Personalized Pediatric Oncology: What are the Targets?

Synergy Satellite: Targeted Drugs - scattered goals
EAHP Hamburg, 16. 3. 2105

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Heidelberg, Germany

Disclosure:
Consultant Novartis
Consultant Astra Zeneca
Research Grant Bayer Healthcare
Pediatric Oncology – a success story in firstline treatment

Relapse - Clinical challenge
NGS: New drug targets

High-grade glioma

Medulloblastoma

Low-grade glioma

Schwartzentruber et al. Nature 2012
Sturm et al. Cancer Cell 2012
Bender et al. Cancer Cell 2013
Fontebasso et al. Nature Genetics 2014

Rausch et al. Cell 2012
Jones et al. Nature 2012
Jones et al. Nature Genetics 2013
Paugh et al. Nature 2012
Kool et al. Cancer Cell 2014
Hovestadt et al., Nature 2014
Northcott et al. Nature 2014

+ Ependymoma

Witt & Mack et al. Cancer Cell 2011
Mack & Witt et al. Nature 2014
Pajtler et al. Cancer Cell 2015

→ In addition to brain tumors: PNET, Wilms, ALL, etc.

Pediatric tumor genomes are „simple“

Alexandrov et al. Nature 2013
INFORM Consortium

INdividualized therapy FOr
Relapsed Malignancies in childhood

INFORM program: 3 steps

Pilot Phase

Feasibility-Registry Study (year 1+2)

Clinical Trial (year 3-5)
Key Inclusion Criteria

• Children, adolescents, young adults, 1-40 years
• **Refractory/relapsed/progressive oncological disease**
  • (Exception: some primary rhabdomyosarcoma indications and DIPG)
• No established treatment option available
• Life expectancy > 3 months & Lansky / Karnofsky ≥ 50
• First-line treatment in GPOH trial protocol
• Inclusion discussed with respective GPOH Study group
• Current and routine re-biopsy performed (i.e. not part of the study)
  • (Note: non-interventional study, EC approved)
• Solid tumors: measurable disease activity
• Fresh frozen tissue, matching normal tissue and formalin fixed paraffin embedded (FFPE) mandatory
• Informed consent

**INFORM workflow**

Registration Central Database

Clinical Follow Up Documentation

Ped Oncol Center (n=56)

Prioritized Target List Central Database

INFORM Website

Tissue:
1. Malignant tissue
2. Non-malignant tissue (germ-line)
3. Tissue for target verification

Target Decision Board:
- Biology
- Bioinformatics
- Ped Oncology
- Pharmacology/Pharmacy
- Entity Expert

INFORM Website

**CTrials.gov**
Target Selection and Prioritization

Criteria harmonized with Scientific Advisory Board (Jan Molenaar & Hub Caron, NKOC-iTHER project, Holland and Birgit Geoerger, MOSCATO project, France)

<table>
<thead>
<tr>
<th>Target Type</th>
<th>Entity</th>
<th>Target Status</th>
<th>Description</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed driver</td>
<td>Specific</td>
<td>Genetic hit (mutation/rearrangement)</td>
<td>Specific alteration in actionable target confirmed as driving in specific entity</td>
<td>Very high</td>
</tr>
<tr>
<td>Confirmed driver</td>
<td>Other</td>
<td>Genetic hit (focal high-amplitude CNV)</td>
<td>Specific alteration in actionable target confirmed as driving in another entity</td>
<td>High</td>
</tr>
<tr>
<td>Presumed driver</td>
<td>Specific</td>
<td>Genetic hit (mutation/rearrangement)</td>
<td>Specific alteration in actionable target likely activating but not proven</td>
<td>High</td>
</tr>
<tr>
<td>Presumed driver</td>
<td>Other</td>
<td>Genetic hit (focal high-amplitude CNV)</td>
<td>Specific alteration in actionable target likely activating but not proven</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pathway activation, genetic</td>
<td>Specific</td>
<td>Genetic hit incl. focal CNV</td>
<td>Genetic alteration indicating activation of an actionable pathway known to be involved in specific entity; potential drug acting elsewhere in pathway</td>
<td>Moderate</td>
</tr>
<tr>
<td>Synthetic lethal / Predictive marker, genetic</td>
<td>Specific</td>
<td>Genetic hit incl. focal CNV</td>
<td>Genetic alteration in a gene known to induce susceptibility to inhibition of another gene in specific entity</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Pathway activation, genetic</td>
<td>Other</td>
<td>Genetic hit incl. focal CNV</td>
<td>Genetic alteration indicating activation of a potentially actionable pathway known from another entity</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Synthetic lethal / Predictive marker, expression</td>
<td>Specific</td>
<td>Protein/Expression Change</td>
<td>Altered expression of a gene/pathway known to induce susceptibility to inhibition of another gene in specific entity</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Pathway activation, expression</td>
<td>Other</td>
<td>Protein/Expression Change</td>
<td>Altered expression indicating activation of an actionable pathway known from another entity</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Circumstantial evidence</td>
<td>Other</td>
<td>Protein/Expression Change</td>
<td>Alterations with some modest literature evidence of possible pathway activation</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

INFORM – Pilotphase

52 patients screened
sex: female 24 male 28
age: mean 13 years min 2 years max 40 years

7 ineligible
45 patients enrolled
3 insufficient/no tumor
42 patients sequenced (1 patient twice)
1 no tumor (450k)
41 patients analyzed

21 patients actionable alteration identified
B. Worst & C. van Tilburg et al., in preparation
### Targets identified

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amplification</th>
<th>Deletion</th>
<th>SNV/Indel</th>
<th>Fusion</th>
<th>Overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>CCND1/2</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A/B</td>
<td></td>
<td></td>
<td>2</td>
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<td>CDK4</td>
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<tr>
<td>EGFR</td>
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<td>2</td>
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<td>EWSR1</td>
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<td>4</td>
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<tr>
<td>FGFR4</td>
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<td></td>
<td>1</td>
<td>1</td>
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<tr>
<td>HSP90AB1</td>
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<td>KRAS</td>
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<td>1</td>
<td></td>
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<tr>
<td>MET</td>
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<td>2</td>
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<tr>
<td>MLL</td>
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</tr>
<tr>
<td>MYCN</td>
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<td>1</td>
<td></td>
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<td>PDGFRA</td>
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<td>PIK3CA</td>
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<td>PTCH1</td>
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<td>TSC2</td>
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<tr>
<td>VEGFA</td>
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<td>1</td>
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<tr>
<td>VEGFR1</td>
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<tr>
<td><strong>total</strong></td>
<td><strong>7</strong></td>
<td><strong>2</strong></td>
<td><strong>9</strong></td>
<td><strong>8</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

41 patients fully sequenced and analyzed so far, 21 had ≥1 alteration with at least “borderline” evidence

*B. Worst & C. van Tilburg et al., in preparation*

### Drug “wish list”

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound #1</th>
<th>+ Compound #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Crizotinib (Pfizer) Ceritinib (Novartis)</td>
<td>?</td>
</tr>
<tr>
<td>CDK4/6</td>
<td>LEE011 (Novartis) Palbociclib (Pfizer)</td>
<td>?</td>
</tr>
<tr>
<td>FGFR</td>
<td>Regorafenib (Bayer Healthcare) Ponatinib (Ariad)</td>
<td>MEKi</td>
</tr>
<tr>
<td>MET</td>
<td>Cabozatinib (Exelixis) Crizotinib (Pfizer)</td>
<td>MEKi</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Dasatinib (Bristol Myers Squibb)</td>
<td>?</td>
</tr>
<tr>
<td>PIK3</td>
<td>Everolimus (Novartis)</td>
<td>Trametinib (GSK)</td>
</tr>
<tr>
<td>BRAFV600E</td>
<td>Vemurafenib (Hoffmann-La Roche) Dabrafenib (GSK)</td>
<td>MEKi</td>
</tr>
<tr>
<td>Smo+PTCH</td>
<td>LDE225 (Novartis) Vismodegib (Roche)</td>
<td>-</td>
</tr>
<tr>
<td>MYC</td>
<td>Panobinostat (Novartis) CUDC-907 (Curis)</td>
<td>BETi Alisertib (Takeda) Pi3Ki EZH2i</td>
</tr>
</tbody>
</table>
Outlook INFORM²: Basket trial design

Molecular analysis/Target identification

- ALK
- CDK
- FGFR
- MET
- PDGFR
- PIK3

Stratum A: Drug 1 and 2
Stratum B: Drug 3 and 4
Stratum C: Drug 5 and 6
Stratum D: Drug 7 and 8
Stratum E: Drug 9 and 10
Stratum F: Drug 11 and 12

Some preliminary examples...

**Pilot – ES-XXX**
Very large myofibroblastic sarcoma

**INFORM analysis**
- ALK fusion identified by sequencing

**Clinical consequence**
- Recruited to Phase I/II ALKi trial
- PR after 2 months
- CR after 1 year (2nd look surgery)

Courtesy of J. Schulte & G. Fleischhack (Essen)
Pilot – HD-XXX
2011: Metastasized group 3 medulloblastoma
2014: Relapse? + meningeosis

INFORM Analysis:
• Secondary malignancy: glioblastoma!
• PTPRZ1-MET fusion with amplification and corresponding overexpression of MET

Clinical consequence:
• Off label compassionate use: Crizotinib
• Local Partial response, but new metastatic lesions

MET expression

Summary & Challenges

✓ High unmet medical need
✓ Personalized molecular diagnostics: clinically feasible
✓ Targets (being) identified

➢ Access to targeted drugs for children very limited
➢ Almost no approved targeted drugs for children
➢ Limited number of phase I data in ped onc
➢ Combination therapy: different companies
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