Background Immune checkpoint inhibitors (ICI) are very effective in deficient DNA mismatch-repair system (dMMR)/microsatellite instable (MSI) metastatic colorectal cancer (mCRC). About 15% of MSS/pMMR CRCs are highly infiltrated by tumor infiltrating lymphocytes (TIL) with a good prognosis. Some immune scores based on CD3+ and/or CD8+ T-cells infiltration are validated and reproducible, especially TuLIS1 and Immunoscore®.2 No data are available concerning efficacy of ICI in this subpopulation of mCRC. Pembrolizumab, an anti-PD1 (programmed death-1) monoclonal antibody has been recently reported very effective in patients with MSI/dMMR mCRC. Immunogenic cell death induced by chemotherapy, such as oxaliplatin, could increase the efficacy of ICI. We formulated the hypothesis that patients with a pMMR mCRC with a high immune infiltrate can be sensitive to ICI plus oxaliplatin-based chemotherapy.

Methods POCHI is a multicenter, open-label, single-arm phase II trial to evaluate efficacy of pembrolizumab in combination with chemotherapy as first-line treatment of pMMR mCRC with a high immune infiltrate. Primary objective is PFS at 10 months, i.e. number of patients alive and without radiological or/and clinical progression at 10 months evaluated by the investigator. Main secondary objectives are overall survival, secondary resection rate, depth of response and early tumour shrinkage. Main inclusion criteria are pMMR mCRC untreated for metastatic disease and with at least one measurable metastatic target according to RECIST v1.1 criteria. Patients must have resected primary tumor to evaluate two different immune scores (Immunoscore® and TuLIS) and patients are eligible if one score is ‘high’. Patients will receive combination of pembrolizumab (200 mg), bevacizumab (7.5 mg/kg), oxaliplatin (130 mg/m²) and capetcitabine (2000 mg/m²/day, on day 1 to 14). Treatment will be repeated every 3 weeks until disease progression or unacceptable toxicity. The clinical hypotheses are to increase PFS at 10 months from 50% to 70%. With a one-sided type error of 5%, power of 85%, 10% rate of patients lost to follow-up or not evaluable, 55 patients have to be included. If 32 patients or more are alive and without progression at 10 months, the treatment will be considered as effective. Thus, with 15% ‘high’ immune score, about 400 patients must be tested in order to include 55 patients in POCHI trial. The ancillary study will consist to identify predictive biomarkers of response and included expression of PD-L1, circulating lymphocytes circulating tumour DNA, mutational load and gut microbiota. Inclusions will start in September 2020 and theoretical end of recruitment is 2023.