ONT-380 in the Treatment of HER2+ Breast Cancer Central Nervous System (CNS) Metastases (Mets)  
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Background
ONT-380 is a next generation small molecule tyrosine kinase inhibitor with nanomolar potency • SHB1 fold more selective for HER2 compared to EGFR; HER2 IC50<4 nM, EGFR IC50>400 nM • HER2 sensitivity leads to decreased potential for EGFR related toxicities compared to dual inhibitors
• In murine models, ONT-380 monotherapy offered superior antitumor efficacy compared to various other TKI/anti-Her2 combinations (Figure 1)

Case Series Description
Patients with progressive/resistant metastases were selected for inclusion in the case series from the following ongoing phase 1b studies:
• ONT-380 Phase 1a, single-arm study of ONT-380 + site specific/definitive radiation (intracranial/resection; T-DXT)
• Patients with CNS disease who failed prior therapy with both trastuzumab and taxotere
• ONT-380 Phase 1b, Phase 1b, open label study of ONT-380 + C + T
• Patients with HER2+ breast cancer with progression after prior therapy with both trastuzumab and taxotere

Selection of Patients for Case Series
22 of 36 patients treated with ONT-380 failed progressive CNS metastases

Safety Overview
• Central nervous system (CNS) metastases were considered response evaluable if they met either of the following criteria:
  1. Unidimensional/progression in patients with similar number of lesions in both CNS and extra-CNS sites
  2. Progression in new lesions in patients who had received radiotherapy and/or surgery to the CNS
• Progressed lesions were required to have measurable disease at baseline for evaluable CNS response evaluation
• Progressed lesions were required to have CNS lesions that did not have obvious progression or were not considered response evaluable

Study Treatments and Assessments
• All patients treated with ONT-380 (380 mg BID; T-DXT: 540 mg/m²/m2; C: 1050 mg/m²/m²; BID 80 mg BID DI, T: 80 mg/m²/m²; D: 28 mg/m²/m²; CI: 15 mg/m²/m²; C: 15 mg/m²/m²; C: 15 mg/m²/m²)
• No escalation prophylactic anti-emetic mediation
• Safety evaluations including physical exam and laboratory work weekly for the first 6 weeks, then q 6 wks
• UDF by MAGA or ECHO q 3 mos
• CT scan or MRI if feasible q 3 mos
• Progression or response evaluation were performed per RECIST 1.1

Patient Disposition

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<th>Response</th>
<th>No. Patients</th>
<th>T</th>
<th>C</th>
<th>T+C+</th>
<th>T+P+</th>
<th>Control Arms</th>
<th>On-Body</th>
<th>Ps + T+</th>
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Note: Patients with PR or CR were considered responders

Study Endpoints

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<th>T+P+</th>
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<th>On-Body</th>
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Summary and Concluding
• ONT-380 administered with T-DXT, C, T, C has been well tolerated in patients with HER2+ breast cancer metastatic to CNS
• Overall response rate of 29% in CNS metastases (95% CI: 20.0% - 38.4%)
• Ensuring signs of activity in both systemic and CNS while in a heavily pretreated population for all metastatic recurrence
• Increased in size of target lesion (up to 10%) 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 ONT-380 with HER2+ is warranted

Figure 1: Tumor shrinkage in response to ONT-380 treatment