Roche: At the Forefront of R&D Innovation and Breakthrough Treatments

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Member of Corporate Executive Committee (CEC)
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Executive Summary

• Roche Group has an industry leading portfolio:
  – Large and Diverse

• Oncology: Continue to innovate, dominate and expand
  – Cancer Immunotherapy: extensive and combination approach
  – Breast cancer: SERD GDC-0810

• Beyond oncology: Follow the science
  – Neuroscience: Nav1.7
  – Infectious disease: Anti-Flu A

• gRED: Continuing transformative innovation into the future
Deep Biological Insights Drive Disease Strategies

**Oncology**
- Expand dominant leadership
- Explore new MOA: Cancer immunotherapy, SERD, etc.
- Pursue combinations and personalized medicines
- Develop new delivery platforms: ADC, Bi-specific, etc.

**Immunology**
- Grow respiratory and RA franchise
- Expand into other debilitating diseases

**Neuroscience**
- Focus on neurodegenerative disorders and pain

**Ophthalmology**
- Enhance delivery mechanisms
- Expand into dry AMD and GA

**Infectious Disease**
- Combat resistance and take advantage of biologics approach
2016 Onwards: Significant Launch Activities

Outcome studies are event-driven: timelines may change. Standard approval timelines of 1 year assumed.
Roche Has the Most Breakthrough Designations

12 Breakthrough Therapy Designations

<table>
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<th>Rank</th>
<th>Company</th>
<th>#</th>
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<tr>
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<td>BMS</td>
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<td>3</td>
<td>Novartis</td>
<td>6</td>
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<td>Merck</td>
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<tr>
<td>3</td>
<td>Pfizer</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>GSK</td>
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</tbody>
</table>

Year | Molecule                                      |
-----|-----------------------------------------------|
2016 | **Ocrelizumab** (PPMS)                       |
2016 | **Venetoclax** (AML)                         |
2016 | **Venetoclax + Rituxan** (R/R CLL)           |
2015 | **Actemra** (Systemic sclerosis)             |
2015 | **Atezolizumab** (NSCLC)                     |
2015 | **Venetoclax** (R/R CLL 17p del)             |
2014 | **Emicizumab/ACE 910** (Hemophilia A)        |
2014 | **Esbriet** (IPF)                            |
2014 | **Lucentis** (DR)                            |
2013 | **Alectinib** (2L ALK+ NSCLC)                |
2013 | **Gazyva** (1L CLL)                          |

Source: [http://www.focr.org/breakthrough-therapies](http://www.focr.org/breakthrough-therapies) as at 17 February 2016; CLL=Chronic Lymphocytic Leukemia; NSCLC=Non-Small Cell Lung Cancer; IPF=Idiopathic Pulmonary Hypertension; DR=Diabetic Retinopathy
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  – Neuroscience: Nav1.7
  – Infectious disease: Anti-Flu A

• **gRED**: Continuing transformative innovation into the future
CI Strategy: Combinations are the Future

Launched/late-stage portfolio

Chemotherapy combinations approved
Targeted combinations approved
Roche combinations in trials
Chemotherapy combinations in trials
Roche NMEs approval expected in 2016
Roche NMEs early stage
Approved non-Roche drugs
Cancer Immunology Research Focus: The Next Generation

Costimulators:
- Anti-OX40 Ab (Ph 1)
- NME1

Stromal modifiers:
- NME2
- NME3

Inhibitory checkpoints:
- Anti-TIGIT Ab (ED)
- NME4
- NME5
- NME6

T<sub>R</sub> cells:
- Anti-OX40 Ab (Ph 1)
- IDO SMI (Ph 1)
- NME7
- NME8

Cancer cell death and release of cancer proteins

Initiation of Immune Response

T cell activation and expansion

Immune cell trafficking and infiltration

Immune suppression

NMEs
anti-OX40: Dual Action Promotes T cell Activation and T Regulatory Cell Inhibition

anti-OX40: Promising Anti-Tumor Activity as Single Agent and in Combination with anti-PD-L1

Ongoing studies

- Phase 1a (MOXR0916)
- Phase 1b combination (MOXR0916 + atezolizumab)
- Planned (MOXR0916 + GDC-0919)

Jeong Kim et al. AACR 2015

MOXR0916 = anti-OX40
**GDC-0919 is a Potent and Selective IDO1 Inhibitor**

**IDO1:**
- IDO1 activity contributes to maternal-fetal tolerance and tumor immune escape
- Expression correlates with poor patient survival across a range of tumors
- **MOA:** Catabolizes Tryptophan to Kynurenine, suppresses effector T cells and enhances Tregs function

**IDO1 Inhibitor GDC0919 (NLG919):**
- Oral small molecule inhibitor of IDO1
- Being tested in Ph1b in combination with **atezolizumab**
Expanding our Leadership in Breast Cancer

SERDs degrade ER, down-regulate Estrogen Receptor (ER) and antagonize ER transcriptional activity

- atezolizumab (MPDL3280A)
- Ipatasertib (GDC-0068)
- SERD (GDC-0810; GDC-0927)
- Taselisib PI3K Inhibitor (GDC-0032)
- HER2+
- ER+
- TNBC
- Others
- Others 1%
- TNBC 13%
- HER2+ 21%
- ER+ 65%
- Others 13%
- HER2+ 21%
- ER+ 65%
SERD GDC-0810 Anti-tumor Activity in Patient with Mutant ESR1(E380Q)

Pre-treatment at Screening

Abnormal uptake in bone

On-treatment at Cycle 2 Day 3

Resolved uptake in bone

Pre-treatment at Screening

Post-treatment at Cycle 6 Day

CT

45% reduction in target lesions
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  – Neuroscience: Nav1.7
  – Infectious disease: Anti-Flu A

• **gRED: Continuing transformative innovation into the future**
## Beyond Oncology: Robust Portfolio across Multiple TAs

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunology</strong></td>
<td><strong>Ophthalmology</strong></td>
<td><strong>Neuroscience</strong></td>
<td><strong>Cardio Metabolism</strong></td>
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<tr>
<td>Cadherin-11 Mab RA</td>
<td>lebrikizumab - COPD</td>
<td>MabThera pemphigus vulgaris</td>
<td>Actemra – RA</td>
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<td>Cat-5 antag - Autoimmune Diseases</td>
<td>lebrikizumab - Atopic Dermatitis</td>
<td>Actemra giant cell arteritis</td>
<td>Actemra – Polyarticular &amp; Systemic Juvenile Idiopathic Arthritis</td>
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<tr>
<td>NME fibrosis</td>
<td>lebrikizumab +/- Esbriet - IPF</td>
<td>Actemra systemic sclerosis</td>
<td>Rituxan - RA</td>
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<td>IL22 Fc inflammatory disease</td>
<td>obinutuzumab lupus nephritis</td>
<td>Lebrikizumab severe asthma</td>
<td>Rituxan - Granulomatosis w/ Polyangiitis &amp; Microscopic Polyangiitis</td>
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<tr>
<td>Erivedge + Esbriet IPF</td>
<td>nemolizumab (IL-31R) atopic dermatitis</td>
<td>Etrolizumab ulcerative colitis</td>
<td>Esbriet - IPF</td>
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<tr>
<td>obinutuzumab renal transplant</td>
<td>nemolizumab (IL-31R) pruritus dialysis pts</td>
<td>Etrolizumab Chron’s Disease</td>
<td>Xolair – Asthma</td>
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<tr>
<td>BTK Inh autoimmune disease</td>
<td>VAP-1 Inh Inflam. disease</td>
<td>Actemra large vessel vasculitis</td>
<td>Xolair – CIU</td>
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<tr>
<td>NME glaucoma</td>
<td>Lucentis wAMD port delivery</td>
<td>Ilapalizumab - Geographic Atrophy</td>
<td>Lucentis – wAMD</td>
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<td>VEGF-ANG2 biMab - wAMD</td>
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<td>Lucentis – DME</td>
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<td>Lucentis RVO</td>
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<td>Lucentis – Diabetic Retinopathy w/ DME</td>
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<td><strong>Infectious Diseases</strong></td>
<td><strong>Neuroscience</strong></td>
<td><strong>Cardio Metabolism</strong></td>
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<td>alpha Synuclein Mab Parkinsons Disease</td>
<td>olesoxime - Spinal Muscular Atrophy</td>
<td>Ocrelizumab PPMS</td>
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<td>ASO Huntington’s Disease</td>
<td>basimisranil - Down Syndrome</td>
<td>Ocrelizumab RMS</td>
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<td>Nav 1.7 inh (2) pain</td>
<td>V1 recp antag (2) autism</td>
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<tr>
<td>SMN2 splicer (2) spinal muscular atrophy</td>
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<td><strong>Ophthalmology</strong></td>
<td><strong>Cardio Metabolism</strong></td>
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<td>Flu B Mab Influenza B</td>
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<td>NME HBV</td>
<td>danoprevir HCV</td>
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<td>HBV Therapeutic vaccine</td>
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<td>NME infectious disease</td>
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<tr>
<td>FGFR1/KLB Mab metabolic disease</td>
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Pain Remains a Huge Unmet Need

Medical Issue

• 20% of individuals experience pain (majority moderate-severe)

• Current development dominated by reformulated or next gen opioids with similar liabilities to current therapy

Unmet Need

• Only 25% of patients achieve adequate relief with current therapy

• Inadequate response primarily due to insufficient efficacy & narrow safety margins that limit dose

Opportunity

• Pain drugs with new MOAs that:
  – Increase potency
  – Improve safety
  – Limit addiction
Nav1.7 Genetically Validated in Humans

1. Human Nav1.7 mutations
   - Loss of function mutations result in pain insensitivity
     (CIP - congenital insensitivity to pain)
   - Activating mutations cause spontaneous pain syndromes
     (IEM - inherited erythromelalgia, PEPD - paroxysmal extreme pain disorder; SFN - small fiber neuropathy)

2. Mouse Nav1.7 knock-outs show efficacy in:
   - Acute pain models (e.g. burn injury)
   - Inflammatory models (e.g., CFA)
   - Neuropathic models (e.g., SNT and CCI)
gRED has Potent and Selective Nav 1.7 Antagonists

Selectivity profile of GDC-0276
 (>25-fold selective over other Nav channels)

GDC-0276 inhibits pain in an
IEM [Nav1.7(I848T)] transgenic mouse

Clinical Program Summary

- **GDC-0276**: SAD complete and MAD to be completed this year
- **GDC-0310**: A second highly selective and potent Nav1.7 inhibitor in phase 1
- Phase 2 expected in late 2016/early 2017
Severe Influenza – Significant Unmet Need

Epidemiology

- **600,000** hospitalizations in US and EU
- **25,000** deaths in US alone
- Vaccinations: Efficacy dependent on immunocompetence and antigen match
  - 2014: CDC estimate of vaccine effectiveness only 18% against circulating H3N2
- Cases: 80% Influenza A, 20% Influenza B

Unmet need Remains Significant

- **25%** of hospitalized patients require ICU care
  - Mean ICU stay is 7.2 days, median 4 days
- **10% - 30%** mortality rate in the ICU
- No therapy has demonstrated clinical benefit in hospitalized patients with severe influenza

“Spanish Flu” 1918 Influenza Pandemic Millions Dead
Novel Influenza-A Antibody Can Rescue Lethal Infection

Anti-Flu A

- Human antibody binds to a conserved site on the stalk of HA, blocking endosomal fusion required for viral replication
- Neutralizes all tested seasonal and pandemic human influenza A viruses
- Strong pre-clinical survival data as single agent and in combination with Tamiflu

Nakamura, Chai et al, Cell Host Microbe 2013
Anti-Flu A Reduces Viral Load and Symptoms in Humans

Global **Phase 2b ‘Proof of Concept’** study in hospitalized influenza A infected patients **began Q1 2015**

**Composite Symptom Score**

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<tr>
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<th>Placebo</th>
<th>3600mg</th>
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<tr>
<td>Symptom Score</td>
<td>207.7</td>
<td>37.7</td>
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<tr>
<td>% Reduction</td>
<td>81.8%</td>
<td>81.8%</td>
</tr>
<tr>
<td>p-Value</td>
<td>(0.29)</td>
<td>(0.29)</td>
</tr>
</tbody>
</table>

**Median AUC by quantitative PCR**

-97.5%
p=0.0051
gRED: Continuing the transformative innovation into the future

• Innovation is alive and well at gRED: top talent and great portfolio

• Continue to focus on oncology while expanding into broader therapeutic areas by following the science

• gRED is a premier innovation center for Roche with access to Roche’s global leadership and resources
<table>
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<tr>
<th>Early Dev</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td>Avastin</td>
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- **Oncology**
- **Immunology**
- **Neuroscience**
- **Ophthalmology**
- **Metabolism**
- **Infectious Diseases**

- Projects with Companion Diagnostics
Doing now what patients need next