DRUP
The Drug Rediscovery Protocol

A national study on behalf of the Centre for Personalized Cancer Treatment
to facilitate patient access to commercially available, targeted anti-cancer drugs
to determine the potential efficacy in treatment of advanced cancers
with a known molecular tumor profile

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CPCT / HMF sequencing

> 3500 patients included
Background

More extensive genomic sequencing = more ‘uncommon’ findings:

- $\text{BRAF}_{\text{mut}}$ in melanoma vs. $\text{BRAF}_{\text{mut}}$ in NSCLC?
- $\text{HER2}_{\text{ampl}}$ in breast cancer vs. $\text{HER2}_{\text{ampl}}$ in CRC?
- $\text{BRCA}_{\text{mut}}$ in ovarian cancer vs. $\text{BRCA}_{\text{mut}}$ in prostate cancer?

Treating patients based on such findings can be challenging:

- Significance of ‘uncommon’ mutations often unknown
- Limited drug-access outside of the registered indication
- No learning curve for off-label treatment in daily practice
Initiation of DRUP

• Treatment based on tumor and mutational profile
• With approved targeted (or immuno) therapies

→ Access to potentially effective therapy for patients
→ Evaluation of efficacy and toxicity
How does it work?

Patient with advanced cancer who has exhausted standard treatment options and whose molecular tumor profile has been analyzed:

- Submit to DRUP study team:
  - Actionable target present?
  - Matching drug available?
  - Literature / rationale?

If yes:
- Inform and screen patient
- Register patient on-study
- Pre-treatment tumor biopsy

Start treatment
When do we consider a drug effective?

- Patients are enrolled in multiple parallel cohorts
- Cohorts are defined by study drug, histologic tumor type and molecular tumor profile
- Efficacy (defined as CR, PR or SD ≥16 weeks) is analyzed per cohort, with a 2-stage-design:
Current study status & preliminary results

- Study was launched in September 2016
- 34 participating hospitals, of which 27 are open for inclusion

<table>
<thead>
<tr>
<th>Participating sites</th>
<th>Participating sites</th>
<th>Participating sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Currently open for inclusion (n = 27)</strong></td>
<td><strong>Currently open for inclusion (n = 27)</strong></td>
<td><strong>Currently open for inclusion (n = 27)</strong></td>
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<tr>
<td>AVL</td>
<td>Haaglanden MC</td>
<td>NWZ</td>
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<tr>
<td>Amphia</td>
<td>Isala</td>
<td>OLVG</td>
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<tr>
<td>Deventer ZH</td>
<td>Martini</td>
<td>Reinier de Graaf</td>
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<tr>
<td>Erasmus</td>
<td>Maxima MC</td>
<td>Rijnstate</td>
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<tr>
<td>ETZ</td>
<td>MC Leeuwarden</td>
<td>Spaarne Gasthuis</td>
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<tr>
<td>Franciscus</td>
<td>Meander</td>
<td>UMC Groningen</td>
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<tr>
<td>Gelderse Vallei</td>
<td>Nij Smellinghe</td>
<td>UMC Leiden</td>
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<tr>
<td><strong>In preparation (n = 7)</strong></td>
<td><strong>In preparation (n = 7)</strong></td>
<td><strong>In preparation (n = 7)</strong></td>
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<tr>
<td>AMC</td>
<td>Haga ziekenhuis</td>
<td>Treant Zorggroep</td>
</tr>
<tr>
<td>Gelre Ziekenhuizen</td>
<td>Maasstad Zkh</td>
<td>Wilhelmina zkh</td>
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<td>ZG Twente</td>
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</table>
# 20 different drugs

## Available

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug Name</th>
<th>Genes/Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amgen</strong></td>
<td>Panitumumab</td>
<td>KRAS-BRAF-NRAS&lt;sub&gt;WT&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>AZ</strong></td>
<td>Olaparib</td>
<td>BRCA 1/2, ATM</td>
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<tr>
<td><strong>Bayer</strong></td>
<td>Regorafenib</td>
<td>RET, VEGFR1,2,3, KIT, PDGFRB, RAF-1, BRAF</td>
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<tr>
<td><strong>BMS</strong></td>
<td>Nivolumab</td>
<td>MSI or high mutational load</td>
</tr>
<tr>
<td><strong>Roche</strong></td>
<td>Erlotinib</td>
<td>EGFR</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Pertuzumab</td>
<td>HER2</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib + Cobimetinib</td>
<td>BRAF V600</td>
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<tr>
<td></td>
<td>Vismodegib</td>
<td>PTCH1</td>
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<tr>
<td></td>
<td>Dabrafenib</td>
<td>BRAF V600</td>
</tr>
<tr>
<td><strong>Roche</strong></td>
<td>Nilotinib</td>
<td>KIT, ABL1, PDGFR, PDGFRB</td>
</tr>
<tr>
<td></td>
<td>Trametinib</td>
<td>BRAF V600, NRAS</td>
</tr>
<tr>
<td><strong>BI</strong></td>
<td>Afatinib</td>
<td>ERBB4, NRG1</td>
</tr>
<tr>
<td><strong>Eisai</strong></td>
<td>Lenvatinib</td>
<td>FGFR1, 2, 3</td>
</tr>
<tr>
<td><strong>MSD</strong></td>
<td>Pembrolizumab</td>
<td>High mutational load</td>
</tr>
<tr>
<td><strong>Pfizer</strong></td>
<td>Axitinib</td>
<td>VEGFR1, 2, 3</td>
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<tr>
<td></td>
<td>Crizotinib</td>
<td>ALK, MET, MST1R, ROS1</td>
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<tr>
<td></td>
<td>Sunitinib</td>
<td>CSF1R, FGFR1,2,3, VEGFR1, 2, 3, KIT, PDGFR, PDGFRB, RET, VHL</td>
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<tr>
<td><strong>Roche</strong></td>
<td>Palbociclib</td>
<td>CDK4/6, CDKN2A</td>
</tr>
<tr>
<td><strong>Committed:</strong></td>
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</tr>
<tr>
<td><strong>Clovis</strong></td>
<td>Rucaparib</td>
<td>BRCA1/2, ATM</td>
</tr>
<tr>
<td><strong>Ipsen</strong></td>
<td>Cabozantinib</td>
<td>MET, AXL, RET, KIT</td>
</tr>
<tr>
<td><strong>AZ</strong></td>
<td>Durvalumab</td>
<td>MSI</td>
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</tbody>
</table>
700 patients submitted for review

Included: 288 (41%)

Pending: 28 (4%)

Excluded: 384 (55%)
1st successful cohort

• Nivolumab for MSI tumors

  – Clinical benefit at 6 months: 61% (at 16 weeks: 71%)
  – Median PFS: not reached, 50% still on study (mPFS to date: 32.2 weeks)

  – Discussion with ZIN how to proceed
Scientific Excellence
- €120 million
- 560 researchers
- 43 principal investigators
- 9 research institutes
- 6 research themes

Collaboration

Valorization

Common Strategy

Outsmarting cancer
Impacting lives
Scientific themes

Understanding tumor growth & resistance

Identifying critical drug combinations & biomarkers

Developing novel technologies

Mobilizing immune defence

Researching causes & consequences of genetic instability

Analysing network perturbations in tumors & tumor-host interactions
Building a link to the clinic

Why?
Bridging the gap between fundamental and clinical research

How?
Connecting clinicians to fundamental research and basic scientists to clinical research

What?
Training for Oncode researchers about (pre-)clinical research and clinical challenges
Clinical proof of concept programme

Goal:
• Facilitate translation of fundamental research to the clinic

Status:
• 5 proposals approved in first call

Next steps:
• Finalize terms & conditions and set up second call
• Design workshops to address e.g. study design, target product profile

Programme manager: Ester Frische
Affordable health care programme

Goals:
• Make future cancer treatments more (cost-) effective

Status:
• First open call together with ZonMw

Next steps:
• Finalize strategy with programme committee
• Set up training on HTA, patient engagement etc.

Programme manager:
Irene Kanter-Schlifke