Report NCU grant

Report submission date: 120214

Main applicant: Eva Hellström Lindberg

Project title: Investigator-initiated Nordic MDS Group GCP trials to improve outcome for patients with MDS and associated leukemias, and increasing biological understanding through establishment of a Nordic MDS experimental platform.

NCU grant received (€): 50 000

Project commencement and completion dates: Depending on specific aims, se below under “summarize major findings” which follow the initial study plan

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1. **Brief description of the project, written in a language understandable to non-scientists (Maximum length: 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 associated acute myeloid leukaemia (AML), 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. Since the last application, September 2010, 5 clinical and predictive studies have been published, one study has been completed, and another two have been initiated.

2. **Summarize the major findings of the project (Maximum length: 400 words)**

*The first Nordic MDS Group EU GCP clinical trial NMDSG07A study of increasing doses of lenalidomide in high-risk MDS and AML patients with a karyotype including del(5q) was successfully completed and published and has also, as intended, rendered spin-off publications. The results were promising with 35% clinical and cytogenetic response in this very advanced patient group, however, patients with documented TP53 mutation responded less well.

*The Nordic MDS Group reached the goal to initiate a subsequent randomized phase II trial, NMDSG10B, including upfront patients with high-risk MDS and AML with del(5q). This trial will evaluate the combination of azacytidine (standard treatment) ± lenalidomide in 72 patients, including also patients with early and potentially curable disease. The study opened February 7 2012, and will run in Sweden, Norway, Denmark, Finland and UK.

* The project set out to test the hypothesis that refractory transfusion-dependent anemia in low and INT-1 risk MDS can be attributed to epigenetic dysregulation and investigated the

efficacy of treatment with Azacytidine ± EPO. The study, NMDSG08A, has enrolled 30/30 planned patients, have been reported in abstract form Dec 2011, and will be summarized and submitted for publication Q3 2012. The Nordic clinical study structure has functioned in an excellent fashion. The outcome of treatment is poorer than expected, which may lead to the recommendation not to use this treatment in low and INT-1 risk MDS unless specific biomarkers, such as trisomy 8 are present.

* NMDSG has, as intended, launched 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.

* 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. In order to screen for recently identified candidate genes, we have initiated the first studies of a targeted resequencing methodology, analysing 30 candidate genes for mutations. Preliminary results are in validation.

* The strength gained by these IIT studies further supports the international status of NMDSG and the group will be part of 2 important corporate studies evaluating new drugs in MDS; Panabinostat which will be evaluated upfront in combination with azacytidine for high-risk MDS, and oral Tosedostat, which will be evaluated as a rescue treatment after azacytidine failure.

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

- MDS is a severe disease with poor estimated outcome both in INT-2 and high-risk MDS 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 (Maximum length 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 this grant

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

Grövdal M, Khan R, Aggerholm A, Antunovic P, Astermark J, Bernell P, Engström LM, Kjeldsen L, Linder O, Nilsson L, Olsson A, Skov Holm M, Tangen M, Wallvik J, Öberg G, Jacobsen SE, Porwit A, Hokland P, Hellström-Lindberg E. Maintenance treatment with azacytidine for patients with high-risk myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) following MDS in complete remission (CR) after induction chemotherapy. Br J Haematol. 2010;150:293-302. (NMDSG02B)

Gohring G, Giagounidis A, Busche G, Hofmann W, Kreipe HH, Fenaux P, Hellstrom-Lindberg E, Schlegelberger B. Cytogenetic follow-up by karyotyping and fluorescence in situ hybridization: implications for monitoring patients with myelodysplastic syndrome and deletion 5q treated with lenalidomide. Haematologica. 2011;96:319-22.

Jädersten M, Saft L, Smith A, Kulasekararaj A, Pomplun S, Göhring G, Hedlund A, Hast R, Schlegelberger B, Porwit A, Hellström-Lindberg E*, Mufti G*. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. Journal of Clinical Oncology, 2011;29:1971-9.

Möllgård L, Saft L, Bach Treppendahl M, Dybedal I, Maxwell Nørgaard J, Astermark J, Ejerblad E, Garelius H, Høgh Dufva I, Jansson M, Jädersten M, Kjeldsen L, Linder O, Nilsson L, Vestergaard H, Porwit A, Grønbæk K, Hellström Lindberg E. Clinical effect of high-dose Lenalidomide in High-Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia with Chromosome 5 Abnormalities. Haematologica. 2011;96:963-71. (NMDSG07A)

Nilsson-Ehle H, Birgegård G, Samuelsson J. Antunovic P, Astermark J, Garelius H, Engström LM ,Kjeldsen L, Nilsson L, Olsson A, Skov-Holm M, Wallvik J[1], Gulbrandsen N, Hellström-Lindberg E. Quality of life, physical function and MRI T2* in elderly low-risk MDS patients treated to a hemoglobin level of 120 g/l with darbepoetin alfa ± filgrastim, or erythrocyte transfusions. Eur J Haematol. 2011 Sep;87(3):244-52 (NMDSG03A)

Corporate trials published since 2010 leading to further strengthned international position of NMDSG

Kantarjian HM, Fenaux P, Sekeres MA, Becker P, Boruchov A, Bowen D, Hellstrom-Lindberg E, Larson RA, Lyons RM, Muus M, Shammo J, Siegel R, Hu K, Franklin J, and Berger D. Safety and Efficacy of Romiplostim in Patients With Lower-risk Myelodysplastic Syndrome (MDS) and Thrombocytopenia J Clin Oncol. 2010;28:437-44.

Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, Sanz G, List AF, Gore S, Seymour JF, Dombret H, Backstrom J, Zimmerman L, McKenzie D, Beach CL, Silverman LR. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28(4):562-9.

Fenaux P, Giagounidis A, Selleslag D, Beyne-Rauzy O, Mufti G, Mittelman M, Muus P, Te Boekhorst P, Sanz G, Del Cañizo C, Guerci-Bresler A, Nilsson L, Platzbecker U, Lübbert M, Quesnel B, Cazzola M, Ganser A, Bowen D Dr, Schlegelberger B, Aul C, Knight R, Francis J, Fu T, Hellström-Lindberg E. A randomized phase 3 study of lenalidomide versus placebo

in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011;118:3765-3776.

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

Göhring G, Lange K, Hofmann W, Nielsen KV, Hellström-Lindberg E, Roy L, Morgan M, Kreipe H, Büsche G, Giagounidis A, Schlegelberger B. Telomere shortening, clonal evolution and disease progression in myelodysplastic syndrome patients with 5q deletion treated with lenalidomide. Leukemia. 2012 Feb;26(2):356-8.

Treppendahl MB, Qiu X, Søgaard A, Yang X, Nandrup-Bus C, Hother C, Andersen MK, Kjeldsen L, Möllgaard L, Hellström-Lindberg E, Jendholm J, Porse BT, Jones PA, Liang G, Grønbæk K. Allelic methylation levels of the noncoding VTRNA2-1 located on chromosome 5q31.1 predict outcome in AML. Blood. 2012 Jan 5;119(1):206-16.