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Original article

Pseudoprogession in patients treated with immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer

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Author Contributions

T.A, R.C., and Y.M. were involved in the study concept and study design. T.A., R.C., Y.M. were involved in quality control of data and algorithms. T.A., R.C., Y.M., and M.C. were involved in data analysis and interpretation. R.C. and M.C. were involved in statistical

analysis. T.A. and R.C. contributed to manuscript preparation and editing. All authors were involved in data acquisition and manuscript review and approved the final manuscript.

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Highlights

- 10% of patients with MSI metastatic colorectal cancer experience pseudoprogression
- Pseudoprogessions occur within the first 3 months.
- Pseudoprogessions represent most of primary radiological progressions.
- The use of iRECIST criteria should be questioned after 3 months.
- Patients with pseudoprogression in this study population have favorable outcomes

Abstract

Background: The efficacy of immune checkpoint inhibitors (ICIs) in microsatellite instability–high/DNA mismatch repair (MSI/dMMR) metastatic colorectal cancer (mCRC) is well-established. ICIs are responsible for pseudoprogression (PSPD) that complicates clinical decisions. We evaluated the PSPD frequency in MSI/dMMR mCRC patients treated with ICIs.

Patients and methods: Consecutive MSI/dMMR mCRC patients treated with ICIs from February 2015 to December 2019 at Saint-Antoine Hospital were included. Imaging was retrospectively and centrally reviewed according to RECIST 1.1 and iRECIST. PSPD was defined as an unconfirmed disease progression (PD) by iRECIST.

Results: 123 MSI/dMMR mCRC patients were included. Thirty-six patients (29%) had radiological PD according to RECIST 1.1 during the median follow-up of 22.3 months (95% CI, 1.5-62.2), including 22 in the first 3 months (the primary radiological PD). Twenty nine patients continued ICIs beyond PD. Twelve patients experienced PSPD, representing 10% of the population and 52% of the primary radiological PD. Median time to PSPD was 5.7 weeks (95% CI, 4.1-11.4). No pseudoprogression was observed after 3 months. The PSPD incidence was 14.8% in patients treated with anti-PD1 alone (n=9/61) and 4.8% in case of anti-PD1 plus anti-CTLA-4 (n=3/62). Eight PSPD patients experienced an objective response. The 2-years progression-free survival and overall survival rates for PSPD patients were 70.0% (95% CI, 32.9-89.2) and 75.0% (95% CI, 29.8-93.4).

Conclusion: MSI/dMMR mCRC patients treated with ICIs experienced PSPDs. PSPD occurred within the first 3 months and represented most of the primary radiological PDs. The use of iRECIST criteria should be questioned after 3 months.

Key Words: pseudoprogression; microsatellite instability; mismatch repair; immunotherapy; PD-1; CTLA-4;

INTRODUCTION

The efficacy of immune checkpoint inhibitors (ICIs) in microsatellite instability-high/DNA mismatch repair-deficient (MSI/dMMR) metastatic colorectal cancer (mCRC) is well-established[1–7]. In a recent phase III study, pembrolizumab (anti-PD1 antibody) as first-line treatment has been associated with a significant improvement of progression-free survival (PFS) compared to chemotherapy with/without bevacizumab or cetuximab [8].

Radiological assessment of tumor response in patients treated with ICIs is challenging due to the probability of pseudoprogression (PSPD) [9]. The main hypothesis underlying the PSPD phenomenon is that ICIs might initially induce a massive recruitment of T cells to the tumor site, leading to a transient increase in tumor size. Recognition of PSPDs and distinction between PSPDs and true progression is critical to avoid undue discontinuation of an effective drug or, conversely, continuation of an ineffective and potentially toxic treatment. Therefore to overcome this phenomenon, new radiological criteria have been developed. According to iRECIST, PSPD is defined as a radiological progression of lesions that is not confirmed over time, but is followed by a sustained stability or a response to treatment [10]. The major change for iRECIST is the concept of “unconfirmed progressive disease” (iuPD) defined on the basis of RECIST 1.1 disease progression (PD), but requiring confirmation [10,11].

The frequency of PSPD during ICI therapy is poorly known and varies according to cancer types and drugs used, but it never exceeds 15% [12–21]. Concerning MSI/dMMR mCRC, some cases of PSPD have already been reported, however there is no study on the incidence of PSPD in this population [22].

The aim of this study was to estimate the incidence of PSPD under ICI in the MSI/dMMR mCRC population and to describe the characteristics and outcomes of these patients.

METHODS

Patients

All consecutive MSI/dMMR mCRC patients enrolled in ICI trials (anti-PD1 monotherapy or the anti-PD1 plus anti-CTLA-4 combination) or treated with ICI (anti-PD1 monotherapy) under a compassionate use program at Saint-Antoine Hospital from February 2015 to December 2019 were included. This research was approved by the ethics committee (N°2020 – CER 2020-6).

Radiological analyses

Tumors were assessed ≤ 28 days before the first dose (baseline) and every 6 to 10 weeks, thereafter, according to different protocols. The decision to pursue treatment beyond iuPD was at the discretion of the treating physician. Treatment beyond iuPD was conditional to a confirmatory imaging 4 to 8 weeks after the first evidence of progression.

Imaging was retrospectively and centrally reviewed by an experienced radiologist (YM) according to RECIST1.1 and iRECIST. PSPD was defined as an unconfirmed PD according to iRECIST [10]. Primary radiological progression was defined as PD according to RECIST 1.1 within 3 months after ICI-treatment initiation. Confirmed primary progression was defined by progression within 3 months according to iRECIST. All cases of PD and PSPD were reviewed by a second experienced radiologist (AR) unaware of the target and non-target lesions chosen by the first radiologist. In case of discrepancy, a final decision was reached by consensus.

Definition of clinical benefit and carcinoembryonic antigen (CEA) response

Clinical benefit was defined as the improvement of at least one of the following items without degradation of the others: pain/ a decrease in analgesic consumption from baseline, weight/ a weight gain of more than 1 kg from baseline, general condition/ the improvement of Eastern Cooperative Oncology Group performance status (ECOG PS). CEA response was defined as a $>50\%$ decrease from its baseline level; CEA stability was defined as a $<50\%$ variation from its baseline level; and CEA progression was defined as a $>50\%$ increase from its baseline level.

Statistical Analysis

Categorical variables were described by numbers and percentages and continuous variables by means, standard deviations, and minimum and maximum values. Survival curves were generated using the Kaplan Meier method. A log-rank test was used to compare survival between groups. Risk factors for PSPD were studied using a Cox univariate regression model (only) including: age, localization, mucinous, ganglion, the number of metastatic sites (1 or ≥ 2), and treatment (monotherapy or combination). The results were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Log linearity hypothesis was not achieved for age that was therefore studied in quartiles. Risk proportionality hypothesis was achieved for all variables studied. PFS was defined by time from the first injection of ICI to the first PD

per iRECIST or death from any cause. Overall survival (OS) was calculated from the first injection of ICI to death, whatever the cause. All superiority tests were two-sided and p values <0.05 were considered significant. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Population and treatment

A total of 123 consecutive MSI/dMMR mCRC patients treated with ICIs from February 2015 to December 2019 were included and analyzed; 113 were treated in clinical trials (Figure 1). Patient baseline characteristics are summarized in Table 1. The mean age was 57 years and 55% of patients were men ($n = 68$). *RAS* and *BRAF*^{V600E} mutations were respectively detected in 40% ($n = 49$) and 21% ($n = 26$) of patients. Overall, 49% ($n = 61$) of patients received an anti-PD1 monotherapy and 50% ($n = 62$) the anti-PD1 and anti-CTLA4 combination. The median follow-up was 22.3 months (95% CI 1.5-62.2).

The incidence of PSPD

Thirty-six (29%) patients experienced radiological PD per RECIST 1.1, including 22 in the first 3 months of treatment (the primary radiological PD). Seven patients had an obvious clinical PD, which didn't allow treatment beyond PD. Twenty nine patients continued ICIs beyond PD and had a confirmation imaging according to iRECIST after a median time of 6.8 weeks. Twelve patients experienced PSPD, representing 10% of the population and 52% of the primary radiological PD. Median time to PSPD was 5.7 weeks (95% CI, 4.1-11.4). No PSPD was observed after 3 months.

Characteristics of patients with PSPD

Baseline characteristics of patients with PSPD are summarized in Table 1. At the time of PSPD, eight patients showed a clinical benefit; improvement of ECOG PS ($n = 4$) and/or increased weight ($n = 4$), and/or decrease of pain ($n = 8$). Two patients had a clinical deterioration ($n = 1$, weight loss; $n = 1$, increased pain) with mild symptoms allowing treatment beyond iuPD. Of the ten patients presenting an abnormal baseline CEA level, five had decreased CEA, two had unchanged CEA, and two had increased CEA at the time of iuPD. Of the ten patients with confirmed primary progression, six of eight patients with an abnormal baseline CEA level had an increased CEA at the time of iuPD.

The incidence of PSPD with anti-PD1 antibody alone was 14.8% ($n = 9/61$), compared to 4.8% with the anti-PD1 plus anti-CTLA4 combination ($n = 3/62$; $p = 0.08$). The first evaluation was planned later in trials evaluating monotherapy than in those testing a combination of ICIs (median time to the first evaluation was 5.7 vs 8.3 weeks). The ratio of PSPD among primary radiological PD was 52.9% (9/17) with anti-PD1 alone and 60.0% (3/5) with the combination. No association between baseline characteristics and the occurrence of PSPD was detected (Table A1).

Outcomes of patients with or without PSPD

Eight out of the 12 patients with an initial PSPD achieved an objective response (five partial responses and three complete responses), with a median time of 4 months from first injection to partial response. All these patients were alive and free of progression at the data lock. Four patients showed a radiological stability as best response after PSPD, of which two had a confirmed PD during follow-up (9.9 and 12.5 months after baseline). The evolution of each patient is summarized in Figure 2.

In the entire cohort, the 2-year PFS and OS rates were 72.0% (95% CI, 61.2-79.0) and 83.0% (95% CI, 73.4-89.4; Figure A1). Considering patients with PSPD, the 2-year PFS and OS rates were 70.0% (95% CI, 32.9-89.2) and 75.0% (95% CI, 29.8-93.4; Figure 3). The 2-year PFS and OS rates for patients with PSDP, overall response, and stability are compared in Figure 4.

DISCUSSION

Our study shows that PSPD occurs in 10% of patients MSI/dMMR mCRC treated with ICIs. PSPD were always observed during the first 3 months of treatment. To our knowledge, this is the first study evaluating the incidence of PSPD in this population, with a high proportion of patients treated beyond RECIST 1.1 progression (81%). Compared to other classical indications of ICIs, PSPD seems more common in patients with MSI/dMMR mCRC, with an incidence twice as high as in metastatic lung cancers where this phenomenon has been widely explored [16,18,19]. As in metastatic melanoma with 6.7%-10% PSPD, this could be explained by the high mutation load and immune infiltration in MSI/dMMR tumors, which are likely to have immune responses [23–25].

PSPD seems more frequent among patients treated with anti-PD1 monotherapy than those receiving the anti-PD1 and anti-CTLA4 combination (14.8% vs 4.8%). Although this difference did not reach a statistical significance ($p = 0.08$), it is noteworthy to mention that

the frequency of PSPD with anti-PD1 alone might have been underestimated. Indeed, the first evaluation was planned later in trials evaluating monotherapy than in those testing the ICIs combination (median time to the first evaluation: 5.7 weeks vs 8.3 weeks). The higher frequency under monotherapy could be explained by greater immediate efficacy with the combination, even if the median time before response seems similar (2.8 months) in other published studies [6,26]. As well, pseudoprogression seems more frequent in patients with more than one metastatic, even if this difference did not reach a statistical significance.

Our data are support the use of iRECIST criteria in clinical trials evaluating anti-PD1 antibodies as single agent for MSI/dMMR mCRC patients. Studies such as the KEYNOTE-177 phase III trial, which analyzed the activity of pembrolizumab with RECIST 1.1 might have underestimated the response rates and PFS [8].

PSPD in this population is an early phenomenon as no delayed PSPD was reported that makes a difference with other tumor types as melanoma. Within the first 3 months, PSPD seemed more frequent than confirmed progression and the main issue in clinical routine is to distinguish them from PD. We have shown that a clinical benefit and a biological response (CEA) favor the hypothesis of a PSPD. Continuation of ICI therapy and performing confirmation in case of primary radiological progression, as proposed with iRECIST criteria, seems a reasonable strategy in this population. In addition, delaying the first evaluation could be also a way to avoid clinical dilemmas related to PSPD if no clinical deterioration is shown. Conversely, because PSPD does not happen tardily in this population, we can question the usefulness of continuing the iRECIST in case of progression after the 3 first months of treatment [17]. However, translational studies exploring mechanisms underlying PSPD and its prediction are needed. Many potential clinical factors and biomarkers have been studied as ctDNA/cfDNA, mutational status, and soluble immune mediators, but none of these biomarkers has been implemented into clinical practice [27-29]. Recently, radiomic models based on magnetic resonance or positron emission tomography/computed tomography data have also been developed [30, 31].

Patients with PSPD in our cohort often showed a secondary radiological response ($n = 8/12$) and had favorable outcomes. Therefore, confirmed PSPD should be considered as a clue of disease sensitivity to ICI. Still, two patients with PSPD experience secondary progression after a durable response.

There are limitations in the present study. It is monocentric and included mainly patients from clinical trials, which could limit the generalization of our results in the real-world setting. Schedules of evaluation were different according to study protocols implicating

an inhomogeneous follow-up. Moreover, this work concerns only MSI/dMMR mCRC and cannot be applied to all MSI/dMMR cancers. Finally, we acknowledge that our study might be underpowered to detect significant associations between baseline characteristics and PSPD.

To conclude, this study highlights the existence of PSPD, observed only at the first evaluation with an incidence of 10% in MSI/dMMR mCRC patients treated with ICI. PSPDs were observed early and mainly with anti-PD1 monotherapy. PSPD should be systematically considered in case of primary radiological progression, particularly in patients with clinical benefit and without worsening of laboratory values, especially CEA. Outcomes are reassuring, better for patients with PSPD than for those with SD.

Conflict of interest

T.A. reports consulting/advisory role and or received honoraria from Amgen, Bristol-Myers Squibb, Chugai, Clovis, Gristone Oncology, HalioDx, MSD Oncology, Pierre Fabre, Roche/Ventana, Sanofi, Servier, and GSK and has received travel, accommodations, and expenses from Roche/Genentech, MSD Oncology, and Bristol-Myers Squibb. M. S. reports consulting/advisory role and or received honoraria from Bristol-Myers Squibb, Astellas, MSD Oncology, and Sanofi and has received travel, accommodations, and expenses from Bristol-Myers Squibb and Ventana/Roche. R. C. reports consulting/advisory role and or received honoraria from Amgen, Sanofi, and Servier and has received travel, accommodations, and expenses from Sanofi. All other authors declare no conflict of interest.

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Figure 1: Study CONSORT diagram

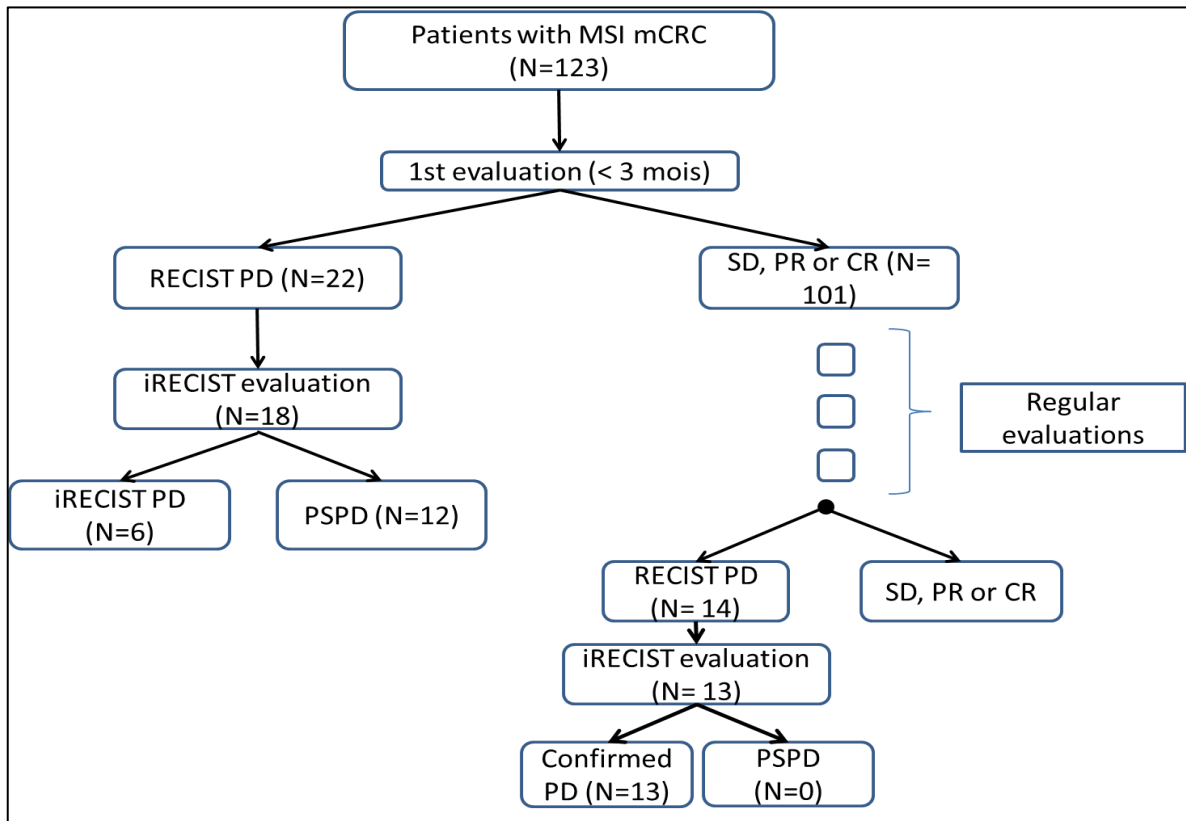


Figure 2: Evolution following pseudoprogression

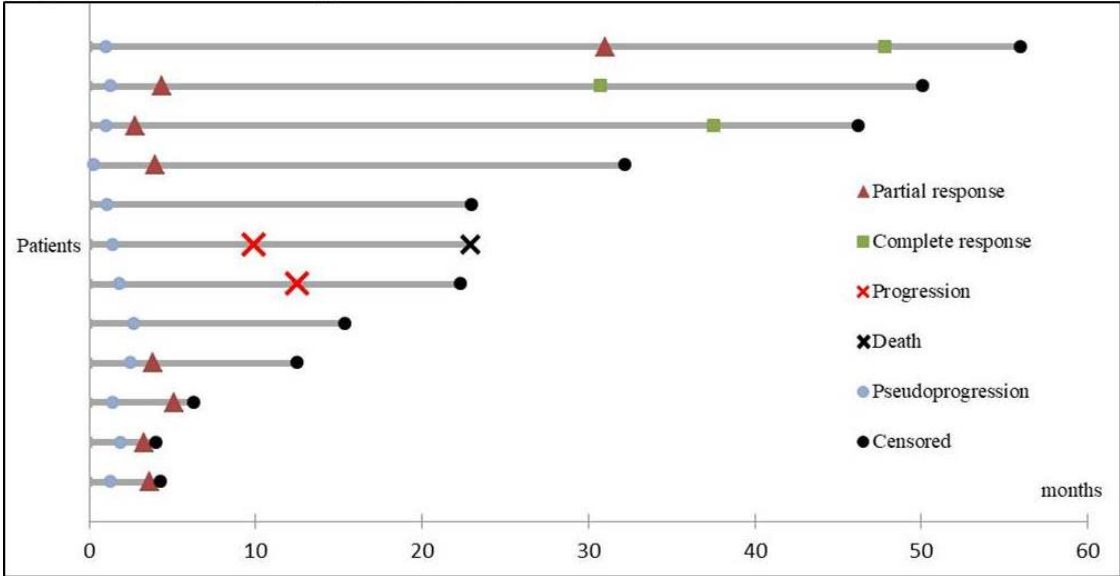


Figure 3: Overall survival (A) and progression-free survival (B) for patients with pseudoprogression

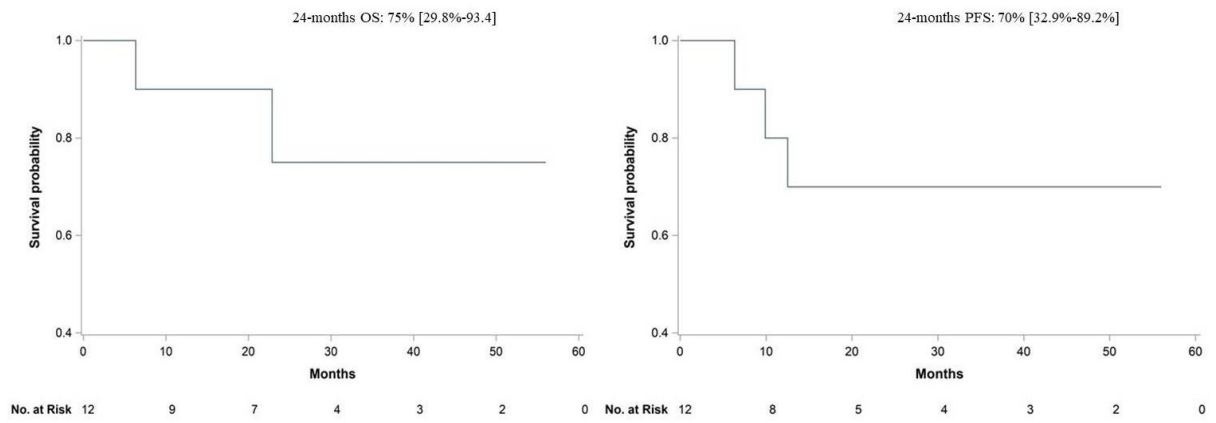
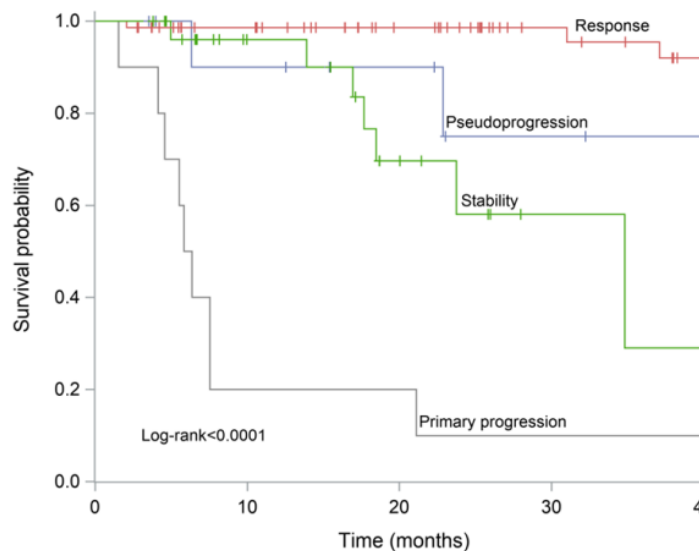


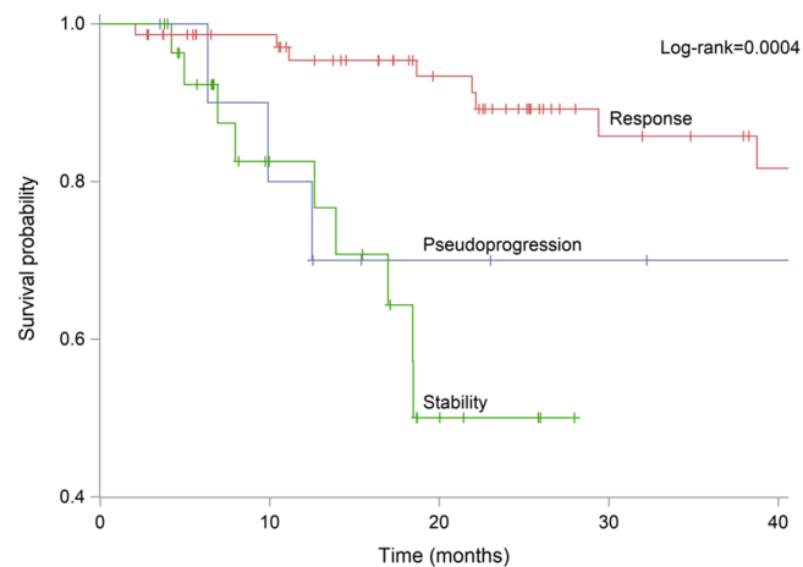
Figure 4: Overall survival (A) and progression-free survival (B) according to radiological response

A



No at risk	0	10	20	30	40
Primary progression	10	2	2	1	
Pseudoprogression	12	9	7	4	
Response	73	62	48	31	
Stability	28	16	8	2	

B



No at risk	0	10	20	30	40
Pseudoprogression	12	8	5	4	3
Response	73	62	45	25	20
Stability	28	14	5	0	

	2-years OS rate	HR		2-years PFS rate	HR
PR + CR	98.6 [90.7;99.8]	1	PR + CR	89.2 [77.3;95.1]	1
PSPD	75.0 [29.8;93.4]	5.0 [0.83 ; 29.96]	PSPD	70.0 [32.9 ; 89.2]	2.9 [0.77;11]
SD	58.0 [26.5;80.0]	10.8 [2.71 ; 42.76]	SD	50.0 [24.6;71.1]	6.2 [2.2;17]
PD	10.0 [0.06;0.36]	54.9 [14.52 ; 207]			

Table 1: Patient baseline characteristics

	All patients N (%)	With PSPD n (%)	Without PSPD n (%)
Number of patients	123	12	111
Age, years (Q1-Q3)	57 (45-65)	53.5 (45-65)	56.5 (45-65)
Gender			
Female	51 (41)	4 (33)	47 (42)
Male	72 (59)	8 (67)	64 (58)
ECOG performance status			
0-1	117 (95)	10 (83)	10 (83)
2-3	6 (5)	2 (17)	4 (4)
Primary tumor location			
Right	78 (63)	7 (58)	71 (64)
Left	41 (34)	4 (32)	37 (33)
Unknown	4 (3)	1 (8)	3 (3)
Number of metastatic sites			
1	39 (32)	1 (8)	38 (34)
2+	84 (68)	11 (92)	73 (66)
Metastatic sites			
Liver	60 (49)	8 (68)	52 (47)
Distant lymph nodes	79 (63)	6 (50)	73 (66)
Lung	18 (14)	2 (17)	16 (14)
Peritoneum	53 (42)	6 (50)	47 (42)
others	29 (24)	3 (25)	26 (23)
Histological feature			
Non-mucinous, non-medullary adenocarcinoma	73 (59)	6 (50)	67 (60)
Medullary adenocarcinoma	7 (6)	0	7 (6)
Mucinous adenocarcinoma	43 (35)	6 (50)	37 (33)
<i>RAS/RAF</i> mutational status			
<i>KRAS/NRAS</i> mutation	49 (40)	3 (25)	46 (41)
<i>BRAF</i> mutation	26 (21)	3 (25)	23 (21)
<i>RAS/RAF</i> wild-type	43 (35)	6 (50)	37 (33)
Unknown	5 (3)	0	5 (5)
Number of prior treatment lines			
0	9 (7)	0 (0)	9 (8)
1	31 (25)	2 (16)	29 (26)

2	54 (44)	5 (42)	49 (44)
3+	29 (24)	5 (42)	24 (22)
Type of checkpoint inhibitor			
Anti-PD1	61 (50)	9 (75)	52 (47)
Anti-PD1 + AntiCTLA4	62 (50)	3 (25)	59 (53)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status