Personalisierte Medizin in der Praxis

Dr. Bernhard Kirschbaum
DVFA Life Science Conference
Frankfurt, 17. Juni 2009
Merck Serono
The largest division of the Merck Group

Merck Group
Revenues FY2008: €7,558m

Business sectors

Pharmaceuticals
Revenues FY2008: €5,429m
Merck Serono
€4,987m

Consumer Health Care
€442m

Chemicals

Liquid Crystals

Performance & Life Science Chemicals

Cross-divisional functions / Central functions
Merck Serono –
Key Facts & Figures

Established: January 5, 2007

Business: Innovative small molecules & biopharmaceuticals

Employees: >17,500

President: Elmar Schnee

Headquarters: Geneva, Switzerland

Key growth drivers: Erbitux, CETUXIMAB, Rebif
**Therapeutic Area Focus:**
From Research and Development to Market

**Research**
- Oncology
- Autoimmune & Inflammatory Diseases (AIID)
- Neurodegenerative diseases
- Fertility
- Endocrinology

**Development**
- Oncology
- Autoimmune & Inflammatory Diseases (AIID)
- Neurodegenerative diseases
- Fertility
- Endocrinology

**Market**
- Oncology
- New Specialist Therapies
  - Osteoarthritis*, Rheumatology*, etc.
- Neurodegenerative diseases
  - Multiple Sclerosis, Parkinson's*
- Fertility
- Endocrinology
- CM Care & local products

* Currently in Development
Stratified Medicine is about adapting the treatment (molecule, dose, schedule,...) according to the patient’s characteristics for better efficacy and less adverse events.

**Personalized Medicine**
- Individual patients,
  - e.g. cancer vaccine
  - made from the patient’s tumor

**Stratified Medicine**
- Patient sub-populations
Stratified Medicine: Basic Principle
How Can Stratified Medicine Help the Patients, Clinicians and Healthcare Systems?

**Patients:**
- More effective & predictive treatment options

**Clinicians:**
- Therapy adjustment based on disease and patient characteristics
- Tool to optimize dosing

**Healthcare Systems:**
- Better return on healthcare expenditure
- More innovation through products with higher medical value using combination of Diagnostics (Dx) and Pharma (Rx)
Stratified Medicine as a Means to Contain Health Care Expenditures

- President Obama’s economical stimulus bill allocates US$1.1bn for comparative effectiveness research (2009)

Early identification of non-responders has double value for the authorities – increasing pressure is expected:
  - Increased patient benefit
  - Health care cost containment

Source: www.whitehouse.gov
Stratified Medicine and Pharma Business – New Opportunities / Added Complexity

**Improved benefit / risk ratio**

Faster, more directed development

Opens doors to new indications

Higher & faster market penetration

Better price and reimbursement

**Business Outcome**

- Smaller target market

- Higher R&D costs

Complication through Dx testing

In practice
Merck Serono Pipeline
as per April 27, 2009

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>in Registration</th>
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</thead>
<tbody>
<tr>
<td>Aurora Kinase Inhibitor AS703569 Solid tumors and hematological malignancies</td>
<td>Atacicept Multiple Sclerosis</td>
<td>Rebitux® (cetuximab) NSCLC 1st line therapy EMEA: Submission filed</td>
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<tr>
<td>NHS-IL2-LT Solid tumors</td>
<td>Erbitux® (cetuximab) Breast cancer</td>
<td>Cladribine tablets Relapsing forms of MS</td>
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<tr>
<td>DI1TE6 Solid tumors</td>
<td>Tucotuzumab celmoleukin (EMD 273066/huKS-IL2), Small cell lung cancer (SCLC)</td>
<td>Cladribine tablets in CIS</td>
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<td>Eg 5 inhibitor Solid tumors and hematological malignancies</td>
<td>EMD 273063 (hu14.18-IL2), Immunocytokine Melanoma</td>
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<td>Survivac Cancer Vaccine Solid tumors</td>
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<td>MEK Inhibitor Solid tumors</td>
<td>Cilengitide SCCCHN</td>
<td>Erbitux® (cetuximab) Adj Colon Cancer</td>
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<tr>
<td>IMO-2055, TLR9 immunomodulator, Solid tumors</td>
<td>Cilengitide NSCLC</td>
<td>Erbitux® (cetuximab) Gastric Cancer</td>
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<td>Sonepcizumab (ASONEPTM) Solid tumors</td>
<td>Adecatumumab (MT201) NSCLC</td>
<td>Cilengitide Glioblastoma</td>
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<td>Fibroblast Growth Factor 18 Osteoarthritis</td>
<td>Atacicept Rheumatoid Arthritis</td>
<td>Stimuvax® NSCLC</td>
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<td>Hyperglycosylated FSH Infertility (ART)</td>
<td>Atacicept Lupus</td>
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<td></td>
<td>ARX 201 Growth hormone deficiencies</td>
<td>Tesamorelin HIV patients with lipodystrophy (US only)</td>
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- Oncology
- Neurodegenerative Diseases
- Autoimmune & Inflammatory Diseases
- Fertility
- Endocrinology
Merck Serono Pipeline
as per April 27, 2009

Phase I
- Aurora Kinase Inhibitor (AST03569)
  Solid tumors and hematological malignancies
- NHS-IL2-LT
  Solid tumors
- DH1E6
  Solid tumors
- Eg 5 inhibitor
  Solid tumors and hematological malignancies
- Survivac Cancer Vaccine
  Solid tumors
- MEK Inhibitor
  Solid tumors
- IMO-2055, TLR9 immunomodulator, Solid tumors
- Sonepcizumab (ASONEPTM)
  Solid tumors
- Fibroblast Growth Factor 18
  Osteoarthritis

Phase II
- Atacicept
  Multiple Sclerosis
- Erbitux® (cetuximab)
  Breast cancer
- Tucotuzumab celmoleukin
  (EMD 273066/huKS-IL2), Small cell lung cancer (SCLC)
- EMD 273063 (hu14.18-IL2),
  Immunocytokine, Pediatric neuroblastoma
- EMD 273063 (hu14.18-IL2),
  Immunocytokine, Melanoma
- Cilengitide
  SCCHN
- Cilengitide
  NSCLC
- Adecatumab (MT201)
  Colorectal Cancer
- Atacicept
  Rheumatoid Arthritis
- Hyperglycosylated FSH
  Infertility (ART)
- ARX 201
  Growth hormone deficiencies

Phase III
- Rebit New Formulation in CIS (REFLEX)
- Cladribine tablets
  Relapsing forms of MS
- Cladribine tablets in CIS
- Safinamide
  Early stage Parkinson’s
- Safinamide
  Mid-to-late stage Parkinson’s
- Erbitux® (cetuximab)
  Ad Colon Cancer
- Erbitux® (cetuximab)
  Gastric Cancer
- Cilengitide
  Glioblastoma
- Stimuvax®
  NSCLC
- Atacicept
  Lupus
- Tesamorelin
  HIV patients with lipodystrophy (US only)

in Registration
- Rebit New Formulation
  Relapsing forms of MS
  FDA: Submission filed
- Erbitux® (cetuximab)
  NSCLC
  1st line therapy
  EMEA: Submission filed

Stratification is an important part of the Merck Serono strategy. Over 60% of our portfolio include Biomarker programs (predictive, mechanistic, surrogates).

Biomarker and or stratification activities
Stratified Medicine: A Reality at Merck Serono

- KRAS stratification for Erbitux® was key to therapeutic expansion.

- Two stratified Phase III programs ongoing in Oncology – Cilengitide and Stimuvax

- Implementation of stratified medicine approach across the whole development portfolio

- Mandatory search for stratification biomarkers in our discovery process.

- Creation of a specialized function dedicated to stratified medicine.
KRAS as a Predictive Marker for Erbitux® Efficacy in Metastatic Colorectal Cancer (mCRC)

Chemotherapy (FOLFIRI) +/- Cetuximab in first line treatment of mCRC

KRAS patient status influences the efficacy of Erbitux®
Improving tumor responses in mCRC: impact of tailored therapy and patient selection


ITT, intent-to-treat population; wt, wild-type; LLD, liver-limited disease

Personalized / tailored therapy – a new era in mCRC
Benefit-effort ratio

Identified 60% pts (KRAS wt) treated with tailored therapy

Target specific patient group (KRAS wt)
- Maximize success in clinical studies
- Good clinical benefit in stratified patients
- Avoid unnecessary adverse effects
- Efficient from health economics perspective

100% pts treated with non-tailored therapy

No indicators to select patients
- Variable success in clinical studies
- Variable clinical benefit in allcomers
- Risk of unnecessary adverse effects
- Inefficient from health economics perspective
Extension of mCRC Indication to 1st Line with KRAS Stratification

1st line 74,200 patients

2nd line 32,200 patients

3rd line 10,200 patients

KRAS wild-type 65%

KRAS mutant 35%

Treatment duration

16 weeks

20 weeks

32 weeks

Treating 2nd and 3rd line, both KRAS wild-type and mutant:
Market = 807,200 weeks treatment

Treating 1st line, KRAS wild-type only:
Market = 1,543,360 weeks treatment

Bigger market enabled by stratification
Higher penetration due to improved efficacy

*Data for biggest 5 countries in Europe, Source: OncFoundation2007 projections for 2008
1 June 2009: Breakthrough for Erbitux in the UK — NICE recommendation thanks to KRAS

85 pieces of coverage for NICE (11 in major newspapers/newswires)
Cilengitide in Glioblastoma

- Glioblastoma is a rare tumor, difficult to treat.
- The methylation of the MGMT* gene promoter is a potential stratification marker.
- Increased likelihood to succeed in Phase III using MGMT stratification.

Stratified medicine helps to meet unmet medical needs and to access additional indications

*O-Methylguanine-DNA Methyltransferase
Consequences of Stratified Medicine Implementation on Technology Management

New capabilities → New complexities

Drug Development

Study Conduct & BM Logistics

Biomarker Technologies

Clinical Study Design

A characteristic that is objectively measured and evaluated as an indicator of
- normal biological processes (+)
- pathologic processes (x)
- pharmacologic responses to a therapeutic intervention (e)
Implementation of Stratified Medicine Has a Strong Impact on Drug Development Process

- Early integration in discovery and development process is important
- Good early PK/PD research is essential
- Competitive advantage to learn the lessons early

- Identification of stratification
- Validation of marker assay
- Analytical validation of diagnostic kit
- Clinical utility assessment for stratification
- Design clinical trials
- Clinical validation of diagnostic kit
- Label consideration based on marker status
- Label consideration based on trial
- Address regulatory requests
- Ensure proper logistics
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Requirements for Stratification Kits in the Pharma Business

<table>
<thead>
<tr>
<th>Conditions for “good stratification kits” from the Rx standpoints:</th>
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<tr>
<td><strong>Technical reliability:</strong></td>
</tr>
<tr>
<td>− Selective</td>
</tr>
<tr>
<td>− Sensitive</td>
</tr>
<tr>
<td>− Reproducible</td>
</tr>
<tr>
<td>− Validated in clinical setting</td>
</tr>
<tr>
<td>− Short turn-around</td>
</tr>
<tr>
<td><strong>Market access:</strong></td>
</tr>
<tr>
<td>− Properly distributed</td>
</tr>
<tr>
<td>− Technically user-friendly</td>
</tr>
<tr>
<td>− Financially affordable</td>
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Alignment of Rx and Dx is important
Are the Current Rx/Dx Business Models Challenged in the Context of Stratified Medicine?

<table>
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<th>Rx reimbursement:</th>
<th>Dx reimbursement:</th>
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<tr>
<td><strong>Value-based system</strong></td>
<td><strong>Cost-based system</strong></td>
</tr>
<tr>
<td>• Price is set according to the medical value</td>
<td>• Price is set according to the product cost</td>
</tr>
<tr>
<td>➢ Innovative drugs increasing the response rate - bringing real added benefit to the patients - will enjoy higher reimbursement</td>
<td>➢ Innovative genotyping kit increasing the response rate will be reimbursed at the level of other genotyping methods</td>
</tr>
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</table>

Will Dx benefit increasingly from value-based recognition?
Dx and Rx Interactions

Two extreme models:

**Invasive model**
- Dx develops stratification markers for marketed drugs without Rx partnership
- Strong impact on Rx business since drug price is unlikely to be renegotiable
- Kit development risk shouldered by Dx
- Risk of double marginalization
- Dx/Rx misalignment might be detrimental for patients benefit

**Collaborative model**
- Dx co-develops stratification markers with Rx
- Higher Dx price negotiable at launch
- Shared development risk, mainly covered by Rx
- Profit sharing & optimization
- Aligned commercialization efforts - Best medical benefit for patients

Stratified Medicine might result in a new Dx/Rx symbiosis.
From Complexity to Oversimplification & Back to Complexity

Genomics Era

Post-Genomics Era
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Thank you for your kind attention!