Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Trastuzumab

Proprietary Product Name: Herceptin

Sponsor: Roche Products Pty Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (Extension of indications)
Decision:	Approved
Date of Decision:	17 September 2010
Active ingredient(s):	Trastuzumab
Product Name(s):	Herceptin
Sponsor's Name and Address:	Roche Products Pty Ltd 4-10 Inman Road, Dee Why, NSW 2099
Dose form(s):	Powder for reconstitution with 7.2 mL sterile water for injections
Strength(s):	150 mg/ 21 mg/mL reconstituted
Container(s):	Vial
Pack size(s):	1s (carton)
Approved Therapeutic use:	In combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.
Route(s) of administration:	Intravenous (IV)
Dosage:	The proposed dose is a loading dose of 8 mg/kg followed by doses of 6 mg/kg at three weekly intervals.
ARTG number(s):	73229

Product Background

Human Epidermal growth factor Receptor 2 (HER-2) is expressed on the cell surface of a number of human epithelial cell types. It is also over-expressed in approximately 6.8-42.6 % of gastric cancers. Trastuzumab is a monoclonal antibody directed against HER-2. It is a humanised murine antibody produced by recombinant deoxyribonucleic acid DNA technology in Chinese Hamster Ovary (CHO) cells.

The drug is currently registered for the treatment of HER-2 positive (+ve) breast cancer in the following situations:

- For the treatment of localised disease, in association with chemotherapy.
- For the treatment of metastatic disease:
  - In combination with taxanes, for patients not previously treated with chemotherapy;
  - As monotherapy, for patients who have received one or more chemotherapy regimens;
  - In combination with an aromatase inhibitor for post-menopausal patients with hormone receptor positive disease.

The current application seeks approval for use in HER2+ gastric/gastro-oesophageal cancer, in combination with a platinum agent and either 5-fluorouracil or capecitabine. A similar

dosing regimen to that used in localised breast cancer is proposed. It is proposed that treatment is continued until disease progression.

Regulatory Status

The sponsor indicated that applications to extend the indications of Herceptin to include HER2 positive advanced gastric cancer have been submitted to the European Medicines Agency (EMA) and are planned for submission to the US FDA. The sponsor warrants that the application "has not been rejected, repeatedly deferred or withdrawn in Canada or denied approval in the USA". Subsequent to the Australian submission, the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a new indication for Herceptin for the treatment of metastatic gastric cancer. The CHMP published this decision on 17 December 2009. The wording of the new CHMP approved indication is - "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-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ [immunohistochemistry] and a confirmatory FISH+ [fluorescence in situ hybridization] result, or IHC3+, as determined by an accurate and validated assay" [Summary of Product Characteristics, EMA Website].

It is noted that the CHMP approved indication refers specifically to cisplatin and not to "platinum agents" as is proposed for Australia.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

There were no new quality data submitted with this application.

III. Nonclinical Findings

There were no new non clinical data submitted with this application.

IV. Clinical Findings

Introduction

The application included one pivotal efficacy and safety study in 594 randomized patients [BO18255; ToGA]. This study was a randomized, open-label, multi-centred, multi-national, comparative Phase III trial designed to evaluate the efficacy and safety of trastuzumab in combination with fluoropyrimidine/cisplatin [FP+H] versus fluoropyrimidine/cisplatin [FP] alone as first-line therapy in patients with inoperable locally advanced or recurrent and/or metastatic HER2-positive adenocarcinoma of the stomach or gastro-oesophageal junction. In this study, HER2 was assessed by both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) and patients were considered eligible for randomization if one or both tests gave a positive result. The pivotal study report indicates that nearly 4000 patients were screened using IHC and FISH assays for study entry and that the overall HER2-positivity rate was 22.1%. The sponsor is proposing that Herceptin be used in patients with gastric cancer who are HER2 positive defined by "ISH" or "IHC". The submission did not include a randomized, controlled, double-blind study investigating the efficacy and safety of the proposed cisplatin (FP) + herceptin (H) regimen for the treatment of HER2 positive advanced carcinoma of the stomach or gastro-oesophageal junction.

The pivotal study included a population pharmacokinetic (PK) analysis of patients taking trastuzumab. The objectives of this analysis were to investigate the PKs of trastuzumab in patients with gastric cancer and to compare these data with PK data in patients with metastatic breast cancer from previous studies. The population PK data included 1419 trastuzumab serum samples from a total of 226 patients with gastric cancer. The results of the analysis were provided in the pivotal study report [BO18255] and in a separate PK population study report [1034808]. The data in these reports have been evaluated, and review and comment provided by the clinical evaluator. No other PK data were provided for evaluation. However, the sponsor's Summary of Clinical Pharmacology Studies included a review of PK data from a sub-study of the pivotal study in Japanese patients comparing exposures of capecitabine and cisplatin given in combination with (n=14) and without trastuzumab (n=8) [JP19959]. It appears that the Australian sponsor does not consider this study to be pivotal or supportive as the reference was not provided but was stated to be "available upon request". The study has not been requested as it does not appear to be directly relevant to the Australian application.

The sponsor's covering letter included reference to "additional supportive data" in the Clinical Overview relating to the use of oxaliplatin as an alternative to cisplatin in combination regimens for the treatment of advanced gastric cancer. The aim of these data was to support the use of the generic term "platinum agents" in the proposed PI rather than limiting the indication to cisplatin. The information in the Clinical Overview supporting the use of oxaliplatin as an alternative to cisplatin has been considered and commented upon by the clinical evaluator (see *Supportive studies*). The sponsor's Summary of Clinical Safety included a summary of Post-Marketing Data. This summary has been reviewed and relevant details included below (under *Post Marketing Experience*).

GCP Aspects

The pivotal study adhered to the principles outlined in the *Guideline for Good Clinical Practice* International Conference on Harmonisation Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the patient.

Pharmacokinetics

Overview

The pivotal study [BO18255] included a population pharmacokinetics (PK) analysis investigating the PKs of trastuzumab in patients with advanced gastric cancer and comparing these with the known PKs of the drug in patients with metastatic breast cancer. The population PK analysis was a pre-specified secondary objective of the pivotal study. The results of the PK analysis were provided in the Clinical Study Report (CSR) for BO18255 and in a separate PK analysis report [Report 1034808]. The posterior Bayesian parameter estimation and the evaluation of the impact of the covariates of interest were performed with NONMEM version 6 Level 1.0[1]. The FOCE INTERACTION method was used for model development and estimation of the reported final population parameters. Graphics and NONMEM datasets were created using SAS and SPLUS version 7.0.

Individual trastuzumab concentration-time data and individual PK parameters were predicted based on posterior Bayesian estimates obtained from the reference population PK model developed from previous Phase III data in patients with metastatic breast cancer. The trastuzumab concentration-time profiles in patients with advanced gastric cancer were adequately described by a two-compartment disposition PK model with first-order

[1] NONMEM® is licensed trademark by Globomax, LLC.

elimination. The structural parameters of the model were clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q), and peripheral volume of distribution (V2). Between-patient variability was estimated on CL, V1, and V2 using exponential error models. The residual error was modelled as proportional error.

The reference model did not adequately describe the data in gastric cancer patients from study BO18255. Visual inspection of the goodness-of-fitness plots from the reference model showed that trastuzumab serum concentrations predicted by the model were higher than trastuzumab serum concentrations observed in BO18255. Diagnostic examination of the model allowed the investigators to conclude that the structural PK model was not mis-specified but that influential covariates were most likely missing from the reference PK model, preventing adequate description of the population of gastric cancer patients. Following further analysis, the investigators introduced additional covariates into the final model in gastric cancer patients. These included the effect of cancer type on clearance (expressed as HER2 shed antigen), the effect of gender on the central volume of distribution (V1), and the effect of Japanese versus non-Japanese ethnicity on the peripheral volume of distribution (V2).

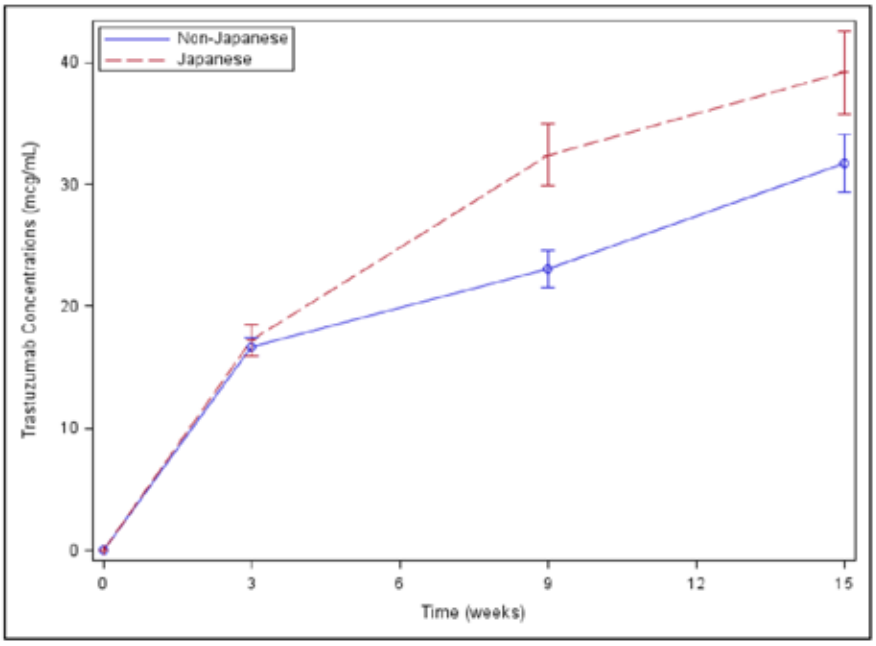
Trastuzumab Serum Concentration – Time Plots

Trastuzumab was administered at a loading dose of 8 mg/kg (on Day 1) followed by a 6 mg/kg IV infusion every 3 weeks. The first infusion was given over 90 minutes and subsequent infusions were given over 30 minutes if the first infusion was well-tolerated. Trastuzumab was continued until disease progression (unless withdrawn earlier due to unmanageable toxicity or withdrawal of patient consent).

The NONMEM PK dataset on which the population PK analysis was performed consisted of 1419 serum samples collected from 266 gastric cancer patients randomized to trastuzumab. There were 207 males and 59 females, and 49 of them were Japanese. The 1419 trastuzumab were distributed as follows: Cycle 1 (pre-dose, end of infusion [244 levels] Day 8 [238 levels], Day 15 [238 levels]); Cycle 2 (pre-dose) [222 levels]; Cycle 4 (pre-dose [175 levels], end of infusion [167 levels]); and Cycle 6 (pre-dose [134 levels]).

The plot of the observed trastuzumab serum concentration versus nominal time profile in Cycle 1 shows bi-exponential decay which is stated to be “in line” with the reference PK model in metastatic breast cancer. The analysis also included plots of observed trastuzumab trough concentrations in males and females over the time period from baseline to 15 weeks after initiation of treatment. These plots showed similar trough concentrations in both males and females to Week 9 after which the serum concentrations began to diverge with concentrations being marginally higher in females than in males. The population PK analysis also included a plot of observed trastuzumab trough concentration in Japanese and non-Japanese patients over the time period from baseline to Week 15. These plots showed similar trough concentrations in both Japanese and non-Japanese patients to Week 3 after which point the concentrations began to separate with higher concentrations being observed in Japanese compared with non-Japanese patients (see Figure 1).

Figure 1: BO18255 – Plot of observed trough trastuzumab serum concentration in Japanese and non-Japanese patients (mean±SEM).



Covariate Analysis in the Population Pharmacokinetic Model

The final PK model included 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 interpretation the effect of cancer type on clearance was complicated by the fact that in patients with advanced gastric cancer HER2 shed antigen levels were not recorded. Consequently, it was not possible to conclude that the effect of cancer type on clearance was due to a true difference in the two cancer populations or due to a difference of HER2 levels or a combination of the two. However, as a difference in HER2 level between the two types of cancer was considered by the investigators to be a reasonable hypothesis, the gastric cancer effect was expressed in term of HER2 shed antigen level. The clearance of trastuzumab in gastric cancer patients based on HER2 shed antigen levels was increased by 56.8 % compared with breast cancer patients [0.378 L/day versus 0.241 L/day, respectively].

The volume of distribution in the central compartment (V1) was 29.6% higher in males (3.91 L) compared with females (3.02 L). The investigators speculate that this could be due to the difference in blood volume between the sexes. The volume of distribution in the peripheral compartment (V2) was 34.7% lower in Japanese compared with non-Japanese patients (1.75 L versus 2.68 L, respectively). The final model estimated between-subject variability in CL of 38.6%, in V1 of 21.4%, and in V2 of 72.6%.

Individual PK parameters at Steady-State in Gastric Cancer Patients

Individual steady-state predicted exposure (area under the concentration-response curve (AUC)), as well as the maximum or "peak" concentration (C_{max}) and the minimum or "trough" concentration (C_{min}) trastuzumab serum concentrations were calculated using the nominal dosage schedule administered as an IV infusion (that is, 6 mg/kg IV administered every 3 weeks). The results for median PK parameters are summarised below in Table 1.

Table 1: Individual Median Steady-State PK parameters in Gastric Cancer Patients

Parameter	Every 3 week dosing regimen of Trastuzumab 6 mg/kg IV in Gastric Cancer Patients Median	5^{th}-95^{th} Percentiles
Steady-State AUC (mg•day/L)	1030	565-1726
C_{min} (mg/L)	23.0	6.4-48.5
C_{max} (mg/L)	128	93.1-178
$t_{1/2}$ days (equilibrium)	14.5	6.2-26.7

$t_{1/2}$=half-life

The predicted steady-state exposures were similar for male and female patients with advanced gastric cancer and in Japanese and non-Japanese patients.

Summary of the PK Data

a. The population PK data showed that a two-compartment bi-exponential model with first-order elimination adequately described the trastuzumab serum concentration-time profile after a loading dose of 8 mg/kg (on Day 1) followed by a 6 mg/kg IV infusion every 3 weeks in patients with gastric cancer.

b. Predicted trastuzumab clearance in patients with gastric cancer was 56.8 % higher than in patients with breast cancer [0.378 L/day versus 0.241 L/day, respectively].

c. Covariate analysis in the final population PK model in patients with gastric cancer showed that sex significantly affected the volume of distribution of the central compartment and ethnicity (Japanese, non-Japanese) significantly affected the volume of distribution in the peripheral compartment. However, predicted steady state exposure to trastuzumab (AUC, C_{min}, and Cmax) and equilibrium half-life were similar in both males and females, and in Japanese and non-Japanese patients.

d. The final population PK model in patients with advanced gastric cancer predicted that for the typical patient (that is, male weighting 68 kg, over-expressing HER2 and having alkaline phosphatase level of 107 U/L), 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.

Evaluator's Overall Conclusions on Pharmacokinetics

The population pharmacokinetic study [BO18255/1034808] was of good quality. The reporting of the study complied with the requirements of the relevant TGA adopted EU CHMP guidance document (*Guideline on Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06*). The purpose of the population PK study was to perform a Bayesian analysis to investigate whether trastuzumab PKs in gastric cancer patients in the pivotal study were comparable with those established mainly in metastatic breast cancer patients in five, previous Phase I-III studies. The reference PK model did not adequately describe the data from the pivotal study as the goodness-of-fit plots showed a systematic over-prediction of trastuzumab serum concentration in patients with advanced gastric cancer. The investigators concluded that influential covariates were missing from the reference model. Consequently, the influence of the covariates cancer type, gender, and ethnicity were investigated. These covariates were not represented in the data from patients

with metastatic breast cancer on which the initial population PK model was based. The final PK model included the effect of cancer type on clearance (expressed as a change of HER2 shed antigen), the effect of gender on volume of distribution in the central compartment, and the effect on ethnicity (that is, Japanese of non-Japanese) on volume of distribution in the peripheral compartment.

Drug Interactions

There were no new data submitted under this heading.

Pharmacodynamics

No new information was submitted under this heading.

Efficacy

Introduction

One, pivotal, efficacy study was submitted (BO18255; ToGA). The submission included no randomized, controlled, double-blind studies, nor did it include any dose response studies.

Main (Pivotal) Study – (Protocol BO18255; ToGA)

Objectives

The *primary objective* was to:

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

The *secondary objectives* were 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;
- evaluate the safety profile in the two treatment arms;
- summarise the quality of life in the two treatment arms;
- evaluate pain intensity, analgesic consumption, and weight gain/loss in the two treatment arms; and
- investigate the pharmacokinetics of trastuzumab in gastric cancer and to compare with historic data in patients with metastatic breast cancer.

Written informed consent was obtained from each patient participating in the study or from legal representatives for patients incapable of giving legal consent. Independent Ethics Committees approved the initial protocol and subsequent amendments. There were audits of 14 investigator sites. There were "major finding(s) involving compliance with GCP[2]" observed at the audited sites, but the sponsor states that "appropriate corrective and preventive actions were undertaken". The results of the study were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2009, and have been published in abstract form (Van Cutsem *et al*, 2009)[3].

[2] Good Clinical Practice

[3] Cutsem Van E, *et al.* (2009). Efficacy results from the ToGA trial: a phase II study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol.* 27:18s (suppl; abstr LBA4509).

Design

The study was a randomized, open-label, multi-centred, multi-national, comparative Phase III trial designed to evaluate the efficacy and safety of trastuzumab added to fluorouracil (5-FU) or capecitabine and cisplatin versus 5-FU or capecitabine and cisplatin as first-line therapy in patients with inoperable locally advanced or recurrent and/or metastatic HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction. Neither patients nor investigators were blinded to treatment.

The study was undertaken in 24 countries at 122 centres, including Australia (4 centres) and the UK (6 centres). The countries providing the most centres were Japan (16), China (15), Russia (12) and Korea (10). Other countries providing centres were located in Western Europe, South America, and Asia. There were no centres in the US or Canada. The study included 594 randomized patients (584 included in the efficacy analysis). Each country recruited between 2 and 125 patients per site with a total of 324 (54%) from Asia and 194 (33%) from Europe. The study ran from September 2005 (1st patient randomized) to 7 January 2009 (clinical cut-off date for analysis).

Randomization was via an interactive voice activation system (IVRS) generated by Clinphone (UK). The eligible patients were randomized (1:1) to either: trastuzumab plus fluoropyrimidine/cisplatin (FP+H) or fluoropyrimidine/cisplatin (FP). The choice of fluoropyrimidine was between 5-FU and capecitabine and was at the discretion of individual investigators on an individual patient basis. Prior to randomization patients were stratified according to the following, Eastern Cooperative Oncology Group (ECOG) criteria[4]: performance status (PS) (0-1 versus 2); chemotherapy regimen (5-FU/cisplatin versus capecitabine/cisplatin); locally advanced versus metastatic disease; stomach versus gastro-oesophageal junction disease; and measurable versus non-measurable evaluable disease. The randomization procedures indicate that investigators were required to have chosen whether a patient was to be treated with capecitabine or 5-FU prior to randomization.

Comment: *The open-label design gives rise to potential patient and/or investigator bias. However, the potential for such bias is mitigated by the fact that the primary objective was overall survival (that is, an objective endpoint). The sponsor considered that it would have been unethical to have included a placebo infusion for the FP group. This is a reasonable position given that the use of combination chemotherapy is generally accepted as standard of care for advanced gastric cancer [Wagner et al, 2006][5], and provides an advantage over best supportive care as regards quality of life (QoL) and survival [Catalano et al, 2009][6].*

[4] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction. 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work. 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. 5 - Dead

[5] Wagner *et al.* (2006). Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol 24:2903-2909.*

[6] Catalano V *et al.* (2005). Gastric cancer. *Critical Reviews in Oncology/Hematology* 54:209–241

However, even with chemotherapy the prognosis of patients with advanced gastric cancer is very poor with a median survival with chemotherapy of 7 to 10 months being reported in most of the larger clinical studies [Wagner et al, 2006].

Subjects

a. Inclusion and Exclusion Criteria

The study included a total of 594 randomized patients, 296 to the FP arm and 298 to the FP+H. The inclusion criteria included male or female patients aged ≥ 18 years; histologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction with inoperable locally advanced or recurrent and/or metastatic disease, not amenable to curative therapy; measurable disease, according to Response Evaluation Criteria in Solid Tumours (RECIST[7]) assessed using computed tomography (CT) or magnetic resonance imaging (MRI), or non-measurable evaluable disease; HER2 positive tumour (primary tumour or metastasis) as assessed by the central laboratory (both IHC and FISH were performed on all tumour samples); ECOG Performance Status (PS) 0, 1 or 2[8]; and life expectancy of at least 3 months. The stratification criteria in the two treatment arms are summarised in Table 2.

Table 2: BO18255 – Stratification criteria (FAS).

[7] The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

[8] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead

	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 exclusion criteria included previous chemotherapy for advanced/metastatic disease (prior adjuvant/neoadjuvant therapy was allowed if at least 6 months had elapsed between completion of adjuvant/neoadjuvant therapy and study enrolment); adjuvant/neoadjuvant therapy with a "platin" was not allowed (exceptionally 1-2 cycles of cisplatin were allowed at the discretion of the investigator). Other notable exclusion criteria included patients with significant cardiovascular disease. While patients with partial or total gastrectomy could enter the study, patients with a jejunostomy probe were excluded as presumably these patients would have been excluded from having the option of being treated with oral capecitabine.

Comment: *The inclusion and exclusion criteria are comprehensive. There are a number of exclusion criteria specific to trastuzumab which reflect the adverse event profile of the drug. These criteria are likely to restrict the use of trastuzumab for this patient population in general clinical practice. The stratification factors were well balanced between treatment arms. Capecitabine was the fluoropyrimidine chosen by most individual investigators for treatment of individual patients (87.5% of all patients) suggesting that total or partial gastrectomy did not act as a disincentive for choosing this orally active drug (22.8% of all patients reported a prior gastrectomy).*

b. Concomitant Medication

Patients were not permitted to receive any other anti-cancer therapy during treatment. However, any other medication which was necessary for patient management could be used at the investigator's discretion. Standard symptomatic treatment was initiated if nausea, vomiting or diarrhoea occurred. Hematopoietic growth factors could be used to treat febrile neutropaenia, according to local institutional or other guidelines, but could not be used as primary or secondary prophylaxis. Growth factors were discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy. Standard precautions were employed when using concomitant medications known to interact with one or more of the study drugs. Palliative surgical procedures were permitted as was palliative radiotherapy (providing it was not to the sole site of disease). Radiotherapy to the sole site of disease was considered disease progression and patients had to discontinue study medication before starting radiotherapy.

Treatment was interrupted for the duration of radiotherapy and until recovery from acute reversible effects.

c. Clinical Assessments

Clinical assessments consisted of tumour response assessment, performance status and safety assessments. There was a schedule of assessment carried out until disease progression.

Tumour response was evaluated according to RECIST which rely on change in tumour size determined by imaging to make response assessments [Therasse P *et al*, 2001][9]. RECIST criteria include four categories of response: complete response (CR), partial response (PR), stable disease (SD), and disease progression (DP). The definition of best response according to RECIST criteria from *Therasse et al (2001)* are summarised below in Table 3.

Table 3: Definition of best response according to RECIST criteria.

Best Response	RECIST Criteria
Complete response (CR)	Disappearance; confirmed at 4 weeks
Partial response (PR)	30% decrease; confirmed at 4 weeks.
Stable disease (SD)	Neither PR nor PD criteria met.
Progressive disease (PD)	20% increase; no CR, PR or SD documented before increased disease.

Source: Therasse *et al*. 2001.

Patients with measurable disease (according to RECIST), or non-measurable evaluable disease were eligible for inclusion in the study. For measurable disease, there must have been at least one measurable lesion assessed by CT or MRI, with the minimum target lesion size being ≥ 10 mm measured by spiral CT, or ≥ 20 mm measured by conventional CT or MRI. In this study, X-rays ultrasound and clinical examination were not considered acceptable for monitoring target lesions, and tumour response was assessed by CT or MRI. The protocol specified that the same method of assessment must be used throughout the entire study for individual patients. If more than one method was used, the protocol specified that the most accurate method according to RECIST criteria was to be selected.

Tumour response was confirmed at a minimum of 4 weeks after the initial response or at the next scheduled tumour assessment if it occurred more than 4 weeks after the initial response. The baseline total tumour burden was assessed within a maximum of 21 days before the first dose of study treatment, and follow-up evaluations were performed at 6 weekly intervals (post-Cycle 2 [pre-Cycle 3], post-Cycle 4 [pre-Cycle 5] and so on until disease progression). All tumour assessments after baseline were to be done preferably within ± 3 days of the scheduled visit. If a scheduled tumour assessment was missed, the protocol specified that the patient could continue treatment until the next scheduled assessment unless clinical signs of disease progression were present. In cases where there was suspicion of progression before the next scheduled assessment, an unscheduled assessment was performed. For patients with non-measurable evaluable disease, disease progression was assessed by the investigator by

[9] Therasse P *et al.,* (2002). Special article: New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Institute* 92: 205-215.

clinical examination, including radiographic evaluation using RECIST criteria for non-target lesions.

Performance status was measured using the ECOG PS scale, and it was recommended that the same person assess an individual's response throughout the study wherever possible. *Safety assessments* are described below.

Comment: *The application of RECIST criteria to the assessment of tumour response was only briefly described in both the Clinical Study Report (CSR) and the Protocol. Both documents referenced the pivotal publication [Therasse et al, 2001] but provided little explanatory discussion of how the principles described in this publication were to be specifically applied in the study. While RECIST is a well known method of assessing disease progression in oncology trials it is considered that the CSR would have been benefited from a more comprehensive description of these criteria to the assessment of advanced gastric carcinoma. RECIST assessments were undertaken unblinded by local investigators rather than by blinded, independent, centralised assessors. This raises the possibility of both bias and variability in interpretation of the imaging results. While the efficacy endpoints based on RECIST criteria were only secondary endpoints the lack of blinded, centralised assessment is considered to significantly weaken the evidentiary strength of these endpoints.*

Treatment

a. Overall

Patients meeting the inclusion and exclusion criteria were randomised (1:1) to one of the two treatment groups: arm A - fluoropyrimidine and cisplatin plus trastuzumab (FP+H); or arm B – fluoropyrimidine and cisplatin (FP). The choice of fluoropyrimidine (5-FU or capecitabine) in combination with cisplatin was at the discretion of individual investigators on an individual patient basis.

b. Treatment Arm A – Trastuzumab plus Fluoropyrimidine and Cisplatin [FP+H]

The FP+H regimen was trastuzumab 8 mg/kg IV loading dose on Day 1, followed by 6 mg/kg IV infusion every 3 weeks *plus* capecitabine 1000 mg/m^2 orally twice daily for 14 days every 3 weeks (from evening on Day 1 to morning on Day 15) or 5-FU 800 mg/m^2/day IV infusion on Days 1-5 *and* cisplatin 80 mg/m^2 IV on Day 1 (30 minutes after infusion of trastuzumab).

Trastuzumab: Trastuzumab was administered as a loading dose of 8 mg/kg (on Day 1) followed by a 6 mg/kg IV infusion every 3 weeks. The first infusion was given over 90 minutes and subsequent infusions given over 30 minutes if the first infusion was well-tolerated. Trastuzumab was continued until disease progression (unless withdrawn earlier due to unmanageable toxicity or withdrawal of patient consent).

5-FU/Cisplatin: The 5-FU infusion could be started at the same time as the cisplatin infusion on Day 1. 5-FU was administered at a dose of 800 mg/m^2/day as a continuous IV infusion over 5 days, given every 3 weeks for 6 cycles (Days 1 to 5 of each cycle). Cisplatin was administered at a dose of 80 mg/m^2 every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2 hour IV infusion with hydration and premedication (steroids and anti-emetics).

Capecitabine/Cisplatin: Capecitabine was administered at a dose of 1000 mg/m^2 orally twice daily (that is, total daily dose 2000 mg/m^2) for 14 days every 3 weeks for 6 cycles (from the evening of Day 1 to the morning of Day 15 of each cycle). Cisplatin was administered at a dose of 80 mg/m^2 every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2 hour IV infusion with hydration and premedication (steroids and anti-emetics).

c. Treatment Arm B - Fluoropyrimidine and Cisplatin [FP]

The 5-FU/cisplatin and capecitabine/cisplatin regimens were the same as those for Arm A.

d. Dose Modifications – Trastuzumab

There were no dose adjustments of trastuzumab for toxicity. If a patient could not tolerate trastuzumab the drug was stopped and not restarted. Trastuzumab treatment was not delayed for toxicities associated with fluoropyrimidine and/or cisplatin that necessitated a delay in treatment with these drugs. In such instances, to keep trastuzumab in synchrony with chemotherapy and to maintain trastuzumab dose intensity, the 6 mg/kg maintenance dose was given at the scheduled time, even through the chemotherapy dose was delayed. When the chemotherapy dose was next given (after resolution of toxicity), the 6 mg/kg maintenance dose of trastuzumab was also given. Subsequent trastuzumab doses were given in synchrony with chemotherapy, every 3 weeks. This meant that trastuzumab doses of 6 mg/kg were occasionally given only one week after the previous trastuzumab dose.

For patients who experienced a life-threatening infusion reaction to the first dose of trastuzumab (for example, tachypnoea, bronchospasm, hypotension, and/or hypoxia), the drug was discontinued and appropriate treatment given. These patients were not re-challenged or censored and were taken off trastuzumab. However, these patients continued in the study until disease progression or death. Trastuzumab was discontinued 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 the left ventricular ejection fraction (LVEF) assessed by multiple-gated radionuclide angiography (MUGA) or echocardiography.

e. Dose Modifications – Fluoropyrimidine/Cisplatin

Treatment with fluoropyrimidine and/or cisplatin was continued at the same dose without reduction or interruption for toxicities if these were considered by the investigator to be unlikely to develop into serious or life-threatening events. No dose-reductions or interruptions were required for anaemia if this could be satisfactorily controlled by blood transfusions. If toxicity required a dosing delay or interruption of both fluoropyrimidine and cisplatin of more than three weeks then both drugs were stopped permanently. In the FP+H arm, treatment with trastuzumab could continue if one or both of fluoropyrimidine or cisplatin was stopped due to toxicity and if continued treatment with trastuzumab was considered to be of clinical benefit.

Haematological Toxicities: The patient could begin a new 3 week treatment cycle if the absolute neutrophil count (ANC) was > 1 x 10^9/L and the platelet count was > 100 x 10^9/L at the start of the cycle. Otherwise, treatment was delayed until the haematological parameters recovered. If recovery had not occurred after a delay of 3 weeks, then chemotherapy was stopped permanently. The protocol specified dose modification instructions due to haematological toxicities on the planned day of treatment. In case of unscheduled assessment in the treatment cycle showing dose limiting toxicity (DLT) the administration of capecitabine/5-FU was interrupted during the cycle, and the doses of capecitabine/5-FU and cisplatin were reduced in subsequent treatment cycles. The protocol also specified dose modification instructions for haematological DLT during a treatment cycle.

Non-Haematological Toxicities: In capecitabine treated patients, if Grade 2, 3 or 4 non-haematological toxicity occurred (that is, Grade 2/3 hand-foot syndrome, diarrhoea, nausea, vomiting, stomatitis, and/or cardiac toxicity) capecitabine was interrupted immediately and the protocol specified instructions were followed. *In 5-FU treated patients*, re-treatment was delayed until all non-haematological toxicities had subsided to Grade 1 or less. Treatment could be delayed for up to 3 weeks after the next scheduled cycle of treatment to allow for

recovery. If re-treatment criteria in this time frame could not be met then 5-FU was discontinued. *In cisplatin treated patients*, if creatinine clearance was < 60 mL/min the dose of cisplatin was adjusted and if it was ≤ 40 mL/min the drug was stopped permanently. In case of ototoxicity or neurotoxicity, cisplatin was discontinued but patients could continue on 5-FU or capecitabine if the investigator considered that this was of clinical benefit.

f. Comment – Treatment

The combination of 5-FU or capecitabine and cisplatin is considered to be an acceptable comparator, given that the first patient in the pivotal study was randomized to treatment in September 2005 and the comparator has been accepted by the EMA. However, it is noted that cisplatin is not specifically approved by the TGA for the treatment of gastric cancer although oxaliplatin is approved for treatment of this condition. Both 5-FU and capecitabine (a pro-drug of 5-FU) are approved for the treatment of gastric cancer. Capecitabine in combination with a "platinum-based regimen" was approved by the TGA in 2009 for the treatment of gastric cancer. The sponsor states that oral capecitabine and continuous IV 5-FU have shown comparable response rates in Phase II trials in advanced gastric cancer. Furthermore, the sponsor states that the combination of capecitabine and cisplatin has shown similar efficacy to the combination of 5-FU and cisplatin in Phase II and III trials in advanced gastric cancer.

The sponsor states that there is currently no "gold standard" chemotherapy treatment for advanced gastric cancer, but notes that 5-FU in combination with cisplatin is "widely accepted worldwide" for the treatment of this condition. At the date of first patient randomization (September 2005), the doublet regimen of 5-FU and cisplatin would have been an accepted standard treatment for advanced gastric cancer. However, over the last few years there has been a general shift from doublet to triplet regimens as standard treatment for this condition [Wagner *et al*, 2006; Catalano *et al* 2005; Wesolowski *et al*, 2009[10]]. In its application letter, the sponsor notes that "the TGA and the Australian Drug Evaluation Committee (ADEC) have previously stated that for the treatment of oesophagogastric cancer 'triplet therapy ECF (epirubicin / cisplatin / fluorouracil) is generally considered better than the two drug combination [presumably cisplatin / flurouracil]'".

In 2006, *Wagner et al* undertook a systematic review and meta-analysis of chemotherapy for advanced gastric cancer and concluded that "best survival results are achieved with three-drug regimens containing FU, an anthracycline, and cisplatin" [Wagner *et al*, 2006]. In 2009, *Morabito et al*[11] reviewed regimens for advanced gastric cancer and concluded that "available date suggest that DCF regimen [docetaxel, cisplatin, fluorouracil] should be considered as the reference schedule for patients with untreated advanced gastric cancer and a good performance status" [Morabito *et al*, 2009]. However, in 2005 *Catalano et al* stated that while chemotherapy produces an advantage over best supportive care as regards quality of life (QoL) and survival in patients with advanced gastric cancer "no clear standard systemic chemotherapy regimen is available". The authors go on to state that "5-FU is one of the most effective and widely used drugs, and a 5-FU based combination therapy should be recommended on a Type-1 level of evidence" [Catalano *et al*, 2005]. In 2009, *Wesolowski et al* stated that "three-drug regimens have shown marginal benefit over traditional doublets, but there is no consensus about which one should be first-line therapy" [Wesolowski *et al*, 2009].

[10] Wesolowski *et al* (2009). Is there a role for second-line therapy in advanced gastric cancer ? *Lancet Oncol* 10:903-12.

[11] Morabito *et al.* (2009). Systemic Treatment of Gastric Cancer. *Critical Reviews in Oncology/Hematology* 70:216-234.

The current National Comprehensive Cancer Network (NCCN) Practice Guidelines (v.2.2010)[12] list three triplet regimens as Category 1 treatments for metastatic or locally advanced cancer, and oxaliplatin plus fluoropyrimidine as a Category 2B treatment. The NCCN guidelines also lists trastuzumab used in combination with systemic chemotherapy for treatment of patients with advanced gastric cancer or gastroesophageal (GE) junction adenocarcinoma that is HER2 positive determined by a standardized method (Category 2A by default).

Primary Efficacy Parameter – Overall Survival (OS)

The primary efficacy parameter was *overall survival (OS)*. It was defined as the time from the date of randomization to the date of 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 Efficacy Parameters

a. Progression Free Survival (PFS)

Progression free-survival (PFS) was defined as the time between the day of randomization and the first documentation of progressive disease (PD) or date of death, whichever occurred first. Patients who had neither progressed nor died at the time of the analysis or who were lost to follow-up were censored at the date of "last tumour assessment" or "last date in drug log" or "last date of assessment for progressive disease in survival follow-up".

Progression-free survival during first-line therapy was defined as the time between randomization and the first date of progressive disease or death (whichever occurred first), but only if it occurred before the start of non-study anti-cancer treatment. This endpoint was considered to be a sensitivity analysis for PFS. If a patient received any anti-cancer treatment after stopping study medication then the patient was censored at the first date the patient received "additional drug therapy", "additional radiotherapy" or "additional surgery". If a patient did not receive any anti-cancer treatment after stopping study medication then the censoring dates were the last date of "last tumour assessment" or "last date in drug log" or "last date of assessment for progressive disease in survival follow-up".

b. Time to Progression (TTP)

Time to progression (TTP) was defined as the time between randomization and the first occurrence of PD. Censoring was as for PFS. *Time to Progression during first-line therapy* was defined as the time between randomization and the first occurrence of progressive disease, but only if it occurred before the start of non-study anti-cancer treatment. This endpoint was considered to be a sensitivity analysis for time to progression. Censoring was as for PFS during first-line therapy.

c. Best Overall Response

The analysis of tumour response was based on the *best overall response*. This was defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death, taking as reference for PD the smallest measurements recorded since the start of treatment. To be assigned a status of partial response (PR) or complete response (CR), changes in tumour measurements had to be confirmed by repeat assessments performed no less than 28 days after the response criteria were first met.

[12] http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

The following algorithm outlines how best overall response was determined from the overall tumour assessments. The hierarchy used to determine best overall response was complete response (CR)>partial response (PR)>stable disease (SD)>progressive disease (PD).

- A patient was assigned a best overall response of CR if they had a response assessment of CR at two consecutive visits at least 28 days apart.
- A patient was assigned a best overall response of PR if they had a response assessment of PR/CR followed by PR or a response assessment of PR followed by CR at two consecutive visits at least 28 days apart.
- A patient was assigned a best overall response of SD if they had a response assessment of SD, PR, or CR at one or more visits at least 42 days (6 weeks) after start of study medication, but were not a confirmed CR or PR.
- A patient was assigned a best overall response of PD if they had a response assessment of PD at any visit, and not a best overall response of CR, PR or SD.
- A patient without any post-baseline tumour assessments, or an assessment of SD, PR or CR in the first 42 days (6 weeks) after start of study medication and no further tumour assessments thereafter had insufficient post-baseline information. The best overall response was set as missing.

A patient was considered to be a responder if best overall response was either confirmed complete response (CR) or confirmed partial response (PR) as determined by RECIST criteria from confirmed evaluations of target and non-target lesions. Patients with a best overall response of stable disease (SD), progressive disease (PD) or insufficient post-baseline information were considered to be non-responders. Patients with measurable disease only at screening were also evaluated for overall tumour response.

d. Duration of Response

Duration of response was defined as the time from first documentation of response (CR or PR) to the first documentation of disease progression. This was calculated only for patients who had a best overall response of CR or PR. Patients who had neither progressed nor died at the time of study analysis or who were lost to follow-up were censored at the date of "last tumour assessment", "last date in drug log", or "last date of assessment for progressive disease in survival follow-up". Patients with measurable disease only at screening were also evaluated for the duration of response.

e. Clinical Benefit Rate (CBR)

Clinical benefit rate (CBR) was defined as stable disease (SD) for 6 weeks or longer, or a response assessment of CR or PR as determined by RECIST criteria.

f. Other Secondary Parameters

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer EORTC-QLQ-C30 and EORTC-QLQ-STO22 questionnaires and was performed according to the EORTC Scoring and Reference Values Manual. The EORTC QLQ-C30 questionnaire is a validated, cancer specific instrument designed for prospective clinical trials. The questionnaire incorporates five functional scales (physical, role, emotional, social and cognitive), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status/QOL scale, and six single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). QOL was also assessed by the EQ-5D (EuroQol Group), but the results were not provided in the study report with the sponsor's intention being to report these results

separately. *Pain intensity* was performed using a Visual Analog Scale (VAS) on a line from 0 mm ("no pain") to 100 mm ("unbearable pain"). *Analgesic medication use* was reported until disease progression; and *weight* was recorded at baseline and at 3 week intervals until disease progression.

Statistical Methods, Sample Size, and Interim Analyses

a. Statistical Methods

The *null hypothesis* was that the survival distribution of overall survival time was the same in the two treatment groups (that is, FP+H compared with FP). The null hypothesis was tested using a two-tailed non-stratified log-rank test (5% significance level), and the estimated hazard ratio (95% confidence interval). The *Kaplan-Meier curves* for each of the treatment groups showed median overall survival, censored observations and p-values for the comparison of survival functions. The primary analyses of OS were performed in the full analysis set (FAS) population, and the supporting analyses were performed in the per-protocol set (PPS) population (see below for definitions). The secondary efficacy endpoints of PFS, TTP, and duration of response were analysed using the same methodology as used for OS.

For the analysis of overall tumour response, a summary table presenting the number and proportion of responders and non-responders in each treatment group, together with the two-sided 95% CI intervals for response rates was provided. The rates and the corresponding 95% CIs for each of the response categories (CR, PR, SD, PD, and Missing) by treatment group were also presented. A Chi-squared test was performed to compare the various response rates in the two treatment groups. The clinical benefit rate was analysed using the same methodology as used for the response rates. There was no statistical adjustment for multiplicity of testing.

The study defined three populations for analysis. The *full analysis set* (FAS) included all patients who were randomized and received study medication at least once (that is, a modified intention-to-treat analysis). The *per-protocol set* (PPS, evaluable patients set) included all FAS patients except those who met specified exclusion criteria (that is, prior chemotherapy for advanced/metastatic disease as listed in the inclusion/exclusion criteria of the protocol; no study medication received; incorrect medication received; failed to meet the tumour assessment criteria specified in the inclusion/exclusion criteria; absence of documentation of overexpression/amplification of HER2; baseline LVEF < 50%; and ECOG PS > 2). The *safety analysis population* (SAP) included all patients who were randomized and received study medication at least once with groups being defined by the actual received medication rather than the medication to which they had been randomized.

b. Sample Size

The planned sample size was 292 patients per treatment arm. This was based on an α-level of 0.05 and a power of 80% to show a significant difference with respect to the primary endpoint of overall survival. The calculation of the sample size was based on the following two assumptions: a 1-year survival of 43.5% in the FP arm and 52.7% in FP+H arm, corresponding to a median overall survival time of 10 months and 13 months, respectively; and an exponential distribution of survival. The protocol regarded a 3 month survival advantage as being "clinically meaningful". Based on the assumptions used to calculate the sample size it was estimated that a total of 460 deaths would be required to satisfactorily demonstrate a statistically significant difference between the two treatment arms.

c. Interim Analyses

The study included three interim safety analyses and two interim safety and efficacy analyses. These analyses were undertaken by an Independent Data Monitoring Committee (IDMC) consisting of four oncologists, one cardiologist, and one statistician. The protocol included stopping rules for the study based on the statistical analysis of the number of deaths reported at the interim analyses. The initial protocol included only one interim efficacy and safety analysis to be performed after 50% (that is, 124) of 248 deaths (that is, the number specified in the initial protocol but subsequently amended). However, at the third interim safety review (31 May 2007) the IDMC noted that, based on the reported number of events (deaths), the overall median survival time for the total population was in excess of 12 months. Consequently, the IDMC had concerns about the initial sample size of 187 patients per treatment arm based on the assumptions of median OS times of 7 months with FP and 10 months with FP+H. Therefore, the IDMC recommended an increase in sample size which would allow for the detection of a difference in median overall survival between treatment arms, now assumed to be 10 months with FP versus 13 months with FP+H. Based on the new assumptions for the median OS in the two treatment arms, the sample size was increased to 584 patients and the total number of events to 460. The protocol was amended to incorporate these changes in patient and event numbers (Protocol version C), and the planned interim efficacy and safety analysis was now to be after 230 events (that is, 50% of 460) rather than 124 events.

The first interim efficacy and safety analysis (26-27 July 2008) was performed after 230 deaths (that is, 50%) of the protocol amended number of 460. The dataset provided to the IDMC was based on 241 events. It was considered that there were no concerns regarding the quality and integrity of the data and no reasons to alter the trial conduct based on toxicity and adverse events. The IDMC strongly recommended an additional interim efficacy and safety analysis after 75% of events (345 deaths) or not later than a data lock date of 18 weeks from the first treatment of the last randomized patient. Following the recommendation of the IDMC, the protocol and statistical analysis plan were amended (Protocol amendment E). At the second interim efficacy and safety analysis (14-15 March 2009), the efficacy data was evaluated at 348 events (deaths). The IDMC advised that the efficacy data for the primary endpoint was now mature, and that analysis favoured the experimental arm (that is, FP+H) and exceeded the pre-specified statistical requirements for stopping the study. To control the overall type I error at the significance level of 0.05, the p value at 348 events was 0.0188 in favour of the FP+H arm. Consequently, the second interim analysis was considered as the definitive analysis and the study did not proceed to the protocol specified analysis at 460 deaths. The significance level for the interim efficacy analysis was determined by applying the Lan-De Mets method and an O'Brien-Fleming alpha spending function using the actual number of events.

Comment: *The procedures for the interim analyses were pre-specified and clearly outlined. The statistical methodology adopted for the analyses is considered to be consistent with standard approaches to such analyses.*

Patient Disposition

The first patient was randomized in September 2005 and the last patient in December 2008. The clinical cut-off date for the analysis presented in the Clinical Study Report was 7 January 2009. After further data cleaning was conducted, the data transfer for analyses was April 17, 2009.

The study included 594 randomized patients: 296 to FP and 298 to FP+H. A total of 10 patients (6 [2%] FP; 4 [1%] FP+H) were excluded from the analysis because they did not receive any study drug. The reasons were: violation of selection entry criteria (2 FP+H);

administration/other (1 FP); refusal of treatment (1 FP); withdrew consent (3 FP; 2 FP+H); and other violation (1 FP). In view of the 10 excluded patients, the primary efficacy population (FAS) consisted of 584 of the 594 randomized patients (290 FP, 294 FP+H). During the study, 3 patients in the FP arm switched the type of fluoropyrimidine taken (2 from capecitabine to 5-FU and 1 from 5-FU to capecitabine).

Two main study phases were defined for each patient: *a treatment phase until disease progression* lasting from randomization until disease progression irrespective of whether treatment was given throughout the entire treatment phase in the FP+H arm or for only 6 cycles followed by no treatment in the FP arm; and *a follow-up phase* lasting from after disease progression until death, with patients being assessed for status (alive or dead) at 6 weekly intervals. Both phases were truncated at the clinical cut-off date for the analysis (7 January 2009) unless patients withdrew, progressed or died.

The number of patients completing at least 6-cycles of treatment was higher in the FP+H arm (63% [186/294]) compared with the FP arm (50% [144/290]), and more patients in the FP+H arm (18% [54/294]) were still in the treatment phase at the clinical cut-off compared with those in the FP arm (12% [34/290]). Fewer patients withdrew prematurely from treatment in the FP+H arm (20% [59/294]) compared with the FP arm (27% [79/290]), but the rates for premature withdrawal were high in both arms.

The median time (days) between randomization and first treatment administration was similar for both arms being 1 [range 0-15] day for FP and 1 [range 0-17] day for FP+H. At the clinical cut-off date, the median duration of follow-up was 17.1 [range 0-31] months in the FP arm and 18.6 [range 1-34] months in the FP+H arm. More patients were alive either in follow-up or on treatment in the FP+H arm (21%, [61/294] and 18% [54/294], respectively) compared with the FP arm (19% [54/290] and 12% [34/290], respectively). The proportion of patients in each treatment arm reported as being lost to follow-up was 2.4% (7/294) for FP+H and 3.4% (10/290) for FP.

At the clinical cut-off date, death had occurred in 62.8% (182/290) of FP treated patients and 56.8% (167/294) of FP+H treated patients, and disease progression (including death) had occurred in 74.1% (215/290) of FP treated patients and 70.7% (208/294) of FP+H treated patients.

Patient Demographics and Baseline Characteristics

a. Overall

The two treatment arms were well balanced as regards ***baseline demographic characteristics***. The mean±standard deviation age in the FP arm was 58.5±11.2 years and 59.4±10.6 years in the FP+H arm, and the percentage of males in the arms was 75% (n=218) and 77% (n=226), respectively. The higher percentage of males in the study compared with females reflects the higher worldwide incidence of males with the condition. The majority of the population was "oriental" (54% FP, 51% FP+H) with the remainder being predominantly Caucasian (36% FP, 39% FP+H).

The two treatment arms were well balanced as regards ***stratification factors***. Nearly all patients in both arms had metastatic disease (96.6% both arms) with the primary site being predominantly stomach (83.4% FP, 80.3% FP+H). The disease was measurable in the majority of patients (88.6% FP, 91.5% FP+H), and most patients had ECOG performance status 0-1 (90.7% FP, 89.8%). The most commonly used fluoropyrimidine was capecitabine (87.9% FP, 87.1%), which most likely reflects the convenience of oral capecitabine administration compared with IV infusion for 5-FU.

The two treatment arms were well balanced as regards ***baseline disease characteristics***. There were notable discrepancies in the histological type of tumour as assessed by local laboratories compared with the central laboratory for both intestinal and diffuse types. The local laboratories provided no information on histological type for 24.5% of patients in the FP arm and 18.4% of patients in the FP+H arm, while the central laboratory provided information on type in all patients (intestinal, diffuse, or mixed). The central laboratory assessment of histological tumour type was used in the analyses. The percentage of patients who had undergone gastrectomy was 21.4% in the FP arm and 24.1% in the FP+H treatment arm. The percentage of patients who had undergone prior chemotherapy was 4.1% in the FP treatment arm and 9.2% in the FP+H treatment arm, with the respective figures for prior radiotherapy being 2.4% and 1.7% and prior anthracycline therapy being 0.7% in both arms. The median number of ***target lesions at baseline*** was 5 [range 1-16] in the FP arm and 5 [range 1-20] in the FP+H arm, and the median number of sites per patient were 2 [range 1-8] and 2 [1-7] respectively. Visceral (lung or liver metastases) were present in 59.3% of patients in the FP arm and 57.5% of patients in the FP+H arm.

b. HER2 Status

HER2 testing was undertaken at a central laboratory using both IHC and FISH. Prior to the clinical study, a validation study was undertaken to develop a HER2 scoring system for gastric cancer and a consensus panel was established to analyse and interpret the data generated by this study. As a result of the validation study scoring for evaluation of IHC staining was modified as compared with established scoring for evaluation of breast cancer [Hofman *et al*, 2008[13]]. Taking into account the different nature of gastric cancer tissue (for example, higher rate of tumour heterogeneity[14]) the consensus panel recommended to use both tests in the BO18255 study to ensure that complete information on protein overexpression and gene amplification is collected. Patients were considered eligible for randomization if one or both tests gave a positive result.

Patients were considered eligible for randomization if one or both tests gave a positive result. The assays used in the pivotal study were HercepTest and HER2 FISH pharmDx, both from DakoCytomation. The validation study indicated that concordance between the FISH and IHC tests that were subsequently used in the pivotal study was 93.5% in 168 evaluable samples, with 11 samples being scored as FISH+ but IHC- or equivocal [Hofmann *et al*, 2008]. The sponsor also added that in the ToGA screening phase, the concordance figure was 87.2%. The consensus panel recommendations for HER2 scoring for gastric cancer are included in the Australian Product Information (Table 6). The HER2 status for the patients analysed for efficacy is summarised below in Table 4.

[13] Hofmann M *et al.,* (2008). Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 52 (7):797-805.

[14] The sponsor also added that gastric cancer tissue has limited HER2 receptor accessibility using the available IHC methods as well as a faster rate of protein degradation due to it being enzymatically more active than breast cancer tissue.

Table 4: Summary of HER2 status (FAS).

Result	FP (n=290)	FP+H (n=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%)

There was one HER2 negative patient from a Russian site who was included in the FAS (assessment error in central laboratory analysis). HER2 negativity was a major protocol violation and this patient (FP+H arm) should have been excluded from the FAS population. However, a *post-hoc* analysis excluding this patient showed that the efficacy results were not affected. The study included a *post-hoc* exploratory efficacy and safety analysis in HER2 subgroups based on low HER2 overexpression (IHC0/FISH+ and IHC 1+/FISH+) and high HER2 overexpression (IHC 2+/FISH+, IHC 3+/FISH+, IHC 3+/FISH-, or IHC 3+/FISH no result). The proportion of patients with low HER2 overexpression was 24.1% (70/290) in the FP arm compared with 20.7% (61/294) in the FP+H arm, and the respective proportion of patients with high overexpression was 75.2% (218/290) and 77.6% (228/294). The results of the *post-hoc* HER2 analysis are reviewed below.

Comment: *The Product Information (PI) indicates that the prevalence of HER2 overexpression or gene amplification in patients with advanced gastric cancer ranges from 6.8% to 42.6%. These figures are based on–studies that have shown that HER2 positivity rates in gastric cancer using* IHC *and FISH or chromogenic in situ hybridization (CISH) vary from 6.8% to 34.0% for* IHC *and from 7.1% to 42.6% for FISH. The sponsor added that these figures were based on literature data applying mainly breast cancer scoring criteria or different HER2 testing principles and should be interpreted with caution. Data, taken from the Hofmann et al (2008) study, identified 16* IHC *studies comprising 3264 samples with a mean rate of 17.6% [range: 6.8% to 34.0%], and 9 FISH or CISH studies comprising 1232 samples with a mean of 19.2% [range: 7.1-42.6%] [Hofmann et al, 2008]. The pivotal study report and validation study [Hofmann et al, 2008] both referred to conflicting evidence in the literature showing that HER2 positivity is a negative prognostic factor in patients with gastric cancer. The Hofmann et al (2008) study validated the Hercept-Test for the identification of HER2+ gastric tumours for the pivotal trial, with modifications to the* IHC *scoring system. However, at the date of the submission, the sponsor stated that the HER2 ISH testing algorithm for the identification of HER positive gastric tumours had not yet been defined.*

The pivotal study report stated that nearly 4000 patients with advanced gastric cancer were screened for HER2 positivity with IHC *and FISH and that the overall HER2 positivity rate was 22.1%. The report referred to published data which showed that HER2 over-expression is more often seen in the intestinal histological subtype compared with the diffuse histological subtype [Hofmann et al, 2008]. The published data indicated that in the* IHC *group, 83.3% of*

tumours were intestinal type adenocarcinomas and 16.7% were diffuse type adenocarcinomas. The investigators note that greater HER2 positivity rates in intestinal tumour might have biased selection toward patients with this subtype rather than the diffuse subtype, 75% (438/584) of the total population were classified by the central laboratory as having the intestinal subtype.

c. Concomitant Disease and Concomitant Medication

Previous or concurrent cardiovascular disease was reported in a higher percentage of patients in the FP+H arm (36% [105/294]) than in the FP arm (30% [88/290]). The most frequently reported cardiovascular diseases were vascular disorders (27% FP, 30% FP+H), and within vascular disorders the most common condition was hypertension (26% FP, 29% FP+H). Cardiac disorders were reported in 8% of patients in the FP arm and 11% of patients in the FP+H arm. Active cardiovascular disease (as allowed per protocol) at baseline was recorded by 25% [72/290] of patients in the FP arm and 28% [83/294] of patients in the FP+H arm. The most common active cardiovascular condition was hypertension (22% FP, 24% FP+H), respectively. Active cardiac disorders (as allowed per protocol) were recorded by 5% of patients in each treatment arm.

Previous or concurrent disease other than gastric cancer or cardiovascular disease was reported in a higher percentage of patients in the FP+H arm (73% [215/294]) than in the FP arm (68% [196/290]). The most frequently recorded disorders were gastrointestinal (35% FP, 36% FP+H), metabolism and nutrition (25% FP, 22% FP+H), blood and lymphatic system (14% FP, 17% FP+H), and infections and infestations (13% in FP, 14% in FP+H).

Previous treatment not associated with gastric cancer was reported in 35% of patients in both arms (FP 102/290, FP+H 102/294). These treatments included a range of surgical procedures, blood product transfusions, vitamins and minerals, and prescription medications. The range of previous treatments was well balanced between the treatments arms.

New concomitant medications started during the study were reported in 96% (278/290) of FP treated patients and 97% (286/294) of FP+H treated patients. The most common new concomitant medications were (shown as FP versus FP+H): 5-HT_3 antagonists (84% versus 87%); corticosteroids (81% versus 87%); electrolyte, glucose and other metabolic supplements (60% versus 67%); anti-emetics other than $5HT_3$ antagonists (63% versus 64%); loop diuretics (47% versus 54%); osmotic diuretics (35% versus 36%) and vitamins and minerals (31% versus 33%). An extensive range of other concomitant medications were used including analgesics, opioid analgesics, anti-histamines, blood products, NSAIDs, and PPIs.

Concomitant medications initiated for adverse events during the study were reported in 88% (259/294) of FP+H treated patients and 83% (241/290) of FP treated patients. The most frequently used treatments were (FP versus FP+H): anti-emetics (32% versus 35%); supplements (27% versus 36%); corticosteroids (21% versus 28%); blood products (17% versus 24%); laxatives and stool softeners (22% versus 16%); NSAIDs (14% versus 23%); 5-HT_3 antagonists (18% both arms); analgesics (17% versus 18%); vitamins and minerals (16% versus 18%); surgical and medical procedures (12% versus 20%); anti-diarrhoeals (11% versus 20%), antihistamines (11% versus 17%); quinolone antibiotics (9% versus 16%); and opioid analgesics (12% both arms).

Subsequent treatment for gastric cancer was reported in 45.2% (131/290) of FP treated patients and 41.5% (122/294) of FP+H treated patients. The subsequent therapies were (shown as FP versus FP+H): chemotherapy (42.8% versus 38.4%); radiotherapy (5.9% versus 5.8%) and surgery (4.5% versus 2.7%). The majority of subsequent chemotherapy treatments included (shown as FP versus FP+H): taxanes 25% versus 24%; anti-metabolites (21% both

arms); topoisomerase inhibitors (22% versus 18%); folic acid derivatives (14% both arms); platinum compounds (14% versus 11%); anti-neoplastic agents (9% versus 7%); cytotoxic antibiotics (5% versus 3%); tyrosine kinase inhibitors (2% versus 1%); and a range of other treatments with an incidence of≤ 1% in one or both treatment arms.

Primary Efficacy Endpoint - Overall Survival - Results

The primary efficacy analysis was based on a non-stratified, two-sided log-rank test (5% significance level) of overall survival. The primary efficacy parameter of overall survival (OS) was statistically significantly improved in the FP+H arm compared with the FP arm (see Table 5, below). The median survival time was 11.1 months [95%CI: 10, 13] with FP and 13.8 months [95%CI: 12, 16] with FP+H; p = 0.0046 log-rank test. The hazard ratio (HR) indicated a 26% reduction in the risk of death for patients in the FP+H arm compared with the FP arm: HR=0.74; 95% CI [0.60-0.91].

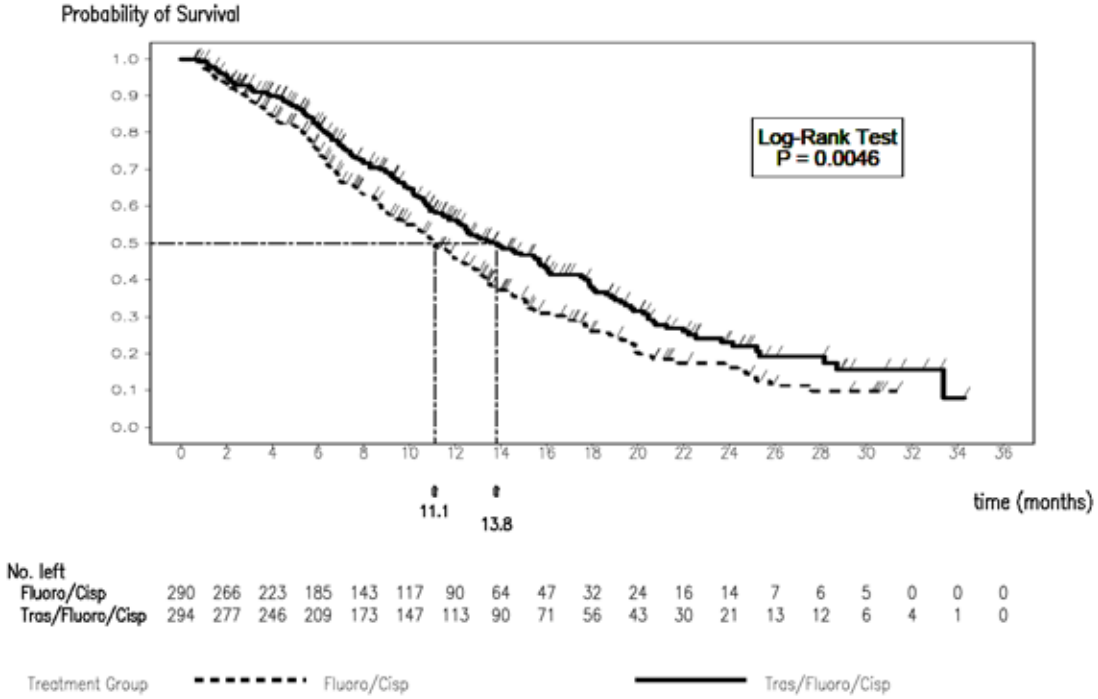
Table 5: Overall Survival (OS). Primary efficacy analysis non-stratified, two-sided log-rank test.

	FP (n=290)	FP + H (n=294)
Patients with event (death)	182 (62.8 %)	167 (56.8 %)
Patients without event *	108 (37.2 %)	127 (43.2 %)
Time to events (months) median #	11.1 [95%CI: 10, 13]	13.8 [95%CI: 12, 16]
Range ##	[Range: 0 to 31]	[Range: 1 to 34]
p-value (log-rank test)	0.0046	
Hazard Ratio	0.74 [95%CI: 0.60, 0.91]	

* Censored; # Kaplan-Meier estimate; ## Including censored observations.

The Kaplan-Meier curves for overall survival are provided below in Figure 2. The curves separated at about 2 months and remained separated for the duration of treatment. The Kaplan-Meier estimated survivals at 6, 12, 18, 24, and 30 months were, FP versus FP+H: 74% versus 82%; 45%, versus 56%; 26% versus 38%; 16% versus 23%; and 10% versus 16%.

Figure 2: Kaplan-Meier curves for overall survival (FAS).



In the stratified analysis of OS the hazard ratio indicated 29% reduction in the risk of death for patients in the FP arm compared with the FP+H arm: HR=0.71 [95%CI: 0.57, 0.88]. The results for the stratified analysis were similar to those for the non-stratified analysis. The analysis of OS in the PPS was consistent with the primary (FAS) analysis and showed that the risk of death was reduced by 27% for patients in the FP+H arm compared with the FP arm: HR=0.73 [95%CI: 0.59, 0.9]. In the PPS, at the time of analysis, death had occurred in 62.6% (179/286) of patients in the FP arm and 56.3% (161/286) of patients in the FP+H arm.

Comment: *The results in the non-stratified and stratified analyses in the FAS population were similar. This is not surprising as the total non-stratified population included, as regards the stratification factors, 97% of patients with metastatic disease, 82% with primary site stomach, 90% with ECOG 0-1, and 88% treated with capecitabine rather than 5-FU.*

Secondary Efficacy Parameters – Results

a. Progression-Free Survival

In the non-stratified analysis, median PFS was statistically significantly longer in the FP+H arm compared with the FP arm. The median PFS was 5.5 [95%CI: 5, 6] months with FP and 6.7 [95% CI: 6, 8] months with FP+H; p=0.0002 log-rank test. The risk of having a PFS event (progression of disease or death, whichever occurred first) was significantly reduced by 29% in the FP+H arm compared with the FP arm: HR=0.71 [95%CI: 0.59-0.85]. There were 235/290 (81.0%) events (213 PD, 22 deaths) in the FP arm and 226 (79.6%) events (206 PD, 20 deaths) in the FP+H arm. The results of the stratified analysis of PFS were similar to the non-stratified analysis.

In the non-stratified sensitivity analysis of PFS during first-line therapy, the risk of a PFS event was statistically significantly reduced by 32% in the FP+H arm compared with the FP arm: HR=0.68 [95%CI: 0.56, 0.83]. The median time to the event was 5.4 [95%CI: 5, 6] months with FP and 6.8 [95%CI: 6, 8] months with FP+H; p < 0.0001 log-rank test. The PFS during first line-therapy was defined as the time between randomization and the first date of progressive disease or death, but only if it occurred before the start of non-study anti-cancer

treatment. There were 217/290 (74.8%) patients with events in the FP arm compared with 213/294 (72.4%) patients in the FP+H arm.

b. Time to Disease Progression

In the non-stratified analysis, the median time to disease progression was statistically significantly longer in the FP+H arm compared with the FP arm. The median time to disease progression was 5.6 [95%CI: 5, 6] months in the FP arm and 7.1 [95%CI: 6, 8] months in the FP+H arm; p=0.0003 log-rank test. The risk of disease progression was significantly reduced by 30% in the FP+H arm compared with the FP arm: HR=0.70 [95%CI: 0.58, 0.85]. The results of the stratified analysis of time to disease progression were similar to the non-stratified analysis. The sensitivity analysis of time to disease progression during first line therapy showed that the risk of an event was reduced by 32% in the FP+H arm compared with the FP arm: HR=0.68 [95%CI: 0.55, 0.83].

c. Overall Tumour Response Rate

The *responder rate* (best overall confirmed response of CR or PR) was 47.3% (139/294) in the FP+H arm and 34.5% (100/290) in the FP arm: difference = 12.8% [95%CI: 4.7, 20.9]; p=0.0017, Chi-squared test. The *complete response (CR) rate* was 5.4% (16/294) in the FP+H arm and 2.4% (7/290) in the FP arm: difference = 3.03% [95%CI: -0.3, +6.3]; p=0.0599, Chi-squared test. The *partial response (PR) rate* was 41.8% (123/294) in the FP+H arm and 32.1% (93/290) in the FP arm: difference = 9.77% [95%CI: 1.8, 17.7]; p=0.0145, Chi-squared test. The *stable disease (SD) rates* were 31.6% (93/294) for FP+H and 34.8% (101/290) for FP. The *progressive disease (PD) rates* were 11.9% (35/294) for FP+H and 18.3% for FP. *No response assessments* were more frequent in the FP arm than in the FP+H arm (12.4% versus 9.2%). The main reason for "missing" response assessments was that a patient might not have had a post-baseline assessment at the date of data transfer or, if a patient had an SD, PR, or CR assessment within the first 6 weeks which was not confirmed 6 weeks after baseline it was categorized as a missing value for best overall response. The results for tumour response rates in the stratified analysis were generally similar to those in the non-stratified analysis.

d. 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 in the non-stratified analysis was significantly longer in the FP+H arm than in the FP arm: 6.9 [95%CI: 6,8] months versus 4.8 [95%CI: 6, 8] months, respectively, p<0.0001 log-rank test. The HR was 0.54 [95%CI: 0.40, 0.73]. The Kaplan-Meier curves show separation from about 3 to 16 months. The Kaplan-Meier estimated rates for 12 month duration of response were 8% for the FP arm and 27% for the FP+H arm.

e. Clinical Benefit Rate

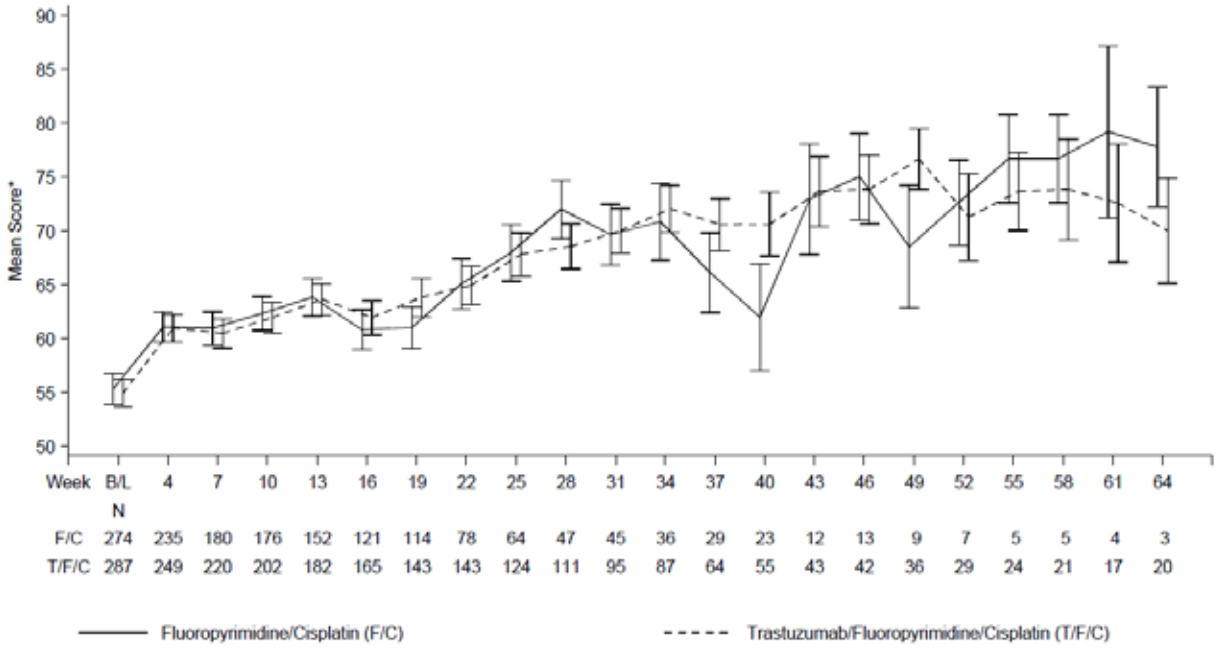
Patients who had stable disease for at least 6 weeks or a response assessment of CR or PR were deemed to have clinical benefit. Patients in the FP+H arm had a statistically significantly higher rate of clinical benefit than patients in the FP arm. In the non-stratified analysis, the clinical benefit rate in the FP+H arm was 78.9% (232/294) compared with 69.3% (201/290) in the FP arm: difference = 9.60% [95% CI: 2.4, 16.9]; p=0.0081 Chi-squared test. The HR was 1.66 [95% CI: 1.14, 2.41]. The results in the stratified analysis were similar to those in the non-stratified analysis.

Other Outcomes (QoL, Pain Intensity, Weight)

Quality of life (QoL) was a secondary objective and was assessed using the EORTC QLQ-C30 and EORTC QLQ-ST022 questionnaires. The results were presented in a qualitative

rather than analytical fashion. The QLQ-C30 Global Health Status contains two items rating "overall health" and "overall quality of life" during the previous week. The Global Health Status scores showed a slight improvement from the start of treatment until Week 19 (around end of chemotherapy) for both arms; from 55% to 61% in the FP arm and from 55% to 64% in the FP+H arm. The scores subsequently increased to 71% in the FP arm and 72% in the FP+H arm at Week 34. Improvement in both arms stabilized at Week 34, but at this time, patient numbers were low, particularly in the FP arm. The EORTC-30 results are summarised in the Figure 3.

Figure 3: BO18255 – Plot of global health score, QoL mean±SEM over time (EORTC QLQ-C30).



Fluoropyrimidine: Investigator's preference of Capecitabine or 5-FU
B/L: Baseline
* For Global Health Status Scales a higher score indicates better QoL

The *QLC-C30 scores* for physical, role, emotional and social function improved after chemotherapy from around Week 19 for both arms, while cognitive function scores remained largely unchanged throughout the treatment phase for both arms. The QLC-C30 scores for dysphagia, reflux, eating restriction and anxiety decreased after the first cycle of treatment in both arms. In both arms, dry mouth, taste, body image and hair loss scores decreased around the end of chemotherapy (Week 16-19). In comparison with patients in the FP arm, patients in the FP+H arm had a lower score for hair loss during the phase of chemotherapy (until about Week 19), while patients in the FP arm had slightly better scores for dysphagia, taste, reflux and eating restrictions. However, subsequent to the end of the chemotherapy phase (Week 19 onwards), the scores were similar in both arms. There were no differences in scores for body image, dry mouth and anxiety between arms.

Pain intensity scores were assessed using the Visual Analogue Scale (VAS) and no difference in pain intensity scores (change from baseline) was observed between the two arms over time. *Analgesic medications* were taken by 29% (84/290) of patients in the FP arm and 29.3% (86/294) of patients in the FP+H arm. In the FP arm, 17.2% (50/290) of patients had to increase analgesic dose or add at least one medication compared with 20.1% (59/294) of patients in the FP+H arm.

Body weight was recorded at baseline and then at 3 weekly intervals until disease progression. The median body weight at screening was 60 kg [range: 28-105] in the FP arm and 61 kg [range: 35-110] in the FP+H arm. No significant difference was observed between the two arms as regards body weight during the study. Approximately half the patients in both arms had no change in body weight throughout the study (FP 51.6% [141/290]; FP+H 50.5% [143/294]), with most of the remaining patients in both treatment arms experiencing a greater than 5% decrease in weight (FP 46.9% [128/290]; FP+H 48.4% [137/294]).

Comment: *The QOL results suggest that both treatments were associated with improvement over the course of the study. However, the results were descriptive rather than analytic and no definitive conclusions can be made. Overall, it appears that small to moderate improvements occurred with both FP and FP+H over the course of the study. Pain intensity scores and analgesic use were similar for both treatment arms. There was no significant difference between treatment arms as regards weight change over the course of the study.*

Exploratory and Subgroup Analyses

The study report included a number of exploratory (Cox regression[15], interaction) and subgroup analyses of the primary and secondary efficacy parameters. The results of the analyses relating to the primary efficacy endpoint of overall survival (OS) are discussed briefly below. The secondary efficacy parameters were analysed in a similar fashion to the primary efficacy parameter, but will not be discussed here as the results for the OS analyses are considered to be representative of all exploratory and subgroup analyses.

In a multiple Cox regression analysis of OS adjusting for all covariates, the HR for FP+H compared with FP was 0.72 [95%CI: 0.58, 0.90]. This result was consistent with the unadjusted primary OS analysis (that is, HR=0.74 [95%CI: 0.60, 0.91]. The results for the multiple Cox regression analysis showed that ECOG PS, region, prior gastrectomy, number of metastatic sites and HER2 status all had a significant effect on overall survival, when adjusting for all other covariates and treatment.

In a univariate Cox regression analysis the effect of each pre-specified covariate on OS was investigated. The univariate results showed that ECOG PS, chemotherapy regimen, region, type of gastric cancer, prior gastrectomy, number of metastatic sites, number of metastatic lesions and HER2 status all had significant effects on overall survival. In an analysis of OS, the unadjusted HR of 0.74 [95%CI: 0.60, 0.91] for FP+H compared with FP was similar to the HR for the comparison adjusted for each individual covariate.

In an interaction analysis between treatment and covariate on overall survival, significant interactions were observed between treatment and measurability of disease (p=0.0061) and between treatment and number of metastatic sites (p=0.0318). These exploratory results suggest that patients with measurable disease had a greater survival benefit from the addition of trastuzumab (HR=0.66 [95% CI: 0.53, 0.82], n=526) compared with patients with non-measurable disease (HR=1.78 [95% CI: 0.87, 3.66], n=58. In addition, the exploratory results for patients with > 2 metastatic sites suggested a greater survival benefit from the addition of trastuzumab (HR=0.57 [95% CI: 0.43, 0.77], n=295) compared with patients with 1-2 metastatic sites (HR=0.93 [95% CI: 0.68-1.26], n=298).

There were a number of subgroup analyses which showed that the risk of death was statistically significantly lower in patients in the FP+H arm compared with patients in the FP arm for most of the 36 subgroups tested.

[15] Cox regression (or proportional hazards regression) is method for investigating the effect of several variables upon the time a specified event takes to happen.

Comment: *The regression, interaction and subgroup analyses are considered to be exploratory rather than definitive. There were 15 separate interaction assessments and no statistical adjustment was made for multiple testing. Consequently, it could be expected that one of the 15 interaction assessments would have been statistically significant due to chance alone. In addition, in the significant interaction analysis involving measurability of disease there was a marked imbalance between the number of patients with measurable disease (n=526) and the number of patients with non-measurable disease (n=58). As regards the subgroup analyses, it is worth noting that the study report stated, "the analyses were not adequately powered to detect minimally clinically meaningful differences between the FP+H and FP arms for each of the pre-defined subgroups. As there were few patients and few deaths that occurred in each of the treatment arms in these subgroups, comparisons of outcomes between subgroups should be interpreted with caution". Overall, it is considered that the regression, interaction, and subgroup analyses provide information which might usefully be followed up in subsequent definitive studies.*

Post-Hoc Overall Survival Analysis by HER2 Status

The results of the *pre-specified HER2* subgroup analysis showed little contribution to the overall increase in FP+H efficacy from subgroups with low HER2 expression (that is, IHC 0/FISH+: HR 0.92; IHC 1+/FISH+: HR 1.24), and demonstrated that the main effect was derived from subgroups with high HER2 expression (that is, IHC 2+/FISH+: HR 0.75; IHC 3+/FISH+: HR 0.58). The interaction test between treatment and HER2 status on overall survival was not statistically significant (p=0.2877) indicating that in the pre-specified analysis there was no difference between the hazard ratios (FP versus FP+H) for the five different HER2 groups as regards effects on OS.

In view of the differential effect of FP+H on OS of HER2 expression, an exploratory *post-hoc analysis* of overall survival and PFS, by low and high expressing HER2 subgroups was undertaken. The low HER2 expressing group consisted of IHC 0/FISH+ and IHC 1+/FISH+, and the high HER2 expressing group consisted of IHC 2+/FISH+, IHC3+/FISH+, IHC3+/FISH-, and IHC3+/FISH no result. The results for the *post-hoc* analysis for overall survival are described below. The results for the PFS have not been presented here but were consistent with those for OS.

In the non-stratified *post-hoc* analysis, the median survival time for the high HER2 expressing group was 11.8 months in the FP arm (n=218, 136 deaths) and 16.0 months in the FP+H arm (n=228, 120 deaths): HR = 0.65 [95%CI: 0.51, 0.83]; p=0.0006. The Kaplan-Meier estimated 12-month survival rates were 48% for the FP arm and 64% for the FP+H arm. The results in the stratified analysis were similar to those in the non-stratified analysis. In the non-stratified analysis, the median survival time for the low HER2 expressing group was 8.7 months in the FP arm (n=70, 45 deaths) and 10.0 months in the FP+H arm (n=61, 43 deaths): HR = 1.07 95%CI: 0.70, 1.62]. The interaction test of the treatment effect and the HER2 category on overall survival was statistically significant (p = 0.0368) indicating that there was a difference between the hazard ratios of the high and low HER2 expression subgroups.

Comment: *The post-hoc analysis indicated that high HER2 expressing patients treated with FP+H had a significant overall survival benefit compared with FP treated patients, while in low HER2 expressing patients there was no significant difference in overall survival between the two treatments. These results should be interpreted cautiously as the analysis was not pre-specified. The patients were not selected or stratified on the basis of high or low HER2 expression. The p-values were presented for descriptive purposes only. The results of this study should be considered to be exploratory and not definitive. However, the results are*

interesting and of potential clinical importance and it would be worthwhile following up these exploratory results in subsequent studies of patients with advanced gastric cancer.

Clinical Studies in Special Populations

There were no clinical studies in special populations in the submission.

Analysis Performed Across Trials

There were no analyses performed across trials (that is, pooled analyses or meta-analysis) in the submission.

Supportive Studies

Overview

The sponsor is seeking approval of a triplet treatment regimen which includes a "platinum agent" (unspecified). In support of this proposal, the sponsor's Clinical Overview included a brief summary of the published data from seven Phase II and two Phase III studies which were claimed to show that oxaliplatin and cisplatin regimens were of similar efficacy in the treatment of advanced gastric cancer. The sponsor's Clinical Overview stated that the Phase II studies "consistently suggested that oxaliplatin efficacy in gastric cancer was non-inferior to that of cisplatin while overall toxicities were reduced. In addition, due to substantially better ease of administration of oxaliplatin, there was a favourable effect on the use of treatment center (hospital, outpatient chemotherapy department) resources". No evaluation of the Phase II studies was provided in the sponsor's Clinical Overview. However, the clinical overview included brief summaries of the two Phase III studies claimed to demonstrate "that oxaliplatin can be substituted for cisplatin in the treatment of gastric cancer" [that is, Cunningham *et al*, 2008; Al-Batran *et al*, 2008[16]]. These two studies have been briefly reviewed below.

Phase III Studies

a. Cunningham et al, 2008 [REAL-2]

This Phase III study (REAL-2) included patients who were at least 18 years of age with histologically proven adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the oesophagus, gastro-oesophageal junction, or stomach that was locally advanced (inoperable) or metastatic. The study was designed to determine whether fluorouracil can be replaced by capecitabine and cisplatin by oxaliplatin in the triple regimen of epirubicin, cisplatin and fluorouracil (ECF). The study was 2x2 design in which 1002 patients were randomly assigned to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil or capecitabine (that is, ECF or ECX, respectively) or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil or capecitabine (that is, EOF or EOX, respectively). The median number of cycles administered was six in each study group. The

[16] Cunningham D *et al.* (2008). Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Eng J Med.*358:36-46.

Al-Batran *et al.* (2008). Phase III Trial in Metastatic Gastroesophageal Adenocarcinoma with Fluorouracil, Leucovorin Plus Either Oxaliplatin or Cisplatin: A Study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 26:1435-1442.

median actual dose intensities of the epirubicin, platinum, and fluoropyrimidine drugs were similar in all groups

The primary endpoint was non-inferiority in overall survival for the triplet therapies containing capecitabine compared with those containing flurouracil, and for those containing oxaliplatin compared with those containing cisplatin. For the primary endpoint, the unadjusted hazard ratio for death for the non-inferiority comparison of capecitabine with fluorouracil was 0.86 [95% CI: 0.80 to 0.99]; for the comparison of oxaliplatin with cisplatin, the hazard ratio was 0.92 [95% CI: 0.80 to 1.10]. The upper limits of the 95% confidence intervals for both hazard ratios were below the pre-specified non-inferiority margin of 1.23. Consequently, the primary endpoint analyses showed non-inferiority of oxaliplatin versus cisplatin, and capecitabine versus fluorouracil in the tested triplet regimens. Median survival times in the ECF, ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively; survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. As compared with cisplatin, oxaliplatin was associated with significantly less Grade 3 or 4 neutropaenia and alopecia, but significantly more Grade 3 or 4 diarrhoea and peripheral neuropathy. The incidence of nausea and vomiting was not decreased in the oxaliplatin group compared with the cisplatin group. The author's were surprised by this finding and commented that this "may reflect improvements in antiemetic therapy".

Comment: *This was a good quality study. It demonstrated non-inferiority as regards overall survival of triplet regimens containing oxaliplatin (EOF, EOX) compared with triplet regimens containing cisplatin (ECF, ECX).*

b. Al-Batran et al, 2008

This Phase III study included patients who were aged more than 18 years with histologically confirmed locally advanced or metastatic adenocarcinoma of the stomach or oesophageal-gastric junction. The study was designed to compare the triplet regimens of fluorouracil, leucovorin, and oxaliplatin (FLO) with fluorouracil, leucovorin, and cisplatin (FLP) in patients with advanced gastric cancer. Patients with previously untreated advanced adenocarcinoma of the stomach or esophagogastric junction were randomly assigned to receive either fluorouracil 2,600 mg/m^2 via 24-hour infusion, leucovorin 200 mg/m^2, and oxaliplatin 85 mg/m^2 (FLO) every 2 weeks or fluorouracil 2,000 mg/m^2 via 24-hour infusion, leucovorin 200 mg/m^2 weekly, and cisplatin 50 mg/m^2 every 2 weeks (FLP).

The primary end point was superiority of FLO (n=112) over FLP (n=106) in terms of median progression free survival (PFS). The study was designed to detect differences in PFS using a one-sided log-rank test. Tumour response was classified according to World Health Organization (WHO) criteria with CT or MRI imaging of target areas pre-treatment and then every 6 weeks. PFS was measured from the date of randomization until disease progression or death of any cause. The median PFS was 5.8 months [95% CI: 4.5, 6.6] with FLO and 3.9 months [95%CI: 3.1, 4.8] with FLP (p=0.0.765; one-sided log-rank test). The median cumulative doses per patient for oxaliplatin and cisplatin were 759.5 mg/m^2 and 295.2 mg/m^2, respectively.

Overall, 214 patients were assessable for toxicity. The treatment was generally well tolerated, and the incidence of Grade 3 to 4 toxicities was relatively low in the two treatment arms: FLO 0-14.3%; FLP 0-14.7%. The incidences (FLO versus FLP) of all grades of toxicity were: 28.6% versus 37.3% for neutropaenia; 40.2% versus 52.0% for leucopaenia; 44.6% versus 42.2% for thrombocytopaenia; and 53.6% versus 71.6% for anaemia. Nausea, vomiting and diarrhoea all occurred more commonly with FLP than with FLO. However,

increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) levels occurred more commonly with FLO than with FLP. Overall, FLO was better tolerated than FLP.

Comment: *This was a study of reasonable quality which showed that the triplet regimens FLO and FLP were comparable as regards PFS, and that the FLO regimen was generally better tolerated than the FLP regimen. The primary endpoint was not met as superiority of FLO over FPO for PFS was not demonstrated using the pre-specified one-sided log-rank test. Furthermore, it is considered that OS would have been preferable to PFS as the primary endpoint as it is free from bias. The study was inadequately powered to detect a statistically significant difference in overall survival between the two treatment arms (FLO, 10.7 months [95% CI: 8.5, 13.9] versus FLP, 8.8 months [95% CI: 7.7, 12.0]). However, despite the methodological issues the results suggest that the two regimens are of similar clinical efficacy. The incidences of six clinically important toxicities, including anaemia, nausea, vomiting, alopecia, fatigue, and renal toxicity, were significantly lower with FLO compared with FLP, as was the incidence of serious adverse events related to the treatment.*

Comment

The supportive data suggest that specific treatment regimens for advanced gastric cancer differing only by the inclusion of oxaliplatin or cisplatin have similar efficacy, while tolerability is generally better in those regimens including oxaliplatin than those including cisplatin. However, there are no pivotal data providing comparison of triplet regimens of trastuzumab, fluoropyrimidine and cisplatin with trastuzumab, fluoropyrimidine, and oxaliplatin for the treatment of patients with HER2 positive advanced gastric cancer. Consequently, it cannot be definitively determined whether these two triplet regimens would be of similar efficacy and safety for this condition.

Evaluator's Overall Conclusion on Efficacy

The pivotal study showed that median overall survival was statistically significantly longer in the FP+H treatment arm compared with the FP treatment arm: 13.8 [95%CI: 12, 16] months versus 11.1 [95%CI: 10, 13]; p=0.0046 log-rank test. The hazard ratio showed that FP+H reduced the risk of death by 26% compared with FP: HR=0.74 [95%CI: 0.60, 0.91]. The increase in median overall survival of 2.7 months is considered to be clinically meaningful. The protocol indicated that a difference of 3 months in median overall survival between FP+H and FP was clinically meaningful, based on the assumption that respective median survival times would be 13 months and 10 months. The observed median survival times in both treatment arms were longer than the assumed median survival times. The Kaplan-Meier estimated 12 month survival rates were 45% in the FP arm and 56% in the FP+H, and respective 30 month survivals were 10% and 16%. The premature withdrawal rates in both arms were ≥ 20% (FP 27%, FP+H 20%), and rates of these levels always raise some concerns about the overall validity of the planned statistical analysis. Nevertheless, it is considered that the observed results in this study are acceptable.

The secondary efficacy endpoints analyses showed that the results for the FP+H versus FP arm were statistically significantly superior ($p < 0.05$) for median progression free survival (6.7 versus 5.5 months), median time to disease progression (7.1 versus 5.6 months), partial response rate (41.8% versus 32.1%), response rate (47.3% versus 34.5%), clinical benefit rate (78.9% versus 69.3%), and median duration of response (6.9 versus 4.8 months). However, these results should be interpreted with caution as the endpoints were based on assessment of tumour response using RECIST criteria undertaken by unblinded local investigators rather than blinded centralised reviewers. This has the potential to bias the assessment and to increase variability of reporting.

The descriptive results for quality of life, pain intensity, analgesic use and weight change during treatment were similar for the two arms. There were a number of exploratory, subgroup, and *post-hoc* analyses which provide ideas for future investigation, but cannot be considered definitive as regards the comparative efficacy of the two treatment arms.

Safety

Introduction

The safety evaluation of the proposed FP+H treatment regimen is based on the safety data from the pivotal study [BO18255]. The study included 584 patients in the safety analysis population (SAP) at the clinical cut-off date for analysis of 7 January 2009. More patients in the FP+H arm received 6 cycles of chemotherapy compared to the FP arm (59.5% versus 49.3% for capecitabine/5-FU and 56.5% versus 48.3% for cisplatin. In the FP+H arm, 50% of patients received trastuzumab for at least 8 cycles. The safety experience is summarised below in Table 6. Overall, almost all patients in each treatment arm experienced an adverse event (AE), and the safety profiles of FP+H and FP were similar with regards to frequency, severity, discontinuations due to AEs, SAEs, dose modifications and AEs leading to death.

Table 6: B018255 – Overview of safety experience in treated patients.

	FP (n=290)	FP+H (n=294)
Any AEs	284 (98%)	292 (99%)
Grade ≥ 3 AEs	198 (68%)	201 (68%)
Serious AEs	81 (28%)	95 (32%)
AEs leading to discontinuation of at least one treatment	48 (17%)	48 (16%)
AEs leading to dose modifications/interruptions	237 (82%)	246 (84%)
AEs leading to death	14 (5%)	17 (6%)

Patient Exposure

Trastuzumab Exposure

At the time of the clinical cut-off, a total of 294 patients with advanced gastric cancer had received at least one treatment cycle of trastuzumab in combination with a fluoropyrimidine and cisplatin. The median number of trastuzumab treatment cycles was 8 [range: 1-49], the median duration of trastuzumab treatment was 4.9 months [range: 0.03-33.18], and the mean total dose of trastuzumab was 3581 mg [range: 280-22798]. The median dose intensity for trastuzumab treatment was 100.1% [range: 84.8%-156.7%]. Dose intensity was defined as the planned versus received dose. The planned dose was defined as the dose that would be given if no doses were missed and/or no dose reductions were made for the number of cycles started by each patient. Dose reductions were not permitted for trastuzumab. The mean cumulative dose intensity for trastuzumab could be > 100% since more than one trastuzumab administration could be given to adjust for fluoropyrimidine and/or cisplatin dosing changes within a given cycle. The mean infusion rates of trastuzumab per cycle increased from 5.39 mg/min at Cycle 1 to 9.08 mg/min at Cycle 2, then increased slightly over the course of treatment (9.57 mg/min at Cycle 3 to 12.12 mg/min at Cycle 40).

Cisplatin Exposure

The median number of cisplatin cycles was 5 [range: 1-16] for the FP arm (n=290) and 6 [range: 1-14] for the FP+H arm (n=294), the median duration of cisplatin treatment was 3.4 months [range: 0.03-15.18] for the FP arm and 3.5 months [range: 0.03-12.88] for the FP+H arm, the mean total dose of cisplatin was 547 mg [range 30-1709] for the FP arm and 550 mg [range: 96-1530] for the FP+H arm. The median dose intensities for cisplatin treatment were 91.1% [range: 23.5%-103.7%] for the FP arm and 89.4% [range: 52.0%-108.6%] for the FP+H arm. Overall, the cisplatin exposure parameters were similar for the two treatment arms.

Fluoropyrimidine Exposure

a. Capecitabine

The median number of capecitabine cycles was 5 [range: 1-20] for both the FP (n=256) and the FP+H arms (n=255), the median duration of capecitabine treatment was 3.9 months [range: 0.03-15.64] for the FP arm and 3.9 months [range: 0.10-16.82] for the FP+H arm, and the mean total capecitabine dose was 193342 mg [range 1650-921000] for the FP arm and 197596 [range: 6000-648200] for the FP+H arm. The median dose intensities were 86.7% [range: 3.6-110.0] for the FP arm and 85.9% [range: 14.3-107.5%] for the FP+H arm. Overall, the capecitabine exposure parameters were similar for the two treatment arms.

b. 5-FU

The median number of 5-FU cycles was 4 [range: 1-11] for the FP arm (n=37) and 6 [range: 1-6] for the FP+H arm (n=38), the median duration of 5-FU treatment was 2.0 months [range: 0.13-7.56] for the FP arm and 3.6 months [range: 0.16-5.09] for the FP+H arm, and the mean total 5-FU dose was 28016 mg [range: 3752-80000] for the FP arm and 31784 mg [range: 4800-47040] for the FP+H arm. The median dose intensities were 90.2% [range: 33.4%-102.0%] for the FP arm and 93.3% [range: 61.1%-101.5%] for the FP+H arm. Overall, exposure to 5-FU was marginally greater in the FP+H arm compared with the FP arm. However, this is unlikely to be clinically significant.

Dose Delays and Interruptions

No dose interruptions within a treatment cycle were observed with cisplatin or 5-FU in the FP or FP+H treatment arms. In Cycle 1, eight patients (2.7%) had a trastuzumab infusion interruption of < 1 day. No other dose interruptions were observed with trastuzumab in all other treatment cycles. Capecitabine treatment had to be interrupted for 1-5 days in nearly every cycle. However, the number of patients experiencing capecitabine treatment interruptions of 1-5 days was similar in both the FP and FP+H arms.

Adverse Events

Overall Pattern of Adverse Events

In the pivotal study, all adverse events (AEs) occurring during the study and for up to 6 months after the last dose of study medication were reported. After the 6 month period, treatment related AEs and unrelated severe or life-threatening AEs were followed-up until resolution or improvement to baseline. AEs were defined as untoward medical occurrences irrespective of causal relationship to treatment. Pre-existing conditions which worsened during the study were also reported as AEs. Preferred terms were assigned to the original investigator reported AE using Version 11.1 of the Medical Dictionary for Regulatory Activities (MedDRA). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0 (Grade 1 to 4), with the exception of cardiac failure, which was graded according to the New York Heart Association (NYHA) classification system. Death (that is, NCI-CTCAE Grade 5) was captured as a

separate outcome. The CTCAE v3.0 displays Grades 1-5 with unique clinical descriptions of severity for each AE based on the general guideline of: Grade 1 (mild AE); Grade 2 (moderate AE); Grade 3 (severe AE); Grade 4 (life threatening or disabling AE); and Grade 5 (death). AEs not listed on the CTCAE were graded from 1 (mild) to 5 (death) using the CTCAE general criteria.

Almost all patients experienced at least one adverse event: 98% (284/290) in the FP arm and 99% (292/294) in the FP+H arm). Overall, patients in the FP+H arm experienced about 22% more AEs than patients in the FP arm (2812 AEs versus 2308 AEs). The most commonly reported AEs in the following body systems were (shown as FP versus FP+H):

- *Gastrointestinal disorders (86% versus 91%)*: most frequently, nausea (63% versus 67%), vomiting (46% versus 50%), diarrhoea (28% versus 37%), constipation (32% versus 26%), stomatitis (15% versus 24%) and abdominal pain (14% versus 16%). All except constipation had a higher incidence in the FP+H than in the FP arm.
- *Blood and lymphatic system disorders (71% in each arm)*: most frequently haematological AEs, such as neutropaenia (57% versus 53%), anaemia (21% versus 28%) and thrombocytopaenia (11% versus 16%).
- *General disorders and administration site conditions (57% versus 69%)*: fatigue (28% versus 35%), pyrexia (12% versus 18%) and mucosal inflammation (6% versus 13%) had a higher incidence in the FP+H arm, while asthenia (18% versus 19%) had a similar incidence in the two arms. An increase in the incidence of chills was observed in the FP+H arm (8%) compared with the FP arm (0%).
- *Metabolism and nutrition disorders (53% versus 58%)*: A high proportion of patients had anorexia (46% in each arm).
- *Skin and subcutaneous tissue disorders (37% versus 44%)*: This imbalance between the arms reflected an increased incidence of palmar-plantar erythrodysaesthesia syndrome (22% versus 26%).
- *Nervous system disorders (37% versus 41%)*: The most frequent AE in both arms was dizziness (10% versus 11%), and the major contributor to the higher incidence of nervous system disorders in the FP+H arm was dysgeusia (5% versus 10%).
- *Respiratory, thoracic and mediastinal disorders (25% versus 28%)*: The most frequent AE in both arms was hiccups (10% versus 12%).
- *Infections and infestations (20% versus 32%)*: The most frequent AE in both arms was nasopharyngitis (6% versus 13%).
- *Renal and urinary disorders (22% versus 28%)*: The most frequent AE in both arms was renal impairment (13% versus 16%).
- *Investigations (29% versus 39%)*: Within this category, a difference between the arms was observed with respect to the proportion of patients reporting weight decrease (14% versus 23%).

Adverse Events Related to Study Treatment

The relationship of an AE to study treatment was assessed by the investigator as either Yes (related) or No (unrelated). Of the total number of AEs, 63% in the FP arm and 65% in the FP+H arm were considered to be related to study treatment (trastuzumab, cisplatin or fluoropyrimidine). The AEs most commonly considered related to treatment were: nausea, vomiting, diarrhoea and stomatitis (SOC GI disorders); neutropaenia and thrombocytopaenia

(SOC blood and lymphatic disorders); fatigue, asthenia, mucosal inflammation and chills (SOC general disorders and administration site conditions); anorexia (SOC metabolism and nutrition disorders); palmar-plantar erythrodysaesthesia syndrome and alopecia (SOC skin and subcutaneous tissue disorders); decreased renal creatinine clearance (SOC investigations); and renal impairment (SOC renal and urinary disorders). The majority of these treatment related AEs occurred at a similar frequency in both treatment groups. Treatment related AEs of nausea, diarrhoea, stomatitis, anaemia, thrombocytopaenia, fatigue, pyrexia, mucosal inflammation, chills and, weight decrease were more common in the FP+H arm than in the FP arm.

Grade ≥ 3 Adverse Events (NCI-CTC)

The incidence of Grade≥ 3 AEs was 68% in both treatment arms: 198/290 in the FP arm and 201/294 in the FP+H arm. The most commonly reported Grade≥ 3 AEs were (shown as FP versus FP+H): blood and lymphatic system disorders (38% [111/290] versus 40% [118/294]); gastrointestinal disorders (21% [61/290] versus 26% [77/294]); metabolism and nutrition disorders (11% [31/290] versus 14% [42/294]); and general disorders and administration site conditions (9% [25/290] versus 13% [37/294]). The most commonly reported Grade ≥ 3 AEs (FP versus FP+H) were neutropaenia (30% versus 27%) and anaemia (10% versus 12%). Most of the total number of Grade ≥ 3 AEs were considered by the investigator to be related to treatment with the proportion being similar for the two treatment arms: 67% (262/389) in the FP arm, and 69% [324/470] in FP+H arm.

Cardiac Adverse Events

In the FP arm, 18/290 (6%) patients experienced 21 cardiac AEs compared with 17/294 (6%) patients in the FP+H arm who experienced 20 AEs. In the FP arm, 9 (3.1%) patients experienced at least one cardiac Grade≥ 3 AE compared with 4 (1.4%) patients in the FP+H arm. In the FP arm, nine events were Grade≥ 3 (2x cardiac failure; 2x myocardial infarction; 1x arteriospasm coronary; 1x atrial flutter, 1x cardiac arrest, 1x cardio-respiratory arrest; 1x Prinzmetal angina). In the FP+H arm, there were five Grade≥ 3 events (1x cardiac failure; 1x acute myocardial infarction; 1x unstable angina; 1x myocardial ischemia; 1x tachycardia). Of the total number of Grade≥ 3 card iac AEs, 5/14 were fatal: two in the FP arm (1x cardiac arrest; 1x cardio-respiratory arrest) and three in the FP+H arm (1x cardiac failure; 1x unstable angina; 1x acute myocardial infarction). Cardiac SAEs were reported in six patients in the FP arm (2x cardiac failure, 2x myocardial infarction, 1x cardiac arrest, 1x cardio-respiratory arrest), and two patients in the FP+H arm (1x cardiac failure and unstable angina; 1x acute myocardial infarction)

Left Ventricular Ejection Fraction (%)

Patients entering the study were required to have LVEF≥ 50% at baseline. LVEF was measured at baseline and every 12 weeks by MUGA or echocardiography using the same technique throughout the study in an individual patient. Trastuzumab was to be discontinued in any patient who developed clinical signs and symptoms of congestive heart failure, and an algorithm was provided for the discontinuation of trastuzumab in individual patients based on interval LVEF assessments. At screening, the median LVEF was 64% [range: 48%-90%] in the FP arm and 65% [range: 50%-86%] in the FP+H arm. During the study, 1.1% (2/187) of patients in the FP arm with a post-screening value had a drop in LVEF of≥ 10% to a LVEF value < 50% compared with 11/237 (4.6%) patients in the FP+H arm. In the FP arm, 11.8% (22 /187) patients had a drop in LVEF of≥ 10% to a LVEF ≥ 50% compared with 16.5% (39/237) patients in the FP+H arm. The mean LVEF remained relatively constant over time (screening to Week 73) in both treatment arms with values fluctuating between 60% and

70%. Overall, 187 FP treated patients and 239 FP+H treated patients had both initial and post-screening LVEF values assessed by the same methods.

Infusion Related Reactions

The study included an AE analysis of typical pre-specified symptoms of infusion related reaction that were reported on the same day of the trastuzumab infusion or the day after the infusion. There were 337 AEs of all grades reported the day of, or the day after, a trastuzumab infusion in 172/294 (59%) patients at any cycle. Of these AEs, 291 AEs (86%) were considered related to study medication. The most common infusion related AEs involved the gastro-intestinal system (45% [131/294], patients) and consisted primarily of nausea (40% [118/294], patients) and vomiting (24% [70/294], patients). The highest proportion of patients with at least one infusion AE occurred in Cycle 1 (41%), and the proportion of patients with at least one AE decreased with subsequent cycles (in Cycles 2-8 the proportions were 20%, 18%, 15%, 15%, 15%, 3%, 2%, respectively).

The first trastuzumab infusion lasted 90 minutes in 76% (225/294) of patients, 120 minutes in 14% (41/294), 60 minutes in 4% (11/294), and 30 minutes in 1% (4/294). Of the 225 patients in whom the first trastuzumab infusion lasted 90 minutes, 39% had at least one AE (gastrointestinal disorders [34%] including nausea and vomiting; general disorders, such as fatigue, and administration site conditions [18%]). After Cycle 1, the majority of the patients had infusions lasting 30 minutes (51% [151/294]), and of these patients 44% (n=66) had at least one AE (gastrointestinal disorders [30%]; general disorders and administration site conditions [19%]). Grade $\geq$ 3 AE on the day of, or the day after, a trastuzumab infusion were experienced by 6% (17/294) of patients and the most common of these were nausea (2% [7/294]) and vomiting (2% [5/294]).

Serious Adverse Events (SAEs) and Deaths

Deaths

At the time of the clinical cut-off (7 January 2009), a total of 349 patients had died. The incidence of death was greater in the FP arm than the FP+H arm (63% [182/290] versus 57% [167/294], respectively). Gastric cancer was the most common cause of death in both treatment arms (FP 92% [167/182]; FP+H 89% [148/167]). Overall, 58% (167/294) of patients in the FP arm died due to progression of gastric cancer compared with 50% (148/294) of patients in the FP+H arm. Death during the treatment phase occurred in 9% (25/290) of patients in the FP arm and 6% (18/294) of patients in the FP+H arm. Death during the follow-up phase occurred in 54% (157/290) of patients in the FP arm and 51% (149/294) of patients in the FP+H arm. The incidence of death within the first 60 days of the first administration of study drug was 6.9% in the FP arm and 5.1% in the FP+H arm.

Death due to AEs occurred in 5% (14/290) patients in the FP arm (14 events) and 6% (17/294) patients in the FP+H arm (18 events). Fatal AEs occurring in at least 2 patients in one or both treatment arms were septic shock (2 FP, 1 FP+H), pneumonia (0 FP, 2 FP+H), and pulmonary embolism (2 FP, 0 FP+H). There were 4 instances of “death” given as the cause of death when the cause was unknown. There were also 3 reports of death due to unknown causes. The investigator judged the cause of death to be related to study treatment in 1% (3/290) of patients in the FP arm (3 events: 1x septic shock, 1x death; 1x pancytopaenia), and 3% (10/294) in the FP+H arm (11 events: 2x pneumonia; 2x death; 1x acute myocardial infarction 1x unstable angina; 1x cardiac failure; 1x gastric haemorrhage; 1x depressed level of consciousness; 1x thrombocytopaenia; 1x renal failure).

Serious Adverse Events (SAEs)

SAEs were reported in 28% (81/290) of patients in the FP arm (122 events) and 32% (95/294) of patients in the FP+H arm (174 events). The most commonly occurring SAEs (shown as FP versus FP+H) were diarrhoea (2% versus 6%), vomiting (1% versus 3%), dysphagia (0% versus 3%), febrile neutropaenia (3% versus 4%), anaemia (2% versus 1%), septic shock (2% versus <1%), and dehydration (2% versus 2%). Fatal SAEs were experienced by 4% of patients in the FP arm and 6% of patients in the FP+H arm.

Laboratory Findings

The shifts from baseline to worsened haematology parameters (Grade ≥ 3) during treatment are summarised below in Table 7. The recorded Grade 3/4 shifts were marginally higher for the four haematology parameters in patients in the FP+H arm compared with the FP arm. In general, the recorded Grade 3/4 shifts were marginally higher in most of the blood chemistry parameters in patients in the FP+H arm compared with the FP arm.

Table 7: Summary of Newly Occurring Grade ≥ 3 Haematology Values During Treatment (Shift Table; SAP).

	FP			FP+H		
	n	Grade 3, n (%)	Grade 4, n (%) *	n	Grade 3, n (%)	Grade 4, n (%) *
↓ Haemoglobin	285	40 (14%)	6 (2%)	292	46 (16%)	11 (4%)
↓ WBC	285	22 (8%)	7 (2%)	292	22 (8%)	8 (3%)
↓ Neutrophils	284	68 (24%)	15 (5%)	289	80 (28%)	21 (7%)
↓ Platelets	285	10 (4%)	1 (< 1%)	292	9 (3%)	7 (2%)

* Excluding shifts from Grade 3 to Grade 4. WBC=white blood cells.

The most common Grade ≥ 3 haematological toxicities were neutropaenia and anaemia, both of which had a slightly higher incidence in the FP+H arm compared with the FP arm (35% versus 29%, and 22% versus 18%, respectively). The Grade ≥ 3 toxicities for reduced haemoglobin were 16% for FP and 20% for FP+H and for reduced platelets were 4% for FP and 5% and for FP+H. The most common Grade ≥ 3 blood chemistry abnormalities were decreased sodium (14% FP versus 16% FP+H), decreased potassium (6% FP versus 10% FP+H) and decreased calcium (2% FP versus 5% FP+H). None of the other recorded Grade ≥ 3 blood chemistry abnormalities occurred with an incidence of > 5% in either of the two treatment arms.

ECG, CXR, Vital Signs

Abnormal electrocardiograms (ECGs) pre- versus post-screening were reported in 9.7% (28/290) and 1.7% (5/290) of patients in the FP arm, with the corresponding values for the FP+H arm being 7.1% (21/294) and 2.7% (8/294). *Abnormal CXRs pre- versus post-screening* were reported in 7.9% (23/290) and 2.8% (8/290) of patients in the FP arm, with the corresponding values for FP+H arm being 12.6% (37/294) and 3.4% (10/294). The change in mean value from screening over time for temperature, pulse rate, and blood pressure have been examined for both treatment groups and no clinically relevant differences were noted.

Safety in Special Populations

There were no pre-specified safety analyses in special populations. The pivotal study included a *post-hoc* safety analysis in patients in both the high and low HER2 expressing groups treated with either FP or FP+H. The safety results from this analysis have been examined. No obvious significant differences in the safety profiles in the high and low HER2 expressing groups could be identified. Overall, the results appeared to be consistent with those for the total safety population. The safety information from this *post-hoc* analysis will not be discussed further.

Immunological Events

No new information reported.

Safety Related to Drug-Drug Interactions and Other Interactions

No new information reported.

Discontinuation due to Adverse Events

Discontinuations of at least one study drug due to AEs occurred in 17% (48/290) of patients treated with FP (50 events) and 16% (48/294) of patients treated with FP+H (53 events). The most common AEs leading to treatment discontinuation were gastrointestinal disorders (2% FP, 4% FP+H), such as diarrhoea and dysphagia; renal and urinary disorders (1% FP, 3%, FP+H) such as renal impairment; blood and lymphatic system disorders (3% FP, 1% FP+H), such as thrombocytopenia and febrile neutropaenia. Overall, treatment discontinuations were similar in the two treatment arms.

Adverse events led to dose modifications or treatment interruptions of at least one component of study treatment occurred in 82% (237/290; 530) of patients in the FP arm and 84% (246/294; 661 events) of patients in the FP+H arm. The most common reasons for dose modification or interruption in the two arms were (shown as FP versus FP+H): blood and lymphatic system disorders (60% versus 58%), such as neutropaenia (54% versus 50%), thrombocytopenia (8% versus 11%), anaemia (3% versus 5%); gastrointestinal disorders (28% versus 29%) including nausea (13% in each arm), vomiting (11% in each arm), diarrhoea (4% versus 9%); renal and urinary disorders (16% versus 20%), such as renal impairment (13% versus 14%); investigations (11% versus 24%), driven by body weight reduction (3% versus 13%), creatinine renal clearance decreased (6% versus 7%); general disorders and administration site conditions (10% versus 17%) including asthenia (4% in each arm) and fatigue (4% versus 3%); metabolism and nutrition disorders (7% versus 10%) such as anorexia (5% versus 7%).

Post Marketing Experience

There were no specific post marketing safety data relating to the use of trastuzumab for the treatment of HER2 positive advanced gastric cancer as the drug was not approved for this indication in any country at the time of the submission. The sponsor's global trastuzumab safety data base as of 29 June 2009 included a total of 11240 adverse events of which 7981 (71%) were considered to be serious. The sponsor estimates that the database represents approximately 650,000 patient years of exposure to trastuzumab. The most frequently reported AEs (that is, $\geq$ 10%) were categorized under the following SOCs: general disorders and administration site condition 1615 events (14.4%); cardiac disorders 1374 events (12.2%); investigations 1281 events (11.4%); and respiratory thoracic and mediastinal disorders 1235 events (11.0%).

The most frequently reported *general disorders and administration site conditions* were: pyrexia 418 (26%); chills 223 (14%); and infusion related reactions 101 (6%). Of the total number of these events (1615), 956 (59%) were SAEs and 669 (41%) non-serious AEs. The

most frequently reported *cardiac disorders* were: cardiac failure 278 (20%); and cardiac failure congestive 205 (15%). Of the total number of these events (1374), 1302 (95%) were SAEs and 72 (5%) non-serious AEs. The most frequently reported *investigation* related AE was ejection fraction decreased 530 (41%). Of the total number of these events (1281), 817 (64%) were SAEs and 464 (36%) non-serious AEs. The most frequently reported *respiratory, thoracic and mediastinal disorders* were: dyspnoea 354 (29%); and pleural effusion 109 (9%). Of the total number of these events (1235), 1056 (86%) were SAEs and 179 (14%) non-serious AEs.

Evaluator's Overall Clinical Comment on Safety

In the pivotal study, the safety profile of FP+H was generally similar to that of FP. Almost all patients in both arms experienced at least one adverse event: FP 98% (284/290) versus FP+H 99% (292/294). Patients in the FP+H arm experienced about 22% more AEs than patients in the FP arm (2812 AEs versus 2308 AEs). The most common adverse events reported in both arms (FP versus FP+H) were gastrointestinal disorders (86% versus 91%), followed by blood and lymphatic system disorders (71% both arms).

The incidence of NCI-CTC Grade ≥ 3 AEs was 68% in both treatment arms (FP 198/290; FP+H 201/294). The most commonly reported Grade ≥ 3 AEs (FP versus FP+H) were neutropaenia (30% versus 27%) and anaemia (10% versus 12%). Cardiac AEs were reported by 6% (18/290) of patients in the FP arm (21 events) and 6% (17/294) of patients in the FP+H arm (20 events). The percentage of patients experiencing a reduction in LVEF ≥ 10% resulting in LVEF < 50% was 1.1% (2/187) in the FP arm and 4.6% (11/237) in the FP+H arm.

There were more deaths in the FP arm (63% [182/290]) than in the FP+H arm (57% [167/294]), and most of the deaths in both arms were related to gastric cancer. SAEs were reported in 28% (81/290) of patients in the FP arm and 32% (95/194) of patients in the FP+H arm. The discontinuation of at least one study drug due to AEs were similar in both arms (FP 17% [48/290]; FP+H 16% [48/294]).

Clinical Summary and Conclusions

Clinical Aspects

Efficacy

The prognosis of patients with advanced gastric cancer is very poor with a median survival with chemotherapy of 7 to 10 months in most of the larger clinical studies [Wagner *et al*, 2006]. The pivotal study showed that median overall survival was statistically significantly longer in the FP+H treatment arm compared with the FP treatment arm: 13.8 [95% CI: 12, 16] months versus 11.1 [95%CI: 10, 13]; p=0.0046 log-rank test. The hazard ratio showed that FP+H reduced the risk of death by 26% compared with FP: HR=0.74 [95%CI: 0.60, 0.91]. The increase in median overall survival of 2.7 months is considered to be clinically meaningful. The protocol indicated that a difference of 3 months in median overall survival between FP+H and FP was clinically meaningful, based on the assumption that respective median survival would be 13 months and 10 months. The observed median survival times in both treatment arms were longer than the respective assumed median survival times. The Kaplan-Meier estimated 12 month survival rates were 45% in the FP arm and 56% in the FP+H, and respective 30 month survival rated were 10% and 16%. The pivotal study was open-label which had the potential to bias the results. However, the choice of overall survival as the primary efficacy parameter (that is, an unequivocal objective endpoint) is considered to satisfactorily mitigate the potential for bias in this particular study. The pivotal study was stopped prematurely on advice from the IDMC following the second interim efficacy and

safety analysis (that is, the study was stopped before a total of 460 deaths specified in the amended protocol had occurred). At this interim analysis, the statistically significant difference in overall survival in favour of the FP+H arm satisfied the pre-specified stopping rules. The study was analysed based on the efficacy and safety data at the second interim analysis.

The statistically significant positive finding for the primary efficacy endpoints of overall survival was supported by statistically significant ($p < 0.05$) differences in the secondary efficacy endpoints (shown as FP+H versus FP) of median progression free survival (6.7 versus 5.5 months), median time to disease progression (7.1 versus 5.6 months), partial response rate (41.8% versus 32.1%), response rate (47.3% versus 34.5%), clinical benefit rate (78.9% versus 69.3%), and median duration of response (6.9 versus 4.8 months). However, the differences between treatments for the secondary efficacy endpoints were small and of borderline clinical significance. Furthermore, the results of the secondary efficacy endpoint analyses should be interpreted with caution as the endpoints were based on tumour response using RECIST criteria assessed by unblinded local investigators rather than blinded centralised reviewers. This has the potential to both bias the assessment of tumour response and to increase variability of reporting tumour response among treatment centres.

The descriptive results for quality of life, pain intensity, analgesic use and weight change during treatment were similar for the two arms. There were a number of exploratory, subgroup, and *post-hoc* analyses which provide ideas for future investigation but cannot be considered definitive as regards the comparative efficacy of the two treatment arms. In particular, the *post-hoc* analysis of overexpression of HER2 suggested that patients with gastric or gastro-oesophageal adenocarcinoma who are high HER2 overexpressers might benefit more from the FP+H treatment regimen than patients who are low HER2 overexpressers.

The comparator treatment of cisplatin/fluoropyrimidine is considered acceptable given that the first patient was randomized to treatment in 2005 and that the combination would have been a widely accepted standard regimen for advanced gastric cancer at that time. However, the current standard of treatment for advanced gastric cancer suggests that a triplet rather than a doublet regimen is now the most suitable comparator for the investigation of new treatments. Investigators selected capecitabine in preference to 5-FU for combination with cisplatin in both the FP (87.9% [255/290]) and FP+H (87.1% [256/294]) treatment arms. The preference for capecitabine most likely reflects the convenience of oral administration with the drug compared with continuous IV infusion required for 5-FU.

There were no pivotal studies comparing the efficacy and safety of triplet regimens of trastuzumab, fluoropyrimidine and cisplatin with trastuzumab, fluoropyrimidine, and oxaliplatin. Consequently, the sponsor's proposal to include the generic term "platinum agents" in the indication rather than cisplatin is not supported. The clinical overview referred to published Phase II and III studies which suggest that oxaliplatin and cisplatin are of similar efficacy when included in comparable doublet and triplet regimens for the treatment of advanced gastric cancer. The published data also suggest that oxaliplatin is better tolerated than cisplatin when included in comparable doublet and triplet regimens. However, it is considered that it cannot be inferred from the supportive data that cisplatin and oxaliplatin are interchangeable "platinum agents" when combined with trastuzumab and capecitabine or 5-FU for the treatment of HER2 positive advanced gastric cancer.

Safety

In the pivotal study, the safety profile of FP+H was similar to that of FP. In general, the addition of trastuzumab to FP did not significantly affect the safety profile of FP alone with regards to the frequency, severity, and discontinuations due to AEs, SAEs, dose modifications and AEs leading to death. The study did not raise new safety signals relating to trastuzumab when combined with FP for the treatment of advanced gastric cancer. The dose intensity (planned versus received) was 100% for trastuzumab, 90% for cisplatin, 86% for capecitabine and 97% for 5-FU.

Almost all patients in both treatment arms experienced at least one adverse event: 98% (284/290) in the FP arm and 99% (292/294) in FP+H). Overall, patients in the FP+H arm experienced about 22% more AEs than patients in the FP arm (2812 AEs versus 2308 AEs). The most common adverse events reported in both treatment arms (FP versus FP+H) were gastrointestinal disorders (86% versus 91%), followed by blood and lymphatic system disorders (71% both arms). The most commonly occurring AEs (FP versus FP+H) were nausea (63% versus 67%), neutropaenia (57% versus 53%), vomiting (46% versus 50%), anorexia (46% both arms), diarrhoea (28% versus 37%), fatigue (28% versus 35%) constipation (32% versus 26%), anaemia (21% versus 28%), palmar-plantar erythrodysaesthesia (22% versus 26%), stomatitis (15% versus 24%), and weight loss (14% versus 23%).

The incidence of NCI-CTC Grade $\geq$ 3 AEs was 68% in both treatment arms (FP 198/290; FP+H 201/294). The most commonly reported Grade $\geq$ 3 AEs (FP versus FP+H) were neutropaenia (30% versus 27%) and anaemia (10% versus 12%). Cardiac AEs were reported by 6% (18/290) of patients in the FP arm (21 events) and 6% (17/294) of patients in the FP+H arm (20 events). The percentage of patients experiencing a reduction in LVEF $\geq$ 10% resulting in LVEF < 50% was 1.1% (2/187) in the FP arm and 4.6% (11/237) in the FP+H arm.

There were more deaths in the FP arm (63% [182/290]) than in the FP+H arm (57% [167/294]), and most of the deaths in both arms were related to the underlying advanced gastric cancer. SAEs were reported in 28% (81/290) of patients in the FP arm and 32% (95/194) of patients in the FP+H arm. Discontinuation of at least one study drug due to AEs was similar in both arms (FP 17% [48/290]; FP+H 16% [48/294]). Adverse events resulting in dose modifications or treatment interruptions of at least one component of study treatment were common and occurred in 82% (237/290; 530 events) of patients in the FP arm and 84% (246/294; 661 events) of patients in the FP+H arm.

Infusion related reactions occurred with trastuzumab in 59% (172/294; 337 events) of patients in any cycle (day of, or day after treatment). Infusion reactions occurred most commonly in the first cycle (41% of patients) and decreased in subsequent cycles. The most common infusion reactions were nausea (40% of patients) and vomiting (24% of patients).

The reported post-marketing adverse events for trastuzumab are consistent with the known safety profile of the drug.

Benefit Risk Assessment

Benefits

The pivotal study showed that patients treated with FP+H had a small but clinically meaningful overall survival benefit (primary efficacy parameter) compared with patients treated with FP: 13.8 versus 11.1 months; p=0.0046 log-rank test. The hazard ratio showed that the risk of death was 26% lower in patients treated with FP+H compared with patients treated with FP: HR=0.74 [95%CI: 0.60, 0.74]. The secondary efficacy endpoints (FP+H versus FP) of median progression free survival (6.7 versus 5.5 months), median time to

disease progression (7.1 versus 5.6 months), partial response rate (41.8% versus 32.1%), response rate (47.3% versus 34.5%), clinical benefit rate (78.9% versus 69.3%), and median duration of response (6.9 versus 4.8 months) were all statistically significantly better with FP+H compared with FP, but these benefits were of borderline clinical significance.

Risks

The risks of FP+H treatment are similar to those of FP treatment. In the pivotal study, nearly all patients who were treated with the regimen experienced at least one AE (99% [292/294]). The most commonly occurring AEs in FP+H treated patients were gastrointestinal disorders (91%) consisting predominantly of nausea (67%), vomiting (46%) and anorexia (46%). Blood and lymphatic system disorders occurred in 71% of FP+H treated patients consisting predominantly of neutropaenia (53%) and anaemia. The incidence of NCI-CTC Grade $\geq$ 3 AEs was 68% in FP+H treated patients with the most commonly reported being neutropaenia (27%) and anaemia (12%). In FP+H treated patients, 4.6% were reported as experiencing a reduction in LVEF $\geq$ 10% resulting in LVEF < 50%. Death occurred in 57% of FP+H treated patients and was most commonly related to the underlying advanced gastric cancer. SAEs were reported in 32% of FP+H treated patients and involved mainly the gastrointestinal and haematological systems. Infusion reactions (mainly nausea and vomiting) occurred in at least one cycle in 59% of patients and were more common in the first cycle (41% of patients) than in subsequent cycles.

Safety Specifications

No additional safety specifications.

Balance

It is considered that the benefit-risk balance for the FP+H regimen is favourable.

Conclusions

It is considered that the FP+H treatment regimen has demonstrated a small but clinically meaningful increase in median overall survival of 2.7 months compared with the FP regimen in advanced gastric carcinoma, a disease with a uniformly poor prognosis. The sponsor added that the increase in median overall survival was more pronounced in patients with higher levels of HER2 protein expression leading to a median overall survival increase of 4.2 months. The safety profile of the FP+H regimen is similar to that of the FP regimen, and the regimen raises no new safety signals for trastuzumab.

Recommended Conditions for Registration

It is recommended that Herceptin (trastuzumab) in combination with capecitabine or 5-FU and cisplatin be approved for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. The treatment regimens should be those used in the pivotal study [BO18255; ToGA].

V. Pharmacovigilance Findings

The following Safety concerns were identified by the Sponsor:

1. Cardiotoxicity;
2. Infusion-related reactions;
3. Haematological toxicity; and
4. Oligohydramnios.

Routine pharmacovigilance activities practices were proposed for all but cardiotoxicity. Additional pharmacovigilance activities for cardiotoxicity include an ongoing clinical study (B20652). A treatment algorithm is also provided in product labelling and is available to prescribers globally via package inserts. The objective of this algorithm is to provide clinicians with a clear set of instructions as to how best to deal with left ventricle ejection fraction (LVEF) decreases that are associated with the cardiotoxicity of Herceptin.

Risk Management Plan

An updated RMP, to reflect the Australian context and the Australian proposed PI, was submitted by the sponsor upon a requested by the Office of Medicines Safety Monitoring evaluator (Australian RMP version 1.0).

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no new quality data submitted.

Nonclinical

There were no new nonclinical data submitted.

Clinical

The application is based on a single open, randomised, controlled trial (BO 18255 aka the **ToGA trial**). The study does not appear to have been published other than in abstract form. The clinical evaluator has recommended approval of the application, with a more restricted indication than that proposed by the sponsor.

Pharmacokinetics The submission included a population pharmacokinetic study conducted on trastuzumab-treated patients enrolled in the pivotal trial. The study suggested that clearance in gastric cancer patients may be higher than that previously observed in breast cancer patients (0.378 L/day versus 0.241 L/day).

Efficacy The ToGA trial enrolled subjects with locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, who had not received prior chemotherapy for their advanced/metastatic disease. Patients were eligible for inclusion if their tumours were HER2+ as determined by:

- a 3+ score for HER2 protein overexpression by immunohistochemistry (IHC); or
- a positive FISH result for HER2 gene amplification.

All subjects received 6 cycles of:

·	Cisplatin	80 mg/m2	Day 1	21-day cycle; AND
·	5-fluorouracil	800 mg/m2/day	Days 1-5	21-day cycle; OR
	Capecitabine	1000 mg/m2 BD	Days 1-14	21-day cycle.

Subjects were randomised (1:1) to receive trastuzumab or no additional treatment. Trastuzumab infusions were continued until disease progression.

The primary endpoint was overall survival. Trastuzumab treatment was associated with a statistically significant prolongation in overall survival (HR 0.74; 95%CI 0.60 – 0.91; p = 0.0046). Median overall survival was prolonged by 2.7 months (13.8 versus 11.1 months). One year survival was increased by 11% (56 versus 45%) and 2-year survival by 7% (23 versus 16%).

The sponsor is seeking approval for Herceptin to be used in patients with gastric cancer who are HER2 positive defined by "ISH" or "IHC".

Trastuzumab treatment was associated with statistically significant benefit on several secondary endpoints. However, these endpoints were based on assessments of tumour response and progression made by the study investigators, who were not blinded to treatment allocation. Results may therefore have been subject to bias. Quality of life parameters suggested no significant differences between the two treatments.

Safety A total of 294 subjects received trastuzumab in the submitted study. Treatment with trastuzumab was not associated with any overall increase in adverse events (AEs), grade ³ 3 AEs, AEs leading to discontinuations or AEs leading to death. There was a slight excess of serious adverse events (32% versus 28%).

With respect to individual adverse events, the drug was associated with increased incidences of:

- Gastrointestinal AEs – diarrhoea, stomatitis
- Pyrexia and chills;
- Fatigue;
- Anaemia (28% versus 21%) and thrombocytopaenia (16% versus 11%)[17].

Individual grade ³ 3 AEs were not notably increased in the trastuzumab group with the possible exception of grade ³ 3 diarrhoea (9% versus 4%).

Trastuzumab has previously been shown to be associated with cardiotoxicity (cardiac failure) in breast cancer patients. In the submitted trial there was an increased incidence of patients experiencing a ³ 10% drop in left ventricular ejection fraction (LVEF). There was no increase in the overall incidence of cardiac adverse events.

RMP

The sponsor has submitted a risk management plan which has been evaluated by the TGA's OMSM. Approval of the application will be subject to finalisation of the RMP to the satisfaction of the OMSM.

Risk-Benefit Analysis

1. Overall risk-benefit

   Trastuzumab treatment was associated with a statistically significant improvement in overall survival. Median survival was increased by 2.7 months and 1-year survival by 11%. This efficacy benefit is considered clinically significant. Excluding patients with IHC 0+/FISH+ and IHC 1+/FISH+ disease should improve the efficacy profile of the drug.

   The additional toxicity caused by the addition of trastuzumab to chemotherapy appears modest and does not outweigh the efficacy benefits. The Delegate therefore considered the risk-benefit to be positive and proposed to approve the application.

2. Indication

   The sponsor is seeking approval for the following indication:

   > *"HERCEPTIN is indicated in combination with capecitabine or 5-FU and a platinum agent for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease."*

[17] Shown as FP+H versus FP.

As indicated by the clinical evaluator, trastuzumab has not been studied in gastric cancer in combination with any platinum agent other than cisplatin. The Delegate therefore proposed to restrict the indication to use with cisplatin, as follows:

> *"HERCEPTIN is indicated in combination with cisplatin and either capecitabine or 5-FU ~~and a platinum agent~~ for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease."*

3. Comparator regimen used
The ADEC has previously expressed the view that a triple combination regimen (for example, ECF: epirubicin/cisplatin/5-FU) should nowadays be considered standard treatment for advanced gastric cancer. This view was based upon a meta-analysis published in June 2006[18]. However, the ToGA trial began enrolling patients in September 2005 when a doublet combination such as cisplatin plus 5FU would have been considered a standard therapy. The choice of comparator is therefore considered acceptable.

Proposed action:

Subject to satisfactory finalisation of the risk management plan, the Delegate proposed to approve the application with the amended indication outlined above. The advice of the Committee is requested.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Roche Products Pty Ltd to register an extension of indications for Trastuzumab (HERCEPTIN) powder for injection 150 mg to include the indication:

> For use in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

In making this recommendation, the ACPM considered that an overall positive risk benefit profile for the new indication was demonstrated for the target population.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Herceptin containing 150 mg trastuzumab for intravenous administration, indicated for:

> Use in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.

For the current Product Information please refer to the TGA website at www.tga.gov.au.

[18] (1) Wagner AD *et al* (2006). *J Clin Oncol* 24:2903-2909; also referred to in the clinical evaluation.

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NAME OF THE MEDICINE

HERCEPTIN®

trastuzumab

CAS-180288-69-1

HERCEPTIN (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2. Trastuzumab is composed of 1,328 amino acids and has a molecular weight of ~148 kDa.

The humanized antibody against HER2 is produced by recombinant mammalian cells (Chinese hamster ovary (rch)) in suspension culture in a nutrient medium and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

DESCRIPTION

HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) infusion.

Each vial of HERCEPTIN contains 150 mg trastuzumab with excipients histidine hydrochloride, histidine, trehalose dihydrate and polysorbate 20. Reconstitution with 7.2 mL of sterile water for injection yields 7.4 mL of a single-dose solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4% ensures that the labelled dose of 150 mg can be withdrawn from each vial.

PHARMACOLOGY

Pharmacodynamics

The HER2 (or c-erbB2) proto-oncogene encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 25% - 30% of primary breast and 6.8% - 42.6% of advanced gastric cancers. A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 receptor.

Studies indicate that patients whose tumours have amplification or overexpress HER2 have a particularly aggressive form of tumour and a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpress HER2. HER2 overexpression or amplification can be diagnosed using an immunohistochemistry-based (IHC) assessment of fixed tumour blocks or In Situ Hybridization (ISH) technology.

Trastuzumab has been shown, both in *in-vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. In animal

models *in vivo*, murine anti-HER2 antibody inhibited the growth of human tumours overexpressing HER2, indicating that the humanized antibody (trastuzumab) is likely also to have anti-proliferative activity *in vivo* against human breast tumours expressing high levels of HER2.

Pharmacokinetics

The pharmacokinetics of trastuzumab have been studied in breast cancer patients with metastatic breast cancer and localised breast cancer. In Phase I studies, single dose intravenous infusions of 1, 2, 4, and 8 mg/kg and short duration intravenous infusions of 10, 50, 100, 250, and 500 mg trastuzumab once weekly in patients demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increased dose level.

Steady State Pharmacokinetics in Breast Cancer

A population pharmacokinetic method, using data from Phase I, Phase II and pivotal Phase III studies, was used to estimate the steady state pharmacokinetics in patients with metastatic breast cancer administered HERCEPTIN at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.225 L/day and the typical volume of distribution was 2.95 L, with a corresponding terminal half-life of 28.5 days (95% confidence interval, 25.5 – 32.8 days). Simulations based on a two compartment pharmacokinetic model show that after a dose change (increase or decrease) it takes approximately 22 weeks to reach steady state (defined as 90% of the AUC at absolute steady state). This estimate is consistent with the value obtained from 5 times the terminal phase half-life (mean 20.3; 95% CI: 18.2 to 23.4 weeks) based on the population pharmacokinetic analysis. At steady state weekly AUC of 578 mg•day/L, peak concentrations of 110 mg/L and trough concentrations of 66 mg/L are expected. The same time interval would be predicted for trastuzumab elimination after discontinuation of HERCEPTIN therapy. It is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state approximately 20 weeks after a dose discontinuation.

An assessment in localised breast cancer patients administered HERCEPTIN at an initial loading dose of 8 mg/kg followed by a 3-weekly dose of 6 mg/kg achieved steady state trough concentrations of 63 mg/L, by cycle 13. The concentrations were comparable to those reported previously in patients with metastatic breast cancer.

The administration of concomitant chemotherapy (either anthracycline or cyclophosphamide) did not appear to influence the pharmacokinetics of trastuzumab.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumours. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of trastuzumab (>20 mg/L) by week 6.

Steady State Pharmacokinetics in Advanced Gastric Cancer

A two compartment population pharmacokinetic method, using data from the Phase III study BO18255 (ToGA) was used to estimate the steady state pharmacokinetics in patients with advanced gastric cancer administered HERCEPTIN 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. In this assessment, for a typical patient with gastric cancer (male weighing 68 kg and over expressing HER2), the clearance of trastuzumab was 0.378 L/day and the volume of distribution in the central compartment was 3.91 L, with a corresponding median elimination half-life of 14.5 days. The median predicted steady-state AUC values (over a period of 3

weeks at steady state) is equal to 1030 mg•day/L, the median steady-state C_{max} is equal to 128 mg/L and the median steady-state C_{min} values is equal to 23 mg/L.

Pharmacokinetics in Special Populations
Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Use in Elderly: Age has been shown to have no effect on the disposition of trastuzumab (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Localised Breast Cancer

Localised breast cancer is defined as non-metastatic, primary, invasive carcinoma of the breast. The use of HERCEPTIN in the setting of localised breast cancer (after surgery and in association with chemotherapy and, if applicable, radiotherapy) has been studied in three randomized controlled trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, localised breast cancer was limited to operable, primary adenocarcinoma of the breast with positive axillary nodes or node negative disease with additional indicators of a higher degree of risk. The design and results of these studies are summarized in Table 11.

Table 11: Clinical Trials in Localised Breast Cancer

	HERA trial n=3386	**B31 and N9831 trials (joint analysis) n=3763**
Eligible patients	Node positive (or node negative [n=1098] and tumour size >1 cm; the protocol was initially unrestricted but then amended - 93 [8.5%] node negative patients with tumours ≤1 cm and 509 [46.4%] node negative patients with tumours >1 cm and ≤2 cm were included)	Node positive (or node negative [n=190] and tumour size • >2 cm and ER or PR +ve; or • >1 cm and ER or PR –ve [n=63 node-negative and tumour size ≤2 cm])
Herceptin dosage regimen	3-weekly	Weekly
Duration of Herceptin treatment	52 weeks	52 weeks
Chemotherapy regimen(s)	Various	Doxorubicin + cyclophosphamide (AC) followed by paclitaxel
Timing of Herceptin in relation to chemotherapy	After completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy	After completion of 4 cycles of AC and concurrent with 12 weeks of paclitaxel (either weekly or 3-weekly)
Median follow-up	1 year (initial evaluation) [2 years (follow-up evaluation [a])]	2 years
Disease recurrence: Rate (Herceptin vs. control)	7.5% vs. 12.9% [12.8% vs. 18.9% [a]]	8.0% vs. 15.5%

Hazard ratio (95% CI) *p*-value	0.54 (0.44-0.67) *p*<0.0001 [0.64 (0.54-0.76) [a]] [*p*<0.0001 [a]]	0.48 (0.39-0.59) *p*<0.0001
Survival: Deaths (Herceptin vs. control)	1.8% vs. 2.4% [3.5% vs. 5.3% [a]]	3.7% vs. 5.5%
Hazard ratio (95% CI) *p*-value	0.75 (0.47-1.21) *p*=0.24 [0.66 (0.47-0.91) [a]] [*p*=0.0115 [a]]	0.67 (0.48-0.92) *p*=0.014

[a] The 2 year follow-up analysis of the 1 year treatment and observation arms of the HERA study had data based on published literature and was not evaluated in detail by the TGA.

The HERA study included a subgroup of patients (n = 602) with small tumours (<2 cm) and node-negative disease. In this subgroup, the relative risk reduction was similar to the overall trial population (HR = 0.50; 95% CI 0.21 - 1.15). However, the benefit in terms of absolute difference in rate of recurrence after 1 year of follow-up was smaller (2.7% recurrence rate with Herceptin vs. 5.5% with observation).

The optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials. Outcomes of an alternative dosage schedule involving treatment for nine weeks are reported in a published paper of trial data (Joensuu et al, 2006. *NEJM).*

Metastatic Breast Cancer

There are no data available to establish the efficacy of HERCEPTIN for the treatment of metastatic disease in patients who have previously received the medicine for the treatment of localised disease.

The safety and efficacy of HERCEPTIN has been studied in randomized, controlled clinical trials in combination with chemotherapy (Studies H0648g, M77001 and TaNDEM) and in an open-label monotherapy clinical trial (Study H0649g) for the treatment of metastatic breast cancer. All trials studied patients with metastatic breast cancer whose tumours overexpress HER2. Patients were eligible if they had 2+ or 3+ levels of overexpression based on a 0 - 3+ scale by immunohistochemical (IHC) assessment of tumour tissue or whose tumours have HER2 gene amplification as determined by Fluorescence In Situ Hybridization (FISH) test (see **PRECAUTIONS, Detection of HER2 Overexpression or HER2 Gene Amplification**).

HERCEPTIN in Combination with Chemotherapy

Study H0648g was an open-label, randomized controlled, multinational trial of chemotherapy-alone and in combination with HERCEPTIN. Patients with previously untreated metastatic breast cancer were treated with either an anthracycline (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2) plus cyclophosphamide (600 mg/m^2) with or without HERCEPTIN or paclitaxel (175 mg/m^2 infused over 3 hours) with or without HERCEPTIN. Patients on HERCEPTIN treatment received 4 mg/kg intravenous loading dose on Day 0, followed by weekly infusions of 2 mg/kg from Day 7, which they could continue to receive until evidence of disease progression. Patients who had previously received anthracycline based adjuvant therapy were treated with paclitaxel whereas those who were anthracycline naïve were treated with an anthracycline + cyclophosphamide.

The prospectively defined, primary intent-to-treat analysis indicated that the combination of HERCEPTIN and chemotherapy significantly prolonged time to disease progression (progression-free survival) compared with chemotherapy-alone as first-line treatment of women with metastatic breast cancer who had tumours that overexpressed HER2. The addition of HERCEPTIN to chemotherapy extended the median time to disease progression by 2.8 months representing a 61% increase (p=0.0001).

Both anthracycline-treated and paclitaxel-treated patients benefited from HERCEPTIN treatment, although the effect appeared to be greater in the paclitaxel stratum. The efficacy of HERCEPTIN treatment was further supported by the secondary endpoints of response rate, duration of response and one-year survival (see Table 22 below).

One-year survival rates (the prospectively defined survival endpoint) were significantly better for the HERCEPTIN + chemotherapy versus chemotherapy-alone (79% vs. 68%; p=0.008). With a median follow-up of approximately two years, overall survival is improved for patients initially treated with HERCEPTIN + chemotherapy compared with those receiving chemotherapy-alone (25.4 vs. 20.3 months; p=0.025) with a relative risk of death of 0.769 (95% CI 0.607 - 0.973; p=0.028).

Figure 1 Survival Time: Anthracycline ± HERCEPTIN (Study H0648g)

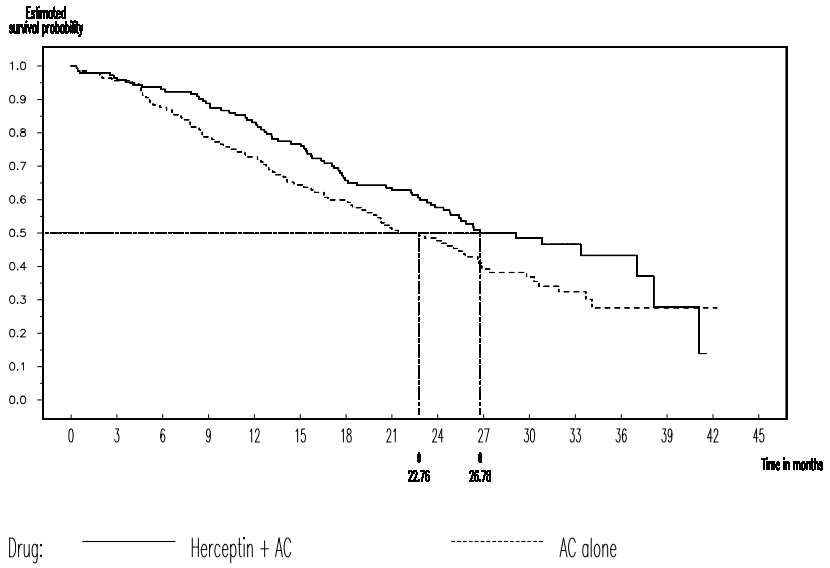
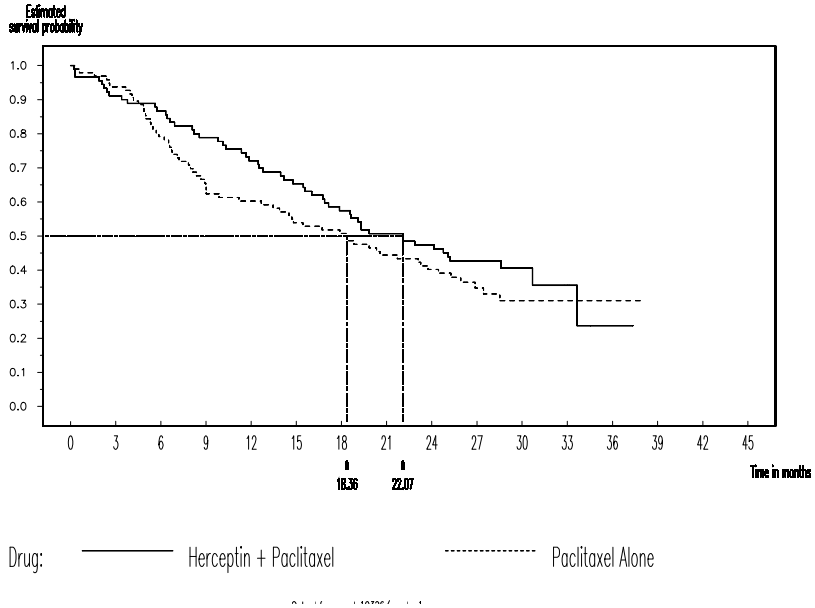


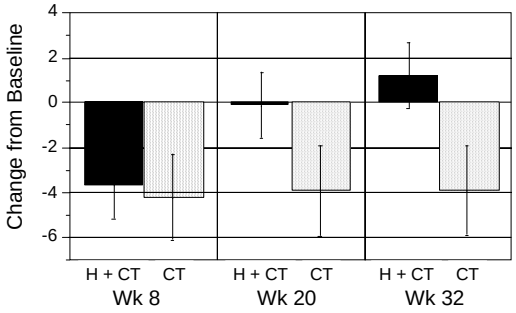
Figure 2 Survival Time: Paclitaxel ± HERCEPTIN (Study H0648g)



The relative overall survival advantage with the addition of HERCEPTIN was observed in both subgroups: AC [26.8 months (H + AC) vs. 22.8 months (AC-alone); *p*=0.052] and paclitaxel [22.1 months (H + P) vs. 18.4 months (P-alone); *p*=0.273] (see also Figures 1 and 2). The analysis of overall survival was, however, greatly confounded by subsequent HERCEPTIN treatment of each of control arms' patients, following disease progression, in the open-label extension study, H0659g (59% of patients in the AC-alone group, and 75% of patients in the paclitaxel-alone group subsequently received HERCEPTIN). Hence, the survival advantage seen above, for HERCEPTIN + chemotherapy treatment versus chemotherapy-alone (which includes patients who subsequently received HERCEPTIN) may underestimate the benefit to patients.

Importantly, the efficacy described above was obtained without a significant negative impact on the quality of life. Global quality of life decreased equally in both the chemotherapy-alone group and the HERCEPTIN + chemotherapy group and was most likely related to the effects of cytotoxic chemotherapy. However, at weeks 20 and 32, the global quality of life score had returned to baseline or better than baseline in the group receiving HERCEPTIN + chemotherapy, while it remained low in the chemotherapy-alone arm (see Figure 3 below).

Figure 3 Changes from Baseline in Health-Related Quality-of-Life Scores in Study H0648g

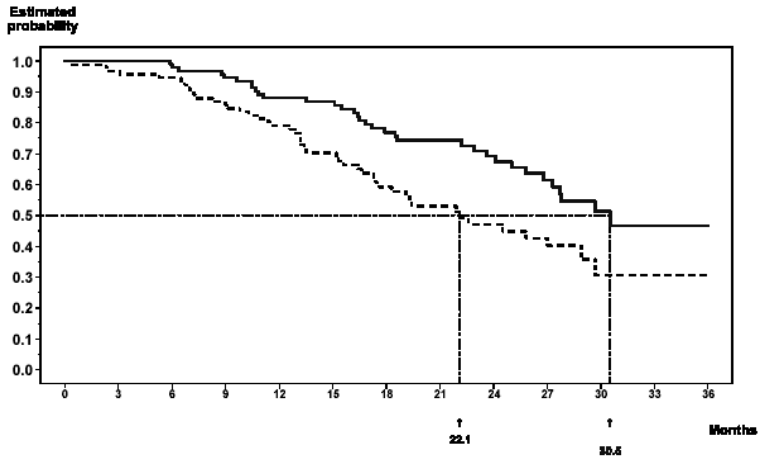


H = HERCEPTIN; CT = chemotherapy

Study M77001 was a multinational, multi-centre, randomized, controlled trial investigating the safety and efficacy of HERCEPTIN in combination with docetaxel, as first-line treatment in HER2 positive metastatic breast cancer patients. One hundred and eighty six patients received docetaxel (100 mg/m^2 infused over 1 hour on Day 2) with or without HERCEPTIN (4 mg/kg loading dose, followed by 2 mg/kg weekly). Sixty percent of patients had received prior anthracycline based adjuvant chemotherapy. HERCEPTIN with docetaxel was shown to be efficacious in patients whether or not they had received prior adjuvant anthracyclines and regardless of their estrogen and/or progesterone receptor status.

The combination of HERCEPTIN + docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression by 4.9 months compared with patients treated with docetaxel-alone (see Table 22). Median survival was also significantly increased in patients receiving the combination therapy compared with those receiving docetaxel-alone (30.5 months vs. 22.1 months) (see Figure 4).

Figure 4 Survival Time: Docetaxel ± HERCEPTIN (Study M77001)



Drug: ——— Herceptin + docetaxel ---------- docetaxel-alone

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Table 22: Efficacy Outcomes with Combination Therapy for Metastatic Breast Cancer

	H0648g						M77001	
	H + chemo n=235	**Chemo alone** n=234	**H + AC** n=143	**AC alone** n=138	**H + P** n=92	**P alone** n=96	**H + D** n=92	**D alone** n=94
Median Time to Disease Progression (months, 95% CI)	7.4 (7.0, 9.0)	4.6 (4.4, 5.4)	7.8 (7.3, 9.4)	6.1 (4.9, 7.1)	6.9 (5.3, 9.9)	3.0 (2.1, 4.3)	10.6 (7.6, 12.9)	5.7 (5, 6.5)
***p*-value** [a]	p=0.0001		p=0.0004		p=0.0001		p=0.0001	
Response Rate (%)	50	32	56	42	41	17	61	34
***p*-value** [b]	p<0.0001		p=0.0197		p=0.0002		p=0.0002	
Median Duration of Response (months, 95% CI)	9.1 (7.7,11)	6.1 (5.5,7.8)	9.1 (7.4,12.2)	6.7 (5.8, 8.2)	10.5 (7.3, 12.5)	4.5 (3.9, 6.4)	11.4 (8.3, 15.0)	5.5 (4.4, 6.2)
***p*-value** [a]	p=0.0002		p=0.0047		p=0.0124		p=0.0002	
Overall Survival (months, 95% CI)	24.8 (22.3,33.7)	20.5 (17.9,25.3)	33.4 (22.8,38.1)	22.8 (18.3,29.8)	22.1 (16.9,33.7)	18.4 (12.7,23.8)	30.5 (26.8, ne)	22.1 (17.6, 28.9)
***p*-value** [a]	p=0.0540		p=0.1021		p=0.2597		p=0.0062	

H = HERCEPTIN; Chemo = chemotherapy; AC = anthracycline + cyclophosphamide; P = paclitaxel; D = docetaxel
[a] p = log-rank test; [b] p = Chi-square test, ne = could not be estimated or not yet reached.

HERCEPTIN in Combination with Anastrozole

The TAnDEM trial was a multi-centre, randomized, open-label, phase III study comparing HERCEPTIN + anastrozole with anastrozole-alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)) positive post-menopausal patients. Two hundred and seven patients were randomized to receive oral anastrozole (1 mg/day) with or without HERCEPTIN (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had received HERCEPTIN for localised disease were excluded from this trial.

Median progression free survival was doubled in the HERCEPTIN + anastrozole arm compared to the anastrozole-alone arm (4.8 months vs. 2.4 months; $p = 0.0016$). For the other parameters the improvements seen for HERCEPTIN + anastrozole were; overall response (16.5% vs. 6.7%); clinical benefit rate (42.7% vs. 27.9%); time to progression (4.8 months vs. 2.4 months). For time to response and duration of response no difference could be recorded between the arms. There was no significant difference in overall survival, however more than half of the patients in the anastrozole-alone arm crossed over to a HERCEPTIN-containing regimen after progression of disease.

HERCEPTIN Monotherapy

Study H0649g was a multinational, multi-centre, single arm trial of HERCEPTIN as monotherapy in 222 women with HER2 overexpressing metastatic breast cancer. All patients had relapsed following treatment with the best available agents (e.g. anthracyclines and taxanes) and were heavily pre-treated. Two-thirds of the patients had prior adjuvant chemotherapy and all patients had tumour progression following at least one prior regimen of cytotoxic chemotherapy for metastatic disease. Ninety-four percent of the patients had prior anthracycline therapy, approximately 60% had prior paclitaxel therapy and 26% had prior bone marrow or stem cell transplants. Together with HER2

overexpression, which is associated with poorer clinical outcomes, aggressive disease was also suggested by nodal status at diagnosis and by the disease-free interval. Twenty-seven percent of patients had 10 or more positive nodes at the time of diagnosis. Thirty-eight percent of patients had a disease-free interval of less than one year prior to enrolment.

Patients received an intravenous loading dose of 4 mg/kg HERCEPTIN on Day 0, followed by weekly intravenous infusions of 2 mg/kg until there was evidence of disease progression. Patients who developed progressive disease could stop treatment, continue on the 2 mg/kg weekly dose or receive an increased intravenous dose of 4 mg/kg, as the investigator deemed appropriate. The primary efficacy parameter was tumour response rate.

HERCEPTIN as second- or third-line therapy induced objective, durable tumour responses in women with metastatic breast cancer who had tumours that overexpressed HER2. There were 8 complete responses and 26 partial responses yielding an overall response rate of 15%. The durability of the responses was particularly notable. The median duration of the responses was 9.1 months at the cut-off date for analysis (see Table 33 below).

Table 33: Efficacy Outcomes with Monotherapy Study H0649g

Outcome Measure	n	Time (months) Kaplan-Meier Estimate of Median (range)
Duration of response	34	9.1 (2–26+)
Time to disease progression	213	3.1 (0–28+)
Time to Treatment Failure	213	2.4 (0–28+)
Survival Time	213	12.8 (0.5–30+)

The clinical significance of the objective tumour responses in this group of patients was supported by the quality-of-life and survival data. Responders had clinically meaningful improvements in physical function, role function, social function, global quality of life and fatigue scale scores during HERCEPTIN treatment. Most responders were still alive at data cut-off (28/34; 82%). The Kaplan-Meier estimate of median survival for all treated patients at the data cut-off date was 12.8 months.

Evidence of efficacy for HERCEPTIN monotherapy is based upon response rates. No data are available to demonstrate improvement in survival or quality of life.

Advanced Gastric Cancer

Study BO18255 (ToGA) was a randomized, open-label, multicentre phase III study investigating HERCEPTIN in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone as first-line therapy in patients with HER2 positive, inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Patients were eligible if they had 3+ levels of HER2 overexpression based on a 0 - 3+ scale by IHC assessment of tumour tissue and/or those whose tumours had HER2 gene amplification as determined by a FISH test (see **PRECAUTIONS, Detection of HER2 Overexpression or HER2 Gene Amplification**).

After satisfying the screening eligibility criteria, including assessment of HER2 status, patients were randomly assigned (1:1) to receive either HERCEPTIN (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) + fluoropyrimidine/cisplatin (FP+H) or FP alone. The chemotherapy regimen was

chosen between 5-FU/cisplatin and capecitabine/cisplatin at the investigator's discretion and could be determined on an individual patient basis.

The efficacy results from ToGA are summarized in Table 44. The primary endpoint was overall survival, defined as the time from the date of randomization to the date of death from any cause. At the time of 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.

Overall survival was significantly improved in the FP + H arm compared to the FP arm ($p = 0.0046$, log-rank test). The median survival time was 11.1 months with FP and 13.8 months with FP + H. The risk of death was decreased by 26% (HR = 0.74; 95% CI 0.60 - 0.91) for patients in the FP + H arm compared to the FP arm (4).

Post-hoc subgroup analyses indicate that targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of FISH status) results in a greater treatment effect. 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 vs. 7.6 months, HR = 0.64 (95% CI 0.51 - 0.79).

Table 44: Summary of Efficacy from Study BO18255

Herceptin dosage regimen	Every 3 weeks			
Chemotherapy regimens (FP)	• Capecitabine: 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle). • 5-FU: 800 mg/m^2/day as a continuous IV infusion over 5 days, given every 3 weeks for 6 cycles (Days 1 to 5 of each cycle). The 5-FU infusion could be started at the same time as the cisplatin infusion on Day 1. • Cisplatin: 80 mg/m^2 every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2h IV infusion with hydration and premedication (steroids and anti-emetics).			
Efficacy Parameters	**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: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + HERCEPTIN; [a] Odds ratio
Progression-free-survival: time between day of randomization and first documentation of progressive disease (PD) or date of death, whichever occurred first. *Time to disease progression:* time between randomization and first occurrence of PD. *Overall response:* occurrence of either a confirmed complete (CR) or a partial (PR) best overall response as determined by RECIST criteria from confirmed radiographic evaluations of target and non-target lesions. *Duration of response:* time from when response (CR or PR) was first documented to the first documented disease progression. This was only calculated for patients who had a best overall response of CR or PR.

Immunogenicity

Nine hundred and three patients treated with HERCEPTIN, alone or in combination with chemotherapy, have been evaluated for antibody production. Human anti-trastuzumab antibodies were detected in 1 patient, who had no allergic manifestations.

INDICATIONS

Localised Breast Cancer

HERCEPTIN is indicated for the treatment of patients with HER2 positive localised breast cancer following surgery and in association with chemotherapy and, if applicable, radiotherapy.

Metastatic Breast Cancer

HERCEPTIN is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;

b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or

c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Advanced Gastric Cancer

*HERCEPTIN is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.**

CONTRAINDICATIONS

HERCEPTIN is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary cell proteins or to any other component of the product.

In the treatment of localised breast cancer, HERCEPTIN is contraindicated in patients with a left ventricular ejection fraction of less than 45% and those with symptomatic heart failure.

PRECAUTIONS

General

HERCEPTIN therapy should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Usual clinical care should be taken to prevent microbial contamination of the intravenous access sites used to deliver HERCEPTIN therapy. *HERCEPTIN should be administered by a healthcare professional prepared to manage anaphylaxis and adequate life support facilities should be available*.* Treatment may be administered in an outpatient setting.

If HERCEPTIN is used concurrently with cytotoxic chemotherapy, the specific guidelines used to reduce or hold the dose of chemotherapy should be followed. Patients may continue HERCEPTIN therapy during periods of reversible chemotherapy-induced myelosuppression, renal toxicity or hepatic toxicity.

Detection of HER2 Overexpression or HER2 Gene Amplification

HERCEPTIN should only be used in patients whose tumours have HER2 overexpression or HER2

gene amplification. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using in situ hybridization (ISH) of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH).

The recommended scoring systems to evaluate IHC staining patterns are shown below in Table 55 (breast cancer) and Table 66 (advanced gastric cancer).

In general, FISH is considered to show gene amplification if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.2, or if there are more than 6 copies of the HER2 gene per tumour cell, if no chromosome 17 control is used.

In general, CISH and SISH are considered to show gene amplification if there are more than 6 copies of the HER2 gene per nucleus in greater than 50% and 30% of tumour cells respectively.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH,CISH and SISH assays.

To ensure accurate and reproducible results, the testing must be performed in a specialized laboratory, which can ensure validation of the testing procedures.

Breast Cancer

HERCEPTIN treatment is only appropriate if there is strong HER2 overexpression, as described by a 3+ score by IHC or a positive ISH result. For patients with an intensity score of 2+ on IHC, confirmation of HER2 positive status by ISH is mandatory. It is also recommended for patients with 3+ staining by IHC.

Table 55: Scoring of IHC Staining Patterns for Breast Cancer Tumour Samples

Staining Intensity Score	Staining pattern	HER2 Overexpression Assessment
0	No staining is observed or membrane staining is observed in <10% of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in >10% of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10% of the tumour cells.	Equivocal
3+	A strong complete membrane staining is detected in >10% of the tumour cells.	Strong overexpression

Adapted from DAKO HercepTest™ package insert

Advanced Gastric Cancer

*HERCEPTIN treatment is only appropriate if there is HER2 overexpression, as described by a 3+ IHC score. For cases with a score of less than 3+ by IHC, confirmation of HER2 positive status by ISH is mandatory.**

Table 66: Scoring of IHC Staining Patterns for Gastric Cancer Tumour Samples

Staining Intensity Score	Staining pattern	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of tumour cells	Negative
1+	Faint/barely perceptible membranous reactivity in >10% of tumour cells; cells are reactive only in part of their membrane	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in >10% of tumour cells	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in >10% of tumour cells Biopsy (not surgery) samples with cohesive IHC 3+ clones are considered positive irrespective of percentage of tumour cells stained	Positive

Cardiotoxicity

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving HERCEPTIN therapy alone or in combination with chemotherapy. This may be moderate to severe and has been associated with death.

Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension, or documented coronary artery disease. Candidates for treatment with HERCEPTIN, especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, and/or MUGA scan. A careful risk-benefit assessment should be made before deciding to treat with HERCEPTIN. Cardiac function should be further monitored during treatment (e.g. every 3 months). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of HERCEPTIN therapy has been seen.

If LVEF drops 10 percentage points from baseline (and to below 50% in patients with a normal baseline measurement) HERCEPTIN should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of HERCEPTIN should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

If symptomatic cardiac failure develops during HERCEPTIN therapy, it should be treated with the standard medications for this purpose. Discontinuation of HERCEPTIN therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of HERCEPTIN in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment. This included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of HERCEPTIN treatment continued on weekly therapy with HERCEPTIN without additional clinical cardiac events.

Breast Cancer

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. As the mean terminal half-life of HERCEPTIN is 28.5 days (95% CI, 25.5 - 32.8 days), trastuzumab may persist in the circulation for up to 20 weeks (95% CI, 18.2 - 23.4 weeks) after stopping treatment (see **Pharmacokinetics**). Since the use of an anthracycline during this period could possibly be associated with an increased risk of cardiac dysfunction, a thorough assessment of the risks versus the potential benefits is recommended in addition to careful cardiac monitoring. The data also suggests that advanced age may increase the probability of cardiac dysfunction.

For localised breast cancer, all patients should have a determination of left ventricular ejection fraction (LVEF) prior to treatment. Use of HERCEPTIN is contraindicated in patients with localised disease and a LVEF of less than 45% and those with symptomatic heart failure. Patients with a LVEF of 45 - 55% at baseline should be monitored regularly for symptoms of heart failure during HERCEPTIN treatment.

In localised breast cancer, the following patients were excluded from the HERA trial, therefore there are no data about the risk/benefit ratio and, consequently, treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Advanced Gastric Cancer

In advanced gastric cancer, the following patients were excluded from Study BO18255 (ToGA) according to the study protocol;

- History of documented congestive heart failure
- Angina pectoris requiring medication
- Evidence of transmural myocardial infarction on ECG
- Poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >100 mmHg)
- Clinically significant valvular heart disease
- High risk uncontrollable arrhythmias
- Baseline LVEF <50% (measured by echocardiography or MUGA).

Hypersensitivity Reactions including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

HERCEPTIN infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include adrenaline, corticosteroids, diphenhydramine, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Infusion Reactions

In clinical trials, infusion reactions consisted of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumour sites), headache, dizziness, dyspnoea, hypotension, rash, asthenia and hypertension. These reactions were usually mild to moderate in severity (see **ADVERSE EFFECTS**).

In the post-marketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of HERCEPTIN. More severe adverse reactions to HERCEPTIN infusion reported include bronchospasm, hypoxia and severe hypotension. These severe reactions were usually associated with the initial infusion of HERCEPTIN and generally occurred during or immediately following the infusion. However, the onset and clinical course were variable. For some patients, symptoms progressively worsened and led to further pulmonary complications (see **Pulmonary Events**). In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. Delayed post-infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culminated in death within hours or up to one week following an infusion.

HERCEPTIN should be discontinued in the event of a severe infusion related reaction, until resolution of the symptoms. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, beta-agonists and corticosteroids.

Pulmonary Events

Severe pulmonary events leading to death have been reported with the use of HERCEPTIN in the post-marketing setting. Signs, symptoms and clinical findings include dyspnoea, *interstitial lung disease** including pulmonary infiltrates, pleural effusions, respiratory distress, non-cardiogenic pulmonary oedema, pulmonary insufficiency, hypoxia, pneumonitis, pulmonary fibrosis and acute respiratory distress syndrome and pneumonia. Interstitial pneumonitis has been reported as a rare but serious complication in clinical trials of HERCEPTIN in localised breast cancer. These events may occur as part of an infusion-related reaction (see **Infusion Reactions**) or with a delayed onset. Patients with symptomatic intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions and should only be treated with HERCEPTIN following consideration of the risk versus benefit.

Paediatric Use

The safety and efficacy of HERCEPTIN in patients under the age of 18 years have not been established.

Use in Elderly

HERCEPTIN has been administered to 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in elderly patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients. Elderly patients did not receive reduced doses of HERCEPTIN in clinical trials. However, greater sensitivity to HERCEPTIN in some older patients cannot be ruled out.

Use in Renal Impairment

Data suggest that the disposition of HERCEPTIN is not altered based on serum creatinine levels up to 177 μmol/L (see **Pharmacokinetics**).

Use in Hepatic Impairment

The use of HERCEPTIN in patients with hepatic impairment has not been studied.

Carcinogenicity

No studies on the carcinogenic potential of HERCEPTIN have been conducted to date.

Genotoxicity

Trastuzumab did not induce gene mutations in bacteria, nor did it cause chromosomal damage *in vitro* (chromosome aberration assay in human lymphocytes) or *in vivo* (mouse micronucleus test).

Effects on Fertility

A study in female cynomolgus monkeys revealed no evidence of impaired fertility at intravenous trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear (see **Use in Pregnancy**).

Use in Pregnancy – Category B2

In studies in cynomolgus monkeys, placental transfer of trastuzumab was observed during the early (days 20 - 50 of gestation) and late (days 120 - 150 of gestation) foetal development period. No evidence of harm to the foetus was seen in cynomolgus monkeys at intravenous trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

It is not known whether HERCEPTIN can cause foetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. As the animal studies of trastuzumab may not be relevant to human, HERCEPTIN should be avoided during pregnancy and since trastuzumab may persist in the circulation for up to 20 weeks, *pregnancy should be avoided for 6 months after the last dose of HERCEPTIN*,* unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

In the post-marketing setting, cases of oligohydramnios, *some associated with fatal pulmonary hypoplasia of the foetus*,* have been reported in pregnant women receiving HERCEPTIN. *Women of childbearing potential should be advised to use effective contraception during treatment with HERCEPTIN and for at least 6 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with HERCEPTIN, close monitoring by a multidisciplinary team is desirable.**

Use in Lactation

A study conducted in lactating cynomolgus monkeys dosed intravenously with trastuzumab at 25 mg/kg twice weekly (serum C_{min} about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg) demonstrated that trastuzumab is excreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with adverse effects on their growth or development from birth to 1 month of age. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

It is not known whether trastuzumab is excreted in human milk. As human IgG is secreted into human milk and the potential for harm to the infant is unknown, breast-feeding should be avoided during HERCEPTIN therapy *and for 6 months after the last dose of HERCEPTIN.**

Interactions with Other Medicines

No formal drug interaction studies have been performed with HERCEPTIN in humans. Clinically significant interactions with concomitant medication used in clinical trials have not been observed. A comparison of serum levels of HERCEPTIN given in combination with cisplatin, doxorubicin or epirubicin-plus-cyclophosphamide has not suggested the possibility of any interaction.

Administration of paclitaxel in combination with HERCEPTIN resulted in a slightly less than two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies (see **Pharmacokinetics**). Paclitaxel pharmacokinetics determined during the fourth cycle of the alternative 3-weekly HERCEPTIN regimen (n = 25) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of HERCEPTIN. Similarly, docetaxel pharmacokinetics determined during the first dose of HERCEPTIN in the standard weekly regimen (n = 10) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel-alone.

Ability to Drive and Use Machines

It is not known whether HERCEPTIN has an effect on the ability to drive and to use machines, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

ADVERSE EFFECTS

Clinical Trial Experience

Localised Breast Cancer

The HERA trial is a multicentre randomized, open label study in patients with HER2 positive localised breast cancer (see **CLINICAL TRIALS**). Table 77 displays adverse events which were reported at 1 year in ≥1% of patients, by study treatment.

Table 77: Adverse Events Reported ≥1% of Patients Treated for Localised Breast Cancer (at 1 year)

Body System / Adverse Event	Observation Arm n=1708 n (%)	HERCEPTIN Arm n=1678 n (%)
Musculoskeletal and connective tissue disorders		
arthralgia[#]	98 (6)	137 (8)
back pain[#]	59 (3)	91 (5)
pain in extremity	45 (3)	60 (4)
myalgia[#]	17 (<1)	63 (4)
bone pain	26 (2)	49 (3)
shoulder pain	29 (2)	30 (2)

Body System / Adverse Event	Observation Arm n=1708 n (%)	HERCEPTIN Arm n=1678 n (%)
chest wall pain	24 (1)	26 (2)
muscle spasms[#]	3 (<1)	45 (3)
musculoskeletal pain	11 (<1)	17 (1)
Infections and infestations		
nasopharyngitis[#]	43 (3)	135 (8)
influenza[#]	9 (<1)	69 (4)
upper respiratory tract infection[#]	20 (1)	46 (3)
urinary tract infection	13 (<1)	39 (2)
rhinitis	6 (<1)	36 (2)
sinusitis	5 (<1)	26 (2)
cystitis	11 (<1)	19 (1)
pharyngitis	9 (<1)	20 (1)
bronchitis	9 (<1)	18 (1)
herpes zoster	9 (<1)	17 (1)
General disorders and administration site conditions		
fatigue[#]	44 (3)	128 (8)
oedema peripheral[#]	38 (2)	79 (5)
pyrexia[#]	6 (<1)	100 (6)
asthenia[#]	30 (2)	75 (4)
chills[#]	-	85 (5)
chest pain[#]	22 (1)	45 (3)
influenza illness	3 (<1)	40 (2)
oedema	7 (<1)	18 (1)
chest discomfort	2 (<1)	20 (1)
Gastrointestinal disorders		
diarrhoea[#]	16 (<1)	123 (7)
nausea[#]	19 (1)	108 (6)
vomiting[#]	10 (<1)	58 (3)
abdominal pain	16 (<1)	40 (2)
constipation	17 (<1)	33 (2)
abdominal pain upper	15 (<1)	29 (2)
dyspepsia	9 (<1)	30 (2)
gastritis	11 (<1)	20 (1)

Body System / Adverse Event	Observation Arm n=1708 n (%)	HERCEPTIN Arm n=1678 n (%)
stomatitis	1 (<1)	26 (2)
Nervous system disorders		
headache[#]	49 (3)	161 (10)
dizziness[#]	29 (2)	60 (4)
paraesthesia	11 (<1)	29 (2)
vertigo	7 (<1)	25 (1)
Vascular disorders		
hot flush	84 (5)	98 (6)
hypertension[#]	35 (2)	64 (4)
lymphoedema	40 (2)	42 (3)
Skin and subcutaneous tissue		
rash[#]	10 (<1)	70 (4)
pruritus	10 (<1)	40 (2)
nail disorder[#]	-	43 (3)
onychorrhexis	1 (<1)	36 (2)
erythema	7 (<1)	24 (1)
Respiratory, thoracic and mediastinal disorders		
cough[#]	34 (2)	81 (5)
dyspnoea	26 (2)	56 (3)
pharyngolaryngeal pain	8 (<1)	32 (2)
dyspnoea exertional	15 (<1)	21 (1)
rhinorrhoea	5 (<1)	24 (1)
epistaxis	1 (<1)	24 (1)
Reproductive system and breast disorders		
breast pain	19 (1)	24 (1)
Psychiatric		
insomnia	31 (2)	58 (3)
depression	34 (2)	51 (3)
anxiety	19 (1)	39 (2)
Cardiac disorders		
palpitations[#]	12 (<1)	48 (3)
cardiac failure congestive	5 (<1)	30 (2)

Body System / Adverse Event	Observation Arm n=1708 n (%)	HERCEPTIN Arm n=1678 n (%)
tachycardia	5 (<1)	20 (1)
Investigations		
ejection fraction decreased[#]	11 (<1)	58 (3)
weight increased	17 (<1)	29 (2)
Renal and urinary disorders		
dysuria	2 (<1)	17 (1)

[#] Adverse Events that were reported at higher incidence (≥2% difference) in the HERCEPTIN group compared with the observation group and therefore may be attributable to HERCEPTIN.

Metastatic Breast Cancer

HERCEPTIN in Combination with Chemotherapy

The adverse event data reflect the clinical trial experience of 903 patients using HERCEPTIN at the recommended dose regimen, either alone or in combination with chemotherapy. Adverse events which occurred in ≥ 10% of patients regardless of causality are described in Table 88.

Table 88: Adverse Events Occurring in ≥10% of Patients Treated for Metastatic Breast Cancer

Body System / Adverse Event	H0649g	H0648g				M77001	
	H alone n = 213 %	H + AC n = 143 %	AC alone n = 135 %	H + P n = 91 %	P alone n = 95 %	H + D n = 92 %	D alone n = 94 %
General disorders							
abdominal pain	22	23	19	34	22	12	12
accidental injury	6	9	4	13	3	-	-
asthenia	47	55	55	62	57	45	41
chills	36	35	11	42	4	-	-
fever	39	56	33	47	23	30	15
influenza-like illness	11	12	6	12	5	10	-
headache	26	44	31	36	28	21	18
mucous membrane disorder	2	22	19	11	7	24	22
pain	49	57	42	60	61	11	9
chest pain	22	20	21	30	27	10	5
fatigue	-	-	-	-	-	24	21
rigors	-	-	-	-	-	11	1
increased weight	2	3	2	2	2	16	6

Body System / Adverse Event	H0649g	H0648g				M77001	
	H alone n = 213 %	H + AC n = 143 %	AC alone n = 135 %	H + P n = 91 %	P alone n = 95 %	H + D n = 92 %	D alone n = 94 %
Cardiac disorders							
congestive heart failure	2	12	2	2	1	-	-
left ventricular failure	-	10	5	6	-	1	-
tachycardia	6	10	5	12	4	7	-
vasodilation	8	18	16	22	20	-	-
lymphoedema	-	-	-	-	-	11	6
Digestive							
constipation	<1	36	28	25	27	27	23
diarrhoea	13	45	25	45	30	43	36
dyspepsia	8	22	20	18	16	14	5
mouth ulceration	2	12	14	4	1	4	2
nausea	37	76	79	51	48	45	41
nausea and vomiting	8	18	9	14	12	-	-
stomatitis	4	30	31	10	7	20	14
vomiting	28	53	49	37	28	29	22
Haem and Lymphatic							
anaemia	4	35	25	14	10	15	7
leukopenia	3	52	33	24	17	12	3
thrombocytopenia	<1	11	9	3	3	2	-
neutropenia	-	-	-	-	-	33	30
febrile neutropenia	-	-	-	-	-	20	11
Metabolic							
anorexia	13	31	26	24	16	22	13
dehydration	2	11	4	9	10	1	-
hypokalaemia	<1	13	4	2	3	2	1
oedema	8	11	5	10	8	5	4
peripheral oedema	10	20	17	22	20	40	35
Musculoskeletal							
arthralgia	6	8	10	37	21	27	20
bone pain	9	7	7	24	18	14	6
back pain	21	27	16	36	31	11	14
neck pain	5	11	8	9	5	5	-

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Body System / Adverse Event	H0649g	H0648g				M77001	
	H alone n = 213 %	H + AC n = 143 %	AC alone n = 135 %	H + P n = 91 %	P alone n = 95 %	H + D n = 92 %	D alone n = 94 %
myalgia	8	13	13	39	36	27	26
pain in extremity	-	-	-	-	-	16	16
Nervous							
anxiety	13	18	14	19	15	9	4
depression	8	20	12	12	13	9	6
dizziness	13	24	18	22	24	7	10
hypertonia	4	8	2	11	3	-	-
insomnia	16	29	16	25	13	12	4
neuropathy	2	4	4	13	5	4	3
paraesthesia	9	17	11	47	39	32	21
peripheral neuropathy	2	2	2	23	16	10	6
somnolence	7	11	15	10	10	1	-
dysgeusia	-	-	-	-	-	14	12
hypoaesthesia	-	-	-	-	-	11	5
Respiratory							
cough increased	28	43	28	42	22	13	16
dyspnoea	23	42	24	28	26	14	15
epistaxis	6	7	6	18	4	20	5
pharyngeal pain	-	-	-	-	-	16	9
rhinorrhoea	-	-	-	-	-	12	1
Skin and Appendages							
acne	2	3	<1	11	3	1	-
alopecia	1	58	59	56	56	67	54
pruritis	11	8	6	14	13	5	3
rash	14	27	17	39	18	24	12
nail disorder	7	4	4	4	1	16	19
erythaema	-	-	-	-	-	23	11
Special Senses							
taste perversion	2	11	13	6	3	-	-
increased lacrimation	5	5	9	3	0	21	10
conjunctivitis	7	8	7	6	2	12	7
Infections							

Body System / Adverse Event	H0649g	H0648g				M77001	
	H alone n = 213 %	H + AC n = 143 %	AC alone n = 135 %	H + P n = 91 %	P alone n = 95 %	H + D n = 92 %	D alone n = 94 %
urinary tract infection	3	13	7	19	14	5	4
herpes simplex	2	7	8	12	3	2	2
infection	20	47	30	46	27	3	-
pharyngitis	13	30	19	22	14	3	2
sinusitis	12	13	6	21	7	1	2
rhinitis	16	22	16	22	5	8	1
nasopharyngitis	-	-	-	-	-	15	6

- not reported

HERCEPTIN in Combination with Anastrozole

The TAnDEM trial was a randomized open-label study, comparing HERCEPTIN + anastrozole with anastrozole-alone in patients with metastatic breast cancer (see **CLINICAL TRIALS**). In the TAnDEM trial, there was no change in the nature or frequency of adverse effects compared with previous trials in the metastatic population.

Adverse reactions attributed to HERCEPTIN in >1% and <10% of patients treated for metastatic breast cancer were the following:

General disorders: back pain, influenza-like illness, infection, neck pain, malaise, hypersensitivity reaction

Cardiovascular: vasodilation, supraventricular tachyarrhythmia, hypotension, heart failure, cardiomyopathy, palpitation

Digestive: anorexia, constipation, dyspepsia

Haem and lymphatic: leukopenia

Metabolic: peripheral oedema, oedema

Musculoskeletal: bone pain

Nervous: anxiety, depression, dizziness, insomnia, paraesthesia, somnolence, hypertonia, peripheral neuropathy

Respiratory: asthma, cough increased, dyspnoea, epistaxis, lung disorders, pleural effusion, pharyngitis, rhinitis, sinusitis

Urogenital: urinary tract infection

Skin and appendages: pruritus, sweating, nail disorder, dry skin, alopecia, acne, maculopapular rash

Advanced Gastric Cancer

Study BO18255 (ToGA) trial was a randomized, open-label study of HERCEPTIN in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone in patients with advanced gastric cancer (see **CLINICAL TRIALS**). The common adverse events (>10%) are presented in Table 99.

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Table 99: Adverse Events Occurring in ≥10% of Patients Treated for Advanced Gastric Cancer

Body System/ Adverse Event	FP (n=290) n (%)	HERCEPTIN + FP (n=294) n (%)
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)
Blood And Lymphatic System Disorders		
Neutropenia	165 (57)	157 (53)
Anaemia	61 (21)	81 (28)
Thrombocytopenia	33 (11)	47 (16)
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)
Metabolism And Nutrition Disorders		
Anorexia	133 (46)	135 (46)
Skin And Subcutaneous Tissue Disorders		
*Palmar-Plantar Erythrodysaesthesia Syndrome**	64 (22)	75 (26)
Alopecia	27 (9)	32 (11)
Investigations		
*Weight Decreased**	40 (14)	69 (23)
Renal And Urinary Disorders		
Renal Impairment *	39 (13)	47 (16)
Respiratory, Thoracic And Mediastinal Disorders		
Hiccups	28 (10)	34 (12)
Nervous System Disorders		
Dizziness	28 (10)	31 (11)
Infections And Infestations		
Nasopharyngitis	17 (6)	37 (13)

FP: Fluoropyrimidine/cisplatin

The following information is relevant to all indications.

Infusion Reactions

During the first infusion of HERCEPTIN chills and/or fever are observed commonly in patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, asthenia and hypertension. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent HERCEPTIN infusions. These symptoms can be treated with an analgesic/antipyretic such as paracetamol or pethidine and an antihistamine such as diphenhydramine (see **Dosage**). Some adverse reactions to HERCEPTIN infusions including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal (see **PRECAUTIONS**).

Hypersensitivity Reactions

Anaphylactoid reactions were observed in isolated cases (see **PRECAUTIONS**).

Cardiac Toxicity

Breast Cancer

Cardiac dysfunction was observed during clinical trials in patients treated with HERCEPTIN (see **PRECAUTIONS**). Reduced ejection fraction and signs and symptoms of heart failure, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, and S_3 gallop, have been observed in patients treated with HERCEPTIN. Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the HERCEPTIN + paclitaxel subgroup, compared with 1% - 4% for the paclitaxel-alone subgroup. For HERCEPTIN monotherapy, the rate was 6 - 9%. The highest rate of cardiac dysfunction was seen in patients receiving HERCEPTIN + anthracycline/cyclophosphamide (27 - 28%), which was significantly higher than the rate reported for patients in the anthracycline/cyclophosphamide-alone subgroup (7 - 10%). In study M77001 with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving HERCEPTIN and docetaxel, compared with 0% in patients receiving docetaxel-alone.

The incidence of cardiac adverse events from retrospective analysis of data from the study of HERCEPTIN + paclitaxel versus paclitaxel alone and the HERCEPTIN monotherapy study is shown in Table 10.

Table 1010: Overview of Cardiac Adverse Event Incidence (n, %) [95% CI]

	H0648g						H0649g
	H + P n=91	**P alone n=95**	***p*-value (χ2)**	**H + AC n=143**	**AC n=135**	***p*-value (χ2)**	**H alone n=21**
Symptomatic heart failure "anthracycline typical" (a)	8 (8.8) [3.9-16.6]	4 (4.2) [1.2-10.4]	0.204	40 (28.0) [20.8-36.1]	13 (9.6) [5.2-15.9]	<0.001	18 (8.5) [5.1-13.0]
Cardiac diagnosis other than heart failure (b)	4 (4.4) [1.2-10.9]	7 (7.4) [3.0-14.6]	0.390	8 (5.6) [2.5-10.7]	9 (6.7) [3.1-12.3]	0.709	7 (3.3) [1.3-6.7]

H+P: HERCEPTIN + paclitaxel; P alone: paclitaxel alone; H+AC: HERCEPTIN + anthracyclines; H alone: Herceptin monotherapy; Categories are mutually exclusive: patients assigned in hierarchical fashion according to ranking in table.

a preferred terms: congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung oedema or other search terms and CRF information indicating cardiac failure (eg. a combination of shortness of breath, dyspnoea, cough increased, pulmonary congestion on X-ray, echo or MUGA findings).

b cardiac condition most likely not related to adriamycin toxicity (eg. pericardial tamponade, syncope, stroke, angina pectoris, myocardial ischemia, myocardial infarction, ascites).
Includes preferred terms: cardiovascular disorder, shock, respiratory failure, respiratory distress, hypoxia, asthma, dyspnoea, cough increased, oedema, peripheral oedema, heart arrest, hypotension, palpitation, bradycardia, tachycardia,

arrhythmia which are not further specified in the text of the adverse event forms in the CRF as being definitely related to malignant disease. Any other events with insufficient information for assessment of aetiology.

The incidence of symptomatic congestive heart failure in the study of HERCEPTIN + docetaxel versus docetaxel alone (M77001) is shown in Table 1111:

Table 1111: Overview of Cardiac Adverse Event Incidence (n, %)

	HERCEPTIN +Docetaxel n=92	Docetaxel n=94
Symptomatic heart failure	2 (2.2%)	0%

In this study, all patients had a baseline cardiac ejection fraction of greater than 50%. In the HERCEPTIN + docetaxel arm, 64% had received a prior anthracycline compared with 55% in the docetaxel-alone arm.

For HERCEPTIN + anastrozole, the rate of symptomatic congestive heart failure was <1% versus 0% in the anastrozole-alone arm. Asymptomatic LVEF drops were experienced by 5.8% of patients in the HERCEPTIN + anastrozole arm versus 0% in the anastrozole-alone arm.

Cardiac endpoints measured during the HERA trial in patients with localised breast cancer are shown in Table 1212 below.

Table 1212: Primary and Secondary Cardiac Endpoints Measured During the HERA Trial

	Observation n=1708 n (%)	HERCEPTIN 1 Year n=1678 n (%)
Incidence of Primary Cardiac Endpoint†	1 (0.1)	10 (0.6)
Incidence of Secondary Cardiac Endpoint‡	9 (0.5)	51 (3.0)

†symptomatic CHF (NYHA class III or IV) and a drop in LVEF of at least 10 points from baseline and to below 50% or cardiac death; ‡ significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) LVEF drop

The incidence of NYHA Class III or IV heart failure (or cardiac death) in the B31 and N9831 trials for HERCEPTIN in localised breast cancer was 3.8% and 3.0% respectively (AC-TH), compared with 1.1% and 0% in the respective observation groups (AC-T). In a published trial (Joensuu et al, 2006, *NEJM*) no patients who received nine weeks of HERCEPTIN experienced cardiac failure.

Advanced Gastric Cancer

In Study BO18255 (ToGA), at screening, the median LVEF value was 64% (range 48% - 90%) in the FP arm and 65% (range 50% - 86%) in the HERCEPTIN + FP arm.

The majority of the LVEF decreases noted in ToGA were asymptomatic, with the exception of 1 patient in the HERCEPTIN arm whose LVEF decrease coincided with cardiac failure.

Table 1313: Summary of LVEF Change from Screening

LVEF Decrease[#]: Lowest Post-screening Value	FP (n=290) (% of patients in each treatment arm)	FP + H (n=294) (% of patients in each treatment arm)
LVEF decrease ≥10% to <50%	2 (1.1%)	11(4.6%)
Absolute Value <50%	2 (1.1%)	14 (5.9%)

LVEF decrease ≥ 10% to ≥ 50%	22 (11.8%)	39 (16.5%)

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + HERCEPTIN; #Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP: n = 187 and FP + H: n = 237)

Table 1414: Cardiac Adverse Events

	FP (n=290) (% of patients in each treatment arm)	**FP +H (n=294) (% of patients in each treatment arm)**
Total Cardiac Events	6%[a]	6%[b]
≥ Grade 3[c]	3%	1%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + HERCEPTIN; [a] 9 patients experienced 9 Events; [b] 4 patients experienced 5 Events; [c] NCI-CTC criteria (V3.0)

Overall, there were no significant differences in cardiotoxicity between the treatment arm and the comparator arm.

Haematological Toxicity

Breast Cancer

Monotherapy– Study H0649g
Haematological toxicity is infrequent following the administration of HERCEPTIN as monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in <1% of patients. No WHO Grade 4 toxicities were observed.

Combination Therapy – Studies H0648g and M77001
WHO Grade 3 or 4 haematological toxicity was observed in 63% of patients treated with HERCEPTIN and an anthracycline/cyclophosphamide compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide combination without HERCEPTIN.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of HERCEPTIN and paclitaxel compared with patients receiving paclitaxel-alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving HERCEPTIN and docetaxel, compared with docetaxel-alone (32% grade 3/4 neutropenia vs. 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% vs. 17% for patients treated with docetaxel-alone).

Localised Setting – HERA Study
Using NCI-CTC criteria, in the HERA trial, 0.4% of HERCEPTIN treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer

The most frequently reported adverse events categorized under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below (Table 1515) by trial treatment.

Table 1515: Blood and Lymphatic System Disorders (SOC) Adverse Events >1%

	FP (n=290) (% of patients in each treatment arm)	**FP + H (n=294) (% of patients in each treatment arm)**
Neutropenia	30%	27%

Anaemia	10%	12%
Febrile Neutropenia	3%	5%
Thrombocytopenia	3%	5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + HERCEPTIN

The total percentage of patients who experienced an adverse event of ≥ Grade 3 NCI CTCAE v3.0 categorized under this SOC were 38% in the FP arm and 40% in the FP + H arm.

Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

Hepatic and Renal Toxicity

Breast Cancer

Monotherapy– Study H0649g
WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of HERCEPTIN as monotherapy in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients. No WHO Grade 3 or 4 renal toxicity was observed.

Combination Therapy – Study H0648g
WHO Grade 3 or 4 hepatic toxicity was observed in 6% of patients treated with HERCEPTIN and an anthracycline/cyclophosphamide compared with an incidence of 8% in patients treated with the anthracycline/cyclophosphamide combination without HERCEPTIN. No WHO Grade 3 or 4 renal toxicity was observed.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving HERCEPTIN and paclitaxel than among patients receiving paclitaxel-alone (7% vs.15%). No WHO Grade 3 or 4 renal toxicity was observed.

Advanced Gastric Cancer

In Study BO18255 **(**ToGA) no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

Grade ≥3 renal toxicity was not significantly higher in patients receiving HERCEPTIN than those in the fluoropyrimidine/cisplatin arm (3% and 2% respectively).

Grade ≥3 adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported adverse event and was not significantly higher in patients receiving HERCEPTIN than those in the fluoropyrimidine/cisplatin arm (1% and <1% respectively).

Diarrhoea

Breast Cancer

Monotherapy– Study H0649g
Of patients treated with HERCEPTIN monotherapy in the metastatic setting, 27% experienced diarrhoea.

Combination Therapy – Studies H0648g and M77001
An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving HERCEPTIN in combination with chemotherapy compared with patients receiving chemotherapy-alone or HERCEPTIN-alone.

Localised Setting – HERA Study
In the HERA trial, 7% of HERCEPTIN treated patients experienced diarrhoea.

Advanced Gastric Cancer

In Study BO18255 (ToGA), 109 patients (37%) in the HERCEPTIN treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Four percent (4%) of patients in the fluoropyrimidine/cisplatin arm experienced Grade ≥ 3 diarrhoea vs. 9% in the HERCEPTIN arm.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed primarily in patients treated with HERCEPTIN + chemotherapy compared with patients receiving chemotherapy-alone or HERCEPTIN-alone.

Serious Adverse Reactions and Post-Marketing Experience

At least one case of the following serious adverse reactions has occurred in patients treated with HERCEPTIN-alone or in combination with chemotherapy in clinical trials or has been reported during post-marketing experience.

General disorders: hypersensitivity reactions, anaphylaxis and anaphylactic shock, angioedema, ataxia, sepsis, chills and fever, asthenia, fever, rigor, headache, paresis, chest pain, fatigue, infusion-related symptoms, peripheral oedema, bone pain, coma, meningitis, cerebral oedema, abnormal thinking, progression of neoplasia

Cardiovascular: cardiomyopathy, congestive heart failure, increased congestive heart failure, decreased ejection fraction, hypotension, pericardial effusion, bradycardia, cerebrovascular disorder, cardiac failure, cardiogenic shock, pericarditis, hypertension

Digestive: hepatocellular damage, liver tenderness, diarrhoea, nausea and vomiting, pancreatitis, hepatic failure, jaundice

Haem and Lymphatic: leukaemia, febrile neutropenia, neutropenia, thrombocytopenia, anaemia, hypoprothrombinaemia

Infections: cellulites, erysipelas

Metabolic: hyperkalaemia

Musculoskeletal: myalgia

Nervous: paraneoplastic cerebellar degeneration

Respiratory: bronchospasm, *interstitial lung disease including** respiratory distress, acute pulmonary oedema, respiratory insufficiency oedema, dyspnoea, hypoxia, laryngeal oedema, acute respiratory distress, adult respiratory distress syndrome, pleural effusion, pulmonary infiltrates, pneumonia, pneumonitis, pulmonary fibrosis

Skin and Appendages: rash, dermatitis, urticaria

Special Senses: papilloedema, abnormal lacrimation, retinal haemorrhage, deafness

Urogenital: membranous glomerulonephritis, glomerulonephropathy, renal failure

Interstitial lung disease

*Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy.**

DOSAGE AND ADMINISTRATION

HER2 testing is mandatory prior to initiation of HERCEPTIN therapy.

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Dosage

The loading and subsequent doses are recommended for monotherapy and combination treatment.

DO NOT ADMINISTER HERCEPTIN AS AN INTRAVENOUS PUSH OR BOLUS.

Patients should be observed for fever and chills or other infusion-associated symptoms (see **ADVERSE EFFECTS**). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

Localised Breast Cancer

The optimal dosage regimen and treatment duration have not been defined. A favourable risk/benefit ratio has been demonstrated with the following regimens (see **CLINICAL TRIALS**).

Three weekly regimen (HERA trial)

Treatment with HERCEPTIN was commenced following surgery and completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy.

Loading Dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent Doses: 6 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes. *If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.**

Patients were treated for 1 year.

Weekly regimen (B31/N9831 trials)

Treatment with HERCEPTIN was commenced following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide (AC) chemotherapy, then together with paclitaxel (paclitaxel given on a weekly or 3-weekly schedule) for 12 weeks, then as a single agent for a further 40 weeks.

Loading dose: an initial dose of 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent doses: 2 mg/kg body weight at weekly intervals. *If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.**

Metastatic Breast Cancer

Loading Dose: The recommended initial loading dose is HERCEPTIN 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent Doses: The recommended weekly dose of HERCEPTIN is 2 mg/kg body weight given at weekly intervals. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

In clinical trials, patients with metastatic breast cancer were treated with HERCEPTIN until progression of disease.

Advanced Gastric Cancer

Initial loading dose of HERCEPTIN is 8 mg/kg body weight, followed by 6 mg/kg body weight three weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over

*approximately 90 minutes. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.**

In clinical trials, patients with advanced gastric cancer were treated with HERCEPTIN until progression of disease.

Refer to the **CLINICAL TRIALS, Advanced Gastric Cancer** section for chemotherapy combination dosing.

Missed Doses

If the patient misses a dose of HERCEPTIN by one week or less, then the usual maintenance dose of HERCEPTIN (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should be given as soon as possible (do not wait until the next planned cycle). Subsequent maintenance doses (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should then be given according to the previous schedule.

If the patient misses a dose of HERCEPTIN by more than one week, a re-loading dose of HERCEPTIN should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly: 8 mg/kg). Subsequent maintenance doses (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should then be given according to the previous schedule.

Preparation for Administration

Reconstituting the Powder

Appropriate aseptic technique should be used.

HERCEPTIN should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted HERCEPTIN may result in problems with the amount of HERCEPTIN that can be withdrawn from the vial.

Each 150 mg vial should be reconstituted with 7.2 mL of sterile water for injections as the solvent. The use of other solvents should be avoided. The resultant solution is 7.4 mL of approximately 21 mg/mL trastuzumab. A 4% overage is included to ensure withdrawal of the labelled dose of 150 mg.

Instructions for Reconstitution

1) Using a sterile syringe, slowly inject 7.2 mL of sterile water for injections in the vial containing the lyophilized HERCEPTIN, directing the stream into the lyophilized cake.

2) Swirl vial gently to aid reconstitution. HERCEPTIN may be sensitive to shear-induced stress, e.g. agitation or rapid expulsion from a syringe. DO NOT SHAKE.

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted preparation results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Instructions for Dilution

Weekly Regimen: Determine the volume of the reconstituted solution required based on a loading dose of trastuzumab 4 mg/kg body weight, or a maintenance dose of trastuzumab 2 mg/kg body weight:

Volume (mL) = **Body weight** (kg) x **dose** (**4** mg/kg for loading or **2** mg/kg for maintenance)

21 (mg/mL, concentration of reconstituted solution)

Three-Weekly Regimen: Determine the volume of the reconstituted solution required based on a loading dose of trastuzumab 8 mg/kg body weight, or subsequent every 3 weeks dose of 6 mg/kg body weight:

Volume (mL) = **Body weight** (kg) x **dose** (**8** mg/kg for loading or **6** mg/kg for maintenance)

21 (mg/mL, concentration of reconstituted solution)

Preparation and Stability of the Admixture

The appropriate amount of the reconstituted solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride.

Dextrose (5%) solution should not be used since it causes aggregation of the protein. HERCEPTIN SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES. No incompatibilities between HERCEPTIN and polyvinylchloride, polyethylene or polypropylene bags have been observed.

The infusion bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

From a microbiological point of view, the HERCEPTIN infusion solution should be used immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8°C.

Dose Reduction

No reductions in the dose of HERCEPTIN were made during clinical trials. Patients may continue HERCEPTIN therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be carefully monitored for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Use in Elderly: Age has been shown to have no effect on the disposition of trastuzumab (see **DOSAGE AND ADMINISTRATION**).

Data suggest that the disposition of HERCEPTIN is not altered based on age or serum creatinine (see **Pharmacokinetics**). In clinical trials, elderly patients did not receive reduced doses of HERCEPTIN.

OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Each carton contains one single-dose vial of HERCEPTIN (trastuzumab).

The single-dose vial of HERCEPTIN contains 150 mg of trastuzumab (reconstituted HERCEPTIN concentrate contains approximately 21 mg/mL of trastuzumab). The contents of the vial appear as a sterile, lyophilized, white to pale yellow powder.

Storage

Store HERCEPTIN vials at 2 to 8°C. Refrigerate. Do not freeze. Do not use beyond the expiration date stamped on the vial.

Reconstituted Solution

A vial of HERCEPTIN reconstituted with sterile water for injections without preservative should be used immediately and any unused portion must be discarded. Do not freeze the reconstituted solution.

Diluted Solution for Infusion

Solutions of HERCEPTIN for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing 0.9% sodium chloride at 2 to 8°C for 24 hours. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at temperatures up to 30°C. From a microbiological point of view, the HERCEPTIN infusion solution should be diluted and used immediately. The product is not intended to be stored after dilution unless the dilution has taken place under controlled and validated aseptic conditions.

Disposal of Medicines

The release of medicines into the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099

Customer Enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF APPROVAL

TGA Approval Date: 17 September 2010

** Please note changes in Product Information*

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au