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Review Article

Pharmacology of Dostarlimab: A Review

Arnab Roy[1,*], Akash Chaurasiya[2]

[1]*Department of Pharmacology, Gautam Institute of Pharmacy, Jaitpur, Nalanda, 801307, Saidbarhi, Bihar, India.*
[2]*Department of Pharmaceutics, Gautam Institute of Pharmacy, Jaitpur, Nalanda, 801307, Saidbarhi, Bihar, India.*

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* *Corresponding author.*
Arnab Roy
arnabroy208@gmail.com

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ABSTRACT

Dostarlimab is a humanised anti-PD-1 immunoglobulin (IgG4) monoclonal antibody (mAb). It has a high affinity for the PD-1 receptor and effectively inhibits interactions with PD-L1 and PD-L2 by blocking their binding to the PD-1 receptor. Programmed cell death 1 (PD-1) is an immunological checkpoint receptor that transmits inhibitory signals to limit local inflammatory responses and preserve self-tolerance. It is found on antigen-activated and fatigued T cells. When the PD-1 receptor binds to the tumor-expressed ligands PD-L1 and PD-L2, T-cell proliferation and cytokine production are suppressed.

Keywords: Dostarlimab; PD1 immunoglobulin; T - cell proliferation

INTRODUCTION

Dostarlimab is a humanised IgG4 monoclonal antibody that was created from a mouse hybridoma utilising the SHM-XEL method.[1] In vitro and in vivo investigations that demonstrate a significant anti tumor effect and CD8+ T-cell infiltration without significantly reducing body weight have been done as part of investigational new medication enabling pre-medical procedures.[2] Dostarlimab shows excessive affinity for PD-1 in Cynomolgus monkey and humanresearch, as assessed by floor plasmon resonance to recombinant PD-1 and float cytometry using Chinese Hamster Ovary-K1 cell lines overexpressing recombinant PD-1 or binding to local protein on peripheral blood mononuclear cells (PBMC). In addition to PD-1, it also prevents PD-L1 and PD-L2 from interacting with PD-1.[2,3] Dostarlimab displayed 100% PD-1 receptor occupancy and PD-1 antagonism via enhanced IL-2 production, according to in vitro responses of primary human CD4+ T-cells in a mixed lymphocyte response assay.[4] In the presence of anti-TIM3 or anti-LAG3 antibodies, there was no significant cytokine release from human PBMCs, and Dostarlimab showed increased interest. Dostarlimab was well-tolerated in extensive toxicological studies with single- and repeat-dose intravenous infusions in cynomolgus monkeys.[1–5]

PHARMACOLOGICAL PROFILES

Dostarlimab is a humanised monoclonal antibody that blocks the activation of the programmed cell death protein-1 (PD-1) receptor by the ligand PD-L1. The checkpoint receptor PD-1 suppresses cancer-specific immune responses.[4,6]

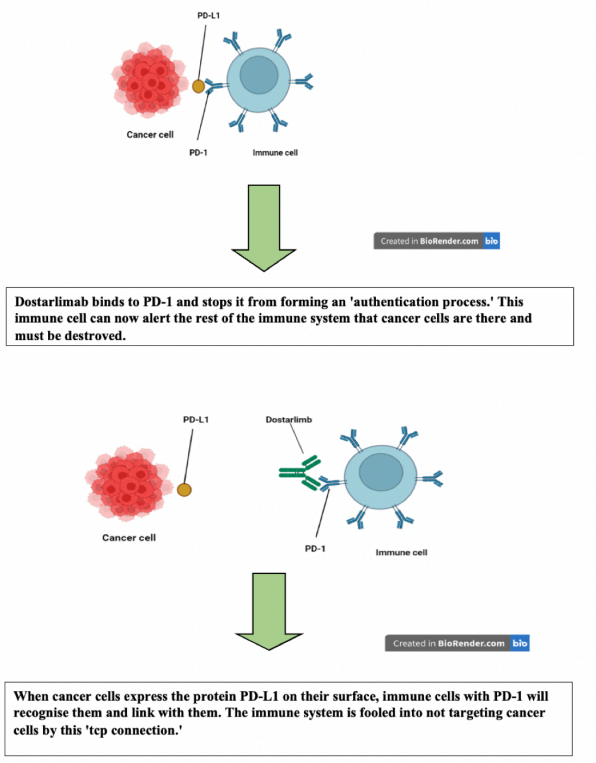
MECHANISM OF ACTION

The T cell PD-1 receptor is activated when the PD-1 ligands PD-L1 and PD-L2 bind to it. This inhibition of T-cell proliferation and cytokine production occurs.[6] In some malignancies, PD-1 ligands are upregulated, and signalling through this route can contribute to the suppression of active T-cell immune responses.[7] Monitoring of malignancies — dostarlimab is an IgG4 monoclonal antibody that has been humanised. PD-1 pathway-mediated immune response suppression, including the immune system's antitumor

response, is released by an isotype that binds to the PD-1 receptor and stops it from interacting with the PD-L1 and PD-L2 receptors. In syngeneic mouse tumour models, tumour growth is reduced by blocking PD-1 activation.[4,8]

Pharmacodynamics

According to surface plasmon resonance, flow cytometry employing cell lines overexpressing recombinant PD-1, or binding to the native protein on peripheral blood mononuclear cells (PBMC), dostarlimab bound to both human and cynomolgus monkey PD-1 with great affinity. The antibody also prevented PD-L1 and PD-L2 from interacting with the receptor. In a human CD4+ mixed lymphocyte response assay, dostarlimab acted as a powerful functional antagonist, resulting in enhanced IL-2 production. In this test, the addition of anti-TIM3 or anti-LAG3 antibodies increased the activity of dostarlimab. Dostarlimab incubation of human PBMCs as a single agent did not result in significant cytokine release stimulation.[8,9]



Pharmacokinetics

The pharmacokinetics of Dostarlimab was studied in 150 individuals with EC who had a variety of solid tumours. Over the dose range of 1.0 to 10 mg/kg, mean C_{max}, $AUC_{0-\infty}$, and $AUC_{0-\tau}$ increased correspondingly. At a dose of 500 mg once every 3 weeks, the Cycle 1 mean (coefficient of variation [percent CV]) C_{max} and $AUC_{0-\tau}$ of Dostarlimab are 171 mcg/mL (20%) and 35,730 mcg*h/mL (20%), respectively, while at a dose of 1,000 mg once every 6 weeks, these are 309 mcg/mL (31%) and 95,820 mcg*.[8,10]

Distribution, Metabolism and Elimination of Dostarlimab

At steady state, the mean (% CV) volume of distribution of Dostarlimabis 5.3 L. (12%).[9] Incase of metabolism catabolic mechanisms are expected to break down Dostarlimab into tiny peptides and amino acids[11] and finally at steady state, Dostarlimab has a terminal elimination half-life of 25.4 days and a mean (% CV) clearance of 0.007 L/h (31%).[12]

THERAPEUTIC TRIALS

Endometrial cancer

In a preliminary examination of data from the dMMR endometrial cancer cohort of the single-group phase I GARNET study, Dostarlimab as monotherapy was linked with meaningful and persistent clinical activity (NCT02715284). Dostarlimab at the prescribed dose was given to patients (n = 104) with recurrent or advanced dMMR tumours who had progressed on platinum-based doublet chemotherapy. At an interim analysis, 30 patients with a 6-month follow-up (n = 71) had an objective response after 11.2 median months of follow-up (range 0.03–22.11 months), with 9 and 21 verified full and partial responses, respectively. At the time of data cut-off (8 July 2019), all confirmed complete replies were still being processed, and the median response time had not yet been attained.[9]

The disease control rate was 57.7% and the median progression-free survival was 8.1 months, respectively. A more recent study looked at data from 103 and 142 patients with dMMR and MMRp endometrial cancer, respectively (data cut-off one March 2020). The overall response rate was 44.7 % and 13.4% after 16.3 and 11.5 months of follow-up, respectively. There were 41 and 12 patients who had a continuing response, respectively.[11,13]

Other types of tumours

Patients with dMMR or POLEmut non-endometrial solid tumours were enrolled in Cohort F of GARNET, with the majority (99 of 106 included in the efficacy analysis) having gastrointestinal tumours. A confirmed overall response was obtained in 41 patients (38.7%), with a 7.5 percent complete response rate. At the time of data cut-off, the median response duration had not been reached (median duration of follow-up 12.4 months). Patients with previously treated recurrent/ advanced NSCLC were enrolled in the GARNET study's NSCLC expansion cohort (n = 67).[14]

The epidermal growth factor receptor (EGFR) was found to be positive in 3% of patients, whereas the status of EGFR was uncertain in 18%. In 18 (27 percent) of the patients, an

immune-related overall response rate of 2 complete and 16 partial responses was reported; 24 patients had stable illness. The overall duration of remission was 11.6 months after a median follow-up of 13.8 months, with response continuing in nine individuals.[15] In patients with NSCLC who have progressed after receiving anti-PD-1 therapy, part two of the phase I AMBER (NCT02817633) trial is evaluating Dostarlimab in conjunction with the anti-TIM-3 antibody Cobolimab (TSR-022). Dostarlimab 500 mg was given once every three weeks in combination with Cobolimab 100 (n = 14) or 300 mg (n = 25) to patients. One of 11 evaluable patients treated with Dostarlimab + Cobolimab 100 mg exhibited a confirmed partial response according to immune-related RECIST criteria at the time of data cut-off, while three others had stable illness. Three of the 20 patients treated Dostarlimab with Cobolimab 300 mg had confirmed partial responses, while the other eight had stable illness. All of the patients that had objective responses had PD-L1 positive tumours, implying that biomarker amplification could be possible.[1]

ADVERSE EVENTS

In the GARNET study (n = 104), nausea (30 %, 0 percent), diarrhoea (26 %, 1.9 %), anaemia (all grades 24 %, grade 3–4 13 %), constipation (20 %, 0.9 %), decreased appetite (14 %, 1.9 %), vomiting (18 %, 0 percent), fatigue (48 %, 1 %), urinary tract infection (13 %, 1.9 %), fatigue (48 %, 1 %), urinary tract infection (13 (14 % , 1 percent). Lymphopenia (37 %, 9%), Leukopenia (21 %, 2.9 percent), Hypoalbuminemia (30 %, 2.9 %), Hypercalcaemia (15 %, 1.9 %) increased alkaline phosphatase (25 %, 2.9 percent), increased creatinine levels (27 %, 2.9 %), hyponatraemia (26 %, 4.8 %) were among the laboratory abnormalities that worsened from baseline to grade three or four in 1%.[16]

In the GARNET study, 34% of patients with dMMR endometrial cancer treated with Dostarlimab reported significant adverse effects, with urinary tract infection (2.9%), sepsis (2.9%), abdominal pain (2.9%), acute renal injury (2.9%), and pyrexia (2.9%) occurring in more than 2% of patients (2.9 percent). Because of adverse responses such as elevated transaminase levels, sepsis, bronchitis, and pneumonitis, five (4.8%) individuals had to stop using Dostarlimab permanently. An adverse reaction such as anaemia, diarrhoea, elevated lipase levels, or pyrexia (all occurring in less than 1% of patients) prompted dosage interruptions in 23% of patients.[12]

RECENT BIOMEDICAL ADVANCEMENTS

Participants in the trial had to be adults with advanced solid tumours. The study does not include patients with a particular type of endometrial cancer who have a deficient mismatch repair (dMMR) status. Dostarlimab, an experimental therapy, was given to the patients (also known by the brand name Jemperli). Dostarlimab has been licenced in the United States as a single therapy for adult patients with dMMR recurrent or advanced endometrial cancer who have progressed on or after platinum-based chemotherapy.

Dostarlimab is approved as a single therapy in the European Union for adult patients with recurrent or advanced dMMR/microsatellite instability-high (MSI-H) endometrial cancer who have progressed during or following treatment with a platinum-containing regimen. Dostarlimab was given intravenously to patients with dMMR endometrial cancer from seven countries in the GARNET trial. Dostarlimab was shown to be effective in reducing tumours in 42 percent of the participants in the study. In general, the percentage of individuals who suffered medical difficulties (also known as side effects) was minimal, which was to be expected given the nature of the treatment.[17]

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