Author response to Colle *et al*

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ABSTRACT

The event of pseudoprogression is rare in patients with MSI-high metastatic colorectal cancer receiving immune checkpoint inhibitors. In this response to the Letter to the Editor by Colle *et al*, we highlight that the timing of disease re-assessment may influence the incidence of pseudoprogression, with early assessments being associated with higher incidence. Such dynamics should be considered when interpreting the efficacy of treatment.

Dear Editor,

We read with interest the letter from Colle *et al*¹ highlighting the lack of pseudoprogression (PSPD) events reported in our study on the prognostic impact of the radiological tumor response dynamics in patients with microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) metastatic colorectal cancer (mCRC) receiving immune checkpoint inhibitors (ICIs).² Our patients discontinued ICIs immediately after the evidence of progressive disease (PD) and, in most of the cases, the radiological PD was paralleled by the worsening of their clinical conditions, especially for heavily pretreated patients with primary PD.

We agree with Colle *et al* that the discrepancy between the prevalence of PSPD previously reported by their group in a similar retrospective population (about 10%) might be explained largely by the difference in the timing of the first radiological evaluation.³ Indeed, the authors observed that, in their study population, the median time to PSPD was 5.7 weeks (95% CI 4.1 to 11.4) and no PSPD was detected after 3 months. In our study, the first disease reassessment was performed, as per clinical practice, at 8/9 weeks from treatment initiation and may have missed the events of PSPD.

We would like to thank Colle *et al* for having stimulated an open scientific discussion about the importance of the timing of the first radiological reassessment in patients with MSI-H/dMMR mCRC treated with ICIs; taken together, the data from our studies suggest that, in the absence of clinical

suspicion, the first radiological evaluation should be performed not prior to 9/12 weeks from treatment initiation, whereas (as pointed out by Colle *et al*) iRECIST criteria⁴ should be considered if the first evaluation is made at an earlier time point. Moreover, data from randomized clinical trials are needed to clearly assess early tumor dynamics, especially for treatment-naïve patients who may cross-over prematurely to less effective chemotherapy-based regimens if PSPD is not promptly recognized.

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