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)

Cristiano Ferrario[a], Erika Hamilton[b,c], Nathalie Aucoin[d], Carla I Falkson[e], Qamar Khan[f], Ian Krop[g], Stephen Welch[h], Philippe L Bedard[i], Alison Conlin[i], Jorge Chaves[k], Alex Vo[l], Luke Walker[l], Virginia F Borges[m]

[a] Segal Cancer Centre - Jewish General Hospital, Montreal, QC H3T 1E2; [b] Sarah Cannon Research Institute, Nashville, TN 37203; [c] Tennessee Oncology, PLLC, Nashville, TN 37203; [d] Hopital de la Cite-de-la Sante, Laval, Quebec H7M 3L9; [e] University of Alabama Comprehensive Cancer Center, Birmingham, AL 35294; [f] University of Kansas Medical Center, Westwood, Kansas 66205; [g] Dana-Farber Cancer Institute, Boston, MA 02215; [h] London Regional Cancer Program, London Health Sciences Centre, London, Ontario, N6A 4L6; [i] Princess Margaret Cancer Center – University Health Network, Toronto, Ontario, M5G 2M9; [j] Providence Oncology and Hematology Care Clinic, Eastside, Portland, OR 97214; [k] Northwest Medical Specialties, Tacoma, WA 98405; [l] Oncothyreon Inc., Seattle, WA 98121; [m] University of Colorado Cancer Center, Aurora, CO 80045

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Background and Study Rationale

Despite recent progress, medical need persists for patients with HER2+ metastatic breast cancer (MBC), particularly those with CNS metastases[1,2]

ONT-380

- HER2 selective small molecule tyrosine kinase inhibitor (TKI) with nanomolar potency[3]
  - Highly selective for HER2 than EGFR (HER2 IC_{50}: 8 nM; EGFR IC_{50}: >10,000 nM)
  - HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- Highly active in murine tumor models of HER2+ disease
  - Synergy with trastuzumab and chemotherapy[4]
  - Improved survival compared to lapatinib and neratinib in a preclinical model of HER2+ CNS disease[5]
- In a Phase 1 single-agent study, clinical benefit seen with no treatment-related Grade 3 diarrhea in heavily pre-treated patients[6]

Trastuzumab emtansine (T-DM1; Kadcyla®*)

- Approved SOC for patients with HER2+ breast cancer with progression following prior therapy with trastuzumab and a taxane[7,8]
- Anecdotal data suggest T-DM1 may have activity against CNS metastases[9,10]

Study Rationale

- Based on preclinical data showing synergy of ONT-380 in combination with trastuzumab and cytotoxic therapy, as well as the potential for CNS activity, the safety, tolerability, and anti-tumor activity of ONT-380 in combination with T-DM1 was evaluated in patients with HER2+ MBC with or without CNS metastases[11]

Study Overview

Patient Population

- HER2+ MBC with progression after prior therapy with trastuzumab and a taxane, separately or in combination
- Patients with brain metastases eligible, including untreated metastases or metastases progressive after prior treatment

Study Design

- 3+3 dose escalation of ONT-380 tablets in combination with approved dose of T-DM1 3.6 mg/kg IV q21 days
  - Dose level 1: ONT-380 300 mg PO BID + T-DM1
  - Dose level 2: ONT-380 350 mg PO BID + T-DM1
- Expansion cohorts at the MTD in patients with and without CNS metastases

Selected Study Objectives

- Determine MTD/recommended dose (RD) of ONT-380 to be given in combination with approved dose of T-DM1
- Evaluate safety of ONT-380 in combination with T-DM1
- Explore anti-tumor activity based on assessment of response by RECIST 1.1
- Explore effect of combination on CNS metastases

Selected Eligibility Criteria

CNS	• Untreated asymptomatic metastases not needing immediate local therapy or progressive metastases following local therapy allowed

Inclusion	• Prior therapy with trastuzumab and a taxane for metastatic disease
	  • Patients with active CNS metastases may have received trastuzumab/taxane in neo-adjuvant/adjuvant setting
	  • Prior pertuzumab and prior lapatinib or other HER2-TKI allowed
	• Target or non-target lesions per RECIST 1.1
	• ECOG 0 or 1
	• Total bilirubin ≤1.5 × ULN
	• ALT and AST ≤1.5 × ULN (<2.5 × ULN if liver metastases present)
	• Normal LVEF

Exclusion	• Previous treatment with T-DM1 at any time, or with any HER2 Inhibitor within 4 weeks prior to study • Prior exposure to cumulative doxorubicin dose (or equivalent) >360 mg/m²

Treatments

- All treatments given over a 21-day cycle
- ONT-380 administered PO BID with no food restrictions
- Dose reductions of ONT-380 and T-DM1 permitted
  - Initial ONT-380 dose reduction schedule: 300 mg to 150 mg
  - Following manufacture of 50 mg tablets: up to 3 dose reductions allowed to minimum dose of 150 mg BID
  - T-DM1 dose reduction per manufacturer's instruction, up to 2 dose reductions allowed
  - Patients permitted to discontinue T-DM1 and continue ONT-380 as a single agent
- Prophylactic anti-diarrheal medication not required

Study Assessments

- ***Safety***: adverse events (AEs) including DLTs, laboratory assessments, physical exam, LVEF by MUGA or ECHO
  - DLT defined as protocol-specified events in 1st treatment cycle
- ***Anti-tumor activity***: Overall (RECIST 1.1) and CNS-specific response every 2 cycles through Cycle 6, and every 3 cycles thereafter
  - Brain MRI in all patients at baseline with follow-up MRI in patients with CNS metastases
  - Patients were considered "CNS assessable" if they had untreated CNS lesions and/or progressive CNS lesions after prior treatment
  - CNS response assessed using Sum of Longest Diameters (SLD) of target CNS lesions and status of non-target CNS lesions compared to baseline (≥20% increase = PD, ≥30% decrease = PR)
    - Untreated or progressive lesions <1 cm were considered assessable (but non-target) lesions

Results

Patient Characteristics

	ONT-380 Dose + T-DM1			
	MTD Cohort (n = 31)	300 mg CNS Exp (n = 19[a])	300 mg Total (n = 50)	350 mg (n = 7)
Age, median (range)	50 (31-71)	53 (30-72)	51 (30-72)	51 (31-66)
ECOG 0/1 (n)	13/18	9/10	22/28	1/6
Hormone receptor positive (n)	21	13	34	4
# of prior nonhormonal systemic treatment for metastatic disease, median (range)[b]	2 (1-6)	1 (0-5)	2 (0-6)	3 (2-10)
Trastuzumab (n)	31	19	50 (100%)	7
Pertuzumab (n)	14	9	23 (46%)	1
Lapatinib (n)	6	4	10 (20%)	1
CNS metastases (n)	11	19	30 (60%)	2
Prior treatment for CNS metastases (n)	10	9	19 (38%)	2
CNS metastases evaluable for response (n)	2	19	21 (42%)	0

[a] 1 patient withdrawn after receiving 1 ONT-380 dose (no T-DM1 administered) for reasons other than AE or PD, included in safety but not efficacy analyses
[b] 3 patients treated in 1st-line metastatic setting; all with active CNS metastases after having received trastuzumab/taxane in neo-adjuvant/adjuvant setting

Dose Escalation and Dose Limiting Toxicity (DLT)

ONT-380 MTD in combination with T-DM1 determined to be 300 mg BID

- ONT-380 300 mg BID + T-DM1
  - DLT in 1/6 patients in initial dose escalation cohort (Grade 3 ALT/AST)
  - DLT in 5/44 patients in MTD/CNS expansion cohorts (Grade 3 ALT and/or AST (n = 3); Grade 4 ALT/Grade 3 AST (n = 1); Grade 2 vomiting and diarrhea (n = 1))
- ONT-380 350 mg BID + T-DM1
  - DLT in 3/7 patients; cohort closed (Grade 3 vomiting (n = 1); Grade 3 fatigue (n = 1); Grade 3 hypersensitivity (n = 1))
- Safety and efficacy data presented are from the 50 patients treated at ONT-380 MTD of 300 mg BID

Patient Disposition at ONT-380 MTD

	ONT-380 Dose + T-DM1		
	MTD Cohort (n = 31)	300 mg CNS Exp (n = 19)	300 mg Total (n = 50)
Patients active on treatment (n)	13	12	25
Median number of cycles (n, range)	7 (1-29+)	7 (1-15+)	7 (1-29+)
Patients off treatment (n)	18	7	25
Progressive disease	14	2	16
Physician decision	0	1	1
Patient decision	1	2	3
Adverse event	3	2	5

Dose Reductions and Treatment Discontinuations Due to AEs at ONT-380 MTD

	ONT-380 Dose + T-DM1		
	MTD Cohort (n = 31)	300 mg CNS Exp (n = 19)	300 mg Total (n = 50)
Patients requiring dose reduction			
ONT-380 + T-DM1	4	3	7
ONT-380 alone	3	0	3
T-DM1 alone	5	2	7
Patients requiring discontinuation of study drug due to AE			
ONT-380 + T-DM1	3	1	4
ONT-380 alone	0	1	1
T-DM1 alone	2	2	4

- Most common reason for dose reduction were asymptomatic lab abnormalities
  - Reduction of ONT-380 and T-DM1: ALT/AST increases; reduction of T-DM1 alone: thrombocytopenia
- AEs leading to treatment discontinuation:
  - ONT-380 + T-DM1: ALT/AST increase (n = 1); hematoma (n = 1); Grade 1 heart failure/asymptomatic LVEF decrease (n = 1); intermittent vomiting (n = 1)
  - ONT-380 alone: ALT/AST increase (n = 1)
  - T-DM1 alone: pulmonary infiltrate (n = 2); ALT/AST (n = 1); Grade 1 heart failure/asymptomatic LVEF decrease (n = 1)

Safety Overview for Patients Treated at ONT-380 MTD

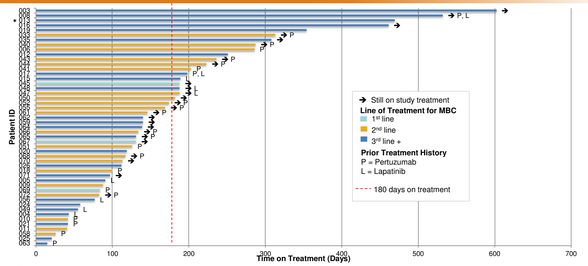
- Majority of AEs Grade 1 in severity
- Most common AEs (reported in >20% of patients) regardless of study drug relationship were nausea, fatigue, diarrhea, vomiting, thrombocytopenia, ALT/AST elevation, decreased appetite, constipation, and hypokalemia
  - Grade 3 clinical (non-laboratory) AEs reported as related to ONT-380 included fatigue (n = 2); and pneumonia, vomiting, and diarrhea (n = 1 each)
  - 2 events of asymptomatic LVEF decrease (reported as Grade 1 heart failure) in patients with prior history of trastuzumab and pertuzumab treatment
- Most lab abnormalities Grade 1 or 2 in severity
  - Most common ≥Grade 3 lab abnormalities were decreased platelets (n = 18); decreased phosphorus (n = 12); elevated ALT/AST (n = 10); decreased lymphocytes (n = 7); and decreased potassium (n = 6)
- All ≥Grade 3 ALT/AST elevations reversible with dose interruption, except in setting of progressive liver disease
  - Majority of patients able to resume treatment with reduced dose ONT-380 and/or T-DM1

Best Overall RECIST 1.1 Response at ONT-380 MTD

Best response	ONT-380 + T-DM1		
	MTD Cohort (n = 31)	300 mg CNS Exp (n = 19)	300 mg Total (n = 50)
Evaluable patients, n (%)	30	18	48[a]
Patients with non-target lesions only	10	4	14
Non-CR/Non-PD	10	4	14
Patients with measurable lesions	20	14	34
cPR (ORR)	9/20 (45%)	5/14 (36%)	14/34 (41%)
SD	7	8	15
PD	4	1	5
CBR[b] (defined as CR or cPR, or SD or non-CR/non-PD for ≥6 months)	15/25 (60%)	8/14 (57%)	23/39 (59%)

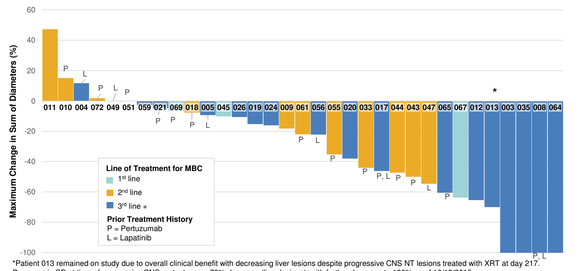
[a] Two patients without follow-up scans due to reasons unrelated to AE or PD
[b] Not including patients with SD active on study for <6 months

Time on Treatment: Patients Treated at ONT-380 MTD



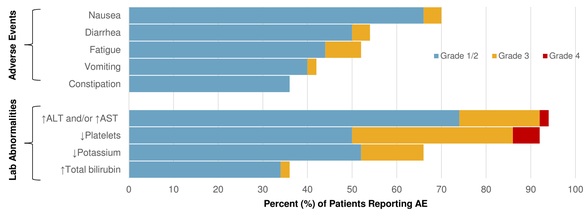
*Patient 013 remained on study due to overall clinical benefit in opinion of treating physician with decreasing liver lesions despite progressive CNS NT lesions treated with XRT at day 217

Maximal Change in Measurable Disease at ONT-380 MTD



*Patient 013 remained on study due to overall clinical benefit with decreasing liver lesions despite progressive CNS NT lesions treated with XRT at day 217. Decrease in SD at time of progressive CNS metastases = 70% decrease (liver lesions), with further decrease to 100% as of 10/12/2015

Selected AEs at ONT-380 MTD (Regardless of Relationship to Study Drug)

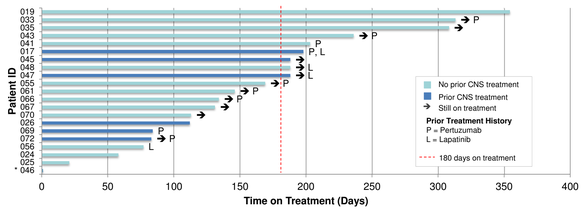


Best CNS Response at ONT-380 MTD

	ONT-380 Dose + T-DM1		
	MTD Cohort (n = 31)	300 mg CNS Exp (n = 19)	300 mg Total (n = 50)
Patients with response-assessable CNS metastases (untreated or progressive after treatment) (n)	2	18[a]	20
Patients with non-target CNS lesions only at baseline (n)	0	7	7
Non-CR/non-PD (n)	0	7	7
Patients with measureable CNS target lesions at baseline (n)	2	11	13
No f/u CNS scan (n)	0	1	1
Overall CNS response rate	0/2	4/10	4/12 (33%)
CR (n)	0	1	1
cPR (n)	0	3	3
SD (n)	2	6	8
PD (n)	0	0	0
CNS CBR[b] (not including active patients with SD <6 months)	2/2 (100%)	7/12 (58%)	9/14 (64%)

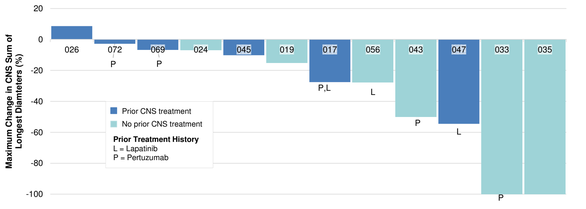
[a] 1 patient withdrawn prior to first follow-up scan for reason other than AE or PD
[b] CBR = CR, cPR, or SD (or non-CR/non-PD) ≥6 months; denominator includes one patient with no f/u CNS scan due to AE

Time on Treatment: Patients with Assessable CNS Metastases



* Patient 046 withdrawn prior to first follow-up scan for reason other than AE or PD

Maximum Change in SLD of CNS Lesions



Summary and Conclusions

The combination of ONT-380 and T-DM1 in this Phase 1b study demonstrates encouraging anti-tumor activity in a high-risk patient population

- Clinical benefit in patients with progressing HER2+ MBC, including those with CNS metastases
  - ORR 41%
  - Median PFS not yet reached
  - Clinical benefit rate 59%; CNS clinical benefit rate 64%
- High-risk patient population
  - 60% of patients with any history of CNS metastases
  - 42% of patients with untreated or progressive CNS metastases
  - Median of 2 prior non-hormonal therapies for MBC
    - 46% of patients with prior pertuzumab
- Combination was well-tolerated
  - Majority of AEs were Grade 1, with most dose reductions due to asymptomatic reversible lab abnormalities

References

[1] O'Sullivan et al. *Curr Breast Canc Rep.* 2014;6(3):169-182; [2] Peddi et al. *Ther Adv Med Oncol.* 2014;6(5):202-209; [3] Moulder et al. AACR-NCI-EORTC 2011; [4] Koch et al. AACR 2011; [5] Dinkel et al. AACR 2012; [6] Borges et al. AACR Special Conf. on Advances in Breast Cancer Research 2013; [7] Kadcyla® package insert. 2015; [8] NCCN Breast Cancer Guidelines. V3.2015; [9] Bartsch et al. *N Neurooncol.* 2014;116(1):205-206; [10] Piccart. ASCO 2013. Oral Presentation; [11] ClinicalTrials.gov. NCT01983501

* Kadcyla® is a registered trademark of Genentech, Inc.

All data presented from an unlocked database as of October 12, 2015 and subject to change.

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