NOPHO

Nordic Society of Paediatric Haematology and Oncology

ANNUAL REPORT 2020

Childhood Cancer in the Nordic and Baltic Countries
Report on Epidemiologic and Therapeutic Results from Registries and Working Groups

This report is published with financial support from:
The Swedish Childhood Cancer Foundation

Cover page: Designed by creative32965 / Freepik

Foreword

Dear NOPHO friends and colleagues

On behalf of all of you and the registration team in Stockholm, I am happy to present the NOPHO Annual Report 2020.

NOPHO was formally established in 1984, and I believe that ever since, the members have gathered each year to share their experiences, research results and to do networking – all with the aim of improving treatment outcomes including survival and minimizing the risk of late effects for our patients. Over the last few months we have experienced the danger of the COVID-19 pandemic, which has limited our participation in NOPHO working group meetings as well as international meetings. Arranging working group meetings as Zoom-meetings have become very popular, and it has proved very useful instead of physical meetings, mainly because we are a society, where we know each other very well.

The Annual Meeting 2020 (the 38th NOPHO Annual meeting and 13th NOBOS Biannual meeting) was planned to take place in Trondheim, but it has been cancelled due to the pandemic. The organizing committees for NOPHO and NOBOS have been working hard planning the scientific program and social events, and thanks to the great kindness and flexibility of the next two years organizers in Kuopio and Lund, it has been possible to push the meeting in Trondheim a year and thus the subsequent two meetings.

Even though the Annual Meeting 2020 is cancelled, the Annual Report is hereby presented with the core of our efforts over in the past year and many years before that. The annual report is the result of great dedication among research nurses, doctors, the registration team in Stockholm, our webmaster and everyone involved in paediatric haematology and oncology in the Nordic and Baltic countries.

The efforts for creating a broader international network and treatment protocols are important for movement of the results even more. However, our close collaboration in the Nordic and Baltic countries remains extremely important in maintaining enthusiasm and commitment within the society.

As always, it is a great pleasure and honor for me to work with my Nordic and Baltic colleagues in our joint cause of improving the lives of our patients.

Take care – and see you physically after the COVID-19 crises.

Aarhus, April 15th 2020

Birgitte Klug Albertsen
Secretary General

Contents

Contents

NOPHO Board

Members 2019 - May 2020		
Secretary--general	Birgitte Klug Albertsen	elected 2018
-elect	Trond Flaegstad	elected 2018
Treasurer	Mathias Rathe	elected 2019
Auditors of accounts	Gustaf Ljungman	elected 2005
	Peder Skov Wehner	elected 2019
Stand in auditor of accounts	Svein Kolmannskog	elected 2005
Denmark	Bodil Als-Nielsen	elected 2018
	Mathias Rathe	elected 2019
	Yasmin Lassen (radiotherapy)	elected 2018
Finland	Kaisa Vepsäläinen	elected 2016
	Mikko Arola	elected 2017
Iceland	Ólafur Gísli Jónsson	elected 2000
	Sólveig Hafsteinsdóttir	elected 2013
Lithuania	Goda Vaitkeviciene	elected 2016
	Rolanda Nemaniene	elected 2019
Norway	Anne Grete Bechensteen	elected 2017
	Tove Nystad	elected 2017
Sweden	Helena Mörse	elected 2018
	Tony Frisk	elected 2019
Pediatric surgery	Jakob Stenman	elected 2019
Young NOPHO	Laura Madanat-Harjuoja	elected 2018

NOPHO Secretariat and Webmaster

NOPHO Secretariat

Jenny Juhlin/Mats Heyman
Karolinska Institutet
Department of Women's and Children's Health
Childhood Cancer Research Unit
Tomtebodavägen 18 A
SE-17177 Stockholm
Sweden
jenny.juhlin@ki.se
mats.heyman@ki.se

NOPHO Webmaster

Elisabeth Jensen-Broby Heldrup
Simply Web
Sallerup 5010
SE-24193 Eslöv
Sweden
Tel: + 46 413 55 56 50
Mobile: + 46 705 18 70 34
Elisabeth.Jensen-BrobyHeldrup@skane.se

NOPHO Scientific committee

Members 2019-2020

Sweden	Kees-Jan Pronk (co-chair -exited SciCom beginning of 2020) Anna Nilsson (since autumn 2019)
Denmark	Bodil Als-Nielsen
Finland	Matti Korhonen
Iceland	Ragnar Bjarnason
Lithuania	Sonata Trakymiene
Norway	Maria Winther Gunnes
Young NOPHO	Nikolas Herold, SE (co-chair until beginning of 2020, currently only chair)

The deadline for applications for NOPHO studies is about 2 months before each NOPHO board meeting (but can be adjusted if circumstances require), often just following the LL-Biology group meeting as many of the applications often also require to be presented at that meeting. For the June 2019 term, 16 new applications were submitted of which 9 were accepted and 7 have been given the possibility to re-submit a revised proposal; in addition, 4 re-submitted and revised proposals from previous rounds have been accepted. For the November 2019 term, 6 new applications were submitted and evaluated, 5 of which were accepted. For the June 2020 term, the deadline for the applications is March 16th. All newly and previously accepted NOPHO projects from 2008 onwards can be seen at https://www.nopho.org/member_pages/member_area/science/nopho_sc_study_db/Archive/Default.aspx.

Projects were uploaded using the platform: https://manuscriptmanager.net/nopho. The applications are sent to all members of the Scientific Committee, as well as to relevant external reviewers (i.e. non-members of the SciCom) with the appropriate competence and/or position within NOPHO. For each application term, the scientific committee has held a 1-2 hour telephone conference some weeks after the application deadline, where the applications have been thoroughly discussed before evaluation notes were subsequently drafted, and circulated to the NOPHO Board to make a final decision on the applications.

During last year's period, SciCom was co-chaired by Kees-Jan Pronk and Nikolas Herold.

During the November 2019 telephone meeting, all proposed candidates for the 2020 NOPHO Lecturer prize were discussed. 3 candidates were selected and presented to the NOPHO board, that subsequently decided on the eventual 2020 NOPHO Lecturer.

Prior to the application deadline March 2020, Anna Nilsson succeeded Kees-Jan Pronk as Swedish representative, and we thank Kees-Jan for his 5 years of contribution to the Scientific Committee, the last three years of which as chair of the SciCom.

Stockholm, March 9th, 2020
Nikolas Herold, on behalf of the SciCom of NOPHO

Young NOPHO

Young NOPHO Board in 2019-2020

Denmark	Stine Nygaard Nielsen, Sofie Gottschalk Højfeldt
Finland	Anu Suominen, Laura Madanat-Harjuoja (chair)
Iceland	Thorgerdur Gudmundsdottir
Lithuania	Monica Kapitancuke
Norway	Simon Kranz, Kirsten Brunsvig Jarvis
Sweden	Nikolas Herold, Mari Wilhelmsson

Last year the annual meeting of Young NOPHO (YN) was held on the 3rd of May, 2019 at the annual NOPHO meeting in Aalborg, Denmark. The minutes from the meeting and the regulations of YN can be found at the NOPHO website. After the annual meeting the YN members had a group photo in the evening followed by an invitation for an annual YN dinner sponsored by Barncancerfonden.

A total of 13 people participated in the meeting. As on previous years, this year we used the topics from the Annual NOPHO meeting in planning our meeting program. Thus the Annual YN meeting which preceded the Annual NOPHO meeting served as an introduction hereto. As participants include young clinicians specializing in pediatrics or pediatric oncology or PhD students, this type of an introduction to the subject seemed relevant to the audience.

The annual YN meeting program was divided into a clinical and a research session. The topics of the clinical session were: introduction to central nervous system tumors, an introduction to diagnosing and treating hemophilia (presented by pediatric hematologist-oncologist Satu Långström), and one clinical case on hemophilia and one brain tumor case. During the annual YN meeting the YN board members (Nikolas Herold on behalf of Simon Kranz) presented the introduction to CNS tumors and the relevant clinical case on hemophilia was presented by YN member Liisa Järvelä.

The clinical session was followed by a research session, in which the YN board selected two abstracts for oral presentation. Laura Seppälä presented her PhD project on preterm birth and risk of childhood cancer.

Jonathan Gronbaek presented the Nordic-European study of the Cerebellar Mutism Syndrome. YN Board member Mari Wilhelmsson presented on hospitalizations in long term survivors of childhood AML – A report from the ALiCCs study. After the meeting, 8 participants joined us for a networking dinner.

The fall Young NOPHO meeting, held from the 15th to the 17th of November, 2019 was organized in Stockholm, Sweden. The meeting began on Friday with a brainstorming dinner followed by an educational component in the form of an Educational day on Pediatric Hematopoietic Stem Cell Transplantation at Karolinska Hospital in Stockholm. A total of 28 participants (including 4 lecturers) took part in the educational day, including colleagues working in pediatric oncology in Stockholm, Uppsala, Umeå, Helsinki, Oslo, Tromsø, Bergen and Estonia. Nurses and researchers in the field of pediatric oncology also took part in the educational day. Mikael Sundin gave a lecture on Hematopoietic Stem Cell Transplantation: the indications, auto vs. allo, choosing a donor, conditioning, the procedure, practical aspects" as well as "Acute toxicities, Graft-versus- Host Disease". Per Ljungman spoke about "Viral infections after HSCT", Mari Wilhelmsson a YN Board member gave a talk on "Late effects after pediatric HSCT" and Stephan Mielke gave a lecture on "The role of CAR T-cells". The seminar was followed by a networking dinner.

The Working Group Board meeting was held on the 17th of November with the main goal of planning the next Annual Young NOPHO Meeting program to be held in Trondheim, Norway on the 8th of May 2020. Apart from organizational and constitutional points the following key aspects were discussed:

A. The theme of the next YN meeting was decided on as "Genetic Predisposition to Childhood Cancer and Targeted Therapies"
B. Possible lecturers were discussed and organizational tasks for the YN meeting were delegated to YN Board members
C. Discussion on how to increase collaboration across boarders. We talked about the possibility of initiating a fellowship exchange between the Nordic countries allowing fellows to learn from the expertise of other Nordic centers in the form of a 1-2 week observership
D. We discussed how to increase participation in Young Nopho
E. A proposition of having the next Board meeting and Educational day in Tromsø in 2020, as the next chair, Simon Kranz is based there

All in all, we had a productive working group meeting. It is our mission to increase collaboration between Young NOPHO members also in between the annual NOPHO meetings and to catalyze Young NOPHO- driven research and education. We have to increase the active participation of Young NOPHO members. This is a challenge due to the large geographical distances and busy clinical schedules. Nevertheless, we already have substantial improvements and want to follow up on this development.

The YN board would like to thank the Swedish Childhood Cancer Foundation (Barncancerfonden) for supporting all YN related meetings in 2019 and 2020 and the next annual meeting in Trondheim, Norway that has been postponed due to the corona virus pandemic to the 7th of May 2021.

Last but not least we would like to thank all YN members for their activities and energy invested in 2019 to 2020, for making YN a more active and collaborative WG. Thank you!

10th of May, 2020
On behalf of the YN board,
Laura Madanat-Harjuoja Finland, YN Chair

Participating clinics/institutions/physicians

Through the years, many colleagues in NOPHO have been involved in treating and reporting of childhood cancer. The main contributors are listed below:

Denmark	Copenhagen	Kjeld Schmiegelow, Karsten Nysom, Birgitte Lausen, Astrid Sehested, Marianne Ifversen, Lisa Hjalgrim, Jesper Brok, Rene Mathiasen, Bodil Als-Nielsen, Marianne Hoffmann, Mimi Kjærsgaard, Katja Harder
	Odense	Peder Skov Wehner, Eckhard Schomerus, Niels Fisker, Michael Callesen, Mathias Rathe, Dorthe Grosen
	Aarhus	Henrik Hasle, Birgitte Klug Albertsen, Torben Mikkelsen, Pernille Edslev Wendtland, Karin Bækgaard Nissen, Ines Kristenen, Torjus Skajaa, Louise Lindholdt Hansen, Louise Tram Henriksen
	Aalborg	Steen Rosthøj, Ruta Tuckuviene
Finland	Helsinki	Mervi Taskinen, Kim Vettenranta, Pasi Huttunen, Jukka Kanerva, Kirsi Jahnukainen, Virve Pentikäinen, Minna Koskenvuo, Samppa Ryhänen, Helena Olkinuora, Satu Långström, Pauliina Utriainen, Adam Alexandersson, Anu Suominen, Antti Kyrönlahti
	Turku	Päivi Lähteenmäki, Marika Grönroos, Anu Huurre, Laura Korhonen, Linnea Schuez-Havupalo, Liisa Järvelä
	Oulu	Riitta Niinimäki, Hanna Juntti, Anne Hekkala, Elli-Maija Ukonmaanaho, Henri Aarnivala
	Tampere	Olli Lohi, Mikko Arola, Katriina Parto, Päivi Raittinen, Sauli Palmu, Niina Valtanen, Kristiina Nordfors
	Kuopio	Pekka Riikonen, Kaisa Vepsäläinen, Jouni Pesola, Tuuli Pöyhönen, Stefan Becker
Iceland	Reykjavik	Ólafur G. Jónsson, Halldóra K. Thórarinsdóttir, Sólveig Hafsteinsdóttir, Ragnar Bjarnason, Jón Jóhannes Jónsson
Lithuania	Kaunas	Giedre Rutkauskiene, Rosita Kiudeliene, Egle Ramanauskiene, Sonata Argustaite, Justina Klimaite, Ruta Radaviciute
	Vilnius	Jelena Rascon, Goda Vaitkevičienė, Gražina Kleinotienė, Audronė Mulevičienė, Indrė Tamulienė, Natalija Šestel, Ramunė Pasaulienė, Rolanda Nemanienė, Sigita Stankevičienė, Sonata Šaulytė Trakymienė, Vilma Rutkauskaitė, Ignė Kairenė
Norway	Oslo	Anne Grete Bechensteen, Ellen Ruud, Heidi Glosli, Bernward Zeller, Inga Maria Johannsdottir, Einar Stensvold, Jochen Büchner, Monica Cheng Munthe-Kaas, Aina Ulvmoen, Charlotte Alme, Marta Burman, Kirsten Jarvis, Ida Knapstad, Tale Torjussen, Anja Lee, Christina Elisabeth Bjerring Opheim Associate members: Marit Hellebostad, Finn Wesenberg, Eva Widing

	Trondheim	Bendik Lund, Ann Elisabeth Åsberg, Svein Kolmannsskog, Erling Moe, Kristin Solem, Magnus Aassved Hjort
	Bergen	Maria W Gunnes, Dorota Malgorzata Wojcik, Anita Andrejeva, Ingrid Kristin Torsvik
	Tromsø	Tore Stokland, Trond Flaegstad, Niklas Stabell, Tove Nystad, Simon Kranz, Ole Mikal Wormdal
Sweden	Stockholm, Solna	Pernilla Grillner, Mats Heyman, Stefan Söderhäll, Niklas Pal, Klas Blomgren, Stefan Holm, Johan Malmros, Per Kogner, Jonas Karlén, Jan-Inge Henter, Ingrid Öra, Petter Svenberg, Karin Strålin, Trausti Óskarsson, Tatiana Greenwood, Susanna Ranta, Tony Frisk, Tomas Bexelius, Christina Egnell, Johan Hamrin, Nina Mogensen, Mari Wilhelmsson, Clary Georgantzi, Karin Henning, Lena-Maria Carlson
	Stockholm, Huddinge	Mikael Sundin, Jacek Winiarski, Peter Priftakis, Kim Ramme, Petra Byström, Gauti Rafn Vilbergsson, Susan Farmand
	Lund	Anders Castor, Jacek Toporski, Lars Hjorth, Helena Mörse, Kees-Jan Pronk, Dominik Turkiewicz, Ingrid Öra, Ulf Tedgård, Annika Mårtensson, Marie Eliasson Hofvander, Johan Svahn, Patrik Romerius, Joakim Wille, Ladislav Krol, Joana Makari, Nadine Gretenkort Andersson, Anna Sällfors Holmqvist, Charlotte Ragnarsson
	Uppsala	Josefine Palle, Britt-Marie Frost, Gustaf Ljungman, Johan Arvidson, Per Frisk, Åke Jakobson, Anders Öberg, Annika Englund, Natalja Jackmann, Britt Gustafsson, Tania Christofo-raki, Arja Harila-Saari, Mia Giertz, Gustaf Leijonhufvud, Geraldine Giraud
	Gothenburg	Karin Mellgren, Jonas Abrahamsson, Gustaf Österlundh, Marianne Jarfelt, Magnus Sabel, Magnus Göransson, Cecilia Langenskiöld, Lene Karlsson, Elizabeth Schepke, Lars Kawan, Torben Ek, Cecilia Petersen, Diana Ljung-Sass, Lisa Mellström, Aron Onerup, Martin Dalin, Jerker Isaksson, Monika Renkiel-ska, Jonathan Källström
	Umeå	Ulrika Norén Nyström, Per-Erik Sandström, Caroline Björklund, Magnus Borssén, Frans Nilsson, Fredrik Bäckström
	Linköping	Mikael Behrendtz, Britt-Marie Holmqvist, Per Nyman Hartmut Vogt, Lisa Törnudd, Oskar Lundgren

The Leukemia Registry

Mats Heyman
Karolinska Institutet
Dept. of Women's and Children's Health
Childhood Cancer Research Unit
Tomtebodavägen 18 A
SE-17177 Stockholm
Sweden

Solid and Brain Tumour Working Groups

Solid Tumour Committee

Chair	Jukka Kanerva (SE) *2019-05*
Denmark	Jesper Brok *2019* Lisa Hjalgrim *2016* Karin Bækgaard Nissen *2018*
Finland	Kirsi Jahnukainen *2016* Hanna Juntti *2016* Jukka Kanerva *2016* Päivi Lähteenmäki *2016* (ST-registry repr.)
Iceland	Halldora Thorarinsdottir *2016* Solveig Hafsteinsdottir *2016* Ólafur G. Jónsson *2016*
Lithuania	Giedre Rutkauskiene *2016* Indre Tamuliene *2016* Rolanda Nemaniene *2016*
Norway	Bem Zeller *2016* Tove Nystad *2016* Dorota Wojcik *2017*
Sweden	Patrik Romerius *2020* Lisa Törnudd *2020* Caroline Björklund *2020*
Young NOPHO	Sauli Palmu *2018*

STC goals:

- STC is a forum for clinical and strategic discussions.
- STC is a forum to form ad hoc WGs for upcoming protocols or other burning issues.
- STC works side by side with the NOPHO Solid tumor registry group.
- STC creates consultation networks within NOPHO for discussion of difficult cases
- NOPHO countries do not have to join the same international protocols, but if there is consensus, it is possible with NOPHO representatives. Currently, Jesper Brok is representing NOPHO in the UMBRELLA consortium and Jukka Kanerva in the rEECur protocol.
- At least yearly meetings, generally two per year with one meeting at the annual meeting and another one in parallel to the LCC and BTC meetings.
- It is important to have own studies within the group and studies connected to the registry. The idea of a project to make a common Nordic registration legal and feasible was launched; the NOPHOCARE project. STC will work actively within the NOPHOmatch project.

All Nordic countries have appointed three formal representatives that form the back-bone of the STC, but it has been decided to have an open attitude and invite all those with a special interest in the area to participate and contribute. In addition, it has been decided that it would be valuable to have members from other disciplines such as radiotherapy, pediatric surgery, pathology, genetics, radiology, etc. involved

in the group to mimic the situation in the tumor board as the solid tumor work indeed is multidisciplinary. STC will increase its collaboration with the NOPHO RT WG. STC has a mailing list of approximately 60 individuals for networking.

The chair shall be nominated by the national groups rotating between the NOPHO countries in a fashion similar to that in other groups. The term for the chair is two years. Next chair will be from Denmark confirmed at the annual meeting 2021 in Kuopio.

During the past year the STC has had two meetings, one at the annual meeting in Aalborg in May 2019 and one in Oslo in November 2019.
At the May meeting we had reports from NOPHOmatch (project aiming at matching patients with early phase trials), updates of early phase trials and treatment protocols open/used in NOPHO countries. Several interesting case reports were presented.
At the November meeting we had an update of the NOPHO-CARE project, update of treatment protocols open/used in NOPHO countries. Jakob Stenman presented a study proposal for relapsed or refractory HR neuroblastoma (Lu-DOTATATE; peptide receptor radionucleotide); STC supports conducting the study. Presentation of drug screening combined with genetic profiling. Update of CWS and EpSSG activities in soft tissue sarcoma. Updates of Ewing sarcoma and extracranial germ cell tumors.

During the next year, we will have a short meeting during Trondheim annual meeting in May and a longer meeting in the fall in Helsinki combined with the NOPHO Board meeting.

Helsinki 15 March 2020

Jukka Kanerva

Brain Tumour Committee

Brain Tumour Committee
Coordinator Virve Pentikäinen (FI)
Denmark René Mathiassen, Helle Broholm (neuropathologist)
Finland Mikko Arola, Virve Pentikäinen, Anne Hekkala, Mia Westerholm-Ormio (neurologist)
Iceland Halldora Thorarinsdottir
Norway Ingrid Kristin Torsvik, Kristin Solem, Petter Brandal (radiotherapist)
Sweden Stefan Holm, Irene Devenney, Christoffer Ehrstedt, Bengt Gustavsson (neurosurgeon)
Lithuania Rosita Kiudeliene, Giedre Rutkauskiene
Estonia Kadri Saks
Latvia Zhanna Kovalova
Young NOPHO Kristiina Nordfors (FI), Satu Långström (FI), Michael Callesen (DK), Geraldine Giraud (SE)
NOPHO Solid Tumor Registry Mats Heyman

Change of members:
Mia Westerholm-Ormio (FI, neurologist), Kristin Solem (NO) and Geraldine Giraud (SE, young NOPHO) joined as new members. Tore Stokland (NO), Tuula Lönnqvist (FI) and Christine Dahl (DK) stepped down.

Brain Tumour Network
NOPHO Brain Tumour Network is a group open to any NOPHO member working with pediatric brain tumors. Brain Tumour Committee meetings are open to Network members. BTC members in each country keep their own list of national Network members and forward relevant messages.

SIOP-E BT working group members from NOPHO (also national coordinators of SIOP CNS tumor protocols where relevant)
Medulloblastoma/PNET: Magnus Sabel (SE), Anne Vestli (NO), Astrid Sehested (DK), Virve Pentikäinen, Mia Westerholm-Ormio (FI)
Low Grade Glioma: Astrid Sehested (chair), Kamilla Rothe Nissen (opthalmologist) (DK), Tore Stokland, Ole Mikal Wormdal (NO), Pernilla Grillner (SE), Päivi Lähteenmäki, Tuire Lähdesmäki (FI)
High Grade Glioma / DIPG: Stefan Holm, Klas Blomgren (SE), Karsten Nysom (DK), Ingrid Kristin Torsvik (NO), Virve Pentikäinen (FI)
Ependymoma: Ingrid Kristin Torsvik (NO), Helena Morse (SE), Pernille Wendtland Edslev (DK), Satu Långström (FI)
CNS Germ cell tumors: Astrid Sehested (DK), Kristin Solem (NO), Irene Devenney (SE), Anne Hekkala (FI)
Craniopharyngioma: Bengt Gustavsson (SE) Tore Stokland (NO)
AT/RT: Karsten Nysom (DK), Clary Georgantzi (SE), Satu Långström (FI), Anne Grethe Bechensteen (NO)
Quality of Survival: Christoffer Ehrstedt (SE)
Radiotherapy: Kristina Nilsson (SE), Henriette Magelssen (NO), Yasmin Lassen (DK)

Meetings

Brain tumour committee meetings:
BTC meeting was held in Aalborg, Denmark, May 3rd 2019 before NOPHO annual meeting. The next BTC meeting is planned to be in Trondheim, Norway May 8th 2020 but may be postponed because of Covid-19 virus related restrictions.

Other brain tumour meetings:

SIOP-E Brain Tumour Group annual meeting was held in Budapest, Hungary 5th -6th April 2019.
PaeNNO 2019 meeting was held in Helsinki, Finland 4th – 6th September 2019.
SIOP-E HGG working group meeting was held in Utrecht, Netherlands, 20th -21th January 2020.

Upcoming brain tumour meetings:

SIOP-E Brain Tumour Group annual meeting 2020 was postponed due to Covid-19 and the time of next SIOP-E BTG meeting will be announced later.
ISPNO 2020 meeting was also postponed due to Covid-19 and will take place in Karuizawa, Japan, 13th – 16th December 2020.
PaeNNO 2021 meeting will take place in Denmark. Tentative dates 8th-10th September 2021.

CNS Tumour molecular classification and related germ line testing

The WHO 2016 classification of the central nervous system tumours reclassifies the major histological brain tumour diagnoses and uses molecular parameters in addition to histology to define tumour entities. Molecular classification has a major impact on prognosis and treatment of pediatric brain tumours. Accordingly, integrated histological and molecular diagnosis is required in new international brain tumour treatment protocols. This defines a need for molecular diagnostic methods (gene sequencing, DNA methylation array etc) which are often required in rapid timetable within study protocols. These are now well available in NOPHO area. Centralization of certain analyses such as methylation array allows sufficient sample numbers for cost-effective and rapid turnover. An updated list of available molecular diagnostic methods for molecular classification in NOPHO area is found on NOPHO web pages under Brain Tumor Committee area.

Moreover, identification of cancer predisposing alterations in germ line if noticed in the tumor is becoming important and also mandatory in many brain tumor protocols. This means that genetic counselling has to be easily available when these alterations are found. Discussion on this issue is ongoing.

Participation in brain tumour protocols

The SIOP-E brain tumor group works towards international cooperative protocols and registries to improve treatment of pediatric brain tumour patients. The NOPHO Brain tumor group participates in this work through encouraging NOPHO countries to join SIOP-E protocols and through elected NOPHO representatives in disease specific working groups. National protocol coordinators from each participating country are also members of the corresponding SIOP-E working groups.

In the beginning of 2020, three phase II-III protocols are open in NOPHO area: SIOP PNET5 medulloblastoma in Denmark, Finland, Norway and Sweden, Ependymoma II in Finland and BIOMEDE in Denmark and Sweden. In addition, several relapse and phase I-II protocols are open and several protocols will be opened in the near future.

Medulloblastoma

SIOP PNET5 protocol for low-risk and standard-risk medulloblastoma contains upfront analysis of molecular markers of tumour biology to stratify patients for low risk and standard risk treatment. The main study questions are about 1) lowering the dose of therapy for low-risk patients to decrease the late effects while maintaining the excellent survival rate and 2) randomising concomitant carboplatin during radiotherapy for standard-risk patients to increase the effectiveness of the treatment. New amendment version 12 of the protocol contains more profound molecular subgrouping and germ line (blood control) preinclusion testing for cancer predisposing syndromes in certain molecular subtypes of medulloblastoma. In addition, new patient groups are included (clinically high risk patients with favourable WNT activation, TP53 mutated – SHH activated medulloblastomas with very poor prognosis, and registry for medulloblastoma patients with cancer predisposing alteration other than TP53 mutation).

During version 11 and 12 of the protocol there have been 7 cases of PRES after radiotherapy, during first chemotherapy cycle. These have been documented as SUSAR because their frequent rate. In the upcoming version 13 of the protocol the order of chemotherapy cycles has been changed to avoid repeated doses of vincristine soon after radiotherapy which has been considered as a risk factor for PRES.

PNET5 protocol version 11 has been running in Finland and Sweden for several years and is now open in Norway. Denmark has opened version 12 and submission of new protocol version is planned/ongoing in other participating NOPHO countries. Recruitment has been extended until at least the end of 2021.

SIOP HR-MB protocol is for clinical HR medulloblastoma patients over 3 – 5 years with non-WNT biology. The main aim is to test systematically whether any of strategies used for HR medulloblastoma offers a survival advantage and to compare toxicities. It will include randomisation to HART (hyperfractionated accelerated radiation therapy) or standard radiotherapy or high dose chemotherapy and standard radiotherapy. Full protocol version 2.0 (June 2019) has received funding in UK for running the trial and has been accepted by UK authorities. It is expected to be opened in the UK by the end of May 2020 and will be submitted in NOPHO countries after that.

SIOP YC-MB protocol for infant/young children (YC) medulloblastoma is in development. The protocol will have biologically stratified treatment groups and will include radiotherapy for patients over 18 months with poorest prognosis. Study design for infant HR-group is ready but there has been a delay in start of the protocol due to questions regarding risk-stratification of patients in infant SHH-medulloblastoma (non-HR) group. Aim is to have randomized trial to better define neurotoxicity of inraventricular MTX and alternative treatment options in this group. Funding has been applied for general structures of the trial for biological (850K methylation array) and neuropsychological assessments for all European patients.

Atypical teratoid rhabdoid tumour (AT/RT)

European Rhabdoid Registry (EU-RHAB) contains a registry and treatment recommendations. We continue to recommend that patients are discussed with Michael Frühwald in Augsburg, who coordinates the registry, and that patients are reported to the registry. European protocol for AT/RT, SIOPE ATRT01 is being developed and has been submitted for funding and to the authorities in Germany. NOPHO Brain Tumor Committee supports the concept of the trial.

Ependymoma

SIOP Ependymoma II protocol is open in several European countries, was opened in Finland in the end of 2019 and will be soon opened in Sweden and Norway, and is in the process of submission in Denmark. This protocol has three different strata (risk categories) with separate randomisations in each strata. It does not contain novel therapies apart from valproic acid as HDAC-inhibitor and does not require tumour biology testing for risk stratification. Biological samples, however, are mandatory and will sent to BIOMECA core laboratories.

Low Grade Glioma (LGG)

SIOP-LOGGIC trial for LGG patients with non-NF1 LGG gr I-II and indication to treat is close to opening and will be opened in several NOPHO countries. Randomisation is between treatment with standard vincristine-carboplatin or vinblastine monotherapy or trametinib (MEK inhibitor). In addition to PFS as defined by MRI imaging, visual and neurological outcome will be included as primary outcome measures. This will necessitate close cooperation with study ophthalmologists for patients with a visual pathway tumour.

It is an inclusion criteria for LOGGIC Europe trial that the patient is first included in the **LOGGIC Core** Bioclinical database with mandatory 1st level molecular investigations (methylation array and basic molecular changes) as well as submission of frozen tumor tissue to 2nd level central tumor assessment in Heidelberg. The 1st level investigation has to be carried out at a LOGGIC molecular hub. At present Copenhagen (DK) is registered as a molecular hub and can perform testing for other countries (price not determined yet, there is some central funding for the first patients), but this can most likely be expanded to other centres in NOPHO as well. It is therefore necessary to open LOGGIC Core as well as LOGGIC Europe to be able to include patients into the randomised trial. All details are ready to be able to open LOGGIC Core and all countries are encouraged to get started on this to be able to be ready for LOGGIC trial. The LOGGIC trial is not yet ready for submission to the authorities, but it is expected that this will be the case within the next few months, and a VHP is planned.

Until opening of the LOGGIC protocol, recommended standard treatment for LGG is according to SIOP-LGG 2004 protocol, which was closed for randomisation in 2013.

LGG patients with BRAFV600E mutation in their tumor are excluded from LOGGIC and go to their own protocols. **Protocol for BRAFV600E positive LGG** including randomisation between standard vincristine-carboplatin and targeted dabrafenib-trametinib treatment is open in Copenhagen (DK) and Tampere (FI).

Protocol for neurofibromatosis 1 and low-grade glioma is also being developed together with the COG as a SIOP-COG cooperation. The trial has just opened in the US for NF-1 LGG patients with an indication for non-surgical therapy, chemotherapy is randomised between VCR-carboplatin (US schedule) and selumetinib, a MEK-inhibitor from AstraZeneca. Like the LOGGIC trial, visual function is an end-point. Birmingham will be European sponsor. Trial will probably not be ready to open in Europe before 2021.

High grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG)

SIOPE Infant HGG protocol was agreed but did not get enough funding and is planned to be opened as a registry containing treatment recommendation.

DIPG registry developed by the SIOPE DIPG network was published in January 2017 and is ready for use in each participating country after approval of national authorities. It has been submitted in Norway, and is planned in Sweden, Denmark and Finland.

BIOMEDE (Biological Medicine for DIPG eradication) is originally a protocol for H3K27M positive pontine gliomas and currently includes H3 K27M-mutant diffuse midline gliomas outside of pons as well. The protocol contains tumor biopsy and preinclusion screening of tumour biology. There was a biology dependent randomization for targeted medication combined with radiation therapy. Randomisation was paused and recruitment continues to single arm study (everolimus combined with radiotherapy) until opening of the BIOMEDE2 trial, which will include a novel drug ONC201. In NOPHO, BIOMEDE is open in Copenhagen (DK) and in Stockholm/Sweden. BIOMEDE2 will also be opened in Helsinki/Finland.

Trial of **dabrafenib + trametinib** for BRAF V600 mutant relapsed or refractory HGG is open in Copenhagen (DK), Stockholm (SE) and Tampere (FI).

There is still no open protocol for other HGG patients after HERBY-protocol in which no benefit from bevacizumab added to radiation therapy and temozolomide was received. Consensus for postoperative treatment of new HGG patient (other than midline H3K27M mutated glioma or infant HGG or rare HGGs with options for targeted treatment) in Europe and NOPHO is still radiation therapy and temozolomide with possible combination of lomustine.

CNS Germ Cell tumours (GCT)

SIOP CNS GCT II protocol for patients with CNS germ cell tumours was open in several countries including Sweden and Norway. The trial was closed in June 2018. The British group´s suggestion for treatment of these patients during the interim phase between protocols is to keep chemotherapy unchanged and, regarding radiotherapy, boost pure germ cell tumors also in cases of complete remission until outcome reports from the trial are available and for non-disseminated non-germinomas give whole ventricular radiation and boost to the tumor bed. NOPHO radiation therapy group recommends to do the same.

Early phase protocols

Regarding possible experimental therapies in NOPHO, the file ”NOPHO novel therapy trials overview” can be found on www.nopho.org under “protocols” and is updated by Karsten Nysom continuously.

A phase 1 trial with **afatinib** for relapsed or progressive ERB receptor positive tumors, which was open in Copenhagen (DK), is paused since Dec 23rd 2019.

MEMMAT protocol is a phase 2 trial of multidrug antiangiogenic approach for patients with recurrent or progressive medulloblastoma. The trial is open in Copenhagen (DK), Bergen (NO) and in all 6 Swedish centers.

A trial of PD1 inhibitor (**pembrolizumab**) in relapsed/progressive PD1 positive solid tumors including brain tumors is open in Lund (SE).

A phase 2 trial of **larotrectinib** for tumors harboring NTRK fusions is open in Copenhagen (DK).

A phase 1-2 trial of **LOXO-195** for tumors with NTRK fusions and resistance to larotrectinib is open in Copenhagen (DK).

A phase 2 trial of **dabrafenib and trametinib** for BRAF V600 mutant relapsed or refractory high grade glioma as well as BRAF V600 mutant low grade gliomas needing non-surgical therapy (randomized against vincristine + carboplatin) is open in Copenhagen (DK), Stockholm (SE) and Tampere (FI).

A phase 2 trial of **nivolumab** (anti-PD1) and ipilimumab (anti-CTLA4) for tumors with high tumor mutational burden without further standard of care treatment is open in Copenhagen (DK).

Radiotherapy

Protons are increasingly used for radiation therapy in pediatric patients, especially in case of very young patients and with close proximity of critical organs at risk. The Skandion Clinic in Uppsala opened in June 2015, is running and treating pediatric patients. Proton therapy centre in Aarhus opened in January 2019, first treated adults and teenagers with brain tumors and from August 2019 also treats younger children needing anesthesia. Pediatric patients from Finland have been sent to West German Proton Therapy Centre Essen (WPE), which treats pediatric brain tumor patients from several European countries. In Norway a political decision to build two proton centres has been made. Until that, pediatric patients are sent to WPE or Skandion Clinic.

QUARTET is a prospective SIOPE driven radiotherapy quality assurance program in which radiotherapy dose plans of patients included in SIOPE protocols are previewed on the EORTC data platform by appointed pediatric radiation oncologists to see if they are planned according to the radiotherapy protocol description. QUARTET is already implemented in neuroblastoma LINES protocol, is being implemented in PNET5 version 12, Ependymoma II and HR-MB protocols and planned in the new EPSSG rhabdomyosarcoma protocol.

NOPHO CNS research projects

The Nordic study of Cerebellar Mutism Syndrome (CMS) in children with brain tumours of the posterior fossa is open in Denmark, Sweden, Finland, Norway, Lithuania, Netherlands, UK and Hungary. The protocol and forms are on the NOPHO web site under "protocols". Patient accrual is going well.

Lithium in the treatment of cognitive late effects after cranial radiotherapy is a study proposed by Klas Blomgren and accepted as a NOPHO study by the NOPHO scientific committee and is planned to run in cooperation with Institut Gustave Roussy in Paris and Hospital for Sick Children in Toronto. Applications have been submitted.

DNA methylation classification of newly diagnosed pediatric CNS tumors in NOPHO study is open and running in Gothenburg (PIs Elizabeth Schepke, Magnus Sabel, Birgitta Lannering). This is a Swedish pilot first.

NOPHOmatch is a project for all relapsed / refractory pediatric cancers. Aim is to match children with R/R cancer to phase 1/2 trials through 1) opening of two large trials for targeted therapies in NOPHO area (ESMART and INFORM2) and 2) establishing weekly Nordic video conferences to assure matching of molecular tumor profiles to targeted treatment within trials. The project was selected for funding from NordForsk 2019-2022.

Nordic publications on pediatric CNS tumors (2019 – 2020):

E. Stensvold et al 2019: *Children treated for medulloblastoma and supratentorial PNET in Norway from 1974 through 2013: Unexplainable regional differences in survival.* Pediatr Blood Cancer 66(10):e279110.

Use of the NOPHO web in CNS tumour work

We continue to encourage that active SIOPE protocols will be put on the NOPHO web with permission of the protocol PI. Minutes of working group meetings should also be posted if permission is granted by the working group chair. In addition, we will keep updated lists of available molecular diagnostic methods on NOPHO web pages.

Virve Pentikäinen
Helsinki, March 17th, 2020

Solid Tumour Registry (NOPHO-Care Task force)

Chair	Päivi Lähteenmäki PI of NOPHO Care
Denmark	Lisa Hjalgrim, 2018
Finland	Päivi Lähteenmäki , 2013
Iceland	Ólafur G. Jónsson
Lithuania	Jelena Rascon, 2020
Norway	Bem Zeller, 2016
Sweden	Cecilia Petersen, 2020 Päivi Lähteenmäki CCEG registry
Young NOPHO	Thorgerdur Gudmundsdottir

The Nordic Childhood Solid Tumor Registry (STR) was started up and maintained since 1982 by the Norwegian Cancer Registry. Annual reports have been included in the NOPHO Report since 1995. The NOPHO Board has earlier decided to transfer the responsibility and future maintenance of the Nordic Solid Tumor Registry from the Norwegian Cancer Registry in Oslo to the Childhood Cancer Research Unit in Stockholm, and a comprehensive analysis of the available Nordic data (1982-2014) was performed for the STR group by our esteemed colleague Göran Gustafsson. The results were published in the Annual Report of 2016.

At that time point, it had become clear that the registration of the patients in practice is only possible to the national quality registries and to specifically defined research project databases (not to be called as registries). Thus, NOPHO wanted to investigate the possibilities to facilitate international collaborations outside NOPHO as well as inside the society. A "Nordic Study Day" was organized on January 28th 2016 in Stockholm by NOPHO GS, NOPHO-registry (CCEG-group) and LLC together with representatives from ethics committees, MPAs, biobank authorities and data regulation expertise from different NOPHO countries in order to try to clarify what is allowed, what is not allowed and how we can overcome obstacles to collaboration in the interest of our patients.

The minutes of the meeting as well as the case-discussions can be found under the Board on the NOPHO-web. Two out of many decision points were:

- In terms related to data protection "language ", NOPHO-registry is the data controller for all Nordic centers. The centers are data processors and there needs to be a formal contract between each processor and the controller.
- NOPHO should design long term registry-based studies. A proposition, "NOPHO-CARE", is under development.

After creating the project group and finalizing the protocol, NOPHO-CARE study proposal was accepted by the official processes within NOPHO. The NOPHO-CARE study has the overall goal of analyzing factors of importance for the event-free and overall survival as well as describing the cost of disease (acute toxicity leading to death, late-effects, late appearing second malignancies) of children with leukemias, lymphomas and solid tumors, and specific rare non-malignant hematological disorders (e.g.

aplastic anemia, thalassemia major, sickle cell disease, DBA). Specific Aims are:

- To study event-free (EFS) and overall (OS) survival in all children with malignancies and specific non-malignant hematological disorders within NOPHO countries.
- To study the effect on survival of the time lapse between diagnosis (as defined by international standards) and start of anticancer treatment
- To study the effects of background variables (patient age at diagnosis, gender, country of residence, disease presentation (molecular biology of the disease, morphology and sub-site localization of the tumor, stage, risk category, given therapy) on EFS and OS.
- To study in more detail the background variables (described above) for those diagnostic subgroups where EFS and OS in NOPHO countries seem to be below those of the best countries in EURO-CARE reports.
- To analyze the causes of death and their possible changes over the decades when treatments and environmental factors have changed. (Progressive cancer/disease, toxicity of treatment, secondary cancer, other causes of death)
- To produce data on cancer prevalence in NOPHO countries (complete and by disease duration)
- To produce validated data on incidence, survival and prevalence of rare cancers and rare non-malignant hematological disorders in NOPHO countries.
- To produce validated data on the proportion of cancer patients and transplanted patients with non-malignant hematological disorders who are cured of their disease and may be in need for specialized late-effect follow-up services in each country.
- To estimate and analyze the number and proportion of avoidable deaths.
- To create a platform for further studying the biology, optimal treatment and final outcomes of non-malignant hematological diseases in a broad enough population (NOPHO-countries).
- To create a platform for discussion on the introduction of further common NOPHO treatment protocols (primary and relapsed diseases) with a wider European/worldwide collaboration.

NOPHO-CARE has two different settings. A registry based part for leukemias, lymphomas and solid tumors: Patients (both alive and deceased) with leukemia, lymphoma, and solid tumors (CNS and extracranial) diagnosed since 1982 whose data need to be collected from national cancer registries, national and local quality registries, and local cancer registries including NOPHO-leukemia databases for ALL and AML. Data in leukemia databases are also needed in the development of future protocols as control material. The development of the treatment of solid tumors in the Nordic level needs compact data on the present treatment results. The high number of patients and inclusion of deceased cases is a reason for not being able to get informed consents for this retrospective study data. The prospective part of the study: Collecting more detailed data (not available in national or local registries) on treatments, toxicities, relapse treatment, and biological aspects from patients with all childhood /adolescent/young adult malignancies who give consent for the NOPHO-CARE study, including patients with non-malignant hematological disorders (e.g. aplastic anemia (SAA), thalassemia major, sickle cell disease, DBA).

In March 2020 we can report that Sweden, Finland, and Lithuania are ready with their national permissions, and Denmark, Iceland and Norway have got agreement for some parts of the project but some details are pending. CCEG has been studying four different solutions for the building up of the new study database. Funding for that is granted from Barncancerfonden, and the final decision will be made in April 2020. Thus, the NOPHO-CARE Task force looks forward getting the study started during 2020.

On behalf of the group
Päivi Lähteenmäki

Lymphoma Working Group

Hodgkin and Non-Hodgkin lymphoma

Chair	Lisa Hjalgrim DK (2015)
Denmark	Peder Skov Wehner Lisa Lyngsie Hjalgrim
Finland	Päivi Lätheenmäki Pasi Huttunen Päivi Raittinen Kaisa Vepsäläinen
Iceland	Ólafur G. Jónsson Sólveig Hafsteinsdóttir
Norway	Maria Gunnes Monica Cheng Munthe-Kaas
Sweden	Karin Mellgren Susanna Ranta Annika Englund Fredrik Becklund
Young NOPHO	Diana Ljung Sass (SE)
Reference pathologist	Ulrika Hansson (SE)

Introduction

The NOPHO Lymphoma group is the combination of the previous Hodgkin Lymphoma (HL) (est. 2014) and non-Hodgkin Lymphoma (NHL) (est. 1992) working groups. It was decided to fuse the two fora at the annual NOPHO meeting in Oulu in May 2015. The Lymphoma working group goals are:

- To share patient experiences and discuss difficult patients
- To involve the Nordic countries in international lymphoma protocols and scientific projects
- To have treatment guidelines also for patients with rare lymphomas
- To have an infrastructure for handling, shipment, and analyses of bio-samples from patients with various types of malignant lymphoma
- To have NOPHO representatives in international collaborations
- To update and expand the former NOPHO NHL registry to be a common Nordic Lymphoma registration within the NOPHOCARE project
- To have 2- 3 yearly meetings
- Finally, to have an updated Lymphoma working group NOPHO webpage within the NOPHO webpage

Over the last two decades, the treatment of both HL and NHL in children and adolescents has followed European protocols.

In 2019 the NOPHO Lymphoma WG had 3 meetings and the main focus of the group has been to open the international lymphoblast lymphoma trial "LBL2018" and to run the common NOPHO and BFM mature B-cell lymphoma trial "B-NHL 2013".

The Lymphoma Registry

The NOPHO NHL-group has been working with on-line registration of patients for a long time and the web-based register has been open for many years, making reporting easier for all clinics. However, change of the NOPHO lymphoma Registry is in process. The registry will include both Hodgkin (HL) and non-Hodgkin (NHL) lymphoma patients. The aim is to have more simple registration for all lymphoma patients, with type of lymphoma, disease characteristics, treatment strategy, and importantly better registration of relapse patients and the relapse treatment strategy. At the moment there is no registration of HL patients in the NOPHO registry (besides Swedish patients) and importantly the registration of NHL patients in registry is dropping. Hopefully, coverage will be improved with new international trials opening and the common "NOPHO Care project".

Hodgkin Lymphoma

Since October 2015, the **Euro-Net-PHL-C2 protocol** has opened and all the Nordic countries are now joining, establishing uniform diagnostic risk stratification and treatment of all Nordic HL patients age 0-18 years at diagnosis.

A common feasibility NOPHO study (Teddi) using breath hold technique during delivery of radiation to thorax and upper abdomen is running in Denmark and Finland.

Non-Hodgkin Lymphoma

Lymphoblast lymphoma: All Nordic countries opened the **LBL 2018 protocol** during 2019 and are recruiting patients into this trial, which is expected to include patients until summer 2024.

Mature B-cell lymphomas and leukemia: The **NOPHO and BFM B-NHL 2013** was approved in all of the Nordic countries in 2017 and all Nordic countries are now open and recruiting patients into this trial, which is expected to include patients until the end of 2023.

Registration of patient data in these protocols are through the Marvin database and NOPHO database. Several NOPHO add on studies are part of these protocols (Quality of life study, immune reconstitution study and CNS flow study). The coordinating NOPHO center is Gothenburg for both the LBL2018 and the BFM2013 trial .

It is expected that a new international protocol for the treatment of **ALCL** will open during 2020

Overall conclusions

NOPHO takes part in international collaborations for the treatment of HL and NHL. Such cooperations are necessary to identify patients with specific risk-factors within the very heterogeneous group of lymphoma patients. This year work in the lymphoma group has mostly been concentrating on opening the LBL2018 trial and recruiting patient to this trial and the B-NHL 2013 trial. Moreover, improvement in registration of lymphoma patients in the NOPHO CARE project will increase the possibility of better surveillance of lymphoma patients within the Nordic region and make it possible for NOPHO to conduct studies and contribute with data to international studies. For some NHL subtypes there is clearly need of new treatment protocols not least treatment protocols for relapsed patients.

Lisa Lyngsie Hjalgrim
Chair
Copenhagen, March 2020

Leukaemia Working Groups

Leukemia and Lymphoma Committee

Chair	Inga Maria Johannsdottir (NO) 2018
Denmark	Peder Skov Wehner, Bodil Elise Thorhauge Als-Nielsen 2019
Finland	Mervi Taskinen (re-elected 2017), Riitta Niinimäki 2019, Päivi Lähteenmäki 2014
Iceland	Ólafur G. Jónsson, Sólveig Hafsteinsdóttir 2013
Lithuania	Ramune Pasauliene 2016, Igne Kairiene 2019
Norway	Bendik Lund 2016, Monica Munthe-Kaas 2018
Sweden	Jonas Abrahamsson, Karin Mellgren 2016, Arja Harila-Saari 2016
Young NOPHO	Audrone Muleviciene (LT)
NOPHO WG-Chairs	
ALL-2008 PI	Kjeld Schmiegelow
ALLTogether	Mats Heyman
ALL Relapse	Petter Svenberg
ALL WG	Mats Heyman
Adult-ALL-group	Nina Toft
LL-Biology	Linda Fogelstrand and Olli Lohi
AML	Josefine Palle and Kees-Jan Pronk
Biobank	Trond Flægstad
Board chair	Birgitte Klug Albertsen
Leukemia genetics	Ulrika Norén-Nyström
Event Group	Arja Harila-Saari
Infant ALL	Birgitte Lausen
Leukemia registration	Mats Heyman
Lymphoma working group	Lisa Lyngsie Hjalgrim
NOPHO MRD group	Hanne Marquart
Ph-ALL/CML	Dominik Turkiewicz
Pharmacology	Goda Vaitkeviciene
SCT	Dominik Turkiewicz

The LLC meets twice a year in connection with the Board meeting. The meetings in 2019 were held in Aarhus (May 3rd) and in Oslo (November 5th). Minutes and presentations from both meetings can be found on the NOPHO website. The main focus at the meetings has been the follow-up of the Nordic leukemia/lymphoma protocols, the proceedings of ALLTogether and new lymphoma protocols, and the reports of leukemia/lymphoma – related working groups.
These groups report their detailed achievements and efforts under their own sections in this annual report.

ALLTogether pilot protocol has been opened in Denmark, Sweden, Norway and Lithuania. The Master protocol is being prepared in most of the participating countries and hopefully will be able to start in Q2 or Q3 this year.

According to NOPHO statutes, leukemia- and lymphoma-related NOPHO studies are always evaluated by the LLC before they go to the Board.
There are an increasing number of non-NOPHO initiated studies connected to the new ALL-Together

(A2G) protocol. LLC has discussed how to organize these studies within NOPHO and decided that these should be treated like other NOPHO studies with approval from WG --> SciCom -> LLC -> Board.

There are two large ALL – late effect studies ongoing and somewhat overlapping, ALLSTAR and HALLON. The study groups are discussing a possible cooperation.

LLC chair has represented NOPHO at the yearly I-BFM board meetings and in 2019 this meeting was held in connection with the first one-week European Childhood Cancer (SIOPE) meeting in Prague on 20th-24th of May. Young active people should be introduced to the SIOPE network, and encouraged to attend the working groups and meetings.

Finally, the LLC has been discussing what is the spirit of NOPHO. NOPHO is not a legal entity and does not own its data, particularly not registry data or biobank material. We need structural changes and to build strong Nordic databases. NOPHO has no legal way of enforcing decisions and LLC admitted a suggestion to the board to establish a working group with national representatives that can define NOPHO and its aims and work on making it a legal entity. We have to think Nordic before local and think Nordic before European.

Oslo
March 2020

Inga Maria Johannsdottir
LLC-chair

ALL Working Group

Coordinator	Mats Heyman
Denmark	Birgitte Klug Albertsen
	Thomas Frandsen
Estonia	Mari Punab
	Kristi Lepik
Finland	Päivi Lähteenmäki
	Mervi Taskinen
Iceland	Ólafur Gísli Jónsson
Lithuania	Goda Vaitkeviciene
Norway	Inga Maria Rinvoll Johannsdottir
	Trond Flaegstad
	Bendik Lund
Sweden	Jonas Abrahamsson
	Anders Castor
	Johan Malmros
Young NOPHO	Adam Alexandersson (FI)
	Nikolas Herold (SE)
Adult representatives	
Denmark	Nina Toft, Ulrik Overgaard
Estonia	Katrin Palk
Finland	Ulla Wartiovaara-Kautto
Norway	Petter Quist Paulsen
Sweden	Helene Hallböök
Lithuania	Laimonas Griskevicius
Chair of the	
Leukemia and Lymphoma committee	Inga Maria Rinvoll Johannsdottir
ALL 2008 protocol committee	Kjeld Schmiegelow
Event group	Arja Harila-Saari
Infant ALL	Birgitte Lausen
ALL relapse	Petter Svenberg
Ph+ ALL/CML	Anders Castor
MRD group	Hanne Marquart
Cytogenetic group	Ulrika Noren Nyström, Bertil Johansson
Pharmacology group	Goda Vaitkeviciene
LL-Biology	Olli Lohi, Linda Fogelstrand
A representative from	
NOPHO registry	Mats Heyman
Secretary general	Birgitte Klug Albertsen

The ALL group meets twice yearly, the day after the Leukaemia & Lymphoma Biology group meetings. The meetings during the year from the last report have been held at Arlanda airport (25th of September 2019 and 10th of March 2020) and have been amalgamated with the NOPHO ALLTogether working group meetings.

The main task of the working-group is to coordinate ALL-directed activities within NOPHO and to prepare issues for decision by the LLC and the NOPHO board.

The present ALL protocol (NOPHO ALL-2008)

ALL WG has cooperated with the NOPHO ALL 2008 PI-group in the follow-up of the ALL2008 protocol.

The study protocol has recruited 2648 patients from 1.7.2008 to 31.12.2019. Out of those 2211 were children 1-17.99 years from the Nordic and Baltic countries, 437 adults (age 18-45) from the Nordic and Baltic countries. We no longer separate the Baltic patients from the rest of NOPHO in the evaluations, but Lithuania and Estonia did not take part in the randomizations in the NOPHO ALL-2008 protocol. The randomized parts of the protocol have now been closed since 1.3.2016, but the protocol is used as standard of care (SOC) until the introduction of the ALLTogether protocol.

EFS at five years is stable as expected: children: 0.86 (SE 0.01), adults: 0.67 (SE 0.03).

pOS at five years: overall: children: 0.93 (SE 0.01), adults: 0.74 (0.03).

The NOPHO ALL-2008 patients have been considered as three defined cohorts:
Cohort 1: Diagnosis 1.7.2008-31.12.2014 (overall publication of outcome comparing children <18 years with young adults 18-45 years). Publication: Toft et al. Results of NOPHO ALL2008 Treatment for Patients Aged 1-45 Years With Acute Lymphoblastic Leukemia. Leukemia. 2018 Mar;32(3):606-615.

Cohort 2: Diagnosis 1.7.2008-1.3.2016 ("randomization cohort" - with randomized parts starting recruitment from 1.1.2009 in Denmark and Sweden, 11.2.2009 in Norway, 1.6.2009 in Finland and 7.1.2010 in Iceland). Most publications from the NOPHO ALL-2008 will have this cohort as recruitment base.

Cohort 3: Diagnosis 1.7.2008- ongoing ("continuation" population-based cohort until the start of ALLTogether Pilot/Main study).

The final composition of cohort 1 and 2 is in principle fixed, but further scrutiny may still change details in the registration. Among other things, the scrutiny of the genetic findings in order to publish the NOPHO ALL-2008 results have changed the genetic label of some patients.

The randomized parts (R1: treatment with or without 6MP increments during consolidation for SR and IR-patients has now been published: Tulstrup et al, Individualized 6-mercaptopurine Increments in Consolidation Treatment of Childhood Acute Lymphoblastic Leukemia: A NOPHO Randomized Controlled Trial, Eur J Haematol. 2018 Jan;100(1):53-60.

R2: 2-weekly (total 15 doses) vs 6-weekly (total 8 doses) PEG-Asp during post-consolidation therapy for SR and IR-patients) has been published in Journal of Clinical Oncology: Klug Albertsen et al, JCO. 2019; 37(19):1638-1646.

The third randomization exploring the addition of Depocyte to high-risk patients in Maintenance has also been published: Levinsen et al. J Pediatr Hematol Oncol. 2016 Nov;38(8):602-609.

A large number of additional papers have been published or are planned based on the protocol – most of those will be based on Cohort 2, but some add-on studies may extend into Cohort 3, which is one of the reasons why the protocol stratification and treatment intentions should be kept.

The MRD group and database

The focus is on preparations for the ALLTogether protocol – both the Pilot- and the Main study. Hanne Marquart has an important role in this group as NOPHO-representative and advocate for flow-cytometry MRD. NOPHO's MRD-database is in the process of being updated with options to include the timepoints relevant for ALLTogether. Eventually, these data will be imported into the ALLTogether study database by automated transfer. For the Pilot Study and the early part of the Main Study, the essential stratifying MRD-data will still have to be entered manually.

The Cytogenetic group and database

The Cytogenetic group performs annual central review of the genetic aberrations in the ALL-cohort (both adults and children) in all Nordic countries. This review has the last years been extended to the Baltic countries thanks to the work by Ulrika Norén Nyström and Bertil Johansson.

The database, which has been managed for many years by Erik Forestier is now prospectively stored in the MySQL database together with the rest of the NOPHO ALL-data in Stockholm. For this purpose, a web-based access has been developed, so that genetic labs can enter data directly into the database and the central review of genetic data is now also performed on-line from the review-meetings. The legacy data from the cytogenetic group is planned to be added to this system, but for practical reasons and time-constraints, this work is still pending for many patients.
The NOPHO-registration system has been fully updated to accommodate the new registration parameters necessary for ALLTogether participation. Eventually these data will be (in analogy with the MRD-data), imported into the ALLTogether Castor database. However, like for the MRD-data, this link is still not operational.

Therapeutic drug monitoring of Asparaginase-activity and Asparaginase-related studies

NOPHO has a great tradition of Asparaginase-related research, mainly based in Aarhus and conducted by Birgitte Klug Albertsen. With the advent of the ALLTogether protocol, there will be monitoring of Asparaginase-activity to identify silent inactivators and distinguish "genunine" allergic reactions (with inactivation of Asp-activity) from "allergy-like" reactions (with retained Asp-activity). Some additional time-points will be added to 1) identify inactivation to the first dose of PEG-Asp and 2) relate peak-level Asparaginase-activity to toxicity and anti-leukaemic activity.

These measurements will be carried out for all of NOPHO in Aarhus and will be recorded in a separate RedCap database – eventually feeding into Castor as the NOPHO MRD- and Cytogenetic applications. Analyses will be systematic in ALLTogether, but the analyses are also performed on patients from other protocols (for instance NOPHO ALL-2008) with reactions. Some of these patients may also qualify for inclusion in the GRASPA-study with red-cell encapsulated E.coli Asparaginase.

Other Asp-related studies include correlation of Asp-activity to toxicity and the exploration of the role of Asp-truncation (due to toxicity) for prognosis in the NOPHO ALL-2008 cohort.

Preservation of old (and new) NOPHO-data and NOPHO-Care

NOPHO has developed leukaemia-treatment for children since the early 1980s and this development is in fact an important reason for the existence of NOPHO as an organisation. This has accumulated a series of leukaemia-protocol cohorts with detailed registration of clinical characteristics, treatment and outcome data – usually referred to as the NOPHO-registry. The legal status of this database has been difficult to establish and with the advent of ever stricter measures to control registration of personalised data, an urgent need for preservation of these data – preferably together with solid tumour data has been a NOPHO priority. This has resulted in a new long-term research project, NOPHO-Care with the aim to conduct long-term follow-up of NOPHO children with childhood cancer. The leukaemia-registries for ALL and AML will constitute an important part of NOPHO-Care. The infrastructure for this long-term storage is being set up with the Childhood Cancer Research Unit in Stockholm under Päivi Lähteenmäki and with a commitment to collect study-data from studies both retrospectively and prospectively.

International Collaborations

Internationally, the NOPHO ALL working group has been represented in the I-BFM collaborative ALL working group (various), the Interfant 2006- (Birgitte Lausen), EsPhALL (Anders Castor) and IntReALL relapse- (Petter Svenberg, Päivi Lähteenmäki, Thomas Frandsen, Inga Maria Johannsdottir) study groups as well as the Ponte-di-Legno (PdL) group (Kjeld Schmiegelow, Mervi Taskinen and Mats Heyman).

Interfant 2006: Patient inclusion has stopped. Several pilot-studies are ongoing, no new protocol proposal yet. The Swedish adaptation of the NOPHO ALL-2008 protocol is used for Swedish infants.

EsPhALL: The new EsPhALL-protocol (in collaboration with COG) with Imatinib for all patients and a randomisation between EsPhALL-therapy and the COG High-risk backbone is on its way to be implemented.

IntReALL: Denmark, Finland and Norway are recruiting patients into the SR-arm of IntReALL. Sweden has not started recruiting and this study is likely to stop recruiting in 2020 or 2021. The HR-study is presently evaluated for a possible amendment, since very good results have been obtained by COG using Blinatumomab for consolidation of HR-patients before allo-HSCT. No consensus exists at the moment with regard to the HR-arm.

PdL: Several projects are underway with collection of data from rare sub-sets of patients.

PdL-toxicity group: An additional important contribution is the initiative from Kjeld Schmiegelow to the PdL-group to coordinate toxicity-registration internationally. Ater an initional consensus paper describing definitions of 14 toxicities (Schmiegelow et al. Lancet Oncol. 2016 Jun;17(6):e231-e239) several projects have been carried out (pancreatitis, several projects are underway: thrombosis, osteonecrosis, neurotoxicity, Asp-related hypersensitivity, Mtx-nefrotoxicity and delayed excretion. The group has also decided to try to define uniform ways to report protocol data and unacceptable long-term toxicities ("Quality Survival").

The next ALL-protocol - ALLTogether

The international collaboration, which started in 2013 to form a consortium ("ALLTogether") for a common ALL protocol has continued. The study was approved in 12 countries (apart from the NOPHO-group including Estonia: Germany, Belgium, the UK, Portugal and Ireland) in October 2019 through a "voluntary harmonised procedure" (VHP) and the Netherlands has approved the protocol separately shortly thereafter. The consortium now consists of 8 study-groups NOPHO, UKALL, DCOG, COALL, BSPHO, SHOP, PHOAI and SFCE. Recently Spain and Cyprus has joined as observers, with the intention to use the master protocol without the experimental interventions (analogous to the NOPHO-pilot described below).

Mainly logistic hurdles (necessary contracts between sponsor and the participating countries, approvals from ethical review boards and in some countries biobank and data-protection authorities), but also the lack of some essential documents and necessary changes to the registration system have held up the start of the main study, but it is now scheduled for start in the first countries in early June 2020.

The first complete draft of the protocol has been in use as a pilot-study, partly to gain experience from the stratification and therapy and partly to test the logistics of the new diagnostics in genetics and MRD. The pilot was implemented first in Denmark (autumn 2018), Lithuania (January 2019), Sweden, Norway and Iceland (autumn 2019). Estonia will join the pilot shortly and will join the main study in 2021. Finland is planning to join the main study directly.

ALLTogether is also meant to be a platform for further ALL research. There has been a call for add-on studies and >30 such studies have been suggested. Several of these studies have been suggested by NOPHO researchers and NOPHO has taken the stance that NOPHO-participation in such studies should be approved by the NOPHO scientific committee. Such approved studies include:

- a study continuing the evaluation of leukaemic contamination of the CSF
- the analysis of the impact of asparaginase-activity (a spin-off of therapeutic drug-monitoring)
- maintenance monitoring (sprung from the NOPHO maintenance study)
- a study on the efficacy of Imatinib (in vitro and in vivo) for patients wit ABL-class fusions in the leukaemic cells
- BRAIN – a study on cognitive long-term effects of ALL-treatment

Mats Heyman, Kjeld Schmiegelow and Mervi Taskinen are the NOPHO representatives for paediatric patients, Helene Hallböök, Nina Toft and Ulla Wartiovaara-Kautto represent NOPHO adult haematologists in the ALLTogether steering committee. Mats Heyman is the chief investigator (CI).

National PI:s are: Johan Malmros (paed S), Helene Hallböök (adult S), Bodil Als-Nielsen (paed DK), Ulrik Malthe Overgaard (adult DK), Inga Maria Rinvoll Johannsdottir (paed N), Hilde Skuterud Wik (adult N), Mervi Taskinen (paed FIN), Ulla Wartiovaara-Kautto (adult FIN), Goda Vaitkeviciene (paed LT), Laimonas Griskevicius (adult LT), Kristi Lepik (paed EE), Mari Punab (adult EE).

The NOPHO biobank

The biobank is going through an overhaul with improved logistics and capability for storage of not only cells, but also primary derivatives such as DNA and RNA – and in ALLTogether also CSF. The biobank receives structural support from the Swedish Childhood Cancer Fund securing its existence and development.

The ALL-WG as an ALL forum

Several working- and ad hoc groups - the LL-biology group, the pharmacology group and the event-group have presented their projects to the ALL-group for feedback and discussion.

The ALL WG has also served as discussion-forum for NOPHO-studies pertaining to ALL-issues giving approvals and recommendations for amendments and further handling by the LLC.

Stockholm, Springtime, 2020
Mats Heyman

Leukemia - ALL Registration Working Group

Coordinator	Mats Heyman
Denmark	Birgitte Klug Albertsen
Finland	Kim Vettenranta
Iceland	Ólafur Gísli Jónsson
Norway	Inga María Jóhannsdóttir
Sweden	Jonas Abrahamsson, Mats Heyman

Data management group Stockholm

Mats Heyman
Trausti Óskarsson
Päivi Lähteenmäki
Göran Gustafsson
Lili Zheng
Shahid Tarar
Nima Behnam Makoi
Mats Nordström
Matteo Bottai
Ida Hed Myrberg
Adrian Levitsky (Head Data Manager, ALLTogether Pilot Study)

Data checks Copenhagen (NOPHO ALL-08)

Kjeld Schmiegelow (PI, NOPHO ALL-08)
Thomas Frandsen
Louise Rold Helt
Kirsten Kørup Rasmussen
Nina Toft

Introduction

We are now clearly in a transition-phase: The NOPHO ALL-2008 trial was closed for recruitment into the randomised sub-studies 1.3.2016, but has continued as standard of care and recruited patients until the end of 2019 (the end of this survey) in Sweden, Norway, Finland, Iceland and Estonia. In Denmark, patients have been included in the ALLTogether Pilot Protocol since late 2018 and recruitment in Lithuania started in 2019. Unfortunately, registration of those patients is lagging behind for legal and logistic reasons. This survey contains the registered patients at the time of extraction of the databases. Registration is important for all patients, but obviously more urgent for the new protocol patients, who experience therapy that is new to the treating centres. The survey is limited in scope and volume this time, mostly because of the situation with shifting priorities and lack of effective registration in the new protocol.

One of the purposes of the Pilot Study was the practice of the new diagnostics, stratification, therapy, but also registration. Even if data is somewhat sparse, important feedback for re-design of the registration system has contributed to big improvements.

Figure 1. NOPHO ALL-2008 trial enrollment and exclusions.

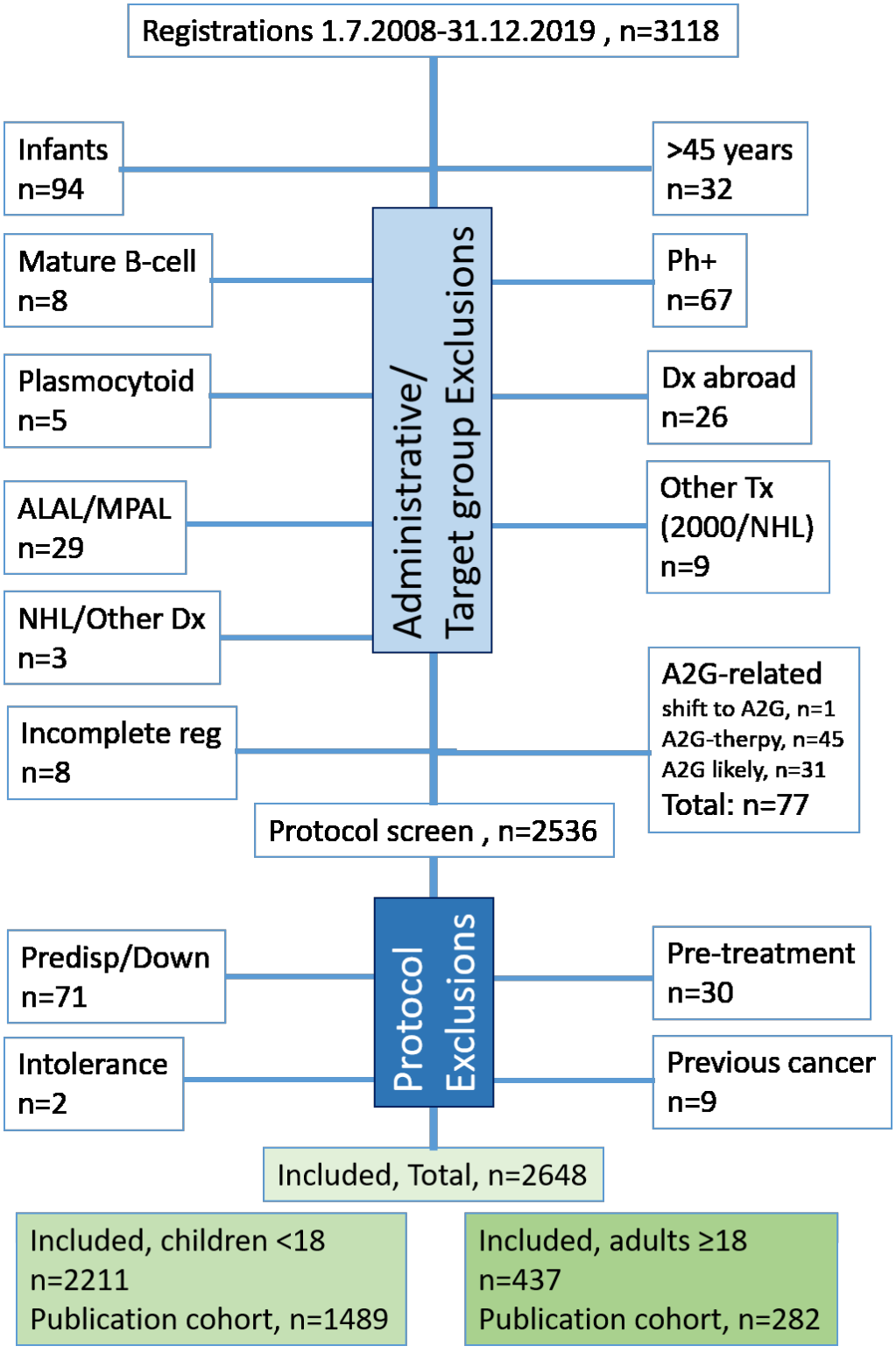


Table 1. Events and outcome NOPHO ALL-2008 – all patients.

Event	Age 1-15 n=2115		Age 16-24 n=291	Age 25-45 n=242	Total n=2648
Non-responders	0		0	0	0
Death in induction	16 (0.8)		2 (0.7)	3 (1.2)	21 (0.8)
CR-reached	**2099**		**289**	**283**	**2627**
Remission %	**99.4**		**99.3**	**98.8**	**99.2**
CR1, no RG d29*	4		0	0	4
Final risk stratification	**SR n=1188 (n=1072)****	**IR n=930 (n=716)****	**HR-chemo n=317 (n=208)****	**HR-HSCT n=188 (99)****	**CR1 n=2623 (2095)****
Death in CR1	11 (9)	23 (15)	29 (20)	15 (8)	78 (52)
Relapses	64 (49)	99 (61)	65 (40)	37 (14)	265 (164)
iBM	28 (19)	51 (29)	46 (9)	28 (12)	153 (89)
iCNS	15 (15)	21 (15)	7 (5)	0 (0)	43 (35)
Testis	2 (0)	1 (0)	1 (1)	0 (0)	4 (1)
BM+CNS	9 (6)	16 (13)	6 (4)	2 (1)	33 (24)
BM+testis	4 (4)	1 (1)	0 (0)	0 (0)	5 (5)
BM+CNS+testis	2 (2)	1 (1)	1 (1)	0 (0)	4 (4)
BM+Other site	2 (1)	3 (2)	0 (0)	3 (1)	8 (4)
Other site	0 (0)	4 (0)	4 (1)	3 (0)	11 (1)
Not registered	2 (2)	1 (0)	0 (0)	1 (0)	4 (2)
SR relapse (IntReALL)	49 (39)	57 (38)	4 (2)	1 (1)	111 (80)
HR relapse (IntReALL)	15 (10)	40 (23)	57 (38)	13 (4)	125 (78)
Relapse after SCT	0 (0)	2 (0)	4 (1)	23 (9)	29 (10)
SMN	11 (10)	2 (2)	3 (1)	0 (0)	16 (13)
MDS	4 (3)	0 (0)	1 (1)	0 (0)	5 (4)
AML	3 (3)	1 (1)	1 (1)	0 (0)	5 (5)
Other	3 (3)	1 (1)	1 (0)	0 (0)	5 (4)
All events	86 (68)	124 (78)	97 (62)	52 (22)	383 (249)
CCR number	1102 (1004)	806 (638)	220 (146)	136 (77)	2265 (1866)
CCR %	92.8 (93.7)	88.3 (89.1)	69.4 (70.2)	72.3 (77.8)	85.5 (88.2)
pDFS (60 mo) all	0.91 (0.01)	0.84 (0.01)	0.65 (0.03)	0.67 (0.04)	0.84 (0.01)
pDFS (60 mo) <16	0.92 (0.01)	0.87 (0.02)	0.66 (0.04)	0.74 (0.05)	0.87 (0.01)
pDFS (60 mo) ≥16	0.78 (0.05)	0.75 (0.04)	0.63 (0.05)	0.57 (0.06)	0.70 (0.02)
pEFS (60 mo) all	-	-	-	-	0.83 (0.01)
pEFS (60 mo) <16	-	-	-	-	0.86 (0.01)
pEFS (60 mo) ≥16	-	-	-	-	0.70 (0.02)
All dead	33 (22)	63 (31)	78 (49)	42 (99)	239 (136)
All alive	1155 (1050)	867 (685)	239 (159)	146 (83)	2409 (1979)
alive %	97.2 (97.9)	93.2 (95.7)	75.4 (76.4)	77.7 (83.8)	91.0 (93.6)
pOS (60 Mo) all	0.97 (0.01)	0.92 (0.01)	0.71 (0.03)	0.74 (0.04)	0.90 (0.01)
pOS (60 mo) <16	0.98 (0.01)	0.95 (0.01)	0.72 (0.03)	0.82 (0.04)	0.93 (0.01)
pOS (60 mo) ≥16	0.86 (0.04)	0.82 (0.03)	0.69 (0.05)	0.64 (0.06)	0.76 (0.02)

*Four patients had very severe infectious complications during induction and could not be assigned a risk-group. They are included in the total number of patients reaching CR1. Three of these patients have relapsed. ** Figures in parenthesis are patients 1-15 at diagnosis for counts and standard error for estimates. The count in "All Events", "CCR number", "All dead", "All Alive" and "alive %" also include the induction deaths as well as the outliers described above.

Table 2. Primary events (NOPHO-2008 cohort) since the previous report.

Event	SR (<16)	IR (<16)	HR-chemo (<16)	HR-SCT (<16)	Total (<16)
Relapse	14 (11)	18 (13)	9 (4)	5 (4)	46 (32)
DCR1	1 (1)	0 (0)	2 (2)	2 (1)	5 (4)
SMN	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)
Total	16 (13)	19 (14)	11 (6)	7 (5)	53 (38)

Numbers in parenthesis refers to patients <16 years at diagnosis.

The annual tally of primary events has increased somewhat compared with the report 2019 (54 vs 43 events). This is not primarily due to late reporting, Only 4 of these events occurred in 2018 and were missed in last years' reporting. As the protocol progresses, one would expect a larger fraction of later relapses, particularly in the lower risk-groups. However, the risk-group distribution is more or less as expected from the initial stratification. A little more than half of the relapses (25/46) were defined as "early" (<36 months from diagnosis and this was, as expected, more common in the higher risk-groups.

One additional relapse occurred in a patient without risk-group and adapted therapy and is thus not included in table 2.

Quality of follow-up - Follow-up of living patients

Median follow-up for all patients (extraction 6th of May):

All patients 1609 days – 4.4 years (19-4290).
For patients <16 years 1783 days – 4.9 years (19-4290).
For patients ≥16 years 1526 days - 4.2 years (27-3952).

These medians seem low for a protocol that started 2008 and prompted an analysis of what fraction of patients have adequate follow-up recorded.

Table 3. Quality of follow-up for living patients diagnosed <2019 and not lost to follow-up before the 1st of January 2019.

	<16 years (%)	≥16years (%)	Total (%)
FU <1019	635 (35.1)	98 (26.6)	733 (33.6)
FU Q1 2019	9 (0.5)	29 (7.9)	38 (1.7)
FU Q2 2019	69 (3.8)	14 (3.8)	83 (3.8)
FU Q3 2019	190 (10.5)	44 (11.9)	234 (10.7)
FU Q4 2019	381 (21.0)	20 (5.4)	401 (18.4)
FU 2020	526 (29.1)	164 (44.4)	690 (31.7)
Total	1810 (100)	369 (100)	2179 (100)

Table 4. Quality of follow-up for living patients diagnosed <2019 and not lost to follow-up before the 1st of January 2019. Publication cohort only

	<16 years (%)	≥16years (%)	Total (%)
FU <1019	524 (41.6)	77 (32.4)	601 (40.1)
FU Q1 2019	6 (0.5)	18 (7.6)	24 (1.6)
FU Q2 2019	51 (4.0)	11 (4.6)	62 (4.1)
FU Q3 2019	131 (10.4)	22 (9.2)	153 (10.2)
FU Q4 2019	235 (18.6)	6 (2.5)	241 (16.1)
FU 2020	314 (24.9)	104 (43.7)	418 (27.9)
Total	1261 (100)	238 (100)	1499 (100)

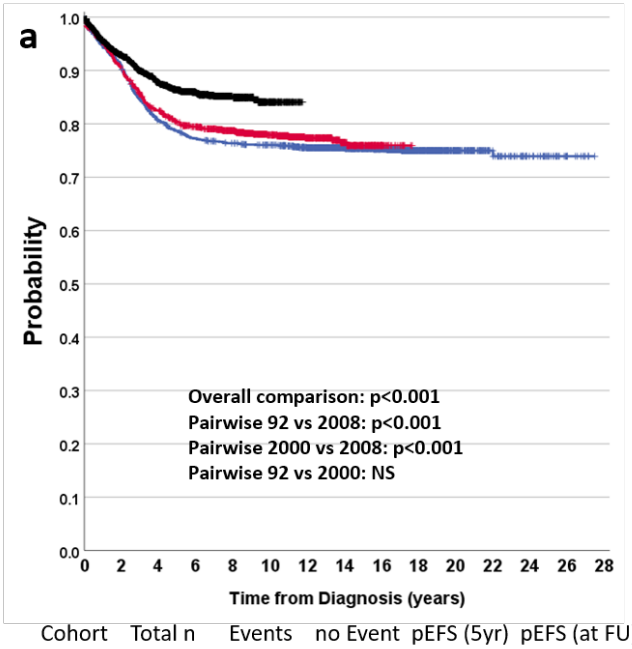
More than a third of our patients have follow-up that is older than one year. The publication-cohort has even less diligent follow-up. This may reflect the relative focus on more recent patients, but will affect our ability to conduct studies on the NOPHO ALL-2008 material. There does not seem to be any major difference in quality of follow-up between paediatric and adult centres.

Table 5. Quality of follow-up for patients with a registered relapse, who are registered as alive at the time of follow-up. Relapses later than 1st of October 2019 excluded.

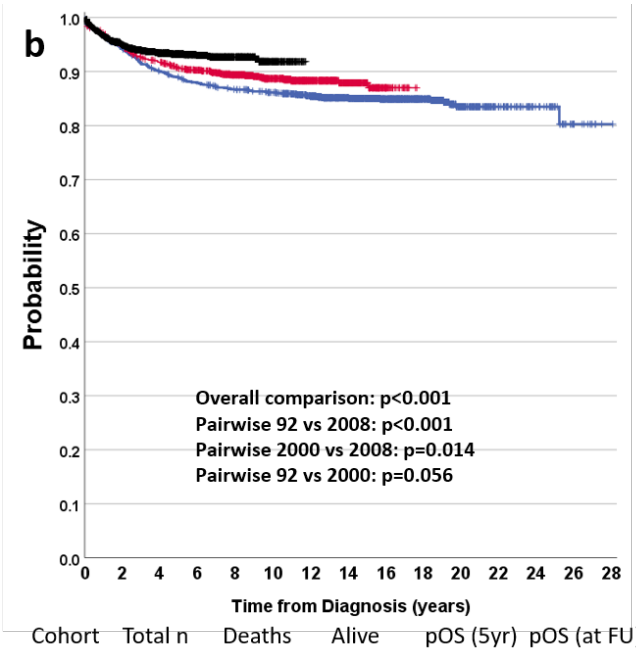
	<16 years (%)	≥16years (%)	Total (%)
FU Rel = 0 days	8 (9.4)	5 (19.9)	13 (11.5)
FU Rel 0-6 mo	5 (5.9)	5 (19.9)	10 (8.8)
FU Rel 6-12 mo	10 (11.8)	5 (19.9)	15 (13.3)
FU Rel >1 year	62 (72.9)	13 (46.4)	75 (66.4)
Total	85 (100)	28 (100)	113 (100)

Follow-up for relapsed patients is clearly insufficient. Particularly the patients that are not followed up at all after relapse (FU after relapse = 0 days) is problematic. This shortcoming affects the credibility of our OS-figures in particular.

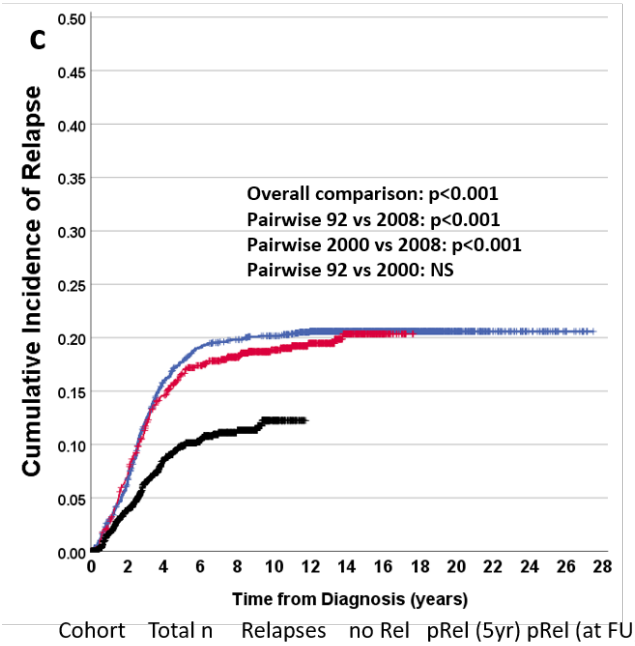
Figure 2. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. (a) EFS, (b) OS, (c) cum inc of relapse, and (d) DCR1.



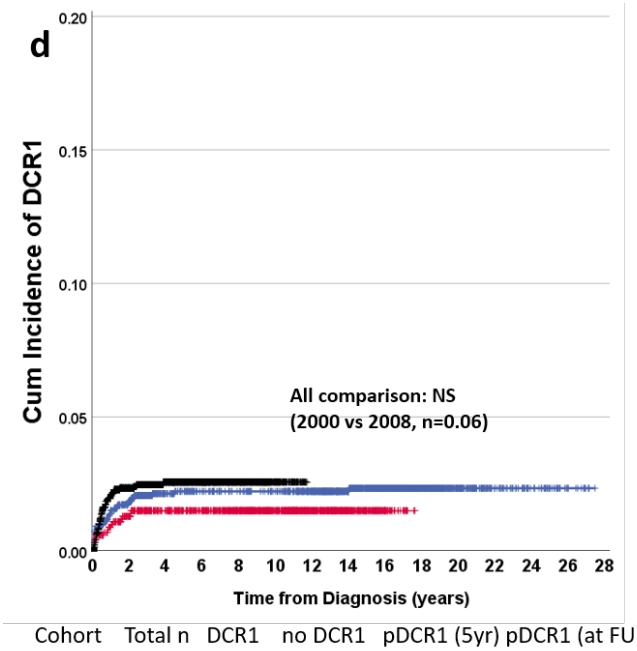
Cohort	Total n	Events	no Event	pEFS (5yr)	pEFS (at FU)
92	1559	384	1175	0.79	0.74
2000	1055	232	823	0.80	0.76
2008	2063	237	1826	0.86	0.84



Cohort	Total n	Deaths	Alive	pOS (5yr)	pOS (at FU)
92	1559	236	1323	0.89	0.80
2000	1055	119	936	0.91	0.87
2008	2063	126	1937	0.93	0.92



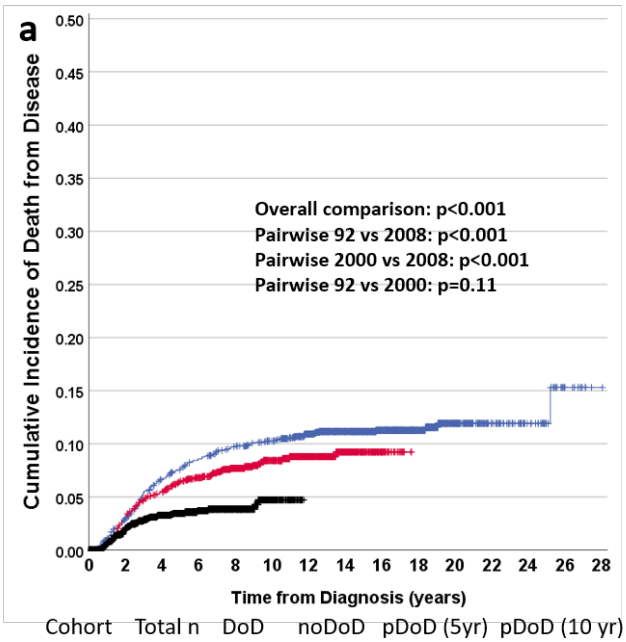
Cohort	Total n	Relapses	no Rel	pRel (5yr)	pRel (at FU)
92	1559	309	1250	0.18	0.21
2000	1055	192	863	0.17	0.20
2008	2063	161	1902	0.10	0.12



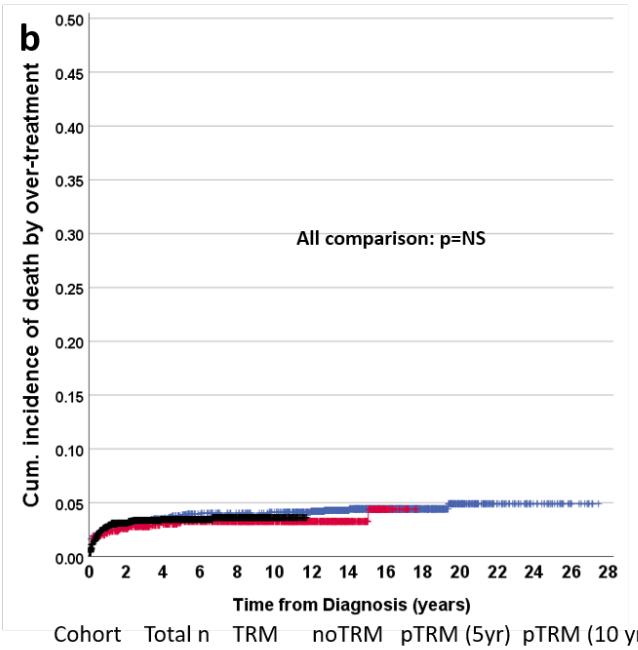
Cohort	Total n	DCR1	no DCR1	pDCR1 (5yr)	pDCR1 (at FU)
92	1559	34	1525	0.022	0.023
2000	1055	15	1040	0.015	0.015
2008	2063	47	2016	0.026	0.026

The overall results are stable as expected. A few late relapses cause disproportionate dents in the graphs, which will be corrected with longer follow-up – if this is completed.

Figure 3. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. a) Under-treatment – death after relapse b) Death from over-treatment (induction-death, death in CR1 and after SMN) by Cohort.



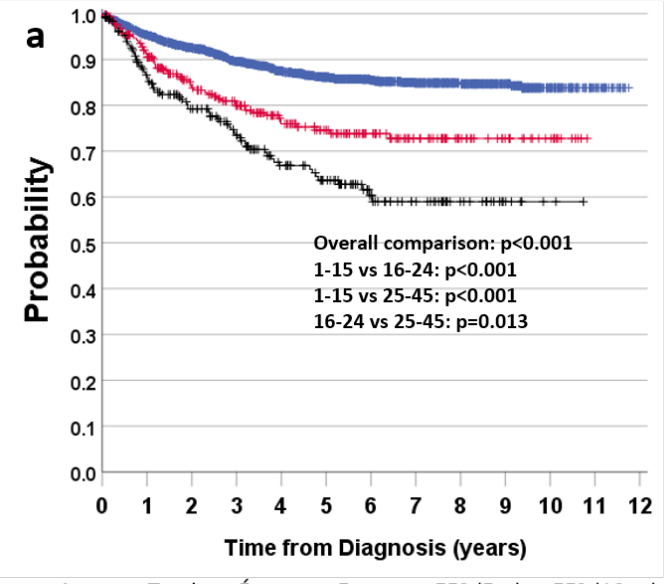
Cohort	Total n	DoD	noDoD	pDoD (5yr)	pDoD (10 yr)
92	1559	170	1389	0.077	0.103
2000	1055	85	970	0.065	0.084
2008	2063	60	2003	0.035	0.047



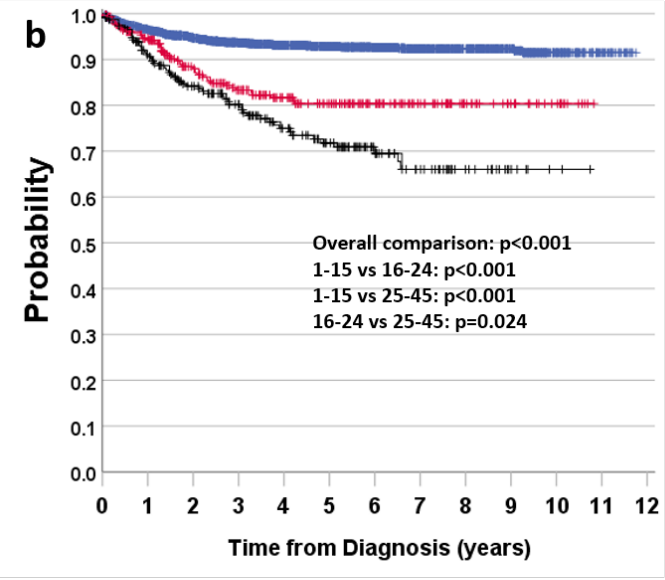
Cohort	Total n	TRM	noTRM	pTRM (5yr)	pTRM (10 yr)
92	1559	65	1494	0.039	0.041
2000	1055	34	1021	0.033	0.033
2008	2063	66	1997	0.035	0.036

In the under-treatment analysis, the "over-treatment events" (induction death, DCR1 and SMN) are censored observations and, conversely, in the over-treatment analysis, patients are censored at the time of relapse, when they are no longer at risk of dying from over-treatment. It is not formally compensated for the competing events, but the estimates correspond well with overall survival.
It illustrates how we have improved in the fight against relapse, but that the price in terms of treatment-related mortality remains constant. The nearly equalised risk indicates that the therapeutic window for an increase in treatment intensity is closing. The way forward is not obvious, but the very similar overall survival results from international groups with different overall treatment-intensities indicate that you can reach at least as far with less intensive therapy. This is an important foundation for the thinking around the ALLTogether protocol.

Figure 4. ALL-2008, Non-B cell ALL 1-<45 years at diagnosis. a) EFS b) OS by age-groups in the ALLTogether1 protocol.



Age	Total n	Évent	noEvent	pEFS (5yr)	pEFS (10 yr)
1-15	2115	249	1866	0.86	0.84
16-24	291	61	230	0.75	0.73
25-45	242	73	169	0.64	0.59



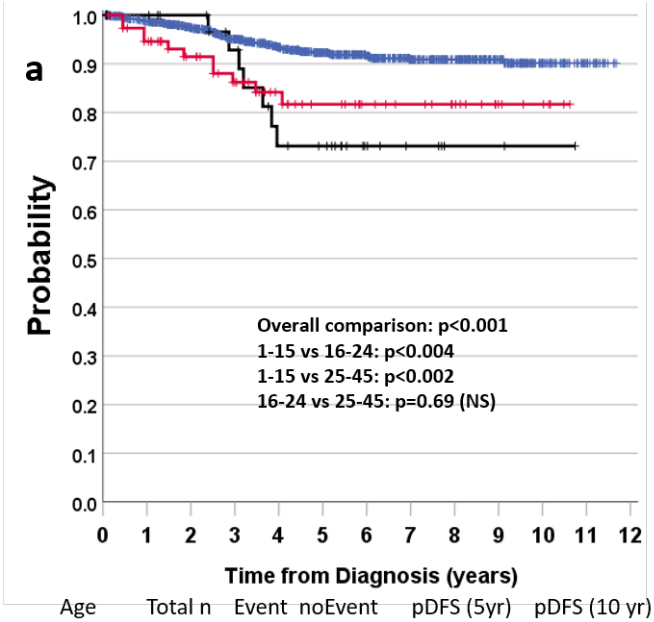
Age	Total n	Dead	Alive	pOS (5yr)	pOS (10 yr)
1-15	2115	136	1979	0.93	0.92
16-24	291	46	245	0.80	0.80
25-45	242	57	185	0.72	0.66

We have known for a long time that older patients fared worse and there was a lot of data supporting the notion that children and adults had biologically different features, but since stratification and treatment were different it was difficult to draw firm conclusions. The NOPHO ALL-2008 protocol provided a platform for (almost) uniform stratification and therapy and provided a firm foundation for very different risk-group profiles in the different age-groups:

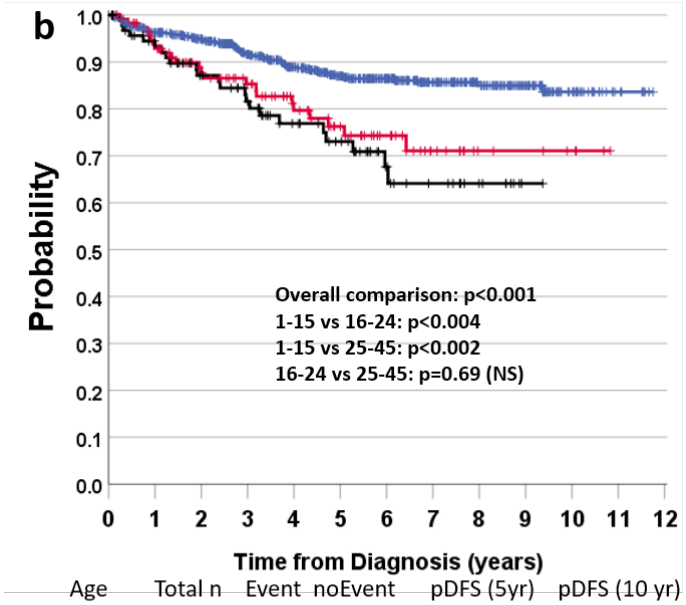
Table 6. Risk-group in NOPHO ALL-2008 by ALLTogether age-groups.

	<16 years (%)	16-24 years (%)	25-45 years (%)	Total (%)
SR	**1072 (51)**	**79 (27)**	**37 (15)**	1188 (45)
IR	**716 (34)**	**119 (41)**	**95 (40)**	930 (36)
HR-chemo	**208 (10)**	**52 (18)**	**57 (24)**	317 (12)
HR-SCT	**99 (5)**	**39 (13)**	**50 (21)**	188 (7)
Total	**2095 (100)**	**289 (100)**	**239 (100)**	2623 (100)

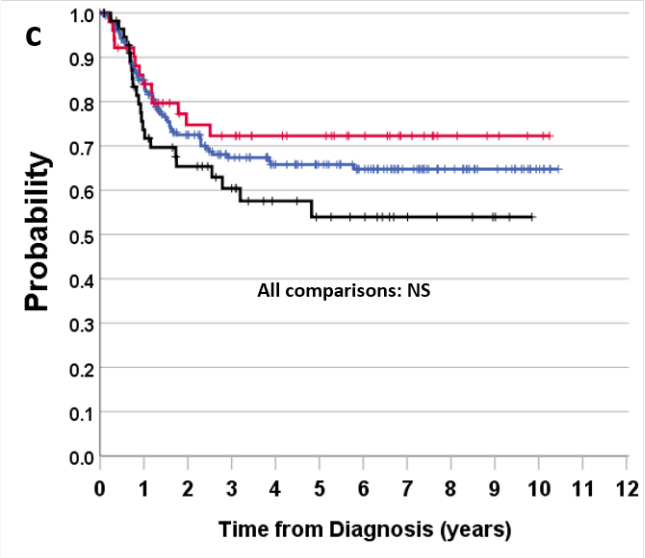
Figure 5. ALL-2008, Non-B cell ALL 1-<45 years at diagnosis DFS for A2G age-groups stratified by risk-group. a) SR-patients b) IR-patients c) HR-chemo patients d) HSCT-patients.



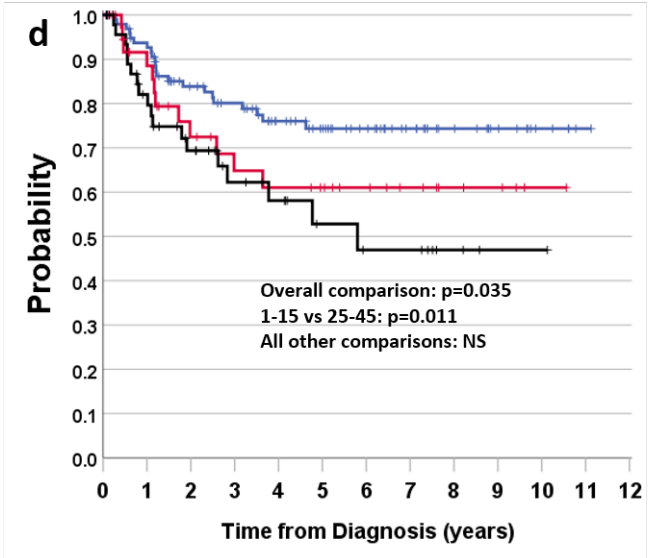
Age	Total n	Event	noEvent	pDFS (5yr)	pDFS (10 yr)
1-15	1072	68	1004	0.92	0.90
16-24	79	11	68	0.82	0.82
25-45	37	7	30	0.73	0.73



Age	Total n	Event	noEvent	pDFS (5yr)	pDFS (10 yr)
1-15	716	78	638	0.87	0.84
16-24	119	23	96	0.76	0.71
25-45	95	23	72	0.73	0.64



Age	Total n	Event	noEvent	pDFS (5yr)	pDFS (10 yr)
1-15	208	62	146	0.66	0.65
16-24	52	13	39	0.72	0.72
25-45	57	22	35	0.54	0.54



Age	Total n	Event	noEvent	pDFS (5yr)	pDFS (10 yr)
1-15	99	22	77	0.74	0.74
16-24	39	12	27	0.61	0.61
25-45	50	18	32	0.53	0.47

The differences in the overall results were largely explained by differences in risk-group fractions by age-group, but with time it has become apparent that fairly substantial differences remain. All risk-groups have these differences, even if lack of power prevents statistical significance in some of the sub-groups. These differences remain almost unchanged if the bulk of the paediatric patients from the incidence-peak 2-5 years – the high hyperdiploid and ETV6-RUNX1 patients are excluded from the analyses (not shown).

Some differences attributable to age remain and continued cooperation between paediatric- and adult haematologists is necessary to identify the critical points. Even with these differences, the results in the adult group is among the best in the world for this age-group. Also the paediatric results compare well with other international results.

Figure 7. ALLTogether1 Pilot study enrollment and exclusions.

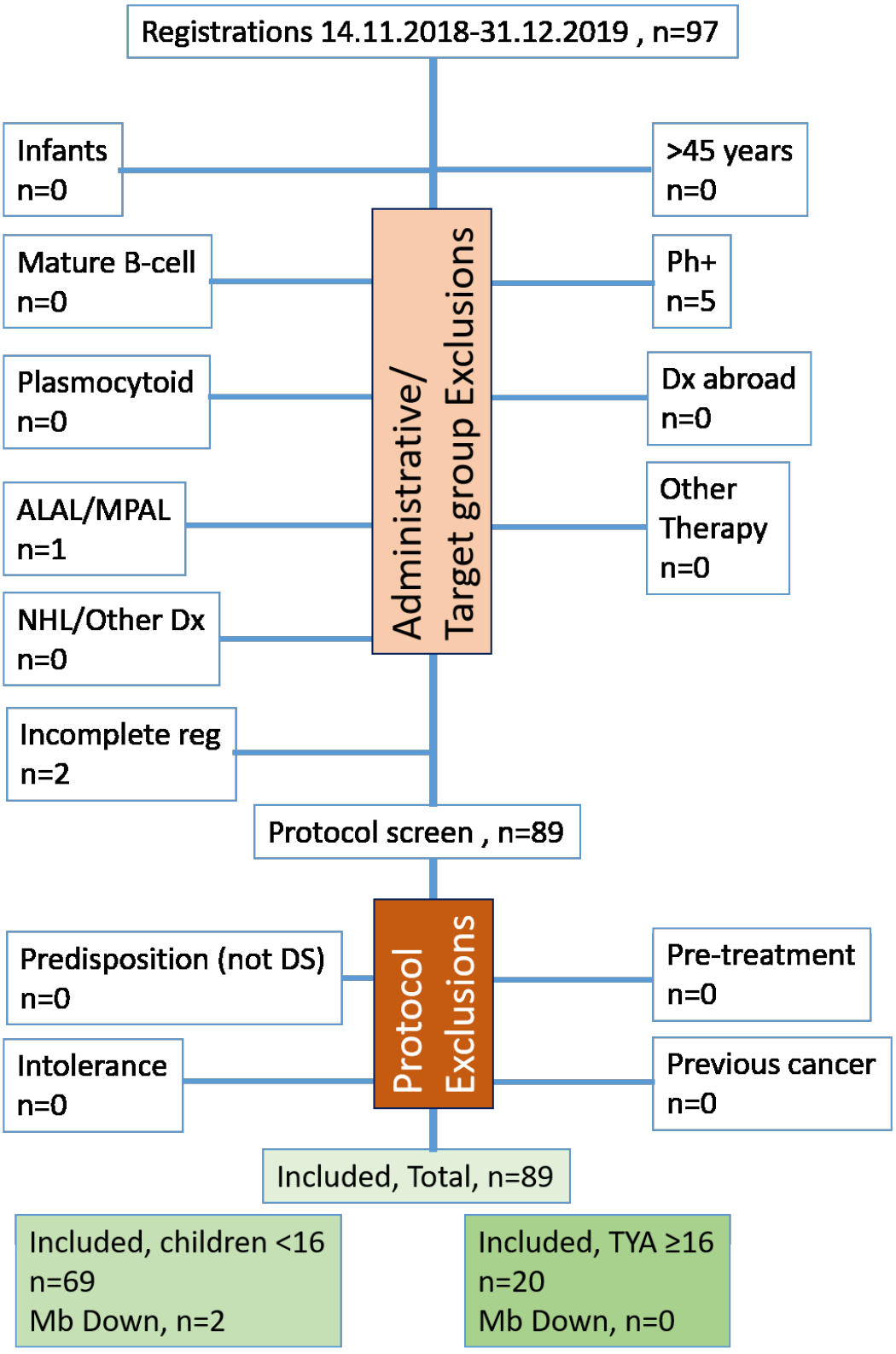


Table 7. Clinical characteristics of ALLTogether Pilot patients.

	<16 years (%) n=69	≥16years (%) n=20	Total (%) n=89
Age			
<10	56 (81)	-	**56 (63)**
10-15	13 (19)	-	**13 (15)**
16-24	-	9 (45)	**9 (10)**
25-45	-	11 (55)	**11 (12)**
WBC			
<50	55 (80)	16 (80)	**71 (80)**
≥50	14 (20)	4 (20)	**18 (20)**
Immunphenotype			
BCP	64 (93)	14 (70)	**78 (88)**
T-cell	5 (7)	6 (30)	**11 (12)**
CNS			
CNS1	43 (62)	12 (60)	**55 (62)**
TLP-	12 (18)	4 (20)	**16 (18)**
CNS2	7 (10)	1 (5)	**8 (9)**
TLP <5 WBC	2 (3)	2 (10)	**4 (4)**
CNS3	1 (1)	0 (0)	**1 (1)**
TLP≥5 WBC	4 (6)	1 (5)	**5 (6)**
Genetics			
HeH/ETV6-RUNX1	38 (55)	0 (0)	**38 (43)**
HR-genetics	5 (7)	4 (20)	**9 (10)**
B-other	14 (21)	7 (35)	**21 (24)**
T-cell NOS	5 (7)	4 (20)	**9 (10)**
Missing	7 (10)	5 (25)	**12 (13)**
Induction			
3-drug	45 (69)	0 (0)	**45 (54)**
4-drug	19 (29)	19 (100)	**38 (45)**
Down	1 (2)	0	**1 (1)**
Missing	4	1	**5**
Strat/Therapy d29			
SR-consolidation	26 (42)	2 (17)	**28 (38)**
IR/HR-consolidation	35 (56)	10 (83)	**45 (61)**
Other	1 (2)	0 (0)	**1 (1)**
Missing	7	8	**15**
Strat/Therapy d71			
SR	20 (38)	2 (18)	**22** (36)
IR-low	11 (21)	0 (0)	**11** (18)
IR-high	17 (33)	6 (55)	**23** (37)
IR-Down	2 (4)	0 (0)	**2** (3)
HR-HSCT	1 (2)	3 (27)	**4** (6)
Protocol Therapy Failure	1 (2)	0 (0)	**0** (0)
Missing	17	9	**26**

Numbers are small yet, but there is a surprisingly high fraction of SR-patients. MRD-data will have to be scrutinised, but we expect this fraction to go down. Registration of data is lagging behind and needs to improve. This may also partly be due to data-management, which is effectively not in place yet, because of the need for work on the registration-system ahead of the start of the main study.

Leukaemic adverse events

There have been four adverse events among the ALLTogether Pilot patients: 1 Protocol Therapy Failure (PTF - resistant disease), 2 relapses and one death in CR1.

- SR: 0 events
- IR-low: 0 events
- IR-high: 2 relapses
- HR-chemo: 0 patients
- HR-HSCT: 1 PTF, 1 DCR1

The PTF was a T-cell patient <16 years at diagnosis with hyperleukocytosis. Therapy was not completely according to protocol, but the disease was obviously highly resistant and is assessed as PTF. The patient went into remission after extensive off-protocol therapy, but relapsed and died of progressive disease.

Both relapses occurred in the IR-high group, were early isolated BM-relapses, one in a TYA T-cell patient (16-24 years old) with hyperleukocytosis at diagnosis and the other in a child <16 years at diagnosis with B-other BCP-ALL. Both patients died of progressive disease.

The death in CR1 was post HSCT and occurred in a patient 25-45 years at diagnosis.

Toxicity

The only treatment-related mortality in the cohort diagnosed up to December 2019 is the DCR1 described above after HSCT.

A new important feature of the registration-system is the possibility to report Adverse Events of Special Interest (AESIs) linked to a treatment phase (mostly sub-lethal toxicity). There is an obvious paucity of registrations for the later parts of the protocol, but induction and Consolidation 1 are new to NOPHO and therefore of great interest.

Table 8. Induction toxicity by age-group (all toxicities by protocol definitions)

Toxicity (induction)	**<16 years (%) n=69**	**≥16years (%) n=20**	**Total (%) n=89**
ICU Ass ventil*	1	0	0
ICU Pressure sup*	0	0	0
Allergy	1	0	1
Heart failure	0	0	0
Kidney failure	0	0	0
Hypertension	0	0	0
Pancreatitis	1	0	1
Diabetes (IDDM)	5	5	10
Enterocolitis	0	0	0
Liver failure	0	1	1
SOS/VOD	0	0	0
VTE	2	3	5
Osteonecrosis	0	0	0
CNS-toxicity	0	1	1
Peripheral neurop	1	0	1
Invasive fungal inf	1	0	1
PJP-pneumonia	0	0	0
Failure to report	8 (12)	7 (35)	15 (17)

*ICU does not refer to the treating unit, but to the need for either assisted ventilation (CPAP, mechanical ventilation or ECMO) or inotropic pressure support.

The change in induction therapy has led to some Asparaginase-related events recorded in induction. The dominating toxicity so far is the need for insulin, which may be related to the change to Dexamethasone for most patients.

Off the record, adult haematologists have reported a high frequency of Asparaginase-related complications – mostly liver-toxicity during induction and also one induction death in a patient diagnosed in 2020. This may lead to a need for adaption of the toxicity-registration and a special survey is urgently on the way to address this problem.

Registration needs to improve, particularly in the adult group. More than a third of the adult group – possibly in most need of the protection of the surveillance – are missing the toxicity-registration altogether.

Table 9. Toxicity associated with Consolidation 1.

Toxicity (induction)	<16 years (%) n=69	≥16years (%) n=20	Total (%) n=89
ICU Ventilation	1	0	1
ICU Pressure supp	1	0	1
Allergy	1	3	4
Heart failure	0	0	0
Kidney failure	0	0	0
Hypertension	0	0	0
Pancreatitis	1	0	1
Diabetes (IDDM)	0	1	1
Enterocolitis	2	0	2
Liver failure	0	2	2
SOS/VOD	2	1	3
VTE	2	4	6
Osteonecrosis	0	0	0
CNS-toxicity	0	0	0
Peripheral neurop	0	1	1
Invasive fungal inf	1	0	1
PJP-pneumonia	0	0	0
Failure to report	16 (23)	10 (50)	26 (29)

Reporting is clearly lagging behind. The low number of registered patients and events precludes firm conclusions, but severe liver toxicity may be more frequent than in previous protocols as mentioned above.

Concluding remarks

With a focus on the implementation of the new protocol, resources seem to be stretched when it comes to taking care of the routines of registration.
This is unfortunate – our concluding research-projects summing up the NOPHO ALL-2008 experience will be lacking important follow-up parameters. Apart from making sure that primary events – and the corresponding follow-up in first remission is up-to-date, it is particularly urgent to register follow-up after primary events, since it affects the overall survival. It is almost for certain that we have missed some deaths after relapse in the present survey. It is of utmost importance to understand if patients are salvageable to evaluate if primary therapy can be de-escalated or not.

For the ALLTogether patients, registration is potentially even more important. The therapy administered is new to the treating centres and we have a unique chance to identify problems. This is particularly important for patents older than 24 years, who have not been treated with the protocol serving as a template for the early parts of the protocol, UKALL2003 and UKALL2011 before.

Nevertheless, the early registration of ALLTogether Pilot Protocol patients and the feedback from registering centres have been invaluable to identify problems, ambiguities and necessary alterations in the structure, since we are now in the process of identifying the desired final alterations to the ALLTogether1 registration system and implement them before study start.

We would like to thank all who participate in the work with registration and other contributions to the completeness and quality of the NOPHO ALL registry. We hope that the NOPHO collaboration will continue to be fruitful also in the context of the coming ALLTogether wider collaboration.

For the registration group, Stockholm, springtime 2020

Mats Heyman

NOPHO ALL-2008 PI Working Group

Members		
Chair	Kjeld Schmiegelow (ALL2008 Protocol chair)	kschmiegelow@rh.dk
Denmark	Birgitte Klug Albertsen (PI asparaginase study)	biralber@rm.dk
	Ulrik Malthe Overgaard (PI adults Denmark)	ulrik.malthe.overgaard@regionh.dk
	Thomas Frandsen (6MP study & event group chair)	t-frandsen@dadlnet.dk
	Hanne Marquart (MRD coordinator flow)	hanne.marquart@dadlnet.dk
	Hans Ole Madsen (MRD coordinator PCR)	hans.o.madsen@regionh.dk
	Nina Toft (Nordic Adult coordinator)	ninatoft@yahoo.com
Estonia	Kaie Pruunsild (PI Estonia)	kaie.pruunsild@lastehaigla.ee
	Katrin Palk (PI adults Estonia)	katrin.palk@regionaalhaigla.ee
Finland	Arja Harila-Saari (PI Depocyte study)	arja.harila-saari@kbh.uu.se
	Kim Vettenranta (PI Finland)	kim.vettenranta@hus.fi
	Ulla Wartiovaara-Kautto (PI adults Finland)	ulla.wartiovaara-kautto@hus.fi
	Johanna Rimpiläinen	johanna.rimpilainen@pshp.fi
Iceland	Ólafur Gísli Jónsson (PI Iceland)	olafurgi@landspitali.is
Lithuania	Goda Vaitkeviciene (PI Lithuania)	goda.vaitkeviciene@vuvl.lt
	Laimonas Griskevicius (PI adults Lithuania)	laimonas.griskevicius@santa.lt
Norway	Bendik Lund (PI Norway)	bendik.lund@ntnu.no
	Inga Maria Rinvoll Johannsdottir (LLC chair)	inga@rinvoll.com
	Petter Quist-Paulsen (PI adults Norway)	petter.quist-paulsen@ntnu.no
Sweden	Jonas Abrahamsson (PI Sweden)	jonas.abrahamsson@vgregion.se
	Helene Hallböök (PI adults Sweden)	helene.hallbook@medsci.uu.se
	Mats Heyman (ALL registry, ALL WG, ALLTogether WG)	mats.heyman@ki.se

For details on recruitment and outcome see NOPHO Annual Report ALL2008-section and presentations from previous ALL2008 WG meetings at www.nopho.org.

Meetings

The ALL2008 study committee has merged with the ALL working group, and updates and research on ALL2008 patients are presented at ALL working group meetings and subsequently posted as part of the ALL working group meeting minutes at www.nopho.org. In addition, results and challenges relating to NOPHO ALL2008 have been presented at various meetings in pharmacology WG, MRD WG, ALL event WG, ALL biology WG, and adult ALL meetings. Focus is now only on scientific data exploration and publications.

Protocol/study cohort

By March 1st 2016 (when randomisations were closed) a total of 1908 patients had been registered in the NOPHO ALL2008 register. Of these 141 (7.4%) are excluded from the ALL2008 study cohort due to Down and other ALL prone syndromes, previous cancer, mixed phenotype ALL, pre-treatment etc., thus leaving 1469 children and 298 adults in the core cohort for publications. The baseline results of ALL2008 for children and adults have been published (Toft, Leukemia 2018).

Randomisations

The protocol was opened July 1st 2008. The three randomised studies opened for children January 1st 2009, but with some delays in entering of patients depending on the approval process in the involved countries. Recruitment has been somewhat below what was projected. Not least R2 (asparaginase at 2 vs. 6 wks intervals) would need several more years of accrual for the study to be sufficiently powered. This reflects poorer recruitment rates (explained by parental refusal and toxicities during consolidation) and somewhat lower relapse rate than originally anticipated. A detailed report was filed to the DSMC

December 2015 presenting outcome and toxicity data. Based on these data the DSMC recommended closure of the Rx1 and Rx2, and both studies were closed March 1st 2016.

Low dose 6MP and intermittent asparaginase became standard of care. 788 patients have been randomised to Rx1 and 625 to Rx2.

Rx1 has been published (Tulstrup, Eur J Haematol 2018) – although 6MP provided borderline significant improvements in fraction of MRD negative patients day 79, no benefit with respect to pEFS was detected.

Rx2: Intermittent asparaginase became the standard of care (Albertsen J Clin Oncol 2019).

Rx3 (+/- Depocyte in HR maintenance) was closed due to insufficient recruitment and problems with drug supply. The Rx3 study showed borderline significant benefit of Depocyte (Levinsen, J Ped Hematol Oncol 2016).

MRD

The T-ALL MRD data has been published in detailed covering both PCR and flow cytometry. They are equally predictive of outcome and support the choice of 10-3 as the cut-off (Modvig, Leukemia 2018). A similar study is being performed for BCP-ALL and is expected to be submitted for publication before the summer 2020.

Toxicity

The compliance to toxicity registration (20 specified toxicities to be registered at 3 months intervals) has been excellent, but reliability differs between the various toxicities. Toxicity profiles for children and adults have been published (Toft, Eur J Haematol 2016; Toft, Leukemia 2018; Rank, Blood 2018). Scrutinization of patient files has revealed that for some toxicities (e.g. peripheral neuropathy) the toxicity data that are routinely captured do not reflect the true incidence. For others including allergy, pancreatitis, thrombosis, and osteonecrosis, the reported toxicity frequencies seem reliable. Approximately 50% of all patients experience one or more of the 20 toxicities. Several of these have been registered in more than 50 patients (allergy, thrombosis, pancreatitis etc) and are being or have been scrutinised in detail (and published). In addition, data on pancreatitis (Wolthers Lancet Oncology 2017), osteonecrosis, neurotoxicity, thromboembolism, invasive fungal infections, induction deaths, asparaginase hypersensitivity, and HD-MTX associated acute nephrotoxicity are part of the Ponte di Legno Toxicity Working group activities. In general, adults are not more burdened by toxicities than adolescents, but experience more thromboembolism (Rank, Blood 2018). Although the simplified MRD-based risk stratification and the major changes in the ALL2008 protocol compared to our previous treatment strategies seem to have reduced the overall relapse rate (especially for T-ALL), the protocol have been somewhat burdened by toxic death. Several amendments to the blocks have aimed to counteract this, and since the latest amendments November 2011 (see www.nopho.org) the toxic death rate for HR-ALL has been acceptable (<5%).

Add-on research

Three large add-on studies are integrated into ALL2008 (see publications):

a. Host genomics: Host DNA has been collected from approximately 90% of the patients. The first ~1300 patients have been exome-enriched SNP-profiled (Illumina Human OmniExome 2.5M). The phenotypes currently addressed are pancreatitis, hyperleukocytosis, CNS leukemia, thrombosis, osteonecrosis, asparaginase allergy, neurotoxicity, high-dose MTX clearance, MTX/6MP metabolism, MRD and relapse rates. The first paper on AAP has been published and results are now being validated and expanded in a Ponte di Legno study. SNP profiling will be a research project in the ALLTogether study, being coordinated from Copenhagen.
b. Maintenance therapy monitoring: Blood sampling has been somewhat below the set target with wide variation between countries and centers. The study has demonstrated strong associations between upstream metabolites and DNA-TGN. This has subsequently been validated in an independent cohort and at strong significant association between DNA-TGN and relapse risk has been shown (HR 0.72 per 100 fmol/micromole DNA for d29 MRD positive patients) (Nielsen, Lancet Oncol

2017). These findings have been confirmed in a large international meta-analysis (to be published). The benefit of adding 6TG to MTX/6MP based maintenance therapy to increase DNA-TGN will be tested in a randomized trial ("TEAM") as part of the ALLTogether protocol. Furthermore, in the ALLTogether protocol all 7,000+ patients will be monitored for MTX/thiopurine metabolites with feedback to the clinicians if results indicate poor treatment adherence (low metabolite levels).

c. Asparaginase antibody and activity monitoring: Sampling has been satisfactory with approximately 8-9 samples having been received per patient. The activity monitoring (by Birgitte Klug Albertsen) will be carried forward in the ALLTogether protocol.

d. CSF flow cytometry: The study has been finalized and demonstrated a highly significant association between CSF positivity and risk of both BM and CNS relapse (Thastrup, Leukemia 2020).

Publications based on ALL2008 protocol data

1. **Raja R, Schmiegelow K, Frandsen T**. *Asparaginase-associated pancreatitis in children.* Br J Haematol 2012;159:18-27.
2. **Toft N, Birgens H, Abrahamsson J, Bernell P, Griškevičius L, Hallböök H, Heyman M, Holm MS, Hulegårdh E, Klausen TW, Marquart HV, Jónsson OG, Nielsen OJ, Paulsen PQ, Taskinen M, Vaitkeviciene G, Vettenranta K, Åsberg A, Schmiegelow K,** *Risk group assignment differs for children and adults 1–45 years with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol.* Eur J Haematol 2013; 90: 404-12.
3. **Ebbesen MS, Nersting J, Jacobsen JH, Frandsen TL, Vettenranta K, Abramsson J, Wesenberg F, Schmiegelow K.** *Incorporation of 6-thioguanine nucleotides into DNA during maintenance therapy of childhood acute lymphoblastic leukemia – the influence of thiopurine methyltransferase genotypes.* J Clin Pharmacol 2013; 53: 670-4.
4. **Rasmussen MM, Christensen RH, Gregers J, Heldrup J, Nersting J, Schmiegelow K.** *Can SLC19A1 80G>A polymorphisms predict risk of extremely delayed MTX-excretion after high dose Methotrexate?* J Ped Hematol Oncol 2013; 35: 417-8.
5. **Vaitkeviciene G, Heyman M, Jonsson OG, Lausen B, Harila-Saari A, Stenmarker M, Taskinen M, Zvirblis T, Asberg A, Groth-Pedersen L, Rageliene L, Schmiegelow K.** *Early morbidity and mortality in childhood acute lymphoblastic leukemia with very high white blood cell cou*nt. Leukemia 2013; 27: 2259-62.
6. **Frandsen TL, Heyman M, Abrahamsson J, Vettenranta K, Åsberg A, Vaitkeviciene G, Pruunsild K, Toft N, Helt L, Bach KF, Schmiegelow K.** *Complying with the European Clinical Trials Directive while surviving the administrative pressure - an alternative approach to toxicity registration in a cancer trial.* Eur J Cancer 2014; 50: 251-9.
7. **Raja RA, Schmiegelow K, Albertsen BK, Prunsild K, Zeller B, Vaitkeviciene G, Abrahamsson J, Heyman M, Taskinen M, Harila-Saari A, Kanerva J, Frandsen TL.** *Asparaginase associated Pancreatitis in Children with Acute Lymphoblastic Leukaemia in the NOPHO ALL2008 Protocol.* Br J Haematol 2014; 165: 126-33.
8. **Levinsen M, Taskinen M, Abrahamsson J, Forestier E, Frandsen TL, Harila-Saari A, Heyman M, Jonsson OG, Lähteenmäki PM, Lausen B, Vaitkevičienė G, Asberg A, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Central nervous system involvement in childhood acute lymphoblastic leukemia at diagnosis: Clinical features and early treatment response.* Pediatr Blood Cancer. 2014; 61:1416-21.
9. **Henriksen LT, Nersting J, Raja RA, Frandsen TL, Rosthøj S, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *Cerebrospinal fluid asparagine depletion during pegylated asparaginase therapy in children with acute lymphoblastic leukaemia.* Br J Haematol. 2014;166: 213-20.
10. **Vaitkeviciene G, Matuzeviciene R, Stoskus M, Zvirblis T, Rageliene L, Schmiegelow K.** *Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol.* Medicina (Kaunas) 2014; 50: 28-36.
11. **Henriksen LT, Harila-Saari A, Ruud E, Abrahamsson J, Pruunsild K, Vaitkeviciene G, Jónsson ÓG, Schmiegelow K, Heyman M, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol.* Pediatr Blood Cancer 2015; 62: 427-33.
12. **Ranta S, Tuckuviene R, Mäkipernaa A, Albertsen BK, Frisk T, Tedgård U, Jónsson ÓG, Pruun-**

sild K, Gretenkort Andersson N, Winther Gunnes M, Saulyte Trakymiene S, Frandsen T, Heyman M, Ruud E, Helgestad J. *Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia - a multicentre study from the Nordic Society of Paediatric Haematology and Oncology.* Br J Haematol 2015; 168:547-52.

13. **Tulstrup M, Larsen HB, Castor A, Rossel P, Grell K, Heyman M, Abrahamsson J, Söderhäll S, Åsberg A, Jonsson OG, Vettenranta K, Frandsen TL, Albertsen BK, Schmiegelow K; Nordic Society of Paediatric Haematology, and Oncology (NOPHO).** *Parents' and Adolescents' Preferences for Intensified or Reduced Treatment in Randomized Lymphoblastic Leukemia Trials.* Pediatr Blood Cancer 2016; 63:865-71.
14. **Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson ÓG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Asberg A, Helt LR, Frandsen T,Schmiegelow K.** *Toxicity profile and treatment delays in NOPHO ALL2008-comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia.* Eur J Haematol 2016; 96:160-9.
15. **Tuckuviene R, Ranta S, Albertsen BK, Andersson NG, Bendtsen MD, Frisk T, Gunnes MW, Helgestad J, Heyman MM, Jonsson OG, Mäkipernaa A, Pruunsild K, Tedgård U, Trakymiene SS, Ruud E.** *Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study.* J Thromb Haemost 2016;14485-94.
16. **Borssén M, Haider Z, Landfors M, Norén-Nyström U, Schmiegelow K, Åsberg AE, Kanerva J, Madsen HO, Marquart H, Heyman M, Hultdin M, Roos G, Forestier E, Degerman S.** *DNA Methylation Adds Prognostic Value to Minimal Residual Disease Status in Pediatric T-Cell Acute Lymphoblastic Leukemia.* Ped Blood Cancer 2016; 63: 1185-92.
17. **Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, Vettenranta K, Åsberg A, Risteli J, Heldrup J, Schmiegelow K.** *Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia.* J Ped Hematol Oncol 2016; 38:602-9.
18. **Levinsen M, Marquart HV, Groth-Pedersen L, Abrahamsson J, Albertsen BK, Andersen MK, Frandsen TL, Harila-Saari A, Pronk C, Ulvmoen A, Vaitkevičienė G, Lähteenmäki PM, Niinimäki R, Taskinen M, Jeppesen M, Schmiegelow K - for the Nordic Society of Pediatric Hematology and Oncology (NOPHO).** *Leukemic blasts are present at low levels in spinal fluid in one third of childhood acute lymphoblastic leukemia cases.* Ped Blood Cancer 2016; 63:1935-1942.
19. **Nielsen SN, Grell K, Nersting J, Frandsen TL, Hjalgrim LL, Schmiegelow K.** *Measures of 6-mercaptopurine and methotrexate maintenance therapy intensity in childhood acute lymphoblastic leukemia.* Cancer Chemother Pharmacol 2016; 78:983-94.
20. **Ranta S, Palomäki M, Levinsen M, Taskinen M, Abrahamsson J, Mellgren K, Niinimäki R, Schmiegelow K, Heyman M, Harila-Saari A.** *Role of neuroimaging in children with acute lymphoblastic leukemia and central nervous system involvement at diagnosis.* Ped Blood Cancer 2017; 64:64-70.
21. **Mogensen SS, Schmiegelow K, Grell K, Albertsen BK, Wehner PS, Kampmann P, Frandsen TL.** *Hyperlipidemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukemia.* Haematologica 2017; 102: e175-8.
22. **Wolthers BO, Frandsen T, Abrahamsson J, Albertsen B, Helt L, Heyman M, Jonsson O, Kőrgvee L-T, Lund B, Raja B, Rasmussen K, Taskinen M, Tulstrup M, Vaitkeviciene G, Yadav R, Gupta R, Schmiegelow K.** *Asparaginase-associated pancreatitis A study on pheno- and genotype in the NOPHO ALL2008 protocol.* Leukemia 2017; 31:325-332.
23. **Svahn T, Mellgren K, Harila-Saari A, Åsberg A, Kanerva J, Jónsson O, Vaitkeviciene G, Mikkelssen TS, Schmiegelow K, Heldrup J.** *Delayed elimination of high dose methotrexate and use of Carboxypeptidase G2 in pediatric patients during treatment for acute lymphoblastic leukemia.* Ped Blood Cancer 2017; 64: e26395.
24. **Nielsen SN, Eriksson F, Rosthoej S, Andersen MK, Forestier E, Hasle H, Hjalgrim LL, Aasberg A, Abrahamsson J, Heyman M, Jónsson OG, Pruunsild K, Vaitkeviciené GE, Vettenranta K, Schmiegelow K.** *Children with low-risk acute lymphoblastic leukemia are at highest risk of second cancers.* Ped Blood Cancer 2017; 64: e26518.
25. **Nielsen SN, Grell K, Nersting J, Abrahamson J, Lund B, Kanerva J, Jónsson OG, Vaitkeviciene**

G, Pruunsild K,Hjalgrim LL, Schmiegelow K. *Population-based, prospective analysis of DNA thioguanine nucleotide levels during maintenance therapy of childhood acute lymphoblastic leukemia*. Lancet Oncol 2017; 18:515-24.

26. **Raja RA, Schmiegelow K, Sørensen DN, Frandsen TL.** A*sparaginase associated pancreatitis is not predicted by Hypertriglyceridemia or Pancreas enzyme levels in children with acute lymphoblastic leukemia.* Ped Blood Cancer 2017; 64: 32-8.
27. **Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson OG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Marquart HV, Madsen HO, Norén-Nyström U, Schmiegelow K.** *Results of NOPHO ALL2008 Treatment for Patients 1-45 years with Acute Lymphoblastic Leukemia.* Leukemia 2018; 32: 606-15.
28. **Toksvang LN, De Pietri S, Nielsen SN, Nersting J, Albertsen BK, Wehner PS, Rosthøj S, Lähteenmäki PM, Nilsson D, Nystad TA, Grell K, Frandsen TL, Schmiegelow K.** *Hepatic sinusoidal obstruction syndrome during maintenance therapy of childhood acute lymphoblastic leukemia is associated with continuous asparaginase therapy and mercaptopurine metabolites.* Ped Blood Cancer 2017; 64: e26519.
29. **Mogensen SS, Harila-Saari A, Frandsen TL, Lähteenmäki P, Castor A, Kohonen I, Schmiegelow K, Mäkitie O.** *Early presentation of osteonecrosis in acute lymphoblastic leukemia: Two children from the Nordic and Baltic cohort.* Ped Blood Cancer 2017; 64: e26624..
30. **Henriksen LT, Hojfeldt SG, Schmiegelow K, Frandsen TL, Wehner PS, Schroder H, Albertsen BL - on behalf of the Nordic Society of Paediatric Haematology and Oncology, NOPHO, group.** *Prolonged first-line PEG-asparaginase treatment in paediatric acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol - pharmacokinetics and antibody formation.* Ped Blood Cancer 2017;64(12).
31. **Schmiegelow K, Nielsen SN, Grell K.** *Do cytogenetics of acute lymphoblastic leukaemia blasts affect required duration and intensity of maintenance therapy? - Authors' reply.* Lancet Oncol 2017;18(6):e292
32. **Wolthers BO, Frandsen TL, Baruchel A, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grell K, Inaba H, Kovacs G, Liang D-C, Mateos M, Mondelaers V, Möricke A, Ociepa T, Samarasinghe S, Silverman LB, van der Sluis IM, Stanulla M, Vrooman LM, Yano M, Zapotocka E, Schmiegelow K.** *Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: a Ponte di Legno toxicity working group report.* Lancet Oncol 2017; 18: 1238-48.
33. **Ramsey LB, Vinks AA, Schmiegelow K, Pauley JL, Bleyer A, Balis FM, Askenazi D, Bergeron S, Shirali A, Schwartz S, Widemann B, Heldrup J.** *Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance.* The Oncologist 2018; 23: 52-61.
34. **Tulstrup M, Frandsen TL, Abrahamsson J, Lund B, Vettenranta K, Jonsson OG, Marquart HVH, Albertsen BK, Heyman M, Schmiegelow K - on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Individualized 6-mercaptopurine dose increments in consolidation treatment of childhood acute lymphoblastic leukemia: a NOPHO ALL2008 randomized controlled trial.* Eur J Haematol 2018; 100: 53-60.
35. **Gerbek T, Ebbesen M, Nersting J, Frandsen TL, Appell ML, Schmiegelow K.** *Role of TPMT and ITPA variants in mercaptopurine disposition.* Cancer Chemother Pharmacol 2018;81:579-86.
36. **Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL.** *Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia.* Ped Blood Cancer 2018; 65: e27071.
37. **Wolthers BO, Mogensen PR, Frandsen TL, Abrahamsson J, Behrendtz M, Heyman M, Lohi O, Norén-Nyström U, Ruud E, Schmiegelow K.** *Insulin dependent diabetes - a chronic complication to acute pancreatitis in childhood acute lymphoblastic leukemia.* Ped Blood Cancer 2019; 66:e27437.
38. **Rank CU, Toft N, Tuckuviene R, Grell K, Nielsen OJ, Frandsen TL, Marquart HVH, Albertsen BK, Tedgård U, Hallböök H, Ruud E, Jarvis KB, Quist-Paulsen P, Huttunen P, Wartiovaara-Kautto U, Jónsson OG, Trakymiene SS, Griškevičius L, Saks K, Punab M, Schmiegelow K.** *Thromboembolism in Acute Lymphoblastic Leukemia: Results of NOPHO ALL2008 Protocol Treatment in Patients 1–45 Years.* Blood 2018; 131:2475-84.
39. **Hrusak O, Haas VD, Stancikova J, Janotova I, Mejstrikova E, Capek V, Trka J, Zaliova M, Luks A, Bleckmann K, Möricke A, Irving J, Konatkowska B, Alexander TB, Inaba H, Schmiegelow**

K, Stokley S, Zemanova Z, Moorman AV, Rossi JG, Felice MS, Dalla-Pozza L, Morales J, Dworzak M, Buldini B, Basso G, Campbell M, Cabrera ME, Marinov N, Elitzur S, Izraeli S, Luria D, Feuerstein T, Kolenova A, Svec P, Kreminska E, Rabin KR, Polychronopoulou S, da Costa E, Marquart HV, Kattamis A, Ratei R, Reinhardt D, Choi JK, Schrappe M, Stary J. *International cooperative study identifies treatment strategy in childhood ambiguous lineage leukemia.* Blood 2018; 132: 264-76.

40. **Mogensen SS, Harila-Saari A, Schmiegelow K, Mäkitie O, Myrberg IH, Niinimäki R, Ruud E, Hafsteinsdottir S, Griškevicius L, Saks K, Hallböök H, Retpen J, Helt LR, Frandsen TL.** *Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia.* Ped Blood Cancer 2018; 65: e27300.
41. **Tulstrup M, Grosjean M, Nielsen SN, Grell K, Wolthers BO, Wegener PS, Jonsson OG, Lund B, Harila-Saari A, Abrahamsson J, Vaitkeviciene G, Pruunsild K, Toft N, Holm M, Hulegårdh E, Liestøl S, Griskevicius L, Punab M, Wang J, Carroll WL, Zhang Z, Dalgaard MD, Gupta R, Nersting J, Schmiegelow K.** *NT5C2 germline variants alter thiopurine metabolism and are associated with acquired NT5C2 relapse mutations in childhood acute lymphoblastic leukaemia.* Leukemia 2018; 32: 2527-35.
42. **Højfeldt SG, Wolthers BO, Tulstrup M, Abrahamsson J, Gupta R, Harila-Saari A, Heyman M, Henriksen LT, Jónsson OG, Lähteenmäki PM, Lund B, Pruunsild K, Vaitkeviciene G, Schmiegelow K, Albertsen BK - on behalf of the Nordic Society of Pediatric Hematology and Oncology, NOPHO group.** *Genetic predisposition to PEG-Asparaginase Hypersensitivity in Children treated according to NOPHO ALL2008,* Br J Haematol 2019; 184: 405-17.
43. **Nersting J, Nielsen SN, Grell K, Pærregaard M, Abrahamsson J, Lund B, Jonsson OG, Pruunsild K, Vaitkeviciene G, Kanerva J, Schmiegelow K.** *Methotrexate polyglutamate levels and co-distributions in childhood acute lymphoblastic leukemia maintenance therapy.* Cancer Chemother Pharm 2019; 83:53-60.
44. **Wolthers BO, Frandsen TL, Patel CJ, Abaji R, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grosjean M, Krajinovic M, Larsen E, Liang D-C, Möricke A, Rasmussen KK, Samarasinghe S, Silverman LB, van der Sluis IM, StanullaM, Tulstrup M, Yadav R, Yang W, Zapotocka E, Gupta R, Schmiegelow K.** *Trypsin Encoding PRSS1-PRSS2 Variation Influence the risk of Aspar¬¬aginase-associated Pancreatitis in Children with Acute Lymphoblastic Leukemia: a Ponte di Legno Toxicity Working Group Report.* Haematologica 2019;104:556-63.
45. **Modvig S, Madsen HO, Siitonen S, Rosthoej S, Tierens A, Juvonen V, Osnes L, Valerhaugen H, Hultdin M, Thörn I, Matuzeviciene R, Stoskus M, Marincevic M, Fogelstrand L, Lilleorg A, Toft N, Jonsson OG, Pruunsild K, Vaitkeviciene G, Vettenranta K, Lund B, Abrahamsson B, Schmiegelow K, Marquart HV.** *Minimal Residual Disease Quantification by Flow Cytometry Provides Reliable Risk Stratification in T-cell Acute Lymphoblastic Leukemia.* Leukemia 2019; 33: 1324-36.
46. **Anastasopoulou S, Eriksson MA, Heyman M, Wang C, Niinimäki R, Mikkel S, Vaitkevičienė GE, Johansdottir IM, Myrberg IH, Jonsson OG, Als-Nielsen B, Schmiegelow K, Banerjee J, Harila-Saari A, Ranta S.** *Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: Clinical characteristics, risk factors, course and outcome of disease.* Ped Blood Cancer 2019;66:e27594.
47. **Ifversen M, Turkiewicz D, Marquart HV, Winiarski J, Buechner J, Mellgren K, Arvidson J, Rascon J, Körgvee LT, Madsen HO, Abrahamsson J, Lund B, Jonsson OG, Heilmann C, Heyman M, Schmiegelow K, Vettenranta K.** *Low burden of minimal residual disease prior to transplantation in children with very high risk acute lymphoblastic leukaemia: The NOPHO ALL2008 experience.* Br J Haematol 20192019;184:982-93.
48. **Thastrup M, Marquart HV, Levinsen L, Grell K, Abrahamsson J, Albertsen BK, Frandsen TL, Harila-Saari A, Lähteenmäki PM, Niinimäki R, Pronk CJ, Ulvmoen A, Vaitkevičienė G, Taskinen M, Schmiegelow K.** *Flow cytometric detection of leukemic blasts in cerebrospinal fluid predicts risk of relapse in childhood acute lymphoblastic leukemia – A Nordic Society for Paediatric Haematology/Oncology study.* Leukemia 2020; 34:336-346.
49. **Albertsen BK, Grell K, Abrahamsson J, Lund B, Vettenranta K, Jónsson OG, Frandsen TL, Wolthers BO, Heyman M, Schmiegelow K.** *Intermittent versus Continuous PEG-asparaginase to Reduce Asparaginase-Associated Toxicities: A NOPHO ALL2008 Randomized Study.* J Clin Oncol 2019; 37: 1638-46.

50. **Quist-Paulsen P, Toft N, Heyman M, Abrahamsson J, Griskevicius L, Hallböök H, Jonsson O, Palk K, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen T, Opdahl S, Marquart HV, Siitonen S, Osnes LT, Hultdin M, Overgaard U, Wartiovaara-Kautto U, Schmiegelow K.** *T cell acute lymphoblastic leukemia in patients 1-45 years treated with the pediatric NOPHO ALL2008 protocol.* Leukemia (In press).
51. **Rank CU, Wolthers BO, Grell K, Albertsen BK, Frandsen TL, Overgaard UM, Toft N, Nielsen OJ, Wehner PS, Harila-Saari A, Grillner P, Abrahamsson J, Norén-Nyström U, Tomaszewska-Toporska B, Lund B, Jarvis KB, Quist-Paulsen P, Vaitkevičienė GE, Griškevičius L, Taskinen M, Wartiovaara-Kautto U, Lepik K, Punab M, Jónsson OG, Schmiegelow K.** *Asparaginase-associated Pancreatitis in Acute Lymphoblastic Leukemia: Results from the NOPHO ALL2008 Treatment of Patients 1–45 Years.* J Clin Oncol 2020; 38: 145-54.
52. **Jarvis KB, LeBlanc M, Tulstrup M, Nielsen RL, Albertsen BK, Gupta R, Huttunen P, Jónsson ÓG, Rank CU, Ranta S, Ruud E, Saks K, Trakymiene SS, Tuckuviene R, Schmiegelow K.** *Candidate Single Nucleotide Polymorphisms and Thromboembolism in Acute Lymphoblastic Leukemia - A NOPHO ALL2008 Study.* Thrombosis Research 2019;184:92-98.
53. **Enshaei A, O'Connor D, Bartram J, Hancock J, Harrison C, Hough R, Samarasinghe S, Den Boer M, Boer J, de Groot-Kruseman H, Marquart HV, Noren-Nystrom U, Schmiegelow K, Schwab C, Horstmann M, Escherich G, Heyman M, Pieters R, Vora A, Moppett J, Moorman A.** *A validated novel continuous prognostic index to deliver stratified medicine in pediatric acute lymphoblastic leukemia.* Blood 2020 (In press).
54. **Anastasopoulou S, Heyman M, Eriksson MA, Niinimäki R, Taskinen M, Mikkel S, Vaitkeviciene GE, Johannsdottir IM, Myrberg IH, Jonsson OG, Als-Nielsen B, Schmiegelow K, Banerjee J, Ranta S, Harila-Saari A.** *Seizures during treatment of childhood acute lymphoblastic leukemia: a population-based cohort study.* Eur J Ped Neurol 2020 (In press)
55. **Tulstrup M, Moriyama T, Jiang C, Grosjean M, Nersting J, Abrahamsson J, Grell K, Hjalgrim LL, Jónsson OG, Kanerva J, Lund B, Nielsen SN, Nielsen RL, Overgaard U, Paulsen PQ, Pruunsild K, Vaitkeviciene G, Wolthers BO, Zhang H, Gupta R, Yang JJ, Schmiegelow K.** *Effects of germline variants in DHFR and FPGS on methotrexate metabolism and relapse of leukemia.* Blood 2020 (In press).

ALL Relapse Working Group

Members
(email addresses: see NOPHO website)

Sweden	Petter Svenberg (Chair 2019-2020, PI SR, HR) Mats Heyman Trausti Óskarsson
Denmark	Bodil Elise Thorhaug Als-Nielsen (PI SR) Peder Skov Wehner
Finland	Päivi Lähteenmäki (PI SR, HR) Laura Korhonen
Iceland	Ólafur Gísli Jónsson
Lithuania	Goda Vaitkeviciene
Norway	Inga Maria Johannsdottir (PI SR) Jochen Büchner (SCT, CART-cell therapy) Dorota Malgorzata-Wojcik

The NOPHO ALL relapse WG has had 4 telephone conferences (please visit the NOPHO website under NOPHO Working groups for meeting minutes) since the last report. In May 2019 Petter Svenberg was chosen to replace Päivi Lähteenmäki as the WG-chair.

Status of IntReALL SR –study: Denmark, Norway and Finland are recruiting, Sweden has finalized the contracting process. Randomization one is still ongoing but the second randomization (epratuzumab) is closed. The sponsor of the study (Berlin Charité) has informed that IntReALL 2010 SR study will close in July 2020.

Status of IntReALL HR -study: Finland is ready for patient recruitment but none so far and Sweden has finalized the contract process. Norway and Denmark will not participate.

The field of BCP-ALL relapse treatment is rapidly changing. During the ASH meeting 2019, the childrens oncology group presented the AALL1331-study. The design was IR/HR- patients in 1st relapse was randomized after induction to either receiving 2 blocks of chemotherapy or two rounds of Blinatumomab during consolidation. The study was recommended early closure due to shown superiority of the Blinatumomab-arm regarding DFS, OS, adverse advents and MRD clearance. The IntReALL-group has already decided to replace the third (HC3) consolidation in the HR-study block with Blinatumomab (off-study) and we now await a substantial amendment for the HR consolidation treatment. In the mean time, treatment for HR patients in the near future will partially differ in the NOPHO countries. In order to learn in this emerging field, the group has been encouraged to discuss and share challenging cases and have done so throughout the year.

Optional HR ALL-relapse treatment studies are open, such as Daratumomab (Stockholm), Isutuximab (Oslo and Gothenburg), Inotuzumab ozogamicin (Copenhagen, Helsinki and Stockholm), Carfilzomib (Copenhagen) and CAR-T-cells (Oslo, Stockholm, Helsinki and Copenhagen).

The IBFM-SG resistant disease committee/ IntReALL meeting took place in Nice (France) 15-16/11.2019, and Petter Svenberg represented the WG there. One topic of discussion was the new protocol (IntReALL 2020), which is under construction. To date, the present design will entail two separate protocols for patients with T-cell and BCP-ALL relapse. Also, BCP ALL patients will be stratified in three groups (SR, HR and VHR). Not yet resolved is weather Inotuzumab ozogamicin will be included in a randomization during induction and weather there will be a randomization between SCT and CAR T-cell therapy at EOI for the HR patients.

In 2019, NOPHO joined the IntReALL-related virtual biobank system (ViBe/Scopeland) and the first payment was taken care of with a Finnish research grant. A previous WG decision was that if further payments are needed, grant application would be an option.

The ALL-SCT-PED2012-FORUM study for relapsed ALL patients with an indication for SCT was halted due to shown superiority, with regards to OS and EFS, of the standard arm (VP16+TBI conditioning) compared to the experimental arm (Busulfan/Thiotepa/Fludarabin but no TBI).

The present Covid -19 pandemia may prevent the next scheduled WG-meeting in Trondheim during the NOPHO Annual meeting on Friday May 8th from 0930 to 11 o'clock (before LLC). We will see.

For the working group
Petter Svenberg
Stockholm, March 2020

Events Working Group (EWG)

Members	
Sweden	Arja Harila-Saari (chair) Anna Nilsson Cecilia Langenskiöld Mats Heyman (ALLTogether) Mia Giertz (Osteonecrosis, secretary for the group)
Denmark	Bodil Thorhauge Als-Nielsen Birgitte Klug Albertsen Kjeld Schmiegelow Ruta Tuckuviene (Thrombosis group)
Norway	Bendik Lund Niklas Bernhard Stabell
Finland	Riitta Niinimäki Anu Huurre
Lithuania	Goda Vaitkeviciene

Arja Harila-Saari was elected to chair the group after Thomas Frandsen who stepped down in February 2019. The group has had two meetings: 16 September with 18 participants and 17 February with 12 participants. Both meetings were arranged at the Arlanda airport, Stockholm.

The main focus areas of the group are follow-up and definitions of events in leukemia protocols, as well as toxicity reporting, follow-up and guidelines for the treatment of the adverse events. The group has mainly but not only worked with acute lymphoblastic leukemia (ALL).

1. Treatment-related mortality (TRM) ALL 2008 GWAS study (Bendik Lund)

The plan is to identify SNPs/genes/pathways identifying death from treatment and not cancer. This case-control study has been approved by NOPHO SC May 2019. The plan is to collect DNA from the local labs for patients who have not a sample sent for the NOPHO ALL2008 "SNP study" during 2020 to be able to do the sequencing. The study cohort includes 72 patients, most of whom have died of infections. The most common cause of death is infection. NOPHO data will contribute to a larger study with several international participants.

2. A study on febrile neutropenia within the Nordic countries

A newly established Nordic pediatric infectious diseases (NORDPID) group plans to start a prospective randomized study with Finland, Sweden, Denmark, Norway, and Iceland on the treatment of neutropenic fever. Event group members Anna Nilsson and Bendik Lund are members of the NORDPID group. The group will start by performing a literature review and collecting data on the standard of care (SOC) in different centers. Thereafter a randomized study is planned, but the exact design is still open.

3. Intensive care and ECMO treatments in Swedish leukemia patients (Susanna Ranta).

Susanna Ranta is leading a national study on intensive care in children with leukemia/NH lymphoma. It combines information from the Swedish intensive care register with the Swedish childhood cancer registry and questionnaires to each center. The first results show that 12/964 (1.2%) of non-transplanted children with leukemia are treated with ECMO in Sweden. Overall survival has been 50% after ECMO, which is in line with survival in other pediatric ECMO treated patients As many as 15% of ALL patients received intensive care during first-line treatment.

4. Impact of BMI on SAEs and outcome in ALL (Christina Egnell Gustafsson)

Data on BMI at diagnosis in the NOPHO ALL 92/2000/2008 protocols shows that obesity at diagnosis of ALL is a risk factor in older children 10-17 y, and especially the risk of relapse is increased. Also, underweight children are at-risk of events. In the study on BMI and toxicity in the NOPHO ALL2008 protocol; 1353 patients 2-18 years old are included from 2008-2016. Preliminary results show that only 2,6% (35pts) were obese; the most common SAE was kidney dysfunction and abdominal problems leading to laparotomy. No difference in the incidence of ON, thrombosis, pancreatitis. The plan is to look more in detail at the obese patients: the toxicities, weight development, MTX concentrations/dosing in relation to body surface area.

Study on MTX pharmacokinetics and toxicity in obese NOPHO ALL2008-patients aims to collect data from the centers on them, and merging data from the previous MTX databases.

5. Hyperleukocytosis in ALL survey (Ignas Kléjus)

85 patients with ALL and hyperleukocytosis from 6 NOPHO-countries were included. 14 of them were treated in ICU (13 before chemotherapy, 1 after chemotherapy). Results showed T-cell patients have higher WBC at diagnosis and a higher risk of tumor lysis syndrome. An important message of the study is that the start of chemotherapy should not be delayed.

6. Leukemia events and SAEs in the ALLTogether protocol (Mats Heyman)

The role of the group is dealing with leukemia events and SAEs and look at guidelines in the ALLTogether. The group has gone through the events: Induction death, Resistant disease, Relapse, death in complete remission 1 (DCR1), secondary malignancies (SMN) and their definitions as well as bone marrow (BM) remission, BM resistant disease, CNS-remission.

Amendments to the ALLTogether protocol version 4.1 will be sent. The following suggestions were supported: Down patients with ALL fulfill criteria for protocol therapy failure when MRD >/= 1% EOC (day 99) or off protocol d57. Most Down patients who do not reach CR at TP1 (MRD pos but <5% or MRD >/= 5%- <25%) will get Blinatumomab 1-2 cycles and then continue with the protocol. Clarification of wording about mediastinal mass in BCP-patients. Definition of relapse: if MRD >/=5% only one technique is needed to confirm, but if MRD >/=1% a repeated BM with another technique within 1-4 weeks is needed. The group will follow closely the Castor toxicity reporting functions and suggest additional information to help function when a need is found.

7. Osteonecrosis (Mia Giertz)

BISON-study (RCT about bisphosphonates to ALL-patients with ON) is paused because an abstract published in 2018 showed poorer outcomes in murine models who were given bisphosphonates during induction therapy for ALL. Waiting for other studies to be presented before going forward with the study. The plan is now to start with a follow-up study on NOPHO ALL 2008-cohort, incidence, treatment and radiological classification of ON which is seen as a late-effect study.

A study on osteonecrosis and venous thrombosis in children and young adults treated for Hodgkin lymphoma in Sweden, Finland and Denmark is initiated. Patient questionnaires and CRFs will be sent out to study incidence, treatment and outcome of venous thrombosis and osteonecrosis. MRT-scans will be reviewed to determine the radiological progress and predictive value of the Niinimäki radiological classification system. NOPHO-study status has been applied, if any other Nordic country is interested, please contact Mia.

8. Asparaginase studies (Birgitte Klug Albertsen)

The risk of relapse after truncation of asparaginase treatment in the ALLTogether protocol will be studied in detail. NOPHO ALL 2008 showed that 8 compared to 15 doses of Asp gave the same outcome but fewer toxicities. There is an increased risk of relapse when truncated after 5 doses. Unpublished data from truncated Asp treatment shows that enzyme activity is important. A study in ALLTogether is planned to include 6000 patients during 5 years. Plan to identify the length of Asp treatment needed to cure the patients.

A study comparing of hypersensitivity reactions after intravenous and intramuscular administration of asparaginase in the ALLTogether protocol is proposed as an add-on study in ALLTogether. Several studies have tried to compare reactions on Asp administered IV or IM. Observation from ALLTogether pilot in Denmark shows true allergic reactions in 14.8%. 6/8 reactions were severe after iv administration. The reactions come later, after 4 doses vs 2 in the NOPHO ALL2008. UKALL will administrate asparaginase intramuscularly, meanwhile, the other countries use intravenous administration; the aim is to compare the incidence between the groups.

9. CNS flow and acute neurotoxicity in ALL (Susanna Ranta)

CNS involvement at ALL-diagnosis is associated with neurotoxicity/PRES. The objective is to merge data from 2 studies to look at FCM and the presence of seizures, PRES or another neurotoxicity. Only previous data, no extra workload but needs a National representative and ethical permission from each country.

10. Omega-3 fish oil (Bodil Als-Nielsen)

A randomized trial that has started in Copenhagen and is aimed to be expanded to a NOPHO study. Fish oil supplement is given to children with ALL treated for SR, IR-low and IR-high in the ALLTogether protocol, to look at the effect on the hypertriglyceridemia as the primary endpoint. Other endpoints osteonecrosis, pancreatitis and thrombosis. Planning to recruit 100 patients, (50/50 – fish oil/placebo). The study will be difficult to conduct in Norway where most children already receive fish oil supplements.

11. Study proposal on pancreatitis (Pernille Rydebeck)

Study on late effects in NOPHO ALL 2008 survivors with pancreatitis during therapy. 168 patients have had pancreatitis, both children and adults. Assessment of endocrine and exocrine pancreatic function after pancreatitis with glucose tolerance and insulin resistance. The study is intended to become a NOPHO study. The data collection is suggested to be coordinated with other ongoing late effect studies, like ALLSTAR and HALLON.

12. Thrombosis (Ruta Tuckuviene)

A prospective thrombosis study is the plan is to collect more detailed data about thrombosis in the ALL-Together protocol in the NOPHO-countries. Application for NOPHO-study will be sent in. A substudy will be looking at the re-exposure of Asparaginase in patients treated for venous sinus thrombosis.

13. Next Event group meeting will be 14th of September 2020 in Stockholm

NOPHO ALLTogether Working Group

Coordinators	Mats Heyman
Denmark	Kjeld Schmiegelow
	Birgitte Klug Albertsen
	Bodil Elise Thorhauge Als-Nielsen
Estonia	Kristi Lepik
Finland	Mervi Taskinen
	Olli Lohi
	Päivi Lähteenmäki
Iceland	Ólafur Gísli Jónsson
Lithuania	Goda Vaitkeviciene
Norway	Inga Maria Rinvoll Johansdottir
	Trond Flaegstad
Sweden	Mats Heyman
	Johan Malmros
	Arja Harila-Saari
	Lene Karlsson
Adult representatives	Helene Hallböök (Sweden)
	Nina Toft (Denmark)
	Ulrik Overgaard (Denmark)
	Ulla Wartiovaara-Kautto (Finland)
	Hilde Skuterud Wik (Norway)
	Laimonas Griskevicius (Lithuania)
	Mari Punab (Estonia)

Representatives in ALLTogether task-forces	
Cytogenetics	Bertil Johansson
MRD	Hanne Marquart, Hans Ole Madsen
CAR-T	Jochen Büchner
Toxicity	Jukka Kanerva, Arja Harila-Saari
Asp-TDM	Birgitte Klug Albertsen
SCT	Marianne Ifversen
Osteonecrosis	Riitta Niinimäki
HDM	Torben Stam Mikkelsen, Kjeld Schmiegelow
Maintenance	Kjeld Schmiegelow
CNS	Mervi Taskinen
Trial Manager	Karin Flood
Regulatory	Mats Heyman
Statistics	Mats Heyman, Matteo Bottai, Ida Hed Myrberg

The Group

The ALLTogether-group was formed when NOPHO decided to join the ALLTogether consortium and then took over from the "NOPHO next protocol ALL-2016 group". After most of the structure of the ALLTogether protocol has been finalised, the NOPHO ALLTogether group meetings have in the last three years merged with the ALL working-group meetings. This adds the input from the ALL-working-group members, who are not members of the ALLTogether working group and it also economises on travelling, but there is of course an obvious risk of over-loading the agenda and not getting enough time for the specific items for each group.

Meetings have taken place at Arlanda airport (25th of September 2019 and 10th of March 2020).

The group serves as an important reference-group for NOPHO opinions regarding changes in the protocol and the structure of the collaboration and prepares decisions taken by the LLC and the board regarding ALLTogether issues that need NOPHO-approval.

Very important aspects of the protocol work take place in the working-groups of ALLTogether, where procedures, routines as well as documentation are worked and prepared for decision by the protocol group/steering committee. The members of the NOPHO ALLTogether working-group shoulder an impressive responsibility and make important contributions to this work.

The ALLTogether Protocol and the Pilot Study

The protocol was finalised in the summer of 2019 and submitted for regulatory approval in August 2019 through a "voluntary harmonised procedure" (VHP). A number of points raised by the competent authority appointed as responsible for the approval resulted in significant changes, the most important was that the TEAM-arm had to be removed from randomisation 3, since the IMPD for the liquid preparation of 6-Thioguanin was not available at the time of submission. All questions were eventually answered and the protocol was approved on the 18th of November 2019.

Since then, various mainly logistic hurdles (necessary contracts between sponsor and the participating countries, approvals from ethical review boards and in some countries biobank and data-protection authorities), but also the lack of some essential documents and necessary changes to the registration system have held up the start of the study, but it is now scheduled for start in the first countries in early June 2020.

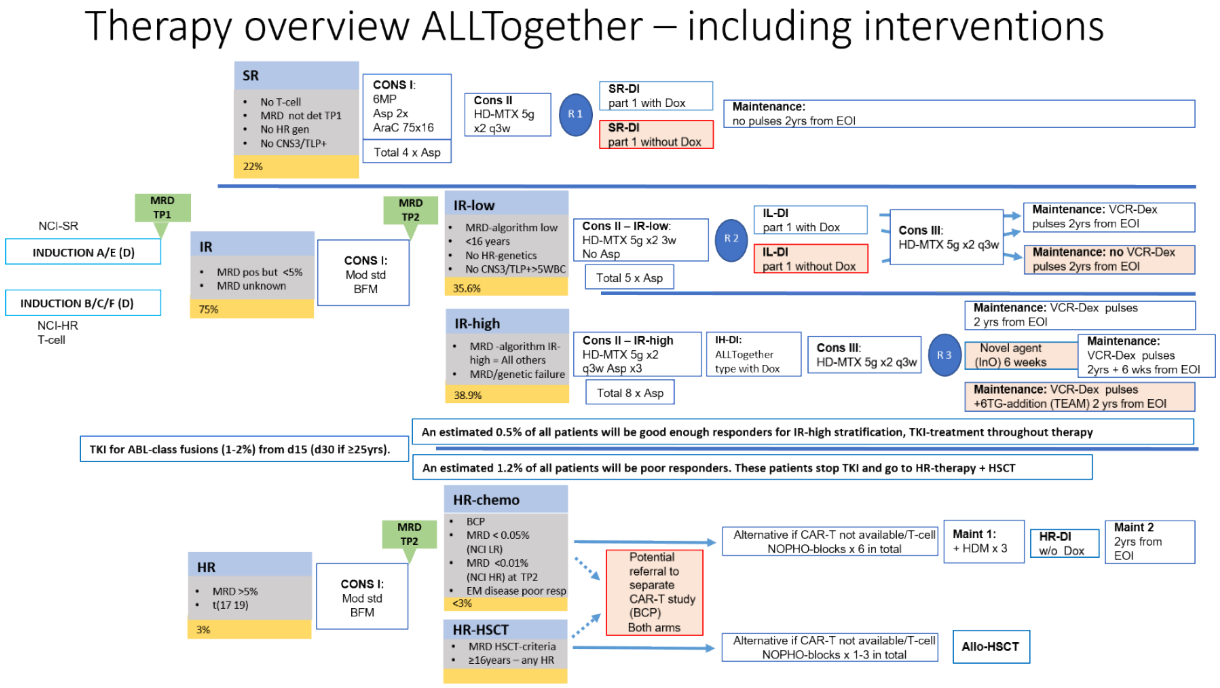
Meanwhile, the first complete draft of the protocol has been in use as a pilot-study, partly to gain experience from the stratification and therapy and partly to test the logistics of the new diagnostics in genetics and MRD. The pilot was implemented first in Denmark (autumn 2018), Lithuania (January 2019), Sweden, Norway and Iceland (autumn 2019). Estonia will join the pilot shortly and will join the main study in 2021. Finland will not implement the pilot-study and will instead join the main study directly.

Amendment of TEAM and Blinatumomab for Down patients

The omission of the TEAM-part of the study has led to the need for an early substantial amendment, when the necessary regulatory documents could be produced.
At the same a new intervention has been developed by Sujith Samarasinghe in the UK with the support from the manufacturer of Blinatumomab (Amgen) for patients with Down Syndrome (DS) and remaining MRD at the end of induction. The intervention consists of the non-randomised replacement of Consolidation 1 and 2 with two blocks of Blinatumomab with the aim to increase the fraction of DS patients achieving MRD-negative status and thereby improving their prognosis. A secondary aim is to reduce the toxicity. The proposal was discussed and approved by all national group, including the NOPHO ALLTogether wg, LLC and board as well as by the ALLTogether protocol group. The TEAM-element was of course a part of the original ALLTogether design and as such needed no approval.

An application for regulatory approval of this substantial amendment has been submitted in late April 2020 and the CA-decision is thus still pending.

Figure 1. Treatment overview of the ALLTogether protocol including interventions – and the TEAM amendment element in R3

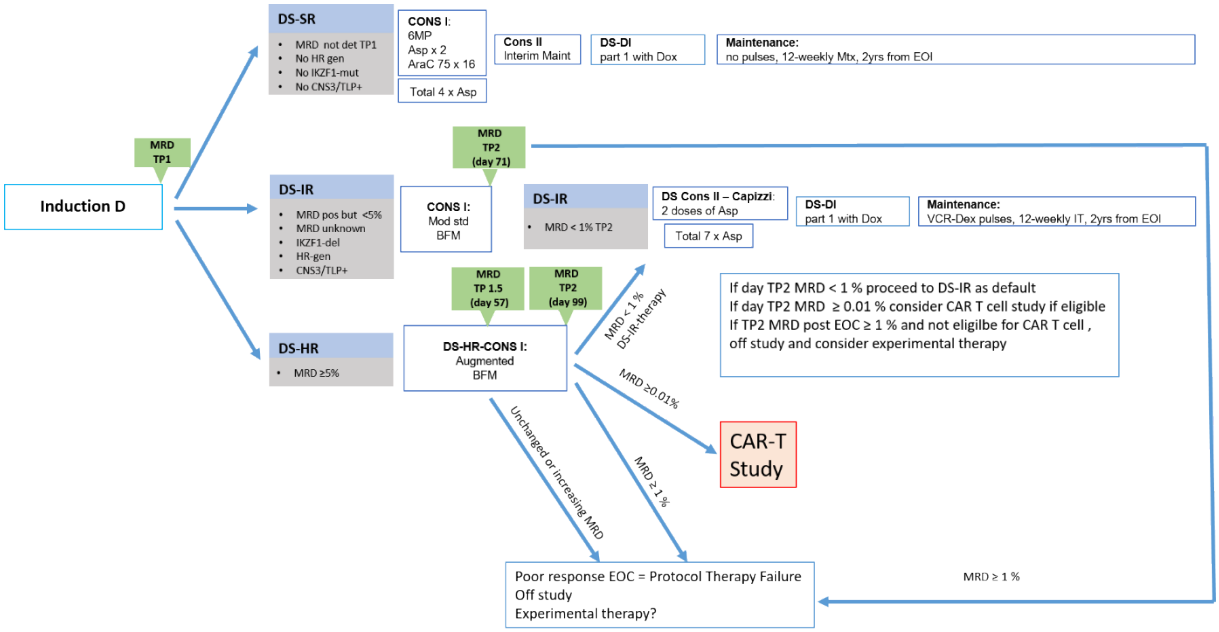


The Pilot study consists of the same elements but with the interventions removed:

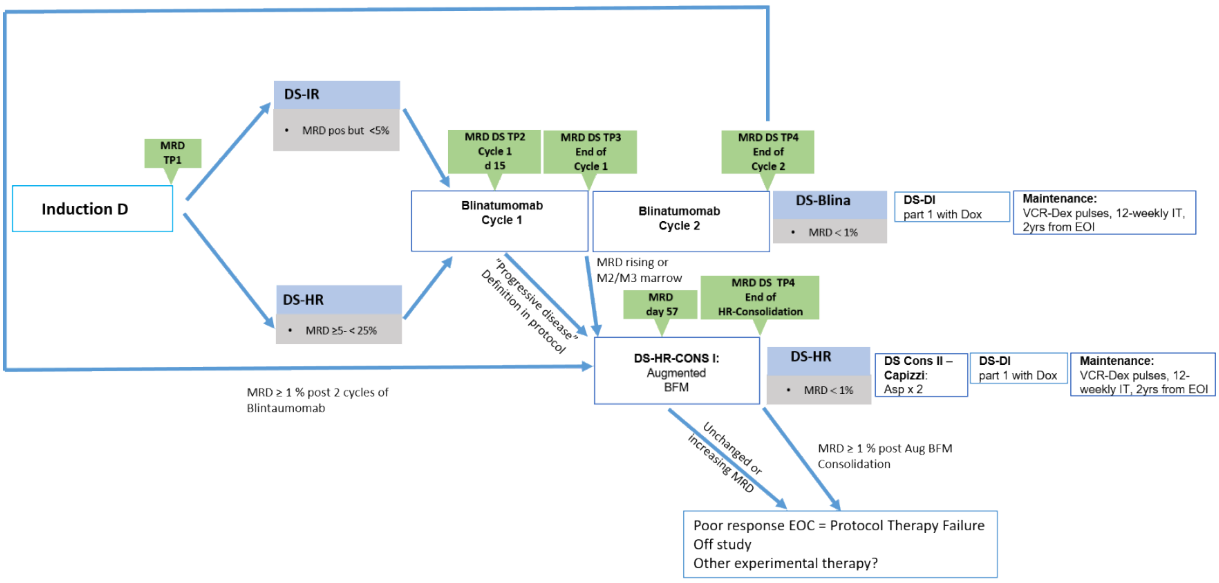
- No R1 randomisation in the SR-arm – all patients receive standard DI
- No R2 randomisation in the IR-low arm – all patients receive standard DI and VCR-Dexa pulses in maintenance (no Inotuzumab, no TEAM addition of 6-Thioguanine to maintenance therapy)
- No R3 randomisation in the IR-high arm – all patients receive standard maintenance
- No addition of TKI for ABL-class fusion patients

Figure 2. Treatment overview of the ALLTogether protocol adaption for children with Down syndrome

a) standard therapy



b) proposed amendment including Blinatumomab



ALLTogether and additional research

The ALLTogether is also meant to be a platform for further ALL research. There has been a call for add-on studies and >30 such studies have been suggested. Several of these studies have been suggested by NOPHO researchers and NOPHO has taken the stance that NOPHO-participation in such studies should be approved by the NOPHO scientific committee.
The studies approved so far as sub-studies, such approved studies include:

- a study continuing the evaluation of leukaemic contamination of the CSF
- the analysis of the impact of asparaginase-activity (a spin-off of therapeutic drug-monitoring)
- maintenance monitoring (sprung from the NOPHO maintenance study)
- a study on the efficacy of Imatinib (in vitro and in vivo) for patients wit ABL-class fusions in the leukaemic cells
- BRAIN – a study on cognitive long-term effects of ALL-treatment

Practical aspects – clinically and administratively

The challenge now is to get NOPHO ready to start full participation in the study. This means major adaption of processes locally and nationally:

- The use of a new registration system (Castor)
- The implementation of therapeutic drug monitoring of Asparaginase activity by the lab in Aarhus lead by Birgitte Klug Albertsen for all of NOPHO, including new registration in the RedCap system
- The implementation of MRD both by PCR and Flow cytometry as basis for treatment decision
- The application of GCP-principles to a larger part of the protocol – and for the randomised parts an increase in the burden of registration
- Future challenges include the full implementation of transfer of data from the MRD- and Cytogenetic NOPHO registration systems

As before, the NOPHO-representation in the protocol-group of ALLTogether is Mats Heyman, Mervi Taskinen and Kjeld Schmiegelow for paediatrics, Helene Hallböök, Nina Toft and Ulla Wartiovaara-Kautto for adult haematology. The representatives in the ALLTogether task-forces are listed above.

National PI:s for ALLTogether are: Johan Malmros (paed S), Helene Hallböök (adult S), Bodil Als-Nielsen (paed DK), Ulrik Malthe Overgaard (adult DK), Inga Maria Rinvoll Johannsdottir (paed N), Hilde Skuterud Wik (adult N), Mervi Taskinen (paed FIN), Ulla Wartiovaara-Kautto (adult FIN), Goda Vaitkeviciene (paed LT), Laimonas Griskevicius (adult LT), Kristi Lepik (paed EE), Mari Punab (adult EE).

Because of the very considerable administrative burden, a central trial office structure is needed. Karin Flood is heading this work as Trial Manager. The help of Jenny Juhlin from her position in the NOPHO secretariat with time dedicated to support for regulatory issues within NOPHO has also been extremely valuable. Adrian Levitsky is the head Data Manager and is as such in charge of design of the registration system – and will also be in charge of data-checks and controls of data. Because of the anticipated workload, a second data-manager is under recruitment.

Springtime 2020
Mats Heyman

AML Working Group

Coordinator	Jonas Abrahamsson	vobjab@gmail.com
National coordinators		
Denmark	Birgitte Lausen	birgitte.lausen@rh.regionh.dk
Estonia	Kadri Saks	kadri.saks@lastehaigla.ee
Finland	Kirsi Jahnukainen	kirsi.jahnukainen@kbh.ki.se
Iceland	Ólafur Gísli Jónsson	olafurgi@landspitali.is
Norway	Bem Zeller	bem.zeller@rikshospitalet.no
Sweden	Josefine Palle	josefine.palle@akademiska.se
Hong Kong	Daniel Cheukk	cheukkld@hku.hk
Latvia	Zhanna Kovalova	zhanna.k@inbox.lv
Lithuania	Ramune Pasauliene	ramune.pasauliene@vuvl.lt
The Netherlands	Gertjan Kaspers	GJL.Kaspers@vumc.nl
Belgium	Barbara De Moerloose	Barbara.DeMoerloose@UGent.be
Israel	Nira Arad-Cohen	n_arad-cohen@rambam.health.gov.il
Spain	José Maria Fernandez	chemafer@me.com
Data manager	Henrik Hasle	hasle@dadlnet.dk
Cytogenetics	Ulrika Norén-Nyström	ulrika.norennystrom@pediatri.umu.se
MRD flow	Anne Tierens	anne.tierens@uhn.ca
Young NOPHO		
Denmark	Kristian Løvvik Juul-Dam	krijuuld@rm.dk
Finland	Minna Koskenvuo	minna.koskenvuo@hus.fi
Norway	Marta Maria Dirdal	mardir@ous-hf.no
Sweden	Kees-Jan Pronk	kees-jan.pronk@med.lu.se

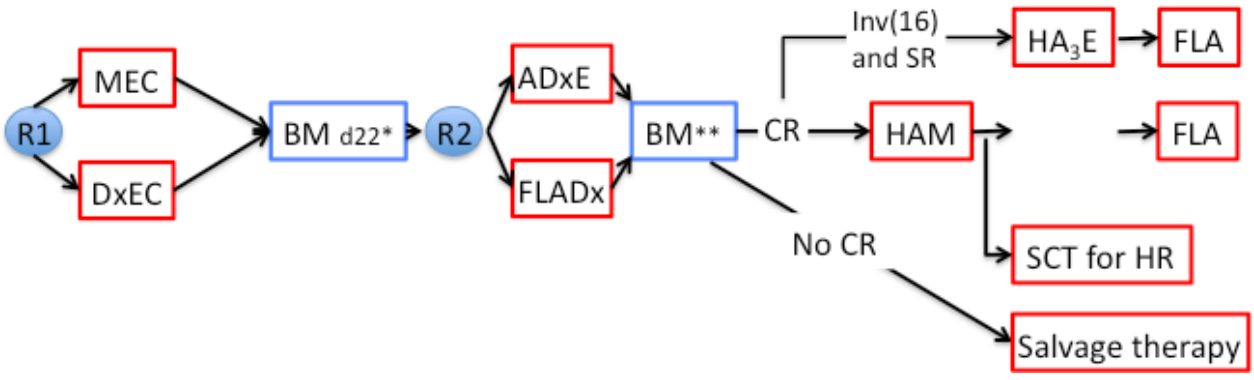


Figure 1. Overview of the current clinical research protocol NOPHO-DBH AML 2012. Evaluation of therapy response is performed on day 22 after the first course and immediately before consolidation. Patients are randomized to receive mitoxantrone or liposomal daunorubicin in course one and to receive ADxE or FLADx as second course. MEC and ADxE are standard arms in non-randomized patients.

Organisation

The group has held two meetings during 2019. One in Helsinki, Finland and one in Copenhagen, Denmark. The meetings have functioned as PI meetings for the coordination and supervision of the treatment protocol NOPHO-DBH AML2012. During 2019 Spain has continued to open centers and at present treat patients at 17 centers. Portugal has still not opened the protocol officially.

We have continued to act as a platform for facilitating both biological and clinical research in pediatric AML and to include our new collaborators in AML2012 in NOPHO research as well as commencing new research activities together with the Belgian, Dutch, Hong Kong, Israeli and Spanish national AML groups. All NOPHO projects are discussed and coordinated with the leukemia biology group which allows for increased collaboration and scientific quality.

Several NOPHO AML research projects have been started and pursued during the year and NOPHO has participated in international collaborative scientific studies. The current AML2012 treatment study is expected to recruit patients to the second randomization during 2020 but the group has started to prepare for the next treatment protocol. A common aim within the group is to try to perform such as study with the countries currently involved in our consortium. At present, it seems likely that a new protocol will continue to rely on conventional drugs since few new drugs exist with documented efficacy to allow incorporation in an upfront protocol. An exception is FLT3 inhibitors which can be combined with conventional therapy and have promising efficacy. Therefore, the group has during 2019 initiated cooperation with the company Daiichi Sankyo who manufacture Quizartinib. The aim is to launch an upfront treatment study in FLT3-ITD positive patients based on addition of Quizartinib to the AML2012 backbone. One of the main reasons that the company chooses to cooperate with our group is that we use a highly effective standard therapy and can provide excellent historical controls for evaluation of MRD and other efficacy endpoints.

As usual, between meetings, members have frequent mail discussions both regarding individual patient treatment decisions and research issues.

Jonas Abrahamsson has decided to step down after being NOPHO AML group chair for more than 8 years. The group has suggested and received approval from LLC to appoint Josefine Palle as new chair and also that a position as vice chair is established and appointed Kees-Jan Pronk .

Introduction

NOPHO has from 1984 until 2013 treated children with AML on four common protocols: NOPHO-AML84, -88-. -93 and -2004. The outline for treatment in the respective protocols is demonstrated in figure 2. All protocols have been based on induction therapy with anthracycline, cytarabine and 6-thioguanin with etoposide added from 1988 followed by consolidation based on high-dose cytarabine. Since 1993 a response guided induction strategy has been used, allowing hematological recovery for children in remission after the first course prior to giving the second course. Compared to the previous intensively timed induction this markedly reduced mortality in induction.

From NOPHO-AML84 to NOPHO-AML93, outcome improved significantly and the NOPHO-AML93 had a 5 year EFS of 50%. Overall survival was 65% which at that time was the highest reported in childhood AML.

However, the steady trend towards improvement was broken with the NOPHO AML 2004 protocol. Although survival increased to 70% the EFS5y was disappointingly low at 47%. When analyzing the relatively poor outcome the main conclusions were that the second induction course in the AML 2004 protocol was not intensive enough and that idarubicin seemed to be less effective in patients with RUNX1/RUNX1T1 (t8;21) AML. Therefore, the group worked intensely to produce the new protocol which was finalized in December 2012. The first patients were treated in March 2013.

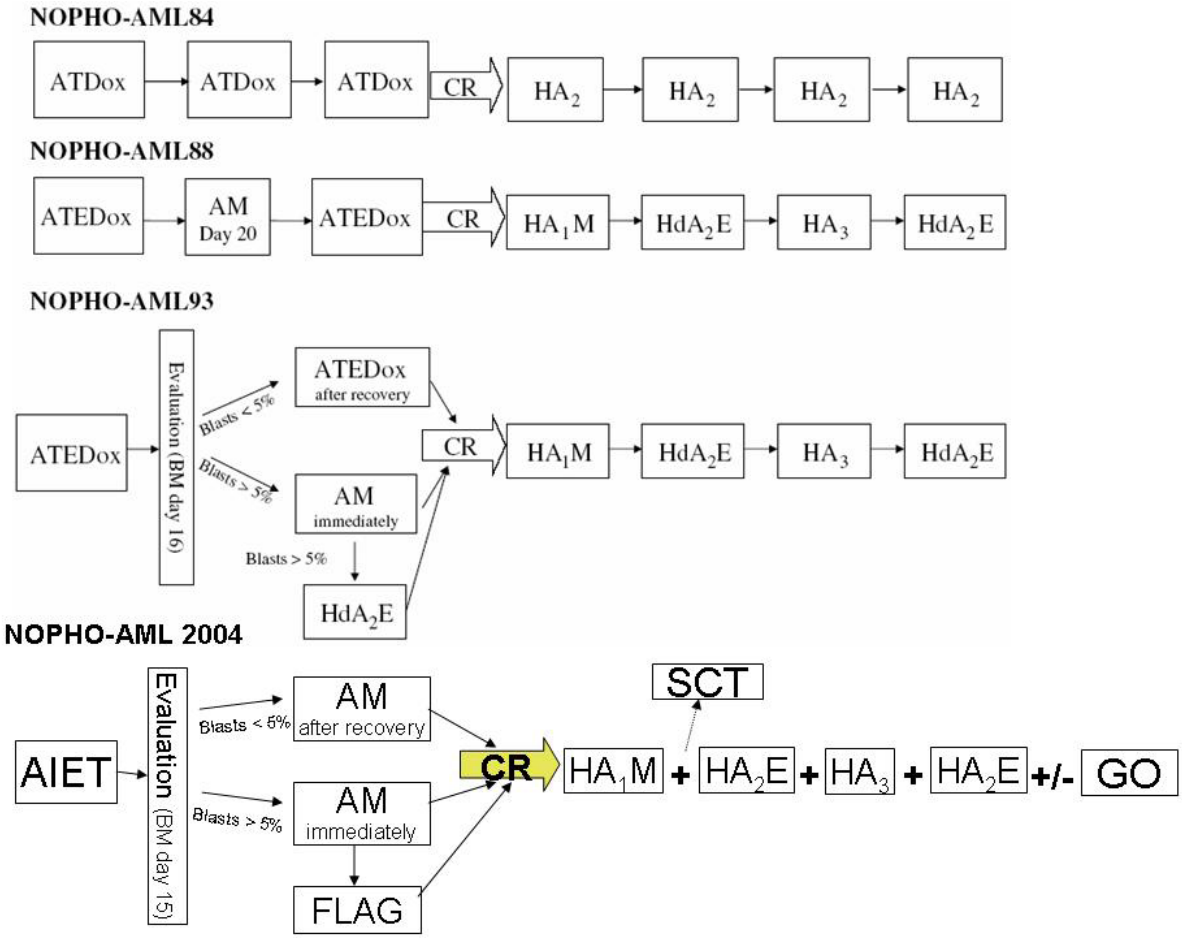


Figure 2. Overview of previous NOPHO treatment protocols from 1984-2012. In AML88 all patients received intensively timed induction with early start of course 2. Since AML93 all protocols have adopted a response-guided timing of the second course, allowing good responding patients to recover peripheral blood values before starting course two.

During 2019 the main work in the AML group has focused on

1. Supervising the efficiency, toxicity and logistic framework for the NOPHO-DBH AML2012 protocol. A major task here is to assure complete registration in all databases including the clinical and laboratory (MRD) databases.
2. Adapting the AML2012 protocol to the unavailability of DaunoXome. This included termination of the first randomization since mitoxantrone in course 1 showed superior efficacy to liposomal daunorubicin and substitution of liposomal with convention daunorubicin in the courses that are compared in the second randomization (FLADx and ADxE).
3. Evaluation of how NOPHO and the entire consortium can participate in two major international projects. The first is PedAL which aims at building a master trial for relapsed AML throughout the world and Data Commons which aims at creating a large set of data from pediatric AML de novo trials throughout the world.
4. Increasing the scientific collaboration with preclinical researchers and between NOPHO and the Belgian, Dutch, Hong Kong, Israeli and Spanish groups.
5. Participation in international collaborative research projects.
6. Continued analysis of data generated from previous NOPHO AML protocols.

NOPHO-AML2004

The protocol opened in January 2004 and was officially closed in December 2013. Hong Kong continued to use the protocol as standard of care until September 2016 at which time AML2012 was opened. The 2004 protocol with flow charts and amendments can be accessed at www.nopho.org. The outcome data are mature and much work has been done within the group also during 2019 to analyze and publish data on outcome, disease biology and toxicity.

Patient accrual

NOPHO AML-2004 included a randomized comparison of the potential benefit of Gemtuzumab as post-consolidation therapy for standard risk AML. Late 2010, the randomized study had accrued the target number of 120 and therefore was closed for randomization but continued to be used as standard therapy without Gemtuzumab. Between 2004 and December 2013, when the protocol was officially closed, 323 protocol patients were registered from the Nordic countries and Hong Kong. The protocol was also used as standard therapy for childhood AML in Estonia and Latvia. During 2010-2013 both the Netherlands and Belgium conducted a study based on a modified version of NOPHO-AML2004 (identical treatment except for omission of the third course HAM and no stem cell transplant in first remission). This study recruited 112 patients and had an EFS of 53.5% and OS of 74.5% at three years.

Toxicity

The toxic death rate in AML2004 was relatively low with 3.1% induction deaths and 2.8% deaths in CR1. The frequency of resistant disease was 5%, second malignancy 1.9% and 45% experienced relapse.

As the treatment blocks were very intensive, bone marrow aplasia was long and the rate of neutropenic fever very high after each block ranging from almost 100% after the first induction course to 74% after HA3. The acute and long-term cardiac toxicity has been very low but a NOPHO publication in 2016 from the NOPHO-AML88, -93 and -04 protocols showed that, although most patients had normal cardiac function and no cardiac symptoms, left ventricular function was significantly reduced compared to controls.

Outcome

The overall results are stable with a five year EFS of 47% compared to 50% in NOPHO-AML93. The overall survival improved to 69% from 65% in AML93. Figure 3 shows event-free survival and overall survival compared to previous protocols.

When analyzing the relatively poor EFS it was found that patients with an intermediate response to AIET had a very high relapse rate as did patients with RUNX1/RUNX1T1 regardless of response. The AML group concluded that the second induction course – AM – was too weak in these patient subsets and in 2010 an amendment was made recommending FLADx as second course for patients with RUNX1/RUNX1T1 or an intermediate response to AIET. This seemed to markedly improve prognosis for these patients. Similar results were seen in the Dutch/Belgian AML01 protocol which used AIET as first course followed by FLA or FLADx in RUNX1/RUNX1T1 AML.

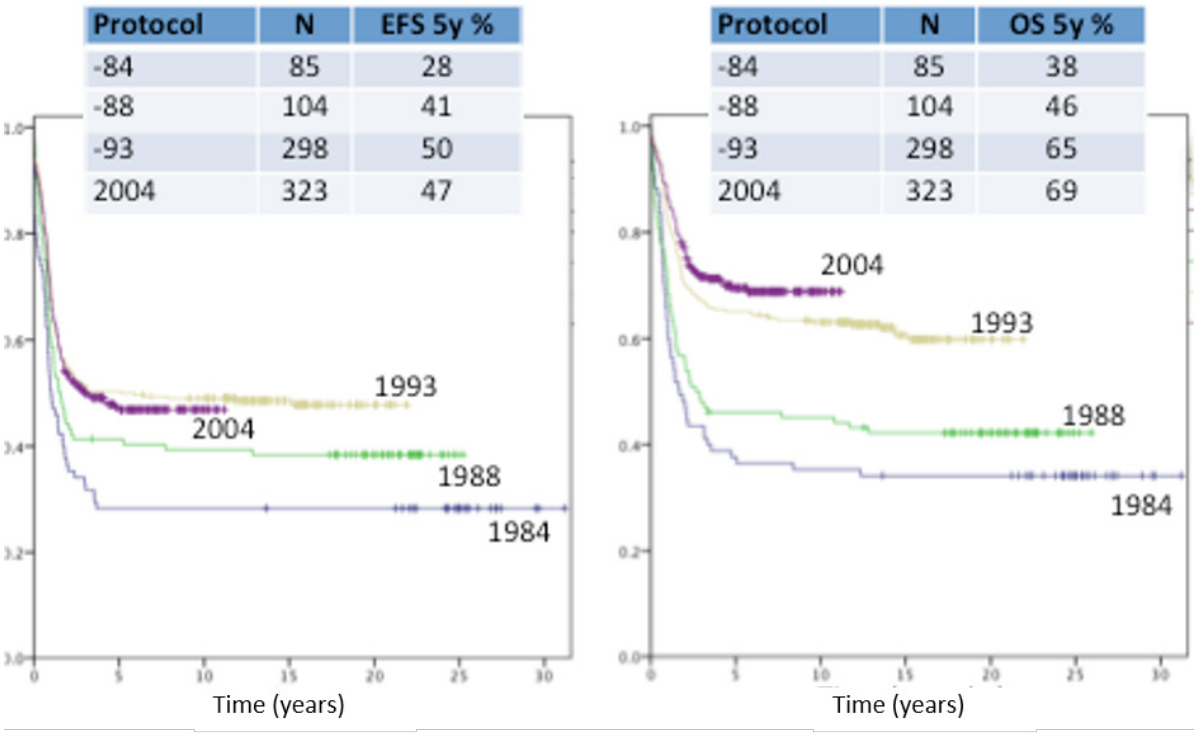


Figure 3. Overall survival (right figure) and event-free survival (left figure) in NOPHO-AML2004 (purple), NOPHO-AML93 (beige), NOPHO-AML88 (green) and NOPHO-AML84 (blue).

Analysis of the results with respect to subgroups is still on-going but it is evident that the changes in induction made in the 2004 protocol affected survival differently for several cytogenetic subgroups. An important conclusion is therefore that, even when using conventional chemotherapy for AML, patients in different subgroups may benefit from tailored therapy.

Stem cell transplant in CR1

In NOPHO-AML2004 high-risk patients were recommended SCT with any matched donor. Initially KMT2A aberration other than KMT2A/MLLT3 was a high risk criterion but interim analysis showed that compliance to the SCT recommendation in these patients was poor and consolidation with chemotherapy resulted in a satisfactory outcome. Thus, an amendment in 2009 removed KMT2A aberrations as a high-risk criterion.

At the same time accumulating evidence indicated that patients with FLT3-ITD mutations without concomitant NPM1 mutation had a very poor prognosis which might be improved by stem cell transplant. Therefore, FLT3-ITD mutations were added as a high risk criterion in an amendment in 2010. In total, only 17% of patients received SCT as consolidation in CR1 or following resistant disease. This is a low rate compared to most other childhood AML protocols.

Gemtuzumab randomization

The results from the randomized study including 120 patients were published 2012 (Hasle et. al. Blood). Gemtuzumab was well tolerated with no toxic deaths. Although GO treated patients had a tendency for later relapses, no effect was observed on either EFS or OS. Thus, the conclusion is that Gemtuzumab neither reduces the relapse rate nor increases survival when administered as post-consolidation therapy. In 2016 we could also show that patients relapsing after GO therapy did not have a significantly worse outcome than patients not receiving GO.

NOPHO-DBH AML2012

The protocol was finalized in December 2012 and the AML2012 database was opened in March 2013. The study has EUDract number 2012-002934-35 and clinical trials identifier NCT01828489. After approval by the competent authorities and setting up of national GCP monitoring the protocol opened in Denmark and Sweden in March 2013, followed by Finland in April and Norway in June. The Netherlands started recruiting patients Jan 2014 and Belgium in May 2014. Hong Kong started recruiting in Sep 2016 and Israel started using the protocol in summer 2016 but randomizations are not planned to be performed. The larger centers in Spain started using the protocol in Nov 2017 following relevant approvals from competent authorities and in Oct 2019 17 centers were recruiting patients. Spain is also not randomizing patients. The MRD group and NOPHO registry continuously work very hard in order to ensure standardization of MRD flow analyses and curate the MRD database.

The study was expected to recruit 300 randomized patients within a time frame of six years but due to the problems with DaunoXome shortage randomizations were on hold for more than a year and resumed in 2019. Depending on approvals from national authorities the countries re-started randomizaions at different timepoints during spring 2019.

The main assumptions, which to a large extent were deduced from experiences from AML2004, behind the major changes in standard treatment in AML2012 as compared to AML2004 are that:

- prognosis can be improved by using more intensive induction therapy
- detection of minimal residual disease ≥0.1% by flow cytometry, following the two induction courses identifies a subset of patients with a very poor prognosis when treated with chemotherapy alone
- stem cell transplant can reduce the negative prognostic impact of a poor response to induction therapy

The risk stratification in AML2012 is mainly based on treatment response which we assumed would be possible to evaluate by flow cytometry in the majority of patients. Since MRD flow is very difficult in AML the MRD group have set up strict logistics and a standardized protocol but continuously strive to improve by several quality control procedures. We can already state that this part of the protocol has been a success since around 90% of patients have an evaluable MRD investigation with a sensitivity of 0.1%. The MRD group meets twice each year and all laboratories partake in twinning so that each patients MRD data at critical protocol timepoints is reviewed by two centers. Furthermore, quality control rounds are performed twice yearly where all laboratories review the same data files. All MRD data files are accessible through a common server.

Children with ≥15% leukemic cells after the first course or ≥ 0.1% after the second course are classified as high risk (HR). In addition, patients with FLT3-ITD and no NPM1 mutation are HR patients regardless of response. This is slightly different from more recent AML trials in children that also incorporate more rare gene aberrations with putative poor outcome. However, whether these small subgroups really have poor prognosis with modern treatment and in what way prognosis interacts with treatment response is largely unknown. Given these uncertainties, the NOPHO AML group has decided to keep the risk stratification as originally planned in AML2012. There has been some treatment violations in the protocol where clinicians at times have given HR therapy including SCT to patients with these alleged poor risk genetic aberrations. Acknowledging that patient numbers are small, none of the individual study groups will be able to define the “true” prognostic impact of these aberrations and we will share our data in collaborative inter-group studies to extend our knowledge. However, the protocol group carefully supervise outcome in these patient groups and as of yet results seem satisfactory even in these genetic groups.

Children and adolescents in the HR group are recommended allogeneic stem cell transplant. All other patients are classified as standard risk and receive consolidation therapy with three blocks containing high dose cytarabine. An exception is standard risk patients with CFBB-MYH11 (inv(16)) who only receive two consolidation blocks.

AML2012 includes two randomized studies both aiming at improving treatment outcome. The efficacy and toxicity (in particular cardiac) of mitoxantrone and DaunoXome in the first induction course are compared. The second study compares the efficacy and toxicity of FLADx to the course ADxE. Both studies are evaluated by using MRD flow after the respective courses as primary endpoint.
AML2012 has three other important research aims

1. to evaluate the prognostic significance of measurement of fusion gene transcript levels after the first and second course
2. to perform a comprehensive genetic characterization of the leukemic cells
3. to use fusion gene transcript determinations to detect molecular relapse of AML during follow-up.

As of Oct 2019, 504 patients have been treated on the protocol. A major setback has been that the company producing DaunoXome has had manufacturing problems and no drug has been available since 1 Nov 2017. Initially we believed that the drug would soon be available again. Therefore, randomizations were put on hold and an amendment was made giving guidelines how to treat patients until the drug became available again. This involved giving the standard arm to all as first course and giving a modified block (ADE - cytarabine, daunorubicin, etoposide) as second course while pausing all randomizations. However, in late 2018 it became clear that it was unlikely that the drug would be available again. At the same time, the annual interim analysis in Oct 2018 clearly showed that mitoxantrone treatment gave a significantly better EFS than DaunoXome in the 194 patients who were randomized prior to the shortage. Therefore, after consulting the DMC, the first randomization was officially closed in Dec 2018 and in order to be able to continue the 2nd randomization, a second amendment was made allowing for substitution of daunorubicin for DaunoXome in both treatment arms in course 2. This amendment was approved in all countries participating in randomizations during spring 2019.

The data given below includes all 504 patients treated on AML2012 until October 2019. 224 have been enrolled in the second randomization and with an accrual of 50 patients annually it will take another 18 months before the study is completed. The age distribution is as expected with 23% below two years. More centers now use NGS panels for diagnostics so 87% of patients have AML specific genetic aberrations. At present, 10% have CBFB/MYH11 which in good responding patients stratifies to only two consolidation courses. A further 13% have RUNX1/RUNX1T1, 10% KMT2A/MLLT3, 14% other KMT2A rearrangements and 11% FLT3-ITD mutations without concomitant NPM1 mutation. The latter subgroup is stratified to high-risk therapy in AML2012.

Adherence to protocol diagnostic and MRD guidelines is excellent. Figure 4 shows that following course one, 92% have an informative MRD examination and that of these 60% have MRD < 0.1%.

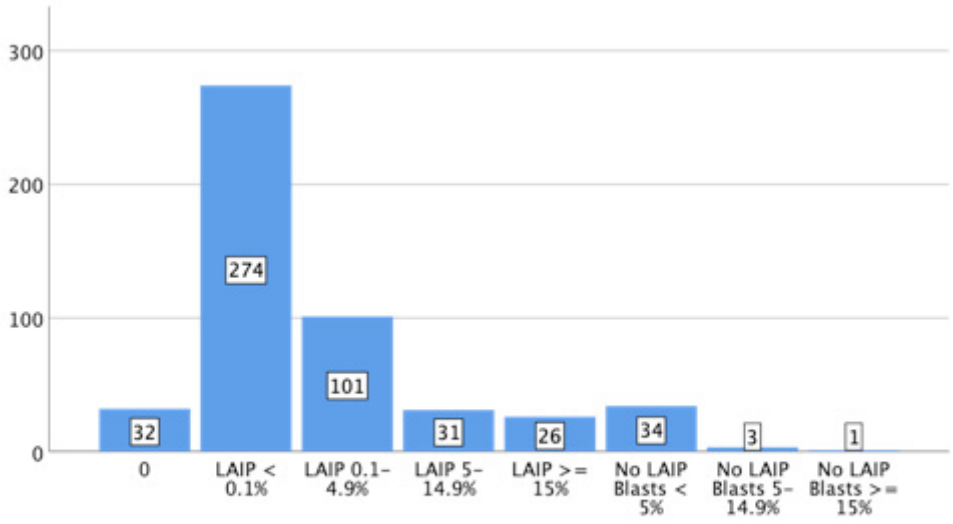


Figure 4. Response to course 1 in AML2012. 0 depicts patients lacking registration. LAIP - leukemia associated immunophenotype. 58% of evaluable patients have MRD < 0.1%.

After course 1, over 85% reached CR which is a high fraction. Overall, AML2012 has very high anti-leukemic effect and following the two induction courses 93.3% reached complete remission. The frequency of resistant disease was 4.2%. Of all patients, 75% were stratified to the standard risk and 18% to the high risk group. As can be seen in figure 5, that shows Kaplan-Meier plots of three year disease-free and overall survival according to risk group, the risk stratification virtually eliminates the previous difference in outcome.

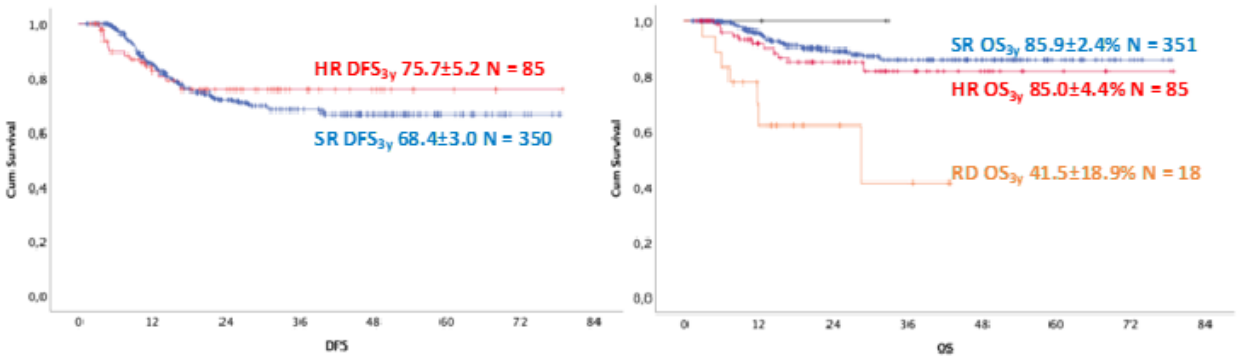


Figure 5. Estimated disease-free survival (left) and overall survival (right) at three years are almost equal in both risk groups. Overall survival is shown also for patients with resistant disease (RD). Blue curve - standard risk, red - high risk, orange - resistant disease. The black curve at the top is two unclassifiable patients.

The toxicity in AML2012 is, as expected, high but manageable. The frequency of induction death is 2.4% and the cumulative risk of treatment-related mortality is 4.8%. This includes deaths after SCT in HR patients.

The overall treatment-related mortality compares favorably to published data in AML. Registration of specific toxicities shows that after each of the first two courses around 45% of patients have documented blood-stream infections. After the first course, 15% have typhlitis and 20% require care at ICU. The frequency of specific toxicities declines with subsequent courses. However, induction therapy for AML is very intensive and many patients experience potentially life-threatening emergencies. Therefore, continued vigilance is necessary and supportive care must be of the highest standard in these patients. Data have been collected to further explore the characteristics, outcome and treatment of patients with typhlitis and/or with ICU admission. Toxicity registration still tends to be delayed for the consolidation courses which is not acceptable in a clinical trial conducted according to good clinical practice. However, this is continuously improving.

The follow-up is now sufficiently long to interpret event-free survival in the protocol. Over 90% of relapses in AML2012 occur within 24 months from diagnosis. Also, the data for overall survival are now beginning to have adequate follow-up although they must be viewed more cautiously. Fig 6 shows a EFS and OS at 3 years in the entire AML 2012 cohort. As can be seen EFS at 3 years is 65.3% and OS at 81.4%. The corresponding values for AML2004 were 49.8% and 73.7% respectively, both significantly lower.

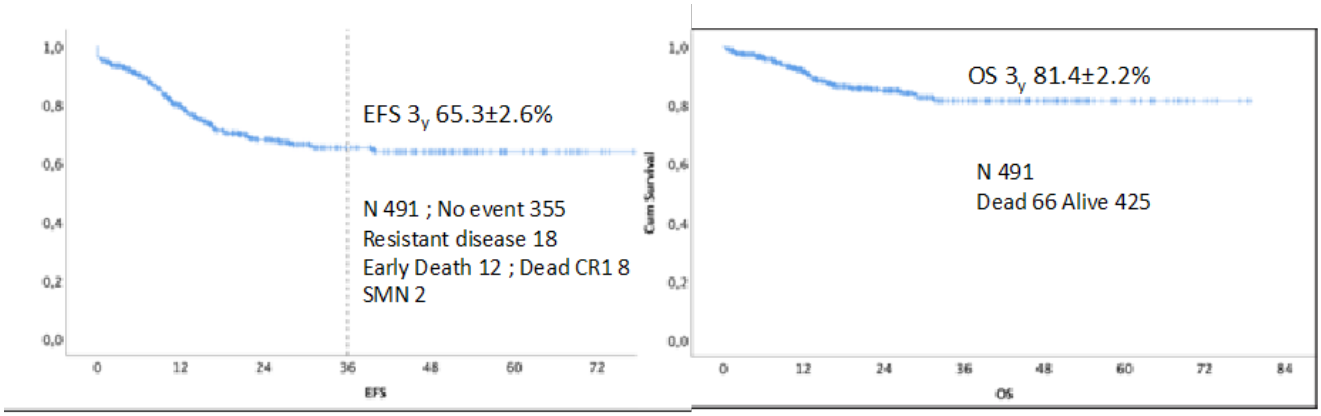


Figure 6. Kaplan-Meier estimates of event-free survival (left) and overall survival (right) for AML2012. Estimates are at three years.

Randomization between mitoxantrone and liposomal daunorubicin

In Oct 2018, 194 patients had been included in the first randomization in AML2012. The last patient was included in Oct 2017. All patients had a minimum follow-up of almost 12 months with a median follow-up time of 30 months in patients without event. For the primary endpoint, the fraction of patients with MRD < 0.1% on day 22 after start of course 1, there was no difference between the treatment arms. However, as shown in figure 7 there was a large and statistically significant difference in event-free survival, estimated at three years, between the treatment arms. Thus, EFS3y was 76.6±4.4% for the MEC arm and 57.0±5.6% for the DxEC arm (Log rank P = 0.017).

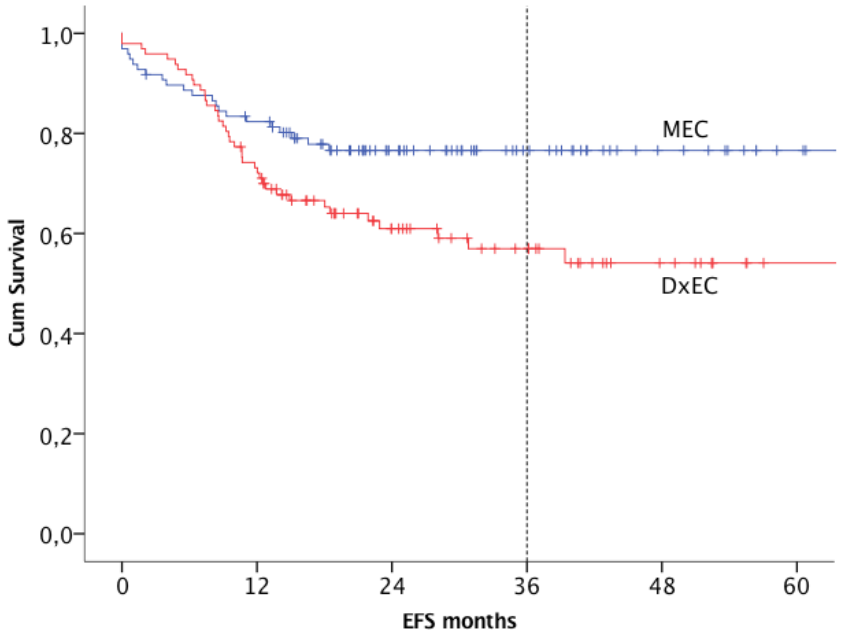


Figure 7. EFS in 194 patients randomized between MEC and DxEC in R1 and with outcome data. MEC (blue line) had an EFS3y of 76.6±4.4% and DxEC had an EFS3y of 57.0±5.6%. Log rank test is significant with P=0.017. The number at risk at three years was 27 for MEC and 23 for DxEC with a median observation time of 30 months in patients without events.

In total, there were 39 events in the DxEC arm and 22 in the MEC which is a statistically significant difference (P=0.021 Chi^2). Further analysis of the events showed, as demonstrated in figure 8, that the difference in EFS3y was caused by a higher cumulative incidence of relapses (CIR3y) in the DxEC arm. CIR3y was 17.4±4.0% for MEC and 39.1±5.7% for DxEC (P=0.004).

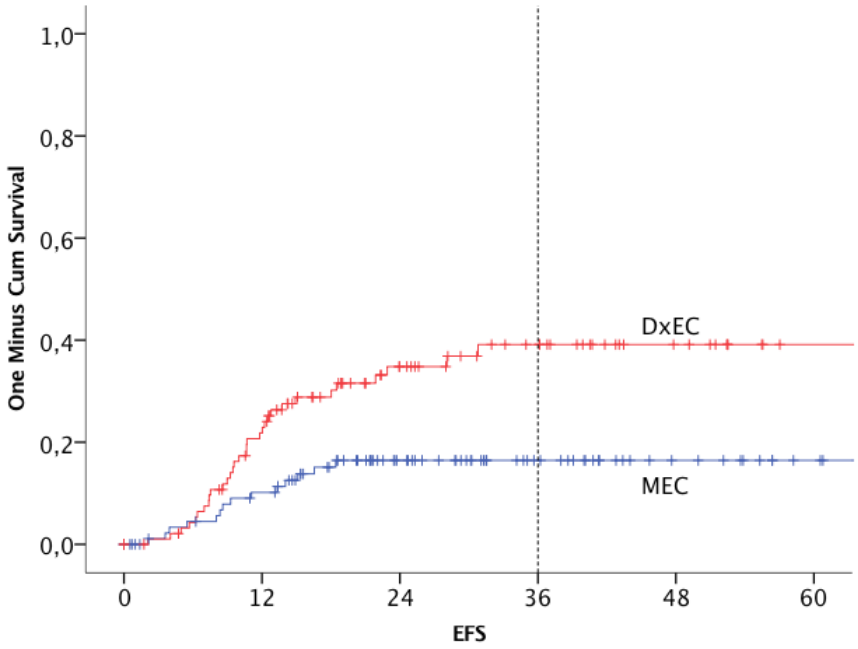


Figure 8. CIR3y in 194 patients randomized between MEC and DxEC in R1 and with outcome data. MEC (blue line) had a CIR3y of 17.4±4.0% and DxEC had an CIR3y of 39.1±5.7%. Log rank is significant with P=0.004. Since the sum of the cumulative incidences of cause-specific events and EFS at three years was close to 100% no attempt to correct for competing events was made.

Multivariate analysis confirmed that the difference in EFS was due to treatment and there was also a trend to increased survival in patients treated with mitoxantrone (OS3y MEC 85.9±3.9% vs DxEC 75.2±5.0%, Log rank test P=0.105).

In conclusion, the NOPHO-DBH AML2012 protocol has improved outcome in children with AML significantly. The study has shown that mitoxantrone, when given as part of the first course, is more effective than DaunoXome. An independent data safety committee continues to review the results from the second randomization annually and supports continuation of this part of the study. We hope that this randomization will reach target accrual by end of 2020. The protocol logistics are well functioning and one of our main goals, namely to show that a very demanding flow cytometric MRD determination can be performed in a multi-center setting, has been accomplished. The treatment efficacy is much better than in previous NOPHO protocols.

Intergroup studies and collaborations

PedAL study and Data Commons

Several large cooperative initiatives are currently being discussed both within Europe and worldwide within the developed countries. The PedAL project is a US initiative for children with relapsed/refractory AML aiming to improve outcome through a comprehensive effort including development of biomarkers, preclinical research, informatics and clinical trials. The ultimate aim is to start a master trial for R/R AML including both a base therapy and trials of innovative therapies from several companies in one trial. This is not least important since the relapse trial with Essen as sponsor now has been terminated prematurely mainly due to the unavailability of DaunoXome. Until relapse trials are commenced, NOPHO recommendations for relapse treatment can be found at www.nopho.org.

Closely related is the project Data Commons which aims at creating a common data dictionary with uniform definitions of variables so that study groups can send their data to a common database. The purpose of this database is to increase patient numbers in order to facilitate research regarding disease and treatment elements. The AML group recognizes that there are many difficulties including logistic and legal issues but consider it extremely important that NOPHO participates and helps drive these projects. This is one of the most important tasks for the NOPHO AML group the next years.

Myeloid leukemia of Down syndrome

The International DS study ML-DS 2006, which reduced the dose in each course and the total number of courses from 6 to 4 has now been published showing excellent results with an EFS at 5 years of 87% and a cumulative incidence of relapse/non-response of 6% in a cohort of 170 children. A new protocol is under development but the ML-DS 2006 is still used for treatment. The protocol is found at www.nopho.org.

AML-M3 APL

In 2009, The NOPHO-AML group recommended joining the international ICC APL study 01 as a registration only study. The outcome in this protocol has been excellent with an OS of 94% at three years. A new protocol, ICC APL study 02, is now finalized and will be recommended as standard therapy in NOPHO. Individual countries will participate fully in the study according to decisions from the national groups. A major change is that patients with standard risk APL are treated only with retinoic acid and arsenic trioxide. The APL study group issued interim guidelines already in 2015 for treatment of patients with SR APL. In late 2019 the full ICC APL Study 02 was uploaded on the NOPHO web and recommended for all APL patients.

Publications involving the NOPHO AML WG from 2018

1. **Espersen ADL, Norén-Nyström U, Abrahamsson J, Ha SY, Pronk KJ, Jahnukainen K, Jónsson ÒG, Lausen B, Palmqvist L, Hasle H.** *AML with t(7;12)(q36;p13) is associated with infancy and trisomy 19. Data from NOPHO-AML and review of the literature.* Genes Chromosomes Cancer. 2018 Jul;57(7):359-365.
2. **Løhmann D, Asdahl PH, Abrahamsson J, Ha SY, Jónsson OG, Kaspers GK, Koskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Hasle H.** *Associations between Neutrophil Recovery Time, Infections and Relapse in Paediatric Acute Myeloid Leukemia.* Pediatr Blood Cancer. 2018 Sep;65(9):e27231. doi: 10.1002/pbc.27231
3. **Klein K, Hasle H, Abrahamsson J, De Moerloose B, Kaspers GK.** *Differences in Infection Prophylaxis Measures Between Pediatric AML Study Groups Within the I-BFM Study Group.* Br J Haematology 2018, 183, 87–95. doi: 10.1111/bjh.15499
4. **Noort S, Zimmermann M, Reinhardt D, Cuccuini W, Pigazzi M, Smith J, Ries RE, Alonzo TA, Hirsch B, Tomizawa D, Locatelli F, Gruber TA, Raimondi S, Sonneveld E, Cheuk DK, Dworzak M, Stary J, Abrahamsson J, Arad-Cohen N, Balwierz W, De Moerloose B, Hasle H, Meshinchi S, van den Heuvel-Eibrink M, Zwaan M.** *Prognostic impact of t(16;21)(p11;q22) and t(16;21)(q24;q22) in pediatric AML: a retrospective study by the I-BFM SG.* Blood 2018 132:1584-1592; doi: https://doi-org.ezproxy.ub.gu.se/10.1182/blood-2018-05-849059
5. **Mari Wilhelmsson , Heidi Glosli, Marianne Ifversen, Jonas Abrahamsson, Jacek Winiarski, Kirsi Jahnukainen, Henrik Hasle.** *On behalf of the Nordic Society of Pediatric Hematology and Oncology (NOPHO). Long-term health outcomes in survivors of childhood AML treated with allogeneic HSCT: A NOPHO –AML Study.* Bone Marrow Transpl 2018. Sep 21. doi: 10.1038/s41409-018-0337-8.
6. **Bager N, Juul-Dam KL, Julie D. Sandahl JD, Abrahamsson J, Beverloo B, de Bont ESJM, Ha SY, Jahnukainen K, Jónsson ÓG, Kaspers G, Kovalova Z, Lausen B, De Moerloose B, Noren-Nyström U, Palle J, Saks K, Zeller B, Kjeldsen E, Hasle H.** *Complex and monosomal karyotype are distinct cytogenetic entities with an adverse prognostic impact in paediatric acute myeloid leukaemia. A NOPHO-DBH-AML study.* Br J Haematology 2018 2018 Nov;183(4):618-628. doi: 10.1111/bjh.15587.
7. **Skou AS, Olsen SØ, Nielsen LH, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros J, Nysom K, Hasle H; Nordic Society of Pediatric Hematology and Oncology (NOPHO).** *Hearing Status in Survivors of Childhood Acute Myeloid Leukemia Treated With Chemotherapy Only: A NOPHO-AML Study.* J Pediatr Hematol Oncol. 2019 Jan;41(1):e12-e17
8. **Testi AM, Pession A, Diverio D, Grimwade D, Gibson B, de Azevedo AC, Moran L, Leverger G, Elitzur S, Hasle H, van der Werff ten Bosch J, Smith O, De Rosa M, Piciocchi A, Lo Coco F, Foà R, Locatelli F, Kaspers GJL.** *Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL.* Blood 2018 132(4):405-412. doi: 10.1182/blood-2018-03-836528.
9. **Løhmann DJA, Asdahl PH, Abrahamsson J, Ha SY, Jónsson ÓG, Kaspers GJL, Koskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Hasle H.** *Use of granulocyte colony stimulating factor and risk of relapse in pediatric patients treated for acute myeloid leukemia according to NOPHO-AML 2004 and DB AML-01.* Pediatric Blood Cancer 2019 Jan 41(1).
10. **Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros J, Nysom K, Hasle H.** *Hearing Status in Survivors of Childhood Acute Myeloid Leukemia Treated With Chemotherapy Only: A NOPHO-AML Study.* J Pediatr Hematol Oncol. 2019 Mar 7
11. **Löhmann DJA, Asdahl PH, Abrahamsson J, Ha SY, Jonsson OG, Kaspers GJL, Konskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Sung L, Hasle H.** *Associations between pre-therapeutic body mass index, outcome and cytogenetic abnormalities in pediatric acute myeloid leukemia.* Cancer Med. 2019 Nov;8(15):6634-6643. doi: 10.1002/cam4.2554. Epub 2019 Sep 18.
12. **Uden T, Bertaina A, Abrahamsson J, Ansari M, Balduzzi A, Bourquin JP, Gerhardt C, Bierings M, Hasle H, Lankester A, Mischke K, Moore AS, Nivison-Smith I, Pieczonka A, Peters C, Sedlacek P, Reinhardt D, Stein J, Versluys B, Wachowiak J, Wiilems L, Zimmermann M, Locatelli F, Sauer M.** *Outcome of Children Relapsing after First Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Acute Myeloid Leukemia: A Retrospective I-BFM Analysis of 333 Children.* Br J Haematol 2020 Feb 3.

13. **KL Juul-Dahm Hans Beier Ommen, Charlotte Guldborg Nyvold, Christiane Walter, Helen Vålerhaugen, Veli Kairisto, Jonas Abrahamsson, Sofie Johansson Alm, Kirsi Jahnukainen, Birgitte Lausen1, Dirk Reinhardt, Bernward Zeller, Nils Von Neuhoff, Linda Fogelstrand, Henrik Hasle.** *Measurable residual disease assessment by qPCR in peripheral blood is an informative tool for disease surveillance in childhood acute myeloid leukemia.* Br J Haematol 2020 In press.

Leukemia Genetics Working Group

Coordinator	Ulrika Norén Nyström	ulrika.noren-nystrom@umu.se
Sweden	Bertil Johansson	bertil.johansson@med.lu.se
	Gisela Barbany Bustinza	gisela.barbany@ki.se
	Lucia Cavelier	lucia.cavelier@igp.uu.se
	Marie Engvall	marie.engvall@akademiska.se
	Helene Sjögren	helene.sjogren@vgregion.se
	Lars Palmqvist	lars.palmqvist@clinchem.gu.se
	Irina Golovleva	irina.golovleva@vll.se
	Anna Norberg	anna.norberg@vll.se
Denmark	Eigil Kjeldsen	eigikjel@rm.dk
	Mette Klarskov Andersen	mette.klarskov.andersen@rh.regionh.dk
Norway	Randi Hovland	randi.hovland@helse-bergen.no
	Martine Eilert-Olsen	mareil@ous-hf.no
Finland	Anne Juvonen	anne.juvonen@hus.fi
	Satu Häikiö	satu.susanna.haikio@tyks.fi
	Kati Pulkkinen	kati.pulkkinen@islab.fi
	Ritva Karhu	ritva.karhu@fimlab.fi
	Hannele Räsänen	hannele.rasanen@nordlab.fi
Iceland	Jón Jóhannes Jónsen	jonjj@landspitali.is
Estonia	Pille Tammur	pille.tammur@kliinikum.ee
Lithuania	Vaidas Dirse	vaidas.dirse@santa.lt

The Leukemia Genetics working group meet once a year. The meeting is divided in two two-day-meetings. All participants (besides the coordinator) are clinical geneticists working at the laboratories responsible for the genetic diagnostics in the Nordic countries. The coordinator, Ulrika Norén Nyström (pediatric oncologist) participate together with Prof. Bertil Johansson in both meetings. In March and April 2019, the meetings took place at Arlanda Airport in Sweden and the Swedish leukemia patients diagnosed in 2018 were reviewed during the first meeting and the rest of the Nordic and Baltic leukemia patients at the second meeting. All pediatric AML patients as well as both pediatric and adult ALL patients were evaluated. During the review meetings all diagnostic genetic results are reviewed, such as karyograms, targeted analyses for the mandatory aberrations (FISH- and/or PCR), but also, if they exist, results from SNP-arrays or other types of analyses done at diagnosis are discussed. A complete karyotype is decided, considering all diagnostic results we know of for each patient. The genetic group defining the patient in the treatment protocol is finally decided by the "worst counts" –principle. Representatives from the Baltic ALL genetic laboratories (Estonia and Lithuania) always participates in the meetings since 2018.

Cytogenetic results for NOPHO patients diagnosed with ALL and AML in 2018

The genetic results at diagnosis in totally 10 infants, 244 children and 55 adults diagnosed with ALL, and 49 children with AML were reviewed at our meetings.

Genetic group - ALL (all ages)	n	%
t(9;22)	7	2,3
KMT2A-rearrangement	10	3,2
Low hypodiploidy (30-39)	4	1,3
Near hapodiploidy (23-29)	0	0
iAMP21	2	0,6
dic(9;20)	9	2,9
t(1;19)	7	2,3
t(12;21)	37	12
High hyperdiploidy (51-67)	79	25,6
Other clonal aberration	111	35,9
Normal	35	11,3
No result / unknown	8	2,6
Total	309	100

Genetic group AML	n	%
t(8;21)	4	8,2
inv (16)	2	4,1
t(9;11)	5	10,2
KMT2A other than t(9;11)	9	18,4
t(15:17)	0	0
FLT3-ITD pos / NPM1wt	2	4,1
Other clonal aberration	18	36,7
Normal	9	18,4
Total	49	100

The Cytogentic application in the NOPHO registry

All genetic laboratories are now successfully reporting the diagnostic genetic results for ALL and AML in the cytogenetic registration application in the CCEG. A new application with modifications according to the ALLTogether protocol was discussed and planned at the meetings.

Umeå 18-03-2020
Ulrika Norén Nyström

Publications involving the Leukemia Genetics wg from 2018

1. **Toft N, Birgens H, Abrahamsson J, Grišķevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson ÓG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Marquart HV, Madsen HO, Norén-Nyström U, Schmiegelow K.** *Results of NOPHO ALL2008 treatment for patients 1-45 years with acute lymphoblastic leukemia.* Leukemia. 2018 Mar;32(3):606-615.
2. **Borssén M, Nordlund J, Haider Z, Landfors M, Larsson P, Kanerva J, Schmiegelow K, Flaegstad T, Jónsson ÓG, Frost BM, Palle J, Forestier E, Heyman M, Hultdin M, Lönnerholm G, Degerman S.** *DNA methylation holds prognostic information in relapsed precursor B-cell acute lymphoblastic leukemia.* Clin Epigenetics. 2018 Mar 5;10:31.
3. **Oskarsson T, Söderhäll S, Arvidson J, Forestier E, Frandsen TL, Hellebostad M, Lähteenmäki P, Jónsson ÓG, Myrberg IH, Heyman M; Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL Relapse Working Group.** *Treatment-related mortality in relapsed childhood acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2018 Apr;65(4).
4. **Espersen ADL, Norén-Nyström U, Abrahamsson J, Ha SY, Pronk CJ, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Palmqvist L, Hasle H.** *AML with t(7;12)(q36;p13) is associated with infancy and trisomy 19. Data from NOPHO-AML and review of the literature.* Genes Chromosomes Cancer. 2018 Jul;57(7):359-365.
5. **Olsson L, Lundin-Ström KB, Castor A, Behrendtz M, Biloglav A, Norén-Nyström U, Paulsson K, Johansson B.** I*mproved cytogenetic characterization and risk stratification of pediatric acute lymphoblastic leukemia using single nucleotide polymorphism array analysis: A single center experience of 296 cases.* Genes Chromosomes Cancer. 2018 Nov;57(11):604-607.
6. **Bager N, Juul-Dam KL, Sandahl JD, Abrahamsson J, Beverloo B, de Bont ESJM, Ha SY, Jahnukainen K, Jónsson ÓG, Kaspers GL, Kovalova Z, Lausen B, De Moerloose B, Noren-Nyström U, Palle J, Saks K, Zeller B, Kjeldsen E, Hasle H.** *Complex and monosomal karyotype are distinct cytogenetic entities with an adverse prognostic impact in paediatric acute myeloid leukaemia. A NOPHO-DBH-AML study.* Br J Haematol. 2018 Nov;183(4):618-628.
7. **Nordlund J, Marincevic-Zuniga Y, Cavelier L, Raine A, Martin T, Lundmark A, Abrahamsson J, Norén-Nyström U, Lönnerholm G, Syvänen AC.** *Refined detection and phasing of structural aberrations in pediatric acute lymphoblastic leukemia by linked-read whole-genome sequencing.* Sci Rep. 2020 Feb 13;10(1):2512.

NOPHO Leukemia Biobank Working Group

Members of the board		
Chair	Trond Flægstad	Trond.Flaegstad@unn.no
Denmark	Henrik Hasle	hasle@dadlnet.dk
Finland	Olli Lohi	olli.lohi@tuni.fi
Iceland	Ólafur G. Jónsson	olafurgi@landspitali.is
Norway	Trond Flægstad	Trond.Flaegstad@unn.no
Sweden	Britt-Marie Frost	britt-marie.frost@kbh.uu.se
Estonia will be appointed -	Kristi Lepik	kristi.lepik@lastehaigla.ee
Latvia will be appointed		
Lithuania will be appointed		
Young NOPHO clinical	Morten Herlin	mortherl@rm.dk
Young NOPHO laboratory	Maike Bensberg	maike.bensberg@liu.se
Scientific committee	Kees-Jan Pronk	kees-jan.pronk@med.lu.se
Leukemia registry	Mats Heyman	Mats.Heyman@ki.se
Leukemia Biology	Sofie Degerman	sofie.degerman@umu.se
NOPHO cytogenetics group	Ulrika Noren-Nyström	ulrika.norennystrom@umu.se
Coordinator	Victoria Wennberg (f.d. Larsson)	victoria.larsson@akademiska.se

NOPHO
Leukemia Biobank

Victoria Wennberg, Mats Heyman, Britt-Marie Frost, Henrik Hasle and Trond Flægstad at NOPHO biobank meeting 2018 in Aalborg, Denmark.

LLC (Leukemia and Lymphoma Committee) and NOPHO board decided in 2006 to build a Nordic biobank for the future collaborative NOPHO-studies of childhood ALL and AML.

Samples as part of a research project, Lönnerholm et al., have been collected since the beginning of the 90s. These samples have been included in NOPHO leukemia biobank.

The biobank is located in Uppsala Biobank, Uppsala Sweden. The samples are received and prepared at UCR (Uppsala Clinical Research Center).

During 2019 the bank was moved from Pathology department of the Academic Hospital, Uppsala to UCR.

An extensive work has been done and is ongoing to modernize banking procedure and the data storage. As well as updating and controlling data.
A new safe laboratory management software (FreezerPro®) is installed.

Åsa Forsberg and Ninni Pudas are ready to prepare cells from submitted patient material.
Sofia Gustavsson arranges cell aliquots in the nitrogen tanks.

ALLTogether

The Biobank will collect bone marrow and blood samples at diagnosis and relapse from the Nordic and Baltic countries, both for children and adults up to 45 years.
ALLTogether: samples from diagnosis, day 15, d 29 and d 71 (remission).
There will be an amendment to the protocol with sampling procedures, where spinal fluid also will be included.

Constitutional DNA in addition to leukemic DNA

The Biobank want to sample constitutional DNA. For the new ALLTogether protocol, this should be included in the protocol and the informed consent.
It is suitable to take a remission blood sample 71 days after diagnosis.

How to retrieve samples from the Biobank

The study proposal must be accepted as a NOPHO project by the scientific committee and the board, it will then be reviewed by the biobank board. The Biobank must be acknowledged in scientific papers if the samples are retrieved.
Exception: International studies on rare leukemias where a few samples are asked for.

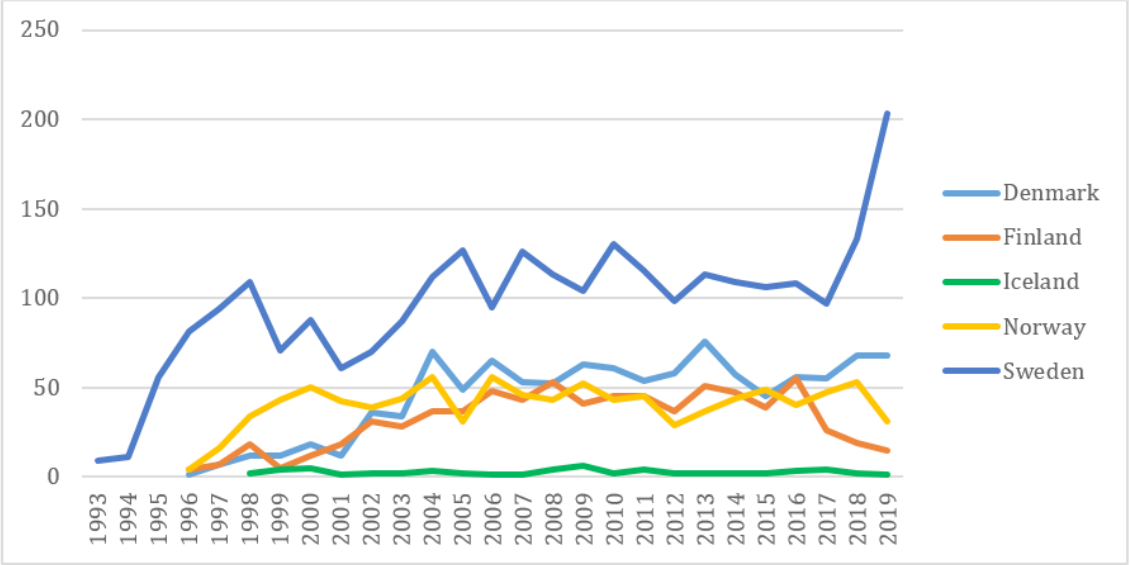
Finnish samples

We are planning to collect all the Finnish samples into Finnish Hematology Registry and Clinical Biobank (FHRB) in Helsinki. Turku & Oulu are still considering.
The sample collection, processing and storing are paid by the public sector (communities), so that is a big advantage. The samples will be marked with the NOPHO/A2G code, and can be retrieved on the basis of NOPHO/A2G approval and after acceptance by FHRB Scientific committee.

A2G biobank group

Member from NOPHO are Britt-Marie Frost and Victoria Wennberg.

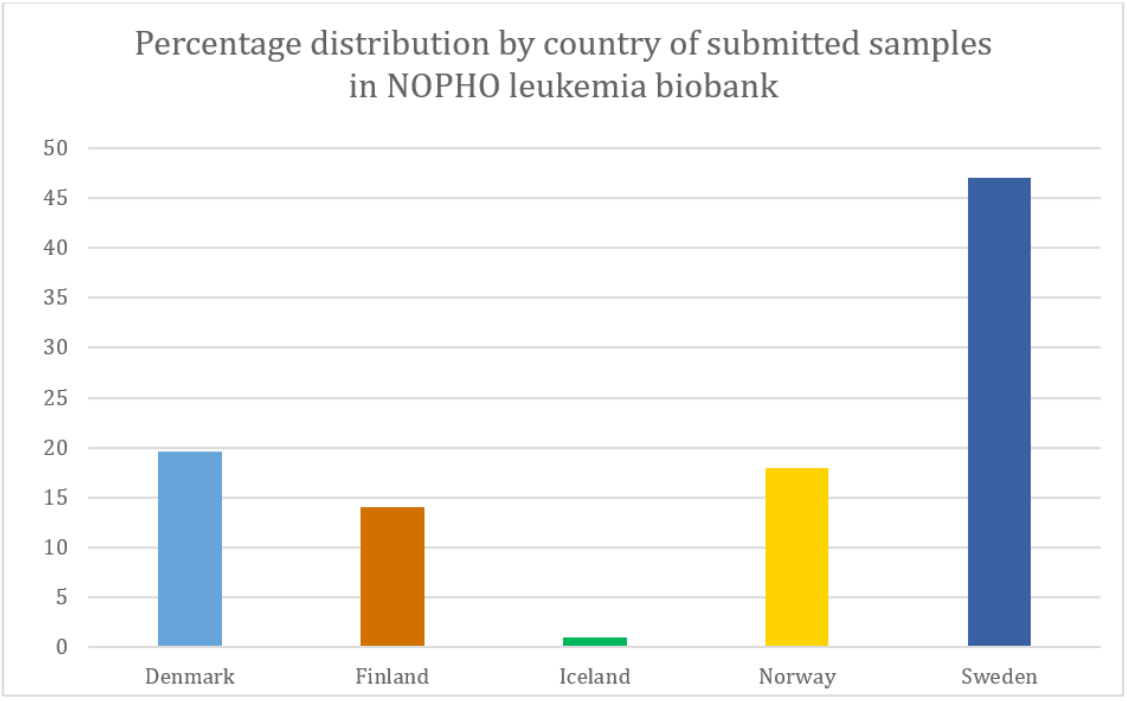
Current content in the biobank: 5654 samples (years 1993-2019).
Extracted DNA in biobank is now available from more than 1800 samples and some of them even RNA.
Yearly collected: approx. 270 samples.
No of samples used in research studies: 1165 (cell pellets/DMSO frozen cells).



The samples before 2006 are imported samples from FMCA.

Since the start of NOPHO biobank, the number of submitted samples has remained stable until recent years, when there has been a decrease in samples from Finland and Norway.

The increase of number of samples from Sweden can be explained by referral tests and start of ALLTogether.



LL Biology Working Group

Linda Fogelstrand	Linda.Fogelstrand@vgregion.se	(chair)
Olli Lohi	olli.lohi@tuni.fi	(chair)
Alessandro Camponeschi	alessandro.camponeschi@gu.se	
Anders Castor	anders.castor@med.lu.se	
Andreas Lennartsson	andreas.lennartsson@ki.se	
Ann Nordgren	ann.nordgren@ki.se	
Ann Elisabeth Åsberg	anneliasgm@gmail.com	
Anna Andersson Anna	anna.andersson@med.lu.se	
Anna Poluha Anna	anna.poluha@akademiska.se	
Ann-Christine Syvänen	Ann-Christine.Syvanen@medsci.uu.se	
Bertil Johansson	bertil.johansson@med.lu.se	
Birgitte Klug Albertsen	biralber@rm.dk	
Colm Nestor	colm.nestor@liu.se	
Dongfeng Chen	dongfeng.chen@gu.se	
Erik Forestier	erik.forestier@medbio.umu.se	
Erik Malmberg Delsing	erik.malmberg@gu.se	
Gisela Barbany	gisela.barbany@ki.se	
Goda Vaitkeviciene	goda.vaitkeviciene@vuvl.lt	
Gudmar Lönnerholm	gudmar.lonnerholm@kbh.uu.se	
Hanne V. Marquart	hanne.marquart@dadlnet.dk	
Hans O. Madsen	hans.o.madsen@regionh.dk	
Hartmut Vogt	hartmut.vogt@liu.se	
Henrik Hasle	hasle@dadlnet.dk	
Inga Maria Rinvoll Johannsdottir	inga@rinvoll.com	
Ingegerd Öfverholm	ingegerd.ofverholm@ki.se	
Jessica Nordlund	jessica.nordlund@medsci.uu.se	
Johan Malmros	johan.malmros@ki.se	
Jonas Abrahamsson	vobjab@gmail.com	
Josefine Palle	josefine.palle@akademiska.se	
Jukka Kanerva	jukka.kanerva@fimnet.fi	
Kajsa Paulsson	kajsa.paulsson@med.lu.se	
Karin Mellgren	karin.mellgren@vgregion.se	
Katrine Ask	katrine.ask@regionh.dk	
Kees-Jan Cornelis Pronk	kees-jan.pronk@med.lu.se	
Kimmo Porkka	kimmo.porkka@helsinki.fi	
Kjeld Schmiegelow	kschmiegelow@rh.dk	
Kristian Løvvik Juul-Dam	juuldamk@gmail.com	
Lars Palmqvist	lars.palmqvist@clinchem.gu.se	
Linda Holmfeldt	linda.holmfeldt@igp.uu.se	
Line Groth-Pedersen Line	line.grothpedersen@rh.regionh.dk	
Magnus Hultdin	magnus.hultdin@vll.se	
Maria Thastrup	maria.thastrup@regionh.dk	
Matilda Degn	matilda.degn.vinther@regionh.dk	
Mats Heyman	mats.heyman@ki.se	
Mervi Taskinen	mervi.taskinen@hus.fi	
Mette Klarskov Andersen	mette.klarskov@dadlnet.dk	
Mindaugas Stoskus	mindaugas.stoskus@santa.lt	
Morten Herlin	m.herlin@rn.dk	
Nikolas Herold	nikolas.herold@ki.se	
Nina Friesgaard Øbro	nina.friesgaard@rh.regionh.dk	

Olle Sangfelt	olle.sangfelt@ki.se
Randi Hovland	randi.hovland@helse-bergen.no
Samppa Ryhänen	samppa.ryhanen@hus.fi
Shumaila Sayyab	shumaila.sayyab@medsci.uu.se
Signe Modvig	signemodvig@gmail.com
Sofie Degerman	sofie.degerman@medbio.umu.se
Tekla Harju	tekla.harju@oulu.fi
Thomas Frandsen	thomas.leth.frandsen@regionh.dk
Trond Flægstad Trond	trond.flaegstad@unn.no
Ulla Wartiovaara-Kautto	Ulla.Wartiovaara-Kautto@hus.fi
Ulrika Norén-Nystrom	ulrika.norennystrom@pediatri.umu.se
Vaidas Dirse	Vaidas.Dirse@santa.lt
Vasilios Zachariadis	vasilios.zachariadis@ki.se
Yanara Marincevic-Zuniga Yanara	yanara.marincevic_zuniga@medsci.uu.se
Zahra Haider	zahra.haider@umu.se

Organization

The group **Leukaemia & Lymphoma Biology Working Group (LL Biology WG)** includes ALL, AML and lymphoma researchers ranging from experimental researchers to pediatric oncologists.

The group is open for all NOPHO members and their coworkers with an interest in biology research on leukemia/lymphoma. Group members therefore shift over time. Also non-NOPHO members are welcome for an initial meeting before applying for NOPHO membership. The co-chairs Linda Fogelstrand and Olli Lohi have strong backgrounds in basic research and represent diagnostics (LF) and clinical (OL) expertise, and research focus primarily on ALL (OL) and AML (LF). OL is also a member of the ALLTogether scientific committee.

The LL Biology WG reports to the LLC, but many of the items are also discussed in the ALL-WG and AML-WG.

Aims

The aims of the group are:

- Bring together clinicians, experimental researchers and diagnostic experts on childhood leukemia and lymphoma
- Increase knowledge of ongoing NOPHO biology-related research projects by regular updates
- Foster collaboration; increase shared projects, technolocy/expertise and funding applications
- Enhance and coordinate utilization of NOPHO biobank material and already obtained data including genomic data
- Plan novel research projects in conjunction with upcoming/ongoing protocols
- Avoid parallel studies
- Assist the NOPHO Scientific committee in evaluating project proposals and if requested aid in ranking research proposals for the NOPHO Biobank

Meetings and results

The group gathers at biannual meetings which are held back-to-back with the ALL/ALLTogether WG meetings. The meetings have a common structure; one scientific theme with invited speaker, presentations of new project proposals (NOPHO projects and local projects), updates of ongoing NOPHO projects and update from the NOPHO biobank. In 2019, the WG held two meetings; in March and September, both at Arlanda, Stockholm, Sweden.

The theme for the meeting in March 2019 was studies connected to ALLTogether. The invited speaker Frank van Leeuwen from Utrecht, The Netherlands, presented on Xenograft banking of high risk ALL. Nikolas Herold from Stockholm presented his ongoing and planned studies on SAMHD1 in ALL and AML, and Arja Harila-Saari from Uppsala presented a project about novel biomarkers for neurotoxicity in ALL. The group discussed how to work on project proposals, in order to give the best output when new projects are presented before they are sumitted to the NOPHO Scientific committee. Several proposed ALLTogether studies were presented by other members fo the group, as were updates of ongoing NOPHO studies on ALL and AML.

The 2019 September meeting was centered on the protein machinery of the cells. The invited speaker Pekka Jaako from Gothenburg presented on 'Linking defective ribosome assembly to acute leukemia'. This was followed by a presentation from Olle Sangfelt, Stockholm on 'Targeting oncogenic SCF Ubiquitin Ligases for cancer therapy'. The ubiquination theme was continued by Aljona Maljukova from Stockholm presenting on WEE1 kinase - a therapeutic target in MLL acute lymphoblastic leukemia through regulation of RUNX1? Andreas Lennartsson then continued with a presentation of his projects on MLL (KMT2A)-translocatios in AML. Ongoing, new and updated projects on both ALL and AML were presented by members of the group.

The 2019 meetings were financed by planning grant from the Swedish Childhood Cancer Foundation (3 year grant 2017-2019). Around 32 and 24 participant attended the two different meetings. In addition to discussions on techniques, new and updated projects, the group has also been given regular updates from the Biobank WG. During the year, LL Biology WG has contributed a young laboratory-focused member to the Biobank WG.

Future perspectives

Meetings will continue to be held biannually, in March and September 2020, the first at Arlanda Airport. Meetings will be financed by the planning grant from the Swedish Childhood Cancer Foundation, which has been extended to 2020. Travel expenses are covered by the institutions of the participants. The theme of the first meeting 2020 will be 'Novel targeted therapies in early phase clinical trials'. Invited speakers are Karsten Nysom, Copenhagen, and Torben Ek, Gothenburg.

Olli Lohi and Linda Fogelstrand
March 2020

Infant Leukemia Working Group

Coordinator	Birgitte Lausen (DK)
Denmark	Birgitte Lausen
Finland	Olli Lohi
Iceland	Solveig Hafsteinsdottir
Norway	Anne Grete Bechensteen
Sweden	Anders Castor
	Ulrika Noren Nyström (cytogenetics)
	Mats Heyman (data center)
Young NOPHO	Sauli Palmu, Finland

The main activity of the NOPHO Infant Leukemia group is to take care of the international Interfant studies. The group had a meeting in January 2019. The annual meeting in the international Interfant group was held in May 2019 during the SIOPe meeting in Prag.

Status of Interfant-06

The current protocol opened in 2006 with Rob Pieters as chair of the study. The randomization was closed pr. 1st Aug. 2016 when the target sample size was reached. The latest version of the Interfant-06-protocol (version 17) was released in April 2017 with changes in the Asparaginase treatment; only PEG-asparaginase should be used, doses should not be dose-adjusted according to age, and asparaginase drug- and antibody levels should be monitored.

The Interfant-06 Study Report released in May 2018 with the final report from the randomized study closed in Aug. 2016 showing no significant better survival in the experimental arm. Overall outcome is not different from the Interfant-99 protocol, apart from a slight increase in overall survival for the "original" groups.

Until a new Infant ALL protocol will be released it is still recommended to continue Interfant-06 version 17 and continue registration. For new infant ALL patients treated according to Interfant-06 protocol in Europe and Australia with KMT2A-mutations it is possible to participate in a Phase 1-2 study with Blinatumomab as monotherapy, a 4-week continuous infusion between induction an Phase 1B (The Nordic site is at Rigshospitalet in Copenhagen).

A manuscript describing the results from the Interfant-06 study is recently published in JCO.

Publications on Infant ALL-studies, where NOPHO is involved

- **Pieters R, De Lorenzo P, Ancliffe P, Aversa LA, Brethon B, Biondi A, Campbell M, Escherich G, Ferster A, Gardner RA, Kotecha RS, Lausen B, Li CK, Locatelli F, Attarbaschi A, Peters C, Rubnitz JE, Silverman LB, Stary J, Szczepanski T, Vora A, Schrappe M, Valsecchi MG.** *Outcome of Infants Younger Than 1 Year with Acute Lymphoblastic Leukemia Treated with the Interfant-06 Protocol: Results from an International Phase III Randomized Study.* J Clin Oncol. 2019 Sep 1;37(25):2246-2256. doi: 10.1200/JCO.19.00261. Epub 2019 Jul 8.
- **Albertsen BK, Harila-Saari A, Jahnukainen K, Lähteenmäki P, Riikonen P, Möttönen M, Lausen B.** *Asparaginase treatment in infants with acute lymphoblastic leukemia; pharmacokinetics and asparaginase hypersensitivity in Interfant-06.* Leuk Lymphoma. 2019 Jan 11:1-7.
- **Mann G, Attarbaschi A, Peters C, Schrappe M, Lorenzo P De, Hann I, Rossi G De, Felice M, Lausen B, LeBlanc T, Szczepanski T, Ferster A, Janka-Schaub G, Rubnitz J, Silverman L B, Stary J, Campbell M, Li C K, Suppiah R, Biondi A, Vora A, Valsecchi MG and Pieters R on behalf of the Interfant-99 Study Group.** *Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia - Results from the Interfant-99 Study.* Blood 2010; 116 (15): 2644-2650
- **Van der Linden M, Valsecchi MG, De Lorenzo P, Möricke A, Janka G, Leblanc TM, Felice M, Biondi A, Campbell M, Hann I, Rubnitz JE, Stary J, Szczepanski T, Vora A, Ferster A, Hovi L, Silverman LB and Pieters R.** *Outcome of congenital acute lymphoblastic leukaemia treated on the Interfant-99 protocol.* Blood 2009; 114: 3764-3768.
- **Lönnerholm G, Valsecchi MG, De Lorenzo P, Schrappe M, Hovi L, Campbell M, Mann G, Janka-Schaub G, Li CK, Stary J, Hann I, Pieters R; Interfant-99 study group.** *Pharmacokinetics of high-dose methotrexate in infants treated for acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2009 May; 52(5): 596-601.
- **Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG.** *A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.* Lancet 2007; 370: 240-250.

Copenhagen 20th March 2020
Birgitte Lausen
Chair of the NOPHO Infant Leukemia working group

Pharmacology Working Group

Chair	Goda Vaitkeviciene
Denmark	Birgitte Klug Albertsen
	Kjeld Schmiegelow
	Henrik Schrøder
Finland	Jukka Kanerva
	Riitta Niinimäki
	Samppa Ryhänen
Iceland	Ólafur G. Jónsson
Norway	Bendik Lund
	Tove Anita Nystad
	Stein Bergan
Lithuania	Goda Vaitkeviciene
Sweden	Arja Harila-Saari
	Cecilia Langenskiöld
	Johan Malmros
	Nina Mogensen
	Jesper Heldrup (MTX)
	Per Rydberg (Lab representative)
	Ranaa El-Edelbi (Chair of Pharmacists WG)
	Staffan Eksborg
Young NOPHO	Stine Nygaard Nielsen
	Rikke Hebo Larsen
	Cecilie Utke Rank (Adult haematologies)

NOPHO Pharmacology group met twice since the last report, on September 17, 2019 and February 18, 2020 in Stockholm.

Changes in the list of the members of the group:
1. Malin Lindqvist Appell, Linköping, Sweden – stepped down as a Swedish representative;
2. Stein Bergan, professor in clinical pharmacology in Oslo University – joined the group as the representative from Norway.

The main areas of interest in the Pharmacology group remained: PK/PD studies in ALL maintenance therapy, asparaginase and high dose methotrexate; association of body mass index with pharmacokinetics of antileukemic drugs (VCR, HD MTX) and subsequently with the outcome of the disease.

Maintenance therapy

1. DNA-thioguanine nucleotide concentration as a predictor of relapse revealed reduction of the risk of relapse by 28% for every 100 fmol/µg DNA-TG increment in the MRD positive pediatric cohort of the NOPHO ALL2008 protocol (Nielsen et al., Lancet Oncology, 2017). Meta-analysis is performed to investigate the findings in a larger patient group (children and young adults) across different treatment protocols. Preliminary results from the analysis of 14,897 DNA-TG measurements from 1957 patients in six international cohorts show an increment of every 100 fmol/µg DNA-TG to remain as a significant risk factor for relapse (Linea Natalie Toksvang, PhD student, Copenhagen).
2. Pilot feasibility study of TEAM strategy (Thiopurine Enhanced ALL Maintenance therapy) – adding

6-thioguanine (2.5–12.5 mg/m^2/day) to concurrent conventional 6MP/MTX maintenance therapy was carried out in Copenhagen (led by Kjeld Schmiegelow and PhD student Rikke Hebo Larsen). Inclusion is completed: 33 patients included (five adults). Last patient completes therapy in March, 2020. Documented adverse events: four SAEs (one early CNS-relapse, one renewed symptoms of pancreatitis (hepatic and kidney affection), one osteonecrosis (adult) and one frontal sinuitis (adult)) and no SUSARs.

3. TEAM study as a part of the randomization in ALLTogether protocol (R3) is undergoing final preparational works. The aim is to initiate TEAM study before 01-10-2020. ALLTogether Master protocol TEAM study National PIs meeting is planned for May 26, Tuesday, in Copenhagen.
4. ALLTogether Master protocol maintenance therapy pharmacokinetics/-dynamics substudy. Since maintenance therapy is important for all risk groups and ages, 6MP/MTX metabolite concentrations will be monitored at three months intervals for all the ~8,000 patients anticipated to be included in A2G. The study is going to explore a detailed map and association of 6MP/MTX metabolite profiles to risk of toxicities and primary A2G events.
5. Recruitment to the Pilot study on Allopurinol use during ALL maintenance phase is continued (Jonas Abrahamsson/ Torben Ek). The study is investigating if adding of allopurinol in patients with wildtype TPMT leads to an increment in 6TG and reduction in 6MMP levels without increasing myelosuppression or other side effects. Opened in Sweden and Finland. So far 35 children included (out of 60 planned). No SUSARs or unexpected toxicity. Patients without central line are eligible as capillary sampling is possible. Three EDTA-tubes with capillary blood (BD 500 µL/tube) should be sent to BONKOLAB.

Asparaginase studies

1. GRASPA study (NOR-GRASPALL 2016 Asparaginase encapsulated in erythrocytes (GRASPA®)) (Line S. Lynggaard, PhD student and Birgitte Klug Andersen). Open in all seven countries using the NOPHO ALL2008 and/or ALLTogether Pilot protocol. Aiming to include 50 patients, 45 included until March, 2020. One severe hypersensitivity reaction so far. No SUSARs.
2. Asparaginase TDM (Birgitte Klug Andersen). Analysis of the NOPHO ALL2008 data (by Sofie Gottschalk Højfeldt, PhD student) showed a significantly increased risk of relapse in the group of the patients with truncated asparaginase and confirmed the importance of asparaginase TDM.
3. Extended sampling during asparaginase treatment since 01/02/2017 for pharmacokinetic studies of PEG-asparaginase after i.m. administration in patients (children and adults) treated on the ALL2008 protocol (Birgitte Klug Albertsen).
4. The Association Between Asparaginase Enzyme Activity Levels and Toxicities in Childhood Acute Lymphoblastic Leukaemia in NOPHO ALL2008 (Line S. Lynggaard and Birgitte Klug Albertsen).
5. Pharmacokinetics and immunogenicity of the first dose of PEG-asparaginase. An ALLTogether pilot study (Birgitte Klug Albertsen).
6. Asparaginase started measuring for all patients treated according to the ALLTogether Pilot protocol. Registration in the RedCap system. Reported back from the lab if no asparaginase activity is detected. Plans for the scientific studies in ALLTogether cohort – to compare effect as well as side effects for i.m. vs i.v. asparaginase infusion; to continue asparaginase PK investigations.

Methotrexate studies

1. The study proposal on severely delayed methotrexate with renal toxicity. Initiative by the PdL Toxicity working group in collaboration with I-BFM. NOPHO representative Torben Mikkelsen. According to the study plan, it is suggested that PI's from each country or international protocol would collect clinical and lab data on patients with severely delayed MTX elimination. Pharmacology group decided, as the data needed to be collected for the study are intensive, participation in the study should be discussed within the NOPHO national groups. Co-authorship of the national PIs will also need to be discussed.
2. As a result of the collaboration with Cincinnati group (Jesper Heldrup as a NOPHO representative) where the NOPHO HD MTX data were used for analysis, web-based tool as a quantitative model of the three-compartment high dose methotrexate PK had been developed. The tool is now freely accessible on the web: mtxpk.org. The aim of the software is to guide glucarpidase dosing in patients with ALL.

3. It was decided by the Pharmacology group, agreed by Jesper Heldrup and by the national representatives, that HD MTX data collected so far from the NOPHO ALL-92, -2000 and -2008 protocols patients would be downloaded into the NOPHO database (e.g. NOPHO-CARE or other, to be decided). Access to the data will be provided to the PIs of the studies that will be approved by the NOPHO SC and national ECs.
4. BMI and the association with high dose MTX (HD-MTX) in NOPHO ALL2008-protocol (Christina Egnell, PhD student, supervised and in collaboration with Susanna Ranta, Arja Harila Saari, Mats Heyman, Staffan Eksborg, Jesper Heldrup and Torben Mikkelsen). The project is dedicated to explore the effect of BMI on outcome and toxicities as well as drug pharmacokinetics. Results from the study of -92, -2000 and -2008 data revealed obesity at diagnosis of ALL to be an independent prognostic risk factor in older children aged 10 to 17 years (Egnell C, Ranta S et al, manuscript in preparation). Preliminary data by Jesper Heldrup from NOPHO ALL92, 2000 and 2008 showed no difference in MTX elimination or nephrotoxicity in obese patients. Hypothesis that BMI is associated with the altered PK through different kinds of HD-MTX associated toxicities (neutropenic fever, mucositis, liver toxicity etc.) and subsequent longer intervals between treatments is going to be checked in detailed evaluation of 44 obese patients in NOPHO ALL2008 protocol.

Collaboration with the Pharmacists group (Chair Ranaa El Edelbi)

The group continues working on the study on Improving handling for oral anticancer drugs used in hospital and home setting (part of the Ranaa El Edelbi PhD study). A project with the aim to prepare the handling procedures for the medical staff as well as for the parents on preparation and delivery of oral cytotoxic drugs, including reconstitution, protective personal equipment and handling patient waste (e.g. vomiting, diapers) and drug spill. Written recommendations and video material is under preparation.

Next meeting: Tuesday September 15, 2020 in Stockholm.

Goda Vaitkevičienė
Chair of the NOPHO Pharmacology WG
March 14, 2020

Other Disease Working Groups

Histiocytosis Working Group

Coordinator	Jan-Inge Henter	jan-inge.henter@ki.se
Denmark	Marianne Ifversen (HLH) Bodil Als-Nielsen (LCH)	marianne.ifversen@regionh.dk bodil.elise.thorhauge.als-nielsen@regionh.dk
Finland	Marika Grönroos Helena Olkinuora	marika.gronroos@tyks.fi helena.olkinuora@hus.fi
Iceland	Halldóra Þórarinsdóttir	halldorathorarins@yahoo.com
Norway	Maria Gunnes (HLH) Monica Cheng Munthe-Kaas (LCH)	maria.winther.gunnes@helse-bergen.no uxmomu@ous-hf.no
Sweden	Jan-Inge Henter Tatiana Greenwood	jan-inge.henter@ki.se tatiana.greenwood@ki.se
Lithuania	Jelena Rascon	jelena.rascon@gmail.com
Young NOPHO	Nikolas Herold	nikolas.herold@ki.se

Langerhans cell histiocytosis (LCH)

LCH-IV

For LCH-IV, each country has separate national coordinator(s). Finland is planning to enter LCH-IV.

Denmark: Karsten Nysom (karsten.nysom@regionh.dk) and Bodil Als-Nielsen (bodil.elise.thorhauge.als-nielsen@regionh.dk)
Sweden: Jan-Inge Henter (jan-inge.henter@ki.se), Désirée Gavhed (desiree.gavhed@ki.se). and applied for: Tatiana Greenwood (tatiana.greenwood@ki.se)
Norway: Monica Munthe-Kaas (uxmomu@ous-hf.no) and Bem Zeller (bzeller@ous-hf.no)

LCH-IV includes altogether seven interconnected studies "strata" *(in italics: enrolled Oct 7th, 2019):*

STRATUM I:	First-Line Treatment *(Group 1, n = 256; Group 2, n = 337)*
STRATUM II:	Second Line Treatment for non-risk LCH *(n = 77)*
STRATUM III:	Salvage Treatment for Risk LCH *(n = 15, all <2 years)*
STRATUM IV:	Stem Cell Transplantation for Risk LCH (HSCT) *(n = 0)*
STRATUM V:	Monitoring and Treatment of Isolated Tumorous and ND CNS-LCH *(n = 11)*
STRATUM VI:	Natural History and Management of "Other" SS-LCH *(n = 429)*
STRATUM VII:	Long-Term Follow-up *(n = x,*including dabrafenib=17 and vemurafenib=43 pts).

Recruitment is slower than expected. For Stratum I, Group 1 and 2, it will take another 4-5 years and 2-3 years, respectively, to reach the final sample size of 400 pat each, For Stratum II, about 3-4 more years will be needed (as a randomized phase II study instead of phase III, and with lower significance level, now at 20%). For Stratum III, it is considered probable to reach to planned 30 patients.
REMINDER: Amendment in Stratum II, Initial course: "Add PRED to all VCR/ARA-C pulses until week 24".

Some studies on LCH and MAPK inhibitors in the literature

Treatment for patients with BRAF V600 inhibitors such as with vemurafenib has been reported to have remarkable efficacy in adult patients with BRAF V600-mutant Erdheim-Chester Disease (ECD) (n=22) and LCH (n=4); Diamond EL, et al. JAMA Oncol 2018;4:384-388. Later the same remarkable efficacy was also observed in 54 children with refractory MS-LCH; Donadieu J, et al J Clin Oncol 2019;37:2857-2865.

Interestingly, it has also been reported that treatment with the MEK inhibitor cobimetinib was efficacious regardless of genotype, and responses were observed in patients (ECD =12, LCH =2, other histiocytoses =4) with ARAF, BRAF, RAF1, NRAS, KRAS, MEK1 (also known as MAP2K1) and MEK2 (also known as MAP2K2) mutations (Diamond EL, et al. Nature 2019;567:521-524).

The role of BRAF/MAPK inhibition in the treatment of LCH has also been reviewed in

- Héritier S, et al. BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. J Clin Oncol. 2016; 34: 3023-30
- Kolenová A, et al. Targeted inhibition of the MAPK pathway: emerging salvage option for progressive life-threatening multisystem LCH. Blood Adv. 2017; 1: 352-56
- Allen C, et al. Langerhans-Cell Histiocytosis. N Engl J Med 2018; 379: 856-68.
- Hogstad B, et al. RAF/MEK/extracellular signal-related kinase pathway suppresses dendritic cell migration and traps dendritic cells in Langerhans cell histiocytosis lesions. J Exp Med. 2018;215:319-36

Notably, although it appears as if BRAF and MEK inhibitors successfully can stabilize the clinical condition also of patients with severe LCH, they do not seem to cure the patients and it is as yet unknown when and how to stop these inhibitor treatments. See: Schwentner R, et al. Longitudinal assessment of peripheral blood BRAFV600E levels in patients with Langerhans cell histiocytosis. Pediatr Res. 2019 May;85(6):856-864.

From the Histiocyte Society Meeting 2018 on LCH

Donadieu J, et al (France): 53 children with refractory LCH and BRAFV600E mutation treated with Vemurafenib. Active Refractory Disease (ARD) (n=47) included 38 patients with and 9 without Risk Organ (RO), all refractory to at least one induction of vinblastine and steroid. Response was complete in 29 and partial in 18. No grade 3 or 4 side effect was observed during first 8 weeks. One death was observed in a patient who had a partial response and later received clofarabine. In symptomatic neurodegenerative CNS (ND) (n=6), shortly after onset two patients withdrew therapy for grade 3 side effect (severe weakness in one, skin rash in one). When provided for long term (n=4) a limited subjective improvement was observed but overall stable in 3 and improved in one, i.e. a limited impact on CNS ND LCH. The safety profile appears good with mainly grade 1 and 2 side effects.

Tardieu M, et al (France): 53 pediatric LCH patients treated since 2013 with vemurafenib for refractory BRAF (V600E) mutated LCH. Data available for 38 patients. 30/38 had skin reactions (rash, photosensitivity, xerosis, panniculitis), but no grade 4/5. 10% had dose reductions. There were no (pre)cancerous skin lesions.

Yang Y, et al (China): Dabrafenib in 21 patients with BRAFV600E+. There were 13 responses, 6 stable disease and 2 failures.

Eckstein O, et al (US): Altogether 18 patients treated with MAPK-inhibitor; ten patients had LCH-neurodegenerative disease (LCH-ND) diagnosed clinically and/or by imaging, while the remaining 8 patients had systemic disease with no LCH-ND. Two patients (11%) achieved a CR, 6 patients achieved a PR (33%), 3 patients only achieved stable disease (17%), and 7 patients experienced progression (38%). Of patients with LCH-ND, all 10 achieved at least PR (40%) or SD (60%), but 4 of these patients eventually progressed. Overall survival was 94% with a median follow-up of 20 months (range 1-42 months). Four of the 18 patients (22%) had a Grade 3-4 toxicity; 2 patients (11%) required dose reduction.

Marshall K, et al (UK): Started with MAPK inhibitors in 2015 and have a total of 14 patients (11 refractory MS, 2 ND-CNS, 1 missing info); 2 vemurafenib, 8 dabrafenib, 3 dabrafenib + trametinib. Median treatment 21 months. No patient discontinued treatment due to lack of response or toxicity. 2 children await response assessment. Treatment withdrawal was attempted in only 1 patient, after 6 and again after 22 months of vemurafenib, leading to disease reactivation within days on both occasions; thus it is unclear when treatment can be withdrawn.

Kumar A, et al (US): 5 children with MS RO+ LCH, BRAFV600E+. Four patients with HLH-2004 criteria (i.e. LCH-HLH). All in remission with dabrafenib.

Santa-Maria V, et al (Spain): Reported on 4 pat with neurodegenerative CNS-LCH (2018). Patients with radiological changes and neurological/neurophysiological abnormalities or neurocognitive dysfunction were treated with MAPK inhibitors (Dabrafenib or Trametinib). ND-LCH MRI changes were present in 4/128 (3%) patients. After 6 mo of treatment, 3/4 pat showed radiological improvement and 2/4 neurocognitive amelioration. After 6 months of treatment, 3/4 patients showed radiological improvement and 2/4 neurocognitive amelioration. The pat with the longest history of ND-LCH (8.5 yrs) had no evidence of clinico-radiological response.

Svojgr K, et al (Czech Republic): BMT and targeted therapy did not eradicate refractory LCH clone measured by BRAF positivity in peripheral blood.

From the Histiocyte Society Meeting 2019 on LCH

NACHO (North American Consortium for Histiocytosis) is preparing a Phase II Study of Cobimetinib in refractory LCH, ND-LCH and other histiocytic disorders (NACHO-COBI); 12 cycles (3 w therapy, 1 w off) 12 mo and then observation 12 mo.

Stephan Ladisch et al from the LCH-III study group reported that 12/43 (28%) deaths occurred the first 6 weeks of therapy, all <2-years old (and 21% during weeks 7–13). During the first 6 weeks all patients received weekly vinblastine + daily prednisolone and randomized to also receive 2-weekly methotrexate or not. All 12 had multisystem disease, and 11/12 RO+. The median therapy duration at death 18 days (7-39). The recorded causes of death were: disease progression and infection (4), disease progression (3), infection (2), disease related respiratory failure (1), thrombocytopenia and pulmonary haemorrhage (1), data unavailable (1). It was concluded that the response assessment at 6 weeks was too late, and an early change to inhibitors is suggested.

Ulrike Pötschger and LCH study group reported retrospective analyses on the impact of GI-involvement at diagnosis on overall survival in LCH patients and concluded that GI-involvement is associated with poorer survival and an independent prognostic risk factor (HR:2.5).

Lei Cui et al from Beijing reported on 102 LCH patients with successfully determined BRAF status. Cell-free (cf)BRAF-V600E at diagnosis was detected positive in 68% (55/81) of BRAF-V600E-mutated LCH patients. cfBRAFV600E was identified in 92% (23/25) of patients with MS RO+ LCH, 83% (19/23) of patients with MS RO- LCH, and 39% (13/33) of patients with SS LCH (P<0.001). The 6-week response rate was much lower in children with positive cfBRAF-V600E (35% vs 65%, P = 0.032). 2-year progression-free survival (PFS) was much lower in the cfBRAF-V600E positive group (35% ± 7.3% and 92% ± 5.2%, respectively; P < 0.001). Moreover, PFS was clearly worse in cfBRAF-V600E positive SS LCH patients (45% ± 20% vs. 100%, P = 0.003). cfBRAF-V600E positivity at week 6, week 12, week 52 of the first-line therapy or course 8 in the second-line therapy was also closely correlated to worse outcome of LCH patients.

Li Na et al from Beijing and Shanxi hospitals reported on 58 children evaluated for osteopontin (OPN) in the CSF and found that OPN was higher in patients with MS, RO+ and CNS risk lesions, and that it correlated with pituitary involvement.

Kenichi Sakamoto et al, for Japanese LCH study group reported on the incidence of ND-LCH and risk factors for development of ND-LCH based on 317 children (111 MFB, 196 MS) included in the JSLG 96/02 protocols 1996-2009, which is ARA-C based chemotherapy. The incidence of CNS-related permanent consequences was 9% in MFB and 28% in MS patients. The 10-year cumulative incidence of DI was 16% and of ND 4%. They had 15 pat with clinical ND-LCH. DI was a risk factor for ND-LCH development (HR: 9.3). No patient developed clinical ND-LCH prior to DI,

Hemophagocytic lymphohistiocytosis (HLH)

HLH-94: The Histiocyte Society protocol HLH-94 was based on the combination of chemotherapy and immunotherapy (VP-16, steroids and cyclosporin A), followed by HSCT. This protocol was succeeded by the HLH-2004 protocol. The final HLH-94 study summary was published in 2011 *(Trottestam H, et al. Blood 2011;118:4577-84).*

HLH-2004: This study was opened in January 2004 and closed for recruitment Dec 31, 2011. The main difference compared to the HLH-94 protocol was that cyclosporin A (CSA) was initiated upfront instead of at week 9. Five-year survival in children with (n = 168) and without (n = 201) family history/genetically verified FHL was 59% and 64%, respectively. The results are presented in *Bergsten E, et al. Blood 2017;130:2728-2738.*

NOTE: The Histiocyte Society recommends the HLH-94 protocol as standard of care, since it could not be shown that HLH-2004 was superior to HLH-94. Many nevertheless use CSA as a bridge to HSCT in primary HLH, starting not earlier than week 3, when dexamethasone is tapered (see guidelines below). The HLH-2004 diagnostic criteria (5/8 criteria) are still recommended.

There is no new international treatment study on HLH planned. Currently minor studies are performed on alemtuzumab in primary HLH and ruxolitinib (a Janus kinase (JAK) 1/2 inhibitor) in both primary and secondary HLH. Studies on anakinra in MAS-HLH (macrophage activation syndrome) is ongoing. Emapalumab (anti-IFN-gamma) has been approved by the FDA in the US, and application for approval in the EU has been submitted.

Recommendations on the use of the HLH-94 protocol: Guidelines on the use of the HLH-94 protocol in clinical practice has been prepared by the HLH Steering Committee of the Histiocyte Society (*Ehl S, et al. J Allergy Clin Immunol Pract 2018; 6: 1508-1517*).

Recommendations for management of HLH in adults: Guidelines have been published (*La Rosée P, et al. Blood. 2019 Jun 6;133(23):2465-2477*).

Recommendations for management of HLH at the ICU: Guidelines have been submitted.

HLH Registry: In preparing for a new international HLH study an HLH Registry is open for (1) all patients with primary immunodeficiencies predisposing to HLH, and (2) patients with active HLH that is not secondary to underlying conditions such as rheumatological disease, malignancy, metabolic disease or Leishmania infection. The study center is in Germany, and a nation-wide ethical application has been approved in Sweden. The study objectives include to:

- Collect data relevant for the assessment of feasibility and design of future interventional studies on the treatment of HLH, and the international patient recruitment potential for a future trial
- Collect data on current standard of care, time to transplant, and outcome after 1 year

In case of clinical questions you are welcome to contact *Jan-Inge.Henter@ki.se* or *Tatiana.Greenwood@ki.se*.

For diagnostic pre-treatment lymphocyte function (cytotoxicity) analyses, contact *Yenan.Bryceson@ki.se* at Karolinska Institutet. For sequencing of HLH-casing genes, you can contact *BiancaTesi@ki.se* at the clinical genetic laboratory at the Karolinska University Hospital.

Thrombosis and Haemostasis Working Group

Chair	Ruta Tuckuviene (DK)
Denmark	Birgitte Klug Albertsen, Marianne Hutchings Hoffmann
Estonia	Kadri Saks
Finland	Pasi Huttunen
Iceland	Olafur Gislí Jonsson
Norway	Ellen Ruud
Lithuania	Sonata Saulyte Trakymiene
Sweden	Susanna Ranta, Ulf Tedgård, Tony Frisk
Young NOPHO	Nadine Gretenkort Andersson (SE), Kirsten Jarvis (NO), Cecilie Utke Rank (DK), and Satu Långström (FI)

Meetings

Last meeting was held in Copenhagen 27st August 2019. The next meeting is planned on 9th of May 2020 in Trondheim.

Members

No changes.

Benign Haematology Committee

Benign Haematology Committee has been established. The main goal of the Committee is to represent benign Haematology in NOPHO and to support a collaboration between NOPHO WGs for Benign Haematology. Ulf Tedgård is the representative from Thrombosis and Haemostasis WG.

Registration of thromboses. WG (by Satu Långström) applies to NOPHO Scientific Committee on Registration of Thromboembolism (TE) in ALLTogether protocol in ALL patients (1-45 years old) in Nordic and Baltic countries.

Other planned studies

1. Long-term follow-up after DVT and PE in children and adults with ALL (Merete Eybye Dam)
   - Focus: Post-thrombotic syndrome (PTS) and QoL.
   - Inclusion: ALL patients aged 1-45 years, diagnosed 2008- 2016, treated according to the NOPHO ALL2008 protocol, and diagnosed with DVT and/or PE (N=177).
   - Approved by the NOPHO ALL WG and TE WG. National authorities will be applied.

2. Re-exposure with asparaginase after cerebral sinovenous thrombosis (CSVT) (Mette Tiedemann Skipper)
   - The primary aim is to explore the safety of re-exposure with asparaginase after clinical stabilization/normalization of symptoms after CSVT.
   - Inclusion: ALL patients aged 1-45 years, diagnosed 2008- 2017, treated according to the NOPHO ALL2008 protocol, and diagnosed with CSVT.
   - Approved by the NOPHO ALL WG; Events WG and TE WG.

3. Status of CSVT follow-up study – neurocognitive testing of neurotoxicity (Susanna Ranta and

Stavroula Anastasopoulou) ALL patients diagnosed 2008-2016 and treated according to the NOPHO ALL2008.

4. Cochrane systematic review on thromboprophylaxis in adult ALL patients treated with asparaginase. Protocol published (cochranelibrary.com). Cecilie Utke Rank: Review in progress.

5. Retrospective multicenter observational study of asymptomatic right atrial TE in children with ALL treated according NOPHO ALL2008 protocol (Kirsten Jarvis).

6. TE in Ponte di Legno (PdL)/ I-BFM. TE is the toxicity of interest in PdL. The data form is now on pilot study by PdL toxicity group.

Publications since March 2019

Jarvis KB, LeBlanc M, Tulstrup M, Nielsen RL, Albertsen BK, Gupta R, Huttunen P, Jónsson ÓG, Rank CU, Ranta S, Ruud E, Saks K, Trakymiene SS, Tuckuviene R, Schmiegelow K. *Candidate single nucleotide polymorphisms and thromboembolism in acute lymphoblastic leukemia - A NOPHO ALL2008 study.* Thromb Res. 2019 Dec;184:92-98.

Aalborg, March 2020
Ruta Tuckuviene
Chair of the NOPHO Thrombosis and Haemostasis Working Group

Late Effect Working Group

Chair	Riitta Niinimäki
Denmark	Catherine Rechnitzer Katja Majlund Harder
Finland	Mervi Taskinen Kirsi Jahnukainen
Iceland	Halldora Thorarinsdottir Solveig Hafsteindottir
Norway	Inga Maria Johannsdottir Einar Stensvold
Sweden	Cecilia Petersen Marianne Jarfelt
NOPHO leukaemia registry	Mats Heyman (SE)
Young NOPHO	Gitte Sorensen (DK) Jan Bernd Stukenborg (SE) Liisa Järvelä (FI) Pauliina Utriainen (FI) Simon Kranz (NO) Thorgerdur Gudmundsdottir (IC)

The group had two meetings in 2019:
One day meeting, Helsinki 15th of January.
Meeting during the NOPHO Annual meeting, Aalborg 4th of May 2019.

The main focus areas of the group are late effects related to the cancer treatment and long-term follow-up clinics in NOPHO countries.

Long-term follow-up (LTFU) clinics in NOPHO countries

The goal of the LE WG is that the collaboration between LTFU clinics in NOPHO countries will increase both clinically and scientifically.

Pancare activities

Pancare had 23rd meeting in Opatija, Croatia, April 24-26 and 24th meeting in Basel, Switzerland, September 11-13.

Collaboration with NOBOS

Collaboration with NOBOS is ongoing and the LE WG meetings are joint meetings.

Ongoing late effects studies in Nordic countries (presented in the meetings)

- Acute Lymphoblastic Leukemia Survivor Trial and Rehabilitation (ALL-STAR) study in Denmark (Liv Andrés-Jensen)
- HALLON study, late effects in ALL2008 HR chemo patients (Arja Harila-Saari/Päivi Lähteenmäki)
- Late effects in survivors of neuroblastoma in the Nordic countries – a study within ALiCCS (Filippa Norsker)
- NORDFERTIL (Jan Bernd Stukenborg)
- BRAIN SAVE: Late effects in brain tumor patients treated with proton versus photon therapy (Arja Harila-Saari)
- Late effects after treatment for childhood brain tumor (Anne Sophie Fischer)
- Gut microbiota during and after cancer treatment in childhood: Associations with cardiometabolic health and immunological recovery (Liisa Järvelä)
- Late effects in survivors of childhood acute lymphoblastic leukemia (Gitte Sorensen)

Next late effect meeting will be 12th of January 2021 in Helsinki.

Oulu, March, 2020

Riitta Niinimäki
Chair of the NOPHO Late Effect working group

Pharmacists Working Group

Sweden	Ranaa Akkawi El Edelbi (Chair) Magnus Dahlander Hilanah Shabo Tamara Al-Ani Sofia Jönsson Madeleine Persson Paula Hansson
Norway	Margrete Einen Gunn-Therese Lund Sørland Siri Utby Maria Larsen Kajsa Rinstad
Lithuania	Goda Vaitkeviciene Monika Grigentyte Laimis Dambrauskas
Finland	Sanna Veijalainen Ulla Taipale Taija Heikkinen
Denmark	Sigrid Otnes Søren Bisgaard Johansen Kathrine Bruun Svan Louise Larsen Maria Kaaberbøl Thorberg

Meeting

The Pharmacists Working Group has had two physical meetings, the 10th of April in Gothenburg and the 5th of December 2019 in Stockholm. We have also had monthly meetings via Lync/Skype.

Projects

The focus of the working group is the development of an educational session for the extravasation guideline (online education).
Status: still ongoing.

We are also working with a second project, the oral chemotherapy project where we want to collect and share information concerning reconstitution and handling of oral cytotoxic agents in the Scandinavian countries.
Status: We are now preparing patient specific leaflets and video films concerning the handling of cytotoxic drugs in home setting.

- A consensus document was achieved by the NOPHO pharmacist group on how oral anticancer drugs should be handled at home.
- Preparing training guidelines for nurses to train the caregivers in the handling procedures of oral anticancer drugs in home setting.
- Educational material is prepared for the nurses on how oral anticancer drugs should be handled at home.

Ranaa and Magnus are also helping the NOPHO pharmacology group to set an education in pharmacology and pharmacokinetics for both pharmacists and doctors.

Ranaa Akkawi El Edelbi
Chair of the NOPHO Pharmacists WG
Stockholm, March 4, 2020

NOPHO/NOBOS Working Group on Ethics (WGE)

Chair	Lisa Törnudd, elected 2018
Secretary	Cecilia Bartholdson, elected 2018
Denmark	Trine Brøner Gitte Petersen Astrid Sehested Pernille Wendtland Edslev
Finland	Marika Grönroos Kristian Juusola Johanna Viitanen
Iceland	Sigrún Þóroddsdóttir
Norway	Grete Ringheim Anne Gro Wesenberg Rognlien
Sweden	Johan Arvidson Anders Castor Sara Karlsson Frans Nilsson Pernilla Pergert Jennie Stigmar

The intention of the NOPHO/NOBOS Working Group on Ethics (WGE) is to support the knowledge in ethics and promote clinical ethics support (CES) in paediatric oncology as well as identifying and raising ethical questions within the field.

Organization

The group has had one 2-day meeting, one 3-day meeting and has delivered the first part of the second two-part ethics-training program.

Meetings of the WGE during 2019

17-19 Mar 2019, Stockholm, Sweden. The theme of the meeting was genetics and the ethics of screening for cancer predisposing conditions.
17-20 Nov 2019, Turku, Finland. The theme of the meeting was human dignity and teaching ethics in the clinical setting.
In addition, working meetings for the course organizers were held.

Completed course arranged by the WGE

1-4 Oct 2019, Sollentuna, Sweden (Second course: Guiding Ethics Case Reflection Rounds, part I)

Upcoming meetings of the WGE

26-28 Apr, 2020, Sweden
15-18 Nov 2020, Norway

Upcoming course arranged by the WGE

25-27 Mar 2020, Guiding Ethics Case Reflection Rounds, part II

Funding

Pergert (co-applicant: Castor) has received a grant for the WGE for 2018-2020 (PL2017-0002) from the Swedish Childhood Cancer Foundation.

Annual Report 2019

Activities of the WGE during the last year

Two new members had been recruited to the group.

The members, who have been inspired and enabled by their participation in the WGE, perform much of the CES locally.

The local CES projects performed by members includes: organizing and facilitating ECR rounds on several levels in the healthcare structure; arranging and contributing to ethical education of healthcare professionals and students; serving as members on national, regional and local ethics committees or societies; preforming and contributing to research projects.

Two members (Bartholdson & Nilsson) has taught clinical ethics, on three occasions during 2019, at the short introduction courses on paediatric oncology for nurses. Two other members (Pergert & Castor) taught clinical ethics at the national education in paediatric oncology for nurses, On the Nordic level, one of the focuses of the group has been to organize the second course in guiding ethics case reflection (ECR).

Among the 22 participants are 11 nurses, 9 physicians, 1 nursing assistant and 1 play-therapist. Most participants come from Sweden (n=16), 2 are from Finland and 4 from Denmark. The course briefly cover the theory of ECR rounds but is first and foremost a skills course; including the implementation of ECR rounds at the paediatric oncology centres. The first part of the course was a 3-day introduction (Oct 2019) to guiding ECR rounds followed by a period in which the participants practice and implement ECR rounds in their clinical setting. The second part of the course is a 2-day follow-up (will be held in march 2020) where participants will fine-tune their knowledge and skills. The WGE is collaborating with Professor Molewijk at VU University in Amsterdam, and the course management team consisted of, apart from Bert Molewijk, Anders Castor, Pernilla Pergert, Cecilia Bartholdson and Lisa Törnudd.

Cecilia Bartholdson et al. is continuing the evaluation of the training and the implemented ECR rounds as a larger research project and Pergert has been granted separate funding from the Swedish Childhood Cancer Fund (PR2016-0020) for the research project entitled “Evaluation of ethics support – What is the impact of moral case deliberations on paediatric oncology?”

The WGE has been an expert reference group in a multi-site cross-sectional Nordic survey on communication over language barriers, moral distress and the ethical climate in childhood cancer care. In 2019, four articles with results from Sweden has been published (and one more in 2020) and the research project is continuing through Pernilla Pergert et al. and is now focusing on the other Nordic countries, in collaboration with national coordinators (NC) from the WGE. Data collection is ongoing in Finland (NC: Kristian Juusola) and Denmark (NC: Gitte Petersen), and is about to start in Norway (NC: Anne Gro Wesenberg Rognlien).

A new version of the website that will be easier to find and navigate is under construction.

Presentations on ethics at international conferences from the group or with group members as co-authors during 2019

Members have participated and presented research at various conferences on clinical ethics. Two members (Pergert & Bartholdson) participated at the International Conference on Clinical Ethics Consulta-

tion (ICCEC) in Vienna. During the conference they participated in an expert meeting about revising the Euro-MCD instrument. Bartholdson gave an oral presentation with the title "How Can the Immediate Management of the Organisation Influence the Ethical Climate?" Pergert also, as a member of the ECEN Steering Committee, participated at the ECEN Open Forum Day in Oxford with the theme Qualifying Ethics Support Services and Training Ethics Consultants. At SIOP, Bartholdson and Pergert presented research on clinical ethics.

Published congress abstracts (on ethics, presented by members)

- **af Sandeberg, M., Bartholdson, C. & Pergert, P.** (2019) Situations important to capture moral distress in paediatric oncology - A national cross-sectional survey. (SIOP Meeting Abstract) Pediatric Blood & Cancer, 66, (Suppl. 4), p.S94.
- **Bartholdson, C., af Sandeberg, M., Molewijk, B. & Pergert, P.** (2019) Ethical decision-making in paediatric oncology - Do participation in ethics case reflection rounds increase perceptions of involvement, possibility to influence, responsibility and understanding? (SIOP Meeting Abstract) Pediatric Blood & Cancer, 66, (Suppl. 4), p.S95.

Publications from the Nordic project and on clinical ethics from the group or with group members as co-authors, Original articles 2019

- **Pergert, P., Bartholdson, C., Blomgren, K., & af Sandeberg, M.** *Moral distress in paediatric oncology: Contributing factors and group differences*, Nursing Ethics. 2019 26(7-8):2351-2363.
- **Pergert, P., Bartholdson, C., & af Sandeberg, M.** *The ethical climate in paediatric oncology—A national cross-sectional survey of health-care personnel.* Psycho-Oncology. 2019 Apr;28(4):735-741. DOI:10.1002/pon.5009
- **Schröder Håkansson, A., Pergert, P, Abrahamsson, J., Stenmarker, M.** *Balancing values and obligations when obtaining informed consent: healthcare professionals' experiences in Swedish paediatric oncology.* Acta Paediatrica, 2019; Accepted. DOI: 10.1111/apa.15010
- **Granhagen Jungner, J., Tiselius, E., Blomgren, K., Lützén, K., Pergert, P.** *Language barriers and the use of professional interpreters: A national multisite cross-sectional survey in paediatric oncology care.* Acta Oncologica. 2019; 58(7), 1015–1020.
- **af Sandeberg, M., Bartholdson, C. & Pergert, P.** *Important situations that capture moral distress in paediatric oncology.* BMC Med Ethics. 2020;21(1):6.

Other publications

- **Pergert, P. & Tiselius, E.** *Intercultural competence and communication over language barriers.* In: Kate A. Mazur & Stacey Berg, Ethical Issues in Pediatric Hematology/Oncology. Switzerland: Springer; 2020.
- **Tiselius, E., Hägglund, E. & Pergert, P.** *Distressful situations, non-supportive work climate, threats to professional and private integrity - Healthcare interpreting in Sweden.* In: Izabel Souza, I & Fragkou, E.E Handbook of Research on Medical Interpreting. Hershey, PA: IGI Global, 2020, p 54-79.
- **Pergert, P., Sullivan, CE., Adde, M., Afungchwi GM., Downing, J., Hollis, R., Ilbawi , A., Morrissey, L., Punjwani, R. & Challinor, J.** *An ethical imperative: Safety and specialization as nursing priorities of WHO Global Initiative for Childhood Cancer.* Pediatr Blood Cancer. 2019;e28143.

Publications

NOPHO Publications

Publications based on cooperative projects within NOPHO.

1983

Moe PJ. *Combined Nordic Meeting of Pediatric Hematology and Oncology.* Am J Hematol Oncol 1983; 4:438.

1986

Moe PJ, Hertz H, Ludvigsson J, Siimes M, Jonmundsson G. *Feilmedisinering hos barn – profylakse og terapi.* Nordisk Medicin 1986; 101:8-9.

1987

Gustafsson G, Garwicz S, Hertz H, Jonmundsson G, Johanesson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M and Åhström L for NOPHO. *A Population-based study of childhood acute lymphoblastic leukemia diagnosed from July 1981 through June 1985 in the five Nordic countries.* Acta Paediatr Scand 1987; 76: 781-788.

1989

Gustafsson G, Berglund G, Garwicz S, Hertz H, Jonmundsson G, Moe PJ, Salmi TT, Seip M, Siimes MA, Yssing M for NOPHO. *A population-based study of children with standard risk acute lymphoblastic leukemia in the five Nordic countries.* Acta Paediatr Scand 1989; 78: 104-109.

Nygaard R, Moe PJ. *Outcome after cessation of therapy in childhood leukemia. A population-based Nordic study of 986 patients. I and II.* Acta Paediatr Scand 1989, Suppl. 354:1-24.

Nygaard R, Moe PJ, Brincker H, Clausen N, Nyman R, Perkkiö M, Eilertsen ME, Johansen OJ, Väre M, Brinch L, Siimes MA. *Late relapses after treatment for acute lymphoblastic leukemia in childhood. A population-based study from the Nordic countries.* Med Ped Oncol 1989;17:45-47.

Schmiegelow K, Siimes MA, Agertoft L, Berglund L, Storm-Mathiesen I, Andreassen M, Salmi TT, Nygaard R, Wiebe T, Kreuger A, Hayder S. *Radio-Iodobenzylguanidine scintigraphy of neuroblastoma: Conflicting results, when compared with standard investigations.* Med Ped Oncol 1989;17:126-130.

1990

Clausen N, Garwicz S, Glomsten A, Jonmundsson G, Kruus S, Yssing M. *Medulloblastoma in Nordic children, I. Incidence and mortality*. Acta Pædiatr Scand 1990, suppl.371:5-11.

Jacobsen BB, Garwicz S, Glomstein A, Jonmundsson G, Kruus S, Yssing M. *Medulloblastoma in Nordic children. III. Long term growth and endocrine sequelae.* Acta Pædiatr Scand 1990;271:20-27.

Lie S, Berglund G, Gustafsson G, Jonmundsson G, Siimes M, Yssing M for NOPHO. *High dose ARA-C as a single agent consolidation therapy in childhood AML. In: Haematology and Blood Transfusion.* Acute Leukemia II. pp 215-221. Springer Verlag, 1990.

Yssing M, Garwicz S, Glomstein A, Jonmundsson G, Kruus S. *Medulloblastoma in Nordic children. II. Neurologic and social prognosis in long term survivors.* Acta Pædiatr Scand 1990, suppl.371:12-19.

1991

Kreuger A, Garwitz S, Hertz H, Jonmundsson G, Lanning M, Lie SO, Moe PJ, Salmi TT, Schroeder H, Siimes MA, Wesenberg F, Yssing M, Åhström L and Gustafsson G for NOPHO. *CNS disease in childhood acute lymphoblastic leukemia. Prognostic factors and treatment results.* Pediatr Hem Oncol 1991; 8:291-299.

Lie SO on behalf of the Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Progress in treatment of childhood leukemias.* Eur J Cancer 1991; suppl.2:11.

Nygaard R. *Long-term survival in childhood leukemia. Relapses and late effects after completed therapy.* Thesis, University of Trondheim, Tapir, 1991.

Nygaard R, Clausen N, Siimes MA, Marky I, Skjeldestad FE, Kristinsson JR, Vuoristo A, Wegelius R, Moe PJ. *Reproduction following treatment for childhood leukemia: A population-*

based prospective cohort study of fertility and offspring. Med Ped Oncol 1991;19:459-466.

Nygaard R, Garwicz S, Haldorsen T, Hertz H, Jonmundsson GK, Lanning M, Moe PJ. *Second malignant neoplasms in patients treated for childhood leukemia. A population-based cohort study from the Nordic countries.* Acta Pædiatr Scand 1991;80:1220-1228.

1992

Lanning M, Garwitz S, Hertz H, Jonmundsson G, Kreuger A, Lie SO, Moe PJ, Salmi TT, Schröder H, Siimes M, Wesenberg F, Yssing M, Åhström L and Gustafsson G for NOPHO. *Superior treatment results in girls with high risk acute lymphoblastic leukemia compared to boys.* Acta Paediatr Scand 1992; 81:66-68.

Lie Sverre and Gustafsson Göran on behalf of the Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Progress in the treatment of childhood leukemias.* Review article Annals of Medicin 1992; 24:319-323.

1993

Siimes MA, Lie SO, Andersen O, Marky I, Rautonen J, Hertz H. *Prophylactic cranial irradiation increases the risk of testicular damage in adult males surviving ALL in childhood.* Med Ped Oncol 1993;21:117-121.

Olsen JH, Garwicz S, Hertz H, Jonmundsson G, Langmark F, Lanning M, Lie SO, Moe PJ, Möller T, Sankila R and Tullinius H. *Second malignant neoplasma after cancer in childhood or adolescence.* Br Med J 1993; 307: 1030-1036.

1994

Moell C, Marky I, Hovi L, Kristinsson J, Rix M, Moe PJ and Garwicz S. *Cerebral irradiation causes blunted pubertal growth in girls treated for acute leukemia.* Med Pediatr Oncol 1994;22:375-379.

1995

Schröder H, Garwicz S, Gustafsson G, Kristinsson J, Siiemes MA and Wesenberg F on behalf of NOPHO. *Outcome after relapse in children with acute lymphoblastic leukemia.* Med Ped Onc 1995; 25:372-378.

Schmiegelow K, Schröder H, Gustafsson G, Kristinsson J, Glomstein A, Salmi T, and Wranne L for NOPHO. *Risk of relapse in childhood acute lymphoblastic leukemia is related to RBC methotrexate and mercaptopurine metabolites during maintenance chemotherapy. Nordic Society for Pediatric Hematology and Oncology.* Journal Clin Oncol 1995; 13:345-351.

Marky I, Jonsson O, Kreuger A, Gustafsson G, Perkkio M, Schmiegelow K, Storm-Mathiesen I and Langmark F. *Childhood Non Hodgkin´s Lymphoma (NHL) in the five Nordic countries. A five year population based study.* Am Journal Pediatr Hem/Onc.; 17(2): 163-166, 1995.

1996

Saarinen U, Mellander L, Nyström K, Ringden O, Schroeder H, Glomstein A and Gustafsson G for NOPHO. *Allogeneic bone marrow transplantation in first remission for children with very high risk acute lymphoblastic leukemia: A retrospective case-control study in the Nordic countries.* Bone Marrow Transplantation; 17 (3):357-363 1996.

Lie S, Jonmundsson G, Mellander L, Siimes MA, Yssing M and Gustafsson G on behalf of NOPHO. *A population based study of 272 children with acute myeloid leukemia treated on two consecutive protocols with different intensity: Best outcome in girls, infants and in children with Down´s syndrom.* Br Journal of Hematology 1996; 94:82-88

Clausen N, Kreuger A, Salmi T, Storm-Mathisen I, Johannesson G. *Severe aplastic anaemia in the Nordic countries: a population based study of incidence, presentation, course, and outcome.* Arch Dis Child 1996;74; 319-22

Sankila R, Garwicz S, Olsen JH, Dollner H, Hertz H, Kreuger A, Langmark F, Lanning M, Moller T and Tulinius H. *Risk of subsequent malignant neoplasms among 1641 Hodgkin´s disease patients diagnosed in childhood and adolescence. A population based cohort study in the five Nordic countries.* JCO, 1996;14(5):1442-46.

1997

Schmiegelow K, Glomstein A, Kristinsson J, Salmi T, Schroder H, Bjork O. *Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. Nordic Society for Pediatric Hematology and Oncology (NOPHO).* J Ped Hematol Oncol, 1997;19(2):102-9.

Lie SO, Jonmundsson GK, Mellander L, Siimes MA, Yssing M, Gustafsson G. *Chemotherapy of acute myelocytic leukemia in children.* Ann N Y Acad Sci. 1997;824:84-90. Review.

1998

Gustafsson G, Lie SO. *Acute leukemias. In: Cancer in children, clinical management, 4th edn. (ed PA Voute, C Kalifa, A Barrett).* Oxford University Press, London, 1998, 99-118.

Sankila R, Olsen JH, Anderson H, Garwicz S, Glattre E, Hertz H, Langmark F, Lanning M, Möller T and Tulinius H. *Risk of cancer among offsprings of childhood-cancer survivors.* New Engl J Med, 1998;338:1339.

Gustafsson G, Kreuger A, Clausen N, Garwicz S, Kristinsson J, Lie SO, Moe PJ, Perkkiö M, Yssing M and Saarinen-Pihkala U. *Intensified treatment of acute childhood lymphoblastic leukemia has improved prognosis, especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996.* Acta Paediatr, 1998;87:1151-61.

Jahnukainen K, Salmi TT, Kristinsson J, Müller J, Madsen B, Gustafsson G. *The clinical indications for identical pathogenesis of isolated and non-isolated testicular relapse in acute lymphoblastic leukemia.* Acta Paediatr,1998,87:638-643

1999

Schroeder H, Gustafsson G, Saarinen-Pihkala U, Glomstein A, Jonmundsson G, Nysom K, Ringden O and Mellander L. *Allogeneic bone marrow transplantation in second remission of childhood acute lymphoblastic leukemia: a population-based case control study from the Nordic countries.* Bone Marrow Transplant, 1999,Mar;23(6):555-560

2000

Garwicz S, Anderson H, Olsen JH, Döllner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Möller T, Sankila R, Tulinius H. *Second malignant neoplasms after cancer in childhood and adolescence: A population-based case-control study in the 5 nordic countries.* Int J Cancer 88: 672-678, 2000.

Möller TR, Garwicz S, Barlow L, Falck Winther J, Glattre E, Olafsdottir G, Olsen JH, Perfekt R, Ritvanen A, Sankila R, Tulinius H. *Decreasing late mortality among 5-year survivors of cancer in childhood and adolescence: A population-based study in the Nordic countries.* J Clin Oncol (in press).

Forestier E, Johansson B, Borgstrom G, Kerndrup G, Johansson J, Heim S. *Cytogenetic findings in a population-based series of 787 childhood acute lymphoblastic leukemias from the Nordic countries. The NOPHO Leukemia Cytogenetic Study Group.* Eur J Haematol. 2000 Mar;64(3):194-200.

Forestier E, Johansson B, Gustafsson G, Borgstrom G, Kerndrup G, Johannsson J, Heim S. P*rognostic impact of karyotypic findings in childhood acute lymphoblastic leukaemia: a Nordic series comparing two treatment periods. For the Nordic Society of Paediatric Haematology and Oncology (NOPHO) Leukaemia Cytogenetic Study Group.* Br J Haematol. 2000 Jul;110(1):147-53.

Gustafsson G, Schmiegelow K, Forestier E, Clausen N, Glomstein A, Jonmundsson G, Mellander L, Mäkipernaa A, Nygaard R, Saarinen-Pihkala U-M. *Improving outcome through two decades in childhood ALL in the Nordic countries: the impacr of high-dose methotrexate in the reduction of CNS irradiation.* Leukemia, 2000, 14: 2267-2275.

2001

Lie SO, Clausen N, Jonmundsson G, Mellander L, Siimes MA, Gustafsson G, on behalf of the Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Early response to therapy is the strongest prognostic factor in childhood AML. Acute Leukemias VIII.* Prognostic and Treatment Strategies, Springer 2001; 499-507

Saarinen-Pihkala UM, Gustafsson G, Ringdén O. et al. *No disadvantage in outcome of using matched unrelated donors as compared with matched sibling donors for bone marrow transplantation in children with acute lymphoblastic leukemia in second remission.* J Clin Oncol 19:3406-3414, 2001.

Möller TR, Garwicz S, Barlow L, Falck Winther J, Glattre E, Olafsdottir G, Olsen JH, Perfekt R, Ritvanen A, Sankila R, Tulinius H. *Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: A population-based study in the Nordic countries.* J Clin Oncol 19: 3173-81, 2001.

2002

T M Calero Moreno, G Gustafsson, S Garwicz, D Grandér, G K Jonmundsson, B-M Frost, A Mäkipernaa, O Rasool, E-R Savolainen, K Schmiegelow, S Söderhäll, Vettenranta, F Wesenberg, S Einhorn, M Heyman. *Deletion of the ink4-locus (the p16ink4a, p14ARF and ND p15ink4b genes) predicts relapse in children with ALL treated according to the Nordic Protocols NOPHO-86 and NOPHO-92.* Leukemia, 16, 2037-2045, 2002.

Nyvold C, Madsen HO, Ryder LP, Seyfarth J, Svejgaard A, Clausen N, Wesenberg F, Jonsson OG, Forestier E, Schmiegelow K. *Precise quantification of minimal residual disease at day 29 allows identification of children with acute lymphoblastic leukemia and an excellent outcome.* Blood 2002; 99: 1253-1258.

2003

Seyfarth J, Madsen HO, Nyvold C, Ryder LP, Clausen N, Jonmundsson G, Wesenberg F, Schmiegelow K. *Post-induction residual disease in translocation t(12;21)-positive childhood ALL.* Med Ped Oncol 2003; 40: 82-7.

Kristensen T, Wesenberg F, Jonsson OG, Carlsen NT, Forestier E, Kirchhoff M, Lundsteen, Schmiegelow K. *High-resolution comparative genomic hybridisation yields a high detection rate of chromosomal aberrations in childhood acute lymphoblastic leukemia.* Eur J Haem 2003 Jun;70(6):363-72.

Schmiegelow K, Bjork O, Glomstein A, Gustafsson G, Keiding N, Kristinsson J, Makipernaa A, Rosthoj S, Szumlanski C, Sorensen TM, Weinshilboum R. *Intensification of mercaptopurine/methotrexate maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic leukemia.* J Clin Oncol 2003 Apr 1;21(7):1332-.

Rosthøj S, Hedlund-Treutiger I, Rajantie J, Zeller B, Jonsson OG, Elinder G, Wesenberg F, Henter JI, on behalf of the NOPHO ITP Working group and five national study groups. *Duration and morbidity of newly diagnosed idiopathic thrombocytopenic purpura in children: A prospective Nordic study of an unselected cohort.* J Pediatr 2003;143:302-7.

Lie SO, Abrahamsson J, Clausen N, Forestier E, Hasle H, Hovi L, Jonmundsson G, Mellander L and Gustafsson G. *Treatment stratification based on initial in vivo response in acute myeloid leukaemia in children without Down's syndrome: results of NOPHO-AML trials.* Br J Haematol. 2003 Jul; 122(2): 217-

Frost BM, Nygren P, Gustafsson G, Forestier E, Jonsson OG, Kanerva J, Nygaard R, Schmiegelow K, Larsson R, Lönnerholm G. On behalf of NOPHO. *Increased in vitro cellular drug resistance is related to poor outcome in high-risk childhood acute lymphoblastic leukaemia.* Br J Haematol 2003 Aug; 122(3):376-85.

Hjalgrim LL, Rostgaard K, Schmiegelow K, Soderhall S, Kolmannskog S, Vettenranta K, Kristinsson J, Clausen N, Melbye M, Hjalgrim H, Gustafsson G. *Age- and sex-specific incidence of childhood leukemia by immunophenotype in the Nordic countries.* J Natl Cancer Inst. 2003 Oct 15; 95(20): 1539-44.

Guerin S, Dupuy A, Anderson H, Shamsaldin A, Svahn-Tapper G, Moller T, Quiniou E, Garwicz S, Hawkins M, Avril MF, Oberlin O, Chavaudra J, de Vathaire F. *Radiation dose as a risk factor for malignant melanoma following childhood cancer*. Eur J Cancer 39: 2379-86, 2003.

2004

Saarinen-Pihkala UM, Gustafsson G, Carlsen N, Flaegstad T, Glomstein A, Kristinsson J, Lanning M, Schroeder H, Mellander L on behalf of NOPHO. *Outcome of children with high-risk acute lymphoblastic leukemia (HR-ALL): Nordic results on an intensive regimen with restricted central nervous system irradiation.* Ped Blood Cancer 2004; 1: 16-26.

Frost BM, Forestier E, Gustafsson G, Nygren P, Hellebostad M, Jonsson OG, Kanerva J, Schmiegelow K, Larsson R, Lonnerholm G. *Translocation t(12;21) is related to in vitro cellular drug sensitivity to doxorubicin and etoposide in childhood acute lymphoblastic leukemia.* Blood. 2004 Oct 15;104(8):2452-7.

Garwicz S, Moller TR, Olsen JH, Sankila R; Association of the Nordic Cancer Registries; Nordic Society for Paediatric Haematology and Oncology: *Nordic studies on late effects of treatment of cancer in childhood and adolescence.* Acta Oncol. 43: 682-3, 2004.

Möller TR, Garwicz S, Perfekt R, Barlow L, Winther JF, Glattre E, Olafsdottir G, Olsen JH, Ritvanen A, Sankila R. *Late mortality among five-year survivors of cancer in childhood and adolescence: Differences between the Nordic countries.* Acta Oncol. 43: 711-8, 2004.

2005

Rosthøj S, Hedlund-Treutiger I, Rajantie J, Zeller B, Jonsson OG, Henter JI, on behalf of the NOPHO ITP Working Group. *Age-dependent differences in Nordic children with ITP (correspondence).* J Pediatr 2005;146:151-152.

Zeller B, Rajantie J, Hedlund-Treutiger I, Tedgård U, Wesenberg F, Jonsson OG, Henter JI and Rosthøj S, on behalf of the NOPHO ITP Working Group and five national study groups. *Childhood Idiopathic Thrombocytopenic Purpura in the Nordic countries: Epidemiology and predictors of chronic disease.* Acta Pædiatrica 2005;94:178-184.

Frost BM, Forestier E, Gustafsson G, Nygren P, Hellebostad M, Jonmundsson G, Kanerva J, Schmiegelow K, Larsson R, Lonnerholm G; Nordic Society for Paediatric Haematology and Oncology. *Translocation t(1;19) is related to low cellular drug resistance in childhood acute lymphoblastic leukaemia.* Leukemia. 2005 Jan;19(1):165-9.

Zeller B, Gustafsson G, Forestier E, Abrahamsson J, Clausen N, Heldrup J, Hovi L, Jonmundsson G, Lie SO, Glomstein A, Hasle H; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Acute leukaemia in children with Down syndrome: a population-based Nordic study.* Br J Haematol. 2005 Mar;128(6):797-804.

Palle J, Frost BM, Forestier E, Gustafsson G, Nygren P, Hellebostad M, Jonsson OG, Kanerva J, Schmiegelow K, Larsson R, Lonnerholm G; on behalf of the Nordic Society for Paediatric Haematology and Oncology. *Cellular drug sensitivity in MLL-rearranged childhood acute leukaemia is correlated to partner genes and cell lineage.* Br J Haematol. 2005 Apr;129(2):189-98.

Rosthøj S, Hedlund-Treutiger I, Rajantie J, Zeller B, on behalf the NOPHO ITP Working Group. *Factors predicting development of chronic disease in Nordic children with acute onset of idiopathic thrombocytopenic purpura.* Br J Haematol 2005.

Lie SO, Abrahamsson J, Clausen N, Forestier E, Hasle H, Hovi L, Jonmundsson G, Mellander L, Siimes MA, Yssing M, Zeller B, Gustafsson G. *Long-term results in children with AML: NOPHO-AML study group – report of three consecutive trials.* Leukemia 2005; 19:2090-2100.

2006

Palle J, Frost BM, Peterson C, Gustafsson G, Hellebostad M, Kanerva J, Schmiegelow K, Lönnerholm G. *Doxorubicin pharmacokinetics is correlated to the effect of induction therapy in children with acute myeloid leukemia.* Anticancer Drugs 2006; 17:385-392.

Paulsson K, Bekassy AN, Olofsson T, Mitelman F, Johansson B, Panagopoulos I. *A novel and cytogenetically cryptic t(7;21)(p22;q22) in acute myeloid leukemia results in fusion of RUNX1 with the ubiquitin-specific protease gene USP42.* Leukemia 2006; 20:224-229.

Stentoft J, Hokland P, Østergaard M, Hasle H, Nyvold CG. *Minimal residual core binding factor AMLs by real time quantitative PCR - initial response to chemotherapy predicts event free survival and close monitoring of peripheral blood unravels the kinetics of relapse.* Leukemia Research 2006; 30:389-395.

Treutiger I, Rajantie J, Zeller B, Elinder G, Rosthøj S, on behalf of the NOPHO ITP working group. *Initial management of children with newly diagnosed idiopathic thrombocytopenic purpura in the Nordic countries.* Acta Pædiatr 2006; 95(6):726-731.

Saarinen-Pihkala UM, Heilmann C, Winiarski J, Glomstein A, Abrahamsson J, Arvidson J, Békàssy AN, Forestier E, Jonmundson G, Schroeder H, Vettenranta K, Gustafsson G. *Pathways through relapses and deaths of children with acute lymphoblastic leukemia: Role of allogeneic stem-cell transplantation in Nordic data.* J Clin Oncol 24:5750-5762, 2006.

Palle J, Frost BM, Gustafsson G, Hellebostad M, Kanerva J, Liliemark E, Schmiegelow K, Lönnerholm G; Nordic Society of Paediatric Haematology and Oncology. *Etoposide pharmacokinetics in children treated for acute*

myeloid leukemia. Anticancer Drugs. 2006 Oct;17(9):1087-94. Erratum in: Anticancer Drugs. 2010 Jan;21(1):129.

Abildgaard L, Ellebæk E, Gustafsson G, Abrahamsson J, Hovi L, Jonmundsson G, Zeller B, Hasle H. *Optimal treatment intensity in children with Down syndrome and myeloid leukaemia: data from 56 children treated on NOPHO-AML protocols and a review of the literature.* Annals of Hematology 85:275-280. 2006.

Forestier E, Schmiegelow K. *The incidence peaks of the childhood acute leukemias reflect specific cytogenetic aberrations.* J Ped Hematol Oncol, 28:486-95, 2006.

Hasle H, Lund B, Nyvold CG, Hokland P, Østergaard M. *WT1 gene expression in children with Down syndrome and transient myeloproliferative disorder.* Leukemia Research; 30: 543-540, 2006.

Paulsson K, Bekassy AN, Olofsson T, Mitelman F, Johansson B, Panagopoulos I. *A novel and cytogenetically cryptic t(7;21)(p22;q22) in acute myeloid leukemia results in fusion of RUNX1 with the ubiquitin-specific protease gene USP42.* Leukemia 2006; 20:224-22 9.

Stentoft J, Hokland P, Østergaard M, Hasle H, Nyvold CG. *Minimal residual core binding factor AMLs by real time quantitative PCR - initial response to chemotherapy predicts event free survival and close monitoring of peripheral blood unravels the kinetics of relapse.* Leukemia Research 2006; 30:389-395.

Svahn-Tapper G, Garwicz S, Anderson H, Shamsaldin A, De Vathaire F, Olsen JH, Døllner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Sankila R, Möller T. *Radiation dose and relapse are predictors for development of second malignant solid tumors after cancer in childhood and adolescence: A population-based case-control study in the five Nordic countries.* Acta Oncol. 45: 438-448, 2006.

Karrman K, Forestier E, Andersen MK, Autio K, Borgström G, Heim S, Heinonen K, Hovland R, Kerndrup G, Johansson B; Nordic Society of Paediatric Haematology and Oncology (NOPHO) and the NOPHO Leukaemia Cytogenetic Study Group (NLCSG). *High incidence of the ETV6/RUNX1 fusion gene in paediatric precursor B-cell acute lymphoblastic leukaemias with trisomy 21 as the sole cytogenetic change: a Nordic series of cases diagnosed 1989-2005.* Br J Haematol. 2006 Nov;135(3):35

Skärby TV, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia.* Leukemia. 2006 Nov;20(11):1955-62.

2007

Möller TR, Garwicz S, for the Nordic Childhood Cancer Cohort Study Group. *Mortality experiences among 15+ year survivors of childhood and adolescence cancers (Letter to the Editor)* Pediat Blood Cancer 48: 363, 2007.

Hawkins MM, Mertens AC, Möller TR, Garwicz S. *Suicide among survivors of childhood cancer (Letter to the Editor).* J Clin Oncol 25: 731-2, 2007.

Abrahamsson J, Clausen N, Gustafsson G, Hovi L, Jonmundsson G, Zeller B, Forestier E, Heldrup J, Hasle H. *Improved outcome after relapse in children with acute myeloid leukaemia.* British Journal of Haematology 2007; 136: 229-236.

Hasle H, Alonzo TA, Auvrignon A, Behar C, Chang M, Creutzig U, Fischer A, Forestier E, Fynn A, Haas OA, Harbott J, Harrison CJ, Heerema NA, van den Heuvel-Eibrink MM, Kaspers GJ, Locatelli F, Noellke P, Polychronopoulou S, Ravindranath Y, Razzouk B, Reinhardt D, Savva NN, Stark B, Suciu S, Tsukimoto I, Webb DK, Wojcik D, Woods WG, Zimmermann M, Niemeyer CM, Raimondi SC. *Monosomy 7 and deletion 7q in children and adolescents with acute myeloid leukemia: an international retrospective study.* Blood 2007; Feb 13;[Epub ahead of print]

Rajantie J, Zeller B, Treutiger I, Rosthøj S, on behalf of the NOPHO ITP Working Group. *Vaccination associated thrombocytopenic purpura in children.* Vaccine 2007; 26;25:1838-40.

Treutiger I, Rajantie J, Zeller B, Henter JI, Elinder G, Rosthøj S, on behalf of the NOPHO ITP Working Group. *Does treatment of newly diagnosed idiopathic thrombocytopenic*

purpura reduce morbidity? Arch Dis Child 2007; 92(8):704-707.

Edslev PW, Rosthøj S, Treutiger I, Rajantie J, Jonsson OG on behalf of the NOPO ITP Working Group. *A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura.* Br J Haematol 2007;138:513-6.

Forestier E, Andersen MK, Autio K, Blennow E, Borgström G, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kerndrup G, Nordgren A, Rosenquist R, Swolin B, Johansson B; Nordic Society of Pediatric Hematology and Oncology (NOPHO); Swedish Cytogenetic Leukemia Study Group (SCLSG); NOPHO Leukemia Cytogenetic Study Group (NLCSG). *Cytogenetic patterns in ETV6/RUNX1-positive pediatric B-cell precursor acute lymphoblastic leukemia: A Nordic series of 245 cases and review of the literature.* Genes Chromosomes Cancer. 2007 May;46(5):440-50.

Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG. *A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.* Lancet 2007; 370: 240-250.

2008

Forestier E, Gauffin F, Andersen MK, Autio K, Borgström G, Golovleva I, Gustafsson B, Heim S, Heinonen K, Heyman M, Hovland R, Johannsson JH, Kerndrup G, Rosenquist R, Schoumans J, Swolin B, Johansson B, Nordgren A; Nordic Society of Pediatric Hematology and Oncology; Swedish Cytogenetic Leukemia Study Group; NOPHO Leukemia Cytogenetic Study Group. *Clinical and cytogenetic features of pediatric dic(9;20)(p13.2;q11.2)-positive B-cell precursor acute lymphoblastic leukemias: a Nordic series of 24 cases and review of the literature.* Genes Chromosomes Cancer. 2008 Feb;47(2):149-58.

Forestier E, Heyman M, Andersen MK, Autio K, Blennow E, Borgström G, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kerndrup G, Nordgren A, Rosenquist R, Swolin B, Johansson B; Nordic Society of Paediatric Haematology, Oncology (NOPHO); Swedish Cytogenetic Leukaemia Study Group (SCLSG); NOPHO Leukaemia Cytogenetic Study Group (NLCSG). *Outcome of ETV6/RUNX1-positive childhood acute lymphoblastic leukaemia in the NOPHO-ALL-1992 protocol: frequent late relapses but good overall survival.* Br J Haematol. 2008 Mar;140(6):665-72.

Lönnerholm G, Frost BM, Behrendtz M, Abrahamsson J, Forestier E, Castor A, Heyman M, Uges DR, de Graaf SS. *Vincristine pharmacokinetics is related to clinical outcome in children with standard risk acute lymphoblastic leukemia.* Br J Haematol. 2008 Aug;142(4):616-21.

2009

Lönnerholm G, Frost BM, Söderhäll S, de Graaf SS. *Vincristine pharmacokinetics in children with Down syndrome.* Pediatr Blood Cancer. 2009 Jan;52(1):123-5.

Lönnerholm G, Nordgren A, Frost BM, Jonsson OG, Kanerva J, Nygaard R, Schmiegelow K, Larsson R, Forestier E. *Dic(9;20)(p13;q11) in childhood acute lymphoblastic leukaemia is related to low cellular resistance to asparaginase, cytarabine and corticosteroids.* Leukemia. 2009 Jan;23(1):209-12.

Lönnerholm G, Thörn I, Sundström C, Frost BM, Abrahamsson J, Behrendtz M, Heldrup J, Jacobsson S, Li A, Olofsson T, Porwit A, Söderhäll S, Larsson R, Forestier E. *In vitro cellular drug sensitivity at diagnosis is correlated to minimal residual disease at end of induction therapy in childhood acute lymphoblastic leukemia.* Leuk Res. 2009 Jan;33(1):46-53.

Milani L, Lundmark A, Nordlund J, Kiialainen A, Flaegstad T, Jonmundsson G, KanervaJ, Schmiegelow K, Gunderson KL, Lönnerholm G, Syvänen AC. *Allele-specific gene expression patterns in primary leukemic cells reveal regulation of gene expression by CpG site methylation.* Genome Res. 2009 Jan;19(1):1-11.

Schmiegelow K, Forestier E, Kristinsson J, Söderhäll S, Vettenranta K, Weinshilboum R, Wesenberg F; Nordic Society of Paediatric Haematology and Oncology. *Thiopurine methyltransferase activity is related to the risk of relapse*

of childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study. Leukemia. 2009 Mar;23(3):557-64.

Schmiegelow K, Al-Modhwahi I, Andersen MK, Behrendtz M, Forestier E, Hasle H, Heyman M, Kristinsson J, Nersting J, Nygaard R, Svendsen AL, Vettenranta K, Weinshilboum R. *Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia - results from the NOPHO ALL-92 study*. Blood. 2009 Feb 17.

Lönnerholm G, Valsecchi MG, De Lorenzo P, Schrappe M, Hovi L, Campbell Campbell M, Mann G, Janka-Schaub G, Li CK, Stary J, Hann I, Pieters R. *Pharmacokinetics of high-dose methotrexate in infants treated for acute lymphoblastic leukemia. Interfant-99 study group.* Pediatr Blood Cancer. 2009 May;52(5):596-601.

Schmiegelow K, Heyman M, Kristinsson J, Mogensen UB, Rosthøj S, Vettenranta K, Wesenberg F, Saarinen-Pihkala U. *Oral methotrexate/6-mercaptopurine may be superior to a multidrug LSA2L2 Maintenance therapy for higher risk childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study.* J Pediatr Hematol Oncol. 2009 Jun;31(6):385-92.

Schmiegelow K, Al-Modhawi I, Andersen MK, Berendtz M, Forestier E, Hasle H, Heyman M, Kristinsson J, Nersting J, Nygaard R, Svendsen AL, Vettenranta K, Weinshilboum R; Nordic Society for Paediatric Haematology and Oncology. *Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study.* Blood. 2009 Jun 11;113(24):6077-84.

Olsen JH, Möller T, Anderson H, Langmark F, Sankila R, Tryggvadóttír L, Falck Winther J, Rechnitzer C, Jonmundsson G, Christensen J, Garwicz S. *Lifelong cancer incidence in 47 697 patients treated for childhood cancer in the Nordic countries.* J Natl Cancer Inst. 2009 Jun 3;101(11):806-13.

Bjorklund E, Matinlauri I, Tierens A, Axelsson S, Forestier E, Jacobsson S et al. *Quality control of flow cytometry data analysis for evaluation of minimal residual disease in bone marrow from acute leukemia patients during treatment.* J Pediatr Hematol Oncol 2009: 31:406-1.

Van der Linden M, Valsecchi MG, De Lorenzo P, Möricke A, Janka G, Leblanc TM, Felice M, Biondi A, Campbell M, Hann I, Rubnitz JE, Stary J, Szczepanski T, Vora A, Ferster A, Hovi L, Silverman LB and Pieters R. *Outcome of congenital acute lymphoblastic leukaemia treated on the Interfant-99 protocol.* Blood 2009; 114: 3764-3768.

2010

Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Söderhäll S, Taskinen M; Nordic Society of Paediatric Haematology and Oncology. *Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia.* Leukemia 2010; 24:345-54.

Schmiegelow K, Heyman M, Gustafsson G, Lausen B, Wesenberg F, Kristinsson J, Vettenranta K, Schroeder H, Forestier E, Rosthoej S. *The degree of myelosupression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse.* Leukemia 2010; 24:715-20.

Molgaard-Hansen L, Möttönen M, Glosli H, Jonmundsson GK, Abrahamsson J, Hasle H. *Early and treatment-related deaths in childhood acute myeloid leukemia in the Nordic countries: 1984-2003*. Br J Haematol 2010; 151: 147-159.

Mann G, Attarbaschi A, Peters C, Schrappe M, Lorenzo P De, Hann I, Rossi G De, Felice M, Lausen B, LeBlanc T, Szczepanski T, Ferster A, Janka-Schaub G, Rubnitz J, Silverman L B, Stary J, Campbell M, Li C K, Suppiah R, Biondi A, Vora A, Valsecchi MG and Pieters R on behalf of the Interfant-99 Study Group. *Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-line-age-leukemia (MLL)-rearranged acute lymphoblastic leukemia - Results from the Interfant-99 Study*. Blood 2010; 116 (15):2644-2650.

Brüggemann M, Schrauder A; Raff T, Pfeifer H, Dworzak M, Ottmann OG, Asnafi V, Baruchel A, Bassan R; Benoit Y, Biondi A, Cavé H, Dombret H, Fielding AK, Foa R, Gökbuget N, Goldstone AH, Goulden N, Henze G, Hoelzer D, Janka-Schaub G, Macintyre EA, Pieters R, Rambaldi A, Ribera JM, Schmiegelow K, Spinelli O, Stary J, von

Stackelberg A, Kneba M, Schrappe M, van Dongen JJM, also on behalf of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the International Berlin-Frankfurt-Münster Study Group (I-BFM-SG). *Standardized MRDquantification in European ALL trials – proceedings of the second international symposium on MRD assessment in Kiel, Germany, 18-20 September 2008.* Leukemia 2010; 24:521-35.

2011

Molgaard-Hansen L, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros-Svennilson J, Nysom K, Hasle H; Nordic Society of Pediatric Hematology and Oncology. *Quality of health in survivors of childhood acute myeloid leukemia treated with chemotherapy only: a NOPHO-AML study.* Pediatr Blood Cancer. 2011 Dec 15;57(7):1222-9.

Staffas A, Kanduri M, Hovland R, Rosenquist R, Ommen HB, Abrahamsson J, Forestier E, Jahnukainen K, Jónsson ÓG, Zeller B, Palle J, Lönnerholm G, Hasle H, Palmqvist L, Ehrencrona H; Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Presence of FLT3-ITD and high BAALC expression are independent prognostic markers in childhood acute myeloid leukemia.* Blood. 2011 Nov 24;118(22):5905-13.

Andersen MK, Autio K, Barbany G, Borgström G, Cavelier L, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Johansson B, Kjeldsen E, Nordgren A, Palmqvist L, Forestier E. *Paediatric B-cell precursor acute lymphoblastic leukaemia with t(1;19)(q23;p13): clinical and cytogenetic characteristics of 47 cases from the Nordic countries treated according to NOPHO protocols.* Br J Haematol. 2011 Oct;155(2):235-43.

Frandsen TL, Abrahamsson J, Lausen B, Vettenranta K, Heyman M, Behrentz M, Castor A, Wehner PS, Frost BM, Andersen EW, Schmiegelow K. *Individualized toxicity-titrated 6-mercaptopurine increments during high-dose methotrexate consolidation treatment of lower risk childhood acute lymphoblastic leukaemia. A Nordic Society of Paediatric Haematology and Oncology (NOPHO) pilot study.* Br J Haematol. 2011 Oct;155(2):244-7.

Schmiegelow K. *Epidemiology of therapy-related myeloid neoplasms after treatment for pediatric acute lymphoblastic leukemia in the nordic countries.* Mediterr J Hematol Infect Dis. 2011;3(1):e2011020.

Lund B, Åsberg A, Heyman M, Kanerva J, Harila-Saari A, Hasle H, Söderhäll S, Jónsson ÓG, Lydersen S, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology. *Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia.* Pediatr Blood Cancer. 2011 Apr;56(4):551-9.

Zachariadis V, Gauffin F, Kuchinskaya E, Heyman M, Schoumans J, Blennow E, Gustafsson B, Barbany G, Golovleva I, Ehrencrona H, Cavelier L, Palmqvist L, Lönnerholm G, Nordenskjöld M, Johansson B, Forestier E, Nordgren A; Nordic Society of Pediatric Hematology, Oncology (NOPHO); Swedish Cytogenetic Leukemia Study Group (SCLSG). *The frequency and prognostic impact of dic(9;20)(p13.2;q11.2) in childhood B-cell precursor acute lymphoblastic leukemia: results from the NOPHO ALL-2000 trial.* Leukemia. 2011 Apr;25(4):622-8.

Molgaard-Hansen L, Möttönen M, Glosli H, Jónmundsson GK, Abrahamsson J, Hasle H; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Treatment-related deaths in second complete remission in childhood acute myeloid leukaemia.* Br J Haematol. 2011 Mar;152(5):623-30.

Kuchinskaya E, Heyman M, Nordgren A, Söderhäll S, Forestier E, Wehner P, Vettenranta K, Jonsson O, Wesenberg F, Sahlén S, Nordenskjöld M, Blennow E. *Interphase fluorescent in situ hybridization deletion analysis of the 9p21 region and prognosis in childhood acute lymphoblastic leukaemia (ALL): results from a prospective analysis of 519 Nordic patients treated according to the NOPHO-ALL 2000 protocol.* Br J Haematol. 2011 Mar;152(5):615-22.

Abrahamsson J, Forestier E, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B, Hasle H. *Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate.* J Clin Oncol. 2011 Jan 20;29(3):310-5.

Vaitkevičienė G, Forestier E, Hellebostad M, Heyman M, Jonsson OG, Lähteenmäki PM, Rosthoej S, Söderhäll S, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *High white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia: biological background and prognostic impact. Results from the NOPHO ALL-92 and ALL-2000 studies.* Eur J Haematol. 2011 Jan;86(1):38-46.

Wlodarski MW, Mötter J, Gorr TA, Olk-Batz C, Hasle H, Dworzak M, Niemeyer CM, Flotho C. *Abnormal promoter DNA methylation in juvenile myelomonocytic leukemia is not caused by mutation in DNMT3A.* Blood 2011; 118: 4490-4491.

Hasle H, Niemeyer CM. *Advances in the prognostication and management of advanced MDS in children.* British Journal of Haematology 2011; 154: 185-195.

Gustafsson B, Hellebostad M, Ifversen M, Sander B, Hasle H. *Acute respiratory failure in 3 children with juvenile myelomonocytic leukemia.* Journal of Pediatric Hematology & Oncology 2011; 33: e363-e367.

Olk-Batz C, Poetsch AR, Nöllke P, Claus R, Zucknick M, Sandrock I, Witte T, Strahm B, Hasle H, Zecca M, Stary J, Bergstraesser E, De Moerloose B, Trebo M, van den Heuvel-Eibrink MM, Wojcik D, Locatelli F, Plass C, Niemeyer CM, Flotho C. *Aberrant DNA methylation characterizes juvenile myelomonocytic leukemia (JMML) with poor outcome.* Blood 2011; 117: 4871-4880.

Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE. *Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.* Clin Pharmacol Ther. 2011, 89:387-91.

Wesolowska A, Dalgaard MD, Borst L, Gautier L, Bak M, Weinhold N, Nielsen BF, Helt LR, Audouze K, Nersting J, Tommerup N, Brunak S, Ponten TS, Leffers H, Schmiegelow K, Gupta R. *Cost-effective multiplexing before capture allows screening of 25,000 clinical relevant SNPs in childhood acute lymphoblastic leukemia.* Leukemia 2011; 25: 1001-6.

2012

Garwicz S, Anderson H, Olsen JH, Falck Winther J, Sankila R, Langmark F, Tryggvadóttir L, Möller TR; for the Association of the Nordic Cancer Registries (ANCR) and the Nordic Society for Pediatric Hematology Oncology (NOPHO). *Late and very late mortality in 5-year survivors of childhood cancer: Changing pattern over four decades-Experience from the Nordic countries.* Int J Cancer. 2012 Oct 1;131(7):1659-66

Hasle H, Abrahamsson J, Forestier E, Ha SY, Heldrup J, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Gemtuzumab ozogamicin as post-consolidation therapy does not prevent relapse in children with AML: results from NOPHO-AML 2004.* Blood. 2012 Aug 2;120(5):978-84.

Barbany G, Andersen MK, Autio K, Borgström G, Franco LC, Golovleva I, Heim S, Heinonen K, Hovland R, Johansson B, Johannsson JH, Kjeldsen E, Nordgren A, Palmqvist L, Forestier E; on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO), the Swedish Cytogenetic Leukaemia Study Group (SCLSG) and the NOPHO Leukaemia Cytogenetic Study Group (NLCSG). *Additional aberrations of the ETV6 and RUNX1 genes have no prognostic impact in 229 t(12;21)(p13;q22)-positive B-cell precursor acute lymphoblastic leukaemias treated according to the NOPHO-ALL-2000 protocol.* Leuk Res. 2012 Jul;36(7):936-8.

Rosthøj S, Rajantie J, Treutiger I, Zeller B, Tedgård U, Henter JI; on behalf of the NOPHO ITP Working Group. *Duration and morbidity of chronic immune thrombocytopenic purpura in children: Five-year follow-up of a Nordic cohort.* Acta Paediatr. 2012 Jul;101(7):761-6.

Rosthøj S, Keiding N, Schmiegelow K. *Estimation of dynamic treatment strategies for maintenance therapy of children with acute lymphoblastic leukaemia: an application of history-adjusted marginal structural models.* Stat Med. 2012 Feb 28;31(5):470-88.

Levinsen M, Shabaneh D, Bohnstedt C, Harila-Saari A, Jonsson OG, Kanerva J, Lindblom A, Lund B, Andersen EW, Schmiegelow K; Nordic Society of Paediatric Haematology

and Oncology (NOPHO). *Pneumocystis jiroveci pneumonia prophylaxis during maintenance therapy influences methotrexate/6-mercaptopurine dosing but not event-free survival for childhood acute lymphoblastic leukemia.* Eur J Haematol. 2012 Jan;88(1):78-86.

Hirabayashi S, Flotho C, Moetter J, Heuser M, Hasle H, Gruhn B, Klingebiel T, Thol F, Schlegelberger B, Baumann I, Strahm B, Stary J, Locatelli F, Zecca M, Bergstraesser E, Dworzak M, van den Heuvel-Eibrink MM, De Moerloose B, Ogawa S, Niemeyer CM, Wlodarski MW. *Spliceosomal gene aberrations are rare, coexist with oncogenic mutations, and are unlikely to exert a driver effect in childhood MDS and JMML.* Blood 2012: 119; e96-e99.

Baumann, I., Fuhrer, M., Behrendt, S., Campr, V., Csomor, J., Furlan, I., de Haas, V., Kerndrup, G., Leguit, R.J., De Paepe, P., Noellke, P., Niemeyer, C. & Schwarz, S. *Morphological differentiation of severe aplastic anaemia from hypocellular refractory cytopenia of childhood: reproducibility of histopathological diagnostic criteria.* Histopathology 2012; 61: 10-17.

Raja R, Schmiegelow K, Frandsen T. *Asparaginase-associated pancreatitis in children.* Br J Haematol 2012;159:18-27.

Toft N, Schmiegelow K, Klausen TW, Birgens H. *A national population-based retrospective study on acute lymphoblastic leukaemia in Denmark 1998-2008.* Br J Med 2012; 175: 87-104.

Jacobsen JH, Schmiegelow K, Nersting J. *Liquid chromatography-tandem mass spectrometry quantification of 6-thioguanine in DNA using endogenous guanine as internal standard.* J Chromatogr B 2012; 15: 881-2.

2013

Wareham NE, Heilmann C, Abrahamsson J, Forestier E, Gustafsson B, Ha SY, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B, Hasle H. *Outcome of poor response paediatric AML using early SCT.* Eur J Haematol. 2013 Mar;90(3):187-94.

Ofverholm I, Tran AN, Heyman M, Zachariadis V, Nordenskjöld M, Nordgren A, Barbany G. *Impact of IKZF1 deletions and PAX5 amplifications in pediatric B-cell precursor ALL treated according to NOPHO protocols.* Leukemia. 2013 Sep;27(9):1936-9.

Toft N, Birgens H, Abrahamsson J, Bernell P, Griškevičius L, Hallböök H, Heyman M, Holm MS, Hulegårdh E, Klausen TW, Marquart HV, Jónsson OG, Nielsen OJ, Paulsen PQ, Taskinen M, Vaitkeviciene G, Vettenranta K, Åsberg A, Schmiegelow K. *Risk group assignment differs for children and adults 1–45 years with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol.* Eur J Haematol 2013; 90: 404-12.

Bohnstedt C, Levinsen M, Rosthøj S, Zeller B, Taskinen M, Hafsteinsdottir S, Björgvinsdóttir H, Heyman M, Schmiegelow K. *Physicians compliance during maintenance therapy in children with Down syndrome and acute lymphoblastic leukemia.* Leukemia. 2013 Apr;27(4):866-70.

Johannsen KH, Handrup MM, Lausen B, Schrøder H, Hasle H. *High frequency of streptococcal bacteraemia during childhood AML therapy irrespective of dose of cytarabine.* Pediatr Blood Cancer. 2013 Jul;60(7):1154-60.

Attarbaschi A, Mann G, Rosolen A, Horibe K, Uyttebroeck A, Beishuizen A, Niggli F, Csoka M, Krenova Z, Mellgren K, Kabickova E, Chaing A, Reiter A, Williams D and Burkhardt B. *Children and adolescents with follicular lymphoma (FL) have an excellent prognosis with limited chemotherapy or with a "watch and wait" strategy after complete resection.* Ann Hematol. 2013 Nov;92(11):1537-1541.

Rasmussen MM, Christensen RH, Gregers J, Heldrup J, Nersting J, Schmiegelow K. *Can SLC19A1 80G>A polymorphisms predict risk of extremely delayed MTX-excretion after high dose Methotrexate?* J Ped Hematol Oncol 2013; 35: 417-8.

Wennerstrand P, Mårtensson LG, Söderhäll S, Zimdahl A, Appell ML. *Methotrexate binds to recombinant thiopurine S-methyltransferase and inhibits enzyme activity after high-dose infusions in childhood leukaemia.* Eur J Clin Pharmacol. 2013 Sep;69(9):1641-9.

Paulsson K, Forestier E, Andersen MK, Autio K, Barbany G, Borgström G, Cavelier L, Golovleva I, Heim S, Heinonen K, Hovland R, Johannsson JH, Kjeldsen E, Nordgren A, Palmqvist L, Johansson B; Nordic Society of Pediatric Hematology and Oncology

(NOPHO); Swedish Cytogenetic Leukemia Study Group (SCLSG); NOPHO Leukemia Cytogenetic Study Group (NLCSG). *High modal number and triple trisomies are highly correlated favorable factors in childhood B-cell precursor high hyperdiploid acute lymphoblastic leukemia treated according to the NOPHO ALL 1992/2000 protocols.* Haematologica. 2013 Sep;98(9):1424-32

Vaitkeviciene G, Heyman M, Jonsson OG, Lausen B, Harila-Saari A, Stenmarker M, Taskinen M, Zvirblis T, Asberg A, Groth-Pedersen L, Rageliene L, Schmiegelow K. *Early morbidity and mortality in childhood acute lymphoblastic leukemia with very high white blood cell count.* Leukemia 2013; 27: 2259-62

Ebbesen MS, Nersting J, Jacobsen JH, Frandsen TL, Vettenranta K, Abramsson J, Wesenberg F, Schmiegelow K. *Incorporation of 6-thioguanine nucleotides into DNA during maintenance therapy of childhood acute lymphoblastic leukemia – the influence of thiopurine methyltransferase genotypes.* J Clin Pharmacol 2013; 53: 670-4.

Aalbers AM, van den Heuvel-Eibrink MM, de Haas V, Te Marvelde JG, de Jong AX, van der Burg M, Dworzak M, Hasle H, Locatelli F, De Moerloose B, Schmugge M, Stary J, Zecca M, Zwaan CM, van de Loosdrecht AA, van Dongen JJ, Niemeyer CM, van der Velden VH. *Applicability of a reproducible flow cytometry scoring system in the diagnosis of refractory cytopenia of childhood.* Leukemia. 2013; 27: 1923-1925.

Molgaard-Hansen L, Skou AS, Juul A, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros J, Nysom K, Hasle H; Nordic Society of Pediatric Hematology and Oncology. *Pubertal development and fertility in survivors of childhood acute myeloid leukemia treated with chemotherapy only: a NOPHO-AML study.* Pediatr Blood Cancer. 2013 Dec;60(12):1988-95.

Schmiegelow K, Levinsen M, Attarbaschi A, Baruchel A, Devidas M, Escherich G, Gibson B, Heydrich C, Horibe K, Ishida Y, Liang D-C, Locatelli F, Michel G, Pieters T, Piette C, Pui C-H, Raimondi S, Silverman L, Stanulla M, Stark B, Winick N, Valsecchi MG. *Second Neoplasms after Treatment of Childhood Acute Lymphoblastic Leukemia.* J Clin Oncol 2013; 31: 2468-76.

2014

Frandsen TL, Heyman M, Abrahamsson J, Vettenranta K, Åsberg A, Vaitkeviciene G, Pruunsild K, Toft N, Helt L, Bach KF, Schmiegelow K. *Complying with the European Clinical Trials Directive while surviving the administrative pressure - an alternative approach to toxicity registration in a cancer trial.* Eur J Cancer 2014; 50: 251-9.

Levinsen M, Taskinen M, Abrahamsson J, Forestier E, Frandsen TL, Harila-Saari A, Heyman M, Jonsson OG, Lähteenmäki PM, Lausen B, Vaitkevičienė G, Asberg A, Schmiegelow K; on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Clinical features and early treatment response of central nervous system involvement in childhood acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2014 Aug;61(8):1416-21.

Raja RA, Schmiegelow K, Albertsen BK, Prunsild K, Zeller B, Vaitkeviciene G, Abrahamsson J, Heyman M, Taskinen M, Harila-Saari A, Kanerva J, Frandsen TL. *Asparaginase associated Pancreatitis in Children with Acute Lymphoblastic Leukaemia in the NOPHO ALL2008 Protocol.* Br J Haematol 2014; 165: 126-33.

Fogelstrand L, Staffas A, Wasslavik C, Sjögren H, Söderhäll S, Frost BM, Forestier E, Degerman S, Behrendtz M, Heldrup J, Karrman K, Johansson B, Heyman M, Abrahamsson J, Palmqvist L. *Prognostic implications of mutations in NOTCH1 and FBXW7 in childhood T-ALL treated according to the NOPHO ALL-1992 and ALL-2000 protocols.* Pediatr Blood Cancer. 2014 Mar;61(3):424-30.

Sandahl JD, Kjeldsen E, Abrahamsson J, Ha SY, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H. *Ploidy and clinical characteristics of childhood acute myeloid leukemia: A NOPHO-AML study.* Genes Chromosomes Cancer. 2014 Aug;53(8):667-75.

Aalbers AM, van der Velden VH, Yoshimi A, Fischer A, Noellke P, Zwaan CM, Baumann I, Beverloo HB, Dworzak M, Hasle H, Locatelli F, De Moerloose B, Gohring G, Schmugge M, Stary J, Zecca M, Langerak AW, van Dongen JJ, Pieters R, Niemeyer CM, van den Heuvel-Eibrink MM. *The clinical relevance of minor*

paroxysmal nocturnal hemoglobinuria clones in refractory cytopenia of childhood: a prospective study by EWOG-MDS. Leukemia 2014; 28: 189-192.

Vaitkevičienė G, Matuzevičienė R, Stoškus M, Žvirblis T, Ragelienė L, Schmiegelow K. *Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol.* Medicina (Kaunas). 2014;50(1):28-36.

Yoshimi A, van den Heuvel-Eibrink MM, Baumann I, Schwarz S, Simonitsch-Klupp I, de Paepe P, Campr, V, Birk Kerndrup G, O'Sullivan M, Devito R, Leguit R, Hernandez M, Dworzak M, de Moerloose B, Stary J, Hasle H, Smith OP, Zecca M, Catala A, Schmugge M, Locatelli F, Fuhrer M, Fischer A, Guderle A, Nollke P, Strahm B, Niemeyer CM. *Comparison of horse and rabbit anti-thymocyte globulin in immunosuppressive therapy for refractory cytopenia of childhood.* Haematologica. 2014 Apr;99(4):656-63.

Henriksen LT, Nersting J, Raja RA, Frandsen TL, Rosthøj S, Schrøder H, Albertsen BK; on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO) group. *Cerebrospinal fluid asparagine depletion during pegylated asparaginase therapy in children with acute lymphoblastic leukaemia.* Br J Haematol. 2014 Jul;166(2):213-20.

Clemmensen KK, Christensen RH, Shabaneh DN, Harila-Saari A, Heyman M, Jonsson OG, Wesenberg F, Rosthøj S, Schmiegelow K; Nordic Society of Pediatric Hematology, Oncology (NOPHO). *The circadian schedule for childhood acute lymphoblastic leukemia maintenance therapy does not influence event-free survival in the NOPHO ALL92 protocol.*Pediatr Blood Cancer. 2014 Apr;61(4):653-8.

Levinsen M, Rotevatn EØ, Rosthøj S, Nersting J, Abrahamsson J, Appell ML, Bergan S, Bechensteen AG, Harila-Saari A, Heyman M, Jonsson OG, Maxild JB, Niemi M, Söderhäll S, Schmiegelow K; Nordic Society of Paediatric Haematology, Oncology (NOPHO). *Pharmacogenetically based dosing of thiopurines in childhood acute lymphoblastic leukemia: Influence on cure rates and risk of second cancer.* Pediatr Blood Cancer. 2014 May;61(5):797-802.

Bartuma K, Pal N, Kosek S, Holm S, All-Ericsson C. *A 10-year experience of outcome in chemotherapy-treated hereditary retinoblastoma.* Acta Ophthalmol. 2014 Aug;92(5):404-11.

Skou AS, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros-Svennilson J, Nysom K, Hasle H. *Renal, gastrointestinal, and hepatic late effects in survivors of childhood acute myeloid leukemia treated with chemotherapy only--a NOPHO-AML study.* Pediatr Blood Cancer. 2014 Sep;61(9):1638-43.

Schmiegelow K, Nielsen SN, Frandsen TL, Nersting J. *Mercaptopurine/ Methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction.* J Pediatr Hematol Oncol 2014; 36:503-17.

2015

Henriksen LT, Harila-Saari A, Ruud E, Abrahamsson J, Pruunsild K, Vaitkeviciene G, Jónsson ÓG, Schmiegelow K, Heyman M, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group. *PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol.* Pediatr Blood Cancer 2015; 62: 427-33.

Vang SI, Schmiegelow K, Frandsen T, Rosthøj S, Nersting J. *Mercaptopurine metabolite levels are predictors of bone marrow toxicity following high-dose methotrexate therapy of childhood acute lymphoblastic leukaemia.* Cancer Chemother Pharmacol. 2015 May;75(5):1089-93.

Ranta S, Tuckuviene R, Mäkipernaa A, Albertsen BK, Frisk T, Tedgård U, Jónsson ÓG, Pruunsild K, Gretenkort Andersson N, Winther Gunnes M, Saulyte Trakymiene S, Frandsen T, Heyman M, Ruud E, Helgestad J. *Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia - a multicentre study from the Nordic Society of Paediatric Haematology and Oncology.* Br J Haematol. 2015 Feb;168 (4):547-52.

Sandahl JD, Kjeldsen E, Abrahamsson J, Ha SY, Heldrup J, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H. *The applicability of the WHO classification in paediatric AML. A NOPHO-AML study.* Br J Haematol. 2015 Mar 29.

Niemeyer CM, Loh ML, Cseh A, Cooper T, Dvorak CC, Chan R, Xicoy B, Germing U, Kojima S, Manabe A, Dworzak M, De Moerloose B, Starý J, Smith OP, Masetti R, Catala A, Bergstraesser E, Ussowicz M, Fabri O, Baruchel A, Cavé H, Zwaan M, Locatelli F, Hasle H, van den Heuvel-Eibrink MM, Flotho C, Yoshimi A. *Criteria for evaluating response and outcome in clinical trials for children with juvenile myelomonocytic leukemia.* Haematologica. 2015; 100: 17-22.

Aalbers AM, van den Heuvel-Eibrink MM, Baumann I, Dworzak M, Hasle H, Locatelli F, De Moerloose B, Schmugge M, Mejstrikova E, Nováková M, Zecca M, Zwaan CM, Te Marvelde JG, Langerak AW, van Dongen JJ, Pieters R, Niemeyer CM, van der Velden VH. *Bone marrow immunophenotyping by flow cytometry in refractory cytopenia of childhood.* Haematologica 2015;100:315-23.

Cseh A, A, Niemeyer CM, Yoshimi A, Dworzak M, Hasle H, van den Heuvel-Eibrink MM, Locatelli F, Masetti R, Schmugge M, Groß-Wieltsch U, Candás A, Kulozik AE, Olcay L, Suttorp M, Furlan I, Strahm B, Flotho C. *Bridging to transplant with azacitidine in juvenile myeloproliferative leukemia: a retrospective analysis of the EWOG-MDS study group.* Blood 2015; 125: 2311-3.

Bartholdson C, Lützén K, Blomgren K, Pergert P. *Experiences of ethical issues when caring for children with cancer.* Cancer Nursing, 2015 Mar-Apr;38(2):125-32.

Uldall P, Andersen M, Greisen G, Hagelund Hansen B, Holte Kofoed E, Bresson Ladegaard Knox J, Nabe-Nielsen H, Petersen G, Ploug T, Sehested A. *Landets første klinisk etisk komite for pædiatri.* 2015 Ugeskrift for læger.

Inaba H, Zhou Y, Abla O, Adachi S, Auvrignon A, Beverloo HB, de Bont E, Chang TT, Creutzig U, Dworzak M, Elitzur S, Fynn A, Forestier E, Hasle H, Liang DC, Lee V, Locatelli F, Masetti R, De Moerloose B, Reinhardt D, Rodriguez L, Van Roy N, Shen S, Taga T, Tomizawa D, Yeoh AE, Zimmermann M, Raimondi SC. *Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study.* Blood 2015 126(13):1575-84.

Hersby DS, Sehested A, Kristensen K, Schmiegelow K. *T-cell ALL in Ataxia Telangiectasia Cured With Only 7 Weeks of Anti-leukemic Therapy.* J Pediatr Hematol Oncol. 2015 Mar;37(2):154-5

Zwaan CM, Kolb EA, Reinhardt D, Abrahamsson J, Adachi S, Aplenc R, De Bont ES, De Moerloose B, Dworzak M, Gibson BE, Hasle H, Leverger G, Locatelli F, Ragu C, Ribeiro RC, Rizzari C, Rubnitz JE, Smith OP, Sung L, Tomizawa D, van-denHeuvel-Eibrink MM, Creutzig U, Kaspers GJ. *Collaborative Efforts Driving Progress In Pediatric Acute Myeloid Leukemia.* J Clin Oncol 2015 33(27):2949-62.

Alexander S, Pole JD, Gibson P, Lee M, Hesser T, Chi SN, Dvorak CC, Fisher B, Hasle H, Kanerva J, Möricke A, Phillips B, Raetz E,Rodriguez-Galindo C, Samarasinghe S, Schmiegelow K, Tissing W, Lehrnbecher T, Sung L; International Pediatric Oncology Mortality Classification Group. *Classification of treatment-related mortality in children with cancer: a systematic assessment.* Lancet Oncol. 2015 Dec;16(16):e604-10.

Wesołowska-Andersen A, Borst L, Dalgaard MD, Yadav R, Rasmussen KK, Wehner PS, Rasmussen M, Ørntoft TF, Nordentoft I, Koehler R, Bartram CR, Schrappe M, Sicheritz-Ponten T, Gautier L, Marquart H, Madsen HO, Brunak S, Stanulla M, Gupta R, Schmiegelow K. *Genomic profiling of thousands of candidate polymorphisms predicts risk of relapse in 778 Danish and German childhood acute lymphoblastic leukemia patients.* Leukemia 2015; 29:297-303.

Lindqvist CM, Nordlund J, Ekman D, Johansson A, Moghadam BT, Raine A, Övernäs E, Dahlberg J, Wahlberg P, Henriksson N, Abrahamsson J, Frost BM, Grandér D, Heyman M, Larsson R, Palle J, Söderhäll S, Forestier E, Lönnerholm G, Syvänen AC, Berglund EC. *The mutational landscape in pediatric acute lymphoblastic leukemiadeciphered by whole genome sequencing.* Hum Mutat. 2015 Jan;36(1):118-28.

Nordlund J, Bäcklin CL, Zachariadis V, Cavelier L, Dahlberg J, Öfverholm I, Barbany G, Nordgren A, Övernäs E, Abrahamsson J, Flaegstad T, Heyman MM, Jónsson ÓG,

Kanerva J, Larsson R, Palle J, Schmiegelow K, Gustafsson MG, Lönnerholm G, Forestier E, Syvänen AC. *DNA methylation-based subtype prediction for pediatric acute lymphoblastic leukemia.* Clin Epigenetics. 2015 Feb 17;7(1):11

Nielsen SN, Frandsen TL, Nersting J, Hjalgrim LL, Schmiegelow K. *Pharmacokinetics of 6-Thioguanine and 6-Mercaptopurine Combination Maintenance Therapy of Childhood ALL: Hypothesis and Case Report.* J Pediatr Hematol Oncol. 2015 Apr;37(3):e206-9.

Svedberg, P., Einberg, E-L., Wärnestål, P., Stigmar, J., Castor, A., Enskär, K., & Nygren, JM. *Support from healthcare services during transition to adulthood – Experiences of young adult survivors of pediatric cancer.* (2016) European Journal of Oncology Nursing Apr;21:105-12.

2016

Wlodarski MW, Hirabayashi S, Pastor V, Starý J, Hasle H, Masetti R, Dworzak M, Schmugge M, van den Heuvel-Eibrink M, Ussowicz M, De Moerloose B, Catala A, Smith OP, Sedlacek P, Lankester AC, Zecca M, Bordon V, Matthes-Martin S, Abrahamsson J, Kühl JS, Sykora KW, Albert MH, Przychodzien B, Maciejewski J, Schwarz S, Göhring G, Schlegelberger B, Cseh A, Noellke P, Yoshimi A, Locatelli F, Baumann I, Strahm B, Niemeyer CM. *Prevalence, clinical characteristics and prognosis of GATA2-related MDS in children and adolescents.* Blood 2016; 127: 1387-97.

Oskarsson T, Söderhäll S, Arvidson J, Forestier E, Montgomery S, Bottai M, Lausen B, Carlsen N, Hellebostad M, Lähteenmäki P, Saarinen-Pihkala UM, Jónsson ÓG, Heyman M; Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL relapse working group. *Relapsed childhood acute lymphoblastic leukemia in the Nordic countries: prognostic factors, treatment and outcome.* Haematologica. 2016 Jan;101(1):68-76.

Jarfelt M, Andersen NH, Glosli H, Jahnukainen K, Jónmundsson GK, Malmros J, Nysom K, Hasle H. *Cardiac function in survivors of childhood acute myeloid leukemia treated with chemotherapy only: A NOPHO-AML study.* Eur J Haematol. 2016 Jul;97(1):55-62.

Cseh AM, Niemeyer CM, Yoshimi A, Catala A, Frühwald MC, Hasle H, van den Heuvel-Eibrink MM, Lauten M, De Moerloose B, Smith OP, Bernig T, Gruhn B, Kulozik AE, Metzler M, Olcay L, Suttorp M, Furlan I, Strahm B, Flotho C. *Therapy with low-dose azacitidine for MDS in children and young adults: a retrospective analysis of the EWOG-MDS study group.* British Journal of Haematology 2016; 172: 930–6.

Bartholdson C, Lützén K, Blomgren K, Pergert P. *Clarifying perspectives: ethics case reflection sessions in childhood cancer care.* Nurs Ethics. 2016 Jun;23(4):421-31.

Bartholdson C, af Sandeberg M, Lützén, K, Blomgren K, Pergert P. *Healthcare professionals' perceptions of the ethical climate in paediatric cancer care.* Nurs Ethics. 2016 Dec;23(8):877-888.

Gregersen PA, Urbak SF, Funding M, Overgaard J, Jensen UB, Alsner J. *Danish retinoblastoma patients 1943-2013 - genetic testing and clinical implications.* Acta Oncol. 2016;55(4):412-7.

Tuckuviene R, Ranta S, Albertsen BK, Andersson NG, Bendtsen MD, Frisk T, Gunnes MW, Helgestad J, Heyman MM, Jonsson OG, Mäkipernaa A, Pruunsild K, Tedgård U, Trakymiene SS, Ruud E. *Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study.* J Thromb Haemost. 2016 Mar;14(3):485-94.

Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson ÓG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Asberg A, Helt LR, Frandsen T, Schmiegelow K. *Toxicity profile and treatment delays in NOPHO ALL2008 – comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia.* Eur J Haematol 2016; 96:160-9.

Tulstrup M, Larsen HB, Castor A, Rossel P, Grell K, Heyman M, Abrahamsson J, Söderhäll S, Åsberg A, Jonsson OG, Vettenranta K, Frandsen TL, Albertsen BK, Schmiegelow K; Nordic Society of Paediatric Haematology, and Oncology (NOPHO). *Parents' and Adolescents' Preferences for Intensified or Reduced Treatment in Randomized Lymphoblastic Leukemia Trials.* Pediatr Blood Cancer 2016; 63:865-71.

Schmiegelow K, Attarbaschi A, Barzilai S, Escherich G, Frandsen TL, Halsey C, Hough R, Jeha S, Kato M, Liang D-C, Mikkelsen TS, Möricke A, Niinimäki R, Piette C, Putti MC, Raetz E, Silverman LB, Skinner R, Tuckuviene R, van der Sluis I, Zapotocka E - on behalf of the Ponte di Legno toxicity working group. *Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus.* Lancet Oncol. 2016 Jun;17(6):e231-9.

Ceppi F, Weitzman S, Woessmann W, Davies K, Lassaletta A, Bettina R, Mellgren K, Uyttebroeck A, Maia I, Abdullah S, Miakova N, Glaser D, Cohn R, Abla O, Attarbaschi A, Alexander S. *Safety and efficacy of intrathecal rituximab in children with B cell lymphoid CD20+ malignancies: An international retrospective study.* Am J Hematol. 2016 May;91(5):486-91.

Mellgren K, Attarbaschi A, Abla O, Alexander S, Bomken S, Brugieres L, Bubanska E, Chiang A , Csóka, M, Fedorova A, Kabickova E, Kobayashi R, Krenova, Z, Meyer-Wentrup F, Miakova N, Pillon M, Uyttebroeck A, Williams D, Wróbel G, and Kontny U on behalf of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the International Berlin-Frankfurt-Münster (I-BFM) Group. *Non-anaplastic peripheral T-cell lymphoma in children and adolescents – an international review of 143 cases.* Ann Hematol. 2016 Aug;95(8):1295-305.

Wennstrom L, Wendtlant Edsløv P, Abrahamsson J, Maxweell Nørgaard J, Fløisand Y, Forestier E, Gustafsson G, Heldrup J, Hovi L, Jahnukainen K, Jonsson OG, Lausen B, Palle J, Zeller B, Holmberg E, Juliuson G, Stockelberg D, Hasle H. *Acute myeloid leukemia in adolescents and young adults in the nordic countries – outcome according to pediatric and adult treatment protocols.* Pediatr Blood & Cancer 2016 63(1):83-92.

Tierens A, Bjørklund E, Siitonen S, Marquart HV, Wulff-Juergensen G, Pelliniemi TT, Forestier E, Hasle H, Jahnukainen K, Lausen B, Jonsson OG, Palle J, Zeller B, Fogelstrand L, Abrahamsson J. *Residual disease detected by flow cytometry is an independent predictor of survival in childhood acute myeloid leukaemia; results of the NOPHO-AML 2004 study.* Br J Haematol. 2016 Aug;174(4):600-9.

Laursen AC, Sandahl JD, Kjeldsen E, Abrahamsson J, Asdahl P, Ha SY, Heldrup J, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H. *Trisomy 8 in Pediatric Acute Myeloid Leukemia. A NOPHO-AML Study.* Genes Chromosomes Cancer. 2016 Sep;55(9):719-26.

Borssén M, Haider Z, Landfors M, Norén-Nyström U, Schmiegelow K, Åsberg AE, Kanerva J, Madsen HO, Marquart H, Heyman M, Hultdin M, Roos G, Forestier E, Degerman S. *DNA Methylation Adds Prognostic Value to Minimal Residual Disease Status in Pediatric T-Cell Acute Lymphoblastic Leukemia.* Pediatr Blood Cancer. 2016 Jul;63(7):1185-92.

Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson ÓG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Asberg A, Helt LR, Frandsen T, Schmiegelow K. *Toxicity profile and treatment delays in NOPHO ALL2008 – comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia.* Eur J Haematol. 2016 Feb;96(2):160-9.

Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, Vettenranta K, Åsberg A, Risteli J, Heldrup J, Schmiegelow K. *Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia.* J Ped Hematol Oncol 2016; 38:602-9.

Levinsen M, Marquart HV, Groth-Pedersen L, Abrahamsson J, Albertsen BK, Andersen MK, Frandsen TL, Harila-Saari A, Pronk C, Ulvmoen A, Vaitkevičienė G, Lähteenmäki PM, Niinimäki R, Taskinen M, Jeppesen M, Schmiegelow K - for the Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Leukemic blasts are present at low levels in spinal fluid in one third of childhood acute lymphoblastic leukemia cases.* Ped Blood Cancer 2016; 63:1935-1942.

Nielsen SN, Grell K, Nersting J, Frandsen TL, Hjalgrim LL, Schmiegelow K. *Measures of 6-mercaptopurine and methotrexate maintenance therapy intensity in childhood acute lymphoblastic leukemia.* Cancer Chemother Pharmacol 2016; 78:983-94.

Løhmann DJ, Abrahamsson J, Ha SY, Jónsson ÓG, Koskenvuo M, Lausen B, Palle J, Zeller B, Hasle H. *Effect of age and body weight on toxicity and survival in pediatric acute myeloid leukemia: results from NOPHO-AML 2004.* Haematologica. 2016 Nov;101(11):1359-1367.

2017

Taskinen M, Oskarsson T, Levinsen M, Bottai M, Hellebostad M, Jonsson OG, Lähteenmäki P, Schmiegelow K, Heyman M. *The effect of central nervous system involvement and irradiation in childhood ALL: Lessons from the NOPHO ALL-92 and ALL-2000 protocols.* Pediatr Blood Cancer. 2017 Feb;64(2):242-249.

Ranta S, Palomäki M, Levinsen M, Taskinen M, Abrahamsson J, Mellgren K, Niinimäki R, Schmiegelow K, Heyman M, Harila-Saari A. *Role of neuroimaging in children with acute lymphoblastic leukemia and central nervous system involvement at diagnosis.* Ped Blood Cancer 2017; 64:64-70.

Mogensen SS, Schmiegelow K, Grell K, Albertsen BK, Wehner PS, Kampmann P, Frandsen TL. *Hyperlipidemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukemia.* Haematologica 2017 (in press).

Wolthers BO, Frandsen T, Abrahamsson J, Albertsen B, Helt L, Heyman M, Jonsson O, Kõrgvee L-T, Lund B, Raja B, Rasmussen K, Taskinen M, Tulstrup M, Vaitkeviciene G, Yadav R, Gupta R, Schmiegelow K. *Asparaginase-associated pancreatitis A study on pheno- and genotype in the NOPHO ALL2008 protocol.* Leukemia 2017;31:325-332.

Svahn T, Mellgren K, Harila-Saari A, Åsberg A, Kanerva J, Jónsson O, Vaitkeviciene G, Mikkelssen TS, Schmiegelow K, Heldrup J. *Delayed elimination of high dose methotrexate and use of Carboxypeptidase G2 in pediatric patients during treatment for acute lymphoblastic leukemia.* Ped Blood Cancer 2017 (in press).

Nielsen SN, Eriksson F, Rosthoej S, Andersen MK, Forestier E, Hasle H, Hjalgrim LL, Aasberg A, Abrahamsson J, Heyman M, Jónsson OG, Pruunsild K, Vaitkevicienė GE, Vettenranta K, Schmiegelow K. *Children with low risk acute lymphoblastic leukemia are at highest risk of second cancers.* Ped Blood Cancer 2017 (In press).

Nielsen SN, Grell K, Nersting J, Abrahamson J, Lund B, Kanerva J, Jónsson OG, Vaitkeviciene G, Pruunsild K, Hjalgrim LL, Schmiegelow K. *DNA-thioguanine nucleotide concentration and relapse-free survival during maintenance therapy of childhood acute lymphoblastic leukaemia (NOPHO ALL2008): a prospective substudy of a phase 3 trial.* Lancet Oncol. 2017 Apr;18(4):515-524

Støve HK, Sandahl JD, Abrahamsson J, Asdahl PH, Forestier E, Ha SY, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Hasle H. *Extramedullary leukemia in children with acute myeloid leukemia: A population-based cohort study from the Nordic Society of Pediatric Hematology and Oncology (NOPHO).* Pediatr Blood Cancer. 2017 Dec;64(12).

Karlsson L, Forestier E, Hasle H, Jahnukainen K, Jónsson OG, Lausen B, Norén Nyström U, Palle J, Tierens A, Bernward Zeller, Jonas Abrahamsson. *Outcome after intensive reinduction therapy and allogeneic stem cell transplant in pediatric relapsed acute myeloid leukemia*. Br J Haematol 2017 Aug;178(4):592-602.

Ebbesen MS, Nygaard U, Rosthøj S, Sørensen D, Nersting J, Vettenranta K, Wesenberg F, Kristinsson J, Harila-Saari A, Schmiegelow K. *Hepatotoxicity During Maintenance Therapy and Prognosis in Children With Acute Lymphoblastic Leukemia.* J Pediatr Hematol Oncol. 2017 Apr;39(3):161-166.

Ranta S, Palomäki M, Levinsen M, Taskinen M, Abrahamsson J, Hasle H, Jahnukainen K, Heyman M, Harila-Saari A; Nordic Society of Pediatric Haematology and Oncology (NOPHO). *Presenting features and imaging in childhood acute myeloid leukemia with central nervous system involvement.* Pediatr Blood Cancer. 2017 Dec;64(12).

Uffmann M, Rasche M, Zimmermann M, von Neuhoff C, Creutzig U, Dworzak M, Scheffers L, Hasle H, Zwaan CM, Reinhardt D, Klusmann JH. *Therapy reduction in patients with Down syndrome and myeloid leukemia: the international ML-DS 2006 trial.* Blood 2017 Jun 22;129(25):3314-

Creutzig U, Zimmerman M, Reinhardt D, Dworzak M, Sramkova L, Bourquin JP, Hasle H, Abrahamsson J, Kaspers GJ, van

den Heuvel MM, Reedijk A, De Moerloose B, Locatelli F, Masetti R. *Characteristics and outcome in patients with central nervous system involvement treated in European pediatric acute myeloid leukemia groups*. Pediatric Blood Cancer 2017 Dec 64;12

af Sandeberg M, Bartholdson C, Wenemark M, Lutzen K, Pergert P (2017): *To change or not to change – Translating and culturally adapting the paediatric version of the Moral Distress Scale-Revised (MDS-R).* BMC Medical Ethics (2017) Feb 20;18, 14.

Toksvang LN, Pietri SD, Nygaard SN, Nersting J, Albertsen BK, Wehner PS, Rosthøj S, Lähteenmäki PM, Nilsson D, Nystad TA, Grell K, Frandsen TL, Schmiegelow K. *Hepatic sinusoidal obstruction syndrome during maintenance therapy of childhood acute lymphoblastic leukaemia is associated with continuous asparaginase therapy and mercaptopurine metabolites.* Pediatr Blood Cancer. 2017 Apr 19. doi: 10.1002/pbc.26519. [Epub ahead of print] PubMed PMID: 28423235

Zeller B, Glosli H, Forestier E, Ha SY, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Hasle H, Abrahamsson J; NOPHO AML working group. *Hyperleucocytosis in paediatric acute myeloid leukaemia - the challenge of white blood cell counts above 200 × 10⁹ /l. The NOPHO experience 1984-2014.* Br J Haematol. 2017 Aug;178(3):448-456.

Mogensen SS, Harila-Saari A, Frandsen TL, Lähteenmäki P, Castor A, Kohonen I, Schmiegelow K, Mäkitie O. *Early presentation of osteonecrosis in acute lymphoblastic leukemia: Two children from the Nordic and Baltic cohort*. Pediatr Blood Cancer. 2017 Nov;64(11).

Wolthers BO, Frandsen TL, Baruchel A, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grell K, Inaba H, Kovacs G, Liang DC, Mateos M, Mondelaers V, Möricke A, Ociepa T, Samarasinghe S, Silverman LB, van der Sluis IM, Stanulla M, Vrooman LM, Yano M, Zapotocka E, Schmiegelow K; Ponte di Legno Toxicity Working Group. *Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study.* Lancet Oncol. 2017 Sep;18(9):1238-1248.

Tram Henriksen L, Gottschalk Højfeldt S, Schmiegelow K, Frandsen TL, Skov Wehner P, Schrøder H, Klug Albertsen B; Nordic Society of Pediatric Hematology and Oncology, NOPHO Group. *Prolonged first-line PEG-asparaginase treatment in pediatric acute lymphoblastic leukemia in the NOPHO ALL2008 protocol-Pharmacokinetics and antibody formation.* Pediatr Blood Cancer. 2017 Dec;64(12)

Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, Ishii E, Janka G, Ladisch S, Lehmberg K, McClain KL, Minkov M, Montgomery S, Nanduri V, Rosso D, Henter JI. *Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study.* Blood. 2017 Dec 21;130(25):2728-2738.

Nielsen SN, Grell K, Nersting J, Abrahamson J, Lund B, Kanerva J, Jónsson OG, Vaitkeviciene G, Pruunsild K,Hjalgrim LL, Schmiegelow K. *Population-based, prospective analysis of dna thioguanine nucleotide levels during maintenance therapy of childhood acute lymphoblastic leukemia.* Lancet Oncol 2017 (In press).

Raja RA, Schmiegelow K, Sørensen DN, Frandsen TL. *Asparaginase associated pancreatitis is not predicted by Hypertriglyceridemia or Pancreas enzyme levels in children with acute lymphoblastic leukemia.* Ped Blood Cancer 2017; 64: 32-8.

Schmiegelow K, Nielsen SN, Grell K. *Do cytogenetics of acute lymphoblastic leukaemia blasts affect required duration and intensity of maintenance therapy? - Authors' reply.* Lancet Oncol. 2017 Jun;18(6):e292.

2018

Banerjee JS, Heyman M, Palomäki M, Lähteenmäki P, Arola M, Riikonen PV, Möttönen MI, Lönnqvist T, Taskinen MH, Harila-Saari AH. *Posterior Reversible Encephalopathy Syndrome: Risk Factors and Impact on the Outcome in Children With Acute Lymphoblastic Leukemia Treated With Nordic Protocols.* J Pediatr Hematol Oncol. 2018 Jan;40(1):e13-e18.

Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson ÓG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Marquart

HV, Madsen HO, Norén-Nyström U, Schmiegelow K. *Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia.* Leukemia. 2018 Mar;32(3):606-615.

Bartholdson, C., Molewijk, B., Lützén, K., Blomgren, K., Pergert, P. *Ethics case reflection sessions: Enablers and barriers*. Nursing Ethics, 2018 25(2):199-211.

Oskarsson T, Söderhäll S, Arvidson J, Forestier E, Frandsen TL, Hellebostad M, Lähteenmäki P, Jónsson ÓG, Myrberg IH, Heyman M; Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL Relapse Working Group. *Treatment-related mortality in relapsed childhood acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2018 Apr;65(4).

Landsend ES, Utheim OA, Pedersen HR, Lagali N, Baraas RC, Utheim TP. *The genetics of congenital aniridia-a guide for the ophthalmologist.* Surv Ophthalmol. 2018;63(1):105-13.

Englund A, Glimelius I, Rostgaard K, Smedby KE, Eloranta S, Molin D, Kuusk T, de Nully Brown P, Kamper P, Hjalgrim H, Ljungman G, Hjalgrim LL: *Hodgkin lymphoma in children, adolescents and young adults- a comparative study of treatment outcome and clinical presentation*, Acta Oncol. 2018 Feb;57(2):276-282.

Lundgaard AY, Hjalgrim LL, Rechner LA, Josipovic M, Joergensen M, Aznar MC, Berthelsen AK, Borgwardt L, Johansen C, Loft A, Safwat A, Vaalavirta L, Specht L, Maraldo MV: *TEDDI: radiotherapy delivery in deep inspiration for pediatric patients - a NOPHO feasibility study.* Radiat Oncol. 2018 Mar 27;13(1):56

Landmann E, Burkhardt B, Zimmermann M, Meyer U, Woessmann W, Klapper W, Wrobel G, Rosolen A, Pillon M, Escherich G, Attarbaschi A, Beishuizen A, Mellgren K, Wynn R, Ratei R, Plesa A, Schrappe M, Reiter A, Bergeron C, Patte C, Bertrand Y: *Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma*, Hematologica, 2017.

Espersen ADL, Norén-Nyström U, Abrahamsson J, Ha SY, Pronk KJ, Jahnukainen K, Jónsson ÒG, Lausen B, Palmqvist L, Hasle H. *AML with t(7;12)(q36;p13) is associated with infancy and trisomy 19. Data from NOPHO-AML and review of the literature*. Genes Chromosomes & Cancer 2018.

Gerbek T, Ebbesen M, Nersting J, Frandsen TL, Appell ML, Schmiegelow K. *Role of TPMT and ITPA variants in mercaptopurine disposition.* Cancer Chemother Pharmacol 2018 (In press).

Ramsey LB, Vinks AA, Schmiegelow K, Pauley JL, Bleyer A, Balis FM, Askenazi D, Bergeron S, Shirali A, Schwartz S, Widemann B, Heldrup J. *Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance.* The Oncologist 2018; 23: 52-61.

Tulstrup M, Frandsen TL, Abrahamsson J, Lund B, Vettenranta K, Jonsson OG, Marquart HVH, Albertsen BK, Heyman M, Schmiegelow K - on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Individualized 6-mercaptopurine dose increments in consolidation treatment of childhood acute lymphoblastic leukemia: a NOPHO ALL2008 randomized controlled trial.* Eur J Haematol 2018; 100: 53-60.

Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL. *Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia.* Ped Blood Cancer 2018; 65: e27071.

Wolthers BO, Mogensen PR, Frandsen TL, Abrahamsson J, Behrendtz M, Heyman M, Lohi O, Norén-Nyström U, Ruud E, Schmiegelow K. *Insulin dependent diabetes - a chronic complication to acute pancreatitis in childhood acute lymphoblastic leukemia.* Ped Blood Cancer 2019; 66(1):e27437.

Rank CU, Toft N, Tuckuviene R, Grell K, Nielsen OJ, Frandsen TL, Marquart HVH, Albertsen BK, Tedgård U, Hallböök H, Ruud E, Jarvis KB, Quist-Paulsen P, Huttunen P, Wartiovaara-Kautto U, Jónsson OG, Trakymiene SS, Griškevičius L, Saks K, Punab M, Schmiegelow K. *Thromboembolism in Acute Lymphoblastic Leukemia: Results of NOPHO ALL2008 Protocol Treatment in*

Patients 1–45 Years. Blood 2018 May 31; 131 (22):2475-84.

Hrusak O, Haas VD, Stancikova J, Janotova I, Mejstrikova E, Capek V, Trka J, Zaliova M, Luks A, Bleckmann K, Möricke A, Irving J, Konatkowska B, Alexander TB, Inaba H, Schmiegelow K, Stokley S, Zemanova Z, Moorman AV, Rossi JG, Felice MS, Dalla-Pozza L, Morales J, Dworzak M, Buldini B, Basso G, Campbell M, Cabrera ME, Marinov N, Elitzur S, Izraeli S, Luria D, Feuerstein T, Kolenova A, Svec P, Kreminska E, Rabin KR, Polychronopoulou S, da Costa E, Marquart HV, Kattamis A, Ratei R, Reinhardt D, Choi JK, Schrappe M, Stary J. *International cooperative study identifies treatment strategy in childhood ambiguous lineage leukemia.* Blood 2018; 132: 264-76.

Mogensen SS, Harila-Saari A, Schmiegelow K, Mäkitie O, Myrberg IH, Niinimäki R, Ruud E, Hafsteinsdottir S, Griškevicius L, Saks K, Hallböök H, Retpen J, Helt LR, Frandsen TL. *Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia.* Ped Blood Cancer 2018 Oct;65(10): e27300.

Tulstrup M, Grosjean M, Nielsen SN, Grell K, Wolthers BO, Wegener PS, Jonsson OG, Lund B, Harila-Saari A, Abrahamsson J, Vaitkeviciene G, Pruunsild K, Toft N, Holm M, Hulegårdh E, Liestøl S, Griskevicius L, Punab M, Wang J, Carroll WL, Zhang Z, Dalgaard MD, Gupta R, Nersting J, Schmiegelow. *NT5C2 germline variants alter thiopurine metabolism and are associated with acquired NT5C2 relapse mutations in childhood acute lymphoblastic leukaemia.* Leukemia 2018; 32: 2527-35.

Nersting J, Nielsen SN, Grell K, Pærregaard M, Abrahamsson J, Lund B, Jonsson OG, Pruunsild K, Vaitkeviciene G, Kanerva J, Schmiegelow K. *Methotrexate polyglutamate levels and co-distributions in childhood acute lymphoblastic leukemia maintenance therapy*. Cancer Chemother Pharm (In press).

Løhmann D, Asdahl PH, Abrahamsson J, Ha SY, Jónsson OG, Kaspers GK, Koskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Hasle H. *Associations between Neutrophil Recovery Time, Infections and Relapse in Paediatric Acute Myeloid Leukemia.* Pediatr Blood Cancer. 2018 Sep;65(9):e27231. doi: 10.1002/pbc.27231

Klein K, Hasle H, Abrahamsson J, De Moerloose B, Kaspers GK. *Differences in Infection Prophylaxis Measures Between Pediatric AML Study Groups Within the I-BFM Study Group.* Br J Haematology 2018, 183, 87–95. doi: 10.1111/bjh.15499

Noort S, Zimmermann M, Reinhardt D, Cuccuini W, Pigazzi M, Smith J, Ries RE, Alonzo TA, Hirsch B, Tomizawa D, Locatelli F, Gruber TA, Raimondi S, Sonneveld E, Cheuk DK, Dworzak M, Stary J, Abrahamsson J, Arad-Cohen N, Balwierz W, De Moerloose B, Hasle H, Meshinchi S, van den Heuvel-Eibrink M, Zwaan M. *Prognostic impact of t(16;21)(p11;q22) and t(16;21)(q24;q22) in pediatric AML: a retrospective study by the I-BFM SG.* Blood 2018 132:1584-1592; doi: https://doi-org.ezproxy.ub.gu.se/10.1182/blood-2018-05-849059

Mari Wilhelmsson, Heidi Glosli, Marianne Ifversen, Jonas Abrahamsson, Jacek Winiarski, Kirsi Jahnukainen, Henrik Hasle on behalf of the Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Long-term health outcomes in survivors of childhood AML treated with allogeneic HSCT: A NOPHO –AML Study.* Bone Marrow Transplant. 2019 May;54(5):726-736.

Bager N, Juul-Dam KL, Julie D. Sandahl JD, Abrahamsson J, Beverloo B, de Bont ESJM, Ha SY, Jahnukainen K, Jónsson ÓG, Kaspers G, Kovalova Z, Lausen B, De Moerloose B, Noren-Nyström U, Palle J, Saks K, Zeller B, Kjeldsen E, Hasle H. *Complex and monosomal karyotype are distinct cytogenetic entities with an adverse prognostic impact in paediatric acute myeloid leukaemia. A NOPHO-DBH-AML study.* Br J Haematology 2018 2018 Nov;183(4):618-628. doi: 10.1111/bjh.15587.

Testi AM, Pession A, Diverio D, Grimwade D, Gibson B, de Azevedo AC, Moran L, Leverger G, Elitzur S, Hasle H, van der Werff ten Bosch J, Smith O, De Rosa M, Piciocchi A, Lo Coco F, Foà R, Locatelli F, Kaspers GJL. *Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL.* Blood 2018 132(4):405-412. doi: 10.1182/blood-2018-03-836528.

Pergert, P., Bartholdson, C., Wenemark, M., Lützén, K., & af Sandeberg, M. *(2018) Translating and culturally adapting the shortened version of the Hospital Ethical Climate Survey (HECS-S) – Retaining or modifying validated instruments,* BMC Medical Ethics 19(1):35

Pergert, P., Bartholdson, C., Blomgren, K., & af Sandeberg, M. *(2018) Moral distress in paediatric oncology: Contributing factors and group differences,* Nursing Ethics, [Epub ahead of print] 9 Nov

Borssén M, Nordlund J, Haider Z, Landfors M, Larsson P, Kanerva J, Schmiegelow K, Flaegstad T, Jónsson ÓG, Frost BM, Palle J, Forestier E, Heyman M, Hultdin M, Lönnerholm G, Degerman S. *DNA methylation holds prognostic information in relapsed precursor B-cell acute lymphoblastic leukemia.* Clin Epigenetics. 2018 Mar 5;10:31.

Olsson L, Lundin-Ström KB, Castor A, Behrendtz M, Biloglav A, Norén-Nyström U, Paulsson K, Johansson B. I*mproved cytogenetic characterization and risk stratification of pediatric acute lymphoblastic leukemia using single nucleotide polymorphism array analysis: A single center experience of 296 cases.* Genes Chromosomes Cancer. 2018 Nov;57(11):604-607.

2019

Modvig S, Madsen HO, Siitonen S, Rosthoej S, Tierens A, Juvonen V, Osnes L, Valerhaugen H, Hultdin M, Thörn I, Matuzeviciene R, Stoskus M, Marincevic M, Fogelstrand L, Lilleorg A, Toft N, Jonsson OG, Pruunsild K, Vaitkeviciene G, Vettenranta K, Lund B, Abrahamsson B, Schmiegelow K, Marquart HV. *Minimal Residual Disease Quantification by Flow Cytometry Provides Reliable Risk Stratification in T-cell Acute Lymphoblastic Leukemia.* Leukemia. 2019 Jun;33(6):1324-1336. Erratum in: Leukemia. 2019 Dec 10.

Anastasopoulou S, Eriksson MA, Heyman M, Wang C, Niinimäki R, Mikkel S, Vaitkevičienė GE, Johansdottir IM, Myrberg IH, Jonsson OG, Als-Nielsen B, Schmiegelow K, Banerjee J, Harila-Saari A, Ranta S. *Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: Clinical characteristics, risk factors, course and outcome of disease.* Pediatr Blood Cancer. 2019 May;66(5):e27594.

Ifversen M, Turkiewicz D, Marquart HV, Winiarski J, Buechner J, Mellgren K, Arvidson J, Rascon J, Körgvee LT, Madsen HO, Abrahamsson J, Lund B, Jonsson OG, Heilmann C, Heyman M, Schmiegelow K, Vettenranta K. *Low burden of minimal residual disease prior to transplantation in children with very high risk acute lymphoblastic leukaemia: The NOPHO ALL2008 experience.* Br J Haematol 2019 (In press).

Albertsen BK, Harila-Saari A, Jahnukainen K, Lähteenmäki P, Riikonen P, Möttönen M, Lausen B. *Asparaginase treatment in infants with acute lymphoblastic leukemia; pharmacokinetics and asparaginase hypersensitivity in Interfant-06.* Leuk Lymphoma. 2019 Jan 11:1-7.

Løhmann DJA, Asdahl PH, Abrahamsson J, Ha SY, Jónsson ÓG, Kaspers GJL, Koskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Hasle H. *Use of granulocyte colony stimulating factor and risk of relapse in pediatric patients treated for acute myeloid leukemia according to NOPHO-AML 2004 and DB AML-01.* Pediatric Blood Cancer 2019 Jan 41(1).

Wolthers BO, Frandsen TL, Patel CJ, Abaji R, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grosjean M, Krajinovic M, Larsen E, Liang D-C, Möricke A, Rasmussen KK, Samarasinghe S, Silverman LB, van der Sluis IM, StanullaM, Tulstrup M, Yadav R, Yang W, Zapotocka E, Gupta R, Schmiegelow K. *Trypsin Encoding PRSS1-PRSS2 Variation Influence the risk of Asparaginase-associated Pancreatitis in Children with Acute Lymphoblastic Leukemia: a Ponte di Legno Toxicity Working Group Report.* Haematologica. 2019 Mar;104(3):556-563.

Skou AS, Olsen SØ, Nielsen LH, Glosli H, Jahnukainen K, Jarfelt M, Jónmundsson GK, Malmros J, Nysom K, Hasle H; Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Hearing Status in Survivors of Childhood Acute Myeloid Leukemia Treated With Chemotherapy Only: A NOPHO-AML Study.* J Pediatr Hematol Oncol. 2019 Jan;41(1):e12-e17.

Højfeldt SG, Wolthers BO, Tulstrup M, Abrahamsson J, Gupta R, Harila-Saari A, Heyman M, Henriksen LT, Jónsson OG, Lähteenmäki PM, Lund B, Pruunsild K, Vaitkeviciene G, Schmiegelow K, Albertsen BK - on behalf of

the Nordic Society of Pediatric Hematology and Oncology, NOPHO group. *Genetic predisposition to PEG-Asparaginase Hypersensitivity in Children treated according to NOPHO ALL2008*. Br J Haematol 2019; 184: 405-17.

Nersting J, Nielsen SN, Grell K, Paerregaard M, Abrahamsson J, Lund B, Jonsson OG, Pruunsild K, Vaitkeviciene G, Kanerva J, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Methotrexate polyglutamate levels and co-distributions in childhood acute lymphoblastic leukemia maintenance therapy.* Cancer Chemother Pharmacol. 2019 Jan;83(1):53-60.

Jarvis KB, LeBlanc M, Tulstrup M, Nielsen RL, Albertsen BK, Gupta R, Huttunen P, Jónsson ÓG, Rank CU, Ranta S, Ruud E, Saks K, Trakymiene SS, Tuckuviene R, Schmiegelow K. *Candidate single nucleotide polymorphisms and thromboembolism in acute lymphoblastic leukemia - A NOPHO ALL2008 study.* Thromb Res. 2019 Dec;184:92-98.

Pieters R, De Lorenzo P, Ancliffe P, Aversa LA, Brethon B, Biondi A, Campbell M, Escherich G, Ferster A, Gardner RA, Kotecha RS, Lausen B, Li CK, Locatelli F, Attarbaschi A, Peters C, Rubnitz JE, Silverman LB, Stary J, Szczepanski T, Vora A, Schrappe M, Valsecchi MG. *Outcome of Infants Younger Than 1 Year with Acute Lymphoblastic Leukemia Treated with the Interfant-06 Protocol: Results from an International Phase III Randomized Study.* J Clin Oncol. 2019 Sep 1;37(25):2246-2256. doi: 10.1200/JCO.19.00261. Epub 2019 Jul 8.

Pergert, P., Bartholdson, C., Blomgren, K., & af Sandeberg, M. *Moral distress in paediatric oncology: Contributing factors and group differences*, Nursing Ethics. 2019 26(7-8):2351-2363.

Pergert, P., Bartholdson, C., & af Sandeberg, M. *The ethical climate in paediatric oncology—A national cross-sectional survey of health-care personnel.* Psycho-Oncology. 2019 Apr;28(4):735-741. DOI:10.1002/pon.5009

Schröder Håkansson, A., Pergert, P, Abrahamsson, J., Stenmarker, M. *Balancing values and obligations when obtaining informed consent: healthcare professionals' experiences in Swedish paediatric oncology.* Acta Paediatrica, 2019; Accepted. DOI: 10.1111/apa.15010

Granhagen Jungner, J., Tiselius, E., Blomgren, K., Lützén, K., Pergert, P. *Language barriers and the use of professional interpreters: A national multisite cross-sectional survey in paediatric oncology care.* Acta Oncologica. 2019; 58(7), 1015–1020.

af Sandeberg, M., Bartholdson, C. & Pergert, P. *Important situations that capture moral distress in paediatric oncology.* BMC Med Ethics. 2020;21(1):6.

Pergert, P., Sullivan, CE., Adde, M., Afungchwi GM., Downing, J., Hollis, R., Ilbawi , A., Morrissey, L., Punjwani, R. & Challinor, J. *An ethical imperative: Safety and specialization as nursing priorities of WHO Global Initiative for Childhood Cancer.* Pediatr Blood Cancer. 2019;e28143.

Stensvold E, Myklebust TÅ, Cappelen J, Due-Tønnessen BJ, Due-Tønnessen P, Kepka A, Johannesen TB, Krossnes B, Lundar T, Maric S, Miletic H, Moholdt V, Myrmel KS, Nordberg T, Rydland J, Stokland T, Solem K, Solheim O, Torsvik I, Wikran GC, Zeller B, Wesenberg F, Bechensteen AG, Brandal P. *Children treated for medulloblastoma and supratentorial PNET in Norway from 1974 through 2013: Unexplainable regional differences in survival.* Pediatr Blood Cancer. 2019 Oct;66(10):e27910.

Löhmann DJA, Asdahl PH, Abrahamsson J, Ha SY, Jonsson OG, Kaspers GJL, Konskenvuo M, Lausen B, De Moerloose B, Palle J, Zeller B, Sung L, Hasle H. *Associations between pre-therapeutic body mass index, outcome and cytogenetic abnormalities in pediatric acute myeloid leukemia.* Cancer Med. 2019 Nov;8(15):6634-6643. doi: 10.1002/cam4.2554. Epub 2019 Sep 18.

Albertsen BK, Grell K, Abrahamsson J, Lund B, Vettenranta K, Jónsson ÓG, Frandsen TL, Wolthers BO, Heyman M, Schmiegelow K. *Intermittent Versus Continuous PEG-Asparaginase to Reduce Asparaginase-Associated Toxicities: A NOPHO ALL2008 Randomized Study.* J Clin Oncol. 2019 Jul 1;37(19):1638-1646.

Schmidt D, Kristensen K, Schroeder H, Wehner PS, Rosthøj S, Heldrup J, Damsgaard L, Schmiegelow K, Mikkelsen TS. *Plasma creati-*

nine as predictor of delayed elimination of high-dose methotrexate in childhood acute lymphoblastic leukemia: A Danish population-based study. Pediatr Blood Cancer. 2019 Jun;66(6):e27637.

2020

Nordlund J, Marincevic-Zuniga Y, Cavelier L, Raine A, Martin T, Lundmark A, Abrahamsson J, Norén-Nyström U, Lönnerholm G, Syvänen AC. *Refined detection and phasing of structural aberrations in pediatric acute lymphoblastic leukemia by linked-read whole-genome sequencing.* Sci Rep. 2020 Feb 13;10(1):2512.

Uden T, Bertaina A, Abrahamsson J, Ansari M, Balduzzi A, Bourquin JP, Gerhardt C, Bierings M, Hasle H, Lankester A, Mischke K, Moore AS, Nivison-Smith I, Pieczonka A, Peters C, Sedlacek P, Reinhardt D, Stein J, Versluys B, Wachowiak J, Wiilems L, Zimmermann M, Locatelli F, Sauer M. *Outcome of Children Relapsing after First Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Acute Myeloid Leukemia: A Retrospective I-BFM Analysis of 333 Children.* Br J Haematol 2020 Feb 3.

KL Juul-Dahm Hans Beier Ommen, Charlotte Guldborg Nyvold, Christiane Walter, Helen Vålerhaugen, Veli Kairisto, Jonas Abrahamsson, Sofie Johansson Alm, Kirsi Jahnukainen, Birgitte Lausen1, Dirk Reinhardt, Bernward Zeller, Nils Von Neuhoff, Linda Fogelstrand, Henrik Hasle. *Measurable residual disease assessment by qPCR in peripheral blood is an informative tool for disease surveillance in childhood acute myeloid leukemia.* Br J Haematol 2020 In press.

Anastasopoulou S, Heyman M, Eriksson MA, Niinimäki R, Taskinen M, Mikkel S, Vaitkeviciene GE, Johannsdottir IM, Myrberg IH, Jonsson OG, Als-Nielsen B, Schmiegelow K, Banerjee J, Ranta S, Harila-Saari A. *Seizures during treatment of childhood acute lymphoblastic leukemia: A population-based cohort study.* Eur J Paediatr Neurol. 2020 Apr 18.

Rank CU, Wolthers BO, Grell K, Albertsen BK, Frandsen TL, Overgaard UM, Toft N, Nielsen OJ, Wehner PS, Harila-Saari A, Heyman MM, Malmros J, Abrahamsson J, Norén-Nyström U, Tomaszewska-Toporska B, Lund B, Jarvis KB, Quist-Paulsen P, Vaitkevičienė GE, Griškevičius L, Taskinen M, Wartiovaara-Kautto U, Lepik K, Punab M, Jónsson ÓG, Schmiegelow K. *Asparaginase-Associated Pancreatitis in Acute Lymphoblastic Leukemia: Results From the NOPHO ALL2008 Treatment of Patients 1-45 Years of Age.* J Clin Oncol. 2020 Jan 10;38(2):145-154.

Wahlund M, Nilsson A, Kahlin AZ, Broliden K, Myrberg IH, Appell ML, Berggren A. *The Role of TPMT, ITPA, and NUDT15 Variants during Mercaptopurine Treatment of Swedish Pediatric Patients with Acute Lymphoblastic Leukemia.* J Pediatr. 2020 Jan;216:150-157.e1.

Mogensen PR, Grell K, Schmiegelow K, Overgaard UM, Wolthers BO, Mogensen SS, Vaag A, Frandsen TL. *Dyslipidemia at diagnosis of childhood acute lymphoblastic leukemia.* PLoS One. 2020 Apr 6;15(4):e0231209.

Quist-Paulsen P, Toft N, Heyman M, Abrahamsson J, Griškevičius L, Hallböök H, Jónsson ÓG, Palk K, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Opdahl S, Marquart HV, Siitonen S, Osnes LT, Hultdin M, Overgaard UM, Wartiovaara-Kautto U, Schmiegelow K. *T-cell acute lymphoblastic leukemia in patients 1-45 years treated with the pediatric NOPHO ALL2008 protocol.* Leukemia. 2020 Feb;34(2):347-357.

Thastrup M, Marquart HV, Levinsen M, Grell K, Abrahamsson J, Albertsen BK, Frandsen TL, Harila-Saari A, Lähteenmäki PM, Niinimäki R, Pronk CJ, Ulvmoen A, Vaitkevičienė G, Taskinen M, Schmiegelow K; Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Flow cytometric detection of leukemic blasts in cerebrospinal fluid predicts risk of relapse in childhood acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology study.* Leukemia. 2020 Feb;34(2):336-346.

Zachary L. Taylor, Tomoyuki Mizuno, Nieko C. Punt, Balaji Baskaran, Adriana Navarro Sainz, William Shuman, Nicholas Felicelli, Alexander A. Vinks, Jesper Heldrup, Laura B. Ramsey. *MTXPK.org: A clinical decision support tool evaluating high-dose methotrexate pharmacokinetics to inform post-infusion care and use of glucarpidase.* In press Clinical Pharmacology & Therapeutics. https://doi.org/10.1101/2020.04.08.20056713

Enshaei A, O'Connor D, Bartram J, Hancock J, Harrison CJ, Hough R, Samarasinghe S, den Boer ML, Boer JM, de Groot-Kruseman HA, Marquart HV, Noren-Nystrom U, Schmiegelow K, Schwab C, Horstmann MA, Escherich G, Heyman M, Pieters R, Vora A, Moppett J, Moorman AV. *A validated novel continuous prognostic index to deliver stratified medicine in pediatric acute lymphoblastic leukemia.* Blood. 2020 Apr 23;135(17):1438-1446.

Tulstrup M, Moriyama T, Jiang C, Grosjean M, Nersting J, Abrahamsson J, Grell K, Hjalgrim LL, Jónsson OG, Kanerva J, Lund B, Nielsen SN, Nielsen RL, Overgaard U, Paulsen PQ, Pruunsild K, Vaitkeviciene G, Wolthers BO, Zhang H, Gupta R, Yang JJ, Schmiegelow K. *Effects of germline variants in DHFR and FPGS on methotrexate metabolism and relapse of leukemia.* Blood 2020 (In press).