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

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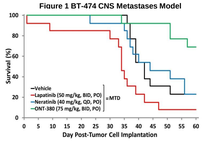
Abstract/Poster No. 612

## 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 $IC_{50}$: 8 nM; EGFR $IC_{50}$: 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

Figure 1 BT-474 CNS Metastases Model




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 | | | | |
|---|---|---|---|---|---|
| | + T-DM1 | + C | + T | + C + T | Total |
| 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$^2$ 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

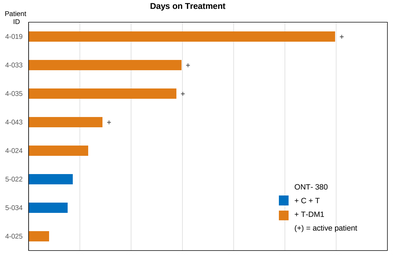
- Majority of AEs Grades 1 or 2 in severity, with no Grade 3 diarrhea
  - Most common AEs across both studies (≥ 4 patients overall): diarrhea, nausea, fatigue, constipation, dyspepsia, headache, abdominal pain, GERD, blurred vision, and vomiting
- 7 SAEs overall
  - 1 related SAE of reversible Grade 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

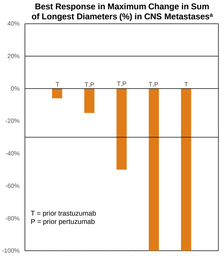
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Disease Characteristics & Prior Treatment | | | | | | | On Study | | | |
| | | | | | | Last Tx (Duration) | | | | | | |
| Treatment | ID | Yrs Since Met Dx | HR | # Prior Nonhorm Tx for Met Dis | Prior HER2 Tx | Regime | (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 |
| | 4-025 | 8 | + | 3 | T | pac | 4 | 1 | Br; Lu; Liv; Bo | 0.7 | CNS not re-scanned | CNS NE | CNS NE | PD in liver after drugs held for Gr 3 LFTs |
| 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)

Days on Treatment




Best Response in Maximum Change in Sum of Longest Diameters (%) in CNS Metastases[a]




[a] 3 pts not shown: 1 non-target lesions only, 2 without f/u CNS scans at time of systemic PD

## 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[a] | 0 | 1 | 1 | 0 |
| Clinical Progression | 1 | 0 | 0 | 0 |
| Physician Decision | 2 | 0 | 2 | 0 |
| Adverse Event | 0 | 0 | 0 | 1 |

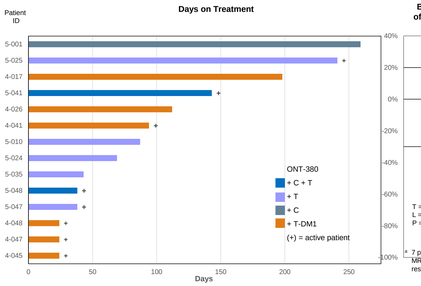
[a] Defined as ≥ 20% increase in target lesions sum of diameters with ≥ 5 mm absolute increase in the sum of all target lesions, or unequivocal progression of non-target lesions

## Patient Summaries: Progressive CNS Lesions after Local Therapy

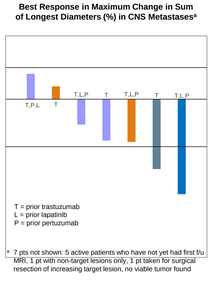
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Disease Characteristics & Prior Treatment | | | | | | | | On Study | | | | | |
| | | | | | CNS Tx Prior to Study Start | | | # Prior Nonhorm Tx for Met Dis | | Last Tx (Duration) | | | Best Response Max Δ in CNS SLD | | |
| Treatment | ID | Yrs Since Met Dx | HR | | Tx | Time (mos) | | Prior HER2 Tx | | Regime | (mos) | PS | Sites of dis | Time on Tx (mos) | Absolute (mm) | (%) | Best CNS Response | Status |
| ONT-380 + T-DM1 | 4-041 | 1 | + | | WBRT | 14 | 1 | T, P | | T+ P+doce | 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; Liv; Bo; LN | 6.6 | 29→21 | -27% | SD | Clin Prog |
| | 4-026 | 3 | + | | WBRT | 4 | 2 | T | | T+pac+nav | 8 | 1 | Br; Lu; Bo | 3.7 | 12→13 | 8% | SD | Phys Dec |
| ONT-380 + C | 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 lesion after C4 |
| | 5-035 | 2 | - | | SRS | 16 | 2 | T,L,K | | K | 13 | 1 | Br | 1.4 | 13 →15 (before surgery) | NA | NE | Phys Dec; resection of target lesion due to CNS symptms; no viable tumor found |
| 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)

Days on Treatment




Best Response in Maximum Change in Sum of Longest Diameters (%) in CNS Metastases[a]



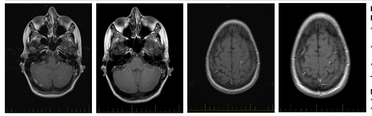

[a] 7 pts not shown: 5 active patients who have not yet had first f/u MRI, 1 pt with non-target lesions only, 1 pt taken for surgical resection of increasing target lesion, no viable tumor found

## 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[a] | 6 | 5[b] |
| NE | 2[c] | 0 | 1[d] | 0 |
| PD | 0 | 2 | 0 | 0 |
| Too early to evaluate | 0 | 0 | 5 | 5 |

[a] Includes one pt with unconfirmed PR who went off study for AE of palmar-plantar erythrodysesthesia syndrome
[b] Includes 1 pt with non-CR non-PD (i.e., has non-target lesions only)
[c] 2 pts with systemic PD but without follow up CNS scan on study
[d] 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

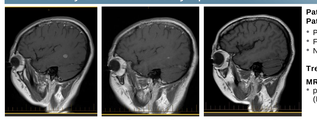



**Patient ID: 4-035**
**Patient History:**
- 3 prior systemic regimens for metastatic disease including T combined with: vinorelbine, C, and paclitaxel
- Found to have new asx CNS mets at time of study screening with target lesions located in cerebellum
- No history of prior CNS XRT

**Treatment: ONT-380 + T-DM1**

**MRI:**
- 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

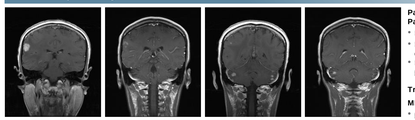



**Patient ID: 4-033**
**Patient History:**
- Previously treated with T, paclitaxel and pertuzumab for 11 mos
- Found to have new asx CNS mets at the time of study screening
- No history of prior CNS XRT

**Treatment: ONT-380 + T-DM1**

**MRI:**
- 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

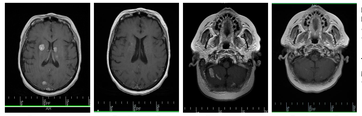



**Patient ID: 5-010**
**Patient History:**
- Prior tx with T and P
- Hx WBRT 15 mos before study entry and SRS of cerebellar lesion 8 mos before study entry
- Progression in CNS after 3 mos tx with C + L just prior to study entry

**Treatment: ONT-380 + T**

**MRI:**
- 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**

**MRI:**
- 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



All data presented from an unlocked database as of May 1, 2015 and subject to change.