Editorial

Rethinking clinical trial design: maximizing the results from each clinical trial participant

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Comment on: Rugo HS, Olopade OI, DeMichele A, *et al.* Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. N Engl J Med 2016;375:23-34.

Submitted Oct 01, 2016. Accepted for publication Oct 13, 2016.
doi: 10.21037/tcr.2016.11.48
View this article at: http://dx.doi.org/10.21037/tcr.2016.11.48

Breast cancer remains the most common cancer diagnosed in women. Triple negative breast cancers (TNBC) especially remain difficult to treat with poorer prognosis than hormone receptor and HER2-neu positive tumors. Although relatively responsive to neoadjuvant chemotherapy with pathological complete response (pCR) of up to 50%, for those who don't achieve a pCR the outcome is poor (1). The hallmark of TNBC is the development of chemoresistant metastatic disease, with the highest frequency of metastases in the first 1–2 years after completing chemotherapy, a rate 2–3 times higher than non-TNBC subtypes (2). The median overall survival for women with metastatic TNBC remains a dismal 12 months, with worse outcomes in patients with CNS metastases (3). As such, the need for developing new therapies TNBC is particularly pressing.

Typically, investigational therapies are tested first in phase I and II trials, with the most promising drugs making it to phase III trials where they are randomized against an accepted standard treatment. Unfortunately, this process typically takes up to 7 years or longer and requires thousands of patients, thus limiting the introduction of promising therapies in a timely fashion (4). There have been efforts to streamline the clinical trial process in the interest of expediting the introduction of new therapies. The FDA introduced the Fast Track designation in 1997 to facilitate expedited review of new drugs for serious medical conditions without a reasonable standard of care, with or without available clinical data. This is in contrast to Priority Review, which is for drugs that have clinical data suggesting improvement over a preexisting standard of care, and the Accelerated Approval Pathway is for drugs with reasonable evidence of clinical benefit based on surrogate end points. In 2012, the Breakthrough Designation was introduced allowing the FDA to further accelerate the approval of drugs for serious conditions on the basis of preliminary clinical data that suggests improvement over the standard of care (4). Should a drug obtain this designation, the FDA works to expedite trials and approval, thus decreasing patients' exposure to a presumably less effective treatment.

To rapidly identify patients who might benefit from investigational agents or treatment regimens novel trial designs have been introduced. One such example, adaptive randomization, uses Bayesian analysis to modify an ongoing trial based on accumulating results, allowing for assessment of superiority, inferiority or futility with a smaller number of patients (5). Responding populations and active compounds can be identified earlier and futile therapies abandoned sooner, facilitating drug development by getting the most effective drugs into phase III trials sooner.

One such example of adaptive randomization is the I-SPY 2 trial published recently in the *New England Journal of Medicine* by Rugo *et al.* (6) I-SPY-2 is a multicenter trial to compare several different investigational drugs combined with standard paclitaxel 80 mg/m^2 IV for 12 doses followed by doxorubicin and cyclophosphamide in the neoadjuvant setting for women with stages II–II breast cancers. Accrual took place between May 2010 and July 2012 and the primary endpoint was pCR. Hormone receptor status, HER2 expression and the MammaPrint 70 gene signature

were assessed and the women were randomized to either the experimental or standard treatment arms. Any combination therapy that achieved pCR with "an 85% Bayesian predictive probability of success in a simulated 300-patient, randomized, phase III trial with a traditional statistical design", would be considered a candidate for further clinical trials.

The NEJM paper reported the results of veliparib, a poly ADP ribose polymerase (PARP) inhibitor, combined with carboplatin, as compared to standard neoadjuvant treatment. Seventy-two women were assigned to the veliparib-carboplatin arm and 44 were allocated to the control group. Of note, the randomized women were similar in age and race, but BRCA 1 and 2 mutation carriers were overrepresented in the experimental arm (17% *vs.* 5%). Additionally, dose reductions of paclitaxel were necessary in 32% of the veliparib-carboplatin group as compared to none in the control group, and 18% of the women with hormone receptor positive breast cancers discontinued treatment early, a finding not observed in the TNBC cohort.

The pCR across all HER2 negative study participants was 33% (95% Bayesian probability interval of 23–43%), however, in the triple negative cohort it was 51% (95% Bayesian probability interval 36–66%). They report that "in the triple negative signature, the probability that veliparib-carboplatin was superior to control was 99%, and its probability of statistical success in a randomized, phase III trial including 300 patients was 88%". Based on this, a phase III neoadjuvant trial is ongoing comparing standard chemotherapy with carboplatin versus standard therapy plus carboplatin and veliparib with the primary end being pCR.

The ISPY 2 trial does have some limitations. The imbalance in the experimental arm of BRCA 1 and 2 mutant carriers may have skewed the data in favor of the carboplatin and veliparib cohort. In particular, both carboplatin and PARP inhibitors are thought to have increased anti-tumor effects in these women (7). Similarly, carboplatin was not added to standard neoadjuvant chemotherapy in this adaptive trial. This is unfortunate, as a neoadjuvant regimen with carboplatin alone *vs.* carboplatin and veliparib may have performed similarly.

pCR is accepted by the FDA a surrogate endpoint for progression-free and overall survival and may be used to accelerate approval for drugs that lead higher pCR (8,9). However, recently this premise has been questioned and as such there is a degree of uncertainty that pCR will predict long-term clinical outcomes (10,11). An example of this is despite the findings that carboplatin increases the pCR in neoadjuvant trials (12,13), a large adjuvant trial is currently ongoing (NRG-BR003) in early stage women with TNBC directly testing the hypothesis that after an anthracycline-based regimen, carboplatin in combination with a taxane improves invasive disease-free survival and overall survival (14).

Nonetheless, adaptive trial design based on Bayesian analysis holds great promise for identifying those who would benefit the most from new therapies decreasing the exposure to futile drugs, and accelerates the time course for performing phase III trials. Thus, ISPY 2 trial makes a potentially significant and important contribution to the ongoing effort to overhaul clinical trial design, but only time will tell.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor San-Gang Wu (Department of Radiation Oncology, Xiamen Cancer Center, the First Affiliated Hospital of Xiamen University, Xiamen, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.11.48). The authors have 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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Cite this article as: Etra A, Shapiro CL. Rethinking clinical trial design: maximizing the results from each clinical trial participant. Transl Cancer Res 2016;5(Suppl 6):S1044-S1046. doi: 10.21037/tcr.2016.11.48