Genentech Research and Early Development (gRED)

Investor Relations Event
February 18, 2020
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Agenda

Welcome
  • Karl Mahler, Head of Investor Relations

Overview and introduction to Genentech (gRED)
  Michael Varney, Head of Genentech Research and Early Development

Non-Oncology Pipeline Overview
  Andy Chan, Senior Vice President, Research Biology

Oncology pipeline Overview
  Stuart Lutzker, Vice President, Oncology Early Research and Development and ad interim Head of Early Clinical Development

Cancer Immunotherapy
  Ira Mellman, Vice President, Cancer Immunology and Exploratory Clinical Development

Q&A Panel and Closing
Strong short term news flow

Diversifying the late stage pipeline and setting new standards of care

<table>
<thead>
<tr>
<th>Product</th>
<th>Timing</th>
<th>Source: Roche/Genentech, incidence/prevalence in the major markets (US, FR, DE, IT, ES, GB); 1 including China; SOC=standard of care; SMA=spinal muscular atrophy; NMOSD=neuromyelitis optica spectrum disorder; UC=ulcerative colitis; CD=Crohn’s disease; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; HCC=hepatocellular carcinoma; TNBC=triple-negative breast cancer; FL=front line; R/R AML=relapsed/refractory acute myeloid leukemia; FDC=fixed dose combination; HR=hormone receptor; mCRPC=metastatic castration resistant prostate cancer; DLBCL=diffuse large B-cell lymphoma; NSCLC=non-small cell lung cancer; AC=all comers</th>
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</thead>
<tbody>
<tr>
<td>risdiplam in SMA</td>
<td>Filed for Type 1/2/3</td>
<td></td>
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<tr>
<td>satralizumab in NMOSD</td>
<td>Filed</td>
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<tr>
<td>HTT-ASO in Huntington’s</td>
<td>Ph II &amp; III ongoing; filing latest 2022</td>
<td></td>
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<tr>
<td>Gazyva in lupus nephritis</td>
<td>initiating Ph III</td>
<td></td>
</tr>
<tr>
<td>etrolizumab in UC and Crohn's Disease</td>
<td>filing in UC in 2020</td>
<td></td>
</tr>
<tr>
<td>PDS in nAMD</td>
<td>fully recruited; filing in 2020</td>
<td></td>
</tr>
<tr>
<td>faricimab in DME/nAMD</td>
<td>recruitment ahead of plan; filing in 2021</td>
<td></td>
</tr>
<tr>
<td>Tecentriq in 1L HCC</td>
<td>Filed</td>
<td></td>
</tr>
<tr>
<td>Tecentriq in neoadj TNBC</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Tecentriq in 1L melanoma</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Tecentriq in FL ovarian cancer</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>idasanutlin in R/R AML</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Perjeta + Herceptin FDC-SC</td>
<td>Filed</td>
<td></td>
</tr>
<tr>
<td>ipatasertib 1/2L TNBC</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>ipatasertib 1L+ HR+ (chemo treated only)</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>ipatasertib in 1L mCRPC</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Polivy in 1L DLBCL</td>
<td>2020/21</td>
<td></td>
</tr>
<tr>
<td>Tecentriq in (neo)adj NSCLC</td>
<td>2021/22</td>
<td></td>
</tr>
</tbody>
</table>
gRED leading the industry in scientific achievements
Consistent publication record in major scientific journals

The international journal of science / 5 December 2019
Vol. 576, No. 7785
£10.00 nature.com
Introduction to Genentech Pharma Research and Early Development (gRED)

Michael Varney | Head of Genentech Research and Early Development
Executive Summary

• Genentech and Roche Are Innovation Companies
  – Drill-Deep science delivers breakthrough and transformative medicines
  – Substantial innovation-focused investment fuels growth

• Robust Portfolio in Immunology, Ophthalmology, Neurodegeneration and Infectious Diseases

• Continued Oncology Leadership
  – Focus on both Molecular Oncology and Immuno-Oncology
  – Pioneer novel technology platforms
Multiple R&D Centers Drive Global Innovation

**Autonomous innovation centers**

- gRED
- pRED
- Chugai

**Worldwide execution**

- Global Product Development
- Manufacturing
- Commercialization

**Research Early Development**

**Diversity, Creativity, Experimentation**

**Scale, Reach, Delivery**

**Notes:**
- gRED=Genentech Research and Early Development; pRED=Pharma Research and Early Development
Premier Innovation Center
Created the world’s largest biotech hub

San Francisco Bay Area

Genentech Research and Early Development

Key Benefits
- Team: 2,200 doing pioneering science
- Innovation: ~20,000 patents granted
- Publication: ~400 publications/year
- Collaborations: >120 globally

Bay Area Life Science Hub*
- Employees: 82,568
- Funding: >$5B VC + >$1B NIH

*California Life Sciences Industry 2018 and 2019 Reports
GRED Is a Publication Powerhouse

~400 Publications in 2019
13 in Cell, Nature and Science

Key Benefits

- Progress science
- Recruit top talent
- Recognition for scientists
- Attract partners to collaborate and expand business opportunities
Innovation Propels Roche Growth

All absolute values are presented in CHFm reported; 1 Erivedge, Perjeta, Kadcyla, Gazyva, Esbriet, Cotellic, Alecensa, Tecentriq, Ocrevus, Hemlibra, Xofluza, Polivy, and Rozlytrek; 2 MabThera and Herceptin in Europe and Japan; 3 Avastin and Herceptin in US Jul-Dec & MabThera/Rituxan in US Nov-Dec
Foundation for gRED Early Drug Development
Building the Pipeline of the Future

Treat * Restore * Cure
Putting the patient first

Science without Borders
Being a Partner of Choice

Human – Machine Partnership
Novel ways of new target discovery

Drug the Undruggable
Focus on increasingly difficult targets

Clear the Path
We Are Creating the Next Wave of Transformative Medicines

Oncology
- Immunotherapy, Solid Tumors, Hematology

Neuroscience
- Neuroprotection, Pain

Ophthalmology
- AMD, Geographic Atrophy, Diabetic Retinopathy

Immunology
- Respiratory, Gastrointestinal, Rheumatology, Allergy

Infectious Diseases
- ATB-resistant Gram negative bacteria, Microbiome

Opportunistic
- Nonalcoholic steatohepatitis, Ischemic heart disease

Treat * Restore * Cure
gRED’s **Drill-Deep Science Creates Transformative Medicines**

- **Scientific insight**
- **Initial product**
- **Label expansion**
- **New drug**
- **New area**

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**HER-2 BC biology & ADC technology**
- Earlier line breast cancer
- Gastric cancer

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**B-cell biology**
- Earlier line NHL
- CLL

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**Immunology**
- Multiple Sclerosis
~70% of Genentech/Roche Molecules Are First-in-Class
Our Science Makes Us the Partner of Choice for Outside Innovation
We Focus On Increasingly Difficult Targets

We play here

Drug the Undruggable

~20,000 genes

Disease Modifying
4,000 (20%)  

"Undruggable"
Hard-to-Drug
3,000 (75%)

Drugged
1,000
(25%)
Platform Diversity Drives Success in Attacking Difficult Targets

- **Macrocycles**
  - DNA Encoded Library Platform
  - Quadrillion of Molecules

- **CIDES**
  - Chemical Inducer of Degradation

- **CKPs**
  - Cystine Knot Peptides

- **Others Undisclosed**

- **Tissue Targeting & Tumor Inducible Activation**

- **RNA Disrupters**

- **Antibody-Mediated Delivery**

- **Biomaterials for LM, SM Delivery**
  - Immune Tolerance
  - Peptide coated MHC nanoparticles Vaccines

Drugs the Undruggable
### Robust gRED Portfolio Across Therapeutic Areas

<table>
<thead>
<tr>
<th>Early Dev</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NME</td>
<td>Anti-FcRH5/CD3</td>
<td>iNeST (PCV)</td>
<td>ipatasertib</td>
<td>Avastin</td>
<td></td>
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<tr>
<td>NME</td>
<td>Anti-HER2/CD3 TDB</td>
<td>Anti-ST2</td>
<td>mPI3K alpha (GDC-0077)</td>
<td>Cotellic</td>
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<tr>
<td>NME</td>
<td>belvarafenib</td>
<td>fenebrutinib</td>
<td>SERD (GDC-9545)</td>
<td>Erivedge</td>
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<tr>
<td>NME</td>
<td>IL15/IL15-Ra-Fc</td>
<td>IL22 Fc</td>
<td>tiragolumab</td>
<td>Herceptin</td>
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<tr>
<td>NME</td>
<td>MAGE-A4 ImmTAC</td>
<td>NME (RG6173)</td>
<td>etrolizumab</td>
<td>Kadryla</td>
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<td>NME</td>
<td>mosunetuzumab</td>
<td>NME (RG6147)</td>
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<td>Perjeta</td>
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<td>NME</td>
<td>NME (RG6151)</td>
<td>Anti-FGFR1/KLB</td>
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<td>Polivy</td>
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<tr>
<td>NME</td>
<td>NME (RG6244)</td>
<td>NME (RG6147)</td>
<td></td>
<td>Tarceva</td>
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<tr>
<td>NME</td>
<td>NME (RG6287)</td>
<td>Semorinemab (Anti-Tau)</td>
<td></td>
<td>Tecentriq</td>
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<tr>
<td>NME</td>
<td>DLK Inh</td>
<td></td>
<td></td>
<td>Venclexta</td>
<td></td>
</tr>
<tr>
<td>NME</td>
<td>Anti-S. Aureus TAC</td>
<td></td>
<td></td>
<td>Rituxan/Mabthera</td>
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</tr>
</tbody>
</table>

**Therapeutic Areas:**
- Oncology
- Immunology
- Neuroscience
- Ophthalmology
- Metabolism
- Infectious Diseases

**Marketed Drugs:**
- Avastin
- Cotellic
- Erivedge
- Herceptin
- Kadryla
- Perjeta
- Polivy
- Tarceva
- Tecentriq
- Venclexta
- Rituxan/Mabthera
- Pulmozyme
- Xolair
- Ocrevus
- Lucentis
- Activase
- Nutropin
- TNKase
Non-Oncology Pipeline Overview

Andy Chan | Senior Vice President, Research Biology
Creating New Opportunities Across Therapeutic Areas

<table>
<thead>
<tr>
<th>Neuroscience</th>
<th>Ophthalmology</th>
<th>Immunology</th>
<th>Infectious Diseases</th>
<th>Opportunistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodegeneration, Pain</td>
<td>AMD, Geographic Atrophy, Diabetic Retinopathy</td>
<td>Rheumatology, Allergy, Gastroenterology, Respiratory</td>
<td>ATB-resistant Gram negative bacteria Microbiome</td>
<td>Non-alcoholic steatohepatitis Ischemic heart disease</td>
</tr>
</tbody>
</table>
IBD is a severely debilitating and complex disease.

Approximately 1.3 million IBD patients have moderate-severe disease.

### Disease Background

**Ulcerative Colitis**
- Mucosal inflammation
- Age of onset 20-30 years
- Adult pop: 1.2M (US+EU5)
- 50% with moderate/severe disease
- Bloody diarrhea with urgency
- Repeated flares
- Increase risk of colon cancer

**Crohn’s Disease**
- Transmural inflammation
- Age of onset 15-30 years
- Adult pop: 1.1M (US+EU5)
- 50% with moderate/severe disease
- Abdominal pain, diarrhea sometimes bloody
- Frequent surgical interventions

### Need for multifactorial treatments
Etrolizumab: First dual-action anti-integrin targeting α4β7/αEβ7

Targets two sources of inflammation with potential for best-in-class efficacy

Vedolizumab (anti-α4β7)

Etrolizumab (anti-β7)

Anti-β7 (α4β7 & αEβ7) is superior to anti-α4β7 in limiting intestinal inflammation

*P < 0.05, ***P < 0.001
Etrolizumab Phase 3 in UC and Crohn’s Disease
A broad and landmark program in inflammatory bowel diseases

**Etrolizumab Phase III Development Program**

**ULCERATIVE COLITIS**

**HIBISCUS I:** Induction trial comparing etro vs. adalimumab vs placebo in anti-TNF naïve patients

**HIBISCUS II:** Induction trial comparing etro vs. adalimumab vs placebo in anti-TNF naïve patients

**LAUREL:** Maintenance trial evaluating etro vs. placebo in anti-TNF naïve patients

**HICKORY:** Induction and maintenance; etro vs. placebo in anti-TNF incomplete responders

**GARDENIA:** Sustained remission evaluating etro vs. infliximab in anti-TNF naïve patients

**COTTONWOOD:** Roll-over, open-label extension trial evaluating safety

**CROHN’S DISEASE**

**BERGAMOT:** Induction and maintenance trial of etro vs. placebo in anti-TNF naïve and IRs

**JUNIPER:** Roll-over, open-label extension trial evaluating safety

**BERGAMOT Phase III results**

**Symptomatic Remission**

<table>
<thead>
<tr>
<th>Week 6</th>
<th>Week 10</th>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9%</td>
<td>15.0%</td>
<td>11.9%</td>
</tr>
<tr>
<td>15.8%</td>
<td>25.9%</td>
<td>20.8%</td>
</tr>
<tr>
<td>8.5%</td>
<td>19.3%</td>
<td>24.9%</td>
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</tbody>
</table>

**Delta:**

- Week 6: 17.1%
- Week 10: 18.9%
- Week 14: 12.9%

**Endoscopic Improvement**

<table>
<thead>
<tr>
<th>Week 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4%</td>
</tr>
<tr>
<td>21.0%</td>
</tr>
<tr>
<td>17.4%</td>
</tr>
</tbody>
</table>

**Delta:**

- Week 14: 14.0%

*For endoscopic analyses, 1 patient receiving Etro 105 mg had a SES-CD score of 0 at baseline and was excluded (n = 119).

**Notes:**

- BERGAMOT Cohort 1 enrolled over 70% of patients who were anti-TNF IR’s
- Symptomatic remission seen as early as week 6 and was observed consistently through week 14
- Well tolerated, with frequency of adverse events comparable with placebo
- Study is continuing to enroll with data in 2021

TNF IR is defined as patients who are refractory to or intolerant of TNF inhibitors

25
IL22-Fc Targets the Epithelium and Dysbiosis

**IL22-Fc is non-immunosuppressive**

Non-clinical studies demonstrate that IL22-Fc:

- **Stimulates tissue regeneration** by increasing epithelial cell proliferation
- **Strengthens intestinal barrier** through increasing mucus production
- **Modulates gut dysbiosis** through stimulating production of anti-microbial peptides

**Phase 1:**
IL22-Fc demonstrated acceptable safety and dose-dependent pharmacologic activity in both healthy volunteers and ulcerative colitis patients

**Day 0**
- Mayo clinic score = 8
- Gross blood in stool
- ≥ 5 stools/day above normal

**Day 80**
- Mayo clinic score = 1
- No blood in stool
- 1-2 stools/day above normal
**IL22-Fc: Phase 2 Study Design in Ulcerative Colitis**

*Proof of concept, dose ranging, head-to-head comparison*

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Treatment/Condition</th>
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</thead>
<tbody>
<tr>
<td>Wk -4 Wk 0</td>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td>Wk 8</td>
<td><strong>Induction</strong></td>
</tr>
<tr>
<td>Wk 8 1°EP</td>
<td><strong>Durability of response</strong></td>
</tr>
<tr>
<td>Wk 30</td>
<td><strong>FPI: Oct 26th, 2018</strong></td>
</tr>
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</table>

- **IL-22**
  - 30µg/kg q4w x3 N=60
  - 60µg/kg IV q8wk (n=30)
  - Placebo (n=30)

- **IL-22**
  - 60µg/kg q4w x3 N=60
  - 60µg/kg IV q8wk (n=30)
  - Placebo (n=30)

- **IL-22**
  - 90µg/kg q4w x3 N=60
  - 60µg/kg IV q8wk (n=30)
  - Placebo (n=30)

- **Vedolizumab** (n=60)

- **Placebo** (n=30)

- **Note:**
  - Moderate to Severe UC
  - mMCS 4-9 (central endoscopic score ≥ 2)

- **Non-responders eligible to rollover to OLE (GA40209) at week 8**
A Multi-Prong Approach to Inflammatory Bowel Disease (IBD)

**IBD Portfolio**

- **Etrolizumab**
  - Ph 3
  - First α4β7/αEβ7 dual anti-integrin
  - Gut-selective mechanism
  - Ph3 in UC+CD, 6 trials, N~3200

- **IL22–Fc (RG7880)**
  - Ph 2
  - Novel non-immunosuppressive
  - Restores epithelial integrity and gut protective mechanisms
  - Ph2b in UC ongoing, N~270

- **GDC-8264, RO7288817**
  - Ph 1
  - Novel non-immunosuppressive
  - Preserves epithelial cell survival
  - Ph1 ongoing
Tau - a Major Component of Neurofibrillary Tangles in Alzheimer’s Disease

**Neurofibrillary tangles**
- Intracellular aggregates of Tau protein in Alzheimer’s Disease
- Abundance is correlated with disease stage and cognitive deficit
- Point mutations cause autosomal dominant frontotemporal dementia (FTD)

![Diagram of Tau protein isoforms](image)

![Stage I, II](image)

![Stage III, IV](image)

![Stage V, VI](image)

Nelson et al., 2012
Detection of Tau with $[^{18}\text{F}]$GTP1 to Support Alzheimer’s Disease Drug Development
Semorinemab (anti-tau antibody) Phase 1 Results

**Pharmacokinetics**

**Pharmacodynamics**

**PK/PD at 8400 mg**

**Phase 1 key results:**
- Well tolerated at single doses up to 16,800 mg and 4 x QW doses of 8,400 mg
- PD response based on plasma accumulation of target appeared to saturate at 4,200 mg
- Max Plasma tau concentration achieved as a PD response in AD was 1.75x higher than in HVs

Semorinemab in Alzheimer’s Disease – Phase II Trial Designs

Evaluating patients with Prodromal to Mild and Moderate AD

**Tauriel**
Prodromal to Mild AD  
N=457

**Lauriet**
Moderate AD  
N=260
HtrA1 (High temperature requirement A1)
A novel target for age-related macular degeneration

Therapeutic Hypothesis: HtrA1 contributes to conversion from intermediate AMD and GA to advanced AMD

HtrA1, a serine protease, can induce breakdown and destruction of extracellular matrix protein, resulting in photoreceptor, retinal pigmented epithelium, Bruch’s membrane, and choroid atrophy
Single dose of FHTR2163, a humanized Fab, inhibits HtrA1 activity
Being evaluated for Geographic Atrophy

Phases 1 in patients with GA secondary to AMD

- SADs (1 to 20 mg) and MAD of 20 mg Q4W x 3
- Well tolerated
- No dose-limiting toxicities
- No study drug-related ocular or systemic AEs or SAEs
- PD suggests potential for Q8W dosing

Angiogenesis 2020
Commitment to Antibiotic-Resistant Gram Negative Bacteria Infections

1. CDC report on Antibiotic Resistance Threats in the United States, 2019
2. WHO report Feb 27, 2017

- Antibiotic-resistant bacteria and fungi cause >2.8 million infections and 35,000 deaths in the US in 2017

- G0775, an arylomycin analog, targets a bacteria-specific type 1 Signal peptidase that is essential and conserved across bacterial species

- G0755 has low intrinsic resistance and overcomes pre-existing resistance mechanisms

<table>
<thead>
<tr>
<th>WHO priority 1 bacteria</th>
<th>G0775 MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> ATCC 43816</td>
<td>0.125</td>
</tr>
<tr>
<td><em>K. pneumonia</em> ATCC 43816</td>
<td>0.125</td>
</tr>
<tr>
<td><em>A. baumannii</em> ATCC 17978</td>
<td>1</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> ATCC 27853</td>
<td>1</td>
</tr>
</tbody>
</table>

1. CDC report on Antibiotic Resistance Threats in the United States, 2019
2. WHO report Feb 27, 2017
Robust gRED "OMNI" Portfolio Across Therapeutic Areas

Early Dev | Phase 1 | Phase 2 | Phase 3 | Registration | Marketed
---|---|---|---|---|---
NME | Anti-FcRh5/CD3 | iNeST (PCV) | ipatasertib |  | Avastin
NME | Anti-HER2/CD3 TDB | Anti-ST2 | mPi3K alpha (GDC-0077) |  | Cotellic
NME | belvarafenib | fenebrutinib | SERD (GDC-9545) |  | Erivedge
NME | IL15/IL15-Ra-Fc | IL22 Fc | tiragolumab |  | Herceptin
NME | MAGE-A4 ImmTAC | NME (RG6173) | etrolizumab |  | Kadcyla
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NME | NME (RG6151) | NME (RG6147) | |  | Polivy
NME | NME (RG6244) | Semorinemab (Anti-Tau) | |  | Tarceva
NME | NME (RG6287) | | |  | Tecentriq
NME | DLK Inh | | |  | Venclexta
NME | Anti-S. Aureus TAC | | |  | Anti-FcRH5/CD3

- Oncology
- Immunology
- Neuroscience
- Ophthalmology
- Metabolism
- Infectious Diseases
Oncology Pipeline Overview

Stuart Lutzker | Vice President, Oncology Early Research and Development
Ad interim Head of Early Clinical Development
gRED utilizes many differentiated platforms to benefit cancer patients

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Bi-specifics</th>
<th>Engineered cytokines</th>
<th>mAb</th>
<th>ADC</th>
<th>Personalized mRNA vaccine</th>
<th>Personalized Engineered T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>ipatasertib (PI3Kα inhibitor SERD)</td>
<td>Mosunetuzumab (FcR:5 x CD3 HER2 x CD3)</td>
<td>IL-15&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Tecentriq (atTIGIT (tiragolumab))</td>
<td>Polivy (Kadcyla)</td>
<td>iNeST&lt;sup&gt;2&lt;/sup&gt; platform: mRNA-LPX Liposome</td>
<td>Activated T cell with neoantigen specificity</td>
</tr>
</tbody>
</table>

- Target oncogenes, suppress tumor growth
- Engage and activate immune cells to kill tumor cells
- Amplify immune response
- Targeted toxic payload
- Patient’s neo-antigens for anti-tumor immune response

<sup>1</sup> in collaboration with Xencore; <sup>2</sup> in collaboration with BioNTech; <sup>3</sup> in collaboration with Adaptive Biotechnologies
PI3K/AKT is the most frequently altered pathway in cancer

14 million cancer patients diagnosed annually worldwide, ~17% are PIK3CA mutant ~2.4M patients

**PI3K pathway**

**Frequency of PIK3CA mutations across tumor types**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>PIK3CA mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+ Breast Cancer</td>
<td>~40%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>~33%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>~25%</td>
</tr>
<tr>
<td>HER2+ Breast Cancer</td>
<td>~25%</td>
</tr>
<tr>
<td>Colon</td>
<td>~20%</td>
</tr>
<tr>
<td>Bladder</td>
<td>~20%</td>
</tr>
<tr>
<td>Cervix</td>
<td>~20%</td>
</tr>
<tr>
<td>HNSCC</td>
<td>~15%</td>
</tr>
<tr>
<td>TNBC</td>
<td>~8%</td>
</tr>
<tr>
<td>Gastric</td>
<td>~7%</td>
</tr>
</tbody>
</table>

HR+ = hormone receptor positive; HNSCC = head and neck squamous cell carcinoma; TNBC = triple negative breast cancer
GDC-0077 in *PIK3CA*-mutant HR+/HER2- mBC

**GDC-0077**

Best in-class molecular properties:
- More selective for PI3Kα
- Degradation of mutant PI3Kα
- Greater, more durable target inhibition

Potential for clinical differentiation:
- Increased efficacy
- Greater safety margins
- Combination with CDK4/6i + ET

**Ph 1 development program**

Dose escalation data from single agent GDC-077 and combinations with letrozole and palbociclib + letrozole presented at SABCS 2019

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HR=hormone receptor; BC=breast cancer; ET=endocrine therapy
GDC-0077 + CDK4/6i + ET demonstrates encouraging activity

- GDC-0077 + palbociclib + letrozole

  B (fully enrolled)
  GDC-0077 + palbociclib + letrozole
  Stage 1

  EXPANSION n = 20
  Palbociclib dose
  9 mg

  6 mg

  3 mg

  TOTAL n = 33

  Arm B can safely combine at its single agent recommended Ph 2 dose with palbo + letrozole at standard approved doses

  ORR: 52%*

Jhaveri, K., et al, SABCS 2019 *Confirmed ORR in patients with measurable disease; HR=hormone receptor; BC=breast cancer; ORR=overall response rate
GDC-0077 in PIK3CA-mutant HR+/HER2- mBC

Ph III study in 1L PIK3CA-mutant HR+/HER2- mBC

HR+/HER2- Locally Advanced/ Metastatic Breast Cancer

- PIK3CA mutation in tumor tissue or ctDNA
- Pre/peri-menopausal on LHRH agonist or postmenopausal females or males
- Progression during or within 12 months of completion of adjuvant endocrine therapy
- No prior systemic therapy for metastatic disease

N = 400

GDC-0077 9 mg QD + palbociclib 125 mg QD 21/7 + fulvestrant 500 mg IM Q4wks

Placebo QD + palbociclib 125 mg QD 21/7 + fulvestrant 500 mg IM Q4wks

NCT04191499

HR=hormone receptor; mBC=metastatic breast cancer; Ph 1 combination data with palbociclib + fulvestrant not yet presented; NCT04191499
GDC-9545 (SERD) in HR+/HER2- mBC

GDC-9545 has best-in-class potential

- Oral route of administration
- Highly potent and improved efficacy *in vivo* vs. other SERDs
- Full ER pathway blockade
- Superior PK results in efficacy at low doses in vivo
- Wide nonclinical safety margins

Jhaveri, K., et al, SABCS 2019; Guan et al, 2019
HR=hormone receptor; mBC=metastatic breast cancer; ER=estrogen receptor; PK=pharmacokinetics
GDC-9545 (SERD) in HR+/HER2- mBC

Ph 1 dose escalation: tumor responses

- Responses observed in pts with prior CDK4/6i and fulvestrant, and in pts with ESR1m
- Dose expansion cohorts with or without palbociclib are ongoing

Safety

<table>
<thead>
<tr>
<th>AEs related to GDC-9545</th>
<th>Grade 3</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bradycardia$^a$</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>0</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

- Treatment related AEs were all Gr 1-2
- No patients withdrew or reduced dose due to AE
- Bradycardia was all Gr 1, asymptomatic, reversible

Program advancing to Phase III

Jhaveri, K., et al, SABCS 2019
HR=hormone receptor; BC=breast cancer; PK=pharmacokinetics; AE=adverse event
Immune cell bispecifics platform

Multiple new therapies and a developing pipeline

**Clinical stage**

- **CD20XCD3 (mosunetuzumab)**: B-cell malignancies
- **FcRH5XCD3**: Multiple Myeloma
- **HER2XCD3**: Breast cancer

**Pre-clinical stage**

Various solid and liquid tumor targets

CD3 and CD16A for T and NK cell activation
Mosunetuzumab

Anti-CD20/CD3 bispecific antibody simultaneously bind T-cells and B-cells

- Optimized binding affinities for improved therapeutic index
- Fast, universal, off-the-shelf solution, with mAb dosing and PK properties
- Potential for use as a single agent and in combination with manageable CRS and neurotoxicity profiles

Currently being assessed in iNHL/aNHL as monotherapy and in combination

iNHL=indolent Non-Hodgkin’s lymphoma; aNHL=aggressive Non-Hodgkin’s lymphoma; CRS=cytokine release syndrome, mAb = monoclonal antibody; TCB = T-cell bispecific
Mosunetuzumab: in aggressive NHL
Complete responses appear durable; dose-escalation is ongoing

Best change (%) in SPD from baseline in aNHL

Investigator-assessed best objective response
(pooled data from 2.8mg to 40.5mg cohorts)

<table>
<thead>
<tr>
<th></th>
<th>N*</th>
<th>ORR, n (%)</th>
<th>CR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive NHL</td>
<td>124</td>
<td>46 (37.1%)</td>
<td>24† (19.4%)</td>
</tr>
<tr>
<td>DLBCL/trFL after ≥ 2 lines</td>
<td>98</td>
<td>37 (37.8%)</td>
<td>20 (20.4%)</td>
</tr>
<tr>
<td>• Refractory to anti-CD20</td>
<td>88/98</td>
<td>32 (36.4%)</td>
<td>18 (20.5%)</td>
</tr>
<tr>
<td>• With prior auto SCT</td>
<td>32/98</td>
<td>17 (53.1%)</td>
<td>11 (34.3%)</td>
</tr>
</tbody>
</table>

• †17 CR pts (70.8%) remain in complete remission (up to 16 months off initial treatment)
• Dose-optimization ongoing; increased efficacy observed in patients with higher exposure to mosunetuzumab as measured by CD20 receptor occupancy (RO%)²

*Efficacy- evaluable pts: pts who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause
aNHL = aggressive NHL; DLBCL = diffuse large b-cell lymphoma; trFL =transformed follicular lymphoma; SCT = stem cell transplant; SPD = sum of the product of the diameters

¹Shuster, S.J., et al., ASH 2019; CCOD: Aug 9, 2019; ²Li et al. ASH 2019 P-1285
**Individualized Neoantigen Specific immune Therapy (iNeST*)**

*Uniquely manufactured for each patient*

- **Tumor Biopsy**
- **Mutation Identification**
- **Vaccine Design**
- **Vaccine Synthesis**

- mRNA backbone
  - Neo-antigen 1
  - Neo-antigen 2
  - Neo-antigen 3...
  - Neo-antigen 10...
  - Neo-antigen 20
  - mRNA backbone

- **Fully individualized vaccine** (mRNA vectors provide patient specific therapy)
- **On demand-production** (highly iterated and reproducible with low failure rate)
- Liposomal formulation for systemic delivery
- Phase II studies underway in 1L melanoma and high risk ctDNA+ adjuvant NSCLC

In collaboration with BioNTech
Immunotherapy Pipeline Overview

Ira Mellman | Vice President, Cancer Immunology
Cancer Immunotherapy is the fastest growing segment in oncology.

Competition places a premium on being smart and fast.

- **Historical data**
  - Total Onc Market: 94B CHF
  - CIT: 6.5B CHF

- **Projected data**
  - Total Onc Market: 106B CHF
  - Total Onc Market: 125B CHF
  - Total Onc Market: 155B CHF
  - CIT: 29B CHF

- **Analyst range**: 30-113B CHF

*Based on analyst models; CIT=Cancer Immunotherapy*
Learning from Tecentriq, gRED’s first approved cancer immunotherapy

Insights from the clinic inform research & development

**Wave 1**
- Monotherapy

**Wave 2**
- Combinations

**Wave 3**
- Next generation CIT

**Wave 4**
- Personalized CIT

CIT = Cancer Immunotherapy
A systematic strategy for discovery and development for the future of IO

Wave 1
Establish single agent activity in major indications

- Tecentriq in PD-L1+ NSCLC
- Monotherapy in NCSLC, mUC; being evaluated for adjuvant NSCLC, adjuvant HNSCC, RCC

Wave 2
Combine with existing medications

- Tecentriq + Avastin in HCC
- Medically meaningful improvement
- Immune doublets: Tecentriq + Bispecifics, aTIGIT, IL-2, IL-15, stromal modulators, antigen presentation agonists

Wave 3
Expand to novel CITs

- Personalized neo-antigen-specific CIT
- iNeST-RNA (vaccine)
- Neo-T (TCR-directed cell therapy)

Wave 4

Opportunity / Cure Rate

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; TNBC=triple-negative breast cancer; HCC=hepatocellular carcinoma; mUC=metastatic urothelial carcinoma; HNSCC=head and neck squamous cell carcinoma; mCRPC=metastatic castration-resistant prostate cancer
All tumors exhibit one of three basic immune phenotypes

Provides mechanistic context for response and lack of response to CIT
Strategies to promote an antitumor immune response by phenotype: Target “rate limiting steps” associated with primary and secondary resistance

**IMMUNE DESERT**
- Generate/release/deliver antigens
- Enhance antigen presentation and T-cell priming
- Redirect and engage T cells

**IMMUNE EXCLUDED**
- Recruit T cells to tumour
- Address stromal barrier
- Redirect and engage T cells

**INFLAMED**
- Invigorate T cell response
- Redirect and engage T cells

Some patients may only require targeting of negative regulator (aPD-L1 monotherapy) to enable cancer immunity

Some patients will need two or more therapies to enable cancer immunity (e.g., to drive infiltration, boost MHC expression, etc)

Investigating a diverse range of targets based on the characteristics of each immune phenotype

**TREATMENT STRATEGIES**

**Generate/release/deliver antigens**
- Personalised cancer vaccine
- Neo-T
- CAR-T*
- Epigenetic modifiers (HDACi,* EZH2i*, DNMTi*)
- Chemotherapy*
- Radiotherapy*
- Targeted therapies: EGFR-TKI, ALKi, PARPi*, AKTi, PI3Ki, MEKi, BRAFi, cabo

**Enhance antigen presentation and T-cell priming**
- Anti-CD40
- Dendritic cell-targeted NMEs
- Anti-PDL1
- Anti-TIGIT

**Synthetic immunity**
- T-cell bispecifics (CD20XCD3, HER2XCD3 TDB), Mosunetuzumab
- NK cell bispecific engagers

---

**IMMUNE DESERT**

**Recruit T cells to tumour**
- Anti-VEGF
- Chemokine modifier NME’s

**Address stromal barrier**
- Stromal modifying NME’s
- Suppressive myeloid/fibroblast modifier NME’s

**Synthetic immunity**
- T-cell bispecifics (CD20XCD3, HER2XCD3 TDB, Mosunetuzumab)
- NK cell bispecific engagers

---

**INFLAMED**

**Invigorate T cells**
- Anti-PDL1
- Anti-TIGIT
- IL15βγ/IL15Rα
- NME – small molecules
- NME – biotherapeutics

**Synthetic immunity**
- T-cell bispecifics (CD3-CD20 TDB, HER2-CD3 TDB)
- NK cell bispecific engagers

---

*Clinical collaborations
There are many T cell checkpoints, including TIGIT

**T-cell regulation**

- **TIGIT** (T cell immunoreceptor with Ig and ITIM domains) is an **inhibitory receptor**, discovered at Genentech.
- **TIGIT** acts as a specific negative regulator of the CD226 costimulatory receptor.
- **TIGIT** is expressed on multiple immune cells, including **CD8+ T cell** (effector memory), **CD4+ T cells** (effector memory and regulatory), **Tfh cells**, and **NK cells**.
- **TIGIT** is expressed on a new population of T cells, **stem-like memory cells**, that may be the preferred targets for anti-PDx efficacy.

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Ig, immunoglobulin; ITIM, immunoreceptor tyrosine-based inhibition motif; Tfh, T follicular helper cell; NK, natural killer

TIGIT – expressed in multiple tumor types

Model for TIGIT regulation of T cell responses

- TIGIT is highly expressed in T-cell infiltrated
  - Lung squamous cell cancer
  - Colon cancer
  - Uterine endometrioid carcinoma
  - Breast cancer

Johnson et al. Cancer Cell 2014
TIGIT and PD-L1 blockade synergistically improves tumor control
Prolongs survival in CT26 models

Blockade of TIGIT and PD-L1 showed a 75% decrease in mean tumor volume after 16 days of treatment.

Unlike PD-1, TIGIT is also expressed by NK cells, which may also contribute to anti-tumor activity in combination.

Rationale for Tecentriq + TIGIT

*T stem-like memory cells are positive for TIGIT*

Anti-PD-L1 expands a key population of PD-1-positive T stem-like cells, which also express TIGIT but no other negative regulator

- T-cell expansion
- Prevent/reverse T-cell exhaustion

Other potential MOA
- Myeloid cell reprogramming
- T regulatory cell reprogramming

Phase Ib and II data to be presented in H1 2020

Modified from Chen and Mellman Nature 2017
IL-15bg/IL-15Ra
An IL-2-like cytokine

- IL-15βγ/IL-15Rα promotes T cell memory, does not stimulate T regs, and avoids vascular leak associated with IL-2

- Can combine with anti-TIGIT & Tecentriq to facilitate CD8 T cell and NK cell expansion
IL-15γ/IL-15Rα
Engineered to extend half-life and increase therapeutic index
Mutant neo-antigens are validated targets for T cell immunity

Rationale for individualized neoantigen-specific therapy (iNeST)

**Stronger T cells against neoantigens**

*Ex vivo* responses

- Shared
- Neo-epitope

**TECENTRIQ: bladder cancer**

Infusion of CD8 T cells specific for KRAS G12D/HLA-C8:02 induces tumor regression

- Mutations that accumulate in cancer can be presented and recognized by T cells
- High tumor mutation burden correlates with clinical response to immune checkpoint blockade
- Infusion of neoantigen-specific T cells induces tumor regression
- iNeST offers the opportunity to target tumors by effectively and specifically promoting tumor neoantigen specific T cell responses

- IFN-g spots per 3x10^6 cells
- Mutation load per megabase
- Clinical benefit

Rosenberg et al. 2016. *Lancet*
Intravenously administered iNeST stimulates innate immunity and encodes antigens for presentation to immune cells.

Neoantigen immune response following iNeST-RNA vaccination

Production of strong T cell responses in every patient

PCV induces T cell immunity

- 32% de novo
- 68% pre-formed

T cells

- 26% CD4
- 57% CD8

Neoepitopes

Number of mutations
13 patients with Stage III and IV melanoma

Initial Phase 1b Tecentriq combo monitoring data expected at AACR 2020

- successful implementation of personalized workflow (TAT 4-6 wks)
- ~120 patients
- Data from initial study informs next generation modifications

PCV=Personalized cancer vaccine; PCV in collaboration with BioNTech
Neo-antigen-specific cell therapy
Increasing cell number beyond the capacity of therapeutic vaccines

**CAR-T**¹

- Chimeric antigen receptor
- Limited to surface antigen
- Clinically proven in heme indications
- Limited activity in solid tumors

**TIL**²

- Isolated from tumor and expanded
- Endogenous T cell receptor (TCR)
- Some clinical activity
- Cellular fitness is unclear

**TCR-T**³

- T cells from patient’s blood
- Engineered tumor-specific TCR
- Better cellular fitness
- Clinical activity is unproven

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¹. Chimeric antigen receptor therapy; 2. Tumor-infiltrating lymphocytes; 3. T-cell receptor therapy
NEO-T cells: a personalized TCR-engineered T cell therapy

Shared Antigens
- Pre-build a library with TCRs for different neoantigens and HLA.

Private Antigens
- Select TCR from the library for each patient.

Select TCR from the library for each patient.

Apheresis → Isolate & stimulate T cells → TCR gene editing → Expand T cells → Infuse

- Determine mutations
- TCR identification/selection

In collaboration with Adaptive Biotechnologies
A clear strategic vision guides the gRED CIT portfolio

Evolving capabilities

- **Immunomodulators**: Foundational understanding of cancer immunity
- **Tumor directed bispecifics**: Tumor-associated antigen targeting
- **Personalized cancer vaccine**: Neoantigen discovery, precision drug design, novel manufacturing
- **Cell therapies**: Overcoming immunosuppression and stromal barriers; Combinations

- **Potential for application across all cancer patients**
  - Synthetic immunity to tumor targets
  - T cell priming and activation
  - Universal
  - Personalized
  - Curative

Potential for application across all cancer patients
Doing now what patients need next