Analysis of DNA repair deficiency biomarkers as predictors of response to the PD1 inhibitor pembrolizumab: Results from the neoadjuvant I-SPY 2 TRIAL for Stage II-III high-risk breast cancer

Background

Pembrolizumab (P), an anti-PD-1 immune checkpoint inhibitor, has been approved for treatment of microsatellite instability-high and mismatch repair deficient cancers. In I-SPY 2, patients were randomized to receive standard chemotherapy alone or in combination with an experimental agent. P was one of the experimental agents evaluated in HER2+ patients and was included in the TN, HR+/HER2-, and HER2+ signatures predicted to respond to veliparib/carboplatin chemotherapy alone or in combination with an experimental agent. P was deficient in a given subtype for each agent.

Method

Data from 248 patients (P: 69; controls: 179) were available. Pre-treatment biopsies were assayed using Agilent gene expression arrays. All I-SPY 2 qualifying biomarker (DB) analyses follow a pre-specified analysis plan. We used logistic modeling to assess biomarker performance. A biomarker is considered as a specific predictor of P response if it associates with response in the P arm but not the control arm, and if the biomarker x treatment interaction is significant (likelihood ratio test, \( p < 0.05 \)). This analysis is also performed adjusting for HR status as covariates, and within receptor subgroups. For successful biomarkers, we use Bayesian modeling to estimate the pCR rates of ‘predicted sensitive’ patients in each arm. Our statistics are descriptive rather than inferential and do not adjust for multiplicities of other biomarkers outside this study.

MP2 and PARP17

Association with Response

Pembrolizumab (P) did not improve performance over MP2 as a single biomarker

Table 1: Bayesian predictive probabilities of success of Pembrolizumab in Phase 3 with single agent MP2

<table>
<thead>
<tr>
<th>HR-HER2-</th>
<th>HER2+</th>
<th>MP2</th>
<th>PARP17</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-HER2-</td>
<td>0.82</td>
<td>0.68</td>
<td>0.65</td>
<td>0.70</td>
</tr>
<tr>
<td>HER2+</td>
<td>0.70</td>
<td>0.63</td>
<td>0.60</td>
<td>0.70</td>
</tr>
</tbody>
</table>

MP2 status associates with pCR in the P arm (OR=2.4; \( p = 0.045 \)) and to a lesser extent in the control arm (OR=2.4; \( p = 0.045 \)).

DNA Repair Pathway Signatures

DNA Repair Pathway Signatures

Association with Response

Of the 9 DDR pathway signatures tested, both BER and DDS associate with pCR in P, but only DDS associates with pCR in the P arm, and not the control arm, with a significant interaction treatment that retains significance in a model adjusting for HR status.

Conclusions

In this small study, MP2 status and a DNA damage sensing pathway but not the PARP17 or other repair pathways show promise as predictive biomarkers for immune checkpoint inhibition therapy in breast cancer.

I-SPY 2 Trial

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