“Towards personalised medicine in Nordic clinical trials cooperation: NTA 2.0”

Cross-Nordic participation in clinical trials

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Oslo University Hospital
Number of clinical trial applications to Regulatory Authorities in the Nordic Region

Dept. of Early Cancer Trials

Oslo University Hospital
## Number of New Clinical Trials in Norway

<table>
<thead>
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<th></th>
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<tbody>
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<td>5</td>
<td>13</td>
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<td>6</td>
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<td>Phase 2</td>
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<td>Phase 3</td>
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<td><strong>129</strong></td>
<td><strong>142</strong></td>
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</table>

Norwegian Medicine Authorities
Clinical trial collaboration in the Nordics

• Strengths
  – Very similar treatment cultures and same healthcare systems
  – Personal 11 digit id number
  – Patient registries, excellent for obtaining Real World Data
  – High standards of clinical research
  – High patients compliance in trials
  – Trials performed rapidly and with high quality
  – English speaking professionals

• Weakness
  – Region regarded as expensive for clinical trials
  – Small populations in each country

"Nordic Cooperation in Clinical Research – Opportunities and Challenges": SWOT analysis, Stina Gestrelius, 2009, Modified
Ways of increasing the number of clinical trials in the Nordic Region

• Simplified approval procedures
  • Mutual recognition of Medicine Authorites approvals among the Nordic countries
  • Harmonized Ethical trial approvals in Nordics?

• Simplify cross-border procedure for patient referral for clinical trial participation

• Creating clinical trial networks – Nordic Trial Alliance (NTA) Nordic NECT, (ECRIN) …
Changing landscape of clinical trials

- Patient selection based on mutational status in tumor rather than tumor type
- Often low frequency of driver mutations in the different tumor types
Genomic Alterations in Common Solid Tumors

- **A. Lung Adenocarcinoma**
  - KRAS
  - EGFR
  - FGFR
  - PIK3CA
  - Other?

- **B. Lung Squamous Cancer**
  - KRAS
  - EGFR
  - FGFR
  - PIK3CA
  - Other?
  - ERBB2
  - TOR
  - MAPK

- **C. Breast Cancer**
  - KRAS
  - EGFR
  - FGFR
  - PIK3CA
  - Other?
  - ERBB2
  - AKT
  - PTEN

- **D. Colorectal Cancer**
  - KRAS
  - NRAS
  - ERBB2/3
  - Other?
  - BRAF

- **E. Melanoma**
  - KRAS
  - NRAS
  - PTEN
  - Other?
  - KIT
  - NF1

- **F. Head and Neck Squamous Cancer**
  - PTEN
  - CDKN2A
  - CCND1
  - PIK3CA
  - Other?

- **G. Ovarian Cancer**
  - BRCA1/2
  - PIK3CA
  - PTEN
  - AKT
  - NFI
  - KRAS
  - CDKN2A
  - CCND1
  - PIK3CA
  - Other?

- **H. Glioblastoma Multiforme**
  - EGFR
  - ERBB2
  - PDGFRA
  - MET
  - NFI
  - NRAS
  - PIK3CA
  - CDKN2A
  - CCND1
  - PTEN
  - Other?

Garraway L A JCO 2013;31:1806-1814

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Presented By Richard Schilsky at 2014 ASCO Annual Meeting
## Drivers in Lung Adenocarcinoma

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>Percentage</th>
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<tr>
<td>RIT1</td>
<td>2.2%</td>
</tr>
<tr>
<td>ERBB2 amp</td>
<td>0.9%</td>
</tr>
<tr>
<td>MET amp</td>
<td>2.2%</td>
</tr>
<tr>
<td>NF1</td>
<td>8.3%</td>
</tr>
<tr>
<td>HRAS</td>
<td>0.4%</td>
</tr>
<tr>
<td>NRAS</td>
<td>0.4%</td>
</tr>
<tr>
<td>RET fusion</td>
<td>0.9%</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>0.9%</td>
</tr>
<tr>
<td>ALK fusion</td>
<td>1.3%</td>
</tr>
<tr>
<td>ROS1 fusion</td>
<td>1.7%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>1.7%</td>
</tr>
<tr>
<td>MET ex14</td>
<td>4.3%</td>
</tr>
<tr>
<td>BRAF</td>
<td>7.0%</td>
</tr>
<tr>
<td>EGFR</td>
<td>11.3%</td>
</tr>
<tr>
<td>KRAS</td>
<td>32.2%</td>
</tr>
<tr>
<td>None</td>
<td>24.4%</td>
</tr>
</tbody>
</table>

Changing landscape of clinical trials

• Patient selection based on mutational status in tumor rather than tumor type
• Often low frequency of driver mutations in the different tumor types
• Low number of patients within each Nordic country - need to recruit patients from a larger population!
Nordic Region

Populations (Jan. 2017)

- Sweden: 9.9
- Denmark: 5.7
- Finland: 5.5
- Norway: 5.3
- Iceland: 0.3
- Total: 26.7

Similar treatment cultures
Nordic Network for Early Cancer Trials

Nordic NECT

Nordic Network for Early Cancer Trials
*Nordic-NECT*¹

- **Objectives**
  - Establish and develop a network to perform state-of-art phase I and early phase II trials in oncology to ensure all patients access to new investigational therapies.
  - Work for a bilateral agreement between the Nordic countries allowing inclusion and treatment of patients in early clinical trial protocols cross borders.
  - Promote “One point of entry” for early clinical trials and common approvals for the Nordic countries.
  - Establish a WEB-site with information about the trial sites and ongoing trials.

- **Activity**
  - Standard phase I (-II) studies
  - “First-in-man” through proof of concept programs
  - Other complex studies requiring special scientific expertise

1) Supported by Norwegian Cancer Society, Radiumhospital Research Foundation, and Nordic Cancer Union
Directive 2011/24/EU on patients’ rights in cross-border healthcare

- EU Cross Border Directive 2011/24/EU allows patients to receive treatments in other countries within the EU, but does not apply to patients participating in clinical trial.
Nordic Cross Border Trial Collaboration

Challenges

• **Legal hurdles**, different legislation in the Nordic countries
  • Denmark
  • Sweden
  • Finland
  • Norway

• **Costs?**
  – Drugs in clinical trial are provided by Pharma for free
  – Travel costs
  – **Todays** drugs commonly have low frequency toxicity, administered ambulatory

• **Risks?**
  – Who will carry incurring extra cost in case of complications - intensive care treatment
Developing Cross-Nordic Trial Collaboration

• Draw on the Danish experience and NordicNECT experience to develop simple procedures for sending patients

• Identify requirements: approvals by Ethical comitees? - Medicine Authorities? - Patients information sheets translated and other hurdles hampering collaboration (supported by NTA/Nordforsk)
  – Workshop during NRI (Nordic Health Research and Innovation Network) meeting in Oslo May 19th. Topic: Precision Medicine
Denmark

Herlev Hospital

Center for Cancer Research
Herlev Hospital
Copenhagen

The Phase I Unit
Rigshospitalet
Copenhagen

Clinical Trial Unit
Aarhus University Hospital

FINLAND

Clinical Trial Unit
Helsinki University Central Hospital

NORWAY

Clinical Cancer Research Unit
Osla University Hospital

Clinical Res. Unit
Haukeland University Hospital

SWEDEN

Early Clinical Trial Unit
Karolinska University Hospital, Stockholm

Rigshospitalet

Ulrik Lassen
MD, Ph.D.
Head of Phase I Unit

Gudrun Daugaard
Head of Clinical Research Unit

Lone Jensen
Head of Study Nurses

Aarhus University Hospital

Francesco d'Amore
MD DMScI
Head of Lymphoma Section Early Phase Trials

Helle Toldsbøl
MS, PhD
Clinical Trial Manager Early Phase Trials
Directive on Cross-Border Healthcare

- If entitled to a treatment in home country may be reimbursed if then they will be by their home country.
- Reimbursement will be up to the cost of that treatment at home. (may need prior authorization)
Directive on Cross-Border Healthcare

- Law clarifies patients' rights to access safe and good quality treatment across EU borders, and be reimbursed for it.
- Patients travelling to another EU country for medical care will enjoy equal treatment with the citizens of the country in which they are treated.
- *If entitled to that healthcare at home, then they will be reimbursed by their home country.*
- Reimbursement will be up to the cost of that treatment at home. *(may need prior authorization)*
Directive on Cross-Border Healthcare

- Make it easier for patients to access information on healthcare in another EU country, and thus increase their treatment options.
- Make it easier for national health authorities to work closer together and exchange information on quality and safety standards of healthcare.
- It will support the development of "European Reference Networks" bringing together, on a voluntary basis, specialised centres of expertise already recognised in Europe.
Arguments for drug development in the Nordic Region?

- Very good healthcare systems at all levels providing services for all patients
- Homogeneous, stable and well educated population
- Excellent Cancer Registries (100% of the cases)
- All individuals identified by a 11 digit id number
- Very few patients lost to follow-up
- A general positive attitude to clinical research in the population
- May recruit patients from a 25 million population
**SWOT analysis**

**Nordic Cooperation in Clinical Research – Opportunities and Challenges**

Based on the governmental/regional visions, reports from industry associations and statements from sponsors or Contract Research Organisations, the following SWOT is proposed for discussion:

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>WEAKNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent standard of authorities</td>
<td>Small populations (and small markets)</td>
</tr>
<tr>
<td>Excellent biobanks and registries</td>
<td>National approvals</td>
</tr>
<tr>
<td>High scientific standard of medical research</td>
<td>Ethics committees may be slow or require translated protocols</td>
</tr>
<tr>
<td>High standard of clinical research</td>
<td>Studies regarded expensive</td>
</tr>
<tr>
<td>Studies performed rapidly and with high quality</td>
<td>Low funding for investigator-initiated studies</td>
</tr>
<tr>
<td>High compliance of patients</td>
<td>Limited time and interest in clinical research</td>
</tr>
<tr>
<td>English-speaking professionals</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OPPORTUNITY</th>
<th>THREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population of 25 million</td>
<td>Legal obstacles</td>
</tr>
<tr>
<td>Improved infrastructure for Nordic trial units</td>
<td>Regional and national competition</td>
</tr>
<tr>
<td>Improved, standardised procedures</td>
<td>Even fewer Nordic offices for CROs and big pharmaceutical companies</td>
</tr>
<tr>
<td>Nordic co-funding of non-commercial studies</td>
<td></td>
</tr>
<tr>
<td>Better/larger/more rapid trials possible</td>
<td></td>
</tr>
<tr>
<td>Advantage for public health in Nordic countries</td>
<td></td>
</tr>
<tr>
<td>Advantage for Nordic medical research</td>
<td></td>
</tr>
<tr>
<td>Advantage for CROs and sponsors</td>
<td></td>
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</table>
Declining number of clinical trials in the Nordic region

*Why?*

- Nordic countries expensive compared to Eastern Europe, Baltic states and Asia?
- Emerging Asian markets with huge populations (India and China)
- Pharmaceutical companies scaling down in the Nordic region - BMS, Astra Zeneca, Pfizer...
- Very limited funding for non-pharma/investigator-driven clinical trials
- Lower hospital budgets “Production rather than research”
- Dwindling physician interest in clinical trials?
Declining number of clinical trials in the Nordic region

Consequences

- Delayed access to new drugs for patients (up to 5-6 years..)
- Delayed implementation of new drugs
- Quality of care offered to patients is closely elated to clinical research and clinical trial participation
- Missed opportunities for important translational research
- Missed opportunities for international collaboration
The number of drugs in clinical development is increasing.

**The big C**

Drugs in development*, 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
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<tr>
<td>Cancer</td>
<td>800</td>
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<tr>
<td>Central nervous system</td>
<td>600</td>
</tr>
<tr>
<td>Infections</td>
<td>400</td>
</tr>
<tr>
<td>Pain and inflammation</td>
<td>200</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes and metabolism</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>40</td>
</tr>
<tr>
<td>Respiratory</td>
<td>30</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>20</td>
</tr>
<tr>
<td>Dermatological</td>
<td>10</td>
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</table>

*Top ten therapeutic areas for the world’s big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval.

Source: Medco, R&D Directions

Courtesy of Alain Herrera
Changing landscape of cancer trials

*Personalized Medicine*

- Patient selection based on mutational status in tumor rather than tumor type
- Low number of patients in each trial due to rarity of the mutations (rare cancers or low frequency of mutation in common cancers)
- Number of patients with the specific (rare) mutations in each Nordic country may be very low (1-2% within one tumor type)
The number of drugs in clinical development is increasing
Participant in clinical trials

Regions

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<tr>
<th>Region</th>
<th>2005</th>
<th>2011</th>
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<tr>
<td>Mittlerer Osten/asiat.-pazif. Raum</td>
<td>0.8%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Zentral- und Südamerika</td>
<td>15.1%</td>
<td>12.8%</td>
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<tr>
<td>USA</td>
<td>38.8%</td>
<td>13.6%</td>
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<tr>
<td>Westeuropa</td>
<td>31.2%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Sonstige</td>
<td>7.0%</td>
<td>31.2%</td>
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Quelle: European Medicines Agency

Published in Der Spiegel
15.12 2014
# New Cancer Trials in Norway

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<th>tot</th>
<th>fase I</th>
<th>fase II</th>
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<td>27</td>
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Norwegian Medicine Authorities