Genentech Research and Early Development  

At the Forefront of R&D Innovation and Breakthrough Treatments

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Executive Summary

- Genentech and Roche have an industry leading portfolio
  - Ongoing track record of success
  - Continued commitment to innovation for patients
  - In-depth biology and immunology expertise

- Oncology: build on our strength in cancer immunotherapy
  - Focus on combinations
  - Leverage expertise in biomarkers and diagnostics
  - Pioneer novel approaches

- Beyond Oncology: follow the science
Most Breakthrough Designations in the Industry
70% of Launches Have Been 1st in Class

Breakthrough Designations

- BTDs on additional indications
- Molecule with BTD

Year | Molecule
--- | ---
2016 | Actemra (Giant cell arthritis)
| Alecensa (1L ALK+ NSCLC)
| Ocrelizumab (PPMS)
| Venclexta (AML)
| Venclexta + Rituxan (R/R CLL)
2015 | Actemra (Systemic sclerosis)
| Tecentriq (NSCLC)
| Venclexta (R/R CLL 17p del)
| Emicizumab/ACE 910 (Hemophilia A)
2014 | Esbriet (IPF)
| Lucentis (DR)
| Tecentriq (Bladder cancer)
2013 | Alecensa (2L ALK+ NSCLC)
| Gazyva (1L CLL)
Genentech Leads the Industry in Scientific Publications

~580 Publications/yr
~17 in Cell, Nature and Science/yr

Key Benefits

- Progress science
- Recruit top talent
- External recognition for scientists
- Engage investigators’ interest to enhance collaboration
Our Drill-Deep Strategy Creates Transformative Medicines

Scientific insights

Initial product

Label expansion

New drugs

New Therapeutic Areas

Her-2 BC biology and ADC technology

• Earlier Line Breast
• Gastric cancer

B-cell biology

• Earlier Line NHL
• CLL

Immunoology

Ocrevus Multiple Sclerosis
Deep Biological Insights Drive Disease Strategies

**ONCOLOGY:** Integrate targeted and cancer immunotherapy to develop best-in-disease therapies

**IMMUNOLOGY:** Integration of human genetics, interrogation of human disease samples and immunology pathways to develop best-in-disease therapies for patient subsets

**NEUROSCIENCE:** Alter the course of neurodegenerative diseases and transform pain therapy through novel genetic, biological and clinical insights

**OPHTHALMOLOGY:** Harness human genetics and biological insights in inflammation and angiogenesis combined with long-acting drug delivery

**INFECTIOUS DISEASES:** Novel therapeutics for difficult to treat bacterial infections through bacterial genetics, novel chemical material, and membrane and immunology expertise
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- **Beyond Oncology: follow the science**
Immune System Fights Cancer
Genomic Instability Drives Escape

Immune Response

Tumor cells
Dendritic cells
T cells

Growing tumor
Tumor cell death
Elimination
Escape
Multiple Intervention Points Available for Boosting Tumor Cell Killing

1. Antigen release
2. Antigen presentation
3. Priming & activation
4. Trafficking
5. T cell infiltration
6. Cancer T cell recognition
7. T cell killing

Recognition

Action

Chen & Mellman (2013) Immunity
Combinations Are Required to Maximize Tumor Killing

**CIT Combination Partner**

- Chemotherapy
- Targeted therapy
- Immunotherapy

**Combination Rationale**

- Standard-of-care
- Enhancing antigen release by killing tumor
- Immuno-stimulatory effects
- More targeted tumor killing
- Immuno-stimulatory effects
- Targeting complementary steps of the immune system
Roche has the Most Combination Opportunities
We Use Science to Select the Best

telasib
ipatasertib
taselisib

Immunotherapy
- cemtrumab amunaleukin
- emactuzumab
- aFAP-IL2v FP
- aCD40
- aOX40
- aCEA/CD3 TCB
- aCD20/CD3
- aTIGIT
- PCV

Targeted therapy
- idasanutlin
- polatuzumab vedotin
- lenalidomide
- azacitidine
- daratumumab
- azacitidine
- lenalidomide
- idasanutlin
- polatuzumab vedotin
Patient Samples Drive Insights for Cancer Immunotherapy Opportunities

**Inflamed**
- CD8+ T cells infiltrated but non-functional

**Immune Excluded**
- CD8+ T cells accumulated but not efficiently infiltrated

**Immune Desert**
- CD8+ T cells absent from tumor and its periphery

**Enhance or remove blockade of T-cell action**
**Bring T-cells in contact with cancer cells**
**Generate and expand antigen specific T-cells**
Patient Samples Drive Insights for Cancer Immunotherapy Opportunities

- Identify **novel targets**
- Understand the role of **biomarkers**
- Understand **escape mechanisms**
- Choose the **best combinations**

**Patient Samples**

**Molecular Insights and Tumor Mutational Burden**

**Opportunities**

- gRED Phase I/II clinical trials
- Smaller patient numbers but less restricted data compared to Phase III

Patient Samples Drive Insights for Cancer Immunotherapy Opportunities
gRED’s Next-Generation CIT Pipeline Targets Different Recognition and Action Steps

**Recognition**

- Anti-OX40 (agonist)
- Personalized cancer vaccine

**Action**

- Trafficking of T cells to tumors (CTLs)
- Infiltration of T cells into tumors (CTLs, endothelial cells)
- Recognition of cancer cells by T cells (CTLs, cancer cells)

**Today’s highlights**

- Anti-CD20/CD3 bispecific
- Anti-PD-L1/Tecentriq
- IDOi
- Anti-OX40
- Anti-TIGIT

Chen & Mellman (2013) Immunity
Anti-TIGIT Enhances Tumor Killing by a Mechanism Distinct from Tecentriq

**Mechanism of Action**

1. TIGIT competes with CD226 for poliovirus receptor (PVR)
2. TIGIT disrupts CD226 mediated T Cell activation
3. TIGIT directly inhibits CD8+ T cell function
4. Anti-TIGIT binds to TIGIT blocking its inhibition of T cells
Anti-TIGIT is First-in-Class and Has Rapidly Progressed into Combination Study with Tecentriq

First anti-TIGIT to enter human study (May 2016)
Currently being dosed as a single agent and in combination with Tecentriq

Preclinical data in anti-PD-L1 non-responsive model

![Graph showing tumor volume over time for control, Anti-PD-L1, TIGIT, and Anti-PD-L1 + TIGIT groups. The graph indicates complete remission (CR) for the combination treatment.](image)
gRED’s Next-Generation CIT Pipeline Targets Different Recognition and Action Steps

**Recognition**

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)

**Action**

5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Personalized cancer vaccine

Chen & Mellman (2013) Immunity
BioNTech is the Leader in Personalized Cancer Vaccines

Expand gRED’s drug discovery platform

Tumor Biopsy

Mutation Identification

Vaccine Design

Vaccine Synthesis

Neo-antigen 1

Neo-antigen 2

Neo-antigen 3

Neo-antigen 4

Neo-antigen 5

mRNA backbone

mRNA backbone
Enhanced Antigen Recognition May Benefit All Immunological Phenotypes

**Immune Desert**

**Immune Excluded**

**Inflamed**

Generate and expand antigen specific T cells
Our Vaccines Have Demonstrated Activity In Patients Combinations are Imminent

**Immune Desert**

**Immune Excluded**

**Inflamed**

Our vaccines have demonstrated:

- Neo-antigen specific T cell responses in all tested patients
- Ability to enhance pre-existing and elicit de novo responses
- Both CD4 and CD8 responses

**Ph1 trial in combination with Tecentriq expected 2H2017**
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BTK Inhibitor Could Transform Rheumatoid Arthritis and Lupus Treatment

**Therapeutic Hypothesis**

- **B cells and myeloid cells** mediate rheumatoid arthritis and lupus.
- **BTK** is essential for BCR signaling in **B cells** and FcγR signaling in **myeloid cells**.

**BTK** is a kinase expressed in most hematopoietic cells except in T cells.

Our **BTKi GDC-0853** is designed to be reversible and highly selective.

RA: Severe Arthritis

Lupus: Disfiguring rash

Genentech
A Member of the Roche Group
BTKi Showed Strong Preclinical Data In Rheumatoid Arthritis and Lupus

- **GDC-0853** showed promising PK, target engagement and tolerability in Phase 1
- Large Phase 2 program ongoing
gRED Pioneers Transformative Innovation

- **Innovation is thriving** at gRED with **drill-deep science** and a **robust portfolio**

- We continue to **lead in 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**