Patients achieving a pathologic complete response (pCR) following neoadjuvant therapy have significantly improved event-free survival relative to those who do not, and pCR is an FDA-approved endpoint to support accelerated approval of novel agents/combinations in the neoadjuvant treatment of high-risk early stage breast cancer. Previous studies have shown that recurrence risk increased with decreasing pCR rate if tested in a neoadjuvant setting (as assessed by the RCB index). As well, these studies suggest that patients with minimal residual disease (RCB class II) have favorable outcomes comparable to those achieving a pCR with high risk tumor subtypes. In this study, we assess whether integrating RCB with MRI functional tumor volume (FTV), which in itself is prognostic, can improve prediction of distant recurrence free survival (DRFS) and identify a subset of patients with minimal residual disease with comparable DRFS as those who achieved a pCR. Imaging tools can then be used to identify the subset that will do well early and guide the timing of surgical therapy.

**Methods**

We performed a pooled analysis of 649 patients from the SPY2 TRIAL with RCB, pre-surgical MRI FTV and known follow-up (data cutoff date: June 2015, median 2.8 years). We first assessed whether FTV predicts residual disease (pCR or pCR/RCB II/III) using ROC analysis. We then applied a power transformation to normalize the pre-surgical FTV distribution, and assessed its association with adverse outcome using a Cox proportional hazards model adjusted for HR/HER2 subtypes. We also fitted a Cox model of RCB index adjusting for subtype, and assessed whether adding pre-surgical FTV to this model further improves association with DRFS using a likelihood ratio (LR) test. For the Cox modeling, we also have favorable outcomes comparable to those achieving a pCR within a given risk group.

**MRI FTV as Predictor of Response**

MRI FTV is more effective at predicting pCR/RCB than predicting pCR alone.

**Cox Model Coefficient Wald test p**

<table>
<thead>
<tr>
<th></th>
<th>Linear Effect</th>
<th>Non-Linear Effect</th>
<th>Non-Linear F-test p</th>
</tr>
</thead>
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<tr>
<td>Transformed pre-surgical FTV(pFTV)</td>
<td>Linear Effect</td>
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<td>0.164</td>
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<tr>
<td></td>
<td>Non-Linear Effect</td>
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<tr>
<td>MRI (pCR)</td>
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<tr>
<td>HER2 (Re: HER2)</td>
<td>Non-Linear Effect</td>
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</tbody>
</table>

**CONCLUSIONS**

- Pre-surgical MRI FTV is effective at predicting minimal residual disease (R0/C0) in the SPY 2 TRIAL.
- Despite the association between FTV and RCB, FTV appears to provide independent added prognostic value (to RCB and subtype), suggesting that integrating MRI volume measures and RCB into a composite predictor may improve DRFS prediction.

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**SPY2 TRIAL**

The SPY2 Trial was supported by Agendia, Inc. Significant contributions to the SPY2 TRIAL were made by David G. Agus, MD, Jon E. Perlstein, MD, Joseph L. Bae, and Stephen H. Pearlman, PhD. Genentech, Inc. sponsored the SPY2 TRIAL in support of experimental drugs for the treatment of breast cancer. The SPY2 TRIAL was conducted with support of Genentech, Inc., Alexion Pharmaceuticals, Inc., and Seattle Genetics.

**Disclosure**

We have no conflicts of interest to declare for this manuscript. SPY2 study schema. Figure 1: SPY2 study schema. Figure 2: iRCB prediction of pCR (top) and pCR/RCB II/III (bottom), for both the trial setting and surgical setting. Figure 3: Kaplan Meier plot of DRFS by pre-surgical FTV (up) and iRCB (down). Figure 4: Kaplan Meier plot of DRFS by pCR (up) and iRCB (down). RCB Corresponding RCB classes for pre-surgical imaging cut-off is in the full color.