Genentech: Pipeline with focus on Partnering

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Senior Vice President of Genentech Partnering
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Research and early-stage development

- Genentech (gRED)
  - Genentech Partnering
- Roche Pharma (pRED)
  - Roche Partnering
- Chugai Pharmaceutical

Late-stage development

- Roche Pharmaceuticals
- Roche Diagnostics
Partnering is Essential, and We Partner Early

50% of pipeline and marketed products derive from successful collaborations

~50 active collaborations with companies and institutions from around the world

90% of product deals are pre-clinical
Genentech Track Record of Successful Innovation

- Genentech Founded
- Rituxan (rituximab) Proven. Promising.
- ACTIVASE® (alteplase) A recombinant version of alteplase.
- Pulmozyme® (dornase alfa) Enzyme that breaks down DNA in the lungs.
- TNKase® (tenecteplase) The one shot for AMI.
- Xolair (omalizumab) For severe allergens use.
- AVASTIN® (bevacizumab) ado-trastuzumab emtansine.
- PERJETA™ (pertuzumab) Pertuzumab.
- LUCENTIS® (ranibizumab injection)
- Tarceva® (erlotinib) Tablets.
- ZELBORAF® (vemurafenib) Tablets.
- GAZYVA® (obinutuzumab injection)

Timeline:
- '76
- '85
- '87
- '93
- '96
- '97
- '98
- '00
- '01
- '03
- '04
- '06
- '12
- '13
Maximize Value for Each Partner

- We don’t believe in a “one size fits all” solution
- We design deals to fit the science and the needs of both companies
- As investors have become less patient with the length of time - and cost - involved in developing new medicines, smaller biotech companies are seeking innovative ways to structure deals
gRED Portfolio

31 molecules from Early Development to Phase 2 (20 with Collaborators)

<table>
<thead>
<tr>
<th>Early Devt (16)</th>
<th>Phase 1 (10)</th>
<th>Phase 2 (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NME</td>
<td>Anti-CD20/CD3</td>
<td>Lifastuzumab Vedotin (Anti-NaPi2b ADC)</td>
</tr>
<tr>
<td>NME</td>
<td>ChK-1 inh (GDC-0575)</td>
<td>Ipatasertib (GDC-0068)</td>
</tr>
<tr>
<td>NME</td>
<td>ERK inh (GDC-0994)</td>
<td>SERD (GDC-0810)</td>
</tr>
<tr>
<td>NME</td>
<td>IDO Inh (GDC-0919)</td>
<td>Anti-Influenza A</td>
</tr>
<tr>
<td>NME</td>
<td>Anti-OX40</td>
<td></td>
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<tr>
<td>NME</td>
<td>SERD (GDC-0927)</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Anti-STEAP1 ADC</td>
<td></td>
</tr>
<tr>
<td>NME (GDC-3280)</td>
<td>NME ADC</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>NME ADC</td>
<td></td>
</tr>
<tr>
<td>NME (GDC-0276)</td>
<td>Anti-HER3 EGFR DAF</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>NME (GDC-0310)</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Anti-Influenza B</td>
<td></td>
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<tr>
<td>NME</td>
<td>Anti-Influenza B</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Nav1.7 (GDC-0276)</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Nav1.7 (GDC-0310)</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Anti-Influenza A</td>
<td></td>
</tr>
</tbody>
</table>

Source: active gRED molecules as of September 30, 2015. Phase is based on FPI.
Genentech Portfolio Strategy

**gRED’s focus is to:**

1. Remain the leader in Oncology
2. Continue to deliver diagnostic-based therapies in Immunology & Ophthalmology
3. Make significant advances in Neuroscience, Infectious Diseases, and other key areas

**R&D highlights:**

- Robust portfolio of large molecules and small molecules
- Advances in antibody engineering
- Personalized Health Care: right medicine for the right patient
Outline: Project Highlights

- **Oncology:**
  - Selective Estrogen Receptor Degrader (SERD) GDC-0810
  - Venetoclax: BCL-2 Inhibitor GDC-0199

- **Neuroscience:**
  - Ocrelizumab
  - Nav1.7
Seragon: Selective Estrogen Receptor Degrader (GDC-0810)

Expanding our Leadership in Breast Cancer
Breast cancer: Still high unmet medical need

Roche proposing solutions for most segments

- ER+/PR+/Her2- (11%)
- ER+/PR-/Her2- (10%)
- ER-/PR+/Her2+ (7%)
- ER-/PR-/Her2+ (2%)
- ER-/PR+/Her2+ (1%)
- ER+/PR-/Her2- (13%)
- ER+/PR+/Her2+ (55%)

Taselisib
PI3K inhibitor
Expanding Our Leadership in Breast Cancer

- Genentech acquired Seragon Pharmaceuticals in August 2014, which included two Selective Estrogen Receptor Degrader (SERD) molecules: GDC-0810 and GDC-0927

- SERDs increase the rate of ER degradation and prevent estrogen from binding to and activating the ER

- ER activity is a critical driver in the 60-70% of patients that are ER +

- Inhibition of estrogen binding to the ER or inhibition of estrogen synthesis is mainstay therapeutic strategy in treatment of ER+ BC

SERD GDC-0810 Demonstrates Tumor Regressions in Tamoxifen Sensitive and Tamoxifen Resistant Breast Cancer Animal Models

ER+ BC xenograft model

GDC-0810 is superior in treating tamoxifen-resistant BC xenografts

Tamoxifen resistance @ ~70 days

GDC-0810 time to tumor progression >1yr

GDC-0810 @ 30 mg/kg and 100 mg/kg
SERD GDC-0810 FES-PET Response and Anti-tumor Activity in Patient with ESR1 E380Q Mutant Tumor

Pre-treatment at Screening

Abnormal uptake in bone

On-treatment at Cycle 2

Resolved uptake in bone

Pre-treatment at Screening

CT

Post-treatment at Cycle 5

CT
Venetoclax: Bcl-2 inhibitor

Expanding our Leadership in Hematology
Hematology: Expanding Our Franchise

Replace CD20 backbone

Extend

Replace and extend

Medical value

Rituxan®/MabThera®

Gazyva®/Gazyvaro™

Rituxan®/MabThera®

Venetoclax (GDC-0199)
Anti-CD79b ADC
Other molecules

Gazyva®/Gazyvaro™

CLL11 study etc.

MURANO Study

CLL14 study, etc.
B-cell Hematologic Malignancies:
Our Portfolio Addresses Multiple Drug Targets

Adapted from Zenz et al., Nature Reviews Cancer, 2010, p. 37-50
Venetoclax Bcl-2 inhibitor (GDC-0199) + Rituxan® in R/R CLL: Deep Reductions in Bone Marrow Infiltrates & Nodal Masses

34/49 (69%) patients achieved complete marrow clearance by morphology and IHC
- Median time to complete marrow clearance was 7 months (range: 6 – 16)

20/49 (41%) patients achieved reduction in all target lesions to ≤1.5 cm
- Median (range) time to normalization was 8 months (6 – 18)

Roberts et al, EHA 2015
## Objective Responses

<table>
<thead>
<tr>
<th>Best Objective Response, n (%)</th>
<th>All Patients n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td></td>
</tr>
<tr>
<td>Complete response, CR (includes 6 CRi)</td>
<td>41 (84)</td>
</tr>
<tr>
<td>Partial response, PR (includes 1 nPR)</td>
<td>20 (41)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Death (TLS) a</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*a Fatal TLS event previously reported; no other fatal TLS events occurred after May 2013 protocol amendment*

- 38 patients remain on study
- 11 discontinued (6 due to PD; 3 withdrew consent; 2 due to AE)
Bone Marrow Minimal Residual Disease (MRD) at 7 Months

MRD was assessed in 15 patients with CR/CRi and 22 patients with a PR using local institutional methods and sensitivity $\leq 10^{-4}$

<table>
<thead>
<tr>
<th>Response Classification</th>
<th>Evaluated Patients</th>
<th>MRD Negative</th>
<th>MRD Positive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15</td>
<td>9</td>
<td>6 (range: 0.003% – 2.3%)</td>
<td>• 1/6 became MRD-negative at 14 months</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
<td>8 (range: 0.05 – 0.44%)</td>
<td>14</td>
<td>• 4/8 with MRD-negative disease have one remaining lymph node &gt;1.5 cm as the only remaining evidence of disease</td>
</tr>
</tbody>
</table>

a Remaining lymph node sizes for the 8 patients with MRD negative PR:
   4 patients with a single lymph node (1.7, 2.2, 2.3 and 2.7 cm)
   4 patients with multiple (2-4) lymph nodes (largest of which is 2.2, 2.3, 2.3, and 2.4 cm)
   the last patient also has splenic involvement

Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed / Refractory CLL
Venetoclax Met Phase 2 Primary Endpoint in CLL - Filings planned in 2015

- Small molecule inhibitor of BCL-2
- Pivotal phase 2 study met primary endpoint in a hard-to-treat type of CLL
- Regulatory submissions planned in US and EU by end of 2015
- Phase 2 and 3 studies in several types of blood cancer

In collaboration with AbbVie (ABT-199). J.E. Seymour, ASCO 2014, abstract # 7015
R/R CLL: relapsed/refractory chronic lymphocytic leukemia.
Neuroscience: Ocrelizumab

Phase 3 studies in RMS and PPMS
RMS and PPMS

*Distinct diseases with different need*

**RMS**
- Characterized by clearly defined attacks of worsening neurologic function followed by increasing disability later
- Patients usually diagnosed in 20s and 30s
- 12 approved treatment options demonstrated reduction in relapses, progression and number of brain MRI lesions
- Safer high efficacy medicines are needed for earlier treatment

**PPMS**
- Characterized by steady progression of disability from beginning, mostly without relapses
- About 15% of overall MS cases
- Patients usually diagnosed in 40s and 50s
- To date there is no approved disease-modifying treatment, several medicines have failed Ph3 trials
B cells can contribute to the pathophysiology of MS

Targeting CD20⁺ B cells may preserve B cell reconstitution and long-term immune memory

Ocrelizumab is a humanised monoclonal antibody that selectively depletes CD20⁺ B cells

OPERA I and II: Two identical studies evaluating the efficacy and safety of ocrelizumab in RMS

1:1 Randomisation

- RMS diagnosis
- 18–55 yrs
- ≥2 clinical relapses within last 2 yrs or 1 relapse in last yr
- EDSS of 0.0–5.5

Double-blind Double-dummy Treatment Period

Ocrelizumab
Dose 1: 300 mg i.v. x 2 (days 1 & 15)
Doses 2-4: 600 mg i.v. x 1

IFN β-1a
Dosed 44 µg s.c. 3 x per week

1 Randomisation

OLE screening period

Safety follow-up
≈48 weeks from date of last infusion

B-cell monitoring‡

‡Continued monitoring occurs if B cells are not repleted.
EDSS, Expanded Disability Status Scale; IFN, interferon; i.v., intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; s.c., subcutaneous.
OPERA I and II: Two identical studies evaluating efficacy and safety of ocrelizumab in RMS

Primary endpoint: Significant reduction in Annual Relapse Rate compared with IFN β-1a

\[ \text{ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; IFN, interferon; ROW, rest of the world.} \]

\[ \text{ITT} \]

*Adjusted ARR calculated by negative binomial regression and adjusted for baseline EDSS score (<4.0 vs ≥4.0), and geographic region (US vs ROW).

\[ \text{ARR reduction vs IFN β-1a p<0.0001} \]

46% ARR reduction vs IFN β-1a

47% ARR reduction vs IFN β-1a
ORATORIO: Phase III Study in primary progressive MS (PPMS)

Diagnosis of PPMS (2005 revised McDonald criteria)¹
- Age 18–55 years
- EDSS 3.0–6.5
- CSF: elevated IgG index or ≥1 oligoclonal bands
- No history of RRMS, SPMS, or PRMS
- No treatment with other MS DMTs at screening

2:1 Randomisation

Blinded Treatment Period
Minimum five 24-week treatment doses for a total of 120 weeks†

OCRELIZUMAB 600mg i.v. infusions every 24 weeks*

DOSE 1  DOSE 2  DOSE 3  DOSE 4  DOSE 5  DOSE N

WEEK  BL  2  24  26  48  50  72  74  96  98  120+

MRI  MRI  MRI

PLACEBO

Patients discontinuing treatment enter safety follow-up

Safety follow-up
≥48 weeks from date of last infusion

B-cell monitoring‡

BL, baseline; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; i.v., intravenous; MRI, magnetic resonance imaging.

ORATORIO: Phase III study in primary progressive MS (PPMS)

Primary endpoint: Significant reduction in 12-week CDP

Time to 12-week Confirmed Disability Progression

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

- 24% reduction in risk of CDP
  HR (95% CI): 0.76 (0.59, 0.98); p=0.0321

Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression. CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.
Neuroscience: Nav1.7

Voltage-gated sodium channel for pain indications
Pain is a huge unmet need

- Pain is a significant medical issue
  - 20% of individuals experience pain (majority moderate-severe)
- There is a substantial unmet medical need for novel pain drugs
  - Only 25% of people with pain achieve adequate relief with current therapy
  - Driven primarily by insufficient efficacy & narrow safety margins that limit dose
- Clinical studies are primarily dominated by reformulated or next generation opioids with similar liabilities to current therapy
- There is a huge opportunity for novel pain drugs with new mechanisms of action
Evolutionary Experiment Validates Na\textsubscript{v}1.7 as Pain Target

Loss of function mutations in humans results in no pain of any kind (CiP)

Gain of function mutations result in:

1. Inherited Erythromelalgia (IEM)
2. Paroxysmal Extreme Pain disorder
**Na_v1.7: Excellent Drug Target for Pain**

Pain sensing receptors begin to depolarize the nerve. Nav1.7 senses the change in polarization and then opens.

Signal propagates down the nerve. Inactivated state

**Phase 1 study is ongoing**

**Lead compound: Selectivity relative to other Na_v channels**

**Lead compound: Oral dosing results in significant reduction in pain behavior**

<table>
<thead>
<tr>
<th>Lead compound: Selectivity relative to other Na_v channels</th>
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<tbody>
<tr>
<td>CNS Na_v</td>
</tr>
<tr>
<td>CNS Na_v</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>CNS Na_v</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normalized log [Na_v inhibitor]</th>
<th>Normalized Current</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
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<table>
<thead>
<tr>
<th>Nociceptive Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
</tr>
<tr>
<td>Na_v inhibitor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0-5</th>
<th>5-10</th>
<th>10-15</th>
<th>15-20</th>
<th>20-25</th>
<th>25-30</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>250</td>
<td>200</td>
<td>150</td>
<td>100</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Na_v inhibitor</td>
<td>250</td>
<td>200</td>
<td>150</td>
<td>100</td>
<td>50</td>
<td>0</td>
</tr>
</tbody>
</table>
Collaboration Structure

XENON

- Helped discover human genetic evidence implicating Nav1.7 as compelling pain target
- Deep expertise in pain and ion channels
- Compelling early stage inhibitor molecules

Genentech

- Consider Nav1.7 to be best novel, biologically validated pain target
- Pain is re-emerging area, looking to leverage partner’s know-how

Integrated collaboration maximizes PTS for first-in-class and/or best-in-class compound for high-priority, highly-competitive target

COLLABORATION TO PURSUE EMERGING BIOLOGY

- Upfront payment, research funding
- Eligible for milestone payments that could reach $650MM
- Royalties

- Exclusive license to all collaboration compounds
- Exclusive access to know-how and proprietary research technologies
Genome Sequencing
Strengthening Our Drug Discovery and Development

Critical for the continued success of our molecules in the clinic:
- Disease understanding
- Target identification and validation
- Clinical trial enrichment for personalized health care
- Companion diagnostics

Whole Genome Sequencing 3,000 Parkinson’s Disease patients

Whole Genome Sequencing 16,000 clinical trial patients over next two years

Targeted sequencing Immunotherapy program companion diagnostic development blood-based monitoring
Roche/FMI R&D Collaboration

1. Comprehensive tumor analysis in Roche` Clinical Trials
   DNA & RNA sequencing

2. We will innovate together
   Immunotherapy Panel
   Blood based continuous monitoring

- Our Phase 3 anti-PDL1 program is a primary focus of the collaboration
- We will use FMI's FoundationOne next generation DNA sequencing to look at a spectrum of DNA mutations
- We will also be working with Foundation Medicine to develop RNA signatures that may be predictive of patient benefit
Summary

- External innovation is an integral part of our R&D effort: over 50% of the Genentech portfolio reflects partnering and collaboration activities.

- Most of our partnerships are for assets and technologies with a strategic fit with our internal portfolio and discovery effort.

- We selectively partner for assets outside of our areas of research when science is compelling and work closely with the partner to advance the asset.

- Our recent effort into exploring human genetics is well positioned to aid in characterizing the complexity of various diseases and discovery of new therapeutic targets.
Q&A