SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL BO22280)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): Pertuzumab, Trastuzumab, docetaxel, FEC, carboplatin.	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomised, multicentre, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab given either concomitantly or sequentially with standard anthracycline-based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer. Report No: [redacted] May 2012		
INVESTIGATORS / CENTERS AND COUNTRIES	Patients were recruited at 44 centers across 19 countries (Bahamas, Bosnia and Herzegovina, Brazil, Canada, Croatia, Germany, Great Britain, Italy, Mexico, New Zealand, Portugal, Republic of China, Republic of Korea, Republic of Serbia, Romania, South Africa, Spain, Sweden, Switzerland).		
PUBLICATION (REFERENCE)			
PERIOD OF TRIAL	26 Nov 09 – 21 Jun 11 (Clinical cut off)	CLINICAL PHASE	II
OBJECTIVES	The primary objective was to make a preliminary assessment of the tolerability of neoadjuvant treatment with one of the following treatment regimens: **Arm A:** 5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. **Arm B:** FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. **Arm C:** Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles. The primary objective was evaluated when all patients had received six cycles of neoadjuvant treatment, had their surgery and all necessary samples taken, or withdrew from the study whichever was earlier.		

	The secondary objectives were: • To make a preliminary assessment of the activity associated with each regimen as indicated by the rate of pathological complete response (pCR; defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery, following primary systemic therapy) in the breast. • To evaluate the safety profiles of each treatment regimen, including pre-operative (neoadjuvant) and post-operative (adjuvant) treatment (ie, trastuzumab). • To investigate the overall survival (OS), the time to clinical response (CR), time-to-response, disease-free survival (DFS) and progression-free survival (PFS) for each treatment arm. • To investigate the biomarkers that may be associated with primary and secondary efficacy endpoints in accordance with each treatment arm. • To investigate the rate of breast conserving surgery for all patients with T2 3 tumors for whom mastectomy was planned at diagnosis.
STUDY DESIGN	This was a Phase II, open-label, randomized, multinational, multi-center trial to evaluate the tolerability and activity associated with trastuzumab and pertuzumab when used in addition to anthracycline-based or carboplatin-based chemotherapy regimens as neoadjuvant therapy in patients with HER2-positive breast cancer which is early stage and >2cm in diameter or locally advanced or inflammatory. To participate in the trial, a patient must have fulfilled all inclusion/exclusion criteria and consented to the collection and storage of serum and tumor tissue samples for biomarker research. Eligible patients were randomized to one of three treatment arms described above. All patients were scheduled to receive trastuzumab, every three weeks up to one year from the start of trastuzumab treatment, regardless of any additional chemotherapy. For any patients who were also considered to require further post-surgery chemotherapy in addition to the standard six cycle neoadjuvant regimen, the recommendation was that the patients who received anthracycline-based neoadjuvant therapy (FEC) were given cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the patients who received carboplatin-based neoadjuvant therapy (TCH), were given FEC. After the completion of surgery (and post-operative chemotherapy if required), patients received radiotherapy as per standard local clinical practice. Patients whose tumors were estrogen-receptor positive received hormone manipulation as per standard local clinical practice.

	Patients whose neoadjuvant study treatment was discontinued prior to surgery were managed as per standard local clinical practice. Approximately 28 days after the last dose of study medication, patients underwent a final safety assessment (called Final Visit). After completion of the study treatment, patients were to be followed until disease progression or until five years after randomization of the last patient, whichever was earlier. After a patient had progressed they were to be followed for survival until the end of study. In case of withdrawal from the trial due to cardiac toxicity the patient was followed up for cardiac outcome, whenever possible. Any patients whose disease progressed before the end of neoadjuvant therapy were withdrawn from study and treated as clinically indicated. Patients who completed chemotherapy and surgery, but then relapsed (either during or at any time after completion of the follow-up treatment) were to be treated as clinically indicated and follow-up information about subsequent therapies and outcomes collected.
NUMBER OF SUBJECTS	A total of 300 patients with early stage HER2-positive breast cancer were screened, of whom 225 were randomized.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	INCLUSION CRITERIA 1. Female patients with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive breast cancer. The initial breast cancer assessment had to be performed by a physician with experience in surgery for breast cancer. Patients with inflammatory breast cancer must have had a core needle biopsy. 2. Primary tumor > 2cm in diameter. 3. HER2-positive breast cancer confirmed by a central laboratory. Tumors must be HER2 3+ by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH)/ chromogenic in situ hybridization (CISH positive). FISH/CISH positivity mandatory for HER2 2+ tumors. 4. Availability of FFPE tissue (buffered formalin method of fixation was accepted) for central confirmation of HER2 eligibility (FFPE tumor tissue was subsequently used for assessing status of biomarkers). 5. Female patients, age ≥ 18 years. 6. Baseline LVEF ≥ 55% (measured by echocardiography or MUGA). 7. ECOG Performance Status ≤ 1 8. At least four weeks since major unrelated surgery, with full recovery. 9. A negative pregnancy test must have been available for pre-menopausal women and for women less than 12 months after the onset of menopause. 10. For women of childbearing potential, agreement to use a “highly-effective”, non-hormonal form of contraception or two “effective” forms of non-hormonal contraception by the patient and/or partner.

	Contraception had to be continued for the duration of study treatment and for at least six months after the last dose of study treatment. 11. Signed informed consent. EXCLUSION CRITERIA 1. Metastatic disease (Stage IV) or bilateral breast cancer. 2. Previous anticancer therapy or radiotherapy for any malignancy. 3. Other malignancy, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin. 4. Inadequate bone marrow function (eg, absolute neutrophil count (ANC) < 1.5 x 10^9/L, platelet count < 100 x 10^9/L and Hb < 9 g/dL). 5. Impaired liver function: (eg, serum [total] bilirubin > 1.25 x upper limit of normal (ULN) (with the exception of Gilbert's syndrome), AST, ALT > 1.25 x ULN, albumin < 25 g/L. 6. Inadequate renal function, serum creatinine > 1.5 x ULN. 7. Uncontrolled hypertension (systolic > 150 and/or diastolic > 100), unstable angina, congestive heart failure (CHF) of any New York Heart Association (NYHA) classification, serious cardiac arrhythmia requiring treatment (exceptions: atrial fibrillation, paroxysmal supraventricular tachycardia), history of myocardial infarction within six months of enrollment, or LVEF < 55%. 8. Dyspnea at rest or other diseases which require continuous oxygen therapy. 9. Severe uncontrolled systemic disease (eg, hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture). 10. Patients with insulin-dependent diabetes. 11. Pregnant and/or lactating women. 12. Patients with reproductive potential not willing to use a 'highly effective' method of contraception or two 'effective' methods of contraception. 13. Received any investigational treatment within four weeks of study start. 14. Patients with known infection with HIV, HBV, HCV. 15. Current chronic daily treatment with corticosteroids (dose of >10 mg methylprednisolone, or equivalent [excluding inhaled steroids]) 16. Known hypersensitivity to any of the study drugs or excipients. 17. Patients assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
TRIAL DRUG / STROKE (BATCH) No.	Pertuzumab: [redacted] Trastuzumab (Herceptin®): [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Pertuzumab 840 mg loading dose IV, then 420 mg IV 3-weekly; Trastuzumab (Herceptin®) 8 mg/kg loading dose IV, then 6 mg/kg every 3 weeks.

REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2) ; Docetaxel (75 mg/m^2 for the first dose; 100 mg/m^2 if no dose limiting toxicity occurs); TCH (trastuzumab followed by carboplatin AUC 6 and docetaxel at a starting dose of 75 mg/m^2). All treatments were given every three weeks by the IV route.
CRITERIA FOR EVALUATION	
SAFETY:	The following safety endpoints were of primary importance for the evaluation of the primary objective: • Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD) • Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%). Secondary safety endpoints of the study related to the safety of the treatment regimen, during both the pre-operative (neoadjuvant) and post-operative (adjuvant) treatment phases, as evaluated by the following endpoints: • Incidence of symptomatic cardiac events and asymptomatic LVEF events • LVEF measures over the course of the study • Incidence and severity of AEs and SAEs • Laboratory test abnormalities
EFFICACY:	The main efficacy endpoint was the pCR rate in the breast, evaluated after six cycles of treatment and surgery or following withdrawal from the study, whichever occurred sooner. pCR was defined at the time of surgery and the rate is the proportion of the ITT population that achieved a pCR. A 95% confidence interval (CI) was calculated around the observed pCR rate for each treatment arm in order to show the variability associated with the point estimate. Secondary Efficacy Endpoints Clinical response (CR) rate, time to clinical response, the proportion of patients achieving breast conserving surgery, overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) and an evaluation of biomarkers associated with response.
PHARMACODYNAMICS:	There were no pharmacodynamic assessments in this study
PHARMACOKINETICS:	There were no pharmacokinetic assessments in this study.
STATISTICAL METHODS	The sample size was based on the primary (safety) endpoint. Approximately 75 patients per arm were planned to be recruited into the study (225 in all).

Formal hypothesis testing was not planned. However, for pCR (the main efficacy endpoint) the approximate expected pCR rates were: Arm A: 50%, Arm B: 45% and Arm C: 40%. With this planned sample size, if these response rates were observed, the minimum true efficacy (lower bound of exact 95% confidence interval) of the estimates would be approximately A: 38.9% B: 33.8% C: 28.9%

For the assessment of incidence of symptomatic left ventricular systolic dysfunction (LVSD), if the true underlying incidence was 3%, the probability of observing more than five such events in a treatment arm was 0.025.

The Kaplan-Meier approach was used to estimate median PFS, DFS and time to clinical response for each treatment arm. The Cox proportional hazard model, stratified by operable, locally advanced, inflammatory breast cancer and estrogen and or progesterone receptor positivity were used to estimate the HR (i.e. the magnitude of treatment effect) and its 95% confidence interval (CI), for description purposes only.

To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes were summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers (exploratory biomarker analyses). Markers to be considered include the status of HER receptors, HER ligands, shed antigens (e.g. ECD/HER2), and other markers relevant for the HER family pathway. Efficacy outcomes considered for this analysis may include primary and secondary efficacy endpoints such as: pathological complete response rate, PFS, DFS and time to clinical response.

SAFETY RESULTS:

The primary objective of the study was to evaluate tolerability, particularly with respect to cardiac function, of the three treatment regimens during the neoadjuvant period of the study. Overall, there were no unexpected findings regarding acute cardiac toxicity, in the neoadjuvant period, in any of the treatment arms. In the neoadjuvant period, two patients in Arm B had Grade 3, symptomatic LVSD. Both events led to treatment withdrawal but resolved without sequelae. Four patients in Arm A, four in Arm B and three in Arm C reported LVEF declines of at least 10% points from baseline to below 50%.

Nearly all patients (96%-100%) had an AE (all grades) during the neoadjuvant period. The most common AE in the neoadjuvant period was diarrhea (in 61% - 72% of patients).

Incidence of most AEs was similar across the treatment arms. However, diarrhea, anemia, dysgeusia, insomnia and thrombocytopenia occurred with a greater incidence in Arm C (ie, occurred in at least 10% more patients in Arm C than in any of the other arms).

In addition, dyspepsia, decreased appetite and rash occurred with a lower incidence in Arm B (ie, occurred in at least 10% fewer patients than in at least one of the other two arms), but were broadly comparable in Arms A and C.

The proportion of patients experiencing an AE of Grade ≥ 3 was 69% in Arm A, 60% in Arm B and 74% in Arm C. Grade ≥ 3 events were predominately blood and lymphatic system disorders, with neutropenia the most commonly reported term across the three treatment arms (43%-47%), followed by febrile neutropenia (9% - 18%).

The incidence of SAEs was highest in Arm C (36%), followed by Arm A (28%) and then Arm B (20%). The most common SAE was febrile neutropenia, and this was lower in Arm B (5%) than in Arms A and C (14%, 15%, respectively). Three patients had SAEs suggestive of CHF (Patient [redacted] in Arm A with Grade 2 LVSD [who was also reported with a significant LVEF decline], and patients [redacted] in Arm B with Grade 3 LVSD). Patient [redacted] had not met protocol requirements for study entry (ie, entered the study with a baseline LVEF reading of < 55%).

No patient died on treatment up to the clinical cut-off date. Three patients (2 in Arm B, 1 in Arm C) died as a result of disease recurrence in the treatment follow-up period

The number of patients discontinuing any study medication was low across all the arms (4, 5 and 6 patients in Arms A, B and C, respectively). AEs leading to discontinuation in more than one patient were LVD, drug hypersensitivity and neutropenia. The number of patients with AEs requiring dose interruption/modification was greatest in Arm C (50%, vs 36% and 29% in Arms A and B, respectively), and were mostly due to neutropenia, anemia and thrombocytopenia.

Overall, there were few Events to Monitor leading to discontinuation of any study medication in the neoadjuvant period and, with the exception of leucopenic AEs (which led to dose modifications in 16% - 20% of patients, across treatment arms), the number of patients with Events to Monitor requiring dose modifications was low. In Arm C, 5% of patients had hepatic-related events (SMQ 'Drug-related hepatic dysfunction'), against 1% in both Arm A and Arm B.

EFFICACY RESULTS:

All three treatment regimens were active, with the majority of patients achieving a pCR . pCR rates were similar across the arms (Arm A: 61.6%; Arm B: 57.3%; Arm C: 66.2% in the ITT population).

Approximately half of all patients in each treatment arm achieved pCR together with all negative lymph nodes and no residual DCIS/LCIS at surgery (50.7% in Arm A, 45.3% in Arm B, 51.9% in Arm C).

Of those patients without pCR, the majority had a distinct single tumor nodule remaining, which was characterized as invasive ductal carcinoma.

pCR rates in the subgroups of patients with operable or with locally-advanced disease were broadly comparable with those in the ITT population.

The three treatment regimens were active both in hormone receptor-positive and hormone receptor-negative patients. However, pCR rates were higher in those patients with hormone receptor-negative disease (65%-84% across arms) than in patients with hormone receptor-positive disease (46%-50% across arms).

Nearly all patients responded to treatment: the clinical response rate was 91.8% in Arm A, 94.7% in Arm B and 89.6% in Arm C.

Median time to clinical response was shortest in Arm A (3.6 weeks; range 3-18 weeks), followed by Arm C (4.9 weeks; range 3-18 weeks) and longest in Arm B (6.9 weeks; range 3-20 weeks), although, the range in time to response in each arm was wide.

Within the ITT population, the proportion of patients who were able to have BCS (ie, quadrantectomy or lumpectomy), within the subgroup of 182 patients who had T2-T3 tumors and for whom mastectomy was originally planned (ie, 61 patients in Arm A, 63 in Arm B and 58 in Arm C), was 75.4% (46/61), 57.1% (36/63), and 63.8% (37/58) in Arms A, B, and C respectively.

PHARMACODYNAMIC RESULTS: No pharmacodynamic data were collected in this study

PHARMACOKINETIC RESULTS: No pharmacokinetic data were collected in this study

CONCLUSIONS:

In patients selected with a good cardiac reserve, pertuzumab and trastuzumab were generally well-tolerated, with low and similar rates of LVSD, regardless of whether they were given sequentially after, or concomitantly, with anthracycline treatment or with carboplatin-based treatment. The combination of pertuzumab plus trastuzumab, given with anthracycline-based or carboplatin-based chemotherapy regimens as neoadjuvant therapy did not identify any unexpected findings regarding cardiac safety in patients with HER2-positive EBC.

The overall safety profile of each regimen was consistent with the known toxicities of the individual treatments regimens, and there were few patients who had to withdraw from study treatment due to an AE.

All three regimens were active, with the majority of patients achieving a pCR (57.3%- 66.2% across arms), and the majority of patients having a clinical response (89.6%- 94.7%).

The results of the study support tolerability and activity of pertuzumab and trastuzumab in combination with different standard neoadjuvant chemotherapy treatment regimens in patients with HER2-positive EBC.