The ISP2 trial demonstrated that functional tumor volume (FTV) measured by dynamic contrast-enhanced (DCE) MRI during neoadjuvant chemotherapy (NAC) predicts patients with non-pCR residual disease with high accuracy, supporting the concept of NAC use in clinically identified breast cancer patients [14]. The SPY2’s ADAPTIVE TRIAL DESIGN

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**BACKGROUND**

The ISP2 TRIAL demonstrated that functional tumor volume (FTV) measured by dynamic contrast-enhanced (DCE) MRI during neoadjuvant chemotherapy (NAC) predicts patients with non-pCR residual disease with high accuracy, supporting the concept of NAC use in clinically identified breast cancer patients [14]. The SPY2’s ADAPTIVE TRIAL DESIGN

**ELIGIBILITY/ENROLLMENT/DISPOSITION**

Eligible patients include those with one of the following criteria: Stage II or III, or T4, any N, M0, including clinical or pathological inflammatory cancer or Regional Stage IV, where supraventricular lymph nodes are the only sites metastasis.

A sub-cohort of 311 patients who had completed therapies with investigational or control regimens were included in this study. Table 1 shows number of patients with breast cancer subtypes defined by HR & HER2 status and patients treated with experimental vs. control regimens (Exp/Rct) in each subtype category, pCR rates in the full cohort and by subtype are also shown in Table 1.

**SPY2’S ADAPTIVE TRIAL DESIGN**

ISP2 is a 2+1 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 (FIG. I). Within each subgroup rate an adaptive randomization scheme is used to control the type I error probabilities or the control regimens. 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 & MammoPrint (MP).

Regimens may knock the trial off 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 ≥0%).

**MABRI PROGRESS AND QUANTIFICATION**

MRI was acquired at 4 time points: pre-NAC (T0), early-treatment (T1), inter-regimen (T2), and post-NAC (T3) (FIG1). MRI imaging was performed at 1.5T or 3T across a variety of vendor platforms. The standard breast MRI protocol included a localisation scan, a T-weighted sequence, DW-MRI and DCE-MRI. The percent change of FTV and mean ADC at T1 (%FTV0% and %ADC0%) and T2 (%FTV2% and %ADC2%) were compared to the pre-NAC (T0) to evaluate predictors for pCR.

- **Functional tumor volume (FTV)**: FTV-MRI was calculated by the sum of voxels with enhancement above defined thresholds (FIG2a).
- **Apparent diffusion coefficient (ADC)** map was generated from DW-MRI with 2 values (b=0 and b=1000 s/mm²). Mean ADC was calculated by averaging ADC values within the whole tumor ROI (FIG2c).

**RESULTS**

- **Univariate analysis**

The values of percent change of FTV and ADC at early-treatment time point T1 (%FTV0% and %ADC0%) and at inter-regimen time point T2 (%FTV2% and %ADC2%) were plotted in FIG3. Corresponding AUCs for predicting pCR are listed in Table 2.

**Table 2 AUCs for logistic regression model with single predictor**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Single predictor AUC</th>
<th>%FTV0%</th>
<th>%FTV2%</th>
<th>%ADC0%</th>
<th>%ADC2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change of FTV</td>
<td>0.64 (0.57, 0.70)</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
</tr>
<tr>
<td>Percent change of ADC</td>
<td>0.64 (0.57, 0.70)</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Figure 2** MRI imaging acquired of all NAC, or no evaluable stage III breast MRI. FTV was calculated by the sum of voxels within the region of interest (ROI) (FIG2a). Corresponding maps from DW-MRI (b=0 and b=1000 s/mm²) show a tumor with FTV measurement. Logistic regression model and area under the receiver operating characteristic curve (AUC) were used in analysis. AUCs of multivariate models were calculated using logistic regression predicted values from 10-fold cross-validation. The statistical significant level for all testing was set at 0.05.

**Figure 3** FTV and ADC changes at treatment time point T1 (left) and T2 (right) for patients having or not having pCR in all. In the full cohort, both FTV and ADC percent change at T1 or T2 are strong predictors for pCR. However, their predictive performance varied in breast cancer subtypes. AUCs are higher at T1 than at T2.

**Table 4 AUCs for multivariate analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariate AUC</th>
<th>%FTV0%</th>
<th>%FTV2%</th>
<th>%ADC0%</th>
<th>%ADC2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTV + ADC</td>
<td>0.84 (0.73, 0.93)</td>
<td>0.84</td>
<td>0.84</td>
<td>0.84</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

The addition of ADC to standard FTV MRI may help refine the prediction of treatment response. Further improvement can be achieved by adjusting the model for breast cancer subtype. The effect of different novel agents should be considered in future study on a larger cohort.

**REFERENCES**


**ACKNOWLEDGEMENTS:**

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