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

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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 along with a cytotoxic agent to lead to increased clinical benefit, ONT-380 is now being evaluated in a Phase 1b study in combination with trastuzumab and capecitabine

Figure 1 BT 474 Model

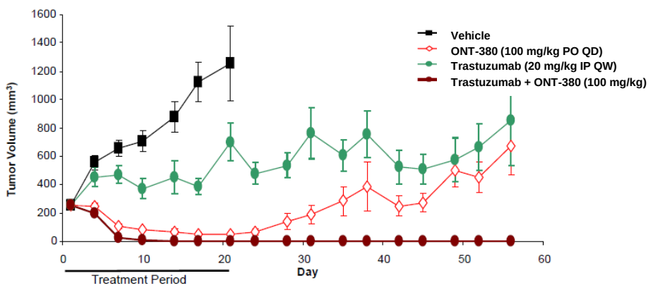
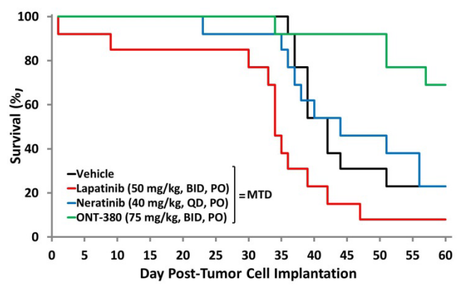


Figure 2 BT-474 CNS Metastases Model



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

Study Overview

- Phase 1b 3+3 open-label dose escalation design to evaluate up to three dose levels of ONT-380 given in combination with:
  - Capecitabine (Combination 1)
  - Trastuzumab (Combination 2)
  - Capecitabine and trastuzumab (Combination 3)
- Cohorts using Combinations 1 and 2 will be filled in a parallel alternating fashion, with capecitabine cohorts being filled preferentially
- Once MTDs have been reached in Combinations 1 and 2, the lower of the two MTDs of ONT-380 will be used for the first cohort of Combination 3
- Patient must have progressive HER2+ metastatic breast cancer and have received prior treatments with both trastuzumab and ado-trastuzumab emtansine (T-DM1) for metastatic disease
- Pharmacokinetic assessments will be performed on Combination 1 (ONT-380 + capecitabine) patients enrolled in a dose escalation cohort or MTD/RP2D expansion cohort
- Additional expansion cohorts may be enrolled, including an expansion cohort at the MTD/RP2D and a CNS expansion cohort

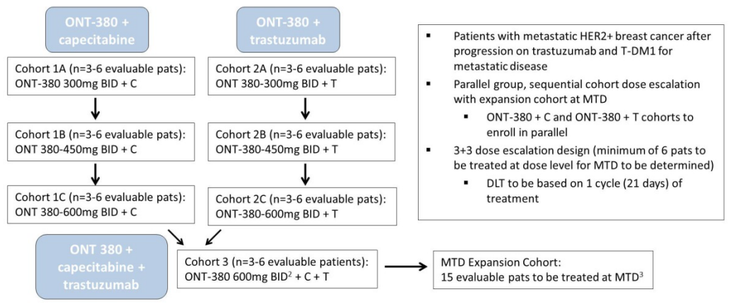
Objectives

- Primary:
  - Identify the MTD/RP2D of ONT-380 to be given in all Combinations
- Secondary:
  - Evaluate the safety and preliminary anti-tumor activity of all Combinations
  - Examine the effects of combination therapy on the pharmacokinetics of ONT-380 and capecitabine when given in combination
- Exploratory
  - Assess HER2 mutations and the presence of other potential biomarkers of response in archived tumor biopsy specimens
  - Assess preliminary CNS anti-tumor activity of all Combinations

Treatment

- ONT-380 administered orally, twice daily (PO BID) at 300 mg, 450 mg, or 600 mg on a 21-day cycle
- Capecitabine administered at 1000 mg/m^2 PO BID on Days 1–14 of each cycle
- Trastuzumab administered at a loading dose of 8 mg/kg intravenously followed by 6 mg/kg once every 21 days
- If Combination 1 and Combination 2 are found to be tolerable, then the lowest ONT-380 dose will be used with both capecitabine and trastuzumab in Combination 3

Study Schema



1. C = Capecitabine; T = trastuzumab.
2. ONT 380 dose = lowest MTD from either doublet. Option for additional cohorts to evaluable possible lower doses of capecitabine or ONT 380 if needed.
3. Patients treated at MTD in Part 1 will be included in total of 15 evaluable patients

Major Eligibility Criteria

Major Inclusion Criteria

- Patients with progressive HER2+ MBC who have previously received T-DM1 and trastuzumab 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

Major Exclusion Criteria

- 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
- Patients previously treated with capecitabine for metastatic disease at any time are eligible for Combination 2 cohorts only
- Patients who have received capecitabine for adjuvant or neoadjuvant treatment > 12 months prior to starting study treatment are eligible to enroll in all cohorts
- 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/m^2 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

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 of 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

Enrollment

- Enrollment is ongoing
- Current planned enrollment is approximately 50 patients

Clinical Trial Registry Number

- NCT02025192

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