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Chicago, IL
ASCO 2009

- Acute Myeloid Leukemia (*Abs* 7000, 7002, 7003, 7015)
- Chronic Myeloid Leukemia (*Abs* 7007)
- Myelodysplastic Syndromes (*Abs* 7010, 7011)
- Chronic Lymphocytic Leukemia (*Abs* 7043, 7044)
Acute Myeloid Leukemia

ASCO 2009
PROGNOSIS IN AML

• Traditionally has relied on cytogenetics, WBC, age, response to therapy

• Cytogenetics most powerful

• However, 40-50% of patients have normal karyotype at diagnosis

• New molecular markers beginning to define new prognostic subgroups
A schematic diagram of the FLT3 receptor tyrosine kinase showing the location of the internal tandem duplication of genes within the juxtamembrane domain and point mutations and gene insertions in the second kinase domain. Illustration by Kenneth Probst. From Litzow, MR. Blood 106:3331, 2005.
Cytoplasmic Nucleophosmin in Acute Myelogenous Leukemia with a Normal Karyotype

• Mutations in exon 12 of NPM1 seen in 50% of normal karyotype AML and are a favorable prognostic factor in AML if FLT3 neg

• Dutch and German studies in Blood confirm favorable prognosis of mutant NPM if FLT3 negative

NEJM 352:254-266, January, 2005
NPM1 gene above
Shuttling mechanism of NPM1 protein below
Model of leukemogenesis with two cooperating classes of mutations

Dohner, Hematology 2007;2007:509-520
NPM1 mutations as an independent prognosticator for older cytogenetically normal acute myeloid leukemia (CN AML).

**ABSTRACT 7000**

**• Background:** In young CN, FLT3-patients NPM1 mutations have better outcomes. What about older patients?

**• Methods:** NPM1 mutation analysis at baseline in 189 older (>60)
  • ARA-C/DNM Induction (7day)
  • 2 different consolidation schedules on CALGB 9720 and 10201

Becker et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7000)
<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>RFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>P</td>
<td>HR**</td>
</tr>
<tr>
<td>NPM1, mutated v wild type</td>
<td>10.1</td>
<td>&lt;0.0001</td>
<td>0.36</td>
</tr>
<tr>
<td>FLT3-ITD, ITD v No ITD</td>
<td>-</td>
<td>-</td>
<td>1.86</td>
</tr>
<tr>
<td>WBC [10^9/L], each 50 unit increase</td>
<td>0.47</td>
<td>0.002</td>
<td>1.82</td>
</tr>
<tr>
<td>Platelets [10^9/L], each 50 unit increase</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Race, white v non-white</td>
<td>-</td>
<td>-</td>
<td>2.52</td>
</tr>
</tbody>
</table>

CR Rate: Mutated (54% of pts) 85%, unmated 45% (p<0.0001)
RFS: 23% vs 10% (P=0.02)
OS: at 3 years 34% vs 7%

NB: NPM1 rare in sAML (15%). High HOX expression decreased Bcl-2

Becker et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7000)
Improving the molecular risk classification for younger (<60 years) de novo cytogenetically normal acute myeloid leukemia (CN AML) patients (pts).

ABSTRACT 7002

• Background: Young CN Patients

• Low risk (FLT3-/ NPM1 Mut)

• High risk (FLT3 + or NPM1 WT)
  • New Factors
    • Low ERG and CEBPA mut (with above Risk Groups)
    • WT 1 Mut poor regardless of FLT3 and NPM status

Marcucci et. 21. J Clin Oncol 27:15s, 2009 (suppl; abstr 7002)
Improving the molecular risk classification for younger (<60 years) de novo cytogenetically normal acute myeloid leukemia (CN AML) patients (pts).

**ABSTRACT 7002**

- **Methods:** 143 CN AML (<age 60)
  - FLT3, NPM1, CEBPA, WT1, ERG, BAALC on CALG 9621 and 19808

- 2 risk groups
  - **Group 1 (n=56)**
    - Low Risk plus low ERG
    - High risk plus CEBPA mut
  - **Group 2 (n=870)**
    - WT1 mut patients
    - Low risk plus high ERG
    - High risk plus CEBPAwt

Marcucci et. 21. J Clin Oncol 27:15s, 2009 (suppl; abstr 7002)
### Multivariable analyses for CR, DFS & OS

<table>
<thead>
<tr>
<th>Variables in Final Models</th>
<th>CR</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>P</td>
<td>HR†</td>
</tr>
<tr>
<td>CALGB Group I vs Group II</td>
<td>6.5</td>
<td>.02</td>
<td>0.28</td>
</tr>
<tr>
<td>BAALC (low vs high)</td>
<td>6.6</td>
<td>.008</td>
<td>-</td>
</tr>
<tr>
<td>WBC [10e09/L] (each 50 unit increase)</td>
<td>0.5</td>
<td>.01</td>
<td>-</td>
</tr>
<tr>
<td>Age (each 10 year increase)</td>
<td>0.4</td>
<td>.01</td>
<td>-</td>
</tr>
</tbody>
</table>

**CR Rate:** Group 1 (54% of pts) 96% vs Grp 279% (p=0.005)
DFS at 5 years: 69% vs 21% (P < 0.0001)
OS at 5 years: 70% vs. 31% (p<0.0001)

Marcucci et al. 2l. J Clin Oncol 27:15s, 2009 (suppl; abstr 7002)
Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia (AML).

ABSTRACT 7015

• **Background:** What are the impact of FLT3 mutations on AML patients (non CN)?

• **Methods:** 481 AML Patients
  • Good (t(8;21), INV 16/t(16;16)) (N=65)
  • Int (diploid, -Y) (N=272)
  • Poor (-5, -7, 11q abn) (N=144)
<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>FLT3-All, n (%)</th>
<th>FLT3-ITD, n (%)</th>
<th>FLT3-TKD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Risk</td>
<td>13 (20)</td>
<td>5 (7.6)</td>
<td>11 (17)*</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>87 (32)</td>
<td>67 (25)</td>
<td>28 (10)**</td>
</tr>
<tr>
<td>Poor Risk</td>
<td>11 (7.6)</td>
<td>3 (2)</td>
<td>8 (5.5)</td>
</tr>
</tbody>
</table>

* - 3 pts: double positive; ** - 8 pts: double positive

No difference in OS in good or poor risk groups
Int Med Risk: OS worse in FLT3-ITD 33 vs 89 weeks, p<0.0001)
(not in FLT-3 TKD)
A randomized trial of anthracycline dose intensification during induction of younger patients with acute myeloid leukemia: Results of Eastern Cooperative Oncology Group study E1900.

**ABSTRACT 7003**

- In younger adults (<60 years old) with newly diagnosed AML:
  - Daunorubicin 45mg/m2/day CR rates of 50 -75%
  - Anthracycline dose-intensification during induction may improve CR:
    - SWOG daunorubicin 70mg/m2/d
      - High CR rates in young group
    - CALGB 9621- daunorubicin 90-95mg/m2/d
      - High CR rates/ tolerable toxicity
  - OS improvement not demonstrated in a prospective randomized trial.

Fernandez et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7003)
E1900: Objectives

Primary Objective:

- To compare OS between two induction regimens daunorubicin 45mg/m² vs. 90mg/m²/d
- Evaluate impact pre HSCT GO on DFS

Secondary Objectives:

- Evaluate impact of allogeneic SCT in AML patients with unfavorable prognostic factors

Planned accrual goal: 830 patients

Closed November 2008- 657 patients.
ECOG Protocol E1900: Schema

**Risk Allocation**

**Daunorubicin**
- 45 mg/m²/day x 3
- or
- 90 mg/m²/day x 3
  + Cytarabine 100 mg/m²/day x 7

**High Intermediate**

CR

**Allogeneic HSCT**

**HiDAC x 2; PBSC Harvest after 2nd course**

**Autologous SCT**
- Busulfan IV 0.8 mg/kg
- Every 6 hrs x 16 doses
- Cyclophosphamide 60 mg/kg/d x 2

**Persistent AML:**
- 2nd cycle of
  - Daunorubicin 45 mg/m²/d x 3
  - Cytarabine 100 mg/m²/d x 7

**Gemtuzumab Ozogamicin**
- 6 mg/m² IV x 1

Closed 10/2007
Disposition of Patients

Entered
657

Randomized to 45mg/m²
330

Evaluable for Response
293

Complete Remission
168 (57.3%)

Randomized to 90mg/m²
327

Evaluable for Response
289

Complete Remission
204 (70.6%)
Results: Toxicity

• Induction deaths were similar
  • 45mg/m² : 4.5%;
  • 90mg/m² : 5.5%

• Grade 3/4 toxicity similar

• High-dose daunorubicin arm
  • Cardiac toxicity not increased
    • 0.3 vs 1.6% LVEF% ↓ (p=0.12)
  • Did not impact delivery of HSCT
Post-remission

- Patients allocated to:
  - Allogeneic: Inc WBC, unfavorable, intermediate
  - Autologous: favorable, intermediate
- Recovered from induction toxicity
- 352/657 (53.6%) registered to second step
  - 53.1% transplanted
    - 36 received allogeneic transplant
    - 141 received autologous transplant
OS by Induction-All Patients

Overall Survival by Induction Treatment-All Patients

Log Rank Test p=0.003
OS by Induction: Favorable and Intermediate

Probability

Log Rank Test p=0.004

Months

Induction Treatment  45 mg/m²/day  90 mg/m²/day
TOTAL  180  178
FAIL  95  71
CNSR  85  107
MEDIAN  20.7  34.3
OS by Induction: Unfavorable

Log Rank Test p=0.45

<table>
<thead>
<tr>
<th>Induction Treatment</th>
<th>TOTAL</th>
<th>FAIL</th>
<th>CNSR</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg/m²/day</td>
<td>59</td>
<td>46</td>
<td>13</td>
<td>10.2</td>
</tr>
<tr>
<td>90 mg/m²/day</td>
<td>63</td>
<td>45</td>
<td>18</td>
<td>10.4</td>
</tr>
</tbody>
</table>
OS Daunorubicin 90mg/m²/d: FLT3 Status

Overall Survival by FLT3 at the high dose

Log Rank Test p=0.009

Probabilities by FLT3 status:
- FLT3 ITD Negative: 241 total, 116 failed, 125 censored, median 28.6 months
- FLT3 ITD Positive: 64 total, 39 failed, 25 censored, median 15.2 months

Graph shows the survival probabilities over months for patients with FLT3 ITD negative and positive, with the Log Rank Test indicating a statistically significant difference in survival (p=0.009).
Conclusions

• In AML patients <60 years, induction therapy with daunorubicin 90mg/m²/d:
  • Is safe
  • Improves CR rates: 70.6% vs. 57.3%
  • Improves OS: 23.7 vs. 15.7 mo.
  • 45mg/m²/d is no longer the standard dose
Chronic Myeloid Leukemia

ASCO 2009
IRIS 6 yr Update: EFS and PFS

Estimated rate at 72 months (with 95% CI)

- **PFS (without AP/BC)**: 93% (90-95)
- **EFS (without event)**: 83% (80-86)

AP/BC, accelerated phase blast crisis; EFS, event-free survival; PFS, progression-free survival

IRIS 6 yr Update: Patients on Study / Discontinuations

<table>
<thead>
<tr>
<th>At 6 Years</th>
<th>First-Line Imatinib N = 553</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On imatinib study treatment</strong></td>
<td><strong>66%</strong></td>
</tr>
<tr>
<td>Discontinuation/crossover</td>
<td><strong>34%</strong></td>
</tr>
<tr>
<td>- Side effects/other AEs</td>
<td><strong>5%</strong></td>
</tr>
<tr>
<td>- Deaths (CML – unrelated)</td>
<td><strong>2%</strong></td>
</tr>
<tr>
<td>- Lack of efficacy / progression</td>
<td><strong>14%</strong></td>
</tr>
<tr>
<td>- Withdrawal of consent</td>
<td><strong>6%</strong></td>
</tr>
<tr>
<td>- Other reason (incl. SCT, lost to follow-up)</td>
<td><strong>8%</strong></td>
</tr>
</tbody>
</table>

AE, adverse event; CML, chronic myeloid leukemia; SCT, stem cell transplant

Targeting BCR-ABL in CML

- Imatinib
  - Resistance
  - Increased Imatinib
  - Allo SCT
- Nilotinib
  - Resistance
- Dasatinib
- Bosutinib
  - INNO-406
  - PHA-739358
  - Omacetaxine
  - MK-0457
  - HHT
  - Others
Figure 1. Kaplan–Meier Analysis of Progression-free Survival among Patients with CML or ALL Associated with Dasatinib.

Efficacy of Dasatinib in Patients (pts) with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP)

• **Background:**
  - Dasatinib is effective in imatinib intolerant and most resistant patients

• **Methods:**
  - Untreated CP-CML
    - Dasatinib 100mg/day
    - Dasatinib 50mg 2x/ Day

Cortes et al. Blood 2008;112(11):a182
Dasatinib in Early CP CML
Non-Hematologic Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pl. effusion</td>
<td>4</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>21</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Musc/Skel pain</td>
<td>21</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Neuro</td>
<td>25</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Skin</td>
<td>44</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>29</td>
<td>8</td>
</tr>
</tbody>
</table>

Cortes et al. Blood 2008;112(11):a182
Complete Cytogenetic Response in Early CP CML by Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percent CCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM 400</td>
</tr>
<tr>
<td></td>
<td>N=50</td>
</tr>
<tr>
<td>3 mo</td>
<td>37</td>
</tr>
<tr>
<td>6 mo</td>
<td>54</td>
</tr>
<tr>
<td>12 mo</td>
<td>65</td>
</tr>
<tr>
<td>18 mo</td>
<td>68</td>
</tr>
</tbody>
</table>

* Evaluable: 48 at 3 mo, 43 at 6 mo, 37 at 12 mo, 32 at 18 mo

Cortes et al. Blood 2008;112(11):a182
# Major Molecular Response in Early CP CML by Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percent MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM 400 N=50</td>
</tr>
<tr>
<td>6 mo</td>
<td>0</td>
</tr>
<tr>
<td>12 mo</td>
<td>24</td>
</tr>
<tr>
<td>18 mo</td>
<td>42</td>
</tr>
</tbody>
</table>

* Evaluable: 45 at 6 mo, 36 at 12 mo, 30 at 18 mo

Cortes et al. Blood 2008;112(11):a182
Dasatinib dose-optimization study in chronic phase chronic myeloid leukemia (CML-CP): Three-year follow-up with dasatinib 100 mg once daily and landmark analysis of cytogenetic response and progression-free survival (PFS).

**ABSTRACT 7007**

• **Background:** what is optimal dose of dasatinib in CML-CP

• **Methods:** Randomized 2x2 design
  - 100 qd (n=167)
  - 140 qd (n=167)
  - 70 bid (n=168)
  - 50 bid (n=168)

Stone et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7007)
- 24 Months of follow up
- PFS
  - 80% (100mg QD)
  - 75-76% (other arms)
- OS similar across arms
- Lowest rates of toxicity in 100mg QD
  - Pleural effusion (P=0.049)
  - Cytopenias (p=0.003)
  - Lowest rates treatment reduction and interruption

Stone et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7007)
Myelodysplastic Syndromes

ASCO 2009
Natural History of MDS

Anemia Only MDS

Short Term: Transfusion Dependence

Lead Time: Typically years (>10) to ∞

Advanced MDS

Iron Overload

Thrombocytopenia and Bleeding

Leukopenia and Infection

Leukemic Transformation

Premature Death

Time: Variable months to years common

32% Conley et al.¹ Heme Related Death Increasing Over Time

MDS Treatment Goals

- Correct Threatening Cytopenias
- Alleviate Symptoms
- Delay Disease Progression
- Increase Survival
- Cure

Evaluating MDS Rx?
AZA-001 Overall Survival: Azacitidine vs “Conventional Care”

Log-Rank  $P = .0001$

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: Aza = 82, Control = 113

Difference: 9.4 months

Efficacy of a novel schedule of decitabine in previously untreated AML, age 60 or older.

ABSTRACT 7010

• **Background:** Decitabine is active in MDS, what would role be in AML >60 years of age?

• **Methods:** Non induction candidates, 20mg/m2/IV days 1-10. 4 week cycles. Consolidations 3-5 days long
  - Good (t(8;21), INV 16/t(16;16)) (N=65)
  - Int (diploid, -Y) (N=272)
  - Poor (-5, -7, 11q abn) (N=144)

Blum et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7000)
Efficacy of a novel schedule of decitabine in previously untreated AML, age 60 or older.

ABSTRACT 7010

• Results:
  • 33 pts (median age 74: 60-83)
  • 13 with complex karyotype
  • 31/33 patients with high risk features

• CR rate of 42%
  • Median duration 2->14 months
  • Median OS not reached
  • Median FU 8 months

• Median number of cycles 5 (1-10)
• 9/14 CRs occurred with 1 cycle (rest needed median 1 (1-3))
• Death <8 weeks 15%
• Neutropenic fever rate 24/33 patients

Blum et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7000)
Clinical experience with different dosing schedules of decitabine in patients with myelodysplastic syndromes (MDS)

**ABSTRACT 7011**

- **Background:** Decitabine is active in MDS, what is the optimal dose between:
  - 15mg/m2 over 3 hours Q 8 hours for 3 days
  - 20mg/m2/daily x 5 days?

Steensma et. al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7011)
# Overview of Decitabine Clinical Trials in the Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient Population</th>
<th>Decitabine Dosing Schedule</th>
<th>Comparator Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-0007</td>
<td>Multicenter, open-label, randomized phase 3 study</td>
<td>Patients aged ≥ 18 years who were diagnosed with <em>de novo</em> or secondary intermediate- or high-risk MDS, including CMML with a white blood count &lt;12 x 10^9/L</td>
<td>15 mg/m² IV dosed over 3 hours every 8 hours for 3 consecutive days every 6 weeks</td>
<td>Supportive care</td>
</tr>
<tr>
<td>EORTC-06011</td>
<td>Multicenter, open-label, randomized phase 3 study</td>
<td>Patients aged ≥ 60 years who were diagnosed with <em>de novo</em> or secondary MDS, including CMML</td>
<td>15 mg/m² IV dosed over 4 hours every 8 hours for 3 consecutive days every 6 weeks</td>
<td>Supportive care</td>
</tr>
<tr>
<td>DACO-020</td>
<td>Multicenter, open-label, nonrandomized phase 2 study</td>
<td>Patients aged ≥ 18 years who were diagnosed with <em>de novo</em> or secondary MDS of any FAB subtype, including CMML with a white blood count &lt;12 x 10^9/L</td>
<td>20 mg/m² IV dosed over 1 hour once daily for 5 consecutive days every 4 weeks</td>
<td>None</td>
</tr>
</tbody>
</table>
| ID03-0180   | Single-site, open-label, randomized phase 2 study | Patients aged ≥ 16 years who were diagnosed with *de novo* or secondary IPSS intermediate- or high-risk MDS, including CMML | 20 mg/m² IV dosed over 1 hour once daily for 5 consecutive days every 4 weeks | • 20 mg/m²/day SQ (given in 2 doses) for 5 consecutive days every 4 weeks  
• 10 mg/m² IV dosed over 1 hour once daily for 10 consecutive days every 4 weeks |
## Endpoint Results of the Decitabine Clinical Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3-Day Decitabine Regimen (N = 89)</th>
<th>5-Day Decitabine Regimen (N = 99)</th>
<th>5-Day Decitabine Regimen (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of decitabine cycles</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Overall improvement, %</td>
<td>30</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>- CR</td>
<td>9</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>- PR</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>- HI</td>
<td>13</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Median time to best response, mo (95% CI)</td>
<td>2.9 (1.4-3.2)</td>
<td>3.8 (3.0-5.7)</td>
<td>2.0 (1.4-2.8)</td>
</tr>
<tr>
<td>Median duration of best response, mo (95% CI)</td>
<td>9.9 (7.9-11.1)</td>
<td>8.6 (6.1-12.6)</td>
<td>NE (4.2-NE)</td>
</tr>
<tr>
<td>Time to AML or death, mo (95% CI)</td>
<td>10.0 (7.6-11.2)</td>
<td>8.8 (6.3-11.9)</td>
<td>12.1 (9.7-16.4)</td>
</tr>
<tr>
<td>PFS, mo (95% CI)</td>
<td>7.3 (5.2-9.7)</td>
<td>6.6 (4.7-8.5)</td>
<td>8.1 (6.7-9.9)</td>
</tr>
<tr>
<td>OS, mo (95% CI)</td>
<td>12.8 (10.3-16.1)</td>
<td>10.1 (8.0-14.0)</td>
<td>17.8 (13.8-NE)</td>
</tr>
<tr>
<td>RBC transfusion independence, %</td>
<td>23</td>
<td>34</td>
<td>33</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, not available; NE, not estimable.
## Treatment-Emergent Grade 3/4 Adverse Events Occurring in ≥ 5% of Subjects

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>3-Day Decitabine Regimen (n = 197)</th>
<th>5-Day Decitabine Regimen (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (5)</td>
<td>73 (37)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33 (17)</td>
<td>58 (29)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>39 (20)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>23 (12)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8 (4)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Infections</td>
<td>68 (35)</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (6)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3-day regimen</td>
<td>Median # of cycles</td>
<td>Overall CR (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>D-0007 (N=89)</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>EORTC-06011 (N=119)</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>5-day regimen</td>
<td>DACO-020 (N=99)</td>
<td>5</td>
</tr>
<tr>
<td>ID03-0180 (N=93)</td>
<td>7</td>
<td>37</td>
</tr>
</tbody>
</table>

<sup>a</sup>As measured by IWG 2000 criteria; <sup>b</sup>Patients who became RBC transfusion independent while on-study
Conclusions

• Overall improvement rates determined using IWG 2000 criteria reached or exceeded 30% in all 4 clinical studies in which decitabine was dosed at 15 mg/m² IV over 3-4 hours every 8 hours for 3 days every 6 weeks or 20 mg/m² IV over 1 hour once daily for 5 consecutive days every 4 weeks.

• Higher overall improvement rates corresponded to an increased median number of treatment cycles.
  • Patients in study ID03-0189 who received a median of 7 cycles of the 5-day decitabine regimen demonstrated the highest overall improvement rate of 65%.

• The 5-day decitabine regimen appears to be at least as active, if not more so, compared with the 3-day regimen and allowed for greater decitabine exposure without compromising safety.

  • The findings from this study suggest that increasing the number of decitabine treatment cycles, which may be facilitated by using a 5-day versus 3-day dosing schedule, may provide additional clinical benefit to patients with MDS.
Chronic Lymphocytic Leukemia

ASCO 2009
Indications for Treatment 2009

- Marrow failure
  - Plt<100
  - Hg<11

- Massive/progressive adenopathy or splenomegaly

- Constitutional symptoms
  - Profound fatigue
  - Wt Loss >10% in 6 mo
  - Night sweats
  - Fever

- LDT <6 months

Shanafelt et al. MCP 79:388
How we select first-line therapy

CLL Patient Requiring Treatment (NCI 1996)

Life expectancy unrelated to CLL

<2 years

Options:
- Supportive care
- Rituximab
- Chlorambucil
- Fludarabine

>2 years

FISH Analysis

No 17p-

Options:
- Clinical trial
- FCR
- FR
- FC

17p13-

Clinical trial

Options:
- Clinical trial
- PCR
- Fludarabine +/- Rituximab
- Chlorambucil

AIHA

Steroid, rituximab, alkylator combo and/or splenectomy

Age

<70

≥70

Shanafelt, ASH Education Book, 2007
Selecting Salvage Therapy After CIT

**Options:**
- Evaluate for SCT
- Reevaluate similar regimen:
  - FCR
  - PCR
- Alem/Ritux
- Medrol/Ritux

**Transplant candidate**
- Yes
  - Options:
    - Evaluate for SCT
    - Pre-transplant debulking options
- No
  - Trt Free Interval Last Therapy
    - <18 months
      - 17p-
        - Yes
          - Options:
            - Clinical trial
            - Medrol/Ritux
            - Alem/Ritux
            - Aggressive regimen:
              - CFAR
              - OFAR
        - No
          - Bulky nodes
            - Yes
              - Options:
                - Clinical trial
                - Medrol/Ritux
                - Lenalidomide
                - Aggressive regimen:
                  - CFAR
            - No
              - Options:
                - Clinical trial
                - Alem/Ritux
                - Medrol/Ritux
                - Revlamid

- No
  - >18 months
    - Options:
      - Retreat similar regimen:
        - FCR
        - PCR
        - Alem/Ritux
        - Medrol/Ritux
Clinical improvement with a novel CD20 mAb, ofatumumab, in fludarabine-refractory chronic lymphocytic leukemia (CLL) also refractory to alemtuzumab or with bulky lymphadenopathy

ABSTRACT 7043

• **Background:** Ofatumumab is human anti CD20 ab, ? More potent than rituximab for B cells

• **Methods:** Patients with double refractory or bulky fludarabine refractory (DR or BFR) CLL
  • 8 weekly then 4 Monthly ofatumumab infusions
    • Dose 1 1300 mg
    • Dose 2-12; 2000mg
138 Patients (DR = 59; BFR = 79)
63% Rai III/IV - Median 5 prior therapies
ORR 58% (40.74% 99% CI) in DR, 47% (32.62) in BFR

<table>
<thead>
<tr>
<th>Measures of clinical improvements with a minimum duration of 2 months*</th>
<th>DR group</th>
<th>BFR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in clinical parameters</td>
<td>N⁺ %</td>
<td>N⁺ %</td>
</tr>
<tr>
<td>Complete resolution of B-symptoms</td>
<td>31 48</td>
<td>46 63</td>
</tr>
<tr>
<td>Complete resolution of lymphadenopathy (&lt;1 cm nodes)</td>
<td>55 16</td>
<td>74 11</td>
</tr>
<tr>
<td>≥50% improvement in lymphadenopathy</td>
<td>55 62</td>
<td>74 49</td>
</tr>
<tr>
<td>Complete resolution of splenomegaly</td>
<td>30 47</td>
<td>46 35</td>
</tr>
<tr>
<td>Complete resolution of hepatomegaly</td>
<td>18 50</td>
<td>21 52</td>
</tr>
<tr>
<td>Neutrophil count from $&lt;1.5 \times 10^9$/L to $&gt;1.5 \times 10^9$/L</td>
<td>19 5</td>
<td>17 29</td>
</tr>
<tr>
<td>Hemoglobin from $&lt;11$g/dL to $&gt;11$g/dL</td>
<td>27 30</td>
<td>43 26</td>
</tr>
<tr>
<td>Improvement in platelet count from $&lt;100 \times 10^9$/L to 50% increase or $&gt;100 \times 10^9$/L</td>
<td>29 41</td>
<td>44 39</td>
</tr>
</tbody>
</table>
Activity of ofatumumab, a novel CD20 mAb, and prior rituximab exposure in patients with fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory chronic lymphocytic leukemia (CLL).

ABSTRACT 7044

• Background: Ofatumumab is human anti CD20 ab, ? More potent than rituximab for B cells

• Methods: Patients with double refractory or bulky fludarabine refractory (DR or BFR) CLL
  • 8 weekly then 4 Monthly ofatumumab infusions
    • Dose 1 1300 mg
    • Dose 2-12; 2000mg

Becker et. Al. J Clin Oncol 27:15s, 2009 (suppl; abstr 7044)
### Efficacy outcomes by RTX exposure

<table>
<thead>
<tr>
<th>Prior RTX</th>
<th>DR (N=59)</th>
<th>BFR (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR, %</td>
<td>Median PFS, mo</td>
</tr>
<tr>
<td></td>
<td>N (95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Any prior RTX*</td>
<td>35 54</td>
<td>5.5 (3.7, 8.0)</td>
</tr>
<tr>
<td>FR†</td>
<td>18 50</td>
<td>5.5 (2.8, 8.3)</td>
</tr>
<tr>
<td>FCR‡</td>
<td>16 50</td>
<td>4.6 (2.3, 6.4)</td>
</tr>
<tr>
<td>No prior RTX</td>
<td>24 63</td>
<td>7.1 (4.8, 8.7)</td>
</tr>
</tbody>
</table>
Conclusions

• Panels of new molecular markers have significant prognostic significance in CN AML
• Higher dose DNM in AML induction probably is best
• Dasatinib 100mg/ daily is likely optimal dose when used in CML CP
• Decitabine 20mg/m2/day x 5 day likely best for MDS, and may have role in longer schedules for AML
• Ofatumumab active in refractory CLL and is undergoing further exploration alone and in combinations