Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Jemperli

Active ingredients: Dostarlimab

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ADA	Anti-drug antibody
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration time curve
$AUC_{0\text{-}inf}$	Area under the concentration time curve from time zero to infinity
$AUC_{0\text{-}tau}$	Area under the concentration time curve from time zero to the end of the dosing period
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency (European Union))
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CMI	Consumer Medicines Information
CPD	Certified Product Details
DLP	Data lock point
dMMR	DNA mismatch repair deficient
DNA	Deoxyribonucleic acid
EC	Endometrial cancer
EC_{50}	Half maximal effective concentration
EMA	European Medicines Agency (European Union)
EU	European Union
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices

Abbreviation	Meaning
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
IFN	Interferon
IgG1	Immunoglobulin G1
IgG4	Immunoglobulin G4
IL	Interleukin
K_D	Dissociation constant
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PD-1	Programmed cell death receptor-1
PDF	Portable document format
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PI	Product Information
PK	Pharmacokinetic(s)
PMS2	Post-meiotic segregation increased 2
PopPK	Pharmacokinetic(s)
PSUR	Periodic safety update report
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
RMP	Risk management plan
TNF	Tumour necrosis factor
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Jemperli
Active ingredient:	Dostarlimab
Decision:	Approved for provisional registration
Date of decision:	15 February 2022
Date of entry onto ARTG:	17 February 2022
ARTG number:	352631
, *Black Triangle Scheme:*	Yes. As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration.
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 4, 436 Johnston Street, Abbotsford VIC 3067
Dose form:	Solution for infusion (concentrate)
Strength:	500 mg/10 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.* *This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*
Route of administration:	Intravenous
Dosage:	Jemperli is administered as monotherapy via intravenous infusion and is to be given as cycles. The recommended dose and schedule are 500 mg dostarlimab administered over 30 minutes and given once

every 3 weeks, for the first 4 cycles. For Cycle 5 onwards, the recommended dose and schedule is 1000 mg given every 6 weeks. See the following for further details.

Cycle	*Week*	*Dosage*
1	1	**500 mg once every 3 weeks** (Each cycle = 3 weeks duration, from Cycle 1 to 4)
2	4	
3	7	
4	10	
5*	13*	**1,000 mg once every 6 weeks** (Each cycle = 6 weeks duration, from Cycle 5 onwards)
6	19	
7	25	

Administration of dostarlimab should continue according to the recommended dose and schedule until disease progression or unacceptable toxicity.

* Note: Cycle 5 should be given 3 weeks following Cycle 4. Cycle 6 and all subsequent cycles are given once every 6 weeks.

Dose modifications

Dose reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 2 of the Product Information. Detailed guidelines for the management of immune-related adverse reactions and infusion-related reactions are described in Section 4.4 Special Warnings and Precautions of the Product Information.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Jemperli (dostarlimab) 500 mg/10 mL, solution for infusion for the following proposed indication:

> *Jemperli is indicated as monotherapy for the treatment of patients with recurrent or advanced mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) endometrial cancer (EC) who have progressed on or after treatment with a platinum-containing regimen.*

Deficiencies in deoxyribonucleic acid (DNA) mismatch repair processes lead to an accumulation of mutations, which are typically short repetitive DNA sequences and single nucleotide substitutions. Lynch syndrome results from pathogenic germline mutations in any one of the five DNA mismatch repair genes, *MLH1, MSH2, MSH6, PMS2* and *EPCAM.* Such mutations are associated with an increased risk of cancer, most commonly colorectal and endometrial cancer; other cancers may occur, with differing frequencies depending upon the particular gene involved. Sporadic DNA mismatch repair deficient tumours arise where there is either epigenetic inactivation of these genes (for example, methylation of *MLH1*), or occasionally where somatic mutations may be acquired as part of an ultra-mutated phenotype arising from a pathogenic germline mutation in other genes such as those for DNA polymerase epsilon.

The most common subtype of endometrial cancer associated with DNA mismatch repair deficient tumours is endometrioid endometrial carcinoma. Endometrial cancers arising from mutations in the polymerase proofreading domains of the DNA polymerase epsilon gene have the highest number of somatic mutations (ultramutated) and are associated with a prolonged survival,[1] whereas those with mismatch repair deficiency due to the absence of *MLH1* or *MSH2* (either loss of heterozygosity in an individual with Lynch syndrome or somatic mutations or *MLH1* methylation) have an microsatellite instability (MSI)-high phenotype but are associated with a poorer prognosis. Germline pathogenic variants in either the *MSH6* or the *PMS2* gene are associated with an increased risk of endometrial cancer but do not necessarily give rise to an MSI-high phenotype and more often result in a MSI-intermediate or MSI-stable phenotype.[2]

Thus, a single test approach to identifying patients with mismatch repair deficiency has its limitations. Loss of protein expression of one of more of the four proteins by immunohistochemistry will detect the majority of cases and is recommended as routine to identify those requiring further testing for potential Lynch syndrome, but may yield false positive results where the protein is expressed but not functional. Assessing MSI status has significant limitations as only a proportion of endometrial cancer that harbours a mismatch repair deficiency will have an MSI-high phenotype reliance upon this to identify eligible patients will not identify the majority of *MSH6* or *PMS2* mutated endometrial cancers which more often have a microsatellite stable phenotype.[2]

Currently approved options for these patients as a second line therapy or beyond include the programmed cell death receptor-1 (PD-1) checkpoint inhibitor, Keytruda (pembrolizumab).[3] Keytruda is indicated for use in adult and paediatric patients for the treatment of unresectable or metastatic solid tumours that are determined as MSI-high or DNA mismatch repair deficient as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment

[1] Lu, K.H. and Broaddus, R.R. Endometrial Cancer, *N Engl J Med*, 2020; 383: 2053-2064.
[2] Latham, A. et al. Microsatellite Instability is Associated with the Presence of Lynch Syndrome Pan-Cancer, *J Clin Oncol*, 2019; 37(4): 286-295.
[3] Australian Product Information - Keytruda (pembrolizumab (rch)). Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01639-1&d=202106071016933 (accessed 3 June 2021).

options. This indication was approved via the TGA's provisional approval pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single arm trial. Sample sizes for individual tissue types were too small to provide data on clinical utility of the MSI/ DNA mismatch repair deficient tests for each of the tissue types, individually. The assumption that MSI-high/ DNA mismatch repair deficient status is predictive of the treatment effect of Keytruda for every tissue type has not been verified. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials. The Keytruda Product Information (PI) reports an objective response rate of 54% (95% confidence interval (CI): 33%, 74%) for MSI-high, including DNA mismatch repair deficient endometrial cancer.

Programmed cell death protein 1 (PD-1) is an immune checkpoint protein and cell surface receptor. Binding of the PD-1 ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2), to the PD-1 receptor found on T-cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. PD-1 and PD-L1 inhibitors are a class of drugs used in certain types of cancer that can block PD-1 and its inhibition of the immune system in order to activate the immune system to target tumour cells. The mode of action of Jemperli (dostarlimab) is consistent with other PD-1 inhibitors such as nivolumab (Opdivo) and pembrolizumab (Keytruda).

Dostarlimab is a humanised monoclonal antibody of immunoglobulin G4 (IgG4) isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2, releasing inhibition of PD-1 pathway mediated immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, similar submissions were under consideration in the United States of America (USA) (submitted on 19 December 2019), the European Union (EU) (submitted on 6 March 2020) and Brazil (submitted on 20 August 2020).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for Submission PM-2020-06455-1-4

Provisional review pathway

Description	Date
Determination (Provisional)	15 September 2020

Description	Date
Submission dossier accepted and first round evaluation commenced	1 February 2021
First round evaluation completed	30 June 2021
Sponsor provides responses on questions raised in first round evaluation	31 August 2021
Second round evaluation completed	6 October 2021
Delegate's Overall benefit-risk assessment	6 January 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 February 2022
Completion of administrative activities and registration on the ARTG	17 February 2022
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed as follows:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man, Methodological Consideration for Using Progression-Free Survival (PFS) or Disease-Free Survival (DFS) in Confirmatory Trials, EMA/CHMP/27994/2008/Rev.1, 13 December 2012.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the Evaluation of Anticancer Medicinal Products in Man, EMA/CHMP/205/95/Rev.4, 13 December 2012.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.

Quality

Dostarlimab is a glycosylated IgG4 monoclonal antibody that selectively binds to PD-1. The molecular weight is approximately 144 kD comprising 2 identical heavy chains and 2 identical light chains linked through intra- and inter-chain disulfide bonds.

The active ingredient was produced using recombinant DNA technology. Information about the manufacturing, storage and control facilities for the active substance have been provided.

The dostarlimab active substance is manufactured from Chinese hamster ovary cells in distinct batches.

Dostarlimab active substance is in drug substance bottles stored at and shipped in qualified containers that maintain temperatures of -35°C or less. From the available information the risk for patients due to substances leaching into dostarlimab active substance is negligible.

The overall quality of the active substance was demonstrated via adequate control of the starting material, control of critical steps and intermediates, process validation, extensive characterisation using orthogonal and state of the art analytical methods, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

The proposed release specification for the active substance is found acceptable, with respect to test methods chosen. The proposed specification limits are based on batch analysis and stability study results. This approach is considered acceptable.

Dostarlimab drug product is presented as a clear, to slightly opalescent colourless to yellow solution essentially free from visible particles, for intravenous administration. The primary container closure system for the dostarlimab 50 mg/mL drug product is a clear glass vial with a chlorobutyl elastomer stopper and an aluminium overseal with a flip-off cap. The drug product is provided as a sterile liquid solution for infusion and does not require reconstitution with a diluent.

All excipients are well known pharmaceutical ingredients and their quality is compliant with international pharmacopoeial standards. The container closure is considered suitable for its intended use as demonstrated by compatibility and stability studies.

The manufacturing process and finished product comparability studies were assessed and considered satisfactory. All analytical methods used for testing of the finished product are satisfactorily described in the dossier and non-compendial methods have been validated. The reference standard used in the testing and release of dostarlimab finished product is the same as the one used for the testing and release of dostarlimab active substance. The finished product quality control for batch release includes identity, potency, purity, impurities, sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and several other general tests.

Based upon stability data submitted by the sponsor, the recommended shelf life and storage conditions for the drug substance is 30 months when stored at -35°C to -90°C. The recommended shelf life and storage conditions for the drug product is 30 months when stored at 2°C to 8°C. No temperature excursion from the approved conditions is allowable.

One vial of Jemperli 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab (50 mg/mL) as the active ingredient and is formulated with sodium citrate dehydrate, citric acid monohydrate, arginine hydrochloride, sodium chloride, polysorbate 80 and water for injection.

The finished product is supplied in a sealed 10 mL Type I borosilicate clear glass vial, with a grey stopper and an aluminium flip-off cap.

Precautions and conditions for storage are as follows:

- Jemperli should be store in a refrigerator 2°C to 8°C and not frozen. Store in the original carton until time of preparation in order to protect from light.
- The prepared dose may be stored either
  - At room temperature up to 25°C for no more than 6 hours from the time of dilution until the end of infusion.; or
  - under refrigeration at 2°C to 8°C for no more than 24 hours from time of dilution until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- After preparation of infusion:
  - To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation.
  - If not used immediately, in-use chemical and physical stability have been demonstrated for up to 24 hours at 2°C to 8°C and up to 6 hours at room temperature (up to 25°C) from time of vial puncture to the end of administration. Due to the lack of preservative, the product must not be used beyond these storage times. Product is for single use in one patient only, discard any residue.

Conclusions and recommendation

The quality evaluator recommended approval of dostarlimab provided the Good Manufacturing Practice (GMP)[4] certification for all sites is obtained. GMP certification has been provided to the TGA prior to approval.

Quality related conditions of registration

- Laboratory testing and compliance with Certified Product Details (CPD)
  - All batches of Jemperli dostarlimab 500 mg solution for infusion 10 mL vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in portable document format (PDF), for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to

[4] **Good Manufacturing Practice (GMP)** describes a set of principles and procedures that when followed helps ensure that therapeutic goods are of high quality.

finished product specifications and test methods are approved in a Category 3 application;[5] or notified through a self-assessable change.

The CPD should be emailed to biochemistry.testing@health.gov.au as a single PDF document.

Nonclinical

The nonclinical evaluation raised no objections to the registration of dostarlimab.

The key findings from the nonclinical evaluation are summarised below.

The overall quality of the nonclinical dossier was high, all pivotal safety related studies were Good Laboratory Practice;[6] compliant and the dossier was in accordance with the relevant International Council for Harmonisation (ICH);[7] guideline.[8]

The primary pharmacology studies broadly supported the proposed mechanism of action for dostarlimab. In *in vitro* binding studies, dostarlimab demonstrated binding to human PD-1 at an average `half maximal effective concentration (EC_{50}) of 2.8 nM and, blocking of PD-L1 and PD-L2 binding with an half maximal inhibitory concentration (IC_{50}) of 1.8 nM and 1.5 nM, respectively. The dissociation constant (K_D) for PD-1 receptor binding was 2 to 4 nM, which is comparable to that of nivolumab (at 3.06 nM). An *in vitro* functional assay found that dostarlimab enhanced human CD4+ T cell activation based on interleukin (IL)-2 secretion in mixed lymphocyte reaction assays (EC_{50} 0.13 to 2 nM, comparable to nivolumab). Cross species reactivity studies demonstrated high levels of cynomolgus monkey and human peripheral blood mononuclear cells (PBMC) binding compared with mouse, rat and dog. The extent of occupancy and saturation of binding was comparable between monkey and human PBMCs. These findings support the use of cynomolgus monkey in the toxicology studies. *In vivo*, the surrogate dostarlimab antibody decreased tumour load and increased survival following murine colon carcinoma grafts.

The pharmacokinetics (PK) of dostarlimab in monkeys and human subjects was generally consistent with the protein nature of the drug.

Dostarlimab is unlikely to demonstrate complement dependent cytotoxicity due to negligible binding to C1q. Dostarlimab demonstrated a low affinity for Fc-γ receptor compared with immunoglobulin G1 isotype (IgG1) antibodies as control, thus suggesting lower potential for antibody-dependent cell mediated cytotoxicity than is generally found with IgG1 antibodies. Dostarlimab is also unlikely to induce excessive cytokine release, since *in vitro* incubation with donor PBMCs did not induce significant production of interferon (IFN) gamma, tumour necrosis factor (TNF) alpha, and interleukin (IL)-2, IL-4, IL-6, and IL-10. Immunohistochemical assays examining cross reactivity revealed no off-target binding for dostarlimab, with staining limited to CD4+ T-cells, CD8+ T-cells, natural killer T-cells, B-cells, and monocytes, consistent with the known tissue expression of PD-1.

[5] A **Category 3 application** relates to updates to the quality data of medicines already included on the Australian Register of Therapeutic Goods (ARTG) which, in the opinion of the TGA, do not need to be supported by clinical, non-clinical or bioequivalence data.
[6] **Good Laboratory Practice (GLP)** is a code of standards following the International Council on Harmonisation (ICH) relevant to testing of medicines in laboratories during drug development.
[7] The **International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.
[8] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.

Examination of safety pharmacology (incorporated into the repeat dose toxicity studies) revealed no effects of dostarlimab on central nervous system, respiratory function, or the electrocardiogram in monkeys.

Following repeat dose administration to monkeys, the increase in dostarlimab exposure was broadly dose proportional from 10 mg/kg, 30 mg/kg through to 100 mg/kg weekly doses. No gender differences were observed in the pharmacokinetic (PK) parameters. An increase in exposure over the treatment period suggested an accumulation of dostarlimab, which also occurs in humans. While the presence of anti-dostarlimab antibodies was detected in most animals, the titre was generally low. No difference in exposure (by area under the curve) were observed between dose matched anti-drug antibody (ADA) positive animals compared with ADA negative animals. Thus, the ADA response in these animals did not appear to impact the PK of dostarlimab.

No local tolerance issues were identified in the repeat dose toxicity studies.

Repeat dose toxicity studies by the intravenous route were conducted in cynomolgus monkeys (up to 13 weeks). The studies were adequately conducted, achieving high relative exposures. A single incidence of severe skin irritation was noted which resulted in premature termination of the animal.

Minimal to moderate mononuclear cell infiltrates were observed in most tissues in the 13-week monkey study, with mild to moderate mononuclear cell infiltrates observed in kidney, liver and heart of some animals in the mid-dose and high dose groups. The kidney, liver and heart findings are likely to be dostarlimab related, or a dostarlimab related exacerbation of background finding for this species. The cell infiltrates could be attributed to a pharmacological effect of dostarlimab. However, an ADA-related effect could not be precluded given the higher incidence of ADAs detected in these dose groups, despite the low ADA titres throughout the study. Minimal perivascular mononuclear cell infiltrate was also observed in brain of some mid-dose and high dose animals. The observed effects were likely due to the pharmacological effect of dostarlimab.

No dedicated immunotoxicity studies were performed. However, endpoints related to assessment of immunotoxicity were examined in the *in vitro* pharmacology studies and as part of single or repeat dose toxicity studies in cynomolgus monkeys. While the *in vitro* studies (binding to FcγR1 (CD64), binding to complement component C1q, and effect on cytokine release by human PBMCs) did not demonstrate significant immunotoxicity potential, skin findings consistent with the features of an immune reaction were noted in some animals in the 13-week repeat dose toxicity study. In addition, sporadic microscopic findings of an immune mediated nature were noted in the kidney, liver, or heart of one to two animals per group dosed with dostarlimab. PD-L1 blockade has also been shown to supress immunity of mice against intracellular bacterial infection by *Listeria monocytogenes* suggesting increased severity of some infections, and PD-1 deficient mice with tuberculosis infection have been shown to have reduced survival compared with wildtype mice associated with heightened inflammatory responses. Therefore, treatment with dostarlimab has the potential for enhanced immune response to infection or impaired antimicrobial immune responses.

No genotoxicity studies were conducted. Given the protein nature of the drug, this is considered acceptable. No carcinogenicity studies were conducted. No proliferative lesions were seen in the repeat dose toxicity study.

Reproductive and development studies were not performed owing to the potential adverse effects of the blockade of PD-1/PD-L1 (PD-1 ligand) pathway on the immune tolerance at the maternal-fetal interface; this is reasonable.

The sponsor has proposed Pregnancy Category D.[9] While no dedicated reproductive development studies were conducted, given the importance of checkpoint inhibitors at the maternal fetal interface, the proposed pregnancy classification is acceptable. This category is also consistent with other products in this drug class, such as the PD-(L)1 inhibitors pembrolizumab, cemiplimab and nivolumab.

Dostarlimab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Clinical

Summary of clinical studies

The following Phase I clinical study is relevant to this submission: Study 4010-01-001 (also known as the GARNET trial)

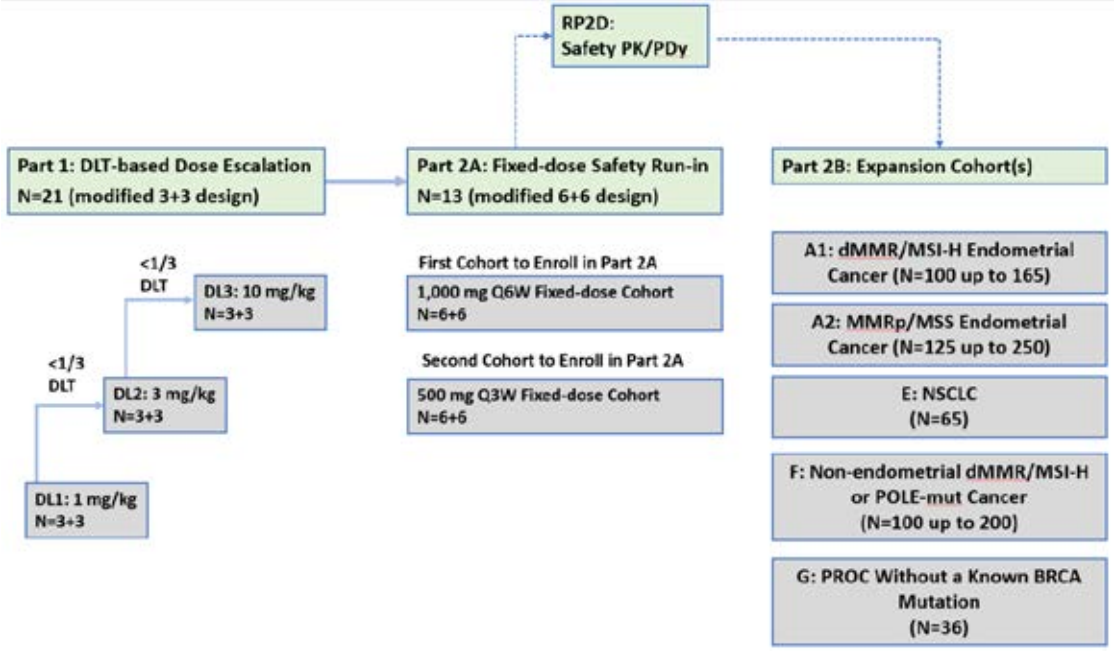
Study 4010-01-001 (GARNET trial)

The GARNET trial provides the pharmacology and clinical data that support the requested indication. This is an ongoing, multicentre, multinational, open label, first in human study with dose escalation and expansion cohorts in patients with recurrent or advanced solid tumours, conducted in two main parts.

Part 1 of the study (ascending dose study) provides safety, and pharmacokinetic (PK) and pharmacodynamics (PD) data about dostarlimab. Part 2 of the study is divided into two parts, Part 2A and Part 2B. Part 2A investigated the safety, tolerability and added further PK data for two flat dosing cohorts. Part 2B investigated the clinical activity by solid tumour type in the recommended therapeutic dosing of 500 mg every 3 weeks for 4 cycles followed by 1,000 mg every 6 weeks for all subsequent cycles, for up to 2 years in the study, but longer if the treating physician and the sponsor agree that the subject continues to benefit.

[9] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Figure 1: Study 4010-01-001 (GARNET trial) Study schema



Abbreviations: DL = dose level; DLT = dose-limiting toxicity; dMMR = DNA mismatch repair deficient; MSI-H = microsatellite instability-high; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSCLC = non-small cell lung cancer; N = number (of patients); PDy = pharmacodynamic; PK = pharmacokinetic; POLE-mut = polymerase epsilon mutation; Q3W = every 3 weeks; Q6W = every 6 weeks; RP2D = recommended Phase II dose, also known as recommended therapeutic dose: 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W thereafter.

Pharmacology

Dostarlimab is a humanised monoclonal antibody of the IgG4 isotype. Dostarlimab binds with high affinity and specificity to PD-1, a cell surface receptor expressed on activated T-cells.

The pharmacokinetics were described from the GARNET trial observations. In Part 1, 6 patients were dosed at 1 mg/kg (3 patients were dose-limiting toxicity evaluable, 3 were PK/PD evaluable), 3 patients were dosed at 3 mg/kg bodyweight, and 12 patients were dosed at 10 mg/kg (6 dose-limiting toxicity evaluable, 6 PK/PD evaluable).

In Part 2A, 6 patients received 500 mg every 3 weeks and 7 patients received 1,000 mg every 6 weeks. The PK was further characterised using population pharmacokinetic (PopPK) modelling. The PD were described from the GARNET trial and exposure response analyses.

Features of the pharmacology described in the submission include:

- Maximum observed plasma concentration (C_{max}) occurs at the end of the 30-minute infusion, with a bi-exponential decline in concentration.
- Maximum concentration, area under the concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$), and area under the concentration time curve from time zero to the end of the dosing period ($AUC_{0\text{-}tau}$) were dose proportional over the 1 mg/kg to 10 mg/kg dose range.
- The Cycle 1 geometric mean half-life ranged between 244.4 to 491.0 hours (10.2 to 20.5 days) for Part 1 and Part 2A.

- Following multiple dose administration in Part 1 and 2A, based on limited available data, accumulation ranged between 180% to 374% for $AUC_{0\text{-}tau}$ and 126% to 259% for C_{max}.
- The dostarlimab PK profile was described in a two-compartment population pharmacokinetics (PopPK model), with time-dependent linear elimination. Time dependency in clearance was described by a sigmoid E_{max} model.
- Dostarlimab clearance at steady state (full effect of time dependent clearance) and volume of distribution at steady state were estimated to be 0.00682 L/h and 5.26 L, respectively, with a half-life of 23.5 days.
- Linear regression of natural log transformed clearance versus natural log transformed body weight indicated a trend of increasing clearance with increasing baseline body weight. However, this relationship was not statistically significant at the p = 0.05 level. This is the basis of progressing flat dosing.
- No adjustment in dose or dosing regimen is deemed warranted based on other covariates, including age, race, gender, or ethnicity.
- Time varying albumin demonstrated the largest impact on exposure with 25.9% lower and 15.5% higher area under the concentration time curve (AUC) in a typical patient with the fifth and ninety-fifth percentiles of the covariate value, respectively.
- No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found on dostarlimab PK. Therefore, no dose adjustment is needed for patients with mild or moderate renal impairment or for patients with mild hepatic impairment. There are limited data in patients with severe renal impairment, end stage renal disease undergoing dialysis and moderate hepatic impairment and no data in patients with severe hepatic impairment.
- Dostarlimab produces a sustained, consistent engagement of the receptor and functional effects at all dose levels studied. The regimen of 500 mg every 3 weeks followed by 1,000 mg every 6 weeks results in full target engagement for the duration of treatment.
- The assessment of the exposure response relationships is limited because much of the observational data are derived using the single dosing regimen in the main part of the study. Nevertheless, univariate logistic regression of objective response rate in patients from Part 2B of the GARNET trial showed no exposure response relationship for the full dataset nor for the subgroup analysis with only endometrial cancer patients. Assessment of duration of response exposure is limited by the smaller number of patients with duration of response reported (compared with overall response rate) and the truncation of duration of response at the time of the data cut-off. None of the tested exposure metrics had a statistically significant relationship with any of the five most common drug related adverse events.
- There were no electrocardiogram changes that suggested a clinically signification prolongation of QT interval corrected for heart rate using Fridericia's formula (QTcF);[10] or pro-arrhythmic effect of dostarlimab at the concentrations achieved with the currently proposed dosing regimen.

[10] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The QTcF is the QT interval corrected for heart rate according to Fridericia's formula.

Immunogenicity

The clinical evaluation found limitations in the immunogenicity findings in the submission and based on the current characterisation was unable to draw any conclusions regarding the impact on safety and efficacy. In Part 2B of the study incidence of treatment-emergent positive antidrug antibody (ADA) samples was low (8 patients, 2.1%), however 26% of patients had no post-baseline measurement addition uncertainty to this finding. In Part B, 4 of the 8 patients with ADA had neutralising antibodies but most of these patients had pre-existing ADA with no post-baseline change in titre. Due to a limited number of ADA positive (neutralising antibody negative or positive) pre-dose data, the clinical evaluator was unable to determine the impact of immunogenicity on PK.

Dose for the main study

The objectives of the GARNET trial (Study 4010-01-001) included determining a safe and efficacious dose of dostarlimab in participants with recurrent or advanced solid tumours. PK and PD data from the initial Part 1 of the study informed the doses selected for assessment in Part 2A, which were then used to refine the dose schedule applied in the expansion cohort in Part 2B.

Part 2B of the study explores initial signs of efficacy in prespecified tumour types using the recommended Phase 2 dose determined from Part 1 and Part 2A. In Part 2B of the study, patients received 500 mg every 3 weeks for 4 cycles followed by 1,000 mg every six weeks thereafter, which was the recommended therapeutic dose determined from Part 1 and Part 2A data.

Dose selection was guided by receptor occupancy analyses in peripheral blood cells that suggested full receptor occupancy occurred at dostarlimab concentrations of 2.435 µg/mL. The population PK model predicted steady state trough concentrations of 51.1 and 29.2 µg/mL for the 500 mg every 3 weeks and 1,000 mg every 6 weeks dosing respectively.[11]

Efficacy

Following the second round of evaluation, the sponsor has narrowed the requested scope of the indication to include only patients whose tumours are mismatch repair deficient. Limited results from the unknown DNA mismatch repair/microsatellite instability (MSI)-high status patients (2 patients) are presented for completeness in the Delegate's overview, but the results focus on the requested DNA mismatch repair deficient population.

Part 2B of the study, the most relevant for the efficacy assessment supporting the requested indication, was initiated at 123 sites in 9 countries. The first patient enrolled on 10 April 2017. The data cut-off date for the clinical study report dated 16 November 2020 is 1 March 2020. The submission includes an analysis of all of Cohort A but only Cohort A1 relates to the requested indication, so is the main focus of the efficacy and safety summaries in this document is Cohort A1.

Study treatment

Dostarlimab 500 mg every 3 weeks (Day 1 of each 21-day cycle) for the first 4 cycles then 1,000 mg every 6 weeks thereafter.

[11] Sponsor clarification: the sponsor wished to comment that the observed mean trough concentration values for patients in Part 2B of this study are greater than the PK/PD model predicted concentrations that are required for full target engagement of 54 µg/mL at the tumour site and 18 µg/mL at peripheral sites.

Protocol amendments

Part 2B participants were enrolled from Global Amendment 2 (Version 3.0, October 2016). Key protocol amendments are shown in the following table.

Table 2: Study 4010-01-001 (GARNET trial) Key protocol amendments

Amendment	Change relevant to this submission
Global Amendment 2 (Version 3.0, October 2016)	To split the endometrial cancer Cohorts into A1 and A2 based on MSI status (MSI-H patients were placed in Cohort A1) To clarify allowed prior treatments, To exclude endometrial sarcoma, To require known tumour MSI status prior to the first dose of study treatment.
Protocol Version 4.0 (September 2017)	Allow interim analysis of patients with MSI-H from Cohort A1 and F, combined for administrative purposes.
Global Amendment 4 (Version 5.1, July 2018)	Increased the enrolment of Cohort A1 based on an interim analysis Increased Cohort A2 to allow a more precise estimate of objective response rate, without changing the overall sample size of the study.
Global Amendment 5 (Version 6.0, May 2019)	Required tumour status to be determined by MMR status based on the results from immunohistochemistry testing. Cohort A1 included patients with dMMR endometrial cancer or in the absence of known MMR status, MSI-H endometrial cancer. Cohort A2 included patients s with MMR-proficient endometrial cancer or, in the absence of known MMR status, Microsatellite Stable endometrial cancer. Sample size of Cohort A1 also increased with the potential for up to 165 patients. Patient reported outcome became an exploratory endpoint.
Global Amendment 6 (Version 7.0, January 2020)	Added Cohort G Added safety and tolerability as primary objectives of Part 2B Added two further interim analyses of Cohorts A1 and F after 200 and 300 participants with measurable disease at Baseline and had at least 24 weeks of follow-up.

Abbreviations: dMMR = DNA mismatch repair deficient; MMR = DNA mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability-high.

Sample size

The maximum enrolment for Part 2B is up to 716 patients. A cohort A1 sample size of approximately 100 participants and with a potential for up to 165 participants. With 65 participants Cohort A1 had 92% power to rule out a ≤ 20% objective response rate (null hypothesis; expected for conventional therapy) when the true objective response rate is 40% at the 2.5% Type I error rate (one-sided).

Inclusion and exclusion criteria

The inclusion and exclusion criteria are included in Table 3. This table includes the changes made at Global Amendment 6 (discussed in Table 2, above).

Table 3: Study 4010-01-001 (GARNET trial) Key inclusion and exclusion criteria for Cohort A1

Inclusion criteria	Exclusion criteria
Age ≥ 18 years Advanced/metastatic dMMR/MSI-H endometrial cancer with measurable disease per RECIST 1.1 and disease progression on or after platinum-based chemotherapy, but not more than 2 lines of anticancer therapy for recurrent/advanced disease (prior hormone therapies acceptable). All endometrial cancers except endometrial sarcoma (including carcinosarcoma), two scans showing increase in tumour measurement and at least one lesion confirmed by central review. dMMR/MSI-H screen locally using immunohistochemistry, polymerase chain reaction or next generation sequencing but eligibility determine by MMR immunohistochemistry results. Archival tissue (formalin fixed, paraffin embedded) or new biopsy prior to study treatment No pregnant or of nonchildbearing potential ECOG;[12] 0 or 1 Adequate organ function	Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 Uncontrolled central nervous system metastases Known additional malignancy (except basal cell carcinoma skin or squamous cell carcinoma of skin with curative therapy or carcinoma in situ of cervix) Poor risk due to underlying medical risk (examples given) Pregnant or breastfeeding Diagnosed immunodeficiency or receiving immunosuppressive therapy within 7 days of first study treatment Known human immunodeficiency virus, hepatitis B, or hepatitis C Active autoimmune disease requiring systemic treatment. Replacement therapy (thyroid replacement, insulin or physiological doses of corticosteroids acceptable). Interstitial lung disease Not recovered to ≤ Baseline or Grade 1 event from radiation or systemic anticancer therapy, or surgery Other anticancer therapy within 21 days or 5 half-lives of the therapy

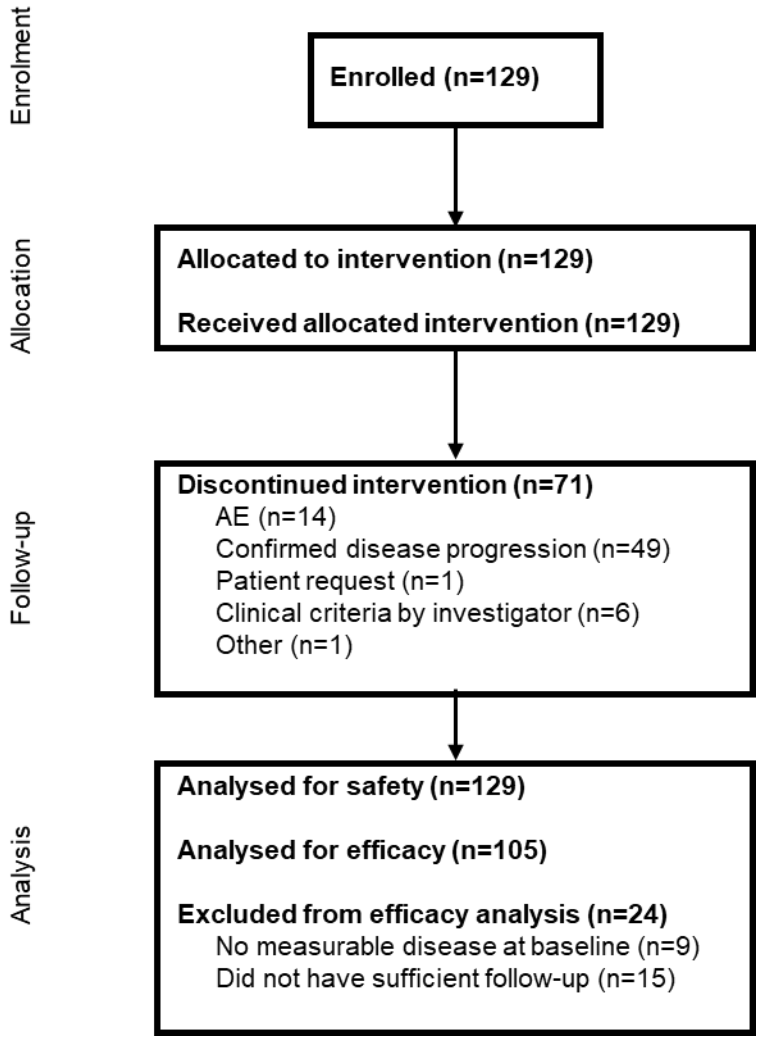
Abbreviations: dMMR = DNA mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; MMR = DNA mismatch repair; MSI-H = microsatellite instability-high; PD-1 = programmed cell death receptor-1; PD-L1 = programmed cell death ligand-1; PD-L2 = programmed cell death ligand-2; RECIST = Response Evaluation Criteria In Solid Tumours criteria.

Patient flow

Figure 2 below summarises the participant flow through the study.

[12] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 – Dead

Figure 2: Study 4010-01-001 (GARNET trial) Participant flow



Abbreviations: AE = adverse event; n = number of subjects in group.

Baseline characteristics

The baseline characteristics of patients in Cohort A1 are summarised in Table 4, below.

Table 4: Study 4010-01-001 (Garnet trial) Baseline characteristics for Cohort A1

		dMMR (n=103)	MMR-unknown / MSI-H (n=2)	Total (n=105)
Age	Median, years (range)	65 (39, 80)	54 (54, 54)	64 (39, 80)
Age group	<65 years	51 (49.5%)	2 (100%)	53 (50.5%)
	≥65 to < 75 years	41 (39.8%)	0	41 (39.0%)
	≥ 75 years	11 (10.7%)	0	11 (10.5%)
Race	White	80 (77.7%)	2 (100%)	82 (78.1%)
	Black	2 (1.9%)	0	2 (1.9%)

		dMMR (n=103)	MMR-unknown / MSI-H (n=2)	Total (n=105)
	Asian	4 (3.9%)	0	4 (3.8%)
	American Indian or Alaska Native	3 (2.9%)	0	3 (2.9%)
	Not reported	14 (13.6%)	0	14 (13.3%)
ECOG status;[12]	0	40 (38.8%)	2 (100%)	42 (40.0%)
	1	63 (61.2%)	0	63 (60.0%)
Disease subtype	Endometrial carcinoma type I	70 (68.0%)	1 (50%)	71 (67.6%)
	Endometrial carcinoma type II	32 (31.1%)	1 (50%)	33 (31.4%)
	Serous carcinoma	4 (3.9%)	0	4 (3.8%)
	Clear cell carcinoma	1 (1.0%)	0	1 (1.0%)
	Squamous carcinoma	1 (1.0%)	0	1 (1.0%)
	Undifferentiated	4 (3.9%)	0	4 (3.8%)
	Mixed	4 (3.9%)	0	4 (3.8%)
	Unspecified	14 (13.6%)	0	14 (13.3%)
	Other;[a]	4 (3.9%)	1 (50.0%)	5 (4.8%)
	Unknown	1 (1.0%)	0	1 (1.0%)
Most recent FIGO stage	Stage I	12 (11.7%)	0	12 (11.4%)
	Stage II	3 (2.9%)	1 (50.0%)	4 (3.8%)
	Stage III	16 (15.5%)	0	16 (15.2%)
	Stage IV	70 (68.0%)	1 (50.0%)	71 (67.6%)
	Unknown	2 (1.9%)	0	2 (1.9%)
Grade of Disease	Grade 1	31 (30.1%)	0	31 (29.5%)
	Grade 2	40 (38.8%)	1 (50.0%)	41 (39.0%)
	Grade 3	27 (26.2%)	1 (50.0%)	28 (26.7%)
	Not assessable	5 (4.9%)	0	5 (4.8%)

Abbreviations: dMMR = DNA mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; MMR = DNA mismatch repair; MSI-H = microsatellite instability-high; n = number of subjects in group.

a. an 'Other' may include adenocarcinoma; adenocarcinoma with ambiguous differentiation; biopsies showed a high-grade adenocarcinoma, which can be seen with tumours of Mullerian origin; carcinoma epidermoid; endometrial adenocarcinoma; endometrial adenocarcinoma not otherwise specified; endometrial neuroendocrine carcinoma; endometrioid adenocarcinoma; high-grade uterine carcinoma; moderately differentiated adenocarcinoma; papillary serous carcinoma; and undifferentiated clear cell carcinoma.

All patients had prior anticancer therapy (62.9% had one prior regimen, 25.7% had two prior regimens, 8.6% had 3 prior regimens, and 2.9% had ≥ 4 prior regimens), 90.5% had surgery and 70.5% had prior radiotherapy.

The sponsor used the Ventana MMR RxDx Panel assay to confirm the DNA mismatch repair deficient status of the tumours.[13]

Primary endpoint

The interim analysis with a data cut-off date was the basis of the clinical evaluation and the clinical evaluator's recommendations.

The median duration of follow-up at the data cut-off date was 16.3 months.

The primary efficacy endpoint was objective response rate, defined as the proportion of participants achieving best overall response of complete response or partial response per Response Evaluation Criteria In Solid Tumours (RECIST);[14] version 1.1 by blinded independent centralised review. Results of the 105 patients are presented in Table 5.

Table 5: Study 4010-01-001 (GARNET trial) Efficacy for Cohort A1

Variable	dMMR (N=103)	MMR-unk/ MSI-H (N=2)	Total (N=105)
BOR by RECIST v1.1, n (%)			
CR	11 (10.7)	0	11 (10.5)
PR	35 (34.0)	1 (50.0)	36 (34.3)
SD	13 (12.6)	0	13 (12.4)
PD	39 (37.9)	0	39 (37.1)
NE	3 (2.9)	0	3 (2.9)
Not done	2 (1.9)	1 (50.0)	3 (2.9)
Confirmed ORR by RECIST v1.1, n (%)	46 (44.7)	1 (50.0)	47 (44.8)
95% CI[a]	(34.9, 54.8)	(1.3, 98.7)	(35.0, 54.8)
Response ongoing[b]	41 (89.1)	1 (100)	42 (89.4)
DCR by RECIST v1.1, n (%)	59 (57.3)	1 (50.0)	60 (57.1)
95% CI[a]	(47.2, 67.0)	(1.3, 98.7)	(47.1, 66.8)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; dMMR = DNA mismatch repair deficient; MMR-unk = unknown mismatch repair tumour status; MSI-H = microsatellite instability high; N= number of subjects; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumours version 1.1; SD = stable disease.

Objective response rate (ORR) was defined as the percentage of participants with a RECIST;[14] v1.1 confirmed CR or PR. DCR was defined as the percentage of participants with a RECIST v1.1 confirmed PR, confirmed CR, or SD. Response assessments were based on blinded independent central review (BICR).

a Exact 2-sided 95% CI for the binomial proportion.

[13] The **Ventana MMR RxDx Panel** is a laboratory test designed to detect mismatch repair (MMR) proteins (MSH6, PMS2, MSH2 and MLH1) in patients diagnosed with solid tumours that have reoccurred multiple times (recurrent) or those who have advanced solid tumour growth.

[14] The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

b All responders who have not yet died or progressed (including clinical progression); the denominator for the percentage is the number of responders.

At the data cut-off the median duration of response had not been reached, but 78.3% of responders with DNA mismatch repair deficient endometrial cancer had a minimum duration of response that exceeded 6 months. At the time of the data cut-off, 89.1% of responders had an ongoing response.

Table 6 summarises the duration of response data for Cohort A1 for patients who had an objective response summarised in Table 5.

Table 6: Study 4010-01-001 (GARNET trial) Duration of response for Cohort A1

Variable	dMMR (N=46)	MMR-unk/ MSI-H (N=1)	Total (N=47)
Median duration of follow-up (months)	16.3	11.1	16.3
DOR status, n (%)			
Events observed	5 (10.9)	0 (0.0)	5 (10.6)
Censored	41 (89.1)	1 (100.0)	42 (89.4)
DOR (months)			
Min, max	2.63, 28.09+	19.32+, 19.32+	2.63, 28.09+
Quartile (95% CI[a])			
25%	NR (9.8, NR)	NR (NR, NR)	NR (9.8, NR)
50%	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
75%	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Duration ≥6 months, n (%)	36 (78.3)	1 (100.0)	37 (78.7)
DOR distribution function (95% CI)			
Month 6	97.8 (85.6, 99.7)	100.0 (100.0, 100.0)	97.9 (85.8, 99.7)
Month 12	90.6 (72.9, 97.0)	100.0 (100.0, 100.0)	90.9 (73.7, 97.1)
Month 18	79.2 (54.9, 91.3)	100.0 (100.0, 100.0)	80.1 (56.8, 91.7)

Abbreviations: CI = confidence interval; dMMR = DNA mismatch repair deficient; DOR = duration of response; max = maximum; min = minimum; MMR-unk = unknown mismatch repair tumour status; MSI-H = microsatellite instability-high; N = number of subjects; NR = not reached.

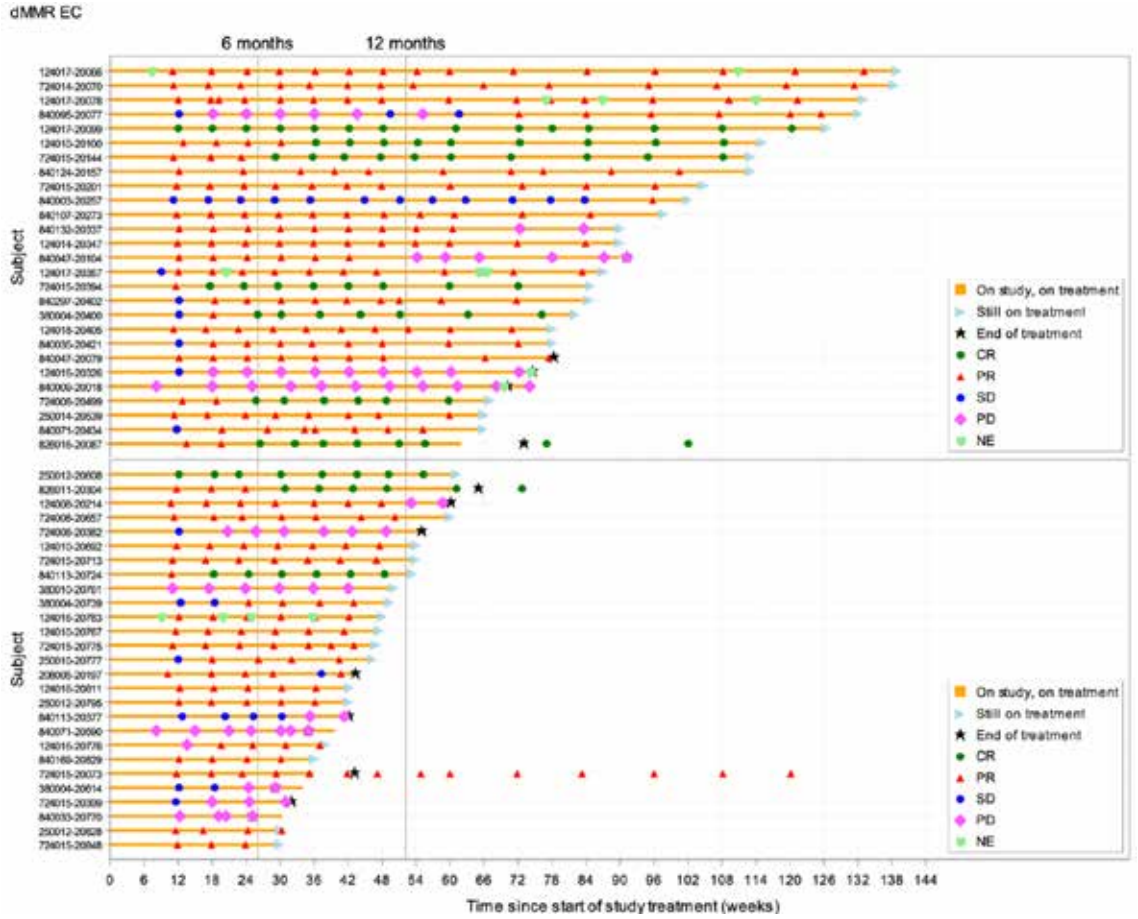
Duration of response (DOR) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) was based on blinded independent central review (BICR). A '+' indicates that the participant's response is ongoing.

a 95% CIs were generated using the method of Brookmeyer and Crowley (1982).[15]

These data for DNA mismatch repair deficient patients are also presented in a swimmer's plot (see Figure 3 below).

[15] Brookmeyer, R. and Crowley, J. A Confidence Interval for the Median Survival Time, Biometrics, 1982; 38(1): 29-41.

Figure 3: Study 4010-01-001 (GARNET trial) Duration of treatment (Swimmer's plot) for Cohort A1



Abbreviations: CR = complete response; dMMR = DNA mismatch repair deficient; EC = endometrial cancer; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

It the last cycle of treatment is ≤ 4 cycles, duration of treatment = last dose date minus start date plus 21 weeks. If the last cycle of treatment is ≥ 5 cycles, duration of treatment = last dose date minus start date plus 42 weeks.

Data cut-off date: 1 March 2020.

At the time of the data cut-off, the median overall survival had not been reached in participants with DNA mismatch repair deficient endometrial cancer. Kaplan-Meier estimates of the probability of survival were 80.7% at Month 6, 74.9% at Month 9, and 68.5% at Month 12 in participants with DNA mismatch repair deficient endometrial cancer in the primary efficacy analysis set. The median progression free survival was 5.5 months in participants with DNA mismatch repair deficient endometrial cancer.

The clinical evaluation raised concerns about the use of polymerase chain reaction or next generation sequencing to detect microsatellite instability (MSI)-'high' status. This issue is considered resolved in the context of the submission after the narrowing of the scope of the indication to omit patients identified by MSI-high tumour status from the indication.

In response to questions the sponsor presented objective response rate results for each of the actual DNA mismatch repair proteins missing.

Table 7: Study 4010-01-001 (GARNET trial) Response to questions tumour response by mismatch repair protein loss

dMMR EC (N=103)

Variable	MLH1 (N=82)	MSH2 (N=21)	MSH6 (N=22)	PMS2 (N=83)
Best Overall Response by RECIST v1.1 [n(%)][a]				
CR	8 (9.8)	3 (14.3)	3 (13.6)	9 (10.8)
PR	27 (32.9)	7 (33.3)	6 (27.3)	28 (33.7)
SD	7 (8.5)	5 (23.8)	6 (27.3)	9 (10.8)
PD	35 (42.7)	5 (23.8)	7 (31.8)	33 (39.8)
Not Evaluable	3 (3.7)	0	0	2 (2.4)
Not Done	2 (2.4)	1 (4.8)	0	2 (2.4)
Confirmed Objective Response Rate by RECIST v1.1 (ORR)				
n(%)	35 (42.7)	10 (47.6)	9 (40.9)	37 (44.6)
95% CI[b]	(31.8, 54.1)	(25.7, 70.2)	(20.7, 63.6)	(33.7, 55.9)
Response Ongoing[c]	31/35 (88.6)	9/10 (90.0)	8/9 (88.9)	33/37 (89.2)
Disease Control Rate by RECIST v1.1 (DCR)				
n(%)	42 (51.2)	15 (71.4)	15 (68.2)	46 (55.4)
95% CI[b]	(39.9, 62.4)	(47.8, 88.7)	(45.1, 86.1)	(44.1, 66.3)

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; dMMR = DNA mismatch repair deficient; EC = endometrial cancer; MLH1 = *mutL* homologue 1; MSH2 = *mutS* homologue 2; MSH6 = *mutS* homologue 6; n= number of subjects in group; ORR = objective response rate; PD = progressive disease; PMS2 = post-meiotic segregation increased 2; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SD = stable disease.

Objective response rate (ORR) is defined as the percentage of patients with a RECIST version 1.1 confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST version 1.1 confirmed PR, confirmed CR, SD. Response assessments are based on blinded independent central review (BICR).

a Complete response (CR), PR, SD and PD.

b Exact 2-sided 95% confidence interval for the binomial propotion.

C All responders who have not yet died or progressed (including clinical progression), denominator for percentage is number of responders.

Data cut-off date: 1 March 2020.

The clinical evaluator noted that MSH6 binds to MSH2 and PMS2 binds to MLH1, so if MSH2 or MSH1 is missing the specimen will not stain for it or its partner protein. Similarity across the subgroups by DNA mismatch repair deficient protein was noted, including the persistence in response in the responder analysis.

Safety

Exposure

Direct support for the safety of dostarlimab in the proposed population was derived from 129 patients from Cohort A1. Overall, 515 patients have been exposed to at least one dose of dostarlimab at the recommended dose.

In the Cohort A1 safety set for the indication the median duration of exposure was 26.0 weeks (range: 3.0 to 138.9 weeks). Only 35 patients (27.1%) had an exposure of greater than 54 weeks, and 53.5% of the dostarlimab patients were exposed for between 19 and 24 weeks.

Just over half of all participants had discontinued treatment, and approximately one-third had discontinued the study. The most common reason for treatment discontinuation was disease progression (38.0%), and the most common reason for study discontinuation was death (27.9%).

Adverse events

Table 8: Study 4010-01-001 (GARNET trial) Summary of safety information

	dMMR (n = 126)	MMR-unknown / MSI-H (n = 3)	Cohort A1 Total (n = 129)
Treatment-emergent adverse events			
Any treatment-emergent adverse event	120 (95.2%)	3 (100%)	123 (95.3%)
Most common adverse events in 10% or more of Cohort A1			
Nausea	31.7%	66.7%	32.6%
Diarrhoea	27.8%	33.3%	27.9%
Anaemia	27.8%	0	27.1%
Fatigue	24.6%	33.3%	24.8%
Asthenia	22.2%	0	21.7%
Constipation	19.8%	0	19.4%
Vomiting	19.0%	0	18.6%
Abdominal pain	16.7%	0	16.3%
Cough	15.1%	66.7%	16.3%
Arthralgia	14.3%	66.7%	15.5%
Urinary tract infection	15.1%	33.3%	15.5%
Back pain	15.1%	0	14.7%
Pruritus	14.3%	0	14.0%
Decreased appetite	12.7%	0	12.4%
Myalgia	10.3%	33.3%	10.9%
Pyrexia	10.3%	33.3%	10.9%
Oedema peripheral	8.7%	66.7%	10.1%
Rash	10.3%	0	10.1%
Grade 3 to 5 events	48.4%	33.3%	48.1%
Most common adverse events of Grade 3 severity or higher (in 2% or more of Cohort A1)			
Anaemia	15.1%	0	14.7%
Abdominal pain	5.6%	0	5.4%

Hyponatraemia	3.2%	33.3%	3.9%
Acute kidney injury	3.2%	0	3.1%
Back pain	3.2%	0	3.1%
Pulmonary embolism	3.2%	0	3.1%
Sepsis	3.2%	0	3.1%
Alanine aminotransferase increased	2.4%	0	2.3%
Diarrhoea	2.4%	0	2.3%
Hypertension	2.4%	0	2.3%
Lipase increased	2.4%	0	2.3%
Pneumonia	2.4%	0	2.3%
Urinary tract infection	2.4%	0	2.3%
Treatment-related adverse events			
Any treatment related adverse event	63.5%	66.7%	63.6%
Most common treatment related adverse events (in 5% or more of Cohort A1)			
Diarrhoea	15.9%	33.3%	16.3%
Asthenia	14.3%	0	14.0%
Fatigue	13.5%	0	13.2%
Nausea	12.7%	0	12.4%
Arthralgia	8.7%	0	8.5%
Pruritus	8.7%	0	8.5%
Anaemia	7.1%	0	7.0%
Hypothyroidism	6.3%	33.3%	7.0%
Rash	5.6%	0	5.4%
Any CTCAE Grade 3 to 5 treatment-related adverse event	13.5%	0	13.2%
Serious adverse events			
Any serious adverse events	34.1%	33.3%	34.1%
Serious adverse events in 2% or more of Cohort A1			

Abdominal pain	3.2%	0	3.1%
Acute kidney injury	3.2%	0	3.1%
Sepsis	3.2%	0	3.1%
Pulmonary embolism	2.4%	0	2.3%
Pyrexia	2.4%	0	2.3%
Urinary tract infection	2.4%	0	2.3%
Serious treatment-related adverse events			
Any serious treatment-related adverse event	9.5%	0	9.3%
Most common serious treatment-related adverse events in more than one patient			
Colitis	1.6%	0	1.6%
Deaths			
Fatal adverse events	4.0%	0	3.9%
Fatal treatment-related adverse events	0	0	0
Discontinuation of study treatment			
Due to an adverse event	11.9%	0	11.6%
Due to treatment-related adverse event	4.0%	0	3.9%
Drug dosing interruption			
Treatment-emergent adverse event interrupted infusion	0.8%	0	0.8%
Treatment-emergent adverse event interrupted study treatment	24.6%	0	24.0%
Note: drug dosing reduction was not allowed in the protocol			
Immune-related adverse events			
Any event	34.9%	33.3%	34.9%
Any treatment-related event	21.4%	33.3%	21.7%

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse event; dMMR = DNA mismatch repair deficient; irAE = immune related adverse effects; MMR-unk = unknown mismatch repair tumour status; MSI-H = microsatellite instability-high; n = number of subjects in group; SAE = serious adverse events; TEAE = treatment-emergent adverse event; TRAE = treatment related adverse event.

Causes of dose interruption included anaemia, pneumonitis, diarrhoea, adrenal insufficiency and increased transaminases. Immune related adverse events are expected

with this class of drugs and included transaminase elevation, diarrhoea and hypothyroidism. Of these most were Grade 1 to Grade 2 events, and were managed with dose interruption, corticosteroids and hormone replacement where needed.

Overall, the safety profile was considered consistent with other PD-1 or PD-L1 inhibitors, however the clinical evaluator noted cardiac safety, and in particular immune mediated cardiac events had not been well characterised, and the immunogenicity information was limited precluding meaningful assessment.

Safety update

Three additional safety changes were provided after the completion of the evaluation phase:

- Amendment to the advice for the dosing advice for endocrinopathies, myocarditis, and severe neurological toxicities, and more precise characterising of immune mediated exfoliative dermatologic conditions (for example, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms).
- A strengthening of the advice to use contraception to avoid pregnancy when prescribed dostarlimab.
- Updates to the frequencies of some immune-mediated adverse events in the PI.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.2 (no date as yet; data lock point (DLP) 1 March 2020) and Australia specific annex (ASA) version 1.0 (dated 7 December 2020) in support of this application. In response to a TGA request for information, the sponsor submitted EU-RMP version 1.1 (dated 12 April 2021; DLP 1 March 2020) and ASA version 2.0 (dated July 2021) in support of this application. At second round of evaluation, the sponsor has submitted ASA version 3.0 (dated October 2021) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immune related adverse reactions (IrARs) (such as immune-related pneumonitis, colitis, endocrinopathies, immune-related skin adverse reactions, nephritis, systemic inflammatory response syndrome, myositis and other irARs)	ü	–	ü	ü*
	Infusion-related reactions	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	None	ü	–	ü	–
Missing information	Long-term safety	–	–	–	–

*Patient Alert Card.

- The summary of safety concerns is satisfactory and include 'systemic inflammatory response syndrome and myositis' in the list of 'immune related adverse reactions' consistent with the latest EU-RMP.[16]
- Routine pharmacovigilance activities only have been proposed. This is acceptable considering the safety concerns proposed and is consistent with the EU-RMP.
- Routine risk minimisation activities have been proposed. In addition, the sponsor proposes a Patient Card as an additional risk minimisation activity to inform patients about the important identified risk of immune related adverse reactions. The Patient Card will be distributed to physicians with the effectiveness assessed by routine pharmacovigilance. This is acceptable.

Risk-benefit analysis

Delegate's considerations

The provisional registration of dostarlimab is supported by single arm data. As a general principle the presentation of single arm data in the provisional registration setting is considered sufficient to demonstrate promising evidence of effect and an early assessment of the safety profile of the product.

The patient characteristics and prior treatments are considered sufficiently generalisable to the Australian context given the submission is seeking provisional registration.

After a median duration of follow-up of 16.3 months, dostarlimab treatment resulted in an objective response in 46 of 103 participants with DNA mismatch repair deficient endometrial cancer, with an objective response rate of 44.7% (95% CI: 34.9%, 54.8%). The median duration of response had not been reached, and 78.3% of responders with DNA mismatch repair deficient endometrial cancer.[17] Kaplan-Meier estimates of the probability of survival were 80.7% at Month 6, 74.9% at Month 9, and 68.5% at Month 12 in participants with DNA mismatch repair deficient endometrial cancer in the primary efficacy analysis set. The median progression free survival was 5.5 months in participants with DNA mismatch repair deficient endometrial cancer.

Study 4010-01-001 (the GARNET trial) data are immature, for example, the median duration of response was not estimable at the interim analysis presented. There are also the limitations of single arm data to consider in weighing up the efficacy evidence. It is noted the sponsor is collecting further data from the GARNET trial as the patients are followed for longer periods. Further information to characterise the comparative efficacy

[16] European Union-risk management plan version 1.1 (dated 12 April 2021; data lock point 1 March 2020).
[17] Sponsor clarification: the sponsor wished to state that the duration of response for these 78.3% of responders was for at least 6 months.

of dostarlimab with chemotherapy, and to further characterise the activity of dostarlimab in endometrial cancer are proposed for the clinical development plan supporting provisional registration. The findings of these studies may serve to reduce some of the residual uncertainty about the use of dostarlimab in the DNA mismatch repair deficient endometrial cancer population. In general, however, the efficacy data presented is supportive preliminary evidence of a meaningful clinical benefit of dostarlimab in this patient group and is sufficient to support provisional registration.

While the safety profile specific to the indicated DNA mismatch repair deficient endometrial cancer population was based on data from 126 patients from cohort A1, 515 patients have been exposed to at least one dose of dostarlimab in the clinical development program. The types of events are consistent with those seem in other drugs in the class although the proportions are higher than generally seen, particularly with gastrointestinal events. This could reflect patients with a later line of therapy, and the contribution of disease to reported adverse events is difficult to ascertain from single-arm data. While strategies to monitor adverse events include dose interruption, steroids and hormone replacement, depending on the specific events, approximately one fourth of the patients had a dose interruption during the study. The clinical evaluation highlighted limitations in the safety information, pointing specifically to a limited understanding of immune related cardiac events and limits to the immunogenicity data so far in the study program. The sponsor has amended the frequencies of these events in the latest safety update and further safety data are expected from an increased duration of exposure in the current study and comparative safety data are expected from Study 4010-03-001 (the RUBY trial; also discussed in section: Clinical study plan, below),[18] each part of the clinical development plan to support provisional registration.

Indication

The indication proposed by the sponsor, below, at the end of second round of evaluation is considered acceptable.

> *Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.*
>
> *This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

Dose

The proposed dose is 500 mg by intravenous infusion over 30 minutes every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks for all cycles thereafter.

The proposed dose is that used in Part 2B of the GARNET trial, and that proposed for the RUBY trial.[18] There are insufficient data to comment on the efficacy with alterative weight based dosing. There are no objections to the flat dosing approach, or the regimen proposed by the sponsor.

Clinical study plan

Study 4010-03-001 (the RUBY trial) is a randomised, Phase III study of dostarlimab in combination with chemotherapy versus chemotherapy alone in patients with recurrent (first recurrence only) or primary advanced (Stage III or IV) endometrial cancer. The

[18] Study 4010-03-001: A Phase III, randomised, double-blind, multicentre study of dostarlimab (TSR-042) plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer (the RUBY trial). ClinicalTrials.gov Identifier: NCT03981796.

RUBY trial was opened for enrolment in July 2019. Patients in the study will be stratified by microsatellite instability (MSI)/DNA mismatch repair status.

Additional data supporting the benefit of dostarlimab will be provided via additional patients with recurrent or advanced DNA mismatch repair deficient / microsatellite instability 'high' status endometrial cancer that have progressed following prior treatment with a platinum-containing regimen from the ongoing GARNET trial, but there is no confirmatory study for patient who have already undergone treatment with platinum based chemotherapy. The sponsor is asked for clarification on this point.

At this time both studies are considered part of the clinical study plan for dostarlimab. In the event of failure of the RUBY trial, additional data from Cohort A1 of the GARNET trial is unlikely to be sufficient to support full registration.

Proposed action

The Delegate proposes to approve the registration of the product for the following indication.

> *Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.*
>
> *This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***The evaluator found the clinical immunogenicity data had limitations that precluded conclusions regarding its impact of efficacy and safety.***

   Does the sponsor have plans to further characterise the immunogenicity of dostarlimab in its clinical development program?

   If so, how will these data be provided to the TGA?

The sponsor can commit to monitoring and analysing immunogenicity in ongoing and relevant future Jemperli clinical trials. An integrated analysis may be generated and will be shared with TGA as relevant ADA data from clinical trials data become available.

2. ***Please provide a copy of the protocol for Study 4010-03-001 (the RUBY trial) or indicate its location in the dossier.***

A copy of the protocol for Study 4010-03-001 (the RUBY) was provided for evaluation by the TGA with the sponsor's response.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Jemperli (dostarlimab) 500 mg/10 mL, solution for infusion, vial, indicated for:

> *Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.*
>
> *This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

Specific conditions of registration applying to these goods

- Jemperli (dostarlimab) is to be included in the Black Triangle Scheme. The PI and CMI [Consumer Medicines Information] for Jemperli must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- The Jemperli EU-risk management plan (RMP) (version 1.1, dated 12 April 2021, data lock point 1 March 2020), with Australian specific annex (version 3.0 dated October 2021), included with Submission PM-2020-06455-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically, the sponsor must conduct studies as described in the clinical study plan in version 3.0 (dated October 2021) of the Australia specific annex. The following study reports should be submitted to TGA:

  – Study 4010-01-001 [the GARNET trial] by date 14 January 2028, and
  – Study 4010-03-001 [the RUBY trial] by date 14 January 2028

  Further guidance for sponsors is available on the TGA website.

- Laboratory testing & compliance with Certified Product Details (CPD)
  - All batches of Jemperli dostarlimab 500 mg solution for infusion 10 mL vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change. The CPD should be emailed to biochemistry.testing@health.gov.au as a single PDF document.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Jemperli approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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