Andreas Wicki
University Hospital Basel
Switzerland
Disclosures

Funding of research projects:
Piqur Therapeutics

Consultancy:
Actelion Pharmaceuticals
Predictive Biomarkers for Targeted Therapy in Oncology

Andreas Wicki, MD, PhD
University Hospital, Basel
topics

• Established predictive biomarkers in oncology
• The nature of biomarkers in oncology
• How should we test biomarkers in oncology?
• What is the ideal source of biomarkers?
• Biomarker-evaluation in early trials
Predictive vs prognostic biomarkers in oncology

A

Biomarker Negative

Biomarker Positive

Proportion Surviving vs Time (years)

Treated vs Not treated

Ballman KV, J Clin Oncol, 2015
Established predictive biomarkers in oncology

**Established predictive biomarkers**
- Ras (colon)
- EGFR (lung)
- ROS (lung)
- Alk (lung)
- ER/PR (breast)
- Her2 (breast)
- Braf (melanoma)
- BRCA (ovary)

**All other biomarkers?**
No clear predictive role has been assigned to other molecular aberrations in cancer cells.
Example: Ras status as a predictive biomarker for response to anti-EGFR antibodies

- **Benefit**
  - Ras wildtype colorectal cancer
  - Ras mutant colorectal cancer

- **Malefit**
  - Testing matters!

Van Cutsem, JCO, 2015
The nature of biomarkers in oncology

Barallobre-Barreiro J et al., Rev Esp Cardiol, 2013
## The nature of biomarkers in oncology

### Search NCBI databases

<table>
<thead>
<tr>
<th>Literature</th>
<th>Genes</th>
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<tbody>
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<td>Books</td>
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Results found in 21 databases for "genomics cancer therapy"
The nature of biomarkers in oncology

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Search NCBI databases

proteomics cancer therapy

Results found in 22 databases for "proteomics cancer therapy"

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<th>Description</th>
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The nature of biomarkers in oncology

Search NCBI databases

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Results found in 23 databases for "metabolomics cancer therapy"

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<td>HomoloGene</td>
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</tbody>
</table>
How many potential genomic markers are there?

- Best guess: $10^6$ mutations in all cancer types?
- How many combinations of mutations are there? $10^8$?
- $3.3 \times 10^7$ cancer patients worldwide (WHO 2012).

Tan H et al., Nat Scientific Reports, 2015
EPFL, laboratory for communications and applications
Genomic biomarkers show patterns of interaction

We need to define a hierarchy of biomarkers and assign relative relevance to each.

Combinatorial patterns are due to selective pressure.

Yeang CH et al., FASEB J, 2008
Schubert M et al., Future Med, 2014

**TABLE 6. Number of mutational patterns connecting pathways**

<table>
<thead>
<tr>
<th></th>
<th>Cell cycle</th>
<th>Stress response</th>
<th>Ras</th>
<th>IGF-AKT</th>
<th>Wnt</th>
<th>TGFB</th>
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<td><strong>Co-occurrence</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Cell cycle</td>
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<td>21</td>
<td>13</td>
<td>12</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Stress response</td>
<td>21</td>
<td>0</td>
<td>13</td>
<td>14</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ras</td>
<td>13</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>IGF-AKT</td>
<td>12</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Wnt</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>TGFB</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

|               |            |                |     |         |     |      |
| **Mutual exclusion** |      |                |     |         |     |      |
| Cell cycle    | 2          | 0              | 0   | 0       | 0   | 0    |
| Stress response | 0         | 0              | 0   | 0       | 0   | 0    |
| Ras           | 0          | 0              | 16  | 1       | 1   | 0    |
| IGF-AKT       | 0          | 0              | 1   | 0       | 0   | 0    |
| Wnt           | 0          | 0              | 1   | 0       | 1   | 0    |
| TGFB          | 0          | 0              | 0   | 0       | 0   | 0    |
How should we test predictive biomarkers in oncology?

Principles of biomarker evaluation in oncology:

1. Hypothesis generation
2. Clinical testing:
   - prospective
   - stratify for biomarker
   - randomize strata
Hypothesis generation: identify driver mutations

1. **Hypothesis-generation in the lab**
   = make use of preclinical models of human cancer

2. **Hypothesis-generation in the clinic**
   (A) Building databases from NGS and CGH data from individual patients (prospective)
   (B) Following-up on patients responding in clinical trials, particularly phase 1 trials (retrospective)
Prediction from the lab (1)

Human tumours
- Copy number alterations
- Mutations
- Translocations
- Methylation alterations
- mRNA alterations
- MicroRNA alterations

Pathways
- NetBox
- MEMo
- PARADIGM

Key transcriptional regulators
- ARACNE
- MINDy
- CONEXIC

Driver missense mutations
- CHASM
- GISTIC

Significant copy number alterations

Prediction from the lab (2)

Prediction from the lab (3)

- Transduced cancer cells
  - N population doublings
- Surviving cancer cells
  - Isolation of genomic DNA and PCR to recover shRNA sequences
  - NGS to determine relative shRNA abundance
- Pooled shRNA library

- Tumour cell dependencies
- Genotype-selective dependencies
- Altered genes

- Human tumours
  - Copy number alterations
  - Mutations
  - Translocations
  - Methylation alterations
  - mRNA alterations
  - MicroRNA alterations

List of altered genes

Prediction from the clinic

(A) Building databases from NGS and CGH data from individual patients (prospective)

Individual patient

Biopsies of multiple tumor sites

Next generation Sequencing

Algorithms for target identification:

1. Is somatic alteration actionable?
2. If actionable, what is the level of evidence?
3. Evidence that somatic alteration is clonal?
4. Evidence that somatic alteration changes function

molecular tumor board

ctDNA

TARGET

5. subclonal drivers?

Treatment

Follow-up/clinical annotation of molecular data

Next generation Sequencing

Biopsies of resistant sites

Adapted from André et al., Ann Oncol, 2014
Prediction from the clinic

(A) Building databases from NGS and CGH data from individual patients (prospective)

Databases, exemplary:

Project of the Swiss Academy of Medical Sciences and the Swiss Confederation: Personalized Health Initiative, including building a national database for clinically annotated –omics data
Finding drivers the old-fashioned way: Following up on patients responding in clinical trials

(B) Following-up on patients responding in clinical trials, particularly phase 1 trials (retrospective)

*Historic efficacy data of phase 1 trials in oncology (mid 90's)*

6% ORR, 0.5% death rate on trial\(^1\)

*Recent data on efficacy in phase 1 trials (2000 onwards)*

10% ORR, 0.5% death rate on trial\(^2\)

General: Mahipal & Nguyen, Risks and Benefits of Phase 1 Clinical Trial Participation. Cancer Control, 2014


First-in-man trial: PQR309-001

Adapted, Wicki, SMW, 2010
Response upon therapy with PQR309 in a patient with thymoma

Up to now -60% tumor volume, duration of response of 9 months (ongoing)

Kristeleit, Wicki, ASCO 2015, abstr 2592
Response upon therapy with PQR309 in a patient with thymoma

Up to now -60% tumor volume, duration of response of 9 months (ongoing)

Kristeleit, Wicki, ASCO 2015, abstr 2592
How should we test predictive biomarkers in oncology?

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   - randomize strata
Clinical testing of predictive markers

Hot Topic

Clinical trial designs incorporating predictive biomarkers

Lindsay A. Renfro a,⁎, Himel Mallick b, c, Ming-Wen An d, Daniel J. Sargent a, Sumithra J. Mandrekar a

a Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
b Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA
c The Broad Institute of MIT and Harvard, Cambridge, MA, USA
d Department of Mathematics and Statistics, Vassar College, Poughkeepsie, NY, USA

Cancer Treatment Reviews, 2016
Clinical testing of predictive markers

(A) Test Marker
- M+
  - Randomize
    - Targeted
    - Standard of Care
- M-
  - Off Study

(B) Test Marker
- M+
  - Randomize
    - Targeted
    - Standard of Care
- M-
  - Randomize
    - Targeted
    - Standard of Care

(D) Test Marker
- M+
  - Randomize
- M-
  - Randomize
  - Treatment 1 (e.g., Targeted)
  - Treatment 2 (e.g., Non-Targeted)

Interim Analysis: Futility in M-Cohort?
- Yes: Stop Enrolling M- and Enrich Primary Final Analysis in the M-Cohort. Futility Analysis in M+ May Also Be Performed
- No: Continue Unselected Enrollment and Perform Final Primary Analysis in Overall Cohort (With Possible Subgroup Analysis in M+)

Renfro, LA, et al., Cancer Treatment Reviews, 2016
Clinical testing of predictive markers

TAILORx Trial
ER-positive and/or PR-positive Breast Cancer
HER2-negative
LN-negative

Recurrence score testing

Primary Study Group
Recurrence Score 11 to 25

Secondary Study Group 1
Recurrence Score < 11
29%
Arm A
Hormonal Therapy

Secondary Study Group 2
Recurrence Score > 25
27%
Arm D
Chemotherapy + Hormonal Therapy

Randomization

Primary Study Group
Recurrence Score 11 to 25

Secondary Study Group 1
Recurrence Score < 11
29%
Arm A
Hormonal Therapy

Secondary Study Group 2
Recurrence Score > 25
27%
Arm D
Chemotherapy + Hormonal Therapy

Arm C
Chemotherapy + Hormonal Therapy

Sparano JA et al., NEJM, 2015

waiting for results
What is the ideal source of biomarkers?

Concordance of genomic biomarkers in different solid tumor samples of the same patient

Concordance of PI3K-axis mutations in primary breast cancer biopsies and metastases:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primary</th>
<th>Met</th>
<th>Primary</th>
<th>Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>AKT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Discordance rate of Braf mutations in primary melanoma and metastases:

16-19% in different case series  Although this is a strong driver mutation!

Bradish J, et al., Mod Pathol, 2015
Are genomic markers from liquid biopsies more reliable than those from solid tissue?

**BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population**

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided P value 0.003)
- Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

<table>
<thead>
<tr>
<th></th>
<th>Full Population (N=1147)</th>
<th>Buparlisib + Fulvestrant n=576</th>
<th>Placebo + Fulvestrant n=571</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9</td>
<td>6.9 (6.8–7.8)</td>
<td>5.0 (4.0–5.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.67–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-sided P value</td>
<td>&lt;0.001</td>
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</table>
Are genomic markers from liquid biopsies more reliable than those from solid tissue?
Are genomic markers from liquid biopsies more reliable than those from solid tissue?
However,…

- Cell-free tumor DNA often represents <1% of all cell free DNA.
- Cell-free tumor DNA shedding rate depends on the tumor entity, its location, size (tumor load) and vascularity.

Diaz LA et al., J Clin Oncol, 2014
Biomarker-evaluation in early trials

Analysis of Impact of Post-Treatment Biopsies in Phase I Clinical Trials

Randy E. Sweis, Michael W. Drazer, and Mark J. Ratain

No. of Studies

Year

2003 2004 2005 2006 2007 2008 2009 2010

Biopsy
No biopsy
Critics of biology in early trials

- **Identification**
  - Phase I oncology abstracts downloaded from PubMed (N = 4,840)
    - Excluded (n = 4,256)
      - No mention of biomarker, surrogate, pharmacodynamic, or biopsy within abstract text
    - Manually reviewed (n = 584)
    - Excluded (n = 519)
      - Pediatric populations
      - Hematologic malignancies
      - Immune or gene therapy
      - No post-treatment biopsy

- **Analysis**
  - Study included post-treatment biopsy (n = 72)
    - Articles citing (n = 54)
      - biopsy biomarkers
  - Statistically significant biomarker result (n = 12)
Supporters of biology in early trials

industrial corner: perspectives and controversies

Oncology 2020: a drug development and approval paradigm

confirmatory trials to convert to full approval based on more traditional end points. This strategy significantly reduced the time to first approval for a number of important drugs in the 1990s and 2000s. However, over the years, this paradigm has increasing-
Supporters of biology in early trials
Supporters of biology in early trials

Oncology 2020
Integrated, continuous development of drugs and diagnostics

POM = Proof of mechanism; POE = Proof of efficacy
Summary: three hypotheses

• We need more biology (including biomarker research) in both early and late clinical trials.

• We need to broaden the spectrum of biomarkers that are assessed (not only genomic markers).

• We need to move away from testing single drugs in single indications and move rather towards clinical trials evaluating biomarker-based treatment algorithms in cancer.
Thank you!

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