Combinational therapy and newer agents in MDS-

Prof Ghulam J. Mufti
MDS foundation
ASH 2011
My Disclosures

- Advisory board member of GSK, Novartis, Roche and Celgene
- Unrestricted educational grants from Celgene
## Spectrum of MDS

### Asymptomatic, IPSS Low/Int-1
- BM function
- Transfusion

### Symptomatic, IPSS Int-2/High Risk

<table>
<thead>
<tr>
<th>IPSS-R</th>
<th>Median (Years)</th>
<th>Survival</th>
<th>25% AML Transform</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Very Low (0-2)</td>
<td>6.8</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Low (3-5)</td>
<td>4.3</td>
<td>10.1</td>
</tr>
<tr>
<td>3</td>
<td>Intermediate (6-7)</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>High (8-9)</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>V. High (10-18)</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

### International MDS Risk Classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Low</td>
<td>267 pts</td>
</tr>
<tr>
<td>Int-1</td>
<td>314 pts</td>
</tr>
<tr>
<td>Int-2</td>
<td>179 pts</td>
</tr>
<tr>
<td>High</td>
<td>56 pts</td>
</tr>
</tbody>
</table>

### WHO

#### Survival

- Low
- Int-1
- Int-2
- High

#### WPSS

- Very low
- Low
- Intermediate
- High
- V. high

### References
Endosteal and Vascular Niches

Effector T-cells

Cytokine milieu

IFN-γ

IL-6

IL-32

No

TPO mimetics

Growth factors

PARP inhibition

TPO-R

Apoptosis

Proliferation and survival

IFN-R

TNF-α

RNK

ROS

TPO-R

GF-Rs

Dysplastic

HSCs

Genetic mutations

Differentiation defects

Epigenetic mutations

Telomere attrition

Signal transducers and RTKases

Self-renewal

DNA repair

Endosteal and Vascular Niches

Trabecular bone

Endosteum

Sinusoid

Central sinus

Medullary artery

Self-renewal

DNA repair
‘Low risk’ MDS

Normal Environment

- Normal Tregs
- Normal Th17
- Normal Cytokines level
- Oligoclonal CD8+ T cells

Low Risk

- Inflammatory Environment
- Low to Normal Tregs
- Increased Th17
- Monocytes
- NK cells

Immune mediated
- IST- ATG, CyA
- Anti-TNF (Etanercept)
- Anti-IL6 (Siltuximab)
- Lenalidomide
- Campath
- P38α MAPK inhibitors (SCIO-469)

Growth and Differentiation factors
- Epo plus GCSF
- Eltrombopag/Romiplostim

Stromal modulation
- Myeloid derived suppressor Cells (MDSCs) and IDO1 inhibitor (INCB24360)

Others
- Ezatiostat Hydrochloride (Telintra®, TLK199)- GSTP1 inhibitor
- Neddylation inhibitors
- Kinase Inhibitors- ON-01910 (PLK1 & Cdc25C Inhibition), Sorafanib, Erlotinib
Erythropoietin ± G-CSF in MDS-

**Treatment response score**

- **RA, RARS, RAEB**
  - Score > +1
    - Good response (74%, n=34)
  - Score –1 to +1
    - Intermediate response (23%, n=31)
  - Score < –1
    - Poor response (7%, n=29)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Score adjustment</th>
</tr>
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<tbody>
<tr>
<td>s-epo</td>
<td>&lt;100</td>
<td>+2</td>
</tr>
<tr>
<td>U/L</td>
<td>100–500</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>−3</td>
</tr>
<tr>
<td>Transf</td>
<td>&lt;2 units/m</td>
<td>+2</td>
</tr>
<tr>
<td>U RBC/m</td>
<td>= or &gt;2 units/m</td>
<td>−2</td>
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</table>

# Lenalidomide MDS-002 Study
## Erythroid Responses at 24 wks

<table>
<thead>
<tr>
<th>Erythroid response</th>
<th>Transfusion indep</th>
<th>Minor (&gt;50% ↓)</th>
<th>Transfusion indep + minor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58 (27%)</td>
<td>36 (17%)</td>
<td>94 (44%)</td>
</tr>
</tbody>
</table>

- Median duration of transfusion independence: 43 wk
- Median Hgb rise: 3.3 g/dL (1.0–9.8)
- Median time to response: 4.5 wk (0.3–39.1)

- GEP from Lenalidomide–responsive patients lacking 5q deletions have a defect in erythroid differentiation analogous to the ineffective erythropoiesis in patients with 5q deletions.

- Ongoing Lenalidomide + EPO trials

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Raza, Blood 2007 and Ebert, PLOS Medicine 2007
Phase 1 Dose-Ranging Study of Oral Ezatiostat Hydrochloride (Telintra®, TLK199) in Combination with Lenalidomide (Revlimid®) in Patients with Non-Deletion(5q) Low to Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Ezatiostat, a glutathione S-transferase P1-1 (GST P1-1) inhibitor, activates Jun kinase and MAPK.
- promoting the growth and maturation of hematopoietic progenitors
- induces apoptosis in malignant cells

• Proven to be an effective single agent therapy for low/Int1 risk MDS (n=75)
• Induces transfusion independence in 30% of patients.
• HI-E 19% and HI-N 16%.
• Median duration of response 34 weeks (2-63 wks)
• Grade 1 to 2 – nausea, vomiting and diarrhoea

• Combination therapy with Lenalidomide is well tolerated
• HI-Erythroid response of 43%
• Ezatiostat may also have the potential to enhance lenalidomide's efficacy.
• ‘Go forward’ dose is ezatiostat/lenalidomide 2000/10 mg

# Romiplostim-Single agent and combination

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>End Point</th>
<th>Bleeding events</th>
<th>Blasts</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romiplostim 4w / Extension 1 year</td>
<td>44</td>
<td>46% durable response</td>
<td>4.3/100 patient week</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Azacitidine + Placebo/Romiplostim</td>
<td>40</td>
<td>85% Vs 62-71% Thromocytopenic events</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lenalidomide+ Placebo/Romiplostim</td>
<td>39</td>
<td>67% vs 57% Thromocytopenic events</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Decitabine + Placebo/Romiplostim</td>
<td>29</td>
<td>79% Vs 80% Thromocytopenic events</td>
<td>43% Vs 27%</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Romiplostim Vs Placebo</td>
<td>250</td>
<td>Efficacy NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Responders to ATG

Table 3  Univariate and multivariate analysis of factors predicting response to ATG

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease stage</td>
<td>0.46 (0.13-1.55)</td>
</tr>
<tr>
<td>IPSS</td>
<td>0.09 (0.01-0.88)</td>
</tr>
<tr>
<td>BM cellularity</td>
<td>0.51 (0.29-0.87)</td>
</tr>
<tr>
<td>Age</td>
<td>0.64 (0.28-1.47)</td>
</tr>
<tr>
<td>HLA-DRB1 status</td>
<td>0.75 (0.19-2.96)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>0.78 (0.31-1.97)</td>
</tr>
<tr>
<td>Transfusion dependence</td>
<td>1.74 (0.01-4.99)</td>
</tr>
<tr>
<td>Platelet dependence</td>
<td>1.06 (0.47-2.40)</td>
</tr>
</tbody>
</table>

Univariate analysis variables

Multivariate analysis variables:
- IPSS
  - Low/Int-1
  - Int-2/High
- BM cellularity
  - Hypocellular
  - Normo/Hypercellular

Effect of IST on survival of 96 MDS patients and predictive factors for the response to treatment

ZY Lim et al Leukemia 2007

Clinical outcomes of 89 NIH immunosuppressive therapy (IST) and 55 International Myelodysplasia Risk Analysis Workshop (IMRAW) patients <= 60 years of age with intermediate-1 MDS

Sloand. E et al JCO 2009
### Phase II Studies of Etanarcept and Siltuximab (Anti-IL6) in Lower Risk MDS

#### Etanarcept

<table>
<thead>
<tr>
<th>Etanarcept</th>
<th>Soluble fusion protein against TNF alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>RBC-TD, Low/Int-1 risk IPSS</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>25mg sc twice weekly 16 weeks</td>
</tr>
<tr>
<td><strong>No. Patients</strong></td>
<td>N=12</td>
</tr>
<tr>
<td><strong>Responses</strong></td>
<td>HI-E-3, HI-N=2 and HI-P=2</td>
</tr>
</tbody>
</table>

#### Siltuximab

<table>
<thead>
<tr>
<th>Siltuximab (CNTO 328)</th>
<th>Chimeric mur/hu-monoclonal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>RBC-TD, Low/Int-1 risk IPSS</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized 2:1 vs Placebo q 4 wk</td>
</tr>
<tr>
<td><strong>No. Patients</strong></td>
<td>N=75</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>HI-Erythroid</td>
</tr>
</tbody>
</table>

Deeg, Leukaemia 2002 and CNTO328 courtesy of Alan List
Medullary p38α/MAPK Phosphorylation
Relationship to Apoptotic Fraction


Courtesy of Alan List
Phase I/II Study of SCIO-469 in Low/Int-1 MDS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number (%) or Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>P38α MAPK inhibitor</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Low/Int-1 MDS with ESA failure</td>
</tr>
<tr>
<td>Design</td>
<td>TID oral (90.180, 270 &amp; 360 mg/d)</td>
</tr>
<tr>
<td>No. Patients</td>
<td>N=62</td>
</tr>
<tr>
<td>AEs all grades</td>
<td>GI (constipation, nausea, diarrhea ≤15%)</td>
</tr>
<tr>
<td>DLT</td>
<td>None defined</td>
</tr>
<tr>
<td>Week 16 Response</td>
<td>HI-P (12%), HI-N (28%), 1CR, 1 cytogenetic-CR</td>
</tr>
</tbody>
</table>

Sokol and List, 2011.
Paradigm of ‘cancer’ chemotherapy

- Synergism if not at least additive, hope not antagonistic!
- Reduce toxicity and dose, non overlapping actions
Combination Therapies in MDS

<table>
<thead>
<tr>
<th>Intensive chemotherapy (n=42)</th>
<th>Aza-001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azacitidine (n=17)</strong></td>
<td><strong>Intensive chemotherapy (n=25)</strong></td>
</tr>
<tr>
<td>25.1 (10.0–NR)</td>
<td>15.7 (8.2–24.1)</td>
</tr>
<tr>
<td>23.1 (6.4–25.4)</td>
<td>10.7 (4.6–15.4)</td>
</tr>
<tr>
<td>HR (95% CI) p value</td>
<td>0.76 (0.33–1.74) 0.51</td>
</tr>
<tr>
<td>0.48 (0.16–1.45)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MDACC, Courtesy GG Manero

**Alternating schedule**

**Induction:**
- Clofarabine 20mg/m² IV QD x 5 d
- Cytarabine 20mg SC BID x 10 d

**Consolidation:**
- Clofarabine 20mg/m² IV QD x 3 d
- Cytarabine 20mg SC BID x 5 d

*Alternating with*
- Decitabine 20 mg/m² IV QD x 5 d

**Low Dose Ara-C + Tipifarnib**
**Low Dose Ara-C + Arsenic Trioxide**
**Low Dose Ara-C + Mylotarg**
**Low Dose Ara-C**
**Low Dose Clofarabine**
**Sapacitabine**
**Drug X**

Fenaux, Lancet Oncol, 2009, and Burnett & Hills, Blood 2011
Paradigm of ‘cancer’ chemotherapy

- Synergism if not at lease additive, hope not antagonistic!
- Reduce toxicity and dose, non overlapping actions.
- Epigenetic models and genetic mutation directed therapy
Normal and Tumour cells- DNA methylation and chromatin modifications

CA = transcriptional coactivators, HAT = histone acetyltransferase activity, TF = transcription factors, HDAC = histone deacetylases, MBPs = methylcytosine-binding proteins, CR = transcriptional corepressors, DNMTs = DNA methyltransferases

Herman and Baylin, NEJM 2003
Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study.

Fenaux, Lancet Oncol, 2009
Molecular predictors of response to DAC and AZA

- GFM(DAC)- 39 advanced CMML
- ORR of 38%
- 8 gene mutations did not predict response or survival (incl ASXL1/TET2/RUNX1,RAS)
- Lower CJUN and CMYB expression predicted improved OS

- Kings(Aza)- 63 high risk MDS
- ORR of 49%
- 10 gene mutations incl. TP53
- Presence of EZH2 mutations associated with response
- Better OS in patients with EZH2/ASXL1 mutation.
- P53 mutations adversely affected survival

Braun, Blood, 2011 and Kulasekararaj, ASH, 2010
Foxp3 expression increased BUT more IL-17 secretion

HD PBMCs

t₀
Non-treated

HD PBMCs

t+96 h
Non-treated

HD PBMCs

t+96 h
Treated

5-Azacytidine Specifically Depletes Regulatory T Cells (Tregs) in Myelodysplastic Syndrome (MDS) Patients (Abstract 276)

Benedetta Costantini, Shahram Y Kordasti, Austin G Kulasekararaj, Jie Jiang, PhD, Thomas Seidl, Pilar Perez Abellan, Janet Hayden, Farzin Farzaneh and Ghulam J. Mufti.
5-Azacytidine Specifically Depletes Regulatory T Cells (Tregs) in Myelodysplastic Syndrome (MDS) Patients (Abstract 276)

Benedetta Costantini, Shahram Y Kordasti, Austin G Kulasekaran, Jie Jiang, PhD, Thomas Seidl, Pilar Perez Abellan, Janet Hayden, Farzin Farzaneh and Ghulam J. Mufti.
Phase I Combination Trial of Lenalidomide and Azacitididine in Patients With Higher-Risk Myelodysplastic Syndromes and Update from Phase II

N=18 (phase I) +18 (phase II)
Median age 68 years (47-78)
Time from diagnosis 8 weeks (2-106)
Blast % (median) 12%
IPSS: Int-2/High risk -31/36
Median F/U 15 months (2-60)

ORR = 25/36 (71%)
- 14 CR (40%)
- 11 HI (31%)
Median time to response -3 months (range 1-7 months)
Median OS for responders is 27 months (range, 7-55)

Sekeres et al. JCO 2010 and ASH abstract 607, Mon, Dec 12, 2011
Toxicity of combination Len plus Aza

- No DLTs reached through all dosing cohorts in Phase I
- Grade 3/4 non-hematologic AEs: cardiac (11%), febrile neutropenia (31%), other infection (8%), pulmonary (11%), vascular access-related thrombosis (6%), CNS hemorrhage (6%).
- Median ANC decrease 35% and median Plt decrease 18%

Sekeres et al. JCO 2010 and ASH abstract 607, Mon, Dec 12, 2011
<table>
<thead>
<tr>
<th>Sub</th>
<th>Cytogenetics#</th>
<th>c-Cbl/b-Cbl/Jak2</th>
<th>TET2</th>
<th>Response</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>47, xy, +8 [20] UPD19p13-11p12</td>
<td>Wt</td>
<td>Wt</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>46, xy [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>46, xy [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>46, xy [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>46, xy [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>CR</td>
</tr>
<tr>
<td>7</td>
<td>46,xy del(5q31q35)[2] 46,xy,[18] UPD6P25-3P22.1, UPD8q24.3</td>
<td>Wt</td>
<td>Wt</td>
<td>CR</td>
</tr>
<tr>
<td>9</td>
<td>Complex, UPD11q24.2-q25</td>
<td>Wt</td>
<td>Wt</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>46,xx [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>HI</td>
</tr>
<tr>
<td>11</td>
<td>46,xy [20]</td>
<td>Wt</td>
<td>Wt</td>
<td>HI</td>
</tr>
<tr>
<td>12</td>
<td>Complex ^</td>
<td>Wt</td>
<td>N.D</td>
<td>HI</td>
</tr>
<tr>
<td>13</td>
<td>Complex ^</td>
<td>Wt</td>
<td>N.D</td>
<td>HI</td>
</tr>
<tr>
<td>14</td>
<td>47, xx, +8 [20]</td>
<td>Wt</td>
<td>Heterozygous V1417F</td>
<td>NR</td>
</tr>
</tbody>
</table>

Sekeres et al. JCO 2010. Slides courtesy M.Sekeres
Azacitidine plus HDACi

- Aza/DAC +SAHA- (ORR approx=60%) Silverman ASH 2008
- Aza +Entinostat- E1905 (US leukaemia Intergroup trial)
- Aza + Panabinostat (LBH 589)- abstract 1529
- Aza/DAC + Valproic acid (+/- ATRA)
- Aza + MS-275
- Aza + MGCD0103

Other Combinations

- Possible combination with effective Oral Nucleoside analogues like Clofarabine and Sapacitabine
- Aza plus Romiplostim
- Aza plus Etanarcept
- Aza plus EGFR-TKIs (Abstract 2790)
5-Azacitidine and Vorinostat in Patients (pts) with Newly Diagnosed MDS or AML Not Eligible for Clinical Trials Because Poor Performance and Presence of Other Comorbidities

- Untreated AML/MDS
  - Not eligible for other clinical trials
- 5-azacitidine 75 mg/m² IV daily x 5 every 3 to 6 weeks and Vorinostat 200 mg orally TID

Responses: Aza +SAHA

- 24 (80%) survived longer than 60 days with median survival of 7 months (1 to 16).
- ORR 9 (30%)-CR 8 +m CR 1
- Additionally, 8 had stable disease of the 16 non-responding patients.
- No correlation with pharmacodynamic end points.
Single agent Lenalidomide in high risk MDS with del 5q - Prognostic factors for achieving CR

N=47
ORR of 27% and 25% achieved TI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>n</th>
<th>No. of CRs</th>
<th>CR, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytogenetic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated del 5q</td>
<td></td>
<td>9</td>
<td>6</td>
<td>67</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Single additional abnormality</td>
<td></td>
<td>11</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 additional abnormalities</td>
<td></td>
<td>27</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Bone marrow blasts, %</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 20%</td>
<td></td>
<td>29</td>
<td>6</td>
<td>21</td>
<td>.16</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td></td>
<td>18</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline platelet count, G/L</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100</td>
<td></td>
<td>20</td>
<td>7</td>
<td>35</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&lt; 100</td>
<td></td>
<td>27</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

SPMs in Lenalidomide treated Low or Int-1 risk MDS patients

- Median Time 13.5 m
- n=557

- Invasive SPM n=17
- B cell malignancies (n=2)
- Solid tumours (n=15)

- Non Melanoma skin cancer n=12

Median age 71 (range 27-95 yrs)
MDS-001 to -004 & -007
88(16%) had prior history of malignancies

Incidence rate is 2.6/100 patient years
(SEER data 2.1/100 patient years for >65 years)

Giagounidis et al, Abstract 1704, Saturday, Dec 10, ASH, 2011
Outcomes after 5-Azacitidiné (AZA) or Decitabine (DAC) failure

Median survival 4.3 months
1 year survival 28%
ORR to Cytarabine salvage 20%

Median OS 5.6 months
2yr survival -15%

Prébet T et al. JCO 2011
Jabbour, Cancer 2010
Outcomes after salvage therapy post 5-azacitidine failure

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>0/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>8.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2*†</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5*†</td>
</tr>
</tbody>
</table>
NOVEL Nucleoside analogues

SAPACITABINE

Tosedostat-Aminopepdidase inhibitor

-Response Rates of around 30%.

CLOFARABINE


Is there a role for GO?

1. CD33 expression level
2. CD33 saturation
3. Internalization
4. Activation of calicheamicin
5. New expression of CD33
6. Binding of GO
7. Efflux of calicheamicin
8. Induction of DNA breaks


Lowenberg B, JCO 2010.
Clofarabine

- Clofarabine for 5 days every 4-6 weekly
  - Oral 40/30/20 mg/m2 – Faderl, JCO 2010
  - IV 15/30 mg/m2 – Kantarjian, JCO 2010
  - Fixed oral dose – Sekeres, ASH 2010

- CR rates 25%, with ORR 43% (ORAL) and 36% (for IV)
- Median OS 5-9 months
- Med OS in Complete Responders is 20-24 months
- ORR is only 25% in AZA/DAC failure group.
- Side-effects: Transaminitis, febrile neutropenia, Nausea
Sapacitabine
Orally Bioavailable and resistant to deamination

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Nucleoside analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Phase I, Relapsed AML or high risk MDS</td>
</tr>
<tr>
<td>Design</td>
<td>Daily oral BD X 3-4 wk</td>
</tr>
<tr>
<td>No. Patients</td>
<td>N=47</td>
</tr>
<tr>
<td>MTD</td>
<td>Arm A 325 (7 days)</td>
</tr>
<tr>
<td></td>
<td>Arm B 425mg (6 days)</td>
</tr>
<tr>
<td>DLT</td>
<td>GI and Hepatic</td>
</tr>
<tr>
<td>Response</td>
<td>28%: 9%CR, 4%CRp, 15%CRi</td>
</tr>
<tr>
<td>4wk mortality</td>
<td>4%</td>
</tr>
</tbody>
</table>

Kantarjian, JCO 2010
## Phase I/II Study of Tosedostat in MDS & AML

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Amintopeptidase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>Relapsed AML or high risk MDS</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Daily oral (60-180mg/d)</td>
</tr>
<tr>
<td><strong>No. Patients</strong></td>
<td>N=44</td>
</tr>
<tr>
<td><strong>MTD</strong></td>
<td>180 mg (130 mg phase II)</td>
</tr>
<tr>
<td><strong>DLT</strong></td>
<td>Hepatic (ALT)</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>14 (32%): 3CR, 4mCR, 7PR</td>
</tr>
</tbody>
</table>

ON-01910 - Multikinase Inhibitor

- PLK1 and Cdc25C inhibitor
- ON 01910 inhibits PLK1 activation of Chk1 & Cdc25C → G2/M arrest

Phase I Study of Oral Azacitidine in MDS, CMML and AML

- Cycle 1 sc Aza followed by Oral Aza (Cycle 2 onwards) at doses of 120 to 600mg (7 days of 28 day cycle)

- 41 patients received SC and oral azacitidine (MDS, n = 29; CMML, n = 4; AML, n = 8)

- DLT (diarrhoea) at the 600mg dose and MTD was 480 mg

- Most common grade 3/4 adverse events were diarrhoea (12.2%), nausea (7.3%), vomiting (7.3%), febrile neutropenia (19.5%), and fatigue (9.8%)

- Overall response rate was 35% in previously treated patients and 73% in previously untreated patients.

Garcia-Manero G et al. JCO 2011
**Plasma concentration and Blood Methylation patterns.**

- Azacitidine exposure increased with escalating oral doses.
- Mean relative oral bioavailability ranged from **6.3% to 20%**.
- Oral and SC azacitidine decreased DNA methylation in blood, with maximum effect at day 15 of each cycle.

Garcia-Manero G et al. JCO 2011
Poly ADP-ribose polymerase 1 (PARP-1)

- Polymerization of ADP-ribose onto surrounding histones, transcription factors and itself
- DNA damage sensor of single strand breaks (SSB) involved in base excision repair
- ADP-ribose polymerization results in relaxation of chromatin and active recruitment of SSB repair factors to SSB.
Targeting of specific homologous recombination defects in cancer, ‘synthetic lethality’

Homologous recombination, replication re-start, Cell survival

Replication failure. Absence of repair or Illegitimate repair via NHEJ. Chromosomal Aberrations, Cell death

BrCA2−/− or BrCA1−/−

SSB repair

ATM Mre11

BrCA1

BrCA2

Rad51

Collapsed replication fork


Microsatellite Instability Induced Mutation in DNA Repair Genes, CtiP and Mre11 Confer Hypersensitivity to PARP Inhibitors in Myeloid Malignancies (Abstract 276)-Gaymes et al
Correlation of PARPi sensitivity in primary AML to MSI dependent abrogation of DNA repair, n=18

Microsatellite Instability Induced Mutation in DNA Repair Genes, CTiP and Mre11 Confer Hypersensitivity to PARP Inhibitors in Myeloid Malignancies (Abstract 276)-Gaymes et al
Post-Transplant combination strategies for relapse

- DLI plus chemotherapy
- DLI plus vaccination studies
- Post transplant Azacitidine +/- DLI (Azarale study, Abstract 656)
- Post Transplant Lenalidomide
- Adoptive immune therapy
- WT1 peptide Vaccination
Conclusions

- Combination therapy needs to be optimised especially in ‘high risk’ MDS patients.
- Further large prospective studies might help identify molecular predictors of response to therapy.
- Non-overlapping mechanisms of actions and toxicities is important.
- Emerging efficacy of novel nucleoside analogues as single agents is promising.
- PARP inhibitors are a novel class of agents and their efficacy in myeloid malignancies is been assessed.
Acknowledgements

Kings Health Partners

Leukaemia & Lymphoma Research
BEATING BLOOD CANCERS

Elimination of Leukaemia Fund
Advancing the care and treatment of leukaemia

Department of Health

EPSRC Engineering and Physical Sciences Research Council

Cancer Research UK

The Wellcome Trust

Charles Wolfson Trust

John and Holly Burton Trust

The Kay Kendall Leukaemia Fund

King’s College London
Founded 1829
University of London
Mutations in MDS

Effects of Reduced Expression of Ribosomal Proteins (RPs) on p53 Activation

P53 activation by Nutlin-3 mimics effect of ↓RPs

P53 anti sense; Dexamethasone

Neddylation Inhibition MLN4924

Adapted from Ellis, S. R. Blood 2011;117:2558.
RFUSIN2 Lentiviral Vector - B7.1/IL-2 transduced AML Cell Vaccine

Chan, Hardwick, Ingram et al: Mol Ther 2005; J. Virol 2006; BJ Haem 2009; Can Imm Immth 2010

Allogeneic – Post-transplant relapsed AML

Study Protocol

PRE-STUDY ENTRY CONDITIONS
- Relapsed AML / MDS
- Post-allogeneic HCT
- 50% donor CD3 chimera in relapse
- <5% BM blast following cytokinductive chemotherapy
- >50% blasts in relapse: low dose chem
>50% blasts in relapse: intensive chem

STUDY ENTRY

<table>
<thead>
<tr>
<th>Week</th>
<th>Arm A. DLI only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DLU $5 \times 10^5$</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td>19</td>
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</tr>
</tbody>
</table>

$DLU$ will be delivered in escalating doses (CD3=kg): $5 \times 10^5$, $5 \times 10^4$, $5 \times 10^3$, $5 \times 10^2$, $5 \times 10^1$ at 6 weekly basis (weeks 1, 7, 13, and 19).
AML B7-IL-2 cell vaccine will be given on the same days as DLI at 4 escalating doses as above.

Chan, Hardwick, Ingram et al: Mol Ther 2005; J. Virol 2006; BJ Haem 2009; Can Imm Immth 2010
## Patient Characteristics: Aza + SAHA

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Total N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>74 (44-83)</td>
</tr>
<tr>
<td>Median WBC</td>
<td>3 K/UL (0.6-112)</td>
</tr>
<tr>
<td>Median BM blasts</td>
<td>10% (1-78)</td>
</tr>
<tr>
<td>Complex cytogenetics</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>CMML</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>AML</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Prior Malignancy</td>
<td>16 (53%)</td>
</tr>
</tbody>
</table>