Challenges and Opportunities in Development of Personalized Medicine

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What's our job?

Transform research and discovery to patient benefit in the real world health care setting as soon and safe as possible.
Efficacy of Medicines in Different Therapeutic Areas

modified from Spear et al., Trends in Molecular Medicine, 2001, Vol 7: 201-204
Traditional Strategies Failed to Significantly Improve the Outcomes of Lung Cancer Patients

- Lung cancer is the most common cause of cancer death

- Over the last decade, ~27,000 NSCLC patients have been enrolled in negative phase 3 trials

- Minimal gain in 5-year OS over the past 3 decades in lung cancer

1. Soria J. Presented at Clinical Science Symposium at ASCO 2011
Traditional drug development

Preclinical research

Discovery

IND

Phase I (n=50–100)

Phase II (n=100–300)

Phase III (n=1000–5000)

Approval

Phase IV and Pharmacovigilance

First In Human

Time (years)

2–10

4

1

2

3

1,5

Källa: PhRMA. Tufts Center for the Study of Drug Development.
Targeted Drugs Applied Without a Biomarker

• Gefitinib single agent

<table>
<thead>
<tr>
<th>Sites</th>
<th>Japan ¹</th>
<th>Europe ¹</th>
<th>United States ²</th>
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<tbody>
<tr>
<td>Patients entered</td>
<td>106</td>
<td>102</td>
<td>216</td>
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<tr>
<td>Response rate</td>
<td>28%</td>
<td>10%</td>
<td>10%</td>
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1) Fukuoka et al JCO 2003
2) Kris et al JAMA 2003
3) Herbst JCO 2004
4) Giaccone JCO 2004

• Gefitinib combination with Chemotherapy

- + carboplatin/paclitaxel³

- + cisplatin/gemcitabine⁴
A First Breakthrough with Biomarkers in Lung Cancer: Activating Mutations in the EGFR Gene

Activating mutations in the EGFR drive the disease
This oncogeneic driver can be identified with a diagnostic test
Targeted therapy to silence the activated EGFR

1. Mok et al., NEJM 2009; 361: 947-957
A more Personalized Medicine R&D Approach

- Critical focus on human biology and pathogenic mechanisms
- Effective interpretation and application of genomic information
- Application of this knowledge to every stage of drug discovery and development
Benefits of Drug Development Linked to a Biomarker

**Benefit to Clinical Development**
- Bigger Treatment Effect
- Smaller Clinical Trials
- Faster Trial Completion

**Benefit to Patients**
- Earlier Regulatory Submission + patient access
- More Dramatic Effect in Treated Patients
- Minimized exposure to drugs if not likely to benefit and
- Unnecessary costs to patients and payers

- Patients Treated More Likely to Benefit
- Longer Time on Treatment

**Graphs**
- # Patients vs. Months
  - 400 vs. 800
  - 18 vs. 30 Months
Molecular selection may enable faster drug development

**Development of crizotinib**

Lead compound identified | Clinical Trials started | Discovery of EML4-ALK Fusion Gene | First clinical responses in ALK+ tumours

2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012

Start of a Biomarker Driven Drug Development

- **First subject May 2006**
- **EML4-ALK described August 2007**
- **Expanded Cohort started**

- **Cohort 3**
  - 200 mg QD
  - 1 DLT: grade 3 ALT elevation

- **Cohort 4**
  - 200 mg BID

- **Cohort 5**
  - 300 mg BID
  - 2 DLTs: grade 3 fatigue

- **Cohort 6**
  - 250 mg BID
  - MTD / RP2D
  - **Part 2:** Expanded, molecularly enriched cohort

Enrolling patients with ALK-positive NSCLC after preliminary observation clear activity in a few patients
Molecular selection and collaboration enable faster drug development

Development of crizotinib

- Lead compound identified
- Clinical Trials started
- Discovery of EML4-ALK Fusion Gene
- First clinical responses in ALK+ tumours
- Phase 3-studies initiated ALK+NSCLC incl. Karolinska
- NEJM publication of ALK+ cohort\(^1\)
- FDA Accelerated approval
- CHMP positive opinion Europe

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Abbott Laboratories develop diagnostic test 2009 ->

Best % change in target lesions
Ph 1 PROFILE1001

- Progressive disease
- Stable disease
- Partial response
- Complete response

Additional references:
Kim, et al, ASCO 2012 #7533 (PROFILE1005)

A new vision for future trials

Experience to date

- **Identification of targets and biomarkers**
  - Not always a sequential process
  - Often easier said than done

- **Considerable areas of unmet need with no identified biomarkers**

- **Cost, speed of discovery and development**
  - Still an emerging picture, but so far not always clear advantages in cost and speed

- **The Regulatory Environment important for**
  - the development process and
  - the review process of the Marketing Authorization Application
Companion Diagnostics

- A validated specific target is necessary for development of Companion Diagnostics (CDx)

- CDx are currently regulated through the In Vitro Diagnostic Directive (IVDD) in the framework of Medical Devices (MD) legislation

- Role of EMA / national board of health
  - Guidance and review
  - Flexible approach needed regarding developing CDx in parallel to drug development
    - A CE marked CDx may not be available at the time of the Marketing Authorization Application – or the best one is yet to come…
From research to everyday health care
Practical management and collaboration

- Amount of tissue needed
- Accuracy and availability of the test
- What is the best method?
- Reporting time vs need to start treatment
- Interpretation of pathology reports
- Change of clinical practice and logistics
- Who should be tested?

Molecular Diagnostic Pathology
Report from the MSKCC, NY

Who are the discussion partners during planning and introduction of a new drug / biomarker / CDx?
Who makes decisions?
Communication and knowledge?
Quality?
From research to everyday health care
What about cost?

Diagnostic Access

- Lack of transparent system for reimbursement of diagnostic costs
- Risk of suboptimal diagnosis and treatment, inequality

Value and the cost/benefit of drugs

- Society perspective: We want innovation but new therapies are considered expensive
  - Not every patient responds – initial or acquired resistance / patients eventually progress
  - Reimbursement and Guideline recommendations - when is a yes a yes?
- Pharma perspective: Proven efficacy and safety basis for approval, responsibility for providing safety and efficacy data remains the same regardless of population size
  - Data evolve over time
- Personalized medicines have a targeted, self-limiting patient population and predictable budget impact
Learn more from every patient in every day health care

**Clinical trials**
- Nurse led clinic – coaching
- Toxicity management
- Compliance

**Advisory boards**

**Physician**
- Instruments for optimizing treatment:
  - Treatment selection
  - Toxicity management, concomitant medication
  - Individualized dosing

**Nurse**
- Well informed
- Prepared for treatment
- Active and motivated

**Patient**

**Structured Data**
- Data mining from registrars, biobanks and other databases
- A national longitudinal patient cohort

**Other Specialists**
- Can treatment be optimized by a multidisciplinary approach?
- Support in toxicity management

**Translational Expert group**
- HOW DO WE GET FURTHER?
- Understand drivers for efficacy, patient selection and causes of AEs
- Long term responder - What do they have in common?
- Early relapse - Why?
- Overcome mechanism of resistance in order to prolong treatment
- Supporting preclinical data for further development?

**Pathologists & molecular biologists**
- High quality tissue and testing
- Molecular characterisation, diagnosis and prognosis
- Support treatment decisions
- Method development
Potential Benefits From Biomarker-driven Treatment Approaches

- Reduced toxicities
- Higher response rates and greater treatment benefits
- Smaller and more ethical clinical trials
- Faster drug development
- Reduced costs for companies and payers

- Multidisciplinary collaboration is key for successful implementation
- Learn more from every patient – also in everyday health care
Thank you for your attention!