SYNOPSIS

Title	**FFCD 1703 - POCHI** **PEMBROLIZUMAB IN COMBINATION WITH XELOX OR FOLFOX BEVACIZUMAB IN PATIENTS WITH MICROSATELLITE STABLE (MSS) METASTATIC COLORECTAL CANCER AND A HIGH IMMUNE INFILTRATE: "A PROOF OF CONCEPT STUDY"**
Sponsor	French Federation of Digestive Oncology (FFCD)
Design	A single arm, open-label, multi-centre phase II study
Study objectives	**Primary objective:** To evaluate the efficacy of pembrolizumab in combination with XELOX or FOLFOX and bevacizumab as 1st line treatment of microsatellite stable (MSS) metastatic colorectal cancer (mCRC) with a high immune infiltrate. Efficacy will be determined by analysis of the number of patients alive and without radiological and/or clinical progression at 10 months (based on RECIST 1.1 criteria evaluated by the investigator). **Secondary objectives:** - Overall survival (median) - Serious adverse events evaluated according to NCI-CTC v4.0 - Histological response in case of secondary resection (TRG criteria) - Secondary resection rate (R0 and R1) - Outcome of tumour markers (CEA and CA19.9) **Evaluated according to the investigator and centralised review (according to RECIST V1.1 criteria):** - Percentage of patients alive and without radiological progression at 10 months (centralised review) - Progression-free survival (median) - Time to radiological progression - Time to objective response - Best response during treatment - Depth of response - Early tumour shrinkage at 9 weeks **Evaluated according to centralised review according to iRECIST criteria:** - Percentage of patients alive and without radiological progression at 10 months - Progression-free survival (median) - Time to radiological progression - Early tumour shrinkage at 9 weeks Exploratory analyses of primary and secondary endpoints will also included investigation of prognostic and predictive values according to sub-classes of Immunoscore® and TuLIS score for all patients with the following criteria: - Percentage of patients alive and without progression at 10 months - Progression-free survival - Overall survival - Best response during treatment
Criteria for inclusion	- Age ≥ 18 years - Both MSS and pMMR metastatic colorectal adenocarcinoma (metachronous or synchronous metastases), histologically proven - Patients who have had adjuvant/post-operative chemotherapy and/or post-operative radiotherapy for the treatment of their primary tumor or R0 resected metastatic lesions can be included if they have a recurrence more than 6 months after the end of this treatment. High immune response defined as the immune infiltration score obtained

	on the primary tumour (resection of primary tumour containing at least 2 mm of tumour-free margin between the tumour and non-tumour area) - Unresectable cancer with at least one measurable metastatic target according to RECIST v1.1 criteria - WHO PS ≤ 1 - Absence severe neuropathy (≥ grade 2) (chemo-induced or not) - Life expectancy ≥ 3 months - Adequate haematological function: neutrophils ≥ 1,500 /mm^3, platelets ≥ 100,000/mm^3, Hb > 9 g/dL - Adequate liver function: AST/ALT ≤ 5xULN, total bilirubin ≤ 2xULN, Alkaline phosphatase ≤ 5xULN - Creatinine clearance ≥ 50 mL/min according to the CKD-EPI formula - Proteinuria <2+ (dipstick urinalysis) or ≤1g/24hour - Patient who is a beneficiary of the social security system - Information provided to patient and signature of the informed consent form
Criteria for non-inclusion	- Active infection requiring intravenous antibiotics at day 1 of cycle 1 - Active or untreated central nervous system metastases - Another concomitant cancer or history of cancer during the last 5 years, except for carcinoma *in situ* of the uterine cervix or a basal cell or squamous cell skin carcinoma or any other carcinoma *in situ* considered as cured - Previous bone marrow allogenic stem cell transplantation or previous organ transplantation - History of idiopathic pulmonary fibrosis, medicinal product-related pneumonia or proof of active pneumonia or pneumonitis on a chest CT-scan prior to therapy - HIV infection, active hepatitis B or C infection, active tuberculosis - Colorectal cancer with microsatellite instability (dMMR and/or MSI) - Patient eligible for curative treatment (resection and/or thermal ablation according to the opinion of the local multidisciplinary tumour meeting board) and patient with *RAS* wild-type tumour for whom a tumour shrinkage with an anti-EGFR is necessary to perhaps obtain a downstaging for a secondary surgery (according to the opinion of the local multidisciplinary tumour meeting board and/or at investigator's discretion) - Patient with only primary tumour biopsies available or only a sample of a metastasis (no surgical resection of the primary tumour) - Previous treatment with anti-PD1 or anti-PDL1 or another immunotherapy - An auto-immune disease which may worsen during treatment with an immune-stimulating agent (patients with type I diabetes, vitiligo, psoriasis, hypo or hyperthyroidism not requiring immunosuppressant therapy are eligible) - Long-term immunosuppressant therapy (patients requiring corticosteroid therapy are eligible if administration at a dose ≤ 10 mg prednisone equivalent dose per day, administration of steroids by a route of administration resulting in minimal systemic exposure (cutaneous, rectal, ocular or inhalation) is authorised) - Known severe hypersensitivity to monoclonal antibodies, to one of the medicinal products used or to one of the excipients in the products used or a history of anaphylactic shock or of uncontrolled asthma - Vaccinations (live vaccine) within 30 days prior to start of treatment - Dihydropyrimidine Dehydrogenase (DPD) deficiency defined by uracilemy level ≥ 16 ng/mL - QT/QTc interval > 450 msec in men and > 470 msec in women - One of the following disorders during the 6 months prior to inclusion: myocardial infarction, unstable/severe angina pectoris, coronary artery bypass grafting, NYHA class II, III or IV congestive heart failure, stroke or transient ischaemic attack - All uncontrolled progressive disorders during the last 6 months: hepatic insufficiency, renal insufficiency, respiratory insufficiency, arterial hypertension - History of an inflammatory digestive disease, obstruction or sub-obstruction not resolved with symptomatic treatment - Peptic ulcer disease not healed before the treatment - Not controlled HTA

	- Patient already enrolled in another therapeutic trial with an ongoing investigational drug or whose treatment ended less than 4 weeks before inclusion - Absence of effective contraception in patients (male and/or female patients) of childbearing potential, a pregnant or breastfeeding woman, women of childbearing potential and who have not had a pregnancy test - Impossibility to submit to medical follow-up of the trial due to geographic, social or psychological reasons - Neo-adjuvant treatment (chemotherapy or radiotherapy) of primary tumor - Concomitant treatment with brivudine or Brivudine within 4 weeks before capecitabine or 5FU initiation - Poor nutritional status (albuminemia < 25 g/l or weight loss > 10% during the last month)
Study treatment	**<u>Investigator will have the choice between treatment with XELOX or FOLFOX plus bevacizumab and pembrolizumab</u>** **<u>Xelox bevacizumab plus pembrolizumab</u>:** - Pembrolizumab: 200 mg by IV infusion over 30 minutes, on day 1 of each cycle - Bevacizumab: 7.5 mg/kg by IV infusion over 60 minutes, on day 1 of each cycle - Oxaliplatin: 130 mg/m² by IV infusion over 2 hours, on day 1 of each cycle - Capecitabine: 2000 mg/m²/day, on day 1 to 14 of each cycle Treatment will be repeated every 3 weeks up until disease progression, unacceptable toxicity or refusal by the patient. **Folfox bevacizumab plus pembrolizumab:** - Pembrolizumab: 400 mg by IV infusion over 30 minutes every 3 cycles (every 6 weeks, at cycle 3, 6, 9, 12…) - Bevacizumab: 5 mg/kg by IV infusion over 60 minutes, on day 1 of each cycle - Oxaliplatin: 85 mg/m² by IV infusion over 2 hours, on day 1 of each cycle - Folinic acid: 400 mg/m² (or 200 mg/m² if Elvorine) IV over 2 hours of each cycle - 5FU bolus: 400 mg/m² IV bolus over 10 minutes of each cycle - 5FU continuous: 2,400 mg/m² IV over 46 hours of each cycle Treatment will be repeated **every 2 weeks** up until disease progression, unacceptable toxicity or refusal by the patient. Except for pembrolizumab, all drugs (capecitabine, oxaliplatin and bevacizumab) will be administered in the setting of its MA (marketing authorisation) in France. Two analysis of safety will be performed: • when 5 patients have been treated for 3 months. • when 10 patients have been treated for 3 months
Rationale for calculation of sample size	One of the specific aspects of this trial is based on determination of immune infiltration scores necessary at time of inclusion. Two different scores (Immunoscore® described by Galon et al. and TuLIS score described by Emile et al.) were used and patients are eligible if one of these two scores is high. About 5% of patients will have a dMMR tumour, 95% a pMMR tumour and 14% will have a high immune infiltrate with CD3+ and/or CD8+ T cells. Thus, 393 patients must be tested in order to include 55 patients in this trial. There are about 20,000 new mCRC per year in France and about 10% are enrolled in therapeutic trials. There is no competitive trial in patients presenting with a mCRC with a high immune infiltrate. The strong scientific rationale for use of an immune checkpoint inhibitor is an additional argument to ensure good recruitment.
Hypothesis and calculation of sample size	The clinical hypotheses for design of the study are as follows: H0: percentage of patients alive and without radiological and/or clinical progression at 10 months of 50% or less is insufficient. H1: percentage of patients alive and without radiological and/or clinical progression at 10 months greater than 50% is expected (treatment efficacy); a 70% rate is hoped.

	With a risk α of 5% (one-sided) and a power of 85%, using an exact binomial method, 50 patients are necessary. Taking into account that 10% of patients will not be evaluable or lost to follow-up at 10 months, 55 patients will have to be included. The conclusion of the study will be defined according to the following rule; on the 50 evaluable patients: if 32 patients or more are alive and without radiological and/or clinical progression at 10 months, then the treatment will be considered effective.
Statistical analysis	The analyses will be performed by modified intention to treat (mITT) on patients included, whatever their eligibility and who have received at least one dose of treatment (whatever the dose and the treatment).
Ancillary study	The ancillary study on biological samples (blood and stool) and tumour samples (primary tumours) will consist at least of analysis of histological (others immune scores, immunohistochemistry of PD-L1 and PD-L2), phenotypal (circulating lymphocytes and gut microbiota) and molecular biomarkers (circulating tumour DNA, mutational load, expression and/or amplification of PD-L1 and PD-L2). The primary objective of these studies is to identify prognostic biomarkers or predictive biomarkers of response to therapy with an immune checkpoint inhibitor. We are seeking to detect an association between the hypermutated characteristic, a high immune response and clinical response to anti-PD1 therapy (pembrolizumab), as described in other tumours.
Number of patients	55 patients
Duration of inclusion and of participation of each patient	Theoretical inclusion rate: 1 or 2 patients per month Theoretical number of centres: 25 centres Start of inclusions: April 2021 Theoretical end of inclusions: 63 months after start of inclusions, i.e. July 2026 Theoretical date of the end of study (analysis of primary endpoint and secondary endpoints): July 2027