New drugs in MDS treatment

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Challenge of MDS treatment

- elderly
- comorbidities
- chromosomal abnormalities
- not eligible for intensive treatment
Where do we stand?

MDS del(5q) → Lenalidomide

MDS non-del(5q) → ESA

Higher risk MDS → Demethylating agents

Failure/relapse

New drugs
Pathomechanisms in MDS

- Chromosomal aberrations
- Gene mutations
- Immunological processes
- Genetic instability
- Aberrant DNA methylation
- Mitochondrial defects
- Aberrant histone acetylation
- Microenvironment

MDS
Currently recruiting trials

- 434 trials on ClinicalTrials.gov addressing „MDS“
- 507 trials on ClinicalTrials.gov addressing „AML“
- 408 trials on ClinicalTrials.gov addressing „NHL“
Low risk MDS
TGF-β signaling

• TGF-β is a myelosuppressive cytokine

• TGF-β receptor I and Smad upregulated and activated in MDS bone marrow progenitors

• suppresses hematopoiesis in MDS
ACE-536
Low risk MDS

ACE-536:
- Modified ActRII
- Human IgG-Fc

Ligand (GDF):
- Type I & Type 2 Activin Receptors
- Smad2

Inhibited
- Smad2 Signaling

Hemoglobin Production

EPO Responsive Proliferation
- BFU-E → CFU-E → Pro E

ACE-536 Responsive Differentiation
- Baso E → Poly E → Ortho E → Retic → RBC
ACE-536
Low risk MDS

Multiple Ascending Dose Phase

Low to Int-1 MDS

Cohort 1
0.125mg/kg*
(n=3-6)

Cohort 2
0.25mg/kg*
(n=3-6)

Cohort 3, etc.
0.50mg/kg*
(n=3-6)

Expansion Phase
Individually Titrated Dose

Expansion Cohort
Starting Dose TBD**
(n = 30)
Targeting apoptosis

Early MDS without expansion of blasts

Advanced MDS with expansion of blasts

Block of differentiation

Apoptosis
APG101
Low risk MDS
APG101
Low risk MDS

CD34+/CD71-

CD34-/CD71+

CD71+/GPA-

CD71+/GPA+
APG101
Low risk MDS

![Graph showing CFU-E and APG101 concentration in μg/l. The x-axis represents APG101 concentration in μg/l, while the y-axis represents mean number.](image)
APG101
Low risk MDS

• Pilot study
  – planned: 18 patients with low and intermediate-1 MDS
  – medullary blast count < 5% and no tMDS or sMDS
  – 100 mg APG101 once weekly i.v.
  – enrolled: n=3
  – excellent tolerability
Thrombocytopenia
Eltrombopag

Kühne T et al., Ann Hematol 2010
Eltrombopag
Low risk MDS

• Phase II trial

• randomized (2:1)
  – arm A: Eltrombopag
  – arm B: placebo

• platelets < 30,000/µL

• 50 mg daily starting dose

Oliva E et al., Leuk Res 2013
Eltrombopag
Low risk MDS

- Arm A: n=17 (total 26 patients)
  - mean age 65 years
  - mean baseline platelet count: 16,000/µL
- 14 patients reached 16-week follow-up:
  - 8/9 cases in arm A: platelet response at median 75 mg dosing
  - mean increase in platelets: 82,000/µL (SD 69/nL)
  - reduction in blast count in 2 patients
Eltrombopag
High risk MDS

- inhibition of leukemia cells in vitro
- induces differentiation of leukemic cells
- prolongs survival in murine transplant models

Roth M et al., Blood 2012
Eltrombopag
High risk MDS

Screening → Randomize

Eltrombopag + Supportive SOC

Placebo + Supportive SOC

2:1 N=140
12 week treatment

Extension

Eltrombopag
High risk MDS
Rigosertib

- Non-adenosine triphosphate (ATP)-competitive small-molecule multi-TKI
- Potent inhibitor of tumor growth in animal models
- Synergism with chemotherapeutic agents
Rigosertib

- exerts activity through:
  - inhibiting polo-like kinase 1 (PLK1) causing mitotic spindle arrest and apoptosis
  - cyclin D1 suppression
  - modulation of PI3K-Akt/mTORC pathway including dephosphorylation of Akt
Rigosertib
Trials

• Phase I/II trial:
  – intravenous
  – up to 1800 mg/day x 3 days every 2 weeks/month
  – 13 high risk MDS pts.
  – refractory to HMA
  – stable disease in 8 pts.
  – 4 pts marrow CR
  – responses irrespective of subgroup
  Seetharam M et al., 2012

• Phase I trial:
  – intravenous
  – dose escalation; up to 1000 mg/m² for 5 days every two weeks
  – 12 high risk MDS pts.
  – 2 AML pts with +8
  – 3 pts ≥ 50% marrow blast reduction
  – 3 pts hematologic improvement
  Olnes MJ et al., 2012
# Oral Rigosertib

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Total patients</td>
<td>37</td>
</tr>
<tr>
<td>Male/female</td>
<td>23/14</td>
</tr>
<tr>
<td>Median age, yrs (range)</td>
<td>74 (53-89)</td>
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<tr>
<td>WHO</td>
<td></td>
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<tr>
<td>RCMD</td>
<td>21</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>7</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>9</td>
</tr>
<tr>
<td>IPSS</td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>7</td>
</tr>
<tr>
<td>intermediate-1</td>
<td>16</td>
</tr>
<tr>
<td>intermediate-2</td>
<td>10</td>
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<tr>
<td>high</td>
<td>4</td>
</tr>
<tr>
<td>Prior 5-Azacitidine</td>
<td>27</td>
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</tbody>
</table>

Komrokji RS et al., 2013
Oral Rigosertib
Pharmacokinetics

• rapid absorption after single fasting dose ($T_{max}$ 1 h)
• linear increase of systemic exposure and dose dependent
• plasma half-life: 2.79 hrs
• bioavailability: 35%
  – significantly reduced after administration after meal

Komrokji RS et al., 2013
Rigosertib
Adverse events

• intravenous:
  – cardiac
  – infections
  – inflammations

• oral:
  – dose dependent
  – urinary tract incl. dysuria, hematuria, nocturia, cystitis

Seetharam M et al., 2012  Olnes MJ et al., 2012  Komrokji RS et al., 2013
Rigosertib

• effective even in pretreated patients

• favorable risk profile particularly with regard to hematological toxicity
Tosedostat

Löwenberg B et al. JCO 2010
Tosedostat

• Orally available

• depletion of amino acids predominantly in tumor cells
  – antiproliferative
  – apoptotic

Löwenberg B et al. 2010
### Table 1. Characteristics of Patients Treated on Study (n = 57)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Phase I</th>
<th>Phase II</th>
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<tbody>
<tr>
<td></td>
<td>60 mg (n = 3)</td>
<td>90 mg (n = 4)</td>
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<tr>
<td>AML</td>
<td>No.</td>
<td>%</td>
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<tr>
<td>MDS</td>
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<td>0</td>
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<tr>
<td>MM</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Median age</td>
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<tr>
<td>Range</td>
<td>45-74</td>
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<td>ECOG score</td>
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<td></td>
<td>(n = 2)</td>
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<tr>
<td>AML treatment status</td>
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<tr>
<td>First salvage</td>
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<td>0</td>
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<tr>
<td>Second or more salvage</td>
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<td>100</td>
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<tr>
<td>Refractory</td>
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<td>0</td>
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<td>Chemotherapy naive</td>
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<td>AML cytogenetics*</td>
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<tr>
<td>Favorable</td>
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<td>0</td>
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<tr>
<td>Intermediate</td>
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<td>50</td>
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<tr>
<td>Unfavorable</td>
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<td>50</td>
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<tr>
<td>Unknown</td>
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</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; ECOG, Eastern Cooperative Oncology Group.

*See section “Study Population” for details of cytogenetic abnormalities.

Löwenberg B et al. 2010
<table>
<thead>
<tr>
<th>Phase</th>
<th>Patient Number</th>
<th>Dose (mg)</th>
<th>Age (years)</th>
<th>Baseline Marrow Blasts (%)</th>
<th>Best Marrow Blasts (%)</th>
<th>Best Marrow Blasts on Day</th>
<th>Marrow Response</th>
<th>Response Duration (days)*</th>
<th>Baseline Karyotype</th>
<th>Salvage Attempt</th>
<th>Overall Survival (days)</th>
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<tbody>
<tr>
<td>I</td>
<td>01-01</td>
<td>60</td>
<td>74</td>
<td>32</td>
<td>2</td>
<td>56</td>
<td>Complete</td>
<td>29</td>
<td>del(7q)</td>
<td>Second</td>
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<td>06-03</td>
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<td>68</td>
<td>31</td>
<td>2</td>
<td>84</td>
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<td>04-09</td>
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<td>67</td>
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<td>Complete†</td>
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<td>03-13</td>
<td>130</td>
<td>73</td>
<td>8</td>
<td>&lt; 1</td>
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<td>36</td>
<td>Normal</td>
<td>First</td>
<td>73</td>
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<td>II</td>
<td>03-30</td>
<td>130</td>
<td>79</td>
<td>31</td>
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<td>&lt; 5</td>
<td>84</td>
<td>Complete</td>
<td>62</td>
<td>47, XY, +1, der(1;16) (q10, p10) + 19†</td>
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<td>66</td>
<td>13</td>
<td>&lt; 2</td>
<td>56</td>
<td>Complete†</td>
<td>449</td>
<td>Normal</td>
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<td>835§</td>
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<td>03-20</td>
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<td>71</td>
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<td>10</td>
<td>56</td>
<td>Partial</td>
<td>161</td>
<td>Normal</td>
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<td>60</td>
<td>34</td>
<td>11</td>
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<td>Partial</td>
<td>100</td>
<td>Normal</td>
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<td>LTFU</td>
<td>Normal</td>
<td>Second</td>
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<td>10</td>
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<td>Partial</td>
<td>31</td>
<td>Normal</td>
<td>None</td>
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<td>13</td>
<td>56</td>
<td>Partial</td>
<td>28</td>
<td>Normal</td>
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<td>69</td>
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<td>9</td>
<td>28</td>
<td>Partial</td>
<td>95</td>
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<td>First</td>
<td>122</td>
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<td>04-58</td>
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<td>67</td>
<td>15</td>
<td>5</td>
<td>28</td>
<td>Partial</td>
<td>478</td>
<td>Normal</td>
<td>First</td>
<td>505</td>
</tr>
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</table>
Table 4. Incidence of CTC Grades 3 to 5 AEs in > 10% of Patients (n = 57)

<table>
<thead>
<tr>
<th>AE</th>
<th>Regardless of Relation</th>
<th>Tosedostat-Related*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. †</td>
<td>%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32</td>
<td>56</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Febrile neutropenia‡</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: CTC, Common Terminology Criteria for Adverse Events, version 2; AE, adverse event.
*As interpreted by the local investigator.
†Each patient is only counted once per AE.
‡All events of febrile neutropenia resulted in patient hospitalization.

Löwenberg B et al. 2010
Tosedostat

- Tosedostat shows high activity as an orally available monotherapy in heavily pretreated patients with AML and MDS

- managable risk profile
Inclusion criteria of clinical trials do not meet the real MDS population. A registry-based simulation.

- 2308 MDS patients from the Düsseldorf registry

- evaluation whether in- and exclusion criteria of 6 recruiting trials (in 2012) allow for participation of patients
Inclusion criteria of clinical trials do not meet the real MDS population. A registry-based simulation.

LEMON 5 EUDRACT 2008-001866-10  
Study drug: Lenalidomide **Eligible 2%**

EPOANE EUDRACT 2010-022884-36  
Study drug: Erythropoietin **Eligible 11%**

MDS005 EUDRACT 2009-011513-24  
Study drug: Lenalidomide **Eligible 5%**

VALENA EUDRACT 2008-002388-14  
Study drugs: Lenalidomide and Valproic acid **Eligible 8%**

ASPIRE EUDRACT 2011-000114-19  
Study drug: Eltrombopag **Eligible 4%**

ONCONOVA EUDRACT 2010-019755-21  
Study drug: Rigosertib **Eligible 2%**

About 65% of pts do not fulfil inclusion criteria for a clinical trial!
Inclusion criteria of clinical trials do not meet the real MDS population. A registry-based simulation.

- Main reason for exclusion:
  - diagnosis of CMML
  - tMDS
  - cell counts not matching
  - pre-treatment not allowed
  - special karyotypes
  - unsuccessful pretreatment
Conclusion

• several new drugs show promising activity in MDS

• combination regimens might further improve response to treatment

• drugs should be evaluated in high quality trials

• trials should be better adapted to clinical need and „real-life“
İlginiz için çok teşekkür ederim!