Efficacy Results of a Phase 1b Study of ONT-380, a CNS-Penetrant TKI, in Combination with T-DM1 in HER2+ Metastatic Breast Cancer (MBC), Including Patients With Brain Metastases

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**Summary and Conclusions**

- Of 36 patients with brain mets: 14 had measurable brain mets and 10 had no measurable brain mets
- Many patients with measurable brain mets had reduction in brain mets regardless of CNS-related toxicity
- Of the patients with non-measurable brain mets, 19/30 (63%) had stable disease in brain ≥6 months
- Many patients with prior HER2 agent had major response in brain mets with T-DM1
- Superior activity compared to other agents in preclinical models of HER2+ CNS disease
- Objective response of brain mets (5 of 14 patients; 36%) and stable disease ≥6 months in brain (9 of 14 patients; 64%) among patients with measurable brain mets
- All patients with brain mets +380 dose reduction maintained disease control at lower dose

**Safety Results**

- ONT-380 is an orally administrable, highly-potent HER2 inhibitor with brain penetration
- High sensitivity for HER2 (IC50 = 0.06 nM, > 400X) and EGFR (IC50 = <0.05 nM, > 1500X), demonstrated potential for EGFR- related toxicities (e.g., diarrhea)
- Active in murine tumor models of HER2+ disease as a single agent and in combination with certain anti-HER2 treatments
- Superior activity compared to lapatinib or pertuzumab in preclinical models of HER2+ CNS disease
- Clinical benefit in patients with brain mets and patients with measurable brain mets (n=30) underwent serial brain MRI and had the following at baseline:
  - 16 patients with measurable brain mets and 14 patients without measurable brain mets
  - Median PFS calculated for all 50 patients, including 16/50 patients (32%) followed for progression of non-CNS disease

**Study Overview**

- All patients treated at RP2D (380 mg ond day 1, 380 mg on day 4)
- 50 patients treated at ONT-380 RP2D (380 mg ond day 1, 380 mg on day 4)
- Activity Assessed Overall and in Subset of Patients With Brain Mets
- Analyses in All Patients Treated at RP2D
- Activity Assessed Overall and in Subset of Patients With Brain Mets
- Subset Analyses in Patients With Brain Mets
- Progression-free survival (PFS)
- Progression-free survival analysis in patients with pembrolizumab
- Objective response of brain mets in patients with measurable disease in brain per modified CNS RECIST 1.1
- Baseline Patient Demographics
  - Many patients had multiple prior HER2 agents and most patients had brain mets

**Overall Efficacy Results**

- Overall response and prolongation of stable disease were observed in the overall population
- 24/50 patients (48%) had measurable disease evaluable for response per RECIST 1.1
- Median PFS calculated for all patients, including 16/50 patients (32%) followed for progression of non-measurable disease (e.g., previously radiated or lesions <1 cm)

**Patients Requiring Dose Reduction**

- Most Patients Who Required an ONT-380 Dose Reduction Able to Continue Treatment at Lower Dose
- Patients with brain mets: 23 of 30 (77%)
- Patients without brain mets: 4 of 20 (20%)
- Patients with measurable brain mets: 11 of 16 (69%)
- Patients without measurable brain mets: 12 of 14 (86%)

**Adverse Events**

- Most common reasons for ONT-380 dose reductions were toxicity (n=6)
- Toxicities related to ONT-380 dose reduction: thrombocytopenia (n=2), fatigue (n=1), neutropenia (n=2)
- Toxicities not related to ONT-380 dose reduction: thrombocytopenia (n=1), fatigue (n=5), neutropenia (n=2), anemia (n=2), diarrhea (n=2), nausea (n=2), vomiting (n=2), headache (n=1), and urinary tract infections (n=1)
- Grade 3 related AEs: fatigue (n=2)