Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2014
Søknad	Biomarker-driven, risk-adapted trials in aggressive lymphomas and Hodgkin lymphoma
Søknadsid	154848
Innsendt av	Peter de Nully Brown - for the Nordic Lymphoma Group

Oppgave: Progress report

Tilordnet	Peter de Nully Brown - for the Nordic Lymphoma Group
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RAPPORT

Briefly describe the project in a language understandable to non-scientists

The Nordic Lymphoma Group (NLG) is the only organization providing the logistic and scientific infrastructure necessary to carry out investigator-initiated Nordic trials in patients with lymphoid malignancies. The aims of NLG research are:
(1) to search for novel biomarkers and outcome predictors to guide the selection of better interventional strategies in order to improve outcome and quality of life in patient with lymphoid malignancies of aggressive histology
(2) to initiate and perform collaborative Nordic interventional clinical trials, based on the generated translational data, involving the research community within the four Nordic countries participating in the NLG collaboration

Summarize the major findings of the project

Large cell lymphoma:

Correlative studies on the basis of CRY-04 trial material - Recent publications demonstrate survival association of tumor associated macrophages and MYC, BCL-2 and TP53 alterations in clinically high risk DLBCL. Several other manuscripts describing for example plasma protein and miRNA profiles, and survival associated mutations in patients with high risk DLBCL have been submitted for publication. CHIC study was closed for recruitment on Dec 2014. Total of 143 patients were included. Results from the second interim analyses on Feb 2015 showed satisfactory response rates and reasonable toxicity (Abstract in ICML-13). A new biomarker-driven and risk-adapted phase II study for DLBCL patients will start in Q2 2016.

T-cell lymphoma:

The NLG coordinated ACT-1 trial ended its recruitment in Dec 2013 (N=257) and the final analysis, ‘unsupervised’ for the CD52 bio-feature of the tumor specimens, was performed in Q2 2015. Collection of biological material for the completion of the ‘supervised’ final analysis is currently ongoing and is expected to be completed within the current calendar year. Correlative studies on biology, diagnostic imaging etc. will ensue. Data on the late follow-up (median 9.5 years) of the NLG-T-01 study cohort was presented as a plenary oral paper at the 14th International Congress of Malignant Lymphoma in Lugano, Switzerland, and a manuscript is in preparation. The NLG-T-01 correlative studies are ongoing based on the construction of a common trial-specific tissue micro array. The construction of the trial-specific TMA, performed by a PhD student travelling to the relevant pathology departments of participating Nordic centers to collect, with appropriate authorizations, cores from trial samples, and the subsequent laboratory tests, are achievements almost entirely related and made possible by the NCU funding. A new phase I/phase II treatment protocol for relapsed/refractory aggressive lymphomas has been written, submitted to national authorities and finally approved (1st approval country: DK). The trial will be coordinated (overall PI) by the NLG and conducted in the Nordic countries (NLG), the Netherlands (HOVON group) and in single additional centers in countries outside the two consortia. The trial will test the feasibility and efficacy of a combination regimen consisting of pixantrone, etoposide, bendamustine and, in CD20+ tumors, rituximab in relapsed/refractory aggressive lymphomas of both B- and T-cell origin. A new ‘adaptive design’ front-line trial for treatment-naïve PTCL belonging to all age strata is under preparation within the T-cell Working Group along with a randomized phase II trial for relapsed/refractory CD30+ PTCL/CD30+ aggressive lymphomas.

Hodgkin lymphoma:

New protocol for elderly patients with HL is starting, including brentuximab vedotin and chemotherapy. The study will explore the substitution of vincristin by brentuximab vedotin in CHOP, a regimen commonly used for elderly HL patients in the Nordic countries. Patients not fit for chemotherapy will be offered brentuximab alone. The first patients have been included in this trial

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

Effective treatments are available for some lymphoid cancers and may cure a fraction of patients, however, current treatments may still be unsuccessful and/or difficult to tolerate, so that ultimately only 40-50% of the entire patient cohort may achieve cure. There is still a largely unmet clinical need for identifying biomarkers that can be used both as targets and/or outcome predictors for biomarker-driven, risk-stratified interventional clinical trials. In this context, aggressive lymphoma entities such as diffuse large B-cell lymphoma (DLBCL) (ca 30% of all lymphomas in Nordic countries), mantle cell lymphoma (MCL) (ca 10-15% of all lymphomas in Nordic countries) and peripheral T-cell lymphoma (PTCL) (ca 10-15% of all lymphomas in Nordic countries) represent, taken together, more than half of all lymphoid malignancies. NLG protocols provide new effective treatment schedules for the aggressive lymphomas and the previous protocols are clinical routine in Nordic countries.

Outline how Nordic cooperation has added value to this project

The number of cases diagnosed annually countrywise within each subtype is often too small to allow the conduct of medium-large size clinical trials. In order to gain increased knowledge, particularly at subtype level, large, homogeneously treated patient cohorts with a possibility for long-term follow-up are needed.

The Nordic collaboration provided by the NLG framework enables us to recruit patient cohorts of sufficient size to study lymphoma subtypes clinically and molecularly, and to follow them prospectively in order to gain clinically relevant new translational knowledge. Also, the Nordic group contributes substantially with patient accrual into collaborative European randomised trials.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
Pedersen MØ, Poulsen TS, Gang AO, Knudsen H, Lauritzen AF, Pedersen M, Nielsen SL, Brown P, Høgdall E, Nørgaard P. Lack of topoisomerase copy number changes in patients with de novo and relapsed diffuse large B-cell lymphoma. Exp Hematol. 2015 Jul;43(7):534-6	25931012
Mylam KJ, Kostakoglu L, Hutchings M, Coleman M, Lamonica D, Czuczman MS, Diehl LF, Nielsen AL, Jensen P, Loft A, Hendel HW, Iyer V, Leppä S, Jyrkkiö S, Holte H, Eriksson M, Gillstrøm D, Hansen PB, Seppänen M, Hjorthaug K, Brown Pde N, Pedersen LM(18)F-fluorodeoxyglucose-positron emission tomography/computed tomography after one cycle of chemotherapy in patients with diffuse large B-cell lymphoma: results of a Nordic/US intergroup study. Leuk Lymphoma. 2015 Jul;56(7):2005-12	25330442
Blaker YN, Brodtkorb M, Maddison J, Hveem TS, Nesheim JA, Mohn HM, Kolstad A, Geisler CH, Liestøl K, Smeland EB, Holte H, Delabie J, Danielsen H. Computerized image analysis of the Ki-67 proliferation index in mantle cell lymphoma. Histopathology. 2015 Jul;67(1):62-9	25431344
Ellin F, Landström J, Jerkeman M, Relander T. Central nervous system relapse in peripheral T-cell lymphomas: a Swedish Lymphoma Registry study. Blood. 2015 Jul 2;126(1):36-41.	25957393
Husby S, Ralfkiaer U, Garde C, Zandi R, Ek S, Kolstad A, Jerkeman M, Laurell A, Räty R, Pedersen LB, Pedersen A, Ehinger M, Sundström C, Karjalainen-Lindsberg ML, Delabie J, Clasen-Linde E, Brown P, Cowland JB, Workman CT, Geisler CH, Grønbæk K. miR-18b overexpression identifies mantle cell lymphoma patients with poor outcome and improves the MIPI-B prognosticator. Blood. 2015 Apr 23;125(17):2669-77	25736311
Combining MYC, BCL2 and TP53 gene and protein expression alterations improves risk stratification in diffuse large B-cell lymphoma. Fiskvik I, Beiske K, Delabie J, Yri O, Spetalen S, Karjalainen-Lindsberg ML, Leppä S, Liestøl K, Smeland EB, Holte H. Leuk Lymphoma. 2015 Jun;56(6):1742-9.	25284491
Pulczynski EJ, Kuittinen O, Erlanson M, Hagberg H, Fosså A, Eriksson M, Nordstrøm M, Østenstad B, Fluge Ø, Leppä S, Fiirgaard B, Bersvendsen H, Fagerli UM. Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group. Haematologica. 2015 Apr;100(4):534-40.	25480497
Riihijärvi S, Fiskvik I, Taskinen M, Vajavaara H, Tikkala M, Yri O, Karjalainen-Lindsberg ML, Delabie J, Smeland E, Holte H, Leppä S. Prognostic influence of macrophages in patients with diffuse large B-cell lymphoma: a correlative study from a Nordic phase II trial. Haematologica. 2015 Feb;100(2):238-45.	25381134
Andersen MD, Kamper P, Nielsen PS, Bendix K, Riber-Hansen R, Steiniche T, Hamilton-Dutoit S, Clausen M, d'Amore F. Tumour-associated mast cells in classical Hodgkin's lymphoma: correlation with histological subtype, other tumour-infiltrating inflammatory cell subsets and outcome. Eur J Haematol. 2016 Mar;96(3):252-9	25963595

Brief overview of expenditures for last year 1 vedlegg (NLG NCU account 2015.pdf)

NCU Grant account 2015	Euro
Tissue Micro array	
Lab technician	7500
Travelling costs	2000
Freezer storage	1000
equipment/reagents	2000
Data Management and statistics (IMISE, Leipzig	27500
Total	40000