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## **A Phase II trial of Ganetespib: Efficacy and safety in patients (pts) with metastatic breast cancer (MBC).**

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**Body:** Background: Heat shock protein 90 (Hsp90) is a molecular chaperone that maintains the stability of a number of key cellular oncoproteins (client proteins). When Hsp90 is inhibited, its client proteins undergo ubiquitination and degradation. HER2 is one of the most sensitive client proteins of Hsp90 and we have previously shown that tanespimycin, a geldanamycin-based Hsp90 inhibitor, is active in trastuzumab-refractory HER2+ MBC, with a RR of 22% and clinical benefit rate of 59%. Ganetespib is a synthetic, small molecule, IV administered, non-geldanamycin Hsp90 inhibitor which has broader inhibitory effects on oncoproteins with pre-clinical antitumor activity in more breast cancer (BC) subtypes, including triple negative breast cancer (TNBC). We therefore tested ganetespib in an unselected cohort of patients with advanced BC.

**Methods:** Pts with locally advanced or MBC were treated with single agent ganetespib at 200mg/m<sup>2</sup> once weekly for 3 weeks, on a 28 day cycle. The primary endpoint of the trial was overall response rate using RECIST 1.1. Pts with HER2+ BC were required to have received prior therapy with trastuzumab. No more than 3 lines of chemotherapy in the metastatic setting were permitted and there was no limit on prior lines of hormone therapy. Pts were evaluated for response after 2 cycles. The trial used a Simon two-stage design requiring at least 3 responses among the first 22 pts, to allow expansion to a total of 40 pts.

**Results:** A total of 14 pts have been treated thus far with a median age of 45.3 years (36.6 to 59.1) and the following subtypes: 8 ER+/HER2+, 3 ER-/HER2+, 1 ER+/HER2- and 2 TNBC. Pts received a median of 1.84 cycles (0.33 to 4). The most common treatment-related AEs were Grade 1/2 and included the following: diarrhea (64%), fatigue (50%), nausea (35%), vomiting (14%), insomnia (14%) and hypersensitivity reactions (35%). The diarrhea had an early onset (< 24 hrs) and lasted up to 48 hrs post-infusion and was managed with either Imodium or similar anti-diarrheal medication. Pts who developed a hypersensitivity reaction were successfully re-challenged following pre-medication using dexamethasone plus H1/H2 antagonists. Grade 3 AEs were limited to 2 pts: 1 with an asymptomatic and reversible elevation in serum amylase, and the other with abdominal pain and diarrhea requiring a dose reduction to 175mg/m<sup>2</sup>. Of the 10 pts

evaluable for efficacy, there is 1 confirmed partial response (PR), 1 minor response (MR) and 2 pts with stable disease (14%). The pt with MR had TNBC and was taken off-study due to a complicated pneumonia requiring hospitalization (unrelated). The remaining 3 pts had HER2+ BC; 2 of these 3 pts (1 PR, 1 SD) are continuing on study and have completed 4 cycles thus far. Updated toxicity and efficacy data will be presented.

**Conclusions:** These data show activity for single agent ganetespib in different subtypes of breast cancer. Ganetespib was well tolerated, with expected gastrointestinal toxicity that was mild in nature and manageable in all patients. Accrual continues and we will present updated data at the meeting.