Efficacy of Hsp90 inhibitor Ganetespib plus Standard Neoadjuvant Therapy in High-Risk Breast Cancer: Results from the I-SPY 2 TRIAL

Background and Rationale: I-SPY 2

- 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 (FIG.1).
- 20% of patients are assigned to treatment.
- Within each patient subtype the other 80% are assigned to experimental therapy based on the relative performances of the various therapies so far in the trial.
- Randomization probabilities are in proportion to the current probabilities that the respective therapy has a higher pathological complete remission (pCR) rate than the control rate in the respective subtypes.

Investigational Agent Evaluation: Hsp90 inhibitor Ganetespib

- Ganetespib, a selective inhibitor of Hsp90, induces the degradation/activation of key drivers of tumor initiation, progression, angiogenesis, and metastasis including HER2, p53/Her2, ESR1, ER, PIK3, AKT, MET and VEGFR. The combination of Hsp90 inhibitors and taxanes has shown promise in preclinical evaluations.
- Ganetespib in combination with taxanes previously has resulted in a superior therapeutic response compared to monotherapy in multiple solid tumor models including Breast Cancer (NCT010677455).
- In this intent-to-treat analysis, patients were considered evaluable if they received any protocol therapy. A non-pCR was assigned if patients received any therapy and withdrew consent, progressed, changed to non-protocol therapy or left the treating institution.

Eligibility and Methods

- Women with invasive breast cancer ≥2.5 cm who were randomly assigned to 12 weekly cycles of paclitaxel (T) and/or (C) or in combination with Ganetespib (G) (weekly 1-3, 5-7, 9-11) followed by doxorubicin/cyclophosphamide (AC) x 4 with serial biomarkers (biopsies, blood draw and MRI scans). (FIG. 1)
- MP low/HER2+ tumors were ineligible for randomization.
- Patients were stratified to 8 subtypes (Table 1) based on hormone-receptor, HER2, and MammPrint gene profiling score (high-1 [MP2] vs high-2 [MP2]), with combinations of subtypes defining 10 agent signatures.

Table 1: Biomarker Subtypes with Overall Response in I-SPY 2 from the beginning of trial to Ganetespib until the final PD (Oct 2015)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Enrolment/Dispos.</th>
<th>Arm</th>
<th>Estimated pCR Rate (% in (95% PI))</th>
<th>Probability (Probability Distribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-</td>
<td>MP high-1 (MP1)</td>
<td>Control</td>
<td>0.16 (0.08 - 0.26)</td>
<td>0.90</td>
</tr>
<tr>
<td>HER2+</td>
<td>MP high-1 (MP1)</td>
<td>Ganetespib</td>
<td>0.36 (0.16 - 0.37)</td>
<td>0.90</td>
</tr>
<tr>
<td>HER2-</td>
<td>MP high-2 (MP2)</td>
<td>Control</td>
<td>0.22 (0.09 - 0.35)</td>
<td>0.90</td>
</tr>
<tr>
<td>HER2+</td>
<td>MP high-2 (MP2)</td>
<td>Ganetespib</td>
<td>0.38 (0.23 - 0.53)</td>
<td>0.90</td>
</tr>
<tr>
<td>HER2-</td>
<td>Total</td>
<td>Control</td>
<td>0.14 (0.04 - 0.24)</td>
<td>0.90</td>
</tr>
<tr>
<td>HER2+</td>
<td>Total</td>
<td>Ganetespib</td>
<td>0.15 (0.04 - 0.27)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Results: Efficiency

The primary endpoint pCR at surgery (no residual invasive disease in breast or nodes).

- 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 & MammPrint (MP).

- Regimens may be dropped for four primary reasons:
  - Graduates (as described above).
  - Drop for futility (10% probability of success in all subtypes).
  - Following accrual of maximum sample size, n = 75, (120 if drug is evaluated across risk stage II/III breast cancer) no residual invasive disease in breast or nodes in 20% of patients are assigned to control.

- Within patient longitudinal modeling of MRI volume was used during the trial to predict whether the patient would experience a pCR and improve the efficiency of adaptive treatment assignments.
- Adaptive assignment to the experimental arms was based on current Bayesian probability of superiority over control.
- Facilitated + Ganetespib (TG) assigned to HER2- patients.
- We report results of TG evaluated in the 3 HER2- subtypes (HER2-HER2- & HER2-HR-).

- In the intent-to-treat analysis, patients were considered evaluable if they received any protocol therapy. A non-pCR was assigned if patients received any therapy and withdrew consent, progressed, changed to non-protocol therapy or left the treating institution.

Figure 3: Bayesian pCR Probability Distributions

Figure 4: pCR Probability Distribution

Results: Safety and Tolerability

Table 2: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Ganetespib n=112</th>
<th>Control n=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hematologic AE</td>
<td>91 (81%)</td>
<td>127 (75%)</td>
</tr>
<tr>
<td>Neutrophil count decrease</td>
<td>19 (17%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>White blood cell decrease</td>
<td>9 (10%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (7%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Periop sensory neuropathy</td>
<td>6 (7%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>ACT increased</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Non-baseline AE of any grade</td>
<td>73 (67%)</td>
<td>51 (40%)</td>
</tr>
</tbody>
</table>

Enrollment/Disposition for TG vs. Control (T)

Figure 2: CONSORT

Legend:
- Estimated (mean) pCR rates are included on curve labels
- 95% PI: 95% Bayesian Probability Interval
- Probability (pCR): Probability of success in a 1:1 randomized 2 arm 300 patient phase 3 trial within the respective subtype population

Conclusions

- I-SPY 2 is a phase 2-3 randomization process that attempts to match experimental therapies with responding patient subtypes.
- I-SPY 2’s adaptive randomization was successful in efficiently evaluating Paclitaxel + Ganetespib (TG) in the setting of HER2- neoadjuvant breast cancer.
- TG combination was well tolerated.
- TG + AC did not meet the graduation threshold in any of the 3 HER2- signatures (HER2+, HER2+/HR+, HER2-/HR-).
- TG did demonstrate activity in the HR-/HER2- signature. Qualifying biomarker analyses are underway to determine if there are clues for how to improve the targeting or combinatorial impact of this agent.

Acknowledgements

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