52nd ASCO Annual Meeting, Chicago

Roche Analyst Event
Sunday, 5 June 2016
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6. increased government pricing pressures;
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Introduction

Karl Mahler
Head of Investor Relations
Agenda

Welcome
Karl Mahler, Head of Investor Relations

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

Roche highlights in cancer immunotherapy
Daniel S. Chen, M.D., Ph.D., VP, Global Head of Cancer Immunotherapy, Global Product Development

Early pipeline update: Assets and strategies
Ira Mellman, gRED: Ph.D., VP, Cancer Immunology, Genentech
William Pao, pRED: M.D., Ph.D., Global Head Oncology Discovery and Translational Area, Roche

Targeted therapies and future combinations
Sandra Horning, M.D., Chief Medical Officer and Head Global Product Development

Q&A
Investigating tumor specific strategies

Size of bubble constitutes patient population

*TNBC mutation frequency is estimated

5YR RELATIVE SURVIVAL

RELATIVE SOMATIC MUTATION FREQUENCY
Oncology strategy and outlook

Daniel O’Day
CEO Roche Pharmaceuticals
Managing increasing complexity in cancer care

Our strategy to maintain innovation leadership

Outlook
Tremendous progress made in cancer treatment
*Increasing patients’ chances for survival*

**Chemotherapy**

**Targeted medicines**

**Targeted medicines + immunotherapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Months</th>
<th>Drug</th>
<th>Months</th>
<th>Drug</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td>OS</td>
<td></td>
<td>OS</td>
<td></td>
</tr>
</tbody>
</table>

Improving SOC
With progress comes increasing complexity

**Example: Implications on clinical trials**

<table>
<thead>
<tr>
<th>Clinical trial population/size</th>
<th>Chemotherapy</th>
<th>Targeted medicines</th>
<th>Targeted medicines + immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified / Large</td>
<td>No diagnostics</td>
<td>Single disease marker</td>
<td>Individual patients / Medium - Small</td>
</tr>
<tr>
<td>Patient sub-groups / Medium</td>
<td>Phase I, II, III</td>
<td>Phase I, II, III</td>
<td>Comprehensive genomic sequencing &amp; response monitoring</td>
</tr>
</tbody>
</table>

Phase I, II, III basket / umbrella studies
Managing increasing complexity in cancer care

Our strategy to maintain innovation leadership

Outlook
Roche: Strong history of innovation
Leading evolution of cancer treatment

Oncology: 9 NMEs launched in 5 years, overall >30% market share

1. Pharmaceuticals, excluding generics
Source: Evaluate Pharma, companies' annual reports & investor presentations; value in USD bn
Our innovation strategy remains unchanged

*Increasing focus on data analytics*

**Pipeline delivery**
- Diverse, differentiated treatment approaches
- Strategic life-cycle mgmt.

**Data & analytics**
- Smart, more efficient R&D
- Access & personalized patient care

**Increased productivity**
- Innovative trial design
- Prioritization & improved decision-making

**Outstanding talent that drives innovation & execution**
Different mechanisms to target cancer
Roche investing in diverse approaches & combinations

**Targeted medicines**

<table>
<thead>
<tr>
<th>Oncogenes</th>
<th>aHER2, MEKi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-angiogenesis</td>
<td>aAng2/VEGF</td>
</tr>
<tr>
<td>Tumor suppressors</td>
<td>MDM2 antagonist</td>
</tr>
<tr>
<td>Epigenetic</td>
<td>BETi</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>BCL2i</td>
</tr>
<tr>
<td>Tumor specific cytotoxicity</td>
<td>aCD20</td>
</tr>
</tbody>
</table>

**Immunotherapy**

- **Activate**
  - aOX40, aCD40, aCEA-IL2v FP, aFAP-IL2v FP
- **Modulate**
  - aPD-L1, aCSF-1R, IDOi, aTIGIT
- **T cell bispecifics**
  - aCEA/CD3 TCB, aCD20/CD3 TCB

**Combinations**

[Image showing different mechanisms and combinations]
10 novel CIT assets in clinical development

Maximize portfolio through combinations

emactuzumab (aCSF-1R); cergutuzumab amunaleukin (aCEA-IL2v FP); vanucizumab (aAng2/VEGF); polatuzumab vedotin (aCD79b ADC); taselisib (PI3Ki); ipatasertib (AKTii); SERD (selective estrogen receptor degrader); idasanutlin (MDM2 antagonist); Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Alecensa in collaboration with Chugai; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; polatuzumab in collaboration with Seattle Genetics; ipatasertib in collaboration with Array Biopharma; IDOi in collaboration with NewLink; daratumumab in collaboration with Janssen (J&J)
Broad coverage across approaches & tumor types

*To benefit our patients*

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Targeted therapies</th>
<th>CIT / Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>aNHL</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>iNHL</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AML</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MM</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MDS</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung</th>
<th>Targeted therapies</th>
<th>CIT / Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ALK+</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>EGFR+</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PDL1+</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breast</th>
<th>Targeted therapies</th>
<th>CIT / Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HER2-/ER+</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TNBC</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bladder/Gastric</th>
<th>Targeted therapies</th>
<th>CIT / Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>UBC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MIBC PDL1+</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Targeted therapies</th>
<th>CIT / Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ovarian</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prostate</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Melanoma (BRAF+)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ Clinical studies ongoing
Substantial investments in underlying technology

Novel antibody platforms supporting research

<table>
<thead>
<tr>
<th>Targeted medicines</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogenes</td>
<td>Activate</td>
</tr>
<tr>
<td>Anti-angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Tumor suppressors</td>
<td></td>
</tr>
<tr>
<td>Epigenetic</td>
<td>Modulate</td>
</tr>
<tr>
<td>Apoptosis</td>
<td></td>
</tr>
<tr>
<td>Tumor specific Cytotoxicity</td>
<td>T cell Bispecifics</td>
</tr>
</tbody>
</table>

**Combinations**

<table>
<thead>
<tr>
<th>Monoclonal antibodies (MAb)</th>
<th>Antibody drug conjugates (ADC)</th>
<th>Glyco-engineered antibodies</th>
<th>Fab fragments</th>
<th>Antibodies with modified Fc part</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Monoclonal antibodies" /></td>
<td><img src="image2" alt="Antibody drug conjugates" /></td>
<td><img src="image3" alt="Glyco-engineered antibodies" /></td>
<td><img src="image4" alt="Fab fragments" /></td>
<td><img src="image5" alt="Antibodies with modified Fc part" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibody cytokine fusion proteins (FP)</th>
<th>(1) Bispecific antibodies (biMAb)</th>
<th>(2) Bispecific antibodies (biMAb)</th>
<th>(1) T cell bispecifics</th>
<th>(2) T cell bispecifics</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6" alt="Antibody cytokine fusion proteins" /></td>
<td><img src="image7" alt="Bispecific antibodies (biMAb)" /></td>
<td><img src="image8" alt="Bispecific antibodies (biMAb)" /></td>
<td><img src="image9" alt="T cell bispecifics" /></td>
<td><img src="image10" alt="T cell bispecifics" /></td>
</tr>
</tbody>
</table>
Innovation strategy remains unchanged

Increasing focus on data analytics

Pipeline delivery

- Diverse, differentiated treatment approaches
- Strategic life-cycle mgmt.

Data & analytics

- Smart, more efficient R&D
- Access & personalized patient care

Increased productivity

- Innovative trial design
- Prioritization & improved decision-making

Outstanding talent that drives innovation & execution
Strategic approach to life-cycle management

Third positive readout for Gazyva - GALLIUM in iNHL

Convenience benefit through subcutaneous injection

Gazyva: Establish new SoC (GALLIUM & GOYA)

Venclexta: Improve on SoC in NHL & CLL; expand into AML and MM

Protect

MabThera

MabThera SC

Gazyva

Venclexta

Tecentriq

polatuzumab vedotin

aCD20/CD3

Replace

Gazyva

MabThera SC

Replace

Gazyva

MabThera SC

Extend

Venclexta

Tecentriq

polatuzumab vedotin

aCD20/CD3

Medical value

Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Polatuzumab in collaboration with Seattle Genetics; SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin’s lymphoma; AML=acute myeloid leukemia; MM=multiple myeloma
Innovation strategy remains unchanged

*Increasing focus on data analytics*

- **Pipeline delivery**
  - Diverse, differentiated treatment approaches
  - Strategic life-cycle mgmt.

- **Data & analytics**
  - Smart, more efficient R&D
  - Access & personalized patient care

- **Increased productivity**
  - Innovative trial design
  - Prioritization & improved decision-making

**Outstanding talent that drives innovation & execution**
Continuously improving our R&D processes

*Improved decision-making and innovative trial design*

**Improved decision-making**

- Cross-Roche strategy
- Early selection of priority candidates
- Seamless development

**Innovative trial design**

- Umbrella / basket studies
- Protocol design & endpoints
- Real world data
Innovation strategy remains unchanged

**Increasing focus on data analytics**

**Pipeline delivery**
- Diverse, differentiated treatment approaches
- Strategic life-cycle mgmt.

**Data & analytics**
- Smart, more efficient R&D
- Access & personalized patient care

**Increased productivity**
- Innovative trial design
- Prioritization & improved decision-making

**Outstanding talent that drives innovation & execution**
Advanced data analytics core to our strategy

Improve R&D efficiency and personalized patient care

Access meaningful data

Diagnostic Data
Clinical Trial Data
Real World Data

Create insights

Advanced analytics of integrated data

Realise value from insights

Smarter, more efficient R&D
Improved access & personalised patient care
Collaboration with Foundation Medicine
Next generation Dx and molecular info insights

Data analytics
Hypothesis generation and trial design

Novel Dx development
CIT Dx and blood-based monitoring

Novel Dx uptake
FDA approval and launch
Collaboration with Flatiron

Leveraging insights from real world data

<table>
<thead>
<tr>
<th>Clinical trial design and recruitment</th>
<th>Real world data based studies</th>
<th>Real world data based submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq NSCLC</td>
<td>CLL, NSCLC &amp; mBC</td>
<td>Cost-effectiveness, safety, efficacy</td>
</tr>
</tbody>
</table>

- **Clinical trial design and recruitment**: Tecentriq NSCLC
- **Real world data based studies**: CLL, NSCLC & mBC
- **Real world data based submissions**: Cost-effectiveness, safety, efficacy
Managing increasing complexity in cancer care

Our strategy to maintain innovation leadership

Outlook
### A strong start to the year

**Selected pipeline highlights**

<table>
<thead>
<tr>
<th>Product</th>
<th>Therapy Area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gazyva</strong></td>
<td>1L iNHL</td>
</tr>
<tr>
<td><strong>Tecentriq</strong></td>
<td>Bladder, NSCLC</td>
</tr>
<tr>
<td><strong>Alecensa</strong></td>
<td>ALK+ NSCLC</td>
</tr>
<tr>
<td><strong>Venclexta</strong></td>
<td>AML, NHL, CLL</td>
</tr>
<tr>
<td><strong>Cotellic + Zelboraf</strong></td>
<td>BRAF+ Melanoma</td>
</tr>
</tbody>
</table>

**Continuing to improve on standard of care**

Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon
# Oncology: Significant launch activities ahead

**Bringing innovative medicines to our patients**

<table>
<thead>
<tr>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venclexta</td>
<td>R/R CLL with 17p del</td>
<td>Perjeta + Herceptin Adjuvant BC HER2+ (APHINITY)</td>
<td>Tecentriq + chemo +/- Avastin 1L NSCLC (IMpower)</td>
</tr>
<tr>
<td>Cotellic + Zelboraf</td>
<td>BRAF+ melanoma</td>
<td>Gazyva 1L aNHL (GOYA)</td>
<td>Tecentriq + Avastin 1L RCC (IMmotion)</td>
</tr>
<tr>
<td>Alecensa</td>
<td>2L ALK+ NSCLC</td>
<td>Gazyva 1L iNHL (GALLIUM)</td>
<td>Alecensa 1L ALK+ NSCLC (ALEX)</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>2L+ NSCLC and bladder cancer</td>
<td>Gazyva Refractory iNHL (GADOLIN)</td>
<td></td>
</tr>
</tbody>
</table>

Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon
Cancer immunotherapy highlights

Daniel Chen, M.D., Ph.D.
VP, Global Head of Cancer Immunotherapy
Global Product Development
Our initial cancer immunotherapy strategy has laid the cornerstone for our programs…

Initial Roche CIT strategy

**Biology**
- Understand human cancer immunity
- Mandatory tumor biopsy & blood samples pre-treatment
- On treatment biopsies & blood samples
- Progression samples
- Annotated non-trial tumor specimens

**Development**
- Rapidly develop Tecentriq & CIT pipeline
- Prioritize responding tumor types: Lung, bladder, RCC, TNBC, melanoma
- Seek accelerated and full approvals
- Establish utility of Dx for ORR, PFS & OS
- Develop endpoints for CIT

**Technology**
- Develop human immunity tools
- PDL1 Immunohistochemistry assay
- Gene expression/immune chips
- Blood-based assays
- Imaging
- Mutation analysis

Improving SoC

<1990s 2000s 2011

- Chemo
- Targeted medicines
- Targeted medicines + immunotherapy

Complexity

Genomic sequencing & response monitoring

X

single disease marker
Our learnings lead to the tumor immunity continuum framework for combinations

Modified from Hegde PS et al. (2016) Clin Canc Res
Targeting treatment options to different patients and cancer types

**Inflamed**
- CD8+ T cells infiltrated, but non-functional
- Accelerate or remove brakes on T-cell response
  - e.g. IDOi, aTIGIT, aCSF-1R

**Immune Excluded**
- CD8+ T cells accumulated but not efficiently infiltrated
- Bring T-cells in contact with cancer cells
  - e.g. aVEGF, chemokine agonists/antagonists, TCBs

**Immune Desert**
- CD8+ T cells absent from tumor and periphery
- Increase number of antigen-specific T-cells or increase antigen presentation
  - e.g. aOX40, aCD40, aCEA/FAP IL-2v, chemo, targeted therapies, vaccines
Our cancer immunotherapy strategy today

Cancer immunity cycle

1. Antigen release
2. Antigen presentation
3. Priming & Activation
4. T cell trafficking
5. T cell infiltration
6. T cell recognition
7. T cell killing
8. Blood vessel
9. Lymph node
10. Tumor

Our CIT strategy

- Establish Tecentriq as foundation
- Unlock CI cycle: Tecentriq combos
- Personalized cancer immunotherapy paradigm

Chen and Mellman. *Immunity* 2013
Tecentriq in NSCLC

Study Design – POPLAR randomized phase II in all-comer population

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on prior platinum therapy
N=287

Stratification Factors
• PD-L1 IC expression (0 vs 1 vs 2 vs 3)
• Histology (squamous vs non squamous)
• Prior chemotherapy regimens (1 vs 2)

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m² IV q3w
until disease progression
POPLAR: Updated mOS in PD-L1 subgroups
Efficacy increasing with higher PD-L1 expression

Updated analysis (Event / N=70%): Minimum follow-up 20 months

<table>
<thead>
<tr>
<th>Subgroup (% of enrolled patients)</th>
<th>Updated median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3 (16%)</td>
<td>Atezolizumab n = 144</td>
</tr>
<tr>
<td></td>
<td>NE (9.8, NE)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel n = 143</td>
</tr>
<tr>
<td></td>
<td>11.1 (6.7, 14.4)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (37%)</td>
<td>15.1 (8.4, NE)</td>
</tr>
<tr>
<td></td>
<td>7.4 (6.0, 12.5)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (68%)</td>
<td>15.1 (11.0, NE)</td>
</tr>
<tr>
<td></td>
<td>9.2 (7.3, 12.8)</td>
</tr>
<tr>
<td>TC0 and IC0 (32%)</td>
<td>9.7 (6.7, 12.0)</td>
</tr>
<tr>
<td></td>
<td>9.7 (6.8, 12.0)</td>
</tr>
<tr>
<td>ITT (N = 287)</td>
<td>12.6 (9.7, 16.0)</td>
</tr>
<tr>
<td></td>
<td>9.7 (8.6, 12.0)</td>
</tr>
</tbody>
</table>

Hazard Ratio

In favor of atezolizumab

In favor of docetaxel

Stratified HR for ITT and unstratified HRs for PD-L1 subgroups; NE, not estimable; Data cut-off: December 1, 2015
Time shows true size of the treatment effect

Example: Tecentriq overall survival in lung cancer

Hazard Ratio

Date

06/14 08/14 01/15 05/15 12/15

0.89 0.83 0.77 0.73 0.69

% of events/patients

0% 20% 30% 53% 60% 70%
POPLAR: Updated mOS in PD-L1 subgroups

OS curves separate in all subgroups incl. TC0/IC0 over time

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS (95% CI)</th>
<th>HRa (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3 (n = 47)</td>
<td>Median 11.1 mo (6.7, 14.4)</td>
<td>HRa = 0.45 (0.22, 0.95)</td>
<td>P value = 0.033</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (n = 105)</td>
<td>Median 7.4 mo (8.0, 12.5)</td>
<td>HRa = 0.50 (0.31, 0.80)</td>
<td>P value = 0.003</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (n = 195)</td>
<td>Median 9.2 mo (7.3, 12.8)</td>
<td>HRa = 0.59 (0.41, 0.83)</td>
<td>P value = 0.003</td>
</tr>
<tr>
<td>TC0 and IC0 (n = 92)</td>
<td>Median 9.7 mo (6.7, 12.0)</td>
<td>HRa = 0.88 (0.55, 1.42)</td>
<td>P value = 0.0601</td>
</tr>
</tbody>
</table>

a Unstratified HR; Data cut-off: December 1, 2015
Study Design – Phase II IMvigor210

**IMvigor210**
- Locally advanced or metastatic urothelial carcinoma
- Predominantly TCC histology
- Tumor tissue evaluable for PD-L1 testing

**Cohort 1 (N=119)**
- 1L cisplatin ineligible
- Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

**Cohort 2 (N=310)**
- Platinum-treated mUC
- Atezolizumab 1200 mg IV q3w until loss of clinical benefit
Imvigor210: Cohort 2 update

Ongoing & durable responses across all subgroups

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 (n = 100)</th>
<th>IC1/2/3 (n = 207)</th>
<th>All(^a) (N = 310)</th>
<th>IC1 (n = 107)</th>
<th>IC0 (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR: confirmed IRF RECIST v1.1 (95% CI)</td>
<td>28% (19, 38)</td>
<td>19% (14, 25)</td>
<td>16% (12, 20)</td>
<td>11% (6, 19)</td>
<td>9% (4, 16)</td>
</tr>
<tr>
<td>CR rate: confirmed IRF RECIST v1.1 (95% CI)</td>
<td>15% (9, 24)</td>
<td>9% (6, 14)</td>
<td>7% (4, 10)</td>
<td>4% (1, 9)</td>
<td>2% (0, 7)</td>
</tr>
</tbody>
</table>

Median follow-up: 17.5 months (range, 0.2+ to 21.1 mo)

- 71% of responses (35/49) were ongoing
  - 86% of CRs ongoing
- mDOR was not yet reached in any PD-L1 IC subgroup (range, 2.1+ to 19.2+ mo)\(^a\)

---

\(^a\) Per IRF RECIST v1.1
\(^b\) Discontinuation symbol does not indicating timing.
\(^c\) No PD or death only. Data cutoff: Mar. 14, 2016.
Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have…

• …disease progression during or following platinum-containing chemotherapy

• …disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
IMvigor210: Cohort 1 response rate & durability
Confirmed responses, incl. CRs observed in all subgroups

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 (n = 32)</th>
<th>IC1/2/3 (n = 80)</th>
<th>All Patients (N = 119)</th>
<th>IC1 (n = 48)</th>
<th>IC0 (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR(^a) (95% CI)</td>
<td>28% (14, 47)</td>
<td>25% (16, 36)</td>
<td>24% (16, 32)</td>
<td>23% (12, 37)</td>
<td>21% (9, 36)</td>
</tr>
<tr>
<td>CR</td>
<td>6%</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>PR</td>
<td>22%</td>
<td>19%</td>
<td>17%</td>
<td>17%</td>
<td>13%</td>
</tr>
</tbody>
</table>

\(^a\) Includes 19 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. PD-L1 IC status: IC2/3 (≥ 5%), IC1 (≥ 1 but < 5%), IC0 (< 1%). Data cut-off: March 14, 2016

- mOS in all patients was 14.8 mo with a median follow-up of 14.4 mo
Ways to unlock the cancer immunity cycle

Combining cancer immunotherapy assets with...

Chen and Mellman. *Immunity* 2013
Tecentriq chemo combo in TNBC

**Study Design – atezolizumab + nab-paclitaxel Phase Ib (Arm F)**

- Phase Ib atezolizumab + nab-paclitaxel in 1-3L+TNBC
  - N=32
  - Atezolizumab 800mg/d q2w
  - Nab-paclitaxel 125mg/m2 q4w
  - until loss of clinical benefit
Tecentriq + Abraxane in TNBC
Response rate and duration of response

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>1L (n = 13)</th>
<th>2L (n = 9(^b))</th>
<th>3L+ (n = 10)</th>
<th>All Patients (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR (95% CI)(^a)</strong></td>
<td>46% (19, 75)</td>
<td>22% (3, 60)</td>
<td>40% (12, 74)</td>
<td>38% (21-56)</td>
</tr>
<tr>
<td>CR</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>PR</td>
<td>38%</td>
<td>22%</td>
<td>40%</td>
<td>34%</td>
</tr>
<tr>
<td>SD</td>
<td>38%</td>
<td>67%</td>
<td>30%</td>
<td>44%</td>
</tr>
<tr>
<td>PD</td>
<td>15%</td>
<td>0%</td>
<td>30%</td>
<td>16%</td>
</tr>
<tr>
<td>Missing or NE</td>
<td>0%</td>
<td>11%</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

\(^a\) Confirmed ORR defined as ≥ 2 consecutive assessments of CR or PR; \(^b\) One patient discontinued with clinical progression before first on-treatment tumor assessment. Data cutoff date: Jan 14, 2016

Phase 3 IMpassion 130 in 1L TNBC patients ongoing

1L Patients

| Phase 3 IMpassion 130 in 1L TNBC patients ongoing

<table>
<thead>
<tr>
<th>Change in sum of largest diameters from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on study (mo)</td>
</tr>
</tbody>
</table>

- PR/CR
- SD
- PD
- Discontinued atezolizumab
- New Lesion
- Unknown
Tecentriq + Cotellic in CRC

Phase Ib dose escalation and cohort expansion study

- **Dose-Escalation Stage (3 + 3)**
  - n = 2
    - 1 KRASmt; 1 wt
    - 20 mg cobi PO QD\(^a\)
    - 800 mg atezo IV q2w
  - 40 mg cobi PO QD\(^a\)
  - 800 mg atezo IV q2w

- **Dose-Expansion Stage**
  - n = 1
    - 1 KRASmt
    - 60 mg cobi PO QD\(^a\)
    - 800 mg atezo IV q2w

**DLT window of 28 days until MTD for combination is defined**

**Dose-Expansion Stage**

- KRASmt mCRC
- NSCLC
- Metastatic Melanoma
- Solid tumors serial biopsy

- n = 20
### Biomarkers: CD8 T-cell accumulation and MHC I expression

<table>
<thead>
<tr>
<th>KRAS&lt;sup&gt;a&lt;/sup&gt; responder&lt;sup&gt;a&lt;/sup&gt; (mCRC cohort)</th>
<th>Clear cell sarcoma patient&lt;sup&gt;b&lt;/sup&gt; (Solid tumors serial biopsy cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="cd8_baseline.png" alt="Baseline" /> <img src="cd8_cobi_atezo.png" alt="Cobi+Atezo" /></td>
<td><img src="cd8_archival.png" alt="Archival" /> <img src="cd8_cobi.png" alt="Cobi" /> <img src="cd8_cobi_atezo.png" alt="Cobi+Atezo" /></td>
</tr>
<tr>
<td><img src="perk_baseline.png" alt="Baseline" /> <img src="perk_cobi_atezo.png" alt="Cobi+Atezo" /></td>
<td><img src="perk_archival.png" alt="Archival" /> <img src="perk_cobi.png" alt="Cobi" /> <img src="perk_cobi_atezo.png" alt="Cobi+Atezo" /></td>
</tr>
<tr>
<td>CD8</td>
<td>CD8</td>
</tr>
<tr>
<td>0.03%</td>
<td>0.08%</td>
</tr>
<tr>
<td>1.72%</td>
<td>12.3%</td>
</tr>
<tr>
<td>pERK</td>
<td>MHC</td>
</tr>
<tr>
<td>H=151</td>
<td>H=60</td>
</tr>
<tr>
<td>H=26</td>
<td>H=300</td>
</tr>
<tr>
<td>H=300</td>
<td>H=300</td>
</tr>
<tr>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td>IC0</td>
<td>IC0</td>
</tr>
<tr>
<td></td>
<td>IC3</td>
</tr>
</tbody>
</table>

- Increased intratumoral CD8 T-cell infiltration and MHC I expression were observed with cobimetinib alone
- Further enhancement seen with cobimetinib + atezolizumab
- Similar results were seen in 75% of patients in the biopsy cohort

<sup>a</sup> Sarah Cannon Research Institute/Tennessee Oncology (J. Bendell)  
<sup>b</sup> Princess Margaret Cancer Center (J. Lewin, Lillian Siu)
**Tecentriq + Cotellic Phase Ib efficacy in CRC**

**Confirmed objective response**

<table>
<thead>
<tr>
<th>Confirmed response per RECIST v1.1</th>
<th>KRAS mt CRC cohort (N = 20)</th>
<th>All CRC patients (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>20% (5.7, 43.7)</td>
<td>17% (5.0, 38.8)</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>SD</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>PD</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>NE</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Phase 3 study in chemo-refractory mCRC is open and actively recruiting**

---

Confirmed per RECIST v1.1.

Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.
# Cancer immunotherapy portfolio by tumor type

## Solid tumors

<table>
<thead>
<tr>
<th>Lung (NSCLC &amp; SCLC)</th>
<th>Breast (TNBC &amp; HER2+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq 2L/3L</td>
<td>Tecentriq (TNBC) + chemo Ph3</td>
</tr>
<tr>
<td>Tecentriq 1L Dx+</td>
<td>Tecentriq + Kadcyla or (HER2+) Herceptin + Perjeta Ph1</td>
</tr>
<tr>
<td>Tecentriq + chemo (x3 1L trials)</td>
<td>Tecentriq + entinostat* Ph2</td>
</tr>
<tr>
<td>Tecentriq + chemo ± Avastin (1L)</td>
<td>Tecentriq</td>
</tr>
<tr>
<td>Tecentriq Adjuvant</td>
<td>Tecentriq</td>
</tr>
<tr>
<td>Tecentriq + Tarceva or Alecensa</td>
<td>Tecentriq</td>
</tr>
<tr>
<td>Tecentriq + chemo</td>
<td>Tecentriq</td>
</tr>
<tr>
<td>Tecentriq + epacadostat*</td>
<td>Tecentriq</td>
</tr>
</tbody>
</table>

## RCC

| Tecentriq ± Avastin | Ph2 |
| Tecentriq ± Avastin | Ph3 |

## Hematological tumors

| Tecentriq | Lenalidomide + daratumumab* | Ph1 (MM) |
| Tecentriq | ± azacitidine | Ph1 (MM) |
| Tecentriq | + Gazyva (lymphoma) | Ph1 (Heme) |
| Tecentriq | + Gazyva + polatuzumab (r/r FL / DLBCL) | Ph1/2 (Heme) |
| Tecentriq | + Gazyva + lenalidomide (r/r FL) | Ph1 (Heme) |
| Tecentriq | + Gazyva + CHOP (1L FL / DLBCL) | Ph1 (Heme) |
| aCD20 CD3 | + Tecentriq | |
| Tecentriq | + CD19 CAR-T (refractory aNHL)* | Ph1 (Heme) |

## Other CIT

| Collaboration |

## As of June 2016
## Phase 3 CIT trials: Planned data read-outs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Trial Name</th>
<th>Est. Trial readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>IMpower 150</td>
<td>Tecentriq + carbo/pac +/- Avastin</td>
</tr>
<tr>
<td></td>
<td>IMpower 130</td>
<td>Tecentriq + carbo + Abraxane</td>
</tr>
<tr>
<td></td>
<td>IMpower 131</td>
<td>Tecentriq + carbo + pac/Abraxane</td>
</tr>
<tr>
<td></td>
<td>IMpower 132</td>
<td>Tecentriq + cis/carbo + pem</td>
</tr>
<tr>
<td></td>
<td>IMpower 110/111</td>
<td>Tecentriq monotherapy</td>
</tr>
<tr>
<td>Adj NSCLC</td>
<td>IMpower 010</td>
<td>Tecentriq monotherapy</td>
</tr>
<tr>
<td>1L SCLC</td>
<td>IMpower 133</td>
<td>Tecentriq+ carbo + etoposide</td>
</tr>
<tr>
<td>2L + NSCLC</td>
<td>OAK</td>
<td>Tecentriq monotherapy</td>
</tr>
</tbody>
</table>

**Bladder**

|           | IMvigor 211 | Tecentriq monotherapy | 2017 |
| Adj MIBC | IMvigor 010 | Tecentriq monotherapy | Post 2018 |

**RCC**

| 1L RCC | IMmotion 151 | Tecentriq + Avastin | 2017 |

**Breast**

| 1L TNBC | IMpassion 130 | Tecentriq + Abraxane | 2018 |

**Colon**

| 3L+ mCRC | COTEZO | Tecentriq + Cotellic | 2018 |

---

As per Q1 2016; Outcome studies are event driven, timelines may change
Towards a personalized CIT paradigm

*HYPOTHETICAL TREATMENT ALGORITHM

INFLAMED

Strong PD-L1 & high mutational load
- Anti-PDL1/PD1

Weak PD-L1 expression
- Anti-PDL1/PD1 + Other CIT (IDOi, aTIGIT, aCSF1R, TCBs, IL2v)

No identified target
- Anti-PDL1/PD1 + Chemo /targeted therapy/XRT

EXCLUDED

T Cells at Periphery
- Anti-PDL1/PD1 + antiangiogenic + anti-stromal agents

No identified target
- Anti-PDL1/PD1 + Chemo /targeted therapy/XRT

IMMUNE DESERT

No Effectors
- Anti-PDL1/PD1 + aOX40 (or aCD40, aCTLA4, IL2v, vaccine)

MHC Loss
- Anti-PDL1/PD1 + TCBs (or IFN, CART, MEKi)

Early pipeline update: The learning loop in action

Ira Mellman, Ph.D.
VP, Cancer Immunology, Genentech
CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

How do clinical biomarker data define next steps?
T cells in action: the basis of all cancer immunotherapy

Alex Ritter, Genentech
Implementation of a learning loop to inform both drug discovery and clinical development

“Reverse Translation” for disease understanding, target selection and prioritization
CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

How do clinical biomarker data define next steps?
gRED CIT portfolio is prioritized by the cancer immunity cycle

**Primming & activation**
- anti-OX40
- anti-CD27* (Cellidex)
- entinostat* (Syndax)

**Antigen presentation**
- T-Vec oncolytic virus* (Amgen)
- INFα
- CMB305 vaccine* (Immune Design)

**Antigen release**
- EGFRi (Tarceva)
- ALKi (Alecensa)
- BRAFi (Zelboraf)
- MEKi (Cotellic)
- anti-CD20 (Gazyva)
- anti-HER2 (Herceptin; Kadcyla; Perjeta)
- various chemotherapies
- lenalidomide* (Celgene)
- rucaparib* (Clovis)
- daratumumab* (Janssen)

**T cell trafficking**
- anti-VEGF (Avastin)

**T cell infiltration**

**Cancer T cell recognition**
- anti-CD20/CD3 TCB
- KTE-C19* (Kite Pharma)
- ImmTAC* (Immunocore)

**T cell killing**
- Tecentriq (atezolizumab)
- IDOi (NewLink)
- anti-TIGIT
- IDOi* (Incyte)
- CPI-444* (Corvus)
- TDOi (NewLink)
- IDO1/TDOi (NewLink)

---

Chen and Mellman. *Immunity* 2013
CIT=cancer immunotherapy; FP=fusion protein; TCB=T-cell bispecific
gRED CIT portfolio is prioritized by the cancer immunity cycle

Antigen presentation
- T-Vec oncolytic virus* (Amgen)
- INFα
- CMB305 vaccine* (Immune Design)

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- MEKi (Cotellic)
- anti-CD20 (Gazyva)
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- various chemotherapies
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- daratumumab* (Janssen)

T cell Trafficking

T cell infiltration
- anti-VEGF (Avastin)

Cancer T cell recognition
- anti-CD20/CD3 TCB
- KTE-C19* (Kite Pharma)
- ImmTAC* (Immunocore)

T cell killing
- Tecentriq (atezolizumab)
- IDOi (NewLink)
- anti-TIGIT
- IDOi* (Incyte)
- CPI-444* (Corvus)
- TDOi (NewLink)
- IDO1/TDOi (NewLink)

Priming & activation
- anti-OX40
- anti-CD27* (Cellnex)
- entinostat* (Syndax)

Marketed
- Clinical development
- Preclinical development
- Established therapies
- In-house CIT NMEs
- Partnered or external

Chen and Mellman, Immunity 2013
CIT=cancer immunotherapy; FP=fusion protein; TCB=T-cell bispecific
aTIGIT: A second potent negative T cell regulator
FPI achieved in May 2016

- Tumor-infiltrating CD8+ T cells and NK cells express high levels of TIGIT
- Antibody co-blockade of TIGIT and PD-L1 elicits tumor rejection in preclinical models
- TIGIT limits the effector function of chronically stimulated CD8+ T cells
- TIGIT restricts CD226 costimulatory signaling by competing for a common ligand (PVR); CD226 signaling is required for activity

TIGIT=T cell immunoreceptor with Ig and ITIM domains; DC=dendritic cell; CD8+ T cell=cytotoxic T lymphocyte (CTL)
aTIGIT preclinical data

*aTIGIT + aPD-L1 effective in animal model*

- aTIGIT + aPD-L1 combination active in a PD-L1 non-responsive model
- Elevated expression of TIGIT by T cells in human cancers
- TIGIT ligand (PVR) widely expressed by many human tumors

Johnson et al (2014) *Cancer Cell*; TIGIT = T cell immunoreceptor with Ig and ITIM domains
aCD20/CD3 TCB: An alternative to CAR-Ts

Entered phase I – Combo with Tecentriq planned

- Fully humanized IgG1
- PK typical of conventional IgG
- No homodimers or aggregate
- Data presentation planned at ASH

1. aCD20/CD3 TCB binds to tumor cells or CD8+ T cells
2. Pulls together the malignant B cell and the T cell
3. Enables T cell killing via CD3 stimulation

Carter et al. 1997 J Mol Biol; Scheer et al. 2013 Nat Biotechnol; TCB=T cell bispecific; CAR=chimeric antigen receptor; CD8+ T cell=cytotoxic T lymphocyte (CTL)
aCD20/CD3 TCB: An alternative to CAR-Ts

Impressive efficacy in humanized mice

aCD20/CD3 TCB activity vs Rituxan

aCD20/CD3 TCB prevents tumor growth in vivo

T cell activation in blood

Sun L.L. et al., Science translational Medicine, May 2015; TCB=T cell bispecific; CD8+ T cell=cytotoxic T lymphocyte (CTL); CD4+ T cell=T helper cells
aOX40 exhibits a dual mechanism of action

Promote antigen dependent T cell activation and regulatory T cell inhibition

1. Antigen dependent T cell activation
2. OX40L/OX40 costimulation promotes T cell activation
3. Inhibition of regulatory T cells

MC38 CRC mouse model

- 2/10 CR for aOX40 treatment
- 9/10 CR for aOX40 + PD-L1 treatment

APC=antigen presenting cell; CD8+ T cell=cytotoxic T lymphocyte (CTL); T reg=regulatory T cell; Adapted from Nature Rev Immunol. 4:420 (2004); Infante J.R. et al., ASCO 2016
Early aOX40 + Tecentriq combination data

aOX40 and Tecentriq upregulates PD-L1 following aPD-1 or aOX40 monotherapy

Infante J.R. et al., ASCO 2016
CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

How do clinical biomarker data define next steps?
Learning loop story 1: Chemo as immunotherapy

Platins effect preclinical efficacy and immunobiology

Camidge et al., WLCL 2015
Chemo combinations in immunotherapy

The field is confirming in house findings

- Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade
- Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents
- The interaction of anticancer therapies with tumor-associated macrophages
- Anticancer Chemotherapy-Induced Intratumoral Recruitment and Differentiation of Antigen-Presenting Cells
Learning loop story 2: MEKi+Tecentriq

Although MEK inhibition should block T cell function

MEKi + aPD-L1 combo shows preclinical efficacy

Primary tumor challenge of aPD-L1 + MEKi (BT26 model)

1. MEK inhibition should block T cell function
2. PD-L1/PD-1 regulates signaling by costimulatory molecules via the PI3 kinase pathway

Ebert et al. *Immunity* 2016; BT26 (KRASmt) colorectal mouse model
MEKi combines with aPD-L1 preclinically
Positive impact on tumor antigen presentation and accumulation of intra-tumoral T cell effectors

Upregulation of tumor MHC class I and antigen presentation

Ras/MAPK pathway activation down regulates MHC class I; MEKi reverses

MEK inhibition causes an increase in incompletely exhausted PD-1\text{low} CD8+ T cells in tumors

Ebert et al. *Immunity* 2016
MEKi is an unexpected combo partner for aPD-L1

Blocks naive T cell priming but inhibits T cell exhaustion

- Likely explains increase in intratumoral T cells
- No effect on CTL killing of tumor cells

Ebert et al. *Immunity* 2016
CIT has changed the oncology paradigm

Update gRED CIT portfolio

The learning loop: Clinical data informs combinations and NME selection

How do clinical biomarker data define next steps?
Human tumors can be classified according to three generalized “immune profiles”

**Inflamed**
- CD8+ T cells infiltrated, but non-functional

**Immune Excluded**
- CD8+ T cells accumulated but have not efficiently infiltrated

**Immune Desert**
- CD8+ T cells absent from tumor and its periphery

---

**Tecentriq response rate**

**CD8+ / IFN-γ / PDL1**

**Angiogenesis / MDSC / stroma**

**Low MHC class I / tumor proliferation**

**Mutation rate**

MDSC = myeloid-derived suppressor cells
Clinical findings define the rate limiting steps on the Cancer Immunity Cycle, and what to do next

**Immune desert**
Insufficient T cell response

- Vaccines
- Chemo
- Pro-inflammatory strategies
- TCB’s

**Excluded infiltrate**
Inadequate T cell homing

- Anti-angiogenics
- Stromal targets
- Chemokines
- Vaccines

**Inflamed**
Inactivated T cell response: Tecentriq most effective

- Negative regulators
- Vaccines
Realizing the potential of cancer immunotherapy

The learning loop will guide CIT progress

First generation
- Checkpoint Inhibitors Monotherapy
  - PD-L1 IHC
    - Tecentriq (2016)

Second generation
- Combine with Existing Medications
  - Teff Signatures
    - Tecentriq + chemo
    - Tecentriq + Avastin, Cotellic, Zelboraf, Tarceva, Alecensa, Gazyva, Herceptin, Perjeta, Kadcyla

Third generation
- Expand to Novel CITs
  - Immune Landscape Signature Dx
    - Immune doublets: Tecentriq + CIT 1, CIT 2...
    - Immune doublets: CIT 1 + CIT 2

Fourth generation
- Personalized CIT
  - FoundationCI, RNAseq
  - Combos/NMEs targeted at defined immune profiles and mutant neoantigens

NME=new molecular entity
Early pipeline update: Assets and strategies

William Pao, M.D., Ph.D.
Global Head Oncology Discovery and Translational Area, Roche pRED
Develop the right drug with the right format against the right target.
Following the science

Understanding patient, tumor and immune context are key to developing new molecules
Following the science

Understanding patient, tumor and immune context are key to developing new molecules.
Following the science
Understanding patient, tumor and immune context are key to developing new molecules
Idasanutlin

**Novel MDM2 antagonist for activating tumor suppressor p53**

**Mechanism of action**


- Among first small molecules to disrupt a non-enzyme **protein:protein interaction** (Vassilev et al., Science 2004)

**Status of idasanutlin**

- Ph Ib study in **relapsed/refractory AML** showed promising activity as monotherapy and with cytarabine

- **Phase III** (MIRROS) study in AML started Jan 2016

- Additional **combination** studies ongoing in myeloproliferative neoplasms (with PEG-IFN), elderly unfit AML (with Venclexta), and NHL (with Gazyva)
Update of idasanutlin responses in AML (Ph1/1b)

Median duration of response > 7 months

**Single agent**

- ORR (CR/CRp+CRI/MLFS) 17% (8/46)
- CR/CRp: 7% (3/46)
- 33/46 patients with evaluable bone marrows ORR 24% (8/33)

**Combo with Ara-C**

- ORR (CR/CRp+CRI/MLFS) 31% (23/75)
- CR/CRp: 27% (20/75)
- 53/75 patients with evaluable bone marrows ORR 43% (23/53)

**Response definitions:**
- **CR**: < 5% marrow blasts with complete recovery of peripheral counts
- **CRp**: CR with incomplete platelet recovery
- **CRI/MLFS**: < 5% marrow blasts with incomplete / no recovery of peripheral counts, morphologic leukemia free state
- **PR**: > 50% decrease in marrow blasts

1CR defined as marrow assessment after cycle 1 with a second marrow assessment > 28 d after initial assessment
Idasanutlin: Phase 3 MIRROS study in R/R AML

• Study design

Multi-center, double-blind, randomized, pbo-controlled phase III in relapsed/refractory AML* (N=440)

Primary outcome measures
• OS in TP53 wild-type population

Key secondary outcome measures
• OS in overall population, CRi, ORR, including CR, CRp and CRi, EFS

R/R AML – relapsed/refractory acute myeloid leukemia; *Non-US trial
Vanucizumab
Bispecific antibody against Ang-2 and VEGF-A

Mechanism of action
• Binds to both angiopoietin-2 and VEGF-A, neutralizing two complementary angiogenic factors
• Additional potential immunomodulatory effects through inhibition of Ang-2 and VEGF-A
• First Roche antibody to use CrossMab technology

Status of vanucizumab
• Ph II (McCave) study in 1L CRC H2H against Avastin ongoing
• Phase Ib in platinum-resistant ovarian cancer showed 29% RR*
• Ph Ib with CD40 in solid tumors ongoing
• Ph Ib with Tecentriq in solid tumors ongoing

Kienast et al., CCR 2013; *Oaknin et al., PASCO ‘15
Vanucizumab: 1L CRC, McCAVE Phase 2 Study
Data expected in late 2016

Open Label Safety Run-in
2 cycles (4 wks)

1L mCRC
N=190

Induction
Up to 8 cycles
(16 wks)

Maintenance
until PD, max.
24 mths

First-line mCRC
vanucizumab + mFOLFOX-6

IMC Review

Bevacizumab + mFOLFOX-6*

Bevacizumab + 5-FU/LV

Vanucizumab + mFOLFOX-6*

Vanucizumab + 5-FU/LV

Primary outcome measures
• PFS

Key secondary outcome measures
• Safety and tolerability, RECIST ORR, OS and duration of response, PK

* mFOLFOX-6: 85 mg/m² Oxaliplatin; 400 mg folinic acid i.v. over 2 hrs; 400 mg/m² 5-FU as bolus, 2.400 mg/m² 5-FU as 46-hrs permanent infusion
Roche pRED CIT molecules in the clinic
Targeting multiple steps of the cancer-immune cycle

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

Macrophages (M2)
- emactuzumab

Vasculature barrier to T-cells
- vanucizumab

Tumor-targeted cytokine
- cergutuzumab amunaleukin
- FAP-IL2v FP

APC stimulators
- CD40 MAb

T cell engagers
- CEA CD3 TCB

Adapted from Chen & Mellman, Immunity '13
APC=antigen presenting cell; CD=classification determinant; CEA=carcinoembryonic antigen; CIT=cancer immune therapy; FAP=fibroblast activation protein; TCB=T cell bispecific
Ongoing or planned pRED immune doublets
Seven novel combinations in the clinic

**Combinations**

<table>
<thead>
<tr>
<th>Modulator</th>
<th>Generator</th>
<th>Engager</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol 1</td>
<td>Mol 2</td>
<td>Mol 3</td>
</tr>
<tr>
<td>Mol 4</td>
<td>Mol 5</td>
<td>Mol 6</td>
</tr>
<tr>
<td>Mol 7</td>
<td>Mol 8</td>
<td>Mol 9</td>
</tr>
<tr>
<td>Mol 10</td>
<td>Mol 11</td>
<td>Mol 12</td>
</tr>
</tbody>
</table>

**With Tecentriq**

- ✓ aCSF-1R
- ✓ aCD40
- ✓ CEA-IL2v FP
- ✓ CEA CD3 TCB
- ✓ Ang2-VEGF biMAb
- ✓ FAP-IL2v FP

**Other**

- ✓ aCD40/aCSF-1R
- ✓ aCD40/Ang2-VEGF biMAb
- ✓ aCSF-1R/Avastin (IST)
- ✓ aFAP-IL2v/cetuximab

✓ Phase I ongoing
Emactuzumab eliminates T cell suppressive macrophages and enhances anti-tumor immunity

Tumor-derived macrophages suppress T cell proliferation

aCSF-1R antibody treatment increases lymphocyte infiltration in colon cancer mouse model

aCSF1R + aPD-L1 combination in colon cancer mouse model

Phase Ib study combining emactuzumab and atezolizumab in solid tumors ongoing

Ries et al., Cancer Cell '14
CIT combos may yield long-term benefits

\(aCSF1R + aCD40\) doublet induces immunologic “memory” in mice – tumors rejected on re-challenge

Emactuzumab + aCD40 in colon cancer mouse model

100% second tumor rejection in combo pre-treated vs. naïve mice

Phase Ib study combining emactuzumab and aCD40 in solid tumors ongoing
IL2v fusion protein platform

Two targeted molecules in development

Advantages over proleukin

- **Higher** exposure
- More **favorable PD** effects: NK / immune-effector > suppressor-cells
- Clinical evidence for **tumor targeting**
- Better **safety** profile

CEA vs FAP targeting

- **CEA - tumor cells**
- **FAP - stromal cells**

Mechanisms of action

- Phase Ib study combining cergutuzumab amunaleukin and atezolizumab ongoing
- Phase I with FAP-IL2v FP ongoing; combination of FAP-IL2v FP and atezolizumab planned

Tabernero et al., ECC ’15; Nicolini et al., AACR ’16
CEA CD3 T cell bispecific for solid tumors

Using innovative engineering from pRED to develop best-in-class platform

<table>
<thead>
<tr>
<th>Tumor histology</th>
<th>Inflamed</th>
<th>Immune Excluded</th>
<th>Immune Desert</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA CD3 TCB</td>
<td>Mono/combo potential</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Binding simultaneously to tumor and T cells by CEA CD3 TCB results in:

- T cell engagement, activation and **killing of tumor cells** by delivery of cytotoxic granules
- **T cell proliferation** (expansion) selectively at site of activation

CIT=cancer immune therapy; TCB=T cell bispecific antibody; Hegde et al., CCR ’16; Bacac et al., CCR ’16
Combination of CEA CD3 TCB + atezolizumab elicits superior anti-tumor activity

Upregulation of PD-L1 and PD-1 by TCB consistent with MoA

CEA CD3 TCB: induces PD-1 on T cells and PD-L1 on tumor cells in preclinical models

CEA CD3 TCB + aPD-L1 in fully humanized PD-L1-resistant xenograft model

Vehicle
CEA CD3 TCB
atezolizumab
CEA CD3 TCB + aPD-L1

PD-1 staining (brown) of tumors at termination

Tumor volume (mm$^3$)

PD-1 on tumor-infiltrating T cells

Vehicle
CEA CD3 TCB

% human CD8+PD-1+

Vehicle
CEA CD3 TCB

Study day

Phase Ib study combining CEA CD3 TCB and atezolizumab ongoing in CEA+ tumors

CEA=carcinoembryonic antigen; MoA=mode of action; PD-1=programmed death 1;
PD-L1=Programmed death ligand 1; TCB=T cell bispecific antibody; Bacac et al., AACR ’16
### Tecentriq combination studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Molecule</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>*Expected readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>enactment (aCSF-1R)</td>
<td>Safety</td>
<td>FPI Q1 2015</td>
<td>2017</td>
</tr>
<tr>
<td>N=110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>CD40 MAb</td>
<td>Safety, PD, efficacy</td>
<td>FPI Q4 2014</td>
<td>2017</td>
</tr>
<tr>
<td>N=160</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>CEA CD3 TCB</td>
<td>Safety, PK, PD, imaging, biomarkers</td>
<td>FPI Q1 2016</td>
<td>2017</td>
</tr>
<tr>
<td>N=100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>cergutuzumab amunaleukin (CEA-IL2v)</td>
<td>Safety, efficacy, PK, PD</td>
<td>FPI Q2 2015</td>
<td>2017</td>
</tr>
<tr>
<td>N=75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>vanucizumab</td>
<td>Safety, efficacy</td>
<td>FPI Q2 2016</td>
<td>2017</td>
</tr>
<tr>
<td>N~40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### aCD40 combination studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Molecule</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>*Expected readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>enactment</td>
<td>Safety, PK, PD</td>
<td>FPI Q2 2016</td>
<td>2017</td>
</tr>
<tr>
<td>N~120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>vanucizumab</td>
<td>Safety, PD, efficacy</td>
<td>FPI Q1 2016</td>
<td>2017</td>
</tr>
<tr>
<td>N=170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Event-driven, timelines may change*
Targeted therapies and future combinations

Sandra Horning, M.D.
Executive VP
Chief Medical Officer and Head Global Product Development
Introduction: Portfolio progress

**Lung:** Alecensa (J-ALEX)

**Melanoma:** Cotellic + Zelboraf

**Breast:** Cotellic, Perjeta (PHEREXA)

**Hematology:** Gazyva, Venclexta

**Summary**
2016 onwards: Significant launch activities

- **Venclexta**: R/R CLL with 17p del
- **Cotellic + Zelboraf**: BRAF+ melanoma
- **Alecensa**: 2L ALK+ NSCLC
- **Tecentriq**: 2L+ lung and bladder cancer
- **Emicizumab (ACE910)**: Hemophilia A
- **Lebrikizumab**: Severe Asthma
- **Ocrelizumab**: RMS/ PPMS
- **Lampalizumab**: Geographic atrophy

<table>
<thead>
<tr>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazyva: Refractory iNHL (GADOLIN)</td>
<td>Gazyva: 1L iNHL (GALLIUM)</td>
<td>Tecentriq + chemo +/- Avastin: 1L NSCLC (IMpower)</td>
</tr>
<tr>
<td>Perjeta + Herceptin: eBC HER2+ (APHINITY)</td>
<td>Tecentriq + Avastin: 1L RCC (IMmotion)</td>
<td>Alecensa: 1L ALK+ NSCLC (ALEX)</td>
</tr>
<tr>
<td>Gazyva: 1L aNHL (GOYA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actemra: Giant cell arteritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Oncology** | **Non-oncology** | **FDA Breakthrough Therapy Designation**

Outcome studies are event-driven: timelines may change. Standard approval timelines of 1 year assumed; Alecensa and emicizumab in collaboration with Chugai; Venclexta in collaboration with AbbVie; Cotellic in collaboration with Exelixis; Gazyva in collaboration with Biogen.
Roche significantly advancing patient care
Recognition for innovation 2013-present

12 Breakthrough Therapy Designations

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Roche</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Novartis</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>BMS</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Merck</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Pfizer</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>GSK</td>
<td>5</td>
</tr>
</tbody>
</table>

Source: [http://www.focr.org/breakthrough-therapies](http://www.focr.org/breakthrough-therapies) as at June 2016; PPMS=Primary Progressive Multiple Sclerosis; CLL=Chronic Lymphocytic Leukemia; NSCLC=Non-Small Cell Lung Cancer; IPF=Idiopathic Pulmonary Fibrosis
Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary
Lung cancer: Still high unmet medical need

*Incidence cases reach 560,000 pts*¹

- **SCLC (NSCLC)**: 15%
- **KRAS+ adenocarcinoma (NSCLC)**: 10%
- **EGFR+ adenocarcinoma (NSCLC)**: 9%
- **ALK+ adenocarcinoma (NSCLC)**: 3%
- **HER2+ adenocarcinoma (NSCLC)**: 2%
- **BRAF+ adenocarcinoma (NSCLC)**: 1%
- **unknown adenocarcinoma (NSCLC)**: 1%
- **large cell carcinoma (NSCLC)**: 15%
- **squamous cell carcinoma (NSCLC)**: 30%

¹ Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; Alecensa in collaboration with Chugai; Cotellc in collaboration with Exelixis

---

= Roche marketed  = Roche in development
Alecensa: ALKi with excellent CNS disease control

Outstanding head-to-head data in 1L ALK+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Alecensa</th>
<th>crizotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR by IRF* (%)</td>
<td>91.6 (n=83)</td>
<td>78.9 (n=90)</td>
</tr>
<tr>
<td>Median PFS (95% CI) by IRF in ITT</td>
<td>NR (20.3-NR) (n=103)</td>
<td>10.2 (8.2-12.0) (n=104)</td>
</tr>
</tbody>
</table>

* In measurable lesions at baseline by IRF

Progression free survival

Japanese Phase III results (J-ALEX)

- PFS HR of 0.34 versus crizotinib exceeds targeted HR of 0.64 (mPFS was not reached)
- Favorable safety profile compared to crizotinib
- US launch in 2L off to a strong start with 19% share of new patients
- H2H 1L data from global study (ALEX) expected beginning 2017

Nokihara H. *et al*, ASCO 2016; Alecensa (alectinib) in collaboration with Chugai
Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary
Melanoma: Still high unmet medical need

*Incidence cases reach 125,000 pts*¹

¹ Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon
**Cotellic+Zelboraf in BRAF+ melanoma**

**PFS and OS subgroup analysis**

### Median OS (months) (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>PBO+Z</th>
<th>C+Z</th>
<th>PBO+Z</th>
<th>C+Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT</strong></td>
<td>248</td>
<td>247</td>
<td>17.4</td>
<td>22.3</td>
</tr>
<tr>
<td>LDH level: &lt;0.8 ULN</td>
<td>84</td>
<td>76</td>
<td>25</td>
<td>NR</td>
</tr>
<tr>
<td>LDH level: &gt;2x ULN</td>
<td>38</td>
<td>31</td>
<td>6.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Stage M1c+LDH&lt;ULN</td>
<td>68</td>
<td>58</td>
<td>18.0</td>
<td>NR</td>
</tr>
<tr>
<td>Stage M1c+LDH&gt;ULN</td>
<td>82</td>
<td>86</td>
<td>8.3</td>
<td>14.5</td>
</tr>
<tr>
<td>No liver metastases</td>
<td>170</td>
<td>164</td>
<td>19.8</td>
<td>NR</td>
</tr>
<tr>
<td>With liver metastases</td>
<td>78</td>
<td>83</td>
<td>12.7</td>
<td>18.5</td>
</tr>
<tr>
<td>Baseline SLD &lt;median</td>
<td>127</td>
<td>121</td>
<td>24.9</td>
<td>NR</td>
</tr>
<tr>
<td>Baseline SLD &gt;median</td>
<td>119</td>
<td>125</td>
<td>13.5</td>
<td>18.6</td>
</tr>
</tbody>
</table>

**Phase III coBRIM subgroup analysis**

- ITT population: mOS of 22.3 months (HR=0.7)
- Across all subsets, Cotellic+Zelboraf showed mPFS and mOS benefit
- US: +6% share of new patients achieved in 1L and 2L after launch

**Phase Ib BRIM7 OS update**

- BRIM7 update (single arm Ph1b): mOS in BRAFi naive patients exceeded 2.5 years

Atkinson V. et al, SMR 2015; McArthur G. et al, ASCO 2016; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; PBO=placebo; M1c (disease stage); LDH=lactate dehydrogenase; ULN=upper limit of normal; SLD=sum of longest diameters
Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREZA)

Hematology: Gazyva, Venclexta

Summary
Breast cancer: Still high unmet medical need
*Incidences cases reach 490,000 pts*¹

**Pie Chart: Breast Cancer Subtypes**

- **ER+/PR+/Her2+:** 55%
- **ER-/PR-/Her2+:** 13%
- **ER+/PR-/Her2+:** 11%
- **ER-/PR+/Her2+:** 7%
- **ER+/PR+/Her2:*** 2%
- **ER-/PR+/Her2+:** 1%

1. **TNBC (triple negative breast cancer):** 13%
2. **ER+/PR+/Her2+:** 11%
3. **ER-/PR-/Her2+:** 7%
4. **ER+/PR-/Her2+:** 2%
5. **ER-/PR+/Her2+:** 1%

**Legend:**

- **= Roche marketed**
- **= Roche in development**

---

1. Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); ER=estrogen receptor; PR=progesterone receptor; TNBC=triple negative breast cancer; Ipatasertib in collaboration with Array BioPharma.
Cotellic + paclitaxel in 1L TNBC
Overcoming potential resistance mechanism

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Cotellic + paclitaxel (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>8 (50)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (50)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (19)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Not done</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

Phase II (COLET); Safety run-in results
- Resistance to 1L taxane therapy is thought to be caused by MAPK pathway upregulation
- ORR of 50%
- Responses were durable up to 30 weeks
- Manageable safety-profile
- Randomized P2 (COLET) ongoing (n=100)

Bruksy A. et al., ASCO 2016; Cotellic in collaboration with Exelisix; MAPK=mitogen-activated protein kinase
Perjeta + Herceptin in 2L HER2+ mBC

**PHEREXA phase III results**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Herceptin + Xeloda (n=224)</th>
<th>Herceptin + Perjeta + Xeloda (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS by IRF</td>
<td>9.0</td>
<td>11.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.65-1.02)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>PFS by investigator</td>
<td>9.0</td>
<td>11.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.66-1.00) *</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>28.1</td>
<td>36.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.51-0.90) *</td>
<td></td>
</tr>
</tbody>
</table>

* Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint

**Phase III PHEREXA results**

- Primary endpoint: Independent review facility assessed mPFS was not statistically significant
- 8-month increase in mOS to 36.1 months was observed
- Magnitude of the OS benefit is in line with prior experience of Perjeta in mBC

Urruticoechea et al., ASCO 2016; H=Herceptin; P=Perjeta; X=xeloda; IRF=independent review facility
Perjeta in neoadjuvant HER2+ eBC

KRISTINE results support NEOSPHERE

Phase III KRISTINE results
- Herceptin + Perjeta + docetaxel + carboplatin was superior to Perjeta + Kadcyla
- Herceptin + Perjeta + docetaxel + carboplatin achieved higher breast conservation rate (52.6% vs 41.7%)

Hurvitz et al., ASCO 2016; H=Herceptin; P=Perjeta; DTX=docetaxel; C=carboplatin; pCR=pathologic complete response
HER2 franchise evolution
Further improving the standard of care

- Phase III results (APHINITY) for Perjeta + Herceptin in the adjuvant setting expected end of 2016

mBC=metastatic breast cancer; SC=subcutaneous; SoC=standard of care
Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotellic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary
Blood cancer: Still high unmet medical need

Incidences cases reach 330,000 pts\(^1\)

\(¹\) Datamonitor; incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); NHL= non-hodgkin’s lymphoma; DLBCL (aNHL)= diffuse large B-cell lymphoma; FL (iNHL)= follicular lymphoma; ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; CLL= chronic lymphoid leukemia; MM= multiple myeloma; MDS= myelodysplastic syndrome; Venclexta in collaboration with AbbVie; Cotellic in collaboration with Exelixis; Gazyva in collaboration with Biogen; polatuzumab vedotin in collaboration with Seattle Genetics; LSD1 inhibitor in collaboration with Oryzon Genomics
Establishing Gazyva as the new CD20 backbone
From good to great

Rituxan sales split by indication

Gazyva approved in Rituxan-refractory FL (iNHL)
Gazyva in FL (iNHL) (GALLIUM)

Gazyva approved in 1L CLL
Venclexta approved in R/R CLL 17p del

Gazyva approved in 1L CLL
Gazyva in DLBCL (aNHL) (GOYA)

CLL=chronic lymphocytic leukemia; iNHL=indolent non-hodgkin’s lymphoma; FL=follicular lymphoma; aNHL=aggressive NHL; DLBCL=diffuse large B cell lymphoma; Gazyva in collaboration with Biogen; Venclexta in collaboration with AbbVie
Third positive readout for Gazyva

**GALLIUM in 1L iNHL**

### Primary end-point:

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

**1L iNHL**

- **n=1401**

  
  **Induction**
  - Rituxan + CHOP or
  - Rituxan + CVP or
  - Rituxan + bendamustine

  **Maintenance**
  - Gazyva + CHOP or
  - Gazyva + bendamustine

  
  PFS
  - Stopped at interim analysis

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

**Rituxan-refractory iNHL**

- **n=411**

  
  **Induction**
  - Gazyva + CHOP or
  - Gazyva + CVP or
  - Gazyva + bendamustine

  **Maintenance**
  - Gazyva q2mo x 2 years

  
  PFS
  - Approved in Q1 2016

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

**Front-line DLBCL**

- (aggressive NHL)

- **n=1418**

  
  **Induction**
  - Gazyva + CHOP
  - Rituxan + CHOP

  
  PFS
  - Data expected in H2 2016

Gazyva in collaboration with Biogen; CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone
Venclexta* + R/G-CHOP in 1L NHL
First efficacy data in combination with CD20 backbone

Phase Ib results (CAVALLI)
- Venclexta + R/G-CHOP was tolerable with discontinuous Venclexta dosing
- Both combinations showed strong ORR, especially CR
- Ph2 study for Venclexta + R-CHOP at 800mg Venclexta (recommended dose) has been initiated
- Dose-finding on-going for Venclexta + G-CHOP

Zelenetz A. et al., ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; R=Rituxan; G=Gazyva; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone
Venclexta* + hypomethylating agents in 1L AML
New options for chemo-unfit elderly

Phase Ib results

- 90% of patients achieved significant reduction in bone marrow blast counts
- ORR of 62% taking both hypomethylating agent combinations together
- Tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Safety expansion with both hypomethylating agents at 2 Venclexta doses ongoing (n=100)

Response, n (%) | Venclexta + decitabine (n=23) | Venclexta + azacitidine (n=22) | Total (n=45)
--- | --- | --- | ---
ORR | 16 (70) | 12 (55) | 28 (62)
CR/CRi | 15 (65) | 12 (55) | 27 (60)
CR | 5 (22) | 7 (32) | 12 (27)
CRi | 10 (44) | 5 (23) | 15 (33)
PR | 1 (4) | 0 (0) | 1 (2)

Bone marrow blast count

*Venclexta (venetoclax) in collaboration with AbbVie; CRi=complete remission with incomplete marrow recovery

Pollyea D. *et al.*, ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; CRi=complete remission with incomplete marrow recovery
**Venclexta** + LDAC in 1L AML

**ORR of 68% achieved in patients with no prior MPN**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Venclexta + LDAC All patients (n=26)</th>
<th>Venclexta + LDAC Patients with no prior MPN (n=22)</th>
<th>Venclexta + LDAC Patients with no prior HMA (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>15 (58)</td>
<td>15 (68)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>14 (54)</td>
<td>14 (64)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>CR</td>
<td>6 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRi</td>
<td>8 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blast count &lt;5%</td>
<td>21 (81)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phase Ib results**

- Majority of patients achieved significant reduction in BM and peripheral blast counts
- ORR of 68% in patients with not prior MPN
- Combination demonstrates a tolerable safety profile for treatment-naive chemo-unfit patients aged ≥65y
- Ph2 expansion on-going (n=50)

Lin T. et al., ASCO 2016; *Venclexta (venetoclax) in collaboration with AbbVie; LDAC=low dose cytarabine; MPN=myeloproliferative neoplasm; HMA=hypomethylating agent; CRi=complete remission with incomplete marrow recovery; BM=bone marrow
## Development plan I: Hematology franchise

### 8 novel molecules in the clinic

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Study name</th>
<th>Indication</th>
<th>Ph1</th>
<th>Ph2</th>
<th>Ph3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazyva</td>
<td>+bendamustine</td>
<td>GADOLIN</td>
<td>FL (iNHL) (Rituxan refractory)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazyva</td>
<td>+CHOP</td>
<td>GOYA</td>
<td>DLBCL (aNHL)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Gazyva</td>
<td>+chemo</td>
<td>GALLIUM</td>
<td>1L FL (iNHL)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Gazyva</td>
<td>+chemo</td>
<td>CLL11</td>
<td>CLL</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Gazyva</td>
<td>+FC/bendamustin/Cib</td>
<td>GREEN</td>
<td>CLL and R/R CLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venclexta*</td>
<td>+Rituxan/+Rituxan+bendamustine</td>
<td>CONTRALTO</td>
<td>R/R FL (iNHL)</td>
<td></td>
<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Rituxan+CHOP/Gazyva+CHOP</td>
<td>CAVALLI</td>
<td>1L aNHL</td>
<td></td>
<td>✓</td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Rituxan+bendamustine</td>
<td></td>
<td>R/R NHL</td>
<td></td>
<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Gazyva+polatuzumab vedotin</td>
<td></td>
<td>aNHL and iNHL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Gazyva+polatuzumab vedotin</td>
<td></td>
<td>R/R aNHL and R/R iNHL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Rituxan</td>
<td></td>
<td>R/R CLL and SLL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Gazyva</td>
<td>CLL14</td>
<td>CLL</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Rituxan</td>
<td>MURANO</td>
<td>R/R CLL</td>
<td></td>
<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td></td>
<td></td>
<td>R/R CLL 17p</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Rituxan+bendamustine</td>
<td></td>
<td>R/R CLL after ibru/idel</td>
<td></td>
<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+Gazyva</td>
<td></td>
<td>R/R CLL and CLL</td>
<td></td>
<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td></td>
<td></td>
<td>R/R CLL and CLL</td>
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<td></td>
<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+bortezomib+dexamethasone</td>
<td></td>
<td>R/R MM</td>
<td></td>
<td></td>
<td>ASCO</td>
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<tr>
<td>Venclexta</td>
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<td></td>
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<td></td>
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<tr>
<td>Venclexta</td>
<td></td>
<td></td>
<td>AML</td>
<td></td>
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<td>ASCO</td>
</tr>
<tr>
<td>Venclexta</td>
<td>+decitabine/+azacitidine/+LdAraC</td>
<td></td>
<td>AML</td>
<td></td>
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<td>ASCO</td>
</tr>
</tbody>
</table>

iNHL = indolent non-Hodgkin's lymphoma; aNHL = aggressive NHL; CLL = chronic lymphoid leukemia; R/R CLL = relapsed/refractory CLL; MM = multiple myeloma; AML = acute myeloid leukemia; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; FC = fludarabine, cyclophosphamide; LDAC = low dose cytarabine; *Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; polatuzumab in collaboration with Seattle Genetics

For further details, please refer to ASCO presentations.
## Development plan hematology franchise II
### 8 novel molecules in the clinic

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Study name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>polatuzumab</td>
<td>+Rituxan/Gazyva</td>
<td>ROMULUS</td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+benda/Rituxan+benda</td>
<td></td>
<td>R/R FL (iNHL) and aNHL</td>
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<tr>
<td>polatuzumab</td>
<td>+Gazyva+CHP/Rituxan+CHP</td>
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<td>1L aNHL</td>
</tr>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+lenalidomide</td>
<td></td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+Venclexta</td>
<td></td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+Gazyva</td>
<td></td>
<td>R/R FL (iNHL) and aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+Gazyva+lenalidomide</td>
<td></td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+CHOP</td>
<td></td>
<td>aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+bendamustine</td>
<td></td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+Gazyva+polatuzumab</td>
<td></td>
<td>R/R FL and aNHL</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+lenalidomide</td>
<td></td>
<td>MM</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>+daratumumab+/−lenalidomide or +/−pomalidomide</td>
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<td>R/R MM</td>
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<td>Tecentriq</td>
<td>+azacitidine</td>
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<td>MDS</td>
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<tr>
<td>aCD20/CD3 biMab</td>
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<td></td>
<td>Heme tumors</td>
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<tr>
<td>LSD1 inhibitor</td>
<td></td>
<td></td>
<td>AML</td>
</tr>
<tr>
<td>idasanutlin</td>
<td>+Gazyva</td>
<td></td>
<td>R/R FL (iNHL) and aNHL</td>
</tr>
<tr>
<td>idasanutlin</td>
<td>+Venclexta</td>
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<td>Chemo unfit R/R AML</td>
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<tr>
<td>idasanutlin</td>
<td>+cytarabine</td>
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<td>R/R AML</td>
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<tr>
<td>undisclosed ADC</td>
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<td></td>
<td>R/R NHL</td>
</tr>
</tbody>
</table>

Venclexta in collaboration with AbbVie; Polatuzumab vedotin in collaboration with Seattle Genetics; LSD1 inhibitor in collaboration with Oryzon Genomics; daratumumab in collaboration with Janssen (J&J); iNHL=indolent non-hodgkin’s lymphoma; R/R FL=relapsed/refractory follicular lymphoma; aNHL=aggressive NHL (DLBCL); MM=multiple myeloma; MDS=myelodysplastic syndrom; AML=acute myeloid leukemia;
Introduction: Portfolio progress

Lung: Alecensa (J-ALEX)

Melanoma: Cotelic + Zelboraf

Breast: Cotellic, Perjeta (PHEREXA)

Hematology: Gazyva, Venclexta

Summary
Combination in development

Chemo combination in development

Combination approved

Chemo combination approved

Roche NME late stage

Roche NME early stage

Non-Roche approved drugs

eamactuzumab (aCSF-1R); cergutuzumab amunaleukin (aCEA-IL2v FP); vanucizumab (aAng2/VEGF); polatuzumab veditin (aCD79b ADC); taselisib (PI3Ki); ipatasertib (AKTi); SERD (selective estrogen receptor degrader); idasanutlin (MDM2 antagonist); Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Alecensa in collaboration with Chugai; Cotellic in collaboration with Exelixis; Zelboraf in collaboration with Plexxikon; polatuzumab in collaboration with Seattle Genetics; ipatasertib in collaboration with Array Biopharma; IDOi in collaboration with NewLink; daratumumab in collaboration with Janssen (J&J)
Doing now what patients need next