Precision medicine in cancer: future or illusion?

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BSMO
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Or already present?
Precision medicine in oncology is already happening, the only question is: **what is affordable?**

1. Patient characteristics
2. Cancer type
3. Immunohistochemical markers (ER)
4. Genotyping (RNA/DNA)
5. Immune biomarkers: TIL/PD-L1 expression for immune checkpoint inhibitors
Current cancer treatments

• Local: surgery and radiotherapy

• **Systemic treatments**
  1. Chemo
  2. Hormonal
  3. Targeted
  4. Immunotherapy
     1. Immune checkpoint inhibitor
     2. Personalized cell therapies
Prediction response to immune checkpoint inhibitors

Mutation load and neo-antigens

Lymphocytic infiltrates

PD-L1 expression
Therapeutic targets: oncogenes that drive the cancer

1. Targeted gene sequencing
2. Gene panels
3. Whole exome or genome
Treatments

• Monoclonal antibodies
  • Surface oncogenic receptors

• Small molecules
  • Intracellular targets
Both somatic mutations in cancer genes and germline mutations in cancer predisposition genes can be therapeutic targets.
Predictive power of genotyping for targeted treatments: varying magnitude

• Mutant protein
  • Mutant c-kit in GIST
  • bcr-abl in CML
  • Mutant EGFR in lung cancer
  • ALK-fusion in lung cancer
  • ......

• Overexpression < gene amplification
  • HER-2 in breast cancer

• Driven expression
  • VEGF in RCC, brain tumors and OVCA

• Physiological expression of wild-type protein
  • EGFR in NSCLC
Important genomic stratification of lung cancer

All actionable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
But also in many other cancers

Garraway jco 2013
Impressive therapeutic results

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
Erlotinib in EGFR mutated lung cancer

Alk targeting: crizotinib

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\textsuperscript{a}

\begin{table}
\centering
\begin{tabular}{llll}
\hline
 & \textbf{Crizotinib (n=162)} & \textbf{Chemotherapy (n=151)} \\
\hline
\textbf{Events, n (%)} & 91 (56) & 111 (74) \\
\textbf{Median, mo} & 5.6 & 1.4 \\
\textbf{HR (95% CI)} & 0.54 (0.40 to 0.71) & \\
\textbf{P} & \textless 0.0001 & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Composite of chest pain, cough, and dyspnea

ESMO 2012
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.
Also active in the brain

Response in 1 mth; 8+ mth

Second generation: alectinib

A Progression-free Survival

B Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>364/303</td>
<td>0.48 (0.35–0.66)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>125/230</td>
<td>0.48 (0.34–0.70)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>239/77</td>
<td>0.45 (0.24–0.87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91/171</td>
<td>0.39 (0.25–0.60)</td>
</tr>
<tr>
<td>Male</td>
<td>73/132</td>
<td>0.61 (0.38–0.98)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>72/138</td>
<td>0.46 (0.28–0.75)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>92/165</td>
<td>0.49 (0.32–0.75)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td>12/17</td>
<td>1.16 (0.35–3.90)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>101/190</td>
<td>0.44 (0.29–0.66)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>49/96</td>
<td>0.42 (0.21–0.77)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44/97</td>
<td>0.40 (0.21–0.77)</td>
</tr>
<tr>
<td>1</td>
<td>102/186</td>
<td>0.48 (0.32–0.71)</td>
</tr>
<tr>
<td>2</td>
<td>11/20</td>
<td>0.74 (0.35–2.25)</td>
</tr>
<tr>
<td>CNS metastases at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78/122</td>
<td>0.40 (0.25–0.64)</td>
</tr>
<tr>
<td>No</td>
<td>86/181</td>
<td>0.51 (0.33–0.80)</td>
</tr>
<tr>
<td>Previous brain radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26/47</td>
<td>0.33 (0.14–0.74)</td>
</tr>
<tr>
<td>No</td>
<td>138/256</td>
<td>0.52 (0.36–0.73)</td>
</tr>
</tbody>
</table>

C Cumulative Incidence of CNS Progression

D Overall Survival

Hazard ratio for death, 0.76 (95% CI), 0.48–1.00
P=0.24 by log-rank test

No. at Risk

Alectinib: 152 142 131 127 119 107 87 81 73 61 24 5

Crizotinib: 151 141 137 115 103 95 73 33 13 1

Peters et al, NEJM 2017
Some targets are rare

Alle actionable (routine or investigational)

Presented By Charles Rudin at 2014 ASCO Annual Meeting
Some targets are rare

**ROS1 rearrangements in NSCLC**

- ROS1 is receptor tyrosine kinase of the insulin receptor family
- *ROS1* gene fusions are potential driver mutations and are present in ~1% of NSCLC cases
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

But they respond as well
Levels of genomic analysis

1. *Companion diagnostics* for individual reimbursed drugs

2. Next Generation Sequencing (NGS)
   - Organ-oriented panels for reimbursed drugs
     - Aline Herbrant, Els Vanvalckenborg, Sciensano
     - Anouk Waeytens, Compermed & RIZIV
   - Organ-agnostic panels (independent of tumor type)
   - Broad panels for all actionable genes
     - Including investigational drugs in development
   - Panels also including explorative targets

3. Whole genome/exome
Current Clinical practice

1. *Companion diagnostics* for reimbursed drugs

2. NGS (not yet reimbursed)
   - Organ-oriented panels for reimbursed drugs
     - Aline Herbrant, Els Vanvalckenborg, Sciensano
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Current Clinical practice

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3. Whole genome/exome
Everything that is missed

• Other cancer types (than the ones specifically foreseen for reimbursement) can carry the same mutations

• Mutations selecting for novel therapies
  • Ad hoc searching for patients that have these mutations in their tumor or germline is like looking for a needle in a haystack & severely hampers accrual in genotype-driven clinical trials
Mutations that are typically associated with particular cancer types also can be found in many other cancer types with variable therapeutic sensitivity.

**BRAF targeting**

• Yes, they are all rare, but there are many different ones

• Many rare ones together make a big one

• Even rare patients have a right to the most effective therapy
Example of rare mutation

• SN, female, 50 yrs

• Pancreatic cancer, 6 cm with diffuse liver mets
  • Pain and pressure on the stomach > feeding problems

• Molecular typing
  • KRAS : no mutation
  • Academic NGS sequencing (50+ genes): no mutations

• Chemotherapy
  • Response with disappearance of symptoms
  • Disease progression after 5 months
Example of rare mutation
Example of rare mutation

• Broader sequencing (FoundationOne) (> 300 genes)
  • RET rearrangement
  • RET mutated/rearranged in 1% of pancreatic cancers
Example of rare mutation

Genomic Alterations Identified†

* RET  GP2-RET fusion
* CDKN2A  loss
* GATA1  L136* – subclonal*
* SPTA1  Q2384K

Additional Findings†

* Microsatellite status  MS-Stable
* Tumor Mutation Burden  TMB-Low; 5 Muts/Mb

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix
* See Appendix for details
Example of rare mutation

<table>
<thead>
<tr>
<th>Genomic Findings Detected</th>
<th>FDA-Approved Therapies (in patient’s tumor type)</th>
<th>FDA-Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>None</td>
<td>Cabozantinib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>GP2-RET fusion</td>
<td></td>
<td>Lenvatinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ponatinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vandetanib</td>
<td></td>
</tr>
<tr>
<td>CDKN2A loss</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CDKN2A loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GATA1 L136* - subclonal</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Microsatellite status</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>MS-Stable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPTA1 Q2384K</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Example of rare mutation

• R/ Alectinib
  • PR> focal progression> chemo-embolisation> alectinib continued
  • Now nine months symptom-free
RET mutations/rearrangements occur in many other cancer types

The prevalence of RET alterations varies by tumor type

**RET fusions**
- NSCLC (≈1% to 2%)\(^1\)
- PTC (≈10%)\(^1,2\)

**RET mutations**
- MTC (Approx. 60%)\(^1\)
- Meningioma (5.6%)\(^2\)
- Esophageal adenocarcinoma (1.4%)\(^2\)
- Breast carcinoma (0.2%)\(^2\)
- Melanoma (0.7%) and basal cell carcinoma (12.5%)\(^2\)
- Gastric adenocarcinoma (0.7%)\(^2\)
- Ureter urothelial carcinoma (16.7%)
- Colorectal adenocarcinoma (0.7%)\(^2\)

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PTC, papillary thyroid cancer.
RET mutations/rearrangements are actionable independent of cancer type

LOXO-292: agnostic activity in RET fusion+ cancers

Histology-agnostic activity of LOXO-292 in RET fusion+ cancers

Diagram showing the maximum change in tumor size across different tumor types (NSCLC, Thyroid, Pancreatic). The graph indicates a decrease in tumor size for all types, with Thyroid and Pancreatic tumors showing the most significant changes.
Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach
Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach

Integrated dataset: Larotrectinib is efficacious regardless of tumor type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Maximum Change in Tumor Size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile fibroblastoma</td>
<td>+53.2</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>-15</td>
</tr>
<tr>
<td>Thyroid</td>
<td>-10</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>-5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-5</td>
</tr>
<tr>
<td>Breast</td>
<td>-5</td>
</tr>
<tr>
<td>Appendix</td>
<td>-5</td>
</tr>
<tr>
<td>Colon</td>
<td>-5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>-5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>-5</td>
</tr>
<tr>
<td>Congenital mesoblastic nephroma</td>
<td>-5</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>-5</td>
</tr>
<tr>
<td>Bone sarcoma</td>
<td>-5</td>
</tr>
</tbody>
</table>

ORR (95% CI) 81% (72-86%)

Best response:
- PR 83%
- CR 17%

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements. CR, complete response; ORR, objective response rate; PR, partial response.
Pembrolizumab: agnostic activity in MSI-high cancers


Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

Le et al
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Frequency, % (n)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>13% (1066)</td>
<td>Hampel et al. (72)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>22% (543), 33% (446)</td>
<td>Zighelboim et al. (73), Hampel et al. (74)</td>
</tr>
<tr>
<td>Gastric</td>
<td>22% (295)</td>
<td>TCGA (75)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>16% (37)(^a)</td>
<td>Chiappini et al. (76)</td>
</tr>
<tr>
<td>Ampullary carcinoma</td>
<td>10% (144)</td>
<td>Ruemmele et al. (77)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>63% (30)(^a)</td>
<td>Mitmaker et al. (78)</td>
</tr>
<tr>
<td>Skin (sebaceous tumors)</td>
<td>35% (20)(^a), 60% (25)(^a)</td>
<td>Cesinaro et al. (79), Kruse et al (80)</td>
</tr>
<tr>
<td>Skin (melanoma)</td>
<td>11% (56)(^a)</td>
<td>Palmieri et al. (81)</td>
</tr>
</tbody>
</table>

\(^a\) Studies of less than 100 patients.
Table 2. Cancers with an MSI-H frequency between 2% and 10%

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Frequency, % (n)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>10% (1234)</td>
<td>Murphy and Wentzensen (82)</td>
</tr>
<tr>
<td>Cervical</td>
<td>8% (344)</td>
<td>Lazo (83)</td>
</tr>
<tr>
<td>Esophageal adenocarcinoma</td>
<td>7% (76)</td>
<td>Farris et al. (84)</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>5% (40)</td>
<td>Kawaguchi et al. (85)</td>
</tr>
<tr>
<td>Head and neck SCC</td>
<td>3% (153)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Glavac et al. (86)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>2% (152)</td>
<td>Hammerschmied et al. (87)</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>2% (55)</td>
<td>Alldinger et al. (88)</td>
</tr>
</tbody>
</table>

Table 3. Cancers with an MSI-H frequency less than 2%

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Frequency, % (n)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (squamous cell)</td>
<td>0% (30), 0% (56)</td>
<td>Reuschenbach et al. (89)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Skin (basal cell)</td>
<td>0% (53), 2% (104)</td>
<td>Reuschenbach et al. (89)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prostate</td>
<td>1% (79)</td>
<td>Burger et al. (90)</td>
</tr>
<tr>
<td>Lung</td>
<td>0% (80), 2% (55)</td>
<td>Okuda et al. (91), Ninomiya et al. (92)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0% (68)</td>
<td>Entz-Werle et al. (93)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>0% (109)</td>
<td>Martinez et al. (94)</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>0%-2% (338)</td>
<td>Laghi et al. (95)</td>
</tr>
<tr>
<td>Breast</td>
<td>0% (267), 0% (34), 0% (52), 1% (100)</td>
<td>Anbazhagan et al. (96), Adem et al. (97), Kuligina et al. (98), Toyama et al. (99)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1% (84)</td>
<td>Catto et al. (100)</td>
</tr>
<tr>
<td>Testicular germ cell</td>
<td>0% (100)</td>
<td>Mayer et al. (70)</td>
</tr>
</tbody>
</table>
Many rare ones together make a big one

There is a ‘long tail’ of hotspot mutations across different cancers

- KRAS G12
- BRAF V600
- IDH1 R132
- PIK3CA H1047
- PIK3CA E545
- TP53 R273
- NRAS Q61

85% of all hotspot mutations affect <5% of any cancer type in which they are found

Presented at: 2018 ASCO Annual Meeting
Presented by: Dr. Alexander Drilon
Broad agnostic sequencing and clinical translation needed

Actionable alterations can be detected across cancers in the clinic

10,000 clinical samples of advanced solid tumors profiled by MSK-IMPACT next-gen sequencing

Level 1: FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A: Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B: Standard of care biomarker for an FDA-approved drug in another indication
Level 3A: Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B: Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication

Matched therapies identified

Zehir et al, Nature Med 2017

Presented By Alexander Drilon at 2018 ASCO Annual Meeting
Further validation of yet unexplored cancer type-genotype associations

Tumor agnostic therapy = targeting oncogenic drivers regardless of tissue histology

**Tumor agnostic drug development can address the ‘long tail’**

- **Histology-specific drug development**
  - Traditional designs
  - Umbrella trials

- **Alteration-specific drug development (agnostic of tumor type)**

**BASKET TRIAL**
- One qualifying group of alterations
- Tumor agnostic patient accrual

Drillon A ASCO 2018
Clinical Trials in the Era of Genomics and Personalized Medicine

Biomarker Clinical Qualification

1. Preclinical studies
   - Proof-of-concept clinical trials
2. Adaptive trials
   - Umbrella studies
   - Confirmatory studies (phase III trials)

Exceptional responders series
Basket trials

Post-Marketing Evaluation

Exceptional circumstances (i.e. low prevalent disease, uncommon biomarker)

Mateo, ASCO edu 2016
Belgian Society of Medical Oncology
The Precision initiative

a collaboration between Belgian university hospitals and pharmaceutical industry to give cancer patients access to a broader spectrum of cancer medicines
Precision steering committee

• Philippe Aftimos - Bordet, Precision 1
• Cauwelier Barbara – Hemato-oncology
• Joelle Collignon - CHU Liege
• Francois Duhoux - UC Louvain
• Sandra Jacobs - Pediatric oncology
• Jacques De Grève - Chair
• Lore Decoster - UZBrussel, precision 2
• Kevin Punie- KU Leuven
• Marika Rasschaert- UZ Antwerpen
• Sylvie Rottey - UGent
• Roberto Salgado - Molecular pathology
• Marc Van den Bulcke - Cancer Centre
• Didier Vandersteichele - STK/FCC
Precision Belgium components

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

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

• Precision 1
  • Establish benefits of genotype driven treatment
  • Interinstitutional Molecular tumor board

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

Philippe Aftimos
Lore Decoster
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
Ongoing Precision studies

- Afatinib in HER1,2 or 3 mutations in any cancer type
  - Recruiting
- Olaparib in cancers with HRD gene mutations
  - Activated

Proposed Precision studies

- Imatinib in KIT, PDGFR, bcr-abl mutated cancers
- Dabrafenib/Trametinib in non-V600 BRAF mutant cancers
- Alpelisib in Pi3K mutant cancers
- Ret inhibitor in RET mutant/rearranged cancers
Advantages (of tissue-agnostic testing) for stakeholders

• Patients
  • Access to additional therapeutic options

• Pharma
  • Patient selection (for trials)
  • Data on efficacy in rare cancer-genotype associations

• Academic research
  • Platform also for scientific collaborators

• Authorities
  • Better insights in real world
To be able to conduct these trials or serve patients in whose disease the specific gene already has been validated as actionable, we need a systematic tissue-agnostic approach to sequencing.
What we need: broad agnostic somatic gene panel

1. *Companion diagnostics* for reimbursed drugs

2. **NGS**
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   - Agnostic panels (independent of tumor type)
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3. Whole genome/exome
Obstacles for Precision

• Content
  • Absence of tumor-agnostic sequencing
  • Absence of many actionable genes, even in academic gene panels
  • Amount of tissue

• Politics
  • Conservative attitude in pathology and genetics
    • A genomic test is NOT research, only the subsequent use could be research
  • Budget
Staged agnostic sequencing in cancer

Proposal

Belgian Precision study

BSMO in collaboration with the Cancer Centre
Rationale

- **Broader panels** applied by some Belgian platforms (+/- 50 genes), sometimes in an agnostic approach, do not cover all potentially actionable genes or not all types of sensitizing mutations in these genes.

- **Rearrangements** which are highly actionable are not systematically covered in NGS testing, but rely on less sensitive immunohistochemistry (if done at all).

- **Belgian NGS labs** are accredited but have heterogeneous methodology and it has been reported that the mutation detection rate varies from one region to another, pointing possibly towards methodological issues.
Rationale

- **More comprehensive commercial platforms** that cover all actionable genes (up to hundreds of genes) and the various types of mutations in these genes: sequence alterations, rearrangements, resulting in fusion genes, and gene amplifications
  - These commercial vendors have adequate comprehensive methodology but are currently too expensive (at their current public pricing) for general application

- **Example: Foundation Medicine (FoundationOne)**
  - builds on a large experience in variant annotation in the US and includes probably most if not all current actionable targets including gene mutations, fusions, MSI, a surrogate for tumor mutational burden etc., all at once in one result
  - Report actionability and indicates established or clinical trial treatment options
Hypothesis

• We expect that up to 20% of patients who failed in the reimbursed organ-specific NGS could have a mutation that is someway actionable

• Test would be applicable to an estimated 5-10K patients with advanced cancer per year
  – high attrition rate after baseline diagnostics and standard therapies, as many patients are not eligible for further line therapies
  – no utility of genotype targeted therapies in end-stage patients or patients with a poor performance status
Study

- **Eligibility**
  - Advanced cancer patients that have failed at least one first-line standard treatment
  - Patients have had a reimbursed organ-specific sequencing panel that was negative
  - Life expectancy of at least 3 months
  - Open to all patients

- **Eligible patients will**
  - Have FoundationOne sequencing (epithelial/sarcoma) on their tumor
  - Treatment based on the FoundationOne result

- **Explorative study in 1000 patients**

- **24 months for recruitment through the Precision network**

- **The commercial partner would provide the testing at a reduced rate (compared to public pricing)**
  - increases the potential for maximizing the return on investment
Measurable outcomes

• **What is the added value of comprehensive and agnostic NGS after reimbursed NGS**
  – Document magnitude of the real life need & the utility of this approach
  – Provide an estimate of the budgetary implications
  – Comparator is the first-line genomic testing using reimbursed NGS
  – Quality and sensitivity control on reimbursed NGS

• **The study would inform the authorities (RIZIV) about the amplitude and cost-effectiveness of comprehensive sequencing**

• **Academic platforms would gain knowledge from the exercise**
Example

• Male patient, 30 years with ultrarare disease
  – Multiple fibroblastic tumors
  – One cervical spine location, next to CNS: needs carbon therapy in Heidelberg

• Academic panel sequencing: no mutations

• FoundationOne: PDGFRβ pathogenic mutation

• Can be treated with imatinib
Conclusion

• Precision medicine is there

• Routine genomic diagnosis does not implement all what is possible, withholding significant treatments for patients and severely hampering clinical trial accrual

• Because of budgetary concerns we propose a prospective staged large panel sequencing project that could inform about the utility and improve current practice
Current routine standard for every cancer patient should be:

1. Broad agnostic tumor panel sequencing of the tumor DNA/RNA

2. Whole genome sequencing of the germline DNA with cancer gene panel analysis
Personalized application of sequencing: mutanome

- Immune therapy (TMB)
- Mutanome vaccination
- Expansion of mutation-directed TILS

Zacharakis, Nature medicine 2018
Future: whole genome

• 9,423 tumor exomes en 26 computational tools to catalog driver genes and mutations

• 299 driver genes with therapeutic/clinical implications

• >3,400 putative missense driver mutations
  • 60%–85% of predicted mutations likely drivers
  • 300 MSI tumors are associated with high PD-1/PD-L1,

• 57% of tumors analyzed harbor putative clinically actionable events

Bailey et al., 2018, Cell 173, 371–385