# Nordic Lymphoma Group

## Newsletter June 2021

www.nordic-lymphoma.org

*Dear members of the NLG society,*

All members of NLG and representatives of collaborating companies are welcome to the next NLG Plenary meeting November 10-11, 2021. This year, we plan for a regular physical meeting, at the the new Scandic Strandpark Hotel, close to Copenhagen Airport. The preliminary program is enclosed. However, some things will remain the same. 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/nlg2021

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 2021

10-11 November 2021

| 10.11.2021 | | |
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| 1000-1200 | CTO session (research nurses/coordinators) | |
| 1200-1300 | **Registration and lunch** | |
| 1300-1330 | Indolent group | Moderator: Peter Brown |
| 1330-1400 | T-cell group | |
| 1400-1430 | Large cell group | |
| 1430-1500 | **Coffee break** | |
| 1500-1600 | *Invited speaker*<br>Veronica Bachanova<br>Advances in NK cell therapies | Moderator: Mats Jerkeman |
| 1600-1800 | Free papers | Moderator: Björn Wahlin |
| 1800-1830 | Business meeting | |

| 11.11.2021 | | |
|---|---|---|
| 0900-1000 | *Invited speaker*<br>Marco Ruella<br>Advances in CAR-T therapies | Moderator: Sirpa Leppä |
| 1000-1030 | **Coffee break** | |
| 1030-1100 | Pathology Group | |
| 1100-1130 | CNS group | |
| 1130-1200 | Epidemiology group | |
| 1200-1300 | L**unch** | |
| 1300-1330 | Hodgkin group | Moderator: Arne Kolstad |
| 1330-1400 | Mantle cell group | |
| 1330-1500 | Controversies in primary CNS lymphoma | |

## 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 has reached the target accrual of 190 patients in 2020. The primary endpoint is CR at 24 months and will not be reached before June 2022. No efficacy data will be available before that.

The study group is working on the development of new clinical studies.
In follicular lymphoma (FL) a new 1st line study (FLAME) may enroll all patients, but treated according to a risk-based algorithm, introducing new drugs. Another study will focus on the poor prognostic group of rituximab refractory/early recurrent (R/R) patients. The final design is not yet determined.

### Large cell group

Clinical studies –NLG-LBC-05 (CHIC) trial demonstrating favourable impact of dose dense chemoimmunotherapy with early systemic CNS prophylaxis on FFS and lower number of CNS recurrences rates in high risk DLBCL patients less than 65 years has been published (Leppä et al., 2020). The subsequent phase II trial, NLG-LBC-06 (BIO-CHIC), 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 and was closed for recruitment in Feb 2021. Results from the first efficacy analysis will be presented in June 2021 at the ICML.

A phase II trial, NLG-LBC-07 (ILIAD), testing the safety and efficacy of oral PI3K inhibitor idelalisib as a monotherapy in the frail patients with relapsed or refractory DLBCL enrolled 36 patients and was closed for recruitment in March 2020.

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, 20 of the planned 200 patients have been included from the Nordic area and from Italy.

After Bio-CHIC trial, we plan to conduct a ctDNA-guided phase III 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.

Correlative studies on the basis of trial material - Several trial-related molecular projects are ongoing. To date, the studies have demonstrated for example survival association of tumour infiltrating immune cells, MYC, BCL2, and TP53 alterations, soluble CD163, soluble PD1 and circulating tumor DNA levels.

**CNS-lymphoma group**

A randomized phase II IELSG45 study (FIORELLA) evaluates the efficacy of fitness- and comorbidity -tailored treatment in elderly patients with newly diagnosed PCNSL, and is ongoing in Denmark, Finland, Israel, Italy, and Switzerland. The study is currently recruiting with an estimated primary completion date in October 2023. The previous IELSG43 (MATRix) study, a phase III study designed to compare two consolidation policies in younger PCNSL patients, is in the follow-up phase with data analysis planned for the Q4 2022.

The working group sees an existing need for a trial for patients with refractory/relapsed PCNSL. Due to a lack of financial support and/or collaborating working groups interested in starting such a trial, the efforts of starting a R/R trial have not been successful so far.

Unfortunately, both Danish members of the working group had to leave the working group, and new members from Denmark are warmly welcomed to join.

**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.

Elderly patients: Since December 2017, NLG has participated in the ENRICH trial, with Simon Rule, Plymouth, as sponsor. This is a randomized phase III trial, comparing rituximab+ibrutinib with rituximab-chemo (either R-bendamustine or R-CHOP). At this point we are very close to finalizing enrolment of the 400 patients, of which 121, so far, are from NLG centres. Enrolment will end 30-JUN-2021.

When ENRICH has been concluded, we will launch a new trial for elderly patients, >60 years, first line, with the 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. This trial, NLG-MCL8, ALTAMIRA, will start recruitment in Q3 2021. It is already approved in Sweden.

The NLG trial for relapsed MCL, NLG-MCL7, VALERIA, exploring the combination of venetoclax, lenalidomide and rituximab, started in June 2019. This is a phase I-II trial, for patients with relapsed MCL, and a population of untreated MCL, ineligible for combination chemotherapy. This trial will also explore a novel treatment strategy for MCL, an MRD-driven approach, where treatment will be stopped following molecular remission. The phase 1 part of the study was presented at ASH 2020, where we were able to show the feasibility of stopping treatment in MRD-negative patients. The enrolment was concluded in April 2021, with 59 patients. Final results are expected to be presented at ASH 2022.

**T cell group**

*ACT trial:*
The final analysis of the ACT-2 trial (elderly patients; >60 yrs) has recently been published in Leukemia (april 2020) and can be found on PubMed (Wulf G et al). The final analysis paper of the ACT-1 trial is in preparation and still waits for the final details regarding the gene expression data characterizing the "predictor of alemtuzumab response (PAR)", which will be included in the paper. The ACT-1 final analysis data were presented, with a preliminary version of PAR, as an oral paper at ASH in December 2018.
Additional translational studies based on the ACT-1 trial biospecimens are ongoing.

*NLG-T-01 trial:*
A manuscript with late 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, has been drafted and will be circulated among working group members shortly. The data set will be presented for the single PTCL subtypes, including ALK-negative ALCL (ALK-positive ALCL patients were excluded from the study due to an expected better prognosis, which did not justify upfront ASCT). 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.
Additional translational studies based on the NLG-T-01 trial biospecimens are ongoing.

*P[R]EBEN trial*
The phase 1b/2a P[R]EBEN protocol in relapsed aggressive B- and T-cell lymphomas has now been completed, after accrual of 60 patients. The manuscript with the final analysis of the study will combine the results of the phase 1b part of the trial with the results of the phase 2 part. Patients have been accrued in various centers from the 4 Nordic countries and from HOVON centers in the Netherlands. Results from correlative biological data regarding per protocol gene expression profile analyses performed at Helsinki University Hospital were presented at the 4$^{th}$ Nordic Meeting on Tumor Microenvironment in Lymphoma and at ASH 2019. This data will also be included in the final analysis paper.
Additional translational studies based on the P[R]EBEN trial biospecimens are ongoing.

*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. Two applications for academic funding of the trial are currently submitted. Further funding will be negotiated with potential partners from the pharmaceutical industry. The new PANTHEON trial will address three main questions: (i) does a pre-induction antiviral pre-phase (steroid+rituximab) improve performance score and disease status prior to induction start along with schedule adherence during induction, in patients who are EBV viremic at diagnosis?; (ii) does measurement of minimal residual disease by means of liquid biopsies (ctDNA) improve response assessment compared to the current standard-of-care (PET/CT)?; (iii) 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 'very frail'. The induction treatment in the trial aims at being as flexible as possible 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 discussion.
There will be one group meeting in September/October 2021 (date not yet specified) to discuss the new trial proposal prior to the next plenary meeting.

**Hodgkin group**

The BVB trial on the use of Brentuximab vedotin 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 work load from the Covid-19 pandemic.

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 Brentuximab vedotin based variant called BrECADD. The study has completed recruitment and the results are awaited.

A subanalysis of the 50-60 year old patients receiving BrECADD in HD21 showed a favorable toxicity profile. To evaluate BrECADD for elderly patients 61-75 years, the trial has been amended and allows for elderly patients to be enrolled in the BrECADD arm without randomization. This part of the study opened in 2020 and will go one for one year.

The "Nordic trial" on stage I-IIA Hodgkin lymphoma was initiated as a treatment recommendation in 1997. The patients treated in the first decade after initiation of the recommendation have been evaluated for relative survival and mortality rates. The final publication has been published in 2020.

**PTLD group**

The group was formally initiated during the NLG meeting in Stockholm 2014. Initial work has mainly been focused on joining the German PTLD-2 trial. Due to issues with funding this will not be possible, and the group will examine the possibility of a Nordic PTLD trial in the relapsed setting.

**Epidemiology group**

The group is working with several projects using data from the national lymphoma registers in Denmark, Sweden, and Norway as well as clinical data being assembled in Finland. The group has regular digital meetings 3-4 times a year.

If you have a lymphoma epi project idea or wishes to get epidemiological input, get on touch with the group chair Karin E Smedby (Karin.ekstrom.smedby@ki.se).

Ongoing or recently completed projects include:

- Life after lymphoma – survivorship aspects including childbearing, second malignancies and infections. We are currently working on several manuscripts. The project was funded by the NCU for the third year this year.
- Treatment and survival among very elderly lymphoma patients (Published, Wasterlid et al, British Journal of Hematology 2020)