50th ASCO Annual Meeting, Chicago

Roche Analyst Event
Sunday, 1 June 2014
Welcome and introduction

Karl Mahler  
Head of Investor Relations, Roche
Agenda

Welcome and introduction
Karl Mahler, Head of Investor Relations, Roche

Realizing the promise of cancer immunotherapy: translating science into medical benefit
Ira Mellman, Vice President, Cancer Immunology, Genentech
Hy Levitsky, Head, Cancer Immunotherapy Experimental Medicine, pRED

ASCO 2014 Roche highlights: setting new standards of care
Sandra Horning, Chief Medical Officer and Head Global Product Development

Oncology strategy and outlook
Daniel O’Day, Chief Operating Officer, Roche Pharmaceuticals

Q&A
Roche oncology: continued sales growth
A portfolio of differentiated medicines

Sales at 2013 exchange rates
Science is continually evolving

Classification of lung adenocarcinomas

2004

2014

Future

PDL1 positive

No oncogenic driver detected: 35%
KRAS: 25%
EGFR: 17%
ALK: 8%
EGFR (other): 4%
HER2: 3%
PIK3CA: 1%
MET: 1%
NRAS: 1%
MEK1: <1%
>1 mutated gene: 3%
Unknown: 35%

Pao & Girard, Lancet Oncol 2011; Johnson, et al. ASCO 2013
Roche’s cancer immunotherapy community

Concerted actions while valuing diversity of approaches
Cancer immunotherapy today

*Approved in monotherapy, one cancer type, few patients*
Cancer immunotherapy in the future

Better patient selection, combinations, broader use?
Realizing the Promise of Cancer Immunotherapy: Translating science into medical benefit (I)

Ira Mellman, Ph.D.
Vice President, Cancer Immunology, Genentech
Mechanistic basis of cancer immunotherapy

The cancer immunity cycle strategy

Different drugs target distinct steps

CEA-IL2v

vaccines
adjuvants
anti-CD40

Avastin

immuno-suppression

anti-PDL1
anti-CSF-1R

Chen & Mellman (2013) Immunity
Using patient data to understand cancer immunity and find new treatments

**MPDL3280A Phase 1 Data: Urothelial Bladder Cancer Patients**

- **Progressive Disease (PD)**
  - Why do many patients not respond?
  - No pre-existing immunity?

- **Stable disease (SD)**
  - What combinations will promote PRs & CRs?
  - Insufficient T cell immunity?
  - Multiple negative regulators?

- **Monotherapy durable responses (PR/CR)**
  - What are the drivers of single agent response?
  - How can PRs be enhanced to CRs?
  - Insufficient T cell immunity?
  - Multiple negative regulators?
Comprehensive approach to biomarker discovery

**Gene Expression - iChip**
High throughput and comprehensive evaluation of tumor and immune genes

**CD8 IHC**
Spatial assessment of CD8 in response to treatment

**Target expression**
Dx grade assays for assessment of target expression

**Molecular Imaging**
Live CD8 T cell PET under development

**Multiplex Immune IHC**
12 marker assay for evaluation of multiple immune cell subsets, endothelial cells, and tumor cells Enables spatial assessment of TILs
On-treatment biomarker profile defines response and lack of response

Responder

Non-responder
Expression of different immune inhibitory factors may not correlate with lack of response to anti-PDL1

Summary of Best Response in lung cancer

<table>
<thead>
<tr>
<th>Biomarker status</th>
<th>ORR(^a) RECIST 1.1</th>
<th>PD rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L2 high(^b)</td>
<td>20% (13/66)</td>
<td>35% (23/66)</td>
</tr>
<tr>
<td>PD-L2 low(^b)</td>
<td>19% (12/63)</td>
<td>46% (29/63)</td>
</tr>
<tr>
<td>All(^c)</td>
<td>21% (36/175)</td>
<td>37% (65/175)</td>
</tr>
</tbody>
</table>

\(^a\) ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1.

\(^b\) PD-L2 low/high is defined as patients with tumor PD-L2 level lower/equal to or higher than the median PD-L2 level in all patients.

\(^c\) All patients include PD-L2–high patients, PD-L2–low patients and patients with unknown tumor PD-L2 status.

Patients first dosed at 1-20 mg/kg prior to October 1, 2012; data cutoff April 30, 2013.

Kohrt et al. SITC 2013
PD-L1 patient immune biomarker analysis guides research and clinical development

**Immune marker expression analysis (illustrative)**

**Targets elevated in non-responders**

Compounds moving into clinic
- Negative regulator NME1
- Anti-cytokine NME2
- Positive regulator NME3
Example: NME1 is a negative regulator discovered from biomarker analysis

Negative regulator combines in PD-L1 non-responsive model
NME3: positive regulator targeting two steps in the cycle – anti-OX40

Accelerate T cell response to antigen

anti-OX40

Anti-PDL1
Inhibit T regs
anti-OX40
OX40 function and potential in oncology
Promote antigen dependent effector T cell activation and T regulatory cell inhibition

Rationale for targeting OX40 in oncology
- Dual mode of action:
  Co-stimulation of effector T cells
  Inhibition of regulatory T cells
- Reduced risk of toxicity
- Complementary MoA to blocking inhibitory receptors
- Potential to overcome suppressive signals from multiple inhibitory receptors

Potential for activity in multiple tumor types

Pre-clinical efficacy and durability of response

**OX40 is expressed in a variety of tumors**

*Colorectal cancer*

*Breast cancer*

**Anti-OX40 increases intratumor $T_{eff}$ cells while depleting $T_{regs}$**

**Increase in intratumoral $T_{eff}$ cells (CD4+CD8)**

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>a-OX40</th>
<th>day 2</th>
<th>control</th>
<th>a-OX40</th>
<th>day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ Fold Change (Rel to Avg Control)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Decrease in intratumoral $T_{regs}$ cells (FoxP3+)**

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>a-OX40</th>
<th>day 2</th>
<th>control</th>
<th>a-OX40</th>
<th>day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>FoxP3/CD4(%)</td>
<td></td>
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</tbody>
</table>
Anti-OX40 can induce durable responses and immunity as a single agent
Pre-clinical efficacy and generation of tumor-specific immunity

**Primary Tumor Challenge (EMT6)**
- Tumor Volume (mm$^3$) vs. day
- Control
- Anti-mouse OX40

**Re-challenge (EMT6 or CT26)**
- Tumor Volume (mm$^3$) vs. day
- CT26 Secondary
- EMT6 Secondary
- EMT6 Primary

*No Treatment*
Increase in $T_{\text{eff}}$ cells by anti-OX40 may create need to combine with anti-PDL1

Chen & Mellman (2013) Immunity
Can combination of anti-PDL1 with chemo- and targeted agents extend benefit to more patients?

- Agents must be safe in combination with anti-PD-L1
- Targeted/chemo therapy should not interfere with immune response or immunotherapeutic mechanism of action
Combinations may extend the benefit of anti-PDL1 Chemo and targeted therapies

Biomarker analysis in progress to identify combinations with enhanced efficacy
Recognition of cancer cells in the absence of T cell immunity
*ImmTACs and bispecifics*
Recognition of cancer cells
*In collaboration with Immunocore

**ImmTACs and bispecifics**

*Targeting intracellular tumor markers*

Cancer cell

ImmTAC

Redirected T cell

KILL

*Targeting extracellular tumor markers*

Cancer cell

Tumor antigen

Knob into holes

full-length IgG

T cell

**Immune-mobilizing mTCR Against Cancer***

**T-cell Dependent Bispecific**

*In collaboration with Immunocore*
Examples: B-cell and HER2 bispecifics

Killing of endogenous B-cells by endogenous T-cells in healthy donor PBMCs

- Target 1: 8.0 pM
- Target 2: 22 pM
- Target 3: 70 pM
- Target 4: 8.6 pM
- Target 5: 426 pM

24 hour assay

Tumor vol. (% change)

- Vehicle
- TBD

Days post treatment

PBMC=Peripheral blood mononuclear cell
The cancer immunity cycle

Many known targets, and likely many “unknown”

Biomarker analysis will aid in prioritizing targets and combinations
Realizing the promise of cancer immunotherapy: Translating science into medical benefit (II)

Hy Levitsky, MD
Head, Cancer Immunology Experimental Medicine, Roche, Pharma Research and Early Development (pRED)
The cancer-immunity cycle

**Priming and activation**
- Anti-CTLA4
- Anti-CD137 (agonist)
- Anti-CD27 (agonist)
- IL-2
- IL-12

**Cancer antigen presentation**
- Vaccines (IMA942 & INO-5150)
- Anti-CD40 (agonist)
- TLR agonists
- IFN-α

**Release of cancer cell antigens**
- Chemotherapy
- Radiation therapy
- Targeted therapy

**Recognition of cancer cells by T cells**
- CARs
- T cell bispecifics
- ImmTACs

**Killing of cancer cells**
- Anti-PD-L1
- Anti-PD-1
- IDO inhibitors

**Neg. Regulator** (NME 1)
- Anti-CSF1R (RG7155)
- Anti-CEA IL2v (RG7813)
- Anti-Cytokine (NME 2)

**Infiltration of T cells into tumors**
- Anti-VEGF
- Neo-vascular activators

**Trafficking of T cells to tumors**

**REDS**
- clinical
- preclinical

**Infiltration of T cells**
- Anti-VEGF
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**Recognition of cancer cells by T cells**
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**Neg. Regulator** (NME 1)
- Anti-CSF1R (RG7155)
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- Anti-Cytokine (NME 2)
1) Inflammatory tumor microenvironment

Tumors induce an immunosuppressive environment by recruitment of myeloid cells

- **A** Depletion
  - Anti-growth factor receptors
  - Targeting lineage antigens

- **B** Inhibition
  - Chemokine receptor blockade
  - Inhibitory receptor agonists

- **C** Switching
  - TLR agonists

TLR - toll-like receptor
Anti-CSF1R phase I proof-of-mechanism

**RG7155 decreases tumor-associated macrophages in patients with various solid tumor types**

Pleural Mesothelioma, 900 mg RG7155

*pre- vs on-treatment tumor biopsies at 4 weeks, i.e. two cycles of treatment; Mφ – macrophage cell line; CSF1R – colony stimulating factor 1 receptor

Significant reduction of tumor-associated macrophages in 11/13 patients treated in monotherapy and 15/15 patients treated in combination with SoC

Ries et al., Cancer Cell 2014 (in press)
Anti-CSF1R phase I proof-of-mechanism in PVNS
From model disease to development opportunity

PVNS - pigmented villonodular synovitis

- Locally aggressive inflammatory joint disorder
- Neoplastic proliferation with overexpression of CSF-1

| Patients | %
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>15/18</td>
</tr>
<tr>
<td>Partial Metabolic Response</td>
<td>15/17</td>
</tr>
<tr>
<td>Clinically progression-free*</td>
<td>17/18</td>
</tr>
</tbody>
</table>

Rapid onset of measurable tumor shrinkage; associated with early functional and symptomatic improvement

Ries et al., Cancer Cell 2014 (in press); * longest follow-up 22 months
2) Tumor targeted antibody-based immunotherapy of cancer

A. ADCC: recruit effector cells (NK, MØ) via FcγRIIIa
   - Glycoengineered IgG1s

B. Support T-cells: supply cytokines and co-stimulatory signals
   - Antibody-cytokine fusions, co-stimulatory antibodies

C. Activate T-cells: stimulate TCR on T cell
   - T cell bispecific antibodies
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- T cell bispecific antibodies
Gazyva: first glyco-engineered antibody approved by FDA

Obinutuzumab (Gazyva)

Glyco-engineered to better engage immune cells

(ADCC = Antibody-Dependent Cell-mediated Cytotoxicity)

Unequivocal clinical benefit demonstrated in Phase III (CLL)
Out-performed Rituxan/Mabthera in H2H Phase III
Glyco-engineered for improved ADCC

2) Tumor targeted antibody-based immunotherapy of cancer

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C. Activate T-cells: stimulate TCR on T cell
   - T cell bispecific antibodies
Amplifying T cell responses in the tumor

IL-2 variant immunocytokine

- High binding affinity to **CEA** for tumor targeting
- **Inert Fc-part** for improved PK & safety
- **IL-2 variant** (diminished CD25 binding) to increase number & activity of effector cells vs. immuno-suppressive cells

- Ideal combination partner for ADCC competent antibodies such as Herceptin, obinutuzumab
- Phase I initiated Dec 2013

Klein et al., abstract number 486, AACR April 6-10, 2013, Washington, DC, USA
**Antibody-targeted IL-2 variant**

*Preferentially stimulating immune cells in tumors*

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**Tumor-targeted cytokine**

- High affinity for CEA\(^1\) (tumor antigen)
- IL2v engineered to boost effector immune cells

---

**Increasing T-cells in tumors**

- Targets to tumors *in vivo* (preclinical)
- Synergistic with ADCC mediated therapeutic mAbs (preclinical)
- Phase 1 initiated Dec 2013

---

\(^1\) carcinoembryonic antigen
Two major categories of solid tumors have been observed at diagnosis

- **20-30 % of patients**
  - T cell markers
  - Expression of chemokines (attract leukocytes)
  - Other immuno-regulatory factors (PD-L1, IDO, FoxP3)

- **70-80% of patients**
  - No lymphocytic infiltrates

![Tumor phenotype by T cell staining](image)

- ✓ single agent immunotherapies
- rarely clinical response to single agent immunotherapies
Most tumors lack tumor specific T cell infiltrates

A potential role for vaccination

• Increase frequency of relevant effector cells

• Change character of immune response: functional differentiation

• Alter lymphocyte trafficking

• Generate long-lived immunologic memory

Drive cancer antigen-specific T cells into tumors
3) Tumor vaccines and immunoadjuvants
Providing specificity and memory to combination immunotherapy

Antigen(s)

Delivery Vehicle (platform)

APC Activators

Antigen Discovery

Naked Peptides

DNA/RNA

Nano-particles

Activators of innate immunity ("adjuvants")

CD40 agonist mAb

Normal tissues

Cancer tumors

Expression relative to healthy kidney:
X absent, P present, F marginal

Roche
Cancer vaccines strategy at Roche

Incorporating rich antigen portfolio into alternative targeting platforms

Exploiting *complementary strengths* with our partners to *co-develop* combination assets
Anti-CD40 agonistic IgG2 mAb
Compelling combination partner for cancer immunotherapy

Multiple immune doublet opportunities
Seeking Synergy

NME 1: T and NK cell amplification

NME 2: antigen presenting cell activation

NME 3: blocking immune checkpoints

NME 4: depleting suppressive macrophages

therapeutic vaccine: tumor antigen specific T cell priming

Numbering of NMEs is for illustrative purposes only
The immunotherapist’s dilemma

....circa 2014
ASCO 2014 Roche highlights: Setting new standards of care

Sandra Horning, M.D.
Executive Vice President
Chief Medical Officer and Head Global Product Development
Agenda

Setting new standards of care

Update on immunotherapy and bladder cancer results

Lung: Tarceva +/- Avastin, alectinib

Colorectal: Avastin and anti-VEGF/Ang2

Melanoma: cobimetinib in combination with Zelboraf

Hematology: Bcl-2i and polatuzumab ADC (CD79b)
# Cancer immunotherapy at Roche

## Pipeline overview

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>ImmTAC</td>
<td>Anti-PDL1 Solid tumors</td>
<td>Anti-PDL1 NSCLC (Dx+)</td>
<td>Anti-PDL1 NSCLC 2/3 L</td>
</tr>
<tr>
<td>Neg. Regulator NME 1</td>
<td>Anti-PDL1 + Avastin Solid tumors</td>
<td>Anti-PDL1 NSCLC</td>
<td>Anti-PDL1 Bladder</td>
</tr>
<tr>
<td>IMA 942</td>
<td>Anti-PDL1 + cobimetinib Solid tumors</td>
<td>Anti-PDL1 + Avastin Renal</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td>Anti-cytokine NME 2</td>
<td>Anti-PDL1 + Zelboraf Met. Melanoma</td>
<td>Anti-PDL1 + Avastin Bladder</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td>T-cell bispecific</td>
<td>Anti-PDL1 + Tarceva NSCLC</td>
<td>Anti-PDL1 NSCLC 2/3 L</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>Anti-PDL1 + immune m. Solid tumors</td>
<td>Anti-PDL1 + Avastin Bladder</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>Anti-PDL1 + Gazyva Heme tumors</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>CSF1R huMAb</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>CEA IL-2v</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>Anti-OX40</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>Anti-CD40</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
<tr>
<td></td>
<td>INO-5150</td>
<td>Anti-PDL1 + Avastin NSCLC</td>
<td>Anti-PDL1</td>
</tr>
</tbody>
</table>

Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov
Urothelial bladder carcinoma (UBC)
High unmet need for patients with advanced disease

New therapies in RCC, prostate and bladder cancer

- US: 74,690 new cases/year\(^1\)
  - 5% metastatic, 20% muscle invasive
- Metastatic UBC prognosis:
  - 5-year OS ~5%\(^2\)
- US: no therapies approved for patients who relapse on cisplatin-based chemo

**MPDL3280A (anti-PDL1) in metastatic UBC**

*Response by PD-L1 IHC status*

- **2** complete responses in the IHC 2 / 3 cohort
- **16** of **17** responding patients had ongoing responses at the time of data cut-off

* Patients with complete responses. Patients with a CR had < 100% reduction of the target lesions due to lymph node target lesions. All lymph nodes returned to normal size as per RECIST v1.1 IC; tumor-infiltrating immune cells. Best response is not known for 7 patients.

Diagnostic PD-L1-positive: IHC 2 (≥ 5% but < 10% ICs); IHC 3 (≥ 10%). PD-L1 negative: IHC 0 (< 1% of ICs) and IHC 1 (≥ 1% but < 5%).

Patients dosed by Nov 20, 2013 with a baseline tumor assessment. Clinical data cut-off was Jan 1, 2014.
MPDL3280A (anti-PDL1) in metastatic UBC

Treatment related adverse events

<table>
<thead>
<tr>
<th></th>
<th>All Grade n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>39 (57%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>Decreased Appetite</strong></td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pyrexia</strong></td>
<td>6 (9%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Asthenia</strong></td>
<td>5 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Chills</strong></td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Influenza-like illness</strong></td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Lethargy</strong></td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Safety profile in bladder cohort consistent with safety in overall phase I population
- No new safety signals identified in the bladder cohort

Clinical data cutoff Jan 1, 2014. Includes events occurring in 3 or more patients. Additional grade 3 or 4 events included thrombocytopenia and decreased blood phosphorus.
**MPDL3280A (anti-PDL1) in locally advanced and metastatic UBC: next steps in development**

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### Phase I

- Phase I results warrant move into pivotal studies
- Results observed to date suggest higher response rate in PD-L1+ patients

### Phase II

<table>
<thead>
<tr>
<th>Locally Advanced or Metastatic UBC</th>
<th>Anti-PDL1 1200 mg IV Q3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=330</td>
<td></td>
</tr>
</tbody>
</table>

**Primary end-point:**
- Overall Response Rate

**FPI:** Q2 2014

### Phase III

**In preparation, expect start in 2014**

---

Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov
Anti-PDL1 in metastatic non-small cell lung cancer (mNSCLC)

**FIR: Phase II Dx-positive advanced mNSCLC**

- **PDL1-positive NSCLC**
  - *n = 130*
- Anti-PDL1 1200 mg IV Q3 weeks
- **Primary end-point:** ORR
- **FPI Q2 2013**
- **Data in-house end ‘14**

**BIRCH: Phase II Dx-positive advanced mNSCLC**

- **PDL1-positive NSCLC**
  - *n = 300*
- Anti-PDL1 1200 mg IV Q3 weeks
- **Primary end-point:** ORR
- **FPI Q1 2014**

**POPLAR: Phase II 2/3L mNSCLC**

- **All comers 2,3L NSCLC**
  - *n = 287*
- Docetaxel
  - 75 mg/m2 IV Q3 wk
- Anti-PDL1
  - 1200 mg IV Q3 wk
- **Primary end-point:** OS
- **FPI Q1 2014**
- **Enrollment complete**

**OAK: Phase III 2/3L mNSCLC**

- **All comers 2,3L NSCLC**
  - *n = 850*
- Docetaxel
  - 75 mg/m2 IV Q3 wk
- Anti-PDL1
  - 1200 mg IV Q3 wk
- **Primary end-point:** OS
- **FPI Q1 2014**

**Phase III trials in first line NSCLC in preparation**

Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov
**MPDL3280A (anti-PDL1) diagnostic program**

*Development of the right assay*

<table>
<thead>
<tr>
<th>Available lab tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control (293)</td>
</tr>
<tr>
<td>Positive control (293-PDL1)</td>
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<tr>
<td>Positive tissue control (Placenta)</td>
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</tbody>
</table>

**Three pillars of the successful IHC test:**

- **Sensitivity:** Detects signal from a few cells
- **Specificity:** Detects PD-L1 protein only
- **Precision:** Reproducibly assigns cases to well-defined categories (IHC 0,1,2,3)

*Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov*
MPDL3280A (anti-PDL1) development

*Readouts over the next 12 months*

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Readout</th>
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</thead>
<tbody>
<tr>
<td><strong>Anti-PDL1 as single agent</strong></td>
<td></td>
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</tr>
<tr>
<td>Phase I</td>
<td>New tumor type</td>
<td>First readout</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Follow-up data</td>
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<tr>
<td></td>
<td>Renal</td>
<td>Follow-up data</td>
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<tr>
<td></td>
<td>Bladder</td>
<td>Follow-up data</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>Follow-up data</td>
</tr>
<tr>
<td>Phase II (FIR)</td>
<td>NSCLC (PD-L1+)</td>
<td>First readout</td>
</tr>
<tr>
<td>Phase II (POPLAR)</td>
<td>2/3L NSCLC</td>
<td>First readout</td>
</tr>
<tr>
<td><strong>Anti-PDL1 in combination</strong></td>
<td></td>
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</tr>
<tr>
<td>Phase Ib</td>
<td>Multiple tumor types</td>
<td>First readout</td>
</tr>
</tbody>
</table>

Outcome studies are event driven, timelines may change
# Agenda

*Setting new standards of care*

## Update on Immuno-oncology and Bladder cancer results

<table>
<thead>
<tr>
<th><strong>Lung:</strong></th>
<th>Tarceva +/- Avastin, alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal:</strong></td>
<td>Avastin and anti-VEGF/Ang2</td>
</tr>
<tr>
<td><strong>Melanoma:</strong></td>
<td>cobimetinib in combination with Zelboraf</td>
</tr>
<tr>
<td><strong>Hematology:</strong></td>
<td>Bcl-2i and polatuzumab ADC (CD79b)</td>
</tr>
</tbody>
</table>
Lung cancer disease area

Targeting multiple hallmarks of cancer

10 HALLMARKS OF CANCER

TARGETING MULTIPLE HALLMARKS TO ADDRESS:

HETEROGENEITY

COMPLEXITY

RESISTANCE

Alectinib

Sustaining proliferative signaling

Deregulating cellular energetics

Resisting cell death

Genome instability & mutation

Inducing angiogenesis

Activation invasion & metastasis

Tarceva

Evading growth suppressors

Avoiding immune destruction

Enabling replicative immortality

Tumor-promoting inflammation

Avastin

aPD-L1

Tarceva plus Avastin in EGFR+ mNSCLC

**Japanese study JO25567**

- **Primary endpoint**: Progression free survival
- **Secondary endpoint**: Overall survival, Objective Response (Response Rate, Disease Control Rate, Response Duration), QOL, Safety
- **Exploratory**: Biomarker analysis
- **Stratification**: Gender, stage, smoking status, EGFR mutation type

Study conducted by Chugai

- Non-squamous NSCLC Stage IIIB / IV or postop. recurrence
- Chemo naïve, PS 0-1
- Active EGFR mutation - exon 19 del or L858R without T790M
  - N=150

- Tarceva 150 mg daily
  - + Avastin 15mg/kg q3W
  - N=150

- Progression free survival (PD)

Study conducted by Chugai
Tarceva plus Avastin in EGFR+ mNSCLC

Japanese study JO 25567

Superior efficacy of A+T combination compared to Tarceva single agent in EGFR+ patients

Study conducted by Chugai
Alectinib in ALK+ve NSCLC
Brain-penetrant ALKi with promising efficacy & safety

Crizotinib-naïve ALK-positive patients post-chemotherapy

Study conducted by Chugai

Study results

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crizotinib-naïve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>93.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Crizotinib-failures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>54.5%</td>
<td>52%</td>
</tr>
<tr>
<td>CNS Objective Response Rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Next steps

- Filed in Japan in Oct. 2013
- Global Phase I/II study expected to readout in 2014
- Start of Phase III in 2014

---

Update on Immuno-oncology and Bladder cancer results

**Lung:** Tarceva +/- Avastin, alectinib

**Colorectal:** Avastin and anti-VEGF/Ang2

**Melanoma:** cobimetinib in combination with Zelboraf

**Hematology:** Bcl-2i and polatuzumab ADC (CD79b)
Avastin in KRAS wt met. colorectal cancer

*Impact of the CALGB study*

### Study design

- **Untreated KRAS wt advanced or mCRC**
  - N=1'142

### Results

<table>
<thead>
<tr>
<th></th>
<th>Avastin+ chemo</th>
<th>Cetuximab+ chemo</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>29.0</td>
<td>29.9</td>
<td>0.925</td>
<td>0.34</td>
</tr>
<tr>
<td>PFS</td>
<td>10.8</td>
<td>10.4</td>
<td>1.04</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**Primary endpoint:** Overall survival

90% powered to detect a HR of 0.80 (2-sided $\alpha=0.05$), assumption: OS 22 months to 27.5 months, $\Delta=5.5$ months

- Cetuximab failed to demonstrate survival benefit over Avastin
- Avastin survival benefit in metastatic colorectal cancer in 1L, 2L and TML\(^1-3\)

\(^1\)Hurwitz, *et al.* NEJM 2004; \(^2\)Giantonio *et al.*, JCO, 2007; \(^3\) D. Arnold *et al.*, JCO, 2012
CrossMAb: bispecific anti-VEGF & Ang2 antibody
Neutralizing two complementary angiogenic factors

Phase II trial design

**Open Label Safety Run-in**
- 2 Cycles (4 wks)

**Induction**
- Up to 8 Cycles (16 wks)
- Avastin + mFOLFOX-6
- A2V + mFOLFOX-6

**Maintenance**
- Avastin + 5-FU/LV
- A2V + 5-FU/LV

**Primary endpoint:**
Median progression free survival (mPFS)

**Secondary endpoints:**
Safety & tolerability, RECIST ORR, OS & duration of response, PK

CrossMAb is listed as RO5520985 in clinicaltrials.gov
ASCO 2014: Manuel Hidalgo, abstract #2525
Agenda
Setting new standards of care

Update on Immuno-oncology and bladder cancer results

Lung: Tarceva +/- Avastin, alectinib

Colorectal: Avastin and anti-VEGF/Ang2

Melanoma: cobimetinib in combination with Zelboraf

Hematology: Bcl-2i and polatuzumab ADC (CD79b)
Cobimetinib plus Zelboraf

Encouraging results of phase I in BRAF+ve mMelanoma

Presented at EADO May 7, 2014

1 Applicable to PFS

<table>
<thead>
<tr>
<th>BRAFi-naïve patients</th>
<th>BRAFi– naïve (n = 63)</th>
<th>Vem-Progression (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events¹</td>
<td>33 (52.4%)</td>
<td>58 (87.9%)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>13.7</td>
<td>2.8</td>
</tr>
<tr>
<td>95% CI for Median PFS</td>
<td>10.1 – 17.5</td>
<td>2.6 – 3.4</td>
</tr>
<tr>
<td>Response rate</td>
<td>87.3%</td>
<td>15.2%</td>
</tr>
<tr>
<td>% pts alive at 1 year</td>
<td>83%</td>
<td>32%</td>
</tr>
<tr>
<td>95% CI for 1 year survival</td>
<td>73-93</td>
<td>19-45</td>
</tr>
</tbody>
</table>

Readout of Phase III trial co-BRIM expected later in 2014
Agenda

Setting new standards of care

Update on Immuno-oncology and Bladder cancer results

Lung: Tarceva +/- Avastin, alectinib

Colorectal: Avastin and anti-VEGF/Ang2

Melanoma: Cobimetinib in combination with Zelboraf

Hematology: Bcl-2i and polatuzumab ADC (CD79b)
Strategies beyond great medicines

**Hematology**

- **BCL-2i**
- **ADCs**
- **ADC 79b**
- **ADC 22**

**Replace**
- **MabThera**
- **Gazyva**

**Extend**
- **Chemo**
- **MabThera**
- **Gazyva**
- **GALLIUM**
- **GADOLIN**

**Replace and extend**
- **BCL-2i**
- **ADCs**
- **ADC 79b**
- **ADC 22**

- **Phase Ib CLL (G+Bcl-2i)**

Bcl-2 i. in collaboration with AbbVie (ABT-199)
B-cell hematologic malignancies
A portfolio addressing multiple drug targets

Anti CD22 ADC
polatuzumab ved.

ROMULUS: Phase II head to head study in NHL

Study design

- R/R FL, n= 41
- 2/3+L DLBCL, n= 81

Rituximab (375 mg/m²) + ADC (2.4 mg/kg) administered in every 21-day cycles

Morschhauser, F., ASCO 2014, abstract #8519

FL: follicular lymphoma, DLBCL: diffuse large B-cell lymphoma
ROMULUS: Phase II head to head study in NHL
Promising results for polatuzumab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>R/R DLBCL</th>
<th>R/R FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>polatuzumab vedotin + rituximab</td>
<td>ORR = 56%</td>
<td>ORR = 70%</td>
</tr>
<tr>
<td></td>
<td>CR = 15%</td>
<td>CR = 40%</td>
</tr>
<tr>
<td>anti-CD22 ADC + rituximab</td>
<td>ORR = 57%</td>
<td>ORR = 62%</td>
</tr>
<tr>
<td></td>
<td>CR = 24%</td>
<td>CR = 10%</td>
</tr>
</tbody>
</table>

Polatuzumab ved. selected for late stage development based on high level of anti-tumor activity

Morschhauser, F., ASCO 2014, abstract #8519
## Bcl-2 inhibitor (GDC-0199) single agent in R/R CLL

*Encouraging responses across patient subgroups*

<table>
<thead>
<tr>
<th>Responses</th>
<th>All n (%)</th>
<th>del (17p) n (%)</th>
<th>F-Refractory n (%)</th>
<th>IGHV Unmutated n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response</strong></td>
<td>60 (77)</td>
<td>15 (79)</td>
<td>31 (76)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Complete response</td>
<td>18 (23)</td>
<td>5 (26)</td>
<td>9 (22)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Partial response*</td>
<td>42 (54)</td>
<td>10 (53)</td>
<td>22 (54)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (13)</td>
<td>2 (11)</td>
<td>7 (17)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>D/C Prior to first (W6) assessment</td>
<td>6 (8)</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Median PFS for patients treated at or above 400 mg has not been reached.

In collaboration with AbbVie (ABT-199). J.F Seymour, ASCO 2014, abstract # 7015

R/R CLL: relapsed/refractory chronic lymphocytic leukemia.
Bcl-2 inhibitor (GDC-0199)+R in R/R CLL

Efficacy in combining with an anti-CD 20 antibody

Best % change from baseline in Lymphocyte Count

<table>
<thead>
<tr>
<th>Response</th>
<th>Evaluable* n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Discontinued prior to assessment</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

* Evaluable pts have reached the month 7 bone marrow assessment, discontinued, or progressed on therapy

• High level of complete response and MRD (6/8 CR, 75%)
• Results supported move into phase III (MURANO) study in R/R CLL

In collaboration with AbbVie (ABT 199). Shuo Ma, ASCO 2014, abstract #7013, R: rituximab. MRD: minimal residual disease (PB or BM)
Bcl-2 inhibitor (GDC-0199) +R in R/R CLL

**Encouraging duration of response**

In collaboration with AbbVie (ABT-199). Shuo Ma ASCO 2014, abstract # 7013

R/R CLL: relapsed/refractory chronic lymphocytic leukemia. SE: safety expansion

Most patients are still progression-free, even those on lower doses
Bcl-2 inhibitor (GDC-0199)

Safety update

- No further clinical TLS\textsuperscript{1} cases since program restart (120 new patients treated)

- New revised monitoring agreed with FDA:
  - No hospitalization for low/medium risk patients
  - Hospitalization for high risk patients\textsuperscript{2}: at treatment initiation and first escalation one week later

In collaboration with AbbVie (ABT-199).
\textsuperscript{1}TLS: Tumor lysis syndrome. \textsuperscript{2}High risk is currently defined at those patients who have large tumors (10+ cm) and those patients who have tumors 5-10 cm and high circulating lymphocyte counts
Bcl-2 (GDC-0199) development

Next steps

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Status</th>
<th>Readout (exp.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td>17p del</td>
<td>Enrolment complete</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Phase III combo with R (MURANO)</strong></td>
<td>R/R CLL</td>
<td>Enrolling</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Phase III combo with Gazyva</strong></td>
<td>1L CLL</td>
<td>Start planned in 2014</td>
<td>2017 and beyond</td>
</tr>
<tr>
<td><strong>NHL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase II + R, +BR</strong></td>
<td>Follicular lymphoma</td>
<td>Start planned in 2014</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Phase Ib/II +R-/G- CHOP</strong></td>
<td>DLBCL</td>
<td>Start planned in 2014</td>
<td>2016</td>
</tr>
</tbody>
</table>

In collaboration with AbbVie (ABT-199)

Outcome studies are event driven, timelines may change. R=rituximab, G=obinutuzumab, B=bendamustine
Roche hematology pipeline

*Broad range of indications and approaches*

### Phase I
- **Bcl-2 inh (GDC 199) + Gazyva**
  - CLL
- **Bcl-2 inh (GDC 199)**
  - NHL
- **Bcl-2 inh (GDC 199)**
  - AML
- **Bcl-2 inh (GDC 199)**
  - Multiple myeloma
- **LSD1 inh (RG6016)**
  - AML
- **MDM2 (RG738)**
  - AML
- **ADC (RG7598)**
  - Multiple myeloma
- **ChK1 inh (RG7741)**
  - Lymphoma
- **RG 7845**
  - Heme tumors

### Phase II
- **Bcl-2 inh (GDC 199)**
  - CLL R/R 17p del
- **Erivedge**
  - AML
- **Polatuzumab ved. (CD 79b)**
  - NHL
- **Pinatuzumab ved. (CD22)**
  - NHL

### Phase III
- **Gazyva**
  - DLBCL
- **Gazyva**
  - iNHL relapsed
- **Gazyva**
  - iNHL front-line
- **Bcl-2 inh. (GDC 199)**
  - CLL R/R

### Registration
- **Gazyva**
  - CLL

---

1 Approved in US, submitted in EU
Oncology strategy and outlook

Daniel O’Day
Chief Operating Officer, Roche Pharmaceuticals
Roche oncology: continued sales growth
A portfolio of differentiated medicines

Sales at 2013 exchange rates
Evolution of science and market in oncology

Increasing competition and scientific complexity

<table>
<thead>
<tr>
<th>Year</th>
<th>Anatomic Diseases</th>
<th>Disease Subsets</th>
<th>Oncogenic Mutations &amp; Emerging Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Little Competition</td>
<td>73 Key Players</td>
<td>30% of Industry Pipelines</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Today</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increasing complexity in science

Increasing market competition
Roche strategy in oncology

Summary
Key success factors in the new environment

Best Science
- Integrated biomarker expertise
- Top tier scientific talent

Smart Development
- First or best in class
- Shift paradigms in development
- Leverage Combinations

Innovative Business Model
- Tailored approaches to access
Best science: integrated biomarker expertise

Personalized Healthcare at Roche

- Supports development of medically differentiated therapies
- PHC strategy applied to vast majority of pipeline molecules
- Leverage fully integrated biomarker and diagnostic expertise
Best science: need top tier scientists
Strong foundation in science key to guide decisions

Hypothetical Example MoAs

Strategy 1: Try everything
• High cost approach

Strategy 2: Focus on the most promising combinations
• Requires scientific expertise and smart development
Smart development: aim at first and best in class

Focus on most promising molecules

Major Oncology Drug Launches

Source: Evaluate Pharma, Decision Resources, Roche internal analysis
Note: *Market shares represent either % sales of target product relative to sales competing products in similar indications or patient shares
Smart development: paradigm shift I
Adaptive clinical trials: “Learning on the go”

Past

Time/trial size

• Small phase I ➔ Proof-of-concept in phase II ➔ Large phase III
• Similar path for each new indication

Present / Future

Pivotal ph II/III – indication 1
Pivotal ph II/III – indication 2
Pivotal ph II/III – indication 3

• Large phase I, proof-of-concept for multiple indications ➔
  Multiple pivotal phase II/III with adaptive trial design
Smart development: paradigm shift I

Learning on the go in PD-L1

**Past**

*Time/trial size*

- Small phase I ➔ Proof-of-concept in phase II ➔ Large phase III
- Similar path for each new indication

**Example – PDL1 NSCLC diagnostic approach**

- Data from Phase Ia NSCLC, FIR and POPLAR can be used to *modify* BIRCH and OAK before they read out
Smart development: paradigm shift II
Surrogate end-points: fast readout of clinical efficacy

Good surrogate endpoint in the causal pathway of the disease

Disease → Surrogate endpoint → True clinical outcome

**Eg Early Breast Cancer PCR**
- Neo-adjuvant treatment
  - Pre-surgery, 4-6 cycles
- **SURGERY**
- Adjuvant treatment
  - Post-surgery up to 1 year

**PCR:** Pathological Complete Response – Absence of cancer cells

**Eg Hematology MRD**
- Early relapse vs Late relapse
- Cytomorphology detection limit
- Immunophenotypic and PCR detection limit

Relative frequency of leukemic cells vs Follow-up time

- Induction
- Maintenance
- "Cut"
**Smart development: paradigm shift II**

**Surrogate end-points with Perjeta and Gazya**

**Good surrogate endpoint in the causal pathway of the disease**

Disease → Surrogate endpoint → True clinical outcome

---

**E.g. early breast cancer (Perjeta) PCR**

**PCR**: Pathological Complete Response – Absence of cancer cells

- US approval for Perjeta Sept 2013

<table>
<thead>
<tr>
<th></th>
<th>Herceptin + docetaxel</th>
<th>Herceptin &amp; Perjeta + docetaxel</th>
<th>Herceptin &amp; Perjeta + docetaxel</th>
<th>Perjeta + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological complete response</td>
<td>29.0%</td>
<td>45.8%</td>
<td>16.8%</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

---

**E.g. hematology (Gazyva) MRD**

**MRD**: Minimal Residual Disease

- Provided strong confidence in results earlier

<table>
<thead>
<tr>
<th></th>
<th>Stage Ia</th>
<th>Stage Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cib (n = 100)</td>
<td>Cib (n = 110)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0 (0/80)</td>
<td>0 (0/80)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0 (0/30)</td>
<td>0 (0/32)</td>
</tr>
</tbody>
</table>
## Smart development: paradigm shift III

**Disease area approaches – hematology example**

<table>
<thead>
<tr>
<th>MabThera/Rituxan</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polatuzumab vedotin anti-CD79b-ADC</td>
<td>NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazyva</td>
<td>CLL approved in US; ongoing in NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDC-0199 BCL-2 inhibitor</td>
<td>NHL, CLL, MM, AML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDM2 antagonist</td>
<td>AML and solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erivedge</td>
<td>AML, solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PDL1</td>
<td>Heme Malignancies &amp; solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC (RG7598)</td>
<td>MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RG7845</td>
<td>Heme malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-Cell Dependent Bi-specific (TDB) AB, PIM, CD44, Others</td>
<td>Heme malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADC=Antibody-Drug Conjugate; AML=Acute Myeloid Leukemia; CLL=Chronic Lymphocytic Leukemia; NHL=Non-Hodgkin’s Lymphoma;
*Co-development molecule with AbbVie
## Smart development: leverage combinations

26 disclosed combinations in 9+ tumor types

### Solid tumors

#### Breast cancer

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Perjeta</td>
<td>Herceptin</td>
<td>✓</td>
</tr>
<tr>
<td>Perjeta</td>
<td>Herceptin</td>
<td>✓</td>
</tr>
<tr>
<td>Kadcyla</td>
<td>Perjeta</td>
<td>Ph3</td>
</tr>
<tr>
<td>Kadcyla</td>
<td>Perjeta</td>
<td>Ph3</td>
</tr>
<tr>
<td>Perjeta</td>
<td>Herceptin</td>
<td>Ph2, 3</td>
</tr>
<tr>
<td>Perjeta</td>
<td>Herceptin</td>
<td>Ph3</td>
</tr>
<tr>
<td>GE-anti-HER3</td>
<td>Perjeta</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

#### Colon cancer

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PDL1</td>
<td>Avastin</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

#### Lung cancer

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>Tarceva</td>
<td>Ph2</td>
</tr>
<tr>
<td>Anti-PDL1</td>
<td>Tarceva</td>
<td>Ph2</td>
</tr>
<tr>
<td>Pictilisib (PI3Ki)</td>
<td>Avastin</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

#### Melanoma

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobimetinib</td>
<td>Zelboraf</td>
<td>Ph3</td>
</tr>
<tr>
<td>Anti-PDL1</td>
<td>Zelboraf</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

### Gastric, brain, kidney and others

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Perjeta</td>
<td>Herceptin</td>
<td>Ph3</td>
</tr>
<tr>
<td>Anti-PDL1</td>
<td>Avastin</td>
<td>Ph2</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>AKT inh</td>
<td>Ph1</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Pictilisib (PI3Ki)</td>
<td>Ph1</td>
</tr>
<tr>
<td>GE-anti-HER3</td>
<td>Tarceva</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

### Hematological tumors

#### Lymphoma

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD22 ADC</td>
<td>Rituxan</td>
<td>Ph2</td>
</tr>
<tr>
<td>Anti-CD79b ADC</td>
<td>Rituxan</td>
<td>Ph2</td>
</tr>
<tr>
<td>Bcl2 inh</td>
<td>Rituxan (+B)</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

#### Leukemia

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcl2 inh</td>
<td>Gazyva</td>
<td>Ph1</td>
</tr>
<tr>
<td>Bcl2 inh</td>
<td>Rituxan</td>
<td>Ph1</td>
</tr>
<tr>
<td>Bcl2 inh</td>
<td>Rituxan (+B)</td>
<td>Ph1, 3</td>
</tr>
</tbody>
</table>

### Locally advanced solid tumors

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Anti-PDL1</td>
<td>Cobimetinib</td>
<td>Ph1</td>
</tr>
<tr>
<td>Anti-HER3/EGFR</td>
<td>Cobimetinib</td>
<td>Ph1</td>
</tr>
</tbody>
</table>

✓ Studies read out/filed/approved
Innovative business models: tailored access

*Developed markets - access through innovative pricing*

**Pack based pricing**
- Undifferentiated $$ by vial

**Value based pricing**

- **Personalized Reimbursement Models**
- **Episode-of-care based**

- **Combinations**

- **Indication based**

**Need for data from healthcare systems**
## Innovative business models: tailored access

### Developing markets – multiple approaches

### Examples of approaches

<table>
<thead>
<tr>
<th>Patient assistance programs</th>
<th>Differential pricing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partnership with Cancer Foundation, Ministry of Health</td>
<td>Access to the public reimbursement</td>
</tr>
<tr>
<td>&gt;24,000 more patients treated since 2011</td>
<td>&gt;1,900 more patients treated since 2013</td>
</tr>
</tbody>
</table>

- Multiple approaches to ensure access to medicines in emerging markets
- No ‘one-size fits all’ solution – depends on market characteristics and segments

Note: Incremental patients treated are current estimates based upon available new patient starts data through YE 2013
**Key success factors in the new environment**

<table>
<thead>
<tr>
<th>Best Science</th>
<th>Smart Development</th>
<th>Innovative Business Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Integrated biomarker expertise</td>
<td>• First or best in class</td>
<td>• Tailored approaches to access</td>
</tr>
<tr>
<td>• Top tier scientific talent</td>
<td>• Shift paradigms in development</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leverage Combinations</td>
<td></td>
</tr>
</tbody>
</table>
Roche strategy in oncology

Summary
Comprehensive approach to cancer…

Multiple ways to target cancer

- Tumor microenvironment
- Angiogenic signaling
- HER2 signaling
- PI3K/AKT/mTOR
- Antibody-drug conjugates
- Cell death “apoptosis“
- Cancer immunotherapy
- Activating immune system


...enabling a disease area approach

*Focused and distinct projects per disease area*

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Global incidence (%)</th>
<th>Late stage projects</th>
<th>Early stage projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal &amp; gastric</td>
<td>22</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Breast</td>
<td>11</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Ovarian/GYN</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hematology</td>
<td>7</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

*Total* 40 55

Multiple assets require disease area strategies
## 2014: Key upcoming oncology readouts

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>cobimetinib (MEKi)</td>
<td>Met. melanoma</td>
<td>Ph III (co-BRIM)</td>
</tr>
<tr>
<td>Kadcyla &amp; Perjeta</td>
<td>HER2+ mBC (1 Line)</td>
<td>Ph III MARIANNE</td>
</tr>
<tr>
<td>alectinib (ALKi)</td>
<td>NSCLC</td>
<td>Ph II</td>
</tr>
<tr>
<td>anti-HER3 EGFR DAF</td>
<td>Head and neck, colorectal cancer</td>
<td>Ph II (MEHGAN, DARECK)</td>
</tr>
<tr>
<td>anti-PDL1</td>
<td>Solid tumors</td>
<td>Ph I/II updates</td>
</tr>
</tbody>
</table>

Outcome studies are event driven, timelines may change
Oncology strategy summary

1. **Best science:**
   - Leveraging our top oncology talent to focus on the most promising molecules and combinations

2. **Smart clinical development:**
   - Delivering first and/or best in class medicines
   - Making smart development decisions and trial designs
   - Using a disease area approach and leveraging combinations

3. **Innovative business models:**
   - Tailoring approaches to ensure access in both developed and developing markets
Doing now what patients need next