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Editorial Board

Dear Editors,

I am pleased to submit the revised version of our manuscript "Efficacy of Olaparib in colorectal cancer patients with alteration in homologous repair protein"

According to reviewer request we make appropriate correction.

I am looking forward to receiving your comments on our manuscript.

Thank you for your time. With my personal regards,

Professor François Ghiringhelli MD, PhD

Director INSERM Team CRI866.

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Reviewer_01441415:

1. Although the treatment experience by olaparib is less novel, because Phase II trial of olaparib in CRC has already reported (Leichman L, et al. Oncologist 2016), the therapeutic concept of exome analysis-guided selection of molecular targeted agent has a considerable potential of future treatment strategy.
   Response: We agree with the reviewer point and we add this reference in the discussion of the manuscript. In this paper the treatment is no guide by molecular analysis so we discuss than maybe molecular analysis could help us to perform drug repositioning.

2. This manuscript is written in acceptable language quality and well-written discussion. Authors are recommended to incorporate the past knowledge and future perspectives regarding combination therapy with olaparib, such as irinotecan.
   Response : according to reviewer request we add in the discussion that olaparib could also be used with classical chemotherapies as previously described in the recent paper from Chen et al (Chen EX, et al. Invest New Drugs. 2016)

Reviewer **00057695 :**

1. However, the most challenging issue of using exome sequencing for the purpose of cancer-causing variant detection is analyzing and filtering the large number of detected variants. This needs to be highlighted in the discussion.
   Response: Accordingly, we highlight this point in the discussion. We add the sentence: "The use of exome sequencing in cancer has largely taken place in the setting of research studies such as The Cancer Genome Atlas (TCGA). However, Integration of exome sequencing into precision cancer care remain a challenging issue because samples such as small and poor quality from formalin-fixed (FFPE) tissues are difficult to analyses. In addition, bioinformatics approaches required to detect the wide-spectrum of mutations with the ability to identify actionable mutations at an acceptable sensitivity remain an issue."

2. Also, the use of targeted therapy such as poly ADP ribose polymerase (PARP) inhibitor therapy such as olaparib 400 mg p.o. b.i.d, in patients with colorectal cancer and inefficient tumor DNA repair mechanisms, such as those with microsatellite instability (MSI-H) has been studied in a phase II study. It was found that single-agent olaparib delivered after failure of standard systemic therapy did not demonstrate activity for CRC patients, regardless of microsatellite status (Leichman L, et al. Oncologist. 2016). Unfortunately, such trial was not alluded to in the discussion.
   Response: We agree with the reviewer point an add this reference in the discussion of the manuscript. In this paper the treatment is no guide by molecular analysis so we discuss than maybe molecular analysis could help us to perform drug repositioning.

3. Also, another recent Phase 1 study (Chen EX, et al. Invest New Drugs. 2016) was conducted to evaluate the safety and tolerability of olaparib, but in combination with irinotecan in patients with advanced colorectal cancer whose disease progressed after at

least one systemic therapy regimen. Again, this study was not referred to in the discussion.

Response : according to reviewer request we add in the discussion tha olaparib could also be used with classical chemotherapies as previously describe in the recent paper from Chen et al (Chen EX, et al. Invest New Drugs. 2016)

4. Other comments: 1. Indicate the dose of olaparib given to both patients.
   Response: We add the dosage (400mg Bid) in the manuscript
5. Although, the drug worked for Case 1, albeit for a short period of time, its use failed in case 2.
   Response: This point is important and we believe that it is one of the important part of the manuscript. We highlight that determination of homologous repair protein defect is important to predict efficacy of olaparib therapy. However, such anomalies are not sufficient to predict efficacy of olaparib. TP53BP1 mutations were previously described to blunt olaparib efficacy in BRCA deficient mice so we report here that such event is also true in human. These data underline that large genetic testing are required before introducing such target therapy for better understanding the molecular mechanism of resistance.

6. What is the cost of conducting the exome analysis? Also indicate the cost of olaparib course and the expected side-effects.
   Response: Exome analysis cost is 1000 euros and 6400 euros par mois.
7. The language needs polishing in certain areas of the “Case Report: patient 1 and patient 2). Also, in the discussion.
   Response: Language was polished as requested.