MINISTRY OF HEALTH, RUSSIA

N.N. PETROV INSTITUTE OF ONCOLOGY

Pesochny-2, St.-Petersburg
197758, Russia

Tel.: +7-(812)-439-9515
Fax: +7-(812)-596-8947

Prof. Evgeny N. Imyanitov
Head of the Department of Tumor Growth Biology
N.N. Petrov Institute of Oncology
RU-197758, Pesochny-2
St.-Petersburg, RUSSIA
Phone: + 7-812-4399528
Email: evgeny@imyanitov.spb.ru

Prof. Hiten RH Patel
Editor-in-Chief
World J Clin Oncol
Prof. Lian-Sheng Ma
Science Editor, Company Editor-in-Chief, Editorial Office
Baishideng Publishing Group Inc

Dear Prof. Patel,
Dear Prof. Ma,

We appreciate greatly your positive consideration of our manuscript #63832 entitled "Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors".

We have managed to address the issues raised during the evaluation process:

Comment: The manuscript clearly described the mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors. They also give clinical relevance and potential future study. it is well written review with. One question for the authors. could they discuss more detail or explain why "The platinum-induced selection of pre-existing BRCA-proficient cells has been demonstrated only for the BRCA1 gene. It is not self-explanatory that the same phenomenon is applicable to BRCA2-driven cancers. "(in page 9), and the difference of resistant mechanisms between brca1 and 2.

Response: To address this suggestion, we have incorporated the following paragraph:

The platinum-induced selection of pre-existing BRCA-proficient cells has been demonstrated only for the BRCA1 *gene, while similarly designed studies have not been performed yet for BRCA2-associated tumors. It is not self-explanatory that the same phenomenon is applicable to BRCA2-driven cancers. Indeed, although both* BRCA1 and BRCA2 *proteins are involved in the response to DNA damage, they have essential dissimilarities in their structure and function [14]. Consequently, they demonstrate differences regarding the spectrum of associated tumors, with prostate and pancreatic cancer been strongly linked to* BRCA2 *but not* BRCA1 *heterozygosity [7]. Breast carcinomas arising in*

BRCA1 *germ-line mutation carriers are usually triple-negative with regard to the receptor status (ER, PgR and HER2), while* BRCA2 *pathogenic alleles are generally associated with the development of tumors expressing steroid hormone receptors [10,11]. BRCA1 but not BRCA2 is essential for taxane-mediated cell death, so the resistance to taxanes is characteristic for BRCA1- but not for BRCA2-deficient cells [12]. The emergence of ORF-restoring secondary mutations in heavily pretreated tumors appears to be somewhat more common for* BRCA2 *than for* BRCA1 *gene [26,27]. BRCA1 deficiency is lethal for normal cells; therefore, the development of cancers in* BRCA1 *germ-line mutation carriers always involves mutation-driven inactivation of the* TP53 *gene, which results in down-regulation of apoptosis and provides the ground for the survival of BRCA1-null cells. In contrast, BRCA2 inactivation is compatible with cell viability, so BRCA2-associated tumors often have wild-type* TP53 *status [47]. While the persistence of BRCA1-proficient cells in chemonaive BRCA1-driven tumors is essential for the adaptation of OC to platinum-based therapy, it is unclear how this intratumoral heterogeneity supports the maintenance of tumor mass in "natural" conditions. This intratumoral heterogeneity may not necessarily be characteristic for the cancers arising in* BRCA2 *germ-line mutation carriers. Further studies are needed to reveal whether the persistence of isolated HR-proficient "stem" cells is relevant for BRCA2-driven tumors or sporadic OCs with BRCAness phenotype.*

We hope that the manuscript is now acceptable for publication and look forward to the decision of the Editorial Board.

With best regards,

Evgeny Imyanitov