Aplastic Anemia: Current Thinking on the Disease, Diagnosis, and Non-Transplant Treatment

Bogdan Dumitriu, MD
Hematology Branch
National, Heart, Lung and Blood Institute
National Institutes of Health

BONE MARROW FAILURE SYNDROMES

SDS
DKC
AA
AA/PNH
PNH
MDS
AML
hypocellular MDS
AID: MS, IBD, uveitis, DM type 1, etc.

APLASTIC ANEMIA = LOW BLOOD COUNTS

Hemoglobin – variable, around 7-8 g/dL (>13 g/dL)
  weakness, fatigue, shortness of breath, lack of energy
Neutrophils – under 500/uL (>1500/uL)
  infections, mouth ulcers
Platelets – under 10,000/uL (>150,000/uL)
  bleeding (gums, nose, skin)
CLINICAL MANIFESTATIONS OF BONE MARROW FAILURE

anemia, bleeding, infection

AGE AT DIAGNOSIS
Aplastic Anemia Admissions to NIH Clinical Center

*NATURAL HISTORY* OF APLASTIC ANEMIA

Severity Criteria (two of three):
- platelets <20k/μL
- reticulocytes <1% (60k/μL)
- ANC <500/μL

Very severe: ANC <200/μL
**Pathophysiology of Aplastic Anemia**

- Immune attack
- Stem cells
- Hematopoietic progenitors
- Circulating blood cells

**Causes of Aplastic Anemia**

- Most of the cases of Aplastic Anemia have no identifiable cause
- There are inherited (genetic) causes of aplastic anemia/bone marrow failure
- Pregnancy, eosinophilic fasciitis, and seronegative hepatitis are associated with AA
- Drugs and chemicals have been reported as well (Benzene, Chloramphenicol)
- All identifiable causes explain very few cases of AA
• 1960’s → 10% survival in 1 year

• 2010 → 90% survival in 1 year

• Immunosuppressive therapy
• Bone marrow transplantation
• Supportive care
• Novel agents

SAA treatment algorithm

1. Biopsy/HCT
2. SAA diagnosis
3. NHL with inoperable disease, HCT in consultation
4. Children and young adults with newly diagnosed disease
5. SAA with inoperable disease, HCT in consultation
6. SAA with inoperable disease

Immunosuppressive therapy

- Anti-thymocyte globulin (ATG)
  - Horse
  - Rabbit

- Cyclosporine (CsA)
- Campath
- Others (MMF, sirolimus, tacrolimus, cyclophosphamide)

Immunosuppressive therapy

- First line of treatment (vs. transplant)
- Salvage for treatment-refractory patients
- Treatment for relapsed disease

Anti-thymocyte Globulin (ATG) Production

- Immunization with human thymocytes
- Anti-human thymocytes antibodies
- Purification of sera
- Cytotoxicity assay
- ATG
- IgG
RESPONSE OF SEVERE APLASTIC ANEMIA TO INTENSIVE IMMUNOSUPPRESSION

Immunosuppressive therapy at diagnosis of SAA

ATG AND CSA FOR SEVERE APLASTIC ANEMIA
OVERALL SURVIVAL

60% response rate
## INTENSIVE IMMUNOSUPPRESSION FOR SAA
### COMPARISON OF RESULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>N</th>
<th>Median Age (years)</th>
<th>Response</th>
<th>Relapse</th>
<th>Clonal Evolution</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>1986-1989</td>
<td>84</td>
<td>32</td>
<td>65%</td>
<td>13%</td>
<td>8%</td>
<td>58% at 11 yrs</td>
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<tr>
<td>NIH</td>
<td>1991-1998</td>
<td>122</td>
<td>35</td>
<td>61%</td>
<td>15%</td>
<td>11%</td>
<td>50% at 7 yrs</td>
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<tr>
<td>EGMBT</td>
<td>1991-1998</td>
<td>100</td>
<td>15</td>
<td>77%</td>
<td>12%</td>
<td>11%</td>
<td>87% at 5 yrs</td>
</tr>
<tr>
<td>Japan</td>
<td>1992-1997</td>
<td>119</td>
<td>9</td>
<td>66%</td>
<td>22%</td>
<td>6%</td>
<td>88% at 3 yrs</td>
</tr>
<tr>
<td>German/Austrian</td>
<td>1993-1997</td>
<td>114</td>
<td>9</td>
<td>77%</td>
<td>12%</td>
<td>6%</td>
<td>87% at 4 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>1996-2000</td>
<td>101</td>
<td>54</td>
<td>74%</td>
<td>42%</td>
<td>6%</td>
<td>88% at 4 yrs</td>
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<tr>
<td>NIH</td>
<td>1998-2002</td>
<td>104</td>
<td>30</td>
<td>80%</td>
<td>37%</td>
<td>9%</td>
<td>85% at 4 yrs</td>
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<tr>
<td>EGMBT</td>
<td>2002-2006</td>
<td>182</td>
<td>46</td>
<td>70%</td>
<td>33%</td>
<td>4%</td>
<td>76% at 6 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>2003-2005</td>
<td>77</td>
<td>28</td>
<td>57%</td>
<td>26%</td>
<td>10%</td>
<td>90% at 3 yrs</td>
</tr>
<tr>
<td>NIH</td>
<td>2005-2010</td>
<td>130</td>
<td>25</td>
<td>68%</td>
<td>39%</td>
<td>21%</td>
<td>96% at 3 yrs</td>
</tr>
</tbody>
</table>

Young NS, Calado RT, Scheinberg P, Blood 2011

## NEW DIRECTIONS IN TREATMENT FOR APLASTIC ANEMIA

- **Add to horse ATG + CsA platform**
  - G-CSF (Neupogen)
  - Mycophenolate mofetil
  - Sirolimus
  - Long course immunosuppression
- **Augment initial lymphocytotoxicity**
  - Rabbit ATG
  - Campath

## A Randomized Trial of H-ATG vs. R-ATG in SAA
### Patients and Methods

- 120 consecutive patients (60 per arm)
- NIH Clinical Center
- 1:1 randomization
- Primary objective –response at 6 months

Scheinberg et al. NEJM 2011
A Randomized Trial of H-ATG vs. R-ATG in SAA
Hematologic Responses at 3 and 6 months

<table>
<thead>
<tr>
<th></th>
<th>Horse ATG</th>
<th>Rabbit ATG</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>3 months</td>
<td>37/60 (62%)</td>
<td>20/60 (33%)</td>
<td>0.003</td>
</tr>
<tr>
<td>6 months</td>
<td>41/60 (68%)</td>
<td>22/60 (37%)</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

A Randomized Trial of H-ATG vs. R-ATG in SAA
Blood Count Recovery in Responders

For new diagnosed SAA recommended/preferred immunosuppression regimen is horse ATG/CSA
Immunosuppressive therapy for refractory SAA

Survival of refractory SAA following retreatment with rabbit ATG + CsA (salvage)

Scheinberg P, Young NS. Br J Haematol 2006

Alemtuzumab (Campath-1H)

- Anti-CD52 Antibody
- Murine hypervariable regions fused into human IgG1
- CD52 expressed:
  - B and T cells
  - NK cells, dendritic cells
  - Monocytes, macrophages
  - Plasma cells, Eos
- No CD52 expression on:
  - RBCs, platelets
  - Hematopoietic stem cells

Ravandi and Brien, Cancer Invest. 2007 24: 718-725
Hernández-Campo RM, Guzmán B. Zin Cytom. 2006 70:71
SECOND IMMUNOSUPPRESSION FOR REFRACTORY SAA

<table>
<thead>
<tr>
<th>Treatment arm (N=54)</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>rabbit ATG (N=27)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>alemtuzumab (N=27)</td>
<td>10 (37%)</td>
</tr>
</tbody>
</table>

For refractory SAA salvage immunosuppression with either rabbit ATG or Campath rescues 1/3 of patients

Immunosuppressive therapy for relapsed SAA

- cyclosporine
- rabbit ATG
- alemtuzumab
ATG AND CSA FOR SEVERE APLASTIC ANEMIA

RELAPSE

Proportion relapsing

Days

RELAPSE AFTER ATG + CSA

Cyclosporine-dependence Post-1st-relapse

<table>
<thead>
<tr>
<th>Years post-relapse</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>Patients on CsA</td>
<td>20/22</td>
<td>19/20</td>
<td>14/18</td>
<td>11/17</td>
<td>11/14</td>
<td>7/11</td>
<td>4/7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(86%)</td>
<td>(91)</td>
<td>(78)</td>
<td>(65)</td>
<td>(79)</td>
<td>(64)</td>
<td>(57)</td>
<td></td>
</tr>
</tbody>
</table>

Retreatment with rabbit ATG + CsA Post-1st-relapse → 2/3 response

Rosenfeld S, Follmann D, Nunez O, Young NS. JAMA 2003
Scheinberg P, Nunez O, Young NS. Br J Haematol 2006

CAMPATH IMMUNOSUPPRESSION FOR RELAPSED SAA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath (N=25)</td>
<td>14 (56%)</td>
</tr>
</tbody>
</table>

Scheinberg et al, Blood 2012
For relapsed SAA treatment with either rabbit ATG or Campath rescues 2/3 of patients

Conclusion/Take home points

SAA is a rare disease

SAA is not cancer

Treatments are effective but do not work in 100% of patients

Immunosuppression works in 2/3 of patients and is less toxic than stem cell transplant but it is not curative (disease can relapse)

Better immunosuppression treatments might be coming soon
Conclusion/Take home points

If you relapse after treatment or if you do not respond to immunosuppression there are treatment options.

Thank you!

New Directions in Aplastic Anemia: What's on the Horizon

Bogdan Dumitriu, MD
Hematology Branch
National, Heart, Lung and Blood Institute
National Institutes of Health
Pathophysiology of Aplastic Anemia

HEMATOPOIETIC GROWTH FACTORS AS THERAPY FOR SAA

Ganser A et al, Blood 1990; 76:1287: IL-3 pilots
Kojima S et al, Blood 2002; 100:796: G-CSF→monosomy 7
Tichelli A et al, Blood 2011; 117:4434: G-CSF shows no survival benefit

THROMBOPOIETIN

- Principal endogenous regulator of platelet production.
- Binds to megakaryocyte promotes production of platelets and mature megakaryocytes.
- Stimulatory effects on multilineage progenitors in vitro and in animal models.
- Clinically maybe beneficial to treat patients with thrombocytopenia (post-chemo, ITP)
Clinical development of THROMBOPOIETIN

- 1994-cloned by 5 independent groups
- 1996-clinical trials with mammalian cell-line produced or e. coli-produced full length thrombopoietin
  - Clear stimulated platelet production in laboratory animals, normal volunteers given single doses
  - Not particularly effective to speed platelet recovery post-chemotherapy
- 1999-2000 Serious adverse events reported in platelet donors
  - Normal platelet donors given repeated subcutaneous doses developed profound, long-lasting thrombocytopenia
  - Due to stimulation of cross-reacting autoantibodies against endogenous TPO (Li et al, BLOOD, 2001)
  - Ended clinical development of recombinant thrombopoietin

2nd generation TPO agonists

- Romiplostim (Nplate): IV/SC, chronic refractory ITP
- Eltrombopag (Promacta): oral, chronic refractory ITP

ELTROMBOPAG FOR REFRACTORY SEVERE APLASTIC ANEMIA

Hematologic Response Criteria
- Platelets: >20K/uL increase, or transfusion-independence
- RBCs: >1.5 g/dL increase in Hb, or transfusion-independence
- ANC: >100% increase if severe neutropenia, or >500/uL increase

NHL Protocol 09-02194: ClinicalTrials.gov identifier: NCT00522083
PATIENTS CHARACTERISTICS

<table>
<thead>
<tr>
<th>Age: median, range</th>
<th>44, (18-77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: number, (%)</td>
<td>14, (54%)</td>
</tr>
<tr>
<td>Transfusion Dependent Number, (%)</td>
<td>26, (100%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>23, (88%)</td>
</tr>
<tr>
<td>Baseline Parameters</td>
<td>Median, range</td>
</tr>
<tr>
<td>Platelets (K/uL)</td>
<td>9, (5-15)</td>
</tr>
<tr>
<td>Neutrophils (K/uL)</td>
<td>0.8, (0.07-2.8)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.0, (8.0-13.8)</td>
</tr>
<tr>
<td>Months from last IST</td>
<td>Median, range: 12, (8-55)</td>
</tr>
</tbody>
</table>

REFRACTORY SAA ELTROMBOPAG STUDY RESULTS

Censure date 11/1/2011

- 26 patients enrolled
- 1 patient ineligible, not treated
- 25 evaluable patients

11 responders (44%)
- 9 platelet responses
- 2 hemoglobin responses
- 4 neutrophil responses

14 non-responders
- 10 stable disease
- 2 died of progression
- 3 clonal evolution to MDS
- 1 HSCT

Median follow up 13 months (range 4-28 months)

PLATELET RESPONSES
Hemoglobin, gr/dL

HEMOGLOBIN INCREASES AFTER ELTROMBOPAG

Median hemoglobin increase 3.6 g/dL (range 1.5-8.2 g/dL)

NEUTROPHIL INCREASES AFTER ELTROMBOPAG

Median ANC increase 590/dL (460-990/ul)

BONE MARROW CELLULARITY AT ONE YEAR

Pre-treatment Post-treatment Pre-treatment Post-treatment

Pre-treatment Post-treatment Pre-treatment Post-treatment
RESPONSE SUMMARY OF EXPANDED COHORT

- Median follow-up 9 months (range 3-47 months)
- 17 responders (40%)
  - 11 platelet responses
  - 4 erythroid responses
  - 8 neutrophil responses
  - Additional 7 at >16wks
- 26 non-responders
  - 2 responded >16 weeks
  - 1 died of progression
  - 3 deaths from sepsis
  - 6 clonal evolution

44 patients enrolled
1 patient ineligible, not treated
43 evaluable patients
1 patient ineligible, not treated

LINEAGE CHARACTERISTICS OF RESPONSES

12 Weeks-Primary Endpoint
Best Response at Follow-up

- Platelets
- Neutrophils
- Hemoglobin

INSIGHTS INTO SAA PATHOPHYSIOLOGY FROM ELTROMBOPEG RESPONSIVENESS

- Stem cell number
- Correlation with blood counts, age, telomere length
- HSC growth factor (+)
- IST (-)
- ↑ probability of failure
- ↑ probability of recovery
- Immune attack
DR[2] Includes those who lost their response as having a response, therefore 'best response'
Desmond, Ronan (NIH/NHLBI) [E], 5/23/2013

Desmond, Ronan (NIH/NHLBI) [E], 5/30/2013
SUMMARY

• Eltrombopag can promote tri-lineage hematopoiesis in SAA patients refractory to IST
  – 44% clinical response rate
  – Transfusion independence
  – Well-tolerated

• Eltrombopag stimulation may expand the HSC pool in humans

• Addition of Eltrombopag early in SAA may increase response rate, decrease time to response, prevent HSC depletion, and avoid clonal progression

FDA Approval of Eltrombopag (Promacta) for Refractory Aplastic Anemia

ELTROMBOPAG FOR MODERATE AA
NHLBI 09-H-0154

Eltrombopag, dose escalation to 150 mg QD by mouth
>18 years old; platelet count <30,000/uL
Assessment by blood counts and BM at 3 and 6 months

Horse ATG + CSA and ELTROMBOPAG for treatment-naïve SAA
NHLBI 12-H-0150

Add eltrombopag to existing horse ATG + CSA platform will increase overall response and decrease relapses
TELOMERE STRUCTURE AND BIOLOGY

- Cap chromosome ends
- Tandem TTAGGG repeats
- Bound to array of proteins: telomerase complex
- Forms higher order chromatin T loop
- Shields 3’ end to prevent recognition as a DNA “break” by non-homologous end joining machinery
- TTAGGG loss with proliferation: “end replication problem”

TELOMERE AND BONE MARROW FAILURE

DYSKERATOSIS CONGENITA

- Leukopenia
- Nail dystrophy
- Hyperpigmentation

TELOMERE LENGTH IN TERT MUTATION LEUCOCYTES

- Various mutations affecting TERT gene
- Analysis of telomere length in patients
- Controls vs. patients comparison

(Images and diagrams not transcribed due to text-only format)
LATE PRESENTATION OF DYSGERATOSIS CONGENITA

37 y/o US Army officer in Afghanistan
tongue ulcer, diagnosed as squamous cell carcinoma
single round of chemotherapy and radiation resulted in unexpected extreme,
persistent pancytopenia. Later, pulmonary metastases
novel Val329Gly mutation in DKC1

Thrombocytopenia, gray hair, very short telomeres, TERT mutation

Peripheral Blood Telomere Length

Telomere disease spectrum

- Moderate to severe aplastic anemia (low platelets only)
- Liver cirrhosis
- Lung fibrosis/IPF
- Skin/nail changes
- Skin/oral cancers
- Leukemia
### Androgens for telomeropathy

Telomere elongation and clinical response to androgen treatment in a patient with aplastic anemia and a heterozygous hTERT gene mutation

**Patrick Flager, Robert Schimassek, Jindřich Lichterová, Tomáš Hrubý, Jana Benešová, Jana Paně, Jana Vilímová, Miroslava Viktorová, Štěpánka Plachýová, Jan Filip, Miroslav Trubač, Jan B. Dikanovič, František Pětka**

**Blood** 2009

#### Table

<table>
<thead>
<tr>
<th>Compound</th>
<th>Androgens</th>
<th>Calardo RT et al, Blood 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td></td>
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</tr>
<tr>
<td>Methyltrienolone (synth.)</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>Nandrolone</td>
<td>600</td>
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<tr>
<td>6β-Hydroxy-Testosterone</td>
<td>300</td>
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<tr>
<td>β-Estradiol</td>
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</table>

#### Diagram

**SEX HORMONES INCREASE TELOMerase Activity IN CULTURED HUMAN LYMPHOCYTES**

Calardo RT et al, Blood 2009
DANAZOL FOR TELOMEROPATHIES

11-H-0209: "Danazol for Genetic Bone Marrow and Lung Disorders"
Danazol, 800 mg/d x 2 yrs for patients with short telomeres +/- mutations
Phase II/III design, N=31
Primary biologic end point: telomere maintenance/elongation
Secondary clinical end points: toxicity, efficacy (blood counts/PFT and CT)
Protocol opened in August 2011; 27 patients enrolled to date
Modest drug toxicity (minimal LFTs, mild headaches, muscle cramps)

ClinicalTrials.gov identifier: NCT01441037

Conclusion/Take home points

Eltrombopag works as a stem cell booster

Addition of Eltrombopag to standard hATG+Csa will likely improve response rate and decrease long-term complications

Conclusion/Take home points

10% of aplastic anemia might be inherited (genetic cause)

Important to diagnose:
- Treatment implications
- Family/genetic counseling
Thank you!

Severe Aplastic Anemia (SAA)

Treatment-Naïve

NCT01623167 “Eltrombopag with Standard Immunosuppression for Aplastic Anemia”

Indication: SAA
Exclusions: Prior Treatment (ATG, high dose cyclophosphamide, alemtuzumab), Fanconi Anemia, liver cirrhosis

Inclusions:
• > 2 yrs
• Bone marrow cellularity < 30%
• At least two of the following:
  - ANC < 500/microl
  - Platelets < 20,000/microl
  - ARC < 60,000/microl

Purpose: To improve hematologic response by adding eltrombopag (oral growth factor) to standard immunosuppressive therapy
Type: Inpatient and Outpatient, Non-Randomized
Duration: 10-14 days inpatient for horse-ATG, CSA+ eltrombopag for 6 months, with 3 month, 6 month and annual follow-up visits

Severe Aplastic Anemia (SAA)

Refractory

NCT00922883 “A Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia”

Indication: SAA with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine.
Exclusions: Treatment with horse or rabbit ATG or Campath within 6 months of study entry, Fanconi Anemia, liver cirrhosis, PNH clone size greater than 50%

Inclusions:
• Diagnosis of aplastic anemia, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine.
• Platelet count ≤ 30,000/microl
• Age ≥ 18 years old

Purpose: To improve platelet counts with eltrombopag (oral growth factor) in patients with thrombocytopenia after immunosuppressive therapy
Type: Outpatient, Non-Randomized
Duration: 3 months of therapy. Monthly visits to NIH.
Moderate Aplastic Anemia (MAA)

NCT01328587 “Eltrombopag for Moderate Aplastic Anemia”

Indication: MAA with thrombocytopenia or anemia.

Exclusions: Fanconi Anemia, liver cirrhosis, PNH clone size greater than 50%.

Inclusions: Current diagnosis of moderate aplastic anemia and
• Age ≥ 18 years old
• One or more of platelet count less than or equal to 30,000/μL; Hemoglobin less than or equal to 8.5 g/dl OR platelet and/or red cell transfusion dependent

Purpose: To improve platelet counts with eltrombopag (oral growth factor).

Type: Outpatient, Non-Randomized.

Duration: 4 months of therapy. Monthly visits to NIH.

T-cell Large Granular Lymphocytosis (T-LGL)

NCT00345345 “Alemtuzumab to Treat T-Large Granular Lymphocytosis”

Indication: T-LGL, Neutropenia, Anemia

Inclusions:
1. T-LGL clone detectable by peripheral blood flow cytometry and TCR gene rearrangements
2. At least one cytopenia:
   • ANC < 500/μL
   • Platelets < 20 k/μL or < 50 k/μL with bleeding
   • Hemoglobin < 9 g/dL or anemia requiring >2 units of RBCs/month transfusions

Purpose: To characterize response (improvement of blood counts) to immunosuppression (Campath) in patients with T-LGL

Type: Inpatient and Outpatient, Non-Randomized

Duration: 11 days inpatient, with 3 month, 6 month and annual follow-up visits

Myelodysplastic syndrome (MDS)

A Pilot Study of a Thrombopoietin-Receptor Agonist, Eltrombopag, in Patients With Low to Int-2 Risk MDS

NCT00961064

Purpose of this study is to see if eltrombopag can increase platelet counts in patients with MDS

Inclusion criteria:
• Patients 18 years of age and older who have platelet count of less than 30 that has not responded to conventional treatment

Outpatient study:
• Treatment with eltrombopag once per day for 16 weeks
• Evaluations at NIH every 4 weeks
  • If response, then follow up every 3 months
  • If no response then follow up at 1 and 6 months off drug
Myelodysplastic syndrome (MDS)

Clofarabine followed by high-dose lenalidomide for high risk MDS, CMMoL and AML

NCT01629882
• Phase I
• Single course of IV clofarabine (5mg/m² x 5) for cytoreduction
• Oral lenalidomide consolidation with dose escalation from 25mg daily for 21/28 days for 1 cycle in the first cohort up to 50mg daily for 28/28 days for 2 cycles in the fourth cohort.
• Oral lenalidomide maintenance, starting at a dose of 10mg daily in 28 day cycles, with dose adjustments, for up to 12 cycles.

• Inclusion criteria:
  – MDS: Int-2 IPSS and higher
  – CMMoL
  – AML
  – ECOG 0 to 2
  – Unresponsive to, or unable to receive, DNA hypomethylating agents or standard intensive induction chemotherapy (i.e. “7+3” cytarabine/anthracycline chemotherapy)

• Outpatient study:
  – Needs to stay locally for monthly revlimid prescription refills.