Adaptively randomized trial of neoadjuvant chemotherapy with or without the Akt inhibitor MK-2206: Graduation results from the I-SPY 2 Trial

Debra Tripodo¹, Amy Le Drouin², Nicole Penson³, Meredith B. Baxter⁴, Cheryl Ann Drigan⁵, Anne M. Wallace⁶, Andrea Forrest⁷, Henry G. Kaplan⁸, Rita Nanda⁹, Kathy S. Albin⁵, Stacy L. Moulder⁸, Barbara B. Haley⁹, Angela De Michele⁹, William Fraser Syron⁵,1⁰, Laura van ’t Veer², Melissa Pathanii⁹, Laura Esserman¹, Donald A. Berry¹, Douglas N. Yendt¹

1A. Abramson Cancer Center, Hospital, TX; University of California at San Francisco, San Francisco, CA; 2B. San Diego Cancer Center, La Jolla, CA; 3A. University of Alabama at Birmingham School of Medicine, Birmingham, AL; 3B. Swedish Cancer Institute, Seattle, WA; 4A. University of Chicago, Chicago, IL; 5A. Baylor College of Medicine, Houston, TX; 6A. The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas at Dallas, TX; University of Pennsylvania, Philadelphia, PA

Background and Rationale

- The Akt axis/threonine kinase is a key node for growth factor receptor-initiated signaling and activates mTOR and downstream effectors. (Fig. 1)
- Complete pathologic response (pCR) to neoadjuvant chemotherapy is a predictor of long-term outcome and can therefore be used to test the potential benefit of novel targeted therapies when added to standard chemotherapy.
- MK-2206 is a selective allosteric inhibitor of Akt1, Akt2, and less so Akt3. MK-2206 does not bind to the active site of Akt, and consequently does not compete with either ATP or peptide substrate for binding to Akt.

Methods

- Women with invasive breast cancer ≥2.5 cm in diameter or ≥3 cm on imaging were adaptively randomized to 12 weekly paclitaxel (control) or in combination with one of several experimental agents followed by doxorubicin/cyclophosphamide (AC) x 4, with serial biopsies (biopsies, blood draw and MRI scans).
- Patients were stratified to 8 subsets (Table 1) based on hormone-receptors, HER2, and mammographic/proliferation score (hormone receptors positive, MPM-2d, with combinations of sub-subsets defining 10 agent signatures).
- Primary endpoint was pCR (no residual invasive disease in breast or nodes) and evaluable patients received an axillary +/- diagnostic investigation.
- 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.
- Patients who progressed, changed to non-protocol therapy or left the treating institution were evaluable and counted as not having a pCR. Patients who withdrew consent prior to surgery (with or without randomization to non-protocol therapy) were considered non-evaluable for pCR.
- The report results of the I-SPY 2 135 mg daily by mouth evaluated in all 8 subsets. Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superior over control.
- Graduation by signature is based on Bayesian predictive probability >85% for success in a 2-arm, N=303 Phase 3 randomized 1:1 trial with pCR endpoint. Futility stopping when the probability of success is >53% in all 10 signatures.

Results

Table 1: Biomarker Subtypes and Overall Prevalence for Entire Trial

| Biomarker Subtype | MP-1 (%) | MP-2 (%) | MK-2206 (%) | N (%)
|-------------------|----------|----------|-------------|-----
| HER2+             | 120 (33%) | 41 (15%) | 13 (19%) | 255 (28%) |
| HER2-             | 227 (72%) | 54 (20%) | 7 (6%)  | 302 (33%) |
| Total             | 337 (100%) | 95 (100%) | 20 (100%) | 486 (100%) |

Table 2: Enrollment/Disposition for MK-2206 and Control Arms

| Enrollment/Disposition | N (%)
|-------------------------|-----
| Eligible                | 486 (100%)
| Enrolled                | 486 (100%)
| Evaluable               | 486 (100%)
| pCR Available           | 486 (100%)
| pCR Evaluated           | 486 (100%)

Table 3: Efficacy Results (Evaluation Highlighted)

| Signature | MK-2206 n=27 | Control n=27 | N (%)
|-----------|---------------|--------------|-----
| pCR Rate  | 94 (54%)      | 41 (13%)     | 142 (46%) |
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Conclusions

- In this adaptively designed trial, the allosteric Akt inhibitor MK-2206 graduated in 3 biomarker signatures on the basis of its predictive probability of statistical success in a 303-patient randomized Phase 3 trial.
- The three signatures for MK-2206 (HER2+/HR-, HR+ and HER2+) indicate activity in both HR+ and HER2+ disease.
- Toxics seen are those previously described including mucocutaneous toxicities and cytopenias, with the possible exception of more mucositis seen in this trial.
- This adaptive randomised trial provides a platform to rapidly ascertain promising therapies for larger scale studies and to match experimental therapies with responding patient subtypes.

References