Genentech: Pipeline with focus to role of Partnering

James Sabry, MD, PhD
Senior Vice President of Genentech Partnering
Roche Group

Unique diversity of approaches

Academia & industry

Over 150 partners

Independent centers for research and early development

Global Product Development

Manufacturing

Commercialisation

Roche Diagnostics
gRED Portfolio
34 molecules from ED to Ph2 (18 with Collaborators)

Early Devel (9)
- NME

Phase 1 (13)
- Anti-ETBR ADC
- Anti-MUC16 ADC
- Anti-NaPi ADC
- Anti-STEAP1 ADC
- ChK-1 inh (GDC-0425)
- ChK-1 inh (GDC-0575)
- PI3K inh (GDC-0032)
- PI3K inh (GDC-0084)
- Anti-IL17
- NME

Phase 2 (12)
- Pinatuzumab vedotin (Anti-CD22 ADC)
- Polatuzumab vedotin (Anti-CD79b ADC)
- Anti-HER3 EGFR DAF
- Apitolisib (GDC-0980)
- Ipatasertib (GDC-0068)
- Pictilisib (GDC-0941)
- Quilizumab (Anti-M1 prime)
- Rontalizumab (Anti-IFNα)
- Crenezumab (Anti-Aβ)
- Lampalizumab (Anti-Factor D)
- Anti-PCSK9
- NME targeting CMV

Source: Roche Q3 2013 Investors Update; October 17, 2013
Genentech Portfolio Strategy

Genentech’s focus is to:
- Remain the leader in Oncology
- Continue to deliver diagnostic-based therapies in Immunology
- Make significant advances in Neuroscience, Infectious Diseases, Ophthalmology, and other key areas

R&D highlights:
- Robust portfolio of “large molecules” and “small molecules”
- Advances in antibody engineering
- Personalized Health Care (PHC): right medicine for the right patient
Expanding Our Leadership in Oncology

**Future:** Leading in further outcome improvements

<table>
<thead>
<tr>
<th>Combinations</th>
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<tbody>
<tr>
<td>Immunotherapy (anti-PDL1, NMEs)</td>
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<tr>
<td>Antibody Drug Conjugates (ADCs)</td>
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<tr>
<td>New pathways (MET, PI3K, apoptosis)</td>
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**Present:** Transformative approaches

<table>
<thead>
<tr>
<th>HER2 Pathway</th>
<th>Heme Franchise</th>
<th>Anti-angiogenesis</th>
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<tbody>
<tr>
<td>Herceptin, Kadcyla, Perjeta</td>
<td>Rituxan, Gazyva, Bcl-2, ADCs</td>
<td>Avastin</td>
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</table>
Advances in Antibody Engineering

**Antibody Drug Conjugate**
- Antibody + linker + cytotoxic agent
- Example: Kadcyla for HER2+ breast cancer

**Dual-Action Antibodies**
- Designed to target two receptors, inhibiting ligand binding to both receptors
- Example: Anti-HER3/EGFR DAF for solid tumors

**Monovalent Antibodies**
- Monovalent (one-armed), monoclonal antibody – can inhibit binding
- Example: Onartuzumab (MetMAb) for lung and other major cancers
Oncology

Ophthalmology

Immunology

Neuroscience
**ADC’s: Multiple Interconnected Alliances**

**Antibody Drug Conjugates (Armed Antibodies)**

- **Immunogen:** License to Maytansinoid Conjugates
- **SGEN:** License to Auristatin Conjugates
- **Nerviano:** Anthracycline Conjugates
- **XXXX:** MTA for proprietary linker-drug reagents
- **SGEN:** Negotiating amendment to obtain option to name additional targets
- **XXXX, Spirogen, XXXX:** MTAs for proprietary DNA-damaging linker-drug reagents
- **Spirogen:** PBD Conjugates
- **Nerviano:** Manufacturing anthracycline conjugates

**Deal Activity**

- '00
- '01
- '02
- '03
- '05
- '07
- '08
- '09
- '10
- '11

**Clinical Data**

- Positive T-DM1 Ph. II results
- Positive Ph. I SGEN35 results
**Antibody Drug Conjugate (ADC) Portfolio**

*Extensive pipeline of ADCs for oncology indications*

<table>
<thead>
<tr>
<th>Early Development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III/Launched</th>
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<tr>
<td><strong>Solid Tumors</strong></td>
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<tr>
<td>ADC NME</td>
<td>Anti-STEAP1</td>
<td>Anti-NaPi2b</td>
<td>Kadcyla* HER2+ Breast</td>
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<tr>
<td>Breast</td>
<td>Prostate</td>
<td>Ovarian</td>
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<td></td>
<td>Anti-MUC16</td>
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<td></td>
<td>Pancreatic</td>
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<td>Anti-NaPi2b</td>
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<td>Lung</td>
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<td>Melanoma</td>
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<td>Multiple Myeloma</td>
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<td><strong>Heme Malignancies</strong></td>
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<td>Anti-CD79b</td>
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<td>NHL</td>
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<td>Anti-CD22</td>
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<td>NHL</td>
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<tr>
<td><strong>Infectious Diseases</strong></td>
<td>Antibody Antibiotic</td>
<td>Expand Heme</td>
<td>Build on strength in HER2+ mBC</td>
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<tr>
<td>Conjugate NME</td>
<td>Conjugate NME</td>
<td>franchise</td>
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**Strategy**

*Extend ADC benefit to additional tumor types; Explore platform for antibiotics (AAC)*

* Kadcyla approved in US Feb. 2013
ADCs in hematology: Anti-CD22 and anti-CD79b

Phase I responses in multiple histologies

Anti-tumor responses observed by histology

ADCs in collaboration with Seattle Genetics

Presented at ICML 2013
ADCs in hematological cancers: Anti-CD22 and anti-CD79b

ROMULUS phase II

NHL (R/R FL and 2/3 line DLBCL)  
N=120

- anti-CD22 ADC + rituximab  
- anti-CD79b ADC + rituximab

Primary end-point: Progression Free Survival  
Expect data: 2014
Lampalizumab

Anti-factor D in Geographic Atrophy
Clinical spectrum of AMD

- Initially, visual acuity minimally affected; signs are anatomic (drusen and pigmentary changes) with symptoms of visual function impairment (e.g., dark adaptation, contrast sensitivity)

Advanced AMD

Geographic Atrophy
- non fovea-threatening
- fovea-threatening
- fovea-involved

Wet AMD

Arch Ophthalmol 2001;119:1417-1436
Lampalizumab (anti-factor D): Selective inhibitor of the alternative complement pathway

**Molecule**
- Fab of a humanized monoclonal antibody
- Targets complement factor D of the alternative pathway

**Target**
- Complement factor D is a rate-limiting enzyme in the alternative pathway and present in relatively low abundance

MAC=Membrane Attack Complex; MBL=mannose-binding lectin
MAHALO Phase II study

**Study design**

- **Phase Ib**
  - Open-label safety run-In (N=14)

- **Phase II (N=129)**
  - Randomized 1:2:1:2

  - Sham
    - Monthly
    - N=21

  - Lampalizumab
    - 10 mg, monthly
    - N=43

  - Sham
    - Every 2 mths
    - N=21

  - Lampalizumab
    - 10 mg, every 2 mths
    - N=44

**Primary Endpoint**

- Mean change in GA area from baseline to Month 18 assessed by fundus autofluorescence (FAF)

*N = 123* for pre-specified modified intent-to-treat population, which is the primary efficacy analysis population.

**AMD risk has a strong genetic component**

*Identifying patients that benefit the most*

- Genetic factors account for \(~55\%\) of total variability in disease risk
- Lifetime AMD risk for individual of affected family member 50% compared to 12% for relatives of controls

19 confirmed loci in pathways related to:
- **Complement**
- **Lipid metabolism**
- **Angiogenesis**
- **Apoptosis**
- **Extracellular matrix**

- **Strong biological rationale for lampalizumab biomarker**
- **To be presented at AAO, November 16-19**

Lampalizumab in Geographic Atrophy (GA)
Targeting alternative complement pathway

**GA Progression: Patient’s Perspective**

Phase 2 MAHALO study demonstrated efficacy in slowing GA area progression
- 20.4% benefit in all patients
- 44% benefit in biomarker positive subpopulation
- 54% benefit in biomarker positive subpopulation with better vision
Etrolizumab

Anti-β7 Integrin in Inflammatory Bowel Disease
### Inflammatory Bowel Disease (IBD) overview

**Two distinct diseases with high unmet medical need**

<table>
<thead>
<tr>
<th><strong>Ulcerative colitis</strong></th>
<th><strong>Crohn’s disease</strong></th>
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<tbody>
<tr>
<td>Age of onset 20-30 yrs</td>
<td>Age of onset 15-30 yrs</td>
</tr>
<tr>
<td>Continuous mucosal distal disease</td>
<td>Patchy transmural disease</td>
</tr>
<tr>
<td>Confined to sigmoid/colon</td>
<td>Most common in ileum and ascending colon</td>
</tr>
<tr>
<td>Bloody, frequent bowel movements</td>
<td>Abdominal pain, diarrhea, vomiting, weight loss</td>
</tr>
<tr>
<td>Progressive over time</td>
<td>Fistulae and strictures</td>
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</table>

**Medical need**
- Higher sustained remission rates
- Decreased risk of severe infections
- Avoidance of surgery and hospitalizations
Etrolizumab: Gut-selective anti-β7 integrin with dual mode of action and no expected CNS effect

**Etrolizumab: Anti-β7**
Blocks leukocyte trafficking and lymphocyte retention

**Vedolizumab: Anti-α4β7**
a. Blocks leukocyte trafficking only
No apparent effect on CNS

**Natalizumab (Tysabri): Anti-α4**
a. Blocks leukocyte trafficking only
b. Affects trafficking to CNS, associated with PML
Etrolizumab phase II study in Ulcerative Colitis
Compelling remission rates

Clinical remission by MCS, Week 10

- Placebo
- Etrolizumab 100mg
- Etrolizumab 300mg+LD

MCS=Mayo Clinic Score, using central endoscopy reading; * 14 week remission as assessed by partial MCS
αEβ7 may predict remission in TNF-naive patients: Potential for PHC approach

Remission at 10 weeks

Note: ~10% and 40% of patients were missing qPCR and IHC data, respectively
Phase III outlook

Best-in-disease in Inflammatory Bowel Disease
>3000 patients program

- First subcutaneous gut-selective anti-integrin
- Better safety profile with reduced risk of severe infection or malignancy
- PHC through αE expression as potential companion diagnostics
- Further details after discussions with healthcare authorities

FPI 1H 2014. Expect first data 2018
Nav1.7

Voltage-gated sodium channel for pain indications
Collaboration Structure

- 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

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

Helped discover human genetic evidence implicating Nav1.7 as compelling pain target

Deep expertise in pain and ion channels

Compelling early stage inhibitor molecules

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
Nav1.7: a Voltage Gated Sodium Channel Involved in the Propagation of Pain Signals

Pain sensing receptors begin to depolarize the nerve.

Nav1.7 opens in response to a change in polarization.

Closed state

Open state

Inactivated state
Nav1.7 is an Extremely Well Validated Pain Target

1. Inactivating mutations of Nav1.7 in humans cause complete insensitivity to pain (homozygous)
   - Congenital insensitivity to pain (CIP)
   - Besides anosmia, they are otherwise normal

2. Activating mutations cause spontaneous pain syndromes
   - Inherited Erythromelalgia (IEM)
   - Paroxysmal extreme pain disorder (PEPD)
   - Small fiber neuropathy (SFN)

3. Conditional KO of Nav1.7 in mice show effects in traditional pain models of the three categories of pain:
   - Acute (burn-injury-induced pain models)
   - Inflammatory (complete Freund’s adjuvant - CFA)
   - Neuropathic (L5 spinal nerve transection - SNT)

Ashlyn Blocker, a CIP patient who has complete loss of function of both Nav1.7 alleles
Summary

• 50% of the Genentech portfolio reflects partnering activities
  
  • Blend of internal and external innovation drives pipeline growth

• Advancing leadership in Oncology through new Pathways, ADCs, Combination trials and Immunotherapy

• Transformative clinical outcomes achieved in GA and UC enabled by PHC approach

• Positioned well to deliver innovative and differentiated therapies to improve patient’s lives