Real-world data on dostarlimab in post-platinum mismatch repair deficient (dMMR)/microsatellite instability high (MSI-H) advanced/recurrent (A/R) endometrial cancer: descriptive analysis of the French cohort Temporary Authorization of Use (cATU)

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Background

Dostarlimab is an anti-programmed cell death protein-1 (anti–PD-1) antibody approved by the European Medicines Agency in April 2021 as monotherapy for patients with mismatch repair deficient/high microsatellite instability (dMMR/MSI-H) advanced or recurrent (A/R) endometrial cancer (EC) who have progressed on or after platinum-based therapy,[1] based on the results of the GARNET trial[2] (NCT02715284).

Clinical outcomes are poor for patients with A/R EC who have progressed following prior treatment with chemotherapy, with a typical median overall survival of <1 year.[3-4]

The French Health Authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) thereby granted cohort temporary authorization of use (cATU) for dostarlimab in Oct 2020 for patients with dMMR/MSI-H A/R EC who had no alternative treatment options and met the eligibility criteria.[5]

Objectives

We report patient characteristics, efficacy and safety of dostarlimab for patients with dMMR/MSI-H A/R EC enrolled in the early access cATU program in France from Nov 3, 2020, to Jun 30, 2021, and who were considered to have received dostarlimab treatment.

Eligibility criteria for French early access cATU program

- Adult patients with primary A/R EC
- dMMR/MSI-H tumour determined using a validated testing method
- Progression on or after platinum-containing chemotherapy
- ≤2 lines of anti-cancer therapy for recurrent or advanced disease
- Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- No hypersensitivity to the active substance or to any of the excipients
- Patients not eligible for clinical trials
- No breast feeding/avoidance of breast feeding for ≥4 months after the last dose of dostarlimab
- Negative pregnancy test in women of childbearing age
- Adequate organ system functions at treatment initiation:
  1. Hemoglobin ≥9 g/dL
  2. Polynuclear neutrophils ≥1.5 × 10^9/L
  3. Platelets ≥100 × 10^9/L
  4. Hepatic and renal function:
     - Total bilirubin ≤1.5 × upper limit of normal (ULN) and direct bilirubin ≤1.0 × ULN
     - Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN (or ≤5 × ULN if documented liver metastasis)
     - Creatinine clearance ≥50 mL/min

Methods

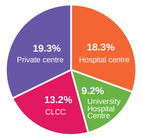
cATU requests

- A total of 95 cATU requests were made by 80 oncologists from 59 different sites throughout France (**Figure 1**).
- Overall, 87 cATU requests were accepted for inclusion in the cohort expanded access scheme; 4 cATU requests were not completed and 4 cATU requests were declined due to patients not meeting the eligibility criteria.
- Nominative ATU (nATU) was authorized for patients with dMMR A/R EC from May 2020 to November 2020, before opening of the cATU; 4 patients that met the eligibility criteria for the cATU switched from nATU to cATU.

Dostarlimab treatment regimen

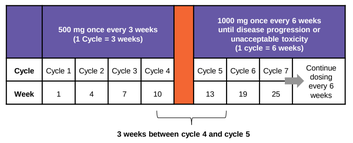
- The dose regimen for dostarlimab treatment is shown in **Figure 2**. Overall, N=80/87 patients included in the cohort expanded access scheme were considered to have received dostarlimab treatment (treatment was provided at least once by laboratory).
- Physicians could complete follow-up forms at each cycle to report clinical follow-up information, efficacy, and safety; safety and disease progression were also captured through pharmacovigilance reports.

Figure 1. Distribution of the types of institutions of requesting physicians in the cohort expanded access scheme (N=59)



CLCC, Centre de Lutte Contre le Cancer (cancer centre).

Figure 2. Dose regimen for patients treated with dostarlimab



Results

Baseline characteristics

Baseline characteristics of the 80 patients considered to have received dostarlimab treatment in the cATU are shown in **Table 1**.

Table 1. Baseline characteristics of patients treated with dostarlimab in the cohort expanded access scheme

Baseline characteristic	N=80*
Age (years) at inclusion in the cATU, median (min, max)	69 (41, 93)
ECOG performance status, n (%)	
0	22 (28)
1	58 (73)
Weight (kg), median (min, max)	67 (45, 130)
HNPCC/Lynch syndrome, n (%)	7 (9)
Missing values	1 (1)
FIGO type at diagnosis, n (%)	
I and II	14 (25)
IIIA and B	4 (8)
IIIC1 and 2	9 (16)
IVA and B	27 (49)
Missing values	25 (31)
Presence of metastases at the time of cATU request, n (%)	69 (86)
Sites of metastases at relapse, n (%)	
Lymph nodes	33 (48)
Peritoneum	31 (45)
Lung	21 (30)
Vagina	3 (4)
Other	17 (25)
Missing values	11 (14)
Type of endometrial cancer, n (%)	
Type I	51 (64)
Type II	29 (36)
Type of histology, n (%)	
Endometrioid	65 (81)
Papillary serous	6 (8)
Clear cell	3 (4)
Other	6 (8)
Type of dMMR status tests, n (%)	
IHC	67 (84)
PCR	26 (33)
NGS	3 (4)
IHC and PCR	13 (16)
Previous treatments, n (%)	
Surgery	58 (73)
Radiotherapy	43 (54)
Brachytherapy	32 (41)
≥1 neoadjuvant chemotherapy	12 (15)
≥1 adjuvant chemotherapy	28 (35)
≥1 chemo-radiotherapy	4 (5)
≥1 chemotherapy following metastasis	34 (43)
Last previous treatment received, n (%)	
Carboplatin-paclitaxel	46 (64)
Other chemotherapy	11 (15)
Tamoxifen	5 (7)
Megestrol acetate	3 (4)
Other hormone therapy	6 (8)
Bevacizumab	1 (1)
Missing values	8 (10)
≥1 concomitant treatment, n (%)	31 (39)
Systemic glucocorticoid	4 (5)
Antibiotics	2 (3)
Other	25 (31)
Blood pressure (mmHg), median (min, max),	
Systolic	130 (105, 150)
Diastolic	75 (59, 95)
Missing values	5 (6)

*Baseline characteristics were based upon N=80 patients unless otherwise specified.
FIGO, International Federation of Gynecology and Obstetrics; HNPCC, hereditary non-polyposis colorectal cancer; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

Median age of patients at time of cATU request was 69 (range 41–93) years and median weight was 67 (range 45–130) kg; 73% (n=58) and 28% (n=22) of patients had ECOG performance status of 1 and 0, respectively.

Overall, 81% (n=65) of patients had endometrioid histology, 8% (n=6) papillary serous, 4% (n=3) clear cell, and 8% (n=6) other. A total of 9% (n=7/79) of patients had a Lynch syndrome diagnosis.

Most patients had stage IV tumours at diagnosis (49%; n=27/55), 25% (n=14) were stages I and II, 8% (n=4) were stages IIIA and B, and 16% (n=9) were stages IIIC1 and 2, based on International Federation of Gynecology and Obstetrics (FIGO) staging. At the time of cATU request, 86% (n=69) of patients had metastases.

Previous treatments included surgery (73%; n=58), radiotherapy (54%; n=43), brachytherapy (41%; n=32), and chemotherapy (100%, n=80): neoadjuvant chemotherapy (15%; n=12), adjuvant chemotherapy (35%; n=28), chemo-radiotherapy (5%; n=4), and chemotherapy for metastatic disease (43%; n=34).

Last previous treatments received included carboplatin-paclitaxel (64%; n=46), other chemotherapy (15%, n=11), tamoxifen (7%, n=5), megestrol acetate (4%, n=3), other hormone therapy (8%, n=6), and bevacizumab (1%, n=1).

Dostarlimab exposure

For patients included in the cohort early access scheme, the maximum possible duration of dostarlimab exposure was 33.6 weeks, corresponding to the time between the first and last day of the cATU.

The median duration of dostarlimab exposure (regardless of whether patients discontinued treatment) was 16.1 weeks (range 0–32 weeks) for patients in the cohort expanded access scheme (n=76) and 35.6 weeks (range 32–41 weeks) for patients who had already started treatment in the nATU (n=4).

Overall, 21% (n=17) of patients permanently discontinued treatment during the cATU. Patients who were still on dostarlimab treatment on the cut-off date of June 30 were permitted to continue treatment outside of the cATU program; however, no information related to treatment duration and efficacy was permitted to be collected after this date, as per the cATU protocol.

Efficacy

Of the 80 patients who received treatment with dostarlimab during the cATU, 54% (n=43) undertook a treatment response assessment before the end of the cATU program (**Table 2**).

The mean (standard deviation) time from treatment initiation to response evaluation was 10.6 (5.6) weeks.

A disease control rate of 56% (n=24) was observed. The overall response rate was 35% (n=15); 5% (n=2) of patients had a complete response to treatment, 30% (n=13) had a partial response, 21% (n=9) had stable disease, and 44% (n=19) had disease progression.

Table 2. Treatment response assessment during follow-up in patients treated with dostarlimab

Total number of patients with at least one treatment response assessment, n (%)	N=43/80 (54)
Response	
Complete response	2 (5)
Partial response	13 (30)
Stable disease	9 (21)
Progression	19 (44)
Overall response rate	15 (35)
Disease control rate	24 (56)
Mean time from treatment initiation to response evaluation (weeks)	
Mean (SD)	10.6 (5.6)
Median (min, max)	9.6 (0.9, 27.1)

Response evaluation was based on both PV cases (n=14 progressions declared as PV cases) and follow-up forms (evaluation of response available for n=41 patients). Only response evaluations during the period of the cATU were considered; if several response evaluations were available, the later evaluation in the period was considered. PV, pharmacovigilance; SD, standard deviation.

Safety

Overall, 29% (n=23/80) of patients presented with at least one adverse event (AE); AEs considered to be related or possibly related to dostarlimab treatment by the treating physician were reported in 14% (n=11) of patients (**Table 3**).

Table 3. Proportion of patients presenting adverse events and treatment-related adverse events (n=80)

All AEs	n (%)	
Any grade AE	23 (29)	
Serious AE	10 (12.5)	
Death	6 (8)	
All TRAEs, n (%)	**Causality reported by the treating physician (yes, possible, probable)**	**Causality reported by the treating physician (unknown)***
Any grade TRAE	11 (14)	7 (9)
Treatment-related SAE	4 (5)	4 (5)
Any TRAE leading to discontinuation	4 (5)	2 (2.5)
Any TRAE leading to treatment interruption/modification	2 (3)	0
TRAE leading to death	1 (1)	2 (2.5)†

PV cases related to disease progression were removed from the safety analysis and presented in the efficacy analysis. A medication error (maximum time between dostarlimab dosing exceeded) was removed from the safety analysis. *AEs declared by physicians as causality to treatment "unknown" were included in the PV database as AEs related to treatment. †For one patient, no information was available on cause of death, and the other patient, the AE was subocclusive syndrome linked to disease progression. AE, adverse event; PV, pharmacovigilance; SAE, serious adverse event; TRAE, treatment-related adverse event.

Serious AEs (SAEs) were reported in 12.5% of patients (n=10), with SAEs considered to be related or possibly related to dostarlimab treatment by the treating physician reported in 5% (n=4) of these patients.

Overall, 5% (n=4) of patients discontinued treatment as a result of a possible treatment-related AE.

A total of 6 patients (8%) died; one patient died due to a possible treatment-related AE (cardiac arrest).

The most frequent AEs that were assessed as related or possibly related to dostarlimab were skin and subcutaneous tissue disorders and thyroid disorders, each observed in 3.8% (n=3) of patients; pneumopathy, hyperglycemia, arthralgia, and diarrhea were each observed in 2.5% (n=2) of patients (**Table 4**).

The most frequent SAE that was deemed related or possibly related to dostarlimab was pneumopathy, observed in 2.5% (n=2) of patients; the majority of reported treatment-related AEs (70% of patients; n=14/20) were not considered to be serious.

Table 4. Proportion of patients presenting treatment-related adverse events (n=80)

	Causality reported by the treating physician (yes, possible, probable)		Causality reported by the treating physician (unknown)	
Parameter, n (%)	**All events**	**Serious**	**All events**	**Serious**
Skin and subcutaneous tissue disorder*	3 (3.8)	1 (1.3)	0	0
Thyroid disorder	3 (3.8)	1 (1.3)	0	0
Pneumopathy	2 (2.5)	2 (2.5)	0	0
Hyperglycemia	2 (2.5)	0	0	0
Arthralgia	2 (2.5)	0	0	0
Diarrhea	2 (2.5)	0	0	0
Asthenia	1 (1.3)	1 (1.3)	0	0
Cardiac arrest	1 (1.3)†	1 (1.3)†	0	0
Hemoglobin abnormal	1 (1.3)	0	1 (1.3)	0
Chills, influenza-like illness	1 (1.3)	0	0	0
Platelet count abnormal	1 (1.3)	0	0	0
Myalgia	1 (1.3)	0	0	0
Hot flush, night sweats	0	0	1 (1.3)	0
Decreased appetite	0	0	1 (1.3)	0
Nausea	0	0	1 (1.3)	0
Papilloedema	0	0	1 (1.3)	1 (1.3)
COVID-19	0	0	1 (1.3)	0
Dyspnoea at rest	0	0	1 (1.3)	1 (1.3)
Neutrophil count abnormal	0	0	1 (1.3)	0
Blood creatinine abnormal	0	0	1 (1.3)	0

*AEs by preferred term: toxicoderma (n=1), urticaria (n=1), drug eruption (n=1), and pruritus (n=2) (1 of the 4 patients experienced multiple AEs). †Patient was also treated with salbutamol for an unknown indication; cardiac arrest was reported as also possibly related to salbutamol.

Conclusions

This program was the first to allow access to immunotherapy for adult patients with dMMR/MSI-H A/R EC outside the clinical trial setting.

During the 8-month period of the cATU, 80 patients with dMMR/MSI-H A/R EC were included in this early access program, highlighting the high unmet medical need for these patients.

Most patients were highly pretreated and presented with advanced disease at the time of inclusion in the cATU.

The disease control rate of dostarlimab in patients with dMMR/MSI-H A/R EC treated in France in the cATU was 56% (in the 54% of patients with response assessments performed), which is consistent with that previously observed in the GARNET trial.[2] Long-term response data could not be collected per the cATU protocol; therefore, conclusions on treatment durability cannot be made.

No new safety signals were observed in the current real-world access program compared with the GARNET trial[2]; the majority of AEs thought to be related to dostarlimab were not serious. Rates of discontinuations due to AEs thought to be related to dostarlimab were low, demonstrating a manageable safety profile with dostarlimab.

Clinical trials are currently ongoing in France[6] and worldwide[7] to assess the efficacy and safety of dostarlimab and other immune therapies alone or in combination with chemotherapy as first-line treatment in patients with and without dMMR/MSI-H EC.

Disclosures

MR declares research funding from Bristol Myers Squibb and Merck, participation in drug advisory boards for AstraZeneca, Merck, and GSK, and speaker fees from AstraZeneca, Merck, GSK, and Immunocore. **LE** declares no conflict of interest. **PF** declares participation in drug advisory boards for AstraZeneca, speaker fees from Eisai, GSK, and Merck, congress invitation from Gilead, and consultancy fees from Clovis and Novartis. **VB** declares participation in drug advisory boards for Novartis. **LG** and **VJ** are employees of GSK. **CT** is an employee of GSK and holds stocks/shares. **NEM** is an employee of GSK. **PB** declares no conflict of interest. **FF** declares participation in drug advisory boards for AstraZeneca, Clovis, GSK, Lilly, Novartis, and Pfizer. **EA** declares participation as a reviewer for Avicenne Hospital. **SR** and **CD** declare no conflicts of interest. **ND** declares participation in drug advisory boards for AstraZeneca, Clovis Oncology, GSK, and Merck, congress invitation from GSK, and personal fees from GSK. **RS** declares research funding from AstraZeneca and Eisai, speaker fees from Clovis, Eisai, GSK, and Novartis, and consultancy fees from GSK. **RF** declares consultancy fees from IPSEN, Bayer, Merck, and Janssen. **TDLMR** declares research funding from Novartis, Pfizer, Seagen, and MSD, participation in advisory boards for Pfizer, AstraZeneca, GSK Clovis Oncology, Roche, MSD, Mylan, Tesaro, French National Cancer Institute, and Unicancer, and institutional funding from Roche, AstraZeneca, GSK, Merck, Pfizer, and Netris Pharma.

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