An Update on RACE: the European Trial combining Eltrombopag and Immunosuppression

Bone Marrow Failure Disease Scientific Symposium
Bethesda, March 17-18th 2016

Antonio M. Risitano, M.D., Ph.D.
Regis Peffault De Latour
On behalf of the SAAWP of the EBMT
Chair: Carlo Dufour
# EBMT studies for AA

<table>
<thead>
<tr>
<th>moderate AA (EMAA)</th>
<th>vSAA / SAA (RACE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THE EMAA trial

Eltrombopag in moderate Aplastic Anemia (MAA) and Supportive Care in Aplastic Anemia

Britta Höchsmann & Hubert Schrezenmeier

Institute of Clinical Transfusion Medicine and Immunogenetics Ulm
German Red Cross Blood Donor Services Baden-Wuerttemberg - Hessia
& Institute of Transfusion Medicine, University Hospital of Ulm
Type of trial:
This is a prospective, randomized, placebo-controlled, double-blind multicenter study.

Patient numbers: 116 evaluable patients (58 each group)

Treatment:
Patients are randomized to receive either Cyclosporine + Eltrombopag or Cyclosporine + placebo
Eltrombopag (or Placebo) starting dose: of 150 mg orally per day
Option of dose modification regarding to response
| Primary objective | The primary objective of this trial is the evaluation of the superiority of the combination therapy Eltrombopag + Ciclosporin (CSA) regarding hematologic response (PR + CR) at 6 months in comparison with treatment with CSA alone in untreated MAA patient. |
EMAA-Study: secondary endpoints

Secondary endpoints are:

- Trilineage (CR and PR) and single lineage hematological response rate at 3, 6, 12 and 18 months.
- Cumulative incidence of response
- Time to best hematological and single lineage response
- Proportion of patients with need for transfusions and number of units transfused (PRBC and PC) since start of treatment
- Cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG
- Toxicity profile as measured using the CTCAE criteria
- Relapse rate at 6, 12 and 18 months cumulative incidence of relapse (from best trilineage hematological response)
- Overall survival
- Failure-free survival
- Telomere lengths and presence of telomerase mutations as biomarkers for response.
- Quality of life as assessed by quality of life instruments (FACIT-F SCALE and EORTC QLQ-C30, in some countries in addition with the QLQ-AA/PNH)
- Pharmacokinetic studies for assessment of dose dependency regarding efficiency and safety in a part of the patients
MAA is defined as Aplastic Anemia fulfilling the following criteria:

- no evidence for other disease causing marrow failure
- hypocellular bone marrow for age
- depression of at least two out of three peripheral blood counts below the normal values:
  - absolute neutrophil count (ANC) < 1.2 G/L
  - platelet count < 70 G/L
  - absolute reticulocyte count < 60 G/L

without fulfilling the criteria for SAA
Moderate Aplastic Anemia  *without prior specific therapy* and need for treatment. In this study need for treatment is defined as:

**a) transfusion-independent MAA and:**

- ANC < 1.0 G/L
- or hemoglobin < 8.5 g/dl and reticulocyte count < 60 G/L
- or platelet count < 30 G/L
- or significant clinical symptoms (infections, bleeding, anemia)

**b) transfusion-dependent moderate aplastic anemia**

Platelet transfusion dependency is defined as prophylactic transfusion (platelet counts < 10 G/L with no bleeding) or therapeutic transfusion.

Red cell transfusion dependency is defined as transfusion of at least 4 units of packed red blood cell concentrates (PRBC) in the 12 weeks prior to study entry.
EMAA-Study: randomization

Randomization will take in account patient’s age and disease severity by stratifying into 4 block combinations to ensure homogeneity between treatment arms, according to the following subgroups:

<table>
<thead>
<tr>
<th>Block 1:</th>
<th>Block 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>transfusion-independent MAA</td>
<td>transfusion-independent MAA</td>
</tr>
<tr>
<td>18-60 years old</td>
<td>&gt; 60 years old</td>
</tr>
<tr>
<td>Block 3:</td>
<td>Block 4:</td>
</tr>
<tr>
<td>transfusion-dependent</td>
<td>transfusion-dependent</td>
</tr>
<tr>
<td>18-60 years old</td>
<td>&gt; 60 years old</td>
</tr>
</tbody>
</table>

After 6 months of treatment within the study as well as completing and documentation of the 6 months assessment the study will be unblinded.
EMAA-Study: schedule

MAA with clinical significant cytopenia without prior specific therapy

Informed consent, screening for enrollment

Inclusion criteria fulfilled, no exclusion criteria present => study office => double blinded randomization

CSA + Placebo

Evaluation 3 months after therapy start => Dose escalation?

6 months after therapy start => evaluation and report of remission status to the study office => unblinding by the study office

A) No Complete Remission:
   Eltrombopag + CSA Evaluation 3 months after therapy start => dose escalation?

B) Complete Remission:
   slow tapering of CSA => end of study treatment

C) Partial & Complete Remission:
   Ongoing Eltrombopag & slow tapering of CSA

D) No Complete or Partial Remission:
   End of Study treatment

12 months after therapy start => evaluation and report of remission status to the study office

A1) No Complete or Partial Remission:
   => End of Study treatment

A2) Complete and Partial Remission:
   Ongoing Eltrombopag & slow tapering
   Tapering/End of Study treatment 12 months after start of eltrombopag (18 months after study start)

Complete and Partial Remission:
   => Tapering/End of Study treatment

18 months after therapy start => evaluation and report of remission status to the study office

Last Follow up 24 months after end of study treatment
**Eltrombopag** (or Placebo) daily starting dose:
150 mg daily (Olnes et al NEJM 2012).

Option of dose escalation to 225 mg daily after 3 months:
- if no trilineage response occurs
- and the platelet count remains < 70 G/L

**CSA** initial daily dose:
5 mg/kg/daily  aim of a trough CSA blood level of 200–400 ng/mL (using a polyclonal assay) or 150–250 ng/mL (using a monoclonal assay).
EMAA- study: status

Switzerland: Basel
France: Paris, Bordeaux
Italy: Genua, Neapel, Rom
Netherlands: Leiden, Groningen
Great Britain: Leeds
Germany: Aachen, Berlin, Essen, Hamburg, Hannover,
Ulm (7 pts. enrolled, 5 pts. on treatment)
THE RACE trial

A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) ± Eltrombopag as front-line therapy for severe aplastic anemia patients.

PRINCIPAL INVESTIGATORS

Regis Peffault de Latour (Paris)  Antonio M Risitano (Naples)
A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients – RACE STUDY(1)

**RACE Trial**

11 March 2016

<table>
<thead>
<tr>
<th>Working party</th>
<th>Principal investigators</th>
<th>Trial Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA-WP</td>
<td>Antonio M Risitano / Regis Peffault de Latour</td>
<td>Marleen van Os</td>
</tr>
</tbody>
</table>

To investigate whether Eltrombopag (Revolade, GSK) added to standard immune-suppressive treatment, CsA + hATG (ATGAM, Pfizer) increases the rate of early complete response in untreated AA patients*

* Patients will be stratified by age and disease severity

Participating countries

- France
- Italy
- Germany
- United Kingdom
- Spain
- Switzerland
- Netherlands
Study TIMELINES

December 2014 - January 2015
Submission to French authorities
Favourable opinion EC received
Awaiting CA decision

February - March 2015
Submission to Italian authorities
Awaiting decision

15 April 2015
Kick-off meeting
Saint Louis Hospital, Paris

June - October 2015
All Participating centers open for subject enrollment

March - July 2015
Submission to all MS completed
- UK
- NL
- CH

April - May 2015
France: 1st subject, 1st visit
Italy: 1st subject, 1st visit
**THE EBMT RACE STUDY**

**Study design**

- **An EBMT Severe Aplastic Anemia Working Party study** (approved by the CTO), entirely funded by Novartis and Pfizer

- **Aim of the study:** to improve the current standard treatment for SAA
  - To improve the **robustness of hematological response** of SAA patients receiving IST

- **Prospective, open label, phase III randomized study**
  - **Control arm:** horse ATG (40 mg/kg x 4dd, iv) + cyclosporine (5 mg/kg, os)
  - **Investigational arm:** horse ATG + cyclosporine + eltrombopag (150 mg/die, os)

- **Type B trial,** because eltrombopag may theoretically result in a somewhat higher risk (mostly clonal evolution) in comparison to standard medical care

- **Participating centers:** 30 sites from 7 EU Countries (France, Italy, UK, Germany, Spain, Netherlands, Switzerland)
THE EBMT RACE STUDY
Statistical design

✓ Superiority study
✓ Sample size calculation
  ✓ Aiming to increase the 3m CR rate from 7% (Scheinberg, Haematologica 2010) to 21% (current NIH data)
  ✓ Sample size to reject the null hypothesis at 5% significance level (alpha-error) and with 80% power (two-sided test) is n=96 patients for treatment arm
  ✓ Sample size increased by 4% to compensate for possibly not evaluable patients: total number of 200 patients (100 each arm)
✓ Randomization
  ✓ 1:1 randomization, including a stratified block design
  ✓ Stratification according to:
    • Disease severity:
      − Severe aplastic anemia (SAA)
      − Very severe aplastic anemia (VSAA: SAA plus ANC <200/μL)
    • Age:
      − >=15 and <40 year old
      − >=40 year old
✓ No stopping rules (study continuation led to discretion of the DMSB)
✓ No interim analysis
THE EBMT RACE STUDY
Eligibility criteria

✓ Inclusion criteria

1. Diagnosis of severe or very severe aplastic anemia
   - At least two of the following:
     - ANC <0.5 x 10^9/L (severe) or <0.2 x 10^9/L (very severe)
     - Platelet counts <20 x 10^9/L
     - Reticulocyte counts <60 x 10^9/L (automatic counter)
   - Hypocellular bone marrow (<30% cellularity), without evidences of fibrosis or malignant cells

2. Male or female age >= 15 years;

3. Written informed consent

4. Willing and able to comply with all of the requirements and visits in the protocol

5. Understands that they can be randomised to either treatment arm

6. Negative pregnancy test for women of child bearing age
THE EBMT RACE STUDY

Eligibility criteria

✓ Exclusion criteria

1. Prior immunosuppressive therapy with ATG, alemtuzumab or cyclophosphamide
2. Eligibility to a sibling allogeneic stem cell transplantation
3. Evidence of a myelodysplastic syndrome
4. History or clinical suspect of constitutional aplastic anemia (i.e. FA or DKC)
5. History of malignant tumors with active disease within 5 years from enrollment
6. Previous history of stem cell transplantation
7. Treatment with cyclosporin A <2 weeks before enrollment
8. CMV viremia, as defined by positive PCR or pp65 test
9. WHO performance status >=3
10. Pregnant or breast feeding patients
11. Patients with hepatic, renal or cardiac failure, or other life-threatening concurrent disease
12. Patients with HIV infection
13. Patients without social health care assistance
14. Patients for whom there is no availability of horse-ATG (ATGAM)
15. Participation in another clinical trial within 1 month before the start of this trial
16. Patients and/or female partners of male patients not using method of birth control
17. Subjects with known hypersensitivity to any of the component medications

The presence of a PNH clone is not an exclusion criterion
Primary endpoint

✓ 3-month complete remission (NIH criteria: normal CBC without transfusions)

Secondary endpoints

✓ Time to first hematological response (complete or partial)
✓ Time to best hematological response
✓ Time to complete response
✓ Rates of hematological response (ORR, CRR, PRR) at 6, 12, 18, 24 months
✓ Overall survival probability
✓ Event-free survival probability
✓ Cumulative incidence of clonal evolution
✓ Cumulative incidence of PNH clone and clinical PNH occurrence
✓ Cumulative incidence of relapse
✓ Cumulative incidence of discontinuation of immunosuppressive therapy
✓ Rate of CsA-independent hematological response at 24 months
✓ Need for and number of transfusions required from treatment
✓ Need for any supportive care, including hospitalization
✓ Quality of life (by the validated EORTC QLQ-C30 questionnaire)
✓ Safety and tolerability of the investigational treatment, including SAE
THE EBMT RACE STUDY

Study flow-chart

Initial treatment

3 month evaluation: primary endpoint

6 month evaluation: stop eltrombopag
Possible cross-over (standard arm only)

12 month evaluation:
Relapse: possible eltrombopag re-starting (investigational arm only)

24 month evaluation: end of the study
TREATMENT Scheme

Randomisation

- Steroids
- hATG
- Steroids
- hATG

Cyclosporin A

Eltrombopag

Primary endpoint 3m CR

+1 // +14 // +3m // +24m

No CR

CR

continue

stop
RACE trial – participating sites

<table>
<thead>
<tr>
<th>Country</th>
<th># sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>6</td>
</tr>
<tr>
<td>Germany</td>
<td>5</td>
</tr>
<tr>
<td>Italy</td>
<td>6</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4</td>
</tr>
<tr>
<td>Spain</td>
<td>5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>
RACE trial – required documents

1. National Competent Authority approval
2. Central Ethics approval
3. Local requirements
4. Site agreement with EBMT (contract)
5. Essential documents
6. Initiation
RACE trial – Flower diagram

November 2015

1. NCA
2. EC
3. Local
4. Contract
5. Essential docs
6. Initiation
RACE trial – Flower diagram

March 2016

1. NCA
2. EC
3. Local
4. Contract
5. Essential docs
6. Initiation
RACE trial – Flower diagram
RACE trial – Flower diagram

1. NCA
2. EC
3. Local
4. Contract
5. Essential docs
6. Initiation
## RACE trial – status overview

<table>
<thead>
<tr>
<th>Country</th>
<th>Approval</th>
<th>Sites open</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>NCA &amp; EC</td>
<td>4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>NCA &amp; EC</td>
<td>2</td>
</tr>
<tr>
<td>Spain</td>
<td>NCA &amp; EC</td>
<td>0</td>
</tr>
<tr>
<td>Italy</td>
<td>NCA &amp; EC</td>
<td>1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>NCA &amp; EC</td>
<td>1</td>
</tr>
<tr>
<td>Germany</td>
<td>submitting</td>
<td>0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>submitting</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>
RACE trial - accrual

<table>
<thead>
<tr>
<th>Hospital</th>
<th># pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordeaux</td>
<td>1</td>
</tr>
<tr>
<td>Leeds</td>
<td>3</td>
</tr>
<tr>
<td>Leiden</td>
<td>1</td>
</tr>
<tr>
<td>Lyon</td>
<td>4</td>
</tr>
<tr>
<td>Naples</td>
<td>2</td>
</tr>
<tr>
<td>Paris</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
</tr>
</tbody>
</table>

RACE trial, 11 March 2016
RACE trial - accrual

Actual Accrual

Expected Accrual according to Protocol

Expected accrual sites open till June (exc. DE/CH/IT)

Patients included

Date

7/1/2015 1/1/2016 7/1/2016 1/1/2017 7/1/2017 1/1/2018 7/1/2018
RACE trial – ancillary biological study (King’s College)

**MYELOID NEOPLASIA**

Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome

Austin G, Kulasekararaj, 1,2 Je Jiang, 1,2 Alexander E. Smith, 1,2 Azim M. Mohamudial 1,2, Syed Mian, 1 Shroyans Gandhi, 1,2 Joop Gisseling, 1 Barbara Czopikowski, 1 Judith G. W. Marsh, 1,2 and Ghalam J. Mufli 1,2

1Department of Haematological Medicine, King’s College London School of Medicine, London, United Kingdom; and 2Department of Haematology, King’s College Hospitals, London, United Kingdom.

Table 3. Details of all the somatic mutations in the study

<table>
<thead>
<tr>
<th>UPN</th>
<th>Gene</th>
<th>Mutant allele burden (%)</th>
<th>Variant class</th>
<th>Nucleotide and protein change</th>
<th>Constitutional DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2*</td>
<td>ASXL1</td>
<td>30</td>
<td>Frameshift insertion</td>
<td>c.1927_1928insG;p.G643fs</td>
<td>Skin</td>
</tr>
<tr>
<td>2*</td>
<td>DNMT3A</td>
<td>42</td>
<td>Non-synonymous SNV</td>
<td>c.C1540G;p.L514V</td>
<td>Skin</td>
</tr>
<tr>
<td>2*</td>
<td>ERBB2</td>
<td>44</td>
<td>Non-synonymous SNV</td>
<td>c.G922A;p.V308M</td>
<td>Skin</td>
</tr>
<tr>
<td>5*</td>
<td>TET2</td>
<td>5</td>
<td>Stopgain SNV</td>
<td>c.C3107T;p.Q1034X</td>
<td>Skin</td>
</tr>
<tr>
<td>6*</td>
<td>ASXL1</td>
<td>38</td>
<td>Stopgain SNV</td>
<td>c.C2242T;p.G748X</td>
<td>Buccal</td>
</tr>
<tr>
<td>10*</td>
<td>SRSF2</td>
<td>43</td>
<td>Non-synonymous SNV</td>
<td>c.C264T;p.Q96L</td>
<td>Buccal</td>
</tr>
<tr>
<td>16*</td>
<td>ASXL1</td>
<td>23</td>
<td>Frameshift insertion</td>
<td>c.2469_2470insAG;p.L823fs</td>
<td>Skin</td>
</tr>
<tr>
<td>18*</td>
<td>DNMT3A</td>
<td>31</td>
<td>Non-synonymous SNV</td>
<td>c.C264T;p.R882C</td>
<td>Skin</td>
</tr>
<tr>
<td>19*</td>
<td>IKZF1</td>
<td>14</td>
<td>Non-synonymous SNV</td>
<td>c.C640G;p.H214D</td>
<td>Skin</td>
</tr>
<tr>
<td>21*</td>
<td>BCOR</td>
<td>5</td>
<td>Stopgain SNV</td>
<td>c.C526T;p.Q176X</td>
<td>Buccal</td>
</tr>
<tr>
<td>29*</td>
<td>ASXL1</td>
<td>41</td>
<td>Stopgain SNV</td>
<td>c.G406A;p.W1356X</td>
<td>Skin</td>
</tr>
<tr>
<td>33*</td>
<td>BCOR</td>
<td>68</td>
<td>Stopgain SNV</td>
<td>c.G4832A;p.W1611X</td>
<td>Skin</td>
</tr>
<tr>
<td>40*</td>
<td>ASXL1</td>
<td>31</td>
<td>Non-frameshift deletion</td>
<td>c.2894_2896del;p.966_966del</td>
<td>Buccal</td>
</tr>
<tr>
<td>46*</td>
<td>MPL</td>
<td>10</td>
<td>Non-synonymous SNV</td>
<td>c.G1544T;p.W515L</td>
<td>Buccal</td>
</tr>
<tr>
<td>64</td>
<td>DNMT3A</td>
<td>47</td>
<td>Non-synonymous SNV</td>
<td>c.C264T;p.R882C</td>
<td>Skin</td>
</tr>
<tr>
<td>66</td>
<td>ASXL1</td>
<td>37</td>
<td>Frameshift deletion</td>
<td>c.2433delT;p.N811fs</td>
<td>Skin</td>
</tr>
<tr>
<td>67</td>
<td>U2AF1</td>
<td>19</td>
<td>Non-synonymous SNV</td>
<td>c.C101A;p.S34Y</td>
<td>Skin</td>
</tr>
<tr>
<td>69</td>
<td>ASXL1</td>
<td>34</td>
<td>Stopgain SNV</td>
<td>c.C2077T;p.R693X</td>
<td>Buccal</td>
</tr>
<tr>
<td>70</td>
<td>ASXL1</td>
<td>2</td>
<td>Stopgain SNV</td>
<td>c.G2026T;p.E676X</td>
<td>Buccal</td>
</tr>
<tr>
<td>70</td>
<td>BCOR</td>
<td>14</td>
<td>Stopgain SNV</td>
<td>c.T912G;p.Y304X</td>
<td>Buccal</td>
</tr>
<tr>
<td>73</td>
<td>BCOR</td>
<td>6</td>
<td>Frameshift deletion</td>
<td>c.4634_4835insC;p.L1612fs</td>
<td>Skin</td>
</tr>
<tr>
<td>79</td>
<td>ASXL1</td>
<td>36</td>
<td>Stopgain SNV</td>
<td>c.G2026T;p.E676X</td>
<td>Buccal</td>
</tr>
<tr>
<td>81</td>
<td>ASXL1</td>
<td>3</td>
<td>Stopgain SNV</td>
<td>c.T2324G;p.L775X</td>
<td>Skin</td>
</tr>
<tr>
<td>88</td>
<td>ASXL1</td>
<td>7</td>
<td>Frameshift deletion</td>
<td>c.2129delC;p.A709fs</td>
<td>Skin</td>
</tr>
<tr>
<td>93</td>
<td>DNMT3A</td>
<td>8</td>
<td>Stopgain SNV</td>
<td>c.S3111T;p.R771X</td>
<td>Skin</td>
</tr>
<tr>
<td>94</td>
<td>BCOR</td>
<td>30</td>
<td>Splice site</td>
<td>splice site c.3052-2A&gt;G</td>
<td>Skin</td>
</tr>
<tr>
<td>97</td>
<td>DNMT3A</td>
<td>7</td>
<td>Non-synonymous SNV</td>
<td>c.C264T;p.R882C</td>
<td>Buccal</td>
</tr>
<tr>
<td>107</td>
<td>ASXL1</td>
<td>30</td>
<td>Stopgain SNV</td>
<td>c.T2468G;p.L823X</td>
<td>Buccal</td>
</tr>
<tr>
<td>129</td>
<td>DNMT3A</td>
<td>5</td>
<td>Non-synonymous SNV</td>
<td>c.G2027A;p.R736H</td>
<td>Skin</td>
</tr>
<tr>
<td>130</td>
<td>DNMT3A</td>
<td>5</td>
<td>Non-synonymous SNV</td>
<td>c.G2845A;p.R882H</td>
<td>Skin</td>
</tr>
<tr>
<td>140</td>
<td>BCOR</td>
<td>5</td>
<td>Frameshift deletion</td>
<td>c.4760delC;p.P1587fs</td>
<td>Buccal</td>
</tr>
<tr>
<td>142</td>
<td>DNMT3A</td>
<td>1.5</td>
<td>Non-synonymous SNV</td>
<td>c.C2644T;p.R882C</td>
<td>Buccal</td>
</tr>
</tbody>
</table>
Hematopoiesis, immunity and (clonal) evolution
Risitano and Peffault De Latour, in press

A

IST

Threshold for cytopenia

Normal AA Hematological response Full recovery? Relapse? Clonal evolution?
Hematopoiesis, immunity and (clonal) evolution

Risitano and Peffault De Latour, in press
Hematopoiesis, immunity and (clonal) evolution

Risitano and Peffault De Latour, in press
Eltrombopag: increased proliferation of residual HSCs vs increased number of recruited HSCs?
## EBMT studies for AA

<table>
<thead>
<tr>
<th>Modality</th>
<th>moderate AA (EMAA)</th>
<th>vSAA / SAA (RACE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective</strong></td>
<td>PR + CR at 6 months</td>
<td>CR at 3 months</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>- age &gt; 18 years &lt;br&gt;- Treatment requiring MAA &lt;br&gt;(transfusion dependency or ANC &lt; 1G/l or Thrombo &lt; 30G/l or Hb &lt; 8,5g/dl &amp; Reti &lt; 60G/l)</td>
<td>- age &gt; 15 years &lt;br&gt;- SAA/ vSAA &lt;br&gt;- No primary allo-SCT</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>CsA + Eltrombopag &lt;br&gt;versus CsA + Placebo</td>
<td>hATG (ATGAM) + CsA + Eltrombopag &lt;br&gt;versus h ATG + CsA</td>
</tr>
<tr>
<td><strong>Eltrombopag Dosage</strong></td>
<td>150 mg (225 mg)</td>
<td>150 mg</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Placebo controlled</td>
<td>Open lable</td>
</tr>
<tr>
<td><strong>Patient number</strong></td>
<td>2 x 58</td>
<td>2 x 100</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>University hospital Ulm</td>
<td>EBMT</td>
</tr>
</tbody>
</table>
The target of clinical translation

**Preclinical: laboratory**

**Preclinical: animals**

**Phase I: healthy subjects**

**Phase I: PNH**

**Phase II**

**Phase II PNH**

**Phase III**

**Approved**

- TT30
- AMY-201
- Mirococept
- CDX-1135
- Lampalizumab
- Achillion CompdA
- Novartis anti-FD
- Novelmed anti-P

**Anti-CCP**
- TNT009

**Anti-C3**
- AMY-101
- APL-2
- ALXN1210
- LFG316
- ALN-CC5
- Coversin
- ALXN5500
- SOBI002
- ARC1905
- RA101348

**Anti-CAP**

**Anti-C5**