Editorial

Role of adaptive randomization in developing novel therapies for patients with breast cancer

Robert S. Meehan[1], Alice P. Chen[1], James H. Doroshow[1,2]

[1]Division of Cancer Treatment and Diagnosis, [2]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Correspondence to: James H. Doroshow, MD. Division of Cancer Treatment and Diagnosis, Rom 3A-44, Bldg. 31, 31 Center Drive, NCI, NIH, Bethesda, MD 20892, USA. Email: doroshoj@mail.nih.gov.

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The rapidly expanding number of new, molecularly-targeted treatments for patients with breast cancer has dramatically increased the pressure to evaluate safety and efficacy for these compounds in a more efficient fashion (1). Moving quickly from early phase, proof-of-mechanism studies to more definitive therapeutic trials has become an important focus of cancer drug development efforts over the past decade (2). New clinical trial designs that explore testing of several new agents simultaneously in a single "umbrella" or "basket" study are currently being explored as a means to this end (3).

A recent study by Esserman and colleagues (4) evaluated the addition of the combination of a poly (ADP-ribose) polymerase inhibitor (veliparib) and a DNA damaging drug (carboplatin) to paclitaxel as initial neo-adjuvant treatment (prior to a standard four cycles of doxorubicin and cyclophosphamide) for women with stage II or III breast cancer [ClinicalTrials.gov number, NCT01042379]. This trial, I Spy (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) 2 (5), is of particular interest because it is being performed using a novel clinical trial infrastructure and an adaptive randomization approach that were developed to improve the speed with which a series of concurrent studies investigating the safety and efficacy of multiple new anticancer agents could be assessed. The trials conducted under the I-SPY 2 umbrella are performed using a master agreement with multiple pharmaceutical partners, template protocols, a network of investigators, and a series of pre-treatment biomarkers for patient selection. Biomarker assessment based on human epidermal growth factor receptor 2 (HER2) and hormone-receptor status, and a 70-gene profile using the MammaPrint® platform (Agendia) (6) is performed on pre-treatment core biopsies to classify patients according to prospectively-defined breast cancer subtypes. Using pathological complete response (pCR) as the primary study endpoint provides a surrogate marker for therapeutic benefit and allows for more rapid identification of agents or combinations that should be investigated further in phase III trials.

I-SPY 2 was designed using a Bayesian statistical approach that adapts patient accrual to individual treatment arms based on continuous evaluation of new efficacy results, enhancing recruitment to more effective therapeutic programs with the goal of attempting to measure the probability that a specific agent or combination might be superior to control therapy in a future phase III study (7). Bayesian (predicative probability) trial design has been heralded as an improvement over traditional frequentist approaches, overcoming some of the perceived limitations of standard clinical trial designs, while remaining robust in controlling type I and type II error rates (8). Therapies that reach pre-specified thresholds of efficacy in one or more patient groups defined by specific biomarker signatures "graduate" from I-SPY 2 and are considered for a future phase III study.

The novel agent evaluated in the study by Esserman and associates is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP). PARP, which was first described over 50 years ago by Chambon (9), recognizes

DNA single strand breaks (ssDNA) and effects DNA repair through the base excision repair pathway (BER). PARP inhibitors are cytotoxic for cells deficient in the capacity to repair DNA double strand breaks using alternate repair strategies, such as the homologous recombination (HR) pathway, as is the case for tumor cells carrying functional mutations in *BRCA1* or *2* genes (10).

There appear to be two primary mechanisms by which PARP inhibition is cytotoxic for tumor cells; the drugs either poison the catalytic activity of the enzyme or they form a complex with the enzyme and DNA (so-called PARP trapping) which blocks the activity of the DNA replication fork, inhibiting DNA synthesis (11). The first PARP inhibitor approved by the United States Food and Drug Administration was olaparib, which demonstrated clinical benefit in patients with ovarian and breast cancers carrying *BRCA* mutations (12); it is available for use as monotherapy in patients with advanced ovarian cancer whose tumors demonstrate functional or suspected deleterious *BRCA* mutations and who have been treated with three or more prior lines of chemotherapy. Other investigational PARP inhibitors include veliparib, rucaparib, niraparib, and talazoparib; of these agents, veliparib, which was used in the Esserman study, has the weakest PARP trapping capacity, but a similar ability to inhibit the enzymatic activity of PARP (13). It has been suggested that the combination of enzymatic and DNA trapping activities may enhance the therapeutic efficacy of this class of drugs when they are used in combination with certain, specific types of DNA-damaging antineoplastic agents (13).

Veliparib has been combined with a substantial number of chemotherapeutic drugs; except for the combination of veliparib and topotecan (14), most combinations can be delivered by themselves without undue toxicity. In Essermans' veliparib study, 72 patients with triple-negative breast cancer received the investigational combination of veliparib and carboplatin, together with paclitaxel, followed by a standard "backbone" of doxorubicin and cyclophosphamide; 44 patients received paclitaxel only followed by standard therapy. The addition of veliparib and carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide increased the pCR rate from 26% *vs.* 51% (95% Bayesian probability interval, 36–66%). Bayesian analysis predicted an 88% probability of success for the addition of the veliparib/carboplatin combination in any subsequent phase III study (4).

The results of the veliparib/carboplatin arm of the I-SPY 2 trial are of real interest because of the novelty of both the investigational platform and the statistical approach employed; however, from the standpoint of the actual clinical results reported, several caveats are warranted. First, and most important, the number of patients entered on the veliparib/carboplatin arm in the triple negative breast cancer (TNBC) cohort for whom predefined statistical endpoints were reached was only 51, with a 26-patient standard therapy control. Second, there was an imbalance in the number of *BRCA* mutations observed in the investigational versus control arm of the study (17% *vs.* 5%). As noted above, increased efficacy of a PARP inhibitor in patients with tumors harboring *BRCA* mutations would be expected; it is unclear whether the extent of this imbalance is sufficient to diminish the overall conclusions of the study, but it is a matter of concern (15,16). Third, in pre-clinical studies, the ability of veliparib to enhance DNA damage from carboplatin has come under question (13), which could have an impact on the interpretation of the results of this trial. Fourth, the true benefit of adding veliparib to carboplatin in a TNBC population is also clouded because of the lack of a carboplatin only arm in the study. Carboplatin has been shown to significantly enhance standard neoadjuvant therapy in patients with TNBC, producing pCR rates equivalent to the veliparib/carboplatin arm of the current trial (17-19). Hence, the contribution of veliparib to the veliparib/carboplatin treatment program remains unclear. With regard to the last point, the authors correctly note that in the absence of a randomized comparison between carboplatin and veliparib/carboplatin no conclusion regarding which drug is adding to the reported results is possible.

Although the value of adding a PARP inhibitor to a DNA damaging agent has been tested in various venues, the Esserman study is one of the few randomized trials that suggest an improvement in outcome related to PARP inhibition. A recent, randomized phase II study examined the value of adding the PARP inhibitor olaparib to chemotherapy (paclitaxel and carboplatin) in patients with recurrent platinum-sensitive ovarian cancer, some of whom (38%) carried *BRCA1/2* mutations; the benefit of treatment with olaparib (in terms of improving progression free survival) was greatest for women with *BRCA* mutations (12). However, in another randomized phase II trial, where veliparib was combined with the alkylating agent cyclophosphamide and compared with cyclophosphamide alone in patients with advanced TNBC, the addition of veliparib did not improve the efficacy of DNA damaging chemotherapy (20). While the effect of veliparib/carboplatin

on therapeutic efficacy in the I-SPY 2 trial—in terms of clinical benefit—remains to be determined, it is clear that the addition of this combination to paclitaxel increased the hematopoietic toxicity of the overall treatment program (4); hence, defining the overall risk/benefit ratio for the additional therapy will need to be much better defined in the phase III setting.

Finally, it is appropriate to point out that the neoadjuvant chemotherapy setting (that employs pCR as the primary endpoint) may not produce results that are easily translated into long term clinical improvement for patients (21). Data from neoadjuvant trials do not necessarily predict the clinical utility of a therapy in the adjuvant or metastatic setting. Thus, the use of pCR rate, as defined by the FDA, provides a useful surrogate outcome in the drug development setting of I-SPY 2 without, necessarily, predicting an effect on overall survival (22).

In conclusion, the I-SPY 2 trial umbrella is providing an important evaluation of the applicability of adaptive clinical trial designs for the testing of novel breast cancer therapies. The goal of shortening drug development timelines through the use of this Bayesian platform is noteworthy. While for all of the reasons outlined above, the combination of veliparib and carboplatin may or may not prove to be a major therapeutic gain in the treatment of locally-advanced breast cancer, the adaptive clinical trial platform exemplified by I-SPY 2 appears to be robust enough for further evaluation across a variety of oncologic clinical trial settings.

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