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Immunotherapy in MSI metastatic colorectal cancer: current status and future perspectives

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Immunotherapy in colorectal cancer: current status and future perspectives
Journal of Clinical and Translational Research

Dear Dr. Sotelo ,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jun 24, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This is an interesting article to be published in this journal. The authors make a complete review about immunotherapy in colorectal cancer, including translational data to understand the role of immune checkpoint inhibitors in this disease.
Also an effort have been made to analyze published data from many clinical trials in this scenario and inform future perspectives regarding immunotherapy in colorectal cancer.

Consider these suggestions that could help enhance the value of this article:

* Summarize the section on biomarkers related to immune checkpoint inhibition in colorectal cancer. (Suggestion: POLE, microbiome, MSI, TMB, immune-score)
* Add a brief summary on immunotherapy resistances in this scenario (Intrinsic and acquired i.e. mutations in β2M, MHC-I, IFNγ/JAK1 mutations, etc).
* Updated info of approvals and indications by main regulatory agencies (FDA, EMA) of immunotherapy in colorectal cancer.

Reviewer #2: Dear authors,

I have reviwed your job with great interest. Immunotherapy in mCRC is an amazing issue. However, some minor and major changes should be done:

Minor comments:
1.- Gene names should be italicized
2.- Regarding targeted therapy in KRAS and BRAF you should add KRAS-G12C and always BRAF-V600E,
3.- Pag 2, 3th parragraph: sideness should be included as a significant prognostic and predictive biomarker
4.- MSI should be more described in the introduction, the role of MSI in localized colon cancer stage II and stage III, what does it's meaning in localized colon cancer regarding prognostic and treatment...
5.- At the end of page 3 "in the past decade an attempt was made...". Several molecular classification has been published, you should delate "an"
6.- A mention to the colorrectal TCGA classification could be mentioned: hypermutated vs no hypermutated tumors.
7.- Pag 4: not a half of the mCRC patients have a molecular alteration that could be druggable.
8.- pag 5 1st parragraph: right-sided CRC respond less (instead of "do not respond") to antiEGFR
9.- Parragraph 2 pag 5: add % for each molecular alteration
10.- Parragraph 3: MSI in mCRC represents up to 5-7%, in the localized scenario is 15-20%,

please change it
11.- Last parragraph page 5: NGS is every day more accessible!
12.- pag 6: regarding nivo, pembro, durva and atezo you should describe if each one of these is antiPD1 or antiPDL1
13.- Table 1: erase keynote028, you already have included the keynote028 update
14.- If you want to talk about immunotherapy in MSS population you should mention CCTG CO.26, the Cotezo (Bendell ESMO GI 2018) and the REGONIVO clinical trials.
15.- Pag 15 Regarding the dose of nivo and ipi there is a confusion with the dose in the text (nivo 1 mg/kg should be change to 3 mg/kg and the same with ipi)
16.- the keynote-177 has been a practice changing trial, this should be reflected in the text. Moreover, RAS mutant patient didn't achieve a big benefit but in my opinion, because is a not pre-planned analysis you should state that KRAS subgroup achieve less benefit instead of "no benefit" and this result should be confirmed in further clinical trials.
17.- Regarding Biespecific antibodis in my opinion you should comment it with more detail, the flair effect, studies that are on-going...
18: ACT: may be you can also include Van Cutsem ESMO GI 2019...
19.- As I suggest before, MSI should be explain with more detail in localized scenario ,%, clinical meaning...
20.- Regarding the techniques for MSI detection such as PCR and IHQ: concordance between both techniques is needed

Major concerns:
1.- This review is focus in a really hot topic in colorectal cancer. However this review lacks of detail and it only comments briefly important points
2.- Although this review is focus on MSS/MSI mCRC only few ideas of MSS patients are commented. I will recommend to change the topic to a "Immunotherapy in MSI mCRC) or to work deeper in the MSS part.
3.- Recent publications suggest that TMB could not be useful in CRC, this papers should be commented: NEJM and Annals of Oncology
4.- Finally, both the introduction and the conclusions seems to be like "bullet points" may be could be changed to a more "history" explanation.

Reviewer #3: The present paper reviews the interesting topic of the current role and future perspectives of immunotherapy in colorectal cancer. Authors made an outstanding review of the available evidence analyzing the rationale and efficacy of immunotherapy in this setting. The article generally looks good in terms of spelling and language. This review article is clearly presented and will be of interest to readers of the journal.

Reviewer #4: Authors performed a comprehensive review on immunotherapy in colorectal cancer, with a focus on molecular biology, evidence on approved clinical trial and discussion of novel possible strategies.
The paper is clear and well written.
As minor revision:
page 3 line 59: ...in those with KRAS, BRAF... please add mutant after BRAF

In general, the terminology regarding microsatellite instability is not homogeneous. Please revise it along the text.

Authors' response

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Lima, 20 June 2021

Re: revision JCTRes-D-21-00048

Dear Dr. Michal Heger

Thank you for giving us an opportunity to resubmit a revised version of our manuscript entitled "Immunotherapy in MSI metastatic colorectal cancer: current status and future perspectives." We have addressed all comments of the reviewers, highlighting the changes in yellow. Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red.

We are grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved.

On behalf of the authors, kindest regards,

Miguel J. Sotelo

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REVIEWER COMMENTS

Reviewer #1:

Comments:

1) Summarize the section on biomarkers related to immune checkpoint inhibition in colorectal cancer (Suggestion: POLE, microbiome, MSI, TMB, immune-score).

We have included a summary of biomarkers related to immune checkpoint inhibition in colorectal cancer.

“However, reported response rates to anti-PD1 are variable and often <50% in patients with MSI-H, suggesting that additional predictive biomarkers are needed. Recent studies point out that tumor mutational burden (TMB) appears to be an important predictive biomarker of response to immunotherapy in multiple tumor types independent of MSI status or PD-L1 expression. TMB-high tumors are thought to harbor an increased neoantigen burden, making them immunogenic, and responsive to immunotherapy. Studies have shown that TMB in MSI-H mCRC is generally elevated, but still quite variable. Although still a few and small-sized studies have addressed this issue, TMB-high mCRC shows a strong association with higher objective response and longer PFS with immunotherapy in comparison with TMB-low mCRC, marking TMB a potential predictive biomarker in this population. Increasing evidence demonstrates that the cancer evolution is strongly dependent on the complex tumor microenvironment in which it develops. Although not standardized yet, the immunoscore (IS) is a direct measure of T-cell infiltration into tumors, based on the amount of lymphocyte populations, specially CD3 and CD8-positive T cells, commonly found in high amounts in MSI-H or dMMR patients. The immunoscore provides a scoring system ranging from low to high, helping to predict and stratify patients who could benefit from immunotherapy. In addition, up to 20% of MSS CRC harbor a similar profile to MSI-H tumors. Among these, a small percentage of MSS CRC (< 1%) are secondary to POL-E and POL-D mutations, characterized by an ultra-mutator phenotype, and have also been shown to respond to PD-1 inhibitors. Is well known that there is an important association between lifestyle factors and the risk of developing CRC, especially dietary factors. Human body is colonized by more than 100 trillion microbes most of which are bacteria, of eukaryotic and archaeal species, many of which are in the gut. Gut microbiota colonization starts at birth and is remodeled according to diet, lifestyle, disease, aging, drug consumption and other environmental factors. The gut of a healthy individual is mainly composed of a specific type and number of microbes, that help to regulate homeostasis, inflammation, metabolism and immunity. The role of gut microbiota in such mechanisms is a relatively new research field, but as an immuno and metabolic modulator, could potentially

affect the efficacy of immunotherapy in cancer patients. Further prospective studies are needed to validate immunoscore, POL-E and POL-D mutations and microbiota as predictive factors."

2) Add a brief summary on immunotherapy resistances in this scenario (Intrinsic and acquired i.e. mutations in β2M, MHC-I, IFNγ/JAK1 mutations, etc).

A brief paragraph regarding the mechanisms of resistance to immunotherapy was included.

"Although immunotherapy has demonstrated being a new option of therapy, markers of resistance to immunotherapy have been discovered in patients with solid tumors. Deletions or mutations in JAK1/2, IFNGR1/2, and IRF1118 have been reported, particularly JAK1 and JAK2. Mutations that inactivate JAK1 or JAK2 lead to both acquired as well as primary resistance to anti- PD1 therapy. Truncating mutations in B2M lead to impaired MHC class I antigen presentation and generation of immune escape variants that fail to elicit a T cell response. Stability of chromatin remodeling complexes (PBRM1, ARID2, and BRD7) in tumors contributes to immunotherapy resistance, which inabilities the recruitment of mismatch repair genes during DNA repair and subsequently diminish the neoantigen load. Furthermore, immunoediting has been reported as a mechanism for resistance. Immunoediting suggests that constant interactions between the immune system and cancer cells result in selection of subclones within the tumor that lack expression of neoantigens, conferring poor immunogenicity and resistance to immunotherapy. Mechanisms of resistance for immunotherapy in CRC is still unclear and further studies must be done to acknowledge this topic".

3) Updated info of approvals and indications by main regulatory agencies (FDA, EMA) of immunotherapy in colorectal cancer.

The approval of immunotherapy agents by the FDA and EMA is updated.

"FDA approval of pembrolizumab (May 2017), nivolumab (August 2017) and nivolumab combined with low-dose ipilimumab (July 2018) in the second-line setting for MSI-H/MMRd mCRC [9]. Recently, the EMA has also approved these agents in MSI-H/MMRd mCRC."

"The FDA (June 2020) and EMA (January 2021) approved pembrolizumab for first-line treatment of MSI-H/dMMR CRC."

Reviewer #2:

Minor comments:

1. Gene names should be italicized

   Changed accordingly, thank you.
2. Regarding targeted therapy in KRAS and BRAF you should add KRAS-G12C and always BRAF-V600E.

   We appreciate your comment, we have added information about KRAS-G12C and BRAF-V600E.

   "During decades KRAS mutation has been considerate "undruggable". However, recent in vitro evidence suggests that targeting the cysteine in the mutated KRAS-G12C increases the apoptosis of G12C-containing cancer cell lines. Although, KRAS-G12C is a rare mutation in mCRC, this result hopefully helps to open a decade lock door in mCRC treatment"

   "BRAF mutations develop in 8-10% of cases, the majority (90%) in the V600E locus. BRAF V600E mutations account for 90% of BRAF mutations in CRC, with a 10-fold more activity compared to the wild-type counterpart"
3. Pag 2, 3th paragraph: sidedness should be included as a significant prognostic and predictive biomarker

   We appreciate your comment, sidedness has been included as a prognostic / predictor factor within the article.

   "Several predictive biomarkers have emerged to aid in the therapeutic decision-making in metastatic CRC, such as KRAS (40%), NRAS (5-10%) and BRAF (8-10%) mutation status, tumor sidedness, microsatellite instability (MSI), and other less common alterations such as HER2 (2%), MET (2%), NTRK (0.2-2.4%), ALK (0.2-2.4%), and ROS1 (0.2-2.4%)"
4. MSI should be more described in the introduction, the role of MSI in localized colon cancer stage II and stage III, what does it's meaning in localized colon cancer regarding prognostic and treatment...

   We appreciate your comment, the role of MSI in clinical stage II and III colorectal cancer has been described in more detail.

   "MSI has an incidence of up to 15-20% in local colorectal cancer and has clinical relevance in early stages. Stage III MSI tumors exhibit higher rates of lymphovascular invasion and perineural invasion. However, there is no clear association between MSI-

h stage III CRC and benefit from adjuvant chemotherapy. In addition, MSI-h is associated with poor response to chemotherapy in stage II tumors. This may be due to the solid evidence indicating that MSI-h stage II or III CRC are associated with fewer odds of relapse and death compared to MSS CRC. Therefore, MSI-h status in stage II or III CRC, may allow to de-escalate adjuvant treatment in selected cases"

5. At the end of page 3 "in the past decade an attempt was made...". Several molecular classification has been published, you should delate "an"

   Changed accordingly, thank you.

   "In the past decade, several attempts have been made to understand and classify CRC based on its molecular profile and in search of possible therapeutic targets"

6. A mention to the colorectal TCGA classification could be mentioned: hypermutated vs no hypermutated tumors

   The TCGA classification of colorectal cancer was reviewed and each group was briefly explained.

   "The TCGA classification (2013) groups patients into chromosomal instability (84%), hypermutated (13%) and ultramutated (3%) profiles. The hypermutated group is characterized by dMMR, MSI, MLH1-sll, CIMP-h, BRAF-mut and SCNA-low''

7. Pag 4: not a half of the mCRC patients have a molecular alteration that could be druggable.

   This information has been removed and the paragraph has been modified, thank you.

   "Around 75% of advanced CRC harbor predictive biomarkers that allow choosing the best therapeutic option. KRAS mutations occur in 40% of CRC, with a up to 85-90% of them, occurring in exon 2, codons 12 and 13, and the remainder in exons 3 and 4. For decades, KRAS mutations have been considered "undruggable". However, sotorasib a KRAS-G12C mutation inhibitor has been recently approved by the FDA for KRAS-G12C-mutant non-small cell lung cancer (NSCLC), after demonstrating high response and survival rates. Although, KRAS-G12C is a rare mutation in mCRC, this results in NSCLC provide a prove of concept that targeting KRAS may also be feasible in other entities, such as mCRC. NRAS mutations occur in 5-10% of patients, in exons 2, 3 and 4. BRAF mutations develop in 8-10% of cases, the majority (90%) in the V600E locus, meanwhile BRAF V600E mutations account for 90% of BRAF mutations in CRC, with a 10-fold more activity compared to the wild-type counterpart".

8. Page 5 1st paragraph: right-sided CRC respond less (instead of "do not respond") to antiEGFR

Changed accordingly, thank you.

"right-sided CRC respond less to anti-EGFR agents"

9. Paragraph 2 pag 5: add % for each molecular alteration

   Thanks for your comment, the percentage was added to each molecular alteration.

   "Several predictive biomarkers have emerged to aid in the therapeutic decision-making in metastatic CRC, such as *KRAS* (40%), *NRAS* (5-10%) and *BRAF* (8-10%) mutation status, tumor sidedness, microsatellite instability (MSI), and other less common alterations such as *HER2* (2%), *MET* (2%), *NTRK* (0.2-2.4%), *ALK* (0.2-2.4%), and *ROS*1 (0.2-2.4%)"

10. Parragraph 3: MSI in mCRC represents up to 5-7%, in the localized scenario is 15-20%, please change it

    Changed accordingly, thank you.

11. Last parragraph page 5: NGS is every day more accessible!

    Changed accordingly, thank you.

    "Next generation sequencing (NGS), a third alternative method, everyday more accessible, has shown high concordance rates with the former methods"

12. Pag 6: regarding nivo, pembro, durva and atezo you should describe if each one of these is antiPD1 or antiPDL1

    It was specifically described whether the mechanism of the immunotherapy agents is PD1 or PDL1.

    "PD-1 (nivolumab or pembrolizumab) and PD-L1 (durvalumab, atezolizumab or avelumab) inhibitors"

13. Table 1: erase keynote028, you already have included the keynote028 update.

    Changed accordingly, thank you.

14. If you want to talk about immunotherapy in MSS population you should mention CCTG CO.26, the Cotezo (Bendell ESMO GI 2018) and the REGONIVO clinical trials.

    The mentioned studies were reviewed and added in the corresponding section of the manuscript. Thank you very much for the suggestion of the studies.

    "Regorafenib is a multi-tyrosine kinase inhibitor that blocks many pathways, including CSF1R, whose inhibition may reduce the recruitment of immune-suppressive tumor-associated macrophages (TAMs) to the tumor microenvironment. A phase I/IB trial evaluated the combination of nivolumab and regorafenib in refractory pMMR mCRC, where 28 patients received nivolumab 240mg IV q2wk and regorafenib according to a dose escalation design. The combination was considered safe. Dose modifications

(reductions or interruptions) for drug-related adverse events occurred in 4 patients. mPFS was 5.7 months and mOS was not reached after a median follow-up of 4.6 months. REGONIVO, a phase Ib trial, evaluated dose-limiting toxicity during the first 4 weeks of treatment with the same regimen in 50 pretreated patients [25 mCRC and 26 metastatic gastric cancer (mGC)] in order to estimate the maximum tolerated dose. One patient had MSI while the rest had MSS/MMR-p tumors. The combination of regorafenib/nivolumab had a manageable safety profile and encouraging antitumor activity. The most common grade 3 treatment-related adverse events were rash (12%), proteinuria (12%), and palmar-plantar erythrodysesthesia (10%). ORR was 40%, and mPFS achieved 5.6 months and 7.9 months in patients with mGC and mCRC, respectively.

The CCTG CO.26 study, investigated somatic variants contributing to plasma tumor mutational burden (pTMB) in MSS patients using cell-free DNA (cfDNA) analysis performed with the GuardantOMNITM test. Patients with pTMB > 28 mutations/megabase (21% of them with MSS tumors) had the greatest OS benefit for durvalumab and tremelimumab (HR 0.34, 90% CI, 0.18-0.63, p = 0.070) with a worse OS in the best supportive care arm (HR 2.59, 90% CI, 1.46-4.62). Of 4044 mutations detected, 67.2% were subclonal and after removing them from pTMB calculation, median pTMB decreased 5.8 mutations/megabase. However, this clonal pTMB remained predictive of durvalumab and tremelimumab improving OS (HR 0.19, 90% CI 0.08-0.45, p = 0.039) with pTMB > 10.6 mutations/megabase (14.1% pts). This study suggests that subclonal and clonal mutations could have a predictive value for immunotherapy in MSS mCRC patients.”.

15. Pag 15 Regarding the dose of nivo and ipi there is a confusion with the dose in the text (nivo 1 mg/kg should be change to 3 mg/kg and the same with ipi)
Changed accordingly, thank you.
“Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg”
16. The keynote-177 has been a practice changing trial, this should be reflected in the text. Moreover, RAS mutant patient didn't achieve a big benefit but, in my opinion, because is a not pre-planned analysis you should state that KRAS subgroup achieve less benefit instead of "no benefit" and this result should be confirmed in further clinical trials.
We appreciate your accurate comment, indeed patients with a KRAS mutation have less benefit. This line has been modified in the article. In the same way, the importance of the Keynote 177 study was emphasized, as they point out.

"This is a practice-changing trial and its results probably establish pembrolizumab as a new first-line standard in MSH-I/MMRd CRC"

"Interestingly, all subgroups benefited from pembrolizumab in terms of PFS. However, the KRAS/NRAS-mutant subgroup achieved less benefit, a result that merits confirmation in further clinical trials"

17. Regarding Bispecific antibodies in my opinion, you should comment it with more detail, the flair effect, studies that are on-going...

    Bispecific antibodies were discussed in more detail, in the same way we included the on-going studies.

    "T cell-dependent bispecific antibody (TDB)-induced T cell activation, which can eliminate tumor cells independent of MHC engagement, is expected to be a novel breakthrough immunotherapy against refractory cancer. In vitro and ex-vivo data suggest that a prolonged presence of the drug in target tissues may result in significant T-cell recruitment, activation and expansion to/in target tissues, potentially resulting in substantial anti-tumor activity." "Ongoing trials are trying to assess the pharmacokinetics, safety and tolerability bispecific monoclonal antibodies like MT110, MGD019 or ZW25; alone or with chemotherapy/immunotherapy in mCRC, mainly heavily pretreated patients, and other solid neoplasms (NCT00895323, NCT03866239, NCT00635596, NCT03761017, NCT03929666)."

18. ACT: maybe you can also include Van Cutsem ESMO GI 2019.

    Results of the phase 1 study, presented by Van Cutsem at ESMO GI 2019, were added.

    "T cell-dependent bispecific antibody (TDB)-induced T cell activation, which can eliminate tumor cells independent of MHC engagement, is expected to be a novel breakthrough immunotherapy against refractory cancer. In vitro and ex-vivo data suggest that a prolonged presence of the drug in target tissues may result in significant T-cell recruitment, activation and expansion to/in target tissues, potentially resulting in substantial anti-tumor activity." "Ongoing trials are trying to assess the pharmacokinetics, safety and tolerability bispecific monoclonal antibodies like MT110, MGD019 or ZW25; alone or with chemotherapy/immunotherapy in mCRC, mainly heavily pretreated patients, and other solid neoplasms (NCT00895323, NCT03866239, NCT00635596, NCT03761017, NCT03929666)."

19. As I suggest before, MSI should be explain with more detail in localized scenario, %, clinical meaning.

We appreciate your valuable comment. MSI has been described in more detail in the early stage, including the percentage.

"MSI has an incidence of up to 15-20% in local colorectal cancer and has clinical relevance in early stages. Stage III MSI tumors exhibit higher rates of lymphovascular invasion and perineural invasion. However, there is no clear association between MSI-h stage III CRC and benefit from adjuvant chemotherapy. In addition, MSI-h is associated with poor response to chemotherapy in stage II tumors. This may be due to the solid evidence indicating that MSI-h stage II or III CRC are associated with fewer odds of relapse and death compared to MSS CRC. Therefore, MSI-h status in stage II or III CRC, may allow to de-escalate adjuvant treatment in selected cases"

20. Regarding the techniques for MSI detection such as PCR and IHQ: concordance between both techniques is needed

Thanks for the comment, we have added the concordance between PCR and IHC for MSI detection in the article.

"NGS has a sensitivity of 95.8% and specificity of 99.4%, with a positive predictive value of 94.5%, and negative predictive value of 99.2% as compared to PCR. For IHC, sensitivity ranged from 80.8%-100.0% and specificity ranged from 80.5%-91.9%"

Major concerns:

1. This review is focus in a really hot topic in colorectal cancer. However, this review lacks of detail and it only comments briefly important points

   We appreciate your honest comment, we have tried to detail and deepen the most relevant points, to improve the manuscript.

2. Although this review is focus on MSS/MSI mCRC only few ideas of MSS patients are commented. I will recommend to change the topic to a "Immunotherapy in MSI mCRC) or to work deeper in the MSS part.

   We appreciate your thoughtful comment. We have changed the title of the article to "Immunotherapy in MSI metastatic colorectal cancer: current status and future perspectives"

3. Recent publications suggest that TMB could not be useful in CRC, these papers should be commented: NEJM and Annals of Oncology

   The information was reviewed and added. Thank you for your comment.

   "TMB-high tumors are thought to harbor an increased neoantigen burden, making them immunogenic, and responsive to immunotherapy. Studies have shown that TMB in MSI-H mCRC is generally elevated, but still quite variable. Although still

a few and small-sized studies have addressed this issue, TMB-high mCRC shows a strong association with higher objective response and longer PFS with immunotherapy in comparison with TMB-low mCRC, marking TMB a potential predictive biomarker in this population"

4. Finally, both the introduction and the conclusions seem to be like "bullet points" may be could be changed to a more "history" explanation.
   Changed accordingly, thank you.

Reviewer #3:

The present paper reviews the interesting topic of the current role and future perspectives of immunotherapy in colorectal cancer. Authors made an outstanding review of the available evidence analyzing the rationale and efficacy of immunotherapy in this setting. The article generally looks good in terms of spelling and language. This review article is clearly presented and will be of interest to readers of the journal.

Thank you very much for your comment.

Reviewer #4:

1) The paper is clear and well written. As minor revision:
   page 3 line 59: ...in those with KRAS, BRAF... please add mutant after BRAF.
   Changed accordingly, thank you.
   "CMS1 is associated with a poor prognosis in those with *KRAS, BRAF mutant"*
2) In general, the terminology regarding microsatellite instability is not homogeneous. Please revise it along the text.
   Thank you for your comment. We add in the article that the definition of MSI is heterogeneous.
   "The terminology regarding microsatellite instability (MSI) is not homogeneous. MSI is commonly described as a hyper-mutable phenotype, resulting from a defective DNA mismatch repair (MMR) system, that leads to the presence of alternate sized repetitive DNA sequences that may (Lynch syndrome) or may not (sporadic cases) be present in the corresponding germline DNA".

2nd Editorial decision
18-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00048R1
Immunotherapy in MSI metastatic colorectal cancer: current status and future perspectives
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: This articles summarize correctly current status of immunotherapy in CRC. It will be very interesting for readers this amazing topic.
Regarding corrections, everythings has been taken care of and now i think the article has increased its value and is ready to publish.
Congratulations to the authors for the efforts and results.

Reviewer #3: In the paper entitled "Immunotherapy in MSI metastatic colorectal cancer: current status and future perspectives", the authors do a comprehensive review of the evidence supporting the benefit of immunotherapy in a subgroup of patients with advanced colorectal cancer. In addition, they analyze future therapies in this scenario. The changes made to the original manuscript have notably improved the level of the paper, so it should be considered for publication.

Reviewer #4: The authors addressed all the required changes.