Initial Therapy of Acute Myeloid Leukemia: Finally, A Trip Beyond 7+3

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Duke University
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Disclosures of Potential Conflicts of Interest

• Speaker Bureau: AbbVie, Agios, BMS/Celgene, Incyte, Jazz, Novartis

• Consultant: AbbVie, Agios, Astellas, BMS/Celgene, Daiichi Sankyo, Glycomimetics, Immunogen, Incyte, Jazz, Kura Oncology, MacroGenics, Novartis, Pfizer, Syros, Takeda, Trillium

• Contracted Research: AbbVie, ALX Oncology, Amgen, Daiichi Sankyo, Forma, Forty Seven / Gilead, Glycomimetics, Immunogen, Jazz, MacroGenics, Novartis, PTC

• Other: BMS/Celgene (Chair, AML Registry Steering Committee), AbbVie (Chair, IRC for VIALE A and VIALE C Phase III studies), Glycomimetics (Scientific Steering Committee)
The AML Treatment Algorithm, Pre 2018

AML Dx

Fit for intensive chemotherapy

AML Dx

Unfit for intensive chemotherapy

7+3 induction chemotherapy

Consolidation chemotherapy

CR

OBSERVATION

ALLOGENEIC STEM CELL TRANSPLANT

Response

CONTINUED THERAPY

Azacitidine
Decitabine
Low Dose Cytarabine
AML-001 Study: Aza vs CCR in Older AML Patients

**Overall Survival (ITT)**
HR = 0.85 (p = 0.1009)

**Overall Survival (censor at subsequent AML Tx)**
HR = 0.76 (p = 0.0190)

Median follow-up 24.4 months, with 193 deaths in AZA arm (80.1%) and 201 deaths in the CCR arm (81.4%). Stratified by ECOG PS and cytogenetic risk.

<table>
<thead>
<tr>
<th></th>
<th>AZA (27.8%)</th>
<th>CR/Cri (25.1%)</th>
<th>RBC TI (38.5%)</th>
<th>PLT TI (40.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR (24.7%)</td>
<td>40.6%</td>
<td>38.5%</td>
<td>27.6%</td>
<td>29.3%</td>
</tr>
</tbody>
</table>

### Survival of Older AML Patients: Population Based Study

<table>
<thead>
<tr>
<th>Study cohort (n=5480)</th>
<th>Untreated group (n=3367)</th>
<th>Treated group (n=2113)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>65-69</td>
<td>763 (13.9)</td>
<td>251 (7.5)</td>
<td>512 (24.2)</td>
</tr>
<tr>
<td>70-74</td>
<td>1139 (20.8)</td>
<td>512 (15.2)</td>
<td>627 (29.7)</td>
</tr>
<tr>
<td>75-79</td>
<td>1293 (23.6)</td>
<td>768 (22.8)</td>
<td>525 (24.8)</td>
</tr>
<tr>
<td>≥80</td>
<td>2285 (41.7)</td>
<td>1836 (54.85)</td>
<td>449 (21.3)</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index (CCI) score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3017 (55.0)</td>
<td>1720 (51.1)</td>
<td>1297 (61.4)</td>
</tr>
<tr>
<td>1</td>
<td>1324 (24.2)</td>
<td>835 (24.8)</td>
<td>489 (23.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>1139 (20.8)</td>
<td>812 (24.1)</td>
<td>327 (15.5)</td>
</tr>
<tr>
<td><strong>Previous myelodysplastic syndrome</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>4524 (82.5)</td>
<td>2698 (80.1)</td>
<td>1826 (86.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>959 (17.5)</td>
<td>669 (19.9)</td>
<td>287 (13.6)</td>
</tr>
<tr>
<td><strong>Use of hypomethylating agents by diagnosis year</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2005</td>
<td>18 (2.7)</td>
<td>-</td>
<td>18 (7.3)</td>
</tr>
<tr>
<td>2006</td>
<td>41 (6.2)</td>
<td>-</td>
<td>41 (15.9)</td>
</tr>
<tr>
<td>2007</td>
<td>69 (10.4)</td>
<td>-</td>
<td>69 (24.3)</td>
</tr>
</tbody>
</table>

SEER-Medicare 2000-2007
38.6% received therapy
Median age: 78 years
Median OS: 3 mos.
OS treated: 6 mos.
OS untreated: 2 mos.
Allo HSCT: 0.8%

Oran and Weisdorf. *Haematologica* 2012; 97 (12): 1916-1924
The Current AML Treatment Algorithm

AML Dx

Fit (appropriate) for intensive chemotherapy

Induction chemotherapy

CR

Consolidation chemotherapy

CR

CR

ALLOGENEIC STEM CELL TRANSPLANT

OBSERVATION OR MAINTENANCE THERAPY

Unfit (inappropriate) for intensive chemotherapy

AML Dx

HMA or LoDAC
HMA/venetoclax
LoDAC/venetoclax
LoDAC/glasdegib
Gemtuzumab ozogamicin
FLT3m, IDH1m, IDH2m inhibitors

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VIALE-A Study Design

**Eligibility**

**Inclusion**
- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

**Exclusion**
- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

**Treatment**

**Randomization 2:1**

- **Venetoclax + Azacitidine** *(N=286)*
  - Venetoclax 400 mg PO, daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

- **Placebo + Azacitidine** *(N=145)*
  - Placebo daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

**Endpoints**

**Primary**
- Overall survival

**Secondary**
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

**Randomization Stratification Factors**
- Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region
- Venetoclax dosing ramp-up
  - **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
  - **Cycle 2** Day 1-28: 400 mg

VIALE A: Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of events/No. of patients (%)</th>
<th>Median duration of study treatment, months (range)</th>
<th>Median overall survival, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aza+Ven</td>
<td>161/286 (56)</td>
<td>7.6 (&lt;0.1 – 30.7)</td>
<td>14.7 (11.9 – 18.7)</td>
</tr>
<tr>
<td>Aza+Pbo</td>
<td>109/145 (75)</td>
<td>4.3 (0.1 – 24.0)</td>
<td>9.6 (7.4 – 12.7)</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

**VIALE A: Overall Survival in Selected Subsets**

<table>
<thead>
<tr>
<th></th>
<th>Aza+Ven</th>
<th>Aza+Pbo</th>
<th>HR [95% CI] Aza+Ven vs. Aza+Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Subjects</strong></td>
<td>161/286 (56.3)</td>
<td>109/145 (75.2)</td>
<td>0.64 (0.50, 0.82)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61/114 (53.5)</td>
<td>41/58 (70.7)</td>
<td>0.68 (0.46, 1.02)</td>
</tr>
<tr>
<td>Male</td>
<td>100/172 (58.1)</td>
<td>68/87 (78.2)</td>
<td>0.62 (0.46, 0.85)</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75</td>
<td>66/112 (58.9)</td>
<td>36/58 (62.1)</td>
<td>0.89 (0.59, 1.33)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>95/174 (54.6)</td>
<td>73/87 (83.9)</td>
<td>0.54 (0.39, 0.73)</td>
</tr>
<tr>
<td><strong>Type of AML</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Novo</td>
<td>120/214 (56.1)</td>
<td>80/110 (72.7)</td>
<td>0.67 (0.51, 0.90)</td>
</tr>
<tr>
<td>Secondary</td>
<td>41/72 (56.9)</td>
<td>29/35 (82.9)</td>
<td>0.56 (0.35, 0.91)</td>
</tr>
<tr>
<td><strong>Cytogenetic Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>84/182 (46.2)</td>
<td>62/89 (69.7)</td>
<td>0.57 (0.41, 0.79)</td>
</tr>
<tr>
<td>Poor</td>
<td>77/104 (74.0)</td>
<td>47/56 (83.9)</td>
<td>0.78 (0.54, 1.12)</td>
</tr>
<tr>
<td><strong>Molecular Marker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLT3</td>
<td>19/29 (65.5)</td>
<td>19/22 (86.4)</td>
<td>0.66 (0.35, 1.26)</td>
</tr>
<tr>
<td>IDH1</td>
<td>15/23 (65.2)</td>
<td>11/11 (100.0)</td>
<td>0.28 (0.12, 0.65)</td>
</tr>
<tr>
<td>IDH2</td>
<td>15/40 (37.5)</td>
<td>14/18 (77.8)</td>
<td>0.34 (0.16, 0.71)</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>29/61 (47.5)</td>
<td>24/28 (85.7)</td>
<td>0.34 (0.20, 0.60)</td>
</tr>
<tr>
<td>TP53</td>
<td>34/38 (89.5)</td>
<td>13/14 (92.9)</td>
<td>0.76 (0.40, 1.45)</td>
</tr>
<tr>
<td>NPM1</td>
<td>16/27 (59.3)</td>
<td>14/17 (82.4)</td>
<td>0.73 (0.36, 1.51)</td>
</tr>
</tbody>
</table>

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete count recovery; CR was defined as absolute neutrophil count >10^3/μL, platelets >10^5/μL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/μL or thrombocytopenia ≤10^5/μL.

CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18–< 75, ≥ 75) and cytogenetic risk (intermediate, poor).

## VIALE A: Serious Adverse Events and Dose Modifications

<table>
<thead>
<tr>
<th>Serious AEs in ≥5% of patients, n (%)</th>
<th>Aza+Ven N = 283</th>
<th>Aza+Pbo N = 144</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All serious AEs</strong></td>
<td>235 (83)</td>
<td>105 (73)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>84 (30)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (5)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>47 (17)</td>
<td>32 (22)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16 (6)</td>
<td>12 (8)</td>
</tr>
<tr>
<td><strong>Any AE leading to:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose discontinuation</td>
<td>69 (24)</td>
<td>29 (20)</td>
</tr>
<tr>
<td>Dose interruption*</td>
<td>204 (72)</td>
<td>82 (57)</td>
</tr>
<tr>
<td>Dose reduction†</td>
<td>7 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td><strong>Deaths, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 days after first dose of study drug</td>
<td>21 (7)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>≤60 days after first dose of study drug</td>
<td>43 (15)</td>
<td>24 (17)</td>
</tr>
<tr>
<td><strong>Other, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor lysis syndrome††</td>
<td>3 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Dose interruptions commonly due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%); interruptions include delays between cycles and reduced duration from 28 to 21 days per cycle for count recovery after marrow leukemia clearance; †Dose reduction for AEs or other medications; †† 3 cases of TLS during ramp up.

Overall Survival from Venetoclax Initiation with Allo HSCT

- **68%** (21/31) of patients remained alive at 12 months posttransplant

- **55%** (17/31) of patients that had SCT had posttransplant remission of ≥12 months and **71%** (12/17) of those patients remained in remission for ≥2 years

- **69%** (18/26) and **59%** (13/22) of patients that achieved CR/CRi and CR/CRh, respectively, maintained remission for ≥12 months posttransplant

Pratz K et al. Outcomes after SCT in patients with AML treated with venetoclax-based therapies. ASH 2019
Phase II Study of LoDAC +/- Glasdegib: Overall Survival

Should therapy with HMA/venetoclax await mutational analysis in older, **UNFIT**, treatment-naïve AML patients?
**VIALE A: Response and Survival in IDH1/2m+ AML**

- **CR+CRh:**
  - Median time to first response, mo. (min, max): 1.0 (0.7, 9.6)
  - Median DoR, mo. (95% CI)*: 29.6 (16.7, NE)

- **CR + CRi:**
  - Median time to first response, mo. (min, max): 1.1 (0.7, 8.8)
  - Median DoR, mo. (95% CI)*: 29.5 (16.7, NE)

**Median treatment cycles (min, max):**
- Ven+Aza: 8.0 (1, 37)
- Pbo+Aza: 2.5 (1, 18)

**Results generated using data of responders only**

**Survival Estimate (%) (95% CI)**

- **Month 6:** 82.3 (71.9, 89.1)
- **Month 12:** 69.3 (57.8, 78.3)
- **Month 24:** 52.4 (40.4, 63.1)

Pollyea DA et al. ASH 2020;Abstract 461.
Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant AML

- IDH1-mutant newly diagnosed AML
- Ineligible for standard therapy
- N=34

56% aged ≥75 years
47% prior exposure to HMA
76% secondary AML

Mutant IDH1 inhibitor ivosidenib 500 mg once daily

- Of the patients who were transfusion-dependent at baseline, 43% became transfusion independent

Response rate, %

- CR
- CRh
- ORR

Prior hypomethylating agent

Median overall survival 12.6 months (95% CI, 4.5-25.7)

Number of patients at risk:
33 28 24 19 16 15 12 12 11 11 8 6 5 4 4 3 2 2 1 0

Robox GJ et al. Blood 2020; 135(7): 463
### Response with Ivo/Aza for Treatment Naïve, IC-Unfit AML

<table>
<thead>
<tr>
<th>Response parameter</th>
<th>All patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR, n (%) [95% CI]</strong></td>
<td>13 (56.5) [34.5, 76.8]</td>
<td></td>
</tr>
<tr>
<td>Time to CR, median (range), months</td>
<td>3.5 (0.8–6.0)</td>
<td></td>
</tr>
<tr>
<td>Duration of CR, median [95% CI], months</td>
<td>NE [7.7, NE]</td>
<td></td>
</tr>
<tr>
<td><strong>CR+CRh, a n (%) [95% CI]</strong></td>
<td>15 (65.2) [42.7, 83.6]</td>
<td></td>
</tr>
<tr>
<td>Time to CR+CRh, median (range), months</td>
<td>2.2 (0.8–6.0)</td>
<td></td>
</tr>
<tr>
<td>Duration of CR+CRh, median [95% CI], months</td>
<td>NE [7.7, NE]</td>
<td></td>
</tr>
<tr>
<td>CRh, n (%)</td>
<td>2 (8.7)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, n (%) [95% CI]</strong></td>
<td>18 (78.3) [56.3, 92.5]</td>
<td></td>
</tr>
<tr>
<td>Time to response, median (range), months</td>
<td>1.8 (0.7–3.8)</td>
<td></td>
</tr>
<tr>
<td>Duration of response, median [95% CI], months</td>
<td>NE [9.5, NE]</td>
<td></td>
</tr>
<tr>
<td><strong>Best response</strong>b</td>
<td>13 (56.5) [34.5, 76.8]</td>
<td></td>
</tr>
<tr>
<td>CR, n (%) [95% CI]</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>CRi/CRp, n (%)</td>
<td>2 (8.7)</td>
<td></td>
</tr>
<tr>
<td>MLFS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**OS, 12-month rate, % [95% CI]**c</td>
<td>82 [59, 93]</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, median (range), months</td>
<td>9.5 (1.3–24.0)</td>
<td></td>
</tr>
</tbody>
</table>

DiNardo C et al. Acute Leukemias XVII, Munich, Germany, February, 2019
### Newly Diagnosed *IDH2*\(^m\) AML Unfit for Intensive Chemotherapy: Responses in BEAT AML S3 Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase 2</th>
<th></th>
<th>Phase 1b</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enasidenib 100mg/day</td>
<td>N=60</td>
<td>Enasidenib + Azacitidine</td>
<td>(n=17)</td>
</tr>
<tr>
<td>CR/CRi, n/N (%), 95% CI</td>
<td>28/60</td>
<td>(47%, 34-60)</td>
<td>7/17</td>
<td>(41%, 18-67)</td>
</tr>
<tr>
<td>Overall Response Rate [CR/CRi/MLFS], n/N (%), 95% CI</td>
<td>30/60</td>
<td>(50%, 37-63)</td>
<td>8/17</td>
<td>(47%, 23-72)</td>
</tr>
<tr>
<td>Duration of Response (months) Median, 95% CI</td>
<td>NR, 7.1-NR</td>
<td></td>
<td>NR, 2.5 – NR</td>
<td></td>
</tr>
<tr>
<td>Overall Survival (months) Median, 95% CI</td>
<td>24.4, 10.6-NE</td>
<td></td>
<td>8.9, 5.2-NE</td>
<td></td>
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</tbody>
</table>

Stein EM et al. ASH 2020; abstract 636.
<table>
<thead>
<tr>
<th>Overall response (CR, CRi/CRp, PR, MLFS), n (%)</th>
<th>ENA + AZA (n=68)</th>
<th>AZA Only (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ORR 95%CI]</td>
<td>[58, 81]</td>
<td>[26, 61]</td>
<td>0.0064</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>36 (53)</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>[CR rate 95%CI]</td>
<td>[41, 65]</td>
<td>[3, 28]</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRi/CRp, n (%)</td>
<td>7 (10)</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>3 (4)</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>MLFS, n (%)</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>13 (19)</td>
<td>13 (39)</td>
<td></td>
</tr>
<tr>
<td>Disease progression, n (%)</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable / Missing, n (%)</td>
<td>5 (7)</td>
<td>5 (15)</td>
<td></td>
</tr>
<tr>
<td>Time to first response, months, median (range)</td>
<td>1.9 (0.7–9.0)</td>
<td>2.0 (0.8–5.8)</td>
<td></td>
</tr>
<tr>
<td>Time to CR, months, median (range)</td>
<td>5.5 (0.7–19.5)</td>
<td>3.7 (3.0–4.1)</td>
<td></td>
</tr>
<tr>
<td>Duration of response, months, median [95%CI]</td>
<td>24.1 [11.1, NR]</td>
<td>12.1 [2.8, 14.6]</td>
<td></td>
</tr>
</tbody>
</table>

DiNardo C et al. EHA 2019, presentation S139
Enasidenib Plus Azacitidine versus AZA Monotherapy in *IDH2m+* Newly Diagnosed AML

**Overall survival**

<table>
<thead>
<tr>
<th>Pts at risk:</th>
<th>Time (months)</th>
<th>Survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENA + AZA 68</td>
<td>68</td>
<td>0.6</td>
</tr>
<tr>
<td>AZA Only 33</td>
<td>33</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ENAsardenib (ENA) + Azacitidine (AZA)

AZA Only

**Event-free survival**

<table>
<thead>
<tr>
<th>Pts at risk:</th>
<th>Time (months)</th>
<th>Probability of event-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENA + AZA 68</td>
<td>49</td>
<td>0.8</td>
</tr>
<tr>
<td>AZA Only 33</td>
<td>33</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Data cutoff:** August 19, 2019

**EFS:** time from randomization to AML relapse, disease progression (IWG AML 2003 criteria), or death from any cause, whichever occurred first.

**DiNardo CD, et al.** EHA 2019, presentation S139
**VIALE A: Response and Survival in FLT3m+ AML**

40 FLT3m+ pts (28 ITD) in AZA/VEN, 22 (13 ITD) in AZA/PBO

![Graph showing CR+CRh and CR+Cri](image)

Median treatment duration of 7 mo
Median time to CR/CRh of 1 m (0.8-4.8 mo)
Median DOR of CRh 18.3 mo (17.4 in ITD)
Median OS 13.3 mo/11.5 ITD

**A. FLT3mut**

Median OS, months (95% CI)
- **CR+CRh**: 13.3 (8.4 – 23.5)
- **CR+Cri**: 14.1 (10.6 – 18.7)

**B. FLT3mut vs. wt in Ven+Aza**

Median OS, months (95% CI)
- **Ven+Aza**: 11.5 (6.4 – 23.5)
- **Pbo+Aza**: 19.2 (1.8 – NR)

**C. FLT3-ITD**

Median OS, months (95% CI)
- **Ven+Aza**: 10.0 (0.2 – 14.7)

**D. FLT3-TKD**

**VIALE-A: In all patients (not just FLT3) with composite complete remission, MRD neg occurred in 23.4% (95% CI, 18.6 to 28.8)**

MRD assessed by flow cytometry, with negativity defined according to ELN guidelines

Konopleva M et al. ASH 2020
Treatment-naïve $FLT3_m$ AML: LACEWING Study

**Randomization Cohort**
Randomize 2:1 (N=250)

**Arm A**
Gilteritinib (120 mg/d PO; days 1–28) + Azacitidine (75 mg/m$^2$/d SC/IV; days 1–7)
28-day cycles until lack of clinical benefit or unacceptable toxicity
30-day follow-up
Follow-up every 3 months

**Arm AC**
Gilteritinib (120 mg/d PO; days 1–28) + Azacitidine (75 mg/m$^2$/d SC/IV; days 1–7)
28-day cycles until lack of clinical benefit or unacceptable toxicity
30-day follow-up
Follow-up every 3 months

**Arm C**
Azacitidine (75 mg/m$^2$/d SC/IV; days 1–7)
28-day cycles until lack of clinical benefit or unacceptable toxicity
30-day follow-up
Follow-up every 3 months

**Safety Cohort**
Gilteritinib (80 mg/d PO; days 1–28; dose escalation to 120 mg/d) + Azacitidine (75 mg/m$^2$/d SC/IV; days 1–7) (N=15)

**Newly diagnosed $FLT3_m$ AML ineligible for intensive induction chemotherapy**

**Arm A (Gilt alone) closed by sponsor.**
Aza/Gilt CR 33% (5/15), CR/CRi 67% (10/15)
Trial stopped due to no survival difference between Aza/Gilt and Aza alone

Wang ES et al. *ASH Meeting 2020*, abstract 27
The Current AML Treatment Algorithm

AML Dx

Fit (appropriate) for intensive chemotherapy → Induction chemotherapy → Consolidation chemotherapy → CR → Allogeneic Stem Cell Transplant

Unfit (inappropriate) for intensive chemotherapy → HMA or LoDAC → HMA/venetoclax → LoDAC/venetoclax → LoDAC/glasdegib → Gemtuzumab ozogamicin → FLT3m, IDH1m, IDH2m inhibitors → Observation or Maintenance Therapy → Consolidation chemotherapy → CR → Continued Therapy
Induction Therapy for IC-Eligible Adult AML

Prior leukemogenic therapy
Antecedent MDS or MDS/MPN
Cytogenetic Analysis / FISH
FLT3 mutation

AML-MRC, tAML
Poor risk karyotype

CBF AML

FLT3 Mutated

Marker Negative

APL

ATRA / ATO
+/- GO or Ida

CPX 351

DNR / Ara-C + GO

DNR / AraC + midostaurin

DNR / Ara-C
Randomized, Phase 3 Study of CPX-351 vs 7+3: Design

Key eligibility:
- Previously untreated high-risk/sAML
- 60-75 years of age
- Able to tolerate intensive therapy
- ECOG PS 0-2

Patients with documented complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) were eligible for consolidation if they had left ventricular ejection fraction of ≥50%, ECOG PS of 0-2, absolute neutrophil count recovered to >500/μL, and platelet count recovered to >50,000/μL. CR was defined as having bone marrow blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥100 × 10^9/L, and independence from red cell transfusions; CRi was defined as having all CR criteria except residual neutropenia (<1.0 × 10^9/L) or thrombocytopenia (<100 × 10^9/L).

This analysis reports the prospectively planned final 5-year follow-up results.

Subgroup analyses were conducted in patients who achieved remission, those aged 60 to 69 years and 70 to 75 years, and those who proceeded to HCT.

CPX-351

Administered as a 90-minute infusion

Induction: 100 units/m² on Days 1, 3, and 5 (Days 1 and 3 for 2nd induction)
Consolidation: 65 units/m² on Days 1 and 3

7+3

Cytarabine 100 mg/m²/day continuous infusion + daunorubicin 60 mg/m²/day
Induction: 7+3 schedule (5+2 for 2nd induction)
Consolidation: 5+2 schedule

5 Year Update of the Phase 3 Study of CPX-351 vs 7+3: Overall Survival

CPX-351 7+3
---
Events/N: 124/153, 145/156
Median OS (95% CI): 9.33 (6.37, 11.86), 5.95 (4.99, 7.75)
HR (95% CI): 0.70 (0.55, 0.91)

3-year KM-estimated survival rate: 21%, 9%
5-year KM-estimated survival rate: 18%, 8%

Phase 3 Study of CPX-351 vs 7+3: Overall Survival Landmark from HSCT

Induction Therapy for IC-Eligible Adult AML

Prior leukemogenic therapy
Antecedent MDS or MDS/MPN
Cytogenetic Analysis / FISH
FLT3 mutation

AML-MRC, tAML
Poor risk karyotype

CBF AML

DNR / Ara-C + GO

FLT3 Mutated
DNR / AraC + midostaurin

Marker Negative
DNR / Ara-C

APL
ATRA / ATO +/- GO or Ida

AML-MRC, tAML
CPX 351
ALFA 0701: Update Event free and Overall Survival

- 280 patients with treatment naïve *de novo* AML, age 50-70
- Induction: DNR 60 mg/m²/d x 3 and Ara-C 200 mg/m²/d x 7 +/- GO 3 mg/m² d 1, 4, 7
- Consolidation: DNR 60 mg/m² d 1 and Ara-C 1 gram/m² q12 hr d 1-4 +/- GO 3 mg/m² d 1
- Only 11 patients proceeded to allo HSCT in CR1 during consolidation
Addition of Gemtuzumab Ozogamicin (GO), an anti CD33 ADC, to AML Induction Chemotherapy

Induction Therapy for IC-Eligible Adult AML

Prior leukemogenic therapy
Antecedent MDS or MDS/MPN
Cytogenetic Analysis / FISH
FLT3 mutation

- APL
- AML-MRC, tAML
  - Poor risk karyotype
- CBF AML
- FLT3 Mutated
- Marker Negative

- ATRA / ATO +/- GO or Ida
- CPX 351
- DNR / Ara-C + GO
- DNR / AraC + midostaurin
- DNR / Ara-C
RATIFY (CALGB 10603): Chemotherapy + Midostaurin or Placebo Newly Diagnosed Patients < 60 Years With FLT3-Mutated AML

Induction

Daunorubicin Cytarabine plus Placebo

Consolidation x 4

High-Dose Cytarabine plus Placebo

Maintenance

Placebo

Midostaurin

ND AML

FLT3-ITD / TKD+ (Mutation Screening Within 48 Hours)

Age 16-59 years

n = 717

1:1

3277 subjects screened; 896 FLT3 mutation positive; 717 randomized (80% selection bias)

– Collaboration with 13 international cooperative groups; 225 sites from 17 countries
  • Alliance, SWOG, ECOG, NCIC CTG, GIMEMA, EORTC, AMLSG, SAL, OSHO, PETHEMA, CETLAM
  • 9 academic FLT3 screening laboratories worldwide

Chemotherapy plus Midostaurin/Placebo for Treatment-Naïve FLT3m AML: RATIFY (CALGB 10603)

Median OS

Midostaurin: 74.7 mo (95% CI, 31.5–NR)
Placebo: 25.6 mo (95% CI, 18.6–42.9)
One-sided P=0.009 by stratified log-rank test

51% for Midostaurin
44% for Placebo

OS Subgroup Analysis

No difference in early mortality
Higher rate of rash and anemia with mido
Chemotherapy/midostaurin for older FLT3 ITD + AML:
Event free survival compared with historical controls

Age 61-70

Induction: 7+3, midostaurin 50 mg bid day 8 -
Consolidation: Cytarabine bid days 1, 3, 5 (3 gm/m² age 61-65, 1 gram/m² age 66-70), midostaurin 50 mg bid day 6 -
Maintenance: Midostaurin 50 mg bid for 365 days (after consolidation or after allo HSCT)


Age 61-70, censor at HSCT

HR 0.42
p < 0.001

HR 0.41
p = 0.00002
QUAZAR AML-001: Study design

International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

PRE-RANDOMIZATION

Screening

Key eligibility criteria:
- First CR / CRi with IC ± consolidation
- Age ≥55 years
- de novo or secondary AML
- ECOG PS score 0-3
- Intermediate- or poor-risk cytogenetics
- Ineligible for HSCT
- Adequate bone marrow recovery (ANC ≥0.5 × 10^9/L, platelet count ≥20 × 10^9/L)

RANDOMIZATION

Randomization (1:1)
Within 4 months (± 7 days) of CR/CRi
Stratified by:
- Age: 55–64 / ≥ 65
- Prior MDS/CMML: Y / N
- Cytogenetic risk: Intermediate / Poor
- Consolidation: Y / N

TREATMENT PHASE

Response Assessment
Every 3 Cycles

28-day cycles

CC-486 300 mg
QD × 14 days

Placebo
QD × 14 days

CR/CRi

5%–15% BM Blasts
(Required) CC-486/PBO × 21 days

> 15% BM Blasts

Stop Treatment

End of Study

Continue Treatment

Optional Treatment

FOLLOW-UP

- Follow until death, withdrawal of consent, study termination, or loss to follow-up

QUAZAR: Overall and Relapse-free Survival

Oral AZA 300 mg QD was associated with significantly improved overall survival (OS) ($P = 0.0009$) and relapse-free survival (RFS) ($P = 0.0001$) vs. PBO.

*RFS estimates were derived using Kaplan–Meier methods and compared for Oral-AZA vs. placebo using log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

QUAZAR: Overall survival by baseline MRD status and treatment arm

Treatment with Oral AZA (CC-486) resulted in improved OS from time of randomization compared with PBO in pts who were MRD+ or MRD– at study entry.

Treatement with Oral AZA (CC-486) resulted in improved OS from time of randomization compared with PBO in pts who were MRD+ or MRD– at study entry.
# QUAZAR: Effect of AZA/PBO on OS and RFS by NPM1 mutation status

<table>
<thead>
<tr>
<th></th>
<th>Median OS (months)</th>
<th>Median RFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZA</td>
<td>PBO</td>
</tr>
<tr>
<td>NPM1 mutated</td>
<td>46.1</td>
<td>15.9</td>
</tr>
<tr>
<td>NPM1 wild type</td>
<td>19.6</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Dohner H, et al. EHA 2021, abstract S131
QUAZAR: Safety

- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>CC-486 n = 236</th>
<th>Placebo n = 233</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td><strong>Patients with ≥1 AE</strong></td>
<td>231 (98)</td>
<td>169 (72)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>153 (65)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>141 (60)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>119 (50)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>91 (39)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>105 (45)</td>
<td>97 (41)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>79 (34)</td>
<td>53 (23)</td>
</tr>
<tr>
<td>Anemia</td>
<td>48 (20)</td>
<td>33 (14)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>70 (30)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>44 (19)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (15)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

Adverse events reported in ≥15% of patients in either arm

Treatment of AML in Adults

• First, determine the goal of therapy based on patient’s clinical status, disease biology, and wishes.
• Some older patients may be cured with time-limited therapy without allo HSCT.
  – Oral azacitidiné maintenance therapy delays relapse and can improve survival.
• Older patients may be candidates for allo HSCT after either intensive or less intensive therapies.
• HMA/venetoclax has changed the treatment options for older AML patients.
  – Clinical trials with anti CD47 antibodies, IDHm inhibitors, FLT3m inhibitors, and other targeted therapies may further improve the outcome of these patients