Belgian Society of Medical Oncology

The Precision initiative

a collaboration between Belgian university and their network hospitals and the pharmaceutical industry to give cancer patients access to a broader spectrum of cancer medicines

Jacques De Grève MD, PhD
Jacques.degreve@uzbrussel.be

For the Precision Steering committee
Cancer registry
Cancer

• Second cause of disease related fatality

• Local treatments: surgery and radiotherapy

• Systemic treatments
  1. Chemo
  2. Hormonal
  3. Targeted
  4. Immunotherapy
Cancer

• Second cause of disease related fatality

• Local treatments: surgery and radiotherapy

• **Systemic treatments**
  1. Chemo
  2. Hormonal
  3. **Targeted**
  4. Immunotherapy
Basis of treatment choices

1. Clinical criteria
   - Disease stage
   - Performance status

2. Pathological criteria
   - Cancer type
   - Therapeutic target expressed:
     - Estrogen receptor
     - PDL1
     - ....

3. Genomic criteria
   - Cancer gene mutations

Which drugs can target the aberrant proteins
Targeted therapies

• Monoclonal antibodies
  – Surface receptors

• Small molecules
  – Intracellular targets
Impressive therapeutic results with targeted therapies

Erlotinib in EGFR mutant lung cancers

Crizotinib in ALK mutant lung cancers

Rosel et al., *Lancet Oncol* 2012

Kwak et al., *N Engl J Med* 2010

Presented By Charles Rudin at 2014 ASCO Annual Meeting
Crizotinib in ALK translocated NSCLC

Shaw et al N Eng J Med; Solomon et al N Eng J Med
Improved quality of life

Time to Deterioration in Lung Cancer Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=162)</th>
<th>Chemotherapy (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>91 (56)</td>
<td>111 (74)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>5.6</td>
<td>1.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.54 (0.40 to 0.71)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>162</td>
<td>151</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>71</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Composite of chest pain, cough, and dyspnea
Also active in brain metastases

Response in 1 mth; 8+ mth

Fig 4. Response of an ROS1-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.
Many targets in lung cancer

All targetable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
Rare mutations

- None (24.4%)
- KRAS (32.2%)
- EGFR (11.3%)
- BRAF (7.0%)
- MET ex14 (4.3%)
- ROS1 fusion (1.7%)
- ALK fusion (1.3%)
- MAP2K1 (0.9%)
- NRAS (0.4%)
- HRAS (0.4%)
- RET fusion (0.9%)
- ERBB2 amp (0.9%)
- MET amp (2.2%)
- RIT1 (2.2%)
- NF1 (8.3%)

All targetable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
Rare mutations respond as well
Same mutations also occur in children

**Pediatric patients in trial**

11 patients (7 boys)  
Median age 9 y [3 – 16]

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>molecular alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>2</td>
<td>2 ALK trans</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>2</td>
<td>2 ALK mt</td>
</tr>
<tr>
<td>IMT</td>
<td>2</td>
<td>1 ALK trans, 1 ROS1 trans</td>
</tr>
<tr>
<td>High Grade Glioma</td>
<td>3</td>
<td>1 MET amp, 1 MET trans, 1 MET amp+trans</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>1</td>
<td>ALK trans</td>
</tr>
<tr>
<td>Atypical meningioma</td>
<td>1</td>
<td>ROS1 trans</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>6 ALK+, 3 MET+, 2 ROS1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease characteristic</th>
<th>Total N=11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor still in place at inclusion</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Missing or not applicable</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic disease at inclusion</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Missing or not applicable</td>
<td>1</td>
</tr>
<tr>
<td>Time between metastatic diagnosis and inclusion (months) Median</td>
<td>25 (10 ; 37)</td>
</tr>
<tr>
<td>Number of Metastatic sites at inclusion</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>4</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>

ALCL, anaplastic large cell lymphoma  
IMT, inflammatory myofibroblastic tumor

Presented By Gilles Vassal at 2016 ASCO Annual Meeting
Same mutations also occur in children

**Efficacy: best response**

1 CR, 4 PR, 2 SD, 4 PD

**ORR = 5/11 ; 0.45 [0.17 – 0.77]**

<table>
<thead>
<tr>
<th></th>
<th>Best response</th>
<th>PFS (months)</th>
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</thead>
<tbody>
<tr>
<td>ALC L</td>
<td>CR</td>
<td>9.5+</td>
</tr>
<tr>
<td>ALC L</td>
<td>PR</td>
<td>13.4+</td>
</tr>
<tr>
<td>IMT ROS1 trans</td>
<td>PR</td>
<td>16.7+</td>
</tr>
<tr>
<td>IMT ALK trans</td>
<td>PR</td>
<td>5.5+</td>
</tr>
<tr>
<td>Meningioma ROS1 trans</td>
<td>PR</td>
<td>9.3+</td>
</tr>
<tr>
<td>Mesothelioma ALK trans</td>
<td>SD</td>
<td>24.8+</td>
</tr>
<tr>
<td>HGG MET trans+amp</td>
<td>SD</td>
<td>6.7+</td>
</tr>
</tbody>
</table>

5 patients are still on treatment
Such actionable mutations are found in all cancer types.
Actionable mutations are frequent or rare

Boland, Oncotarget. 2015 Aug 21;6(24):20099-110
Actionable mutations are frequent or rare breast cancer

Stephens, Nature 2012
Currently approved major targeted therapies

Targetable Oncogenic Drivers in Human Cancers

- CML
  - BCR-ABL

- GIST
  - CKIT

- Melanoma
  - BRAF

- Breast
  - HER2

- Lung
  - EGFR
  - ALK
  - ROS1
Many more genes are actionable

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Aberration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>EGFR Activating Mutations</td>
</tr>
<tr>
<td>Afatinib</td>
<td>HER2 Activating Mutations</td>
</tr>
<tr>
<td>AZD9291</td>
<td>EGFR Mutations (T790M/Rare Activating)</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK Translocations</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ROS1 Translocations</td>
</tr>
<tr>
<td>Dabrafenib and Trametinib</td>
<td>BRAF V600K/V600E Mutations</td>
</tr>
<tr>
<td>GDC-0032 (taselisib)</td>
<td>PIK3CA Mutations</td>
</tr>
<tr>
<td>GSK2636771</td>
<td>PTEN Mutation or Deletion w/ PTEN Expression on IHC</td>
</tr>
<tr>
<td>GSK2636771</td>
<td>PTEN Loss by IHC</td>
</tr>
<tr>
<td>T-DM1</td>
<td>HER2 Amplification</td>
</tr>
<tr>
<td>Trametinib</td>
<td>BRAF Fusions or non-V600K/non-V600E Mutations</td>
</tr>
<tr>
<td>Trametinib</td>
<td>NF1 Mutations</td>
</tr>
<tr>
<td>Trametinib</td>
<td>GNAQ/GNA11 Mutations</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>SMO/PTCH1 Mutations</td>
</tr>
<tr>
<td>Defactinib</td>
<td>NF2 Loss</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>cKIT Mutations</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>DDR2 Mutations</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>MET Amplification</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Exon 14 Skipping</td>
</tr>
<tr>
<td>AZD4547</td>
<td>FGFR Fusions, Mutations, and Amplifications</td>
</tr>
<tr>
<td>AZD5363</td>
<td>AKT Mutations</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>NRAS Mutations Awaiting CRADA.</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>CCND1,2,3 Amplification(and Rb protein expression by IHC)</td>
</tr>
</tbody>
</table>
| Nivolumab                     | MMR deficiency (IHC: MLH1, MSH2)                                        | 24 genes
Many more genes are actionable

Actionable Mutations of Interest in NCI-MATCH and Estimated Prevalence

aMOIs (actionable mutations of interest):
- ALK translocations - (4%)
- BRAF fusions or non-V600E, non-V600K mutations - (2.79%)
- BRAF V600E or V600K - (1-12%)
- cKIT mutations - (4%)
- DDR2 mutations - (2%)
- EGFR activating mutations - (1-4%)
- EGFR T790M mutations - (1-2%)
- FGFR amplifications or FGFR mutations - (5%)
- GNA11 mutations - (1.6%)
- GNAQ mutations - (2%)
- HER2 activating mutations - (2-5%)
- HER2 amplifications - (5%)
- MET amplifications - (4%)
- mTOR mutations - (5%)
- NF1 mutations - (7.7%)
- NF2 loss - (2%)
- PIK3CA mutations or amplifications - (17-18%)
- PTEN mutations or deletions - (11%)
- ROS1 translocations - (5%)
- SMO or PTCH1 mutations - (2.63 and 3.76%)
- TSC1 or TSC2 mutations - (2.6-3.5%)

Presented By Lillian Siu at 2016 ASCO Annual Meeting
Why precision?

- Targeted drugs follow a path of development addressing most frequent **genotype-cancer type** associations and are registered and marketed in these indications
  - In rare cancers if homogeneously mutated

- **Rare mutations or rare cancer type-genotype** associations do not enter such a development path easily

- The **same actionable mutations can occur in any cancer type**, not just in the registered cancer type

- Although there is a **high plausibility that the same drugs will work in these off-label indications**, the patients concerned remain without access to these treatments for a very long time
Precision Belgium components

• Implementing gene panel sequencing
  – Ongoing evaluation of NEXTgen platforms
  – Sequencing all established and emerging actionable genes
  – Cancer Centre > RIZIV/INAMI

• Establish national real-time shared database
  – Clinical data
  – Genomic data
  – Connected to e-health and Cancer Registry
  – Accessible to all investigators/oncologists

• Precision 1
  – Establish benefits of approach
  – Interinstitutional Molecular tumor board

• Precision 2
  – Establish new evidence on efficacy in specific genotype-cancer type associations
Actionable mutation identified

• Eligible for registered/marketed drug

• Eligible for ongoing pharma-sponsored trial
  – Precision 1

• Creation of multicohort basket trials
  – Precision 2
  – Open in each centre > ease of patient access
Multicohort basket trials

Figure 3: Basket clinical trial based on tumour genotype

Source: http://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials
Basket trial can demonstrate activity in off-label indications

Heyman et al n engl j med 373;8 August 20, 2015
Precision Belgium

Precision 1

- No actionable mutation
- Existing clinical trial matched drug
- Approved drug indication
- Actionable, but non-matched drug given

Precision 2

- Phase II with drug matched for specific mutation

Other mutation identification source

- Drugs registered in specific indication
- Involvement of all universities and their networks
- National coordinator
Current

Specific drug-tumor type- genotype combination
Development of new therapeutic gene targets
Expanding current drugs to all cancers with same mutation
Examples of precision 2 studies in process of activation

• Afatinib in HER1,2 or 3 mutated any cancer type
  – Boehringer Ingelheim

• Imatinib in KIT, PDGFR, bcr-abl mutated cancers
  – Novartis

• Olaparib in cancers with HRD gene mutations
  – Astrazeneca

• Dabrafenib/Trametinib in non-V600 BRAF mutant cancers
  – Novartis

• Other trials in development
Deliverables of Precision

• Large genotype-tumor type cohorts
  – Create evidence for drug registration

• Small genotype-tumor type cohorts
  – Pool evidence with similar international efforts

• Tapur, US; France, Netherlands,...
Advantages for all stakeholders

• **Patients**
  – Access to additional therapeutic options

• **Research**
  – Broad cooperation will generate a context on which fundamental projects can be grafted

• **Government**
  – Collaboration with Federal health care stakeholders at the early stage of development of this program will set the stage to develop an adequate health care infrastructure in Belgium suitable to implement all aspects of Precision medicine, not limited to sequencing technologies

• **Pharma**
  – Access to new evidence created on off-label drug activity
  – Systematic sequencing makes our patient population more attractive for pharma-sponsored trials
Additional path to registering drugs in specific genotype-cancer type associations
Other applications of sequencing

• Determine sensitivity/resistance to classical therapies
  – Olaparib: targeted agent and chemotherapy
  – Hormonal therapy breast cancer
    • ESR1 mutations

• Sequencing of circulating tumor DNA
  – Following disease response easily
  – Early detection of cancer
  – Selection for immunotherapies
Cancers with high mutation rate

Immunotherapy
- Checkpoint inhibitors
- Mutanome vaccination
Acknowledgements

• BSMO initiative
• Seven University Medical Oncology departments and their networks
  – Including pediatric oncology and hematology
• Supported by the Foundation against cancer
• In collaboration with the Cancer Centre
  – Maggie De Block investment in Personalized Medicine
• In collaboration with Pharma (drugs)
Precision executive committee

– Roberto Salgado
– Lore Decoster, Philippe Aftimos
– Marc Vanden Bulcke (Cancer Centre)
– Jacques De Grève (BSMO)
Precision steering committee

- Ahmad Awada - Bordet
- Philippe Aftimos – Precision 1
- Cauwelier Barbara – Hemato-oncology
- Guy Berchem – CH Luxembourg
- Joelle Collignon - CHU Liege
- Lore Decoster – Precision 2
- Jacques De Grève – UZ Brussel, Precision Chair
- Francois Duhoux - UC Louvain
- Sandra Jacobs - Pediatric oncology
- Kevin Punie- KU Leuven
- Christian Rolfo - UZ Antwerpen
- Sylvie Rottey – UZ Gent
- Roberto Salgado – Molecular pathology
- Marc Van den Bulcke - Cancer Centre
- Didier Vandersteichele - STK/FCC