Efficacy Results of a Phase 1b Study of Tucatinib (ONT-380), an Oral HER2-Specific Inhibitor, in Combination With Capecitabine and Trastuzumab in HER2+ Metastatic Breast Cancer, Including Patients With Brain Metastases

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Tucatinib Background

- Tucatinib is an orally bioavailable, potent HER2 selective tyrosine kinase inhibitor
  - Selective for HER2 (IC50 8 nM) > EGFR (IC50 >10,000 nM); decreased potential for EGFR-related toxicities (e.g. diarrhea, skin rash)
  - Active in murine HER2+ tumor models as a single agent and synergistic in combination with trastuzumab or chemotherapy[1]
  - Improved outcome compared to lapatinib or neratinib in preclinical HER2+ CNS models[2]
  - Initial Phase 1 single-agent study showed objective responses with no treatment-related Grade 3 diarrhea[3]
  - 172 patients have been treated at the recommended Phase 2 dose (RP2D) of 300 mg BID or above
- This Phase 1b study explored tucatinib in combination with capecitabine and trastuzumab to provide dual HER2 inhibition in conjunction with a cytotoxic agent

[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, taxane, and T-DM1 (unless contraindicated)
- Baseline brain MRIs; patients with brain metastases (mets) eligible, including untreated or progressive brain mets after prior CNS-directed treatment
- Prior pertuzumab or lapatinib permitted

Treatment

- Tucatinib was studied in doublet cohorts in combination with capecitabine or trastuzumab, followed by triplet cohort in combination with capecitabine and trastuzumab
  - Tucatinib 300 mg PO BID (all combinations) or 350 mg PO BID (doublets)
  - Capecitabine (C) 1000 mg/m^2 PO BID for 14 days of a 21-day cycle
  - Trastuzumab (Tz) 8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days
- No anti-diarrheal prophylaxis required

Analyses in all patients treated at RP2D

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

Subset analyses in patients with brain mets

- Outcomes in patients with vs. without brain mets at baseline
- Response of brain mets in patients with measurable disease in brain per Modified CNS RECIST 1.1

Baseline Patient Demographics

	Tucatinib 300 mg BID		
	+ C (N = 7)	+ Tz (N = 18)	+ C + Tz (N = 27)
Age, median (range)	52 (38-70)	46 (35-67)	50 (35-67)
ECOG 0/1, n (%)	3 (43%)/4 (57%)	9 (50%)/9 (50%)	14 (52%)/13 (48%)
Hormone receptor positive, n (%)	5 (71%)	14 (78%)	15 (56%)
# of prior regimens for metastatic disease, median (range)	3 (1-5)	6 (2-13)	3 (0-8)
# of prior HER2 agents, median (range)	2 (2-3)	3 (2-4)	3 (2-4)
Trastuzumab, n (%)	7 (100%)	18 (100%)	27 (100%)
Pertuzumab, n (%)	4 (57%)	9 (50%)	20 (74%)
T-DM1, n (%)	7 (100%)	16 (89%)	27 (100%)
Lapatinib, n (%)	2 (29%)	17 (94%)	10 (37%)
Brain mets, n (%)	2 (29%)	16 (89%)	11 (41%)
Stable, treated mets, n (%)	1 (14%)	7 (39%)	4 (15%)
Untreated mets, n (%)	0	1 (6%)	4 (15%)
Progressive mets after prior tx, n (%)	1 (14%)	8 (44%)	3 (11%)

*2 patients did not have prior T-DM1 due to contraindication

Safety Results

Overall Safety Results

- Tucatinib has an acceptable safety profile at the RP2D (300 mg BID)
- Most (~70%) treatment-emergent adverse events (TEAEs) at the RP2D were Grade 1
- No instances of cardiac failures were reported
- Safety profile consistent with previous studies using tucatinib and known side effects of capecitabine and trastuzumab
- No deaths due to TEAEs

Drug Limiting Toxicities

- 1 DLT of cerebral edema in triplet cohort
- 3 patients had Grade 3 ALT/AST elevations
  - All 3 patients recovered after tucatinib held and treatment resumed after dose reduction
- 3 patients had Grade 3 diarrhea
  - Seen only in capecitabine-containing cohorts and at rates consistent with single agent capecitabine treatment
  - No serious events were observed

Severity of Most Common Adverse Events and LFT Abnormalities

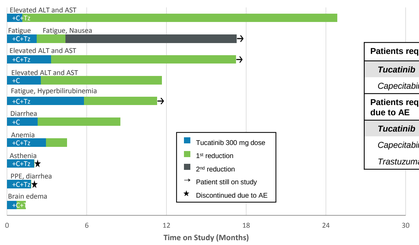
Adverse Events Reported in ≥ 20% Patients in Triplet Cohort	Tucatinib 300 mg BID		
	+ C (N = 7)	+ Tz (N = 18)	+ C + Tz (N = 27)
Diarrhea	5 (71%)	10 (56%)	21 (78%)
Grade 1	4	7	14
Grade 2	1	3	4
Grade 3	0	0	3
Nausea	5 (71%)	6 (33%)	20 (74%)
Grade 1	4	6	13
Grade 2	1	0	7
Grade 3	0	0	0
PPE	5 (71%)	0	18 (67%)
Grade 1	1	0	2
Grade 2	3	0	13
Grade 3	1	0	3
Vomiting	2 (19%)	4 (22%)	13 (48%)
Grade 1	2	2	11
Grade 2	0	1	2
Grade 3	0	1	0
Fatigue	5 (71%)	3 (17%)	11 (41%)
Grade 1	2	2	4
Grade 2	3	1	3
Grade 3	0	0	4

Adverse Events Reported in ≥ 20% Patients in Triplet Cohort	Tucatinib 300 mg BID		
	+ C (N = 7)	+ Tz (N = 18)	+ C + Tz (N = 27)
Decreased appetite	2 (29%)	0	8 (30%)
Grade 1	2	0	4
Grade 2	0	0	4
Grade 3	0	0	0
Upper respiratory tract infection	0	3 (17%)	6 (22%)
Grade 1	0	2	3
Grade 2	0	1	3
Grade 3	0	0	0
LFT Abnormalities			
Increased ALT	5 (71%)	5 (28%)	19 (70%)
Grade 1	3	4	15
Grade 2	1	1	2
Grade 3	1	0	2
Increased AST	6 (86%)	9 (50%)	23 (85%)
Grade 1	3	9	15
Grade 2	2	0	6
Grade 3	1	0	2
Increased Bilirubin	3 (43%)	4 (22%)	14 (52%)
Grade 1	3	3	7
Grade 2	0	1	5
Grade 3	0	0	2

PPE = palmar-plantar erythrodysaesthesia
The following Grade 4 events were reported:
- Tucatinib 300 mg BID + C: cardiac arrest (n = 1) unrelated per investigator
- Tucatinib 300 mg BID + Tz: brain edema (n = 1) unrelated per investigator
- Tucatinib 300 mg BID + C + Tz: breast implant infection (n = 1) unrelated per investigator; brain edema (n = 1) probably related per investigator

Tucatinib Dose Reductions and Discontinuations due to an Adverse Event

In 10 of 52 patients (shown below) treated at RP2D:
- 8 patients had tucatinib dose reductions
- 2 patients discontinued tucatinib treatment due to an adverse event



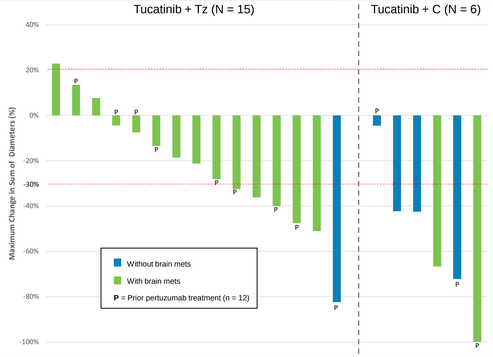
	+ C (N = 7)	+ Tz (N = 18)	+ C + Tz (N = 27)
Patients requiring dose reduction			
Tucatinib	**2**	**0**	**6**
Capecitabine	6	--	17
Patients requiring discontinuation of study drug due to AE			
Tucatinib	**0**	**0**	**2**
Capecitabine	0	--	3
Trastuzumab	--	2	2

Efficacy Results

Best Response in Patients with Measurable Disease

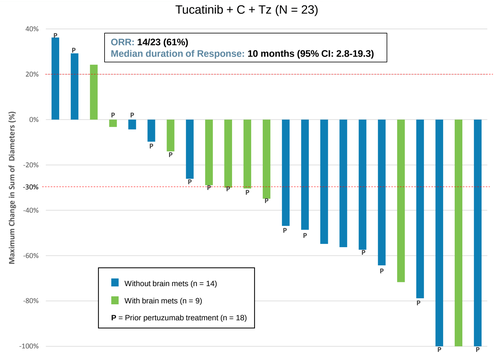
Best Response in Patients with Measurable Lesions	Tucatinib 300 mg BID		
	+ C (N = 6)	+ Tz (N = 15)	+ C + Tz (N = 23)
Objective Response Rate (ORR)	5 (83%)	6 (40%)	14 (61%)
Complete Response (CR)	0	0	1
Partial Response (PR)	5	6	13
Stable Disease (SD)	1 (17%)	7 (47%)	6 (26%)
Progressive Disease (PD)	0	2 (13%)	3 (13%)

Response in Patients with Measurable Disease in Doublet Cohorts



Note: Bars represent change in measurable lesions but some patients also have nonmeasurable lesions. In addition, 3 patients in the Tucatinib + Tz and 1 patient in the Tucatinib + C cohorts had nonmeasurable lesions only and are therefore not able to be represented on the waterfall.

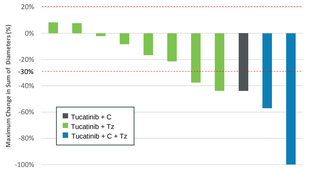
Response in Patients with Measurable Disease in Triplet Cohort



Note: Bars represent change in measurable lesions but some patients also have nonmeasurable lesions. In addition, 4 patients in the Triplet cohort had nonmeasurable lesions only and are therefore not able to be represented on the waterfall.

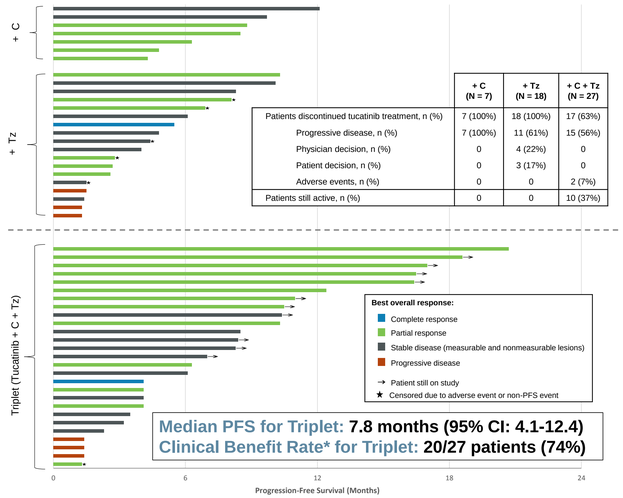
Brain Mets Response by Cohort at RP2D

- 29 of 52 patients with brain mets at baseline:
  - 12 had measurable CNS disease (defined as >1 cm and untreated/progressive), and were evaluable for CNS response, with a response rate of 5/12 (42%)
  - Remaining 17 patients had nonmeasurable lesions only, which were followed for progression, as assessed by PFS



Note: 1 patient had measurable CNS disease at baseline but did not have a follow-up scan

Progression-Free Survival

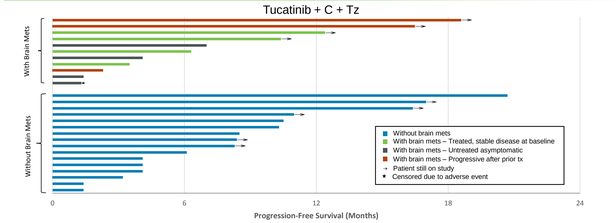


	+ C (N = 7)	+ Tz (N = 18)	+ C + Tz (N = 27)
Patients discontinued tucatinib treatment, n (%)	7 (100%)	18 (100%)	17 (63%)
Progressive disease, n (%)	7 (100%)	11 (61%)	15 (56%)
Physician decision, n (%)	0	4 (22%)	0
Patient decision, n (%)	0	3 (17%)	0
Adverse events, n (%)	0	0	2 (7%)
Patients still active, n (%)	0	0	10 (37%)

Median PFS for Triplet: 7.8 months (95% CI: 4.1-12.4)
Clinical Benefit Rate* for Triplet: 20/27 patients (74%)

* Clinical Benefit Rate is defined as SD ≥6 mos, PR, or CR

Progression-Free Survival in Triplet Cohort by Brain Mets Status



Conclusions

- Combination of tucatinib with capecitabine + trastuzumab was well tolerated
  - Majority of AEs were Grade 1 and majority not requiring dose reduction
- Encouraging anti-tumor activity seen in the triplet combination, in a heavily pre-treated population including those with brain mets
  - Objective Response Rate of 61%
  - Median Duration of Response of 10 months
  - Median PFS 7.8 months overall
  - Clinical Benefit Rate of 74%
- Clinical benefit in patients with brain mets
  - Outcomes of patients with brain mets similar to those without
  - Responses and long-term stable disease seen in patients with brain mets
- Activity and tolerability support the use of this combination in a pivotal randomized trial (HER2CLIMB; NCT02614794)

CASCADIAN THERAPEUTICS

All data presented from an unlocked database as of 10 October 2016 and subject to change.

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