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Title: Residual cancer burden (RCB) with veliparib/carboplatin in the I-SPY2 trial

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Body: Background: I-SPY2 is a multicenter phase 2 trial in high risk stage II/III breast cancer (BC) using adaptive randomization within biomarker subtypes to evaluate novel agents added to standard neoadjuvant chemotherapy. The first regimen to graduate based on the predicted probability of a higher pCR rate within predefined subsets was veliparib/carboplatin + paclitaxel (VC+T→AC vs T→AC) in triple negative BC (TNBC). In TNBC the residual cancer burden (RCB) is prognostic, whether as a continuous index or grouped into classes, with pCR (RCB-0) and RCB-I classes having identical survival. Therefore, we evaluated the use of RCB to further discriminate between investigational and control arms.

Methods: Site pathologists reported RCB for 99% of subjects in the primary efficacy analysis based on pCR (n=114/115). We compared the distribution of RCB reported as a continuous index in each treatment-subset combination to matched concurrently randomized controls using the Wilcoxon rank sum test for RCB index, and Fisher's Exact test for RCB classes (RCB-0/I vs RCB-II/III). The statistics are descriptive rather than inferential, and given the small sample size have no claim on generalizability. We modified the Bayesian model used to compute the estimated probability of success in a future, randomized, phase 3 trial of 300 subjects, if response were defined by either pCR or RCB-I (RCB0/I), or separately if it were defined by pCR alone.

Results: VC+T→AC led to a significantly lower RCB index than T→AC in TNBC (p=0.0021), with a near-significant trend when those with pCR were excluded (p=0.06). There was no significant difference in RCB distributions in the other breast cancer subtypes treated. In TNBC, the odds ratio (OR) for achieving RCB-0/I in the VC+T→AC arm vs control was 8.2 (95% confidence interval (CI): 2.1–35), whereas the OR for achieving pCR was 4.56 (95% CI: 1.25–19.53). The simulations using response information from I-SPY2 to predict the probability of success for VC+T→AC for TNBC in a future phase 3 trial estimated this probability to be 0.99 if modeled using RCB-0/I as the response endpoint, and 0.90 if modeled using pCR as the response endpoint.

Conclusions: Use of RCB index and classes provided additional insight into the effect of adding VC to T, appearing to magnify the improved treatment response that had been observed with pCR rates in TNBC. It will be important to test in randomized trials whether a decrease in the RCB index relative to controls, and/or increased rates of RCB-0/I class, are predictive of survival benefit in TNBC.