



Precision medicine for pancreatic cancer: real-world evidence from the Know Your Tumor programme

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Comment on: Pishvaian MJ, Blais EM, Brody JR. Overall Survival in Patients With Pancreatic Cancer Receiving Matched Therapies Following Molecular Profiling: A Retrospective Analysis of the Know Your Tumor Registry Trial. *Lancet Oncol* 2020;21:508-18.

Received: 02 June 2020; Accepted: 19 June 2020; Published: 30 December 2020.

doi: 10.21037/dmr-2020-20

View this article at: <http://dx.doi.org/10.21037/dmr-2020-20>

Pancreatic ductal adenocarcinoma (PDAC) is predicted to become the 2nd most common cause of cancer-related death by 2030 (1). The majority of pancreatic tumours are unresectable at time of diagnosis and median survival of patients in the advanced disease setting is just 12 months despite combination chemotherapy (2,3). There is a clear unmet need for the development of novel, innovative approaches to systemic therapy for patients with PDAC. Pathogenic alterations in genes involved in the DNA damage response (DDR), including *BRCA1*, *BRCA2*, *ATM*, *PALB2* amongst others, are associated with sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors (4). NCCN guidelines now recommend universal testing of PDAC patients for pathogenic germline alterations in *BRCA1* and *BRCA2*. In 2019 the FDA approved the use of PARPi Olaparib for treatment of patients with germline *BRCA1/2*-mutation and metastatic PDAC who had not progressed on platinum-based chemotherapy. This was based on demonstration of a significant improvement in progression-free survival among patients receiving maintenance Olaparib compared to placebo in the randomised phase III POLO study. This was the first and only approval of a molecularly targeted agent in PDAC to date (5). Somatic tumour mutational profiling in PDAC is more exploratory but up to 25% of PDAC patients may harbour ‘actionable’ variants (6,7), defined as those with clinical or strong preclinical evidence of a response to therapy. Significant responses to biomarker-based tumour agnostic therapies have been reported in PDAC; including immune checkpoint inhibitors for high microsatellite

instability (MSI-H) tumours and TRK inhibitors for *NTRK1*, *NTRK2*, *NTRK3*, or *ROS1* fusions (8-10). However, implementation of a precision oncology treatment paradigm for pancreatic cancer remains challenging, however, in large part due to the near ubiquity of KRAS alterations and rapidly progressive nature of the disease (11).

In this context, Pishvaian *et al.* (12) report the overall survival (OS) results of the Know Your Tumor (KYT) registry trial in *The Lancet Oncology*. The KYT programme enrolled 1856 patients based on voluntary calls to Pancreatic Cancer Action Network call centre. Tumour samples within the previous year underwent clinical genomic testing, and germline genetic testing was encouraged but not mandated. This information was collected into a personalised report, where a molecular tumour board consisting of oncologists, bioinformaticians and cancer biologists ranked therapy options on a case-by-case basis and returned this information to the patient and treating oncologist. As this was a real-world registry study, there were no uniform baseline characteristics, including performance status, CA19-9 levels, sites of metastases and specific dosing, routes and frequencies of therapies administered. To account for this variation, OS was measured from the date of initial diagnosis of advanced, unresectable or metastatic disease.

Of these 1,856 patients initially enrolled, 1,082 (58%) patients received molecular testing results and actionable variants were identified in 282 (26%) of 1,082 samples. Clinical outcomes were available for 677 patients that received 1 or more line of therapy in the advanced setting and had sufficient follow up. Of the 189 patients in this

group with an actionable alteration, 46 (24%) received a targeted therapy (the 'matched' group) while 143 (76%) did not receive molecularly matched therapy (the 'unmatched' group). At a median follow up of 383 days, median OS was significantly longer in the matched group compared to the unmatched group (2.58 *vs.* 1.51 years; HR 0.42; 95% CI: 0.26–0.68; $P=0.0004$), and those without an actionable alteration (HR 0.34; 95% CI: 0.22–0.53; $P<0.0001$). Median OS of the unmatched group did not differ significantly (0.82; 95% CI: 0.64–1.04; $P=0.1$) from those without an actionable alteration (the 'no marker' group).

As this was not a randomised trial, the authors explored whether baseline differences in matched, unmatched and no markers groups could account for observed OS differences. No significant imbalances were detected in sex, age at diagnosis and surgical status. However, in the matched group there was a higher frequency of patients exposed to platinum therapy or treated with >2 lines of treatment. A secondary analysis of patients that received >2 lines of treatment found that there still was a longer OS (1.81 *vs.* 0.85 years; HR 0.37; 0.22–0.63; $P=0.0002$) in the matched group compared to the unmatched and the no marker groups. Alterations in the DDR pathway were present in 94 (50%) of 189 patients with actionable mutations and median survival of those that received a PARP or ATR inhibitor was longer than those in the unmatched group (3.81 *vs.* 1.71 years; HR 0.48; 0.24–0.94; $P=0.0001$). Among 95 patients with an actionable alteration outside of the DDR pathway, there was increased survival compared to those in the no marker group (2.39 *vs.* 1.31 years; HR 0.40; 0.20–0.78; $P=0.0076$).

This study has important implications for a precision medicine approach to pancreatic cancer. It suggests that up to 26% of PDAC patients harbour a clinically actionable alteration, and administration of biomarker directed therapies may confer an OS benefit. Overall, 8% of patients profiled were eligible for PARP inhibitors, immune checkpoint inhibitors and TRK inhibitors. Other more exploratory matched targeted therapies were also employed, including CDK4/6 inhibitors for those harbouring CDK4 mutations and dual RAF/MEK inhibition for patients with *BRAF*^{V600E} alterations. As promising as these results are, several caveats remain. First, a relatively small fraction (46; 2%) of the 1836 patients referred ultimately received a matched therapy. This highlights the real-world barriers to implementing a precision oncology approach in PDAC. Secondly, this was a registry protocol where patients were enrolled at varying stages in their disease course, and the

study was non-interventional with respect to treatment availability. This could have introduced a bias where patients in the matched group had a better performance status and more favourable disease biology thus making them more eligible for enrolment into clinical trials of matched therapies. Finally, matched treatments were often combined with chemotherapy, and 351 patients were not included in this analysis due to missing longitudinal data, which both may have affected overall survival results. In light of the small sample size and exploratory nature of this prospective analysis, the overall survival gains can be interpreted as hypothesis-generating, rather than a new standard-of-care. This provides a rationale for prospective umbrella trials in PDAC, where real-time tumour molecular profiling and germline genetic testing could inform allocation of patients into separate treatment arms informed by results. Important studies such as the Precision-Panc trial (ISRCTN14879538), which has enrolled 300 patients as of March 4th 2020 illustrate such an approach, whereby PDAC patients undergo somatic and germline molecular profiling, and are assigned to one of five randomised trials to evaluate molecular determinants of response to molecularly targeted and traditional cytotoxic therapy (13).

As pancreatic cancer treatment moves into the era of precision medicine, incorporating real-world evidence with results of prospective trials is necessary. This study by Pishvaian *et al.* is a systematic comparison of survival following actionable therapy allocation in PDAC, and a proof-of-concept that tumour profiling may improve outcomes in a subset of patients. This provides a rationale for future adaptive precision medicine trials, incorporating basic and translational study endpoints to further characterise mechanisms of resistance and predictors of response. However, the relatively low proportion (2%) of patients enrolled who ultimately received matched therapy draws attention to the systemic barriers that patients encounter in seeking personalised treatments. Going forward, addressing these barriers will prove equal in importance to trial design in leveraging precision medicine to improve patient outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/dmr-2020-20>). MAL reports other from Agios pharmaceuticals, other from Roche, outside the submitted work. RP has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-2020-20

Cite this article as: Power R, Lowery MA. Precision medicine for pancreatic cancer: real-world evidence from the Know Your Tumor programme. *Dig Med Res* 2020;3:88.