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REVIEW

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Dostarlimab: From preclinical investigation to drug approval and future directions

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ABSTRACT

Immune checkpoint blockers (ICB) act by reverting the immunosuppressive phenotype of cancer cells, thus allowing host immune system to generate an immune response to the tumor. One of the key mechanisms targeted by ICB is the PD-1/PD-L1 axis, which lies onto the interaction between the programmed-cell death protein 1 and its ligand, overexpressed in several tumor types. This interaction leads to the inhibition of T-cell proliferation and their apoptosis and exhaustion. Anti-PD-1/PD-L1 monoclonal antibodies are now the mainstay of treatment for several advanced stage tumors. Dostarlimab is a novel IgG4 anti-PD-1 antibody which has yielded remarkable results in mismatch-repair deficient endometrial cancer and locally advanced rectal cancer. This product review will illustrate the preclinical development of dostarlimab and its pharmacological characteristics, the clinical trials published so far and the ongoing clinical investigations.

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Introduction

Since the first FDA approval of ipilimumab for the treatment of advanced melanoma in 2011, the introduction of immune checkpoint blockers (ICB) into the oncological practice has radically reshaped the management of several solid tumors. This category encompasses a broad group of agents whose mechanism of action consists in inhibiting the immune regulatory checkpoints, thus overcoming the negative regulation of immune cell activation and fostering the development of an immune response against tumor cells.

One of the key immune checkpoints contributing to the inhibition of T cell proliferation and activation is the PD-1/PD-L1 axis. PD-1 (programmed cell death protein 1) is a transmembrane receptor expressed on active T-cells; after the interaction with its ligand PD-L1 (programmed death-ligand 1), the phosphorylation of tyrosine residues in the intracellular inhibitory tyrosine-switch motif (ITSM) of PD-1 results in the recruitment of SHP2 (Src homology-2 domain-containing tyrosine phosphatase) which is one of the key mediators of PD-1-induced immune negative regulation. In particular, the main outcomes of the PD-1/SHP2 interaction are the reduction of T-cell proliferation and activation, the inhibition of cytokine production and cell cycle blockade, which ultimately lead to T-cell apoptosis and exhaustion, thus allowing tumor cells to elude the host immune surveillance.[1] PD-L1 expression is constitutively absent in most healthy tissues, but it can be upregulated in tumor cells in different ways one of which involves the release of interferon-gamma (IFN-γ) by the tumor-infiltrating lymphocytes (TILs). PD-L1 overexpression in neoplastic cells is also induced by TILs-independent mechanisms, such as oncogenic gene mutations in key signaling pathways or micro-RNA regulation.[2]

Currently, antibodies targeting the PD-1/PD-L1 interaction are the backbone of the first-line therapy in advanced melanoma, non-small cell lung cancer and kidney cancer, amongst others; while in some indications their use is restricted by the expression of the biomarker (such as, but not only, PD-L1 expression on tumor cells), in many tumor types they can be administered without a biomarker testing. Moreover, anti-PD-1/PD-L1 agents have demonstrated a synergism with several other anticancer drugs, such as tyrosine-kinase inhibitors (TKI) in renal cell cancer or chemotherapy in head and neck squamous cell carcinoma. This product review will focus on preclinical investigation, published results and ongoing investigations of dostarlimab, a novel PD-1 monoclonal antibody with a peculiar administration schedule.

Preclinical investigation

Dostarlimab (TSR-042) is an Ig-G4 humanized anti-PD-1 monoclonal antibody generated from a mouse hybridoma. Preclinical characterization of the drug was carried out in vitro and in vivo models by Laken et al.[3] Dostarlimab binds with high affinity (K_D 300 pM) with human and cynomolgus monkey PD-1, while it does not cross-react to the mouse species orthologue. Both in human and cynomolgus monkey CD3+ cell surface, Dostarlimab binds rapidly to PD-1

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with a slow dissociation rate from the target.[4] In preclinical models, Dostarlimab has shown to inhibit the interaction of both PD-L1 and PD-L2 with the PD-1 receptor. The anti-PD-1 activity of dostarlimab has been characterized in immunogenicity assays, resulting in an increased T-cell activation measured through an increased IL-2 production from CD4+ lymphocytes; IL-2 production was enhanced in presence of anti-TIM3 or anti-LAG3 antibodies, which counteract the activity of known immune checkpoint molecules. Dostarlimab also induces an antigen-specific T-cell activation as demonstrated by a flu/PPD/TT activation assay in which incubation with dostarlimab determined an increase of IFN-γ release. The choice of the IgG4 isotype relied on the minimization of the Fc domain-mediated function, which may lead to a depletion of tumor-reactive T-cells. On the other hand, when incubated as a single agent with healthy donor peripheral blood mononuclear cells (PBMCs), it does not elicit a nonspecific T-cell response in an antigen-independent context, thus lacking T-cell agonist properties.[4]

In vivo antitumor activity was initially assessed in humanized mouse models of human breast and lung cancer. In both models, compared to the IgG4 isotype control, treatment with dostarlimab resulted in a significantly reduced tumor growth; post-treatment pharmacodynamic evaluation of tumor xenografts demonstrated an increased infiltration of CD8+ cells along with a reduction in the regulatory T-cell population.

Preliminary toxicity evaluation was conducted in cynomolgus monkeys through a single- and 1 month- repeat dose at doses of 10, 30 and 100 mg/kg. Dostarlimab was well tolerated with no unexpected deaths and no effect of body weight. An important concern in the field of anti-PD-1 or anti-PD-L1 monoclonal antibodies (mAbs) is the development of an immunogenic response through the generation of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), which may affect pharmacokinetics, drug toxicity, and efficacy parameters. Immunogenicity evaluation of dostarlimab was performed in the pivotal phase I GARNET trial (see below). The incidence of dostarlimab-emergent ADAs (including both the treatment-induced and the treatment-boosted ADAs) was of 2.5%, which is globally comparable to other mAbs directed against the same target; moreover, the development of ADAs did not affect significantly dostarlimab pharmacokinetics nor had an impact on safety and efficacy measures.[5]

Preliminary clinical data and published results

The disruption of DNA repair machinery has been established as a potential mechanism of response to immune checkpoint blockers. Alterations in DNA damage response pathways enhance tumor immune detection by increasing the mutational rate and, consequently, by generating tumor neoantigens, which can be recognized by the immune system of the host.[6,7] Mismatch repair (MMR)-deficient tumors (also called microsatellite instability high tumors-MSI-H) are enriched in mutation-associated neoantigens (MANAs) and exhibit a significantly higher number of T-cells infiltrate as well as apoptotic tumor cell death.[8] Based on these findings, a proof-of-concept study of immune checkpoint blockade with an anti-PD-1 antibody (pembrolizumab) in patients with MMR-deficient solid tumors was designed. The most frequent tumor types were colorectal and endometrial cancer; all patients had received at least one previous line of treatment. The results of this trial showed a remarkable 53% overall response rate (ORR), with 21% of patients achieving a complete response (CR). T-cell receptor sequencing assay (TCRseq) and neoantigen reactivity tests demonstrated that treatment with ICB induces a peripheral expansion of MANAs-directed tumor-specific T cells, confirming that the response to ICB in MMR deficient tumors is mainly driven by the formations of neoepitopes.[9] Upon these results, many clinical trials were launched in order to assess the activity and efficacy of ICB in dMMR tumors.

Immunotherapy in endometrial cancer

Endometrial cancer (EC) is a tumor with a relevant frequency of microsatellite instability, especially in the endometrioid histotype (up to 40% of cases reported as MSI-H).[10] Most commonly, MSI-H endometrial cancer is associated with the methylation of MLH1 promoter.[11,12] MSI-H endometrial cancers are characterized by lower stage and intermediate prognosis.[13,14] In the Le et al. study, endometrial cancer represented the second most common malignancy with MMR deficiency, accounting for 17% of the enrolled patients ($N = 15$). In these patients, response rates were in line with those reported in overall MSI-H population, with an ORR of 53% and 20% complete responses (CR).

Following these results, the activity of pembrolizumab in dMMR EC was evaluated into the open-label, phase II KEYNOTE-158 study. In this multi-cohort trial, patients with non-colorectal MSI-H/dMMR with disease progression or intolerance to prior therapy were treated with 3-weekly pembrolizumab (200 mg flat dose) for a maximum of 35 cycles or until disease progression, unacceptable toxicity or death; patients with endometrial carcinoma (excluding sarcomas and mesenchymal tumors) participated in cohort D. Primary endpoint was the ORR which occurred in 57.1% (95% CI, 42.2–71.2%) of EC patients, with 8/49 patients achieving a CR. The median DOR was not reached in this cohort (95% CI, 2.9–27+).[15]

These results led to the FDA approval of Pembrolizumab for the treatment of MSI-H/dMMR advanced EC with disease progressing after a previous line of therapy.

At a recent update of the trial, after a median follow-up of 42.6 months, the median progression-free survival (PFS) was 13.1 months (95% CI, 4.3–34.4 months) and the median overall survival (OS) was not reached (95% CI, 27.2 months-NR). In the whole dMMR EC patients, the ORR was 48% (95% CI, 37–60%) Pembrolizumab yielded high ORR both in patients with <2 lines of previous therapy (53%, 95% CI 36–69%) and in patients with 2 or more lines of previous therapy (44%, 95% CI 28–60%).[16]

The activity of the anti-PD-L1 antibody avelumab for patients with pretreated dMMR EC was assessed in one cohort of a phase II study by Konstantinopoulos et al. The dMMR cohort also included patients with POLE mutation, although no patient with such alteration were enrolled. In this cohort ($N = 15$), ORR was 26.7% (95% CI, 7.8–55.1%). The trial had also a cohort dedicated to pMMR (proficient) patients, which was closed after a futility assessment.[17]

In a similar fashion, the two-cohort PHAEDRA study evaluated the activity of the anti-PD-L1 durvalumab both in patients with dMMR and pMMR EC; of note, in the dMMR cohort, untreated patients were eligible. Primary endpoint was ORR by immune-related RECIST (iRECIST). 21/36 (60%) patients in the dMMR cohort had not received any previous line of treatment for advanced disease. ORR by iRECIST was observed in 47% of patients (95% CI, 32–63%) with 6 CR and 11 partial responses (PR). After stratification for previous therapies, treatment-naïve patients showed a 57% ORR compared to 38% ORR observed in pretreated patients. The pMMR cohort of the PHAEDRA trial also underlined the negligible activity of anti-PD-L1 drugs in these patients, with 3% of pMMR EC patients ($N = 35$) achieving a PR (95% 1–15%).[18]

Dostarlimab activity in endometrial cancer

Based on the preliminary findings of the pivotal study by Le et al[9] and given the results of the previously mentioned studies, the safety and activity of dostarlimab was assessed across multiple solid tumors in the open-label, single-arm multicohort phase I GARNET trial (NCT02715284). The study was developed in sequential stages. Part 1 ($N = 21$) assessed the dose limiting toxicity (DLT) of weight-bases doses of dostarlimab administered every 2 weeks with a starting dose of 1 mg/kg with subsequent dose escalation to 3 and 10 mg/kg. After the completion of this stage, in part 2A safety and tolerability of fixed-dose schedules were assessed: the 13 patients enrolled were treated with dostarlimab with either a 500 mg-dose administered every three weeks (Q3W) ($N = 6$) or a 1000 mg-dose administered every 6 weeks (Q6W) ($N = 7$).[19] The ongoing phase 2B is exploring the antitumor activity and safety of dostarlimab with the recommended therapeutic dose (RTD) assessed during part 2A, which consists in four cycles of dostarlimab 500 mg Q3W followed by 1000 mg Q6W until disease progression, unacceptable toxicity or death. In this stage, patients were enrolled into different expansion cohorts according to tumor type and MMR status: cohort A1 and A2 enrolled patients with dMMR and pMMR EC, respectively; cohort E enrolled patients with non-small cell lung cancer (NSCLC) and cohort F enrolled patients with MSI-H/dMMR non-endometrial solid neoplasms.

The results of the first interim analysis of cohort A1 published in 2020, showed a meaningful activity of dostarlimab in MMRd/MSI-h subset of patients.[20] This cohort enrolled women with recurrent EC that progressed on or after platinum-based chemotherapy and with evidence of MMR deficiency using immunohistochemistry (IHC) performed by a certified local or a central laboratory; if MMR results were inconclusive or unavailable (MMRunk), the patients were classified by their MSI status (patient with MSI-H were included into the dMMR group, while patients with no MSI were assigned to the pMMR group). Patients must have been treated with no more than 2 lines of therapy for advanced disease. Primary endpoints of the phase 2B were ORR and duration of response (DOR). 104 patients were enrolled, 71 of which had at least one measurable lesion and were therefore included in the analysis. Dostarlimab yielded an ORR of 42.3% (95% CI, 30.6–54.6%) with 9/71 patients (12.7%) achieving a CR and 21/71 patients (29.6) achieving PR, confirmed by a blinded independent central review (BICR). The disease control rate (DCR) (CR + PR + stable disease) was 57.7% (95% CI, 45.4–69.4%). The most frequent treatment-related adverse events (TRAEs) (reported in $\geq$ 10% of patients) were asthenia, diarrhea, fatigue, and nausea. Most TRAEs were grade 1 or grade 2. Grade 3 or higher TRAEs were reported in 11.5% of patients; the most frequent were anemia (2.9%), colitis, diarrhea, increased lipase and increased transaminase (1.9% each). TRAE-related discontinuations of study drug occurred in two patients (1.9%), both for increased transaminase levels. Immune-related adverse events (irAEs) were reported in 23.1% of patients, with diarrhea (5.8%) and hypothyroidism (5.8%) being the most frequent. Grade 3 or higher irAEs occurred in 7.7% of patients, the most common being diarrhea (2.9%). IrAE-related discontinuation occurred in 2 patients for G3 transaminase level increase (1.9%).

Patients with pMMR EC showed lower ORR compared to patients with dMMR EC, in both cohorts.[21] 156 out of the 161 patients enrolled in cohort A2 were included in this analysis. With a longer median follow-up of 16.3 months, the ORR in cohort A1 was in line with the first interim analysis (43.5%, 95% CI, 34–53.4%) with 10.2% CR; in cohort A2 (pMMR patients), after a median follow-up of 11.5 months the ORR was 14.1% (95% CI, 9.1–20.6%) with 1.9% CR and 12.2% PR. The DCR was 55.7% (95% CI, 45.7–65.1%) in cohort A1 and 34.6% (95% CI, 27.2–42.6%) in cohort A2. In both cohorts, the median DOR was not reached. The safety analysis was conducted considering all EC patients as a single group and was comparable to the first report of the cohort A1. No toxic deaths have been reported so far. At the most recent interim analysis (median follow-up 27.6 months), dostarlimab reported an ORR of 45.5% in cohort A1 (95% CI, 37.1–54%) with 16.1% CR and 29.4% PR; response was ongoing in 83.1% of patients. Patients in cohort A2 showed a 15.4% ORR (95% CI, 10.1–22%) with 2.6% CR and 12.8% PR.[22]

In addition, at ESMO 2022 meeting the results of a post-hoc analysis on dostarlimab activity according to the molecular profiling of endometrial cancer, were disclosed. Based on the Cancer Genome Atlas (TCGA) and its surrogate classifications, EC were classified as POLE-mutated, dMMR/MSI-H, TP53-mutated and tumors with no specific mutation profile (NSMP). In the GARNET trial the ORR did not highlight any significant differences of dostarlimab efficacy according to the molecular profiling neither hormonal receptor status did seem to influence the response to dostarlimab.[23]

The meaningful responses observed with anti-PD-1 or anti-PD-L1 monoclonal antibodies in women with dMMR endometrial cancer strongly underscore the activity of ICB in this biomarker-selected population. Reported ORR ranges from 26.7% to 48%; this heterogeneity might be explained by the differences between trials in terms of the pretreated patients. In the avelumab trial, for example, 20% and 40% of patients had received 2 and 3 or more previous lines of treatment, respectively, and the patients with disease progressing after several lines of treatment may exhibit a more aggressive phenotype with poor response to treatment. Another possible explanation may be related to the different IgG isotype: dostarlimab and pembrolizumab, which yielded the highest responses rates, are both IgG4 anti-PD-1 antibodies, while avelumab and

durvalumab belong to the IgG1 family. As stated before, IgG4 antibodies do not retain all the Fc-mediated properties, therefore reducing the risk of tumor-reactive T-cell depletion. The higher response rate obtained by dostarlimab and pembrolizumab in dMMR EC patients might suggest a different efficacy of the drugs according to the target antigen; PD-1 targeting seems a more fruitful strategy than PD-L1 targeting as also reported by other authors in different conditions.[24,25] Moreover, the number of patients enrolled in these trials is limited and does not permit to establish a legitimate comparison between these agents. (Table 1) Nevertheless, it must be underlined that mismatch-repair deficiency does not univocally predict response to ICB in all patients. Several mechanisms of resistance to immunotherapy have emerged in this population of patients; one of this is the discrepancy between the MMR status and the TMB, which could explain the lack of benefit from ICB in some dMMR patients who show a low TMB.[26,27] PTEN mutations have also been linked to a poor response to immunotherapy in dMMR cancers, especially those located in the phosphatase domain which are related to a immunosuppressive phenotype.[27]

Dostarlimab activity in rectal cancer

The outstanding results achieved by PD-1 blockade in the context of advanced dMMR colorectal cancer[28] have paved the way for the assessment of the efficacy of immune checkpoint blockade in earlier stages of the disease. The standard of care for locally advanced rectal cancer (LARC) consists in neoadjuvant fluoropyrimidine-based chemotherapy followed by chemoradiation and surgery. This approach carries nevertheless a significant burden of acute and long-term toxicities, due to chemotherapy and radiation therapy side effects; in addition, surgery often requires a permanent diverting colostomy, which may entail a meaningful deterioration in the quality of life. Based on these premises, there has been an increasing interest in developing radiation- and/or surgery-sparing strategies. Intriguingly, the achievement of a clinical complete response assessed radiologically and/or endoscopically is currently accepted as a surrogate for pathological complete response in patients with LARC not undergoing operative management with a well-recognized impact on survival. The phase II NCT04165772 trial enrolled patients with dMMR LARC as assessed by local IHC testing. Patients were to receive dostarlimab 500 mg every 3 weeks for 9 cycles (6-months course) followed by chemoradiation and total mesorectal excision. Patients who achieved a clinical CR after either the neoadjuvant dostarlimab or chemoradiotherapy underwent non-operative management. Responses were assessed by means of rectal digital and endoscopic examination and by rectal MRI. The study had two primary endpoints: 1. the sustained clinical response 12 months after completion of dostarlimab therapy (in patients who did not undergo surgery) or pathological complete response in patients undergoing surgery; 2. clinical responses to neoadjuvant dostarlimab with or without chemoradiation. The results of the latter endpoint have been recently published, after a median follow-up of 12 months. All the 12 patients which had completed the dostarlimab course achieved a clinical complete response (CR rate 100%, 95% CI, 74–100%); at the data cutoff, none of the patients had undergone chemoradiotherapy or surgery. Five out of 12 patients achieved an early clinical CR, assessed at the 3-month evaluation. Symptoms relieve was also obtained rapidly, with 81% of patients reporting resolution of symptoms within the 9th week after the start of neoadjuvant therapy. Dostarlimab treatment did not produce any grade 3 or higher adverse events; most common toxicities were Grade 1–2 skin rash (31%), pruritus (25%) and fatigue (25%).[29] On treatment tumor biopsies showed that clinical response was associated with an enrichment in the CD8+ T lymphocyte population and with the formation of tertiary lymphoid structure, a known biomarker of response in other cancer types such as melanoma and sarcoma.[30]

Dostarlimab activity in other solid neoplasms

The cohort E of the phase I GARNET trial enrolled patients with non-small cell lung cancer (NSCLC) who had disease progression after at least 1 line of platinum-based chemotherapy; patients with EGFR or ALK mutated NSCLC were admitted if they had received both a tyrosine-kinase inhibitor (TKI) and a chemotherapy regimen. Dostarlimab was administered at the

Table 1. Summary of patient characteristics and key outcomes of trials with anti-PD-1/PD-L1 monoclonal antibodies in mismatch-repair deficient (dMMR) endometrial cancer (EC).

	KEYNOTE-158[15, 16]	NCT02912572[17]	PHAEDRA[18]	GARNET[19–22]
Study drug	Pembrolizumab	Avelumab	Durvalumab	Dostarlimab
Target antigen	PD-1	PD-L1	PD-L1	PD-1
Trial design	Phase II non-randomized	Phase II non-randomized	Phase II non-randomized	Phase I
Median follow-up time, months	42.6	18.6	19	27.6
dMMR EC patients, n	79	15	36	143
Number of previous lines allowed	≥1	≥1	0–3	1–2
Treatment-naïve patients, n (%)	0	0	21 (60)	0
ORR, n (%; 95%CI)	38 (**48**; 37–60)	4 (**26.7**; 7.8–55.1)	17 (**47**; 32–63)*	65 (**45.5;** 37.1–54)
• CR, n(%)	• 11 (14)	• 1 (6.7)	• 6 (17)	• 23 (16.1)
• PR, n(%)	• 27 (34)	• 3 (20)	• 11 (31)	• 42 (29.4)
PFS, months (95% CI)	13.1 (4.3–34.4)	4.4 (1.7 – NR)	8.3 (2.4 – NR)*	6.0 (4.1–18.0)
OS, months (95% CI)	NR (27.2 – NR)	NR	NR*	NR (25.7 – NR)
TRAE all grades, % (Grade 3 or higher, %)	76 (12)	71 (19.4)	93 (36)	63.6 (13.2)

Abbreviations: CI, confidence interval; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse events.
*Assessed by iRECIST.

same schedule reported for endometrial cancer and the response rate was assessed exclusively by irRECIST criteria. This cohort included 67 patients; the majority (35.8%) had a PD-L1 Tumor Proportion Score (TPS) $\leq$ 1%, 20 patients (29.9%) had a PD-L1 TPS between 1 and 49% and 5 patients (7.5%) had a PD-L1 TPS $\geq$ 50%. PD-L1 TPS was unknown for 18 patients (26.9%). After a median follow-up of 13.8 months, irORR was 26.9% (95% CI, 16.8–39.1%); 2 patients achieved an irCR. irDCR was 62.7% (95% CI, 50–74.2%). Tumor response was observed in all PD-L1 expression subgroups; a correlation between PD-L1 expression and response to dostarlimab has not been established.

The safety profile in cohort E was similar to that observed in patients with endometrial cancer. The most common any-grade TRAEs were fatigue (16.4%), hypothyroidism (14.9%) and asthenia (13.4%); grade 3 or higher TRAEs were reported in 11.9% of patients, with fatigue being the most common (4.5%). TRAE-related discontinuations of treatment occurred in four patients (5.9%).[31]

The results of the efficacy and safety analysis of Cohort F were presented at the 2021 ASCO Gastrointestinal Cancer Symposium. This cohort enrolled patients with non-endometrial solid tumors harboring MMR deficiency or POLE-mutations. The majority of patients included in the safety analysis ($N = 106$) had a gastrointestinal tumor (93.4%) being colorectal cancer the most common subtype ($N = 69$). In this cohort, the ORR was 38.7% (95% CI, 29.4–48.6%) with 7.5% CR. At the data cutoff, after a median follow-up of 12.4 months the median DOR was not reached. Safety profile was consistent with that reported in the other cohorts of the trial.[32]

Pharmacokinetics and pharmacodynamics

Pharmacokinetic (PK) parameters of dostarlimab were assessed in the patients enrolled in the phase I GARNET trial (see above).[19] Maximum drug concentration was reached rapidly both in part 1 (weight-based schedule) and in part 2 (fixed doses); the median t_{max} value ranged from 1.50 to 2.96 h for part 1 and from 0.96 to 1.52 h in part 2A (500 and 1000 mg dose, respectively) after the infusion of the first cycle. PK studies did not demonstrate a dose effect on steady-state volume of distribution, clearance and terminal elimination half-life. Pharmacodynamics (PD) was assessed through flow cytometry analysis of PD-1 receptor occupancy (RO) on CD3+ peripheral blood mononuclear cells. For the evaluation of functional RO, patient T-cells incubated with superantigen staphylococcal enterotoxin B were tested with dostarlimab and an isotype control; dostarlimab RO was calculated through the ratio of interleukin-2 concentration saturating with dostarlimab versus isotype control. Maximal RO was assessed in patients enrolled in part 1 and 2A of the trial and was achieved in all but one patient, who was subsequently evaluated for the presence of dostarlimab-ADA and tested positive. The establishment of the fixed dose regimen for the part 2 of the GARNET trial has been determined observing a no statistically significant clearance difference in a body weight range of 45.6–145.6 kg; moreover, the achieved concentration of dostarlimab were several-fold higher than those required for maximal RO. No significant PK or PD differences between the 500 and the 1000 mg dose regimens emerged. In addition, while the 3-weekly administration for the first cycles consents a more intensive monitoring of safety and tolerability, the subsequent 6-week cycles allow a reduction of the burden to patients and healthcare provisioners.

The population pharmacokinetic (PopPK) model built on the data of the patients enrolled in the GARNET trial support the recommended schedule. In this model, time-dependent concentration of dostarlimab dropped to a maximum of 14.9%, a decrease which is lower than those reported in pharmacokinetic analysis of other ICB (20 to 35.9%). Moreover, this model explored the possible roles of patient covariates of disease characteristics on dostarlimab PK; however, none of the coviarates taken into consideration showed an impact on PK parameters. In addition, there was no significant efficacy and safety exposure/response relationship, confirming the feasibility and the efficacy of the administered schedule.[33]

Key ongoing clinical trials

Several clinical trials are assessing the activity and efficacy of dostarlimab in solid tumors, both as a monotherapy or in combination with other target therapies.

Dostarlimab in gynecological malignancies

The significant response rates observed in the EC cohort of the GARNET trial have warranted the further exploration of dostarlimab in earlier lines of treatment, both as a monotherapy and as part of a combination therapy. The relationship between the malfunctioning of the DNA repair mechanisms and the response to immunotherapy has been intensively investigated and provides a robust preclinical rationale for the exploitation of ICB in combination with drugs interfering with the DNA damage repair. In this context, the combination of ICB and PARP inhibitors is a promising strategy which has already proven some evidence of a synergism.[34] The RUBY trial (NCT039817896) is a quadruple-blinded, phase III randomized trial which enrolls patients with recurrent or primary advanced, treatment-naïve EC. The study is designed as a two-part randomized trial. In the first part, patients are randomized to receive standard of care (SoC) chemotherapy plus dostarlimab IV or placebo followed by dostarlimab/placebo maintenance; in the second part, limited to the maintenance phase, patients are randomized to receive dostarlimab plus niraparib or matched IV and oral placebo, respectively. The study has PFS and OS as coprimary endpoints.[35]

A French trial is assessing the efficacy of single-agent dostarlimab in advanced/recurrent chemonaive dMMR EC patients. The DOMENICA trial (NCT05201547; https://clinicaltrials.gov/ct2/show/NCT05201547) is an open-label, multicenter phase III trial that randomizes (1:1) patients to receive front-line treatment with dostarlimab or SoC carboplatin-paclitaxel chemotherapy. Primary endpoint is PFS.

The existence of a synergism between immunotherapy and radiotherapy is widely recognized and relies on several biological mechanisms, such as the upregulation of PD-1 and the induction of immunogenic cell death.[36] The combination of ICB with radiotherapy is under investigation in several malignancies. An ongoing single-arm phase II trial (NCT04774419;

https://clinicaltrials.gov/ct2/show/NCT04774419) is exploring the safety and efficacy of dostarlimab with radiotherapy in patients with locally advanced dMMR endometrial cancer. The trial will enroll patients with surgically staged III/IVA disease (with or without residual tumor) that will receive 4 cycles of dostarlimab 500 mg every 3 weeks and an additional fifth cycle at the dose of 1000 mg with concomitant intensity-modulated radiotherapy (IMRT) to pelvic nodes and vaginal cuff. Primary endpoints are PFS and safety.

PARP inhibitors have been already approved as a maintenance treatment in ovarian cancer (OC) for patients who do not progress to first-line chemotherapy. The synergism between ICB and PARP inhibitors in women with OC has been reported in vitro and in vivo preclinical models and it is under evaluation in several clinical trials, both in chemo-naive and pretreated patients.[37] The ENGOT-Ov44/FIRST trial (NCT03602859) is a phase III study which randomizes treatment-naïve OC patients to receive SoC chemotherapy (± bevacizumab) followed by niraparib maintenance or the combination of SoC chemotherapy (± bevacizumab) plus dostarlimab followed by maintenance with niraparib plus dostarlimab. The original design of the study included also a third arm of SoC chemotherapy followed by placebo maintenance; this arm was later discontinued in light of the outcome of the PRIMA and PAOLA-1 trials,[38,39] which established maintenance treatment with PARP inhibitors alone or in combination with antiangiogenic agent bevacizumab as the standard of care for high-grade OC. Coprimary endpoints of the trials are the PFS in the intention-to-treat (ITT) population and in PD-L1 positive patients.[40]

The NITCHE/MITO-33 trial (NCT04679064) will evaluate the efficacy of the PARP inhibitor-ICI combination in pretreated, platinum-resistant OC patients. In this trial, women with recurrent/relapsed OC not suitable for platinum retreatment are randomized to receive SoC chemotherapy at physician's choice (between weekly paclitaxel, pegylated liposomal doxorubicin, gemcitabine and topotecan) or the combination of niraparib and dostarlimab. Patients with previous treatment with a PARP inhibitor or an ICB are eligible. OS will serve as the primary endpoint of the trial.[41] The combination of niraparib and dostarlimab in platinum-resistant OC (PROC) has already been investigated in two phase II studies. The OPAL trial evaluated the combination of dostarlimab (with the GARNET schedule) plus 3-weekly bevacizumab plus oral niraparib. The combination yielded an ORR of 17.9% (95% CI, 8.7–31.1%); the authors underlined that most patients were BRCA wildtype or homologous repair defects (HRD)-negative.[42] However, niraparib plus dostarlimab failed to demonstrate any benefit in patients with PROC and BRCA wildtype tumors in the MOONSTONE phase II trial. In the interim analysis of the study, the combination showed an unsatisfactory 7.3% ORR (95% CI, 1.5–19.9%) which led to trial discontinuation for futility. PD-L1 status did not predict the response.[43]

Several ongoing studies are assessing the efficacy of the combination of dostarlimab and niraparib in different solid tumors including head and neck squamous cell carcinoma (HNSCC), penile cancer and small cell lung cancer among others.

From an immunological standpoint, squamous cell carcinoma (SCC) of the cervix displays features which may suggest a biological rationale for the use of ICB. In particular, the overexpression of PD-1/PD-L1, which has been detected in more than 50% of cervical SCC, might play a role in the evasion from immune surveillance of the HPV-infected cells.[44] Therefore, many ICBs have been evaluated in phase II trials for women with advanced cervical cancer progressing to first-line chemotherapy, with response rates ranging from 15 to 26.3%.[45–47] More recently, in the phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial, the anti-PD-1 cemiplimab have demonstrated a significant survival advantage over second-line chemotherapy in this setting (median OS 12.0 vs 8.5 months, hazard ratio (HR) for death 0.69, 95% CI 0.56–0.84; $p < .001$).[48]

In view of these results, a phase II trial is currently assessing the safety and efficacy of dostarlimab in high-risk locally advanced cervical cancer, defined by a FIGO Stage III-IV or by pelvic or para-aoritc lymph-node involvement regardless of FIGO stage. The ATOMICC trial will randomize 2:1 patients who achieved CR or PR to SOC chemoradiation to receive maintenance treatment with dostarlimab for 2 years or observation as per standard of care. Primary endpoint is PFS.[49]

Dostarlimab in other solid neoplasms

The observation of the enhanced activity of dostarlimab in the presence of other ICB inhibitors such as anti-TIM-3 antibodies in preclinical models have fostered the design of several clinical trials evaluating this combinations in solid tumors. The AMBER trial (NCT02817633) is assessing the combination of the TIM-3 inhibitor cobolimab (TSR-022) alone or with dostarlimab in patients with solid tumors. The trial was conceived as a two part-study, starting with a multicohort dose escalation part followed by a multicohort dose expansion part. At 2022 ASCO Annual Meeting, the preliminary results of the combination of dostarlimab and cobolimab in patients with advanced and metastatic melanoma were presented. Patients received dostarlimab 500 mg q3w with cobolimab IV q3w at three different dose levels (100, 300, and 900 mg). The ORR for all the evaluable patients (N = 28) was 42.9.[50] The combination of an anti-PD-1 and an anti-TIM-3 antibody is also under evaluation in patients with resectable stage III or oligometastatic stage IV melanoma in the randomized phase II NEO-MEL-T trial (NCT04139902; https://www.clinicaltrials.gov/ct2/show/NCT04139902). The patients will receive neoadjuvant dostarlimab or the combination of dostarlimab plus cobolimab for 2 cycles (6 weeks) prior to the planned surgery followed by adjuvant dostarlimab for 6 cycles every 6 weeks (48 weeks). Primary endpoint of the trial is the major pathologic response (MPR) defined as a residual volume of viable tumor < 10% in the resected specimen.

The IOLite trial was an open-label phase 1b trial evaluating the safety and the efficacy of dostarlimab in advanced solid tumors. The study had four arms of dostarlimab in combination with niraparib or with bevacizumab (Cohort A and C respectively) and with carboplatin/paclitaxel alone or combined with bevacizumab (Cohort B and D respectively). In parts A and C, up to 4 lines of previous treatment are allowed,

Table 2. Key ongoing phase III and randomized phase II clinical trials of dostarlimab as a monotherapy or in combination with other agents in solid tumors.

NCT Number, Name (if available)	Phase	Target condition(s)	Study arm(s)	Primary endpoint(s)
NCT05201547, DOMENICA	III	Stage IV treatment-naïve dMMR EC	Dostarlimab vs SoC ChT	PFS
NCT04679064, NITCHE/MITO-33	III	Recurrent/advanced EC	Dostarlimab vs SoC ChT	OS
NCT04655946, COSTAR Lung	III	Stage IV NSCLC progressed after anti-PD(L)1 therapy and chemotherapy	ChT vs ChT + Dostarlimab ± Cobolimab	OS
NCT03602859, ENGOT-Ov44/FIRST	III	Stage III-IV treatment-naïve OC	SoC ± Dostarlimab followed by maintenance with Niraparib ± Dostarlimab	PFS in PD-L1 + pts, PFS in ITT
NCT03981796, RUBY	III	Recurrent/advanced EC	SoC ± dostarlimab followed by maintenance with placebo vs dostarlimab ± niraparib	PFS, OS
NCT04139902, NEO-MEL-T	II-R	Stage III-IV unresected melanoma	Dostarlimab ± Cobolimab	MPR
NCT03833479, ATOMICC	II-R	High risk LACC	Dostarlimab vs observation	PFS

Abbreviations: ChT, chemotherapy; dMMR, mismatch-repair deficient; EC, endometrial cancer; II-R, phase II randomized; ITT, intention-to-treat population; LACC, locally advanced cervical cancer; MPR, major pathological response; OC, ovarian cancer; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

Table 3. Summary of clinical outcomes in patients treated with dostarlimab monotherapy in the clinical trials published so far.

Condition[reference]	N	ORR (95% CI)	DCR (95% CI)	DOR, months (range)	mPFS (95%CI), months	mOS (95%CI), months
dMMR Endometrial Cancer[22]	143	45.5% (37.1–54.0%)	60.1% (51.6–68.2%)	NR (1.18+ to 47.21+)	6.0 (4.1–18.0)	NR (25.7–NR)
pMMR Endometrial Cancer[22]	156	15.4% (10.1–22.0%)	34.0% (26.6–42.0%)	19.4 (2.8–47.18+)	2.7 (2.6–2.8)	16.9 (13.0–21.8)
Locally advanced Rectal Cancer[29]	12	100% (74–100%)	100% (74–100%)	NA	NA	NA
Non-Small Cell Lung Cancer[31]	67	26.9% * (16.8–39.1%)	62.7% * (50.0–74.2%)	11.6 * (2.8–19.4+)	7.0 (4.3–9.5)	18.8 (11.4–20.3)
dMMR Non-EC Solid Tumors[32]	106	38.7% (29.4–48.6%)	NA	NR	NA	NA

Abbreviations: DCR, disease control rate; dMMR, mismatch-repair deficient; DOR, duration of response; EC, endometrial cancer; OS, overall survival; NA, not assessed; NR, not reached; pMMR, mismatch-repair proficient; PFS, progression-free survival.
*Assessed per iRECIST.

while in the chemotherapy arms patients could have received only one line of previous treatment. Primary endpoints were the assessment of the recommended phase 2 dose (RP2D), safety and preliminary efficacy. Fifty-five patients were enrolled: ORR was achieved in 18.2%, 42.9%, 30.8% and 50% of patients in cohort A to D, respectively. Two CR were reported: a patient with vulvar cancer in the cohort B and a patient with a head/neck squamous cell carcinoma in cohort D. No new safety signals emerged from the trial.[51]

The characteristics and primary endpoints of the key ongoing phase II- III randomized clinical trials are summarized in Table 2.

Approval and availability

Based on the preliminary results of cohort A1 of the GARNET trial, in April 2021 the Food & Drug Administration (FDA) granted accelerated approval for dostarlimab for the treatment of patients with dMMR advanced or recurrent endometrial cancer with disease progressing after platinum-based chemotherapy. Four months later, after the disclosure of the results of non-EC patients in the GARNET trial, the drug underwent FDA accelerated approval for all type of solid tumors harboring mismatch-repair deficiency which have progressed to prior treatment and with no valid treatment options.[52]

The European Medicine Agency (EMA) has granted dostarlimab a conditional marketing authorization for the treatment of patients with dMMR advanced or recurrent EC which progressed after platinum-based chemotherapy in April 2021. The concession of a standard authorization will be subjected to a longer follow-up of the Cohort A1 of the GARNET trial and to the preliminary results of the RUBY trial, both of which are expected to be disclosed by the end of 2022. At the time of writing this manuscript, in Europe dostarlimab did not receive any type of authorization for non-EC solid tumors.[53]

Conclusions and future directions

Dostarlimab is a novel anti-PD1 IgG4 antibody characterized by a high affinity to the receptor and a favorable pharmacokinetic profile. Preliminary results in women with advanced dMMR EC suggest a remarkable activity in this population of patients, thus providing an active and tolerable treatment option in these patients; on the other hand, the impressive 100% CR rate observed in patients with LARC warrants further development of this treatment in the context of offering patients a surgery-sparing strategy. Dostarlimab also showed interesting activity signals in dMMR non-EC tumors. These results (summarized in Table 3), alongside with the favorable toxicity profile and the possibility to switch to a 6-weekly schedule, make the development of this drug particularly interesting, especially in this biomarker-selected population; although the GARNET trial have undoubtedly showed activity in dMMR EC, leading to its approval both from FDA and EMA, the role of dostarlimab in dMMR non-EC tumors and the combination strategy will be defined by the results of the

ongoing phase II and III trials. In addition, the identification of the mechanisms of ICB resistance in dMMR tumors should be a prioritary effort in order to design strategies to overcome it and to improve ICB outcomes.

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