Minutes of WP8 MDS during the 10th Annual Meeting of the European LeukemiaNet, Tuesday, February 5, 2013

1) **Progress studies in EU-MDS Registry: report from Academy meeting in Nijmegen 30-01-13**

   a) **General overview of EU-MDS registry** (David Bowen, Louise de Swart): The accrual of new patients has remained steady after the inclusion of first 1,000 patients. Currently more than 1,400 patients have been reported in the registry (January 2013). Serbia has joined the Registry and it will start reporting patients in a few months. Croatia has applied to become a member. It has completed the application form. Croatia will be visited by the monitor before final approval. Dr Gevorg Tamamyan from Armenia has shown interest to join the EU-MDS Registry. He will contact Dr Jackie Droste for the application procedure. Israel has included 24 patients last year. The draft of the first manuscript has been discussed including the issue of the implementation of the new IPSS-R. Louise de Swart has completed the updated cytogenetic file. Detlef Haase is checking the new cytogenetic classification of the file: to be completed before the end of February.

   b) **Impact of transfusion on biology and progression** (Tom Johnston, Louise de Swart): the reporting of the transfusion history is almost 100% complete in the EU-MDS Registry. Since administration of Red Blood Cell transfusions (RBC) is a time dependent variable, specific statistical adjustments are necessary to perform appropriate analyses to assess the role of RBC in the outcome of lower risk MDS patients. In the most recent analysis Tom Johnston could show that the intensity of RBC transfusions was a very important prognostic factor in predicting survival with a very poor 4-year survival of less than 20% in patients who received more than 4 units of RBC per month. A full manuscript will be submitted for publication later this year.

   c) **European pattern and impact of the use of erythropoietic stimulating agents (ESAs) in low and INT-1 risk MDS** (Hege Garelius, Eva Hellström, Alex Smith): Admistration of ESA's in MDS varies significantly in the various countries within the EU-MDS Registry ranging from less than 20% in Poland to > 60% in several countries, including Greece. The chance of an MDS patient of being treated is dependent on several factors, including age, country and other factors. To correct for these factors, a propensity score for being treated with ESA's was developed. Correction for these factors showed a 15% survival benefit of patients who have been treated with ESA's, but this difference was not significant due to the broad confidence interval range. Patients with nontransfusion dependent anemia responding to ESA treatment had a 24 month longer duration before the first administered RBC.

   d) **Quality of Life (QoL) is influenced by RBC transfusions in time** (Reinhard Stauder): the EQ5D and the Visual Analogue Score (VAS) are reported in more than 80% of the patients in the Registry. VAS appear to be associated with the hemoglobin levels as expected (R: 0.22). VAS is negatively associated with the

intensity of RBC transfusions, but it levels off at more than 2 units/months. VAS showed a downward trend over time in both transfusion dependent and independent groups. The difference in this rate between the groups is 0.2 VAS units faster decrease per month in the transfused patients, 95% CI: 0.3 to 0.1 faster rate per month.

e) **The prognostic relevance of declining cytopenias in lower risk MDS** (Raphael Itzykson): RI presented this study at the ASH Annual Meeting, Dec 10th 2012, Atlanta (Abstract #700) and during the ELN breakfast meeting at ASH, Atlanta. He clearly showed that the kinetics of worsening of neutropenia and thrombocytopenia have prognostic value in lower-risk MDS. This prognostic value was independent of usual prognostic scoring systems, including: Revised IPSS, low-risk dedicated score LRPSS, time-dependent scores (WPSS). The kinetics of anemia was not interpretable because of the influence of RBC transfusions and treatment with ESA's.

f) **Progress of Iron Chelation Study with Novartis** (Theo de Witte, Alex Smith, Krista McKerracher): the first iron chelation analysis performed in 2011 when 55 patients had already received iron chelation showed interesting results. We developed an analysis plan which includes a propensity model to replace the matched pair analysis approach. Currently more than 100 patients have received iron chelation. AS will develop a draft analysis plan based on the current data. This plan will be discussed during a meeting of a task force from the EU-MDS Registry and collaborators from Novartis at Schiphol Airport March 15, 2013.

g) **Report on Cytomorphology review** (Marius MacKenzie, Ulrich Germing): MM and UG reported on the first Central morphologic review ELN EU-MDS Registry by the expert panel Morphology Review Panel in Düsseldorf 27-29 August, 2012. The 11 members of the panel reviewed 100 randomly selected slides. The data of the review have been entered into the database of the EU-MDS Registry in York. Further steps are to compare the original diagnoses with the diagnoses of the expert panel, to perform analyses of the single items, including dysplasia, to correlate quality of material and availability of staining (iron!). This will result in a final report. MM and UG will organize a second workshop including histology aiming at assessment of fibrosis, assessment of cellularity, cross validation cytology-histology.

h) **Future of Registry: report from steering committee meeting 31-1-13** in Nijmegen (David Bowen, Theo de Witte): the sponsor (RUNMC) has signed a contract with Novartis to further support the Registry: follow-up reports of 4th and 5th year follow-up of the first 1,000 patients. This will allow substantial support of the national coordinators, reporting fees, monitoring and the University of York until 2016. Support for the next cohort of 500 patients is in an advanced stage. Extension of the Registry to higher risk patients is still explored, but external funding remains unsettled until now.

2) **Report of the fifth international ELN workshop of FCM in MDS**, October 26-27, 2012 and presentation of new plans (Arjan van de Loosdrecht): the flowcytometry working group has discussed the possibilities to extend the flow score to the erythroid lineage as well. They defined the altered differentiation pattern in the erythroid lineages which might be incorporated in the flow score (manuscript in preparation). In addition

the absence of B-cell precursors in the CD34 population was identified as very specific for MDS. FC diagnostic score has been implemented in a prospective study. AvdL and W. Kern will organise 6th ELN MDS flow meeting at the MLL in Munich, Germany on October 25-26, 2013.

3) **Progress of the Trial Platform: EMSCO and discussion of planned trial(s)**
Uwe Platzbecker , Pierre Fenaux, Moshe Mittelmann, introduced Sonya Faber, the Head of Business Development of EMSCO. UP, PF and MM have developed an ELN-based MDS clinical trial coordinating office in Dresden. The main aims are: 1. to facilitate research, accelerate translation and optimize trial recruitment in MDS research in an ideal time frame, a coordinated collaboration and partnership between scientific study groups in Europe; 2. to prevent trial duplication and 3. to offer a focal point for trial design and consultation between major European MDS groups.
Phase 2 (2013) will consist of: solliciting additional funding from Pharma to make EMSCO financially independent; to develop Website and logo and to set-up a common trial (GFM/GMDS-SG) sharing biostatistician, possibly CRAs, data collection and management with the goal to identify hurdles and practical problems (e.g. submission to IRB and national authorities, insurance, central randomization, monitoring etc.). Two studies have been identified as potentially interesting for EMSCO: combination of lenalidomide with vidaza in 5q- syndrome who failed to respond to lenalidimide alone and combination of vidaza with a second drug: the pick a winner approach in high risk patients who failed vidaza alone.

4) **Progress ELN diagnostic and therapeutic guidelines and new plans, including specific guidelines for allogenetic SCT in MDS**
Luca Malcovati, Eva Hellstrom, Theo de Witte have completed the manuscript on the diagnostic and therapeutic guidelines. The manuscript has been sent to all co-authors and is ready for submission to Blood. The future plans are to develop a web-based scenario analysis aimed at evaluating the implementation of the guidelines, and the adherence to the recommendations in a large set of centers in Europe. In addition the EBMT has launched the idea to develop specific and detailed SCT guidelines as a further elaboration of the general ELN MDS guidelines. Theo de Witte has developed a draft programme and draft topics for the scenario analyses. The drafts will be circulated to the task force consisting of 6 to 8 experts from the EBMT MDS subcommittee and the ELN MDS Work Package 8.

5) **Optima: FP7 Application and beyond** - Joop Jansen
A grant application to the last of the 7th FP of the EU called: "Optimized personalized management of Lower-risk Myelodysplastic Syndrome patients leading to improved quality of life and supportive care based on scientific evidence (OPTIMA) has been submitted on October 2, 2012. Unfortunately the application did not pass the first stage (December 8, 2012). JJ has identified the 27 most frequently occurring mutated genes in MDS. He tested the amplification of these genes on material obtained from unstained smears. The DNA was of sufficient quality to allow deep sequencing of this material using the Roche 454 platform. He is currently testing the cheaper Ion-Torrent platform. He will also test deep sequencing on DNA from stained bone-marrow slides and from paraffin-embedded material. A pilot study will be performed on 30 to 50 patients from a few selected sites. Further develop database and automated analysis for known-SNPs Informed consents Status of new application.