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ASSESSMENT REPORT FOR HERCEPTIN

International non-proprietary name/Common name: trastuzumab

Procedure No. EMEA/H/C/278/II/0047

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Trastuzumab is currently approved for the treatment of HER2 over-expressing metastatic breast cancer, either as monotherapy if therapy with anthracycline and taxanes has failed or is contraindicated, or in combination with paclitaxel inpatients who have not received prior chemotherapy for metastatic disease and for whom an anthracycline is not suitable or in combination with docetaxel in patients who have not received prior chemotherapy for metastatic disease.
Trastuzumab is also indicated for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)

The MAH has submitted data from the ToGA trial (study BO18255) trial to support an extension of the indication for the use of Herceptin in combination with capecitabine or intravenous 5-fluorouracil and a platinum agent for the treatment of patients with HER2-positive advanced adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Aside from changes to section 4.1 consequential changes in section 4.2 (choice of posology), section 4.8 (results from the ToGA study), section 5.1 (results from the ToGA study), section 5.2 (results from the ToGA study) as well as editorial and formatting changes to update the SPC to the current QRD template are requested.

1.2 Clinical aspects

Gastric cancer (GC) remains one of the most common malignancies in the world with an estimated one million new cases in 2007. GC is the second leading cause of cancer-related death in men and fourth among women, with more than 800,000 deaths worldwide in 2007. Incidence of GC varies widely across geographic regions. The highest rates are in Eastern Asia (Japan, Korea and China), Eastern Europe and certain countries in Central and South America. Rates are lower in the United States, Northern and Western Europe and Australia/New Zealand. The incidence in women is about 50% lower than in men and generally follows a similar geographic pattern.

Studies of HER2-positivity rates in GC using immunohistochemistry (IHC) and in situ hybridization (ISH, using fluorescence [FISH] or chromogenic labels [CISH]) have shown a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH. Good concordance of HER2-positivity has been reported between the results obtained by IHC and FISH (86.9%), and also between surgically resected samples and biopsies (88.5%). At the time the ToGA trial was set up, an estimate of 18% HER2-positivity was taken as an average of the available data for gastric cancer. While some studies have failed to find a direct correlation between HER2-positivity and prognosis, several studies have shown HER2 overexpression to be associated with poorer prognosis and survival.

A validation study has been conducted to define HER2 scoring in GC, as recommended by a consensus panel. The screening programme for the phase III pivotal study of Herceptin in GC, the ToGA trial, is the largest study of HER2-positivity in AGC to date. Three thousand six hundred and sixty seven evaluable samples were assessed. Eight hundred and ten were defined as HER2-positive (IHC3+ and/or FISH+), giving an overall HER2-positivity rate of 22.1%, which is comparable to breast cancer. HER2-positivity rates were similar between Europe and Asia, but varied between countries due to different histology. A higher HER2-positivity rate was seen in cancer of the GEJ than in stomach cancer (n=2759, 33.2% vs 20.9%). In the screened population for ToGA histological subtypes were evaluable for 3619 cases (including HER2-positive and HER2-negative). Based on this data set the occurrence of intestinal tumour type (according to the Lauren classification) was higher than the diffuse type (52.1% vs 30.3%). Additionally, intestinal-type gastric cancers show a significantly higher HER2 positivity rate than diffuse or mixed type tumours (intestinal: 32.2%, diffuse: 6.1%, mixed: 20.4%).

The biological effect of Herceptin has been demonstrated in pre-clinical studies using HER2 positive gastric cancer lines of Western, Japanese and Korean origin. A small amount of published clinical data is already available, evaluating the efficacy and safety of Herceptin in combination with various chemotherapy regimens in patients with HER2-positive GC, with beneficial effects reported in French and Japanese patients with HER2 overexpressing AGC.

Currently, the only potentially curative treatment for gastric cancer is surgery. Unfortunately, in Europe, the USA and developing countries, GC is often diagnosed at a stage beyond resectability and the overall 5-year survival does not exceed 25%. Regardless of their geographic region, patients with unresectable disease due to locally advanced growth or metastatic spread have a poor prognosis with overall 5-year survival in the range of 5%-15%**.** For these patients, and patients with recurrent disease after surgery, the main therapeutic option is chemotherapy.

5-fluorouracil (5-FU) remains the backbone of chemotherapy in AGC, having the highest activity of any single agent, with a 20% response rate and 5 to 7 months median survival in phase III randomised trials. Poly-chemotherapy using 5-FU in 2- or 3-drug combinations (including doxorubicin, mitomycin, cisplatin, methotrexate, leucovirin, epirubicin or etoposide) has generally produced higher response rates and disease-free survival times (DFS) compared to 5-FU alone but no significant overall survival (OS) advantage in randomised trials. The combination of 5-FU plus cisplatin (FC) is the most commonly used in routine clinical practice in the majority of countries for first-line treatment of AGC due to its accessibility and consistent efficacy results, with response rates of 20%-51% and median OS times of 7.2 to 8.6 months**.**

During the last 10 years, several new cytotoxic drugs have been shown in phase III trials to be active in gastric cancer, including docetaxel, irinotecan, oxaliplatin and capecitabine. Although there is currently no global gold-standard chemotherapy treatment for AGC, infusional 5-FU in combination with cisplatin therapy is widely accepted worldwide for AGC, including GEJ adenocarcinoma. The National Comprehensive Cancer Network (NCCN) guidelines (in the USA) for AGC propose several possible chemotherapy combinations: oxaliplatin with a fluoropyrimidine (5-FU or capecitabine), FC plus docetaxel, FC plus epirubicin, irinotecan in combination with cisplatin or fluoropyrimidine, or paclitaxel-based regimens.

Data submitted

The data submitted within the application dossier support the use of Herceptin to treat patients with HER2-positive AGC. The application centres on the results of a planned interim efficacy analysis from one pivotal study, the ToGA trial (study BO18255). ToGA is an open-label, randomised, multicentre, phase III study evaluating the efficacy and safety of Herceptin in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone as first-line therapy in patients with advanced or metastatic HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction. Summarised pharmacokinetic (PK) results from the ToGA trial were included within the dossier and were presented side-by-side with PK parameters that were common to two studies using the same dosing regimen performed in female patients with MBC.

To support the use of platinum agents other than cisplatin within the Herceptin containing combination regimen for AGC from ToGA, data from published studies evaluating use of Herceptin in combination with chemotherapy regimens containing oxaliplatin or carboplatin to treat HER2-positive breast cancer patients were submitted. Finally, data demonstrating non-inferior efficacy and reduced toxicity when cisplatin is substituted with oxaliplatin in chemotherapy treatment regimens for AGC are also included in the dossier.

Paediatric Investigation Plan

The MAH submitted written EMEA communication, dated 4 June 2008, confirming applicability to Herceptin of the EMEA Decision (dated 21 April 2008) regarding a paediatric investigational plan class

waiver for products intended to treat breast and gastric cancer, in accordance with Regulation (EC) No 1901/2006 as amended.

1. 2. 1. Pharmacokinetics

Pharmacokinetics of trastuzumab has been evaluated previously in patients with metastatic breast cancer (MBC) and in the adjuvant setting in early breast cancer (EBC) after completed chemotherapy. Posology in metastatic breast cancer is a loading dose of 4 mg/kg followed by weekly infusion at a dose of 2 mg/kg. Initially pharmacokinetic analysis using a one-compartmental model gave a half-life estimate of 6-8 days which was included in the initial SPC. A reassessment using a two-compartmental model gave a half-life estimate of 28.5 days. Posology in the adjuvant setting is a 8 mg/kg loading dose and a 6 mg/kg dose that is administered every 3 weeks. The reason for the different posology in the adjuvant setting appeared to be convenience for the patient and the revised data on pharmacokinetic parameters, in particular the longer half-life.

The ToGA trial (study BO18255) contained pharmacokinetic data from patients with HER2-positive advanced gastric cancer (AGC) in combination with chemotherapy. The posology is the same as in the EBC setting (Q3W regimen, 6 mg/kg IV). Pharmacokinetic data from two studies (BO15935 and WO16229) using the same posology in the metastatic breast cancer setting have been submitted for comparison.
In addition, data from study JP19959 on the PK of capecitabine and cisplatin in the presence and absence of trastuzumab were submitted.

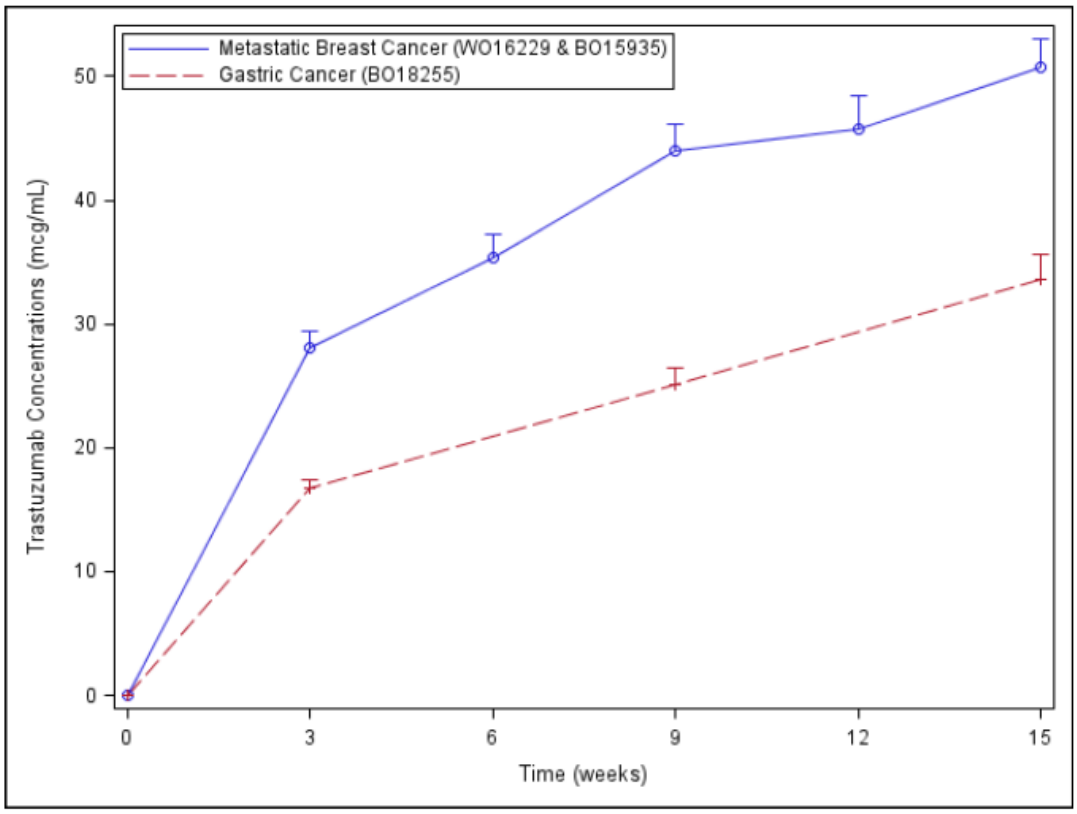
Serum concentrations of trastuzumab were determined by a validated enzyme-linked immunosorbent assay (ELISA). The stationary phase of this assay was a recombinant version of the extra-cellular domain (ECD) of the p185HER2 receptor. The limit of quantification for trastuzumab was 156 ng/mL.

In total, 294 AGC patients received treatment with trastuzumab in combination with chemotherapy (cisplatin plus 5-FU/capecitabine). The first dose of trastuzumab (8 mg/kg) was followed at three-weekly intervals by up to 5 doses of 6 mg/kg trastuzumab administered iv over a 90-minute period. Treatment was continued as a three-weekly regimen until disease progression, unacceptable toxicity or the patient wished to leave the study. Blood samples for PK assessments were collected at Cycle 1 (pre-dose, end of infusion, Day 8, Day 15), Cycle 2 (pre-dose), Cycle 4 (pre-dose, end of infusion) and Cycle 6 (pre-dose).
In total, 1780 identified serum concentrations from 272 AGC patients at the time of database closure were measured: 1524 concentrations in 272 patients were above the limit of quantification (LOQ = 156 ng/mL) and 254 concentrations in 250 patients were below the LOQ (BLQ).

Pharmacokinetic parameters were derived by population PK methods. A Bayesian feedback population pharmacokinetic analysis was performed on trastuzumab PK data from BO18255 study. The NONMEM PK dataset on which the population PK analysis was performed was composed of 1419 serum concentrations collected from 266 gastric cancer patients.

Individual trastuzumab concentration-time data and individual PK parameters were predicted based on posterior Bayesian estimates obtained from the reference population PK model developed on previous phase III data and fitted to the BO18255 data by fixing the population parameter values (i.e. fixed and random effect parameters) to their values obtained in the reference PK model. The reference model was a two-compartment disposition pharmacokinetic model with first-order elimination with the structural parameters drug clearance CL, central volume of distribution V1, the inter-compartmental clearance Q, and the peripheral volume of distribution V2. A comparison of the profile of the observed trough concentrations vs. nominal times in gastric cancer patients with the profile in metastatic breast cancer patients that received the same 3 weekly regimen (i.e. WO16229 and BO15935) is presented in Figure 1. The plot shows lower trastuzumab levels in gastric cancer patients compared to metastatic breast cancer patients.

Figure 2 **Comparison of the Mean Profile (SE) of the Observed Trastuzumab Trough Concentrations between gastric cancer (BO18255) and metastatic breast cancer patients (WO16229 and BO15935)**



The purpose of the PK analysis was to perform a Bayesian analysis to investigate whether trastuzumab pharmacokinetics characterized in gastric cancer patients in study BO18255 was comparable with the trastuzumab pharmacokinetics established mainly in metastatic breast cancer patients in the previous five phase I-III studies.
The final PK model includes the effect of cancer type on clearance (expressed as a change of HER2 shed antigen), the effect of gender on volume of central compartment, and the effect on ethnicity on volume of peripheral compartment. The inclusion of the 3 covariates in the final PK model has corrected the bias observed when fitting the reference PK model to the gastric cancer patients data.
For the typical patient with gastric cancer, eg, a male patient weighting 68 kg, overexpressing HER2, the trastuzumab clearance (CL) is 0.378 L/day, the volume of the central compartment (V1) is 3.91 L and the volume of the peripheral compartment (V2) is 2.68 L. The between-subject variability in clearance is equal to 38.6% and in central volume of distribution is 21.4%. A higher between-patient variability is estimated for the peripheral volume of distribution, 72.6%.

The interpretation of cancer type effect on clearance was complicated by the fact that in the BO18255 study the levels of HER2 shed antigen were not recorded. It was not possible to conclude that the cancer type effect on clearance was due to a true difference in the two cancer populations or due to a difference of HER2 level or a combination of the two. As a difference in HER2 level between the 2 types of cancer was considered as a reasonable hypothesis, the gastric cancer effect was expressed in term of HER2 Shed antigen level. The clearance in BO18255 patients is increased by 56.8 % compared to breast cancer patients; this translates into a median level of HER2 shed antigen of 1480 ng/mL in BO18255 compared to 17.9 ng/mL in the metastatic breast cancer population. This value is large but has been observed in some patients with breast cancer.

Individual predicted steady-state exposure (AUC), as well as expected Cmax and Cmin trastuzumab concentrations were calculated for all treated patients using the individual posthoc parameter estimates on CL, V1, and V2 and using the nominal dosage schedule administered as an i.v. infusion. It is noticed that the impact of gender and ethnicity on the PK in AGC patients was low. Thus, neither gender nor race can explain the PK differences observed between AGC and MBC/EBC patients.

Influence on PK of capecitabine and cisplatin (study JP19959)

The exposures of capecitabine (Xeloda®)and cisplatin when given in combination in the presence (XP+H; N=14) and absence of trastuzumab (XP; N=8) are shown in Figure 4 and Figure 5, respectively. There were no clinically relevant changes in exposure to capecitabine or cisplatin; AUC, Cmax, tmax, mean clearance values (CL) and mean half-lives (t1/2) were similar without and with trastuzumab.

Discussion on Clinical Pharmacokinetics

Sparse sampling was applied for determination of trastuzumab serum concentrations after a loading dose of 8 mg/kg (on day 1) followed by 6 mg/kg i.v. infusion every 3 weeks in patients with advanced gastric cancer. Resulting median trastuzumab trough concentrations from cycle 1 to 5 were about half the size of the corresponding values in MBC patients using the same posology. In both populations trough levels increased continuously from cycle 1 up to cycle 5 (week 15) indicating that steady state is not reached until that time point. This is consistent with a half life of 26 days. Corresponding levels in cycle 1 and the time course of trough levels in EBC patients using the same posology (preliminary data from the HERA study) prove that in early breast cancer patients trastuzumab levels are at least as high as in MBC patients..

The MAH has performed a population PK analysis of blood samples collected over the first 6 cycles of treatment. A population PK two-compartment model assuming first-order elimination derived from modelling of PK data from MBC patients was used to describe the trastuzumab serum concentration-time profiles in patients with gastric cancer. The goodness-of-fit plots of the Bayesian feedback showed a systematic over-prediction of trastuzumab concentrations which indicated that the reference PK model could not adequately describe the data from study BO18255.
The influence of the covariates cancer type, gender, ethnicity and race, that were not represented in the metastatic breast cancer population, were therefore investigated. They were found statistically significant and were included in the final model. The influence of gender and race were rather small. The covariate "cancer type" allowed to estimate higher CL values in AGC patients:

Estimation of trastuzumab clearance in gastric cancer patients by the final model (0.378 L/day) was ~57% higher than that in metastatic breast cancer patients (0.241 L/day), leading to markedly (about 50%) lower predicted values of AUC, Cmax and Cmin at steady state in gastric cancer (1030 mg*day/L, 128 and 23 mg/L) compared to metastatic breast cancer patients (1793 mg*day/L , 189 and 47.3 mg/L) using the same posology. Mean observed steady state values after 13 cycles in early breast cancer patients using the same posology were even higher (2255 mg*day/L, 216 and 63.2 mg/L, respectively; preliminary data from the BO16348/HERA study) than those predicted for MBC patients

This means that steady state exposure (based on AUCss and Cmin) of trastuzumab is 54 to 64 % (43 to 51%) lower in AGC compared to EBC (MBC) patients using the same posology.

The covariate "cancer type" is assumed to represent differences in shed HER2 receptor levels between the cancer types. The MAH postulates that the increased clearance of trastuzumab in AGC (about 57% according to their PK model) is due to higher levels of circulating extra-cellular domain of the HER2 receptor (shed antigen), and indeed, women with MBC and higher baseline shed antigen were more likely to have lower serum trough concentrations. However, there are no data to support this interpretation. An increased binding/distribution of trastuzumab to cellular HER2 receptors cannot be ruled out.
It is well-known from other receptor-binding monoclonal antibodies that receptor-mediated clearance plays a role in the elimination of the drug. This leads to a nonlinear portion of the total clearance occurring

outside the central compartment which is in contrast to the assumption of first-order elimination from the central compartment. The role of the nonlinear CL is thought to be more prominent at low concentrations and at high receptor concentrations (tumour load).
Therefore, the difference in total CL found between AGC and MBC patients might also plausibly be explained by differences in receptor density between the two subpopulations. Therefore, it would be of interest whether a model allowing for a nonlinear (saturable) portion of the total clearance (with Vmax dependent on the total receptor concentration) could satisfactorily describe the differences found between AGC and MBC data.
Since in the BO18255 study the levels of HER2 shed antigen were not recorded, it was not possible to conclude that the cancer type effect on clearance was due to a true difference in the two cancer populations or due to a difference of HER2 level or a combination of the two. Under the assumption that HER2 shed antigen level is fully responsible for the difference in plasma concentrations found, a median level of HER2 shed antigen of 1480 ng/mL in BO18255 compared to 17.9 ng/mL in the metastatic breast cancer population was estimated.
An elimination half-life of 14.5 days was estimated. This in contrast to the observed continuous increase in Ctrough levels up to week 15, indicating that steady state has not been reached until that time point. Therefore, a prediction for the time to reach steady state cannot be made on the basis of these data. There is no supportive evidence for the assumption that half-life in AGC patients is shorter than the equilibrium half life obtained from population PK analysis in metastatic breast cancer patients (26.3 days).

Further, it would be of interest to more fully comprehend possible interactions of all concomitant medications and the possible impact of hydration volume on trastuzumab levels in individual patient groups.

The main question is whether the depletion of free serum trastuzumab in AGC patients (possibly due to binding to high levels of shed HER2 or altered hydration volumes) would reflect a decrease in pharmacodynamically active drug and could mean a possible underexposure of trastuzumab in these patients. If this was true, the levels of shed HER2 could be a prerequisite for an appropriate calculation of dose in different cancer patients.

In addition, data were presented from a second study investigating the possible influence of trastuzumab on the PK of the concomitant chemotherapeutics capecitabine and cisplatin. The results show that the exposure of capecitabine and cisplatin were similar in the presence and in the absence of trastuzumab.

Sufficient explanation for the observed differences in PK of trastuzumab in gastric cancer compared to breast cancer has not been provided. The hypothesis that shed HER2 leads to higher trastuzumab clearance could not be substantiated by data. In addition the statements as regards the time to steady state that are proposed are inconclusive and not supported by the supplied data. Proposed changes to the SmPC on PK in breast cancer are not endorsed and are not substantiated by data. Although trastuzumab has demonstrated efficacy in the gastric cancer setting there is remaining concern that the chosen dose is not optimal in gastric cancer patients. The MAH therefore committed to submit a plan with actions and timelines to further investigate the PK issues. This may include consideration of further exploration of dose.

1. 2. 2. Clinical efficacy

- Main study ToGA trial (BO18255)

The ToGA trial (BO18255) is a randomised, open-label multicentre phase III study of trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone as first-line therapy in patients with HER2 positive advanced gastric cancer.
The trial was conducted in 24 countries (excluding the USA). A total of 594 patients were randomized in a 1:1 ratio to each of the two treatment arms between September 2005 and December 2008.
Patients were stratified prior to randomization for a number of prognostic and other factors that could affect outcome: Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2), chemotherapy regimen (5-FU + cisplatin vs capecitabine + cisplatin), locally advanced versus metastatic

disease, stomach versus gastro-esophageal junction, and measurable versus non-measurable evaluable disease.

Main Inclusion criteria

1. Histologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction with inoperable locally advanced or recurrent and/or metastatic disease, not amenable to curative therapy.
2. Measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), assessed using imaging techniques (CT or MRI), or non-measurable evaluable disease.
3. HER2-positive tumour (primary tumour or metastasis) as assessed by the central laboratory. (Both IHC and FISH were performed on all tumour samples in the central laboratory).
4. ECOG Performance Status 0, 1 or 2
5. Life expectancy of at least 3 months.
6. Male or female. Age ≥ 18 years

Patients in both arms followed the same schedule of visits and underwent the same safety and efficacy assessments (every three weeks until disease progression and every six weeks thereafter until death), thus helping to reduce the potential for bias for both efficacy endpoints and adverse event reporting.

An interim analysis was recommended by the IDMC following the results of the first interim analysis. While it can not be excluded that this recommendation was influenced by the results of the 1st interim analysis (and thus the type I errror might no longer be preserved exactly), the impact on the type I error can be considered quite small as mentioned in Lan KKG DeMets DL: Changing the frequency of interim analysis in sequential monitoring. Biometrics, 45, 1017- 1020 (1989).

Treatment

All patients were scheduled to receive six cycles of chemotherapy comprising a fluoropyrimidine (capecitabine, 1000 mg/m2 given orally twice daily for 14 days every 3 weeks, or 5-fluorouracil, 800 mg/m2/day administered as a continuous IV infusion over 5 days, given every 3 weeks) and cisplatin, administered at a dose of 80 mg/m2 every 3 weeks as a 2 hour IV infusion. The choice of fluoropyrimidine was decided by the investigator on an individual patient basis.

Patients randomized to receive trastuzumab were administered a loading dose of 8 mg/kg (on day 1) followed by 6 mg/kg every 3 weeks by IV infusion. The first infusion was given over 90 minutes, with subsequent infusions given over 30 minutes if the first infusion was well tolerated. Trastuzumab treatment continued until disease progression (unless withdrawn earlier due to unmanageable toxicity).

There were no dose adjustments of trastuzumab foreseen for toxicity. If a patient could not tolerate trastuzumab infusions, trastuzumab treatment was stopped completely. All patients enrolled in the study must have had a baseline LVEF ≥ 50%. In the case of cardiac toxicity a detailed algorithm was used to define discontinuation/continuation/stopping rules for trastuzumab.

Primary objectives

To compare the overall survival (OS) for patients treated with trastuzumab combined with 5-FU or capecitabine plus cisplatin, versus 5-FU or capecitabine plus cisplatin.

Secondary objectives

To evaluate progression-free survival (PFS), time to progression (TTP), overall response rate (complete response [CR] + partial response [PR]), clinical benefit rate (CR + PR + stable disease [SD]), and duration of response in the two treatment arms.
• To evaluate the safety profile in the two treatment arms.
• To summarize the quality of life in the two treatment arms.
• To evaluate pain intensity, analgesic consumption, and weight gain/loss in the two treatment arms.

• To investigate the pharmacokinetics of trastuzumab in gastric cancer and to compare with historic data in patients with metastatic and adjuvant breast cancer.

Primary endpoint

The primary efficacy parameter was **overall survival** (OS). It was defined as the time from the date of randomization to the date of the death (from any cause). Patients who had not been reported as having died at the time of the analysis were censored at the date they were last known to be alive.

Secondary endpoint

Secondary efficacy variables were progression-free survival [the time between the day of randomization and the first documentation of progressive disease (PD) or date of death, whichever occurred first], time to progression (the time between randomization and the first occurrence of progressive disease), overall response rate (the occurrence of a confirmed CR or PR as determined by the RECIST criteria from confirmed radiographic evaluations of target and non-target lesions), clinical benefit rate (SD for 6 weeks or longer, CR plus PR as determined by the RECIST criteria), and duration of response (the time from the date the CR or PR was first recorded to the date on which PD is first noted).

The study also evaluated the safety profile, quality of life, and pain, analgesic consumption and weight gain/loss in the two treatment arms, and investigated the pharmacokinetics of trastuzumab in patients with gastric cancer.

Sample size

Initially sample size was calculated assuming a median overall survival of 7 months for patients in the fluoropyrimidine/cisplatin treatment arm and 10 months in the trastuzumab plus fluoropyrimidine /cisplatin arm. In order to detect this difference with 80% by means of a two-sided log-rank test 248 events where needed ($\alpha = 0.05$). One interim efficacy and safety analysis was foreseen in the original protocol (performed after 50% of events). During the course of the trial it became obvious (from other clinical trials as well as from the overall survival rate of the recent trial) that the assumption about the median survival duration especially for the comparator group was to liberal. Following the advice of the IDMC the sample size was increased to allow for the observation of 460 events. This was done to achieve 80% power to detect a difference of overall survival anticipating a median overall survival in the fluoropyrimidine/cisplatin treatment arm of 10 months compared to 13 months in the the trastuzumab plus fluoropyrimidine /cisplatin arm (log-rank test, $\alpha = 0.05$)

Patients were centrally randomised 1:1 (Trastuzumab: Placebo) by means of an IVRS Approximately three-quarters of all patients were male (75% in the FP arm and 77% in the FP+H arm). The majority of patients were oriental (54% in the FP arm and 51% in the FP+H arm) or Caucasian (36% and 39%, respectively). The median age of patients was 59 years in the FP arm and 61 years in the FP+H arm.

Patients were stratified at randomization on the basis of ECOG performance status, locally advanced versus metastatic disease, stomach versus GEJ, measurable versus nonmeasurable evaluable disease, and the chemotherapy regimen (capecitabine or 5-FU,decided by the investigator)

Statistical methods

The primary analysis was based on the full analysis set. For the primary analysis, an unstratified log-rank test was used to assess whether there is a difference in overall survival (OS) between both treatment groups. Further analyses (e.g. COX-regression) accounting for the stratification factors and pre-specified covariables support the primary analysis. In addition, various subgroup analyses were performed to assess the consistency of the study results.
In general survival methods were used to analyse time to event data; categorical data were compared between treatment groups by means of χ^2-tests. Treatment effects are described by appropriate point estimates including their 95% confidence intervals.

To account for interim analyses an α-spending function of the O'Brien-Fleming type was applied. Following the 1st interim analysis (after 50% of planned events) the IDMC recommended an additional interim analysis when 75% of the planned events had been observed.

Efficacy analysis populations

The **Full Analysis Set** (**FAS**, intent to treat population) included all patients who were randomized and received study medication at least once.

The **Per Protocol Set** included all patients of the FAS, but patients who fulfilled any of the following criteria were excluded:

1. Prior chemotherapy for advanced/metastatic disease as listed in the inclusion/exclusion criteria of the protocol
2. No study medication received.
3. Incorrect medication received given randomization.
4. Patients who failed to meet the tumour assessment criteria specified in the inclusion/exclusion criteria.
5. Absence of documentation of overexpression/amplification of HER2.
6. Baseline LVEF < 50%.
7. ECOG PS > 2

The **Safety Analysis Population** included all patients who were randomized and received study medication at least once. Groups were defined by the actual received medication rather than randomization arm.

RESULTS

The trial was started in September 2005. A total of 594 patients enrolled and at the time of the analysis, a total of 349 randomized patients had died (63% in FP and 57% in FP+H).

The primary patient population analyzed was the full analysis set (FAS). Other patient populations analyzed were the per protocol set (PPS) and the safety population (SAP).

The FAS population comprised all patients who were randomized in the study and received study medication at least once. Of 594 patients enrolled to the trial, a total of 10 patients were excluded from the FAS (10 patients did not receive any study medication) Thus, the FAS population comprised 584 patients; the number of patients in the FP and FP+H arms were 290 and 294, respectively

Baseline characteristics for the used stratification factors are shown in the following table.

	Fluoro-pyrimidine/ Cisplatin N = 290	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294
Sex		
MALE	218 (75%)	226 (77%)
FEMALE	72 (25%)	68 (23%)
n	290	294
Race		
BLACK	2 (<1%)	1 (<1%)
CAUCASIAN	105 (36%)	115 (39%)
ORIENTAL	158 (54%)	151 (51%)
OTHER	25 (9%)	27 (9%)
n	290	294
Age in years		
Mean	58.5	59.4
SD	11.22	10.75
SEM	0.66	0.63
Median	59.0	61.0
Min-Max	21 - 82	23 - 83
n	290	294
Weight in kg		
Mean	63.17	62.08
SD	13.034	12.594
SEM	0.765	0.735
Median	60.30	61.45
Min-Max	28.0 - 105.0	35.0 - 110.0
n	290	294
Height in cm		
Mean	166.4	166.3
SD	8.85	8.26
SEM	0.52	0.48
Median	167.0	166.0
Min-Max	128 - 190	146 - 198
n	290	294

n represents number of patients contributing to summary statistics.

The following table shows the summary of stratification factors (FAS)

	Fluoropyrimidine/ Cisplatin N=290	Trastuzumab/Fluoro- pyrimidine/Cisplatin N=294
Extent of Disease		
n	290	294
Locally Advanced	10 (3.4%)	10 (3.4%)
Metastatic	280 (96.6%)	284 (96.6%)
Primary Site		
n	290	294
Stomach	242 (83.4%)	236 (80.3%)
GE Junction	48 (16.6%)	58 (19.7%)
Measurability		
n	290	294
Measurable	257 (88.6%)	269 (91.5%)
Non-measurable	33 (11.4%)	25 (8.5%)
ECOG Performance Status		
n	290	294
0-1	263 (90.7%)	264 (89.8%)
2	27 (9.3%)	30 (10.2%)
Chemotherapy Regimen		
n	290	294
Capecitabine	255 (87.9%)	256 (87.1%)
5-FU	35 (12.1%)	38 (12.9%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

The following table shows the summary of baseline disease characteristics (FAS)

	Fluoropyrimidine/ Cisplatin N=290	Trastuzumab/Fluoro- pyrimidine/Cisplatin N=294
Time from First Diagnosis of Gastric Cancer to Randomisation (months)		
n	290	294
Median	1.2	1.5
Range	0.2-65.6	0.3-309.3
Time from Diagnosis of Locally Advanced or Recurrent/Metastatic Disease to Randomisation (months		
n	290	294
Median	1.0	1.0
Range	0.1-7.5	0.2-26.7
Extent of Disease at Study Entry		
n	290	294
Locally Advanced	10 (3.4%)	10 (3.4%)
Metastatic	280 (96.6%)	284 (96.6%)
Primary Site		
n	290	294
Stomach	242 (83.4%)	236 (80.3%)
GE Junction	48 (16.6%)	58 (19.7%)
Type of Gastric Cancer (assessed by local laboratory)		
n	290	294
Intestinal	131 (45.2%)	132 (44.9%)
Diffuse	88 (30.3%)	108 (36.7%)
Not Assessed	71 (24.5%)	54 (18.4%)
Type of Gastric Cancer (assessed by central laboratory)		
n	287	293
Intestinal	213 (74.2%)	225 (76.8%)
Diffuse	25 (8.7%)	26 (8.9%)
Mixed	49 (17.1%)	42 (14.3%)
Measurability		
n	290	294
Measurable	257 (88.6%)	269 (91.5%)
Non-measurable	33 (11.4%)	25 (8.5%)
Prior Radiotherapy		
n	290	294
Yes	7 (2.4%)	5 (1.7%)
No	283 (97.6%)	289 (98.3%)
Prior Anthracycline Therapy		
n	290	294
Yes	2 (0.7%)	2 (0.7%)
No	288 (99.3%)	292 (99.3%)
Prior Chemotherapy		
n	290	294
Yes	12 (4.1%)	27 (9.2%)
No	278 (95.9%)	267 (90.8%)
Prior Gastrectomy		
n	290	294
Yes	62 (21.4%)	71 (24.1%)
No	228 (78.6%)	223 (75.9%)
ECOG Performance Status		
n	290	294
0	105 (36.2%)	101 (34.4%)
1	158 (54.5%)	163 (55.4%)
2	27 (9.3%)	30 (10.2%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Prior Gastrectomy includes Preferred Terms: Gastrectomy and Oesophagogastrectomy

HER2 status at baseline (FAS population)

Combined FISH / IHC Result	Fluoropyrimidine/ Cisplatin N=290		Trastuzumab/Fluoro-pyrimidine/Cisplatin N=294	
n	290		294	
FISH+/IHC0	38	(13.1%)	23	(7.8%)
FISH+/IHC1+	32	(11.0%)	38	(12.9%)
FISH+/IHC2+	79	(27.2%)	80	(27.2%)
FISH+/IHC3+	125	(43.1%)	131	(44.6%)
FISH-/IHC3+	6	(2.1%)	9	(3.1%)
FISH+/IHC no result	2	(0.7%)	5	(1.7%)
FISH no result/IHC3+	8	(2.8%)	8	(2.7%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Following the HER2 testing, patients were classified in different HER2 subgroups. Overall, the proportion of patients with low HER2 overexpression (IHC 0/FISH+ and IHC 1+/FISH+) was small (**22%** [131/584]) as compared to patients with high HER2 overexpression (IHC 2+/FISH+ and IHC 3+ including IHC 3+/FISH negative or FISH no result; **76%** [446/584]). Seven patients (1%) were classified as IHC no result/FISH+.

Prior treatment

Overall, 7% of patients (4% in FP, 9% in FP+H) across the two treatment groups had a previous adjuvant chemotherapy, 2% had previous radiotherapy and 40% had surgery (mainly driven by gastrectomy 23% 132/584) for gastric cancer. All other surgical procedures included a variety of interventions without curative intent.

Previous treatments for gastric cancer (FAS)

Previous Treatment	**FP N = 290**	**FP+H N = 294**
Adjuvant Chemotherapy	12 (4%)	27 (9%)
Radiotherapy	7 (2%)	5 (2%)
Surgery	102 (35%)	129 (44%)

Patients prematurely discontinuing study treatment

Of those patients starting study treatment, more patients from the FP arm (146/290 pts [50%]) had not completed six cycles of therapy at the clinical cut-off compared to the FP+H arm (108/294 pts [37%])

Summary of patient disposition

	Fluoropyrimidine/ Cisplatin N=296	Trastuzumab/Fluoro-pyrimidine/Cisplatin N=298
No. of Patients Randomised	296	298
No. of Patients with at Least One Dose	290	294
No. of Patients Discontinued Study Treatment due to PD	177	181
No. of Patients Prematurely Discontinued Study Treatment	79	59
No. of Patients Ongoing in Treatment Period	34	54
No. of Patients Completing <6 Cycles	146	108
No. of Patients Completing 6 Cycles	114	28
No. of Patients Completing >6 Cycles	30	158
No. of Patients Entered Follow-up	221	217
No. of Patients Died in Follow-up	157	149
No. of Patients Lost to Follow-up	10	7
No. of Patients Alive in Follow-up	54	61
No. of Patients Not Entered Follow-up	69	77
No. of Patients Died during Treatment Period	25	18
No. of Patients Ongoing in Treatment Period	34	54
No. of Patients between Treatment Period and Follow-up	10	5

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Treatment phase until disease progression: From randomization until disease progression irrespective of whether treatment was given throughout the entire treatment phase in the FP+H arm or only for 6 cycles followed by no treatment in the FP arm. Patients discontinued the treatment because of disease progression or withdrawal for reasons listed on the withdrawal page of the CRF
Follow-up phase: After disease progression and until death, patients were assessed for their alive status at 6 weekly intervals

More patients in the FP+H arm received 6 cycles of chemotherapy compared to the FP arm (59.5% vs 49.3% for capecitabine/5-FU and 56.5% vs 48.3% for cisplatin). No major differences in adverse events leading to treatment discontinuation of at least one study drug were demonstrated between the two treatment arms (50 AEs in FP, 53 AEs in FP+H).The number of patients who discontinued treatment due to AEs (any grade) was similar between the two treatment arms (48 pts [17%] in FP, 48 pts [16%] in FP+H).The most common AEs that led to treatment discontinuation were gastrointestinal disorders (2% in FP, 4% in FP+H), such as diarrhoea, and dysphagia; renal and urinary disorders (1% in FP, 3% in FP+H) such as renal impairment; blood and lymphatic system disorders (3% in FP, 1% in FP+H), such as thrombocytopenia and febrile neutropenia.

A total of 253 patients (43%) received at least one subsequent treatment for gastric cancer (45%) in FP and (42%) in FP+H.

Efficacy Results

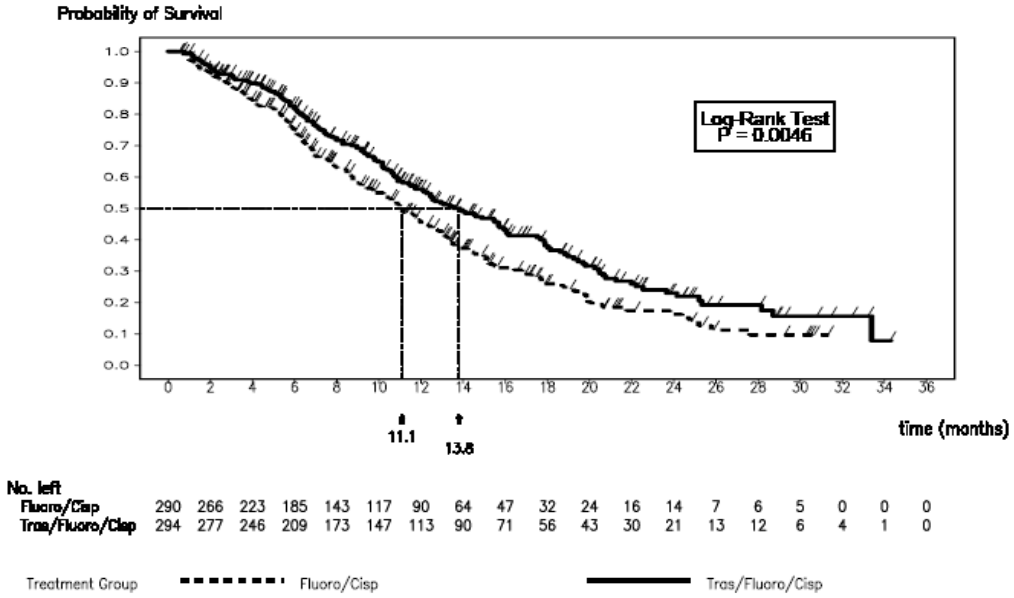
The second interim efficacy analysis was performed after 349 events (patient deaths), corresponding to 75.9% of the planned 460 events, had been reported in the study across the two treatment arms. The results were reviewed by the IDMC, who recommended that the study be terminated.

At the time of the clinical cut-off (January 7, 2009), a total of 349 patients had died. There were more deaths in the FP arm (63% [182/290]) compared to the FP+H arm (57% [167/294]). There were 315 out of 349 deaths due to progressive disease (gastric cancer), 58% [167/290] in the FP arm and 50% [148/294] in the FP+H arm. Overall, 34 patients died due to causes not related to or not reported as disease progression. Thirty-one patients died due to adverse events (14 pts in FP, 17 pts in FP+H) Three patients died due to an unknown reason.

The median duration of follow-up was 17.1 months in the FC arm and 18.6 months in the FP+H arm.

Treatment with trastuzumab in combination with FP chemotherapy resulted in a significant improvement in overall survival compared to treatment with FP alone. At the time of analysis, 182 patients (62.8%) in the FP arm and 167 patients (56.8%) in the FP+H arm had died. In addition to fewer deaths, the median overall survival time in the FP+H arm was extended to 13.8 months compared to 11.1 months in the FP arm. This corresponds to a statistically significant reduction in the risk of death by 26% for patients treated with trastuzumab plus FP (hazard ratio = 0.74; 95% CI [0.60-0.91], p = 0.0046). The difference in overall survival between the two treatment groups (ie, separation of the curves in the Kaplan-Meier plot) is seen early on and appears to be maintained over time.

Figure: Kaplan Meier Plot of Overall Survival (FAS)



Secondary efficacy parameters

At the time of the analysis (clinical cut-off January 7, 2009), a total of 461 patients had progressed (419 patients) or died (42 patients) Of those patients, 81% had progressed in the FP arm and 77% in the FP+H arm and 42 patients died (22 pts in FP, 20 pts in FP+H). A summary of the secondary efficacy assessments (FAS) is presented below:

Secondary Efficacy Parameter	Fluoropyrimidine/Cisplatin N=290	Trastuzumab/Fluoropyrimidine /Cisplatin N=294
Progression-free survival		
No. of patients with event	235 (81.0%)	226 (76.9%)
No. of patients without event	55 (19.0%)	68 (23.1%)
Median time to event	5.5	6.7
p value (log-rank test)	0.0002	
Hazard Ratio [95% CI]	0.71 [0.59, 0.85]	
Time to Progression		
No. of patients with event	215 (74.1%)	208 (70.7%)
No. of patients without event	75 (25.9%)	86 (29.3%)
Median time to event	5.6	7.1
p value (log-rank test)	0.0003	
Hazard Ratio [95% CI]	0.70 [0.58, 0.85]	
Overall Response Rate		
No. of patients with:		
Complete Response (CR)	7 (2.4%)	16 (5.4%)
Partial Response (PR)	93 (32.1%)	123 (41.8%)
Stable Disease (SD)	101 (34.8%)	93 (31.6%)
Progressive Disease (PD)	53 (18.3%)	35 (11.9%)
Missing assessment	36 (12.4%)	27 (9.2%)
Responders (CR+PR)	100 (34.5%)	139 (47.3%)
Non-responders	190 (65.5%)	155 (52.7%)
Difference in Response Rate	12.80	
p value (Chi-squared test)	0.0017	
Odds Ratio [95% CI]	1.70 [1.22, 2.38]	
Duration of Response		
No. of patients included in analysis (Pts with CR/PR)	100 (100.0%)	139 (100.0%)
No. of patients with event	80 (80.0%)	100 (71.9%)
No. of patients without event	20 (20.0%)	39 (28.1%)
Median time to event	4.8	6.9
p value (log-rank test)	<0.0001	
Hazard Ratio [95% CI]	0.54 [0.40, 0.73]	
Clinical Benefit Rate		
Patients with Clinical Benefit (CR+PR+SD)	201 (69.3%)	232 (78.9%)
Patients with no Clinical Benefit	89 (30.7%)	62 (21.1%)
Difference in Clinical Benefit	9.60	
p value (Chi-squared test)	0.0081	
Odds Ratio [95% CI]	1.66 [1.14, 2.41]	

In summary, significant benefit from the addition of trastuzumab to FP therapy was seen for the secondary endpoints of **progression-free survival** (median 6.7 months for the FP+H arm vs 5.5 months for the FP arm; p= 0.0002 and hazard ratio 0.71 [0.59, 0.85]); **overall response rate** (47.3% vs 34.5%, difference in

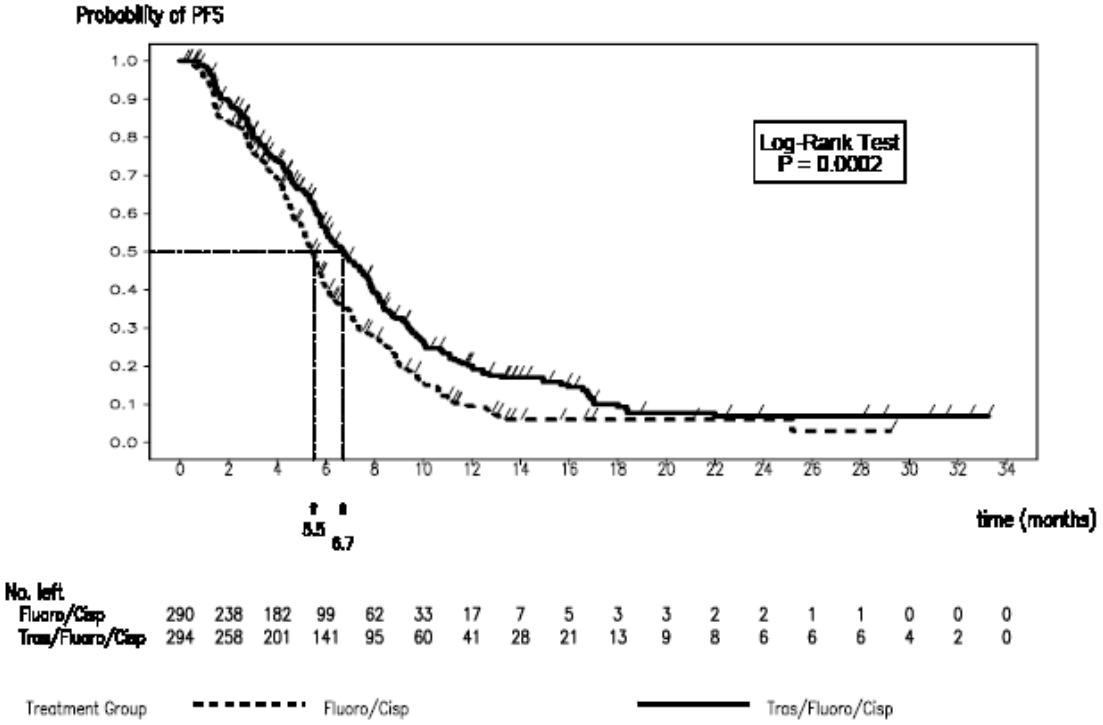
response rate: p= 0.0017 and odds ratio 1.70 [1.22, 2.38]**);** **time to progression** (median 7.1 months vs 5.6 months, p= 0,0003 and 0.70 [0.58, 0.85]), **duration of response** (median 6.9 months vs 4.8 months, p<0.0001 and hazard ratio 0.54 [0.40, 0.73]) and **clinical benefit rate** (78.9% vs 69.3%, p=0.0081 and odds ratio 1.66 [1.14, 2.41])

Progression free survival

At the time of the analysis (clinical cut-off January 7, 2009), a total of 461 patients (81% [235/290] in FP, 77% [226/294] in FP+H) had progressed (213 pts in FP, 206 pts in FP+H) or died (22 pts in FP, 20 pts in FP+H)

In the unstratified analysis, the addition of trastuzumab to the FP regimen significantly prolonged the median PFS when compared to the FP regimen alone. The median PFS was 5.5 months with FP and 6.7 months with FP+H. The risk of having a PFS event (progression or death, whichever occurred first) significantly decreased by 29% (HR 0.71; 95% CI [0.59-0.85]; p = 0.0002) in the FP+H arm

The Kaplan-Meier curves for the duration of PFS (FAS) are shown below



The results of the stratified (extent of disease/primary site/measurability/ECOG PS/chemotherapy regimen) analysis of PFS were similar to the non-stratified analysis, as seen in the following table

Tras/Fluoro/Cisp vs. Fluoro/Cisp	Log-rank test (p-value)	Cox Regression		
		Hazard Ratio	95% CI	p-value
No Stratification	0.0002	0.71	[0.59;0.85]	0.0002
With Stratification*	0.0004	0.71	[0.59;0.86]	0.0005

* stratified by Extent of Disease (LA vs Metastatic) and Primary Site (Stomach vs GE Junction) and Measurability (Measurable vs Non-meas.) and ECOG Performance Status (0-1 vs 2) and Chemo. Regimen (Cap/Cisp vs 5-FU/Cisp)
Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

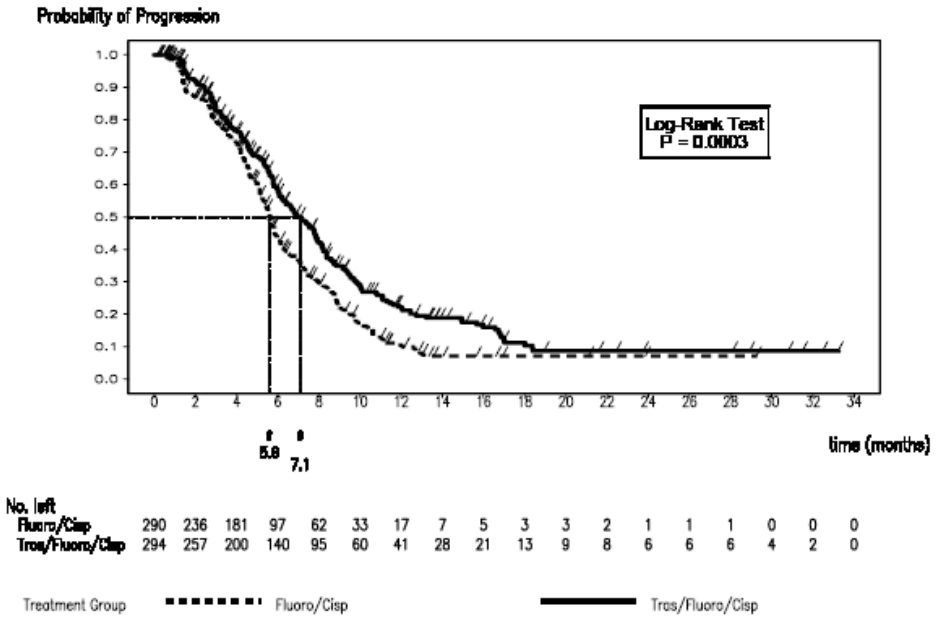
Sensitivity analysis of PFS

The robustness of the PFS analysis was confirmed by performing a sensitivity analysis of PFS during first-line therapy. This was defined as the time between randomization and the first date of progressive disease or death, whichever occurred first, and only including patients that obtained no further anti-cancer treatment since stopping study medication. The unstratified analysis showed that the risk of a PFS event during first-line therapy was reduced by 32% for the FP+H arm (HR 0.68; 95% CI [0.56-0.83]; p < 0.0001).

Time to Disease Progression

At the time of the clinical cut-off, a total of 423 patients had a disease progression (74% [215/290] in FP, 71% [208/294] in FP+H). The median time to disease progression was 5.6 months for the FP arm and 7.1 months for the FP+H arm . With the addition of trastuzumab to the FP regimen, the risk was significantly reduced by 30% (HR 0.70; 95% CI [0.58-0.85]; p = 0.0003).

The Kaplan Meier curve of time to progression is presented below:



The results of the stratified analysis (hazard ratio: 0.69, p=0.0003) of time to disease progression were similar to the non-stratified analysis (hazard ratio: 0.70, p=0.0003)

The robustness of the time to disease progression analysis was confirmed by analyzing the time to disease progression during first-line therapy. The analysis showed that the risk of an event during first-line therapy was reduced by 32% for the FP+H arm (HR 0.68; 95% CI [0.55-0.83]; p = 0.0001)

Overall tumour response rate

When ananlysing the FAS, the incidence of patients with an objective response (CR/PR) was higher in the trastuzumab arm (47.3% [139/294]) compared to the control arm (34.5% [100/290])

The difference in response rate was 12.8% (95% CI [4.7; 20.9]; p = 0.0017). The complete response rate was more than doubled in the FP+H arm (5.4%) compared to the FP arm (2.4%) (p = 0.0599, Chi-squared test). There were more patients with a partial response in the FP+H arm (41.8%) compared to the FP arm (32.1%) (p = 0.0145, Chi-squared test). A higher incidence of patients in the FP arm had stable disease (34.8%) and progressive disease (18.3%) compared to the FP+H arm (31.6% and 11.9%, respectively).

Summary of overall tumour response rate

	Fluoropyrimidine/ Cisplatin (N=290)		Trastuzumab/Fluoro- pyrimidine/Cisplatin (N=294)
Responders$	100 (34.5 %)		139 (47.3 %)
Non-Responders	190 (65.5 %)		155 (52.7 %)
95% CI for Response Rates*	[29.0; 40.3]		[41.5; 53.2]
Difference in Response Rates		12.80	
95% CI for Difference in Response Rates#		[4.7; 20.9]	
p-Value (Chi-squared Test)		0.0017	
Odds Ratio		1.70	
95% CI for Odds Ratio		[1.22;2.38]	
Complete Response (CR)	7 (2.4 %)		16 (5.4 %)
95% CI for CR Rates*	[1.0; 4.9]		[3.1; 8.7]
Difference in CR Rates		3.03	
95% CI for Difference in CR Rates#		[-0.3; 6.3]	
p-Value (Chi-squared Test)		0.0599	
Odds Ratio		2.33	
95% CI for Odds Ratio		[0.94;5.74]	
Partial Response (PR)	93 (32.1 %)		123 (41.8 %)
95% CI for PR Rates*	[26.7; 37.8]		[36.1; 47.7]
Difference in PR Rates		9.77	
95% CI for Difference in PR Rates#		[1.8; 17.7]	
p-Value (Chi-squared Test)		0.0145	
Odds Ratio		1.52	
95% CI for Odds Ratio		[1.09;2.14]	
Stable Disease (SD)	101 (34.8 %)		93 (31.6 %)
95% CI for SD Rates*	[29.4; 40.6]		[26.4; 37.3]
Progressive Disease (PD)	53 (18.3 %)		35 (11.9 %)
95% CI for PD Rates*	[14.0; 23.2]		[8.4; 16.2]
Missing (No Response Assessment)	36 (12.4 %)		27 (9.2 %)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

$ Patients with best overall response of confirmed CR or PR
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

• Stratified Analysis of Overall Tumor Response Rate
The results based on the stratified analysis (stratified by Extent of Disease (LA vs Metastatic) and Primary Site (Stomach vs GE Junction) and Measurability (Measurable vs Non-meas.) and ECOG Performance Status (0-1 vs 2) and Chemo. Regimen (Cap/Cisp vs 5-FU/Cisp) were similar to those based on the unstratified analysis.

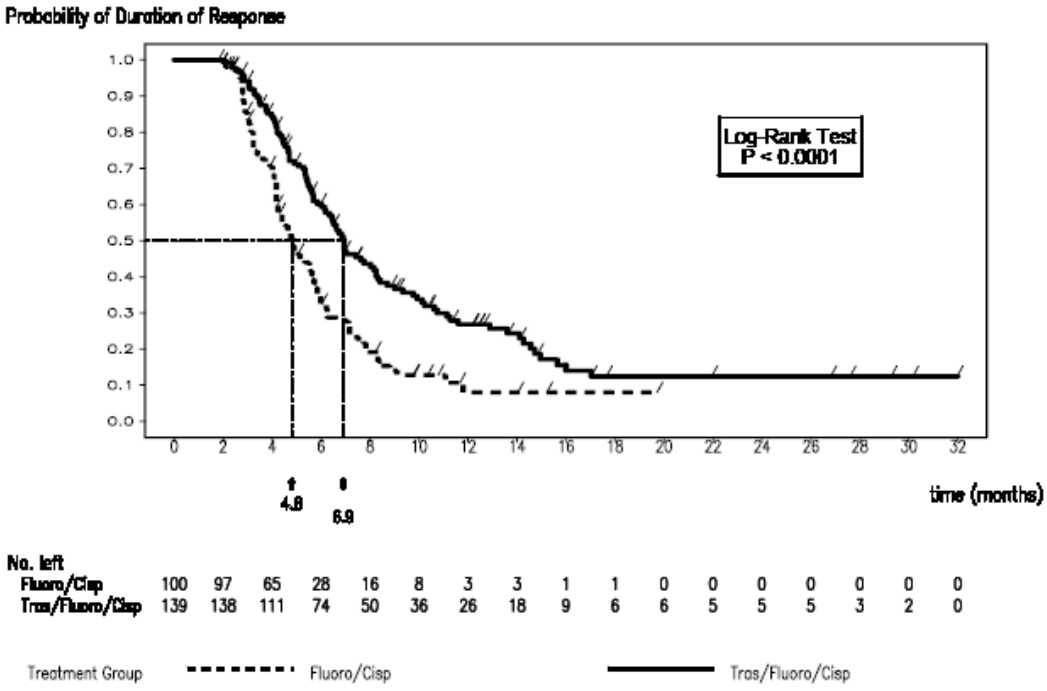
• Exploratory analysis of Overall Tumor Response Rate in patients with measurable disease
The results based on this subpopulation of patients(FP arm: 257 of 290 patients and FP+H arm: : 269 of 294 patients) with measurable disease were similar to those based on the intent-to-treat population.

In summary, the observed treatment effect is highly significant in all three analyses performed (FAS unstratified (p=0.0017), FAS stratified (p=0.0048) and exploratory analysis in patients with measurable disease at baseline(p= 0.0017))

Duration of response

The duration of response was assessed in patients who had a best overall response of CR or PR. The median duration of response was significantly longer in the FP+H arm (6.9 months) than in the FP arm (4.8 months). The Hazard Ratio was 0.54 (95% CI [0.40; 0.73]; p < 0.0001).

The Kaplan-Meier plots of **duration of response** (see graph below) showed a separation of the curves for the FP and FP+H groups from 3 months to 16 months Responses were maintained at a higher rate in the FP+H arm than in the FP arm during that time period.



Clinical benefit rate

Patients who had stable disease for at least 6 weeks or a response assessment of CR or PR were deemed to have clinical benefit. Patients treated with trastuzumab plus FP exhibited a significantly (p = 0.0081, Chi-Squared test) higher incidence of clinical benefit (78.9% [232/294]) compared to the patients treated with FP alone (69.3% [201/290])

Summary of quality of life in the two treatment arms and evaluation of pain intensity, analgesic consumption, and weight gain/loss in the two treatment arms

Quality of life was assessed using the EORTC QLQ-C30 and gastric module ST022 questionnaire

Utility assessment was performed using the EQ-5D self-report questionnaire, which consists of two pages comprising the EQ-5D descriptive system and the EQ visual analogue scale (VAS). It provides a single descriptive profile and a single index value for health status.

Assessment of pain intensity was performed using the VAS at baseline on day 1 prior to first dose of study drug, and then 3-weekly at each visit (on day 1 of each cycle prior to
dosing) until disease progression.

The actual scores and change from baseline scores in both EORTC QLQ-C30 and EORTC QLQ-STO22 indicated improved quality of life in both arms over time, especially at the end of chemotherapy.

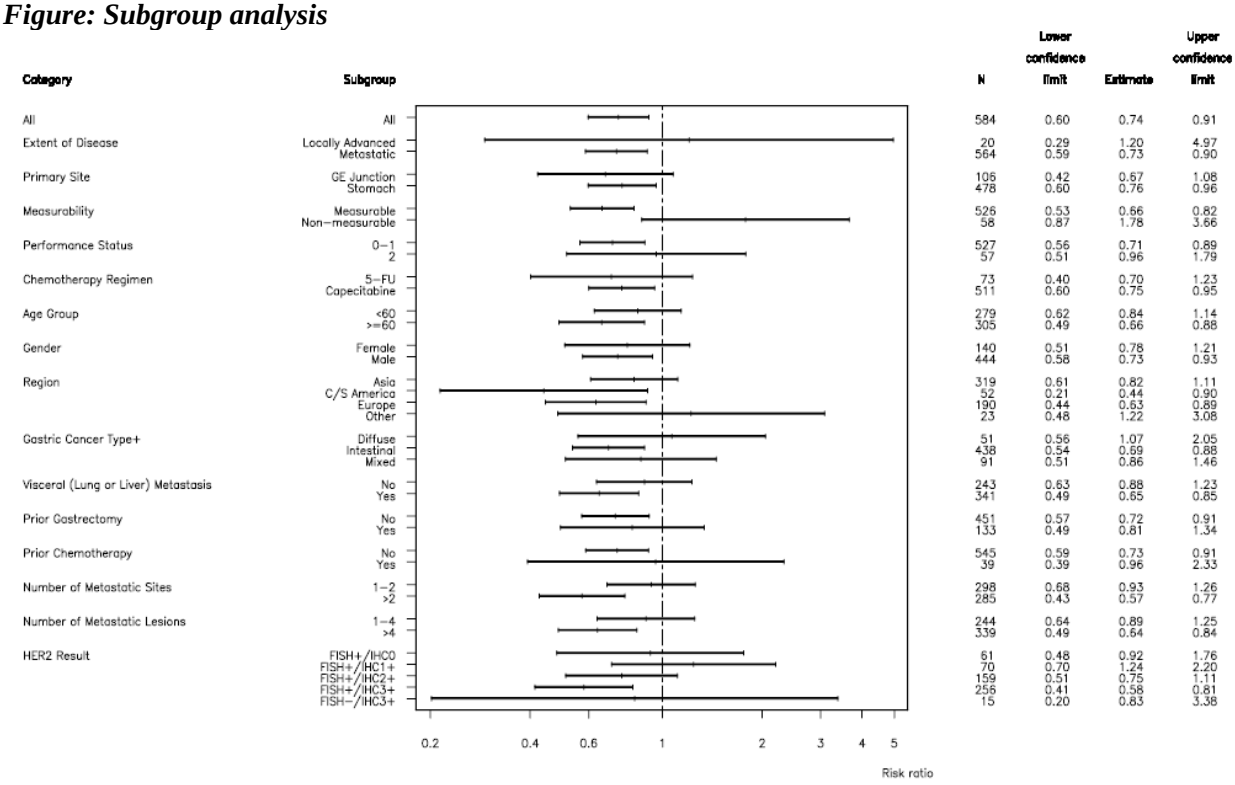
Gastrointestinal symptom scores were slightly better in the FP arm during chemotherapy compared to the FP+H arm which correlates with the slight increased frequency of gastrointestinal AEs observed in the FP+H arm. The FP+H arm scored less for hair loss compared to the FP arm.

Pain scores and use of analgesics were similar in both arms.

Subgroup and Exploratory analysis

Results of subgroup analyses suggest that benefit is substantially increased for those patients with tumours characterized as IHC 3+/FISH positive. The subgroup analyses, whilst understandably limited in their power to detect significant differences between the two study arms, have created some doubt regarding the benefit of add-on Herceptin treatment in particular subgroups; for instance those with locally advanced disease, non-measurable disease, IHC 1+ tumour staining and ECOG 2 performance scores. Insignificant differences seen in OS and PFS between contralateral subgroups and in some cases better median survival times for the dual therapy subgroups, save the small patient numbers and events, remain largely unexplained.

Figure: Subgroup analysis



Summary of Multiple Cox regression for overall survival

Effect/ Covariate included in the Model	Hazard Ratio	95% CI for Hazard Ratio	p-Value
Trastuzumab/Fluoropyrimidine/Cisplatin vs Fluoropyrimidine/Cisplatin	0.72	[0.58;0.90]	0.0036
Extent of Disease (LA vs Metastatic)	0.95	[0.45;2.02]	0.8986
Primary Site (Stomach vs GE Junction)	1.24	[0.90;1.71]	0.1823
Measurability (Measurable vs Non-meas.)	1.12	[0.72;1.72]	0.6248
ECOG Performance Status (0-1 vs 2)	0.40	[0.28;0.59]	<.0001
Chemo. Regimen (Cap/Cisp vs 5-FU/Cisp)	0.80	[0.54;1.16]	0.2365
Age (<60 vs >=60)	1.03	[0.82;1.28]	0.8205
Gender (Male vs Female)	0.95	[0.72;1.25]	0.6998
Region (C/S America vs Asia)	2.04	[1.35;3.09]	0.0007
Region (Europe vs Asia)	1.56	[1.18;2.06]	0.0017
Region (Other vs Asia)	1.98	[1.16;3.40]	0.0128
Type of GC (Diffuse vs Intestinal)	1.17	[0.78;1.73]	0.4466
Type of GC (Mixed vs Intestinal)	1.16	[0.84;1.59]	0.3599
Visceral Metastasis (Yes vs No)	1.13	[0.88;1.46]	0.3475
Prior Gastrectomy (Yes vs No)	0.56	[0.40;0.79]	0.0008
Prior Chemotherapy (Yes vs No)	1.29	[0.79;2.13]	0.3094
Number of Metastatic Sites (1-2 vs >2)	0.77	[0.59;1.00]	0.0477
Number of Metastatic Lesions (1-4 vs >4)	0.91	[0.70;1.19]	0.4892
HER2 Result (FISH+/IHC0 vs FISH+/IHC3+)	1.74	[1.17;2.57]	0.0056
HER2 Result (FISH+/IHC1+ vs FISH+/IHC3+)	1.93	[1.36;2.74]	0.0002
HER2 Result (FISH+/IHC2+ vs FISH+/IHC3+)	1.37	[1.05;1.77]	0.0188
HER2 Result (FISH-/IHC3+ vs FISH+/IHC3+)	1.25	[0.62;2.50]	0.5286

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU
LA=Locally Advanced, GE=Gastroesophageal, GC=Gastric Cancer (assessed by central laboratory)

Similarly, in the multiple Cox regression analysis for PFS, when adjusting for all covariates, a significant p-value for the IHC 3+/FISH+ category indicated that this group had a better PFS compared to the IHC 0/FISH+ (p = 0.0008), IHC 1+/FISH+ (p = 0.0008) and IHC 2+/FISH+ (p = 0.0002) categories.

Definition of two HER2 subgroups:
Based on the observation that limited treatment effect could be identified in the low HER2-expressing subgroup, the MAH proposed to re-define HER2-positive patients, and therefore the target population. Two new subgroups were defined based on IHC scoring (if not otherwise indicated all patients were FISH positive):

- **Group 1 ("low HER2 expressing group"):**
  IHC 0/FISH+ and IHC 1+/FISH+
  (70 patients in FP, 61 patients in FP+H)

- **Group 2 ("high HER2 expressing group")**:
  IHC 2+/FISH+ and
  IHC 3+ including IHC 3+/FISH negative or IHC 3+/FISH no result
  (218 patients in FP, 228 patients in FP+H)

The low HER2 expressing group comprised 70 patients in the FP arm and 61 patients in the FP+H arm. The high HER2 expressing group comprised 218 patients in the FP arm and 228 patients in the FP+H arm. Two patients in the FP arm and five patients in the FP+H arm had no IHC score recorded and were therefore not included in either of these subgroups.

Hazard Ratios and 95% Confidence Intervals for Overall Survival by HER2 Status-IHC 0, IHC 1+ versus IHC 3+, IHC 2+/FISH+ (FAS)

Subgroup		Fluoropyrimidine/ Cisplatin: Patients per group	N Events	Median time	Trastuzumab/Fluoro-pyrimidine/Cisplatin: Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		290	182	11.1	294	167	13.8	0.74	[0.60;0.91]
HER2 Result	FISH+/IHC0 or 1+	70	45	8.7	61	43	10.0	1.07	[0.70;1.62]
	FISH- or + or no result/IHC2+ or 3+	218	136	11.8	228	120	16.0	0.65	[0.51;0.83]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Program : $PROD/cdpl2032/bo18255/ehcowd_16.sas / Output : $PROD/cdpl2032/bo18255/reports/ehcowd_16_2001.lst
27APR2009 8:28

Using the protocol-defined inclusion criteria of HER2-positivity, i.e. a positive test result by either IHC (IHC 3+) or FISH, **22% of AGC patients screened were eligible for inclusion** into this study. However, using a definition of high HER2 expressing tumours based on the post-hoc analysis (ie, IHC 2+/FISH+ or IHC 3+ including IHC 3+/FISH negative and IHC 3+/FISH no result), the **HER2 positivity rate in advanced gastric cancer was found to be 16%.**

In this subgroup of patients with high HER2 expressing tumours, a median overall survival of 16.0 months was observed in the FP+H arm compared with 11.8 months in the FP arm (HR 0.65 [95% CI 0.51-0.83]). In contrast, in patients whose tumours would be classified as HER2-negative using this revised definition, ie, patients with low HER2-expressing tumours (IHC 0/FISH+ and IHC 1+/FISH+), limited treatment benefit was observed (median survival times of 8.7 and 10 months in the FP and FP+H arms, respectively, HR 1.07 [95% CI 0.70; 1.62]).

Discussion on Clinical Efficacy

Therapy for gastric cancer has evolved recently and combination of either docetaxel, cisplatinum and 5-FU or epirubicin, cisplatinum and 5-FU are commonly used, however it is debatable if there exists a clear therapeutic standard. At the time the ToGa trial was started the baseline therapy was an accepted standard. The addition of docetaxel to cisplatinum/5-FU lead to an increase of mean survival from 8.6 months to 9.2 months (p=0.02, J Clin Oncol. 2006;24:4991-4997). There are no data comparing 5-FU/cisplatinum therapy to the combination of epirubicin, cisplatinum and 5-FU. Therefore the combination of trastuzumab with 5-FU/cisplatinum is considered appropriate.
The MAH has provided the results from an interim analysis of one pivotal study (ToGA) for the evaluation of safety and efficacy of trastuzumab in combination with capecitabine or intravenous 5-fluorouracil and cisplatin for the treatment of patients with HER2-positive advanced adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease. The study had a randomised, open design.

The conduct of these studies is acceptable and no deviations from GCP are apparent.

The ToGA trial has demonstrated a survival benefit for patients with gastric cancer treated with trastuzumab in combination with 5-FU/capecitabine and cisplatin. The observed survival benefit is considered clinically relevant. Consistent effects were observed in the secondary endpoints. A further refinement of the criteria for HER2 positivity leads to definition of a patient population with increased survival benefit.

Pertinent baseline data show an even distribution between the two treatment arms (FP vs FP + H) and define a clinically relevant population. Of note, most patients had metastatic disease (97% both arms) , the primary site was gastric cancer (83%; 80%), disease was mostly measurable (89%; 92%) ECOG performance was mostly very good (91%, 90%) and notably, capecitabine was the preferred fluoropyrimidine (FP) treatment in the study (88%, 87%). The proportion of patients with low HER2

overexpression (IHC 0/FISH+ and IHC 1+/FISH+) was small (22% [131/584]) as compared to patients with high HER2 overexpression (IHC 2+/FISH+ and IHC 3+ including IHC 3+/FISH negative or FISH no result; 76% [446/584]). Seven patients (1%) were classified as IHC no result/FISH+.

The primary endpoint OS is acceptable. Hazard ratio was 0.74 (95% CI 0.60-0.91, p = 0.0046), corresponding to a median OS prolongation by 2.7 months (13.8 months in the FP+H group, 11.1 months in the FP group). This difference is considered clinically meaningful. Analyses of secondary endpoints (PFS, TTP, ORR) gave consistent results.

The MAH has also analysed the data on the basis of FISH and IHC results and proposes a classification that allows for a better definition of patients likely to benefit from therapyMain determinant of this classification for HER2 positivity is ICH; therefore patients with FISH+ but IHC 0 or 1+ tumours are excluded from therapy. This new classification is supported for the gastric cancer population.

This study demonstrates that addition of Herceptin to 5-FU or capecitabine, and cisplatin dual therapy for patients with AGC provides additional benefit of increased survival time over that seen with the dual therapy alone. The 3-weekly dosing regimens used for the fluoropyrimidine (capecitabine or 5-FU) and cisplatin treatments are commonly used clinical regimens for this indication, and have been shown to be effective as first-line therapy of advanced gastric cancer (Kang Y; JCO, 2006). Six cycles of chemotherapy are in line with generally accepted routine clinical practice for the treatment of AGC in the first line metastatic setting The survival data are well supported by the positive results of the 'time to event' and 'response rate' analyses.

Even though some systematic reviews and meta analyses report best results of chemotherapy with three-drug regimens containing FU, an anthracycline and cisplatin (Wagner, A. et al, JCO 2006), both treatment arms in ToGA were offered the same regimens and therefore no bias with regard to treatment effect of trastuzumab is introduced. At the time of initiation of the ToGA trial standard therapy consisted of double therapy, it was therefore an acceptable choice for standard therapy. Therapy has evolved over time and triple therapy (either epirubicin, cisplatin, 5-FU or docetaxel, cisplatin, 5-FU) is considered current standard of care by many physicians in Europe. However, the combination of epirubicin, cisplatin and 5-FU has not been subject of a licensing procedure and there is no formal demonstration that triplets are superior to doublet therapy with cisplatin and 5-FU. The addition of docetaxel to cisplatinum/5-FU lead to an increase of mean survival from 8.6 months to 9.2 months (p=0.02, J Clin Oncol. 2006;24:4991-4997). Therefore, the estimation of benefit for these patients in comparison with the standard of care for first-line medical treatment of AGC is difficult.

The MAH initially proposed a therapeutic indication in which Herceptin is used in combination with fluoropyrimidine and 'a platinum agent'. However, it is unclear that sufficient evidence exists to support extrapolation of data from ToGA to combinations of Herceptin, fluoropyrimidine and either oxaliplatin or carboplatin. Currently there are neither robust safety data for combinations of oxaliplatin and Herceptin, nor efficacy data for carboplatin in gastric cancer. Use of platinum agents in a number of indications has demonstrated distinct safety profiles for each agent and likely differences in efficacy. Further, these agents are not used interchangeably within treatment combinations and algorithms in standard oncology practice.

Given the above, the CHMP agreed to limit the indication of Herceptin in combination with the agents evaluated in ToGA.

Based on the data submitted, there is insufficient evidence of efficacy in patients with locally advanced disease and therefore this group was excluded from the therapeutic indication. Also, insufficient evidence of efficacy were presented for the subgroup of patients with non-measurable disease, and this has been reflected in the SPC (see sSPC section 5.1).

Similarly, there remmain uncertainties about the efficacy in patients with ECOG performance status >=2 (see SPC section 5.1).

The efficacy of Herceptin has been established in patients whose tumours are characterised by IHC3+ or IHC2+ confirmed by FISH+ staining and this is reflected in the therapeutic indication.

Patients who are FISH positive but only insufficiently express the HER 2 protein (IHC 0/FISH+ or IHC 1+/FISH+) should not be treated with Trastuzumab. This is also supported from a biological perspective as the HER2 protein is the direct target for trastuzumab. In this subgroup of patients, clinically meaningful benefit can be observed. Together with the recommended scoring system (separated for breast cancer and gastric cancer) the Her 2 positivity algorithm must be reflected in Section 5.1 of the SmPC.

1. 2. 3. Clinical Safety

This submission includes the clinical safety data from 584 patients with AGC from the ToGA trial who were included in the second interim analysis (clinical cut off date January 7, 2009), 294 of whom received trastuzumab in addition to fluoropyrimidine and cisplatin.

Adverse events

At the time of clinical cut-off, almost all patients in both treatment arms had experienced at least one adverse event. The incidence of serious adverse events was slightly higher in the FP+H arm than in the FP arm (32% vs 28%). A similar proportion of adverse events leading to death were seen in each arm (5% in the FP arm and 6% in the FP+H arm). Slightly fewer patients were withdrawn from the FP+H arm than the FP arm as a result of adverse events (11% vs 15%).

Overview of Adverse Events

Number of Patients (%) with	Fluoropyrimidine/ Cisplatin N=290	Trastuzumab/ Fluoropyrimidine/ Cisplatin N=294
Any AEs	284 (98%)	292 (99%)
Grade 3/4 AEs	198 (68%)	201 (68%)
Related AEs	271 (93%)	283 (96%)
Serious AEs	81 (28%)	95 (32%)
AEs leading to withdrawal from study	43 (15%)	32 (11%)
AEs leading to discontinuation of at least 1 treatment component	48 (17%)	48 (16%)
AEs leading to dose modifications/ interruptions	237 (82%)	246 (84%)
AEs with fatal outcome	14 (5%)	17 (6%)

The most common AEs recorded during the study (occurring with an incidence of ≥ 5%) are summarized by SOC below. The most common AEs in both treatment arms were nausea, vomiting, neutropenia and anorexia. Adverse events which occurred with a higher frequency in the FP+H arm than the FP arm (≥ 5% difference) included diarrhea, stomatitis, anemia, thrombocytopenia, fatigue, pyrexia, mucosal inflammation, chills, dysgeusia, weight decrease and nasopharyngitis.

Body System/ Adverse Event	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
GASTROINTESTINAL DISORDERS		
NAUSEA	184 (63)	197 (67)
VOMITING	134 (46)	147 (50)
DIARRHOEA	80 (28)	109 (37)
CONSTIPATION	93 (32)	75 (26)
STOMATITIS	43 (15)	72 (24)
ABDOMINAL PAIN	42 (14)	46 (16)
ABDOMINAL PAIN UPPER	15 (5)	27 (9)
DYSPEPSIA	16 (6)	18 (6)
DYSPHAGIA	10 (3)	19 (6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	165 (57)	157 (53)
ANAEMIA	61 (21)	81 (28)
THROMBOCYTOPENIA	33 (11)	47 (16)
FEBRILE NEUTROPENIA	8 (3)	15 (5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	82 (28)	102 (35)
ASTHENIA	53 (18)	55 (19)
PYREXIA	36 (12)	54 (18)
MUCOSAL INFLAMMATION	18 (6)	37 (13)
OEDEMA	25 (9)	22 (7)
OEDEMA PERIPHERAL	12 (4)	17 (6)
CHILLS	-	23 (8)
METABOLISM AND NUTRITION DISORDERS		
ANOREXIA	133 (46)	135 (46)
HYPOKALAEMIA	13 (4)	22 (7)
DEHYDRATION	16 (6)	18 (6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	64 (22)	75 (26)
ALOPECIA	27 (9)	32 (11)
PIGMENTATION DISORDER	16 (6)	19 (6)
RASH	12 (4)	16 (5)
NERVOUS SYSTEM DISORDERS		
DIZZINESS	28 (10)	31 (11)
PERIPHERAL SENSORY NEUROPATHY	24 (8)	23 (8)
NEUROPATHY PERIPHERAL	21 (7)	24 (8)
DYSGEUSIA	14 (5)	28 (10)
HEADACHE	19 (7)	14 (5)
INVESTIGATIONS		
WEIGHT DECREASED	40 (14)	69 (23)
CREATININE RENAL CLEARANCE DECREASED	19 (7)	24 (8)
WEIGHT INCREASED	15 (5)	21 (7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
HICCUPS	28 (10)	34 (12)
COUGH	17 (6)	19 (6)
DYSPNOEA	16 (6)	9 (3)
RENAL AND URINARY DISORDERS		
RENAL IMPAIRMENT	39 (13)	47 (16)
NEPHROPATHY TOXIC	12 (4)	18 (6)
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	17 (6)	37 (13)
UPPER RESPIRATORY TRACT INFECTION	10 (3)	15 (5)
PSYCHIATRIC DISORDERS		
INSOMNIA	20 (7)	24 (8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	15 (5)	12 (4)

Overall, the incidence of Grade ≥ 3 AEs was similar in the two treatment groups (68% in each arm). Grade 3 or 4 AEs that occurred in ≥ 1% of patients in either treatment group are summarized below.

There was an increased incidence of Grade ≥ 3 AEs in the FP+H arm compared to the FP arm in body systems such as gastrointestinal disorders (21% in FP, 26% in FP+H) with Grade 3 or 4 diarrhea reported by 9% of patients in the FP+H arm compared with 4% of patients in the FP arm. Metabolism and nutrition disorders were seen in 11% in FP, 14% in FP+H and general disorders and administration site conditions were reported for 9% in FPand 13% in FP+H.

Neutropenia, commonly associated with fluoropyrimidine plus platinum therapy, was the most common Grade ≥ 3 event in both treatment arms (29% in FP, 35% in FP+H).

Summary of Grade ≥ 3 AEs occurring with an incidence of at least 1% by trial treatment (SAP)

Body System/ Adverse Event	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	88 (30)	79 (27)
ANAEMIA	30 (10)	36 (12)
FEBRILE NEUTROPENIA	8 (3)	15 (5)
THROMBOCYTOPENIA	8 (3)	14 (5)
LEUKOPENIA	2 (<1)	7 (2)
PANCYTOPENIA	3 (1)	-
GASTROINTESTINAL DISORDERS		
NAUSEA	21 (7)	22 (7)
VOMITING	22 (8)	18 (6)
DIARRHOEA	11 (4)	27 (9)
ABDOMINAL PAIN	4 (1)	4 (1)
DYSPHAGIA	1 (<1)	7 (2)
STOMATITIS	6 (2)	2 (<1)
CONSTIPATION	5 (2)	2 (<1)
GASTROINTESTINAL HAEMORRHAGE	3 (1)	4 (1)
ABDOMINAL PAIN UPPER	1 (<1)	3 (1)
METABOLISM AND NUTRITION DISORDERS		
ANOREXIA	18 (6)	19 (6)
HYPOKALAEMIA	7 (2)	13 (4)
HYPONATRAEMIA	6 (2)	11 (4)
DEHYDRATION	5 (2)	7 (2)
HYPOALBUMINAEMIA	2 (<1)	5 (2)
HYPOCALCAEMIA	1 (<1)	3 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
ASTHENIA	10 (3)	14 (5)
FATIGUE	7 (2)	12 (4)
MUCOSAL INFLAMMATION	2 (<1)	6 (2)
DEATH	1 (<1)	3 (1)
PYREXIA	-	3 (1)
INVESTIGATIONS		
WEIGHT DECREASED	7 (2)	6 (2)
HAEMOGLOBIN DECREASED	-	4 (1)
NERVOUS SYSTEM DISORDERS		
LETHARGY	1 (<1)	3 (1)
DEPRESSED LEVEL OF CONSCIOUSNESS	-	3 (1)
INFECTIONS AND INFESTATIONS		
SEPTIC SHOCK	5 (2)	1 (<1)
ORAL CANDIDIASIS	-	3 (1)
PNEUMONIA	-	3 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	4 (1)	4 (1)
DYSPNOEA	5 (2)	1 (<1)
VASCULAR DISORDERS		
DEEP VEIN THROMBOSIS	2 (<1)	3 (1)
RENAL AND URINARY DISORDERS		
RENAL FAILURE ACUTE	2 (<1)	3 (1)
RENAL IMPAIRMENT	3 (1)	2 (<1)
RENAL FAILURE	-	3 (1)
HEPATOBILIARY DISORDERS		
HYPERBILIRUBINAEMIA	1 (<1)	4 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	5 (2)	4 (1)

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Data Source: ae11ctc_3001

Definition of Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

– is fatal;

– is life-threatening

– required in-patient hospitalization or prolongation of existing hospitalization;
– results in persistent or significant disability/incapacity;
– is a congenital anomaly/birth defect;
– is medically significant or requires intervention to prevent one or other of the outcomes listed above

Summary of SAEs with an incidence rate of at least 1% in at least one treatment arm (SAP)

Body System/ Adverse Event	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	81 (28)	95 (32)
Total Number of AEs	122	174
GASTROINTESTINAL DISORDERS		
DIARRHOEA	6 (2)	17 (6)
VOMITING	3 (1)	8 (3)
DYSPHAGIA	-	8 (3)
NAUSEA	4 (1)	3 (1)
ABDOMINAL PAIN	3 (1)	1 (<1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
FEBRILE NEUTROPENIA	8 (3)	11 (4)
ANAEMIA	7 (2)	3 (1)
NEUTROPENIA	3 (1)	2 (<1)
PANCYTOPENIA	3 (1)	-
INFECTIONS AND INFESTATIONS		
PNEUMONIA	-	6 (2)
SEPTIC SHOCK	5 (2)	1 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
ASTHENIA	3 (1)	3 (1)
MUCOSAL INFLAMMATION	3 (1)	2 (<1)
PYREXIA	2 (<1)	3 (1)
DEATH	1 (<1)	3 (1)
METABOLISM AND NUTRITION DISORDERS		
DEHYDRATION	6 (2)	5 (2)
ANOREXIA	3 (1)	4 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	3 (1)	3 (1)
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	4 (1)	7 (2)
RENAL FAILURE ACUTE	1 (<1)	3 (1)

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

There were 95 patients (32%) with a total of 174 SAEs in the FP + H arm and 81 patients (28%) with a total of 122 SAEs in the FP arm .

Fifty-two percent (63/122) of SAEs in the FP arm and 55% (**96/174**) of SAEs in the FP+H arm were considered by the investigator to be related to treatment

Relationship of Adverse Events to Treatment

Investigators classified adverse events as either unrelated to treatment or related to treatment. Treatment included trastuzumab as well as FP.

Sixty-three percent and 65% of AEs were considered related to the treatment in the FP arm and the FP+H arm, respectively. The majority of these AEs were classified as gastrointestinal disorders (67% in FP, 70% in (FP+H), blood and lymphatic system disorders (86% in FP, 86% in FP+H), general disorders and administration site conditions (58% in FP, 67% in FP+H), metabolism and nutrition disorders (71% in FP, 72% in FP+H), skin and subcutaneous tissue disorders (84% in FP, 78% in FP+H) and nervous system disorders (62% in FP, 63% in FP+H).

Overall, fewer patients in the FP+H arm (32 patients, 11%) were withdrawn from the study as a result of an AE than in the FP arm (43 patients, 15%).

Dose modifications or treatment interruptions of at least one component of study treatment were also recorded by a similar proportion of patients in each group (82% of patients in the FP arm and 84% of patients in the FP+H arm).

The most common reasons for dose modification or interruption in the two study arms were: neutropenia (54% in FP, 50% in FP+H), thrombocytopenia (8% in FP, 11% in FP+H), nausea (13% in each arm), vomiting (11% in each arm), renal impairment (13% in FP, 14% in FP+H) and weight decrease (3% in FP, 13% in FP+H).

Summary of Adverse events leading to discontinuation of at least one trial treatment

Body System/ Adverse Event	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	48 (17)	48 (16)
Total Number of AEs	50	53
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	7 (2)	12 (4)
DIARRHOEA	-	4 (1)
DYSPHAGIA	-	2 (<1)
ENTERITIS	1 (<1)	1 (<1)
GASTRIC HAEMORRHAGE	1 (<1)	1 (<1)
NAUSEA	1 (<1)	1 (<1)
GASTROINTESTINAL HAEMORRHAGE	-	1 (<1)
ILEUS	-	1 (<1)
OBSTRUCTION GASTRIC	1 (<1)	-
PANCREATITIS ACUTE	1 (<1)	-
PERITONITIS	1 (<1)	-
STOMATITIS	1 (<1)	-
UPPER GASTROINTESTINAL HAEMORRHAGE	-	1 (<1)
Total Number of AEs	7	12
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	4 (1)	9 (3)
RENAL IMPAIRMENT	1 (<1)	4 (1)
NEPHROPATHY TOXIC	2 (<1)	2 (<1)
RENAL FAILURE ACUTE	1 (<1)	2 (<1)
RENAL FAILURE	-	1 (<1)
Total Number of AEs	4	9
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	8 (3)	4 (1)
THROMBOCYTOPENIA	5 (2)	2 (<1)
FEBRILE NEUTROPENIA	-	2 (<1)
ANAEMIA	1 (<1)	-
NEUTROPENIA	1 (<1)	-
PANCYTOPENIA	1 (<1)	-
Total Number of AEs	8	4
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	6 (2)	4 (1)
PERIPHERAL MOTOR NEUROPATHY	1 (<1)	2 (<1)
CEREBROVASCULAR ACCIDENT	1 (<1)	1 (<1)
CEREBRAL INFARCTION	1 (<1)	-
DEPRESSED LEVEL OF CONSCIOUSNESS	-	1 (<1)
HYPOGLYCAEMIC COMA	1 (<1)	-
LETHARGY	1 (<1)	-
PARAESTHESIA	1 (<1)	-
PERIPHERAL SENSORY NEUROPATHY	-	1 (<1)
Total Number of AEs	6	5
CARDIAC DISORDERS		
Total Pts With at Least one AE	6 (2)	2 (<1)
MYOCARDIAL INFARCTION	2 (<1)	-
ACUTE MYOCARDIAL INFARCTION	-	1 (<1)
CARDIAC ARREST	1 (<1)	-
CARDIAC FAILURE	1 (<1)	-
CARDIO-RESPIRATORY ARREST	1 (<1)	-
MYOCARDIAL ISCHAEMIA	-	1 (<1)
PRINZMETAL ANGINA	1 (<1)	-
Total Number of AEs	6	2

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU.

Infusion reactions

Seventeen patients (6%) experienced at least one typical infusion-related AE of CTC Grade ≥ 3 on the day of or the day after a trastuzumab infusion. The reported events were gastrointestinal disorders (nausea or vomiting, 11 patients), general disorders and administration site conditions (asthenia, fatigue or chills, 9 patients) and immune system disorders (hypersensitivity, 1 patient). None of them was fatal. The proportion of patients experiencing typical infusion-related AEs starting on the day of or the day after trastuzumab infusion after each infusion was summarized by treatment cycle .

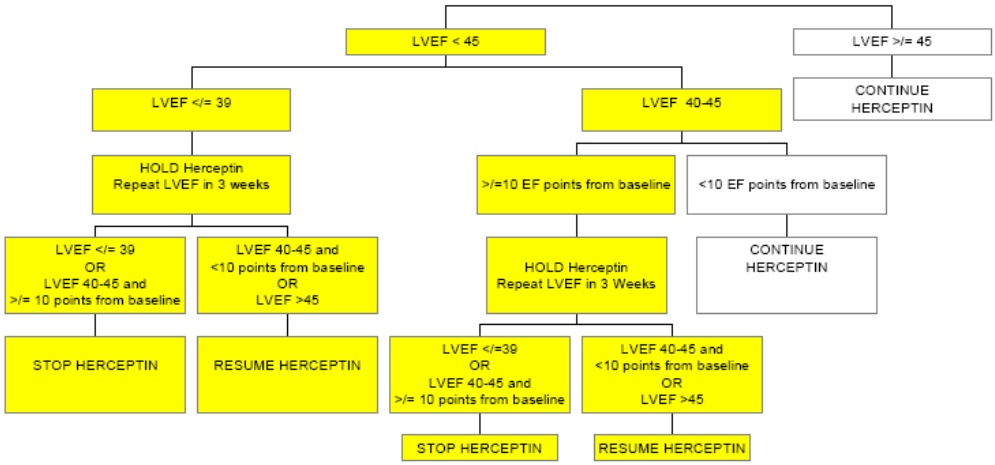
The proportion of patients experiencing these events generally decreased with each infusion: 41% of patients in the FP+H arm reported a typical infusion-related event on the day of or the day after the first infusion, while only 2% of patients reported such an AE after the eighth infusion.

Cardiac safety

Cardiotoxicity is a known risk of treatment with trastuzumab. The current SmPC states that all candidates for treatment should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram and/or MUGA scan, and a careful risk-benefit assessment conducted prior to starting treatment with trastuzumab. It is also recommended that cardiac function be monitored regularly (e.g. every three months) during treatment, and patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). Discontinuation of treatment should be considered in patients who develop cardiac failure or who have a continued decrease in LVEF.

In order to monitor cardiac safety in the ToGA trial, LVEF measurements were performed using MUGA or echocardiography, and the same technique used throughout the study for each individual patient. All patients were required to have a baseline LVEF of ≥ 50%. LVEF was monitored every 12 weeks during the study. Additional LVEF measurements were performed at the investigator's discretion in the case of concerns that an AE may be related to cardiac dysfunction.

Trastuzumab was discontinued in all patients for whom a drop of LVEF to a value below 40% was documented and confirmed with a repeat assessment within 3 weeks of the first assessment, and in any patient who developed clinical symptoms and signs suggesting congestive heart failure, with the diagnosis confirmed by chest X-ray, and a drop in LVEF by MUGA or echocardiography.



Note: LVEF assessment results must be available before/on the day of the next scheduled trastuzumab administration, and a decision to give or withhold that dose must be made based on this algorithm.

Cardiac adverse events

Overall, 33% (193/584) of patients were recorded to have a previous or concurrent cardiovascular disease with a slightly higher incidence in the FP+H arm (30% [88/290] in
FP, 36% [105/294] in FP+H;). The most frequently observed cardiovascular diseases were vascular disorders (27% in FP, 30% in FP+H), amongst which hypertension was the dominant component (26% in FP, 29% in FP+H), and cardiac disorders (8% in FP, 11% in FP+H).
Eight percent of patients in the FP arm and 11% patients in the FP+H arm reported aprevious cardiovascular disease which was no longer active at the start of study. These consisted of cardiac disorders (4% in FP, 6% in FP+H), including myocardial infarction (2% in FP+H and none on FP), and vascular disorders (4% in FP, 5% in FP+H) with 4% and 5% of patients in the FP arm and the FP+H arm, respectively,having hypertension.
Active cardiovascular diseases (as allowed per protocol) at baseline was recorded by 25% of patients in the FP arm and 28% of patients in the FP+H arm. The most common condition was hypertension, reported by 22% and 24% of patients in the FP and FP+H arms, respectively. Active cardiac disorders (as allowed per protocol) were recorded by 5% of patients in each treatment arm.
Six percent of patients in both treatment groups experienced cardiac adverse events. Four patients (1%) in the FP+H arm recorded a Grade ≥ 3 cardiac event, compared with nine patients (3%) in the FP arm. Two patients in each group died as a result of cardiac events: cardiac arrest and cardio-respiratory arrest in the FP arm and, in the FP+H arm, cardiac failure plus unstable angina, and acute myocardial infarction.

Summary of grade > 3 cardiac adverse events

Body System/ Adverse Event	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
CARDIAC DISORDERS		
Total Pts With at Least one AE	9 (3)	4 (1)
CARDIAC FAILURE	2 (<1)	1 (<1)
MYOCARDIAL INFARCTION	2 (<1)	-
ACUTE MYOCARDIAL INFARCTION	-	1 (<1)
ANGINA UNSTABLE	-	1 (<1)
ARTERIOSPASM CORONARY	1 (<1)	-
ATRIAL FLUTTER	1 (<1)	-
CARDIAC ARREST	1 (<1)	-
CARDIO-RESPIRATORY ARREST	1 (<1)	-
MYOCARDIAL ISCHAEMIA	-	1 (<1)
PRINZMETAL ANGINA	1 (<1)	-
TACHYCARDIA	-	1 (<1)
Total Number of AEs	9	5

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Neither of the two patients in the FP+H group who had received prior anthracycline therapy experienced cardiac disorders during the study.

Assessment of LVEF change

At screening, the median LVEF value was 64% in the FP arm and 65% in the FP+H arm.

Significant decreases in LVEF (ie, a decrease of ≥ 10% resulting in a LVEF value of < 50%) were recorded on at least one occasion during the study by 11 patients (**4.6%)** in the FP+H arm compared to 2 patients (**1.1%)** in the FP arm (table below).

A further 39 patients (**16.5%**) in the FP+H arm experienced decreases in LVEF of ≥ 10% from screening (with LVEF ≥ 50%), compared to 22 patients (**11.8%)** in the FP arm.

LVEF measurements are summarized showing median and range for baseline values, and frequency of absolute drop in **LVEF of ≥ 10%,** and drops to **a value < 50%.**

Summary of LVEF Change from Screening Over Time

	Fluoropyrimidine/ Cisplatin N=290	Trastuzumab/ Fluoropyrimidine/ Cisplatin N=294
Screening		
n	287	293
Median	64	65
Range	48-90	50-86
Lowest Post-Screening Value		
n (with Screening and Post-Screening Values)*	187	237
Absolute Decrease >=10% and Absolute Value <50%	2 (1.1%)	11 (4.6%)
Absolute Decrease >=10% and Absolute Value >=50%	22 (11.8%)	39 (16.5%)
Absolute Decrease <10%	88 (47.1%)	108 (45.6%)
No Change	14 (7.5%)	13 (5.5%)
Absolute Increase	61 (32.6%)	66 (27.8%)
n (with Post-Screening Values)	190	239
Absolute Value <50%	2 (1.1%)	14 (5.9%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

* Only includes patients whose method of assessment at that visit is the same as at their initial assessment

Deaths

At the time of clinical cut-off, 182 patients (63%) in the FP arm and 167 patients (57%) in the FP+H arm had died (see table).Disease progression of the underlying gastric cancer accounted for the majority of these deaths: 167 deaths in the FP arm and 148 deaths in the trastuzumab arm.

Summary of causes of deaths

Cause of Death	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
Total No. of Deaths	182 (63)	167 (57)
GASTRIC CANCER	167 (58)	148 (50)
DEATH	1 (<1)	3 (1)
NK	1 (<1)	2 (<1)
SEPTIC SHOCK	2 (<1)	1 (<1)
PNEUMONIA	-	2 (<1)
PULMONARY EMBOLISM	2 (<1)	-
ACUTE MYOCARDIAL INFARCTION	-	1 (<1)
ANGINA UNSTABLE	-	1 (<1)
BILIARY SEPSIS	-	1 (<1)
BLOOD PRESSURE DECREASED	1 (<1)	-
CARDIAC ARREST	1 (<1)	-
CARDIO-RESPIRATORY ARREST	1 (<1)	-
CEREBRAL INFARCTION	1 (<1)	-
CEREBROVASCULAR ACCIDENT	1 (<1)	-
COMPLETED SUICIDE	1 (<1)	-
DEPRESSED LEVEL OF CONSCIOUSNESS	-	1 (<1)
DYSPHAGIA	-	1 (<1)
GASTRIC HAEMORRHAGE	-	1 (<1)
GASTROINTESTINAL PERFORATION	-	1 (<1)
HAEMORRHAGE INTRACRANIAL	1 (<1)	-
ILEUS	-	1 (<1)
PANCYTOPENIA	1 (<1)	-
PARANEOPLASTIC SYNDROME	-	1 (<1)
PYLORIC STENOSIS	1 (<1)	-
RENAL FAILURE	-	1 (<1)
THROMBOCYTOPENIA	-	1 (<1)

Investigator text for Cause of Death encoded using MedDRA version 11.1.
Percentages are based on N.
Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU.
Cause of Death for Patient 63685/2063 was CARDIAC FAILURE (not shown) as well as ANGINA UNSTABLE (as shown)
NK = cause of death not known
DD11 20APR2009:07:42:18 dd11_3001

Overall, 34 patients died due to causes not reported as or not related to disease progression. **Fourteen (14)** patients in the FP arm and **17** patients in the FP+H arm died as a result of an adverse event. The cause of death was "not known" in a further **three** patients.

A total of **ten deaths (10/17 or 59%)** in the FP+H arm were considered to be due to treatment-related AEs (2 cases of "death", 2 cases of pneumonia, one case of cardiac failure plus unstable angina, and one case each of acute myocardial infarction, gastric hemorrhage, depressed level of consciousness, thrombocytopenia and renal failure), compared to **three deaths (3/14 or 21%)** in the FP arm ("death", septic shock and pancytopenia).
Narratives, summary table and a listing of deaths resulting from adverse events are presented in the study report. 32 outcomes of death are listed for 31 patients. (with one patient having two adverse events that led to death and considered by the investigator to be both related to study medication).

Summary of treatment related adverse events leading to death.

Cause of death	Fluoro-pyrimidine/ Cisplatin N = 290 No. (%)	Trastuzumab/ Fluoro-pyrimidine/ Cisplatin N = 294 No. (%)
Total Pts with at Least one AE	3 (1)	10 (3)
Total Number of AEs	3	11
SEPTIC SHOCK	1 (<1)	-
PNEUMONIA	-	2 (<1)
ACUTE MYOCARDIAL INFARCTION	-	1 (<1)
ANGINA UNSTABLE	-	1 (<1)
CARDIAC FAILURE	-	1 (<1)
GASTRIC HAEMORRHAGE	-	1 (<1)
DEATH	1 (<1)	2 (<1)
DEPRESSED LEVEL OF CONSCIOUSNESS	-	1 (<1)
PANCYTOPENIA	1 (<1)	-
THROMBOCYTOPENIA	-	1 (<1)
RENAL FAILURE	-	1 (<1)

Most of the fatal treatment related AEs were due to

• infections and infestations: **1** patient with septic shock in the FP arm and **2** patients with pneumonia in the FP+H arm
• cardiac disorders: **2** patients with 3 Aes in the FP+H arm (cardiac failure and unstable angina , acute myocardial infarction)
• gastrointestinal disorders: **1** patient in the FP+H arm (gastric hemorrhage).
• general disorders and administration site conditions: **1** patient in the FP arm and **2** patients in the FP+H arm (death).
• nervous system disorders: **1** patient in the FP+H arm (depressed level of consciousness)
• blood/lymphatic system disorders: **1** patient with pancytopenia in the FP arm and **1** patient with thrombocytopenia in the FP+H arm
• renal and urinary disorders: **1** patient with renal failure in the FP+H arm

However, considering the full analysis set (FAS) there was no difference between treatment arms in the incidence of death within 60 days of first administration of study drug (6.9% in FP, 5.1% in FP+H) as well as during treatment or within 6 months (37.2% in FP, 35.4% in FP+H

HER2 Subgroup Safety Analysis

A similar incidence of Grade ≥ 3 AEs was observed in both subgroups: 67% [47/70] in FP, 69% [42/61] in FP+H in the low HER2 expressing group and 69% [150/218] in FP, 68% [154/228] in FP+H for the high HER2 expressing group. Blood and lymphatic disorders were the most common Grade ≥ 3 events, occurring at a similar frequency between treatment arms in both the low and high HER2 expressing subgroups.
In the high HER2 expressing group, 10 patients experienced 10 Grade ≥ 3 cardiac AEs (7 pts [3%] in FP, 3 pts [1%] in FP+H) In the FP arm, 7 events were Grade ≥ 3 In the FP+H arm, there were 3 Grade ≥ 3 events. In the low HER2 expressing group, two patients in the FP arm experienced a Grade ≥ 3 cardiac event and one patient in the FP+H arm experienced two events.

Serious adverse events were reported by a total of 38 patients in the low HER2 expressing group (24% [17/70] in FP, 34% [21/61] in FP+H). A total of 227 SAEs in 133 patients with high expressing HER2 tumours were reported across the two treatment arms. A similar number of patients experiencing SAEs was observed in the two arms (29% [64/218] in FP, 30% [69/228] in FP+H)

At the time of the clinical cut-off (January 7, 2009), 88 patients in the low HER2 expressing group had died. Six of these deaths were due to adverse events (2 pts in FP, 4 pts in FP+H). In the high expressing HER2 group, a total of 256 patients had died, 23 patients in this group died due to adverse events (12 pts in FP, 11 pts in FP+H).

The incidence of Grade ≥ 3 laboratory abnormalities during the study was similar between treatment arms in both the low HER2 and high HER2 expressing group.

Laboratory findings

During the study the majority of patients in either study arm did not exhibit a shift from their baseline laboratory test parameter values or exhibited a shift of 2 grades or less between baseline and their worst test value.

The most common Grade ≥ 3 hematologic toxicity was low neutrophils and low hemoglobin which had a slightly higher incidence in the FP+H arm compared to the FP arm (35% vs 29% and 22% vs 18%, respectively). These Grade 3/4 shifts are correlated with reported Grade ≥ 3 AEs of neutropenia and anemia.

Blood chemistry parameters with Grade ≥ 3 during the treatment period show a potential influence of trastuzumab (FP+H vs FP) on lower potassium (10% vs 6%) , lower sodium (16% vs 14%), lower calcium (5% vs 2%) and albumin levels (3% vs <1%). The incidence of other Grade ≥ 3 abnormalities for other laboratory parameters was low and not markedly different between the two treatment arms.

Pharmacovigilance/Risk Management Plan

The applicant has provided an updated Risk Management Plan with the application for an extension of indication. Version 5.0 of the RMP is presented in a structure completely different from the previous version.
A number of changes and corrections are requested for the updated RMP taking into account the information from the new indication.

Risk Management Plan

- **Safety Specification**

An updated RMP, Version 5.0 with data lock point 18.04.2009 has been provided.

1. Safety Specification

No changes of non-clinical data to version 4.0

Limitation of the Human Safety Database
Exposure for early and metastatic breast cancer has reached approximately 645,505 patient years in the post-marketing setting and in clinical trials.
Exposure data are presented with regard to indication, treatment duration and dosing schedule. In USA in 2009 distribution was 80% adjuvant and 20% for metastatic breast cancer. Outside USA it is assumed that 62% of patients will be treated for early breast cancer and 38% for metastatic breast cancer, except Japan, where the split is 70%:30%.
The Applicant assumed that safety data from patients treated for early and metastatic breast cancer could be extrapolated to the intended population in gastric cancer.

Gastric cancer
In study BO18255 (ToGA) 584 patients had been treated, whereof 294 patients received trastuzumab, additionally to treatment with Fluoropyrimidine and cisplatin. 77% of patients were male and 23% were female. There is a difference in gender distribution with regard to exposure data up to now. The Applicant does not anticipate any specific difference in the safety profile with regard to the gender distribution.

The accuracy of HER2 testing in human gastric tumours including GE junction is crucial to select the right patient for HER2 target therapy with Herceptin. The quality of HER2 testing results can be affected by several factors, such as the fixative reagent used or the duration of fixation. If validated assays are not used, the accuracy can be affected as well.

Adverse events/adverse reactions
No new safety concern had been identified.

Identified risks

Cardiotoxicity
Early breast cancer
The incidence of grade III and IV congestive heart failure was 0-0.49% among patients not treated with trastuzumab. The incidence of LVEF decrease of more than 10% in patients receiving trastuzumab ranged from 2.2 to 17%.

Metastatic breast cancer
The incidence of congestive heart failure was 3.9-5% in patients not receiving trastuzumab, depending on the administered treatment regimen. The incidence was 1% in patients treated with paclitaxel only. LVEF decreases of more than 10% occurred in 19% of patients receiving trastuzumab.

Gastric cancer
1.1% of patients not receiving trastuzumab experienced a drop of LVEF from baseline of at least 10% to an absolute LVEF value below 50% compared to 4.6% of patients receiving trastuzumab. As risk factors for occurrence of cardiotoxicity the age above 50 years, prior anti-hypertensive medication used or low LVEF prior to or following paclitaxel administration had been reported, as well as previous anthracycline therapy.

Infusion-related reactions
The Applicant performed a search of the safety database.
Out of 5035 identified events of infusion related reactions 129 events had a fatal outcome.
No data on infusion related reactions in BO18255 had been presented.

Haematotoxicity
In all clinical trials in the indication breast cancer, an increased incidence of haematotoxicity in patients treated with trastuzumab, compared with those not receiving trastuzumab, has been observed, although no underlying mechanism for haematotoxicity has been identified yet.

Oligohydramnios
Up to the cut off date of 08.08.2008 11 cases of oligohydramnios, out of about 150 pregnancies, had been identified, whereof 2 infants died, one due to complications of premature birth and the other one because of pulmonary hypoplasia.
As requested by FDA, the Applicant started a pregnancy registry for patients becoming pregnant during treatment or within 6 months after end of therapy with trastuzumab.

Interactions with other medicinal products, food and other substances
No formal drug interaction studies had been performed.´

Epidemiology of the indication
Breast cancer
In Europe, breast cancer is the most commonly diagnosed cancer in women (429,000 new breast cancers in 2006 or 28.9% of total cancers in Europe. It has been estimated tha t approximately 25-30% of diagnosed breast cancers are HER2-positive.
In Europe, breast cancer was the third leading cause of death (131,900 new deaths) in 2006. 5-year survival of patients with early breast cancer is greater 85%, compared to about 25% of patients with metastatic disease.
HER2 overexpression of breast cancer is associated with poorer prognosis.
48% of patients with HER2+ breast cancer are 55 years old or older and the majority (80%) are white.

Gastric cancer
In Europe gastric cancer is the fifth most common cancer with about 150,000 new cases per year. HER2 is overexpressed in approximately 20% of all gastric cancer.
Mortality rates are 18.1 per 100,000 in men and 8.3 per 100,000 in women in Europe. Gastric cancer accounts for approximately 6-7% of cancer deaths. 5-year survival does not exceed 25%.
Incidences of gastric cancer increases with age, with a peak between 50-70 years.
High risk areas include Japan, China, Eastern Europe and some countries in Central and South America.
Risk factors are smoking, lower socioeconomic status, Helicobacter pylori infection, and diet factors such as salty food as well as obesity.

Relevant comorbidities in the target population
Data form eight US cancer care centers suggest that hypertension is the most common comorbidity in breast cancer patients (34.5%)
For gastric cancer data from Netherlands suggest that cardiovascular diseases (19-21%) and hypertension (15-19%) are the most common comorbidities.

Epidemiology in unexposed target population
Cardiotoxicity

General breast cancer patients
Data from Netherlands suggests, that patients treated with cardiotoxic chemotherapy had rates of 69.3/1000 patient years (PY) for any cardiovascular hospitalisation, 3.6/1000PY for heart failure and 21.5/1000 PY for other cardiovascular disease. Patients treated with non-cardiotoxic chemotherapy had nearly similar hospitalisation rates, 98.3/1000 PY for any cardiovascular hospitalisation, 8.3/1000 PY for cerebrovascular disease and 29.5/1000 PY for other cardiovascular disease.
Early breast cancer HER+
Data form 3 trials in US, Canada and Europe showed incidences of grade III/IV congestive heart failure of 0-0.49% among patients not treated with trastuzumab. The incidence of LVEF decrease of more than 105 ranged from 2.2% to 17% with mortality ranging form 0.06-0.15%

Metastatic breast cancer
Data from 3 trials in US, Canada and Europe showed incidences of congestive heart failure of 3.9-5%, depending on chemotherapeutic regimen and was 1% in patients only receiving paclitaxel. Drop of LVEF more than 10% occurred at an incidence of 19%. Mortality rate was 0.43%.

Gastric cancer
One clinical trial reported a 1.1% incidence of decreased LVEF among patients with advanced HER2+ gastric cancer.

Haematological toxicity

Early breast cancer
The incidence of neurtropenia in 2 trials in US, Canada and Europe ranged from 0.7% (grade 4-5) to 4.5% (grades 2-5).
Metastatic breast cancer, HER+
The incidence of neutropenia was 26%.
Cancer patients in general with febrile neutropenia have a risk for mortality ranging form 2.6% up to 21.4%, depending on comorbidities.

Gastric cancer
One clinical trial showed incidence of r neutropenia ranging from 59-80%, depending on chemotherapeutic regimen. Mortality rates in general range from 2.6% to 21.4%, depending on comorbidities.

2. Pharmacovigilance Plan

Summary of safety concerns and planned pharmacovigilance actions

Safety Concern	**Planned Action(s)**
Important Identified Risks	
1. Cardiotoxicity	Study BO20652 is currently ongoing. First and second interim analyses have been submitted with the corresponding PSURs with a September 25 DLP. Ongoing use of guided questionnaire in an effort to better characterise cardiotoxicity associated with Herceptin use. Treatment algorithm describing actions to be taken in the event of onset of decreased ejection fractions.
2. Infusion Related Reactions	Routine pharmacovigilance practices.
3. Haematotoxicity	Routine pharmacovigilance practices.
4. Oligohydramnios	Routine pharmacovigilance practices.

Pharmacovigilance action plan for cardiotoxicity

Safety Concern	**Cardiotoxicity**
Action(s) Proposed	Cardiac AE specific safety study BO20652 (OHERA)
Objective of Proposed Action(s)	**Primary objective**: • To observe the incidence of symptomatic congestive heart failure (CHF) (NYHA class II, III and IV) and cardiac death in patients treated with Herceptin® in routine clinical practice setting. **Secondary objectives**: • To explore potential risk factors for symptomatic congestive heart failure. • To observe the time to onset and the time to recovery of symptomatic congestive heart failure. • To observe the incidence of asymptomatic cardiac failure and other significant cardiac conditions. • To observe the incidence of asymptomatic cardiac failure

Rationale for Proposed Action(s)	The incidence of asymptomatic left ventricular dysfunction and symptomatic CHF was very low in the Herceptin® treated patients participating in the HERA study. However, the likelihood exists that cardiac failure may occur at a higher rate in ordinary clinical practice than in the setting of a randomized controlled clinical trial with strict entry criteria. This observational, single cohort safety study has been designed to observe the occurrence of cardiac events in patients with HER2 positive early breast cancer treated with Herceptin® in daily clinical practice. It is a non-interventional, observational study that serves as a commitment study to the EMEA approval in early breast cancer.
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Professional labelling may be altered in response to the results of this study following consultation with the relevant competent authorities.
Milestone for evaluation and reporting including justification for choice of milestones	Baseline information will be collected from all enrolled patients who signed the informed consent form. All patients receiving Herceptin® will be treated and monitored according to the local clinical practice. Data will be collected from centre's medical records for up to 5 years or death, unless they are lost to follow-up or withdraw the informed consent. Patients will be monitored irrespective of actual treatment regimen they receive for the early as well as recurrent or metastatic disease. Once a year the data will be analyzed and presented to Competent Authorities for review.
Titles of protocol	An Observational Study Of Cardiac Events In Patients With HER2 Positive Early Breast Cancer Treated With Herceptin®.

Overview of study protocols for the pharmacovigilance plan

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
BO20652 (OHERA)	Version A	Active	Annually with the September PSUR (DLP 25 Sep)	Circa 2014

Summary of outstanding actions, including milestones

Actions	Milestones / Exposure	Milestones / Calendar Time	Study Status
Annual analysis	N/A	With the PSUR – data lock point 25 September.	Ongoing

3. Evaluation of the need for risk minimisation measures

Summary of planned risk minimisation actions

Safety Concern	Are Routine Risk Minimisation Activities Sufficient?	**Proposed Actions**
Important Identified Risks		
5. Cardiotoxicity	No	Algorithm is provided in professional labelling and is available to prescribers globally via package inserts. **Criteria to be Used to Verify the Success of Proposed Risk Minimisation Activity** Analysis annually with the scheduled PSURs of the actions taken with Herceptin by prescribers globally in response to decreased LVEF and the outcome of the reported adverse event.

		Additional Risk Minimisation: **Clinical Recommendation Algorithm** **Proposed Review Period** Annually with the PSUR
6. Infusion related reactions	Yes	Current professional labelling states that Herceptin treatment should only be initiated by physicians experienced in the treatment of cancer patients. It is advised that Herceptin be discontinued until resolution of serious adverse events associated with infusion and that patients experiencing dyspnoea at rest should be only be treated following consideration of the risk versus benefit, given their possibly increased susceptibility to IRRs.
7. Haematotoxicity	Yes	Given that most chemotherapy regimen are likely to induce haematotoxicity, it is considered sufficient that routine monitoring of lab test values is sufficient to allow for appropriate measures to be taken locally following onset.
8. Oligohydramnios	Yes	Current professional labelling indicates that Herceptin treatment should only be initiated/ maintained during pregnancy if the potential benefit to the mother outweighs the potential risk to the foetus. The MAHs licensing partner in the USA, Genentech, Inc., has initiated a pregnancy registry in an effort to better characterise the use and potential risks associated with Herceptin use during pregnancy.

B. Risk Minimisation

4. Risk Minimisation Plan

Additional risk minimisation measures: Cardiotoxicity

Additional Risk Minimisation: • **Clinical Recommendation Algorithm**	**Objective and Rationale** The objective of this algorithm is to provide clinicians with a clear set of instructions as to how best to deal with LVEF decreases that are associated with the cardiotoxicity of trastuzumab.
	Proposed Actions Algorithm is provided in professional labelling and is available to prescribers globally via package inserts.
	Criteria to be Used to Verify the Success of Proposed Risk Minimisation Activity Analysis annually with the scheduled PSURs of the actions taken with Herceptin by prescribers globally in response to decreased LVEF and the outcome of the reported adverse event.
	Proposed Review Period Annually with the PSUR.

Discussion on the RMP

Version 5.0 of the RMP is presented in a structure completely different from the previous version. In general it is not very concise to present the data with regard to the incidences of identified and potential

risk by several tables for each single study. A pooled analysis of study data with regard to the indications would have been preferred.

The cut-off dates are different for the several presented data. 18.04.2009 is reported as data lock point for the RMP, but cut off date for example for the presented cases of oligohydramnios is mentioned as 08.08.2008. The data lock point of the RMP and the cut off dates for the data presented in the RMP should be congruent.

Patients with previous chemotherapy for advanced/metastatic disease were excluded in the trial (prior adjuvant/neoadjuvant therapy was allowed if at least 6 months had elapsed between completion of adjuvant/neoadjuvant therapy and enrollment into the study). Patients with a lack of physical integrity of the upper GI tract or malabsorption syndrome, and patients with active gastrointestinal bleeding were not allowed to enter the study. Therefore the target patient population may be not representative for patients treated after marketing authorization. Physical integrity could be affected by the underlying cancer. Additionally, patient with gastric cancer are at risk for developing gastrointestinal bleeding. Therefore, additional safety data are required and the MAH will continue enhanced pharmacovigilance measures which include targeted guided questionnaires designed to characterize identified risks. With regard to risk factors for cardiotoxicity a joint analysis of studies with 1799 patients is mentioned in table 6, but the studies included in the joint analysis are reported. The Applicant should specify the studies included in the joint analysis. In general, an overview of identified risks and potential risks should be presented by a pooled analysis of all trials performed. The RMP should be updated accordingly.

No presentation of safety profile with regard to the new indication, including a comprehensive discussion of potential differences is presented. The Applicant is asked to present an overview of safety profile in patients treated for gastric cancer in comparison to the approved indications, including a comprehensive discussion of the differences observed.

In the ToGA trial the frequency of infections was higher in patients treated with fluoropyrimidine, cisplatin and trastuzumab, compared with those treated with fluoropyrimidine and cisplatin (32% versus 20%) and 2 patients in the trastuzumab containing arm died because of pneumonia, versus none in the fluoropyrimidine and cisplatin arm. Therefore infections should be addressed as potential risk in the RMP.

Because the number of patients (294 patients) treated for gastric cancer is small, the median treatment duration (4.9 months) was short and the extent of the population intend for treatment is high, additional actions to collect further safety data, especially with regard to identified risk are necessary. The MAH will continue enhanced pharmacovigilance measures which include targeted guided questionnaires designed to characterize identified risks.

With regard to outstanding actions including milestone, annual analysis, to be presented with PSURs is reported, but it is not specified which analysis will be performed. The MAH is requested to specify annual analysis.

In Appendix 2 of the RMP a lot of ongoing clinical trials are mentioned, e.g. study H4613g AKA Her-Q-Les addressing cardiotoxicity and drug interactions, as well as the pregnancy registry. All of these studies are neither included in the table of study protocols for the pharmacovigilance plan, nor in the detailed action plan for safety concerns and also not in the table of outstanding actions and milestones. The Applicant should update the tables of the RMP with the information on these studies.

Study ML20529, addressing relevant literature findings of association of genetic polymorphism of HER2 and cardiotoxicity has been mentioned in previous PSURs and discussed in the PSUR assessment reports, but this study is not reported in the RMP, neither with regard to activities for safety concerns nor in Appendix 2, although this study will collect relevant data on cardiotoxicity. This study should be included in the RMP and should be discussed in relation to cardiotoxicity, as well as the literature finding of association of genetic polymorphism of HER2 and cardiotoxicity.

Appendix 6 of the RMP gives HER2 testing recommendations in gastric cancer.
It is mentioned that the accuracy of HER2 testing in human gastric tumours including GE junction is crucial to select the right patient for HER2 target therapy with Herceptin. The quality of HER2 testing results can be affected by several factors, such as the fixative reagent used or the duration of fixation. If

validated assays are not used, the accuracy can be affected as well. To guarantee proper HER2 testing the guidelines on both preanalytical factors and validated assays have been mentioned to be followed.
In Section 1.3.1 of the RMP it has been reported that detailed educational material regarding HER2 testing will be made available to prescribers, but this educational material has not been included in section risk minimisation activities. The RMP should be updated accordingly.
Additional the general consideration for HER2 testing as given "Before pathology laboratories embark on HER2 testing in gastric cancer, laboratory personal should be specifically trained. To ensure consistent HER2 testing quality it is recommended that pathology labs should participate in regular QC programs." should also be included in the section risk minimisation activities.

Of note, each updated RMP should include a presentation of changes, either by submitting a version where the changes are highlighted or by presenting the changes in the format of a table.

Overall Discussion on Clinical safety

Safety data from the ToGA trial suggest that there are no additional significant safety issues with Herceptin used in the treatment of advanced gastric cancer over and above those seen when it is used to treat breast cancer. Therefore, risks of cardiac dysfunction and pulmonary, gastrointestinal and infusion related adverse reactions persist. However, the safety profile of Herceptin in breast cancer is considered relatively well-established and well-defined risk minimisation strategies exist and are detailed within the risk management plan, product information and within clinical guidelines.

Overall Discussion and Benefit-Risk assessment

Herceptin has been investigated in one randomised, open-label phase III trial ToGA (BO18255) in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous i.v. infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m2 every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in the following table:

Parameter	FP N = 290	FP +H N = 294	HR (95% CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5%	47.3%	1.70[a] (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	< 0.0001

FP + H: Fluoropyrimidine/cisplatin + Herceptin
FP: Fluoropyrimidine/cisplatin

a Odds ratio

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8 %) in the control arm and 167 patients (56.8 %) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of the FISH status). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95 % CI 0.51-0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95 % CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95% CI 0.41-0.81) in the IHC 3+/FISH+ group

In an exploratory subgroup analysis performed in the TOGA (BO18255) trial there was no apparent benefit with the addition of Herceptin in patients with ECOG PS 2 at baseline, non measurable and locally advanced disease.

Analysis of PK in gastric cancer gave remarkable differences to PK in breast cancer, e.g. lower trough concentrations and further clarification on the involved mechanisms is needed.

Regarding PK/PD, there are still open issues remaining, concerning low serum levels (AGC is 54 % (43 %) -lower compared to breast cancer patients), lower T1/2 (14,5 days AGC vs 28,5 days for EBC and MBC) and clearance (role of shed Ag, tumour mass, prehydration with cisplatinum Rx,..). A post-approval follow-up measure on PK/PD should address a number of points such as:

- distinction between biologically active and inactive forms of the drug
- suitability of a non-linear PK model to decribe trastuzumab pharmacokinetics
- investigation of PK/PD relationship based on other parameters

On the basis of the above analysis, the MAH agreed to further investigate the PK issues. This may include consideration of further exploration of dose.

In conclusion, the Overall benefit is clearly demonstrated and differential treatment effects are addressed in SmPC. The open issues related to pharmacokinetics will be resolved post – approval as FUMs, the risk is relatively well known and a further RMP revision is expected as a FUM, therefore the benefit/risk evaluation is considered favourable in the indication:

Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

II. CONCLUSION

On 17 December 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.