A phase 1b study of ONT-380, an oral HER2-specific inhibitor, combined with ado-trastuzumab emtansine (T-DM1), in HER2+ metastatic breast cancer (MBC)

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Poster Board: #121A
Abstract ID: TPS662

Scientific Background/Rationale

- ONT-380 (also known as ARRY-380) is a selective small molecule inhibitor of HER2 kinase with nanomolar potency and decreased potential for EGFR-related toxicities
- 500-fold more selective for HER2 compared to EGFR in *in vitro* assays†
  - HER2 IC50: 8 nM, EGFR IC_{50}: 4000 nM
  - Equipotent against truncated p95-HER2 and WT-HER2
- ONT-380 is highly active in tumor models of HER2+ disease (see Figures 1 and 2)†
  - In tumor models of systemic HER2+ disease, ONT-380 demonstrated synergistic activity with trastuzumab
  - In a tumor model of HER2+ CNS metastases, ONT-380 was associated with markedly improved survival compared to both lapatinib and neratinib
- In Phase 1 single-agent study ONT-380 was well tolerated and provided clinical benefit with minimal EGFR-related toxicities
- Based on potential for dual blockade of HER2 to lead to increased clinical benefit, ONT-380 is now being evaluated in a Phase 1b study in combination with T-DM1

Figure 1 BT 474 Model

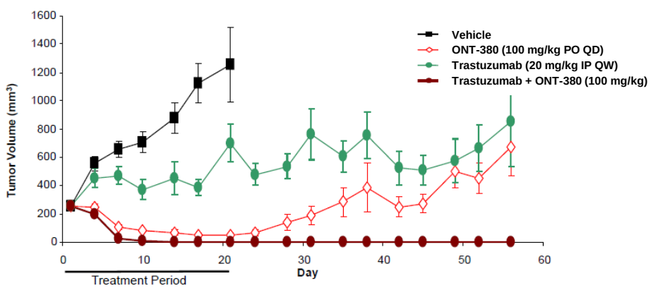
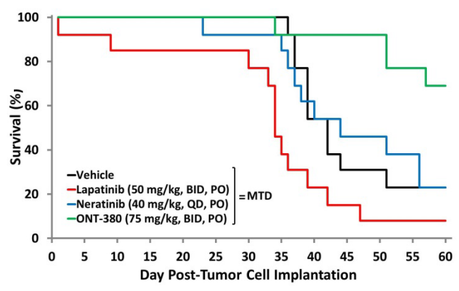


Figure 2 BT-474 CNS Metastases Model



†Data provided by Array BioPharma; AACR 2012 Poster #852

Study Overview

- Phase 1b 3+3 dose escalation design to evaluate up to three dose levels of ONT-380 in combination with T-DM1 at the approved single agent dose
- Patients must have progressive HER2+ metastatic breast cancer and have previously received trastuzumab and a taxane, separately or in combination, as therapy for metastatic disease
- Additional expansion cohorts may be enrolled, including an expansion cohort at the MTD/RP2D and a CNS expansion cohort

Objectives

- Primary:
  - Determine the MTD/RP2D of ONT-380 to be given in combination with the approved dose of T-DM1
- Secondary:
  - Evaluate the safety and preliminary anti-tumor activity of ONT-380 given at the MTD/RP2D in combination with T-DM1
- Exploratory:
  - Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens
  - Examine the effects of combination therapy on the pharmacokinetics of ONT-380 and T-DM1
  - Evaluate the effect of ONT-380 in combination with T-DM1 on CNS metastases

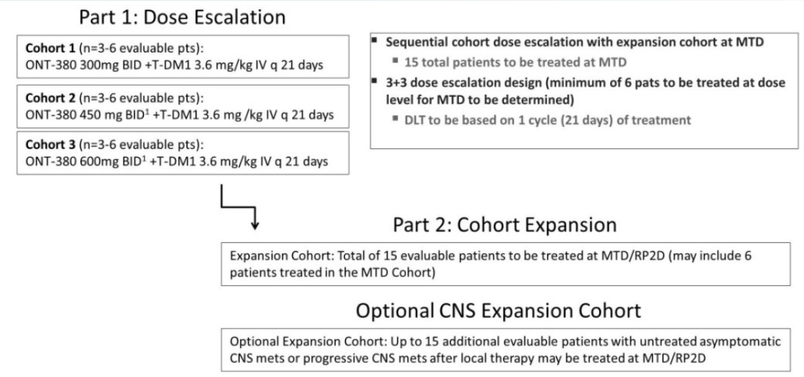
Treatment

- Treatment cycle is 21 days
- T-DM1 administered intravenously on Day 1 of each cycle (except in Cycle 1, when it will be administered on Day 2 to allow pharmacokinetic assessments of ONT-380 alone)
- ONT-380 administered orally, twice per day on Days 1–21 of each cycle
- Treatment to continue until disease progression, unacceptable toxicity, or withdrawal of consent

Assessments

- CT/MRI body every other cycle until Cycle 6, then every 3rd cycle
- MRI brain at baseline for all patients. In patients with baseline CNS disease, MRI brain every other cycle until Cycle 6, then every 3rd cycle
- ECHO/MUGA every 3 months
- CNS disease will be assessed per RECIST 1.1 for treatment decisions. However, CNS responses will also be assessed per both modified RECIST criteria for CNS disease and by volumetric measurements
- Weekly visits required in first 2 cycles, then only on day 1 of each cycle

Study Schema



1. If ONT-380 300 mg BID and T-DM1 not tolerated, option to de-escalate ONT-380 dose to 150 mg BID

Major Eligibility Criteria

Major Inclusion Criteria

- Patients with progressive HER2+ MBC who have previously received trastuzumab and a taxane, separately or in combination, for metastatic disease
  - HER2+ documented by FISH and/or 3+ IHC staining
- Target and/or non-target lesions per RECIST 1.1
- Eastern Cooperative Oncology Group performance status of 0 of 1
- Left ventricular ejection fraction must be within institutional limits of normal as assessed by echocardiogram or multigated acquisition scan documented within 4 weeks prior to first dose of study drug
- Adequate hepatic function as defined by: total bilirubin ≤ 1.5 x ULN and transaminases ≤ 1.5 x ULN (< 2.5 x ULN if liver metastases are present)

Major Exclusion Criteria

- Previous treatment with T-DM1 at any time
- Known carriers of Hepatitis B or C, or known HIV+
- Known impaired cardiac function or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, congestive heart failure and uncontrolled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)
- Myocardial infarction or unstable angina within 6 months prior to the first dose of study drug

Allowances for Prior Therapy

- Treatment with other small molecule HER2 inhibitors (including but not limited to, lapatinib, neratinib, or afatinib) is permitted > 4 weeks prior to study treatment
- Previous treatment with trastuzumab must be > 3 weeks prior to study treatment
- Treatment with either chemotherapy or hormonal cancer therapy must be > 2 weeks prior to study treatment
- Previous treatment with anthracyclines must be at a total exposure of < 360 mg/m² of doxorubicin or its equivalent
- Radiation is permitted > 14 days prior to study treatment

CNS Disease

- Dose escalation and MTD/RP2D expansion cohort:
  - Patients with symptomatic CNS metastases are excluded. Patients with treated CNS metastases or untreated asymptomatic CNS metastases not requiring immediate local therapy may be eligible
- Optional CNS disease expansion cohort:
  - Patients with asymptomatic untreated CNS metastases not needing immediate local therapy or patients with progressive CNS disease following local therapy may be eligible
- Patients with leptomeningeal disease are excluded

Enrollment

- Enrollment is ongoing in the US and Canada
- Current planned enrollment is approximately 50 patients

Clinical Trial Registry Number

- NCT01983501