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REVIEW ARTICLE

Dostarlimab as a promising immunotherapy for endometrial cancer treatment – literature review

Kamila Derlatka[1,A-D] ✉, Justyna Tasior[1,A-D], Marika Kulczycka[1,A-D], Wioletta Pasieczna[1,A-D], Monika Prendecka-Wróbel[2,E-F]

[1] *Student Research Group / Physiology Department, Medical University, Lublin, Poland*
[2] *Physiology Department, Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. Endometrial cancer, a leading gynecological malignancy, is on the rise globally. Existing treatments for advanced cases have limited effectiveness and notable side-effects. Dostarlimab, a monoclonal antibody, enhances the immune response against tumuors by blocking the PD-1/PD-L1/PD-L2 interaction. This review examines dostarlimab's role, mechanism, clinical trials, and safety in endometrial cancer.

Review Methods. A search was conducted using PubMed and Google Scholar databases to evaluate dostarlimab's therapeutic potential in endometrial cancer. The review encompasses studies detailing its mechanism of action, clinical trial outcomes, and safety data.

Brief description of the state of knowledge. Endometrial cancer, the foremost gynecological malignancy in developed countries, has seen a surge in global incidence. Traditional treatments for advanced or recurrent cases exhibit limited efficacy and notable toxicity. Dostarlimab, an innovative monoclonal antibody, intervenes in the PD-1/PD-L1/PD-L2 axis, augmenting anti-tumour immune responses and fostering tumour regression. In April 2021, accelerated FDA approval was granted for dostarlimab in mismatch repair deficient recurrent or advanced endometrial cancer, post-platinum regimen. Subsequently, on 9 February 2023, FDA approval was extended to a broader patient cohort, encompassing those ineligible for curative surgery or radiation.

Summary. Dostarlimab, targeting PD-1/PD-L1/PD-L2, shows promise in treating advanced endometrial cancer. Mechanism, trials, and safety are explored. FDA approvals highlight its potential. Ongoing trials and combination therapies suggest a dynamic role in management. Dostarlimab offers renewed hope for patients.

Key words

immunotherapy, immune checkpoint inhibitor, endometrial cancer, dostarlimab, TSR-042

INTRODUCTION

Globally, endometrial cancer (EC) is a significant issue and for many years has remained the second most common cancer, after cervical cancer, of the reproductive organs in women. In developed countries where screening for HPV infection and cervical cancer is maintained at a satisfactory level, EC is the leading cancer of the reproductive organs. According to the World Health Organization's International Agency for Research on Cancer, 417,367 (4.5%) cases of EC were registered in 2020, making it the sixth most common cancer among women. The highest burden of EC is recorded in North America and Western Europe, with the mortality rate in the EC in 2020 at 97,370, with the peak incidence occurring between the ages of 55–59 [1, 2].

EC is typically manifested by bleeding and spotting from the genital tract, which can cause anxiety in postmenopausal women and prompt them to seek help quickly. As a result, most ECs are detected at an early stage, with a 5-year overall survival rate of about 89%, and close to 100% in locally limited stages. In the advanced stage, however, the prognosis is poor. The term 'endometrial cancer' encompasses a polymorphic group of tumours that are significantly different in molecular characteristics, response to treatment, and prognosis. The division into type I, underpinned by estrogen-progesterone imbalance, ove-expression of hormone receptors, and a better prognosis, and type II hormone-independent with a worse prognosis, is now considered historical or is only a preliminary predictive factor [3].

The division of cancer by histological type proposed by the World Health Organisation into endometroid, mucinous, clear cell, squamous cell, and serous carcinomas, appears suboptimal accordingn to today's knowledge. Above all, it is prone to human error. Moreover, within a single histological type, we have to deal with high molecular heterogeneity of cells. Therefore, to effectively treat EC, therapy must be optimized against each cell individually. Nowadays, a division that takes into account the genetic and epigenetic features of cancer cells distinguishes four molecular subtypes: polymerase e hypermethylation (POLE), microsatellite instability (MSI-H), mismatch repair deficiency (dMMR), and alterations in the p53 gene (*The Cancer Genome Atlas*) seems to be more up-to-date [1, 4]

✉ Address for correspondence: Kamila Derlatka, Student Research Group / Physiology Department, Medical University, Lublin, Poland
E-mail: kamila.derlatka515@gmail.com

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DMMR cancers often co-exist with high-stage and recurrent disease, and are highly prone to microsatellite instability and neoantigen formation [5]. Nevertheless, old but often reliable methods of conventional chemotherapy, radiotherapy or hormone therapy are still used today. The standard for EC chemotherapy is the combination of taxane and platinum. Unfortunately, reports of chemotherapy resistance in dMMR tumours are becoming more frequent. Patients with metastatic EC have significantly lower 5-year survival rates, a higher recurrence rate with a tendency to recur outside the pelvis, and a poorer response to treatment.

The new phenotype of cancer cells is forcing us to evaluate our knowledge and explore new therapeutic methods. Immunotherapy is one such method that has recently been increasingly discussed tly in the context of EC. Currently, this innovative drug therapy is being used in recurrent EC, advanced cases that have progressed despite traditional treatment, or with dMMR/MSH-I tumours, although the indications for immunotherapy are constantly expanding as needed. Interest in immunotherapy as a treatment option for dMMR/MSH-I tumours is based on the known characteristics of their cells containing a higher neoantigen load, increased PD-1/PDL-1 expression, and significant infiltration of the tumour environment with lymphocytes. Up to 30% of ECs are now thought to have high levels of microsatellite instability or deficient base mismatch repair, making it the most common cancer with this molecular profile [6].

PD-1/PD-L1 pathway. The programmed cell death protein (PD-1), which belongs to the immunoglobulin superfamily, is considered one of the most essential inhibitory checkpoints. PD-1 expression occurs on T, B, myeloid and Natural Killer (NK) cells and interacting with its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), negatively regulates the adaptive immune response. The strength of TCR signaling is correlated with the level of PD-1 expression in order to limit excessive T cell activation [7, 8, 9].

Research showed that both PD-L1 and PD-L2 can be expressed on cancer cells

[10, 11]. Hence, the prolonged exposure to tumour antigens and the tumour immunosuppressive environment can lead to the inhibition of immune response and impaired T cell function, including activation, proliferation, and cytokine production [7, 12]. A pivotal research on animal models demonstrated that interaction between PD-L1 on tumour cells and PD-1 on cytotoxic T cells resulted in accelerated tumour growth [13]. Human studies subsequently showed that expression of PD-L1 and PD-L2 is associated with a poor disease prognosis in many cancers [14–16]. Therefore, antibodies blocking PD-1 or its ligand PD-L1 have been approved in order to block tumour-generated immunosuppression and treat various cancers [12].

PD-1/PD-L pathway and endometrial cancer. In 2017, the Proactive Molecular Risk Classifier for Endometrial Cancer described four molecular prognostic groups, consistent with *The Cancer Genome Atlas* of 2013: ultramutated DNA polymerase epsilon (POLE) tumours which are associated with the best prognosis, microsatellite instability (MSI) or mismatch repair (MMR)-deficient (MMRd) hypermutated tumours with intermediate prognosis, p53 abnormal tumours with the worst prognosis, and tumours with copy-number low alterations with good to intermediate prognosis [17].

It is known that in carcinomas, particularly in recurrent cases, the tumour mass undergoes increased infiltration by CD8+ lymphocytes. Similar features are observed in EC types MSI-H or dMMR. The immune system's activated cells contain checkpoint receptors known as PD-1 programmed cell death receptors. They provide signals to T lymphocytes that are necessary for the body's self-tolerance to its antigens, and to prevent excessive inflammatory response. When tumour cells up-regulate PDL-1/PDL-2 molecules, they become ligands for the PD-1 receptor on lymphocytes, leading to the body's self-tolerance towards itself. This results in pathologically-altered cells escaping from the body's natural defence mechanisms. Blocking the PD-1/PDL-1 pathway enhances the cytotoxic activity of lymphocytes, bringing tumour cells back under immune surveillance [18].

Researchers have observed increased expression of PD-L1 in the peritumoural or tumoural compartment of MMRd [19, 20]. Thus, immune checkpoint pathways such as PD-1/PD-L1 became the main target for immunotherapy in endometrial cancer (EC) [17].

Preclinical characteristics and pharmacokinetics. Early reports that initiated the significant role of immune checkpoint inhibitors indicate pembrolizumab for patients with progressive metastatic carcinoma, showing that the MMR status was predictive of the clinical benefit of Pembrolizumab. Subsequently, (FDA) approved Pembrolizumab for patients with unresectable or metastatic, MSI-H or dMMR solid tumours that have progressed following prior treatment, or for which no other alternative therapies are possible. This encouraged the following exploration of immunotherapeutic agents in this patient population [22]

Dostarlimab (TSR-042) was pre-clinically characterized as a selective, IgG4 humanized monoclonal antibody generated from a mouse hybridoma. It exhibits a similarly strong affinity to both human and cynomolgus monkey PD-1. These antibodies have shown an effective blockade of PD-1 and PD-L1/L2 interaction. Functional analyses showed that dostarlimab increases the T-cell function *in vitro* by the improvement of IL-2 production interferon (IFN)-γ release in the absence of T-cell agonist activity of this mAb. Due to lack of cross-reaction to the mouse species orthologue, its anti-cancer activity was assessed in humanized mouse models of breast and lung cancer, resulting in inhibition of tumour growth [23]

The pharmacokinetics and toxicity of TSR-042 in cynomolgus monkeys was described by S. Kumar et al., who concluded that with increasing the dosage from 10 to 100 mg/kg, maximum concentration [C_{max}] and area under the concentration–time curve [AUC], increased in an approximately dose-proportional manner. Moreover, based on the CL and Vss, dostarlimab is determined to be a typical mAb. During the testing in a 1-month repeat-dose study assessing toxicology, dostarlimab was well tolerated when administered once a week to male and female cynomolgus monkeys via intravenous infusion at doses of 10, 30, or 100 mg/kg. As reported, the researchers did not observe any unexpected deaths, drug-related clinical symptoms, or effect on body weight. Owing to its pre-clinical properties this antibody of 500 mg administered every 3 weeks, followed by 1,000 mg every 6 weeks [24].

Based on the GARNET research, Murad Melhem et al. developed pharmacological characteristics described

by a 2-compartment model with time-dependent linear elimination. Time-dependent clearance declined over time to a maximum of 14.9%. Estimated dostarlimab geometric mean coefficient of variation % clearance was 0.179 (30.2%) L d^{-1}; volume of distribution – 5.3 (14.2%), L and terminal elimination half-life – 23.5 (22.4%) days at steady state. This report also proves that pharmacokinetics (PK) of dostarlimab is similar to other PD-1 antibodies [25].

CLINICAL TRIALS

Dostarlimab in monotherapy. GARNET is the largest, multi-centre, open label, I phase clinical trial examining the use of dostarlimab in monotherapy of advanced solid tumours. The study began in March 2016 and was divided into 2 parts, with Part 1 focusing on evaluating the safety, pharmacokinetics, and pharmacodynamics of increasing doses of dostarlimab at intravenous, ascending, weight-based doses 1 mg/kg, 3 mg/kg and 10 mg/kg until the maximum tolerated dose (20 mg/kg) is reached. Part 2 consists of 2 subparts, with Part 2A assessing the safety and tolerability of fixed doses of dostarlimab – 500 mg administered every 3 weeks (Q3W) or 1,000 mg administered every 6 weeks (Q6W), and Part 2B examining its clinical activity in 5 cohorts (A1, A2, E, F,G) of participants with specific types of advanced solid tumours: dMMR/MSI-H EC (A1), MMRp/MMS EC (A2), NSCLC (E), non-endometrial dMMR/MSI-H and POLE mutant cancers (F), and platinum-resistant ovarian cancer BRCA-wild type (G).

A1 and A2 patients with advanced or recurrent EC who had progressed on or after platinum-based chemotherapy and had not previously received immune checkpoint inhibitors (ICI) therapy were enrolled. The key inclusion criteria was also measurable disease at baseline confirmed by blinded independent central review (BICR). All histological subtypes, except sarcoma and carcinosarcoma, were eligible. [18, 26].

In the second part, patients received 500mg Q3W for the first 4 cycles and 1,000mg Q6W thereafter. Anti-tumour activity was assessed by immune-related Response Evaluation Criteria in Solid Tumours (irRECIST). An objective response rate (ORR) and duration of response (DOR) were established as primary endpoints. The preliminary results were first published in 2018 [27] and 2019 [28], followed by another publication in 2020 [29]. Finally, in early 2022, the latest results were shown, which included the largest group of patients studied.

129 patients with dMMR/MSI-H EC (cohort A1) and 161 patients with MMRp/MMS EC (cohort A2) were treated with dostarlimab; however, there were 108 and 156 individuals in the efficacy population, respectively. Among the efficacy-evaluable patients, the median follow-up time was 16.3 months for A1, while it was 11.5 months for the A2. The calculated median age in both cohorts was the same and amounted to 65.5 years. All patients who received at least one dose of dostarlimab underwent safety analyses. Moreover, 65.7% of dMMR/MSI-H EC patients (71 out of 108) were diagnosed with low-grade endometrioid carcinoma (grade 1 or 2). In contrast, MMRp/MSS EC patients showed more diverse histologic subtypes, with high-grade tumours being common, especially the serous subtype (37.8%; 59/156). According to RECIST 1.1, the study revealed an ORR of 43.5% (95% CI 34.0%-53.4%) in dMMR/MSI-H EC patients, with 11 (10.2%) confirmed complete responses (CR) and 36 (33.3%) confirmed partial responses (PR). Conversely, MMRp/MSS EC patients showed an ORR of 14.1% (95% CI 0.1%-20.6%), with 3 (1.9%) CR and 19 (12.2%) confirmed PR. The median time to response was 11.9 weeks in the dMMR EC patients and 12.1 weeks in the MMRp EC patients. Notably, the median duration of response (DOR) was not reached in either cohort. While the disease control rate (DCR) was 55.6% (95% CI 45.7%-65.1%) in A1, in A2 it was 34.6% (95% CI 27.2%-42.6%).

The following were established as key secondary endpoints: immune-related objective response rate (irORR), duration of response (irDOR), and disease control rate (irDCR). In the A1 cohort, the following were obtained: 44.8%, SD (stable disease), 63.7%, meanwhile in cohort A2: 14.4%, 9 months, 40.6%.

In dMMR/MSI-H EC, the likelihood of PFS (progression-free survival) was 49.5%, 48.0%, and 46.4% at 6, 9, and 12 months, while in MMRp/MSS EC, the corresponding probabilities were 35.8%, 31.3%, and 29.4%.

In the study, a total of 27 patients (8.6%) discontinued treatment due to a treatment-related adverse event (TRAE), with 13 cases in the dMMR/MSI-H group and 14 cases in the MMRp/MSS group. The most common TRAEs leading to discontinuation were ALT increase (1.0%), aspartate transaminase (AST) increase (0.7%), and transaminase increase. TRAEs were consistent between the dMMR/MSI-H and MMRp/MSS cohorts. Most of them were grade 1 or 2, and the most common TRAEs of any grade were fatigue (56; 17.8%), diarrhea (46; 14.6%), and nausea (43; 13.7%). The most frequent any-grade immune-related adverse event (irAE) was hypothyroidism, which occurred in 12 patients (8%). There were no deaths in the EC cohorts attributed to dostarlimab.

In the GARNET clinical trial, dostarlimab was shown to have long-lasting anti-tumour effects in both dMMR/MSI-H and MMRp/MSS AR EC. However, better outcomes were observed in the first group, including a higher response rate and longer progression-free survival (PFS) and overall survival (OS). Throughout the study, no new safety signals were observed, and the safety profile was considered manageable. Most TRAEs reported were of low grade, and their incidence was similar across both study cohorts [6, 30, 31].

These results are consistent with the known characteristics of dMMR/MSI tumours, which exhibit increased tumour neoantigen load, tumour-infiltrating lymphocytes, and increased expression of PD-1 and PD-L1. These features can enhance the response to immune checkpoint inhibitors, highlighting the potential of Dostarlimab as a therapeutic option for patients with dMMR/MSI-H AR EC [32, 33]

A patient-reported outcome (PRO) is a measure of a patient's health status reported directly by the patient, rather than being interpreted or evaluated by a healthcare professional or a third party. PROs can be used to evaluate a patient's symptoms, functioning, quality of life, and satisfaction with treatment, among other things. They are often used in clinical trials and other research studies to assess the effectiveness of treatments and interventions from the patient's perspective [34].

In the GARNET trial, PROs were measured in dMMR/MSI-H EC patients using the validated European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) at each dose of dostarlimab and during follow-up.

Table 1.

Clinical trial (NCT No.)	Study design	Phase	Type of neoplasm	Drugs	Results	References
GARNET (NCT 02715284)	multicentre open-label, first-in-human, non-randomized, two-part	1	dMMR/MSI-H EC (A1), MMRp/MMS EC (A2), NSCLC (E), non-endometrial dMMR/MSI-H and POLE mutant cancers (F), platinum-resistant ovarian cancer BRCA-wild type (G)	*Part 1*: dostarlimab IV in increasing doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg (max. 20 mg/kg) on day 1 and 15 of a 28-day cycle *Part 2A:* fixed dose of dostarlimab of either 500 mg Q3W (21-day cycle) or 1000 mg Q6W (42-day cycle) on day 1 of each cycle. *Part 2B* (cohorts A1, A2, E, F, G): dostarlimab 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for all subsequent cycles.	Cohort A1: ORR 43.5% with CR 10.2% and PR 33.3%; DCR 55.6%. Cohort A2: ORR 14.1% with CR 1.9% and PR 12.2%; DCR 34.6 %	[6],[18],[26-31]
DORA (NCT05728814)	multicentre, retrospective, observational (non-interventional)	-	dMMR/MSI-H recurrent or advanced EC	Treatment under observation is dostarlimab administered on day 1 of each treatment cycle until disease progression, unacceptable toxicity or patient/doctor's decision. Dostarlimab administered 500 mg Q3W for 4 cycles followed by 1000 mg Q6W for all subsequent cycles.	No results have been posted yet	[37]
NEC (NCT03016338)	Open-label, single-arm, two-part	2	epithelial endometrial cancer except for endometrial sarcoma, carcinosarcoma, clear cell, mixed and adenosquamous tumours	*Part 1:* niraparib 200 or 300 mg each day. Part 2: dostarlimab 500 mg Q3W for 4 cycles, then 1000 mg Q6W; and niraparib 200 or 300 mg each day	*Part 1:* CBR 20% with median CB of 5.3 months, ORR 4% *Part 2:* CBR 31.8% with median CB of 6.8 months, ORR 14%	[43]
ROSCAN (NCT03651206)	multicentre, open-label, multicentre, randomized, two-part	2/3	progressive or recurrent uterine or ovarian carcinosarcoma	*Phase 2:* Arm 1: niraparib 200 or 300 mg each day Arm 2: dostarlimab 500 mg Q3W for 4 cycles, then 1000 mg Q6W; and niraparib 200 or 300 mg each day Arm 3: Chemotherapy (doxorubicin, paclitaxel. topotecan or gemcitabine) *Phase 3:* Arm 1: Arm 1 or 2 from phase 2 with superior efficacy Arm 2: Chemotherapy (doxorubicin, paclitaxel. topotecan or gemcitabine)	No results have been posted yet	[44]
NCT05559879	open-label, single-arm	1/2	carcinosarcoma	cabozantinib 40mg PO daily and dostarlimab 500mg IV Q3W followed by maintenance therapy with cabozantinib 40mg PO daily and dostarlimab 1000mg IV Q6W for up to 2 years.	No results have been posted yet	[49]
NCT03955978	open-label. single-arm	1	clinical stage I or II endometrial carcinoma	Brachytherapy (IMRT technique) 6 weekly fractions of 6 Gy per fraction (total 36Gy) and dostarlimab given before and during radiation (total 4 doses)	No results have been posted yet	[53]
NCT04774419	open-label, single-arm	2	endometrial cancer: all histologies and stage III/IVA disease	Radiation (IMRT technique) total dose of 45-50.4Gy at 1.8 Gy per fraction) for 5-6 weeks and dostarlimab Q3W for 4 cycles followed by 1 dose of 1,000mg (max. 5 cycles of dostarlimab)	No results have been posted yet	[54]
DOMENICA (NCT05201547)	multicenter, open-label, randomized	3	endometrial adenocarcinoma with recurrent or advanced disease	Arm A: dostarlimab IV 500 mg Q3W for 4 cycles followed by 1000 mg Q6W; thereafter, Arm B: carboplatin AUC 5 or 6 plus paclitaxel 175 mg/m2, every 3 weeks (6 cycles)	No results have been posted yet	[57]
NCT05819892	open-label, single-arm, randomized	1	endometrial cancer of any histologic subtype	Adjuvant therapy during radiation and after radiation, immunotherapy after radiation and chemotherapy. Drugs IV: paclitaxel, carboplatin, dostarlimab, cisplatin. 6 cycles of active treatment followed by 14 cycles of maintenance as long as the disease remains stable.	No results have been posted yet	[58]
IOLite (NCT03307785)	multicenter, open-label,non-randomized, multi-arm	1b	advanced (unresectable) or metastatic cancer	Experimental: Part A: dostarlimab and niraparib 200 mg QD *Experimental: Part A:* dostarlimab and niraparib 300 mg QD (n=22) *Experimental: Part B:* dostarlimab and carboplatin-paclitaxel (n=14) *Experimental: Part C:* dostarlimab, niraparib 200 mg QD and bevacizumab *Experimental: Part C:* dostarlimab, niraparib 300 mg QD and bevacizumab (n=13) *Experimental: Part D:* dostarlimab, carboplatin-paclitaxel and bevacizumab (n=6)	DLTs in 2, 1, 2, and 0 patients, in parts A-D. Preliminary antitumor activity was observed, with confirmed RECIST v1.1 CR/PR reported in 4 of 22 (18.2%), 6 of 14 (42.9%), 4 of 13 (30.8%), and 3 of 6 (50.0%) patients, in parts A-D. DCRs were 40.9%, 57.1%, 84.6%, and 83.3%, in parts A-D	[59]

Clinical trial (NCT No.)	Study design	Phase	Type of neoplasm	Drugs	Results	References
AMBER (NCT02817633)	multi-centre, open-label, non-randomized, first-in-human phase 1	1	advanced or metastatic solid tumour	1A: cobolimab (IV Q2W) monotherapy at 7 doses (6 weight-based [0.03–10 mg/kg] and 1 flat [1200 mg] dose) 1B: cobolimab (1 mg/kg) + nivolumab (3 mg/kg IV Q2W); and (1C) cobolimab (100, 300, or 900 mg) + dostarlimab (500 mg IV Q3W).	Cobolimab + dostarlimab was well tolerated and showed preliminary anti-tumour activity	[60]
RUBY (NCT03981796)	multicentre, randomized, double-blind	3	endometrial cancer with recurrent or advanced disease	Active Comparator: Arm 1) Participants receiving dostarlimab + Carboplatin-paclitaxel followed by dostarlimab Placebo Comparator: Arm 2) Participants receiving placebo + carboplatin-paclitaxel followed by placebo Active Comparator: Arm 3) Participants receiving dostarlimab + carboplatin-paclitaxel followed by dostarlimab+niraparib Placebo Comparator: Arm 4) Participants receiving placebo + carboplatin-paclitaxel followed by placebo	In the dMMR-MSI-H population, PFS at 24 months 61.4% in the dostarlimab group and 15.7% in the placebo group. In the overall population, PFS at 24 months 36.1% in the dostarlimab group and 18.1% in the placebo group Overall survival at 24 months was 71.3% with dostarlimab and 56.0% with placebo	[56]

IV – intravenously; Q3W – every 3 weeks; Q6W - every 6 weeks; PO – per orale; IMRT – intensity modulated radiation therapy; AUC – area under the curve; ORR – objective response rate; PR – partial response; CR – complete response; DCR – disease control rate; CBR – clinical benefit rate; CB – clinical benefit; DLTs – dose-limiting toxicities; QD – once a day; RECIST – Response Evaluation Criteria In Solid Tumours

The completion rate of PROs among 88 patients was >95.5%. The results showed significant improvement in quality of life, emotional and social functioning, and stable or improved symptom scores throughout cycle 7 of the trial. Among the patients who reported a worsening in their response categories, only a small percentage experienced a 2-category worsening (≤7.4%) or a 3-category worsening (≤2.5%) [35,36].

In February 2023, a multicentre, retrospective, observational (non-interventional) study DORA was registered examining the effectiveness of treatment with dostarlimab monotherapy in an expanded access programme (EAP) among women with dMMR/MSI-H EC, who progressed during or after previous treatment with a platinum-containing regimen. The programme was available in Spain from January 2021 – September 2022. The primary clinical objectives were established as ORR and DOR, which were measured using RECIST 1.1 criteria. The study is still in the patient recruitment phase [37].

PARP inhibitors. Poly (ADP-ribose) polymerase (PARP) inhibitors, such as niraparib, olaparib, and rucaparib, have been shown to block the PARP enzymes by inhibiting their catalytic activity, as well as trapping PARP-DNA complexes at sites of DNA damage, thereby preventing DNA repair, replication, and transcription [38]. Niraparib has been approved by the FDA for use in recurrent ovarian and breast cancer [39], which has led to attempts to use it in other types of cancer. Moreover, studies have shown that DNA damage can enhance the immune response by increasing the expression PD1 and PD-L1 [40, 41, 42]. Consequently, the combination of PARP inhibitors with anti-PD-1/PD-L1 antibodies is being explored as a potential strategy for treating patients with EC. There is a phase-2 study NEC investigating the efficiency of niraparib in monotherapy (cohort C1–25 patients), or in combination with dostarlimab (cohort C2–22 patients) in patients with recurrent/advanced EC, who have previously received platinum-based chemotherapy. Niraparib as a single agent showed modest activity with CBR 20% and median clinical benefit (CB) duration of 5.3 months, meanwhile the combination with dostarlimab demonstrated CBR of 31.8% and median CB duration of 6.8 months. There was no significant correlation observed between CB rate and either IHC markers (PTEN, p53, MMR, PDL-1) or NGS (PTEN, TP53, HR genes, TMB-high) in both cohorts. Furthermore, none of these biomarkers showed a statistically significant association with longer PFS [43]. The effectiveness of niraparib and dostarlimab is currently being studied in a phase-2/3 clinical trial ROSCAN in patients with endometrial and ovarian carcinosarcoma who have progressed after previous platinum-based chemotherapy [44].

VEGF inhibitors. Cabozantinib is a tyrosine kinase inhibitor that works by blocking the activity of certain proteins involved in the growth and spread of cancer cells, including VEGFR, MET, and AXL. In endometrial cancer, over-expression of these proteins is associated with poor prognosis and resistance to standard treatments [45]. The combination of cabozantinib and immunotherapy has shown promise in the treatment of certain types of cancer, including advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) [46–48]. There is a phase Ib/II, single arm study investigating the efficiency of cabozantinib plus dostarlimab in women with recurrent gynecologic carcinosarcoma. The primary outcome measure is the proportion of patients who survive progression-free for at least 6 months from the start of treatment. No results have been posted so far [49].

Radiotherapy. Radiation enhances immune responses by promoting tumour-cell death, dendritic cell activation, antigen cross-presentation, and cytotoxic T-cell activation. It also modulates the expression of immune checkpoint ligands, including PD-L1, on tumour cells and immune cells in the tumour microenvironment [50, 51]. Antibody binding alone is not cytotoxic, but it can trigger antibody-dependent cellular cytotoxicity and non-cell-mediated cytolysis. Anti-PD-L1 antibodies currently in development do not mediate antibody-dependent cellular cytotoxicity, but

new reagents optimized for this purpose could potentially be combined with local radiation to enhance PD-L1 expression [52]. Therefore, a phase-1 clinical trial is being conducted to evaluate the safety and efficacy of dostarlimab in conjunction with brachytherapy using the intensity modulated radiation therapy (IMRT) technique for patients with inoperable EC. Safety and tolerability of the regimen were established as primary endpoints, using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [53].

Another single-arm phase-2 trial aims to test the safety and effectiveness of combining IMRT and dostarlimab in women with dMMR/MSI-H EC who have recently undergone surgery. The study focuses on women with stage III-IVA EC, and the primary endpoint is disease-free survival rate at 24 months after surgery [54].

Chemotherapy. In advanced-stage and high-risk endometrial cancer, adjuvant treatment is the standard of care and generally includes chemotherapy with or without radiotherapy. The best application of these 2 methods together or separately is still the object of study [55]. Moreover, according to the latest research, synergistic use of chemotherapy and immunotherapy is a promising alternative for standard chemotherapy. Namely, dostarlimab plus carboplatin–paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer, with a strong benefit in the dMMR–MSI-H population. In the phase 3, randomized, double-blind, multicentre RUBY trial, patients were randomly allocated in a 1:1 ratio to receive dostarlimab (500 mg) or placebo intravenously, in combination with carboplatin at an area under the curve of 5 mg per milliliter per minute, and paclitaxel at a dose of 175 mg per square meter of body-surface area intravenously every 3 weeks for the first 6 cycles, followed by dostarlimab (1,000 mg) or placebo intravenously every 6 weeks for up to 3 years, or until disease progression, treatment discontinuation caused by toxic effects, patient or investigator withdrawal, or death. The most relevant endpoints were progression-free survival as assessed by the researcher according to Response Evaluation Criteria in Solid Tumours (RECIST), safety and overall survival [56].

In order to compare chemotherapy as a Carboplatin-Paclitaxel with dostarlimab in the first line, another clinical trial is currently underway and will end in October 2029. The multicentre, open-label, randomized study is assessing the efficacy and safety of dostarlimab versus carboplatin-paclitaxel in patients with MMR deficient relapse, or advanced endometrial cancer [57].

Another open-label, randomized, 1-phase and single arm clinical trial is being conducted in patients with lymph node metastases with stage IIIC of endometrial cancer. The purpose of the study is to explore the relevance and safety of radiochemotherapy plus concurrent immunotherapy, including dostarlimab, followed by chemotherapy plus concurrent immunotherapy and subsequent immunotherapy maintenance [58].

Dostarlimab in combinations. Timothy A. Yap (IOLite) designed a multicentre, open-label, multi-arm phase 1b study with the aim of specifying the recommended dose (RP2D), safety, PK, and preliminary efficacy of dostarlimab in combination with approved cancer therapies for patients with advanced or metastatic different types of cancer. 55 of the enrolled patients received dostarlimab and: (1) niraparib in part A (n=22); (2) carboplatin–paclitaxel in part B (n=14); (3); niraparib plus bevacizumab in part C (n=13); (4) carboplatin–paclitaxel plus bevacizumab in part D (n=6). All combinations were safe and tolerable.

Dostarlimab exhibited promising anti-tumour activity in double and triplet regimens in combination with niraparib, with or without bevacizumab, or in combination with carboplatin-paclitaxel with or without bevacizumab [59]. Interestingly, the results of this study are validated in patients with endometrial cancer in the larger, phase 3 RUBY trial mentioned above [56].

Dostarlimab was also assessed in combination with cobolimab in Part 2 (1C) of multi-centre, open-label AMBER study in 104 patients (1A (n=46), 1B (n=7), or 1C (n=55)). The 1C group comprised patients with NSCLC, skin, and peritoneal mesothelioma. The results showed that cobolimab plus dostarlimab was well tolerated and showed preliminary anti-tumour activity [60]. Another anti-cancer medication combinated with dostarlimab is niraparib – a PARP inhibitor used in the above-described RUBY study [56].

FDA approval of Jemperli (dostarlimab-gxly) for dMMR endometrial cancer. In April 2021 dostarlimab received accelerated approval for the treatment of recurrent or advanced endometrial cancer in adult patients who have a deficiency in mismatch repair, and have previously been treated with platinum-containing drugs. On 9 February 2023, the FDA approved the drug for use in adult patients who have progressed on or after platinum-containing treatment and are not eligible for curative surgery or radiation, thus expanding its approved use.

Main advantages and disadvantages of dostarlimab – profitability and cost of treatment. Although the history of dostarlimab is short, it appears to hold promise. However, it also poses a challenge and should warrant greater vigilance among researchers due to the antibody's rapid registration and short follow-up period, which do not allow for definitive conclusions to be drawn regarding long-term efficacy or potential delayed side-effects. Additionally, there is currently insufficient data on the safety of its use in the elderly, one of the primary target groups. One major risk associated with dostarlimab therapy is the lack of stratification of the risk of body immunization and potential immunological adverse reactions. Limited clinical studies have reported the possibility of severe, life-threatening immune reactions, even after discontinuation of PD-1 inhibitor treatment. Treated patients have also experienced non-infectious pneumonia, immune-mediated colitis, and hepatitis.

Immunological endocrinopathies have been observed during the use of dostarlimab, including in type I diabetes, hyperthyroidism, hypothyroidism, adrenal insufficiency, and inflammation of the thyroid and pituitary glands. Patients should be monitored for joint pain, immune-mediated rashes, as well as other less common complications. A serious side-effect can be the rejection of a parenchymal organ transplant or the development of graft-versus-host disease. Another issue is the lack of data on interactions with other drugs. Additionally, as EC is occurring in an increasingly younger age group, attention must be paid to female fertility and pregnancy. The lack of reliable data does not allow for conclusive statements about the harmfulness of the therapy,

but due to the structure of dostarlimab as an IgG4 protein, it can diffuse through the placenta and potentially pose a risk to the foetus. A limitation of the therapy is the need for contraception in women of childbearing age and the contraindication of use during pregnancy. There are no available data on fertility or the permeation of the drug or its metabolites into a woman's breast milk.

No studies have been conducted on the potential carcinogenicity or genotoxicity of dostarlimab. Another inconvenience in the use of the drug, in addition to the limited availability of data, is the need for precise patient selection. Cancer treatment in this case requires double precision, with patients and drugs needing to be mutually matched in terms of therapeutic goals. The clear advantage of dostarlimab is its high efficacy in dMMR and/or MSI tumours, which often allows for regression when standard treatment has failed. It is the first drug to achieve complete tumour ablation with a concomitant lack of recurrence.

In addition, all of this is achieved by utilizing the patient's own immune reserves, without leading to the severe and almost certain side-effects of classical chemotherapy. An essential issue is immune matching between the tumour environment and the drug, which enables it to act within the pathological tissue without damaging healthy cells, thus bypassing potential immune reactions. What remains clinically significant is an easy drug delivery regimen, independence of dostarlimab clearance from renal or hepatic capacity, and intravenous delivery, which maintains a constant drug concentration. The only contraindication to the use of the drug is a hypersensitivity reaction, which does not limit clinical use. Paradoxically, the drug's relatively low awareness is an advantage as it holds the promise of significant success in oncology [61].

Although acess to innovative therapies is a major opportunity for public health, it also means significant expense. In the United States, the average cost of a single dose of the antibody is approximately $11,000, resulting in a high cost of therapy. Currently, the drug remains at full-price, but there is increasing discussion of the possibility of reimbursement for dostarlimab therapy in the near future [62].

Dostarlimab in other cancers. Currently, the FDA has approved 6 different PD-1 and PDL-1 inhibitors for clinical use, which are a great alternative to conventional treatment. There is a strong up-regulation of PDL-1 receptors in many types of cancer cells, which is why PD-1/PDL-1 pathway inhibitors currently have applications in the treatment of many cancers, and more niches for their use are still being sought. Therapy with drugs that modulate the immune micro-environment of tumours is often used as a treatment of last resort or as adjuvant therapy. Immune checkpoint blockade appears to be a highly effective approach against treatment-resistant and rapidly progressing tumours with base-matching deficiency. Dostarlimab is used in the treatment of locally advanced rectal cancer with base-matching deficiency showing remarkable efficacy. In locally advanced dMMR cancer, conventional induction chemotherapy as part of standard multimodal treatment often fails due to poor anti-tumour response. This has necessitated the search for other solutions, and nowadays, dostarlimab monotherapy can be considered a first-line neoadjuvant treatment in rectal cancer with rule mismatch. PD-1 blockade alone has been shown to lead not only to a benefit in terms of reduced tumour mass and improved surgical respectability, but even to complete tumour immunoablation. This was the first time in science that a drug in clinical trials completely destroyed a tumour, and there was no recurrence. Admittedly, with the high local advancement of rectal cancer, the results are no longer so optimistic, but this creates great opportunities. The success of neoadjuvant immunotherapy in rectal cancer has focused interest on dostarlimab [63].

Based on the promising results of the PD-1 inhibitor in rectal cancer treatment, there is increasing interest in its use in other dMMR/MSI-H tumours. It has now shown promising results in ovarian cancer, melanoma, head and neck cancer, breast cancer, small cell and non-small cell lung cancer, pancreatic cancer, squamous cell carcinoma, and many others. Dostarlimab is used both in monotherapy and in combination with other drugs, mainly anti-angiogenic drugs and classical chemotherapy. Testing different drug combinations allows searching for the optimal treatment [5, 64].

CONCLUSIONS

Dostarlimab is a promising treatment option for patients with recurrent or advanced endometrial cancer, particularly those with mismatch repair deficiency (dMMR) who have previously received platinum-containing regimens, and are not candidates for surgery or radiation. Its recent FDA approval underscores its importance in managing endometrial cancer, and ongoing clinical trials are exploring its potential in various settings and combinations with other therapies.

Dostarlimab offers several notable advantages. It exhibits high efficacy against dMMR and/or MSI tumours, achieving complete regression even after failed standard treatments, while sparing patients from the severe side-effects commonly associated with traditional chemotherapy. Its precise targeting of tumour cells without harming healthy tissue is a significant therapeutic benefit. The simplicity of its delivery, independence from renal or hepatic capacity, and ease of administration via intravenous infusion, contribute to its clinical significance.

However, this promising therapy has limitations. Limited long-term efficacy and safety data, especially in elderly patients, raise concerns. The risk of immunological adverse reactions, including severe immune responses, pneumonia, colitis, and hepatitis, necessitates careful monitoring. Immunological endocrinopathies and potential impacts on fertility and pregnancy require consideration. The lack of information regarding drug interactions, carcinogenicity, and genotoxicity adds to the uncertainty surrounding its use. Precise patient selection is crucial for matching patients and drugs based on therapeutic goals.

Despite impressive response rates in clinical trials, dostarlimab's long-term safety and efficacy warrant further investigation. Optimal patient selection criteria and mechanisms of response and resistance require deeper understanding. Evaluating cost-effectiveness and quality of life impact is also essential.

In the light of these challenges, dostarlimab represents a significant advancement in the treatment of endometrial cancer, and providing hope to patients with this type of cancer. Ongoing research on dostarlimab and other

immunotherapy agents will lead to improved outcomes for endometrial cancer patients.

This review is significant in oncology as it underscores dostarlimab's promise in treating advanced or recurrent endometrial cancer, supported by a thorough examination of its mechanism, clinical trials, and FDA approvals. It envisions a dynamic role for dostarlimab in endometrial cancer management, offering renewed hope to patients in critical need.

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