Examples of personalized Healthcare implementation At Roche: Statistical perspectives

Laurent Essioux, BBS 4th June 2019
Personalized Health Care evolution at Roche

Drug and Diagnostics co development

Identification of biomarkers associated with Immune related adverse effects
MDM2 Antagonist (idasanutlin) Program Background

- MDM2 is a key negative regulator of the p53 tumor suppressor
- Idasanutlin blocks the MDM2-p53 interaction leading to stabilization and activation of p53 and tumor cell cycle arrest and apoptosis
- RO5045337 / MDM2(2) was the first MDM2 antagonist taken into the clinic
  - Showed exciting activity in AML Phase 1
  - Limited clinical development potential
- RO5503781 / Idasanutlin is an optimized new generation MDM2 antagonist with same MOA
  - New chemical class, enhanced binding specificity and increased potency

Idasanutlin in Accelerated development in AML pivotal Phase 3 trial
Idasanutlin response biomarker strategy
Targeting patients with active p53 in Acute Myeloid Lymphoma (AML)

1 - Selection of p53 wild type patients using sequence-based test (83% of AML patients p53 wt)

2- Selection patients with activated p53 pathway

Can a gene expression-based signature informing p53 pathway activation status, prior to therapy, with clinical useful predictive value of response to MDM2 inhibitor be developed?

- Can it outperform / complement p53 somatic mutation test?
- Does it outperform single gene assessment? (e.g MDM2 amplification assay)

➔ How to develop it using Phase I data to input Phase 3 assessment?
MDM2 inhibitor sensitivity variable selection procedure

- Tumor growth inhibition assay – mdm2 (2) inhibitor

287 tumor cell lines
- RNA-sequencing -> building block of the expression-based signature
- Exome Sequencing -> p53 status

Univariate filtering step
- Spearman correlation (IC50, RNA-seq)
- Logistic regression: Sensitivity~gene expression

Union the list with fdr<=0.05: 35 genes

Functional annotation
- p53-MDM2 pathway
  - 19 genes

Multivariate Variable selection
- Stepwise Multivariate regression selection (IC50)
- Stepwise Multivariate logistic regression selection (sens. vs res.)
  - BIC criteria & biological interpretation

MDM2, CDKNa1, XPC, BBC3 (PUMA)
Increasing Signature Score

Increasing Sensitivity

**IC50 MDM2(2) Log2 scale**

**MDM2(2), R=-0.70, P<2e-16**

*Multivariate Regression of molecular signature of MDM2 inh. Sensitivity:* Score = $g_{MDM2} + g_{XPC} + g_{BBC3} - g_{CDKN2A}$

• p53 mutation status and RNA signature not completely redundant
• The signature was not associated with chemotherapy sensitivity (data not shown)
Translation to Phase I clinical trial

**- NO212179 – mdm2 inh. (2)/ RO5045337**

28 refractory/relapsed AML patients

QD Treatment at MTD

x 10d + 18 d rest

Overall remission*

at end of C1 (28 days)

4-gene Score computation

**- NP28679 – Idasanutlin/ RO5503781**

21 refractory/relapsed AML patients

QD X 5 days +

1g/m² cytarabine X 6 days

Overall remission*

at end C1 (28-42 days)

4-gene Score computation

* Overall remission: Bone marrow blast ≤5%, with or without complete blood count recovery and with/without platelet count recovery
**Level of Evidence for MDM2 Signature**

*Reproducible signature in the two MDM2 antagonists*

**Gene Signature included as an exploratory endpoint in the Phase III trial**

> To be developed as a *complementary* diagnostic
Guidance to iDMC to assess biomarker utility at IA
For AML Phase III Pivotal Study
2:1 randomization idasanutlin + Cytarabine vs Cytarabine

Probability for each recommendation (bold = correct decision):
Interim Analysis after 120 patients, response after two cycles (d56)

<table>
<thead>
<tr>
<th>Truth</th>
<th>P(declare useless)</th>
<th>P(declare Case 1)</th>
<th>P(declare Case 2)</th>
<th>P(declare Case 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>score useless</td>
<td>0.95</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
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<tr>
<td>score prognostic</td>
<td>0</td>
<td>0.62</td>
<td>0.31</td>
<td>0.07</td>
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<td>score predictive, less correlation in controls</td>
<td>0</td>
<td>0.21</td>
<td><strong>0.39</strong></td>
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<tr>
<td>score predictive</td>
<td>0.01</td>
<td>0.04</td>
<td>0.16</td>
<td><strong>0.79</strong></td>
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Conclusions – Part I

• Development of response/predictive biomarkers requires a tight collaboration between biological research, clinical research, and statistical analysis rigor
  – Importance of analysis transparency
  – Pre-specification in hypothesis testing
  – Data exploration needs to be contained, especially with Sparse data

• The development of predictive markers is contingent on the development plan and available data, which can be limiting
  – In vitro data suggested that the mdm2 inhibitor response signature was not associated with chemotherapy, its prognosis value could not be tested before the phase III design
  – Limited information of the association with p53 mutations in AML
Moving into the ‘data’ era – The hidden cost of clinical trial data

**Planned**

- CRF Data: curation, mapping transformation of data from CRF to SDTM to ADAM dataset, and documentation
- Exploratory biomarkers: Procuring and managing patient samples, Running the assay (e.g., WGS, RNA)

**Unplanned**

- Variation on adherence to standards
- Secondary use of data (e.g. data harmonization)
- Data cataloging and curation of exploratory biomarkers
- Integration
- Enabling infrastructure (e.g. network, storage, compute)
EDIS intends to make our internal data **F.A.I.R.** and **SHARED** to accelerate generating meaningful insights from the data we have access to for R&D.

**Enhanced Data and Insights Sharing (EDIS)**

*Accelerate reliable insights generation from data*

Using insights from clinical trials and clinical practice to further research and development.

Using translational research to inform clinical trials and clinical practice.

**Mechanisms of Sharing**

- **Data Integration**
- **Data Management**
- **Single Point of Truth**

**Clinical Setting**

Clinical studies and real-world clinical experience to assess utility

**Forward Translation**

Using translational research to inform clinical trials and clinical practice.

**Reverse Translation**

Using insights from clinical trials and clinical practice to further research and development.

**Research & Development**

Better understand diseases and underlying drug response

**FAIR***: Findable, Accessible, Interoperable and Reproducible
The integrated Data Mart Portfolio

**Data mart Portfolio**

- Cancer immunotherapy
- Cancer Immunotherapy Safety
- Heme (NHL/FL)
- Breast Cancer (TNBC)
- Autism
- Ophthalmology
- Asthma/COPD
- Inflammatory Bowel Disease
- MIND4AD (AD)
Cancer immunotherapy and immune related adverse effect

Background

- Immune Check point inhibitor (PD-1 /PD-L1 inhibitor, CTLA4-inhibitor) increases anti-tumor immunity
- The activation of the immune system can lead to inflammatory side effects called immune related adverse effects

Objectives:

Identification of factors associated with occurrence of IrAEs upon PD-L1 inhibitor treatment

Identification of high-risk patients

→ Improve patient monitoring and selection, and differentiation of risk/benefit ratio

→ Based on patient’s baseline and on-treatment characteristics

Most frequent IrAE (PD-L1 inh.)
- Skin (Rash),
- Liver (Hepatitis)
- Endocriinal (hypo/hyperthyroidism)

9 RCTs with PD-L1 inhibitor (>6000 patients, lung and bladder)

<table>
<thead>
<tr>
<th>Multi-dimensional Data</th>
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<tbody>
<tr>
<td>Treatment regimens</td>
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<tr>
<td>Presence/Absence of AEs and/or ADA</td>
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<tr>
<td>Demographics and clinical information</td>
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<tr>
<td>Medicinal chemistry, blood flow cytometry</td>
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<tr>
<td>Germline DNA sequencing (HLA, WGS)</td>
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<td>(Microbiome)</td>
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<td>tumor genomic</td>
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<tr>
<td>• RNA seq.</td>
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<td>• Somatic mutation panel</td>
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Statistical approach

*Time to first Immune related Adverse effect*

- **Exploratory Data Analysis**
  - Define the right follow-up time window
  - Incidence between indications, treatment arms
  - Descriptive analysis of covariates….

- For selected sets of covariates
  - Use an Individual Participant Data (IPD) meta-analysis framework

\[
\ln(\lambda_{ij}) = \ln(\lambda_{0j}(t)) + \tilde{\theta}_j x_{ij} + \gamma_i^T X_{ij} + \varepsilon_{ij}
\]

- Flexible modeling to account for the adjustment covariates \((\gamma_{ij})\) and estimation of the parameter of interest \((\theta_{ij})\)
- One-step IPD meta-analysis favored: some organ-specific IrAEs have small # of events
Conclusions

• Use of existing clinical data is a key component of the PHC strategy evolution at Roche
  – Legacy RCT is a key data source

• Allows to enrich the development of the co-development of compounds and diagnostics

• Allows to extend the scope of clinical research questions
  – Assess benefit/risk ratio depending on patient’s characteristics
  – Identify prognostic / predictive biomarkers

• Brings new statistical challenges…
Doing now what patients need next