Treatment of Adult AML Patients Appropriate for Intensive Therapy: It isn’t just 7+3 anymore!

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The Current AML Treatment Algorithm

AML Dx

Fit (appropriate) for intensive chemotherapy

Induction chemotherapy

CR

Consolidation chemotherapy

CR

Allogeneic HSCT

OBSERVATION OR MAINTENANCE THERAPY

Unfit (inappropriate) for intensive chemotherapy

Refractory

HMA or LoDAC

HMA/venetoclax

LoDAC/venetoclax

LoDAC/glasdegib

Gemtuzumab ozogamicin

FLT3m, IDH1m, IDH2m inhibitors

Response

Continued Therapy

Relapse

Salvage therapy

Refractory

Response

Continued Therapy

Reflexive

AML Dx

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AML Dx
Case #1: Maintenance therapy for AML

- 73-year-old man without any significant medical history presented with pancytopenia and peripheral blood myeloblasts.
- Bone marrow biopsy: acute myeloid leukemia with normal karyotype
- Myeloid gene panel detects six pathogenic mutations: NPM1, FLT3 ITD (AR 0.08), IDH2 R140Q, JAK2 V617F, SRSF2 P95R, and TET2 A1863V
- He received cytarabine and daunorubicin (7+3) with midostaurin.
- He achieved first complete remission following one cycle induction therapy.
- He then received two cycles of cytarabine 1.5 gram/m²/dose x 6 doses
- End-of-consolidation bone marrow biopsy: 10-20% cellularity, trilineage hematopoiesis, focal reticulin fibrosis
  - Flow cytometry negative for leukemic blast population
  - SRSF2 (VAF 41.5%), JAK2 (VAF 5.6%) , and TET2 (VAF 27.4%) variants still present.
Randomized Maintenance Therapy with Azacitidine (Vidaza) in Older Patients (≥ 60 years of age) with Acute Myeloid Leukemia (AML) and Refractory Anemia with Excess of Blasts (RAEB, RAEB-t). Results of the HOVON97 Phase III Randomized Multicentre Study (EudraCT 2008-001290-15)


No improvement in overall survival, even if censored at time of allo HSCT
CC-486

• CC-486 is an oral hypomethylating agent with a distinct PK/PD profile from injectable azacitidine\textsuperscript{1,2}

• CC-486 has demonstrated clinical activity in patients with hematologic malignancies\textsuperscript{1–4}

• Oral dosing of CC-486 allows for extended drug exposure during each treatment cycle to prolong therapeutic activity\textsuperscript{1,2}

• We hypothesized that prolonged treatment with CC-486 could be effective as post-remission maintenance in AML


AML, acute myeloid leukemia; DNMT, DNA methyltransferase; PD, pharmacodynamic; PK, pharmacokinetic.
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 (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

- > 15% BM Blasts
  - Stop Treatment
  - End of Study
- 5%–15% BM Blasts
  - CC-486/PBO × 21 days
  - Optional Treatment
  - Continue Treatment
- CR/CRi
  - CC-486 300 mg QD × 14 days
  - Placebo QD × 14 days
  - 28-day cycles

**Follow-up**

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

QUAZAR AML-001: 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.

QUAZAR AML-001: RFS by Number of Consolidation Cycles

*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 AML-001: 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

Roboz GR et al. ASH 2020; abstract 692
QUAZAR AML-001: Effect of AZA/PBO on OS and RFS based on NPM1 mutations status

Median OS (months, oral Aza)
- NPM1 Mut: 46.1
- NPM1 WT: 15.9

Median RFS (months, oral Aza)
- NPM1 Mut: 23.2
- NPM1 WT: 16.9

Dohner H, et al. EHA 2021, abstract S131
<table>
<thead>
<tr>
<th>Preferred term</th>
<th>CC-486 n = 236</th>
<th>Placebo n = 233</th>
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<tbody>
<tr>
<td>Patients with ≥1 AE</td>
<td></td>
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<tr>
<td>All Grades</td>
<td>231 (98)</td>
<td>225 (97)</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>169 (72)</td>
<td>147 (63)</td>
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<tr>
<td>Gastrointestinal</td>
<td></td>
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</tr>
<tr>
<td>Nausea</td>
<td>153 (65)</td>
<td>55 (24)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>141 (60)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>119 (50)</td>
<td>50 (22)</td>
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<tr>
<td>Constipation</td>
<td>91 (39)</td>
<td>56 (24)</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Neutropenia</td>
<td>105 (45)</td>
<td>61 (26)</td>
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<tr>
<td>Neutropenia</td>
<td>97 (41)</td>
<td>55 (24)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>79 (34)</td>
<td>63 (27)</td>
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<tr>
<td>Anemia</td>
<td>48 (20)</td>
<td>42 (18)</td>
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<tr>
<td>Other</td>
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<tr>
<td>Fatigue</td>
<td>70 (30)</td>
<td>45 (19)</td>
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<tr>
<td>Askenia</td>
<td>44 (19)</td>
<td>13 (6)</td>
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<tr>
<td>Pyrexia</td>
<td>36 (15)</td>
<td>44 (19)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (12)</td>
<td>39 (17)</td>
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</table>

- 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

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

Case #1: Maintenance therapy for AML

- A 73-year-old man with acute myeloid leukemia with normal karyotype and NPM1, FLT3 ITD (AR 0.08), IDH2 R140Q, JAK2 V617F, SRSF2 P95R, and TET2 A1863V
- 7+3 with midostaurin followed by 2 cycles of high dose cytarabine
- End-of-consolidation bone marrow biopsy: 10-20% cellularity, trilineage hematopoiesis, focal reticulin fibrosis
  - Flow cytometry negative for leukemic blast population
  - SRSF2 (VAF 41.5%), JAK2 (VAF 5.6%) , and TET2 (VAF 27.4%) variants still present.
- Maintenance therapy with oral azacitidine
  - Cycle 1 complicated by nausea, constipation
  - Cycle 2 complicated by prolonged cytopenias
  - Now cycle 6 after dose adjustment and tolerating well
Case #2: Secondary AML

- A 74-year-old man without any medical comorbid illness
- Absolute monocytosis for 2 years, mild thrombocytopenia for 6 years
- He develops fatigue (PS 1), night sweats, unintentional weight loss, and myalgias
- **CBC**: leukocytosis (WBC 30,000 with 45% monocytes atypical)
- **BM biopsy**: AML with severe fibrosis
- **Cytogenetics**: 46, XY [20]
- **NGS**: ASXL1, SRSF2, TET2, and CBL
Liposomal Daunorubicin and Cytarabine (CPX-351)

- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100-nm bilamellar liposomes
- 1 vial = 44 mg daunorubicin plus 100 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

Randomized, Phase 3 Study of CPX-351 vs 7+3: Design

**Study 301**

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

**Primary endpoint:** OS (event driven)

**Stratifications:**
- Therapy-related AML
- AML with history of MDS
  - With prior HMA
  - Without prior HMA
- AML with history of CMML
- de novo AML with MDS karyotype
- 60-69 years of age
- 70-75 years of age

**CPX-351 (n = 153)**

**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

**Follow-up:**
- Death OR 5 years

**Patients in CR or CRi: consolidation (1-2 cycles)**

**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

**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

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*1 unit = 0.44 mg daunorubicin + 1 mg cytarabine.*

Overall remission rate was also significantly higher with CPX-351 vs 7+3: 47.7% vs 33.3%
Phase 3 Study of CPX-351 vs 7+3: Overall Survival Landmark from HSCT

Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed Secondary AML: OS by Age

Study 301

Case #2: Secondary AML (Continued)

- A 74-year-old man without medical comorbid illness
- Absolute monocytosis for 2 years, mild thrombocytopenia for 6 years
- He develops fatigue (PS 1), night sweats, unintentional weight loss, and myalgias
- **CBC**: leukocytosis (WBC 30,000 with 45% monocytes atypical)
- **BM biopsy**: AML with severe fibrosis
- **Cytogenetics**: 46, XY [20]
- **NGS**: ASXL1, SRSF2, TET2, and CBL

Receives CPX-351 on 5/20/19 as outpatient
- Culture negative for febrile neutropenia
- 06/28/19: BM CRp by 07/16/19
- 07/24/19: CPX-351 consolidation as outpatient
- 08/28/19: BM CR (NGS panel is negative)

**Proceeds to allogeneic HCT**
- 10/18/19: preparative regimen fludarabine/melphalan
- 10/23/19: haplo (son) alloHCT
- Cyclophosphamide post cells
- Last visit, 02/10/20: doing well