MINI REVIEW

Immune Checkpoint mAb Cancer Therapies approved by FDA

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In 1893 the surgeon William Coley (1) reported that injection of inactivated bacteria into sarcoma could lead to tumor shrinkage, since then immunology and oncology have been linked together, the intersection between immune surveillance and tumor growth and development has made exponential advances, leading to broad immunotherapeutic advances in all cancer types. This mini review focus on immune checkpoint inhibitor monoclonal antibody (mAb) approved by FDA so far.

According to NCI, A type of drug that blocks proteins called checkpoints, such as Programmed cell death 1 (PD-1), Cytotoxic T-lymphocyte antigen 4 (CTLA-4), and Lymphocyte activation gene 3 (LAG3), that are made by some types of immune system cells, such as T cells, and some cancer cells. These checkpoints help keep immune responses from being too strong and sometimes can keep T cells from killing cancer cells. When these checkpoints are blocked, T cells can kill cancer cells better.(2) (10)

PD-1 is a transmembrane protein expressed on T cells, B cells,NK cells. monocytes, and dendritic cells. PD-1 is an inhibitory molecule that binds to the programmed cell death ligand 1 (PD-L1; also known as B7-H1) and PD-L2 (B7-H2). PD-L1 is expressed on the surface of multiple tissue types, including hematopoietic cells. PD-L1 is also expressed in many tumor cells; PD-L2 is more restricted to hematopoietic cells. The PD-1:PD-L1/2 interaction directly inhibits apoptosis of the tumor cell, promotes peripheral T effector cell exhaustion, and promotes conversion of T effector cells to Treg cells. (3~9)

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response. The expression of CTLA-4 is upregulated by the degree of T cell receptor (TCR) activation and cytokines such as IL-12 and IFN gamma, forming a feedback inhibition loop on activated T effector cells. As a result, CTLA-4 can be broadly considered a physiologic "brake" on the CD4+ and CD8+ T cell activation that is triggered by APCs. (2)

LAG3 is expressed by B cells, some T cells, NK cells, and tumor-infiltrating lymphocytes (TILs), is used to regulate immune checkpoint pathways. The LAG3 protein enhances Treg activity by binding major histocompatibility complex (MHC) class II and hampering T cell differentiation and proliferation LAG-3 blocking antibodies restore the effect or function of exhausted T cells and increases their ability to attack tumor cells.(10)

Monoclonal antibody (mAb) technique was created by Georges Köhler, César Milstein, and Niels Kaj Jerne in 1975 by using a mouse x mouse hybridoma. In 1984 they were awarded the Nobel Prize in Medicine for the discovery. Eight years later, in 1992 US FDA approved the first therapeutic mAb muromonab-CD3 (trade name Orthoclone OKT3) to reduce acute rejection in patients with organ transplants. Since then, as of December 31, 2021, FDA has approved 136 therapeutic mAbs, 50 were approved for cancer therapy (11), among them 9 targets at immune checkpoints, listed here (2~10). In March 2022, FDA approved OPDUALAG, targeting two checkpoints PD-1 and LAG3 (10), it will potentially raise a new wave of combined therapy.

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DOI: 10.33309/2639-8583.040204

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Aproval on	**MAH**	**Drug Name**	**Active Ingredients**	**Target**	**Indication**	**Warning and Precausion**	**Adverse Events 1st Five**
3/25/2011	BMS	YERVOY	ipilimumab (CTLA-4)	CTLA-4	Melanoma; RCC; CC; HC; NSCLC; MPM	IMAE; IRR; Complications of allogeneic HSCT; EFT	fatigue, diarrhea, pruritus, rash, colitis
9/4/2014	MSD	KEYTRUDA	pembrolizumab (PD-1)	PD-1	Melanoma et al >18 cancers	IMAE; IRR; Complications of allogeneic HSCT; EFT	fatigue, MSP, rash, diarrhea, pyrexia
3/4/2015	BMS	OPDIVO	nivolumab (PD-1)	PD-1	Melanoma; NSCLC	IMAE; EFT	NSCLC >20%: fatigue, dyspnea, MSP, decreased appetite, cough
5/18/2016	GENEN TECH	TECENTRIQ	atezolizuma (PD-L1)	PD-L1	UC; NSCLC; SCLC; HC; Melanoma	IMAE; IRR; Complications of allogeneic HSCT; EFT	fatigue/ asthenia, decreased appetite, nausea, cough, dyspnea
3/23/2017	EMD SERONO	BAVENCIO	avelumab (PD-L1)	PD-L1	MCC; UC; RCC	IMAE; IRR; Complications of allogeneic HSCT; MACE; EFT	MCC: fatigue, MSP, diarrhea, nausea, IRR
5/1/2017	ASTRA ZENECA	IMFINZI	durvalumab (PD-L1)	PD-L1	Non-Small Cell Lung Cancer; Small Cell Lung Cancer	IMAE; IRR; Complications of allogeneic HSCT; EFT	NSCLC: cough, fatigue, pneumonitis, URTI, dyspnea
9/28/2018	RE GENERON	LIBTAYO	cemiplimab-rwlc (PD-1)	PD-L1	CSCC; BCC; NSCLC	IMAE; IRR; Complications of allogeneic HSCT; EFT	≥15%: MSP, fatigue, rash, and diarrhea
4/22/2021	GSK	JEMPERLI	dostarlimab-gxly (PD-1)	PD-L1	dMMR endometrial cancer	IMAE; IRR; Complications of allogeneic HSCT; EFT	≥20%: fatigue, nause, diarrhea, anemia, constipation.
3/18/2022	BMS	OPDUALAG	nivolumab and relatlimab-rmbw	PD-1 and LAG3	unresectable or metastatic melanoma	IMAE; IRR; HSCT; EFT	pain, fatigue, rash, pruritus, diarrhea.

*Melanoma1.2 Non-Small Cell Lung Cancer1.3 Head and Neck Squamous Cell Cancer1.4 Classical Hodgkin Lymphoma1.5 Primary Mediastinal Large B-Cell Lymphoma1.6 Urothelial Carcinoma1.7 Microsatellite Instability-High or Mismatch Repair DeficientCancer1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer1.9 Gastric Cancer1.10 Esophageal Cancer1.11 Cervical Cancer1.12 Hepatocellular Carcinoma1.13 Merkel Cell Carcinoma1.14 Renal Cell Carcinoma1.15 Endometrial Carcinoma1.16 Tumor Mutational Burden-High Cancer1.17 Cutaneous Squamous Cell Carcinoma1.18 Triple-Negative Breast Cancer.

Abbreviation for the table
BCC Basal Cell Carcinoma
CC Colorectal Cancer
CSCC Cutaneous Squamous Cell Carcinoma
CTLA-4 cytotoxic T-lymphocyte antigen 4
dMMR mismatch repair deficient
EFT Embryo-fetal toxicity
HC Hepatocellular Carcinoma
HSCT hematopoietic stem cell transplantation
IMAE Immune-Mediated Adverse Reactions
IRR Infusion-related reactions
LAG3 lymphocyte activation gene-3
MACE Major adverse cardiovascular events
MCC Merkel Cell Carcinoma
MPM Malignant Pleural Mesothelioma
MSP musculoskeletal pain
NSCLC Non-Small Cell Lung Cancer
RCC Renal Cell Carcinoma
UC Urothelial Carcinoma
URTI upper respiratory

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How to cite this article Cai H H, Pandit A A. Immune Checkpoint mAb Cancer Therapies Approved by FDA. Clin Res Immunol 2022;4(2):12-14.
DOI: 10.33309/2639-8583.040204