Treatment of AML in the elderly: intensive or not?

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## Conflicts of interest

<table>
<thead>
<tr>
<th>Company name</th>
<th>Research support</th>
<th>Consultant</th>
<th>Advisory board</th>
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<td>MERUS</td>
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</tbody>
</table>
Erythrocytes

Oxygen transport

Leukocytes

Resistance

Platelets

hemostasis

Erythrocytes

Leukocytes

Platelets

Normal bone marrow

Acute leukemia

Maturation disturbance

Anemia

Bleeding

Infections

Acute leukemia

Maturation disturbance

Anemia

Bleeding

Infections

Acute leukemia

Maturation disturbance

Anemia

Bleeding

Infections

Acute leukemia

Maturation disturbance

Anemia

Bleeding

Infections
Outcome of cytogenetic entities recognised in 2008 WHO classification

MRC/NCRI AML Trials: Overall Survival
Ages 16–59

Analysis of 5,876 cases entered in MRC AML10, 12 & 15 trials

Genomic landscape of adult AML

- Targeted resequencing of 111 myeloid cancer genes (combined with cytogenetic profiles) in 1540 AML
- 5236 driver mutations (i.e., fusion genes, copy number alterations, gene mutations) involving 77 loci
- 6 genes mutated in >10% pts; 13 genes 5-10% pts; 24 genes 2-5% pts; 37 genes <2% pts

2017 ELN Prognostic Stratification of AML

**Favourable**
- t(8;21)(q22;q22.1); RUNX1-RUNX1T1
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- Mutated NPM1 without FLT3-ITD or with FLT3-ITD\(^\text{low}\)
- Biallelic mutated CEBPA

**Intermediate**
- Mutated NPM1 and FLT3-ITD\(^\text{high}\)
- Wild-type NPM1 without FLT3-ITD or with FLT3-ITD\(^\text{low}\) (without adverse-risk genetic lesions)
- t(9;11)(p21.3;q23.3); MLLT3-KMT2A
- Cytogenetic abnormalities not classified as favourable or adverse

**Adverse**
- t(6;9)(p23;q34.1); DEK-NUP214
- t(v;11q23.3); KMT2A rearranged
- t(9;22)(q34.1;q11.2); BCR-ABL1
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype, monosomal karyotype
- Wild-type NPM1 and FLT3-ITD\(^\text{high}\)
- Mutated RUNX1¶
- Mutated ASXL1¶
- Mutated TP53

FLT3-ITD allelic ratio defined as: low, <0.5; high, ≥0.5. ¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. Döhner H et al. Blood 2017;129:424–447.
Overall survival according to ELN 2017 in 3679 newly diagnosed AML patients treated in HOVON studies

Patient data derived from AML29, AML42, AML92 and AML102 HOVON-SAKK studies
“I Am Older, Not Elderly,” Said the Patient With Acute Myeloid Leukemia

Charles A. Schiffer, Division of Hematology/Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI
Median age at diagnosis: 68-70+ years

5-yr survival is 28.3%

Incidence of AML by Age Group

5-Year Survival of Newly Dx AML, Stratified by Age at Diagnosis (2007-2013)

SEER 2018 data
Ageing is a biological dynamic process beyond human control and there is no general prognosis of the age at which a person becomes old.

Life Expectancy

http://www.rivm.nl/vtv/object_document/o2309n18838.html
Characteristics AML in Elderly

• Disease related factors
  – Antecedent Hematological Disorder
  – Adverse Prognostic Cytogenetic Profile
  – Overexpression MDR1 gene
  – Gene Expression Profile differences
  \( \rightarrow \) **Chemotherapy less effective**

• Host related factors
  – Worse performance status
  – More co-morbidity
  – PK and PD changes
  \( \rightarrow \) **Increased Toxicity of Chemotherapy**
Age-related frequency of gene mutations

Analysis based on 10,622 AML patients from the AMLSG data base
Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; >70 yrs, n=2,485

Bullinger et al. J Clin Oncol 2017
Fit or Unfit
Elderly
HCT-CI predicts early mortality and survival

- Prospective study n=177
- AML pts ≥ 60 years who received induction chemotherapy

<table>
<thead>
<tr>
<th>HCT-CI score</th>
<th>30-day mortality %</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>1-2</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>≥ 3</td>
<td>29</td>
<td>19</td>
</tr>
</tbody>
</table>

P-value: P<0.001  p=-0.04

Giles et al. BJH 2006
Augmented HCT-CI + age + cytogenetic/molecular risks


http://www.amlcompositemodel.org/
Differentiating fit from unfit requires a comprehensive approach

Comorbidity

Cognitive function

Psychological Health

Physical function

Nutrition

Treatment outcome

Social support

H. Klepin ASH 2014
Geriatric assessment predicts survival in older AML patients receiving induction therapy

• N=74, prospective single institution study, median age 68.8 years

• GA done within 5 days of admission for induction chemotherapy

• Cognitive function was assessed using the 100-point Modified Mini-Mental State (3MS)

• SPPB assessed using a short walk (4 m), repeated chair stands, grip strength and balance test

Klepin et al Blood 2013;121:4287
Objectively measured physical and cognitive function were more important than chronologic age in predicting survival.

**Objective physical function**
Kaplan-Meier Survival Estimates by SPPB

**Cognitive function**
Kaplan-Meier Survival Estimates by 3MS Score

P=0.018

P=0.002

Klepin et al Blood 2013;121:4287
**HOVON 43: Daunorubicin Dose Intensification in elderly AML**

**Induction cycle I**
- DNR 45 mg/m² x3
- Ara-C 200 mg/m² x7

**Induction cycle II**
- Ara-C 1 g/m² q12 hrs x 6 days
- DNR 90 mg/m² x3
- Ara-C 200 mg/m² x7

**Post induction**
- none
- GO 6 mg/m² q 4 weeks x 3
- RIC-SCT (optional)

*Lowenberg, Ossenkoppele et al, NEJM 2009:361:1235*
HOVON 43: Daunorubicin Dose Intensification in elderly AML: OS

Lowenberg, Ossenkoppele et al, NEJM 2009:361:1235
New Trial Design in Elderly AML

Octopus design: HOVON 103

- DNR/ARA-C
- DNR/ARA-C + Bevacizumab
- DNR/ARA-C + Lenalidomide
- DNR/ARA-C + Tosedostat
- DNR/ARA-C + Selinexor

Randomized Phase II
Winner X vs Y
(Survival)
HOVON 103 Lenalidomide
Overall Survival

Ossenkoppele Leukemia 2020
HOVON 103 Lenalidomide
Overall Survival

Overall survival
Risk AML (as in HO102)

Cumulative percentage

Good 100
Intermediate 75
Poor 50
VeryPoor 25

0

Good
Intermediate
Poor
VeryPoor

At risk:
Good 32
Intermediate 30
Poor 112
VeryPoor 48

N 32 16
Intermediate 30 15
Poor 112 95
VeryPoor 48 43

Logrank P < .001

Ossenkoppele Leukemia 2020
Change in overall survival in time age 15-59 yrs

Age over 60 years
New Treatment Modalities!!!
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 unit = 0.44 mg daunorubicin plus 1.0 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors
Phase 3 Study of CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed High-Risk AML

Key eligibility:
- Previously untreated
- Aged 60-75 years
- Able to tolerate intensive therapy
- 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
- Aged 60-69 years
- Aged 70-75 years

Induction:
- CPX-351 44 mg/100 mg per m² IV days 1, 3, 5
- Cytarabine 100 mg/m²/day x 7 plus daunorubicin 60 mg/m²/day x 3

Consolidation:
- CPX-351 29 mg/65 mg per m² IV days 1, 3
- Cytarabine 100 mg/m²/day x 5 plus daunorubicin 60 mg/m²/day x 2

Primary endpoint: Overall survival

Follow-up:
- Death or
- 5 years

Phase 3 Study of CPX-351 Vs 7+3 in High-Risk AML: Response Rate

- CPX-351 (n = 153)
- 7+3 (n = 156)

### CR
- CPX-351: 37.3%
- 7+3: 25.6%
- Odds ratio (95% CI): 1.69 (1.03, 2.78)
- P = .040

### CR + CRi
- CPX-351: 47.7%
- 7+3: 33.3%
- Odds ratio (95% CI): 1.77 (1.11, 2.81)
- P = .016

CPX-351 Improves Survival Among Older, High-Risk AML

Kaplan-Meier Curve for OS: ITT Analysis Population

- **CPX-351**: 104/153 events, median survival 9.56 months (95% CI 6.60-11.86)
- **7+3**: 132/156 events, median survival 5.95 months (95% CI 4.99-7.75)
- Hazard Ratio (HR) = 0.69
- *P* = 0.005

“Current” standard for unfit elderly

• Prospective randomized trials in unfit AML:

  ◆ Low dose Ara-C superior to BSC
    (Burnett et al. Cancer. 2007)

  ◆ Decitabine 5-days 20 mg/m^2 superior to CC
    (Kantarjian et al. JCO. 2012)

  ◆ Azacytidine 7-days 75mg/m2 superior to CC
    (Dombret et al. Blood 2015)
Frontline treatment for elderly patients with AML unfit for Intensive Chemotherapy

Azacytidine vs CCR\(^2\)

Decitabine vs TC\(^1\)

## Recent approvals in AML

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Approval</th>
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</thead>
<tbody>
<tr>
<td><strong>Midostaurin</strong>¹²</td>
<td><em>De novo</em> AML with FLT3 mutation</td>
<td>FDA: 2017 EMA: 2017</td>
</tr>
<tr>
<td><strong>Gemtuzumab ozogamicin</strong>³⁴</td>
<td><em>De novo</em> CD33+ AML (also R/R AML in the US)</td>
<td>FDA: 2017 EMA: 2018</td>
</tr>
<tr>
<td><strong>CPX-351</strong>⁵⁶</td>
<td><em>De novo</em> t-AML or MRC-AML</td>
<td>FDA: 2017 EMA: 2018</td>
</tr>
<tr>
<td><strong>Ivosidenib</strong>⁷</td>
<td><em>De novo</em> R/R AML with IDH1 mutation</td>
<td>FDA: 2018</td>
</tr>
<tr>
<td><strong>Enasidenib</strong>⁸</td>
<td>R/R AML with IDH2 mutation</td>
<td>FDA: 2017</td>
</tr>
<tr>
<td><strong>Gilteritinib</strong>⁹</td>
<td>R/R AML with FLT3 mutation</td>
<td>FDA: 2018</td>
</tr>
<tr>
<td><strong>Glasdegib</strong>¹⁰</td>
<td>(+LDAC) <em>De novo</em> AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy</td>
<td>FDA: 2018</td>
</tr>
<tr>
<td><strong>Venetoclax</strong>¹¹</td>
<td>(+LDAC/HMA) <em>De novo</em> AML in patients ≥75 years old or who have comorbidities precluding use of intensive chemotherapy</td>
<td>FDA: 2018</td>
</tr>
<tr>
<td><strong>Tagraxofusp</strong>: fusion protein of IL-3 and diphtheria toxin</td>
<td>Blastic Plasmacytoid Dendritic Cell Neoplasm</td>
<td>FDA: 2018</td>
</tr>
</tbody>
</table>

Venetoclax: selective bcl-2 inhibitor

Many tumors overexpress bcl-2

Cancer cell survival

BCL-2

Pro-apoptotic protein

Cancer cell apoptosis

Venetoclax

BCL-2

Apoptosis initiation

Pro-apoptotic protein

Activation of caspases

Cytochrome c

BAX

BAK

pro-apoptotic proteins are released from BCL-2 binding

Konopleva M. Cancer Discovery 2016
A Randomized, Double-blind, Placebo-controlled Study of Venetoclax with Azacitidine vs Azacitidine in Treatment-naïve Patients with Acute Myeloid Leukemia Ineligible for Intensive Therapy: VIALE-A

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**
N=433*

**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+Crh 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

Courtesy C.Dinardo

Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/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>
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</tbody>
</table>

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

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

Courtesy C.Dinardo

Composite Response Rate (CR+CRi)

CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 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>

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test.

Courtesy C.Dinardo

Duration of Response After Achieving CR/CRi

<table>
<thead>
<tr>
<th></th>
<th>Median duration of CR/CRi, months (95% CI)</th>
<th>Median duration of CR, months (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Aza+Ven (n=286)</td>
<td>17.5 (13.6 – NE)</td>
<td>17.5 (15.3 – NE)</td>
</tr>
<tr>
<td>Aza+Pbo (n=145)</td>
<td>13.4 (5.8 – 15.5)</td>
<td>13.3 (8.5 – 17.6)</td>
</tr>
</tbody>
</table>

Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete count recovery; NE: Not estimable; Pbo: Placebo; Ven: Venetoclax


Courtesy C. Dinardo

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>190</th>
<th>161</th>
<th>133</th>
<th>101</th>
<th>85</th>
<th>72</th>
<th>44</th>
<th>23</th>
<th>4</th>
<th>2</th>
<th>0</th>
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<tbody>
<tr>
<td>Aza+Ven</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aza+Pbo</td>
<td>41</td>
<td>31</td>
<td>20</td>
<td>17</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Combination of venetoclax plus an HMA is the new gold standard for unfit AML

- Azacitidine and venetoclax combination significantly extended survival in treatment-naïve patients with AML ineligible for standard induction therapy compared to azacitidine and placebo.

- Patients treated with azacitidine and venetoclax combination had significantly higher remission rates and transfusion independence.

- The adverse events with azacitidine and venetoclax combination were similar to previously reported experiences.
FLT3-ITD Mutations in AML

- FLT3 internal tandem duplication (ITD) occurs in ≈ 25% of younger adult patients with AML (28%-34% CN-AML)
- FLT3 TKD mutations (5-10%)
  - ligand-independent dimerization and constitutive activation of the tyrosine kinase domain
    - factor-independent growth
    - block in myeloid differentiation
- Associated with adverse prognosis
RATIFY (CALGB 10603): Overall Survival

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

22% reduced risk of death in the midostaurin arm)

OS Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>717</td>
<td>0.78 (0.63–0.96)</td>
<td>0.009 (one-sided)</td>
</tr>
<tr>
<td>ITD (high)</td>
<td>214</td>
<td>0.80 (0.57–1.12)</td>
<td>0.19 (two-sided)</td>
</tr>
<tr>
<td>ITD (low)</td>
<td>341</td>
<td>0.81 (0.60–1.11)</td>
<td>0.19 (two-sided)</td>
</tr>
<tr>
<td>TKD</td>
<td>162</td>
<td>0.65 (0.39–1.08)</td>
<td>0.10 (two-sided)</td>
</tr>
</tbody>
</table>

Toxicity

- No difference in early mortality
- Higher rate of rash and GI toxicity with mido

Midostaurin Plus Chemotherapy for FLT3-ITD+ AML AMLSG 16-10 Trial

**Induction (1-2 cycles)**
- **Midostaurin** (50 mg bid, day 8 until 48h before start of subsequent cycle)
- **Daunorubicin** (60 mg/m²/day, days 1-3)
- **Cytarabine** (200 mg/m²/day, days 1-7)

**Consolidation (1 cycle)**
- **Midostaurin** (50 mg bid, day 6 until 48h before start of subsequent cycle)
- **HiDAC** (aged-based dosing, days 1, 3, and 5)

**Consolidation (first priority)**
- **Allogeneic HSCT**
- **Midostaurin** (50 mg bid, day 6 until 48h before start of subsequent cycle)
- **HiDAC** (aged-based dosing, days 1, 3, and 5)

**Consolidation (second priority; × 3 cycles)**
- **Midostaurin** (50 mg bid, day 6 until 48h before start of subsequent cycle)
- **HiDAC** (aged-based dosing, days 1, 3, and 5)

**Maintenance (up to 1 year)**
- **Midostaurin** (50 mg bid, days 1-28)

**Patients with FLT3-ITD+ AML**
- Aged 18-70 years (N = 440)

**Primary endpoint:** EFS

**Secondary endpoints:** CR, RFS, OS, CIR

---

CIR, cumulative incidence of relapse.

a FLT3 screening results within 48 hours; FLT3-ITD/-WT ratio > 0.05 by GeneScan-based fragment length analysis required to be FLT3-ITD+.

b During induction, patients achieving PR after cycle 1 can receive an optional cycle 2.

c For patients eligible for alloSCT, 1 course of HiDAC is optional before alloSCT.

d Age-appropriate cytarabine dose on days 1, 3, and 5: 18-65 years, 3 g/m² q12h (total dose 18 g/m²); > 65 years, 1 g/m² q12h (total dose 6 g/m²).

Comparison AMLSG 16-10 vs Historical Control
Propensity Score Weighting Analysis*

HR = 0.70 (95 CI, 0.535-0.920)

HR = 0.49 (95% CI, 0.316-0.753)

*Propensity score weighting on age, gender, WBC, marrow blasts, NPM1 mutations

Unpublished data.
ClinicalTrials.gov: NCT01477606 (active)
Older pts with Newly Diagnosed $\text{FLT3}^{\text{mut}}$ AML
Frontline FLT3i + Lower Intensity Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Age</th>
<th>CR/CRI (%)</th>
<th>Median OS, mo</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>SORAFINIB + AZA</td>
<td>64 (24-87)</td>
<td>43</td>
<td>6.2</td>
<td>43 (6 were ND)</td>
</tr>
<tr>
<td>MIDOSTAURIN + AZA</td>
<td>65 (21-85)</td>
<td>26</td>
<td>5.1</td>
<td>54 (14 were ND)</td>
</tr>
<tr>
<td>GILTERITINIB + AZA (LACEWING)</td>
<td>76 (65-86)</td>
<td>67</td>
<td>8.7</td>
<td>15</td>
</tr>
<tr>
<td>QUIZARTINIB + AZA/LDAC</td>
<td>68 (&gt;60)</td>
<td>83</td>
<td>21.1</td>
<td>12</td>
</tr>
<tr>
<td>AZA/DAC + VEN</td>
<td>&gt;65</td>
<td>53-65</td>
<td>12-13</td>
<td>30</td>
</tr>
<tr>
<td>TKI + DEC10-VEN</td>
<td>70 (64-80)</td>
<td>100</td>
<td>NR</td>
<td>10</td>
</tr>
</tbody>
</table>

Courtesy Dr Dinardo

Role of IDH in Cancer

- IDH is a critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Mutation frequency in AML (n=2,464 pts)²

Enasidenib and ivosidenib in R/R AML

<table>
<thead>
<tr>
<th></th>
<th>Enasidenib 100 mg (n=214) (Stein et al, Blood 2017/2019)</th>
<th>Ivosidenib 500 mg (n=125) (DiNardo et al, NEJM 2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (number, %)</td>
<td>83 (38.8%)</td>
<td>52 (41.6%)</td>
</tr>
<tr>
<td>CR (number, %)</td>
<td>42 (19.6%)</td>
<td>27 (21.6%)</td>
</tr>
<tr>
<td>CRi or CRp (number, %)</td>
<td>20 (9.3%)</td>
<td>16 (12.8%)</td>
</tr>
<tr>
<td>Time to first response, median (months, range)</td>
<td>1.9 (0.5 – 9.4)</td>
<td>1.9 (0.8 – 4.7)</td>
</tr>
<tr>
<td>Duration of response, median (months, 95% CI)</td>
<td>5.6 (3.8 – 7.4)</td>
<td>6.5 (4.6 – 9.3)</td>
</tr>
<tr>
<td>Duration of response in patients with CR (months, 95% CI)</td>
<td>8.8 (5.6 – NR)</td>
<td>9.3 (5.6 – 18.3)</td>
</tr>
<tr>
<td>Median overall survival (months, 95% CI)</td>
<td>8.8 (7.7 – 9.6)</td>
<td>8.8 (6.7 – 10.2)</td>
</tr>
</tbody>
</table>
Enasidenib (AG-221) and Ivosidenib (AG-120) in mutant IDH2 and IDH1 relapsed or refractory AML

Enasidenib in r/r IDH2^{mut} AML
Overall response rate (CR, CRi, PR, MLFS): 40.3%

Median OS: 9.3 months (95%CI 8.2, 10.9)


Ivosidenib in r/r IDH1^{mut} AML
Overall response rate (CR, CRi, PR, MLFS): 41.6%

Median OS: 8.2 months (95%CI 5.5, 12.0)

### Ivosidinib in untreated AML

<table>
<thead>
<tr>
<th></th>
<th>N=34</th>
<th></th>
<th>N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>76.5 yrs (range 64-87)</td>
<td></td>
<td>76 yrs (range 61-88)</td>
</tr>
<tr>
<td><strong>sec AML</strong></td>
<td>76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>prior MDS</strong></td>
<td>53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall response rate, n (%)</strong></td>
<td>55%</td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>30%</td>
<td></td>
<td>57%</td>
</tr>
<tr>
<td><strong>CR+CRh</strong></td>
<td>42%</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td><strong>Duration of CR, months</strong></td>
<td>NE</td>
<td></td>
<td>1.8 months</td>
</tr>
<tr>
<td><strong>12-months duration of response,</strong></td>
<td>78%</td>
<td></td>
<td>3.5 months</td>
</tr>
<tr>
<td><strong>mIDH1 clearance in CR+CRh patients</strong></td>
<td>9/14</td>
<td></td>
<td>10/16 (63%)</td>
</tr>
</tbody>
</table>

G.Roboz EHA 2019 PS1025  
C.Dinardo EHA 2019 PS 1023
Targeting TP53 mutations in MDS/AML via APR-246

APR-246 binds covalently to p53...

...restores wt p53 conformation & activity...

...and triggers cell cycle arrest and apoptosis

APR-246 Combined with Azacitidine (AZA) in TP53 Mutated Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). A Phase 2 Study By the Groupe Francophone Des Myélodysplasies (GFM)

Thomas Cluzeau, Marie Sebert, Ramy Rahmé, Stefania Cuzzubbo, Anouk Walter-Petrich, Jacqueline Lehmann-Che, Isabelle Madelaine, Pierre Peterlin, Blandine Bève, Habiba Attalah, Fatiha Chermat, Elsa Miekoutima, Odile Beyne Rauzy, Christian Recher, Aspasia Stamatoullas, Lise Willems, Emmanuel Raffoux, Céline Berthon, Bruno Quesnel, Antoine F. Carpentier, David A. Sallman, Sylvie Chevret, Lionel Ades, Pierre Fenaux

Université Côte d’Azur; CHU of Nice, Hematology department; Mediterranean center of molecular medicine, INSERM U1065; Groupe Francophone des Myélodysplasies (GFM)
GFM-APR phase 2 study design

- APR-246 4500mg/d IV over 6 hours days 1-4
- AZA 75mg/m² SC daily days 4-10
- 28 day cycles
- Maintenance treatment after Allogeneic SCT for 12 months:
  - Azacitidine 36mg/m² SC daily days 1-5
  - APR-246 3700mg/d IV over 6 hours days 1-4

MDS intermediate, high and very high IPSS-R and AML (including with > 30% marrow blasts) with TP53 mutation

* Bone marrow evaluation
### Response to Treatment in Evaluable Patients (n=45) receiving AZA + APR-246

#### Evaluable patients, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>MDS</th>
<th>AML</th>
<th>MDS-MPN + CMML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate patients, n</td>
<td>45</td>
<td>33</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Overall response rate, n (%)</td>
<td>39 (87)</td>
<td>29 (88)</td>
<td>7 (88)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>CR rate, n (%)</td>
<td>24 (53)</td>
<td>20 (61)</td>
<td>4 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Duration of CR, months (median) [95% CI]</td>
<td>7.3 [5.8 – N.E.]</td>
<td>7.3 [5.8 – N.E.]</td>
<td>7.0 [3.3 – N.E.]</td>
<td>N.E.</td>
</tr>
<tr>
<td>Discontinued for transplant, n (%)</td>
<td>22 (49)</td>
<td>17 (52)</td>
<td>4 (50)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Median duration of follow-up = 10.8 months
Azacitidine + CD47 Antibody Magrolimab for MDS/AML

- CD47 is a “don’t eat me” signal on cancer cells that enables macrophage evasion
- Magrolimub (Hu5F9-G4) targets CD47 on tumor cells, inducing macrophage phagocytosis

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>MDS (n=33)</th>
<th>AML (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>30 (91%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (42%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>CRi</td>
<td>-</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>MLFS/marrow CR</td>
<td>8 (24%)</td>
<td>1 (%)</td>
</tr>
<tr>
<td>Median time to first response (range), months</td>
<td>1.9 mo</td>
<td></td>
</tr>
<tr>
<td>MRD-neg in responders, n/N (%)</td>
<td>6/30 (20%)</td>
<td>8/16 (50)</td>
</tr>
<tr>
<td>Median follow-up (range), months</td>
<td>5.8 (2.0-15)</td>
<td>9.4 (1.9-16.9)</td>
</tr>
<tr>
<td>Median DOR (range), months</td>
<td>NR (0.03-10.4+)</td>
<td>NR (0.03-15.1+)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

- In patients with TP53-mutated AML (n=12), the ORR was 75% and the median DOR and OS were not reached
- 6- mo OS 91% in TP53-mutated AML
- CD34+CD38- LSC were eliminated in 40% of patients overall
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

CR/CRi

5%–15% BM Blasts

(Optional) CC-486/PBO × 21 days

Stop Treatment

End of Study

Continue Treatment

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

AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.
PATIENT DISPOSITION

Screened: N = 555

Screened but not randomized n = 83

Randomized N = 472

Discontinued treatment: n = 193
- Disease relapse 60%
- Adverse events 12%
- Withdrew consent 4%
- Physician decision† 3%
- Other 2%
- Death 0.4%

Discontinued treatment: n = 208
- Disease relapse 77%
- Withdrew consent 6%
- Adverse events 5%
- Other 1%
- Death 1%
- Physician decision† 0%

CC-486 n = 238
- Treatment ongoing* n = 45

Placebo n = 234
- Treatment ongoing* n = 26

*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment.
PRIMARY ENDPOINT: OVERALL SURVIVAL FROM RANDOMIZATION

- Median follow-up: 41.2 months

Stratified \( P \) value: 0.0009
Stratified HR: 0.69 [95% CI 0.55, 0.86]

\[ \Delta 9.9 \text{ months} \]

\[ \Delta 24.7 \text{ months} \]

[95% CI 11.7, 17.6]

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95% CIs were generated using a stratified Cox proportional hazards model.

95% CI, 95% confidence interval; HR, hazard ratio.
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. 95% CIs were generated using a stratified Cox proportional hazards model.

95% CI, 95% confidence interval.
Maintenance therapy with CC-486 represents a new potential therapeutic standard for patients aged ≥55 years with AML in first remission

- CC-486 is the first maintenance therapy to provide statistically significant and clinically meaningful improvements in both OS and RFS in a broad range of patients with AML in remission following intensive chemotherapy, with or without consolidation
  - OS and RFS benefits with CC-486 were observed across key patient subgroups

- The safety and tolerability of CC-486 was manageable, with no unexpected adverse events

- CC-486 preserved overall HRQoL vs. placebo
Take Home messages

• Fully characterize AML also in the elderly

• Intensive or non-intensive approaches for older pts?
  • How to determine fitness?
  • Intensive chemotherapy no longer required prior to SCT?

• What is the preferred regimen for FLT3 and IDH mutant AML?
  • Targeted Tx with intensive chemo for the fit?
  • AZA + targeted tx & AZA + venetoclax both effective
  • Triplet combinations?

• Can we change the natural history of TP53 mutant AML?
  • APR-286 and Magrolimab are potential candidates

  How do we best incorporate maintenance therapy, immunotherapy
thank you