A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, January 11, 2020, 8:00 AM – 4:00 PM
Houston, Texas

Faculty

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Robert L Coleman, MD
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Harry P Erba, MD, PhD
Erika Hamilton, MD
Sara Hurvitz, MD

Mark Levis, MD, PhD
Stephen V Liu, MD, PhD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
Philip A Philip, MD, PhD, FRCP
Gregory J Riely, MD, PhD
Sonali M Smith, MD

Moderator
Neil Love, MD
Agenda

Module 1 — Lymphomas and Chronic Lymphocytic Leukemia: Drs Cheson, Nastoupil and Smith

Module 2 — Breast Cancer: Drs Hamilton and Hurvitz

Module 3 — Acute Leukemias: Drs Erba and Levis

Module 4 — Gastrointestinal Cancers: Drs Bekaii-Saab, Bendell and Philip

Module 5 — Genitourinary Cancers: Drs Drake and Oh

Module 6 — Lung Cancer: Drs Liu and Riely

Module 7 — Gynecologic Cancers: Drs Coleman and Moore
Harry P Erba, MD, PhD
Professor, Department of Medicine
Director of the Leukemia Program
Division of Hematologic Malignancies and Cellular Therapy
Duke Cancer Institute
Duke University School of Medicine
Durham, North Carolina
## Disclosures

<table>
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<tr>
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<td><strong>Contracted Research</strong></td>
<td>AbbVie Inc, Daiichi Sankyo Inc, ImmunoGen Inc, MacroGenics Inc</td>
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<td>GlycoMimetics Inc</td>
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<td><strong>IRC</strong></td>
<td>AbbVie Inc, Covance</td>
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<td><strong>Speakers Bureau</strong></td>
<td>Agios Pharmaceuticals Inc, Celgene Corporation, Incyte Corporation, Jazz Pharmaceuticals Inc, Novartis</td>
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Mark Levis, MD, PhD
Director, Adult Leukemia Program
Co-Division Director, Hematologic Malignancies
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland
## Disclosures

<table>
<thead>
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Acute Leukemias — Drs Erba and Levis

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia
Venetoclax Combined with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia¹

Venetoclax Combined with Low-Dose Cytarabine for Previously Untreated Patients with Acute Myeloid Leukemia: Results from a Phase Ib/II Study²

¹ DiNardo CD et al.  

² Wei AH et al.  
Venetoclax with either Azacitidine or Decitabine\(^1\) versus Low-Dose Cytarabine\(^2\): Response Rates by Subgroup

**Azacitidine or Decitabine\(^1\)**

- **Complete remission (CR)**
  - All Patients: 67%, N = 145
  - Cytogenetic risk:
    - Intrmed: 43%, n = 74
    - Poor: 28%, n = 71
  - AML:
    - De novo: 67%, n = 109
    - 2\(^{nd}\): 67%, n = 36
  - Age:
    - <75: 69%, n = 83
    - ≥75: 64%, n = 62

- **CR with incomplete blood count recovery (CRi)**
  - All Patients: 37%, N = 145
  - Cytogenetic risk:
    - Intrmed: 31%, n = 74
    - Poor: 28%, n = 71
  - AML:
    - De novo: 32%, n = 109
    - 2\(^{nd}\): 22%, n = 36
  - Age:
    - <75: 34%, n = 83
    - ≥75: 24%, n = 62

**Cytarabine\(^2\)**

- **Complete remission (CR)**
  - All Patients: 54%, N = 82
  - Cytogenetic risk:
    - Intrmed: 26%, n = 49
    - Poor: 29%, n = 26
  - Prior HMA:
    - Yes: 15%, n = 24
    - No: 42%, n = 58
  - AML:
    - De novo: 63%, n = 42
    - 2\(^{nd}\): 45%, n = 40

- **CR with incomplete blood count recovery (CRi)**
  - All Patients: 28%, N = 82
  - Cytogenetic risk:
    - Intrmed: 29%, n = 49
    - Poor: 27%, n = 26
  - Prior HMA:
    - Yes: 4%, n = 24
    - No: 29%, n = 58
  - AML:
    - De novo: 26%, n = 42
    - 2\(^{nd}\): 30%, n = 40

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Venetoclax (VEN) with Either Azacitidinedine (AZA) or Decitabine (DEC)\(^1\) versus Low-Dose Cytarabine (LDAC)\(^2\): Select Adverse Events

<table>
<thead>
<tr>
<th>Grade 3/4 AEs</th>
<th>VEN 400 mg DEC (n = 31)</th>
<th>VEN 400 mg AZA (n = 29)</th>
<th>VEN 800 mg DEC (n = 37)</th>
<th>VEN 800 mg AZA (n = 37)</th>
<th>VEN 1,200 mg DEC (n = 5)</th>
<th>VEN 1,200 mg AZA (n = 6)</th>
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<tr>
<td>Febrile neutropenia</td>
<td>19 (61%)</td>
<td>11 (38%)</td>
<td>15 (41%)</td>
<td>13 (35%)</td>
<td>2 (40%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Decreased WBC count</td>
<td>13 (42%)</td>
<td>7 (24%)</td>
<td>10 (27%)</td>
<td>12 (32%)</td>
<td>2 (40%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
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<table>
<thead>
<tr>
<th>Grade ≥3 AEs</th>
<th>VEN 600 mg + LDAC (n = 82)</th>
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<tr>
<td>Febrile neutropenia</td>
<td>34 (42%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31 (28%)</td>
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<tr>
<td>Decreased WBC count</td>
<td>28 (34%)</td>
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## Select Ongoing Phase III Trials of Venetoclax-Based Therapies for Treatment-Naïve AML Ineligible for Intensive Chemotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Randomization</th>
<th>Estimated primary completion</th>
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<tr>
<td>M15-656</td>
<td>443</td>
<td>Venetoclax → azacitidine</td>
<td>February 2020</td>
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<tr>
<td>(NCT02993523)</td>
<td></td>
<td>Placebo → azacitidine</td>
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<tr>
<td>M16-043</td>
<td>211</td>
<td>Venetoclax + low-dose cytarabine</td>
<td>July 2020</td>
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<tr>
<td>(NCT03069352)</td>
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<td>Placebo + low-dose cytarabine</td>
<td></td>
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<tr>
<td>M19-072</td>
<td>60</td>
<td>Venetoclax + azacitidine</td>
<td>November 2020</td>
</tr>
<tr>
<td>(NCT03941964)</td>
<td></td>
<td>Venetoclax + decitabine</td>
<td></td>
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Venetoclax is an orally bioavailable small molecule inhibitor of Bcl-2. In a phase I/II study in relapsed/refractory AML patients, single-agent venetoclax demonstrated minimal evidence of activity (less than 20% response rate). However, even as a single agent, 4 of 6 subjects with an IDH mutation had a response. In phase Ib studies leading to FDA approval, venetoclax was combined with less-intensive therapies for treatment-naïve older or unfit AML patients, including azacitidine, decitabine and low dose cytarabine (LoDAC). The rationale was not based on preclinical data, but instead the combinations were studied in an effort to improve the poor outcomes seen with the less intensive standard-of-care therapies. Although the optimal dose of venetoclax was evaluated in these phase Ib studies, the optimal dosing schedule (concurrent, sequential, or both as well as duration of venetoclax therapy) was not evaluated. The overall response rate with hypomethylating agents (HMA) plus venetoclax is remarkable, 71% CR/CRi.
The median time to response was short, 1-2 months. The responses also appeared durable, and the median overall survival was 16 months with HMA plus venetoclax. Although response rates greater than 50% were observed in the phase Ib study across mutational subsets, including TP53, the response rates were highest among patients with IDH1, IDH2 and NPM1 mutations. The 30-day mortality in the azacitidine plus venetoclax arm was less than 5%. AML patients previously treated with HMA for myelodysplastic syndrome were excluded from the HMA plus venetoclax phase Ib study. However, such patients were treated with LoDAC plus venetoclax; the overall response rate in these patients was only 33%, with only 1 of 24 subjects achieving CR. Single-institution data supports the use of HMA plus venetoclax in patients with relapsed/refractory AML or in AML patients previously treated with an HMA.
Two potential toxicities should be considered with these combinations: tumor lysis syndrome (TLS) and myelosuppression. Tumor lysis syndrome was not observed in the HMA plus venetoclax phase Ib study. However, the study required subjects to have a WBC count less than 25,000/microliter. Although hydroxyurea was allowed prior to treatment, only 10% of the subjects received hydroxyurea. In fact, 25%-30% subjects had only 20%-30% marrow blasts, and less than 50% of subjects in both phase Ib studies had over 50% marrow blasts. Patients receiving venetoclax with HMA or LoDAC should be monitored closely for TLS. Great caution should be exercised if using venetoclax with HMA or LoDAC in the setting of uncontrolled leukocytosis or renal insufficiency. Venetoclax will contribute to myelosuppression, especially neutropenia. The risk of hematologic toxicity appeared higher in the decitabine/venetoclax arm compared with the azacitidine/venetoclax arm of the phase Ib study.
Two thirds of subjects in the HMA/venetoclax phase Ib study required dose interruption. There are no formal guidelines on the management of cytopenias during maintenance therapy with venetoclax plus HMA or LoDAC. The prescribing information suggests the use of myeloid growth factors, but dose reductions may also be considered. Since myelosuppression is uncommon with single-agent HMA once a remission has been achieved, and the optimal number of days of venetoclax was not studied, I prefer to limit the number of days of venetoclax therapy during subsequent cycles. CYP3A4 inhibitors will increase exposure to, and toxicity from, venetoclax. The dose of venetoclax should be reduced to 50-100 mg daily with concomitant use of a strong CYP3A4 inhibitor. Two international phase III studies of azacitidine with venetoclax/placebo and LoDAC with venetoclax/placebo have completed enrollment. The primary endpoint of these two studies includes overall survival.
Since the median survival of AML patients in the phase Ib studies exceeded 12 months, it is anticipated that these two studies will be positive. However, a phase III study of standard therapy with venetoclax vs placebo in relapsed myeloma was halted due to worse survival in the experimental arm, despite a higher response rate. If the phase III studies of these venetoclax combinations in treatment-naïve, older and/or unfit AML patients are negative and do not confirm a survival benefit, these combinations may still provide benefit based on the rapid achievement of remission in a high percentage of patients without early induction mortality.

Venetoclax inhibits the anti-apoptotic protein Bcl-2. Therefore, this agent may act synergistically with other cytotoxic or targeted agents in AML. Phase I studies combining venetoclax with FLT3 inhibitors, IDH inhibitors and standard cytotoxic chemotherapy such as 7+3 are under way.
Response to Venetoclax in Combination with Low Intensity Therapy (LDAC or HMA) in Untreated Patients with Acute Myeloid Leukemia with IDH, FLT3 and Other Mutations and Correlations with BCL2 Family Expression

Chyla BJ et al.
ASH 2019;Abstract 546.
## Phase Ib/II Trial: Molecular Marker-Defined Subgroup Analysis of Clinical Outcomes with Venetoclax + HMA or LDAC

<table>
<thead>
<tr>
<th>Molecular marker*</th>
<th>CR/CRi</th>
<th>Median OS</th>
<th>Median TTFR</th>
<th>DoR</th>
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<tbody>
<tr>
<td>Molecular marker cohort (n = 167)</td>
<td>109 (65.3%)</td>
<td>12.5 mo</td>
<td>1.2 mo</td>
<td>15.0 mo</td>
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<tr>
<td>IDH1/IDH2 mutation (n = 43)</td>
<td>36 (83.7%)</td>
<td>NR</td>
<td>1.1 mo</td>
<td>NR</td>
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<tr>
<td>NPM1 mutation (n = 26)</td>
<td>22 (84.6%)</td>
<td>NR</td>
<td>1.3 mo</td>
<td>NR</td>
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<tr>
<td>TP53 mutation (n = 37)</td>
<td>22 (59.5%)</td>
<td>8.9 mo</td>
<td>1.5 mo</td>
<td>5.6 mo</td>
</tr>
<tr>
<td>FLT3 mutation (n = 30)</td>
<td>16 (53.3%)</td>
<td>12.4 mo</td>
<td>1.8 mo</td>
<td>19.9 mo</td>
</tr>
</tbody>
</table>

NR = Not reached; CRi = incomplete complete remission; TTFR = time to first response; DoR = duration of response.

* Pts with co-expressing mutations are represented more than once.

* VEN + HMA or LDAC has efficacy across multiple molecular markers in AML.

* Activity with VEN + HMA or LDAC is rapid and durable, and is observed across different levels of BCL2 expression in AML blasts.

Chyla BJ et al. ASH 2019;Abstract 546.
HMA with venetoclax has rapidly been adopted by U.S. oncologists as a standard of care for treatment-naïve, older AML patients who are not fit for intensive chemotherapy, based on an expansion of a phase IB study. The high responses rates (70% CR/CRi), rapid time to response (1-2 months), low early mortality (5%), durable responses, and median survival of 15-18 months can all be cited as reasons for adopting this regimen, even though there is still no phase III data demonstrating an overall survival (OS) benefit compared with HMA alone. The results of the phase III study of azacitidine with either venetoclax or placebo are expected soon. The presentation by Chyla and colleagues provide some insight into response rates and duration of response (DOR) in certain subsets of patients treated with either an HMA or LoDAC with venetoclax. The rate of CR/CRi in patients with NPM1-, IDH1-, or IDH2-mutated disease was over 80%; whereas, 50-60% of those with TP53 or FLT3 mutations had a response following HMA/LoDAC with venetoclax.
The DOR and OS were impressive in those with NPM1, IDH1, and IDH2 mutations (the median DOR and median OS had not been reached). However, median DOR was shorter for those with FLT3 mutations and much shorter for those with TP53 mutations (less than six months). The median survival for those with TP53 mutations was 8.9 months. Bcl-2 mRNA expression did not correlate with response. However, other assays of Bcl-2 inhibitor sensitivity were not reported. This data raises several important questions. There is no single definition of unfit for intensive chemotherapy, creating uncertainty in how to identify these patients. Early mortality is also low with 7+3 induction chemotherapy for well-selected older AML patients. Older AML patients with NPM1-mutated AML can be cured with standard 7+3 induction followed by intermediate-dose cytarabine consolidation. Although the data for the NPM1 subset with HMA/ven or LoDAC/ven is impressive, we should not ignore the opportunity to potentially cure an older patient with NPM1-mutated AML with time-limited chemotherapy.
We do not have any quality-of-life data for older patients subjected to indefinite maintenance therapy with HMA or LoDAC with venetoclax. IDH-mutated AML is highly sensitive to venetoclax as a single agent and to the combinations of HMA or LoDAC with venetoclax. However, the combination of HMA with ivosidenib in IDH1-mutated AML and with enasidenib in IDH2-mutated AML also leads to high response rates with over 50% of patients alive at one year. Furthermore, the combination of azacitidine with ivosidenib does not appear to produce recurrent myelosuppression during maintenance therapy. In fact, the blood counts appear to recover quickly during the first cycle based on data presented by Courtney DiNardo at EHA 2019. Ivosidenib has been FDA-approved for previously untreated older AML patients unfit for chemotherapy. A number of questions arise: Should the clinician await the IDH mutation data before choosing the induction regimen? If an IDH mutation is detected, which regimen should be chosen first? If these agents are used in sequence, it is not clear which should be used first.
However, venetoclax is not FDA approved for relapsed/refractory AML. Would clinicians consider combining both venetoclax and an IDH inhibitor with either LoDAC or HMA? Is combination “superior” to considering a sequential approach? How would we judge “superior,” since toxicity is unlikely to be less with a combination of two active agents, and the DOR and OS with HMA/ven is already very impressive? The response rate in TP53-mutated AML is over 50%, but not clearly different from what can be achieved with intensive chemotherapy. The DOR is short. At this time, allogeneic hematopoietic stem cell transplantation (allo HSCT) is the only potentially curative option for these patients. The quality of the remission prior to allo HSCT affects ultimate outcome with allo HSCT. Patients in an MRD-negative CR appear to derive the greatest benefit from allo HSCT. It is not clear if the quality of the remissions following intensive chemotherapy or venetoclax with HMA/LoDAC are different. There is no data regarding outcomes with allo HSCT for TP53-mutated patients treated with HMA/ven versus intensive chemotherapy.
Clearly, novel approaches are needed in this subset of patients. Recent data with the TP53 modulator, APR246, and the anti-CD47 (Don’t Eat Me) monoclonal antibody, magrolimab, in patients with TP53-mutated myeloid neoplasm is intriguing. Patients with TP53-mutated AML should be considered for available clinical trials. The response rate and DOR observed with HMA/ven or LoDAC/ven are clearly affected by mutational profile. If investigators selected subjects for the phase III studies of azacitidine/venetoclax or LoDAC/venetoclax based on mutational profile, this unmeasured selection bias could potentially affect the OS benefit of the venetoclax combination in either a positive (if IDH- or NPM1-mutated patients selected) or negative (if TP53-mutated patients selected) manner.
Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: phase 2 study results

Jorge E. Cortes, MD,1 B. Douglas Smith, MD,2 Eunice S. Wang, MD,3 Akil Merchant, MD,4 Vivian G. Oehler, MD,5 Martha Arellano, MD,6 Daniel J. DeAngelo, MD,7 Daniel A. Pollyea, MD,8 Mikkael A. Sekeres, MD,9 Tadeusz Robak, MD,10 Weidong Wendy Ma, PhD,11 Mirjana Zeremski, MD,11 M. Naveed Shaik, PhD,11 A. Douglas Laird, PhD11 Ashleigh O’Connell, BSc,11 Geoffrey Chan, MD,11 and Mark A. Schroeder, MD12

BRIGHT AML 1003: Glasdegib with Chemotherapy for Untreated AML or High-Risk MDS

<table>
<thead>
<tr>
<th>Select adverse events</th>
<th>Glasdegib + chemotherapy (n = 69)</th>
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<td>Any grade</td>
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<tr>
<td>Any adverse event</td>
<td>100%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>71.0%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>63.8%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>53.6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>40.6%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

| Median OS (n = 69)                    | 14.9 mo    |
| CR (n = 69)                           | 46.4%      |
| CR in patients ≥55 years old (n = 60) | 40.0%      |

BRIGHT AML1019: Ongoing Phase III Trial Design

Primary endpoint: Overall survival

Target accrual (N = 720)
- Previously untreated AML
- Adequate organ function
- No APL
- No AML with BCR ABL1 or t(9;22)(q34;q11.2) as sole abnormality
- No active CNS leukemia

Glasdegib + 7+3 induction (intensive study) or Glasdegib + azacitidine (non-intensive study)
Placebo + 7+3 induction (intensive study) or Placebo + azacitidine (non-intensive study)

Glasdegib is an orally bioavailable inhibitor of Smoothened, a component of the Hedgehog pathway. Preclinical studies of this agent do not show convincing evidence of a direct effect on the AML leukemic cell or even normal hematopoiesis. On the other hand, it has been postulated that glasdegib may interfere with the interaction between the leukemic stem cells and the bone marrow microenvironment. Glasdegib has been FDA approved based on the results of a randomized, phase II study in treatment-naïve, older, unfit AML patients. Patients were randomly assigned in a 2:1 fashion to receive either low dose cytarabine (LoDAC) with glasdegib 100 mg once daily continuously or low dose cytarabine alone, respectively. There was no placebo control; patients and their physicians were not blinded to the treatment assignment. The primary endpoint of the study was met with improvement in median survival from 4 months to 8.3 months with the addition of glasdegib.
However, the complete remission rate in the control arm was less than 5%, lower than that observed in several other studies with low dose cytarabine alone. This suggests that subjects assigned to single-agent LoDAC may have been removed from the study before a response could be achieved. Glasdegib was associated with GI toxicity including dysgeusia, nausea and diarrhea, as well as alopecia and muscle cramps. Cortes and colleagues have published the results of a phase II study of glasdegib in combination with daunorubicin and cytarabine induction therapy followed by intermediate-dose cytarabine consolidation (2-4 cycles). Subjects in CR not proceeding to allogeneic hematopoietic stem cell transplant (allo HSCT) then received six 28-day cycles of glasdegib maintenance. The primary endpoint of the study was improvement in the CR rate to greater than 54% for the 60 evaluable patients aged 55 years and older.
The primary endpoint was not achieved; only 40% of the patients achieved a CR. Although the authors report that the CR rate was not affected by the identified mutations in these patients, the CR rate in patients with poor-risk karyotype was only 18% (3 of 17 patients). On the other hand, the authors were encouraged by a median survival of 14.7 months in patients aged 55 years and older. They suggest that glasdegib may exert a benefit by affecting the survival of the leukemic stem cell through an effect on paracrine signaling in the marrow microenvironment. In this way, glasdegib may affect risk of relapse and overall survival more than CR rate. However, median duration of CR was short (100 days), potentially due to methodologic issues. The protocol-defined pharmacodynamics studies on peripheral blood samples could not demonstrate an effect of glasdegib on Hedgehog signaling due to low baseline expression of GLI proteins.
Other than the expected hematologic toxicity of intensive chemotherapy, there was expected GI toxicity (dysgeusia, nausea, anorexia). The authors conclude that the addition of glasdegib was well tolerated, since these toxicities were generally grade 1-2. The true benefit of glasdegib in AML has not yet been established. We eagerly await the results of the BRIGHT AML randomized trials to assess the benefit of Hedgehog inhibition in AML.
FDA Approves Addition of Survival Data to Gilteritinib Label for Relapsed or Refractory AML with a FLT3 Mutation
Press Release – May 29, 2019

“On May 29, 2019, the Food and Drug Administration approved the addition of overall survival data in labeling for gilteritinib, indicated for adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.

Approval was based on the ADMIRAL trial (NCT02421939), which included 371 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay. Patients were randomized (2:1) to receive gilteritinib 120 mg once daily (n = 247) over continuous 28-day cycles or prespecified salvage chemotherapy (n = 124). Salvage chemotherapy included either intensive cytotoxic chemotherapy or a low-intensity regimen. For the analysis, overall survival (OS) was measured from the randomization date until death by any cause. After a median follow-up of 17.8 months, median OS was 9.3 months for patients receiving gilteritinib and 5.6 months for those on the chemotherapy arm (HR 0.64; p = 0.0004).”

Gilteritinib was initially approved on November 28, 2018 based on an interim analysis of response rates from ADMIRAL. After a median follow-up of 4.6 months, 29 patients achieved complete remission (CR) or CR with partial hematologic recovery (CRh) (21%).
Phase III QUAZAR AML-001 Study of Oral Azacitidine (CC-486) as Maintenance Therapy for Newly Diagnosed AML Meets Primary and Secondary Endpoints
Press Release – September 12, 2019

Top-line results were announced from the international Phase III randomized, double-blind, placebo-controlled study, QUAZAR, that evaluated the efficacy and safety of the investigational therapy CC-486 as maintenance therapy in patients with newly diagnosed AML who achieved first complete response (CR) or complete response with incomplete blood count recovery (CRi) with induction chemotherapy (with or without consolidation). The study enrolled 472 patients, randomized 1:1 to receive either oral CC-486 300 mg or placebo once daily for 14 days of a 28-day cycle plus best supportive care until disease relapse. Maintenance treatment with CC-486 resulted in a highly statistically significant and clinically meaningful improvement in overall survival compared to placebo. The key secondary endpoint of relapse-free survival (RFS) also showed a statistically significant improvement. CC-486 was well tolerated, and there were no unexpected safety events in QUAZAR AML-001.

Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML

Perl AE et al.  
ADMIRAL: Phase III Trial Efficacy Results

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Gilteritinib (n = 247)</th>
<th>Chemo (n = 124)</th>
<th>HR* or RD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median EFS</td>
<td>2.8 mo</td>
<td>0.7 mo</td>
<td>0.79*</td>
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<tr>
<td>Median LFS</td>
<td>4.4 mo</td>
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<td>NE</td>
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<tr>
<td>ORR</td>
<td>67.6%</td>
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<td>21.8%</td>
<td>32.5*</td>
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<tr>
<td>PR</td>
<td>13.4%</td>
<td>4.0%</td>
<td>ND</td>
</tr>
<tr>
<td>Median DoR</td>
<td>11.0 mo</td>
<td>NE</td>
<td>NE</td>
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HR = hazard ratio; RD = risk difference; EFS = event-free survival; LFS = leukemia-free survival; NE = not estimable; ORR = overall response rate; CRp = CR with incomplete platelet recovery; CRc = composite CR; CRi = CR with incomplete hematologic recovery; ND = not determined; DoR = duration of remission

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<th>Grade ≥3 (Gilteritinib)</th>
<th>All grades (Salvage Chemotherapy n = 109)</th>
<th>Grade ≥3 (Salvage Chemotherapy)</th>
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<td>45.9%</td>
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<td>Anemia</td>
<td>47.2%</td>
<td>40.7%</td>
<td>34.9%</td>
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<td>Pyrexia</td>
<td>42.7%</td>
<td>3.3%</td>
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<td>13.8%</td>
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<tr>
<td>Increased AST</td>
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<tr>
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<td>Dyspnea</td>
<td>23.6%</td>
<td>4.1%</td>
<td>6.4%</td>
<td>2.8%</td>
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Select Ongoing Phase III Trials of Gilteritinib-Based Therapies for AML with FLT3 Mutation

<table>
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<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Randomization</th>
<th>Estimated primary completion</th>
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<tr>
<td>2215-CL-0303 (NCT03182244)</td>
<td>318</td>
<td>Refractory to first-line tx with or without HSCT</td>
<td>Gilteritinib Salvage chemotherapy</td>
<td>March 2020</td>
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<td>2215-CL-0304 (NCT02997202)</td>
<td>346</td>
<td>Maintenance tx following allogeneic transplant</td>
<td>Gilteritinib Placebo</td>
<td>April 2025</td>
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<tr>
<td>2215-CL-0201 (NCT02752035)</td>
<td>323</td>
<td>Newly diagnosed Intensive chemo ineligible</td>
<td>Gilteritinib Gilteritinib + azacitidine Azacitidine</td>
<td>April 2021</td>
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<tr>
<td>HOVON 156 AML (NCT04027309)</td>
<td>768</td>
<td>Newly diagnosed Intensive chemo eligible</td>
<td>Gilteritinib* + chemotherapy Midostaurin* + chemotherapy</td>
<td>May 2023</td>
</tr>
</tbody>
</table>

* Administered sequentially to standard induction and consolidation chemotherapy; patients who achieve CR/CRi/MLFS will receive maintenance gilteritinib or midostaurin

Activating mutations of FLT3 occur in about one third of AML patients. The more common mutation is an internal tandem duplication (ITD) in the juxtamembrane region, encoded by exons 14 and 15. FLT3 tyrosine kinase domain (TKD) mutations are identified in 5%-10% of AML patients. The presence of the FLT3 ITD mutation has been associated with a worse overall survival due to higher risk of relapse. Midostaurin was FDA approved in April 2017 for treatment-naïve AML patients with either a FLT3 ITD or TKD mutation in combination with standard daunorubicin and cytarabine induction therapy and cytarabine consolidation, based on the results of the RATIFY trial. Although the CR rate was not improved by the addition of midostaurin to standard induction therapy, the survival of patients at 4 years was superior with midostaurin compared with placebo (51% vs 44%). The survival benefit was most apparent for patients receiving midostaurin-containing therapy who proceeded to allo HSCT in first CR.
Midostaurin is a first-generation type I inhibitor. First-generation FLT3 inhibitors are less selective. In fact, some have speculated that the survival benefit observed with midostaurin in the RATIFY trial may be due to its activity against a broad range of both tyrosine and serine-threonine kinases. Type I inhibitors interfere with the ATP binding site and are active against both ITD- and TKD-mutant enzymes. Gilteritinib is an orally bioavailable, type I, second-generation FLT3 inhibitor with greater specificity for FLT3 than midostaurin. Gilteritinib was compared with either intensive (MEC, IdaFLAG) or less intensive (azacitidine, low dose cytarabine) salvage therapy for FLT3-mutated AML patients with refractory or first relapse disease in a 2:1 randomization, respectively. Gilteritinib was superior to salvage chemotherapy in terms of efficacy: higher CR rate (21% vs 11%), higher CR + CRh rate (34% vs 15%), improvement in median overall survival (9.3 vs 5.6 months), improvement in one-year survival (37% vs 17%) and higher number of patients able to proceed to allo HSCT (26% vs 15%), the only potentially curative option.
Patients who continued gilteritinib after allo HSCT had a better overall survival compared to those who did not, but the true benefit of gilteritinib maintenance post allo HSCT is difficult to discern given the selection bias inherent in this type of comparison. The BMT CTN trial is evaluating gilteritinib post allo HSCT in a placebo-controlled randomized phase III trial. The benefit of gilteritinib over salvage chemotherapy was observed regardless of co-mutations (NPM1, DNMT3A, WT1) and high vs low FLT3 allelic ratio. There was no significant safety signal, although gilteritinib has been associated with differentiation syndrome. I believe this data strongly supports the use of gilteritinib (over chemotherapy alone) in this population. However, the survival of patients with FLT3-mutated AML who received either gilteritinib or salvage chemotherapy was dismal at 2 years (approximately 10%). Since FLT3 mutation appears to be a late event in leukemogenesis, it is not surprising that targeting a single mutation will not result in long-term benefit. Clearly, other interventions are required. Gilteritinib is being studied in combination with chemotherapy as well as MDM2 and Bcl-2 inhibitors.
Other FLT3 inhibitors are in development, including quizartinib and crenolanib. Quizartinib is arguably the most potent of the selective FLT3 inhibitors. As a type II inhibitor, it is only active against the FLT3 ITD mutation. Nonetheless, in the initial phase I studies of quizartinib, AML patients with a FLT3 ITD variant allelic frequency less than 10% also responded. The QuANTUM-R study compared quizartinib to salvage chemotherapy in a design nearly identical to the ADMIRAL trial. The primary endpoint of the study was achieved, with improvement in median overall survival (27 weeks vs 20 weeks). The response rate was also higher with quizartinib than chemotherapy (48% vs 27%), and more patients were able to proceed to allo HSCT after quizartinib therapy (32% vs 12%). The magnitude of the survival benefit seemed less than that observed with gilteritinib. However, the survival of patients in the QuANTUM-R study may have been affected by 23% of subjects assigned to the chemotherapy arm not accepting their treatment assignment. In terms of toxicity, quizartinib has been associated with QT prolongation, especially at higher doses explored in the initial phase I studies.
In QUANTUM-R only 3% of subjects experienced asymptomatic prolongation of the QTc interval to greater than 500 milliseconds. Although ODAC advised against approval of quizartinib based on uncertain benefit-to-risk ratio, the drug has been approved in Japan.
FDA Approval of Ivosidenib as First-Line Treatment for AML with IDH1 Mutation
Press Release – May 2, 2019

“On May 2, 2019, the Food and Drug Administration approved ivosidenib for newly-diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA-approved test, in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Approval was based on an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of single-agent ivosidenib for newly-diagnosed AML with an IDH1 mutation.

The adverse reactions that occurred in at least 25% of patients were diarrhea, fatigue, edema, decreased appetite, leukocytosis, nausea, arthralgia, abdominal pain, dyspnea, differentiation syndrome and myalgia. Prescribing information contains a Boxed Warning alerting health care professionals and patients about the risk of differentiation syndrome which may be life-threatening or fatal.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation
Mutant IDH1 Inhibitor Ivosidenib (IVO; AG-120) in Combination with Azacitididine (AZA) for Newly Diagnosed Acute Myeloid Leukemia (ND AML)

Dinardo CD et al.
*Proc ASCO 2019;Abstract 7011.*
Ivosidenib and Azacitidine in Newly Diagnosed AML with IDH1 Mutation: Treatment Duration and Best Overall Response

**ORR = 78.3%**

<table>
<thead>
<tr>
<th>Response</th>
<th>CR</th>
<th>CRi/CRp</th>
<th>MLFS</th>
<th>SD</th>
<th>NE</th>
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<tbody>
<tr>
<td>ORR</td>
<td>78.3%</td>
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</tr>
<tr>
<td>CR</td>
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<td>CRi/CRp</td>
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<td>MLFS</td>
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<td>SD</td>
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<tr>
<td>NE</td>
<td></td>
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</table>

**Treatment duration (months)**

- SD
- CR
- CRi/CRp
- MLFS
- SD
- NE
- MLFS
- SD
- SD

**a** Patient continued on commercially available ivosidenib

**b** Patient had mIDH1 clearance in PBMCs only (BMMCs not available); all other patients had mIDH1 clearance in both BMMCs and PBMCs

NA = not assessed; NE = not evaluable

Dinardo CD et al. *Proc ASCO* 2019;Abstract 7011.
Ivosidenib Induces Deep Durable Remissions in Patients with Newly Diagnosed IDH1-Mutant Acute Myeloid Leukemia

Roboz GJ et al.  
*Blood* 2019;[Epub ahead of print].
Ivosidenib in Newly Diagnosed AML with IDH1 Mutation: Best Response, Overall Survival and Tolerability


- Median OS = 12.6 mo
- Ivosidenib monotherapy was well tolerated.

Best response

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib (n = 33)</th>
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<tbody>
<tr>
<td>ORR</td>
<td>18 (54.5%)</td>
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<tr>
<td>CR</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>CRi/CRp</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>MLFS</td>
<td>1 (3.0%)</td>
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</table>

CRi = CR with hematologic recovery
CRp = CR with incomplete platelet recovery
MLFS = morphologic leukemia-free state
Ivosidenib in Newly Diagnosed AML with IDH1 Mutation: Transfusion Independence


Transfusion Independence

Patients Dependent at Baseline (n = 21)

Achieved transfusion independence (n = 9)

IDH1 mutation clearance 9/14 pts with CR+CR with partial hematologic recovery

Postbaseline transfusion independence, %

CR (n = 10)
CRh (n = 4)
Non-CR/CRh responders (n = 4)
Nonresponders (n = 15)
Overall (n = 33)

Platelet (n = 14)
Red blood cell (n = 16)
Both (n = 21)
Both ivosidenib and enasidenib have been listed in NCCN AML practice guidelines for the treatment of treatment naïve, older, IDH mutated AML patients unable to tolerate intensive chemotherapy. Roboz et al report the efficacy and safety of single-agent ivosidenib in treatment naïve IDH1m AML patients. The rate of CR/CRh with single-agent ivosidenib is 42% with 30% CR. The median time to CR/CRh response was almost 3 months. Two thirds of IDH1m AML patients achieving a CR or CRh were still in a response at 12 months. Mutational clearance was achieved in 64% of the CR/CRh patients. The adverse event profile is similar to that observed in R/R IDH1m AML. However, the combination of HMA with venetoclax has been associated with a very high response rate (over 90% CR/CRi) in treatment-naïve IDHm AML patients. Responses with HMA/venetoclax are often seen after only one cycle of therapy.
Since AML patients previously treated with an HMA for MDS were excluded from the phase I/II study of HMA/venetoclax, this data supports the use of ivosidenib for initial therapy of AML patients who have already progressed from myelodysplastic syndrome after having received an HMA. IDH mutations are not infrequently discovered at the time of progression of MDS to AML. Ivosidenib is now FDA approved for initial treatment of IDH1m AML patients based on this single-agent data. The combinations of azacitidine with full doses of the IDHm inhibitors appear safe based on the results of a phase Ib study. DiNardo et al have presented the results of an expanded cohort (N = 23) of treatment-naïve, older/unfit IDH1m AML patients treated with azacitidine and ivosidenib. The response rates are higher than expected with either agent alone (70% CR/CRh and 78% ORR). Furthermore, 63% of CR/CRh patients achieved MRD-negative remissions as judged by clearance of the IDH1 mutant allele by digital PCR assay.
Median duration of response has not been reached, with seven of the CR/CRi patients with ongoing responses for more than 12 months. Importantly, neutrophil counts improved during the first cycle of therapy and remained above 500/mm$^3$ in the responders with subsequent cycles of therapy. Rapid and sustained blood count recovery may be a point of distinction between azacitidine with ivosidenib versus HMA with venetoclax. The toxicity profile was similar to that expected with either drug alone. Differentiation syndrome occurred in 17% of subjects and grade 3/4 QT prolongation in 13%. Ideally, we would want to compare the outcomes of patients given azacitidine with either placebo or an IDHm inhibitor. The AGILE trial is attempting to address this question with ivosidenib in treatment-naïve, IDH1 mutated, older AML patients unfit for intensive chemotherapy. However, there are significant challenges affecting accrual to the study. First, less than 10% of AML patients will have an IDH1 R132 mutation necessary for treatment on the study.
Second, other agents are being combined with HMA, such as the Bcl-2 inhibitor venetoclax and the Smoothen inhibitor glasdegib. Based on very encouraging response rates and median survival in phase Ib studies, some clinicians are treating older unfit patients, regardless of mutational status, with the combination of azacitidine with venetoclax. Third, if a patient is not responding on study, then ethically the subject needs to be told if he/she has been randomized to ivosidenib or placebo, since ivosidenib would be an available option for the patient randomized to receive placebo. Therefore, the blind would need to be broken. How long would an investigator allow their patient to remain on such a blinded study without a response, knowing the subject may have been randomized to placebo? One cycle, two cycles? Finally, overall survival is the primary endpoint of the AGILE trial. An OS benefit may be obscured by available salvage therapies following treatment on the AGILE trial, such as ivosidenib itself, Bcl-2 inhibitors, and immunotherapeutic approaches with BiTE, DART and antibody-drug conjugates.
Event-free survival could circumvent this problem and decrease the sample size. However, complete response rate already appears to be lower with azacitidine alone (20%) compared with azacitidine with ivosidenib. Therefore, EFS would likely show a benefit of the combination but predominantly due to difference in CR. Ultimately, these obstacles may be insurmountable, indicating the need for alternative approaches to FDA approval and/or clinical adoption of novel therapeutic options for AML patients. Finally, assuming that the phase III studies of HMA or LoDAC with venetoclax show a survival benefit over single-agent HMA or LoDAC alone, the phase III study would ideally compare azacitidine plus ivosidenib to azacitidine plus venetoclax. A phase Ib study has shown that both ivosidenib and enasidenib can also be safely combined with 7+3 induction and high dose cytarabine consolidation therapies in treatment-naïve IDH1m and IDH2m AML patients, respectively.
The investigators reported the rates of response, including MRD-negative responses (using both flow cytometry and digital PCR assays) and survival at one year (over 75% in both groups of patients). However, the benefit of adding IDHm inhibitors to standard AML therapy can only be truly discerned from placebo-controlled, double-blind, randomized phase III trials. The HOVON has launched such a trial. These trials will exclude subjects with a concomitant FLT3 mutation, since midostaurin is approved in Europe for these patients.
Enasidenib, an Inhibitor of Mutant IDH2 Proteins, Induces Durable Remissions in Older Patients with Newly Diagnosed Acute Myeloid Leukemia

Enasidenib for Older Patients Newly Diagnosed with AML with IDH2 Mutation: Survival Outcomes

**Overall Survival**

- N = 39
- Median OS 11.3 months (95% CI 5.7, 15.1)

**Event-Free Survival**

- N = 39
- Median EFS 5.7 months (95% CI 2.8, 16.0)
The Phase I studies of ivosidenib and enasidenib in the respectively IDH1 and IDH2 mutated, relapsed and refractory (R/R) AML patients have produced very similar results. 33% of IDH1m+ R/R AML patients and 25% of IDH2m+ R/R AML patients achieve a complete remission or complete remission with partial hematologic recovery (CRh, ANC over 500/mm³ AND platelets over 50,000/mm³). The median time to CR + CRh is 2 months with ivosidenib and almost 4 months with enasidenib. The majority, if not all, of the responses will be seen by 6 months. Furthermore, transfusion dependent AML patients may become transfusion independent, even without achieving CR or CRh. The median duration of response has been approximately 6-9 months; however, some patients have been in remission for over 1.5 years. The major toxicity to consider with both ivosidenib and enasidenib is differentiation syndrome (DS), occurring in 10% to 20% of patients, depending on grade, often associated with hyperleukocytosis.
DS may occur as early as the first week of therapy and as late as several months into therapy. The signs of DS include fluid retention with pulmonary edema, pleural/pericardial effusions, fever, dyspnea, hypoxia, hypotension and renal insufficiency. When DS is suspected, the patient should be monitored closely and started on dexamethasone 10 mg IV twice daily. If the WBC count is increasing, hydroxyurea should be started. Unlike APL, only half of the patients experiencing DS will actually achieve remission. There are several potential explanations for this observation. There may be multiple subclones of the disease at the time of relapse, some of which may not respond to the IDHm inhibitors due to the presence of other drivers, while the IDHm-driven disease does respond. It is also possible that the signs of disease progression may be mistaken for those of DS. There is no laboratory evaluation that allows us to definitively diagnose DS.
The diagnosis of DS (as opposed to AML progression) may be favored if there are signs of granulocytic differentiation in the blood smear. Also, DS tends to respond within the first few days of steroid therapy, whereas AML progression will not respond. Stein et al have updated results from the phase I/II study of enasidenib in R/R AML patients. The response rates did not change (20% CR, 40% ORR). There were a few important observations. A significant minority of patients (38%) only maintained stable disease during the first 90 days on study. However, 30% of these patients (N = 25) achieved an IWG-defined response in the next 90 days, including CR in 16 of these 25 patients. Subjects with three or fewer mutations were more likely to have a response (29% CR, 55% ORR) compared with those with six or more mutations (16% CR, 31% ORR). FLT3 ITD or TKD co-mutation was associated with lower chance of remission.
Mutations in the genes for spliceosome enzymes and receptor kinase signaling pathways were associated with lower chance of response. Subjects achieving a molecular remission by PCR had a better survival than those who did not. These patients were also likely to have achieved a CR. However, there was no difference in the survival of morphologic CR patients either achieving a molecular remission or not. This analysis did show that lower VAF was associated with greater chance of achieving a response (statistically significant only for the R140 mutation). However, the significant overlap in the range of VAF among responders and non-responders make this observation of limited clinical value. High baseline 2HG levels were associated with a greater chance of remission for the IDH2 R172 population only. Rapid, significant suppression of 2-HG levels was observed regardless of response in IDH2 R140-mutant AML patients. However, suppression of the 2-HG levels correlated with response in the R172 group.
Although this observation suggests a different mechanism of action of enasidenib in these two subgroups, the authors make no comment about this difference between the R140 and R172 groups. The response rate was nominally higher in the R172 group, but this was likely due to a lower number of co-mutations. Although these correlative studies are interesting and may provide insight into mechanism of action, these features do not allow us to select patients who should or should not receive enasidenib. Both ivosidenib and enasidenib have been listed in NCCN AML practice guidelines for the initial treatment of older, IDH-mutated AML patients unable to tolerate intensive chemotherapy. Pollyea et al report the efficacy and safety of single-agent enasidenib in treatment-naïve IDH2m AML patients. The overall response rate (31% CR, CRi, PR and MLFS) is similar to that observed in the cohort of the phase I study of R/R AML patients; only 18% achieved a CR.
The time to first response was just under 2 months and time to best response almost 4 months. The BEAT AML study has demonstrated similar efficacy of enasidenib in this patient population. If no response after four cycles, azacitidine would be added to enasidenib in the BEAT AML study. The adverse event profile is similar that observed in R/R IDH2m AML. However, the combination of HMA with venetoclax has been associated with a very high response rate (CR/CRi) in treatment-naïve AML patients with IDH mutations. Responses with HMA/venetoclax are often seen after only one cycle of therapy. On the other hand, since AML patients previously treated with an HMA for MDS were excluded from the phase I/II study of HMA/venetoclax, this data supports the use of enasidenib in AML patients who have already progressed from myelodysplastic syndrome and have received hypomethylating agents (HMA). Not infrequently, IDH mutations are discovered at the time of progression of MDS to AML.
A phase Ib study has shown that both ivosidenib and enasidenib can be safely combined with 7+3 induction and high dose cytarabine consolidation therapies in treatment-naïve IDH1m and IDH2m AML patients, respectively. The investigators reported the rates of response, including MRD-negative responses (using both flow cytometry and digital PCR assays) and survival at one year (over 75% in both groups of patients). However, the benefit of adding IDHm inhibitors to standard AML therapy can be truly discerned only from placebo-controlled, double-blind, randomized phase III trials. The HOVON has launched such a trial. These trials will exclude subjects with a concomitant FLT3 mutation, since midostaurin is approved in Europe for these patients.
Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results from an Ongoing, Randomized Study

DiNardo CD et al.  
Proc ASH 2019;Abstract 643.
Results from an Ongoing Phase II Trial of Enasidenib/Azacitidine versus Azacitidine Alone for Newly Diagnosed AML with IDH2 Mutation

<table>
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<tr>
<th>Response</th>
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<th>AZA (n = 33)</th>
<th>p-value</th>
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<td>Overall response rate</td>
<td>46 (68%)</td>
<td>14 (42%)</td>
<td>0.0155</td>
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<td><strong>Best response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>34 (50%)</td>
<td>4 (12%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>CRi/CRp</td>
<td>6 (9%)</td>
<td>4 (12%)</td>
<td>—</td>
</tr>
<tr>
<td>PR</td>
<td>3 (4%)</td>
<td>4 (12%)</td>
<td>—</td>
</tr>
<tr>
<td>Morphologic leukemia-free state</td>
<td>3 (4%)</td>
<td>2 (6%)</td>
<td>—</td>
</tr>
</tbody>
</table>

CRi/CRp = CR with incomplete recovery

- Median time to CR = 5.0 mo (Enasidenib/AZA) vs 3.7 mo (AZA)
- Median TTFR = 1.9 mo (Enasidenib/AZA) vs 2.0 mo (AZA)
- Median DoR = NR (Enasidenib/AZA) vs 10.2 mo (AZA)
- Combination therapy was generally well tolerated, with a safety profile similar to that reported for either monotherapy.

DiNardo CD et al. *Proc ASH 2019;Abstract 643.*
The IDH inhibitors, enasidenib and ivosidenib, have been evaluated in combination with azacitidine in separate studies. The azacitidine combinations with full dose of enasidenib or ivosidenib were found to be safe in a phase Ib study. The sponsor of the IDH1 inhibitor ivosidenib then performed a single-arm expansion study of azacitidine with ivosidenib in treatment-naïve, older, unfit IDH1-mutated AML patients. Courtney DiNardo has previously presented the data from the 23 subjects treated on this phase 2 expansion. The CR/CRh rate was 65% and CR rate 55%. The 12-month survival was 82%. The blood counts in responders appeared to steadily improve during the first cycle of therapy, and there did not appear to be treatment-related myelosuppression in subsequent maintenance cycles. The randomized phase II study of enasidenib with azacitidine also demonstrated a high rate of response in IDH2-mutated patients (63% CR/CRi, 53% CR), significantly higher than that achieved with single-agent azacitidine alone. The responses with the combination were also deeper with a higher rate of clearance of the variant allele compared with azacitidine alone.

Editorial — Dr Erba

The IDH inhibitors, enasidenib and ivosidenib, have been evaluated in combination with azacitidine in separate studies. The azacitidine combinations with full dose of enasidenib or ivosidenib were found to be safe in a phase Ib study. The sponsor of the IDH1 inhibitor ivosidenib then performed a single-arm expansion study of azacitidine with ivosidenib in treatment-naïve, older, unfit IDH1-mutated AML patients. Courtney DiNardo has previously presented the data from the 23 subjects treated on this phase 2 expansion. The CR/CRh rate was 65% and CR rate 55%. The 12-month survival was 82%. The blood counts in responders appeared to steadily improve during the first cycle of therapy, and there did not appear to be treatment-related myelosuppression in subsequent maintenance cycles. The randomized phase II study of enasidenib with azacitidine also demonstrated a high rate of response in IDH2-mutated patients (63% CR/CRi, 53% CR), significantly higher than that achieved with single-agent azacitidine alone. The responses with the combination were also deeper with a higher rate of clearance of the variant allele compared with azacitidine alone.
Responses were seen even in the subset with RAS mutations. However, the OS was identical; the median OS was 22 months in both arms. A similar number of subjects had died, but more patients had died on treatment with the combination than with azacitidine alone. The authors did not provide details of blood count recovery over time. The similarity in the median survival is likely due to the ability to salvage azacitidine failures with enasidenib alone or even other effective regimens such as venetoclax combinations. It is not clear from this data if azacitidine is actually required. Enasidenib should be compared with the combination of enasidenib and azacitidine. Nevertheless, the availability of effective salvage therapies for older AML patients may obscure any potential effect on OS. This fact illustrates the importance of incorporating quality of life and patient-reported outcomes into future clinical trials for older AML patients who are not pursuing curative therapy for their disease.
Genetic Characteristics and Outcomes by Mutation Status in a Phase 3 Study of CPX-351 versus 7+3 in Older Adults with Newly Diagnosed, High-Risk/Secondary Acute Myeloid Leukemia (AML)

Lindsley RC et al.
Proc ASH 2019;Abstract 15.
### Outcomes with CPX-351 versus 7+3 in Older Patients with Newly Diagnosed High-Risk/Secondary AML: By Most Frequently Occurring Mutation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASXL1</th>
<th>DNMT3A</th>
<th>RUNX1</th>
<th>TET2</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPX-351 (n = 30)</td>
<td>7+3 (n = 20)</td>
<td>CPX-351 (n = 20)</td>
<td>7+3 (n = 21)</td>
<td>CPX-351 (n = 21)</td>
</tr>
<tr>
<td>CR</td>
<td>17%</td>
<td>20%</td>
<td>35%</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.80</td>
<td>0.49</td>
<td>0.83</td>
<td>0.34</td>
<td>0.79</td>
</tr>
<tr>
<td>CR+CRi</td>
<td>37%</td>
<td>35%</td>
<td>60%</td>
<td>57%</td>
<td>33%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.08</td>
<td>1.13</td>
<td>1.07</td>
<td>0.60</td>
<td>0.62</td>
</tr>
<tr>
<td>Transplant</td>
<td>27%</td>
<td>30%</td>
<td>55%</td>
<td>38%</td>
<td>29%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.85</td>
<td>1.99</td>
<td>1.80</td>
<td>1.40</td>
<td>0.31</td>
</tr>
<tr>
<td>Median OS</td>
<td>9.1 mo</td>
<td>6.3 mo</td>
<td>12.6 mo</td>
<td>5.5 mo</td>
<td>8.9 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.67</td>
<td>0.41</td>
<td>0.58</td>
<td>0.47</td>
<td>1.19</td>
</tr>
<tr>
<td>Median EFS</td>
<td>1.6 mo</td>
<td>1.4 mo</td>
<td>6.0 mo</td>
<td>3.6 mo</td>
<td>2.0 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.79</td>
<td>0.45</td>
<td>0.57</td>
<td>0.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Median remission duration</td>
<td>6.4 mo</td>
<td>4.1 mo</td>
<td>9.9 mo</td>
<td>4.3 mo</td>
<td>8.1 mo</td>
</tr>
</tbody>
</table>

Editorial — Dr DiNardo

Older patients make up the majority of all patients with AML, with a median age of 68 years. In older adults, and for patients with secondary AML (i.e., AML evolving from an antecedent hematologic disorder or developing as a complication of previous chemotherapy or radiotherapy), standard 7+3 chemotherapy is associated with poor outcomes related to both increased toxicities and lower response and overall survival. Results of the Phase III trial of 7+3 versus CPX-351, a liposomal encapsulation of cytarabine plus daunorubicin at a fixed 5:1 molar ratio, demonstrated improved response (CR/CRi 48% versus 33%) and survival (median OS 9.56 versus 5.95 months; P = 0.003) in fit patients 60-75 years of age with secondary AML or AML with MDS-related cytogenetic abnormalities. Notably, while CPX-351 was identified to be effective in nearly all subpopulations evaluated, patients who had previously received hypomethylating agents had no obvious survival benefits from CPX-351 compared with 7+3 chemotherapy, thus confirming an unfortunately high unmet clinical need for these patients.
The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitididine) in Patients with Acute Myeloid Leukemia (AML) in First Remission

Wei AH et al.
*Proc ASH 2019;Abstract LBA-3.*
QUAZAR AML-001: Survival Outcomes at a Median Follow-Up of 41.2 Months


RFS = Relapse-free survival

Stratified $p$-value: 0.0009
Stratified HR 0.69

CC-486 Placebo
24.7 months 10.2 months

Stratified $p$-value: 0.0001
Stratified HR 0.69

CC-486 Placebo
14.8 months 4.8 months

OS

Survival probability

Stratified $p$-value: 0.0009
Stratified HR 0.69

CC-486 Placebo
24.7 months

(n = 238)

OS

Survival probability

(n = 234)

RFS

Relapse-free survival probability

(n = 238)

(n = 234)
### Quazar AML-001: Safety

<table>
<thead>
<tr>
<th>Select Grade 1/2 AEs</th>
<th>CC-486 (n = 238)</th>
<th>Placebo (n = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>64%</td>
<td>23%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49%</td>
<td>21%</td>
</tr>
<tr>
<td>Select Grade 3/4 AEs</td>
<td>n = 238</td>
<td>n = 234</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41%</td>
<td>24%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>n = 238</td>
<td>n = 234</td>
</tr>
<tr>
<td>Infections</td>
<td>17%</td>
<td>8%</td>
</tr>
</tbody>
</table>

- Few AEs led to treatment discontinuation, most often GI events (CC-486, 5%; PBO, 0.4%).

CC-486 is an oral formulation of azacitidine. My review of the early phase studies of this agent suggest that it achieves pretty much the same biologic effect as IV or SQ azacitidine, causing some nausea in patients but otherwise very well tolerated. This trial was touted at ASH as being the first example of a successful maintenance therapy in AML. I confess I am underwhelmed by their claims. Patients were eligible for this trial if they achieved remission with intensive chemotherapy and were deemed ineligible for allogeneic transplant. Most patients had intermediate-risk AML and had complete induction and one or two cycles of consolidation. That is, they had AML that was theoretically curable, but had incomplete therapy. The age range was typical for AML: median 68, range 55-86 years. Patients were randomized to receive placebo or 300 mg per day of CC-486 for 14 out of 28-day cycles. The trial took four and a half years to accrue, and small wonder — these are rather difficult patients to find.
The results showed a 10-month overall survival advantage for CC-486, although the survival curves came together after about 4 years (meaning most patients eventually still died). These data are reminiscent of the results of decitabine maintenance in the ECOG-E2906 trial. In E2906, patients were randomized to induction with clofarabine or 7+3. Clofarabine was clearly inferior, but all patients were then grouped and re-randomized to decitabine maintenance or nothing. Decitabine conferred a survival benefit, but since it was being used following an inferior/incomplete therapy, no one was all that surprised. So my conclusion from this QUAZAR trial is that if you have an AML patient in remission after intensive therapy who simply can’t tolerate any more intensive therapy, maintenance with a hypomethylating agent will confer a survival benefit, and oral azacitidine seems a convenient way to accomplish this. However, while I’m not particularly excited or surprised by this trial, I’m quite excited about this drug.
It offers an oral replacement for what is otherwise a tedious aspect of the treatment of older patients with MDS and AML, namely having to trudge into clinic daily for 7 days of each month for an injection. Given the efficacy of azacitidine combined with venetoclax, we have here the potential to treat a large fraction of older AML patients with an entirely oral regimen. I think this is the big deal about CC-486.
Acute Leukemias — Drs Erba and Levis

Acute Myeloid Leukemia

Acute Lymphoblastic Leukemia
FDA Authorizes First Next-Generation Sequencing (NGS)-Based Test for Very Low Levels of Remaining Cells in ALL or Multiple Myeloma (MM)

Press Release – September 28, 2018

“The Food and Drug Administration permitted marketing of ClonoSEQ assay, an NGS-based test for minimal residual disease (MRD) in patients with acute lymphoblastic leukemia (ALL) or MM. MRD is a measure of the amount of cancer cells remaining in a person’s bone marrow.

[The] approval is an important step forward for patients with ALL and MM. Determining whether a patient has residual cancer cells remaining after treatment provides information on how well a patient has responded to therapy and how long remission may last. Having a highly sensitive test available to measure MRD in ALL or MM patients can help providers manage their patients’ care.”

ClonoSEQ Assay for the Detection of Lymphoid Malignancies

Monter A, Nomdedéu JF. 
The use of MRD to assess response and guide therapeutic decisions can now be considered a standard of care in the management of patients with ALL. While no single assay platform or method has been established as definitively better than any other, worldwide, most centers use flow cytometry for MRD in ALL. The unique features of this disease lend itself to identification of a leukemia-associated phenotype that can be detected at a level of 1 cell in 10,000 and can be followed throughout treatment. The ClonoSEQ® platform authorized by the FDA is DNA-based, in that it uses a combination of multiplex PCR (meaning PCR with multiple sets of primers) and NGS to detect unique immunoglobulin sequences within the malignant lymphocyte clone. Those unique sequences are then tracked (with a sensitivity of up to 1 cell in a million) over time. There are other, similar commercially available platforms. We know that the presence/persistence of MRD in patients who have otherwise achieved a morphologic (ie, microscopic) response predicts for a much worse outcome.
While virtually all major academic centers treating this disease use MRD in management of ALL, the exact use varies widely. At our center, we use flow-based MRD. A typical scenario might be as follows. A 31-year-old patient with Ph- B-ALL is treated according to a pediatric regimen. After induction and consolidation, a bone marrow biopsy reveals MRD at a level of 0.06%. Planning for an allogeneic transplant gets under way, and a cycle (or two) of blinatumomab is administered. The bone marrow is now MRD-negative, and the patient undergoes transplant. It is assumed that having a blinatumomab-induced MRD-negative marrow will improve outcomes from the transplant — but that is only an assumption, and really requires prospective clinical data for validation.
Blinatumomab for Minimal Residual Disease (MRD) in Adults with B-Cell Precursor Acute Lymphoblastic Leukemia (BCPALL): Median Overall Survival (OS) Not Reached at 5 Years for Complete MRD Responders

Goekbuget N et al.  
*Proc EHA* 2019;Abstract S1619.
Blinatumomab in B-Cell ALL: Survival According to MRD Response

Study month

Number of subjects at risk:

1: MRD responder at cycle 1 (N = 48) Median 95% CI – (29.5, -)
2: MRD nonresponder at cycle 1 (N = 23) Median 95% CI 14.4 (3.8, 32.3)

p-value for log-rank test: 0.002
Censor indicated by vertical bar; CI = confidence interval
ECOG-E1910: Ongoing Phase III Trial Design

Eligibility (N = 488)

- Newly diagnosed B-lineage ALL
- BCR-ABL-negative disease
- No concurrent active cancer
- No history of recent myocardial infarction (within 3 months)
- ECOG PS 0-3

Primary endpoint: Overall survival

Chemotherapy

Blinatumomab + chemotherapy
This abstract provides follow-up data from the BLAST study, in which patients with B-ALL in morphologic remission but with MRD were treated with blinatumomab. Previously this group reported that 78% of these patients achieved MRD negativity with blinatumomab treatment. The issue is whether or not that results in an improvement in survival. The median survival of the 84 MRD-negative patients wasn’t reached, whereas it was 14.4 months for those failing to become MRD negative after blinatumomab. This result implies that “scrubbing” a marrow clean of MRD with blinatumomab is a good thing. However, everyone received blinatumomab, and the persistent MRD in the “non-responders” may have just been a marker of worse disease. The simplest explanation, however, is that the elimination of MRD by blinatumomab is what resulted in the improved outcome.
Randomized data is really what is needed here, and the results of the ECOG-E1910 trial, which has just finished accrual in the US, may provide that data. While blinatumomab is often very well tolerated, there is still likely some underlying toxicity — 74 patients in the BLAST study went to transplant after blinatumomab, with a 36.5% rate of treatment-related mortality. This is quite a high rate, and one wonders if depletion of immunoglobulin (an effect of blinatumomab) increases transplant risk.
A Randomized Phase 3 Trial of Blinatumomab vs. Chemotherapy as Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children’s Oncology Group Study AALL1331

Brown PA et al.
ASH 2019;Abstract LBA-1.
Among patients with detectable MRD (≥0.01%) at the completion of Block 1 chemo, the proportion with undetectable MRD (<0.01%) after Block 2 (Arm A) vs. Blina cycle 1 (Arm B) was 21% vs. 79% (p < 0.0001).

The rates of MRD response were similar with Block 3 or Blina cycle 2.
### AALL1331: Safety

<table>
<thead>
<tr>
<th>Select Grade ≥3 AEs</th>
<th>Arm A (UKALLR3 Chemo)</th>
<th>Arm B (Blinatumomab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Block 2</td>
<td>Block 3</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>Infections*</td>
<td>41%</td>
<td>61%</td>
</tr>
<tr>
<td>Sepsis*</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>CRS</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Seizure</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Other neurotoxicity+</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* *p < 0.001; +Including cognitive disturbance, tremor, ataxia and dysarthria

- All blinatumomab-related AEs fully resolved
- The rate of patients successfully proceeding from randomization to HSCT (data cut-off 9/30/19) was strikingly different between arms.
  - On Arm A, only 45% (44 of 98 who received randomized therapy) proceeded to HSCT.
  - On Arm B, 73% (75 of 103 who received randomized therapy) proceeded to HSCT (*p < 0.0001*).
Blinatumumab is a BiTE (a “bi-specific T-cell engager”) approved for use in adults with relapsed B-ALL. Based on my experience with this agent, I believe it has led to an across-the-board improvement in overall survival for adults with B-ALL. In this study, pediatric and AYA patients with B-ALL in first relapse all received a single round of intensive salvage chemotherapy. Those patients achieving some semblance of a response (i.e., marrow blasts reduced to 25% or less) were randomized to receive either two courses of standard intensive chemotherapy or two 28-day infusions of blinatumumab. Patients were then taken to allogeneic transplant if eligible. The trial was stopped early by the DSM committee because of improved DFS, OS, clearance of MRD, and lower toxicity in the blinatumumab arm. The survival curves show a very believable 20% improvement in the blinatumumab arm, a result not surprising to any adult oncologist who has used this novel immunotherapy since its initial U.S. approval in 2014.
I would say these survival curves mirror the magnitude of improvement we see at my institution in terms of the overall benefit in our adult patients in whatever manner the BitE is used. While these findings aren’t particularly earth-shattering, they offer further evidence that this is an incredibly active agent in this disease and should be a component of therapy for newly diagnosed patients. On an additional note, a concern has often been raised about how to incorporate this type of immunotherapy into conventional ALL treatment. The BiTE relies on T-cells, and T-cells are presumably depleted by conventional ALL chemotherapy. Nonetheless, that doesn’t seem to have been a problem in this trial, in which all patients had a lymphocyte-directed regimen prior to blinatumumab, and yet the agent was still highly effective. This is still an area of debate, requiring more research.
End of Phase I Results of ZUMA-3, A Phase 1/2 Study of KTE-X19, Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients (Pts) with Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia (ALL)\textsuperscript{1}

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: End of Phase 1 Results of ZUMA-3\textsuperscript{2}

\textsuperscript{1} Shah BD et al. 
Proc ASCO 2019;Abstract 7006.

\textsuperscript{2} Shah BD et al. 
Proc EHA 2019;Abstract PS945.
ZUMA-3: A Phase I/II Trial Design

**CONSORT Diagram for ZUMA-3**

- Not dosed due to AE (n = 3)
- Withdrawn consent (n = 1)
- Found ineligible after leukapheresis (n = 1)

- Not dosed due to AE (n = 2)
- Moved to compassionate use before dosing (n = 1)
- Initiated new therapy (n = 1)

**Enrolled/leukapheresed (N = 54)**

**Conditioning chemotherapy (N = 49)**

**Received KTE-X19 (N = 45)**

- Data cutoff: September 27, 2018
- Safety analysis (n = 45)
- Efficacy\(^a\) (n = 41)
  - Median follow-up from KTE-X19 dosing: 16 months (range, 1-30 months)

- 100% manufacturing success for all enrolled/leukapheresed patients
  - Only 2 patients required additional leukapheresis for product manufacturing
- Overall, 83% of patients received KTE-X19
- The primary reason for not receiving KTE-X19 was AEs (n = 5)

\(^a\) Patients were eligible for efficacy analysis after 8 weeks of follow-up; the efficacy-evaluable population includes all patients with a minimum of 2 months of follow-up.

AE = adverse event

Shah BD et al. *Proc ASCO* 2019;Abstract 7006.
ZUMA-3: Incidence of Treatment-Emergent Cytokine Release Syndrome (CRS)- and Neurologic Event (NE)-Specific Symptoms

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Any CRS&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Any Pryrexia</th>
<th>Any Hypotension</th>
<th>Any Sinus tachycardia</th>
<th>Any Chills</th>
<th>Any NE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Any Encephalopathy</th>
<th>Any Confusional state</th>
<th>Any Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>100 50 100 26 81 25 93 29</td>
<td>100 50 87 39 63 31 80 38</td>
<td>67 50 74 39 50 19 64 33</td>
<td>33 0 43 4 13 0 31 2</td>
<td>17 0 39 0 13 0 27 0</td>
<td>83 50 87 43 63 25 78 38</td>
<td>67 33 48 26 13 13 38 22</td>
<td>33 17 39 4 31 13 36 9</td>
<td>17 0 35 0 25 0 29 0</td>
</tr>
<tr>
<td>Any CRS&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>100 50</td>
<td>100 26</td>
<td>81 25</td>
<td>93 29</td>
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<td>87 39</td>
<td>63 31</td>
<td>80 38</td>
<td>67 50</td>
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<tr>
<td>Any Pryrexia</td>
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<td>87 39</td>
<td>63 31</td>
<td>80 38</td>
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<td>74 39</td>
<td>50 19</td>
<td>64 33</td>
<td>33 0</td>
</tr>
<tr>
<td>Any Hypotension</td>
<td>67 50</td>
<td>74 39</td>
<td>50 19</td>
<td>64 33</td>
<td>33 0</td>
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<td>13 0</td>
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<td>17 0</td>
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<tr>
<td>Any Sinus tachycardia</td>
<td>33 0</td>
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<td>13 0</td>
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<td>27 0</td>
<td>83 50</td>
<td>87 43</td>
<td>63 25</td>
<td>78 38</td>
<td>38 22</td>
</tr>
</tbody>
</table>

- Of 41 patients with ≥2 months of follow-up, 68% had CR/CRi and 73% had undetectable MRD.

<sup>a</sup> CRS was graded per a modified grading system proposed by Lee DW, et al. Blood 2014;124:188-95; <sup>b</sup> Individual symptoms of CRS and NEs were graded per National Cancer Institute’s Common Terminology Criteria for Adverse Events, v 4.03.

CRS = cytokine release syndrome; NE = neurologic event

Tisagenlecleucel Appears Effective and Safe in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia with High-Risk Cytogenetic Abnormalities

Grupp S et al.  
*Proc EHA 2019;Abstract S1618.*
ELIANA and ENSIGN Phase II Studies of Tisagenlecleucel in Relapsed/Refractory ALL: Pooled Efficacy Data in Patients with High-Risk (HR) Cytogenetic Abnormalities

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>N = 29 With HR cytogenetics</th>
<th>N = 108 Without HR cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed remission per IRC assessment MRD-negative</td>
<td>19 (65.5%)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>Not reached</td>
<td>—</td>
</tr>
<tr>
<td>12-mo relapse-free probability</td>
<td>74.6%</td>
<td>61.7%</td>
</tr>
<tr>
<td>24-mo relapse-free probability</td>
<td>74.6%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>Not reached</td>
<td>—</td>
</tr>
<tr>
<td>12-mo survival probability</td>
<td>74.9%</td>
<td>70.7%</td>
</tr>
<tr>
<td>24-mo survival probability</td>
<td>66.6%</td>
<td>58.8%</td>
</tr>
</tbody>
</table>
OBERON: Ongoing Phase III Trial Design

Target accrual (N = 220)

- Patients with CD19-expressing B-cell precursor ALL AND
  - Untreated first or second relapse or
  - Refractory disease to primary induction therapy or
  - Refractory disease to first salvage therapy or
  - Relapse after allogeneic stem cell transplant
- No untreated first relapse of ALL more than 24 months after initial diagnosis

Primary endpoint: Overall survival

This abstract reports the results of a post-hoc subgroup analysis of outcomes from two CAR T-cell (tisagenlecleucel) trials enrolling pediatric and young adult relapsed/refractory B-ALL patients. The subgroup of interest was defined as having high-risk cytogenetics/mutations (BCR-ABL, MLL, CRLF2, TP53, etc). They identified 29 such patients and reported that 19 of these achieved a CR, 18 of whom were MRD negative. The 24-month survival for the patients in this high-risk group ended up actually being higher than for those patients lacking high-risk features. This data highlights the remarkable efficacy of this therapeutic approach — provided patients can actually make it through the long process of getting to a CAR T-cell infusion.