Prolonged Progression-Free Survival (PFS) in Advanced HER2+ Metastatic Breast Cancer with or without Brain Metastases: A Pooled Analysis of Tucatinib Phase 1b Studies

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Background and Study Overview

Clinical Context

- Advances in the treatment of HER2+ breast cancer using sequential HER2 targeted therapies has resulted in overall improvements in outcome
- Nonetheless, treatment of HER2+ metastatic breast cancer (MBC) following trastuzumab, pertuzumab and T-DM1 is therapeutically challenging
- Currently there is no consensus regarding a single standard of care for these patients including those with brain metastases (BM)
  - Up to 50% of patients will develop BM during the course of their disease[a]
- Tucatinib is an investigational, oral, potent, highly selective HER2+ oral tyrosine kinase inhibitor that in combination has shown promising results in the treatment of HER2+ MBC in patients with and without BM with acceptable safety

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Methods

- Two Phase 1b studies of tucatinib, ONT-380-004 and ONT-380-005, were pooled to identify and characterize the subgroup of patients with prolonged PFS
- Prolonged PFS was defined as patients achieving twice the observed median PFS
  - Modeled after the ASCO Framework Guidelines for randomized trials
- Baseline disease characteristics and radiology findings were compared between the subgroup of patients with or without prolonged PFS

Treatment

- Study ONT-380-004: tucatinib + T-DM1 (N=50)
  - Tucatinib 300 mg PO BID
  - T-DM1 3.6 mg/kg IV once every 21 days
- Study ONT-380-005: tucatinib + capecitabine + trastuzumab cohort (N=27)
  - Tucatinib 300 mg PO BID (all combinations)
  - Capecitabine 1000 mg/m2 PO BID for 14 days of a 21-day cycle
  - Trastuzumab 8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days

Assessments

- Brain and body imaging
  - Contrast MRI of brain and CT of chest, abdomen and pelvis was obtained in all patients at baseline
  - In patients with baseline BM, MRI was obtained every 6 weeks for first 6 cycles, then every 9 weeks thereafter
  - In patients without baseline BM, MRI was obtained if clinically indicated
  - In all patients, contrast CT of chest abdomen and pelvis was obtained every 6 weeks for first 6 cycles, then every 9 weeks thereafter
- RECIST 1.1 was used for response assessment

Results

Prolonged PFS Subgroup

- 77 patients were analyzed
  - 50 from the Study 004 (tucatinib + T-DM1)
  - 27 from the Study 005 (tucatinib + trastuzumab + capecitabine cohort)
- Patients received a median of 2 prior therapies including a taxane, trastuzumab, pertuzumab, T-DM1 (Study 005 only), and lapatinib
- Median PFS was
  - 8.2 months in the MTD cohort in Study 004
  - 7.8 months in the triplet cohort in Study 005
- 17 patients (22%) demonstrated PFS ≥ 17 months, operationally defined as a prolonged PFS subgroup
  - 10/50 (20%) from Study 004
  - 7/27 (26%) from Study 005

Prolonged PFS Subgroup Comparison with Baseline Characteristics and Radiology Findings

- No differences were seen in comparing the total population with that of the prolonged PFS cohort in the distribution of
  - presence of brain metastases
  - hormone receptor status (positive or negative)
  - presence of visceral metastases
  - number of prior HER2 regimens
  - time from diagnosis (initial and metastatic) to study initiation
  - metastatic disease burden at diagnosis (LDH, number of target and nontarget lesions, sum of diameters of target lesions)
  - age

Similarity of Demographics by Subgroup

Parameter		PFS < 17 months (N = 60)	PFS ≥ 17 months (N = 17)
Age, median (range)		50 (30-72)	53 (31-65)
ECOG, n (%)	*0*	25 (42%)	12 (71%)
	1	35 (58%)	5 (29%)
Distant metastases, n (%)	*Yes*	59 (98%)	17 (100%)
Hormone receptor status, n (%)	*Positive*	36 (60%)	13 (76%)
	Negative	24 (40%)	4 (24%)
# distinct HER2 therapies, n (%)	*1*	16 (27%)	5 (29%)
	2	27 (45%)	7 (41%)
	3	11 (18%)	4 (24%)
	4	6 (10%)	1 (6%)
Prior pertuzumab therapy		35 (58%)	8 (47%)
Median duration of last prior treatment (months)		6.05	9.03

Similarity of Demographics by Subgroup

Parameter	PFS < 17 months (N = 60)	PFS ≥ 17 months (N = 17)
Elevated LDH	20 (33%)	4 (24%)
Visceral disease, n (%)	43 (72%)	12 (71%)
Measurable disease	48 (80%)	10 (59%)
# of body target lesions, median (range)	2 (0-5)	1 (0-4)
# of body non-target lesions, median (range)	2 (0-10)	2 (0-5)
Total # of body target and non-target lesions, median (range)	4 (1-14)	3 (1-6)
Sum of the diameters of body target lesions, median (range)	38mm (16-157)	42mm (17-66)

Comparability of Brain Metastases Characteristics by Subgroup

- Of the prolonged PFS patients, 41% had baseline BM, comparable to the percentage of all patients entering the trial at baseline (53%)

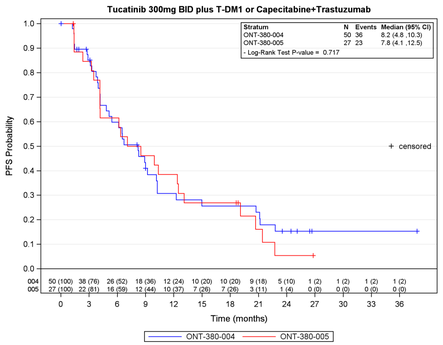
Parameter		Patients with BM	
		PFS < 17 months (N =34)	PFS ≥ 17 months (N = 7)
Hormone receptor status, n (%)	*Positive*	20 (59%)	4 (57%)
Measurable disease in brain		26 (76%)	5 (71%)
# of brain target lesions, median (range)		2 (1-3)	2.5 (2-3)
# of brain non-target lesions, median (range)		2 (1-9)	1 (1-3)
Total # of brain target and non-target lesions, median (range)		3 (1-11)	2.5 (1-4)
Sum of the diameters of brain target lesions, median (range)		34 mm (10-68)	35 mm (11-49)
Time from last brain radiotherapy (months), median (range)		4.6 (0.5-59.6)	13.4 (0.9-21.4)
Number of prior SRS	*1*	6 (18%)	3 (43%)
	2	2 (6%)	1 (14%)
Number of prior WBRT, n (%)	*1*	15 (44%)	2 (29%)
Category of brain metastases			
	Untreated asymptomatic	12 (35%)	1 (14%)
	Treated stable	11 (32%)	2 (28%)
	Treated progressive	11 (32%)	4 (57%)

Subject Disposition at End of Study

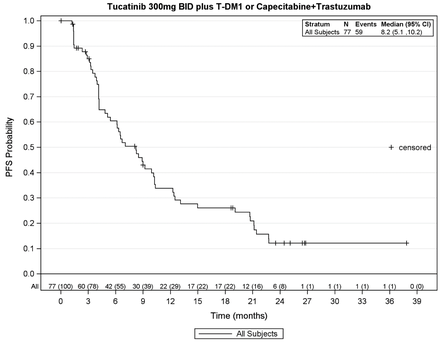
Disposition	< 17 months (N=60)	≥ 17 months (N=17)
Continuing On Study	1 (2%)	10 (59%)
Discontinued due to:		
Progressive Disease	43 (72%)	5 (29%)
Adverse Event	5 (8%)	0
Death	5 (8%)	0
Physician Decision	2 (3%)	1 (6%)
Lost To Follow-Up	2 (3%)	0
Informed Consent Withdrawn	1 (2%)	0
Other	0	1 (6%)
Subject Decision To Discontinue Treatment	1 (2%)	0

Efficacy Results

Similar PFS in Studies ONT-380-004 and ONT-380-005



Pooled Analysis of Progression-Free Survival in Patients Treated at 300 mg BID



Conclusions

- 22% of patients treated with tucatinib in combination for late stage MBC demonstrate prolonged PFS defined as ≥ 17 months, representing a significant subgroup of patients who have extended disease control
- Patient characteristics such as hormone receptor status, presence of visceral disease, burden of disease, and age, often predictive for limited survival, were not predictive of prolonged PFS on tucatinib
- Baseline BM did not differentiate patients who achieved prolonged PFS, although the presence of BM historically has negatively impacted PFS
- Further molecular characterization of the prolonged PFS cohort may help to identify this patient group
- These data support the evaluation of tucatinib in patients with and without BM in the accruing HER2CLIMB pivotal trial

All data presented from an unlocked database as of 05 September 2017 and subject to change.

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