Roche Foundation Medicine:

Diagnostic innovation and personalised therapeutic opportunities for cancer patients

Roberto Scalamogna, Biomarkers Leader

June 7TH 2018
The benefit of personalized therapy

346 phase I trials, 13,202 patients

Treatment-related mortality: 1.9 vs 2.3%, p=0.31

Schwaederle et al. ASCO 2016; Abstract 11520
The benefit of personalized therapy

570 phase II trials, 32,149 patients

Treatment-related death rate: 1.5 vs 2.3%, p<0.001

Treating Lung Cancer patients based on their tumour profiling results improves outcomes

Kris MG et al (2014); JAMA 311 (19)
Barlesi R et al (2016); Lancet So140-6736
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Molecular Pathway</th>
<th>Clinical Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>ALK</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cotellic</td>
<td>MEK</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>hedgehog</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Obinutuzumab &amp; Rituximab</td>
<td>CD20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ipatasertib</td>
<td>PI3K/AKT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab, Pertuzumab, TDM-1</td>
<td>HER2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PDL1/TMB</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Polatuzumab Vedotin</td>
<td>CD79b</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>NTRK/ROS1/ALK</td>
<td>+</td>
<td>+</td>
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</table>
We are uniquely positioned to lead in PHC 2.0

Roche Group

Our science and products

Our partners
Diagnostic Capabilities Enable Precision Medicine

Cancer Biomarker Panel

Tumor
- Gene Expression
- CD8 IHC
- Target expression
- Multiplex Immune IHC
- Molecular Imaging

Blood
- Cytokines/chemokines
- Immune Cell Subsets
- Gene Expression
- Multiplex Immune IHC
- Molecular Imaging

CD8 IHC
- Target expression
- Multiplex Immune IHC
- Immune Cell Subsets
Cancer Treatment in the Future?

"Here's my sequence"

A. Bacall, The New Yorker
Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study

John D. Hainsworth, Funda Meric-Bernstam, Charles Swanton, Herbert Hurwitz, David R. Spigel, Christopher Sweeney, Howard Burris, Ron Bose, Bongin Yoo, Alisha Stein, Mary Beattie, and Razzelle Kurzrock


**HER2 amplified / overexpressing**

• CRC1 38% ORR overall; 50% CBR; DOR = 10 months ()
• Salivary cancer2 63% ORR; 88% CBR; DOR = 9 months
• Bladder cancer3 33% ORR; 56% CBR; DOR = 6 months
• Biliary cancer4: 38% ORR; 75% CBR; DOR = 3 months

**BRAF V600E NSCLC**

• NSCLC5 Vemurafenib monotherapy: 40% ORR; 53% CBR; DOR = 5 months
Driving personalized healthcare forward

*Personalize treatment through understanding of a patient’s tumor*

### Blockbuster medicines

- Large: unspecified

### Targeted therapies

- Medium: sub-group
- Single disease marker

### Personalized treatments

- Small: individual patient
- Comprehensive NGS & response monitoring
- Personalized combos of targeted & CIT agents

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**Target population**

- Large: unspecified
- Medium: sub-group
- Small: individual patient

**Diagnostics**

- No specific biomarkers
- Single disease marker
- Comprehensive NGS & response monitoring

**Treatment**

- One medicine fits all
- Targeted agents
- Personalized combos of targeted & CIT agents

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NGS=Next generation sequencing; CIT=Cancer Immunotherapy
Foundation Medicine
A new molecular information

- Founded 2010 in Cambridge, MA, USA
- Proprietary molecular information platform
- 200,000+ clinical cases profiled
- 30+ pharmaceutical clinical trial partners
- Roche collaboration for R&D and commercialization outside USA
Applies next-generation sequencing to identify genomic alterations across 315 cancer-related genes known to be drivers of solid tumors plus select introns of 28 genes.

Designed to analyze and interpret DNA sequence information of 405 genes and RNA sequence (cDNA) information of 265 commonly rearranged genes in hematologic malignancies.

A liquid biopsy Assay for Circulating Tumor DNA, interrogating all known classes of genomic alteration across 62 genes. Provides validated, blood-based profiling when tissue biopsy may not be feasible.

Microsatellite instability (MSI)
Tumor mutational burden (TMB)

A single solution for simultaneous assessment of MSI and TMB biomarkers – previously separate and time- and labor-intensive tests. Will provide additional and relevant genomic clues as to which patients may benefit the most from certain immunotherapies.

FMI’s current services
Comprehensive Dx and molecular information

NEW PLATFORM

NEWLY IMPLEMENTED FEATURE OF FOUNDATIONONE®
**Foundation Medicine:**

*CGP solutions for Oncology*

### Patient Information

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Not Given</th>
<th>Medical Facility</th>
<th>Not Given</th>
<th>Report Date</th>
<th>02 September 2015</th>
<th>Tumor Type</th>
<th>Lung adenocarcinoma</th>
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<tbody>
<tr>
<td>Sex</td>
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<td>Ordering Physician</td>
<td>Not Given</td>
<td>Specimen Received</td>
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<td>Specimen Site</td>
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<td>FMI Case #</td>
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<td>Date of Collection</td>
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<td>Specimen Type</td>
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<td>Specimen ID</td>
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<td>Pathologist</td>
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</tbody>
</table>

### About the Test:

FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

### Tumor Type: Lung Adenocarcinoma

#### Genomic Alterations Identified

- ERBB2 A775_G776insYVMA
- CTNNB1 S37F
- MDM2 amplification
- FRS2 amplification
- NFKB1 amplification
- MET amplification
- SLT2 A170F
- U2AF1 S34F

#### Additional Disease-relevant Genes with No Reportable Alterations Identified

- ALK
- KRAS
- RET
- EGFR
- BRAF

### Patient Results

- 8 genomic alterations
- 4 therapies associated with potential clinical benefit
- 1 therapy associated with lack of response
- 12 clinical trials

### Therapeutic Implications

<table>
<thead>
<tr>
<th>Genomic Alterations 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>ERBB2 A775_G776insYVMA</td>
<td>Afatinib</td>
<td>Ado-trastuzumab emtansine</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(+) Lapatinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pertuzumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>CTNNB1 S37F</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>MDM2 amplification</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>FRS2 amplification</td>
<td>None</td>
<td>None</td>
<td>None</td>
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</table>
Cancer of unknown primary (CUP)

Cancer spreads from an unknown site to other parts of the body

Brain metastasis

Lung metastasis

Unknown primary tumour

‘CUP’ is defined by the lack of a primary site

Survival for patients with CUP is not improving

CUP cases from the Swedish Cancer Registry

- Relative 1-year-survival ~20%
- Relative 5-year-survival ~10% - 15%

CUP: cancer of unknown primary
A multi-arm trial in cancer of unknown primary patients based on molecular profiling

**Study overview**

**Eligibility review**
- Histologically-confirmed CUP (non-specific subset)
- Confirmation of CUP (non-specific subset) at central laboratory
- No prior lines of therapy
- ECOG PS 0 - 1
- ≥ 1 measurable lesion
- Tumour tissue sample
- Blood sample

**Platinum-based chemotherapy (3 cycles)**

**MTB recommendation Investigator decision**

**Molecularly-guided therapy**

Loss of clinical benefit

**Category 1 patients**

**Category 2 patients**

**Day 1**

**EOI & PT Work-ups**

**Treatment Period**

**EOT**

**EOS**

**Screening Period**

**Induction Period**

## Therapy options

### Molecularly-guided therapies

<table>
<thead>
<tr>
<th>Targeted therapies</th>
<th>Identified actionable alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>ALK, RET rearrangements</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Inactivating <em>PTCH1</em>, activating <em>SMO</em> alterations</td>
</tr>
<tr>
<td>Ipatasertib*</td>
<td><em>AKT1</em>, <em>PI3K</em></td>
</tr>
<tr>
<td>Olaparib</td>
<td><em>BRCA1</em>, <em>BRCA2</em> or homologous recombination deficiency based on LOH</td>
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<tr>
<td>Vemurafenib + cobimetinib</td>
<td><em>BRAF</em> V600</td>
</tr>
<tr>
<td>Erlotinib + bevacizumab</td>
<td><em>EGFR</em></td>
</tr>
<tr>
<td>Trastuzumab SC + pertuzumab +</td>
<td><em>ERBB2</em> / <em>ERB3</em></td>
</tr>
<tr>
<td>chemotherapy a</td>
<td></td>
</tr>
</tbody>
</table>

### Immunotherapy

| Atezolizumab                        | TMB–High (≥ 16 mutations / Mb), MSI–High                             |
| Atezolizumab + chemotherapy a        | TMB–Low or Unknown (< 16 mutations / Mb)                              |

### Alternative therapies

Only if the investigator in consultation with the "Molecular Tumor Board" has strong evidence to support a therapy not represented in the nine investigational treatment arms above
Our stakeholders are moving to this future state

**Patients**
Increasingly generating/using technology and data to manage health

**Payers/Governments**
Embracing use of RWD for access and reimbursement, investing in PHC

**Physicians & Providers**
Growing interest in ‘big data’ & decision support tools

**Regulators**
Establishing regulatory frameworks that use RWD
Our Personalized Health Care aspiration
Increased patient impact

- Better Diagnosis
- BETTER PROGNOSIS
- Effective Clinical Trial Participation
- FEWER ADVERSE EVENTS
- Better Disease Monitoring
- OPTIMIZE TREATMENT SELECTION
- Improved Access to Therapies
Why not just perform a phase III trial?

- **RWD provides** a much larger and more heterogeneous patient pool, across various cancers
- Running **trials** are **costly**

Large, **independent** data pool of patient profiles creates **opportunities** to **demonstrate the value** of and further **develop personalised healthcare** in oncology.
Future healthcare data
Broad, deep, linked, and real-time data

<table>
<thead>
<tr>
<th>Total population in healthcare system</th>
<th>Today</th>
<th>Future</th>
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<tbody>
<tr>
<td>Intermittent, not real-time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mostly sub-scale</td>
<td></td>
<td></td>
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<tr>
<td>Not generalizable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data Access</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous, real-time</td>
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<td></td>
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<tr>
<td>Meaningful data at scale (MDAS)</td>
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<td></td>
</tr>
<tr>
<td>(depth, breadth &amp; quality)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalizable</td>
<td></td>
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</table>

Deep, linked data  Clinical data only
Our industry is accelerating

Top 20 Biopharma

Deals

- Comprehensive Diagnostics
- Genomic Data
- RWE
- Advanced Analytics
- Digital Health


2 12 18 34 ~60

Microsoft, Amazon, IBM, Apple, Facebook, Intel, BGI, NVIDIA, Alphabet, Baidu

SANOFI, Novartis, Merck, Lilly, Pfizer, Bristol-Myers Squibb
Ideal PHC healthcare ecosystem

Select, comprehensive partnerships to rapidly demonstrate full PHC environment

- **Data & insights sharing**
- **Value-based pricing**
- **Real time outcomes tracking**
- **Disease monitoring**
- **Policy/Legal changes to support PHC**

**Patient-linked cinico-genomic databases**

**Decision support**
Meaningful Data At Scale (MDAS)

Clinical Data

‘Omics

Imaging

Digital Health

LONGITUDINAL DATA OVER TIME

Understanding of disease and patient heterogeneity at unprecedented resolution

Rapid identification of patients for trial enrollment

Generalizable data for value-based care and patient access
Why is RWD particularly important for Roche FMI?

- Comprehensive genomic profiling (CGP)
- Patient report: Linking alterations to targeted therapies
- Treatment decisions
- Patient outcomes
- Pharmaco-economic outcomes

**RWD** needed to **bridge the evidence gap** between **CGP** and **beneficial outcomes**

- To further **develop** FMI services
- To demonstrate to **HCPs** the benefit of CGP and to provide them **support** on **clinical decision making**
- To demonstrate to **payers** the **added value of CGP**

**Interest to track** treatment decisions and outcomes after FMI profiling
Partnering with Flatiron
An example of an existing data source

Flatiron Health is a health technology company that creates **infrastructure** that can **organise, track** and **analyse anonymised data from cancer patients**, enabling researchers to **learn from real-world treatment experience**.

**Flatiron Provider Network**
Darkest color density represents highest patient concentration

- **265** Cancer clinics
- **2,500** Clinicians
- **1.7M** Active cancer patients in network

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Access an Integrated Patient Record
Streamline the Molecular Tumor Board
Identify Candidates for Clinical Trials

Gain Insights from Similar Patients
Analyze Real-World Outcomes
Identify Candidates for Molecular Testing

Aggregate Clinical Data
Integrate Structured Molecular Data
Our vision

*Innovation based on data insights*

*Improve R&D efficiency, access, & personalise patient care*
Building a bigger picture
For the benefit of the individual patient

The greater the collective amount of patient profiles, treatment and subsequent outcome data we have, the greater the picture we can build of cancer.

.. and the higher the likelihood of delivering a successful treatment plan for each individual patient.
Doing now what patients need next