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

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ONT-380 Background

- ONT-380 (also known as ARRY-380) is a selective small molecule inhibitor of HER2 kinase with nanomolar potency
- ONT-380 is 500-fold more selective for HER2 compared to EGFR
  - HER2 IC50 (BT474 cells): 8 nM
  - EGFR IC50 (A431 cells): 4000 nM
  - Equipotent against truncated p95-HER2 and WT-HER2
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- Highly active in mouse tumor xenograft models of HER2+ disease
  - In models of systemic HER2+ disease, ONT-380 demonstrated synergistic activity with trastuzumab (Figure 1)
  - In a model of HER2+ CNS disease, ONT-380 was associated with improved survival compared to both lapatinib and neratinib (Figure 2)

Figure 1 BT 474 Subcutaneous Model

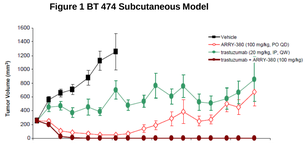
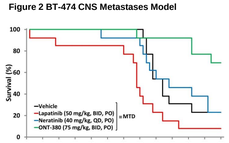


Figure 2 BT-474 CNS Metastases Model



- In an initial Phase 1 single-agent study using a powder-in-capsule (PIC) formulation, ONT-380 was well tolerated and provided clinical benefit with no treatment-related Grade 3 diarrhea[a]
  - Maximum tolerated dose (MTD) for PIC formulation = 600 mg BID
  - Dose limiting toxicities (DLT) = reversible Grade 3 ALT/AST elevations
- New tablet formulation developed with improved pharmacokinetic (PK) characteristics
  - ~ 2-fold greater bioavailability with decreased inter- and intra-patient variability

Based on potential clinical benefit from dual blockade of HER2, ONT-380 is now being evaluated in a Phase 1b study in combination with ado-trastuzumab emtansine (T-DM1) in patients with HER2+ metastatic breast cancer with and without CNS metastases using the new tablet formulation

a Borges VF et al, Poster A050 presented at AACR Special Conference on Advances in Breast Cancer Research 2013

Study Overview

Design

- 3+3 dose escalation of ONT-380 tablets in combination with approved dose of T-DM1
  - ONT-380 (300 mg or 350 mg) PO BID + T-DM1 3.6 mg/kg IV q 21 days
- Expansion cohorts in patients with and without CNS metastases

Objectives

- Identify maximum tolerated dose (MTD) / recommended Phase 2 dose (RP2D) of ONT-380 tablets administered in combination with T-DM1
- Characterize PK of ONT-380 (new tablet formulation) and evaluate effects of ONT-380 on emtansine PK
- Explore anti-tumor activity based on assessment of response by RECIST 1.1

Patient Population

- HER2+ breast cancer with progression after prior therapy with trastuzumab and a taxane, together or separately, for metastatic disease
- Prior treatment with small molecule HER2 inhibitor (including lapatinib) allowed

Selected Eligibility Criteria

Inclusion	Exclusion

• Target or non-target lesions per RECIST 1.1
• ECOG performance status 0 or 1
• Total bilirubin ≤1.5 × ULN
• ALT and AST ≤1.5 × ULN (<2.5 × ULN if liver metastases present)
• Normal LVEF
	• Prior exposure to cumulative doxorubicin dose (or equivalent) >360 mg/m²
	• CNS disease:
	  • Dose escalation and "Non-CNS" Expansion Cohorts: treated, stable CNS metastases or untreated asymptomatic metastases allowed
	  • CNS Expansion Cohort: untreated asymptomatic metastases or progressive metastases after prior whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) allowed
	  • Leptomeningeal disease excluded from all cohorts

Study Assessments

- Safety: labs, physical exam, LVEF by MUGA or ECHO
- Anti-tumor activity: RECIST 1.1 every 2 cycles through Cycle 6, thereafter every 3 cycles
- Pharmacokinetics
  - ONT-380 drug levels: Day 1 (Cycles 1 – 6)
  - Emtansine levels: Cycle 1 Days 2, 8, 15; Cycle 2 Days 1, 8, 15

Study Overview (continued)

DLT Definition

- Events occurring during Cycle 1 considered related to treatment with ONT-380 and T-DM1 meeting the following criteria:
  - ≥Grade 3 AEs
  - Grade 2 nausea with ≥Grade 1 diarrhea
  - Treatment-related AEs of any grade leading to >2 week delay in therapy

Dose Modifications

- Dose reductions of both ONT-380 and T-DM1 required for treatment-related non-hematologic Grade 3 AEs, Grade 3 ALT or AST elevations, and Grade 3 bilirubin elevation
- T-DM1 dose modifications required for Grade 4 thrombocytopenia
- Treatment discontinuation required for study-treatment related:
  - Grade 4 AEs
  - Grade 4 ALT, AST, or bilirubin elevation
  - ALT/AST >3 × ULN + bilirubin >2 × ULN
  - Symptomatic congestive heart failure or confirmed decreases in LVEF <40% or LVEF 40 to ≤45% and ≥10% decrease from baseline

Study Status

Cohort	Status	
	Dose Escalation	Dose Expansion
ONT-380 300 mg BID + T-DM1	Enrollment complete	Enrollment complete
ONT-380 350 mg BID + T-DM1	Enrollment ongoing	--
CNS Cohort (ONT-380 300 mg BID + T-DM1)	Enrollment ongoing	--

Results

Patient Characteristics

	ONT-380 300 mg + T-DM1 (n = 17)
Age, mean (range)	53 (31, 71)
Ethnicity, n	
Caucasian	14
Asian	2
African American	1
ECOG 0/1, n	6/11
Hormone receptor positive, n	12
Number of prior systemic treatments for metastatic disease, median (range)	2 (1, 6)
Patients with prior pertuzumab, n	6
Patients with prior lapatinib, n	5
History of prior or active CNS metastases, n	9
History of prior treatment for CNS metastases, n	7
Treatment of CNS metastases within 6 months of study entry, n	6

Exposure and Patient Characteristics

	ONT-380 300 mg + T-DM1 (n = 17)
Median # cycles received (range)	5 (2, 13)
Patients active on treatment, n	10
Patients discontinued from treatment (all due to PD), n	7

Dose Limiting Toxicity and Dose Reductions

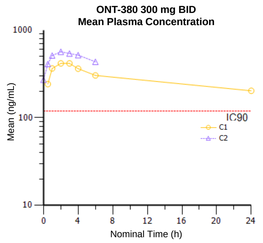
300 mg ONT-380 BID: DLT in 2/17 patients treated in non-CNS cohort

- 1 of 6 initial patients treated with DLT of reversible Grade 3 elevations in ALT and AST
  - Cohort expanded to allow further characterization of safety and PK
- Second patient with DLT of Grade 2 nausea and Grade 2 diarrhea
- Both patients experiencing DLT remain active on study after dose reduction of ONT-380 and T-DM1

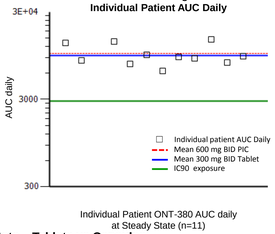
Dose Reductions	ONT-380 300 mg + T-DM1 (n = 17)
Patients requiring dose reduction of (n):	
ONT-380 alone	2
T-DM1 alone	3
ONT-380 + T-DM1	3

ONT-380 Pharmacokinetics

ONT-380 300 mg BID Mean Plasma Concentration



ONT-380 300 mg BID Individual Patient AUC Daily



Mean ONT-380 Plasma PK Parameters at Steady State – Tablets vs Capsules

ONT-380 Dose Form	Dose	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{Daily} (hr*µg/mL)	AUC CV (%)
Tablet	300 mg BID	735	2	6	9593	28
Powder in capsule (PIC)	600 mg BID	835	2	5	10020	85

PK Summary

- At steady state, dosing with 300 mg BID tablets yielded similar drug exposure to dosing with the original PIC formulation at 600 mg BID (single agent study MTD)
- The PK parameters (AUC, C_{max} & T_{max}) have reduced variability at steady state using the tablet formulation compared to PIC formulation
- Drug exposure using 300 mg tablets BID is well above the level corresponding to 90% inhibition of HER2 (cellular potency in 50% human serum)

ONT-380 Safety Overview

- Most common AEs, regardless of relationship to study drug
  - Nausea, diarrhea, vomiting, fatigue, thrombocytopenia, decreased appetite, hypokalemia, constipation
  - Majority Grade 1 or Grade 2 in severity
  - No Grade 3 diarrhea or rash
- 5 SAEs reported in 5 patients
  - All unrelated to treatment with exception of Grade 3 pneumonia considered related to both ONT-380 and T-DM1 per investigator assessment
- No significant changes in LVEF

Most Frequent (>20%) Adverse Events Overall	ONT-380 300 mg + T-DM1 (n = 17)		
	Any Grade	Grade 3	Grade 4
Nausea	14	--	--
Diarrhea	10	--	--
Vomiting	9	--	--
Fatigue	7	--	--
Thrombocytopenia	6	5	--
Decreased Appetite	5	--	--
Hypokalemia	5	2	--
Constipation	4	--	--
Headache	4	--	--
Epistaxis	4	--	--
Oropharyngeal Pain	4	--	--

Selected Laboratory Toxicities	ONT-380 300 mg + T-DM1 (n = 17)		
	Any Grade	Grade 3	Grade 4
Platelets decreased	13	5	1
ALT increased	15	3	--
AST increased	16	2	--
Total bilirubin increased	5	1	--
Potassium decreased	10	2	--

Anti-Tumor Activity

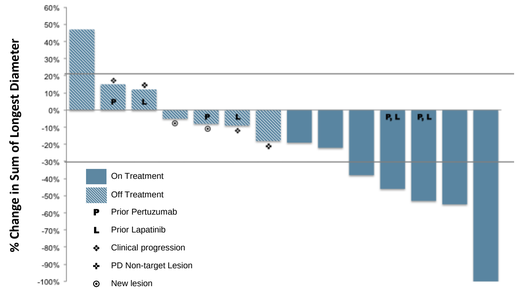
	ONT-380 300 mg + T-DM1 (n = 17)
Best response (RECIST 1.1)	
Evaluable patients[a], n	16
PR	5
SD[b]	7
PD	4
Clinical Benefit Rate (PR or SD >6 months)	6/13[c] (46%)

a One patient on study but without evaluable follow-up scans
b SD includes one patient with non-target lesions only without progression.
c Three active patients with SD on study for <6 months; 3 patients with SD as best response now off study due to progression

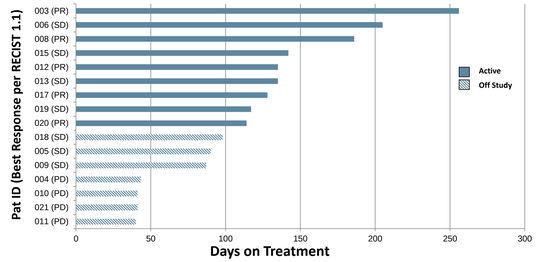
CNS Disease Control

- 9 of 17 patients with history of CNS metastases
- 4 patients with evaluable CNS target lesions per modified RECIST 1.1
  - Best CNS response: SD in 3 patients; PD in 1 patient
    - Decrease in target lesions in 2 of 3 patients
  - All patients with SD still active on study

Change in Measurable Disease



Time on Treatment



Summary and Conclusions

- ONT-380 + T-DM1 has been well tolerated in patients with HER2+ metastatic breast cancer
  - Majority of AEs Grade 1 or 2 in severity
  - No Grade 3 diarrhea, with no required concomitant medication
  - Safety profile consistent with single-agent experience for both drugs
- The tablet formulation yields approximately the same exposure at half the PIC formulation dose
- Encouraging signs of preliminary efficacy in a heavily pre-treated population
  - Many patients receiving 3rd-line or greater treatment for metastatic disease, and >50% with history of treated and/or active CNS metastases
  - Clinical benefit and response seen in patients previously treated with pertuzumab and/or lapatinib
- Disease stabilization seen in patients with measurable CNS disease
  - CNS cohort enrolling to allow for better characterization of activity in the CNS

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All data presented from an unlocked database as of October 31, 2014 and subject to change.

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