CAR T Cell Therapy
Chimeric Antigen Receptor T cell therapy, or CAR T cell therapy, is an immunotherapy approach to treat cancer.

CAR T Cell Therapy Production
The production of CAR T cell therapy involves a number of steps.¹ ²

Allogeneic
Allogeneic CAR T cells are engineered using T cells from a single donor that are utilized in multiple patients.

Autologous
Autologous CAR T cells are engineered using a patient’s own T cells.

Approaches to CAR T Cell Therapy Development
There are two approaches to the production of CAR T cell therapy. More research is needed to better understand the potential benefits and disadvantages of each approach.

Pfizer is Actively Pursuing Allogeneic CAR T Cell Therapy
Through collaborations with Cellectis and Servier, Pfizer is actively investigating allogeneic CAR T cell therapies across several targets.

Cellectis’s CAR T platform technology provides a proprietary, allogeneic approach to developing CAR T cell therapies that seeks to make genetically-engineered immunotherapy treatments that could potentially be used by multiple patients.

The collaboration with Servier enables us to co-develop and potentially commercialize UCART19, an investigational allogeneic CAR T cell therapy.

PF-04136309 CCR2 Inhibitor

**PF-04136309 (PF-6309)** is an investigational small-molecule antagonist of the human chemokine (C-C motif) receptor 2 (CCR2) – a type of receptor that binds to cytokines (proteins that are involved in cell signaling).\(^1,2\)

**PF-6309 Mechanism of Action**

CCL2 is a chemoattractant that is released by tumor cells and binds to CCR2, which is expressed on the surface of monocytes (types of white blood cells) in the bone marrow. CCL2 is thought to play a role in the recruitment of monocytes from the bone marrow to the tumors, where these cells then become tumor associated macrophages (TAM). They in turn, have been observed to limit the effectiveness of anti-tumor immune responses, leading to tumor progression and chemoresistance.\(^3\)

**PF-6309** binds to CCR2 and has been observed to inhibit the binding of CCL2 to its receptor CCR2. The inhibition of CCR2 is thought to stop the recruitment of monocytes and reverse immune suppression within the tumor microenvironment.\(^3,4,5\)

**The Potential of CCR2 Inhibition**

Studies suggest that inhibition of CCR2 may have application in a variety of diseases, including cancer. Pre-clinical studies of **PF-6309** show anti-tumor activity in localized pancreatic cancer. **PF-6309** has also been evaluated in an investigator-initiated Phase 1b dose escalation study in pancreatic cancer. More research is needed to fully understand the potential of CCR2 inhibition in cancer and identify potential immunotherapy combinations.

**Clinical Study**

**PF-6309** is currently being studied in a Phase 1b/2 trial (dose escalation study followed by randomized Phase 2) for pancreatic cancer (NCT02732938).\(^6\)

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PF-6309 is an investigational compound.
UTOMILUMAB (PF-05082566)

Utomilumab is the proposed non-proprietary name for PF-05082566, an investigational immunotherapy and fully humanized monoclonal antibody (mAb) administered intravenously that stimulates signaling through 4-1BB (CD-137), a protein expressed in many immune cells.

Mechanism of Action

The 4-1BB (CD-137) protein receptor is found on CD8+ and CD4+ T cells and natural killer cells.1,2 Based on pre-clinical data, when utomilumab (PF-05082566) binds to 4-1BB, it has been observed to stimulate and increase the number of immune cells.1 This may provide enhanced anti-tumor immune function.1

The Potential of Combination Approach

Preclinical studies suggest that combining utomilumab (PF-05082566) with a checkpoint inhibitor, such as anti-PD-L1, or other immunotherapies may be able to amplify the immune response.4,5,6 Further understanding the biology of how the immune system attacks tumors and ways by which tumors evade the immune system may lead to new investigational compounds.

CLINICAL STUDIES

Pfizer is exploring the potential of utomilumab (PF-05082566) in a clinical development program to determine:

• maximum tolerated dose
• anti-tumor activity and safety profile
• therapeutic potential in combination with other therapies

Phase 1

Data from a Phase 1 study that evaluated utomilumab (PF-05082566) in combination with rituximab in patients with relapsed or refractory CD20+ non-Hodgkin's lymphoma (NHL) showed that utomilumab (PF-05082566) had anti-tumor activity.7

• No dose-limiting toxicities were observed and no patients discontinued treatment due to treatment-related adverse events.
• These results characterize the potential activity for this investigational immunotherapy when used in combination with a drug such as rituximab that has a different MOA.7

Future studies

Pfizer will further explore utomilumab (PF-05082566) in order to better understand its efficacy and safety when used as both a single agent and in combination with other anti-cancer therapies, including immunotherapies, in several types of studies:

• A Phase I study as a single agent in multiple tumor types and in combination with rituximab in lymphoma patients
• A Phase 1 combination study with Merck (U.S.) for pembrolizumab (anti-PD-1) in solid tumors
• A Phase 1 combination study with mogamulizumab (anti-CCR4) in collaboration with KHK
• A Phase 1 combination study with Merck KGaA and Pfizer's PD-L1 avelumab

For more information, please visit www.pfizercancertrials.com or www.clinicaltrials.gov or call toll-free 1-877-369-9753 (in the United States and Canada) or +1-646-277-4066 (outside of the United States and Canada).


PF-8600 (OX40 AGONIST)

PF-04518600 (PF-8600) is an investigational immunotherapy monoclonal antibody (mAb) that targets the human OX40 protein (CD134), a receptor that is expressed on several types of T cells (types of immune cells).

**Mechanism of Action**

OX40 protein is mostly expressed on T cells (CD4+ and CD8+) that have recently been exposed to antigens, for example, tumor cells. When an OX40 agonist, such as PF-8600, binds to the OX40 protein receptor it triggers a co-stimulatory signal that is observed to be associated with increased production of T cells and inflammatory cytokines. This mechanism is thought to activate the dormant immune settings, which then may help fight cancer cells. Furthermore, in the tumor microenvironment (the cellular environment in which the tumor exists) OX40 agonist antibodies may suppress and/or reduce the regulatory T cells (Treg), which tend to inhibit effector T cell functions.

**The Potential of Combination Approach**

Preclinical studies suggest that combining PF-8600 with a checkpoint inhibitor, such as anti PD-1/anti-PD-L1, or other immunotherapies may be able to amplify the immune response, and show additive activity in syngeneic tumor models. More research, however, is needed to fully understand the mechanism of action of these potential combination approaches.

**Clinical Study**

**Phase 1**

In 2015, Pfizer initiated a Phase 1 trial of PF-8600 in patients with select advanced solid tumors, such as hepatocellular carcinoma, melanoma, clear cell renal cell carcinoma, or squamous cell head and neck cancer. The estimated enrollment is 180 patients.