Roche late-stage pipeline update
London, 9 December 2010
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2. legislative and regulatory developments and economic conditions;
3. delay or inability in obtaining regulatory approvals or bringing products to market;
4. fluctuations in currency exchange rates and general financial market conditions;
5. uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6. increased government pricing pressures;
7. interruptions in production;
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9. litigation;
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Roche late-stage pipeline update

Agenda

09.00-9.05  Introduction  
            Karl Mahler, Head of Investor Relations

09.05-9.45  Oncology late-stage portfolio update  
            Hal Barron, MD Global Development and Chief Medical Officer

09.45-10.05  Q&A

10.05-10.40  CNS pipeline update  
            Eugene Tierney, Global Product Strategy TA Head, CNS

10.40-11.00  Q&A
Late-stage pipeline progressing well

Number of NMEs

- Virology
- CNS
- Metabolic
- Inflammation
- Oncology

2007 2008 2009 2010E

- Number of NMEs:
  - 2 NMEs in 2007: ocrelizumab, dalcetrapib
  - 4 NMEs in 2008: ocrelizumab, dalcetrapib, taspoglutide, pertuzumab
  - 10 NMEs in 2009: ocrelizumab, dalcetrapib, taspoglutide, pertuzumab, taspoglutide, Actemra, ocrelizumab, lebrikizumab
  - Up to 14 NMEs in 2010E: HCV pol inh, ocrelizumab MS, Glycine reuptake inh, SGLT2 inh, aleglitazar, taspoglutide, dalcetrapib, lebrikizumab

1 LIP decision made, phase III pending; 2 LIP and phase III decision pending
Our strategic franchises
Focus on areas with high unmet medical need

<table>
<thead>
<tr>
<th>Franchise</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>High unmet medical need - high risk/high reward “The new oncology?”</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Only dalcetrapib targets primary care. Aleglitazar: specialty product.</td>
</tr>
<tr>
<td>Virology</td>
<td>Focus on hepatitis; existing infrastructure to launch new products.</td>
</tr>
<tr>
<td>Inflammation</td>
<td>RA biologics: area of high growth – Actemra strongly positioned</td>
</tr>
<tr>
<td>Oncology</td>
<td>Leader in oncology with strong pipeline–Regulatory requirements evolving, raising the bar for new products (including competition)</td>
</tr>
</tbody>
</table>
# Major clinical news flow for our late-stage NMEs in 2011/2012

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Compound</th>
<th>Indication</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Hedgehog Pathway Inh</td>
<td>advanced BCC</td>
<td>Ph II – Pivotal study</td>
</tr>
<tr>
<td></td>
<td>T-DM1</td>
<td>1st line HER2+ mBC</td>
<td>Ph II - final data</td>
</tr>
<tr>
<td></td>
<td>GA101</td>
<td>Relapsed indolent NHL</td>
<td>Ph II Head-to-Head with Rituxan</td>
</tr>
<tr>
<td></td>
<td>MetMab</td>
<td>NSCLC 2nd / 3rd line</td>
<td>Ph II - final data</td>
</tr>
<tr>
<td></td>
<td>Lebrikizumab</td>
<td>asthma</td>
<td>Ph II MILLY</td>
</tr>
<tr>
<td></td>
<td>Nucleoside Pol Inh</td>
<td>Hepatitis C</td>
<td>Ph IIb PROPEL</td>
</tr>
<tr>
<td></td>
<td>Dalcetrapib</td>
<td>Atheroclerosis CV risk red.</td>
<td>Ph IIb dal-VESSEL; dal-PLAQUE</td>
</tr>
<tr>
<td></td>
<td>Lucentis</td>
<td>diabetic macular edema</td>
<td>Ph III RIDE &amp; RISE</td>
</tr>
<tr>
<td></td>
<td>Avastin</td>
<td>relapsed ovarian cancer</td>
<td>Ph III OCEANS</td>
</tr>
<tr>
<td></td>
<td>BRAF inh</td>
<td>1st line met melanoma</td>
<td>Ph III BRIM3</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab + Herceptin</td>
<td>1st line HER2+ mBC</td>
<td>Ph III CLEOPATRA</td>
</tr>
<tr>
<td></td>
<td>Avastin + Herceptin</td>
<td>1st line HER2+ BC</td>
<td>Ph III AVEREL</td>
</tr>
<tr>
<td></td>
<td>Herceptin</td>
<td>adj HER2+BC sc</td>
<td>Ph III HANNAH</td>
</tr>
<tr>
<td>2012</td>
<td>T-DM1</td>
<td>2nd line HER2+ mBC</td>
<td>Ph III EMILIA</td>
</tr>
<tr>
<td></td>
<td>Avastin</td>
<td>mCRC</td>
<td>Ph III TML*</td>
</tr>
<tr>
<td></td>
<td>Actemra</td>
<td>RA DMARD IR</td>
<td>Ph III Head-to-Head with Humira</td>
</tr>
<tr>
<td></td>
<td>Actemra</td>
<td>RA sc formulation</td>
<td>Ph III</td>
</tr>
<tr>
<td></td>
<td>Herceptin</td>
<td>adj HER2+BC 2 yrs vs 1 yr</td>
<td>Ph III HERA</td>
</tr>
<tr>
<td>2012/13</td>
<td>Dalcetrapib</td>
<td>Atheroclerosis CV risk red.</td>
<td>Ph III dal-OUTCOMES final analysis</td>
</tr>
</tbody>
</table>

*TML = treatment through multiple lines; Oncology and CV outcome studies are event driven, timelines may change*
Oncology pipeline update

Hal Barron, MD
Global Development and Chief Medical Officer
**Late-stage pipelines update**

### Oncology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MetMAb</strong></td>
<td>III</td>
<td>NCSLC and triple neg. mBC</td>
</tr>
<tr>
<td><strong>T-DM1</strong></td>
<td>III</td>
<td>HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td><strong>Pertuzumab</strong></td>
<td>III</td>
<td>HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td><strong>GA101 (RG7159)</strong></td>
<td>III</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td><strong>BRAF inhibitor</strong></td>
<td>III</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td><strong>Hedgehog inhibitor</strong></td>
<td>PIV</td>
<td>Basal cell carcinoma</td>
</tr>
</tbody>
</table>

### Metabolism, Immunology & Virology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Polymerase inhibitor</strong></td>
<td>II</td>
<td>Chronic Hepatitis C</td>
</tr>
<tr>
<td><strong>Aleglitazar</strong></td>
<td>III</td>
<td>CV high-risk in Type 2 Diabetes</td>
</tr>
<tr>
<td><strong>Dalceprapib</strong></td>
<td>III</td>
<td>Dyslipidemia / CV high-risk</td>
</tr>
<tr>
<td><strong>Lebrikizumab</strong></td>
<td>II</td>
<td>Asthma</td>
</tr>
</tbody>
</table>

### CNS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycine reuptake inhibitor</strong></td>
<td>III</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td><strong>Ocrelizumab</strong></td>
<td>III</td>
<td>Multiple Sclerosis</td>
</tr>
</tbody>
</table>

* First in class  
^ LIP decision made, phase III pending,  
# LIP and phase III decision pending
# Late-stage pipelines update

## Oncology

| MetMAb | Phase III  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NCSLC and triple neg. mBC</td>
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</table>

| T-DM1* | Phase III  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive metastatic breast cancer</td>
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</table>

| Pertuzumab* | Phase III  
<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive metastatic breast cancer</td>
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</table>

| GA101 (RG7159)* | Phase III  
<table>
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<th></th>
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<tbody>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
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| BRAF inhibitor* | Phase III  
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<th></th>
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<tbody>
<tr>
<td>Malignant melanoma</td>
</tr>
</tbody>
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| Hedgehog inhibitor | Pivotal Phase II  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
</tr>
</tbody>
</table>

## Metabolism, Immunology & Virology

| Nucleoside Polymerase inhibitor* | Phase II  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Hepatitis C</td>
</tr>
</tbody>
</table>

| Aleglitazar | Phase III  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>CV high-risk in Type 2 Diabetes</td>
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</table>

| Dalceprapib* | Phase III  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia / CV high-risk</td>
</tr>
</tbody>
</table>

| Lebrikizumab # | Phase II Asthma |

## CNS

| Glycine reuptake inhibitor | Phase III  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

| Ocrelizumab | Phase III  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Multiple Sclerosis</td>
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</tbody>
</table>

* First in class  
^ LIP decision made, phase III pending, # LIP and phase III decision pending
MetMAb
Monovalent anti-Met antibody
MetMAb: a new compound that inhibits HGF-mediated activation

**MetMAb**
- Monovalent format designed to prevent HGF-mediated stimulation of pathway
- Preclinical activity across multiple tumor models

**Cancers in which Met potentially plays role**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Non-small cell lung carcinoma (NSCLC)</th>
<th>Triple negative metastatic breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma (RCC)</td>
<td>Gastric cancer</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer (CRC)</td>
<td>Met Autocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma multiforme (brain cancer)</td>
<td>Head and neck squamous cell cancer</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>Ovarian cancer</td>
<td></td>
</tr>
</tbody>
</table>

**Rationale for targeting Met**
- Met is amplified, mutated, overexpressed or uniquely activated in various cancers
- Met overexpression associated with worse prognosis in many cancers

HGF=Hepatocyte Growth Factor
MetMAb + Tarceva in lung cancer
Efficacy analysis in overall population

Early analysis of all patients
2nd/3rd line mNSCLC

PFS HR=1.09

OS HR=1.09

23 patients from the erlotinib+placebo arm crossed over to MetMAb.

Median PFS and OS are consistent with previously reported findings in similar disease setting.

Spigel et al, ESMO 2010
Diagnostic companion test
Understanding the biology of Met signalling

**NSCLC: Intensity of Met staining on tumor cells scored on 0–3 scale**

- 1+
- 2+
- 3+

‘Met high’ definition: \( \geq 50\% \) tumor cells with a staining intensity of 2+ or 3+

- Phase III in NSCLC with prospective testing of Met receptor over-expression
- Estimated that about one-half of NSCLC patients have Met high tumours
- Met IHC assay will be a companion test for the approval for MetMAb in NSCLC

Spigel et al, ESMO 2010
MetMAb + Tarceva in lung cancer
New example of Personalised Healthcare approach

Early analysis of Met High Patients
2nd/3rd line mNSCLC

PFS HR=0.56
OS HR=0.55

- 54% patients had ‘Met High’ NSCLC
- 12/23 patients from the Tarceva+placebo arm who crossed over to MetMAb were Met High.
- Final analysis to be presented at an upcoming medical meeting

Spigel et al, ESMO 2010
## MetMAb development plan

**NSCLC and triple-negative mBC**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>2nd and 3rd line Metastatic Non-small Cell Lung Cancer</th>
<th>1st and 2nd line Triple Negative Metastatic Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>Phase III</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Over-expressing Met Receptor</td>
<td>N=180</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>• <strong>ARM A</strong>: Tarceva plus MetMAb</td>
<td>• <strong>ARM A</strong>: Avastin and paclitaxel plus MetMAb</td>
</tr>
<tr>
<td></td>
<td>• <strong>ARM B</strong>: Tarceva plus placebo</td>
<td>• <strong>ARM B</strong>: Avastin and paclitaxel plus placebo</td>
</tr>
<tr>
<td></td>
<td>Prospective Met status testing.</td>
<td>• <strong>ARM C</strong>: paclitaxel plus MetMAb</td>
</tr>
<tr>
<td><strong>Primary end-point</strong></td>
<td>• Overall survival</td>
<td>• Progression-free survival</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>• Expect FPI in 2011</td>
<td>• Expect FPI Q1 2011</td>
</tr>
</tbody>
</table>
Pertuzumab and T-DM1
Advancing the HER2 franchise

T-DM1 in collaboration with ImmunoGen
HER2-positive breast cancer
Current treatment options

HER2-positive drug treated incidence

- **Late-lines of therapy**: high unmet medical need, novel therapies needed
- **Second line**: Xeloda + lapatinib is standard of care for patients who progressed on Herceptin
- **First line**: Standard of care is highly efficacious Herceptin + chemotherapy; poorly tolerated side effects of chemotherapy component
- **Adjuvant**: standard of care: Herceptin

Source: Roche estimates
HER2 franchise
Building on the strength of Herceptin

Pertuzumab
- Disrupts HER2:HER3 receptor dimers and downstream signaling
- In combination with Herceptin: potential to create new standard of care for women with HER2-positive metastatic BC

T-DM1
- Retains Herceptin’s biologic activity
- Targeted intracellular delivery of a potent cell-killing agent, DM1
- No need for conventional chemotherapy
HER2-positive breast cancer
Improving the standard of care

**2nd line mBC**
- Xeloda + lapatinib
- T-DM1 (EMILIA)

**1st line mBC**
- Herceptin + chemotherapy
- Herceptin & pertuzumab + chemotherapy (CLEOPATRA)
- T-DM1 & pertuzumab (MARIANNE)
- Herceptin + Avastin + chemotherapy (AVEREL)

**Early (adjuvant) BC**
- Herceptin + chemotherapy
- Herceptin Subcutaneous + chemotherapy
- Herceptin + Avastin + chemotherapy (BETH)

Timelines refer to the expected dates of first filing
# Herceptin & pertuzumab

Enhancing the HER2 blockade

## Timelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Early (adjuvant) BC</th>
<th>1st line mBC</th>
<th>2nd line mBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Herceptin + Avastin + chemotherapy (AVEREL)</td>
<td>Herceptin &amp; pertuzumab + chemotherapy (CLEOPATRA)</td>
<td>Xeloda + lapatinib</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td>T-DM1 &amp; pertuzumab (EMILIA)</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
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<td>2015</td>
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<tr>
<td>2016</td>
<td></td>
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</tbody>
</table>

Timelines refer to the expected dates of first filing.
Herceptin & pertuzumab: complementary mechanism of actions

**Herceptin:**
- prevents HER2 activation
- inhibits ligand-independent HER2 signalling and flags cells for destruction by the immune system

**Pertuzumab:**
- inhibits ligand-activated HER2 dimerisation
- flags cells for destruction by the immune system
- suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER2-driven signalling

---

Herceptin & Pertuzumab:
higher efficacy than individual compounds

Herceptin & Pertuzumab:
antitumour effect following progression on Herceptin alone

*KPL-4 breast cancer xenograft model; SEM = standard error of the mean

Herceptin & pertuzumab demonstrate encouraging efficacy in proof of concept phase II study

- Phase II in patients with HER2+ mBC who progressed on Herceptin-based therapy
- Cohort 3 received pertuzumab only; after disease progression moved to pertuzumab & Herceptin

 Depends on [chart]

ORR=25% CBR=50%

ORR=3% CBR=10%

ORR=21% CBR=43%

*aOnly 27 patients are evaluable: 1 patient did not progress on pertuzumab monotherapy before moving on to combination therapy and 1 patient’s tumour was unassessable after Cycle 2

*b*n=14 as at data cut-off; 1 patient had not reached overall best response endpoint (8 cycles of assessment during this phase) and 1 patient died before efficacy assessment; ORR=Objective Response Rate; CBR=Clinical Benefit Rate

Baselga et al. SABCS 2009. Abstract 5114
Herceptin & pertuzumab in neoadjuvant HER2+ BC
An important result from NEOSPHERE trial

Neoadjuvant treatment

- Herceptin q3w for 1 year
- Docetaxel q3w x 4
- Pertuzumab q3w x 4

N=417

Adjuvant treatment

- Herceptin q3w for 1 year
- FEC x 3 q3w
- Docetaxel x 4 q3w
- FEC x 3 q3w

Primary endpoint: pCR rate at time of surgery
Data to be presented tomorrow at SABCS

EBC = early-stage breast cancer; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; pCR = pathological complete response (tumour eradication); q3w = every 3 weeks
First line HER2-positive metastatic BC
Herceptin and pertuzumab: CLEOPATRA trial

Primary endpoint:
- Progression-free survival

- Enrolment completed Q2 2010
- Expect PFS data 2011
- Filing in 2011
Herceptin & pertuzumab in adjuvant setting
Potentially increasing the cure rate

HER2-positive early breast cancer
N=~4000

Primary end-point:
- 3 year Disease Free Survival

Herceptin + chemotherapy

Herceptin & pertuzumab + chemotherapy

Chemotherapy: FEC x 3 → TH x 3 or AC x 4 → TH x 4 or TCH x 6; Total duration of Herceptin treatment=1 year
FEC = 5-fluorouracil, Epirubicin, Cyclophosphamide; TH=Taxotere, Herceptin; AC=cyclophosphamide, doxorubicin; TCH=Taxotere, Carboplatin, Herceptin

FPI: Q3 2011
Follow-up: 3 years (median)
Expect data 2016
T-DM1 in HER2-positive breast cancer treatment
Overcoming the hurdles of conventional chemotherapy

2nd line mBC
- Xeloda + lapatinib
- T-DM1 (EMILIA)

1st line mBC
- Herceptin + chemotherapy
- Herceptin & pertuzumab + chemotherapy (CLEOPATRA)
- Herceptin + Avastin (AVAREL)
- T-DM1 & pertuzumab (MARIANNE)

Early (adjuvant) BC
- Herceptin + chemotherapy
- Herceptin Subcutaneous + chemotherapy
- Herceptin & pertuzumab + chemotherapy
- Herceptin + Avastin + chemotherapy (BETH)

Timelines refer to the expected dates of first filing
T-DM1 in late lines metastatic setting
Strong efficacy in highly pretreated patients

**HER2-positive mBC patients:**

- Median number of prior agents for metastatic disease: 7
- Prior exposure to an anthracycline, a taxane, capecitabine, lapatinib and trastuzumab.
- Received two HER2-directed regimens in the metastatic setting.

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>IRF (N=110)</th>
<th>Investigator (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate, %</strong></td>
<td>34.5</td>
<td>32.7</td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td>(26.1–43.9)</td>
<td>(24.1–42.1)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate, %</strong></td>
<td>48.2</td>
<td>46.4</td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td>(38.8–57.9)</td>
<td>(37.1–56.1)</td>
</tr>
</tbody>
</table>

TDM4374g: SABCS 2009, updated at ESMO 2010

IRF=Independent Review Facility

Objective Response=complete or partial response determined by two consecutive tumor assessments at least 28 days apart.

Clinical Benefit=objective response or stable disease maintained for at least 6 months.
Second line HER2-positive metastatic breast cancer
T-DM1 to demonstrate benefit over standard of care

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Second-line&lt;sup&gt;1&lt;/sup&gt; HER2-positive Metastatic Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase/Study</td>
<td>Phase III EMILIA</td>
</tr>
<tr>
<td># of Patients</td>
<td>N=580</td>
</tr>
</tbody>
</table>
| Design             | • ARM A: T-DM1  
                     • ARM B: Xeloda plus lapatinib                              |
| Primary Endpoint   | • Progression-free survival                                  |
| Status             | • FPI Q1 2009                                               
                     • Expect data early 2012                                  |

<table>
<thead>
<tr>
<th>Second-line&lt;sup&gt;1&lt;/sup&gt; HER2-positive Metastatic Breast Cancer</th>
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<tbody>
<tr>
<td>Phase III EMILIA</td>
</tr>
<tr>
<td>N=980</td>
</tr>
</tbody>
</table>
| • ARM A: T-DM1  
                     • ARM B: Xeloda plus lapatinib                              |
| Co-primary endpoints:                                       |
| • Progression-free survival                                 |
| • Overall survival                                          |
| • FPI Q1 2009                                               |
| • Expect PFS data 2012                                       |

- Trial recruiting well.
- Filing for accelerated approval expected in 2012, with mature PFS data.
- OS data to be provided within 1.5 years thereafter.

<sup>1</sup> Patients must have received prior treatment which included both: a taxane, alone or in combination with another agent, and trastuzumab in the adjuvant, locally advanced, or metastatic setting.
First line: T-DM1 vs. Herceptin+docetaxel
Robust efficacy and lower rate of chemo-related side effects

**HER2+ recurrent locally advanced BC or MBC (N=137)**

**T-DM1**
3.6 mg/kg Q3W until PD (N=67)

**Herceptin**
8 mg/kg dose; 6 mg/kg Q3W + Docetaxel
75 or 100 mg/m² Q3W (N=70)

<table>
<thead>
<tr>
<th>Safety evaluable patients</th>
<th>T-DM1</th>
<th>Herceptin + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=67</td>
<td>n=68</td>
<td></td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>63 (94.0)</td>
<td>68 (100.0)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>25 (37.3)</td>
<td>51 (75.0)</td>
</tr>
<tr>
<td>Serious AE*</td>
<td>13 (19.4)</td>
<td>15 (22.1)</td>
</tr>
</tbody>
</table>

Objective Response*

**32 (47.8%)**

**29 (41.4%)**

* assessed before cross-over

Perez et al. ESMO 2010
First line: T-DM1 vs. Herceptin+docetaxel

Safety and selected side effects of T-DM1

Overall, T-DM1 appears to be far better tolerated than Docetaxel- Trastuzumab. Rate of Grade 3-4 Events decreased by ~50%

Eric Winer, Discussion of 4450 study at ESMO 2010

LFT=Liver Function Test
First-line HER2-positive mBC: MARIANNE trial
T-DM1 and pertuzumab vs standard of care

Primary end-point:
- Progression-free survival
- Recruitment started Q3 2010
- Expect data 2014
Redefining HER2 blockade: pertuzumab and T-DM1
Increasing the efficacy and tolerability in first line
BRAF inhibitor in melanoma
PLX4032, RG7204
Metastatic melanoma

- Major cause of death from skin cancer
- Incidence has increased significantly, on average 4% p.a. in US

Incidence of first-line metastatic melanoma

2010E Number of patients

Drug-treated Incidence

Top 5 EU: 7200
BRAF Mutation Positive

US: 6900

Top 5 EU: 3800
BRAF Mutation Positive

US: 3600
The Target: BRAF Kinase
An important mediator of cellular proliferation

- Oncogenic mutation of BRAF
  ~8% of all solid tumors
  ~50% of malignant melanomas

- shRNA knock down experiments support its role in neoplastic behavior

- BRAF mutation knock-in mice develop melanoma-like malignancies

- RG7204 arrests abnormal cell growth in melanoma models

Sosman et al, Int. Melanoma Congress 2010
BRAF mutation analysis for patient selection
Development of companion diagnostic

- FFPE Tumor Block
- Tissue Preparation
- Genomic DNA Extraction
- TaqMan Real-time PCR

BRAF mutation testing in BRIM2 trial
- cobas® 4800 BRAF V600 Mutation Test
- Designed to detect V600E (1799 T>A) mutation
- Samples analyzed at central labs
- 324 samples screened; 183 mutation-positive (56%)

FFPE=Formalin-Fixed Paraffin-Embedded
Sosman et al, Int. Melanoma Congress 2010
BRIM2: single arm study in mutation positive patients
Tumor responses assessed by IRC

- Best Overall Response Rate: 52% by IRC*
- Best Overall Response Rate: 55% by investigator assessments (INV)
- Response Rate: 68% (INV), including unconfirmed

BORR=Best Overall Response Rate; IRC=Independent Review Committee;
*6 patients were unevaluable; bars represent 90% confidence interval

Sosman et al, Int. Melanoma Congress 2010
Tumor regression occurred in majority of patients

- 7 patients had 100% tumor shrinkage, 3 of which had confirmed CR;
- 1 patient had unconfirmed CR and 3 patients had non-target lesions present
- 122 patients had baseline and ≥ 1 post-baseline scan with measurable disease

Sosman et al, Int. Melanoma Congress 2010
BRAF inhibitor safety profile

Cutaneous SCC: Keratoacanthoma (KA) Subtype

Adverse events in BRIM2

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All grades</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia (joint pain)</td>
<td>57.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Rash</td>
<td>51.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>49.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Alopecia (hair loss)</td>
<td>33.3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cutaneous SCC</strong></td>
<td><strong>24.2</strong></td>
<td><strong>24.2</strong></td>
</tr>
<tr>
<td>Pruritis (itching)</td>
<td>27.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Skin papilloma (verruca)</td>
<td>27.3</td>
<td>0</td>
</tr>
</tbody>
</table>

- 130 patients experienced at least one drug-related AE

Characteristics of KA subtype
- Raised button-like, central crater
- Well-differentiated neoplasm with low probability of invasion/metastasis
- Can grow rapidly; may involute and regress
- Typically treated by excision
- Observed with other agents (e.g., sorafenib)

KA in the Phase I RG7204 Trial
- Occurred on sun-exposed skin
- Did not result in treatment discontinuation

SCC=Squamous Cell Carcinoma
# BRAF inhibitor development

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Second- and Third line Malignant Melanoma BRAF mutation positive</th>
<th>First-line Malignant Melanoma BRAF mutation positive</th>
<th>Previously treated metastatic melanoma BRAF mutation positive</th>
<th>First-line Malignant Melanoma BRAF mutation positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase/Study</strong></td>
<td><strong>Phase II BRIM2</strong></td>
<td><strong>Phase III BRIM3</strong></td>
<td><strong>Patient Access Program</strong></td>
<td><strong>Patient Access Program</strong></td>
</tr>
<tr>
<td><strong># of Patients</strong></td>
<td>N=132</td>
<td>N=~680</td>
<td>N=400 (US)</td>
<td>N=1,000 (exUS)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>• <strong>Single ARM</strong>: RG7204</td>
<td>• <strong>ARM A</strong>: RG7204</td>
<td>• <strong>Single ARM</strong>: RG7204</td>
<td>• <strong>Single ARM</strong>: RG7204</td>
</tr>
<tr>
<td></td>
<td>• <strong>ARM B</strong>: dacarbazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>• Best overall response rate assessed by IRC using RECIST criteria</td>
<td>• Overall survival</td>
<td>• Safety</td>
<td>• Safety</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>• Presented at Int. Melanoma Congress 2010</td>
<td>• FPI Q1 2010</td>
<td>• US site open for enrollment Q4 2010</td>
<td>• Expect to open access program as soon as the Phase III BRIM3 study results are available</td>
</tr>
</tbody>
</table>

---

**BRIM2 data shared with healthcare authorities (FDA and EMA)**

Further regulatory steps under evaluation
GA101
Type II, glycoengineered anti-CD20 monoclonal antibody

In collaboration with Biogen Idec
GA101: a type II, glycoengineered anti-CD20
Increasing efficacy vs. rituximab

**Increased direct cell death**
Type II vs. Type I antibody

**Enhanced ADCC**
Glycoengineering for increased affinity to FcyRIIIa

**Lower CDC activity**
Type II vs. Type I antibody

ADCC=Antibody-Dependent Cell-mediated Cytotoxicity; CDC= Complement Dependent Cytotoxicity

*Mössner E, et al. Blood. 2010; June 3; 115:4393-4402*
GA101: superior in vitro and in vivo efficacy compared to Type I CD20 antibodies

GA101 shows superior direct cell death induction

Superior tumor growth inhibition vs. Type I CD20 antibodies

Panel of NHL cell lines; measured by AxV/PI exposure

SU-DHL4 xenografts

Rajie et al., 52st ASH annual meeting 2010, Orlando, Poster #3925,
Preclinical summary of GA101
A differentiated anti-CD20 monoclonal antibody

- Increased direct cell death induction due to type II mode of binding
- Increased ADCC due to glycoengineering (stronger affinity to FcγRIIIa)
- Superior B-cell depletion demonstrated in whole-blood assay as well as lymphoid tissue in cynomolgus monkeys
- Superior tumour remissions in various NHL xenograft models (incl. DLBCL, MCL, and follicular Lymphoma)

ADCC=Antibody-Dependent Cell-mediated Cytotoxicity; CDC= Complement Dependent Cytotoxicity
GA101 in relapsed/refractory indolent NHL
High response rates in heavily pretreated patients

GAUGUIN phase II results
1600/800 mg

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
<th>Unknown</th>
<th>ORR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>iNHL 1600 mg/800mg (n=22)</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>55%</td>
</tr>
<tr>
<td>Rituximab-refractory iNHL 1600 mg/800 mg (n=11)</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>50%</td>
</tr>
<tr>
<td>Median PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.3 months</td>
</tr>
</tbody>
</table>

†Overall Response Rate based on evaluable patients

Salles G, et al. ASH 2010; Abstract 2868
GA101 in relapsed/refractory aggressive NHL
Promising response rates in heavily pretreated patients

**GAUGUIN phase II results in aNHL**
**1600/800 mg**

| Cohort (n=19) (1600 mg/800 mg) | Complete Response/ Complete Response unconfirmed | Partial Response | Stable Disease | Progressive Disease | ORR  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=19)</td>
<td>-</td>
<td>6</td>
<td>1</td>
<td>12</td>
<td><strong>32%</strong></td>
</tr>
<tr>
<td>Mantle-cell Lymphoma (n=4)</td>
<td>-</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td><strong>50%</strong></td>
</tr>
<tr>
<td>Diffuse large B-cell Lymphoma (n=15)</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td><strong>27%</strong></td>
</tr>
<tr>
<td>Rituximab-refractory (n=12)</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td><strong>25%</strong></td>
</tr>
</tbody>
</table>

Median of 4 prior therapies

## GA101 in NHL and CLL: development plan

**Aiming to show superiority versus current standard of care**

### Ongoing trials

<table>
<thead>
<tr>
<th>Front-line CLL</th>
<th>Indolent NHL MabThera/Rituxan Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III CLL11</strong></td>
<td><strong>Phase III GADOLIN</strong></td>
</tr>
<tr>
<td>N=780</td>
<td>N=360</td>
</tr>
<tr>
<td><strong>ARM A:</strong> GA101 plus chlorambucil</td>
<td><strong>ARM A:</strong> GA101 plus Bendamustine</td>
</tr>
<tr>
<td><strong>ARM B:</strong> MabThera/Rituxan plus chlorambucil</td>
<td><strong>ARM B:</strong> Bendamustine</td>
</tr>
<tr>
<td><strong>ARM C:</strong> Chlorambucil alone</td>
<td></td>
</tr>
<tr>
<td>•Progression-free survival</td>
<td>•Progression-free survival</td>
</tr>
<tr>
<td>•FPI Q4 2009</td>
<td>•FPI Q2 2010</td>
</tr>
<tr>
<td>•Expect data 2013</td>
<td>•Expect data 2015</td>
</tr>
</tbody>
</table>

### To start in 2011

<table>
<thead>
<tr>
<th>1st Line indolent NHL</th>
<th>1st Line aggressive NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III</strong></td>
<td><strong>Phase III</strong></td>
</tr>
<tr>
<td>•<strong>ARM A:</strong> GA101 + chemotherapy followed by GA101 maintenance</td>
<td>•<strong>ARM A:</strong> GA101 + chemotherapy</td>
</tr>
<tr>
<td>•<strong>ARM B:</strong> MabThera/Rituxan + chemotherapy followed by MabThera/Rituxan maintenance</td>
<td>•<strong>ARM B:</strong> MabThera/Rituxan + chemotherapy</td>
</tr>
<tr>
<td>•FPI planned 2011</td>
<td>•FPI planned 2011</td>
</tr>
</tbody>
</table>

**Ongoing trials**

**Front-line CLL**
- Patients with comorbidities

**Indolent NHL MabThera/Rituxan Refractory**

**ARM A:** GA101 plus chlorambucil
**ARM B:** MabThera/Rituxan plus chlorambucil
**ARM C:** Chlorambucil alone

- Progression-free survival
- FPI Q4 2009
- Expect data 2013
- FPI Q2 2010
- Expect data 2015

---

**To start in 2011**

**1st Line indolent NHL**
- FPI planned 2011

**1st Line aggressive NHL**
- FPI planned 2011
Hedgehog pathway inhibitor
RG3616
**Hedgehog pathway inhibitor in basal cell carcinoma**

**Phase I efficacy data**

- RG3616 is efficacious in treating advanced basal cell carcinoma
  - 33 BCC patients treated in Phase I*
  - >50% had a response to therapy (IRF assessed)
    - 2 (6.1%) complete response
    - 16 (48.5%) partial response
  - Median duration of response >8.8 months
  - Well-tolerated with reversible, mild adverse events

---

* Von Hoff, et al., *New England Journal of Medicine, September 2009*
## Hedgehog Pathway Inhibitor GDC-0449
### Development plan

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Advanced Basal Cell Carcinoma</th>
<th>Operable Basal Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase/Study</td>
<td>Pivotal Phase II</td>
<td>Phase II</td>
</tr>
<tr>
<td># of Patients</td>
<td>N=100</td>
<td>N=49</td>
</tr>
<tr>
<td>Design</td>
<td>• <strong>Single ARM: GDC-0449</strong></td>
<td>• <strong>Single ARM: GDC-0449</strong></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>• Overall response rate</td>
<td>• COHORT 1: Complete clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• COHORT 2: Durable complete clearance</td>
</tr>
<tr>
<td>Status</td>
<td>• Enrolment completed Q1 2010</td>
<td>• FPI Q4 2010</td>
</tr>
<tr>
<td></td>
<td>• Expect data results H1 2011</td>
<td></td>
</tr>
</tbody>
</table>
## Late-stage portfolio update

### Metabolism, Immunology & Virology

<table>
<thead>
<tr>
<th>Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MetMAb</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>NCSLC and 3N mBC</td>
</tr>
<tr>
<td><strong>T-DM1</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td><strong>Pertuzumab</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td><strong>GA101 (RG7159)</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td><strong>BRAF inhibitor</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Malignant melanoma</td>
</tr>
<tr>
<td><strong>Hedgehog inhibitor</strong></td>
</tr>
<tr>
<td>Pivotal Phase II</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism, Immunology &amp; Virology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Polymerase inhibitor</strong></td>
</tr>
<tr>
<td>Phase II</td>
</tr>
<tr>
<td>Chronic Hepatitis C</td>
</tr>
<tr>
<td><strong>Aleglitazar</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>CV high-risk in Type 2 Diabetes</td>
</tr>
<tr>
<td><strong>Dalcetrapib</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Dyslipidemia / CV high-risk</td>
</tr>
<tr>
<td><strong>Lebrikizumab</strong></td>
</tr>
<tr>
<td>Phase II Asthma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycine reuptake inhibitor</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td><strong>Ocrelizumab</strong></td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
</tr>
</tbody>
</table>

* First in class  
^ LIP decision made, phase III pending, # LIP and phase III decision pending
RG7128: novel NS5B nucleoside polymerase inhibitor of HCV

- Active against HCV genotypes 1, 2, 3 and 4\(^1-3\)
- No evidence of baseline or treatment-emergent resistance\(^4,5\)
- Renally excreted
- Not metabolized by liver enzymes
- Low potential for drug–drug interactions
- 12 weeks interim analysis presented at AASLD show excellent efficacy
- Final data 2011

**Aleglitazar**

**Effects of $\alpha/\gamma$ PPAR activation**

**Primary $\alpha$ effect:**
- Improve plasma lipid profile
  - $\uparrow$ Fatty acid uptake
  - $\uparrow$ Fatty acid oxidation
  - $\uparrow$ apo AI, HDL
  - $\downarrow$ VLDL-TG
  - $\downarrow$ apo-CIII
  - Anti-inflammatory

**Primary $\gamma$ effect:**
- Improve insulin sensitivity
  - $\uparrow$ Fatty acid uptake
  - $\uparrow$ Beta cell function
  - $\uparrow$ Adiponectin secretion
  - Anti-inflammatory

**Heart, liver, muscle, vasculature**

**Adipocytes**

**Muscle**

Roche
Aleglitazar development in patients with high CV risk
Phase III CV outcomes study

**Design**
- Double-blind, placebo-controlled study on top of standard of care
- Treatment duration: At least 2.5 years
- \( N = 6,000 \)

**Patients**
- Type 2 diabetes (known and recently diagnosed)
- Hospitalized for acute coronary syndrome

<table>
<thead>
<tr>
<th>Screening/ placebo run-in period</th>
<th>Treatment period</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aleglitazar 150 ( \mu )g or placebo</td>
<td>Standard of care (diabetes and other cardiovascular risk factors)</td>
<td>At least 2.5 years</td>
</tr>
</tbody>
</table>

**Primary endpoint**
- Composite endpoint of reduction in cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke (MACE)
CETP activity: transfer of neutral lipids among all lipoproteins

Lipid-poor ApoA-I (pre-β HDL) → HDL3c → HDL3b → HDL3a → HDL2a → HDL2b

CETP

VLDL → LDL

Modulating Cholesteryl Ester Transfer Protein Activity Maintains Efficient Pre-β HDL Formation and Increases Reverse Cholesterol Transport

CETP modulation vs. CETP inhibition

By modulating CETP, dalcetrapib does not inhibit pre-beta-HDL formation and cholesteryl ester (CE) transfer between HDL particles, while decreasing CE transfer to LDL/VLDL.
Dalcetrapib positive effect on pre-β HDL formation and reverse cholesterol transfer

Effect of Dalcetrapib, Torcetrapib, and Anacetrapib on pre-β HDL Formation in Human Plasma In Vitro
Without addition of exogenous CETP

Relationship Between HDL AUC and Fecal Labelled Sterols

* P < 0.01 (HDL·AUC); # P < 0.01 (radioactivity of fecal total sterols) vs. control (Dunnett test)

Dalcetrapib (RG1658)
Development program

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>dal-HEART Programme Global Research Initiative</th>
</tr>
</thead>
</table>
| **Phase/Study**     | **Phase IIb** dal-VESEL
Endothelial Function study | **Phase IIb** dal-PLAQUE
Imaging study | **Phase III**
dal-OUTCOMES
Mortality and Morbidity study | **Phase III**
dal-PLAQUE 2*
Imaging study |
| **# of Patients**   | N=476                                | N=130                                | N=15,600                              | N=900                                 |
| **Design**          | In addition to standard medication (including statins): 36 weeks treatment duration
- ARM A: Dalcetrapib
- ARM B: Placebo | In addition to standard medication (including statins): 24 months treatment duration
- ARM A: Dalcetrapib
- ARM B: Placebo | In addition to standard medication for ACS (including statins): Minimum of 24 months treatment duration
- ARM A: Dalcetrapib
- ARM B: Placebo | In addition to standard medication (including statins): 24 months treatment duration
Uses both IMT and IVUS ultrasound imaging techniques
- ARM A: Dalcetrapib
- ARM B: Placebo |
| **Primary Endpoint**| Change from baseline in mean blood pressure (4 weeks)
Change from baseline in % flow mediated dilatation (12 weeks) | Change from baseline of MRI plaque size/burden (12 months)
Change from baseline in plaque to background (blood) ratio from an index vessel by PET/CT (6 months) | Time to first occurrence of any component of the composite cardiovascular event | Assess the change from baseline in the progression of atherosclerosis using IMT and IVUS in coronary and carotid vascular beds in the same patients |
| **Status**          | Initiated Q2 2008
Enrolment completed Q3 2009
Expect data in 2011 | Initiated Q1 2008
Enrolment completed Q4 2008
Expect data in 2011 | Initiated Q2 2008
Enrolment completed Q2 2010
Expect interim analysis in 2011* | Initiated Q4 2009 |

In collaboration with Japan Tobacco

*Study being conducted in collaboration with the Canadian Atherosclerosis Imaging Network and Montreal Heart Institute
CHD = Stable coronary heart disease; PET/CT = Positron Emission Tomography/Computed Tomography; MRI = Magnetic Resonance Imaging; ACS = Acute Coronary Syndrome; CAD = Coronary artery disease; IMT = Intima-Media Thickness; IVUS = Intravascular Ultrasound.

*Event driven interim analysis
**Lebrikizumab: anti-IL13 antibody**

**Serum periostin levels may serve as a surrogate for anti-IL13 responsive patients**

1. Asthma is a heterogeneous disease
2. Serum periostin and/or other markers may serve as a serum surrogate for gene signature
3. Identification of predictive diagnostic marker may predict improved clinical responses to lebrikizumab (anti-IL13)
## Lebrikizumab development programme

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Adult Patients Who Are Inadequately Controlled on Inhaled Corticosteroids</th>
<th>Adult Patients Who Are Not Taking Inhaled Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase/Study</strong></td>
<td>Phase II MILLY <em>Proof of concept Study</em></td>
<td>Phase II MOLLY <em>Dose-ranging Study</em></td>
</tr>
<tr>
<td># of Patients</td>
<td>N=218</td>
<td>N=200</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>• ARM A: Lebrikizumab</td>
<td>• ARM A: Lebrikizumab (low dose)</td>
</tr>
<tr>
<td></td>
<td>• ARM B: Placebo</td>
<td>• ARM B: Lebrikizumab (medium dose)</td>
</tr>
<tr>
<td></td>
<td>• ARM C: Lebrikizumab (high dose)</td>
<td>• ARM C: Lebrikizumab (high dose)</td>
</tr>
<tr>
<td></td>
<td>• ARM D: Placebo</td>
<td>• ARM D: Placebo</td>
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<tr>
<td><strong>Status</strong></td>
<td>• FPI Q3 2009</td>
<td>• FPI Q4 2009</td>
</tr>
<tr>
<td></td>
<td>• Enrolment completed Q1 2010</td>
<td>• Enrolment completed Q3 2010</td>
</tr>
</tbody>
</table>

Data to be presented in 2011
Results from 10 key trials in Q4

Short-term newsflow

• **Breast Cancer: T-DM1 in 1st line HER2-positive breast cancer**
  - randomised Phase II data - first cut; RR but not yet PFS or OS – ESMO (October 8-12, Milano)

• **Non-Small Cell Lung Cancer: MetMab in 2nd/ 3rd line NSCLC**
  - randomised Phase II - ESMO

• **Ovarian Cancer: ICON7 Avastin in front line ovarian cancer**
  - Phase III pivotal data - ESMO

• **Multiple Sclerosis: Ocrelizumab in RRMS**
  - randomised Phase II - ECTRIMS (15 October, Gothenburg)

• **Hepatitis C: Nucleoside Polymerase inh (RG7128)**
  - randomised Phase IIb PROPEL interim data – AASLD (October 28-Nov 2, Boston)

• **Metastatic Melanoma: BRAF inh**
  - Phase II BRIM2 data; Intl. Melanoma Research Congress (November 4-9, Sydney)

• **Non-Hodgkin's Lymphoma: GA101 in aNHL**
  - randomised Phase II data – ASH (December 4-7, 2010, Orlando)

• **Schizophrenia: Glycine reuptake inh**
  - randomised Phase II data - ACNP (December 5-9, Miami)

• **Breast Cancer: Pertuzumab neoadjuvant**
  - randomised Phase II data - NEOSPHERE- SABCS (December 8-12, San Antonio)

• **Asthma: Lebrikizumab**
  - randomised Phase II MILLY – data in house
Roche

We Innovate Healthcare
CNS
Glycine reuptake inhibitor and Ocrelizumab

Eugene Tierney
Global Product Strategy TA Head, CNS
**Late-stage pipelines update**

**CNS**

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Metabolism, Immunology &amp; Virology</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MetMAb</strong>&lt;br&gt;Phase III&lt;br&gt;<em>NCSLC and 3N mBC</em></td>
<td><strong>Nucleoside Polymerase inhibitor</strong>^&lt;br&gt;Phase II&lt;br&gt;<em>Chronic Hepatitis C</em></td>
<td><strong>Glycine reuptake inhibitor</strong>&lt;br&gt;Phase III&lt;br&gt;<em>Schizophrenia</em></td>
</tr>
<tr>
<td><strong>T-DM1</strong>*&lt;br&gt;Phase III&lt;br&gt;<em>HER2-positive metastatic breast cancer</em></td>
<td><strong>Aleglitazar</strong>&lt;br&gt;Phase III&lt;br&gt;<em>CV high-risk in Type 2 Diabetes</em></td>
<td><strong>Ocrelizumab</strong>&lt;br&gt;Phase III&lt;br&gt;<em>Multiple Sclerosis</em></td>
</tr>
<tr>
<td><strong>Pertuzumab</strong>*&lt;br&gt;Phase III&lt;br&gt;<em>HER2-positive metastatic breast cancer</em></td>
<td><strong>Dalcetrapib</strong>*&lt;br&gt;Phase III&lt;br&gt;<em>Dyslipidemia / CV high-risk</em></td>
<td></td>
</tr>
<tr>
<td><strong>GA101 (RG7159)</strong>*&lt;br&gt;Phase III&lt;br&gt;<em>Non-Hodgkin’s lymphoma</em></td>
<td><strong>Lebrikizumab</strong> #&lt;br&gt;Phase II&lt;br&gt;<em>Asthma</em></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF inhibitor</strong>*&lt;br&gt;Phase III&lt;br&gt;<em>Malignant melanoma</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hedgehog inhibitor</strong>&lt;br&gt;Pivotal Phase II&lt;br&gt;<em>Basal cell carcinoma</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* First in class<br>^ LIP decision made, phase III pending, # LIP and phase III decision pending
Glycine reuptake inhibitor (GlyT-1)
RG1678, the first GRI in schizophrenia
Schizophrenia
Disease and epidemiology

Multiple symptoms

POSITIVE
• Hallucinations
• Delusions
• Thought disorder
• Bizarre behavior

NEGATIVE
• Anhedonia
• Social withdrawal
• Self-neglect

MOOD
• Anxiety
• Depression

COGNITIVE
• Attention deficits
• Poor executive function
• Poor working memory

Epidemiology*

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnosed Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>0.7</td>
</tr>
<tr>
<td>Japan</td>
<td>0.8</td>
</tr>
<tr>
<td>France</td>
<td>0.7</td>
</tr>
<tr>
<td>Germany</td>
<td>0.8</td>
</tr>
<tr>
<td>Italy</td>
<td>0.8</td>
</tr>
<tr>
<td>Spain</td>
<td>0.7</td>
</tr>
<tr>
<td>UK</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Source: Decision Resources, Jan. 2010
Available treatment options

Only positive symptoms addressed by antipsychotics

**Dual-dopamine/5HT2 antagonists:**
- Poor efficacy in negative and cognitive symptoms
- Low tolerability: EPS (movement disorders), hypotension, obesity, diabetes, QTc prolongations

**Better treatment for positive symptoms needed:**
- Widespread use of combination therapy (app. 60 % *)
- No safety data for D2 combinations
- No controlled studies with combinations in schizophrenia

Schizophrenia is associated with NMDA receptor dysfunction

**Genetic and environmental factors**

- **Glutamate site activation**
  - Risk of neurotoxicity (too much calcium entry)

- **Modulation via glycine reuptake**
  - Safe way to enhance NMDA activity

**Current treatment**
- Dopamine receptor blockade

**NMDA dysfunction**

- Sensory deficit
- Generalized cognitive deficit
- Impaired learning and memory
- Thought disorder
- Negative symptoms
- **Positive symptoms**
- **Gating deficit**
- **Executive dysfunction**

**Risk of neurotoxicity** (too much calcium entry)

**Modulation via glycine reuptake**

- Safe way to enhance NMDA activity

Modified from: Kantrowitz JT, Brain research Bulletin 2010
Glutamate/NMDA hypothesis of schizophrenia

GRI increases signaling through NMDA receptor

Both Glutamate and Glycine are needed for NMDA receptor function

NMDA= N-methyl-D-aspartate; GRI=glycine reuptake inhibitor; GlyT-1=type-1 glycine transporter

GlyT-1 potentially benefits both positive and negative symptoms

Healthy

- Decreases dopamine levels in the striatum (nucleus accumbens) where it impacts positive symptoms

Schizophrenia

- GlyT-1 activates NMDA receptors on GABA and dopaminergic neurons and excite them
  - Decreases dopamine levels in the striatum (nucleus accumbens) where it impacts positive symptoms
  - Increases dopamine levels in the prefrontal cortex where it benefits negative symptoms

GlyT-1 shows efficacy in pre-clinical models thought to predict efficacy in positive symptoms

GRI modulates dopamine transmission without blocking D2 receptors

GRI can enhance the efficacy of antipsychotics

<table>
<thead>
<tr>
<th>Compound</th>
<th>ED90, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlyT-1</td>
<td>0.3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.55</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.2</td>
</tr>
</tbody>
</table>

# = p < 0.05 vs Vehicle; * = p < 0.05; ** = p < 0.01; *** = p < 0.001 vs Amphetamine
Level of receptor occupancy determines efficacy. ~50% sufficient for full efficacy in all animal models.

Rat in vivo binding

Monkey PET

Human PET

Optimal predicted human dose: 10–30 mg range
GlyT-1 in negative symptoms of schizophrenia
Phase 2 Proof-of-Concept study design

**Screening & Run-in**

- Screening
  - 4 weeks

**8 Week Treatment**

- Placebo (N=81)
- 10 mg (N=82)
- 30 mg (N=81)
- 60 mg (N=79)

**Follow-up**

- 4 weeks

**Population**
- Patients with predominant negative symptoms, stabilised on antipsychotic medication

**Primary endpoint**
- PANSS Negative Symptom Factor Score

**Secondary endpoints**
- CGI-S/I for Negative Symptoms
- PSP
- CNSVitalSigns

**Negative symptoms**

**Clinical assessment**

**Function**

**Cognition**

75
GlyT-1 in negative symptoms of schizophrenia

Significant reduction in negative symptom factor score*

Effect Size (Week 8): 10 mg = 0.37, 30 mg = 0.40

*PP population
Consistent effects on all measured outcomes*

**Response rate**

- Placebo: 43%
- RG1678 10mg/day: 65%
- RG1678 30mg/day: 60%
- RG1678 60mg/day: 43%

*p=0.0126
p=0.0882

**CGI-I of negative symptoms**

- Placebo: p=0.0255
- RG1678 10mg/day: p=0.0126
- RG1678 30mg/day: p=0.0882
- RG1678 60mg/day: p=0.061

**Change in function (PSP)**

- Placebo: Week 4 = 54, Week 8 = 56
- RG1678 10mg/day: Week 4 = 55, Week 8 = 58
- RG1678 30mg/day: Week 4 = 53, Week 8 = 57
- RG1678 60mg/day: Week 4 = 52, Week 8 = 56

*PP population; Response rate: ≥ 20% improvement in NSFS; PSP=Personal and Social Performance; CGI-I=Clinical Global Impression-Improvement
GlyT-1: placebo-like safety profile

Adverse events by body system during treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10 mg/day</th>
<th>30 mg/day</th>
<th>60 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients with ≥ one AE</td>
<td>40</td>
<td>41</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>Nervous system</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>Infectious</td>
<td>10</td>
<td>13</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>11</td>
<td>6</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>General disorder</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Musculo-skeletal-connective</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
GlyT-1 in positive symptoms of schizophrenia
Phase II: trend in reduction of positive symptoms

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>RG1678 10mg/day</th>
<th>RG1678 30mg/day</th>
<th>RG1678 60mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Mean change from baseline

Placebo
RG1678 10mg/day
RG1678 30mg/day
RG1678 60mg/day

ES = –0.38

*PP population; patients with baseline positive symptom factor score ≥ 18 (median split 30-35 patients/arm)
## GlyT-1 in phase III: exploring two indications

### Negative symptoms and sub-optimally controlled patients

<table>
<thead>
<tr>
<th>Negative symptoms of schizophrenia (3 trials)</th>
<th>Patients with sub-optimally controlled symptoms of schizophrenia (3 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td><strong>No. of patients</strong></td>
</tr>
<tr>
<td>2x</td>
<td>2x</td>
</tr>
<tr>
<td>N=620</td>
<td>N=600</td>
</tr>
<tr>
<td>1:1:1 randomisation</td>
<td>1:1:1 randomisation</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td>PANSS negative symptoms factor score at week 24</td>
<td>PANSS positive symptoms factor score at week 12</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>ARM A: 10 mg GlyT-1</td>
<td>ARM A: 10 mg GlyT-1</td>
</tr>
<tr>
<td>ARM B: 20 mg GlyT-1</td>
<td>ARM B: 5 mg GlyT-1</td>
</tr>
<tr>
<td>ARM C: placebo</td>
<td>ARM C: placebo</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td><strong>Status</strong></td>
</tr>
<tr>
<td>FPI Q4 2010; Expect data 2013</td>
<td>FPI Q4 2010; Expect data 2013</td>
</tr>
</tbody>
</table>

### Two new indications, study designs and patient populations agreed with health authorities in US (SPA), Europe and Japan
GlyT-1 development: optimizing the data quality
Synergies in study design and patient recruitment

Studies for negative symptoms and partial responders developed in parallel at the same clinical sites:

- High unmet medical need in both indications
- Creates broad safety data base
- Synergy in recruitment: reduced risk of rater inflation/deflation
Treatment goal in schizophrenia
Restoring patient autonomy

Conclusions: GlyT-1 in schizophrenia

- Robust, consistent and clinically meaningful reduction in negative symptoms (Per Protocol population) with trend improvement in functioning

- Preclinical and clinical data indicate ~50% target occupancy as optimal for efficacy of Glyt-1

- Overall, well tolerated, benign safety profile with few drop outs

- A trend seen in the subgroup of patients with moderately high positive symptoms is supportive of potential in positive symptoms control

- Phase III trials started in Q4 2010 with the potential to deliver two new indications in schizophrenia where patients currently have no approved treatment options

- The new MOA could show benefit in other psychiatric indications based on potential efficacy on motivation and positive symptoms
Ocrelizumab
Humanized anti-CD20 antibody
Multiple Sclerosis
Debilitating disease affecting adults in prime of life

- Chronic inflammatory and demyelinating disease of the CNS
- Affects mainly Caucasians and predominately in Northern hemisphere
- Diagnosis typically at ages 20-50:
  - 85% Relapse-Remitting MS; women >60%
  - 15% Primary Progressive MS; men >60%
- Unpredictable, inflammatory “attacks” leave scars (sclerosis) and various levels of disability

Source: Decision Resources
Three major types of Multiple Sclerosis

Relapse-Remitting (RRMS) (60-65%)
Clearly defined relapses (attacks) with remissions initially returning to baseline but gradually result in sustained disability.

Secondary Progressive (SPMS) (20-25%)
Initial RRMS followed by disability accumulation. Still experience relapses which eventually stop.

Primary Progressive (PPMS) (10-15%)
Slow but nearly continuous worsening of disease from outset (no relapses).

Marketplace
- High unmet need:
  - high efficacy therapies for relapsing forms have major safety issues
  - no treatment for primary progressive disease
  - diagnosis and classification is difficult, often retrospective and can take 2-5 years
- Treatment decisions concentrated mainly in MS centers/hospitals
- Payers pressure has been limited; patients’ advocacy groups powerful in access

Adapted from Lublin 1996, Arnold 2004
Current treatment dominated by ABCR cycling
“Between a rock and a hard place”

Available treatment options

- **Avonex**
  - interferon β1a
- **Betaferon**
  - interferon β1b
- **Copaxone**
  - glatiramer acetate
- **Rebif**
  - interferon β1a
- **Gilenya**
  - fingolimod
- **Tysabri**
  - natalizumab

Treatment choice:

- Efficacy/safety trade-off
- Potential risks:
  - ABCR: Injection site reactions
  - Tysabri: opport. infect.: PML, liver toxicity
  - Gilenya: cardiovascular-, respiratory effects, livertoxicity, macular edema, lymphomas, fetal risk

Cycle / Switch

Initial management
Switches due to flu, injection site reactions or injection frequency

Failure-switch
based on ABCR efficacy or tolerability issues
Ocrelizumab in phase II for RRMS
Study design for the first 2 treatment cycles

<table>
<thead>
<tr>
<th>Screening</th>
<th>Randomisation</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days</td>
<td>Group</td>
<td>1st cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 15</td>
</tr>
<tr>
<td></td>
<td>Double blind</td>
<td>Placebo i.v.</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo i.v.</td>
</tr>
<tr>
<td></td>
<td>Ocrelizumab 600 mg</td>
<td>Ocrelizumab 300 mg i.v.</td>
</tr>
<tr>
<td></td>
<td>Ocrelizumab 2000 mg</td>
<td>Ocrelizumab 1000 mg i.v.</td>
</tr>
<tr>
<td>Open label</td>
<td>IFN beta-1a</td>
<td>IFN beta-1a 30 µg i.m. every week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocrelizumab 300 mg i.v.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocrelizumab 300 mg i.v.</td>
</tr>
</tbody>
</table>

1:1:1:1 Randomization stratified by geographic region.
Ocrelizumab in phase II
Efficacy amongst the highest seen in RRMS

Mean no. T1 Gd-enhancing lesions

- Placebo (n=54)
- Ocrelizumab 600 mg (n=51)
- Ocrelizumab 2000 mg (n=52)
- IFN beta-1a (n=55)

Primary end point

Reductions of 96% (2000mg) and 89% (600mg); p<0.0001 for both ocrelizumab doses vs placebo

Annualized Relapse Rate (ARR)
Secondary end point

- Placebo: 0.636
- Ocrelizumab 600 mg: 0.125
- Ocrelizumab 2000 mg: 0.169
- IFN beta-1a: 0.364

Kappos et al, ECTRIMS 2010

Gd=Gadolinium; IFN beta-1a arm was open label, all efficacy comparisons were exploratory
Ocrelizumab in phase II
Safety Summary

Adverse Events (AEs)
- No imbalance in AEs
- No imbalance in the number of infections
- No opportunistic infections were reported
- Higher incidence of Infusion Related Reactions only at first infusion of Cycle 1 (34.5% in 600 mg, 43.6% in 2000 mg)
  IRR rates were not different to placebo for second infusion of Cycle 1

Serious Adverse Events (SAEs)
- 8 SAEs: 2 in placebo, 1 in 600 mg, 3 in 2000 mg, 2 in IFN beta-1a
- 1 SAE considered to be infection related in placebo group
- 1 death in the 2000 mg ocrelizumab dose group at Week 14, disease onset at Week 12:
  - Systemic Inflammatory Response Syndrome with disseminated intravascular coagulation and multi-organ dysfunction syndrome
  - No signs of viral infection found prior to and during hospitalisation, and in autopsy specimen
  - At Day 11 of hospitalisation, the patient had developed bacterial pneumonia
  - Immediate cause of death: transcranial herniation due to brain oedema

- Ocrelizumab was generally well tolerated
- No safety signal limiting further investigation was observed
Ocrelizumab safety in MS patients
Phase III design leverages RA safety findings

- Ocrelizumab RA trials suggest that lower dose (similar to planned MS dose) does not cause imbalance in serious infections

<table>
<thead>
<tr>
<th>Serious Infections rate per 100 patient-years</th>
<th>Pooled pivotal RA studies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Ocrelizumab 2 x 200 mg</td>
</tr>
<tr>
<td>3.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

- Although 2 x 200mg ocrelizumab showed an acceptable safety profile, the efficacy in RA was not competitive with rituximab

Other significant variables:
- Concomitant use of immunosuppressants significantly higher in RA than MS
- Age: RA patients tend to be older than MS
- Risk of infections in general higher in RA than in MS

Lower dose, younger patient population and the absence of concomitant immunosuppressants may result in better safety profile in MS patients

* SCRIPT, STAGE, FEATURE, FILM; data presented at ACR 2010
Ocrelizumab in RRMS
Looking for the next step in MS therapy

Relative reduction in Annualized Relapse Rate vs placebo in a range of phase 2/3 trials

NOTES:
- **Pattern**: Solid bars represent Phase III studies; pattern = Phase II
- **Trial durations** vary from 6 mos. to 3 yrs; studies included different patient populations, different in/exclusion criteria, different ARR definitions and data were collected over a time span of more than 20 years
- **Ph II** trials of laquinimod, teriflunomide, and BG12 did not show significantly better efficacy on ARR than placebo and are not included in comparison figures
## Moving ocrelizumab to phase III: RRMS

Two global studies to start in 2011

<table>
<thead>
<tr>
<th>Twin Global Studies</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>&quot;A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Ocrelizumab In Comparison To Interferon Beta-1a (Rebif®) In Patients With RRMS&quot;</td>
<td></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>interferon β1a (Rebif®)</td>
<td>interferon β1a (Rebif®)</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>N=800 1:1 randomization</td>
<td>N=800 1:1 randomization</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Annualized Relapse Rate at 96 weeks Each study powered separately for primary endpoint</td>
<td></td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>FPI H1 2011; Expect data 2014</td>
<td></td>
</tr>
</tbody>
</table>
Some PPMS patients benefit from anti-CD20 therapy

OLYMPUS trial (rituximab in PPMS)

All Intent-to-Treat Patients (N=439)

- Non-significant primary result on time to confirmed disease progression (CDP)

Age <51; Gd Lesions ≥1 (N=72)

- Pre-planned subgroup analysis indicates that in younger patients with 1 or more Gd lesion, rituximab significantly delayed time to CDP

PPMS is biologically heterogeneous
Treatment success depends on better patient selection

Gd=Gadolinium
Moving ocrelizumab to phase III: PPMS
Learning from OLYMPUS trial

Modified Inclusion/Exclusion criteria select active population in OLYMPUS trial

Inclusion Criteria:
- Age 18-55 (*Olympus* = 65)
- Baseline EDSS 3.0 - 6.5 (*Olympus* = 2.0-6.5)

Exclusion Criteria
- Patients with EDSS ≥ 5 and time since disease onset ≥ 15 yrs
- Patients with EDSS <5 and time since disease onset ≥ 10 yrs

OLYPUS impact on ocrelizumab PPMS phase III
- Select younger patients
- Select patients with active disease (*Olympus: median 2-yr EDSS change in the placebo group was 0*)
- Increase the length of treatment to 2.5 years (*Olympus: 2 years*)

EDSS = Expended Disability Status Scale
Ocrelizumab PPMS Phase III Clinical Program
Development plan features

Double Blind Placebo-controlled Pivotal Ph III Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Progressive Multiple Sclerosis (PPMS) ORATORIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>• Age 18 to 50</td>
</tr>
<tr>
<td></td>
<td>• Baseline EDSS 3.0-6.5</td>
</tr>
<tr>
<td></td>
<td>• Disease duration from the onset of MS symptoms</td>
</tr>
<tr>
<td></td>
<td>• Less than 15 years in patients with EDSS &gt;5.0</td>
</tr>
<tr>
<td></td>
<td>• Less than 10 years in patients with EDSS ≤5.0</td>
</tr>
<tr>
<td>No. of patients</td>
<td>N ~ 630, 2:1 randomization</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo infusion</td>
</tr>
<tr>
<td>Study duration</td>
<td>Minimum 120 week treatment period (2.5 years)</td>
</tr>
<tr>
<td>Schedule &amp; Dose</td>
<td>300 mg x 2 (two weeks apart) for first cycle followed by 600 mg IV single infusion Q24 wks</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Time to sustained disability progression</td>
</tr>
<tr>
<td>Status:</td>
<td>FPI Q1 2011; Expect data 2014</td>
</tr>
</tbody>
</table>

EDSS = Expended Disability Status Scale
Conclusions
Ocrelizumab in MS

- Phase II efficacy data for ocrelizumab amongst the highest seen in relapsing-remitting multiple sclerosis (RRMS)

- Phase II results suggest ocrelizumab is generally well tolerated and has an acceptable safety profile in MS

- Ocrelizumab Phase III trials will start in 2011 (Q1 PPMS and Q2 RMS)

- We have confidence in achieving success in Phase III and in bringing a new treatment option to patients with MS based on:
  - The selected dose of 2x300 mg has shown to be efficacious in Phase II
  - 2x300 mg is close to the dose found to have a safety profile comparable to placebo in Phase III RA trials
Roche

We Innovate Healthcare