Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Progress report

Avelumab versus standard second line treatment chemotherapy in metastatic colorectal cancer patients with microsatellite instability: The SAMCO-PRODIGE 54 randomised phase II trial

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ARTICLE INFO

Article history:
Received 13 November 2020
Accepted 26 November 2020
Available online xxx

Keywords:
Anti-PDL1
Immunotherapy
Metastatic colon cancer
Microsatellite instability
Second-line treatment

ABSTRACT

Immune checkpoint inhibitors have failed in treating metastatic colorectal cancer (mCRC) patients except those with dMMR/MSI tumors. However, until very recently we had only non-comparative promising data in this population with anti-programmed cell death 1/ programmed cell death ligand 1 (PD1/PD-L1) antibodies alone or combined with anti- cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies.

This comparative phase II trial (NCT 03186326), conducted in more than 100 centers in France, will include dMMR/MSI mCRC patients with progression after a first-line treatment with chemotherapy ± targeted therapies, to evaluate efficacy and safety of the anti-PDL1 Avelumab versus a standard second-line treatment. Main inclusion criteria were patients aged 18 to 75 years, ECOG performance status ≤2, dMMR/MSI mCRC and failure of a standard first-line regimen. Patient will be randomised to receive Avelumab 10 mg/kg versus standard second-line doublet chemotherapy plus a targeted agent according to tumor *RAS* status. Patients will be followed for 4 years. A gain of 5 months in median PFS is expected in favour of the Avelumab arm (12 vs 7 months; HR=0.58). Secondary endpoints include objective response rate, overall survival, quality of life and toxicity. In addition, circulating tumour DNA and microbiota will be explored to test their potential prognostic and predictive values. The study was opened in March 2018.

1. Rationale and aims

Human tumors escape immunosurveillance in order to progress and spread. One of the major mechanisms involved in this immune-escape phenomenon is the activation of immune system regulatory checkpoints. The PD1/PD-L1 (Program Death - Ligand

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https://doi.org/10.1016/j.dld.2020.11.031
1590-8658/

1) axis is one of the most well described example of these immune checkpoints and interaction between PD-1 and PD-L1 was shown to lead the activated cytotoxic CD8+ T cells to a state of anergy inefficient against tumor cells. Blocking PD-1/PD-L1 has recently emerged as a highly promising option for the treatment of an ever-increasing number of malignancies, including melanoma, non-small cell lung carcinoma, bladder carcinoma, Hodgkin lymphoma, triple-negative breast carcinoma, as well as head and neck cancer [1]. In fact, anti-PD1 and anti-PD-L1 monoclonal antibodies (mAbs), called immune checkpoint inhibitors (ICIs), have consequently been designed to restore T cell activity. Only a fraction of patients with these neoplasms respond to ICI but robust and durable objective responses, with sometimes-complete responses, and no relapse are not anymore considered as impossible.

Multiple anti-PD1 and anti-PD-L1 mAbs are under evaluation in digestive cancers [2,24]. Nonetheless, few successes have been reported to date in unselected metastatic colorectal cancer (mCRC) patients. The fact that CRC does not respond to ICI appears somehow paradoxical, since the first sophisticated analyses of the immunological tumor microenvironment have been performed on CRC specimens, yielding the conclusion that the “immune contexture” has a critical impact on the outcome of the patients [3,25,26].

Approximately 15% of the CRC are deficient for the DNA mismatch repair (dMMR) system inducing a state of genetic instability, also called MSI-H (high microsatellite instability) or MSI (microsatellite instable) CRC. MMR gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*) inactivation is due to either a germline mutation in Lynch syndrome or a somatic inactivation in sporadic case mostly owing to *MLH1* hypermethylation. This deficiency is responsible for the high mutational load observed in these tumours and the generation of several neoantigens, which drives a high anti-tumor immune response and an abundant peri– and intra-tumor infiltrating lymphocyte (TIL) [4–6]. In addition, strong PD-L1 expression was found in dMMR CRC as compare to proficient MMR/microsatellite stable (pMMR/MSS) CRC [7]. Localised dMMR CRC have a better prognosis than pMMR CRC, probably because this neoantigens are associated with cytotoxic T CD8+ specific immune response against tumor cell [8,9]. In metastatic CRC (mCRC) things are a bit different as i) the frequency of dMMR/ is only 4–7%, ii) the good prognosis conferred by dMMR status is more controversial and iii) dMMR mCRC are possibly associated with chemoresistance to standard treatment [10–13].

Since defective in mismatch repair system largely increases mutational load with several immunogenic neoantigens preliminary results suggests that patients with chemoresistant dMMR mCRC benefit from the administration of anti-PD-1/PD-L1 mAbs [14–16]. These encouraging results have been recently confirmed by non-randomised trial with anti-PD1/PD-L1 mAbs alone or in combination with anti-CTLA-4 (Cytotoxic T lymphocyte associated antigen 4) mAbs in both metastatic [17] and localised CRC patients [18]. The first phase III trial dedicated to dMMR mCCR comparing in first line pembrolizumab with chemotherary ± bevacizumab or cetuximab was recently presented at American Society of Medical Oncology. Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS compared to chemotherary ± bevacizumab or cetuximab [19].

The Avelumab anti-PD-L1 mAb has been recently tested in many different tumor types with promising results with significant efficacy and acceptable safety profile [20]. Avelumab is currently under investigation in many phase III trials, but no comparative data on the efficacy of this immune checkpoint inhibitor in dMMR mCRC are currently available.

We thus propose in the SAMCO-PRODIGE 54 trial to evaluate efficacy and safety of Avelumab as a second-line treatment in dMMR mCRC patients, who have failed to a standard first-line treatment, in comparison to a standard second-line treatment with chemotherapy ± targeted therapy.

2. Patients and study design

The SAMCO-PRODIGE 54 study is an open-label randomised phase II trial conducted in France, sponsored by the FFCD and support by the PRODIGE French intergroup (FFCD, UNICANCER GI and GERCOR), comparing the anti-PDL-1 Avelumab (10 mg/kg q2w) to a standard second-line doublet chemotherapy ± targeted agent, in dMMR/ mCRC that have failed a first-line standard chemotherapy ± targeted agent.

The study was opened to inclusion in the end of April 2018. Overall, 100 centers will be opened in France. The end of inclusions is scheduled for July 2021.

2.1. Inclusion and non-inclusion criteria

Main inclusion and non-inclusion criteria are summarised in Table-1. It is worthy to note that initially mCRC were eligible if dMMR status was assessed by immunohistochemistry (extinction of one MMR proteins) or by molecular biology (2 instable loci among the 5 tested) but the protocol has been amended to include only dMMR mCRC if 2 methods for assessing the MMR status were concordant due to possible discrepant results between theses 2 methods and a lack of response to ICIs in this situation, as recently published [21].

Patients will be randomised in a 1:1 ratio (“Second-line Chemotherapy” versus “Avelumab”) using the minimisation technique. Randomisation will be stratified based on: center**,** WHO PS (0–1 versus 2)**,** *BRAF* status (non-mutated *BRAF* versus mutated *BRAF*), and age (<70 versus ≥ 70).

Trial started in April 2018 and primary endpoint analysis is planned for July 2022.

2.2. Study treatments

In the experimental arm (arm A), patients will receive intravenous (IV) infusion of Avelumab at 10 mg/kg every 14 days (Fig. 1).

In the control arm (arm B), patients will receive an IV infusion of chemotherapy +/- targeted therapy. Chemotherapy allowed are FOLFIRI (if the patient was treated with FOLFOX in first-line) or FOLFOX (if the patient was treated with FOLFIRI in first-line) and left at the investigator decision if the patient received fluoropyrimidine alone in first-line setting. Targeted treatment is investigators' choice according to *RAS* status and targeted therapy used in first-line. Targeted therapy allowed are Cetuximab (500 mg/m^2), Panitumumab (6 mg/kg), Bevacizumab (5 mg/kg) or Aflibercept (4 mg/kg) every 14 days.

Cycles will be repeated in the two treatment arms until disease progression, unacceptable toxicity (grade 4 toxicity or grade 3 toxicity after the dose has been adjusted twice), patient refusal or upon investigator decision.

All toxicities requiring dose adjustment will be evaluated according to the NCI-CTCAE v4.03 criteria and managed as usually recommended.

This study (clinicaltrials.gov NCT 03186326) is performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines (ICH–E6, 17/07/96). This protocol received approval from an Institutional Review Board, Comité de Protection des Personnes sud mediterranee III (CCP) on April 27, 2017.

All patients have to provide written informed consent before starting the study.

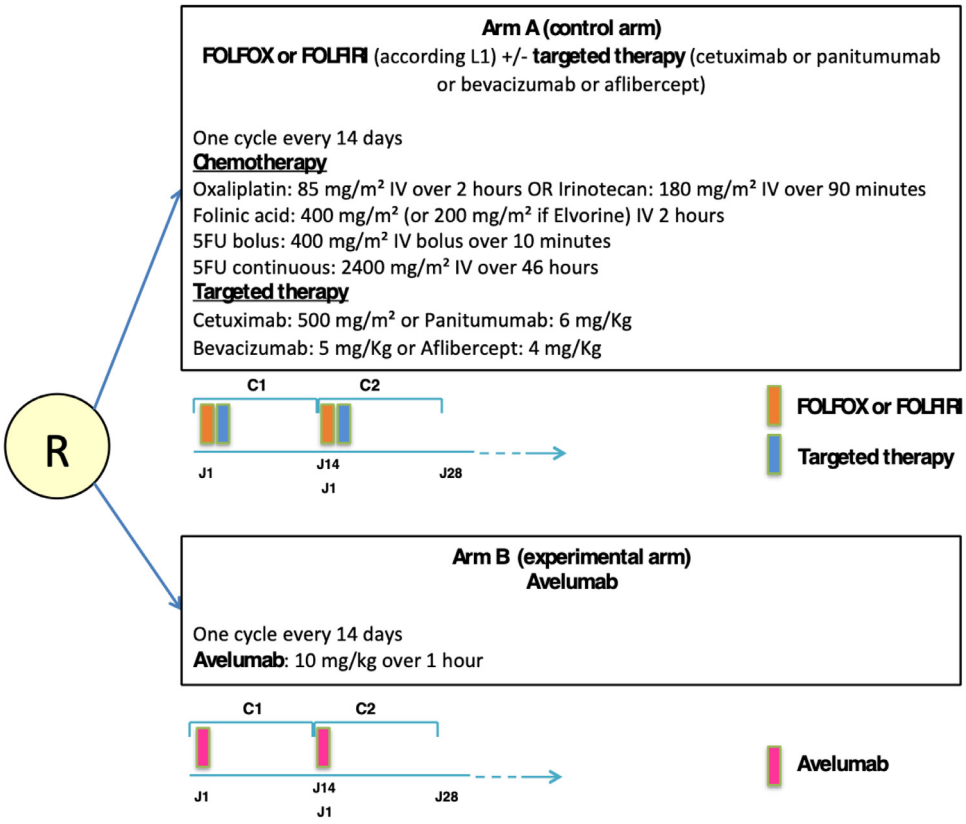

Fig. 1. Study design and treatments.

2.3. Trial objectives and endpoints

The primary objective is to compare between the two treatment arms (Arm A: second-line chemotherapy, Arm B: Avelumab) progression-free survival (PFS) by local assessment using RECIST 1.1. PFS will be defined as the time from the date of randomisation to the date of first disease progression or death, from any cause including treatment-related death. Patients alive without progression will be censored on the date of last news. Second cancers will not be taken into account.

Secondary objectives will include: time-to-progression (according to RECIST and iRECIST), overall survival, time to best response (according to RECIST and iRECIST), objective response rate (according to RECIST and iRECIST), best response under treatment (according to RECIST and iRECIST), PFS by central review (RECIST 1.1 for Arm A and iRECIST for Arm B), toxicity according to NCI-CTC v4.03, depth of response, early tumor shrinkage at 8 weeks, secondary resection rate (R0 and R1), histological response in case of secondary resection (tumor regression grade (TRG) and modified TRG criteria), evolution of carcinoembryonic antigen and quality of life using EORTC QLQ-C30.

2.4. Monitoring of patients

The initial biological (complete blood count, uracilemia, creatinine clearance (MDRD formula), liver function tests, lactate dehydrogenase (LDH), albumin and TSH) and clinical (medical history, weight, height and body surface area, WHO performance status and QLQ-C30 questionnaire) assessments should take place within 2 weeks prior to randomisation.

Tumor assessment is recommended to be performed within 3 weeks prior to randomisation and every 2 months, with thoraco-abdominal and pelvic CT-scan and CEA level assessments.

2.5. Calculation of sample size and statistical analysis plan

We expect an improvement of 5 months in PFS, in favour of Arm B (Avelumab), from 7 to 12 months as compared Arm B (standard second-line treatment), with a hazard ration (HR) of 0.58. Using a fixed design by the Schoenfeld method (and considering a bilateral alpha risk of 5% and a power of 80%), 106 events (progression or death) are needed to demonstrate this difference.

With an estimated recruitment rate of 3 patients per month, a follow-up period for each patient of 24 months, and a percentage of patients lost to follow-up or not evaluable of 15%, 132 patients must be randomised. Indeed, we plan to enroll a total of 66 patients per arm.

For all endpoints, a two-sided 95% confidence interval (CI) will be calculated. Survival criteria (PFS, overall survival, time-to-progression) will be estimated using the Kaplan-Meier method and described by medians and their 95% CI. Comparisons by treatment arm will be conducted using the log-rank test. The hazard ratio for the treatment effect will be calculated using a Cox model.

Follow-up will be estimated by the reversed Kaplan–Meier method. Analyses of primary and secondary efficacy endpoints will be conducted in the modified intention-to-treat (mITT) population i.e. all CCRm patients with double checked MSI regardless of their eligibility criteria and who have had received at least one dose of treatment in the study. Patients will be analysed according to the allocated group by randomisation.

A Per-Protocol (PP) analysis of the primary endpoint will also be done. PP population is defined as all CCRm patients with double checked MSI with all eligibility criteria, who will receive at least one dose of treatment and who will have at least one tumor evaluation. Patients will be analyzed according to treatment received.

Best response rate, toxicities and other baseline variables will be reported using usual descriptive statistics for quantitative

Table 1
Main eligibility criteria.

Main inclusion criteria

- Histologically proven colorectal adenocarcinoma with non-resectable metastasis(es)
- dMMR status determined by immunohistochemistry (loss of expression of MLH1, MSH2, MSH6 and/or PMS2) and MSI status determined by molecular biology in each center
- At least one measurable target (primary tumour or metastasis) according to RECIST v1.1 criteria
- Known *RAS* and *BRAF* mutational status
- Age $\geq$ 18
- WHO PS $\leq$ 2
- Life expectancy $\geq$ 3 months
- First-line treatment failure (progression or unacceptable toxicity) of chemotherapy containing fluoropyrimidine (capecitabine or 5FU) +/- irinotecan +/- oxaliplatin with or without cetuximab, bevacizumab, panitumumab or aflibercept (patients with disease progression during, or within 6 months after, discontinuation of adjuvant chemotherapy are eligible)
- Adequate haematological, renal and liver functions

Main non-inclusion criteria

- Patient eligible for immediate curative therapy (surgical and/or percutaneous) according to local multidisciplinary team meeting
- Patient having progressed under first-line treatment with FOLFIRINOX or FOLFOXIRI +/- target agent (patients with progression during maintenance treatment after a triplet chemotherapy are eligible)
- Previous treatment with immune checkpoint inhibitor
- Active or prior documented autoimmune or inflammatory disorders (patients with alopecia, vitiligo, controlled hypo or hyperthyroidism, any chronic skin condition not requiring immunosuppressant therapy are eligible)
- Current immunosuppressive treatment (patients with current steroid medication are eligible if they have a dose $<$ or $=$ to the equivalent of 10 mg of prednisone daily, administration of steroids by a route resulting in minimal systemic exposure (local, intra-anal, intraocular or inhalation) are allowed)
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation, or immunodeficiency syndromes
- Positive test for HIV, active hepatitis B or hepatitis C, active tuberculosis
- Peripheral sensory neuropathy with functional impairment
- Known partial or total dihydropyrimidine dehydrogenase (DPD) enzyme deficiencies.
- Vaccination during the 4 weeks preceding the start of treatment
- DPD partial or total deficiency (defined by uracilemia $\geq$ 16 ng/ml)
- Any severe intercurrent illness not stabilised over the past 6 months (hepatic, cardiac, renal or respiratory failure)
- History of interstitial pneumonitis or pulmonary fibrosis or any other known severe respiratory insufficiency
- History of inflammatory bowel disease or unresolved occlusion or sub-occlusion with symptomatic treatment
- Other malignancy within 5 years prior to study enrolment, except for localised cancer in situ, basal or squamous cell skin cancer, properly treated

variables (mean, standard deviation, median, inter-quartile interval and range) and for qualitative variables (frequencies and percentages). Comparisons by treatment arm will be performed for the quantitative variables, using a Student or Wilcoxon test and for qualitative variables, using a chi2 test or a Fisher exact test.

Safety analyses will be done on all CCRm patients randomised receiving at least one dose of treatment. Patients will be analyzed according to treatment received. Safety analyses will also be performed on the mITT population.

2.6. Ancillary study: biomarker analysis

All patients enrolled in this trial will be proposed to consent for their participation to a biological ancillary study. Prognostic and predictive biomarkers can be studied on blood, stool and tumor-derived samples.

These biomarker analyses on tumor samples will include at least determination of immune cells infiltrate by immunohistochemistry (PD-1, PD-L1, PD-L2, CD8, CD4, CD3, FoxP3), immune scores and genetic/genomic assessments (tumor mutational burden (TMB), CpG island methylator phenotype (CIMP) and consensus molecular subtypes (CMS) classification) with a first goal of hypothesis generating for the determination of future predictive biomarkers for immune checkpoint inhibitors efficacy.

Circulating tumor DNA (ctDNA) is a potential surrogate of solid biopsy for detecting important theranostic genetic alterations. Preliminary results in CRC showing that the normalisation of ctDNA after 4 weeks of treatment is highly predictive of PFS and OS [22]. Very few data are available on ctDNA in dMMR/MSI mCRC and the SAMCO trial represents an opportunity to study ctDNA in dMMR/MSI mCRC. We investigate the prognostic value of the detection and quantification of ctDNA at the time of inclusion in the trial, and also to test the predictive impact of an early decrease in the amount of ctDNA. An analysis of ctDNA will be performed before the first cycle of treatment, before the third cycle of treatment and at progression.

Microbiota ancillary study (stool sampling) will study the relationship between the composition of the intestinal microbiota (before treatment, before the third cycle of treatment and at progression) and the antitumor response and tolerability to Avelumab or chemotherapy. The results of this study could open new perspectives to identify of ICI responders but also the manipulation of the intestinal microbiota (for example: fecal transplantation or microbiota complementation) to increase their efficacy and tolerability.

All analyses will be conducted in a centralised manner.

3. Discussion

Many non-randomised trials suggest a high efficacy of anti-PD1/PD-L1 mAbs alone or in combination with anti-CTLA-4 mAbs in dMMR/MSI mCRC [14–17]. Nevertheless, due to the lack of randomised trial versus standard of care there is no approval in most European countries by contrast to the US or Japan. In Europe, this promising treatment should be only considered in a clinical trial pending marketing authorization [23].

The KEYNOTE-177 trial, a phase 3, open-label, randomised study of first-line Pembrolizumab (anti-PD1) versus investigator-choice chemotherapy for dMMR or MSI mCRC has recently been communicated as positive for its primary endpoint (PFS) showing a superiority of Pembrolizumab at the ASCO 2020 virtual meeting. The market authorization in Europe is still pending. SAMCO remains an important randomised trial to confirm benefit of ICI, using in this case an anti-PDL-1, versus standard treatment in

mCRC patients already treated with a first line standard regimen. Moreover, SAMCO will also identify potential relevant predictive biomarkers of efficacy and tolerability of ICI.

4. Conclusion

PRODIGE54-SAMCO is a randomised phase II trial evaluating, in patients with MSI/dMMR mCRC and after failure of a first-line standard therapy, the benefit of the anti-PDL-1 Avelumab compared to standard second-line treatments. SAMCO is the first randomised trial comparing ICI versus standard treatment in second-line setting in MSI/dMMR mCRC (Table 1).

Financial support

This study was supported by MERK-KGAa. Fédération Francophone de Cancérologie Digestive (FFCD) is funding the bio-bank and molecular analysis.

Declaration of Competing Interest

JT has received honoraria for speaker or advisory role from Sanofi, Roche, Merck Serono, Amgen, Servier, Pierre Fabre, Lilly, Astra Zeneca and MSD.

LE has received honoraria for speaker or advisory role Servier, Merck Serono, Amgen.

PLP is a consultant/advisory board member for Merck Serono, Astrazeneca Amgen, Boehringer Ingelheim, Biocartis, Roche, Bristol-Myers Squibb, Pierre Fabre, Servierand MSD.

CL has served in a consulting/advisory role and or received honoraria for, Amgen, Pierre Fabre, Novartis, AAA.

FE has received honoraria for speaker and/or advisory role from Ipsen, Merck, Bayer, Sanofi and Servier.

OB has received honoraria for speaker and/or advisory role from Merck KGaA, Roche Genentech, Bayer, Astra-Zeneca, Grunenthal, MSD, Amgen, Servier, and Pierre Fabre,

TA has served in a consulting/advisory role and/or received honoraria from Amgen, Bristol-Myers Squibb, Chugai, Clovis, Halliodx, MSD, Pierre Fabre, Roche/Ventana, Sanofi, Servier and has received travel, accommodations, and expenses from Roche/Ventana, MSD Oncology, and Bristol-Myers Squibb.

DT has served in a consulting/advisory role and/or received honoraria from Amgen, Bristol-Myers Squibb, MSD Oncology, Roche/Ventana, Sanofi, Servier, Novartis, Merck Serono and Astra Zeneca.

HP has served in a consulting/advisory role and/or received honoraria from Amgen, Sanofi, Servier, Merck Serono and Roche.

SK has received honoraria for speaker and/or advisory role from Amgen, Ipsen, MSD, Pfizer, Sanofi, and Servier.

EB, JFE, JB, MC and FD have nothing to disclose.

CT has received honoraria for speaker or advisory role from Merck, Sanofi, MSD, Ipsen, Amgen, Servier, and Bristol-Myers Squibb.

This research was financially supported by Merck Santé S.A.S., an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.

Acknowledgements

We thank all physicians who participate in the SAMCO trial. We also thank all the cooperative groups (FFCD – UNICANCER GI – GERCOR) for their contribution and participation to the present trial, especially Jérémie Bez our FFCD SAMCO manager. Finally, we thank MERK-KGAa and the “Ligue nationale contre le cancer” for their support.

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