NCU – Summative report for 2013

Report submission date: 22.02.14

Principal investigator: Eva Hellström Lindberg

Project title: *Nordic MDS Group (NMDSG) Clinical Trial program and new biobank and molecular platform to improve outcome for patients with MDS*

NCU grant received (€): 70 000

Project commencement and completion dates:

---

1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

The Nordic MDS Group performs investigator-initiated clinical trials aiming to improve symptom-free survival and cure rate for patients with myelodysplastic syndromes (MDS), and to increase clinical and biological understanding of these diseases through establishment of a clinical study database and a Nordic biobank platform. The study program encompasses new treatment against the severe anemia of low-risk MDS, as well as the very poor prognosis of high-risk MDS. A novel component of this project is to create a population-based DNA biobank from patients with MDS in the Nordic region in order to understand how different treatments should be selected in the future.

2. Summarize the major findings of the project (max. 400 words)

*Based on previous studies in the group, we have further evaluated and confirmed the strong negative impact of small TP53 mutated subclones in del(5q) low-risk MDS, a group that should not be treated with lenalidomide. This has been implemented in the Nordic Guidelines (www.nmds.org). The study has been accepted for publication

*The NMDSG randomized phase II trial, NMDSG10B, has been launched in all participating countries and enrolled close to 1/3 of planned patients. This study includes newly diagnosed patients with high-risk MDS and AML with del(5q) and evaluates the combination of azacytidine (standard treatment) ± lenalidomide in 72 patients, including also patients with early and potentially curable disease.

* The clinical phase II trial NMDSG08A tested the hypothesis that refractory transfusion-dependent anemia in low and INT-1 risk MDS can be attributed to epigenetic dysregulation and respond to treatment with Azacytidine ± EPO. The study enrolled 30/30 planned patients, showed overall negative results, which has led to modifications of the Nordic Guidelines. The study has been accepted for publication

* NMDSG has completed its first phase I dose finding study of eltrombopag in patients who have an indication for azacytidine and a pre-existing platelet count <75 x 10E9/l and to prepare

for a phase II study (new). 25% of intended patients have been recruited. Results were favourable and the ms has been submitted for publication

* All NMDSG trials render a common biobank with well-annotated MDS patients and we have developed an experimental platform that is shared between all researchers and enables genetic, epigenetic and stem cell studies. We have during 2013 tested and validated the Haloplex platform for 42 genes in 450 MDS samples from the NMDSG database and Stockholm region, as well as a new Haloplex kit of 72 genes. Moreover, all 4 participating countries have identified national population-based sample collections, and received ethical permit for targeted sequencing. The first analysis of approx. 200 Nordic patients will be analysed Q2 2014.

* NMDSG is working with new protocols for CMML and del(5q) MDS

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)

- MDS is a severe disease with poor estimated outcome both in INT-2 and high-risk MDS (approximately one year) and in lower risk groups with regular transfusion need. Moreover, patients with a regular transfusion need have a much poorer quality of life. The clinical trial program aims to improve symptoms and prognosis and cure rate in patients with MDS.
- The clinical trial program builds up a biobank, which is used to support biological studies across the Nordic region. These studies may lead to a better understanding both of basic biology of the disease and of mechanisms for response to various treatment alternatives.
- The Nordic MDS Group collaborators published since almost 10 years Nordic Guidelines for management of MDS, which serves to inform the haematological community about optimal management of the disease. Through these guidelines, new clinical findings are effectively implemented.

4. Outline how Nordic cooperation has added value to this project (max. 100 words)

- The incidence of MDS (4/100 000) makes Nordic corporation necessary if qualitative studies are to be performed. NMDSG is considered as one of the best clinical MDS groups in the world, much thanks to the long-standing support from NCU
- Part of the recent grant has been used to bring junior collaborators to the bi-annual meeting, which also includes sessions for junior research projects. This will ensure the survival" of NMDSG in the future.
- The results obtained from the studies are rapidly implemented in the clinical practise due to the Nordic Guidelines for MDS.
- During the last project period NMDSG has also formalised the preclinical collaboration and access to biobank material

5. Publications resulting from the NCU research grant

Nordic MDS Group IIT studies and predictive studies published since application 2010

1. Tobiasson M, Dybedahl I, Skov Holm M, Karimi M, Brandefors L, Garelius H, Grövdal M, Høgh Dufva I, Grønbæk K, Jansson M, Marcher C, Nilsson L, Olsnes A, Porwit A, Saft L,

Möllgård L, **Hellström-Lindberg E**. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor resistent, low and INT-1 risk MDS. Results from the Nordic NMDSG08A clinical Phase 2 trial. Accepted Blood Cancer Journal, 2014

2. Saft L, Karimi M, Ghaderi M, Matolscy A, Fenaux P, Mufti G, Giagounidis A, Selleslag D, Muus P, Sanz G, Mittelman M, Bowen D, Porwit A, Fu T, Backstrom J, MacBeth K, **Hellström-Lindberg E**. P53 Protein Expression is a strong predictor of outcome and cytogenetic response in patients with Low-/INT-1 risk myelodysplastic syndromes treated with Lenalidomide. Accepted, Haematologica, 2014
3. Svensson T , Chowdhury O, Garelius H, Lorenz F, Saft L, Jacobsen SEW, Eva Hellström Lindberg[6] and Cherif H. A pilot phase I dose finding safety study of the thrombopoietin-receptor agonist, eltrombopag, in patients with myelodysplastic syndrome treated with azacitidine. Submitted for publication

Corporate trials and international guidelines leading to further strengthend international position of NMDSG

4. Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Aug 26. [Epub ahead of print]

Translational studies made possible through sharing of biobank material from NMDSG trials.

5. Grövdal M, Karimi M, Tobiasson M, Johansson LE, Nikpour M, Luttrop K, Jansson M, Forsblom AM, Ungerstedt J, Kere J, Greco D, **Hellström-Lindberg E**. Azacitidine induces profound genome-wide hypomethylation in primary myelodysplastic bone marrow cell cultures. Leukemia. 2014;28:411-3
6. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, Yoon CJ, Ellis P, Wedge DC, Pellagatti A, Shlien A, Groves MJ, Forbes SA, Raine K, Hinton J, Mudie LJ, McLaren S, Hardy C, Latimer C, Della Porta MG, O'Meara S, Ambaglio I, Galli A, Butler AP, Waldin G, Teague JW, Quek L, Sternberg A, Gambacorti-Passerini C, Cross NC, Green AR, Boultwood J, Vyas P, **Hellstrom-Lindberg E**, Bowen D, Cazzola M, Stratton MR, Campbell PJ. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013 Sep 12. [Epub ahead of print]
7. Pellagatti A, Benner A, Mills KI, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, Jädersten M, Verma A, McDonald EJ, Killick S, **Hellström-Lindberg E**, Bullinger L, Wainscoat JS, Boultwood J. Identification of Gene Expression-Based Prognostic Markers in the Hematopoietic Stem Cells of Patients With Myelodysplastic Syndromes. J Clin Oncol. 2013 Sep 3. [Epub ahead of print]