51st ASCO Annual Meeting, Chicago

Roche Analyst Event
Sunday, 31 May 2015
Welcome
Karl Mahler, Head of Investor Relations

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

Working along the cancer immunity-cycle: Strategies and new agents
Ira Mellman, gRED: Ph.D., Vice President, Cancer Immunology, Genentech
William Pao, pRED: M.D., Ph.D., Global Head Oncology Discovery and Translational Area, Roche

ASCO 2015 Roche highlights: Setting new standards, developing combinations
Sandra Horning, M.D., Chief Medical Officer and Head Global Product Development

Growing importance of molecular information in cancer immunotherapy
Garret Hampton, Ph.D., Vice President, Oncology Biomarker Development and Companion Diagnostics

Summary and Q&A
Karl Mahler, Head of Investor Relations
Oncology strategy and outlook

Daniel O’Day
Chief Operating Officer, Roche Pharmaceuticals
Roche oncology: Continued sales growth

A portfolio of differentiated medicines
Oncology continues to become more complex
Science, clinical practice evolving with understanding of disease biology

Classification of lung adenocarcinomas

2004
Unknown
KRAS
EGFR

2014
No oncogenic driver detected 35%
KRAS 25%
EGFR 17%
ALK 8%
PD-L1 positive (illustrative)
EGFR (other) 4%
HER2 3%
NRAS 1%
MET 1%
PI3KCA
MEK1 <1%
>1 mutated gene 3%
No oncogenic driver detected

Today

Roche’s oncology strategy has remained constant
Today’s presentations highlight the results of our strategy across key programs

**Follow the science**
- Bringing our best minds together
- Science driven programs

**Personalized healthcare**
- Differentiation via biomarkers
- Experts integrated in R&D

**Strong portfolio & development**
- Comprehensive pipeline and active partnering
- Smart trial design

**Higher certainty of patient benefit:** Better for patients and for reimbursement
Strategy in action - Immunotherapy

Perspectives in key franchises

Summary
Strategy into action: Learning loop
Comprehensive and scientifically driven strategies – crafted by our best minds

Research
(gRED, pRED, Chugai & external)

Immunotherapy & Combinations

Development
(early and late)

Partnering
(Genentech and Roche)

Clinical Insights & Biomarkers
(internal and external)

We bring our best scientists & clinicians together for:

- Ideation
- Decision making
- Quick & efficient pursuit of promising ideas
...and we dedicate budget for rapid proof of concept studies (Ph1)
Atezolizumab (aPD-L1, MPDL3280A) strategy
Biomarker selection and combinations

Our vision: Bringing the potential for transformative benefit to a broad patient population either in mono therapy or combinations

Diagnostic selection to identify patients most likely to benefit from atezolizumab as a monotherapy

Improve survival using well-tolerated combinations with existing and emerging therapies
Atezolizumab in 2/3L NSCLC (POPLAR)
Clinical outcomes correlate with PD-L1 expression

**Overall Survival**

- **ITT n=287**
- TC3 or IC3: 16%*  (0.46)
- TC2/3 or IC2/3: 37%*  (0.56)
- TC1/2/3 or IC1/2/3: 67%*  (0.63)
- TC0 and IC0: 32%*  (1.12)

**Progression Free Survival**

- In favor of atezolizumab: HRa = 0.98
- In favor of docetaxel: HRa = 0.57

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\( \text{a = Unstratified HR; * = eligible patient population} \)

Spira A. et al, ASCO 2015
Atezolizumab strategy: Combinations

Scientifically driven strategy that combines with chemo, targeted therapy, and other immunotherapy

- **pRED**
- **gRED**
- **Both**

**Costimulatory antibodies**
- Anti-OX40 (agonist)

**APC stimulators**
- Anti-CD40 (agonist)

**Clinical phase molecules**

**Eliminate M2 Macrophages**
- Anti-CSF-1R

**T cell bispecifics**
- Anti-CEA/CD3 TCB

**Tumor-targeted cytokines**
- Anti-CEA-IL2v FP
- Anti-FAP-IL2v FP

**Checkpoint Inhibitors**
- Anti-PD-L1
- Anti-TIGIT
- IDOi
- Anti-OX40

Chen & Mellman (2013) *Immunity*
Atezolizumab strategy: Programs by disease

Focused strategy: Going deep in diseases where we have strong scientific rationale

15 Roche / Genentech Phase 2 or 3 Studies

**LUNG**
- 2L+ single-arm Ph2 (x2)
- 2L+ rand Ph2 and rand Ph3
- 1L single-agent Ph3 (x2)
- 1L w/chemo, Avastin Ph3 (x3)

**BLADDER**
- 2L+ & 1L cis-inel single-arm Ph2
- 2L+ rand Ph3
- Adjuvant Ph3

**KIDNEY**
- 1L w/Avastin Ph2
- 1L w/Avastin Ph3

**BREAST**
- 1L w/Abraxane Ph3
Atezolizumab strategy: Summary
Comprehensive, science-driven program

Strategic pillars of our PD-L1 development approach

**Dx + Monotherapy**
- Examples:
  - mRCC (Ph II)
  - mUBC (Ph II)
  - 2L mNSCLC (Ph II ‘BIRCH’, ‘POPLAR’, ‘FIR’, Ph III ‘OAK’)
  - Dx+ 1L NSCLC (2x: Sq/NSq, Ph III)
  - Dx+ mUBC (Ph III)

**Immune Doublets**
- Examples:
  - Loc adv/ metastatic solid tumors with ipilimumab or Interferon alfa-2b (Ph Ib)
  - Combination with anti-CSF-1R (Ph Ib)
  - Combination with anti-CD40 (Ph Ib)
  - Combination with Incyte’s IDOi (Ph Ib)
  - Combination with anti-OX40 (Ph Ib)
  - Combination with CEA-IL2v (Ph Ib)
  - Combination with Celldex anti-CD27

**Chemotherapy Combinations**

**Targeted Therapy Combinations**

**Combination with Chemotherapy**
- Examples:
  - 1L NSCLC Squamous and Non-Squamous with platinum doublets (x3, Ph III)
  - 1L TNBC with Abraxane (Ph III)

**Combination with Targeted Therapy**
- Examples:
  - mRCC with Avastin (Ph II)
  - mRCC with Avastin (Ph III)
  - EGFR+ NSCLC w/Tarceva (Ph Ib)
  - ALK+ NSCLC w/alectinib (Ph Ib)
  - Solid tumors with Avastin (Ph Ib)
  - Solid tumors w/cobimetinib (Ph Ib)
  - Lymphoma with Gazyva (Ph Ib)
Strategy in action - Immunotherapy

Perspectives in key franchises

Summary
Hematology strategy on track
Strong pipeline and programs across key indications

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Indication</th>
<th>P 1</th>
<th>P 2</th>
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Data presented at ASCO

* venetoclax in collaboration with AbbVie
BR = bendamustine+Rituxan

venetoclax (Bcl2 inhibitor); polatuzumab vedotin (CD79b ADC)
HER2 franchise outlook
Complete portfolio of innovative drugs

2nd line mBC
- Xeloda + lapatinib
- Kadcyla (EMILIA)

1st line mBC
- Herceptin + chemo
- Herceptin & Perjeta + chemo (CLEOPATRA)
- Kadcyla & Perjeta (MARIANNE)

Adjuvant BC
- Herceptin + chemo
- Herceptin sc + chemo (HannaH)
- Herceptin & Perjeta + chemo (APHINITY)

Neoadjuvant BC
- Herceptin + chemo (NOAH)¹
- Herceptin & Perjeta + chemo (Neosphere, Tryphaena)
- Kadcyla & Perjeta (KRISTINE)
- Kadcyla (KATHERINE)
- Kadcyla & Perjeta (KAITLIN)

Established standard of care
New standard of care
Trials in progress

¹ Neoadjuvant BC
HER2 franchise: Perjeta commercial uptake strong

Next Milestone: eBC readout (APHINITY) in 2016

Perjeta US Neoadj Approval

Perjeta Cleopatra OS Readout

NEOSPHERE OS Data at this ASCO

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CHFm

Q1

Q4

Q2

Q3

Q1

Kadcyla

Perjeta

Herceptin

Neoadjuvant approval

Cleopatra OS readout

NEOSPHERE OS data at this ASCO

Next Milestone: eBC readout (APHINITY) in 2016
Avastin franchise
Continues to be the most studied molecule at ASCO

Continued growth fueled by recent launches in cervical, ovarian cancers

Avastin Mesothelioma data presented at ASCO 2015

Sales at 2014 average exchange rates
Strategy in action - Immunotherapy
Perspectives in key franchises

Summary
ASCO 2015: Roche highlights

- More than 275 abstracts, Avastin most quoted drug

- Potential improvements on current standard of care:
  - Cobimetinib / Zelboraf in 1L skin cancer (targeted therapies)
  - Alectinib in 2L ALK mutated lung cancer

- New treatment options:
  - Atezolizumab in 2L lung cancer (vs chemo)
  - Atezolizumab combinations with chemo in lung and TNBC
  - Avastin in mesothelioma
  - Gazyva in R/R indolent NHL

- Several filings resulting from data presented at the meeting
Roche’s oncology strategy has remained constant

Today’s presentations highlight the results of our strategy across key programs

Follow the science

• Bringing our best minds together
• Science driven programs

Personalized healthcare

• Differentiation via biomarkers
• Experts integrated in R&D

Strong portfolio & development

• Comprehensive pipeline and active partnering
• Smart trial design

Higher certainty of patient benefit: Better for patients and for reimbursement
Working along the cancer immunity-cycle: Strategies and new agents I

Ira Mellman

Vice President, Cancer Immunology, Genentech
The renaissance of immunotherapy is a revolution for cancer patients
Early data suggests that anti-PD-L1/PD-1 is active across a wide range of tumor types.

Broad activity but only subset of patients benefit.

ORR ~10-30%

Most patients will need biomarker selection and combination therapy: Strategy now supported by clinical results.
Using patient data to understand cancer immunity-cycle

Atezolizumab 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?*

Powles et al., *Nature* 2014
Combinations of immunotherapeutics

*Partnered programs

**Immunity**

Chen & Mellman (2013) *Immunity*
**IDO (indoleamine di-oxygenase)**

* A suppressor of effector T cells

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**Adaptive expression of PD-L1**

- IFNγ-mediated up-regulation of tumor PD-L1
- MAPK PI3K pathways
- CD8+ Cytotoxic T Lymphocyte (CTL)

**Adaptive expression of IDO**

- IFNγ-mediated up-regulation of tumor IDO
- Kynurenine ↑ Tryptophan ↓
- IDO
- MAPK PI3K pathways
- CD8+ Cytotoxic T Lymphocyte (CTL)

* T cell suppression*
Pre-clinical data shows promising activity for IDO inhibition (GDC-0919)

- Plasma kynurenine decrease
- T regulatory cells decrease
- T effector cells show increased proliferation & CTL function
- Enhanced anti-tumor efficacy with anti-PD-L1 and anti-CTLA4

Ongoing studies
- Phase 1a (GDC-0919)
- Phase 1b combination (GDC-0919 + atezolizumab)
- Phase 1b combination (INCB024360 + atezolizumab)

GDC-0919 in collaboration with NewLink; INCB024360 in collaboration with Incyte
TIGIT

A second potent negative regulator of T cell responses

- Human and murine tumor-infiltrating CD8+ T cells express high levels of TIGIT
- Antibody co-blockade of TIGIT and PD-L1 elicits tumor rejection in preclinical models
- TIGIT selectively limits the effector function of chronically stimulated CD8+ T cells
- TIGIT interacts with CD226 in cis and disrupts CD226 homodimerization

1. Competes with CD226 for PVR
2. Disrupts CD226 activation
3. Directly inhibits T cells in cis

TIGIT = T cell immunoreceptor with Ig and ITIM domains
TIGIT

aTIGIT and aPD-L1 combination effective in PD-L1 non-responsive model

1. Competes with CD226 for PVR
2. Disrupts CD226 activation
3. Directly inhibits T cells in cis

Median tumor volume (mm$^3$)

Complete remission (CR)

Day
Elevated expression of TIGIT by T cells in human cancer supports combination with atezolizumab

Lung squamous cell carcinoma

OX40 exhibits a dual mechanism of action
Promote antigen dependent effector T cell activation and T regulatory cell inhibition

Increase in T effector cells by aOX40 may create need to combine with aPD-L1
Promising pre-clinical efficacy of an aOX40/aPD-L1 combination model

Ongoing studies

- Phase 1a (MOXR0916)
- Phase 1b combination (MOXR0916 + atezolizumab)
- Planned (MOXR0916 + GDC-0919)

MOXR0916 = anti-OX40
Combinations with chemotherapy

*Induced inflammation & antigen release may enhance atezolizumab efficacy*

1. **Release of cancer cell antigens**
   (Immune and cancer cells)

2. **Cancer antigen presentation**
   (dendritic cells/APCs)

3. **Priming and activation**
   (APCs & T cells)

4. ** Trafficking of T cells to tumors**
   (CTLs)

5. **Infiltration of T cells into tumors**
   (CTLs, endothelial cells)

6. **Recognition of cancer cells by T cells**
   (CTLs, cancer cells)

7. **Killing of cancer cells**
   (Immune and cancer cells)

Chen & Mellman (2013) *Immunity*
Combinations may extend the benefit of aPD-L1

Preclinical synergy with selected chemo and targeted therapies

**Oxaliplatin chemotherapy**

**MEKi targeted therapy**

CT26 (Krasmut)

Dosing
Combinations with chemotherapy appear to extend the benefit of atezolizumab in NSCLC patients

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Atezolizumab + carboplatin/paclitaxel
- CR/PR (n=3)
- SD (n=2)
- PD (n=0)

Atezolizumab + carboplatin/pemetrexed
- CR/PR (n=9)
- SD (n=1)
- PD (n=1)

Atezolizumab + carboplatin/nab-paclitaxel
- CR/PR (n=8)
- SD (n=4)
- PD (n=1)

Chemotherapy can promote Th1-type inflammation in tumors

Liu et al. ASCO 2015
Strategic vision: Lead by developing best-in-class combination therapies

**Combinations with immunotherapies**
- aCD40
- Vaccines, Oncolytic Viruses
- aCTLA4
- aOX40
- aCD27
- aCEA/FAP-IL2v
- T Cell Bispecifics
- ImmTACs Planned
- IDOi
- aCSF1R
- aTIGIT
- Cytokines, anti-cytokines Planned

**Combinations with other agents**
- aVEGF
- EGFRi Planned
- ALKi
- BRAFi
- MEKi
- BTKi
- aCD20
- aHER2
- Chemo
- HDAC
- A2V

- Partnered external combo
- Internal combo

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- **Clinical development**
- **Preclinical development**
- **Partnered projects**
Working along the cancer immunity-cycle: Strategies and new agents II

William Pao, M.D., Ph.D.
Global Head Oncology Discovery and Translational Area, Roche pRED
### Cancer immunotherapy at pRED

**Distinct MoAs with potential for combinations**

<table>
<thead>
<tr>
<th><strong>aCSF-1R</strong></th>
<th><strong>aCEA-IL2v FP</strong></th>
<th><strong>aCEA/CD3 TCB</strong></th>
<th><strong>aCD40</strong></th>
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<tbody>
<tr>
<td>First antibody shown to eliminate tumor-associated macrophages</td>
<td>Designed to amplify immune response</td>
<td>First anti-tumor T-cell engager from Roche to enter clinical trials</td>
<td>Best/first in class immuno-activating Ab</td>
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<tr>
<td>Proof of biological activity established in rare disease (PVNS)</td>
<td>Novel recombinant immunocytokine with superior safety, PK, and tumor targeting</td>
<td>Best-in-class TCB platform</td>
<td>Activates antigen presenting cells to jumpstart adaptive immunity</td>
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Tumor-associated macrophages
A promising new target in oncology
Emactuzumab (aCSF-1R)

Proof of biological activity shown in PVNS*

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<tr>
<th>Clinical benefit</th>
<th>Patients</th>
<th>%</th>
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<tr>
<td>Objective response</td>
<td>24/28</td>
<td>86</td>
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<tr>
<td>Complete response</td>
<td>2/28</td>
<td>7</td>
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<td>Partial metabolic response</td>
<td>24/26</td>
<td>92</td>
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<tr>
<td>Clinically progression-free</td>
<td>27/28</td>
<td>96</td>
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*PVNS - pigmented villonodular synovitis, emactuzumab = anti-CSF-1R (RG7155)

CSF1R Inhibition with Emactuzumab in Locally Advanced Diffuse-type Tenosynovial Giant Cell Tumors of the soft tissue: a phase 1, dose escalation and expansion study, Cassier P. et al. (2015), Lancet Oncology, in press
Emactuzumab: Elimination of tumor-associated macrophages in solid tumors – phase I data

Depletion of CSF-1 dependent macrophages in solid tumors

- Proof of biological activity in wide range of tumor types
- Potentially synergistic with atezolizumab
  - Phase I combination study: dose escalation with atezolizumab ongoing
  - No severe immune-related AE reported to date
  - Multiple extensions to start Q3 2015

Macrophages suppress T cell proliferation in vitro

atezolizumab = anti-PD-L1 (MPDL3280A)
Gomez-Roca, CA: Phase I study of RG7155, a novel anti-CSF1R antibody, in patients with advanced/metastatic solid tumors, 2015 ASCO
Tumor targeted IL2v cytokine fusion proteins
A platform to amplify and activate immune effectors in tumors

Mechanism of Action
- Binds to target to deliver novel variant of IL-2 to the tumor
- Recruits killer T and Natural Killer (NK) cells to the tumor

Features
- Compared to standard IL-2-based therapy, it shows:
  - Superior expansion of immune effectors
  - Less activation of suppressive T-cells
  - Better tolerability
  - Better tumor targeting

IL2v – interleukin-2 variant

Novel tumor-targeted, engineered IL-2 variant (IL-2v)-based immunocytokines for immunotherapy of cancer:
Christian Klein et al., ASH, 2013, Blood 122 (21), 2278-2278
aCEA-IL2v – phase I data

Tumor targeting and intra-tumoral T cell activation

Increased CD8 densities and CD8:CD4 ratio confirm intra-tumoral immune activation at doses ≥ 20 mg

**aCEA-IL2v is an ideal combination partner for atezolizumab: Phase I combination starting**

CEA - carcinoembryonic antigen; *Quantitative data from 2 CEA-ve patients pending, no tumor uptake on visual assessment

*Schellens, Jan H. M. et al., CEA--targeted engineered IL2: Clinical confirmation of tumor targeting and evidence of intra-tumoral immune activation; 2015 ASCO
aFAP-IL2v: A complementary approach targeting tumor stroma

FAP staining

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<tr>
<th>Parameter</th>
<th>CEA-IL2v</th>
<th>FAP-IL2v</th>
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<tr>
<td>Target cell</td>
<td>Cancer cells (CEA)</td>
<td>Tumor stromal cells (FAP)</td>
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<tr>
<td>Target expression</td>
<td>Heterogeneous</td>
<td>Homogeneous</td>
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<tr>
<td>Target density</td>
<td>Medium</td>
<td>High</td>
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<tr>
<td>Indications</td>
<td>Mainly GI indications: GC, PaC, CRC</td>
<td>Very broadly expressed: High expression in e.g. H&amp;N, sq NSCLC, BC</td>
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- FAP-IL2v phase I start: planned in 2015

FAP – fibroblast-activation protein
T cell engaging therapies in development

**CAR T cells versus T cell bispecific antibodies**

### Engineered T cells (CARS)

- High interest, outstanding clinical efficacy with CD19 CARs in **hematology**
- Activity associated with high **toxicity**
- Challenging manufacturing and regulatory processes

### T cell engaging bispecific antibodies

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<th>Potency</th>
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CEA-TCB: First “2:1” T cell bispecific in the clinic

Targets CEA-expressing tumors to induce localized T cell-mediated killing

**Mechanism of Action**

- Binds T cells and tumor cells simultaneously
- Results in T cell activation/proliferation and killing of tumor cells
- Does not require MHC:peptide complex presentation by tumor cells
- T cell engagement independent of specificity and activation status

**Features**

- Entry into human – study started in Dec 2014
- Combination with IL2v & PD-L1 planned early in clinical development
- Broad, early pipeline of several TCBs addressing solid & hematological malignancies
CEA-TCB: Novel mode of action

From poorly inflamed to highly inflamed tumors

- Recruits new T cells and/or expands pre-existing ones
- Induces T cell re-localization from tumor periphery to tumor bed
- Activates intra-tumor T cells to become differentiated towards effector memory phenotype

Intravital two-photon imaging 24 h after CEA-CD3 therapy. Red: Tumor cells (LS174T RFP). Green: Human T cells

Bacac M. et al., submitted
Roche cancer immunotherapy pipeline
Abundant opportunities for combinations

- Checkpoint Inhibitors
  - Anti-PD-L1
  - Anti-TIGIT
  - IDOi
  - Anti-OX40

- Eliminate M2 Macrophages
  - Anti-CSF-1R

- Tumor-targeted cytokines
  - Anti-CEA-IL2v FP
  - Anti-FAP-IL2v FP

- T cell bispecifics
  - Anti-CEA/CD3 TCB

- APC stimulators
  - Anti-CD40 (agonist)

- Costimulatory antibodies
  - Anti-OX40 (agonist)

- Clinical phase molecules
  - pRED
  - gRED
  - Both

- Priming & activation
- T cell Trafficking
- T cell infiltration
- T cell recognition
- Antigen presentation
- Antigen release
- T cell killing

Chen & Mellman (2013) *Immunity*
Cancer immunotherapy program growing strongly

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Indication</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td></td>
<td>+ chemo</td>
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<tr>
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<td>+ Avastin+chemo</td>
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<td>Mono</td>
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<td>+ Avastin</td>
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<tr>
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<td>+ Zelboraf</td>
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<td></td>
</tr>
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<td></td>
<td>+ Zelboraf+cobimetinib</td>
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</tr>
<tr>
<td></td>
<td>Mono</td>
<td>Solid tumors</td>
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<tr>
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<td>+ Avastin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>+ cobimetinib</td>
<td></td>
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<tr>
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<td>+ ipilimumab</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>+ IFN alpha-2b</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>+ aCD40</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>+ aOX40</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>+ aCSF-1R</td>
<td></td>
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<tr>
<td></td>
<td>+ aCEA-IL2v FP</td>
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<td></td>
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<tr>
<td></td>
<td>+ Gazyva</td>
<td>Hematology</td>
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<td>Mono</td>
<td>Triple neg. breast cancer</td>
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<td></td>
<td>+ chemo</td>
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<tr>
<td><strong>aCSF-1R</strong></td>
<td>Mono</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ aCD40</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>acea-IL2v FP</strong></td>
<td>Mono</td>
<td>Solid tumors</td>
<td></td>
<td></td>
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<tr>
<td><strong>afaP-IL2v FP</strong></td>
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<td>Solid tumors</td>
<td></td>
<td></td>
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<tr>
<td><strong>aOX40</strong></td>
<td>Mono</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>acea/CD3 TCB</strong></td>
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<td>Solid tumors</td>
<td></td>
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<tr>
<td><strong>IDO</strong></td>
<td>Mono</td>
<td>Solid tumors</td>
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<tr>
<td><strong>IDO (Incyte)</strong></td>
<td>+ aPD-L1</td>
<td>Solid tumors</td>
<td></td>
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<tr>
<td><strong>Varilumab (Celldex)</strong></td>
<td>+ aPD-L1</td>
<td>Solid tumors</td>
<td></td>
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</tr>
</tbody>
</table>

Study ongoing | Study imminent | * External collaboration
ASCO 2015 Roche highlights: Setting new standards, developing combinations

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

Setting new standards, developing combinations

Cancer immunotherapy

Roche program update
Atezolizumab in lung cancer
Atezolizumab in bladder cancer

Targeted therapies and combinations

Alectinib in ALK-positive lung cancer
Cobimetinib + Zelboraf in melanoma
Kadcyla, Perjeta, Herceptin in HER2+ breast cancer

Hematology

Gazyva in NHL
Roche cancer immunotherapy program

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>aPD-L1</td>
<td>aPD-L1</td>
<td>aPD-L1</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Solid tumors (Dx+)</td>
<td>2/3L NSCLC</td>
</tr>
<tr>
<td>aPD-L1+chemo</td>
<td>aPD-L1+ipilimumab</td>
<td>aPD-L1**</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Solid tumors</td>
<td>2/3L Bladder</td>
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<tr>
<td>aPD-L1+Ilenalidomide**</td>
<td>aPD-L1+IFN-alfa</td>
<td>aPD-L1+Avastin</td>
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<tr>
<td>MM</td>
<td>Solid tumors</td>
<td>1L Renal</td>
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<tr>
<td>aPD-L1+Tarceva</td>
<td>aPD-L1+aCD40</td>
<td>aPD-L1</td>
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<td>NSCLC</td>
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<td>1/2L Bladder</td>
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<td>aPD-L1+Zelboraf</td>
<td>aPD-L1+aOX40**</td>
<td>aPD-L1+chemo**</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Solid tumors</td>
<td>1L non sq NSCLC</td>
</tr>
<tr>
<td>aPD-L1+cobimetinib</td>
<td>aPD-L1+aCSF-1R**</td>
<td>aPD-L1+chemo**</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Solid tumors</td>
<td>1L non sq NSCLC</td>
</tr>
<tr>
<td>aPD-L1+Avastin</td>
<td>aPD-L1+aCEA-IL2v FP**</td>
<td>aPD-L1+chemo**</td>
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<tr>
<td>Solid tumors</td>
<td>Solid tumors</td>
<td>1L sq NSCLC</td>
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<tr>
<td>aPD-L1 + Gazyva</td>
<td>aPD-L1**</td>
<td>aPD-L1**</td>
</tr>
<tr>
<td>R/R FL / aNHL</td>
<td>tba</td>
<td>1L non sq NSCLC (Dx+)</td>
</tr>
<tr>
<td>aPD-L1+Avastin+chemo</td>
<td>aPD-L1**</td>
<td>aPD-L1**</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>tba</td>
<td>1L non sq NSCLC (Dx+)</td>
</tr>
<tr>
<td>aPD-L1+Zelboraf+cobi**</td>
<td>aPD-L1**</td>
<td>aPD-L1+Avastin**</td>
</tr>
<tr>
<td>Melanoma</td>
<td>tba</td>
<td>1L TNBC</td>
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<td>aCSF-1R</td>
<td>aPD-L1**</td>
<td>aPD-L1+chemo**</td>
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<tr>
<td>Solid tumors</td>
<td>tba</td>
<td>1L RCC</td>
</tr>
<tr>
<td>aCEA-IL2v FP</td>
<td>aPD-L1**</td>
<td>aPD-L1**</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>tba</td>
<td>Adjuvant MIBC (Dx+)</td>
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<td>aOX40</td>
<td>aPD-L1**</td>
<td>tba</td>
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<td>Solid tumors</td>
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</tr>
<tr>
<td>aCEA/CD3 TCB</td>
<td>NME**</td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>tba</td>
<td></td>
</tr>
</tbody>
</table>

Status as at May 31, 2015

- aPD-L1 trials
- NMEs monotherapy
- Immune doublets
- 2015 readout expected
- ** Study start in 2015
- ✓ Data at ASCO 2015
Biomarker development for atezolizumab

*PD-L1 expression on different cell types*

<table>
<thead>
<tr>
<th>IC Score</th>
<th>PD-L1 staining</th>
<th>TC Score</th>
<th>PD-L1 staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC3</td>
<td>IC ≥ 10%</td>
<td>TC3</td>
<td>TC ≥ 50%</td>
</tr>
<tr>
<td>IC2</td>
<td>IC ≥ 5% and &lt; 10%</td>
<td>TC2</td>
<td>TC ≥ 5% and &lt; 50%</td>
</tr>
<tr>
<td>IC1</td>
<td>IC ≥ 1% and &lt; 5%</td>
<td>TC1</td>
<td>TC ≥ 1% and &lt; 5%</td>
</tr>
<tr>
<td>IC0</td>
<td>IC &lt; 1%</td>
<td>TC0</td>
<td>TC &lt; 1%</td>
</tr>
</tbody>
</table>

Assessed by immunohistochemistry using SP142, a sensitive and specific proprietary monoclonal antibody assay against PD-L1

*Immune cell staining*  
*Tumor cell staining*

Gettinger S. *et al*, ASCO 2015
### Atezolizumab clinical program in 2/3L NSCLC

**Breakthrough designation in PD-L1+ patients**

#### Primary end-point:

| Trial | Phase | PD-L1-selected mNSCLC n=138 | Atezolizumab 1200 mg IV Q3 weeks | ORR
|-------|-------|-----------------------------|---------------------------------|-------|
| **FIR** | Phase II | PD-L1-selected mNSCLC n=138 | Atezolizumab 1200 mg IV Q3 weeks | ORR
| **POPLAR** | Phase II | All comers 2/3L mNSCLC n=287 PD-L1 stratified | Atezolizumab 1200 mg IV Q3 weeks, Docetaxel 75 mg/m² IV Q3 weeks | OS Interim data at ASCO Final data in H2 2015 |
| **BIRCH** | Phase II | PD-L1-selected mNSCLC n=667 | Atezolizumab 1200 mg IV Q3 weeks | ORR Data in Q3 2015 |
| **OAK** | Phase III | All comers 2/3L mNSCLC n=1100 PD-L1 stratified | Atezolizumab 1200 mg IV Q3 weeks, Docetaxel 75 mg/m² IV Q3 weeks | OS Data expected 2016 |

**Note:** Atezolizumab (Anti-PD-L1) is listed as MPDL3280A in clinicaltrials.gov

mNSCLC = metastatic Non Small-Cell Lung Cancer
Atezolizumab in 2/3L NSCLC (POPLAR)
Clinical outcomes correlate with PD-L1 expression

Overall survival

<table>
<thead>
<tr>
<th>ITT</th>
<th>n=287</th>
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<tbody>
<tr>
<td>TC3 or IC3</td>
<td>16%*</td>
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<tr>
<td>0.46</td>
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<tr>
<td>0.77</td>
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</tr>
<tr>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td>1.93</td>
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</table>

In favor of atezolizumab
In favor of docetaxel

Progression-free survival

<table>
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<tr>
<th>ITT</th>
<th>0.98</th>
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<td>0.57</td>
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<tr>
<td>0.70</td>
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<tr>
<td>0.87</td>
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<tr>
<td>1.17</td>
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</tr>
<tr>
<td>1.87</td>
<td></td>
</tr>
</tbody>
</table>

In favor of atezolizumab
In favor of docetaxel

*= unstratified HR; * = eligible patient population
Spira A. et al, ASCO 2015
Atezolizumab in 2/3L NSCLC (POPLAR)

Overall survival correlates with PD-L1 expression

- Final POPLAR and BIRCH read-outs in H2 15
- Phase III (OAK) in all comers (stratified by PD-L1 expression): Data in 2016

\[9.1 \text{ mo } (7.4, 12.8)\]

\[9.7 \text{ mo } (6.7, 11.4)\]

\[9.7 \text{ mo } (8.6, 12.0)\]

\[\text{Not Reached } (11.0, \text{ NE})\]

\[= \text{ Unstratified HR}\]

Spira A. et al, ASCO 2015
Atezolizumab + chemotherapy in 1L NSCLC (Ph1)

Well tolerated with no unexpected toxicities

The addition of atezolizumab to standard 1L chemotherapy was well tolerated throughout the course of treatment, including maintenance therapy, with no unexpected toxicities

No autoimmune renal toxicity or pneumonitis was observed

Liu S. et al, ASCO 2015
Atezolizumab + chemotherapy in 1L NSCLC (Ph1)
Efficacy unrelated to PD-L1 expression

ORR across all arms = 67% (48-82)
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
Liu S. et al, ASCO 2015
Atezolizumab phase III program in 1L NSCLC
Developing combinations, building on predictive PD-L1 biomarker

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Treatment arms</th>
<th>Primary completion*</th>
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<tr>
<td><strong>Combination studies – All comers (PD-L1 subgroup analysis)</strong></td>
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<tr>
<td>GO29436</td>
<td>Non-squamous</td>
<td>Atezo + Carbo + Pac Atezo + Carbo + Pac + Avastin  Carbo + Pac + Avastin</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=1200</td>
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<tr>
<td>GO29537</td>
<td>Non-squamous</td>
<td>Atezo + Carbo + Nab-pac Carbo + Nab-pac</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=550</td>
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<tr>
<td>GO29437</td>
<td>Squamous</td>
<td>Atezo + Carbo + Pac Atezo + Carbo + Nab-pac Carbo + Nab-pac</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=1200</td>
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<tr>
<td><strong>Monotherapy studies – PD-L1 Selected</strong></td>
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<td>Non-squamous</td>
<td>Atezo Cis or Carbo + Pem</td>
<td>2017 (PFS)</td>
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<td>n=400</td>
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<tr>
<td>GO29432</td>
<td>Squamous</td>
<td>Atezo Cis or Carbo + Gem</td>
<td>2017 (PFS)</td>
</tr>
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<td>n=400</td>
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</tbody>
</table>

* Outcome studies are event driven, timelines may change, OS endpoint included for all studies

Atezo=atezolizumab; Carbo=Carboplatin; Pac=Paclitaxel; Nab-pac= Nab-paclitaxel; Cis=Cisplatin; Pem=Pemetrexed; Gem=Gemcitabine
Note: Atezolizumab (Anti-PD-L1) is listed as MPDL3280A in clinicaltrials.gov
Atezolizumab in 2L UBC (Ph1)
ORR correlates with PD-L1 expression

Atezolizumab responses by PD-L1 biomarker status

<table>
<thead>
<tr>
<th>PD-L1 IHC n=87</th>
<th>ORR, % (95% CI)</th>
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<tbody>
<tr>
<td>IC3 (n=12)</td>
<td>67% (35, 90)</td>
</tr>
<tr>
<td>IC2 (n=34)</td>
<td>44% (27, 62)</td>
</tr>
<tr>
<td>IC1 (n=26)</td>
<td>19% (7, 39)</td>
</tr>
<tr>
<td>IC0 (n=15)</td>
<td>13% (2, 40)</td>
</tr>
</tbody>
</table>

• Response rates correlate with PD-L1 status; 20% CR in IHC2/3
• Responses observed with visceral metastases: 38% RR in IHC2/3
• Well tolerated with 5% Gr3/4 immune-related adverse events

UBC = urothelial bladder Cancer; IC = immune cells; ORR = overall response rate
Petrylak D. et al, ASCO 2015
Atezolizumab in 2L UBC (Ph1)

Survival correlates with PD-L1 expression

Survival\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>IC2/3</th>
<th>IC0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 92)</td>
<td>(n = 48)</td>
<td>(n = 44)</td>
</tr>
</tbody>
</table>

**OS**

- Median OS (range): Not reached (1 to 20+ mo) vs. 8 mo (1 to 15+ mo)
- 1-y survival (95% CI): 57% (41-73) vs. 38% (19-56)

- **PD-L1** is a predictive biomarker for ORR, PFS and OS in 2L bladder cancer
- **Phase II study** (NCT02108652) in 1/2L bladder: Read-out H2 2015
- **Phase III studies** in 2/3L bladder and high risk muscle invasive bladder after cystectomy (adjuvant) started in 2015

Petrylak D. *et al*, ASCO 2015
Agenda
Setting new standards, developing combinations

Cancer immunotherapy
Roche program update
Atezolizumab in lung cancer
Atezolizumab in bladder cancer

Targeted therapies and combinations
Alectinib in ALK-positive lung cancer
Cobimetinib + Zelboraf in melanoma
Kadcyla, Perjeta, Herceptin in HER2+ breast cancer

Hematology
Gazyva in NHL
Alectinib in ALK+ NSCLC after crizotinib failure

Strong efficacy in two phase 2 studies

- Alectinib, next generation, brain penetrant ALK inhibitor
- Two P2 studies (global and US) show high systemic and CNS response rates in crizotinib-failed patients
- Median PFS: 8.9m & 6.3m (global & US study, respectively)
- Good tolerability with minimal dose modifications
- Final duration of response and PFS results expected in H2 2015

Alectinib in ALK+ NSCLC after crizotinib failure

Excellent CNS disease control

- Both global and US studies show high ORR (57-69%) in measurable CNS disease; disease control rates 80-100%
- Median duration of response in measurable CNS disease was 10.3 months in the global study
- Filing planned 2015
- Global phase III study in 1L ALK+ NSCLC (Alex) on-going: alectinib vs crizotinib

Cobimetinib + Zelboraf in Melanoma (coBRIM)
Update confirms benefit in BRAF\textsuperscript{V600}+ patients

- Median PFS of ~1 year in Cobimetinib + Zelboraf arm with longer follow-up (14.2 m)
- OS data not yet mature
- Filed in US and EU

<table>
<thead>
<tr>
<th></th>
<th>Cobimetinib + Zelboraf (n = 247)</th>
<th>Zelboraf + Placebo (n = 248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ORR</td>
<td>69.6</td>
<td>50.0</td>
</tr>
<tr>
<td>% CR</td>
<td>15.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Median PFS</td>
<td>12.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Median DoR in months</td>
<td>13.0</td>
<td>9.2</td>
</tr>
</tbody>
</table>

**ORR = overall response rate; CR = complete response; PR = partial response; DoR = duration of response**

Larkin J. et al, ASCO 2015
Cobimetinib+Zelboraf in Melanoma (BRIM7)
Phase I update shows strong efficacy

Two-year survival rate demonstrates benefit of cobimetinib + Zelboraf
Projected 28.5 m median OS compares to historical 13.6 m with Zelboraf alone
Results show importance of combination vs sequential use of targeted therapy in melanoma

<table>
<thead>
<tr>
<th></th>
<th>BRAF inhibitor -naive (n=63)</th>
<th>Zelboraf-Progressors (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR%</td>
<td>87.3</td>
<td>15.2</td>
</tr>
<tr>
<td>CR%</td>
<td>15.9</td>
<td>1.5</td>
</tr>
<tr>
<td>mPFS (m)</td>
<td>13.8</td>
<td>2.8</td>
</tr>
<tr>
<td>mOS (m)</td>
<td>28.5</td>
<td>8.4</td>
</tr>
<tr>
<td>1-yr OS%</td>
<td>82.5</td>
<td>34.7</td>
</tr>
<tr>
<td>2-yr OS%</td>
<td>61.1</td>
<td>15.1</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
Pavlick A. et al, ASCO 2015
Kadcyla + Perjeta in 1L HER2+ mBC (MARIANNE)

Non-inferior PFS for Kadcyla or Kadcyla + Perjeta

- K and K + P achieved non-inferiority but not superiority to H + T
- Addition of Perjeta to Kadcyla did not improve PFS
- Kadcyla was better tolerated and maintained health-related quality of life for a longer duration

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (m)</th>
<th>HR vs H+T</th>
<th>HR vs K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin + docetaxel (H+T)</td>
<td>13.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m2 q3w) OR Herceptin + paclitaxel (H+T)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4 mg/kg LD then 2 mg/kg + 80 mg/m2 qw)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kadcyla + placebo (K)</td>
<td>14.1</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>(3.6mg/kg + 840 mg LD then 420 mg q3w)</td>
<td></td>
<td>p=0.31</td>
<td>p=0.14</td>
</tr>
<tr>
<td>Kadcyla + Perjeta (K+P)</td>
<td>15.2</td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>(3.6mg/kg + 840 mg LD then 420 mg q3w)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ellis P. et al, ASCO 2015
Perjeta + Herceptin in HER2+ eBC (NEOSPHERE) 5yr follow-up shows lasting benefit in neoadjuvant setting

Perjeta + Herceptin + docetaxel

- PFS and DFS benefit of neoadjuvant Perjeta + Herceptin + docetaxel - despite identical adjuvant therapy
- No new safety concerns with longer follow-up
- APHINITY adjuvant study results in 2016

FEC = 5-fluorouracil, Epirubicin, Cyclophosphamide; pCR = pathologic complete response; PFS = progression free survival; DFS = disease free survival
Gianni L. et al, ASCO 2015
* PT arm also received docetaxel q3w X 4
HER2 franchise outlook
Complete portfolio of innovative drugs

- APHINITY, KRISTINE results in 2016
- NEOSPHERE update ASCO 2015
Agenda

Setting new standards, developing combinations

Cancer immunotherapy
- Roche program update
- Atezolizumab in lung cancer
- Atezolizumab in bladder cancer

Targeted therapies and combinations
- Alectinib in ALK-positive lung cancer
- Cobimetinib + Zelboraf in melanoma
- Kadcyla, Perjeta, Herceptin in HER2+ breast cancer

Hematology
- Gazyva in NHL
Hematology franchise
A broad portfolio of innovative drugs

Breakthrough therapy designation for venetoclax in R/R CLL 17p

Biosimilars delayed to 2017

* venetoclax in collaboration with AbbVie
BR = bendamustine+Rituxan

venetoclax (Bcl2 inhibitor); polatuzumab vedotin (CD79b ADC)

**Data presented at ASCO**
Second positive readout for Gazyva

**GADOLIN in Rituxan-refractory iNHL**

**Primary end-point:**

**CLL11: Ph III Chronic Lymphocytic Leukemia (CLL)**

1L CLL  
\[ n=781 \]

- Gazyva + chlorambucil
- Rituxan + chlorambucil
- chlorambucil

**GADOLIN: Ph III Recurrent Indolent NHL (iNHL)**

Rituxan-refractory iNHL  
\[ n=411 \]

**Induction**

- Gazyva + bendamustine  
- bendamustine

**Maintenance**

- Gazyva q2mo x 2 years

**GOYA: Ph III 1L Diffuse Large B-cell Lymphoma (DLBCL)**

Front-line DLBCL (aggressive NHL)  
\[ n=1418 \]

- Gazyva + CHOP
- Rituxan + CHOP

**GALLIUM: Ph III 1L Indolent NHL (iNHL)**

1L iNHL  
\[ n=1401 \]

**Induction**

- Gazyva + CHOP or
- Gazyva + CVP or
- Gazyva + bendamustine
- Rituxan + CHOP or
- Rituxan or
- Rituxan + bendamustine

**Maintenance**

- Gazyva q2mo x 2 years
- Rituxan q2mo x 2 years

In collaboration with Biogen Idec  
CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone
Gazyva in Rituxan-refractory iNHL (GADOLIN)

Significant PFS improvement achieved

IFR-assessed PFS

OS

HR² = 0.55 (0.40–0.74)

- PFS significantly prolonged by independent (HR=0.55) and investigator (HR 0.52) assessment
- Median PFS was ~ doubled by investigator assessment (29 versus 14 months)
- OS data immature
- Filing planned in 2015

¹ = Stratified HR
Sehn L. et al, ASCO 2015
Setting new standards, developing combinations
Driven by the breadth of our portfolio
Growing importance of molecular information in cancer immunotherapy

Garret Hampton, Ph.D.
Vice President, Oncology Biomarker Development and Companion Diagnostics
Personalized healthcare
A cornerstone of our strategy

> 60% of current drugs in our development portfolio have a companion diagnostic

Right patient – right drug

4 of 5 BTD were enabled by having a Dx that identified patients most likely to benefit

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazyva</td>
<td>CLL</td>
</tr>
<tr>
<td>Alectinib</td>
<td>ALK+ NSCLC</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1+ NSCLC</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1+ UBC</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>17p- CLL</td>
</tr>
</tbody>
</table>
Oncology is evolving
More complex science with better patient outcomes

Disease heterogeneity in lung cancer

Overall survival in EGFR mut+ lung cancer

Erlotinib (n = 86)
Chemotherapy (n = 87)
HR 0.37 (95% CI 0.25–0.54);
log-rank $p < 0.0001$

Number at risk
Erlotinib 86 63 54 32 21 17 9 7 4 2 2 0 0 0
Chemotherapy 87 49 20 8 5 4 3 1 0 0 0 0 0 0

Rosell et al. (2012) The Lancet
Biomarker discovery and development at Genentech/Roche

**Understand disease biology**
- Biomarker prevalence
- Prognostic significance
- Subsets of unmet need
- Pipeline opportunities
- Dx hypotheses

**Identify biomarkers**
- Pharmacodynamic
- Predictive
- Response surrogate
- Resistance (innate/acquired)

**Define diagnostic endpoints**
- Companion Dx endpoints
- Response surrogates

**Develop new technologies**
- Multiplex assays
- Real-time Dx
- Monitoring
Predictive markers – tissue staining for PD-L1
Cancer and/or immune cell expression of PD-L1 can correlate with clinical benefit

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n</th>
<th>% of PD-L1–positive (immune cells)</th>
<th>% of PD-L1–positive (tumor cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>184</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>RCC</td>
<td>88</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>59</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>HNSCC</td>
<td>101</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Gastric</td>
<td>141</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>CRC</td>
<td>77</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>83</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>205</td>
<td>27</td>
<td>11</td>
</tr>
</tbody>
</table>

Patient selection enriches for benefit

**PD-L1-selected lung (TC & IC) and bladder cancer (IC)**

<table>
<thead>
<tr>
<th>PD-L1 TC staining</th>
<th>Score</th>
<th>PD-L1 IC staining</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC ≥ 50%</td>
<td>TC3</td>
<td>IC ≥ 10%</td>
<td>IC3</td>
</tr>
<tr>
<td>TC ≥ 5% and &lt; 50%</td>
<td>TC2</td>
<td>IC ≥ 5% and &lt; 10%</td>
<td>IC2</td>
</tr>
<tr>
<td>TC ≥ 1% and &lt; 5%</td>
<td>TC1</td>
<td>IC ≥ %1 and &lt; 5%</td>
<td>IC1</td>
</tr>
<tr>
<td>TC &lt; 1%</td>
<td>TC0</td>
<td>IC &lt; 1%</td>
<td>IC0</td>
</tr>
</tbody>
</table>

**Lung cancer: Survival hazard ratio***

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>TC3 or IC3</th>
<th>TC2/3 or IC2/3</th>
<th>TC1/2/3 or IC1/2/3</th>
<th>TC0 and IC0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.46</td>
<td>0.56</td>
<td>0.63</td>
<td>1.12</td>
<td></td>
</tr>
</tbody>
</table>

**Bladder cancer: Overall survival***

- Median OS 7.6 mo
  - (95% CI, 4.7-NE)
- Median OS Not Reached
  - (95% CI, 9.0-NE)

* Monotherapy data
Using patient data to understand cancer immunity-cycle

Atezolizumab 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?

Powles et al., Nature 2014
Biomarker discovery and development

Integral part of the cancer immunotherapy learning organization

Research
(gRED, pRED, Chugai & external)

Development
(early and late)

Cancer Immunotherapy Committee

Partnering
(Genernetch and Roche)

Clinical Insights & Biomarkers
(internal and external)
Combination with Avastin

*Increasing response rates by keeping cancer immunity-cycle turning*

On-treatment biopsies show absence of T cells in tumor bed before and after treatment with PD-L1

Lack of T cell infiltration may limit response to checkpoint inhibitors

**Herbst et al. (2014) Nature**

**Chen & Mellman (2013) Immunity**
Combination with Avastin

*Increased T cell infiltration and clinical activity*

On-treatment biopsies show increased infiltrate and reduction in tumor vasculature

Combination regimen benefits most patients irrespective of PD-L1 status

Phase 2 in RCC ongoing (n= 300); Phase 3 initiated
Clinical data guides combinations

Identifying potentially synergistic combinations

Myeloid signature associated with lack of response to atezolizumab in bladder cancer

Complementary mechanisms of action to enhance benefit from immunotherapies

Phase I combination study of anti-CSF-1R and atezolizumab ongoing
Roche and FMI will innovate together

Exclusive development of immunotherapy panel

Tumor profiling with RNA sequencing

Immune marker expression (illustrative)

Myeloid signature: IL1B, IL8, CCL2.

Mutation-load and neo-antigen discovery

Identifying immunogenic mutations by structure-guided algorithms

Predictive biomarkers & new combinations

Identifying immunogenic mutations by structure-guided algorithms

Schumacher and Schreiber (2015) Science
Our vision for cancer immunotherapy

A personalized approach to treatment

*Hypothetical algorithm

---

1. **Strong PD-L1**
   - Tx with aPD-L1/PD-1

2. **Weak PD-L1**
   - Are suppressive myeloid cells present?
     - No
       - Are T cells at tumor periphery?
         - No
           - MHC loss?
             - No
               - No T cells?
                 - No identifiable immune targets
               - Yes
                 - No identifiable immune targets
             - Yes
               - Antigen experienced?
                 - Yes
                   - T cell BiSpecific+ Atezolizumab
                 - No
                   - Anti-OX40+ Atezolizumab
         - Yes
           - Tumor antigen expression?
             - Yes
               - Anti-CSF-1R+ Atezolizumab
             - No
               - IDO1+ Atezolizumab
     - Yes
       - IDO/kyneurinin expressed?
         - No
           - Chemo+ Atezolizumab
         - Yes
           - No identifiable immune targets

3. **No PD-L1**
   - No identifiable immune targets

4. **No identifiable immune targets**
   - Chemo+ Atezolizumab

---

*Evaluate tumor:
Is the tumor inflamed?

---

1. **Inflamed**

2. **Weak PD-L1**
   - Are suppressive myeloid cells present?
     - No
       - MHC loss?
         - No
           - No T cells?
             - No identifiable immune targets
           - Yes
             - Antigen experienced?
               - Yes
                 - T cell BiSpecific+ Atezolizumab
               - No
                 - Anti-OX40+ Atezolizumab
         - Yes
           - Tumor antigen expression?
             - Yes
               - Anti-CSF-1R+ Atezolizumab
             - No
               - IDO1+ Atezolizumab
     - Yes
       - IDO/kyneurinin expressed?
         - No
           - Chemo+ Atezolizumab
         - Yes
           - No identifiable immune targets

3. **Non-Inflamed**

---

*Hypothetical algorithm
Patient journey tomorrow
Bridging comprehensive testing and drug development

Molecular monitoring
Patient care
Clinical decision
Comprehensive testing

R&D insights
Summary and Q&A

Karl Mahler  
*Head of Investor Relations, Roche*
<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin cancer</strong></td>
</tr>
<tr>
<td><strong>cobimetinib + Zelboraf:</strong> Ph III <em>(coBRIM)</em> in 1L BRAF+ mM; PFS &amp; biomarker update</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
</tr>
<tr>
<td><strong>alectinib:</strong> two Ph II in 2L ALK+ NSCLC</td>
</tr>
<tr>
<td><strong>Atezolizumab (anti-PDL1):</strong> POPLAR, COMBO, FIR</td>
</tr>
<tr>
<td><strong>Avastin:</strong> mesothelioma</td>
</tr>
<tr>
<td><strong>Bladder cancer</strong></td>
</tr>
<tr>
<td><strong>Atezolizumab (anti-PDL1):</strong> Ph I update in bladder</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
</tr>
<tr>
<td><strong>Kadcyla:</strong> Ph II <em>(ADAPT)</em> neoadjuvant 12 weeks HER2+ HR+ BC</td>
</tr>
<tr>
<td><strong>Kadcyla + Perjeta:</strong> Ph III <em>(MARIANNE)</em> in 1L HER2+ mBC</td>
</tr>
<tr>
<td><strong>Herceptin + Perjeta:</strong> Ph II <em>(NEOPSPHERE)</em> in neoadjuvant HER2+ BC</td>
</tr>
<tr>
<td><strong>Avastin + Letrozole:</strong> Ph III <em>(CALGB40503)</em> in 1L HR+ mBC</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
</tr>
<tr>
<td><strong>Gazyva:</strong> Ph III <em>(GADOLIN)</em> in R/R iNHL</td>
</tr>
<tr>
<td><strong>Venetoclax:</strong> Ph I in R/R NHL and R/R MM</td>
</tr>
</tbody>
</table>
Cancer immunotherapy: Encouraging early data in monotherapy across various cancer types

Range across various studies

<table>
<thead>
<tr>
<th>NSCLC 2L</th>
<th>ORR range</th>
<th>mPFS range</th>
<th>mOS* range</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Un-stratified</td>
<td>~ 15%</td>
<td>~ 3 m</td>
<td>~ 9-11 m</td>
<td>~ 15%</td>
</tr>
<tr>
<td>Stratified</td>
<td>40-45%</td>
<td>~ 6-8 m</td>
<td>Not reached</td>
<td>~20-30%</td>
</tr>
</tbody>
</table>

Range across various studies

<table>
<thead>
<tr>
<th>Bladder 2L</th>
<th>ORR range</th>
<th>mPFS range</th>
<th>mOS range</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified</td>
<td>25-45%</td>
<td>~ 2-5.5 m</td>
<td>Not reached</td>
<td>~30%</td>
</tr>
</tbody>
</table>

* Comparisons based on publicly available competitor data sets. Significant limitations with these cross-trial comparisons; significant variability in baseline population demographics further limit conclusions.

Note: CheckMate 057 2L+ non-squamous NSCLC trial was stopped early because the study met its OS endpoint.
Cancer immunotherapy: Still many open questions

The Cancer-Immunity Cycle

The generation of immunity to cancer is a cyclic process that can be self-propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and the anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells; CTLs, cytotoxic T lymphocytes.

How can we convert unresponsive tumors into responsive tumors?

Can we modulate/monitor T-cell responses?

What are the factors affecting T-cell infiltration?

Can we create a personalized immunotherapy paradigm?

Can we convert an unresponsive tumor to a responsive one?

What influences durability of response?
Doing now what patients need next