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The journey of dostarlimab: a successful weapon for cancer treatment

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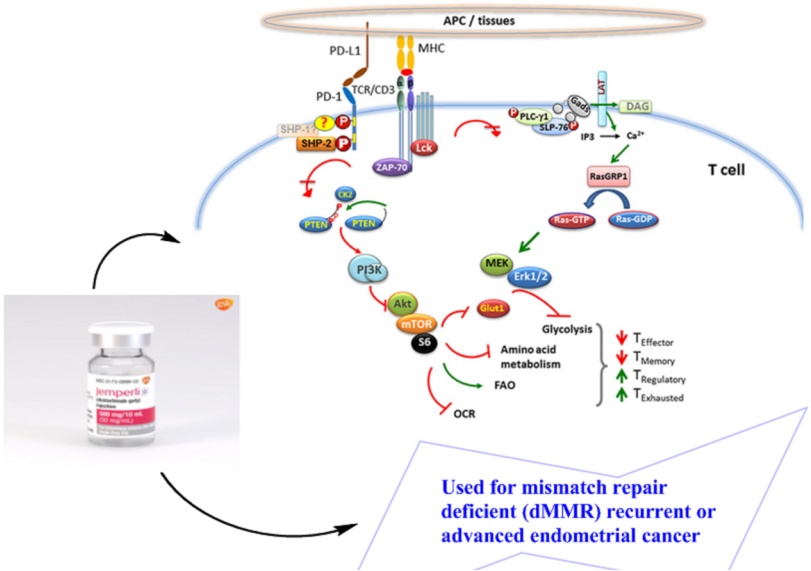
Abstract

In a number of malignancies, new immuno-oncology therapies that focus on the programmed cell death 1 (PD-1) have improvised the patient condition along with a positive aftereffect. Monoclonal antibodies (mAbs) directed against PD-1 and its ligand (PD-L1), have been widely used to treat a variety of malignancies, including melanoma, renal cancer, and non-small cell lung cancer (NSCLC). Dostarlimab, a therapeutic anti-PD-1 antibody, was authorised by the United States Food and Drug Administration (FDA) in April 2021 under the trade name JEMPERLI. It is a humanised contrary PD-1 immunoglobulin G 4 (IgG4) mAb, which successfully blocks interaction with PD-L1 and PD-L2 by binding tightly to the PD-1 receptor. This article summarizes the different aspects associated with the dostarlimab, including currently available anti-PD-1/PD-L1 antibodies, pharmacokinetics (PK), pharmacodynamics, adverse reaction, and mechanism of action of dostarlimab, as well as various reported clinical trials.



Graphical abstract. Role of dostarlimab in cancer

Keywords

Programmed cell death receptor 1, cancer therapy, monoclonal antibodies, programmed cell death 1 ligand 1, dostarlimab, clinical trials

Introduction

The therapy options available to cancer patients have undergone a significant change as a result of programmed cell death 1 (PD-1) receptor and its ligand (PD-L1) inhibitors. PD-1 is an inhibitory immune checkpoint receptor, which is expressed by the activated T cells. The PD-1 receptor through interactions with PD-L1 and PD-L2 prevents activated effector T-cell cytokine production, proliferation, and cytotoxic activity [1, 2]. Numerous malignancies that upregulate PD-L1 are able to subvert the PD-1/PD-L1 pathway, which reduces the response of cytotoxic T-cells in the tumour microenvironment and has been linked to a poor prognosis [3, 4]. By blocking the binding of PD-1/PD-L1, immune evasion is reversed and an adaptive immune response against the tumour is restored [5]. Interestingly, PD-L1 monoclonal antibodies (mAbs) have shown anticancer efficacy in individuals with diverse solid tumours.

Currently, four anti-PD-1 antibodies got approval for use in cancer immunotherapy throughout the world. In 2014, pembrolizumab (KEYTRUDA®) and nivolumab (OPDIVO®) were approved by United States Food and Drug Administration (FDA) for treating non-small cell lung cancer (NSCLC) and melanoma. Since then, the antibodies' indications have been increased to treat a variety of tumours such as breast cancer, classical Hodgkin lymphoma (CHL), urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), esophageal carcinoma, head carcinoma, endometrial cancer, renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC), either alone or in combination with other medications. In 2018, cemiplimab (LIBTAYO®) received approval from FDA for treating squamous cell carcinoma. Furthermore, the FDA has granted cemiplimab's enlarged indication for the diagnosis of basal cell carcinoma as well as NSCLC. Dostarlimab (JEMPERLI), the fourth PD-1 mAb, was approved by the FDA in April 2021 for the cure of mismatch repair deficient (dMMR) solid tumours and dMMR endometrial cancer [6–12]. It is being developed by GlaxoSmithKline (GSK) under a license from AnaptysBio Inc. (AnaptysBio) to treat a variety of cancers, including ovarian cancer, NSCLC, pancreatic cancer, malignant melanoma, squamous cell cancer (SCC), peritoneal cancer, small-cell lung cancer (SCLC), endometrial cancer, and cancer of the neck and head. Dostarlimab is an immunoglobulin G 4 (IgG4) mAb that has been humanized and was produced from the hybridoma of a mouse. Dostarlimab is approved for the treatment of adult patients with advanced or recurrent endometrial cancer who have a dMMR mutation. Dostarlimab should be used in the following amounts: every three weeks 500 mg for the first four doses, followed by 1,000 mg every six weeks starting three weeks after dose four, or until the disease progresses or the side effects become intolerable. Numerous immune-related side effects have been linked to dostarlimab use, which may necessitate stopping the drug temporarily or permanently [13]. Two signalling motifs can be found in the cytoplasmic tail of PD-1. An immunoreceptor tyrosine-based switch motif (ITSM) and an immunoreceptor tyrosine-based inhibitory motif (ITIM) are the two types. The binding of PD-L1 or PD-L2 to PD-1 on activated T cells and T cell receptor (TCR) signalling result in the tyrosine phosphorylation of the cytoplasmic domain tyrosines and the recruitment of an Src homology 2-containing tyrosine phosphatase (SHP-2) to the ITSM. Downstream signalling is suppressed as a result of SHP-2's dephosphorylation of TCR-associated *CD-3z* and zeta-chain-associated protein kinase 70 (ZAP-70). This includes the inhibition of Protein kinase B (Akt) and phosphoinositide 3-kinase (PI3K) activity, which impairs glucose metabolism and interleukin-2 (IL-2) release. The development of mAbs for cancer immunotherapy involves improving T cell activity by preventing the binding of PD-1 and PD-L1 or PD-L2 [14]. The currently available drugs that target PD-1/PD-L1 pathway and comparison are shown in Table 1.

Table 1. Currently available drugs that target PD-1/PD-L1 pathway

Drugs	Approved indication	Dosage	Route of administration	Side effects
Nivolumab (brand name "OPDIVO®", fully human IgG4 mAb)	Metastatic NSCLC, metastatic melanoma, CHL, malignant pleural mesothelioma, RCC, HNSCC, urothelial carcinoma, HCC, esophageal cancer, dMMR, or MSI-H metastatic colorectal cancer, gastric cancer, and gastroesophageal junction cancer	For melanoma, RCC, HNSCC, NSCLC, urothelial carcinoma, CHL, esophageal cancer, and gastroesophageal junction cancer: every two weeks 240 mg Pediatric patients with MSI-H or dMMR metastatic colorectal cancer: every two weeks 3 mg/kg	Intravenous (i.v.)	Back pain, blurred vision, change or loss of taste, depressed mood, cough, dry skin and hair, irregular heartbeat and pulse, loss of appetite, itching, nausea, muscle cramps and stiffness, red, irritated eyes, swelling, redness, the pain of the skin, weight gain, vomiting, chest pain, trouble sleeping, tenderness, bloody or cloudy urine, drowsiness, trouble breathing
Pembrolizumab (brand name "KEYTRUDA®", humanized IgG4 mAb)	Metastatic NSCLC, Metastatic melanoma, urothelial carcinoma, esophageal cancer, PMBCL, HNSCC, MSI-H or dMMR cancer, HCC, gastric cancer, cervical cancer, CHL, RCC, MCC, endometrial carcinoma, TMB-H cancer, triple-negative breast cancer, and CSCC	For adult metastatic melanoma patients: every 3 weeks 200 mg Adult patients with HNSCC, NSCLC, PMBCL, esophageal cancer, dMMR or MSI-H cancer, cervical cancer, TMB-H, HCC, urothelial carcinoma, MCC, CHL, CSCC: every 3 weeks 200 mg or every 6 weeks 400 mg Pediatric patients with PMBCL, MSI-H or dMMR cancer, CHL, TMB-H, MCC: every 3 weeks 2 mg/kg Pediatric melanoma patients: every 3 weeks 2 mg/kg	i.v.	Bladder pain, blurred vision, itching, swelling of the face, hands, arms, lower legs, or feet, loss of voice, body aches or pain, confusion, decreased appetite, cough, difficulty with breathing, depressed mood, dry mouth, feeling cold, joint or bone pain, painful or difficult urination, lower back or side pain, slow or fast heartbeat, stomach cramps, vomiting, weakness in the arms, yellow eyes or skin, sneezing, muscle weakness, trouble sleeping, severe or sudden headache, drowsiness
Cemiplimab (brand name "LIBTAYO®", humanized IgG4 mAb)	Metastatic or locally advanced CSCC	Until illness development or toxicity, 350 mg once every three weeks	i.v.	Diarrhea, fatigue, musculoskeletal pain, rash, nausea, constipation, pruritus, immune-mediated adverse reactions
Atezolizumab (brand name "TECENTRIQ®", humanized IgG1 mAb)	SCLC, urothelial carcinoma, metastatic NSCLC, HCC, and melanoma	Every 3 weeks 1,200 mg	i.v	Nausea, lower back or side pain, difficulty in breathing, diarrhea, body aches or pain, slow and fast heartbeat, burning or painful urination, fever, stomach cramps, rapid weight gain, headache, unusual tiredness or weakness, vomiting, confusion, depressed mood, facial swelling, trouble sleeping, yellow eyes and skin, increased thirst, muscle pain, redness of the skin
Avelumab (brand name "BAVENCIO®", fully human IgG1 mAb)	MCC, RCC, Metastatic urothelial carcinoma	10 mg/kg every two weeks until the condition progresses or there is toxicity	i.v.	Headache, muscle, bone, or joint pain, nausea, constipation, tiredness, vomiting, and weight loss
Durvalumab (brand name "IMFINZI®", humanized IgG1 mAb)	Metastatic urothelial carcinoma, NSCLC, SCLC	Every 2 weeks 10 mg/kg	i.v.	Bladder pain, fever, dry skin and hair, slowed heartbeat, tenderness, stomach cramps, bloody or cloudy urine, burning, or painful urination, rapid weight gain, chest pain, cough, difficult breathing, sweating, trouble sleeping, blurred vision, headache, chest tightness, pale skin, redness of the eye

Table 1. Currently available drugs that target PD-1/PD-L1 pathway (*continued*)

Drugs	Approved indication	Dosage	Route of administration	Side effects
Dostarlimab (brand name "JEMPERLI", humanized IgG4 mAb)	dMMR endometrial cancer and dMMR solid tumours	Every 3 weeks 500 mg	i.v.	Bladder pain, burning or painful urination, feeling cold, constipation, hair loss, muscle cramps and stiffness, trouble breathing, weight gain, unusual tiredness or weakness, pale skin, chest pain or tightness, confusion, coma, cough, fever, diarrhea, headache, irritability, nausea, trouble sleeping, sweating, anxiety, change in vision, dry mouth, joint pain, drowsiness

CSCC: cutaneous squamous cell carcinoma; MCC: Merkel cell carcinoma; MSI-H: microsatellite instability-high; PMBCL: primary mediastinal large B-cell lymphoma; TMB-H: tumour mutational burden-high cancer

Pathophysiology

The T cell protein is phosphorylated as a result of TCR/CD3 chains oligomerizing (TCR) in response to a foreign antigen recognized by a T cell that has been presented by major histocompatibility complex (MHC) on the surface of an antigen-presenting cell (APC). This is followed by the recruitment of activated lymphocyte-specific protein tyrosine kinase (Lck) and zeta-chain-associated protein kinase 70 (Zap-70) to the phosphorylated immunoreceptor tyrosine-based activation motifs (ITAM) of the TCR tail, which starts the subsequent TCR-signaling cascade. SHP-2 is drawn to the ITSM by the phosphorylation of the two tyrosine residues on PD-1's cytoplasmic tail when it engages with its ligands during TCR bridge (also possibly SHP-1). Zap-70 and Lck are thus dephosphorylated. Additionally, PD-1 ligation inhibits the PI3K/Akt/mammalian target of rapamycin (mTOR) and Ras/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) pathways, which causes a decrease in metabolism of amino acids and glycolysis and an increase in fatty acid oxidation in T cells. The course of T cell development may be impacted by this alteration in metabolic reprogramming, which could reduce the formation of effector & memory T cells while promoting the production of regulatory T cells and weary T cells (Figure 1) [15].

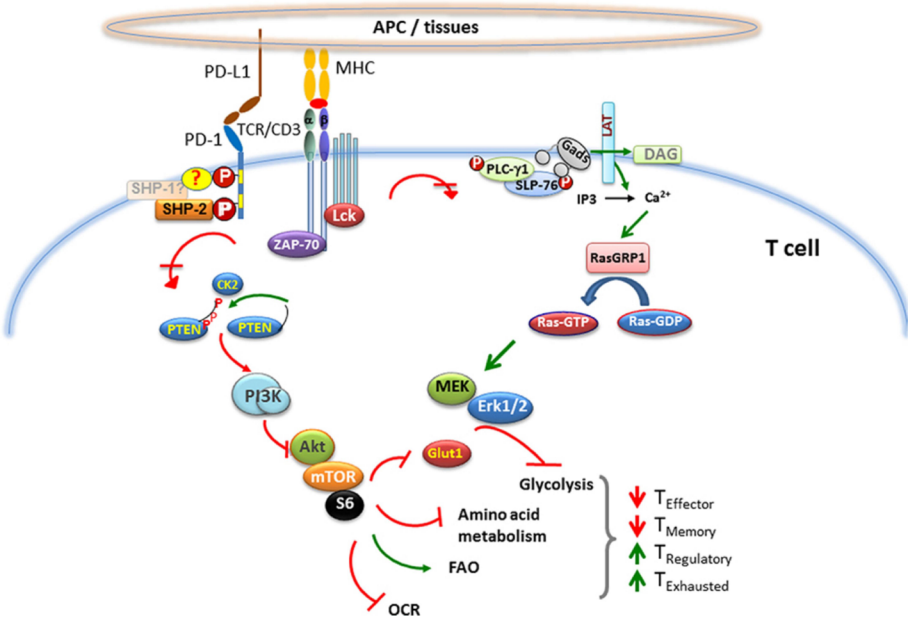


Figure 1. Pathophysiology of PD-1. CK2: casein kinase-2; DAG: diacylglycerol; FAO: fatty acid oxidation; Gads: GRB2-related adaptor downstream of Shc; GDP: guanosine diphosphate; Glut1: glucose transporter 1; GTP: guanosine triphosphate; IP3: inositol 1,4,5-trisphosphate; MEK: mitogen-activated protein kinase kinase; OCR: oxygen consumption rate; P: phosphorylated; PI3K: phosphoinositide 3-kinase; PLC-γ1: phospholipase C-gamma 1; PTEN: phosphatase and tensin homolog; RasGRP: Ras guanil releasing protein; LAT: linker for activation of T cells; SLP-76: SH2 domain-containing leukocyte phosphoprotein of 76kDa; ?: possibility of any of the options

Pharmacology

Mechanism of action

The PD-1 ligands PD-L1 and PD-L2 suppress cytokine production and T-cell proliferation when they attach to the PD-1 receptor on T cells. Some cancers that exhibit upregulation of PD-1 ligands and signaling via this route may help to reduce active T-cell immune monitoring of malignancies. Dostarlimab, a humanised IgG4 mAb, suppresses the immune response, as well as the anti-tumour immune response, by binding to the PD-1 protein and preventing it from binding with PD-L1 and PD-L2. In animal tumour models using genetically identical tissues, inhibiting PD-1 activation decreased tumour growth [12].

Pharmacodynamics

Dostarlimab binds with high affinity to both cynomolgus monkey and human PD-1, as per surface plasmon resonance, through cell lines that overexpress chimeric PD-1 in flow cytometry, or attaching to the natural protein on peripheral blood mononuclear cells (PBMC). Additionally, in order to bind by the receptor, PD-L1 and PD-L2 were inhibited through antibody. Dostarlimab exhibited potent functional antagonistic behaviour with mixed lymphocyte response assay (LRA) in a human $CD4^+$, increasing the production of IL-2. Dostarlimab was more active in this experiment when anti-LAG3 or anti-TIM3 antibodies were present. Human PBMCs were treated with dostarlimab, although the release of cytokines was not noticeably increased.

Pharmacokinetics

Pharmacokinetics (PK) of dostarlimab in patients with various solid tumours, including 150 people with endometrial cancer (EC), were investigated. The dosing range was 1–10 mg/kg. $AUC_{0\text{-inf}}$, the C_{max} mean, and $AUC_{0\text{-tau}}$ all dose increased proportionally. Dostarlimab $AUC_{0\text{-tau}}$ and mean cycle C_{max} are 35,730 μg × h/mL (20%) and 171 μg/mL (20%) at the 500 mg dose once every three weeks and 95,820 μg × h/mL (29%) and 309 μg/mL (31%) at the 1,000 mg dose once every six weeks, respectively [12].

Distribution: dostarlimab's mean steady-state distribution volume is 5.3 L (12%).

Metabolism: catabolic mechanisms are anticipated to break down dostarlimab into minor amino acids and peptides.

Elimination: at a steady state, the mean maximal elimination half-life of dostarlimab is 25.4 days and a mean clearance of 0.007 L/h (31%).

Specific Populations: based on tumour kinds, age (24–86 years), sex (females made up 79%), race/ethnicity, or age, there were no clinically significant changes in the dostarlimab PK (78% White, 4% African American, 2% Asian, and 16% other), or estimated creatinine clearance (CLCR, severe: CLCR = 15–29 mL/min, *n* = 3; moderate: CLCR = 30–59 mL/min, *n* = 90; mild: CLCR = 60–89 mL/min, *n* = 210; normal: CLCR 90 mL/min, *n* = 173).

Adverse reactions

Immune-mediated adverse reactions

Dostarlimab is a mAb that belongs to a group of drugs that binds to either PD-L1 or PD-1, disrupting the PD-L1/PD-1 pathway, eliminating immune response suppression, potentially rupturing peripheral tolerance, and producing immunological-mediated side effects. Any tissue or organ system might have immune-mediated adverse effects that can be serious or lethal. Immune-mediated side effects might occur at any point after initiating use of PD-L1/PD-1 blocking antibody. Although immune-mediated side effects of PD-L1/PD-1 blocking antibody therapy may emerge at any point during or after treatment, they frequently do so during diagnosis. To ensure the safe use of blocking antibodies of PD-L1/PD-1, early detection, and control of immune-mediated negative effects are crucial. A close eye has to be kept out for any symptoms or indications that ought to be outward signals of an underlying immune-mediated adverse event. Screening for thyroid, liver, and creatinine function have to be done at the beginning of treatment and on a regular basis after that. There is a need to start the necessary workup in situations of suspected immune-mediated adverse

reactions to rule out other causes, like an infection. Medical management should be implemented as soon as possible, along with specialist advice as necessary. The drug should be withheld or ceased permanently depending on the severity. In general, systemic corticosteroids (1–2 mg/kg per day prednisone or similar) should be given if dostarlimab needs to be interrupted or discontinued until improvement to Grade 1 or less. The corticosteroids should be tapered off for a month when the condition improves to Grade 1 or less. If corticosteroids are unable to treat an immune-mediated adverse effect in a patient, administration of additional systemic immunosuppressants could be considered. Patients on PD-L1/PD-1 inhibitors, such as dostarlimab, may have a higher risk of developing deadly immune-mediated pneumonitis if they had previously undergone thoracic radiation treatment [12].

Hypophysitis

Dostarlimab may cause immune-mediated hypophysitis. Acute mass effect symptoms like headaches, photophobia, or visual field cuts can be a sign of hypophysitis. The hypophysitis may also result in hypopituitarism. Hormone replacement therapy should be stated if necessary. If dostarlimab is not clinically stable, it should be withheld.

Thyroid disorders

Immune-mediated thyroid diseases can be caused by dostarlimab. Endocrinopathy may or may not accompany thyroiditis in a patient. After hyperthyroidism, hypothyroidism can occur. As clinically warranted, the hormone replacement therapy should be started or the medical treatment of hyperthyroidism should be done. The drug dostarlimab should be withheld if not clinically stable.

Thyroiditis

Around 0.5% (2/444) of individuals on dostarlimab have been reported to experience Grade 2 thyroiditis. There were no discontinuations of dostarlimab as a result of thyroiditis in either of the two thyroiditis events that occurred.

Hypothyroidism

It was found that 5.6% (25/444) of the patients using dostarlimab had Grade 2 hypothyroidism. In 40% of the 25 individuals, hypothyroidism was cured without the need to stop taking dostarlimab. None of the 25 hypothyroid patients needed to take systemic corticosteroids [12].

Type 1 diabetes mellitus

Diabetic Ketoacidosis: dostarlimab may present this problem with Type 1 Diabetes Mellitus. Hyperglycaemia or other diabetes-related symptoms should be properly monitored in patients. Insulin therapy should be started as soon as it is clinically appropriate. Dostarlimab may be discontinued completely or temporarily depending on the severity.

Other immune-mediated adverse reactions

Incidences of lymphadenitis, immunological thrombocytopenia, sarcoidosis, and solid organ transplant rejection have all been reported as clinically significant immune-mediated adverse events.

Effects involving nervous system include encephalitis, meningitis, myasthenia gravis, myelitis and demyelination, nerve paresis, Guillain-Barre syndrome, and autoimmune neuropathy are among the illnesses that can affect people. The vascular/cardiac symptoms include vasculitis, pericarditis, and myocarditis. Ocular effects include iritis, uveitis, and other ocular inflammatory toxicities. Retinal detachment may be seen in some cases. If uveitis develops in conjunction with other immune-mediated adverse responses, it could result in Vogt-Koyanagi-Harada syndrome, which may need systemic steroids to lessen the risk of irreversible vision loss. The connective tissue and musculoskeletal effects include rhabdomyolysis, polymyositis/myositis, and associated sequelae including polymyalgia rheumatic, arthritis, and renal failure. The gastrointestinal effects may include gastritis, increase in the levels of serum amylase and lipase, pancreatitis, and duodenitis.

Endocrine system may lead to hypoparathyroidism. Other (immune/hematologic) effects could be aplastic anemia, systemic inflammatory response syndrome, hemolytic anemia, hemophagocytic lymphohistiocytosis, histiocytic necrotizing lymphadenitis, solid organ transplant rejection, immune thrombocytopenia.

Infusion-related reactions

With PD-L1/PD-1 blocking antibodies, serious or life-threatening infusion-related events have been documented. 0.2% (1/444) of patients taking dostarlimab experienced severe infusion-related events (Grade 3). The infusion-related reactions were all overcome by the patients. Patients need to be monitored for indications of infusion-related reactions. Depending on the severity of the reaction, the rate of infusion of dostarlimab should be stopped or decreased, or even permanently withdrawn [12].

Clinical trials

In a preliminary examination of data from the single-group phase I GARNET trial's dMMR EC cohort, dostarlimab as monotherapy was linked to significant and long-lasting clinical activity (NCT02715284). Dostarlimab was administered at the prescribed dosage to 104 participants with advanced or recurrent dMMR tumours who had developed on platinum-based doublet chemotherapy. Persons with a six-month follow-up (n = 71) showed an objective response in 30 participants in a brief study after 11.2 median months of follow-up (from 0.03 months to 22.11 months), including of 9 and 21 certified complete and partial response, respectively. At the time of the data cut-off (8 July 2019), all confirmed complete responses were still being processed, and the median response time had not been attained. The rates of disease control and median progression-free survival were, respectively, 57.7% and 8.1 months. In a more recent investigation, information was gathered from 103 and 142 participants, respectively, who had mismatch repair proficient (MMRp) and dMMR EC. The overall response rate was 44.7% [35 (34%) partial and 11 (10.7%) complete responses] and 13.4% [16 (11.3%) partial and 3 (2.1%) complete responses], after 16.3 and 11.5 months of follow-up. There was a continued response in 41 and 12 patients, respectively [16–18]. In a small trial carried out by the Memorial Sloan Kettering Cancer Center (MSKCC) in 2022, it was observed that all 18 patients with rectal cancer experienced complete recovery of their cancer, 6 months after taking an experimental dose of dostarlimab. For the first time in history, this clinical trials of dostarlimab demonstrated complete elimination of the cancer disease in patients [19]. The various reported clinical trials of dostarlimab are summarized in Table 2.

Table 2. Trials of dostarlimab

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 2	NCT04068753	Recurrent cervix cancer	65	University of Oklahoma	To evaluate the safety of dostarlimab and niraparib used in combination therapy and determine the effects (both positive and negative) that this therapy has on individuals with progressive or recurrent cervix cancer	Recruiting	July 2025
Phase 2	NCT05405192	GTN	24	University of Miami	To determine whether Dostarlimab is a successful therapy for GTN	Not yet recruiting	December 1, 2028

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 2	NCT04313504	Head and neck cancer	23	Trisha Wise-Draper	To identify which niraparib and dostarlimab combination provides individuals with recurrent or metastatic HNSCC with the greatest overall outcome	Recruiting	June 1, 2027
Phase 1	NCT04544995	Neoplasms	116	GSK	To identify the optimal Phase 2 dose and assess the safety, PK, and effectiveness of niraparib combined with dostarlimab in children with resistant or recurrent solid tumours	Recruiting	March 15, 2030
Phase 2	NCT04139902	Melanoma stage III; melanoma stage IV	56	Diwakar Davar	To evaluate the efficacy of anti-PD-1/anti-TIM-3 (TSR-042/TSR-022) or anti-PI-1 inhibitor (TSR-042) combo in operable melanoma patients	Recruiting	October 2027
Phase 2	NCT04409002	Pancreatic cancer; metastatic pancreatic cancer	25	Massachusetts General Hospital	To examines the efficacy of RT, niraparib, and dostarlimab in the treatment of metastatic pancreatic cancer	Active, not recruiting	October 1, 2026
Phase 2 Phase 3	NCT04655976	Lung cancer, non-small cell	250	GSK	To see how cobolimab combined with docetaxel and dostarlimab works in individuals with NSCLC who have developed on the previous anti-PD-L1 treatment and chemotherapy	Recruiting	January 1, 2026
Phase 2	NCT04701307	Lung small cell carcinoma	48	MD Anderson Cancer Center	To investigate the efficacy of dostarlimab and niraparib in the treatment of SCLC	Recruiting	May 30, 2025
Phase 3	NCT05201547	Endometrial cancer	142	Arcagy-Gineco GROUP	To compare effectiveness of dostarlimab to carboplatin-paclitaxel in advanced endometrial cancer or dMMR relapse patients	Recruiting	May 2029

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 2	NCT03955471	Ovarian neoplasms	41	Tesaro, Inc.	To assess the safety and efficacy of dostarlimab and niraparib in patients with relapsed, advanced, fallopian tube, endometrioid, high-grade ovarian, clear cell, or primary peritoneal cancer who do not have a known BRCA mutation, have a platinum-resistant disease, and have also undergone bevacizumab treatment in the past	Terminated	January 12, 2022
Phase 2	NCT05126342	Recurrent ovarian cancer	100	AGO Research GmbH	To gather proof of the effectiveness of dostarlimab and niraparib in two experimental cohorts of relapsed ovarian cancer patients	Not yet recruiting	November 1, 2026
Phase 2	NCT04581824	Lung cancer, non-small cell	243	GSK	To compare the safety and effectiveness of the PD-1 inhibitors pembrolizumab and dostarlimab when given along with chemotherapy to patients with non-squamous NSCLC who do not have a known sensitizing *ALK*, *EGFR*, *ROS-1*, *BRAF* V600E mutation	Active, not recruiting	October 20, 2025
Phase 1 Phase 2	NCT04926324	Rectal neoplasm malignant	38	Joseph Caster, Ph.D., M.D.	To establish the maximum tolerable dose of niraparib for locally advanced rectal cancer when treated with dostarlimab and hypofractionated radiotherapy	Recruiting	December 31, 2026
Phase 2	NCT04983745	Homologous recombination deficient solid tumours	30	West Cancer Center	To assess the dostarlimab and niraparib effectiveness and safety in metastatic, recurrent, or unresectable solid tumours patients that have a suspected pathogenic, pathogenic, somatic *HRD* gene mutation	Not yet recruiting	August 2025

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 2	NCT04493060	Metastatic pancreatic ductal adenocarcinoma	20	Mayo Clinic	To evaluate the efficacy of dostarlimab and niraparib in the treatment of individuals with germline or somatic PALB2 and BRCA1/2 mutant pancreatic cancer that has progressed to other parts of the body	Recruiting	December 1, 2022
Phase 3	NCT04679064	Ovarian cancer	427	Fondazione Policlinico Universitario Agostino Gemelli IRCCS	To compare chemotherapy given at the doctor's discretion with niraparib plus dostarlimab in the treatment of patients with primary peritoneal cancer when platinum is not an option	Recruiting	January 1, 2025
Phase 2	NCT04895046	*HRD*; cholangiocarcinoma; metastatic cancer	47	Walid Shaib, M.D.	To evaluate HRD patient selection in molecularly chosen immune-based combination therapy for advanced cholangiocarcinoma maintenance therapies	Withdrawn	September 2023
Phase 2	NCT04837209	Breast cancer	32	Massachusetts General Hospital	To evaluate the safety and efficacy of niraparib and dostarlimab in combination with RT in patients with metastatic triple-negative breast cancer	Recruiting	December 1, 2029
Phase 2	NCT03680508	Adult primary liver cancer	42	University of Hawaii	To examine the efficacy of dostarlimab and cobolimab in treating locally advanced or metastatic liver cancer patients	Recruiting	October 2023
Phase 1	NCT02715284	Neoplasms	740	Tesaro, Inc.	To assess the dostarlimab in advanced solid tumour patients who have few other alternatives for therapy	Recruiting	July 30, 2024
Phase 2	NCT04681469	HNSCC	49	Gruppo Oncologico del Nord-Ovest	To assess the effectiveness and safety of a short course of the drug combination dostarlimab and niraparib	Recruiting	June 2028

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 1	NCT03843359	Neoplasms	300	GSK	To assess the tolerability, safety, and early clinical efficacy of GSK3745417 whether given alone (Part 1A) or in combination (Part 2A) with dostarlimab in refractory/relapsed solid tumours patients	Recruiting	May 22, 2025
Phase 2	NCT04584255	Breast cancer	62	Dana-Farber Cancer Institute	To evaluate the safety and efficacy of using dostarlimab plus niraparib as a neoadjuvant treatment for BRCA-mutated breast cancer patients	Recruiting	July 17, 2029
Phase 3	NCT03602859	Ovarian neoplasms	1405	Tesaro, Inc.	To compare the effectiveness of dostarlimab and niraparib for platinum-based therapy with platinum-based therapy as the standard of care for treating stage III or stage IV nonmucinous epithelial ovarian cancer	Active, not recruiting	June 22, 2026
Phase 1	NCT04446351	Neoplasms	178	GSK	To assess GSK6097608's safety, tolerability, PD, PK, and preliminary clinical efficacy in advanced solid tumour patients when it is administered alone and in combination with dostarlimab	Recruiting	August 29, 2024
Phase 2	NCT04165772	Rectal adeno carcinoma	30	Memorial Sloan Kettering Cancer Center	To investigate the efficacy of dostarlimab as a treatment for advanced dMMR solid tumours in comparison to standard surgery and standard chemoradiotherapy (capecitabine + RT)	Recruiting	November 30, 2025
Phase 2	NCT03308942	Neoplasms	53	Tesaro, Inc.	To assess the effectiveness and safety of niraparib in combination and alone with PD-1 inhibitors in patients with metastatic and locally advanced NSCLC	Completed	August 31, 2021

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 1	NCT05277051	Neoplasms	126	GSK	To examine the PK, safety, immunogenicity, and tolerability of GSK4381562 in certain metastatic or locoregionally recurrent solid tumours patients for whom no other effective or conventional treatment choices remain	Recruiting	February 26, 2027
Phase 1	NCT03250832	Neoplasms	111	Tesaro, Inc.	To assess the TSR-033 alone and in combination with dostarlimab and combination with FOL/leucovorin, dostarlimab, 5-fluorouracil, and OX and bevacizumab in an individual with advanced solid tumours	Active, not recruiting	November 14, 2022
Phase 1	NCT04673448	Breast cancer	18	University of Washington	To assess the effectiveness of niraparib and TSR-042 in treating individuals with primary peritoneal, pancreas, fallopian tube BRCA-mutated breast, ovary cancer	Recruiting	March 30, 2026
Phase 1 Phase 2	NCT04126200	Multiple myeloma	464	GSK	To assess the impact of belantamab mafodotin in conjunction with other anti-cancer medications in refractory/ relapsed multiple myeloma patients	Recruiting	February 23, 2028
Phase 2	NCT03016338	Endometrial cancer	51	University Health Network, Toronto	To determine the effectiveness of dostarlimab with the experimental medication niraparib in recurrent/advanced endometrial cancer patients	Active, not recruiting	December 2023

Table 2. Trials of dostarlimab (*continued*)

Phase	Trial code	Cancer type	Participants	Sponsor	Purpose of study	Current status	Completion date
Phase 1 Phase 2	NCT05060432	Advanced cancer	376	iTeos Belgium SA	To assess EOS-448's safety, RP2D, tolerability, pharmacodynamics, PK, and anticancer efficacy in patients with advanced solid tumours who are receiving routine medical treatment and experimental medicines	Recruiting	September 2024

BRAF: B-Raf proto-oncogene, serine/threonine kinase; BRCA: breast cancer; EGFR: epidermal growth factor receptor; GTN: gestational trophoblastic neoplasia; HRD: homologous recombination deficiency; OX: oxaliplatin; PALB: partner and localizer of breast cancer 2; FOL: folinic acid; ROS-1: c-ros oncogene 1; RP2D: recommended phase 2 dose; RT: radiation therapy; TSR: anticancer treatment being developed by Tesaro to treat various types of cancer

Conclusions

Dostarlimab is a novel humanized anti-PD-1 that is approved for the treatment of different types of cancers such as ovarian cancer, NSCLC, SCC, malignant melanoma, SCLC, and peritoneal cancer, endometrial cancer, pancreatic cancer, fallopian tube cancer, and cancer of the neck and head. For the first time, small clinical studies of dostarlimab demonstrated complete elimination of the cancer disease in patients. In this review, we have summarized all aspects of dostarlimab including PK, pharmacodynamics, adverse reaction, and mechanism of action of dostarlimab, as well as various reported clinical trials. Additionally, monotherapy of dostarlimab demonstrated encouraging anticancer efficacy in patients with advanced cancers, positive PK, proof-of-concept pharmacodynamics, and safety.

Abbreviations

CHL: classical Hodgkin lymphoma

CLCR: creatinine clearance

dMMR: mismatch repair deficient

FDA: Food and Drug Administration

GSK: GlaxoSmithKline

HCC: hepatocellular carcinoma

HNSCC: head and neck squamous cell carcinoma

IgG4: immunoglobulin G 4

ITSM: immunoreceptor tyrosine-based switch motif

Lck: lymphocyte-specific protein tyrosine kinase

mAbs: monoclonal Antibodies

MCC: Merkel cell carcinoma

MSI-H: microsatellite instability-high

NSCLC: non-small cell lung cancer

PD-1: programmed cell death 1

PD-L1: programmed cell death ligand-1

PK: pharmacokinetics

PMBCL: primary mediastinal large B-cell lymphoma

RCC: renal cell carcinoma

SCLC: small-cell lung cancer

TCR: T cell Receptor

TMB-H: tumour mutational burden-high cancer

ZAP-70: zeta-chain-associated protein kinase 70

Declarations

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Author contributions

RA: Conceptualization. SAV: Data curation. PAC: Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Not applicable.

Consent to participate

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Availability of data and materials

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