Overview

• Conventional & novel hypomethylating agents

• Novel targeted therapies

• AML founding mutations and HSC
RESULTS OF A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF AZACITIDINE (AZA) VS CONVENTIONAL CARE REGIMENS (CCR) IN OLDER PATIENTS WITH NEWLY DIAGNOSED AML

Late Breaking Abstract
#6212

Dombret H et al.
(International study)
BACKGROUND

• Compared to conventional care regimens (CCR) Azacitidine (AZA) prolonged OS in older AML pts with low bone marrow (BM) blast percentage (20-30%)

• No large R studies area available in elderly AML with>30% blasts
AIM AND METHODS

• Multicenter, randomized, open-label Phase III study
• ≥65 yrs with de novo or sAML (>30% BM blasts)*, ineligible for allogeneic stem cell transplant
• Primary endpoint: OS
• Randomized to receive:
  1. CCRs per investigator choice of best treatment: intensive chemotherapy (standard 7+3 regimen), LDAC (20 mg SC BID x10d/28d cycle), or BSC
  2. AZA (75 mg/m²/d SC x7d/28d cycle)

*low risk K and wbc >15,000 excluded
## BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AZA (n=241)</th>
<th>CCR (n=247)</th>
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<tbody>
<tr>
<td><strong>Age (yrs), median (min, max)</strong></td>
<td>75.0 (64, 91)</td>
<td>75.0 (65, 89)</td>
</tr>
<tr>
<td><strong>WHO AML classification, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Not otherwise specified (NOS)</td>
<td>153 (63.5)</td>
<td>143 (57.9)</td>
</tr>
<tr>
<td>Myelodysplasia-related changes</td>
<td>75 (31.1)</td>
<td>83 (33.6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (5.4)</td>
<td>21 (8.5)</td>
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<tr>
<td><strong>Bone marrow blasts %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (min, max)</td>
<td>70.0 (2, 100)</td>
<td>74.0 (4, 100)</td>
</tr>
<tr>
<td><strong>Cytogenetic risk, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>155 (64.3)</td>
<td>160 (64.8)</td>
</tr>
<tr>
<td>Poor*</td>
<td>85 (35.3)</td>
<td>85 (34.4)</td>
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</table>
RESULTS (I)

- 488 randomized patients

Median OS (95%CI) in the AZA arm was 10.4 mos vs. 6.5 mos with CCR (unstratified HR=0.84 [95%CI 0.69, 1.02], p=0.08
RESULTS (II) AND CONCLUSIONS

• One-yr survival was 47% with AZA vs 34% with CCR: Although NS, clinically meaningful OS difference

• Rates of grade 3-4 hematologic AEs were higher with AZA than BSC, and similar to LDAC and IC, and consistent with previous experience
A RANDOMIZED MULTICENTER PHASE II STUDY OF A 5-DAY REGIMEN OF SGI-110, A NOVEL HYPMETHYLATING AGENT, IN NAÏVE ELDERLY AML

Abs # 3416

Yee K et al. (MDACC, Houston)
BACKGROUND

- SGI-110: a 2nd generation HMA which prolongs half-life and extends exposure to decitabine

- In a phase I study, SGI-110 given daily for 5 d produced potent hypomethylation and clinical responses in MDS and AML previously treated with 1st generation HMAs*

*Kantarjian et al., 2012
AIMS AND STUDY DESIGN

• Randomized Phase II study in treatment naïve elderly (≥ 65 years) AML patients not suitable for intensive induction chemotherapy

• Efficacy and safety of 2 doses of SGI-110 (60 mg/m2 or 90 mg/m2) given as a 5-day sc regimen every 28 days until progression

• Primary endpoint: Overall Complete Remission (CR+CRi +CRp)
RESULTS AND CONCLUSION

• 51 patients treated: 24 and 27 patients randomized to 60 and 90 mg/m² doses

• Overall CR in 12 (8 CR+4CRi, 50%) and 12 (9CR+3CRi, 44%) for 60 and 90 mg/m²

• Low all-cause mortality (compared to intensive chemotherapy) at 30/60 days of 5.9% and 15%

• Phase III trial with 60 mg/m² ongoing for confirmation of results
PHASE I/II STUDY OF VOLASERTIB, A POLO-LIKE KINASE INHIBITOR (PLK), IN PATIENTS WITH RELAPSED/REFRACTORY AML: UPDATED PHASE I RESULTS FOR VOLASERTIB MONOTHERAPY

Abs # 4277

Döhner H et al.
German-Austrian AMLSG
BACKGROUND AND AIMS

- Volasertib is a selective and potent cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Plk.

- Updated phase I results of volasertib monotherapy in rel/ref AML ineligible for intensive salvage therapy.

- Determine the maximum tolerated dose (MTD), safety, and pharmacokinetics (PK) of volasertib monotherapy.
RESULTS AND CONCLUSION

• 56 pts treated (median age: 70 yrs, 84% aged ≥65 yrs). All failed prior AML treatment (median: 2 previous lines).

• At higher volasertib doses (≥350 mg), 5/43 pts (12%) achieved a complete remission with incomplete blood count recovery (Cri).

• Grade ≥3 drug-related AEs (occurring in ≥3 pts) included neutropenia and thrombocytopenia (25%), anemia (21%), leukopenia (13%), mucosal inflammation (7%), and pneumonia (5%).
• Phase III trial with low dose cytarabine, with or without volasertib, in older untreated pts with AML ineligible for intensive therapy*

* Preliminary results reported in Blood 2014
ATRA AS ADJUNCT TO INTENSIVE TREATMENT IN YOUNGER ADULT PTS WITH AML-FINAL RESULTS OF THE AMLSG 07-04 RANDOMIZED TRIAL

Abs # 4480

Schlenk R et al.
BACKGROUND AND AIMS

• Among elderly AML patients, those with NPM1+ve/FLT3wt, significantly benefit from ATRA as adjunct to chemotherapy*

• Evaluate the impact of ATRA combined with CHT on outcome, and assess the NPM1 mutational status in relation to ATRA as a biomarker of response in younger adult AML pts entered in the prospective randomized trial AMLSG 07-04

*Schlenk et al. Haematologica 2009
METHODS

• Age 18-60 yrs

• Induction therapy: 2 cycles of ICE

• Consolidation therapy: high-risk AML assigned to allo-HSCT from a MRD or MUD. All other assigned to 3 cycles of high-dose ARA-C or, if an MRD was available, to allo-HSCT in intermediate-risk AML.

• Randomized up-front for ATRA 45mg/m² d 6-8, 15mg/m² d 9-21

• Primary and secondary end points: EFS, CR rate, CIR and OS
RESULTS

- 1100 patients randomized, 556 in the standard and 544 in the ATRA-arm. *NPM1* +ve in 29% of pts

- In multivariable analyses, ATRA neither as single factor nor as interaction term with *NPM1* had a significant impact on CR and EFS on an ITT basis.

- In contrast, a PP analysis revealed a significant impact of the ATRA-*NPM1* interaction (OR, 2.07; p=0.03) indicating a higher CR probability and EFS for AML-*NPM1*+ for pts treated with ATRA (p=0.04)
CONCLUSIONS

- ATRA as adjunct to chemotherapy improved responses to induction therapy and EFS in \textit{NPM1} mutated-AML
FLT3-ITD INDUCED MYELOPROLIFERATION CAUSES A CELL EXTRINSIC DEPLETION OF HAEMATOPOIETIC STEM CELLS

Abs # 3998

Mead AJ. et al.
(UK and Sweden)
• FLT3-ITD frequently occur in AML and are associated with a high relapse risk

• The ability of FLT3-ITD to transform progenitor cells and impact of mutant FLT3-ITD within the HSC compartment is unclear
AIM AND METHODS

• To investigate whether FLT3-ITDs confer aberrant self-renewal properties to progenitor cells and to determine the expression pattern of FLT3 in the HSC compartment

• Murine knock-in model of FLT3-ITD myeloproliferation

• Phenotypic and functional stem cell assays and single-cell gene expression analysis of over 1000 HSC to understand the expression pattern related to FLT3-ITDs
RESULTS

• Loss of functional HSCs in adult Flt3-ITD mice

• Single HSCs from FLT3-ITD mice show less frequent expression of stem-cell associated genes

• Competitive transplantation using FLT3-ITD fetal liver cells, with wt competitor HSCs, resulted in FLT3-ITD myeloproliferation and associated, marked cell-extrinsic suppression of wild-type competitor HSCs

• FLT3-ITD mice showed disruption of the niche elements (loss of endothelial cells and mesenchymal stem cells)
CONCLUSIONS

• Flt3-ITDs might exert a clonal advantage over normal HSCs by
  - expanding aberrant myeloid-biased multipotent progenitors
  - extrinsic suppression of non-malignant, Flt3-negative HSCs through disruption of the niche
NPM1 AND FLT3-ITD MUTATIONS COOPERATE TO IMPAIR HEMATOPOIETIC STEM/PROGENITOR CELLS DIFFERENTIATION AND DEREGULATE GATA1 IN A MOUSE MODEL OF AML

Abs # 3744

Sportoletti P et al.
(Univ. of Perugia)
BACKGROUND

• NPM1 and FLT3-ITD mutations frequently coexist in human AML

• The molecular and cellular mechanisms of mutation cooperation remain unclear
AIM AND METHODS

• Generation of an AML model using knock-in mouse (crossing NPM1 and FLT3 mutant mice*) to study:

  - Mechanisms of NPM1 and FLT3-ITD mutations cooperation
  - Cellular origin of leukemia
  - Identification of novel molecular targets of NPM1/FLT3-ITD mutations-driven leukemia

*Sportoletti et al., Blood 2013, Lee et al., Cancer Cell 2007
RESULTS (I)

• Concomitant expressions of NPM1 and FLT3-ITD mutant proteins in HSCs led to leukemia development with massive splenomegaly, leukocytosis, anemia and thrombocytopenia

• Pre-leukemic mice displayed a significant reduction of long term HSCs and a significant increase in frequency of multipotent progenitors (MPP)

• CMP and GMP compartments were expanded more than two-fold in NPM1/FLT3-ITD mice while immature megakaryocytic and erythroid compartments were significantly reduced
RESULTS (II)

• Complete loss of GATA1 (master regulator of erythroid and megakaryocytic differentiation) expression in the BM both at the mRNA and protein levels

• In vivo, AC220 induced a reduction of WBC counts accompanied by a partial GATA1 re-expression

• Further studies to investigate the mechanism of GATA1 deregulation are ongoing
A PHASE I STUDY OF AG-221, A FIRST IN CLASS, POTENT INHIBITOR OF THE IDH2-MUTANT PROTEIN, IN PATIENTS WITH IDH2 MUTANT POSITIVE ADVANCED HEMATOLOGIC MALIGNANCIES

Late Breaking Abst
#3416

Agresta S et al.
BACKGROUND

- Somatic point mutations in the metabolic enzymes IDH1/2 confer a novel gain-of-function in cancer cells resulting in accumulation and secretion of the onco-metabolite 2-HG

- AG-221 is an oral, potent, reversible, and selective inhibitor of mutated IDH2 protein which demonstrated a survival benefit in a primary human AML xenograft model and reduced 2-HG levels
AIMS

• First phase I study of oral AG-221 in humans to evaluate safety, pharmacokinetics, pharmacodynamics (including 2-HG levels) and clinical activity

• AG-221 administered orally once or twice per day in continuous 28-day cycles
RESULTS

- Therapy has been well tolerated with no dose-limiting toxicities
- 10 AML patients were treated: (N=5 at 30 mg BID, N=5 at 50 mg BID), median age of 62.5 years. 8 pts had an R140Q mutation, 2 had a R172K mutation.
- Median number of prior regimens was 2
- Efficacy data in the 2 cohorts:

<table>
<thead>
<tr>
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<th>30 mg BID N=5</th>
<th>50 mg BID N=5</th>
<th>Total N=10</th>
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<tbody>
<tr>
<td>CR</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CRp</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NE</td>
<td>3</td>
<td>-</td>
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<tr>
<td><strong>Overall Response Rate</strong></td>
<td><strong>2/2</strong></td>
<td><strong>4/5</strong></td>
<td><strong>6/7</strong></td>
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</table>
CONCLUSIONS

• AG-221 is well tolerated and leads to objective responses in AML pts including complete remissions

• Mutant IDH2 is a valid therapeutic target in cancer
SOME OPEN ISSUES

• Aza in front-line therapy of elderly AML:
  
  Is Aza to be further explored in this subset?  
  Which pt subgroups are more likely to benefit?  
  Which combinatorial strategies?

• Is there a role for ATRA in \textit{NPM1}c AML?

• Is IDH2 inhibition a valid therapeutic approach in AML?