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Avelumab vs Standard Second-Line Chemotherapy in Patients With Metastatic Colorectal Cancer and Microsatellite Instability
A Randomized Clinical Trial

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IMPORTANCE Only 1 randomized clinical trial has shown the superiority of immune checkpoint inhibitors in patients with deficient mismatch repair and/or microsatellite instability (dMMR/MSI) metastatic colorectal cancer (mCRC) in the first-line setting.

OBJECTIVES To determine whether avelumab (an anti–programmed cell death ligand 1 antibody) improves progression-free survival (PFS) compared with standard second-line chemotherapy in patients with dMMR/MSI mCRC.

DESIGN, SETTING, AND PARTICIPANTS The SAMCO-PRODIGE 54 trial is a national open-label phase 2 randomized clinical trial that was conducted from April 24, 2018, to April 29, 2021, at 49 French sites. Patients with dMMR/MSI mCRC who experienced progression while receiving standard first-line therapy were included in the analysis.

INTERVENTIONS Patients were randomized to receive standard second-line therapy or avelumab every 2 weeks until progression, unacceptable toxic effects, or patient refusal.

MAIN OUTCOME AND MEASURES The primary end point was PFS according to RECIST (Response Evaluation Criteria in Solid Tumours), version 1.1, evaluated by investigators in patients with mCRC and confirmed dMMR and MSI status who received at least 1 dose of treatment (modified intention-to-treat [mITT] population).

RESULTS A total of 122 patients were enrolled in the mITT population. Median age was 66 (IQR, 56-76) years, 65 patients (53.3%) were women, 100 (82.0%) had a right-sided tumor, and 52 (42.6%) had *BRAF V600E*–mutated tumors. There was no difference in patients and tumor characteristics between treatment groups. No new safety concerns in either group were detected, with fewer treatment-related adverse events of at least grade 3 in the avelumab group than in the chemotherapy group (20 [31.7%] vs 34 [53.1%]; $P = .02$). After a median follow-up of 33.3 (95% CI, 28.3-34.8) months, avelumab was superior to chemotherapy with or without targeted agents with respect to PFS (15 [24.6%] vs 5 [8.2%] among patients without progression; $P = .03$). Rates of PFS rates at 12 months were 31.2% (95% CI, 20.1%-42.9%) and 19.4% (95% CI, 10.6%-30.2%) in the avelumab and control groups, respectively, and 27.4% (95% CI, 16.8%-39.0%) and 9.1% (95% CI, 3.2%-18.8%) at 18 months. Objective response rates were similar in both groups (18 [29.5%] vs 16 [26.2%]; $P = .45$). Among patients with disease control, 18 (75.7%) in the avelumab group compared with 9 (19.1%) in the control group had ongoing disease control at 18 months.

CONCLUSIONS The SAMCO-PRODIGE 54 phase 2 randomized clinical trial showed, in patients with dMMR/MSI mCRC, better PFS and disease control duration with avelumab over standard second-line treatment, with a favorable safety profile.

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Visual Abstract

Supplemental content

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The activation of immune checkpoints is an important mechanism for human tumors to escape immune surveillance to progress and spread. The programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) axis is one of the most described examples of these immune checkpoints. Blocking the PD-1-PD-L1 axis has emerged during the past decade as a highly promising option for the treatment of an ever-increasing number of malignant neoplasms.[1] Nonetheless, few successes have been reported to date in unselected patients with metastatic colorectal cancer (mCRC), though 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 effect on the outcome of the patients.[2]

Approximately 15% of CRCs are deficient for the DNA mismatch repair (dMMR) system, which induces a state of genetic instability, also called microsatellite instability (MSI). Inactivation of the *MMR* gene is due to either a germline mutation in Lynch syndrome or a somatic inactivation in sporadic cases.[3] This deficiency is responsible for a high tumor mutational burden and the generation of several neoantigens, which drive a high antitumor immune response and an abundant number of tumor-infiltrating lymphocytes with strong PD-L1 expression.[4-7] In mCRC, the frequency of dMMR/MSI status is 4% to 7% and is possibly associated with chemoresistance to fluoropyrimidines and specific outcomes.[8-13]

The first results of the immune checkpoint inhibitor (ICI) anti-PD-1 and anti-PD-L1 monoclonal antibodies (mAbs) suggest that patients with dMMR/MSI mCRC have a prolonged survival with these treatments.[12,14,15] These encouraging results have been recently confirmed by a single randomized clinical trial dedicated to dMMR/MSI mCRC comparing first-line anti-PD-1 pembrolizumab with first-line standard of care (SOC) chemotherapy with or without targeted therapy.[16] Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS compared with chemotherapy with or without targeted therapy (median, 16.5 vs 8.2 months; $P < .001$) and was associated with fewer treatment-related adverse events and improved patient quality of life.

Avelumab is an anti-PD-L1 mAb that has been recently evaluated in many tumor types with promising results with significant efficacy and an acceptable safety profile.[17] No comparative data on the efficacy of these ICIs vs SOC in dMMR/MSI mCRC are currently available in the second-line setting. The SAMCO-PRODIGE 54 (Partenariat de Recherche en Oncologie Digestive) trial evaluated the efficacy and safety of avelumab as a second-line treatment in patients with dMMR/MSI mCRC not previously treated with immunotherapeutic agents and in whom standard first-line treatment failed, compared with a standard second-line treatment.

Key Points

Question Are checkpoint inhibitors better than chemotherapy in the second-line setting for deficient mismatch repair and/or microsatellite instability (dMMR/MSI) metastatic colorectal cancer (mCRC)?

Findings In this phase 2 randomized clinical trial including 122 patients, avelumab, an anti–programmed cell death ligand 1 antibody, was associated with significantly better progression-free survival and disease control duration than standard second-line treatment. In addition, avelumab had a favorable safety profile in the second-line setting of dMMR/MSI mCRC.

Meaning These findings suggest that for patients with dMMR/MSI mCRC not treated with pembrolizumab in the first-line setting, immune checkpoint inhibitors may be an option in the second-line setting, with better efficacy and tolerability than the current standard of care.

Methods

Patients

The SAMCO-PRODIGE 54 study is an open-label phase 2 randomized clinical trial that was conducted at 40 sites in France, sponsored by the Fédération Francophone de Cancérologie Digestive. The trial protocol is provided in Supplement 1. The SAMCO-PRODIGE 54 study was performed in accordance with the Declaration of Helsinki[18] and International Conference on Harmonization Good Clinical Practice Guidelines. This protocol received approval from the ethics committee of Comite de Protection des Personnes Sud Mediterranee III. All patients provided written informed consent. Eligible patients were 18 years or older and had an unresectable dMMR/MSI stage IV CRC with measurable disease according to Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1; a World Health Organization (WHO) performance status (PS) score of 0 to 1; and adequate organ function.[19] All patients were treated with a first-line standard chemotherapy regimen with or without a targeted agent according to *RAS* status.

Mismatch repair status was determined locally by immunohistochemistry of the 4 MLH1, MSH2, MSH6, and PMS2 proteins; MSI status was determined locally by polymerase chain reaction–based analysis of 5 tumor microsatellite loci.[20] Patients with discordant tumor results between MSI and MMR immunohistochemistry tests were excluded from the modified intention-to-treat (mITT) population. Tumor assessment was performed within 3 weeks before randomization and every 2 months, with thoracoabdominal and pelvic computed tomographic scans and blood carcinoembryonic antigen assessments.[19]

Treatments

Patients were randomly assigned in a 1:1 ratio, using the minimization technique, to avelumab at a dose of 10 mg/kg every 2 weeks intravenously or to the investigator's choice of second-line chemotherapy with or without a targeted agent determined according to the first-line treatment regimen and *RAS*/*BRAF* status. Randomization was stratified based on center, WHO PS, *BRAF* status, and age (eFigure 1 in Supplement 2).

The choices of chemotherapy, repeated every 2 weeks, were as follows: leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (modified FOLFOX-6); modified FOLFOX-6 plus bevacizumab; modified FOLFOX-6 plus cetuximab; leucovorin calcium (folinic acid), fluorouracil, and irinotecan hy-

drochloride (FOLFIRI); FOLFIRI plus bevacizumab; and FOLFIRI plus cetuximab. Treatment was continued until disease progression according to RECIST, version 1.1, unacceptable toxic effects, or a decision by the physician or patient to withdraw from the trial. Patients randomly assigned to the chemotherapy group could receive an ICI after disease progression at the discretion of the investigator.

End Points

The primary end point of this trial was PFS defined as the time from randomization to first disease progression, as assessed by investigators according to RECIST, version 1.1, or death from any cause. Patients alive without progression were censored on the date of last news. Second cancers were not considered. Secondary end points were overall survival (OS), overall response rate, time to best response (time from randomization to best response), duration of disease control (time from randomization to first disease progression in patients without progression at first disease assessment) and safety. Adverse events were evaluated throughout the trial and at 30 days after treatment discontinuation and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Calculation of Sample Size

We expected an improvement in PFS, in favor of avelumab, with a hazard ratio (HR) of 0.58. Considering a fixed design with a 2-sided α risk of 5% and a power of 80%, 106 events (progression or death) are needed to demonstrate this difference based on the Schoenfeld method. 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 had to be randomized, and we planned to enroll a total of 66 patients per group.

Statistical Analysis

For all end points, a 2-sided 95% CI was calculated. Survival was estimated using the Kaplan-Meier method. Comparisons by treatment group were performed using the log-rank test. The HR for the treatment effect was calculated using a Cox proportional hazards model if conditions of the model validity were applicable.

Analyses of primary and secondary efficacy end points were planned to be conducted on the mITT population (ie, all patients with mCRC and MSI and dMMR status using immunohistochemistry and polymerase chain reaction analysis), regardless of their eligibility criteria, and who received at least 1 dose of treatment in the study. Patients were analyzed according to the allocated group by randomization.

Safety analyses were performed on all patients receiving at least 1 dose of treatment. Patients were analyzed according to treatment received.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc), and R software, version 2023.06.0 (R Project for Statistical Computing). A 2-sided $P < .05$ was considered statistically significant.

Results

Study Population and Treatment

Between April 24, 2018, and April 29, 2021, 132 patients were randomized to receive avelumab (65 patients) or chemotherapy with or without a targeted agent (67 patients). Ten patients (6 in the chemotherapy group and 4 in the avelumab group) were excluded from the mITT population for the following reasons: 5 patients had microsatellite-stable disease, and 5 did not receive any study treatment due to early deaths (n = 3), consent withdrawal and inclusion in another trial (n = 1), and clinical progression precluding treatment administration (n = 1). According to the predefined mITT population of 122 patients (57 men [46.7%] and 65 women [53.3%]; median age, 66 [IQR, 56-76] years), 61 patients were finally randomized in each study group. All patients received their treatment according to treatment allocation at randomization (**Figure 1**).

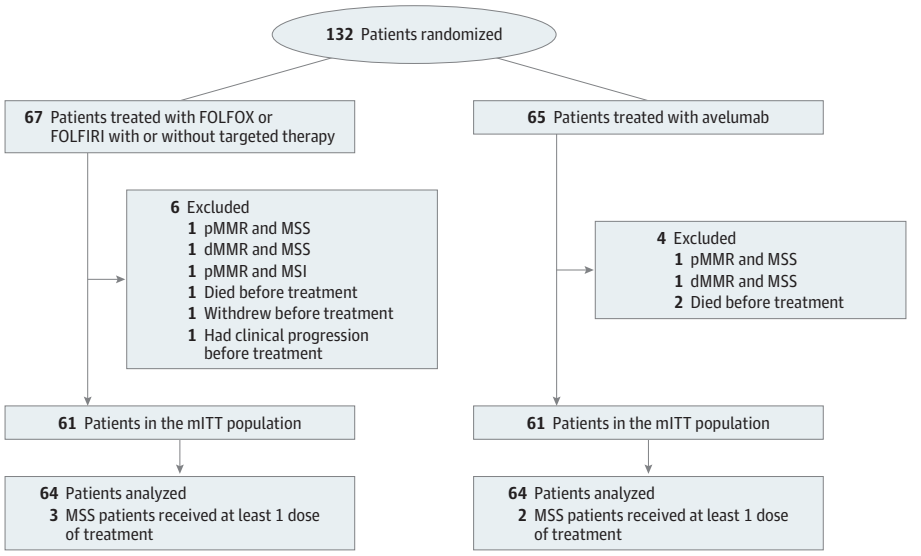
All demographic and baseline characteristics, including the previous line of therapy, were well balanced between the 2 groups, as shown in eTable 1 in Supplement 2. Eleven patients (9.0%) had WHO PS 2, though it was an exclusion criterion for the study. In the chemotherapy group, patients were treated with FOLFIRI plus bevacizumab (20 [32.8%]), FOLFIRI plus aflibercept (14 [22.9%]), FOLFIRI plus an anti-epidermal growth factor receptor (12 [19.7%]), FOLFOX plus bevacizumab (X [16.4%]), FOLFOX alone (1 [1.6%]), or FOLFIRI alone (4 [6.6%]).

At the data cutoff date of May 23, 2022, the median follow-up was 33.3 (95% CI, 28.3-34.8) months. The median duration of treatment was 7.4 (range, 0.03-46.5) months in the avelumab group and 5.1 (range, 0.03-19.7) months in the chemotherapy group. Length of treatment is summarized in eTable 2 in Supplement 2.

Progression-Free Survival

The median PFS in the avelumab group was 4.1 (range, 2.31-5.68) months; in the chemotherapy group, it was 6.2 (range, 4.11-7.29) months. Due to Kaplan-Meier curves crossing at 7.3 months corresponding to a PFS rate of 36%, the log-rank test and the HR of PFS analyses were not appropriate (log-rank $P = .30$), and various alternative approaches have been proposed in the literature to deal with such a feature of survival curves.[21-24] In this particular situation, the Qiu and Sheng test seems recommended.[21,22] Using this appropriate statistical test, avelumab was superior to chemotherapy with respect to PFS ($P = .03$) (**Figure 2**A). The estimated percentages of patients alive and progression free were 31.2% (95% CI, 20.1%-42.9%) at 12 months and 27.4% (95% CI, 16.8%-39.0%) at 18 months in the avelumab group; estimated percentages were 19.4% (95% CI, 10.6%-30.2%) at 12 months and 9.1% (95% CI, 3.2%-18.8%) at 18 months in the chemotherapy group. The estimated restricted mean survival time for PFS was also assessed, and after 36 months of follow-up also favored avelumab: 12.3 (95% CI, 8.7-15.8) months in the avelumab group compared with 8.1 (95% CI, 6.2-10.0) months in the chemotherapy group ($P = .04$).

Figure 1. Study Flowchart



dMMR indicates deficient mismatch repair; FOLFIRI, leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX, leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; mITT, modified intention to treat; MSI, microsatellite instability; MSS, microsatellite stability; pMMR, proficient MMR.

Response to Treatment

Overall response rate (18 [29.5%] vs 16 [26.2%]) and disease control rates (43 [70.5%] vs 47 [77.0%]), according to RECIST, version 1.1, were similar in the avelumab and chemotherapy groups, respectively (**Table 1**). The median time to best response was 2.0 (IQR, 1.8-2.5) months in the chemotherapy group vs 3.5 (IQR, 2.0-8.0) months in the avelumab group (P = .002). The percentage of patients with progressive disease as the best response was numerically higher in the avelumab group than in the chemotherapy group (17 [27.9%] vs 10 [16.4%]) (Table 1). Four patients in the chemotherapy group and 1 in the avelumab group died before first computed tomographic scan assessment.

Among patients with disease control, 28 (75.7%) in the avelumab group vs 9 (19.1%) in the chemotherapy group had ongoing disease control at 18 months. The median duration of disease control was 16.7 (IQR, 5.7-33.4) months in the avelumab group and 7.3 (IQR, 4.9-11.9) months in the chemotherapy group (P < .001) (Figure 2B and C).

Overall Survival

Overall survival was not different between treatment groups, with a median OS of 25.8 (95% CI, 14.1 to not reported [NR]) months in the avelumab group and 23.4 (95% CI, 13.0-NR) months in the chemotherapy group (HR, 0.94 [95% CI, 0.57-1.53]; P = .79) (eFigure 2 in Supplement 2). As of the cutoff date, 32 patients in each group (64 [52.5%]) had died.

At the time of data cutoff, 31 of 61 patients (50.8%) randomly assigned to the chemotherapy group had received an ICI in a subsequent line of therapy. Two were treated with durvalumab, 6 with dostarlimab, 10 with pembrolizumab, and 13 with nivolumab. Altogether, 31 patients in the chemotherapy group (83.8%) reaching a subsequent line of treatment received an ICI. At the time of data cutoff, in the avelumab group, 18 patients (29.5%) were still being treated with avelumab and 23 of the 43 remaining patients (53.5%) with progressive disease were able to receive subsequent anticancer therapy.

Safety

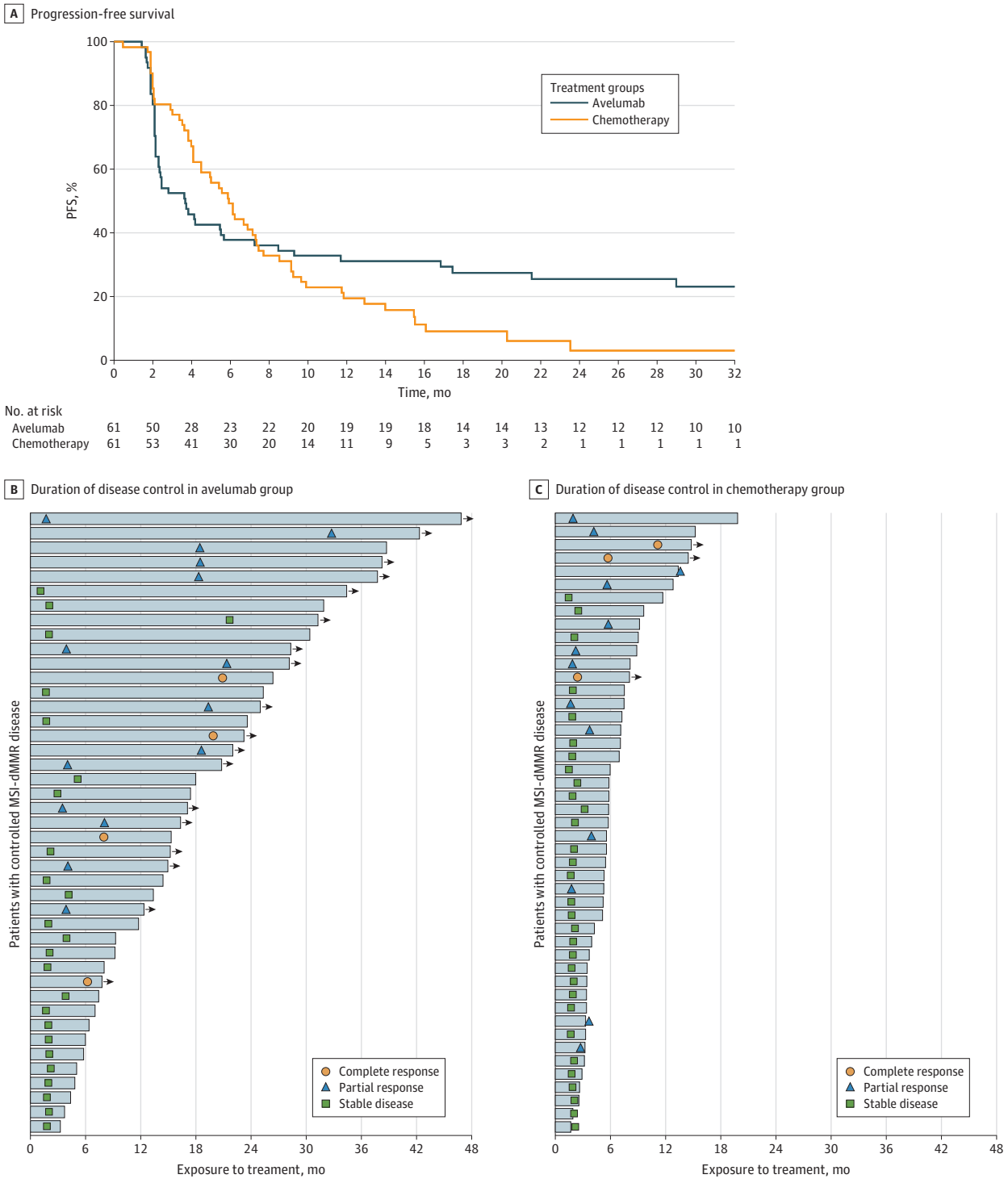
All patients receiving at least 1 dose of treatment were analyzed for safety. Treatment-related adverse events occurred in 56 of 63 patients (88.9%) in the avelumab group and in 63 of 64 patients (98.4%) in the chemotherapy group (P = .05). Adverse events of grade 3 or higher occurred in 20 patients (31.7%) in the avelumab group compared with 34 (53.1%) in the chemotherapy group (P = .02). The most common grade 3 or higher adverse events are summarized in **Table 2.** A total of 6 patients (9.5%) in the avelumab group and 7 (10.9%) in the chemotherapy group discontinued treatment owing to adverse events. No grade 5 adverse events occurred.

Immune-mediated adverse events (8 patients [12.7%]) and infusion reactions (3 patients [4.8%]) occurred in 11 of 63 patients (17.5%)—including 6 with grade 1 to 2 hypothyroidism, 5 with grade 1 to 2 hyperthyroidism, 1 with grade 3 colitis, and 2 with grade 2 and 1 with grade 3 infusion-related reactions (3 patients presented with >1 immune-mediated adverse event)—in the avelumab group compared with 2 of 64 patients (3.1%) with cetuximab infusion-related reactions in the chemotherapy group. No grade 5 immune-mediated adverse events or infusion reactions were observed.

Discussion

In this phase 2 randomized clinical trial, second-line avelumab was superior to chemotherapy with or without targeted agents with respect to PFS in patients with dMMR/MSI mCRC. This result is in line with previous reports on ICI efficacy in dMMR/MSI mCRC in different treatment lines.[12,15,16] To our knowledge, this is the second randomized study dedicated to this very specific population. Although PFS curves that cross late (7.3 months) preclude the use of HRs and medians to report the results, the difference in PFS between Kaplan-Meier curves from both treatment groups was statistically significant, and the du-

Figure 2. Progression-Free Survival and Duration of Disease Control in the Avelumab Group and the Chemotherapy Group



For duration of disease control, each bar represents 1 patient in the study. Rightward arrows indicate continuing treatment. dMMR indicates deficient mismatch repair; MSI, microsatellite instability; PFS, progression-free survival.

ration of disease control also clearly favored the avelumab group. In addition, the difference in restricted mean survival time, a complementary analysis for PFS performed when the proportional hazards assumption is violated, favored the use of avelumab. Tolerability also favored the avelumab group, with a difference in treatment-related grades 3 to 4 adverse events that is statistically significant and clinically relevant (31.7% vs 53.1%; $P = .02$). This rate of treatment-related adverse events of grade

Table 1. Response to Treatment per RECIST, Version 1.1[a]

Response	Treatment group	
	Avelumab (n = 61)	Chemotherapy (n = 61)
Response to treatment		
Complete response	4 (6.6)	3 (4.9)
Partial response	14 (23.0)	13 (21.3)
Stable disease	25 (41.0)	31 (50.8)
Progressive disease	17 (27.9)	10 (16.4)
Objective response rate	18 (29.5)	16 (26.2)
Disease control rate	43 (70.5)	47 (77.0)
Time to best response, median (IQR), mo	3.5 (2.0-8.0)	2.0 (1.8-2.5)

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumours.

[a] Unless indicated otherwise, data are expressed as No. (%) of patients.

Table 2. Treatment-Related Grades 3 and 4 Adverse Events[a]

Adverse event	Treatment group	
	Avelumab group (n = 63)	Chemotherapy group (n = 64)
All grades 3 and 4	20 (31.7)	34 (53.1)
Nausea and/or vomiting	0	2 (3.1)
Diarrhea	3 (4.8)	5 (7.8)
Stomatitis	0	2 (3.1)
Neutropenia	0	12 (18.8)
Neurotoxicity	1 (1.6)	2 (3.1)
Fatigue	0	7 (10.9)
Hypertension	1 (1.6)	7 (10.9)
Abnormal liver test results	5 (7.9)	1 (1.6)

[a] Graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Data are expressed as No. (%) of patients.

3 or higher is in accordance with those observed with other ICIs evaluated in dMMR/MSI mCRC, which ranged between 16% and 33%.[12,15,16] In addition, immune-related adverse events and infusion-related reactions were rare in patients treated with avelumab (12.7% and 4.8%, respectively) and mostly of grades 1 to 2. Altogether, the safety profile of avelumab in the current trial is consistent with that observed with avelumab across multiple tumor types.[16]

This trial also provides prospective data on PFS with chemotherapy alone or in combination with antiangiogenic or anti-epidermal growth factor receptor drugs in patients with dMMR/MSI mCRC as second-line treatment. The median PFS of 6.2 months and the objective response rate of 26.2% observed with chemotherapy are consistent with or even better than previously published data[25-28] suggesting the efficacy of chemotherapy with or without targeted agents in the second-line setting for these particular patients with mCRC.

When looking at the shape of the curves, we also observed progressive disease at first disease assessment in 27.8% of patients, which is superior to immediate progression in patients treated with SOC seen in 16.4% of patients. This percentage is very similar to that reported in the KEYNOTE-177 study, in which 29.4% of patients experienced immediate progression compared with only 12.0% of patients treated with SOC agents in the first-line setting.[16] This underlines the importance of identifying patients with dMMR/MSI status and upfront resistance to immunotherapy to select them for different treatment approaches such as immunotherapy combined with standard chemotherapeutic regimens or combinations of PD-1 or PD-L1 and CTLA-4 inhibitors or other immune-active compounds, currently explored in ongoing phase 3 studies.[29,30] Many markers of progressive disease during the first 2 months of PD-1 blockade therapy have been explored to date, but no clear marker of resistance has been identified.[28,31-33] The 1-year PFS rate is only 31%, suggesting that secondary resistance is also observed in a substantial number of patients. In the KEYNOTE-177 study, 1-year PFS rate was approximately 50%. This difference between the 2 studies may be due to several factors. First, avelumab is an anti-PD-L1 antibody, whereas pembrolizumab targets PD-1, and efficacy may differ between the 2 antibodies.[34] Second, at the time of this trial, immunotherapy was not available in France for patients with dMMR/MSI mCRC, and investigators may have selected patients with poor condition inappropriately to obtain such treatment for their patients. This is suggested by nearly 10% of patients with WHO PS 2, though PS 2 was an exclusion criterion and 10 patients experienced death within 60 days from treatment start. The discrepancy between 1-year PFS rates in our study and the first-line KEYNOTE-177 study may also indirectly suggest that using ICI in earlier lines of treatment is associated with higher rates and longer duration of disease control. The excellent results reported in the neoadjuvant setting also suggest that better outcomes can be obtained when treating patients with dMMR/MSI CRC and limited disease burden.[35]

In the present study, OS was not different between the 2 treatment groups, with median OS of 25.8 (95% CI, 14.1-NR) and 23.4 (95% CI, 13.0-NR) months in the avelumab and chemotherapy groups, respectively. However, 83.7% of patients from the chemotherapy group eligible for a subsequent treatment received an ICI in a later line of treatment. This important crossover rate may explain the absence of a difference in OS between our 2 study groups. Similarly, no significant differences in OS were observed in the KEYNOTE-177 study, with a median OS not reached (95% CI, 49.2-NR months) with pembrolizumab vs 36.7 (95% CI, 27.6-NR) months with chemotherapy.[36] In addition, it is of note that such survivals were never reported in a second-line trial for patients with mCRC. In the VELOUR[25] and RAISE[26] trials testing antiangiogenic drugs in the second-line setting in all-comer (MSI and microsatellite stable) patients with mCRC, survival ranged from 11.7 to 13.3 months. Reaching a median survival of about 2 years in the second-line setting underlines the important therapeutic effect of ICIs in dMMR-MSI mCRC, even beyond first-line treatment.

Strengths and Limitations

A major strength of the SAMCO-PRODIGE 54 study is the randomization between SOC and ICIs. Many nonrandomized trials suggest high efficacy of anti-PD-1 and anti-PD-L1 mAbs alone or in combination with anti-CTLA-4 mAbs in dMMR/MSI mCRC,[12,37] but evidence-based medicine usually requires randomized trials. The SAMCO-PRODIGE 54 trial is, to our knowledge, the second randomized clinical trial evaluating an ICI and the first in the second-line setting in these patients. The main study limitation is the probable inclusion of patients not meet-

ing all study inclusion criteria, as suggested by the number of patients with a WHO PS of 2 and presenting early death (within 2 months after enrollment).

Conclusions

Although pembrolizumab is generally used as a first-line treatment, it still happens that patients are not tested for MMR IHC or MSI status upfront and are thus treated with standard first-line chemotherapy regimens with or without targeted agents and are referred to expert centers after a first-line treatment not containing an ICI. The findings of this randomized clinical trial show that in such patients, avelumab led to significantly longer PFS and fewer treatment-related adverse events than chemotherapy and justifies the use of ICIs in such patients rather than standard second-line treatments.

ARTICLE INFORMATION

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