Stock, MD, MA

Not long after this year's American Society of Hematology (ASH) meeting, we gathered 6 clinical investigators for our first ever think tank focused exclusively on leukemias and myelodysplastic syndromes (MDS). Although a lot of the excitement during this closed recording session centered on new agents and therapies — particularly the explosion of encouraging clinical research in acute lymphoblastic leukemia (ALL) with both CAR T-cell immunotherapy and the bispecific T-cell engager antibody blinatumomab (see below) — it was also fascinating to hear that an older drug that has sometimes gotten a bad rap — sorafenib (sor) — may have a new role as part of up-front treatment for acute myeloid leukemia (AML).

ALL is an uncommon disease that many oncologists appropriately triage to tertiary centers, but AML — particularly in elderly patients — is an important part of general oncology practice. As such, even though the randomized, Phase II trial of sor presented at ASH as a plenary was not the "home run" that we are beginning to see more frequently with immunotherapy in many diseases, from a practical clinical perspective the study findings may be among the most important in any cancer this year.

For that reason, we lead off this year's acute leukemia/MDS ASH summary by focusing on that work. But as always, we also created teaching slide sets and obtained perspectives from a noted clinical investigator — in this case Mikkael Sekeres — for a number of the most important presentations, which are outlined below:

Mikkael A Sekeres, MD, MS

AML

Sor up front in AML

About 20% of patients with AML have activating mutations in the FMS-like tyrosine kinase 3 (FLT3), and a number of FLT3 inhibitors are in various states of development. Sor targets this kinase, among others, and for that reason this **Phase II placebo-controlled German trial** evaluated the addition of sor to standard induction and consolidation treatment (followed by maintenance with sor) in 267 adult patients with

newly diagnosed AML age 60 years and younger. Importantly, individuals both with and without FLT3-internal tandem duplication (ITD) mutations were eligible for and enrolled in the study. With a median follow-up of 3 years, the trial met its primary endpoint of event-free survival (EFS), demonstrating a significant improvement in favor of sor (median EFS 20.5 months versus 9.2 months, $p = 0.013$). Interestingly and quite unexpectedly, there was a suggestion that the benefit was, if anything, more impressive in patients without FLT3-ITD mutations. The one sticking point is, to date there is no overall survival (OS) advantage, which is concerning to Dr Sekeres and has informed his current decision not to use up-front sor outside of a clinical trial.

Click here to see Dr Kantarjian's comment

However, at the think tank the reaction to these data was quite different, as Dr Hagop Kantarjian noted that since 2005, he and his MD Anderson colleagues have been routinely using FLT3 inhibitors in patients with FLT3-ITD mutations and that the outcomes appear indirectly to be improved compared to earlier series. The think tank faculty speculated on possible biologic explanations for these compelling findings, including the presence of other kinase targets or inhibition of wild-type FLT3 kinase activation, but most seemed to agree that these new data at the very least deserve careful consideration in patients with and without these abnormalities. To further drive home this point, Dr Kantarjian made an impassioned plea for "leukemia doctors to act more like those focused on solid tumors" and seek small research advances that, when coupled together, create a major positive effect for patients, as seen, for example, in renal cell carcinoma.

VALOR trial of vosaroxin

VALOR is a large, **international Phase III study** evaluating cytarabine with or without vosaroxin, a first-in-class anticancer quinolone derivative, in patients with relapsed/refractory AML. On the surface things look straightforward, as the trial did not reach its primary endpoint of improved OS. However, the data also demonstrated that complete remission rates were improved with vosaroxin/cytarabine, and a preplanned survival subgroup analysis censoring patients at allogeneic transplant showed a statistically significant 1.4-month advantage (hazard ratio 0.83, $p = 0.02$). Dr Sekeres is not convinced these improvements are clinically meaningful, but Dr Kantarjian — whose group has done a lot of this research — believes vosaroxin has important value and should be made available to clinicians.

MDS

Lenalidomide (len) in non-del(5q) disease

While the role of this immunomodulatory agent is well established and approved in patients with del(5q), mainly for management of anemia, a prior Phase II trial

suggested clear-cut benefit in non-del(5q) disease. **This Italian Phase III study** almost duplicated the results seen in the Phase II effort and demonstrated a ≥56-day transfusion independence rate of 27% with len compared to a 2.5% rate with placebo. These findings will undoubtedly lead clinicians to want to use this drug in this situation, and think tank participant Dr David Steensma endorses this approach. However, he cautions that "platelets need to be at a reasonable level" to use len.

Azacitidine (aza) alone or with len or vorinostat (vor) in higher-risk MDS and chronic myelomonocytic leukemia

At ASH Dr Sekeres presented the first results from the largest prospective study in higher-risk MDS ever conducted in North America — **SWOG-S1117** — which demonstrated a modest signal for improvement in disease-related outcomes with the 2 combinations. Unfortunately, a greater likelihood to discontinue treatment due to toxicity was also seen (9% aza, 23% aza/len, 24% aza/vor). In discussing this work, Dr Sekeres pointed out that these data will continue to mature, and he believes it is possible that with better management of side effects, these and other combinations may be successfully incorporated into treatment.

ATRA/arsenic trioxide (AAT) in acute promyelocytic leukemia (APL)

At the 2012 ASH meeting, the initial findings from the landmark Phase III Italian-German APL0406 trial in low/intermediate-risk APL comparing AAT as induction and consolidation to ATRA/idarubicin as induction, consolidation and maintenance therapy grabbed headlines and led many oncologists to change their practices. Dr Sekeres and his Cleveland Clinic group, however, wanted to see more follow-up before following suit. That information came **at this year's meeting** as excellent outcomes (now with 254 patients evaluable for response at 3 years) were observed with both therapies, but there appeared to be a suggestion of greater benefit with AAT (complete response [CR] 100% versus 97%; 2-year EFS rate 98% versus 84.9%, $p = 0.0002$; 2-year OS rate 99.1% versus 94.4%, $p = 0.01$). This has now given Dr Sekeres and his group enough supporting evidence to offer the chemotherapy-free AAT combination as standard induction and postremission therapy to patients with low/intermediate-risk APL.

ALL

Treatment for older adolescents and young adults (AYAs)

For years, a fundamental issue in this disease has been whether more intensive pediatric regimens should be used in AYAs. At ASH we saw relevant findings from the single-arm **US Intergroup trial C10403** of 296 patients age 16 to 39 who received a pediatric regimen administered by adult hematologist-oncologists. The 2-year EFS of 66% seen in this study represents a significant improvement compared to 34% EFS observed in historical controls, and globally the outcomes, including toxicities, were similar to what has been documented in other prospective international studies of pediatric regimens in AYAs.

As a result of these important findings, Dr Sekeres and the think tank faculty, including Dr Wendy Stock, who presented these data at ASH, all support the use of this approach moving forward both in clinical practice and in trials attempting to integrate new agents. It should also be noted that Dr Kantarjian believes that hyper-CVAD is an equivalent alternative.

CD19-targeted 19-28z CAR-modified autologous T cells in adult patients with relapsed, refractory B-cell ALL

A number of our CME programs have helped chronicle the amazing story of CAR T-cell therapy, and we would be remiss to not provide an update coming out of the year's biggest meeting. As previously mentioned, ALL is the locus where this therapy has taken off, and in San Francisco we saw extended follow-up from a **Phase I Memorial Sloan Kettering study** in this disease. Of the 22 patients evaluable for response, many of whom had heavily pretreated disease, an impressive 91% (20 patients) achieved CR after CAR T-cell infusion, with 90% (18 patients) of those being MRD-negative. Ten of the 13 transplant-eligible patients subsequently went on to successfully receive an allogeneic hematopoietic cell transplant.

In terms of complications, patients with MRD at the time of treatment did not experience cytokine release syndrome (CRS), and for those with morphologic disease at the time of T-cell infusion, a temporal relationship between serum IL-6 levels and CRS suggests that early intervention with IL-6-directed therapy might be effective in ameliorating related neurologic toxicities.

In commenting on this study, Dr Sekeres cautions that currently CAR T-cell therapy requires specialized administration logistics and the capability to manage potentially challenging cytokine-mediated toxicities. He also questions the long-term durability of response and envisions a future for this approach as a bridge to transplant but is uncertain as to whether CAR T-cell therapy will one day have a role as a stand-alone treatment or as part of induction.

Blinatumomab

At ASH we saw the presentation of the **Phase II BLAST trial** of 116 patients who were MRD-positive ($\geq 10^{-3}$) after having received at least 3 prior intensive chemotherapy regimens. The MRD CR after 1 cycle of blinatumomab was 78% and did not differ across multiple patient demographics, including those with higher MRD burden. However, the adverse event (AE) profile (mainly related to cytokine release) is not insignificant. Importantly, in this trial serious AEs occurred in 60% of patients, with 2 fatalities.

In discussing the recent FDA accelerated approval of the drug at the think tank, the faculty noted its impressive effectiveness as a salvage therapy but also related the challenges they have faced in managing toxicities. In this regard, Dr Steensma emphasized the role of corticosteroids in mitigating side effects such as fever and impaired mental function. Not surprisingly, a number of current trials combine

blinatumomab with chemotherapy in both the salvage and front-line settings, including a Phase III trial in newly diagnosed ALL (**NCT02003222**).

Be on the lookout for the entire think tank program this summer, but next on this series, we talk about new agents in multiple myeloma, particularly the search for the "rituximab of myeloma" that includes a new wave of monoclonal antibodies such as elotuzumab and daratumumab.

Neil Love, MD
Research To Practice
Miami, Florida

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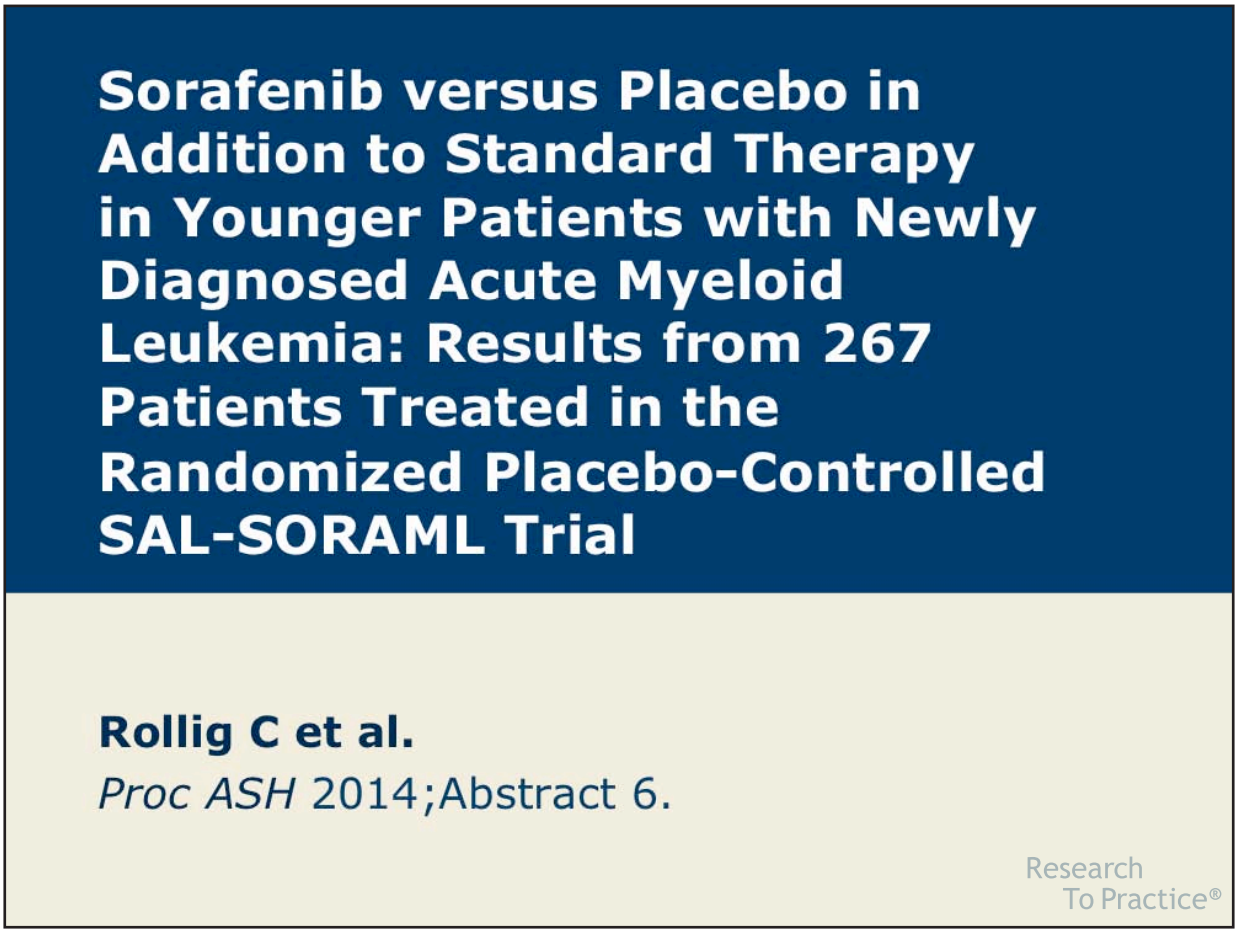
Phase II SORAML Trial of Sorafenib versus Placebo in Addition to Standard Therapy for Younger Patients with Newly Diagnosed AML

Presentation discussed in this issue

Rollig C et al. **Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: Results from 267 patients treated in the randomized placebo-controlled SAL-SORAML trial.** *Proc ASH* 2014;**Abstract 6**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Mikkael A Sekeres, MD, MS (1/20/15)



Background

- Sorafenib is a multikinase inhibitor with activity against several oncogenic kinases that may play a role in the pathogenesis of acute myeloid leukemia (AML).
- Data from in vitro studies and nonrandomized clinical trials suggest that sorafenib might be an effective drug for the treatment of AML (*Biol Blood Marrow Transplant* 2014;20:1687; 2042).
- **Study objective:** To determine the efficacy of sorafenib added to standard primary induction and consolidation therapy for patients ≤60 years of age with newly diagnosed AML.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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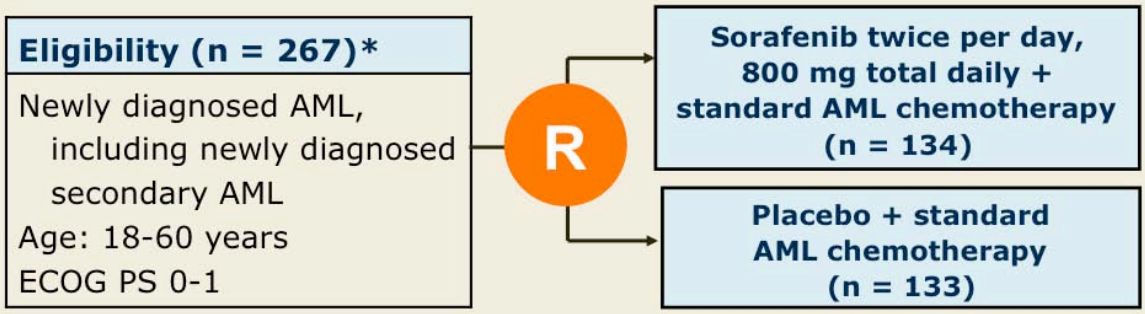
Phase II SORAML Trial Design (NCT00893373)



* Out of 276 enrolled patients, 267 received the study treatment.

- **Primary endpoint:** Event-free survival (EFS)
- Treatment plan for all patients included 2 cycles of induction with DA (daunorubicin 60 mg/m^2 d3-5 + cytarabine 100 mg/m^2 continuous IV d1-7)
  → 3 cycles of high-dose cytarabine consolidation (3 g/m^2 BID d1, 3, 5).
- Patients without response after DA I received second induction with HAM (cytarabine 3 g/m^2 BID d1-3 + mitoxantrone 10 mg/m^2 d3-5).
- Allogeneic stem cell transplantation was scheduled for all patients with intermediate-risk AML in first complete remission with a sibling donor and for all patients at high risk with a matched related or unrelated donor.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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Patient Demographics and Treatment Characteristics

- Demographic and disease characteristics were equally distributed between the 2 arms.
  - The incidence of the FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutation was 17% in both arms.
- Among 46 patients with FLT3-ITD-positive AML, there was no difference in EFS:
  - A trend in favor of sorafenib was observed for prolonged relapse-free survival and overall survival.
- The median follow-up time was 36 months.
- The median cumulative dose of administered study medication was similar in both arms.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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Clinical Outcomes

Outcome	Sorafenib	Placebo	*p*-value
Complete response (CR)	60%	59%	0.764
Median EFS* 3-year EFS	20.5 mo 40%	9.2 mo 22%	0.013
Median RFS 3-year RFS	NYR 56%	23 mo 38%	0.017
Median OS 3-year OS	NYR 63%	NYR 56%	0.382

RFS = relapse-free survival; NYR = not yet reached; OS = overall survival

* An event is defined as failure to achieve CR after induction, relapse or death.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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Adverse Events

- The most common reported Grade ≥3 adverse events were:
  - Fever (40%)
  - Infections (22%)
  - Bleeding events (2%)
- The risk for fever, bleeding events and hand-foot syndrome was significantly higher in the sorafenib arm.
- The incidence of all other adverse events showed no significant differences.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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Author Conclusions

- For younger patients with AML, the sequential addition of sorafenib to standard chemotherapy is feasible and associated with antileukemic efficacy.
- A higher incidence of infections and bleeding events was associated with sorafenib therapy.
- Although overall survival in both treatment arms was similar, sorafenib treatment resulted in significantly prolonged event-free and relapse-free survival.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

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Investigator Commentary: Results from the Phase II SORAML Trial of Sorafenib in Patients with Newly Diagnosed AML

The results from the SORAML trial were presented at the plenary session at ASH 2014. Patients received sorafenib or placebo in addition to primary induction and consolidation therapy. Induction included treatment with 2 cycles of DA followed by 3 cycles of high-dose cytarabine consolidation therapy. The CR rates in both arms were identical at 59% with placebo versus 60% with sorafenib. All patients were followed for 36 months. A statistically significant difference was reported in median EFS, which was 9.2 months in the placebo arm versus 20.5 months in the sorafenib arm. The 3-year relapse-free survival was statistically different at 38% in the placebo arm and 56% with sorafenib.

Importantly, among the 46 patients with FLT3-ITD abnormalities, no difference was reported in EFS between the 2 treatment arms. Overall, there appears to be an advantage for patients who received sorafenib versus placebo regardless of FLT3-ITD status. However, no overall survival data are available because the median had not yet been reached. The 3-year overall survival was 63% with the addition of sorafenib versus 56% in the placebo arm.

Interview with Mikkael A Sekeres, MD, MS, January 20, 2015

continued

Investigator Commentary: Results from the Phase II SORAML Trial of Sorafenib in Patients with Newly Diagnosed AML (continued)

The "money page" in AML is overall survival, and historically we've always been able to get better results with more therapy earlier on, but this is usually at the cost of some toxicity that limits survival. We need to see how the survival data with the addition of sorafenib in this study mature. It's perplexing that we didn't see more of a signal with sorafenib therapy in those patients who had FLT3-ITD abnormalities.

The addition of sorafenib during induction and consolidation therapy did not add much toxicity. As a side note, assessing adverse events in patients who are receiving intensive induction chemotherapy is mind-bogglingly difficult because by design we're creating side effects. We're even creating a measurable amount of mortality associated with therapy. In this study the most common adverse events of Grade 3 or higher included fever, which is usually observed in leukemia studies, and, not surprisingly, infections and bleeding events. The rates of fever, bleeding events and hand-foot syndrome were significantly higher in the sorafenib arm. Overall, there was not much of a difference in the observed adverse events between the treatment arms.

Interview with Mikkael A Sekeres, MD, MS, January 20, 2015