Genentech: Pipeline with focus on 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
Genentech
gRED
Roche
pRED
Chugai

Worldwide execution
Global Product Development
Manufacturing
Commercialisation

Roche Diagnostics
# gRED Portfolio

*33 molecules from Early Development to Phase 2 (18 with Collaborators)*

## Early Devt (16)

- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME
- NME

## Phase 1 (10)

- Anti-MUC16 ADC
- Anti-STEAP1 ADC
- ChK-1 inh (GDC-0575)
- ERK inh (GDC-0994)
- NME ADC
- NME ADC
- Anti-OX40
- SERD (GDC-0810)
- Anti-IL17
- NME

## Phase 2 (7)

- Pinatuzumab vedotin (Anti-CD22 ADC)
- Anti-NaPi ADC
- Anti-HER3 EGFR DAF
- Ipatasertib (GDC-0068)
- Quilizumab (Anti-M1 prime)
- Crenezumab (Anti-Ab)
- Anti-FluA

### Legend:

- Collaborator(s)

Source: Roche Q3 2014 Investors Update, October 15, 2014. Phase 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
Expanding Our Leadership in Oncology

Future: Leading in further outcome improvements

- Immunotherapy (anti-PDL1, anti-ox40, IDO, NMEs)
- Combinations
- Antibody Drug Conjugates (ADCs)
- New pathways (PI3K, SERDs, apoptosis)

Present: Transformative approaches

- HER2 Pathway
  - Herceptin®
  - Kadcyla®
  - Perjeta®
- Heme Franchise
  - Rituxan®/MabThera®
  - Gazyva®
  - Gazyvaro™
  - Bcl-2 ADCs
- Anti-angiogenesis
  - Avastin®
Outline: Project Highlights

- **Oncology:**
  - Cancer Immunotherapies
  - Seragon ARN-810
  - HER2 Therapies: Herceptin, Perjeta, Kadcyla

- **Neuroscience:** Nav1.7
Cancer Immunotherapies

*anti-PD-L1 (MPDL3280A)*, *anti-OX40*, *NLG919 IDO Inhibitor*
The Cancer Immunity Cycle: Immunosuppression is the rate limiting step to effective anti-tumor immunity

Chen & Mellman (2013) Immunity

Immunosuppression
Targeting immunosuppression by blocking the PD-L1/PD-1 pathway

- PD-1/PD-L1 interaction inhibits T cell activation, attenuates target killing: prevents overstimulation of T cells during acute virus infection

- A large percentage of tumors also up-regulate PD-L1 and evade killing by T cells

- Blocking PD-1 binding restores effector T cell activity
Rapid and Sustained Response in an NSCLC Patient Treated With MPDL3280A Monotherapy

64-year-old male with squamous NSCLC s/p R lobectomy; cisplatin + gemcitabine, docetaxel, erlotinib; PD-L1 positive

Herbst et al. MPDL3280A Anti-PDL1 Phase I ASCO 2013
PD-L1 positive kidney cancer patient with a rapid response to MPDL3280A

Biomarkers at baseline:

Biomarkers at week 4 post C1D1:

51-year-old male with RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus

Carolina BioOncology Institute (Powderly)

Cho et al., J Clin Oncol. 31, 2013 (suppl; abstr 4505)
Using patient data to understand cancer immunity and find new targets

**Anti-PDL1 Phase I data**
urothelial bladder cancer

- **Progressive Disease (PD)**
  - Why do many patients not respond?

- **Stable disease (SD)**
  - What combinations will promote PRs & CRs?

- **Monotherapy durable responses (PR/CR)**
  - What are the drivers of single agent response?

**Awarded FDA Breakthrough Status, May 2014**

T cell-directed Therapeutics: Multiple Possibilities

Safety issues

Clinical validation

Anti-OX40 can induce durable responses and immunity as a single agent: Pre-clinical efficacy and durability of response

**Primary Tumor Challenge**

- **Control**
- **Anti-mouse OX40**

**Re-challenge**

- **CT26 Secondary**
- **EMT6 Secondary**
- **EMT6 Primary**

Recently initiated enrollment in the Phase 1 clinical trial GO29313
http://clinicaltrials.gov/show/NCT02219724
gRED recently licensed new cancer immunotherapy molecule, NLG919 IDO Inhibitor

**IDO (indoleamine di-oxygenase) is induced by IFNg and acts with PD-L1 to suppress effector T cells**

- Adaptive expression of PD-L1
- Adaptive expression of IDO

IDO (indoleamine di-oxygenase) is induced by IFNg and acts with PD-L1 to suppress effector T cells.
IDO mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine

*IDO* mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine.

Free tryptophan

- **High**
  - mTOR
  - Promote translation

- **Low**
  - Uncharged Tryptophanol-tRNA
  - GCN2 kinase
  - Stress response
  - Suppress T effectors
  - Enhance T reg

Kynurenine

- Arylhydrocarbon receptor
- Suppressive cytokines
- FOXP3
- Enhance T reg

Tumor cells

- IFNg activates IDO expression

Dendritic cells

- mTOR

Macrophages

- TDO (tryptophan dioxygenase) is a second related target to IDO
Seragon: ARN-810
Targeting Estrogen Receptor positive Breast Cancer

Targeting ligand dependent ERα Activity

- Aromatase Inhibitors (letrozole) – block synthesis of estrogens
- ERα Antagonists (tamoxifen) – compete with estrogens for binding to Erα
- SERDs – selective estrogen receptor degraders

Targeting ligand-independent ERα Activity

- SERDs – selective estrogen receptor degraders (fulvestrant)

Seragon ARN-810 is an ER modulator with a dual mechanism of action: blocks the activation of ERα and induces the degradation of ERα by the proteosome
**ARN-810 Demonstrates Tumor Regressions in Tamoxifen Sensitive and Tamoxifen Resistant Breast Cancer Models**

**Chronic daily dosing of ARN-810 in ER+ xenograft model**
- Tumor regression followed by long durable response
- Study followed out to 1 yr

**Median TTP for ARN-810 >1yr**

**Chronic dosing of Tamoxifen**
- Emergence of resistance @ approx. 70 days

**Not all SERM/SERDs are created equally. In tamoxifen-resistant xenografts:**
- ARN-810 at 100 mg/kg QD regress all tumors
- Modest effect of Fulvestrant (SERD) and pipendoxifene (SERM Wyeth terminated post Phase I)
- No effect for Arzoxifene (SERM Lilly failed in mBC Phase 3)
Identification of mutations in ERα in patients with acquired resistance to endocrine therapies

- Estimate that ~22% of ER+ patients acquire activating mutations in ERα
- ERα LBD mutations are ligand independent and constitutively active

- ARN-810, an orally administered, selective ER antagonist/degrader (SERD) is in Phase 1 (FPI April 2013)
- SRN-927, a next generation SERD from different chemical series, is in Early Development
Cross-talk between ERα and PI3K pathways offer strong rationale for combination

**Plasma membrane**
- Androstenedione
- Testosterone
- Aromatase
- Estrogen
- Letrozole
- Tamoxifen

**Cytoplasm**
- ER
- ARN-810
- GDC-0032
- PI3K
- PDK1
- AKT
- PIP2
- PIP3
- PTEN

**Nucleus**
- ER
- ER
- Response Element
- Proliferation, growth, and survival

**Response Element**
HER2 Therapies: Herceptin, Perjeta, Kadcyla
Continuing to raise the efficacy bar in HER2-positive metastatic breast cancer

- Illustrative. MARIANNE trial ongoing, results are not yet available.
CLEOPATRA: Perjeta + Herceptin Overall survival (OS) final analysis (Feb 2014)

- First-line treatment with pertuzumab, trastuzumab, and docetaxel significantly improved OS for patients with HER2-positive MBC compared with placebo, trastuzumab, and docetaxel

- The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC

Randomised treatment

- Ptz + T + D: median 56.5 months
- Pla + T + D: median 40.8 months

Δ 15.7 months

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

Median follow-up of 50 months (range 0–70 months) at final analysis
Improving standard of care in HER2-positive breast cancer in all lines of treatment

Established standard of care

Potential new standard of care

Potential future standard of care

NEOSPHERE study filed for neoadjuvant breast cancer indication in EU

Timelines refer to the expected dates of first filing; ¹ approved in JP since 2011, in EU 2012; ² approved in US since 2013
Neuroscience: Nav1.7

Voltage-gated sodium channel for pain indications
Why are we interested in treating pain?

- 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
**Na\textsubscript{v}1.7 Function: Voltage gated sodium channel that drives pain signaling**

Pain sensing receptors begin to depolarize the nerve.

Nav1.7 senses the change in polarization and then opens.

Closed state

Open state

Inactivated state

Signal propagates down the nerve.
Na\textsubscript{v}1.7: Pain target identified from experiment of nature

**Na\textsubscript{v}1.7 Biology**
- Voltage-gated Na\textsuperscript{+} channel (generation of action potential)
- Expressed in pain-sensing nerve fibers
  - Selectivity relative to other Na\textsubscript{v} channels will be important for optimal safety profile

**Na\textsubscript{v}1.7 Human Genetics**
- Loss-of-function mutations in Na\textsubscript{v}1.7 results in Congenital Indifference to Pain (CIP)
  - Recessive disorder; no pain from birth
  - Defective olfaction (anosmia); Otherwise physiologically normal
- Activating mutations cause spontaneous pain syndromes (IEM-inherited erythromelalgia, PEPD- paroxysmal extreme pain disorder; SFN- small fiber neuropathy)

**Na\textsubscript{v}1.7 knockout mice show reduced pain behavior**
- Acute, inflammatory, and neuropathic pain models

Based on this promising biology, Genentech is collaborating with Xenon Pharmaceuticals to discover selective and orally available Na\textsubscript{v}1.7 inhibitors
Collaboration Structure

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

• 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

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
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, Combination trials and Cancer Immunotherapy

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