Clinical Development at Roche: Driving the paradigm shift
Jean-Jacques Garaud, MD
Global Head Pharma Development, Chief Medical Officer Roche
Sell sider breakfast Paris, October 23, 2008

Personalized healthcare: Fashion or substance?
Where the value goes
Where we stand at Roche
Pipeline update
Key Drivers of Change in Our Industry

Healthcare Pressures: Benefit-Risk Ratio
Economic Pressures: Benefit-Cost Ratio
New Technologies: Expanded Capabilities

Healthcare pressures intensify focus on improved benefit-risk ratio

Patients are different, diseases are heterogeneous

However, most medicines are not differentiated
Key Drivers of Change in Our Industry
A call for more effective and safer drugs

Efficacy

Drug Response Rate, %

60
80
40
20
0

Safety

GSK

Sanofi aventis

Novartis

Bayer

Novartis

1 Spears et al., Trends Mol Med, 2001; 2 Lazarou et al., JAMA, 1998

Key Drivers of Change in Our Industry
Economic pressures intensify focus on improved benefit-cost ratio

U.S. Healthcare Spend as % of GDP

2000 2008 2015

14% 16% 20%

U.S. Healthcare Spending, US$ Billions

2000 2008 2015

1500 2500 4000

Source: Centers for Medicare and Medicaid, Office of the Actuary, National Health Statistics Group
**Key Drivers of Change in Our Industry**

*Step-change needed in Pharma development*

- **New Molecular Entities (NME)**
  - 53 in 1996
  - 17 in 2007

- **R&D Spend**
  - $17 Bn in 1996
  - $47 Bn in 2007

*Sources: FDA/CDER Data, PhRMA data, Price Waterhouse Coopers analysis, Pharma 2020*

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**Key Drivers of Change Towards PHC**

*PHC is key to enabling highly differentiated medicines*

- **Healthcare Pressures:** Benefit-Risk Ratio
- **Economic Pressures:** Benefit-Cost Ratio
- **New Technologies:** Expanded Capabilities

*Need for highly differentiated medicines that impact positively public health*

*Payors will reward innovation*
Personalized Healthcare: Fashion or substance?

Where the value goes

Where we stand at Roche

Pipeline update

Defining Value

*For patients and payors, better clinical outcomes and improved quality of life*

**Benefit to Patients & Payors can be:**

- Better and more predictable clinical outcomes
- Quality of life and life-years gained
- Reduced morbidity
- Reduced unnecessary treatment/side effects and associated costs
- Better compliance
Defining Value
For Roche Pharma, faster market access and penetration

Benefit to Roche Pharma can be:
- Faster access to market
- Better and more stable pricing
- Faster penetration into market
- Increased market share
- Better compliance
- Longer duration of therapy

Pharmacoeconomics of Therapeutic Stratification
Reduced patient populations offset by increased total revenue and patient benefit
Defining Value
For Roche Diagnostics, high medical value tests yield higher growth and increased market share

Benefit to Roche Dx can be:
- New business with strategic growth
- Higher medical value tests, leading to premium pricing
- Higher placements of platforms
- Increased market share

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**PHC in Roche – The Roche Group**

Two highly complementary divisions that represent a natural fit

Built on a foundation of expertise in molecular biology and technologies

**Pharma 2015 – New R&D Model**

*Bringing the right disciplines together at the center-stage of drug discovery & development*

Innovation that results in higher quality candidate selection
Collaboration Pharma and Diagnostics

Biomarker programs for all pharma projects

Example Oncology

<table>
<thead>
<tr>
<th>Phase I and II</th>
<th>Phase III / market</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1R mAb (R1807)</td>
<td>Herceptin</td>
</tr>
<tr>
<td>MDM2 antag (R7112)</td>
<td>Avastin</td>
</tr>
<tr>
<td>PLX4032 (R7204)</td>
<td>Pertuzumab</td>
</tr>
<tr>
<td>T-DM1 (R3502)</td>
<td>Tarceva</td>
</tr>
<tr>
<td>• Range of candidate markers</td>
<td>• HER2 expression</td>
</tr>
<tr>
<td>• P53 wild-type</td>
<td>• HER2 gene amplification</td>
</tr>
<tr>
<td>• BRAF V600E gene mutation</td>
<td>• Range of candidate markers for hypothesis investigation</td>
</tr>
<tr>
<td>• HER2 expression</td>
<td>• Range of candidate markers</td>
</tr>
<tr>
<td>• HER2 gene amplification</td>
<td>• EGFR expression (IHC)</td>
</tr>
</tbody>
</table>

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Summary …
… in a few words

1. It is Real!
2. Optimal value: Start early, own IP and co-launch
3. Our unique position: Pharma and Dx, new R&D model

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Personalized Healthcare: Fashion or substance?

Where the value goes

Where we stand at Roche

Roche Pharma pipeline overview

Focused on five Disease Biology Areas

**Oncology**
- MabThera
- Avastin
- Herceptin
- Tarceva
- Pertuzumab

**RA/Inflammation**
- Actemra
- R1507 (IGF-1R mAb)
- R1594 ocrelizumab

**Metabolic**
- R667 RARg

**Virology**
- Tamiflu
- Pegasy
- R248A HPV16
- R1655 CEPI Inh.

**CNS**
- Pegasys
- R3487 Alzheimer’s
- R1678 Schizophrenia

**Emerging**
- MabThera
- Actinon
- R1564 ocrelizumab
- R827 RAAmg

**Early Stage**
- On Hand Promising
- 11 ph. I compounds

**Mid-Term**
- 9 phase I compounds

**On Hand**
- 11 ph. I compounds

**Emerging**
- 11 ph. I compounds
Pipeline: 54 NMEs and 58 additional indications

Staying strong in oncology and diversifying into new areas

Key drivers for long term development in place

Develop the short term drivers while not ‘leaving ‘the others
Oncology: Q3 ‘08 pipeline update

Significant newsflow before end of year

**MabThera in relapsed CLL: REACH**
Randomized ph. III, 552 patients
Fludarabine+cyclophosphamide +/- MabThera
met primary endpoint (PFS)
Filing 2009

**Tarceva+Avastin in 2nd line NSCLC: BETA lung**
Tarceva +/- Avastin
improvement in PFS / RR benefit
OS not significant
EU filing under evaluation

**Avastin in 1st line mBC: RIBBON-1**
Phase III study, 1238 patients,
2 primary analyses:
Anthraccline/-taxane-based +/- Avastin, and Xeloda +/- Avastin
Expect topline data Q4 ‘08

**Tarceva 1st line maintenance NSCLC: SATURN**
4 chemo cycles followed by T vs. placebo
Enrollment completed Q2 ’08
Potentially label-enabling for Tarceva
Expect topline data Q4 ’08

Avastin still early in its journey
Realising full potential across tumour types

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Early/adjuvant (Potential for cure)</th>
<th>Advanced/metastatic (Extending life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon, colorectal</td>
<td></td>
<td>[EU, US, JP: broad label in 1st and subsequent lines]</td>
</tr>
<tr>
<td>Lung (NSCLC)</td>
<td>Phase III (E1505)</td>
<td>[EU majority of chemos, US carboplatin/paclitaxel]</td>
</tr>
<tr>
<td>Breast (HER2-)</td>
<td>Phase III (BEATRICE, E5103)</td>
<td>[EU US w/paclitaxel]</td>
</tr>
<tr>
<td>Breast (HER2+)</td>
<td>Phase III (BETH w/Herceptin)</td>
<td>[EU US w/paclitaxel]</td>
</tr>
<tr>
<td>Kidney (RCC)</td>
<td>–</td>
<td>Phase III (RIBBON-2, incl. w/Xeloda)</td>
</tr>
</tbody>
</table>

Avastin also tested in gastric, ovarian and prostate cancer, aNHL, and brain (GBM)

(Trial names) [Approval status]. More trials are ongoing than listed above.
Avastin in Refractory Glioblastoma Multiforme (GBM)

High unmet medical need

- Incident Primary Brain Tumors population in line with mRCC
  - 20,000 incident patients in top 5 EU countries (mRCC: 17,000)
- Phase II data demonstrated encouraging six-month PFS and ORR in patients with relapsed GBM, exceeding historical estimates of 15%
- Avastin in relapsed GBM ph. II data on track to be filed by end 2008
- Phase III in first-line Glioblastoma in preparation

T. F. Cloughesy et al., ASCO 2008, abstract 2010b (Monday)

Maintaining leadership in oncology

Building on our key areas of expertise

<table>
<thead>
<tr>
<th>New molecular entities</th>
<th>Key features</th>
<th>Potential patient benefit</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-CD 20</strong> (building on MabThera)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R7159/GA101 (3rd generation)</td>
<td>Glyco-engineered type II antibody, fully humanized; ADCC, CDC, direct cell death</td>
<td>Significantly improved efficacy</td>
<td>ph. I/II NHL, CLL</td>
</tr>
<tr>
<td><strong>Anti-HER2</strong> (building on Herceptin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Inhibition of HER2 dimerisation</td>
<td>Improved efficacy in combo with Herceptin</td>
<td>ph. III mBC mNSCLC</td>
</tr>
<tr>
<td>Trastuzumab-DM1</td>
<td>Anti-microtubule linked to Herceptin</td>
<td>Reduced side effects, superior efficacy</td>
<td>ph. II mBC ph. III 'go'</td>
</tr>
<tr>
<td><strong>Angiogenesis (building on Avastin)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R7334 / TB-403</td>
<td>mAb against placental growth factor (PIGF); blocks a pro-angiogenic factor</td>
<td>Adding efficacy to Avastin in combo or sequentially</td>
<td>ph. I</td>
</tr>
<tr>
<td>Anti-PlGF mAb</td>
<td></td>
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Key drivers for long term development in place

Develop the short term drivers while not ‘leaving’ the others

- Virology
- CNS
- Metabolic
- Inflammation
- Oncology

ILLUSTRATIVE

Inherent development risk

Maturity of portfolio

Early Phases

Low

High

Existing

Rheumatoid Arthritis: Not all patients respond to current therapy

Gold standard therapy

anti-TNF + MTX

Unmet Medical Need

Only 1 of 3 patients receives significant benefit

% ACR70 Responders

ACR 70 = 70% Improvement in:

disease activity - patient

disease activity - physician

Patient assessment of pain

Physical disability

Acute phase reactants - CRP, ESR
Actemra: The first IL-6 receptor inhibitor
Unprecedented level of remission in moderate to severe patients with RA

- Largest clinical programme of any biologic for RA
- Consistently high & durable remission rates - across different disease stages
- Rapid treatment response - as early as 2 weeks

New data presented at EULAR 2008:
- RADIATE: Rapid and significant improvements in patients who have failed up to 3 anti-TNF inhibitors
- AMBITION: Only biologic to have demonstrated superiority vs. methotrexate as monotherapy
- Regulatory update: Positive FDA panel on July 29th, 2008; CRL received; working with FDA to address outstanding matters, EU review on track

1 Emery et al., EULAR 2008, Abstract OP-0251
2 Jones et al., EULAR 2008, Abstract OP-0131
3 Complete response letter

Key drivers for long term development in place
Develop the short term drivers while not ‘leaving‘ the others

Virology
CNS
Metabolic
Inflammation
Oncology

Inherent development risk
High
Low
existing
Earlier Phases
Maturity of portfolio

ILLUSTRATIVE
CETP Inhibitor

**R1658 is a unique CETPi**

- In contrast to the majority of other CETPi, R1658 has a different chemical backbone to Torcetrapib
- In patients treated with R1658, HDL is of normal composition
- In pre-clinical models and in clinical trials up to phase II, data showed that R1658 at therapeutic doses had a similar safety profile to placebo, including effects on blood pressure and RAAS activation

**Relationship Between Changes in LDL-C and HDL-C Levels and CHD Risk**

1% decrease in LDL-C reduces CHD risk by 1%
1% increase in HDL-C reduces CHD risk by 1%


**Large mortality and morbidity study running**

- Only true evaluation of the CV benefits of raising HDL-C by CETPi
- R1658 is being investigated to reduce CV risk on top of current recommended standard of care for CV risk factors
- Currently the only route to approval of CETPi
**Taspoglutide: investigational once-weekly GLP-1 analogue for the treatment of type-II diabetes**

- Significantly reduces blood glucose over only eight weeks
- Provides substantial weight loss in a dose-response fashion
- Additional titration study confirmed the safety and tolerability of taspoglutide
- Efficacy, safety and tolerability profile encouraging
- Phase III recruitment started in Q3 2008

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- Virology
- CNS
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<table>
<thead>
<tr>
<th>Inherent development risk</th>
<th>Low</th>
<th>High</th>
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<tr>
<td>Maturity of portfolio</td>
<td>existing</td>
<td>Earlier Phases</td>
</tr>
</tbody>
</table>
CD20 targeting: new treatment strategy for MS
Very promising signals from Phase II with rituximab

- Total cumulative mean number of gadolinium lesions was reduced by 91% (p<0.0001)
- Patients with relapses over 24 weeks in the treated arm was 14.5% compared to 34.3% in the placebo (58 percent relative reduction, p = 0.0238)

Ocrelizumab: Phase II placebo-controlled program in RRMS

Roche R&D opportunities in summary

- Innovation-driven business focused on differentiated products that add medical value
- Network approach to foster innovation and build on our core business
- Leverage combination of Pharmaceuticals and Diagnostics in-house to develop more targeted treatment options (personalized healthcare)
- Numerous short- and mid-term drivers of growth with low development risk
- Broad pipeline for long-term sustainable growth

Our unique strategy provides Roche with a competitive edge for sustainable outperformance
We Innovate Healthcare