# Agenda

## Morning session

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:30 – 10:35</td>
<td>Welcome</td>
<td>Karl Mahler</td>
</tr>
<tr>
<td>10:35 – 11:05</td>
<td>Pharma strategy &amp; productivity</td>
<td>Daniel O’Day</td>
</tr>
<tr>
<td>11:05 – 12:00</td>
<td>Late-stage pipeline</td>
<td>Sandra Horning</td>
</tr>
<tr>
<td>12:00 – 12:45</td>
<td>Lunch break</td>
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</tbody>
</table>

## Afternoon session

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:45 – 13:30</td>
<td>Cancer immunotherapy</td>
<td>Dan Chen / Cathi Ahearn</td>
</tr>
<tr>
<td>13:30 – 14:20</td>
<td>Life cycle management &amp; new market opportunities</td>
<td>Bill Anderson</td>
</tr>
<tr>
<td>14:20 – 14:45</td>
<td>Break</td>
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## Breakout sessions

<table>
<thead>
<tr>
<th>Breakout</th>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>Breakout 1</td>
<td>Hematology</td>
<td>David Traub / Cindy Perettie</td>
</tr>
<tr>
<td>Breakout 1</td>
<td>Molecular Information</td>
<td>Garrett Hampton</td>
</tr>
<tr>
<td>Breakout 1</td>
<td>Biosimilars</td>
<td>Fermin Ruiz de Erenchun</td>
</tr>
<tr>
<td>Breakout 2</td>
<td>Hematology</td>
<td>David Traub / Cindy Perettie</td>
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<tr>
<td>Breakout 2</td>
<td>Molecular Information</td>
<td>Garrett Hampton</td>
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<td>Breakout 2</td>
<td>Biosimilars</td>
<td>Fermin Ruiz de Erenchun</td>
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<tr>
<td>Breakout 2</td>
<td>Buffet reception</td>
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</table>

15:45 – 16:15  Buffet reception
Roche Pharma Day 2015
Pharma strategy & productivity

Daniel O’Day | Chief Operating Officer
Pharmaceuticals Division
This presentation contains certain forward-looking statements. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1 pricing and product initiatives of competitors;
2 legislative and regulatory developments and economic conditions;
3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6 increased government pricing pressures;
7 interruptions in production;
8 loss of or inability to obtain adequate protection for intellectual property rights;
9 litigation;
10 loss of key executives or other employees; and
11 adverse publicity and news coverage.

Any statements regarding earnings per share growth is not a profit forecast and should not be interpreted to mean that Roche’s earnings or earnings per share for this year or any subsequent period will necessarily match or exceed the historical published earnings or earnings per share of Roche.

For marketed products discussed in this presentation, please see full prescribing information on our website www.roche.com

All mentioned trademarks are legally protected.
Roche has a strong track record of innovation
*Industry leading medicines as basis for our continuous growth*

Sales excluding OTC at 2014 average exchange rates;
Note: Approved medicines shown do not represent the entire portfolio rather a selection; timeline reflects year of approval
Roche’s strategy remains unchanged
Success hinges on excellence in innovation & execution

- Differentiated molecules
- Commercial excellence
- R&D 2.0
- Personalize patient care
- Innovative ways of working
- Do more with less

Outstanding talent that drives innovation & execution
Roche’s strategy remains unchanged
Success hinges on excellence in innovation & execution

Pipeline & execution

- Focus investment on **differentiated molecules**
- Drive **excellence in commercial execution**
Diversified approach towards innovation

**Belief: Exploring broad BUT prioritizing rigorously**

**We invest more than others in the early stage**

<table>
<thead>
<tr>
<th>% of budget dedicated R&amp;D phases</th>
<th>Research engines identified a growing n° of diverse solutions to patients’ needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>R &amp; Early D 54%</td>
<td>Genentech &amp; Roche &amp; CHUGAI</td>
</tr>
<tr>
<td>Late D 46%</td>
<td>Industry avg.</td>
</tr>
<tr>
<td>Industry avg 40%</td>
<td>Roche</td>
</tr>
<tr>
<td>Industry avg 60%</td>
<td>2011 11</td>
</tr>
<tr>
<td>Roche 54%</td>
<td>2012 18</td>
</tr>
<tr>
<td>19</td>
<td>2013</td>
</tr>
</tbody>
</table>

External sources: Investment split based on the CMR Pharmaceutical R&D Factbook (data from 10 companies, 2014); Number of entries into Pre-clinical for Industry based on data from KMR, data for 2011-2013.
However, we set a high bar for our R&D pipeline …

Targeting clear differentiation in areas of unmet need

Assessment for late stage entry candidates & line extensions

<table>
<thead>
<tr>
<th>Unmet medical need</th>
<th>Clinical differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

Illustrative

Greater differentiation

Total sales potential

Sales

Time

Continued

Disqualified
…and rigorously prioritize our R&D activities

*Focused investments on the most promising candidates*

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**Late stage portfolio overview**

**Go, Wait, Gate Examples**

- **Go**
  - Move fast and make broad investments – *example Immunotherapy*

- **Mitigate Risk: Wait**
  - Waiting until we get further data to initiate programs – *example Polatuzumab*

- **Mitigate Risk: Gate**
  - Gate larger investments on further data, for example interim readouts, safety analyses, or different studies – *example Alzheimer's*
Leading to highly differentiated portfolio
Of both, pipeline and in-market products

<table>
<thead>
<tr>
<th>Oncology / Heme</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 NMEs + 8 AIs</td>
<td>tamelisib</td>
<td>atezolizumab</td>
<td>Avastin</td>
</tr>
<tr>
<td></td>
<td>venetoclax</td>
<td></td>
<td>Rituxan/MabThera</td>
</tr>
<tr>
<td></td>
<td>Cotellel</td>
<td></td>
<td>Herceptin</td>
</tr>
<tr>
<td></td>
<td>alectinib</td>
<td></td>
<td>Xeloda</td>
</tr>
<tr>
<td></td>
<td>ACE 910</td>
<td></td>
<td>Tarceva</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunology</th>
<th>1 NME + 5 AIs</th>
<th>lebrikizumab</th>
<th>Esbriet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>etrolizumab</td>
<td></td>
<td>Pulmozyme</td>
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<td></td>
<td></td>
<td></td>
<td>Xolair</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Ophthalmology</th>
<th>1 NME + 1 AI</th>
<th>lampalizumab</th>
<th>Actemra/RoActemra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lucentis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuroscience</th>
<th>5 NMEs</th>
<th>ocrelizumab</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>gantenerumab</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>crenezumab</td>
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<td></td>
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</tbody>
</table>

AI=additional indication; NME=new molecular entity
We pay great attention to upcoming launches … to guarantee broad access to our medicines

### Atezolizumab

**Targeting first line in a competitive space**

- Fast to market entry via biomarker and targeting first line

### Lebrikizumab

**Entering a new therapeutic area**

*Example: Specialists*

- Several companies launching in the coming years

### Ocrelizumab

**Entering a new therapeutic area**

*Example: MS Treatment Centers*

- Will be 13th brand entering MS

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Launching clearly differentiated medicines in a competitive market still requires adequate funding

*Source: Roche analysis*
Resources shifted to new & strategic products…
…while overall spend only increases slightly

Product Marketing and Medical Costs (2012 – 2015)
Roche’s strategy remains unchanged
Success hinges on excellence in innovation & execution

Data & analytics

☑️ R&D 2.0: Data to increase our R&D efficiency and identify innovative medicines

☑️ Data to personalize patient care
Data and analytics as key opportunity

*Improve R&D efficiency and patient care*

Roche is uniquely positioned: Pharma, Diagnostics, FMI

1. Diagnostics information
2. Clinical trial data
3. Real-world data

Analytics & Insights

- Smarter, more efficient R&D
- Improved access & patient care
Roche is uniquely positioned to participate
Our strategy as these trends evolve

- Ensure adoption into clinical practice
- Further drive personalized HC strategy

Data generation & analytics

- Push for (high) data standards
- Continue to expand our internal data mgmt & analytics capabilities

Smarter, more efficient R&D

- Further incorporate analytics in hypothesis generation
- Identify innovative ways to improve clinical trial designs

Improved access & patient care

- Leverage data to support access
- Ensure benefit/risk/cost are appropriately reflected
Roche’s strategy remains unchanged
Success hinges on excellence in innovation & execution

Increased efficiency

☑️ Identify innovative ways of working

☑️ Determine how to do more with less
We are innovating in the way we work (1)

Leveraging molecular information for trial design

Example umbrella studies

Cancer patients screened for a series of biomarkers and allocated to the best therapies within the trial architecture

Clear benefits

• Accelerated hypothesis generation

• Shortened trial timelines: faster testing for medicines & combinations

• Reduction of development costs

Examples: LUNG-MAP, MY PATHWAY
We are innovating in the way we work (2)
Replacing clinical trials with real world evidence

Situation

- EMA requested **evaluation of Kadcyla in a new group of patients**
- Recruitment to a new trial challenging due to the small population

Solution & Benefit

- 60 out of 2000 **patients with reduced heart function identified** in medical affairs database
- **Real world data substituted** for a clinical trial

Leveraging real world data saved CHF 5.4 m on clinical trial costs
We are also driving operational efficiencies (1)
*Select examples R&D*

**Lean Protocol Design**
Rethinking protocol design to reduce complexity

**Sourcing Strategy**
Outsourcing transactional clinical operations roles

**Partnerships**
Industry consortium (20 companies) to drive trial efficiency

*All programs implementing lean protocols*


*Other topics: Risk based monitoring, industry wide registries, etc.*

Resulting in ~100m per year in savings
We are also driving operational efficiencies (2)

Select examples Technical Operations

**Network efficiencies**

Improve capacity planning across the network & align to future needs

**Complexity reduction**

Remove >40% of all presentations by streamlining the EP¹ portfolio (<0.1% sales impact²)

**Continuous process improvement**

Implement lean principles, e.g. to decrease end-to-end cycle time by up to 50%³

---

Source: 1. Established Products  2. In 2016  3. For processes in scope
Roche’s strategy remains unchanged

Success hinges on excellence in innovation & execution

Outstanding talent

- Ensure talent development and retention
- Foster diversity to drive innovation
We are expanding and diversifying our talent base
Talent diversity as backbone of our strategy

Creating a great place to work …

... to expand our diverse talent base

Number of key positions

<table>
<thead>
<tr>
<th>Year</th>
<th>Female (%)</th>
<th>Male (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>32%</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>2012</td>
<td>37%</td>
<td>63%</td>
<td>100%</td>
</tr>
<tr>
<td>2013</td>
<td>40%</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>2014</td>
<td>41%</td>
<td>59%</td>
<td>100%</td>
</tr>
</tbody>
</table>

~20% increase in female representation over the years.
A selection of our talents are here today

**Sandra J. Horning**
- Chief Medical Officer & Head of Global Product Development
- Emerita professor of medicine at Stanford for more than two decades
- More than 35 years industry experience

**Bill N. Anderson**
- Head of Global Product Strategy
- Senior Vice President for the BioOncology Business Unit in the U.S.
- Before joining Genentech in 2006 as SVP of the Immunology and Ophthalmology Business Unit, Vice President of the Neurology Business Unit at Biogen Idec.

**Daniel Chen**
- Cancer Immunotherapy Franchise Head, Product Development Oncology
- Adjunct Clinical Faculty at Stanford University Cancer Center
- 10 years experience with Genentech

**Cathi Ahearn**
- Lifecycle Leader, Atezolizumab Lung and GU Cancers
- Senior Director, Global Product Strategy
- 15 years experience with Genentech
A selection of our talents are here today

Fermin Ruiz de Erenchun
• Global Head Biologic Strategy
• Lifecycle Leader Avastin
• 20 years experience with Roche

Garret Hampton
• Vice President, Oncology Biomarker Development & Companion Diagnostics
• Executive Director Translational Sciences at Celgene
• 20 years of industry experience; 6 years at Genentech

David Traub
• Lifecycle Leader Gazyva, MabThera/Rituxan
• Medical Director Oncology/Hematology
• 10 years experience with Roche

Cindy Perettie
• Vice President Global Product Strategy, Hematology, Genentech
• President of Global Development Innovations at Sarah Cannon Research Institute
• 10 years experience with Genentech
Despite some set-backs, Roche continues to stay ahead of the industry.

Note: Success rates calculated at the project/indication level for overlapping 5-year periods (9 data points between 2002-14) based on KMR data (with 13 Industry peers and Roche). From 2009 all Genentech projects are included; before that only those opted-in by Roche.
Achievements: Differentiation
Leading Breakthrough Therapy Designations

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>#</th>
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<tbody>
<tr>
<td>1</td>
<td>Roche</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>BMS</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Novartis</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Merck</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>GSK</td>
<td>5</td>
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<tr>
<td>5</td>
<td>JNJ</td>
<td>4</td>
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<tr>
<td>5</td>
<td>Pfizer</td>
<td>4</td>
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**Breakthrough Therapy Designations**

- **YTD 2015**
  - **Actemra** (Systemic sclerosis)
  - **Venetoclax** (R/R CLL 17p)
  - **Atezolizumab** (NSCLC)
  - **ACE 910** (Hemophilia)

- **2014**
  - **Esbriet** (IPF)
  - **Lucentis** (DR)
  - **Atezolizumab** (Bladder)

- **2013**
  - **Alectinib** (2L ALK+ NSCLC)
  - **Gazyva** (1L CLL)

Source: http://www.focr.org/breakthrough-therapies as at 2 November 2015; CLL=Chronic Lymphocytic Leukemia; NSCLC=Non-Small Cell Lung Cancer; IPF=Idiopathic Pulmonary Hypertension; DR=Diabetic Retinopathy
Achievements: Productivity

_Doubled number of projects at same costs_

Late stage development costs & number of projects

Excludes Chugai, pRED and gRED, Medical Affairs and PTD
Source: Roche internal development data
Positive outlook

Strong pipeline mitigates biosimilar impact

- NME launches: Venetoclax, Alectinib, Cotellic, Ocrelizumab, Atezolizumab, Lebrikizumab, ACE910, Lampalizumab
- Biosimilars: MabThera, Herceptin, Avastin
Roche Pharma Day 2015

Late-stage pipeline

Sandra Horning  |  Chief Medical Officer & Head of Development Pharmaceuticals Division
Late-stage development program
13 NMEs in late-stage development

NME=new molecular entity; Timeline indicates year of expected filing or pivotal data readout
Major line extension: 2016 (APHINITY; GOYA); 2017 (IMpower 1L lung cancer; GALLIUM)
Late-stage development program
Molecules covered in this section...

- alectinib
- Oncology/hematology
- 2015
- Herceptin + Perjeta
- Gazyva

- ocrelizumab
- Neuroscience
- 2016
- Atezolizumab + chemo
- Gazyva

- ACE910
- Ophthalmology
- 2017
- Atezolizumab
- Gazyva

- lampalizumab
- Immunology
- Post 2017
- Crenezumab
- Etrolizumab
- Gantenerumab
- Taselisib
# Alectinib in crizotinib-failed ALK+ NSCLC

*A novel best-in-class drug in lung cancer*

<table>
<thead>
<tr>
<th>NMEs</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Post 2017</th>
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<tr>
<td></td>
<td>alectinib</td>
<td>ocrelizumab</td>
<td>ACE910</td>
<td>gantenerumab</td>
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<td>crenezumab</td>
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<td>venetoclax</td>
<td>lebrikizumab</td>
<td>olesoxime</td>
<td>taselisib</td>
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<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td>etrolizumab</td>
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<tr>
<td>2016</td>
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</tr>
<tr>
<td>2017</td>
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<tr>
<td>Post</td>
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</table>

- **Herceptin** + **Perjeta**
- **Gazyva**
- **Gazyva**
- **atezolizumab + chemo**

**NSCLC** = non-small cell lung cancer
MoA: Alectinib (ALK inhibitor)
Inhibiting signaling of ALK fusion proteins

Alectinib, next generation, highly selective brain penetrant ALK inhibitor

MOA=mechanism of action; NSCLC=non-small cell lung cancer; Xalkori® (crizotinib)
Alectinib in ALK+ NSCLC after crizotinib failure
Strong efficacy with excellent CNS disease control

Phase II US and Global Studies

- High systemic and CNS response rates in crizotinib-failed patients
- Median PFS: 8.1m (US), 8.9m (global)
- Median DOR: 13.5m (US), 14.1m (global)
- Favourable safety and tolerability with minimal dose modification
- Filed in the US/EU in Q3

ORR=overall response rate; CR=complete responses; CNS=central nervous system; PFS=progression free survival; DOR=duration of response; Shaw A. et al, WCLC 2015; Barlesi F. et al, ESMO/ECC 2015
Development plan: Alectinib
1L setting and immunotherapy combinations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Study name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>alectinib*</td>
<td>ALEX</td>
<td>1L ALK+ NSCLC</td>
<td></td>
</tr>
<tr>
<td>alectinib</td>
<td>AF-001JP</td>
<td>crizotinib-naive ALK+ NSCLC</td>
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<tr>
<td>alectinib</td>
<td>AF-002JG/NP28761 (US)</td>
<td>crizotinib-failed ALK+ NSCLC</td>
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<tr>
<td>alectinib</td>
<td>ACCALIA/NP28673 (global)</td>
<td>crizotinib-failed ALK+ NSCLC</td>
<td></td>
</tr>
<tr>
<td>alectinib</td>
<td>+atezolizumab</td>
<td>NSCLC</td>
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= filed

atezolizumab (aPD-L1 mAb); NSCLC=non-small cell lung cancer; * in collaboration with Chugai
**Cotellic+Zelboraf in BRAF^{V600}+ melanoma**

*A competitive combination in melanoma*

**NMEs**

- alectinib
- ocrelizumab
- ACE910
- crenezumab
- gantenerumab
- venetoclax
- atezolizumab
- lampalizumab
- taselisib
- etrolizumab
- lebrikizumab
- olesoxime
- Herceptin + Perjeta
- Gazyva
- Gazyva

**Year**

- 2015
- 2016
- 2017
- Post 2017

- **Cotellic**
- **Herceptin + Perjeta**
- **Gazyva**

- **A competitive combination in melanoma**
MoA: Zelboraf (BRAFi)+Cotellic (MEKi)  
Inhibiting mutant BRAF and MEK in parallel

• BRAF mutations lead to uncontrolled signaling and cell proliferation in the absence of any growth factors
• Zelboraf targets mutated BRAFV600 and blocks downstream MEK/ERK signaling

• Most common mechanism of acquired resistance to Zelboraf is ERK reactivation through alternative MEK signaling
• Cotellic (cobimetinib) is an inhibitor of MEK which prevents ERK reactivation

MOA=mechanism of action; Zelboraf (vemurafenib); Cotellic (cobimetinib)  
http://www.biooncology.com
Cotellic+Zelboraf in melanoma

*Update confirms benefit in BRAF$^{V600+}$ patients*

**Progression free survival**

<table>
<thead>
<tr>
<th></th>
<th>Zelboraf + Cotellic (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>

**coBRIM phase III results:**

- OS endpoint met (data to be presented at SMR conference)
- Median PFS ~1 year with 14m follow-up
- Filed in US and EU

Cotellic (cobimetinib); ORR=overall response rate; CR=complete response; PFS=progression free survival; DoR=duration of response; OS=overall survival; SMR=society for melanoma research; Larkin J. *et al*, ASCO 2015
Development plan: Cotellic & melanoma franchise

*Triple combination started with atezolizumab*

<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>Cotellic</td>
<td>+Zelboraf*</td>
<td>coBRIM</td>
<td>1L mM BRAFV600+</td>
<td>⊗</td>
<td>⊗</td>
<td>✓</td>
</tr>
<tr>
<td>Cotellic</td>
<td>+atezolizumab</td>
<td></td>
<td>KRASmut+ mM, NSCLC, CRC</td>
<td>⊗</td>
<td>⊗</td>
<td></td>
</tr>
<tr>
<td>Cotellic</td>
<td>+atezolizumab+Zelboraf</td>
<td></td>
<td>1L mM BRAFV600+</td>
<td>⊗</td>
<td>⊗</td>
<td></td>
</tr>
<tr>
<td>Cotellic</td>
<td>+paclitaxel</td>
<td></td>
<td>TNBC</td>
<td>⊗</td>
<td></td>
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</tr>
<tr>
<td>Cotellic</td>
<td>+duligotuzumab</td>
<td></td>
<td>KRAS+ solid tumors</td>
<td>⊗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotellic</td>
<td>+ERK inhibitor**</td>
<td></td>
<td>Solid tumors</td>
<td>⊗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotellic</td>
<td>+idasanutlin</td>
<td></td>
<td>Solid tumors</td>
<td>⊗</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓ = filed

= trial starting in coming quarters

---

Cotellic (cobimetinib); atezolizumab (aPD-L1 mAb); duligotuzumab (HER3/EGFR biMab; RG7597); ERKinhibitor (RG7842); SMR=society for melanoma research; *in collaboration with Plexxikon (Daiichi Sankyo Group); **in collaboration with Array BioPharma
**Venetoclax in R/R CLL with 17p deletion**

*A unique Bcl-2 inhibitor with significant upside*

<table>
<thead>
<tr>
<th>NMEs</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Post 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>alectinib</td>
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<td>taselisib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>etrolizumab</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herceptin + Perjeta</td>
<td>atezolizumab + chemo</td>
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</tr>
<tr>
<td>Gazyva</td>
<td></td>
<td>Gazyva</td>
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</tr>
</tbody>
</table>

Venetoclax in R/R CLL with 17p deletion:

- A unique Bcl-2 inhibitor with significant upside.

**Key Points**:

- **2015**: Venetoclax
- **2016**: A unique Bcl-2 inhibitor with significant upside
- **2017**: Further advancements and extensions
- **Post 2017**: Ongoing research and developments
MoA: Venetoclax* (Bcl-2 inhibitor)

Starting apoptosis through the apoptosome

Product profile

- Venetoclax designed to selectively bind and inhibit Bcl-2
- Inhibiting Bcl-2 releases pro-apoptotic proteins, which trigger apoptosis through the apoptosome

MOA=mechanism of action; * venetoclax in collaboration with AbbVie
http://www.biooncology.com
Venetoclax+BR in R/R NHL

Early and long lasting responses

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>R/R aNHL (n=11)</th>
<th>R/R FL (n=21)</th>
<th>R/R Marginal Zone Lymphoma (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>5 (45)</td>
<td>15 (71)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (9)</td>
<td>6 (29)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (36)</td>
<td>9 (43)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (18)</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (36)</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discontinued (no assessment)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Phase I preliminary results:

- Early and long-lasting responses were seen across dose cohorts in heavily pre-treated patients
- Preliminary data demonstrate a tolerable safety profile of venetoclax+BR
- Phase II (CONTRALTO) started in R/R FL (iNHL)
- Phase II (CAVALLI) started in 1L DLBCL (aNHL)

BR=bendamustin/Rituxan; R/R aNHL=relapsed/refractory aggressive non-hodgkin’s lymphoma (R/R DLBCL); R/R FL=relapsed/refractory follicular lymphoma; iNHL=indolent NHL; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; de Vos S. et al, presented at International Conference on Malignant Lymphoma Lugano, Jun 2015; data cut-off April 2nd
Venetoclax+Rituxan in R/R CLL

Deep responses in the majority of patients

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>R/R CLL (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>41 (84)</td>
</tr>
<tr>
<td>CR (includes 6 CRi)</td>
<td>20 (41)</td>
</tr>
<tr>
<td>PR/nodular PR</td>
<td>21 (43)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (10)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Bone marrow MRD-negative</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Bone marrow MRD-positive</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Bone marrow MRD not evaluable</td>
<td>9 (18)</td>
</tr>
</tbody>
</table>

**Phase Ib results:**
- ORR of 84% including 41% CR/CRi
- 49% of patients are MRD negative
- Well tolerated with no new toxicities
- Phase III (MURANO) started in R/R CLL
- Phase III (CLL14) started in 1L CLL

R/R CLL=relapsed/refractory chronic lymphoid leukemia; ORR=overall response rate; CR=complete response; CRi=CR with incomplete blood count recovery; PR=partial response; SD=stable disease; PD=progressive disease; MRD=minimal residual disease; Roberts. *et al,* presented at EHA 2015.
### Development plan I: Hematology franchise

**8 NMEs 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><strong>NHL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gazyva</td>
<td>+bendamustine</td>
<td>GADOLIN</td>
<td>iNHL (Rituxan refractory)</td>
<td>☑️</td>
<td>☑️</td>
<td>☑️</td>
</tr>
<tr>
<td>Gazyva</td>
<td>+CHOP</td>
<td>GOYA</td>
<td>aNHL</td>
<td></td>
<td></td>
<td>☑️</td>
</tr>
<tr>
<td>Gazyva</td>
<td>+chemo</td>
<td>GALLIUM</td>
<td>1L iNHL</td>
<td></td>
<td>☑️</td>
<td>☑️</td>
</tr>
<tr>
<td>Gazyva</td>
<td>+FC/bendamustin/Clb</td>
<td>GREEN</td>
<td>CLL and R/R CLL</td>
<td>☑️</td>
<td>☑️</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>CLL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax*</td>
<td>+Rituxan/+Rituxan +bendamustine</td>
<td>CONTRALTO</td>
<td>R/R FL (iNHL)</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan +CHOP/Gazyva +CHOP</td>
<td>CAVALLI</td>
<td>1L aNHL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan +bendamustine</td>
<td></td>
<td>R/R NHL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td></td>
<td></td>
<td>R/R CLL and R/R NHL</td>
<td></td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan</td>
<td></td>
<td>R/R CLL and SLL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Gazyva</td>
<td>CLL14</td>
<td>R/R CLL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan</td>
<td>MURANO</td>
<td>R/R CLL 17p</td>
<td>☑️</td>
<td>☑️</td>
<td>☑️</td>
</tr>
<tr>
<td>venetoclax</td>
<td></td>
<td></td>
<td>R/R CLL after ibru/idel</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan +bendamustine</td>
<td></td>
<td>R/R CLL and CLL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Gazyva</td>
<td></td>
<td>R/R CLL and CLL</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
<tr>
<td><strong>MM</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>venetoclax</td>
<td>+bortezomib+dexamethasone</td>
<td></td>
<td>R/R MM</td>
<td>☑️</td>
<td>☑️</td>
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</tr>
<tr>
<td><strong>AML</strong></td>
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<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+decitabine/+azacitidine/+LdAraC</td>
<td></td>
<td>AML</td>
<td>☑️</td>
<td>☑️</td>
<td></td>
</tr>
</tbody>
</table>

- **NME** = new molecular entity; **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; **LdAraC** = low dose cytarabine; * venetoclax in collaboration with AbbVie
# Development plan II: Hematology franchise

8 NMEs 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>polatuzumab*</td>
<td>+Rituxan/Gazyva</td>
<td>ROMULUS</td>
<td>R/R FL and aNHL</td>
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<td></td>
<td></td>
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<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>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+CHP/Rituxan+CHP</td>
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<td>1L aNHL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+lenalidomide</td>
<td></td>
<td>R/R FL and aNHL</td>
<td>Q4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>polatuzumab</td>
<td>+Gazyva+venetoclax</td>
<td></td>
<td>R/R FL and aNHL</td>
<td>Q4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>undisclosed ADC</td>
<td></td>
<td></td>
<td>R/R NHL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atezolizumab</td>
<td>+Gazyva</td>
<td></td>
<td>R/R FL (iNHL) and aNHL</td>
<td></td>
<td></td>
<td>Q4</td>
</tr>
<tr>
<td>atezolizumab</td>
<td>+Gazyva+lenalidomide</td>
<td></td>
<td>R/R FL and aNHL</td>
<td></td>
<td></td>
<td>Q4</td>
</tr>
<tr>
<td>atezolizumab</td>
<td>+CHOP</td>
<td></td>
<td>aNHL</td>
<td></td>
<td>Q4</td>
<td></td>
</tr>
<tr>
<td>atezolizumab</td>
<td>+bendamustine</td>
<td></td>
<td>R/R FL and aNHL</td>
<td></td>
<td>Q4</td>
<td></td>
</tr>
<tr>
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<td>+Gazyva+polatuzumab</td>
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<td>MM</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>atezolizumab</td>
<td>+azacitidine</td>
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<td>MDS</td>
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<tr>
<td>aCD20/CD3 biMab</td>
<td></td>
<td></td>
<td>Heme tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSD1 inhibitor**</td>
<td></td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>idasanutlin</td>
<td></td>
<td></td>
<td>Heme tumors</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

= additional trials starting in coming quarters

polatuzumab vedotin (aCD79b ADC); atezolizumab (aPD-L1 MAb); aCD20/CD3 biMAb (RG7828); LSD1 inhibitor (RG6016); idasanutlin (MDM2 antagonist); iNHL=indolent non-hodgkin’s lymphoma; R/R FL=relapsed/refractory follicular lymphoma; aNHL=agressive NHL (DLBCL); MM=multiple myeloma; MDS=myelodysplastic syndrom; AML=acute myeloid leukemia; *in collaboration with Seattle Genetics; ** in collaboration with Oryzon Genomics
Ocrelizumab in multiple sclerosis

*First drug active in both RMS & PPMS*

<table>
<thead>
<tr>
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<td>Taselisib</td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>lebrikizumab</td>
<td>Olesoxime</td>
<td>Etrolizumab</td>
<td></td>
</tr>
<tr>
<td><strong>2015</strong></td>
<td><strong>2016</strong></td>
<td><strong>2017</strong></td>
<td><strong>Post 2017</strong></td>
<td></td>
</tr>
<tr>
<td>Herceptin + Perjeta</td>
<td>Atezolizumab + chemo</td>
<td><strong>Gazyva</strong></td>
<td><strong>Gazyva</strong></td>
<td></td>
</tr>
</tbody>
</table>

RMS=relapsing forms of multiple sclerosis (MS) which includes patients with RRMS and SPMS with superimposed relapses; PPMS=primary progressive MS
MoA Ocrelizumab (humanized anti-CD20 MAb)

Results confirm central role of B cells in MS

Product profile
- Humanised anti-CD20 antibody
- Selective depletion of a B cell subset leaving the ability to generate new B cells intact
- Administered IV twice yearly

MOA=mechanism of action; RMS=relapsing forms of multiple sclerosis (MS) which includes patients with RRMS and SPMS with superimposed relapses; RRMS=relapsing-remitting MS; SPMS=secondary progressive MS; PPMS=primary progressive MS; IV=intravenous; Adapted from Lublin 1996, Arnold 2004
Ocrelizumab in RMS
Superior efficacy, similar safety to Rebif®

<table>
<thead>
<tr>
<th>Study Endpoint</th>
<th>Relative Risk Reduction versus Rebif®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPERA I</td>
</tr>
<tr>
<td>1 EP ARR</td>
<td>-46%</td>
</tr>
<tr>
<td>Key 2 EP</td>
<td></td>
</tr>
<tr>
<td>CDP (12 wks)</td>
<td>-43%</td>
</tr>
<tr>
<td>CDP (24 wks)</td>
<td>-43%</td>
</tr>
<tr>
<td>T1 Gd-enhancing lesions</td>
<td>-94%</td>
</tr>
<tr>
<td>New and/or enlarging T2 lesions</td>
<td>-77%</td>
</tr>
</tbody>
</table>

**OPERA I/II results**

- Ocrelizumab superior to Rebif® (interferon beta-1a) in substantially reducing the three major markers of disease activity:
  - Annualized relapse rate
  - Confirmed Disability Progression for both 12 and 24 weeks
  - MRI outcomes of brain inflammation and damage
- Similar safety to interferon beta-1a over the two-year controlled treatment period

RMS=relapsing forms of multiple sclerosis; ARR=annualized relapse rate; CDP=confirmed disability progression; MRI=magnetic resonance imaging; IFN=interferon; *Adjusted ARR calculated by negative binomial regression and adjusted for baseline EDSS score (<4.0 vs ≥4.0), and geographic region (US vs ROW); EDSS=expanded disability status scale
Ocrelizumab in PPMS
*First positive efficacy outcome*

<table>
<thead>
<tr>
<th>Study Endpoint</th>
<th>Relative Risk Reduction versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORATORIO</td>
<td></td>
</tr>
<tr>
<td>1 EP</td>
<td></td>
</tr>
<tr>
<td>CDP (12 wks)</td>
<td>24%</td>
</tr>
<tr>
<td>CDP (24 wks)</td>
<td>25%</td>
</tr>
<tr>
<td>Timed 25-foot walk (baseline to wk 120)</td>
<td>29%</td>
</tr>
<tr>
<td>Key 2 EP</td>
<td></td>
</tr>
<tr>
<td>T2 lesion volume (baseline to wk 120)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Whole brain volume (wk 24 to wk 120)</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

**Key**

- **EP**: Endpoint
- **CDP**: Confirmed Disability Progression

**ORATORIO results:**

- Data establishes role of B cells in PPMS
- Significant risk reductions on primary and key secondary endpoints
- Favourable safety profile: Serious infections similar to placebo during a mean treatment duration of 3 years

**Time to 12-week Confirmed Disability Progression**

- Placebo (n=244)
- Ocrelizumab 600mg (n=488)

*24% reduction in risk of CDP HR: 0.76; p=0.0321*

**PPMS**=primary progressive multiple sclerosis; **CDP**=confirmed disability progression
# Lebrikizumab in asthma

*First-in-class molecule in an expanding market*

<table>
<thead>
<tr>
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<td>etrolizumab</td>
</tr>
<tr>
<td>venetoclax</td>
<td><strong>lebrikizumab</strong></td>
<td>olesoxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2015</strong></td>
<td><strong>2016</strong></td>
<td><strong>2017</strong></td>
<td><strong>Post 2017</strong></td>
<td></td>
</tr>
<tr>
<td>Herceptin + Perjeta</td>
<td>Gazyva</td>
<td>atezolizumab + chemo</td>
<td>Gazyva</td>
<td></td>
</tr>
<tr>
<td><strong>line extensions</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
MoA: Lebrikizumab (anti-IL13 MAb)
Inhibiting IL-13 in type 2 asthma patients

Product profile

- First-in-class aIL13 MAb with potential for broader efficacy than aIL5 MAbs
- High unmet need in severe uncontrolled asthma
- Periostin as potential biomarker of exacerbation risk and lung function decline
- Establish strong efficacy profile in patients with high periostin or high eosinophils (biomarkers of type 2 inflammation)
- Targeted for safety and efficacy by inhibiting IL13 only vs blocking IL4/13 which may reduce immune defense

MOA=mechanism of action; IL=interleukin
Lebrikizumab in severe uncontrolled asthma
High efficacy and improved convenience

Summary phase II results:

• Exacerbation reduction of 60%
• Early onset of lung function improvement (FEV1)
• Prefilled syringe and Q4W subcutaneous delivery for improved convenience

Q4W = monthly dosing; FEV= forced expiratory volume; LUTE/VERSE results presented at AAAAI 2014; Thomas NC. et al., Biologics 2012; Hanania NA. et al., Thorax 2015
## Development plan: Lebrikizumab

*Programs in asthma, IPF, atopic dermatitis and COPD*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year</th>
<th>Study</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe uncontrolled asthma Adults</td>
<td>2015</td>
<td>LAVOLTA I/II</td>
<td>Phase III</td>
</tr>
<tr>
<td>Mild to moderate asthma Adults</td>
<td>2016</td>
<td>STRETTO</td>
<td>Phase III</td>
</tr>
<tr>
<td>Severe uncontrolled asthma Adolescents</td>
<td>2017</td>
<td>ACOUSTICS</td>
<td>Phase III</td>
</tr>
<tr>
<td>Asthma Adults (OCS-sparing)</td>
<td>2018</td>
<td>VOCALS</td>
<td>Phase II</td>
</tr>
<tr>
<td>Asthma Biomarker</td>
<td></td>
<td>CLAVIER</td>
<td>Phase I</td>
</tr>
<tr>
<td>IPF Mono and lebrikizumab+Esbriet</td>
<td></td>
<td>RIFF</td>
<td>Phase III</td>
</tr>
<tr>
<td>Moderate to severe atopic dermatitis</td>
<td></td>
<td>TREBLE</td>
<td>Phase II</td>
</tr>
<tr>
<td>Moderate to severe atopic dermatitis</td>
<td></td>
<td>ARBAN</td>
<td>Phase III</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td>VALETA</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Q4W=monthly dosing; PK=pharmacokinetic study; IPF=idiopathic pulmonary fibrosis; COPD=chronic obstructive pulmonary disease; OCS=oral corticosteroid
ACE910 in hemophilia A
A game changing molecule with a unique mechanism

- alectinib
- Cotellic
- venetoclax
- ocrelizumab
- atezolizumab
- lebrikizumab
- ACE910
- lampalizumab
- etrolizumab
- gantenerumab
- crenezumab
- taselisib

Year
- 2015
- 2016
- 2017
- Post 2017

- Herceptin + Perjeta
- Gazyva
- atezolizumab + chemo
- Gazyva

line extensions

NMEs
MoA: ACE910* (anti-FIXa/FX bispecific MAb) 
Mimicking FVIIIa in blood clotting

1. Normal clotting pathway: FVIIIa enables FIXa/FX interaction

2. ACE910 supports FIXa/FX interaction

Product profile
- Weekly to monthly SC dosing (Half-life of 28 to 34 days)
- No neutralizing antibodies to ACE910 in phase I study
- No potential to induce FVIII inhibitors
- Works in presence of FVIII inhibitors

ACE910 in Hemophilia A

Extension study confirms excellent efficacy

**Phase I results:**
- 95% to 100% ABR reduction in inhibitor and non-inhibitor patients
- No thromboembolic AEs when given with rFVIII
Development plan: ACE910
Changing the standard of care in hemophilia A

Japanese studies Chugai
Inhibitor Non-interventional
Inhibitor (≥12 yrs) Weight based QW dosing
Non-inhibitor (≥12 yrs) Weight based QW and Q2W dosing
Pediatrics Inhibitor
(Q4W dosing study planned)

2015
2016
2017
2018

OLE

Phase I
Phase II
Phase III
Patient transfer

QW=weekly dosing; Q2W= dosing every 2 weeks; Q4W=monthly dosing; PK=pharmacokinetic study; OLE=open label extension
Lampalizumab in geographic atrophy
A unique Factor D inhibitor for a high unmet need

- alectinib
- Cotellic
- venetoclax
- ocrelizumab
- atezolizumab
- lebrikizumab
- ACE910
- lampalizumab
- gantenerumab
- crenezumab
- taselisib
- etrolizumab

- Herceptin + Perjeta
- Gazyva
- atezolizumab + chemo
- Gazyva
- Post 2017
MoA: Lampalizumab (anti-FactorD MAb)

Blocking the alternative complement pathway

MoA=mechanism of action
MoA: Lampalizumab (anti-FactorD MAb)
Blocking the alternative complement pathway
Lampalizumab in geographic atrophy

First phase II study with positive results in GA

**MAHALO phase II results:**

- 20% reduction in GA area progression in all-comers
- 44% reduction in GA area progression in CFI+ patients
- CFI+ patients appeared to progress faster compared to CFI- patients

GA=geographic atrophy; CFI=complement factor I biomarker; *Based on mITT population with last observation carried forward data. Adjusted mean is the least squares mean from the stratified analysis of variance model adjusted for baseline GA. Vertical bars are ±1 standard error of the least squares mean; **Not adjusted for multiplicity. Vertical bars are 95% CI of the least squares mean.
Development plan: Lampalizumab

Phase III studies reading out in 2017

GA=geographic atrophy; OLE=open label extension
Gantenerumab and crenezumab in AD
Two shots on a high-risk high-reward goal

AD=alzheimer’s disease
MoA: Gantenerumab/crenezumab (anti-Αβ MAbs)

Inhibiting different species of Aβ in the brain

**Amyloid pathway and targets**

Disease involvement of Aβ oligomerization & plaque formation:

- Mutations in the amyloid precursor protein can protect against AD\(^1\) or increase AD susceptibility\(^2\)
- Aggregated Aβ plaques have been shown to be neurotoxic\(^3\)

Development plan: Crenezumab & Gantenerumab

Dose escalation to inform phase III development

---

**Phase I**
- **Crenezumab**
  - Phase Ib safety
  - (Phase III planned)
  - (Phase III tbd)
- **Gantenerumab**
  - DIAN-TU (autosomal dominant AD)
  - Scarlet RoAD
  - Marguerite RoAD
  - (Phase III tbd)

**Phase II**
- **Crenezumab**
- **Gantenerumab**

**Phase III**
- **Crenezumab**
- **Gantenerumab**

**OLE**
- **Crenezumab**
- **Gantenerumab**

**Gated decision**
- **Crenezumab**
- **Gantenerumab**

---

AD = alzheimer’s disease; OLE = open label extension; tbd = to be decided
Late-stage development program
A new kinase inhibitor in late-stage

<table>
<thead>
<tr>
<th>NMEs</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Post 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcensa/alectinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotellic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ocrelizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atezolizumab</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>lebrikizumab</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACE910</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lampalizumab</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>olesoxime</td>
<td></td>
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</tr>
<tr>
<td>etrolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gantenerumab</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>crenezumab</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>taselisib</td>
<td></td>
<td></td>
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<tr>
<td>Herceptin + Perjeta</td>
<td></td>
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<tr>
<td>Gazyva</td>
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<td></td>
</tr>
<tr>
<td>atezolizumab + chemo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gazyva</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
MoA: Taselisib (PI3K inhibitor)

Mutant-selective PI3 kinase inhibitor

Product profile

- PI3K-alpha mutations present in many cancers
- Taselisib was designed to specifically bind the ATP-binding pocket of mutated PI3K thereby preventing Akt signaling leading to cell growth and inhibition of apoptosis
- Mutant-selective PI3K inhibitors are expected to show greater target inhibition with fewer adverse events

MoA = mechanism of action; PI3K = phosphatidylinositol 3-kinase
http://www.biooncology.com
Development plan: Taselisib

First phase III started in HER2-/ER+ breast cancer

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Study name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>tasilisib</td>
<td>+fulvestrant</td>
<td>SANDPIPER</td>
<td>2L HER2-/ER+ mBC</td>
</tr>
<tr>
<td>tasilisib</td>
<td>+letrozole</td>
<td>LORELEI</td>
<td>Neoadjuvant HER2-/ER+ BC</td>
</tr>
<tr>
<td>tasilisib</td>
<td>+letrozole/fulvestrant</td>
<td></td>
<td>HER2-/HR+ BC</td>
</tr>
<tr>
<td>tasilisib</td>
<td>+docetaxel/paclitaxel</td>
<td></td>
<td>HER2-/HR+ locally recurrent or mBC</td>
</tr>
<tr>
<td>tasilisib</td>
<td></td>
<td>Lung-MAP</td>
<td>Pi3KCAmut+ 2L+ sq NSCLC</td>
</tr>
</tbody>
</table>

Sq NSCLC=squamous non-small cell lung cancer; mBC=metastatic breast cancer; ER=estrogen receptor; HR=hormone receptor
Etrolizumab in inflammatory bowel disease

A highly differentiated molecule in a growing market
MoA: Etrolizumab (anti-β7 integrin mAb)
Gut-selective dual MoA with no expected CNS effect

**Product profile**
- Selectively blocking lymphocyte trafficking and retention in the gut
- No impact on lymphocyte trafficking in the CNS

MoA=mechanism of action; CNS=central nervous system
Etrolizumab in ulcerative colitis

**Compelling remission rates**

**EUCALYPTUS phase II results:**

- 44% remission reduction in TNF-naive patients
- Biomarker: αEβ7 may predict remission rate in TNF-naive patients

TNF=interferon-alpha; TNF-IR=interferon-alpha intolerant/refractory; αE=Integrin αE β7; qPCR=quantitative polymerase chain reaction; MCS=Mayo Clinic Score, using central endoscopy reading; *~10% and 40% of patients were missing qPCR and IHC data; Vermeire S. et al., Lancet 2014
Development plan: Etrolizumab

Programs in ulcerative colitis and Crohn`s disease

1L = TNF naive
2L = TNF intolerant/refractory

TNF=interferon alpha; UC=ulcerative colitis; CD=crohn`s disease
Late-stage development program
80% of NMEs developed with companion diagnostics

NMEs developed along with companion diagnostic
Late-stage development program
Differentiated by mechanism of action (MoA)

- alectinib
- ocrelizumab
- ACE910
- gantenerumab
- crenezumab
- taselisib
- etrolizumab
- venetoclax
- atezolizumab
- lampalizumab
- olesoxime
- lebrikizumab
- Gazyva
- Herceptin + Perjeta
- atezolizumab + chemo
- Gazyva
- Gazyva

- best-in-class profile
- highly differentiated MoA from class competition
- no class competition (unique MoA)
- breakthrough therapy designation
**Newsflow in H2 2015**

Vienna, 25 -29 Sep
- **atezolizumab (+chemo)**
  - NSCLC: POPLAR, BIRCH, P1b chemo combo update
  - Bladder: P2 (2L cohort)
- **alectinib**
  - ALK+ NSCLC: P2 update
- **CEA-IL2v FP; IDOi**
  - solid tumors: P1 updates

Barcelona, 7-10 Oct
- **ocrelizumab**
  - RMS: P3 OPERA I/II
  - PPMS: P3 ORATORIO

San Francisco, 18-21 Nov
- **atezolizumab + Zelboraf**
  - mM: P1
- **Cotellic + Zelboraf**
  - BRAF+mM: coBRIM OS data

San Antonio, 19-22 Nov
- **atezolizumab**
  - GBM: P1

San Antonio, 8-12 Dec
- **Atezolizumab + chemo**
  - TNBC: P1b abraxane combo

**Presentations planned**
Roche Pharma Day 2015
Cancer Immunotherapy

Daniel S. Chen | Cancer Immunotherapy Franchise Head
Product Development, Genentech/Roche
Immunotherapy is changing the face of cancer treatment

**Understanding of the biology has reached an inflection point**

...translating into remarkable benefit for patients

Response in NSCLC to atezolizumab monotherapy

Anti-CTLA4 (ipilimumab)
Melanoma

Pooled OS (1861 patients)
Median OS, months (95% CI): 11.4 (10.7–12.1)
3-year OS rate, % (95% CI): 22 (20–24)

Schadendorf et al (2015) JCO
Intense industry effort resulted in demonstrated benefit in a large number of tumor types

- Melanoma
- Bladder
- Lymphoma
- Breast cancer
- Gastric cancer
- Cervical cancer
- Ovarian cancer
- Glioblastoma
- Lung cancer
- Renal cancer
- Head and neck cancer
- Pancreatic cancer
- Colorectal cancer
- Cervical cancer
- Renal cancer
- Bladder

>20 companies

>30 CIT targets

>400 studies

~$4bn in R&D*

Internal estimates
CIT=cancer immunotherapy; *Annual spend
## Significant complexity remains

### Scientific
- Each tumor with distinct immune biology
- Patients with the same tumor type respond differently
- Pre-clinical models poorly predict efficacy in humans

### Clinical
- New endpoints needed to detect benefit of CIT agents
- Achieve synergies through combination regiments
- Combination toxicity not predictable

### Commercial
- Market becoming more competitive
- New pricing models needed for combination regimens
- Treatment paradigm changes requires continuous education for physicians
Traditional drug development

Linear development approach is not suited to address these challenges

Generate Hypothesis

Test Hypothesis

Verify Hypothesis

Launch

Research

Early Development

Late Development

Marketing
Cancer immunotherapy committee (CITC)
Focused on knowledge exchange, speed and efficiency

**Research**
Better understand the underlying immune response to tumor cells

**Clinical**
Design studies demonstrating program activity and informing immune system biology

**Biomarker Data / Biological Insights**

*Targets, Drugs and Combinations*

- Development Strategy
- Biomarkers
- Market Insights
- Scientific Understanding
CITC contributing to advancement of the field

Selecting patients

Improving outcomes

Improving SoC

Tumor cells (TCs)

Immune cells (ICs)

Tumor and immune cells (TCs and ICs)

Bladder cancer

Lung cancer

NSCLC (TC3 or IC3)

\[ HR^2 = 0.49 \ (0.22, 1.07) \]

\[ P \text{ value} = 0.068 \]

Median 15.5 mo (9.8, NE)

Median 11.1 mo (6.7, 14.4)

Median follow up: 7 mo (range, 0–11 mo), 142 events

Bladder cancer

Overall Survival

ORR = 50.0% (4/8)

ORR = 76.5% (13/17)

ORR = 56.3% (9/16)
Leveraging basic science to identify and prioritize innovative therapies

Patient subgroups

- RCC: 59%, 15% IC>1%, 2% TC>1%
- UBC: 68%, 22% IC>1%, 1% TC>1%
- NSCLC: 57%, 38% IC>1%, 11% TC>1%
- TNBC: 58%, 1% IC>1%, 3.5% TC>1%

Novel targets

- Effector T cell
- TCR
- Antigen Presenting Cell
- Ox40
- Ox40L
- IFN-γ
- aCSF-1R
- aCEA-IL2v FP
- aCEA/CD3 TCB

Combinations

- Anti-OX40
- aPD-L1
- aPD-L1 + Chemo
- combo
POPLAR: Overall survival by PD-L1 subgroups

Efficacy increasing with higher PD-L1 expression

<table>
<thead>
<tr>
<th>Subgroup (% of enrolled patients)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT (N = 287)</strong></td>
<td></td>
</tr>
<tr>
<td>TC0 and IC0 (32%)</td>
<td>9.7 (6.7, 12.0)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (68%)</td>
<td>15.5 (11.0, NE)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (37%)</td>
<td>15.1 (8.4, NE)</td>
</tr>
<tr>
<td>TC3 or IC3 (16%)</td>
<td>15.5 (9.8, NE)</td>
</tr>
<tr>
<td><strong>Atezolizumab</strong></td>
<td></td>
</tr>
<tr>
<td>n = 144</td>
<td>9.7 (8.6, 12.0)</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
</tr>
<tr>
<td>n = 143</td>
<td>11.1 (6.7, 14.4)</td>
</tr>
</tbody>
</table>

Atezolizumab: Doubled likelihood of survival in PD-L1-high tumors (IC2/3 or TC2/3)
POPLAR: PD-L1/PD-1 ligand and receptor family members predict clinical benefit in NSCLC

**PD-L1**
- **OS HR: 0.46** (95%CI: 0.27 – 0.78)

**PD-1**
- **OS HR: 0.43** (95%CI: 0.24 – 0.76)

**B7.1**
- **OS HR: 0.44** (95%CI: 0.26 – 0.77)

**PD-L2**
- **OS HR: 0.39** (95%CI: 0.22 – 0.69)
Comprehensive biomarker effort
Cornerstone of our R&D strategy

**DNA-mutation & CNVs**
Ex: EGFR, BRAF
DNA sequencing

**mRNA-expression**
Cell signatures, targets
RNA sequencing

**Protein-expression**
PDL1, other CI targets
Multiplex IHC

**Cell free tumor DNA**
Ex: EGFR, BRAF
Blood DNA sequencing

**Imaging**
Ex: ImmunoPET
Imaging

---

**To advance science**

---

**To aid development**

---

**To improve patient care**

---
Unlocking full value of immunotherapy through combinations

**Broadest industry portfolio in oncology**

**Antigen presentation**
- T-Vec oncolytic viruses* (Amgen)
- INFα
- anti-CD40
- CMB305 vaccine* (Immune Design)

**Antigen release**
- EGFRi (Tarceva)
- ALKi (Alectinib)
- BRAFi (Zelboraf)
- MEKi (Cotellic)
- anti-CD20 (Gazyva)
- anti-HER2 (Herceptin; Kadcyla; Perjeta)
- various chemotherapies
- lenalidomide*
- rociletinib* (Clovis)

**Priming & activation**
- anti-CEA-IL2v FP
- anti-OX40
- anti-CD27* (Celldex)
- entinostat* (Syndax)

**T cell Trafficking**

**T cell infiltration**
- anti-VEGF (Avastin)
- anti-Ang2/VEGF (vanucizumab)

**Cancer T cell recognition**
- anti-CEA/CD3 TCB
- anti-CD20/CD3 TCB
- anti-HER2/CD3 TCB
- ImmTAC* (Immunocore)

**T cell killing**
- anti-PDL1 (atezolizumab)
- anti-CSF-1R (emactuzumab)
- IDOi (NewLink)
- IDOi* (Incyte)
- CPI-444* (Corvus)
- anti-TIGIT
- IDO1/TDOI* (Curadev)
Chemotherapy combinations
Creation of the favourable immune profile

**Pre-clinical data**

**Tumor CD8+ (T cells)**

**Platinum doublet 1**

**Platinum doublet 2**

**On-treatment biopsy**

**Pre-treatment**

**Post FOLFOX**
Chemotherapy combination in NSCLC

Atezolizumab and a standard of care

1L NSCLC  
\( n = 37 \)

4–6 cycles

\[
\text{atezolizumab 15mg/kg IV q3w} + \\
\text{carboplatin q3w + paclitaxel q3w}
\]

Maintenance

\[
\text{atezolizumab} +/- \\
\text{pemetrexed}
\]

\[
\text{Treat to PD} \\
\text{or} \\
\text{loss of clinical benefit}
\]

\[
\text{Treat to PD} \\
\text{or} \\
\text{loss of clinical benefit}
\]

\[
\text{Treat to PD} \\
\text{or} \\
\text{loss of clinical benefit}
\]

\[
\text{PR/CR} (n=4) \\
\text{Stable disease} (n=4) \\
\text{Discontinued} \\
\text{New lesion}
\]

\[
\text{PD} (n=2) \\
\text{PR/CR} (n=13) \\
\text{Stable disease} (n=1) \\
\text{Discontinued} \\
\text{New lesion}
\]

\[
\text{PD} (n=2) \\
\text{PR/CR} (n=9) \\
\text{Stable disease} (n=4) \\
\text{Discontinued} \\
\text{New lesion}
\]

\[
\text{CB/pac (N=8)} \\
\text{CB/pem (N=17)} \\
\text{CB/nab (N=16)}
\]

**ORR = 50.0% (4/8)**

**ORR = 76.5% (13/17)**

**ORR = 56.3% (9/16)**
Combination with Avastin

Aiding T-cell infiltration results in encouraging activity in RCC

Combination regimen benefits most patients irrespective of PD-L1 status

![Diagram illustrating immune response cycle]

- **1. Antigen release**
- **2. Antigen presentation**
- **3. Priming & activation**
- **4. T cell trafficking**
- **5. T cell infiltration**
- **6. Immuno-suppression**
- **7. Cancer cell killing**

**T cell infiltration**

**anti-VEGF**

**IHC 0**

**IHC 1**

**IHC 2**

**IHC 3**

**Discontin.**

![Graph showing change in sum of largest diameters from baseline (%)]

- **PR**
- **SD**
- **PD**

Time on study (days)

0 42 84 126 168 210 252 294 336 378

AACR 2015
Combinations with targeted agents
Potential for enhanced efficacy

**Antigen release**

- **BRAFi (Zelboraf)**
- **EGFRi (Tarceva)**
- **ALKi (Alectinib)**
- **MEKi (Cotellic)**
- anti-CD20 (Gazyva)
- various chemotherapies
- lenalidomide
- rociletinib* (Clovis)

---

**Cohort**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Regimen</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N=3)</td>
<td>Concurrent</td>
<td>33%</td>
</tr>
<tr>
<td>2 (N=8)</td>
<td>56 day run-in</td>
<td>75%</td>
</tr>
<tr>
<td>3 (N=6)</td>
<td>28 day run-in</td>
<td>100%</td>
</tr>
<tr>
<td>All (N=17)</td>
<td></td>
<td>76%</td>
</tr>
</tbody>
</table>

- **mPFS=12.2mo, DoR=20.9mo**
- Staggered dosing was better tolerated
- **AEs** were manageable and generally reversible

---

Full data including biomarkers at SMR 2015

---

Chen and Mellman, *Immunity* 2013
Enhancing atezolizumab efficacy through immunotherapy combinations

Atezolizumab

**Clinical development**
- Anti-CEA-IL2v FP
- Anti-OX40
- Anti-CD27* (Celldix)
- Estinostat* (Syndax)

**Preclinical development**
- Partnered or external therapies

**Established therapies**
- Anti-CEA (Amgen)
- Anti-CD40

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

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- Anti-CD20/CD3 TCB
- Anti-HER2/CD3 TCB

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- Anti-CEA-CD3 TCB
- Anti-CD20/CD3 TCB
- Anti-HER2/CD3 TCB

**ImmTAC**
- Anti-TIGIT
- IDO1/TDO1* (Curadev)

**Seven immune doublets in clinic**

---

**aOX40 pre-clinical data**

Control
- anti-PD-L1
- aOX40
- aOX40
- aOX40

Median tumor volume (mm$^3$)

0 10 20 30 40 60

Day

Complete Remission (CR)
**Personalized Cancer Immunotherapy**

**Evaluate tumor:**

is the tumor inflamed?*

1. **Strong PD-L1**
   - **Anti-PDL1/PD1**
   - **plus**
     - Anti-CSF1R
   - **or**
     - Anti-IDO inhibitor
   - **or**
     - Chemo
   - **plus**
     - Radiotherapy
   - **plus**
     - Targeted therapy

2. **Weak PD-L1**
   - **Anti-PDL1/PD1**
   - **plus**
     - Anti-OX40
   - **plus**
     - Anti-CTLA4
   - **plus**
     - Anti-CD40
   - **plus**
     - Anti-CEA-IL2v
   - **plus**
     - Vaccines

3. **No PD-L1**
   - **Anti-PDL1/PD1**
   - **plus**
     - Anti-angiogenics
   - **plus**
     - Anti-T cell bispecifics

4. **No identifiable immune targets**
   - **Anti-PDL1/PD1**
   - **plus**
     - Anti-angiogenics
   - **plus**
     - Anti-T cell bispecifics

**Non-inflamed**

1. **Are T cells at tumor periphery?**
   - **MHC loss?**
     - **No T cells?**
       - **No identifiable immune targets**
     - **Tumor antigen expression?**
       - **Antigen experienced?**

**Possible hypothetical algorithm**
Leverage two businesses to deliver all tools for better patient care

**Tools to characterize individual’s disease**

- DNA-Mutation & CNVs
  - Ex: EGFR, BRAF
  - DNA Sequencing
- mRNA-Expression
  - Cell signatures, targets
  - RNA Sequencing
- Protein-Expression
  - PDL1, other CI targets
  - Multiplex IHC
- Cell free Tumor DNA
  - Ex: EGFR, BRAF
  - Blood DNA Sequencing
- Imaging
  - Ex: ImmunoPET
  - Imaging

**Personalized treatment options**

- T cell Trafficking
- T cell infiltration
- T cell recognition
- T cell killing
- Antigen presentation
- Antigen release

*Evaluate tumor: Is the tumor influenced?*

- High PDL1 expression
- Low/No PDL1 expression
- No unidentified target
- T cells at Periphery
- No Effector
- MHC Lack
- No unidentified target

- Assay + Other CIT (EROT, DNA, TKI)
- Assay + Other CIT (pH3, HER, EGFR)
- Assay + Chemo / SOC
- Assay + NAbitin (or NAb)
- Assay + erd1069 (or erd1069)
- Assay + ToCes (or ToCes)
- Assay + Chemo / SOC
Roche Pharma Day 2015

Cathi Ahearn | Lifecycle Leader Atezolizumab, Lung and GU
Genentech/Roche
### Roche cancer immunotherapy beginning 2015

#### Status as at December 31, 2014

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
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<tbody>
<tr>
<td><strong>atezo</strong></td>
<td><strong>atezo+IFN-alfa</strong></td>
<td><strong>atezo</strong></td>
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<tr>
<td>Solid tumors</td>
<td>Solid tumors</td>
<td>NSCLC (Dx+)</td>
</tr>
<tr>
<td><strong>atezo+chemo</strong></td>
<td><strong>atezo+aCD40</strong></td>
<td><strong>atezo</strong></td>
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<td>2/3L NSCLC</td>
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<td></td>
<td><strong>atezo</strong></td>
</tr>
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<td></td>
<td>1/2L Bladder</td>
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<td></td>
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<tr>
<td><strong>atezo+Avastin</strong></td>
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<td>Solid tumors</td>
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<td>R/R FL / aNHL</td>
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<td></td>
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<tr>
<td><strong>atezo+Avastin+chemo</strong></td>
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<tr>
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<td><strong>aCEA-IL2v FP</strong></td>
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<td><strong>aOX40</strong></td>
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<td>Solid tumors</td>
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<tr>
<td><strong>aCEA/CD3 TCB</strong></td>
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<td><strong>IDO</strong></td>
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<tr>
<td><strong>atezo+ipilimumab</strong></td>
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<tr>
<td>Solid tumors</td>
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</tr>
</tbody>
</table>

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**Legend:**
- **atezolizumab trials**
- **NMEs monotherapy**
- **Immune doublets**
Roche cancer immunotherapy today

### Phase I
- atezolizumab (atezo)
- Solid tumors
- atezolizumab + chemo
- Solid tumors
- atezolizumab + Tarceva
- NSCLC
- atezolizumab + Zelboraf
- Melanoma
- atezolizumab + Cotillic
- Solid tumors
- atezolizumab + Avastin
- Solid tumors
- atezolizumab + Gazyva
- Solid tumors
- atezolizumab + Avastin + chemo
- Solid tumors
- atezolizumab + lenalidomide
- MM
- atezolizumab + Zelboraf + Cotillic
- Melanoma
- atezolizumab + alectinib
- ALK+ NSCLC
- atezolizumab +/- azacitidine
- MDS
- atezolizumab + Gazyva + chemo
- R/R FL/aNHL
- atezolizumab + Gazyva + lenalidomide
- R/R FL/aNHL
- atezolizumab + Herceptin + Perjeta
- HER2+ eBC/mBC
- atezolizumab + Kadryla
- HER2+ eBC/mBC
- aCEA-IL2v FP
- Solid tumors
- aOX40
- Solid tumors
- aCEA/CD3 TCB
- Solid tumors
- IDO
- Solid tumors
- aCSF-1R
- Solid tumors
- aCD20/CD3 TCB
- heme tumors
- atezolizumab + ipilimumab
- Solid tumors
- atezolizumab + IFN-alfa
- Solid tumors
- atezolizumab + aCD40
- Solid tumors
- atezolizumab + aOX40
- Solid tumors
- atezolizumab + aCSF-1R
- Solid tumors
- atezolizumab + aCEA-IL2v FP
- Solid tumors
- atezolizumab + IDO
- Solid tumors

### Phase II
- atezolizumab NSCLC (Dx+)
- atezolizumab 2/3L NSCLC
- atezolizumab + Avastin
- 1L Renal
- atezolizumab 1/2L Bladder

### Phase III
- atezolizumab 2/3L NSCLC
- atezolizumab 2/3L Bladder
- atezolizumab + Avastin + chemo
- 1L non sq NSCLC
- atezolizumab + chemo
- 1L non sq NSCLC
- atezolizumab + chemo
- 1L sq NSCLC
- atezolizumab
- 1L non sq NSCLC (Dx+)
- atezolizumab
- 1L sq NSCLC (Dx+)
- atezolizumab + Avastin
- 1L TNBC
- atezolizumab + chemo
- 1L RCC
- atezolizumab
- Adjuvant MIBC (Dx+)
- atezolizumab
- Adjuvant NSCLC (Dx+)

Status as of Nov 5, 2015

- **atezolizumab trials**
- **NME monotherapy**
- **Immune doublets**
- **Additions in 2015**
Non-small cell lung cancer

*Cause of the highest number of cancer related deaths*

433,800 patients diagnosed each year

- One of the highest incidence rates
- Highly heterogeneous disease
- Treatment becoming increasingly personalized based on molecular profile of each cancer
- Significant unmet need exist for therapies that extend lives

**Atezolizumab Phase III studies**

**Adjuvant:** Stage IB-IIIA

**1L metastatic:** Stage IV

**2L+ metastatic:** Stage IV

Decision resources 2015
# Atezolizumab NSCLC programme

*Studies addressing all patient subgroups*

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Filing</th>
<th>Data</th>
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<tbody>
<tr>
<td>Atezo Monotherapy</td>
<td>IMpower010</td>
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<td>Atezo + carbo + nab-pac</td>
<td>IMpower 130</td>
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<tr>
<td>Atezo + carbo + pac/nab-pac</td>
<td>IMpower 131</td>
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<td>Atezo + cis/carbo + pem</td>
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<table>
<thead>
<tr>
<th>1L</th>
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| | IMpower 110 | | | | 2017 |

<table>
<thead>
<tr>
<th>2L+</th>
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<td>Atezo NSq/Sq Monotherapy Randomized Ph3</td>
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<tr>
<td>Various combinations</td>
<td>targeted, CI and chemo</td>
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</tr>
</tbody>
</table>

**NSCLC** = non-small cell lung cancer
Bladder cancer treatment flow today

Incident NMIBC (~70%, 127K)  
Neoadj + surg (~40%)  
Surg only (~30%)  
Surg+Adj (~30%)  
mUBC (~35K, de novo and relapsed)  
1L prior-platinum (~30%)  
1L platinum-naïve (~70%)  
2L/3L (~60%)

Incident MIBC (~20%, 28K)

Incident mUBC (~10%, 13K)

NMIBC=non-muscle invasive bladder cancer; MIBC=muscle invasive bladder cancer; Roche internal estimates (Mar 2014)
Atezolizumab bladder programme
Monotherapy and combination studies

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Filing</th>
<th>Data</th>
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<tr>
<td><strong>MIBC adj.</strong></td>
<td>Atezo Monotherapy IMvigor 010</td>
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<td><strong>1L cis-ineligible</strong></td>
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<td>Atezo monotherapy Single-Arm Ph2 IMvigor210 Cohort 2</td>
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<tr>
<td></td>
<td>Various combinations CI</td>
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</tbody>
</table>

MIBC=muscle invasive bladder cancer

- PD-L1-selected
- all-comers
- first-to-market
- rolling filing
Renal cell carcinoma (RCC)

Increasing market with need for agents that improve survival

- ~15% of RCC patients are diagnosed with metastatic disease
- mRCC population is expected to grow due to population ageing
- There is a need for well tolerated, efficacious treatments in 1L
- Atezolizumab + Avastin combination demonstrated high diseases control rate (PR=40%, SD=50%)*

Decision resources 2014; *ASCO GU 2015
Triple negative breast cancer (TNBC)

*Disease with high unmet medical need*

- Accounts for 10-20% of breast cancer
- Defined by lack of expression of ER, PR and HER2
- Median OS ~12months
- No standard of care, no unique targeted therapies
- Atezolizumab demonstrated single-agent activity in phase I (ORR=19%)*

*Emens, AACR 2015; ER=estrogen receptor; PR=progesterone receptor*
# Atezolizumab RCC and TNBC programmes

## Monotherapy and combination studies

### Renal cell carcinoma (RCC)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Monotherapy/Combination</th>
<th>1L</th>
<th>2L+</th>
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<tbody>
<tr>
<td>1L</td>
<td>Atezo+Avastin</td>
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<td>Atezo+Avastin / Atezo Monotherapy Randomized Ph2</td>
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<td>IMmotion150</td>
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<td>2L+</td>
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### Triple negative breast cancer (TNBC)

<table>
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<tr>
<th>Phase</th>
<th>Monotherapy/Combination</th>
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<th>2L+</th>
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<td>1L</td>
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<tr>
<td>2L+</td>
<td>Various combinations</td>
<td></td>
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</tr>
</tbody>
</table>
Increasing value of cancer immunotherapy

Earlier lines, new indications, combinations

Opportunity

2016

Launch

2L NSCLC Dx+
2L bladder Dx+

Expand & Lead

1L NSCLC allcomers
1L TNBC allcomers
1L RCC allcomers

Transform

Adjuvant NSCLC
Adjuvant bladder
New indications
CI combinations

2020
Setting new standards, developing combinations
Driven by the breadth of our in-house portfolio
# Cancer immunotherapy newsflow in 2015

<table>
<thead>
<tr>
<th>Event</th>
<th>Presentation Details</th>
<th>Location</th>
<th>Dates</th>
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<tbody>
<tr>
<td><a href="#">Society for Melanoma Research (SMR) 2015 Congress</a></td>
<td><strong>atezolizumab + Zelboraf</strong> - mM: Phase I</td>
<td>San Francisco, 18-21 Nov</td>
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<td><a href="#">Society for NeuroOncology</a></td>
<td><strong>atezolizumab</strong> - GBM: Phase I</td>
<td>San Antonio, 19-22 Nov</td>
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<td><a href="#">San Antonio Breast Cancer Symposium</a></td>
<td><strong>atezolizumab + abraxane</strong> - TNBC: Phase Ib</td>
<td>San Antonio, 8-12 Dec</td>
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<td><a href="#">2016 Genitourinary Cancers Symposium</a></td>
<td><strong>atezolizumab</strong> - mUC: IMvigor 210</td>
<td>San Francisco, 7-9 Jan</td>
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</table>
Roche Pharma Day 2015

Life cycle management & new market opportunities

Bill Anderson | Chief Marketing Officer
Pharmaceuticals Division
Maximising existing franchises

New growth opportunities

Access in a changing healthcare environment
**Multiple major pivotal trials reading out near term**

**Significant filing and launch activities ahead**

<table>
<thead>
<tr>
<th>Year</th>
<th>Molecule</th>
<th>Indication</th>
<th>Market opportunity</th>
<th>Incremental infrastructure</th>
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<tr>
<td>2015</td>
<td>Alectinib</td>
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<td>Cotellic/Zelboraf</td>
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<td></td>
<td>Venetoclax</td>
<td>Hematology (CLL 17p del)*</td>
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<td>Ocrelizumab</td>
<td>Multiple Sclerosis</td>
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<td>Atezolizumab</td>
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<td>Lebrikizumab</td>
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<td>Large</td>
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<td></td>
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<td>Adj HER2+ breast cancer</td>
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<td>GOYA</td>
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<td></td>
<td>Idasanutlin (MDM2)</td>
<td>Acute myeloid leukemia</td>
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**Legend**

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Neuroscience</th>
<th>Ophthalmology</th>
<th>Immunology</th>
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<tr>
<td><img src="icon.png" alt="Small: up to CHF 0.5 bn" /></td>
<td><img src="icon.png" alt="Medium= CHF 0.5 to CHF 1bn" /></td>
<td><img src="icon.png" alt="Large &gt; CHF1bn" /></td>
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</tbody>
</table>

NSCLC=non-small cell lung cancer; CLL=chronic lymphocytic leukemia; AD=atopic dermatitis; IPF=idiopathic pulmonary fibrosis; COPD=chronic obstructive pulmonary disease; NHL=non-hodgkin's lymphoma; * first indication
Roche’s approach in oncology: First- and best-in-class necessary for success

Data sources: Evaluate Pharma, Decision Resources, Roche/Genentech PMR launch trackers
Note: *Market shares represent either % sales of target product relative to sales competing products in similar indications or patient shares from Roche PMR trackers; sales data are actuals (≤ 2013) + consensus broker forecasts (2013-2020) where applicable
Anti-CD20: Multiple approaches across the franchise

Rapidly and sustainably convert market to SC
Gazyva (GALLIUM) (improve > SoC)

Gazyva (GREEN)- Extend chemo backbone
Venetoclax – Extend efficacy

Rapidly and sustainably convert market to SC
GAZYVA (GOYA) in aNHL (improve > SoC)

Broad development program for venetoclax as add on and in new tumour types

SoC=standard of care; SC=subcutaneous; CLL=chronic lymphocytic leukemia; iNHL=indolent non-hodgkin’s lymphoma; aNHL=aggressive NHL
Anti-CD20 franchise
*Strategies for long term growth*

**Protect**
- MabThera
- MabThera SC

**Replace**
- Gazyva

**Extend**
- Gazyva
- Venetoclax
- Polatuzumab
- Atezolizumab

Rapidly and sustainably convert the market to SC
 Await GOYA and GALLIUM Extend Gazyva with GREEN
 Increase medical benefit with Venetoclax in NHL, CLL and expand into new diseases e.g. Multiple Myeloma

Venetoclax in collaboration with AbbVie; SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin’s lymphoma
HER2+ breast cancer adjuvant: Still high medical need despite major advances

**Adjuvant - HERA trial**

![Graph showing Disease-Free Survival](image)

- HR = 0.76 (95% CI: 0.67-0.86)
- P < 0.0001

**Neoadjuvant - NOAH trial**

![Graph showing Event-Free Survival](image)

- HR = 0.64 (95% CI: 0.44-0.93)
- P = 0.016

---

1. Roche data on file; 2. L. Gianni et al, ASCO Annual Meeting 2013
HER2 franchise: Strengthening standard of care  
Franchise expected to grow further

**Market (Product launches)**

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

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

- **Adjuvant BC**
  - Herceptin + chemo
  - Herceptin sc + chemo (HannaH)

- **Neoadjuvant BC**
  - Herceptin + chemo (NOAH)\(^1\)
  - Herceptin & Perjeta + chemo (Neosphere, Tryphaena)\(^2\)

- **Pipeline (Trial starts)**
  - **eBC/mBC**
    - atezolizumab + Herceptin + Perjeta
    - atezolizumab + Kadcyla

**Timeline**

- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019

- **Established SoC**
- **Potentially new SoC**
- **New trials**

atezolizumab (aPD-L1 MAb); SoC=standard of care
HER2 franchise: Significant growth opportunities in current indications

- Increased patient share
- Longer treatment duration
- Emerging markets

Patient shares

<table>
<thead>
<tr>
<th>Drug</th>
<th>US</th>
<th>EU5</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin Adjuvant</td>
<td>96%</td>
<td>93%</td>
<td>25%</td>
</tr>
<tr>
<td>Perjeta Neoadjuvant</td>
<td>84%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>1L Perjeta mBC</td>
<td>63%</td>
<td>51%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2L Kadcyla</td>
<td>58%</td>
<td>58%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Sources: Market research tracking studies; Latest quarter Q315 in EU5 and US
Franchise strategies for long term growth
*New indications and longer duration*

<table>
<thead>
<tr>
<th>Growth opportunity</th>
<th>Indication</th>
<th>Global peak sales potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2</td>
<td>Perjeta adjuvant (APHINITY)</td>
<td>⬤⬤⬤</td>
</tr>
<tr>
<td>Potential and new indications</td>
<td>Herceptin SC*</td>
<td>⬤⬤⬤</td>
</tr>
<tr>
<td>CD20</td>
<td>Gazyva aNHL (GOYA)</td>
<td>⬤⬤⬤</td>
</tr>
<tr>
<td>Potential and new indications</td>
<td>Gazyva iNHL (GALLIUM)</td>
<td>⬤⬤⬤</td>
</tr>
<tr>
<td></td>
<td>MabThera SC*</td>
<td>⬤⬤⬤</td>
</tr>
<tr>
<td></td>
<td>Venetoclax</td>
<td>⬤⬤⬤</td>
</tr>
</tbody>
</table>

*Small: up to CHF 0.5 bn  medium = CHF 0.5 to CHF 1bn  large > CHF1bn

*Sales replacing current IV products; SC=subcutaneous; iNHL=indolent non-hodgkin’s lymphoma; aNHL=aggressive NHL*
Avastin: Further growth opportunities

Existing markets
• Continued growth in emerging markets
• Continued uptake in lung, ovarian and cervical cancer

New indications
• Avastin + Tarceva (filed in EU)
• Mesothelioma (filing ongoing)

Market extension
• Avastin + Atezolizumab in lung, renal, colorectal

Avastin global sales (incl. Chugai) at 2014 average exchange rates; NSCLC=non-small cell lung cancer; mCRC=metastatic colorectal cancer; RCC=renal cell carcinoma; BC=breast cancer; OC=ovarian cancer; GBM=glioblastoma; CC=cervical cancer
What does it take to succeed in chronic diseases?
Importance of incremental differentiation

Humira in TNF-α Inhibitors

- SC vs Remicade’s IV
- Less frequent dosing than Enbrel

Tecfidera in MS

- Better efficacy than 1st gen
- Better safety than 2nd gen

Victoza in T2D

- Better device
- QD vs. BID

MS=multiple sclerosis; T2D=type 2 diabetes; SC=subcutaneous; IV=intravenous; QD=once a day dosing; BID=twice a day dosing
Actemra: Success in a competitive space
Focus on differentiation

Clear positioning: Focus on monotherapy

“ADACTA Study Shows Actemra Superior in Monotherapy”

“Monotherapy: for patients who cannot tolerate Methotrexate”

Share of Voice

US Share of Voice

In 2010

4%

In 2011

10%

Continued evidence generation

<table>
<thead>
<tr>
<th>Key Ph IV Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy Efficacy</td>
<td>&gt;8,500</td>
</tr>
<tr>
<td>Monotherapy H2H vs Humira</td>
<td>~320</td>
</tr>
<tr>
<td>Early RA monotherapy</td>
<td>~1,500</td>
</tr>
</tbody>
</table>

• EULAR Guidelines: Recommended for monotherapy

Source for share of voice: IMS SPD, Q1 2015 & US PMR 2010-11
**Actemra: Increasing patient shares through smart clinical development and focused marketing**

**Patient shares in EU5 in rheumatoid arthritis monotherapy**

- **Strategy: Focus on monotherapy**
- **H2H superiority in 1L monotherapy**
- **Leveraging sub-cutaneous formulation**

Source: GFK quarterly tracker Q1’15, based on survey of Roche targeted accounts
Maximising existing franchises

New growth opportunities

Access in a changing healthcare environment
## New growth opportunities outside oncology

<table>
<thead>
<tr>
<th>NMEs</th>
<th>Line extensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>alectinib</td>
<td>Gazyva</td>
</tr>
<tr>
<td>Cotellic</td>
<td>Herceptin + Perjeta</td>
</tr>
<tr>
<td>venetoclax</td>
<td>Gazyva</td>
</tr>
<tr>
<td><strong>ocrelizumab</strong></td>
<td><strong>Gazyva</strong></td>
</tr>
<tr>
<td><strong>ATEZOLIZUMAB</strong></td>
<td><strong>atezolizumab + chemo</strong></td>
</tr>
<tr>
<td><strong>LEBRIKIZUMAB</strong></td>
<td><strong>Gazyva</strong></td>
</tr>
<tr>
<td>ACE910</td>
<td><strong>Gazyva</strong></td>
</tr>
<tr>
<td>crenezumab</td>
<td><strong>Gazyva</strong></td>
</tr>
<tr>
<td>taselisib</td>
<td><strong>Gazyva</strong></td>
</tr>
<tr>
<td>lampalizumab</td>
<td>Post 2017</td>
</tr>
<tr>
<td>olesoxime</td>
<td>post 2017</td>
</tr>
<tr>
<td>etrolizumab</td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacological Areas:**
- **Oncology/hematology**
- **Neuroscience**
- **Ophthalmology**
- **Immunology**
Multiple sclerosis (MS): Level of differentiation important for new entrants

Global market shares Q2 2015

- Multiple treatment options in Relapsing and Remitting MS
- Continued high unmet medical need
- Primary Progressive MS (PPMS) – no approved treatments for this indication

1 Source: Evaluate Pharma Multiples Sclerosis report, October 2015. Note: Market shares based on value (sales)
2 ABCR's refers to Avonex®, Betaferon® / Betaseron®, Copaxone®, Rebin®, Extavia®, Plegridy®
Multiple Sclerosis: Improvements over SoC driving market growth

Global sales (lc) USDm

Source: Evaluate Pharma Multiple Sclerosis report, October 2015; * Includes Imusera sales; SoC=standard of care
Range of treatment options in RMS
Varying efficacy and safety profiles

ILLUSTRATIVE

More

Alemtuzumab
Natalizumab
(NCV+)

Natalizumab
(NCV-)

Fingolimod

Dimethyl fumarate

Teriflunomide

Less

Unmet need

SAFETY/ USE

More / Earlier

Less / Later

Orals  New biologics  ABCRs

RMS=relapsing forms of multiple sclerosis; ABCR=Avonex®; Betaseron®; Copaxon®; Rebif®;
Ocrelizumab: Effective, safe, convenient

**Efficacy***
- Superior to standard of care DMT

**RMS**
- Superior to standard of care DMT

**PPMS**
- First investigational treatment to show efficacy

**Safety**
- Incidence of adverse events & serious adverse events (incl. serious infections) similar to interferon beta-1a in both RMS studies and similar to placebo in PPMS

**Convenience**
- IV – Twice yearly

*Based on ARR, CDP, T1/T2 lesions; DMT=disease modifying treatment; AE=adverse event; CDP=confirmed disability progression; PPMS=primary progressive multiple sclerosis; SAE=serious adverse event; IV=intravenous
New growth opportunities outside oncology

<table>
<thead>
<tr>
<th>Year</th>
<th>NMEs</th>
<th>Line extensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>alectinib, Cotellic, venetoclax</td>
<td>Herceptin + Perjeta, Gazyva</td>
</tr>
<tr>
<td>2016</td>
<td>ocrelizumab, lebrikizumab</td>
<td>Gazyva</td>
</tr>
<tr>
<td>2017</td>
<td>ACE910, atezolizumab, lampalizumab</td>
<td>Gazyva, atezolizumab + chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post 2017</td>
</tr>
<tr>
<td></td>
<td>gantenerumab, crenezumab, taselisib, etrolizumab</td>
<td></td>
</tr>
</tbody>
</table>

- Oncology/hematology
- Neuroscience
- Ophthalmology
- Immunology
Severe asthma: High unmet need in growing market

Global asthma market 2014 vs 2020

- Approx. 300m patients worldwide and growing strongly
- 5-10% asthma patients have severe disease, and ~30% of severe disease is uncontrolled despite maximal therapy
- Over 4.5m severe asthmatics with uncontrolled disease

Note: Market shares based on value (sales); Source: Evaluate; defined by daily use of ≥500ug ICS + LABA
**Asthma: >CHF 15bn market**

*Small molecules majority of SoC*

<table>
<thead>
<tr>
<th>GINA</th>
<th>NHLBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
<td><strong>Step 4</strong></td>
</tr>
<tr>
<td><strong>Step 5</strong></td>
<td><strong>Step 5</strong></td>
</tr>
</tbody>
</table>

**GINA guidelines**

**NHLBI guidelines**

---

**GINA guidelines in Global initiative for asthma 2012, NHLBI guidelines from Asthma Care September 2012 and International ERS/ATS guidelines published in ERJ on Dec. 12, 2013, *Evaluate Pharma 2013; SoC=standard of care; OCS=oral corticosteroid; ICS=inhalable corticosteroid**
Asthma: Biologic market expected to grow strongly to CHF 5bn by 2020

New guidelines

New biologics with different MoAs within 5yrs

Biomarkers: Emergence of phenotyping

1. Decision resources, Asthma (Moderate to Severe), April 2014. Timeframe considered = when mepolizumab, reslizumab and lebrikizumab will be available; 2. Evaluate pharma, analysis on January 28th 2015; OCS=oral corticosteroid; MoA=mechanism of action
Lebrikizumab: Differentiated mode of action with solid dual biomarker profile

**Efficacy**
- Efficacy beyond clinical asthma exacerbations (CAE) reduction
- Broad development beyond asthma in related diseases

**Safety**
- Improve on significant side effects associated with oral corticosteroid (OCS) use

**Biomarker**
- Biomarkers to show clinically meaningful effect in distinct populations
Lebrikizumab in atopic dermatitis

Chronic disease with high unmet medical need

**Disease**
- Inflamed skin, chronic, relapsing
- Severe itching, poor sleep, psycho-social dysfunction
- Th2 driven disease, with high expression of IL-13

**Prevalence**
- Most common dermatologic disease (~2x psoriasis)
- 20-30% moderate to severe

**Unmet need**
- Current treatment options: Burdersome, non-targeted, significant toxicity
- Up to 60% with moderate-severe disease do not adequately respond
New growth opportunities outside oncology

- alectinib
- ocrelizumab
- Cotellic
- atezolizumab
- venetoclax
- lebrikizumab
- NMEs
- 2015
  - Herceptin + Perjeta
  - Gazyva
- 2016
  - atezolizumab + chemo
  - Gazyva
- 2017
  - Gazyva
- Post 2017
  - gantenerumab
  - crenezumab
  - taselisib
  - lampalizumab
  - olesoxime
  - etrolizumab

Line extensions

- Oncology/hematology
- Neuroscience
- Ophthalmology
- Immunology
Hemophilia A: Current treatment strategies

Episodic (on demand) treatment
• Patients treated only when they bleed
• Can be up to 30-60 times per year

Prophylaxis
• Goal is to prevent bleeds
• IV infusion 2-3 times per week
• Can reduce bleed rate to 0-2 per year for non-inhibitor patients
• Should be the standard, but is still not used in ~35% of patients (treatment burden, adherence, IV access issues)
Hemophilia A: There are significant limitations of current treatment options

**FVIII market (USD 6.1bn in 2012)**

- **Current FVIII treatments**
  - Limited half-life of only 8-12 hrs
  - Frequent IV injections
  - Induce neutralizing antibodies, which inhibit their function

**By-passing agent market (USD 2.1bn)**

- **Current bypassing treatments**
  - Much shorter half-life of ~4-6 hrs
  - Multiple frequent IV infusions
  - Long infusion times (30+mins) for FEIBA
  - Unstable efficacy compared to FVIII

*Company reported sales; ^1EvaluatePharma consensus analyst estimates
ACE910 can address the major medical needs for both inhibitor and non-inhibitor patients.

**Non-Inhibitor**
- **On-demand treatment**
  - 1-3 times/bleeding event, IV
- **Prophylaxis treatment**
  - 3 times/week, IV

**Inhibitor**
- **On-demand treatment with by-passing agents**
  - 2-3h intervals, IV
- **Prophylaxis with by-passing agents**
  - Every other day, IV

**Inhibiting Factor VIII antibodies in 20-30% of the patients**

**ACE 910**
- Less frequent & SC injection
- No potential to induce FVIII inhibitor
- Potentially more effective prophylaxis

**Immune Tolerance Induction**
- 70-80% success rate
- limitation due to very high cost and heavy burden for patients
ACE 910: Differentiated mode of action with less frequent dosing

**MoA**
- Bi-specific fully humanized antibody designed to promote clot formation at site of injury
- Novel approach that promotes FX activation, a key step in acceleration of coagulation and stable clot formation

**Efficacy**
- More effective prophylaxis for inhibitor patients
- Substantial improvement in bleed rates

**Safety / Convenience**
- No potential to induce FVIII inhibitors
- Subcutaneous administration
- Less frequent dosing (potentially Q4W) due to long half life
- Allow more non-inhibitor patients to be on prophylaxis

Q4w = monthly dosing
New growth opportunities outside oncology

NMEs
- alectinib
- ocrelizumab
- Cotellic
- atezolizumab
- venetoclax
- lebrikizumab
- 2015
- Herceptin + Perjeta
- Gazyva
- 2016
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- 2017
- atezolizumab + chemo
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- taselisib
- lebrikizumab
- olesoxime
- etrolizumab
- Oncology/hematology
- Neuroscience
- Ophthalmology
- Immunology
Geographic Atrophy (GA): Significant unmet need with no approved treatments

**AMD Market overview**

- **Geographic Atrophy (GA)**
  - 5m+ pts
  - GA is a progressive, irreversible disorder severely impacting visual function and patient quality of life

- **Neovascular AMD**
  - Neovascularization

- Lampalizumab
  - CFI biomarker profile +ve
  - CFI biomarker profile -ve
  - other

- Phase III study population

- AMD prevalence is estimated to be similar to the prevalence of neovascular AMD

- **AMD**
  - 30-50m pts
  - Initially, visual function minimally affected; signs are anatomic (drusen)

- **Roche**

- **Progressive and irreversible disease, responsible for 20% of legal blindness**

- **Currently no effective therapies approved**

- **Lampalizumab**: Selective inhibitor of the alternative complement pathway

**AMD**=age-related macular degeneration; **CFI**=Complement Factor I
Lampalizumab: First-in-class disease modifying therapy

**Efficacy**
- Phase II showed promising efficacy in all comers; higher efficacy in exploratory biomarker group

**Safety / Convenience**
- No unexpected or unmanageable SAEs

**Biomarker**
- CFI profile biomarker included in pivotal trials
Maximising existing franchises

New growth opportunities

Access in a changing healthcare environment
The key challenge to access: Differentiated solutions across geographic clusters

United States (US)
(35% of world market, 5% of population)
- Free, stable pricing

Developed countries ex-US
(37% of world market, 10% of population)
- Payers negotiate price

Emerging Markets
(28% of world market, 85% of population)
- Spend limited by GDP per capita
Roche’s solution: Personalised reimbursement models

- Pay for performance
- Multiple-indication pricing
- Combinations

- Pricing according to benefits delivered to patients in different indications and combinations
- Personalised reimbursement models include:
  - Pay for performance
  - Multiple-indication pricing
  - Combination pricing
Pay for performance

“Level of reimbursement based on a patient’s response to a medicine over a specified time period”

AIFA - Payment by Results procedure

- Start of the new treatment in all eligible patients
- Evaluation after x days/cycles
- Non-responders: Treatment is stopped
- The overall patient's cost of treatment is not reimbursed
- Pay-back by Market Authorization Holder to public hospital
- Responders: Treatment is continued
- Treatment is reimbursed by NHS

(+)
- Fair reimbursement for patients on an individual level

(-)
- Only a few healthcare systems technically support reimbursement at patient level
- Which outcome is important?
Multiple-indication pricing

“Allows a medicine approved in different indications and combinations to be priced according to benefits delivered in each indication and combination”

**Now** – unit of drug has same price across all indications

- All indications
- List price (invoice price)

**Future** – single or combination drug price varies by indication based on benefit

- Indication A: Price X
- Indication B: Price Y
- Indication C: Price Z
- Other: Price X

**(+)**
- Best reflects reality of current treatment paradigms, particularly in oncology

**(-)**
- Requires drug-utilisation tracking substantial at patient level
Combination pricing

“Ensures benefits of combination therapies are reflected while considering the limits of healthcare budgets”

*Now* – unit of drug has same price, whether used as single agent or in combination

- Single use or combination
  - List price product A (invoice price)
- List price product B (invoice price)

*Future* – price varies by single or combination use based on benefit

- Product A
- Product B
- Product A + B (without PRM)
- Product A + B (with PRM)

- Price X
- Price Y
- Price Z
- Potential Price

**(+)**
- Addresses the reality of combination treatments, particularly oncology
- Takes healthcare budget into consideration

**(-)**
- Not all drug combos are from the same company
- High complexity with many possible combinations
Positive outlook

Strong pipeline mitigates biosimilar impact

NME launches
Venetoclax, Alectinib, Cotellic, Ocrelizumab, Atezolizumab, Lebrikizumab, ACE910, Lampalizumab

Biosimilars
MabThera, Herceptin, Avastin

Sales

Conceptual

Pipeline

Marketed products

Late-stage development program
Market opportunities through to 2017

NMEs

- alectinib
- Cotellic
- venetoclax

- ocrelizumab
- atezolizumab
- lebrikizumab

- ACE910
- lampalizumab
- olesoxime

- gantenerumab
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line extensions

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