# 5 Minute JournalClub

**POST-ASH** Issue 5, 2015

# Results from an Ongoing Phase I Trial in Relapsed/Refractory B-Cell ALL and the Phase II BLAST Trial of Blinatumomab in B-Precursor ALL

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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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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**.

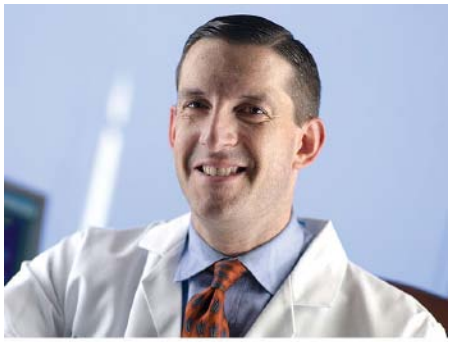
**Leukemias and Myelodysplastic Syndromes Think Tank Faculty**
January 29, 2015

**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:



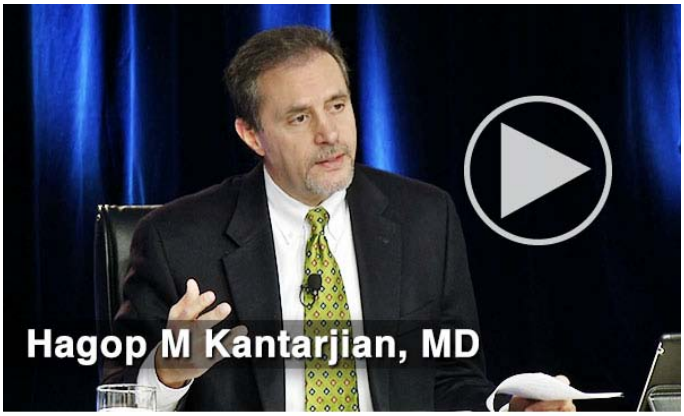
**Mikkael A Sekeres, MD, MS**

## 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
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# Results from an Ongoing Phase I Trial in Relapsed/ Refractory B-Cell ALL and the Phase II BLAST Trial of Blinatumomab in B-Precursor ALL

## Presentations discussed in this issue

Park JH et al. **CD19-targeted 19-28z CAR modified autologous T cells induce high rates of complete remission and durable responses in adult patients with relapsed, refractory B-cell ALL.** *Proc ASH* 2014;**Abstract 382**.

Goekbuget N et al. **BLAST: A confirmatory, single-arm, phase 2 study of blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL).** *Proc ASH* 2014;**Abstract 379**.

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

**CD19-Targeted 19-28z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL[1]**

**BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL)[2]**

**[1] Park JH et al.**
*Proc ASH* 2014;Abstract 382.

**[2] Goekbuget N et al.**
*Proc ASH* 2014;Abstract 379.

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# CD19-Targeted 19-28z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL

**Park JH et al.**

*Proc ASH* 2014;Abstract 382.



## Background

- Relapsed adult acute lymphoblastic leukemia (ALL) is associated with high reinduction mortality, chemotherapy resistance and dismal prognosis:
  - Median overall survival (OS) <6 months
  - 5-year OS ≤10%
- High antitumor activity of autologous T cells genetically modified to express 19-28z chimeric antigen receptor (CAR) targeting CD19 was previously reported in adult patients with CLL and ALL (*Blood* 2011;118:4817; *Sci Transl Med* 2014;6(224):224ra25).
- **Study objective:** To report long-term outcomes with 19-28z CAR in adult patients with relapsed/refractory (R/R) ALL, including analysis of the potential predictive markers of response and neurologic toxicities.

# Ongoing Phase I Trial Design (NCT01044069)

| Eligibility (Target accrual: n = 40) |
|---|
| R/R B-cell ALL<br>Age: ≥18 years<br>Patients with minimal residual disease (MRD) or in first complete response (CR)<br>Karnofsky PS >70 |

→ **19-28z CAR therapy**

**24 patients have received treatment**

- Eligible patients underwent leukapheresis, and T cells were transduced with a retrovirus encoding a CAR construct composed of anti-CD19 scFV linked to CD28 and CD3ζ signaling domains (19-28z).
- All patients received lymphodepleting chemotherapy followed 2 days later by infusion with 1 x $10^6$ to 3 x $10^6$ 19-28z CAR T cells/kg.
- **Primary endpoints:** Safety and antitumor activity of 19-28z CAR T cells
- Post-treatment MRD was assessed at day 14 to 28 in the bone marrow samples.

Park JH et al. *Proc ASH* 2014;Abstract 382; www.clinicaltrials.gov, accessed May 2015.

# Patient Characteristics

| Characteristic | n = 24 |
|---|---|
| Median age (range) | 56 years (23-74) |
| Ph+ B-cell ALL<br>BCR-ABL T315I mutation | 25%<br>8% |
| Prior allo-HSCT | 25% |
| ≥3 prior lines of ALL therapy before receiving 19-28z CAR T-cell therapy | 46% |

Allo-HSCT = allogeneic hematopoietic stem cell transplant

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

# Responses

| At time of 19-28z CAR T infusion | n = 22* |
|---|---|
| Patients with morphologic disease† | 12 (54.5%) |
| Patients with MRD | 10 (45.5%) |
| **After 19-28z CAR T infusion** | **n = 22*** |
| Patients in CR | 20 (91%) |
| Achieved MRD-negative CR | 18 (82%) |
| **Transplant-eligible patients (after infusion)** | **n = 13** |
| Successfully underwent allo-HSCT | 10 (77%) |

* Evaluable patients; † 6%-97% blasts in the bone marrow

- As of July 1, 2014, the median follow-up was 7.4 months (range, 1-34)
- Patients with ≥6 months of follow-up (n = 13)
- Responses appeared to be durable with 6 patients disease free >1 year

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

# Outcomes

- Median OS was 9 months
- Patients who relapsed during follow-up (n = 5)
  - This includes patients with CD19-negative relapse (n = 1)
  - Patients re-treated with CAR T cells (n = 3)
    - Patients who achieved a second CR (n = 2)
- For responders versus nonresponders, there was no association between response and:
  - Age (<60 vs ≥60 years)
  - Prior allo-HSCT
  - Number of prior therapies
  - Pretreatment blast percentage

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

## Treatment-Related Adverse Events

- None of the 10 patients with MRD at the time of T-cell infusion developed cytokine release syndrome (CRS).
- 9 of 13 (69%) patients with morphologic disease at the time of T-cell infusion developed CRS with or without neurological symptoms that required intervention with an interleukin (IL)-6R antagonist or corticosteroid.
- A detailed analysis of serum cytokines demonstrated a consistent peak of IL-6 (22.2- to 553-fold increase) immediately prior to the development of neurological toxicities.
- Based on these data, a multidisciplinary CRS management algorithm was developed for patients at high risk in order to reduce the severity of CRS and improve safety of the 19-28z CAR T-cell therapy.

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

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## Author Conclusions

- While longer follow-up is needed to confirm the durability of the observed responses, the potent induction of MRD-negative responses and the successful long-term outcomes, including subsequent allo-HSCT without apparent additional post-transplant toxicities, strongly support the use of 19-28z CAR T cells in adult patients with B-ALL.
- A temporal relationship between serum IL-6 levels and neurological toxicities indicates that early intervention with IL-6-directed therapy may be more effective in ameliorating neurological toxicities in patients with morphologic disease at the time of T-cell infusion.
- These findings need to be evaluated systematically and confirmed in a larger Phase II trial.

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

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**Investigator Commentary: Efficacy and Safety Results from a Phase I Trial of CAR T Cells in R/R B-Cell ALL**

CAR T-cell therapy has been a hot topic for the past couple of years. The median age of patients on the study was 56 years, so young and old patients were included (range 23-74). Remarkably, of 22 evaluable patients, 20 achieved CR after the infusion of CAR T cells, and 18 of these patients achieved MRD-negative CR. Of 13 transplant-eligible patients, 10 underwent allo-HSCT after CAR T-cell therapy.

With a median follow-up of 7.4 months, 6 patients remain disease free beyond 1 year. This is interesting, but interpretation depends on whether one is a "glass-half-full" or a "glass-half-empty" kind of person. Although the investigators state that the responses were durable, I don't know if I would call 6 out of 22 evaluable patients remaining disease free beyond a year "durable." We will have to wait to see how CAR T-cell therapy will be incorporated into the treatment algorithm, but it appears to have a role as a bridge to transplant.

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

continued

**Investigator Commentary: Efficacy and Safety Results from a Phase I Trial of CAR T Cells in R/R B-Cell ALL**

In terms of toxicity, 9 out of 13 patients with morphologic disease at the time of infusion developed CRS. You have to administer this type of therapeutic approach either in a bone marrow transplant unit with intensive care capacity or in an intensive care unit. This is not a foreign concept because patients who have received IL-2 therapy for other types of cancer have had to go through this. It's a doable approach, but it's not doable at every treatment center. It is a specialized, "boutique" approach to the treatment of lymphoid cancers. Also, some patients developed neurologic toxicities, and this is probably related to the CRS observed.

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

# BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL)

**Goekbuget N et al.**

*Proc ASH* 2014;Abstract 379.



## Background

- Patients with ALL with persistent/recurrent minimal residual disease (MRD) after induction therapy have a higher risk of relapse than those with no detectable MRD.
- Treatment for patients with MRD aims to avoid hematologic relapse, reduce MRD load and provide a bridge to subsequent hematopoietic stem cell transplant (HSCT).
- Blinatumomab is a recently approved, bispecific T-cell-engaging monoclonal antibody construct that redirects CD3-positive T cells to CD19-positive target cells, resulting in the serial lysis of CD19-positive B cells.
- In a Phase II study of first-line blinatumomab in 21 patients with MRD-positive ALL, 80% of evaluable patients achieved a complete MRD response (*JCO* 2011;29(18):2493-8).
- **Study objective:** To confirm whether blinatumomab is effective, safe and tolerable in patients with MRD-positive ALL.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379.

# Phase II BLAST Trial Design (NCT01207388)

**Eligibility (n = 116)**

B-precursor ALL in hematologic complete response (<5% blasts in bone marrow) after ≥3 intensive chemotherapy treatments

MRD $\geq 10^{-3}$

No prior allo-HSCT; not eligible for tyrosine kinase inhibitor therapy

→ **Blinatumomab (IV)**
15 µg/m² per day for 4 weeks → 2 weeks off (for ≤4 cycles or ≥1 cycle → HSCT)

- Responders could receive ≤4 cycles of treatment or undergo HSCT after ≥1 cycle; patients with hematologic relapse discontinued treatment.
- **Primary endpoint:** Rate of complete MRD response within the first treatment cycle
- **Secondary endpoints** include overall survival, relapse-free survival, duration of complete MRD response, incidence and safety of adverse events
- As of Feb 2014, 106 patients had ended treatment: 74 completed and 32 discontinued

Goekbuget N et al. *Proc ASH* 2014;Abstract 379.

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# Efficacy

- Patients excluded from study (n = 3)
  - No central laboratory assay results (n = 1)
  - Assay results with a sensitivity of $5 \times 10^{-4}$ (n = 2)
- Patients included in efficacy analysis (n = 113)
  - Patients who achieved complete MRD response after 1 cycle of treatment: 88 (78%)
    - The lower confidence interval limit exceeded 44% (the null hypothesis for response rate)
  - Patients who achieved complete MRD response after >1 cycle of treatment: 80%
- The rate of complete MRD response did not differ significantly across age, sex, line of treatment and MRD burden categories.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

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# MRD Response with Blinatumomab Therapy

| Complete response in which treatment was administered (n = 116, 113) | Baseline n (%) | MRD response % (95% CI) |
|---|---|---|
| First | 75 (65%) | 82% (72%-90%) |
| Second | 39 (34%) | 71% (54%-85%) |
| Third | 2 (2%) | 50% (1%-99%) |
| **Baseline MRD level*** | **n (%)** | **MRD response** |
| $\geq 10^{-1}$ to $<1$ | 9 (8%) | 67% (30%-93%) |
| $\geq 10^{-2}$ to $<10^{-1}$ | 45 (39%) | 82% (67%-92%) |
| $\geq 10^{-3}$ to $<10^{-2}$ | 52 (45%) | 78% (65%-89%) |

* 10 (9%) patients had MRD $<10^{-3}$, below the lower limit of quantitation, or unknown MRD status.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

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# Select Adverse Events (AEs)

| AE | Occurring in ≥20% (All grades) | Occurring in ≥5% (Serious AEs) |
|---|---|---|
| Pyrexia | 88% | 15% |
| Headache | 38% | Not reported (NR) |
| Tremor | 29% | 7% |
| Chills | 25% | NR |
| Fatigue | 24% | NR |
| Nausea | 22% | NR |
| Vomiting | 22% | NR |
| Aphasia | NR | 5% |
| Encephalopathy | NR | 5% |

- All patients experienced ≥1 AE; 60% experienced serious AEs; 2 fatal AEs occurred on treatment.
- 5% of patients experienced overdose.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

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# Author Conclusions

- This is the largest prospective trial with an experimental compound in MRD-positive ALL.
- Blinatumomab treatment resulted in complete MRD response across multiple patient demographics, including patients in second-line treatment and those with high MRD burden.
- With a complete MRD response rate of 78%, the study met its primary objective.
- Among patients with a complete MRD response, 98% had a response within the first treatment cycle.
- After intensive therapy for patients with MRD-positive ALL, rapid MRD response induced by blinatumomab has the potential to improve patient outcomes.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

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**Investigator Commentary: Efficacy and Safety Results from the Phase II BLAST Trial of Blinatumomab in B-Precursor ALL**

On December 3, 2014 the FDA granted accelerated approval for blinatumomab for Philadelphia chromosome-negative relapsed or refractory precursor B-cell ALL. It's a clever strategy to use such a drug to kill leukemia cells. Of 113 patients, 88 (78%) achieved a complete MRD response after 1 cycle of treatment with blinatumomab. This is a high response rate, including a low disease burden. Across all cycles beyond cycle 1, the MRD response rate was 80%. Adverse events occurring in 20% or more of patients included pyrexia (88%), headache, tremor, chills and fatigue.

In my experience, an infusion-related reaction is associated with blinatumomab, and our approach is to hospitalize patients for 9 days, take them through an initial dose-escalation period, discharge them and administer the agent in an outpatient setting. Blinatumomab is administered continuously over 28 days, and the FDA recommends changing the infusion bag every 48 hours. It is an intensive approach that requires a specialty center and that patients live close to the center. The current approval in the relapsed/refractory setting is based on patients previously achieving MRD, and the goal is to eliminate MRD-positive ALL while focusing on longer-term outcomes.

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