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Abstract

Immune checkpoint inhibitors (ICI) have high efficacy in metastatic colorectal cancer (mCRC) with microsatellite instability (MSI) but not in microsatellite stable (MSS) tumour due to the low tumour mutational burden. Selective internal radiation therapy (SIRT) could enhance neoantigen production thus triggering systemic anti-tumoral immune response (abscopal effect). In addition, Oxalipatin can induce immunogenic cell death and Bevacizumab can decrease the exhaustion of tumour infiltrating lymphocyte. In combination, these treatments could act synergistically to sensitize MSS mCRCs to ICI

SIRTCI is a prospective, multicentre, open-label, phase II, non-comparative single-arm study evaluating the efficacy and safety of SIRT plus Xelox, Bevacizumab and Atezolizumab (anti-programmed death-ligand 1) in patients with liver-dominant MSS mCRC. The primary objective is progression-free survival at 9 months. The main inclusion criteria are patients with MSS mCRC with liver-dominant disease, initially unresectable disease and with no prior oncologic treatment for metastatic disease. The trial started in November 2020 and has included 10 out of the 52 planned patients.

Keywords:

Colorectal cancer, Immune checkpoint inhibitor, Liver metastases, Selective internal radiation therapy

Abbreviations

No keyword abbreviations are available

1 Background

About 50% of patients with colorectal cancer (CRC) will develop a metastatic disease. The majority of patients have unresectable metastatic disease and unresectable liver-dominant disease represents 25% of all metastatic CRCs (mCRCs). Morbidity and mortality in patients with a mCRC are mainly due to unresectable liver metastases [1]. In the first-line setting the recommended treatment for mCRC is Oxaliplatin- and/or Irinotecan-based chemotherapy associated with targeted therapy according to *KRAS* status [2,3]. Selected patients could also receive triplet chemotherapy or intra-arterial chemotherapy plus targeted therapy. In this setting, median progression-free survival (PFS) of mCRC patients with unresectable disease is about 10 months and median overall survival (OS) around 30 months [4–6]. Bevacizumab improves clinical outcomes when combined with any of the fluoropyrimidine and oxaliplatin and/or irinotecan

combinations (FOLFOX/XELOX, FOLFIRI or FOLFOXIRI) as well as with single-agent 5-FU or capecitabine [7]. Hepatic intra-arterial treatments have not proven their efficacy in first-line treatment in patients with unresectable liver-dominant disease as phase III trials concerning hepatic intra-arterial chemotherapy with 5FU or FUDR are obsolete considering the standard treatment and not conclusive in a meta-analysis [8], and a phase III with oxaliplatin is still ongoing [9], and selective internal radiation therapy (SIRT) has failed to increase OS [10,11].

Tumour progression involves the escape from immunosurveillance mainly through the activation of immune checkpoint inhibitory activity. An immune checkpoint inhibitor (ICI) mediated by programmed death-1 (PD-1), Pembrolizumab, was recently approved as first-line treatment of mCRC with deficient mismatch repair system/microsatellite instability (dMMR/MSI) [12]. ICIs have high efficacy in hypermutated tumours, which produce many tumour neoantigens such as dMMR/MSI mCRC. Chemotherapy with the targeted agent remains the standard of care in mCRCs with proficient mismatch repair system/microsatellite stability (pMMR/MSS), which do not respond to ICIs due in part to the low level of tumour neoantigens. Some therapies seem to be able to convert a "non-immunogenic" neoplasm into an "immunogenic" neoplasm. ICIs were first proposed in combination with radiotherapy due to noted abscopal effects, where local radiation induces immunogenic cell death and systemic immune-mediated anti-tumour response distant from the irradiated lesion, called abscopal effects [13–15]. Local radiation induces an anti-tumour immune responses by promoting recruitment and activation of T cells within the tumour microenvironment [13]. Palliative radiotherapy given concurrently with an ICI in patients with melanoma has caused regression of the targeted irradiated lesion as well as marked abscopal effects with regression of distant metastases [16,17]. The combination of local radiotherapy and immune-modulation can increase local tumour control and cause distant anti-tumour effects (abscopal effects) through diverse mechanisms: increased tumour-antigen release and cross-presentation, improved dendritic-cell function, enhanced T cell priming, improved trafficking of lymphocytes into the tumour microenvironment and inducing positive immunomodulatory pathways [14,15]. In a phase I trial, ICI plus radiation of one metastatic site in 35 patients with chemoresistant cancers, including four patients with mCRC, demonstrated a 33% clinical benefit (defined as partial response or stable disease lasting ≥6 months) outside the radiation field [18]. A recent phase II study evaluated abscopal effects of ICI after radiation in patients with chemoresistant pMMR mCRC and demonstrated an increase in systemic anti-tumour immune response and a regression of non-irradiated lesions [19]. All of these results support the hypothesis that radiation can allow the tumour to become sensitive to ICI and that ICI can increase abscopal the anti-tumour effects of radiation.

SIRT, also called radioembolization, which involves the injection of Yttrium-90 (Y90) microspheres (SIRSphere® and TheraSphere®) into the hepatic artery of patients with unresectable liver tumours, showed significant efficacy in liver-dominant mCRC. In the first-line setting in patients with liver-dominant mCRC, adding SIRT to chemotherapy (FOLFOX ± Bevacizumab) was well-tolerated and demonstrated significantly delayed disease progression in the liver but unfortunately with no OS improvement [10,11]. By contrast, in chemoresistant mCRC with liver dominant-disease, SIRT demonstrated an improvement in OS as compared to chemotherapy alone [20] and is officially approved in Europe. SIRT has shown significant abscopal effects [21]. SIRT, with average estimated tumour doses of 200–300 Gy, offers a powerful means of eliciting an immune response. In addition, the embolization portion of radioembolization offers a second means of creating cell death and generating a pro-inflammatory environment.

Bevacizumab has immunomodulatory properties including the increased trafficking of T cells into tumours, and a reduction of suppressive cytokines, infiltrating T regulatory cells and myeloid-derived suppressor cells and it yields decreased CD8 T cell exhaustion, as well [22–25] Oxalipatin has been shown to increase immunogenic tumour cell death and sensitizes tumours to checkpoint blockade therapy [26]. In a recent randomized phase II trial, the addition of an ICI, Atezolizumab (anti-programmed death-ligand 1, anti-PD-L1) to Capecitabine and Bevacizumab resulted in prolonged PFS in the 82 patients with a chemoresistant mCRC receiving the three therapies, as compared with 46 patients receiving chemotherapy only (4.4 months versus 3.3 months) [27,28]. Finally, all of these data suggest a synergistic effect of SIRT, Bevacizumab, Oxaliplatin and ICI combination to convert a "non-immunogenic" pMMR/MSS mCRC into an "immunogenic" neoplasm.

The aim of the SIRTCI trial is to demonstrate the synergistic anti-tumour efficacy of SIRT, ICI, Oxaliplatin and Bevacizumab in patients with unresectable liver-dominant mCRC so as to obtain high tumour regression of both hepatic and extra-hepatic diseases, using immunogenic cell death and abscopal effects.

2 Design

2.1 Study objectives and endpoints

The primary endpoint is PFS at 9 months according to response evaluation criteria in solid tumours (RECIST) 1.1 criteria evaluated by the investigators. PFS is defined as the time interval between date of inclusion and date of first radiological progression according to RECIST1.1 or death, whichever comes first. Patients alive and without progression will be censored at the date of last follow-up exam. PFS at 9 months is defined as the percentage of patients alive and without radiological progression (either hepatic or extra-hepatic) 9 months after inclusion using RECIST v1.1 criteria.

Secondary endpoints are: safety profile according to common terminology criteria for adverse event v4.0 (CTCAE), median PFS, hepatic PFS (time interval between inclusion and first liver progression), extra-hepatic PFS (time interval between inclusion and first extra-hepatic progression), best response rate over all time point assessments, and overall response rates (ORR) at weeks 9, 18 and 27. These criteria will be evaluated according to the RECIST 1.1 and immune-RECIST (iRECIST) criteria, not only by the investigators, but also by central review [29]. Other secondary endpoints are OS, early tumour shrinkage (defined as a response >20% at week 9), depth of tumour response (defined as the percentage of tumour shrinkage observed at the nadir of the response), secondary resection rate, time to treatment strategy failure (defined as the time between inclusion and the date of definitive stop of the experimental treatment) and biomarker analyses (see ancillary studies).

2.2 Ancillary studies

Blood, stool, and tumour samples will be collected in order to identify predictive factors of treatment response, prognostic factors and/or biomarkers of treatment toxicity. Each biomarker will be correlated with primary endpoint (PFS at 9 months) and with several secondary endpoints (median PFS according to RECIST 1.1 and iRECIST criteria, OS and ORR).

Biomarker analysis of the tumour (immunohistochemistry (IHC) and/or tumour DNA) will include mutational status analysis (at minimum *RAS, BRAF* and consensus molecular subtype classification), tumour mutation burden (TMB) determination and immune response analysis (expression at least of CD3, CD4, CD8, FoxP3, CD20, PD-L1, PD1 and immune scores).

Blood samples to analyse pharmacokinetics of Atezolizumab will be collected at cycles 1, 2, 5 and 8. Blood samples for circulating tumour DNA (ctDNA) analysis will be collected before first, second and third cycle of treatment and at progression. Systemic immune response (soluble PD-L1 and blood leucocyte subpopulations) will be analysed through blood samples collected before the first and the fourth cycle.

Stool samples will be collected prospectively in all patients (before treatment and at week 9 before the first evaluation of treatment efficacy) to analyse microbiota (16S rRNA sequencing).

All radiological evaluations will be collected to be reviewed (centralized review) and for radiomic analyses including all CT-scan (every 9 weeks) and MRI (before treatment and at week 36) until progression. Y90 positron emission tomography-computed tomography (PET-CT) will be performed within 24 h after the SIRT and a (18)F-fluorodeoxyglucose (FDG) PET-CT will be performed before treatment and at weeks 9 and 18 for correlation with treatment efficacy and toxicity.

2.3 Population and patient selection

The main inclusion criteria are histologically proven pMMR/MSS mCRC with liver-dominant non-resectable disease (Table 1). Liver-dominant disease is defined as up to 6 extra-hepatic lesions (only peritoneal lesions are not allowed) if asymptomatic and without organ dysfunction. Patients must have initially unresectable disease according to the local multidisciplinary team and be eligible for SIRT according to the radiologist's opinion. No prior oncologic treatment for metastatic disease is allowed (i.e. chemotherapy, radiotherapy or investigational drug).

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Table 1

Main inclusion and exclusion criteria.

Inclusion Criteria
- Age ≥18 years. - Histologically proven mismatch repair proficient metastatic colorectal cancer (pMMR and/or MSS). - Liver-dominant disease with up to 6 extra-hepatic lesions (only peritoneal lesions are not allowed) if asymptomatic and without organ dysfunction. - Measurable disease according to RECIST 1.1 criteria. - Patient with initially unresectable disease according to the local multidisciplinary team and eligible for radioembolization according to the radiologist's opinion. - Tumour volume <50% of total liver volume. - No prior oncologic treatment for metastatic disease (i.e. chemotherapy, radiotherapy or investigational drug). Patients may have received adjuvant chemotherapy or (neo)adjuvant radiochemotherapy to the pelvis (tumour of the rectum), but the last dose of chemotherapy/radiotherapy must be administered at least 6 months prior to entry into this study. - WHO performance status ≤1. - Estimated life expectancy ≥3 months. - Adequate haematological function (neutrophils ≥1500/mm^3, platelet count ≥100,000/mm^3, haemoglobin >9 g/dL) - Adequate hepatic function (AST and ALT ≤5 x ULN, total bilirubin ≤2 x UNL, alkaline phosphatase ≤5 x ULN) - Adequate renal function (creatinine clearance ≥50 ml/min according MDRD formula)
Exclusion Criteria
- Positive tests for HIV or other immunodeficiency syndromes, active hepatitis B or hepatitis C and active tuberculosis. - Active autoimmune disease. - Bone marrow allograft or solid organ transplant history. - Symptomatic or untreated central nervous system metastasis. - Concomitant or previous malignant disease, except adequately treated in situ carcinoma of the uterine cervix, basal or squamous cell carcinoma of the skin, or cancer in complete remission for ≥5 years. - History of idiopathic pulmonary fibrosis, evidence of active pneumonitis on screening chest CT-scan and any severe chronic respiratory insufficiency. - Patient with contraindication to angiography and/or selective hepatic catheterization such as coagulopathy with serious bleeding risk that is not correctable by usual therapy of haemostatic agents. - Patients on anticoagulant therapy different from LMWH cannot be included. Relaying these

anticoagulants to a LMWH before inclusion is allowed. In addition, it must be possible to stop the LMWH 24 h before invasive procedures according to the usual recommendations (before the work-up and before the SIRT).

- Significant presence of ascites, cirrhosis, portal hypertension and main portal venous tumour involvement or thrombosis.
- Long-term immunosuppressive/steroid medication (patients requiring corticosteroid therapy are eligible if they receive a dose equivalent to no more than 10 mg of prednisone per day).
- Partial or complete dihydropyrimidine dehydrogenase deficiency.

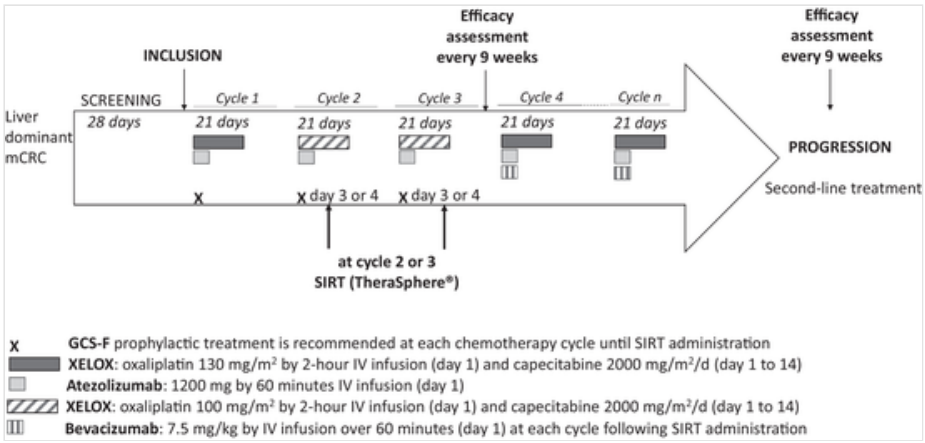
pMMR: proficient mismatch repair; MSS: microsatellite stability; RECIST: response evaluation criteria in solid tumours; WHO: world health organization; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; MDRD: modification of diet in renal disease; HIV: human immunodeficiency virus; CT: computed tomography; SIRT: selective internal radiation therapy; LMWH: low-molecular-weight heparin.

2.4 Study treatments

Patients will receive XELOX regimen with Oxaliplatin at 130 mg/m^2 by 2-hour intra-venous (IV) infusion and Capecitabine at 2000 mg/m^2 per day from day 1 to day 14, with Atezolizumab 1200 mg by 60minute IV infusion at day 1, during the cycles before SIRT (Fig. 1). For the cycle just before SIRT administration, Oxaliplatin will be administered at 100 mg/m^2. In addition, a granulocyte-macrophage colony-stimulating factor prophylactic treatment is recommended at each chemotherapy cycle until SIRT administration to prevent neutropenia. After SIRT, Bevacizumab 7.5 mg/kg by IV infusion over 60 min will be added at day 1 of each cycle. Treatment will be repeated every 3 weeks up to disease progression, unacceptable toxicity, refusal by the patient, withdrawal of consent, pregnancy or at investigator decision. After 4 cycles of XELOX, oxaliplatin could be suspended, at the discretion of the investigator. Atezolizumab will be administrated for a maximal treatment duration of 2 years.

alt-text: Fig 1

Fig. 1



Study Design
GCS-F: granulocyte colony stimulating-factor.

SIRT will be performed after a work-up, to map the hepatic vessels, determine the variant arteries that may lead to extra-hepatic microsphere deposition, determine lung shunting and treatment dose. SIRT will be administrated once only, 3 or 4 days after day 1 of cycle 2 or 3. The TheraSphere® procedure will be performed according to the current guidelines in order to obtain a dose of 180–200 Gy in liver metastases and less than 80 Gy in non-tumoral liver. In

addition, the tumour volume of liver metastases should be lower than 50% of total liver volume. An information document on dosimetry within the framework of the SIRTCI protocol is provided to nuclear medicine physicians.

2.5 Patient follow-up

Within 28 days before inclusion, patients must undergo a thoraco-abdomino-pelvic CT-scan, hepatic MRI and 18 fluoro-D-glucose positron emission tomography/CT-scan (FDG PET/CT) (Table 2).

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Table 2

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Main examination and follow-up schedule.

	BEFORE TREATMENT		DURING TREATMENT		AFTER PROGRESSION
	Within 28 days before inclusion	Within 14 days before inclusion	Before each course	Every 9 weeks	Every 3 months for a maximum of 12 months
Clinical and biological informed consent	X				
CLINICAL EXAMINATION					
WHO performance status		X	X	X	X (30 days after the end of treatment)
Evaluation of NCI-CTCAE version 4.0 toxicities			X	X	
BIOLOGICAL ASSESSMENT					
Laboratory assessment		X*	X*	X*	X (30 days after the end of treatment)
DPD deficiency assessment	X				
CEA and CA19.9 markers		X		X	X
PARACLINICAL REVIEWS					
Thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication)	X			X	
Hepatic MRI	X			X (at week 36)	
18 fluoro-D-glucose positron emission tomography/CT-scan (FDG PET/CT)	X			X (at week 9 and 18)	
Yttrium (Y90) PET/CT			X (within 24 h after SIRT)		
ANCILLARY STUDIES					
Blood samples (ctDNA, pharmacokinetic of Atezolizumab and immune response analysis)		X	X		
Stools (microbiome study)		X		X (at week 9)	

NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; WHO: World Health Organization; MRI: Magnetic resonance imaging; DPD: Dihydropyrimidine dehydrogenase.

Table Footnotes

* Before each cycle: Haematology panel (white blood cell count with differential, platelet count, haematocrit and haemoglobin), coagulation (prothrombin time and activated clotting time), chemistry panel (serum electrolyte levels, serum creatinine, creatinine clearance (MDRD), blood urea and calcemia), liver panel (aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, conjugated bilirubin, gamma-glutamyl transferase and alkaline phosphatase) and only before each cycle with Bevacizumab: urine dipstick (proteinuria) and at baseline then every 9 weeks: LDH and TSH.

Patients are evaluated every 9 weeks for clinical examination, laboratory assessment and morphological assessment. Briefly, the clinical examination includes Eastern Cooperative Oncology Group - Performance Status (ECOG PS) and toxicities evaluated by NCI-CTC v4.0 classification. Morphological assessment is based on thoraco-abdomino-pelvic CT according to RECIST 1.1 criteria. In addition, Y90 PET/CT will be performed within 24 h after SIRT, FDG PET/CT at weeks 9 and 18 and a hepatic MRI at week 36 to evaluate treatment efficacy.

2.6 Patient monitoring

An independent data and safety monitoring board (DSMB) has been set up and the committee ~~will~~ meet after 6 patients have been treated to review safety analysis of the data from their first cycles including SIRT. The committee will then meet at least once a year or more often if the sponsor deems it necessary to analyse serious adverse events (SAEs). The first DSMB meeting was conducted on October 21, 2021 to review safety data on the first 6 patients included. Nine SAEs were reported in five patients. Since 7 SAEs related to the treatment were observed and considered expected with this treatment combination (one peripheral sensory neuropathy, abdominal pain, cholangitis, hepatic vein thrombosis, hepatic cytolysis, prostatitis and one pyrexia), the DSMB recommended continuation of the study without any modification.

2.7 Data management

For each patient enrolled in the study, all required data will be entered in electronic case report form (eCRF), accessible only by authorized persons via secured web connection. The investigator is responsible for its completion and its approval. Once completed, eCRF will be locked and monitored by a clinical research assistant mandated by the Fédération Francophone de Cancérologie Digestive (FFCD).

2.8 Statistical considerations

Median PFS in first-line setting with a combination of recent chemotherapy and targeted therapy in mCRC patients with unresectable liver-dominant disease is about 10 months [6,8,9]. PFS is a surrogate marker of OS and a primary endpoint commonly used in phase II trials. Indeed, the clinical hypotheses for sample size calculation are:

H0: 50% of patients alive and without progression at 9 months is not acceptable.

H1: 70% of patients alive and without progression at 9 months is expected.

With an alpha risk (one-sided) of 5%, a power of 85% and according to minimax 2-steps Simon design, 44 evaluable patients are needed. Assuming 20% of non-evaluable patients or lost to follow-up, 52 patients will be included. Patient is defined as evaluable if they have received SIRT.

An interim analysis is planned to evaluate safety and efficacy of the combination after inclusion of 22 evaluable patients. Inclusions will be stopped until the results of the first step are available. The DSMB will review the efficacy and the safety results to decide whether to continue the study or not. For the efficacy evaluation, if 12 or more patients (amongst the 22 evaluable patients) are alive and without progression at 9 months, then the trial will continue.

At the final step, after 44 evaluable patients will be included, if 28 or more patients are alive without progression at 9 months, then the strategy will be considered as effective.

2.9 Administrative considerations

The study sponsor is the FFCD. The study was registered under EudraCT 2019–002,400–40 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 Ouest III on June 17, 2020 and from the ANSM on July 27, 2020.

The trial has started in November 2020 and has already included 10 out of the 52 planned patients.

3 Discussion

Treatment of liver-dominant mCRC remains a challenge as liver metastases are often involved in morbidity and mortality of mCRC patients. Given the survival improvement [12] achieved in patients with dMMR/MSI mCRC thanks to ICI, turning pMMR/MSS mCRC, which do not respond to ICI, into immunosensitive tumours would transform patients' prognosis. Furthermore, the feasibility of locoregional treatments of liver-dominant mCRC such as hepatic intra-arterial chemotherapy or SIRT should not be assessed [30,31]. The target population of SIRT is restricted to the patient with liver-dominant mCRC and chemoresistance to standard chemotherapies and targeted therapies. Nevertheless, radiation induces an immunogenic cell death able to convert a "non-immunogenic" neoplasm into an "immunogenic" neoplasm and Oxaliplatin and Bevacizumab could also help to increase immune response in combination with SIRT and Atezolizumab.

SIRTCI is the first trial to assess the association of SIRT with chemotherapy, anti-angiogenic and immunotherapy in mCRC. The combination of SIRT and ICI could increase the immune abscopal anti-tumour effects of radiation. Once activated in one place (liver), the immune system can attack tumour lesions anywhere else in the body (lung, peritoneum) through this abscopal effect. SIRT will be assessed both as a local treatment, which may improve liver response (increased local SIRT efficacy with ICI) and as a trigger of the abscopal effect, which may improve overall response outside the liver (increased abscopal effects of SIRT with ICI) and patient survival. Therefore, the study includes patients with liver-dominant disease since the aim of the SIRTCI trial is to induce immune abscopal anti-tumour effects of radiation. Patients with hepatic and up to 6 extra-hepatic lesions are included if extra-hepatic lesions are not symptomatic and if there is no organ dysfunction.

A recent phase II study evaluated Durvalumab (anti-PDL1) and Tremelimumab (anti-CTLA4) with concurrent radiotherapy in patients with chemoresistant metastatic pMMR CRC and demonstrated a tolerable safety profile [32]. Radiotherapy does not seem to increase immune-mediated AEs related to the ICI with 25% of patients with grade 3–4 treatment-related AEs. In addition, in the AtezoTRIBE trial combining FOLFOXIRI plus bevacizumab plus Atezolizumab versus FOLFOXIRI plus bevacizumab, as first-line treatment of unresectable mCRC patients, no safety issue was reported [33].

SIRT has already been tested in combination with chemotherapy (Gemcitabine and Cisplatine) in the first-line treatment of unresectable intra-hepatic cholangiocarcinoma [34]. The safety profile was acceptable with some restriction in cirrhotic patients, the combination was successful with 90% of tumour control and 30% of secondary resection. In the first-line setting in patients with liver-dominant mCRC, adding SIRT to chemotherapy demonstrated an improvement of hepatic PFS, but no benefit on PFS and OS. In this study, SIRT and chemotherapy are done simultaneously (SIRT administered on the 3rd or 4th day of the chemotherapy cycle) and there was no increase of AEs as compared to chemotherapy alone [10,11]. Treatment-related grade 3 or more adverse events were reported in 73.4% of patients in the FOLFOX group and 85.4% in the FOLFOX plus SIRT group. The most frequently reported AEs were neutropenia, neuropathy, fatigue, nausea and diarrhoea. The most frequent grade 3–4 AE was neutropenia, 24.2% in chemotherapy alone group versus 36.7% in the chemotherapy plus SIRT group. In the SIRTCI trial to minimize the risk of complication related to neutropenia, the Oxaliplatin dose is decreased before SIRT and granulocyte-macrophage colony-stimulating factor prophylactic treatment is recommended at each chemotherapy cycle until SIRT administration. Bevacizumab is added only after SIRT treatment (to prevent bleeding during work-up and SIRT). Capecitabine has a hepatic metabolism and up until now there is no~~t~~ data concerning combination of SIRT and capecitabine. Capecitabine could lead to~~give~~ an increase in~~of~~ liver toxicity of SIRT. A~~Indeed, a~~ safety analysis has been performed after the inclusion of 6 patients. Since all SAEs related to the treatment were considered expected the DSMB recommended continuation of the study without any modification. Next step is now the interim analysis planned to assess safety and efficacy of the strategy.

In second-line treatment of mCRC combination of SIRT, chemotherapy and targeted therapy (EPOCH Phase III trial) demonstrated an improvement in PFS and hepatic PFS versus chemotherapy +/- targeted therapy alone [35]. Rather than hepatic PFS, which only reflects local control, we have chosen PFS at 9 months as primary endpoint because PFS can evaluate abscopal effect (extra-hepatic response) and is also a surrogate marker of OS. Median PFS in first-line setting with a doublet plus a targeted agent is from 9 to 12 months in unresectable liver-dominant mCRC [6,10–11], corresponding to a PFS of 50%–60% at 9 months. PFS is more reliable than response rate at 2–3 months given that the treatments used can induce tumour necrosis (SIRT). In addition, most patients will have a disease control/response at 2–3 months with this combination. We are aware that this single-arm study will include selected patients as in all innovative phase II trials but a randomized phase II study with a large population does not seem appropriate in view of the limited literature on the safety and efficacy of this combination. The clinical hypothesis to obtain 70% of patients alive and without progression at 9 months is ambitious and currently not achieved with current chemotherapies plus a targeted agent in mCRC.

Ancillary studies will allow assessment of the local (tumour) and systemic immune response (blood) and other predictive biomarkers of response to ICI, XELOX, SIRT and Bevacizumab combination in pMMR/MSS mCRC. All well-known predictive biomarkers of chemotherapy (mutational status, circulating tumour DNA) and ICI (tumour mutational load, PD-L1 expression and immune response) efficacy will be analysed [36–38]. Additionally, we will perform pharmacokinetic analyses of Atezolizumab and centralized imaging review to evaluate morphologic and metabolic predictive markers (CT-scan, MRI, FDG PET/CT and Y90 PET/CT) of SIRT plus ICI efficacy [39,40]. In addition, the innate and adaptive immune system activation state and repertoire may be altered, based on local microbiota leading to differential activity of Bevacizumab and/or ICI in CRC subjects. Some studies suggest that gut microbiota might be involved in the efficacy and toxicity of chemotherapies and ICIs [41–43]. The small number of patients included in this phase II trial will limit the power of these investigations. However, these exploratory ancillary studies will be of major interest to drive analyses that should be used for the forthcoming phase III trial.

The results of the SIRTCI trial should provide a rationale for a randomized phase III study comparing chemotherapy alone (doublet or triplet) plus targeted agent according to *RAS* status versus chemotherapy, Bevacizumab, SIRT and ICI combination in mCRC patients with unresectable liver-dominant disease.

Funding

This study was supported in part by Roche and Biocompatibles UK Ltd, a wholly owned subsidiary of Boston Scientific Corporation. *Fédération Francophone de Cancérologie Digestive* (FFCD) is funding the bio-bank and molecular analysis.

Declaration of Competing Interest

None declared.

Acknowledgements

We thank all physicians who are participating in the SIRTCI trial. We thank Flore Geillon and Manon Pelkowski the FFCD SIRTCI project managers, Paolo Carni the data manager and the FFCD clinical research associates. Finally, we thank Biocompatibles UK Ltd, Roche and the "*Ligue nationale contre le cancer*" for their support.

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