

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



Angela Dalia Ricci, Alessandro Rizzo , Giovanni Brandi

**To cite:** Ricci AD, Rizzo A, Brandi G. The DNA damage repair (DDR) pathway in biliary tract cancer (BTC): a new Pandora's box? *ESMO Open* 2020;5:e001042. doi:10.1136/esmoopen-2020-001042

ADR and AR contributed equally.

Received 12 September 2020  
Accepted 12 September 2020

Published online  
29 September 2020

We read with great interest the article 'Molecular profile of BRCA-mutated biliary tract cancers' by Spizzo and colleagues.<sup>1</sup> 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.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to

© Author (s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ on behalf of the European Society for Medical Oncology.

Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi University Hospital, Bologna, Italy

**Correspondence to**  
Dr Angela Dalia Ricci;  
dalia.ricci@gmail.com



distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, any changes made are indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Alessandro Rizzo <http://orcid.org/0000-0002-0701-6764>

#### REFERENCES

- 1 Spizzo G, Puccini A, Xiu J, *et al*. Molecular profile of BRCA-mutated biliary tract cancers. *ESMO Open* 2020;5:e000682.
- 2 Heeke AL, Pishvaian MJ, Lynce F, *et al*. Prevalence of homologous Recombination-Related gene mutations across multiple cancer types. *JCO Precis Oncol* 2018;2018:1–13.
- 3 Park W, Chen J, Chou JF, *et al*. Genomic methods identify homologous recombination deficiency in pancreas adenocarcinoma and optimize treatment selection. *Clin Cancer Res* 2020;26:3239–47.
- 4 Kim RD, Chung V, Alese OB, *et al*. A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. *JAMA Oncol* 2020;6:1–8.
- 5 Shim JH, Kim HS, Cha H, *et al*. HLA-corrected tumor mutation burden and homologous recombination deficiency for the prediction of response to PD-(L)1 blockade in advanced non-small-cell lung cancer patients. *Ann Oncol* 2020;31:902–11.