Letter to the Editor

Clinical Cancer Research

Molecular Profiling of Pancreatic Cancer Patients—Response

Michael J. Pishvaian[1,2] and Emanuel Petricoin III[2,3]

We appreciate the opportunity to address the comments raised by Drs. Sahin and Elias. First, we are aware of the data surrounding the use of PARP inhibitors for HR-deficient pancreatic ductal adenocarcinoma (PDA; refs. 1, 2). We acknowledge that for patients with HR-deficient disease whose tumors have progressed on prior platinum there is often a lack of response to PARP inhibitors. Indeed, a critical part of the KYT process is that our disease-specific experts review the patient's treatment history and, if there was progression on prior platinum therapy, then a PARP inhibitor–based option is not considered. Such patients would indeed be appropriately placed in the "unmatched" therapy group if there was no other matched therapy to consider. Of the 640 patients we presented, only 2 patients with HR-deficient tumors received a PARP inhibitor after progressing on a platinum-based therapy, and removing these 2 patients does not affect the survival outcomes ($P = 0.004$ instead of $P = 0.03$).

With regards to the prognostic value of *BRCA* mutations, Dr. Golan demonstrated an improvement in outcomes for patients treated with platinum versus nonplatinum therapy, but any survival benefit was clearly confounded by the known predictive value of platinums in these patients. In contrast, the median overall survival for the surgically resected *BRCA* mutation carriers who did not receive platinum therapy was only 13 months. This observation was later confirmed in a matched case–control study (3). To our knowledge, there are no definitive data of the pure prognostic value of *BRCA* mutations in PDA.

Finally, while sonic hedgehog (SHH) inhibitors are active in basal cell carcinoma, this activity was not linked to the identification of an associated biomarker. In the absence of any predictive biomarker, our disease-specific experts would not present such an option. Accordingly, despite their availability in multiple umbrella studies, we never recommended SHH inhibitors in the KYT cohort.

We appreciate the concern that biomarker-directed therapies that work for one disease may not necessarily work in PDA, and we acknowledge that there is still much to "prove" prospectively. Nevertheless, a key goal of the KYT program is to identify biomarker-specific trials, which may yield unexpectedly positive outcomes, as we are starting to observe for some PDA patients, [e.g., the enrollment of 4 PDA patients in the pembrolizumab MSI-high trial (4); and our recent publication of entrectanib in ROS/NTRK fusion-harboring PDA patients (5)]. These patients would have never benefitted from these novel agents if the treating physician had not considered biomarker-driven therapy.

Disclosure of Potential Conflicts of Interest

E.F. Petricoin is an employee of Ceres Nanosciences, reports receiving other commercial research support from Abbvie, Inc, Genentech, Inc., and Symphogen, Inc., holds ownership interest (including patents) in Ceres Nanosciences, Inc. and Perthera, Inc., and is a consultant/advisory board member for ADVX Investors Group, LLC, AzGen, Inc., Ceres Nanosciences, Inc. and Perthera. No potential conflicts of interest were disclosed by the other authors.

[1]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center Washington, D.C. [2]Perthera, Inc, McLean, Virginia. [3]George Mason University, Fairfax, Virginia.

Corresponding Author: Michael J. Pishvaian, Podium B, Lombardi Comprehensive Cancer Center, 3800 Reservoir Road, NW, Washington, DC 20007. Phone: 202-444-1212; Fax: 202-4440-9429; E-mail: pishvaim@georgetown.edu.

doi: 10.1158/1078-0432.CCR-18-2645

Received August 13, 2018; revised August 17, 2018; accepted August 17, 2018; published first December 14, 2018.

References

1. Pishvaian MJ, Biankin AV, Bailey P, Chang DK, Laheru D, Wolfgang CL, et al. BRCA2 secondary mutation-mediated resistance to platinum and PARP inhibitor-based therapy in pancreatic cancer. Br J Cancer 2017;116:1021–6.
2. Chand SN, Zarei M, Schiewer MJ, Kamath AR, Romeo C, Lal S, et al. Posttranscriptional regulation of PARG mRNA by HuR facilitates DNA repair and resistance to PARP inhibitors. Cancer Res 2017;77:5011–25.
3. Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, Kelsen DP, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. Br J Cancer 2017;116:697–702.
4. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
5. Pishvaian MJ G-LI, Liu SV, Multani PS, Chow-Maneval E, Rolfo C. Entrectinib in TRK and ROS1 fusion-positive metastatic pancreatic cancer. JCO Precis Oncol 2018;doi: 10.1200/PO.18.00039.