Background

The I-SPY 2 TRIAL enrolls women with locally advanced, molecular high-risk breast cancer. An Integrated Residual Cancer Burden (RCB), based on MR volume change through treatment, is used to predict pathologic complete response (pCR) in the randomization/evaluation Bayesian engine. With the goal of effective de-escalation of treatment for patients exhibiting an early response, biomarkers are being assessed for their ability to predict pCR, alone or with MR data, during treatment. Here, we present the results of a pilot study to examine if invasive tumor cellularity in mid-treatment core tissue biopsies predicts pCR in a 40-patient cohort of I-SPY 2 patients. Other pathologic variables evaluated include Ki67, morphologic features of tumor, and atonal tumor-infiltrating lymphocytes (TILs).

Methods

I-SPY 2 TRIAL pathologists (N=4) were provided with scanned images of H&E and Ki67 (DAKO/Agilent, clone MIB-1) sections of biopsies from patients exhibiting an early response, defined by hormone cancer (N=40 patients, 12 weeks). Agreement between pathologists was high (>90%) for both pCR (Figure 1). In total, images from 153 cores were evaluated.

Criteria assessed: For each core, pathologists were asked to score the % area occupied by tumor bed (treatment changes and/or residual cancer), % of viable invasive tumor (0-100%), overall % Ki67 labelled, and %TILs, using standardized guidelines.

Analysis: Concordance between pathologists was assessed for all scored criteria, using % agreement for dichotomous variables, and Pearson correlation (r/slope/d) or Kolmogorov-Smirnov test for continuous variables. The maximum and average cellularity recorded over all cores/patient, averaged over all pathologists, were analyzed for association with pCR using t-tests (significance threshold p<0.05). Fisher’s Exact test was used for dichotomous variables, and Pearson’s correlation for association of continuous variables with the residual cancer burden (RCB) index.

Results: Concordance

Pathologists were in general agreement about the presence of tumor, tissue bed, with greater than 80% agreement between any two (p<0.05), and an overall agreement of 78%.

Results: Response Prediction

Absence of invasive cancer is predictive of pCR

We also treated invasive cellularity as a dichotomous variable (percent Ki67). With 68% of patients scored by all pathologists in the invasive tumor cell (Ki67) achieved a pCR, as opposed to 0% of patients scored on invasive cellularity by one or more pathologists (Fisher, p<0.001), pending a positive predictive value for pCR of 0.9.

Conclusion

In this pilot study we demonstrate that the absence of residual invasive tumor cells within identified tumor bed in mid-treatment core biopsy samples is highly predictive of pCR.

Advocate Perspective

Diagnostic tools that predict outcome during treatment can be used to adapt therapy for patients. Combining biomarker with other tools, such as MRI, can redirect or de-escalate therapy, and move forward more targeted treatments to prolong life or cure breast cancer.

Acknowledgements

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Assessing biomarkers to inform treatment de-escalation: mid-treatment biopsy cellularity predicts pCR in the I-SPY 2 TRIAL


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Results:

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