Evaluation of the PD-1 Inhibitor Celimipilin in Early-stage, High-risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

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BACKGROUND

I-SPY 2 (Figure 1): A multicenter, phase 2 trial using response-adaptive randomization in biomarker subtypes defined by hormone-receptor (HR), HER2, and MammPrint (MP) status to evaluate novel agents as neoadjuvant therapy for women with high-risk breast cancer.

Celimipilin (Cemi) is a PD-1 inhibitor approved for the treatment of metastatic basal cancer, cutaneous squamous cell carcinoma, and NRCLC.1,2 Here, we report current efficacy rates of Cemi in combination with paclitaxel followed by AC in early stage high-risk breast cancer.

Inclusion criteria: Tumor Size ≥ 2.5 cm; hormone-receptor (HR)+HER2- MammPrint (MP) high risk, HR-HER2+ or HER2+.

Primary Endpoint: Pathological complete response (pCR). To identify (graduate) regimens that have ≥85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by Roswell Park status and MP.

Control Arm for HER2+ patients: Weekly paclitaxel x12 followed by doxorubicin + cyclophosphamide (AC) q2-3 weeks x 4.

Statistical Methods

Serial MRI imaging (at 3 weeks, 12 weeks and prior to surgery) were used along with accumulating pCR data to continuously update and estimate pCR rates for trinomial analysis. Treatment was modified intent to treat. Patients who switched to non-protoct treatment were not censored.

Graduate regimens with ≥85% Bayesian predictive probability of success (i.e. demonstrating superiority in one of the three future 300-patient phase 3 neoadjuvant trial with a pCR endpoint within response signatures).

Cemi was eligible to graduate in 3 pre-defined signatures: HER2-, HER2+ and HER2+. To adapt to changing standard of care, we constructed “dynamic controls” comprising best available therapeutic strategies using I-SPY 2 and external data and estimated the probability of Cemi being superior to the dynamic control.

RESULTS

Primary Efficacy Analysis

62 HER2+ patients (39 HR+ and 23 HR-) received Cemi arm treatment.

The control group included 350 patients with HER2+ tumors (195 HR+ and 155 HR-) enrolled since March 2010.

Estimated pCR rates (as of June 2022) are summarized in the table.

<table>
<thead>
<tr>
<th>HER2-</th>
<th>HER2+</th>
<th>HR-HER2+</th>
</tr>
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<tbody>
<tr>
<td>Control: 31% (95% CI: 27%–35%)</td>
<td>Control: 29% (95% CI: 22%–37%)</td>
<td>Control: 14% (95% CI: 9%–20%)</td>
</tr>
</tbody>
</table>

Figure 2: Estimated pCR rates in the Cemi and control arms at the time of arm closure. A time-adjusted Bayesian logistic model, based on all pcr with information at the time of closure of the Cemi arm, was used to estimate pCR rates. The posterior pCR probability distribution with 95% credible interval, along with the probability that Cemi is superior to control, denoted as Pr(Pr>C), and the predictive probability of success in a 300-patient 1 randomized Phase III trial, denoted as Pr(Pr>0.5), are shown for the HER2- (left), HR-HER2+ (middle), and HR-HER2+ (right) signatures.

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR Rate (95% CI)</th>
<th>Probability of Cemi Superior to Control</th>
<th>Probability of Success in Phase 3 (relative to Control)</th>
<th>Probability of Cemi Superior to Dynamic Control</th>
</tr>
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<tbody>
<tr>
<td>HER2-</td>
<td>52% (35%–69%)</td>
<td>0.961</td>
<td>0.620</td>
<td>0.413</td>
</tr>
<tr>
<td>HR-HER2+</td>
<td>29% (17%–45%)</td>
<td>0.990</td>
<td>0.913</td>
<td>0.374</td>
</tr>
<tr>
<td>HR-HER2-</td>
<td>14% (9%–21%)</td>
<td>0.574</td>
<td>0.089</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 1: Estimated pCR rates for the HER2-, HR-HER2+, and HR-HER2+ breast cancer subtypes.

ImPrint-53: Gene signature of Neoadjuvant Immunotherapy Response

CONCLUSIONS

Anti-PD-1 therapy with Cemi resulted in a higher predicted pCR rate in the HR-/HER2- breast cancer subtype at 53% compared to control at 29%.

Cemi gradated in HR-HER2- signature.

We did not observe a response in the HR+/HER2+ likely due to limited numbers in the randomized arm and the adaptive randomization to the Cemi/LAG-3 arm.

The Immunomarker identifies the patients with the greatest treatment with RCB 0 or >4%.

Immunemediated AE’s were similar to other single IO agents + chemotherapy.13

Table 1 is consistent with previously published data using check point inhibitors in early-stage HR-HER2- breast cancer.


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The right drug, the right patient, the right time...now.

I-SPY2Trials