A Phase 1b Study of ONT-380, an Oral HER2-Specific Inhibitor, in Combination with Capecitabine (C) and Trastuzumab (T) in 3rd Line+ Treatment of HER2+ Metastatic Breast Cancer (MBC)

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ASCO Abstract/Poster No. 602

ONT-380 Background

- ONT-380 is a HER2 selective small molecule tyrosine kinase inhibitor with nanomolar potency
  - ONT-380 is 500-fold more selective for HER2 versus EGFR
  - HER2 IC_{50}: 8 nM; EGFR IC_{50}: 4000 nM
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- Highly active in tumor models of HER2+ disease
  - Synergy with trastuzumab and chemotherapy
  - Improved survival compared to either lapatinib or neratinib in a preclinical model of CNS disease[a]
- In a Phase 1 single-agent study, associated with anti-tumor activity with no treatment-related Grade 3 diarrhea in heavily pre-treated patients[b]
  - Dose limiting toxicity (DLT) = reversible Grade 3 ALT/AST elevations
- Based on potential for increased anti-tumor activity with dual blockade of HER2 as well as synergy with chemotherapy, ONT-380 is being evaluated in a Phase 1b study in combination with capecitabine (C) and trastuzumab (T)
- Parallel 3+3 dose escalation of ONT-380 in combination with either C alone or T alone, followed by evaluation in combination with both C and T
  - Initial safety, PK, and anti-tumor activity of ONT-380 at 300 mg PO BID combined with either C or T presented at SABCS 2014
    - No observed drug-drug interaction with capecitabine
  - Updated data now presented here

[a] Dinkel et al, AACR 2012
[b] Borges et al, AACR Special Conference on Advances in Breast Cancer Research 2013

Study Overview

Selected Study Objectives

- Evaluate safety of ONT-380 in combination with C and T
- 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 T-DM1 for metastatic disease
- Prior treatment with small molecule HER2 inhibitor (including lapatinib) allowed

Selected Eligibility Criteria

- **Inclusion**
  - Target or non-target lesions per RECIST 1.1
  - ECOG 0 or 1
  - Total bilirubin ≤1.5 × ULN
  - ALT and AST ≤2.5 × ULN (<5 × ULN if liver metastases present)
  - Normal LVEF
- **Exclusion**
  - Prior exposure to cumulative doxorubicin dose (or equivalent) >360 mg/m^2
  - Prior treatment with capecitabine (for capecitabine containing cohorts only)
- **CNS disease:**
  - Untreated asymptomatic metastases *or* progressive metastases after prior whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) allowed

Treatments

- 21-day cycle
- ONT-380 300 mg PO BID (no food restrictions)
- Capecitabine 1000 mg/m^2 BID Days 1-14
- Trastuzumab 8 mg/kg IV Cycle 1 Day 1, then 6 mg/kg q 21 days starting Cycle 2
- Dose reductions of ONT-380 and capecitabine permitted
- Prophylactic anti-diarrheal medication not required

Study Assessments

- Safety: labs, physical exam, LVEF by MUGA or ECHO
- Anti-tumor activity: RECIST 1.1 every 2 cycles through Cycle 6, every 3 cycles thereafter
- PK analyses from capecitabine-containing cohorts (presented previously)

ONT-380 is being developed by Oncothyreon under a licensing agreement with Array Biopharma

Results

Patient Characteristics

	ONT-380 +		
	C (n = 7)	T (n = 13)	C + T (n = 12)
Age, median (range)	54 (38-70)	49 (35-67)	48 (36-67)
ECOG 0/1 (n)	3/4	5/8	8/4
Hormone receptor positive (n)	5	10	8
# of prior nonhormonal systemic Tx for metastatic disease, median (range)	3 (2-7)	4 (2-9)	3 (2-6)
Trastuzumab (n)	7	13	12
Pertuzumab (n)	4	6	7
T-DM1 (n)	7	12	12
Lapatinib (n)	3	12	4
CNS metastases (n)	2	11	6
Prior treatment for CNS metastases (n)	2	11	4

Patient Disposition

	ONT-380 +		
	C (n = 7)	T (n = 13)	C + T (n = 12)
Patients active on treatment (n)	0	4	7
Patients off treatment (n)	7	9	5
Radiographic PD	5	5	4
Clinical PD	1	1	0
Physician Decision	1	2	0
Patient Decision	0	1	0
Adverse Event	0	0	1

Dose Reductions and Discontinuations

	ONT-380 +		
	C (n = 7)	T (n = 13)	C + T (n = 12)
Patients requiring dose reduction of:			
ONT-380	2	0	2
Capecitabine	5	n/a	6
Patients requiring discontinuation of:			
ONT-380	0	0	0
Capecitabine	0	n/a	1
Trastuzumab	0	0	0

ONT-380 Safety Overview[a]

- Majority of AEs Grade 1 or 2 in severity; no Grade 3 diarrhea
- Most common AEs overall (in ≥5 pts)
  - Diarrhea, nausea, constipation, fatigue, palmar-plantar erythrodysesthesia syndrome (PPE), vomiting, headache, dyspepsia, dizziness, hot flush, and arthralgia
- 11 SAEs overall
  - 10 SAEs considered unrelated to study drugs
  - 1 SAE in pt treated with ONT-380 300 mg BID + C + T considered related to both ONT-380 and capecitabine
    - Reversible Gr 4 edema at site of pre-existing untreated asymptomatic thalamic metastasis; considered possible treatment effect
    - Considered a DLT; no other DLTs on study
- No significant changes in LVEF

[a]ONT-380 300 mg BID

Most Common AEs* by Study Treatment

	ONT-380 +					
	C (n = 7)		T (n = 13)		C + T (n = 12)	
Adverse Events	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Diarrhea	5	0	8	0	8	0
Nausea	4	0	3	0	7	0
Constipation	4	0	5	0	2	0
Fatigue	5	0	1	0	4	0
PPE	4	1	0	0	6	0
Vomiting	2	0	2	0	4	0
Selected Laboratory Toxicities						
↑ALT	5	1[a]	6	0	8	1[b]
↑AST	6	1[a]	10	0	11	1[b]
↑Total bilirubin	3	0	4	0	7	1[c]

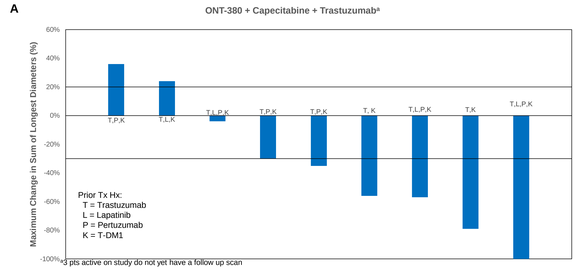
*No Grade 4 or 5 AEs among most common AEs; 1 event each of Gr 4 cerebral edema (DLT); cardiac arrest (unrel); and breast infxn (unrel)
[a]Occurred during Cycle 3. Patient continued on study for 346 days with SD following dose reductions of ONT-380 to 150 mg BID and capecitabine to 750 mg/m^2
[b]Occurred during Cycle 2. Patient remains on study after 13 cycles with a cPR following dose reductions of ONT-380 to 150 mg BID and capecitabine to 750 mg/m^2
[c]Noted on patient's off-study visit; pt with progression in liver.

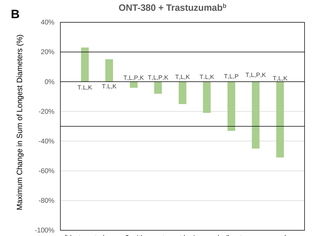
Anti-Tumor Activity

	ONT-380 +		
	C (n = 7)	T (n =13)	C + T (n = 12)
Best overall response (RECIST 1.1)			
Evaluable patients, (n)	7	11	9
CR	0	1	1
cPR	5	3	4
SD or non-CR non-PD	2	5	2[a]
PD	0	2	2
Too early to evaluate	0	2	3

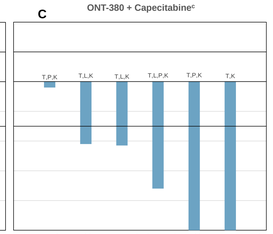
[a]Includes pt with unconfirmed PR without follow-up scan

Best Response in Measurable Disease





[b]4 pts not shown: 2 with non-target lesions only (best responses: 1 non-CR/non-PD, 1 CR), and 2 active on study who do not yet have a follow up scan

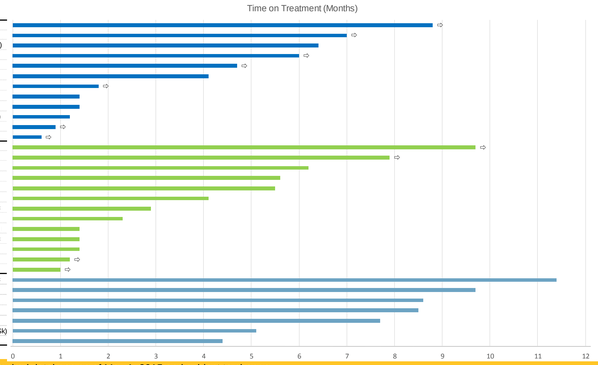


[c]1 pt not shown with non-target lesions only and best response of non-CR/non-PD

Patient Summaries and Time on Treatment

Treatment Group	Pt ID	Disease Characteristics & Prior Treament: Time Since Met Dx (Years)	HR	# Prior Nonhormonal Metastatic Tx	Prior HER2 Treatment	Last Treatment: Regimen	Duration (months)	On Study: PS	Sites of Disease	Evaluable CNS Mets	Time on Treatment (months)	Best Response	Status
ONT-380 + C + T	021	2	-	2	T,K	K	8	0	Br; Lu; Liv; Bo; LN	N	8.9	cPR	Active
	027	2	+	6	T,K	K	7	0	Lu; Bo; LN	N	7.1	cPR	Active
	023	2	-	3	T,P,K	lip dox	3	0	Br; Lu; LN	N	6.5	cPR	PD (LuBo)
	031	5	+	5	T,L,P,K	T, P	6	0	Lu; Liv; Bo; Sk; LN	N	6.1	cPR	Active
	041	5	+	5	T,L,P,K	L,cabaz	4	1	Br; Liv; Bo	Y	4.8	SD	Active
	032	1	-	3	T,L,P,K	L, entin	7	1	Sk; LN	N	4.2	CR	PD (Sk)
	046	1	+	3	T,P,K	K	7	0	Liv; Bo; LN	N	1.8	ND	Active
	022	7	+	5	T,L,K	L,T, entin	8	0	Br; Lu; Liv; Bo; LN	Y	1.4	PD	PD (Liv)
	028	1	-	3	T,P,K	K	2	0	Liv	N	1.4	PD	PD (Liv)
	034	1	+	2	T,P,K	K	7	1	Br; Liv	Y	1.3	uPR	AE (PPE)
	050	5	+	2	T,K	K	5	0	Bo	N	0.9	ND	Active
	048	2	+	2	T,K	K	6	1	Br; Lu; Liv; Bo; LN; Chest wall	Y	0.6	ND	Active
ONT-380 + T	015	2	-	2	T,L,K	K	1	1	Br; Lu; Liv; LN	N	9.8	cPR	Active
	025	14	+	9	T,L,P,K	TPI-287	2	0	Br; Lu; Liv; Bo; LN	Y	8.0	cPR	Active
	006	3	+	6	T,L,K	T, vin	5	1	Br; Lu; LN	N	6.3	SD	PD
	008	6	+	4	T,L,K	K	13	0	Br; Bo; Sk; LN	N	5.7	nCR /nPD	Pt Dec
	009	3	+	3	T,K	K	7	0	Liv; Bo; Sk; LN	N	5.6	CR	PD (LN)
	016	3	+	3	T,L,K	T,L,C	9	1	Br; Lu; LN	N	4.2	SD	PD (Br)
	010	2	+	2	T,L,P	L,C	3	1	Br; Liv; Bo; LN	Y	2.9	cPR	Phys Dec
	024	5	+	7	T,L,P,K	T,nab-pac	8	0	Br; Lu; Liv; Bo; LN	Y	2.3	SD	PD (Lu)
	007	5	+	5	T,L,P,K	T,P	3	0	Br; Liv; Bo; LN; Ov	N	1.4	PD	Clin Prog
	035	2	-	2	T,L,K	K	13	1	Br	Y	1.4	SD	Phys Dec
	019	5	+	6	T,L,K	T, pac	1	1	Br; Liv; Bo; LN	N	1.4	PD	PD
	047	4	-	4	T,L,P,K	T, P	4	1	Br; Lu; Liv; LN	Y	1.3	ND	Active
	049	3	+	6	T,L,P,K	enib	16	1	Sk	N	1.0	ND	Active
ONT-380 + C	003	2	+	2	T,P,K	K	3	0	Lu; LN	N	11.6	SD	Phys Dec
	002	1	+	2	T,P,K	K	4	1	Bo	N	9.8	nCR /nPD	PD (Bo)
	005	1	+	3	T,L,P,K	K	4	0	Bo; LN	N	8.7	cPR	PD (LN)
	001	2	+	4	T,K	cisplat	2	1	Br; Bo	Y	8.6	cPR	PD (Br)
	012	2	-	7	T,L,K	enib	1	1	Lu; LN	N	7.8	cPR	PD (Lu)
	018	3	-	3	T,L,K	T,L	4	1	Bo; Sk	N	5.1	cPR	Clin Prog (Sk)
	017	1	+	2	T,P,K	K	1	0	Br; Lu; Liv; Bo; Sk; LN	N	4.4	cPR	PD (Br)

Abbreviations: capecitabine (C), pertuzumab (P), T-DM1 (K), lapatinib (L) / bone (Bo), brain (Br), liver (Liv), lung (Lu), lymph node (LN), ovary (Ov), skin (Sk)



Summary and Conclusions

- ONT-380 in combination with capecitabine and/or trastuzumab has been well tolerated in patients with advanced HER2+ breast cancer
  - Majority of AEs Grade 1 or 2 in severity
  - No Grade 3 diarrhea, with no mandated anti-diarrheal medication
- Encouraging signs of anti-tumor activity in a heavily pre-treated population
  - Many patients receiving 3rd-line or greater treatment for metastatic disease; >50% with history of CNS metastases
  - Clinical benefit and response seen in patients previously treated with trastuzumab, pertuzumab, T-DM1, and/or lapatinib
- Evaluation of CNS anti-tumor activity ongoing (see ASCO poster 612)
- Based on observed clinical benefit and responses seen, a Phase 2 study to further evaluate the activity of ONT-380 in patients with advanced HER2+ breast cancer is planned

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