Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2015
Søknad	Clinical trial-based precision medicine in the Nordic countries for patients with aggressive lymphomas
Søknadsid	176832
Innsendt av	Peter de Nully Brown - for the Nordic Lymphoma Group

Oppgave: Progress report

Tilordnet	Peter de Nully Brown - for the Nordic Lymphoma Group
Status	Løst
Opprettet	10.02.2017

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:

CHIC study testing the impact of dose dense chemoimmunotherapy with early CNS prophylaxis on the outcome of high risk DLBCL patients was closed for recruitment on Dec 2014. Total of 143 patients were included, and the results from the final analyses presented at ASH 2016. A new biomarker-driven and risk-adapted trial for DLBCL patients will open for inclusion in Q2 2017. Correlative studies on the basis of CHIC and a previous CRY-04 trial material are ongoing. To date, the studies have demonstrated survival association of tumor associated macrophages, and MYC, BCL2, TP53 and DTX1 alterations in high risk DLBCL. Several other studies describing for example plasma protein and miRNA profiles, and impact of alternative splicing on survival have been published or submitted for publication.

Mantle cell lymphoma:
The Nordic MCL group will join the upcoming European MCL Net TRIANGLE three-arm trial, testing intensive therapy + ibrutinib in younger untreated patients. The trial will start in autumn 2015 in Germany and France with a safety run in of 50 patients, and inclusion started in the Nordic area in q1 2017. MCL4 1st-line trial “Lena-BeRit” trial completed 2013 with 50 patients, and was published in Blood in 2016. Plan to join ENRICH trial: phase III trial, comparing rituximab+ibrutinib with rituximab-chemo in q3 2017. A second line phase-II trial, NLG-MCL6, “Philemon” opened in May 2015 also with a chemotherapy-free approach: Ibrutinib, rituximab and lenalidomide, followed by ibrutinib+rituximab maintenance, and was concluded one year later, after inclusion of 50 patients.

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 has been published.. A new phase I/phase II treatment protocol for relapsed/refractory aggressive lymphomas has been initiated with ongoing inclusion. 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.

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)
El-Galaly TC, Jakobsen LH, Hutchings M, de Nully Brown P, Nilsson-Ehle H, Székely E, Mylam KJ, Hjalmar V, Johnsen HE, Bøgsted M, Jerkeman M Routine Imaging for Diffuse Large B-Cell Lymphoma in First Complete Remission Does Not Improve Post-Treatment Survival: A Danish-Swedish Population-Based Study. J Clin Oncol	26438115
Eskelund CW, Kolstad A, Jerkeman M, Räty R, Laurell A, Eloranta S, Smedby KE, Husby S, Pedersen LB, Andersen NS, Eriksson M, Kimby E, Bentzen H, Kuittinen O, Lauritzsen GF, Nilsson-Ehle H, Ralfkiaer E, Ehinger M, Sundström C, Delabie J, Karjalainen-Lindsberg ML, Workman CT, Garde C, Elonen E, Brown P, Grønbaek K, Geisler CH.15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol	27378674
Jakobsen LH, Hutchings M, de Nully Brown P, Linderoth J, Mylam KJ, Molin D, Johnsen HE, Bøgsted M, Jerkeman M, El-Galaly TC. No survival benefit associated with routine surveillance imaging for Hodgkin lymphoma in first remission: a Danish-Swedish population-based observational study. Br J Haematol. 2016	26846879
Albertsson-Lindblad A, Kolstad A, Laurell A, Räty R, Grønbæk K, Sundberg J, Pedersen LB, Ralfkiær E, Karjalainen-Lindsberg ML, Sundström C, Ehinger M, Geisler C, Jerkeman M.Lenalidomide-bendamustine-rituximab in untreated mantle cell lymphoma > 65 years, the Nordic Lymphoma Group phase I+II trial NLG-MCL4.Blood. 2016	27354719
Cheah CY, Brockelmann PJ, Chihara D, Moskowitz AJ, Engert A, Jerkeman M, El-Galaly TC, Augustson B, Vose J, Bartlett NL, Villa D, Connors JM, Feldman T, Pinnix CC, Milgrom SA, Dabaja B, Oki Y, Fanale MA. Clinical characteristics and outcomes of patients with Hodgkin lymphoma with central nervous system involvement: An international multicenter collaboration. Am J Hematol. 2016	27222367
Hoster E, Geisler CH, Doorduijn J, van der Holt B, Walewski J, Bloehdorn J, Ribrag V, Salles G, Hallek M, Pott C, Szymczyk M, Kolstad A, Laurell A, Raty R, Jerkeman M, Van't Veer M, Kluin-Nelemans JC, Klapper W, Unterhalt M, Dreyling M, Hermine O. Total body irradiation after high-dose cytarabine in mantle cell lymphoma: a comparison of Nordic MCL2, HOVON-45, and European MCL Younger trials. Leukemia. 2016	26598017
van Imhoff, G. W., McMillan, A., Matasar, M. J., Radford, J., Ardeshna, K. M., Kuliczkowski, K., Kim, W., Hong, X., Goerloev, J. S., Davies, A., Barrigon, M. D., Ogura, M., Leppa, S., Fennessy, M., Liao, Q., van der Holt, B., Lisby, S., and Hagenbeek, A. (2016) Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. J Clin Oncol, 2016	28029326

Brief overview of expenditures for last year 1 vedlegg (NLG NCU account 2016.pdf)

NCU Grant account 2016	Euro
Tissue Micro array	
Lab technician	10000
Travelling costs	5400
Freezer storage	1000
equipment/reagents	2000
Study meeting, 5 timer in 2016	7300
Data Management and statistics	14300
Total	40000