Clofarabine + Ara-C vs Ara-C in Older Patients with Relapsed or Refractory (R/R) AML: Results from the CLASSIC I* Trial

*Clofarabine and Ara-c Studying Survival via Induction and Consolidation

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• Prognosis of patients (pts) with relapsed or refractory (R/R) AML is dismal with median survival of 4.7 months\(^1\)

• Clofarabine (Clo) is a deoxyadenosine analog with activity in adult AML\(^2\)

• Previous single-institution trial of Clo + cytarabine (Ara-C) in R/R AML showed RR of 40% (CR 26%)\(^3\)

• CLASSIC I is an international, multicenter, phase III study to evaluate the efficacy and safety of Clo in combination with Ara-C compared to ara-C alone in older adult pts with R/R AML

Eligibility Criteria

• Patients ≥ 55 years old with R/R AML
• At least 1, but no more than 2, prior induction therapies
• ECOG PS 0-2
• Adequate renal and hepatic function
  GFR ≥ 60 ml/min, serum bilirubin ≤1.5 × ULN; AST, ALT, and alkaline phosphatase ≤ 2.5 × ULN
• No previous Clo or IDAC or HiDAC
• No HSCT in previous 3 months
CLASSIC I Study Design

326 pts from 57 sites (US, CAN, EU) age ≥ 55 yrs and with R/R AML

Randomize

Placebo IV + Ara-C 1g/m² iv daily x 5

Clo 40 mg/m² iv daily x 5 + Ara-C 1 g/m² iv daily x 5

Maximum of 3 cycles of treatment

Stratification: REF: No response or CR1 < 6 mos; REL: CR1 ≥ 6 mos

Primary objective: Overall survival

Secondary objectives: CR rate, ORR, EFS, DFS, DOR, safety
## Patient Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall Population</th>
<th>REF Stratum*</th>
<th>REL Stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clo+Ara-C (n=158)</td>
<td>Ara-C (n=162)</td>
<td>Clo+Ara-C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n=83)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>(range)</td>
<td>(XX-XX)</td>
<td>(XX-XX)</td>
<td>(XX-XX)</td>
</tr>
<tr>
<td>Male, %</td>
<td>64</td>
<td>70</td>
<td>61</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td>49</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>44</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>1st Pre-trial Induction, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>56</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No remission</td>
<td>44</td>
<td>46</td>
<td>84</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*1 patient removed from evaluable patient population because duration of CR1 was unknown
Overall Population

**REF**

- ORR: $p < 0.0001$
- CR: $p = 0.0005$

**REL**

- ORR: $p = 0.0019$
- CR: $p = 0.0096$

*1 patient removed from evaluable patient population because duration of CR1 was unknown*
EFS: Overall Population

HR = 0.63 (0.49, 0.80)

p = 0.0001

Clo+Ara-C

Ara-C
EFS: Randomization Strata

![Graph showing Kaplan-Meier curves for EFS with comparison of Clo+Ara-C REF, Clo+Ara-C REL, Ara-C REF, and Ara-C REL. The hazard ratio (HR) for Clo+Ara-C REF compared to Clo+Ara-C REL is 0.57 (0.40, 0.83) with p=0.0022. The HR for Ara-C REF compared to Ara-C REL is 0.67 (0.49, 0.93) with p=0.0131.]

REF: HR = 0.67 (0.49, 0.93)  
p=0.0131

REL: HR = 0.57 (0.40, 0.83)  
p=0.0022
4-month EFS

Overall Population
p<0.0001

REF Stratum
p=0.0088

REL Stratum
p=0.0017

Percent

40%  38%  35%  41%

Clos+Ara-C (n=162)  Ara-C (n=157)  Clos+Ara-C (n=88)  Ara-C (n=84)  Clos+Ara-C (n=74)  Ara-C (n=74)
Remission Durability (IRRP)

Time (Months)

Percent

- **Clo+Ara-C DFS**
- **Ara-C DFS**
- **Clo+Ara-C DOR**
- **Ara-C DOR**
Survival: Overall Population

HR = 1.00 (0.78, 1.28)
p=0.9951
Survival: Randomization Strata

REF: HR = 1.13 (0.81, 1.57)  
\( p=0.4676 \)

REL: HR = 0.85 (0.55, 1.24)  
\( p=0.3963 \)
### Safety

<table>
<thead>
<tr>
<th>Overall Safety, %*</th>
<th>Clo+Ara-C (n=161)</th>
<th>Ara-C (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 adverse events (AE)</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Discontinuation of drug due to AE</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Serious AE</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>Death due to AE</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Death due to treatment-related AE</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><strong>30-day mortality (%)</strong></td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>60-day mortality (%)</strong></td>
<td>24</td>
<td>16</td>
</tr>
</tbody>
</table>

*Regardless of causality to study drug(s), unless otherwise specified*
# Safety

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Clo+Ara-C (n=161)</th>
<th>Ara-C (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>&gt; Grade 3 AE (non-infectious)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
Conclusions

• OS did not differ between treatment arms

• Statistically significant improvement in secondary endpoints
  – ORR and CR rates doubled
  – Significantly prolonged EFS

• Higher mortality in CLO arm

• Long-term study follow-up continues

• Clofarabine in the treatment of adult patients with AML continues to be investigated in randomized studies by cooperative groups
We thank the patients, investigators and staff from the following institutions for their participation in the CLASSIC I study:

**United States:**
- Mayo Clinical Hospital; Phoenix, AZ
- Arizona Cancer Center; Tucson, AZ
- UA for Medical Sciences, Arkansas Cancer Research Center; Little Rock, AR
- Scripps Cancer Center; La Jolla, CA
- USC, Kenneth Norris Cancer Center; Los Angeles, CA
- UCLA School of Medicine; Los Angeles, CA
- Stanford Comprehensive Cancer Center; Stanford, CA
- UC Health Science Center; Aurora, CO
- Rocky Mountain Cancer Center; Denver, CO
- Cancer Center of Central Connecticut; Southington, CT
- Rush University Medical Center; Chicago, IL
- Northwestern University; Chicago, IL
- Evanston Northwestern Healthcare; Evanston, IL
- University of Kansas Medical Center; Kansas City, KS
- University of Kentucky, Markey Cancer Center; Lexington, KY
- Louisiana State University Health Science Center; Shreveport, LA
- Maine General Medical Center; Waterville, ME
- Beth Israel Deaconess Medical Center; Boston, MA
- Josephine Ford Cancer Center; Detroit, MI
- Dartmouth Hitchcock Medical Center; Lebanon, NH
- The Cancer Center at Hackensack University Medical Center; Hackensack, NJ
- Roswell Park Cancer Center; Buffalo, NY
- Mt. Sinai School of Medicine; New York, NY
- New York Medical Center; Valhalla, NY
- Mecklenburg Medical Group; Charlotte, NC
- Duke University Medical Center; Durham, NC
- Wake Forest University School of Medicine; Winston-Salem, NC
- Gabrial Cancer Center; Canton, OH
- University of Oklahoma Health Sciences Center; Oklahoma City, OK
- Oregon Health Science University; Portland, OR
- MUSC; Charleston, SC
- UT Medical Center; Knoxville, TN
- Sarah Cannon Research Institute; Nashville, TN

**United States (cont):**
- Vanderbilt University Medical Center; Nashville, TN
- UT Southwestern, Simmons Comprehensive Cancer Center; Dallas, TX
- MD Anderson Cancer Center; Houston, TX
- Cancer Care Centers of South Texas; San Antonio, TX
- University of Texas Health Sciences Center; San Antonio, TX
- University of Utah - Huntsman Cancer Institute; Salt Lake City, UT
- WV University Hospitals, Mary Babb Randolph Cancer Center; Morgantown, WV
- Medical College of Wisconsin; Milwaukee, WI

**Canada:**
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- Juravinski Cancer Center; Hamilton, Ontario
- Hopital Maisonneuve-Rosemont; Montreal, Quebec

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- Hopital Claude Huriez CHRU de Lille; Lille
- Hopital Edouard Herriot; Lyon
- Institut Paoli Calmettes; Marseille
- Hopital Hotel Dieu; Nantes
- Hopital Purpan; Toulouse

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- Medizinische Klinik der Technischen Universität München; Munich
- Universitätsklinikum Ulm; Ulm

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- A.O Ospedale Niguarda Ca’Granda; Milano
- A.O San Gerardo; Monza
- Azienda Ospedaliera "Antonio Cardarelli"; Napoli