Background

Neratinib (Puma Biotechnology, Inc.), an irreversible pan-HER tyrosine kinase inhibitor, has been investigated in patients with advanced breast cancer. The multicenter, open-label CONTROL trial is the first-of-its kind study to incorporate neratinib in a first-line non-neoadjuvant setting. The CONTROL trial is a 2-arm, international, open-label, phase II study designed to investigate the incidence and severity of diarrhea in patients with HER2-positive early-stage breast cancer. Recently preclinical studies suggest that multiple mechanisms may be involved in the performance of neratinib induced diarrhea, including elements of inflammatory and diarrheagenic mediators. In particular, in a rat model, inflammation was observed in the colon in association with neratinib treatment. To reduce grade 3 diarrhea both in patients previously treated (13.6%) and not previously treated with pertuzumab (21.7%), the CONTROL study, for which enrollment started near May 2015, was designed to enroll 140 patients (70 per treatment arm) for whom new treatment strategies are needed.

Methods

Study design

CONTROL (PUMA-HER-005) is an international, open-label, phase II study that incorporates a randomized, 1:1 allocation of patients to loperamide prophylaxis for 1–2 cycles: 4 mg initial dose, then 4 mg tid days 1–14 (i.e. 12 mg/day), then 4 mg bid days 15–56 (i.e. 8 mg/day) (protocol amendment 3). Open-label loperamide for 1 cycle (protocol amendment 2). Two loperamide schedules have been described: (1) loperamide 4 mg tid days 1–14 plus budesonide (budesonide cohort), and (2) loperamide 4 mg tid days 1–14 followed by 4 mg bid days 15–56 (protocol amendment 3). Recent preclinical studies suggest that multiple mechanisms may be involved in the performance of neratinib induced diarrhea, including elements of inflammatory and diarrheagenic mediators. In particular, in a rat model, inflammation was observed in the colon in association with neratinib treatment. 

In the loperamide cohort, 18% of patients had previously received pertuzumab (16.7%). Adherence to loperamide prophylaxis was assessed based on total daily dose of prophylactic loperamide administered. In the budesonide cohort, 18% of patients had previously received pertuzumab (16.7%). In the loperamide cohort, 10% of patients had previously received pertuzumab (16.7%). In the budesonide cohort, 10% of patients had previously received pertuzumab (16.7%). In the loperamide cohort, 10% of patients had previously received pertuzumab (16.7%). In the budesonide cohort, 10% of patients had previously received pertuzumab (16.7%). In the loperamide cohort, 10% of patients had previously received pertuzumab (16.7%). In the budesonide cohort, 10% of patients had previously received pertuzumab (16.7%). In the loperamide cohort, 10% of patients had previously received pertuzumab (16.7%). In the budesonide cohort, 10% of patients had previously received pertuzumab (16.7%).

Patient population

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