Residual Cancer Burden (RCB) with Veliparib/Carboplatin in the I-SPY2 Trial

Registration Number: NCT01042379

Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2

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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 97% of subjects in the primary efficacy analysis based on pCR (n=113/116). 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.

I-SPY2 Schema

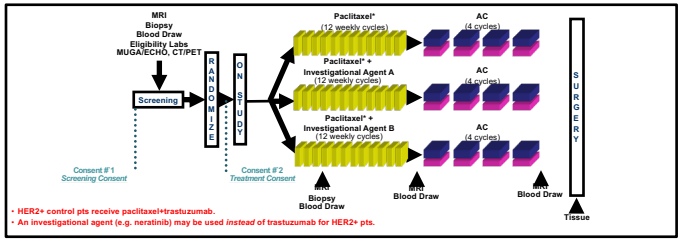
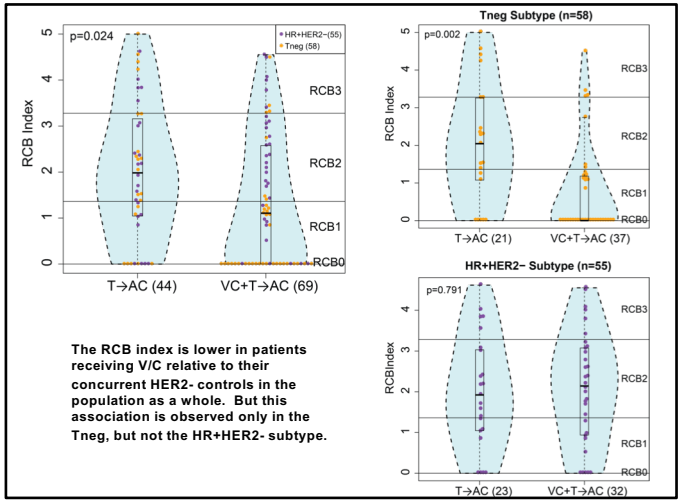
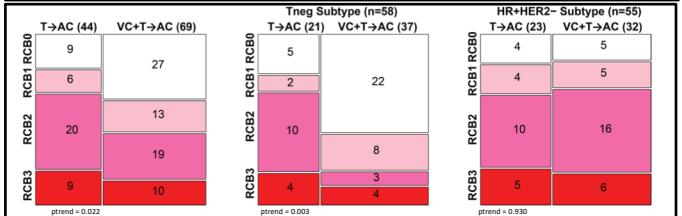


FIGURE 1



The RCB index is lower in patients receiving V/C relative to their concurrent HER2- controls in the population as a whole. But this association is observed only in the Tneg, but not the HR+HER2- subtype.

FIGURE 2



Consistent with the continuous index, differences in categorical RCB classes proportions are observed overall, but the association is driven by the Tneg subtype

FIGURE 3

	Control (n=44)	V+C (n=69)
RCB0/1	15	40
RCB2/3	29	29

OR = 2.64 (1.14-6.34), Fisher test p = 0.020
Compared to pCR: 2.48 (0.97 - 6.82), Fisher test p=0.041

Tneg

	Control (n=21)	V+C (n=37)
RCB0/1	7	30
RCB2/3	14	7

OR: 8.19 (2.17-35.03), Fisher test p = 0.0005
Compared to pCR: 4.56 (1.25 – 19.53), Fisher test p=0.013

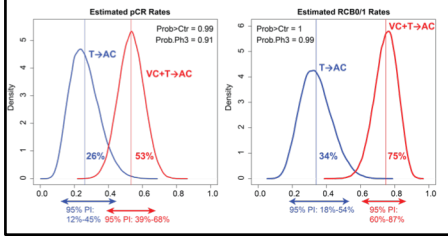
HR+HER2-

	Control (n=23)	V+C (n=32)
RCB0/1	8	10
RCB2/3	15	22

OR = 0.85 (0.24-3.13), Fisher test p = 1
Compared to pCR: 0.88 (0.16 – 5.06), Fisher test p=1

Similarly, differences in dichotomized RCB groups proportions are observed overall, but the association is driven by the Tneg subtype.

FIGURE 4



Using RCB0/1 as a secondary efficacy endpoint, the probability of V/C demonstrating superiority to control is >0.999 within the graduating triple negative signature, which is higher than that observed with the primary pCR endpoint (0.992).

The probability of success of a 300-patient 1:1 randomized phase 3 trial of HR-HER2+ patients increases from 0.91 to 0.99 when we consider the RCB0/1 endpoint as opposed to pCR.

SUMMARY OF FINDINGS

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.

I-SPY…The Right Drug, The Right Patient, The Right Time…NOW!

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