Agenda

Welcome
Karl Mahler, Head of Investor Relations

Roche in immunology – overview
Mark Eisner, M.D. Global Head of Product Development – Immunology, Infectious Disease & Ophthalmology

Phase II Nobility data - efficacy and safety of obinutuzumab or placebo in combination with mycophenolate mofetil in patients with Lupus Nephritis
Larry Tsai, M.D., Global Head of Rheumatology & Respiratory Development

Q&A
Karl Mahler, Head of Investor Relations
Welcome
Karl Mahler
Head of Investor Relations
Rich pipeline newsflow in 2019
Upcoming conferences and IR events*

**Today**

- **Gazyva + SOC**: Ph II (*NOBILITY*) in lupus nephritis

**November 8 - 13**

- **CD20 x CD3 bispecifics mosunetuzumab and RG6026**: Ph I mono and combo data in R/R NHL
- **Polivy + bendamustine**: Ph Ib/II update in R/R DLBCL
- **Venclexta**: Ph III updates in R/R and 1L CLL (MURANO, CLL14); Ph I data in MDS, MM, AML

**Upcoming conferences and IR events**

- **KIDNEY WEEK 2019**
  - November 8 - 13
  - **November 8 - 13**

- **ACR ARP ANNUAL MEETING**

- **ESMO ASIA 2019**
  - Save the date!
  - **November 22-24, 2019**

- **SABCS**
  - **December 10-14, 2019**
  - **December 7-10, 2019 | ORLANDO, FL**

- **TECENTRIQ + AVASTIN**: Ph III (IMbrave150) in 1L HCC

- **PERJETA + HERCEPTIN**: Ph III (APHINITY) 2nd interim OS / iDFS update in HER2+ eBC
- **P+H FDC subcut**: Ph III (FeDeriCa) in HER2+ eBC
- **PI3Ki RG6114**: Ph I data in PIK3CA-mutated HR+ BC
- **SERDI RG6171**: Ph I data in HR+ BC

* Planned submissions (to be confirmed)
Roche: Strong presence in immunology
Annualized sales approaching CHF 9bn

Immunology Q3 2019 update

**Esbriet (+6%)**
- Growth in mild to moderate segments

**Actemra (+9%)**
- EU: Remains leader in overall and 1L monotherapy RA
- Growth driven by RA new patient starts and GCA launches

**Xolair (+3%)**
- Growth driven by CIU
- Positive Ph III (POLYP I/II) results in nasal polyps filed in the US

**Gazyva (lupus nephritis)**
- BTD received; data presented at ASN and ACR/ARP 2019

CER=Constant Exchange Rates; RA=rheumatoid arthritis; GCA=giant cell arteritis; CIU=chronic idiopathic urticaria; BTD=breakthrough therapy designation; ASN=American Society of Nephrology; ACR/ARP=American College of Rheumatology/Association for Rheumatology Professionals
Roche in immunology – overview

Mark Eisner, M.D.
Global Head of Product Development - Immunology, Infectious Disease & Ophthalmology
Roche legacy in immunology

- Organ rejection in patients receiving kidney, heart, or liver transplants.
- Rheumatoid arthritis
- Granulomatosis with Polyangiitis
- Microscopic Polyangiitis
- Pemphigus Vulgaris
- Cystic fibrosis.
- Moderate to severe persistent allergic asthma
- Chronic idiopathic urticaria.
- Rheumatoid arthritis
- Paediatric juvenile idiopathic arthritis
- Systemic juvenile idiopathic arthritis
- Giant cell arteritis
- CAR-T cell-induced cytokine release syndrome.
- Idiopathic pulmonary fibrosis.
Creating new opportunities across therapeutic areas

**Xolair**
- Selectively blocks human IgE-mediated mast cell activation
- Positive Ph III data in nasal polyps, US filing on track for Q4 2019
- BTD in food allergy Q3 2019, Ph III pivotal study ongoing

**Etrolizumab**
- Anti-β7 integrin with dual MoA - blocks leukocyte trafficking and lymphocyte retention
- Extensive Ph III program in ulcerative colitis and Crohn’s disease
- Data readout in UC expected in 2020

**Gazyva**
- Type II anti-CD20 provides enhanced B cell depletion
- Positive Ph II data in lupus nephritis with enhanced efficacy vs SOC in complete renal response at 1 year
- Ph III to start Q1 2020
Immunology pipeline

**Indication**

- **asthma**
- **inflammatory diseases**
- **Autoimmune diseases**
- **Rheumatoid arthritis**
- **Lupus nephritis**
- **Ulcerative colitis**
- **Crohn’s disease**
- **Nasal polyps**
- **Food allergy**
- **CIU**
- **IPF**

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**Phase I**

- **NME (RG6151)**
- **NME (RG6244)**
- **NME (RG6173)**
- **NME (RG7835)**

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**Phase II**

- **ST2 MAb (RG6149)**
- **IL-22 Fc (RG7880)**
- **fenebrutinib (RG7845)**
- **Gazyva (RG7159)**

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**Phase III**

- **etrolizumab (RG7413)**
- **etrolizumab (RG7413)**
- **Xolair (RG3648)**
- **Xolair (RG3648)**

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**Approved**

- **Xolair (RG3648)**
- **Actemra (RG1569)**
- **MabThera (RG105)**
- **etrolizumab (RG7413)**
- **etrolizumab (RG7413)**
- **Xolair (RG3648)**
- **Xolair (RG3648)**
- **Xolair (RG3648)**
- **Esbriet (RG6062)**
Etrolizumab: First dual-action anti-Integrin targeting α4β7/αEβ7
Potential for best in class efficacy targeting two sources of inflammation

Etrolizumab Ph3 program in UC and Crohn’s disease
A landmark program designed to generate compelling claims

**Etrolizumab phase 3 program**

**ULCERATIVE COLITIS**

- **HIBISCUS I** induction trial comparing etro vs placebo and etro vs. adalimumab in anti-TNF naïve patients
- **HIBISCUS II** induction trial comparing etro vs. placebo and etro vs. adalimumab in anti-TNF naïve patients
- **LAUREL** maintenance trial evaluating etro vs. placebo in anti-TNF naïve patients
- **HICKORY** induction and maintenance; etro vs. placebo in anti-TNF-IR patients
- **GARDENIA** sustained remission evaluating etro vs infliximab in anti-TNF naïve patients
- **COTTONWOOD** open-label extension evaluating safety in pts previously enrolled in etro Ph 2 or 3

**CROHN’S DISEASE**

- **BERGAMOT** induction and maintenance trial of etro vs. placebo in anti-TNF naïve and IRs
- **JUNIPER** open-label extension trial evaluating safety in patients enrolled from BERGAMOT

**Comprehensive IBD dataset**

- 8 clinical studies
  - 6 Ph3 trials, 2 open-label extension studies
  - TNF-naïve and TNF-IR
- Longitudinal dataset with clinical data, imaging, histology, multiomics, microbiome

**Program of firsts**

- First head-to-head comparisons vs. both Humira and Remicade (anti-TNFs) in randomized, controlled pivotal studies in UC
- First to evaluate endoscopic improvement in Crohn’s disease
- First to use central endoscopy reading for patient eligibility and endpoint assessment

• Phase 3 data in ulcerative colitis expected in 2020

Anti-TNF-IR patients are patients who are refractory to or intolerant of TNF inhibitors
Lupus Nephritis
Autoimmune disease with significant unmet medical need

- **Lupus nephritis (LN)** is characterized by:
  - Protein and blood in the urine
  - Progressive loss of kidney function

- Prevalence ~500,000 in US, EU, Brazil, and China
  - Young women of color at greatest risk
  - ~50-60% of patients with systemic lupus erythematosus progress to LN

- **8x risk of death** vs. the general population, due to:
  - Uncontrolled disease, complications of treatment or dialysis
  - Cardiovascular disease

- **No approved therapies**
  - Unapproved SOC is only partially effective despite high rates of toxicities

Lupus Nephritis
Significant morbidity and mortality due to end-stage renal disease (ESRD)

>20% risk of ESRD within 15 years in patients with LN

Increased risk of death in patients on dialysis due to ESRD

1. Source: Tektonidou et al. Arthritis & Rheumatology 2016; ESRD - End-stage renal disease
2. Source: Special analyses, USRDS ESRD Database and Medicare 5 percent sample, 2012. All-cause mortality in the ESRD and Medicare populations with specific comorbid conditions identified in the preceding year, point prevalent sample on January 1, 2012, adjusted for race. TIA: transient ischemic attack CVA: cerebral vascular accident; AMI: acute myocardial infarction
Phase II Nobility data - efficacy and safety of obinutuzumab or placebo in combination with mycophenolate mofetil in patients with Lupus Nephritis

Larry Tsai, M.D.
Global Head of Rheumatology & Respiratory Development
A Phase II Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Obinutuzumab or Placebo in Combination with Mycophenolate Mofetil in Patients with Active Class III or IV Lupus Nephritis

Richard Furie,1 Gustavo Aroca,2 Analía Alvarez,3 Hilda Fragoso-Loyo,4 Elizabeth Zuta Santillán,5 Brad H. Rovin,6 Thomas Schindler,7 Imran Hassan,8 Matthew D. Cascino,9 Jay P. Garg,9 and Ana Malvar10

Disclosures

• This study was funded by Genentech, Inc.
• R Furie: Genentech.
• BH Rovin: Genentech, Aurinia, BristolMyersSquibb, Biogen, Pfizer, Eli Lilly, GlaxoSmithKline, Mallinckrodt, EMD Serono, Omeros, Calliditas, Retrophin, BioMarin.
• PG Brunetta: former employee of Genentech.
• T Schindler, I Hassan: employees of Roche.
• MD Cascino, JP Garg: employees of Genentech.
B-cell depletion in lupus nephritis

- End-stage renal disease risk from proliferative lupus nephritis (LN) remains high\(^1\)

- B-cells are central to LN pathogenesis but RCTs of Type I anti-CD20 antibodies rituximab and ocrelizumab showed mixed results\(^2,3\)

- Variability in B-cell depletion with Type I anti-CD20 antibodies in SLE may be responsible for inconsistent clinical responses\(^4,5\)

- It is hypothesized that greater B-cell depletion in peripheral blood and tissue may lead to improved clinical responses\(^4,6\)

Obinutuzumab

- Obinutuzumab is a humanized Type II anti-CD20 approved for combination treatment of CLL and follicular lymphoma\(^1\)

- Enhanced B-cell depletion vs. rituximab and ofatumumab:
  - **Glycoengineering**: Up to 100x antibody-dependent cytotoxicity\(^2,3\)
  - **Type II binding conformation**: Greater direct cell death, reduced internalization, lower complement-dependent cytotoxicity\(^2,3\)

- Greater B-cell depletion than rituximab in tissue\(^3\) and SLE patient samples\(^4\)

- Superior to rituximab in H2H trials in B-cell malignancies\(^5,6\)

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**NOBILITY design**

**Key inclusion criteria:**
- ISN/RPS Class III or IV LN within six months, concomitant class V permitted
- UPCR ≥1 on 24-hour collection

**Key exclusion criteria:**
- Rapidly progressive glomerulonephritis
- eGFR <30 mL/min/1.73 m²
- >50% of glomeruli with sclerosis

**Primary endpoint:**
- Complete renal response (CRR) at week 52

**Key secondary endpoints:**
- Overall renal response (CRR or PRR)
- Change in levels of dsDNA, C3, C4

* Prespecified alpha level = 0.2

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**104 week double-blind period**

<table>
<thead>
<tr>
<th>Obinutuzumab 1000 mg + MMF (n=63)</th>
<th>Placebo + MMF (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients received MMF, 1000 mg methylprednisolone, and a prednisone taper*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OBI or PBO infusions</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24</th>
<th>26</th>
<th>36</th>
<th>Week 52</th>
<th>Week 76</th>
<th>104</th>
</tr>
</thead>
</table>

* MMF target dose 2-2.5g, oral prednisone 0.5 mg/kg/day tapered to 7.5 mg/day by Week 12 and held until Week 52. NCT02550652
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab + MMF (n=63)</th>
<th>Placebo + MMF (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>55 (87%)</td>
<td>51 (82%)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>42 (67%)</td>
<td>49 (79%)</td>
</tr>
<tr>
<td>White</td>
<td>10 (16%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td><strong>Prior history of LN</strong></td>
<td>32 (51%)</td>
<td>32 (52%)</td>
</tr>
<tr>
<td><strong>Class IV LN</strong></td>
<td>49 (78%)</td>
<td>44 (71%)</td>
</tr>
<tr>
<td><strong>Concomitant class V LN</strong></td>
<td>20 (32%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td><strong>Serum creatinine – mg/dL</strong></td>
<td>0.87 ± 0.34</td>
<td>0.80 ± 0.33</td>
</tr>
<tr>
<td><strong>Serum creatinine ≤ ULN</strong></td>
<td>51 (81%)</td>
<td>55 (89%)</td>
</tr>
<tr>
<td><strong>UPCR</strong></td>
<td>3.3 ± 2.7</td>
<td>2.9 ± 2.5</td>
</tr>
<tr>
<td><strong>Anti-dsDNA positive</strong></td>
<td>31 (49%)</td>
<td>36 (58%)</td>
</tr>
<tr>
<td><strong>C3 &lt; 90 mg/dL</strong></td>
<td>43 (68%)</td>
<td>37 (60%)</td>
</tr>
<tr>
<td><strong>C4 &lt; 16 mg/dL</strong></td>
<td>37 (59%)</td>
<td>44 (71%)</td>
</tr>
</tbody>
</table>

All categorical variables are reported as n (%). Continuous variables are reported as mean ± SD. ULN = upper limit of normal
**Exposure and disposition**

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab + MMF (n=63)</th>
<th>Placebo + MMF (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received four study drug infusions</td>
<td>57 (90%)</td>
<td>54 (87%)</td>
</tr>
<tr>
<td>MMF exposure – median</td>
<td>2.0 g/day</td>
<td>2.0 g/day</td>
</tr>
<tr>
<td>Corticosteroid exposure through Week 52 – median</td>
<td>4008 mg</td>
<td>4009 mg</td>
</tr>
<tr>
<td>Completed 52 weeks of follow-up</td>
<td>59 (94%)</td>
<td>56 (90%)</td>
</tr>
<tr>
<td>Completed 76 weeks of follow-up</td>
<td>58 (92%)</td>
<td>52 (84%)</td>
</tr>
<tr>
<td>Died</td>
<td>1 (2%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Required any rescue therapy</td>
<td>6 (10%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Required cyclophosphamide rescue</td>
<td>2 (3%)</td>
<td>6 (10%)</td>
</tr>
</tbody>
</table>

All categorical variables are reported as n (%). Prespecified rescue therapies included pulse steroids, cyclophosphamide, and rituximab.
Renal response endpoints

**Complete renal response (CRR)**

- **CRR required all of:**
  - UPCR < 0.5
  - Serum creatinine ≤ upper limit of normal
  - Serum creatinine ≤ 115% of baseline value
  - <10 RBC/hpf without RBC casts

- **Week 52:**
  - Obinutuzumab + MMF: 35%
  - Placebo + MMF: 23%
  - Δ12%, P=0.11

- **Week 76:**
  - Obinutuzumab + MMF: 40%
  - Placebo + MMF: 18%
  - Δ22%, P=0.007

**Overall renal response (CRR or PRR)**

- **PRR required all of:**
  - UPCR ≥ 50% reduction to <1 (to <3 if baseline ≥3)
  - Serum creatinine ≤ 115% of baseline value
  - RBC ≤50% above baseline or <10 RBC/hpf

- **Week 52:**
  - Obinutuzumab + MMF: 56%
  - Placebo + MMF: 36%
  - Δ20%, P=0.02

- **Week 76:**
  - Obinutuzumab + MMF: 51%
  - Placebo + MMF: 29%
  - Δ22%, P=0.02

PRR = partial renal response
Alternative complete response definitions at Week 76

- **CRR**:
  - UPCR < 0.5
  - SCr ≤ ULN
  - SCr ≤ 115% of baseline
  - <10 RBC/hpf without casts
  - Δ22%, P=0.007

- **Excluding sediment**:
  - UPCR < 0.5
  - SCr ≤ ULN
  - SCr ≤ 115% of baseline
  - Δ25%, P=0.003

- **Permissive SCr criteria**:
  - UPCR < 0.5
  - SCr ≤ ULN
  - Δ20%, P=0.02

SCr = serum creatinine; ULN = upper limit of normal. All endpoint definitions were prespecified in the study protocol.
CRR over time

* P < 0.2; ** P < 0.05; *** P < 0.01 for comparison vs. placebo.
Mean change in laboratory values

Last observation prior to treatment failure is applied for missing data. Comparisons were adjusted for stratification factors (region, race).

* P < 0.02; ** P < 0.05; *** P < 0.01 for comparison vs. placebo.
B-cell depletion in peripheral blood

Mean CD19+ count

Percent with CD19+ count ≤ 5 cells/μL

<table>
<thead>
<tr>
<th>Week</th>
<th>Obinutuzumab + MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>96%</td>
</tr>
<tr>
<td>Week 4</td>
<td>96%</td>
</tr>
<tr>
<td>Week 12</td>
<td>94%</td>
</tr>
<tr>
<td>Week 24</td>
<td>93%</td>
</tr>
<tr>
<td>Week 52</td>
<td>94%</td>
</tr>
</tbody>
</table>
B-cell subsets

Memory B-cells: CD45+, CD19+, CD27+
Naïve B-cells: CD45+, CD19+, IgD+, CD27-, CD38dim/-
Plasmablasts: CD45+, CD19+, CD27+, CD38bright

Obinutuzumab + MMF
Placebo + MMF
Safety summary at Week 76 data cut

<table>
<thead>
<tr>
<th>Event</th>
<th>Obinutuzumab + MMF (n=64)</th>
<th>Placebo + MMF (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration, wks – median</td>
<td>86.6</td>
<td>77.1</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>56 (88%)</td>
<td>55 (90%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (2%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>GI perforation</td>
<td></td>
<td>GI bleed, SLE, PML, Resp. infection</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>15 (23%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Serious infection events</td>
<td>4 (6%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Infection adverse event</td>
<td>45 (70%)</td>
<td>39 (64%)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation from blinded infusions</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10 (16%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Serious infusion-related reaction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

All categorical variables are reported as n (%).
One patient randomized to placebo inadvertently received active obinutuzumab during the first cycle. This patient is included in the obinutuzumab group for safety analyses.
Conclusions

• NOBILITY met its primary and key secondary endpoints

• Obinutuzumab resulted in clinically-meaningful benefits over SOC alone on renal response through Week 76

• Significant improvements in serologies and proteinuria were also observed

• Obinutuzumab resulted in rapid and complete depletion of peripheral B-cells without an increase in serious adverse events, serious infections, or deaths over SOC alone

• Blinded data through Week 104 are forthcoming

• Initiation of a global Phase III trial is planned for early 2020
We thank all study participants and their families, and our investigators and study coordinators

**NOBILITY Investigators**

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Singhal, Atul K.  
Thanou, Aikaterini  
Wallace, Daniel  
Ximenes, Antonio Carlos  
Zazueta, Beatriz  
Zunino, Daltro  
Zuta Santillan, Adolfina
Doing now what patients need next