Nordic Lymphoma Group

Newsletter June 2023

Dear members of the NLG society,

All members of NLG and representatives of collaborating companies are welcome to the next NLG Plenary meeting November 8-9, 2023, at the Scandic Strandpark Hotel, close to Copenhagen Airport, same as last year. The preliminary program is enclosed. Recent lymphoma research will be presented from all countries as in previous years, and invited speakers will inspire, by highlighting current topics on both clinical and translational research on lymphomas.

NLG is hereby also inviting representatives from the pharmaceutical companies, representing relevant products used for diagnosing and treatment of malignant hematological diseases, to participate in our annual plenary meeting.

Wish you all warmly welcome to attend the meeting. Link for participation is found on our homepage, www.Nordic-lymphoma.org and here: https://na.eventscloud.com/nlg2023

Looking forward to seeing you in November!

All the best,

Mats

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NLG Plenary meeting – working groups

Working group meetings may be arranged either physically or virtually in advance of the plenary meeting.

Abstract submission

Please send your abstract and case presentation before October 1st to your national member of the NLG coordination group.

Free papers session

Scientific papers on on-going lymphoma research from each country are appreciated and will be presented in this session.

Young scientists and PhD-students are encouraged to submit abstracts to their national representatives.

NLG Plenary Meeting 2023

08.11.2023		
1000-1200	CTO session (research nurses/coordinators)	
1200-1300	*Registration and lunch*	
1300-1500	***NLG Epidemiology Educational Session***	
1300-1330	Causal inference in real-world studies Sandra Eloranta/Lasse Jakobsen	Moderator: Tarec El-Galaly
1330-1400	Estimand framework and novel trial designs Kasper Rufibach, Biostatistician, Roche, Basel	
1400-1430	*Coffee Break*	
1430-1530	Building real-world data cohorts – LEO/SPORE James Cerhan, Professor, Mayo Clinic, Rochester, US	
1530-1545	*Coffee break*	
1545-1700	Precision medicine in lymphoma Philipp Staber, Ass prof, University of Vienna, Austria	Moderator: Sirpa Leppä
1700-1800	Free papers – session 1	Moderator: Alexander Fosså
1800-1830	Business meeting	

09.11.2023		
0830-0900	Lymphoma management in Estonia Tatjana Tratš	Moderator: Susanna Mannisto
0900-1000	Free papers – session 2	
1000-1030	*Coffee + Poster session*	
1030-1100	Large cell group	Moderator: Björn Wahlin
1100-1130	CNS group	
1130-1200	Mantle cell group	
1200-1300	*Lunch*	
1300-1330	Indolent group	Moderator: Peter Brown
1330-1400	Hodgkin group	
1400-1430	Epidemiology group	
1430-1500	*Coffee break*	
1500-1530	T-cell group	
1530-1600	Pathology group	

Update on working group activities

Indolent group

The SAKK-NLG 35/14 phase II study comparing Rituximab with or without Ibrutinib for untreated patients with advanced follicular lymphoma will present results at the Lugano meeting in a month.

The NLG will open / are opening two new academic studies for follicular lymphoma. MERLIN is for 2nd line treatment in patients with early progression (POD24+) of disease. This is a selected group of patients with a poor prognosis. All included patients will be treated with single-agent mosunetuzumab, a new bispecific CD3/CD20 antibody. Roche contributes funding and drug. The trial is about to start now.

Regarding first-line follicular lymphoma, the FLAME study was cancelled because of company pullout in December 2022, but luckily, we have devised a new proposal called FLIRT which was approved by Incyte this spring. A first protocol version for FLIRT is being finalized and it will be reviewed by the company and regulatory agencies the coming months. FLIRT will have the same division into low-risk and high-risk patients, based on LDH, B2M and urgent need of treatment. High-risk patients will all receive rituximab-lenalidomide + tafasitamab (CD19 antibody) with a short maintenance with lenalidomide-tafasitamab (total treatment one year). Low-risk patients will receive rituximab-lenalidomide and 1:1 randomization to tafasitmab (no maintenance). Primary endpoint is event-free survival at 24 months.

For splenic MZL we will cooperate with IELSG in the RITZ trial, which will start this year (probably). RITZ is a randomized phase III trial for 1st line treatment: rituximab alone or combined with zanubrutinib with a fixed treatment duration.

Large cell group

Clinical studies
Young high-risk patients: NLG-LBC-06 (BIO-CHIC) phase II trial, which is testing whether stratification of the patients according to biological risk factors for different treatment groups can further improve the outcome of the patients with clinically high risk DLBCL enrolled the planned 120 patients in Feb 2021. Results from the safety and efficacy analysis were presented at ASH 2022 in December, showing highly satisfactory FFS, PFS, OS and CNS recurrence rates. Results from the associated substudy, which is exploring the impact of pretreatment and end-of-therapy (MRD) circulating tumor DNA levels on treatment outcome will be presented at ICML 2023 on June.

After Bio-CHIC trial, we plan to conduct a ctDNA-guided phase II trial, where we will determine if ctDNA levels can be used to guide treatment decisions. The patients will be stratified according to their ctDNA levels to different treatment groups, and based on high, intermediate, or low ctDNA levels either de-escalate, continue, or change to experimental therapy.

Elderly patients: The ongoing randomized phase III POLAR BEAR trial for elderly patients with DLBCL (>80 years, or frail >75 years) is comparing standard treatment, R-mini-CHOP with a

regimen where vincristine has been substituted by the anti-CD79b immunoconjugate polatuzumab vedotin. By the end of May 2023, 147 patients have been included from the Nordic area and from Italy. The trial will now be expanded to 300 patients and enroll patients also from Australia. The trial DSMB reviewed safety data from the first 100 patients in August 2022, and recommended continuous enrolment according to protocol. Interim safety data will be presented at EHA 2023 on June.

Correlative studies on the basis of trial material
Several trial-related translational projects are ongoing. To date, the studies have demonstrated for example survival association of tumour infiltrating immune cells, soluble serum proteins and circulating tumor DNA levels.

CNS-lymphoma group

The working group is planning to start a descriptive, prospective 1st line PCNSL trial. In this trial, we will study the outcome, functional and neurological status, and health-related quality of life of newly diagnosed PCNSL patients treated with standard of care therapy in the Nordic countries. In addition, diagnostic and response assessment MRI images, diagnostic tumor tissue, CSF, and peripheral blood (PB) are collected for epidemiological, prognostic, and predictive biological and translational studies.

An update on the previous NLG phase II first line PCNSL study, published in 2015, with a median follow-up of 76 months is under preparation for publication.

MCL group

Younger patients (<65 years): The Nordic MCL group has participated in the European MCL Net TRIANGLE phase III three-arm trial, testing intensive therapy + ibrutinib in younger untreated patients. The trial started in the Nordic area in q4 2016 and was closed for enrolment in January 2021. 870 patients were randomized, making this the largest clinical trial in MCL so far. 111 patients have been enrolled from NLG centres. Data were presented at the ASH meeting in December 2022, showing that addition of ibrutinib to induction and as maintenance, improves failure-free survival, which will likely have impact on clinical practice.

Elderly patients: Since December 2017, NLG has participated in the ENRICH trial, with University of Plymouth as sponsor. This is a randomized phase III trial, comparing rituximab+ibrutinib with rituximab-chemo (either R-bendamustine or R-CHOP). Enrolment was finalized in June 2021, and results are expected in 2024.

In Q4 2021, a new trial for elderly patients, NLG-MCL8, ALTAMIRA, started recruitment.
This includes patients >60 years with untreated MCL, using a novel combination of another BTK-inhibitor, acalabrutinib, and rituximab. This is a phase II trial with a maximum treatment duration of 1 year, except for patients with biological high risk features. By the end of April, 2023, 55 of 80 patients have been enrolled, and is open for centres in Sweden and Norway. Soon, centres in Denmark, Finland and South Korea will be able to enroll patients.

The NLG trial for relapsed MCL, NLG-MCL7, VALERIA, exploring the combination of venetoclax, lenalidomide and rituximab, was concluded in April 2021, with 59 patients. This is a phase I-II trial, for patients with relapsed MCL, and a population of untreated MCL, ineligible for combination chemotherapy. This trial also explores a novel treatment strategy for MCL, an MRD-driven approach, where treatment will be stopped following molecular remission. Final results were presented at ASH 2022, showing that stopping treatment in molecular remission is feasible.

In collaboration with the European MCL Network, we plan to start a phase IB-II trial, PLATO, with a novel combination, glofitamab+pirtobrutinib, initially in patients with R/R MCL, but later on also in previously untreated patients.

T cell group

PANTHEON trial:
The latest trial proposal from the NLGs Working Group on T-cell lymphomas, the PANTHEON trial (**PAN T-H**istological **E**ntities trial **O**f the **N**ordic lymphoma group), has evolved in design and infrastructural planning within the last year. An application for academic funding of the trial is planned for 2023. Further funding will be negotiated with potential partners from the pharmaceutical industry (consolidation part). The PANTHEON trial will address two main questions: (i) does measurement of minimal residual disease by means of liquid biopsies (ctDNA) improve response assessment compared to the current standard-of-care (PET/CT)?; (ii) does a biofeature-driven post-induction consolidation (6 months) reduce the occurrence of post-induction relapses as compared to current standard-of care (observation only)? The PANTHEON trial is designed to include all PTCL subtypes ('PAN T-Histological entities') in the context of a full spectrum of clinical fitness categories, i.e. 'fit', 'frail' and 'vulnerable'. The induction treatment will be given as per national guidelines in order to optimize inclusion of most of the PTCL patients throughout the Nordic countries. Possible collaborations with other countries in Europe and Asia are under consideration. Collaborations with labs within Denmark regarding analysis of ctDNA have been initiated, and pilot samples are sent to professor Niels Pallisgaard's lab in Roskilde, Denmark for optimization of methods.
There have been virtual working group meetings during Q1 and Q2 2023 regarding ongoing and planned projects and additional meetings will take place during the fall.

ACT trial:
The final analysis of the ACT-2 trial (elderly patients; >60 yrs) has been published in Leukemia (Wulf GG et al, Leukemia, 2021). The final analysis paper of the ACT-1 trial is in preparation and still waits for the final details regarding gene expression data characterizing the "predictor of alemtuzumab response (PAR)". The ACT-1 final analysis data were presented as an oral paper at ASH in December 2018.
Additional translational studies based on the ACT-1 trial biospecimens are ongoing in collaboration with Javeed Iqbal in Omaha, Nebraska. A combined analysis of long-term outcome of the ACT-1 and ACT-2 trials is in progress.

NLG-T-01 trial:

Data on long-term follow-up (median 10 years) data from the NLG-T-01 study, including those patients, whose tissue samples have been analyzed for DUSP-22 and TP63 rearrangements, was presented orally at the ASH meeting in 2022. The data set comprises the single PTCL subtypes, including ALK-negative ALCL (ALK-positive ALCL patients were excluded from the study). The possible impact of rearrangements of the DUSP22-gene in ALCL was part of translational studie of NLG-T01. Long-term outcome data from NLG-T-01 will be useful for the coming national and European (ESMO) guidelines since they will allow us to compare outcomes with what reported for ALK-negative ALCL in the ECHELON-2 trial.

P[R]EBEN trial
The phase 1b/2a P[R]EBEN protocol in relapsed aggressive B- and T-cell lymphomas has been completed, after accrual of 60 patients. Patients have been accrued from the 4 Nordic countries and from HOVON centers in the Netherlands. Early results from correlative biological data regarding per protocol gene expression profile analyses performed at Helsinki University Hospital were presented at the 4th Nordic Meeting on Tumor Microenvironment in Lymphoma and at ASH 2019. Translational results from the PREBEN trial including gene expression data from patients with DLBCL or PTCL will be presented as a poster at the ICML-meeting in Lugano in June 2023.

Nordic DUSP22 project
The working group is working on a retrospective study on the impact on outcome of DUSP22 rearrangements in ALK-neg ALCL, including BIA-ALCL and cutaneous ALCL with biospecimens from the Nordic countries. Our aim is to collect a large enough patient cohort with reliable follow-up using the country-specific lymphoma registries. Results regarding the importance of DUSP22 rearrangements are inconclusive and are based on small series of patients, so more solid data is needed, particularly if this marker is to be included in clinical decision making.

Hodgkin group

The BVB trial on the use of Brentuximab vedotin (BV) as first line treatment in elderly patients with HL started in 2015 as a joint German and Nordic study. The study is completed and abstracts covering early results were presented in Cologne in in the fall of 2018 and at ASH in 2018. The publication is postponed due to workload from the Covid-19 pandemic. Manuscripts of the longer follow-up of both the B-CAP and BV monotherapy arms of the study are now in preparation.

The Nordic countries have collectively joined the German Hodgkin Study Group in the HD21 trial for newly diagnosed advanced stage Hodgkin lymphoma comparing escalated BEACOPP to a BV based variant called BrECADD. First results showing superiority of the BrECADD arm in terms of toxicity have been presented at the ISHL in Cologne and at ASH in 2022. The results for the efficacy endpoint are now in preparation and are awaited at the upcoming Lugano meeting in 2023.

The HD21 showed a favorable toxicity profile and was amended to evaluate BrECADD for elderly patients 61-75 years without randomization. This part of the study closed for inclusion in April 2023 after 80 patients were enrolled. Results have not been published so far.

The Swedish Hodgkin Lymphoma Group has run at phase II trial for early stages of HL using proton therapy, the Pro-Hodgkin study. As the other Nordic countries now will get better access to proton

facilities on their own, we plan to expand the study within the NLG. There is also an ongoing epidemiology project for elderly patients with HL headed by the NLG.

Epidemiology group

The group is working with several projects using data from the national lymphoma registers in Denmark, Sweden, and Norway. Clinical data being assembled in Finland. The group has regular digital meetings 3-4 times a year.
Since start of 2023, we have had a group meeting discussing new projects and collaborations. In May, we will have a webinar with attendance of Dutch lymphoma researcher. The Hodgkin fertility study has been published. NCU funding has been renewed and a F2F meeting is being planned prior to the NLG meeting in November 2023
If you have a lymphoma epi project idea or wish to get epidemiological input, get on touch with the group chair Tarec El-Galaly (tceg@rn.dk).