25 February 2021
EMA/176464/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Jemperli

International non-proprietary name: dostarlimab

Procedure No. EMEA/H/C/005204/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| ADCC | antibody dependent cellular cytotoxicity |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALP | alkaline phosphatase |
| BICR | blinded independent central review |
| BOR | best overall response |
| BSA | bovine serum albumin |
| $C_{avg}$ | average dostarlimab exposure |
| CFR | Code of Federal Regulations |
| CFU | colony-forming unit |
| CHMP | Committee for Medicinal Products for Human Use |
| CHO | Chinese hamster ovary |
| CI | confidence interval |
| cIEF | capillary isoelectric focusing |
| CL | clearance |
| CMA | conditional marketing authorisation |
| $C_{max}$ | maximum dostarlimab exposure |
| $C_{min}$ | minimum dostarlimab exposure |
| CPA | critical process attributes |
| CPP | critical process parameter |
| CR | complete response |
| cRO | conventional receptor occupancy |
| CSR | clinical study report |
| DCR | disease control rate |
| dMMR | mismatch repair-deficient |
| DOR | duration of response |
| DP | drug product |
| EC | endometrial cancer |
| ECOG | Eastern Cooperative Oncology Group |
| ELISA | enzyme linked immunosorbent assay |
| EMA | European Medicines Agency |
| ESMO | European Society for Medical Oncology |
| EU | European Union |

| Abbreviation | Definition |
|---|---|
| EU | endotoxin unit |
| FDA | Food and Drug Administration |
| FIGO | International Federation of Gynecology and Obstetrics |
| FIH | first-in-human |
| FMEA | failure mode effect analysis |
| fRO | functional receptor occupancy |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practices |
| GSK | GlaxoSmithKline |
| HC | heavy chain |
| HMW | high molecular weight |
| ICH | International Council for Harmonisation |
| IgG4 | immunoglobulin G4 |
| IHC | immunohistochemistry |
| IL-2 | interleukin-2 |
| IMM | immune modulatory medication |
| IND | Investigational New Drug |
| irAE | immune-related adverse event |
| irBOR | immune-related best overall response |
| irCR | immune-related complete response |
| irDCR | immune-related disease control rate |
| irORR | immune-related objective response rate |
| irPD | immune-related progressive disease |
| irPR | immune-related partial response |
| irRECIST | immune-related RECIST |
| ISF | impurity safety factor |
| IV | intravenous |
| KM | Kaplan-Meier |
| KPA | key process attribute |
| KPP | key process parameter |
| LAL | limulus amebocyte lysate |
| LC | light chain |
| mAb | monoclonal antibody |
| MCB | master cell bank |
| MMR | mismatch repair |
| MSI | microsatellite instability |
| MSI-H | microsatellite instability-high |

| Abbreviation | Definition |
|---|---|
| MSS | microsatellite stable |
| NCCN | National Comprehensive Cancer Network |
| NGHC | non-glycosylated heavy chain |
| NGS | next-generation sequencing |
| NS | normal saline |
| NSCLC | non-small cell lung cancer |
| NTU | nephelometric turbidity unit |
| ORR | objective response rate |
| OS | overall survival |
| PACMP | post-approval change management protocol |
| PAR | proven acceptable range |
| PBMC | peripheral blood mononuclear cells |
| PC | process characterization |
| PCR | polymerase chain reaction |
| PD | progressive disease |
| PD-1 | programmed cell death protein-1 |
| PD-L1 | programmed cell death-ligand 1 |
| PD-L2 | programmed cell death-ligand 2 |
| PD | pharmacodynamic(s) |
| PFI | progression-free interval |
| PFS | progression-free survival |
| Ph.Eur. | european pharmacopoeia |
| PIP | paediatric investigation plan |
| PK | pharmacokinetic(s) |
| POLE | polymerase ε |
| PPQ | process performance qualification |
| PR | partial response |
| PRO | patient-reported outcome |
| ProA | protein A |
| PT | preferred term |
| Q1 | first quartile |
| Q3 | third quartile |
| QbD | quality by design |
| qPCR | quantitative polymerase chain reaction |
| QTcF | corrected QT interval using Fridericia's formula |
| QTPP | quality target product profile |
| Q"X"W | every "X" weeks; X=frequency |

| Abbreviation | Definition |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RO | receptor occupancy |
| RP-HPLC | reversed-phase liquid chromatography |
| RTD | recommended therapeutic dose |
| SAE | serious adverse event |
| SD | stable disease |
| SE-HPLC | size exclusion - high performance liquid chromatography |
| SLDR | sum of diameters of measurable target lesions in mm per RECIST |
| SOC | system organ class |
| SOC | standard of care |
| $t_{½}$ | terminal elimination half-life |
| TEAE | treatment-emergent adverse event |
| TI | tolerance interval |
| TIM-3 | T-cell immunoglobulin and mucin domain 3 |
| TSE | transmissible spongiform encephalopathy |
| UF/DF | ultrafiltration / diafiltration |
| US | United States |
| USP | united states pharmacopoeia |
| UV | ultraviolet |
| V1 | central volume of distribution |
| WCB | working cell bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant GlaxoSmithKline (Ireland) Limited submitted on 6 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Jemperli, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Dostarlimab is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0303/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0303/2019 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Applicant's request(s) for consideration*

## Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

## New active Substance status

The applicant requested the active substance dostarlimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *Scientific advice*

The applicant received the following Scientific advice on the development relevant for the indication sought in the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 22 June 2017 | EMEA/H/SA/3585/1/2017/III | Dr Jan Sjöberg, Dr Helgi Helgason |

The Scientific Advice pertained to the following non-clinical and clinical aspects of the dossier:

- The overall non-clinical safety programme to support MAA in the approved indication.
- The adequacy of the overall clinical pharmacology plan to support MAA.
- The proposed popPK approach and exposure-response analyses.
- The design of the open-label, non-randomised study 4010-01-001, and its potential to provide pivotal data to support an application for CMA.
- The design of Phase 3, open-label, randomized, active-controlled study of dostarlimab in advanced and recurrent endometrial cancer, including the proposed population, endpoints, comparator choice, and statistical analysis, and its potential to provide comprehensive data to convert a potential CMA to full MA.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Blanca García-Ochoa Co-Rapporteur: Sinan B. Sarac

| | |
|---|---|
| The application was received by the EMA on | 6 March 2020 |
| Accelerated Assessment procedure was agreed-upon by CHMP on | 30 January 2020 |
| The procedure started on | 26 March 2020 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 27 May 2020 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 26 May 2020 |
| In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days | 27 May 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 2 June 2020 |

| | |
|---|---|
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 11 June 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant and the CHMP concluded that it was no longer appropriate to pursue accelerated assessment during the meeting on | 23 June 2020 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 9 October 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 17 November 2020 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 26 November 2020 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 10 December 2020 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 22 December 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 15 January 2021 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 28 January 2021 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 02 February 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 10 February 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jemperli on | 25 February 2021 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The claimed indication is: "Dostarlimab is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen."

The population defined as 'recurrent' or 'advanced' endometrial cancer (EC) is constituted by patients with stage ≥ IIIB endometrial cancer that have already received 1 or 2 lines of anti-cancer therapy, out of which one must have been a platinum doublet.

### 2.1.2. Epidemiology and risk factors

Worldwide, there were 417,367 new cases of EC and 97 370 deaths due to EC in 2020. In Europe, there were a total of 130,051 new cases of EC and 29,963 deaths due to EC in 2020 (GLOBOCAN 2020, corpus uteri cancer (ICD-10 category C54)).

Endometrial cancer is predominantly a disease of post-menopausal women and most common in women over 50 years of age. A woman's risk of developing endometrial cancer by the age of 75 is estimated to range from 0.6% in developing countries to 1.6% in developed countries (Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90).

Risk factors include age, obesity, diabetes mellitus, nulliparity, late menopause, unopposed oestrogen intake or oestrogen-producing tumours, a history of breast cancer and the use of tamoxifen (Berek JS, Hacker NF. Berek and Hacker's Gynecologic Oncology. 5th Edition. Lippincott Williams & Wilkins, 2010.).

### 2.1.3. Biologic features

EC can be classified as dMMR or mismatch repair (MMR) proficient based on the absence or presence of proteins that play a critical role in the MMR process. Defective DNA MMR results in genetic hypermutability known as microsatellite instability (MSI). The resulting accumulation of base pair mismatches interferes with DNA replication and drives genome instability (Kloor et all, 2016). Genome instability can manifest within microsatellites, which are repetitive DNA sequences (1 to 6 bases in length) found in coding and noncoding regions throughout the genome, a finding referred to as MSI. In literature and industry guidelines, the terms dMMR and MSI-H are used interchangeably. Tumours with the highest frequency of this biomarker are colorectal, endometrial and other gastrointestinal cancers (Bonneville R et all, 2017).

The European Society for Medical Oncology (ESMO) recommends the MMR immunohistochemistry (IHC) as the first method for MSI testing. National comprehensive Cancer Network (NCCN) colon cancer guidelines note that "IHC for MMR and polymerase chain reaction (PCR) for MSI are different assays measuring the same biological effect".

EC is one of the cancers with a high observed rate of dMMR/MSI-H (average of approximately 34%). The incidence, however, varies depending on histology and tumour grade (Mittica et al, 2017). The rate of dMMR/MSI-H is lower in low-grade endometrial tumours (28.6%) than in high-grade endometrial tumours (54.3%). Although data on MMR/MSI status in the metastatic setting are limited, the rate of dMMR/MSI-H in EC classified as Stage III or IV according to the International Federation of Gynecology and Obstetrics (FIGO) was shown to range from 6% to 17% (Basil et all, 2000).

### 2.1.4. Clinical presentation, diagnosis and stage/prognosis

Endometrial cancer (EC) develops in the lining of the uterus, called the endometrium. This is the most common type of uterine cancer, accounting for more than 90 percent of cases.

Most endometrial carcinomas are diagnosed at an early stage (FIGO stages I or II) since abnormal uterine bleeding is the presenting symptom in 90% of cases (ESMO Clinical practice guideline). However, an estimated 10%-15% of endometrial carcinomas recur and 80%-90% of recurrences occur within 3 years (Sohaib SA et al, 2007).

The overall prognosis of EC is mainly dependent on the stage at diagnosis and tumour histology. Earlier stages and endometrioid histology are associated with better prognosis, whereas advanced stages and non-endometrioid histologies such as serous, clear cell, and mixed are known to be associated with a worse prognosis (Morice P et al, Endometrial cancer. Lancet. 2016 Mar 12;387(10023):1094-1108).

### 2.1.5. Management

Approximately 20% of patients are diagnosed with advanced or metastatic disease (Stage III or IV) and systemic chemotherapy becomes a critical component of initial treatment, as surgery alone is unlikely to cure the disease (Miller DS. 2009;).

Depending on the extent and location of recurrent disease, histology, and patients' overall health, including comorbidities, surgery, radiation therapy, chemotherapy, or hormone therapy can be considered as treatment options:

- For patients with advanced or recurrent disease of any histological subtype, surgery is recommended only when optimal cytoreduction can be achieved.

- Radiation therapy is indicated in patients with an isolated vaginal relapse, and radical radiotherapy may be used as primary treatment in patients with unresectable disease or in those who have medical contraindications to surgery.

- Systemic palliative therapy options include hormone therapy and chemotherapy; treatment selection is based on several factors, including histopathological and clinical features of the patient. Hormone therapy is indicated for patients with advanced or recurrent EC and endometrioid histology and has demonstrated a favourable toxicity profile. Patients with Grade 1 to 2 endometrioid tumours and those with hormone receptor-positive disease are most likely to experience clinical benefit from hormone therapy (ESMO Clinical practice guideline).

Carboplatin and paclitaxel is considered as the standard of care (SOC) in first line setting to treat the advanced or metastatic EC based on its similar efficacy and less toxicity compared to cisplatin, doxorubicin and paclitaxel (ESMO guidance: Colombo, N et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1), 2-30.).

There are no approved therapies or specific regimens recommended by consensus guidelines as standard of care (SOC) for patients who have progressed on or after treatment with a platinum-containing regimen, (Colombo et al. 2016).

Currently available systemic therapy options for recurrent or advanced EC in the second-line setting (prior exposure to platinum-containing therapy) are summarized in the table below. None of the treatments have received approval for use in patients with EC in the EU.

**Table 1: Summary of available endometrial cancer treatments after prior platinum-containing therapy**

| Agent | Endpoint | Summary of Results | Reference |
|---|---|---|---|
| Liposomal doxorubicin | ORR | N=45<br>ORR=9.5%<br>Median DOR=2.7 months<br>Median OS=9.2 months | GOG 129H |
| Oxaliplatin | ORR | N=52<br>ORR=13.5%<br>Median DOR=10.9+ months<br>(range: 4.1 to 50.3+ months) | GOG 129-K |
| Docetaxel | ORR | N=26<br>ORR=7.7%<br>Median OS=6.4 months | GOG 129-N |
| Topotecan | ORR | N=28<br>ORR=9%<br>Median DOR=4.5 months (N=2 responses)<br>Median OS=N/A | GOG 129J |
| Bevacizumab | ORR | N=52<br>ORR=13.5%<br>Median DOR=6 months<br>Median OS=10.6 months | GOG 229-E |

Abbreviations: DOR=duration of response; N=number of patients; N/A=not applicable; NR=not reached; ORR=objective response rate; OS=overall survival.
Of note: none of these therapies are approved for treatment of endometrial cancer.

Note: Only limited data are available for these agents, and these are derived from small single-arm, non-registrational studies.

## *About the product*

Dostarlimab (also referred to as TSR-042) is a humanised mAb of the IgG4 isotype that binds to PD 1 receptors and blocks the interactions of binding with its ligands PD L1 and PD L2. The inhibition of PD 1 pathway mediated immune response results in inhibition of T cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti tumour immuno responses through blockade of PD 1 binding to PD L1 and PD L2. In syngeneic mouse tumour models, blocking PD 1 activity resulted in decreased tumour growth (see SmPC section 5.1).

The recommended indication is as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS* (see section 5.1 for information on assays used in the studies).

*IHC=immunohistochemistry; PCR=polymerase chain reaction; NGS=next-generation sequencing.

The recommended dose as monotherapy is 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

The dosage regimen is presented in Table 2.

**Table 2. Dosage regimen for patients treated with dostarlimab**

| | 500 mg Once Every 3 Weeks (1 Cycle = 3 weeks) | | | | 1000 mg Once Every 6 Weeks until disease progression or unacceptable toxicity (1 cycle = 6 weeks) | | | |
|---|---|---|---|---|---|---|---|---|
| **Cycle** | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Continue dosing Q6W |
| **Week** | 1 | 4 | 7 | 10 | 13 | 19 | 25 | |

**3 weeks between cycle 4 and cycle 5**

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

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 SmPC.

Detailed guidelines for the management of immune-related adverse reactions and infusion-related reactions are described in section 4.4 of the SmPC.

## *Type of Application and aspects on development*

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following aspects:

- there is an unmet medical need for more efficacious treatments in 2nd line of Endometrial cancer considering treatments for second line of EC have a limited efficacy, roughly 15% of ORR, with median of OS not longer than 1 year.

- dostarlimab has the potential to address this unmet medical need. Even though the limited sample size of the GARNET study cannot be considered robust enough to fully characterise the efficacy and safety, the antitumor activity shown by this drug in the specific setting of MSI-H/dMMR 2nd line EC, appears durable and is considered promising.

However, during the assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as major objections were raised and a longer clock stop was requested by the applicant.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. In order to further

confirm the efficacy and safety of dostarlimab for patients in recurrent or advanced dMMR/MSI-H endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen, the Applicant committed to provide the following data:

- Provision of further data from the ongoing GARNET study Cohort A1 expansion of enrolment. They are continuing to enroll patients and as of Aug 30, 2020, 136 patients have been enrolled. This study will provide safety and efficacy data and longer follow up period in the indicated patient population. A primary analysis of ORR and DOR data is expected for Q4 2021 (N=131 with ≥ 12 months follow up from the first time of responses) and submission is planned for Q4 2022.
- Provision of data from Study 4010-03-001 (RUBY), a randomised double-blind Phase III study of dostarlimab in combination with chemotherapy (carboplatin plus paclitaxel considered the SOC) versus chemotherapy alone in subjects with recurrent or primary advanced endometrial cancer. Patients in the study will be stratified by MSI/MMR status. The study was opened for enrolment in July 2019 and is going to enrol 470 subjects. The study as of August 30, 2020 has 264 randomized patients. This study will provide safety and efficacy data of dostarlimab in combination with chemotherapy. The primary analysis of progression-free survival (PFS), as assessed by blinded independent central review (BICR) is foreseen in Q1 2022 (N=470). At that time an interim OS analysis is expected to be performed. The subsequent data submission is planned for Q4 (December) 2022. The final analysis is foreseen for 2024.

- Unmet medical needs will be addressed, as results of GARNET study have shown that dostarlimab has a proven benefit and will substantially advance medical practice for patients with dMMR/MSI-H EC who have progressed on or following a platinum-containing regimen.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Given the lack of approved treatment options and the poor prognosis of these patients, new effective treatment options are urgently needed. Dostarlimab has demonstrated a favourable benefit risk profile that makes it a potential valuable treatment for this patient population with a manageable safety profile. Therefore, taking into account the lack of approved treatment options and in light of the available data, the applicant is of the opinion that granting the approval in this indication for dostarlimab will provide to these patients that are in need a studied therapeutic option, that the benefit to public health outweighs the risk as demonstrated by the benefit risk profile of the product, while additional data will be generated in order to confirm the safety and efficacy of dostarlimab in the pivotal study GARNET and in the Phase III study RUBY.

## 2.2. Quality aspects

### 2.2.1. Introduction

The Jemperli finished product is presented as a concentrate for solution for infusion containing 500 mg of dostarlimab as active substance.

Other ingredients are: trisodium citrate dihydrate, citric acid monohydrate, L-arginine hydrochloride, sodium chloride, polysorbate 80, and water for injection.

The product is available in 10 mL type I borosilicate clear glass vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap containing 500 mg dostarlimab.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

### 2.2.2. Active substance

#### *General information*

Dostarlimab is an anti-programmed cell death protein 1 (PD-1) humanised $IgG_4$ monoclonal antibody, produced in Chinese hamster ovary (CHO) cells. It is a glycosylated homodimer consisting of two identical heavy chains and two identical light chains, with 12 intra-chain disulfide bonds and 4 inter-chain disulfide bonds. The predominant N-linked glycoforms are core fucosylated biantennary glycans with 0 (G0F), 1 (G1F), and 2 (G2F) terminal galactose residues. Lack of dostarlimab ADCC activity has been demonstrated by lack of Fcγ binding (Biacore analysis).

$IgG_4$ is reported to have the tendency to form half-antibodies. To prevent this, each heavy chain contains a serine to proline substitution at amino acid 225, to promote stabilization of disulphide bonds between the two heavy chains.

Dostarlimab is claimed to be a New Active Substance.

#### *Manufacture, process controls and characterisation*

GMP Certificates provided for active substance manufacturing and testing sites are considered acceptable in the context of this procedure.

***Description of manufacturing process and process controls***

The dostarlimab active substance manufacturing process has been adequately described. An active substance batch consists of a pool of harvests from two (2) to three (3) production bioreactors, each inoculated from a culture derived from a single vial of the working cell bank (WCB). Dostarlimab is expressed in a CHO cell line using a fed-batch process.

Main steps are fermentation, recovery and purification. The commercial dostarlimab manufacturing process follows a standard process for monoclonal antibodies production, starting with the thawing of one vial of the working cell bank, followed by several cell expansion steps before inoculating multiple bioreactors. The bioreactors are harvested through centrifugation and depth filtration followed by purification using three chromatography unit operations. After that a UF/DF step is performed followed by polysorbate addition. Low pH inactivation and virus filtration are included as orthogonal dedicated

virus inactivation/elimination steps. Once the active substance is filtered, it is stored frozen at ≤-35˚C prior been shipped to the finished product or active substance storage facilities.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. Critical process parameters (CPP), key process parameters (KPP), critical process attributes (CPA) and key process attributes (KPA), including their proven acceptable ranges have been provided for the vial thaw, seed expansion, production bioreactors, harvest and all the purification steps. Hold studies have been performed to allow the storage of process intermediates based on biochemical and microbial integrity. Reprocessing is allowed for viral filtration step in case a filter integrity fails, or the process is operated outside the validated parameters, and for the bulk fill step, in case the filter integrity fails, or active substance container is unsuitable for use. Reprocessing has been evaluated at lab scale and no impact on product quality has been observed. A protocol to validate three reprocessing operations at commercial scale has been provided. The active substance manufacturing process is considered acceptable.

***Control of materials***

Sufficient information on raw materials, both compendial and non-compendial, used in the active substance manufacturing process has been submitted. Materials are controlled based on a risk assessment. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. The history and characteristics of the host cell bank based on commercial CHO DG44 cells are described. The host cell bank was properly characterised. The master (MCB) and working (WCB) cell banks were produced under GMP conditions and have been characterised for relevant phenotypic and genotypic markers. Characterisation tests include identity (genetic and morphologic identification), DNA sequencing, integration of recombinant transgenes (copy number) and safety (freedom from adventitious agents). An End of Production Cell Bank (EOPCB) was generated. Characterisation of EOPCB demonstrates that there are no significant changes in cell line stability and viral safety when subjected to extra passaging during production, establishing an *in vitro* cell age limit for the dostarlimab manufacturing process. All tests were done according to current guidelines, and the results obtained ensure that both banks meet all required specifications. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

A protocol for generation of future WCBs is provided. It gives high-level information on the cultivation, media used and preparation for storage.

***Control of critical steps and intermediates***

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the dostarlimab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. As part of the development of the control strategy, a series of risk assessments have been performed on each stage of the process to identify the process parameters that impact the critical quality attributes. The acceptable ranges for the process parameters were studied in characterization

studies. Acceptable ranges for the critical process parameters (CPP) and critical process attributes (CPA) have been provided based on results of the process characterization studies.

***Process validation***

The dostarlimab active substance manufacturing process has been validated. The approach taken to validate dostarlimab manufacturing process is based on an enhanced approach, where the process is demonstrated to perform consistently and dostarlimab meets all the biochemical, functional and microbiological acceptance criteria.

Four active substance batches were successfully processed through upstream process and three consecutive batches were fully executed through the downstream process and were successfully processed to active substance. One batch was terminated due to a non-process related contamination in the harvest tank (root cause established). Thus, consistency in production has been shown on three consecutive full-scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces dostarlimab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The dostarlimab active substance process has adequately demonstrated the removal of process related impurities (e.g. host cell proteins (HCP), host cell DNA, media components) at acceptably low levels. Additional impurities risk assessments and spiking studies have been provided.

Concurrent at scale validation protocols have been provided for chromatography resin lifetimes, UF/DF membranes lifetimes and reprocessing for viral filtration and final filtration prior bulk fill. Small scale resin lifetime studies and reprocessing studies have been included. Ongoing process verification will be used to monitor the validated commercial dostarlimab manufacturing process.

***Manufacturing process development***

The commercial active substance manufacturing process was developed in parallel with the clinical development program. Several significant changes have been introduced during the development of the manufacturing process, including a change from MCB to WCB in the upstream process, process upscale, process transfer to different facilities and process condition changes to accommodate the larger manufacturing scale, to improve process yields, and to improve impurity removal capabilities in the purification process. To support those changes an analytical comparability assessment was performed according to guidelines ICH Q5E and ICH Q9, which included comparison of impurity removal, batch analysis data, extended characterization comprising physicochemical tests (e.g. primary sequence analysis, high order structure analysis, glycosylation and sialylation analysis, and stability studies. The results of these studies show that there are no differences in product quality attributes between the clinical development process (single bioreactor) and commercial process.

The development of the control strategy for dostarlimab has been well described. Initially product critical quality attributes (CQA) were identified and failure mode effect analysis (FMEA) risk assessment was performed to select process parameters and raw materials for process characterization (PC) experimental studies. Prior to starting the PC studies small scale models were developed and qualified by adjusting the scale dependent parameters and were used in process characterization studies to establish the proven acceptable ranges (PARs) for the different units of operation. As part of the control strategy an extractable and leachable risk assessment was performed. Based on extractable analysis, threshold of toxicological concerns and permissible daily exposure calculations it was concluded that the risks to patients are low. Overall, the systematic approach taken to develop the control strategy is considered adequate. In-process controls includes what are defined as key- and critical process parameters. A key process parameter (KPP) does not have a meaningful impact on CQAs in the defined range'. A key performance attribute (KPA) should be monitored to assess whether

the process performs predictably and acceptably. The definition of CQA, CPP, KPP, CPA, KPA and proven acceptable ranges is sound and the proposed control strategy for the manufacture of dostarlimab intermediate is endorsed.

***Characterisation***

The dostarlimab active substance has been sufficiently characterised by a wide range of analytical methodologies classified into five categories: structural characterization, physicochemical properties, heterogeneity analysis, bioactivity and degradation products and pathway. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The bioactivity and binding properties of dostarlimab were assessed using various analytical methods. These studies showed that dostarlimab blocks the interaction between programmed cell death protein 1 (PD-1) and its ligand programmed cell death-ligand 1 (PD-L1). Even though, the Applicant also stated that dostarlimab blocks the interaction between PD-1 and its ligand programmed cell death-ligand 2 (PD-L2), no information has been presented in support of this statement.

*Process-related impurities* were assessed based on their potential risk to safety, efficacy, immunogenicity and overall effect on the quality of dostarlimab active substance.

*Product-related impurities* have also been characterised, including size variants as aggregates and fragments whose risk as impurity is high, and charge variants as oxidized and isomerized species whose risk as impurity is low. In addition, *product-related substances* have been characterised, including sialylated glycan species, deamidated species and C-terminal lysine on the heavy chain.

In conclusion, the proposed overall product characterisation strategy is appropriate.

## *Specification*

The specification set for release and stability of dostarlimab active substance have been set in accordance with ICH Q6B and includes suitable physicochemical tests and appropriate tests for identity, purity and potency to control relevant characteristics of monoclonal antibodies.

Overall, the acceptance criteria for the specification are based on active substance batch analyses and considered sufficiently justified. During the evaluation procedure, the adjustment of some active substance specifications (e.g. charged variants, residual protein A content (REC)) was requested to align them with amended specifications for finished product or to better reflect process capability and clinical experience. The data presented show that the active substance is highly pure and of consistent potency.

***Analytical methods***

The analytical methods have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. System suitability criteria and sample acceptance criteria are specified were relevant and the system suitability test ranges have been confirmed during validation of the methods. The system suitability criteria are adequate to confirm that the methods are in control during routine testing.

***Batch analysis***

Batch release data are provided for dostarlimab manufactured for clinical and commercial finished product manufacturing.

Data for all active substance batches presented, show that data is comparable across production scales and are within the specifications and confirm consistency of the manufacturing process.

***Reference materials***

A dostarlimab reference material program has been established that consists of a two-tiered reference material system, consistent with ICH Q6B guidance. The primary and working reference materials were derived from the same dostarlimab active substance at the same time. Future working reference materials will be qualified against the PRM and a protocol has been provided. Overall, the reference standard program is deemed acceptable.

***Container closure***

The container is a polycarbonate bottle. The closure consists of a polypropylene screw cap with a silicone liner. Appropriate validation for extractables and leachables was performed for the container closure system. Prior to use, the containers are released in accordance with established site procedures. Vendor specifications are described.

## *Stability*

The stability results indicate that the active substance is sufficiently stable and justify the proposed maximum storage time in the proposed container, i.e. 36 months when stored at ≤-35°C.

Data from primary stability studies and supporting stability studies are available. Stability test results meet the commercial acceptance criteria at long-term storage conditions for all primary and supporting stability lots. The stability studies have been performed according to ICH Q5C.

The analytical methods used in the stability program are a subset of the validated methods used for release of the active substance for further manufacturing into finished product. These include either dostarlimab-specific analytical methods that were shown to be stability indicating through forced degradation studies or compendial tests suitable for monitoring general characteristics of the product throughout its shelf life.

Accelerated and stressed stability data generated at 5±30°C and 25°C/60% RH is provided for up to 6 months.

Photostability studies, forced degradation studies, and freeze-thaw studies have been performed according to relevant guidelines.

The applicant commits to continue the ongoing stability studies post-approval and to annually add at least one commercial active substance batch to the stability program.

In summary, the stability results indicate that the active substance is sufficiently stable and justify the proposed maximum storage time of 36 months at $\leq$-35°C in the proposed container.

## 2.2.3. Finished medicinal product

### *Description of the product and Pharmaceutical development*

The Jemperli 50 mg/mL finished product is a sterile clear to slightly opalescent, colourless to yellow solution, essentially free from visible particles, and supplied as 10 mL single-use glass vial with a stopper and aluminium seal. Each finished product vial contains 500 mg dostarlimab formulated with trisodium citrate dihydrate, citric acid monohydrate, L-arginine hydrochloride, sodium chloride, and polysorbate-80.

A Quality Target Product Profile (QTPP) as described by the ICH Guideline Q8 (R2) was defined to ensure that the safety and efficacy of Jemperli could be maintained as described in the Target Product Profile (TPP). The QTPP for the finished product was refined over time and was used to guide the product development effort to satisfy clinical and commercial requirements.

Formulation studies were designed to optimise the chemical and physical stability of dostarlimab. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Neither excipients of human or animal origin, or novel excipients are used in the manufacture of the finished product.

An overfill of 0.7 mL is included to allow proper volume withdrawal (10 mL) but no overage.

The primary packaging is a 10 mL type I borosilicate clear glass vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap containing 500 mg dostarlimab. The material complies with Ph. Eur. and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The development of finished product manufacturing process started with the early phase clinical presentation, manufactured at WuXi Biologics (WuXi) in China. For the late phase clinical trials and commercial presentation, a higher protein content per vial was targeted (50 mg/mL dostarlimab, with 10.0 mL delivered volume), with no change in product formulation. In addition, the stored conditions were changed from -40ºC to -80ºC. The comparability of the two storage conditions was demonstrated by stability studies.

A bioanalytical comparability assessment was performed between early and late presentations. The comparability exercise was based on product release, complementary biophysical characterisation and stability studies. Results from these studies demonstrate that the process changes did not adversely impact the quality and safety of the finished product.

The finished product packaging materials and manufacturing process components were evaluated for potential extractables, elemental impurities and leachables using a risk-based approach.

The finished product is a sterile concentrate for solution for infusion and contains no antimicrobial preservatives. Sterility is assured by a validated process. In-use compatibility was demonstrated by evaluating the stability of the finished product with IV bag materials and diluents. The data from the compatibility study supports that the finished product is biochemically stable. The microbial growth potential of the finished product was evaluated when diluted, following Ph. Eur. 5.1.3 recommendations. No significant microbial growth was detected.

The critical quality attributes identified were visible particles, sub-visible particles, extractable volume and sterility and are properly controlled during the finished product manufacturing process.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters.

## *Manufacture of the product and process controls*

The sites involved in manufacturing, in-process testing, testing, labelling and packaging, final batch release and importation are listed in the dossier and are all supported by a valid proof of GMP compliance. GlaxoSmithKline Trading Services, Ltd., Ireland is responsible for final batch release.

The batch formula for Jemperli 50 mg/mL finished product is provided, as well as a batch size range. This range was properly validated during PPQ.

The finished product manufacturing process is described in sufficient detail and includes thawing, pooling and mixing of the active substance, bioburden reduction filtration, sterile filtration, and aseptic filling into the unlabelled primary container. No formulation or dilution steps are included.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

The process does not include any isolated process intermediates. Reprocessing is not allowed.

All vials and vial components, as well as filling machine parts and other product-contact components, are properly prepared and sterilised. The whole process is carried out in qualified facilities, appropriately monitored, using qualified equipment. Key and critical process parameters and performance attributes for every individual process step are properly defined and described.

Process performance qualification (PPQ) of Jemperli finished product was performed with a minimum of three PPQ finished product batches for the common part (BDS thawing, pooling and mixing, and bioburden reduction filtration) and for each filling line and covers the proposed batch size range. Performance consistency was properly demonstrated across filling lines and intra-filling line. The acceptance range for the process parameters were defined according to process control strategy. All acceptance criteria for CPPs, CPAs, KPPs, KPAs, and finished product release criteria were met for all PPQ batches for both filling lines. Some deviations were reported, investigated, and concluded that they have no impact in the process validation.

The validated finished product manufacturing process will be continually monitored.

Bioburden reduction and sterile filtration were properly validated by small-scale filter validation studies. Container closure integrity was demonstrated by a validated headspace gas analysis. Aseptic processing validation of each filling line was performed with three consecutive media fill simulations. In addition, appropriate shipping validation studies were performed for worst-case routes, under temperature-controlled conditions, and exposure stresses of shock, vibration, and pressure changes.

A post-approval change management protocol (PACMP) for a new finished product manufacturing site intended to be implemented is provided.

## *Product specification*

The release and end-of-shelf specifications of the finished product have been provided and cover all the required attributes, including tests for appearance, content, identity, purity, potency and general

compendial tests. The dostarlimab finished product release and shelf-life specifications are considered adequate to ensure the quality of Jemperli finished product.

The majority of methods are used to control both the active substance and finished product, except for quality attributes normally expected for control of finished product (e.g. general pharmaceutical attributes) or active substance (e.g. process related impurities).

The acceptance criteria for finished product specifications were established following accumulated knowledge about the product and a statistical analysis (TI) based on the finished product batches. The TI 95/99 were applied as predictive of future values and used to confirm the ability of future batches to meet the acceptance criteria. The acceptance criteria were also confirmed against data from the stability studies at the long-term condition. The acceptance criteria for impurities are supported by an assessment of all release (reflective of clinical experience) and stability data. Overall, the approach for setting the specification is acceptable and in line with ICH Q6B.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

***Analytical methods***

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The compendial analytical procedures are verified and are performed according to current Ph. Eur. Monographs.

The validation studies and transfer qualification information presented are considered acceptable.

***Batch analysis***

Batch information is provided in the dossier, including the status, manufacturing date, batch size, reference standard used for release testing, active substance manufacturing process, description, manufacturing site, disposition in clinic, PPQ, and stability studies. Batch analysis results of batches of 50 mg/ml dostarlimab finished product are presented in the dossier. Batch analysis data of historical dostarlimab finished product batches have also been provided. The results are within the specifications and confirm consistency of the manufacturing process.

***Reference materials***

Reference standards are identical to the reference standards for the active substance.

## *Stability of the product*

Based on available stability data, the shelf-life of 24 months when stored at 2 – 8 °C in the original package in order to protect from light, as stated in the SmPC is acceptable. Short-term excursions

outside the storage condition are not anticipated to affect the product quality as evidenced by the real-time data obtained at the accelerated and stressed conditions.

The stability of Jemperli 50 mg/mL finished product is evaluated by a stability program in accordance with ICH Q1A (R2) Stability Testing of New Drug Substances and Products and ICH Q5C Stability Testing of Biotechnological/Biological Products. The batches of Jemperli are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability of the finished product is primarily supported by stability studies conducted on clinical finished product with the same components, process and facility as the commercial finished product. Real time/real condition stability data and for accelerated conditions at 25 ± 2°C/60 ± 5% RH and at 40 ± 2°C/75 ± 5% RH according to the ICH guidelines were provided.

All batches placed at the long-term stability condition (5 ± 3°C) remained within specifications for all timepoints tested to date. No discernible trends or change in any of the tested product quality attributes were observed for up to 36 months from one finished product batch, from other batches on stability including two batches with 24 months of data and four additional batches with 18 months of data, where all batches exhibited the same stability characteristics for the timepoints tested.

A photostability study with vials from a selected batch to identify potential sensitivity to light exposure. Results from the photo-stability study confirm that the finished product is not sensitive to light exposure and the data supports the extended stability of finished product to light exposure at room temperature for up to 30 days.

The applicant commits to continue the ongoing stability studies post-approval and to annually add at least one commercial finished product batch to the stability program.

## Post approval change management protocol(s)

The post-approval change management protocol (PACMP) presented in the dossier outlines the comparability plan for the addition and implementation of an alternate commercial site for the production of Jemperli 50 mg/mL finished product. The alternate site will be added post-approval as an additional site of manufacture, primary packaging, inspection, secondary packaging and labelling, storage, and batch release testing of finished product to expand manufacturing capacity and mitigate supply continuity risk. The finished product may in future be sourced from both the finished product sites upon approval of the post-approval variation.

An ongoing process verification approach that integrates process development and process validation/qualification will be included into an overall program aimed at increasing the level of process knowledge and understanding, to ensure that the process is operated under a state of control. The potential differences between the manufacturing process as run at the current finished product site and the process at the alternate site are minimal.

The alternate site will execute batches at commercial scale, after technology transfer of the process to the site. Comparability studies will be performed. The product quality assessment will consist of the release testing results, higher order characterization analysis, and stability study data from the PPQ batches. Overall, the provided information on the PACMP presented is considered sufficient.

### *Adventitious agents*

A comprehensive strategy has been used to ensure the Jemperli 50 mg/mL finished is free from adventitious agents (non-viral and viral adventitious agents). This includes cell bank characterization,

raw material sourcing and testing, production facility controls, manufacturing process monitoring and control, and viral clearance validation studies.

No animal-derived raw materials or resins are used for the manufacture of Jemperli, except for the recombinant CHO production cell line. Based on the information provided, the Jemperli product is considered safe in terms of non-viral adventitious agents.

Extensive viral safety testing was performed on the MCB, WCB and EOPCB (end of production cells) according to ICH guideline Q5A (R1) and EMA guideline EMEA/CHMP/BWP/398498/2005. The results confirm that no infectious endogenous or adventitious viral agents were detected in the MCB or WCB. Unprocessed bulk samples were also tested, and no viral agents were detected.

Viral clearance studies were performed to determine the capacity of the dostarlimab active substance manufacturing process to remove or inactivate potential endogenous and adventitious viruses. The manufacturing process for Jemperli includes steps specifically designed to remove viruses (virus filtration) and inactivate viruses (low pH viral inactivation) and additionally the chromatography steps contribute to the overall virus clearance. For the Virus filtration step, effective virus removal was demonstrated for all types of viruses tested.

The sponsor is committed to re-evaluating the risk to viral safety as part of a process comparability package when significant changes in the active substance production process (either cell culture or downstream purification) are made, as needed.

### *GMO*

Not applicable.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

The Quality documentation in the Jemperli dossier is of acceptable standard. Whilst no Quality Major Objections were raised, the applicant was requested to address a number of Other Concerns/clarifications, which have been successfully resolved during the procedure.

Satisfactory information on development, manufacture and control of the active substance and finished product has been presented. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product will have a satisfactory and uniform performance in clinical use.

The active substance and finished product manufacturing process and process controls are described in sufficient detail and the processes are appropriately validated. A science- and risk-based approach with Quality by Design (QbD) elements was used for process development and process characterization, supporting the proposed manufacturing process and its control strategy as well as demonstrating a solid process understanding. Comparability was demonstrated for material from early development into the commercial active substance process. Characterization of dostarlimab active substance was performed using an extensive panel of appropriate methods.

Overall, the approach for setting the product specifications is acceptable and in line with ICH Q6B. However, the approach used for setting the charge variant specification is not fully agreed. Method variability has been accounted for in setting the specification acceptance limits, although it is already taken into account in the batch data and this results in wide ranges. Despite this, the proposed specification has been accepted as it is not expected to have an impact on product safety/efficacy.

A risk assessment for the formation of nitrosamines have been provided and the applicant concludes that there is no risk of formation of N-nitrosamines taking into consideration the manufacturing process and the container closure system.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. This pertains to the re-assessment of the specifications for residual protein A and host cell protein upon completion of the on-going at scale column resin re-use carryover study. This point is put forward and agreed as recommendations for future quality development.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to consistent clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

## 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. To reassess the residual protein A and host cell protein specification criterion upon completion of the on-going at scale column resin re-use carryover study.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

The non-clinical efficacy and safety of dostarlimab (also referred as APE04443.03 or TSR-042) were characterised through a battery of pharmacology, pharmacokinetics, and toxicology studies.

The mechanism of action for dostarlimab was evaluated in a series of *in vitro* binding studies using surface plasmon resonance (SPR) and flow cytometry to assess the binding kinetics of dostarlimab to human and cynomolgus monkey PD-1 and the ability of dostarlimab to block PD-1/PD-L1 and PD-1/PD-L2 interactions in a competitive setting.

The Pharmacokinetic (Toxicokinetics) characterisation of dostarlimab was carried out through toxicity studies with cynomolgus monkey, no specific pharmacokinetics studies were carried out.

The toxicology of dostarlimab was evaluated through a single dose toxicity study and repeated dose toxicity studies in cynomolgus monkey.

Studies conducted as part of the toxicology program, with the exception of the single-dose study in monkeys and the initial tissue cross-reactivity study in normal human tissues, were conducted in compliance with the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.

### 2.3.2. Pharmacology

#### *Primary pharmacodynamic studies*

The pharmacodynamic activity of dostarlimab was conducted in both *in vitro* and *in vivo* experimental systems.

***In vitro***

*In vitro characterization: binding to human PD-1 and competitive blocking of PD-1 interaction with PD-L1 and PD-L2*

TSR-042 (dostarlimab) was characterized for binding kinetics to human PD-1 using SPR (Report ANA011.003). The results of the three experiments showed that TSR-042 demonstrated a KD of 2-4 nM for binding to monomeric soluble human PD-1 (Study ANA011.003). Dostarlimab Binding to PD-1 Dimeric Fusion Protein showed KD = 0.3 nM; Ka = $5.7 \times 10^5$/Ms and Kd = $1.7 \times 10^{-4}$/s (surface plasma resonance). Under the CHO cell Surface PD-1 system, the EC50 = 2 nM (Study report ANA011.002).

Blocking of the PD-1/PD-L1 and PD-1/PD-L2 binding interaction was assessed by flow cytometry that measured DyLight 650 (DyL650)-labeled PD-L1 or PD-L2 mouse IgG1 Fc fusion protein (PD-L1mFc/PD-L2 mFc) binding to human PD-1-expressing CHO-K1 cells (Study ANA011.002). Compared to an IgG4 isotype control, dostarlimab efficiently blocked PD-1/PD-L1 and PD-1/PD-L2 binding, with IC50 values of 1.8 and 1.5 nM, respectively (Figure 1).

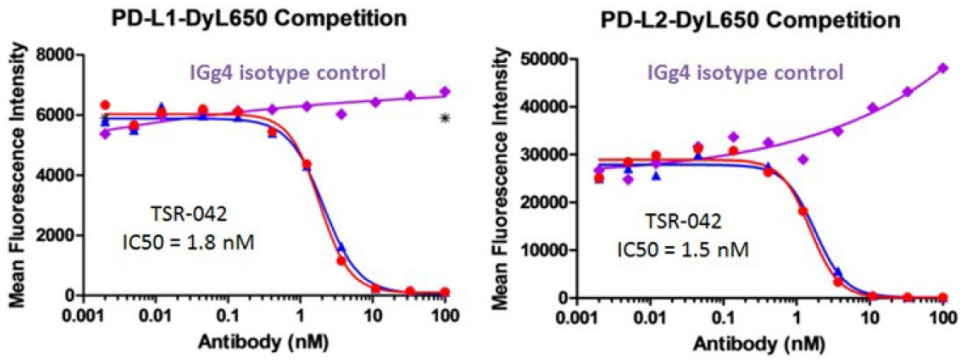



**Figure 1. Competitive Blocking of PD-1 Interaction with PD-L1 and PD-L2 by Dostarlimab**

*In vitro characterisation of dostarlimab in mixed lymphocyte reaction*

Functional antagonist activity of dostarlimab was tested in a human $CD4^+$ T cell mixed lymphocyte reaction (MLR) assay. An isotype control antibody was tested in parallel and the results were compared with historical MLR assay results for APE04443.01 (another lot of TSR-042), APE02479 (another lot of TSR-042), and BMS-936558 (nivolumab) (Report ANA011.003) (see Table 3). For determination of functional potency of TSR-042 (APE04443.03) the EC50 was measured in 3 separate MLR experiments using different human donors. Antagonism of PD-1 in this assay has been shown to result in increased T cell activation as measured by increased IL-2 production.

The EC50 value for dostarlimab was approximately 1nM (ranged from 0.13 to 2 nM).

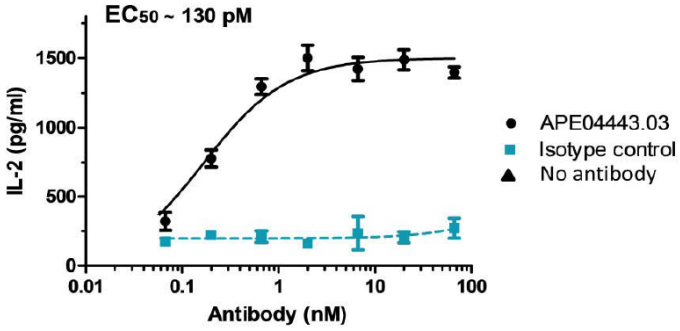



**Figure 2. Activity of dostarlimab in a MLR assay**

**Table 3: Activity of APE04443 in the human mixed lymphocyte reaction**

| Antibody | Expt No. | Human MLR Assay $EC_{50}$ |
|---|---|---|
| APE04443.01 | 1 | 2 nM |
| APE04443.03 | 1 | 0.8 nM |
| APE04443.03 | 2 | 1 nM |
| APE04443.03 | 3 | 0.13 nM |
| APE02479 historical | n=2 | 0.3 nM, 0.07 nM |
| APE02080 nivolumab historical | n=2 | 0.2 nM, 0.3 nM |

*Dostarlimab binding to human/ cynomolgus monkey PBMCs*

The studies XLB-071 and 074X reported the concentration range of dostarlimab (TSR-042) which effectively binds to human/cyno peripheral blood mononuclear cells (PBMCs) (3 donors). This was determined by flow cytometry utilising a CD3 marker and an IgG4 specific antibody.

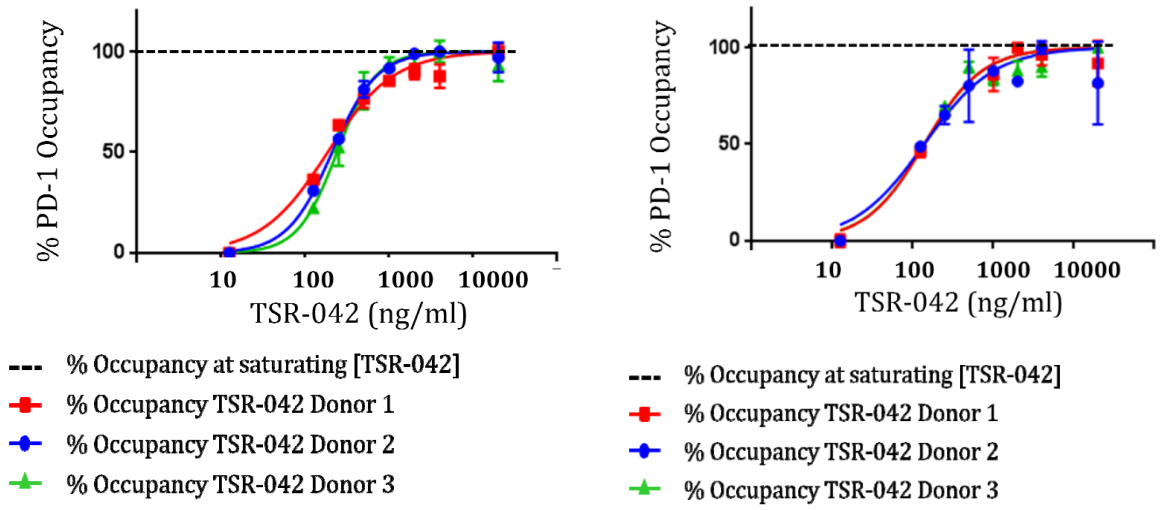



**Figure 3. % Pd-1 occupancy for TSR-042 to human (left) or monkey (right) PBMCs**

*Cross-species binding specificity of dostarlimab*

When binding kinetics to the human and cynomolgus monkey PD-1 dimer were evaluated, there was less than a 2-fold difference in the KD values (0.1-0.3 nM for the human PD-1 dimer as compared to 0.2-0.5 nM for the cynomolgus monkey PD-1 dimer (Table 2). In addition, binding of dostarlimab to human or cynomolgus monkey PD-1, expressed on CHO-K1 cells, was assessed by flow cytometry using phycoerythrin-conjugated mouse anti-human IgG4 to detect antibody binding (Study ANA011.002). Dostarlimab bound to cell surface human and cynomolgus monkey PD-1 with an EC50 of 2.0 and 3.4 nM, respectively.

**Table 4. Dostarlimab Binding to PD-1 Dimeric Fusion Protein (SPR) and Cell Surface PD-1 (Flow Cytometry)**

| | Kinetic Parameters | | | PD-1-Expressing CHO Cells[1] |
|---|---|---|---|---|
| Species | $k_a$ $(Ms)^{-1}$ | $k_d$ $(s^{-1})$ | $K_D$ (nM) | $EC_{50}$ (nM) |
| Human PD-1 | $5.7\times10^{5}$ | $1.7\times10^{-4}$ | 0.30 | 2.0 |
| Cyno PD-1 | $4.3\times10^{5}$ | $2.3\times10^{-4}$ | 0.53 | 3.4 |

Source: Study ANA011.002

The objective of the study XLB-065 was to assess TSR-042 binding to freshly isolated peripheral blood mononuclear cells (PBMCs) from the following: cynomolgous {cyno}, human, beagle, mouse and rat PBMCs. This was determined by flow cytometry utilizing TSR-042 conjugated to the fluorophore FITC over a range of concentrations.

For freshly isolated PBMCs stained with FITC-TSR-042 higher staining was observed with cyno PBMCs and human PBMCs. Lower levels of staining were observed with beagle PBMC and very low levels with both mouse and rat PBMCs (Table 5 and Table 6).

**Table 5: FITC-TSR-042 Diluted 1:10**

| PBMCs | Unstained (FITC Gate) | PBMC + TSR-42-FITC |
|---|---|---|
| | % Cells Detected | % Cells Detected |
| | | |
| Human | 0.0 | 8.0 |
| Cyno | 0.0 | 18.5 |
| Beagle | 0.0 | 4.6 |
| Mouse | 0.0 | 1.3 |
| Rat | 0.1 | 1.2 |

**Table 6**: **FITC-TSR-042 Diluted 1:100**

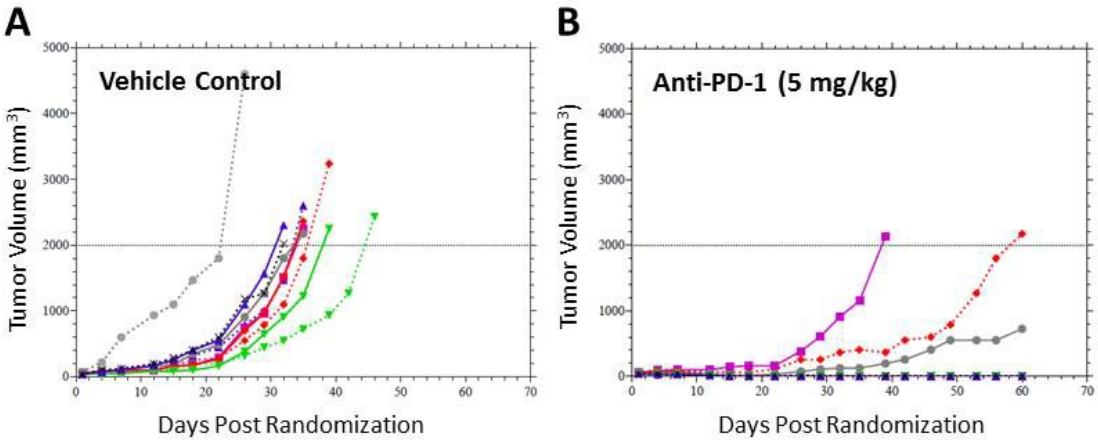
| PBMCs | Unstained (FITC Gate) | PBMC + TSR-42-FITC |
|---|---|---|
| | % Cells Detected | % Cells Detected |
| | | |
| Human | 0.0 | 1.04 |
| Cyno | 0.0 | 10.0 |
| Beagle | 0.0 | 1.72 |
| Mouse | 0.0 | 0.17 |
| Rat | 0.1 | 0.11 |

***In vivo***

Due to the lack of cross-reactivity between anti-human PD-1 antibodies like dostarlimab and mouse PD-1, a commercially available rat anti-mouse surrogate antibody (APE04348) was used to assess the potential for PD-1 inhibition to suppress tumour growth in an MC38 syngeneic mouse tumour model (Study ANA011.E004). Other treatments as well as control negative were used for comparison.

The MC38 cell line was derived from a mouse colon adenocarcinoma. Tumours were initiated by subcutaneously implanting $1\times10^{6}$ MC38 cells into the right flank of each animal, and tumour development was monitored. Mice with tumours measuring 32 to 75 $mm^3$ were randomized and dosed with antibody (5 mg/kg) or vehicle (phosphate-buffered saline) intraperitoneally twice weekly (on Days

1, 4, 8, and 11). Tumours were measured twice a week for up to 60 days (end of study). The time-to-endpoint (TTE) for each mouse was defined as the time when the tumour reached a volume of 2,000 $mm^3$ and the animal was euthanized or on the final day (Day 60), whichever came first. MC38 tumours in vehicle control-treated mice exhibited progressive growth, reaching the 2,000 $mm^3$ volume endpoint at a median of 33.8 days. Anti-mouse-PD-1 suppressed tumour growth. Seven of 10 animals were tumour free after at least 60 days (Figure 4), extending the survival (median TTE 60 days versus 33.8 days in vehicle-treated animals) and resulting in a 78% tumour growth delay, calculated as percent increase in median TTE for treated versus control mice. No treatment-related toxicity or loss of body weight was observed in anti-PD-1-treated animals.




Source: Study ANA011.E004
Abbreviations: PD-1=programmed cell death protein 1.
Each line represents the tumour growth for an individual animal.

**Figure 4: Anti-Tumour Activity of an Anti-Mouse PD-1 Surrogate Antibody in MC38 Tumour-Bearing Mice**

The tumour growth inhibition seen in the anti-PD-1 treatment arm translated into extended long-term survival for these groups (Figure 5A). To confirm that anti-tumour efficacy was mediated by an adaptive immune response, 6 animals from the anti-PD-1 group that were tumour free on Day 81 were re-challenged with 4 times the number of MC38 tumour cells used for the original inoculation ($4\times10^6$ MC38 cells per animal; opposite [left] flank). On the same day, 9 age-matched, female, treatment-naïve mice were inoculated with $4\times10^6$ MC38 cells per animal. All animals were treated with vehicle, and tumours were measured twice weekly for an additional 7 weeks. All 9 (100%) of the treatment-naïve control animals developed tumours and reached the 2,000 $mm^3$ endpoint at a median of 36.9 days (Study ANA001.E005). All animals previously treated with anti-PD-1 and re-challenged with MC38 cells had palpable tumours at 2 to 3 weeks post re-challenge, but by the fourth to fifth week post MC38 cell re-challenge, all animals were again tumour free and remained tumour free until the end of the study (Figure 5B).

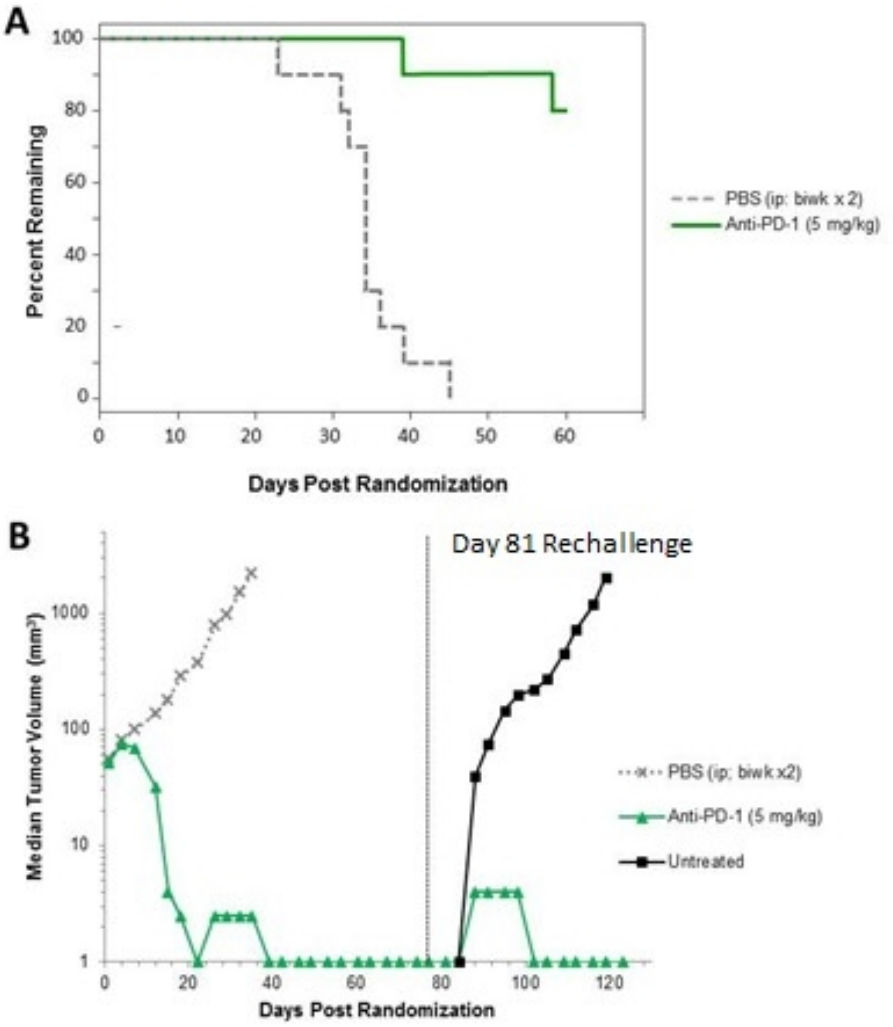



**Figure 5: Survival Curves and Anti-Tumour Memory Response for MC38 Tumour-Bearing Mice Treated with an Anti-PD-1 Surrogate Antibody**

Source: Study ANA011.E004
Abbreviations: Biwk=biweekly; IP=intraperitoneal; PBS=phosphate-buffered saline; PD-1=programmed cell death protein 1.
Panel A: Kaplan-Meier survival curves for mice bearing MC38 tumours treated twice weekly with vehicle (PBS) or 5 mg/kg rat anti-mouse PD-1 surrogate antibody. Panel B: Memory Response. Tumour volume for mice previously treated with anti-PD-1 (5 mg/kg) versus treatment-naïve mice (untreated) following MC38 cell inoculation (re-challenge).

## *Secondary pharmacodynamic studies*

*In vitro stimulation of PBMCs/cytokine production*

An evaluation on whether the compound dostarlimab (TSR-042) would cause stimulation of human PBMCs -as determined by levels of Interferon-γ and IL-2 expression-, and the effect on cytokine release was conducted *in vitro.*

PBMCs from 3 donors were adjusted to a final concentration of 200,000 cells/well and incubated with either TSR-042, or IgG4 at the various concentrations (for 3 days at 37°C in a humidified CO2 incubator). As a positive control either CytoStim (1 uL/well) or CD2/CD3/CD28 beads (4 uL/well) was added to the appropriate wells. IL-2 expression levels or IFN-γ was determined in one aliquot by ELISA. Other aliquots were submitted for multiplex analysis (IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α).

For all donors, low levels of IFN-γ and IL-2 was obtained with all concentrations of TSR-042 (5-2000 µg/mL) and IgG4 evaluated (the same concentration as TSR-042), while high levels of IFN-γ was obtained with CytoStim and CD2/CD3/CD28 beads (0.02%). Only with the CD2/CD3/CD28 beads were significant levels of IL-2 expression obtained.

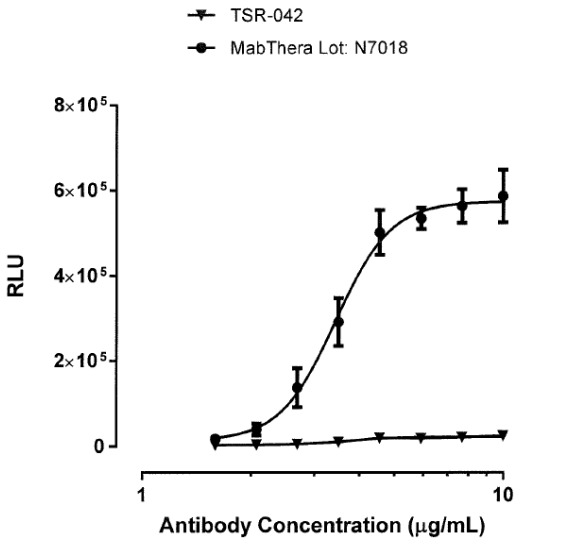
Treatment of PBMCs with either TSR-042 or IgG4 alone generated no enhanced cytokine response or any clear dose response. Only treatment of the PBMCs with CD2/CD3/CD28 beads generated elevated levels of expression the various cytokines evaluated.

In conclusion, TSR-042 caused minimal stimulation of PBMCs/cytokine release at the evaluated concentrations.

*Binding of dostarlimab to complement component C1q*

Dostarlimab binding to complement component C1q was assessed in study 8324-037. A C1q ELISA was developed based on the method described by Idusogie et al., 2000. The target article was coated onto a 96-well polystyrene plate at 8 concentrations: 10, 7.7, 5.9, 4.6, 3.5, 2.7, 2.1, and 1.6 µg/mL. MabThera served as positive control. The EC50 values and 90% confidence intervals (CI) were calculated for each test article.

Luminance increased with the positive control MabThera, however, no reaction occurred with the TSR-042 (Figure 6).




| | MabThera Lot: N7018 | TSR-042 |
|---|---|---|
| EC50 | 3.438 | NA |
| 95% CI | 3.225 to 3.665 | 2.966 to 4.695 |
| Emax | 573301 | 22488 |

**Figure 6: C1Q analysis ($EC_{50}$ Concentration-Response Curves) of MabThera Reference Standard vs TSR-042**

*Binding of dostarlimab to FcγR1 (CD64)*

Study No. 8324-038 assessed dostarlimab binding to FcγRI. A Bio-Layer Interferometry (BLI)-based (Forte Bio Octet Red 96) method for determining binding rate constants (kon, koff, KD) was successfully developed and optimised to provide kinetic data on the interaction between provided monoclonal antibodies, and Human CD64 Protein. MabThera served as positive control.

The TSR-042 average $K_D$ was 16.42 nM (2SD range of 12.31 to 20.52 nM) from n=3. MabThera $K_D$ = 6.94 nM (4.82 to 9.06 nM).

### *Safety pharmacology programme*

Dostarlimab safety pharmacology was assessed within toxicity studies in Cynomolgus Monkeys (Study 273-0016-TX). Three groups of 3 female and 3 male monkeys each received a single administration of dostarlimab at 10, 30, or 100 mg/kg dissolved in Phosphorous buffer saline (PBS, pH7.4). The control animals (3 females and 3 males) received PBS only. Electrocardiograms were obtained from all available animals. ECG data analysis included a description of waveform morphology (for P, QRS, and T waves), but measurements of interval durations (RR, PR, QRS, and QT) and QTc interval duration was not calculated in this study. There were no dostarlimab related effects on electrocardiography following a single intravenous administration of dostarlimab at dose levels up to 100 mg/kg. No dostarlimab systemic adverse effects (clinical signs, body weight, food consumption, ophthalmologic examinations) were noted in the study.

Safety pharmacology parameters (cardiovascular, respiratory, and central nervous systems) were also evaluated in a pivotal GLP toxicity study with monkeys (Study No. 273-022-TX). No treatment-related effects on both quantitative and qualitative ECG parameters, blood pressure parameters, heart rate were observed in this study. No delayed effects were noted in recovery phase. There were no treatment-related effects on respiratory and neurological parameters observed in this study. The no observed adverse-effect level (NOAEL) was determined to be ≥100 mg/kg/dose, based on the lack of test article-related changes for both male and females.

### *Pharmacodynamic drug interactions*

Pharmacodynamic drug interactions studies were not submitted (see discussion on non-clinical aspects).

## 2.3.3. Pharmacokinetics

Pharmacokinetic (toxicokinetics) characterisation of dostarlimab was carried out through toxicity studies with cynomolgus monkey. Dostarlimab was administered intravenously and toxicokinetic parameters were assessed after both single and repeated administration to cynomolgus monkeys. An ELISA method was developed for measuring dostarlimab and anti-dostarlimab antibodies in monkey serum.

No distribution, metabolism, excretion studies were submitted.

**Absorption**

Cynomolgus Monkeys toxicokinetics was firstly addressed through a single intravenous infusion non-GLP study (Study 273-0016-TX). In this study, three groups of 3 female and 3 male monkeys each received a single administration of dostarlimab at 10, 30, or 100 mg/kg dissolved in Phosphorous buffer saline (PBS, pH7.4). The control animals (3 females and 3 males) received PBS only. No significant sex differences in systemic exposure were observed at any dose level. Combined toxicokinetic parameters from male and female monkeys are presented in the Table 7 and Table 8.

**Table 7**: **Pharmacokinetics Parameters of TSR-042 after a Single Intravenous Dose to Cynomolgus Monkeys (Male and Female Separated)**

| Dose (mg/kg) | Sex | Cmax (µg/mL) | Tmax (h) | $T_{1/2}$ (h) | $AUC_{0\text{-}1320h}$ (h*µg/mL) | Vdss (mL/kg) | MRT (h) | Cl (mL/h/kg) |
|---|---|---|---|---|---|---|---|---|
| 10 | Male | 265± 9.87 | 0.5 (0.5 - 1.0) | 31.0 (14.9 - 97.0) | 45700 ± 21800 | 39.9 ± 8.17 | 193 ± 129 | 0.248 ± 0.0933 |
| | Female | **274 ± 6.81** | **0.5 (0.5 - 1.0)** | **168.6 (72.1 -282.6)** | **57400 ± 14400** | **53.1 ± 5.28** | **314 ± 110** | **0.181 ± 0.0547** |
| 30 | Male | 758 ± 77.0 | 0.5 (0.5 - 1.0) | 58.5 (26.8 - 243.2) | 145000 ± 34100 | 48.5 ± 7.90 | 242 ± 99.0 | 0.213 ± 0.0465 |
| | Female | **693 ± 44.7** | **0.5 (0.5- 0.5)** | **123.0 (86.7- 217.2)** | **192000 ± 16500** | 48.3 ± 7.01 | **309 ± 30.6** | **0.156 ± 0.0120** |
| 100 | Male | 3400 ± 80.0 | 1.0 (0.5 - 4.0) | 56.7 (31.1 - 138.7) | 426000 ± 224000 | 39.4 ± 3.92 | **170 ± 96.8** | 0.274 ± 0.114 |
| | Female | **2930 ± 135** | **1.0 (0.5 - 1.0)** | **60.7 (19.9 - 66.2)** | **437000 ± 126000** | 48.4 ± 7.44 | **213 ± 71.9** | **0.242 ± 0.0685** |

**Table 8**: **Pharmacokinetics Parameters of TSR-042 after a Single Intravenous Dose to Cynomolgus Monkeys (Male and Female Combined)**

| Dose (mg/kg) | Sex | Cmax (µg/mL) | Tmax (h) | $T_{1/2}$ (h) | $AUC_{0\text{-}1320h}$ (h*µg/mL) | Vdss (mL/kg) | MRT (h) | Cl (mL/h/kg) |
|---|---|---|---|---|---|---|---|---|
| 10 | Male+Female | **270 ± 8.34** | 0.5 (0.5 - 1.0) | **99.8 (14.9 - 282.6)** | **51600 ± 18100** | **46.5 ± 6.73** | **254 ± 120** | **0.215 ± 0.0740** |
| 30 | Male+Female | **726 ± 60.9** | 0.5 (0.5 - 1.0) | **90.8 (26.8 - 243.2)** | **169000 ± 25300** | **48.4 ± 7.46** | **276 ± 64.8** | **0.185 ± 0.0292** |
| 100 | Male+Female | **3170 ± 108** | 1.0 (0.5 - 4.0) | 58.7 (19.9 - 138.7) | **432000 ± 175000** | **43.9 ± 5.68** | **192 ± 84.4** | **0.258 ± 0.0913** |

Data is presented as mean ± SD for Cmax, $AUC_{0\text{-}1320h}$, Vdss, MRT, and Cl values, and median (range) for Tmax and $T_{1/2}$ values.

Toxicokinetics parameters were also assessed within a GLP toxicity study with cynomolgus monkey (study no. 273-0022-TX, GLP study). Animals were administered 0, 10, 30, or 100 mg/kg/dose TSR-042 once every week for 4 weeks (five doses in total) by 15-minute intravenous infusion.

No significant sex differences in systemic exposure were observed at any dose level, therefore combined toxicokinetic parameters from male and female monkeys are presented in the Table 9.

**Table 9**: **Summary of Toxicokinetic Parameters in Male and Female Monkeys Following Intravenous Administration of TSR-042 once weakly for 4 weeks**

| Dose (mg/kg/dose) | Study Day | Sex | Cmax (µg/mL) | Tmax (h) | $T_{1/2}$ (h) | $AUC_{0\text{-}168h}$ (h*µg/mL) |
|---|---|---|---|---|---|---|
| 10 | 1 | Male+ Female | 265 ± 56.1 | 0.5 (0.5 - 4.0) | 211.9 (133.9 - 597.2) | 18800 ± 3340 |
| | 22 | Male+ Female | 469 ± 44.5 | 0.5 (0.5 - 4.0) | 217.8 (175.3 - 542.3) | 54500 ± 6710 |
| 30 | 1 | Male+ Female | 782 ± 120 | 0.5 (0.5 - 8.0) | 174.9 (107.8 -294.1) | 61200 ± 10300 |
| | 22 | Male+ Female | 1320 ± 224 | 4.0 (0.5 - 8.0) | 318.2 (111.8 -810.2) | 147000 ± 41700 |
| 100 | 1 | Male+ Female | 2620 ± 630 | 0.5 (0.5 - 8.0) | 172.3 (110.3 -305.1) | 197000 ± 15600 |
| | 22 | Male+ Female | 4070 ± 1010 | 4.0 (0.5 - 8.0) | 212.8 (57.1 - 468.6) | 419000 ± 148000 |

Data is presented as mean ± SD for Cmax and $AUC_{0\text{-}168h}$ values, and median (range) for Tmax and $T_{1/2}$ values.

The systemic exposure increased dose-proportionally in both sexes on Days 1 and 22 as the dosage increased from 10 to 100 mg/kg.

The potential toxicity and toxicokinetics of TSR-042, when given intravenously once weekly for 13 weeks (a total of 14 doses) to cynomolgus monkeys, and to evaluate the potential reversibility of any findings were determined in the study report No. 4010-09-003. In males and females across all dose levels tested, Tmax ranged from 5 minutes post-dose to 168 hr post-dose on Day 1 and ranged from 5 minutes post-dose to 96 hr post-dose on Day 85. By Day 85, steady state serum dostarlimab concentration was achieved in males and females in all dose levels tested. Half-life (t1/2), volume of distribution (Vd) and clearance (CL) could not be estimated in any dose levels tested on Days 1 and 85 because of the

sustained serum dostarlimab concentration within the dosing interval. Exposure of dostarlimab as defined by AUC(0-168) increased in a roughly dose-proportional manner in males and females across all dose levels tested on Days 1 and 85.

AUC(0-168) increased in males and females on Day 85 relative to Day 1 in all dose groups, suggesting TSR-042 accumulation following repeated weekly dosing. Mean accumulation ratios for AUC(0-168) ranged from 2.22 to 3.62 in males and females across all dose groups. No relevant gender difference was observed in TSR-042 exposure, as defined by AUC(0-168), across all dose levels tested and gender ratios (male/female) ranged from 0.660 to 1.47.

**Table 10**: **Summary of Toxicokinetic Parameters in Male and Female Monkeys Following Intravenous Administration of TSR-042 once weakly for 13 weeks**

| Gender: | Males | | | Females | | |
|---|---|---|---|---|---|---|
| TSR-042 Dose (mg/kg/week): | 10 | 30[a] | 100 | 10 | 30 | 100 |
| Parameter (Units) | Day 1 | | | | | |
| $T_{max}$ (h) | 42.5 | 3.50 | 1.71 | 1.29 | 24.3 | 0.236 |
| $C_{max}$ (µg/mL) | 437 | 1080 | 2450 | 405 | 874 | 2850 |
| $C_{168}$ (µg/mL) | 181 | 287 | 924 | 95.1 | 403 | 1000 |
| $AUC_{(0-168)}$ (hr*µg/mL) | 34500 | 80100 | 212000 | 23500 | 81700 | 235000 |
| $AUC_{(0-168)}$/D (hr*µg/mL/(mg/kg)) | 3450 | 2670 | 2120 | 2350 | 2720 | 2350 |
| | Day 85 | | | | | |
| $T_{max}$ (h) | 13.3 | 0.0833 | 17.0 | 0.0833 | 2.27 | 1.54 |
| $C_{max}$ (µg/mL) | 937 | 1760 | 6510 | 805 | 3020 | 5960 |
| $C_{168}$ (µg/mL) | 338 | 803 | 3600 | 395 | 1390 | 3310 |
| $AUC_{(0-168)}$ (hr*µg/mL) | 69200 | 180000 | 725000 | 79800 | 272000 | 632000 |
| $AUC_{(0-168)}$/D (hr*µg/mL/(mg/kg)) | 6920 | 5990 | 7250 | 7980 | 9070 | 6320 |
| $R_{AUC}$ (Ratio) | 2.54 | 2.22 | 3.60 | 3.41 | 3.62 | 2.99 |

RAUC = $AUC_{(0-168)}$ on Day 85 / $AUC_{(0-168)}$ on Day 1; - = not applicable.
$T_{1/2}$, Vd and CL were not reported because R-square less than 0.8 or extrapolation exceeded 20%.
[a] Animal No. 3004 was excluded from mean and SD calculation due to potential impact from ATA.

## 2.3.4. Toxicology

### *Single dose toxicity*

A non-GLP study for the evaluation of toxicokinetics, immunogenicity and potential toxicity (Study 273-0016-TX) was conducted in cynomolgus monkeys following single intravenous infusion.

Three groups of 3 female and 3 male monkeys each received a single administration of Dostarlimab. The control animals (3 females and 3 males) received PBS only.

Evaluation included mortality, clinical observations (detailed and cage side), body weights, food consumption during the in-life phase, ophthalmologic examination at the last week of in life (Week 8), clinical pathology evaluations (haematology, coagulation, serum chemistry, urinalysis) on Days 15, 29, and 57, electrocardiography examinations on Day 1 and Day 54, and toxicokinetics (TK) of Dostarlimab at 0 (pre-dose), 0.5 (30 minutes), 1, 4, 24, 48, 96, 168, 240, 336, 504, 672, 1008, and 1320 hours post-dose in serum and anti-TSR-042 antibodies concentration in serum at pre-dose, on Days 15, 29, 42, and 56.

Immunogenicity results are presented under "antigenicity".

There were no TSR-042 related effects on clinical signs, body weight, food consumption, ophthalmologic examinations or electrocardiography following a single intravenous administration of TSR-042 at dose levels up to 100 mg/kg.

One male was found dead after completion of the Ophthalmologic Examinations during pretest and was subsequently replaced. The death of this monkey was not test article-related.

There were no TSR-042 effects on haematology, clinical biochemistry, or urinalysis that were related to a single intravenous administration of TSR-042 at dose levels up to 100 mg/kg.

When compared with the pretest data on Day 15, decreased haematocrit, increased Reticulocytes count, decreased White Blood Cells, including Neutrophils count were noted in all groups including control, this was considered to be caused by blood sampling, and not test article-related.

The administration of TSR-042 by a single intravenous dose to the cynomolgus monkeys at dose levels of 0, 10, 30 or 100 mg/kg did not result in any treatment-related adverse effects on clinical signs, body weight, food consumption, electrocardiography, ophthalmology, or clinical pathology. The no-adverse effect-level (NOAEL) was considered to be 100 mg/kg in this study. At NOAEL, the Cmax and the AUC0-1320h were 3400µg/mL and 426000 h*µg/mL for males, respectively, and 2930 µg/mL and 437000 h*µg/mL for females, respectively.

## *Repeat dose toxicity*

**Study no. 273-0022-TX**

A GLP repeat dose toxicity, toxicokinetics and safety pharmacology study were conducted in the cynomolgus monkey. The study consisted in 4-week repeated intermittent intravenous infusion with 4-week recovery (study no. 273-0022-TX, GLP study).

Forty-eight (48) adult cynomolgus monkeys were randomly assigned to 4 groups, 6/sex/group. Animals were administered 0, 10, 30, or 100 mg/kg/dose TSR-042 once every week for 4 weeks (five doses in total) by 15-minute intravenous infusion.

Four animals/sex/group were subjected to a full gross necropsy on Day 30, 1 day post the last dose (the 5th dose). The remaining 2 animals/sex/group were assigned for a 4 weeks treatment-free recovery period and were subjected to a full gross necropsy on Study Day 58 (end of recovery phase).

Parameters evaluated during the study included mortality, clinical observations including body weights, body weight changes, food evaluation, ophthalmologic examinations, neurological examinations, electrocardiography, blood pressure and respiration, clinical pathology (hematology, clinical chemistry, coagulation, urinalysis), toxicokinetics, and anti-drug-antibody (ADA) analysis, gross pathology, organ weights, and histopathology.

Actual concentration and homogeneity of the formulations met the acceptance criteria (100-104%).

Immunogenicity results are presented under "antigenicity".

There were no test article-related mortality, clinical signs, effects on body weight or appetite, or findings in ophthalmologic examinations, safety pharmacology parameters (neurological examinations, electrocardiography, blood pressure, and respiration), haematology, clinical pathology, urinalysis, gross pathology, histopathology, bone marrow smears, and organ weights during the dosing phase or recovery phase.

At the injection site, minimal to mild haemorrhage, neutrophilic infiltrates, lymphohistiocytic infiltrates, fibrosis, and/or necrosis were observed across all dose groups and were considered to be related to the infusion procedure.

**Study No. 4010-09-003**

A GLP repeat dose toxicity, toxicokinetics and safety pharmacology study were conducted in the cynomolgus monkey. The study consisted in 13-Week Once Weekly Intravenous Toxicity Study in Cynomolgus Monkeys with an 8-Week Recovery Period (GLP).

The objective of this study was to determine the potential toxicity and toxicokinetics of TSR-042, when given intravenously once weekly for 13 weeks (a total of 14 doses) to cynomolgus monkeys and to evaluate the potential reversibility of any findings.

TSR-042 was administered intravenously to cynomolgus monkey (N= 4/sex/dose) once a week for 13 weeks, at doses of 0, 10, 30 and 100 mg/kg. Control and the highest dose had 6 animals/sex/dose, and after the dosing period, 2 animals/sex/dose continued free of TSR-042 for an 8-week recovery period.

The following parameters and endpoints were evaluated in this study: clinical signs, body weights, body weight gain, food evaluation, ophthalmology, electrocardiogram, body temperature, blood pressure and heart rate, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), bioanalysis, toxicokinetic, anti-therapeutic antibody, immunophenotyping, and T-cell dependent antibody response (TDAR), plasma cytokine, gross necropsy findings, organ weights, and histopathologic examinations.

One male dosed at 10 mg/kg/week was euthanized on Day 89 due to chronic, unresolved generalized skin findings and secondary swollen and firm inguinal lymph nodes. Gross findings included generalized pale tan scaling of the skin and dark black thickening of the ears (pinna) and enlargement of inguinal and axillary lymph nodes. Microscopic findings noted in the skin of this animal included moderate mononuclear cell inflammation, acanthosis, single cell keratinocyte death/apoptosis throughout all epidermal layers, hyperkeratosis, superficial dermal oedema, spongiosis, intraepithelial lymphocyte infiltrates, increased pigmentation, perivascular mononuclear cell infiltrate, and deposition of basophilic extracellular matrix in the superficial dermis. Additional microscopic findings noted in this animal included mildly to moderately increased lymphoid cellularity in the axillary, mandibular, and inguinal lymph nodes and minimally increased cellularity in the spleen. These changes were considered secondary to the dermal findings.

All remaining animals survived to their scheduled necropsy.

Liquid faeces was considered a possible TSR-042-related effect at ≥ 30 mg/kg/week given the increased incidence over concurrent controls and timing relative to dosing. This transient, sporadic, clinical sign was not considered adverse since there were no associated changes in food consumption or body weight as well as lack of associated pathology findings.

There were no test article-related changes in body weight, food consumption, electrocardiogram, body temperature, blood pressure, heart rate, clinical pathology, immunophenotyping (T-cells, B-cells, NK cells and monocytes), TDAR, plasma cytokine (IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-10, TNFα, and IL-17), organ weight, or gross findings.

Microscopic findings were observed in the kidney (mild to moderate mononuclear infiltrates in the interstitium of 1 male at 10 mg/kg/week and 1 female at 30 mg/kg/week), liver (mild mixed cell inflammation in 1 male at 30 mg/kg/week) and heart (mild mononuclear cell myocardial infiltrates accompanied by minimal multifocal myocardial degeneration in 1 female at 100 mg/kg/week) at the end of the dosing period. Mild mononuclear cell myocardial infiltrates accompanied by minimal

multifocal myocardial degeneration were also noted in one male at 100 mg/kg/week following the 8-week recovery.

Because of the euthanasia of 1 male at 10 mg/kg/week, the no-observed-adverse-effect level (NOAEL) could not be determined under the conditions of this study.

### *Genotoxicity*

Genotoxicity studies with dostarlimab were not submitted (see discussion on nonclinical aspects).

### *Carcinogenicity*

Carcinogenicity studies with dostarlimab were not submitted (see discussion on nonclinical aspects).

### *Reproduction toxicity*, Fertility and early embryonic development

Studies on reproduction and embryonic development were not submitted (see discussion on nonclinical aspects).

### Embryo-foetal development

Studies on reproduction and embryo-foetal development were not submitted (see discussion on nonclinical aspects).

### Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile animal toxicity studies were provided. (see discussion on nonclinical aspects).

### *Local Tolerance*

No local tolerance study was submitted. The injection sites were monitored and examined in the single-dose and repeat-dose IV monkey toxicity studies (Study 273-0016-TX; Study 273-0022-TX; Study 4010-09-003). No dostarlimab-related local irritation or toxicity was observed.

### *Other toxicity studies*

#### Antigenicity

Antigenicity evaluation was performed within toxicity studies. In the three toxicity studies, cynomolgus monkey were dosed with 0, 10, 30 and 100 mg/kg bw.

**Table 11: Incidence of anti-therapeutic antibody positive results in cynomolgus monkeys administered TSR-042 (single IV administration)**

| Dosage (mg/kg/dose) | Number of animals that developed Anti-Drug antibody | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | | Females | | | | | |
| | Pretest | Day 15 | Day 29 | Day 42 | Day 56 | Percentage[a] (%) | Pretest | Day 15 | Day 29 | Day 42 | Day 56 | Percentage[a] |
| 0 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0.00 | 0/3 | 0/3 | 1/3 | 1/3 | 1/3 | 25.0 |
| 10 | 0/3 | 0/3 | 2/3 | 2/3 | **2/3** | **50.0** | 0/3 | 0/3 | 0/3 | 0/3 | **2/3** | **16.66** |
| 30 | 1/3 | 0/3 | 2/3 | 2/3 | 2/3 | 50.0 | 0/3 | 0/3 | 0/3 | 0/3 | 0/3 | 0.00 |
| 100 | 0/3 | 0/3 | 1/3 | 2/3 | 2/3 | 41.7 | 0/3 | 0/3 | 1/3 | 2/3 | 2/3 | 41.7 |

Note: [a]: percentage= number of positive results / total number of sample

**Table 12: Incidence of anti-therapeutic antibody positive results in cynomolgus monkeys administered TSR-042 (4-week repeated IV administration)**

| Dosage (mg/kg/dose) | Number of animals that developed Anti-Drug antibody | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | | Females | | | | | |
| | Pretest | Day 15 | Day 29 | Day 42 | Day 57 | Percentage[a] (%) | Pretest | Day 15 | Day 29 | Day 42 | Day 57 | Percentage[a] |
| 0 | 0/6 | 0/6 | 0/6 | 0/2 | 0/2 | 0.00 | 0/6 | 0/6 | 0/6 | 0/2 | 0/2 | 0.00 |
| 10 | 0/6 | 0/6 | 1/6 | 0/2 | 0/2 | 6.25 | 1/6 | 3/6 | 0/6 | 0/2 | 0/2 | 18.75 |
| 30 | 0/6 | 0/6 | 0/6 | 0/2 | 0/2 | 0.00 | 0/6 | 0/6 | 0/6 | 1/2 | 1/2 | 12.5 |
| 100 | 0/6 | 0/6 | 0/6 | 0/2 | 0/2 | 0.00 | 1/6 | 1/6 | 1/6 | 0/2 | 0/2 | 12.5 |

**Table 13 Incidence of anti-therapeutic antibody positive results in cynomolgus monkeys administered TSR-042 (13-week repeated IV administration)**

| | Group 1 | | Group 2 | | Group 3 | | Group 4 | |
|---|---|---|---|---|---|---|---|---|
| Study Day | M | F | M | F | M | F | M | F |
| 1 | 0/6 | 0/6 | 0/4 | 0/4 | 1/4 | 0/4 | 1/6 | 1/6 |
| 15 | 0/6 | 0/6 | 1/4 | 1/4 | 3/4 | 2/4 | 3/6 | 2/6 |
| 29 | 0/6 | 0/6 | 1/4 | 3/4 | 4/4 | 2/4 | 4/6 | 3/6 |
| 57 | 0/6 | 0/6 | 1/4 | 3/4 | 4/4 | 0/4 | 2/6 | 3/6 |
| 85 | 0/6 | 0/6 | 1/4 | 2/4 | 2/4 | 0/4 | 1/6 | 3/6 |
| 92 | 0/6 | 0/6 | 0/4 | 2/4 | 1/4 | 0/4 | 0/6 | 2/6 |
| 99 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 1/2 |
| 106 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 2/2 |
| 113 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 1/2 |
| 120 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 1/2 |
| 134 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 1/2 |
| 148 | 0/2 | 0/2 | NA | NA | NA | NA | 0/2 | 2/2 |
| Sub-total | 0/6 | 0/6 | 1/4 | 3/4 | 4/4 | 2/4 | 6/6 | 4/6 |
| Positive Rate (%) | 0% | 0% | 25% | 75% | 100% | 50% | 100% | 67% |

**Immunotoxicity**

Immunotoxicity were integrated in the *in vitro* pharmacology studies (binding to FcγR1 [CD64], binding to complement component C1q, and effect on cytokine release by human PBMCs) and as part of single- or repeat-dose toxicity studies in cynomolgus monkeys (immunophenotyping, immunogenicity [ADA formation], cytokine levels, and TDAR).

In the 13-week toxicity study, skin findings consistent with the features of an immune reaction were noted in 1 low-dose animal. In addition, sporadic microscopic findings of an immune-mediated nature were noted in the kidney, liver, or heart of 1 to 2 animals per group dosed with dostarlimab. The incidence or severity of these findings was not dose-related.

## 2.3.5. Ecotoxicity/environmental risk assessment

The provided ERA consists of a justification for not performing any ERA studies due to the nature of the product being a monoclonal antibody unlikely to result in a significant risk to the environment. Monoclonal antibodies are broken down by proteolysis and the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, dostarlimab is not expected to pose a risk to the environment (see discussion on non-clinical aspects).

## 2.3.6. Discussion on non-clinical aspects

**Pharmacology**

Cross-species binding activity was investigated for humans and different animal species. Findings were consistent with sequence homology, supporting the cynomolgus monkey as an appropriate species for toxicological evaluation.

The potency and selectivity of dostarlimab were evaluated *in vitro* using biochemical and cellular signalling assays and the anti-tumour activity of dostarlimab was evaluated *in vitro*. Due to the lack of reactivity between anti-human PD-1 antibodies like dostarlimab and mouse PD-1, a surrogate rat IgG2a anti-mouse PD-1 antibody was instead used to describe the activity of PD-1 inhibition in a mouse allograft model. From a non-clinical point of view, exposure-response relationship and the posology in patients appear to be justified. *In vitro* and *in vivo* proof of concept is considered established.

Using human PBMCs it was shown that dostarlimab did not induce significant production of cytokines, and it is unlikely that dostarlimab will independently induce cytokine release. Further, it was shown that dostarlimab did not bind to C1q and is thus not likely to activate complement and exert complement-dependent cytotoxicity (CDC). Dostarlimab binding to the low-affinity Fc-γ receptor CD64 (FcγR1) was low and consistent with its IgG4 framework, therefore dostarlimab is unlikely to elicit ADCC.

No dedicated safety pharmacology studies were performed. Safety pharmacology core battery endpoints (CNS, cardiovascular and respiratory) were investigated in the 4-week repeat dose toxicity study (Study 273-0022-TX). No dostarlimab-related effects were observed following administration of 0, 10, 30 or 100 mg/kg/day dostarlimab. Some statistically significant changes were observed sporadically, but as no systematic dose dependent changes were observed, they were deemed not to be related to treatment with dostarlimab.

Pharmacodynamic drug interactions studies were not provided which was considered acceptable as dostarlimab is intended as monotherapy. Furthermore, it is acknowledged that interaction with CYP 450 or drug transporters are unlikely to occur for monoclonal antibodies and no further information is required.

**Pharmacokinetics**

The pharmacokinetics (ADME) of dostarlimab was evaluated as part of the general toxicity studies in cynomolgus monkeys. Distribution, metabolism and excretion was not investigated, which is acceptable according to ICH S6.

The methods developed to measure dostarlimab and anti-dostarlimab antibody in cynomolgus monkey serum in support of the GLP pivotal toxicological studies have been suitably validated.

The PK after both single and repeat dosing appear well described in monkeys with an approximately dose proportional increase in exposure. PK properties of dostarlimab showed long half-life, low

clearance and a low steady state distribution volume in the range of the plasma volume for monkeys, which indicates that dostarlimab remains mainly in the vascular system. There were no significant gender differences. It appeared that accumulation of dostarlimab (2.1 to 3.6-fold) occurred in monkeys in the TK investigations.

Neutralising anti-drug antibodies (ADA) was investigated following single and repeat dose administration. It was found that between 33.3-66.7% of the single dose animals and 8.33-75% of the repeat dose animals developed ADA during the studies. ADA incidences were however correlated with overall TK parameters and compared to animals negative for ADAs and no significant impact on TK were observed. One ADA-positive animal in the 13-week repeat dose study did however show fast clearance of dostarlimab, suggesting that its elimination kinetics were affected by the presence of ADA. This animal was excluded from the group mean analysis. ADA in animals does not necessarily predict the clinical situation, however, in the present studies, ADA development did not affect serum concentration of dostarlimab in general.

The applicant did not submit studies on distribution, metabolism and excretion. This is acceptable as in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6), no tissues distribution studies, metabolism studies, mass balance investigations are considered necessary. The low volume of distribution ranging between 43.9-48.4 mL/kg at steady state suggests that most of the monoclonal antibody remains in the bloodstream. The metabolism and clearance of dostarlimab *in vivo* is expected to follow the degradation route of mABs in general, via biochemical pathways that are independent of metabolising enzymes. Dostarlimab is expected to be degraded into small peptides, amino acids and small carbohydrates, that are eliminated by renal excretion or returned to the nutrient pool.

The lack of PK drug-drug interaction studies is acceptable as it is assumed that interaction with metabolising enzymes and transporters will not occur *in vivo* or via cytokines.

**Toxicology**

Overall the toxicology study package is in line with what is expected based on ICH S9, ICH S6 and ICH M3 (R2) for a monoclonal antibody with only one pharmacologically active species (Cynomolgus monkey), for a biopharmaceutical intended for advanced cancer.

The single dose and repeat dose studies of 4- and 13-week duration were all performed with similar dose levels of dostarlimab (10, 30 and 100 mg/kg).

No adverse toxicities were observed in the single dose toxicity study and the high dose level (100 mg/kg) was considered to be the NOAEL.

Dostarlimab was well tolerated by most animals following repeated dose administration once weekly for 4 or 13 weeks at 10, 30 and 100 mg/kg. No dostarlimab related findings were made in the 4-week toxicity study, where safety pharmacology endpoints were included. Sporadic and dose unrelated macroscopic and/or microscopic findings of an immune-mediated nature were observed in the skin, kidney, liver, or heart of 1 to 2 animals/group dosed with dostarlimab. It was uncertain whether these findings were dostarlimab related as they were not seen in any other dostarlimab dosed animals.

In the 13 weeks study, one male animal presented with a skin-condition during the first week after start of treatment, which despite efforts to treat the skin condition, worsened during the study, and ultimately the animal had to be euthanised on Day 89. Histological findings were consistent with an immune response. The animal did develop ADA, but these were not considered to have contributed to the condition given the low titer of ADA and the lack of correlation between the titer and progression of skin findings. The skin condition could not be excluded to be related to treatment with dostarlimab and

could be due to the pharmacologic effect of dostarlimab. Due to the finding in this animal, no NOAEL could be established for this study.

In general, the exposure margins in animals are considered sufficient. In both the single dose and 2-week repeat dose study, the high dose group (100 mg/kg/day administered once weekly) was established as the NOAEL. This is supported, as no dostarlimab related toxicities were identified in these studies. However, in the 13-week repeat dose study, the NOAEL could not be established, due to the finding described above occurring in one animal in the low dose group (10 mg/kg). At this dose level, the AUC0-168h was 74,500 µg•h/mL, corresponding to approximately 6 and 5 times the clinical exposure at 500 mg Q3W andQ6W. respectively.

Overall, dostarlimab appears to be well tolerated and no special hazard were identified for humans based on repeat-dose toxicity studies of duration up to 3 months in the cynomolgus monkey (see SmPC section 5.3).

No studies have been performed to assess the potential of dostarlimab for carcinogenicity or genotoxicity which was considered acceptable based on ICH S6 (R1). In addition, the ICH S9 guidance for development of therapeutics intended to treat patients with advanced cancer specify that carcinogenicity studies are not needed for these indications.

Animal reproduction and development toxicity studies have not been conducted with dostarlimab. A literature-based risk assessment was provided and identified that there may be a reproductive risk following treatment with dostarlimab, as PD-1/L1 pathway is involved in the foeto-maternal tolerance, and normal function is considered important in upholding a normal pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of dostarlimab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth (see SmPC section 5.3). Therefore, dostarlimab is not recommended during pregnancy and in women of childbearing potential not using contraception (see SmPC section 4.6) and the risks have been reflected in the SmPC.

While fertility studies were not submitted, no notable effects on the male and female reproductive organs were observed in monkeys in the 1 month and 3 month repeat dose toxicology studies; however, these results may not be representative at all of the potential clinical risk because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown (see SmPC section 5.3).

No juvenile animal toxicity studies were provided. Toxicology studies for dostarlimab were performed in cynomolgus monkeys aged 2.5 to 5.1 years. This is equivalent to ≥10 years for humans. No specific issues were observed in the cynomolgus monkeys that warrant studies in younger animals

No additional reproductive and developmental studies are planned in order to reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles (ICH M3 [R2]) which is considered acceptable.

No stand-alone local tolerance studies were performed. Observation of injection site reactions were incorporated in the single and repeated dose toxicity studies. No dostarlimab related local tolerance issues were observed in cynomolgus monkeys.

The lack of any metabolite studies is accepted considering the product being a monoclonal antibody which is expected to be degraded by proteolytic pathways.

Impurities were not studied in the non-clinical setting. The test item batch used in the 13-week repeat dose study was also used in the clinical study GARNET. The test item batch used in the 4-week repeat

dose study, as well as the definitive TCR studies was from an earlier production process; however, it was demonstrated to be comparable to clinical batch.

The tissue-cross reactivity studies performed in human and Cynomolgus monkey tissues did not show any unexpected binding.

No ERA studies were submitted which is acceptable considering the nature of the product in line with the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 21 *). Dostarlimab being a monoclonal antibody is unlikely to result in a significant risk to the environment.

## 2.3.7. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* pharmacology was conducted in disease models for dostarlimab, supporting the intended clinical use. Nonclinical proof of concept as an inhibitor of PD-1 ligand binding appear well-established.

Pharmacokinetics of dostarlimab is well described, and no deficiencies were identified.

An abbreviated toxicology program was performed, in line with the ICH S6, ICH M3 (R2) and ICH S9 guidelines. Safety pharmacology endpoints were included in the 4 week repeat-dose toxicity study. No reproductive investigations were performed, but a literature-based risk assessment was presented. In principle the minimal toxicology program can be considered sufficient.

The SmPC reflects the findings of the toxicity studies, as well as the reproductive risk based on current knowledge from the literature.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Table 14: Tabular overview of clinical studies**

| Phase of Study | Study Identifier Title | Location of Study Report | Study Objective | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Patient Population | Treatment Duration | Study Status; Report Type |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 4010-01-001 (GARNET)<br>A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors | Module 5.3.3.2: Parts 1 + 2A<br><br>Module 5.3.5.2: Part 2B Cohorts A1 + A2<br><br>Module 5.3.5.4: Part 2B Cohort E and Part 2B Cohort F | Part 1/2A: To establish an RP2D for dostarlimab based on safety and tolerability, PK, and PDy in patients with advanced solid tumors<br>Part 2B: To confirm the RP2D and establish the safety and clinical activity of dostarlimab in patients with advanced solid tumors | Multicenter, open-label, first-in-human, 2-part, dose escalating and expansion study | Part 1 (dose escalation): dostarlimab 1, 3, or 10 mg/kg Q2W IV<br>Part 2A (fixed-dose): Q6W Cohort - dostarlimab 1,000 mg Q6W IV; Q3W Cohort - dostarlimab 500 mg Q3W IV<br>Part 2B (expansion): dostarlimab 500 mg Q3W IV for first 4 cycles, dostarlimab 1,000 mg Q6W IV for all subsequent cycles (all cohorts) | Part 1: 21<br>Part 2A: 13<br>Part 2B:<br>Cohort A1 - 107<br>Cohort A2 - 161<br>Cohort E - 67<br>Cohort F - 109 | Parts 1 and 2A: Patients with advanced solid tumors<br>Part 2B:<br>Cohort A1 - Patients with dMMR/ MSI-H endometrial cancer<br>Cohort A2 - Patients with MMRp/ MSS endometrial cancer<br>Cohort E - Patients with NSCLC<br>Cohort F - Patients with dMMR/ MSI-H or POLE-mut solid tumors | Up to 2 years or until the subject meets protocol specific discontinuation criteria | Ongoing;<br>Full CSR Parts 1 + 2A<br><br>Full CSR Part 2B Cohorts A1 + A2<br><br>Synoptic CSR Part 2B Cohort E<br><br>Full CSR Part 2B Cohort F |

### 2.4.2. Pharmacokinetics

Clinical pharmacology data with dostarlimab is available from clinical study 4010-01-001 (GARNET).

Dostarlimab was characterized using population PK analysis from 477 patients with various solid tumours, including 267 patients with EC.

**Analytical Methods**

**PK Assays**

ELISA bioanalytical methods were validated and used for the determination of dostarlimab concentration in human serum.

*Immunogenicity assays*

Two immunogenicity assays were validated. An electrochemiluminescence (ECL) method was utilized to detect, confirm, and determine the titre of anti-dostarlimab antibodies in human serum. The analysis was performed in three stages consisting on an initial screening followed by a confirmatory analysis and a titre analysis.

Positive samples were tested for neutralizing anti-dostarlimab antibodies (NAb) by a competitive ligand-binding assay with ECL. In this method, samples are pre-cleaned to remove dostarlimab from the serum and then mixed with a fixed amount of dostarlimab to form a NAb-drug complex.

## *Absorption*

No studies assessing absorption were submitted as dostarlimab is administered intravenously.

## *Distribution*

Based on POSTHOC parameters, dostarlimab had a mean steady state systemic clearance of 0.00742 L/hr, a steady-state mean volume of distribution of 5.34 L and a mean terminal half-life of 25.4 days. The population clearance estimate was approximately 15.5% lower at steady state when compared to single dose. POSTHOC parameter estimate summaries are presented below.

**Table 15: Dostarlimab POSTHOC PK parameter summary (population PK analysis)**

| Parameter | N | Mean | Sd | CV% | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Clearance (L/HR) | 477 | 0.008778 | 0.002750 | 31.3 | 0.00392 | 0.0209 |
| Central compartment volume (L) | 477 | 3.121 | 0.6581 | 21.1 | 0.888 | 6.08 |
| CLss (L/HR) | 477 | 0.007420 | 0.002325 | 31.3 | 0.00331 | 0.0177 |
| Vss (L) | 477 | 5.344 | 0.6581 | 12.3 | 3.11 | 8.31 |
| Distribution half-life (HR) | 190 | 30.64 | 2.745 | 9.0 | 16.7 | 39.3 |
| Terminal half-life (days) | 190 | 25.39 | 6.088 | 24.0 | 11.3 | 52.2 |

Notes: CV=Coefficient of variation; N=Number of parameters; Sd=Standard Deviation.
Source: Appendix 10.2

Note: POSTHOC: posterior conditional estimation

## *Elimination*

No metabolism or excretion studies with dostarlimab were submitted (see discussion on clinical pharmacology).

*Excretion*

The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects.

In Study 4010-01-001 (GARNET), geometric mean values of CL ranged from 6.677 to 13.60 mL/h for Part 1 and were 9.007 and 8.814 mL/h in Part 2A after 500 mg Q3W and 1000 mg Q6W, respectively.

The half-life ranged from 244.4 to 491.0 hours (10.2 to 20.5 days) in Part 1. For Part 2A, geometric mean values were within the range observed for Part 1 data (346.8 and 469.3 hours for t1/2).

## *Dose proportionality and time dependencies*

### Dose proportionality and Time dependency

Statistical assessment of dostarlimab dose-proportionality for Part 1 over a dose range of 1 mg/kg to 10 mg/kg in Cycle 1 is presented in Table 16 below.

**Table 16: Summary of assessment for Dostarlimab dose proportionality in Part 1 Cycle 1**

| Pharmacokinetic Parameter | n | Slope | | |
|---|---|---|---|---|
| | | Estimate | Standard error | 90% Confidence Interval |
| $C_{max}$ (µg/mL) | 21 | 1.06 | 0.04 | (0.99, 1.13) |
| $AUC_{(0\text{-}inf)}$ (µg*h/mL) | 19 | 1.08 | 0.10 | (0.90, 1.26) |
| $AUC_{(0\text{-}tau)}$ (µg*h/mL) | 20 | 1.10 | 0.08 | (0.96, 1.24) |

Source: Table 14.2.9

Multiple-dose PK data were limited to few subjects for Part 1 and Part 2A (n < 3 per DL for each PK parameter at all levels).

Albeit based on limited available data, in comparison to Cycle 1, data in multiple-dose cycles generally indicated an intra-individual decrease in clearance (with exception of one subject in the 10 mg/kg PK/PDy treatment group).

Following multiple-dose administration, accumulation of dostarlimab ranged between 180% to 374% for AUC(0-tau) and 126% to 259% for Cmax in Part 1 and 2A.

**Table 17: Summary of dostarlimab PK parameters for each treatment for Part 1 Cycle 6**

| | Geometric Mean (GCV%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $AUC_{(0\text{-}tau)}$ (µg*h/mL) | $C_{max}$ (µg/mL) | $t_{max}$ [a] (h) | $C_{min}$ (µg/mL) | $t_{min}$ [a] (h) | $t_{1/2}$ (h) | CL (mL/h) | $V_{ss}$ (mL) | $RAUC_{(0\text{-}tau)}$ (%) | $RC_{max}$ (%) |
| **1 mg/kg, DLT-eval (N = 1)** | 8970 | 42.1 | 1.43 | 17.3 | 336.23 | 292 | 14.9 | 6250 | 184 | 145 |
| **1 mg/kg, PK/PDy (N = 1)** | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) | ND (n=0) |
| **3 mg/kg (N=2)** | 31800 – 43500 | 156 - 186 | 2.27 (1.52 – 3.02) | 71.2 - 110 | 167.19 (0.00 – 334.38) | 423 [b] | 3.68 - 6.67 | 4130 [b] | 328 - 374 | 230 - 259 |
| **10 mg/kg, DLT-eval (N = 1)** | 96000 | 395 | 1.55 | 216 | 0.00 | 595 | 6.25 | 5400 | 302 | 223 |
| **10 mg/kg, PK/PDy (N = 1)** | 121000 | 531 | 1.52 | 214 | 0.00 | 571 | 8.71 | 7000 | 197 | 152 |

[a] Median (range)
[b] n = 1
For n = 2 only minimum and maximum value are presented; for n=1 only the respective value is presented.
Note that $AUC_{(0\text{-}tau)}$ is identical to $AUC_{(0\text{-}last)}$ and hence only one parameter is presented.
Abbreviations: GCV% = geometric coefficient of variation; ND = not determined.
Source: Table 14.2.7.

**Table 18: Summary of dostarlimab PK parameters for each treatment for Part 2A Cycle 5 (Q3W) or Cycle 4 (Q6W)**

| | Geometric Mean (GCV%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $AUC_{(0\text{-}tau)}$ (µg*h/mL) | $C_{max}$ (µg/mL) | $t_{max}$ [a] (h) | $C_{min}$ (µg/mL) | $t_{min}$ [a] (h) | $t_{1/2}$ (h) | CL (mL/h) | $V_{ss}$ (mL) | $RAUC_{(0\text{-}tau)}$ (%) | RCmax (%) |
| **500 mg Q3W (N = 2)** | 53300 - 98000 | 207 - 275 | 47.99 (1.47 – 94.50) | 62.7 - 125 | 252.49 (0.00 – 504.97) | 423 - 454 | 5.10 – 9.38 | 3410 - 5310 | 180 - 239 | 126 – 161 |
| **1000 mg Q6W (N = 1)** | ND (n=0) | 472 | 0.53 | ND (n=0) | ND (n=0) | 715 | ND (n=0) | 3680 | ND (n=0) | 150 |

[a] Median (range)
For n = 2 only minimum and maximum value are presented; for n=1 only the respective value is presented.
Note that $AUC_{(0\text{-}tau)}$ is identical to $AUC_{(0\text{-}last)}$ and hence only one parameter is presented.
Abbreviations: GCV% = geometric coefficient of variation; ND = not determined.
Source: Table 14.2.8.

When dosed at the recommended therapeutic dose (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks), dostarlimab showed an approximate two-fold accumulation ($C_{min}$) starting cycle 4 through cycle 12, consistent with the terminal half-life ($t_{1/2}$).

Exposure (both maximum concentration [$C_{max}$] and the area under the concentration-time curve, [$AUC_{0\text{-}tau}$] and [$AUC_{0\text{-}inf}$]) was approximately dose proportional (see SmPC section 5.2).

**Pharmacokinetics in the target population**

Base population PK model

Inter-individual variability was tested on all central compartment parameters for 1-compartment models and intercompartmental clearances (Q) and the peripheral volumes of distribution (V2) for 2-compartment models. Residual error was modelled as proportional, additive, and additive plus proportional.

The final base model selected was a 2-compartment model with IIV on clearance (CL) and central volume of distribution (V1) with a proportional residual error model (base model 2C11) and an off-diagonal correlation between CL and V1. This term was carried forward for all subsequent model building.

The population typical values and residual variability (RSV) estimates are shown in Table 19 . The precision for all structural model parameters and RSV estimates, as measured by relative standard error (RSE%), was less than 25%. The final base PK model fitted the data adequately. The population typical values and residual variability (RSV) estimates are shown in Table 19. The precision for all structural model parameters and RSV estimates, as measured by relative standard error (RSE%), was less than 25%.

**Table 19: Population PK parameters of base model 2C11**

| | Titles | Error type | Estimate | CV or Sd | SE | RSE (%) | Lower CI | Upper CI |
|---|---|---|---|---|---|---|---|---|
| Output: | | | | | | | | |
| Status: | MINIMIZATION SUCCESSFUL | | | | | | | |
| OFV: | | | 31056.37 | | | | | |
| Condition No: | | | 85.47 | | | | | |
| THETA(1) | Clearance (L/HR) | | 0.00822 | | 0.000258 | 3.141 | 0.007714 | 0.008726 |
| THETA(2) | Central Compartment Volume (L) | | 3.02 | | 0.03354 | 1.111 | 2.954 | 3.086 |
| THETA(3) | Intercompartmental clearance (L/HR) | | 0.0285 | | 0.002629 | 9.225 | 0.02335 | 0.03365 |
| THETA(4) | Peripheral Compartment Volume (L) | | 2.07 | | 0.09986 | 4.824 | 1.874 | 2.266 |
| THETA(5) | Imax | | -0.249 | | 0.03239 | 13.01 | -0.3125 | -0.1855 |
| THETA(6) | TI50 (Hours) | | 2080 | | 209.9 | 10.09 | 1669 | 2491 |
| THETA(7) | Hill coefficient | | 3.7 | | 0.8744 | 23.63 | 1.986 | 5.414 |
| THETA(8) | Weight Scaling on CL | | 0.512 | | 0.06508 | 12.71 | 0.3845 | 0.6395 |
| THETA(9) | Weight Scaling on V1 | | 0.475 | | 0.04198 | 8.837 | 0.3927 | 0.5573 |
| ETA(1) | Between Subject Variability (CL) | Exponential | 0.08388 | CV = 29.58% | 0.006456 | 7.697 | 0.07123 | 0.09653 |
| ETA(1,2) | Off-diagonal correlation (CL-V1) | Off-Diagonal Correlation | 0.02293 | CORR = 0.4185 | 0.003809 | 16.61 | 0.01546 | 0.0304 |
| ETA(2) | Between Subject Variability (V1) | Exponential | 0.03579 | CV = 19.09% | 0.002228 | 6.225 | 0.03142 | 0.04016 |
| EPS(1) | Within Subject Variability | Proportional | 0.03012 | CV = 17.36% | 0.000337 | 1.117 | 0.02946 | 0.03078 |

Notes: CI=Confidence interval; CV=Coefficient of variation; SE=Standard error; RSE=Relative standard error. CI is the parametric 95% confidence interval.
Source: Appendix 5

Final population PK model

The final model incorporated several covariates: albumin on central clearance, alkaline phosphatase on central volume, alkaline phosphatase on central clearance, SLDR on central clearance, sex on central volume, positive ADA on central clearance, and age on central clearance. Its inclusion partially reduced the inter-individual variability on CL (37% to 30%) and V1 (23% to 19%).

**Table 20: population PK parameters of covariate model 814**

| Parameters | Form | Estimate | CV or Sd | SE | RSE | Low CI | Upper CI | shrinkage |
|---|---|---|---|---|---|---|---|---|
| OFV | | 30728.88 | | | | | | |
| Condition No | | 84.83 | | | | | | |
| Clearance (L/HR) | | 0.00687 | | 0.000194 | 2.82 | 0.00649 | 0.00725 | |
| Central Compartment Volume (L) | | 3.22 | | 0.06263 | 1.945 | 3.097 | 3.343 | |
| Intercompartmental Clearance (L/HR) | | 0.0278 | | 0.002158 | 7.764 | 0.02357 | 0.03203 | |
| Peripheral Compartment Volume (L) | | 2.22 | | 0.09004 | 4.056 | 2.044 | 2.396 | |
| Imax | | -0.168 | | 0.02953 | 17.58 | -0.2259 | -0.1101 | |
| TI50 (HR) | | 2180 | | 221.1 | 10.14 | 1747 | 2613 | |
| Hill Coefficient | | 5.01 | | 2.165 | 43.21 | 0.7666 | 9.253 | |
| Weight Scaling on CL | | 0.52 | | 0.06246 | 12.01 | 0.3976 | 0.6424 | |
| Weight Scaling on V1 | | 0.479 | | 0.04211 | 8.791 | 0.3965 | 0.5615 | |
| ALB Scaling on CL | | -0.958 | | 0.05463 | 5.703 | -1.065 | -0.8509 | |
| ALP Scaling on V1 | | 0.0884 | | 0.01407 | 15.92 | 0.06082 | 0.116 | |
| ALP Scaling on CL | | 0.101 | | 0.01533 | 15.18 | 0.07096 | 0.131 | |
| SLDR Scaling on CL | | 0.0722 | | 0.009872 | 13.67 | 0.05285 | 0.09155 | |
| Sex on V1 | | 0.919 | | 0.0197 | 2.143 | 0.8804 | 0.9576 | |
| ADBA on CL | | 1.17 | | 0.05147 | 4.399 | 1.069 | 1.271 | |
| Age Scaling on CL | | -0.251 | | 0.07929 | 31.59 | -0.4064 | -0.09559 | |
| Between Subject Variability (CL) | Exponential | 0.06231 | CV = 25.36% | 0.006163 | 9.891 | 0.05023 | 0.07439 | 17% |
| Off-diagonal Correlation (CL-V1) | Off-Diagonal Correlation | 0.01826 | CORR = 0.3987 | 0.003491 | 19.12 | 0.01142 | 0.0251 | |
| Between Subject Variability (V1) | Exponential | 0.03366 | CV = 18.5% | 0.002128 | 6.322 | 0.02949 | 0.03783 | 9.86% |
| Within Subject Variability | Proportional | 0.0283 | CV = 16.82% | 0.000328 | 1.157 | 0.02766 | 0.02894 | 8.75% |

Notes: ADBA=Anti-drug binding antibody; ALB=Albumin; ALP=Alkaline phosphatase; CI=Confidence interval; CV=Coefficient of variation; IIV=Inter-individual variability; RSE=Relative standard error; Sd=Standard deviation; SE=Standard error; SLDR= Sum of diameters of measurable target lesions - RECIST. CI is the parametric 95% confidence interval.
Source: Appendix 10

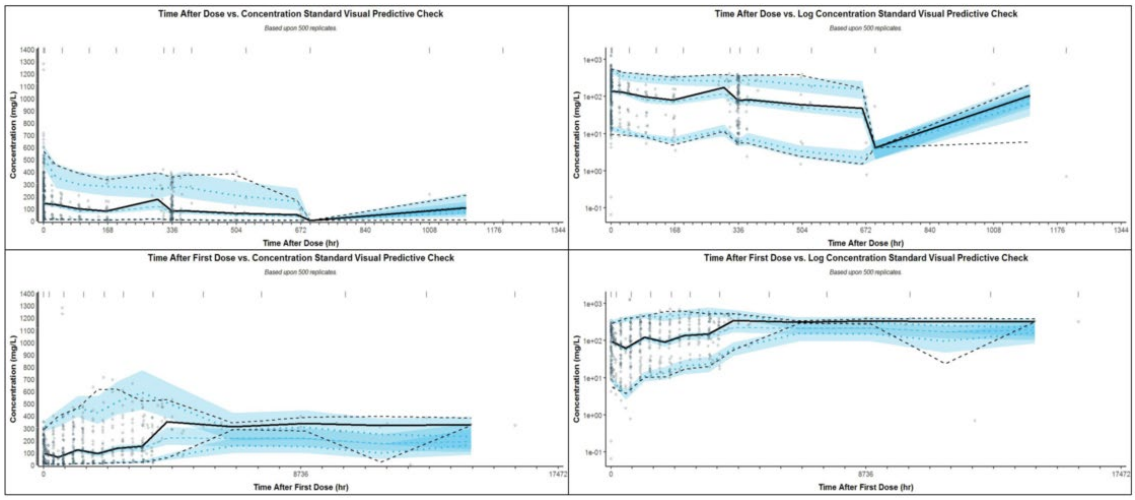



**Figure 7: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) VPC Plots – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after dose (top panel) or time after first dose (bottom panel) data. The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5$^{th}$ and 97.5$^{th}$ observed percentiles. Dashed blue line represent the 50$^{th}$ prediction percentile. Dotted blue lines represent the 2.5$^{th}$ and 97.5$^{th}$ prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5$^{th}$, 50$^{th}$, and 97.5$^{th}$ prediction percentiles. Notches along the top x-axis identify the corresponding bins.

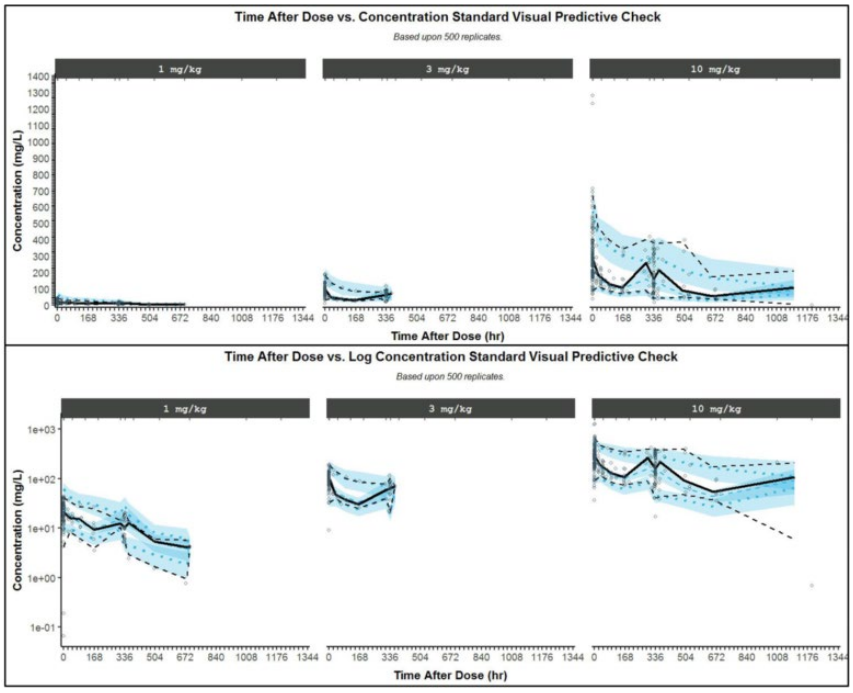



**Figure 8: Time after Dose Linear (Top Panel) and Log (Bottom Panel) VPC Plots Stratified by Dose – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

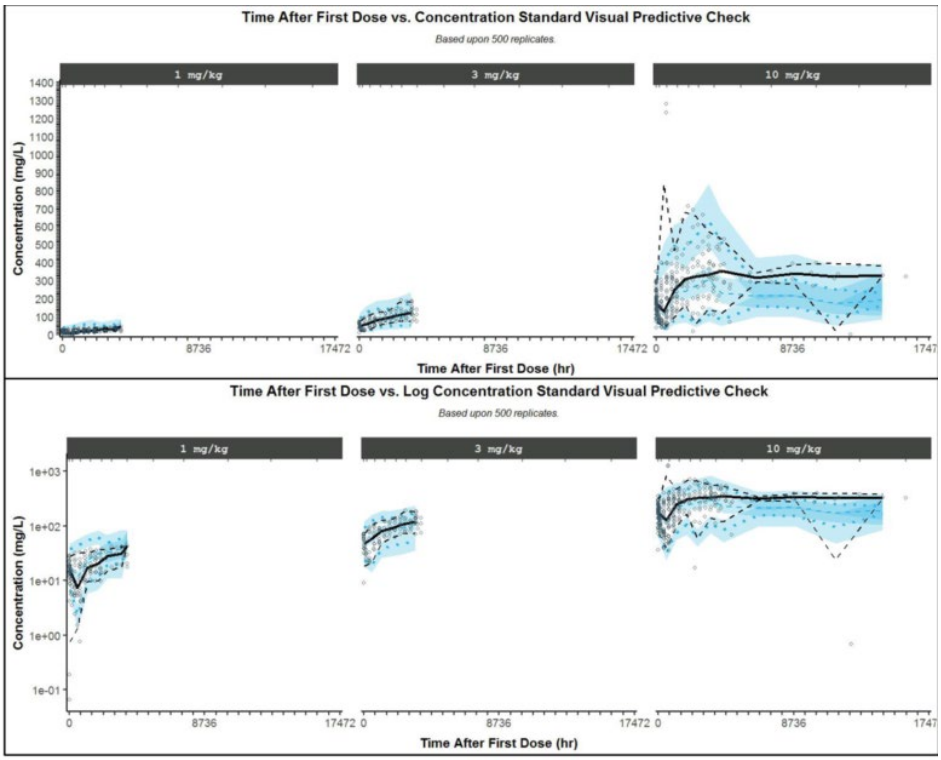



**Figure 9: Time after First Dose Linear (Top Panel) and Log (Bottom Panel) VPC Plots Stratified by Dose – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after first dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

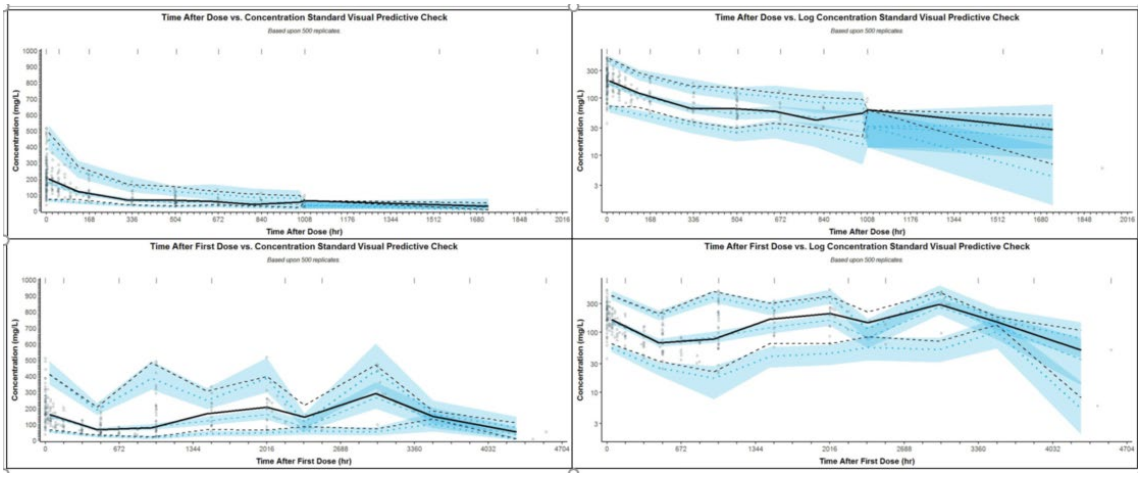



**Figure 10: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) VPC Plots – GARNET Part 2A**

Abbreviation: VPC=visual predictive check Note: Circles represent the individual observed dostarlimab concentration vs time after dose (top panel) or time after first dose (bottom panel) data. The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

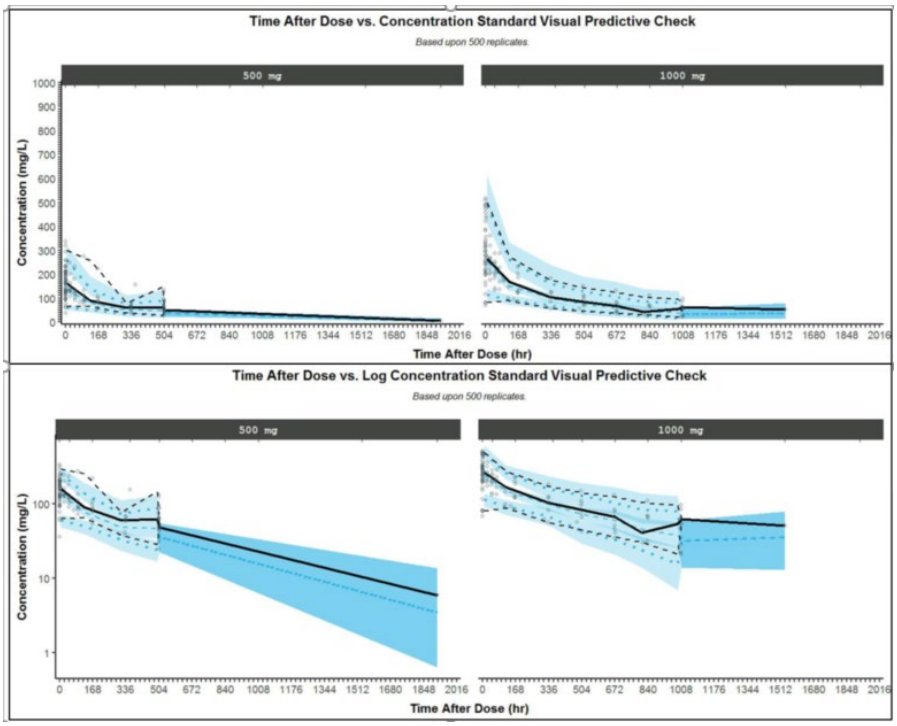



**Figure 11: Time after Dose Linear (Top Panel) and Log (Bottom Panel) VPC Plots Stratified by Dose – GARNET Part 2A**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

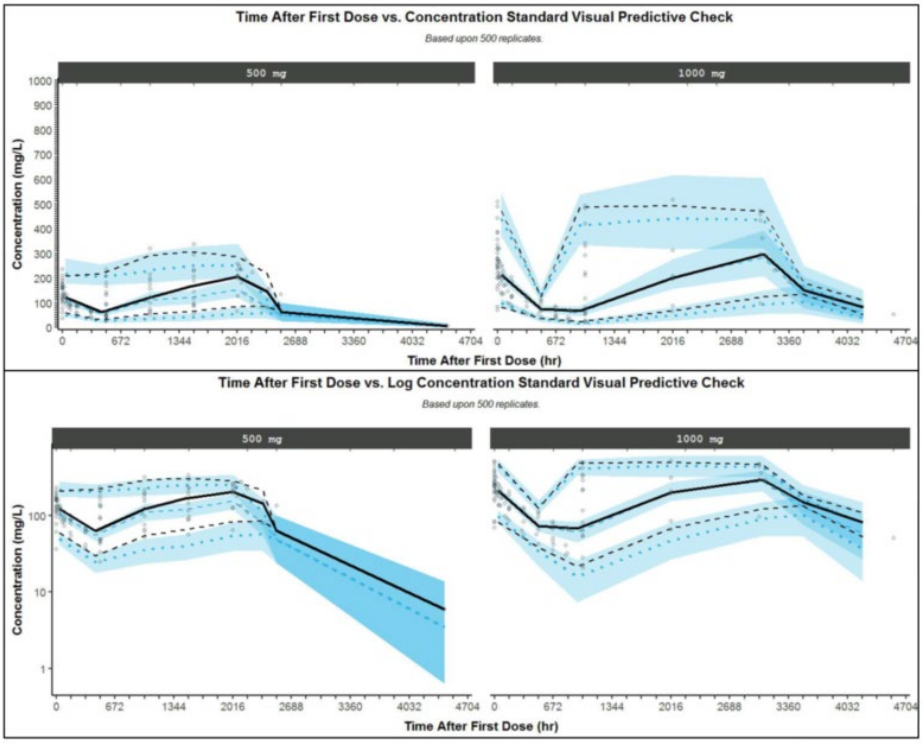



**Figure 12: Time after First Dose Linear (Top Panel) and Log (Bottom Panel) VPC Plots Stratified by Dose – GARNET Part 2A**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after first dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

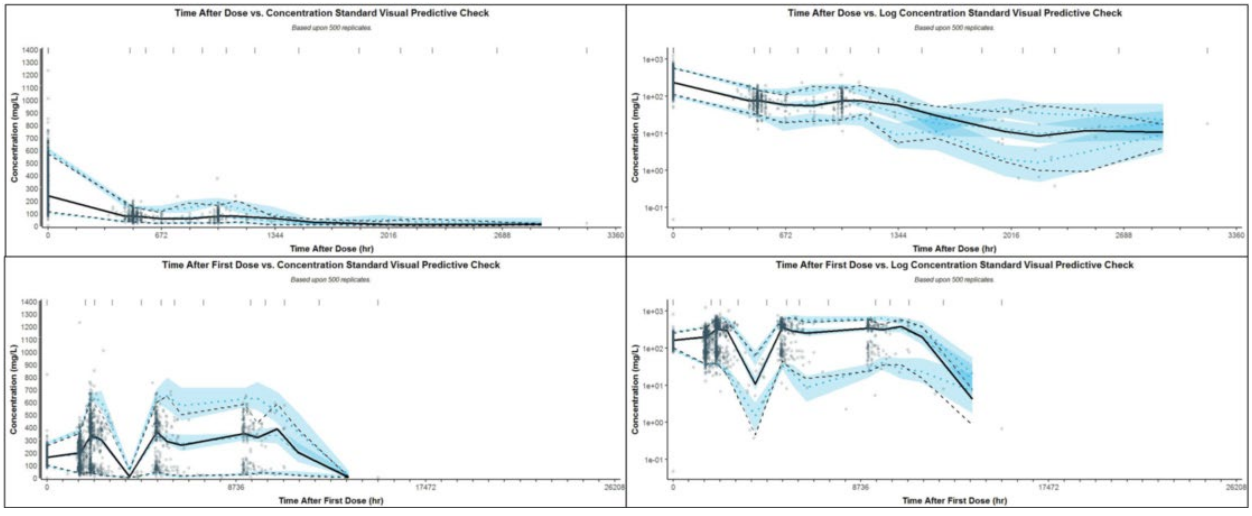



**Figure 13: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) VPC Plots – GARNET Part 2B**

Abbreviation: VPC=visual predictive check.

Note: Circles represent the individual observed dostarlimab concentration vs time after dose (top panel) or time after first dose (bottom panel) data. The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5$^{th}$ and 97.5$^{th}$ observed percentiles. Dashed blue line represent the 50$^{th}$ prediction percentile. Dotted blue lines represent the 2.5$^{th}$ and 97.5$^{th}$ prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5$^{th}$, 50$^{th}$, and 97.5$^{th}$ prediction percentiles. Notches along the top x-axis identify the corresponding bins.

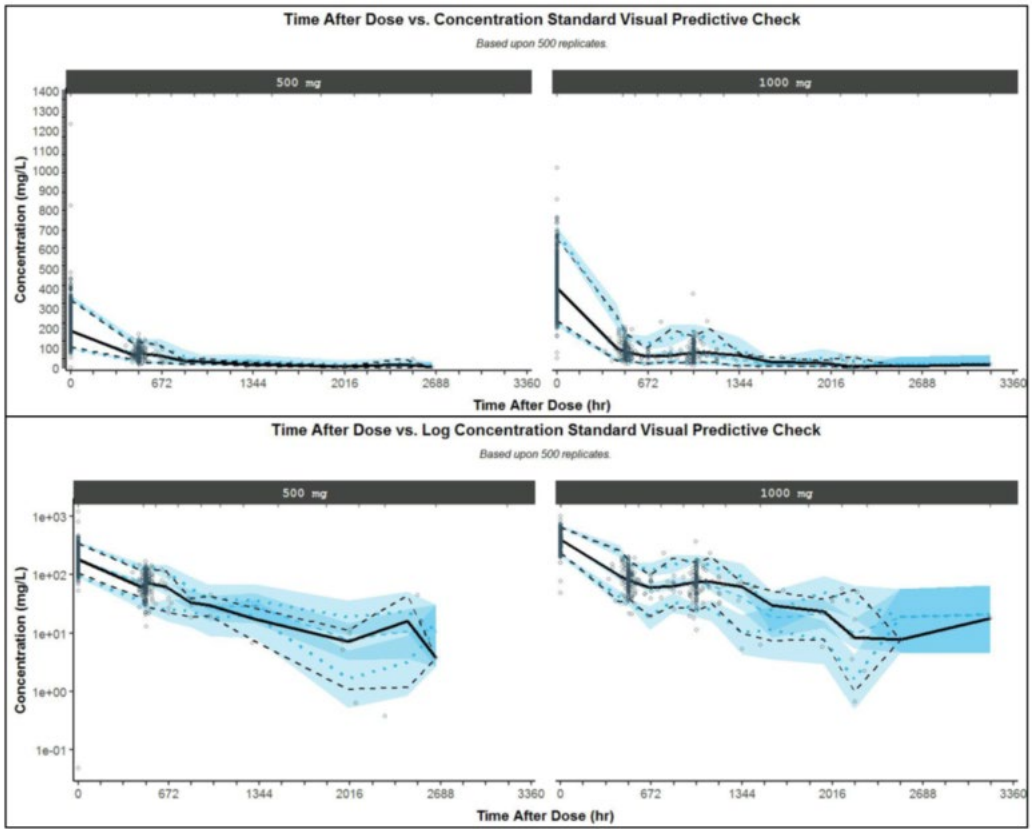



**Figure 14: Time after Dose Linear (Top Panel) and Log (Bottom Panel) VPC Plots Stratified by Dose – GARNET Part 2B**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue line represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

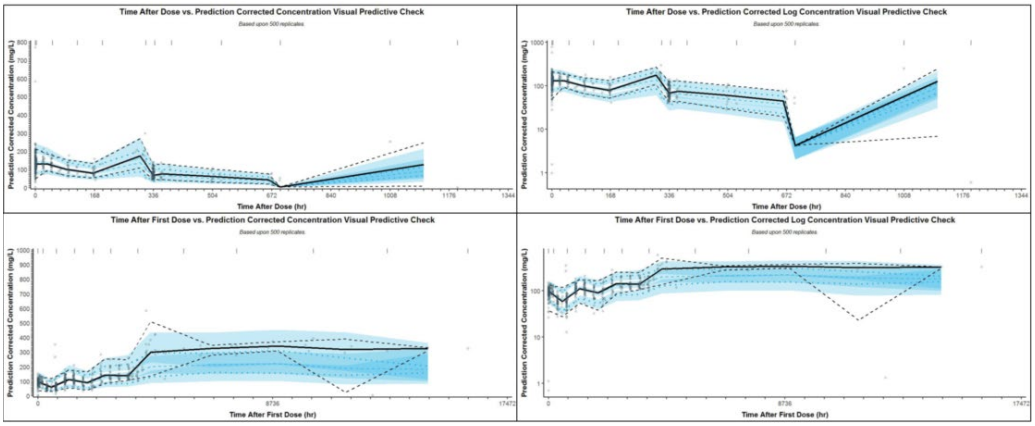



**Figure 15: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) Prediction-Corrected VPC Plots – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose (top panel) and time after first dose (bottom panel) data. The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

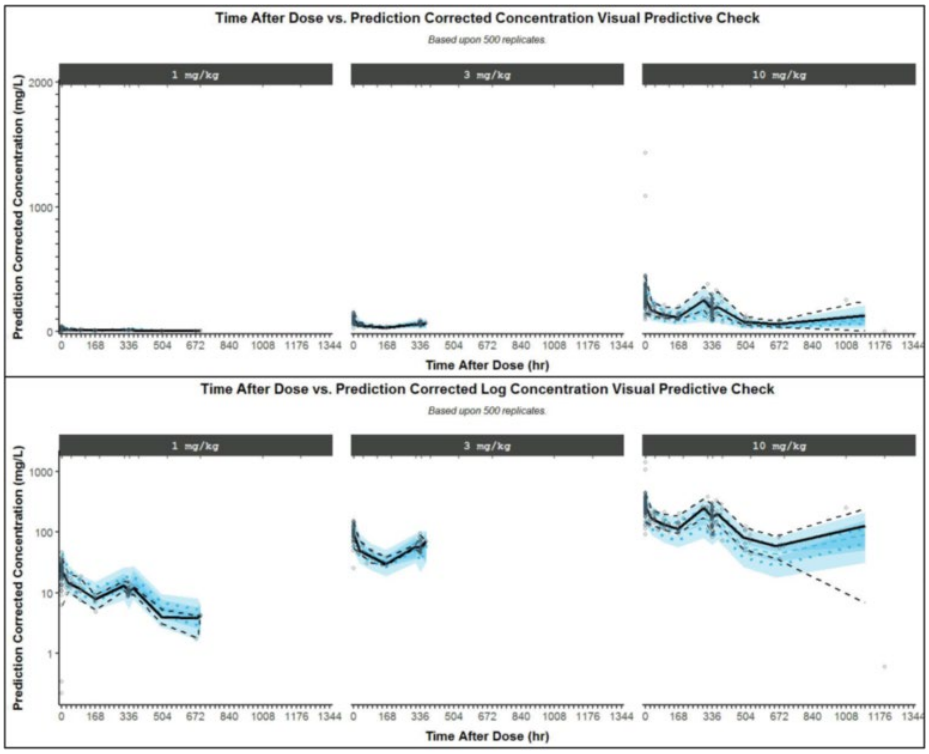



**Figure 16: Time after Dose Linear (Top Panel) and Log (Bottom Panel) Prediction-Corrected VPC Plots Stratified by Dose – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

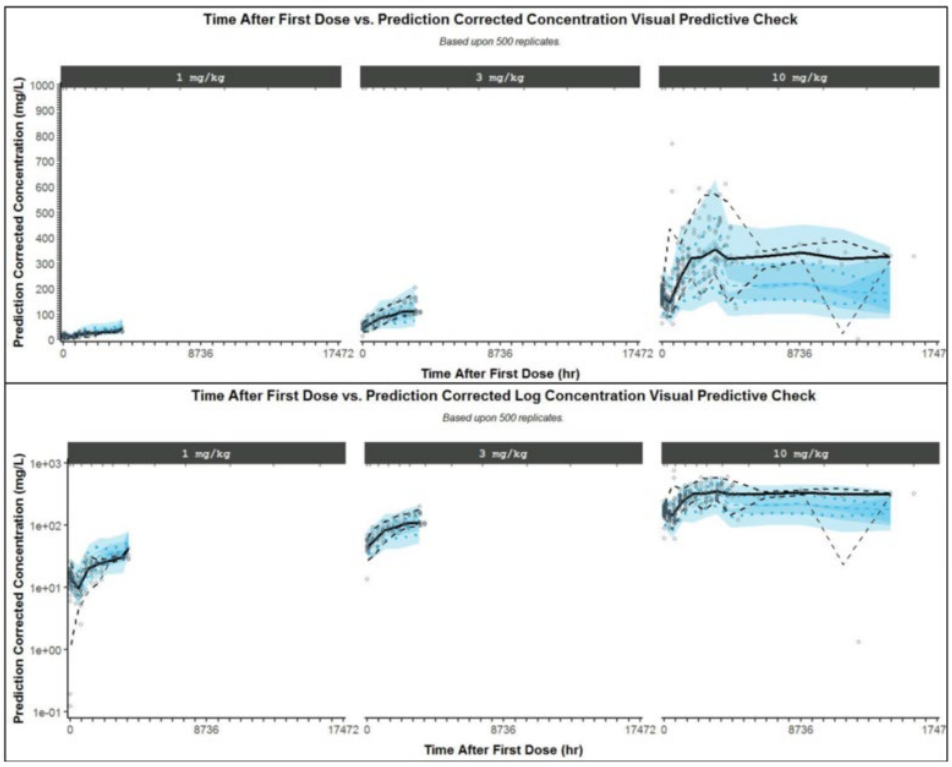



**Figure 17: Time after First Dose Linear (Top Panel) and Log (Bottom Panel) Prediction-Corrected VPC Plots Stratified by Dose – GARNET Part 1**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after first dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

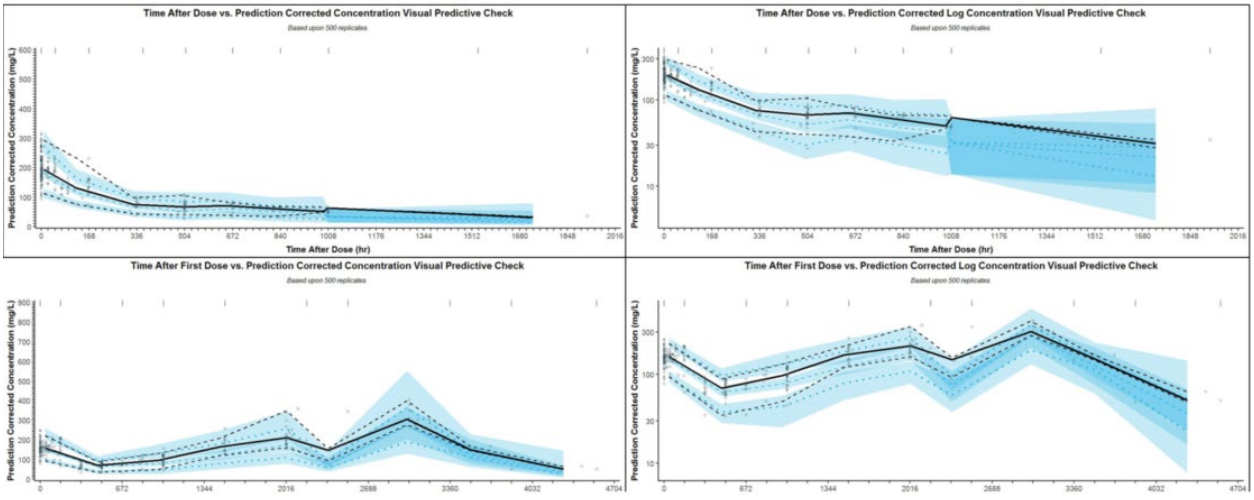



**Figure 18: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) Prediction-Corrected VPC Plots – GARNET Part 2A**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose (top panel) and time after first dose (bottom panel) data. The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

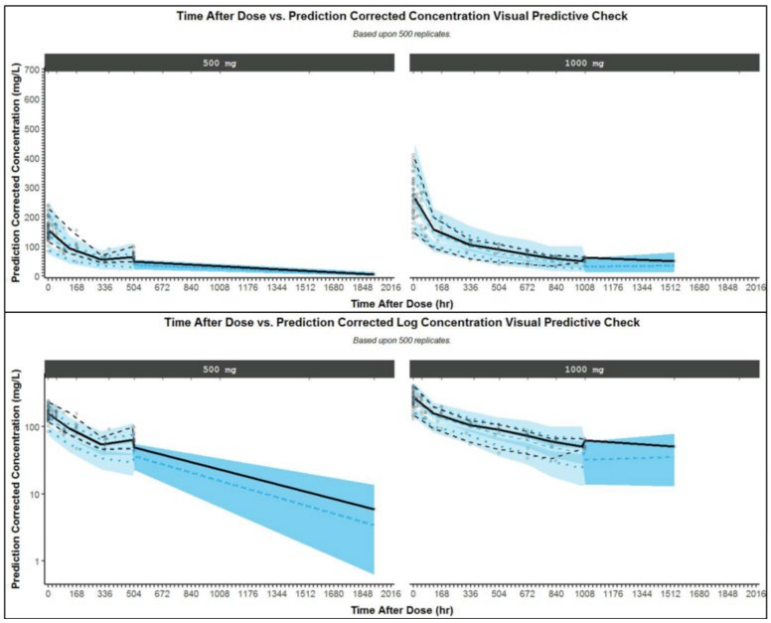



**Figure 19: Time after Dose Linear (Top Panel) and Log (Bottom Panel) Prediction-Corrected VPC Plots Stratified by Dose – GARNET Part 2A**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

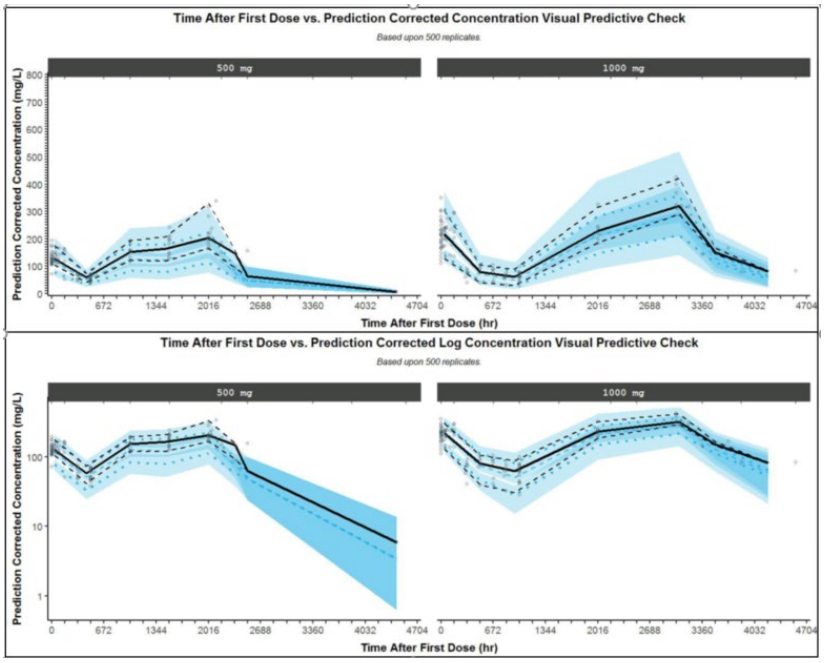



**Figure 22: Time after First Dose Linear (Top Panel) and Log (Bottom Panel) Prediction-Corrected VPC Plots Stratified by Dose – GARNET Part 2A**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after first dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

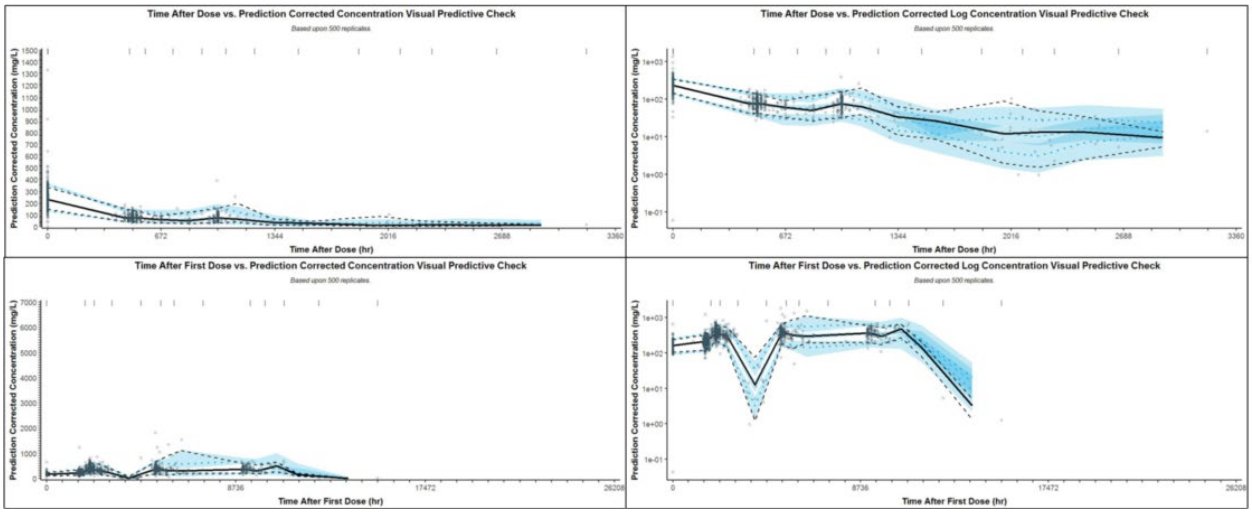



**Figure 20: Time after Dose and Time After First Dose Linear (Left Column) and Log (Right Column) Prediction-Corrected VPC Plots – GARNET Part 2B**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose (top panel) and time after first dose (bottom panel) data. The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

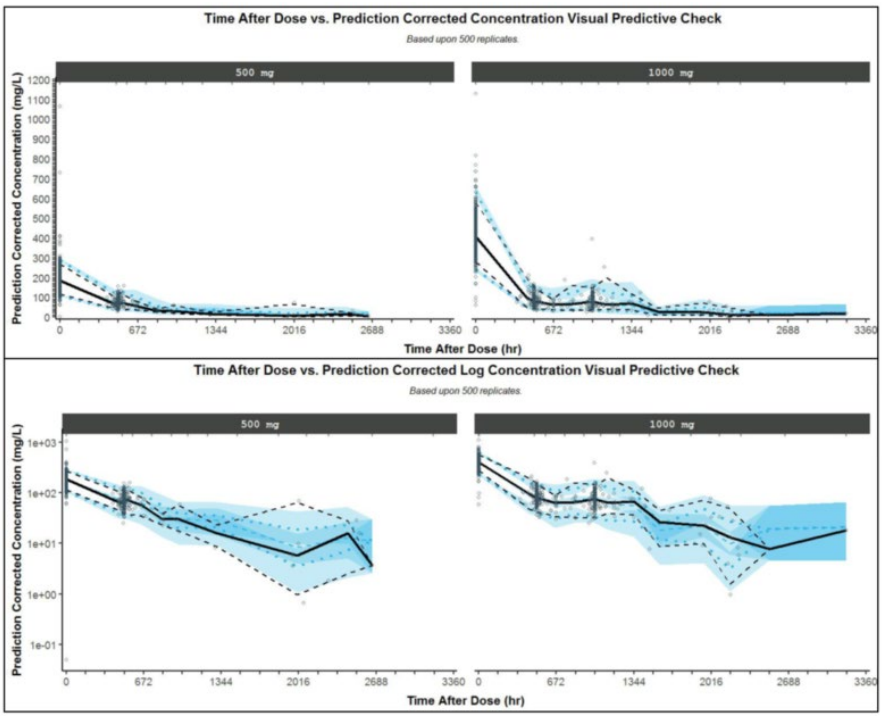



**Figure 21: Time after Dose Linear (Top Panel) and Log (Bottom Panel) Prediction-Corrected VPC Plots Stratified by Dose – GARNET Part 2B**

Abbreviation: VPC=visual predictive check.
Note: Circles represent the individual observed prediction corrected dostarlimab concentration vs time after dose data (linear plots – top panel, log plots – bottom panel). The solid black line represents the median observed prediction corrected dostarlimab concentration. Dashed black lines represent the 2.5th and 97.5th observed percentiles. Dashed blue lines represent the 50th prediction percentile. Dotted blue lines represent the 2.5th and 97.5th prediction percentiles. The blue shaded areas represent the 90% prediction intervals around each of the 2.5th, 50th, and 97.5th prediction percentiles. Notches along the top x-axis identify the corresponding bins.

Part 2A 500 mg Q3W and 1000 mg Q6W VPCs showed overlapping prediction and confidence intervals after 2016 hours post-dose. The protocol defined dosing window for Part 2B after Cycle 1 appeared in the corresponding VPC. The varied dosing times led to multiple peaks before and after the scheduled dosing time as seen in Cycle 2 and the observed data for Cycle 4. An additional VPC was completed for Cycle 4 using time after dose to correct for the dosing time inconsistencies.

Model predictability was demonstrated for the VPC which showed the majority of the observed concentrations were contained within the 95% prediction interval for each presentation.

## *Special populations*

In the PK population, 173 patients had normal renal function, 210 had mild renal impairment, 90 had moderate renal impairment while 3 patients had severe renal impairment and 1 patient had end-stage renal disease. Most patients had normal liver function while 48 had mild liver impairment and 4 had moderate liver impairment. No patients with severe liver impairment were included in the study. Gender was a significant co-variate of V. Almost ¾ of the study population were female. Race was adequately represented in the study population. Weight ranged from 34 kg to 182 kg in the PK population. Dostarlimab was not studied in children.

### Impaired renal function

Dostarlimab PK was similar between patients with normal renal function and those with mild or moderate renal impairment.

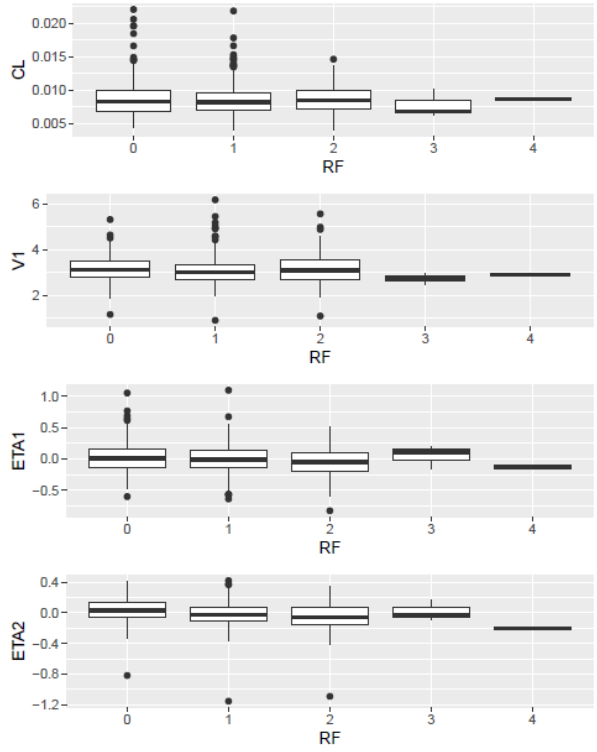



**Figure 22: Boxplot of Random Effects vs Categorical Covariates (Base Model)**

**Impaired hepatic function**

Mild hepatic impairment did not appear to cause a significant change in the PK of dostarlimab when compared to patients with normal hepatic function.

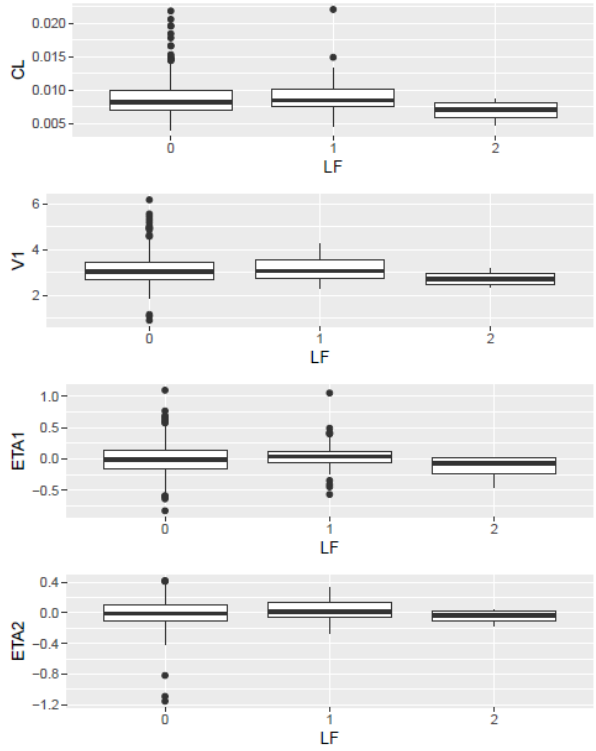



**Figure 23: Boxplot of Random Effects vs Categorical Covariates (Base Model)**

- **Gender**

Female gender was associated with a decrease in the central volume by 8%.

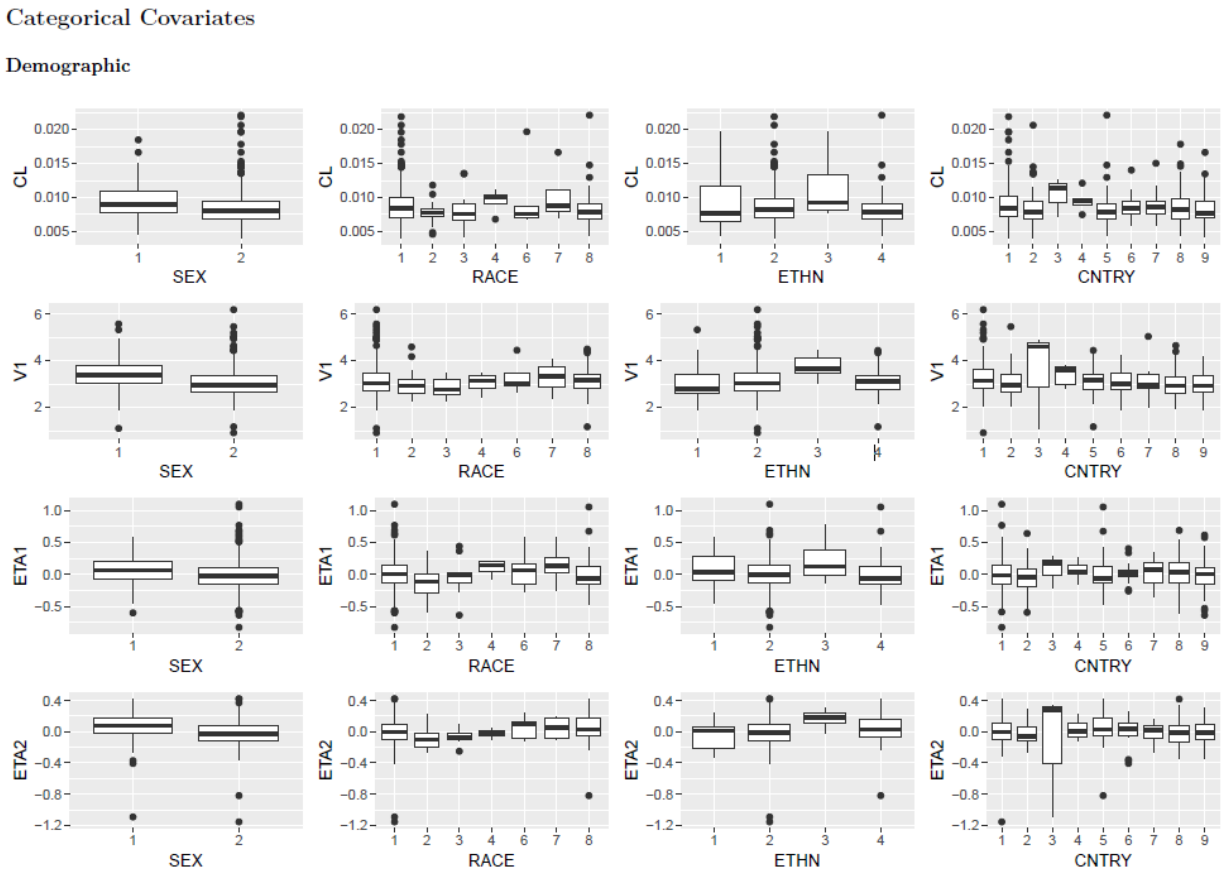



**Figure 24: Categorical Covariates- Demographic**

- **Race**

Race and ethnicity were not statistically significant covariates in the PK population.

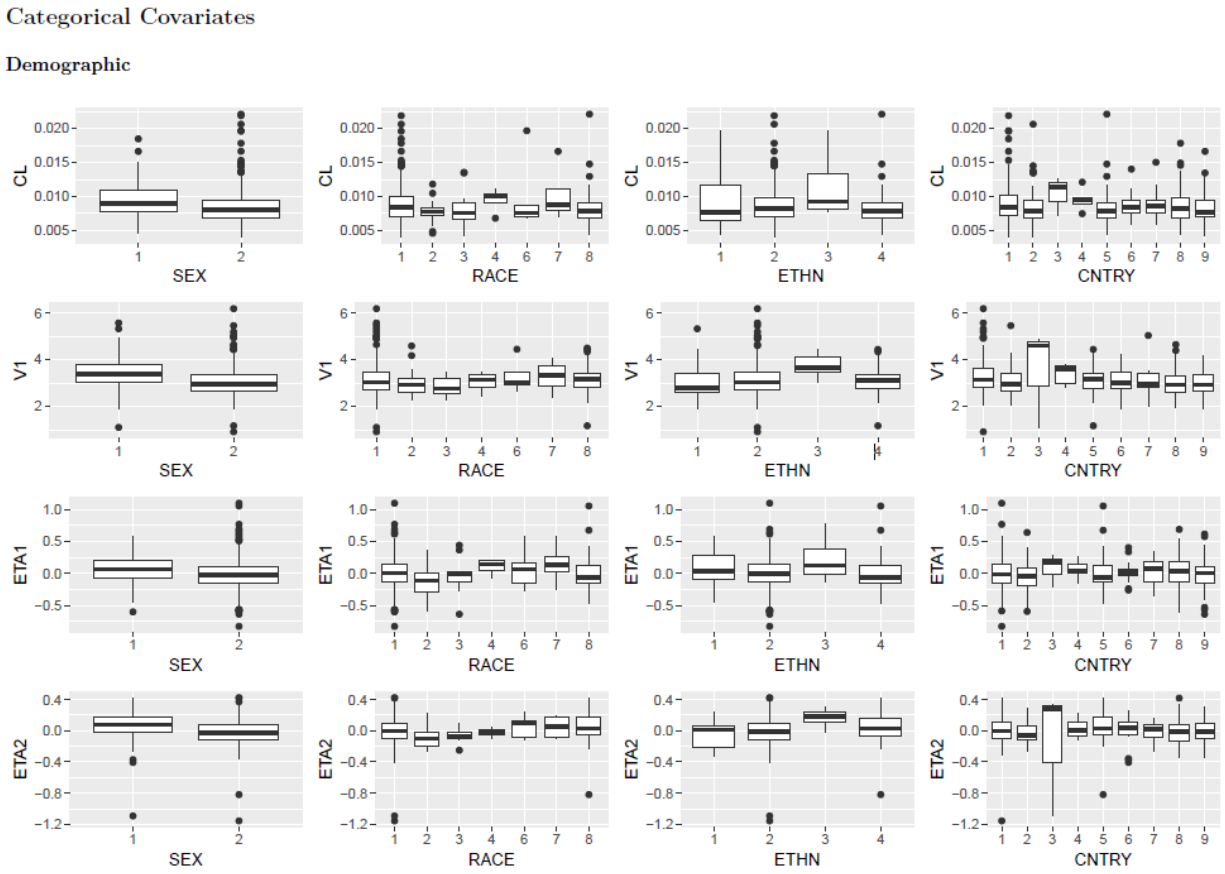



**Figure 25: Categorical Covariates- Demographic**

**Weight**

In Part 1 and 2A over the weight range of 45.6 to 145.6 kg linear regression of natural log transformed CL versus natural log transformed baseline body weight indicated a trend of increasing CL with increasing body weight. However, this relationship was not statistically significant at the 0.05 level.

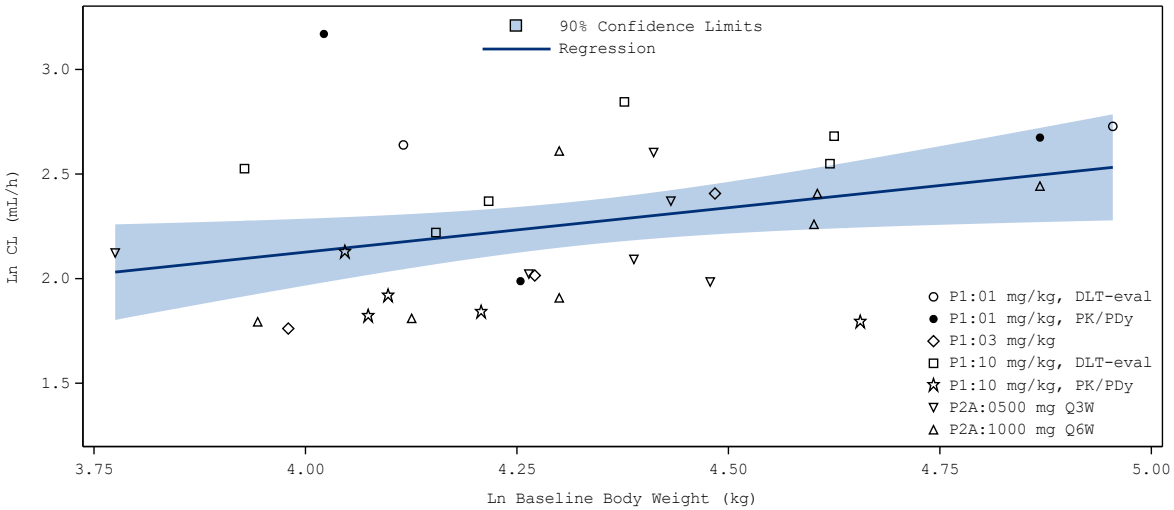



**Figure 26: Individual Dostarlimab CL Versus Body Weight on Cycle 1/Day 1 for Part 1 and Part 2A**

**Elderly**

An increase in age led to a decrease in CL and vice versa, over the observed age range of 24 to 86 years old.

## *Pharmacokinetic interaction studies*

No interaction studies were submitted (see discussion on clinical pharmacology)

## *Immunogenicity*

**Immunogenicity of dostarlimab**

ADA sampling in Study 4010-01-001

For Part 1 and 2A serum samples for the determination of anti-dostarlimab antibodies were the same samples as those collected as for assessment of drug PK. Predose samples and samples at or after 96 hours postdose were included for the analysis. For Part 2B, serum samples for the determination of anti-dostarlimab antibodies were collected predose on Day 1 of Cycle 1 (baseline), Cycle 4 (9 weeks), Cycle 5 (12 weeks), Cycle 8 (30 weeks), and Cycle 12 (54 weeks), and then at a safety follow-up visit approximately 90 days after the last dose of study drug.

There were 1543 samples tested for antibodies to dostarlimab. Of these, 1376 (89.2%) were negative for dostarlimab ADA, 130 (8.4%) confirmed positive, and 37 (2.4%) were inconclusive. Overall, the prevalence of baseline positive samples was 16.5%, ranging from 0.0% in Part 1 to 17.3% in Part 2B. In Part 2B, the prevalence was 17.3% at baseline, but fell to 5.1% at Cycle 4 and 0.0% by Cycle 12.

**Table 21: prevalence of anti-dostarlimab antibodies by visit, Part 2B**

| | Prevalence of Patients who are ADA Positive | |
|---|---|---|
| | n/N | % |
| Cycle 1, Day 1 (Baseline) | 76/440 | 17.3 |
| Cycle 4 Day 1, 0 hour | 16/313 | 5.1 |
| Cycle 5 Day 1, 0 hour | 13/250 | 5.2 |
| Cycle 8 Day 1, 0 hour | 5/109 | 4.6 |
| Cycle 12 Day 1, 0 hour | 0/54 | 0.0 |
| Safety Follow-up | 1/35 | 2.9 |

n=number of patients with positive results; N=Number of patients with sample result at this time point

Of the patients with treatment-emergent ADA, 7 tested positive for NAb at one or more time points. In addition, there were 33 patients who were categorized as having treatment-unaffected ADA (pre-existing ADA with no meaningful increase in titer), who were positive for NAb at one or more time points during the study.

None of the 13 patients with treatment-emergent ADA reported a serious adverse event or infusion reaction. Twelve reported a drug-related AE, 5 reported an immune-related AE, and 1 patient reported hypersensitivity.

There were 4 patients with treatment-emergent ADA in the Part 2B EC cohort. Of these 4 patients, 2 were classified as having complete or partial response (ORR) with 1 patient having a duration of response of at least 6 months.

In the PopPK analysis, inference regarding the effect of ADA was inconclusive. When tested as transient (time-varying positive or negative), ADA was statistically significant leading to a 17% increase in systemic clearance. However, when ADA was tested as persistent (negative until first positive, then carried forward as positive for the rest of the study) or on a subject level (positive for all records if any test result was positive, negative otherwise), the effect was not statistically significant. The final model included ADA as a part of stepwise selection based on numeric criteria (AIC).

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

No clinical studies were submitted.

The mechanism of action for dostarlimab was evaluated in a series of *in vitro* binding studies and *in vivo* studies (see non-clinical section).

### *Primary and Secondary pharmacology*

**Primary pharmacology**

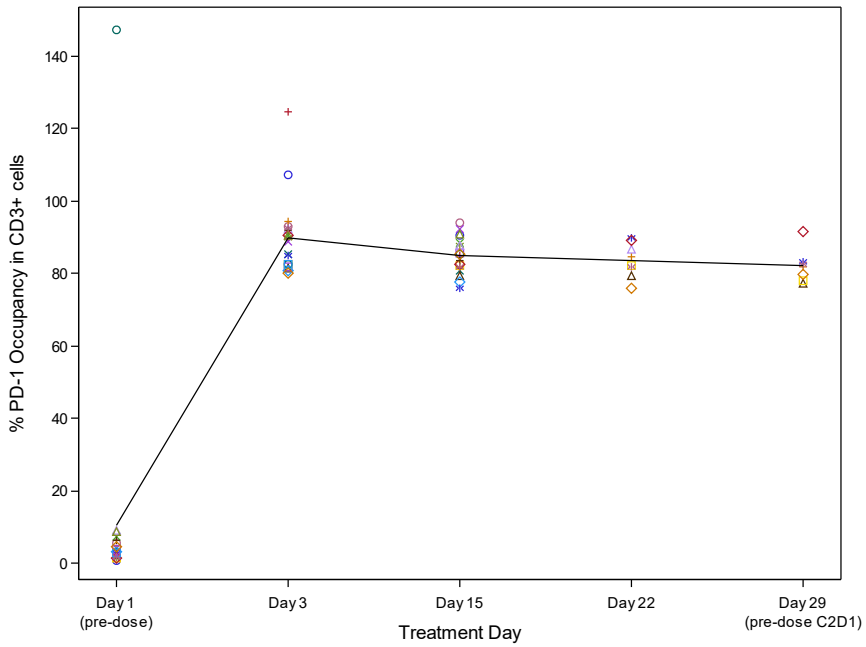
Dostarlimab PD-1 Receptor Occupancy (RO) was determined in peripheral blood from patients following the first dose in Parts 1, 2A and 2B of Study 4010-01-001. Both a conventional receptor occupancy (cRO) assay, which provided a measure of dostarlimab direct binding to CD3+ cells, as well as a functional receptor occupancy (fRO) assay, which measured dostarlimab downstream signal

modulation via IL-2 production, were used for the PD analysis. The cRO and fRO assays were validated.

Conventional Receptor Occupancy (cRO)

The cRO assay was performed by flow cytometry using a qualified phenotyping antibody panel on peripheral blood mononuclear cells isolated from whole blood samples. The binding of dostarlimab was determined for each T cell subset (CD3+, CD3+CD4+, and CD3+CD8+).

Data were available for all 21 patients in Part 1, all 13 patients in Part 2A, and 121 patients in Part 2B. The analysis of Parts 1 and 2A focused on the serial samples collected over the first dosing interval, where maximal RO was obtained at the first post-dose sample and maintained for all doses and dose regimens tested. Part 1 data is presented in Figure 27.




Source: Integrated Receptor Occupancy Report, Figure 2
Abbreviations: CD=cluster of differentiation; PD-1=programmed cell death protein 1; PD=pharmacodynamic(s); PK=pharmacokinetic(s);

**Figure 27: Individual and Mean Percent PD-1 Occupancy for Dostarlimab in CD3+ Cells in Part 1**

In Part 2B of the study, samples were drawn at predose on Days 1 and 22, and at the end of treatment. Maximal PD-1 occupancy was observed following the first dose of 500 mg dostarlimab, directly before the next dose at Day 22 (Figure 28). The results were independent of tumour type.

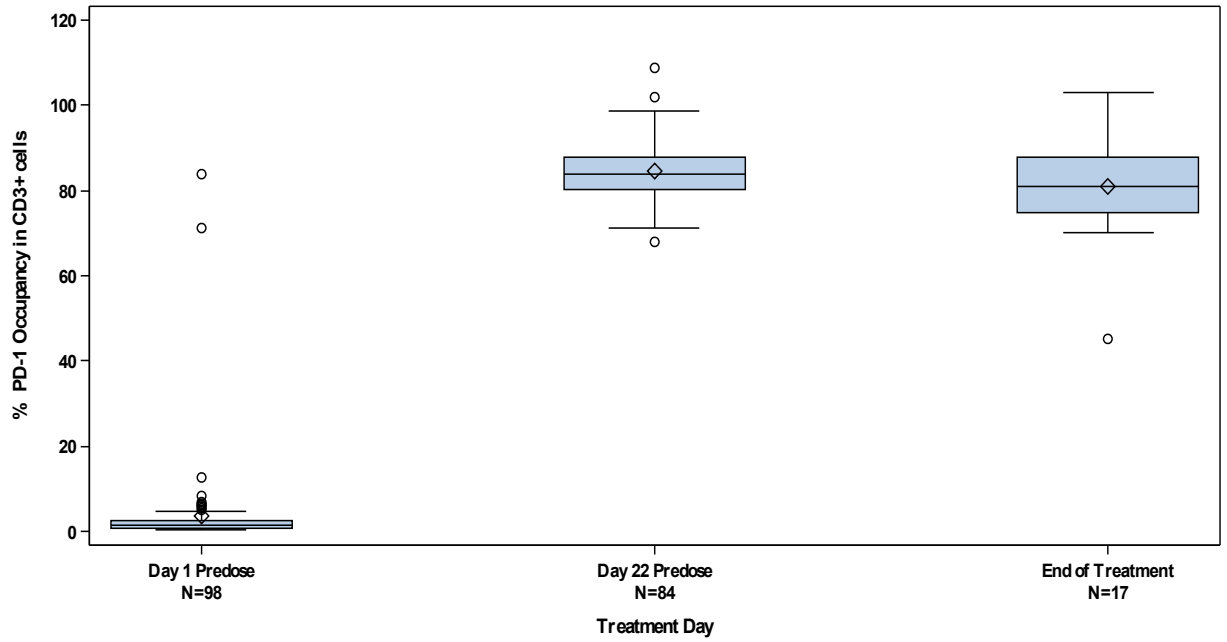



**Figure 28: Individual and Mean Percent PD-1 Occupancy for Dostarlimab in CD3+ Cells in Part 2B**

Source: Integrated Receptor Occupancy Report, Figure 4
Abbreviations: CD=cluster of differentiation; PD-1=programmed cell death protein 1; Q1=first quartile; Q3=third quartile

Functional Receptor Occupancy (fRO)

The fRO assay was used to evaluate the downstream effects of dostarlimab binding on cells derived from patients dosed with dostarlimab, by measuring cytokine (IL-2) secretion by *ex vivo* staphylococcal enterotoxin B (SEB) -stimulated polyclonal T cells in whole blood samples.

Samples were collected in Parts 1 and 2A at the same timepoints as for the cRO assessments. Data was available from 21 patients in Part 1 and 13 patients in Part 2A. Full fRO (ratio of approximately 1) was obtained and maintained for all doses and dose regimens tested. In Part 1, full fRO was achieved following administration of a single dose of dostarlimab and maintained at least until the second scheduled dose of study drug (Figure 29).

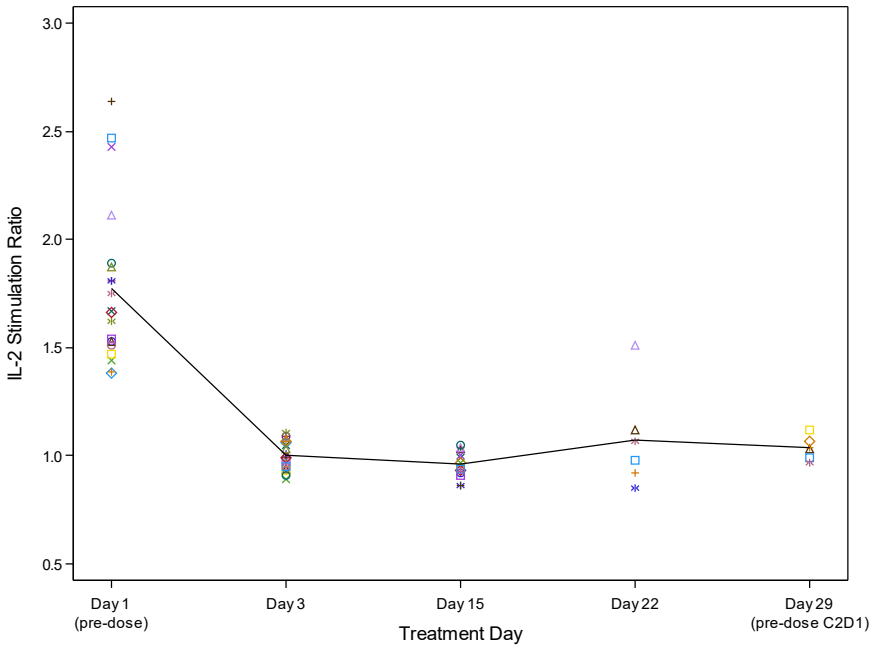



**Figure 29: Individual and Mean IL-2 Stimulation Ratio in fRO Assay in Part 1**

Source: Integrated Receptor Occupancy Report, Figure 5
Abbreviations: C=cycle; D=day; fRO=functional receptor occupancy; IL-2=interleukin-2; PDy=pharmacodynamic(s); PK=pharmacokinetic(s)

Similarly, in Part 2A, full fRO was achieved following administration of a single dose of dostarlimab starting at the first postdose sample and maintained at least until the second scheduled dose of study drug for virtually all patients. No differences were observed in RO between the two dose regimens of 500 mg dostarlimab Q3W and 1000 mg dostarlimab Q6W.

**Secondary pharmacology**

An analysis of potential cardiac effects of dostarlimab was conducted to examine trends and look for a potential relationship between dostarlimab concentrations and effects on QT prolongation. Potential effects were assessed by analysis of central tendency, the incidence of clinical noteworthy ECG values, morphological assessment of rhythm abnormalities at the recommended therapeutic dose, and an analysis of dostarlimab concentration and baseline-corrected QT interval (corrected using Fridericia's formula) (QTcF). Standard 12-lead triplicate ECGs were recorded.

The QTcF change from baseline at predose and at the end-of-infusion on Day 1 of Cycles 1, 4, 5, 8, and 12, and at the end of treatment visit for all patients in Part 2B were used for the analysis of central tendency of QTcF prolongation per ICH E14 Guidance. Cycle 1 Day 1 predose timepoint was considered as baseline. Standard 12-lead triplicate ECGs were recorded and interpreted by a qualified physician at the site.

All of the upper bounds of the 90% 2-sided CI of mean ΔQTcF were below the threshold of 10 milliseconds (msec). The greatest mean QTcF increase from baseline was 5.741 msec (2-sided 90% CI: 3.438, 8.043 msec), observed at the Cycle 5 Day 1, 0.5 hr timepoint. For at all other post-dose timepoints the mean ΔQTcF was less than 5 msec and the upper 90% 2-sided CI ranged from 1.885 to 8.043 msec. Mean change from baseline is presented in Figure 19.

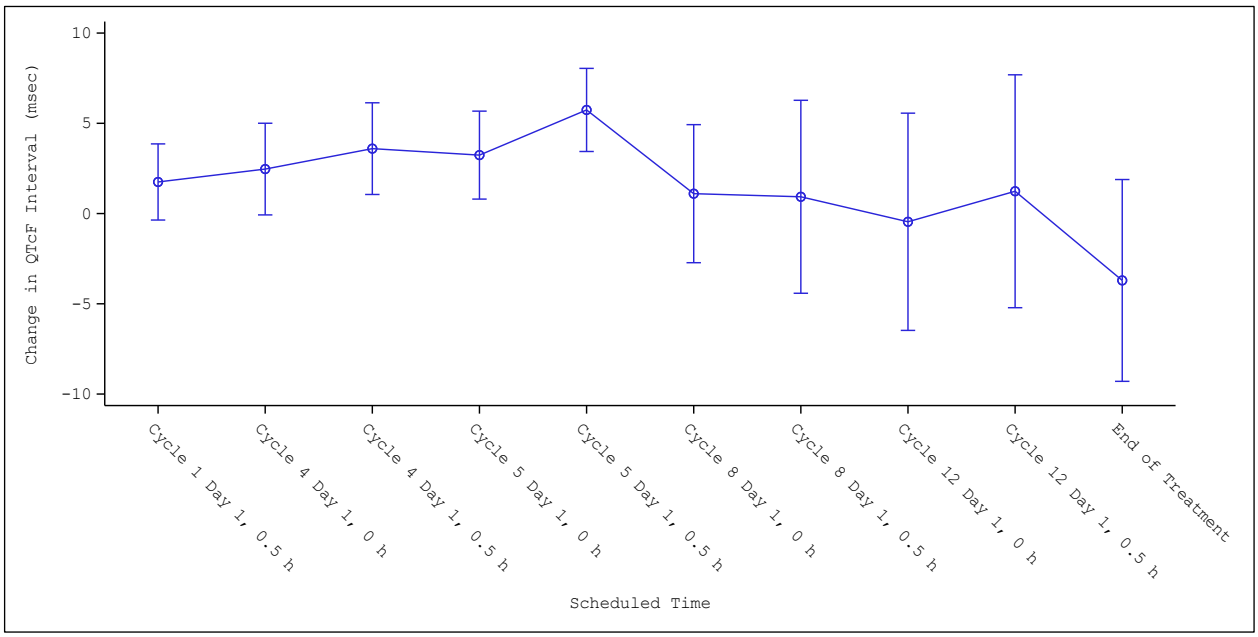



**Figure 30: Mean Change from Baseline QTcF vs Time (with 2-sided 90% CI)**

The relationship between dostarlimab concentrations and the ΔQTcF interval was also evaluated by exposure-response modeling of the predose and end-of-infusion dostarlimab concentrations and corresponding ΔQTcF values collected on Day 1 of Cycles 1, 4, 5, 8, and 12, and at the end of treatment visit for all patients in Part 2B at the recommended therapeutic dose. Cycle 1 Day 1 predose timepoint was considered as baseline. Standard 12-lead triplicate ECGs were recorded and interpreted by a qualified physician at the site.

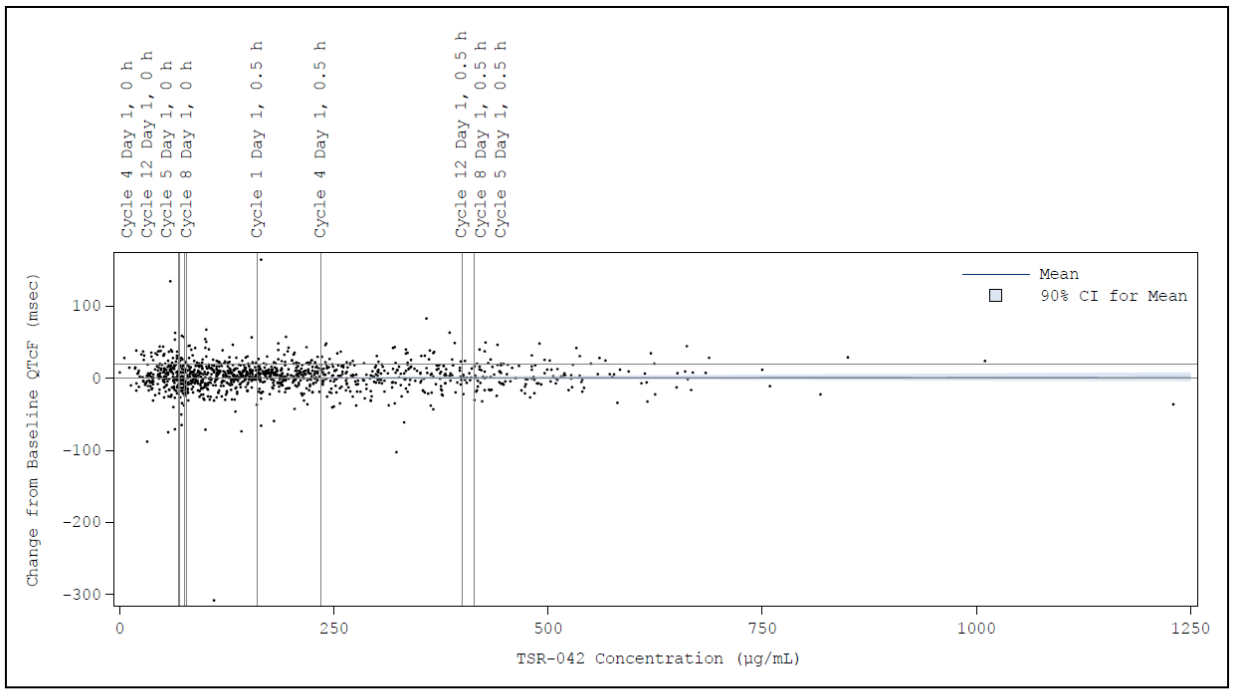
**Table 22: Estimates of changes from baseline QTcF at Geometric Mean TSR-042 Serum Concentration**

| Scheduled Timepoints | N | Geometric Mean Concentration (µg/mL) | Mean Change in QTcF (msec) | 2-sided 90% CI (msec) |
|---|---|---|---|---|
| Cycle 1 Day 1, 0.5 h | 299 | 159.9 | 2.660 | (0.9605, 4.360) |
| Cycle 4 Day 1, 0 h | 211 | 68.75 | 2.516 | (0.7209, 4.310) |
| Cycle 4 Day 1, 0.5 h | 210 | 234.6 | 2.779 | (1.074, 4.485) |
| Cycle 5 Day 1, 0 h | 175 | 75.98 | 2.527 | (0.7437, 4.310) |
| Cycle 5 Day 1, 0.5 h | 168 | 414.1 | 3.064 | (1.058, 5.071) |
| Cycle 8 Day 1, 0 h | 59 | 77.93 | 2.530 | (0.7498, 4.310) |
| Cycle 8 Day 1, 0.5 h | 59 | 399.9 | 3.042 | (1.072, 5.012) |
| Cycle 12 Day 1, 0 h | 21 | 69.41 | 2.517 | (0.7230, 4.310) |
| Cycle 12 Day 1, 0.5 h | 21 | 399.2 | 3.041 | (1.072, 5.009) |

Source: Table 7

The relationship between dostarlimab concentration and ΔQTcF was assessed using a random coefficients mixed effects model for the ΔQTcF values. The slope of the exposure-response relationship between the change from baseline in QTcF interval and dostarlimab concentration was not significantly different from zero (0.001589 msec/µg/mL; 95% CI: -0.004208, 0.007386 msec/µg/mL; p=0.5906) and the intercept estimate was 2.406 msec (95% CI: 0.1037, 4.709 msec).

The mean ΔQTcF increase was less than 5 msec at all scheduled post-dose timepoints with associated drug concentrations. The upper bound of the 2 sided 90% CI was less than 10 msec, below the threshold of regulatory concern per the ICH E14 Guidance.




Note: Population regression line and confidence bands are estimated using a random coefficients linear mixed model. Vertical lines indicate the geometric mean $C_{max}$ at each scheduled time.
Source: Figure 2

**Figure 31: Model-based mean Prediction line of the Mean ΔQTcF values and its 2-sided 90% CIs at Geometric Mean Concentration at scheduled timepoints**

**PK/PD model**

The proposed dose and schedule for dostarlimab is 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for all subsequent cycles. This dose and schedule were determined in the GARNET study based on the PK and RO analysis of Part 1 and Part 2A data during development. Dose selection was guided primarily by the observed RO data from peripheral blood cells. Full RO was achieved at dostarlimab serum concentrations of 2.435 µg/mL and above. One patient with positive ADA at 1 mg/kg with a dostarlimab serum concentration of 1.51 µg/mL did not have full target engagement based on the IL-2 functional assay. At the time of dose selection, PK and RO data from 16 patients from Part 1 were used for dose and exposure projections using PK modelling. The model predicted $C_{trough}$ at steady state for the 500 mg Q3W and 1,000 mg Q6W doses were 51.1 and 29.2 µg/mL with associated 90% CIs of 13.4 and 111.1 µg/mL and 4.1 and 78.5 µg/mL, respectively. Importantly, 90% lower bound of the mean predicted $C_{trough}$ following 500 mg Q3W and 1,000 mg Q6W dosing is 5.5- and 1.7-fold of, respectively, the level required for full target engagement of peripheral blood cells.

A PK/PD model was used to further confirm the projected RTD. In a comparative analysis the PK-target engagement for pembrolizumab and dostarlimab were analysed. First, pembrolizumab data were digitized (Elassaiss-Schaap et al. 2017) and analysed together with dostarlimab interleukin-2 (IL-2) functional assay results. A NONMEM sigmoid $E_{max}$ model was fitted to the data.

Based on the model, concentrations of 54 µg/ml for dostarlimab and 43 µg/ml for pembrolizumab are estimated to maintain 90% of maximal PD-1 suppression in tumours, assuming a 3-fold tissue dilution

for typical mAbs (Shah and Betts 2012). For pembrolizumab at steady state of the 200 mg flat dose, mean $C_{trough}$ is about 29 µg/mL and mean $C_{avg}$ is about 45 µg/mL (Freshwater et al. 2017). For dostarlimab at steady state, both the 500 mg Q3W (model predicted $C_{trough}$ 101 µg/mL, $C_{avg}$ 147 µg/mL) and 1,000 mg Q6W (model predicted $C_{trough}$ 71 µg/mL, $C_{avg}$ 147 µg/mL) doses maintain maximal peripheral PD-1 suppression at maximal levels throughout the respective dosing intervals. The dostarlimab $C_{trough}$ levels for patients in Part 2B (observed data) from Cycle 4 to Cycle 12 were approximately 70 µg/mL on average (predose Cycle 4, 5, 8, and 12: Mean±standard deviation=72.75±26.79 µg/mL, 82.89±35.86 µg/mL, 85.29±46.43 µg/mL, and 77.68±35.10 µg/mL, respectively).

Compared to 1 mg/kg, the observed $C_{trough}$ (Day 22) after a single dose is 4.24 µg/mL with a standard deviation of ±2.38 µg/mL. With about 2-fold accumulation at steady state, the 1 mg/kg dose or the equivalent flat dose will not be able to reach the required full target engagement concentration of 54 µg/mL at tumour sites as well as 18 µg/mL at peripheral sites.

**Relationship between plasma concentration and effect**

Exposure-efficacy

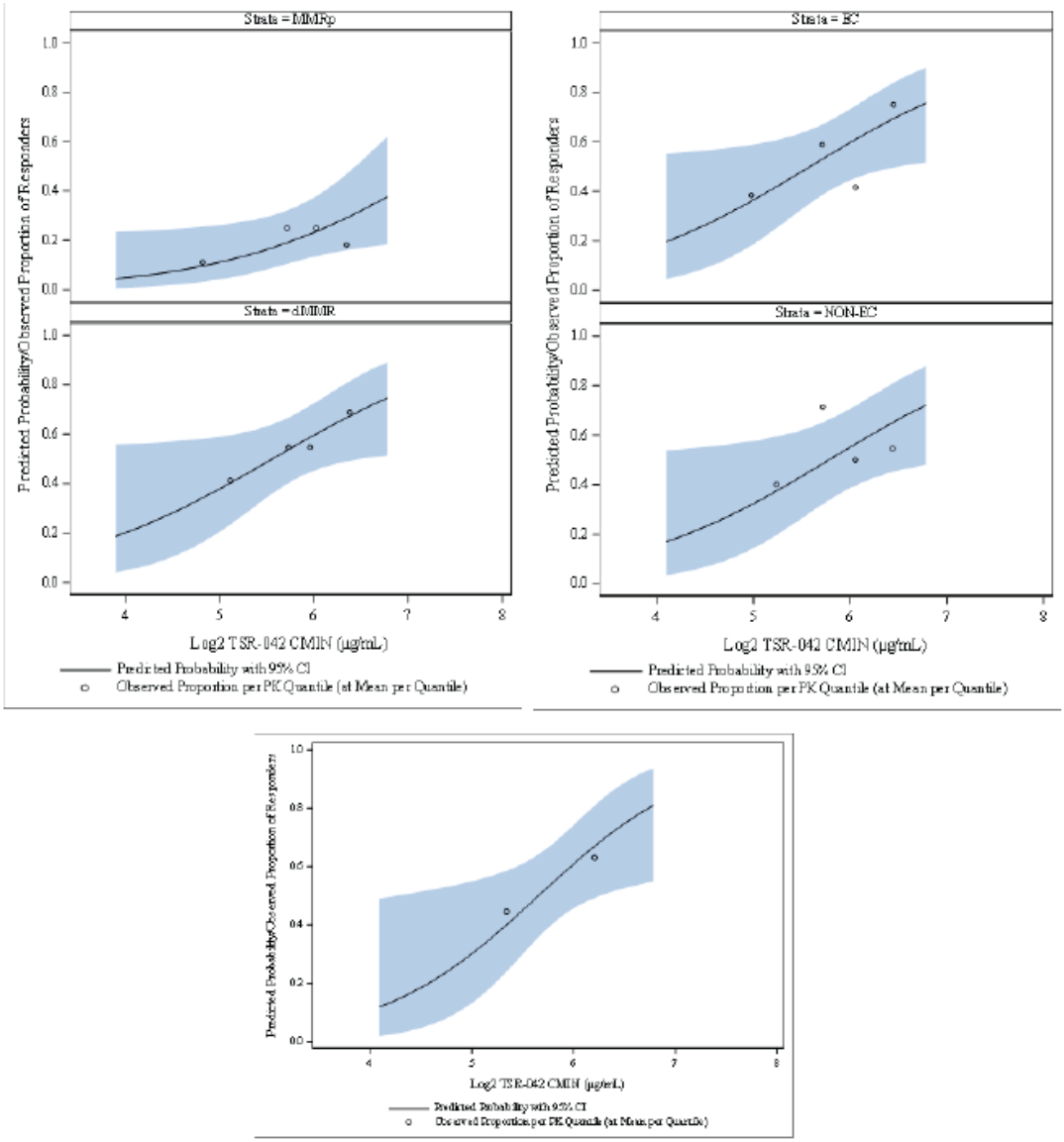
The time to event response (DOR) was to be assessed using Cox proportional hazard models with exposure as the independent predictor. These analyses were restricted to responders, per the OR definition. These analyses were not carried out due to the small number of subjects with a DOR measurement (i.e. losing OR, after achieving it).

ORR was plotted against quantile groups for dostarlimab exposure, overlain with model predicted curves.

**Table 23: Summary of the exposure-Response Logistic Regression for Objective Response-Part 2B**

| Patient Group | Number of ORR Patients/Total Patients in Analysis | PK Parameter | Odds Ratio for Doubling Exposure | 95% CI of Odds Ratio | p-value |
|---|---|---|---|---|---|
| EC | 41/107 | $C_{avg}$ | 3.753 | (0.7444, 18.92) | 0.1091 |
| | | $C_{min}$ | 2.420 | (1.025, 5.716) | **0.0439** |
| EC dMMR | 29/54 | $C_{avg}$ | 5.049 | (0.5428, 46.96) | 0.1547 |
| | | $C_{min}$ | 3.281 | (0.9815, 10.97) | 0.0537 |
| dMMR pan tumor | 50/94 | $C_{avg}$ | 3.707 | (0.7258, 18.94) | 0.1153 |
| | | $C_{min}$ | 2.575 | (1.053, 6.293) | **0.0381** |

Note: Bold indicates p<0.05. Source: Appendix T1_ER Table 1.




Notes: Top left panel: EC subgroup. Top right panel: dMMR pan tumor subgroup. Bottom panel: EC dMMR subgroup. Circles indicate observed proportion of patient showing OR vs mean PK exposure per PK quartile. Results for the EC dMMR subgroup were very similar. Source: Appendix F1_ER Figures 1.2 and 1.6.

**Figure 32: Predicted probability and Observed Proportion of Overall response vs Dostarlimab Cmin for EC and dMMR Pan Tumour Patient Groups-Part 2B**

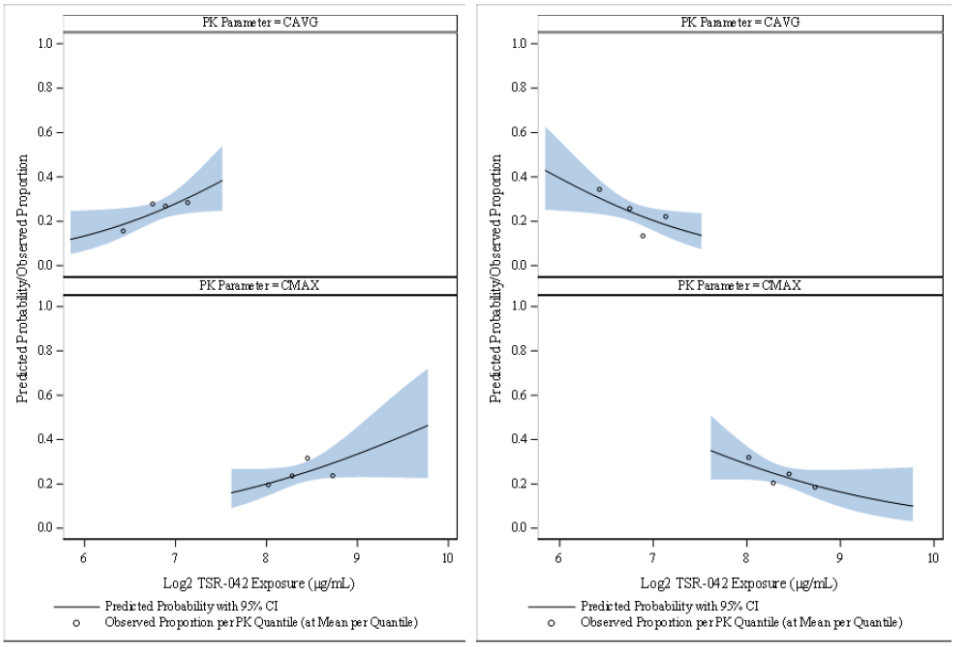
Exposure-safety

The relationship between dostarlimab exposure (Cavg and Cmax for 1000 mg Q6W of Cycle 5 RP2D) and the incidence of selected AEs (the top 5, with respect to incidence, for drug related AEs) was assessed using the same methods specified for dichotomous response efficacy variables. The safety population including Part 2B was used for these analyses, subset to subjects with PK parameters estimated, both for Part 2B in entirety, and for Part B excluding NSCLC patients. For the latter analysis, the same stratification approach for the exposure relationship was used, as for the efficacy analysis.

**Table 24: Summary of the exposure-Response Logistic Regression for Adverse Events-Parts 1,2 and 2B**

| Adverse Event | Number of AE Patients/Total Patients in Analysis | PK Parameter | Odds Ratio for Doubling Exposure | 95% CI of Odds Ratio | p-value |
|---|---|---|---|---|---|
| Fatigue | 99/385 | $C_{avg}$ | 0.894 | (0.394, 2.03) | 0.7897 |
| | | $C_{max}$ | 1.19 | (0.551, 2.56) | 0.6595 |
| Asthenia | 95/385 | $C_{avg}$ | 2.51 | (1.05, 5.99) | **0.0384** |
| | | $C_{max}$ | 2.01 | (0.928, 4.36) | 0.0765 |
| Diarrhoea | 92/385 | $C_{avg}$ | 0.393 | (0.170, 0.907) | **0.0287** |
| | | $C_{max}$ | 0.482 | (0.208, 1.11) | 0.0880 |
| Nausea | 90/385 | $C_{avg}$ | 0.334 | (0.144, 0.779) | **0.0112** |
| | | $C_{max}$ | 0.408 | (0.173, 0.961) | **0.0403** |
| Hypothyroidism | 51/385 | $C_{avg}$ | 2.36 | (0.780, 7.12) | 0.1288 |
| | | $C_{max}$ | 1.10 | (0.408, 2.97) | 0.8495 |

Note: Bold indicates p<0.05. Source: Appendix T3_ER Table 3.




Notes: Left panel: Asthenia. Right panel: Diarrhoea. Circles indicate proportion of patient with AE vs mean PK exposure per PK quartile. Graphial results for nausea were very similar to that of diarrhoea.
Source: Appendix F3_ER Figures 3.3 and 3.2.

**Figure 33: Predicted probability and Observed Proportion of Adverse Events (Asthenia and Diarrhoea) Dostarlimab Cavg and Cmax-Parts 1,2A and 2B**

## 2.4.4. Discussion on clinical pharmacology

Analytical Methods

A ELISA bioanalytical method was submitted for the determination of dostarlimab concentration in support of the study No. 4010-01-001.

In general, the pre-study validation of the analytical methods is satisfactory. In addition, the in-study validation shows acceptable calibration standards and QCs.

Two immunogenicity assays were described and validated. The design of the ADA and NAb detection assays is considered appropriate. Validation reports were provided, showing that the assays are suitable for their intended purpose. However, the Applicant is recommended to improve the 3-tier ADA assays to target a drug tolerance of at least 200 µg/mL of 100 ng/mL positive control. In principle, evaluation of drug tolerance should include additional positive controls with concentrations above and below the target sensitivity level of 100 ng/mL. When substantial improvements in method performance are achieved, the applicant will submit the results of the improved ADA methods once they are validated (REC).

Pharmacokinetics in the target population

Dostarlimab is administered via the intravenous route and therefore estimates of absorption are not applicable (see SmPC section 5.2).

No metabolism or excretion studies with dostarlimab were submitted in accordance with the International Council for Harmonisation (ICH) Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Dostarlimab is a therapeutic mAb IgG4 that is expected to be catabolised into small peptides, amino acids, and small carbohydrates by lysosome through fluid phase or receptor mediated endocytosis. The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects (see SmPC section 5.2).

Dostarlimab was characterised using population PK analysis from 477 patients with various solid tumours. This population PK modelling strategy was implemented to characterise the time-course PK profiles after dostarlimab administration using a sequential modelling approach: first, the base model was developed, then a covariate analysis was performed based on the significant covariate-parameter relationships previously explored and, at the last stage, the final population pharmacokinetic model was evaluated using the standard methodologies.

- Base model

A two compartments model with time-dependency clearance was selected as the base structural PK model. A weight-scaling effect on CL and V1 was incorporated using estimated allometric exponents (0.51 for CL and 0.48 for V1), which differ from the standard allometric exponents. In general, the model seems able to describe the overall tendency of the experimental data and parameters were estimated precisely.

- Final model

The final model incorporates several covariates: albumin on central clearance, alkaline phosphatase on central volume, alkaline phosphatase on central clearance, SLDR on central clearance, sex on central volume, positive ADA on central clearance, and age on central clearance. Its inclusion partially reduced the inter-individual variability on CL (37% to 30%) and V1 (23% to 19%).

Independent visual predictive checks were presented for each dose level and cycle of administration (Part 2A). The Applicant provided Forest plots of relevant covariates (sex, ADA status, weight, albumin,

alkaline phosphatase, age, diameter of target lesions by Response Evaluation Criteria in Solid Tumours (RECIST)) that did not indicate any clinically relevant effect on dostarlimab exposure (Cavg and Cmax) at Cycle 1. Female subjects have lower exposure than male subjects but the effect was within the 0.8 and 1.2 bounds.

Weight evaluated in the range of 47.7-110.8 kg had great impact on dostarlimab exposure as anticipated. Forest plots of the effect of significant covariates on dostarlimab exposure at Cycle 5 were provided (data not shown). These data showed high body weight and low baseline albumin had effect on Cavg outside of the 0.8 bound. Patients of body weight 110.8 kg have dostarlimab Cavg 20.8% lower than the reference patients while patients with baseline ALB 28.9 g/L have dostarlimab Cavg 24.3% lower than the reference patients. The Forest plot of effect on Cmin was not provided. Across the Pop PK population, weights and baseline albumin ranged from 34-182 kg and 19-51 g/L which is somewhat wider than evaluated in the Forest plots.

Special populations

Renal impairment was evaluated based on the estimated creatinine clearance [$CL_{CR}$ mL/min] (normal: $CL_{CR} \geq 90$ mL/min, n = 173; mild: $CL_{CR}$ = 60-89 mL/min, n = 210; moderate: $CL_{CR}$ = 30-59 mL/min, n = 90; severe: $CL_{CR}$ = 15-29 mL/min, n = 3 and ESRD: $CL_{CR} < 15$ mL/min, n = 1). The effect of renal impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of dostarlimab were found between patients with mild or moderate renal impairment and patients with normal renal function. Based on the available data, no dose adjustment is recommended for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment or end-stage renal disease undergoing dialysis (see SmPC sections 4.2 and 5.2).

Hepatic impairment was evaluated as defined using the US National Cancer Institute criteria of hepatic dysfunction by total bilirubin and AST (Normal: total bilirubin (TB) & AST < = upper limit of normal (ULN), n = 425; mild: TB > ULN to 1.5 ULN or AST > ULN, n = 48; and moderate: TB > 1.5-3 ULN, any AST, n = 4). The effect of hepatic impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment compared to patients with normal hepatic function. No clinically important differences in the clearance of dostarlimab were found between patients with mild hepatic impairment and normal hepatic function. Based on the available data, no dose adjustment is recommended for patients with mild hepatic impairment (see SmPC section 4.2). There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment (see SmPC sections 4.2 and 5.2).

Effect of weight was evaluated using data from study Part 1 and 2A and did not indicate any clinically relevant effect. In Study Part 2B, Cmin at Cycle 5 was shown to be significantly related to overall response. A doubling of Cmin increase odds ratio by 2.4-3.3-fold in the endometrial cancer and pan tumour patient groups. Hence Cmin is important for OR. The exposure in over-weighted patients (120-180 kg) at the proposed dosing regimen (RTD) provides for the vast majority of patients (>95.7%) dostarlimab levels above the efficacy threshold (18 mg/L). No obvious trends based on body weight were seen in ORR or in the incidence of TEAEs (data not shown). The patients with body weights >120 kg seemed to have less benefit in terms of ORR. However, there were only 4 very obese patients in the efficacy population which is too low to draw any firm conclusion.

The population PK analysis of the patient data indicates that there are no clinically important effects of age (range: 24 to 86 years), gender or race, ethnicity, or tumour type on the clearance of dostarlimab (see SmPC section 5.2). No dose adjustment is recommended for patients who are aged 65 years or over. There are limited clinical data with dostarlimab in patients aged 75 years or over.

Interactions

No interaction studies have been performed. Monoclonal antibodies (mAb) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies (see SmPC section 4.5).

Primary pharmacology

Dostarlimab is an IgG4-k anti-PD-1 antibody which binds with high affinity to PD-1 to block the interaction between PD-1 and PD-L1/PD-L2 ligands. The required concentration for full target engagement has been determined to 54 µg/mL at tumour sites and 18 µg/mL at peripheral sites. A lower dose e.g. 1 mg/kg or equivalent fixed dose will not be able to maintain full target engagement throughout treatment. Full receptor occupancy as measured by both the direct PD 1 binding and interleukin 2 (IL 2) production functional assay was maintained throughout the dosing interval at the recommended therapeutic dosing regimen (see SmPC section 5.2).

Secondary pharmacology

No clinically relevant QtcF prolongation is expected based on the experimental data provided and the analysis performed.

Exposure-response

Baseline clearance rather than exposure has been identified as a significant predictor of overall survival in subjects treated with nivolumab and pembrolizumab (Bajaj et al. 2017, Wang et al. 2017, Turner et al. 2018)). The clinical relevance of baseline CL could be a confounding factor for the E-R relationship, since CL is highly correlated with patient survival. The use of cycle 5 exposure metrics was justified as the highest exposure level collected and the closest value to the efficacy measurement.

No exposure-efficacy relationship has been established between dostarlimab (Cavg and Cmin) and overall response in any of the populations studied. An exposure-response was estimated between Cmin and odds ratio in EC and pan tumour populations (2.4- and 2.6-fold increase). However, it is unclear how changes in PK parameters due to time-dependency effects, may affect the exposure-efficacy relationship.

No exposure-safety relationship was established between dostarlimab exposure (Cmax and Cavg) and the probability of the most common dostarlimab related adverse events in patients receiving the proposed dosing regimens (Part 2B). An inverse exposure-safety relationship was demonstrated when a full analysis was performed, but no statistically significant relationships were encountered in patients with EC, dMMR/MSI-H EC, and dMMR/MSI-H pan tumour.

Dose selection

Selection of the recommended therapeutic dosing regimen (500 mg Q3W for 4 cycles, followed by 1,000 mg Q6W for all subsequent cycles) was based on the efficacy, safety, receptor occupancy, and population PK analysis of dostarlimab observed to date and is discussed under section 2.5.3.

## 2.4.5. Conclusions on clinical pharmacology

Dostarlimab has been characterised using experimental data from Study 4010-01-001. Data from dose escalation (Part 1A) and proposed dosing regimens after single and multiple dosing regimens of 500

mg Q3W and 1000 mg Q6W have been used. The methodology applied to characterise the pharmacokinetics and interactions through non-compartmental analysis and population approach is generally endorsed.

Exploratory and statistical evaluations were performed between dostarlimab Cavg, Cmin and Cmax and different efficacy and safety endpoints. The lack of a significant exposure-efficacy may limit the conclusions regarding the effective dostarlimab exposure. Despite the limitations it can be concluded that, based on exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety when doubling the exposure of dostarlimab.

## 2.5. Clinical efficacy

### 2.5.1. Dose response study

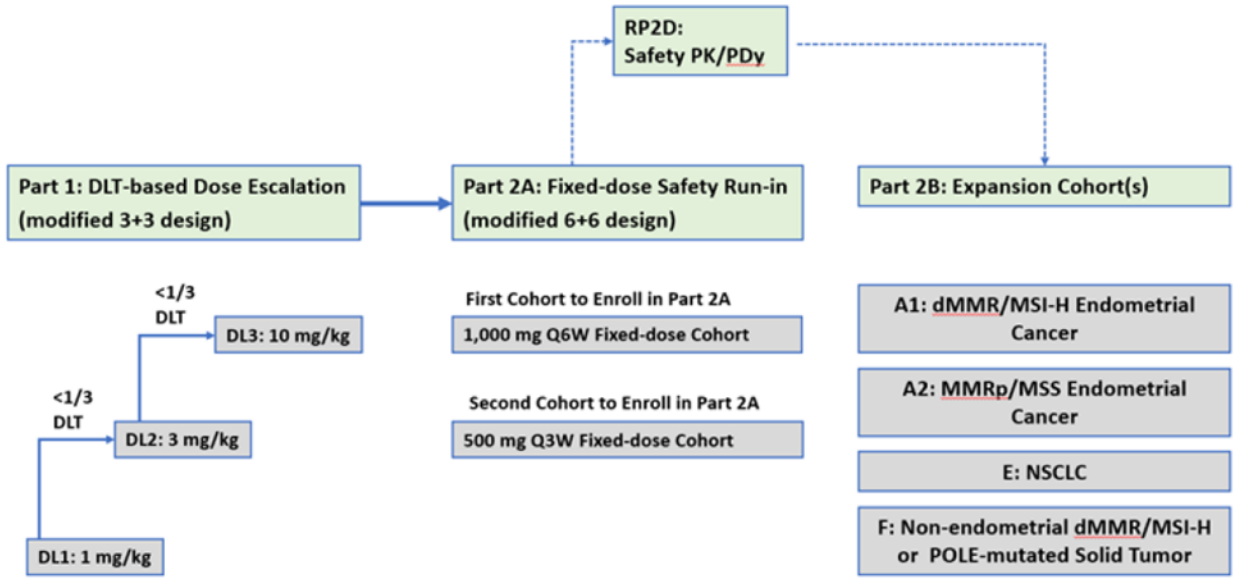
See results presented under clinical pharmacology section.

### 2.5.2. Main study

#### *Study 4010-01-001 (GARNET)*

#### *Methods*

This is a phase 1 Dose Escalation and cohort expansion study of dostarlimab, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumors.




Abbreviations: DL=dose level; DLT=dose-limiting toxicity; dMMR=mismatch repair-deficient; MMRp=mismatch repair-proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; NSCLC=non-small cell lung cancer; PDy=pharmacodynamic(s); PK=pharmacokinetic(s); POLE-mut=polymerase epsilon-mutated; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose.
Note: Expansion Cohort A1 and Cohort F are open to enrolment. Enrolment to Part 1, expansion Cohort A2, and expansion Cohort E is complete. The RP2D is 500 mg dostarlimab Q3W for 4 cycles followed by 1,000 mg dostarlimab Q6W thereafter.

**Figure 34: Study 4010-01-001 (GARNET) Phase 1 study schema**

Study 4010-01-001 is a multicentre, open-label study with expansion cohorts designed to assess the safety, tolerability, PK, PD, and clinical activity of dostarlimab in patients with recurrent or advanced solid tumours who experienced disease progression on or after treatment with available anticancer therapies.

The study is being conducted in 2 parts:

- **Part 1** of the study evaluates dose-limiting toxicities, overall safety, and the PK/PD profile of ascending weight-based doses of dostarlimab.

- **Part 2** of the study is subdivided into Part 2A and Part 2B.

Part 2A (fixed-dose safety evaluation cohorts) of the study evaluated the safety and tolerability of dostarlimab at 2 fixed (flat; non-weight based) doses: 500 mg administered Q3W and 1,000 mg administered Q6W up to 2 years. Subjects in Part 2A who received at least 4 cycles of dostarlimab using the Q3W dosing regimen were allowed to switch to the Q6W dosing regimen.

In Part 2B (expansion cohorts), the clinical activity and safety of dostarlimab at the recommended therapeutic dose is being evaluated in several expansion cohorts. In Part 2B of the study, subjects are enrolled in 1 of 4 expansion cohorts according to the following tumour types: dMMR/MSI-H EC (Cohort A1), MMR-proficient/MSS EC (Cohort A2), non-small cell lung cancer (NSCLC) (Cohort E), and dMMR/MSI-H or POLE-mutated non-EC (Cohort F).

## *Study Participants*

Part 2B of the study was initiated at 123 sites in 9 countries. The study is executed at sites in the US, Europe (Czech Republic, Denmark, France, Italy, Spain, United Kingdom, and Poland), and Canada.

Inclusion criteria

For inclusion into Cohort A1 or Cohort A2 of Part 2B of this study, subjects were required to fulfill all of the following criteria:

1. Subject was at least 18 years old.

2. Subject had proven recurrent or advanced solid tumour and disease progression after treatment with available anticancer therapies or was intolerant to treatment that met the requirements for the part of the study they participated in.

    a. Part 2B: Histologically of cytologically proven recurrent or advanced solid tumour with measurable lesion(s) per RECIST v1.1 and met one of the following disease types:

    The criteria below were met for subjects participating in

        a. Cohort A1 – Subjects with dMMR/MSI-H EC and

        b. Cohort A2 – Subjects with MMR-proficient/MSS EC

• Subjects had progressed on or after platinum doublet therapy.

• Subjects had received no more than 2 lines of anticancer therapy for recurrent or advanced (≥Stage III B) disease. Prior treatment with hormone therapies was acceptable and did not count toward the number of anticancer therapies noted in the criterion above for this cohort.

• All EC histologies were allowed, except endometrial sarcoma (including carcinosarcoma).

• Subjects submitted 2 scans demonstrating an increase in tumour measurement that met criteria for PD on or after the latest systemic anticancer therapy based on RECIST v1.1 to Central Radiology prior to the first dose of dostarlimab.

• Presence of at least 1 measurable lesion on baseline scan was confirmed by Central Radiology review.

• Status of tumour MMR/MSI: Subjects could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but subject eligibility was determined by MMR IHC results. For subjects with available local MMR IHC results for the respective cohort(s), tumour samples were submitted to a central IHC laboratory, and the quality was checked and cleared prior to Cycle 1/Day 1. For subjects without available local MMR IHC test results (ie, subjects with local PCR or NGS test results), tumour samples were submitted directly to a central IHC laboratory, and the central IHC results confirmed eligibility prior to proceeding with other screening procedures. After the central IHC test was completed, remaining tumour tissue may have been sent to a central NGS laboratory for further testing.

3. Part 2B: Subjects had archival tumour tissue available that was formalin fixed and paraffin embedded.

• For subjects who did not have archival tissue, a new biopsy was performed to obtain a tissue sample prior to study treatment initiation. For subjects without available archival tissue, the biopsy was taken from the tumour lesions (either primary or metastatic) that had easy accessibility and low biopsy-associated risks and excluded biopsies of the liver, brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the oesophagus, stomach, or bowel.

4. Female subjects must have had a negative serum pregnancy test within 72 hours prior to the date of the first dose of study medication; unless they were of nonchildbearing potential.

5. Female subjects of childbearing potential (see above) must have agreed to use 1 highly effective form of contraception with their partners starting with the Screening Visit through 150 days after the last dose of study treatment.

6. Subject had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 for Part 1 and ≤1 for Part 2.

7. Subject had adequate organ function, defined as follows:

a. absolute neutrophil count (ANC) ≥1,500/μL

b. platelets ≥100,000/μL

c. haemoglobin ≥9 g/dL or ≥5.6 mmol/L

d. serum creatinine ≤1.5×upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault equation for subjects with creatinine levels >1.5×institutional ULN

e. total bilirubin ≤1.5×ULN AND direct bilirubin ≤1×ULN

f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN, unless liver metastases were present, in which case they must be ≤5×ULN

g. international normalized ratio (INR) or prothrombin time ≤1.5×ULN, unless the subject was receiving anticoagulant therapy or as long as prothrombin time or partial thromboplastin time (PTT) was within the therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT) ≤1.5×ULN, unless the subject was receiving anticoagulant therapy or as long as prothrombin time or PTT was within the therapeutic range of intended use of anticoagulants.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Subject had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

2. Subject had known uncontrolled central nervous system metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may have participated provided they were stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), had no evidence of new or enlarging brain metastases, and were clinically stable off corticosteroids for at least 7 days prior to study treatment. Carcinomatous meningitis precluded a subject from study participation, regardless of clinical stability.

3. Subject had a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy, or in situ cervical cancer.

4. Subject was considered a poor medical risk due to a serious, uncontrolled medical disorder; a non-malignant systemic disease; or an active infection requiring systemic therapy. Specific examples included, but were not limited to, active, non-infectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would have interfered with cooperation with the requirements of the study (including obtaining informed consent).

5. Subject was pregnant or breastfeeding, or expected to conceive children within the projected duration of the study, starting with the Screening Visit through 150 days after the last dose of study treatment.

6. Subject had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

7. Subject had a known history of HIV (HIV 1/2 antibodies).

8. Subject had known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [qualitative] was detected).

9. Subject had an active autoimmune disease that had required systemic treatment in the past 2 years (i.e., with the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) was not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops were allowed.

10. Subject had a history of interstitial lung disease.

11. Subject had not recovered (i.e., to Grade ≤1 or to baseline) from radiation- and chemotherapy-induced AEs or received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.

12. Subject had participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks prior to the first dose of study drug.

13. Subject had received prior anticancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever was shorter. Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may have been allowed.

14. Subject had not recovered adequately (Grade ≤1) from AEs and/or complications from any major surgery prior to starting therapy.

15. Subject had received a live vaccine within 14 days of the planned start of study treatment.

16. Subject had a known hypersensitivity to dostarlimab components or excipients.

## *Treatments*

Dostarlimab is administered intravenously (IV) as a 30-minute infusion to all patients.

The dosing schedule for the Part 2 B of Study 4010-01-001 is as follows:

Dostarlimab is being administered at fixed doses of 500 mg administered Q3W for 4 cycles and 1,000 mg administered Q6W thereafter. Subjects with no unacceptable toxicities or no PD may be treated for up to 2 years in this study. Study treatment may continue beyond 2 years if the treating physician and the Sponsor agree that the subject continues to benefit.

## *Objectives*

The objectives from protocol version 6.0 (amendment 5; 10 May 2019) relevant to Cohorts A1 in Part 2B were the following:

The primary objective was the evaluation of the antitumor activity of dostarlimab in patients with recurrent or advanced dMMR/MSI-H EC (Cohort A1) in terms of objective response rate (ORR) and duration of response (DOR) by blinded independent central review (BICR) using RECIST v1.1.

Secondary objectives

- to characterize the pharmacokinetic (PK) profile of dostarlimab
- to evaluate the immunogenicity of dostarlimab
- to evaluate additional measures of clinical benefit, including the following:

  o immune-related disease control rate (irDCR) based on Investigators' assessment using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

  o immune-related duration of response (irDOR) based on Investigators' assessment using irRECIST

  o immune-related progression-free survival (irPFS) based on Investigators' assessment using irRECIST

  o progression-free survival (PFS) based on BICR using RECIST v1.1

  o immune-related objective response rate (irORR) based on Investigators' assessment using irRECIST

o disease control rate (DCR) based on Investigators' assessment using RECIST v1.1

o overall survival (OS)

Exploratory objectives:

- to characterize the pharmacodynamic (PD) profile of dostarlimab
- to explore changes in intratumoral cells and circulating biomarkers in the blood following treatment with dostarlimab
- to explore the profile of tumor-infiltrating lymphocytes (TILs), tumor cell characteristics including genomic alterations (eg, MMR/microsatellite instability (MSI) and polymerase [POLE]), and/or circulating biomarkers prior to treatment with dostarlimab and to correlate them with clinical benefit
- patient-reported outcomes (PROs) (European Quality of Life scale, 5 Dimensions, 5 Levels [EQ-5D-5L] and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]) in subjects in Cohorts A1 and F enrolled under protocol amendment 3 or subsequent amendments

## *Outcomes/endpoints*

The primary endpoints for Cohort A1 were as follows:

**ORR**, defined as the proportion of patients achieving best overall response (BOR) of complete response (CR) or partial response (PR), as assessed per RECIST v1.1 based on BICR

**DOR**, defined as the time from first documentation of CR or PR, as assessed per RECIST v1.1, until the time of first documentation of PD, as assessed per RECIST v1.1 based on BICR, or death due to any cause

Secondary endpoints for Cohort A1 included (but were not limited to):

**DCR**, defined as the proportion of patients achieving BOR of confirmed CR, PR, or stable disease (SD), as assessed per RECIST v1.1.

**PFS**, defined as the time from date of first dose to the earlier date of assessment of disease progression or death by any cause in the absence of progression based on the time of first documentation of PD per RECIST v1.1 based on BICR.

**OS**, defined as the time from date of first dose of study treatment to the date of death by any cause.

**Immune-related objective response rate (irORR)**, defined as the proportion of patients achieving immune-related best overall response (irBOR) of immune-related complete response (irCR) or immune-related partial response (irPR), as assessed per immune-related RECIST (irRECIST) based on Investigator's assessment.

**Immune-related duration of response**, defined as the time from first documentation of irCR or irPR, as assessed per irRECIST based on Investigator's assessment, until the time of first documentation of immune-related progressive disease (irPD) (subsequently confirmed), as assessed per irRECIST based on Investigator's assessment, or death.

**Immune-related disease control rate (irDCR)**, defined as the proportion of patients achieving irBOR of irCR, irPR, or immune-related SD, as assessed per irRECIST based on Investigator's assessment.

**Immune-related progression-free survival (irPFS)**, defined as the time from date of first dose to the earlier date of assessment of irPD or death by any cause in the absence of progression based on the time of first documentation of irPD (subsequently confirmed) per irRECIST based on Investigator's assessment.

Exploratory endpoints

**PRO:** The European Quality of Life scale, 5 Dimensions, 5 Levels and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire were used to assess cancer-specific health-related quality of life. PRO assessments were added to the study under protocol amendment 3.

## *Sample size*

For Part 2B, a total sample size of up to 680 subjects for the expansion cohorts was estimated to provide assessment of clinical activity of dostarlimab based on ORR.

For Cohort A1, the null hypothesis that the true response rate is ≤20% (H0: p≤0.2) was tested against a one-sided alternative of ≥40% (Ha: p≥0.4). With 65 subjects treated, Cohort A1 has 92% power to rule out a ≤20% ORR (null hypothesis; expected ORR for conventional therapy) when the true ORR is 40% at the 2.5% type I error rate (one-sided). Based on a report that 6 of 9 subjects with MSI-H EC achieved a clinical response following treatment with an anti-PD-1 antibody, the activity of dostarlimab in this subject population was expected to negate the necessity for a 2-stage design and, thus, there was no interim analysis in this cohort.

Under protocol amendment 5, the sample size of Cohort A1 was increased to 100 subjects, with the potential for up to 165 subjects, which allowed the lower-limit boundary of the exact 95% CI excluding a response rate of 25% or less and assuming the observed ORR is 35%.

## *Randomisation*

This was an uncontrolled Cohort Study.

## *Blinding (masking)*

The study was open label.

## *Statistical methods*

The statistical analysis for Study 4010-01-001 was descriptive in nature. In general, categorical data were summarized using number of patients (n), frequency, and percentages, with the denominator for percentages being the number of patients in the analysis set. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method was provided to summarize the binomial proportion of the ORR/immune-related ORR (irORR) and DCR/immune-related DCR (irDCR) for both RECIST v1.1 and immune-related RECIST (irRECIST) assessments, where applicable.

Three interim analyses were planned for dMMR/MSI-H patients from Cohorts A1 and F combined for administrative purposes. The interim analyses were to occur when combined enrollment in the 2 cohorts reached approximately 100, 200, and 300 patients and enrolled patients had been followed up for at least 6 months

Data presented for cohort A1 were based on a prospectively defined interim analysis conducted when 200 patients enrolled in Cohort A1 and Cohort F (combined) had at least 6 months of follow up in order to allow sufficient time to assess tumour response and duration.

*Analysis Sets*

- Primary efficacy analysis set (RECIST 1.1 per BICR): All patients in Safety Analysis Set with measurable disease at baseline (defined at the existence of at least one target lesion at baseline tumor assessment by BICR) who have had the opportunity for at least 24 weeks of tumor assessment at the time of analysis. All patients included in the primary efficacy analysis set had a minimum follow-up period of 24 weeks from first dose, regardless of whether they had a post-treatment scan.

Subjects who did not have a postbaseline radiographic tumour assessment; who received postbaseline antitumor treatments (including surgery or radiation to the tumour lesions) other than the study treatments prior to reaching a CR/irCR or PR/irPR; or who died, progressed, or dropped out for any reason prior to reaching a CR/irCR or PR/irPR were counted as non-responders in the assessment of ORR and irORR.

- Secondary efficacy analysis set (irRECIST per Investigator assessment): All patients in Safety Analysis Set with measurable disease at baseline (defined at the existence of at least one target lesion at baseline tumor assessment by Investigator) who have had the opportunity for at least 24 weeks of tumor assessment at the time of analysis. All patients included in the secondary efficacy analysis set had a minimum follow-up period of 24 weeks from first dose, regardless of whether they had a post-treatment scan.

- Safety analysis set: All patients who received any amount of study drug prior to the data cut-off.

*Efficacy analyses*

The analyses for the efficacy endpoints using RECIST v1.1 and irRECIST were based on the efficacy analysis set. The analyses for OS were based on the primary efficacy analysis set. The key efficacy analyses for Cohort A1 and Cohort A2 were ORR, DCR, DOR, and PFS by RECIST v1.1; irORR, irDCR, irDOR, and irPFS by irRECIST; and OS.

Censoring rules for DOR and irDOR are presented below.

**Table 25: Censoring Rules for DOR, irDOR, PFS, and irPFS**

| Scenario | Date of event/censoring | Outcome |
|---|---|---|
| No baseline assessment | First dose date | Censored |
| No post-baseline evaluable radiologic tumor assessment | First dose date | Censored |
| Prior to 48 weeks tumor assessment:<br>Progression or death ≤ 12 weeks +10 days after prior post-baseline tumor assessment or ≤ 18 weeks after first dose date<br>After 48 weeks tumor assessment:<br>Progression or death ≤24 weeks + 10 days after prior post-baseline tumor assessment | Date of progression or death | Event |
| Prior to 48 weeks tumor assessment:<br>Progression or death > 12 weeks + 10 days after the prior post-baseline tumor assessment<br>After 48 weeks tumor assessment:<br>Progression or death >24 weeks + 10 days after the prior post-baseline tumor assessment | Date of last evaluable radiologic tumor assessment prior to Progression or death | Censored [a] |
| No progression | Date of last evaluable radiologic tumor assessment | Censored |
| New anticancer therapy given | Date of last evaluable radiologic tumor assessment before anticancer therapy given | Censored |

[a] Tumor assessment is based on a CT or MRI scan. If progression/death is determined and 2 previous scans were missing, date of progression is not known.

Censoring for OS was set at the last known date of contact.

### *Results*

Results at the time of data cut-off of 08 July 2019 for patients with dMMR/MSI-H EC enrolled in Cohort A1 of Part 2B of Study 4010-01-001 (GARNET) were initially presented in the application.

During the procedure, updated efficacy data for the GARNET study Cohort A1 (dMMR/MSI-H) EC with a data cutoff date of 01 March 2020 were submitted and are presented below.

Results are presented for the primary efficacy analysis set consisting in patients who had measurable disease and the opportunity for at least 24 weeks of follow-up, including 3 patients who discontinued prematurely due to adverse events or disease progression (N=108).

As of the data cutoff date, 58 participants (45%) were still on study treatment and enrolment is still ongoing.

## Participant flow

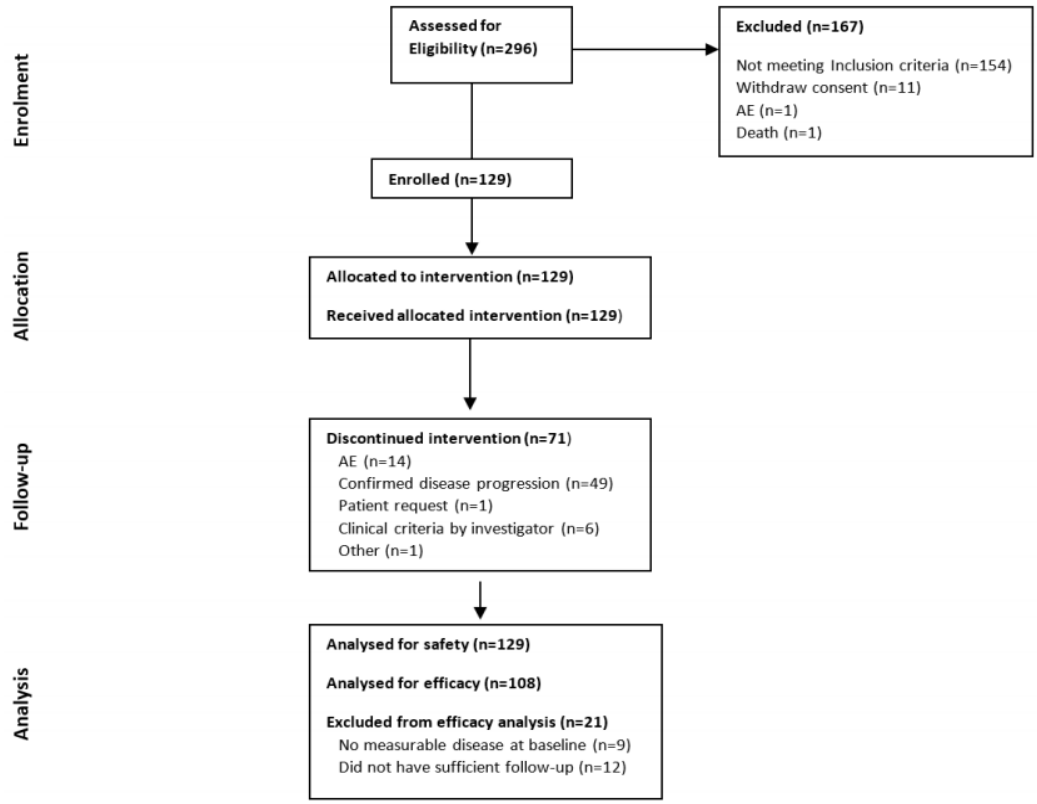



**Figure 35: Participant Workflow: GARNET Study, Patients with Mismatch Repair Deficient/Microsatellite-Instability High Endometrial Cancer**

**Table 26: Patient disposition - Primary Efficacy Population**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Variable**<br>**Reason [n (%)]** | **dMMR**<br>**(N=106)** | **MMR-unk /MSI-H**<br>**(N-2)** | **Total**<br>**(N=108)** |
| Subjects still on treatment | 39 (36.8) | 1 (50.0) | 40 (37.0) |
| Discontinued treatment | 67 (63.2) | 1 (50.0) | 68 (63.0) |
| Adverse event | 14 (13.2) | 0 | 14 (13.0) |
| Confirmed disease progression | 46 (43.4) | 0 | 46 (42.6) |
| Risk to patients as judged by the Investigator and/or Sponsor | 0 | 0 | 0 |
| Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor | 0 | 0 | 0 |
| Patient request | 1 (0.9) | 0 | 1 (0.9) |
| Patient pregnancy | 0 | 0 | 0 |
| Sponsor decision to terminate study | 0 | 0 | 0 |
| Based on clinical criteria by Investigator | 5 (4.7) | 1 (50.0) | 6 (5.6) |
| Other | 1 (0.9) | 0 | 1 (0.9) |
| Discontinued study | 44 (41.5) | 1 (50.0) | 45 (41.7) |
| Withdrawal of consent | 7 (6.6) | 0 | 7 (6.5) |
| Lost to follow-up | 1 (0.9) | 1 (50.0) | 2 (1.9) |
| Sponsor decision to terminate study | 0 | 0 | 0 |
| Death | 35 (33.0) | 0 | 35 (32.4) |
| Other | 1 (0.9) | 0 | 1 (0.9) |
| Subjects treated beyond initial disease progression | 25 (23.6) | 0 | 25 (23.1) |
| Died while on study | 35 (33.0) | 0 | 35 (32.4) |
| Disease progression | 30 (28.3) | 0 | 30 (27.8) |
| Adverse event | 5 (4.7) | 0 | 5 (4.6) |
| Unknown | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |

Source: Table 14.1.3.1a.1.1
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high.
Note: Reasons for discontinuation are based on the Discontinuation of Treatment and Discontinuation of Study CRF page.

## Recruitment

First subject enrolled: 10 April 2017

Last subject completed: Not applicable. Cohort A1 is still open to enrolment. As of the data cutoff date of 01 March 2020, 129 subjects had been enrolled in Cohort A1, and 58 patients were still on treatment. Cohort A2 was closed to enrolment.

Data cut-off date: 01 March 2020

Median follow-up at data cut-off date in Cohort A1: 16.3 months.

## Conduct of the study

Five global protocol amendments were implemented during the study, as follows: protocol version 2.0 (amendment 1, dated 26 January 2016); protocol version 3.0 (amendment 2, dated 31 October 2016, The EC cohort was split into 2 cohorts based on MSI status, Assessment of tumour imaging from Cohort A1 and Cohort A2 by central radiologists based on RECIST v1.1); protocol version 4.1 (amendment 3, dated 09 October 2017: inclusion of PRO, inclusion of an IA in Cohort A1 and F); protocol version 5.1 (amendment 4, dated 03 July 2018: increased enrolment in Cohort A2, stable patients were allow to prolong treatment) and protocol version 6.0 (amendment 5, dated 10 May 2019: The definitions of Cohort A1 and Cohort A2 were updated such that tumour status requirements in the EC cohorts were revised to specify that subject eligibility can only be determined by MMR status based on results from IHC testing).

Subjects participating in Part 2B of the study were enrolled only under protocol versions 3.0, 4.1, and 5.1. No subjects were enrolled under protocol version 6.0 by the data cut-off date for this interim CSR.

*Protocol deviations*

In the safety analysis set, a total of 14 significant protocol deviations were recorded for 13 subjects (4.9%), including 7 significant protocol deviations in 6 subjects (5.8%) with dMMR EC. Most of these significant deviations were related to inclusion/exclusion criteria and included the following:

• Deviation of inclusion criterion 2 (n=8), including progression following more than 2 prior lines of therapy (n=2 [2 subjects with dMMR EC]), no prior platinum doublet therapy (n=1 [1 subject with dMMR EC]), no central radiological confirmation of PD before dosing (n=1 [1 subject with dMMR EC]), no measurable disease at baseline (n=1 [1 subject with dMMR EC]), and subjects with carcinosarcoma (n=3 [3 subjects with MMR-proficient EC]).

• Deviation of exclusion criterion 11: subject has not received transfusion of red blood cells within 3 weeks prior to the first dose of study drug (n=1 [1 subject with MMR-proficient EC]). A second subject with dMMR EC also received transfusion of red blood cells within 3 weeks prior to the first dose of study drug.

• Deviation of exclusion criterion 13: no washout period of 21 days for paclitaxel/carboplatin treatment prior to dosing (n=1 [1 subject with dMMR EC]).

• Subject received dostarlimab before central MSI status confirmation (n=1 [1 subject with MMR-proficient EC]).

• SAE was reported 12 days out of window (n=1 [1 subject with MMR-proficient EC]).

## Baseline data

The demographic characteristics for patients with dMMR/MSI-H EC in the primary efficacy analysis set are summarised in the table below.

**Table 27: Demographic characteristics – patients with dMMR/MSI-H EC (Primary efficacy analysis set) – DCO 1 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Characteristics [n (%)]** | **dMMR (N=106)** | **MMR-unk /MSI-H (N=2)** | **Total (N=108)** |
| Race | | | |
| White | 82 (77.4) | 2 (100.0) | 84 (77.8) |
| Asian | 5 (4.7) | 0 | 5 (4.6) |
| Black | 2 (1.9) | 0 | 2 (1.9) |
| American Indian or | 3 (2.8) | 0 | 3 (2.8) |
| Alaska Native | 0 | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Not reported | 14 (13.2) | 0 | 14 (13.0) |
| Ethnicity | | | |
| Hispanic or Latino | 4 (3.8) | 0 | 4 (3.7) |
| Not Hispanic or Latino | 84 (79.2) | 2 (100.0) | 86 (79.6) |
| Unknown | 3 (2.8) | 0 | 3 (2.8) |
| Not reported | 15 (14.2) | 0 | 15 (13.9) |
| Age (years) | | | |
| n | 106 | 2 | 108 |
| Mean (standard) | 63.4 (8.97) | 54.0 (0.00) | 63.2 (8.98) |
| Median | 65.0 | 54.0 | 64.5 |
| Q1, Q3 | 59.0, 70.0 | 54.0, 54.0 | 58.5, 69.5 |
| Min, max | 39, 80 | 54, 54 | 39, 80 |
| Age group | | | |
| <65 years | 52 (49.1) | 2 (100.0) | 54 (50.0) |
| ≥65 years - <75 years | 43 (40.6) | 0 | 43 (39.8) |
| ≥75 years | 11 (10.4) | 0 | 11 (10.2) |
| Weight (kg) | | | |
| Mean (standard) | 74.19 (21.058) | 67.10 (22.769) | 74.05 (20.998) |
| Median | 71.00 | 67.10 | 71.00 |
| Q1, Q3 | 57.00, 87.00 | 51.00, 83.20 | 57.00, 86.55 |
| Min, max | 34.0, 141.4 | 51.0, 83.2 | 34.0, 141.4 |
| Height (cm) | | | |
| n | 103 | 2 | 105 |

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Characteristics [n (%)]** | **dMMR (N=106)** | **MMR-unk /MSI-H (N=2)** | **Total (N=108)** |
| Mean (standard) | 159.95 (6.930) | 155.10 (0.141) | 159.86 (6.896) |
| Median | 160.00 | 155.10 | 160.00 |
| Q1, Q3 | 155.00, 164.00 | 155.00, 155.20 | 155.00, 163.00 |
| Min, max | 144.0, 182.9 | 155.0, 155.2 | 144.0, 182.9 |
| BMI ($kg/m^2$) | | | |
| n | 103 | 2 | 105 |
| Mean (standard) | 28.97 (7.849) | 27.88 (9.414) | 28.95 (7.830) |
| Median | 27.93 | 27.88 | 27.93 |
| Q1, Q3 | 22.31, 34.05 | 21.23, 34.54 | 22.31, 34.05 |
| Min, max | 13.6, 53.9 | 21.2, 34.5 | 13.6, 53.9 |
| ECOG performance status | | | |
| 0 | 40 (37.7) | 2 (100.0) | 42 (38.9) |
| 1 | 66 (62.3) | 0 | 66 (61.1) |
| 2 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 |

Source: Table 14.1.1.5.2a.1.1
Abbreviations: BMI=body mass index; dMMR=mismatch repair-deficient; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; EU=European Union; max=maximum; min=minimum; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high.

The baseline disease characteristics for patients with dMMR/MSI-H EC in the primary efficacy analysis set are summarised in the table below.

**Table 25: Primary Cancer History: EU Primary Efficacy Population - DCO 1 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Characteristics [n (%)]** | **dMMR (N=106)** | **MMR-unk /MSI-H (N-2)** | **Total (N=108)** |
| FIGO cancer stage at diagnosis | | | |
| Stage I | 41 (38.7) | 0 | 41 (38.0) |
| Stage II | 8 (7.5) | 1 (50.0) | 9 (8.3) |
| Stage III | 37 (34.9) | 1 (50.0) | 38 (35.2) |
| Stage IV | 20 (18.9) | 0 | 20 (18.5) |
| Most Recent FIGO Stage | | | |
| Stage I | 12 (11.3) | 0 | 12 (11.1) |
| Stage II | 3 (2.8) | 1 (50.0) | 4 (3.7) |
| Stage III | 19 (17.9) | 0 | 19 (17.6) |
| Stage IV | 70 (66.0) | 1 (50.0) | 71 (65.7) |
| Unknown | 2 (1.9) | 0 | 2 (1.9) |
| Histology at diagnosis | | | |
| Endometrioid carcinoma type I | 70 (66.0) | 1 (50.0) | 71 (65.7) |
| Endometrial carcinoma type II | 35 (33.0) | 1 (50.0) | 36 (33.3) |
| Serous carcinoma | 5 (4.7) | 0 | 5 (4.6) |
| Clear cell Carcinoma | 1 (0.9) | 0 | 1 (0.9) |
| Squamous carcinoma | 1 (0.9) | 0 | 1 (0.9) |
| Undifferentiated carcinoma | 4 (3.8) | 0 | 4 (3.7) |
| Mixed carcinoma | 6 (5.7) | 0 | 6 (5.6) |
| Unspecified | 14 (13.2) | 0 | 14 (13.0) |
| Other | 4 (3.8) | 1 (50.0) | 5 (4.6) |
| Unknown | 1 (0.9) | 0 | 1 (0.9) |
| Grade of disease at diagnosis | | | |
| Grade 1 | 31 (29.2) | 0 | 31 (28.7) |
| Grade 2 | 41 (38.7) | 1 (50.0) | 42 (38.9) |
| Grade 3 | 29 (27.4) | 1 (50.0) | 30 (27.8) |
| Not assessable | 5 (4.7) | 0 | 5 (4.6) |
| Expression of oestrogen receptors | | | |
| Positive | 51 (48.1) | 0 | 51 (47.2) |
| Negative | 5 (4.7) | 0 | 5 (4.6) |

**Table 25: Primary Cancer History: EU Primary Efficacy Population (Continued)**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Characteristics [n (%)]** | **dMMR (N=106)** | **MMR-unk /MSI-H (N-2)** | **Total (N=108)** |
| Unknown | 50 (47.2) | 2 (100.0) | 52 (48.1) |
| Expression of progesterone receptors | | | |
| Positive | 40 (37.7) | 0 | 40 (37.0) |
| Negative | 10 ( 9.4) | 0 | 10 (9.3) |
| Unknown | 56 (52.8) | 2 (100.0) | 58 (53.7) |
| Expression of HER2/neu | | | |
| Positive | 3 (2.8) | 0 | 3 (2.8) |
| Negative | 2 (1.9) | 0 | 2 (1.9) |
| Unknown | 101 (95.3) | 2 (100.0) | 103 (95.4) |

Source: Table 14.1.1.6.2a.1.1
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; FICO=International Federation of Gynaecology and Obstetrics; HER2=human epidermal growth factor 2; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high.

Prior anticancer treatment for patients with dMMR/MSI-H EC in the primary efficacy analysis set is summarized in the table below.

**Table 29: Primary Anti-Cancer Treatment - Patients with dMMR/MSI-H EC (Primary efficacy analysis set) – DCO 1 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| Variable[n (%)] | dMMR (N=106) | MMR-unk /MSI-H (N=2) | Total (N=108) |
| Any prior anti-cancer treatment | 106 (100) | 2 (100) | 108 (100) |
| Prior surgery for study indication | 96 (90.6) | 2 (100) | 98 (90.7) |
| Any prior anticancer radiotherapy | 76 (71.7) | 1 (50.0) | 77 (71.3) |
| Prior bevacizumab use | 5 (4.7) | 0 | 5 (4.6) |
| Any prior anticancer treatment for adjuvant/neo-adjuvant disease | 57 (53.8) | 2 (100) | 59 (54.6) |
| Number of prior anticancer regimen | | | |
| 0 | 0 | 0 | 0 |
| 1 | 68 (64.2) | 1 (50.0) | 69 (63.9) |
| 2 | 27 (25.5) | 0 | 27 (25.0) |
| 3 | 8 (7.5) | 1 (50.0) | 9 (8.3) |
| ≥4 | 3 (2.8) | 0 | 3 (2.8) |
| Number of prior regimen for metastatic disease[a] | | | |
| 0 | 48 (45.3) | 1 (50.0) | 49 (45.4) |
| 1 | 48 (45.3) | 0 | 48 (44.4) |
| 2 | 9 (8.5) | 1 (50.0) | 10 (9.3) |
| 3 | 1 (0.9) | 0 | 1 (0.9) |
| ≥4 | 0 | 0 | 0 |
| Best overall response from last platinum-containing prior anticancer therapy | | | |
| Complete response | 18 (17.0) | 1 (50.0) | 19 (17.6) |
| Partial response | 26 (24.5) | 0 | 26 (24.1) |
| Progression free interval from last platinum-containing anticancer therapy (months) | | | |
| Mean (standard) | 11.64 (15.868) | 18.87 (22.232) | 11.78 (15.896) |
| Median | 6.6 | 18.9 | 6.6 |
| Q1, Q3 | 4.4, 12.3 | 3.2, 34.6 | 4.4, 12.4 |
| Min, max | 0.2, 123.0 | 3.2, 34.6 | 0.2, 123.0 |

Source: Table 14.1.1.13.2a.1.1
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; max=maximum; min=minimum; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high.
[a] Excluding neo-adjuvant, adjuvant regimens, and hormonal agents.

## Numbers analysed

The safety analysis set for Cohort A1 which was defined as all subjects who received any amount of study drug regardless of follow up time, included 129 subjects.

The primary efficacy analysis set for Cohort A1 was defined as all subjects in the safety analysis set with measurable disease at baseline (defined as the existence of at least 1 target lesion at baseline tumour assessment by BICR) who had the opportunity for at least 24 weeks of tumour assessment at the time of analysis; including patients who discontinued prematurely due to adverse events or disease progression (accounted as non-responders). It comprised 108 subjects: 106 subjects with dMMR EC by IHC and 2 subjects with MSI-H EC by NGS but unknown MMR status.

As of the data cut-off date of 01 March 2020 for this interim CSR, 58 subjects were still on study treatment in Cohort A1. Enrolment is ongoing in Cohort A1.

**Table 26: Reasons participants were excluded from primary efficacy population – Data Cut-off Date 01 March 2020**

| Variable | dMMR (N=20) | MMR-unk /MSI-H (N=1) | Total (N=21) |
|---|---|---|---|
| Subjects who were treated but not included in the efficacy dataset | 20 (100) | 1 (100) | 21 (100) |
| Reasons subjects were excluded from efficacy population | | | |
| Subjects were enrolled after Sept 15, 2019 | 12 (60.0) | 0 | 12 (57.1) |
| Still on treatment | 12 (60.0) | 0 | 12 (57.1) |
| Discontinued treatment due to AE | 0 | 0 | 0 |
| Discontinued treatment due to PD | 0 | 0 | 0 |
| Discontinued treatment due to other reason | 0 | 0 | 0 |
| Subjects did not have measurable disease at baseline per BICR | 8 (40.0) | 1 (100) | 9 (42.9) |
| Still on treatment | 5 (25.0) | 1 (100) | 6 (28.6) |
| Discontinued treatment due to AE | 0 | 0 | 0 |
| Discontinued treatment due to PD | 3 (15.0) | 0 | 3 (14.3) |
| Discontinued treatment due to other reason | 0 | 0 | 0 |
| Subjects received other antitumour treatments | 0 | 0 | 0 |

Source: Table 14.2.33a.1
Abbreviations: AE=adverse event; BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair-deficient; EC=endometrial cancer; MMR-unk=mismatch repair unknown; MSI-H=microsatellite instability-high; PD=progressive disease.

## Outcomes and estimation

Primary efficacy endpoints

- Objective Response Rate

Tumour response by BICR using RECIST v1.1 criteria for patients with dMMR/MSI-H EC in the primary efficacy analysis set is summarized in the tables below.

**Table 27: Tumour Response Summary-RECIST v1.1 Assessed by BICR in Patients with dMMR/MSI-H EC (Primary efficacy analysis set) – DCO 1 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| Variable | dMMR (N=106) | MMR-unk /MSI-H (N=2) | Total (N=108) |
| Best overall response by RECIST v1.1 [n (%)] | | | |
| Complete response | 11 (10.4) | 0 | 11 (10.2) |
| Partial response | 35 (33.0) | 1 (50.0) | 36 (33.3) |
| Stable disease | 13 (12.3) | 0 | 13 (12.0) |
| Progressive disease | 39 (36.8) | 0 | 39 (36.1) |
| Not evaluable | 6 (5.7) | 0 | 6 (5.6) |
| No disease | 0 | 0 | 0 |
| Not done | 2 (1.9) | 1 (50.0) | 3 (2.8) |
| Confirmed objective response rate by RECIST v1.1 | | | |
| n (%) | 46 (43.4) | 1 (50.0) | 47 (43.5) |
| 95% CI[a] | (33.8, 53.4) | (1.3, 98.7) | (34.0, 53.4) |
| Response ongoing[b] | 41/46 (89.1) | 1/1 (100) | 42/47 (89.4) |
| Disease control rate by RECIST v1.1 | | | |
| n (%) | 59 (55.7) | 1 (50.0) | 60 (55.6) |
| 95% CI[a] | (45.7, 65.3) | (1.3, 98.7) | (45.7, 65.1) |

Source: Table 14.2.1a.1.1

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; DCR=disease control rate; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high; RECIST=Response Evaluation Criteria in Solid Tumours; ORR=objective response rate; PFS=Progression free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease.

Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST v1.1 confirmed PR, confirmed CR, SD. Response assessments are based on blinded independent central review (BICR).

[a] Exact 2 sided 95% confidence interval for the binomial proportion.

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

- Duration of Response

At the time of data cut-off 01 March 2020, the median DOR had not been reached and ranged from 2.6 to 28.1+, whereas 78.7% of the responders had a DOR of ≥6 months.

**Table 28: Kaplan-Meier Analysis of duration of response-RECIST v1.1 Assessed by BICR in Patients with dMMR/MSI-H EC (Primary Efficacy Analysis Set-Patients with Objective Response) – DCO 1 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| Variable | dMMR (N=46) | MMR-unk /MSI-H (N=1) | Total (N=47) |
| Median duration of follow-up (months) | 13.8 | 11.1 | 16.3 |
| DOR | | | |
| Status [n (%)] | | | |
| Events observed | 5 (10.9) | 0 | 5 (10.6) |
| Censored | 41 (89.1) | 1 (100) | 42 (89.4) |
| DOR (months) | | | |
| Min, max | 2.6, 28.1+ | 19.3+, 19.3+ | 2.6, 28.1+ |
| 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) | 37 (78.7) |
| DOR distribution function (95% CI) | | | |
| Month 6 | 97.8 (85.6, 99.7) | 100 (100, 100) | 97.9 (85.8, 99.7) |
| Month 12 | 90.6 (72.9, 97.0) | 100 (100, 100) | 90.9 (73.7, 97.1) |
| Month 18 | 79.2 (54.9, 91.3) | 100 (100, 100) | 80.1 (56.8, 91.7) |

Source: Table 14.2.2.12a.1.1
Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair-deficient; DOR=duration of response; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; EU=European Union; max=maximum; min=minimum; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high; NR=not reported; RECIST=Response Evaluation Criteria in Solid Tumours.
Note: DOR: Duration of Response per RECIST v1.1 based on blinded independent central review (BICR).
Note: + Indicates subject's response is ongoing
[a] 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

Secondary Efficacy Endpoints

- Disease Control Rate

At the time of data cut-off of 01 March 2020, the DCR in patients with dMMR/MSI-H EC, including CR, PR, and SD, was 55.6% (95%CI: 45.7, 65.1). Stable disease (SD) was 12% (95%CI: 6.6, 19.7).

- Progression-free Survival

At the time of data cut-off of 01 March 2020, just under half of the patients (47.2%) were censored, and a total of 57 PFS events had been observed. Based on these results, the probability of being free of PD at Month 6, Month 9, and Month 12 was estimated to be 48.6%, 47.5%, and 47.5%, respectively.

**Table 29: Kaplan-Meier Analysis of PFS per RECIST v1.1- Based on BICR in patients with dMMR/MSI-H EC (Primary efficacy analysis set) – DCO 01 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| Variable | dMMR (N=106) | MMR-unk /MSI-H (N=2) | Total (N=108) |
| PFS | | | |
| Status [n (%)] | | | |
| Events observed | 57 (53.8) | 0 | 57 (52.8) |
| Censored | 49 (46.2) | 2 (100) | 51 (47.2) |
| PFS (months) | | | |
| Quartile (95% CI)[a] | | | |
| 25% | 2.7 (2.5, 2.9) | NR (NR, NR) | 2.7 (2.5, 2.9) |
| 50% | 5.5 (3.1, 18.0) | NR (NR, NR) | 5.5 (3.2, NR) |
| 75% | NR (NR, NR) | NR (NR, NR) | NR (NR, NR) |
| PFS distribution function (95% CI) | | | |
| Month 6 | 48.1 (38.0, 57.4) | 100 (100, 100) | 48.6 (38.6, 57.9) |
| Month 9 | 46.9 (36.9, 56.4) | 100 (100, 100) | 47.5 (37.4, 56.8) |
| Month 12 | 46.9 (36.9, 56.4) | 100 (100, 100) | 47.5 (37.4, 56.8) |

Source: Table 14.2.10a.1.1
Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unknown=mismatch repair unknown; MSI-H=microsatellite instability-high; RECIST=Response Evaluation Criteria in Solid Tumours; PFS=Progression free survival; NR=not reported.
Note: PFS response per RECIST v1.1 based on blinded independent central review (BICR).
[a] 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

- Overall Survival

At the time of data cutoff of 01 March 2020, the median OS for patients with dMMR/MSI-H EC had not been reached and only 35 OS events had been observed. Based on these results, the probability of survival at Month 6, Month 9, and Month 12 was estimated to be 81.3%, 75.5%, and 69.2%, respectively.

**Table 30: Kaplan-Meier Analysis of Overall Survival in Patients with dMMR/MSI-H EC (Primary Efficacy Analysis Set) – DCO 01 March 2020**

| | dMMR or (MMR-unk and MSI-H) EC | | |
|---|---|---|---|
| **Variable** | **dMMR (N=106)** | **MMR-unk /MSI-H (N=2)** | **Total (N=108)** |
| **OS** | | | |
| Status [n (%)] | | | |
| Events observed | 35 (33.0) | 0 | 35 (32.4) |
| Censored | 71 (67.0) | 2 (100) | 73 (67.6) |
| OS (months) | | | |
| Quartile (95% CI)[a] | | | |
| 25% | 9.3 (5.2, 15.4) | NR (NR, NR) | 9.3 (5.2, 15.4) |
| 50% | NR (17.1, NR) | NR (NR, NR) | NR (17.1, NR) |
| 75% | NR (NR, NR) | NR (NR, NR) | NR (NR, NR) |
| OS distribution function (95% CI) | | | |
| Month 6 | 81.1 (71.9, 87.5) | 100 (100, 100) | 81.3 (72.2, 87.6) |
| Month 9 | 75.2 (65.2, 82.7) | 100 (100, 100) | 75.5 (65.6, 82.9) |
| Month 12 | 68.8 (58.1, 77.3) | 100 (100, 100) | 69.2 (58.6, 77.6) |

Source: Table 14.2.2.22a.1.1
Abbreviations: CI=confidence interval; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unk=mismatch repair unknown; MSI-H=microsatellite instability-high; NR=not reported; OS=overall survival.
Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST v1.1 confirmed PR, confirmed CR, SD. Response assessments are based on blinded independent central review (BICR).
[a] 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

- Immune-related ORR

Analyses using irRECIST were performed using the secondary efficacy analysis set (N=116), which included all patients with measurable disease at baseline (defined at the existence of at least 1 target lesion at baseline tumour assessment by the Investigator [as opposed to assessment by BICR, i.e., the primary efficacy analysis set (N=108)]) who received the first dose of dostarlimab at least 24 weeks prior to the data cutoff of 01 March 2020.

At the time of data cutoff, the irORR was 44.8% (95%CI 35.6, 54.3), with 6.9% immune-related CRs (irCRs) and 37.9% immune-related PRs (irPRs). A total of 17.2% of patients with dMMR/MSI-H EC had an immune-related BOR (irBOR) of immune-related SD (irSD), and 31.9% had an irBOR of immune-related PD.

- Immune-related DCR, PFS

The irDCR in patients with dMMR/MSI-H EC, including irCR, irPR, and irSD, was 62.1%

The median irPFS had not been reached. Just under half of the patients (44.8%) were censored at this time, and a total of 64 irPFS events had been observed. Based on these results, the probability of being progression free at Month 6, Month 9, and Month 12 was estimated to be 54.3%, 50.4%, and 46.6%, respectively.

## Ancillary analyses

### Subgroup analyses

- Subgroup Analyses of ORR (DCO 1 March 2020)

*ORR by MSI Status in Cohort A1*

As of the data cut-off date for this interim CSR, the ORR in subjects with MSI-H EC based on FoundationOne (NGS) test results (50.0%) was similar to that in subjects with dMMR EC based on local IHC test results (43.4%).

*ORR by Number of Prior Anticancer Therapy Regimens in Cohort A1*

The ORR in subjects with dMMR/MSI-H EC was similar in subjects who received 1 line of prior anticancer therapy (47.8%; 33/69) and subjects who received 2 or more lines of prior anticancer therapy (35.9%; 14/39). When data from subjects with MMR-unknown but MSI-H tumours were pooled with those of subjects with dMMR tumours, the results remained similar.

*ORR by Prior Radiation Therapy in Cohort A1*

The ORR in subjects with dMMR/MSI-H EC was similar in subjects who had received prior radiation (45.5%; N=77) and subjects who had not received prior radiation (38.7%; N=31).

*ORR by Prior Bevacizumab Use in Cohort A1*

A total of 5 subjects with dMMR/MSI-H EC with prior bevacizumab use and 103 subjects with dMMR/MSI-H EC without prior bevacizumab use were included in the primary efficacy analysis set. Evaluation of a potential effect of bevacizumab use on the dostarlimab ORR in subjects with dMMR/MSI-H EC was not possible due to the small sample size of 1 of the 2 subgroups.

*ORR by BOR from Last Platinum-containing Prior Anticancer Therapy in Cohort A1*

Among subjects with dMMR/MSI-H EC in the primary efficacy analysis set, 47 subjects had a BOR from the last platinum-containing prior anticancer therapy of CR or PR, 13 subjects had a BOR from the last platinum-containing prior anticancer therapy of SD, 39 subjects had a BOR from the last platinum-containing prior anticancer therapy of PD, and 9 subjects were missing data on BOR from the last platinum-containing prior anticancer therapy. Due to the small number of subjects within each BOR from last platinum-containing prior anticancer therapy subgroup, a meaningful comparison based on BOR from last platinum-containing anticancer therapy could not be made.

**Table 31: Tumour Response Summary by Best Overall Response from last Platinum-Containing Prior Anticancer Therapy - BICR per RECIST v1.1: Primary Efficacy Population**

| Variable | CR/PR | SD | PD | Missing | Total |
|---|---|---|---|---|---|
| **EC: Total** | **N=45** | **N=21** | **N=15** | **N=27** | **N=108** |
| Best overall response by RECIST v1.1 [n (%)] | | | | | |
| CR | 3 (6.7) | 4 (19.0) | 1 (6.7) | 3 (11.1) | 11 (10.2) |
| PR | 18 (40.0) | 9 (42.9) | 2 (13.3) | 7 (25.9) | 36 (33.3) |
| SD | 6 (13.3) | 2 (9.5) | 0 | 5 (18.5) | 13 (12.0) |
| PD | 15 (33.3) | 4 (19.0) | 9 (60.0) | 11 (40.7) | 39 (36.1) |
| Not evaluable | 3 (6.7) | 1 (4.8) | 1 (6.7) | 1 (3.7) | 6 (5.6) |
| No disease | 0 | 0 | 0 | 0 | 0 |
| Not done | 0 | 1 (4.8) | 2 (13.3) | 0 | 3 (2.8) |
| Confirmed objective response rate by RECIST v1.1 (ORR) | | | | | |
| n (%) | 21 (46.7) | 13 (61.9) | 3 (20.0) | 10 (37.0) | 47 (43.5) |
| 95% CI[a] | (31.7, 62.1) | (38.4, 81.9) | (4.3, 48.1) | (19.4, 57.6) | (34.0, 53.4) |
| Response ongoing[b] | 18/21 (85.7) | 12/13 (92.3) | 2/3 (66.7) | 10/10 (100) | 42/47 (89.4) |
| Disease control rate by RECIST v1.1 (DCR) | | | | | |
| n (%) | 27 (60.0) | 15 (71.4) | 3 (20.0) | 15 (55.6) | 60 (55.6) |
| 95% CI[a] | (44.3, 74.3) | (47.8, 88.7) | (4.3, 48.1) | (35.3, 74.5) | (45.7, 65.1) |

Source: Table 14.2.6a.
Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; DCR=disease control rate; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unk=mismatch repair unknown; MSI-H=microsatellite instability-high; RECIST=Response Evaluation Criteria in Solid Tumours; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.
Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST v1.1 confirmed PR, confirmed CR, SD. Response assessments are based on blinded independent central review (BICR).
[a] Exact 2 sided 95% confidence interval for the binomial proportion.
[b] All responders who have not yet died or progressed (including clinical progression), denominator for

*ORR by Progression-free Interval from Last Platinum-containing Prior Anticancer Therapy in Cohort A1*

The ORR in subjects with dMMR/MSI-H EC was slightly higher in subjects who had a progression-free interval from the last platinum-containing prior anticancer therapy of 6 months or greater (45.5%; N=66) than in subjects who had a progression-free interval of less than 6 months (37.5%; N=40).

*ORR by demographic and disease characteristics*

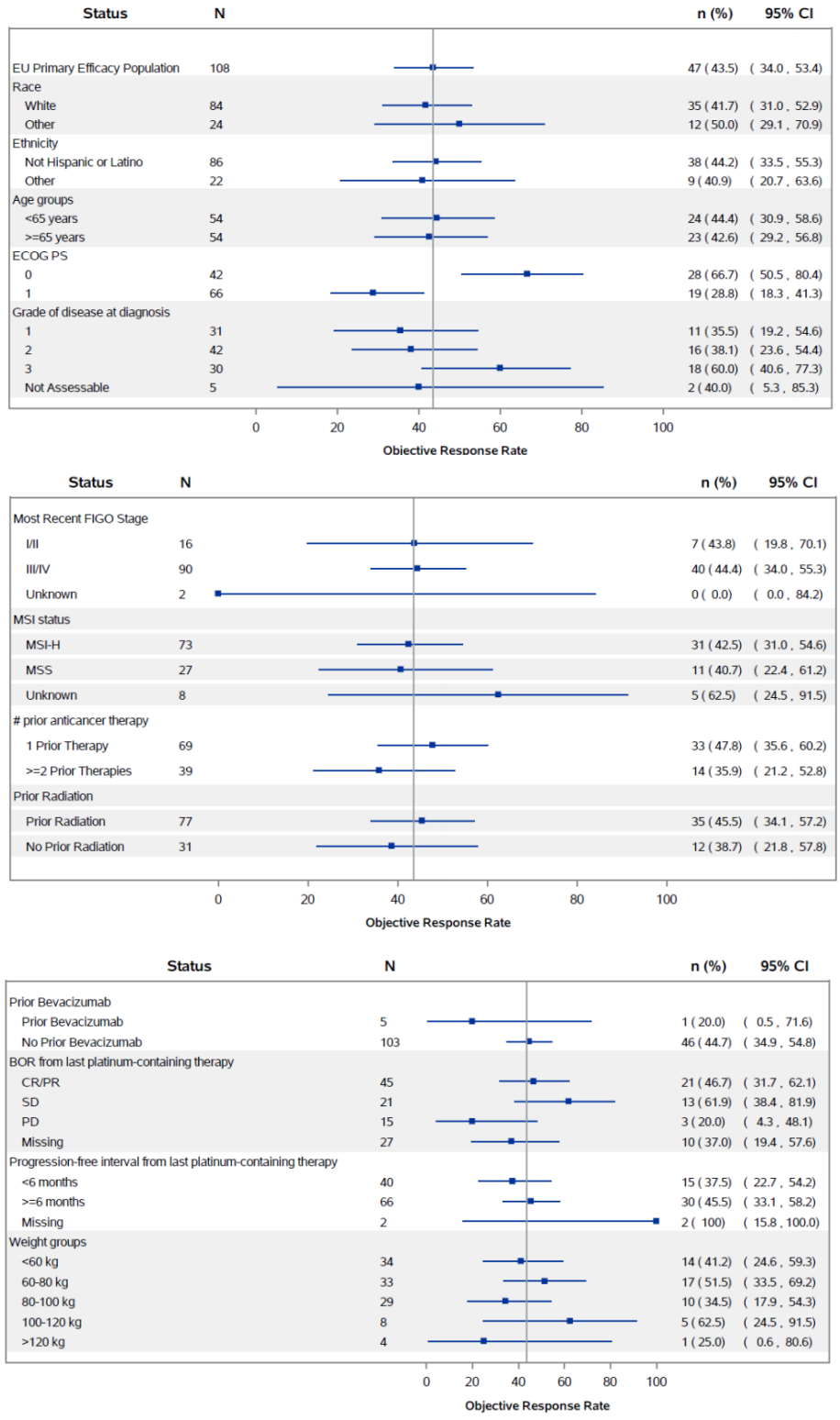



**Figure 36: Forest Plot of Objective Response Rate (Complete Response or Partial Response) and 95% CI by Subgroup on Primary Efficacy Population**

**Additional Exploratory Analyses (post hoc)**

PD-L1 tumour expression was assessed from an exploratory perspective using combined positive score (CPS) cut points of <1% and ≥1%. The testing was performed on samples from Cohorts A1 (dMMR/MSI-H EC) and A2 (MMR proficient EC). All dMMR/MSI-H EC patients with viable samples were included.

- ORR by PD-L1 Tumour Expression in Cohort A1 (DCO 01 March 2020)

PD-L1 tumour expression was assessed using combined positive score (CPS) cut points of <1% and ≥1%. Of the 108 patients with dMMR/MSI-H EC, 58 had a CPS of ≥1% with an ORR of 55.2% and 23/108 patients had a CPS of <1% with an ORR of 30.4%. Twenty seven of the 108 patients had no available PD-L1 tumour expression data.

**Table 32: Tumour Response Summary in dMMR/MSI-H EC Subject by PD-L1 Combined Positive Score- RECIST v1.1 (Primary Efficacy Analysis Set) – DCO 01 March 2020**

| Variable | CPS <1% | CPS ≥1% | CPS Missing | Total |
|---|---|---|---|---|
| **EC: dMMR** | **N=23** | **N=58** | **N=25** | **N=106** |
| Best overall response by RECIST v1.1 [n (%)] | | | | |
| CR | 1 (4.3) | 9 (15.5) | 1 (4.0) | 11 (10.4) |
| PR | 6 (26.1) | 23 (39.7) | 6 (24.0) | 35 (33.0) |
| SD | 2 (8.7) | 7 (12.1) | 4 (16.0) | 13 (12.3) |
| PD | 14 (60.9) | 15 (25.9) | 10 (40.0) | 39 (36.8) |
| Not evaluable | 0 | 1 (1.7) | 2 (8.0) | 3 (2.8) |
| No disease | 0 | 0 | 0 | 0 |
| Not done | 0 | 3 (5.2) | 2 (8.0) | 5 (4.7) |
| Confirmed objective response rate by RECIST v1.1 (ORR) | | | | |
| n (%) | 7 (30.4) | 32 (55.2) | 7 (28.0) | 46 (43.4) |
| 95% CI[a] | (13.2, 52.9) | (41.5, 68.3) | (12.1, 49.4) | (33.8, 53.4) |
| Response ongoing[b] | 6/7 (85.7) | 28/32 (87.5) | 7/7 (100) | 41/46 (89.1) |
| Disease control rate by RECIST v1.1 (DCR) | | | | |
| n (%) | 9 (39.1) | 39 (67.2) | 11 (44.0) | 59 (55.7) |
| 95% CI[a] | (19.7, 61.5) | (53.7, 79.0) | (24.4, 65.1) | (45.7, 65.3) |
| **EC: MMR-unk/MSI-H** | **N=0** | **N=0** | **N=2** | **N=2** |
| Best overall response by RECIST v1.1 [n (%)] | | | | |
| CR | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 1 (50.0) | 1 (50.0) |
| SD | 0 | 0 | 0 | 0 |
| PD | 0 | 0 | 0 | 0 |
| Not evaluable | 0 | 0 | 0 | 0 |
| No disease | 0 | 0 | 0 | 0 |
| Not done | 0 | 0 | 1 (50.0) | 1 (50.0) |
| Confirmed objective response rate by RECIST v1.1 (ORR) | | | | |
| n (%) | 0 | 0 | 1 (50.0) | 1 (50.0) |
| 95% CI[a] | -- | -- | (1.3, 98.7) | (1.3, 98.7) |
| Response ongoing[b] | 0 | 0 | 1/1 (100) | 1/1 (100) |

| Variable | CPS <1% | CPS ≥1% | CPS Missing | Total |
|---|---|---|---|---|
| Disease control rate by RECIST v1.1 (DCR) | | | | |
| n (%) | 0 | 0 | 1 (50.0) | 1 (50.0) |
| 95% CI[a] | -- | -- | (1.3, 98.7) | (1.3, 98.7) |
| **EC: Total** | **N=23** | **N=58** | **N=27** | **N=108** |
| Best overall response by RECIST v1.1 [n (%)] | | | | |
| CR | 1 (4.3) | 9 (15.5) | 1 (3.7) | 11 (10.2) |
| PR | 6 (26.1) | 23 (39.7) | 7 (25.9) | 36 (33.3) |
| SD | 2 (8.7) | 7 (12.1) | 4 (14.8) | 13 (12.0) |
| PD | 14 (60.9) | 15 (25.9) | 10 (37.0) | 39 (36.1) |
| Not evaluable | 0 | 1 (1.7) | 2 (7.4) | 3 (2.8) |
| No disease | 0 | 0 | 0 | 0 |
| Not done | 0 | 3 (5.2) | 3 (11.1) | 6 (5.6) |
| Confirmed objective response rate by RECIST v1.1 (ORR) | | | | |
| n (%) | 7 (30.4) | 32 (55.2) | 8 (29.6) | 47 (43.5) |
| 95% CI[a] | (13.2, 52.9) | (41.5, 68.3) | (13.8, 50.2) | (34.0, 53.4) |
| Response ongoing[b] | 6/7 (85.7) | 28/32 (87.5) | 8/8 (100) | 42/47 (89.4) |
| Disease control rate by RECIST v1.1 (DCR) | | | | |
| n (%) | 9 (39.1) | 39 (67.2) | 12 (44.4) | 60 (55.6) |
| 95% CI[a] | (19.7, 61.5) | (53.7, 79.0) | (25.5, 64.7) | (45.7, 65.1) |

Source: Table 14.2.2.12a.1.2

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; DCR=disease control rate; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-unk=mismatch repair unknown; MSI-H=microsatellite instability-high; RECIST=Response Evaluation Criteria in Solid Tumours; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease.

Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST v1.1 confirmed PR, confirmed CR, SD. Response assessments are based on BICR.

[a] Exact 2 sided 95% confidence interval for the binomial proportion.

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

**Table 33: KM Analysis of Progression Free Survival in Subject with dMMR/MSI-H EC by Combined Positive Score- (Primary Efficacy Analysis Set) – DCO 01 March 2020**

| Variable | CPS <1% | CPS ≥1% | CPS Missing | Total |
|---|---|---|---|---|
| **EC: dMMR** | **N=23** | **N=58** | **N=25** | **N=106** |
| PFS | | | | |
| Status [n (%)] | | | | |
| Events observed | 17 (73.9) | 27 (46.6) | 13 (52.0) | 57 (53.8) |
| Censored | 6 (26.1) | 31 (53.4) | 12 (48.0) | 49 (46.2) |
| PFS (months) | | | | |
| Quartile (95% CI)* | | | | |
| 25% | 2.6 (0.4, 2.8) | 2.9 (2.5, 4.2) | 2.5 (1.1, 2.9) | 2.7 (2.5, 2.9) |
| 50% | 2.9 (2.7, 5.6) | 16.6 (4.2, NR) | 4.2 (2.5, NR) | 5.5 (3.1, 18.0) |
| 75% | 12.2 (3.0, NR) | NR (NR, NR) | NR (4.2, NR) | NR (NR, NR) |
| PFS distribution function (95% CI) | | | | |
| Month 6 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 45.7 (24.6, 64.5) | 48.1 (38.0, 57.4) |
| Month 9 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 39.9 (19.6, 59.6) | 46.9 (36.9, 56.4) |
| Month 12 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 39.9 (19.6, 59.6) | 46.9 (36.9, 56.4) |
| **EC: MMR-unk/MSI-H** | **N=0** | **N=0** | **N=2** | **N=2** |
| PFS | | | | |
| Status [n (%)] | | | | |
| Events observed | -- | -- | 0 | 0 |
| Censored | -- | -- | 2 (100) | 2 (100) |
| PFS (months) | | | | |
| Quartile (95% CI)* | | | | |
| 25% | -- | -- | NR (NR, NR) | NR (NR, NR) |
| 50% | -- | -- | NR (NR, NR) | NR (NR, NR) |
| 75% | -- | -- | NR (NR, NR) | NR (NR, NR) |
| PFS distribution function (95% CI) | | | | |
| Month 6 | -- | -- | 100 (100, 100) | 100 (100, 100) |
| Month 9 | -- | -- | 100 (100, 100) | 100 (100, 100) |
| Month 12 | -- | -- | 100 (100, 100) | 100 (100, 100) |
| **EC: Total** | **N=23** | **N=58** | **N=27** | **N=108** |
| PFS | | | | |
| Status [n (%)] | 17 (73.9) | 27 (46.6) | 13 (48.1) | 57 (52.8) |
| Events observed | 6 (26.1) | 31 (53.4) | 14 (51.9) | 51 (47.2) |
| PFS (months) | | | | |
| Quartile (95% CI)* | | | | |
| 25% | 2.6 (0.4, 2.8) | 2.9 (2.5, 4.2) | 2.5 (1.1, 2.9) | 2.7 (2.5, 2.9) |
| 50% | 2.9 (2.7, 5.6) | 16.6 (4.2, NR) | 4.2 (2.5, NR) | 5.5 (3.2, NR) |
| 75% | 12.2 (3.0, NR) | NR (NR, NR) | NR (8.1, NR) | NR (NR, NR) |
| PFS distribution function (95% CI) | | | | |
| Month 6 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 48.0 (27.0, 66.3) | 48.6 (38.6, 57.9) |
| Month 9 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 42.7 (22.2, 61.7) | 47.5 (37.4, 56.8) |
| Month 12 | 30.4 (13.5, 49.3) | 56.5 (42.4, 68.3) | 42.7 (22.2, 61.7) | 47.5 (37.4, 56.8) |

Source: Table 14.2.10a.1.2

Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR-proficient=mismatch repair proficient; MMR-unk=mismatch repair unknown; MSI-H=microsatellite instability-high; NR=not reported; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours.

Note: PFS per RECIST v1.1 based on blinded independent central review.

* 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

**Additional sensitivity analysis**

The MAH initially presented results from an efficacy analysis set consisting of 105 patients who received the first dose of dostarlimab at least 24 weeks prior to the data cut-off (i.e. excluding 3 patients who discontinued treatment due to AE or clinical progression before 24 weeks follow-up; data not shown). Sensitivity analyses were requested and presented as a side-by-side comparison in Table 34 per the requested exclusions denoted below.

a) **Sensitivity Analysis 1 (SA-1) (n=108):** tumour response summary in all participants in the safety analysis set (ITT) excluding the patients without measurable disease at baseline and who have not had the opportunity to have 24 weeks follow up, but including those patients who discontinued treatment due to AE or clinical progression as non-responders.

b) **Sensitivity Analysis 2-A (SA-2A) (n=117):** All patients in the safety analysis set (ITT) excluding only the 12 patients who have not had the opportunity for at least 24 weeks follow up and were still on treatment at data cut-off. Patients who discontinued due to AEs before 24 weeks (n=2), those who were assessed as PD before 24 weeks (n=1), and patients with without measurable disease at baseline assessed by BICR (n=9) are counted as non-responders.

c) **Sensitivity Analysis 2-B (SA-2B) (n=117):** All patients in the safety analysis set (ITT) excluding only the 12 patients who have not had the opportunity for at least 24 weeks follow up and were still on treatment at data cut-off (n=117). Patients who discontinued due to AEs before 24 weeks (n=2) or were assessed as having PD before 24 weeks (n=1) were counted as non-responders. Patients with non-measurable disease at baseline assessed by BICR (n=9) were included in the denominator, but those who were assessed as CR were counted as responders in the numerator (i.e. even if they were considered not to have measurable disease by the BICR team, but the disease then fully disappeared according to the investigator).

**Table 34: Tumour Response Summary in Participants with dMMR/MSI-H EC – RECIST v1.1 Assessed by BICR – ITT Population minus discontinuations due to AE or clinical progression (DCO 1 March 2020)**

| | dMMR or (MMR-unk & MSI-H) EC | | |
|---|---|---|---|
| | SA-1 | SA-2A | SA-2B |
| Variable | Total (n=108) | Total (n=117) | Total (n=117) |
| Best Overall Response by RECIST v1.1 [n(%)] | | | |
| CR | 11 (10.2) | 11 (9.4) | 12 (10.3) |
| PR | 36 (33.3) | 36 (30.8) | 36 (30.8) |
| SD | 13 (12.0) | 13 (11.1) | 13 (11.1) |
| PD | 39 (36.1) | 39 (33.3) | 39 (33.3) |
| Not Evaluable | 6 (5.6) | 6 (5.1) | 6 (5.1) |
| No Disease | 0 | 0 | 0 |
| Not Done | 3 (2.8) | 3 (2.6) | 3 (2.6) |
| No Measurable Disease at Baseline | -- | 9 (7.7) | 8 (6.8) |
| Confirmed Objective Response Rate by RECIST v1.1 (ORR) | | | |
| n(%) | 47 (43.5) | 47 (40.2) | 48 (41.0) |
| 95% CI[a] | (34.0, 53.4) | (31.2, 49.6) | (32.0, 50.5) |
| Response Ongoing[b] | 42/47 (89.4) | 42/47 (89.4) | 43/48 (89.6) |
| Disease Control Rate by RECIST v1.1 (DCR) | | | |
| n(%) | 60 (55.6) | 60 (51.3) | 61 (52.1) |

| | | | |
|---|---|---|---|
| 95% CI[a] | (45.7, 65.1) | (41.9, 60.6) | (42.7, 61.5) |

Source: Tables 14.2.30a.1, 14.2.30a.2, 14.2.30a.3
Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR.
DCR is defined as the percentage of patients with a RECIST v1.1 confirmed PR, confirmed CR, or SD.
Response assessments are based on blinded independent central review (BICR).
Abbreviations: CR=Complete Response; PR=Partial Response; SD=Stable Disease
[a] Exact 2-sided 95% confidence interval for the binomial proportion.
[b] All responders who have not yet died or progressed (including clinical progression), denominator for the percentage is number of responders.

## Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

| **Title: A phase 1 dose escalation and cohort expansion study of dostarlimab, an anti-pd-1 monoclonal antibody, in patients with advanced solid tumours - Part 2B, endometrial cancer (cohort A1)** | | | |
|---|---|---|---|
| Study identifier | GARNET, study 4010-01-001 (EudraCT 2016-0000320-26) | | |
| Design | Phase 1, open-label, multi-cohort, single-arm treatment | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | Not applicable<br>Not applicable<br><br>Not applicable |
| Hypothesis | Cohort A1 has 92% power to rule out a ≤20% ORR (null hypothesis; expected ORR for conventional therapy) when the true ORR is 40% at the 2.5% type I error rate (one-sided). | | |
| Treatments groups | Cohort A1<br>Patients with recurrent or advanced dMMR/MSI-H endometrial cancer after progress to a platinum containing regimen | | Dostarlimab 500 mg Q3W for the first 4 cycles followed by 1,000 mg Q6W for all subsequent cycles |
| Endpoints and definitions | Primary efficacy endpoints | ORR | Proportion of patients achieving Best Overall Response of complete response (CR) or partial response (PR) per RECIST v1.1 by blinded independent central review (BICR) |
| | | DOR | Time from first documentation of response per RECIST v1.1 by BICR until progressive disease (PD) or death |
| | Secondary efficacy endpoints | PFS | Time from first dose until PD per RECIST v1.1 by BICR or death of any cause |
| | | OS | Time from first dose until death of any cause |
| Clinical cut-off | 1 March 2020 | | |
| Database lock | 9 Aug 2019 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Interim analysis (data cut-off 1 March 2020)** | | |
| Analysis population and time point description | Primary efficacy analysis set from cohort A1 is constituted by patients with measurable disease at baseline by RECIST v1.1 per BICR and with at least 24 weeks of tumour assessment as of the data cut-off date | | |
| Descriptive statistics and estimate variability | Treatment group | | Cohort A1 |
| | Number of subjects | | 108 |
| | ORR, number of subjects (rate) | | 47<br>(43.5%) |
| | 95% CI[a] | | 34.0, 53.4 |
| | Median DOR in responders, months (range) | | Not evaluable (2.6, 28.1+) |
| | 95% CI[b] | | (not evaluable, not evaluable) |
| | Probability of maintaining response at 6 months by K-M (95 % CI) | | 97.9 %<br>(85.8, 99.7) |

| | | |
|---|---|---|
| | Probability of maintaining response at 12 months by K-M (95 % CI) | 90.9 %<br>(73.7, 97.1) |
| Effect estimate per comparison | Not applicable | |
| Notes | [a] Exact 2-sided 95% CI for the binomial proportion<br>[b] 95% CI generated using the method of Brookmeyer-Crowley (1982). | |

## Clinical studies in special populations

Of the 108 patients treated with dostarlimab in the efficacy population, 50.0 % were older than 65 years. Consistent results were observed in the elderly population, where the ORR by BICR (95% CI) was 42.6 % (29.2 %, 56.8 %) in patients ≥ 65 years.

**Table 35: Clinical Studies in Special Populations**

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| **Controlled Trials** | None | None | None |
| **Non Controlled trials** | | | |
| **dMMR/MSI-H EC** | 51/129 | 12/129 | 0 |
| **Total Monotherapy** | 195/515 | 57/515 | 2/515 |

## *Supportive study(ies)*

**Results of Study 4010-01-001 Part 2B – Cohort F Patients with Tumours Classified as dMMR/MSI-H and/or POLE-mutated Non EC (DCO 8 July 2019)**

Cohort F was constituted by patients with recurrent or advanced non-endometrial dMMR/MSI-H or POLE-mutated solid tumours, who had PD following up to 2 prior lines of systemic therapy for recurrent or advanced (≥Stage IIIB) disease; and who had no alternative treatment options.

The safety analysis set of cohort F included 109 patients. Of these, 2 patients had POLE mutated non-EC.

At the time of data cut-off of 8 July 2019, 22.9% of patients had discontinued treatment, and 11.0% had discontinued the study. The most common reason for treatment discontinuation was confirmed PD (15 patients), and the most common reason for study discontinuation was death (8 patients).

Of the 109 patients in the safety analysis set, 50 patients (45.9%) had received at least one dose of dostarlimab and had 6 months of follow up data and were therefore included in the primary efficacy analysis set.

Of these 50 patients, 31 (62%) had colorectal cancer, 8 (16%) small intestine cancer, 4 (8%) gastric cancer, 2 (4%) ovarian cancer and 1 patient (2%) each with genital neoplasm female, pancreatic carcinoma and renal cell carcinoma-sarcoma. 2 patients (4%) had other tumours.

At the data cut-off, confirmed responses had occurred in 22 out of 50 patients, for an ORR of 44% (95% CI 30.0, 58.7) and included 8.0% CRs and 36.0% PRs. Clinical activity was consistent across CRC and other tumour types (ORR 43.3%, and 44.4%, respectively), and comparable to MMR-selected EC in cohort A1 (43.1%).

At the time of data cut-off, 20 out of 22 patients were on ongoing response, so the median DOR had not been reached, ranging from 2.76+ to 13.83+ months.

At the time of data cut-off, the median PFS in patients with dMMR/MSI-H non-EC was 11.0 months. A total of 31 patients with dMMR/MSI-H non-EC (62.0%) were censored at this time, and 19 PFS events had been observed.

At data cut-off, only 8 OS events had occurred in all 109 patients.

**Results of Study 4010-01-001 Part 2B: Cohort A2 Patients with EC (proficient MMR/MSS) - (DCO 8 July 2020)**

*Demographic and Other Baseline Characteristics in Cohort A2*

For subjects with MMR-proficient EC in the primary efficacy population, the median age was 66.0 years (range: 30, 86 years). Most subjects were White. Median weight was 74.90 kg (range: 45.8, 182.3 kg), and median BMI was 28.96 kg/m$^2$ (range: 18.3, 61.6 kg/m$^2$). At study entry, 49.5% of subjects with MMR-proficient EC had an ECOG performance status of 0, and 50.5% of the subjects had an ECOG performance status of 1. When demographics data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remain similar.

The most common histology grade at diagnosis in subjects with MMR-proficient EC was Grade 3 (61.0%), and just over half of all subjects had disease with unfavourable histologic characteristics, such as serous carcinoma (36.2%), clear cell carcinoma (7.6%), or mixed carcinoma (7.6%). Most subjects had FIGO Stage IV (71.4%) disease at the time of study enrollment. When data on disease characteristics from subjects with MMRunknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

All subjects with MMR-proficient EC had received prior anticancer treatment (100.0%), with 54.3% of subjects having received any prior adjuvant/neo-adjuvant anticancer treatment. A total of 43.8% of subjects had 1 anticancer prior regimen and 2 prior regimens each. Less than 13% of subjects with MMR-proficient EC had received 3 or more prior regimens. Approximately two-thirds of subjects with MMR-proficient EC had received prior regimens for metastatic disease. 95.2% of subjects had prior surgery and 65.7% had prior anticancer radiotherapy. The most common BOR from the last platinum-containing anticancer therapy was PD (27.6% of subjects with MMR-proficient EC), followed by CR and PR (20.0% of subjects with MMR-proficient EC each). The median progression-free interval from the last platinum-containing anticancer therapy was 8.41 months (Q1, Q3: 4.4, 11.8 months). When prior anticancer treatment data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

*Analysis of Efficacy in Cohort A2*

The ORR in subjects with MMR-proficient EC was 9.5%, with 1 subject having a BOR of CR and 9 subjects having a BOR of PR. A BOR of SD was observed in 26 subjects (24.8%) (). A total of 56 of subjects had a BOR of PD (53.3%). BOR was not assessed in 13 subjects (12.4%). When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar, with an ORR of 10.0% (MMR-proficient/MSS EC) vs 9.5% (MMR-proficient EC), respectively.

The majority of the subjects with MMR-proficient EC with an objective response (70.0% of responders) had an ongoing response at the time of the data cutoff. A median DOR in these subjects was therefore not evaluable (NE). The DOR in these subjects ranged from 1.41+ to 22.21+ months, with DOR ≥6 months in 5 subjects (50.0% of responders).

The DCR in subjects with MMR-proficient EC was 34.3%, with 1 subject having a BOR of CR, 9 subjects having a BOR of PR, and 26 subjects having a BOR of SD. When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar, with a DCR of 33.6% (MMR-proficient/MSS EC) vs 34.3% (MMR-proficient EC), respectively.

The irORR in subjects with MMR-proficient EC was 11.4%, with 3 subjects having an irBOR of irCR and 9 subjects having an irBOR of irPR. Response was ongoing in 8 subjects (66.7% of responders) at the time of the data cutoff. An irBOR of irSD was observed in 29 subjects with MMR-proficient EC (27.6%). A total of 46 subjects with MMR-proficient EC had an irBOR of irPD (43.8%). irBOR was not assessed in 14 subjects (13.3%) and was NE in 4 subjects (3.8%). When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

The majority of the subjects with MMR-proficient EC with a response by irRECIST (66.7% of responders) had an ongoing response at the time of the data cutoff. A median irDOR in these subjects was therefore NE. The irDOR in subjects with MMR-proficient EC ranged from 1.41+ to 22.21+ months, with 5 subjects (41.7% of responders) having an irDOR ≥6 months.

The irDCR in subjects with MMR-proficient EC was 39.0%, with irBOR of irCR in 3 subjects, irPR in 9 subjects, and irSD in 29 subjects. When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

A total of 87 PFS events were observed, and the median PFS in subjects with MMR-proficient EC was 2.7 months. When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar, with a median PFS of 2.7 months in subjects with MMR-proficient/MSS EC and MMR-proficient EC.

A total of 81 irPFS events were observed, and the median irPFS in subjects with MMR-proficient EC was 2.8 months. When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

Most subjects with MMR-proficient EC in the primary efficacy analysis set (57.1%) were censored at the time of the data cutoff. The median OS in these subjects was 16.0 months.

*Subgroup Analyses in Cohort A2*

At the time of data cutoff, the ORR in subjects with MMR-proficient EC was higher in subjects who had received prior radiation (13.0%; N=69) than in subjects who had not received prior radiation (2.8%; N=36). When data from subjects with MMR-unknown but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar (12.7% [9/71] vs 5.1% [2/39]).

No effect of local (IHC) versus central (FoundationOne NGS) test results, number of prior anticancer therapy regimens, or duration of progression-free interval from last platinum-containing prior anticancer therapy was observed. A total of 6 subjects with MMR-proficient EC with prior bevacizumab use and 99 subjects with MMR-proficient EC without prior bevacizumab use were included in the primary efficacy analysis set. There were few subjects with prior bevacizumab use to determine whether ORR is affected by prior bevacizumab use. Due to the small number of subjects within each BOR from last platinum-containing prior anticancer therapy subgroup, a meaningful comparison based on BOR from last platinum-containing anticancer therapy could not be made. When data from subjects with MMR-unknown

but MSS tumours were pooled with those of subjects with MMR-proficient tumours, the results remained similar.

A median DOR was not reached in the majority of subgroups. A comparison of DOR range between the subgroups was hampered by the small sample size of subjects with MMR-proficient EC who had an objective response (N=10). No evaluation of a potential effect of these variables on the DOR or DOR range was performed in subjects with MMR-proficient/MSS EC.

The outcomes to the last platinum-based regimen were as follows: for Cohort A1 ORR 44.5% (CR 18.1%, PR 26.4%), SD 18.1%, PD 15.3%, median PFS 6.37 months (95%CI 4, 12 months) vs Cohort A2 ORR 40.0% (CR 20%, PR 20%), SD 32.4%, PD 27.6%, median PFS 8.4 months (95%CI 4, 11.8 months).

*Efficacy Results in Patients with EC Overall (Cohorts A1 and A2 of Study 4010-01-001) by MMR/MSI status in EC patients – DCO 01 March 2020*

**Table 36 Summary Efficacy Results by MMR/MSI status in EC Patients (Primary Efficacy Analysis Set) – DCO 01 March 2020**

| Variable | dMMR/MSI-H EC (N=108) | MMR proficient/MSS EC (N=156) | EC Overall (N=264) |
|---|---|---|---|
| Confirmed ORR by RECIST v1.1 | | | |
| n (%) | 47 (43.5) | 22 (14.1) | 69 (26.1) |
| 95% CI[a] | (34.0, 53.4) | (9.1, 20.6) | (20.9, 31.9) |
| Response ongoing[b] | 42/47 (89.4) | 14/22 (63.6) | 56/69 (81.2) |
| PFS (months) | | | |
| median (95% CI)[c] | 5.5 (3.2, NR) | 2.7 (2.6, 2.8) | 3.0 (2.8, 4.0) |
| OS (months) | | | |
| median (95% CI)[c] | NR (17.1, NR) | 16.8 (12.9, 21.4) | 18.5 (16.0, 26.4) |

Source: Table 14.2.32a.1

Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair-deficient; EC=endometrial cancer; EU=European Union; MMR=mismatch repair; MMR-proficient=mismatch repair proficient; MSI=microsatellite instability; MSI-H=microsatellite instability-high; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours.

Note: ORR is defined as the percentage of patients with a RECIST v1.1 confirmed CR or PR. Response assessments are based on BICR.

[a] Exact 2 sided 95% confidence interval for the binomial proportion.

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

[c] 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The main evidence of efficacy submitted to support the claimed indication is Study 4010-01-001 (GARNET), a multicentre, open-label, Phase 1, dose escalation study with expansion cohorts in patients with recurrent or advanced solid tumours who have limited available treatment options. This was a multinational clinical trial, with centres participating from USA, Canada, and Europe.

Study 4010-01-001 was conducted in 2 parts. In Part 1, a modified 3+3 design was used to evaluate ascending weight-based doses of dostarlimab administered by IV infusion. Part 2A evaluated the safety and tolerability of 2 fixed doses of dostarlimab. No dose-limiting toxicities were observed, and the recommended therapeutic dose was determined to be 500 mg Q3W for the first 4 cycles followed by 1,000 mg Q6W for all subsequent cycles. This dosing schedule was used in Part 2B and thus for all patient efficacy data reported in this report.

Selection of the recommended therapeutic dosing regimen (500 mg Q3W for 4 cycles, followed by 1,000 mg Q6W for all subsequent cycles) was based on the efficacy, safety, receptor occupancy, and population PK analysis of dostarlimab observed to date. Receptors are fully occupied at all dose levels studied over the entire dosing interval, including over the entire dosing interval following 500 mg Q3W and 1,000 mg Q6W dosing, the 2 components of the RTD regimen. The exposure response curve is flat for both safety and efficacy. Therefore, the proposed dose regimen is considered acceptable.

The main efficacy data supporting the claimed indication come from Cohort A1 in Part 2B of the study, which includes patients with dMMR/MSI-H EC endometrial cancer.

This was an open-label, multicentre, single-arm cohort study. The primary objective of the analysis for Cohort A1 was the evaluation of the antitumor activity of dostarlimab. The primary endpoints were the proportion of ORR and DOR by BICR using RECIST v1.1. and the secondary endpoints included DCR, PFS, OS, irORR, irPFS, irDOR, and exploratory PROs.

Cohort A1 from part 2B recruited patients with MSI-H endometrial cancer, who have progressed on or after at least 1, but no more than 2 lines of anti-cancer therapy (of which, at least 1 must be a platinum-based therapy). All EC histological types were allowed, except sarcomas. The study was conducted in accordance with the ICH for GCP and the Declaration of Helsinki (Version 2008) and do not raise any particular concerns.

It is noted that patients with the following status were excluded from the GARNET study and therefore no efficacy data is available in these patients (see SmPC section 4.4): ECOG baseline performance score ≥ 2; uncontrolled central nervous system metastases or carcinomatous meningitis; other malignancies within the last 2 years; immunodeficiency or receiving immunosuppressive therapy within 7 days; active HIV, hepatitis B or hepatitis C infection; active autoimmune disease requiring systemic treatment in the past 2 years excluding replacement therapy; history of interstitial lung disease; or receiving live vaccine within 14 days.

ORR and DOR based on blinded independent central review using RECIST 1.1 criteria were selected as primary endpoints providing a reliable estimate of the antitumor activity of dostarlimab in the context of a single arm trial. Secondary endpoints including DCR, PFS, OS, as well as irORR, irDOR, irPFS, plus QoL assessments are considered relevant endpoints.

Overall, the main limitations of the study are the non-randomised nature and the absence of control arm leading to uncertainties on the actual benefit in clinically relevant treatment outcomes, i.e. OS. Furthermore, preliminary efficacy remains limited to 108 patients with dMMR/MSI-H advanced EC. These

limitations could be acceptable in the context of a CMA based on the observed effect on ORR when it is considered outstanding and provided all the criteria for the CMA are fulfilled (see further discussion under efficacy data and additional analyses).

In addition, there were uncertainties related to the prognostic and/or predictive value of dMMR/MSI-H biomarker in the EC population. Data presented indicate that the presence of dMMR/MSI-H is a predictive biomarker of response to immune therapy. Available evidence also suggests that the response to chemotherapy in these patients would be consistent to that seen for patients with MMR proficient status (see under efficacy data and additional analyses).

Local dMMR/MSI-H test results were used for patient selection for efficacy in the GARNET study. Further information related to the methodology used for dMMR/MSI-H alteration diagnosis was provided. While most patients in GARNET were enrolled based on IHC testing, reflecting clinical care, all the different platforms are testing the same phenotype (dMMR/MSI-H) and any of them are considered valid tests.

## *Efficacy data and additional analyses*

The study population is considered a well-defined, homogeneous, and pre-treated population representative of the intended target as defined by the baseline demographic and disease characteristics.

An *administrative* interim analysis was planned to occur when the combined enrolment in cohorts A1 and F of GARNET reached 100 subjects who had been followed for at least 24 weeks.

The applicant submitted results from 129 patients (cohort A1) with cut-off date of 1 March 2020 constituting the intended population for the proposed therapeutic indication.

Out of the safety dataset (N=129), only patients with measurable disease at baseline and who had been followed for at least 24 weeks (or prematurely excluded due to AEs or disease progression) were selected for the efficacy dataset of N=108.

In patients with dMMR/MSI-H EC from Study 4010-01-001 Cohort A1, the ORR as assessed based on RECIST 1.1 by BICR was 43.5% (47 of 108 patients), 95% CI (34.0, 53.4), with 10.2% CRs (11 of 108 patients).

At the time of the data cut-off date of 01 March 2020, the median DOR had not been reached, and 78.3 % of responders had a DOR ≥6 months. Based on Kaplan-Meier estimates, the probability of maintaining a response for 6, and 12 months in patients with dMMR/MSI-H EC was 97.9% and 90.9%, respectively. At the time of the data cut-off date, 89.4 % of responders had an ongoing response.

DCR (BOR of CR, PR, or SD) was observed in 55.6% (60 of 108 patients) of all patients with dMMR/MSI-H EC.

In terms of progression free survival, 47.2% had no PFS event at the data cut-off. Based on these results, the probability of being free of PD at Month 6, Month 9, and Month 12 was estimated to be 48.6%, 47.5%, and 47.5%, respectively.

The majority of patients in the primary efficacy analysis set did not have an OS event (67.6%), and the median OS was not reached. Based on these results, the probability of survival at Month 6, Month 9, and Month 12 was estimated to be 81.3%, 75.5%, and 69.2%, respectively.

Secondary endpoints according to irRECIST based on Investigator assessment (based on secondary analysis set, N=116 patients) were consistent to those primary and key secondary endpoints.

Subgroup analyses defined by tumour MSI status, number of prior anticancer therapy regimens, prior radiation therapy, prior bevacizumab use, BOR from last platinum-containing prior anticancer therapy, and progression-free interval from last platinum containing prior anticancer therapy were conducted.

Overall, results of subgroup analyses for ORR and DOR in the overall population of patients with dMMR/MSI-H EC were consistent with the primary efficacy results. Results were also consistent across the relevant subgroups, the only exception being the subgroup of patients with ECOG PS 0 or 1 where a considerable difference in ORR was observed between the ECOG PS 0 (67% in 42 patients) and ECOG PS 1 (30% in 63 patients) subgroups in patients with dMMR/MSI-H EC. Improved efficacy performance in more fit patients is not unexpected. However, the results should be interpreted with caution in view of the limited sample size.

Furthermore, of the 515 patients treated with dostarlimab monotherapy, 50.7% were under 65 years, 37.9% were 65-75 years, and 11.5% were 75 years or older. Efficacy results by age range of patients separately were requested and showed consistent tumour responses across the spectrum of age.

The efficacy of dostarlimab in children and adolescents aged under 18 years has not been established. No data are available (see SmPC section 4.2).

The prevalence of PD-L1 expression in dMMR EC (A1) and overall 2L EC population (A1+A2) were evaluated by pooling the data from patients with dMMR/MSI-H EC (Cohort A1 of Study 4010-01-001) and patients with MMR proficient/microsatellite stable EC (Cohort A2 of Study 4010-01-001) (data not shown). Preliminary analysis suggested that PD-L1 expression (CPS ≥1%) was more frequently seen in dMMR compared to MMR proficient EC.

PD-L1 IHC results were available for 81 out of 108 patients (75%) from the primary efficacy analysis set from cohort A1 (dMMR/MSI-H EC) and for 104 out of 156 patients (67%) from cohort A2 (MMRp/MSS EC) (data not shown). Subgroup analysis by PD-L1 expression using the threshold of 1% (data cut-off 1 March 2020) showed that PD-L1 positivity drives the ORR benefit: 55.2% vs. 30.4% for A1 and 20% vs. 4% for A2 in the PD-L1 positive vs the PD-L1 negative population. Interestingly, when the whole EC population is pooled (n=261), a similar proportion of ORR benefit is seen from MMR/MS selection [45% for dMMR/MSI-H (n=108) vs. 14% for MMRp/MSS (n=156)] or PD-L1 selection [38% for ≥1% (n=115) vs. 13% for <1% (n=68)]. This observation was further supported by the logistic regression model (data not shown) that evaluated the statistical association between MMR/MS status or PD-L1 status. Regarding alternative cut-off points for PD-L1 status, it is agreed that the ROC curves suggest that the optimal threshold for predicting efficacy benefit in terms of response is 1%.

Overall, although higher tumour responses were observed in patients with higher PD-L1 expression, clinical activity was observed regardless of tumour PD-L1 combined positive score (CPS) by IHC (see Table 32).

The sensitivity analyses conducted applying more conservative censoring rules (

**Table** ) provided consistent results for tumour responses to those initially seen, addressing the doubts raised on the selection of the evaluated population and the interpretation of the results.

In conclusion, ORR results are considered outstanding in patients with recurrent or advanced dMMR/MSI-H EC previously treated with a platinum-containing regimen, given that currently available systemic therapy options for recurrent or advanced EC in the second-line setting provide very limited overall clinical activity and are invariably short-lived, with objective response rates (ORRs) of approximately 7% to 14% and median overall survival (OS) of 6 to 11 months.

However, it was doubted if these same modest results observed in the general EC population are expected in the subset of patients with dMMR/MSI-H EC patients when treated with standard treatments or whether better outcomes might be expected. Based on previous knowledge from other

anti-PD1 inhibitors and on tumour responses observed in the different Cohorts of GARNET Study, it is unquestioned that the presence of dMMR/MSI-H is a biomarker predictive of treatment outcomes to dostarlimab.

In order to investigate whether dMMR/MSI-H is a prognostic or predictive marker of response to standard chemotherapy, the applicant conducted a systematic review aimed to evaluate the available clinical study evidence in the treatment of recurrent or advanced endometrial cancer (data not shown).

Despite the number of studies investigating the prognostic effect of both MMR and MSI status on survival and disease progression, results varied, and there was no strong evidence to suggest that either dMMR or MSI-H status has a significant positive or negative prognostic value in endometrial cancer patients.

Regarding the predictive effect, evidence presented from Cohort A1 (dMMR/MSI-H) and Cohort A2 (MMR-proficient/MSS EC) shows consistent tumour responses from patients who had received platinum-based chemotherapy prior to receiving dostarlimab in both Cohorts (Cohort A1 ORR 44.5% vs Cohort A2 ORR 40%), with consistent Progression Free intervals following last platinum-based regimen (Cohort A1 median PFS 6.37 (95% CI 4, 12) vs Cohort A2 median PFS 8.4 months (95% CI 4, 11.8), thus, regardless of the presence of the MMR/MS status. Even if these two cohorts are not fully comparable with respect to some baseline disease characteristics, in general both are rather similar and represent a heavily pretreated recurrent or advanced EC population previously treated with platinum-based chemotherapy. Results suggest that the presence of MMR-d/MSI-H is not predictive of responses to standard chemotherapy in previous lines. Available literature also suggests that the same applies for chemotherapy in second line. In conclusion, based on available evidence it appears reasonable to conclude that the modest tumour responses and short survival in the overall EC population reported in the literature for available chemotherapies in 2nd line can be applied to the subset of patients with dMMR/MSI-H EC.

With this in mind, the observed tumour responses with dostarlimab are well above those expected with standard treatment and are considered clinically relevant in this condition. However, more comprehensive clinical data are still considered needed in order to firmly conclude on the benefit of dostarlimab in the claimed indication.

### *Additional efficacy data needed in the context of a conditional MA*

As discussed above, there are limitations related to the efficacy of dostarlimab in the claimed indication due to the uncontrolled nature of the pivotal trial, the limited sample size and data immaturity. These limitations hamper the assessment of clinical benefit in terms of relevant clinical outcomes. Therefore, additional clinical data should be provided in order to confirm the benefit of dostarlimab in the claimed indication. In the context of a conditional MA, updated results from study GARNET (Cohort A1) will be provided by 31 December 2022 to confirm the benefits observed with dostarlimab in the target population. At that time, data from at least 131 patients with measurable disease followed for at least 12 months from the onset of response will be available (SOB).

Furthermore, data from study 4010-03-001 (RUBY), a randomised double-blind Phase III study of dostarlimab in combination with chemotherapy (carboplatin plus paclitaxel considered the SOC) versus chemotherapy alone, in chemotherapy-naïve subjects with recurrent or primary advanced endometrial cancer will be provided. This study is expected to include approximately 25% of patients with dMMR/MSI-H EC. Patients will be stratified by MMR/MS status. The results of the primary analysis of progression-free survival (PFS), as assessed by blinded independent central review (BICR) (N=470) together with the results of the interim OS analysis will be submitted by 31 December 2022 (SOB). The final OS analysis is currently foreseen for 2024 (REC).

Although this study is assessing dostarlimab in combination with chemotherapy in a prior line of treatment in EC patients, the results from this study are expected to provide further evidence of safety and efficacy of dostarlimab in the treatment of MSI-H endometrial cancer (EC).

## 2.5.4. Conclusions on the clinical efficacy

Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Results from available literature suggest that single agent chemotherapy provides ORRs of approximately 7% to 14% and median overall survival of 6 to 11 months in 2nd line therapy. There is a clear unmet medical need in this population for which there is currently no approved therapies in the EU.

Preliminary efficacy data from cohort A1 of trial GARNET showed a benefit in terms of ORR and DOR from dostarlimab in the advanced dMMR/MSI-H endometrial cancer setting: ORR of 43.5% and 78.3% of patients with a DOR of ≥6 months. Dostarlimab treatment compares favourably to available, unapproved therapies commonly used in this patient population, for whom consistent results can reasonably be anticipated in the subset of patients with dMMR/MSI-H EC.

Taking into account the disease setting, the limited treatment options available and the size and duration of the observed anti-tumoral effect, dostarlimab is considered to provide a clinically relevant benefit for adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that have progressed on or following prior treatment with a platinum-containing regimen.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit updated results of the GARNET study, Cohort A1, including at least 131 patients with measurable disease followed for at least 12 months from the onset of response. The CSR should be submitted by 31 December 2022.
- In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease. The CSR should be submitted by 31 December 2022).

## 2.6. Clinical safety

Safety data for dostarlimab are organized into 2 groups:

• Patients with dMMR and dMMR/MSI-H Endometrial Cancer (Cohort A1; monotherapy)

• Patients treated with dostarlimab at the recommended therapeutic dose (RTD) (monotherapy): the "RTD" pool comprises patients who were treated with the 500 mg every 3 weeks (Q3W) for 4 doses followed by 1,000 mg every 6 weeks (Q6W) regimen (GARNET Part 2B Schema, see Figure 34).

## *Patient exposure*

**Endometrial Cancer monotherapy group**

**Extent of Exposure**

Treatment exposure for patients with dMMR/MSI-H EC is summarised in Table 37 (data cut-off date of 1 March 2020). The overall median treatment duration for participants with dMMR/MSI-H EC was 26.0 weeks (range: 3 to 139 weeks). Sixty-three participants (48.8%) were exposed to dostarlimab monotherapy for at least 24 weeks, whereas 40 participants (31.0%) and 23 participants (17.8%) were exposure for at least 48 and 72 weeks, respectively.

**Table 37: Duration of Exposure (Safety Analysis Set – Patients with dMMR/MSI-H EC) (DCO 1 March 2020)**

| Parameter | dMMR/MSI-H EC (N=129) |
|---|---|
| Duration of exposure (weeks) | |
| n | 129 |
| Mean (StDev) | 40.8 (36.68) |
| Median | 26.0 |
| Q1, Q3 | 12.0, 60.9 |
| Min, max | 3, 139 |
| Duration of exposure, n (%) | |
| ≥0 weeks | 129 (100.0) |
| ≥6 weeks | 109 (84.5) |
| ≥12 weeks | 89 (69.0) |
| ≥24 weeks | 63 (48.8) |
| ≥36 weeks | 52 (40.3) |
| ≥48 weeks | 40 (31.0) |
| ≥60 weeks | 28 (21.7) |
| ≥72 weeks | 23 (17.8) |
| ≥84 weeks | 17 (13.2) |
| ≥96 weeks | 12 (9.3) |
| Total number of doses received | |
| n | 129 |
| Mean (StDev) | 8.4 (6.20) |
| Median | 6.0 |
| Min, max | 1, 25 |
| Cumulative dose (mg) | |
| n | 129 |
| Mean (StDev) | 6596.9 (5951.65) |
| Median | 4000.0 |
| Min, max | 500, 23000 |
| Relative dose intensity (%) | |
| n | 129 |
| Mean (StDev) | 97.6 (6.30) |
| Median | 100.0 |
| Min, max | 57, 107 |

Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; max=maximum; min=minimum; MSI-H=microsatellite instability-high; Q1=first quarter; Q3=third quarter; StDev=standard deviation.

Regarding treatment modifications, infusion interruptions were infrequent (only 1 notified) and 24.8% patients experience at least 1 infusion delay. Most of the delays were ≥7 days.

**Table 38: Summary of Dose Modifications (Safety Analysis Set – Patients with dMMR/MSI-H EC) (DCO 1 March 2020)**

| Parameter | dMMR/MSI-H EC (N=129) |
|---|---|
| Infusion interruption | |
| 0 | 128 (99.2) |
| 1 | 1 (0.8) |
| 2 | 0 |
| 3 | 0 |
| ≥4 | 0 |
| Infusion delay | |
| 0 | 97 (75.2) |
| 1 | 24 (18.6) |
| 2 | 7 (5.4) |
| 3 | 1 (0.8) |
| ≥4 | 0 |
| Missed dose | |
| 0 | 119 (92.2) |
| 1 | 10 (7.8) |
| 2 | 0 |
| 3 | 0 |
| ≥4 | 0 |
| Patients with at least 1 infusion delay | |
| Worst dose delays | |
| 3-6 days delay | 1 (0.8) |
| 3 days | 1 (0.8) |
| ≥7 days delay | 31 (24.0) |
| 7-13 days | 5 (3.9) |
| 14-20 days | 8 (6.2) |
| 21-27 days | 9 (7.0) |
| ≥28 days | 9 (7.0) |

Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high.
Note: Infusion delays were any delay in infusion of at least 3 days.

**Patients treated with dostarlimab at the RTD**

**Extent of Exposure**

Treatment exposure for patients treated with dostarlimab at the RTD is summarised in Table 39 and Table 40. Patients received doses of 500 mg every 3 weeks for 4 doses followed by 1000 mg every 6 weeks for all cycles thereafter.

The overall median treatment duration for participants treated with dostarlimab as a single agent at the RTD was 20.0 weeks (range: 1 to 146 weeks). Two hundred fifteen participants (41.7%) were exposed to dostarlimab monotherapy for at least 24 weeks, whereas 132 participants (25.6%) and 51 participants (9.9%) were exposed for at least 48 and 72 weeks, respectively.

**Table 39: Duration of Exposure (Safety Analysis Set – Patients Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| Parameter | Dostarlimab Single Agent (N=515) |
|---|---|
| Duration of exposure (weeks) | |
| n | 515 |
| Mean (StDev) | 33.9 (31.48) |
| Median | 20.0 |
| Q1, Q3 | 10.7, 53.9 |
| Min, max | 1, 146 |
| Duration of exposure, n (%) | |
| ≥0 weeks | 515 (100.0) |
| ≥6 weeks | 421 (81.7) |
| ≥12 weeks | 322 (62.5) |
| ≥24 weeks | 215 (41.7) |
| ≥36 weeks | 174 (33.8) |
| ≥48 weeks | 132 (25.6) |
| ≥60 weeks | 82 (15.9) |
| ≥72 weeks | 51 (9.9) |
| ≥84 weeks | 38 (7.4) |
| ≥96 weeks | 26 (5.0) |
| Total number of doses received | |
| n | 515 |
| Mean (StDev) | 7.2 (5.37) |
| Median | 5.0 |
| Min, max | 1, 26 |
| Cumulative dose (mg) | |
| n | 515 |
| Mean (StDev) | 5509.8 (5109.71) |
| Median | 3000.0 |
| Min, max | 500, 24000 |
| Relative dose intensity (%) | |
| n | 515 |
| Mean (StDev) | 98.0 (6.16) |
| Median | 100.0 |
| Min, max | 38, 111 |

Source: LSC102334.Rapp.Q56.t.1 and LSC102334.CoRap.Q47a.t.1
Abbreviations: max=maximum; min=minimum; Q1=first quarter; Q3=third quarter; RTD=recommended therapeutic dose; StDev=standard deviation.

**Table 40: Summary of Dose Modifications (Safety Analysis Set – Patients Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| Parameter | Dostarlimab Single Agent (N=515) |
|---|---|
| Infusion interruption | |
| 0 | 505 (98.1) |
| 1 | 8 (1.6) |
| 2 | 2 (0.4) |
| 3 | 0 |
| ≥4 | 0 |
| Infusion delay | |
| 0 | 421 (81.7) |
| 1 | 73 (14.2) |
| 2 | 19 (3.7) |
| 3 | 2 (0.4) |
| ≥4 | 0 |
| Missed dose | |
| 0 | 470 (91.3) |
| 1 | 44 (8.5) |
| 2 | 1 (0.2) |
| 3 | 0 |
| ≥4 | 0 |
| Patients with at least 1 infusion delay | |
| Worst dose delays | |
| 3-6 days delay | 8 (1.6) |
| 3 days | 8 (1.6) |
| ≥7 days delay | 86 (16.7) |
| 7-13 days | 8 (1.6) |
| 14-20 days | 35 (6.8) |
| 21-27 days | 19 (3.7) |
| ≥28 days | 24 (4.7) |

Source: LSC102334.Rapp.Q56.t.2
Abbreviations: RTD=recommended therapeutic dose.
Note: Infusion delays were any delay in infusion of at least 3 days.

## *Adverse events*

**Endometrial Cancer monotherapy group**

**Adverse events**

Most participants with dMMR/MSI-H EC experienced at least 1 TEAE (95.3%). Treatment-related AEs refer to any TEAE assessed by the investigator as related to study treatment ("Related," "Possibly Related," or missing). Treatment-related TEAEs were reported in 63.6% of participants. The majority of TEAEs were not severe or serious and did not require treatment interruption or discontinuation. TEAEs leading to death were reported in 5 participants (3.9%).

**Table 41: Overview of TEAEs (Safety Analysis Set – Participants with dMMR/MSI-H EC) (DCO 1 March 2020)**

| Events, n (%) | dMMR/MSI-H EC (N=129) |
|---|---|
| Any TEAEs | 123 (95.3) |
| Any Grade ≥3 TEAEs | 62 (48.1) |
| Any TEAEs leading to death | 5 (3.9) |
| Any serious TEAEs | 44 (34.1) |
| Any TEAEs leading to permanent treatment discontinuation | 15 (11.6) |
| Any TEAE leading to study treatment interruption | 31 (24.0) |
| Any treatment-emergent irAE | 47 (36.4) |
| Any dostarlimab infusion-related reactions | 0 |

Source: Table 14.3.1.1a
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; irAE=immune-related adverse event; MSI-H=microsatellite instability-high; TEAE=treatment-emergent adverse event.
Note: For each category, participants were included only once even if they experienced multiple events in that category. AE severity was graded using CTCAE v4.03. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after end of treatment visit (or until the start of alternate anticancer therapy, whichever occurred earlier). AE severity was graded using CTCAE v4.03.

TEAEs reported for participants with dMMR/MSI-H EC are summarised in Table 42 (by SOC and PT; ≥10% of participants).

More than half of the participants with dMMR/MSI-H EC had an event in the SOC of General disorders and administration site conditions (64.3%), with fatigue and asthenia being the most frequently reported TEAEs (≥20%), and/or the SOC of Gastrointestinal disorders (62.8%), with nausea and diarrhoea being the most frequently reported TEAEs.

Overall, the most frequently reported TEAEs (≥20%) in participants with dMMR/MSI-H EC were nausea, diarrhoea, anaemia, fatigue, and asthenia. These common TEAEs were Grade 1 or Grade 2 in severity in most participants for whom the TEAEs were reported, with the exception of anaemia, for which 19 participants (14.7%) had Grade 3 events. Of the other most frequently reported TEAEs, 3 participants (2.3%) had Grade 3 TEAEs of diarrhoea, 1 participant (0.8%) each had Grade 3 TEAEs of asthenia and fatigue, and no participant had TEAEs of Grade ≥3 nausea. For none of the participants who had these most frequently reported TEAEs, the event was Grade 4 or Grade 5.

**Table 42: Common TEAEs by System Organ Class and Preferred Term (≥10% of Participants) (Safety Analysis Set – Participants with dMMR/MSI-H EC) (DCO 1 March 2020)**

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Any TEAEs | 123 (95.3) |
| General disorders and administration site conditions | 83 (64.3) |
| Fatigue | 32 (24.8) |
| Asthenia | 28 (21.7) |
| Pyrexia | 14 (10.9) |
| Oedema peripheral | 13 (10.1) |
| Gastrointestinal disorders | 81 (62.8) |
| Nausea | 42 (32.6) |
| Diarrhoea | 36 (27.9) |
| Constipation | 25 (19.4) |
| Vomiting | 24 (18.6) |
| Abdominal pain | 21 (16.3) |
| Musculoskeletal and connective tissue disorders | 57 (44.2) |
| Arthralgia | 20 (15.5) |
| Back pain | 19 (14.7) |
| Myalgia | 14 (10.9) |
| Infections and infestations | 55 (42.6) |
| Urinary tract infection | 20 (15.5) |
| Respiratory, thoracic, and mediastinal disorders | 44 (34.1) |
| Cough | 21 (16.3) |
| Metabolism and nutrition disorders | 43 (33.3) |
| Decreased appetite | 16 (12.4) |
| Skin and subcutaneous tissue disorders | 41 (31.8) |
| Pruritus | 18 (14.0) |
| Rash | 13 (10.1) |
| Blood and lymphatic system disorders | 40 (31.0) |
| Anaemia | 35 (27.1) |

Source: Table 14.3.1.2a
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high; PT=preferred term; TEAE=treatment-emergent adverse event.
Notes: For each PT, participants were included only once even if they experienced multiple events in that PT.

**Immune-Related AEs (irAEs)**

irAEs experienced by patients with dMMR/MSI-H EC are summarised below.

In patients with dMMR/MSI-H EC, 47 patients (36.4%) reported irAEs. The most frequently reported irAEs (>5%) were diarrhoea (8.5%) and hypothyroidism (7.0%) (Table 27). The median time to onset across events reported in ≥2% patients varied from 19 days (for pruritus) to 380 days (for colitis).Almost half of the patients required treatment with immune modulatory medication (IMM) to manage the irAEs and most of them were resolved at the time of the data cut-off date.

**Table 43: irAE by Category and Preferred Term (≥2% Patients) (Safety Analysis Set - Patients with dMMR/MSI-H EC)(DCO 1 March 2020)**

| | | | Treated with IMM** | | | Not treated with IMM** | | |
|---|---|---|---|---|---|---|---|---|
| **Category Preferred Term, n(%)** | **Overall (N=129) n(%)** | **Median time to onset (days)** | **n(%)** | **Resolved n(%)** | **Median time to resolution (days) 95% CI** | **n(%)** | **Resolved n(%)** | **Median time to resolution (days) 95% CI** |
| Any immune-related TEAE | 47 (36.4) | | | | | | | |
| Immune-mediated Gastrointestinal | 13 (10.1) | | | | | | | |
| Diarrhoea | 11 (8.5) | 70.0 | 0 | 0 | | 11 (100.0) | 10 (90.9) | 6.0 (1.0,26.0) |
| Colitis | 3 (2.3) | 380.0 | 2 (66.7) | 2 (100.0) | 35.0 (24.0,NE) | 1 (33.3) | 0 | NE (NE,NE) |
| Immune-mediated endocrinopathies | 12 (9.3) | | | | | | | |
| Hypothyroidism | 9 (7.0) | 168.0 | 9 (100.0) | 2 (22.2) | NE (63.0,NE) | 0 | 0 | |
| Hyperthyroidism | 4 (3.1) | 53.5 | 2 (50.0) | 2 (100.0) | 42.0 (41.0,NE) | 2 (50.0) | 2 (100.0) | 42.0 (20.0,NE) |
| Immune-mediated musculoskeletal | 7 (5.4) | | | | | | | |
| Arthralgia | 6 (4.7) | 52.0 | 1 (16.7) | 0 | NE (NE,NE) | 5 (83.3) | 3 (60.0) | 366.0 (23.0,NE) |
| Immune-mediated hepatic | 6 (4.7) | | | | | | | |
| Alanine aminotransferase increased | 4 (3.1) | 112.5 | 2 (50.0) | 2 (100.0) | 6.5 (5.0,NE) | 2 (50.0) | 2 (100.0) | 11.0 (8.0,NE) |
| Aspartate aminotransferase increased | 3 (2.3) | 33.0 | 3 (100.0) | 2 (66.7) | 5.0 (3.0,NE) | 0 | 0 | |
| Transaminases increased | 3 (2.3) | 176.0 | 2 (66.7) | 2 (100.0) | 11.0 (7.0,NE) | 1 (33.3) | 1 (100.0) | 14.0 (NE,NE) |
| Immune-mediated pancreatitis | 6 (4.7) | | | | | | | |
| Lipase increased | 4 (3.1) | 108.5 | 0 | 0 | | 4 (100.0) | 4 (100.0) | 42.5 (7.0,NE) |
| Amylase increased | 3 (2.3) | 130.0 | 1 (33.3) | 1 (100.0) | 14.0 (NE,NE) | 2 (66.7) | 1 (50.0) | NE (16.0,NE) |
| Immune-mediated skin adverse reactions | 6 (4.7) | | | | | | | |
| Pruritus | 4 (3.1) | 19.0 | 0 | 0 | | 4 (100.0) | 3 (75.0) | 82.0 (7.0,NE) |
| Immune-mediated renal | 4 (3.1) | | | | | | | |

| | | | Treated with IMM** | | | Not treated with IMM** | | |
|---|---|---|---|---|---|---|---|---|
| **Category Preferred Term, n(%)** | **Overall (N=129) n(%)** | **Median time to onset (days)** | **n(%)** | **Resolved n(%)** | **Median time to resolution (days) 95% CI** | **n(%)** | **Resolved n(%)** | **Median time to resolution (days) 95% CI** |
| Blood creatinine increased | 4 (3.1) | 53.5 | 1 (25.0) | 1 (100.0) | 1.0 (NE,NE) | 3 (75.0) | 2 (66.7) | 13.5 (8.0,NE) |

Abbreviations: AE=adverse event; CI=confidence interval; IMM=immune-modulatory medication; irAE=immune-related adverse event; NE=not evaluable.
Source: Table 14.3.1.25.a
Note: AEs are coded using MedDRA version 23.0. irAEs are identified as any Grade ≥2 AEs based on prespecified preferred terms.
** If a patient experienced the same event multiple times, the highest grade was taken. If a patient experienced the same event with the same grade more than once, the one that was treated with IMM was taken. If a patient experienced the same event with the same grade more than once and treated with the same IMM or no treatment, the longer duration to recovery will be taken.
Percentages are calculated using 'No. of patients with irAE' as denominator. IMM with or without Resolved columns % are calculated using n(%).

**Grade ≥3 Treatment-Emergent Adverse Events by SOC and PT**

Grade ≥3 TEAEs reported in ≥2% of participants with dMMR/MSI-H EC are summarised in Table 44.

Treatment-related Grade ≥3 TEAEs were experienced by 17 participants (13.2%) with dMMR/MSI-H EC. Anaemia (5 participants [3.9%]) and lipase increased (3 participants [2.3%]) were the only treatment-related Grade ≥3 TEAEs reported in >2 participants with dMMR/MSI-H EC.

**Table 44: Grade ≥3 TEAEs by SOC and PT (≥2% of Participants) (Safety Analysis Set - Participants with dMMR/MSI-H EC) (DCO 1 March 2020)**

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Any Grade ≥3 TEAE | 62 (48.1) |
| Blood and lymphatic system disorders | 20 (15.5) |
| Grade ≥3 Anaemia | 19 (14.7) |
| Grade 3 Anaemia | 19 (14.7) |
| Gastrointestinal disorders | 18 (14.0) |
| Grade ≥3 Abdominal pain | 7 (5.4) |
| Grade 3 Abdominal pain | 7 (5.4) |
| Grade ≥3 Diarrhoea | 3 (2.3) |
| Grade 3 Diarrhoea | 3 (2.3) |
| Investigations | 14 (10.9) |
| Grade ≥3 Alanine aminotransferase increased | 3 (2.3) |
| Grade 3 Alanine aminotransferase increased | 3 (2.3) |
| Grade ≥3 Lipase increased | 3 (2.3) |
| Grade 3 Lipase increased | 3 (2.3) |
| Infections and infestations | 12 (9.3) |
| Grade ≥3 Sepsis | 4 (3.1) |
| Grade 4 Sepsis | 3 (2.3) |
| Grade 5 Sepsis | 1 (0.8) |
| Grade ≥3 Pneumonia | 3 (2.3) |
| Grade 3 Pneumonia | 2 (1.6) |
| Grade 5 Pneumonia | 1 (0.8) |
| Grade ≥3 Urinary tract infection | 3 (2.3) |
| Grade 3 Urinary tract infection | 3 (2.3) |
| Metabolism and nutrition disorders | 10 (7.8) |
| Grade ≥3 Hyponatraemia | 5 (3.9) |
| Grade 3 Hyponatraemia | 4 (3.1) |
| Grade 4 Hyponatraemia | 1 (0.8) |
| Musculoskeletal and connective tissue disorders | 9 (7.0) |
| Grade ≥3 Back pain | 4 (3.1) |
| Grade 3 Back pain | 4 (3.1) |

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Respiratory, thoracic, and mediastinal disorders | 8 (6.2) |
| Grade ≥3 Pulmonary embolism | 4 (3.1) |
| Grade 3 Pulmonary embolism | 3 (2.3) |
| Grade 4 Pulmonary embolism | 1 (0.8) |
| Renal and urinary disorders | 7 (5.4) |
| Grade ≥3 Acute kidney injury | 4 (3.1) |
| Grade 3 Acute kidney injury | 4 (3.1) |
| Vascular disorders | 4 (3.1) |
| Grade ≥3 Hypertension | 3 (2.3) |
| Grade 3 Hypertension | 3 (2.3) |

Source: Table 14.3.1.5a
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: AE severity was graded using CTCAE v4.03. For each PT, participants were included only once even if they experienced multiple events in that PT.

**Patients Treated with Dostarlimab at the RTD**

**Adverse Events**

TEAEs reported for participants treated with dostarlimab at the RTD are summarised in **Table 45**.

Most participants who received dostarlimab as a single agent at the RTD experienced at least 1 TEAE (97.9%). Treatment-related TEAEs were reported in 67.2% of participants. The majority of TEAEs were not serious and did not require treatment interruption or discontinuation. SAEs were reported in 39.4% of participants. irAEs were reported in 34.8% of participants, and infusion-related reactions were reported in 1.4% of participants.

TEAEs leading to discontinuation of study treatment were observed in 9.5% of participants. TEAEs that led to study treatment interruption were reported in 22.5% of participants.

**Table 45: Overview of TEAEs (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| Events, n (%) | Dostarlimab Single Agent<br>(N=515) |
|---|---|
| Any TEAEs | 504 (97.9) |
| Any Grade ≥3 TEAEs | 259 (50.3) |
| Any TEAEs leading to death | 14 (2.7) |
| Any serious TEAEs | 203 (39.4) |
| Any TEAEs leading to permanent treatment discontinuation | 49 (9.5) |
| Any TEAEs leading to treatment interruption | 116 (22.5) |
| Any treatment-emergent irAEs | 179 (34.8) |
| Any dostarlimab infusion-related reactions | 7 (1.4) |

Source: Table 14.3.1.1.1
Abbreviations: AE=adverse event; CRF=case report form; CTCAE=Common Terminology Criteria for Adverse Events; irAE=immune-related adverse event; RTD=recommended therapeutic dose; TEAE=treatment-emergent adverse event.
Note: Reasons for discontinuation were based on the Discontinuation of Treatment and Discontinuation of Study CRF page. AE severity was graded using CTCAE v4.03.

TEAEs reported for participants treated with dostarlimab at the RTD are summarised in Table 46. The SOC of General disorders and administration site conditions was the SOC with the highest incidence (>30%) of treatment-related TEAEs, with fatigue being the most frequently reported treatment-related TEAEs in the SOC (15.0%).

**Table 46: Common TEAEs by SOC and PT (≥10% of Participants) (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Participants with at least 1 TEAE | 504 (97.9) |
| Gastrointestinal disorders | 330 (64.1) |
| Nausea | 129 (25.0) |
| Diarrhoea | 116 (22.5) |
| Vomiting | 95 (18.4) |
| Constipation | 86 (16.7) |
| Abdominal pain | 76 (14.8) |
| General disorders and administration site conditions | 304 (59.0) |
| Fatigue | 131 (25.4) |
| Asthenia | 99 (19.2) |
| Pyrexia | 54 (10.5) |
| Infections and infestations | 216 (41.9) |
| Urinary tract infection | 65 (12.6) |
| Musculoskeletal and connective tissue disorders | 207 (40.2) |
| Arthralgia | 71 (13.8) |
| Back pain | 65 (12.6) |
| Metabolism and nutrition disorders | 198 (38.4) |
| Decreased appetite | 90 (17.5) |
| Respiratory, thoracic, and mediastinal disorders | 196 (38.1) |
| Cough | 80 (15.5) |
| Dyspnoea | 66 (12.8) |
| Skin and subcutaneous tissue disorders | 171 (33.2) |
| Pruritus | 59 (11.5) |
| Rash | 57 (11.1) |
| Blood and lymphatic system disorders | 150 (29.1) |
| Anaemia | 132 (25.6) |
| Endocrine disorders | 67 (13.0) |
| Hypothyroidism | 52 (10.1) |

Source: Table 14.3.1.2
Abbreviations: PT=preferred term; RTD=recommended therapeutic dose; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

**Immune-Related AEs**

**Table 47: irAEs by Category and Preferred Term (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (DCO 01 March 2020)**

| Category Preferred Term, n (%) | Overall N=515 n (%) | Median Time to Onset (days) | Treated with an IMM | | | Not treated with an IMM | | |
|---|---|---|---|---|---|---|---|---|
| | | | n (%) | Resolved n (%) | Median Time to Resolution (days) (range) | n (%) | Resolved n (%) | Median Time to Resolution (days) (range) |
| Any Immune Related TEAE | 179 (34.8) | - [a] | 70 (39.1) | 38 (54.3) | 84.0 (1, 698+) | 109 (60.9) | 68 (62.4) | 43.0 (1, 913+) |
| Immune-mediated endocrinopathies | 62 (12.0) | 72 | | | | | | |
| Hypothyroidism | 37 (7.2) | 91 | 36 (97.3) | 13 (36.1) | NE (10, 698+) | 1 (2.7) | 0 | NE (9+, 9+) |
| Hyperglycaemia | 16 (3.1) | 71 | 0 | 0 | - | 16 (100.0) | 13 (81.3) | 22.0 (1, 213+) |
| Hyperthyroidism | 10 (1.9) | 32.5 | 5 (50.0) | 3 (60.0) | 43.0 (6, 313+) | 5 (50.0) | 5 (100.0) | 36.0 (20, 64) |
| Adrenal insufficiency | 7 (1.4) | 249 | 5 (71.4) | 2 (40.0) | NE (15, 451+) | 2 (28.6) | 0 | NE (287+, 333+) |
| Thyroiditis | 2 (0.4) | 33.5 | 2 (100.0) | 0 | NE (38, 133) | 0 | 0 | - |
| Immune-mediated Gastrointestinal | 42 (8.2) | 62.5 | | | | | | |
| Diarrhoea | 37 (7.2) | 61 | 0 | 0 | - | 37 (100.0) | 33 (89.2) | 7.5 (1, 347+) |
| Colitis | 7 (1.4) | 183 | 2 (28.6) | 2 (100.0) | 35.0 (24, 46) | 5 (71.4) | 3 (60.0) | 100.0 (17, 279+) |
| Gastritis | 2 (0.4) | 83 | 0 | 0 | - | 2 (100.0) | 2 (100.0) | 15.5 (9, 22) |
| Gastroenteritis | 1 (0.2) | 327 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 5.0 (5, 5) |
| Immune-mediated hepatic | 26 (5.0) | 76.5 | | | | | | |
| Alanine aminotransferase increased | 15 (2.9) | 76 | 5 (33.3) | 4 (80.0) | 15.0 (5, 88) | 10 (66.7) | 8 (80.0) | 11.0 (2, 22) |
| Aspartate aminotransferase increased | 14 (2.7) | 38.5 | 5 (35.7) | 3 (60.0) | 5.0 (3, 88) | 9 (64.3) | 3 (33.3) | NE (1, 103) |
| Blood bilirubin increased | 5 (1.0) | 43 | 0 | 0 | - | 5 (100.0) | 1 (20.0) | NE (2, 60) |
| Hyperbilirubinaemia | 4 (0.8) | 116.5 | 0 | 0 | - | 4 (100.0) | 2 (50.0) | 91.0 (5, 119+) |
| Transaminases increased | 4 (0.8) | 145.5 | 2 (50.0) | 2 (100.0) | 11.0 (7, 15) | 2 (50.0) | 2 (100.0) | 9.5 (5, 14) |
| Hepatitis | 1 (0.2) | 101 | 1 (100.0) | 1 (100.0) | 11.0 (11, 11) | 0 | 0 | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Immune-mediated pancreatitis | 24 (4.7) | 84.5 | | | | | | |
| Amylase increased | 16 (3.1) | 84.5 | 1 (6.3) | 1 (100.0) | 14.0 (14, 14) | 15 (93.8) | 8 (53.3) | 64.0 (16, 655+) |
| Lipase increased | 9 (1.7) | 84 | 1 (11.1) | 1 (100.0) | 8.0 (8, 8) | 8 (88.9) | 7 (87.5) | 42.5 (1, 107) |
| Pancreatitis | 3 (0.6) | 427 | 1 (33.3) | 1 (100.0) | 15.0 (15, 15) | 2 (66.7) | 2 (100.0) | 7.0 (4, 10) |
| Pancreatitis acute | 3 (0.6) | 89 | 1 (33.3) | 1 (100.0) | 11.0 (11, 11) | 2 (66.7) | 1 (50.0) | NE (6, 6) |
| Immune-mediated skin adverse reactions | 22 (4.3) | 29 | | | | | | |
| Rash | 11 (2.1) | 31 | 4 (36.4) | 4 (100.0) | 15.0 (6, 38) | 7 (63.6) | 6 (85.7) | 30.0 (1, 300+) |
| Pruritus | 6 (1.2) | 19 | 0 | 0 | - | 6 (100.0) | 5 (83.3) | 40.5 (5, 913+) |
| Rash maculo-papular | 3 (0.6) | 25 | 1 (33.3) | 1 (100.0) | 14.0 (14, 14) | 2 (66.7) | 2 (100.0) | 23.0 (2, 44) |
| Pemphigoid | 1 (0.2) | 407 | 1 (100.0) | 0 | NE (454+, 454+) | 0 | 0 | - |
| Rash macular | 1 (0.2) | 57 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 28.0 (28, 28) |
| Rash pruritic | 1 (0.2) | 349 | 0 | 0 | - | 1 (100.0) | 0 | NE (76+, 76+) |
| Immune-mediated renal | 19 (3.7) | 64 | | | | | | |
| Blood creatinine increased | 19 (3.7) | 64 | 1 (5.3) | 1 (100.0) | 1.0 (1, 1) | 18 (94.7) | 10 (55.6) | 57.0 (1, 535+) |
| Nephritis | 2 (0.4) | 260 | 1 (50.0) | 1 (100.0) | 38.0 (38, 38) | 1 (50.0) | 1 (100.0) | 8.0 (8, 8) |
| Immune-mediated nervous system | 13 (2.5) | 75 | | | | | | |
| Neuropathy peripheral | 5 (1.0) | 75 | 1 (20.0) | 0 | NE (46, 46) | 4 (80.0) | 0 | NE (23, 796+) |
| Paraesthesia | 4 (0.8) | 44 | 0 | 0 | - | 4 (100.0) | 3 (75.0) | NE (3, 367) |
| Dysaesthesia | 1 (0.2) | 146 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 105.0 (105, 105) |
| Facial paresis | 1 (0.2) | 41 | 0 | 0 | - | 1 (100.0) | 0 | NE (895+, 895+) |
| Hypoaesthesia | 1 (0.2) | 160 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 3.0 (3, 3) |
| Peripheral sensory neuropathy | 1 (0.2) | 170 | 0 | 0 | - | 1 (100.0) | 0 | NE (313+, 313+) |
| Polyneuropathy | 1 (0.2) | 210 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 8.0 (8, 8) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Immune-mediated Pulmonary | 7 (1.4) | 143 | | | | | | |
| Pneumonitis | 7 (1.4) | 143 | 7 (100.0) | 6 (85.7) | 63.0 (16, 431+) | 0 | 0 | - |
| Hypersensitivity | 4 (0.8) | 22.5 | | | | | | |
| Infusion related reaction | 3 (0.6) | 22 | 1 (33.3) | 1 (100.0) | 1.0 (1, 1) | 2 (66.7) | 2 (100.0) | 1.0 (1, 1) |
| Hypersensitivity | 1 (0.2) | 43 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 1.0 (1, 1) |
| Immune mediated Ocular | 1 (0.2) | 275 | | | | | | |
| Iridocyclitis | 1 (0.2) | 275 | 0 | 0 | - | 1 (100.0) | 1 (100.0) | 28.0 (28, 28) |
| Immune-mediated hematologic | 1 (0.2) | 9 | | | | | | |
| Autoimmune haemolytic anaemia | 1 (0.2) | 9 | 1 (100.0) | 1 (100.0) | 64.0 (64, 64) | 0 | 0 | - |
| Immune-mediated musculoskeletal | 1 (0.2) | 376 | | | | | | |
| Arthritis | 1 (0.2) | 376 | 0 | 0 | - | 1 (100.0) | 0 | NE (17+, 17+) |

Abbreviations: AE=adverse event; IMM=immune-modulatory medication; irAE=immune-related adverse event; NE=not evaluable.
Note: AEs are coded using MedDRA version 23.0. irAEs are identified as any Grade ≥2 AEs based on prespecified preferred terms.
** If a patient experienced the same event multiple times, the highest grade was taken. If a patient experienced the same event with the same grade more than once, the one that was treated with IMM was taken. If a patient experienced the same event with the same grade more than once and treated with the same IMM or no treatment, the longer duration to recovery will be taken.

Percentages are calculated using 'No. of patients with irAE' as denominator. IMM with or without Resolved columns % are calculated using n(%).

*Immune-related pneumonitis*

Immune-related pneumonitis occurred in 7 (1.4 %) of 515 patients, including grade 2 (1.2 %) and grade 3 (0.2 %) pneumonitis. Pneumonitis led to discontinuation of dostarlimab in 3 (0.6 %) patients. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in all 7 patients experiencing pneumonitis. Pneumonitis resolved in 6 (85.7 %) patients.

*Immune-related colitis*

Colitis occurred in 8 (1.6 %) patients, including grade 2 (1.0 %) and grade 3 (0.6 %) colitis. Colitis did not lead to discontinuation of dostarlimab in any patients. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (28.6 %) patients. Colitis resolved in 6 (75.0 %) patients experiencing colitis.

*Immune-related hepatitis*

Hepatitis occurred in 1 (0.2 %) patient, which was grade 3. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required. Hepatitis did not lead to discontinuation of dostarlimab and resolved.

*Immune-mediated endocrinopathies*

Hypothyroidism occurred in 37 (7.2 %) patients, all of which were grade 2. Hypothyroidism did not lead to discontinuation of dostarlimab and resolved in 13 (35.1 %) patients.

Hyperthyroidism occurred in 10 (1.9 %) patients, including grade 2 (1.7 %) and grade 3 (0.2 %). Hyperthyroidism did not lead to discontinuation of dostarlimab and resolved in 8 (80 %) patients.

Thyroiditis occurred in 2 (0.4 %) patients; both were grade 2. Neither event of thyroiditis resolved; there were no discontinuations of dostarlimab due to thyroiditis.

Adrenal insufficiency occurred in 7 (1.4 %) patients, including grade 2 (0.8 %), and grade 3 (0.6 %). Adrenal insufficiency resulted in discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 2 (28.6 %) patients.

*Immune-mediated nephritis*

Nephritis, including tubulointerstitial nephritis, occurred in 3 (0.6 %) patients; all were grade 2. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (66.7 %) patients experiencing nephritis. Nephritis led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 2 of 3 (66.7 %) patients.

*Immune-related rash*

Immune-related rash (rash, rash maculo-papular, rash macular, rash pruritic, pemphigoid) occurred in 17 (3.3 %) patients, including Grade 3 in 6 (1.2 %) patients receiving dostarlimab. The median time to onset of rash was 41 days (range 2 days to 407 days). Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 5 (29 %) patients experiencing rash. Rash did not lead to discontinuation of dostarlimab and resolved in 13 (76.5 %) patients.

*Immune-related arthralgia*

Immune related arthralgia occurred in 21 (4.1 %) patients. Grade 3 immune related arthralgia was reported in 3 (0.6 %) patients receiving dostarlimab. The median time to onset of arthralgia was 87 days (range 1 day to 783 days). Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (9.5 %) patients experiencing arthralgia. Arthralgia did not lead to discontinuation of dostarlimab and resolved in 8 (38 %) patients experiencing arthralgia.

**Subgroup Analysis of Treatment-emergent irAEs**

The incidence of irAEs was analysed by subgroup, defined by sex, age, race, ethnicity, BMI, region, ECOG performance status, baseline kidney function, baseline hepatic function, prior anticancer treatment, prior radiotherapy, prior chemotherapy, and prior immunotherapy. A comparison of irAE incidence in participants treated with dostarlimab as a single agent between the subgroups is hampered by the small sample size (≤30 participants) of some of the subgroups. In subgroups of sufficient size for comparison (>30 participants), the incidence of irAEs was generally similar, with the following exceptions:

- Participants from Western Europe (N=299) had a lower incidence of any irAE than participants from North America (N=198) (29.1% vs 40.9%). This is driven at least in part by differences in the incidence of diarrhoea (Western Europe 4.3%; North America 10.6%).

- Participants with normal kidney function (N=230) and mildly impaired kidney function (N=199) had a lower incidence of any irAE than participants with moderately impaired kidney function (N=83) (30.0% and 35.7% vs 45.8%, respectively). The difference seems to be primarily driven by differences in the incidence of blood creatinine increased (normal kidney function 0.9%; mildly impaired kidney function 3.5%; moderately impaired kidney function 12.0%).

**Infusion-Related Reactions**

A total of 7 participants (1.4%) treated with dostarlimab as a single agent at the RTD reported infusion-related reaction TEAEs. These infusion-related reaction TEAEs were infusion-related reaction (6 participants [1.2%]) and hypersensitivity (1 participant [0.2%]).

Of the 7 participants treated with dostarlimab as a single agent who experienced infusion-related reaction TEAEs, 1 participant (14.3%) with a Grade ≥3 event was treated with an IMM. The event resolved after 1.0 day. Six participants (85.7%) were not treated with an IMM. The events in these participants resolved after a median time to resolution of 1.0 day.

Grade 2 infusion related reaction TEAEs was reported in 1.2% of patients. Grade ≥3 infusion-related reaction TEAEs were reported in 1 participant (0.2%), infusion-related reaction TEAEs leading to treatment interruption were reported in 4 participants (0.8%), and infusion-related reaction TEAEs leading to permanent discontinuation of study treatment were reported in 2 participants (0.4%). The 2 participants with an infusion-related reaction leading to permanent discontinuation of study treatment had treatment interrupted due to the infusion-related reaction prior to permanently discontinuing treatment.

No infusion-related reaction SAEs or infusion-related reaction TEAEs leading to death were reported.

All patients recovered from the infusion-related reaction.

**Grade ≥3 Treatment-Emergent Adverse Events**

Grade ≥3 TEAEs reported for ≥1.5% of participants treated with dostarlimab at the RTD are summarised in Table 48.

A total of 259 participants (50.3%) who received dostarlimab as a single agent at the RTD experienced a Grade ≥3 TEAE. The most frequently reported Grade ≥3 TEAEs (≥3%) in participants treated with dostarlimab as a single agent at the RTD were anaemia, dyspnoea, abdominal pain, and hyponatraemia.

Treatment-related Grade ≥3 TEAEs were experienced by 70 participants (13.6%) treated with dostarlimab as a single agent at the RTD. The most frequently reported treatment-related Grade ≥3 TEAEs (>1.0% of participants) were anaemia (1.7%), fatigue (1.6%), and lipase increased (1.4%).

The only Grade 4 TEAE reported in ≥1% of participants who received dostarlimab as a single agent was sepsis, which was reported in 5 participants (1.0%). Grade 4 TEAEs of hyponatraemia were reported in 4 participants (0.8%), and Grade 4 TEAEs of dyspnoea and lipase increased were reported in 2 participants (0.4%) each. All other Grade 4 TEAEs were reported in 1 participant (0.2%) each.

Among participants who received dostarlimab as a single agent at the RTD, 14 participants had Grade 5 TEAEs: Respiratory failure was reported in 2 participants (0.4%) and aspiration, cerebrovascular accident, haemoptysis, hypoxia, infection, intestinal obstruction, large intestinal obstruction, pleural effusion, pneumonia, renal failure, sepsis, and shock were reported in 1 participant (0.2%) each. None of these Grade 5 TEAEs were considered to be related to dostarlimab by the Investigator.

**Table 48: Grade ≥3 TEAEs by SOC and PT (≥1.5% of Participants) (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| **System Organ Class<br>Preferred Term, n (%)** | **Dostarlimab Single Agent (N=515)** |
|---|---|
| Participants with at least 1 Grade ≥3 TEAE | 259 (50.3) |
| Gastrointestinal disorders | 74 (14.4) |
| Grade ≥3 abdominal pain | 18 (3.5) |
| Grade 3 abdominal pain | 18 (3.5) |
| Grade ≥3 nausea | 10 (1.9) |
| Grade 3 nausea | 10 (1.9) |
| Grade ≥3 vomiting | 8 (1.6) |
| Grade 3 vomiting | 8 (1.6) |
| Investigations | 54 (10.5) |
| Grade ≥3 amylase increased | 8 (1.6) |
| Grade 3 amylase increased | 7 (1.4) |
| Grade 4 amylase increased | 1 (0.2) |
| Grade ≥3 lipase increased | 8 (1.6) |

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Grade 3 lipase increased | 6 (1.2) |
| Grade 4 lipase increased | 2 (0.4) |
| Blood and lymphatic system disorders | 51 (9.9) |
| Grade ≥3 anaemia | 45 (8.7) |
| Grade 3 anaemia | 44 (8.5) |
| Grade 4 anaemia | 1 (0.2) |
| Metabolism and nutrition disorders | 51 (9.9) |
| Grade ≥3 hyponatraemia | 17 (3.3) |
| Grade 3 hyponatraemia | 13 (2.5) |
| Grade 4 hyponatraemia | 4 (0.8) |
| Grade ≥3 hyperglycaemia | 8 (1.6) |
| Grade 3 hyperglycaemia | 7 (1.4) |
| Grade 4 hyperglycaemia | 1 (0.2) |
| Infections and infestations | 50 (9.7) |
| Grade ≥3 pneumonia | 13 (2.5) |
| Grade 3 pneumonia | 12 (2.3) |
| Grade 5 pneumonia | 1 (0.2) |
| Grade ≥3 sepsis | 8 (1.6) |
| Grade 3 sepsis | 2 (0.4) |
| Grade 4 sepsis | 5 (1.0) |
| Grade 5 sepsis | 1 (0.2) |
| Respiratory, thoracic, and mediastinal disorders | 39 (7.6) |
| Grade ≥3 dyspnoea | 19 (3.7) |
| Grade 3 dyspnoea | 17 (3.3) |
| Grade 4 dyspnoea | 2 (0.4) |
| Grade ≥3 pulmonary embolism | 11 (2.1) |
| Grade 3 pulmonary embolism | 10 (1.9) |
| Grade 4 pulmonary embolism | 2 (0.4) |
| General disorders and administration site conditions | 36 (7.0) |
| Grade ≥3 fatigue | 14 (2.7) |
| Grade 3 fatigue | 14 (2.7) |
| Grade ≥3 asthenia | 8 (1.6) |
| Grade 3 asthenia | 7 (1.4) |
| Grade 4 asthenia | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 24 (4.7) |
| Grade ≥3 back pain | 10 (1.9) |
| Grade 3 back pain | 10 (1.9) |
| Vascular disorders | 18 (3.5) |

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Grade ≥3 hypertension | 8 (1.6) |
| Grade 3 hypertension | 8 (1.6) |

Source: Table 14.3.1.4
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; PT=preferred term; RTD=recommended therapeutic dose; SOC=system organ class; TEAE=treatment-emergent adverse event.

Note: AE severity was graded using CTCAE v4.03. For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

**Adverse drug reactions**

Adverse drug reactions (ADRs) to be included in the prescribing information were determined from the frequencies of TEAEs, Grade ≥3 TEAEs, serious TEAEs in the RTD monotherapy pool of the GARNET study (N=515). Because GARNET is a single-arm study with no comparator or placebo arm, the medical history of the study population was considered to provide historical context for AE frequencies reported during the study.

The incidence of investigator assessment of event relationship to drug and the historical frequency from medical history were selected as the primary methods to determine ADRs. In addition, adverse reactions reported for other PD-1/PD-L1 inhibitors were reviewed and considered to be supportive of drug relationship based on mechanism of action and biological plausibility, particularly for AEs occurring at low frequency.

For events fulfilling the causality requirement of ADR, the frequency categories in the tabulated list of adverse reactions (see SmPC section 4.8) was based on the frequencies of all-causality AEs (i.e. irrespective of investigators' assessments of relatedness) calculated based on the RTD monotherapy pool from study GARNET.

Overall, the safety of dostarlimab has been evaluated in 515 patients with endometrial cancer or other advanced solid tumours who received dostarlimab monotherapy in the GARNET study, including 129 patients with advanced or recurrent dMMR/MSI-H endometrial cancer.

Dostarlimab was most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of dostarlimab.

Dostarlimab was permanently discontinued due to adverse reactions in 17 (3.3 %) patients; most of them were immune related events. Adverse reactions were serious in 8.7 % of patients; most serious adverse reactions were immune-related adverse reactions (see SmPC section 4.4).

**Table 49: Dostarlimab Adverse Drug Reactions in Patients with Solid Tumours (Monotherapy, N=515)**

| System Organ Class<br>Preferred Term | Frequency of All Grades n(%) | Frequency of Grades 3-4 n(%) |
|---|---|---|
| Blood and lymphatic system disorders | | |
| Anaemia | 132 (25.6)[a] | 45 (8.7) |
| Endocrine disorders | | |
| Hypothyroidism | 52 (10.1) | 0 |
| Hyperthyroidism | 20 (3.9) | 1 (0.2) |
| Adrenal insufficiency | 7 (1.4) | 3 (0.6) |
| Thyroiditis | 4 (0.8)[b] | 0 |
| Hypophysitis | 2 (0.4) | 0 |
| Metabolism and nutrition disorders | | |
| Type 1 diabetes mellitus | 2 (0.4) | 0 |
| Diabetic ketoacidosis | 1 (0.2) | 0 |
| Eye disorders | | |
| Uveitis | 2 (0.4)[c] | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| Pneumonitis | 15 (2.9)[d] | 1 (0.2) |
| Gastrointestinal disorders | | |
| Nausea | 129 (25.0) | 10 (1.9) |
| Diarrhoea | 116 (22.5) | 6 (1.2) |
| Vomiting | 95 (18.4) | 8 (1.6) |
| Colitis | 12 (2.3)[e] | 3 (0.6) |
| Pancreatitis | 6 (1.2)[f] | 5 (1.0)[f] |
| Hepatobiliary disorders | | |
| Hepatitis | 3 (0.6)[g] | 1 (0.2) |
| Skin and subcutaneous tissue disorders | | |
| Pruritus | 59 (11.5) | 1 (0.2) |
| Rash | 85 (16.5)[h] | 6 (1.2)[i] |
| Musculoskeletal and connective tissue disorders | | |
| Myalgia | 34 (6.6) | 0 |
| Arthralgia | 71 (13.8) | 3 (0.6) |
| Renal and urinary disorders | | |
| Nephritis | 4 (0.8)[j] | 0 |

| System Organ Class<br>Preferred Term | Frequency of All Grades n(%) | Frequency of Grades 3-4 n(%) |
|---|---|---|
| General disorders and administration site conditions | | |
| Pyrexia | 54 (10.5) | 1 (0.2) |
| Chills | 19 (3.7) | 0 |
| Investigations | | |
| Transaminases increased | 63 (12.2)[k] | 13 (2.5)[k] |
| Injury, poisoning and procedural complications | | |
| Infusion related reaction | 6 (1.2) | 1 (0.2) |

Data cut-off date 01 March 2020
[a] Includes Anaemia and Autoimmune haemolytic anaemia
[b] Includes Thyroiditis and Autoimmune thyroiditis
[c] Includes Uveitis and Iridocyclitis
[d] Includes Pneumonitis and Interstitial lung disease
[e] Includes Colitis, Enterocolitis and Enterocolitis haemorrhagic
[f] Includes Pancreatitis and Pancreatitis acute
[g] Includes Hepatitis and Hepatocellular injury
[h] Includes Rash, Rash maculo-papular, Erythema, Rash macular, Rash pruritic, Rash erythematous, Rash papular, Toxic skin eruption, Exfoliative rash and Pemphigoid
[i] Includes Rash and Rash maculo-papular
[j] Includes Nephritis and Tubulointerstitial nephritis
[k] Includes Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased and Hypertransaminasaemia

## Serious adverse events and deaths

**Endometrial Cancer monotherapy group**

**Deaths**

Deaths reported for patients with dMMR/MSI-H EC are summarised in Table 50.

**Table 50: Deaths (Safety Analysis Set – Participants with dMMR/MSI-H EC)**

| Reason, n (%) | dMMR/MSI-H EC (N=129) |
|---|---|
| Overall deaths | 36 (27.9) |
| Primary reason of death | |
| Disease progression | 31 (24.0) |
| Adverse events | 5 (3.9) |

Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high.

Five participants (3.9%) with dMMR/MSI-H EC had a TEAE leading to death. All TEAEs leading to death (aspiration, pleural effusion, pneumonia, sepsis, and shock) were reported in 1 participant each. Of all 5 TEAEs leading to death, 2 each were in the SOCs of Infections and infestations and Respiratory, thoracic, and mediastinal disorders. None of the TEAEs that led to death were assessed by the Investigator as related to dostarlimab or considered to be an irAE.

**SAE**

SAEs reported patients with dMMR/MSI-H EC are summarised in Table 51.

Treatment-related SAEs were experienced by 12 participants (9.3%) with dMMR/MSI-H EC. Colitis was the only treatment-related SAE reported in >1 participant with dMMR/MSI-H EC (2 participants [1.6%]).

**Table 51: SAEs by SOC and PT (Safety Analysis Set – Participants with dMMR/MSI-H EC) (DCO 1 March 2020)**

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Participants with at least 1 SAE | 44 (34.1) |
| Gastrointestinal disorders | 13 (10.1) |
| Abdominal pain | 4 (3.1) |
| Colitis | 2 (1.6) |
| Intestinal obstruction | 2 (1.6) |
| Anal haemorrhage | 1 (0.8) |
| Constipation | 1 (0.8) |
| Gastric ulcer perforation | 1 (0.8) |
| Pancreatitis | 1 (0.8) |
| Pancreatitis acute | 1 (0.8) |
| Infections and infestations | 12 (9.3) |
| Sepsis | 4 (3.1) |
| Urinary tract infection | 3 (2.3) |
| Bronchitis | 2 (1.6) |
| Pneumonia | 2 (1.6) |
| Pyelonephritis | 2 (1.6) |
| Bacteraemia | 1 (0.8) |
| Upper respiratory tract infection | 1 (0.8) |
| General disorders and administration site conditions | 9 (7.0) |
| Pyrexia | 3 (2.3) |
| General physical health deterioration | 2 (1.6) |
| Pain | 2 (1.6) |
| Asthenia | 1 (0.8) |
| Oedema | 1 (0.8) |
| Respiratory, thoracic, and mediastinal disorders | 8 (6.2) |
| Pulmonary embolism | 3 (2.3) |
| Aspiration | 1 (0.8) |
| Dyspnoea | 1 (0.8) |
| Hypoxia | 1 (0.8) |
| Pleural effusion | 1 (0.8) |
| Pneumonitis | 1 (0.8) |
| Renal and urinary disorders | 6 (4.7) |
| Acute kidney injury | 4 (3.1) |

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Renal failure | 1 (0.8) |
| Tubulointerstitial nephritis | 1 (0.8) |
| Urinary tract obstruction | 1 (0.8) |
| Nervous system disorders | 4 (3.1) |
| Apraxia | 1 (0.8) |
| Encephalopathy | 1 (0.8) |
| Epilepsy | 1 (0.8) |
| Facial paresis | 1 (0.8) |
| Metabolism and nutrition disorders | 3 (2.3) |
| Dehydration | 1 (0.8) |
| Hyperglycaemic hyperosmolar nonketotic syndrome | 1 (0.8) |
| Hypophagia | 1 (0.8) |
| Musculoskeletal and connective tissue disorders | 3 (2.3) |
| Back pain | 1 (0.8) |
| Muscular weakness | 1 (0.8) |
| Myalgia | 1 (0.8) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 (2.3) |
| Tumour pain | 2 (1.6) |
| Malignant melanoma | 1 (0.8) |
| Investigations | 2 (1.6) |
| Aspartate aminotransferase increased | 1 (0.8) |
| Transaminases increased | 1 (0.8) |
| Skin and subcutaneous tissue disorders | 2 (1.6) |
| Drug eruption | 1 (0.8) |
| Pemphigoid | 1 (0.8) |
| Cardiac disorders | 1 (0.8) |
| Myocardial infarction | 1 (0.8) |
| Eye disorders | 1 (0.8) |
| Iridocyclitis | 1 (0.8) |
| Hepatobiliary disorders | 1 (0.8) |
| Cholecystitis | 1 (0.8) |
| Vascular disorders | 1 (0.8) |
| Shock | 1 (0.8) |

Source: Table 14.3.1.11a
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
Note: For each PT, participants were included only once even if they experienced multiple events in that PT.

Serious irAEs reported patients with dMMR/MSI-H EC and those in the monotherapy pool are summarised in Table 52.

**Table 52: Serious irAEs by Category and Preferred Term (≥0.5% of Participants) (Safety Analysis Set) (DCO 1 March 2020)**

| Category<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>N=129 |
|---|---|
| Any serious immune-related TEAE | 10 (7.8) |
| Immune-mediated gastrointestinal | 2 (1.6) |
| Colitis | 2 (1.6) |
| Immune-mediated hepatic | 2 (1.6) |
| Aspartate aminotransferase increased | 1 (0.8) |
| Transaminases increased | 1 (0.8) |
| Immune-mediated pancreatitis | 2 (1.6) |
| Pancreatitis | 1 (0.8) |
| Pancreatitis acute | 1 (0.8) |
| Immune-mediated nervous system | 1 (0.8) |
| Facial paresis | 1 (0.8) |
| Immune-mediated ocular | 1 (0.8) |
| Iridocyclitis | 1 (0.8) |
| Immune-mediated pulmonary | 1 (0.8) |
| Pneumonitis | 1 (0.8) |
| Immune-mediated skin adverse reactions | 1 (0.8) |
| Pemphigoid | 1 (0.8) |

Source: Table 14.3.1.19a and Table 14.3.1.18.1
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; irAE=immune-related adverse event; MSI-H=microsatellite instability-high; PT=preferred term; RTD=recommended therapeutic dose; TEAE=treatment-emergent adverse event.
Notes: For each category and PT, a participant was included only once, even if they experienced multiple events in that category or PT.
Ordered by incidence in participants with dMMR/MSI-H EC.
Also see SCS Section 3.1.1.7.1.1 Table 28 (dMMR/MSI-H EC) and Section 3.1.2.7.1.1 Table 42 (RTD).

**Patients Treated with Dostarlimab at the RTD**

**Deaths**

Deaths reported for participants treated with dostarlimab at the RTD are summarised in Table 53.

**Table 53: Deaths (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (1 March 2020)**

| Reason, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Overall death | 182 (35.3) |
| Primary reason of death | |
| Disease progression | 160 (31.1) |
| Adverse event | 17 (3.3) |
| Unknown | 3 (0.6)[a] |
| Other | 2 (0.4)[b] |

Source: LSC102334.CoRap.Q47f.t.2
Abbreviations: EC=endometrial cancer; MMRp=mismatch repair-proficient; NSCLC=non-small cell lung cancer; RTD=recommended therapeutic dose.
[a] One participant with MMRp EC discontinued study treatment due to confirmed disease progression and died during the long-term follow-up period, and 1 participant with MMRp EC discontinued study treatment based on clinical criteria by the Investigator and died during the long-term follow-up period (Listing 16.1.2a). One participant with NSCLC discontinued study treatment due to confirmed disease progression and died during the long-term follow-up period (Table 14.3.1.14, data on file).
[b] One participant with MMRp EC discontinued study treatment based on clinical criteria by the Investigator and died during the 90-day safety follow-up period. One participant with MMRp EC discontinued study treatment due to confirmed disease progression and died during the long-term follow-up period (Listing 16.1.2a).

Fourteen (14) participants treated with dostarlimab as a single agent at the RTD had a TEAE leading to death. TEAEs of respiratory failure led to death in 2 participants. All other TEAEs leading to death were reported in 1 participant each. TEAEs in the SOCs of Respiratory, thoracic, and mediastinal disorders (N=6) and Infections and infestations (N=3) made up two-thirds of all TEAEs leading to death. None of the TEAEs that led to death were assessed by the Investigator as related to dostarlimab or considered to be an irAE.

**SAE**

SAEs reported for ≥1% of participants treated with dostarlimab at the RTD are summarised in Table 54.

Treatment-related SAEs were experienced by 40 participants (7.8%) treated with dostarlimab as a single agent at the RTD. The most frequently reported treatment-related SAEs (≥0.5% of participants) were adrenal insufficiency, pneumonitis, and pyrexia reported in 3 participants (0.6%) each.

**Table 54: SAEs by SOC and PT (≥1% of Participants) (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD)**

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Participants with at least 1 SAE | 203 (39.4) |
| Gastrointestinal disorders | 68 (13.2) |
| Abdominal pain | 16 (3.1) |
| Intestinal obstruction | 8 (1.6) |
| Vomiting | 8 (1.6) |
| Ascites | 7 (1.4) |
| Nausea | 7 (1.4) |
| Infections and infestations | 51 (9.9) |
| Pneumonia | 12 (2.3) |
| Sepsis | 8 (1.6) |
| Urinary tract infection | 5 (1.0) |
| Respiratory, thoracic, and mediastinal disorders | 31 (6.0) |
| Dyspnoea | 11 (2.1) |
| Pulmonary embolism | 7 (1.4) |
| General disorders and administration site conditions | 25 (4.9) |
| Pyrexia | 8 (1.6) |
| Renal and urinary disorders | 12 (2.3) |
| Acute kidney injury | 7 (1.4) |
| Blood and lymphatic system disorders | 6 (1.2) |
| Anaemia | 5 (1.0) |

Source: Table 14.3.1.11
Abbreviations: PT=preferred term; RTD=recommended therapeutic dose; SAE=serious adverse event; SOC=system organ class.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

A total of 26 participants (5.0%) had a serious irAE, with the most frequently reported serious irAEs (>0.5% of participants) being adrenal insufficiency, pancreatitis, pancreatitis acute, and pneumonitis (3 participants [0.6%] each).

**Table 55: Serious irAEs by Category and Preferred Term (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD) (DCO 1 March 2020)**

| Category<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Any serious immune-related TEAE | 26 (5.0) |
| Immune-mediated pancreatitis | 6 (1.2) |
| Pancreatitis | 3 (0.6) |
| Pancreatitis acute | 3 (0.6) |
| Lipase increased | 1 (0.2) |
| Immune-mediated endocrinopathies | 5 (1.0) |
| Adrenal insufficiency | 3 (0.6) |
| Hyperglycaemia | 1 (0.2) |
| Hyperthyroidism | 1 (0.2) |
| Immune-mediated hepatic | 4 (0.8) |
| Transaminases increased | 2 (0.4) |
| Aspartate aminotransferase increased | 1 (0.2) |
| Hepatitis | 1 (0.2) |
| Immune-mediated pulmonary | 3 (0.6) |
| Pneumonitis | 3 (0.6) |
| Immune-mediated skin adverse reactions | 3 (0.6) |
| Rash maculo-papular | 2 (0.4) |
| Pemphigoid | 1 (0.2) |
| Immune-mediated gastrointestinal | 2 (0.4) |
| Colitis | 2 (0.4) |
| Immune-mediated haematologic | 1 (0.2) |
| Autoimmune haemolytic anaemia | 1 (0.2) |
| Immune-mediated nervous system | 1 (0.2) |
| Facial paresis | 1 (0.2) |
| Immune-mediated ocular | 1 (0.2) |
| Iridocyclitis | 1 (0.2) |

Source: Table 14.3.1.18.1
Abbreviations: irAE=immune-related adverse event; PT=preferred term; RTD=recommended therapeutic dose; TEAE=treatment-emergent adverse event.
Note: For each PT, participants were included only once even if they experienced multiple events in that PT.

## Laboratory findings

### Haematology

**Patients with dMMR/MSI-H Endometrial Cancer**

Of the 129 participants with dMMR/MSI-H EC, 1 participant had Grade 3 decreased haemoglobin at baseline, and 2 participants had Grade 3 decreased lymphocytes.

Shifts to Grade 3 or Grade 4 haematology parameters of ≥2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 haematology parameters observed in >1% of participants included shifts from Grade 0 (1.6%), Grade 1 (3.1%), and Grade 2 (10.1%) for decreased haemoglobin; shifts from Grade 0 (1.6%), Grade 1 (1.6%), and Grade 2 (4.7%) for decreased lymphocytes; and shifts from Grade 1 (1.6%) for decreased leukocytes. Shifts to Grade 4 were only observed for decreased lymphocytes (1 participant [0.8%] for shifts from Grade 0, Grade 1, and Grade 2 each).

**Patients Treated with Dostarlimab at the RTD**

Of the 515 participants treated with dostarlimab as a single agent at the RTD, 1 participant had Grade 3 decreased haemoglobin at baseline, and 18 participants had Grade 3 decreased lymphocytes.

Shifts to Grade 3 or Grade 4 haematology parameters of ≥2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 haematology parameters observed in >1% of participants included shifts from Grade 1 (2.5%) and Grade 2 (5.4%) for decreased haemoglobin and shifts from Grade 0 (1.9%), Grade 1 (1.2%), and Grade 2 (3.5%) for decreased lymphocytes. Shifts from Grade 0 to Grade 4 haematology parameters were observed in 2 participants (0.4%) for decreased lymphocytes and 1 participant (0.2%) each for decreased neutrophil count and decreased platelet count. A shift from Grade 1 to Grade 4 was observed in 1 participant (0.2%) for decreased lymphocytes. A shift from Grade 2 to Grade 4 was observed in 1 participant (0.2%) for decreased lymphocytes. No other shifts to Grade 4 haematology values were observed in this population.

### Blood Chemistry

**Patients with dMMR/MSI-H Endometrial Cancer**

For the 129 participants with dMMR/MSI-H EC, Grade 3 baseline chemistry values included decreased potassium (1 participant), decreased magnesium (1 participant), and decreased sodium (2 participants). Grade 4 baseline values included decreased corrected calcium (1 participant).

Shifts to Grade 3 or Grade 4 blood chemistry parameters of ≥2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 chemistry parameters observed in >1% of participants included shifts from Grade 1 and Grade 2 (1.6% of participants each) for decreased albumin, shifts from Grade 2 (1.6% of participants) for increased alkaline phosphatase (ALP), shifts from Grade 0 (1.6% of participants) and Grade 1 (2.3% of participants) for decreased sodium, shifts from Grade 1 (1.6% of participants) for increased creatinine, shifts from Grade 0

(2.3% of participants) for increased alanine aminotransferase (ALT), and shifts from Grade 0 (1.6% of participants) for decreased potassium. Shifts to Grade 4 chemistry parameters observed in >0.5% of participants included shifts from Grade 0 (1.6% of participants) for increased corrected calcium and shifts from Grade 3 (0.8% of participants) for decreased sodium. One participant (0.8%) who had maximum Grade 4 increased magnesium postbaseline was missing a baseline value for the parameter.

Shifts to Grade 3 or Grade 4 blood chemistry parameters in participants with dMMR/MSI-H EC were generally similar to those in participants treated with dostarlimab as a single agent.

**Patients Treated with Dostarlimab at the RTD**

For the 515 participants treated with dostarlimab as a single agent at the RTD, Grade 3 baseline chemistry values included decreased albumin (2 participants), increased alkaline phosphatase (ALP) (3 participants), increased corrected calcium (2 participants), decreased potassium (2 participants), decreased magnesium (3 participants), and decreased sodium (9 participants). Grade 4 baseline values included decreased corrected calcium (1 participant).

Shifts to Grade 3 or Grade 4 blood chemistry parameters of ≥2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 chemistry parameters observed in >1% of participants included shifts from Grade 2 (1.2% of participants) for decreased albumin, shifts from Grade 2 (1.6% of participants) for increased ALP, shifts from Grade 0 and Grade 1 (2.5% of participants each) for decreased sodium, shifts from Grade 0 (1.4% of participants) for increased ALT, and shifts from Grade 0 (1.6% of participants) for increased total bilirubin (TBL). Shifts to Grade 4 chemistry parameters observed in >0.5% of participants included shifts from Grade 0 (0.8% of participants each) for increased corrected calcium and decreased corrected calcium and shifts from Grade 3 (0.6% of participants) for decreased sodium.

Shifts to Grade 3 or Grade 4 blood chemistry parameters in participants treated with dostarlimab as a single agent were generally similar to those in participants with dMMR/MSI-H EC.

**Incidence of Potential Liver Toxicity Events**

**Patients with dMMR/MSI-H Endometrial Cancer**

The incidence of potential liver toxicity events reported for participants with dMMR/MSI-H EC was similar to the one reported in patients treated with Dostarlimab at the RTD (see below).

**Patients Treated with Dostarlimab at the RTD**

The incidence of potential liver toxicity events in participants treated with dostarlimab at the RTD is summarised in Table 56.

**Table 56: Incidence of Potential Liver Toxicity Events (Safety Analysis Set - Patients Treated with Dostarlimab at the RTD)**

| Maximum Elevation Under Treatment, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| ALT | |
| <3×ULN | 483 (93.8) |
| 3×ULN to <5×ULN | 9 (1.7) |
| 5×ULN to <10×ULN | 4 (0.8) |
| 10×ULN to <20×ULN | 4 (0.8) |
| ≥20×ULN | 0 |
| AST | |
| <3×ULN | 480 (93.2) |
| 3×ULN to <5×ULN | 10 (1.9) |
| 5×ULN to <10×ULN | 4 (0.8) |
| 10×ULN to <20×ULN | 4 (0.8) |
| ≥20×ULN | 1 (0.2) |
| ALT or AST | |
| <3×ULN | 475 (92.2) |
| 3×ULN to <5×ULN | 12 (2.3) |
| 5×ULN to <10×ULN | 7 (1.4) |
| 10×ULN to <20×ULN | 5 (1.0) |
| ≥20×ULN | 1 (0.2) |
| Total bilirubin level | |
| <1.5×ULN | 481 (93.4) |
| 1.5×ULN to <2×ULN | 6 (1.2) |
| ≥2×ULN | 13 (2.5) |
| ALP | |
| <1.5×ULN | 381 (74.0) |
| 1.5×ULN to <2×ULN | 42 (8.2) |
| ≥2×ULN | 75 (14.6) |
| Concurrent ALT ≥3×ULN and total bilirubin ≥2×ULN | 5 (1.0) |
| Concurrent AST ≥3×ULN and total bilirubin ≥2×ULN | 7 (1.4) |
| Concurrent ALT or AST ≥3×ULN and total bilirubin ≥2×ULN | 7 (1.4) |
| Concurrent ALT or AST ≥3×ULN and total bilirubin ≥2×ULN and ALP ≥2×ULN | 5 (1.0) |
| Potential Hy's law: concurrent ALT or AST ≥3×ULN and total bilirubin ≥2×ULN and ALP <2×ULN | 1 (0.2) |

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; RTD=recommended therapeutic dose; ULN=upper limit of normal.
Note: Concurrent measurements are those occurring on the same date. Participants can be included in more than 1 category but cannot be included in the same category more than once.

## *Safety in special populations*

**Intrinsic Factors**

TEAEs by Sex, SOC, and PT

The incidence of TEAEs was generally similar between male and female patients treated with dostarlimab as a single agent at the RTD; however, SAEs were more frequent in female participants (41.2%) than in male participants (33.3%). The pattern of TEAEs by PT was similar between female and male participants: The most frequently reported PTs within the SOCs with the highest incidence of TEAEs were the same.

TEAEs by Age, SOC, and PT

Of the 515 patients treated with dostarlimab monotherapy, 51 % were under 65 years, 38 % were 65-<75 years, and 12 % were 75 years or older. No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years).

**Table 57: Overall Summary of TEAEs by Age Group (Safety Analysis Set) (DCO 1 March 2020)**

| Events | dMMR/MSI-H (N=129) n(%) | Total monotherapy (N=515) n(%) |
|---|---|---|
| **Number of Subjects by Sub-Groups [N1 (%)]** | | |
| <65 | 66 (51.2) | 261 (50.7) |
| ≥65 - <75 | 51 (39.5) | 195 (37.9) |
| ≥75 - <85 | 12 (9.3) | 57 (11.1) |
| ≥85 | 0 | 2 (0.4) |
| **Subjects With At Least TEAE** | | |
| <65 | 63 (95.5) | 256 (98.1) |
| ≥65 - <75 | 49 (96.1) | 192 (98.5) |
| ≥75 - <85 | 11 (91.7) | 54 (94.7) |
| ≥85 | 0 | 2 (100.0) |
| **TEAEs Grade ≥3** | | |
| <65 | 27 (40.9) | 126 (48.3) |
| ≥65 - <75 | 28 (54.9) | 105 (53.8) |
| ≥75 - <85 | 7 (58.3) | 27 (47.4) |
| ≥85 | 0 | 1 (50.0) |
| **TEAEs Leading to Permanent Treatment Discontinuation** | | |
| <65 | 6 (9.1) | 23 (8.8) |
| ≥65 - <75 | 6 (11.8) | 20 (10.3) |
| ≥75 - <85 | 3 (25.0) | 6 (10.5) |
| ≥85 | 0 | 0 |
| **Serious TEAEs** | | |
| <65 | 19 (28.8) | 98 (37.5) |
| ≥65 - <75 | 21 (41.2) | 81 (41.5) |
| ≥75 - <85 | 4 (33.3) | 23 (40.4) |
| ≥85 | 0 | 1 (50.0) |
| **TEAEs Leading to Death** | | |
| <65 | 2 (3.0) | 6 (2.3) |
| ≥65 - <75 | 2 (3.9) | 6 (3.1) |

| Events | dMMR/MSI-H (N=129) n(%) | Total monotherapy (N=515) n(%) |
|---|---|---|
| ≥75 - <85 | 1 (8.3) | 2 (3.5) |
| ≥85 | 0 | 0 |
| **Immune-related TEAEs** | | |
| <65 | 24 (36.4) | 87 (33.3) |
| ≥65 - <75 | 19 (37.3) | 72 (36.9) |
| ≥75 - <85 | 2 (16.7) | 18 (31.6) |
| ≥85 | 0 | 2 (100.0) |
| **Infusion-related Reactions** | | |
| <65 | 0 | 3 (1.1) |
| ≥65 - <75 | 0 | 2 (1.0) |
| ≥75 - <85 | 0 | 1 (1.8) |
| ≥85 | 0 | 1 (50.0) |

Treatment-emergent adverse events (TEAEs) were coded using MedDRA version 23.0.
Percentages for TEAEs were based on N1 for each age subgroup.

**Table 58: Overview of Treatment Emergent Adverse Events by Age Group (Safety Population, Monotherapy Pool) (DCO 1 March 2020)**

| Parameter | Age <65 261 (50.7%) | Age 65-74 195 (37.9%) | Age 75-84 57 (11.1%) | Age 85+ 2 (0.4%) |
|---|---|---|---|---|
| **Total TEAEs** | 256 (98.1) | 192 (98.5) | 54 ( 94.7) | 2 (100.0) |
| **Serious TEAEs- Total** | 98 ( 37.5) | 81 ( 41.5) | 23 ( 40.4) | 1 ( 50.0) |
| **- Fatal** | 6 ( 2.3) | 6 ( 3.1) | 2 ( 3.5) | 0 |
| **- Hospitalization/prolong existing hospitalization** | 91 ( 34.9) | 76 ( 39.0) | 20 ( 35.1) | 1 ( 50.0) |
| **- Life-threatening** | 3 ( 1.1) | 8 ( 4.1) | 0 | 0 |
| **- Disability/incapacity** | 1 ( 0.4) | 3 ( 1.5) | 1 ( 1.8) | 0 |
| **- Other(medically significant)** | 8 ( 3.1) | 12 ( 6.2) | 0 | 0 |
| **TEAE leading to drop-out** | 23 ( 8.8) | 20 ( 10.3) | 6 ( 10.5) | 0 |
| **Psychiatric disorders SOC** | 53 ( 20.3) | 31 ( 15.9) | 9 ( 15.8) | 0 |
| **Nervous system disorders SOC** | 69 ( 26.4) | 52 ( 26.7) | 17 ( 29.8) | 1 ( 50.0) |
| **Accident and injuries SMQ** | 17 ( 6.5) | 17 ( 8.7) | 6 ( 10.5) | 0 |
| **Cardiac disorders SOC** | 12 ( 4.6) | 12 ( 6.2) | 2 ( 3.5) | 0 |
| **Vascular disorders SOC** | 41 ( 15.7) | 34 ( 17.4) | 3 ( 5.3) | 0 |
| **Cerebrovascular disorders[1]** | 3 ( 1.1) | 4 ( 2.1) | 0 | 0 |
| **Infections and infestations SOC** | 112 ( 42.9) | 78 ( 40.0) | 26 ( 45.6) | 0 |
| **Anticholinergic syndrome PT** | 0 | 0 | 0 | 0 |

| Parameter | Age <65<br>261 (50.7%) | Age 65-74<br>195 (37.9%) | Age 75-84<br>57 (11.1%) | Age 85+<br>2 (0.4%) |
|---|---|---|---|---|
| **Quality of life decreased PTs[2]** | 0 | 0 | 0 | 0 |
| **Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures[3]** | 17 ( 6.5) | 28 ( 14.4) | 5 ( 8.8) | 1 ( 50.0) |

TEAEs: treatment-emergent adverse events; SOC: system organ class; SMQ: standardized MedDRA queries; PT: preferred term.
1. CNS vascular disorders SMQ
2.Quality of life decreased search terms: Quality of life decreased; Impaired quality of life; Performance status decreased; ECOG performance status worsened
3. Sum of events identified using the following PTs: orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, fracture PTs

TEAEs by Ethnicity, SOC, and PT

Most of the participants treated with dostarlimab as a single agent at the RTD were not Hispanic or Latino (398 participants [77.3%]). For 17.9%, ethnicity was not reported. Due to the small number of participants in ethnicity subgroups other than not Hispanic or Latino and not reported (≤30 participants), a meaningful comparison based on ethnicity could not be made.

TEAEs by Race, SOC, and PT

Most of the participants treated with dostarlimab as a single agent at the RTD were White (379 participants [73.6%]). For 17.5%, race was not reported. Due to the small number of participants in race subgroups other than White or not reported (≤30 participants), a meaningful comparison based on race could not be made.

TEAEs by BMI, SOC, and PT

Of the 515 participants treated with dostarlimab as a single agent at the RTD, 5.4% had underweight BMI status (<18.5 kg/m2), 35.0% had normal BMI status (≥18.5 to <25 kg/m2), 27.0% had overweight BMI status (≥25 to 30 kg/m2), and 30.3% had obese BMI status (≥30 kg/m2).

The incidence of TEAEs in the different TEAE categories by BMI status were generally similar in participants with a normal BMI status, overweight BMI status, and obese BMI status. The incidence of irAEs in participants with a normal BMI status (31.1%) was lower than that in participants with an overweight BMI status (38.8%). The incidence of irAEs in participants with an obese BMI status (35.9%) was between that of participants with normal BMI status and participants with an overweight BMI status.

The incidence of Grade ≥3 TEAEs in participants with a normal BMI status (56.1%) was higher than that in participants with an obese BMI status (42.3%) or overweight BMI status (49.6%). SAEs were reported more frequently in participants with a normal BMI status (40.6%) or overweight BMI status (40.3%) than in participants with an obese BMI status (34.6%). TEAEs leading to treatment interruption were reported less frequently in participants with normal BMI status (20.6%) than in participants with an overweight BMI status (25.9%), but more frequently than in participants with an obese BMI status (16.7%).

The pattern of TEAEs by PT was similar between the different BMI status subgroups: The most frequently reported PTs within the SOCs with the highest incidence of TEAEs were the same.

Due to the small number of participants with an underweight BMI status (≤30 participants), a meaningful comparison could not be made with the other BMI status categories.

TEAEs by Baseline ECOG Performance Status, SOC, and PT

Of the 515 participants treated with dostarlimab single agent at the RTD, 57.3% had a baseline ECOG performance status of 1, and 42.5% of participants had a baseline ECOG performance status of 0. The baseline ECOG performance status was missing in 1 participant (0.2%). The incidence of TEAEs were generally higher in participants with an ECOG performance status of ≥1 compared with those with an ECOG performance status of 0 for participants treated with dostarlimab as a single agent at the RTD (e.g. Grade ≥3 TEAEs: 54.2% vs 44.7%; SAEs: 45.1% vs 31.5%; TEAEs leading to treatment discontinuation: 11.2% vs 7.3%).

The pattern of TEAEs by PT was similar between the 2 baseline ECOG performance status subgroups: The most frequently reported PTs within the SOCs with the highest incidence of TEAEs were the same.

TEAEs by Baseline Kidney Function

Kidney function was defined as normal for creatinine clearance (CrCl) ≥90 mL/min, mildly impaired for CrCl <90 to ≥60 mL/min, moderately impaired for CrCl <60 to ≥30 mL/min, and severely impaired for CrCl <30 mL/min.

In participants treated with dostarlimab as a single agent at the RTD, the incidence of TEAEs in the different TEAE categories was generally similar between participants with normal (N=230), mildly impaired (N=199), or moderately impaired (N=83) baseline kidney function.

The incidence of irAEs in participants with normal baseline kidney function (30.0%) and participants with mildly impaired baseline kidney function (35.7%) was lower than that in participants with moderately impaired baseline kidney function (45.8%). This difference is primarily driven by differences in the incidence of a single PT: blood creatinine increased. The incidence was progressively higher in participants with impaired kidney function (mild 3.5% and moderate 12.0%) compared to participants with normal kidney function (0.9%).

TEAEs leading to study treatment interruption were reported more frequently in participants with moderately impaired baseline kidney function (30.1%) than in participants with mildly impaired baseline kidney function (18.1%).

The pattern of TEAEs by PT was similar between the different baseline kidney function subgroups: The most frequently reported TEAEs within the SOCs with the highest incidence of TEAEs were the same.

There were too few participants with severely impaired kidney function at baseline (≤30 participants) to make meaningful comparisons with other baseline kidney function subgroups.

TEAEs by Baseline Hepatic Function

Hepatic function was defined based on the maximum common toxicity criteria grade for ALT or AST at baseline (normal=Grade 0 to 1, mildly impaired=Grade 2, moderately impaired=Grade 3, severely impaired=Grade 4). The majority of participants treated with dostarlimab as a single agent at the RTD had normal baseline hepatic function (N=512). There were 3 participants with a mildly impaired baseline hepatic function and no participants with moderately or severely impaired baseline hepatic function. Due to the small number of participants with an impaired baseline hepatic function, a meaningful comparison based on baseline hepatic function could not be made.

**Extrinsic Factors**

TEAEs by Geographic Region, SOC, and PT

Of the 515 participants treated with dostarlimab single agent at the RTD, 58.1% were treated in Western Europe, 38.4% were treated in North America, and 3.5% were treated in Eastern Europe.

The incidence of TEAEs was generally similar in participants in North America and participants in Western Europe. irAEs occurred more frequently in participants in North America (40.9%) than in participants in Western Europe (29.1%), which is driven at least in part by differences in the incidence of diarrhoea (Western Europe 4.3%; North America 10.6%).

The pattern of TEAEs by PT was similar between the 2 geographic region subgroups: The most frequently reported TEAEs within the SOCs with the highest incidence of TEAEs were the same.

Due to the small number of participants (≤30 participants) from Eastern Europe, a meaningful comparison based on geographic region could not be made with the other region categories.

TEAEs by Number of Prior Anticancer Treatments

Of the 515 participants treated with dostarlimab single agent at the RTD, 45.4% had received 1 prior anticancer treatment regimen, 37.7% had received 2 prior anticancer treatment regimens, 12.8% had received 3 prior anticancer treatment regimens, and 4.1% had received ≥4 prior anticancer treatment regimens.

The incidence of TEAEs was generally similar in participants who had received 1, 2, or 3 prior anticancer treatment regimens. Grade ≥3 TEAEs occurred less frequently in participants who had received 1 prior anticancer treatment regimen (46.6%) than in participants who had received 2 (53.1%) or 3 (53.0%) prior anticancer treatment regimens. SAEs occurred more frequently in participants who had received 3 prior anticancer treatment regimens (48.5%) than in participants who had received 1 (38.9%) or 2 (37.6%) prior anticancer treatment regimens.

The pattern of TEAEs by PT was similar between the 3 prior anticancer treatment subgroups: The most frequently reported TEAEs within the SOCs with the highest incidence of TEAEs were the same.

Due to the small number of participants (≤30 participants) who had received ≥4 prior anticancer treatment regimens, a meaningful comparison based on this subgroup could not be made.

TEAEs by Prior Radiotherapy, SOC, and PT

Of the 515 participants treated with dostarlimab single agent at the RTD, 265 had received radiotherapy, and 250 had not received radiotherapy.

The incidence of TEAEs was generally similar in participants who had or had not received radiotherapy. Grade ≥3 TEAEs and SAEs occurred less frequently in participants who had not received radiotherapy (46.8% and 35.6%, respectively) than in participants who had received radiotherapy (53.6% and 43.0%, respectively).

The pattern of TEAEs by PT was similar between participants who had or had not received radiotherapy: The most frequently reported TEAEs within the SOCs with the highest incidence of TEAEs were the same.

## *Immunological events*

Immune-mediated AEs have been assessed within the "Adverse Events" section. See also results of immunogenicity analysis under Clinical pharmacology.

## *Safety related to drug-drug interactions and other interactions*

No data were submitted (see discussion on clinical safety).

## *Discontinuation due to adverse events*

**Endometrial Cancer monotherapy group**

**Treatment Interruptions Due to Adverse Events**

TEAEs leading to treatment interruption reported for patients with dMMR/MSI-H EC are summarized in Table 59. TEAEs leading to treatment interruption were experienced by 31 participants (24.0%) with dMMR/MSI-H EC. The most frequently reported TEAEs leading to treatment interruptions (>2%) in participants with dMMR/MSI-H EC were anaemia and diarrhoea.

**Table 59: TEAEs Leading to Treatment Interruption by SOC and PT (≥ 1% of Participants) (Safety Analysis Set – Participants with dMMR/MSI-H EC)**

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC<br>(N=129) |
|---|---|
| Any TEAE leading to study treatment interruption | 31 (24.0) |
| Gastrointestinal disorders | 9 (7.0) |
| Diarrhoea | 3 (2.3) |
| Colitis | 2 (1.6) |
| Blood and lymphatic system disorders | 5 (3.9) |
| Anaemia | 4 (3.1) |
| Infections and infestations | 4 (3.1) |
| Pneumonia | 2 (1.6) |
| Investigations | 4 (3.1) |
| Lipase increased | 2 (1.6) |
| Injury, poisoning, and procedural complications | 2 (1.6) |
| Gastroenteritis radiation | 2 (1.6) |

Source: Table 14.3.1.18a
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each PT, participants were included only once even if they experienced multiple events in that PT.

TEAEs leading to treatment interruption reported for ≥0.5% of participants treated with dostarlimab at the RTD are summarised in Table 60.

**Table 60: TEAEs Leading to Treatment Interruption by SOC and PT (≥0.5% of Participants) (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD)**

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent<br>(N=515) |
|---|---|
| Participants with at least 1 TEAE leading to treatment interruption | 116 (22.5) |
| Gastrointestinal disorders | 28 (5.4) |
| Diarrhoea | 8 (1.6) |
| Abdominal pain | 3 (0.6) |
| Colitis | 3 (0.6) |
| Investigations | 18 (3.5) |
| Aspartate aminotransferase increased | 5 (1.0) |
| Blood creatinine increased | 4 (0.8) |
| Lipase increased | 4 (0.8) |
| Alanine aminotransferase increased | 3 (0.6) |
| Amylase increased | 3 (0.6) |
| Infections and infestations | 17 (3.3) |
| Pneumonia | 5 (1.0) |
| Respiratory, thoracic, and mediastinal disorders | 16 (3.1) |

| System Organ Class<br>Preferred Term, n (%) | Dostarlimab Single Agent (N=515) |
|---|---|
| Pneumonitis | 7 (1.4) |
| Dyspnoea | 3 (0.6) |
| General disorders and administration site conditions | 15 (2.9) |
| Fatigue | 5 (1.0) |
| Asthenia | 3 (0.6) |
| Endocrine disorders | 11 (2.1) |
| Adrenal insufficiency | 4 (0.8) |
| Blood and lymphatic system disorders | 10 (1.9) |
| Anaemia | 8 (1.6) |
| Metabolism and nutrition disorders | 9 (1.7) |
| Hyperglycaemia | 3 (0.6) |
| Musculoskeletal and connective tissue disorders | 6 (1.2) |
| Arthralgia | 4 (0.8) |
| Renal and urinary disorders | 5 (1.0) |
| Acute kidney injury | 3 (0.6) |

Source: Table 14.3.1.6
Abbreviations: PT=preferred term; RTD=recommended therapeutic dose; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

**Treatment Discontinuation Due to Adverse Events**

TEAEs leading to permanent discontinuation of study treatment reported for patients with dMMR/MSI-H EC and those in the monotherapy pool are summarised in Table 61.

**Table 61: TEAEs Leading to Permanent Discontinuation of Study Treatment by SOC and PT (≥0.5% of Participants) (Safety Analysis Set) (DCO 1 March 2020)**

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC (N=129) | Dostarlimab Single Agent (N=515) |
|---|---|---|
| Any TEAE leading to discontinuation of study treatment | 15 (11.6) | 49 (9.5) |
| Investigations | 4 (3.1) | 11 (2.1) |
| Alanine aminotransferase increased | 2 (1.6) | 5 (1.0) |
| Transaminases increased | 2 (1.6) | 3 (0.6) |
| Aspartate aminotransferase increased | 1 (0.8) | 3 (0.6) |
| Gamma-glutamyltransferase increased | 1 (0.8) | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | 3 (2.3) | 7 (1.4) |
| Aspiration | 1 (0.8) | 1 (0.2) |
| Pleural effusion | 1 (0.8) | 2 (0.4) |
| Pneumonitis | 1 (0.8) | 3 (0.6) |

| System Organ Class<br>Preferred Term, n (%) | dMMR/MSI-H EC (N=129) | Dostarlimab Single Agent (N=515) |
|---|---|---|
| Gastrointestinal disorders | 2 (1.6) | 8 (1.6) |
| Intestinal obstruction | 1 (0.8) | 1 (0.2) |
| Pancreatitis | 1 (0.8) | 1 (0.2) |
| Infections and infestations | 2 (1.6) | 2 (0.4) |
| Bronchitis | 1 (0.8) | 1 (0.2) |
| Pneumonia | 1 (0.8) | 1 (0.2) |
| Sepsis | 1 (0.8) | 1 (0.2) |
| Renal and urinary disorders | 2 (1.6) | 3 (0.6) |
| Acute kidney injury | 1 (0.8) | 1 (0.2) |
| Tubulointerstitial nephritis | 1 (0.8) | 1 (0.2) |
| Nervous system disorders | 1 (0.8) | 4 (0.8) |
| Apraxia | 1 (0.8) | 1 (0.2) |
| Vascular disorders | 1 (0.8) | 1 (0.2) |
| Shock | 1 (0.8) | 1 (0.2) |

Source: Table 14.3.1.14a and Table 14.3.1.9
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; MSI-H=microsatellite instability-high; PT=preferred term; RTD=recommended therapeutic dose; SOC=system organ class; TEAE=treatment-emergent adverse event.
Notes: For each SOC and PT, a participant was included only once, even if they experienced multiple events in that SOC or PT.
Ordered by incidence in participants with dMMR/MSI-H EC.

irAEs leading to permanent discontinuation of study treatment reported for patients with dMMR/MSI-H EC and those in the monotherapy pool are summarised in Table 62.

**Table 62: irAEs Leading to Study Treatment Discontinuation by Category and Preferred Term (≥0.5% of Participants) (Safety Analysis Set) (DCO 1 March 2020)**

| Category<br>Preferred Term, n (%) | dMMR/MSI-H EC N=129 | Dostarlimab Single Agent (N=515) |
|---|---|---|
| Any immune-related TEAE leading to study treatment discontinuation | 6 (4.7) | 20 (3.9) |
| Immune-mediated hepatic | 4 (3.1) | 8 (1.6) |
| Alanine aminotransferase increased | 2 (1.6) | 4 (0.8) |
| Transaminases increased | 2 (1.6) | 3 (0.6) |
| Aspartate aminotransferase increased | 1 (0.8) | 2 (0.4) |
| Immune-mediated pancreatitis | 1 (0.8) | 3 (0.6) |
| Pancreatitis | 1 (0.8) | 1 (0.2) |
| Immune-mediated pulmonary | 1 (0.8) | 3 (0.6) |
| Pneumonitis | 1 (0.8) | 3 (0.6) |

Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; irAE=immune-related adverse event; MSI-H=microsatellite instability-high; PT=preferred term; RTD=recommended therapeutic dose; TEAE=treatment-emergent adverse event.
Notes: For each category and PT, a participant was included only once, even if they experienced multiple events in that category or PT. Ordered by incidence in participants with dMMR/MSI-H EC.

### *Post marketing experience*

Not applicable.

## 2.6.1. Discussion on clinical safety

The primary evidence of safety supporting the use of dostarlimab in the intended indication derives from study GARNET, Cohort A1 (part 2B) which includes 129 patients with dMMR/MSI-H EC group and 515 patients in the RTD monotherapy group, with a data cut-off date of 01 March 2020. The median treatment duration is 26.0 weeks for participants with dMMR/MSI-H EC (Cohort A1) and 20.0 weeks for patients in the monotherapy RTD pool.

Additional supportive safety data were provided from the RTD pool plus dostarlimab combination therapy data (data not shown) comprising 719 patients who were treated with the 500 mg every 3 weeks (Q3W) for 4 doses followed by 1,000 mg every 6 weeks (Q6W), or 500 mg Q3W for all doses from the following studies: study GARNET, study 4020-01-001 (AMBER) with dostarlimab in combination with TSR-022±TSR-033 in patients with advanced solid tumours and study 3000 01 002 (IO-Lite) with dostarlimab in combination with niraparib, platinum-based doublet chemotherapy or bevacizumab in patients with metastatic or locally advanced solid tumours.

dMMR/MSI-H EC group (n=129)

*Patients exposure*

At the time of the most recent data cut-off (01 March 2020), 63.6% patients remained in the study and 45% were still on treatment. The primary reason for study discontinuation was death (n=36, 27.9%), followed by withdrawal of consent (n=8, 6.2%). No patients were reported to have discontinued the study due to adverse events. Regarding study treatment, the main reason to discontinue study treatment was disease progression (n=49, 38.0%), followed by AE (n=14, 10.9%).

The median duration of treatment for this patient group was 26 weeks (range: 3.0, 139.0), with a median relative dose intensity of 100% during the first 12 weeks, as well as from week 13 onward. Infusion delays occurred in 24.8% with a ≥7-day delay for most of them (24%). This suggests that most patients received the planned dose, with a low number of delays, which is reassuring.

Overall, 31 patients (24%) had at least 1 dose interruption due to AEs, 15 (11.6%) had an AE that lead to permanent treatment discontinuation, suggesting that dostarlimab is well tolerated.

*Adverse events*

With the most recent cut-off date (1 March 2020) and 129 patients included in the safety data set of the dMMR/MSI-H EC group, 95.3% of patients with dMMR/MSI-H EC population reported any AE, and 48.1% reported Grade≥3 AEs. Most commonly reported AEs (>20% of patients) were nausea (32.6%), diarrhoea (27.9%), fatigue (24.8%), anaemia (27.1%) and asthenia (21.7%). The most commonly reported Grade ≥3 AEs were anaemia (14.7%), abdominal pain (5.4%) and hyponatraemia (3.9%). The uncontrolled nature of the study hampers contextualisation of the safety data with a comparator and thus limit the assessment of treatment-related AEs.

Serious adverse events were reported by 34.1% of patients, the most commonly reported were abdominal pain, acute kidney injury and sepsis (reported by 3.1% of patients, each), followed by pyrexia, urinary tract infection, and pulmonary embolism (2.3%, each).

A total of 36 (27.9%) patients had died at the time of the most recent data cut-off, most of them due to disease progression (n=31, 24.0%). Five (3.9%) patients experienced AEs leading to death,

none of them considered related to dostarlimab. The types of AEs leading to death were pneumonia, shock, sepsis, aspiration bronchial and pleural effusion (each AE was reported in a single patient).

AEs leading to permanent treatment discontinuation were reported for 15 (11.6%) of patients. The most commonly (≥1%) reported AEs leading to study drug discontinuation by PT were transaminases increased and ALT increased (n=2, 1.6%, each). The proportion of patients with any AEs leading to dose interruptions were 24.0%; infusion delays occurred in 24.8% (most of them ≥7 days). The most common AEs leading to dose interruptions were anaemia (3.1%), and diarrhoea (2.3%).

With regards to adverse events of special interest, immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including dostarlimab. Therefore, immune-related AEs (irAE) were considered as AE of special interest according to dostarlimab mechanism of action and pharmacological class. Overall, 36% of patients experienced an irAE (8.5% diarrhoea, 7.0% hypothyroidism). Overall, 4.7% of irAEs led to treatment discontinuation, the most common ones were to transaminases increased and ALT increased (1.6%, n=2, each).

IrARs including immune-related pneumonitis, colitis, endocrinopathies, immune-related skin adverse reactions, nephritis were reported with dostarlimab and are considered important identified risks (see RMP). While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Therefore, important immune-related adverse reactions listed in the SmPC section 4.4 are not inclusive of all possible severe and fatal immune-related reactions.

Early identification and management of immune-related adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Patients should be monitored for symptoms and signs of immune-related adverse reactions. Clinical chemistries, including liver tests and thyroid function tests, should be evaluated at baseline and periodically during treatment. For suspected immune-related adverse reactions, adequate evaluation including specialty consultation should be ensured (see SmPC section 4.4).

The patient's information and early recognition of the signs and symptoms of the most commonly observed immune-related adverse reactions are considered paramount for the safe use of the PD-1 medicinal products. Therefore, a patient card will be put in place to address the important identified risk of immune-related adverse reactions, as additional risk minimisation measure (see RMP). This patient alert card will also include a section for other HCPs with information on the risk of immune-related adverse reactions and the prescriber's contact information. All prescribers of dostarlimab should inform patients about the Patient Alert Card, explaining what to do should they experience any symptom of immune related adverse reactions. The physician will provide the Patient Alert Card to each patient (see SmPC section 4.2).

Based on the severity of the adverse reaction, treatment with dostarlimab should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered (see below and section 4.2). Upon improvement to Grade ≤1, corticosteroid taper should be initiated and continued for 1 month or longer. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Hormone replacement therapy for endocrinopathies should be instituted as warranted (see SmPC section 4.4).

Treatment with dostarlimab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones and unless otherwise specified in Table 2 of the SmPC.

Specific warnings and precautions have also been included in the SmPC to ensure adequate management of immune-related adverse reactions which were reported with dostarlimab including pneumonitis, colitis, hepatitis, endocrinopathies (including hypothyroidism, hyperthyroidism, and adrenal insufficiency), nephritis and rash.

Since pneumonitis has been reported in patients receiving dostarlimab (see SmPC section 4.8), patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (see SmPC section 4.2).

Dostarlimab can cause immune-related colitis (see SmPC section 4.8). Thus, patients should be monitored for signs and symptoms of colitis and managed with dostarlimab treatment modifications, anti-diarrhoeal agents and corticosteroids (see SmPC section 4.2).

Dostarlimab can also cause immune-related hepatitis (see SmPC section 4.8). Patients should be monitored for changes in liver function periodically as indicated, based on clinical evaluation and managed with dostarlimab treatment modifications and corticosteroids (see SmPC section 4.2).

Furthermore, immune-related endocrinopathies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus and adrenal insufficiency, have been reported in patients receiving dostarlimab (see SmPC section 4.8). Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving dostarlimab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended in section 4.2 of the SmPC.

There were also cases of immune-related adrenal insufficiency occurring in patients receiving dostarlimab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in section 4.2 of the SmPC.

Dostarlimab can cause immune-related nephritis (see SmPC section 4.8). Patients should be monitored for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (see section 4.2) of the SmPC.

Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (see SmPC section 4.8). Patients should be monitored for signs and symptoms of rash. Immune-related rash should be managed as recommended in section 4.2 of the SmPC. Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Caution should be used when considering the use of dostarlimab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents (see SmPC section 4.4).

Immune related arthralgia has been reported in patients receiving dostarlimab (see SmPC section 4.8), with approximately one half of these cases considered related to dostarlimab by investigators. Patients should be monitored for signs and symptoms of arthralgia. Suspected immune related arthralgia should be confirmed and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Given the mechanism of action of dostarlimab other potential immune related adverse reactions may occur, including potentially serious events [e.g. myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis]. Clinically significant immune related adverse reactions reported in less than 1 % of patients treated with dostarlimab as monotherapy in clinical studies include autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis and diabetic ketoacidosis. Patients should be monitored for signs and symptoms of immune related adverse reactions and managed as described in section 4.2. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with dostarlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with dostarlimab versus the risk of possible organ rejection should be considered in these patients.

Fatal and other serious complications can occur in patients who receive allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD 1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GvHD), acute GvHD, chronic GvHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. The benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody should be considered prior to or after an allogeneic HSCT.

Although no infusion-related reactions were reported in dMMR/MSI-H EC patients, infusion -related reactions including hypersensitivity occurred in 7 (1.4 %) patients, including grade 2 (1.2 %) and grade 3 (0.2 %) infusion-related reactions in the monotherapy dataset and is considered an important identified risk (see RMP). All patients recovered from the infusion-related reaction. Since dostarlimab can cause infusion-related reactions, which can be severe (see SmPC sections 4.4 and 4.8), a warning has been included in the SmPC. For severe (grade 3) or life-threatening (grade 4) infusion-related reactions, the infusion should be stopped and treatment should be permanently discontinued (see SmPC sections 4.2 and 4.4).

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC is a contraindication (see SmPC section 4.3).

Fluctuation in laboratory parameters, including blood chemistry parameters (e.g., increased transaminases, increased alkaline phosphatase), blood counts (anaemia, lymphopenia, mainly) have been observed during dostarlimab therapy.

Patients with the following status were excluded from the GARNET study and therefore no safety data is available in these patients (see SmPC section 4.4): ECOG baseline performance score ≥ 2; uncontrolled central nervous system metastases or carcinomatous meningitis; other malignancies within the last 2 years; immunodeficiency or receiving immunosuppressive therapy within 7 days; active HIV, hepatitis B or hepatitis C infection; active autoimmune disease requiring systemic treatment in the past 2 years excluding replacement therapy; history of interstitial lung disease; or receiving live vaccine within 14 days.

No participants who received dostarlimab at the RTD experienced overdose of dostarlimab. If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted (see SmPC section 4.9).

Based on the available safety data, dostarlimab has no or negligible influence on the ability to drive and use machines (see SmPC section 4.7).

Regarding the safety in special populations, AEs leading to death and AEs of special interest for the elderly population appear to be slightly more frequent for patients over the age of 65 when compared to younger patients with dMMR/MSI-H EC. The same trend is observed for patients in the monotherapy pool. However, no new safety concerns arose from these data and it is considered that these risks can be adequately managed with the warning and precautions included in the SmPC.

The safety of dostarlimab in children and adolescents aged under 18 years has not been established. No data are available.

There are no or limited amount of data on the use of dostarlimab in pregnant women. Based on its mechanism of action, dostarlimab can cause foetal harmful pharmacological effects when administered during pregnancy (see SmPC section 4.6). Animal reproduction and development studies have not been conducted with dostarlimab; however, inhibition of the PD 1/PD L1 pathway can lead to increased risk of immune mediated rejection of the developing foetus resulting in foetal death (see section on non-clinical aspects and SmPC section 5.3). Human immunoglobulins (IgG4) are known to cross the placental barrier, and therefore, being an IgG4, dostarlimab has the potential to be transmitted from the mother to the developing foetus. Therefore, there is a risk associated with the administration of dostarlimab to women of childbearing potential and dostarlimab is not recommended during pregnancy and in women of childbearing potential not using contraception.Women of childbearing potential must use effective contraception during treatment with dostarlimab and until 4 months after the last dose of Dostarlimab (see SmPC section 4.6).

With regards to breastfeeding, it is unknown whether dostarlimab/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Dostarlimab should not be used during breast feeding and breast feeding should be avoided for at least 4 months after the last dose of dostarlimab.

Furthermore, fertility studies have not been conducted with dostarlimab (see SmPC section 4.6).

With regards to immunogenicity, anti-drug antibodies (ADA) were tested in 315 patients who received dostarlimab and the incidence of dostarlimab treatment emergent ADAs was 2.5 % (see clinical pharmacology section). Neutralising antibodies were detected in 1.3 % of patients. In the patients who developed anti dostarlimab antibodies, there was no evidence of altered efficacy or safety of dostarlimab (see SmPC section 4.8).

Overall, the main evidence to characterise dostarlimab safety profile comes from ongoing, uncontrolled studies hampering a contextualisation of the safety data. Despite this limitation, available information shows that dostarlimab safety profile is consistent with the profile known for its pharmacological class and no new signals have been identified. Furthermore, long-term safety data are missing (see RMP). Although no new safety signals have been identified to date from patients remaining on treatment for >1 year in study GARNET, data from this sub-population is limited to date and long-term safety (>1 year of dostarlimab treatment, >2 years of dostarlimab treatment) will continue to be evaluated by routine pharmacovigilance.

The general safety profile from the GARNET 2B group (monotherapy use) is consistent with that of the dMMR/MSI-H EC patients. The RTD monotherapy group, as the largest currently available safety dataset, was selected as the basis to estimate more accurately the frequencies of ADR described in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Since dostarlimab is a biological product, the tradename and the batch number of the administered product should be clearly recorded in order to improve the traceability (see SmPC section 4.4).

### *Additional safety data needed in the context of a conditional MA*

Dostarlimab is a new agent from an already known pharmacological class (PD-1 inhibitors). The available safety data do not show any new or concerning findings for this type of agents. At present, the limited size of the safety database and long-term data do not allow a comprehensive characterisation of its safety profile. However, the available safety data are considered adequate in the context of a conditional marketing authorisation. Additional safety data will be provided from study GARNET and study RUBY that will allow to further characterise the observed safety profile of dostarlimab.

## 2.6.2. Conclusions on the clinical safety

Overall, the available evidence suggests that dostarlimab safety is consistent with the profile known for its pharmacological class and no new signals have been identified. The safety profile of dostarlimab in the intended indication is considered overall acceptable. Adequate risk minimisation measures are in place to manage the risks associated with dostarlimab, including the important risk of immune related adverse reactions (see RMP and SmPC). Uncertainties remain due to the limited size of the safety database, the lack of direct controls and the missing long-term data.

Long term safety will continue to be monitored through routine pharmacovigilance. Furthermore, the CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit updated results of the GARNET study, Cohort A1, including at least 131 patients with measurable disease followed for at least 12 months from the onset of response. The CSR should be submitted by 31 December 2022.
- In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease. The CSR should be submitted by 31 December 2022).

## 2.7. Risk Management Plan

### Safety concerns

**Table 76: Summary of the safety concerns.**

| *Summary of safety concerns* | |
|---|---|
| Important identified risks | IrARs (such as immune-related pneumonitis, colitis, endocrinopathies, immune-related skin adverse reactions, nephritis, systemic inflammatory response syndrome, myositis and other irARs)<br><br>Infusion-related reactions |
| Important potential risks | None |
| Missing information | Long-term safety |

### Pharmacovigilance plan

The Applicant proposes to monitor and collect data on the product's safety concerns through routine pharmacovigilance activities. No additional pharmacovigilance activities are being proposed, which is considered adequate in light of the currently proposed safety concerns.

### Risk minimisation measures

**Table 77: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| IrARs (such as immune-related pneumonitis, colitis, endocrinopathies, immune-related skin adverse reactions, nephritis, systemic inflammatory response syndrome, myositis and other irARs) | Routine risk minimisation measures:<br><br>*SmPC section 4.2, 4.4 and 4.8*<br><br>*PL Sections: 2, 4*<br><br>*Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4.*<br><br>*Prescription only medicine*<br><br>*Use restricted to physicians experienced in the use of anticancer medicinal products* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None<br><br>Additional pharmacovigilance activities:<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Additional risk minimisation measures:<br>*Patient card* | |
| | Routine risk minimisation measures:<br>*SmPC Sections: 4.2, 4.4, 4.8*<br>*PL Sections: 2, 4*<br>*Recommended treatment modifications are provided in SmPC section 4.2. and 4.4*<br>*Prescription only medicine*<br>*Use restricted to physicians experienced in the use of anticancer medicinal products*<br>Additional risk minimisation measures:<br>*None* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |
| Long-term safety | Routine risk minimisation measures:<br>No risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are

set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

## *2.9. New Active Substance*

The applicant declared that dostarlimab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers dostarlimab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

## *2.10. Product information*

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Jemperli (dostarlimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation [REG Art 14-a].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Dostarlimab is intended as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

### 3.1.2. Available therapies and unmet medical need

Carboplatin in combination with paclitaxel is considered the standard of care (SOC) for first-line treatment of advanced or metastatic EC based on its similar efficacy and improved toxicity compared to cisplatin, doxorubicin, and paclitaxel (ESMO Clinical Practice Guideline for Endometrial cancer, Ann Oncol 2013; 24 (Suppl 6)). For patients with recurrent or advanced EC who have progressed on or after treatment with a platinum-containing regimen, there are no approved therapies or specific regimens recommended by consensus guidelines in the EU. Depending on the extent and location of recurrent disease, histology, and patients' overall health including comorbidities, surgery, radiation therapy, chemotherapy, or hormone therapy can be considered as treatment options.

Currently available systemic therapy options for recurrent or advanced EC in the second-line setting (with prior exposure to platinum-containing therapy) include liposomal doxorubicin, oxaliplatin, docetaxel, topotecan, and bevacizumab (ESMO guidance: Colombo, N et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1), 2-30). Data for these agents, which are derived from small single-arm, non-registrational studies, are limited and show that overall clinical benefit is very limited and invariably short-lived, with ORRs of approximately 7% to 14% and median OS of 6 to 11 months. Even for the agents with a higher ORR (13.5%), the reported median OS was similar to that of agents with relatively lower ORR and remained at <1 year. Additionally, long-term treatment is challenging even for the patients who achieve responses or disease stabilization due to cumulative chemotherapy-related toxicities.

Available evidence from a literature review suggests that similar rates of response would be expected in the subset of dMMR/MSI-H EC with available therapies.

Because there is no approved therapy or recognized SOC for patients with dMMR/MSI-H EC who have progressed on or after treatment with a platinum-containing regimen and available treatment options provide limited clinical activity in terms of ORR and OS, there is a crucial need to develop new therapeutic options that have meaningful and durable clinical activity in this patient population.

### 3.1.3. Main clinical studies

The main evidence of efficacy submitted comes from Study 4010-01-001 (GARNET), a multicentre, open-label, Phase 1, dose escalation study with expansion cohorts in patients with recurrent or advanced solid tumours.

Efficacy data supporting the claimed indication initially included data from 129 patients with dMMR/MSI-H EC in Cohort A1 at the DCO 1 March 2020, of whom 108 constitutes the primary efficacy population (i.e. participants with measurable disease at baseline and the opportunity for at least 24 weeks of follow-up, including those who discontinued prematurely due to AEs or disease progression)**.** Some supportive efficacy data from 50 patients with dMMR/MSI-H non-endometrial cancer (non-EC) advanced solid tumours in Cohort F of Study 4010-01-001 was also provided.

The primary efficacy endpoints for Cohort A1 were Objective Response Rate (ORR) and Duration of Response DOR according to RECIST v1.1 assessed by BICR.

Secondary efficacy endpoints included Disease Control rate, Progression Free Survival and Overall Survival as well as immune-related ORR, DOR, DCR and PFS.

## *3.2. Favourable effects*

In patients with dMMR/MSI-H EC from Study 4010-01-001 Cohort A1, the ORR as assessed based on RECIST 1.1 by BICR was 43.5% (95% CI: 34.0, 53.4) with 10.2% CRs (11 of 108 patients) at the time of the data cutoff date (01 March 2020). The median DOR had not been reached, and 78.7% of responders had a DOR ≥6 months. Based on Kaplan-Meier estimates, the probability of maintaining a response for 6, 12, and 18 months in patients with dMMR/MSI-H EC was 97.9%, 90.9%, and 80.1%, respectively. At the time of the data cutoff date, 89.4% of responders had an ongoing response.

In terms of progression free survival, 47.2% had no PFS event, and longer follow-up is needed for a stable and accurate estimation of PFS. The majority of patients in the primary efficacy analysis set did not have an OS event (67.6%), and the median OS was not reached.

Secondary endpoints according to irRECIST based on Investigator assessment, showed consistent results.

Subgroup analyses defined by tumour MSI status, number of prior anticancer therapy regimens, prior radiation therapy, prior bevacizumab use, BOR from last platinum-containing prior anticancer therapy, and progression-free interval from last platinum containing prior anticancer therapy were conducted. Overall, results of subgroup analyses for ORR and DOR were consistent with the primary efficacy results in the overall population of patients with dMMR/MSI-H EC.

Subgroup analysis by PD-L1 expression (exploratory analysis) showed differences in the rates of tumour responses (PD-L1<1% ORR 30.4% vs PD-L1≥1% 55.2%).

## *3.3. Uncertainties and limitations about favourable effects*

The main source of evidence comes from a non-comparative single arm, open label, phase 1 dose escalation and expansion cohort study, which is currently ongoing. The lack of comparator and the immaturity of data for some relevant outcomes, make interpretation of the actual clinical relevance of the results challenging. These uncertainties are expected to be addressed upon completion of the GARNET Study, where mature results for tumour responses, duration of responses and overall survival results will be available for an extended number of patients with dMMR/MSI-H EC. Furthermore, results from study RUBY, a randomised double-blind Phase III study of dostarlimab in combination with chemotherapy (carboplatin plus paclitaxel considered the SOC) versus chemotherapy alone, in chemotherapy-naïve subjects with recurrent or advanced endometrial

cancer will be submitted to provide further evidence of safety and efficacy of dostarlimab in the treatment of MSI-H endometrial cancer (EC).

## *3.4. Unfavourable effects*

The safety dataset comprised 129 patients with dMMR/MSI-H EC with an overall median treatment duration of 26.0 weeks. Twelve patients (9.3 %) received treatment for a duration ≥ 96 weeks (22 months). 95.3% of patients reported any AE, and 48.1% reported ≥Grade 3 AEs. Treatment-related TEAEs were reported in 63.6% of participants and treatment-related Grade ≥3 TEAEs were experienced by 17 participants (13.2%). Treatment-related SAEs were experienced by 12 participants (9.3%).

AEs leading to permanent treatment discontinuation were reported for 15 (11.6%) of patients. The most commonly (≥1%) reported AEs leading to study drug discontinuation by PT were transaminases increased and ALT increased (n=2, 1.6%, each). The proportion of patients with any AEs leading to dose interruptions were 24.0%; infusion delays occurred in 24.8% (most of them ≥7 days).

Immune-related AEs (irAE) are considered as AE of special interest according to dostarlimab mechanism of action and pharmacological class. Overall, 36.4% patients experienced an irAE (8.5% diarrhoea, 7.0% hypothyroidism). Overall, 4.7% of irAEs led to treatment discontinuation, the most common ones were transaminases increased and ALT increased (1.6%, n=2, each).

In general, the safety profile for patients with dMMR/MSI-H endometrial cancer in the GARNET study was not different from that of the overall RTD monotherapy population (n=515). The median duration of treatment in this population was 20 weeks.

The most common adverse reactions (> 10 %) were anaemia (25.6 %), nausea (25.0 %), diarrhoea (22.5 %), vomiting (18.4 %), arthralgia (13.8%), pruritus (11.5 %), rash (11.1 %), pyrexia (10.5 %) and hypothyroidism (10.1 %).

Adverse reactions were serious in 8.7 % of patients; most serious adverse reactions were immune-related adverse reactions. Most commonly reported Grade 3 and 4 drug related AEs were anaemia (8.7%), transaminases increased (2.5%), nausea (1.9%), vomiting (1.6%), diarrhoea (1.2%) and rash (1.2%).

Dostarlimab was permanently discontinued due to adverse reactions in 17 (3.3 %) patients; most of them were immune-related events.

## *3.5. Uncertainties and limitations about unfavourable effects*

The main evidence to characterise dostarlimab safety profile comes from ongoing, uncontrolled studies, which is a limitation to contextualise the safety findings. Safety data available in the target population (dMMR/MSI-H Endometrial Cancer) is small in size (n=129 with the most recent cut-off date) and long-term exposure is limited. However, the safety data available are considered adequate in the context of a CMA.

Additional data from study GARNET and study RUBY will be submitted post-authorisation which will further characterise the observed safety profile of dostarlimab in the claimed indication.

## *3.6. Effects Table*

**Table 63: Effects Table for dostarlimab in mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen**

| Effect | Short Description | Unit | Dostarlimab | No Control | Uncertainties / Strength of evidence | Referen-ces |
|---|---|---|---|---|---|---|
| **Favourable Effects (DCO: 1 March 2020) (n=108)** | | | | | | |
| ORR | CR+PR<br>by RECIST v1.1 by BICR | proportion | 43.5%, 95% CI (34.0, 53.4)<br>10.2% CR<br>33.3% PR<br>12.0% SD | NA | 60/108. Limited size and uncontrolled data | |
| DOR | Duration of tumour responses | Months (min, max) | NE (2.6, 28.1+) | NA | Uncontrolled and immature data<br>Probability of maintaining response at 6 months by K M (95 % CI): 97.9 % (85.8, 99.7)<br>Probability of maintaining response at 12 months by K-M (95 % CI): 90.9 % (73.7, 97.1) | |
| DCR | CR+PR+SD<br>by RECIST v1.1 | proportion | 55.6%, 95% CI (45.7, 65.1) | NA | Uncontrolled data | |

| Effect | Short Description | Unit | Dostarlimab | No Control | Uncertainties / Strength of evidence | Referen -ces |
|---|---|---|---|---|---|---|
| **Unfavourable Effects (DCO 1 March 2020) (n=129)** | | | | | | |
| Treatment related AE overall | | n (%) | 82 (63.6%) | NA | | |
| Treatment related ≥G3 AEs | | | 17 (13.2%) | | | |
| Treatment related SAEs | | | 12 (9.3%) | | | |
| AE leading to treatment discontinuation | | | 15 (11.6%) | | | |
| AE leading to treatment interruptions | | | 31 (24.0%) | | | |

Abbreviations: DCO: Data cut-off, AE: Adverse event, G3 AE: Grade 3 Adverse events; SAE: Serious adverse event. ORR: Overall response rate, CR: complete response, PR: partial response, DOR: Duration of response, DCR: disease control rate, SD: stable disease, BICR: blinded independent central review, RECIST: Response Evaluation Criteria in Solid Tumors, DCR: disease control rate, PFS: Progression free survival, OS: overall survival, NA: not applicable

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The observed tumour responses rate of 43.5% (95%CI 34.0, 53.5) is considered promising in patients with dMMR/MSI-H recurrent or advanced endometrial cancer (EC) that have progressed on or following prior treatment with a platinum-containing regimen, including 10.2% CR, 33.3% PR, with responses ongoing in 89.4% of responders at the time of the data cut-off date. Median DOR has not been reached yet.

Currently available systemic therapy options (mainly single agent chemotherapy) for recurrent or advanced EC in the second-line setting provide very limited overall clinical activity and invariably short-lived, with objective response rates (ORRs) of approximately 7% to 14% and median overall survival (OS) of 6 to 11 months. Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Available data suggest that the presence of dMMR/MSI-H does not predict better treatment outcomes for chemotherapy. Thus, similar outcomes might be expected for the dMMR/MSI-H subset of advanced EC patients in 2$^{nd}$ line.

In this disease setting, it is emphasised that the observed magnitude of tumour responses, which seem durable, is well above those previously observed with available, unapproved treatment options commonly used in this patient population in the EU. The observed benefit, if confirmed, is

considered clinically relevant as it is reasonable to assume that it will translate into a survival benefit.

Overall, the available information suggests that dostarlimab safety is consistent with the profile known for its pharmacological class and no new signals have been identified. Data available, although limited in size and long-term exposure, appear acceptable and suggest a tolerable profile.

## 3.7.2. Balance of benefits and risks

Results from available literature suggest that single agent chemotherapy provides ORRs of approximately 7% to 14% and median overall survival (OS) of 6 to 11 months in 2nd line therapy. In this context, the observed magnitude of tumour responses following treatment with dostarlimab, which seem durable, is well above those previously observed with available treatment options in the EU. These preliminary results are considered promising and supportive of clinical benefit, as it is reasonable to expect that these will translate into a survival benefit.

The observed safety profile appears consistent with the one expected for its pharmacological class and no new signals have been identified.

Nevertheless, uncertainties on the actual clinical benefit remain due to the immaturity of data and lack of comparator. Furthermore, the safety database is small and limited in terms of long-term exposure. These uncertainties will be addressed by means of the specific obligations which will provide comprehensive efficacy and safety data.

In conclusion, it is considered that preliminary efficacy and safety data support a favourable benefit/risk balance for dostarlimab in the treatment of patients with advanced dMMR/MSI-H EC. Nevertheless, additional comprehensive evidence will be provided in order to establish firm conclusions on the actual benefits and risks of dostarlimab (see SOBs).

## 3.7.3. Additional considerations on the benefit-risk balance

### *Conditional marketing authorisation*

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission for dostarlimab 50 mg/mL concentrate for solution for infusion pursuant to Commission Regulation No 507/2006.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above.
- It is likely that the applicant will be able to provide comprehensive data.

  Further data from the ongoing GARNET study Cohort A1 expansion of enrolment will be submitted. This will provide safety and additional efficacy data, including longer follow up of the study population, i.e. patients with recurrent or advanced dMMR/MSI-H EC that has progressed following prior treatment with a platinum-containing regimen. Therefore, more

robust data on tumour responses, and mature results on the DOR, PFS and OS will be available for an extended database size. For GARNET Cohort A1 (expansion), a primary analysis of ORR and DOR data is foreseen for Q4 2021 including at least 131 patients with measurable disease followed for at least 12 months from the onset of response. The CSR will be submitted by 31 December 2022.

Furthermore, data from study 4010-03-001 (RUBY), a randomised double-blind Phase III study of dostarlimab in combination with chemotherapy (carboplatin plus paclitaxel considered the SOC) versus chemotherapy alone, in chemotherapy-naïve subjects with recurrent or advanced endometrial cancer will be provided. This study is expected to include approximately 25% of patients with dMMR/MSI-H EC. Patients will be stratified by MMR/MS status. The results of the primary analysis of PFS, as assessed by BICR (N=470) together with the results of the interim OS analysis will be submitted by 31 December 2022.

- Unmet medical needs will be addressed, in view of the observed response rates. In the context of patients with recurrent or advanced endometrial cancer progression on or following prior treatment with a platinum containing regimen these results are unprecedented. Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Results from available literature suggest that single agent chemotherapy provides ORRs of approximately 7% to 14% and median overall survival of 6 to 11 months in 2nd line therapy. In this context, it is emphasised that the observed magnitude of tumour responses, which seem durable, is well above to those previously observed with available treatment options in the EU.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In light of the unmet medical need for patients with recurrent or advanced endometrial cancer progression on or following prior treatment with a platinum containing regimen and considering the positive benefit/risk balance for dostarlimab in the intended indication this criterion is considered fulfilled.

### *3.8. Conclusions*

The overall B/R of Jemperli, as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen, is positive.

## 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jemperli is favourable in the following indication:

Jemperli is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability high (MSI H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum containing regimen.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Additional risk minimisation measures**

Prior to the launch of Jemperli (dostarlimab) in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme with the National Competent Authority.

The educational programme is aimed at increasing the awareness of patients about the signs and symptoms of potential immune-related adverse reactions associated with dostarlimab treatment.

The MAH shall ensure that in each Member State where Jemperli is marketed, all healthcare professionals who are expected to prescribe Jemperli are provided with the following educational package:

- Patient Card.

The Patient Card shall contain the following key messages:

- Description of the main signs and symptoms of immune-related adverse reactions.

- The importance of notifying their treating physician/nurse immediately if symptoms occur or worsen, and the importance of not attempting to treat themselves.
- The importance of carrying the Patient Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
- Includes contact details of their Jemperli prescriber and a warning message for healthcare professionals at any time, including in conditions of emergency, that the patient is using Jemperli.

## *Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation*

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| **Description** | **Due date** |
|---|---|
| In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit updated results of the GARNET study, Cohort A1, including at least 131 patients with measurable disease followed for at least 12 months from the onset of response.<br>The CSR should be submitted by: | 31 December 2022 |
| In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease.<br>The CSR should be submitted by: | 31 December 2022 |

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

Not applicable.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that dostarlimab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.