TRANSFORMING THE FUTURE OF CANCER CARE

ROCHE CANCER IMMUNOTHERAPY RESEARCH APPROACH AND PIPELINE
TRANSFORMING THE FUTURE OF CANCER CARE

For more than 50 years, Roche has been at the forefront of oncology research, discovering and developing new cancer treatments and diagnostics. Now, we are expanding the impact of our medicines with a comprehensive cancer immunotherapy program.
At Roche, our goal is to constantly improve options—and outcomes—for patients.

With breakthroughs in research that have translated into the clinic, we are helping set the standard of care with a world-leading oncology portfolio.

- 14 different medicines across tumor types
- Foundational treatments, including anti-CD20, anti-HER2, anti-VEGF, BRAFi, ALKi, EGFRi, and anti-PDL1
- Pioneering companion diagnostics, including HER2, BRAF, and EGFR (first liquid biopsy)

EXPANDING OUR IMPACT
>10 million patients have received Roche cancer medicines since 1995. As we continue research into cancer immunotherapy, Roche aims to help more patients than ever before.

ASPIRING TO ACHIEVE A CURE WITH CANCER IMMUNOTHERAPY

We know that every patient—and every cancer—is unique. Our deep understanding of tumor and immune biology drives our vision of the future: personalized strategies that target both the T-cell and the tumor microenvironment.

Anti-PDL1: our foundation for cancer immunotherapy combinations
Roche developed the first anti-PDL1 cancer immunotherapy approved in multiple tumor types. We continue to build our clinical insights with additional trials of anti-PDL1 as monotherapy or in combination with our portfolio and pipeline agents.

In addition to anti-PDL1, Roche is examining unique immunotherapy targets and exploring their synergistic potential in novel combination regimens and with established medicines.

ROCHE CANCER IMMUNOTHERAPY CLINICAL DEVELOPMENT PROGRAM

NEXT-GENERATION DIAGNOSTIC TOOLS to inform treatment decisions

94% of Q1 2017.

[Image of Roche logo and patient]

<table>
<thead>
<tr>
<th>20+</th>
<th>12</th>
<th>60+</th>
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<tbody>
<tr>
<td>Molecules</td>
<td>Compounds</td>
<td>Trials</td>
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<tr>
<td>in research and development</td>
<td>being tested in clinical studies</td>
<td>ongoing (monotherapy and combination)</td>
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LEADING THE SCIENCE OF CANCER IMMUNOTHERAPY RESEARCH

UNLOCKING CANCER IMMUNITY FOR MORE PATIENTS

To deliver transformative benefit to even more patients, Roche is pursuing research designed to unlock cancer immunity.14,19

The Cancer Immunity Cycle: a series of rate-limiting steps governing the antitumor immune response

For an antitumor immune response to lead to effective killing of cancer cells, the Cancer Immunity Cycle must be initiated and allowed to proceed. There are 3 key T-cell activities required: T-cell generation, T-cell infiltration, and T-cell killing of tumor.14,15,19

3 immune phenotypes and therapeutic strategies

Building on the foundational framework of the Cancer Immunity Cycle, the Roche research team has identified 3 immune phenotypes that describe the level of T-cell presence and activity within the tumor microenvironment. These phenotypes can help determine disruptions or mechanisms of immune escape in cancer immunity.15,20

With these immune phenotypes, we can identify the T-cell activities required to reinitiate the Cancer Immunity Cycle—and the best therapeutic strategies to do so.14,15

IMMUNE DESERT14,15,21

PATTERN OF IMMUNE ACTIVITY
T cells are absent from the tumor and the tumor microenvironment

T-CELL ACTIVITY REQUIRED
GENERATE active, tumor-directed T cells

THERAPEUTIC STRATEGIES
• Generate antigens
• Enhance antigen presentation and T-cell priming
• Redirec and engage T cells

Accumulation of CD8+ T cells that do not penetrate the tumor (arrows).

CD8 immunohistochemistry (IHC). Lack of CD8+ T cells in the tumor or stroma.

IMMUNE INFLAMED14,15,21

PATTERN OF IMMUNE ACTIVITY
T cells have accumulated, but are not efficiently infiltrating the tumor microenvironment

T-CELL ACTIVITY REQUIRED
INFILTRATE tumor

THERAPEUTIC STRATEGIES
• Recruit T cells to the tumor
• Address stromal barrier
• Redirec and engage T cells

Abundance of CD8+ T cells within the tumor (arrows).

IMMUNE EXCLUDED14,15,21

PATTERN OF IMMUNE ACTIVITY
T cells have accumulated, but are not efficiently infiltrating the tumor microenvironment

T-CELL ACTIVITY REQUIRED
INFILTRATE tumor

THERAPEUTIC STRATEGIES
• Recruit T cells to the tumor
• Address stromal barrier
• Redirec and engage T cells

Accumulation of CD8+ T cells that do not penetrate the tumor (arrows).
A COMPREHENSIVE APPROACH TO RESTORING CANCER IMMUNITY

The robust clinical development program at Roche is rationally designed around immune and tumor biology—and the corresponding key therapeutic strategies to reinitiate the antitumor immune response. We are investigating a range of molecules and modalities to understand the best clinical applications within and across phenotypes. We are pursuing some of these molecules with external collaborators.14,16

IMMUNE DESERT

TREATMENT STRATEGIES
GENERATE / RELEASE / DELIVER ANTIGENS
- Personalized cancer vaccine
- Vaccines
- Oncolytic virus*
- CAR-P7
- Epigenetic modifiers:
  - HDACi,*
  - EZH2i,*
  - DNMTi*
- Chemotherapy*
- Radiotherapy*
- MEKi
- Targeted therapies: anti-HER2, BRAFi, EGFR-TKI, ALKi, PARPi,* anti-CD20

ENHANCE ANTEN PRESENTATION & T-CELL PRIMING
- Anti-CD40
- Anti-CD27*

REDIRECT & ENGAGE T CELLS
- T-cell bispecifics
  - (CEA-CD3 TCB, CD20-CD3 TCB, CD20-CD3 TDB)

IMMUNE EXCLUDED

TREATMENT STRATEGIES
RECRUIT T CELLS TO TUMOR
- Anti-VEGF
- Anti-CD40*

ADDRESS STROMAL BARRIER
- Anti-stromal agent

REDIRECT & ENGAGE T CELLS
- T-cell bispecifics
  - (CEA-CD3 TCB, CD20-CD3 TCB, CD20-CD3 TDB)

IMMUNE INFLAMED

TREATMENT STRATEGIES
INVIGORATE T CELLS
- Anti-PDL1
- Anti-VEGF
- Anti-CD40*
- Anti-FAP-IL2v
- Anti-CEA-IL2v
- Anti-CSFR
- Anti-TIGIT
- IDOi*
- Anti-A2A*
- Anti-CD38*

REDIRECT & ENGAGE T CELLS
- T-cell bispecifics
  - (CEA-CD3 TCB, CD20-CD3 TCB, CD20-CD3 TDB)

*Clinical collaborations.
Mapping of approaches to phenotypes based on current lead hypotheses. Does not preclude activity in other phenotypes.
Building on the foundation of PD-L1 checkpoint inhibition, PD-L1 inhibition is a clinically validated approach to invigorating existing immunity. However, tumors employ multiple mechanisms of immune escape, which disrupts the cancer immunity cycle. Therefore, a combination approach based on the immune phenotype may be needed to generate the essential T-cell activities required for each patient.14,16,22-24

### OUR COMBINATION STRATEGY

**Address multiple immune escape mechanisms to restore the cancer immunity cycle**14,15

### PROMOTE T-CELL INFILTRATION

**Generate active antitumor T cells**

**Invigorate T cells**

### EXAMPLES OF COMBINATIONS BY IMMUNE PHENOTYPE

#### IMMUNE EXCLUDED

- **ANTI-VEGF:** Helps increase T-cell infiltration into the tumor microenvironment
- **ANTI-PDL1:** Blocks immunosuppressive signaling in the tumor microenvironment to invigorate T-cell-mediated tumor killing

#### IMMUNE DESERT

- **Chemotherapy/targeted therapy + anti-PDL1:**
  - Promotes tumor cell death, resulting in the release of tumor antigens that can initiate T-cell priming and activation

#### IMMUNE INFLAMED

- **ANTI-PDL1:** Blocks immunosuppressive signaling in the tumor microenvironment to invigorate T-cell-mediated tumor killing

- **ANTI-VEGF:** Helps increase T-cell infiltration into the tumor microenvironment

- **ANTI-PDL1:** Blocks immunosuppressive signaling in the tumor microenvironment to invigorate T-cell-mediated tumor killing

- **IMMUNOTHERAPY + ANTI-PDL1:**
  - Addresses multiple immunosuppressive mechanisms in the tumor microenvironment (eg, expression of IDO, TIGIT) to enhance antitumor activity
**INDICATION** | **INVESTIGATIONAL REGIMEN** | **PHASE I** | **PHASE II** | **PHASE III**
---|---|---|---|---
Bladder Cancer | Anti-PDL1 + chemotherapy | | | |
Breast Cancer | Anti-PDL1 + chemotherapy | | | |
Colorectal Cancer | Anti-PDL1 + MEK inhibitor | | | |
Esophageal Cancer | Anti-PDL1 + chemotherapy | | | |
Gastric Cancer | Anti-PDL1 + anti-VEGF + chemotherapy | | | |
Hematologic Malignancies | Anti-PDL1 + anti-CD20 + chemotherapy | | | |
Hepatocellular Carcinoma | Anti-PDL1 + anti-VEGF | | | |
Melanoma | Anti-PDL1 + BRAF inhibitor + MEK inhibitor | | | |
**INDICATION** | **INVESTIGATIONAL REGIMEN** | **PHASE I** | **PHASE II** | **PHASE III**
---|---|---|---|---
Metastatic Castration-resistant Prostate Cancer | Anti-PDL1 + androgen receptor inhibitor | | | |
Non-Small Cell Lung Cancer | Anti-PDL1 + anti-VEGF + chemotherapy | | | |
Ovarian Cancer | Anti-PDL1 + anti-VEGF | | | |
Pancreatic Cancer | Anti-PDL1 + CXCR4 inhibitor | | | |
Renal Cell Carcinoma | Anti-PDL1 + anti-FAP-IL2v + anti-VEGF | | | |
Soft Tissue Sarcoma | Anti-CD40 + anti-VEGF/Ang2 | | | |
Solid Tumors | Anti-CD137 | | | |
**This compound and the combination of agents and their uses are investigational and have not been approved by regulatory agencies. Efficacy and safety have not been established. The information presented should not be construed as a recommendation for use. The relevance of findings in preclinical studies to humans is currently being evaluated. Information is consistent with ClinicalTrials.gov as of April 27, 2017.**

**Bold typeface** used to indicate development of immunotherapeutic strategies in-house (Roche/Genentech).

**Italic typeface** used to indicate development of multiple immunotherapeutic strategies both in-house (Roche/Genentech) and external collaboration.

**Partnered/external collaborations.**

**NOW ENROLLING:** ROCHE CANCER IMMUNOTHERAPY COMBINATION CLINICAL TRIALS⁵⁶
COLLABORATING FOR A COMMON GOAL

At Roche, we are committed to achieving a cure for cancer—by working together, we can get there faster. We are coordinating a worldwide effort to engage with academic centers, as well as life science and technology companies, in our shared goal to transform patient lives.26-28

Academic alliances
Our vision is to deepen exchange and collaboration across academic institutions to accelerate progress in the field of cancer immunotherapy research.26

imCORE is a global network of cancer research institutes that are working together and with Roche to identify and prioritize the most promising new treatment approaches and to rapidly conduct preclinical and clinical research.26

For enquiries regarding imCORE, contact imCORE@roche.com.

CURRENT imCORE INSTITUTIONS

23 CENTERS
9 COUNTRIES
4 CONTINENTS

COLLABORATE TO ACCELERATE
Connect with us: Contact your local Roche medical science liaison

- For more information about the Roche Cancer Immunotherapy research and pipeline visit www.roche.com/research_and_development, or http://global.researchcancerimmunotherapy.com
- To learn about currently enrolling cancer immunotherapy clinical trials visit www.ClinicalTrials.gov