Roche Pharma Day 2019

Late Stage Immunology and Infectious Disease

Cristin Hubbard | Senior Vice President Immunology, Infectious Disease & Ophthalmology, Global Product Strategy
Zafar Hakim | Senior Director, Disease Area Strategy, Immunology, Infectious Disease & Ophthalmology
Creating new opportunities across therapeutic areas

**Immunology and Infectious disease**

<table>
<thead>
<tr>
<th><strong>Gazyva</strong></th>
<th><strong>Etrolizumab</strong></th>
<th><strong>Xolair</strong></th>
<th><strong>Xofluza</strong></th>
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<td>A type II anti-CD20 that provides enhanced B cell depletion</td>
<td>Gut-selective anti-β7 integrin with dual MoA inhibiting lymphocyte trafficking &amp; retention</td>
<td>Xolair blocks IgE-mediated mast cell activation</td>
<td>CAP-dependent endonuclease inhibitor</td>
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- **Gazyva**
  - Efficacy in lupus nephritis in randomized Ph II trial

- **Etrolizumab**
  - Extensive Ph III program in Ulcerative Colitis and Crohn’s Disease

- **Xolair**
  - Expanding into nasal polyps and food allergies

- **Xofluza**
  - First “single dose” treatment for influenza that shortens flu symptoms

MoA = mechanism of action
Late stage pipeline update

Topics covered in presentations and break-out sessions

1. Hematology franchise
   - CLL: Venclexta Gazyva
   - DLBCL: Polivy, Venclexta
   - NHL, DLBCL: mosunetuzumab, CD20xCD3
   - AML: Venclexta, idasanutlin
   - MM: Venclexta

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   - HER2+: Kadcyla, Perjeta, FDC SC, Tecentriq
   - TNBC: Tecentriq, ipatasertib
   - HR+: ipatasertib; PI3Kα inhibitor

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   - NSCLC: Tecentriq
   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek

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   - OC: Tecentriq, Avastin
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   - MS: Ocrevus update
   - SMA: risdiplam
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10. Oncology / Hematology
    - Immunology
    - Neuroscience
    - Ophthalmology
    - Infectious diseases
    - Immunology

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Lupus Nephritis
A serious condition with high unmet medical need

**500k patients**\(^1\) globally with lupus nephritis

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

- **Young women of color** at greatest risk

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

- **No approved therapies in US**

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suppl 1 Dall’Era 2017; Izmirly 2017; Arnaud 2014; Brinks 2016; CDC’s Morbidity and Mortality Weekly Report – 2002; RBC=red blood cells
Incomplete efficacy in Lupus Nephritis with type I anti-CD20 Abs

**B cells are central to Lupus Nephritis (LN)**

**In lupus, autoreactive B cells:**
- Secrete pathogenic autoantibodies & proinflammatory cytokines
- Present self-antigens
- Activate T cells

**Prior experience with type 1 anti-CD20 therapy**

**Two RCTs failed to confirm clinical benefit of type 1 anti-CD20 therapies in LN**
- LUNAR \((n=144)\): no Complete Renal Response benefit when rituximab added to SOC
- BELONG \((n=367)\): no Complete Renal Response benefit when ocrelizumab added to SOC

**B cell depletion associated with response**

- **Rituximab failed to achieve complete depletion** in many lupus patients when assessed with high sensitivity flow cytometry (HSFC)
- Lupus B cells express mechanisms of resistance to depletion
- Clinical responses appear to be better when complete depletion is achieved as observed in the NOBILITY trial

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Rahman and Isenberg 2008; Rovin 2012; Mysler 2013, Mendez 2018; RCT=randomized controlled trial; SOC=standard of care
Gazyva: A novel glyoengineered type II anti-CD20 Ab
Positive Ph II results in lupus nephritis

Ph II (NOBILITY) results

- Ph II (NOBILITY) met both primary and key secondary endpoints
- High unmet medical need; no treatment approved
- Ph III program to be initiated

Gazyva: Greater B-cell depletion may improve efficacy

Type II anti-CD20 region:
- Increased direct cell death
- Decreased CDC
- Reduced CD20 internalization

Glycoengineered Fc region:
- Higher FcγR affinity
- Enhanced ADCC/ADCP

- Gazyva’s MOA shows greater potency than Rituxan in depleting peripheral and tissue-based B cell populations
- Recent studies suggest that tissue-based B cells play a role in lupus nephritis and that their complete depletion is needed

CDC=complement-dependent cytotoxicity; ADCC=antibody-dependent cell-mediated cytotoxicity; ADCP=antibody-dependent cellular phagocytosis; MOA=mechanism of action; Moessner et al., Blood, 2010; Niederfellner et al., Blood, 2011; Dalle et al., MCT, 2011; Jak et al., Blood, 2011; Alduaij et al., Blood, 2011; Lim et al., Blood, 2011; Honeychurch et al., Blood, 2012; Peviani et al., Blood, 2011; Bologna et al., JI, 2011; Braza et al., Haematologica, 2011; Patz et al., BJH, 2011
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**Ulcerative colitis**
- Age of onset 20-30 years
- Adult pop: 1.2m (US+EU5)
- 50% with moderate/severe disease
- Bloody diarrhea with urgency
- Repeated flares

**Crohn’s Disease**
- Age of onset 15-30 years
- Adult pop: 1.1m (US+EU5)
- 50% with moderate/severe disease
- Abdominal pain, diarrhea sometimes bloody
- Frequent surgical interventions

**Significant disease burden**
- Bowel perforation
- Toxic megacolon
- Fistulae and strictures
- Abscesses
- Colostomy
- Pouchitis

**Quality of life impact**
- Increased risk of colon cancer
- Infertility
- High rates of depression, anxiety, increased suicide
- High rates of severe fatigue, disability, and chronic pain

IBD is a severely debilitating disease that impacts young patients. ~1.3m patients globally with moderate-severe disease.

Loftus et al (2014); Bhandari et al (2017); Gradus et al (2010); Abautret-Daly et al (2017); Morrison et al (2013); Jess et al (2013); InSync Patient Journey Study (2015); Adelphi DSP (2015); IBD=inflammatory bowel disease
High unmet need for improved efficacy in moderate to severe IBD

Low Remission Rates with UC Standard of Care
Many patients lose response over time

- Only 10-20% of patients remain in remission at 1 year
- Onset of some agents are slow, taking up to 12 weeks
- Low rates of endoscopic healing and histological improvement
- Current standard of care increases risk of serious infection and/or malignancy
- No current ability to personalize based on phenotype/biomarker
- Potential to raise the efficacy ceiling with a safe backbone to combine treatments

Adapted from Amiot A. and Peyrin-Biroulet L. Therap Adv Gastroenterol. 2015; 8(2): 66–82; IBD=inflammatory bowel disease; UC=ulcerative colitis
Etrolizumab: First dual-action anti-Integrin targeting α4β7/αEβ7
Potential for best in class efficacy targeting two sources of inflammation

Etrolizumab Ph III program in UC and Crohn’s Disease

A landmark program designed to generate compelling claims

### Etrolizumab Ph III development program

<table>
<thead>
<tr>
<th>Ulcerative colitis (UC)</th>
<th>Comprehensive IBD dataset</th>
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<tbody>
<tr>
<td><strong>HIBISCUS I:</strong> Induction trial comparing etro vs. adalimumab vs. placebo in anti-TNF naïve patients</td>
<td><strong>• 8 clinical studies</strong></td>
</tr>
<tr>
<td><strong>HIBISCUS II:</strong> Induction trial comparing etro vs. adalimumab vs placebo in anti-TNF naïve patients</td>
<td>- 6 Ph III trials, 2 open-label extension studies</td>
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<td><strong>LAUREL:</strong> Maintenance trial evaluating etro vs. placebo in anti-TNF naïve patients</td>
<td>- TNF-naïve and TNF-IR</td>
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<tr>
<td><strong>HICKORY:</strong> Induction and maintenance; etro vs. placebo in anti-TNF incomplete responders</td>
<td><strong>• Longitudinal dataset with clinical data, imaging, histology, multiomics, microbiome</strong></td>
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<td><strong>GARDENIA:</strong> Sustained remission evaluating etro vs infliximab in anti-TNF naïve patients</td>
<td><strong>Program of firsts</strong></td>
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<td><strong>COTTONWOOD:</strong> Roll-over, open-label extension trial evaluating safety</td>
<td><strong>• First head-to-head comparisons vs. both Humira and Remicade (anti-TNFs) in randomized, controlled pivotal studies in UC</strong></td>
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<td><strong>BERGAMOT:</strong> Induction and maintenance trial of etro vs. placebo in anti-TNF naïve and IRs</td>
<td><strong>• First to evaluate endoscopic improvement in Crohn’s disease</strong></td>
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<tr>
<td><strong>JUNIPER:</strong> Roll-over, open-label extension trial evaluating safety</td>
<td><strong>• First to use central endoscopy reading for patient eligibility and endpoint assessment</strong></td>
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<tr>
<td></td>
<td><strong>• Evaluating over 3,000 patients for induction and maintenance of disease remission</strong></td>
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TNF IR is defined as patients who are refractory to or intolerant of TNF inhibitors; etro=etrolizumab; IBD=inflammatory bowel disease
UC: In patients refractory/intolerant to anti-TNF, symptomatic remission started early and continued to increase to Week 14

Ph III HICKORY

- HICKORY is an ongoing Ph III clinical trial in anti-TNF intolerant patients with moderately-to-severe active UC
- In the open-label induction cohort at 14 weeks, etrolizumab treatment resulted in:
  - clinically meaningful rates of endoscopic improvement
  - symptomatic remission
  - improvements in inflammatory biomarkers
- The response rate continues to increase over time
- The maintenance portion of this study is ongoing with data expected in 2020

Stool frequency¹ and rectal bleeding remission rates²

Ph III HICKORY STUDY with etrolizumab 105mg SC monthly

Rectal bleeding remission

- Remission rates increased through week 14
- Remission rates were approximately 30% at week 4 and 50% at week 14

Stool frequency remission

- Remission rates increased through week 14
- Remission rates were approximately 10% at week 4 and 25% at week 14

¹ SF remission defined as a weekly mean score of < 1.5 with ≥ 1-point reduction from baseline; ² RB remission defined as a weekly mean score of < 0.5 with ≥ 0.5-point reduction from baseline; Data presented at 12th Congress of ECCO; 17 February 2017; Barcelona, Spain; TNF intolerant is defined as patients who are refractory to or intolerant of TNF inhibitors; UC=ulcerative colitis; SC=subcutaneous
CD: Symptomatic remission and endoscopic improvement was shown during induction with monthly dosing

Ph III BERGAMOT

- BERGAMOT Cohort 1 enrolled over 70% of patients who were anti-TNF intolerant
- In this induction cohort, etrolizumab demonstrated clinically meaningful endoscopic improvement
- Symptomatic remission seen as early as week 6 and was observed consistently through week 14
- Etrolizumab was well tolerated, with frequency of adverse events comparable with placebo: no deaths, anaphylaxis, or PML were reported
- Study is continuing to enroll with data in 2021

Peyrin-Biroulet et al; 12th Congress of ECCO; 17 February 2017; Barcelona, Spain; TNF IR is defined as patients who are refractory to or intolerant of TNF inhibitors; CD=Crohn’s disease; PML=progressive multifocal leucoencephalopathy
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Continuing to invest in Xolair
New indications and patient convenience

New indications & ease of use

- **Food allergy with high unmet need**
  - Affects > 4.8 million children in US$^{1,2}$ with no approved preventative treatments except avoidance

- **Nasal Polyps**
  - Positive topline results in Q2 (data to be presented at ACAAI in November); US filing in Q4 2019

- **Rapid IgE point of care assay$^3$**
  - 5-minute point-of-care (POC) test to determine total IgE and specific IgE levels to 5 major perennial allergens associated with allergic asthma

- **Home use**
  - EU approval granted in Dec 2018; US filing planned

Food allergy

- **Allergen avoidance is only partially effective**
  - US: Every 3 minutes, someone goes to ER due to an adverse food reaction$^5$ and ~40% of children with food allergy have experienced anaphylaxis$^4,5$

- **Xolair blocks IgE-mediated mast cell activation with data to support efficacy across multiple food allergens$^6$**

- **Phase III OUTMATCH trial initiated Q3 2019**
  - Designed to determine whether Xolair can decrease or prevent allergic reactions to peanut and other food allergens allergens (such as cow’s milk, egg, wheat, cashew, hazelnut etc.)

- **Unique collaboration between NIH, CoFAR and Genentech/Novartis**
  - NIH-sponsored CoFAR (Consortium for Food Allergy Research) as the leading US academic food allergy research centers with established infrastructure and credibility

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Xofluza (baloxavir marboxil)  
A novel treatment for unmet needs in influenza

Influenza is a serious disease

- Annually **1 in 10 people are affected** by influenza, with millions hospitalized and up to **650,000 deaths**\(^1\) every year
- Currently approved antivirals have limitations in terms of efficacy, route of administration, convenience & resistance
- **Burden on the healthcare system**\(^2\), with significant socio-economic impact:
  - Lost workforce productivity
  - Strained healthcare services
- The risk of severe disease increased in **high-risk groups**: elderly, children, pregnant women and people with chronic health conditions

Xofluza is a novel treatment

- **Xofluza** is a potent **single dose** antiviral, significantly reducing time to cessation of viral shedding and reducing viral load significantly faster than the current standard of care
- **First in class** CAP-dependent endonuclease inhibitor
- **Approved in US in 2018**, and multiple countries
- **Xofluza** is safe and effective at reducing the duration of influenza symptoms compared with placebo
- **Xofluza** has been shown in non-clinical studies to have activity against oseltamivir-resistant and avian strains (H7N9, H5N1)

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1. Molinari NA, et al; 2. Estimated to be $87.1B; Baloxavir marboxil co-developed with Shionogi with Roche holding worldwide license excluding Japan and Taiwan
Xofluza with unique MOA: Broad development program
Single dose studied across variety of patient types and clinical settings

Unique mechanism of action

- Xofluza blocks viral mRNA transcription by inhibiting CAP-dependent endonuclease activity

Broad clinical program

Continuing to advance the science and address the largest unmet needs in influenza:

- **Variety of patient types being studied:**
  - Otherwise healthy patients (CAPSTONE-1)
  - High-risk patients (CAPSTONE-2)
  - Pediatric patients (miniSTONE-1)
  - Pediatric patients (miniSTONE-2)
  - Hospitalized patients (FLAGSTONE)

- **Variety of clinical settings being studied**
  - Post-exposure prophylaxis (BLOCKSTONE)
  - Transmission prevention (CENTERSTONE)

- **Pandemic planning**

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Xofluza data across multiple strains of influenza and patient types

**Recent Ph III data readouts**

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<td>Xofluza vs. placebo for <strong>post-exposure prophylaxis (PEP)</strong> study of Xofluza</td>
<td>Xofluza vs. Tamiflu in a <strong>pediatric population</strong></td>
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<td>• Significant reduction in time to alleviation of symptoms by &gt;24 hrs vs placebo</td>
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<td>• PEP with Xofluza reduces the risk of influenza by 86% compared with placebo</td>
<td>• Single-dose efficacy comparable to Tamiflu, a proven effective treatment for children with influenza</td>
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<td>• Time to cessation of viral shedding reduced by 48 hrs vs Tamiflu</td>
<td>• Better efficacy in Type B influenza comp to Tamiflu</td>
<td>• Benefit remains significant regardless of influenza A viral subtype, and is also observed in children &lt;12 years of age and in household contacts at high risk of influenza complications</td>
<td>• Strong reduction of viral shedding compared to Tamiflu</td>
</tr>
<tr>
<td>• Xofluza is well tolerated with no new safety signals</td>
<td>• Reduced use of systemic antibiotics &amp; incidence of influenza-related complications</td>
<td></td>
<td>• Well tolerated</td>
</tr>
</tbody>
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Baloxavir marboxil co-developed with Shionogi with Roche holding worldwide license excluding Japan and Taiwan
### Creating new opportunities across therapeutic areas

*Immunology and Infectious disease key data readouts*

<table>
<thead>
<tr>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
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<tbody>
<tr>
<td>Gazyva Lupus Nephritis</td>
<td><strong>Etrolizumab UC</strong></td>
<td><strong>Xolair Food Allergy</strong></td>
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<td><strong>Nobility</strong></td>
<td><strong>HICKORY</strong></td>
<td><strong>OUTMATCH</strong></td>
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<tr>
<td><strong>Xolair Nasal Polyps</strong></td>
<td><strong>Etrolizumab UC</strong></td>
<td><strong>Etrolizumab CD</strong></td>
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<td><strong>POLYP 1 &amp; POLYP 2</strong></td>
<td><strong>HIBISCUS I &amp; II</strong></td>
<td><strong>BERGAMOT</strong></td>
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<td><strong>Xofluza PEP</strong></td>
<td><strong>Etrolizumab UC</strong></td>
<td><strong>Xolair Hospitalized</strong></td>
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<td><strong>BLOCKSTONE</strong></td>
<td><strong>LAUREL, GARDENIA</strong></td>
<td><strong>FLAGSTONE</strong></td>
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<td><strong>Xofluza Pediatrics (1-12 yr)</strong></td>
<td><strong>Xofluza Pediatrics (0-1 yr)</strong></td>
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<td><strong>miniSTONE-2</strong></td>
<td><strong>MiniSTONE 1</strong></td>
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<td><strong>Xofluza Transmission</strong></td>
<td><strong>CENTERSTONE</strong></td>
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</tbody>
</table>

- Immunology
- Infectious Diseases
Doing now what patients need next