Acute Myeloid Leukemia Trials in Older Adults

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- **Consulting relationships past three years:**
  - AbbVie*; Actinium, Agios*; Amgen; Argenix (DSMB); Arog*; Astellas; AztraZenaca; BerGenBio; Biolinerx, Celgene (includes DSMB and steering committee); Daiici-Sanko; Elevate Bio; Fujifilm; GemoAb; Janssen; Jazz; Juno; Lilly* (only clin res support); Macrogenics; Novartis*; Ortsuka; Pfizer; Roche; Stemline; Syndax; Syntrix (DSMB only); Syros; Takeda (DSMB), Trovagene
  - * denotes support to my institution for clinical trials on which I was local PI

- **Securities, employment, promotional activities, intellectual property, gifts, grants**
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AML: What is it and how did it get there?

• Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated

• Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually); unusual but kindreds exist w germ-line mutations in >10 genes
## Current Risk Assessment in AML

### Key Prognostic Data in AML in 2021

<table>
<thead>
<tr>
<th>Patient age</th>
<th>FH, bleeding hx; Therapy related; Prior MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics / fusion mRNA</td>
<td>screen for APL, MLL, Ph+, CBF</td>
</tr>
<tr>
<td>Multiparameter flow</td>
<td></td>
</tr>
<tr>
<td>Molecular studies:</td>
<td></td>
</tr>
<tr>
<td>• FLT3 ITD (internal tandem duplication) mutation</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>• NPM1 mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>• CEBPA biallelic mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>• RUNX1, TP53, ASXL1 (KIT in CBF)</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

Of Future Importance: mutation status of IDH1/2, DNMT3A, TET2, etc.
Survival in AML in Age ≥ 60 Years (MDACC, 1973-Present, n=1647)
Why Do Older Patients With AML Experience Inferior Outcomes?

- Decreased host tolerance of intensive therapy
  - Impaired hematopoietic stem cell reserve
  - Presence of comorbid diseases
  - Decreased chemotherapy clearance

- Increased resistance of disease to therapy
  - Ratio of favorable (eg, t[8;21]) to unfavorable (eg, -7) cytogenetics is lower than for younger patients
  - Higher expression of drug resistance proteins (eg, PGP)
  - Higher incidence of antecedent hematologic disorders

PGP = p-glycoprotein.
In Elderly de novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes

Heterogeneity and Hope in Older Adults with AML

– Host Factors: Fitness (Geriatric Assessment [Klepin H et al, J Geriatr Oncol, 2020]), comorbidities, age

– Disease Features: Cytogenetic and Molecular features

– 3 new recently approved drugs based on trials for older adults
  - AZA/VEN, upfront age>75, unfit
  - CPX-351, upfront, age 60-75, fit
  - CC-486 (oral aza), maintenance, age >55, fit
CPX-351

• CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity

  – 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing \(\text{in vitro}\)^1

  – In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days^2

  – Selective uptake of liposomes by bone marrow leukemia cells in xenograft models^3

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CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria

Key Eligibility
- Previously untreated
- Ages 60–75 years
- Able to tolerate intensive therapy
- ECOG PS 0–2

Stratifications:
- Therapy-related AML
- AML with history of MDS with and without prior HMA therapy
- AML with history of CMML
- De novo AML with MDS karyotype
  - 60–69 years
  - 70–75 years

Induction (1–2 cycles)
- CPX-351 (n = 153)
- 7+3 (n = 156)

Consolidation (1–2 cycles)
- Patients in CR or CRi:
  - CPX-351 (n = 73)
  - 7+3 (n = 52)

Follow-up:
- Death OR
- 5 years

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

**Overall Clinical Results**

<table>
<thead>
<tr>
<th></th>
<th>CPX-351 (n = 153)</th>
<th>7+3 (n = 156)</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+CRi</td>
<td>47.7%</td>
<td>33.3%</td>
<td>1.77 (1.11, 2.81)</td>
<td>0.016</td>
</tr>
<tr>
<td>HSCT rate</td>
<td>34.0%</td>
<td>25.0%</td>
<td>1.54 (0.92, 2.56)</td>
<td>0.098</td>
</tr>
<tr>
<td>Deaths ≤30 days*</td>
<td>5.9%</td>
<td>10.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths ≤60 days*</td>
<td>13.7%</td>
<td>21.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on Kaplan-Meier estimate for the intent-to-treat population.

Median follow-up in patients who were alive: CPX-351 (n = 49): 589 days (range: 44-1007); 7+3 (n = 24): 601 days (range: 417-917).

CI, confidence interval; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; HSCT, hematopoietic stem cell transplant.

Hazard ratio = 0.69
2-sided P value = 0.005

Lancet et al, ASCO 2016
Survival Landmarked from Time of Transplant

- CPX-351 median OS not reached vs 10.25 months for 7+3
  - HR of 0.46 favoring CPX-351 ($P=0.0046$)
  - Cox proportional hazards HR, including transplant as a time-dependent covariate, was 0.51 (95% CI, 0.35–0.75; $P=0.0007$), favoring CPX-351

Lancet et al, ASH 2016
Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.

Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis.

Azacitidine ± Venetoclax (VIALE-A) Study Design

(NCT02993523)

### 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

- **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

### 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

### 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

DiNardo CD et al. NEJM 2020
AZA ± VEN in AML: Composite Response Rate (CR+CRi)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with $P < .001$ by CMH test.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of treatment cycles, median (range)</th>
<th>Median time to CR/CRi, Months (range)</th>
<th>*CR+CRi by initiation of Cycle 2, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aza + Ven (n = 286)</td>
<td>7.0 (1.0 – 30.0)</td>
<td>1.3 (0.6 – 9.9)</td>
<td>124 (43.4)</td>
</tr>
<tr>
<td>Aza + Pbo (n = 145)</td>
<td>4.5 (1.0 – 26.0)</td>
<td>2.8 (0.8 – 13.2)</td>
<td>11 (7.6)</td>
</tr>
</tbody>
</table>

DiNardo CD et al. NEJM 2020
**AZA ± VEN in AML: Overall Survival**

<table>
<thead>
<tr>
<th>Group</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), \(P < .001\)

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo CD et al. NEJM 2020
AZA ± VEN in AML: Survival by Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Aza+Ven n/N (%)</th>
<th>Aza+Pbo n/N (%)</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>
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</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>
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<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>
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<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>

DiNardo CD et al. NEJM 2020
Oral azacitidine

• Oral azacitidine (Oral-AZA [CC-486]):
  – Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent¹,²
  – Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)³
• Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity¹,²


AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.
QUAZAR AML-001: Study design and eligibility criteria

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC

PRE-RANDOMIZATION

Key eligibility criteria:
- First CR/CRi with IC ± consolidation
- Age ≥55 years
- De novo AML or AML secondary to MDS/CMML
- ECOG PS score 0-3
- Intermediate- or poor-risk cytogenetics
- Not candidate for HSCT
- ANC ≥0.5 × 10^9/L
- Platelets ≥20 × 10^9/L

RANDOMIZATION

1:1 Randomization
Within 4 months (± 7 days) from CR/CRi
Stratified by:
- Age: 55-64 / ≥65 years
- Prior MDS/CMML: Yes / No
- Cytogenetic risk: Intermediate / Poor
- Consolidation: Yes / No

TREATMENT PHASE

Oral-AZA 300 mg QD x 14 Days
Response Assessment (BM Aspirate) Every 3 Cycles

Placebo QD x 14 Days

CR/CRi
5%-15% BM Blasts
(5%-15% BM Blasts)

>15% BM Blasts
Stop Treatment

OPTIONAL

Oral-AZA/PBO x21 Days

End of Study

FOLLOW-UP

Continue Treatment

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\textsuperscript{1}

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**OVERALL SURVIVAL**

- Oral-AZA (n = 238)
- Placebo (n = 234)

**RELAPSE-FREE SURVIVAL**

- Oral-AZA (n = 238)
- Placebo (n = 234)

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No. at risk:
- Oral-AZA
- Placebo

Wei A, et al NEJM, 2020
New RX Algorithm in Older Adults with AML

- FIT, FLT3 mutation (TKD or ITD): 3+7+mido
- FIT, CBF: 3+7+GO
- FIT, MRC-related cytogenetics, h/o MDS, prior rx for CA: CPX-351
- FIT, NOS: 3+7
- UNFIT, or >75 yo: aza (7d) + venetoclax
- UNFIT, IDH1 or IDH2 mut: ivo- or enasidenib
- Post CR
  - alloSCT if poss (Devine et al, JCO 2015)
  - Cont low dose rx (Dinardo et al, NEJM 2020)
  - Maint oral aza (Wei, et al, NEJM 2020)
New CTEP/NCTN Approach in Myeloid Malignancies: MyeloMatch

- 3 Working groups: younger AML, older AML, MDS
- 1 Master screening protocol will assign pts based on age, fitness, AML subtype (rapid cytogenetic and molecular screening)
  - MRD-driven endpoints
    - A fit older adult could be assigned to 3+7 +/- drug X (currently X = the E-selectin inhibitor uproleselan) or to CPX351+ mido v novel FLT3 inhib or CPX v aza/ven (adverse risk)
    - An unfit older adult could be assigned to aza/ven +/- IDH inhibitor or aza/ven +/- anti CD47 or Aza/ven +/- TP53 refolding agent
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