ASH 2012
Update on ACUTE LEUKEMIA

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- Acute Lymphoblastic Leukemia
  - New Antibodies and other tidbits
- Acute Promyelocytic Leukemia
  - Do we need maintenance therapy after all?
- Acute Myeloid Leukemia
  - More on use of high dose ara-C
  - Rising from the ‘ASHes’? Gemtuzumab
  - ATRA beyond APL
  - Novel therapies
Acute Lymphoblastic Leukemia

Acute Lymphoblastic Leukemia: 4 Treatment Subgroups

- Younger (< age 40) Ph-negative
  - Pediatric-Like therapy (lots of non-myelosuppressive chemo)

- Older (>40) Ph-negative
  - Larson/CALGB (5-drug) or HyperCVAD f/b alloSCT

- Younger (< age 55) Ph+
  - Larson or HyperCVAD plus TKI f/b alloSCT

- Older (> 55 yo) Ph+
  - Steroids plus dasatinib plus minimal chemo (Foa et al Blood 2011)
What can we add to make things better?

- **T-cell**: nelarabine (in development, US Intergroup)
- **B-cell**: specific Ab
  - Rituximab for the 40% CD20+ (Thomas JCO 2010)
  - Anti-CD19 biTE (Abstract 252)
  - Anti-CD22 epratuzumab (Abstract 573)
  - Anti-CD22 toxin conjugate inotuzumab ozogamycin (Abstract 875)
MT103-206 Dosing Schedule

- Repeated 4 week cycles continuous intravenous infusion with a 2-week treatment-free interval between cycles
- Consolidation after CR/CRh* within the first two treatment cycles
  - Three additional cycles of blinatumomab
  - Allogeneic HSCT

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Initial Dose Week 1, Cycle 1</th>
<th>Dose Week 2, Cycle 1</th>
<th>Dose Week 3-4, Cycle 1</th>
<th>Subsequent Cycles – Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 µg/m²/d</td>
<td>15 µg/m²/d</td>
<td>15 µg/m²/d</td>
<td>15 µg/m²/d</td>
</tr>
<tr>
<td>2a</td>
<td>5 µg/m²/d</td>
<td>15 µg/m²/d</td>
<td>15 µg/m²/d</td>
<td>15 µg/m²/d</td>
</tr>
<tr>
<td>2b</td>
<td>5 µg/m²/d</td>
<td>15 µg/m²/d</td>
<td>30 µg/m²/d</td>
<td>30 µg/m²/d</td>
</tr>
<tr>
<td>3</td>
<td>Decision about dosing after completion of cohort 1 and 2 a/b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRh*: CR with only partial hematologic recovery: ≤5% blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, partial recovery of peripheral blood counts.

Blinatumomab in CD19+ ALL

- 12/18 CR (67%)
  - 75% heme recovery
  - 100% responders achieved MRD
- Fever/chills most common AE
- Reversible CNS events in 4 pts
- Need low dose during first week due to cytokine release when tumor burden lowered abruptly

Topp et al, Abstract 252
Inotuzumab: Mechanisms of Action

• The antibody-antigen complex is rapidly internalized upon binding to CD22
• Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
• Calicheamicin binds to DNA, inducing double-stranded DNA breaks
• Development of DNA breaks is followed by apoptosis of the tumor cell

Inotuzumab: Background

• CD22 expression in more than 90% of ALL
• Inotuzumab produces high response rate in refractory lymphoma
• Phase II dose 1.8 g/m² IV Q 3-4 weeks
• DLT - thrombocytopenia
Inotuzumab in ALL: Design

- Inotuzumab 1.3 mg/m² in first 3 and 3 pediatric patients; 1.8 mg/m² in others; repeat Q 3-4 wks
  - Pts with refractory ALL and CD22+ by flow cytometry
- If stable or no response post 2 courses:
  - add rituximab 375 mg/m² D1 (Inotuzumab D2)
- Responding patients continue for up to 8 cycles

O'Brien et al, abstract 875

Inotuzumab in ALL. Response (N=49)

<table>
<thead>
<tr>
<th>Response</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>9 (18)</td>
</tr>
<tr>
<td>CRp</td>
<td>14 (29)</td>
</tr>
<tr>
<td>CRi (marrow CR)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>19 (39)</td>
</tr>
<tr>
<td>Death &lt; 4 wks</td>
<td>2 (4)</td>
</tr>
<tr>
<td>OR: 9 CR + 14 CRp + 5 CRi</td>
<td>28 (57)</td>
</tr>
</tbody>
</table>

Better than historical MDA data base

O'Brien et al, abstract 875
Inotuzumab in ALL: Conclusions

- Overall response rate 57%
  - Very high response rate for single agent therapy (incl cytog and MRD responses)
- Correlation of response with drug plasma levels
- Toxicities: thrombocytopenia; LFT
- Plans: weekly schedule, combination with chemotherapy underway

O’Brien et al, abstract 875
Background - Bortezomib for ALL

- Bortezomib may be a new agent for B-cell ALL.

- Preclinical
  - Bortezomib active in Pediatric Preclinical Testing Program. 
  - Bortezomib synergistic with dexamethasone.
  - Bortezomib additive with vincristine, asparaginase, doxorubicin or cytarabine. 

- Clinical
  - Bortezomib - no single agent activity in ALL in phase I trial. 
  - Bortezomib + dexamethasone induce transient response in a child with refractory multiply relapsed ALL. 

Treatment in 22 relapsed pedi-ALL pts

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>11</th>
<th>14</th>
<th>15</th>
<th>18</th>
<th>22</th>
<th>29</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>Bortezomib (1.3 mg/m²)</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vincristine (1.5 mg/m²)</td>
<td>V</td>
<td></td>
<td>V</td>
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<td>V</td>
<td></td>
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<tr>
<td>Doxorubicin (60 mg/m²)</td>
<td>Dox</td>
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<tr>
<td>Dexamethasone (10 mg/m²)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Pegasparginase (2500 U/m²)</td>
<td>PEG</td>
<td>PEG</td>
<td></td>
<td></td>
<td>PEG</td>
<td>PEG</td>
<td></td>
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<tr>
<td>Intrathecal (IT) Ara-C</td>
<td>ITA</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CNS Negative: IT Methotrexate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ITM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Positive: IT Triples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ITT</td>
<td>ITT</td>
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</table>

Evaluation

Messinger et al, abst 251
### T2005-003 Phase II Response

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>B-cell</th>
<th>T-cell</th>
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<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>CR</td>
<td>14 (64%)</td>
<td>14 (70%)</td>
<td>0</td>
</tr>
<tr>
<td>CRp</td>
<td>2 (9%)</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>SD/PD</td>
<td>2 (9%)</td>
<td>0</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (14%)</td>
<td>3 (15%)</td>
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</tr>
<tr>
<td>Unknown</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Benchmark TACL remission rate - 3rd & 4th attempt - 44% & 27% (Ko, J Clin Oncol, 2010)

Messinger et al, abst 251

### Is Bortezomib Worth Evaluating?

1. **Bortezomib + Vincristine, Dexamethasone, Pegasparaginase and Doxorubicin** - sufficiently efficacious (14/22 CR) per study design - allowing early closure.

2. High response rate: 64% CR + 9% CRp better than TACL historical data for similar patients (27% - 44%).

3. Significant activity in B-cell ALL: 70% CR + 10% CRp; 85% bone marrow response.

4. Some Gr 3 peripheral neuropathy
Acute Promyelocytic Leukemia: many ways to get to >80% LT DFS

- US Intergroup: 4+7 +ATRA in'dn f/b 2 cycles of ATO; f/b 2 cycles dauno/ATRA; f/b maintenance for 1 year (Powell Blood 2010)

- PETHEMA: ida/ATRA in'dn; fb ATRA /anthracyline x 3; f/b maint (Sanz Blood 2009)

- French: ida/Ara in'dn; f/b ara-C in consol f/b maint (Ades, Blood 2008)

- No chemo: ATRA/ATO with GO for high WBC (Ravandi JCO 2009)
US Intergroup Randomized Trial

**Induction**
ATRA d1 – CR
DNR + Ara-C (7+3)

**Consolidation**
ATRA + DNR

**Maintenance**
6-MP/MTX
ATRA

**Maintenance**
ATRA

*2 cycles of TRISENOX*® (arsenic trioxide), 25 doses


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**CALGB 9710: DFS by RX and WBC**

![Graph showing DFS by RX and WBC](image)

- **Arsenic**
  - WBC < 10K
  - WBC > 10K

- **No Arsenic**
  - WBC < 10K
  - WBC > 10K

\[ P = 0.0016, \text{HR} \ 2.24 \]

Acute Promyelocytic Leukemia: Is Maintenance Therapy Needed?

- US Intergroup: 4+7 + ATRA induction followed by 2 cycles of ATO; followed by 2 cycles dauno/ATRA; followed by maintenance for 1 year (Powell Blood 2010)
  - Maintenance randomization (for one year) to:
    - ATRA 45 mg/m2/d x 7 every other week
    - Or
    - ATRA 45 mg/m2/d x 7d every other week plus 6MP 60 mg/m2/day plus MTX 20 mg/m2 weekly

Disease-Free Survival (DFS)

<table>
<thead>
<tr>
<th></th>
<th>ATRA</th>
<th>ATRA + Chemo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS events</td>
<td>41/166</td>
<td>30/162</td>
<td>0.134</td>
</tr>
<tr>
<td>DFS events</td>
<td>31/82</td>
<td>26/84</td>
<td>0.191</td>
</tr>
<tr>
<td>(by consolidation)</td>
<td>10/84</td>
<td>4/78</td>
<td>0.128</td>
</tr>
<tr>
<td>Low/Int*</td>
<td>25/128</td>
<td>19/131</td>
<td>0.195</td>
</tr>
<tr>
<td>(by risk group)</td>
<td>16/38</td>
<td>11/31</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Low/Int: WBC ≤ 10,000; High: WBC > 10,000

Powell et al., Abstract 258
### Overall Survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>ATRA</th>
<th>ATRA + Chemo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events</td>
<td>22/166</td>
<td>16/165</td>
<td>0.329</td>
</tr>
<tr>
<td>OS events no ATO</td>
<td>14/82</td>
<td>13/84</td>
<td>0.723</td>
</tr>
<tr>
<td>(by consolidation) ATO</td>
<td>8/84</td>
<td>3/81</td>
<td>0.150</td>
</tr>
<tr>
<td>OS events Low/Int*</td>
<td>14/128</td>
<td>9/134</td>
<td>0.198</td>
</tr>
<tr>
<td>(by risk group)   High*</td>
<td>8/38</td>
<td>7/31</td>
<td>0.731</td>
</tr>
</tbody>
</table>

*Low/Int: WBC ≤ 10,000; High: WBC > 10,000

Powell et al., Abstract 258

### DFS and OS – Initial 50 Patients

<table>
<thead>
<tr>
<th>Observation</th>
<th>ATRA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS a</td>
<td>8/23</td>
<td>7/23</td>
</tr>
<tr>
<td>OS b</td>
<td>4/24</td>
<td>7/26</td>
</tr>
</tbody>
</table>

a. 2, 3, and 5 year DFS similar, p ≥ 0.472
b. 2, 3, and 5 year OS similar, p ≥ 0.336

Powell et al., Abstract 258
Maintenance Rx in APL: Conclusions

- The addition of methotrexate and mercaptopurine to ATRA maintenance did not improve DFS or OS in patients with APL in first CR
  - DFS at 2, 3, and 5 year may be improved in patients on the non ATO consolidation arm
  - there is no suggestion of benefit for patients on the ATO arm

- In a small group of 50 patients ATRA maintenance was not superior to observation

- The addition of ATO consolidation remains the most important determinant of DFS and OS in this trial

Powell et al., Abstract 258

Acute Myelogenous Leukemia
Acute Myeloid Leukemia

- **Younger (age <60)**
  - Induction: dauno 60-90 mg/m² x 3d plus ara-C 100-200 mg/m²/d x 7 d IVCI, reinduction if needed
  - Consolidation: CALGB high dose ara-C x 3-4 cycles OR allo SCT from Sibling or MUD; alloSCT preferred in all except CBF and CN-NPM1+/FLT3-

- **Older (age ≥ 60)**
  - Induction: dauno 60-90 mg/m² x 3d plus ara-C 100-200 mg/m²/d x 7 d IVCI, reinduction as needed, OR
    - low-intensity rx in unfit/unwilling/not likely to benefit (e.g. decitabine/LDAC/clofarabine)
  - Consolidation: modified high dose ara-C, or repeat induction (or other?) OR RIC allo SCT
AML: What Can we Add to Induction to Improve Outcomes?

- High dose ara-C
- Gemtuzumab Ozogamycin
- All-trans retinoic acid
- Histone deacetylase inhibitor
  - SAHA (Vorinostat)+IA (Garcia-Manero et al, abstract 763 - 85% CR/CRp upfront better than historical IA); Future Intergroup randomized trial of IAS v IA v 3+7 planned
  - Panibinostat+MEC (Schlenck et al abst-423 - 55% CR in rel/refr)
- Disrupt leukemic cell in protected niche: CXCR4 inhibition+3+7 (Uy et al, abstract 82 - 67% CR in upfront AML)

AML: Use of High Dose ara-C

- Standard in the US for post-CR non-tx therapy based on CALGB 8525 (Mayer et al, NEJM 1994)
  - 3 gm/m² over 3h q12 h on d1,3,5 x 3-4 cycles
- Can HIDAC be used in induction (instead)?
  - SWOG (Weick et al. Blood 1996) and HOVON (Lowenberg et al., NEJM 2011) studies suggested no
  - Willemze et al, abstract 257, suggests yes, but most of these pts received auto- or allo SCT
**EORTC-GIMEMA AML-12 trial**

First randomization: AraC dose: age <61 (n=1942)

- SD-AraC (100 mg/m² c.i. D 1-10)
- HD-AraC (3 g/m²/12 hrs i.v. D 1, 3, 5, 7)

Dauno : 50 mg/m² i.v. D 1,3,5
Etoposide : 50 mg/m² i.v. D 1-5

SD-AraC vs HD-AraC (3 g/m²/12 hrs i.v. D 1, 3, 5, 7)

Dauno : 50 mg/m² i.v. D 4-6
ID-AraC : 500 mg/m²/12 hrs i.v. D 1-6
IL2 : 4 x 10⁶ IU/m² s.c. D1 + 8 x 10⁶ IU/m² s.c. D2-D5, every 4 weeks, for 1 year

---

**Induction started**

- SD AraC N=969
- HD AraC N=973

<table>
<thead>
<tr>
<th></th>
<th>SD AraC</th>
<th>HD AraC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR after 1 cycle</td>
<td>648 (68.1%)</td>
<td>714 (75.5%)</td>
</tr>
<tr>
<td>Overall CR</td>
<td>684 (71.9%)</td>
<td>746 (78.7%)</td>
</tr>
<tr>
<td>Age &lt; 46 yrs</td>
<td>366 / 484 (75.6%)</td>
<td>399 / 483 (82.6%)</td>
</tr>
<tr>
<td>Age 46-60 yrs</td>
<td>318 / 468 (67.9%)</td>
<td>347 / 465 (74.6%)</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>173 (18.2%)</td>
<td>123 (13.0%)</td>
</tr>
<tr>
<td>Death in Induction</td>
<td>85 (8.9%)</td>
<td>71 (7.5%)</td>
</tr>
<tr>
<td>Hypoplasia &gt;12 wks</td>
<td>5 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Inevaluable</td>
<td>4 (0.4%)</td>
<td>8 (0.8%)</td>
</tr>
</tbody>
</table>

**Willemze et al., abstract 257**
Duration of Survival and of DFS according to 1st Randomization

**AML-12: Duration of Survival**

- Logrank test: $p=0.06$
- HR = 0.89 (0.79, 1.00)
- Adjusted by age, PS, WBC, cytogenetics

**AML-12: DFS from CR**

- Logrank test: $p=0.25$
- HR = 0.92 (0.80, 1.06)

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Duration of Survival/DFS for pts < 46 yrs according to 1st Rand.

**AML-12: Duration of Survival**

- Logrank test: $p=0.009$
- HR = 0.79 (0.63, 1.00)

**AML-12: DFS from CR**

- Logrank test: $p=0.07$
- HR = 0.83 (0.64, 1.08)
Duration of Survival/DFS for pts 46-60 yrs according to 1st Rand.

**AML-12: Duration of Survival**
Age 46 - 60 yrs

- HR = 0.99 (0.81, 1.22)
- Logrank test: p = 0.91
- HR adj = 0.97 (0.79, 1.20)
- P adj = 0.72

**AML-12: DFS from CR**
Age 46 - 60 yrs

- HR = 1.02 (0.80, 1.32)
- Logrank test: p = 0.80

**EORTC/GIMEMA AML-12 trial**
Summary of treatment comparison

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All patients</th>
<th>Age &lt; 46 yrs</th>
<th>Age 46-60 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDAraC</td>
<td>HD AraC</td>
<td>SDAraC</td>
</tr>
<tr>
<td>OS: 6-yr rate</td>
<td>38.7%</td>
<td>42.5%</td>
<td>43.4%</td>
</tr>
<tr>
<td>HR</td>
<td>0.89</td>
<td>0.79</td>
<td>0.99</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.06</td>
<td>0.009</td>
<td>0.91</td>
</tr>
<tr>
<td>DFS: 6-yr rate</td>
<td>41.5%</td>
<td>44.7%</td>
<td>46.4%</td>
</tr>
<tr>
<td>HR</td>
<td>0.92</td>
<td>0.83</td>
<td>1.02</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.25</td>
<td>0.07</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Logrank test

Willemze et al., abstract 257
AML-12 trial (Age<46 yrs)
Overall Survival by Cytogenetic Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>N=304</th>
<th>N=135</th>
<th>N=319</th>
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<tbody>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Risk</td>
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<td></td>
</tr>
<tr>
<td>NN, Y</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- HR=0.73, P=0.04
- HR=0.70, P=0.02
- HR=0.73, P=0.05

AML-12 trial (Age<46 yrs)
Overall Survival by Cytogenetic Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>N=146</th>
<th>N=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Poor</td>
<td></td>
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</tr>
</tbody>
</table>

- HR=0.95, P=0.80
- HR=0.84, P=0.51
- HR=0.84, P=0.51
EORTC-GIMEMA AML-12 trial
Conclusions

EORTC-GIMEMA (AML-12):
SD- vs. HD AraC in the induction treatment shows,
with a median follow-up of 6 years, that the use of HD-
AraC leads to:

1. Significantly higher CR rate (78.7% vs 71.9%, p<0.001)
for all AML-patients, age 15-60 years, without increased
 treatment related mortality

2. An improvement of overall survival rate at 6 years
   - overall population : +3.8% (42.5% vs 38.7%, p=0.06)
   - patients < 46 years: +8.5% (51.9% vs 43.4%, p=0.009)

3. How does this compare with the current use of high-
dose daunorubicin (90 mg/m2)?

Willemze et al., abstract 257

Gemtuzumab Ozogamycin: CD33 Ab-toxin
(calicheamycin) Conjugate

- Approved in 2001 based on 30% CR+CRp rate in
relapsed AML (half were CRp) (9mg/m2 days1 and 14)

- Withdrawn in 2010 since ‘confirmatory’ (SWOG 0106)
study failed to show benefit for addition of GO to
induction chemo. Known marrow and liver toxicity

- 3 abstracts at ASH, including one plenary talk,
suggested re-visitation needed for GO plus chemo
### ALFA 0701: Treatment arms

**Randomization:** untreated AML 50-70

**Arm A:**
- DNR 60 mg/m² D1 to D3
- AraC 200 mg/m² D1 to D7

**Arm B:**
- DNR 60 mg/m² D1 to D3
- AraC 200 mg/m² D1 to D7
- GO 3 mg/m² D1, D4, D7

**2nd course if BM blasts >10% at D15**
- DNR 60 mg/m² D1, D2
- AraC 1g/m²/12h D1 to D3

**CR or CRp**

**1st CONSOLIDATION**
- DNR 60 mg/m² D1
- AraC 1g/m²/12h D1 to D4
- GO 3 mg/m² D1

**2nd CONSOLIDATION**
- DNR 60 mg/m² D1
- AraC 1g/m²/12h D1 à D4
- GO 3 mg/m² D1

---

### ALFA 0701: Event-free Survival

**EFS A (control) (n=139)**
- Events: 104
- Median: 11.9 mo
- 2-year: 16.5%
- HR (95% CI): 1 (0.42-0.77)

**B (GO) (n=139)**
- Events: 76
- Median: 19.6 mo
- 2-year: 41.1%
- HR (95% CI): 0.57 (0.27-0.77)

**P = 0.00018** by the log-rank test

Though CR (75 v 81%), ED (4 v 6.5%) rate not different

---

Castaigne et al, abstract 6
**ALFA 0701: Overall Survival**

![Graph showing overall survival for ALFA 0701 study with control and GO arms.]

<table>
<thead>
<tr>
<th></th>
<th>OS A (control)</th>
<th>B (GO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=139)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>71</td>
<td>59</td>
</tr>
<tr>
<td>Median</td>
<td>19.2 mo</td>
<td>34 mo</td>
</tr>
<tr>
<td>2-year</td>
<td>43.5%</td>
<td>53.1%</td>
</tr>
<tr>
<td>HR</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.50-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

P= 0.046 by the log-rank test

*Castaigne et al., abstract 6*

**OS According to Cytogenetics Risk-Groups**

<table>
<thead>
<tr>
<th>Cytogenetics Risk-Groups</th>
<th>Control arm</th>
<th>GO arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable/intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prolonged thrombocytopenia and rare episodes of VOD were the main GO toxicities.*

*Castaigne et al., abstract 6*
GO plus Induction Chemotherapy: Now What?

- ALFA 0701 suggests benefit in age 50-70

- MRC 15 trial (Burnett et al, JCO 2011) suggested benefit in most younger pts and MRC 16 trial in 1115 pts ages 51-84 (Burnett et al, abstract 582) of chemo (3+7 or 3+clofarabine) +/- 3mg/m² on d1
  - Relapses reduced: 61 v 70%-p=0.004, 2 yr OS improved: 35 v 29%- p=0.04

- GOELAMS AML 2006 IR (n-253, age 18-60, int risk, Delaunay et al, abstract 79)
  - No benefit to GO 6 mg/m² plus ind’n, and consol f/b allo, improved EFS benefit in non-transplanted pt

Randomized Trials Using ATRA in Non-APL AML - Schedule

<table>
<thead>
<tr>
<th></th>
<th>chemo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Estey MDACC ATRA</td>
<td>Fludara/Ara-C/Ida</td>
<td></td>
</tr>
<tr>
<td>Burnett MRC</td>
<td>Dauno/Ara-C/Thioguanine</td>
<td></td>
</tr>
<tr>
<td>Schlenk AMLSG (AMLHD98B)</td>
<td>Ida/Ara-C/Etoposide</td>
<td>Pos in NPM1 mut/FLT3 WT</td>
</tr>
<tr>
<td>Schlenk AMLSG (07-04)</td>
<td>Ida/Ara-C/Etoposide</td>
<td>Abstract 80</td>
</tr>
<tr>
<td>Schlenk et al, abstract 80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MRC AML-12 Trial: Evaluation of ATRA in AML within a 2x2x2x2 Factorial Design

---

**Design: AMLSG 07-04**

**Recruitment:** Between 2004-2006

- **N=374**
- **N=738**
- **N=1112**

**Induction x2**
- ICE
- ICE + ATRA*
- ICE + VPA
- ICE + ATRA*/VPA

**Consolidation x3**
- HiDAC
- HiDAC + ATRA*
- HiDAC + VPA
- HiDAC + ATRA*/VPA

**Genetic Profiling**

- ICE: idarubicin 12mg/m², day 1,3,5 (in induction II reduced to d 1, 3); cytarabine 100mg/m² continuous i.v., day 1 to 7; etoposide 100mg/m², day 1-3; *ATRA 45mg/m², day 6 to 8, and 15mg/m², day 9 to 21
- HiDAC: 3g/m² bid day 1,3,5 or 1,2,3; *ATRA 15mg/m², day 6 to 28

---

**Schlenk et al, abstract 80**

---
Response to Induction Therapy

*per protocol*

<table>
<thead>
<tr>
<th></th>
<th>NPM1-wt</th>
<th>ATRA</th>
<th>NPM1-mut</th>
<th>ATRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ATRA</td>
<td>Control</td>
<td>ATRA</td>
</tr>
<tr>
<td>CR</td>
<td>n=351</td>
<td>n=345</td>
<td>n=141</td>
<td>n=142</td>
</tr>
<tr>
<td></td>
<td>69.5%</td>
<td>69%</td>
<td>84%</td>
<td>90%</td>
</tr>
<tr>
<td>RD</td>
<td>24.5%</td>
<td>27%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>ED</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**multivariable**

<table>
<thead>
<tr>
<th></th>
<th>NPM1-wt</th>
<th>OR</th>
<th>p-value</th>
<th>NPM1-mut</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>OR-wt</td>
<td>1.09</td>
<td>0.66</td>
<td>2.29</td>
<td>0.05</td>
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</tr>
<tr>
<td>FLT3-ITD</td>
<td>0.62</td>
<td>0.12</td>
<td>0.70</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s/t-AML</td>
<td>0.53</td>
<td>0.03</td>
<td>0.32</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log10(WBC)</td>
<td>0.65</td>
<td>0.04</td>
<td>1.90</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>0.99</td>
<td>0.31</td>
<td>0.98</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.66</td>
<td>0.05</td>
<td>1.03</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse</td>
<td>0.44</td>
<td>0.0006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>favorable</td>
<td>3.24</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schlenk et al, abstract 80

Primary Endpoint: Event-free Survival

*Allo-HSCT in 1st CR censored - as treated*

Median follow up for survival
3.55 years
Event free Survival - Multivariable – *per protocol*

<table>
<thead>
<tr>
<th></th>
<th>NPM1-wt</th>
<th></th>
<th>NPM1-mut</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p-value</td>
<td>HR</td>
<td>p-value</td>
</tr>
<tr>
<td>ATRA</td>
<td>1.06</td>
<td>0.56</td>
<td>0.66</td>
<td>0.03</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>1.53</td>
<td>0.02</td>
<td>1.60</td>
<td>0.03</td>
</tr>
<tr>
<td>IDH1&lt;sup&gt;R132&lt;/sup&gt;</td>
<td>1.13</td>
<td>0.66</td>
<td>1.72</td>
<td>0.04</td>
</tr>
<tr>
<td>IDH2&lt;sup&gt;R140&lt;/sup&gt;</td>
<td>0.81</td>
<td>0.48</td>
<td>1.69</td>
<td>0.04</td>
</tr>
<tr>
<td>IDH2&lt;sup&gt;R172&lt;/sup&gt;</td>
<td>1.59</td>
<td>0.11</td>
<td>1.69</td>
<td>0.04</td>
</tr>
<tr>
<td>s/t-AML</td>
<td>1.25</td>
<td>0.12</td>
<td>1.93</td>
<td>0.07</td>
</tr>
<tr>
<td>log&lt;sub&gt;10&lt;/sub&gt;(WBC)</td>
<td>1.08</td>
<td>0.46</td>
<td>1.42</td>
<td>0.05</td>
</tr>
<tr>
<td>Age in years</td>
<td>1.00</td>
<td>0.38</td>
<td>1.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.37</td>
<td>0.002</td>
<td>1.33</td>
<td>0.12</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse</td>
<td>2.28</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>favorable</td>
<td>0.33</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schlenk et al, abstract 80

Secondary Endpoint: Overall Survival

*as treated*

Schlenk et al, abstract 80
AML : Other New Therapies

- CPX 351
- Hedgehog pathway inhibition
- New FLT3 inhibitors (pre-clin PLX3397) (Smith et al, abst 764)
- Tosedostat-amino acid de prv er (Cortes et al, abst 767 - 22% RR in advanced pts)
- mTor inhibition plus chemo (Park et al, abst 845)
- Immunotherapy (non-transplant)
  - Dendritic cell-AML cell fusion vaccine (Rosenblatt et al, abst 948)
  - Tumor-primed NK cell therapy (Kottaridid et al, abst 946)

CPX-351

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
CPX-351 Prior Studies

◆ CPX-351 Phase I Study¹
  – MTD: 101 u/m² on days 1, 3 and 5
  – DLT: Hypertensive crisis, cardiomyopathy, prolonged cytopenia
  – 10/43 (23%) CR/CRp in advanced AML
  – Prolonged exposure to 5:1 ratio documented:
    • t₁/₂ = Cytarabine 31.1 h, Daunorubicin 21.9 h
    • Drug detectable 7 days after last dose
    • 5:1 molar ratio maintained for >24 hours

◆ Study 204: Randomized Phase 2 Study²
  – Newly Diagnosed AML, age 60 to 75 years
  – CPX-351 vs. “7+3”
  – CR + CRi: 56 (67%) vs. 21 (51%) p=0.0712*
  – 60 Day Mortality: 4 (4.7%) vs. 6 (14.6%) p=0.053

* Met protocol specified criteria for success p ≤ 0.1 (one-sided Fisher’s Exact test)

² Lancet et al. ASH Annual Meeting Abstracts, Nov 2010; 116:655

CPX-351 Study 205 - 1st Salvage Study Design

Eligibility
  ◆ Initial CR ≥ 1mo.
  ◆ Ages 18-65
  ◆ Stratified by EPI*
  ◆ PS 0-2

CPX-351 (n=81)
  100 units/m² IV days 1, 3, 5
  Up to 2 inductions and 2 consolidations

Investigator’s Choice (n=44)
  • MEC (n=23)
  • 7+3 (n=7)
  • Other (n=14)

* European Prognostic Index (EPI; Breems, D.A. et al, 2005)
CPX-351 Study 205 - 1st Salvage
Response to Therapy

Cortes et al, abstract 254

<table>
<thead>
<tr>
<th></th>
<th>CPX-351</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=81</td>
<td>n=44</td>
<td></td>
</tr>
<tr>
<td>&lt;5% blasts D14-21</td>
<td>58 / 75* (77)</td>
<td>25 / 42* (60)</td>
</tr>
<tr>
<td>CR+CRi</td>
<td>41 (51)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>CR</td>
<td>31 (38)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>CRi</td>
<td>10 (12)</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Unfavorable EPI pts did better with CPX (41 v 27%); no ED differences
(16 % 60d mortality in each arm); slower heme recov

* (6) CPX-351 pts and (2) Control pts did not have a d14-21 bone marrow performed

CPX-351 Study 205 - 1st Salvage
OS by EPI Risk Group

Unfavorable  Favorable & Intermediate

<table>
<thead>
<tr>
<th></th>
<th>CPX-351: EPI unfav.</th>
<th>Median (mos.)</th>
<th>Standard: EPI unfav.</th>
<th>Median (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6 (5.4,10.2)</td>
<td>4.2 (2.8,5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR= 0.55, p=0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cortes et al, abstract 254
**Hedgehog Inhibitors**

- **PF-04449913** is a novel oral small molecule inhibitor of the Hedgehog pathway
  - Blocks SMO in preclinical in vitro models at nanomolar concentrations in multiple cell-based assays
  - Potent in vivo inhibition of the pathway observed in hematologic and solid tumor models with no inhibition of normal stem cells

- **First-in-patient study** of PF-04449913 administered as single agent to patients with select hematologic malignancies
  - Open label, multi-national, multi-center, dose escalation, Phase 1 study (n=35)
  - 3 + 3 design
  - PF-04449913 administered continuously once daily for 28-day cycles (Cycle 1 also had a single lead-in dose)

---

Acute Leukemia-ASH update: Conclusions

- Antibodies (esp. BiTE and inotuzumab) will be added to chemo in ALL
- Maintenance chemo is irrelevant in APL in the Arsenic era. What about ATRA?
- Will GO (lower dose) be resurrected and become the SOC in chemo-receiving older adults?
- Will ATRA plus chemo be the new standard in NPM1 mut/FLT3 WT AML?

Acute Leukemia-ASH update: Acknowledgements

- The DFCI Leukemia and Transplant teams, DF/HCC collaborators (esp. Stone, Abel, Motyckova, Steensma, Wadleigh; Buchanan, Cahill, Galinsky, Penicaud)
- Investigators around the world who sent slides (Cortes, Willemze, Raetz, O’Brien, Delauany, Schlenk, Garcia-Manero, Castaigne, Messinger, Powell, Jamieson)
- Patients and their families who participated in these clinical trials
The End