Belgian Society of Medical Oncology

“Precision”

Bringing innovation to the patient

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

For the Precision Steering committee
Cancer, a high medical need

![Cancer Incidence and Mortality Diagram]

Cancer registry
Cancer

• Second cause of disease related fatality

• Local treatments: surgery and radiotherapy

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

Rosell 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\(^a\)**

<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>

\(^a\)Composite of chest pain, cough, and dyspnea

No. at risk
- Crizotinib: 162, 71, 40, 17, 9, 2, 0
- Chemotherapy: 151, 30, 13, 3, 1, 1, 0

ESMO 2012
Also active in brain metastases

Response in 1 mth; 8+ mth

Many targets in lung cancer

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

All targetable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
All targetable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
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.
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>Total</td>
<td>11</td>
<td>6 ALK+, 3 MET+, 2 ROS1</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>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>CR</td>
<td>9.5+</td>
</tr>
<tr>
<td>ALCL</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 across cancer types

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

breast cancer

Stephens, Nature 2012
Targetable Oncogenic Drivers in Human Cancers

- **CML**: BCR-ABL
- **GIST**: CKIT
- **Melanoma**: BRAF
- **Breast**: HER2
- **Lung**: EGFR, ALK, ROS1

Currently approved major targeted therapies

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Many more genes are currently 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>
<tr>
<td>Nivolumab</td>
<td>MMR deficiency (IHC: MLH1, MSH2)</td>
</tr>
</tbody>
</table>

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%)

reopened in May 2016 with a total of 24 treatment arms. Each arm expects to enroll a maximum of 35 patients

NCI-Molecular Analysis for Therapy Choice

https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match
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.

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

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

- 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 (years).
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
  – Investigate benefits of approach
  – Interinstitutional Molecular tumor board

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

Philippe Aftimos
Lore Decoster
NGS part

• Cancers systematically sequenced
• Consensus gene panel (Compermed)
• National database healthdata
  – Storage of anonymous information
  – Sequencing results: stored as VCF files
  – Clinical data
• Automated upload from centers
<table>
<thead>
<tr>
<th>Tumor types</th>
<th>Nomenclature (example)</th>
<th>Gene panels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor specific gene panels</td>
<td>ComPerMed gene panel</td>
</tr>
<tr>
<td>Tumor A</td>
<td>300.1</td>
<td>Gene 1, Gene 2, Gene 3, Gene 4, Gene 5, Gene 6, Gene 7, Gene 8, Gene 9, Gene 10</td>
</tr>
<tr>
<td>Tumor B</td>
<td>300.2</td>
<td>Gene 4, Gene 5</td>
</tr>
<tr>
<td>Tumor C</td>
<td>300.3</td>
<td>Gene 4, Gene 3, Gene 6, Gene 7</td>
</tr>
<tr>
<td>Tumor D</td>
<td>300.4</td>
<td>Gene 5, Gene 8, Gene 9, Gene 10</td>
</tr>
</tbody>
</table>

1. **Genes** which **MUST be** analyzed for the analyzed tumor: (level 1 & 2)

2. Laboratories are **allowed** to analyze more genes.

3. Laboratories are allowed to use **either**:
   (a) A tumor specific gene panel **or**
   (b) The ComPerMed gene panel

4. For the reimbursement:
   (a) If < xx kb (calculated on the basis of the minimal set of genes for the analyzed tumor (level 1&2) → amount to be discussed (INAMI/RIZIV)
   (b) If > xx kb (calculated on the basis of the minimal set of genes for the analyzed tumor (level 1&2) OR the ComPerMed gene panel → Reimbursement higher than (a) → amount to be discussed (INAMI/RIZIV)

NB: If laboratories add more genes than those which are present in the ComPerMed gene panel, these will not be reimbursed.

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Laboratory can choose to use either a tumor specific gene panel or the ComPerMed gene panel. The ComPerMed gene panel contains all the genes included in the different tumor specific gene panels.

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**Dr Aline Herbrant**
Cancer center
One gene panel that covers all actionable mutations (established, emerging) in all cancers should be strongly favored

- Currently only 24 genes
- Not that more expensive than tumor-specific panels
- Identification of rare mutations
- Avoids resequencing² efforts
  - Not timely for the patient
  - Added cost
  - Cfr. germline management
- **Precision Belgium impossible without the comprehensive panel**
- **Budgetary concerns to be relativized:**
  - 10K pts x 500€ = 5.000K€
  - Pembrolizumab in first-line lung cancer: 30-50,000K€ (modest estimate)
Actionable mutation identified

1. Eligible for registered/marketed drug
2. Eligible for ongoing pharma-sponsored trial
   Precision 1

3. Creation of multicohort basket trials
   1. Precision 2
   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

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
Clinical Trials in the Era of Genomics and Personalized Medicine

Mateo, ASCO edu 2016
Examples of precision 2 studies in process of activation

- Afatinib in HER1,2 or 3 mutations in any cancer type
  - Boehringer Ingelheim
  - Activation ongoing

- Imatinib in KIT, PDGFR, bcr-abl mutated cancers
  - Novartis
  - In negotiation

- Olaparib in cancers with HRD gene mutations
  - Astrazeneca
  - In development

- Dabrafenib/Trametinib in non-V600 BRAF mutant cancers
  - Novartis
  - In negotiation

- Other trials in development
Precision 2: an open explorative phase 2, open label study on afatinib in the treatment of advanced cancer carrying an EGFR, HER2 or HER3 mutation
Study objectives

• Primary:
  – Response rate on afatinib in cancers harboring an EGFR mutation, a HER2 mutation or a HER3 mutation

• Secondary:
  – Disease control rate
  – PFS and OS
  – Safety
  – To study resistance mechanisms
  – Response and PFS on the combination of afatinib and paclitaxel after progression on afatinib
Main in- and exclusion criteria

- Histologically confirmed advanced cancer harbouring an EGFR, HER2 or HER3 mutation
- Failure of at least one previous line of standard treatment
  - No restriction to the number of previous lines
- No other genomic driven trial for the specific tumor type or patient not eligible
- Age ≥18
- ECOG PS ≤2
- Life expectancy > 3 months
- Adequate organ function
- Measurable lesion
- No EGFR mutant non squamous NSCLC
Treatment

• Treatment period 1
  – All patients treated with afatinib until progression, unacceptable toxicity or withdrawal of consent

• At progression
  – Preferable rebiopsy to study resistance mechanisms
  – Fulfill all eligibility criteria for treatment period 2

• Treatment period 2
  – All patients treated with afatinib in combination with paclitaxel weekly until progression, unacceptable toxicity or withdrawal of consent
Deliverables of Precision

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

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

• Create a platform for scientific collaboration
  – Also fundamental research

• Systematic sequencing makes our population more attractive for pharma-sponsored trials
Advantages for all stakeholders

• Patients
  – Access to additional therapeutic options

• Pharma
  – Access to new evidence created on off-label drug activity

• Research
  – Broad cooperation will generate a platform on which more fundamental projects can be grafted
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
  – Including Luxemburg
• Supported by the Foundation against cancer
• In collaboration with the Cancer Centre
  – Maggie De Block investment in sequencing
• In collaboration with pharma (drugs)
Current infrastructure

• Coordinator
• Part-time datamanagers in each university and its network
• Cancer Centre support
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