

## NCU – Summative report for 2014

Report submission date:

Principal investigator: Hans Erik Johnsen

Project title: *Classification and Prediction of Clinical Resistance in Multiple Myeloma - EMN-02 / NMSG19/10*

NCU grant received (€): 25,000

Project commencement and completion dates: 01.07.2012 – 31.12.2015

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

Previously, we have used a preclinical model of malignant B-cell lines to study molecular mechanisms of resistance in multiple myeloma by combining drug induced growth inhibition and gene expression profiling. The resistance index (RI) has been retrospectively validated in the HOVON65/GMMG-HD4 trial data set. In a multivariate analysis correcting for age, sex and ISS-staging, we found a high RI to melphalan to be an independent variable associated with inferior survival for patients with multiple myeloma (1).

Now, these observations need to be confirmed prospectively in biological tumor material from the current EMN-02 trial biobank material.

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

The EMN-02 study was officially closed for inclusion on 15 April 2014. In the Nordic area we have included 141 patients into the EMN-02 trial, which in total now has 1500 patients enrolled.

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

To be able to use all samples we have modified our technologies, allowing us to use frozen samples from all patients (2) for sorting of minor B-cell subsets for microarray gene expression analysis (3).

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

The trial is running in a sufficient way, with contact to all regional coordinators and research nurses following presentations and discussion during the Nordic meetings in Copenhagen and Stockholm. The Nordic collaboration will deliver about 20% of patients and samples for the trial.

**5. Publications resulting from the NCU research grant**

1. Andersen JP, Bøgsted M, Dybkær K, Mellqvist UH, Morgan GJ, Goldschmidt H, Dimopoulos MA, Einsele H, San Miguel J, Palumbo A, Sonneveld P, Johnsen HE. Global myeloma research clusters, output, and citations: a bibliometric mapping and clustering analysis. PLoS One. 2015 Jan 28;10(1):e0116966.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538-48. doi:10.1016/S1470-2045(14)70442-5. Review.
3. Bøgsted M, Bilgrau AE, Wardell CP, Bertsch U, Schmitz A, et al. (2013) Proof of the concept to use a malignant B cell line drug screen strategy for identification and weight of melphalan resistance genes in multiple myeloma. PLoS One 8: e83252. Available: <http://dx.plos.org/10.1371/journal.pone.0083252>. Accessed 2 January 2014.
4. Rasmussen SM, Bilgrau AE, Schmitz A, Falgreen S, Bergkvist KS, et al. (2014) Stable phenotype of B-cell subsets following cryopreservation and thawing of human lymphocytes stored in a tissue biobank. Submitted Cytometry B Clin Cytom.
5. Bergkvist KS, Nyegaard M, Bøgsted M, Schmitz A, Bødker JS, et al. (2014) Validation and implementation of a method for microarray gene expression profiling of minor B-cell subpopulations in man. BMC Immunol 15: 3. Available: <http://www.biomedcentral.com/1471-2172/15/3>. Accessed 7

February 2014.

6. Engelhardt M, Terpos E, Kleber M, Gay F, Wäsch R, Morgan G, Cavo M, van de Donk N, Beilhack A, Bruno B, Johnsen HE, Hajek R, Driessen C, Ludwig H, Beksac M, Boccadoro M, Straka C, Brighen S, Gramatzki M, Larocca A, Lokhorst H, Magarotto V, Morabito F, Dimopoulos MA, Einsele H, Sonneveld P, Palumbo A; European Myeloma Network. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica*. 2014 Feb;99(2):232-42. doi: 10.3324/haematol.2013.099358. PubMed PMID: 24497560; PubMed Central PMCID: PMC3912952.
7. Johnsen HE, Bergkvist KS, Schmitz A, Kjeldsen MK, Hansen SM, Gaihede M, Nørgaard MA, Bæch J, Grønholdt ML, Jensen FS, Johansen P, Bødker JS, Bøgsted M, Dybkær K; for the Myeloma Stem Cell Network (Mscnet). Cell of origin associated classification of B-cell malignancies by gene signatures of the normal B-cell hierarchy. *Leuk Lymphoma*. 2013 Nov 1. [Epub ahead of print] PubMed PMID:23998255.
8. Lanza F, Campioni DC, Hellmann A, Milone G, Wahlin A, Walewski J, Spedini P, Fiamenghi C, Cuneo A, Knopińska W, Swierkowska-Czeneszew M, Petriz J, Fruehauf S, Farge D, Mohty M, Passweg J, Ruuto T, Madrigal A, Johnsen HE; Quality Assessment of Haematopoietic Stem Cell Grafting Committee of European Blood and Marrow Transplantation Society. Individual quality assessment of autografting by probability estimation for clinical endpoints: a prospective validation study from the European group for blood and marrow transplantation. *Biol Blood Marrow Transplant*. 2013 Dec;19(12):1670-6. doi: 10.1016/j.bbmt.2013.08.005. Epub 2013 Aug 27. PubMed PMID: 23988403.
9. Bødker JS, Gyruup C, Johansen P, Schmitz A, Madsen J, Johnsen HE, Bøgsted M, Dybkær K, Nyegaard M. Performance comparison of Affymetrix SNP6.0 and cytogenetic 2.7M whole-genome microarrays in complex cancer samples. *Cytogenet Genome Res*. 2013;139(2):80-7. doi: 10.1159/000345125. Epub 2012 Nov 20. PubMed PMID: 23182917.
10. Kloster MB, Bilgrau AE, Rodrigo-Domingo M, Bergkvist KS, Schmitz A, Sønderkær M, Bødker JS, Falgreen S, Nyegaard M, Johnsen HE, Nielsen KL, Dybkaer K, Bøgsted M. A model system for assessing and comparing the ability of exon microarray and tag sequencing to detect genes specific for malignant B-cells. *BMC Genomics*. 2012 Nov 5;13:596. doi: 10.1186/1471-2164-13-596. PubMed PMID: 23127183; PubMed Central PMCID: PMC3505742.
11. Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, Chomienne C, Ishikawa F, Schuringa JJ, Stassi G, Huntly B, Herrmann H, Soulier J,

Roesch A, Schuurhuis GJ, Wöhrer S, Arock M, Zuber J, Cerny-Reiterer S, Johnsen HE, Andreeff M, Eaves C. Cancer stem cell definitions and terminology: the devil is in the details. *Nat Rev Cancer*. 2012 Nov;12(11):767-75. doi: 10.1038/nrc3368. Epub 2012 Oct 11. PubMed PMID: 23051844.

12. Ross FM, Avet-Loiseau H, Ameye G, Gutiérrez NC, Liebisch P, O'Connor S, Dalva K, Fabris S, Testi AM, Jarosova M, Hodgkinson C, Collin A, Kerndrup G, Kuglik P, Ladon D, Bernasconi P, Maes B, Zemanova Z, Michalova K, Michau L, Neben K, Hermansen NE, Rack K, Rocci A, Protheroe R, Chiecchio L, Poirel HA, Sonneveld P, Nyegaard M, Johnsen HE; European Myeloma Network. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. *Haematologica*. 2012 Aug;97(8):1272-7. Epub 2012 Feb 27. PubMed PMID: 22371180; PubMed Central PMCID: PMC3409827.