Efficacy Results of a Phase 1b Study of ONT-380, a CNS-Penetrant TKI, in Combination With T-DM1 in HER2+ Metastatic Breast Cancer (MBC), Including Patients With Brain Metastases

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ONT-380 Background

- ONT-380 is an orally bioavailable, highly potent HER2 selective tyrosine kinase inhibitor
  - Highly selective for HER2 (IC_{50} 8 nM) > EGFR (IC_{50} >10,000 nM); decreased potential for EGFR-related toxicities (e.g. diarrhea)
  - Active in murine tumor models of HER2+ disease as a single agent and is synergistic in combination with trastuzumab or chemotherapy[1]
  - Superior activity compared to lapatinib or neratinib in preclinical models of HER2+ CNS disease[2]
  - Initial Phase 1 single-agent study showed objective responses with no treatment-related Grade 3 diarrhea[3]
- Randomized Phase 2 study of ONT-380 vs. placebo with capecitabine and trastuzumab is currently enrolling (NCT02614794)
- We report here mature efficacy and safety results of all patients treated in a Phase 1b trial of ONT-380 + T-DM1 at the ONT-380 recommended Phase 2 dose (RP2D)

[1] Koch et al. AACR 2011; [2] Dinkel et al. AACR 2012 ; [3]Borges et al, AACR Special Conference on Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications 2013

Study Overview

Patient Population

- HER2+ MBC with progression after prior therapy with trastuzumab and a taxane, separately or in combination
- Patients with brain mets eligible, including untreated mets or progressive mets after prior treatment
- Prior pertuzumab, lapatinib, or other anti-HER2 TKI permitted

Treatment

- 50 patients treated at ONT-380 RP2D (300 mg BID) + T-DM1 3.6 mg/kg IV q21 days

Activity Assessed Overall and in Subset of Patients With Brain Mets

Analyses in All Patients Treated at RP2D

- Safety variables
- Objective response in patients with measurable disease per RECIST 1.1
- Progression-free survival (PFS)

Subset Analyses in Patients With Brain Mets

- Progression-free survival in patients with vs. without brain mets
- Objective response of brain mets in patients with measurable disease in brain per Modified CNS RECIST 1.1

Baseline Patient Demographics

- Many patients had multiple prior HER2 agents and most patients had brain mets

	Patients Treated at RP2D (N = 50)
Age, median (range)	51 (30-72)
ECOG 0/1, n (%)	20 (40%)/30 (60%)
Hormone receptor positive, n (%)	34 (68%)
Time since metastatic diagnosis (mos), median (range)	20 (1-93)
Prior HER2 agents, median (range)	2 (1-3)
Trastuzumab (n)	50 (100%)
Pertuzumab (n)	23 (46%)
Lapatinib (n)	10 (20%)
Brain Mets	30 (60%)
Stable, treated brain mets (n)	9 (18%)
Untreated brain mets (n)	11 (22%)
Progressive brain mets (n)	10 (20%)

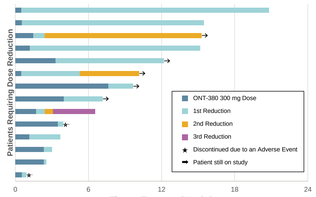
Safety Results

Selected Safety Data

- Safety data were previously reported and the overall safety profile remains unchanged and a detailed summary of safety was presented previously at SABCS 2015[4]
- Majority of AEs were Grade 1
- For patients with brain mets, safety profile was generally consistent with overall population
- Dose reductions of ONT-380 were required in 14/50 patients (28%)
  - Most common reason for ONT-380 dose reduction was elevation of LFTs
- Dose reductions in T-DM1 were required in 19/50 patients (38%)
  - Most common reason for isolated T-DM1 dose reduction was thrombocytopenia
- Drug discontinuations of ONT-380 due to an adverse event (AE) occurred in 5/50 patients (10%); discontinuations of T-DM1 due to AE occurred in 8/50 patients (16%)

[4]Ferrario et al., Poster Session at 38th Annual SABCS, Dec. 8-12, 2015 (P4-14-20)

Most Patients Who Required an ONT-380 Dose Reduction Able to Continue Treatment at Lower Dose



Note: 3 additional patients discontinued due to adverse events but did not have a dose reduction.

Severity of Most Common Adverse Events and LFT Abnormalities

N = 50								
AEs (>40%)					***LFT Abnormalities***				
	Total	**Grade 1/2**	**Grade 3**	**Grade 4**		**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**
Nausea	36 (72%)	35 (70%)	1 (2%)		Incr AST	44 (88%)	37 (74%)	6 (12%)	1 (2%)
Diarrhea	30 (60%)	28 (56%)	2 (4%)		Incr ALT	40 (80%)	32 (64%)	8 (16%)	
Fatigue	28 (56%)	22 (44%)	6 (12%)		Incr Bili	18 (36%)	16 (32%)	2 (4%)	
Headache	22 (44%)	20 (40%)	2 (4%)						
Thrombocytopenia	21 (42%)	7 (14%)	11 (22%)	3 (6%)					
Vomiting	21 (42%)	20 (40%)	1 (2%)						

Abbreviations: Bili = bilirubin; Incr = increased

Overall Efficacy Results

Response Rate and Progression-Free Survival

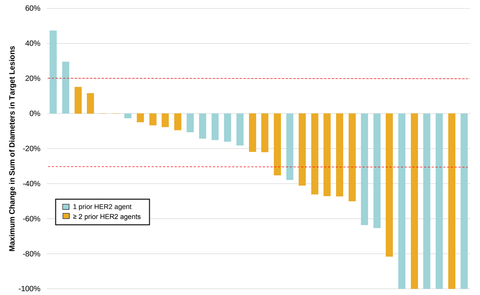
- Objective responses and prolonged stable disease were observed in the overall population
- 34/50 patients (68%) had measurable disease evaluable for response per RECIST 1.1
- Median PFS calculated for all 50 patients, including 16/50 patients (32%) followed for progression of non-measurable disease (e.g. previously radiated or lesions < 1 cm)

Patients with Measurable Lesions	N = 34
Objective Response Rate	16/34 (47%)
Complete Response	1
Partial Response	15
Stable Disease	14 (41%)
Progressive Disease	4 (12%)

All Patients Treated	N = 50
Median PFS (months)	8.2
95% Confidence Interval	(5.1-10.2)
Censored	17
Events	33
Clinical Benefit Rate (SD or non-CR/non-PD ≥6 mos, PR, or CR)	30/50 (60%)

Overall Response in Patients with Measurable Disease

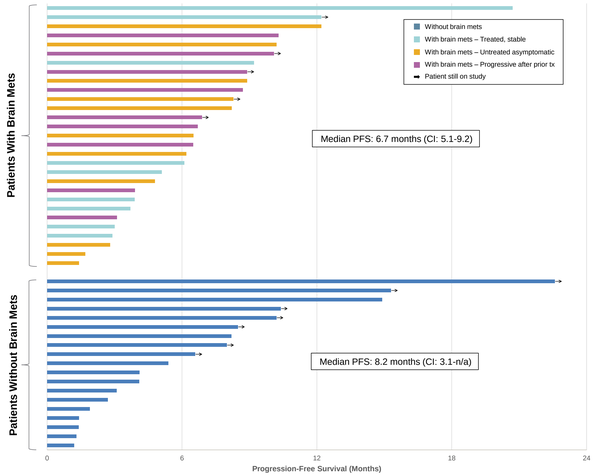
- Similar benefit in patients regardless of number of prior anti-HER2 agents



Subset Analyses in Patients With Brain Mets

Progression-Free Survival in Patients With or Without Brain Mets

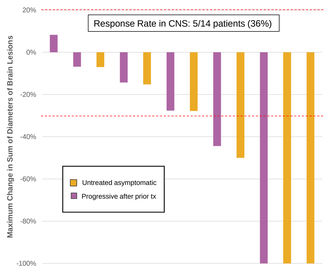
- All study patients had baseline brain MRI
- Patients with brain mets (n=30) underwent serial brain MRI and had the following at baseline:
  - untreated asymptomatic brain mets (n=11)
  - stable treated brain mets (n=9), or
  - brain mets progressive after surgery or radiation (n=10)
- Patients without brain mets (n=20) on baseline MRI did not require a serial brain MRI
- PFS was similar in subset of patients with brain mets (n=30) vs. patients without brain mets (n=20)



Note: 2 patients (one with brain mets and one without) were withdrawn prior to first follow-up scan for reasons other than AE or PD, with censored PFS of 0 days

Response Rates in Measurable Brain Mets per Modified CNS RECIST 1.1

- Of 30 patients with brain mets:14 had measurable brain mets and 16 had non-measurable brain mets
  - Many patients with measurable brain mets had reduction in brain mets regardless of prior CNS treatment, with a CNS response rate of 36%
  - Of the patients with non-measurable brain mets, 10/16 (63%) had stable disease in brain ≥6 months



Note: Two patients with measurable brain mets at baseline had no follow-up brain MRI (one patient with PD systemically and one patient due to patient decision).

Outcome of Patients With Brain Mets

- Many patients with brain mets had long-term control of both brain mets and systemic disease. In the 30 patients with brain mets at baseline:
  - 5 remain active on study without PD
  - 15 with initial control of brain mets eventually developed PD in the brain (+/- systemic PD) but had a median time on treatment of 8 months (range: 3-21 months)
  - 4 are off study for PD outside of the brain only
  - 6 are off study for reasons other than PD
- No patients without brain mets at baseline developed new clinically apparent brain mets while on study

Summary and Conclusions

- Combination of ONT-380 and T-DM1 in this Phase 1b study demonstrates encouraging anti-tumor activity in a high-risk patient population with a median of 2 prior HER2 agents, including almost half treated previously with pertuzumab
  - Objective Response Rate of 47%
  - Median PFS 8.2 months in overall population
- Combination was well tolerated
  - Majority of AEs were Grade 1
  - Most patients who required an ONT-380 dose reduction maintained disease control at lower dose
  - Most common reason for dose reductions of ONT-380 due to reversible lab abnormalities
- Clinical benefit in patients with brain mets
  - Outcomes of patients with brain mets similar to patients without brain mets
  - Response rate of brain lesions 36%, with long-term stable brain mets in many patients
- Study included patients previously treated with pertuzumab and patients with brain mets, which mirrors HER2+ patients seen in clinical practice.
  - Encouraging activity and tolerability warrant further study in these populations.

Acknowledgements: All patients and their families, as well as participating sites.

All data presented are from an unlocked database as of 02 May 2016 and subject to change.

ASCO Abstract/Poster No. 513