The role of BRCA gene mutations as risk factors for breast and ovarian cancer and in surgical decision management for their cancer risk mitigation has been well known for many years (1,2). In addition, the association of BRCA mutations with other malignancies including pancreas, prostate, melanoma, and cholangiocarcinoma is now clear (3-5).

Functionally, BRCA genes are involved in the repair of DNA double stranded breaks (DNA DSBs) and in the activation of DNA damage repair checkpoints (6). Specifically, BRCA 1 and BRCA 2 mutations interfere with homologous recombination repair (HR), creating a specific therapeutic opportunity; namely, the creation of synthetic lethality by treating patients carrying these mutations with agents that further compromise DNA DSB repair. The term “synthetic lethality” is defined as a “type of genetic interaction where the co-occurrence of two genetic events results in organismal or cellular death.” In this context the word “synthetic” is used for its ancient Greek meaning: the combination of two entities to form something new (7).

Following success with the PARP inhibitor, Olaparib, as maintenance therapy for patients with newly diagnosed BRCA related ovarian cancer (12) a decision was taken to apply a maintenance therapy approach with BRCA related pancreatic cancer, leading in 2018 to the results of the POLO (Pancreas Cancer Olaparib Ongoing) trial (13).

This international trial, involving many sites from western Europe, Israel, South Korea and the USA, showed a significant 3.8 months (P=0.004) increase in disease free survival (DFS) among 154 randomized patients (culled from 3,315 screened) with BRCA related pancreatic cancer who remained in remission following 6 months of FOLFIRINOX chemotherapy.

Success as maintenance therapy, suggested the possibility of enhanced effect with concurrent platinum based chemotherapy and PARP inhibition and on January 24,
In this randomized, Phase II trial 50 patients with BRCA related (predominantly BRCA 2) metastatic cancer received initial therapy with either gemcitabine and cis-platinum (600 and 25 mg/sq m, respectively on days 3 and 10) (arm B) or the same chemotherapy with veliparib 80 mg twice daily on days 1 through 12 (arm A). The results are summarized in Table 1. Unfortunately, although there was an enhanced Disease Control Rate (100% vs. 78.3%), this did not translate into a survival effect with either median DFS or median OS. Whether this outcome might have been different if larger patient numbers had been accrued would be interesting speculation. However, given that this trial was already a tour de force across continents to achieve this 50 patient accrual, such speculation presently is unknowable. Thus, in this trial, there was no suggestion of enhanced survival (Table 1).

Table 1 Response, survival, and toxicity by treatment arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>B</th>
<th>A</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Gemcitabine + cis-Platinum</td>
<td>Gemcitabine + cis-Platinum</td>
<td></td>
</tr>
<tr>
<td>PARP inhibitor</td>
<td>None</td>
<td>Veliparib</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>65.2</td>
<td>74.1</td>
<td>0.55</td>
</tr>
<tr>
<td>Disease control rate (%)</td>
<td>78.3</td>
<td>100</td>
<td>0.02</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>9.7</td>
<td>10.1</td>
<td>0.73</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.2–13.6</td>
<td>6.7–11.5</td>
<td></td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>16.4</td>
<td>15.5</td>
<td>0.60</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.7–23.4</td>
<td>12.2–24.3</td>
<td></td>
</tr>
<tr>
<td>Total grade 3–4 hematologic toxicities</td>
<td>22</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Total grade 3–4 non-hematologic toxicities*</td>
<td>35</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>

*, Common Terminology Criteria for Adverse Events, version 4. PFS, progression free survival; OS, overall survival; disease control rate, CR + PR + SD; CI, confidence interval.

pancreatic cancer research: Lustgarten, Reiss, and David M. Rubinstein. In addition, both these investigators and their institutions are known for reliable, solid research with adequate support for data management and administrative attention. That these institutions ran the trial well, and in a manner consistent with all protocol requirements, is strongly supported by a successful NCI data audit. In the spirit of “learning more from our failures than our successes” the authors promise a separate publication on the topic of insights to the lack of success seen. In the interim we are left to speculate on our own.

Although there was enhanced toxicity with the addition of Veliparib to gemcitabine and cis-platinum (arm A), there were no toxic deaths in either arm and neither hematologic or non-hematologic toxicity seems to have contributed to the reported outcomes. As summarized in Table 2, the total amount of chemotherapy received (on average) in both arms was about the same.

Another possibility would be that these results are a false negative result. However, given the use of a standard “minimax” design that set the type II error rate at 0.10, this seems unlikely.

We also need to ask if there is some difference between Veliparib and Olaparib that would account for these results. Murai et al. (15,16) have shown that PARP inhibitors may cause cytotoxicity by both the trapping of PARP—DNA complexes and through their better recognized inhibitory mechanism. Moreover, they also report that Olaparib is
so much more effective at trapping PARP—DNA complexes than veliparib. As will be discussed further (below) there is reason to believe that this mechanism does not likely explain the results in the O'Reilly trial, but is mentioned here only to point out that there are differences among these various PARP inhibitors that likely require further exploration.

So, what is left to consider?

Given that the POLO trial strongly suggests benefit from adding a PARP inhibitor sequentially after platinum based therapy, the possible cause of the disappointing results seen in Dr. O'Reilly’s trial that seems most likely would be a lack of additivity between cis-platinum chemotherapy and PARP inhibition when given concurrently. Is this reasonable? Are there data to suggest such a possibility?

Although the specific mechanisms differ, Platinum based chemotherapy and PARP inhibition, in separate studies, have been shown to have therapeutic advantage in BRCA related malignancies, likely because of both types of agents’ known interference with DNA repair (17). While synergy was hoped for by giving these agents concurrently, there are some, limited data from clinical trials and laboratory studies to support a lack of additivity/synergy. Clinically, the phase III BrighTNess trial (18) in patients with Triple Negative Breast cancer demonstrated that neoadjuvant therapy with a combination of veliparib plus paclitaxel and carboplatin was not superior to combined paclitaxel and carboplatin, although both carboplatin arms were superior to paclitaxel alone (pathological CR rates: paclitaxel alone—31%, paclitaxel + carboplatin—58%, paclitaxel + carboplatin + veliparib—53%). In the lab, Murai et al. (16) report that Olaparib did not enhance cis-platinum cytotoxicity when studied with wild type DT40 cells or DU145 prostate cancer cells. Another in vitro clue is that it has been shown that variation in levels of a newly identified protein involved in DNA damage response, RANBP9, can effect whether non-small cell lung cancer cells are responsive to the combination of olaparib and platinum, as well as platinum alone (19). Finally, again in vitro, discordant sensitivity has been seen in subsets of ovarian cancer cells with an alternate mechanism for dealing with DNA DSB’s (nucleotide excision repair); namely, responsiveness to platinum but resistance to PARP inhibition, even though responsiveness to both is more common (20). In aggregate, these data lend some credence, even if not conclusive, to the notion that PARP inhibitors may very well not demonstrate enhanced therapeutic effect when combined concurrently with platinum chemotherapy.

In summary: This was a great trial done by outstanding investigators using an excellent design and was built on terrific clinical science and clearly well executed. The results are disappointing, but possibly will be instructive. As Robert Burns wrote in 1785 (translated from the Scottish) “The best laid schemes of mice and men oft go awry, and leave us nothing but grief and pain, for promised joy!” (21).

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Footnote

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Tables in this work are original, having been constructed from the data presented in the paper reviewed.

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