Nordic Lymphoma Group

Newsletter June 2024

Dear members of the NLG society,

The NLG Plenary meeting will take place on November 6-7, 2024, at the Scandic Strandpark Hotel, close to Copenhagen Airport, in the same location as last year. All members of NLG are warmly welcome to participate.

We also invite representatives from the collaborating pharmaceutical companies, representing relevant products used for diagnostics, and treatment of malignant hematological diseases, to participate in our meeting.

The program is enclosed. Recent lymphoma research from all countries will be presented in oral and poster sessions, invited speakers will highlight the current topics on clinical and translational research on lymphomas and working groups will give their annual progress reports. This year, the educational topic will be T-cell lymphoma. As a new concept, we have also included a career talk in the program.

The link for the registration is found on our homepage, www.Nordic-lymphoma.org , and here, https://na.eventscloud.com/nlg2024

Looking forward to seeing you in November!

Best regards,

On behalf of the NLG coordinating group

Sirpa Leppä
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NLG Plenary meeting – working groups

Working group meetings will be arranged before the plenary meeting.

CTO session – research nurses and coordinators

CTO session will be arranged before the plenary meeting.

Abstract submission

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

Peter Brown from Denmark
Marjukka Pollari from Finland
Renate Galleberg from Norway
Daniel Molin from Sweden

Free paper and poster sessions

Scientific ongoing lymphoma research from each country is appreciated and will be presented in these sessions.

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

Nordic Lymphoma Group

Plenary Meeting
November 6-7, 2024
Scandic CPH Strandpark
Copenhagen

Wednesday 06.11.2024		
1000-1200	***CTO session (research nurses/coordinators)***	
1200-1300	*Registration and lunch*	
1300-1305	Welcome	Moderator: Sirpa Leppä
1305-1430	Poster pitches and free papers, session 1	
1430-1515	*Coffee break, poster session and exhibition*	
1515-	***T-cell lymphoma Educational Session***	
1515-1600	PTCL pathology/Insights to the latest international classifications Laurence de Leval	Moderator: Thomas Relander
1600-1645	ESMO/EHA PTCL Clinical Practise guidelines Francesco d'Amore	
1645-1715	*Coffee break, poster session, and exhibition*	
1715-1800	Interesting PTCL cases T-cell working group	Moderator: Thomas Relander
1800-1830	Career talk with an aperitif Eva Kimby	Moderator: Björn Wallin
1830-1900	***Business meeting***	
1930	*Dinner*	

Thursday 07.11.2024		
0900-1000	Free papers – session 2	Moderator: Mats Jerkeman
1000-1030	*Coffee break, Poster session, and exhibition*	
1000-1600	***Working group reports***	
1030-1100	Indolent group	Moderator: Daniel Molin
1100-1130	Large cell group	
1130-1150	CNS group	
1200-1300	*Lunch*	
1300-1330	Mantle cell group	Moderator: Troels Hammer
1330-1400	Hodgkin group	
1400-1420	T cell group	
1420-1500	*Coffee break and exhibition*	
1500-1530	Epidemiology group	Moderator: Renate Galleberg
1530-1550	Waldenström group	
1550-1600	Wrap up	Sirpa Leppä

After the Plenary program, Abbvie will organize a 2-hour post-symposium titled *"From one fits all treatment to a tailored approach -What does the future hold for DLBCL"*

Updates of the A-CTO and working group activities

A-CTO

The Clinical Trial Office of the Nordic Lymphoma Group, also called A-CTO, short for Academic Clinical Trial Office, is a part of the Department of Hematology at Aarhus University Hospital. Its purpose is to guide, facilitate, and coordinate the establishment (design, implementation, and performance) of local, national, and Nordic/international academic clinical trials. It was establised in 2014 and has since then grown to a unit with a staff of 5 people: 3 clinical trial managers, 1 scientific coordinator and a quality manager.

NLG Trials in A-CTO:

Study	PI Sponsor	Start enrollment	End enrollment	Status
MERLIN	Marianne Brodtkorb, Oslo	2023		Enrolling
POLAR BEAR	Mats Jerkeman, Lund	2020		Enrolling
ALTAMIRA	Mats Jerkeman, Lund	2021	2023	Treatment ongoing
VALERIA	Mats Jerkeman, Lund	2018	2021	FU ongoing
Bio-CHIC	Sirpa Leppä, Helsinki	2017	2021	FU ongoing
PREBEN	Francesco d'Amore, Aarhus	2016	2020	FU ongoing
ILIAD	Mats Jerkeman, Lund	2017	2021	Closed
PHILEMON	Mats Jerkeman, Lund	2015	2016	Closed
ACT-1	Francesco d'Amore, Aarhus	2008	2013	Closed

Other trials in A-CTO:

Study	PI Sponsor	Start enrollment	End enrollment	Status
ORACLE	Jehan Dupuis, LYSARC	2018/ NLG 2020	2021	Closed in NLG
ENRICH	David Lewis, University Hospitals Plymouth	2015/ NLG 2017	2021	Treatment, FU ongoing
TRIANGLE	Martin Dreyling, LMU Klinikum Munich	2016	2020	FU ongoing

Contact details for the Clinical Trial Office:

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A-CTO has existed for 10 years when we come to the plenary meeting in November!

Working group activities

Indolent group

The NLG have started the MERLIN trial for patients with early progression (POD24+) of follicular lymphoma (2nd line). This is a selected group of patients with a poor prognosis. All included patients are treated with single-agent mosunetuzumab, a new bispecific CD3/CD20 antibody. Roche contributes funding and drug. The trial has included 22/80 patients (2 May 2024) since its start in September 2023.

For first-line treatment, the FLIRT trial protocol is being finalized and it will be reviewed by the company and regulatory agencies the coming months. FLIRT will divide patients 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) followed by a 6 month maintenance lenalidomide-tafasitamab (total treatment one year). Low-risk patients will receive rituximab-lenalidomide and 1:1 randomization to tafasitamab (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 tested whether stratification of the patients according to biological risk factors for different treatment groups can improve the

outcome of the patients with clinically high-risk LBCL was closed for recruitment in Feb 2021. Safety and efficacy data after a median follow-up of 3 years showed highly satisfactory FFS, PFS, OS, and CNS recurrence rates, and were presented at ASH 2022 and a manuscript has been submitted for publication. In addition, results from the associated circulating tumor DNA (ctDNA) substudy were presented at ICML 2023. Results from the long-term follow-up will be presented at EHA 2024 in June.

All fit patients with at least stage II and IPI score ≥1: In the NLG-LBC-09 (CINDERELLA; **CI**rculating d**N**a gui**D**ed th**E**rapy la**R**ge B-c**EL**l **L**ymphom**A**) study, the objective is to use ctDNA-based assessment prospectively to capture LBCL heterogeneity, guide treatment and evaluate response. The study is divided into three parts: First, we will determine disease burden and the cut-off values for high and low ctDNA levels in a population-based cohort. In part 2 (run-in cohort), the primary endpoint is to determine the turnover time and success of the ctDNA assay. Based on the results from parts 1 and 2, we will start the expansion cohort, where the treatment will be ctDNA-guided. The patients will be stratified according to their ctDNA levels and biological risk factors into low, intermediate, or high-risk groups, and based on the risk group, the treatment will be de-escalated, continued, or changed.

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 April 2024, 198 patients have been included from the Nordic area and Italy. The trial has been expanded to 300 patients and is enrolling patients also from Australia. The DSMB reviewed safety data in April 2024, and recommended to continue enrolment according to the protocol.

NLG will also participate in the HOVON-168 study. This is a randomized intergroup phase III trial, comparing R-mini-CHOP with R-mini-CHOP combined with epcoritamab in frail and unfit elderly patients (age ≥ 75 years) with aggressive B-cell lymphoma. The protocol is in preparation and trial is expected to open enrollment Q4/2024.

Correlative studies based on 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 ctDNA levels.

CNS-lymphoma group

A 10-year follow-up on the previous NLG phase II 1st line primary central nervous system lymphoma (PCNSL) study, originally published in 2015, was published with altogether 17 long-term survivors (26% of the patients). The main feature of the trial was its focus on elderly patients that were treated with a de-escalated induction immunochemotherapy followed by maintenance temozolomide. In the entire study population, ECOG performance score, neurocognition, and

functional independence improved or remained unchanged in the majority of the patients. The 10-year OS rate was 29.8%, the 10-year PFS rate 13.3%, and median DOR 13.2 months with a significant proportion of elderly long-term survivors (a 10-year OS rate of 29.8% among the elderly subgroup).

The working group is starting a Nordic prospective, multicenter trial with the aim of characterizing circulating tumor DNA (ctDNA) for early response assessment in PCNSL patients treated with standard of care (SOC) 1st line therapy with a curative intent. Secondary objectives are to assess the clinical characteristics, health-related quality of life (HRQoL), neurological status, and outcome of newly diagnosed PCNSL patients in the Nordic countries. Patients eligible for a curative intent SOC 1st line therapy, such as MATRix + high-dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT), are eligible for the trial. Diagnostic tumor tissue, cerebrospinal fluid (CSF), and plasma samples are collected for ctDNA and translational analyses with the aim describing new prognostic and predictive biomarkers. Treatment responses are assessed with the International PCNSL Collaborative Group (IPCG) response criteria, and diagnostic and response assessment magnetic resonance imaging (MRI) images are centrally analyzed in order to describe new prognostic and predictive markers.

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 published in Lancet April 2024, showing that addition of ibrutinib to induction and as maintenance, clearly 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 will be presented at ASH 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 BTKinhibitor, 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. Enrollment was finalised in December 2023, after recruiting 81 patients in Sweden, Denmark, Norway, Finland and South Korea. Results will be presented at ASH 2024.

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 published in Blood Advances this spring, showing that stopping treatment in molecular remission is feasible. An additional paper on ctDNA studies in VALERIA was also recently submitted for publication.

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. This study is planned to start recruitment in 2025.

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. 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, ddPCR.
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. A manuscript on the long-term results of the NLG-T01 trial including impact of DUSP22 rearrangements in ALCL is under preparation in collaboration with Andy Feldman at the Mayo clinic.

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 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. A final analysis of the trial and its correlative biological data is planned for 2024.

Nordic DUSP22 project

The working group is planning a retrospective study on the impact on the 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 B-CAP 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. 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 first results for the efficacy endpoint were presented at the Lugano meeting in 2023. A superiority analysis will be presented at EHA and ASCO 2024 and a publication is expected soon.

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, Finland, and Norway. It is a multidisciplinary group with participation of clinicians and statisticians. The group meets 3-4 times per year. In 2024, the group had a virtual meeting on "Benchmarking observational data against randomised trials and complementing trial results with observational data" with an external lecture by Anthony Matthews from Karolinska. A meeting in September will focus on Hodgkin lymphoma with presentation of Holistic by Susan Parson. Finally, a F2F meeting is planned before the NLG plenary meeting on November 5th and 6th. The NGL EPI group received a third-year funding for various projects, including meeting activities.
Ongoing projects include projects focusing on late toxicities after high-dose therapy, secondary cancer occurrence and cardiovascular events after treatment for lymphoma. The group has also published a paper on machine learning for prognosis in Hodgkin lymphoma.
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).