Roche Pharma Day 2015

Hematology franchise overview

Cynthia Perettie  |  Global Hematology Franchise Head
David Traub      |  Lifecycle Leader anti-CD20 Franchise
Pharmaceuticals Division
Hematology indications still represent large unmet need

40% of DLBCL patients relapse and succumb to their disease

FL
Still no cure, many patients experience multiple relapses before succumbing to their disease

CLL
Still no cure, many patients achieve incomplete responses and require chronic treatment, many experience multiple relapses

AML/MDS
SOC in AML has made little progress in decades, we believe combinations will significantly improve outcomes for patients

MM
Highly variable disease with driver mutations, current SOC (PI and IMIDs) associated with significant side effects, combinations with targeted therapies will advance SOC

Hemophilia
Existing therapies are hampered by burden on therapy and compliance
# Roche hematology – expanding within and beyond NHL/CLL

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Registration</th>
<th>Approved</th>
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<tbody>
<tr>
<td><strong>NHL</strong></td>
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<tr>
<td>MabThera SC</td>
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<td><strong>CLL</strong></td>
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<tr>
<td>Gazyva</td>
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<td>Type II anti-CD20</td>
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<td>CLL*</td>
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<td></td>
<td>MM</td>
<td></td>
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<td>idasanutlin</td>
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<td>polatuzumab</td>
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<td><strong>MM</strong></td>
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<td><strong>HEMOPHILIA</strong></td>
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<tr>
<td>4 early assets, incl. CD20/CD3</td>
<td>Heme indications</td>
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<td>ACE910</td>
<td>Hemophilia</td>
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</tbody>
</table>

ADC: Antibody-drug Conjugate
*Co-development molecule with Abbvie
MabThera SC

NHL launch ongoing, strong uptake in most markets

- First EU launches in 2014, ongoing or imminent in further countries
- Encouraging initial uptake in majority of markets, comparable to Herceptin SC
- Slower conversion in countries with strong incentives to use IV (Germany) or limited reimbursement (UK)
Advancing the standard of care in NHL & CLL

**Gazyva: Designed to be the superior aCD20**

### CLL 11

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Phase</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L CLL</td>
<td>1L Chronic Lymphocytic Leukemia (CLL)</td>
<td>III</td>
<td>Gazyva + chlorambucil</td>
<td>Launched in Q4 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rituxan + chlorambucil</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chlorambucil</td>
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</table>

### GADOLIN

<table>
<thead>
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<th>Study</th>
<th>Design</th>
<th>Phase</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1L Refractory Indolent NHL (iNHL)</td>
<td>III</td>
<td>Gazyva + bendamustine</td>
<td>Filed Q3 2015</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>bendamustine</td>
<td></td>
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### GOYA

<table>
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<th>Design</th>
<th>Phase</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
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<tr>
<td></td>
<td>1L Diffuse Large B-cell Lymphoma (DLBCL)</td>
<td>III</td>
<td>Gazyva + CHOP</td>
<td>Data expected 2016</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rituxan + CHOP</td>
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</table>

### GALLIUM

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Phase</th>
<th>Induction</th>
<th>Maintenance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1L Indolent NHL (iNHL)</td>
<td>III</td>
<td>Gazyva + CHOP or Gazyva + CVP or Gazyva + bendamustine</td>
<td>Data expected 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rituxan + CHOP or Rituxan or Rituxan + bendamustine</td>
<td></td>
</tr>
</tbody>
</table>

In collaboration with Biogen Idec

CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone
GADOLIN

Strong data for GAZYVA in refractory iNHL

IRF-Assessed PFS MabThera-refractory iNHL (n=396)

Gazvya provides substantial benefit in iNHL patients who did not achieve adequate disease control from a previous MabThera-based regimen

FDA Priority Review granted (10/24/2015)
1L DLBCL

GOYA to include data across cell of origin subtypes

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of incidence</th>
<th>Median OS [months]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Comers</td>
<td>100%</td>
<td>&gt;60</td>
</tr>
<tr>
<td>GCB</td>
<td>55%</td>
<td>&gt;60</td>
</tr>
<tr>
<td>ABC**</td>
<td>30%</td>
<td>30-40</td>
</tr>
<tr>
<td>Double Positive</td>
<td>18-33%</td>
<td>24</td>
</tr>
<tr>
<td>Double-Hit</td>
<td>5-10%</td>
<td>12</td>
</tr>
</tbody>
</table>

** worse outcomes in ABC may be driven by higher proportion of double positive patients

REFERENCES

- Johnson N et al, JCO 2012
- Hu S et al, Blood 2013
- MAIN, GATHER data
- Iqbal J et al. JCO, 2006
- Davis et al. Nature 2010
- Haberman T et al, JCO 2006
- Thieblemont C et al. JCO 2011

* 46% of ABC patients are double positive (Hu S et al. Blood, 2013)

Source: Roche internal data presented during REFORCE F2F Feb-2015
Development vision: Raising the bar for curative therapies in NHL

Pursue compelling combinations with internal and external molecules

- **Anti CD20**
  - MabThera or GAZYVA
  - CD20/CD3
  - TCB

- **Chemo**
  - Eliminate or replace with ADC
  - polatuzumab
  - NME ADC

- **Biologic modifier**
  - Add a targeted agent
  - venetoclax
  - atezolizumab
# Phase Ib/II studies in NHL

**14 unique combinations**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Disease</th>
<th>Status</th>
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<tbody>
<tr>
<td>Doublet</td>
<td>Anti-CD20 + venetoclax</td>
<td>FL</td>
</tr>
<tr>
<td>Doublet</td>
<td>Anti-CD20 + atezolizumab</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Doublet</td>
<td>Anti-CD20 + idasanutlin</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Doublet</td>
<td>Anti-CD20 + polatuzumab vedotin</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + venetoclax + CHOP</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + venetoclax + bendamustine</td>
<td>FL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + polatuzumab vedotin + CHP</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + polatuzumab vedotin + bendamustine</td>
<td>FL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + atezolizumab + CHOP</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Doublet + Chemo</td>
<td>Anti-CD20 + atezolizumab + bendamustine</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Triplet</td>
<td>Anti-CD20 + atezolizumab + lenalidomide</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Triplet</td>
<td>Anti-CD20 + atezolizumab + polatuzumab vedotin</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Triplet</td>
<td>Anti-CD20 + polatuzumab vedotin + venetoclax</td>
<td>FL/DLBCL</td>
</tr>
<tr>
<td>Triplet</td>
<td>Anti-CD20 + polatuzumab vedotin + lenalidomide</td>
<td>FL/DLBCL</td>
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</table>
## Development plan: Venetoclax

**A new cornerstone of the hematology franchise**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Combination</th>
<th>Indication</th>
<th>P 1</th>
<th>P 2</th>
<th>P 3</th>
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<tbody>
<tr>
<td>venetoclax*</td>
<td>+Rituxan MURANO</td>
<td>R/R CLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Gazyva CLL14</td>
<td>1L CLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>Monotherapy</td>
<td>R/R CLL 17pdel</td>
<td>Filing Q4 '15</td>
<td></td>
<td></td>
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<tr>
<td>venetoclax</td>
<td>Monotherapy after ibrutinib/idelalisib tx</td>
<td>R/R CLL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan</td>
<td>R/R CLL and SLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan +/- B CONTRALTO</td>
<td>R/R FL (iNHL)</td>
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</tr>
<tr>
<td>venetoclax</td>
<td>+Rituxan/Gazyva +chemo CAVALLI</td>
<td>1L aNHL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>venetoclax</td>
<td>+ Rituxan + B</td>
<td>R/R NHL</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>venetoclax</td>
<td>+bortezomib+dexamethasone</td>
<td>R/R MM</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>venetoclax</td>
<td>+ hypomethylating agents + LDAC</td>
<td>AML</td>
<td></td>
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</tbody>
</table>

*venetoclax (Bcl2 inhibitor) in collaboration with AbbVie

B = bendamustine
LDAC = low dose Ara C
MRD negative status as surrogate end-point for long-term remission and/or cure

**MRD (Minimal Residual Disease) detection** (illustrative)

- **Early relapse**
- **Late relapse**
- **Cytomorphology detection limit**
- **Immunophenotypic and PCR detection limit**
- ‘Cure’

**MRD as prognostic factor: CLL8 study**

- **Peripheral blood**
- **Bone marrow**

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J Clin Oncol. 2012 Mar 20;30(9):980-8
CLL: Two different treatment paradigms

**Short course combinations** that induce **deep responses** followed by long **treatment-free remissions**

MRD-negative responses followed by long remissions

**Chronic treatments** with agents that are **effective, safe, and convenient**

Long remissions from safe, tolerable, chronic therapy
**CLL: Two different treatment paradigms**

![Image](image-url)

<table>
<thead>
<tr>
<th>Line</th>
<th>R/R</th>
<th>R-/Venetoclax</th>
<th>Gazyva-bendamustine</th>
<th>Gazyva-chlorambucil</th>
<th>R-chlorambucil</th>
<th>R-FC</th>
<th>Ibrutinib</th>
<th>Idelisib</th>
<th>R-Benda-Ibrutinib</th>
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<tr>
<td>N</td>
<td>78</td>
<td>49</td>
<td>158</td>
<td>238</td>
<td>233</td>
<td>408</td>
<td>31</td>
<td>61</td>
<td>54</td>
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<tr>
<td>ORR</td>
<td>77%</td>
<td>86%</td>
<td>78.5%</td>
<td>75.5%</td>
<td>65.9%</td>
<td>90%</td>
<td>71%</td>
<td>67%</td>
<td>56%</td>
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<tr>
<td>CR</td>
<td>23% CR/CRi</td>
<td>41% CR/CRi</td>
<td>32.3%</td>
<td>22.2% CR/CRi</td>
<td>8.3% CR/CRi</td>
<td>44%</td>
<td>10%</td>
<td>3%</td>
<td>4%</td>
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<tr>
<td>MRD-negative</td>
<td>BM: 55% (6/11)*</td>
<td>BM: 75% (15/20)</td>
<td>BM: 27.8% (53%) (ITT)</td>
<td>PB: 58.9%</td>
<td>PB: 31% (41/132)</td>
<td>BM: 17% (15/88)</td>
<td>PB: 2% (3/150)</td>
<td>BM: 3% (2/72)</td>
<td>PB: 63% (90/143)</td>
</tr>
</tbody>
</table>

MRD: minimal residual disease; R/R: relapsed/refractory; 1L: first-line; BM: bone marrow; PB: peripheral blood
*MRD tests performed in local unvalidated laboratories in a small number of patients; in patients with a CR who have been tested

References:
1. John Seymour, EHA 2014
7. Stilgenbauer et al., ASH 2015 (GREEN subgroup analysis)
8. Ma Shuo et al., ASH 2015 (abstract 80273)
Hemophilia A: ACE910 addressing major medical need in highly focused market

### FVIII market ($6.1bn in 2012)†

<table>
<thead>
<tr>
<th>Year</th>
<th>Others</th>
<th>Recombinate</th>
<th>Helixate</th>
<th>Humate P</th>
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<tbody>
<tr>
<td>2009</td>
<td>$5.3 bn</td>
<td>$5.5 bn</td>
<td>$6.0 bn</td>
<td>$6.1 bn</td>
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<tr>
<td>2010</td>
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<td></td>
</tr>
<tr>
<td>2011</td>
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<td></td>
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<tr>
<td>2012</td>
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- Current FVIII treatments
  - Limited half-life of only 8-12 hrs
  - Frequent IV injections
  - Induce neutralizing antibodies, which inhibit their function

### Bypassing agent market ($2.1bn)†

<table>
<thead>
<tr>
<th>Year</th>
<th>FEIBA VH</th>
<th>NovoSeven</th>
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<tbody>
<tr>
<td>2009</td>
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<td>2010</td>
<td>$1.9 bn</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>$2.1 bn</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>$2.1 bn</td>
<td></td>
</tr>
</tbody>
</table>

- 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  ‡EvaluatePharma consensus analyst estimates
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

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
## Roche data highlights at ASH 2015

**Gazyva combinations**
- Rituxan refractory NHL: Phase 3 GADOLIN update
- 1L or R/R CLL: Phase 3 GREEN subgroup analysis with bendamustine
- 1L CLL: Phase 3 CLL14 safety run-in, combo with venetoclax

**venetoclax**
- R/R CLLp17 del: Phase 2 data presentation

**venetoclax combinations**
- 1L AML: Phase 1b with decitabine or azacitidine
- R/R NHL: Phase 1 + Rituxan + bendamustine
- 1L or R/R CLL: Phase 1b with Gazyva

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**Roche curtain raiser highlighting key abstracts on new data at ASH to be released today**
Roche Pharma Day 2015

Molecular Information

Garret Hampton  VP, Oncology Biomarker Development
Pharmaceuticals Division
Personalized healthcare
A cornerstone of the Genentech / Roche strategy

- **60% of pipeline programs are being developed with companion diagnostics**

### Molecule

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
<th>BTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra</td>
<td>(Systemic sclerosis)</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>(R/R CLL 17p)</td>
<td>✓</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>(NSCLC)</td>
<td>✓</td>
</tr>
<tr>
<td>ACE 910</td>
<td>(Hemophilia)</td>
<td></td>
</tr>
<tr>
<td>Esbriet</td>
<td>(IPF)</td>
<td></td>
</tr>
<tr>
<td>Lucentis</td>
<td>(DR)</td>
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<tr>
<td>Atezolizumab</td>
<td>(Bladder)</td>
<td>✓</td>
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<tr>
<td>Alectinib</td>
<td>(ALK+ NSCLC)</td>
<td>✓</td>
</tr>
<tr>
<td>Gazyva</td>
<td>(1L CLL)</td>
<td></td>
</tr>
</tbody>
</table>

**4 out of 9 BTDs enabled by a Dx that identified patients most likely to benefit**
Significant advances in cancer biology

Multiple molecular subsets of disease

**PD-L1 Expression**

- EGFR
- KRAS
- MET
- KIF5B-RET
- ROS1 Fusions
- NRAS
- HER2
- BRAF
- PIK3CA
- AKT1
- MAP2K1
- MET splice site
- ALK Fusions
- Unknown
Molecular Information in oncology

Combination of molecular and patient data will enable change in R&D and clinical practice

- Smarter, more efficient R&D
- Better patient care

- Molecular understanding of cancer
- Database & Analytics interface
- Treatment plan selected
- Patient outcomes
- Patients matched to clinical trials
Multiple capabilities required
Comprehensive tumor analysis and longitudinal assessment

<table>
<thead>
<tr>
<th>Comprehensive tumor analysis</th>
<th>Continuous monitoring over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA-mutation &amp; CNVs</td>
<td>Cell free tumor DNA</td>
</tr>
<tr>
<td>Ex: EGFR, BRAF</td>
<td>Ex: EGFR, BRAF</td>
</tr>
<tr>
<td>DNA sequencing</td>
<td>Blood DNA sequencing</td>
</tr>
<tr>
<td>mRNA-expression</td>
<td>Imaging</td>
</tr>
<tr>
<td>Cell signatures, targets</td>
<td>Ex: ImmunoPet</td>
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<tr>
<td>RNA sequencing</td>
<td></td>
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<td>Protein-expression</td>
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<tr>
<td>PDL1, other CI targets</td>
<td></td>
</tr>
<tr>
<td>Multiplex IHC</td>
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</tr>
</tbody>
</table>

Ex: EGFR, BRAF, PDL1, other CI targets

Imaging Ex: ImmunoPet

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Foundations

Roche

Genentech
FMI R&D collaboration

Our partnership with FMI is key to informing R&D by leveraging molecular information

Comprehensive tumor analysis

<table>
<thead>
<tr>
<th>DNA-mutation &amp; CNVs</th>
<th>mRNA-expression</th>
<th>Protein-expression</th>
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</thead>
<tbody>
<tr>
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<td>Cell signatures, targets</td>
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<td>Multiplex IHC</td>
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Continuous monitoring over time

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<td>Ex: ImmunoPet</td>
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<tr>
<td>Blood DNA sequencing</td>
<td>Imaging</td>
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</table>

Molecular Information from FMI database and GNE/Roche clinical trials (FM1 & FM1 heme)

Immunotherapy panel development (DNA & RNA)

Development of a blood-based molecular assays
Clinical trial data

Roche / FMI database queries

Example: PIK3CA mutations in multiple cancers

50,000+ patient data in FMI database

Cancer indications (with > 50 cases)
Implementation of FMI panels in development

*Focus on high-value clinical samples*

**Current prioritization***:

1. Trials with post-progression biopsy (with archival baseline samples)
2. Phase 3 trial** n>300
3. Phase 2 trial* n>100
4. Phase 1b combos

** Positive trial, evidence of activity or potential identification of subset / high value for informing our pipeline (i.e., importance of disease setting / indication / treatment)
## FMI R&D collaboration

### Immunotherapy R&D collaboration

### Comprehensive tumor analysis

<table>
<thead>
<tr>
<th>DNA-mutation &amp; CNVs</th>
<th>mRNA-expression</th>
<th>Protein-expression</th>
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### Continuous monitoring over time

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**Immunotherapy panel development (DNA & RNA)**

Ex: ImmunoPet
Checkpoint inhibitors

Most effective in “inflamed” tumors

Inflamed
- TILs
- PD-L1 expression
- CD8+ T cells
- Genomic instability
- Pre-existing immunity

Non-inflamed
PD-L1 IHC: Staining for TCs and ICs
Assay sensitivity critical in detecting both cell types

Immune cells (ICs)  Tumor cells (TCs)  Tumor and immune cells (TCs and ICs)

e.g. bladder  e.g. NSCLC

WCLC 2015
1IMvigor 210 ECC 2015, 2POPLAR ECC 2015
Patient selection enriches for benefit

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

**Lung cancer: Survival hazard ratio***

| TC3 or IC3 | 0.49 |
| TC2/3 or IC2/3 | 0.54 |
| TC1/2/3 or IC1/2/3 | 0.59 |
| TC0 and IC0 | 1.04 |

**ITT N=287**

- In favor of atezolizumab
- In favor of docetaxel

**Bladder cancer: Overall survival***

- **Median OS Not Reached** (95% CI, 7.6-NE)
- **Median OS 6.7 mo** (95% CI, 5.7-8.0)

* Monotherapy data

ECC 2015
Benefit is not the same for every patient
Some patients with high expression of PD-L1 do not benefit – why?

Example: Atezolizumab phase 1 data in urothelial bladder cancer patients
Many types of data will be needed to inform patient care including:

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

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

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

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

- **Other Dx & patient data**
  - Ex: Imaging, outcomes etc
  - EMRs

1. **PDL-1 IHC and multiplex IHC**
   - Immune cell types and signatures

2. **Mutation burden & neo-epitope prediction**
Gene expression & combination hypotheses

Understanding the biology of immune cells in tumors enables combination hypotheses.
Gene expression & combination hypotheses

Understanding the biology of immune cells in tumors enables combination hypotheses

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

**Hypothesis:** Anti-CSF-1R removes macrophages which may enable atezolizumab activity

**Myeloid signature:** IL1B, IL8, CCL2

**PD =** Progressive disease  
**SD =** Stable disease  
**CR/PR =** Complete/partial response
Unlocking full value of CI through combinations
Broadest industry portfolio in oncology

1

Chen and Mellman, Immunity 2013; CI=cancer immunotherapy
Gene expression as a predictive biomarker

Presence of INFγ-producing CD8 T-cells predicts benefit in NSCLC treated with atezolizumab

Patients with a high tumor IFNg-associated gene signature derive OS benefit from atezolizumab in NSCLC (POPLAR)
Biomarkers for cancer immunotherapy

Key platforms for discovery and development

Many types of data will be needed to inform patient care including:

1. **Immune cell types and signatures**
2. **Mutation burden & neo-epitope prediction**

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

- **mRNA-expression**
  - Cell signatures, targets
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  - Ex: EGFR, BRAF
  - DNA sequencing

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

- **Other Dx & patient data**
  - Ex: Imaging, outcomes etc
  - EMRs

- **Other**
  - DNA sequencing
  - Protein-expression
  - EMRs
Mutation burden is clinically important

*Tumors with higher numbers of mutation tend to be more sensitive to anti-PDL1 / anti-PD1*

Conclusions

- **Transformational time**
- **Molecular Information**
- **Personalised healthcare**
Roche Pharma Day 2015

Biosimilar market in context

Fermin Ruiz de Erenchun  |  Global Head Biologic Strategy Team
Pharmaceuticals Division
Biosimilars: Ten years in the making

Regulatory environment

Summary
Biosimilars: Ten years in the making

EU pioneered the biosimilar concept
- Six products approved, including the first mAb biosimilar (infliximab)
- Uptake did not achieve saving expectations

WHO leading global efforts; many emerging countries implemented WHO biosimilar guidelines as a reference

US published final biosimilars guideline
- FDA pathway operating, 3 applications pending, one approval

Differential adoption of WHO biosimilar guidelines led to registration of Non-Comparable Biotherapeutic products (NCBs)*, driven by:
- Capacity issues at National Regulatory Agencies
- Local economic development policies

Biosimilar entry timelines delayed (incl. Herceptin & MabThera)

*For definition and industry position on NCBs please refer to IFPMA Policy Statement: http://www.ifpma.org/uploads/media/Non-comparable_Biotherapeutic_Products__English__01.pdf
Current biosimilar trends
So far, sales have not achieved initial expectations

MAT 870 CHFm (June 2015)
(CAGR 25.5%)

*Excludes US as no biosimilars have been approved in the US so far (Omnitrope was approved under the 505(b) pathway)
IMS Health; MAT=moving annual total
Generics vs biosimilars

Clear divide in uptake; complex market drivers

Market share

Driven by price and patient offering
9 innovators, one biosimilar
Efficacy visible only longer term
No switching

Payer driven: 7 biosimilars
Efficacy visible immediately
High turnover of patients

Small molecule
Virtually disappear

Sources: IMS Biosimilar Dashboard, IMS & Roche analysis
1 Volume market share based on EU5 average; 2 Volume market share based on average of France & Germany EPO; 3 Data based on % remaining sales in EU
Despite 10 years of experience in the EU, uptake of biosimilars differs across countries.

Anti-TNF market is not a good analogue for oncology

Infliximab biosimilar could expand beyond its accessible market and obtain market share from Enbrel® and Humira®
Small molecules and biologics
Not all the same

• Small molecule policies allow substituting patients → only the price counts

• For biologics, European Medicine Agency (EMA) does not provide guidance on interchangeability and substitution

• Most countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines
  – Biologics must be prescribed by brand name
  – Laws against substitution
  – Switching remains a physician’s choice
Payer environment is one of multiple drivers for biosimilar uptake

Drivers?

- Payer environment
- Therapeutic area
- Innovation and change in SoC
- Physician’s support
Biosimilars: Ten years in the making

Regulatory environment

Summary
Establishment of biosimilar guidelines has increased driven by WHO efforts
Requirements and study designs are different for biosimilars vs innovator products

<table>
<thead>
<tr>
<th>Aspects of development</th>
<th>Biosimilar</th>
<th>Innovator product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Sensitive and homogeneous (patients are <em>models</em>)</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Clinical design</strong></td>
<td>Comparative versus innovator, normally equivalence</td>
<td>Superiority vs standard of care (SoC*)</td>
</tr>
<tr>
<td><strong>Study endpoints</strong></td>
<td>Sensitive, clinically validated PD markers</td>
<td>Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Similar safety profile to innovator; no new findings</td>
<td>Acceptable benefit/risk profile versus SoC*</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Similar immunogenicity profile to innovator</td>
<td>Acceptable risk/benefit profile versus SoC*</td>
</tr>
<tr>
<td><strong>Extrapolation</strong></td>
<td>Possible if justified</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

* In some cases SoC may not exist
How should extrapolation risk be managed?

The regulator’s perspective
How should extrapolation risk be managed?

The physicians’ perspective

I would like to see a phase III trial for each indication.
# What is the right patient population to establish clinical similarity to Herceptin?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Metastatic population (advanced BC)</th>
<th>Neoadjuvant/Adjuvant population (early BC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PK</strong></td>
<td>✗ Affected by patient’s status &amp; tumor burden</td>
<td>✓ Homogeneous population can be selected</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>✗ Clinically validated PD marker not available</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical efficacy/safety</strong></td>
<td>✗</td>
<td>✓ Populations less likely to be confounded by baseline characteristics and external factors</td>
</tr>
<tr>
<td></td>
<td>• Difficult to select homogeneous group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status…)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Population with heterogeneous characteristics affecting final clinical outcome</td>
<td></td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>✗ Immune system affected by performance status and concomitant chemotherapies received</td>
<td>✓ Immune system impaired during chemotherapy cycles, but likely to recover to <em>normal</em> status thereafter</td>
</tr>
</tbody>
</table>
The regulatory thinking is evolving

The Herceptin case

<table>
<thead>
<tr>
<th>mBC Phase III Start Date</th>
<th>Regulatory Filing</th>
<th>eBC Phase III Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celltrion Q2 2010</td>
<td>x</td>
<td>Q1 2014</td>
</tr>
<tr>
<td>Mylan Q4 2012</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Pfizer Q4 2013</td>
<td></td>
<td>Q2 2014</td>
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Biosimilars: Ten years in the making

Regulatory environment

Summary
Generics, biosimilars: Not all the same

- **Small molecules:** Policies allow fast penetration of generics

- **Biosimilars:** Countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines
  - Biologics must be prescribed by brand name, laws against automatic substitution, switching remains a physician’s choice, EMA - no guidance on interchangeability
  - After 10 years of experience in the EU, uptake of biosimilars differ heavily across countries

- **Regulatory environment:** Still evolving with authorities in the process of finally establishing frameworks; case by case decisions likely