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Interplay between sarcopenia, GDF-15, and the efficacy of nivolumab plus ipilimumab in patients with mismatch repair deficient metastatic colorectal cancer: final survival analysis of the phase II GERCOR NIPICOL study

Leonard Depotte,[1] Paula Nay,[2] Christophe Borg,[3,4] Aurélia Meurisse,[5,6] Julie Henriques,[5,6] Jaafar Bennouna,[7] Christelle De La Fouchardière,[8] David Tougeron ,[9] Thibault Mazard,[10] Benoist Chibaudel,[11] Christophe Tournigand,[1,12] Dewi Vernerey,[5,6] Frédéric Pigneur,[13] Thierry Andre ,[12,14] Romain Cohen [12,14]

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For numbered affiliations see end of article.

Correspondence to
Dr Romain Cohen;
romain.cohen@aphp.fr

ABSTRACT

Background Sarcopenia and growth differentiation factor 15 (GDF-15) are linked to poor cancer survival. In this exploratory analysis, we evaluated their interaction with nivolumab-ipilimumab efficacy in chemoresistant metastatic colorectal cancer (mCRC) harboring microsatellite instability and/or mismatch-repair deficiency (MSI/dMMR), based on the final survival analysis of the NIPICOL phase II trial.

Patients and methods 57 patients with MSI/dMMR chemoresistant mCRC received nivolumab-ipilimumab for 3 months (3M), then, nivolumab alone for 9M. Skeletal muscle mass index (SMI) was evaluated by CT scan at baseline and 12M to assess sarcopenia. GDF-15 levels were assessed at baseline and 3M. Main endpoints were overall survival (OS) and immune Response Evaluation Criteria In Solid Tumors progression-free survival (iPFS).

Results After excluding three patients not confirmed as MSI/dMMR by central review, the overall median follow-up was 60.4 months. The 3-year and 5 year iPFS rates were 72.0% and 65.3%, with OS rates of 77.5% and 73.3%, respectively. Among 49 patients with evaluable GDF-15, high-baseline GDF-15 was associated with poorer survival: 3-year iPFS rate of 56.3% for GDF-15≥2500 versus 81.7% for GDF-15<2500 (PFS HR=2.45, 95% CI 0.91 to 6.55), 3-year OS rates of 61.4% versus 84.5% (OS HR=2.08, 95% CI 0.70 to 6.22). Of the 48 evaluable patients for SMI, 31 (65.0%) displayed sarcopenia at baseline. 11 out of 20 (55%) patients with baseline sarcopenia and assessed for SMI at 12M, reversed sarcopenia by 12M. They had higher baseline GDF-15 levels and greater GDF-15 decrease by 3M (delta mean change: −69.8% vs −40.3%) compared with patients who remained sarcopenic.

Conclusion 1-year nivolumab-ipilimumab demonstrates consistent efficacy after 5-year follow-up in an MSI/dMMR chemoresistant mCRC population. GDF-15 confirms to be a promising biomarker for sarcopenia and survival.

Trial registration number NCT03350126.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Microsatellite instability/mismatch repair deficiency (MSI/dMMR) is a crucial predictive biomarker for the efficacy of immune checkpoint inhibitors, significantly improving survival outcomes in patients with metastatic colorectal cancer (mCRC). Sarcopenia, known for its association with reduced quality of life and higher mortality, is an adverse prognostic factor in cancer, but its specific impact on patients with MSI/dMMR mCRC and its potential reversibility with immunotherapy remain unclear. Additionally, elevated levels of growth differentiation factor 15 (GDF-15) are linked to cancer-related cachexia and immune evasion, although the exact mechanisms are not fully understood, highlighting the need for further research into its role in cancer progression.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that a 1-year fixed duration of nivolumab-ipilimumab therapy provides durable efficacy in patients with MSI/dMMR chemoresistant mCRC, with 5-year progression-free survival (PFS) and overall survival (OS) rates comparable to longer treatments. It highlights the complex relationship between sarcopenia and immunotherapy outcomes, showing that while sarcopenia did not significantly impact treatment efficacy, only half of the patients experienced sarcopenia resolution. Additionally, the study establishes a link between elevated GDF-15 levels, sarcopenia, and poorer survival, indicating that GDF-15 may influence outcomes beyond its role in muscle loss.

INTRODUCTION

The identification of microsatellite instability/mismatch repair deficiency (MSI/

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest a need to reconsider the optimal duration of immunotherapy in MSI/dMMR mCRC, potentially reducing treatment length while maintaining efficacy. The study underscores the importance of accurately diagnosing MSI/dMMR status and monitoring sarcopenia, advocating for early interventions and personalized supportive care strategies. Additionally, it supports the development of targeted therapies against GDF-15, which could improve outcomes in sarcopenic patients and enhance the effectiveness of immune checkpoint inhibitors. These insights may influence future clinical guidelines, encouraging integrated approaches to address sarcopenia and cachexia in cancer treatment.

dMMR) as a predictive biomarker for the efficacy of immune checkpoint blockade represents a breakthrough in recent oncology. MSI/dMMR tumors display high levels of immunogenic neoantigens, resulting in increased tumor infiltration by cytotoxic lymphocytes.[1] In patients with metastatic colorectal cancer (mCRC), pembrolizumab and the nivolumab-ipilimumab combination,[2] both administered for a maximum of 2 years, have significantly improved patients' survival outcomes compared with first-line chemotherapy±targeted therapy.

Sarcopenia is a well-known adverse prognostic factor of patients with cancer, associated with reduced quality of life, increased treatment-related side effects, and higher mortality.[3–6] CT-based measurements[7] have been developed and validated for assessing sarcopenia (using the skeletal muscle mass index (SMI)) throughout cancer treatment. The impact of sarcopenia in patients with MSI/dMMR mCRC and its reversibility on immunotherapy effect remains to be determined.

Growth differentiation factor 15 (GDF-15) is a protein in the transforming growth factor beta (TGF-β) superfamily, functioning as a stress hormone secreted by various tissues in response to pro-inflammatory signals.[8] GDF-15 is significantly elevated in many cancers and is associated with weight loss, reduced physical capacity, and decreased survival.[9] Although its exact mechanisms are not fully understood, GDF-15 plays a crucial role in the development of cancer-associated cachexia, tumor invasion, and immune system evasion.[10]

The GERCOR NIPICOL phase II study evaluated 12 months of therapy with nivolumab-ipilimumab for patients with MSI/dMMR chemoresistant mCRC (NCT033501260).[11] Based on the final survival analysis, we conducted an exploratory study examining the frequency, survival association, and evolution of sarcopenia, along with GDF-15 levels in this patient population.

PATIENTS AND METHODS

Study design and patients

The single-arm, multicenter phase II study evaluated the nivolumab-ipilimumab combination in patients with chemoresistant mCRC with locally determined MSI and/or dMMR status. The main inclusion criteria were histologically confirmed mCRC locally assessed as MSI/dMMR, measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) V.1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and resistance or intolerance to fluoropyrimidines, oxaliplatin, irinotecan, antiangiogenics, and anti-epidermal growth factor receptor agents for *RAS/RAF* wild-type tumors.[11]

Patients received nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for four cycles (induction phase), followed by nivolumab 3 mg/kg intravenously every 2 weeks until disease progression, discontinuation because of toxicity, death, withdrawal of consent, or a maximum of 20 infusions, equivalent to 1 year of therapy.

MSI/dMMR status was centrally confirmed using immunohistochemistry and pentaplex PCR. Misdiagnosed cases (ie, microsatellite stable or mismatch proficient) were excluded from the analyses presented here.

The study was approved by the independent ethics committee and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Sarcopenia diagnosis

CT scans performed at baseline and 12 months (ie, theoretical end of treatment period) were collected to centrally assess muscle mass. Identical CT instrumentation parameters were used for each patient at baseline and month 12 to optimize reproducibility of anthropomorphic measurements. Muscle mass was measured using semi-automatic segmentation on a dedicated post-treatment station (Advantage Window V.4.7, GE Healthcare, Buc, France) as a cross-sectional area at the middle of the L3 level. The total lumbar muscle cross-sectional area (CSA) was measured in cm^2, with a pre-established density threshold of −29 to +150 Hounsfield units (including the external and internal obliques, paraspinal, rectus abdominis, transversus abdominis, and psoas muscles).[12] All CSAs were normalized to stature, following standard body composition evaluation practices, resulting in SMI: SMI=CSA/height^2 (cm^2/m^2). All imaging was reviewed by one expert radiologist blinded to patients' survival status and initial data.[13] SMI cut-offs defined by Martin *et al*[7] were used for sarcopenia diagnosis: L3 SMI<43 cm^2/m^2 in males with body mass index (BMI)<25.0 or <53 cm^2/m^2 in males with BMI≥25, and<41 cm^2/m^2 in females, regardless of BMI.

GDF-15 measurement

Blood samples were collected at baseline and 3 months and processed immediately for plasma freezing. GDF-15 levels were determined using the Human GDF-15 DuoSet ELISA Kit (R&D Systems, DY957), according to the manufacturer's instructions. Each sample was analyzed in duplicate, and robustness was ensured by repeating measures

of a control plasma batch across all plates. Experiments were carried out in a blinded fashion to eliminate bias.

Statistical analysis

The primary endpoint was to evaluate the disease control rate at 12 weeks according to RECIST V.1.1 and immune RECIST (iRECIST) criteria by central review (previously published elsewhere).[11] Secondary endpoints were overall survival (OS), progression-free survival by iRECIST (iPFS) and objective response rate (ORR) as defined in the princeps publication.

The objectives of this post-hoc analysis were (1) to evaluate the frequency of sarcopenia at baseline, its prognostic effect, and its evolution from baseline to the theoretical end of the treatment period (ie, month 12) and (2) to evaluate the survival association of GDF-15 level at baseline and 3 months (end of the induction phase).

Continuous and categorical variables were described by medians (IQR) and frequencies (percentage), respectively, and according to sarcopenic status and GDF-15 level at baseline. Median PFS and OS, and the proportion of patients meeting these endpoints at specific time points, were estimated by the Kaplan-Meier method. The 95% CIs were calculated using log-log transformation. Median follow-up was calculated by the reverse Kaplan-Meier method. The restricted cubic splines method was applied to model the relationship between the baseline value of GDF-15 in its continuous form and to determine optimal cutoffs. The association between sarcopenic status, GDF-15 level, and survival was estimated using univariable Cox proportional hazards regression models, with HR and 95% CI provided.

All statistical analyses were conducted using SAS V.9.4 and R V.4.3.0. Due to the updated nature of the results and the post-hoc context of the analysis, no p values were provided for comparisons, instead, 95% CIs were proposed to quantify the precision of the estimations.

RESULTS

Population

A total of 57 patients with MSI/dMMR mCRC were included from December 2017 to November 2018. Of these, three patients had a tumor reclassified as MSS/pMMR by central assessment and were therefore excluded from the analysis. CT-based body mass composition measurements were performed for 48 patients at baseline and for 32 patients who remained free of progression at 12 months. GDF-15 assays were performed in 49 patients at baseline and in 45 patients at 3 months, resulting in 29 patients with both body composition parameters assessed at baseline and 12 months, as well as GDF-15 levels available at baseline and 3 months (figure 1). Baseline characteristics of the study population are detailed in table 1.

Updated final survival results

Median follow-up was 60.4 months (95% CI 59.5 to 63.1). 36 patients (63.2%) completed 1 year of treatment

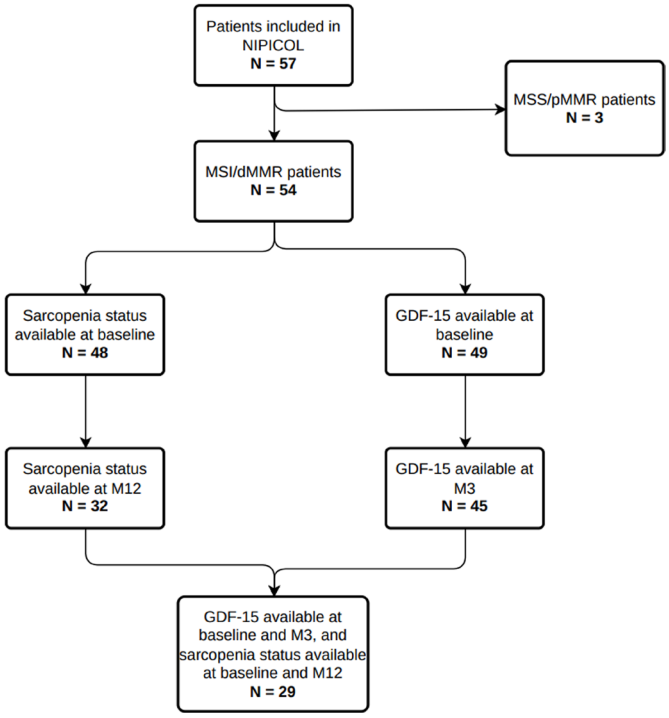

Figure 1 Study flowchart. GDF-15, growth differentiation factor 15; MSI/dMMR, microsatellite instability and/or mismatch-repair deficiency; M3, 3 months; M12, 12 months; N, number of patients.

(figure 2). The 3-year and 5-year iPFS rates were 72.0% (95% CI 57.9% to 82.1%), and 65.3% (95% CI 50.5% to 76.6%), with the 3-year and 5-year OS rates of 77.5% (95% CI 63.8% to 86.5%) and 73.3% (95% CI 59.0% to 83.3%), respectively (figure 3). Concerning the best response rate, 19 (35.2%) patients had complete responses, 21 (38.9%) had partial responses, 9 (16.7%) had stable diseases, and 2 (3.7%) had progressions according to iRECIST criteria. Three (5.6%) were non-evaluable. Six patients experienced disease progression after 12 months (best observed response: partial response=4 and stable disease=2), of which two received a second course of nivolumab, resulting in one partial response and one disease progression (figure 2).

Sarcopenia and GDF-15 at treatment initiation

The prevalence of baseline sarcopenia was 65% (31 of 48 evaluable patients). Performance status was more frequently altered in sarcopenic patients (ECOG PS1: 80.7% vs 35.3% in the non-sarcopenic group). The median BMI was lower in the sarcopenic group (median IQR 21.6 (19.1–23.5) and 24.0 (23.3–27.6) kg/m^2; table 1). Body mass composition measurements by sarcopenic status are provided in online supplemental table 1.

Baseline sarcopenia was associated with a numerically detrimental effect on survival outcomes, with 5-year iPFS rates of 63.1% (95% CI 47.8% to 83.3%) versus 75.5% (95% CI 57.1% to 99.7%; HR=1.83, 95% CI 0.58 to 5.77), and 5-year OS rates of 66.2% (95% CI 51.1% to 85.9%) vs 88.2% (95% CI 74.2% to 100.0%; OS HR=3.14,

Table 1 Patient characteristics at baseline

	NIPICOL MSI/dMMR confirmed population n=54	Sarcopenia status available at baseline n=48		GDF-15 available at baseline n=49	
		Non-sarcopenic patients (n=17)	Sarcopenic patients (n=31)	GDF-15<2500 (n=33)	GDF-15>2500 (n=16)
Age, years median (Q1–Q3)	57.1 (43.7–63.8)	49.7 (37.6–63.1)	56.5 (43.7–63.1)	57.7 (30.6–77.3)	55.5 (22.2–78.5)
Sex, n (%)					
Male	30 (55.6)	13 (76.5)	14 (45.2)	19 (57.6)	9 (56.3)
Female	24 (44.4)	4 (23.5)	17 (54.8)	14 (42.4)	7 (43.8)
ECOG performance status, n (%)					
0	17 (31.5)	11 (64.7)	6 (19.4)	13 (39.4)	2 (12.5)
1	37 (68.5)	6 (35.3)	25 (80.6)	20 (60.6)	14 (87.5)
Body mass index, kg/m², median (Q1–Q3)	22.5 (20.3–24.9)	24.0 (23.3–27.6)	21.6 (19.1–23.5)	22.5 (19.8–26.3)	22.8 (20–25.2)
Primary tumor location, n (%)					
Right-sided	24 (44.4)	10 (58.8)	15 (48.4)	18 (54.5)	8 (50.0)
Left-sided	29 (53.7)	6 (35.3)	16 (51.6)	15 (45.5)	7 (43.8)
Both	1 (1.9)	1 (5.9)	0	0	1 (6.2)
Mutational status, n (%)					
BRAF mutation	9 (16.7)	2 (11.8)	4 (12.9)	6 (18.2)	2 (12.5)
RAS mutation	26 (48.1)	9 (52.9)	16 (51.6)	14 (42.4)	10 (62.5)
RAS/*BRAF* wild-type	18 (33.3)	5 (29.4)	11 (35.5)	13 (39.4)	4 (25)
Unknown	1 (1.9)	1 (5.9)	0 (0)	0 (0)	0 (0)
Tumor grade, n (%)					
Grade 1–2	29 (53.7)	10 (58.8)	14 (45.2)	20 (60.6)	7 (43.8)
Grade 3–4	18 (33.3)	6 (35.3)	11 (35.5)	8 (24.2)	7 (43.8)
Missing	7 (13.0)	1 (5.9)	6 (19.3)	5 (15.2)	2 (12.4)
Stage at diagnosis, n (%)					
II	3 (5.6)	2 (11.8)	1 (3.2)	2 (6.1)	1 (6.3)
III	17 (31.5)	8 (47.0)	7 (22.6)	10 (30.3)	5 (31.3)
IV	26 (48.1)	6 (35.3)	18 (58.1)	16 (48.5)	7 (43.8)
Missing	8 (14.8)	1 (5.9)	5 (16.1)	5 (15.2)	3 (18.8)
Nb of metastatic sites, n (%)					
≤2	39 (72.2)	12 (70.6)	23 (74.2)	22 (66.7)	14 (87.5)
>2	15 (27.8)	5 (29.4)	8 (25.8)	11 (33.3)	2 (12.5)
Nb of prior treatment lines sites, n (%)					
≤2	28 (51.9)	9 (52.9)	17 (54.8)	16 (48.5)	9 (56.3)
>2	25 (46.3)	7 (41.2)	14 (45.2)	17 (51.5)	7 (43.8)
Missing	1 (1.8)	1 (5.9)	0	0	0

ECOG, Eastern Cooperative Oncology Group; GDF-15, growth differentiation factor 15; MSI/dMMR, microsatellite instability and/or mismatch-repair deficiency; N, number.

95% CI 0.69 to 14.36; figure 4). No association between sarcopenia and immune-related adverse event rates was observed.

Among the 49 assessed patients, the median level of GDF-15 at baseline was 1949 pg/mL (IQR 1016–3152). Sarcopenic patients at baseline had a median GDF-15 level of 2206 ng/mL (IQR 1521–3183), compared with 1434 ng/mL (IQR 725–3234) for non-sarcopenic patients. A linear relationship was observed between the risk of progression according to iRECIST criteria and baseline GDF-15 level (online supplemental figure 1), with a threshold value of 2500 pg/mL to best discriminate patients at risk of disease progression or death. Patients with GDF-15≥2500 pg/mL (n=16) exhibited

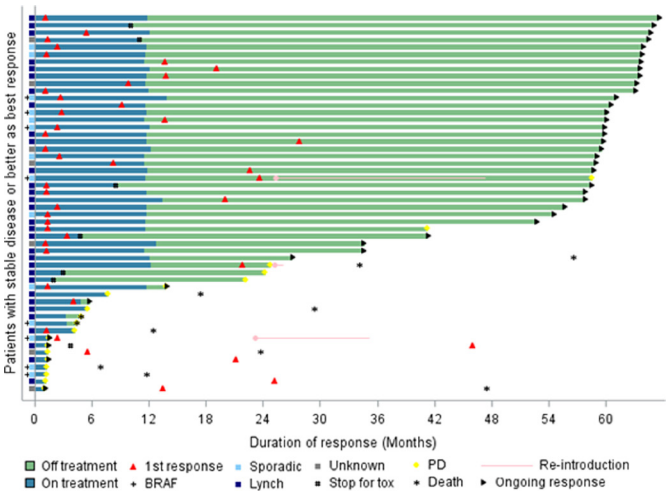

Figure 2 Swimmer plot. BRAF, BRAF V600E mutation; PD, disease progression.

more frequently altered performance status (87.5% vs 60.6%) and higher tumor grade (poorly differentiated or undifferentiated tumor: 43.8% vs 21.2%) compared with those with low baseline GDF-15 level (n=33; table 1). High baseline GDF-15 was associated with shorter iPFS estimations, with the 3-year and 5-year iPFS rates of 56.3% and 49.2% in the high GDF-15 group versus 81.7% and 74.4%, respectively, for patients with low baseline GDF-15. Similar results were observed for OS, with the 3-year and 5-year OS rates of 61.4% and 61.4% in the high GDF-15 group versus 84.5% and 78.0% in the low GDF-15 group (figure 5).

Longitudinal follow-up

No patient developed sarcopenia under immunotherapy (12 patients assessed at 12 months out of 17 patients without baseline sarcopenia), except for one male patient who had stable SMI values but an increased BMI, which surpassed the patient BMI cut-off and consequently changed the SMI threshold according to Martin's criteria.

Among the 31 patients with baseline sarcopenia, 20 were assessed for body mass composition at 12 months: 9 (45.0%) remained sarcopenic at 12 months. Compared with those whose sarcopenia reversed at 12 months, these nine patients had lower baseline SMI and a smaller relative increase in SMI (+4.5% vs +18.6%; online supplemental figure 2). They also had lower baseline GDF-15 levels (median of 1264 (IQR 410–2218) vs 2422 (IQR 1949–3367)) and a smaller relative reduction in GDF-15 between baseline and month 3 (−40.3% vs −69.8%).

Median GDF-15 level at 3 months was 865 pg/mL (IQR 594–1437), with a median relative difference from baseline to month 3 of −48.5% (IQR −70.0 to −6.3). Patients whose GDF-15 increased between baseline and 3 months tended to have poorer survival compared with those whose GDF-15 decreased (online supplemental figure 3).

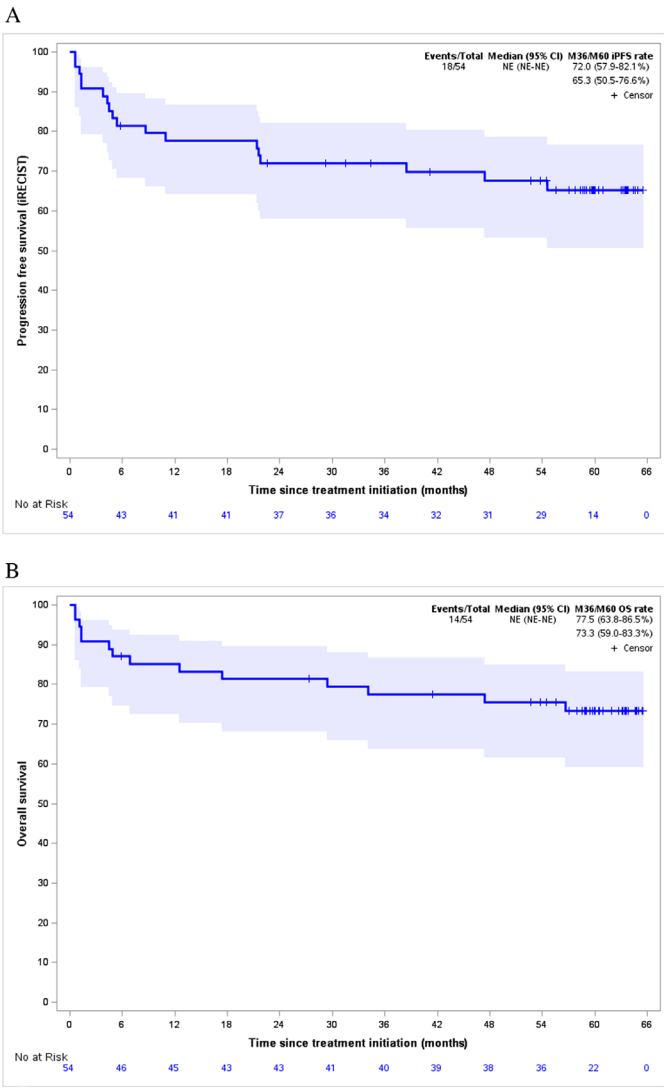

Figure 3 Progression-free survival by iRECIST (A) and overall survival (B) in the MSI/dMMR population. iPFS, iRECIST progression-free survival; iRECIST, immune Response Evaluation Criteria In Solid Tumors; MSI/dMMR, microsatellite instability and/or mismatch-repair deficiency; OS, overall survival.

DISCUSSION

The GERCOR NIPICOL multicenter phase II study demonstrated that the nivolumab-ipilimumab combination with a fixed 1-year treatment duration exhibits robust and durable efficacy in patients with MSI/dMMR chemoresistant mCRC, with 5-year iPFS and OS rates of 65.3% and 73.3%, respectively.

These survival results align with those from other trials testing immune checkpoint inhibitors (ICIs) for 2 years or more. In the non-randomized, multicohort CheckMate-142 trial (locally assessed MSI/dMMR status),[14 15] the 48-month PFS and OS rates were respectively 54% and 71% in the pretreated cohort (second-line or more, n=119), and 51% and 72% in the first-line cohort. Updated results[16] showed the 60-month PFS and OS rates of 55% and 67%, respectively. The NIPICOL trial's fixed 1-year treatment duration raises questions about the optimal

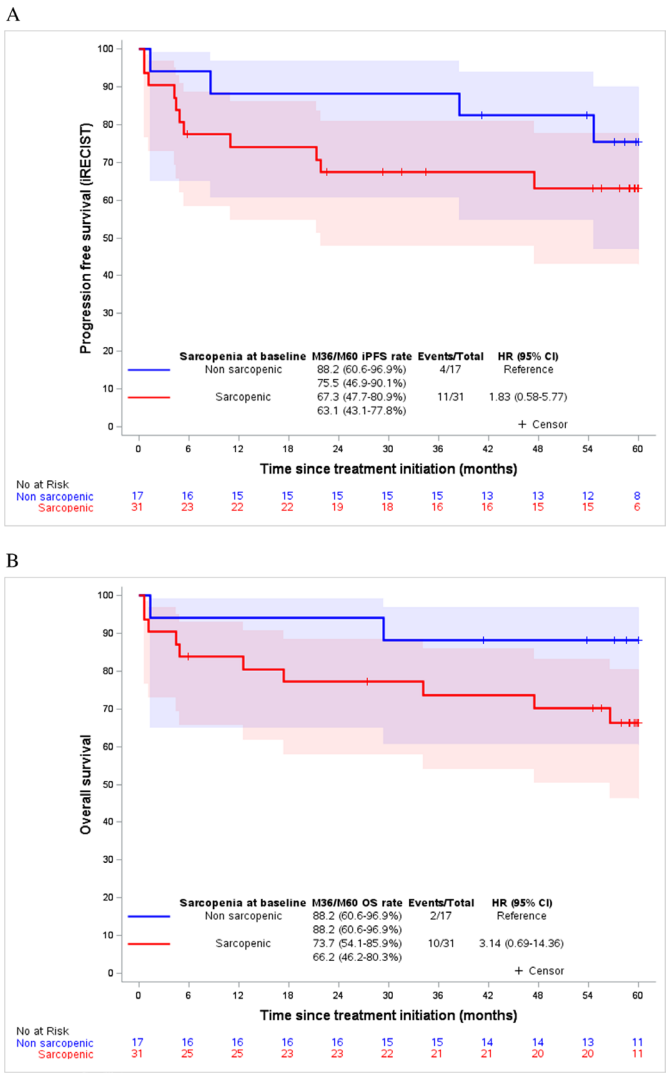

Figure 4 Progression-free survival (A) and overall survival (B) in the sarcopenic (red) and non-sarcopenic group (blue) at baseline. iPFS, iRECIST progression-free survival; iRECIST, immune RECIST; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors.

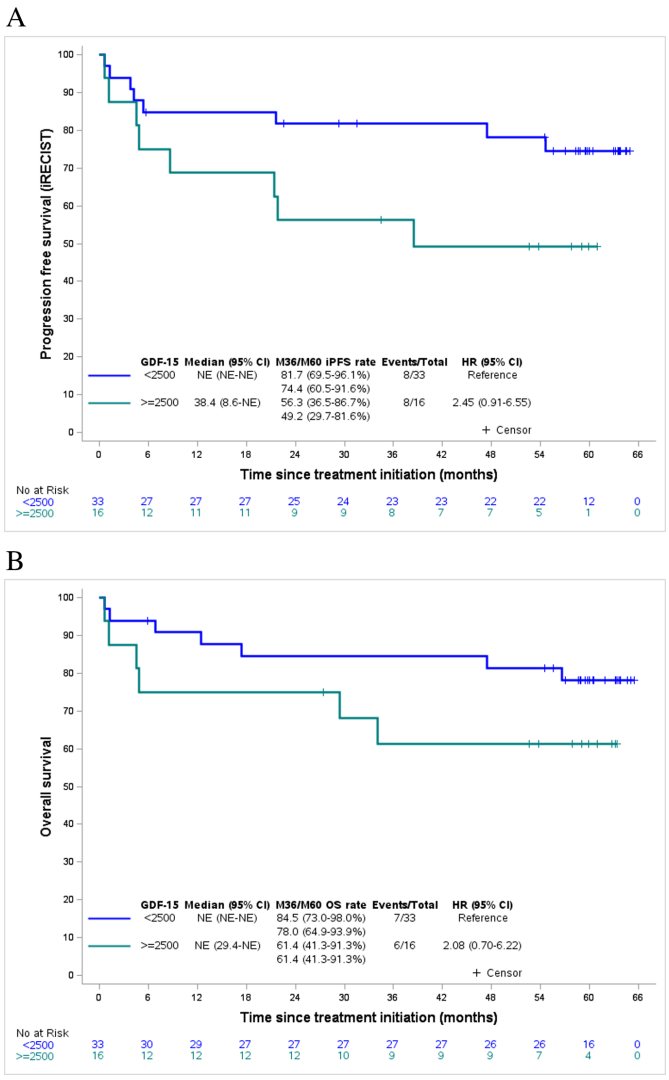

Figure 5 Progression-free survival (A) and overall survival (B) according to baseline GDF-15 levels. GDF-15, growth differentiation factor 15; iPFS, iRECIST progression-free survival; iRECIST, immune RECIST; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors.

duration of nivolumab-ipilimumab therapy for patients with MSI/dMMR mCRC. Importantly, we excluded patients with misdiagnosed MSI/dMMR tumors from this updated survival analysis (3 MSS and pMMR out of 57 included patients), consistent with the CheckMate-8HW phase III trial,[2] which centrally confirmed MSI/dMMR status (15% of patients were not confirmed with MSI/dMMR phenotype). These results emphasize the critical need for optimal diagnostic methods to confirm MSI/dMMR status.[17]

This is the first report on the changes in body composition parameters under immunotherapy in patients with MSI/dMMR mCRC. While ICIs have shown significant survival and quality of life benefits,[2 18] their impact on sarcopenia, a known driver of morbidity and mortality,[19] remains undocumented. Here, two-thirds of patients exhibited sarcopenia at baseline. Among those alive and progression-free at 12 months, half showed resolution of sarcopenia, while 47% remained sarcopenic despite the effectiveness of immunotherapy. Those who did not recover had severe sarcopenia, with significantly lower baseline SMI. Intriguingly, they had lower baseline GDF-15 levels and smaller GDF-15 decreases over time than those who recovered from sarcopenia. One may suggest that they had comorbidities (ie, apart from cancer) partly responsible for sarcopenia in a GDF-15-independent manner. Our findings may help identify these patients at diagnosis, allowing for early intervention to manage sarcopenia.

In this study, baseline sarcopenia did not significantly impact immunotherapy efficacy. Although survival outcomes were numerically lower for sarcopenic patients, the difference was not statistically significant. This contrasts with a recent meta-analysis, which identified sarcopenia as an independent negative prognostic factor in patients receiving ICI as monotherapy across various

cancer types, with reductions of 14.6% in ORR, 21.2% in 1-year PFS, and 23% in 1-year OS.[20] Our study, focusing on dual anti-programmed cell death protein 1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy in a highly responsive population, may have compensated for immune dysfunctions seen in sarcopenic patients, explaining our results.

The role of GDF-15 in cancer-related anorexia, as part of the cachexia phenomenon, is well established, largely due to its impact on appetite-regulating centers in the hypothalamus. However, several preclinical data suggest that GDF-15 may directly contribute to muscle mass loss, and hence to sarcopenia, independently of food intake.[19] In our study, elevated GDF-15 was associated with sarcopenia, and patients who recovered from it showed higher baseline GDF-15 levels and a stronger decrease in GDF-15 over time than those who remained sarcopenic despite immunotherapy. These findings align with recent preclinical and phase 1 studies, reflecting a growing interest in therapies targeting GDF-15. This interest was further enhanced by the positive results of the first randomized, placebo-controlled trial evaluating ponsegromab, a monoclonal antibody targeting GDF-15, in patients with cancer cachexia and GDF-15 level over 1500 pg/mL.[21]

Importantly, GDF-15 was linked to survival, with an optimized threshold of 2500 pg/mL: high baseline GDF-15 and its increase over time were associated with poorer survival outcomes. This threshold is similar to that found in the study by Hong *et al*,[22] which showed that GDF-15 level above 1945 ng/mL was associated with poorer outcomes in patients with advanced lung cancer treated with immunotherapy. However, although sarcopenia and GDF-15 were correlated, the GDF-15 threshold that best predicted sarcopenia (1300 pg/mL) was different from that predicting patients' prognosis (2500 pg/mL). These results suggest that GDF-15's adverse prognostic impact extends beyond its role in sarcopenia, potentially exerting a more direct effect on tumor progression and immune evasion.[10] This hypothesis is being explored by the ongoing GDFather-2 (NCT04725474) and GDFather-Neo (NCT06059547) trials, which are evaluating visugromab (an anti-GDF-15 antibody) in combination with nivolumab in several cancer types, with the objective of increasing tumor sensitivity and thus improving response to anti-PD-1 therapies.

Our study also has several limitations. First, the results of this post-hoc analysis on the association between sarcopenia, GDF-15, and survival should be considered exploratory: the small sample size limited the statistical power, and missing data further reduced the evaluable population. Similarly, we were unable to perform a multivariate analysis due to the low number of events, reflecting the high efficacy of the treatment. Finally, some parameters (eg, muscle strength, nutritional status, and inflammatory markers) were not collected in the NIPICOL study. The absence of these data prevents us from drawing comprehensive conclusions about cachexia, which encompasses all these parameters in its definition.

The 1-year nivolumab-ipilimumab combination demonstrated durable efficacy in patients with MSI/dMMR chemoresistant mCRC. Favorable outcomes were observed despite a high prevalence of sarcopenia, which resolved in only half of the patients with baseline sarcopenia and disease control at 12 months. High levels of the cancer-associated cachexia factor GDF-15 were associated with baseline sarcopenia and poor survival outcomes, but higher probability to recover from baseline sarcopenia under the effect of immunotherapy, emphasizing the need for personalized supportive care and innovative targeted therapeutic approaches.

Author affiliations
[1]Department of Medical Oncology, Univ Paris Est Creteil, INSERM, IMRB, AP-HP, Hopital Henri Mondor, Creteil, Île-de-France, France
[2]Department of Medical Oncology, Hôpital Saint-Antoine, Paris, Île-de-France, France
[3]Medical Oncology, Hôpital Jean Minjoz, Besancon, France
[4]TIMc, UMR 1098, Besancon, Bourgogne-Franche-Comté, France
[5]EFS, INSERM, UMR RIGHT, University of Franche-Comté, Besancon, Bourgogne-Franche-Comté, France
[6]Methodology and Quality of Life Unit in Oncology, Besançon University Hospital Center, Besancon, France
[7]Department of Digestive Oncology, University Hospital Centre Nantes, Nantes, Pays de la Loire, France
[8]Medical Oncology, Centre Leon Berard, Lyon, Rhône-Alpes, France
[9]Department of Hepato-Gastroenterology, CHU Poitiers, Poitiers, France
[10]Department of Medical Oncology, Institut de Recherche en Cancérologie de Montpellier, Montpellier, Languedoc-Roussillon, France
[11]Department of Medical Oncology, Hospital Franco-Britannique, Fondation Cognacq-Jay, Paris, France
[12]GERCOR, Paris, France
[13]Department of Radiology, University Hospital of Henri Mondor, Créteil, France
[14]Department of Medical Oncology, Hôpital Saint-Antoine, AP-HP, and INSERM UMRS 938, Équipe Instabilité des Microsatellites et Cancer, Équipe Labellisée par la Ligue Nationale Contre le Cancer, SIRIC CURAMUS, Centre de recherche Saint Antoine, Sorbonne Universite, Paris, Île-de-France, France

X David Tougeron @david_tougeron

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ORCID iDs
David Tougeron http://orcid.org/0000-0002-8065-9635
Thierry Andre http://orcid.org/0000-0002-5103-7095
Romain Cohen http://orcid.org/0000-0001-9602-5162

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