Progression-Free Survival (PFS) and Site of First Progression in HER2+ Metastatic Breast Cancer (MBC) Patients with or without Brain Metastases: A Pooled Analysis of Tucatinib Phase 1 Studies

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Clinical Context and Tucatinib Background

- Despite improvements in outcome in patients with HER2+ breast cancer, metastatic disease develops in ~ 30%[a]
- In patients with metastatic HER2+ breast cancer, up to 50% develop brain metastases (BM)[b]
- Historically, patients with BM have poorer prognosis than patients without BM[c]
- Current HER2 targeted agents have limited impact on treatment of BM due to restricted entry or rapid receptor-mediated efflux
- There is an unmet medical need for HER2 targeted therapies that are active both systemically and in the brain

Tucatinib is an investigational, orally bioavailable, highly potent HER2 selective tyrosine kinase inhibitor

- Designed to be highly selective for HER2
- Superior activity compared to lapatinib or neratinib in preclinical models of HER2+ brain metastases[d]

a Goldhirsch et al. Lancet. 2013; b Lin Cancer 2013; c Brufsky et al. Clin Cancer Res 2011; d Dinkel et al. AACR 2012

Study Overview

Data from 2 Phase 1b combination studies of tucatinib (ONT-380-004 and ONT-380-005) were pooled to analyze baseline characteristics and outcomes of patients with and without BM

Patient Characteristics

- Patients with HER2+ metastatic breast cancer previously treated with taxane (both studies), trastuzumab (both studies), and T-DM1 (ONT-380-005 only)
- All patients were screened for BM with baseline contrast brain MRI
- All patients were required to have minimal symptoms related to BM
  - If CNS-directed therapy was required, patients treated with radiotherapy before first study treatment

Treatment

- Study ONT-380-004: tucatinib + T-DM1
  - Tucatinib 300 mg PO BID
  - T-DM1 3.6 mg/kg IV once every 21 days
- Study ONT-380-005: tucatinib +/- capecitabine +/- trastuzumab
  - Tucatinib 300 mg PO BID (all combinations)
  - Capecitabine 1000 mg/m^2 PO BID for days 1-14 of a 21-day cycle
  - Trastuzumab 8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days

Assessments

- Brain imaging
  - Contrast MRI 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
- RECIST 1.1 was used for response assessment

Methods

- Based upon historical data suggesting different prognoses, data from both Phase 1b studies were pooled and 4 subgroups of patients were identified retrospectively:
  - No brain metastases
  - Untreated asymptomatic
  - Treated stable*
  - Treated progressive*
- The four subgroups were then compared with respect to baseline characteristics, progression-free survival (PFS), and site of progression
- The safety profiles of these tucatinib studies have previously been shown to be similar in patients with vs without BM[e]

* "Treated" means CNS-directed radiation or surgery; e Murthy et al. SABCS 2015

Results: Comparative Characteristics

Patient Subgroups by Categories of Brain Metastases

Subgroups	Number of Patients (N = 77)
No brain metastases	36 (47%)
Brain metastases	41 (53%)
Untreated Asymptomatic	*13 (17%)*
Treated Stable	*13 (17%)*
Treated Progressive	*15 (19%)*

Demographics by Subgroup

Parameter		No BM (N = 36)	Untreated Asymptomatic (N = 13)	Treated Stable (N = 13)	Treated Progressive (N = 15)
Age, median (range)		49.5 (31-67)	53 (30-72)	47 (36-71)	53 (36-67)
ECOG, n (%)	*0*	17 (47%)	8 (62%)	7 (54%)	5 (33%)
	1	19 (53%)	5 (38%)	6 (46%)	10 (67%)
Race, n (%)	*White*	27 (75%)	8 (62%)	12 (92%)	13 (87%)
	Asian	6 (17%)	1 (8%)	0	0
	Black/African American	3 (8%)	4 (31%)	1 (8%)	1 (7%)
	Unknown	0	0	0	1 (7%)
Hormone Receptor (HR), n (%)					
	Positive	25 (69%)	9 (69%)	5 (38%)	10 (67%)
	Negative	11 (31%)	4 (31%)	8 (62%)	5 (33%)

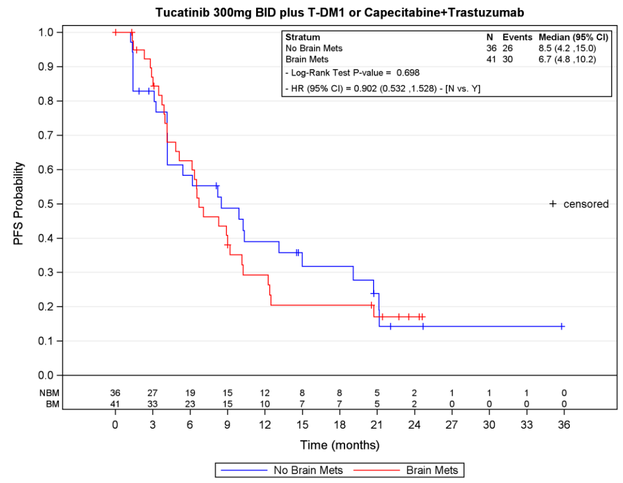
Comparability of Brain Metastases Characteristics by Subgroup

Parameter	No BM (N = 36)	Untreated Asymptomatic (N = 13)	Treated Stable (N = 13)	Treated Progressive (N = 15)
Total # of target and non-target brain lesions, median (range)	0	2 (1-8)	2 (0-8)	2 (1-7)
Sum of diameters – target brain lesions (mm), median (range)	0	27.5 (10-68)	0	35 (11-59)
Last prior radiotherapy for BM, n (%)				
Whole brain	0	0	5 (38%)	9 (60%)
SRS	0	0	7 (54%)	6 (40%)
None	36 (100%)	13 (100%)	1 (8%)[a]	0
Time from last brain radiation (months), median (range)	0	0	1.5 (0.5-59.6)	8.3 (1.1-28.2)
# prior SRS, n (%)[b]				
0	0	0	6 (46%)	9 (60%)
1-3	0	0	7 (54%)	6 (40%)
# prior whole brain irradiation, n (%) [b]				
0	0	0	6 (46%)	4 (32%)
1-2	0	0	7 (54%)	11 (73%)
Both procedures, n (%)[b]				
Yes	0	0	2 (15%)	2 (13%)
No	0	0	10 (77%)	13 (87%)

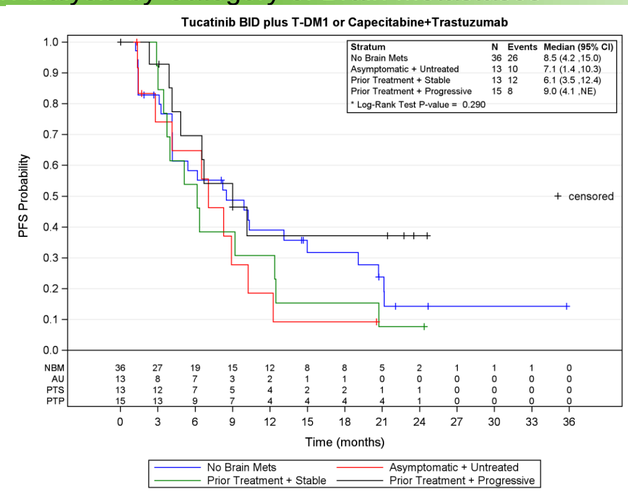
Abbreviations: # = number; BM = brain metastases; SRS = stereotactic radiosurgery; a = lesionectomy only; b = not mutually exclusive

Efficacy Results

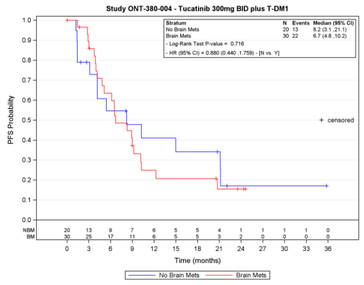
Similar PFS in the Pooled Analysis of Patients With and Without Brain Metastases

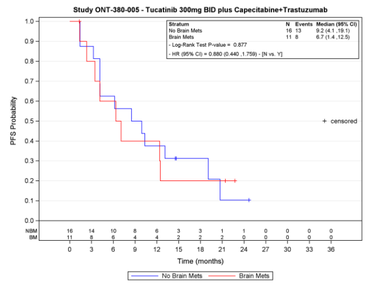


PFS in the Pooled Analysis by Category of Brain Metastases



Similar PFS by Study Comparing Patients With and Without Brain Metastases





Source of PFS or Non-PFS Events

Source of PFS or Non-PFS Events	No Baseline BM (N = 36)	With Baseline BM (N = 41)
# with PFS events – Total, n (%)	27 (75%)	31 (76%)
Radiographic	*26 (72%)*	*28 (68%)*
Death due to progression	*0*	*2 (5%)*
Clinical progression only	*1 (3%)*	*1 (2%)*
# without PFS events – Total, n (%)	9 (25%)	10 (24%)
Active on study	*5 (14%)*	*5 (12%)*
Censored	*4 (11%)*	*5 (12%)*

Site of Progression is Different Between Patients With and Without Brain Metastases

Site of Progression	No Baseline BM (N = 36)	With Baseline BM (N = 41)
# Radiographic PFS Events, n (%)	26 (72%)	28 (68%)
Site of Progression, n (%)		
Brain only	3 (8%)	17 (41%)
Body only	23 (64%)	7 (17%)
Brain and body	0 (0%)	4 (10%)

Summary and Conclusions

- Patients with BM are often excluded from clinical trials, particularly if untreated or treated progressive BM, due to expected poor outcomes
- However, patients with BM in pooled tucatinib studies have similar PFS to patients without BM, including patients with untreated or progressive treated BM
- Baseline characteristics in the 4 subgroups analyzed were not differentiating
- Patients with vs. without BM differ only in the site of disease progression
  - Patients with baseline BM are more likely to progress in brain than those without
  - Patients with BM still frequently progress extracranially, emphasizing the continued importance of systemic disease control in patients with BM
- These results support the further study of tucatinib in patients with BM, including those with untreated BM or progressive BM after radiation
  - Patients with BM are included in the ongoing registrational HER2CLIMB trial, a randomized study of patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1. Patients are treated with capecitabine and trastuzumab in combination with tucatinib vs. placebo

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All data presented from an unlocked database as of 28 June 2017 and subject to change.