NOPHO

Nordic Society of Paediatric Haematology and Oncology

ANNUAL REPORT 2022

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

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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 2022.

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 26 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/Teams-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 2022 (the 39th NOPHO Annual meeting) was planned to take place in Kuopio, but the meeting will be virtual because of the uncertainty of the pandemic.

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.

Tromsø, March 24th 2022
Trond Flægstad
Secretary General

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NOPHO Board

Members 2021 - May 2022		
Secretary-general	Trond Flaegstad	elected 2020
-elect	Mats Heyman	elected 2020
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
Estonia	Sirje Mikkel	elected 2021
Finland	Mikko Arola	elected 2017
	Hanna Juntti	elected 2020
Iceland	Ólafur Gísli Jónsson	elected 2000
	Sólveig Hafsteinsdóttir	elected 2013
Latvia	Anna Valaine	elected 2022
Lithuania	Rolanda Nemaniene	elected 2019
	Igne Kairiené	elected 2020
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	Simon Kranz	elected 2020

NOPHO Webmaster and NOPHO Secretariat

NOPHO Webmaster

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NOPHO Website

During the year, there has been continuously ongoing updates of the basic functions such as support for Working groups, Minutes, Treatment Protocols, Board meetings, General assembly, NOPHO scientific studies, Education, Emergencies guidelines, Young NOPHO, Annual Reports from working groups, Working group Request, Notice Board, Ballots, Abstracts systems, Meetings & Conferences and Jobs in pediatric oncology within the member countries.

Web pages has been created for the NOPHO Annual Meeting in Kuopio 2022 with all information about the event. The webmaster has always a close collaboration with the organizers and provide ongoing support to the organizers and the congress secretariat.

Member messages have been sent out with information about security measures and "to do yourself" call to members for protecting themselves against IT intrusions.

During the year, the webmaster also offers ongoing support to the Secretary-General and to the Board.

The NOPHO Website is under constant development adapted to the user's needs.

To meet future challenges a new NOPHO website is under construction. In parallel with the maintenance of the basic functions of the existing NOPHO web, intense work is going on in addition to create and implement the entire NOPHO web to a new and more secure and modern web platform.

Under 2021 the web solution has been established and is under testing for functionality. A part of our strategy is to continue to simplify the administration and management of this large website with modern updated tools that are available today. The new website solution adapts to rules approved within the NOPHO organization.

The webmaster does the work together with an external consultant. We secure a uniform design, prioritizations, structure and navigation of the entire website. We have created a clear interface with a simplified viewing also between the Open area and the Member-login part, so the NOPHO members easily and quickly can find what they are looking for.

The new IT platform and structure is configured. All the files from the latest 5 year from the 40 Working groups, Bord, General assembly has been posted on the new NOPHO website. New functions are being developed such as an economic system for the NOPHO Secretariat.

The new NOPHO website will at the beginning run parallel with our actual NOPHO website for a period so the members could get a chance to get accustomed with it.

Integration and transferring member database information is ongoing and also preparing of the coming release.

Elisabeth Broby
NOPHO-webmaster

NOPHO Scientific Committee

Members 2021-2022

Sweden	Anna Nilsson
Denmark	Bodil Als-Nielsen
Estonia	Lenne-Triin Kõrgvee
Finland	Matti Korhonen
Iceland	Ragnar Bjarnason (stepping down 2022, no substitution at the moment)
Lithuania	Sonata Trakymiene
Norway	Maria Winther Gunnes
Young NOPHO	Nikolas Herold (chair)
Latvia	No representative

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 spring autumn 2021 term, 5 new applications were submitted of which 2 were accepted and 3 have been given the possibility to re-submit a revised proposal. For the autumn spring 2022 term, 1 new application and 2 amendments for previously accepted studies were submitted and are currently evaluated. 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.

Four candidates have been nominated for the 2022 NOPHO Lecturer prize were discussed. All candidates were discussed, ranked and presented to the NOPHO board, that makes the final decision for NOPHO Lecturer.

Stockholm, March 23rd, 2022.
Nikolas Herold, on behalf of the SciCom of NOPHO

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, Ruta Tuckuviene, Sascha Wiik Michelsen, Raheel Altaf Raja, Peter Erik Lotko Pontoppidan
	Odense	Peder Skov Wehner, Eckhard Schomerus, Niels Fisker, Michael Callesen, Mathias Rathe, Dorthe Grosen, Sine Lykkedegn
	Aarhus	Henrik Hasle, Birgitte Klug Albertsen, Torben Mikkelsen, Pernille Edslev Wendtland, Karin Bækgaard Nissen, Ines Kristensen, Torjus Skajaa, Louise Lindholdt Hansen, Louise Tram Henriksen
	Aalborg	Steen Rosthøj, Christina Friis Jensen, Marianne Olsen
Estonia	Tallinn	Kristi Lepik, Kadri Saks, Maarja Karu, Geerda Ainsoo, Irina Kerna, Keiu Paapsi, Kati Mädo
	Tartu	Sirje Mikkel, Lenne-Triin Kõrgvee, Ain Kaare, Pille Tammur
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, Heljä Lång
	Turku	Päivi Lähteenmäki, Marika Grönroos, Anu Huurre, Laura Korhonen, Linnea Schuez-Havupalo, Liisa Järvelä, Riikka Kuvaja
	Oulu	Riitta Niinimäki, Hanna Juntti, Anne Hekkala, Elli-Maija Ukonmaanaho, Henri Aarnivala
	Tampere	Olli Lohi, Susanna Vuorenoja, Päivi Raittinen, Sauli Palmu, Niina Valtanen, Kristiina Nordfors
	Kuopio	Kaisa Vepsäläinen, Jouni Pesola, Tuuli Pöyhönen, Stefan Becker, Emmi Danner
Iceland	Reykjavik	Ólafur G. Jónsson, Halldóra K. Thórarinsdóttir, Sólveig Hafsteinsdóttir, Ragnar Bjarnason, Jón Jóhannes Jónsson
Latvia	Riga	Anna Valaine, Žanna Kovaļova, Santa Kursīte, Marika Grūtupa, Elizabete Cebura, Zelma Višņevska-Preciniece, Gunita Medne, Irina Voitoviča

Lithuania	Kaunas	Giedre Rutkauskiene, Rosita Kiudeliene, Egle Ramanauskiene, Sonata Argustaite, Justina Klimaite, Ruta Radaviciute, Eglė Bindokaitė, Mantas Simutis
	Vilnius	Jelena Rascon, Goda Vaitkevičienė, Gražina Kleinotienė, Audronė Mulevičienė, Indrė Tamulienė, Ramunė Pasaulienė, Rolanda Nemanienė, Sigita Stankevičienė, Sonata Šaulytė Trakymienė, Vilma Rutkauskaitė, Ignė Kairienė, Edita Rutkauskienė, Monika Kapitančiukė
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, Christina Elisabeth Bjerring Opheim, Anne Gro Wesenberg Rognlien, Ingvild Heier, Anne Vestli
	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, Ingvild B Setså, Christian M Thaulow
	Tromsø	Tore Stokland, Trond Flaegstad, Niklas Stabell, Tove Nystad, Simon Kranz, Ole Mikal Wormdal
Sweden	Stockholm, Solna	Pernilla Grillner, Anna Nilsson, Cecilia Petersen, Mats Heyman, Stefan Söderhäll, Niklas Pal, Klas Blomgren, Stefan Holm, Johan Malmros, Per Kogner, Jonas Karlén, Jan-Inge Henter, Ingrid Öra, Petter Svenberg, Karin Belander Strålin, Trausti Óskarsson, Tatiana Greenwood, Fredrik Bäcklund, Susanna Ranta, Tony Frisk, Tomas Bexelius, Christina Egnell, Johan Hamrin, Nina Mogensen, Mari Wilhelmsson, Clary Georgantzi, Karin Henning, Lena-Maria Carlson, Lovisa Malmqvist, Hans Henningsson, Nikolas Herold
	Stockholm, Huddinge	Mikael Sundin, Jacek Winiarski, Peter Priftakis, Kim Ramme, Petra Byström, Gauti Rafn Vilbergsson, Susan Farmand
	Lund	Anders Castor, 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, Gustav Andersson Sundén
	Uppsala	Josefine Palle, Britt-Marie Frost, Gustaf Ljungman, Johan Arvidson, Per Frisk, Åke Jakobson, Anders Öberg, Annika Englund, Natalja Jackmann, Britt Gustafsson, Tania Christoforaki, 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 Renkielska, Jonathan Källström
Umeå	Ulrika Norén Nyström, Per-Erik Sandström, Caroline Björklund, Magnus Borssén, Frans Nilsson, Fredrik Bäckström
Linköping	Mikael Behrendtz, Per Nyman, Hartmut Vogt, Lisa Törnudd, Oskar Lundgren, Elham Dadfar, Viktor Säll

The Leukemia Registry

Mats Heyman
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Solid and Brain Tumour Working Groups

Solid Tumour Committee

Chair	Tove Nystad 2021-2023
Denmark	Jesper Brok 2019 Mathias Rathe 2020 Lars Rasmussen 2020 (pediatric surgery) Karin Bækgaard Nissen 2018 Lisa Hjalgrim 2016 (ST-registry repr.)
Estonia	Kadri Saks 2021 Maarja Karu 2021 (Young NOPHO)
Finland	Hanna Juntti 2016 Jukka Kanerva 2016 Sauli Palmu 2021 Päivi Lähteenmäki 2016 (ST-registry repr.)
Iceland	Halldora Thorarinsdottir 2016 Solveig Hafsteinsdottir 2016 Ólafur G. Jónsson 2016
Latvia	Marika Grūtupa 2021 Zelma Višņevska 2021
Lithuania	Giedre Rutkauskiene 2016 Indre Tamuliene 2016 Rolanda Nemaniene 2016
Norway	Maria W Gunnes 2021 (KSSB) Dorota Wojcik 2017 Tove Nystad 2016
Sweden	Patrik Romerius 2020 Lisa Törnudd 2020 Caroline Björklund 2020

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 tumour registry group.
- STC creates consultation networks within NOPHO for discussion of difficult cases
- STC publishes on NOPHO web an updated list of treatment protocols open/used in NOPHO countries
- In the sarcoma field STC collaborates with the Scandinavian sarcoma group (SSG)
- 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. Currently this includes the NOPHO-CARE project, Lutetium neuroblastoma study and plans for protocol for extracranial germ cell tumours.

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, paediatric surgery, pathology, genetics, radiology, etc. involved in the group to mimic the situation in the tumour board as the solid tumour work indeed is multidisciplinary. STC will increase its collaboration with the NOPHO RT WG.

STC has a mailing list of approximately 84 individuals for networking.

The chair 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 should be from Denmark but postpone a year. Norway takes the position. At the virtual meeting in November 2021, the decision was made. Tove Nystad from Norway is the new chair.

We have included 4 new members from Estonia and Latvia at the November meeting.

During the past year, the STC has had two virtual meetings: one in May and one in November.

At the May meeting we had an update of BENCHISTA project: a international benchmarking of childhood cancer survival by tumour stage, update of the NOPHO-CARE project, data imported in NOPHO-care RedCap Database form Sweden and Finland, update of CWS status (new registry SoTI-SAR), CWS guidance 2,0 coming (will take time), updates of Ewing protocol status in Europe, 2 protocols in preparation: iEuroEwing and Inter-Ewing 1, update of the Lutetium neuroblastoma study, open in Norway and Denmark, NOPHOmatch (project aiming at matching patients with early phase trials), update of new Phase 1-2 trials, closed trials: BEACON, epizyme tazemetostat and OMS trial with rituximab, update of osteosarcoma collaboration, European consortium on osteosarcoma to be established (very early stage, no funding, no trial yet), status of GCT collaboration, goal to have co-operation with the British group. Responsible individuals for emergency guidelines, find a suitable person in Denmark, and update on treatment protocols on NOPHO web.

At the November meeting we had an update of New phase 1-2 trials, status Europeans osteosarcoma collaboration, consortium: FOSTER Fight Osteosarcoma Through European, 19 countries participate, 8 work packages, update of GCT collaboration, collaboration with UK, negotiations of possibilities to include NOPHO countries in international/UK trials, NOPHO members to UK National advisory panel, Information about inflammatory myofibroblastic tumours and ALKi in NOPHO area, proposal for cases series from NOPHO area, representatives from each country are encouraged to inform of suitable cases, update of NOPHO solid course in Oslo in March 2022. Update NOPHO care, Swedish and Finnish data imported, Denmark and Norway joining. Update NOPHO study day, discussion with legal experts regarding of transferring data gathered from NOPHO leukaemia study protocol internationally. Päivi Lähteenmäki was chosen to represent STC in the group.

During the next year, we will have a meeting during the virtual Kuopio annual meeting in May (6th of May at 09.00-12.00 CET) and a possible face to face meeting in November combined with the NOPHO Board meeting.

Tromsø 27 March 2022
Tove Nystad

Brain Tumour Committee

Brain Tumour Committee

Coordinator Virve Pentikäinen (FI) until May 2022, Clary Georgantzi (SE) will continue since Annual Meeting 2022
Denmark René Mathiassen, Ines Kristensen, Michael Callesen, David Scheie (neuropathologist)
Finland Virve Pentikäinen, Anne Hekkala, Satu Långström, Mia Westerholm-Ormio (neurologist)
Estonia Lenne-Triin Kõrgvee
Iceland Halldora Thorarinsdottir
Latvia Zhanna Kovalova, Elizabete Cebura
Lithuania Rosita Kiudeliene, Giedre Rutkauskiene
Norway Ingrid Kristin Torsvik, Magnus Hjort, Petter Brandal (radiotherapist)
Sweden Magnus Sabel, Stefan Holm, Per Nyman, Christoffer Ehrstedt
Young NOPHO Kristiina Nordfors (FI), Elli-Maija Ukonmaanaho (FI), Geraldine Giraud (SE)
NOPHO Solid Tumor Registry Mats Heyman

Change of members:
Lenne-Triin Kõrgvee (ES), Magnus Hjort (NO) and Anders Öberg (SE) joined as new members. Mikko Arola (FI), Bengt Gustavsson, Kadri Saks (ES) and Kristin Solem (NO) stepped down, and the group warmly thanks them for collaboration.

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.

Collaboration with SIOPE Brain Tumor Group

The SIOPE 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 SIOPE protocols and through NOPHO representatives in disease specific working groups. National protocol coordinators from each participating country are also members of the corresponding SIOPE working groups.

SIOPE Brain tumor working group members from NOPHO:

CNS Embryonal Tumors (formerly Medulloblastoma/PNET): Magnus Sabel, Elizabeth Schepke (SE), Anne Vestli, Einar Stensvold (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), Ines Kristensen (DK), Satu Långström (FI)
CNS Germ cell tumors: Astrid Sehested (DK), Magnus Hjort (NO), Anders Öberg (SE), Anne Hekkala (FI)
Craniopharyngioma: René Mathiassen (DK), Pelle Nilsson (neurosurgeon, SE), Tore Stokland (NO), Atte Karppinen (neurosurgeon, FI)
AT/RT: Karsten Nysom (DK), Clary Georgantzi (SE), Satu Långström (FI), Aina Ulvmoen (NO), Anne Grethe Bechensteen (NO)
Quality of Survival: Christoffer Ehrstedt (SE)
Radiotherapy: Malin Blomstrand (SE), Henriette Magelssen (NO), Yasmin Lassen (DK)

CNS Tumor molecular classification and related germ line testing

The WHO 2016 and the most recent WHO 2021 classifications of the central nervous system tumors reclassify the major histological brain tumor diagnoses and uses molecular parameters in addition to histology to define tumor entities. Molecular classification has a major impact on prognosis and treatment of pediatric brain tumors and is required in new international brain tumor treatment protocols. This defines a need for feasible and rapid molecular diagnostic methods. These are well available in NOPHO area. Centralization of certain analyses such as 850K methylation array allows sufficient sample numbers for cost-effective and rapid turnover.

Moreover, identification of cancer predisposing alterations in germ line is becoming increasingly important and also mandatory in many brain tumor protocols. This means that genetic counselling has to be easily available when these alterations are found.

Pediatric brain tumor protocols in NOPHO

In the beginning of 2022, two phase III protocols are open in NOPHO area: SIOP PNET5 medulloblastoma in Denmark, Finland, Norway and Sweden, and Ependymoma II in Finland, Denmark, Norway and Sweden. LOGGIC Core (bioclinical database with full molecular analysis for newly diagnosed pLGG) is open in Denmark and Norway and planned to be opened in Finland and Sweden. In addition, several relapse and phase I-II protocols are open, and several protocols will be opened.

Medulloblastoma

There are four SIOPE protocols for medulloblastoma. All of them include risk stratification based on tumor biology and use the same methods for molecular diagnosis.

SIOP PNET5 MB protocol is for low-risk (LR) and standard-risk (SR) medulloblastoma patients aged 3 (-5) - 22 years. The main study questions are about 1) lowering the intensity of therapy for LR patients to decrease the late effects while maintaining the excellent survival rate and 2) randomising concomitant carboplatin during radiotherapy for SR patients to increase the effectiveness of the treatment. The amendment version 12 of the protocol contains more profound molecular subgrouping and germ line preinclusion testing for certain cancer predisposing syndromes. In addition, new patient groups are included. The most recent amendment of the protocol is version 13, in which the order of chemotherapy cycles has been changed to minimize the risk of PRES (posterior reversible encephalopathy syndrome), the recruitment period of the trial has been extended until June 2022 and the length of the whole trial has been extended until summer 2026.
Interim analyses of the LR and SR groups show that the benefit risk relation of the trial remains unchanged since the approval of the trial.

All participating countries, including participating NOPHO countries Denmark, Finland, Norway and Sweden, have opened protocol version 13 by the beginning of 2022.

SIOP HR-MB protocol is for clinical high risk (HR) medulloblastoma patients with non-WNT tumor biology, aged 3 (- 5) - 22 years. The main aim is to find out if any of the strategies used for HR medulloblastoma offers a survival advantage and to compare toxicities. The protocol includes randomization to HART (hyperfractionated accelerated radiotherapy, twice daily), which led to concern regarding twice daily anesthesia in small children if randomized to HART. The conclusion is that each participating country may decide whether children needing anesthesia will be included. In NOPHO, Denmark and Norway will not include, Sweden will include these patients, and Finland will go according to Essen proton centre as youngest Finnish medulloblastoma patients receive craniospinal proton therapy in Essen.

The HR-MB protocol is open in UK since spring 2021. Submission process is ongoing in other countries.

SIOP YCMB-LR (low risk) protocol is for young children (YC) <3-5 years with SHH activated medulloblastoma. It is a common trial of SIOPE and HeadStart – groups. The protocol includes randomization to HeadStart chemotherapy with high dose chemotherapy and autologous stem cell

rescue or HIT-SKK therapy with intraventricular methotrexate (i.e., two regimens with equal superior survival rates). Main end point is neurological outcome. The protocol has approved central funding (including some mandatory diagnostic methods such as 850K methylation array for all recruited patients) and national funding applications are requested now. Planned submission in each participating country is during 2022 and planned duration of the trial is 2023 – 2029. Denmark, Finland and Sweden will participate.

SIOP YCMB – HR (high risk) protocol is for infant non-SHH medulloblastoma. The protocol will include induction chemotherapy, randomization between two different high dose regimens, craniospinal radiotherapy for patients who are not in complete remission after induction therapy. The trial design is still under work.

Atypical teratoid rhabdoid tumour (AT/RT)

European Rhabdoid Registry (EU-RHAB) contains a registry and current treatment recommendations. We continue to recommend that patients are discussed with Michael Frühwald in Augsburg, who coordinates the registry.

SIOPE ATRT01 is a European protocol for 0 – 18 y patients with AT/RT. The main question is can 18 – 35 months of age patients with non-metastatic and non-progressive AT/RT be treated without radiotherapy. The protocol has been funded and opened in Germany. Denmark, Finland, Norway and Sweden will open the protocol.

Ependymoma

SIOP Ependymoma II protocol is open in several European countries including Finland, Denmark and Norway. 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. However, it is highly recommended to send biological samples to BIOMECA core laboratories for additional biological study, which is an essential part of the trial.

Low Grade Glioma (LGG)

LOGGIC Core trial is a bioclinical databank for all newly diagnosed LGG patients. It includes blioclinical database with mandatory first level molecular investigations of the tumor biopsy (methylation array and basic molecular changes) as well as submission of frozen tumor tissue to second level central tumor assessment in Heidelberg. It is necessary to get LOGGIC Core up and running to be able to participate in LOGGIC trial. LOGGIC Core is now open in Denmark and Norway, and opening process is ongoing in Finland and Sweden.

LOGGIC trial is for LGG patients with non-NF1 LGG gr I-II and indication to treat. There is randomisation between treatment with standard vincristine-carboplatin or vinblastine monotherapy or MEK inhibitor. In addition to PFS as defined by MRI imaging, visual and neurological outcome will be included as primary outcome measures. Start of the trial has been delayed because there is delay on the experimental drug side. LOGGIC will be opened in Denmark, Finland, Norway and Sweden.

Until opening of the LOGGIC trial, the recommended standard treatment for LGG is vincristine – carboplatin 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. Until 2nd December 2020, such patients could be enrolled into a separate, industry-sponsored **trial for BRAFV600E positive LGG** including randomisation between standard vincristine - carboplatin and targeted dabrafenib – trametinib (BRAF inhibitor – MEK inhibitor/Novartis) treatment. Until the results of the trial randomization are known, the NOPHO CNS tumour group will suggest a standard therapy for such patients.

NF1 LGG trial has been developed as a SIOP - COG cooperation. It offers first line therapy for patients with neurofibromatosis 1 and LGG and includes 2:1 randomization between selumetinib (MEK inhibitor /AstraZeneca) and vincristine – carboplatin. The trial is open in US (ACNS1831) since 2020. The company has decided to support European trial, which will go through Birmingham CTU.

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

SIOPE Infant HGG protocol was agreed but did not get enough funding. Infant HGG is a biological disease entity that differs from HGG of older children and often has favorable prognosis. The proposed SIOPE protocol offers a treatment recommendation for infant HGG.

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 submission is planned in Sweden, Denmark and Finland. Issues regarding registry related laws have postponed progress of the submission process.

BIOMEDE (Biological Medicine for DIPG eradication, Gustave Roussy, France) is originally a protocol for H3K27M positive pontine gliomas, which was amended to include all H3 K27M-mutant diffuse midline gliomas. There was a tumor biology dependent randomization for targeted medication combined with radiation therapy until randomisation was paused and recruitment continued as single arm study (everolimus combined with radiotherapy). The protocol is closed. **BIOMEDE2.0** protocol will include randomization between everolimus and a novel drug ONC201, combined with standard radiotherapy. All patients with H3K27M – mutant diffuse midline gliomas without upper age limit can be included. Opening of the trial was delayed, because company that produced ONC201 was bought by another company. The protocol is now being evaluated by the French authorities. In NOPHO, it is planned to be opened at least in Copenhagen, Stockholm and Helsinki. Awaiting BIOMEDE2.0, several countries recommend radiotherapy combined with sirolimus (sirolimus is considered biologically equivalent to everolimus, but much cheaper).

Other HGGs: There is no open protocol for newly diagnosed HGG patients at the moment. Recommendation of the SIOPE HGG group is under preparation. Until publication of the SIOPE HGG group recommendation the consensus for postoperative treatment of new HGG patient (other than midline H3K27M mutated glioma or infant HGG) in Europe is still radiation therapy combined with temozolomide, with possible combination of lomustine (Neuro-Oncology 18(10), 1442–1450, 2016, doi:10.1093/neuonc/now038). Molecular workup is highly recommended.

CNS Germ Cell tumors (GCT)

SIOP CNS GCT II trial was closed in June 2018 and there is no open protocol for this patient group at the moment. During the interim phase between protocols, the UK group previously recommended to keep chemotherapy unchanged and, regarding radiotherapy, boost pure germinomas also in cases of complete remission until outcome reports from the trial are available. They are now changing their practise as outcome of patients in complete remission after chemotherapy without boosting has been good. There will be a SIOPE + COG consensus conference on the criteria for complete remission, which will be needed for decision of this matter.

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.

Current early phase protocols for brain tumors:

- Roche GO42286 alectinib = second generation ALKi for intra and extracranial tumors with ALK fusion (Copenhagen)
- Y-mAbs 301 ^{177}Lu-DTPA-omburtamab for relapsed or refractory medulloblastoma; radioimmunotherapy via Ommaya, phase 1 (Copenhagen)
- INCB 84344-102 ponatinib for relapsed/refractory childhood cancer (Stockholm)

- AZ Olaparib (PARPi) for relapsed/refractory intra- or extracranial tumors with BRCAness/HRD (Copenhagen)
- MEMMAT: a multidrug antiangiogenic approach for recurrent or progressive ~~medulloblastoma~~, ependymoma and AT/RT (Copenhagen, all 4 Norwegian centres, all 6 Swedish centres).
- INFORM2 NivEnt: Nivolumab and etinostat (HDACi) for relapsed/refractory tumors with full molecular work-up (Stockholm)
- ITCC-053 CRISP: ALK inhibitor for tumors with ALK, ROS1 or MET aberrations except ALCL (Copenhagen)
- FIREFLY-1: DAY101 for advanced solid tumours with activating BRAF alteration
- KEYNOTE-051: Pembrolizumab (PD1 inhibitor) in relapsed/progressive PD1 positive solid tumors including brain tumors (Lund).
- LOXO-TRK-15003: Larotrectinib for NTRK-fusion positive tumors (Copenhagen, Stockholm).
- TRIDENT-1: Repotrectinib for tumors with NTRK fusions, also if previously treated with other TRKi (Copenhagen).
- Libretto-121: selpercatinib (RETi) for relapsed/refractory tumors with RET aberration (Copenhagen)

Radiotherapy

Protons are increasingly used for radiation therapy in pediatric CNS tumor patients, because radiation exposure of healthy tissues and organs at risk is minimized by proton therapy in many situations. In NOPHO, proton therapy is available in Scandion Clinic/Uppsala and in DCPT Århus. Both centres accept foreign pediatric patients. In Norway, two proton centres are planned within the next years. In addition, Essen proton therapy centre WPE treats patients from other countries, including NOPHO countries. Thus, Nordic pediatric brain tumor patients with indication to proton therapy have a feasible access to proton therapy.

Reirradiation guidelines for several tumors have been updated by the Swedish group. These can be found at the NOPHO webpages.

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. Pilot study will be opened in Stockholm and in the future the study is planned to run in cooperation with Institut Gustave Roussy (Paris) and Hospital for Sick Children (Toronto).

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.

The NOPHO experience with new brain tumor entities diagnosed with molecular profiling has been presented by Torben Mikkelsen/Aarhus and Géraldine Giraud/Uppsala. The trial has been approved by the NOPHO Scientific Committee.

NOPHOmatch is a project for relapsed/refractory pediatric cancers including CNS tumors. Aim is to match these patients 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 videoconferences. Currently weekly Nordic videoconferences are running and INFORM2 trial is recruiting in Stockholm.

Meetings

Because of Corona pandemic, all pediatric neuro-oncology meetings have been either virtual or hybrid meetings since spring 2020.

NOPHO Brain tumour committee meetings:

BTC virtual (Teams) meetings were held May 7, 2021, and November 10, 2021. The next BTC meeting will be virtual meeting May 6, 2022, in conjunction with the NOPHO Annual meeting.

Other brain tumour meetings:

- SNO (Society of neuro-oncology) 2021 annual meeting November 19-21, 2021 – Boston
- SIOPE Brain Tumor Group working group virtual meetings in Embryonal tumor group, High grade glioma group and Low grade glioma group.

Upcoming brain tumour meetings:

- NOPHO Brain tumor group meeting, May 6, 2022 – virtual meeting
- SIOPE Brain tumor group 2022 annual meeting, June 11-12, 2022 - Hamburg
- ISPNO 2022, June 13-15, 2022 - Hamburg
- PaeNNO 2022, September 14-16, 2022 - Copenhagen
- NOPHO CNS tumor course, October 24-26, 2022 – Gothenburg
- SNO (Society of neuro-oncology) 2022 annual meeting, November 16-20, 2022 – Tampa Bay, Florida
- BTB (Barntumörbanken) – symposium, December 1-2, 2022 - Stockholm

On behalf of the NOPHO Brain Tumor Group,

Virve Pentikäinen
Helsinki, April 2nd, 2022.

Solid Tumour Registry (NOPHO-Care Task force)

Chair	Päivi Lähteenmäki, PI of NOPHO Care
Denmark	Lisa Hjalgrim, 2018
Estonia	Kadri Saks, 2021, Keiu Paapsi 2021
Finland	Päivi Lähteenmäki, 2013
Iceland	Ólafur G. Jónsson
Latvia	Marika Grutupa
Lithuania	Jelena Rascon, 2020
Norway	Maria Gunnes, 2021
Sweden	Cecilia Petersen, 2020
CCEG registry group	Päivi Lähteenmäki
Young NOPHO	Thorgerdur Gudmundsdottir

The Nordic Childhood Solid Tumor Registry (STR) published an analysis of historical solid tumor survival data 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 decided to design long-term registry-based studies.

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 leukemia, lymphoma and solid tumors, and specific rare non-malignant hematological disorders (e.g. aplastic anemia, thalassemia major, sickle cell disease, DBA).

The specific aims and structure of the two different parts of the NOPHO-CARE project are described in the NOPHO Annual report published in May 2020. The process of collaboration agreements and data transfer agreements between Karolinska Institute and participating countries is ongoing. CCEG has, in June 2020, taken decision on the database structure and the RedCap-based database is built up, and first data from Sweden and Finland have been imported. Barncancerfonden in Sweden has funded the project. Next steps will be the first batch updates from Norwegian and Danish Cancer registries as well as planning of final processes for direct registration of benign hematology cases from centers outside Sweden. Thus, the NOPHO-CARE Task force looks forward getting the whole project up and running during 2022.

On behalf of the group
Päivi Lähteenmäki

Leukaemia Working Groups

Leukemia and Lymphoma Committee

Chair	Inga Maria Johannsdottir
Estonia	Kristi Lepik, Maarja Karu
Denmark	Peder Skov Wehner, Bodil Elise Thorhauge Als-Nielsen, Birgitte Klug Albertsen
Finland	Mervi Taskinen, Riitta Niinimäki, Päivi Lähteenmäki
Iceland	Ólafur G. Jónsson, Sólveig Hafsteinsdóttir
Latvia	Zanna Kovalova, Anna Valaine
Lithuania	Ramune Pasauliene, Ignė Kairienė
Norway	Monica Munthe-Kaas, Magnus Hjort
Sweden	Jonas Abrahamsson, Karin Mellgren, Arja Harila-Saari

WG-Chairs

ALL-2008 PI	Kjeld Schmiegelow
ALLTogether	Mats Heyman
ALL Relapse	Petter Svenberg
ALL WG	Arja Harila-Saari
Adult-ALL-group	Nina Toft
AML	Josefine Palle and Kees-Jan Pronk
Biobank	Henrik Hasle
Board chair	Trond Flægstad
Leukemia genetics	Ulrika Norén Nyström
LL-Biology	Linda Fogelstrand and Olli Lohi
Event Group	Arja Harila-Saari
Infant ALL	Ulrika Norén Nyström
Leukemia registration	Päivi Lähteenmäki
Lymphoma working group	Lisa Lyngsie Hjalgrim
NOPHO MRD group	Hanne Marquart
Ph-ALL	Anders Castor
Pharmacology	Torben Stamm Mikkelsen
SCT	Dominik Turkiewicz
Young NOPHO	Adam Alexandersson (FI)

All Nordic countries have appointed 2-3 representatives to the LLC but the number of mail recipients is larger. Also, others with special interest are welcome to join the meetings. The LLC chair is nominated by the national groups rotating between the NOPHO countries. The term for the chair is four years. The next chair will be from Lithuania and will replace the current chair at the annual meeting in 2022.

The LLC meets twice a year in connection with the Board meeting. Both meetings in 2021 were digital (Zoom-meetings) due to the Covid19 situation, the first was on May 7th and the second on November 9th. 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.

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 ALLTogether (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.

LLC chair has represented NOPHO at the yearly I-BFM board meetings and since 2019 at the new SIOPE meeting.
The next NOPHO annual meeting will be digital and so will the LLC meeting on May 6th.

Oslo
March 2022

Inga Maria Johannsdottir
LLC-chair (stepping down)

ALL Working Group and NOPHO ALLTogether Working Group

ALL Working Group Members

Sweden	Arja Harila-Saari (chair)
	Anders Castor
	Johan Malmros
	Jonas Abrahamsson
Denmark	Birgitte Klug Albertsen
	Thomas Frandsen
Estonia	Mari Punab
	Kristi Lepik
Finland	Päivi Lähteenmäki
	Mervi Taskinen
Iceland	Ólafur Gísli Jónsson
Latvia	Anna Valaine
	Žanna KovaĮova
Lithuania	Goda Vaitkeviciene
Norway	Inga Maria Rinvoll Johannsdottir
	Trond Flægstad
	Bendik Lund
Young NOPHO	Adam Alexandersson
	Nikolas Herold
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
ALLTogether PI	Mats Heyman
ALL 2008 protocol committee	Kjeld Schmiegelow
Event group	Arja Harila-Saari
Infant ALL	Ulrika Norén Nyström
ALL relapse	Petter Svenberg
Ph-ALL/CML	Anders Castor
MRD group	Hanne Marquart
Cytogenetic group	Ulrika Norén Nyström, Bertil Johansson
Pharmacology group	Torben Stamm Mikkelsen
LL-Biology	Olli Lohi, Linda Fogelstrand

ALLTogether Working Group Members

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

NOPHO Representatives in ALLTogether Working Groups/Committees

Cytogenetics	Bertil Johansson
MRD	Hanne Marquart, Hans O. 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	Karin Flood, Mats Heyman, Jenny Juhlin
Statistics	Mats Heyman, Matteo Bottai, Ida Hed Myrberg

The group has had two meetings: 4th November with 22 participants and 15th March with 16 participants. Both sessions were arranged via Zoom and held in combination with the NOPHO ALLTogether working group meetings.

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

International collaborations

The NOPHO-ALL working group is involved in several international collaborations, including I-BFM, the Czech-led project for ALAL (AMBI), and the HARMONY initiative.

For the international I-BFM group ALL-committee ad-hoc T-cell group, Mats Heyman and Kjeld Schmiegelow are the NOPHO representatives. Initial meetings have taken place and the focus is currently on organizing data-sharing for hypothesis-building (clinical, genetic – possibly including research data and MRD). The most reasonable dataset for NOPHO to share would be the NOPHO ALL-2008 dataset. This data-sharing is not primarily aiming at publication, but as working material.

The NOPHO-ALL group is also involved in the international project for patients with ambiguous lineage leukaemia (ALAL), with Ladislav Krol as representative.

For the HARMONY initiative, a pan-European initiative to create a platform of all the data that has already been published by ALL protocol groups, Kjeld Schmiegelow is the NOPHO-ALL representative. In principle, all are in favor of the HARMONY initiative but legal review must be performed from the national perspective to ensure all data-sharing is properly performed.

National parent representation

Briefly, presently parent/patient representatives from Portugal, The Netherlands, Lithuania and Finland have been appointed, but are missing from remaining countries. Parent/patient representatives provided several questions to be discussed in the national groups. Parental representation and parental input on, e.g., the informed consent process and study design, is strongly supported by the NOPHO ALLTogether working group.

A "Terms-of-reference" document has been developed to provide a "job description" to facilitate recruitment. Communication around the findings and ongoing activities to other patients/parents is considered important and it may be beneficial to have multiple representatives covering different competences per country.

Substantial amendment 3 (SA3)

The Voluntary Harmonisation Procedure (VHP) for the clinical trial application has been approved in all NOPHO-countries as well as in most countries in the whole consortium. The most important addition, apart from the confirmation of previous urgent safety measures, is the addition of infants with BCP-ALL and KMT2A germline and all infants with T-cell disease.

As of 8 March 2022, a total of 866 patients have been recruited. A risk-group script is under development, which may aid centers in checking their registration of stratifying parameters. At the moment there is some under-reporting of MRD- and risk-group.

New guidelines for immunological reactions to PEG-Asp have been added. Briefly, Urgent Safety Measure 4 (USM4) was implemented based on observed high toxicity in Consolidation 1; as a result PEG-Asp was removed from Consolidation 1 and re-started in Consolidation 2. The Therapeutic Drug Monitoring (TDM) group has reviewed the result of this change; their results indicate a higher incidence of hypersensitivity reaction (HSR) to PEG-Asp in post-induction than induction, though frequency varied between countries and protocol arms. It is also unclear if the rate of HSR has increased in the 1-2 years (before the start of ALLTogether) – some felt yes, others no. In any case, the change in schedule according to USM4 has yielded a significant increase in HSRs, almost exclusively observed in post-induction phase Consolidation 2 (3rd and 4th dose). This is unlikely to be due to changes in the product and is probably the result of the changes in the protocol and the introduction of an Asp-free interval. The TDM group suggested a short-term plan of action. Regarding intramuscular (IM) administration of Asp: pharmacokinetics indicate peak-level sampling after 1 or 2 days, thus the sampling schedule should be adjusted if IM dosing is used.
Complete registration is crucial for continued evaluation, including both new registration in Castor (premedication administered? Y/N per dose) and complete data entry in RedCap. An update of Castor registration is ongoing, with the aim to have the database in shape for the Progress report and DSMB report

in September. General clinical data checks are ongoing and ideally the key variables from the Genetics, MRD, and TDM groups will be delivered before summer.

A new CCEG ALLTogether MRD database is ready and registration will start soon. It is important that registration is carried out by people with MRD-expertise to ensure data quality. In the long-term, logistics for MRD database reporting should be discussed and there is a need to check that the database is regularly updated, perhaps with help from an algorithm helping the data management. The NOPHO MRD group is interested in studying T-ALL flow cytometry vs PCR data for publication, possibly in collaboration with other groups.

Concerns about cost and quality of life due to every-other-day scheduling of Erwinase have been discussed and remain a continued concern.

International collaborations in the NOPHO ALLTogether group

The NOPHO-ALL working group is involved in several international collaborations, including the AIM study (sub-study to ALLTogether1), the INTERFANT-21 study, and the ELEGANT study.

The AIM study is part of SA3 and has already been accepted by the ALLTogether Scientific Committee and Pharmacology group. Once the substantial amendment 3 is up and running in a country, the AIM study starts in that specific county, unless the country has opted out. In additional to the AIM study, an intervention study based on the AIM study (I-AIM) with both adults and children from Denmark and Norway is also planned, but has not passed the ALLTogether Scientific Committee. The I-AIM study design involves randomization of adults into 2 intervention arms (newly diagnoses vs chronic phase patients with different imatinib dose adjustments) and 1 control arm (no imatinib dose adjustment). For children, it will be observational but imatinib will be adjusted to >1000 ng/ml.

The INTERFANT-21 protocol study requires that for work-up of PCR-based MRD, diagnostic DNA samples are to be sent to Denmark, where they will be analyzed and also further sent to Frankfurt for sequencing (target identification with regard to the genomic KMT2A-rearrangement). If whole genome sequencing identifies the target sequence, this may be used, but the MRD-analysis should be performed in Copenhagen. The INTERFANT-21 protocol is not yet submitted due to ongoing contract negotiations with Amgen (original goal 1 Feb). Estonia will be unable to participate due to lack of resources; Lithuania will participate. The prednisone response will be assessed by morphology (to enable comparison with previous protocols); morphology can be done locally.

The ELEGANT study has received ethical approval in Denmark, but needs approval in all participating countries and the need for regulatory approval needs to be assessed country by country. It is a collaboration among several study consortia and separate from the ALLTogether clinical trial from a regulatory point of view.

There is a proposal for a collaboration between ALLTogether and COG/Janssen to implement a randomized intervention for T-cell patients with high MRD; this proposal is currently in review with the COG scientific committee and is supported by the ALLTogether Protocol Steering Committee (PSC).

International representation and feedback ALLTogether Board

NOPHO representation in the PSC is presently Mervi Taskinen, Kjeld Schmiegelow, and Mats Heyman. A formal decision to nominate two representatives to each of the PSC and ALLTogether Board is planned to be taken in September 2022. The national groups may nominate such candidates.

The ALLTogether annual meeting in Portugal will be in late September, just before the SIOP-meeting.

The next combined ALL-ALLTogether meeting will be on Tuesday, 13th September, and held as a hybrid meeting (Arlanda/Zoom).

Leukemia - ALL Registration Working Group

Coordinator	Mats Heyman
Denmark	Birgitte Klug Albertsen
Estonia	Keiu Papsi
Finland	Kim Vettenranta
Iceland	Ólafur Gísli Jónsson
Norway	Inga María Jóhannsdóttir
Sweden	Jonas Abrahamsson, Mats Heyman
Data compilation and analyses	
	Mats Heyman
	Trausti Óskarsson
Infrastructure Childhood Cancer Epidemiology Group (CCEG)	
	Päivi Lähteenmäki
	Göran Gustafsson
	Lili Zheng
	Shahid Tarar
	Nima Behnam Makoi
	Mats Nordström
Statistics ALLTogether	
	Matteo Bottai
	Ida Hed Myrberg
	Anna Warnqvist
Data Management ALLTogether	
	Antonio Gonzalez Sanchez
	Elisabet Bergsten
	Alexander Phillips
Data checks Copenhagen (NOPHO ALL-08)	
	Kjeld Schmiegelow (PI, NOPHO ALL-08)
	Thomas Frandsen
	Louise Rold Helt
	Kirsten Kørup Rasmussen
	Nina Toft

Introduction

All NOPHO centres, except in Latvia, are now treating their patients according to the ALLTogether protocol and at the time of this report, all these countries are now also recruiting into the main study after an (extended) pilot phase for Estonia, Lithuania and Iceland because of unresolved ethicolegal issues. Latvia is preparing for joining the pilot-study, which has been extended to also include new candidates. For instance, some centres in Spain are planning to join in the autumn of 2022. Most of the focus will then be on the NOPHO ALLTogether patients, but some data on the NOPHO ALL-2008 patients will also be included. Work is ongoing to define this patient cohort down to the last patient.

The NOPHO ALL-2008 patients

From the start of recruitment in 2008 until the end of 2021, 3231 patients have been registered in the NOPHO ALL-2008 registry. Of these 550 patients did not meet the administrative/target group inclusion criteria and the NOPHO ALL-2008 trial inclusion criteria. (**Figure 1**). Age outside the target group, Ph+ALL and Down syndrome have generally been the most common exclusions. In addition, over the last 3 years, during the transition to the ALLTogether trial, a number of patients have been registered partly in the ALL-2008 registry but treated according to the ALLTogether protocol. Some are even registered in the ALL-2008- as well as in the ALLTogether registry (Castor). For this annual report we have tried to identify patients that were truly treated according to the ALL-2008 protocol and reviewed the inclusion criteria for the majority of patients. We included 2681 patients in this part of the report.

Table 1. Patients 1-45 years of age with B-precursor and T-ALL meeting trial criteria and treated according to the NOPHO ALL-2008 protocol.

Year of diagnosis	Total	Sweden	Denmark	Norway	Finland	Iceland	Estonia	Lithuania
2021	1	0	0	1	0	0	0	0
2020	34	0	0	5	29	0	0	0
2019	155	62	5	30	44	1	13	0
2018	253	93	39	53	33	3	10	22
2017	262	76	50	45	48	9	14	20
2016	253	69	48	45	62	5	9	15
2015	218	72	36	46	42	1	5	16
2014	225	87	31	42	34	3	6	22
2013	283	90	66	49	43	2	11	22
2012	213	70	45	35	32	1	8	22
2011	240	83	50	32	33	3	11	28
2010	256	91	53	37	39	3	10	23
2009	206	64	40	31	44	3	3	21
2008	82	29	16	12	19	1	3	2
Total	**2681**	**886**	**479**	**463**	**502**	**35**	**103**	**213**

As previously reported, the outcomes of patients treated according to NOPHO ALL-2008 are in general very good. The 5-year overall survival (OS) is now 90% (±1%), 93% (±1%) for patients 1-15 years of age and 78% (±2%) for patients 16-45 years of age (**Table 2**). The outcome for patients stratified as Standard Risk has been excellent with 5-year OS of 97% (±1%) but the results from the High-Risk Chemo arm are disappointing with 5-year OS of only 73% (±3%), worse than the patients stratified to the High-Risk HSCT-arm (OS 76%±3%) and an even larger difference when only patients <16 are included (5-year OS 74%±3% and 84%±4% respectively). This emphasizes the urgent need for novel therapies for this risk group.

Figure 1. NOPHO ALL-2008 trial enrolment and exclusions

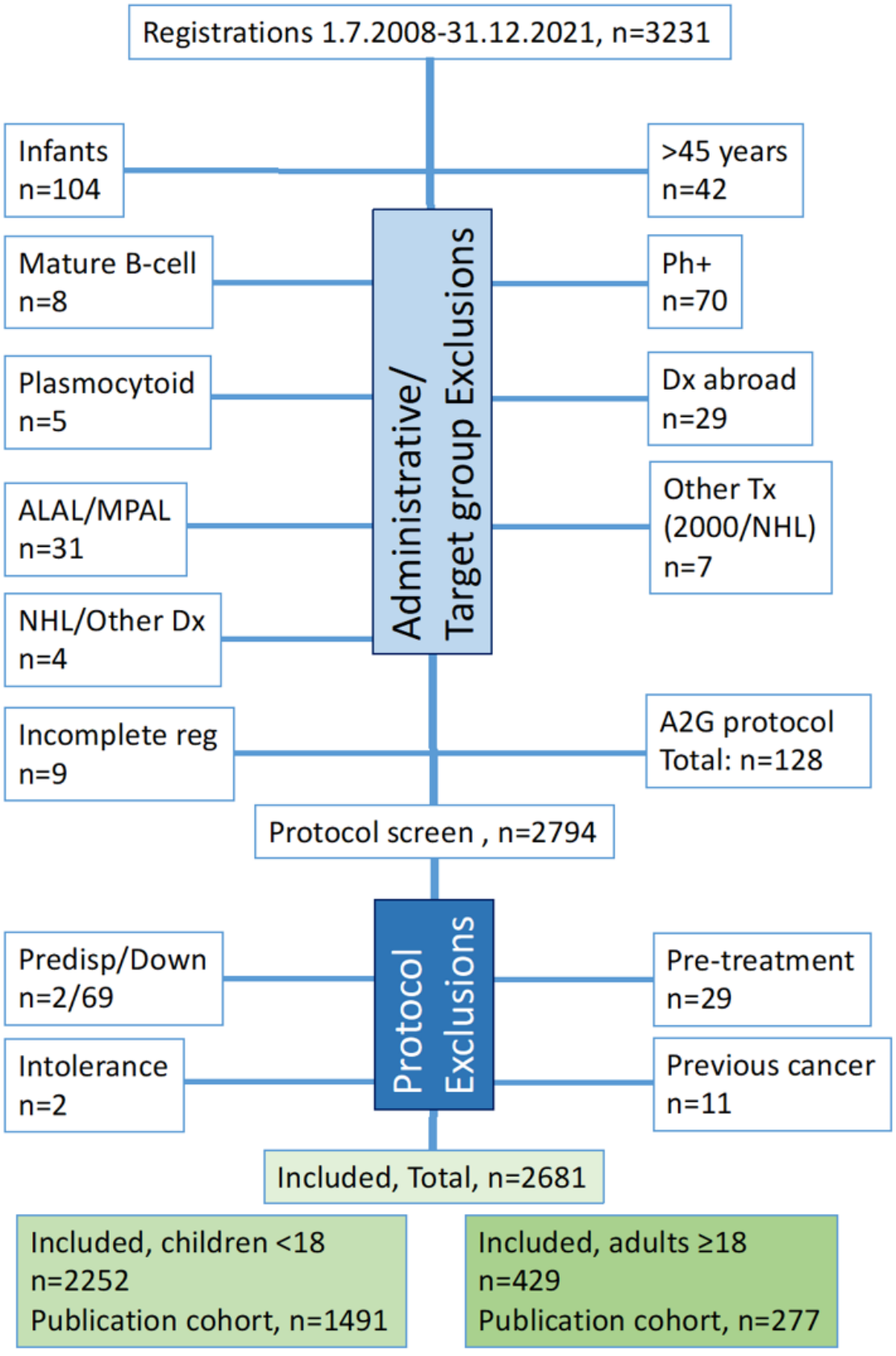


Table 2. Events and outcome NOPHO ALL-2008 – all patients.

Event	Age 1-15 n=2144		Age 16-24 n=294	Age 25-45 n=243	Total n=2681
Non-responders	0		0	0	0
Death in induction	16 (0.7)		2 (0.7)	3 (1.2)	21 (0.8)
CR1-reached	**2128**		**292**	**240**	**2660**
Remission %	**99.3**		**99.3**	**98.8**	**99.2**
CR1, no RG d29*	3		0	0	3
Final risk stratification	**SR n=1207 (n=1092)****	**IR n=937 (n=722)****	**HR-chemo n=322 (n=212)****	**HR-HSCT n=191 (n=99)****	**CR1-reached n=2660* (n=2128)****
Death in CR1	12 (10)	23 (15)	29 (20)	15 (7)	79 (52)
Relapses	79 (59)	121 (73)	71 (44)	38 (14)	312(193)*
isolBM (iBM)	39 (26)	62 (34)	49 (31)	28 (12)	181 (106)*
isolCNS (iCNS)	16 (15)	22 (16)	9 (5)	0 (0)	47 (36)
Testis	3 (1)	2 (0)	1 (1)	0 (0)	6 (2)
BM+CNS	13 (9)	22 (18)	7 (5)	2 (1)	44 (33)
BM+testis	4 (4)	1 (1)	0 (0)	0 (0)	5 (5)
BM+CNS+testis	2 (2)	2 (2)	1 (1)	0 (0)	5 (5)
BM+Other site	3 (2)	4 (2)	0 (0)	3 (1)	10 (5)
Other site	0 (0)	6 (0)	4 (1)	4 (0)	14 (1)
SMN	11(10)	2 (2)	4 (2)	0 (0)	17 (14)
MDS	4 (3)	0 (0)	1 (0)	0 (0)	5 (3)
AML	3 (3)	1 (1)	1 (1)	0 (0)	5 (5)
Other	4 (4)	1 (1)	1 (0)	0 (0)	6 (5)
Unknown	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
All events	102 (79)	146 (90)	104 (66)	53 (21)	408 (259)*
CCR number	1105 (1013)	791 (632)	218 (146)	138 (78)	2252 (1869)*
CCR %	91.5 (92.8)	84.4 (87.5)	67.7 (68.9)	72.3 (78.8)	84.7 (87.8)*
pDFS (60 mo) all	0.93 (0.01)	0.86 (0.01)	0.75 (0.03)	0.75 (0.04)	0.87 (0.01)
pDFS (60 mo) <16	0.94 (0.01)	0.89 (0.01)	0.77 (0.03)	0.83 (0.04)	0.90 (0.01)
pDFS (60 mo) ≥16	0.79 (0.04)	0.76 (0.04)	0.71 (0.05)	0.66 (0.06)	0.74 (0.02)
pEFS (60 mo) all	-	-	-	-	0.83 (0.01)
pEFS (60 mo) <16	-	-	-	-	0.86 (0.01)
pEFS (60 mo) ≥16	-	-	-	-	0.69 (0.02)
All dead	39 (27)	72 (33)	83 (52)	44 (16)	261 (146)*
All alive	1168 (1065)	865 (689)	239 (160)	147 (83)	2420 (1998)*
alive %	96.8 (97.7)	92.3 (95.6)	74.2 (76.2)	77.0 (84.8)	90.3 (93.2)*
pOS (60 Mo) all	0.97 (0.01)	0.92 (0.01)	0.73 (0.03)	0.76 (0.03)	0.90 (0.01)
pOS (60 mo) <16	0.98 (0.01)	0.95 (0.01)	0.74 (0.03)	0.84 (0.04)	0.93 (0.01)
pOS (60 mo) ≥16	0.87 (0.04)	0.83 (0.03)	0.71 (0.05)	0.66 (0.06)	0.78 (0.02)

*Three 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. All three have relapsed (iBM). ** Figures in parenthesis are patients 1-15 at diagnosis for counts or standard error for estimates. The count in "All Events", "CCR number", "All dead", "All Alive" and "alive %" also include the induction deaths and the outliers described above.

As expected, the number of events in the ALL-2008 cohort has decreased since the annual number of recruited patients has decreased successfully since 2018. In 2021, 20 new primary events occurred, 19 relapses and one SMN (**Table 3**).

Table 3. Primary events (NOPHO-2008 cohort) since the previous report.

Event	SR (<16y)	IR (<16y)	HR-chemo (<16y)	HR-SCT (<16y)	Total (<16y)
Relapse	10 (8)	8(5)	1(0)	0 (0)	19 (13)
DCR1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SMN	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Total	11 (9)	8 (5)	1 (0)	0 (0)	20 (14)

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

The current median follow-up for all living patients is 2108 days (range 27-4957 days), 2143 days (range 27-4957) for patients <16 years at diagnosis and 1999 days (range 27-4633) for patients 16-45 years.

The ALLTogether patients

From the start of recruitment of the first pilot patients in Denmark in 2018 until the end of 2021, a total of 813 patients have been registered in the ALLTogether Castor registry, of which 580 were registered within NOPHO. A total of 32 patients did not fulfil inclusion criteria and an additional 17 had to be excluded because of missing information leaving 531 patients for analysis in this report, 269 treated according to the pilot protocol and 262 included in the ALLTogether main study (**Figure 2**).
The start of recruitment in the different countries and the recruitment/country is shown in Table 4.

The ALLTogether Pilot and Main Study

Figure 2. ALLTogether1 Pilot and Main study enrolment and exclusions.

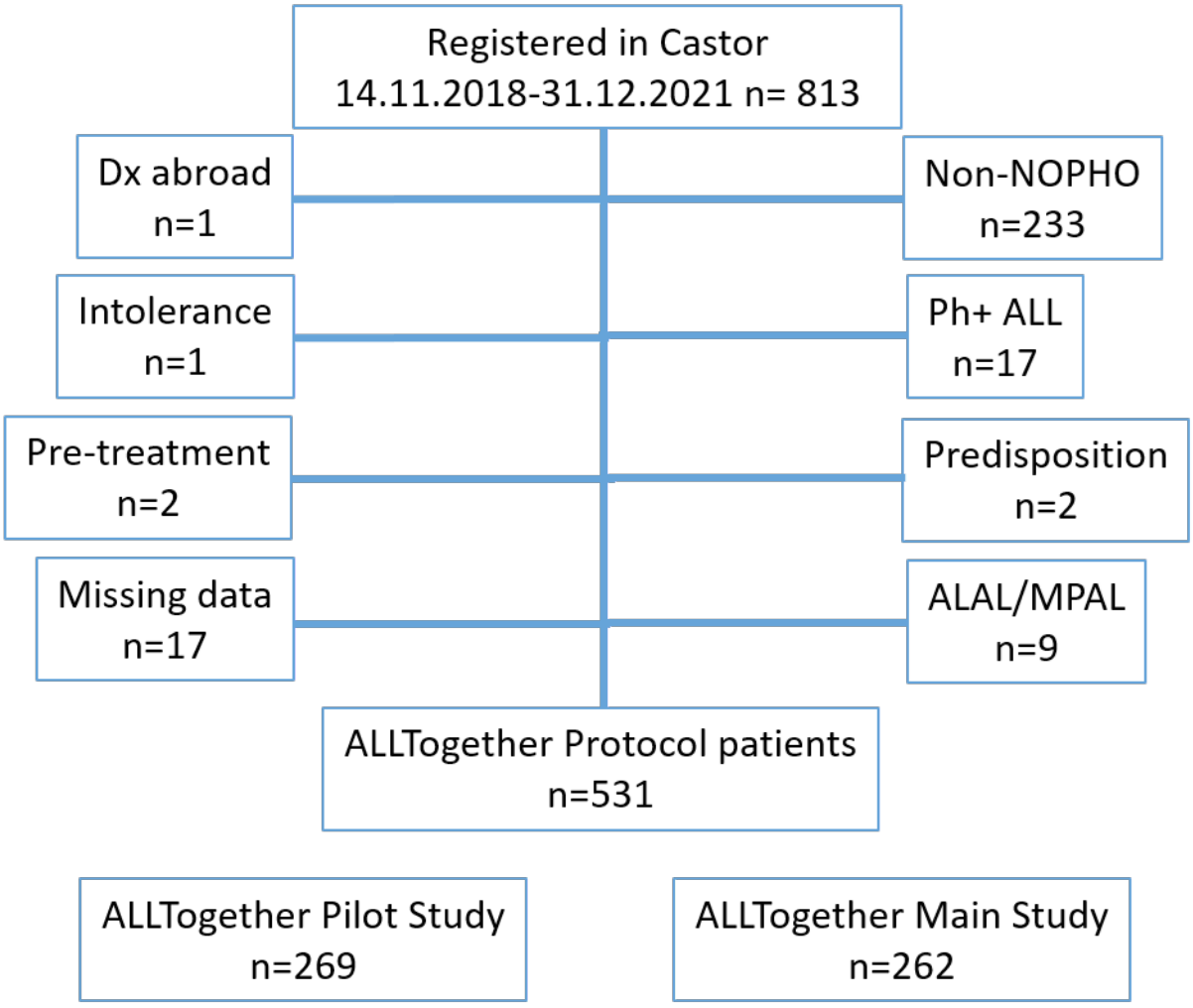


Table 4. Recruitment ALLTogether by country.

Country	Pilot n=269	Date start recruitment	Main n=262	Date start recruitment
Denmark	73	14.11.2018	60	24.7.2020**
Lithuania	41	4.12.2018	0	-
Sweden	105	13.8.2019	112	28.9.2020
Norway	44	23.9.2019	44	12.12.2020
Finland	-	-	46	8.9.2020
Iceland	6	13.01.2020	0	
Non NOPHO	**Pilot n=0**	-	**Main n=221**	**Date start recruitment**
Netherlands	-	-	142	9.7.2020*
Belgium	-	-	62	30.10.2020
UK	-	-	17	11.05.2021
Excluded	-	-	12	

*First patient in ALLTogether1, **First patient ALLTogether1 included in NOPHO.

Table 5. Clinical characteristics at diagnosis, NOPHO ALLTogether Pilot and Main study patients.

	Pilot (%) n=269	Main Study (%) n=262	Total (100 %) n=531
Sex			
Male	166 (62)	151 (58)	**317 (60)**
Female	103 (38)	111 (42)	**213 (40)**
Age			
<10	158 (59)	173 (66)	331 (62)
10-15	43 (16)	47 (18)	90 (17)
16-24	28 (10)	21 (8)	49 (9)
25-45	40 (15)	21 (8)	61 (12)
WBC			
<50	230 (85)	186 (71)	416 (78)
≥50	39 (15)	76 (29)	115 (22)
Immunophenotype			
BCP	238 (88)	218 (83)	456 (86)
T-cell	31 (12)	44 (17)	75 (14)
NCI risk-group (BCP)			
SR	137 (58)	124 (57)	261 (57)
HR	101 (42)	94 (43)	195 (43)
CNS			
CNS1	200 (74.9)	183 (70.4)	383 (72.7)
TLP-	45 (16.9)	41 (15.8)	86 (16.3)
CNS2	10 (3.7)	16 (6.2)	26 (4.9)
TLP+ <5 WBC	2 (0.7)	11 (4.2)	13 (2.5)
CNS3	5 (1.9)	4 (1.5)	9 (1.7)
TLP+ ≥5 WBC	5 (1.9)	5 (1.9)	10 (1.9)
Failed/missing	2	2	4
HR-Genetics screen*			
Screened	264 (98.1)	259 (98.9)	523 (98.5)
Incomplete screen	4 (1.5)	2 (0.8)	6 (1.1)
Incomp canonical abber	1 (0.4)	1 (0.4)	2 (0.4)
Genetics Groups			
ETV6-RUNX1	50 (18.6)	53 (20.2)	103 (19.4)
High Hyperdiploid	81 (30.1)	70 (26.7)	151 (28.4)
Hypodiploid 30-39	6 (2.2)	4 (1.5)	10 (1.9)
Near haploid (<30)	3 (1.1)	4 (1.5)	7 (1.3)
iAMP21	3 (1.1)	8 (3.1)	11 (2.1)
KMT2A-r	10 (3.7)	13 (5.0)	23 (4.3)
t(17;19)	2 (0.7)	0 (0)	2 (0.4)
t(1;19)	11 (4.1)	7 (2.7)	18 (3.4)
ABL-class fusions	1 (0.4)	2 (0.8)	3 (0.6)
Other not stratifying	81 (30.1)	89 (34.0)	170 (32.0)
Screened, aberrations	17 (6.3)	12 (4.6)	29 (5.5)
Failed/missing	4 (1.5)	0	4 (0.8)
CNA-profile (BCP)			
Poor Risk	63 (35)	88 (45)	151 (40)
Good Risk	118 (65)	106 (55)	224 (60)
Inconclusive/missing	57	37	102

*Patients had to be screened for hypodiploidy, near haploidy, iAMP21, KMT2A and t(17;19). Two patients failed some of these analyses, but had a canonical aberration (ETV6-RUNX1) detected, which according to the guidelines is enough to exclude the HR-aberrations.

Since the size of the groups (pilot/main study) is now adequate for comparisons, the distribution becomes more as expected. Completeness of data is reasonable, very few (and seemingly fewer in the recent period) patients have incomplete baseline diagnostics. Very few patients have missing CNS-data, but the interpretation of the grouping is not clear to all. Table 6 shows the discrepancy in the interpretation with discrepant interpretation in 63 (12%) of the cases, potentially changing the stratification in 42 (8%). An

additional two patients had an interpretation registered on insufficient grounds and three had no interpretation despite sufficient information. Particularly the interpretation of TLP +/- seems to be problematic.

This calls for correction of registration and/or improved instructions/education of the registration staff.

Table 6. Interpretation of the CNS-registration ("CNS risk-group") based on registered CNS-data.

CNS-status	CNS1	TLP-	CNS2	TLP+ <5WBC	CNS3	TLP+ >5WBC	Insuff data	No interpret
CNS1	369	21	5	2	0	0	1	0
TLP-	0	47	1	1	0	0	0	0
CNS2	9	1	18	1	0	0	1	0
TLP+ <5WBC	1	15	2	7	0	0	0	0
CNS3	2	1	0	0	9	1	0	0
TLP+ >5WBC	0	1	0	1	0	9	0	0
Insuff data	0	0	0	0	0	0	2	0
No interpret	2	0	0	1	0	0	0	0

Columns=Corrected interpretation
Rows=Interpretation as entered into Castor

Table 7. Initial stratification, early events and treatment response to Induction and Consolidation 1. NOPHO ALLTogether Pilot and Main study.

	Pilot (%) n=269	Main Study (%) n=262	Total (100 %) n=531
Induction type			
3-drug	137 (51)	119 (45)	256 (48)
4-drug	127 (47)	135 (52)	262 (49)
Down	5 (2)	8 (3)	13 (3)
Induction outcomes			
Induction death	2 (0.7)	0	2 (0.4)
Outliers – no risk-group	0	1 (0.4)	1 (0.2)
Remaining for stratific	267	261	528
MRD d29			
Not detectable	73 (27.3)	67 (25.7)	140 (26.5)
<0.01%	49 (18.4)	59 (22.6)	108 (20.5)
0.01-<0.03%	27 (10.1)	36 (13.8)	63 (11.9)
0.03-<0.05%	16 (6.0)	18 (6.9)	34 (6.4)
0.05-<0.1%	9 (3.4)	8 (3.1)	17 (3.2)
0.1-<0.5%	30 (11.2)	30 (11.5)	60 (11.3)
0.5-<5%	24 (9.0)	25 (9.6)	49 (9.3)
5-<25%	8 (3.0)	12 (4.6)	20 (3.8)
≥25%	8 (3.0)	3 (1.1)	11 (2.1)
missing	23 (8.6)	3 (1.1)	26 (4.9)

MRD-registration is much more complete in the main study than in the pilot, which also makes risk-stratification better. It is also notable that an MRD-reading can be obtained for almost all patients, likely due to the use of both FCM and PCR MRD.
The tables 8-10 show the assessment of risk-group from a central review point of view, with the data at hand from the registration.

Table 8. Up- and Down-Grading post Induction and Final stratification. NOPHO ALLTogether Pilot and Main study.

	Pilot (%) n=267	Main Study (%) n=261	Total (100 %) n=528
Up-/Down-Grading			
Down-grading	0	0	0
From IR-low-HSCT	0	1	1
From IR-high-HSCT	11	13	24
Final Risk-Groups			
SR	64 (24.0)	55 (21.1)	119 (22.5)
IR-Low	49 (18.4)	64 (24.5)	113 (21.4)
IR-High	115 (43.1)	99 (37.9)	214 (40.5)
IR-high (TKI)	0	2 (0.8)	2 (0.4)
HR-chemo	2 (0.7)	3 (1.1)	5 (0.9)
HR-HSCT	31 (11.6)	30 (11.5)	61 (11.6)
SR-Down	1 (0.4)	0	1 (0.2)
IR-Down	3 (1.1)	8 (3.1)	11 (2.1)
HR-Down	2 (0.7)	0	2 (0.4)

Table 9. Post Induction Final stratification – patients <16 years.

	Pilot (%) n=201	Main Study (%) n=219	Total (100 %) n=420
SR	55 (27.4)	55 (25.1)	110 (26.2)
IR-Low	49 (24.4)	64 (29.2)	113 (26.9)
IR-High	85 (42.3)	73 (33.3)	158 (37.6)
IR-high (TKI)	0	2 (0.9)	2 (0.5)
HR-chemo	2 (1.0)	3 (1.4)	5 (1.2)
HR-HSCT	6 (3.0)	17 (7.8)	23 (5.5)
SR-Down	1 (0.5)	0	1 (0.2)
IR-Down	1 (0.5)	5 (2.3)	6 (1.4)
HR-Down	2 (1.0)	0	2 (0.5)

Table 10. Post Induction Final stratification – patients ≥16 years.

	Pilot (%) n=66	Main Study (%) n=42	Total (100 %) n=108
SR	9 (13.6)	1 (2.4)	10 (9.3)
IR-Low	-	-	-
IR-High	30 (45.5)	25 (59.5)	55 (50.9)
HR-chemo	-	-	-
HR-HSCT	25 (37.9)	13 (31.0)	38 (35.2)
SR-Down	0	0	0
IR-Down	2 (3.0)	3 (7.1)	5 (4.6)
HR-Down	0	0	0

There is a striking, but expected difference in the distribution of risk-groups between the children and the TYA-patients. With growing recruitment, the real-world data approach the calculated estimates made before the study start. There is still a slightly higher fraction of patient stratified to HSCT than expected and a slightly lower fraction than expected in the IR-Low group. Particularly in the pilot-study, there is a number of patients stratified to the IR-high arm by default because of missing data, particularly regarding MRD.

Stratification is complex and there has been a learning curve. Table 11 indicates the self-reported risk-groups versus the centrally reviewed risk-groups for the pilot-patients and Table 12 for the main study patients.

Table 11. Central Review Risk-Groups vs self-reported Risk-Groups, excluding DS patients. Pilot protocol

Risk-Group	SR	IR-Low	IR-High	HR-chemo	HR-HSCT	Total
SR	46	7	14	0	1	68
IR-Low	4	33	4	2	1	44
IR-High	6	4	79	0	6	94
HR-chemo	0	0	0	0	3	3
HR-HSCT	0	0	0	0	17	17
Not Reported	8	5	18	0	3	34
Total	64	49	115	2	31	261

Columns=Central Review risk-grouping interpretation
Rows=Self-reported risk-grouping
Concordant: 175 (67%), under-stratified 38 (15%), over-stratified: 14 (5%), not reported: 34 (13%).

Table 12. Central Review Risk-Groups vs self-reported Risk-Groups, excluding DS patients. Main Protocol

Risk-Group	SR	IR-Low	IR-High	HR-chemo	HR-HSCT	Total
SR	45	5	3	0	0	53
IR-Low	6	50	1	2	1	60
IR-High	2	3	74	1	1	81
HR-chemo	0	0	0	0	2	2
HR-HSCT	0	0	1	0	24	25
Not Reported	3	6	21	0	2	32
Total	56	64	100	3	30	253

Columns=Central Review risk-grouping interpretation
Rows=Self-reported risk-grouping
Concordant: 193 (76%), under-stratified 16 (6%), over-stratified: 11 (4%), not reported: 32 (13%).

Follow-up

The registration of follow-up is clearly insufficient. Out of 269 pilot patients, 71 (26%) patients had adequate follow-up (after 1.1.2022) or had a registered event with a date, 27 (10%) had an out-dated follow-up and the remaining 171 (64%) had no follow-up. The corresponding figures for the main study patients were 111 (42%) with adequate follow-up and 151 (58%) without follow-up recorded.
Therefore, in this report follow-up had to be based on the assumption that events have been reported and that patients without events remain in CR1 and alive. All events had to be reported within a week and follow-up was extrapolated to 8 days before extraction (3.4.2022), which was also the day after the last recorded adverse event.

Pilot study

For EFS estimates: Median follow-up for pilot patients in CR1 was 760 days (range 107-1236).
For OS estimates: Median follow-up for living patients in the pilot study was 765 days (same range as for EFS).

Main study

For EFS estimates: Median follow-up for main study patients in CR1 was 316 days (range 94-618).
For OS estimates: Median follow-up for living patients in the main study was 318 with the same range as for EFS.

Treatment-results – Events and estimates for EFS and OS

Table 13. Events and overall outcomes by Risk-Groups, Pilot patients, excluding Down syndrome.

Event	Pilot Patients n=263 (non-Down Syndrome)				Total (100 %) n=263
Ind death	2				2 (0.76)
Outliers	0				0
To Risk-Group	261				261
	SR n=64	IR-Low n=49	IR-High n=115	HR (comb) n=33	Total n=261
PTF*	-	-	-	1	1 (0.4)
CR1 (%)	62	47	105	28	242 (92.0)
Relapse	1	1	7	2	11 (4.2)
DCR1	1	1	3	2	7 (2.7)
SMN	0	0	0	0	0
Dead	1 (1.6)	2 (4.1)	6 (5.2)	3 (9.1)	14 (5.3)**
Alive	63 (98.4)	47 (95.9)	109 (94.8)	30 (90.9)	249 (94.7)**
1 yr DFS (SD)	0.97 (0.02)	0.96 (0.03)	0.95 (0.02)	0.87 (0.06)	0.94 (0.02)***
1 yr OS (SD)	0.98 (0.02)	0.96 (0.03)	0.96 (0.02)	0.93 (0.04)	0.95 (0.01)***

*Mandatory stratification as HR.
**Including events before risk-stratification (induction deaths).
***Estimates for the whole patient population include early event and constitute EFS and OS for the whole population.

Table 14. Events and overall outcomes by Risk-Groups, Main study patients, excluding Down.

Event	Main Study Patients n=254 (non-Down Syndrome)				Total (100 %) n=254
Ind death	0				0
Outliers	1				1
To Risk-Group	253				253
	SR n=55	IR-Low n=64	IR-High (+TKI) n=101	HR (comb) n=33	Total n=253
PTF*	-	-	-	1 (3.0)	1 (0.4)
CR1 (%)	55 (100)	63 (98.4)	99 (98.0)	32 (97.0)	249 (98.0)
Relapse	0	1 (1.6)	1 (1.0)	0	2 (0.8)
DCR1	0	0	1 (1.0)	0	1 (0.4)
SMN	0	0	0	0	0
Dead	0	0	1 (1.0)	0	1 (0.4)**
Alive	55 (100)	64 (100)	100 (99.0)	33 (100)	253 (99.6)**
1 yr EFS (SD)	1.0	0.98 (0.02)	0.96 (0.03)	0.96 (0.04)	0.97 (0.01)
1 yr OS (SD)	1.0	1.0	0.98 (0.02)	1.0	0.99 (0.01)

*Mandatory stratification as HR.
**Including events before risk-stratification (induction deaths).

None of the patients with Down syndrome have had any events in any of the study-cohorts and this was also true for patients in the main study with ABL-class fusion and TKI-therapy.

The 1-year EFS and OS for the combined pilot-main study population was 0.96 (SE 0.01) and 0.97 (SE 0.01) respectively.

Sub-lethal toxicity

Figure 3. Induction toxicity by study cohort

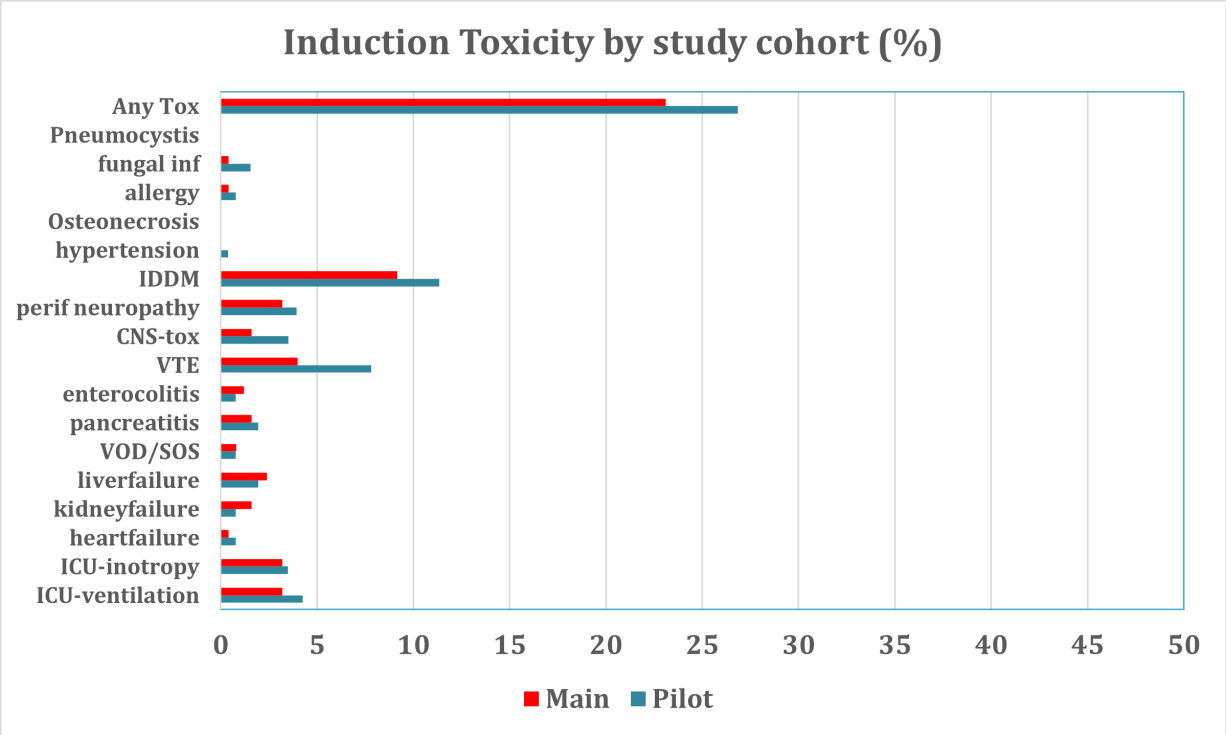
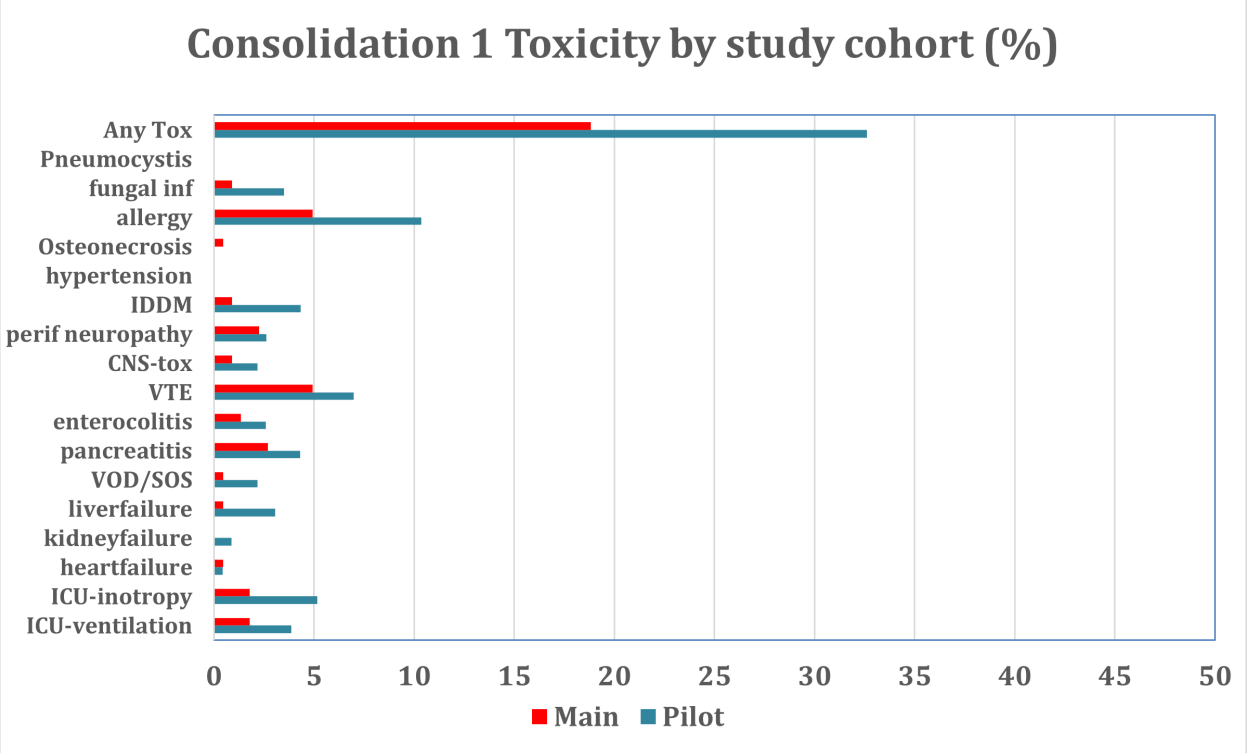


Table 15. The most common Induction Toxicities (AESIs) by cohort. Coverage: 95.5% pilot patients and 95.8% main study patients.

Toxicity	Pilot n=257 (%)	Main Study n=251 (%)	Total n=508 (%)
Any	69 (26.8)	58 (23.1)	127 (25.0)
ICU-press	9 (3.5)	8 (3.2)	17 (3.3)
ICU-vent	11 (4.2)	8 (3.2)	19 (3.7)
IDDM	29 (11.3)	23 (9.2)	52 (10.2)
Liver fail	5 (1.9)	6 (2.4)	11 (2.2)
Pancreatitis	5 (1.9)	4 (1.6)	9 (1.8)
VTE	20 (7.8)	10 (4.0)	30 (5.9)
CNS-tox	9 (3.5)	4 (1.6)	13 (2.6)
Per Neur tox	10 (3.9)	8 (3.2)	18 (3.5)

Diabetes is probably more common than in NOPHO ALL-08 with the universal use of Dexamethasone and the incidence is quite high. The toxicity is slightly higher in the pilot cohort compared with the main study, particulary VTE is more common in the pilot protocol, possibly reflecting the early period when the older patients were treated with two doses of PEG-Asp in induction.
Adherence to registration is generally high.

Figure 4. Consolidation 1 toxicity by age-group



The level of toxicity during Consolidation 1 no longer stands out as higher than during induction – for the main study patients.

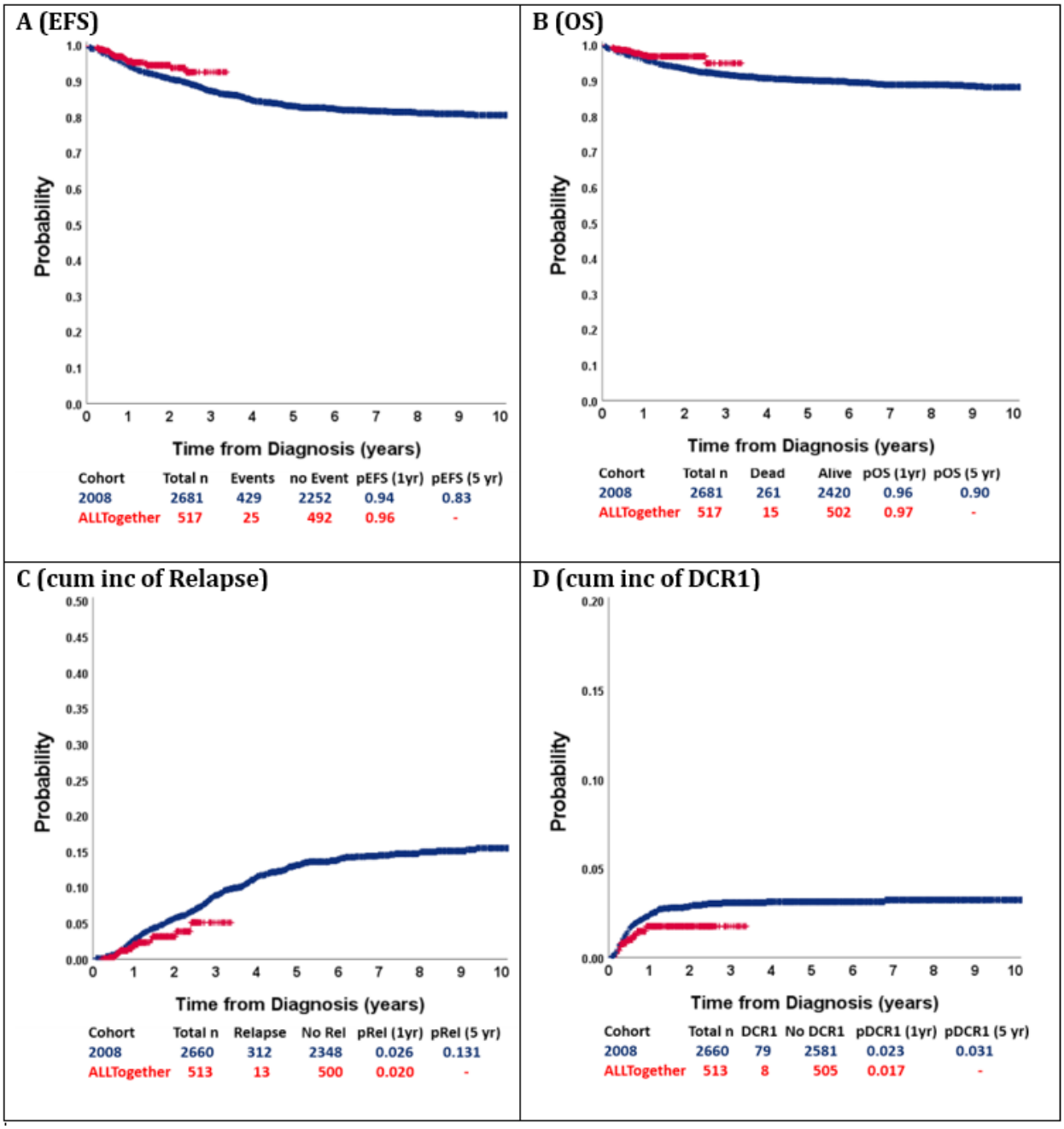
Table 16. The most common Consolidation 1 Toxicities (AESIs) by protocol group. Coverage: 87% pilot patients and 85% main study patients. Induction deaths removed from the denominator.

Toxicity	Pilot n=233 (%)	Main Study n=223 (%)	Total n=456 (%)
Any	76 (32.6)	42 (18.8)	127 (25.9)
ICU-press	12 (5.2)	4 (1.8)	16 (3.5)
ICU-vent	9 (3.9)	4 (1.8)	13 (2.9)
Liver fail	7 (3.1)	1 (0.4)	8 (1.8)
Pancreatitis	10 (4.3)	6 (2.7)	16 (3.5)
Enterocolitis	6 (2.6)	3 (1.3)	9 (2.0)
Fungal inf	8 (3.5)	2 (0.9)	10 (2.2)
VTE	16 (7.0)	11 (4.9)	27 (5.9)
IDDM	10 (4.3)	2 (0.9)	12 (2.6)
Allergy	24 (10.3)	11 (4.9)	35 (7.7)

The toxicity-rate has fallen dramatically in the main study cohort, likely because of the removal of PEG-Asp from this therapy phase. Some Asp-associated toxicities such as allergy, pancreatitis, liver toxicity and VTE have decreased, but also the need for intensive care, which is generally a marker for infectious toxicity.

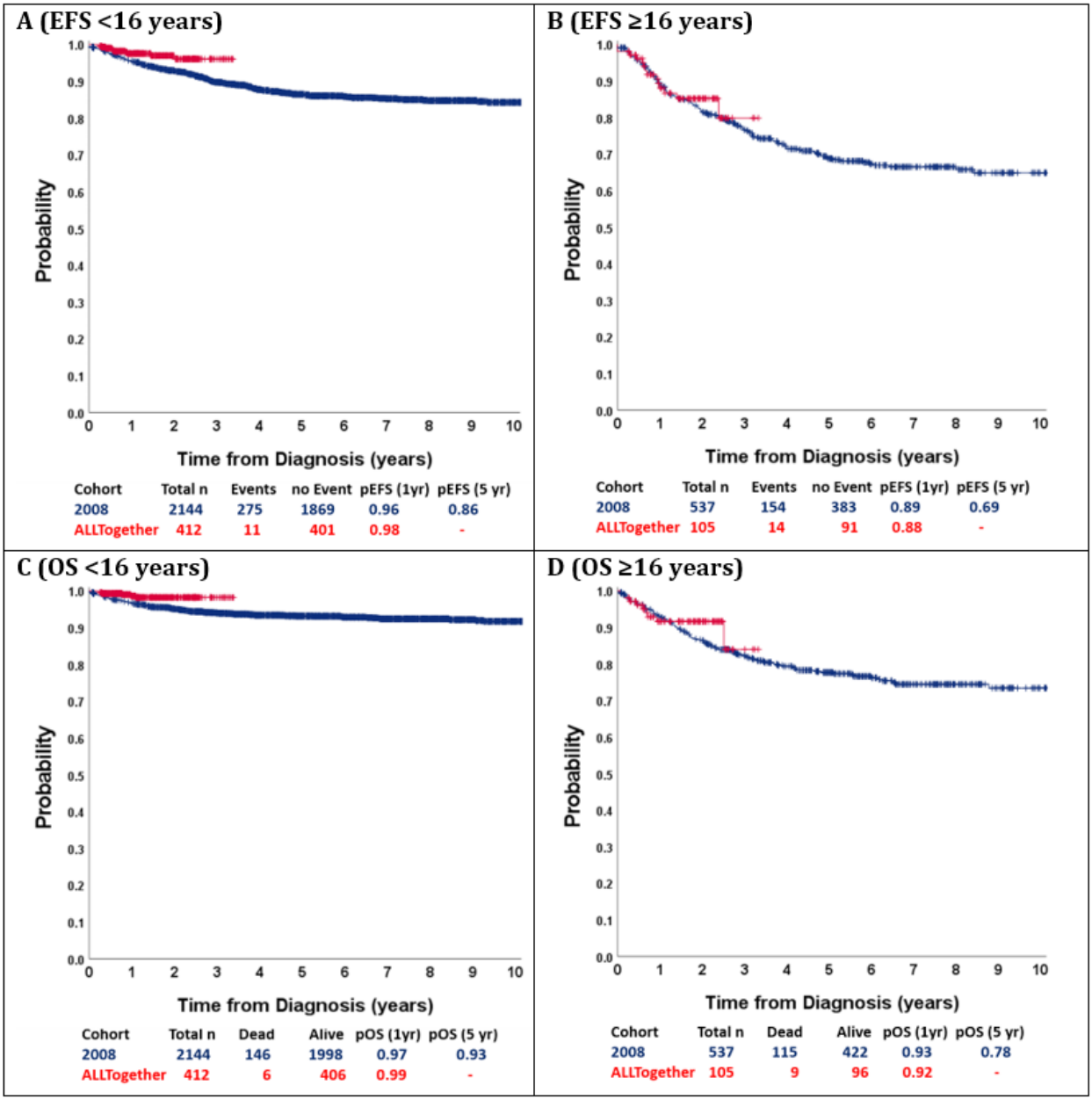
The rate of allergy is of interest and was in the region of 10% in the pilot, obviously lower after PEG-Asp was removed. The allergy-rate in Consolidation 2 was 0.6% in the pilot and presently, in the mixed population pre-/post change 11.2. However, there are many patients without registered AESIs for this phase and the general impression and some preliminary measurements in the whole consortium indicates that it may go up considerably. This will be further explored in the ALLTogether progress- and DSMB-reports.

Figure 5. NOPHO ALL-2008 vs ALLTogether (pilot+main study), Non-B cell ALL 1-<45 years at diagnosis, Mb Down excluded.



The early results of the ALLTogether pilot+early main study patients compared with the NOPHO ALL-2008 results may seem encouraging. However, the follow-up time is limited and the latter part of the curves, particularly after cessation of therapy have very few observations. Early estimates are also dominated by toxicity and it is likely that ALLTogether on average is less toxic than NOPHO ALL-08 because of the lower fraction of HR-patients. More adequate estimates, with potential to change these trends will be available with longer follow-up extending to the period after cessation of therapy, when a better assessment of the risk of relapse can be made. For this reason, no significance-testing have been carried out in these comparisons. Nevertheless, presently, there are no indications that the results will end up much worse than NOPHO ALL-2008 up in time. There was a learning-curve also for the NOPHO ALL-2008 protocol, with a relative excess of early deaths in CR1.

Figure 6. NOPHO ALL-2008 vs ALLTogether (pilot+main study), Non-B cell ALL 1-<16 and 16-45 years at diagnosis, Mb Down excluded.



The tendency for an improved prognosis is more obvious for the younger patients, whereas the graphs for the TYA-patients are essentially superimposable.

Table 17. Event-profile by age-group in the analyses above, ALL-2008 and ALLTogether patients

	ALL-2008		ALLTogether	
	<16 (n=2144)	≥16 (n=537)	<16 (n=412)	≥16 (n=105)
Induction Death	16 (0.7)	5 (0.9)	0 (0)	2 (2)
Protocol Therapy Fail	0 (0)	0 (0)	0 (0)	0 (0)
Relapses	193 (9)	119 (22)	6 (1.5)	7 (7)
DCR1	52 (2.4)	27 (5)	3 (0.7)	5 (5)

It is likely that both relapses and toxicity contribute to the worse results for older patients.

Concluding remarks

The message from the survey 2022 is mixed. We have overall results indicating that the overall results for patients treated according to ALLTogether are at least comparable to the NOPHO ALL-2008 protocol, but it is too early to draw any firm conclusions regarding the long-term outcomes.

On the other hand, it is obvious that the complexity of the protocol and the complex structure with additional diagnostics in the shape of double MRD-measurements and therapeutic drug-monitoring is increasing the burden on the departments. This complexity is also reflected in an increased burden of registration, which shows in an increasing fraction of missing data, some of which are critical for the full analysis of the results.

An additional burden to the logistics and registration has been the important changes in the ALLTogether protocol carried out and the report illustrates the shift in toxicity between the phases of treatment. Further evaluation of these changes will follow in progress- and DSMB-reports from the whole consortium patient material.

It is understandable, particularly at the beginning of the new protocol, that there are teething problems when it comes to understanding the new infrastructure, the complexity of the stratification and organising the logistics.
Hopefully, these initial problems will be possible to resolve soon, since the registration and data-analysis are essential tools for improving the outcome for our patients.

Nevertheless, we would like to thank all who participate in the work with registration and other contributions to the completeness and quality of the registered data.

We also hope that the NOPHO collaboration will continue to be fruitful also in the context of the coming ALLTogether wider collaboration and that NOPHO will contribute to the common activities of the consortium as well as with our own initiatives for the development of care and research in ALL for children and young adults.
We are particularly looking forward to welcoming our Latvian colleagues to the collaboration also in ALL, since Latvia is planning to join the ALLTogether pilot study.

For the registration group, Stockholm, springtime 2022

Mats Heyman and Trausti Óskarsson

ALL Relapse Working Group

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Sweden	Petter Svenberg (Chair since 2019) Mats Heyman Trausti Óskarsson

I addition to the annual NOPHO WG- meeting two additional WG-meetings were held via zoom/ teams. Anna Valaine from Latvia and Samppa Ryhänen from Finland were introduced as new members.

IntReALL studies

The IntReALL 2010 SR –study:

The study is closed (July 2020) and some data has been available and discussed during the fall in IBFM-meetings. For example, the outcome for R1 (randomisation between UKALL3 and ALL REZ backbone) are very similar, however more patients reached CR2 with the UKALL3-arm (Arm B) than with Arm A although TRM was slightly higher, especially during consolidation. As previously stated, due to a significant superior EFS for patients with IEM treated with Arm A compared with Arm B, future patients with IEM will receive Arm A. According to Charité, the results from the SR study will be published later this year.

The IntReALL 2010 HR -study

Finland has included two patients both whom received protocol-violating treatment (Nelarabine in one patient with T-ALL and for the other patient (with BCP-ALL) Blinatumomab was administered during consolidation prior to HC3. Sweden, Norway and Denmark are not participating.

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

The IBFM-SG resistant disease committee/ IntReALL consortium met on numerous occasions via zoom discussing the new protocol.

The relapses of BCP patients will be stratified accordingly, Very high risk (VHR, relapse <18 months from primary diagnose and/or cytogenetic features e.g. p53, hypodiploidy, t(1;19)/(17;19), MLL/AF4. High risk (HR) relapse, early isolated or combined medullary/extra medullary relapse. For patients with late isolated or combined medullary/extra medullary relapses will be stratified as standard risk (SR).

- The IntReALL 2020 SR protocol will be an academic sponsored study including two randomisations, one in the induction and one later on during consolidation. All patients will receive one round of Blinatumomab. The IntReALL 2020 HR study will entail an investigational window during induction where a Pfizer-sponsored randomization will take place.

The intention to participate has been discussed within the WG, however the final commitment to the study will be a national decision.

For the VHR patients, they will be included in the ITCC059 trial where after the intention is to include them in a Rome-sponsored CAR T-cell trial with Miltenyi as the CAR-construct provider. Since there is specific Miltenyi apparatus required, and the patient numbers are small, different options for smaller countries are discussed. Our WG plans to have a separate meeting with the sponsor in order to clarify the best way forward.

- Hem-ISMART is an European initiative for biomarker driven selection and drug response profiling of relapse patients.
First stage focus for the HEM-ISMART is T-ALL and TLL-relapse patients, Next stage BCP-ALL/LL and AML rare subgroups.

- International Leukemia Board (iLB) is a European initiative to address patients to a selected arm of innovative drug combinations in a safe and regulated clinical trail environment. This foresees to reduce off-label and compassionate use in pediatric patients and make safety, toxicity and first efficacy signals rapidly available.

Prospective registration of ALL relapses in the Nordic countries. The WG members have agreed to grasp the treatment burden for relapse patients. At the moment, treatment is not seldom heterogeneous including both chemotherapy, immunotherapy, stem cell transplantation and inclusion in a phase 1/2 trial. Therefore a prospective registration would be the next step, however this can be achieved in numerous ways. The NOPHO CARE study, whose purpose is to study EFS and OS in all children with malignancies within the NOPHO countries, could be the platform needed. The data is imported from national cancer registry, and the Nordic countries except Iceland has ethical permissions already in place that cover data collection of relapsed patients. For the sole purpose to observe if these patient benefit from the different relapse treatment or not and include more variables, the start of a new registry to prospectively register all relapsed ALL patient has been discussed. Lastly, these patients can be registered in the Marvin based IntReALL ALL relapse registry. An effort to start prospectively register relapse patient data will be initiated during 2022.

Due to the Covid pandemic the annual NOPHO WG-meeting in Kuopio, Finland will be virtual.

For the working group
Petter Svenberg,
Stockholm, March 2022

Events Working Group (EWG)

Sweden	Arja Harila-Saari (chair) Anna Nilsson Cecilia Langenskiöld Mats Heyman (ALLTogether) Mia Giertz (Osteonecrosis, Secretary for the group) Susanna Ranta (Thrombosis)
Denmark	Birgitte Klug Albertsen (Asparaginase) Bodil Thorhauge Als-Nielsen Kjeld Schmiegelow
Norway	Bendik Lund Niklas Bernhard Stabell
Finland	Riitta Niinimäki Anu Huurre
Latvia	Elizabete Cebura
Lithuania	Goda Vaitkeviciene
Iceland	Ólafur G. Jónsson
Young NOPHO	Raheel Altaf Raja (Denmark)

The group has had two meetings: 13th September with 26 participants and 7th February with 20 participants. Both sessions were arranged via Zoom.

The groups primary focus areas are follow-up and definitions of events in leukemia protocols and toxicity reporting, follow-up, and guidelines for treating adverse events. The group has mainly but not only worked with acute lymphoblastic leukemia (ALL). A focus of both meetings has been on events related to asparaginase.

1. Asparaginase (Asp)-related studies (Birgitte Klug Albertsen's study group)

At the September meeting, comparisons in hypersensitivity following PEG-Asp treatment in the ALLTogether pilot protocol vs the main protocol were presented and shown to be 17% and 36% hypersensitivity, respectively. Potential mechanisms or causes behind this disparity between protocols were discussed, such as the lack of concurrent use of dexamethasone or potential change in the preparation of Asp, as well as potential next steps, e.g., increasing interval or desensitizing exposure during consolidation 1 in the context of a randomized controlled trial (RCT). At the February meeting, Asp allergy in the ALLTogether protocol was further discussed. Price was mentioned – this may potentially be a political question. Treatment is also experienced as burdensome for the family, if patients need to receive it every other day for several months; possible to take intramuscularly with different dosage. Recombinant E. coli asparaginase may not be an alternative, as it has been shown to be more immunogenic. Birgitte suggested a RCT, e.g., comparison of ERYASPASE to Erwinase, and collecting more CSF samples.

Results from a study cohort of 1155 patients (6944 samples) on the association between asparaginase enzyme activity levels and toxicity in childhood ALL were presented. Briefly, overall toxicity and relapse were not significantly associated with increasing Asp enzyme activity levels for the whole cohort, while risk of pancreatitis and osteonecrosis was significantly associated with increasing enzyme activity levels. The results indicated that some patients might benefit from using therapeutic drug monitoring to identify high enzyme activity levels, to potentially reduce specific toxicities through dose reduction.

Another Asp-related study aimed to investigate safety of asparaginase re-exposure, the clinical decision making of asparaginase re-exposure, and clinical outcome after re-exposure. Of the 46 patients identified and included in the study, the majority were re-exposed to Asp, a low rate of re-thrombosis and low frequency of bleeding complications were detected. No clinical outcomes or imagine findings were associated with re-exposure to Asp.

A new study was proposed: Glucose intolerance and diabetes related to treatment with steroids and PEG-asparaginase in children and adolescents with ALL and lymphoma. The main aim is to investigate the incidence and severity of medication-induced glucose intolerance and diabetes mellitus in children and adolescents (1.0-17.9 years old) treated for ALL or lymphoma in Denmark. Continuous glucose monitoring will be performed using the Dexcom G6 glucose sensor. Ethical approval has been received, patient recruitment expected to start in March. EWG was positive to the study.

2. COVID-19 in pediatric cancer

Collaboration between Uppsala and Karolinska, along with other centers in Sweden. Patient recruitment since June 2020 and 139 patients recruited as of September's meeting (340 samples). Healthy sibling samples will also be collected (n=160) for analysis. Many children developed antibodies against SARS-CoV-2 with minimal (or no) symptoms and despite immunosuppressive treatment. Studies evaluating different covid variants may be performed.

3. Adverse events in ALLTogether

Reported results on toxicity in ALLTogether resulted in a change in the therapy (Asp moved from consolidation 1 for all patients and introduced in consolidation 2). Next steps were proposed: Updated look at toxicity to investigate whether toxicity has changed following change in therapy. In short, the toxicity profile differed between the ALL2008 and ALLTogether protocols, though the overall frequency has not changed significantly. Data collection is still ongoing and aims to include all patients in Sweden. Suggestions to look into the timing of toxicity and potential differences between risk groups, as well as to evaluate potential discrepancies between the reporting in different data sources.

Hyperammonemia has been observed during ALLTogether, especially during Erwinase treatment. Recommendation was to decrease the dose by 25%, give the infusion under 2 hours rather than 1 hour, and consider providing dosage intramuscularly rather than intravenously. May be possible to further decrease dose, but then samples should be checked to ensure that dosage remains sufficient.

Regarding coagulation, differences were observed in bleeding events and thrombotic events between the ALL2008 and ALLTogether treatment protocols.

4. Intensive care in children with acute myeloid leukemia in Sweden

Study cohort of 126 patients with AML, recruited from the Swedish Childhood Cancer Registry, of which 58 were admitted to intensive care (46%). A discrepancy was observed in reported admission rates between data from pediatric oncology treatment centers (29%) and the Swedish Intensive Care Registry (44%). There appears to have been excellent availability to intensive care in Sweden.

5. Single nucleotide polymorphisms and central nervous system toxicities in the ALL-2008 protocol

Neurotoxicity was evaluated in a cohort of 1464 children (1274 with B-ALL and 190 with T-ALL), of whom 135 presented at least one neurotoxicity during treatment course. PRES was the most common neurotoxicity and seizure was the most common neurological symptom. Age was identified as a modifier

of neurotoxicity with an overall higher risk of neurotoxicity in children ≥10 years and possible genetic disposition to seizures in children <10 years. Further GWAS and validation studies in larger cohorts of pediatric patients with ALL are warranted.

6. Body mass index changes as well as in relation to toxicity in the ALL-2008 protocol

Study aim was to describe change in BMI in NOPHO ALL-2008 and association with gender/age/toxicities, using registry data. A total of 1443 patients treated according to the ALL-2008 protocol were included in the study. No significant correlations between BMI and median duration in each treatment phase or median delay to Maintenance 1 were observed. More obese children (72.5%) than children with healthy BMI (51.4%) had one or more toxic event, and older obese children had more Asp-associated toxicities. There was a tendency to increased toxicity in younger underweight children. Severe adverse events of significant included kidney failure, thrombosis (older children), abdominal catastrophe, SUSAR anaphylactic reaction, and bleeding as well as truncation of Asp in older children.

7. Osteonecrosis and thrombosis in children with Hodgkin Lymphoma (Mia Gertz and study group)

Study aim was to investigate the incidence, treatment, and outcome of symptomatic osteonecrosis (ON) in pediatric Hodgkin lymphoma (HL) between 2005-2019 in Sweden, Denmark, and Finland. Preliminary results are that ON is equally common in pediatric HL as pediatric ALL. Girls with HL in/after puberty have a very higher risk of ON, and ON seems to be associated with a significant weight gain during treatment.

The next EWG meeting will be on Monday, 5th September, and held as a Zoom meeting.

Publications involving the work of the Events Working Group

1. **Buchmann S, Schrappe M, Baruchel A, Biondi A, Borowitz M, Campbell M, Cario G, Cazzaniga G, Escherich G, Harrison CJ, Heyman M, Hunger SP, Kiss C, Liu HC, Locatelli F, Loh ML, Manabe A, Mann G, Pieters R, Pui CH, Rives S, Schmiegelow K, Silverman LB, Stary J, Vora A, Brown P.** *Remission, treatment failure, and relapse in pediatric ALL: an international consensus of the Ponte-di-Legno Consortium.* Blood. 2022 Mar 24;139(12):1785-1793. doi: 10.1182/blood.2021012328. PMID: 34192312
2. **Jarvis KB, Andersson NG, Giertz M, Järvelä L, Lindinger O, Långström S, Niinimäki R, Palmu S, Trakymiene SS, Tuckuviene R, Vepsäläinen K, Ranta S, Frisk T.** *Asymptomatic Right Atrial Thrombosis After Acute Lymphoblastic Leukemia Treatment.* J Pediatr Hematol Oncol. 2021 May 1;43(4):e564-e566. doi: 10.1097/MPH.0000000000001848. PMID: 32555028
3. **Laumann RD, Iversen T, Mogensen PR, Lauritzen L, Mølgaard C, Frandsen TL.** *Effect of Fish Oil Supplementation on Hyperlipidemia during Childhood Acute Lymphoblastic Leukemia Treatment - A Pilot Study.* Nutr Cancer. 2021;73(9):1816-1820. doi: 10.1080/01635581.2020.1803934. Epub 2020 Aug 13. PMID: 32791015
4. **Thastrup M, Marquart HV, Levinsen M, Modvig S, Abrahamsson J, Albertsen BK, Frost BM, Harila-Saari A, Pesola J, Ulvmoen A, Wojcik DM, Taskinen M, Hoffmann M, Lausen B, Schmiegelow K; Nordic Society of Paediatric Haematology, Oncology (NOPHO).** *Flow cytometric analysis of cerebrospinal fluid improves detection of leukaemic blasts in infants with acute lymphoblastic leukaemia.* Br J Haematol. 2021 Oct;195(1):119-122. doi: 10.1111/bjh.17769. Epub 2021 Aug 15. PMID: 34396501
5. **Oskarsson T, Duun-Henriksen AK, Bautz A, Montgomery S, Harila-Saari A, Petersen C, Niinimäki R, Madanat-Harjuoja L, Tryggvadóttir L, Holmqvist AS, Hasle H, Heyman M, Winther JF; ALiCCS study group.** *Skeletal adverse events in childhood cancer survivors: An Adult Life after Childhood Cancer in Scandinavia cohort study.* Int J Cancer. 2021 Dec 1;149(11):1863-1876. doi: 10.1002/ijc.33741.Epub 2021 Jul 30. PMID: 34278568
6. **Gottschalk Højfeldt S, Grell K, Abrahamsson J, Lund B, Vettenranta K, Jónsson ÓG, Frandsen TL, Wolthers BO, Marquart HV, Vaitkeviciene G, Lepik K, Heyman M, Schmiegelow K, Albertsen BK.** *Relapse risk following truncation of pegylated asparaginase in childhood acute lymphoblastic leukemia.* Blood. 2021 Apr 29;137(17):2373-2382. doi: 10.1182/blood.2020006583. PMID: 33150360 Clinical Trial.

7. **Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Schmiegelow K, Vedsted P, Albertsen BK, Schrøder H; Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Detection mode of childhood acute lymphoblastic leukaemia relapse and its effect on survival: a Nordic population-based cohort study.* Br J Haematol. 2021 Aug;194(4):734-744. doi: 10.1111/bjh.17555. Epub 2021 May 27. PMID: 34041748
8. **Toksvang LN, Andrés-Jensen L, Rank CU, Niinimäki R, Nersting J, Nielsen SN, Mogensen SS, Harila-Saari A, Abrahamsson J, Joelsson J, Overgaard UM, Quist-Paulsen P, Griškevičius L, Jónsson ÓG, Vaitkevičienė G, Frandsen TL, Toft N, Grell K, Schmiegelow K.** *Maintenance therapy and risk of osteonecrosis in children and young adults with acute lymphoblastic leukemia: a NOPHO ALL2008 sub-study.* Cancer Chemother Pharmacol. 2021 Nov;88(5):911-917. doi: 10.1007/s00280-021-04316-z. Epub 2021 Jun 18. PMID: 34145469 Clinical Trial.
9. **Sági JC, Gézsi A, Egyed B, Jakab Z, Benedek N, Attarbaschi A, Köhrer S, Sipek J, Winkowska L, Zaliova M, Anastasopoulou S, Wolthers BO, Ranta S, Szalai C, Kovács GT, Semsei ÁF, Erdélyi DJ.** *Pharmacogenetics of the Central Nervous System-Toxicity and Relapse Affecting the CNS in Pediatric Acute Lymphoblastic Leukemia.* Cancers (Basel). 2021 May 12;13(10):2333. doi: 10.3390/cancers13102333. PMID: 34066083
10. **Nielsen SN, Toksvang LN, Grell K, Nersting J, Abrahamsson J, Lund B, Kanerva J, Jónsson ÓG, Vaitkeviciene G, Pruunsild K, Appell ML, Hjalgrim LL, Schmiegelow K.** *No association between relapse hazard and thiopurine methyltransferase geno- or phenotypes in non-high risk acute lymphoblastic leukemia: a NOPHO ALL2008 sub-study.* Cancer Chemother Pharmacol. 2021 Aug;88(2):271-279. doi: 10.1007/s00280-021-04281-7. Epub 2021 Apr 29. PMID: 33928426
11. **Andrés-Jensen L, Attarbaschi A, Bardi E, Barzilai-Birenboim S, Bhojwani D, Hagleitner MM, Halsey C, Harila-Saari A, van Litsenburg RRL, Hudson MM, Jeha S, Kato M, Kremer L, Mlynarski W, Möricke A, Pieters R, Piette C, Raetz E, Ronceray L, Toro C, Grazia Valsecchi M, Vrooman LM, Weinreb S, Winick N, Schmiegelow K; Ponte di Legno Severe Toxicity Working Group.** *Severe toxicity free survival: physician-derived definitions of unacceptable long-term toxicities following acute lymphocytic leukaemia.* Lancet Haematol. 2021 Jul;8(7):e513-e523. doi: 10.1016/S2352-3026(21)00136-8. PMID: 34171282 Review.
12. **van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, Hudson MM, Kremer LCM, Skinner R, Wallace WH, Constine LS, Higham CE, Kaste SC, Niinimäki R, Mostoufi-Moab S, Alos N, Fintini D, Templeton KJ, Ward LM, Frey E, Franceschi R, Pavasovic V, Karol SE, Amin NL, Vrooman LM, Harila-Saari A, Demoor-Goldschmidt C, Murray RD, Bardi E, Lequin MH, Faienza MF, Zaikova O, Berger C, Mora S, Ness KK, Neggers SJCMM, Pluijm SMF, Simmons JH, Di Iorgi N.** *Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group.* Lancet Diabetes Endocrinol. 2021 Sep;9(9):622-637. doi: 10.1016/S2213-8587(21)00173-X. Epub 2021 Jul 30. PMID: 34339631 Review.
13. **Toksvang LN, Grell K, Nielsen SN, Nersting J, Murdy D, Moorman AV, Vora A, Schmiegelow K.** *DNA-TG and risk of sinusoidal obstruction syndrome in childhood acute lymphoblastic leukemia.* Leukemia. 2022 Feb;36(2):555-557. doi: 10.1038/s41375-021-01420-0. Epub 2021 Sep 17. PMID: 34535761
14. **Egnell C, Heyman M, Jónsson ÓG, Raja RA, Niinimäki R, Albertsen BK, Schmiegelow K, Stabell N, Vaitkeviciene G, Lepik K, Harila-Saari A, Ranta S.** *Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia.* Br J Haematol. 2022 Mar;196(5):1239-1247. doi: 10.1111/bjh.17936. Epub 2021 Nov 2. PMID: 34726257
15. **Ranta S, Broman LM, Abrahamsson J, Berner J, Fläring U, Hed Myrberg I, Kalzén H, Karlsson L, Mellgren K, Nilsson A, Norén-Nyström U, Palle J, von Schewelov K, Svahn JE, Törnudd L, Heyman M, Harila-Saari A.** *ICU Admission in Children With Acute Lymphoblastic Leukemia in Sweden: Prevalence, Outcome, and Risk Factors.* Pediatr Crit Care Med. 2021 Dec 1;22(12):1050-1060. doi: 10.1097/PCC.0000000000002787. PMID: 34074998
16. **Sørensen GV, Belmonte F, Erdmann F, Mogensen H, Albieri V, Holmqvist AS, Madanat-Harjuoja L, Talbäck M, Heyman MM, Malila N, Feychting M, Schmiegelow K, Winther JF, Hasle H.** *Late mortality among survivors of childhood acute lymphoblastic leukemia diagnosed during 1971-2008 in Denmark, Finland, and Sweden: A population-based cohort study.* Pediatr Blood Cancer. 2022 Jan;69(1):e29356. doi: 10.1002/pbc.29356. Epub 2021 Sep 28. PMID: 34582112

17. **Andrés-Jensen L, Grell K, Rank CU, Albertsen BK, Tuckuviene R, Linnemann Nielsen R, Lynggaard LS, Jarvis KB, Quist-Paulsen P, Trakymiene SS, Semaškevičienė R, Saks K, Jonsson OG, Frandsen TL, Johansson PI, Schmiegelow K.** *Endothelial dysfunction and thromboembolism in children, adolescents, and young adults with acute lymphoblastic leukemia.* Leukemia. 2022 Feb;36(2):361-369. doi: 10.1038/s41375-021-01383-2. Epub 2021 Aug 13. PMID: 34389803
18. **Lynggaard LS, Rank CU, Hansen SN, Gottschalk Højfeldt S, Henriksen LT, Jarvis KB, Ranta S, Niinimäki R, Harila-Saari A, Wolthers BO, Frandsen TL, Heyman M, Schmiegelow K, Albertsen BK.** *Asparaginase enzyme activity levels and toxicity in childhood acute lymphoblastic leukemia: a NOPHO ALL2008 study.* Blood Adv. 2022 Jan 11;6(1):138-147. doi: 10.1182/bloodadvances.2021005631. PMID: 34625787
19. **Nielsen RL, Wolthers BO, Helenius M, Albertsen BK, Clemmensen L, Nielsen K, Kanerva J, Niinimäki R, Frandsen TL, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Aytan-Aktug D, Liu HC, Möricke A, Samarasinghe S, van der Sluis IM, Stanulla M, Tulstrup M, Yadav R, Zapotocka E, Schmiegelow K, Gupta R.** *Can Machine Learning Models Predict Asparaginase-associated Pancreatitis in Childhood Acute Lymphoblastic Leukemia.* J Pediatr Hematol Oncol. 2022 Apr 1;44(3):e628-e636. doi: 10.1097/MPH.0000000000002292. PMID: 35226426
20. **Lynggaard LS, Vaitkeviciene G, Langenskiöld C, Lehmann AK, Lähteenmäki PM, Lepik K, El Hariry I, Schmiegelow K, Albertsen BK.** *Asparaginase encapsulated in erythrocytes as second-line treatment in hypersensitive patients with acute lymphoblastic leukaemia.* Br J Haematol. 2022 Mar 28. doi: 10.1111/bjh.18152. Online ahead of print. PMID: 35344210
21. **Helenius M, Vaitkeviciene G, Abrahamsson J, Jonsson ÓG, Lund B, Harila-Saari A, Vettenranta K, Mikkel S, Stanulla M, Lopez-Lopez E, Waanders E, Madsen HO, Marquart HV, Modvig S, Gupta R, Schmiegelow K, Nielsen RL.** *Characteristics of white blood cell count in acute lymphoblastic leukemia: A COST LEGEND phenotype-genotype study.* Pediatr Blood Cancer. 2022 Mar 22:e29582. doi: 10.1002/pbc.29582. Online ahead of print. PMID: 35316565.
22. **Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Jónsson ÓG, Svenberg P, Schmiegelow K, Heyman M, Norén-Nyström U, Schrøder H, Albertsen BK.** *Temporal changes in incidence of relapse and outcome after relapse of childhood acute lymphoblastic leukemia over three decades; a Nordic population-based cohort study.* Leukemia. 2022 Mar 21. doi: 10.1038/s41375-022-01540-1. Online ahead of print. PMID: 35314777

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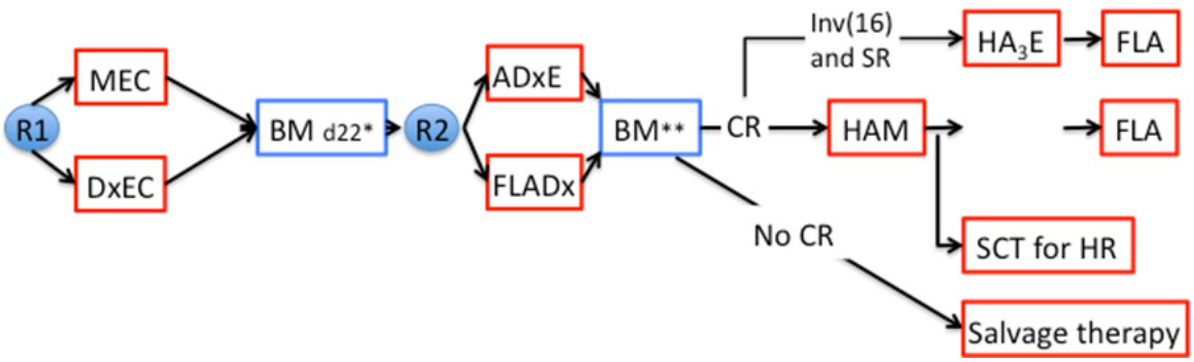


Figure 1. Overview of the current clinical research protocol NOPHO-DBH AML 2012. Evaluation of therapy response is performed on day 22 after the first course and immediately before consolidation. Randomisations R1 and R2 are closed and MEC and ADxE are standard arms in all patients.

Organisation

The group has held two meetings during 2021, 19th of April and 8th of November and they both had to be digital due to the Covidpandemia. The November meeting was joint meeting with the MRD group. At both meetings there were NOPHO AML group meeting before meeting the whole consortium as former decided. The meetings have functioned as PI meetings for the coordination and supervision of the treatment protocol NOPHO-DBH AML2012.

In between these meetings there have been a lot of workning group meetings and activities in the making of a new protocol, the CHIP-AML 22 protocol.

We have continued to act as a platform for facilitating both biological and clinical research in pediatric AML and to include all 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 NOPHO leukemia biology group which allows for increased collaboration and scientific quality. As this report is written there just was a special AML-NOPHO biology meeting 14th of March 2022.

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 still recruiting patients. In summer 2021 randomization 2 was closed as it had recruited all patients. The protocol is open for registration using the standard arms until the next protocol is ready to open. As usual, between meetings, members have frequent mail discussions both regarding individual patient treatment decisions and research issues.

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 EFS_{5y} 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.

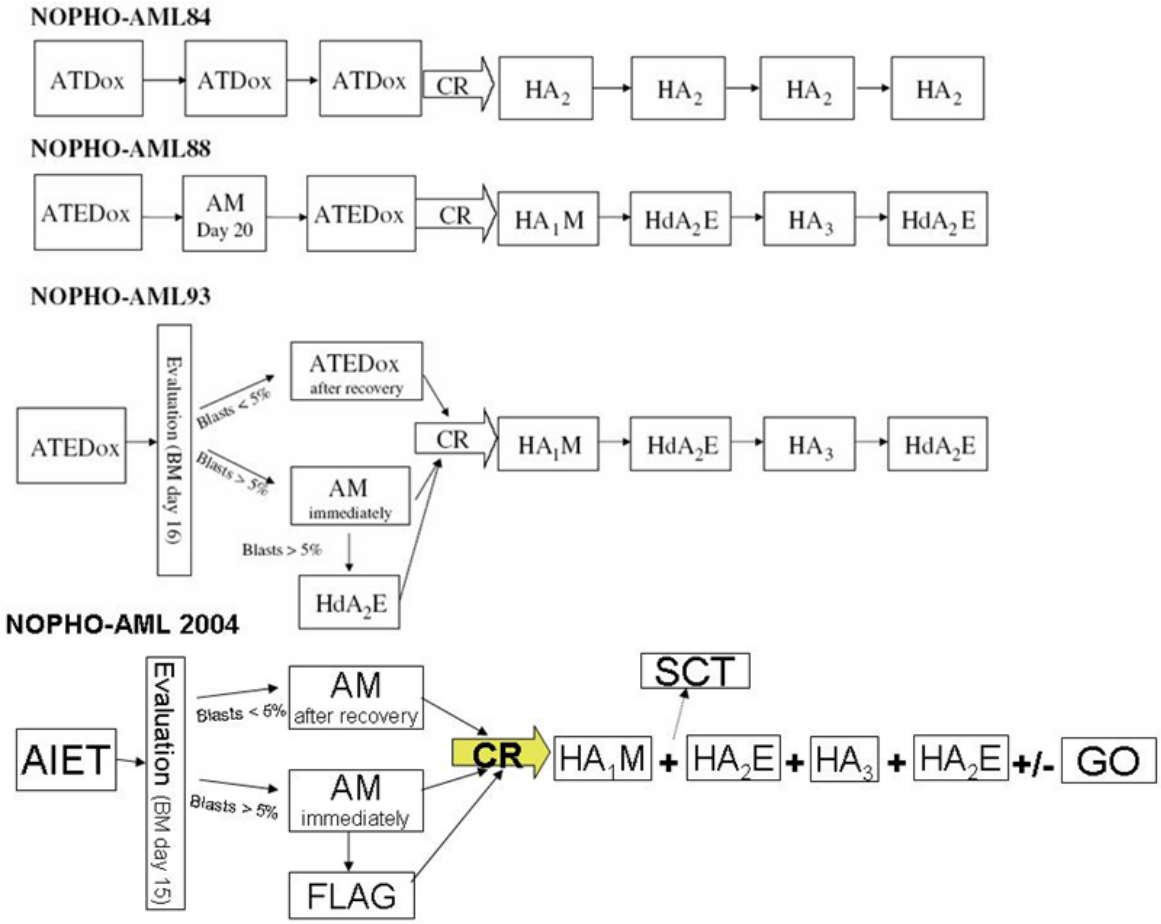


Figure 2. Overview of previous NOPHO treatment protocols from 1984-2012. In AML88 all patients received intensively timed induction with early start of course 2. Since AML93 all protocols have adopted a response-guided timing of the second course, allowing good responding patients to recover peripheral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

During 2021 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. Continuous work so that NOPHO 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 the other is Data Commons which aims at creating a large set of data from pediatric AML trials throughout the world.
3. Increasing the scientific collaboration with preclinical researchers and between NOPHO and the Belgian, Dutch, Hong Kong, Israeli and Spanish groups.
4. Participation in international collaborative research projects.
5. 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 2021 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.

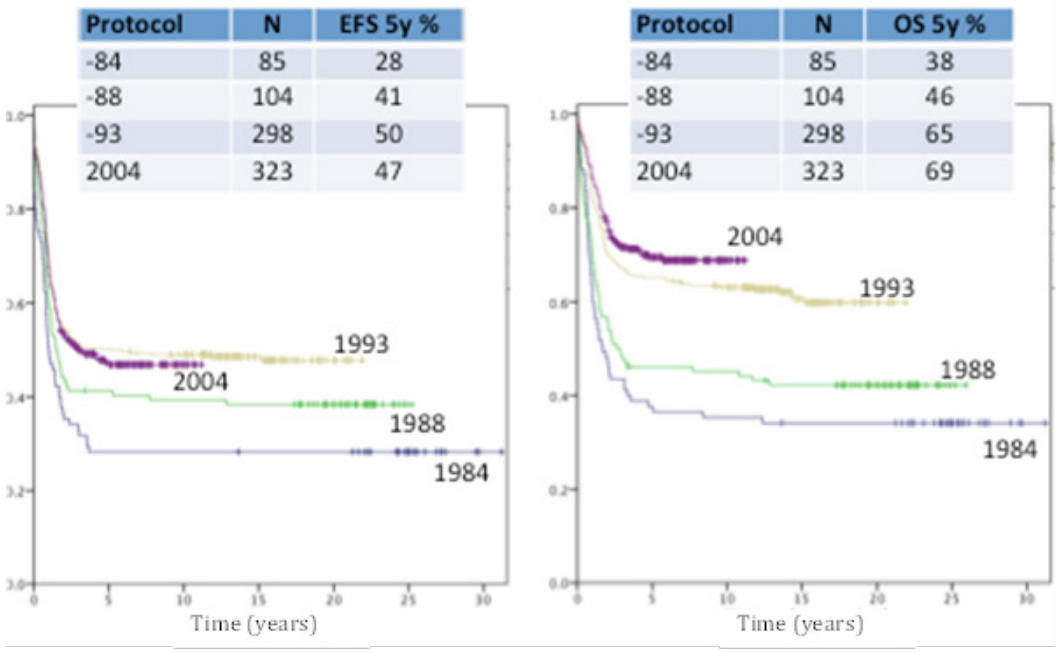


Figure 3. Overall survival (right figure) and event-free survival (left figure) in NOPHO-AML2004 (purple), NOPHO-AML93 (beige), NOPHO-AML88 (green) and NOPHO-AML84 (blue).

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. Randomization 1 was terminated at this point since EFS was significantly higher in the mitoxantrone arm. Depending on approvals from national authorities the countries re-started randomizatons at different timepoints during spring 2019. In summer 2021 randomization 2 was closed as it had recruited all patients. The protocol is open for registration using the standard arms until the next protocol is ready to open. These patients are important to allow subgroup analyses in a larger cohort.

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.

As there is an ongoing discussion about the risk grouping of these patients an analysis of patients with KMT2A and those classified as "highrisk" in other treatment protocols was done. This analysis did not change the decision by the NOPHO AML group to keep the risk stratification as originally planned in AML2012 and it emphasized the importance of MRD analysis and identified some subgroups where MRD < 0,1% after C1 might affect EFS and OS. 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 included 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 were compared. The second study compared 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 Mar 2022, 770 patients have been treated on the protocol. A major setback was that the company producing DaunoXome did not provide the drug 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 DaunoX-

ome 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 770 patients treated on AML2012 until March 2022. 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 64% have MRD < 0.1%.

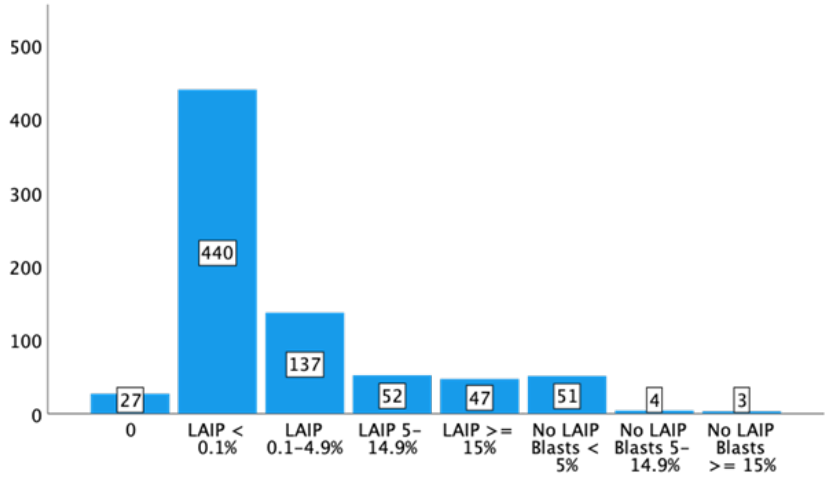


Figure 4. Response to course 1 in AML2012. 0 depicts patients lacking registration. LAIP - leukemia associated immunophenotype. 60 % of all patients have MRD < 0.1%.

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 92 % reached complete remission. The frequency of resistant disease was 5,5 %. Of all patients, 73.9 % 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 event-free and overall survival according to risk group, the risk stratification virtually eliminates the previous difference in outcome.

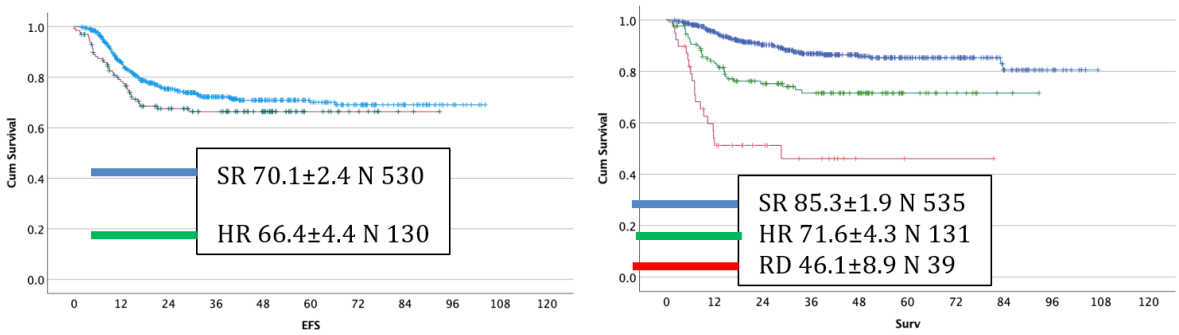


Figure 5. Event -free survival (left) and overall survival (right) are almost equal in both risk groups. Overall survival is shown also for patients with resistant disease (RD). Blue curve - standard risk, green - high risk, red - resistant disease.

The toxicity in AML2012 is, as expected, high but manageable. The frequency of induction death is 2.6% and the cumulative risk of treatment-related mortality is 6 %. 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 22 months from diagnosis. Also, the data for overall survival are now so mature allowing for interpretation. 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 63.6 % and OS at 78.0 %.

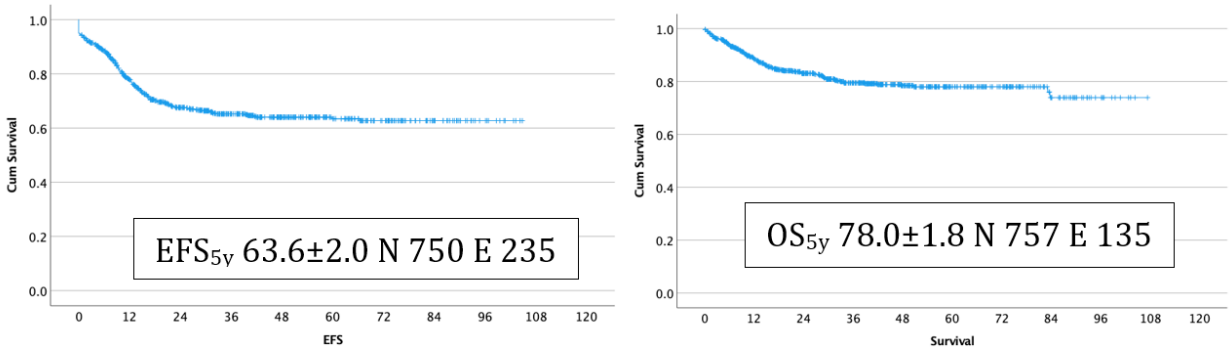


Figure 6. Kaplan-Meier estimates of event-free survival and overall survival for AML2012. Estimates are at five years.

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).

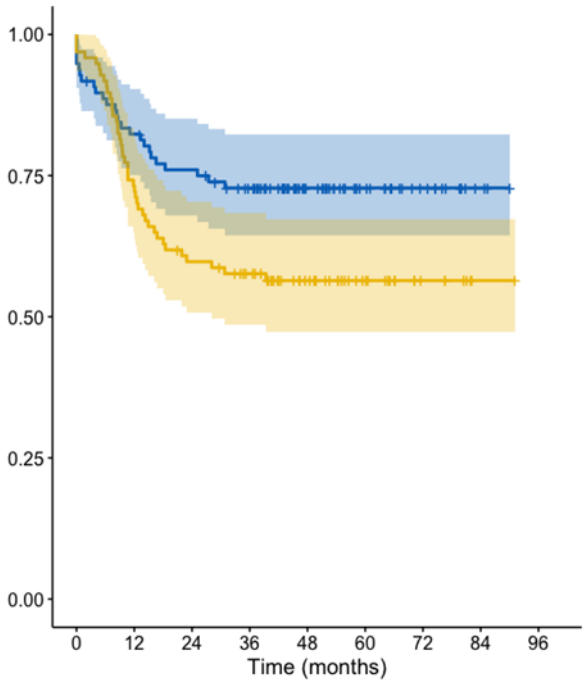


Figure 7. EFS in 194 patients randomized between MEC and DxEC in R1 and with outcome data. MEC (blue line) had an EFS_{5y} of 72.8% (63.9-81.7) and DxEC(yellow line) had an EFS_{5y} of 56.4% (46.5-66.3) Log rank test is significant with P=0.017. The number at risk at three years was 27 for MEC and 23 for DxEC with a median observation time of 30 months in patients without events.

In total, there were 42 events in the DxEC arm and 26 in the MEC which is a statistically significant difference. Further analysis of the events showed, as demonstrated in figure 8, that the difference in EFS_{5y} was caused by a higher cumulative incidence of relapses (CIR_{5y}) in the DxEC arm. CIR_{5y} was 17.5% (10.7-25.7) for MEC and 35.1% (25.7-44.6) for DxEC (P=*0.005*).

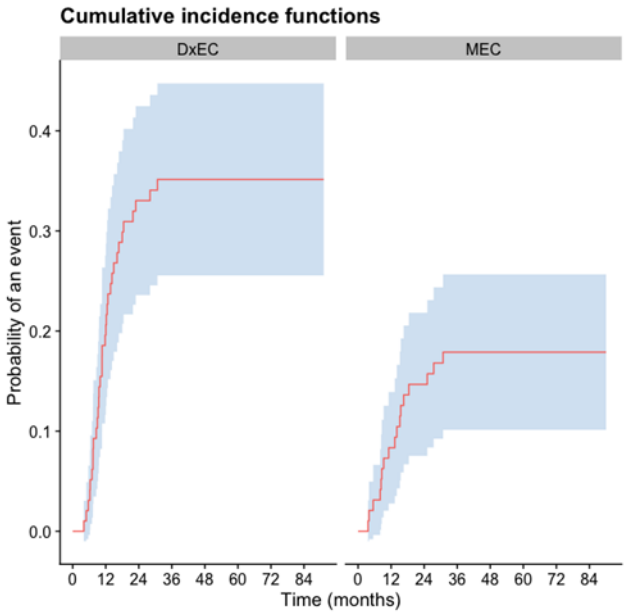


Figure 8. CIR_{5y} in 194 patients randomized between MEC and DxEC in R1 and with outcome data. MEC (right) had a CIR_{5y} of 17.5% (10.7-25.7) and DxEC(left) had an CIR5y of 35.1% (25.7-44.6) Log rank is significant with P=0.005. Analysis is performed with correction for competing events.

Multivariable 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 (OS_{5y} MEC 81.9% (74-89.7) vs DxEC 73.8% (65-82.7).

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. The second randomization reached target accrual in summer 2021 and analyses will be performed 2023. 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.

New AML protocol

NOPHO-DB-SHIP Consortium and upcoming new AML protocol: CHIP-AML22 study

The NOPHO-DBH AML12 protocol was initiated in NOPHO countries, Netherlands, Belgium and Hongkong that all have randomized in the current protocol. The consortium has since been complemented with Spain and Israel who have treated patients on the NOPHO-DBH AML12 protocol, however not joining the randomizations. Lastly, also Portugal has joined the consortium, hence the current consortium name NOPHO-DB-SHIP; NOPHO – Dutch Belgium – Spain Hong Kong Israel Portugal. The aim is that all countries will treat AML patients according to the CHIP-AML22 guidelines, and hopefully as many countries as possible with participate in the study questions.

In April 2020, it was decided to start planning for a new protocol. A steering committee (SC) was formed with representatives from most of the different groups/countries and Dr Jonas Abrahamsson, SE, joined as PI for the current protocol. Dr Gertjan Kaspers, from the Prinses Máxima Center (PMC), Netherlands was appointed CI (Chief Investigator), and Dr Kees-Jan Pronk, SE as vice-PI for the planned protocol. Dr Dominik Turkiewicz, SE, was appointed protocol statistician. The protocol will be named the CHIP-AML22 study: Childhood International Protocol – AML22. Following formation of the SC, a call went out for participants for a number of working groups (WG). The Figure below gives an overview of the SC, the WGs and the participants in those. The SC has focused on what backbone to use and what randomizations to include in the protocol. The SC has cooperated with the different WGs on other more specific issues. The WG diagnostics/risk stratification is working on defining definitions of AML and relapse/refractory disease, working on guidelines for diagnostic workup/MRD-analysis, as well as working to establish a basis to decide on risk stratification. The WG supportive care is writing guidelines for several aspects of supportive care that we aim to include as recommendations in the protocol. The guidelines were also summarized in a expert opinion paper and submitted for publication. The WG alloSCT/Cellular Therapy has at this moment in time a main focus to coordinate the CHIP-AML22 study with the planned SCRIPT-AML study. The SCRIPT-AML study (see further below) will include AML patients that require SCT (either in CR1 or CR2). As the recruiting countries in the SCRIPT-AML study strongly overlap that of the CHIP-AML22, and as HR patients in the CHIP-AML22 likely directly are recruited to the SCRIPT-AML study, coordination between the studies is considered important. Lastly, a WG preclinical and translation Research was established. This group will coordinate proposals for add-on studies. Guidelines for study proposals were established by this group and currently we are working to synchronize this with the NOPHO scientific committee routines.

The major study-questions in the planned CHIP-AML22 study have been identified and a study plan was established. Likely, CHIP-AML22 will be submitted under new EU regulations and likely submitted as Master Protocol with a number of Sub studies. The protocol has not yet been finalized, but the the paragraph below summarizes some of the ideas and proposals for the new CHIP-AML22 study. The backbone will be very similar to the current NOPHO-DBH AML12 study. Apart from the good performance of that protocol, it also allows the SC to make decisions on treatment/risk stratifications/etc based on data from our own protocol. Dr Jonas Abrahamsson has multiple times provided the SC with specific analyses to help planning for the protocol. Currently, the standard arm backbone will be induction with MEC and ADE. Standard risk consolidation with be HAM+ADE+FLA, Risk stratification is somewhat altered; see below figure 9

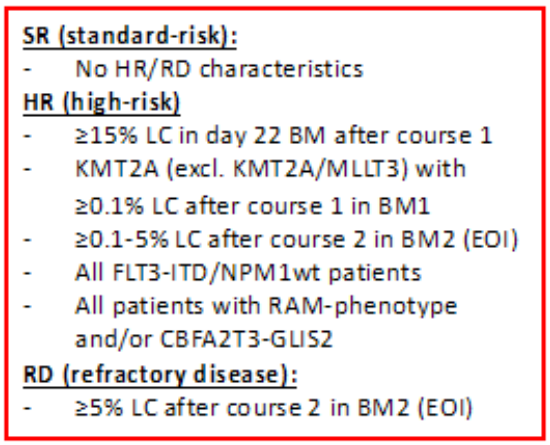


Figure 9: Risk stratification in CHIP-AML22

As before, Flt3-ITD/Npm1wt, >15% after course 1 and >0,1% at end of induction are high risk (HR) patients. Other HR groups are depicted in Figure 9 and these were identified based on the results from the AML12 study. HR patients will receive one consolidation course and proceed thereafter to hematopoietic stem cell transplantation (SCT).

The SC will propose a randomization (R1) during Induction course 1; w/wo GO (Mylotarg). The rationale is that in the AML12, MRD response after induction is a strong predictor of outcome, thus we wish test intensification of induction to increase treatment efficacy. GO has previously been studied in the NOPHO AML2004 study during consolidation without additive value. Several international groups however (including COG) have studied GO already during induction and found GO to have additive value at least in subgroups of patients. However, as the results in the NOPHO-DBH AML12 trail are superior to the results in the groups that published on GO, we plan to study GO in a randomized fashion. Previously, a separate study for Flt3-ITD/NPM1wt patient with the Flt3-inhibitor Quizatinib was planned, but that study never opened. Therefor Flt3-ITD/NPM1wt patients will likely be part of the study. We are currently discussing what patients to expose to an Flt3-inhibitor, and at what dose/schedule. No final decision on the type of Flt3-inhibitor has been taken, but negotiations to include Quizartinib are ongoing. HR patient without Flt3-ITD/Npm1wt, hence based on MRD, will likely be exposed to Bcl2-inhibitor Venetoclax during the first consolidation course (HAM), prior to SCT. As no formulation for smaller children is available on the European market, we are currently discussing with the company to solve this issue. A second randomization (R2) during consolidation is discussed and here the SC considers de-escalation of treatment in good responders, in a non-inferiority designed randomization. There is no final proposal yet on the modality of R2. As R2, being a non-inferiority randomization, requires a larger sample size compared to R1 (which is a superiority design), it is likely possible to start a "second R1" after the "first R1" has recruited sufficient patient numbers. The SC will propose to perform Interrim analyses during all randomizations.

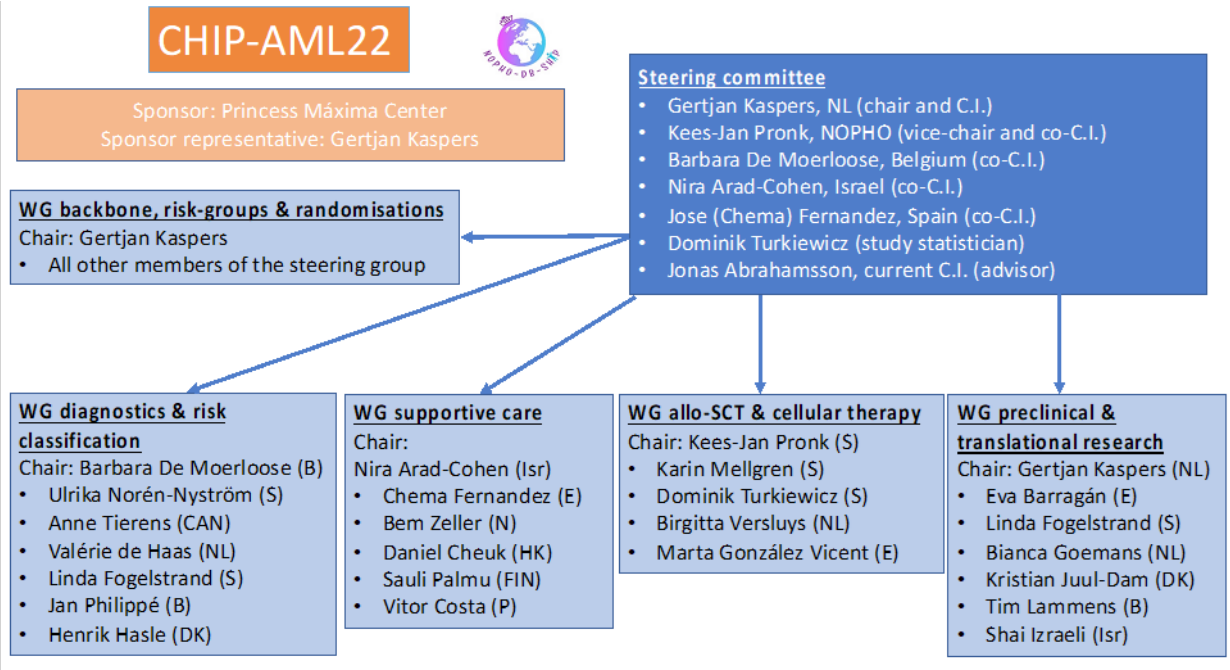


Figure 10. Overview of the organization the the CHIP-AML21 study, including the steering committee and WGs, as well as all participating members in the groups. CHIP-AML 21, Childhood International Protocol – AML21; WG, working group; PMC, Princess Máxima Center.

Intergroup studies and collaborations

PedAL, EUPAL 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.

EUPAL foundation that supports the EUPAL consortium started in May 2020 in Utrecht. The aims to improve survival in pediatric AML, intensify basic, translational and clinical research, bringing innovative therapies to children, improving supportive care, supporting children and families, outreach and twining programs and longterm surveillance.

Kristian Lovvik Juul-Dam has been appointed by the NOPHO AML group as "young investigator" to work together with four colleagues in development of phase I/II trials for new promising drugs in R/R AML and he is currently working on a study with menin inhibitors for patients with KMT2A rearranged AML.

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. All NOPHO countries have had several meetings with Dirk Reinhart in Essen who is responsible for the project and Henrik Hasle have taken the lead in the project of transferring NOPHO AML 2004 data. Still there is no research program which will be needed for several countries before they can apply to ethic committees to be able to transfer the data.

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.

The new protocol, ICC APL study 02, is recommended as standard therapy in NOPHO since 2020. 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 (ATRA) and arsenic trioxide (ATO) and for high risk patients gemtuzumab ozogamicin(GO) is added.

International relapsed AML study

In the beginning of 2020 it was unfortunately decided to stop the relapse protocol that had been delayed since 2016 due to change of sponsor and that was already approved by the competent authorities in Denmark, Finland and Sweden. The plan was to investigate, in a randomized setting, if addition of Gemtuzumab to FLADx could improve early response. The NOPHO guidelines for AML relapse, until a new relapse study is available, can be found on www.nopho.org and hopefully, the new PedAL study for R/R AML, will get started during 2022.

SCRIPT-AML study

Planned 2-arms randomisation to compare different conditioning regimens in AML SCT, Bu-Cy-Mel vs Clo-Flu-Bu. There will also be an observational arm in the study for patients without access to a matched donor. Collaboration between NOPHO-Netherlands, Belgium, Israel, Hong Kong and Spain. PI Karin Mellgren and data manager Dominik Turkiewicz, both Sweden. Co-chair Birgitte Versluys, Utrecht, NL.

Publications involving the NOPHO AML WG from 2019.

1. **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.
2. **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.
3. **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 Jun;66(6):e27701. doi: 10.1002/pbc.27701. Epub 2019 Mar 7.
4. **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.
5. **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.
6. **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 Br J Haematol 2020 Jul;190(2):198-208. doi: 10.1111/bjh.16560. Epub 2020 Mar 16
7. **Wilhelmsson M, Jahnukainen K, Winiarski J, Abrahamsson J, Bautz A, Gudmundsdottir T, Madanat-Harjuoja LM, Holmqvist AS, Winther JF, Hasle H; ALiCCS study group.** *Hospitalizations in long-term survivors of childhood AML treated with allogeneic HCT-An Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study.* Am J Hematol. 2021 Mar 1;96(3):E74-E77. doi:10.1002/ajh.26071. Epub 2021 Jan 28. PMID: 33326137.
8. **Stratmann S, Yones SA, Mayrhofer M, Norgren N, Skaftason A, Sun J, Smolinska K, Komorowski J, Herlin MK, Sundström C, Eriksson A, Höglund M, Palle J, Abrahamsson J, Jahnukainen K, Munthe-Kaas MC, Zeller B, Tamm KP, Cavelier L, Holmfeldt L.** *Genomic characterization of relapsed acute myeloid leukemia reveals novel putative therapeutic targets.* Blood Adv. 2021 Feb 9;5(3):900-912. doi: 10.1182/bloodadvances.2020003709. PMID: 33560403 Free PMC article.
9. **Borgstedt-Bendixen SE, Abrahamsson J, Ha SY, Koskenvuo M, Lausen B, Palle J, Zeller B, Hasle H, Løhmann DJA.** *Abdominal Complications During Treatment for Pediatric Acute Myeloid Leukemia.* J Pediatr Hematol Oncol. 2021 Aug 16. doi: 10.1097/MPH.0000000000002281. Online ahead of print. PMID: 34387627.
10. **White T, Kaspers G, Abrahamsson J, Arad-Cohen N, Cianci D, Fernandez J, Ha SY, Hasle H, De Moerloose B, Zwaan CM, Goemans BF.** *Clinical outcomes of second relapsed and refractory first relapsed paediatric AML: A retrospective study within the NOPHO-DB SHIP consortium.* Br J Haematol. 2022 Feb 4. doi: 10.1111/bjh.18039. Online ahead of print. PMID: 35118649.
11. **Versluys AB, Boelens JJ, Pronk C, Lankester A, Bordon V, Buechner J, Ifversen M, Jackmann N, Sundin M, Vettenranta K, Abrahamsson J, Mellgren K.** *Hematopoietic cell transplant in pediatric acute myeloid leukemia after similar upfront therapy; a comparison of conditioning regimens.* Bone Marrow Transplant. 2021 Jun;56(6):1426-1432. doi: 10.1038/s41409-020-01201-w. Epub 2021 Jan 19. PMID: 33469191.

12. **Fornerod M, Ma J, Noort S, Liu Y, Walsh MP, Shi L, Nance S, Liu Y, Wang Y, Song G, Lamprecht T, Easton J, Mulder HL, Yergeau D, Myers J, Kamens JL, Obeng EA, Pigazzi M, Jarosova M, Kelaidi C, Polychronopoulou S, Lamba JK, Baker SD, Rubnitz JE, Reinhardt D, van den Heuvel-Eibrink MM, Locatelli F, Hasle H, Klco JM, Downing JR, Zhang J, Pounds S, Zwaan CM, Gruber TA; Berlin-Frankfurt-Munster Study Group (BFM); Dutch Children's Oncology Group (DCOG); Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP); Nordic Society for Pediatric Hematology and Oncology (NOPHO); Dutch Children's Oncology Group (DCOG); for St. Jude Children's Research Hospital Study Group (SJCRH).** *Integrative Genomic Analysis of Pediatric Myeloid-Related Acute Leukemias Identifies Novel Subtypes and Prognostic Indicators.* Blood Cancer Discov. 2021 Sep 9;2(6):586-599. doi: 10.1158/2643-3230.BCD-21-0049. eCollection 2021 Nov.PMID: 34778799 Free PMC article.

Leukemia Genetics Working Group

Coordinator	Ulrika Norén Nyström	Umeå
Denmark	Eigil Kjeldsen	Aarhus
	Mette Klarskov Andersen	Copenhagen
	Birgitte Preiss	Odense
Estonia	Pille Tammur	Tallinn
Finland	Jonna Elonen-Jokinen	Turku
	Petra Pasanen	Turku
	Anne Juvonen	Helsinki
	Ritva Karhu	Tampere
	Kati Pulkkinen	Kuopio
	Satu Häikiö	Kuopio
	Hannele Räsänen	Oulu
Iceland	Jón Jóhannes Jónsen	Reykjavik
Latvia	Aigars Dzalbs	Riga
Lithuania	Vaidas Dirse	Vilnius
Norway	Martine Eilert-Olsen	Oslo
	Randi Hovland	Bergen
	Helle Lybaek	Bergen
Sweden	Gisela Barbany Bustinza	Stockholm
	Lucia Cavelier	Uppsala
	Marie Engvall	Uppsala
	Bertil Johansson	Lund
	Linda Arvidsson	Lund
	Irina Golovleva	Umeå
	Anna Norberg	Umeå
	Helene Sjögren	Gothenburg
	Lars Palmqvist	Gothenburg

The Leukemia Genetics working group meet once a year. The meeting is divided in two two-day-meetings. All participants (besides the coordinator) are working at the genetic laboratories responsible for the leukemia genetic diagnostics in the Nordic countries. The coordinator, Ulrika Norén Nyström (pediatric oncologist and coordinator) participate together with Prof. Bertil Johansson (senior expert) in both meetings. In February 2021, the meetings were virtual due to the pandemic. The Swedish leukemia patients diagnosed in 2020 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), results from SNP-arrays and also NGS (new generation sequencing) tecniques 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 for each patient is finally decided by the "worst counts" – principle. Representatives from the 19 genetic labs in the Nordic and Baltic countries participated.

Cytogenetic results for NOPHO patients diagnosed with ALL and AML in 2020

During 2020 the numbers of children registered in both the AML-registry and in the ALL registries decreased as compared to what usually is the case. The reason for this observation is not known, however an epidemiological study led by Anna Nilsson, Stockholm, about the impact of Covid-19 on incidence of ALL in NOPHO, is planned.

At our meetings, 249 ALL patients (4 infants, 195 children and 51 adults) diagnosed during 2020, and 42 children registered in the AML registry were reviewed (some of the NOPHO patients registered have other diagnoses than AML, and only 28 children with de novo AML were registered during 2020). Estonian ALL patients were not fully reviewed because of lack of access to CASTOR in Estonia. Many of the relapses of ALL and AML during 2020 were also reviewed, but not all, because of lack of samples sent to the genetic laboratories at relapse.

The Cytogentic module in the NOPHO registry

All genetic laboratories are now successfully reporting the diagnostic genetic results for ALL and AML in the cytogenetic registration module in the CCEG. For the patients treated according to the ALLTogether protocol in Estonia the review has still not been done (see above).

Umeå 28-03-2022
Ulrika Norén Nyström

Publications involving the work of Leukemia Genetics wg, from 2021 until March 2022

1. **Hirabayashi S, Butler ER, Ohki K, Kiyokawa N, Bergmann AK, Möricke A, Boer JM, Cavé H, Cazzaniga G, Yeoh AEJ, Sanada M, Imamura T, Inaba H, Mullighan C, Loh ML, Norén-Nyström U, Pastorczak A, Shih LY, Zaliova M, Pui CH, Haas OA, Harrison CJ, Moorman AV, Manabe A.** *Clinical characteristics and outcomes of B-ALL with ZNF384 rearrangements: a restrospective analysis by the Ponte di Legno Childhood ALL Working Group.* Leukemia. 2021 Nov;35(11):3272-3277. PMID: 33692463
2. **Krali O, Palle J, Bäcklin CL, Abrahamsson J, Norén-Nyström U, Hasle H, Jahnukainen K, Jónsson ÓG, Hovland R, Lausen B, Larsson R, Palmqvist L, Staffas A, Zeller B, Nordlund J.** *DNA Methylation Signatures Predict Cytogenetic Subtype and Outcome in Pediatric Acute Myeloid Leukemia (AML).* Genes (Basel). 2021 Jun 10;12(6):895. PMID: 34200630.
3. **Sayyab S, Lundmark A, Larsson M, Ringnér M, Nystedt S, Marincevic-Zuniga Y, Tamm KP, Abrahamsson J, Fogelstrand L, Heyman M, Norén-Nyström U, Lönnerholm G, Harila-Saari A, Berglund EC, Nordlund J, Syvänen AC.** *Mutational patterns and clonal evolution from diagnosis to relapse in pediatric acute lymphoblastic leukemia.* Sci Rep. 2021 Aug 6:11(1):15988. PMID: 34362951.
4. **Mukkada S, Bhakta N, Chantada GL, Chen Y, Vedaraju Y, Faughnan L, Homsi MR, Muniz-Talavera H, Ranadive R, Metzger M, Friedrich P, Agulnik A, Jeha S, Lam C, Dalvi R, Hessissen L, Moreira DC, Santana VM, Sullivan M, Bouffet E, Caniza MA, Devidas M, Pritchard-Jones K, Rodriguez-Galindo C.** *Global Registry of COVID-19 in Childhood Cancer. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study.* Lancet Oncol. 2021 Oct;22(10):1216-1426. PMID: 34454651.
5. **Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Jónsson ÓG, Svenberg P, Schmiegelow K, Heyman M, Norén-Nyström U, Schröder H, Albertsen BK.** *Temporal changes in incidence of relapse and outcome after relapse of childhood ALL over three decades; a Nordic population-based cohort study.* Leukemia, 2022 Mars 21. Online ahead of print. PMID: 35314777.

NOPHO Leukemia Biobank Working Group

Members of the working group	
Chair	Henrik Hasle
Past chair	Trond Flægstad
Denmark	Henrik Hasle
Estonia	Kristi Lepik
Finland	Olli Lohi
Iceland	Ólafur Gisli Jónsson
Latvia	To be appointed
Lithuania	Daniel Naumovas
Norway	Niklas Stabell
Sweden	Britt-Marie Frost
Young NOPHO clinical	Morten Krogh Herlin
Young NOPHO laboratory	Maike Bensberg
Scientific committee	Nikolas Herold
Leukemia registry	Mats Heyman
Leukemia Biology	Sofie Degerman
NOPHO cytogenetics group	Ulrika Noren Nyström
Biobank	Elina Chugunova, Victoria Wennberg and Maria Lindström
Coordinator	victoria.wennberg@akademiska.se

NOPHO
LEUKEMIA
BIOBANK

Website

The NOPHO Leukemia Biobank has launched a website, https://nopholeukemiabiobank.org
The first version of the website is in Swedish but will later be translated to English. The website is both for lay people and professionals. It will with time contain updated statistics of the biobank.
It's planned to include a list of all studies retrieving samples from the biobank with the name of the study and the principal investigator.
Please have a look at the website and send your feed-back.

The website is financed by the Swedish Childhood Cancer Fund.

During the last year the biobank group has again only met online.

Patient ID

All patients with material to be saved in the biobank must be reported in a database to get a NOPHO or CASTOR number. This is also true for non-protocol patients, e.g. infant ALL, APL, MDS etc. Patient samples without NOPHO or CASTOR number will be destroyed.

New referral form

A referral form for sending material to the biobank in Uppsala was revised in January 2022. The form in English and Swedish can be found at nopho.org under working groups: Leukemia biobank.

The new form reflects the request to send PB and BM from diagnosis, at remission and at relapse from both ALL and AML. It is recommended to send cerebrospinal fluid (CSF) from diagnosis. CSF should be handled and frozen locally and sent to Uppsala in batches.

It's encouraged to send constitutional DNA from PB in remission.

Details are found in the referral form.

Time for sampling:

	Diagnosis	Day 15	Day 29	Day 50	Remission	Relapse
ALL A2G	Bone marrow, blood, serum, liquor	Bone marrow	Bone marrow	Bone marrow High risk patients	Blood in EDTA or heparin tubes at day 71/78	Bone marrow, blood, serum, liquor
ALL except A2G	Bone marrow, blood, serum, liquor				Blood in EDTA or heparin tubes at consolidation	Bone marrow, blood, serum, liquor
AML	Bone marrow, blood, serum, liquor				Blood in EDTA or heparin tubes at consolidation	Bone marrow, blood, serum, liquor
Other diagnoses	Bone marrow, blood, serum, liquor					Bone marrow, blood, serum, liquor

How to retrieve samples from the Biobank

The study proposal must be accepted as a NOPHO project by the Scientific committee and by the board. The Biobank must be acknowledged in scientific papers if the samples have been retrieved for the study.
International studies on rare leukemias where only a few samples are asked for may be published without acknowledgement of the biobank.

Withdrawal of the last sample from the biobank

In general, it's not allowed to take the last sample.
However, there may be exceptional situations where it may be accepted to withdraw the last sample because the patient sample is essential for the study of that unique type of leukemia.
An example could be an international study of a rare type of leukemia diagnosed in e.g. less than 1 patient per year within NOPHO.

It may be difficult for the biobank or the biobank group to make the decision whether the last sample can be retrieved, therefore it will be a mandatory part of the scrutiny by the NOPHO Scientific committee to make a recommendation of whether the last sample can be withdrawn.

LL Biology Working Group

Members
NOTE; in this WG we don't have appointed country representatives. All NOPHO members are welcome as active members.

Listed members as of March 2022:
Jonas Abrahamsson, Birgitte Klug Albertsen, Anna Andersson, Gisela Barbany, Alessandro Camponeschi, Anders Castor, Sofie Degerman, Matilda Degn, Erik Delsing Malmberg, Vaidas Dirse, Trond Flægstad, Linda Fogelstrand, Erik Forestier, Thomas Frandsen, Line Groth-Pedersen, Tekla Harju, Henrik Hasle, Morten Herlin, Nikolas Herold, Mats Heyman, Linda Holmfeldt, Randi Hovland, Magnus Hultdin, Inga Maria Rinvoll Johannsdottir, Bertil Johansson, Kristian Løvvik Juul-Dam, Mette Klarskov Andersen, Andreas Lennartsson, Olli Lohi, Gudmar Lönnerholm, Hans O. Madsen, Johan Malmros, Hanne V. Marquart, Karin Mellgren, Signe Modvig, Colm Nestor, Ann Nordgren, Jessica Nordlund, Ulrika Norén-Nyström, Josefine Palle, Lars Palmqvist, Kajsa Paulsson, Anna Poluha, Kimmo Porkka, Kees-Jan Cornelis Pronk, Monika Renkielska, Samppa Ryhänen, Olle Sangfelt, Kjeld Schmiegelow, Mindaugas Stoskus, Ann-Christine Syvänen, Mervi Taskinen, Maria Thastrup, Goda Vaitkeviciene, Hartmut Vogt, Ulla Wartiovaara-Kautto, Vasilios Zachariadis, Ann Elisabeth Åsberg, Nina Friesgaard Øbro, Ingegerd Öfverholm.

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 group decided in 2020 to keep on Olli Lohi (OH) and Linda Fogelstrand (LF) as chairs of the group. They have strong backgrounds in basic research and represent diagnostics (LF) and clinical (OL) expertise, and research focus primarily on ALL (OL) and AML (LF). The chairs are also active in the scientific groups connected to ongoing and planned international ALL and AML trials; OL is a member of the ALLTogether Scientific committee, and LF of the CHIP-AML22 WG preclinical and translational research.

The LL Biology WG reports to the LLC, but many of the items are also discussed in the ALL/ALLTogether 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, technology/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. Previously, the meetings have had 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 2021, both WG meetings were virtual due to the pandemic and therefore shorter covering primarily new/ongoing projects. Neither meeting generated costs.

The 2021 March virtual meeting had 26 participants. There were no new project proposals, but updates of two longstanding productive NOPHO projects: 'Methylation profiling of T-ALL samples' by Sofie Degerman, Umeå, and 'Multi-level analysis of acute myeloid leukemia' by Linda Holmfeldt, Uppsala. The latest news from the ALLTogether Scientific Committee were presented by Sofie Degerman and Olli Lohi. ALLTogether SC includes two members from each regional/national group: one clinician and one scientist, currently Olli Lohi and Sofie Degerman from NOPHO. The ALLTogether Scientific Committee will accept applications three times a year and the practical aspects of this have been discussed in several forums during 2021, including LL Biology WG, and continues 2022. The meeting also covered updates from the Biobank group.

Also the 2021 September virtual meeting had 26 participants. One new AML project was proposed; 'TARP as an immunotherapeutic target in pediatric AML: current status and future developments' by Jolien Vanhooren, group Tim Lammens in Ghent, Belgium. Ulrika Norén Nyström, Umeå, who is representing NOPHO in Interfant-21, shortly presented five different suggested add-on studies to the Interfant-21 protocol, proposed by researchers in UK, Netherlands, Italy, and Japan. The LL Biology WG deemed more details necessary before advising NOPHO to embark on these projects, and it was decided to invite PI:s of project to a coming WG meeting (March 2022). In the meeting, there was also an update of the large, longstanding project 'NOPHO study no 56: Genome-wide epigenetic analysis in ALL' by Jessica Nordlund, Uppsala. In the project, the researchers have collected large amounts of DNA methylation and RNA sequencing data on ALL patients from 1992-2012, and Jessica invited interested people to contact her directly if the data could be useful for their projects. The biobank group updated with collected sample types and numbers.

Future perspectives

Meetings will continue to be held biannually, in March and September 2022. The first meeting will be hybrid according to the previous structure with the theme Moving AML forward and invited speaker. Meeting costs during 2022 will be financed by the planning grant from the Swedish Childhood Cancer Foundation (LF). Travel expenses are covered by the institutions of the participants.

Olli Lohi and Linda Fogelstrand
March 2022

Infant Leukemia Working Group

Coordinator/Chair	Ulrika Norén Nyström, Leukemia genetics wg
Denmark	Birgitte Klug Albertsen
Estonia	Kristi Lepik
Finland	Olli Lohi
Iceland	Sólveig Hafsteinsdóttir
Latvia	Anna Valaine
Lithuania	Vilma Rutkauskaite
	Goda Vaitkeviciene
Norway	Magnus Assaved Hjort
Sweden	Anders Castor
	Lene Karlsson
Data center	Mats Heyman
Young NOPHO	Sauli Palmu, Finland

The main activity of the NOPHO Infant Leukemia group is to discuss and manage current international infant ALL protocols.

The group had several virtual meetings during 2021. In June Birgitte Lausen stepped down as chair and Ulrika Norén Nyström was approved as new Chair. During the autumn representatives for the Baltic countries also joined the group. The group has met virtually twice during the autumn and winter, mainly to discuss issues with the planned new Interfant-21 protocol.

At present (March 2022) the Interfant-21 protocol is about to be submitted in the Netherlands. The protocol is based on the promising results of the Phase I/II-study with one cycle of Blinatomumab (28 days continuous infusion) between induction and Phase 1B which has been open for *KMT2A*-rearranged (*KMT2A*-r) infants with BCP-ALL within the Interfant consortium. Princess Maxima in Utrecht will be sponsor for the Interfant-21 trial, that only will include infants with *KMT2A*-r BCP ALL. No randomization will be included and therefore outcome will be compared to well characterized historical controls. The backbone of the protocol is based on the previous Interfant-06. One cycle of Blinatomumab will be recommended to all patients after induction, and a second cycle will replace MARMA for medium risk patients responding well to the first cycle of Blina. Other changes as compared to the Interfant-06 protocol: less stringent adaptation of age-based dose reduction guidelines; allocation to lymphoid or myeloid consolidation therapy based upon EOI MRD; all HR patients and MR patients with insufficient MRD response will be eligible for allo-HSCT and also for experimental therapy prior to SCT.

The protocol sponsor hope to submit the protocol to Dutch regulatory authorities in April/May 2022 and receive the ethical approval in June/July. The NOPHO countries will (hopefully) be able to submit the protocol through the ECTR system from the autumn of 2022, if this plan holds. The NOPHO countries planning to participate in the protocol: Denmark, Finland, Lithuania, Norway, and Sweden.

NB! Infants diagnosed with BCP-ALL without *KMT2A*-r or T-ALL, will be eligible for the ALLTogether1 protocol version 4.0, which is modified to include these infants, and already approved in some of the NOPHO countries. The dosing of infants in ALLTogether1 v.4.0 is adjusted to the dosing that will be used in the Interfant-21 protocol.

Umeå 29th of March
Ulrika Norén Nyström
Chair of the NOPHO Infant Leukemia working group

Other Disease Working Groups

Benign Haematology Committee (BHC)

Chair Ulf Tedgård / Annika Mårtensson (new 2022)

Thrombosis and Haemostasis working group chair Susanna Ranta (new 2021)

Red cell disorders working group chair Annika Mårtensson (new 2022)

Platelet working group chair Mimi Kjærsgaard

Histiocytosis working group chair Jan-Inge Henter / Tatiana von Bahr Greenwood (new 2022)

After the BHC Teams meeting the 28th of April 2022, Annika Mårtensson has accepted to be the new chairman of BHC (from after the NOPHO Board meeting 2022). Annika is from 2022 also chairman of the Red cell working group. Tatiana von Bahr Greenwood will succeed Jan-Inge Henter as chairman of the Histiocytosis working group.

At the BHC meeting in April we also discussed how benign haematology and BHC could become of more interest for all members of NOPHO. An open meeting for all interested in benign haematology in conjunction with the NOPHO annual meeting was one suggestion. A good opportunity to start could be at the 2023 annual meeting held in Lund.

The following is a brief summary in a few points of what the working groups are working on. For more detailed information see each working groups annual report.

Thrombosis and Haemostasis working group

The group consist of representants from each NOPHO country -with Latvia joining 2021- as well as other interested colleagues and had two virtual meetings in 2021.

The main research focus is ALL-related coagulopathy with several ongoing research projects.

The group has initiated more detailed registration of thromboses in CASTOR.

Red Cell Disorders working group

The group consist of representants from each NOPHO country and adult hematologists are associated to the group. Annika Mårtensson, Sweden is new chairman of the group from March 2022.

During 2021 most work has focused on the registry for transfusion dependent anemias (the VPH registry) which is a quality register. The VPH registry is open for registrations since October 2021.

Research regarding data in the VPH registry can be made on patients who have given informed consent to export of data to NOPHO-Care, which the working group participates in. Collaboration with the European research registry RADeep is ongoing and an application to the Ethics Review Board for a study is planned.

Platelet working group

Work is underway to develop NOPHO guidelines for the treatment of acute ITP.

Work is ongoing to develop NOPHO guidelines for the treatment of chronic ITP.

A manuscript on intracranial haemorrhage in ITP is being prepared based on experiences from the Nordic countries.

Histiocytosis working group

Histiocyte Society: The 38th Annual Meeting of the Histiocyte Society will be held in a Nordic Country; in Stockholm, September 18-20, 2022. Welcome! https://www.histiocytesociety.org/Stockholm-2022

LCH-IV: Sweden, Norway and Denmark are approved study centers, and on 31st December 2021 24 countries were participating and altogether n=1719 patients had been recruited. Since recruitment is slower than expected, and for Stratum I group 1 it will take another 2-3 years to reach the planned sample size while it should be reached for Stratum II during 2022. **NOTE:** The current protocol version is 1.6.

HLH studies: For primary HLH, the Histiocyte Society recommends the HLH-94 protocol as standard of care, but with the HLH-2004 diagnostic criteria (5/8 criteria). There is no new international treatment study on HLH planned but the HLH Registry, based in Germany, 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.

ECHO: The European Consortium for Histiocytosis (ECHO) is focusing on LCH, and ongoing relevant studies in ECHO are:

- EU Series/ targeted therapy in LCH Histiocytosis (Jean Donadieau, France); Results being analyzed.
- Mutant BRAF allele load in circulating cell lineages in histiocytic disorders/LCH (Elena Sieni, Italy, and Astrid van Halteren, Netherlands); Enrollment ongoing.
- Clinicogenomic associations in LCH (Astrid van Halteren). In manuscript. Collaboration with Histiocyte Society/LCH-IV.
- There is a newly formed Working Group on Histiocytoses in Adulthood in ECHO. Chair: Polyzois Makras: makras@internet.gr

Lund, May 2022
Ulf Tedgård
Outgoing chairman of the NOPHO Benign Haematology Committee

NOPHO Novel Therapy Working Group

Members 2021-2022

Denmark	Karsten Nysom (chair), Kjeld Schmiegelow
Finland	Olli Lohi
Iceland	Halldóra K. Þórarinsdóttir
Norway	Trond Flægstad, Jochen Büchner
Sweden	Stefan Holm, Ingrid Øra, Jacek Toporski, Mats Heyman, Geraldine Giraud (Young NOPHO)

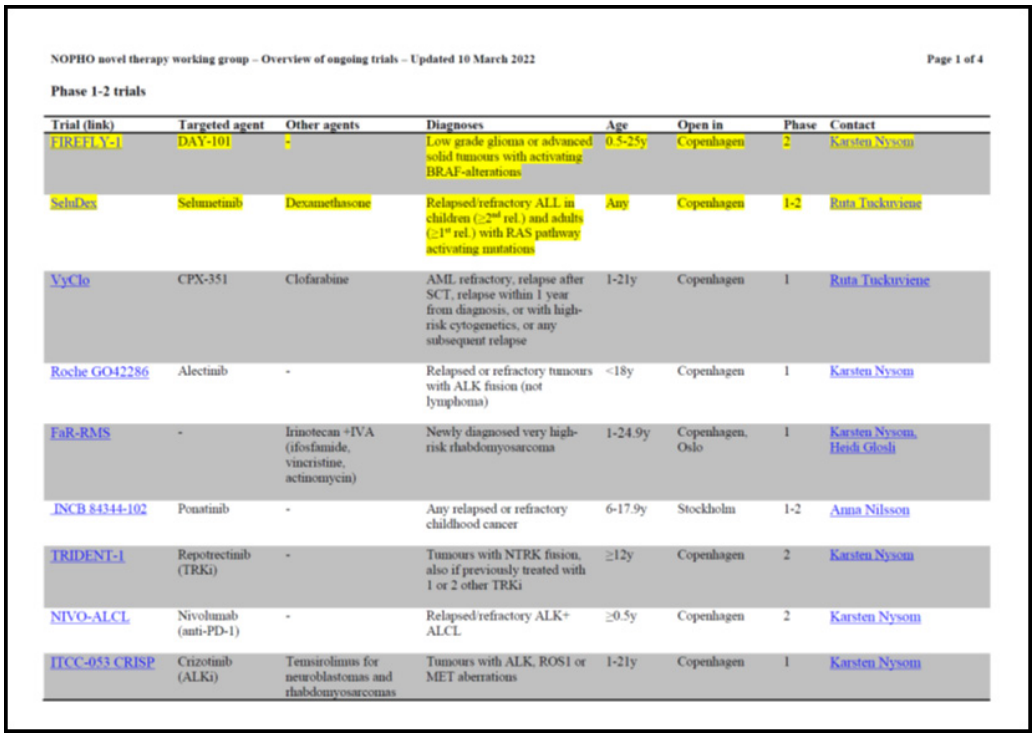
The working group has not had any meetings since the annual meeting in Aalborg in May 2019. This year, a web-based meeting is planned Friday 06 May 08:00-10:00.

There are now Nordic ITCC centres in Copenhagen, Stockholm, Gothenburg, Tampere, Oslo and Helsinki, all of which have tumour samples from high-risk patients and relapses analysed in molecular sequencing programs (INFORM and a Danish programme).

The main progress in the working group's field of interest during the past year was continuation of the NOPHOmatch project, containing weekly Nordic videoconferences on relapsed or refractory childhood cancers (every Wednesday at 13:00 CET, led by Torben Ek, Gothenburg).

The number of phase 1-2 trials for children with cancer recruiting in the Nordic region has been steadily increasing to now 27. An up-to-date overview of all phase 1-2 trials and phase 3 trials with targeted agents, open for children or adolescents with cancer in any Nordic or Baltic country, is available at www.nopho.org under "Protocols".

Copenhagen, March 27th, 2022
Karsten Nysom



NOPHO novel therapy working group – Overview of ongoing trials – Updated 10 March 2022 Page 1 of 4

Phase 1-2 trials

Trial (link)	Targeted agent	Other agents	Diagnoses	Age	Open in	Phase	Contact
FIREFLY-1	DAY-101	-	Low grade glioma or advanced solid tumours with activating BRAF-alterations	0.5-25y	Copenhagen	2	Karsten Nysom
SeluDex	Selumetinib	Dexamethasone	Relapsed/refractory ALL in children (≥2nd rel.) and adults (≥1st rel.) with RAS pathway activating mutations	Any	Copenhagen	1-2	Ruta Tuckuviene
VyClo	CPX-351	Clofarabine	AML refractory, relapse after SCT, relapse within 1 year from diagnosis, or with high-risk cytogenetics, or any subsequent relapse	1-21y	Copenhagen	1	Ruta Tuckuviene
Roche GO42286	Alectinib	-	Relapsed or refractory tumours with ALK fusion (not lymphoma)	<18y	Copenhagen	1	Karsten Nysom
FaR-RMS	-	Irinotecan +IVA (ifosfamide, vincristine, actinomycin)	Newly diagnosed very high-risk rhabdomyosarcoma	1-24.9y	Copenhagen, Oslo	1	Karsten Nysom, Heidi Glosli
INCB 84344-102	Ponatinib	-	Any relapsed or refractory childhood cancer	6-17.9y	Stockholm	1-2	Anna Nilsson
TRIDENT-1	Repotrectinib (TRKi)	-	Tumours with NTRK fusion, also if previously treated with 1 or 2 other TRKi	≥12y	Copenhagen	2	Karsten Nysom
NIVO-ALCL	Nivolumab (anti-PD-1)	-	Relapsed/refractory ALK+ ALCL	≥0.5y	Copenhagen	2	Karsten Nysom
ITCC-053 CRISP	Crizotinib (ALKi)	Temsirolimus for neuroblastomas and rhabdomyosarcomas	Tumours with ALK, ROS1 or MET aberrations	1-21y	Copenhagen	1	Karsten Nysom

Histiocytosis Working Group

Coordinator	Tatiana von Bahr Greenwood
Denmark	Tania Nicole Masmas (HLH) Peter Erik Lotko Pontoppidan (LCH)
Finland	Marika Grönroos Helena Olkinuora
Iceland	Halldóra Þórarinsdóttir Sólveig Hafsteinsdóttir
Lithuania	Jelena Rascon
Norway	Maria Gunnes (HLH) Monica Cheng Munthe-Kaas (LCH)
Sweden	Jan-Inge Henter Tatiana von Bahr Greenwood
Young NOPHO	Nikolas Herold

LANGERHANS CELL HISTIOCYTOSIS (LCH):

LCH-IV study

From the Nordic and Baltic countries Sweden, Norway and Denmark are up and running study centers.

Each country has its separate national coordinator(s):

- **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)

At cut-off date 31st December 2021:

- 24 countries participating
- Total accrual n=1719, accrual 2021 n=278
- Of total accrual, enrolled patients Sweden n=46, Denmark n=46 and Norway n=29
- For treatment Stratum I-VII following was reported, as per 31st Dec 2021:
  - STRATUM I: First-Line Treatment
    - Group 1: n = 422, whereof RO+LCH n=125. Randomised 85%. Deaths n = 5
    - Group 2: n = 545, whereof CNS-risk lesion n = 299. Randomised 93%
  - STRATUM II: Second Line Treatment, RO- LCH n =159. Randomised 86%
  - STRATUM III: Salvage Treatment for RO+ LCH n = 17
  - STRATUM IV: Stem Cell Transplantation for Risk LCH n = 0
  - STRATUM V: Isolated CNS tumorous n = 10 and ND CNS-LCH n = 10
  - STRATUM VI: Natural History and Management of "Other" SS-LCH n = 752
  - STRATUM VII: Long-Term Follow-up

Recruitment is slower than expected. For Stratum I it will take another 2-3 years. Final sample size of 400 randomised patients for Stratum I group 2 has been reached, but much follow-up data is missing that is necessary to reach study endpoint of reactivation rates. For Stratum II, the new randomization sample of 100 patients should be reached during 2022. For Stratum III, it is considered feasible to reach the planned 30 patients.
NOTE: The current protocol version is 1.6.

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 results are presented in:

- **Bergsten E, Horne A, Hed Myrberg I, Arico M, Astigarraga I, Ishii E, et al.** *Stem cell transplantation for children with hemophagocytic lymphohistiocytosis: results from the HLH-2004 study.* Blood advances. 2020;4(15):3754-66.
- **Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, et al.** *Confirmed efficacy of etoposide and dexamethasone in HLH treatment: Long term results of the cooperative HLH-2004 study.* Blood. 2017;130:2728-2738.

NOTE: The Histiocyte Society recommends the HLH-94 protocol as standard of care, but with the HLH-2004 diagnostic criteria (5/8 criteria).

There is no new international treatment study on HLH planned.

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-causing genes, you can contact BiancaTesi@ki.se at the clinical genetic laboratory at the Karolinska University Hospital.

NOPHO Histio represented in other European and International Histiocytosis consortiums:
ECHO – European Consortium for Histiocytosis
Jan-Inge Henter, Tatiana von Bahr Greenwood, Magdalini Lourda (Sweden)
Karsten Nysom and Daniel el Fassi (Denmark)
Monica Cheng Munthe-Kaas (Norway)
Jelena Rascon (Lithuania)
Zhanna Kovalova (Latvia)

- **ECHO Annual Meeting (hybrid) October 15-16, 2021, Athens**
- Ongoing relevant studies in ECHO
  - o EU Series/ targeted therapy in LCH Histiocytosis – Jean Donadieau, France
    Results being analyzed
  - o Mutant BRAF allele load in circulating cell lineages in histiocytic disorders/LCH – Elena Sieni,

Italy, and Astrid van Halteren, Netherlands. Enrollment ongoing.
    - Clinicogenomic associations in LCH – Astrid van Halteren. Study closed. In manuscript. Collaboration with Histiocyte Society/LCH-IV.
- Newly formed **Working Group on Histiocytoses in Adulthood** had a virtual kick-off meeting February 17, 2022. Chair: Polyzois Makras: makras@internet.gr
- Next meeting at the Annual Meeting of Histiocyte Society 2022 in Stockholm.

Histiocyte Society

- **37th Virtual Annual Meeting of the Histiocyte Society October 11-12, 2021.**
  For all meeting abstracts see: https://onlinelibrary.wiley.com/doi/10.1002/pbc.29453
- Ongoing studies
    - See Histiocyte Society website: www.histiocytesociety.org

38th Annual Meeting of the Histiocyte Society September 18-20, 2022

Thrombosis and Haemostasis Working Group

Chair	Susanna Ranta (SE)
Denmark	Birgitte Klug Albertsen, Marianne Hutchings Hoffmann, Ruta Tuckuviene
Estonia	Kadri Saks
Finland	Pasi Huttunen
Iceland	Ólafur Gislí Jonsson
Latvia	Žanna Kovalova, Anna Valaine (joined 2021)
Lithuania	Sonata Saulyte Trakymiene
Norway	Ellen Ruud
Sweden	Tony Frisk, Nadine Gretenkort Andersson, Ulf Tedgård *honor member*
Young NOPHO	Kirsten Jarvis (NO), Cecilie Utke Rank (DK), and Satu Långström (FI)

Other active participants: Merete Dam, Mette Tiedeman Skipper, Liv Andrès-Jensen, Line Stensig Lynggård, Lovisa Malmqvist

Goals of the Thrombosis and Haemostasis Working Group (TE WG):

- TE WG is a forum for clinical discussions and contributes to consultation networks
- TE WG creates clinical guidelines on coagulation for NOPHO members
- At least two-yearly meetings
- The group is a forum for presentation on ongoing studies within the field and contributes to scientific collaboration. The main focus of the research is ALL-related coagulopathy. The group registers data on thrombosis during ALLTogether protocol to be used in creating guidelines and support scientific studie

Meetings: The group met virtually on the 12th February 2021 and September 3rd 2021. The next meeting is planned March the 11th 2022 via zoom.

The TE WG has under 2021 assessed the different routines on hemostasis between ALLTogether treatment centers by a questionnaire via RedCap (Nadine Gretenkort Andersson and Susanna Ranta) 17 pediatric and 12 adult oncology centers responded the survey (Table 1). Most centers test for hemostasis at diagnosis. Only 5/17 pediatric centers use or plan to use thromboprophylaxis in high-risk patients, whereas all but one adult center used thromboprophylaxis either routinely or to high-risk patients. None of the centers used NOACs.

Seven pediatric centers determine antithrombin activity routinely in connection to asparaginase. Six pediatric centers substitute low antithrombin levels in all or selected patients without thrombosis (threshold for substitution 30 -75%), while nine centers give antithrombin to patients with thrombosis and low antithrombin. Seven pediatric centers follow fibrinogen levels under asparaginase, 10 substitute selected patients with low Fibrinogen to prevent bleeds.

Table 1. Survey on clinical praxis and hemostasis during ALLTogether treatment

	Pediatric centers (n=17)	Adult centers (n=12)
Routine laboratory assessment of hemostasis		
At diagnosis	17	12
After diagnosis	10	7
Thromboprophylaxis		
All patients	0	7
Selected high-risk patients	4	4
Follow-up of antithrombin after diagnosis		
All patients	7	3
Selected patients	5	3
Not performed	5	6
Prophylactic antithrombin used to prevent DVT		
All patients	2	1
Selected patients	4	1
Not given	10	10
Antithrombin replacement used after DVT		
All patients	4	3
Selected patients	5	2
Follow-up of Fibrinogen after diagnosis		
All patients	7	5
Not performed	10	7
Prophylactic fibrinogen replacement to prevent bleeds		
All patients	4	2
Selected patients	6	5
Not given	5	5

Doctoral projects:

a) Doctoral thesis "Common Genetic Variation and Thromboembolism in Acute Lymphoblastic Leukemia" Kirsten Jarvis (main supervisor Ellen Ruud). Dissertation on January the 28th, 2021.

b) **NOPHO post thrombotic syndrome study** Merete Eybye Dam (main supervisor Birgitte Klug Albertsen). Ongoing study.
The study aims to describe incidence and severity grade of PTS among children and adults, to identify risk factors for PTS and to evaluate QoL after DVT or PE.

c) **NOPHO cerebral sinovenous thrombosis study** Mette Skipper (main supervisor Birgitte Klug Albertsen) Ongoing study.
The study explores the safety of asparaginase re-exposure, clinical decision making of asparaginase re-exposure and outcome after re-exposure. Manuscript has been submitted.

d) **Coagulation disturbances during ALLTogether** Lovisa Malmqvist (main supervisor Mats Heyman). Planned to start 2022.
The study explores coagulation disturbances during early ALLTogether treatment in Sweden using global hemostasis analyses, microvesicles and proteomics.

Other ongoing projects:

a) **Registration of thromboses.**
NOPHOs Scientific committee has approved to register details on TE within ALLTogether, in NOPHO countries; registration is open in Sweden, Denmark, Island, Lithuania and Norway; Finland is waiting for ethical approval, while the ALLTogether protocol has not been initiated in Estonia or Latvia yet.

b) **NOPHO CSF Asparaginase study** (Birgitte Klug Albertsen)
The aim of the study is to correlate plasma asparaginase enzyme activity with CSF asparaginase levels and CSF MRD flow. The secondary aim is to measure thrombotic markers in the CSF and in blood for CSVT prediction.

c) **Endothelial markers and risk of thrombosis** (Liv Andres-Jensen)
A study proposal on prospective endothelial dysfunction study with aim to assess endothelial markers and their association with various toxicities including TE. The study would use the same samples that are sent to assess ASP activity.

d) **Swedish cohort study on ALLTogether toxicity** (Susanna Ranta)
Sweden is collecting data on early toxicity in ALLTogether protocol including hemostatic complications.

Collaboration outside NOPHO

TE in ponte di Legno (pDL)/ I-BFM. TE is the toxicity of interest in pDL, NOPHO Thrombosis and Haemostasis working group will provide data to the study.

Publications on coagulation involving the NOPHO Thrombosis and Haemostasis Working Group members from 2021

a) **Lynggaard LS, Rank CU, Hansen SN, Gottschalk Højfeldt S, Henriksen LT, Jarvis KB, Ranta S, Niinimäki R, Harila-Saari A, Wolthers BO, Frandsen TL, Heyman M, Schmiegelow K, Albertsen BK.** *Asparaginase Enzyme Activity Levels and Toxicity in Childhood Acute Lymphoblastic Leukemia: a NOPHO ALL2008 study.* Blood Adv. 2021 Epub ahead of print.

b) **Andrés-Jensen L, Grell K, Rank CU, Albertsen BK, Tuckuviene R, Linnemann Nielsen R, Lynggaard LS, Jarvis KB, Quist-Paulsen P, Trakymiene SS, Semaškevičienė R, Saks K, Jonsson OG, Frandsen TL, Johansson PI, Schmiegelow K.** *Endothelial dysfunction and thromboembolism in children, adolescents, and young adults with acute lymphoblastic leukemia.* Leukemia. 2022;36(2):361-369.

c) **Jarvis KB, Andersson NG, Giertz M, Järvelä L, Lindinger O, Långström S, Niinimäki R, Palmu S, Trakymiene SS, Tuckuviene R, Vepsäläinen K, Ranta S, Frisk T.** *Asymptomatic Right Atrial Thrombosis After Acute Lymphoblastic Leukemia Treatment.* J Pediatr Hematol Oncol. 2021;43(4):e564-e566

Stockholm February 2022

Susanna Ranta
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
Latvia	Elizabete Cebura
Norway	Inga Maria Johannsdottir Einar Stensvold
Sweden	Cecilia Petersen Aron Onerup
NOPHO leukaemia registry	Mats Heyman (SE)
Young NOPHO	Gitte Vrelits Sorensen (DK) Jan Bernd Stukenborg (SE) Liisa Järvelä (FI) Monika Kapitančukė (LT) Pauliina Utriainen (FI) Simon Kranz (NO) Thorgerdur Gudmundsdottir (IC)

The group had three virtual meetings in 2021: 12th of January, 27th of May and 3rd of November.

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 organised two online Pancare meetings: 19th of May and 8th of October.

Collaboration with NOBOS

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

Ongoing or planned 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)
- Psychosocial Survey in the Nordic ALLStar project (Päivi Lähteenmäki)
- HALLON study, late effects in ALL2008 HR chemo patients (Liisa Järvelä)

- NORDFERTIL (Jan Bernd Stukenborg)
- Osteonecrosis in patients with Hodgkin lymphoma in Sweden, Finland and Denmark 2005-2019 (Mia Giertz/Henri Aarnivala)
- NOPHO study on re-exposure to asparaginase after cerebral sinus venosus thrombosis (Mette Skipper)
- Post-thrombotic syndrome after deep venous thrombosis and sequalae after pulmonary embolism in association with treatment on the NOPHO ALL2008 protocol (Merete Dam)
- Childhood acute lymphoblastic leukaemia relapse detection and possible effect on prognosis: a Nordic population-based cohort study (Karen Jensen)
- A study proposal on ALLTogether follow-up guidelines (Karen Jensen)
- NORDfertil project (Jan-Bernd Stukenborg)
- Questionnaire for updating the situation of fertility preservation options in Nordic countries (Babak Asadi)

The common NOPHO follow-up guidelines after ALLTogether treatment

The group has an ungergoing project to update guidelines for the follow-up after ALL treatment.

Next short meeting will be in May 2022.
Next full-day meeting will be 10th of January 2023 in Helsinki.

Oulu, February 2022

Riitta Niinimäki
Chair of the NOPHO Late Effect working group

Red Cell Disorders Working Group

Chair	Ulf Tedgård (SE) 2012. Annika Mårtensson new from 2022.
Denmark	Birgitte Lausen, Mimi Kjærsgaard, Pernille Wendtland Edslev
Finland	Kirsi Jahnukainen, Nina Valtanen
Iceland	Ólafur G. Jónsson
Norway	Anne Grete Bechensteen, Einar Stensvold
Sweden	Annika Mårtensson, Magnus Göransson
Young NOPHO	Audrone Muleviciene (LT), Szymon Klafkowski (NO)

Associated members: Jan-Inge Henter (SE), Rolf Ljung (SE), Niels Clausen(DK), Marit Hellebostad (NO)

Associated members from adult hematology: Honar Cherif (SE), Christian Kjellander (SE), Ulla Wartiovaara-Kautto (FI), Andreas Birkedal Glenthøj (DK), Nina Haagenrud Schultz (NO)

Meetings

The group usually has one physical meeting a year but due to the pandemic there has been no such meeting since January 2020. There has instead been Teams-meetings 8th of April 2021, 16th of September 2021, 20th of January 2022 and 31st of March 2022. Minutes from the meetings are available at the NOPHO web page. Adult hematologists are participating at the meetings.

What has happened during 2021

At the latest meeting the 31st of March Annika Mårtensson, Sweden was appointed new chairman of the working group.

During 2021 most work has focused on the registry for transfusion dependent anemias. What was previously named the Nordic Transfusion Registry (NTR) has been moved to INCA (Information-sNätverk för CAncervården) and became a Swedish quality registry named "VPH registret" instead (VPH=Vårdplaneringsgruppen för Pediatrisk hematologi) as it will only involve Swedish patients. The variables in the VPH registry are based on variables in the European registry RADeep which is under construction but still not in final. Peter Priftakis and Ulf Tedgård has together with Tai Wai Cheng and Johan Ivarsson from INCA had monthly contact with the group from RADeep to develop the new platform. New variables have been added to RADeep so that also patients with DBA and spehorcytosis can be included.

The VPH registry is open for registrations since October 2021. The following transfusion dependent anemias can be registered: Thalassemia major and intermedia, SCD (even those without regular transfusions), DBA (even those on steroid treatment without regular transfusions), Enzymopathies (PKD particularly) and Other (Hereditary Spherocytosis and even cases without diagnosis who are on regular transfusions).

Research regarding data in the VPH registry can be made on patients who have given informed consent to export of data to NOPHO-Care. NOPHO-Care is approved by the ethics committee (EPN) and is now also approved for including adult patients. NOPHO-Care Informed consent is available for different ages, parents, and adults, but not in different languages. Peter Priftakis and Ulf Tedgård have participated in the Swedish Childhood Cancer Registry meetings.

Export of data from NOPHO-Care to the European registry RADeep is still under discussion.

Norway, Finland and Denmark will not be able to report to the Swedish VPH registry as it is a quality registry only for Swedish patients. After informed consent data can be exported to NOPHO care so that data for all of NOPHO can be collected. The same goes for RADeep as the variables and specifications are the same as in RADeep making it easy to export data to this European collaboration as long as the patient/caretaker has signed the Informed Consent Form.

Norway are working on their registry and use the same variables as in RADeep and VPH registry. In Finland there is still some uncertainties regarding the legal rules for a national registry. Helsinki is now a member of EuroBloodNet making it hopefully easier to export to RADeep, but the authorities have strict rules for export of data.

For more information regarding EuroBloodNet, ENROL and RADeep, see these internet pages: http://eurobloodnet.eu/, http://eurobloodnet.eu/enrol/, www.radeepnetwork.eu

"Nordic blood disorders forum" has had regular meetings on Teams during 2021 for discussion about difficult cases, where the input from adult hematologists has been of great value.

For the coming year we hope to get registrations going in Sweden, that the rest of the Nordic countries will follow and that it will be possible to have a physical meeting.

Lund, March 2022
Ulf Tedgård
Outgoing chairman of the NOPHO Red Cell Disorders Working Group

NOPHO Radiotherapy Working Group

The group was joined by a new representative from Estonia: Aidi Adamson Raieste and Finland: Sirpa-Liisa Lahtela. We are also looking forward to soon welcome a new member from Latvia.

Radiotherapy wise there is the impression that all modern photon and proton radiotherapy techniques and also brachytherapy and stereotactic radiotherapy are available in the NOPHO countries. The proton center in Uppsala (Skandion clinic) and in Aarhus (DCPT) are accepting patients from other countries. Norway is building two new proton therapy facilities that will become operational in 2024.

We had one virtual meeting in spring 2021 and a virtual scientific day in autumn 2021. At the working group meeting Maja Maraldo gave us an update on "The Teddi Protocol" and we also discussed radiotherapy in infants. Petter Brandal is working together with SIOP Europe on this subject. The scientific day was about "management of the vertebral spine in pediatric radiotherapy for paravertebral and craniospinal irradiations". We had Dr. Bianca Hoeben from Utrecht as a guest lecturer and also interactive contouring and dose planning discussions.

The working group's project concerning interobserver variability in target delineation and doseplanning for childhood ependymoma has been presented at several conferences and was published in Acta Oncologica.(https://doi.org/10.1080/0284186X.2021.2022202).

The Swedish Pediatric Radiotherapy Group has updated their guidelines on reirradiation, the updated version will be sent to the NOPHO website.
We organised a course on "Pediatric Radiotherapy for Pediatric Oncologists" as a "lunch to lunch Young NOPHO Educational Day". It was first planned to be held in November 2021 in combination with a NOPHO Course in Copenhagen, but as this course became a virtual course due to the pandemic and our course was depending on "hands on" teaching sessions, we decided to combine it with the Solid Tumour course in Oslo in April 2022. The course was held on 1st/2nd of April 2022 and was a combination of classical lectures and workshop discussions in small groups. The faculty was formed by members of the working group. The onsite feedback from the participants was very positive and we are now waiting for the feedback in form of a digital questionnairy, once this will be evaluated, we will see if we will continue with this course in this form as part of the NOPHO Curriculum for pediatric oncologists.

Participants from the working group have participated in other NOPHO working groups, like the brain tumour group, the solid tumour group and the late effect group.

Yasmin Lassen Chair for the NOPHO Radiotherapy Working Group

NOPHO/NOBOS Working Group on Ethics (WGE)

Chair	Cecilia Bartoldson, elected 2022
Secretary	Gitte Petersen, elected 2022
Denmark	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
	Frans Nilsson
	Pernilla Pergert
	Jennie Stigmar
	Lisa Törnudd

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.

The working group is the first joint working group with members from both NOPHO and NOBOS. All members are expected to be active. The newest NOPHO-member, Lithuania, is not yet represented in the group but hopefully this will change during the next year.

Completed meetings of the WGE

14-15 Mar 2022, Sweden

Upcoming meetings of the WGE

The group plans to have one 4-day meeting in the fall 2022 and one 3-day meeting in the spring 2023.
9-12 Oct, 2022, Norway
26-28 Mar 2023, Sweden

Completed course arranged by the WGE

Due to restrictions in both travel and meeting the second part of the course "Guiding Ethics Case Reflection Rounds" had to be postponed. To support the participants the group has instead organized other activities, such as a virtual ethics reflection to inspire, support and present tools for facilitating ethics case reflection rounds in a virtual setting.

Upcoming course arranged by the WGE

27-29 Apr 2022, Guiding Ethics Case Reflection Rounds, adjusted part II.
Due to the repeated postponement of the second part of the course and the long time that has passed since part I, the course has been adjusted to include more repetition and also to accommodate participants taking the course for the first time.

Funding

Pergert (co-applicant: Castor) has received a grant for the WGE for 2018-2020 (PL2017-0002) from the Swedish Childhood Cancer Foundation. Since most activities budgeted for in 2020 and 2021 have been postponed, an application to extend the grant to include 2021 has been approved and an application to also include 2022 has been sent.

Annual Report 2021

The work in the group has continued to suffer from the restrictions due to the pandemic. Many or most hospitals have had strict rules on meeting time and the group has not been able to effectively meet in larger scale, even virtually. The members, however, inspired and enabled by their participation in the WGE, has continued to work in ethics locally to the extent this has been possible and approved.

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. Members of the group has also been available to provide support for the facilitator trained in the courses of 2017-2018 and 2019.

At the International Conference on Clinical Ethics and Consultation (ICCEC) hosted in South Africa, members of the group had no less than three oral presentations that were delivered via video

Presentations on ethics at international conferences from the group or with group members as co-authors during 2021

- ICCEC 2021, hybrid/Stellenbosch, South Africa, Nov 30-Dec 3, 2021
    - Pergert, P., Bartholdson, C., af Sandeberg,M., ”Context-specific Situations Important to Capture Moral Distress – A National Cross-Sectional Study in Paediatric Oncology.
    - Törnudd, L., & Bartholdson, C. “Patients on Social Media – Supportive Guidelines For an Ethical And Legal Approach”
    - Bartholdson, C., af Sandeberg, M., Molewijk, B., Pergert, P., ”Perceptions of Ethical Decision Making in Relation to Participation/Non participation in Ethics Case Reflection Rounds Among Healthcare Professional Caring for Children with Cancer”

Publications on ethics from the group or with group members as co-authors, Original articles 2021

1. Weiner C, **Pergert P**, Molewijk B, **Castor A**, **Bartholdson C** (2021) Perceptions of important outcomes of ethics case reflection rounds: a qualitative study among healthcare professionals in childhood cancer care. BMC Medical Ethics.22:(27)
2. **Bartholdson C**, af Sandeberg M, Molewijk B, **Pergert P** (2021) Does participation in ethics discussions have in impact on ethics decision making? A cross-sectional study among healthcare professionals in paediatric oncology. EJON. (52):101950
3. **Bartholdson C**, Billstein I, **Pergert P**, Molewijk B (nd) Healthcare professionals ‘perceptions of ethics case reflection rounds before implementation - A national quantitative study in paediatric oncology. Submitted
4. Weiner C, **Pergert P**, Castor A, Molewijk B, **Bartholdson C** (nd). Difficult situations and moral questions raised during moral case deliberations in Swedish childhood cancer care – a qualitative nationwide overview. Submitted

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 May;102(5):e175-e178.

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.* Pediatr Blood Cancer 2017 Jul;64(7).

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.* Pediatr Blood Cancer. 2017 Oct;64(10).

Nielsen SN, Grell K, Nersting J, Abrahamsson 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 Sep;64(9).

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*, Haematologica 2017 Dec;102(12):2086-2096.

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.

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 Mar;81(3):579-586.

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. 2020 Mar 5;135(10):780. Erratum for: Blood. 2018 May 31;131(22):2475-2484.

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 Pharmacol 2019 Jan;83(1):53-60.

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.

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.

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.

Wilhelmsson M, Glosli H, Ifversen M, Abrahamsson J, Winiarski J, Jahnukainen K, Hasle H 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, 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.

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.

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

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 Mar;184(6):982-993.

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.

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.

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 creatinine 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.

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 Paediatr 2020 May;109(5):1040-1048.

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.

Juul-Dam KL, Ommen HB, Nyvold CG, Walter C, Vålerhaugen H, Kairisto V, Abrahamsson J, Alm SJ, Jahnukainen K, Lausen B, Reinhardt D, Zeller B, von Neuhoff N, Fogelstrand L, Hasle H. *Measurable residual disease assessment by qPCR in peripheral blood is an informative tool for disease surveillance in childhood acute myeloid leukaemia.* Br J Haematol. 2020 Jul;190(2):198-208.

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 Jul;27:72-77.

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 Oct;34(10):2822. Erratum for: Leukemia. 2020 Feb;34(2):336-346.

Taylor ZL, Mizuno T, Punt NC, Baskaran B, Navarro Sainz A, Shuman W, Felicelli N, Vinks AA, Heldrup J, Ramsey LB. *MTXPK.org: A clinical decision support tool evaluating high-dose methotrexate pharmacokinetics to inform post-infusion care and use of glucarpidase.* Clin Pharmacol Ther 2020 Sep;108(3):635-643.

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. Erratum in: Blood. 2020 Sep 17;136(12):1468.

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 Sep 3;136(10):1161-1168.

Dreisig K, Brünner ED, Marquart HV, Helt LR, Nersting J, Frandsen TL, Jonsson OG, Taskinen M, Vaitkeviciene G, Lund B, Abrahamsson J, Lepik K, Schmiegelow K. *TPMT polymorphisms and minimal residual disease after 6-mercaptopurine post-remission consolidation therapy of childhood acute lymphoblastic leukaemia.* Pediatr Hematol Oncol. 2020 Nov 18:1-12.

Brunetti M, Zeller B, Tierens A, Heim S, Micci F, Panagopoulos I. *TYRO3 Truncation Resulting From a t(10;15)(p11;q15) Chromosomal Translocation in Pediatric Acute Myeloid Leukemia.* Anticancer Res. 2020 Nov;40(11):6115-6121

Egnell C, Ranta S, Banerjee J, Merker A, Niinimäki R, Lund B, Mogensen PR, Jonsson ÓG, Vaitkeviciene G, Lepik K, Forslund A, Heyman M, Harila-Saari A. *Impact of body mass index on relapse in children with acute lymphoblastic leukemia treated according to Nordic treatment protocols.* Eur J Haematol. 2020 Dec;105(6):797-807.

Jarvis KB, Nielsen RL, Gupta R, Hede FD, Huttunen P, Jónsson ÓG, Rank CU, Ranta S, Saks K, Trakymiene SS, Tuckuviene R, Tulstrup M; INVENT consortium, Ruud E, Schmiegelow K, LeBlanc M. *Polygenic risk score-analysis of thromboembolism in patients with acute lymphoblastic leukemia.* Thromb Res. 2020 Dec;196:15-20.

Tuckuviene R, Bjerg CL, Jonsson OG, Langstrom S, Rank CU, Ranta S, Saks K, Trakymiene SS, Ruud E. *Pulmonary embolism in acute lymphoblastic leukemia - An observational study of 1685 patients treated according to the NOPHO ALL2008 protocol.* Res Pract Thromb Haemost. 2020 Jun 21;4(5):866-871.

Loimijoki T, Lapatto R, Taskinen M. *Adrenal function after induction therapy for acute lymphoblastic leukemia in children short: adrenal function in ALL.* Eur J Pediatr. 2020 Sep;179(9):1453-1459.

Bergsten E, Horne A, Hed Myrberg I, Arico M, Astigarraga I, Ishii E, et al. *Stem cell transplantation for children with hemophagocytic lymphohistiocytosis: results from the HLH-2004 study.* Blood advances. 2020;4(15):3754-66.

2021

Chan WY, Ho PL, To KK, Lam AY, Ho KW, Lau TW, So NL, Ha SY. *A child with acute myeloid leukemia complicated by calcaneal osteomyelitis due to Mycobacterium abscessus infection after induction chemotherapy successfully salvaged with bedaquiline and clofazimine.* Int J Infect Dis. 2021 Feb;103:9-12.

Østergaard A, Bohnstedt C, Grell K, Degn M, Zeller B, Taskinen M, Hafsteinsdottir S, Björgvinsdóttir H, Heyman M, Hoogerbrugge P, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Acute lymphoblastic leukemia and down syndrome: 6-mercaptopurine and methotrexate metabolites during maintenance therapy.* Leukemia. 2021 Mar;35(3):863-866.

Schmidt DE, Wendtland Edslev P, Heitink-Pollé KMJ, Mertens B, Bruin MCA, Kapur R, Vidarsson G, van der Schoot CE, Porcelijn L, van der Bom JG, Rosthøj S, de Haas M. *A clinical prediction score for transient versus persistent childhood immune thrombocytopenia.* J Thromb Haemost. 2021 Jan;19(1):121-130.

De Pietri S, Frandsen TL, Christensen M, Grell K, Rathe M, Müller K. *Citrulline as a biomarker of bacteraemia during induction treatment for childhood acute lymphoblastic leukaemia.* Pediatr Blood Cancer. 2021 Jan;68(1):e28793.

Jarvis KB, Andersson NG, Giertz M, Järvelä L, Lindinger O, Långström S, Niinimäki R, Palmu S, Trakymiene SS, Tuckuviene R, Vepsäläinen K, Ranta S, Frisk T. *Asymptomatic Right Atrial Thrombosis After Acute Lymphoblastic Leukemia Treatment.* J Pediatr Hematol Oncol. 2021;43(4):e564-e566

Weiner C, Pergert P, Molewijk B, Castor A, Bartholdson C (2021). *Perceptions of important outcomes of ethics case reflection rounds: a qualitative study among healthcare professionals in childhood cancer care.* BMC Medical Ethics.22:(27).

Modvig S, Hallböök H, Madsen HO, Siitonen S, Rosthøj S, Tierens A, Juvonen V, Osnes LTN, Vålerhaugen H, Hultdin M, Matuzeviciene R, Stoskus M, Marincevic M,

Lilleorg A, Ehinger M, Norén-Nystrøm U, Toft N, Taskinen M, Jónsson OG, Pruunsild K, Vaitkeviciene G, Vettenranta K, Lund B, Abrahamsson J, Porwit A, Schmiegelow K, Marquart HV. *Value of flow cytometry for MRD-based relapse prediction in B-cell precursor ALL in a multicenter setting.* Leukemia 2021 Jul;35(7):1894-1906.

Bartholdson C, af Sandeberg M, Molewijk B, Pergert P (2021). *Does participation in ethics discussions have in impact on ethics decision making? A cross-sectional study among healthcare professionals in paediatric oncology.* EJON. (52):101950

Bartholdson C, Billstein I, Pergert P, Molewijk B (nd). *Healthcare professionals 'perceptions of ethics case reflection rounds before implementation - A national quantitative study in paediatric oncology.* Submitted

Weiner C, Pergert P, Castor A, Molewijk B, Bartholdson C (nd). *Difficult situations and moral questions raised during moral case deliberations in Swedish childhood cancer care – a qualitative nationwide overview*. Submitted

Hirabayashi S, Butler ER, Ohki K, Kiyokawa N, Bergmann AK, Möricke A, Boer JM, Cavé H, Cazzaniga G, Yeoh AEJ, Sanada M, Imamura T, Inaba H, Mullighan C, Loh ML, Norén-Nyström U, Pastorczak A, Shih LY, Zaliova M, Pui CH, Haas OA, Harrison CJ, Moorman AV, Manabe A. *Clinical characteristics and outcomes of B-ALL with ZNF384 rearrangements: a restrospective analysis by the Ponte di Legno Childhood ALL Working Group.* Leukemia. 2021 Nov;35(11):3272-3277. PMID: 33692463

Krali O, Palle J, Bäcklin CL, Abrahamsson J, Norén-Nyström U, Hasle H, Jahnukainen K, Jónsson ÓG, Hovland R, Lausen B, Larsson R, Palmqvist L, Staffas A, Zeller B, Nordlund J. *DNA Methylation Signatures Predict Cytogenetic Subtype and Outcome in Pediatric Acute Myeloid Leukemia (AML).* Genes (Basel). 2021 Jun 10;12(6):895. PMID: 34200630.

Sayyab S, Lundmark A, Larsson M, Ringnér M, Nystedt S, Marincevic-Zuniga Y, Tamm KP, Abrahamsson J, Fogelstrand L, Heyman M, Norén-Nyström U, Lönnerholm G, Harila-Saari A, Berglund EC, Nordlund J, Syvänen AC. *Mutational patterns and clonal evolution from diagnosis to relapse in pediatric acute lymphoblastic leukemia.* Sci Rep. 2021 Aug 6:11(1):15988. PMID: 34362951.

Mukkada S, Bhakta N, Chantada GL, Chen Y, Vedaraju Y, Faughnan L, Homsi MR, Muniz-Talavera H, Ranadive R, Metzger M, Friedrich P, Agulnik A, Jeha S, Lam C, Dalvi R, Hessissen L, Moreira DC, Santana VM, Sullivan M, Bouffet E, Caniza MA, Devidas M, Pritchard-Jones K, Rodriguez-Galindo C. *Global Registry of COVID-19 in Childhood Cancer. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study.* Lancet Oncol. 2021 Oct;22(10):1216-1426.

Højfeldt, SG, Grell K, Abrahamsson, J, Lund B, Vettenranta K, Jónsson, O Frandsen, TL, Wolthers BO, Marquart HVM, Vaitkeviciene G, Lepik K, Heyman M, Schmiegelow K, Albertsen BK. *Relapse risk following truncation of PEG-asparaginase in childhood acute lymphoblastic leukemia – results from the NOPHO ALL2008 Protocol.* Blood. 2021, I: Blood. 137, 17, s. 2373-2382 10 s.

Krag S, Larsen D, Albertsen BK, Glerup M. *Risk of ocular hypertension in children treated with systemic glucocorticoid.* 2021. Acta Ophthalmologica. 99, 8, s. e1430-e1434.

Andrés-Jensen L, Skipper MT, Christensen KM, Johnsen PH, Myhr KA, Fridh MK, Grell K, Pedersen AML, Rubak SLM, Ballegaard M, Hørlyck A, Jensen RB, Lambine TL, Nielsen KG, Tuckuviene R, Wehner PS, Albertsen BK , Schmiegelow K, Frandsen TL. *National, clinical cohort study of late effects among survivors of acute lymphoblastic leukaemia: the ALL-STAR study protocol.* BMJ Open. 2021 Feb 9;11(2):e045543.

Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Schmiegelow K, Vedsted P, Albertsen BK, Schrøder H; Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Detection mode of childhood acute lymphoblastic leukaemia relapse and its effect on survival: a Nordic population-based cohort study.* Br J Haematol. 2021 Aug;194(4):734-744.

Jensen KS, Albertsen BK, Schrøder H, Falborg AZ, Schmiegelow K, Rosthøj S, Callesen

MT, Vedsted, P. *Health care utilisation preceding relapse or second malignant neoplasm after childhood acute lymphoblastic leukaemia: a population-based matched cohort study.* BMJ Open 2021 Aug 19;11(8):e050285.

Maarbjerg SF, Thorsted A, Friberg LE, Nielsen EI, Wang M, Schrøder H, Albertsen BK. *Continuous infusion of piperacillin-tazobactam significantly improves target attainment in children with cancer and fever.* Cancer Rep (Hoboken) 2021 Nov 18;e1585.

Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Schmiegelow K, Vedsted P, Albertsen B, Schrøder H. *Doing less, accomplishing more for childhood ALL: response.* Br J Haematol 2022 Apr;197(1):120.

Jensen KS, Albertsen BK, Schrøder H, Falborg AZ, Schmiegelow K, Rosthøj S, Thude Callesen M, Vedsted P. *Health care utilisation following childhood acute lymphoblastic leukaemia: a population-based matched cohort study.* 2021, I: BMJ Open. 11, 11, e049847.

Larsen RH, Rank CU, Grell K, Møller LN, Overgaard UM, Kampmann P, Nersting J, Degn M, Nielsen SN, Holst H, Albertsen BK, Wehner PS, Callesen MT, Kanerva J, Frandsen TL, Als-Nielsen B, Hjalgrim LL, Schmiegelow K. *Increments in DNA-thioguanine level during thiopurine-enhanced maintenance therapy of acute lymphoblastic leukemia.* 2021, I: Haematologica. 106, 11, s. 2824-2833 10 s.

Brix N, Glerup M, Thiel S, Mistegaard CE, Skals RG, Berntson L, Fasth A, Nielsen SM, Nordal E, Rygg M, Hasle H, Albertsen BK, Herlin T, Nordic Study Group of Pediatric Rheumatology (NoSPeR) group. *M-ficolin: a valuable biomarker to identify leukaemia from juvenile idiopathic arthritis.* 2021, I: Archives of Disease in Childhood. Fetal and Neonatal Edition. 6 s., 2021-322114.

Lynggaard LS, Rank CU, Als-Nielsen B, Hoejfeldt SG, Heyman M, Schmiegelow K, Albertsen BK. *PEG-asparaginase treatment for acute lymphoblastic leukaemia in children: a network meta-analysis.* 2021, I: Cochrane Database of Systematic Reviews. 2021, 6, CD014570.

Laumann RD, Iversen T, Mogensen PR, Lauritzen L, Mølgaard C, Frandsen TL. *Effect of Fish Oil Supplementation on Hyperlipidemia during Childhood Acute Lymphoblastic Leukemia Treatment - A Pilot Study.* Nutr Cancer. 2021;73(9):1816-1820.

Thastrup M, Marquart HV, Levinsen M, Modvig S, Abrahamsson J, Albertsen BK, Frost BM, Harila-Saari A, Pesola J, Ulvmoen A, Wojcik DM, Taskinen M, Hoffmann M, Lausen B, Schmiegelow K; Nordic Society of Paediatric Haematology, Oncology (NOPHO). *Flow cytometric analysis of cerebrospinal fluid improves detection of leukaemic blasts in infants with acute lymphoblastic leukaemia.* Br J Haematol. 2021 Oct;195(1):119-122.

Oskarsson T, Duun-Henriksen AK, Bautz A, Montgomery S, Harila-Saari A, Petersen C, Niinimäki R, Madanat-Harjuoja L, Tryggvadóttir L, Holmqvist AS, Hasle H, Heyman M, Winther JF; ALiCCS study group. *Skeletal adverse events in childhood cancer survivors: An Adult Life after Childhood Cancer in Scandinavia cohort study.* Int J Cancer. 2021 Dec 1;149(11):1863-1876.

Gottschalk Højfeldt S, Grell K, Abrahamsson J, Lund B, Vettenranta K, Jónsson ÓG, Frandsen TL, Wolthers BO, Marquart HV, Vaitkeviciene G, Lepik K, Heyman M, Schmiegelow K, Albertsen BK. *Relapse risk following truncation of pegylated asparaginase in childhood acute lymphoblastic leukemia.* Blood. 2021 Apr 29;137(17):2373-2382.

Toksvang LN, Andrés-Jensen L, Rank CU, Niinimäki R, Nersting J, Nielsen SN, Mogensen SS, Harila-Saari A, Abrahamsson J, Joelsson J, Overgaard UM, Quist-Paulsen P, Griškevičius L, Jónsson ÓG, Vaitkevičienė G, Frandsen TL, Toft N, Grell K, Schmiegelow K. *Maintenance therapy and risk of osteonecrosis in children and young adults with acute lymphoblastic leukemia: a NOPHO ALL2008 sub-study.* Cancer Chemother Pharmacol. 2021 Nov;88(5):911-917.

Sági JC, Gézsi A, Egyed B, Jakab Z, Benedek N, Attarbaschi A, Köhrer S, Sipek J, Winkowska L, Zaliova M, Anastasopoulou S, Wolthers BO, Ranta S, Szalai C, Kovács GT, Semsei ÁF, Erdélyi DJ. *Pharmacogenetics of the Central Nervous System-Toxicity and Relapse Affecting the CNS in Pediatric Acute Lymphoblastic Leukemia.* Cancers (Basel). 2021 May 12;13(10):2333.

Nielsen SN, Toksvang LN, Grell K, Nersting J, Abrahamsson J, Lund B, Kanerva J, Jónsson ÓG, Vaitkeviciene G, Pruunsild K, Appell ML, Hjalgrim LL, Schmiegelow K. *No association between relapse hazard and thiopurine methyltransferase geno- or phenotypes in non-high risk acute lymphoblastic leukemia: a NOPHO ALL2008 sub-study.* Cancer Chemother Pharmacol. 2021 Aug;88(2):271-279.

Andrés-Jensen L, Attarbaschi A, Bardi E, Barzilai-Birenboim S, Bhojwani D, Hagleitner MM, Halsey C, Harila-Saari A, van Litsenburg RRL, Hudson MM, Jeha S, Kato M, Kremer L, Mlynarski W, Möricke A, Pieters R, Piette C, Raetz E, Ronceray L, Toro C, Grazia Valsecchi M, Vrooman LM, Weinreb S, Winick N, Schmiegelow K; Ponte di Legno Severe Toxicity Working Group. *Severe toxicity free survival: physician-derived definitions of unacceptable long-term toxicities following acute lymphocytic leukaemia.* Lancet Haematol. 2021 Jul;8(7):e513-e523.

van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, Hudson MM, Kremer LCM, Skinner R, Wallace WH, Constine LS, Higham CE, Kaste SC, Niinimäki R, Mostoufi-Moab S, Alos N, Fintini D, Templeton KJ, Ward LM, Frey E, Franceschi R, Pavasovic V, Karol SE, Amin NL, Vrooman LM, Harila-Saari A, Demoor-Goldschmidt C, Murray RD, Bardi E, Lequin MH, Faienza MF, Zaikova O, Berger C, Mora S, Ness KK, Neggers SJCMM, Pluijm SMF, Simmons JH, Di Iorgi N. *Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group.* Lancet Diabetes Endocrinol. 2021 Sep;9(9):622-637.

Ranta S, Broman LM, Abrahamsson J, Berner J, Fläring U, Hed Myrberg I, Kalzén H, Karlsson L, Mellgren K, Nilsson A, Norén-Nyström U, Palle J, von Schewelov K, Svahn JE, Törnudd L, Heyman M, Harila-Saari A. *ICU Admission in Children With Acute Lymphoblastic Leukemia in Sweden: Prevalence, Outcome, and Risk Factors.* Pediatr Crit Care Med. 2021 Dec 1;22(12):1050-1060.

Fornerod M, Ma J, Noort S, Liu Y, Walsh MP, Shi L, Nance S, Liu Y, Wang Y, Song G, Lamprecht T, Easton J, Mulder HL, Yergeau D, Myers J, Kamens JL, Obeng EA, Pigazzi M, Jarosova M, Kelaidi C, Polychronopoulou S, Lamba JK, Baker SD, Rubnitz JE, Reinhardt D, van den Heuvel-Eibrink MM, Locatelli F, Hasle H, Klco JM, Downing JR, Zhang J, Pounds S, Zwaan CM, Gruber TA; Berlin-Frankfurt-Munster Study Group (BFM); Dutch Children's Oncology Group (DCOG); Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP); Nordic Society for Pediatric Hematology and Oncology (NOPHO); Dutch Children's Oncology Group (DCOG); for St. Jude Children's Research Hospital Study Group (SJCRH). *Integrative Genomic Analysis of Pediatric Myeloid-Related Acute Leukemias Identifies Novel Subtypes and Prognostic Indicators.* Blood Cancer Discov. 2021 Sep 9;2(6):586-599.

Michels N, Boer JM, Enshaei A, Sutton R, Heyman M, Ebert S, Fiocco M, de Groot-Kruseman HA, van der Velden VHJ, Barbany G, Escherich G, Vora A, Trahair T, Dalla-Pozza L, Pieters R, Zur Stadt U, Schmiegelow K, Moorman AV, Zwaan CM, den Boer ML. *Minimal residual disease, long-term outcome, and IKZF1 deletions in children and adolescents with Down syndrome and acute lymphocytic leukaemia: a matched cohort study.* Lancet Haematol. 2021 Oct;8(10):e700-e710.

Borgstedt-Bendixen SE, Abrahamsson J, Ha SY, Koskenvuo M, Lausen B, Palle J, Zeller B, Hasle H, Løhmann DJA. *Abdominal Complications During Treatment for Pediatric Acute Myeloid Leukemia.* J Pediatr Hematol Oncol. 2021 Aug 16.

Immonen E, Nikkilä A, Peltomäki T, Aine L, Lohi O. *Late adverse effects of childhood acute lymphoblastic leukemia treatment on developing dentition.* Pediatr Blood Cancer. 2021 Sep;68(9):e29200.

Wilhelmsson M, Jahnukainen K, Winiarski J, Abrahamsson J, Bautz A, Gudmundsdottir T, Madanat-Harjuoja LM, Holmqvist AS, Winther JF, Hasle H; ALiCCS study group. *Hospitalizations in long-term survivors of childhood AML treated with allogeneic HCT-An Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study.* Am J Hematol. 2021 Mar 1;96(3):E74-E77.

Stratmann S, Yones SA, Mayrhofer M, Norgren N, Skaftason A, Sun J, Smolinska K, Komorowski J, Herlin MK, Sundström C, Eriksson A, Höglund M, Palle J, Abrahamsson J, Jahnukainen K, Munthe-Kaas MC, Zeller B, Tamm KP, Cavelier L, Holmfeldt L. *Genomic characterization of relapsed acute myeloid leukemia reveals novel putative therapeutic targets.* Blood Adv. 2021 Feb 9;5(3):900-912.

Versluys AB, Boelens JJ, Pronk C, Lankester A, Bordon V, Buechner J, Ifversen M, Jackmann N, Sundin M, Vettenranta K, Abrahamsson J, Mellgren K. *Hematopoietic cell transplant in pediatric acute myeloid leukemia after similar upfront therapy; a comparison of conditioning regimens.* Bone Marrow Transplant. 2021 Jun;56(6):1426-1432.

2022

Niinimäki R, Aarnivala H, Banerjee J, Pokka T, Vepsäläinen K, Harila-Saari A. *Reduced dose folinic acid rescue after rapid high-dose methotrexate clearance is not associated with increased toxicity in a pediatric cohort.* Support Care Cancer. 2022 Jan;30(1):127-133.

Maarbjerg SF, Kiefer LV, Albertsen BK, Schrøder H, Wang M.J. *Bloodstream Infections in Children with Cancer: Pathogen Distribution and Antimicrobial Susceptibility Patterns Over a 10-Year Period.* J Pediatr Hematol Oncol 2022 Jan 1;44(1):e160-e167.

Egnell C, Heyman M, Jónsson ÓG, Raja RA, Niinimäki R, Albertsen BK, Schmiegelow K, Stabell N, Vaitkeviciene G, Lepik K, Harila-Saari A, Ranta S. *Obesity as a predictor of treatment-related toxicity in children with acute lymphoblastic leukaemia.* Br J Haematol. 2022 Mar;196(5):1239-1247.

Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Jónsson ÓG, Svenberg P, Schmiegelow K, Heyman M, Norén-Nyström U, Schröder H, Albertsen BK. *Temporal changes in incidence of relapse and outcome after relapse of childhood ALL over three decades; a Nordic population-based cohort study.* Leukemia, 2022 Mars 21. Online ahead of print. PMID: 35314777.

Andrés-Jensen L, Grell K, Rank CU, Albertsen BK, Tuckuviene R, Linnemann Nielsen R, Lynggaard LS, Jarvis KB, Quist-Paulsen P, Trakymiene SS, Semaškevičienė R, Saks K, Jonsson OG, Frandsen TL, Johansson PI, Schmiegelow K. *Endothelial dysfunction and thromboembolism in children, adolescents, and young adults with acute lymphoblastic leukemia.* Leukemia. 2022;36(2):361-369.

Ghannoum M, Roberts DM, Goldfarb DS, Heldrup J, Anseeuw K, Galvao TF, Nolin TD, Hoffman RS, Lavergne V, Meyers P, Gosselin S, Botnaru T, Mardini K, Wood DM; EXTRIP workgroup. *Extracorporeal Treatment for Methotrexate Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup.* Clin J Am Soc Nephrol. 2022 Mar 2:CJN.08030621. doi: 10.2215/CJN.08030621. Online ahead of print.

Buchmann S, Schrappe M, Baruchel A, Biondi A, Borowitz M, Campbell M, Cario G, Cazzaniga G, Escherich G, Harrison CJ, Heyman M, Hunger SP, Kiss C, Liu HC, Locatelli F, Loh ML, Manabe A, Mann G, Pieters R, Pui CH, Rives S, Schmiegelow K, Silverman LB, Stary J, Vora A, Brown P. *Remission, treatment failure, and relapse in pediatric ALL: an international consensus of the Ponte-di-Legno Consortium.* Blood. 2022 Mar 24;139(12):1785-1793.

Toksvang LN, Grell K, Nielsen SN, Nersting J, Murdy D, Moorman AV, Vora A, Schmiegelow K. *DNA-TG and risk of sinusoidal obstruction syndrome in childhood acute lymphoblastic leukemia.* Leukemia. 2022 Feb;36(2):555-557.

Sørensen GV, Belmonte F, Erdmann F, Mogensen H, Albieri V, Holmqvist AS, Madanat-Harjuoja L, Talbäck M, Heyman MM, Malila N, Feychting M, Schmiegelow K, Winther JF, Hasle H. *Late mortality among survivors of childhood acute lymphoblastic leukemia diagnosed during 1971-2008 in Denmark, Finland, and Sweden: A population-based cohort study.* Pediatr Blood Cancer. 2022 Jan;69(1):e29356.

Lynggaard LS, Rank CU, Hansen SN, Gottschalk Højfeldt S, Henriksen LT, Jarvis KB, Ranta S, Niinimäki R, Harila-Saari A, Wolthers BO, Frandsen TL, Heyman M, Schmiegelow K, Albertsen BK. *Asparaginase enzyme activity levels and toxicity in childhood acute lymphoblastic leukemia: a NOPHO ALL2008 study.* Blood Adv. 2022 Jan 11;6(1):138-147.

Nielsen RL, Wolthers BO, Helenius M, Albertsen BK, Clemmensen L, Nielsen K, Kanerva J, Niinimäki R, Frandsen TL, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Aytan-Aktug D, Liu HC, Möricke A, Samarasinghe S, van der Sluis IM, Stanulla M, Tulstrup M, Yadav R, Zapotocka E, Schmiegelow K, Gupta R. *Can Machine Learning Models Predict Asparaginase-associated Pancreatitis in Childhood Acute Lymphoblastic Leukemia.* J Pediatr Hematol Oncol. 2022 Apr 1;44(3):e628-e636.

Lynggaard LS, Vaitkeviciene G, Langenskiöld C, Lehmann AK, Lähteenmäki PM, Lepik K, El Hariry I, Schmiegelow K, Albertsen BK. *Asparaginase encapsulated in erythrocytes as second-line treatment in hypersensitive patients with acute lymphoblastic leukaemia.* Br J Haematol. 2022 Mar 28. doi: 10.1111/bjh.18152. Online ahead of print. PMID: 35344210

Helenius M, Vaitkeviciene G, Abrahamsson J, Jonsson ÓG, Lund B, Harila-Saari A, Vettenranta K, Mikkel S, Stanulla M, Lopez-Lopez E, Waanders E, Madsen HO, Marquart HV, Modvig S, Gupta R, Schmiegelow K, Nielsen RL. *Characteristics of white blood cell count in acute lymphoblastic leukemia: A COST LEGEND phenotype-genotype study.* Pediatr Blood Cancer. 2022 Mar 22:e29582.

Jensen KS, Oskarsson T, Lähteenmäki PM, Flaegstad T, Jónsson ÓG, Svenberg P, Schmiegelow K, Heyman M, Norén-Nyström U, Schrøder H, Albertsen BK. *Temporal changes in incidence of relapse and outcome after relapse of childhood acute lymphoblastic leukemia over three decades; a Nordic population-based cohort study.* Leukemia. 2022 Mar 21. doi: 10.1038/s41375-022-01540-1. Online ahead of print. PMID: 35314777

Sundquist F, Georgantzi K, Jarvis KB, Brok J, Koskenvuo M, Rascon J, van Noesel M, Grybäck P, Nilsson J, Braat A, Sundin M, Wessman S, Herold N, Hjorth L, Kogner P, Granberg D, Gaze M, Stenman J. *A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of ^{177}Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-Risk Neuroblastoma-LuDO-N.* Front Pediatr. 2022 Mar 10;10:836230.

Helenius M, Vaitkeviciene G, Abrahamsson J, Jonsson ÓG, Lund B, Harila-Saari A, Vettenranta K, Mikkel S, Stanulla M, Lopez-Lopez E, Waanders E, Madsen HO, Marquart HV, Modvig S, Gupta R, Schmiegelow K, Nielsen RL. *Characteristics of white blood cell count in acute lymphoblastic leukemia: A COST LEGEND phenotype-genotype study.* Pediatr Blood Cancer. 2022 Mar 22:e29582.

White T, Kaspers G, Abrahamsson J, Arad-Cohen N, Cianci D, Fernandez J, Ha SY, Hasle H, De Moerloose B, Zwaan CM, Goemans BF. *Clinical outcomes of second relapsed and refractory first relapsed paediatric AML: A retrospective study within the NOPHO-DB SHIP consortium.* Br J Haematol. 2022 Feb 4.

Toussaint L, Brandal P, Embring A, Engellau J, Evensen ME, Griskeviskius R, Hansen J, Hietala H, Wickart Johansson G, Jørgensen M, Kramer PH, Kristensen I, Lehtio K, Magelssen H, Maraldo MV, Marienhagen K, Martinsson U, Nilsson K, Peters S, Plaude S, Seiersen K, Sendiuliene D, Smulders B, Edvardsen T, Søbstad JM, Taheri Z, Vaalavirta L, Vestergaard A, Timmermann B, Lassen-Ramshad Y; NOPHO Radiotherapy Working Group. *Inter-observer variation in target delineation and dose trade-off for radiotherapy of paediatric ependymoma.* Acta Oncol. 2022 Feb;61(2):235-238.

Anastasopoulou S, Harila-Saari A, Als-Nielsen B, Eriksson MA, Heyman M, Johannsdottir IM, Marquart HV, Niinimäki R, Pronk CJ, Schmiegelow K, Vaitkeviciene G, Thastrup M, Ranta S. *Does minimal central nervous system involvement in childhood acute lymphoblastic leukemia increase the risk for central nervous system toxicity?* Pediatr Blood Cancer. 2022 Apr 30:e29745.

Anastasopoulou S, Nielsen RL, Als-Nielsen B, Banerjee J, Eriksson MA, Helenius M, Heyman MM, Johannsdottir IM, Jonsson OG, MacGregor S, Mateos MK, Mayoh C, Mikkel S, Myrberg IH, Niinimäki R, Schmiegelow K, Taskinen M, Vaitkeviciene G, Warnqvist A, Wolthers B, Harila-Saari A, Ranta S. *Acute central nervous system toxicity during treatment of pediatric acute lymphoblastic leukemia: phenotypes, risk factors and genotypes.* Haematologica. 2022 Mar 31. doi: 10.3324/haematol.2021.280016. Online ahead of print.

Toksvang LN, Als-Nielsen B, Bacon C, Bertasiute R, Duarte X, Escherich G, Helgadottir EA, Johannsdottir IR, Jónsson ÓG, Kozlowski P, Langenskjöld C, Lepik K, Niinimäki R, Overgaard UM, Punab M, Räty R, Segers H, van der Sluis I, Smith OP, Strullu M, Vaitkevičienė G, Wik HS, Heyman M, Schmiegelow K. *Thiopurine Enhanced ALL Maintenance (TEAM): study protocol for a randomized study to evaluate the improvement in disease-free survival by adding very low dose 6-thioguanine to 6-mercaptopurine/methotrexate-based maintenance therapy in pediatric and adult patients (0-45 years) with newly diagnosed B-cell precursor or T-cell acute lymphoblastic leukemia treated according to the intermediate risk-high group of the ALLTogether1 protocol.* BMC Cancer. 2022 May 2;22(1):483. doi: 10.1186/s12885-022-09522-3.