A Potential First-in-class Anti-VTCN1 Antibody for the Treatment of Solid Tumors

Overview

Drug Name	PTH-0301
Description	PTH-0301 is a recombinant humanized IgG4 monoclonal antibody that can specifically bind to VTCN1 (also known as B7-H4) to block the inhibitory effects on T cell proliferation, activation, and related immune responses mediated by VTCN1. Therefore, PTH-0301 can restore and enhance the anti-tumor immune responses and has broad-spectrum anti-cancer potential. PTH-0301 has received IND approval in the US, and a phase 1 clinical trial is currently undergoing in China.
Target	VTCN1
Drug Modality	Monoclonal antibody
Indication	Solid tumor
Product Category	Immunotherapy
Mechanism of Action	Blocking the immunosuppressive effects mediated by VTCN1
Status	Phase 1 (NMPA); IND (FDA)
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for PTH-0301. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

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VTCN1

Introduction	VTCN1 is one of the most important members of the B7 family. It is often overexpressed in cancer cells and immunosuppressive tumor-associated macrophages (TAMs). Human VTCN1 gene is located on the p13.1 region of chromosome 1. VTCN1 is a transmembrane protein consisting of 282 amino acids. It contains a large hydrophobic transmembrane domain and an intracellular domain containing only 2 amino acids. There are seven potential N-glycosylation sites in its extracellular domain. A large number of studies have shown that VTCN1 plays a crucial role in tumors, inflammation, and autoimmune diseases. VTCN1 negatively regulates the immune response of T cells and promotes immune escape by inhibiting the proliferation, cytokine secretion, and cell cycle of T cells. Therefore, further exploration of VTCN1 may provide new insights and methods for the development of immunotherapy.
Approved Name	V-set domain containing T cell activation inhibitor 1
Official Symbol	VTCN1
Gene Type	gene with protein product
Synonyms	B7-H4; FLJ22418; B7S1; B7x; B7H4
Ensembl	ENSG00000134258
Gene ID	79679
mRNA Refseq	NM_024626
Protein Refseq	NP_078902
OMIM	608162
UniProt ID	Q7Z7D3
Chromosome Location	1p13.1-p12

Clinical Resources

Pathway	Adaptive immune response, immune system process, interleukin-4 production, negative regulation of T cell activation and proliferation, etc.
Major Conditions	Solid tumors

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Drug Modality

Monoclonal Antibody

PTH-0301 is a recombinant humanized IgG4 monoclonal antibody, which can specifically bind to VTCN1 and thereby effectively block the inhibitory effect of VTCN1 on T cell activation and proliferation as well as immune response.

Indication

Solid Tumor

A number of studies have shown that VTCN1 protein is widely expressed in various solid tumors, including ovarian cancer, endometrial cancer, breast cancer, prostate cancer, lung cancer, bladder cancer, etc. The expression of VTCN1 in the tumor microenvironment is not limited to the tumor cells themselves, but also exists on immune cells such as tumor-associated macrophages (TAMs), inhibiting the anti-tumor immune response of T cells and forming an immunosuppressive microenvironment of "cold tumors".

Ovarian Cancer	The high expression rate of VTCN1 in ovarian cancer tissues is closely related to disease progression and drug resistance. Expressed as the mortality-incidence ratio, ovarian cancer is the most lethal form of cancer affecting women. The principal reason why ovarian cancer is so lethal is the lack of clinically specific symptoms leading to detection at early, more successfully treatable stages. According to Globocan data for 2020, the global incidence of ovarian cancer that year was 313,959 and an incidence rate of 6.6 per 100,000 women. According to the prediction of the American Cancer Society, there will be approximately 20,890 new cases in the United States in 2025, and about 12,730 deaths will be caused.
Breast Cancer	Breast cancers are broadly classified as noninvasive, invasive, and metastatic. Among the invasive forms of breast cancer, the most common are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). The treatment strategies for breast cancer include surgery, radiotherapy, hormone therapy, and biological or chemotherapy.

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	According to the International Agency for Research on Cancer, in 2020, female breast cancer pulled ahead of lung cancer as the most commonly diagnosed malignancy worldwide, accounting for 11.7% of all incident cancer cases that year.
Endometrial Cancer	Endometrial cancer currently ranks as the most common gynecologic malignancy in women worldwide and continues to increase in prevalence. Patients with endometrial cancer can generally be treated successfully with surgery alone. Patients with advanced or recurrent disease should receive chemotherapy, and radiation therapy is used along with chemotherapy to treat patients with locally advanced disease. However, very few chemotherapeutic agents have been approved specifically for the indication of endometrial cancer. Over the past three decades, the overall incidence of endometrial cancer worldwide has increased by more than 130%. In the United States, the American Cancer Society estimates that 69,120 new cases of cancer of the uterine corpus, more than 90% of which are endometrial cancers, will be diagnosed in 2025.

Mechanism of Action

Blocking the Immunosuppressive Effects Mediated by VTCN1

VTCN1 is abnormally highly expressed on the surface of various solid tumor cells and tumor-associated macrophages (TAMs). Tumor cells utilize the inhibitory function of VTCN1 to evade the immune response mediated by T cells. The VTCN1 expressed on both tumor cells and host cells reduces the activation and subsequent effector functions of tumor-infiltrating T cells in the tumor, such as inflammatory cytokine production and cytolytic activity. In addition, VTCN1 induces the shifting of effector T cells into an exhausted T cell phenotype co-expressed PD-1 and Tim-3. VTCN1 immune checkpoint also plays a key role in cancer by promoting the proliferation of immunosuppressive cells (including regulatory T cells, myeloid-derived suppressor cells, and macrophages), thereby shaping an immunosuppressive environment.
PTH-0301 is a monoclonal antibody targeting VTCN1, which can highly specifically recognize and bind to VTCN1, occupying its binding site and preventing it from binding to inhibitory receptors on T cells, and blocking the inhibitory signal transmitted by VTCN1 to T cells. The T cells can regain their activity, resume proliferation, and release cytokines to recognize and kill tumor cells expressing VTCN1. In addition, PTH-0301 as a monoclonal antibody can produce antibody-dependent cell-mediated cytotoxicity (ADCC) to kill tumor cells. When the monoclonal antibody binds to VTCN1 on the surface of tumor cells, the Fc segment of PTH-0301 is

exposed. Immune cells such as natural killer cells are activated by binding to the Fc segment, thereby releasing cytotoxic substances like perforin and granzymes, which directly kill tumor cells.

Status

The Status of PTH-0301

The IND approval for PTH-0301 has been received in both China and the United States. A phase 1 clinical trial is being conducted in China to evaluate the safety, tolerability and pharmacokinetic characteristics of PTH-0301 in patients with advanced solid tumors.