

# ONT-380 in the Treatment of HER2+ Breast Cancer Central Nervous System (CNS) Metastases (Mets)

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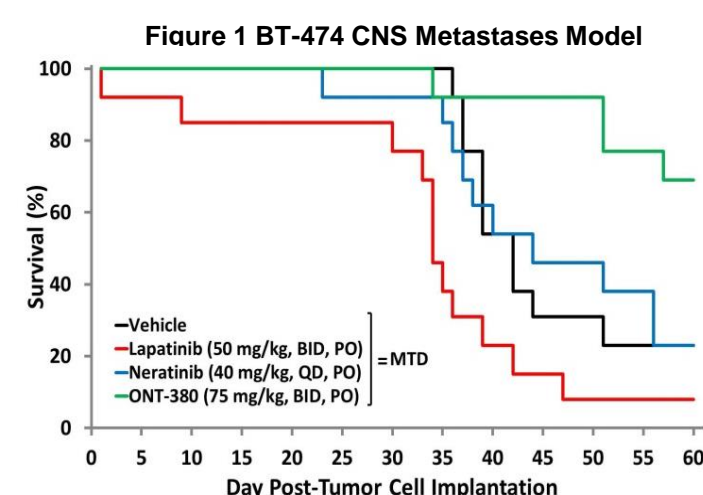
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Abstract/Poster No. 612

## Background

- ONT-380 is a HER2 selective small molecule tyrosine kinase inhibitor with nanomolar potency
  - 500-fold more selective for HER2 compared to EGFR
  - HER2 IC<sub>50</sub>: 8 nM; EGFR IC<sub>50</sub>: 4000 nM
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- In a model of HER2+ CNS metastases, ONT-380 was associated with improved survival compared to either lapatinib or neratinib (Figure 1)
- ONT-380 is currently being evaluated in two ongoing phase 1b combination studies (+ T-DM1 and ± capecitabine [C] ± trastuzumab [T])
- Here we present data from patients in these two studies with response-evaluable CNS metastases treated with ONT-380 300 mg PO BID



Dinkel et al, AACR 2012

## Case Series Description

Patients with response-evaluable CNS metastases were selected for inclusion in this case series from the following ongoing phase 1b studies:

- ONT-380-004: Phase 1b, open-label study of ONT-380 + ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1)
  - Population: Patients with HER2+ breast cancer with progression after prior therapy with both trastuzumab and a taxane
- ONT-380-005: Phase 1b, open-label study of ONT-380 ± C and ± T
  - Population: Patients with HER2+ breast cancer with progression after prior therapy with both T and T-DM1

## Selection of Patients for Case Series

- 22 out of 68 patients had response-evaluable CNS metastases

	ONT-380				Total
	+ T-DM1	+ C	+ T	+ C + T	
Patients enrolled (n)	36	7	13	12	68
No history of CNS metastases (n)	14	5	2	6	27
Stable treated CNS metastases (n) (not evaluable for CNS response)	10	1	6	2	19
Response-evaluable for CNS metastases (n)	12	1	5	4	22
Untreated asymptomatic (n)	6	0	0	2	8
Progression after prior CNS treatment (n)	6	1	5	2	14

- CNS metastases were considered response-evaluable if they met either of the following criteria:
  - Untreated, asymptomatic lesions in patients who had never received radiotherapy or surgery to the CNS
  - Progressive or new lesions in patients who had received radiotherapy and/or surgery to the CNS
- Groups analyzed separately based on data suggesting lower CNS response rates to systemic treatment in previously irradiated patients
- Previously irradiated lesions that did not have obvious progression were not considered response evaluable

## Study Treatments and Assessments

- All patients treated with ONT-380 300 mg BID plus: T-DM1 (3.6 mg/kg IV q 21 d), C (1000 mg/m<sup>2</sup> PO BID D1-14), T (8 mg/kg C1D1; 6 mg/kg q 21 d); or C + T
  - Dose reductions of ONT-380, T-DM1, and C permitted
  - No mandatory prophylactic anti-diarrheal medication
- Safety evaluations including physical exam and labs performed weekly for the first 6 wks, then q 3 wks
- LVEF by MUGA or ECHO q 3 mos
- CT scans and brain MRI at baseline and q 6 wks through cycle 6, then q 9 wks
  - Overall response assessment and treatment decisions per RECIST 1.1
  - CNS response defined as ≥ 30% decrease in sum of the longest diameter (SLD) of CNS target lesions (target lesions must be ≥ 1 cm)
  - CNS progression defined as ≥ 20% increase from nadir and ≥ 5 mm absolute increase in the SLD of all target lesions, or unequivocal progression in non-target lesions

## Patient Characteristics

	ONT-380			
	+ T-DM1 (n = 12)	+ C (n = 1)	+ T (n = 5)	+ C + T (n = 4)
Age, median (range)	57 (30-71)	55	47 (35-67)	48 (45-67)
ECOG 0/1 (n)	6/6	0/1	2/3	1/3
Hormone receptor positive (n)	8	1	3	4
Number of prior nonhormonal systemic treatments for metastatic disease, median (range)	2 (0-5)	4	4 (2-9)	4 (2-5)
Trastuzumab (n)	7	1	5	4
Pertuzumab (n)	4	0	4	2
T-DM1 (n)	0	1	4	4
Lapatinib (n)	1	0	5	2

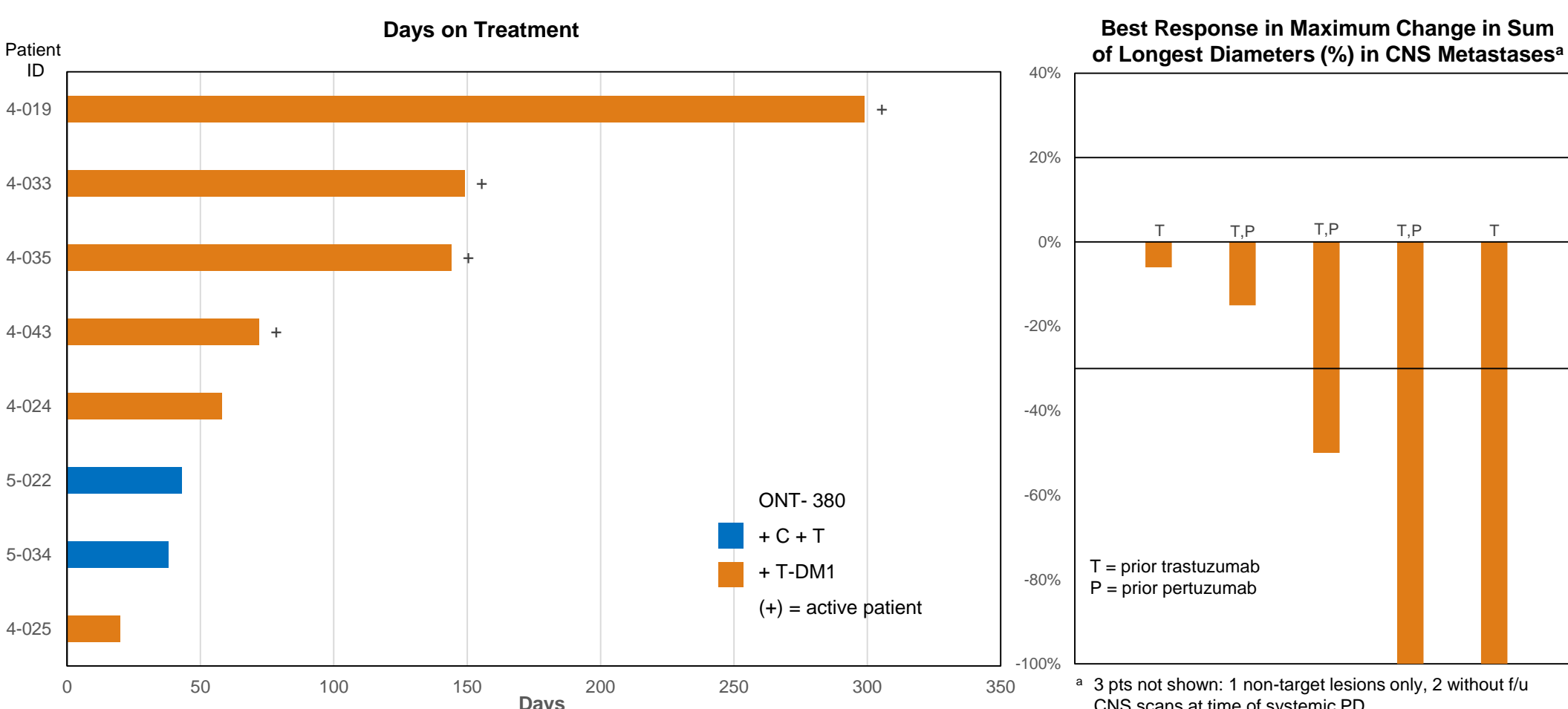
## Safety Overview

- Majority of AEs Grades 1 or 2 in severity, with no Grade 3 diarrhea
  - Most common AEs across both studies (≥ 4 patients overall): diarrhea, nausea, fatigue, constipation, dyspepsia, headache, abdominal pain, GERD, blurred vision, and vomiting
- 7 SAEs overall
  - 1 related SAE of reversible Grade 4 edema at site of untreated asx thalamic metastasis; considered possible treatment effect
  - 6 SAEs considered unrelated to study treatment: seizures (n = 2); visual field defect, loss of coordination, confusion, and respiratory distress (n = 1 each)
- Lab abnormalities included asx, reversible ALT and/or AST elevations, majority Grades 1 or 2
  - 2 pts treated with ONT-380 + T-DM1 with Grade 3 AST and/or ALT
- No significant changes in LVEF

## Patient Summaries: Untreated/Asymptomatic CNS Metastases

Treatment	ID	Disease Characteristics & Prior Treatment				On Study								
		Yrs Since Met Dx	HR	# Prior Nonhorm Tx for Met	Prior HER2 Tx	Regime (mos)	PS	Sites of Disease	Time on Tx (mos)	Best Response Max Δ in CNS SLD Absolute (mm)	%	Best CNS Response	Status	
ONT-380 + T-DM1	4-019	2	+	2	T,P	C + T	3	1	Br; Lu; Bo; LN	10.0	33 → 28	-15%	CNS SD	Active
	4-033	1	+	1	T,P	T+P+doc	11	0	Br; Lu; Bo	5.0	10 → 0	-100%	CNS CR	Active
	4-035	3	-	3	T	pac+T	6	1	Br; Lu; Bo; LN; Pericard eff	4.8	22 → 0	-100%	CNS PR (persistent non-targets lesions)	Active
	4-043	1	-	1	T,P	T+P+doc	7	0	Br; Bo	2.4	10 → 5	-50%	CNS PR	Active
	4-024	3	+	5	T	T + gem	4	1	Br; Liv; Bo	1.9	29 → 27	-6%	CNS SD	Pt with pneumocystis pneumonia; off study Phys Dec
ONT-380 + C + T	5-034	1	+	2	T,P,K	K	7	1	Br; Liv	1.3	< 1 cm only; unchanged after 2 cycles	N/A	CNS SD	AE (PPE)
	5-022	7	+	5	T,L,K	L + entin+T	8	0	Br; Lu; Liv; Bo; LN	1.4	< 1 cm non-target lesion	CNS NE	CNS NE	PD in liver after drugs held for SAE

Abbreviations: brain (Br); bone (Bo); capecitabine (C); ado-trastuzumab emtansine, [T-DM1] (K); lapatinib (L); liver (Liv); lymph node (LN); lung (Lu); pertuzumab (P); trastuzumab (T)



## Patient Disposition

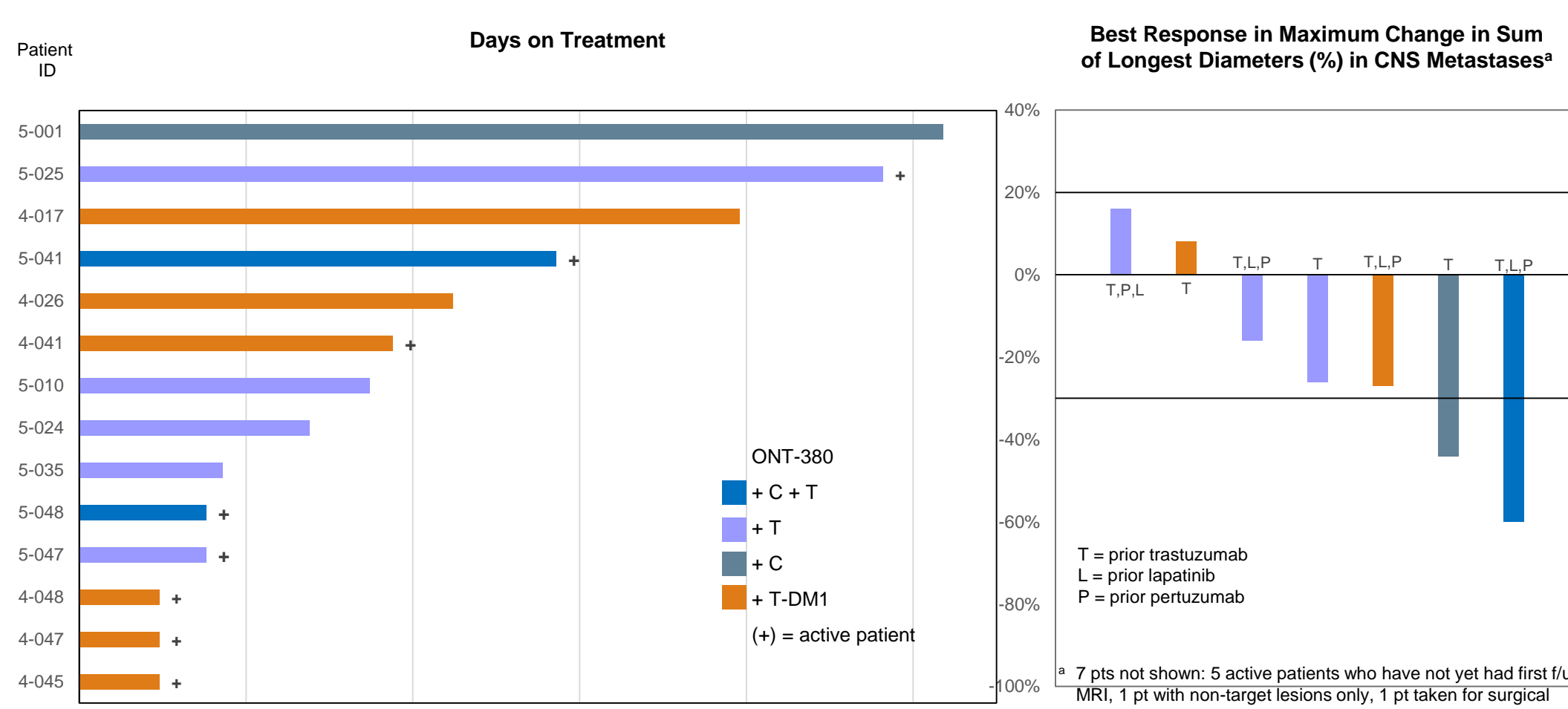
	ONT-380			
	+ T-DM1 (n = 12)	+ C (n = 1)	+ T (n = 5)	+ C + T (n = 4)
Patients active on treatment (n)	8	0	2	2
Patients off treatment (n)	4	1	3	2
Progressive Disease	1	1	1	1
PD in the CNS <sup>a</sup>	0	1	1	0
Clinical Progression	1	0	0	0
Physician Decision	2	0	2	0
Adverse Event	0	0	0	1

<sup>a</sup> Defined as ≥ 20% increase in target lesions sum of diameters with ≥ 5 mm absolute increase in the sum of all target lesions, or unequivocal progression of non-target lesions

## Patient Summaries: Progressive CNS Lesions after Local Therapy

Treatment	ID	Disease Characteristics & Prior Treatment				On Study										
		Yrs Since Met Dx	HR	# Prior Nonhorm Tx for Met	Prior HER2 Tx	Regime (mos)	PS	Sites of Dis	Time on Tx (mos)	Best Response Max Δ in CNS SLD Absolute (mm)	%	Best CNS Response	Status			
ONT-380 + T-DM1	4-041	1	+	WBRT	14	1	T,P	T+P+doc	8	0	Br; Lu	3.1	< 1 cm lesions only	N/A	SD	Active
	4-047	2	-	SRS; craniotomy	9,21,6	1	T,L	T+L	20	0	Br; Bo	0.8	Too early	Too early	Too early	Active
	4-048	5	+	WBRT; SRS	48,9	4	T,L	T+L	14	0	Br; Bo	0.8	Too early	Too early	Too early	Active
	4-045	1	+	WBRT	16	0	T	pac+T	4 (adj)	0	Br	0.8	Too early	Too early	Too early	Active
	4-017	1	-	WBRT; SRS	7,1	2	T,P,L	C+L	3	1	Br; Lu; Bo; LN	6.6	29 → 21	-27%	SD	Clin Prog
ONT-380 + C	4-026	3	+	WBRT	4	2	T	T+pac+nav	8	1	Br; Lu; Bo	3.7	12 → 13	8%	SD	Phys Dec
	5-001	2	+	SRS	12	4	T,K	K	3	1	Br; Bo	8.6	25 → 14	-44%	PR	PD (systemic and CNS)
ONT-380 + T	5-025	14	+	WBRT; SRS	21,8	9	T,P,L,K	TPI-287	2	0	Br; Lu; Liv; Bo; LN	7.1	12 → 10	-16%	SD	Active
	5-047	4	-	SRS	8	4	T,P,L,K	P+T	4	0	Br; Lu; Liv; LN	1.3	Too early	Too early	Too early	Active
	5-010	2	+	WBRT; SRS	16,8	2	T,L,P	C+L	3	1	Br; Lu; Liv; Bo; LN	2.9	15 → 11	-26%	SD	Phys Dec
	5-024	5	+	SRS	5	9	T,P,L,K	T+ nab-pac	8	0	Br; Lu; LN	2.3	12 → 14	16%	SD	SRS to target lesions after C4 Phys Dec; resection of target lesion due to CNS symptoms; no viable tumor found
	5-035	2	-	SRS	16	2	T,L,K	K	13	1	Br	1.4	13 → 15 (before surgery)	NA	NE	
ONT-380 + C + T	5-041	5	+	WBRT	21	2	T,P,L,K	L+cabaz	4	1	Br; Liv; Bo	4.8	35 → 15	-60%	PR	Active
	5-048	2	+	WBRT	4	2	T,K	K	6	1	Br; Lu; Liv; Bo; LN; Ch Wall	1.3	Too early	Too early	Too early	Active

Abbreviations: brain (Br); bone (Bo); capecitabine (C); ado-trastuzumab emtansine, [T-DM1] (K); lapatinib (L); liver (Liv); lymph node (LN); lung (Lu); pertuzumab (P); trastuzumab (T)



## Best Response (CNS and Overall)

	Untreated, Asymptomatic CNS Mets (n = 8)		Progressive/ New CNS Mets after Tx (n = 14)	
	CNS Only	Overall	CNS Only	Overall
CR	1	0	0	0
PR	2	2	2	4
SD	3	4 <sup>a</sup>	6	5 <sup>b</sup>
NE	2 <sup>c</sup>	0	1 <sup>d</sup>	0
PD	0	2	0	0
Too early to evaluate	0	0	5	5

<sup>a</sup> Includes one pt with unconfirmed PR who went off study for AE of palmar-plantar erythrodysesthesia syndrome  
<sup>b</sup> Includes 1 pt with non-CR non-PD (i.e., has non-target lesions only)  
<sup>c</sup> 2 pts with systemic PD but without follow up CNS scan on study  
<sup>d</sup> 1 pt with increasing lesion taken off study for surgical resection. Pathologic dx: treatment-induced necrosis; no viable tumor seen

## Case Study 1: Untreated/Asymptomatic CNS Metastases

**Patient ID: 4-035**  
**Patient History:**  
 • 3 prior systemic regimens for metastatic disease including T combined with: vinorelbine, C, and paclitaxel  
 • Found to have new asx CNS mets at time of study screening with target lesions located in cerebellum  
 • No history of prior CNS XRT  
**Treatment: ONT-380 + T-DM1**  
**MRIs:**  
 • post 2 cycles: -68% CNS target lesions  
 • post 6 cycles: -100% CNS target lesions  
 • (Images selected to demonstrate longest axis of lesions)

## Case Study 2: Untreated/Asymptomatic CNS Metastases

**Patient ID: 4-033**  
**Patient History:**  
 • Previously treated with T, paclitaxel and pertuzumab for 11 mos  
 • Found to have new asx CNS mets at the time of study screening  
 • No history of prior CNS XRT  
**Treatment: ONT-380 + T-DM1**  
**MRIs:**  
 • post 6 cycles: complete resolution of target and non-target lesions in CNS (Images selected to demonstrate longest axis of lesions)

## Case Study 3: Progressive CNS Lesions after Prior XRT

**Patient ID: 5-010**  
**Patient History:**  
 • Prior tx with T and P  
 • Hx WBRT 15 mos before study entry and SRS of cerebellar lesion 8 mos before study entry  
 • Progression in CNS after 3 mos tx with C + L just prior to study entry  
**Treatment: ONT-380 + T**  
**MRIs:**  
 • post 2 cycles: -26% reduction in CNS lesion (Images selected to demonstrate longest axis of lesions)

## Case Study 4: Progressive CNS Lesions after Local Therapy

**Patient ID: 5-041**  
**Patient History:**  
 • WBRT 21 mos prior to study entry  
 • Progression of 4 of 5 known lesions while on L + cabazitaxel for 4 mos, just prior to study enrollment  
**Treatment: ONT-380 + Trastuzumab + Capecitabine**  
**MRIs:**  
 • post 6 cycles: -60% reduction in CNS lesions (Images selected to demonstrate longest axis of lesions)

## Summary and Conclusions

- ONT-380 in combination with either T-DM1, T, C, or T + C has been well tolerated in patients with HER2+ breast cancer metastatic to the CNS
  - Majority of AEs were Grade 1 or 2 in severity, with no Grade 3 diarrhea
- Encouraging signs of activity in both systemic and CNS mets in a heavily pretreated population for all combinations evaluated
- Decrease in size of target CNS lesions (up to 100%) seen in patients with and without prior history of CNS local therapy, with CNS tumor control of > 6 mos in some patients
- Further study of CNS activity of ONT-380 is warranted

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

