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Progress Report

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ABSTRACT

Background: Immune checkpoint inhibitors (ICI) targeting Programmed death-1 (PD-1) have shown their efficacy in advanced MSI/dMMR (microsatellite instability/deficient mismatch repair) tumors. The MSI/dMMR status predicts clinical response to ICI. The promising results evaluating ICI in localized MSI/dMMR tumors in neoadjuvant setting need to be confirmed in MSI/dMMR solid tumors. The aim of the IMHOTEP trial is to assess the efficacy of neoadjuvant anti-PD-1 treatment in MSI/dMMR tumors regarding the pathological complete response rate.

Methods: This study is a prospective, multicenter, phase II study including 120 patients with localized MSI/dMMR carcinomas suitable for curative surgery. A single dose of pembrolizumab will be administered before the surgery planned 6 weeks later. Primary objective is to evaluate the efficacy of neoadjuvant pembrolizumab according to pathological complete tumor response. Secondary objectives are to assess safety, recurrence-free survival and overall survival. Ancillary studies will assess molecular and immunological biomarkers predicting response/resistance to ICI. First patient was enrolled in December 2021.

☆ Trial registration: IMHOTEP trial has been registered on www.clinicaltrials.gov; NCT04795661 (first post: March 12th, 2021).

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Discussion: The IMHOTEP trial will be one of the first clinical trial investigating perioperative ICI in localized MSI/dMMR in a tumor agnostic setting. Assessing neoadjuvant anti-PD-1 is mandatory to improve MSI/dMMR patient's outcomes. The translational program will explore potential biomarker to improve our understanding of immune escape and response in this ICI neoadjuvant setting.

1. Background

Surgery is the gold standard treatment of localized resectable solid tumors. However, overall and progression-free survivals are increased by multimodal therapy combining chemotherapy in the neoadjuvant/perioperative or in adjuvant setting. For example, localized gastric adenocarcinomas are currently treated with perioperative chemotherapy (FLOT regimen) [1]. Six-month of oxaliplatine-based adjuvant chemotherapy is recommended in high-risk-stage II and stage III colon cancers following the results of the MOSAIC study [2]. Recently the treatment duration has been reviewed to 3 months in low-risk stage III and high-risk-stage II colon cancers following the IDEA study results [3]. In the FOxTROT phase III trial evaluating neoadjuvant chemotherapy for patients with locally-advanced colon cancer, the authors reported a significant histological downstaging ($p < 0.001$ for pT and pN) with less incomplete (R1-R2) resections (5% vs. 10%, $p = 0.001$) induced by neoadjuvant chemotherapy. However, there was no significant improvement of the relapse or persistent disease rate after two years following resection (primary endpoint) [4]. In endometrial cancer, a chemotherapy may be proposed in the adjuvant setting for high-risk uterine confined disease [5] but also in neoadjuvant setting for localized bulky disease (stage IIIc). In many tumours types, MSI/dMMR status has been associated with a better overall survival and less recurrence in localized tumours [6]. However, the benefit of (neo)-adjuvant chemotherapy is quite different in localized MSI/dMMR tumors. Indeed, many studies suggest that MSI/dMMR status may be a negative predictive factor for the efficacy of chemotherapy. This was suggested in several tumor types especially in adjuvant or neoadjuvant setting. In stage II MSI/dMMR colorectal cancer (CRC) patients, fluoropyrimidine–based adjuvant chemotherapy was demonstrated ineffective [7–9]. The same observations were reported in MSI/dMMR localized gastric cancer (GC) [10–12]. By contrast, MSI/dMMR status is highly predictive of clinical response to ICI in metastatic solid cancers [13]. Indeed, antibodies blocking programmed death-1 (PD-1) or its ligand programmed death-ligand 1 (PD-L1) +/- combined with Cytotoxic T Lymphocyte Associated-4 (CTLA-4) have been investigated in recent clinical trials in metastatic MSI/dMMR cancers [14–16]. Based on these trials, four drugs have already been FDA-approved in metastatic MSI/dMMR tumors: pembrolizumab, dostarlimab, nivolumab and ipilimumab. The ICI's feasibility and safety in the neoadjuvant setting has been proven in several tumor types in phase II studies [16–21]. In localized colorectal cancer (CRC), the phase II NICHE trial (NCT03026140) [19] investigated the role of a neoadjuvant treatment with nivolumab + ipilimumab (ipilimumab 1 mg/kg on day 1 + nivolumab 3 mg/kg on day 1 and day 15) in early-stage CRC, including 21 MSI/dMMR tumors. All patients with MSI/dMMR CRC (20/20; 100%) had a pathological response including 19/20 major response (defined as ≤10% of viable tumor cells) and 12/20 pathological complete response (pCR) (63%; 95% confidence interval (CI) 36–81%) with a complete pathological response (pCR). In contrast, only 3 major pathological responses were observed in 15 proficient MMR (pMMR) CRCs, with two pCRs and one tumor with 1% residual viable tumor. ICI was well tolerated and all patients underwent radical tumor resection without any delay (median time to surgery =32 days (Interquartile range (IQR) 28–35 days)). Most of the studies evaluating the safety and efficacy of a neoadjuvant ICI therapy have been conducted in high-risk resectable melanoma with PD-1 antibody [20–22]. Interestingly, these studies demonstrated the early effect of a single dose of anti PD-1, occurring as soon as 2 weeks after the treatment injection, both at a clinical and biological level [23]. No unexpected adverse events, no delays in surgery or unexpected surgical complications were observed. Some interesting data are also available in other solid tumors [18,24,25], reinforcing the interest in using ICI in resectable tumours. Based on these results, we hypothesized that one cycle of ICI will benefit to patients with MSI/dMMR tumors at early stages, whatever their anatomical origin, by providing a high rate of pathological complete response and ultimately prolonging patient's survival. This work will also provide molecular and immunological data contributing to identify patients who can benefit more from immunotherapy in the neoadjuvant setting with pCR and furthermore those who could avoid surgery in the future.

2. Methods

2.1. Trial design

This study is a prospective, multicenter, phase II clinical trial aiming to include 120 patients with localized MSI/dMMR carcinomas suitable for curative surgery (Fig. 1). A single dose of pembrolizumab (MK-3475, KEYTRUDA®) will be administered in the neoadjuvant setting and patients will be offered adjuvant pembrolizumab (for 1 year) in absence of disease progression. We anticipated including patients in four cohorts according to primary tumor site: colon, endometrium, gastric and other digestive cancers (miscellaneous origin).

2.2. Study objectives

The primary objective is to evaluate the efficacy of pembrolizumab in the pre-operative setting, defined as pCR, in patients with untreated localized/locally advanced MSI/dMMR carcinomas, independently of their anatomical origin. Secondary objectives are to evaluate: safety of the perioperative treatment, post-operative morbidity, R0 resection rate, major pathological response (≤ 10% residual viable tumor) rate, recurrence-free survival (RFS), disease-free survival (DFS), overall response rate (ORR) at 4 weeks after the injection of pre-operative pembrolizumab, overall and progression-free survivals (OS and PFS) and quality of life (QoL). The objectives of the ancillary program are to assess molecular and immunological predictive biomarkers of pCR and compare the data according to the primary tumor site.

2.3. Study endpoints

Primary endpoint will be the rate of complete pathological response (pCR) defined as 0% viable tumor cells according to central pathological review (F.B.).

Secondary endpoints are:

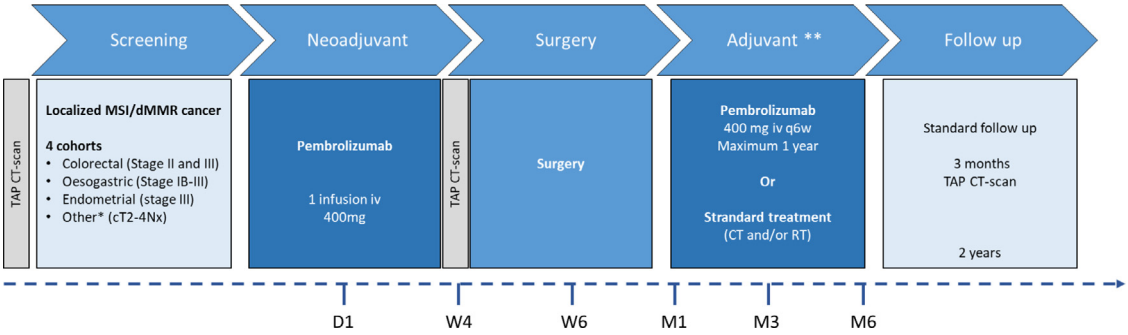

Fig. 1. Timeline and summarized study protocol.
*Biliary tract or pancreas adenocarcinoma, small bowel adenocarcinoma (duodenum, jejunum, ileum). ** Adjuvant therapy depending on localization and ypTN and/or 4-week CT-scan / MRI / endoscopy. D: day; W: week and M: month.

- Safety profile, determined using the National Cancer Institute – Common Terminology Criteria for Adverse Event (NCI-CTC AE) grading scale version 5. Adverse events will be described by their intensity and severity.
- Rate of surgical complications (post-operative morbidity) assessed according to modified Clavien Dindo scoring.
- Percentage of patients with R0 resection.
- Percentage of patients with major pathological response ($\leq$ 10% residual viable tumor).
- Recurrence-free survival, defined as the time from the date of first study treatment administration to the date of first documented recurrence (second cancer are excluded).
- Percentage of patients with objective response at 4 weeks (complete or partial response) after neoadjuvant pembrolizumab, according to RECIST v1.1.
- Percentage of patients with second cancer.
- OS, defined as the time from the date of first study treatment administration to the date of death due to any cause.
- PFS, in patients with recurrence, defined as the time from the date of end of treatment to the date of first documented progression in case of unresectable disease.
- Quality of life (QoL) assessed using the EORTC QLQ-C30 (baseline, before surgery and at 3 and 6 months after surgery).

2.4. Sample calculation

We built our hypothesis on the gastric cancer's data, where a recently published meta-analysis showed a 6.74% average pathological complete response (pCR) rate in gastric or gastroesophageal junction cancer treated with neoadjuvant and radical surgery (range: 3%–15%) [49]. Furthermore, in the FLOT4 phase III randomized study, Al-Batran reported a 25% of pT0/pT1 tumors with the FLOT regimen (versus 15% with ECF; $p = 0.001$) [50]. In localized colon or endometrial cancer, as surgery-first is the standard of care, we have scarce data about neoadjuvant treatment efficacy. We also used the NICHE study results where the complete pathological response rate in MSI/dMMR colon cancer was 60% [35; 51]. A sequential Bayesian design will be used to allow continuous monitoring of the primary endpoint and update knowledge gradually. This approach will enable stopping a cohort as early as possible if no sufficient activity is shown. The successive estimation of the predictive probabilities of efficacy according to the Bayesian inference has no impact on the type I error inflation. Consequently, the number of patients to be included depends on the number of interim analyses. Sample size will be thus evaluated by analogy with an A'Hern's single stage phase II design with P0=25%, P1=50% and 85% power, leading to the inclusion of a maximum of 30 patients by cohort [26]. For each cohort, interim analyses are planned after 6-week follow-up of the first 10 patients (i.e. after surgery) and then every 10 patients. Early stopping will be recommended if there is a high posterior probability ($\geq$90%) given observed data that the rate of complete pathological response is lower than 50%. If no early stopping occurs until the maximum sample size is reached, treatment will be considered worthy for further evaluation if the predictive probability that the complete pathological response rate is higher than 50% is high enough.

2.5. Inclusion and exclusion criteria (Table 1)

All patients (18 years and older, ECOG-performance status 0–1) with histologically proven MSI/dMMR localized non-metastatic tumor included in one of the four cohorts (Table 1):

- Colorectal Cancer (cT3/T4 N0 M0 ou cT N+ M0) or,
- Oesogastric (gastric, gastro-oesophageal or oesophageal) adenocarcinomas (cT2 to cT4 N0/+ M0) or,
- Endometrial carcinoma (stage III) or,
- Other tumor types (cT2 to cT4 N0/+ M0 on TAP CT-scan and echo-endoscopy): biliary tract or pancreas adenocarcinoma and small bowel adenocarcinoma (duodenum, jejunum, ileum).

The MSI/dMMR status will be established by both techniques: immunohistochemistry (IHC) [MMR protein expression] and polymerase chain reaction (PCR) and validated by coordinator's team. MMR proteins expression will be assessed using IHC with four antibodies (anti-MLH1, anti-MSH2, anti-MSH6 and anti-PMS2) and microsatellite instability by PCR (pentaplex panel is recommended: BAT-25, BAT-26, NR-21, NR-24, and NR-27) prior to screening. Loss of MLH1 and PMS2 / or MSH2 and MSH6 / or MSH6 alone / or PMS2 alone protein staining by IHC indicates dMMR, and tumor with $\geq$ 2 unstable markers among 5 microsatellite markers analyzed on PCR (BAT25, BAT26, NR21, NR24, and NR27) proves MSI/dMMR status.

2.6. Procedure

Pembrolizumab will be administered intravenously (iv) at the dose of 400 mg according to recent summary of product characteristics (SPC). A single dose will be administered 6 weeks before the planned surgery. Based on the established exposure-response relationships for pembrolizumab over a 5-fold dose range (2 mg/kg every 3 weeks, Q3W) with similar clinical efficacy and safety of 400 mg every 6 weeks (Q6W) across tumor types [27], the surgery was planned 6 weeks after pembrolizumab infusion. In oesogastric MSI/dMMR cancer, if no tumor regression or downstaging is observed on the 4-week CT-scan/gastroscopy after preoperative pembrolizumab, the standard neoadjuvant chemotherapy (FLOT regimen) could be administered according to investigator's and coordinator's choice. Surgery will be performed during the 6th

Table 1
Inclusion and exclusion criteria for IMHOTEP trial.

Key inclusion criteria	Key exclusion criteria
■Age ≥18 years	■MSS/pMMR tumors
■ECOG-Performance status 0 to 1	■Metastatic disease (stage IV).
■Histologically proven locally advanced non-metastatic tumor included in one of the 4 cohorts:	■Know to active TBC, HBV, HCV
Colorectal Cancer (cT3/T4 N0 M0 ou cT N+ M0 on thoraco-abdomino-pelvic (TAP) computed tomography (CT) scan and echo-endoscopy) OR	■Active HIV with CD4 count < 400 cells/mm3
Oesogastric (gastric, gastro-oesophageal or oesophageal) cancer (cT2 to cT4 N M0 on TAP CT-scan and echo-endoscopy) OR	■Active systemic autoimmune disease
Endometrial carcinoma (stage III) OR	■Interstitial lung disease
Other tumor types (cT2 to cT4 N M0 on TAP CT-scan and echo-endoscopy): biliary tract or pancreas adenocarcinoma, small bowel adenocarcinoma (duodenum, jejunum, ileum), peritoneum adenocarcinoma	■History of severe hypersensitivity to another monoclonal antibody.
■ MSI/dMMR established by IHC and PCR	■Immunosuppressive therapy or corticosteroids (in dosing exceeding 10 mg daily of prednisone equivalent) within the last 2 months before inclusion.
■Adequate bone-marrow, hepatic, and renal functions	■Active infections.
■Patients of childbearing potential accepting to use effective contraceptive measures	■Radiotherapy within the 2 weeks before inclusion.
	■Live vaccine within 30 days prior to the first dose of study drug.
	■Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
	■Pregnant or breastfeeding woman or patient expecting to conceive or father children within the projected duration of the study.
	■Ongoing anti-cancer treatment for another cancer

week after pembrolizumab injection. The study protocol is summarized in Fig. 1.

Adjuvant pembrolizumab will be administered depending on the tumor response on the 4-week CT-scan/MRI/endoscopy, the pathological stage (ypTNM), the tolerance of pre-operative treatment and the ability of the patient to receive the treatment regarding his general post-operative condition.

2.7. Follow up

Patients will be followed-up during 36 months (except in the case of consent's withdrawal): at 1, 3, and 6 months after surgery, and then as recommended by national guidelines (https://www.snfge.org/tncd), with at least a TAP CT-scan every 3 months during the first 2 years. Survival status and date of first recurrence (if applicable) will be updated for all patients once a year until final analyses. Final data will be analysed and the report will be prepared after the end of study visit of the last patient.

2.8. Adverse events

International Conference on Harmonization (ICH) Guidelines for Good Practice requires that both investigators and sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical studies. An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. A value outside the normal or reference range in a routine safety assessment, such as clinical laboratory, vital signs or ECG, may be considered as an adverse event if they are considered medically relevant by the investigator: i.e. symptomatic, requiring corrective treatment, leading to IMP discontinuation/dose modification (reduction and/or delay), and/or fulfilling a seriousness criterion. A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that at any dose results in death is life threatening requires new and prolonged inpatient hospitalization, results in persistent or significant disability/incapacity, is congenital anomaly/birth defect or, any other significant medical condition.

2.9. Translational research

All patients included in the trial will participate to ancillary research program. Blood samples will be collected at inclusion (before first pembrolizumab injection), just before surgery (D-1), at one-month post-surgery (before the first adjuvant injection) and at recurrence.

We will investigate by multi-parametric flow cytometry, the impact of treatment on the frequency of main peripheral immune populations and on the expression of immune checkpoints (inhibitory or stimulatory) on T cell subsets. The impact of treatment on the modulation of peripheral cytokines will be assessed using multiplex (Luminex®). We will also investigate during treatment circulating tumor DNA (ctDNA) (MSI/dMMR) in order to identify if ctDNA is predictive of treatment efficacy and disease recurrence.

Available tumor tissue (archival FFPE block) from pre-treatment biopsies of the primary tumor and from surgical specimens will be collected. Whole exome sequencing and RNAseq will be performed to investigate gene expression involved in anti-tumor response, immune gene signature associated with tumor response/resistance, and tumor mutational burden (TMB).

The objectives of this ancillary program are double: (i) to assess molecular and/or immunological biomarkers before and in the course of treatment that can predict the response and/or resistance to pembrolizumab, (ii) to compare the data according to the primary tumor site.

2.10. Data analysis

Methodology and analysis details will be provided in the Statistical Analysis Plan (SAP), which will be compiled, reviewed and signed off prior to the end of the data management process. Statistical analyses will be performed using SAS® software version 9.4 or later. Qualitative variables will be described using frequency and percentage distributions. The number of missing data will be given, but will not be considered for the calculation of proportions. Quantitative data will be described using the number of observations, mean, standard deviation, median, minimum and maximum values. To perform Bayesian analysis, we assume the pCR rate to be a

random variable following a binomial distribution Bin (n, p) where n is the sample size and p is the true underlying pCR rate. Conclusions and inferences will be conducted on p. The prior distribution of p (representing the knowledge of the pCR rate probability prior to observing the data) will be pre-specified. We assume the prior distribution of p follow a Beta (a,b). Thus, the posterior distribution of p, after observing a certain number of patients m will be estimated from a beta-binomial model [26]: Beta(a+s, b+m-s), where s is the observed number of success among the m patients observed. For each cohort, interim analyses will be planned after 6-week follow up of the first 10 patients (i.e. after surgery) and then every 10 patients. Based on the observed data, the prior distribution of the success will be updated and refined at each interim analysis to obtain the posterior distribution, allowing the estimation of the mean pCR rate with its 95% credible interval (measure of Bayesian precision). At each update of the distribution (every 10 patients), a futility stopping rule will recommend to stop the cohort if there is a high predictive probability that the estimated pCR rate is lower or equal to the futility boundary p0 = 50%: PR (pathological response$\leq$50) $\geq$90%. It means that most of the distribution (90% of it) falls to the left hand side of 50%, indicating that it is very likely that the effect is at best 50%. Sensitivity analyses according to different prior distributions will be performed in order to see the impact of initial distribution Beta (a,b) on interim decision. The study will continue until the stopping rule applied at each interim analysis is not met, or until the maximum sample size is reached. The prior density function and posterior distribution of the true pCR rate across successive interim analyses will be displayed graphically.

Post-operative morbidity rate, R0 resection rate, major pathological response rate, overall response rate before surgery and rate of second cancer will be described using percentages and presented associated with their 95%CI intervals. The Kaplan-Meier (KM) approach will be used to estimate median PFS and OS. Median PFS and OS as well as survival rates at specific timepoints will be presented together with their 95% CI.

2.11. Ethical and regulatory aspects

The study sponsor is the center Léon Bérard (Lyon, France). The study was registered under EudraCT 2020–004957–62 number. This trial is conducted in accordance with the ethical principles of the Helsinki declaration of 1964 and its subsequent revisions and with good clinical practice of the international conference on harmonization (ICH–E6, 17/07/96). The protocol received approval from French ethic committee on 28/05/2021 and from the ANSM on 09/09/2021.

3. Discussion

In MSI/dMMR localized cancers, neoadjuvant/perioperative ICI administration seem to be a promising strategy in order to improve cure, due to high pathological complete response rate observed with these agents in preliminary studies [19,28–30]. However, until now, data are scarce, relying mainly on post-hoc analyses and prospective studies are needed. Furthermore, several challenging questions remain opened in MSI/dMMR tumors, especially (i) how to evaluate tumor response in the localized setting? (ii) is the evaluation with RECIST criteria as valuable with ICI as with chemotherapy?, (iii) how is it possible to predict complete pathological response? Conversely, to metastatic cancers, evaluating tumor response (RECIST 1.1 or iRECIST) in localized cancer is challenging. In the preoperative setting, clinical response (improvement of baseline symptoms), endoscopic considerations and CT-scan showing no progressive disease remain imperfect. In the post-operative setting, tumor response is analysed according to ypTNM stage and tumor regression grade (TRG). The most important factor affecting long-term survival after peri–operative treatment is still unknown but the ypN stage is a major determinant of outcome in many tumor locations. Using only objective response rate (ORR) to evaluate tumor shrinkage and antitumor activity may significantly underestimate the benefits derived from neoadjuvant therapy especially in localized gastrointestinal cancers. Disease-free survival seems preferred to ORR because more correlated to OS. However, timelines to obtain enough events can be long to obtain in dMMR/MSI tumours with good prognosis, and early markers of treatment efficacy are needed to improve standard of care. As in lung cancer [31], we planned to standardize pathological response by assessing the percentages of (1) viable tumor, (2) necrosis, and (3) stroma (including inflammation and fibrosis) with a total adding up to 100%, which can be used for all systemic therapies. Indeed, major pathological response seems to play an important role in long-term survival and it could predict overall survival as a surrogate marker [32,33]. Several studies showed discrepancies between morphological and histological findings after neoadjuvant immunotherapy, with observations of complete pathological responses in cases with residual disease on preoperative CT-scan [18,23,29]. These observations suggest that radical surgical decision cannot be based only on RECIST or iRECIST criteria, our objective being to identify patients with complete tumor response, in order avoiding to operate them. Translational researches are mandatory to find potential biomarkers that may predict pCR and more sensitive than morphological (CT-scan/MRI/PET) monitoring. This trial offers the opportunity to evaluate potential predictive biomarkers associated with pathological tumor response and/or resistance to neoadjuvant pembrolizumab, such as tumor mutational burden, gene expression, MSI score, peripheral immunological markers and circulating tumor DNA (ctDNA). In addition, the data from these different analyses could allow us to identify predictive biomarkers associated with the response in MSI tumors regardless of the primary site of the tumor. The use of ICI as a neoadjuvant treatment in MSI/dMMR cancers showed in recent studies that preoperative immunotherapy could achieve a high rate of pathologic major or complete response in potentially resectable neoplasms and eventually provide a chance to cure the tumor regardless of surgery. As well as in the phase II NICHE trial [19], toripalimab, with or without celecoxib was evaluated in the neoadjuvant setting for resectable dMMR/MSI-high colorectal cancer [28]. The authors showed that 15/17 patients (88% [95% CI 64–99]) in the toripalimab plus celecoxib group and 11/ 17 patients (65% [38–86]) in the toripalimab monotherapy group had a pathological complete response [28]. In a case report series of six patients with resectable locally advanced (cT4N+) MSI gastrointestinal cancers (n = 4 gastric and n = 2 colorectal cancers) treated with anti-PD-1-based regimens (50% received chemotherapy regimens associated to ICI), radical surgery was performed in all of the 6 patients [34]. Among them, 5 (87%) achieved a pCR, whereas the single patient with no pCR had a heterogeneous mixed dMMR-pMMR cancer [34]. The results of a retrospective series of patients with stage IV metastatic MSI colorectal cancer, showed pCR in 13 out of 14 resected metastases and even after a short-duration therapy [29]. Even more recently, the NEONIPIGA phase II trial evaluated neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients with localized MSI/dMMR oeso-gastric adenocarcinoma [30]. Among the 29 patients who underwent surgery 17/29 (59%) had pCR [30]. These results suggest that neoadjuvant ICI in MSI/dMMR tumors may be definitive without need for surgical resection if pCR may be predicted earlier. Several phase II studies are currently exploring the use in the neoadjuvant setting of ICI in the neoadjuvant/adjuvant setting of MSI tumors especially in gastric cancers (NCT04006262, NCT04817826 and NCT04152889). Our study will

provide early results in other digestive tumor types less frequent than colon and gastric cancers.

In conclusion, neoadjuvant pembrolizumab appears as a promising therapeutic approach in MSI/dMMR localized tumors. The goal of neoadjuvant pembrolizumab is to increase tumor responses, induce complete pathological responses, ease the surgeries (especially in delicate locations as rectum and gastric tumors) and cure patients. IMHOTEP study is a tumor agnostic trial on perioperative pembrolizumab that will provide valuable results both on clinical and biological sides. In the long-term perspective, translational analyses of the IMHOTEP trial aim to identify in which patients surgical intervention will remain necessary.

Declaration of Competing Interest

CC declares a consulting and advisory board for Amgen, Servier, and received honoria from Servier, Amgen. TA received honoraria from Servier, Pierre fabre, Amgen, AstraZeneca and declares consulting for Bioven, Servier, SIRTEC, MSD. RC received honoraria from MSD Oncology, Pierre Fabre, and Bristol-Myers Squibb, declares consulting from Exeliom Biosciences, Enterome Bioscience and received research funding from Servier Institute. OD received honoraria from Amgen, Sanofi, Merck Serono, MSD, Servier, Ipsen, Keocyt and declares consulting for Merck Serono, Sanofi, MSD, AstraZeneca, Novartis. LE declares consulting for BMS and Servier. FG declares research grant from Roche, AstraZeneca and consulting for Astrazenca, Roche, Sanofi, BMS, MSD, Merck-Serono, Amgen. EL declares consulting for Roche, Servier, Ipsen, Bayer, BTG, MSD. CN received honoraria from Amgen, AstraZeneca, Baxter, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences, Merck, MSD, Mylan, Novartis, Nutricia, Pierre Fabre, Roche, Sanofi, Servier and research funding from Roche. ES received honoraria from Servier, Amgen, Merck Serono, MSD, Pierre Fabre Oncology BMS, Sanofi, Research funding from Bayer, and declares consulting for Pierre Fabre Oncology. YT declares honoraria from MSD, Astra Zeneca, Bayer, Amgen, Servier, Ipsen, Pierre Fabre, AAA and consulting for Merck. DT received honoraria from Amgen, Roche, Sanofi, Bristol-Myers Squibb, Merck Serono, MSD, Bristol-Myers Squibb, Servier/Pfizer, Ipsen, research funding from AstraZeneca, SERVIER, Roche, MSD, BTG, and declares consulting for Sanofi, MSD, Pierre Fabre, and AstraZeneca. A.Z. declares consulting and/or advisory boards for Amgen, Lilly, Merck, Roche, Sanofi, Servier, Baxter, MSD, Pierre Fabre, Havas Life, Alira Health, Zymeworks, and Daiichi. CDLF received honoraria from Amgen, Astra- Zeneca, Bayer, Bristol-Myers Squibb, Eisai, Incyte Biosciences, Ipsen, Lilly, Merck Serono, MSD, Pierre Fabre Oncologie, Pfizer, Roche, Sanofi-Aventis, Servier. FB, MBZ, SK, EC, PR and ES declares no conflicts of interests.

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