



NOPHO – past, present and future

NOPHO as an example of Nordic clinical trial platform

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NOPHO

Nordic Pediatric Hematology-Oncology association



Original

- Denmark
- Finland
- Iceland
- Norway
- Sweden

New NOPHO

- Lithuania

Close collaborator

- Estonia
- Latvia



Nordic collaboration – motives & aims

- Wish to offer better treatment and change for Nordic children with cancer
- Wish to get patients and treatments registered and to analyze results
- Make contacts and collaborate with the other world
- Teach and learn from each other, be stronger together





NOPHO - History

- **The Nordic Paediatric Society 1916** (Nordic pediatricians with special interest in pediatric hematology)
- **Nordic club of paediatric haematology 1968**
 - no formal membership, no board, no fee...
 - aims
 - 1) to create a forum for scientific discussion and collaboration
 - 2) to build friendships and give young paediatricians the opportunity to present their research within a friendly setting
- **Nordic collaboration in paediatric oncology** (pediatricians, pediatric surgeons, radiotherapists) 1980
- **Nordic society of paediatric haematology and oncology – NOPHO 1984**





Organization today

Sweden	283	• General Assembly-once a year
Denmark	146	• Board-twice a year
Norway	96	• Leukemia-lymphoma committee
Finland	81	• Solid tumor Committee
Island	6	• Brain tumor Committee
Lithuania	38	• Young NOPHO
Others	28	• NOPHO-NOBOS
TOTAL	678	• Working groups 35

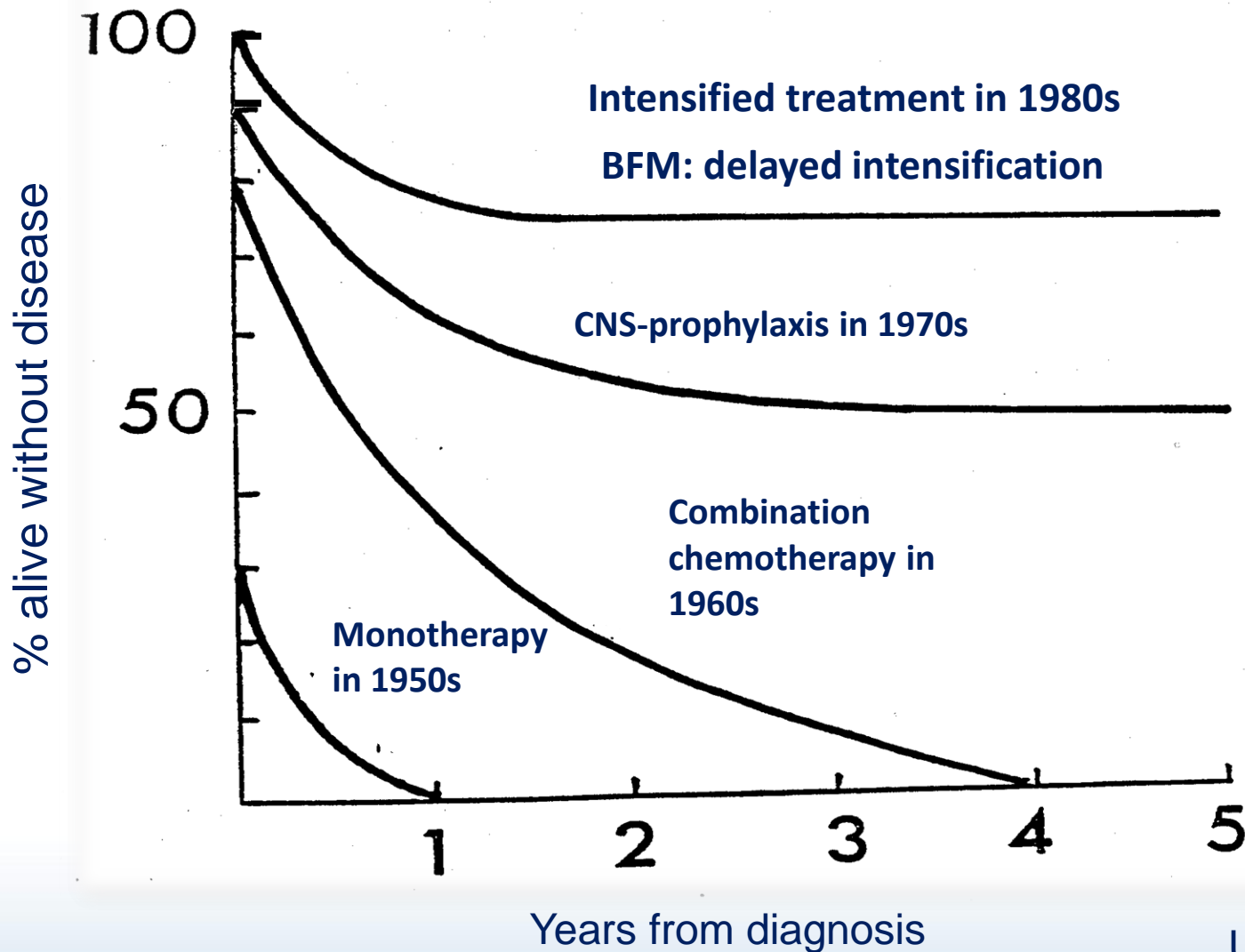


Steps towards successful collaboration and improved treatment results

- **Population-based registration of all Nordic children with leukaemia and solid tumors** (pre-existing population-based national cancer registries)
- **Common Nordic leukaemia treatment protocols**
 - registration 100%, follow-up close to 100%
 - steadily improving treatment results
- **Education of young paediatricians** in hematology-oncology; specialised educational courses (Young NOPHO courses)
- **Member of I-BMF** (international BFM study group for leukaemia and lymphoma) 2006
- **Joining to SIOPE in 2013**
 - all NOPHO members became individual members of SIOPE
 - participation to SIOPE solid tumor protocols and registries
 - pan-European integration of research, care and education

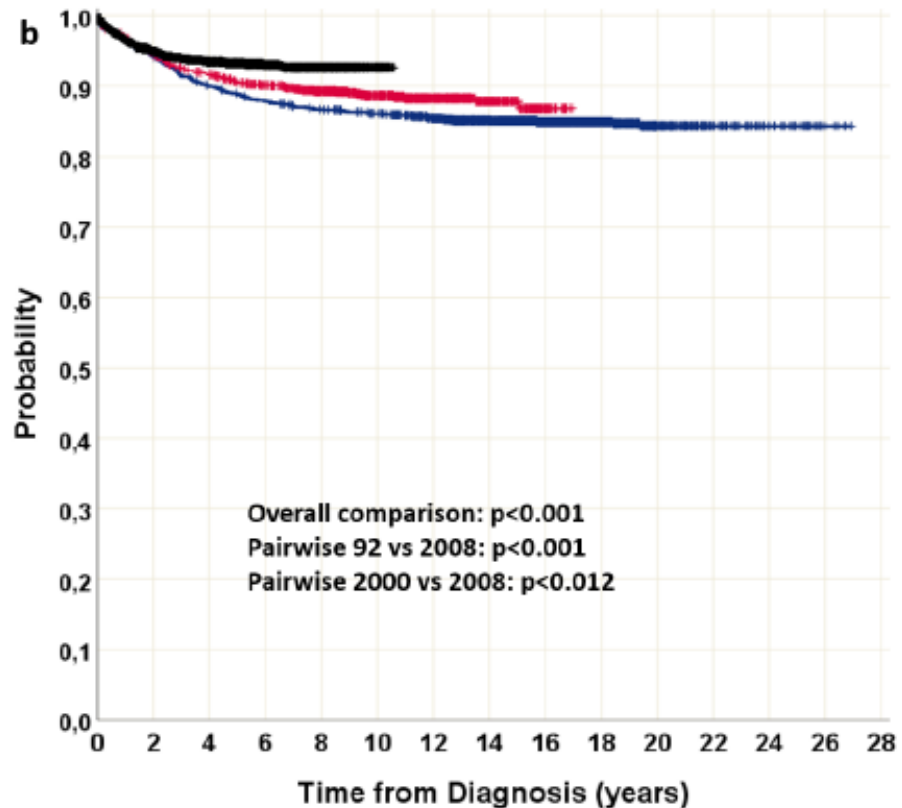


Improvement of childhood ALL treatment





NOPHO ALL-92, -2000 and -2008 protocols; overall survival

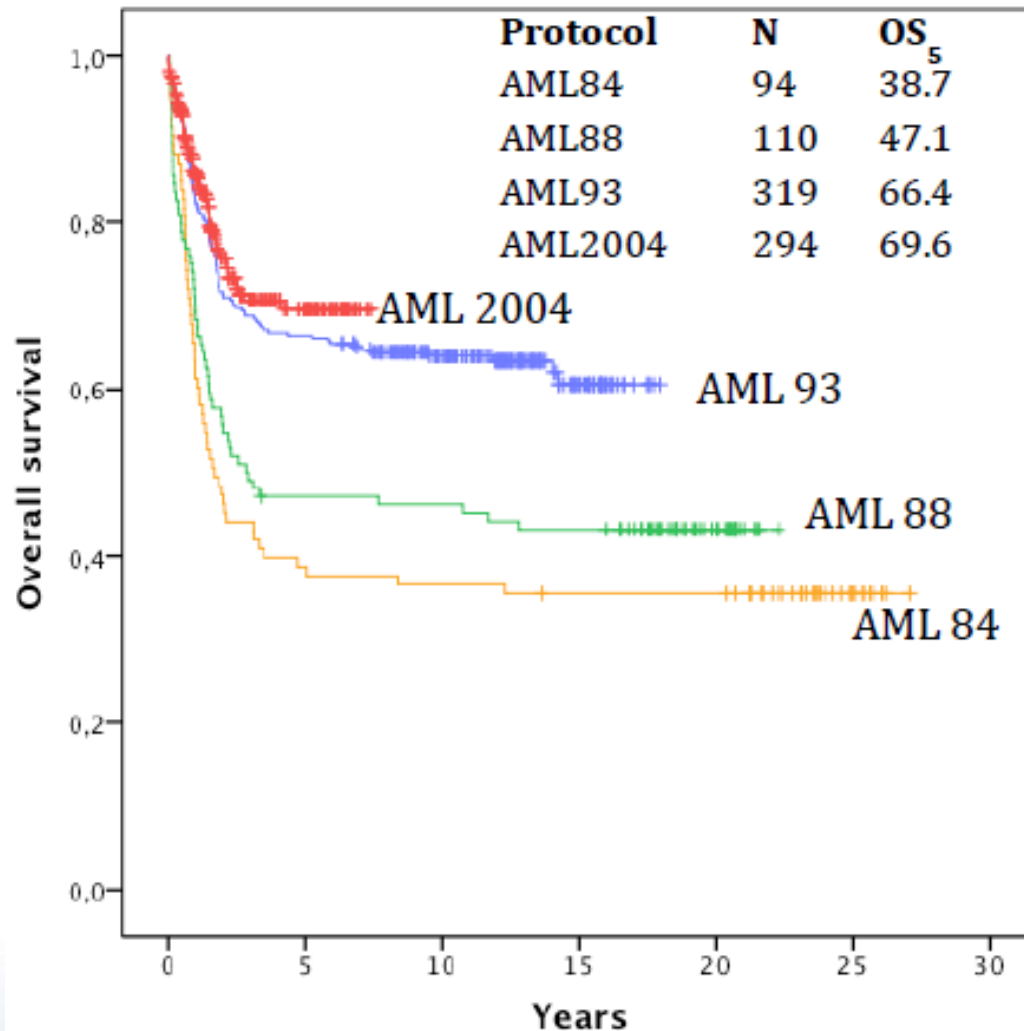


- MRD (minimal residual disease) measurement
- Reponse - guided stratification of treatment

Cohort	Total n	Deaths	Alive	pOS (5yr)	pOS (at FU)
92	1561	234	1327	0.89	0.84
2000	1056	120	936	0.91	0.87
2008	1936	113	1823	0.93	0.93



NOPHO AML studies: a success story



- AML 88: Intensified chemotherapy
- AML 93 and AML 2004: **Response-guided approach** to retain the antileukemic effect while reducing toxicity
- World-leading results
- NOPHO-DBH (Duch Belgian) AML 2012 : aim of better prognosis by better risk stratification based on MRD quantification and more intensive induction



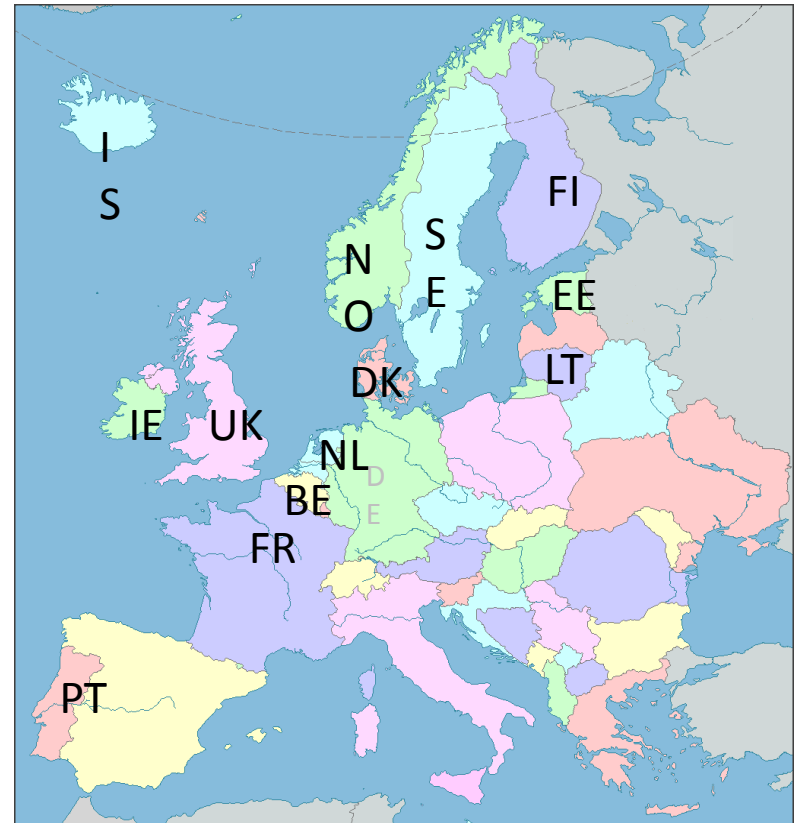
Where are we now – what's next?

- World leading results from NOPHO leukemia protocols
 - annual accrual of patients still too slow – need to join forces with European groups
- Solid tumors – individual entities too rare, need to join international protocols
- Molecular profiling of childhood tumors, novel targetted treatments – need to get all Nordic children an access to these
- Nordic registries of childhood cancer – need to maintain this structure
 - upcoming NOPHO CARE as a common registry and study platform for all pediatric cancers in NOPHO area
- New important aspects of cancer treatment and survival
 - long term side effects of the treatment (cardiac, neurocognitive, growth etc)
 - fertility preservation
 - quality of survival



New ALL protocol (ALLTogether) as part of an international consortium

- NOPHO
- UK-ALL
- DCOG (Dutch)
- CoALL (German)
- Belgian Society for Pediatric Hematology-Oncology
- Irish Society of Pediatric Hematology/Oncology
- Portuguese Society of Pediatric Hematology/Oncology
- FrALLe





Pediatric clinical phase 3 trials in NOPHO

- NOPHO own protocols
 - ALL: NOPHO ALL-82; ALL-86, ALL-92, ALL-2000, ALL-2008 (upcoming ALLTogether)
 - AML: NOPHO AML2006; NOPHO-DBH-2012
- NOPHO as part of international protocols
 - Lymphoma: ALCL99; EuroNet PHL 2.0
 - Histiocytosis: LCH 1-IV; HLH 2004
 - Ph-ALL: EsPhALL
 - Infant-ALL: Interfant 2006
 - CML
 - Allogeneic stem cell transplantation in ALL: Forum
 - Low grade glioma: SIOPE LOGGIC
- National groups as part of international protocols
 - Ewing sarcoma
 - Osteosarcoma
 - Rhabdomyosarcoma: CWS RMS
 - Medulloblastoma: SIOPE PNET5 (upcoming SIOPE HR-MB, SIOPE YC-MB)
 - Ependymoma: SIOPE Ependymoma II
 - AT/RT: EURHAB (upcoming SIOPE AT/RT)



Pediatric phase 1-2 trials and targetted therapy in phase 3 trials in NOPHO: overview on www.nopho.org continuously updated by NOPHO novel therapy working group / Karsten Nysom

NOPHO novel therapy working group – Overview of ongoing trials – Updated 16 September 2019

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Phase 1-2 trials

Trial (link)	Targeted agent	Other agents	Diagnoses	Age	Open in	Phase	Contact
BEACON	Dinutuximab beta (anti-GD2)	Temozolomide, topotecan	Relapsed or refractory HR neuroblastoma	1-21.9y	Copenhagen	2	Karsten Nysom
ITCC-015	Azacitidine	-	Relapsed JMML	1-17.9y	Aarhus	1	Henrik Hasle
BI 1200.120	Afatinib (EGFRi)	-	Relapsed or refractory intra- and extracranial tumours with confirmed ErbB pathway deregulation, shown in study biomarker pre-screening	1-17.9y	Copenhagen	1	Karsten Nysom
rEECur EuroEwing link	-	Topotecan, cyclophosphamide, irinotecan, temozolomide, ifosfamide	Recurrent or primary refractory Ewing sarcoma	4-49.9y	Bergen, Oslo, Trondheim, Tromsø, Copenhagen, Aarhus, Helsinki, Turku, Oulu, Tampere	2	Dorota Malgorzata Wojcik , Heidi Glosli , Erling Moe , Tove Nystad , Karsten Nysom , Henrik Hasle , Jukka Kanerva , Päivi Lähteenmäki , Riitta Niinimäki , Mikko Arola
MEMMAT	Bevacizumab (anti-VEGFR)	Thalidomide, celecoxib, fenofibrate, etoposide, cyclophosphamide, cytarabine	Relapsed or progressed medulloblastoma	0-19.9y at original diagnosis	Copenhagen, Gothenburg, Stockholm, Uppsala, Lund, Umeå, Linköping	2	Karsten Nysom , Magnus Sabel , Stefan Holm , Anders Öberg , Helena Mörse , Mattias Mattsson , Irene Devenney
BIOMEDE	Everolimus	Radiotherapy	Newly diagnosed H3 K27M mutant diffuse midline glioma (including DIPG)	0.5-29.9y	Copenhagen, Stockholm	2	Karsten Nysom , Klas Blomgren
EZH-102	Tazemetostat (EZH2i)	-	Relapsed or refractory INI1 negative tumours (not AT/RT)	0.5-17.9y	Copenhagen	1	Karsten Nysom

etc...

28 trials
9/2019



INFORM

INdividualized therapy FORe Relapsed Malignancies in Childhood

- New treatment strategies for relapsed high risk childhood malignancies
- Objectives:
 - Characterization of high risk refractory/relapsed/progressive pediatric malignancies
 - Identification of
 - targets
 - mechanism-of-action based treatments of interests
 - number of patients per year/entity suitable for clinical trial
- Profound molecular profiling of the tumor to identify actionable alterations → data processing and target analysis → tumor board → report and TC

10/2013

pilot phase

01/2015

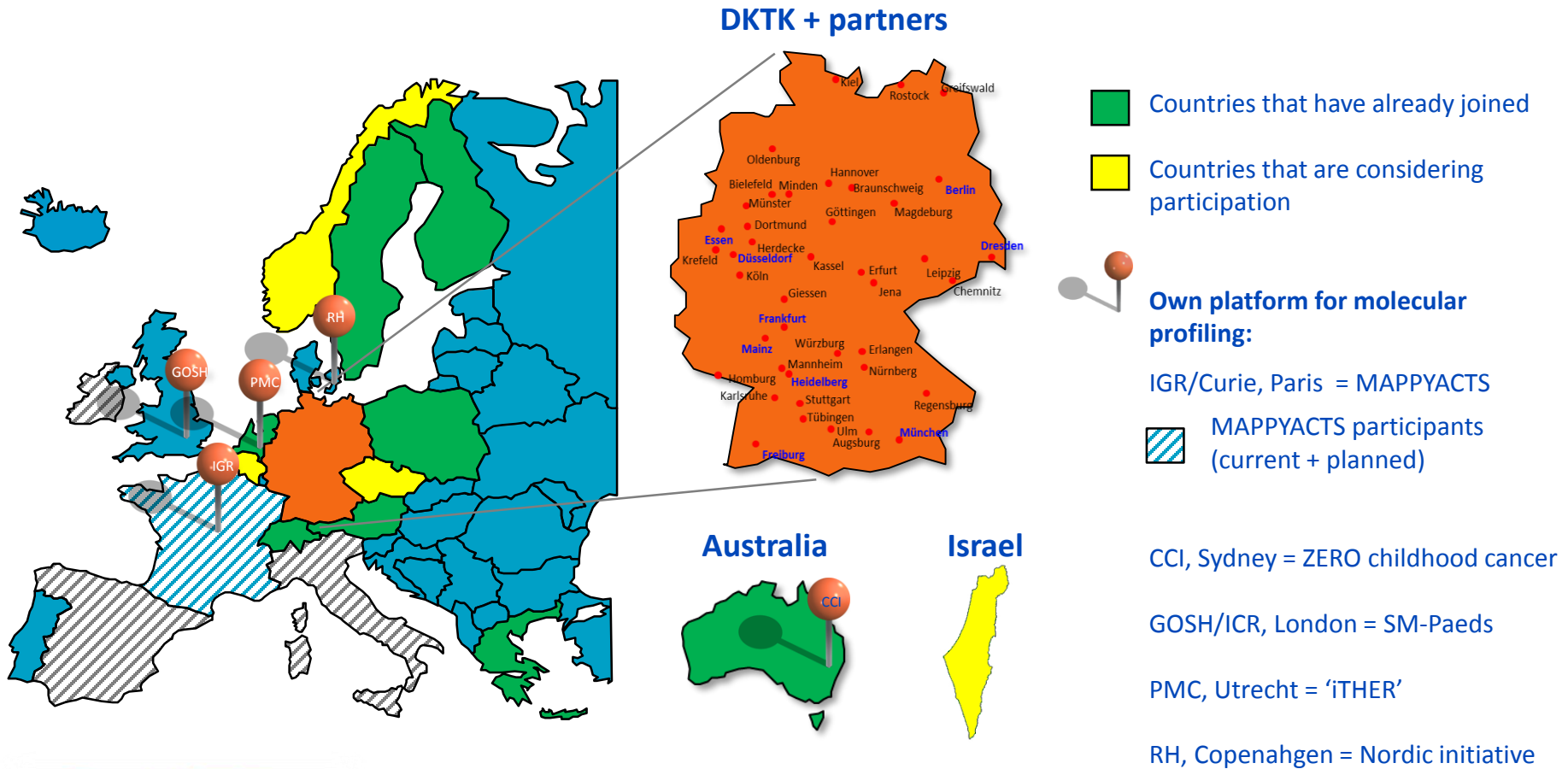
INFORM registry (profiling platform)

INFORM2 clinical trial series

~ 01/2019



INFORM – International collaboration





N



FI



DK



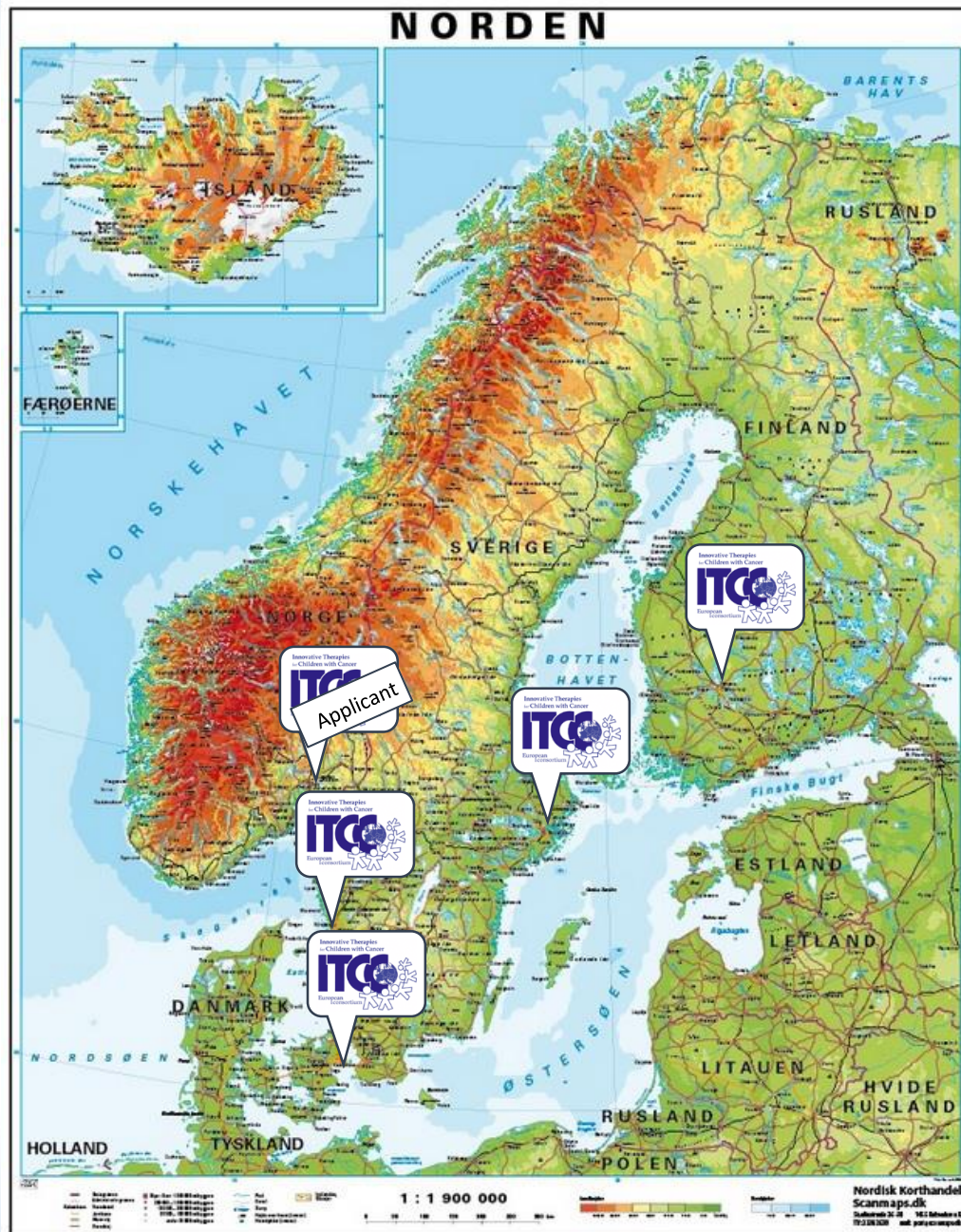
SE

NOPHOmatch

Matching relapsed/refractory cancers with more phase 1-2 clinical trials

“Sharing is better than chairing” (Torben Ek)

Karsten Nysom 2019



- P1 Stockholm
- Ingrid Öra
- P2 Gothenburg
- Torben Ek
- P3 Copenhagen
- Karsten Nysom
- P4 Oslo
- Heidi Glosli
- P5 Tampere
- Sauli Palmu



NOPHOmatch BACKGROUND

- High-quality molecular analysis of relapsed cancers is established in most Nordic centres
 - Denmark own platform
 - Sweden INFORM
 - Finland INFORM
 - Norway INFORM
- A large unmet need of matching targeted therapies



NOPHOmatch

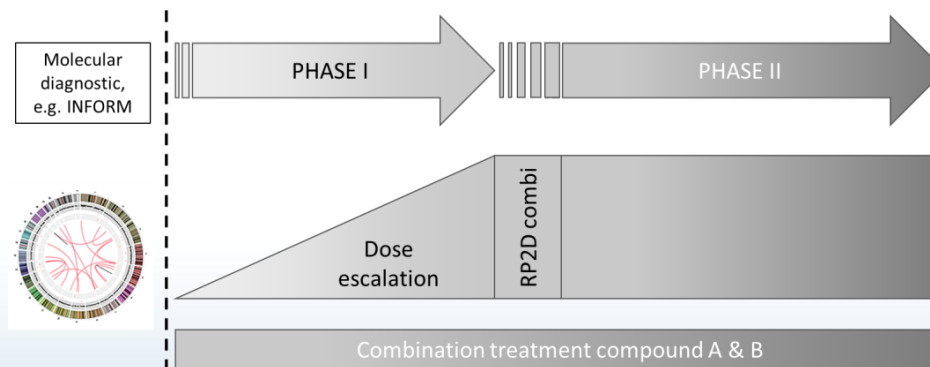
Matching more children with R/R cancer to P1/2 trials through

1. Opening of two large trials for targeted therapies in the Nordic region
 - ESMART (Copenhagen)
 - INFORM2 (Stockholm)
2. Establishing weekly Nordic videoconferences to assure better matching of molecular tumor profiles to targeted treatment within trials (Gothenburg)
 - Further strengthen a Nordic network of trial units that will provide increased access to early trials in a familiar setting



- **ESMART** (European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors)
 - Basket trial to cover targeting of several survival pathways (CDK4/6, WEE1, PARP, IDH2, PD1+KIR) in oncogenesis currently not adequately employed for pediatric patients in Europe
 - NOPHO: Copenhagen

- **INFORM2**
 - Biomarker-driven, multinational phase I/II treatment combination trial series across entities, evaluating preliminary efficacy and safety
 - NOPHO: Stockholm





Conclusions

- NOPHO was formed to create a forum for scientific discussions, collaboration and friendships in pediatric hematology and oncology in Nordic countries
- The main aim is to offer Nordic children with cancer the best available therapy and quality of life
- Strengths
 - common way of thinking
 - common registries for Nordic pediatric patients
 - common, successful own protocols
 - good, established collaboration with European groups
 - warm, encouraging and open atmosphere
- Running a clinical trial, recruitment and treatment of patients in NOPHO is feasible because of open and easy communication between NOPHO countries and centres



Thank you for your attention

