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## The DNA damage repair (DDR) pathway in biliary tract cancer (BTC): a new Pandora's box?

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Received 12 September 2020 Accepted 12 September 2020 We read with great interest the article 'Molecular profile of BRCA-mutated biliary tract cancers' by Spizzo and colleagues. This study provides substantial evidence of the emerging importance of BRCA 1/2 mutations (BRCAm) identification in biliary tract cancers (BTC), suggesting a potential association between BRCAm and response to immune checkpoint inhibitors (ICIs). The emerging role of these genomic alterations as novel therapeutic target in metastatic solid tumours has led to enhance the concept of patient-focused, personalised medicine, paving the way towards new therapeutic scenarios in poor-prognosis malignancies. For this reason, the results reported by Spizzo and colleagues add another significant element to implement tailor-made treatment strategies for patients with BTC. However, some questions remain open.

First, the prevalence of BRCAm fluctuates from 1% to 7% across BTC, while a larger spectrum of genes which compromise DNA damage repair (DDR) pathway have been reported to occur in up to 28.9% patients with newly diagnosed BTC.<sup>2</sup> Interestingly, detection of multiple loss-of-function mutations in other DDR genes, epigenetic inactivation of BRCA1 or methylation of RAD51C promoters may identify candidates for displaying 'BRCAness' phenotype.<sup>2</sup> Nevertheless, there is still no consensus on methods for testing and defining DDR alterations in BTC. A recent study by Park and colleagues<sup>3</sup> proposed a selection of 17 germline and somatic alteration of HRR genes (ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, PALB2, RAD50, RAD51, RAD51C and RTEL1) in addition to BRCAm to evaluate a correlation with genomic instability in patients affected by pancreatic ductal adenocarcinoma. Moreover, despite the exciting therapeutic potential of DNA-damaging agents in these patients with broader evidence of 'BRCAness', how DDR pathway deficiency could associate with clinical responses and patient outcomes in BTC is still unknown.

Another question may deserve attention. Two months ago, Kim and colleagues<sup>4</sup> published results from a multicentre, phase II trial evaluating nivolumab in 54 patients with BTC after progression on 1 up to 3 lines of systemic therapy. According to the results of this study, 22% (10/54) of patients receiving nivolumab achieved objective response per RECIST V.1.1 criteria and, surprisingly, all responders had a mismatch-repair proficient tumour.<sup>4</sup> Therefore, considering the recent results reported by Spizzo et al and the approximate value of prevalence of DDR gene mutations in BTC, it would be interesting to know how many patients with DDR alterations were included in the study and if a proportion of ICIs responders harboured a 'BRCAness' phenotype.

Recently, comprehensive genomic analysis of 198 advanced non-small-cell lung cancer (NSCLC) samples carried out by Shim and colleagues<sup>5</sup> suggested that homologous recombination deficiency (HRD) could influence the response to ICIs by activating the stimulator of interferon genes signalling pathway and HRD could be associated with higher tumour mutation burden and longer progression-free survival in NSCLC. These findings provide an intriguing speculation regarding the potential therapeutic implications of DDR alterations across solid tumours.

In summary, we believe further efforts are needed to ascertain DDR deficiency in a comprehensive and cost-effective approach and to explore the potential role of DDR alterations as potential predictive biomarker in BTC.

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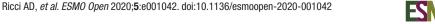
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