New Developments in Acute Myeloid Leukemia: A Review of New Therapies for Treatment

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Objectives

- Describe the currently available treatment strategies for patients with Acute Myeloid Leukemia (AML)
- Describe novel and emerging therapeutic options in AML and their mechanisms of action (MOAs)
- Recognize safety and efficacy data for novel and emerging therapeutic options

Question #1
Which of the following drug oral drug therapies requires upfront medication reconciliation and drug–drug/drug–herbal reviews before initiating chemotherapy.
1. Venetoclax
2. Ivosidenib
3. Enasidenib
4. Midostaurin
5. All of the above

Question #2
Which of the following therapies is an IDH1 inhibitors
1. Ivosidenib
2. Gemtuzumab
3. Midostaurin
4. Gilteritinib

Question #3
Which of the following can cause differentiation syndrome
1. Enasidenib
2. Midostaurin
3. Venetoclax
4. Glasdegib

AML Epidemiology

- Estimated New Cases in 2019: 21,450
- % of All New Cancer Cases: 1.2%
- Estimated Deaths in 2019: 10,920
- % of All Cancer Deaths: 1.8%
- Percent Surviving at 5 years: 28.3%

SEER 21 2012-2016, All Races, Both Sexes
AML Epidemiology

Cytogenetic and molecular findings used in risk stratification for AML

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cytogenetic</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Normal cytogenetics</td>
<td>Normal cytogenetics with isolated biallelic CEBPA mutation</td>
</tr>
<tr>
<td></td>
<td>Isolated t(1;19) or t(1;22)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal cytogenetics</td>
<td>KIT mutation in core binding factor leukemia: inv(16) or (1;14)</td>
</tr>
<tr>
<td></td>
<td>Other non-good and non-poor changes</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (t;12)(p13;q24) Monoosomal karyotype*</td>
<td>Normal cytogenetics with RUNX1/ETO</td>
</tr>
<tr>
<td></td>
<td>(−7/del(7q), −5/del(5q)</td>
<td></td>
</tr>
</tbody>
</table>

*Reference to translocations is based on cytogenetic classification results and may differ from molecular results.

Outcomes in AML modified by clinical, cytogenetic, and molecular features as well as therapy.

Genetic abnormalities that affect acute myeloid leukemia (AML) classification

<table>
<thead>
<tr>
<th>AML with Recurrent Genetic Abnormalities</th>
<th>Complex karyotype (≥5 unrelated abnormalities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1-RUNX1T1</td>
<td>t(8;21)(q22;q22)</td>
</tr>
<tr>
<td>CBFB-MYH11</td>
<td>t(14;17)(q22;p13)</td>
</tr>
<tr>
<td>PML-RARA</td>
<td>t(15;17)(q22;q12)</td>
</tr>
<tr>
<td>NUP214-MDLT2A</td>
<td>t(9;11)(q22;q13)</td>
</tr>
<tr>
<td>EVI1</td>
<td>t(3;3)(q21q26.2)</td>
</tr>
<tr>
<td>RBM15-MKL1</td>
<td>t(1;22)(p13;q13)</td>
</tr>
<tr>
<td>NPM1 gene mutation</td>
<td>t(2;11)(p21;q23)</td>
</tr>
</tbody>
</table>

*Rule out therapy related AML before using any of these three translocations to make a diagnosis of AML with myelodysplasia related changes.

<table>
<thead>
<tr>
<th>Gene Color</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 95% for sec. AML</td>
</tr>
<tr>
<td></td>
<td>&gt; 95% for de novo AML</td>
</tr>
</tbody>
</table>

AML Ontogeny Can Be Mutationally Defined
Molecular classes of AML and concurrent gene mutations in adult patients up to the age of ~65 years.


Outcomes in Older Adults With AML (Aged 65-93 Yrs)


OS After Diagnosis

Early Mortality With Induction Chemotherapy in Pts With AML by ECOG PS and Age


Early Death by ECOG PS, %
Age < 56 Yrs (n = 364) Age 56-65 Yrs (n = 242) Age 66-75 Yrs (n = 270) Age > 75 Yrs (n = 79)
0 2 11 12 14
1 3 5 16 18
2 2 18 31 50
3 0 29 47 82

Mutations in Older Pts With AML


<table>
<thead>
<tr>
<th>Variables</th>
<th>All Older</th>
<th>Younger</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>14.3</td>
<td>24.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>15.2</td>
<td>20.9</td>
<td>.008</td>
</tr>
<tr>
<td>TP53</td>
<td>7.6</td>
<td>13.0</td>
<td>.001</td>
</tr>
<tr>
<td>Cohesin</td>
<td>10.0</td>
<td>9.6</td>
<td>&gt; .999</td>
</tr>
<tr>
<td>FLT3/ITD</td>
<td>22.5</td>
<td>22.6</td>
<td>&gt; .999</td>
</tr>
<tr>
<td>FLT3/TKD</td>
<td>6.5</td>
<td>6.8</td>
<td>.848</td>
</tr>
<tr>
<td>NRAS</td>
<td>12.1</td>
<td>13.0</td>
<td>.662</td>
</tr>
<tr>
<td>KRAS</td>
<td>3.2</td>
<td>2.3</td>
<td>.426</td>
</tr>
<tr>
<td>PTPN11</td>
<td>3.9</td>
<td>6.2</td>
<td>.050</td>
</tr>
<tr>
<td>KIT</td>
<td>3.2</td>
<td>2.3</td>
<td>.426</td>
</tr>
<tr>
<td>JAK2</td>
<td>0.6</td>
<td>0.6</td>
<td>&gt; .999</td>
</tr>
<tr>
<td>WT1</td>
<td>6.9</td>
<td>3.4</td>
<td>.023</td>
</tr>
<tr>
<td>NPM1</td>
<td>22.3</td>
<td>28.2</td>
<td>.021</td>
</tr>
<tr>
<td>CEBPA</td>
<td>14.3</td>
<td>10.2</td>
<td>.055</td>
</tr>
<tr>
<td>RUNX1</td>
<td>13.4</td>
<td>19.8</td>
<td>.002</td>
</tr>
<tr>
<td>MLL/PTD</td>
<td>5.8</td>
<td>6.8</td>
<td>.543</td>
</tr>
<tr>
<td>ASXL1</td>
<td>10.9</td>
<td>17.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IDH1</td>
<td>5.8</td>
<td>6.8</td>
<td>&gt; .999</td>
</tr>
<tr>
<td>IDH2</td>
<td>11.9</td>
<td>14.7</td>
<td>.183</td>
</tr>
</tbody>
</table>

*For all variables except Cohesin, n = 462; for Cohesin, n = 411.

OS (Mos)

P = .042

No adverse genetic alterations (n = 37)
At least 1 adverse genetic alteration (n = 32)

The Challenge of Managing AML

- AML is not one disease, so how to best classify?
  - Cytogenetics define broad groups but don’t help to individualize therapy
  - Molecular genetics can help individualize treatment, but many pts have multiple mutations and most are not “actionable”
  - Disease of older adults, who often have medical comorbidities

- Traditional treatments—hard to know if they’ll work
  - Onset is rapid, significant toxicities, poor outcomes
  - Targeted therapies have yet to fulfill promise

- GOALS: better understanding of AML biology, better drugs, better strategies
FDA AML Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Approval Event</th>
<th>Agent/Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>7+3</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Gemtuzumab Approved</td>
<td>Gemtuzumab ozogamicin</td>
</tr>
<tr>
<td>2017</td>
<td>Midostaurin (FR3)</td>
<td>Midostaurin (FR3)</td>
</tr>
<tr>
<td>2017</td>
<td>Enasidenib (IDH2)</td>
<td>Enasidenib (IDH2)</td>
</tr>
<tr>
<td>2017</td>
<td>Midostaurin (FR3) FRONT LINE</td>
<td>Midostaurin (FR3)</td>
</tr>
<tr>
<td>2017</td>
<td>Gemtuzumab Approved (2nd Approval)</td>
<td>Gemtuzumab ozogamicin</td>
</tr>
<tr>
<td>2018</td>
<td>Venetoclax + Hypomethylating Agent (BCL-2) FRONT LINE</td>
<td>Venetoclax + Hypomethylating Agent (BCL-2)</td>
</tr>
<tr>
<td>2018</td>
<td>Gladeceibr + Low dose Cytarabine (Sonic Hedgehog) FRONT LINE</td>
<td>Gladeceibr + Low dose Cytarabine (Sonic Hedgehog)</td>
</tr>
<tr>
<td>2018</td>
<td>Gilterinib (Flt3)</td>
<td>Gilterinib (Flt3)</td>
</tr>
</tbody>
</table>

Conan’s Arch Nemesis

Gemtuzumab

- Gemtuzumab ozogamicin is a CD33-targeted antibody–drug conjugate
- Approved for AML in 2000, removed from the market in 2010 due to safety concerns (early mortality, sinusoidal obstruction syndrome),
- Reapproved by the FDA in 2017 at a lower dose for newly diagnosed CD33+ AML in adults and relapsed/refractory disease in adults and children.
- “Black box” warning for hepatotoxicity

Gemtuzumab Ozogamicin (GO)

- Recombinant, humanized murine monoclonal anti-CD33 antibody
- CD33 expressed on 90% of blasts from patients with AML
- Absent from normal hematopoietic stem cells
- Calicheamicin derivative is a cytotoxic antibiotic
- Linked by hydrolysable linker
- Shown to be active in AML in first relapse >60 years

Gemtuzumab

- Newly-diagnosed, de novo AML (combination regimen):
  - Induction: 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine
  - Consolidation: 3 mg/m² on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine.
- Newly-diagnosed AML (single-agent regimen):
  - Induction: 6 mg/m² (not limited to one 4.5 mg vial) on Day 1 and 3 mg/m² (not limited to one 4.5 mg vial) on Day 8.
  - Continuation: For patients without evidence of disease progression following induction, up to 8 continuation courses of MYLOTARG 2 mg/m² (not limited to one 4.5 mg vial) on Day 1 every 4 weeks
- Relapsed or refractory AML (single-agent regimen): 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7

Dosage Modifications for Hematologic and Nonhematologic Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent thrombocytopenia</td>
<td>If platelet count does not recover to greater than or equal to 100 within 14 days following the planned start date of the consolidation cycle</td>
</tr>
<tr>
<td>Persistent neutropenia</td>
<td>If neutrophil count does not recover to greater than 0.5 within 14 days following the planned start date of the consolidation cycle</td>
</tr>
<tr>
<td>Total bilirubin greater than 2 × ULN</td>
<td>Delay treatment with MYLOTARG until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. Omit scheduled dose if delayed more than 2 days between sequential infusions.</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Interrupt the infusion and institute appropriate medical management</td>
</tr>
</tbody>
</table>

Lancet. 2012: 379: 1508–16
Standard of Care Induction Chemotherapy ± Gemtuzumab Ozogamicin

- Gemtuzumab ozogamicin 3 mg/m² on Days 1, 4, 7 of induction and Day 1 of each consolidation cycle

OS and Relapse-Free Survival in AML by Genotype

Post-study treatment (mITT population).

GO + Chemotherapy: Toxicity
**VOD/SOS Gemtuzumab ozogamicin**

<table>
<thead>
<tr>
<th>Author</th>
<th>Incidence of VOD/SOS %</th>
<th>Median Time to Onset of VOD/SOS (Range), d</th>
<th>Median Time Between mAb and HSCT (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giles et al, 200145</td>
<td>GO: 14 (12)</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Larsson et al, 200590</td>
<td>HSCT→GO: 8 (8)</td>
<td>NR</td>
<td>11.7 mo (4.3-112.4)</td>
</tr>
<tr>
<td>Rajvanshi et al, 200243</td>
<td>HSCT→GO: 8 (35)</td>
<td>NR</td>
<td>131 d (17-967)</td>
</tr>
<tr>
<td>Tallman et al, 201344</td>
<td>Overall: 44 (9.1)</td>
<td>HSCT→GO: 12 (15.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Wadleigh et al, 200342</td>
<td>HSCT: 4 (8)</td>
<td>GO→HSCT: 9 (64)</td>
<td>22 (10-27)</td>
</tr>
</tbody>
</table>

**Key Takeaway Points Gemtuzumab**

- Right Patient at the Right Time
- Monitoring of Treatment Side Effects
- Addressing Reimbursement
- Consideration for Outpatient Utilization for patients
  - (Key for Many Sites- Especially under an APM)

**FLT3 and AML**

- **FLT3** is a receptor tyrosine kinase
- Normally expressed in myeloid progenitor cells
- Expressed on blasts in most cases of AML
- Promotes growth, blocks differentiation
- Activating mutations in ~ 30% of AML
- 3% FLT3-ITD
- 7% FLT3-TKD
- FLT3 mutations makes everything worse![2]
- High white count
- High relapse rate
- Occur across different subtypes of AML:
  - ~ 30% of NPM1-mutated AML
  - ~ 30% to 40% of APL

**FLT3 Inhibitors**

- Staurosporine
- Lestaurtinib
- Midostaurin
- Sorafenib
- Quizartinib

**Reference compound**

- No activity in relapse
- Active at diagnosis when combined with chemo
- No activity in relapse
- Some activity at relapse . . . but not well tolerated

**RATIFY: First-line Chemotherapy ± Midostaurin in FLT3-Mutated AML**

- Randomized phase III study
- Induction* (1-2 cycles)
- Consolidation (up to 4 cycles)
- Maintenance (12 cycles)

**RATIFY: Overall Survival**

- mOS, MoM (95% CI)
- Midostaurin: 74.4 (51.5-109)
- Placebo: 76 (61.4-97.4)

- **P** = .009 by stratified log-rank test
RATIFY: Summary Adverse Events

<table>
<thead>
<tr>
<th>Grade 3-4 Nonhematologic/AEs (≥10% Pop %)</th>
<th>Midostaurin (n = 355)</th>
<th>Placebo (n = 354)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>10</td>
<td>0.05</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>14</td>
<td>8</td>
<td>0.008</td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>13</td>
<td>9</td>
<td>0.19</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>10</td>
<td>0.53</td>
</tr>
<tr>
<td>Infection</td>
<td>52</td>
<td>50</td>
<td>0.60</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>15</td>
<td>0.92</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81</td>
<td>82</td>
<td>.84</td>
</tr>
</tbody>
</table>

Deaths: 5% (18/355) in midostaurin arm vs 5.3% (19/357) in placebo; leading causes:
- Hemorrhage, CNS (1 midostaurin, 2 placebo)
- Infection (4 midostaurin, 7 placebo), pneumonitis (3 midostaurin, 0 placebo),
- More details provided in the text.

IDH1 and IDH2: Key Research Milestones

- IDH1 and IDH2 mutations identified in AML.
- Germline IDH2 mutations identified in AML.
- Somatic IDH1 mutations identified in glioblastoma.
- IDH1 mutations identified in AML.
- Production of D2HG by mutant IDH enzymes discovered.
- IDH2-mutant mouse model developed.
- Mutated IDH enzymes inhibit many 2-OG-dependent enzymes.
- IDH3: mitochondrial heterotetramer; canonical enzyme of the third step in TCA cycle, converts NAD+ to NADH.
- IDH1/2: metabolic enzymes that interconvert isocitrate and α-ketoglutarate (α-KG) while maintaining normal cellular redox status.
- Mutated IDH2 (mIDH2) observed in 10% to 13% of pts with AML.
- IDH2 functions: metabolism of glucose, glutamine, fatty acids.
- IDH3: mitochondrial heterotetramer; canonical enzyme of the third step in TCA cycle, converts NAD+ to NADH.
- Mutated IDH2 (mIDH2) observed in 10% to 13% of pts with AML.
- IDH2 functions: metabolism of glucose, glutamine, fatty acids.
- Role of IDH Enzymes:
  - IDH1/2: metabolic enzymes that interconvert isocitrate and α-ketoglutarate (α-KG) while reducing NADP to NADPH.
  - IDH3: mitochondrial heterotetramer; canonical enzyme of the third step in TCA cycle, converts NAD+ to NADH.
  - IDH2 functions:
    - Metabolism of glucose, glutamine, fatty acids.
    - Mitochondrial function.
  - NADPH protects against lipid peroxidation and oxidative DNA damage.

Midostaurin

- Dosage: capsule or oral solution containing 50 mg of midostaurin base.
- Administration:
  - Take with food to reduce the risk of nausea and vomiting.
  - Do not break or chew RYDAPT capsules.
  - If a dose is missed or vomited, do not administer.
  - Take the next dose at the usual time.

Role of IDH Enzymes:

- IDH1/2: metabolic enzymes that interconvert isocitrate and α-ketoglutarate (α-KG) while reducing NADP to NADPH.
- IDH3: mitochondrial heterotetramer; canonical enzyme of the third step in TCA cycle, converts NAD+ to NADH.
- IDH2 functions:
  - Metabolism of glucose, glutamine, fatty acids.
  - Maintains normal cellular redox status.
- NADPH protects against lipid peroxidation and oxidative DNA damage.

Enasidenib in IDH2-Mutant R/R AML: Background

- Mutated IDH2 (mIDH2): produces oncometabolite 2-HG which can alter DNA methylation and lead to blocked myeloid differentiation.
- mIDH2 observed in 10%-13% of pts with AML.
- 2-HG can be synthesized from mutated IDH2 (mitochondrial form) or mutated IDH1 (cytoplasmic).
- Enasidenib (AG-221): selective, potent oral inhibitor of mutated IDH2 enzyme.
- Induces leukemic cell differentiation in preclinical models and in pts with R/R AML.
- Current report assessed MTD, PK/PD, safety, clinical activity of enasidenib in IDH2-mutant R/R AML cohort in first phase III trial.

Cancer Cell. 2010 Dec 14;18(6):553-67
Gross et al. J Ex Med 2010
Marcucci et al JCO 2010
Ward et al. Cancer Cell 2010
Enasidenib in IDH2-Mutant R/R AML: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>R/R AML</th>
<th>R/R by Best Response in R/R AML</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk status</td>
<td>Intermediate 0-1</td>
<td>R/R to 0-1 cycles with first-line therapy</td>
<td>0.151 (n = 109)</td>
</tr>
<tr>
<td></td>
<td>Intermediate 1</td>
<td>R/R to ≥ 2 cycles with first-line therapy</td>
<td>0.227 (n = 109)</td>
</tr>
<tr>
<td></td>
<td>High-risk &gt; 1</td>
<td>R/R to ≥ 2 cycles with first-line therapy</td>
<td>0.084 (n = 109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Enasidenib treatment</td>
<td>0.020 (n = 109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enasidenib mut status</td>
<td>Enasidenib mut status</td>
<td>0.432 (n = 109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDH2 R140 mutation</td>
<td>IDH2 R140 mutation</td>
<td>0.166 (n = 109)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDH mutation status</td>
<td>Baseline</td>
<td>0.640 (n = 176)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECOG PS</td>
<td>Female, %</td>
<td>58 (64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age, yrs (range)</td>
<td>67 (19-100)</td>
</tr>
</tbody>
</table>

Enasidenib in IDH2-Mutant R/R AML: Response

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>R/R AML</th>
<th>All Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response, n (%)</td>
<td>176</td>
<td>176</td>
</tr>
<tr>
<td>CR</td>
<td>20 (22.2)</td>
<td>34 (19.2)</td>
</tr>
<tr>
<td>CRp</td>
<td>2 (2.2)</td>
<td>12 (6.6)</td>
</tr>
<tr>
<td>CRi</td>
<td>3 (3.3)</td>
<td>18 (10.1)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (5.5)</td>
<td>80 (45.9)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>NE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Median time to first response, mos (range)</td>
<td>1.0 (0.5-6.4)</td>
<td>1.0 (0.5-9.6)</td>
</tr>
<tr>
<td>Median time to CR, mos (range)</td>
<td>1.0 (0.5-9.4)</td>
<td>1.9 (0.5-9.4)</td>
</tr>
<tr>
<td>Median DoR, mos (95% CI)</td>
<td>5.6 (3.8-9.7)</td>
<td>5.8 (3.9-7.4)</td>
</tr>
<tr>
<td>Median OS, Mos (95% CI)</td>
<td>7.0 (5.0-8.3)</td>
<td>13.8 (8.3-17.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.7 (11.6-NE)</td>
</tr>
</tbody>
</table>

Enasidenib Side Effects

- 8% of pts experienced serious treatment-related IDH inhibitor–associated differentiation syndrome
- ORR: 100 mg/day, 38.5%; all doses, 40.9%
- Platelets, hemoglobin, ANC generally increased with enasidenib cycle number
- Bone marrow blasts decreased over time
- FISH and morphological evidence from individual pts suggested myeloblast differentiation with enasidenib
- Responders and nonresponders had similar BL 2-HL levels, BL-miDNA 14F
- Post-BL transfusion independence rates (per RBC, platelet parameters): ~ 35% in overall pts, ~ 53% with non-CR responders, > 94% in pts with CR

Ivosidenib

<table>
<thead>
<tr>
<th>Indications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Newly diagnosed AML in patients ≥ 75 years or patients ≥ 65 years with comorbidities precluding intensive induction therapy.</td>
</tr>
<tr>
<td></td>
<td>Newly diagnosed AML in patients &gt; 75 years or patients with a life expectancy of &gt; 12 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg/day, once daily</td>
</tr>
<tr>
<td></td>
<td>Treatment for a minimum of 6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Adjustments</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose reduction in patients with unacceptable toxicity, progression or unacceptable toxicity.</td>
</tr>
</tbody>
</table>

Ivosidenib Drug Interactions

- Increases Ivosidenib Exposure
- Dose reduce to 250 mg daily
- Decreases ivosidenib Exposure
- Avoid if possible or monitor
- Increases risk for QTc Prolongation
- Avoid if possible or monitor
**Conclusions**

- IDH 1/2 inhibitors are well tolerated in this patient population.
- Most AEs were not treatment-related and were grade 1-2 in severity.
- In patients with R/R AML, IDH1/2 inhibitors induced durable CRs and were associated with OS > 8 mos.
- Responses to IDH 1/2 inhibitors require several treatment cycles.
- Differentiation appears to drive the clinical efficacy of IDH 1/2 inhibitors.
- Consistent evaluations of dosing and drug interactions remains a key issues for safety management and side effect monitoring.

**Ivosidenib in IDH1-Mutated R/R AML: Overall Survival**

- The slide shows a Kaplan-Meier survival curve for patients treated with ivosidenib.
- The curve indicates OS probability over time, with survival rates shown at various time points.

**Ivosidenib in R/R IDH1-Mutated AML: Most Common AEs (Any Cause)**

- The table lists common adverse events (AEs) and their incidence in patients treated with ivosidenib.
- The most common AEs include diarrhea, pyrexia, and neutropenia.

**Ivosidenib in R/R IDH1-Mutated AML: AE of Special Interest**

- The table highlights specific AEs of interest, such as idiosyncratic idosyncratic intolerance syndrome (IIS), idiosyncratic idiosyncratic intolerance syndrome (IIS), and idiosyncratic idiosyncratic intolerance syndrome (IIS).

**Ivosidenib in IDH1-Mutated R/R AML: Response**

- The slide presents a response analysis for patients treated with ivosidenib.
- The table shows the primary efficacy population by response in primary efficacy population, with outcomes for CR/CRh and CR/CRh.

**Gilteritinib Now FDA Approved for Relapsed/Refractory FLT3-Mutated AML**

- November 28, 2018: FDA approved gilteritinib at 120 mg PO QD for adults with relapsed/refractory AML with an FLT3 mutation detected by FDA-approved test[1,2].
- Approval based on interim analysis of phase III ADMIRAL trial, which included adults with relapsed/refractory AML and an FLT3-ITD, DB35, or 1836 mutation[3,4].
- After median follow-up of 4.6 mos, CR/CRh rate was 21%.
- Conversion to transfusion independence occurred in 31%.
**Gilteritinib**

**Indications**

- 120 mg PO daily with or without food
- Continue until disease progression or unacceptable toxicity
- Treat for a minimum of 6 months

**Dosing**

- QTc prolongation
- Pancreatitis
- Treatment-related ≥ grade 3 toxicities

**Dose Adjustments**

- QTc prolongation
- Pancreatitis
- Treatment-related ≥ grade 2 toxicities

**Gilteritinib Drug Interactions**

- Strong CYP3A4 Inhibitors: Increases Gilteritinib Exposure
  - Avoid if possible
- Strong CYP3A4 Inducers: Decreases Gilteritinib Exposure
  - Avoid if possible or monitor
- QTc Prolonging Drugs: Increases risk for QTc Prolongation
  - Avoid if possible

**Phase III ADMIRAL Study: Gilteritinib in FLT3-Mutant R/R AML**

- Primary endpoints: OS, CR/CRh rate
- Secondary endpoints: EFS, CR rate

**FDA Approval of Glasdegib For AML in Adults With Older Age or Comorbidities**

- November 21, 2018: FDA approved glasdegib at 100 mg PO QD in combination with low-dose cytarabine (LDAC) for newly diagnosed AML in adults either aged ≥ 75 yrs or with comorbidities precluding intensive induction chemotherapy[^1][^2]
- Approval based on multicenter, open-label, randomized phase II BRIGHT AML 1003 trial, which compared glasdegib + LDAC vs LDAC alone in patients newly diagnosed with AML[^1][^2]
  - Inclusion criteria: either aged ≥ 75 yrs, severe cardiac disease, ECOG PS of 2, or serum creatinine > 1.3 mg/dL
  - After a median f/u of 20 mos, the median OS was 8.3 mos with glasdegib + LDAC vs 4.3 mos with LDAC (HR: 0.46; P = .0002)

Glasdegib: Oral Inhibitor of Sonic Hedgehog Pathway

- Glasdegib: selective, potent oral inhibitor of transmembrane protein smoothened (SMO), a component of the Sonic Hedgehog (Hh) signaling pathway
- Decreased expression of genes involved in leukemia stem cell renewal and maintenance
- Overcomes therapy resistance in LSC and bulk AML cells

Sonic Hedgehog Signaling Pathway: Inactive vs. Active

- Inactive (Absence of Hh ligand)
  - PTCH1 inhibits SMO
  - SUFU facilitates degradation of GLI activators → GLI repression → Hh target genes are not expressed
- Active (Presence of Hh ligand)
  - SMO activated
  - GLI activators translocate to nucleus
  - Hh target genes expressed
  - Hh pathway
  - Cell cycle
  - Anti-apoptotic genes

Glasdegib Indications

- Newly Diagnosed AML in patients > 75 or patients with comorbidities precluding intensive induction

Glasdegib Dosing

- Glasdegib 100 mg by mouth daily on days 1-28, without regard to meals
- Cytarabine 20 mg SQ twice daily on days 1-10
- Continued until disease progression or toxicity

Glasdegib Drug Interactions

- Strong CYP3A4 Inhibitors
  - Increases Glasdegib Exposure
  - Avoid if possible or monitor
- Strong CYP3A4 Inducers
  - Decreases Glasdegib Exposure
  - Avoid if possible
- QTc prolonging Drugs
  - Increases risk for QTc Prolongation
  - Avoid if possible or monitor

Glasdegib QTc Prolongation on ≥2 separate ECGs† Management considerations

- >480 to 500 ms
  - Correct potassium and magnesium abnormalities.
  - Review and adjust concomitant medications with known QTc prolongation effects.
  - Continue to monitor: after QTc interval returns to ≤480 ms, patients should have a weekly ECG for 2 further weeks.
- >500 ms
  - Correct potassium and magnesium abnormalities.
  - Review and adjust concomitant medications with known QTc prolongation effects.
  - Continue to monitor: after QTc interval returns to ≤480 ms, patients should have a weekly ECG for 2 further weeks.
  - Interrupt glasdegib.
  - When QTc interval falls either to ≤480 ms or within 30 ms of the patient’s baseline measurement, resume glasdegib at 50 mg qd po.
  - Maintain glasdegib dose at 50 mg qd po unless an alternative cause of QTc prolongation is found, when 100 mg qd po can be reconsidered.

Phase II study in pts with AML and high-risk myelodysplastic syndrome
Phase II study in pts with AML and high-risk myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Phase II study in pts with AML and high-risk myelodysplastic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasdegib 100 mg+LDAC, N = 88</td>
</tr>
</tbody>
</table>

Phases

*Phase II* study in pts with AML and high-risk myelodysplastic syndrome

Glasdegib 100 mg+LDAC, N = 88

LDAC, N = 44

**Patients with CR, n (%)**

- **80% CIa**
  - Good/intermediate: 11.9–22.2
  - Poor cytogenetic risk: 6.9–24.2

- **80% exact CIb**
  - Good/intermediate: 12.3–28.1
  - Poor cytogenetic risk: 6.9–24.2

**Combination versus LDAC**

**Pearson Chi-square test for all enrolled patients (unstratified)**

- **P value**: 0.0142

**Treatment-emergent adverse events**

<table>
<thead>
<tr>
<th>MedDRA preferred term</th>
<th>Grade 1–2 (Glasdegib 100 mg+LDAC, N = 84)</th>
<th>Grade 3–4 (LDAC, N = 41)</th>
<th>Grade 5 Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>6 (7.1)</td>
<td>54 (64.3)</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (3.6)</td>
<td>35 (41.7)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>30 (35.7)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (33.3)</td>
<td>2 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (29.8)</td>
<td>3 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (16.7)</td>
<td>12 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>26 (31.0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (4.8)</td>
<td>14 (16.7)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (22.6)</td>
<td>4 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (25.0)</td>
<td>2 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>22 (26.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (23.8)</td>
<td>1 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>21 (25.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (17.9)</td>
<td>6 (7.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Venetoclax**

- **Indications**
  - Newly diagnosed AML in patients aged ≥ 75 yrs or with comorbidities precluding intensive induction chemotherapy
  - Venetoclax + azacitidine, decitabine, or low-dose cytarabine

- **Dosing**
  - Day 1: 100 mg
  - Day 2: 200 mg
  - Day 3: 400 mg
  - Day 4 and Beyond: 400 mg with hypomethylating agents
  - Concomitant with 600 mg low-dose cytarabine
  - Continued until disease progression or toxicity

- **Dose Adjustments**
  - Hematologic toxicity: Concomitant moderate/strong CYP3A and P-gp inhibition

**FDA Approval of Venetoclax in Combination For Newly Diagnosed AML in Older Adults**

- **November 21, 2018:** FDA expanded indication to include venetoclax in combination with either azacitidine, decitabine, or low-dose cytarabine for newly diagnosed AML in adults who are either aged ≥ 75 yrs or have comorbidities precluding use of intensive induction chemotherapy[1,2]
  - New indication based on 2 open-label, nonrandomized phase I/II trials[2-4]
    - **In the M14-358 trial in newly diagnosed AML**, the CR rate was 37% with venetoclax + azacitidine and 54% with venetoclax + decitabine
    - **In the M14-387 trial in newly diagnosed AML**, including those with prior hypomethylating agent for an antecedent hematologic disorder, venetoclax + low-dose cytarabine was associated with a CR rate of 21%
Venetoclax Drug Interactions

- Strong CYP 3A4 Inhibitors
  - Increases Venetoclax Exposure
  - Decrease Dose by 50%

- Strong CYP3A4 Inducers
  - Increases Venetoclax Exposure
  - Decrease Dose by ~75%

- P-gp Inhibitors
  - Increases Venetoclax Exposure
  - Decrease Dose by 50%

- Moderate/Strong CYP3A Inducers
  - Decreases Venetoclax exposure
  - Avoid if possible

Drug Interaction Dosing

- Day 1 50 mg
- Day 2 100 mg
- Day 3 200 mg
- Day 4+ 200 mg

BCL-2 Expression and Outcomes

- Blood 2016 128:1709

Venetoclax + Hypomethylating Agents for Unfit AML


- Table:

<table>
<thead>
<tr>
<th>CR/CRi</th>
<th>Median OS (mos)</th>
<th>2-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aza2</td>
<td>28%</td>
<td>10.8 mos</td>
</tr>
<tr>
<td>Dec3</td>
<td>17.8%</td>
<td>7.7 mos</td>
</tr>
<tr>
<td>VEN + HMA</td>
<td>67%</td>
<td>17.5 mos</td>
</tr>
</tbody>
</table>

Venetoclax + LDAC in Untreated Older AML Patients: Phase I/II Studies


- Durable Responses

- ORR

- High Response Rate

[Graphs and tables showing response rates and survival outcomes]
Emerging Therapies

The Future

Next Exit

Phase III QUANTUM-R: Quizartinib for Relapsed/Refractory FLT3-ITD AML

- Primary endpoint: OS
- Secondary endpoint: EFS, safety

 Adults with AML ± 1% FLT3-ITD allelic ratio, refractory disease or relapse within 6 mos of CR1 ± HSCT; ≥ 5 cycles of anthracycline- or mitoxantrone-containing induction therapy (N = 367)

Quizartinib or LoDAC: Until unacceptable toxicity, lack of benefit, or HSCT
MEC or FLAG-IDA: up to 2 cycles

Quizartinib 60 mg (n = 245)  
Salvage CT* (n = 122)

Quizartinib: A Great Drug, but Still One With a Couple of Challenges . . .

KIT inhibition leads to hypopigmentation and myelosuppression

Resistance to quizartinib conferred by point mutations in FLT3

Subject No. Age, Yrs Sex New Mutation at Relapse Wks on Study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, Yrs</th>
<th>Sex</th>
<th>New Mutation at Relapse</th>
<th>Wks on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1005-004</td>
<td>60</td>
<td>F</td>
<td>F691l</td>
<td>19</td>
</tr>
<tr>
<td>1005-006</td>
<td>43</td>
<td>M</td>
<td>D835F</td>
<td>6</td>
</tr>
<tr>
<td>1005-007</td>
<td>59</td>
<td>F</td>
<td>D835F</td>
<td>23</td>
</tr>
<tr>
<td>1005-008</td>
<td>69</td>
<td>M</td>
<td>D835F</td>
<td>19</td>
</tr>
<tr>
<td>1005-010</td>
<td>52</td>
<td>M</td>
<td>F691L</td>
<td>26</td>
</tr>
</tbody>
</table>

Flotetuzumab: CD123 × CD3 Bispecific DART Protein

- DART bispecific molecule
- Applications across various diseases
- Predictable manufacturability
- Stable
- Variable light and heavy chain pairing permits greater proximity between effector CD3-positive cells and target CD123-positive cells
- Can adjust half-life, valency
- Flotetuzumab (MGD006/S80880) MoA: mediates T-cell redirection, activation, proliferation, and killing of CD123-positive AML cells

Flotetuzumab Phase I Study: Dosing Scheme

- 4 Days On/2 Days Off
- Cohorts 2a-E: 40-450 ng/kg/day

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dosing Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>40 ng/kg/day</td>
</tr>
<tr>
<td>3</td>
<td>100 ng/kg/day</td>
</tr>
<tr>
<td>4</td>
<td>200 ng/kg/day</td>
</tr>
<tr>
<td>5</td>
<td>400 ng/kg/day</td>
</tr>
</tbody>
</table>

Schedule

- Lead-in dose: 3 days
- Cycle 1 Wks 1-4: 4 days on/3 days off
- Cycle 2 and beyond: 4 days on/3 days off
Flotetuzumab Phase I Study: Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>63.6 (14.28)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>67.0 (29.0-84.0)</td>
</tr>
<tr>
<td>Female gender</td>
<td>25 (43.9)</td>
</tr>
<tr>
<td>AML subclassification</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Refractory</td>
<td>28 (53.8)</td>
</tr>
<tr>
<td>HMA tx failure (≥ 2 cycles)</td>
<td>14 (26.9)</td>
</tr>
</tbody>
</table>

*Abbreviation: AML = acute myeloid leukemia, HMA = hypomethylating agents.

Flotetuzumab Phase I Study: Safety

<table>
<thead>
<tr>
<th>Flotetuzumab-Related AEs in ≥ 10% of Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (N = 57)</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>IRR/CRS</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Platelet count decreased</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
</tr>
</tbody>
</table>

*Abbreviations: IRR = infusion-related reaction, CRS = cytokine release syndrome.

Flotetuzumab: Antileukemic Activity at Threshold Dose ≥ 500 ng/kg

- In dose-escalation phase, 14 patients received at least 1 cycle of flotetuzumab at threshold dose ≥ 500 ng/kg/day and underwent posttreatment BM biopsy
- Most responding patients had rapid responses after 1 cycle of therapy (cycles ≤ 2)
- Antileukemic activity: 8/14 patients (57%)
- ORR (CR + CRi + MLF + PR): 6/14 patients (43%)
- CR + CRi rate: 4/14 (28%)

Immunotherapy for AML

- Phase Ib/II Study of Azacitidine + Nivolumab in Relapsed AML: Response
  - How does this compare?
  - Single-agent AZA/DAC (N = 655) with CR/CRi rate of 16%[2]
  - AZA/DAC + VEN with CR/CRi of 21%[3] to 27%[4]

<table>
<thead>
<tr>
<th>Best Response/Outcome</th>
<th>Evaluable Patients (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>CR/CRi, n (%)</td>
<td>17 (24)</td>
</tr>
<tr>
<td>HI + 50% blast reduction</td>
<td>7 (10)</td>
</tr>
<tr>
<td>HI + 75% blast reduction</td>
<td></td>
</tr>
<tr>
<td>HI + ≥ 80% blast reduction</td>
<td></td>
</tr>
<tr>
<td>HI failure</td>
<td>6 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>41 (59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS of Azacitidine + Nivolumab vs Historical HMA Combinations at MDACC; Censored for SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Total (%)</td>
</tr>
<tr>
<td>OS (mos)</td>
</tr>
<tr>
<td>Median OS</td>
</tr>
<tr>
<td>OS Probability</td>
</tr>
</tbody>
</table>

- Salvage [1]
- Median age: 72 yrs
- Secondary AML: 47%
- Adverse cytogenetics: 35%
- Expected survival in salvage 1/2: 5-7 mos, 12-mo OS (N = 655): 16%[2]
- Survival with HMA + VEN in salvage (off protocol): 3-4 mos[2]
# Frontline Cytarabine, Idarubicin, Nivolumab for AML: Phase II Study Design

**Endpoints:** ORR, DoR, EFS, RFS, OS, characterization of AML progenitors and T-cells, safety

**Patients:** 18-60 yrs of age (or > 60 yrs if very fit) with either AML by WHO criteria or high-risk MDS with ≥ 10% blast cells; ECOG PS 0-2; adequate cardiac, renal, hepatic function (N = 35)

### Induction
- Cytarabine 1.5 g/m² IV D1-4*
- Idarubicin 12 mg/m² IV QD x 3
- Nivolumab 3 mg/kg Q2W starting on D24 ± 2 days

### Consolidation
- Cytarabine 0.75 g/m² IV QD x 3
- Idarubicin 8 mg/m² IV QD x 2

### Maintenance
- ≤ 5 cycles
- Nivolumab 3 mg/kg Q2W ≤ 1 yr

* Cytarabine given over 24 hrs; patients older than 60 yrs of age received 3 days instead of 4.
† First 3 patients treated at run-in phase with nivolumab 1 mg/kg with no drug-related toxicity. The remaining 32 patients treated as noted in schema.

---

### Patient Characteristics

**Characteristic** | Patients (N = 35) | Median age, yrs (range) | Female sex, n (%) | Median WBC, 10⁹/L (range) | Median creatinine, mg/dL (range) | Median bilirubin (range) | Median BM blast, % (range) | AML/MDS, n (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54 (26-65)</td>
<td>20 (57)</td>
<td>5 (0.4-46.1)</td>
<td>0.8 (0.51-1.31)</td>
<td>0.7 (0.2-2.5)</td>
<td>42 (15-96)</td>
<td>26 (74)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Blood Cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Prior therapy for MDS, n (%)

- None
- Hypomethylating agents

26 (74)
4 (11)
2 (6)
3 (9)

---

### Response and Follow-up

**Median follow-up:** 8.4 mos (range: 0.7-21.1)

**Outcome, n (%) Patients (N = 35)**
- CR 21 (62)
- CRp/CRi 5 (14)
- PR/NR 1 (3)/4 (11)
- Early death 3 (9)
- Too soon 1 (3)
- 4-wk/8-wk mortality 2 (6)/1 (3)

**Median no. nivolumab administered (range)**
- 6 (0-13)

**Progressing to alloSCT**
- 9 (26)

**Median EFS, mos (range)**
- 8.3 (0.5-18.0)

**Median RFS (in CR), mos (range)**
- 17.3 (0.6-19.9)

**Median OS, mos (range)**
- 15.8 (0.5-21.1)

### MRD by FCM At CR/CRi/CRp At 1-3 Mos of F/u

<table>
<thead>
<tr>
<th>Negative</th>
<th>Positive</th>
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### Comparison to Idarubicin + Cytarabine

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<th>Remission Duration*</th>
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<td>IA + Nivo</td>
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<td>IA + Nivo</td>
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### Phase I Trial of Anti-CD123 CAR T-Cells: Results

- AML patients refractory after alloSCT with median of 4 earlier therapies, n = 6
- Lentiviral transduction
- Phy/Cy lymphodepletion → 1 infusion
- Antileukemic activity in 4/6 patients (66%) | MLFS, n = 3; CR, n = 1; blast reduction, n = 2
- Cytokine-release syndrome
  - Grade 1, n = 4; grade 2, n = 1; none fatal
- No drug-limiting toxicity, cytopenias

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### Ipilimumab Monotherapy in Patient With Relapsed AML After HSCT

- Phase I/II study, N = 28
  - AML, n = 14; NDS, n = 2; MPN, n = 1
  - Median age: 58 yrs (range: 22-75)
  - Median time since HSCT: 675 days (range: 108-1830)
- Results: CR, n = 5 (21%); PR, n = 2 (8%); SD, n = 6 (27%)
  - 5/12 (42%) patients with extramedullary AML achieved CR
  - Immune-related AE, n = 6 (21%)
    - Death, n = 1; pneumonitis, n = 2; ITP, n = 1; diarrhea, n = 1
    - GVHD, n = 4, precluding treatment

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Conclusions

- New treatments have changed the current regimens in the fight against AML
- Oral therapies continue to dominate the discussion on treatment, but a coinciding focus on adherance, drug interactions and outcomes is essential
- Newer therapies including Bispecific antibodies and Immune checkpoint inhibitors in trials may lead to a potential role for these agents in MRD clearance

Question #1
Which of the following drug oral drug therapies requires upfront medication reconciliation and drug–drug/drug–herbal reviews before initiating chemotherapy.

1. Venetoclax
2. Ivosidenib
3. Enasidenib
4. Midostaurin
5. All of the above

Question #2
Which of the following therapies is an IDH1 inhibitors

1. Ivosidenib
2. Gemtuzumab
3. Midostaurin
4. Gilteritinib

Question #3
Which of the following can cause differentiation syndrome

1. Enasidenib
2. Midostaurin
3. Venetocloax
4. Glasdegib
Questions