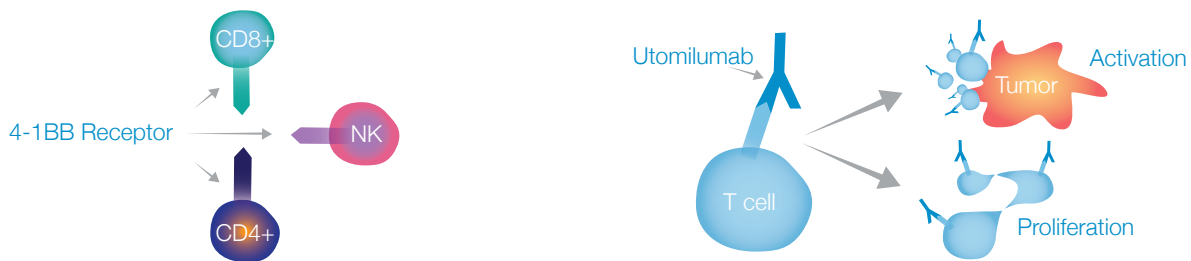


UTOMILUMAB (PF-05082566)

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

¹ Fisher TS, Kamperschroer C, Oliphant T, et al. Targeting of 4-1BB by monoclonal antibody PF-05082566 enhances T-cell function and promotes anti-tumor activity [published online ahead of print March 11, 2012]. *Cancer Immunol Immunother*. doi:10.1007/s00262-012-1237-1.

² Westwood JA, Hunnam TC, Pegram HJ, et al. Routes of delivery for CpG and anti-CD137 for the treatment of orthotopic kidney tumors in mice. *PLoS ONE*. 2014; 9(5):1-10.

³ West, J., et al. Immune Checkpoint inhibitors, *JAMA Oncol*. 2015;1(1):115. doi:10.1001/jamaoncol.2015.0137. Available at <http://oncology.jamanetwork.com/article.aspx?articleid=2174768>.

⁴ Wei H, Zhao L, Li W, et al. Combinatorial PD-1 blockade and CD137 activation has therapeutic efficacy in murine cancer models and synergizes with cisplatin. *PLoS ONE*. 2013; 8(12):1-11.

⁵ Curran MA, Kim M, Montalvo W, et al. Combination CTLA-4 blockage and 4-1BB activation enhances tumor rejection by increasing t-cell infiltration, proliferation, and cytokine production. *PLoS ONE*. 2011; 6(4):1-11.

⁶ Guo Z, Cheng D, Xia Z, et al. Combined TIM-3 blockade and CD137 activation affords the long-term protection in a murine model of ovarian cancer.

⁷ Gopal, A., et al. A phase I study of PF-05082566 (anti-4-1BB) + rituximab in patients with CD20+ NHL. *J Clin Oncol* 33, 2015 (suppl; abstr 3004). Available at http://abstracts.asco.org/156/AbstView_156_147130.html.