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Primary Resistance to Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer-Beyond the Misdiagnosis-In Reply

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1 **AUTHORS' REPLY**

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1 **Primary Resistance to Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer:**

2 **What's Beyond Misdiagnosis. Authors' reply**

3 We thank Jian Xu and colleagues for their interest in our work. We totally agree that, besides
4 misdiagnosing of the MSI/dMMR status, specific mechanisms including those described by
5 Xu et al. may underlie primary resistance of true MSI tumors to immunotherapy. Although it
6 is not *per se* a resistance mechanism, it is likely that the majority of primary resistance to
7 immunotherapy results from such misdiagnoses in clinical trials today. From a clinical point
8 of view, the medical oncologists, pathologists and molecular biologists must be aware of this,
9 so that patients experiencing immediate disease progression after ICKi initiation should be
10 quickly re-assessed for their MSI/dMMR status, even more so since ICKi might be continued
11 potentially until the next radiological evaluation (with the hypothesis of a pseudo-
12 progression).

1 **Routine double mismatch repair testing for checkpoint inhibitors. Authors's reply**

2 Kotoula and colleagues express concern about the small sample size of our study and also the
3 financial cost of a routine double MSI/dMMR status screening using both
4 immunohistochemistry (IHC) and PCR.

5 Though our findings were also based on the screening of a large retrospective tumor
6 collection of MSI colorectal cancers, we totally agree that they have to be further confirmed
7 in the future due to the small size of the study population we prospectively examined in this
8 study.

9 It is true that MSI/dMMR misdiagnosis was mainly related to misinterpretation of pentaplex
10 PCR rather than IHC in this study. Nevertheless, we would like to respectfully remind
11 Kotoula and colleagues that IHC alone has been shown to be associated with several pitfalls
12 (for review see ¹). Consistent with the literature ², we have observed in our cohort
13 approximately 5% of false negatives by IHC, probably related to false sense mutations which
14 did not lead to total inactivation of the corresponding MMR protein in cancer cells.
15 Considering the major and durable clinical benefit of immune checkpoint inhibitors for
16 patients with MSI cancer, we do believe that a 5% false-negative rate is ethically not
17 acceptable and that hence dual screening with both IHC and pentaplex PCR is absolutely
18 necessary. The complementarity of IHC and pentaplex PCR to reach maximum sensitivity
19 and specificity have been already well documented in the literature. ¹ The cost of a combined
20 analysis is of course higher, and we agree that this point has to be taken into consideration,
21 especially as the screening of non-metastatic patients may become more and more
22 indispensable also in pan-cancer in the future.

23 Regarding *HSP110* T17 assay, we show here (and in previously published studies ³) that it is
24 a highly sensitive, helpful microsatellite marker. One might use it as a third confirmatory

1 assay specifically for cases with discrepant results between IHC and pentaplex PCR with a
2 very small extra cost (5 to 10% of all tested specimen). An other possibility would be to
3 include this marker directly in the routine tested panel with almost no additional cost. In any
4 case, the strategy will remain cheaper than commercial next-generation methods that have
5 recently obtained FDA approval for MSI testing and other actionable therapeutic targets ⁴.

6

- 7 1. Svrcek M, Lascols O, Cohen R, et al. MSI/MMR-deficient tumor diagnosis: Which
8 standard for screening and for diagnosis? Diagnostic modalities for the colon and other
9 sites: Differences between tumors. *Bull Cancer (Paris)*. February 2019.
10 doi:10.1016/j.bulcan.2018.12.008
- 11 2. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary
12 nonpolyposis colorectal cancer). *N Engl J Med*. 2005;352(18):1851–1860.
- 13 3. Buhard O, Lagrange A, Guilloux A, et al. HSP110 T17 simplifies and improves the
14 microsatellite instability testing in patients with colorectal cancer. *J Med Genet*.
15 2016;53:377-384. doi:10.1136/jmedgenet-2015-103518
- 16 4. Prasad V. Why the US Centers for Medicare and Medicaid Services (CMS) should have
17 required a randomized trial of Foundation Medicine (F1CDx) before paying for it. *Ann*
18 *Oncol*. 2018;29(2):298-300. doi:10.1093/annonc/mdx786

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