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## RESEARCH ARTICLE

## Cancer Therapy and Prevention

# Complete pathological response after chemotherapy or immune checkpoint inhibitors in deficient MMR metastatic colorectal cancer: Results of a retrospective multicenter study

Pauline Marolleau<sup>1</sup> | David Tougeron<sup>2</sup>  | Benoit Allignet<sup>3</sup> | Romain Cohen<sup>4</sup>  | David Sefrioui<sup>5</sup>  | Blandine Gallet<sup>6</sup> | Frédéric Dumont<sup>7</sup> | Rosine Guimbaud<sup>8</sup> | Emily Alouani<sup>8</sup> | Guillaume Passot<sup>9</sup> | Grégoire Desolneux<sup>10</sup> | François Ghiringhelli<sup>11</sup>  | Frédéric Marchal<sup>12</sup> | Farouk Mourthadhoi<sup>13</sup> | Romain Coriat<sup>14</sup> | Romain Desgrippes<sup>15</sup> | Christophe Locher<sup>16</sup> | Gaël Goujon<sup>17</sup> | Gaëtan Des Guetz<sup>17</sup> | Thomas Aparicio<sup>18</sup>  | Etienne Paubelle<sup>19</sup> | Aurélien Dupré<sup>20</sup> | Christelle de la Fouchardière<sup>1,21</sup> 

<sup>1</sup>Medical Oncology Department, Leon Berard Center, Lyon, France

<sup>2</sup>Gastroenterology and Hepatology Department, Poitiers University Hospital, University of Poitiers, Poitiers, France

<sup>3</sup>Department of Radiation Oncology, Leon Berard Center, Lyon, France

<sup>4</sup>Department of Medical Oncology, Saint-Antoine Hospital, Sorbonne Université, AP-HP, and INSERM, Unité Mixte de Recherche Scientifique 938, Centre de Recherche Saint-Antoine, Equipe Instabilité des Microsatellites et Cancer, Equipe labellisée par la Ligue Nationale contre le Cancer, Paris, France

<sup>5</sup>Normandy Centre for Genomic and Personalized Medicine and Department of Hepatogastroenterology, Normandie Univ, UNIROUEN, Inserm U1245, IRON group, Rouen University Hospital, Rouen, France

<sup>6</sup>Department of Medical Oncology, Val d'Aurelle Center, Montpellier, France

<sup>7</sup>Department of Surgical Oncology, Comprehensive Cancer Center, Institut de Cancérologie de l'Ouest, France

<sup>8</sup>Digestive Oncology Department, Rangueil Hospital, University Hospital of Toulouse, France

## Abstract

About 5% of the patients with metastatic colorectal cancers (mCRC) present microsatellite instability (MSI)/deficient mismatch repair system (dMMR). While metastasectomy is known to improve overall and progression-free survival in mCRC, specific results in selected patients with dMMR/MSI mCRC are lacking. Our study aimed to describe metastasectomy results, characterize histological response and evaluate pathological complete response (pCR) rate in patients with dMMR/MSI mCRC. We retrospectively reviewed data from all consecutive patients with dMMR/MSI mCRC who underwent surgical metastasectomy between January 2010 and June 2021 in 17 French centers. Primary outcome was to assess the pCR rate defined by tumor regression grade (TRG) 0. Secondary endpoints included relapse-free survival (RFS) and overall survival (OS), and explored TRG as predictive factor for RFS and OS. Among the 88 patients operated, 109 metastasectomies were performed in 81 patients after neoadjuvant treatment [chemotherapy ± targeted therapy (CTT): 69, 85.2%; immunotherapy (ICI): 12, 14.8%], and pCR was achieved in 13 (16.1%) patients. Among the latter, pCR rate were 10.2% in the patients having received CTT (N = 7) and 50.0% in the patients treated with ICI (N = 6). Radiological response did not predict TRG. With a median follow-up of 57.9 (IQR 34.2-81.6) months, median RFS was 20.2 (15.4-not reached) months, median OS was not reached. Major pathological responses (TRG0 + TRG1) were significantly associated

**Abbreviations:** dMMR, deficient mismatch repair system; ICI, immune checkpoint inhibitors; LS, Lynch syndrome; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; OS, overall survival; pCR, pathological complete response; pMMR, proficient mismatch repair system; RFS, relapse-free-survival; TRG, tumor regression grade.

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<sup>9</sup>Department of General Surgery and Surgical Oncology, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France

<sup>10</sup>Department of Surgical Oncology, Bergonie Institute, Bordeaux, France

<sup>11</sup>Department of Medical Oncology, GF Leclerc Center, Dijon, France

<sup>12</sup>Department of Surgical Oncology, Lorraine Cancer Center, Vandoeuvre les Nancy, France

<sup>13</sup>Department of General Surgery, Saint Etienne University Hospital, Jean Monnet University, Saint Etienne, France

<sup>14</sup>Gastroenterology Department, Cochin University Hospital, Université de Paris, APHP, Paris, France

<sup>15</sup>Gastroenterology Department, Saint Malo General Hospital, Saint Malo, France

<sup>16</sup>Gastroenterology and Digestive Oncology Department, Meaux Hospital, Meaux, France

<sup>17</sup>Gastroenterology Department, Bichat Hospital, Paris, France

<sup>18</sup>Gastroenterology Department, Saint Louis Hospital, Paris, France

<sup>19</sup>Hematology Department, Amiens University Hospital, Amiens, France

<sup>20</sup>Surgical Department, Centre Léon Bérard, Lyon, France

<sup>21</sup>Medical Oncology Department, Institut Paoli-Calmettes, Marseille, France

#### Correspondence

Christelle de la Fouchardière, Medical Oncology Department, Centre Léon Bérard, 28, rue Laennec, 69373 Lyon cedex 08, France.

Email: [christelle.delafouchardiere@lyon.unicancer.fr](mailto:christelle.delafouchardiere@lyon.unicancer.fr); [delafouchardierec@ipc.unicancer.fr](mailto:delafouchardierec@ipc.unicancer.fr)

with longer RFS (HR 0.12, 95% CI 0.03-0.55;  $P = .006$ ). The pCR rate of 16.1% achieved with neoadjuvant treatment in patients with dMMR/MSI mCRC is consistent with previously reported rates in pMMR/MSS mCRC. Immunotherapy showed better pCR rate than chemotherapy  $\pm$  targeted therapy. Further prospective trials are needed to validate immunotherapy as neoadjuvant treatment in resectable/potentially resectable dMMR/MSI mCRC and identify predictive factors for pCR.

#### KEYWORDS

deficient mismatch repair system, immune checkpoint inhibitors, metastatic colorectal cancer, microsatellite instability, neoadjuvant treatment, pathological complete response

#### What's new?

Pathological responses to neoadjuvant treatment have been shown to predict survival outcome after surgery in metastatic colorectal cancer. However, most of the current data were collected before the approval of immune checkpoint inhibitors as standard treatment for metastatic colorectal cancer in Europe and the use of MMR/MSI status as predictive response factor. This retrospective multicenter study in dMMR/MSI metastatic colorectal cancer patients who underwent metastasectomy shows a pathological complete response rate of 16.1% to neoadjuvant treatment, comparable to that in pMMR/MSS metastatic colorectal cancer patients. Immunotherapy showed a better pathological complete response rate than chemotherapy with or without targeted therapy.

## 1 | INTRODUCTION

Microsatellite instability (MSI) results from impaired DNA mismatch repair (MMR) system. Cells with abnormally functioning MMR are unable to detect and repair errors that spontaneously occur during DNA replication and preferentially in microsatellites due to their repetitive nature.<sup>1</sup> Along with the accumulation of frameshift mutations, neoproteins and potential neoantigen are produced. This high tumoral mutation burden in tumors results in increased sensitivity to immune checkpoint inhibitors (ICI).<sup>2,3</sup> Deficient MMR system (dMMR) is observed in about 5% of the patients with metastatic colorectal cancer (mCRC),<sup>4</sup> either resulting from germline mutation in MMR protein in patients with Lynch syndrome, or from somatic alterations such as hypermethylation in the *MLH1* promoter in sporadic cases. Chemoresistance in localized dMMR/MSI CRC has been suggested and a deleterious effect of 5FU adjuvant therapy in stage II disease has been reported.<sup>5</sup> In metastatic disease, results are still controversial,<sup>4,6-9</sup> however chemotherapy remained until 2020 the standard of care. Indeed, the immune checkpoint inhibitor programmed death 1 (PD-1) changed the therapeutic landscape in

dMMR/MSI tumors, showing a significant survival benefit vs standard chemotherapy alone or combined with targeted therapy, both in progression-free survival and objective response rate (ORR), leading to the recent approval of pembrolizumab as first-line treatment for dMMR/MSI mCRC.<sup>10-12</sup> The rate of radiological complete response with pembrolizumab reached 11% compared to 4% reported with standard chemotherapy regimen.<sup>10</sup> However, the KEYNOTE-177 study reported no results regarding metastasectomies.

In mCRC with microsatellite stability (MSS), also called proficient MMR (pMMR), surgical resection of metastases led to improved OS as marginally reported in small series focusing on dMMR/MSI mCRC.<sup>7,8,13</sup> Neoadjuvant treatment, in addition to increase complete resection rates, allows tumor downstaging and sometimes to achieve pathological complete response (pCR). pCR is associated with increased relapse-free and overall survival with systemic treatment or chemoradiotherapy in several tumor types,<sup>14-16</sup> and more specifically in patients with mCRC.<sup>17-20</sup> pCR is rarely achieved in mCRC patients treated with chemotherapy alone (2.8%) or with targeted therapy like VEGF(R) inhibitors (13%).<sup>17,21,22</sup> Whereas ICI have demonstrated high efficacy in patients with dMMR/MSI mCRC,<sup>23</sup> data relative to pCR achieved after preoperative treatment are scarce.

This retrospective multicentric study aimed to report pathological tumor response in dMMR/MSI mCRC patients treated with neoadjuvant treatment [chemotherapy  $\pm$  targeted therapy (CTT) or ICI], and especially explored pCR rate, as a surrogate marker for relapse-free or overall survival.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

This retrospective multicenter study included all consecutive patients with a histologically proven stage IV dMMR/MSI CRC patients who benefited surgical metastasectomy between January 01, 2010 and June 31, 2021. MSI was detected by PCR in tumoral DNA using a pentaplex panel of five mononucleotide repeat markers (MSI if instability affects at least two markers) and/or by loss of MMR expression in tumor cells using immunohistochemistry (IHC), in primary tumor and/or metastatic sample, as recommended by guidelines. dMMR status was defined as the loss of nuclear expression of at least one MMR protein (MLH1, MSH2, MSH6 and/or PMS2).<sup>24</sup> Tumors with discordant MMR IHC and MSI results were excluded (pMMR/MSI and dMMR/MSS). *RAS* (KRAS exons 3-4 and NRAS exons 2-3-4) and *BRAF* mutational status were collected from molecular biology reports. Lynch syndrome was defined by the presence of a germline *MMR* mutation, and sporadic cases of qualified MLH1/PMS2 negative tumors harboring *BRAF* mutation and/or *MLH1* promotor hypermethylation. Patients were treated according to national French guidelines with standard preoperative treatment: patients with *RAS* and *BRAF* wild-type tumors were treated with chemotherapy combined with an anti-EGFR; patients with mutated *RAS* or *BRAF* tumor usually received chemotherapy combined with bevacizumab. Some patients received immunotherapy, either pembrolizumab upon its approval by the EMA and compassionate use in France, or within clinical trials. Some patients received no neoadjuvant treatment. Detailed data regarding the standard use of CTT were not collected. Patients were classified according to the neoadjuvant treatment received into CTT or ICI group. Responses were assessed with computed tomography scan (CT-scan) and/or with magnetic resonance imaging (MRI) according to standard guidelines, every 2 or 3 months.<sup>25</sup>

### 2.2 | Pathological evaluation

Pathological reports of all the metastasectomies were collected and reviewed locally to assess histological tumor regression according to the American Joint Committee on Cancer/College of American Pathologists score (AJCC/CAP).<sup>21,26</sup> We used a modified 4-point tumor regression grade (TRG) score considering the presence of residual tumor cells and the extent of fibrosis. TRG0 translated the absence of tumor cells (complete response), TRG1 rare residual tumor cells scattered throughout abundant fibrosis (near-complete response), TRG2 large amount of tumor cells outgrown by fibrosis and TRG3 most exclusively tumor cells without fibrosis. In case of discordance between multiple resections samples, the highest TRG score was considered.

### 2.3 | Endpoints

The primary objective was to evaluate the rate of pathological complete response (pCR) after metastasectomy defined with TRG0 after preoperative treatment. Pathological response referred only to tumors treated preoperatively. Secondary objectives included the evaluation of histological response using TRG, the description of morphology (tumor vitality, presence of necrosis, acellular mucin pools and fibrosis), relapse-free-survival (RFS) after the latest surgical metastasectomy and overall survival (OS).

### 2.4 | Statistical analysis

Descriptive statistics were performed for patient and tumor characteristics. The binary data were compared using Fisher or Chi2 tests and continuous data using Mann-Whitney test or Student's *t*-test. Predictive factors of pCR were investigated by univariable and multivariable logistic regression. Median follow-up was determined using the reverse Kaplan-Meier method.<sup>27</sup> OS was defined as the time from diagnosis of metastatic disease to death from any cause, or censored at the date of last follow-up for patients alive. RFS was defined as the time from the latest curative surgery to relapse or death from any cause, or censored at the date of last information. For OS et RFS according to preoperative treatment, in case of multiple surgery, treatment before last surgical management was considered. Survival distribution was estimated by the Kaplan-Meier method and was compared to log-rank test. Hazard ratio (HR) with 95% confidence interval (95% CI) was calculated using Cox models. Multivariate analysis was performed using Cox proportional hazard model and included variables with a *P*-value <.05 in univariable analysis. All analyses were two-sided, with a *P*-value <.05 considered as statistically significant. Statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

## 3 | RESULTS

### 3.1 | Patient and tumor characteristics

The study included 88 dMMR/MSI mCRC patients from 17 French centers treated between January 01, 2010 and June 31, 2021 (missing data for dMMR/MSI status: 0%). Among them, 42 (47.7%) were women. Median age was 55.5 (range 17-94) years (Table 1). Most patients had an ECOG-PS 0-1 (81.8%) at diagnosis of metastatic disease. Overall, 35.2% of patients had Lynch syndrome, 42.1% had a sporadic disease (origin unknown for 22.7%). Loss of MLH1/PMS2 was identified in 42 (47.7%) patients, loss of MSH2/MSH6 in 18 (20.5%) and an isolated loss of one MMR, (PMS2 or MSH6) was reported in 25 (28.4%) patients. One of two patients was diagnosed with synchronous metastatic disease (*n* = 44, 50%), most often located in the liver (*n* = 42, 47.7%) and in the peritoneum (*n* = 47, 53.4%) (Table 2). *RAS* mutations were identified in 27 (30.7%) patients (missing data: 9.1%), and *BRAF* mutations in 22 (25%) patients (missing

**TABLE 1** Patient, treatment and tumor characteristics

Characteristics	Total (N = 88)
Age (years)	55.5 (17-94)
Gender	
Men	46 (52.3%)
Women	42 (47.7%)
Lynch syndrome	
Yes	31 (35.2%)
No	37 (42.1%)
Unknown	20 (22.7%)
Primary tumor site	
Right colon	52 (59.1%)
Left colon	22 (25%)
Rectum	10 (11.4%)
Multifocal	4 (4.5%)
Stage at diagnosis	
I	2 (2.3%)
II	10 (11.4%)
III	29 (32.9%)
IV	44 (50%)
Unknown	3 (3.4%)
Histological subtype	
Adenocarcinoma	56 (63.6%)
Mucinous	28 (31.8%)
Other	3 (3.4%)
Signet-ring cell	1 (1.1%)
Tumor grade	
Well-differentiated	14 (15.9%)
Moderate	37 (42%)
Poorly differentiated	28 (31.8%)
Unknown	9 (10.2%)
Vascular invasion	
Yes	40 (45.5%)
No	36 (40.9%)
Unknown	12 (13.6%)
Perinervous infiltration	
Yes	24 (27.3%)
No	50 (56.8%)
Unknown	14 (15.9%)
MSI status determined by polymerase chain reaction and immunohistochemistry	
Yes	81 (92%)
No	7 (8%)
MMR protein loss	
MLH1/PMS2	42 (47.7%)
MSH2/MSH6	18 (20.5%)
Isolated loss	25 (28.4%)
Unknown	3 (3.4%)
MLH1 promoter methylation	

(Continues)

**TABLE 1** (Continued)

Characteristics	Total (N = 88)
Yes	18 (42.8%)
No	17 (40.5%)
Unknown	7 (16.7%)
BRAF V600E mutation	
Yes	22 (25%)
No	53 (60.2%)
Unknown	13 (14.8%)
RAS mutation	
Yes	27 (30.7%)
No	53 (60.2%)
Unknown	8 (9.1%)
Number of surgical procedures	109
Liver	26 (23.9%)
Peritoneum	10 (9.2%)
Lung	2 (1.8%)
Lymph node	2 (1.8%)
Digestive tract	1 (0.9%)
Other	4 (3.7%)
Multiple sites (≥2)	64 (58.7%)
Number of resected metastases	344

Note: Categorical variables are n (%); continuous variables are median (range).

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; MLH1, MutL Homolog 1; MMR, mismatch repair; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; PMS2, PMS1 Homolog 2; RAS, Rat Sarcoma.

data: 14.8%). In patients with metachronous metastases, metastatic disease occurred in a median time of 8.8 (range 2-168) months after the diagnosis of the primary tumor.

### 3.2 | Neoadjuvant treatment and surgery

Out of the 88 patients, 109 surgeries were performed, including 69 (78.4%) patients with one surgery, 17 (19.3%) with two surgeries and 2 (2.3%) with three surgeries. Overall, 344 metastasectomies were performed, and the median number of metastases resected per surgery was 3.4 (range 1-16). A total of 81 patients received neoadjuvant treatment [CTT: N = 69 (85.2%); ICI: N = 12 (14.8%)]. A mean number of one (range 0-5) treatment line was received before surgery for a median time of 5.1 (0.9-32.8) months. Twenty-eight (25.7%) surgeries were performed without any preoperative therapy (Table 2 and Figure 1).

### 3.3 | Radiological response

Objective response rate reached 43.2% (only partial responses with no complete responses). Overall response rate with ICI was 66.7% (8/12) and 39.1% (27/69) with CTT (Table 3).

### 3.4 | Pathological response

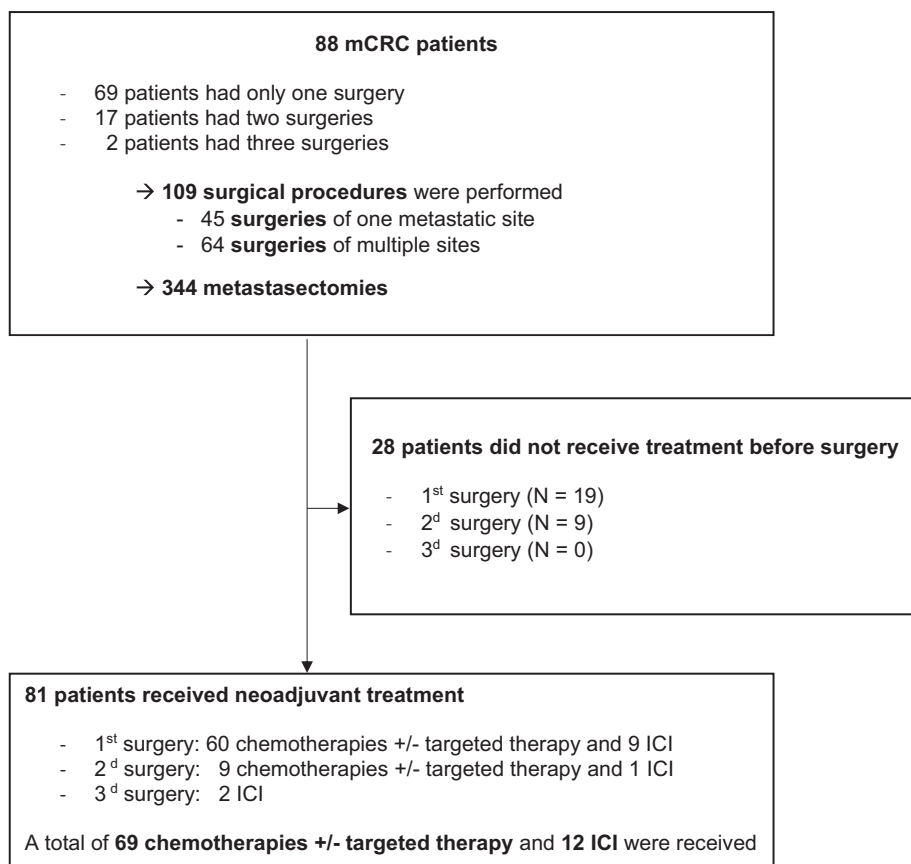
Among the patients having received preoperative treatment ( $N = 81$ ), 13 (16.1%) achieved pCR, seven with CTT and six with immunotherapy. pCR consisted mostly in necrosis ( $n = 8/13$ , 61.5%), fibrosis ( $n = 5/13$ , 38.5%) and mucin pools ( $n = 5/13$ , 38.5%). In patients treated with neoadjuvant ICI, 10 (83.3%) experienced complete or near-complete pathological response (TRG0: 6, 50.0%; TRG1:

4, 33.3%) and 2 were nonresponders (TRG2, 1, 8.3%; TRG3: 1, 8.3%). With CTT, 14 (20.6%) achieved pCR or near pCR (TRG0: 7, 10.3%; TRG1: 7, 10.3%) whereas 54 (79.4%) did not respond to neoadjuvant CTT (TRG2: 21, 30.9%; TRG3: 33, 48.5%; Table 3). Neoadjuvant ICI was associated with a statistically significant pCR rate, compared to CTT ( $P = .002$ ).

Patients with TRG 0/1 were more likely to achieve radiological response or to remain stable, when compared to preoperative imaging

**TABLE 2** Characteristics of surgeries

	Surgery no. 1 (n = 88)	Surgery no. 2 (n = 19)	Surgery no. 3 (n = 2)	Total (n = 109)
<b>Resected metastatic site</b>				
Liver	42	4	0	46
Peritoneum	47	12	1	60
Lymph nodes	53	3	1	57
Pulmonary	0	2	0	2
Digestive tract	35	2	0	37
Other	17	3	1	21
≥2 resected metastatic sites	57 (64.8%)	6 (31.6%)	1 (50%)	64 (58.7%)
<b>Presurgical treatment</b>				
Chemotherapy ± targeted therapy (CTT)	60 (68.2%)	9 (47.4%)	0	69 (63.3%)
Immunotherapy (ICI)	9 (10.2%)	1 (5.2%)	2 (100%)	12 (11%)
None	19 (21.6%)	9 (47.4%)	0	28 (25.7%)



**FIGURE 1** Flowchart



**TABLE 3** Response rates (radiological, pathological) according to surgery and presurgical treatment

	Surgery no. 1 (n = 88)	Surgery no. 2 (n = 18)	Surgery no. 3 (n = 3)	Total (n = 109)	CTT group (N = 69)	ICI group (N = 12)
<b>Radiological response</b>						
Partial response	30	4	1	35 (43.2%)	27 (39.1%)	8 (66.7%)
Stable disease	25	3	0	28 (34.6%)	26 (37.7%)	2 (16.7%)
Progression	2	2	0	4 (4.9%)	3 (4.4%)	1 (8.3%)
No presurgical treatment	19	8	1	28		
Unknown	12	1	1	14 (17.3%)	13 (18.8%)	1 (8.3%)
<b>TRG score</b>						
0	11	1	1	13 (16.1%)	7 (10.2%)	6 (50%)
1	10	0	1	11 (13.6%)	7 (10.2%)	4 (33.3%)
2	18	4	0	22 (27.2%)	21 (30.4%)	1 (8.3%)
3	29	5	0	34 (41.9%)	33 (47.8%)	1 (8.3%)
No presurgical treatment	19	8	1	28		
Unknown	1	0	0	1 (1.2%)	1 (1.4%)	0
<b>Resection type</b>						
0	76	13	3	92 (84.4%)		
1	8	3		11 (10.1%)		
2	1	0		1 (0.9%)		
Unknown	3	2		5 (4.6%)		

Abbreviations: CTT, chemotherapy ± targeted therapy [anti-EGFR and anti-VEGF(R)]; ICI, immune checkpoint inhibitor; TRG, tumor regression grade.

( $P = .044$ ). However, radiological response did not directly correlate with TRG. Indeed, the 35 tumors with radiological response after neoadjuvant treatment were classified as TRG3 (28.6%), TRG2 (25.7%), TRG1 (17.1%) and TRG0 (28.6%). Among patients treated with ICI who achieved partial response ( $N = 8$ ), 50% were TRG0 and 50% TRG1. Among the 46 patients with synchronous metastatic disease, 24 (52.2%) had surgery on the primary tumor and simultaneous metastatic resections. In these cases, TRG were similar in both locations in half of them. In patients without neoadjuvant treatment, pathological reports revealed 100% viable tumoral cells ( $N = 19/19$ ), 10.5% necrosis ( $N = 2/19$ ) and 10.5% fibrosis ( $N = 2/19$ ).

In univariable analysis, loss of MLH1-PMS2 was associated with reduced pCR rate but this variable was not retained in multivariate analysis (Table 4). Among patients with pCR, 3 (23.1%) relapsed ( $N = 3/13$ ); two had another neoadjuvant treatment (CTT:  $N = 2$ ; ICI:  $N = 1$ ) before another metastasectomy (Table S1).

### 3.5 | Survival

With a median follow-up of 57.9 (IQR 34.2–81.6) months, median OS in the overall population was not reached (2.6-NR); 26 deaths and 11 lost-to-follow-up were reported at the data cut-off date (Figure 2). One-year and 2-year OS was 97.7% (95% CI 94.7–100) and 84.1% (95% CI 76.6–92.5), respectively. In univariable and multivariable analyses (Table 4), RFS was correlated to TRG 0–1 (HR 0.12, 95% CI 0.03–0.55;  $P = .006$ ) and ECOG-PS > 1 (HR 6.06, 95% CI 2.43–15.1;

$P = <.001$ ), whereas OS was only related to ECOG-PS > 1 (HR 5.23, 95% CI 1.88–14.6;  $P = .002$ ).

Among patients who experienced recurrence, the median time to first relapse was 14.5 months (range 1.90–7 months) and median time to second relapse was 9.3 months (range 1–20 months). First and second relapses occurred at the same tumor site in 58.8% and 46.7% of the cases, respectively. Median RFS from latest metastasectomy was 20.2 (range 15.4–not reached; 95% CI 28.8–63.6) months. One-year and 2-year RFS were 63.4% (95% CI 53.7–74.8) and 46.9% (95% CI 36.7–59.9), respectively (Figure 2). RFS and OS according to preoperative treatment are presented in Figure S2.

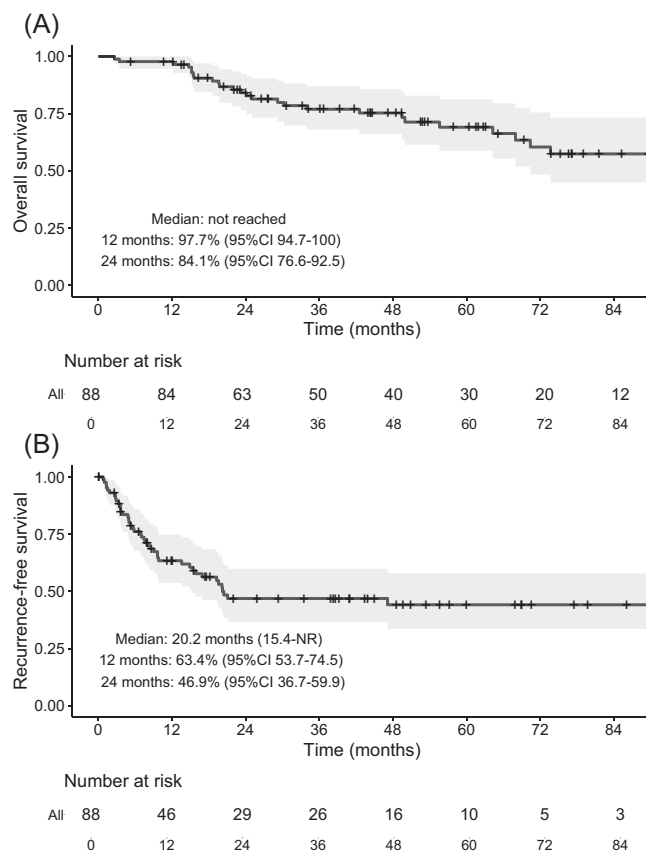
## 4 | DISCUSSION

Surgical treatment of mCRC remains the essential therapeutic approach of offering a chance of cure and provides a significant impact on OS.<sup>28</sup> Surgical metastasectomy is performed when feasible, most often after preoperative CTT. Both radiological and pathological responses to neoadjuvant treatment have been shown to predict survival outcome after surgery.<sup>18,20,29</sup> Most of the current data were collected before the use of MMR/MSI status as predictive factor for ICI and the availability of ICI as standard treatment in patients with mCRC. The European Medicines Agency approved, in December 2020, the use of pembrolizumab in dMMR/MSI mCRC patients in Europe. However, despite the positive opinion for reimbursement provided by the French Transparency Commission in June 2021,

**TABLE 4** Univariable and multivariable analyses of prognostic factors for recurrence-free survival (RFS) and overall survival (OS)

Variables	Recurrence-free survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Tumor regression grade (0-1 vs > 1)	0.17 (0.05-0.55)	<b>.003</b>	0.12 (0.03-0.55)	<b>.006</b>	0.29 (0.09-0.98)	<b>.047</b>	0.26 (0.06-1.18)	.082
ECOG performance status (2 vs 0-1)	4.61 (1.91-11.2)	<b>&lt;.001</b>	6.06 (2.43-15.1)	<b>&lt;.001</b>	4.03 (1.5-10.8)	<b>.006</b>	5.23 (1.88-14.6)	<b>.002</b>
Age at metastatic disease (per year)	1.00 (0.98-1.03)	.7	—	—	1.02 (0.98-1.05)	.3	—	—
Loss of MLH1-PMS2 (yes vs no)	2.08 (1.09-3.98)	<b>.027</b>	1.14 (0.57-2.3)	.7	2.91 (1.23-6.92)	<b>.015</b>	2.23 (0.89-5.59)	.086
Loss of MSH2-MSH6 (yes vs no)	0.61 (0.25-1.45)	.3	—	—	0.48 (0.14-1.63)	.2	—	—
BRAF V600E mutated (yes vs no)	0.52 (0.25-1.1)	.087	—	—	1.4 (0.6-3.28)	.4	—	—
RAS mutated (yes vs no)	1.00 (0.51, 1.94)	.99	—	—	0.64 (0.27-1.55)	.3	—	—
Metastases (at diagnosis vs metachronous)	1.79 (0.97-3.32)	.063	—	—	2.08 (0.94-4.6)	.071	—	—
Sporadic case (yes vs no)	1.07 (0.55-2.08)	.8	—	—	1.78 (0.75-4.24)	.2	—	—
Lynch (yes vs no)	0.92 (0.46-1.83)	.8	—	—	0.46 (0.17-1.2)	.11	—	—

Note: Bold values indicate the statistically significant value.

**FIGURE 2** (A) Overall survival and (B) recurrence-free survival

reimbursement in France is not yet approved, and only compassionate use reimbursed by MSD is possible. Consequently, only few data documented the place of surgery in the treatment sequence in dMMR/MSI mCRC. Furthermore, with only 3%-8% of the mCRC patients identified as dMMR/MSI, clinical studies in this selected subgroup are particularly challenging. Our study gathered data from the

first large group of dMMR/MSI mCRC patients in order to assess the pCR rate in resected metastases. In particular, no data on patients who underwent metastatic surgery in the pivotal study leading to pembrolizumab approval in dMMR/MSI mCRC patients (KEYNOTE-177) are available. We report that ICI showed improved efficacy, with an overall response rate of 66.7%, consistent with the efficacy previously reported for ICI in the literature and confirming an objective response rate with ICI higher than CTT. In addition, we describe an increased pCR rate achieved with neoadjuvant immunotherapy, with one over 2 (50%) patients achieving pCR after ICI compared to only 1 over 10 (10%) with CTT in dMMR/MSI mCRC patients. This result is consistent with the high pCR rate (92.3%) reported with ICI [either PD-1/PD-L1 monotherapy (N = 7) or in combination with CTLA4 inhibitor (N = 6)] in a series of 13 patients dMMR/MSI mCRC.<sup>23</sup> In early-stage dMMR/MSI CRCs, whereas neoadjuvant chemotherapy has not been specifically investigated, the subgroup analysis of the FOXTROT study reported a pCR rate of 4.7% in patients with dMMR/MSI-H CRC.<sup>30</sup> Similarly, a small series suggested a chemoresistance in nonmetastatic dMMR/MSI rectal cancer, with a higher rate of disease progression (29% vs 0%) after neoadjuvant FOLFOX in dMMR/MSI vs pMMR tumors.<sup>31</sup> With the promising pCR rate of 60% reported in the study NICHE,<sup>32</sup> the use of neoadjuvant ICI in patients with localized dMMR/MSI CRC was attractive. Similar pCR rate (N = 15, 57.7%) was recently retrieved in 26 Chinese patients.<sup>33</sup> Furthermore, Cercek et al reported a 100% clinical complete response rate with the PD-1 inhibitor dostarlimab in localized rectal carcinomas.<sup>34</sup> However, these patients were not operated and the median follow-up was short (12 months). Nevertheless, based on these promising results, we initiated the prospective study IMHOTEP (NCT04795661) to evaluate the efficacy of neoadjuvant ICI based on pCR rate assessment in different dMMR/MSI tumors including CRC. In our study, TRG0-1 after preoperative treatment (Table 3) was a significant predictive factor for RFS in dMMR/MSI mCRC. This result is consistent with results reported in other mCRC



series.<sup>23</sup> Furthermore, we observed a median RFS of 20.2 months, longer than the 9.5-month duration previously reported.<sup>13</sup> TRG was not demonstrated to be associated with OS. However, interpretation may be limited by the reduced population size and the short median follow-up. We also confirm the limitation related to the radiological evaluation in dMMR/MSI patients treated with immunotherapy, no complete radiological responses were observed in our cohort. Our results showing a persisting residual disease on preoperative imaging in 12 out of the 13 (92%) patients with pCR are consistent with previous results from the Ludford study.<sup>23</sup> The iRECIST response criteria has not been validated in dMMR/MSI mCRC patients, the NIPICOL study showed only rare pseudo-progressions (3.5%) and did not consider iRECIST as useful.<sup>35</sup> In accordance with our study, CT-scan imaging was not appropriate to predict pathological response. Among the six patients presenting pCR, none had a radiological complete response (4 PR, 1 SD and 1 unknown). Failure to predict pathological tumor response with CT-scan has also been underlined in metastatic melanoma and the most useful imaging modality to identify complete response with ICI was <sup>18</sup>FDG-Pet-CT imaging.<sup>36</sup> In dMMR/MSI mCRC patients treated with ICI, data on metabolic response with <sup>18</sup>FDG-Pet scan are sparse but controversies exist, and complete metabolic response with <sup>18</sup>FDG-Pet-CT did not systematically predict pCR.<sup>37</sup> In dMMR/MSI localized rectal adenocarcinomas, T2-weighted and diffusion-weighted MRI has proven to be appropriate to predict clinical CR in a recently published phase II study but multiple metastatic sites remain a limitation.<sup>34</sup> Indeed, the clinical utility of <sup>18</sup>FDG-Pet CT, whole-body MRI or PET/MR for multiple metastatic sites still has to be refined. Liquid biopsies, and especially circulating tumor DNA (ctDNA) could provide valuable help to predict pCR with ICIs, even if appropriate detection of minimal residual disease in dMMR/MSI mCRC patients has not been addressed yet. ctDNA level was shown to be related to tumor mutational burden and its prognostic role was demonstrated in several CRC, regardless of the TNM stages.<sup>38</sup> After chemotherapy, the presence of ctDNA is associated with shorter PFS and OS.<sup>39-41</sup> After curative surgery, the absence of ctDNA is associated with a decreased relapse risk and a better prognosis; ctDNA detection seems useful to assess minimal residual disease, and to early diagnose relapses.<sup>42</sup> Monitoring ctDNA levels and clearance during immunotherapy could contribute to better predict pCR, even though the high prevalence of peritoneal carcinomatosis and lymph node metastases in dMMR/MSI mCRC is likely to limit its investigation. Indeed, metastatic sites usually associated with low ctDNA levels.<sup>38</sup> Some durable tumor responses with ICI in dMMR/MSI mCRC patients treated have been reported,<sup>43</sup> late tumor responses were also achieved in the CheckMate-142 study with a rate of complete responses increasing from 3% initially to 9% after 21 months<sup>44</sup> and high pCR rates, as observed in our study, could support the possibility of surgical abstention with close monitoring for selected patients. Clinical trials investigating *watch and wait* strategies in dMMR/MSI tumors after neoadjuvant ICI are currently in progress, especially when surgery potentially deleterious in terms of quality of life are anticipated, notably for rectal or gastric localization (NCT04643041; NCT04817826). Limitations of our study include the retrospective

design, excluding valid comparison between patients treated with CTT or ICI and inducing biases due to the selection of patients being operated. It is also limited by the small number of patients treated with ICI in a neoadjuvant setting. As ctDNA has no specific indication and is not eligible for reimbursement in France so far, further evaluation in using ctDNA to predict pCR was not achievable in our study.

In conclusion, patients with dMMR/MSI mCRC showed pCR rate similar to that reported in the literature in all comers mCRC patients (mostly pMMR/MSS) treated with neoadjuvant chemotherapy. With ICI, pCR rate reached up to 50% by contrast to 13% with standard CTT. The predictive value of the CT-scan seems low and alternative radiological examinations should be further evaluated. Prospective, multicentric studies are needed to determine the place of surgery in the curative management of patients with dMMR/MSI mCRC with stable disease or tumor response to ICI.

#### AUTHOR CONTRIBUTIONS

The work reported in this article has been performed by the authors, unless clearly specified in the text. All authors were involved in writing and reviewing the report and in making the decision to submit for publication. Conceptualization (Christelle de la Fouchardière, Pauline Marolleau), Data curation (Christelle de la Fouchardière, Pauline Marolleau), Formal Analysis (Pauline Marolleau, Benoit Allignet), Investigation (all authors), Methodology (Christelle de la Fouchardière, Pauline Marolleau), Supervision (Christelle de la Fouchardière), Validation (all authors), Visualization (Benoit Allignet), Writing – original draft (Pauline Marolleau, Christelle de la Fouchardière), Writing – review and editing (all authors).

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#### CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

#### DATA AVAILABILITY STATEMENT

Anonymized data sets are available upon reasonable request from the data protection officer of the Léon Bérard cancer center at [dpd@lyon.unicancer.fr](mailto:dpd@lyon.unicancer.fr). Further information is available from the corresponding author upon request.

#### ETHICS STATEMENT

This research was conducted in accordance with relevant French and European laws and directives. Namely, the study was conducted with the provisions of French Law of 6 January 1978 “Loi Informatique et Libertés” as amended, and declared to the French data protection authority (*Commission Nationale Informatique et Liberté, CNIL*). The study received GDPR compliance certificate in accordance with the reference methodology MR-004 (registration no. 201-004-036) on February 25, 2020. All data were anonymized. No written informed consent was required, patients have a right of opposition to the data collection.

## ORCID

David Tougeron  <https://orcid.org/0000-0002-8065-9635>

Romain Cohen  <https://orcid.org/0000-0001-9602-5162>

David Sefrioui  <https://orcid.org/0000-0002-0821-5642>

François Ghiringhelli  <https://orcid.org/0000-0002-5465-8305>

Thomas Aparicio  <https://orcid.org/0000-0001-8834-6927>

Christelle de la Fouchardière  <https://orcid.org/0000-0003-2291-5693>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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