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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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Background

The I-SPY 2 TRIAL enrolls women with locally advanced, molecular high-risk breast cancer. An integrated Residual Cancer Burden (iRCB), based on MRI 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 tissue core biopsies predicts pCR in a 40-patient cohort of I-SPY 2 patients. Other pathologic variables evaluated include Ki67, morphologic features of tumor, and stromal tumor-infiltrating lymphocytes (sTILs).

I-SPY2's Adaptive Trial Design

I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast cancers (FIG.1). Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are proportional to current probabilities that the respective therapies have a higher pCR rate than control rate in the respective subtypes. *The primary endpoint is pathologic complete response (pCR, no residual disease in breast or nodes) at surgery*.

The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by hormone-receptor (HR) & HER2 status and MammaPrint (MP).

Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (< 10% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

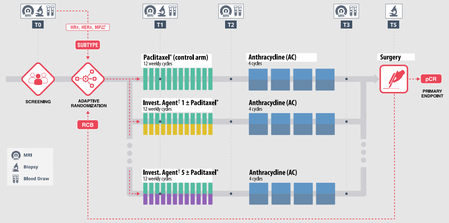
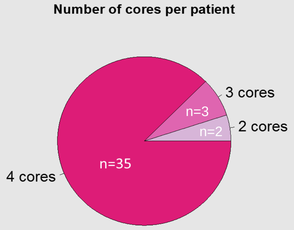


Figure 1: I-SPY2 study schema and adaptive randomization based on probabilities of agents of achieving pCR within a given subtype

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 core biopsy samples from 40 patients, collected ~12-weeks into treatment ("T2" on Figure 1). In total, images from 153 cores were evaluated.

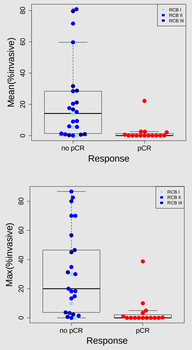


Criteria assessed: For each core, pathologists were asked to score the % area occupied by tumor bed (treatment changes and/or residual cancer), % of viable invasive tumor (0-100%) within tumor bed (with Nottingham grading, % Ki67 labelled, and % sTILs, using standardized guidelines).

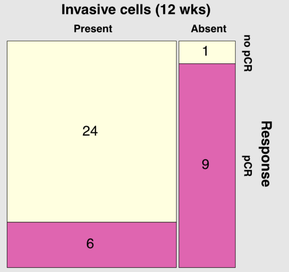
Analysis: Concordance between pathologists was assessed for all scored criteria, using % agreement for dichotomous variables, and Pearson correlation (r)/standard deviation (sd) for continuous variables. The maximum and average cellularity recorded over all cores/patient, averaged over all pathologists, 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- Response Prediction

Absence of invasive cancer is predictive of pCR

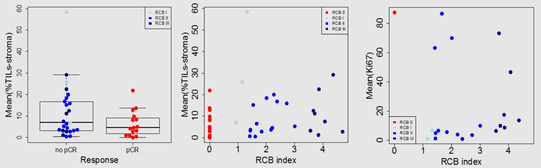


Both the mean (t-test: p=7.59E-05) and maximum (t-test: p=0.0012) %invasive tumor at 12 weeks, scored as an average over all pathologists, were significantly higher in patients who did not achieve pCR than in responders.



We also treated %invasive cellularity as a dichotomous variable (present/absent). 90% (9/10) of patients scored by all pathologists as 0% invasive tumor cells (absent) achieved a pCR, vs only 20% (6/30) of patients scored as >0% invasive cellularity by one or more pathologists (present) (OR=32, Fisher p=0.00015); yielding a positive predictive value for pCR of 0.9.

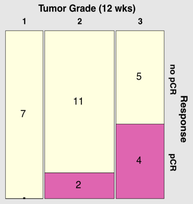
sTILS and Ki67 do not associate with response



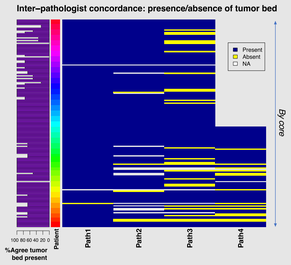
Ki67 and sTILS at 12 weeks were fairly concordant across pathologists ((r,sd)=(0.92, 8.45%) and (0.82,5.5%), respectively), but did not associate with response (p>0.05 for pCR, RCB01, or RCB index).

Grade trends towards association with outcome

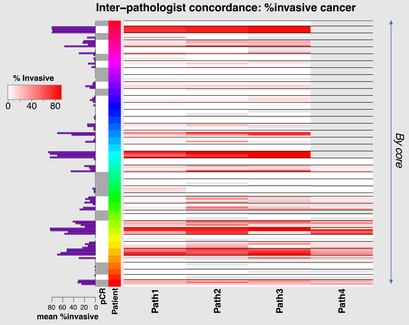
Tumor histologic grade at 12 weeks, assessed in 29/30 patients with non-zero cellularity, trended toward association (Fisher p=0.078): 44% (4/9) with Grade 3 went on to have a pCR, vs. 15% (2/13) with Grade 2 and none in Grade 1.

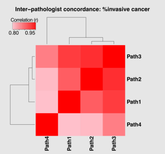


Results- Concordance

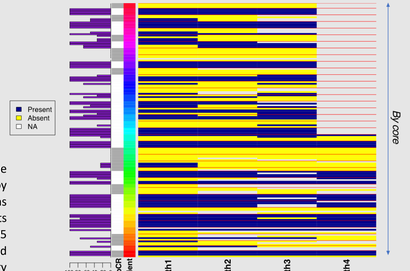


Pathologists were in general agreement about the presence or absence of tumor bed, with greater than 82% agreement between any two (83-96%), and an overall agreement of 77%.





For scoring the % of the tumor bed involved by invasive cancer, correlations between pairs of pathologists ranged from 0.79-0.95 (mean(r)=0.87, sd=5%), and agreement on a binary presence/absence of invasive cancer was 78%.



Limitations in the pilot study contributed to discordance between pathologists: scoring fresh-frozen tissue, access only to lower resolution digital images, lack of confirmatory tests.

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 biopsy cellularity with other tools, such as MRI, can redirect or de-escalate therapy, and move further toward more targeted treatments to prolong life or cure breast cancer.

Acknowledgements

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