TITLE: Phase 1 Study of ONT-380, a HER2 Inhibitor, in Patients with HER2+ Advanced Solid Tumors, with an Expansion Cohort in HER2+ Metastatic Breast Cancer (MBC)

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ABSTRACT

Purpose: ONT-380 (ARRY-380) is a potent and selective oral HER2 inhibitor. This Phase 1 study determined the maximum tolerated dose (MTD), pharmacokinetics (PK) and antitumor activity of ONT-380 in HER2-positive advanced solid tumors, with an expansion cohort of patients with HER2-positive MBC.

Experimental Design: ONT-380 was administered twice daily (BID) in continuous 28-day cycles. After a modified 3+3 dose escalation design determined the MTD, the expansion cohort was enrolled. PK properties of ONT-380 and a metabolite were determined. Response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST).

Results: Fifty patients received ONT-380 (escalation=33; expansion=17); 43 patients had HER2+MBC. Median prior anti-cancer regimens=5. Dose-limiting toxicities of increased transaminases occurred at 800mg BID, thus 600mg BID was the MTD. Common AEs were usually Grade 1/2 in severity and included nausea (56%), diarrhea (52%), fatigue (50%), vomiting (40%) constipation, pain in extremity and cough (20% each). 5 patients (19%) treated at MTD had grade 3 AEs (increased transaminases, rash, night sweats, anemia and hypokalemia). The half-life of ONT-380 was 5.38 hours and increases in exposure were approximately dose proportional. In evaluable HER2+MBC (n=22) treated at doses ≥ MTD, the response rate was 14% [all partial response (PR)] and the clinical benefit rate (PR+stable disease ≥ 24 weeks) was 27%.

Conclusion: ONT-380 had a lower incidence and severity of diarrhea and rash than that typically associated with current dual HER2/EGFR inhibitors and showed notable anti-tumor activity in heavily pretreated HER2+MBC patients, supporting its continued development.

TRANSLATIONAL RELEVANCE

ONT-380 (ARRY-380) selectively inhibits the receptor tyrosine kinase HER2 relative to EGFR. In HER2 overexpressing cell lines, ONT-380 blocked proliferation and the phosphorylation of HER2 and its downstream effector, Akt. By contrast, in the EGFR overexpressing cell lines, it weakly inhibited phosphorylation and proliferation, demonstrating that ONT-380 may have potential to block HER2 signaling without causing the toxicities of EGFR inhibition. Further, one of the key challenges in HER2 metastatic breast cancer remains the identification of molecules that cross the blood brain barrier. In preclinical studies with intracranial tumor models, treatment of mice with ONT-380 compared with lapatinib or neratinib showed a survival benefit when each drug was dosed at the maximum-tolerated dose (MTD). Together, these data support the hypothesis that ONT-380 may be an effective and well tolerated treatment for HER2+ MBC with or without CNS metastasis.

INTRODUCTION

Approximately 15-20% of breast cancers have an amplification of the *HER2/neu* proto-oncogene and/or over-expression of its protein product, HER2 [1, 2], which has been associated with poor prognosis prior to the development of HER2-targeted therapies [3]. While multiple approved strategies exist for disrupting HER2 signaling in HER2-positive (HER2+) metastatic breast cancer (MBC)[4, 5], including monoclonal antibodies such as trastuzumab [6] and pertuzumab [7], the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1) [8], and the small-molecule dual tyrosine kinase inhibitor (TKI) lapatinib [9], several unmet needs exist in this patient population. First, though existing targeted therapies are improving outcomes in patients with HER2+MBC, disease resistance does eventually develop in most patients [10, 11]. Second, toxicity profiles for targeted agents, such as lapatinib, often preclude combination regimens due to off-target effects, such as skin rash and diarrhea, resulting from EGFR inhibition [12-14]. Finally, HER2+ primary tumors carry a predisposition for central nervous system (CNS) metastasis [15, 16], necessitating the development of targeted therapies that can cross the blood-brain barrier.

ONT-380 (also known as ARRY-380) is a potent, selective, ATP-competitive, orally administered small-molecule inhibitor of HER2. ONT-380 has nanomolar activity against purified HER2 enzyme and was approximately 500-fold selective for HER2 versus EGFR in cell-based assays [17], properties that could potentially translate clinically into a favorable toxicity profile in comparison to less specific HER2 TKIs that also inhibit EGFR [12-14]. ONT-380 also significantly inhibited phosphorylation of truncated HER2 (p110/p95), which is thought to be associated with trastuzumab resistance in HER2+ breast cancer. Nonclinical in

vivo pharmacology studies of ONT-380 as a single agent, as well as in combination with standard-of-care therapies, demonstrated significant tumor growth inhibition in HER2-dependent tumor xenograft models, including models of breast cancer [17, 18]. ONT-380 treatment also significantly enhanced survival in HER2-driven intracranial tumor xenograft models [19]. Combined, these preclinical data supported the rationale for the first-in-human Phase 1 study of ONT-380 reported herein.

PATIENTS AND METHODS

This study (NCT00650572) was conducted under all applicable regulatory requirements. The study was approved by the institutional review boards of all participating sites, and patients provided written informed consent prior to the initiation of study-related treatment or procedures.

Study Design and Treatment

This open-label Phase 1 study comprised both dose-escalation and expansion components to determine the maximum tolerated dose (MTD) of ONT-380 and assess the safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of ONT-380. ONT-380 was dosed orally as a powder-in-capsule formulation.

In the dose-escalation component, a modified 3 + 3 dose-escalation design was used to determine the MTD of ONT-380 in patients with advanced HER2+ cancers. This modified design allowed 3 to 4 evaluable patients to be enrolled per cohort, with expansion up to a total of 6 evaluable patients if a dose-limiting toxicity (DLT) was observed. Eligible patients received a single dose of ONT-380 in a fasted state on Cycle 1 Day 1 and, if they did not experience a DLT, twice-daily (BID) dosing in a fed state in continuous 28-day cycles was initiated on Cycle 1 Day 3 and

continued until disease progression, unacceptable toxicity or patient withdrawal of informed consent. A starting dose of 25 mg BID was utilized with additional cohorts at planned dose levels of 50, 100, 200, 300, 500, 650 and 800 mg BID. The MTD was defined as the highest dose of ONT-380 at which no more than 1 of 6 evaluable patients experienced a DLT in Cycle 1. Patients evaluable for DLT determination received at least 1 cycle of ONT-380 without dose reduction in Cycle 1.

Dose-limiting toxicities were any adverse event (AE) not clearly attributable to the patient's disease, including hematologic toxicities of Grade 4 neutropenia ≥ 7 days, Grade 3/4 neutropenia with fever, Grade 4 thrombocytopenia or anemia or any grade thrombocytopenia associated with bleeding; non-hematologic toxicities of Grade 3 or 4 toxicity despite adequate supportive care, Grade 2 vomiting on 2 consecutive days despite anti-emetic therapy and Grade 2 toxicity > 2 weeks; laboratory abnormalities with at least a 2-grade increase that were associated with clinical signs and symptoms that persisted for over 7 days; and interruption of dosing for > 2 weeks if that interruption was secondary to drug-related toxicity. Exceptions included Grade 3 nausea and vomiting in the absence of anti-emetic prophylaxis.

In the expansion cohort, patients with HER2+MBC received ONT-380 at the declared MTD in continuous 28-day cycles without regard to food and continued until disease progression, unacceptable toxicity or patient withdrawal of informed consent.

Patient Population

Patients were ≥ 18 years of age with HER2+ cancer (dose-escalation cohorts) or HER2+MBC with an accessible lesion for biopsy (expansion cohort). Initially, patients with advanced solid

tumors historically known to express HER2 were enrolled (N=19), but the study was later amended to allow only patients with documented HER2+ disease as determined by immunohistochemistry [IHC] 3+, fluorescence in situ hybridization [FISH]+, silver in situ hybridization [SISH]+ (expansion only) and/or chromogenic in situ hybridization [CISH]+ (expansion only).[20, 21] Other key inclusion criteria included disease progression on at least one prior therapeutic regimen (for metastatic disease in the expansion cohort) or no curative therapy available, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2, adequate organ function and left ventricular ejection fraction (LVEF) $\geq$ 40% by cardiac imaging. Patients with HER2+MBC had to receive prior therapy with trastuzumab and lapatinib (if available) or declined those treatments prior to entry into the study. Patients with uncontrolled or symptomatic brain metastases or a history of Gilbert's syndrome or other genetic disorders affecting conjugation of bilirubin were excluded.

Safety Assessments

Safety was continually monitored with assessments occurring in Cycle 1 on Days 1, 2, 3, 8, 15 and 22 (dose-escalation cohorts) and on Days 1, 8 and 15 (expansion cohort). In subsequent cycles, patients in all cohorts were assessed every 28 days. Assessments included the monitoring of AEs, DLTs (in Cycle 1 for dose-escalation cohorts only), clinical laboratory parameters (hematology, chemistry, urinalysis), electrocardiogram (ECG) results, ECOG PS, vital signs, physical examination findings and cardiac imaging to assess LVEF.

The severity of an AE was assessed and reported by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0. A

composite term of "combined rash" included the preferred terms (PTs) of dermatitis acneiform, acne, skin exfoliation and all PTs that included the term "rash".

Response Assessments

Tumor response was assessed every 8 weeks using standard clinical evaluations, including Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0 with modification (dose-escalation cohorts; including a maximum of 3 target lesions and not including clinical lesions as measurable) or RECIST, Version 1.1 (expansion cohort), when applicable. Serological tumor marker levels were incorporated into the overall response assessment per RECIST. Patients who had measurable disease and at least 1 follow-up scan were considered evaluable for response.

Pharmacokinetic Assessments

The PK of ONT-380 and a metabolite were characterized in both the dose-escalation and expansion cohorts. For the dose-escalation cohorts, blood samples were collected on Cycle 1 Day 1 after patients fasted for 2 hours before and 1 hour after a single dose of ONT-380 (fasted assessment; predose and 0.5 to 24 hours postdose), on Cycle 1 Day 3 with food (fed assessment; predose and 1 to 4 hours postdose) and on Cycle 1 Day 15 (predose and 0.5 to 12 hours postdose), with additional trough samples collected predose on Cycle 1 Day 8 and on Day 1 of Cycles 2, 3 and 4. For the expansion cohort, blood samples were collected on Cycle 1 Day 1 (predose), Cycle 1 Day 15 and Cycle 2 Day 1 (for both days: predose and 0.5 to 12 hours postdose), with additional trough samples collected on Day 1 of Cycles 2 through 6. Plasma concentrations were determined using a validated Good Laboratory Practice (GLP) liquid

chromatography with tandem mass spectrometric detection (LC-MS/MS) method. The individual plasma concentration-time data for each analyte were evaluated with noncompartmental analysis using Phoenix WinNonlin®, Version 6.3 (Pharsight Corporation, St. Louis, MO, USA).

RESULTS

Patient Characteristics

Between April 2008 and July 2011, a total of 50 patients (median age 58 years; 90% female) were enrolled at 4 sites in the US and Canada. Thirty-three patients were enrolled in the dose-escalation phase, with an additional 17 patients treated in the expansion phase. Most patients had breast cancer, were heavily pretreated and had a favorable ECOG PS. All patients with breast cancer had received prior trastuzumab and 81% of these patients had received prior lapatinib. Patient characteristics are summarized in **Table 1.**

Dose escalation, DLTs and MTD

Dose escalation proceeded through the planned cohorts of 25 to 650 mg BID, with no DLTs observed. In the 800 mg BID cohort, 2 of 4 patients experienced DLTs (both of Grade 3 increased alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]), thus the 800 mg BID dose was declared not tolerable. Of note, all DLTs resolved within 2 weeks with interruption of dosing and upon re-challenge at a lower dose, patients tolerated continued ONT-380 treatment. Subsequently, the 650 mg BID cohort should have been expanded to include 3 additional patients in order to define the MTD; however, the inventory of 25 mg capsules was limited. Therefore, 7 patients were enrolled into a 600 mg BID dose-escalation cohort. With none of these 7 patients experiencing DLTs, the 600 mg BID dose was declared the

MTD. For the following safety discussion, the 600 and 650 mg dose levels were combined to represent the MTD dose level.

Safety and tolerability

Adverse events are summarized in **Table 2**.The most commonly reported AEs (all grades) were nausea, diarrhea, fatigue, vomiting, rash (combined term), constipation, cough and pain in extremity. Grade 3 AEs were reported in 42% of patients; those occurring in > 1 patient were anemia and cellulitis (3 patients each, 6%) and abdominal pain, hypokalemia, increased ALT, increased AST, musculoskeletal chest pain and vomiting (3 patients each, 4%). Four patients (8%) experienced one Grade 4 event each, none deemed treatment related; these were events of asthenia, diabetes insipidus, hypercalcemia and sepsis. At the MTD, the most common AEs were diarrhea, nausea, fatigue, vomiting, pain in extremity and urinary tract infection (**Table 2**); the majority of these events were Grade 1 or Grade 2 in severity.

The most commonly reported AEs considered treatment-related were nausea (17 patients, 34%), diarrhea (11 patients, 22%), fatigue (10 patients, 20%), and vomiting, increased ALT and increased AST (6 patients each 12%). The severity of treatment-related AEs increased with higher ONT-380 dose, with Grade 3 treatment-related AEs (including hypokalemia, increased ALT and increased AST [4% each]; and rash, night sweats, peripheral edema and anemia [2% each]) reported only in the ≥ 600 mg BID cohorts. At the MTD, the most common AEs considered treatment related by the Investigator were nausea and diarrhea and all of these events were less than Grade 3 in severity (**Table 3**).

Two patients (4%) died of disease progression within 30 days of their last dose of ONT-380, 12 patients (24%) developed SAEs and 5 patients (10%) discontinued ONT-380 due to an AE; none of these events were considered related to ONT-380 by the Investigator.

Fifteen patients (30%) required interruption of ONT-380 due to AEs and 4 patients (8%) underwent a dose reduction. Dose modifications were primarily due to elevations in liver function tests (LFTs) and ONT-380 was almost always re-initiated with tolerability at the initial or lower doses; no elevations in LFTs led to study drug discontinuation.

Typically, elevations in LFTs were observed within a week of ONT-380 initiation and the incidence and severity of these elevations increased with increased dose. Although common (62% of patients treated), elevations in LFTs were mostly Grade 1 and were reversible upon interruption or dose reduction of ONT-380. No Hy's Law cases were observed.

Grade 1/2 shifts in electrolytes (up to 34% of patients) and serum creatinine (48% of patients) were also common and occurred most often at doses ≥ 300 mg BID. Grade 3/4 electrolyte imbalances were rare and occurred only at doses ≥ 500 mg BID. Shifts in these parameters were reversible upon interruption of ONT-380.

Pharmacokinetics

Following a single dose of ONT-380 (Cycle 1 Day 1), the geometric mean plasma concentration-time profiles for ONT-380 were similar in shape across the dose range studied (25 to 800 mg) and geometric mean concentrations tended to increase with increasing dose.

Repeat-dose geometric mean plasma ONT-380 concentration-time profiles (Cycle 1 Day 15) were similar in shape to the Cycle 1 Day 1 profiles and across cohorts, and tended to increase with increasing dose (**Figure 1**). Predose (trough) plasma ONT-380 concentrations on Cycle 1 Day 15 were similar to the 12-hour post-dose mean concentrations of the same day, which is indicative of steady-state exposure. At the MTD, trough concentrations were maintained above the predicted IC_{90} value [22]. The results of the dose proportionality assessment suggest that ONT-380 exposure was approximately dose proportional. Although accumulation was variable, an overall geometric mean R_{AUC} of 1.95 (104% CV) indicated moderate accumulation with repeat dosing. On both Cycle 1 Day 1 and Cycle 1 Day 15, the overall median T_{max} for ONT-380 was approximately 2 hours and the overall median half-life was 5.38 hours. Exposure of the metabolite was approximately 12% that of ONT-380, regardless of day. No significant food effect was observed for ONT-380 or metabolite exposure; however, variability was high.

Response

Among the 35 patients evaluable for response at any dose level, the best tumor response per RECIST was confirmed partial response (PR) in 3 patients (9%) and stable disease (SD) in 20 patients (57%; including 2 patients with unconfirmed PRs). Among the 22 HER2+MBC patients with measurable disease at baseline that were treated at doses of ≥ 600 mg BID, the clinical benefit rate (PR + SD ≥ 24 weeks) was 27% (6 patients), including 3 confirmed PRs and 3 SDs (**Table 4**). Tumor shrinkage was observed in both skin and visceral lesions, including liver metastases. One additional patient without measurable disease at baseline had SD for ≥ 24 weeks. In patients who had not received prior lapatinib (n=7), 1 (14%) had PR, 3 (43%) had SD and 3 (43%) had PD as best response. In the 3 patients with a confirmed PR, the duration of

response was 12.3 weeks (N=1) and 28 weeks (N=2). All 3 of these patients had received prior trastuzumab, and 2 had also received prior lapatinib. **Figure 2** illustrates the change in the sum of longest diameter of target lesions per RECIST in patients with HER2+MBC treated at doses ≥ 600 mg BID with measurable disease and evaluable follow-up scans.

DISCUSSION

This Phase 1 study determined the MTD of the oral HER2-selective inhibitor ONT-380 as 600 mg BID using a powder-in-capsule formulation. Overall, ONT-380 was well tolerated with no treatment-related Grade 4 events, SAEs or AEs leading to discontinuation. Grade 3 elevations in hepatic transaminases were dose limiting at 800 mg BID; however, these elevations were reversible within 2 weeks by holding study drug and did not recur upon re-challenge at the MTD.

ONT-380 was found to have favorable PK properties, although variable exposure was observed. No significant food effect was observed for ONT-380 or metabolite exposure. When dosed at the MTD, mean steady-state ONT-380 concentrations were maintained at or above the predicted IC_{90} for HER2 inhibition. Of note, a tablet formulation demonstrating increased exposure and lower variability [22] is being used in all current clinical studies [23, 24].

Additionally, ONT-380 demonstrated notable single-agent anti-tumor activity in patients with HER2+MBC treated at doses ≥ MTD. In this heavily pretreated population (all had received prior trastuzumab and 84% had received prior lapatinib), there was a clinical benefit rate (PR + SD > 24 weeks) of 27%, including durable confirmed PRs (14%) in patients who received after at least 2 prior HER2-targeted therapies. While response comparisons across clinical studies are difficult due to confounding factors such as prior treatment and other clinical factors, the

response to single-agent ONT-380 is within range of that seen with both lapatinib [25] and neratinib monotherapy [26], though arguably for ONT-380 in a population that had undergone therapy with a higher number of HER2-targeted therapies. Perhaps a more relevant comparison based upon the number of prior therapies is the TH3RESA trial in which heavily pretreated patients with advanced HER2+breast cancer were randomized to receive either ado-trastuzumab emtansine or physician's choice [27]. In TH3RESA, all patients had received prior therapy with both trastuzumab and lapatinib and the use of ado-trastuzumab emtansine was associated with an objective response rate of 31% in patients with measurable disease (N=345) vs. 9% in the physician's choice group (N=163). Though ONT-380 did not have as high a response rate as ado-trastuzumab emtansine, response was higher than that of the physician's choice group, suggesting a potential role for ONT-380 over chemotherapy/trastuzumab-containing regimens as ado-trastuzumab emtansine continues to become an earlier treatment line for HER2+ breast cancer. To this point, a trial of ONT-380 in combination with trastuzumab and/or capecitabine is being conducted in patients with disease progression on ado-trastuzumab emtansine [24].

As important, during treatment with ONT-380, there was a low incidence of Grade 3 toxicities commonly associated with dual EGFR/HER2 inhibitors, with only one patient each experiencing Grade 3 diarrhea and Grade 3 rash. This compares favorably to the ~10 to 30% incidence of Grade 3/4 diarrhea associated with the single-agent recommended Phase 2 dose of lapatinib or neratinib used to treat metastatic breast cancer [25-28]. This noted absence of treatment-related high-grade diarrhea makes ONT-380 a suitable agent for combination therapy with capecitabine or trastuzumab, theoretically, without the relatively high rate of diarrhea (or rash) that has been associated with these agents when given in combination with non-specific HER2 inhibitors [25, 29-31].

In conclusion, this study demonstrated that ONT-380 appears to have a more favorable and manageable toxicity profile compared to either current dual EGFR/HER2 or pan-HER TKIs, with clinical activity in a heavily pretreated HER2+MBC cohort. There is increasing evidence that dual targeting of HER2 (but not EGFR) can lead to further improvements in efficacy. In particular, the combination of a small-molecule inhibitor with an antibody-based therapy may be effective in overcoming resistance; accordingly, ONT-380 is currently undergoing evaluation in patients with HER2+MBC in combination Phase 1b studies with capecitabine and/or trastuzumab (NCT02025192) [24] and ado-trastuzumab emtansine (NCT01983501) [23]. Both studies have completed enrollment with patients continuing to receive treatment. Preliminary data shows that the combination of ONT-380 with other active treatments was well-tolerated and demonstrates encouraging anti-tumor activity in a high risk patient population [24, 32]. Additionally, these studies have enrolled expansion cohorts of patients with CNS metastases based upon preclinical animal models demonstrating adequate CNS penetration for ONT-380 showing preliminary safety and efficacy in this at need patient population with heavily pre-treated HER2+ MBC with CNS metastases [33]. Currently, an international Phase 2 randomized, double-blinded, placebo-controlled study of ONT-380 in combination with trastuzumab and capecitabine in patients with pretreated, unresectable locally advanced or metastatic HER2+ MBC (NCT02614794) is actively recruiting patients. Patients with or without brain metastases are eligible and the primary endpoint is bi-compartmental progression free survival (PFS) based on assessment of both CNS and non-CNS disease [34].

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TABLES

Table 1 Patient Characteristics (N=50)

Characteristic	
Enrollment, n (%)	
dose-escalation phase	33 (66%)
25 mg BID	3 (6%)
50 mg BID	3 (6%)
100 mg BID	3 (6%)
200 mg BID	3 (6%)
300 mg BID	3 (6%)
500 mg BID	4 (8%)
600 mg BID	7 (14%)
650 mg BID	3 (6%)
800 mg BID	4 (8%)
expansion phase	17 (34%)
Median age, years (range)	58 (31 – 77)
Sex, n (%)	
male	5 (10%)
female	45 (90%)
Race, n (%)	
White	40 (80%)
Black/African American	4 (8%)
Asian	4 (8%)
other	2 (4%)
Tumor type, n (%)	
breast	43 (86%)
colorectal	6 (12%)
salivary gland	1 (2%)
ECOG performance status, n (%)	
0	16 (32%)
1	31 (62%)
2	3 (6%)
Median prior systemic (hormonal, chemotherapy, biological) anticancer regimens (range)	5 (1 – 15)
Prior treatments, n (%)	
radiation	38 (76%)
surgery	44 (88%)
HER2+ breast cancer, n	43
median prior HER2 therapy-based regimens (range)	6 (2 - 15)
prior trastuzumab, n (%)	43 (100%)
prior lapatinib, n (%)	36 (84%)

Abbreviations: BID = twice daily; ECOG = Eastern Cooperative Oncology Group; mg = milligram(s)

Table 2 Incidence of Patients with Treatment-emergent Adverse Events, Regardless of Causality, in ≥ 10% of Patients (N=50)

Adverse Event	25 to 500 mg[a] BID ONT-380 (N=19)	600/650 mg[b] BID ONT-380 (N=27)	800 mg BID ONT-380 (N=4)	Total (N=50)
Total Patients With Any AE	19 (100%)	26 (96%)	4 (100%)	49 (98%)
Nausea	11 (58%)	15 (56%)	2 (50%)	28 (56%)
Diarrhea	5 (26%)	18 (67%)	3 (75%)	26 (52%)
Fatigue	11 (58%)	12 (44%)	2 (50%)	25 (50%)
Vomiting	8 (42%)	10 (37%)	2 (50%)	20 (40%)
Combined rash[c]	7 (37%)	4 (15%)	1 (25%)	12 (24%)
Constipation	5 (26%)	4 (15%)	1 (25%)	10 (20%)
Cough	4 (21%)	5 (19%)	1 (25%)	10 (20%)
Pain in extremity	1 (5%)	7 (26%)	2 (50%)	10 (20%)
Back pain	3 (16%)	5 (19%)	1 (25%)	9 (18%)
Headache	5 (26%)	4 (15%)	0	9 (18%)
Urinary tract infection	2 (11%)	7 (26%)	0	9 (18%)
Myalgia	2 (11%)	5 (19%)	1 (25%)	8 (16%)
Musculoskeletal chest pain	3 (16%)	4 (15%)	0	7 (14%)
Abdominal pain	3 (16%)	3 (11%)	0	6 (12%)
Alanine aminotransferase increased	1 (5%)	3 (11%)	2 (50%)	6 (12%)
Anorexia	3 (16%)	3 (11%)	0	6 (12%)
Aspartate aminotransferase increased	1 (5%)	3 (11%)	2 (50%)	6 (12%)
Dizziness	4 (21%)	1 (4%)	1 (25%)	6 (12%)
Dyspnea	1 (5%)	5 (19%)	0	6 (12%)
Erythema	1 (5%)	5 (19%)	0	6 (12%)
Hypomagnesemia	2 (11%)	4 (15%)	0	6 (12%)
Night sweats	0	5 (19%)	0	5 (10%)
Upper respiratory tract infection	1 (5%)	3 (11%)	1 (25%)	5 (10%)

Abbreviations: AE = adverse event; BID = twice daily; mg = milligram(s)

[a] Includes the dose levels of 25 mg (N=3), 50 mg (N=3), 100 mg (N=3), 200 mg (N=3), 300 mg (N=3) and 500 mg (N=4) BID.

[b] The 650 mg BID dose was modified to 600 mg due to lack of availability of 25 mg capsules (650 mg BID [N=3]; 600 mg BID [N=24]).

[c] Combined rash term includes events of acne, dermatitis acneiform, skin exfoliation and all MedDRA preferred terms that included the term "rash".

Table 3 Incidence of Patients with Treatment-related Adverse Events at the Maximum Tolerated Dose of ONT-380 (N=27) in ≥ 10% of Patients, by Maximum Severity

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Total Patients With Any AE	8 (30%)	7 (26%)	5 (19%)	0	20 (57%)
Nausea	7 (26%)	2 (7%)	0	0	9 (33%)
Diarrhea	6 (22%)	1 (4%)	0	0	7 (26%)
Fatigue	2 (7%)	3 (11%)	0	0	5 (19%)
Alanine aminotransferase increased	0	2 (7%)	1 (4%)	0	3 (11%)
Aspartate aminotransferase increased	0	3 (11%)	0	0	3 (11%)
Combined rash[a]	2 (7%)	0	1 (4%)	0	3 (11%)
Vomiting	2 (7%)	1 (4%)	0	0	3 (11%)

Abbreviations: AE = adverse event; BID = twice daily; mg = milligram(s); MTD = maximum tolerated dose

Note: The 600 and 650 mg dose levels were combined to represent the MTD dose level. The 650 mg BID dose was modified to 600 mg due to lack of availability of 25 mg capsules (650 mg BID [N=3]; 600 mg BID [N=24]).

[a] Combined rash term includes events of acne, dermatitis acneiform, skin exfoliation and all MedDRA preferred terms that included the term "rash".

Table 4 Best Overall Tumor Response for HER2-positive Metastatic Breast Cancer Patients with Measurable Disease at Baseline at ONT-380 Doses ≥ 600 mg BID (N=22)

Best Overall Response	600 mg BID ONT-380 (N=18)[a]	800 mg BID ONT-380 (N=4)	Total (N=22)
PR	2 (11%)	1 (25%)	3 (14%)
SD			
< 24 weeks	9 (50%)[b]	0 (0%)	9 (41%)
≥ 24 weeks	2 (11%)	1 (25%)	3 (14%)
PR + SD ≥ 24 weeks	4 (22%)	2 (50%)	6 (27%)
Progressive disease	5 (28%)[c]	1 (25%)	6 (27%)
Not evaluable	0 (0%)	1 (25%)	1 (5%)

Abbreviations: BID = twice daily; mg = milligram(s); PR = partial response; SD = stable disease

[a] No patients in the 650 mg BID cohort had measurable disease.

[b] One patient with SD had an unconfirmed PR.

[c] Includes 1 patient whose target lesions were not evaluable at study termination.

FIGURE LEGENDS

Figure 1 Geometric Mean (SD) Plasma ONT-380 Concentrations on Cycle 1 Day 15 (Semi-log Scale)

Figure 2 Waterfall Plot of Target Lesions in HER2-positive Metastatic Breast Cancer Patients with Measurable Disease Evaluable for Response at ONT-380 Doses ≥ 600 mg BID (N=20)

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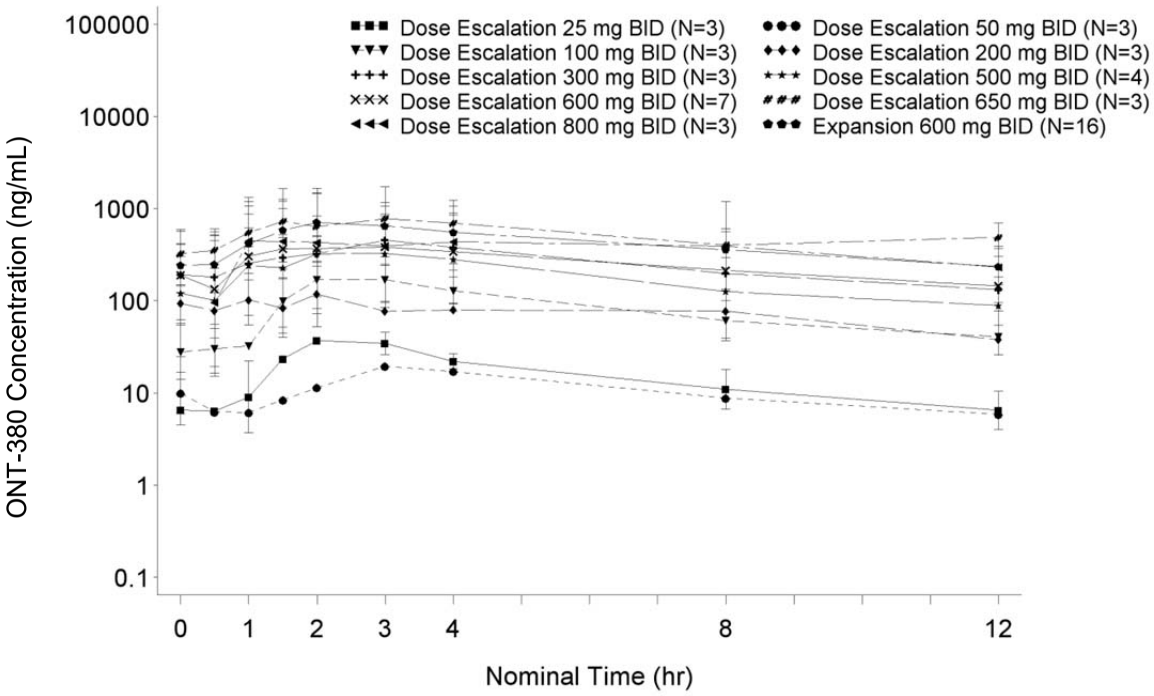
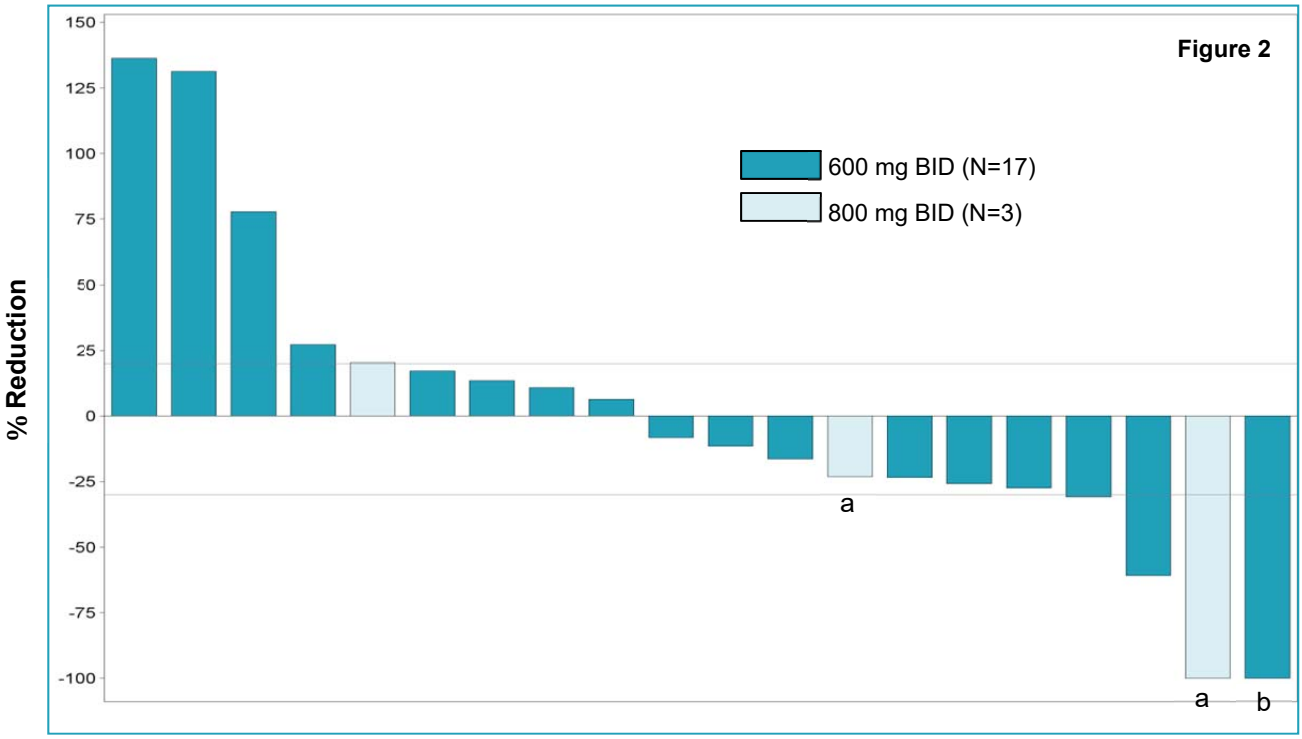
Figure 1





HER2-positive MBC Patients with Measurable Disease Evaluable for Response at Doses ≥ 600 mg BID[c]

[a] Dose was held after approximately 1 week of dosing and then reduced to 600/650 mg BID.
[b] All patients received prior lapatinib with the exception of this patient.
[c] No patients in the 650 mg BID cohort had measurable disease.

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Clinical Cancer Research

Phase 1 Study of ONT-380, a HER2 Inhibitor, in Patients with HER2+ Advanced Solid Tumors, with an Expansion Cohort in HER2+ Metastatic Breast Cancer (MBC)

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