198TiP A randomized, double-blinded, controlled study of tucatinib (ONT-380) vs placebo in combination with capecitabine (C) and trastuzumab (T) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (mBC) (HER2CLIMB)

E. Paplomata[1], T. Bachelot[2], V. Mueller[3], C. Murias[4], R.K. Murthy[5], A.F.C. Okines[6], A.M. Wardley[7], L.N. Walker[8], A.M. Antunes De Melo e Oliveira[9]

[1]Department of Hematology and Medical Oncology, Emory Winship Cancer Institute, Atlanta, GA, USA, [2]Department of Medical Oncology, Centre Léon Bérard, Lyon, France, [3]Department of Gynaecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Medical Oncology, Sarah Cannon Research Institute SCRI UK, London, UK, [5]Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Department of Medicine, Royal Marsden Hospital NHS Foundation Trust, London, UK, [7]The NIHR Manchester Clinical Research Facility at The Christie NHS Foundation Trust and Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology Medicine & Health, University of Manchester, Manchester, UK, [8]Seattle Genetics, Seattle Genetics, Inc., Seattle, WA, USA, [9]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Tucatinib (ONT-380) is a highly selective small molecule inhibitor of HER2 kinase with nanomolar potency. Because tucatinib does not inhibit EGFR at clinically relevant concentrations, it potentially decreases EGFR-related toxicities (severe skin rash, diarrhea). In preclinical studies, tucatinib has demonstrated synergistic activity with T and is active in HER2+ models of brain metastases (BM). In a Phase 1b study, tucatinib showed encouraging antitumor activity when combined with C and T in pts with HER2+ mBC previously treated with ado-trastuzumab emtansine (T-DM1) and T. Objective responses were seen, including in pts with BM. The combination was well tolerated with low rates of Gr 3 diarrhea at the recommended dose (300 mg PO BID, equivalent to the single agent MTD). Tucatinib is being evaluated in an ongoing international randomized, double blind, phase 2 study in combination with C and T (HER2CLIMB).

Trial design: HER2CLIMB is recruiting in North America, Europe, Israel, and Australia. The primary study objective is to assess the effect of tucatinib vs. placebo in combination with C + T on progression-free survival (PFS) based on independent central review. Additional objectives include PFS in pts with BM, overall survival (OS), objective response rate, and safety. To increase the power of key secondary endpoints, the sample size was expanded from 480 to 600 pts. The study population includes adult pts with progressive HER2+ locally advanced or mBC who have had prior treatment with T, pertuzumab, and T-DM1 but not TKIs. A contrast-enhanced brain MRI is required at screening. Pts with untreated or progressive BM may be enrolled if they do not require immediate local therapy. Pts with isolated CNS progression on study may continue study treatment after undergoing local CNS-directed therapy. Pts receive C (1000 mg/mg^2 PO BID for 14 days of a 21-day cycle) and T (6 mg/kg IV once every 21 days after a loading dose of 8 mg/kg IV), and are randomized in a 2:1 ratio to tucatinib 300 mg PO BID or placebo. Safety is monitored by an independent Data Monitoring Committee.

Editorial acknowledgement: Irene Chen (Seattle Genetics, Inc.) and Isabelle Murray (Seattle Genetics, Inc.).

Clinical trial identification: NCT02614794.

Legal entity responsible for the study: Seattle Genetics, Inc.

Funding: Seattle Genetics, Inc.

Disclosure: E. Paplomata: Research funding grants: Novartis, Genentech, Corcept therapeutics, Seattle Genetics, Abbvie, Merck, Hoosier Cancer Research Network. T. Bachelot: Advisory board membership: Seattle Genetics, Roche, Novartis, Pfizer; Honoraria: Roche, Novartis, Pfizer; Research funding grants: Roche, Novartis, Pfizer, AstraZeneca; Travel expenses: Roche, Novartis, Pfizer, AstraZeneca. V. Mueller: Consultancy: Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Tesaro, Nektar; Honoraria: Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Janssen-Cilag. R.K. Murthy: Research funding grants: Genentech, Daiichi Sankyo, Oncothyreon/Seattle Genetics, EMD-Serono, Pfizer/Alliance foundation; Advisory board meetings, honoraria: Genentech, Puma, Daiichi Sankyo. A.F.C. Okines: Research funding grants: Pfizer; Speaker's bureau: Roche. A.M. Wardley: Advisory board membership: Roche, Novartis, AstraZeneca, Lilly, Pfizer, Pierre Fabre, Amgen, MSD, NAPP, ACCORD, Athenex; Sponsorship for meetings: Roche, Daiichi Sankyo; Consultancy: Gerson Lehman Group Guidepoint Global, Coleman Expert Network; Corporate board membership: Director of Andrew Wardley LTD; Honoraria: Roche, Novartis, AstraZeneca, Lilly, Pfizer, Pierre Fabre, Amgen, MSD, NAPP, ACCORD, Athenex, Daiichi Sankyo; Speaker's bureau: Roche, Novartis, AstraZeneca, Lilly, Pfizer; Travel expenses: Daiichi Sankyo. L.N. Walker: Employment: Seattle Genetics. A.M. Antunes De Melo e Oliveira: Consultancy: GSK, Puma Biotechnology, Roche; Research funding grants to the institution: AstraZeneca, Boehringer Ingelheim, Cascadian Therapeutics, Celldex, Genentech, GlaxoSmithKline, Immunomedics, Novartis, Seattle Genetics, Philips Healthcare, Piqur, Puma Biotechnology, Roche, Sanofi; Travel expenses: GP Pharma, Grünenthal, Novartis, Pierre-Fabre, Roche; Honoraria: Roche. All other authors have declared no conflicts of interest.