Cancer Therapy: Clinical

Clinical Cancer Research

Phase I 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 I study determined the MTD, pharmacokinetics (PK) and antitumor activity of ONT-380 in HER2-positive advanced solid tumors, with an expansion cohort of patients with HER2$^+$ 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 anticancer regimens = 5. Dose-limiting toxicities of increased transaminases occurred at 800 mg BID, thus 600 mg 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 $\geq$ MTD, the response rate was 14% [all partial response (PR)] and the clinical benefit rate (PR + stable disease $\geq$ 24 weeks) was 27%.

Conclusions: 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 antitumor activity in heavily pretreated HER2$^+$ MBC patients, supporting its continued development. *Clin Cancer Res; 23(14); 3529–36. ©2017 AACR.*

Introduction

Approximately 15% to 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 before the development of HER2-targeted therapies (3). Although multiple approved strategies exist for disrupting HER2 signaling in HER2-positive (HER2$^+$) metastatic breast cancer (MBC; refs. 4, 5), including mAbs such as trastuzumab (6) and pertuzumab (7), the antibody–drug conjugate ado-trastuzumab emtansine (T-DM1; ref. 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 with 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).

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Note: prior presentation: AACR Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications, San Diego, CA, Oct 3–6, 2013 (abstract A050); and AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, San Francisco, CA, Nov 12–16, 2011 (abstr A143).

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doi: 10.1158/1078-0432.CCR-16-1496

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 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.

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 I 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 before the initiation of study-related treatment or procedures.

Study design and treatment

This open-label Phase I study comprised both dose-escalation and expansion components to determine the 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 used 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.

DLTs were any adverse event (AE) not clearly attributable to the patient's disease, including hematologic toxicities of Grade 4 neutropenia $\geq$ 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 $\geq$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; refs. 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 before 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 (PT) 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).

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 United States 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.

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, y (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).

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 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

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."

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 (LFT) 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 (Fig. 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

Table 3. Incidence of patients with treatment-related adverse events at the MTD 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%)

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 ($N = 24$)].
Abbreviations: AE, adverse event; BID, twice daily; mg, milligram(s); MTD, maximum-tolerated dose.
[a]Combined rash term includes events of acne, dermatitis acneiform, skin exfoliation, and all MedDRA preferred terms that included the term "rash."

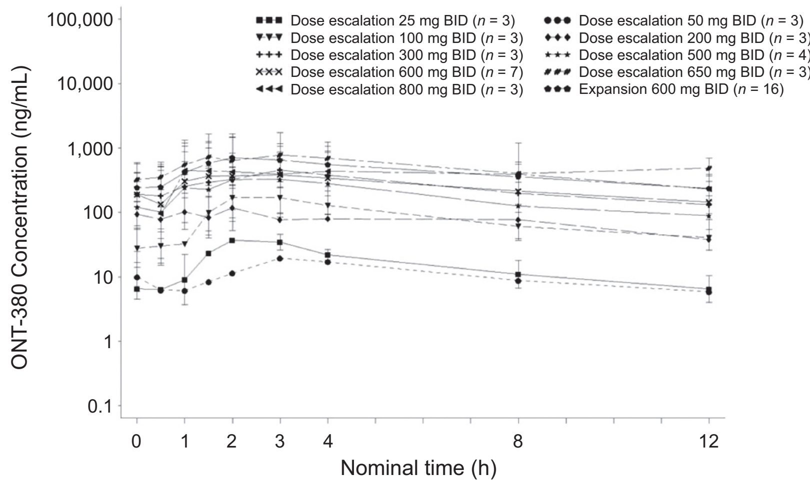


Figure 1.
Geometric mean (SD) plasma ONT-380 concentrations on cycle 1 day 15 (Semi-log Scale).

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

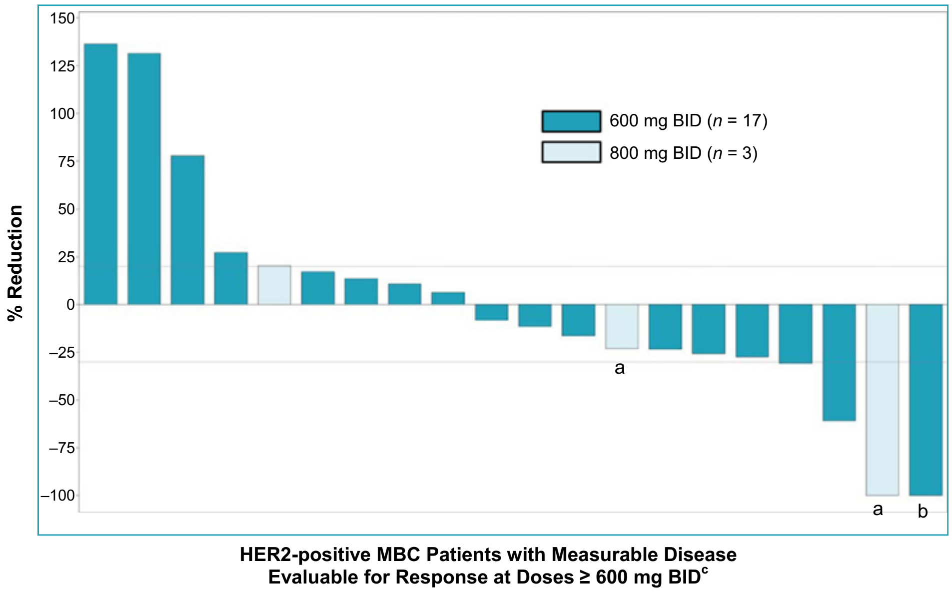
This Phase I study determined the MTD of the oral HER2-selective inhibitor ONT-380 as 600 mg BID using a powder-in-capsule formulation. Overall, ONT-380 was well tolerated with no treatment-related grade 4 events, SAEs or AEs leading to discontinuation. Grade 3 elevations in hepatic transaminases were 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).

Table 4. Best overall tumor response for $HER2^+$ MBC 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.



[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.

Figure 2.
Waterfall plot of target lesions in HER2$^+$ MBC patients with measurable disease evaluable for response at ONT-380 doses ≥600 mg BID (N = 20).

In addition, ONT-380 demonstrated notable single-agent antitumor 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) versus 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 approximately 10% to 30% incidence of Grade 3/4 diarrhea associated with the single-agent recommended Phase II 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 nonspecific HER2 inhibitors (25, 29–31).

In conclusion, this study demonstrated that ONT-380 appears to have a more favorable and manageable toxicity profile compared with 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 Ib studies with capecitabine and/or trastuzumab (NCT02025192; ref. 24) and ado-trastuzumab emtansine (NCT01983501; ref. 23). Both studies have completed enrollment with patients continuing to receive treatment. Preliminary data show that the combination of ONT-380 with other active treatments was well-tolerated and demonstrates encouraging antitumor activity in a high-risk patient population (24, 32). In addition, 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 II 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 bicompartmental progression-free survival based on assessment of both CNS and non-CNS disease (34).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acknowledgments

The authors thank the participating patients, their families, study investigators, the clinic nurses and the study coordinators at all institutions for their invaluable contributions.

Grant Support

This work was supported by Array BioPharma, Inc.. Medical writing support was provided by Allison L. Marlow.

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Received August 10, 2016; revised December 7, 2016; accepted December 14, 2016; published OnlineFirst January 4, 2017.

References

1. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:2078–99.
2. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. J Pathol 2003;200:290–7.
3. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82.
4. Figueroa-Magalhães MC, Jelovac D, Connolly RM, Wolff AC. Treatment of HER2-positive breast cancer. Breast 2014;23:128–36.
5. Li SG, Li L. Targeted therapy in HER2-positive breast cancer. Biomed Rep 2013;1:499–505.
6. HERCEPTIN® (trastuzumab) [Prescribing Information]. South San Genentech, Inc.; 2014. Available from: http://www.gene.com/download/pdf/herceptin_prescribing.pdf.
7. PERJETA® (pertuzumab) [Prescribing Information]. South San Genentech, Inc.; 2013. Available from: http://www.gene.com/download/pdf/perjeta_prescribing.pdf.
8. KADCYLA™ (ado-trastuzumab emtansine) [Prescribing Information]. South San Genentech, Inc.; 2013. Available from: http://www.gene.com/download/pdf/kadcyla_prescribing.pdf.
9. TYKERB® (lapatinib) [Prescribing Information]. Research Triangle GlaxoSmithKline; 2013. Available from: https://www.gsksource.com/gskprm/htdocs/documents/TYKERB-PI-PIL.PDF.
10. Baselga J. Treatment of HER2-overexpressing breast cancer. Ann Oncol 2010;21 Suppl 7: 36–40.
11. Wong AL, Lee SC. Mechanisms of resistance to trastuzumab and novel therapeutic strategies in HER2-positive breast cancer. Int J Breast Cancer 2012;2012:415170.
12. Frankel C, Palmieri FM. Lapatinib side-effect management. Clin J Oncol Nurs 2010;14:223–33.
13. Lucchini E, Pilotto S, Spada E, Melisi D, Bria E, Tortora G. Targeting the epidermal growth factor receptor in solid tumors: focus on safety. Expert Opin Drug Saf 2014;13:535–49.
14. Sandler AB. Nondermatologic adverse events associated with anti-EGFR therapy. Oncology 2006;20:35–40.
15. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J Clin Oncol 2009;27:5278–86.
16. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. Clin Cancer Res 2007;13:1648–55.
17. Pheneger T, Bouhana K, Anderson D, Garrus J, Ahrendt K, Allen S, et al. In vitro and in vivo activity of ARRY-380: A potent, small molecule inhibitor of ErbB2 [abstract]. In: Proceedings of the American Association of Cancer Research 100th Annual Meeting; 2009 Apr 18–22, 2009: AACR; 2009. Abstract nr 1795.
18. Lee P, Anderson D, Pheneger T, Napier C, Garrus J, Avrutskaya A, et al. In vivo activity of ARRY-380: A potent, small molecule inhibitor of ErbB-2 in combination with trastuzumab or docetaxel in a BT-474 human breast carcinoma xenograft model [abstract]. In: Proceedings of the American Association of Cancer Research 100th Annual Meeting; 2009 Apr 18–22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr 5581.
19. Dinkel V, Anderson D, Winski S, Winkler J, Koch K, Lee P. ARRY-380, a potent, small-molecule inhibitor of ErbB2, increases survival in intracranial $ErbB2^+$ xenograft models in mice [abstract]. In: Proceedings of the American Association of Cancer Research 103rd Annual Meeting; 2012 Mar 31–Apr 04; Chicago, IL. Philadelphia (PA): AACR; 2012. Abstract nr 852.
20. Martin V, Cappuzzo F, Mazzucchelli L, Frattini M. HER2 in solid tumors: more than 10 years under the microscope; where are we now? Future Oncol 2014;10:1469–86.
21. Martin V, Landi L, Molinari F, Fountzilas G, Geva R, Riva A, et al. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients. Br J Cancer 2013;108:668–75.
22. Lindemann C, Fry D, Preigh M, Anderson P, Chavira R, Litwiler K, et al. Preclinical and clinical evaluation of the effect of gastric pH on exposure of ARRY-380 formulated as a crystalline freebase and a PVP-VA spray dried dispersion [abstract]. In: Proceedings of the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition; 2013 Nov 10–14; San Antonio, TX: AAPS; 2013. Abstract nr W5276.
23. Borges VF, Hamilton EP, Yardley DA, Moulder SL, Hortobagyi GN, Walker LN, et al. A phase 1b study of ONT-380, an oral HER2 specific inhibitor, combined with ado-trastuzumab (T-DM1), in $HER2^+$ metastatic breast cancer (MBC) [abstract]. In: Proceedings of the 37th Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS); 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; 2014. Abstract nr P4-15-08.
24. Hamilton E, Yardley DA, Hortobagyi G, Walker L, Borges VF, Moulder S. A phase 1b study of ONT-380, an oral HER2-specific inhibitor, combined with capecitabine and/or trastuzumab, in $HER2^+$ metastatic breast cancer (MBC) [abstract]. In: Proceedings of the 37th Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS); 2014 Dec 9–13; San Antonio, TX.
25. Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124–30.
26. Burstein HJ, Sun Y, Dirix LY, Jiang Z, Paridaens R, Tan AR, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. J Clin Oncol 2010;28:1301–7.
27. Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689–99.

28. Crown JP, Burris HA III, Boyle F, Jones S, Koehler M, Newstat BO, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. Breast Cancer Res Treat 2008;112:317–25.
29. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733–43.
30. Saura C, Garcia-Saenz JA, Xu B, Harb W, Moroose R, Pluard T, et al. Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2014;32:3626–33.
31. Swaby R, Blackwell K, Jiang Z, Sun Y, Dieras V, Zaman K, et al. Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: a phase I/II study. J Clin Oncol 27:15s, 2009 (suppl; abstr 1004).
32. Ferrario C, Hamilton E, Aucoin N, Falkson Cl, Khan Q, Krop I, et al. 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) [abstract]. In: Proceedings of the San Antonio Breast Cancer Symposium (SABCS) Annual Meeting; 2015 Dec 8–15; San Antonio, TX: SABCS; 2015. Abstract nr P4-14-20.
33. Murthy RK, Hamilton E, Borges V, Moulder S, Aucoin N, Welch S, et al. ONT-380 in the treatment of $HER2^{+}$ breast cancer central nervous system (CNS) metastases [abstract]. In: Proceedings of the San Antonio Breast Cancer Symposium (SABCS) Annual Meeting; 2015 Dec 8–15; San Antonio, TX: SABCS; 2015. Abstract nr P4 -14-19.
34. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 2015;16:e270–8.