Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Cetuximab

Proprietary Product Name: Erbitux

Sponsor: Merck Serono Australia Pty Ltd

October 2011

TGA Health Safety Regulation

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- 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.

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I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Withdrawn
Date of Decision:	24 August 2011
Active ingredient(s):	Cetuximab
Product Name(s):	Erbitux
Sponsor's Name and Address:	Merck Serono Australia Pty Ltd Units 3-4, 25 Frenchs Forest Road East Frenchs Forest NSW 2086
Dose form(s):	Solution for infusion
Strength(s):	5 mg/mL x 10, 20, 50 and 100 mL
Container(s):	Clear, colourless glass vials with a fluorotec-coated bromobutyl rubber stopper and aluminium/polypropylene seal
Pack size(s):	Single use vial
Approved Therapeutic use:	The existing indications remained unchanged. Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *K-RAS* wild-type metastatic colorectal cancer · in combination with chemotherapy · as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy. Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck · in combination with radiation therapy for locally advanced disease · in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.
Route(s) of administration:	Intravenous
Dosage:	First dose 400 mg/m^2 then 250 mg/m^2 once weekly
ARTG Number (s):	132348, 132393, 132395, 132396

Product Background

Cetuximab is a chimeric monoclonal antibody that binds specifically and with high affinity to the extracellular domain of human epidermal growth factor receptor (EGFR). Cetuximab antagonises receptor binding of cognate EGFR ligands such as epidermal growth factor (EGF) and transforming growth factor (TGF). Because of the diversity of the EGFR dependent intracellular signal pathways, the biological effects of the blockade of ligand receptor binding by cetuximab are varied and comprise most cellular functions implicated in tumour growth and metastasis such as cell proliferation, cell survival, cell motility, cell invasion, tumour angiogenesis and deoxyribonucleic acid (DNA) repair. In

preclinical *in vitro* and *in vivo* studies, it has been shown that cetuximab inhibits tumour growth and metastasis by interfering with all these processes. EGFR is expressed in many normal epithelial tissues including skin and hair follicles. It is also expressed in many human cancers including squamous cell cancer of the head and neck (SCCHN) and colorectal cancer (CRC). Signal transduction through the EGFR results in activation of wild-type K-RAS protein. However, in cells with activating K-RAS mutations, the mutant K-RAS protein is active independent of EGFR regulation.

The current indications are:

KRAS wild-type metastatic colorectal cancer in combination with chemotherapy and as a single agent in patients who have failed or are intolerant to oxaliplatin- and irinotecan-based therapy.

In combination with radiation therapy for locally advanced disease and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease for squamous cell cancer of head and neck.

This AusPAR describes the evaluation of an application by Merck Serono Australia Pty Ltd (the sponsor) to extend the indications to include the use of Erbitux (cetuximab) for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC)

Cetuximab is indicated for the first line treatment of patients with, advanced or metastatic non-small cell lung cancer in combination with platinum-based chemotherapy.

This application was initially lodged in 2009. The sponsor sought broad approval for use in the first line treatment of NSCLC. The clinical evaluator recommended rejection of the application based on a negative balance of benefit and risk. In response, the sponsor submitted additional data from the pivotal studies and proposed a more restricted indication (for use only in patients with *high-EGFR expressing tumours*). There are therefore two clinical evaluations for this application; namely the initial evaluation for the "intent to treat" (ITT) population followed by the evaluation of supplementary data.

The dosage proposed for the new indication is an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 until disease progression. This is the same dosage regimen approved for use in metastatic CRC (mCRC) and SCCHN.

There is one other anti-EGFR antibody registered in Australia: panitumumab (Vectibix). It is not approved for use in NSCLC.

There are two registered small molecule EGFR inhibitors: gefitinib (Iressa) and erlotinib (Tarceva). These agents are both approved for use in NSCLC in various settings. However, both were found to be ineffective in the specific setting of use in combination with chemotherapy for the first line treatment of a broad NSCLC population.

Regulatory Status

Erbitux was originally registered by the TGA for second line treatment of metastatic colorectal cancer in January 2005 and subsequently for treatment of locally advanced head and neck cancer in combination with radiotherapy in January 2007. Later, the indication for both metastatic colorectal cancer and head and neck cancer was extended.[1]

A similar submission was submitted in the European Union (EU) on 10 September 2008 for the indication:

[1] TGA. AusPAR for Cetuximab, February 2010. Available at: http://www.tga.gov.au/pdf/auspar/auspar-erbitux.pdf

Erbitux is indicated for the first line treatment of patients with epidermal growth factor receptor (EGFR)-expressing, advanced or metastatic non small cell lung cancer in combination with platinum based chemotherapy.

It was rejected on 30 November 2009 because the Committee on Human Use of Medicinal Products (CHMP) was of the opinion that the benefits of Erbitux in the treatment of non small cell lung cancer did not outweigh its risks.

A further submission was made to the EU on 18 March 2011 which is under evaluation. The indication in that submission is for:

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non small cell lung cancer with high EGFR-expressing tumours.

The sponsor is not responsible for submissions in the US or Canada.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

No nonclinical studies, but 62 published papers, were submitted in support of the proposed extension to the NSCLC indication. No literature search strategy was provided but this was considered acceptable given the regulatory history of the drug and the purpose of this application.

Since the dosage and administration were not changed from previous applications, the pharmacokinetic and toxicological data as well as general pharmacology data (including the mechanism of action of cetuximab) submitted with previous applications to register cetuximab were considered to also support this application. It was also noted by the sponsor (in its *Nonclinical Overview*) that no data have been reported since then that would result in a revision of the sponsor's evaluation of the general cetuximab pharmacology. Therefore, only those references containing nonclinical data considered to be directly relevant to the new NSCLC indication have been evaluated in this report.

Pharmacology

Primary pharmacodynamics

Anti-tumour activity of cetuximab was demonstrated in a variety of nonclinical *in vitro* and *in vivo* models using various cell lines derived from NSCLC. Since the mean maximum plasma concentration (C_{max}) at the maximum recommended clinical dose (according to the proposed product information [PI]) is 185 µg/mL (~1.2 µM), reduced proliferation was seen in many cell types *in vitro* at clinically relevant concentrations. However, this parameter is less useful for assessing likelihood of efficacy than, for example, the minimum plasma concentration (C_{trough}), because the time at the effective concentration needs to be taken into account. In many of these cell types, a reduction in phosphorylation of epidermal growth factor receptor (EGFR), extracellular signal regulated kinase (ERK), AKT (protein kinase B) and mitogen activated protein kinase (MAPK) were seen following exposure to cetuximab, both *in vitro* in cultured cells and in xenografted NSCLC tumours in athymic mice following cetuximab treatment. These activities were shown in cell lines derived from adenocarcinoma, squamous cell carcinoma and other histologies. While

there were differences in susceptibility between the cell types used in these studies, increased EGFR gene copy number (GCN) was not a prerequisite for cetuximab activity and neither did the extent of inhibition of EGFR phosphorylation necessarily correlate with cell proliferation and viability. However, the H520 cell line, which had no detectable EGFR, was unresponsive to cetuximab (when tested) both *in vitro* and in *in vivo* xenografts. The submitted nonclinical *in vitro* and *in vivo* data indicated that cetuximab was active in cell lines expressing EGFR with mutations, including EGFR with mutations conferring resistance to tyrosine kinase inhibitors (TKIs) as well as EGFR wild type.

In one published study, cetuximab inhibited proliferation *in vitro*, without affecting clonogenic survival in the same cell lines. Cetuximab also mediated antibody dependent cellular cytotoxicity (ADCC) in NSCLC tumour cells, in a manner which generally, but not universally, was dependent on cetuximab concentration and EGFR expression levels at clinically relevant concentrations.

The combination of cetuximab with cisplatin or paclitaxel resulted in apparently synergistic effects in a variety of cell lines *in vitro*. *In vivo*, cetuximab in combination with cisplatin, carboplatin, docetaxel or gemcitabine resulted in greater anti-tumour effects than either agent alone in athymic mice xenografted with H292 cells but against H1975 cells only with gemcitabine and docetaxel. Responsiveness was therefore cell type dependent.

In a previous evaluation, it was noted that the Kirsten rat sarcoma (*KRAS)* gene mutation has significantly associated with an absence of clinical response to cetuximab in CRC patients and may be predictive of resistance to cetuximab. No new nonclinical data were submitted to address the effect of *KRAS* on efficacy in NSCLC.

Nonclinical Summary and Conclusions

No nonclinical safety data in support of the proposed extension to indications were submitted. However, no change is proposed to the dose or dosing regimen. The submitted published literature provided *in vitro* and *in vivo* evidence from multiple cell types in support of the efficacy of cetuximab for extension of indications to include EGFR expressing NSCLC, with and without combination therapy with platinum based chemotherapy. The extent of the response varied with cell type and some NSCLC cell types (including a cell type with no detectable EGFR expression) were resistant to cetuximab treatment.

Cetuximab inhibited proliferation of a number of NSCLC tumour cell lines *in vitro* and inhibited NSCLC xenograft tumour growth *in vivo* as well as downstream EGFR phosphorylation events at clinically relevant concentrations and doses. The *in vitro* and *in vivo* activity of cetuximab against some NSCLC cell lines (but not all) was improved by combination treatment with platinum derivatives (cisplatin, carboplatin and oxaliplatin) *in vitro* and *in vivo*.

A requirement for EGFR testing has not been included for this patient population. The nonclinical data do not support efficacy in non-EGFR NSCLC models.

There were no nonclinical objections to the extension of indications for cetuximab, provided that the safety and efficacy of the new indication is supported by clinical data.

IV. Clinical Findings

Initial Clinical Evaluation of ITT Population - Introduction

The clinical development program of cetuximab in non-small cell lung cancer (NSCLC) consists of 2 Phase Ib/IIa open label single arm (uncontrolled) studies, 2 Phase II

randomised, controlled open label studies and 2 Phase III randomised controlled open label studies. In the 4 later phase trials, 2018 subjects with advanced or metastatic (Stage IIIb or Stage IV) NSCLC were randomised. In all trials, cetuximab was given in combination with two chemotherapy agents, one being platinum based.

Initial Clinical Evaluation - Pharmacokinetics

Introduction

In the submission new pharmacokinetic (PK) data was available from 585 subjects with EGFR expressing NSCLC in four trials (EMR 62 202-046, EMR 62 202-011, IMCL CP02-9925 and ICL CP02-9932). In all four trials the cetuximab dosage regimen was the same: 400 mg/m^2 body surface area initially and then 250 mg/m^2 weekly thereafter via intravenous (IV) infusion. Cetuximab was administered in combination with platinum based chemotherapy doublets in all trials.

Methods

Results from individual studies were analysed by non-compartmental PK analysis or by characterisation of serum cetuximab levels by descriptive statistics. Cetuximab concentration data from studies EMR 62 202-046 and -011 were combined into a common population PK database for an integrated analysis.

Absorption, Distribution, Metabolism, Excretion (ADME)

Cetuximab is administered as an IV infusion. No studies have been performed on metabolism. Antibody metabolism is presumed to involve biodegradation to smaller molecules.

Pharmacokinetics in the target population

Multiple dose PK parameters were assessed in 33 subjects with NSCLC in the Phase II study EMR 62 202-011 during administration of cetuximab (Week 3 of treatment) and during administration of cetuximab together with cisplatin and vinorelbine chemotherapy (Week 4 of treatment). Results are summarised in Table 1. The ratio of PK parameters in Week 4 as a percentage of values in Week 3 ranged from 97.3 to 113.1%. These similar findings in the data from the 2 weeks indicated that the cisplatin/vinorelbine chemotherapy did not have a significant effect on the PK of cetuximab.

Table 1: Multiple dose PK parameters for the target dose of cetuximab in Study EMR 62 202-011

PK parameter	Statistic	Week 3 Cetuximab alone	Week 4 Cetuximab + cisplatin and vinorelbine	Mean ratio % Week 4 / Week 3
		N = 33	N = 33	
C_{max} (µg/mL)	Mean (S.D.)	189 (39)	202 (66)	106.9
	Range	125-267	144-502	
t_{max} (h)	Mean (S.D.)	1.7 (1.2)	1.6 (1.1)	97.9
	Range	1-5.2	0.8-4.8	
AUC_T (µg/mL)	Mean (S.D.)	14660 (4139)	14874 (4746)	101.5
	Range	7583-24653	5711-27657	
$t_{1/2}$ (h)	Mean (S.D.)	83 (23)	92 (21)	111.1
	Range	50-155	56-147	
MRT_{ss} (h)	Mean (S.D.)	122 (33)	134 (31)	109.9
	Range	72-228	82-214	
CL_{ss} (L/h)	Mean (S.D.)	0.033 (0.008)	0.033 (0.011)	101.2
	Range	0.017-0.053	0.015-0.070	
V_{ss} (L)	Mean (S.D.)	3.91 (1.07)	4.42 (1.7)	113.1
	Range	1.84-6	2.02-8.88	

Peak and trough concentrations were determined in studies EMR 62 202-046, IMCL CP02-9925 and IMCL CP02-9932 and are summarised in Table 2. The concomitant chemotherapy was cisplatin and vinorelbine in EMR 62 202-046, gemcitabine and carboplatin in IMCL CP02-9925 and paclitaxel and carboplatin in IMCL CP02-9932. With repeat dosing and concomitant administration of platinum based chemotherapy, the observed cetuximab levels were reasonably constant over time and similar between studies.

Table 2: Mean (SD) trough and peak serum concentrations of cetuximab in NSCLC studies

Study	Timepoint	Trough concentration (µg/mL)			Peak concentration (µg/mL)		
		N	Mean	S.D.	N	Mean	S.D.
EMR 62 202-046	Week 1	486	2.0	10.8	454	223.1	64.6
	Week 7	298	51.5	33.1		n.a.	n.a.
EMR 62 202-011	Week 3	34	38.3	18.1	33	180	43.6
	Week 4	33	42.2	19.4	32	195	64.6
IMCL CP02-9925 [a]	Week 1	20	1.2	1.63		n.a.	n.a.
	Week 3	18	63.2	39.86	14	221.1	62.85
	Week 6	18	86.0	53.85	17	290.0	115.25
	Week 9	20	90.1	54.00	19	308.0	122.31
	Week 12	22	91.9	41.53	19	290.7	97.34
	Week 15	19	107.4	47.31	19	293.7	86.36
	Week 18	16	99.4	44.73	14	325.9	104.42
	Week 21	10	131.1	55.75	9	293.0	118.33
IMCL CP02-9932 [a]	Week 1	28	1.4	2.17		n.a.	n.a.
	Week 3	26	56.5	33.97	23	236.5	74.23
	Week 6	23	111.0	79.41	21	234.1	102.62
	Week 9	19	104.4	64.36	18	251.5	67.24
	Week 12	18	119.9	55.60	18	299.9	129.85
	Week 15	14	137.2	63.08	13	286.7	80.67
	Week 18	14	137.3	46.02	12	324.1	111.33
	Week 21	13	129.7	76.61	12	352.6	154.29

n.a.=not applicable, S.D.=standard deviation

[a] In studies IMCL CP02-9925 and-9932, weeks were calculated based on a cycle length of 3 weeks. Data are shown only up to cycle 7, corresponding to week 21, for clarity. The serum concentrations remained constant through at least 18 cycles of treatment.

The population PK analysis included 524 subjects with NSCLC and 1448 observations from two studies. There were 965 (67%) observations from 485 subjects in the Phase III trial EMR 62 202-046 and 483 (33%) observations from 39 subjects in the Phase II trial EMR 62 202-011. The data were described by a one compartment model with linear clearance. The volume of distribution was estimated to be 3.28 L and the clearance of cetuximab was estimated to be 0.025 L/h. Body surface area was determined to be a significant covariate on clearance and the volume of distribution

Evaluator's Comments

The PKs of cetuximab in NSCLC patients is similar to PKs reported in other populations and was not affected by coadministration of platinum based chemotherapy. Since the body surface area impacts on cetuximab clearance and volume of distribution, the proposed dosage based on mg/m^2 body surface area would ensure consistent exposure in patients with NSCLC.

Initial Clinical Evaluation - Pharmacodynamics

No new pharmacodynamic data were submitted.

Initial Clinical Evaluation - Efficacy

Introduction

The submission contained clinical data from six trials (four controlled and two uncontrolled) in subjects with advanced stage NSCLC. All trials were stated to be carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). Data from these trials have been used for determining clinical efficacy.

Main (pivotal) Studies

EMR 62 202-046 (FLEX)

An open, randomised, controlled, multicentre Phase III study comparing cisplatin/vinorelbine plus cetuximab versus cisplatin/vinorelbine as first line treatment for subjects with EGFR expressing advanced non-small cell lung cancer (NSCLC) ("FLEX").

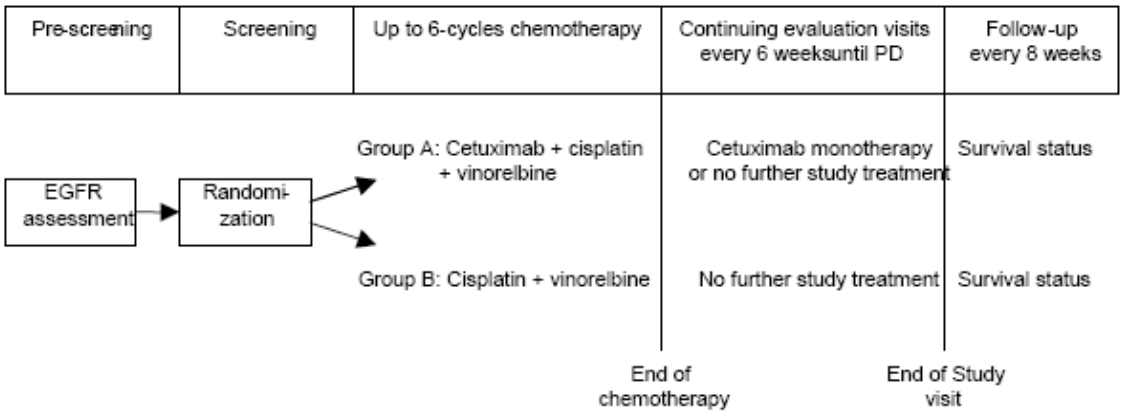
Methods

Subjects were randomised at 155 centres in 30 countries; 21 in Asia/Australia, 120 in Europe and 14 in South America. There was an independent Data Safety Monitoring Board (DSMB) which reviewed data twice during the trial and had no safety concerns to cease the trial.

EGFR expression in tumour biopsies was performed at regional laboratories and analysis of laboratory safety variable were performed locally. Results were sent to a virtual central laboratory that normalised the data. All local laboratories analysed a test sample provided by the virtual central laboratory to allow normalisation factors to be generated for each laboratory. Human anti-chimeric antibody (HACA) status in subjects treated with cetuximab was assessed by a central laboratory in Germany.

A schematic diagram of the study design is shown in Figure 1. The chemotherapy (CTX) phase of the study had a maximum duration of 18 weeks (6 cycles). Subjects then had continuing 6 weekly evaluation visits until documentation of progressive disease (PD) at which point final tumour assessment was performed. An "end of study visit" was carried out after the diagnosis of PD. Subjects were then followed up every 8 weeks for survival status, further anticancer treatment information and the outcome of any adverse events (AEs) related to cetuximab.

Figure 1: Schematic overview of study design EMR 62 202-046



Objectives

The primary objective of the study was to show superiority in terms of overall survival (OS) time for subjects receiving cetuximab + cisplatin + vinorelbine (cetuximab+C/V) as first line treatment compared with subjects receiving cisplatin + vinorelbine (C/V) alone. The secondary objectives were to compare progression free survival (PFS) time, best overall response, disease control, safety and quality of life between the two treatment groups. Cetuximab PK were also evaluated via population PK approach.

Study participants

Inclusion criteria were: ≥18 years of age, histologically or cytologically confirmed NSCLC Stage IIIb with documented malignant pleural effusion or Stage IV; immunohistochemical evidence of EGFR expression on tumour tissue (DakoCytomation EGFR pharmDx™ test kit); presence of at least one bidimensionally measurable index lesion not in a previously irradiated area; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤2 at study entry; white blood cell (WBC) count >3 x 10^9/L, with neutrophils ≥1.5 x 10^9/L, platelets ≥100x 10^9/L, and haemoglobin ≥5.6 mmol/L (9 g/dL); total bilirubin ≤1.5 x upper limit of normal (ULN) range; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 x ULN; serum creatinine ≤1.25 ULN and/or creatinine clearance ≥60 mL/min; and recovery from relevant toxicities before study entry.[2]

Exclusion criteria were: previous exposure to monoclonal antibodies, signal transduction inhibitors or EGFR targeting therapy; previous CTX for NSCLC; major surgery within 4 weeks; prior chest irradiation within 12 weeks (palliative radiation of bone lesions was

[2] 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

allowed); brain metastasis; pre-existing ascites Grade ≥2 and/or pericardial effusion Grade ≥2; previous malignancy; active infection; concurrent chronic systemic immune therapy, CTX, or hormone therapy for cancer treatment; symptomatic peripheral neuropathy of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade ≥2 and/or ototoxicity Grade ≥2; superior vena cava syndrome contraindicating hydration; myocardial infarction within 6 months or uncontrolled congestive heart failure; history of significant neurologic or psychiatric disorders or drug abuse; pregnancy or lactation.[3]

Evaluator's Comments

The population is representative of the target population of advanced NSCLC. EGFR expression on tumour tissue was required for study inclusion though the sponsor has not proposed it as a requirement in the requested indication.

Treatments

Cetuximab was administered IV with an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. Subjects received prophylactic treatment with an antihistamine. Therapy was withheld for Grade 3 skin reactions and discontinued if a Grade 4 reaction occurred. Therapy was continued in the event of toxicity to chemotherapy.

Chemotherapy consisted of 3 weekly cycles of cisplatin 80 mg/m^2 on Day 1 of each cycle and vinorelbine 25 mg/m^2 on Days 1 and 8 of each cycle. The protocol originally stated that the dose of vinorelbine was 30 mg/m^2. However, based on the high incidence of neutropenia and neutropenic fever of any grade, the DSMB recommended that the dose be reduced to 25 mg/m^2. This became effective with Amendment 2 after 1,058 subjects (95%) had actually started on 30 mg/m^2 vinorelbine.

Cisplatin and vinorelbine were given for a maximum of 6 cycles (18 weeks) or until progressive disease (PD), symptomatic deterioration or unacceptable toxicity occurred. Cetuximab treatment could continue as monotherapy after chemotherapy completion or early discontinuation due to intolerance, until PD, symptomatic deterioration or unacceptable toxicity occurred. Additional concurrent CTX, radiation (other than palliative radiotherapy of bone lesions) or hormone therapy for treatment of the malignancy was not allowed.

Evaluator's Comments

Platinum based two drug combinations are standard treatment in Australia for advanced NSCLC. Vinorelbine dosage approved in Australia for NSCLC is 25 to 30 mg/m^2.

Outcomes/endpoints

The primary efficacy variable in this study was the overall survival (OS) time which was defined as the time from randomisation to death from any cause.

The secondary efficacy variables were: PFS time, with time to treatment failure (TTF) as a *post hoc* sensitivity analysis; best overall response; and disease control rate. PFS time was defined as the duration from randomisation until first observation of radiologically confirmed PD or death due to any cause. TTF was defined as the time in months from randomisation until the date of the first occurrence of one of the events defining treatment failure (clinical or radiological PD, death, discontinuation due to an AE, new anticancer

[3] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

treatment commencement or consent withdrawn). Objective response rate (ORR) was defined as the proportion of subjects who had confirmed complete response (CR) or partial response (PR) according to radiological assessment. Disease control rate was defined as the proportion of subjects who had confirmed CR or PR or stable disease (SD) as the best overall response on radiological assessment.

Evaluation of lesions was based on images obtained by either CT or MRI scan and was performed at baseline and every 6 weeks after randomisation until PD and at the final visit. To assess whether there was progression of disease, the tumour burden at baseline was calculated and used for comparison with subsequent measurements. Up to 10 identified index lesions were measured and other lesions (or disease sites) were identified as non-index. Overall response was defined based on the assessments for index and non-index lesions as well as considering the occurrence of new lesions. Definitions are shown in Table 3. For partial response (PR), a 50% or more decrease in index lesion diameter compared to baseline was required. After an overall response was assigned at each follow up time point, the best overall response across all time points was established by applying the Modified WHO criteria (Table 4).

Table 3: Study EMR62202-046 - Evaluation of Response Based on Index and Non-Index Lesions

Index lesions	
Complete Response (CR)	Disappearance of all index lesions.
Partial Response (PR)	A 50% or more decrease in the sum of the products of diameters (SOPD) of index lesions compared to the baseline SOPD, with no evidence of PD.
Stable Disease (SD)	Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD.
Progressive disease (PD)	A 25% or more increase in the SOPD of index lesions, compared to the smallest SOPD recorded for the study period (nadir SOPD).
Non-index lesions	
Complete Response (CR)	Disappearance of all non-index lesions. No new lesions.
No change (NC)	No significant change in non-index lesions to qualify for either CR or PD. No new lesions.
Progressive disease (PD)	Appearance of one or more new lesions, and/or unequivocal progression of existing non-index lesions (worsening or new effusions or ascites is not considered radiologic progression).

Table 4: Study EMR62202-046 – modified WHO criteria

Confirmation Criteria and Best Overall Response

Earlier Best Response (not yet confirmed)	Later Best Response (confirmation)	Best Overall Response
CR	CR	CR
CR	No CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
SD	Not applicable	SD
PD	Not applicable	PD

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the EORTC lung cancer specific QLQ-LC13 and the EuroQoL (EQ-5D) questionnaires were used to assess quality of life (QoL). The QLQ-C30 is a cancer specific self administered core questionnaire. It comprises 30 questions and provides a multidimensional assessment of QoL. Assessment took place at baseline, on Day 1 of the third CTX cycle, at the first 6 weekly evaluation visit after the end of CTX and at continuing evaluation visits at approximately 6 and 12 months after randomisation, and at the final tumour assessment.

Statistical Considerations

Assuming an increase in median duration of survival of 25% (that is, from 8 months in the CTX group to 10 months in the cetuximab + CTX group), α equalling 0.05 (two-sided) and a power of 90%, a sample size of 1,100 subjects (550 per treatment group) was required. This resulted in 845 required events (deaths). It was noted that the study's power would be about 75% if there was a 20% increase in median survival.

Subjects were randomised using an Interactive Voice Response System (IVRS) in a 1:1 ratio. Randomisation was stratified by ECOG PS 0 or 1 versus 2 and disease stage (IIIb with malignant pleural effusion versus IV) as these are important prognostic factors.

This study was open label as most subjects treated with cetuximab experience skin reactions and are thus identifiable.

The "intent to treat" (ITT) population (all subjects randomised to study treatment) was primarily used in the analysis of baseline characteristics and efficacy. Equality of OS time between treatment groups was tested using a two-sided stratified log-rank test (α=5%); strata were as per randomisation (ECOG PS of 0 or 1 versus 2, tumour Stage IIIb versus IV). Kaplan-Meier survival curves were presented by treatment group. The hazard ratio (HR) including 95% confidence interval (CI) of cetuximab and CTX over CTX alone was calculated using Cox's proportional hazards model. Sensitivity analysis using Cox's proportional hazards model adjusted for potential prognostic factors was also done.

For the secondary variables PFS time and TTF, the same analyses as for OS were conducted. The best overall response rate and disease control rate were compared in the Cochran-Mantel-Haenszel (CMH) test (two-sided with α=5%). To adjust for multiplicity when testing the endpoints, the analyses were ranked according to their clinical relevance as follows: OS time, PFS, disease control rate, then best ORR.

In response to US Food and Drug Administration (FDA) questions on cardiopulmonary arrest in relation to the submission on cetuximab treatment for head and neck cancer, an unplanned interim analysis was conducted in 2005 on AEs relating to myocardial infarction, cardiorespiratory arrest and sudden death. These data, without any efficacy data, were reviewed by the DSMB and no concerns regarding study continuation were raised.

Results

Study subjects were enrolled from November 2004 to February 2006 and the clinical cut-off was in July 2007.

There were 1861 subjects pre-screened, 1258 screened, and 1125 randomised with 557 in the cetuximab+CTX group and 568 in the CTX group (ITT population). The primary analysis set was the ITT population. Of the 1688 subjects tested, 1442 (85%) had EGFR expressing tumours. Of these, 321/1442 subjects were not randomised. This was primarily due to not meeting the inclusion/exclusion criteria (57%). There were 15 subjects in the ITT group who did not receive study treatment (6 in cetuximab+CTX and 9 in CTX groups). The main reason for discontinuation from the study was PD or death in 446 (80.1%) subjects in the cetuximab + CTX group and 408 (71.8%) in the CTX group, followed by adverse events in 20 (3.6%) and 43 (7.6%) respectively.

Protocol deviations were documented in 119/557 (21.4%) subjects in the cetuximab + CTX group and 104/568 (18.3%) in the CTX group. The types of deviations were similar between groups. The main reason resulting in exclusion from the per protocol analysis was administration of one cycle or less of study treatment.

Three protocol amendments were issued. Amendment 1 described an ancillary study for mutation analysis of archived tumour biopsies from randomised subjects. The main change in amendment 2 was the reduction in the starting dose of vinorelbine from 30 mg/m^2 to 25 mg/m^2 due to the high incidence of neutropenia and neutropenic fever of any grade (49% and 21%, respectively, pooled analysis of 365 subjects for the DSMB). Amendment 3 described taking tumour samples for KRAS analysis.

Baseline data

In the ITT population, 84% of subjects were Caucasian, 70% male, the median age was 59.2 years and 78.1% were current or former smokers. The treatment groups were similar with respect to randomisation strata (ECOG status and disease stage), ethnic subgroup, gender, age and smoking status. Abnormal physical findings were similar between treatment groups with the most common being those of the respiratory system (55.3% in the cetuximab+CTX group and 56.7% of the CTX group). Lung function at baseline was similar between groups. Prior treatment for NSCLC occurred in 150/557 (26.9%) of the cetuximab+CTX group and 166/568 (29.2%) of the CTX group and consisted mainly of surgery. Relevant prior medical history was similar between groups.

Concomitant medication use was similar during the study apart from systemic antihistamines (96.2% in cetuximab+CTX vs 28.9% in CTX group), antipruritics (63.7% vs 12.1%) and systemic antibacterials (67.1% vs 49.8%). These increased rates in the cetuximab group may be explained by prophylactic antihistamine use prior to infusion, treatment of skin reactions (anti-acne tetracyclines and antipruritics) and the treatment of the increased rate of infectious complications.

Baseline disease characteristics were similar with respect to duration of disease, histology, staging, and location and number of metastases. Most subjects had adenocarcinoma (45.8% in cetuximab+CTX and 48.8% in the CTX group) or squamous cell carcinoma (34.1% and 32.9% respectively). The percentage of subjects with EGFR detectable cells at

baseline was similar between groups and around 70% in each group had ≥40% EGFR detectable cells. The Asian population accounted for 10.8% of the ITT population (121/1125). In this subgroup of Asians there were more women (46.3% versus 29.8% of the overall ITT population), more that had never smoked (52.1% vs 21.7%) and more adenocarcinoma (71.9% vs 47.3%).

There were 299 (53.7%) subjects in the cetuximab+CTX group and 344 (60.6%) in the CTX group who received post-study anticancer treatment. Radiotherapy and CTX were well balanced across the treatment groups, but more subjects in the CTX alone group received anti-EGFR therapy (26.9% versus 16.9%). Post-study anticancer treatment was also higher in the Asian subgroup with 71% of the Asian cetuximab+CTX and 88.1% of the Asian CTX group receiving such treatment compared to 53.7% and 60.6% of the cetuximab+CTX group and CTX group, respectively in the overall ITT analysis. In the Asian group, more patients received anti-EGFR therapy (74.6% versus 50.0%) than CTX alone.

Primary outcome

Overall Survival Time

The median duration of follow up was 23.8 months in both treatment groups. There were 421 (75.6%) deaths in the cetuximab group and 447 (78.7%) deaths in the CTX group. Median overall survival (OS) time in the cetuximab+CTX group was 11.3 months (95% CI: 9.4, 12.4) and in the CTX group was 10.1 months (95% CI: 9.1, 10.9). The hazard ratio (HR) of cetuximab+CTX over CTX was 0.87 (95% CI: 0.76, 0.99]) which just reached statistical significance, p=0.044 (Table 5). Kaplan-Meier estimates are presented in Figure 2. A Cox regression analysis adjusting for the following baseline variables (gender, ethnic origin, ECOG PS, number of organs involved, tumour stage, histology, global QoL and smoking habit) found the HR for cetuximab+CTX over CTX was 0.84 (95% CI: 0.69, 1.03) which was not statistically significant (p=0.102).

Table 5: EMR62-202-046 – summary of primary analysis of OS (ITT population)

Summary statistics[a]	Cetuximab + CTX N=557	CTX N=568
Number of deaths, %	421 (75.6)	447 (78.7)
Log rank p value (stratified)[b]	0.0441	
Hazard ratio (stratified) [95% CI] [b, c]	0.871 [0.762, 0.996]	
Overall survival time, *months, median [95% CI]* [d]	11.3 [9.4, 12.4]	10.1 [9.1, 10.9]
Number of subjects at risk/survival rates up to [95% CI] [d]		
3 months	448 83% [79, 86]	457 82% [79, 86]
6 months	383 71% [67, 75]	383 70% [66, 74]
12 months	251 47% [43, 51]	225 42% [38, 46]
18 months	155 31% [27, 35]	134 26% [22, 30]
24 months	53 20% [17, 24]	48 17% [14, 21]

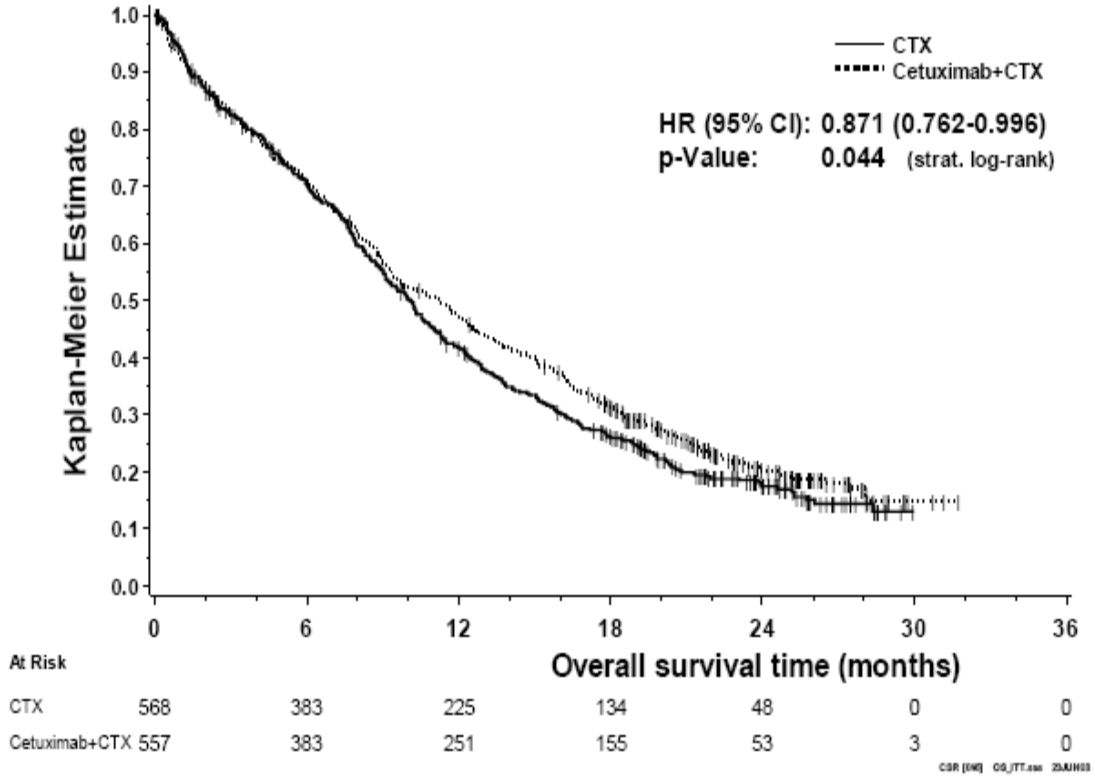
[a] Analysis based on 4 September 2007 snapshot.

[b] Stratification based on ECOG PS and tumor stage as per IVRS.

[c] Hazard ratio of cetuximab + CTX over CTX.

[d] Product-limit (Kaplan-Meier) estimates.

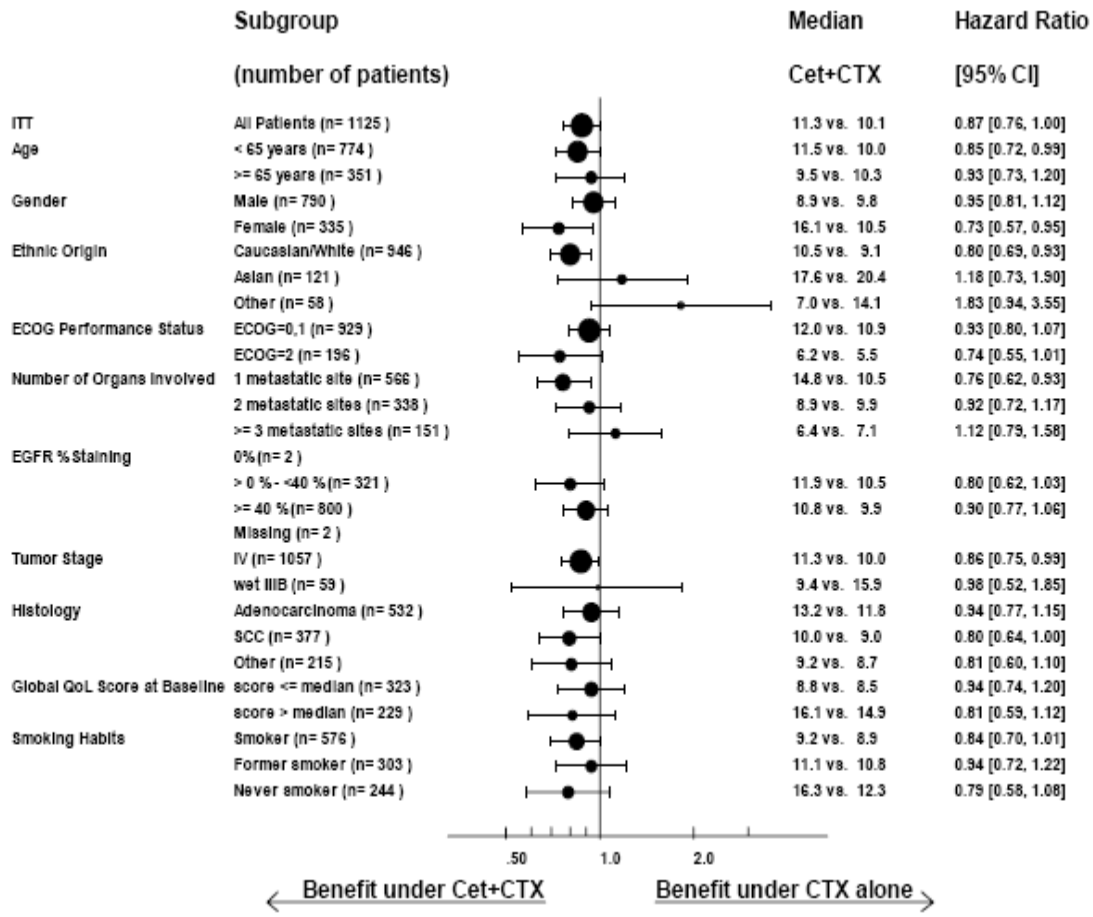
Figure 2: EMR62-202-046 – Kaplan-Meier estimates of OS (ITT population)



Overall Survival Time Subgroup Analysis

The results of subgroup analyses of OS time in the ITT population are summarised in Figure 3. No adjustments for multiplicity were performed for secondary statistical analyses and the subgroup analyses were not powered to detect statistically significant differences.

Figure 3: EMR62-202-046 – OS – results of subgroup analyses (ITT population)



In the Caucasian population, the median duration of follow up was 23.0 months in the cetuximab+CTX group and 23.7 months in the CTX group, with a death event rate of 76.8% and 82.5% respectively. The median OS time in the cetuximab+CTX group was 10.5 months (95% CI: 9.2, 12.0) and in the CTX group was 9.1 months (95% CI: 8.2, 10.1). The HR of cetuximab+CTX over CTX for Caucasians was 0.80 (95% CI: 0.69, 0.93, p=0.003), which was statistically significantly in favour of cetuximab treatment. However, no benefit was seen for the Asian population and in fact the median OS time in those treated with cetuximab+CTX (17.6 months, 95% CI: 12.3, 23.3) and in those treated with CTX was shorter than those treated with CTX (20.4 months, 95% CI: 16.1, 26.1). Furthermore, the OS was non-significantly greater in the CTX group compared to the cetuximab+CTX group (HR = 1.18, 95% CI: 0.73, 1.91). There were also less deaths, 64.5% in the cetuximab+CTX group and 52.5% in the CTX group.

Regarding histology, for subjects with adenocarcinoma (n=532), the OS was 13.2 months in the cetuximab+CTX group and 11.8 months in CTX group with a non statistically significant HR of 0.94 (95%CI: 0.77, 1.15). For those with squamous cell carcinoma (SCC) (n=377), the OS was 10.0 and 9.0 months in the cetuximab+CTX and CTX groups respectively, with a HR of 0.80 (95%CI: 0.64, 1.00). Other subgroups for whom benefit appeared to be greater were those <65 years, females and those with only 1 metastatic site (Figure 2).

All subjects treated with cetuximab who developed acne-like rash between Day 1 and Day 21 of treatment were included in a special analysis of OS time, where Day 22 of treatment was regarded as Day 0. Development of acne-like rash in the first 21 days of treatment was

associated with a longer OS time in the ITT population treated with cetuximab and CTX - 8.1 months in those without the rash versus 14.3 months in those with the rash.

Secondary Outcomes

Progression Free Survival Time

Median PFS time was the same at 4.8 months in both treatment groups and the HR for PFS time for cetuximab+CTX over CTX was 0.94 (95% CI: 0.83, 1.08) which was not statistically significant (p=0.39). The median PFS time in the Caucasian population was similar to that in the ITT group (4.7 months in the cetuximab+CTX group and 4.4 months in the CTX group) and the HR of 0.93 (95% CI: 0.81, 1.08) was not significant (p=0.35). For the Asian population, the PFS time HR was 0.88 (95% CI: 0.58, 1.32 p=0.53). Subgroup analyses for PFS showed results which were mostly similar to those seen for subgroup analysis for OS.

Best Overall Response Rate and Disease Control Rate

In the cetuximab+CTX group the best overall response rate (ORR) was 36.4% (95% CI: 32.4, 40.6) which was slightly higher than the rate of 29.2% (95% CI: 25.5, 33.2) in the CTX group with an odds ratio (OR) of 1.39 (95% CI: 1.08, 1.79, p=0.01). However the disease control rate was equal in both groups (72.5%, 71.5%) with an OR of 1.06 (95%CI: 0.81, 1.37, p= 0.68).

Time to Treatment Failure

There were slightly more subjects in the CTX group who were censored (cetuximab+CTX: 18%; CTX: 24%). The time to treatment failure was therefore calculated as a *post hoc* sensitivity analysis, also taking into account events which were considered signs of clinical progression (non-image-proven PD and start of any new anticancer treatment). The median time to treatment failure was 4.2 months in the cetuximab + CTX group and 3.7 months in the CTX group. The HR for cetuximab + CTX over CTX was 0.86 (95% CI: 0.76, 0.97, p=0.015).

Quality of Life

There were 783 subjects included in the ITT (QLQ-C30) subset population. Of these, 670 subjects had evaluable data (348 in the cetuximab+CTX arm and 322 in the CTX alone arm). There were 1829 questionnaires completed with only 1187 evaluable - 66.6% in the cetuximab+CTX arm and 63.1% in the CTX alone treatment group. There was a significantly worse score on a number of scales (for example, social, role and physical functioning) during treatment Cycle 3 in those treated with cetuximab+CTX. The difference was not, however, evident at 6 months. Sore mouth and dysphagia scales on QLQ-LC13 were also significantly higher in the cetuximab+CTX group.

CA225099

A randomised multicentre Phase III study of taxane/carboplatin/cetuximab versus taxane/carboplatin as first line treatment for patients with advanced metastatic non-small cell lung cancer.

Methods

This study was conducted in the USA at 96 centres. The study was ongoing at the time of the evaluation of the sponsor's *Clinical Study Report (CSR)* so results included an interim analysis of overall survival. Final results will be available when 558 deaths are observed.

Tumour response and progression were based on blinded evaluation by an independent radiology review committee (IRRC). After the CTX phase of the study, participants had tumour assessments (by CT scan or MRI) 6 weekly until disease progression or

commencement of secondary chemotherapy at which point follow up was continued at 3 monthly intervals.

Objectives

The primary objective was to compare progression free survival (PFS) of subjects treated with cetuximab + taxane/carboplatin (cetuximab+T/C) to that of subjects treated with taxane/carboplatin (T/C) alone. The main secondary objectives included comparison between treatment arms for tumour response, disease control, overall survival, lung cancer symptom response and progression and an assessment of safety.

Study participants

As with EMR 62202-046, inclusion criteria were age ≥18 years with histologically or cytologically documented NSCLC who presented with Stage IV or Stage IIIb disease with malignant pleural effusion, or recurrent disease following radiation therapy or surgical resection and a bidimensionally measurable disease. ECOG PS needed to be 0 or 1 at study entry (while PS 2 was also included in EMR 62202-046). Evidence of EGFR expression on tumour tissue was not a required inclusion criterion unlike EMR 62202-046.

The main exclusion criteria were: concurrent malignancy; symptomatic central nervous system (CNS) metastases; uncontrolled cardiovascular disease; peripheral neuropathy ≥Grade 2; inadequate renal, hepatic or haematologic function; prior treatment with cetuximab or EGFR targeted therapy; prior CTX for lung cancer; and previous reaction to monoclonal antibody therapy.

Treatments

As in EMR 62202-046, cetuximab was administered weekly at an initial dose of 400 mg/m^2 IV infusion and a weekly maintenance dose of 250 mg/m^2 IV infusion. Subjects received prophylactic premedication with an antihistamine.

Chemotherapy consisted of taxane and carboplatin administered on Day 1 and then in 3 weekly cycles. The taxane could be IV paclitaxel or IV docetaxel as chosen by the investigator prior to randomisation and could not be revised. Doses were paclitaxel 225 mg/m^2 or docetaxel 75 mg/m^2. The carboplatin dose was calculated using the modified Calvert formula and was based on the target area under the curve (AUC) for each subject. The dose was estimated in milligrams based on the subject's body weight at each treatment visit and the estimated creatinine clearance (CrCl) obtained within one week prior to administration of each dose. The AUC for carboplatin was defined as the carboplatin dose (in mg) divided by [25 + creatinine clearance]). Taxane premedication was used (dexamethasone +/- antihistamine and cimetidine or equivalent).

Taxane and carboplatin were given for a maximum of 6 cycles (18 weeks) or until unacceptable toxicity or documented disease progression. Cetuximab treatment could continue as monotherapy, as in EMR 62202-046, until disease progression or cetuximab toxicity. Treatment starting doses could be reduced by 2 levels to manage toxicity but could not be re-escalated.

Outcomes/endpoints

The primary efficacy endpoint for this study was PFS based on the IRRC assessment. PFS based on the investigator assessment was a secondary endpoint together with response rate (modified WHO criteria), disease control, overall survival, symptom response and symptomatic progression.

Tumour assessment was by MRI or CT scan with the same method used at each assessment. Index lesions were chosen, up to 5 per organ and 10 in total, for reference and for measuring in 2 dimensions during the study. Tumour response was based on change in

the total area of all index lesions as well as the status of non-index and new lesions. Assessment was conducted by the IRRC with 2 primary independent readers and a final assessment with clinical information was performed by an independent oncologist. Assessments were based on the modified WHO criteria. Lung cancer symptoms were measured using the subject-rated Functional Assessment of Cancer Treatment-Lung Cancer Subscale (FACT-LCS) which included 7 items specific to lung cancer.

Statistical Considerations

A two-sided, $\alpha = 0.05$ level, log-rank test, stratified by PS (0 or 1) and intended on-study taxane (docetaxel or paclitaxel), was used to compare the PFS of subjects randomized to cetuximab+T/C to that of subjects randomised to T/C alone. The study required at least 510 events (IRRC progressions or deaths) to ensure that the log rank test would have at least at least 90% power at the 5% level for rejecting the null hypothesis, given a true hazard ratio of 0.75. The clinical cut-off had to be at least 5 months after the randomization of the last subject. A sample size of 660 randomised subjects was chosen to obtain the 510 events.

Survival analyses was planned to be performed after at least 558 subjects had died, which, assuming a true hazard ratio of 0.8, would ensure 75% power for detecting a difference in survival at the 5% level between treatment arms. At the request of the FDA and after the study was already underway, the sponsor agreed to analyse survival at the time of the PFS final analysis, in addition to after 558 deaths.

Subjects were randomised in a 1:1 ratio to receive cetuximab+T/C or T/C alone. Randomisation was stratified by study site, PS (0 or 1) and intended on-study taxane. The taxane could be either paclitaxel or docetaxel, depending on investigator preference and had to be chosen prior to randomisation and could not be revised. Randomisation was achieved using an IVRS. Unlike EMR 62 202-046, there was no stratification by disease stage. This was an open label study.

Efficacy analyses were conducted on the all randomised data set (ITT population). PFS, based on IRRC assessments, was defined, as in FLEX, as the time from randomisation until disease progression or death. The primary analysis was a comparison of PFS between treatment arms by means of a two-sided, $\alpha = 0.05$ level, log-rank test, stratified by PS (0 or 1) and intended on-study taxane (docetaxel or paclitaxel) as recorded at the time of randomisation. Other analyses included Kaplan-Meier estimates of the PFS distribution in each arm and estimates of the hazard ratio (with 95% CI) of cetuximab+T/C over C/T. The HR was estimated by means of a stratified Cox's proportional hazard model with treatment as the single covariate. In addition, the HR was also estimated in a multivariate model in which the treatment effect was adjusted for baseline liver metastases, 4 or more disease sites at baseline, and prior lung surgery. The analyses of overall survival were similar to those done on PFS.

The primary analyses of tumour response were also based on the IRRC assessments. Response rate (and disease control rate) was compared between arms using a CMH (α =0.05 level) test stratified by PS (0 or 1) and intended on-study taxane. A multivariate logistic regression analysis was performed to assess the treatment effect after adjustment for the same prognostic factors as used in the multivariate Cox model for PFS.

Results

Subjects were randomised between December 2004 and November 2006 and the clinical cut-off was April 2007.

There were 755 subjects enrolled, 676 randomised with 645 treated, 325 in the cetuximab+T/C group and 320 in the T/C group. The most common reasons for not

randomising subjects were not meeting inclusion criteria (62.0%) and subject request (21.5%). At the time of data cut-off for the clinical study report, only 13 subjects remained in the study, all in the cetuximab+T/C group. The ITT population consisted of 338 subjects in each treatment group, 31 subjects in the ITT group did not receive study treatment (13 in cetuximab+T/C and 18 in T/C groups). Major protocol deviations were reported in 6/338 (1.8%) of the cetuximab+T/C group and 1/338 (0.3%) of the T/C group. All subjects were included in the efficacy and safety analyses.

There were 4 protocol amendments. Amendment 1 permitted pharmacogenetic studies and amendment 2 allowed more flexible premedication regimens for taxanes. Amendment 3 resulted from discussions with the FDA. This changed the study from Phase II to Phase III changing the primary endpoint from response rate to PFS and increasing the sample size from 300 to 660. Amendment 4 allowed concurrent palliative radiation of metastatic bone lesions.

At the time of this study report there were 429 deaths (214 cetuximab+T/C and 215 T/C). Mature survival data (at 558 deaths) was not provided in a CSR but was presented in the sponsor's *Clinical Overview* with an associated table.

Baseline data

In the ITT population, the majority were Caucasian (88.2%), male (58.6%) and the median age was 65 years. The treatment groups were similar with respect to ethnic group, age, gender, smoking status, NSCLC disease characteristics and prior therapies. As with EMR 62 202-046, most subjects had an adenocarcinoma (50.9% of cetuximab+T/C and 53.8% T/C) followed by squamous cell carcinoma (19.8% cetuximab+T/C and 19.2% T/C). Grade 3 or 4 pre-treatment AEs were reported for 8.3% of subjects in the cetuximab+T/C group and 11.8% of subjects in the T/C group; most were respiratory or general disorders.

Administration of cetuximab did not reduce the administration of chemotherapy based on the percentage of subjects who received at least 80% of the planned CTX dose in the cetuximab+T/C group (paclitaxel 82.5%, docetaxel 79.9%, carboplatin 73.5%) relative to the T/C group (paclitaxel 82.0%, docetaxel 89.3%, carboplatin 81.3%). Subjects in both groups completed a median of 4 cycles of CTX. The percentage of subjects who received subsequent anticancer therapy during follow up was similar in the groups (53.8% cetuximab+T/C; 56.8% T/C). Concomitant medication use was also similar between groups.

Primary outcome

Progression Free Survival

Based on IRRC assessment, there were 284/338 (84.0%) events in the cetuximab+T/C group and 263/338 (77.8%) in the T/C group. The median PFS time was 4.4 months (95% CI: 4.1, 5.1) and 4.2 months (95% CI: 3.9, 4.5) in the cetuximab+T/C and T/C groups respectively. PFS was not significantly better (p=0.236) in the cetuximab group and the HR was 0.90 (95%CI: 0.76, 1.07) and altered little after adjustment for prognostic factors (Table 6). Three, 6 and 9 month PFS rates based on IRRC assessments were similar for the cetuximab+T/C and T/C groups.

Table 6: Study CA225099 – summary of PFS

Summary of Progression-free Survival Based on the IRRC Assessments: All Randomized Subjects

	Cetuximab+ Taxane+Carboplatin N=338	Taxane+Carboplatin N=338
Number of events/Number of subjects (%)	284/338 (84.0)	263/338 (77.8)
Median (months) (95% CI) (1)	4.40 (4.11, 5.06)	4.24 (3.94, 4.63)
Log-rank p-value (2)	0.2358	
Hazard ratio (95% CI) (3) (4)	0.902 (0.761,1.069)	

(1) Confidence interval computed using the Brookmeyer and Crowley method
(2) Stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization
(3) Ratio of cetuximab+taxane+carboplatin to taxane+carboplatin
(4) Estimated using a Cox regression model stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization and with treatment as the only covariate

Subpopulation analyses of PFS suggested a positive effect by adding cetuximab to T/C CTX for those with squamous cell carcinoma (HR 0.70, 95%: CI 0.47, 1.05), ECOG PS of 0 (HR 0.73, 95% CI: 0.54, 0.99) and treatment with docetaxel (HR 0.78, 95% CI: 0.61, 0.99). The median PFS for subjects with baseline PS of 0 was 5.8 months for cetuximab+T/C and 5.3 months for T/C, and for subjects with squamous cell NSCLC was 5.2 and 4.3 months respectively. There was no treatment difference in those with adenocarcinoma and all other subgroups did not reach statistical significance.

An analysis of PFS as based on investigator assessment (rather than IRRC) and therefore not blinded found that the median PFS time was 4.3 months and 3.8 months in the cetuximab+T/C and T/C groups respectively with a statistically significant HR of 0.77 (95%CI 0.65, 0.90, p= 0.002).

Secondary outcomes

Tumour response

Based on IRRC assessment, there was a tumour response rate of 87/338 (25.7%) in the cetuximab+T/C group and 58/338 (17.2%) in the T/C group, odds ratio (OR) of 1.68 (95% CI 1.15, 2.44 p=0.007) (Table 7). The OR showed little change after adjustment for the prognostic factors of liver metastases, number of disease sites and prior lung surgery.

Table 7: Study CA225099 – tumour response

Tumor Response Based on the IRRC Assessment: All Randomized Subjects

	Cetuximab+Taxane+ Carboplatin N = 338	Taxane+Carboplatin N = 338
Best response, number of subjects (%)		
Complete response	0	1 (0.3)
Partial response	87 (25.7)	57 (16.9)
Stable disease	143 (42.3)	154 (45.6)
Progressive disease	54 (16.0)	56 (16.6)
Unable to determine	54 (16.0)	70 (20.7)
Response rate[a]	87/338 (25.7)	58/338 (17.2)
(95% CI)[b]	(21.2, 30.7)	(13.3, 21.6)
Odds ratio[c,d] (95% CI)	1.675 (1.152, 2.436)	
CMH p-value for difference in response[d]	0.0066	

[a] Number of responders (complete response + partial response) / Number of subjects

[b] Confidence interval using the Clopper and Pearson method

[c] Ratio of C/T/C to T/C

[d] Stratified by PS (0 vs 1) and intended on-study taxane (paclitaxel vs docetaxel) at randomization

Overall survival

At data cut-off, 429 of 676 randomised subjects had died, 214/338 in cetuximab+T/C and 215/338 in the T/C group. The median survival was 9.5 and 8.4 months in the cetuximab+T/C and T/C groups respectively and was not significantly different (HR of 0.93, 99.9% CI: 0.64, 1.36 p=0.46). The OS HR was little changed after adjustment for the prognostic factors of liver metastases, 4 or more disease sites and prior lung surgery. Final data were presented in the sponsor's *Clinical Summary* (data cut-off August 2008) and were little changed, with a median survival of 9.7 and 8.4 months and 227/338 and 287/338 deaths in the cetuximab+T/C and T/C groups respectively. The final OS HR of 0.89 was not statistically significant (95% CI: 0.75, 1.05, p=0.17).

Time to treatment failure

Time to treatment failure was not reported in the CSR. It was however reported in the *Clinical Summary* as a *post hoc* analysis. The median TTF was 3.7 months in the cetuximab+T/C group and 2.8 months in the T/C group, with a HR of 0.72 (95% CI 0.62, 0.85, p<0.0001).

KRAS mutational analysis

The Kirsten rat sarcoma gene (KRAS) is a proto-oncogene and mutations of the KRAS gene at certain hotspots result in its activation. In NSCLC the incidence of KRAS mutations is in the range of 15-20% with more adenocarcinomas affected (up to 30%) while the mutation is rare in squamous cell carcinoma (about 5%). The KRAS mutation status helps predict clinical outcome of treatment with the anti-EGFR antibody in patients with metastatic colorectal cancer (CRC) where those with KRAS wild type tumours have a significantly greater benefit from anti-EGFR therapy than those patients with KRAS mutated tumours. (Amado et al, 2007; Benvenuti et al, 2007; Bokemeyer et al, 2008; Cervantes et al, 2008;De

Roock et al, 2007; Di Fiore et al, 2007; Frattini et al, 2007; Khambata-Ford et al, 2007; Lievre et al, 2008; Lievre et al, 2006; Van Cutsem et al, 2008).[4,5,6,7,8,9,10,11,12,13,14]

In the two Phase III studies, KRAS mutational status was assessed in a subset of participants. Status was assessable in 379 subjects (31% of samples were not able to be evaluated). This resulted in mutation status being available for 33.7% (379/1125) of all trial subjects. In CA225099, tumour specimens were evaluable in 202/676 (29.9%) of all trial subjects.

Baseline characteristics of the KRAS evaluable subjects were comparable to the ITT populations in both studies. In EMR 62202-046, KRAS mutations were found in 72/379 (19%) of subjects. In CA225099, KRAS mutation rate was found in 35/202 (17.3%) subjects.

The results by KRAS mutation status are summarised for OS, PFS and ORR in Table 8. In study EMR 62 202-046, the OS time HR was 0.94 in KRAS evaluable subjects, 0.92 in those with KRAS wild type, and 1.04 in those with KRAS mutant tumours. In study CA225099, the PFS time HR was 0.94, 0.95 and 0.88 in the KRAS evaluable, KRAS wild type and KRAS mutant groups respectively. For NSCLC patients with a KRAS wild type tumour there was no improvement in outcomes (as measured by OS, PFS or ORR) when treated with cetuximab and CTX compared to those with a KRAS mutant tumour.

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Table 8: Hazard ratios for OS, PFS and ORR by KRAS status

Hazard Ratios for Overall Survival Time and Progression-free Survival Time, and Objective Response Rates in Studies EMR 62 202-046 and CA225099 (ITT and KRAS-evaluable populations)

Population	N		Hazard ratio			Objective response rate (%)			
			OS time	PFS time		EMR 62 202-046		CA225099	
	EMR 62-202-046	CA 225099	EMR 62-202-046	EMR 62-202-046	CA 225099	Cet + CTX	CTX	Cet + CTX	CTX
ITT	1125	676	0.87	0.94	0.90	36.4	29.2	25.7	17.2
KRAS									
Evaluable	379	202	0.94	0.92	0.97	36.8	26.3	32.7	22.1
Wild-type	307	167	0.92	0.95	1.07	37.2	27.2	32.9	25.6
Mutant	72	35	1.04	0.88	0.64	35.1	22.9	30.8	9.1

Cet=cetuximab, CTX=chemotherapy, ITT=intent-to-treat, OS=overall survival, PFS=progression-free survival

Evaluator's Comments

Unlike in metastatic colorectal cancer, KRAS mutation status is unlikely to be predictive of a positive response to cetuximab therapy in NSCLC.

Analysis performed across trials (pooled analysis and meta-analysis)

The sponsor provided a PowerPoint presentation of a meta-analysis of the four controlled studies which included 2018 subjects. From this meta-analysis, the median OS improvement was 0.9 months, 10.3 months in the cetuximab+CTX group and 9.4 months in the CTX group. The resultant OS HR was statistically significant at 0.88 (95% CI: 0.80-0.97, p=0.010). When examining the subgroup of Caucasians, the OS HR was 0.84 (95% CI: 0.75-0.93, p<0.001) with an improved survival of 1.1 months (9.9 vs 8.8 months).

The meta-analysis states there is a statistically significant improvement for PFS with a HR of 0.90 (95% CI: 0.81-0.99, p=0.036). The meta-analysis for ORR notes an overall OR of 1.46 (95% CI: 1.20-1.78, P<0.001).

Evaluator's Comments

As the formal meta-analysis methodology and report has not been provided it is not possible to draw definitive conclusions from data in this PowerPoint presentation. Given that 56% (1125/2018) of the subjects in the meta-analysis came from trial EMR 62202-046, which had the only significant result on OS, it is likely that results seen have been driven by the size of this study. The meta-analysis presentation states a statistically significant result for PFS HR. This needs to be verified as PFS HRs in all four trials individually were non-significant with all 95% CIs crossing unity.

Supportive studies

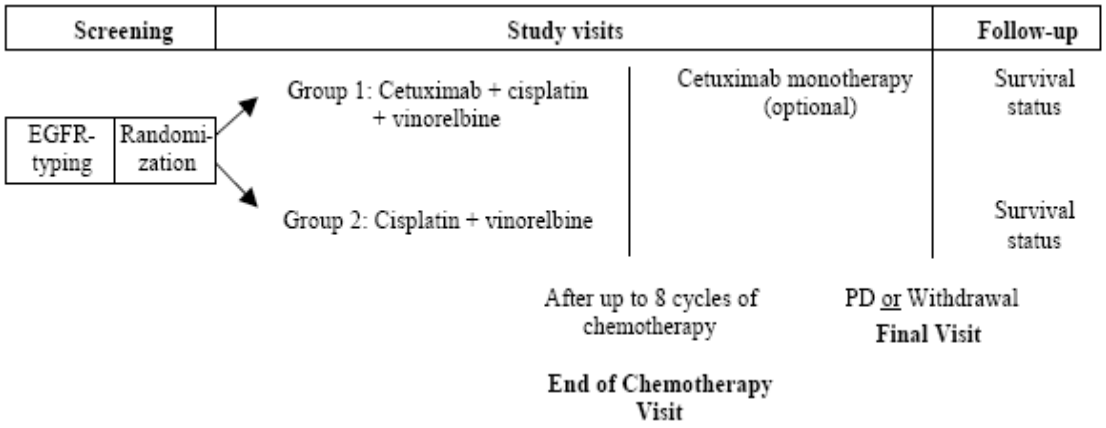
EMR 62202-011 (LUCAS)

An open, randomized Phase II pilot study of cetuximab in combination with cisplatin and vinorelbine or cisplatin and vinorelbine alone, to evaluate their efficacy, safety and pharmacokinetics in patients with advanced epidermal growth factor receptor (EGFR) positive non-small cell lung cancer (NSCLC).

Methods

The study was conducted between March 2002 and October 2004 (survival cut-off) at 17 centres (15 enrolled subjects) in 6 European countries. The study design is illustrated in Figure 4. Subjects were pre-screened for EGFR status in tumour tissue. After randomisation treatment with study medication continued until progressive disease (PD) or unacceptable toxicity for a maximum of 8 cycles (6 months). A final visit was at PD, withdrawal or at the end of the study 6 months post last subject randomisation. Subjects were then followed for survival status and information on further treatments.

Figure 4: EMR 62 202-011 Study Design



Objectives

The primary objective was to determine the objective response rate (ORR) to cetuximab administered in combination with cisplatin and vinorelbine and to cisplatin and vinorelbine alone in patients with advanced EGFR positive NSCLC. The secondary objectives included safety, time to disease progression, median duration of response, TTF and PK.

Study participants

The main inclusion criteria were: ≥18 years of age; diagnosis of histologically confirmed NSCLC, Stage IV or Stage IIIb with documented malignant pleural effusion; presence of at least one unidimensionally measurable lesion; if the index lesion was in an irradiated area, progression of that lesion had to be demonstrated prior to entry; immunohistochemical evidence of EGFR expression; life expectancy of ≥3 months; Karnofsky performance status (KPS) ≥70 at study entry; neutrophils ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, haemoglobin ≥9 g/dL; bilirubin level <1.5 x ULN, AST and ALT ≤3 x ULN (5 x ULN if liver metastases are present), and serum creatinine ≤1.25 ULN and/or creatinine clearance ≥60 mL/min.[15] The main exclusion criteria were any prior chemotherapy, brain metastases, and concurrent chemotherapy, immune or hormone therapy.

[15] Another commonly used performance scale is the Karnofsky performance status. It is similar to the WHO scale, but goes to up 100. Selected levels are shown below.

- 100 – you don't have any evidence of disease and feel well
- 80 – you have some signs or symptoms and it takes a bit of effort to carry on as normal
- 60 – you need help from time to time but can mostly care for yourself
- 40 – you always need help to care for yourself
- 20 – you are ill, in hospital and need a lot of treatment
- 10 – you are very ill and unlikely to recover

Treatments

All treatments were IV infusions. Cetuximab was administered as an initial dose of 400 mg/m2, followed by weekly doses of 250 mg/m^2. Cisplatin was administered at a dose of 80 mg/m^2 on Day 1 of a 3 week cycle and vinorelbine at a dose of 25 mg/m^2 on Day 1 and Day 8 of the 3 week cycle. Up to a maximum of 8 cycles (6 months) of chemotherapy were administered. Cetuximab could then continue weekly as monotherapy for those in the cetuximab+C/V group until PD or unacceptable toxicity occurred.

Outcomes/endpoints

The primary outcome variable for the study was ORR according to the "Response Criteria in Solid Tumors (RECIST)" as determined by the study investigators.[16] This was defined as the best overall tumour response from the start of treatment until disease progression or recurrence. The best overall response rate consisted of those whose best response was CR or PR. Response was defined based on assessment of target and non target lesions as per definitions in Table 9. Secondary efficacy endpoints, also based on investigator assessment, included best overall unconfirmed response, OS, PFS, duration of response, time to response and TTF.

Table 9: Response definitions

Evaluation of response based on target lesions

Complete response (CR)	Disappearance of all target lesions.
Partial response (PR)	A decrease by 30% or more in the sum of the longest diameter of all target lesions taking as reference the baseline sum of longest diameter.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD i.e. a decrease of the sum of longest diameter of all target lesions by less than 30% taking the baseline measurement as reference or an increase of this diameter by less than 20 % taking as reference the smallest sum of longest diameter since treatment started.
Progressive disease (PD)	An increase by 20% or more in the sum of the longest diameter of all target lesions taking as reference the smallest sum of longest diameter recorded since the treatment started.

Evaluation of response based on non-target lesions

Complete response (CR)	Disappearance of all non-target lesions.
Incomplete response (IR) / stable disease (SD)	The persistence of one or more non-target lesion(s)
Progressive disease (PD)	The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

Statistical Considerations

The sample size was fixed without power calculations. A response rate of 25 to 30% was expected and a sample size of 40 subjects per group chosen. In order to recruit 80 EGFR positive patients, it was estimated that about 180 patients had to be screened.

Participants were randomised using an IVRS in a 1:1 ratio between the cetuximab+C/V or cisplatin/vinorelbine (C/V) groups. The study was open label.

Efficacy analyses were conducted on the ITT and per protocol populations. For the primary outcome, best overall response rate point estimates and 2-sided Clopper-Pearson exact 95% CI were calculated. Kaplan-Meier curves were presented for all time to event variables (median, 2-sided 95% CI). Progression free survival rates and survival rates were calculated based on Kaplan-Meier estimates. No formal statistical hypotheses were tested for secondary variables.

Results

Participant flow

Overall, 129 subjects were pre-screened. EGFR status was available in 114 subjects of whom 103 (89.6%) were EGFR expressing. Of these 103 subjects, 86 were randomised (ITT population): 43 to cetuximab+C/V and 43 to C/V treatment. There were 17/103 (16.5%) EGFR expressing subjects who failed to meet eligibility criteria. There were major protocol deviations in 7 (8.1%) of subjects, 4 in the cetuximab+C/V group and 3 in the C/V group. There were 2 randomised patients (1 in each group) who did not have malignant pleural effusions (eligibility deviation); these were included in the ITT population.

Baseline data

The median age of subjects was 58 years, all were Caucasian and there were more males than females (74.4% vs 25.6%). Disease characteristics, including baseline KPS, were similar between treatment groups. The type of tumour and staging was similar between groups; overall 36 (41.9%) patients had a squamous cell carcinoma and 37 (43.0%) patients had an adenocarcinoma. Target lesion evaluation was similar, as was involvement of other organs and EGFR staining. Previous anticancer therapy occurred in 29.1% of subjects; 26.7% with surgery and 2.3% with radiotherapy, this was similar between groups. There were 23 (53.5%) patients from the cetuximab+C/V group and 29 (67.4%) patients from the C/V group who received anticancer post-study therapy. Of these the best response for post-study therapy was CR in 2 (2.3%) patients (both in the cetuximab+C/V group) and PR in 6 patients (3 in each treatment group).

Outcomes

Results are summarised in Table 10. The ORR was 34.9% (95% CI: 21.0, 50.9) in the cetuximab+C/V group and 27.9% (95% CI: 15.3, 43.7) in the C/V group with an odds ratio of 1.38 (95% CI: 0.55, 3.46). Higher responses for those treated with cetuximab+C/V compared to C/V were seen in those <60 years (41.7% vs 25.9%), with adenocarcinoma (35.0% vs 17.7%) and with only one organ involved (75.0% vs 33.3%).

Table 10: Efficacy results for Study EMR 62 202-011 (ITT population)

Response variable	Cetuximab + CTX N=43		CTX alone N=43	
		95% CI		95% CI
Primary variable				
Objective response rate, % subjects	34.9	[21.0, 50.9]	27.9	[15.3, 43.7]
Odds ratio	1.38 [0.55, 3.46]			
Secondary variables				
Progression-free survival time, median (months)	5.0	[4.5, 5.8]	4.6	[2.5, 6.0]
Hazard ratio	0.71 [0.4, 1.2]			
Time to treatment failure, median (months)	3.4	[2.9, 5.0]	2.9	[1.8, 4.5]
Hazard ratio	0.68 [0.4, 1.1]			
Overall survival time, median (months)	8.3	[6.1, 9.9]	7.3	[5.6, 9.5]
Hazard ratio	0.71 [0.5, 1.1]			

CI=confidence interval, CTX=chemotherapy

Skin toxicity occurred in 37 (86.0%) of the cetuximab+C/V group and 3 (7.0%) of the C/V group. A best overall response rate of 100% (5/5) was achieved for patients with skin toxicity severity of Grade 3 (no Grade 4 severity reported) in the cetuximab+C/V group.

The median PFS was 5.0 months (95% CI: 4.5, 5.8) for the cetuximab+C/V group and 4.6 months (95% CI: 2.5, 6.0) for the C/V group, with a HR of 0.71 (95% CI: 0.4, 1.2). TTF was 3.4 months (95% CI: 2.9 to 5.0) and 2.9 months (95% CI: 1.8 to 4.5) for the cetuximab+C/V and C/V groups respectively with a HR of 0.68 (95% CI: 0.4, 1.1). At data cut-off, 88.4% of subjects had died (36 in the cetuximab+C/V group and 40 in the C/V group).

The median survival time for cetuximab+C/V group was 8.3 months (95% CI: 6.1 to 9.9) versus 7.3 months (95% CI; 5.6 to 9.5) in the C/V group with a HR of 0.71 (95% CI: 0.5 to 1.1).

CA225100

A randomized multicentre Phase II study of gemcitabine/platinum/cetuximab versus gemcitabine/platinum as first line treatment for subjects with advanced/metastatic non-small cell lung cancer.

Methods

An abbreviated *Clinical Study Report* was provided in the submission (data cut-off May 2006) together with an addendum to the CSR (final data cut-off December 2006). The study was conducted between January 2005 to May 2006 at 41 sites in the USA and Canada. The study was originally designed to enrol 300 subjects. However after approximately 30 subjects were enrolled, it was decreased to 120 to reflect a change in regulatory strategy since the chemotherapy regimen used in this study (gemcitabine/platinum) did not reflect the current standard of care in the US.

Objectives

The primary objective of the study was to estimate objective response rate (ORR) in each treatment arm (cetuximab/gemcitabine/platinum [cetuximab+G/P] and gemcitabine/platinum [G/P]). Secondary objectives included an estimation of disease control rate, time to response, duration of response, PFS, OS and safety.

Study participants

Subjects were eligible for inclusion if they had: histologically or cytologically documented non-small cell lung cancer (NSCLC); Stage IV disease or Stage IIIB disease with malignant pleural effusion, or recurrent disease following radiation therapy or surgical resection; PS of 0 or 1; and had not received prior chemotherapy, including adjuvant chemotherapy for NSCLC

Treatments

Cetuximab was administered IV at weekly intervals at an initial dose of 400 mg/m^2 and then subsequent weekly doses at 250 mg/m^2. Prior to randomisation, the investigator chose the on-study platinum chemotherapy agent – either cisplatin or carboplatin. Chemotherapy treatment in Week 1 was gemcitabine 1250 mg/m^2 IV + cisplatin 75 mg/m^2 or gemcitabine 1000 mg/m^2 IV + carboplatin (AUC=5) IV and in subsequent weeks was gemcitabine 1250 mg/m^2 IV (in conjunction with cisplatin) or gemcitabine 1000 mg/m^2 IV (in conjunction with carboplatin). Each cycle of therapy was 3 weeks.

Treatment continued until progressive disease (PD) was documented, intolerable toxicity occurred or for a maximum of 6 cycles in the G/P arm. Cetuximab could be continued as monotherapy post CTX as in other studies. Dose reductions in any of the drugs were allowed based on tolerability. If one or more of the study drugs was discontinued because of toxicity, the other agent(s) could be continued.

Outcomes/endpoints

The primary study endpoint was ORR and this was defined as the proportion of subjects who achieved a best response of confirmed CR or PR as defined by the sponsor's response assessment. Secondary endpoints included disease control rate, duration of response, time to response, PFS, OS, symptom response and symptomatic progression.

The sponsor conducted a centralised review, based on investigator tumour evaluations, of tumour response and progression to determine best response and date of progression.

Evaluator's Comments

There is no mention in the CSR whether this centralised review was blinded or not.

Statistical Considerations

A sample size of 60 subjects per treatment group was allocated. There were no formal power calculations undertaken. A response rate in the range of 22 to 47% was expected with a rate of 7% greater in the cetuximab group based on the previous Phase II study EMR 62 202-011 (LUCAS).

Subjects were randomised in a 1:1 ratio to receive cetuximab+G/P or G/P via an IVRS. Randomisation was stratified by site, ECOG performance status (PS) 0 or 1, and the intended on-study platinum agent (choice of cisplatin or carboplatin was made before randomisation). This was an open label study.

Response rates (objective response rate and disease control rate) were estimated along with their exact two-sided, 95% CI calculated using the method of Clopper and Pearson. For time to event variables (PFS, OS, and duration of response), the Kaplan-Meier method was used to estimate the median and its associated two-sided 95% CI. Analyses of demography, baseline characteristics and efficacy were performed on the data set of all randomised subjects (n=131).

Results

Participant flow

There were 32 sites in the US which randomised 131 subjects, 65 to cetuximab+G/P and 66 to G/P treatment. In the cetuximab+G/P group, 7 subjects received cisplatin, and 57 received carboplatin, while in the G/P group 12 received cisplatin and 54 carboplatin.

Major eligibility violations were identified in 2 subjects in the cetuximab+G/P arm; 1 had Stage IIIB disease but did not have malignant pleural effusion and 1 did not have bidimensionally measurable disease. Major protocol deviations were identified in 5 subjects (4 cetuximab+G/P, 1 G/P). Two subjects were not pre-medicated prior to the first cetuximab dose and 3 started therapy more than 6 days after randomisation. All 7 subjects were included in the analyses of efficacy and safety.

There were 2 protocol amendments, the first adding blood sampling for future pharmacogenetic testing. The main changes with the second amendment were a decrease in the sample size from 300 to 120 subjects and removal of the IRRC.

Baseline data

There were more females in the cetuximab+G/P group (61.5%) compared to the G/P group (50%), the median age was similar (66 years), as was ECOG PS and ethnicity (83% White). Disease characteristics were similar between groups, at baseline 110/131 (84%) subjects had Stage IV disease, 46.6% with adenocarcinoma and 21.4% with squamous cell carcinoma. For previous treatment, 28% of cetuximab+G/P and 18% of G/P subjects had prior surgery and 12% of cetuximab+G/P and 18% of G/P subjects had prior radiotherapy.

Adding cetuximab to G/P chemotherapy did not result in reduced ability to administer the chemotherapy. The number of cycles of chemotherapy, duration of therapy and dose intensity was similar between groups. The median number of cetuximab infusions was 12.5 (range 1 to 45).

Outcomes

Results for ORR, PFS and OS are summarised in Table 11. The ORR was 18/65 (27.7%) in the cetuximab+G/P group and 12/66 (18.2%) in the G/P group, with a difference in favour of the cetuximab group of 9.5%, (95% CI: -4.8, 23). The odds ratio for ORR was 1.72 (95% CI: 0.75, 3.92).

Table 11: Efficacy results for Study CA225100 (ITT population)

Response variable	Cetuximab + CTX N=65		CTX alone N=66	
		95% CI		95% CI
Primary variable				
Objective response rate, % subjects	27.7	[17.3, 40.2]	18.2	[9.8, 29.6]
Odds ratio	1.72 [0.75, 3.92]			
Secondary variables				
Progression-free survival time, median (months)	5.1	[4.2, 6.0]	4.2	[3.8, 5.5]
Hazard ratio	0.80 [0.55, 1.16]			
Overall survival time, median (months)	12.0	[8.8, 15.2]	9.3	[7.4, 11.8]
Hazard ratio	0.84 [0.55, 1.27]			

CI=confidence interval, CTX=chemotherapy

Disease control rate was similar in the two groups 49/65 (75.4%) and 49/66 (74.2%) in the cetuximab+G/P and G/P groups respectively. The median time to response (1.6 months cetuximab+G/P, 1.4 months G/P) was similar in both arms, as was the median duration of response (5.1 months cetuximab+G/P, 4.9 months G/P). At the time of final data cut-off, 53/65 (81.5%) of the cetuximab+G/P group and 60/66 (90.9%) of the G/P group had progressed with a median PFS of 5.1 and 4.2 months respectively. The median OS was 12 months for the cetuximab+G/P group and 9.3 months for the G/P group with a HR of 0.84 (95% CI: 0.55, 1.27).

IMCL CP02-9932 and IMCL CP02-9925

These are two open label, single group, Phase Ib/IIa studies of cetuximab in combination with chemotherapy in subjects with advanced NSCLC. The first study was in combination with carboplatin and paclitaxel (C/P) and the second with carboplatin and gemcitabine (C/G). The studies were conducted in the USA between 2000 and 2003.

The primary objective of both studies was to assess the safety profile of cetuximab in combination with the CTX regimen and secondary objectives were to determine the anti-tumour activity, including response rate and duration of response and to assess the effect of cetuximab on the PKs of the chosen chemotherapy.

Subjects in both studies were at least 18 years of age with pathologically confirmed, unidimensionally measurable, chemotherapy-naive, Stage IV NSCLC with immunohistochemical evidence of EGFR expression (≥1+) and an ECOG PS ≤ 2 (study with C/P) or a Karnofsky PS score of 80 to 100 (study with C/G).

Treatment consisted of an initial cetuximab dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. In the first study, carboplatin (AUC=6) and paclitaxel (225 mg/m^2) were administered in 3 week cycles. In the second study, gemcitabine (1000 mg/m^2 on Day 1 and 8) and carboplatin (AUC=5, on Day 1) were administered in 3 week cycles. Treatment was continued until disease progression or unacceptable adverse events.

Tumour response was evaluated via unidimensional measurement (MRI or CT scan) using RECIST criteria at completion of every 2 cycles of CTX.

Study IMCL CP02-9932 (cetuximab+C/P) enrolled 32 subjects and 31 were treated. There were 8/31 partial responses, no complete responses, giving an ORR of 25.8% (95% CI: 11.9, 44.6). The disease control rate was 67.7% (21/31) (95% CI: 48.6, 83.3). The median duration of response was 143 days (4.7 months), the duration of disease control was 186 days, and the median time to disease progression was 168 days. The median PFS was 149 days, median OS was 335 days (11 months) and the OS rate calculated at 12 months was 40.2% (95% CI: 23.0, 56.9).

Study IMCL CP02-9925 (cetuximab+C/G) enrolled 35 subjects. There were no complete responses and partial responses occurred in 8/35 subjects giving an ORR of 22.9% (95% CI: 10.4, 40.1). An additional 20 patients had stable disease producing a disease control rate of 80.0% (95% CI: 63.1. 91.6). The median duration of response was 184 days. The median time to disease progression was 167 days, median PFS (all deaths counted) was 174 days, and the median OS was 310 days. The 1 year survival rate was 45.7% (95% CI: 28.9, 61.0).

Evaluators overall conclusions on clinical efficacy

There were 4 randomised controlled studies presented in the submission, 2 Phase III (EMR 62 202-046, CA225099) and 2 Phase II (CA225100 and EMR 62 202-011). These studies evaluated a total of 2018 subjects, which is considered a sufficiently large population to be able to draw efficacy conclusions in this indication. The studies enrolled

men and women with histologically or cytologically confirmed, advanced (Stage IIIb with malignant pleural effusion or Stage IV) NSCLC. Subjects needed to have a baseline ECOG PS of 0 or 1 in CA225099 and CA225100, KPS of 70-100 in EMR 62202-011, or ECOG PS of 0 to 2 in EMR 62 202-046. EGFR expression on tumour tissue was required for one of the Phase III (EMR 62 202-046) and one of the Phase II studies (EMR 62 202-011) but was not required on the other Phase III (CA225099) or Phase II study (CA225100). Index lesions needed to be bidimensionally measurable, except in EMR62 202-011 where they were unidimensionally measurable. Subjects with prior chemotherapy exposure and brain metastases were excluded.

All studies were open label due to the skin reactions known to occur with cetuximab. Studies were continued until progressive disease or unacceptable toxicity. Platinum based chemotherapy was given for 6 cycles in all studies, except for the Phase II EMR 62 202-011 where it was given for 8 cycles, and afterwards cetuximab could be continued as monotherapy in the cetuximab+CTX group. Tumour assessments, by CT scan or MRI were conducted 6 weekly. Only the Phase III study CA225099 had an IRRC, the other 3 trials used the investigator's assessments of tumour response.

The design of the studies was in accordance with current TGA-adopted EU guidelines for anticancer medicinal products and the pivotal Phase III trials used the clinically relevant endpoints of either OS or PFS as primary and secondary outcome measures.[17] The main efficacy variables are summarised in Table 12.

Table 12: Key efficacy variables in the randomized controlled studies

Variable	EMR 62 202-046	CA225099	CA225100	EMR 62 202-011
OS time	Primary	Secondary	Secondary	Secondary
PFS time	Secondary	Primary	Secondary	Secondary
TTF	Post-hoc sensitivity analysis	Post-hoc sensitivity analysis	Not determined	Secondary
ORR	Secondary	Secondary	Primary	Primary

ORR=objective response rate, OS=overall survival, PFS=progression-free survival, TTF=time to treatment failure

The main efficacy results from the 4 controlled studies are presented in Table 13.

[17] EMEA, Committee for Medicinal Products for Human Use (CHMP), 14 December 2005. Guideline on the Evaluation of Anticancer Agents in Man, CPMP/EWP/205/95/Rev. 3/Corr.

Table 13: Summary of the most important efficacy results in the randomised controlled studies

Efficacy variable / statistic	EMR 62 202-046		CA225099		CA225100		EMR 62 202-011	
	Cet + CTX N=557	CTX N=568	Cet + CTX N=338	CTX N=338	Cet + CTX N=65	CTX N=66	Cet + CTX N=43	CTX N=43
Median OS time, months [a]	11.3	10.1	9.7 (9.5)	8.4 (8.4)	12.0	9.3	8.3	7.3
p-value (stratified log-rank test)	0.044		0.169 (0.464)		Not reported		Not reported	
Hazard ratio	0.87		0.89 (0.93)		0.84		0.71	
Median PFS time, months	4.8	4.8	4.4	4.2	5.1	4.2	5.0	4.6
p-value (stratified log-rank test)	0.387		0.236		Not reported		Not reported	
Hazard ratio	0.94		0.90		0.80		0.71	
Median TTF, months	4.2	3.7	3.7	2.8	Not reported		3.4	2.9
p-value (stratified log-rank test)	0.015		<0.0001				Not reported	
Hazard ratio	0.86		0.72				0.68	
ORR, % subjects	36.4	29.2	25.7	17.2	27.7	18.2	34.9	27.9
p-value (CMH test)	0.010		0.007		Not reported		Not reported	
Odds ratio	1.39		1.68		1.72		1.38	

[a] For study CA225099, the numbers for the final analysis (cut-off 1 August 2008) are given; the numbers for the interim analysis (cut-off 30 April 2007) are given in parentheses.

Cet=cetuximab, CTX=chemotherapy, CMH=Cochran-Mantel-Haenszel test, ITT=intention to treat, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, TTF=time to treatment failure

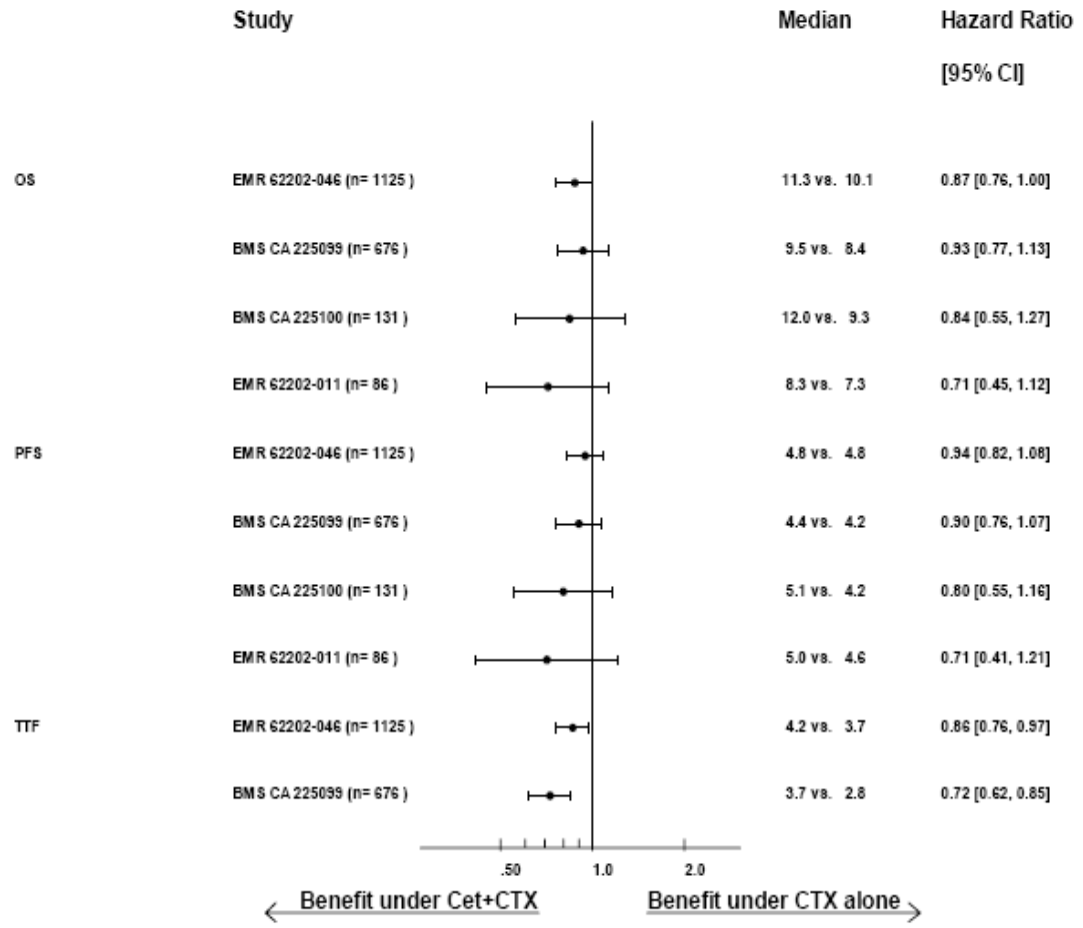
The first pivotal Phase III study EMR 62 202-046 suggests an advantage of cetuximab+CTX on the primary endpoint of OS (HR=0.87 with borderline statistical significance p=0.044) and also for ORR, but not in terms of PFS or disease control rate for patients with advanced EGFR expressing NSCLC. The overall survival benefit was modest with a median survival improvement of 1.2 months (11.3 versus 10.1 months in the cetuximab+CTX and CTX groups respectively).

In the second pivotal Phase III study CA225099, again in for advanced NSCLC though without requiring positive EGFR expression, the primary endpoint of PFS as assessed by an IRRC was not met. The PFS time was 4.4 compared to 4.2 months in the cetuximab+CTX and CTX groups respectively (HR=0.90, p=0.236). In addition, overall survival was not improved (HR=0.93, p=0.464), though an advantage was seen in ORR and TTF (which was a *post hoc* analysis). This was the only study with independent verification of tumour response/progression and given the open label nature of the studies it is important to take this into account when assessing results of this and other studies.

In the two controlled Phase II studies, results showed a modest tendency towards benefit (as measured by ORR) with cetuximab, 7% difference between treatment groups in EMR 62 202-011 and 9.5% in CA225100. These studies were small and had unblinded investigator assessment of the endpoint, thus meaningful conclusions on efficacy are hard to draw. The two Phase Ib/IIa studies both had encouraging results in terms of ORR though were both uncontrolled, small pilot studies.

For the 4 controlled studies, a diagrammatic summary of efficacy results in terms of hazard ratios for time related variables of OS, PFS and TTF, and odds ratios for ORR, are presented in Figures 5 and 6.

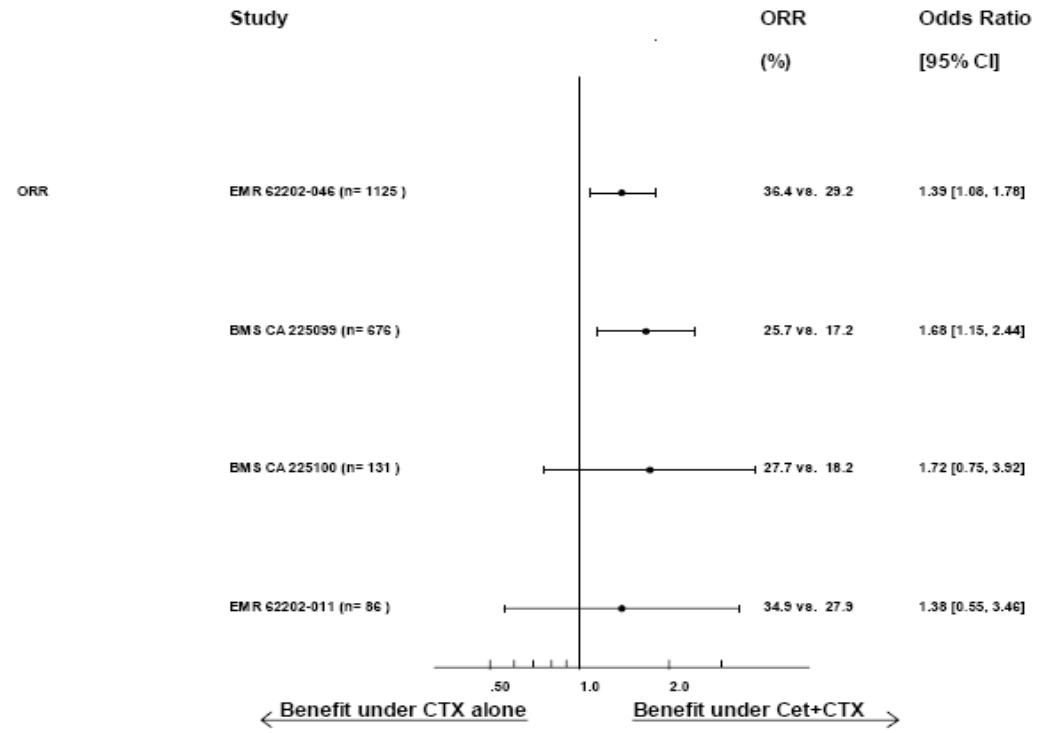
Figure 5: Overview of the OS, PFS and TTF findings in the randomised controlled studies



Note: findings for OS time in study CA225099 are based on an interim analysis after 429 events (deaths). A final analysis of survival will be performed after 558 deaths have occurred.

Cet=cetuximab, CI=confidence interval; CTX=chemotherapy, OS=overall survival, PFS=progression-free survival, TTF=time to treatment failure

Figure 6: Overview of ORR findings in the randomised controlled studies



Cet=cetuximab, CI=confidence interval, CTX=chemotherapy, ORR=objective response rate

There is evidence that cetuximab has activity against NSCLC as shown in the positive effect on ORR in the 4 main studies, though the improvement is modest (7.2% in EMR62202-046, 8.5% in CA225099, 7% in EMR 62202-011 and 9.5% in CA225100). Despite this, cetuximab has only shown borderline activity in terms of OS, with an increased median survival of 1.2 months (about 5 weeks) in one Phase III study but no OS benefit was seen in the secondary endpoint analysis of the other main Phase III trial. In addition, PFS was not shown to be improved in the trial where it was the primary endpoint nor was it improved as secondary endpoint in the other Phase III trial. These are seemingly discordant results between OS and PFS. It could be postulated that the benefit in OS, but in not in PFS, that was seen in EMR 62 202-046 was due to an effect of add-on treatments after completing chemotherapy. The data do not support this hypothesis as more subjects in the CTX alone compared to the cetuximab+CTX group received post-study anticancer treatment (60.6% versus 53.7%) with a similar use of radiotherapy and CTX but greater use of anti-EGFR therapy (26.9% versus 16.9%). Therefore it seems unlikely that additional anticancer therapy resulted in the improved overall survival.

Given these marginal efficacy data, an examination of various subgroups was undertaken by the sponsor in an attempt to identify subgroups of patients who may benefit from cetuximab treatment. In contrast to patients with metastatic colorectal cancer, KRAS mutational status did not affect efficacy results. There was some limited improvement for the Caucasian population in study EMR 62 202-046 with an OS HR of 0.80 (p=0.003) however the PFS HR was not significant at 0.93 (p=0.35).

EGFR expression was only an inclusion criteria in two trials EMR 63 303-046 and EMR 62 202-011 where expression rates were found to be 85% and 90% respectively. EGFR expression was not a requirement for inclusion in the other 2 controlled studies CA225099 and CA225100. The rate of EGFR expression is unknown in these latter 2 trials and it could be postulated that differences in the trial population's EGFR expression may

have impacted on results. However, as it appears EGFR expression occurs in the vast majority of NSCLC tumour cells on balance this is not considered to have been a major contributor to the differences in results seen in the main trials.

In terms of tumour histology, subjects with adenocarcinoma did not receive benefit from treatment with cetuximab. For those with squamous cell carcinoma, there was a suggestion of improved benefit in OS (HR 0.80, 95% CI: 0.69, 1.00) in study EMR62 202-046, although the survival time improvement was only one month (10.0 versus 9.0 months). In study CA225099, PFS was marginally increased in those with SCC (HR 0.70, 95% CI: 0.48, 1.05). Whilst there is a suggestion of improved treatment response in those with SCC, efficacy conclusions cannot be definitely drawn from such secondary analyses. A consideration of pooled efficacy data from the 2 Phase III trials could be helpful to evaluate this further.

From the 2 Phase III trials, there is only one statistically significant, albeit somewhat tenuous at p=0.044, result on a primary outcome measure of OS. This result is not supported by statistically significant results for OS in the other pivotal study or the 2 Phase II trials nor is it supported by any statistically significant improvement in the other main outcome measure of PFS where results are unconvincing in all 4 controlled studies. It is acknowledged that there is some anti-tumour activity of cetuximab in NSCLC as evidenced by the positive results on ORR (including as measured by blinded independent review in CA225099). The meta-analysis of the 4 controlled studies provided is only in a PowerPoint presentation and so cannot be fully evaluated. The results as presented do not alter the findings discussed above.

Clinically, the positive result is only of marginal benefit, with the addition of cetuximab to platinum based chemotherapy resulting in an OS increase of about 5 weeks from 10.1 to 11.3 months.

Initial Clinical Evaluation - Safety

Introduction

In the submitted clinical trials, routine safety assessments included monitoring of all adverse events (AEs), serious adverse events (SAEs), measurement of vital signs, physical examinations and clinical laboratory tests. AEs were recorded at all study visits and followed to resolution or stabilisation. Blood samples for assessment of haematology and serum chemistry were obtained at baseline, prior to each treatment cycle, at end of dosing, and every 6 weeks during follow up. In addition, blood was obtained for weekly haematologic assessment during the first 2 to 3 cycles to monitor possible myelosuppression. AE collection and documentation was more frequent in the cetuximab arm of the studies due to weekly treatment visits and the possibility of continuation on cetuximab as monotherapy. Human anti-chimeric antibody (HACA) assessment was conducted at screening and end of study visits in 2 studies.

The grading of AEs was performed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (studies EMR 62 202-011, EMR 62 202-046, IMCL CP02-9925, and IMCL CP02-9932) or NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 (studies CA225099 and CA225100).[3] Grade 5 was used only in the study reports for the studies CA225099 and CA225100, not in studies EMR 62 202-046 and EMR 62 202-011 because death was an outcome in these studies. For the purposes of comparison across studies, AEs categorised as Grade 5 events were categorised as Grade 4 events.

The AE analyses were based on treatment emergent AEs (TEAEs), which were defined as those AEs that were absent before the start of treatment and emerged during the

treatment phase or that worsened relative to the pre-treatment state. In studies EMR 62 202-046, CA225099 and CA225100, the treatment phase was defined as the time from the first administration of any study treatment until 30 days after the last dose of study treatment. In study EMR 62 202-011, AEs occurring up to 42 days after end of any study drug administration were considered as treatment emergent. It is noted that such definitions may allow a longer observation period for AEs in the subjects treated with cetuximab as they may opt for continuing treatment as monotherapy after completing CTX.

Data from the 6 clinical trials in NSCLC were used in the safety evaluation, with a total of 2036 subjects of whom 1045 were exposed to cetuximab. The data have not been pooled for analysis as different chemotherapy regimens were used in the trials. Overall safety cut-off date used in the sponsor's *Summary of Clinical Safety* was 31 March 2008.

Patient exposure

A summary of the clinical trials and subject exposure is presented in Table 14.

Table 14: Summary of the clinical trials and subject exposure

Study number	Study treatments	ITT pop	No. of subjects exposed Total	No. subjects exposed to Cetuximab	No. of subjects Control	Cetuximab duration in weeks
Active-controlled						
EMR 62 202-046 (FLEX)	Cetuximab + cisplatin + vinorelbine vs cisplatin + vinorelbine	1125	1110	548	562	Median 17.7 (Range 1-135)
CA225099	Cetuximab + taxane (paclitaxel or docetaxel) + carboplatin vs taxane (paclitaxel or docetaxel) + carboplatin	676	645	325	320	Median 12.1 (Range 1-115)
EMR 62 202-011 (LUCAS)	Cetuximab + cisplatin + vinorelbine vs cisplatin + vinorelbine	86	85	42	43	Median 13.6 (Range 1-47)
CA225100	Cetuximab + gemcitabine + platinum (cisplatin or carboplatin) vs gemcitabine + platinum (cisplatin or carboplatin)	131	130	64	66	Median 13.6 (Range 1-69)
Open studies						
IMCL CP02-9932	Cetuximab + paclitaxel + carboplatin	31	31	31	NA	Median 21.0 (Range 2-83)
IMCL CP02-9925	Cetuximab + gemcitabine + carboplatin	35	35	35	NA	Median 21.9 (Range 1-59)
TOTAL		2041	2036	1045	991	

In study EMR 62 202-046, the median duration of cetuximab treatment was 18 weeks, 341/548 (62.2%) subjects received up to 18 infusions and 207/548 (37.8%) received between 19 to 132 infusions. The median cumulative dose was 3761 mg/m^2. There were 241/548 (44.0%) subjects who received cetuximab as monotherapy after cessation of CTX, with a median number of monotherapy infusions per subject of 9 (range 1-110). Adding cetuximab did not impact on CTX (cisplatin and vinorelbine) treatment as the number of infusions, median duration of treatment, cumulative dose, dose intensity and relative dose intensity in the 2 treatment groups were similar.

In the other Phase III study CA225099, 325 subjects were exposed to cetuximab for a median duration of 12.1 weeks and 125/325 (38.5%) received cetuximab as monotherapy after CTX discontinuation with a median of 10 monotherapy infusions (range 1-73). Treatment groups were similar in terms of exposure to CTX.

In study EMR 62 202-011, the median treatment duration for the 42 subjects treated with cetuximab was 13.6 weeks and 11/42 (26.2%) continued on it as monotherapy for a median of 6 infusions (range 1-23). In study CA225100, 64 subjects were exposed to cetuximab for a median duration of 13.6 weeks and 22/64 (34.4%) continued on it as monotherapy for a median of 11 infusions (range 2-48).

Adverse Events

In study EMR 62 202-046, AEs were reported in 99.5% and 97.7% of subjects in the cetuximab+CTX and CTX groups respectively (Table 15). Skin rash occurred in 45.4% of the cetuximab+CTX group compared to 3% of the CTX group. Other more frequently occurring AEs were leukopenia (33.0% vs 28.1%), diarrhoea (24.3% vs 18.7%), febrile neutropenia (22.6% vs 16.4%), pyrexia (22.4% vs 15.1%) and stomatitis (15.5% vs 4.8%). Only anaemia was more frequent in the CTX group (42.2% vs 47.3%) (Table 16). Grade 3 or 4 AEs were more common in the cetuximab+CTX group (91.1%) compared to CTX alone (86.3%) with Grade 4 AEs occurring in 62.4% and 52.3%, respectively. Grade 4 AEs that occurred more frequently (≥5% difference or relative risk >2) in the cetuximab+CTX group than in the CTX group were leukopenia (10.4% vs 5.0%), white blood cell count (WBC) decreased (2.6% vs 0.7%), pulmonary embolism (4.2% vs 2.0%), sepsis (1.8% vs 0.2%), septic shock (1.1% vs 0%), hypocalcaemia (1.3% vs 0.4%) and pneumonia (1.3% vs 0.4%).

Table 15: AEs occurring in ≥10% of subjects in either treatment group in Study EMR 62 202-046

MedDRA preferred term	% of subjects	
	Cetuximab + CTX N=548	CTX N=562
Any AE	**99.5**	**97.7**
Neutropenia	57.5	58.7
Nausea	53.6	54.1
Rash	45.4	3.0
Anemia	42.2	47.3
Vomiting	40.1	40.7
Anorexia	38.1	35.9
Constipation	37.4	33.8
Fatigue	37.2	32.4
Leukopenia	33.0	28.1
Diarrhea	24.3	18.7
Febrile neutropenia	22.6	16.4
Pyrexia	22.4	15.1
Dyspnea	20.6	18.1
Alopecia	19.5	19.0
Cough	17.7	14.4
Asthenia	16.8	17.4
Stomatitis	15.5	4.8
Dizziness	15.0	10.1
Headache	14.6	10.7
Chest pain	13.9	13.0
Dry skin	13.9	1.6
Weight decreased	13.7	8.9
Hypokalemia	13.7	8.7
Dermatitis acneiform	13.7	0.2
Abdominal pain	13.5	13.9
Dyspepsia	12.6	9.8
Pruritus	11.7	2.3
Insomnia	10.6	8.7
Mucosal inflammation	10.6	4.3

Table 16: AEs with frequency difference of ≥5% between treatments in Study EMR 62 202-046

MedDRA preferred term	% of subjects	
	Cetuximab + CTX N=548	CTX N=562
AEs more frequent for cetuximab + CTX		
Rash	45.4	3.0
Diarrhea	24.3	18.7
Febrile neutropenia	22.6	16.4
Pyrexia	22.4	15.1
Stomatitis	15.5	4.8
Dry skin	13.9	1.6
Hypokalemia	13.7	8.7
Dermatitis acneiform	13.7	0.2
Pruritus	11.7	2.3
Mucosal inflammation	10.6	4.3
Hypomagnesemia	9.9	4.8
Paronychia	8.4	0.0
Acne	6.9	0.4
Skin fissures	5.5	0.0
AEs more frequent for CTX		
Anemia	42.2	47.3

In the other Phase III trial CA225099, AEs occurred in 99.7% of both treatment groups (Table 17). AEs occurring at a ≥5% difference between treatment group are summarised in Table 18. AEs not consistent with current product labelling that occurred at a higher frequency in the cetuximab+CTX group were constipation, cough, dehydration, dyspepsia, tachycardia and localised infection. Grade 3 or 4 AEs were again more common in those treated with cetuximab (79.1% compared to 61.3% in the CTX alone group) and 28.6% and 21.9% respectively for Grade 4 AEs. Grade 4 AEs with a higher frequency in the cetuximab+CTX group were neutropenia (5.8% vs 3.8%), pulmonary embolism (2.5% vs 0.3%), pneumonia (1.2% vs 0.3%) and neutrophil count decreased (1.2% vs 0.3%).

Table 17: AEs occurring in ≥10% of subjects in either treatment group in Study CA225099

MedDRA preferred term	% of subjects	
	Cetuximab + CTX N=325	CTX N=320
Any AE	**99.7**	**99.7**
Fatigue	74.8	70.9
Nausea	60.3	50.6
Rash	56.9	14.7
Diarrhea	47.7	32.8
Constipation	45.2	31.3
Anorexia	40.3	30.3
Alopecia	36.3	43.8
Dyspnea	32.9	34.4
Vomiting	32.9	30.0
Cough	30.8	25.3
Dehydration	27.4	16.3
Insomnia	26.5	22.2
Stomatitis	22.2	12.8
Dry skin	20.9	3.4
Weight decreased	20.6	10.0
Dizziness	20.3	14.7
Dysgeusia	18.5	14.4
Dermatitis acneiform	17.5	0.6
Edema peripheral	16.9	14.4
Arthralgia	15.4	15.9
Back pain	15.4	12.8
Mucosal inflammation	15.4	5.9
Dyspepsia	14.8	9.4
Musculoskeletal pain	14.5	9.7
Pruritus	13.8	5.3
Pain in extremity	13.2	10.6
Pyrexia	13.2	9.7
Peripheral sensory neuropathy	12.9	15.9
Abdominal pain	12.9	8.8
Epistaxis	11.7	5.6
Depression	11.4	8.8
Headache	11.1	10.3
Neuropathy	11.1	10.3
Asthenia	11.1	6.9
Hypotension	11.1	5.9
Myalgia	10.2	11.3
Neutropenia	10.2	6.9
Anxiety	9.5	10.3
Neuropathy peripheral	8.6	11.3

Table 18: AEs with frequency difference of ≥5% between treatments in Study CA225099

MedDRA preferred term	% of subjects	
	Cetuximab + CTX N=325	CTX N=320
AEs more frequent for cetuximab + CTX		
Nausea	60.3	50.6
Rash	56.9	14.7
Diarrhea	47.7	32.8
Constipation	45.2	31.3
Anorexia	40.3	30.3
Cough	30.8	25.3
Dehydration	27.4	16.3
Stomatitis	22.2	12.8
Dry skin	20.9	3.4
Weight decreased	20.6	10.0
Dizziness	20.3	14.7
Dermatitis acneiform	17.5	0.6
Mucosal inflammation	15.4	5.9
Dyspepsia	14.8	9.4
Pruritus	13.8	5.3
Epistaxis	11.7	5.6
Hypotension	11.1	5.9
Hypomagnesemia	9.5	0.9
Hypersensitivity	8.6	2.8
Exfoliative rash	8.0	0.3
Tachycardia	7.7	2.2
Localized infection	5.8	0.0
AEs more frequent for CTX		
Alopecia	36.3	43.8

In EMR 62 202-011, skin rash and acne were very frequent in the cetuximab+CTX group (40.5% compared to 2.3% in the CTX group); other AEs that occurred at a higher frequency (difference of ≥10% between groups) were constipation, diarrhoea, stomatitis, neuropathy and dehydration. The overall frequency of Grade 3 or 4 AEs was similar (78.6% cetuximab+CTX vs 79.1% CTX alone) although some occurred at greater frequency including asthenia (19% vs 2.3%), dyspnoea (11.9% vs 2.3%), fever (9.5% vs 4.7), infection (9.5% vs 2.3%) and syncope (7.1% vs 2.3%).

In CA225100, Grade 3 or 4 AEs were reported in 48/64 (75.0%) subjects in the cetuximab+CTX group and 34/66 (51.5%) subjects in the CTX group. Grade 3 or 4 AEs were consistent with the product labelling with the exception of dehydration (10.9% vs 1.5%), back pain (9.4% vs 1.5%) and thrombocytopenia (10.9% vs 6.1%).

Reported AEs that were consistent with the known safety profile of cetuximab included skin related AEs (rash, acne, dry skin, skin fissures, pruritus, paronychia), asthenia, anorexia, diarrhoea with or without hypokalaemia, epistaxis, headache, hypomagnesaemia, mucositis and pyrexia. In these NSCLC studies, AEs occurring more frequently in subjects treated with cetuximab included constipation, dehydration, sepsis

and pneumonia, hyponatraemia, leukopenia and febrile neutropenia, increased creatinine, renal failure, cough, dyspepsia and tachycardia.

AEs of special interest were examined in data combined from the 4 controlled studies. Acne-like rash occurred in 73.5% (720/979) of subjects treated with cetuximab and was generally mild to moderate in severity, although in 10.6% (104/979) of the subjects, it was Grade 3 or 4. Acne-like rash (any grade) resolved in 19.6% (141/720) of subjects during cetuximab treatment and in a further 42.6% (307/720) within 60 days of the last cetuximab dose and was ongoing in 26.9% (194/720) of subjects.

Infusion-related reactions (IRRs) (which include allergy/anaphylaxis, dyspnoea, fever and other) were more common in the cetuximab+CTX groups (Table 19). Overall 4.5% (44/979) of subjects in the cetuximab+CTX group and 1.3% (13/991) of subjects in the CTX group had a Grade 3 or 4 reaction.

Table 19: Number (%) of subjects with infusion related reactions in randomised controlled studies

AE grade /	EMR 62 202-046		EMR 62 202-011		CA225099		CA225100	
medical concept	Cet + CTX N=548	CTX N=562	Cet + CTX N=42	CTX N=43	Cet + CTX N=325	CTX N=320	Cet + CTX N=64	CTX N=66
Any grade	53 (9.7)	17 (3.0)	3 (7.1)	1 (2.3)	52 (16.0)	24 (7.5)	17 (26.6)	4 (6.1)
Allergy/anaphylaxis	24 (4.4)	4 (0.7)	1 (2.4)	0 –	34 (10.5)	11 (3.4)	6 (9.4)	0 –
Dyspnea	8 (1.5)	9 (1.6)	2 (4.8)	1 (2.3)	15 (4.6)	12 (3.8)	10 (15.6)	4 (6.1)
Fever	21 (3.8)	3 (0.5)	0 –	0 –	1 (0.3)	0 –	1 (1.6)	1 (1.5)
Other	5 (0.9)	2 (0.4)	0 –	0 –	3 (0.9)	2 (0.6)	1 (1.6)	0 –
Grade 3 or 4	19 (3.5)	7 (1.2)	1 (2.4)	1 (2.3)	20 (6.2)	5 (1.6)	4 (6.3)	0 –
Allergy/anaphylaxis	14 (2.6)	1 (0.2)	1 (2.4)	0 –	15 (4.6)	2 (0.6)	3 (4.7)	0 –
Dyspnea	3 (0.5)	6 (1.1)	0 –	1 (2.3)	3 (0.9)	1 (0.3)	1 (1.6)	0 –
Fever	0 –	0 –	0 –	0 –	0 –	0 –	0 –	0 –
Other	4 (0.7)	0 –	0 –	0 –	2 (0.6)	2 (0.6)	0 –	0 –

The incidence of mucositis in the cetuximab treated subjects was 28.8% (282/979) with 2.0% (20/979) for Grade 3 events, compared to 12.8% and 0.6% (Grade 3 events) in the CTX groups. The incidence of haemorrhages (for example, epistaxis, haemoptysis, pulmonary haemorrhage) of any grade was 20.5% (201/979 subjects) in the cetuximab treated subjects compared to 12.6% (125/991 subjects) in the CTX groups. Frequency of Grade 3 or 4 haemorrhages was similar but mild to moderate epistaxis occurred more frequently in cetuximab treated subjects (8.8% vs 3.9%). Thromboembolic events were higher in the cetuximab+CTX groups than the CTX groups with deep vein thrombosis occurring in 3.1% (30/979) vs 1.6% (16/991) and pulmonary embolism in 3.8% (37/979) vs 2.4% (24/991) of subjects.

Cardiac events (including arrest, arrhythmia, congestive heart failure, infarction/ischaemia and sudden death) occurred at a similar frequency in 3 of the trials but were more frequent in cetuximab treated subjects in study CA225099 (17.8% and 8.1% in the cetuximab+CTX and CTX groups respectively), with Grade 3 or 4 cardiac events in 6.8% and 3.1% respectively. In this trial, the Grade 3 or 4 cardiac events were more frequent in subjects with a history of cardiac disease treated with cetuximab+CTX (17/22, 77.3%) compared to those treated with CTX (4/10, 40.0%).

Grade 3 or 4 neutropenia, febrile neutropenia and severe infectious complications (pneumonia and septic events) were all notably more frequent in the cetuximab+CTX groups.

Serious Adverse Events and Deaths

Deaths

The sponsor's *Safety Summary* includes all deaths that occurred in the 6 clinical trials up to 30 days after the last dose of study medication; however, to allow for the same duration follow up period, data on deaths that occurred up to 30 days after the last dose of CTX in the cetuximab and CTX group in the 4 controlled studies were reviewed.

The primary reason for death in the 4 controlled studies is summarised in Table 20. In all studies combined, when examining the same follow up period (up to 30 day post CTX) there were 126/979 (12.9%) deaths in the cetuximab+CTX group compared to 115/991 (11.6%) in the CTX group. In study EMR 62 202-046, there was a slighter higher death rate in the 30 days after the last dose of CTX in the cetuximab+CTX group compared to the CTX group (15.5% vs 13.5%) and disease progression or disease related complications were the major causes of death (8.6% and 8.5% of subjects respectively). There was one death due to anaphylactic shock which was considered related to cetuximab treatment. In study CA225099, deaths up to 30 days post CTX were similar in the cetuximab+CTX (9.2%) and CTX groups (8.4%). Most deaths were from tumour related disease, however there were 2 deaths from drug related toxicity in the CTX group. In the 2 uncontrolled studies the main cause of death was related to disease.

Table 20: Deaths up to 30 days after the last dose of study treatment or chemotherapy in the randomised controlled studies

Study / Primary reason for death	No. (%) of subjects who died					
	Up to 30 days after last dose of study treatment				Up to 30 days after last dose of CTX	
	Cetuximab + CTX		CTX		Cetuximab + CTX	
EMR 62 202-046	N=548		N=562		N=548	
All reasons	103	(18.8)	76	(13.5)	85	(15.5)
Disease progression	33	(6.0)	30	(5.3)	22	(4.0)
Disease-related complications	28	(5.1)	18	(3.2)	25	(4.6)
Intercurrent or unrelated illness or event	17	(3.1)	8	(1.4)	15	(2.7)
Events related to chemotherapy	14	(2.6)	10	(1.8)	14	(2.6)
Events related to cetuximab	1 [a]	(0.2)	NA	NA	0	–
Unknown	10	(1.8)	10	(1.8)	9	(1.6)
EMR 62 202-011	N=42		N=43		N=42	
All reasons	6	(14.3)	4	(9.3)	4	(9.5)
Disease progression	2	(4.8)	1	(2.3)	0	–
Disease-related complications	3	(7.1)	1	(2.3)	3	(7.1)
Intercurrent or unrelated event	0	–	1	(2.3)	0	–
Unknown	1	(2.4)	1	(2.3)	1	(2.4)
CA225099	N=325		N=320		N=325	
All reasons	37	(11.4)	27	(8.4)	30	(9.2)
Tumor-related disease	31	(9.5)	19	(5.9)	24	(7.4)
Other	6	(1.8)	6	(1.9)	6	(1.8)
Study drug toxicity	0	–	2	(0.6)	0	–
CA225100	N=64		N=66		N=64	
All reasons	8	(12.5)	8	(12.1)	7	(10.9)
Tumor-related disease	7	(10.9)	7	(10.6)	6	(9.4)
Other or unknown	1	(1.6)	1	(1.5)	1	(1.6)
Study drug toxicity	0	–	0	–	0	–

[a] Subject died after first dose of cetuximab and did not receive CTX.

SAEs

Like data on deaths, it was noted that the observation period for SAEs may be longer in subjects treated with cetuximab due to continuation of treatment as monotherapy. The safety overview does not adjust the data for this difference.

In all 4 studies there were more SAEs and more treatment related SAEs in subjects treated with cetuximab+CTX than in those treated with CTX alone. In the Phase III studies, SAEs occurred in 59.3% vs 43.4% (EMR 62 202-046) and 55.4% vs 37.8% (CA225099) in the cetuximab+CTX and CTX groups, respectively. SAEs were also more frequent in the cetuximab+CTX group in the Phase II studies (47.6% vs 41.9% in EMR 62 202-011 and 48.4% vs 39.4%in CA2225100).

In EMR 62 202-046, the most frequent SAEs were febrile neutropenia (17.5% vs 11.9%), neutropenia (8.6% vs 5.9%), general physical health deterioration (4.0% vs 0.7%) and pulmonary embolism (3.6% vs 2.3%) in the cetuximab+CTX and CTX groups respectively.

In CA225099, SAEs of dehydration (7.4% vs 3.4%), pneumonia (5.5% vs 3.4%), febrile neutropenia (4.3% vs 2.5%), hypersensitivity (3.4% vs 0.3%) and neutropenia (2.8% vs 1.3%) were more frequent in those treated with cetuximab+CTX than CTX alone. The combined frequency in the 2 Phase III studies for neutropenia was 6.4% (56/873) vs 4.2% (37/882), febrile neutropenia 12.6% (110/873) vs 8.5% (75/882) and pneumonia was 4.2% (37/873) vs 2.7% (24/882) subjects in the cetuximab+CTX and CTX groups respectively.

In CA225100, SAEs of pneumonia (7.8% vs 6.1%), thrombocytopenia (4.7% vs 1.5%), dyspnoea (4.7% vs 1.5%), febrile neutropenia (4.7% vs 1.5%), dehydration (4.7% vs 0) and hypersensitivity (4.7% vs 0) were more common in the cetuximab+CTX group. In the other Phase II study EMR 62 202-011, SAEs of leukopenia (21.4% vs 11.6%), infection (7.1% vs 2.3%) and dyspnoea (7.1% vs 4.7%) were more common in the cetuximab+CTX group.

Laboratory findings

There were some differences in sampling schedules of laboratory variables between the studies, for instance haematology measurements were taken weekly during CTX treatment in studies EMR 62 202-046 and EMR 62 202-011 but were restricted to the first 2 to 3 CTX cycles in studies CA225099 and CA225100. After the end of CTX, laboratory measurements were performed at intervals of 6 weeks in study EMR 62 202-046 and at intervals of 3 weeks in studies CA225099.

In EMR 62 202-046, Grade 3 or 4 low haemoglobin was similar between groups (14.8% vs 17.0), while Grade 3 or 4 low WBC and Grade 3 or 4 low neutrophils were higher in the cetuximab+CTX group (65.4% vs 53.7% and 79.1% vs 69.7% respectively). Electrolyte levels were similar between groups, except for magnesium where low levels occurred in 50.9% of cetuximab+CTX subjects compared to 28.1% of the CTX subjects (note only 20% of subjects were tested for magnesium after a protocol amendment). Grade 1 to 4 raised liver function tests (LFTs) were more common in the cetuximab+CTX group however Grade 3 and 4 levels were similar between treatment groups.

In CA225099 as with the other Phase III study, the notable difference was in Grade 3 or 4 low WBC and Grade 3 or 4 low neutrophils which were more frequent in cetuximab treated subjects (44% vs 30.7% and 62.7% vs 55.9% respectively). Low magnesium was also more frequent with Grade 3 or 4 occurring in 8.8% of the cetuximab+CTX compared to 0.7% in the CTX group. High LFTs (any grade) were more frequent in the cetuximab+CTX group, although Grade 3 and 4 raised LFTs were similar between groups.

In EMR 62 202-011, there was a higher rate of Grade 3 and 4 low WBC and low neutrophils in the cetuximab+CTX group. In CA225100, low haematology parameters were similar between treatment groups, except for Grade 3 and 4 thrombocytopenia which was more common in cetuximab+CTX (57.8% vs 43.1%).

Safety in special populations

Age

In EMR 62 202-046, 30.7% (168/548) in the cetuximab+CTX group and 31.3% (176/562) in the CTX group were aged ≥65 years. For subjects treated with cetuximab+CTX, the following Grade 3 or 4 AEs were more common in the elderly compared to those aged <65 years: fatigue (10.7 vs 5.8%), hypokalaemia (10.1% vs 4.5%) and leukopenia (28.0% vs 24.0%). In CA225099, there was a greater proportion of subjects aged ≥65 years - 48.6% (158/325) in the cetuximab+CTX group and 52.2% (167/320) in the CTX group. For those treated with cetuximab+CTX, Grade 3 or 4 AEs were more frequent in the elderly

compared to those aged <65 years (82.3% vs 76%) and included dehydration (15.2% vs 7.8%) and dyspnoea (18.4% vs 6.6%).

Gender

In EMR62 202-046, Grade 3 or 4 febrile neutropenia was more frequent in females (26.8%) than in males (19.5%) treated with cetuximab+CTX as was decreased WBC (9.5% in females vs 3.4% in males).

Race

In EMR 62 202-046, 84% of subjects were Caucasian and 10% were Asian and 5% were of other race. When treated with cetuximab+CTX, there were a number of Grade 3 or 4 AEs which occurred more frequently in Asian subjects compared to Caucasians; these included asthenia, febrile neutropenia, haemoglobin decreased, hypoalbuminaemia, hypokalaemia, hyponatraemia, lymphopenia, nausea, sepsis and decreased WBC. The number of non-Caucasians in study CA225099 was too small to draw meaningful conclusions.

Cardiovascular disease history

Cardiovascular (CV) disease history was present in 57% of subjects in EMR 62 202-046 and 72% of those in CA225099. When treated with cetuximab+CTX compared to CTX alone, subjects with a history of CV disease showed a higher rate of the following Grade 3 or 4 AEs: leukopenia (20.0% vs 18.6%), neutropenia (54.9% vs 48.5%) in EMR 62 202-046; dehydration (14.6% vs 7.6%), fatigue (21.8% vs 15.2%) and neutropenia (9.2% vs 4.9%) in CA225099.

Safety related to drug-drug interactions and other interactions

There were no specific drug interaction studies included on the possible pharmacokinetic interactions between cetuximab and platinum based chemotherapies. In the reviewed NSCLC trials, the frequency of neutropenia and leukopenia in subjects treated with cetuximab and platinum based chemotherapy was notably higher than in those treated with CTX alone, which indicates an important safety issue.

Discontinuation due to adverse events

Cetuximab was discontinued due to AEs in 19.9% (109/548) of subjects in EMR 62 202-046, 30.5% (99/325) of subjects in CA225099, 21.4% (9/42) in EMR 62 202-011 and 37.5% (24/64) in CA225100. In EMR 62 202-046, the most frequently affected System Order Classes (SOCs) were *Infections and Infestations* (3.6%), *General Disorders and Administration Site Conditions* (3.5%), *Respiratory, Thoracic and Mediastinal Disorders* (2.9%), *Nervous System Disorders* (2.7%), *Skin and Subcutaneous System Disorders* (2.6%) and *Immune System Disorders* (2.4%). In CA225099, the most frequently affected SOCs were *General Disorders and Administration Site Conditions* (7.1%), *Respiratory, Thoracic and Mediastinal Disorders* (6.2%); *Gastrointestinal Disorders* (5.5%); *Cardiac Disorders* (5.2%) and *Skin and Subcutaneous System Disorders* (3.4%).

For those treated with cetuximab+CTX compared to CTX alone, the proportion of subjects discontinuing chemotherapy due to an AE was similar in EMR 62 202-046 (20.3% vs 18.9) and EMR 62 202-011 (31.0% vs 30.2%). In CA225099, there were more subjects with AEs leading to discontinuation of chemotherapy in the group treated with cetuximab+CTX (24.6% vs 17.2% for taxane and 24.0% vs 16.5% for carboplatin).

Evaluator's overall conclusions on clinical safety

The safety database for advanced NSCLC included data on 2036 treatment exposed subjects of whom 1045 were exposed to cetuximab. The median cetuximab treatment duration was 17.7 weeks in the largest trial, consisting of half the exposed population, and

12.1 to 13.6 weeks in the other 3 controlled trials. The number of subjects and duration of treatment are adequate to draw safety conclusions for the proposed indication. Due to differing chemotherapy combinations in the 4 controlled trials, data were not pooled.

The AE frequency of over 95% seen in these trials is as would be expected in group of patients with advanced or metastatic cancer and chemotherapy treatment. These AEs led to cessation of cetuximab treatment in around 25% of subjects.

Whilst many of the AEs that were more frequent in those treated with cetuximab were consistent with current product labelling (asthenia, anorexia, diarrhoea with or without hypokalaemia, epistaxis, headache, decreased magnesium, mucositis, raised LFTs , DVT, pulmonary embolism and pyrexia), there were a number of others that occurred more frequently in the NSCLC subjects treated with cetuximab (constipation, sepsis and pneumonia, leukopenia and febrile neutropenia, hyponatraemia, increased creatinine, renal failure, cough, dyspepsia and tachycardia). There is an increased risk of dehydration (perhaps related to mucositis or diarrhoea) and there was also, perhaps related, increased frequency of acute renal failure in study CA225099.

As is known with cetuximab, its addition to treatment resulted in very frequent skin reactions (over 80%) with around 10% of subjects having a Grade 3 or 4 acne-like rash. Such severe rashes may predispose to infections particularly given the reduced immune state noted in subjects. IRRs were also common (4.5% with Grade 3 or 4 IRR) and there was one death from anaphylaxis attributable to cetuximab.

Over all studies there was a notable increase in the frequency of Grade 3 or 4 AEs in those treated with cetuximab. In particular, unlike current product labelling, in the NSCLC population the addition of cetuximab to platinum based chemotherapy resulted in an increased risk of Grade 3 or 4 leukopenia and neutropenia together with the related infectious complications (febrile neutropenia, pneumonia and sepsis). This finding was consistent across the 4 randomised trials and is perhaps a consequence of drug interactions between cetuximab and platinum based chemotherapy.

It was also of major concern that there was a 15.5% increased rate of SAEs across the 4 studies in the cetuximab+CTX groups than in the CTX group; any SAE occurred in 56.8% (556/979) vs 41.3% (409/991) and treatment related SAEs in 36.6% (358/979) vs 23.1% (229/991) of subjects in the groups respectively. Notable SAEs occurring at an increased frequency in cetuximab treated subjects were neutropenia, febrile neutropenia, pneumonia, hypersensitivity, pulmonary embolism and dehydration. It was noted that the observation period for the cetuximab group was longer and adjusted data would be useful. These data were provided to the EMA (but were not in the Australian submission) and the difference in SAE frequency was 10.9% rather than 15%.[18]

When treated with cetuximab, the elderly (≥65 years) suffered more adverse events than their younger counterparts, in particular Grade 3 or 4 fatigue, hypokalaemia, leukopenia, dehydration, dyspnoea were more common. The small numbers of Asian subjects makes drawing conclusions in this population difficult. For subjects with a history of cardiac disease, there was an increased risk of Grade 3 and 4 AEs as well as an increased risk of cardiac events in study CA225099.

No HACAs were detected in 176 NSCLC subjects and the overall positive rate in oncology studies was 3%.

[18] EMA. CHMP variation assessment report - Erbitux/cetuximab. London, November 2009. Doc Ref: EMEA/CHMP/731075/2009.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

A detailed study report for the meta-analysis data (which was only provided as a PowerPoint presentation) should be provided.

Safety

Data on the frequency of SAEs and Grade 4 AEs during the chemotherapy phase of the 4 controlled trials (that is, after adjustment for similar observation periods) should be provided.

Initial Clinical Evaluation - Clinical Summary and Conclusions

Clinical Aspects

Pharmacokinetics

The PK of cetuximab in NSCLC is not affected by addition of platinum based chemotherapy doublets and modelling continues to support dosage based on body surface area (mg/m^2).

Clinical Efficacy

The efficacy of cetuximab as a first line treatment in combination with platinum based chemotherapy doublets was examined in patients with advanced (Stage IIIb with malignant pleural effusion or Stage IV), histologically confirmed NSCLC. Two of the 4 studies (EMR 62202-046 and 011) required EGFR expression on tumour tissue for inclusion. All studies were open label due to the skin reactions known to occur with cetuximab. Only the Phase III study CA225099 had independent assessment of tumour response (assessed 6 weekly by CT scan or MRI); in the other studies response was done by investigator assessment only.

While there is evidence to suggest activity of cetuximab against NSCLC through positive results in ORRs in all 4 trials, the overall efficacy results as measured by the clinically relevant endpoints of OS and PFS, were found to be marginal and discordant between trials. In the larger Phase III trial, EMR 62202-046, there was a modest benefit in terms of OS of 1.2 months (HR=0.87 95% CI: 0.76, 0.99) with borderline significance, p=0.044 but there was no significant improvement in PFS. In the second Phase III trial, CA225099, the primary endpoint of PFS as assessed by an IRRC, was not met and overall survival was not improved. Neither OS nor PFS were significantly improved in the 2 Phase II trials. The reasons for this discordance between OS and PFS in study EMR 62202-046 are unclear. It was not felt likely due to additional post study anticancer treatment as there was no greater use in the cetuximab treated subjects than the CTX treated subjects. Results from the 4 trials for OS, PFS and TTF are summarised in Figure 5. While TTF was significantly improved, results should be interpreted with caution due the *post hoc* nature of analyses in both Phase III studies.

Of interest, subjects who developed an acne-like rash during the first 3 weeks of cetuximab treatment had an improved survival compared to those without a rash. Unlike in colorectal cancer, KRAS mutational status did not affect efficacy results. EGFR expression on tumour tissue was a requirement for study EMR 62 202-046 but not in CA225099.

There was some limited improvement in OS for the Caucasian population in study EMR 62202-046 (OS HR=0.80, p=0.003), however this was not supported by PFS which was not

significant. There was also a suggestion of improved treatment response in those with squamous cell carcinoma (OS HR=0.80 compared to HR=0.87 for the ITT population), however the median increase in survival was only 1 month. Overall secondary, subgroup analyses are not considered sufficient, particularly when the results are still borderline, to enable definitive conclusions to be drawn on efficacy.

A PowerPoint presentation of a meta-analysis of the 4 controlled studies was provided. In this the OS HR was 0.88 (95% CI: 0.80-0.97, p=0.010). As no methodology nor formal report were supplied, a formal evaluation was not possible.

Clinical Safety

Adverse events were virtually universal as would be expected in patients with advanced cancer receiving chemotherapy treatment and resulted in about 25% of subjects ceasing cetuximab. Many of the AEs were consistent with the current product labelling for cetuximab, such as infusion related reactions (4.5% of subjects with Grade 3 or 4 IRR and one death from anaphylaxis) and skin reactions (over 80% of subjects with Grade 3 or 4 acne-like rash in around 10%). It was noted that development of acne-like rash may be associated with an improved treatment response.

There were several new safety concerns which have arisen from these NSCLC studies that are not consistent with current product labelling. When cetuximab is added to platinum based chemotherapy, there was an increased risk of leukopenia and neutropenia (and notably at Grade 3 and 4 levels) together with the related infectious complications (febrile neutropenia, pneumonia and sepsis). There was also an increased risk of dehydration (perhaps related to mucositis or diarrhoea) and acute renal failure. Subjects with cardiac disease were at increased risk of severe AEs and in particular cardiac events, which needs to be further examined.

The major safety concern from these studies was an overall higher rate of Grade 3 and 4 AEs and of SAEs in patients treated with cetuximab. Grade 3 or 4 AEs occurred in 91.1% vs 86.3% in EMR 62202-046, and 79.1% vs 61.3% in CA225099, in cetuximab+CTX and CTX groups respectively. SAEs occurred at a 15.5% higher rate in cetuximab treated subjects (59.3% vs 43.4% in EMR 62202-046 and 55.4% vs 37.8% in CA225099). This SAE rate has not taken into account the increased follow up time for cetuximab subjects and data on comparable observations periods has not been provided (though noted in the EMA review to still be 10.9% higher). The most notable SAEs with increased frequency in cetuximab-treated patients were neutropenia, febrile neutropenia, pneumonia, hypersensitivity, pulmonary embolism and dehydration. Compared to those aged <65 years, the elderly (≥65 years) treated with cetuximab were at greater risk of Grade 3 and 4 AEs with fatigue, dyspnoea, dehydration, hypokalaemia, dyspnoea and leukopenia all being more frequent.

When examining deaths between treatment groups over the same observation period (up to 30 days post last CTX dose), there was a slightly higher rate in cetuximab treated subjects (12.9% vs 11.6%). There was one death due to cetuximab related anaphylaxis. There were no HACAs were detected in 176 NSCLC subjects evaluated and the overall positive rate in oncology studies was 3%.

Benefit risk assessment

Benefits

The addition of cetuximab to platinum based chemotherapy improved OS in the larger Phase III trial by 1.2 months (about 5 weeks) for subjects with Stage IIIb or IV, EGFR-expressing, NSCLC. The median OS was 11.3 months for the cetuximab+CTX group compared to 10.1 months for the CTX group with a resultant HR of 0.87 (95% CI 0.76, 0.99 p=0.044). This is a borderline statistically significant result. The improvement in OS was

not seen in the other Phase III trial and was not supported by an improvement in PFS in any of the 4 trials and, in particular, PFS was not significantly improved in the Phase III study where it was the primary outcome and had independent blinded assessment. There was evidence of cetuximab activity against NSCLC with ORR improvement in all 4 controlled studies though the benefit appeared to be modest (7.2% and 8.5% in the two Phase III trials).

The submission included large and comprehensive randomised controlled trials, with a total of 2018 (979 treated with cetuximab) subjects enrolled in the 4 controlled trials. Due to occurrence of skin reactions with cetuximab, it was not possible to blind the studies and so all were open label. Only one trial (the smaller Phase III) had an independent blinded review for tumour assessment and in the other 3 trials assessment conducted by the investigators was not blinded. This may have allowed the introduction of bias.

There was an emphasis placed on the endpoints of ORR and TTF, however as the main clinically relevant endpoints in advanced malignancy are OS and PFS and the fact that TTF was a *post hoc* analysis, neither provide substantive support for efficacy.[17]

Overall, the benefit of cetuximab treatment on OS of 1.2 months was of borderline statistical significance and not supported by the secondary endpoint of PFS nor the results in the other 3 trials and so does not appear to be convincing.

Risks

Cetuximab has a known risk profile which includes very frequent skin reactions (over 80% of subjects treated) with around 10% of subjects having a Grade 3 or 4 acne-like rash. Infusion related reactions were also common (4.5% of subjects having a Grade 3 or 4 IRR) and there was one death from anaphylaxis in the reported studies. The incidence of DVT and pulmonary embolism was also higher in cetuximab treated subjects (3.1% vs 1.6% and 3.8% vs 2.4% respectively).

The major concern with cetuximab when used concurrently with platinum based chemotherapy in NSCLC is the notably increased rate of Grade 3 or 4 AEs and of SAEs. In the 4 controlled studies there was a 15.5% increased rate of SAEs [56.8% (556/979) in subjects treated with cetuximab+CTX compared to 41.3% (409/991) in those treated with CTX alone]. This increased rate was not due to the longer observation period in subjects treated with cetuximab as in the EMA's evaluation a difference of 10.9% was still noted when adjusting for the difference in observation periods. The increased rate of Grade 4 AEs in cetuximab treated subjects was 10.1 % and 6.7% in EMR 62202-046 and CA225099 respectively. The most frequent Grade 3 and 4 AEs were leukopenia and neutropenia and their infectious complications (Grade 3 or 4 febrile neutropenia, pneumonia and sepsis) were also consistently increased across the 4 main trials.

It was noted that there was a temporary decrease in QoL across a number of scales during Cycle 3 of treatment in subjects receiving cetuximab+CTX. The sponsor proposed that this may be due to skin reactions occurring at this time.

The safety database for NSCLC is large, with a total of 1045 subjects exposed to cetuximab, and a median treatment duration of 17.7 weeks in the largest study containing half the exposed subjects. Due to the differing chemotherapy regimens used in the clinical trials the data were not pooled. It is noted, however, that risks seen were consistent across trials.

The open label nature of the studies may have introduced some bias in reporting of AEs and recording on QoL questionnaires. The longer observation period for AE and SAE collection in the cetuximab treated subjects would have resulted in a greater number of events recorded in this group. Adjustment for this effect was conducted on deaths though

not on SAEs in the data provided. It is noted that this adjustment on SAEs was provided to the EMA and resulted in a reduction from 15.5% to 10.6% in the difference in the rate of SAEs. The QoL questionnaire completion rate was low and this may introduce bias, hence conclusions from QoL data were not weighted heavily.

Balance

Lung cancer is the fifth most common cancer in Australia and the leading cause of cancer deaths.[19] NSCLC accounts for about 80% of lung cancers. Unfortunately lung cancer tends to present late, with most patients having advanced, or even metastatic disease at clinical presentation and as a consequence the 5 year survival is low (11% for males, and 14% for females).[20]

Treatment options are limited for advanced stage disease. The mainstay of first line treatment is cytotoxic platinum chemotherapy doublets. The addition of bevacizumab to chemotherapy has shown a statistically significant 2 month improvement in median OS (12.3 vs 10.3 months) for patients with non-squamous NSCLC. Second line treatment options include the small molecule inhibitors of EGFR tyrosine kinase (erlotinib and gefitinib). For NSCLC patients after failure of at least one CTX regimen, erlotinib improved overall survival by 2 months (6.7 vs 4.7 months) with a significant HR of 0.73 (p=0.001). Gefitinib did not significantly improve OS (HR=0.89, 5.6 versus 5.1 months) in patients with advanced or metastatic NSCLC who had failed chemotherapy and is only approved for use in such patients who have never smoked or who have already had some benefit from this treatment.

Such treatments are only providing small incremental benefits, with OS remaining short therefore treatment of advanced NSCLC presents an obvious unmet medical need. Cetuximab has an obvious attraction in that it presents a potential to fill the gap not covered by bevacizumab as an add-on to chemotherapy in patients with squamous NSCLC.

Cetuximab has shown, in one study, an improvement in overall survival of about 5 weeks (from 10.1 to 11.3 months) which is of borderline statistical significance and has not been supported by the second Phase III trial results nor a significant improvement in PFS in any trial. This modest benefit could be considered significant for a patient with terminal malignancy and could also be argued as an incremental clinical improvement in an area with known unmet need.

On the other side of the balance, the safety risks associated with cetuximab treatment are significant and in particular there is a notably increased risk of Grade 3 and 4 AEs and SAEs. It is acknowledged that skin reactions may be indicative of better treatment response, perhaps a consolation to those experiencing them and that many of the high grade risks seen may be managed with current medical treatment. However, when one considers the short life expectancy of these patients, the increased risk of serious harm and the resultant possibility of hospitalisation and reduced quality of life during the final months of life, it is considered that these harms outweigh the modest, and statistically tenuous, benefit in overall survival.

The evaluation of cetuximab in the NSCLC indication conducted by the EMA and its advisory group on oncology has been conducted and also came to the same negative opinion.[18] A subsequent analysis in greater detail of subgroups, in particular Caucasians, non-adenocarcinoma and those aged ≤65 years failed to alter the benefit risk balance in favour of cetuximab and the negative opinion was upheld in November 2009.[18]

[19] AIHW. Cancer in Australia: an overview, 2008. AIHW cat no CAN 42, Dec 2008.

[20] NHMRC. Clinical practice guidelines for the prevention, diagnosis and management of lung cancer. The Cancer Council Australia. March 2004.

Conclusions

It was concluded that the overall benefit risk balance of cetuximab is negative for the indication of "the first line treatment of patients with advanced or metastatic non-small cell lung cancer in combination with platinum-based chemotherapy".

Supplementary Clinical Evaluation – Introduction

The initial registration application to extend the indication of Erbitux (cetuximab) to include first line treatment for non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy was evaluated in 2010. The clinical evaluator recommended rejection of the application. In response, the sponsor supplied supplementary data and a revised indication. In addition, responses to issues raised in the initial evaluation were included. Subsequent to the initial application, the sponsor compiled new biomarker data which have been analysed and form the basis of this supplementary data package.

The sponsor reported that discussions with the European Medicines Authority (EMA) were held regarding analyses of biomarkers in the NSCLC population in order to identify a more responsive target population. Details of these discussions were not been provided.

The purpose of this application is to extend the indication to include the treatment of non-small cell lung cancer (NSCLC). The original proposed indication was:

Erbitux is indicated for the first-line treatment of patients with advanced or metastatic non-small cell lung cancer in combination with platinum-based chemotherapy.

The revised indication now requested for NSCLC was:

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR-expressing tumours.

Supplementary Clinical Evaluation – Efficacy

Introduction

The initial submission contained clinical data from 6 trials (4 controlled and 2 uncontrolled) in subjects with advanced stage NSCLC. Evaluation of this submission found a negative benefit risk balance. Subsequently, the sponsor analysed biomarker data from the two main clinical trials, EMR 62 202-046 (FLEX) and BMS CA225-099 and this has been submitted for evaluation.

The Phase II study EMR 62202-011 required patients to have EGFR expressing tumour for study inclusion. The sponsor states that, due to methodological differences, EGFR immunohistochemistry (IHC) score calculation from this study was not available. In the other main Phase II study, CA225100, EGFR expression was not an inclusion criterion so subgroup analyses by IHC score were also not available.

Main (pivotal) Studies

EMR 62 202-046 (FLEX)

The FLEX trial was described in the Initial Clinical Evaluation. The primary objective of the study was overall survival (OS) with progression free survival (PFS) as a secondary objective.

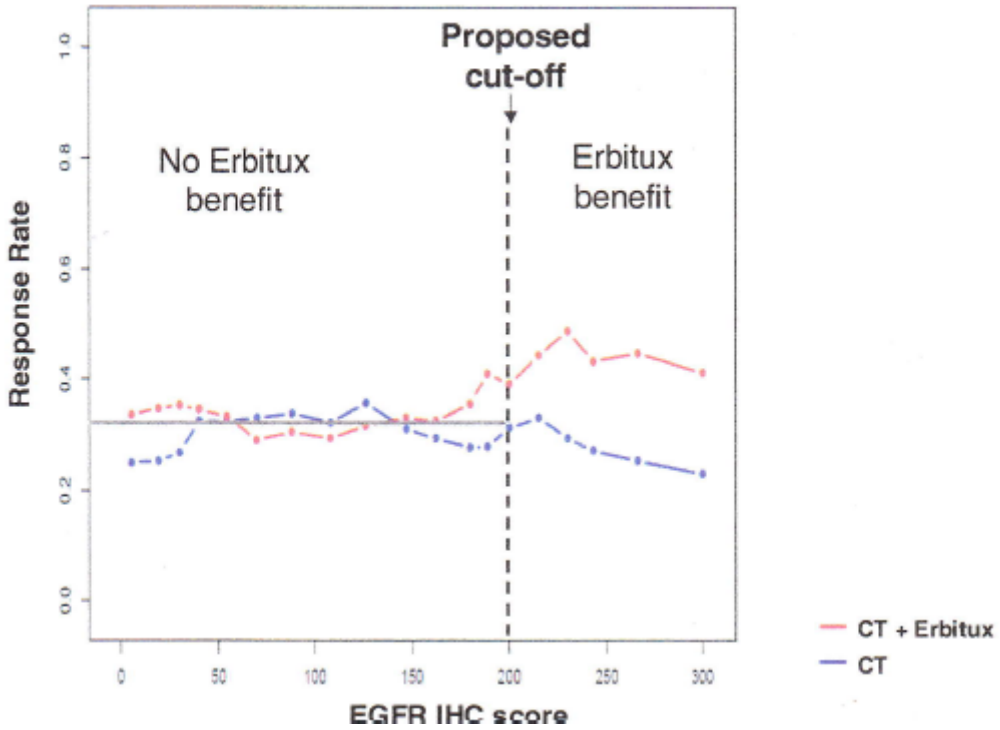
Methodology for EGFR expression and cut-off determination

During the trial EGFR expression in tumour biopsies was performed at four regional laboratories with results then sent to a virtual central laboratory that normalised the data.

All local laboratories analysed a test sample provided by the virtual central laboratory to allow normalisation factors to be generated for each laboratory. Data was collected prospectively as EGFR expression was a trial inclusion criterion.

The sponsor analysed the data for tumour response by EGFR immunohistochemical (IHC) score to establish a level at which the biomarker may have a predictive value for clinical efficacy. The objective response rate (ORR), in 5% percentile steps, by EGFR IHC score is shown in Figure 7. This shows greater tumour response at an EGFR IHC score of at least 200. Subjects were then classified as low EGFR-expressing (EGFR IHC score < 200) and high EGFR-expressing (EGFR IHC score ≥ 200).

Figure 7: Relation between EGFR expression (IHC score) and response rate (RR) (ITT population) – EMR 62 202-046



Participant flow

There were 1861 subjects pre-screened, 1258 screened, and 1125 randomised with 557 in the cetuximab+chemotherapy (CTX) group and 568 in the CTX group (ITT population). Of the 1125 subjects, EGFR expression data were available for 1121 and of these 345 (31%) were high EGFR-expressing and 776 (69%) were low expressing, as based on the cut-off IHC score of 200.

Baseline characteristics

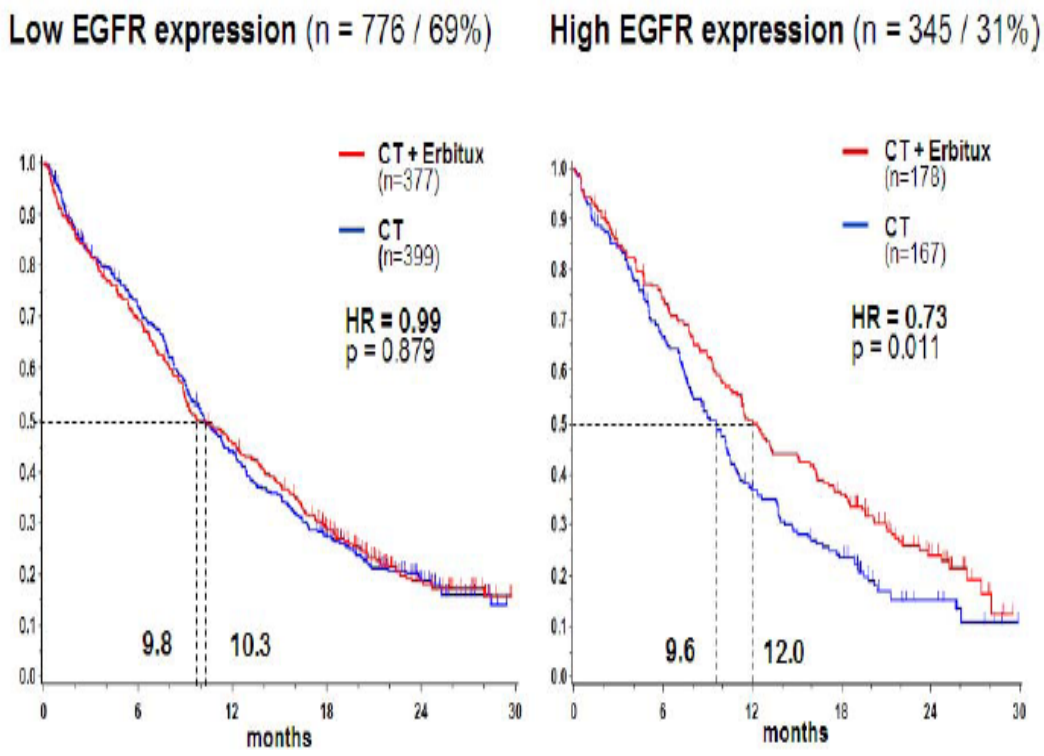
In the high EGFR expressing group, the baseline characteristics of age, gender, race, tumour stage, histology, smoker and ECOG status were balanced between the 2 treatment groups. Therefore it can be assumed that the benefit seen for the treatment cetuximab and CT in the high EGFR expressing group was not influenced by prognostic factors (for example, age, gender and smoking status) or imbalances with respect to EGFR IHC score distribution between both treatment arms.

Outcomes and estimation

In the ITT population, the median overall survival (OS) time in the cetuximab+CTX group was 11.3 months (95% CI: 9.4, 12.4) and in the CTX group was 10.1 months (95% CI: 9.1, 10.9). The hazard ratio (HR) of cetuximab+CTX over CTX was 0.87 (95% CI: 0.76, 0.99) which just reached statistical significance, p=0.044. A Cox regression analysis adjusting for the following baseline variables (gender, ethnic origin, ECOG PS, number of organs involved, tumour stage, histology, global QoL, and smoking habit) found the HR for cetuximab+CTX over CTX was 0.84 (95% CI: 0.69, 1.03) which was not statistically significant p=0.102.

In the high EGFR expression group, the median OS of cetuximab+CTX was 12.0 months (95% CI: 10.2, 15.2) compared to 9.6 months in the CTX group (95% CI: 7.6,10.6) with a HR of 0.73 (95% CI: 0.58, 0.93, p=0.011). In the low EGFR expressing group, the median OS was 9.8 months vs 10.3 months in the cetuximab+CTX and CTX groups, respectively, with a HR of 0.99 (95% CI 0.84,1.16 p=0.879) (Figure 8). Analyses of OS were performed at different IHC score cut-offs and showed that for an IHC score of ≥ 250 the median survival was 11.2 months with cetuximab+CTX compared to 7.6 months (HR 0.63, 95% CI: 0.44,0.90).

Figure 8: OS according to low and high EGFR expression – EMR 62 202-046



In the ITT population, the median PFS time was the same at 4.8 months in both treatment groups and the HR for PFS time for cetuximab+CTX over CTX was 0.94 (95% CI: 0.83, 1.08, p=0.39). In the high EGFR expressing group, the median PFS time was 5.0 months and 4.6 months in the cetuximab+CTX and CTX groups, respectively, HR=0.86 (95% CI: 0.68,1.09,

p=0.216). The median time to treatment failure in the ITT population was 4.2 months in the cetuximab+CTX group and 3.7 months in the CTX group, HR 0.86 (95% CI: 0.76, 0.97, p=0.015). For those with high EGFR expressing tumours the median time to treatment failure was 4.2 months versus 4.0 months, HR was 0.78 (95% CI: 0.63,0.97, p=0.026).

The best overall response rate (ORR) in the ITT population was 36.4% (95% CI: 32.4, 40.60) for those treated with cetuximab+CTX which was slightly greater than CTX alone (ORR=29.2%, 95% CI: 25.5, 33.2) with an odds ratio (OR) of 1.39 (95% CI: 1.08, 1.79, p=0.01). The disease control rate was similar between groups (72.5%, 71.5%) with an OR of 1.06 (95% CI: 0.81, 1.37, p= 0.68). In the high EGFR expressing group, the ORRs were 44.4% and 28.1% in the cetuximab+CTX and CTX groups, respectively (OR 2.04, 95% CI: 1.30,3.19, p=0.002) (Table 21).

Table 21: Improved efficacy across all endpoints in high EGFR expression group compared to ITT population – EMR 62 202-046

	ITT n = 1125				High EGFR expression (EGFR IHC score ≥200) n = 345			
	CT + Erbitux	CT	HR/OR	95% CI	CT + Erbitux	CT	HR/OR	95% CI
OS (months)	11.3	10.1	0.87	0.762 - 0.996	12.0	9.6	0.73	0.58 - 0.93
PFS (months)	4.8	4.8	0.94	0.825 - 1.077	5.0	4.6	0.86	0.68 - 1.09
TTF (months)	4.2	3.7	0.86	0.761 - 0.971	4.2	4.0	0.78	0.63 – 0.97
RR (%)	36.4	29.2	1.39	1.081 - 1.785	44.4	28.1	2.04	1.30 - 3.19

Subgroup analyses

As with the ITT data, the high EGFR expressing subgroups with better OS were <65 years, Caucasians, squamous cell carcinoma and Stage IV. Asian patients showed no benefit for OS, though the numbers with high EGFR expression were low (n=49). Adenocarcinoma had a non-significant improvement in median OS of 20.2 months vs 13.6 months (HR 0.74, 95% CI: 0.48, 1.14) while there was no improvement in low EGFR expressing adenocarcinoma group (11.8 vs 11.5 months). For squamous cell carcinoma with high EGFR expression, the median OS was 11.2 months with cetuximab+CTX compared to 8.9 months with CTX alone, which was statistically significant, (HR 0.62, 95% CI: 0.43,0.88) with no improvement in the SCC group with low EGFR expression.

CA225099

CA225099 was a randomised, multicentre, open label, Phase III study of cetuximab plus taxane/carboplatin versus taxane/carboplatin as first line treatment for patients with advanced metastatic NSCLC which is described in the initial clinical evaluation. Data from this study was used to validate the predictive values of the EGFR expression using the IHC cut-off score of 200. In a subset of patients for whom tumour tissues samples were available, EGFR expression was measured by IHC and analysed by a blinded, independent pathologist

Participant flow

There were evaluable samples from 136 (20%) of patients with 74 (21.9% of randomised) in the cetuximab+CTX group and 62 (18.3%) in the CTX group. There were 39/74 (52.7%) of the cetuximab+CTX group with high EGFR expression and 38/62 (61.2%) of the CTX group.

Baseline characteristics

The high EGFR expressing group was well balanced across baseline characteristics, except for age where there were more younger patients in the cetuximab+CTX group.

Outcomes and estimation

In the validation set (n=136), there was no significant improvement in OS (8.3 vs 9.7 months, HR 1.05, 95% CI: 0.73, 1.51). For the subgroup of patients with high EGFR expressing tumours (n=77), the PFS was similar (4.6 vs 4.2 months, HR 1.01, 95% CI:0.61,1.69) and OS was non-significantly improved (9.3 vs 7.6 months, HR 0.76, 95% CI: 0.47,1.23). In contrast, the addition of cetuximab to CTX in those with low EGFR expression resulted in a non-significant reduction in median survival (8.1 vs 12.4 months). Due to imbalances of age, an analysis with age adjustment was undertaken. This resulted in a reduction in the HR for PFS from 1.01 to 0.84 (95% CI: 0.47,1.51) and increase in the OR for RR from 3.70 to 5.69 (95% CI: 1.55, 20.9), however there was little change in OS HR from 0.76 to 0.77 (95% CI: 0.46, 1.30) (Table 22).

Table 22: Efficacy Results after Adjustment for age low and high EGFR Expression

BMS 099 (adjusted)	Low EGFR expression (EGFR IHC score <200) n = 59				High EGFR expression (EGFR IHC score ≥200) n = 77			
	CT + Erbitux	CT		95% CI	CT + Erbitux	CT		95% CI
OS (months)	8.1	12.4	HR 1.73	0.96 - 3.12	9.3	7.6	HR 0.77	0.46 - 1.30
PFS (IRC) (months)	4.5	6.0	HR 1.09	0.61 - 1.96	4.6	4.2	HR 0.84	0.47 - 1.51
TTF (IRC) (months)	3.4	4.2	HR 1.07	0.62 - 1.82	2.9	2.3	HR 0.59	0.35 - 0.98
RR (IRC; %)	22.9	33.3	OR 0.59	0.18 - 1.89	35.9	13.2	OR 5.69	1.55 - 20.9

Biomarker Analysis

As the section on supportive studies is not applicable, the evaluator has included in this section data on further exploratory biomarker analysis undertaken by the sponsor. Using available tumour tissue from studies EMR 62202-046 and CA225099 the sponsor conducted retrospective analyses of the following biomarkers:

- Biomarkers related to EGFR signalling pathway: KRAS mutation, EGFR mutation, EGFR gene copy number, PTEN protein expression, EGFR polymorphism, EGF polymorphism, CCND1 polymorphism.
- Biomarkers relating to immune effector function (antibody-dependent cellular cytotoxicity): FCGR2A and FCGR3A polymorphisms.
- Biomarkers relating to acne like rash: EGFR polymorphism.

Statistical methods

Statistical analysis included Kaplan-Meier estimates and Cox proportional hazards models for the endpoints of OS and PFS. The ORR was also compared between treatment groups. The analyses for the ITT population and evaluable population were stratified by randomisation strata, however there was no stratification in the biomarker subgroups due to the small numbers.

Results

Unlike data on EGFR expression, none of these biomarkers were found to identify patients who may have an increased likelihood of benefit with cetuximab therapy.

KRAS mutation was found in 19% and 17% of analysed samples in studies EMR62202-046 and CA225099, respectively. As reported in the initial NSCLC evaluation, KRAS mutational status, unlike in CRC, was found not to be predictive of a positive response to cetuximab therapy in NSCLC. This was the case in both adenocarcinoma and non-adenocarcinoma subgroups.

EGFR gene copy number status was assessed by fluorescence in situ hybridisation (FISH) and found to be increased in 37% and 52% of the available samples in EMR 62202-046 and CA225099, respectively. There was no influence of EGFR gene copy number on outcome. In study CA225099, a positive EGFR FISH was found to worsen the response to cetuximab (OS HR 1.92, 95% CI: 1.05, 3.54). There was also no association found between PTEN protein expression status or EGFR kinase domain mutations.

With the single nucleotide polymorphism (SNP) analyses, no associations with cetuximab efficacy were found for FCGR 2A and 3A polymorphisms, EGFR 1562 G/A polymorphisms, or EGF and CCND1 polymorphisms. In addition, no association was found between acne-like rash and EGFR polymorphism.

Due to the knowledge that HER2 gene copy number, as well as HER2 expression, is important in predicting of benefit trastuzumab therapy, the EGFR gene copy status was assessed for cetuximab in EMR 62202-046. For subjects with high EGFR expression, the treatment effect on OS was similar irrespective of gene copy number (HR 0.83 if FISH positive and HR 0.82 if FISH negative). For those with low EGFR expression, there was a trend for more impact if FISH positive than negative (HR0.81 vs HR 0.96).

Evaluators overall conclusions on clinical efficacy

There were 4 randomised, controlled, open label studies presented in the initial NSCLC dossier which included total of 2018 subjects with histologically or cytologically confirmed, advanced (Stage IIIb with malignant pleural effusion or Stage IV) NSCLC. EGFR expression on tumour tissue was required for one of the Phase III (EMR 62 202-046) and one of the Phase II studies (EMR 62 202-011) but was not required on the other Phase III (CA225099) or Phase II study (CA225100). Cetuximab efficacy was assessed in combination with platinum based chemotherapy and could be continued as monotherapy in the cetuximab+CTX group after CTX cycles has been completed. Only the Phase III study CA225099 had an IRRC, the other 3 trials used the investigator's assessments of tumour response.

The first pivotal study (EMR 62202-046) found a modest overall survival benefit of 1.2 months (11.3 versus 10.1 months in the cetuximab+CTX and CTX groups, respectively, HR 0.87 p=0.044). There was no significant improvement in PFS or disease control. The second pivotal study (CA225099) did not meet the primary endpoint of PFS as assessed by an IRRC (4.4 vs 4.2 months in the cetuximab+CTX and CTX groups, respectively HR 0.90, p=0.236). In addition, overall survival was not improved (HR 0.89, p=0.169). There was

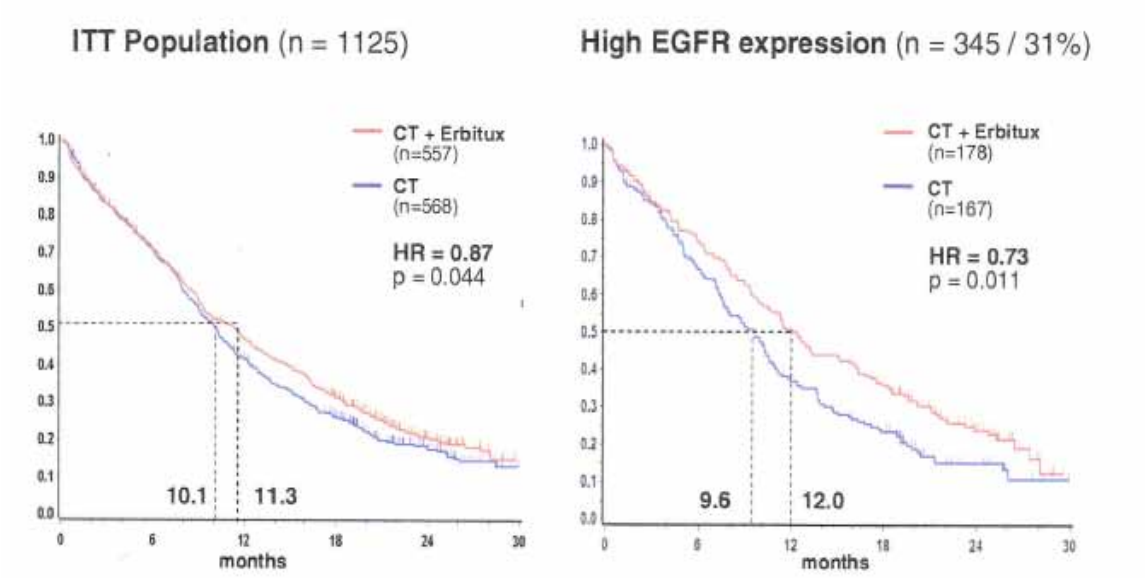
evidence that cetuximab had activity against NSCLC as shown in the positive effect on ORR in the 4 main studies, though the improvement is modest (7.2% in EMR62202-046, 8.5% in CA225099, 7% in EMR 62202-011 and 9.5% in CA225100).

In this submission, new biomarker data from the two pivotal Phase III studies were presented. An IHC score was generated ranging from 0 (no staining) to 300 (100% of cells with strong staining) with a cut-off of 200, based on the ORR, for low and high EGFR expression.

In EMR 62202-046, of the 1125 subjects randomised there were 1121 (99.6%) samples available for testing and 31% were high EGFR expressing. As EGFR expression was not an inclusion criteria in CA225099, of the 676 patients randomised there were evaluable samples from only 136 (20.1%) patients and 56.6% of these were high EGFR expressing.

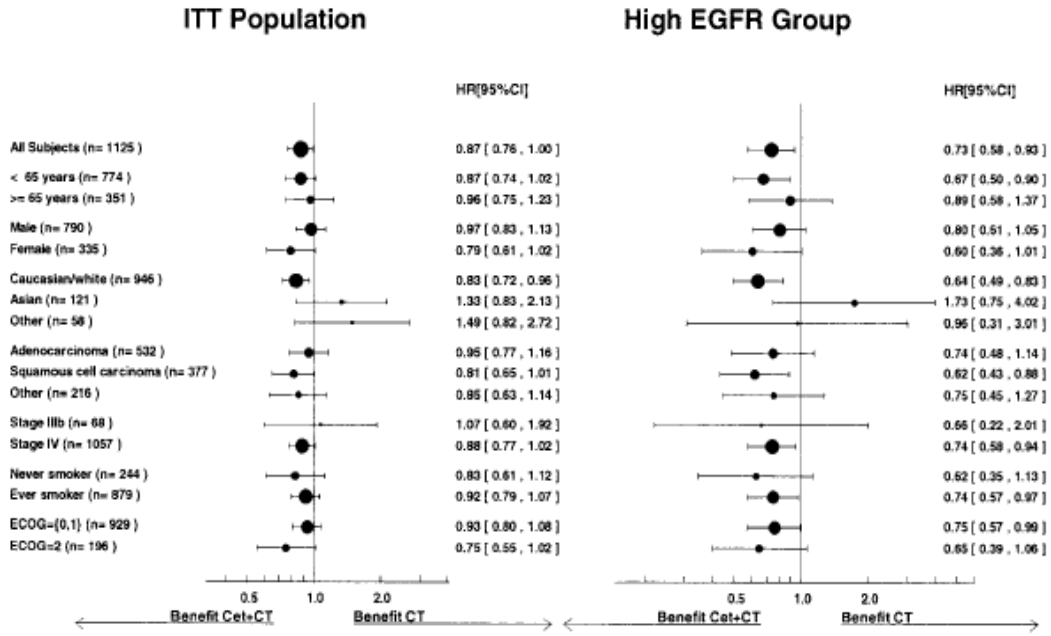
In EMR 62202-046, analysis of this subgroup of high EGFR expression found an improvement in median OS time in those treated with cetuximab+CTX of 2.4 months (12.0 vs 9.6 months) with a HR of 0.73 (95% CI: 0.58, 0.93, p=0.011). In contrast, the low EGFR expressing group had no improvement in OS (9.8 vs 10.3 months, HR=0.99, 95% CI: 0.84,1.16 p=0.879). Figure 9 shows the OS time for the ITT population compared to the high EGFR expression subgroup.

Figure 9: OS – ITT population and high EGFR expression – EMR 62 202-046



The median PFS time was still not significantly improved, (HR=0.86, 95% CI: 0.68,1.09, p=0.216) though there was a modest increase in PFS time (5.0 vs 4.6 months in the cetuximab+CTX and CTX groups, respectively). Subgroup analyses found, as with the data from the whole population, the high EGFR expressing subgroups with better OS were <65 years, Caucasians, squamous cell carcinoma and Stage IV while Asian patients showed no benefit for OS, though the numbers with high EGFR expression were low (n=49) (Figure 10).

Figure 10: Improved efficacy across subgroups in high EGFR expression group compared to ITT population – EMR 62202-046



Study CA225099 was used for validation of data from the main study. In the small group (n=136) where EGFR expression score was available, the age adjusted PFS was 4.6 months for cetuximab+CTX compared to 4.2 months for CTX alone (HR 0.84, 95% CI: 0.47,1.51) and age adjusted OS was 9.3 months and 7.6 months, respectively (HR 0.77, 95% CI: 0.46, 1.30). This showed a modest improvement in findings for the high EGFR expressing subgroup though the numbers are too small to draw conclusions.

A variety of other biomarkers were assessed from available samples from the two studies. These included biomarkers related to EGFR signalling pathway (KRAS mutation, EGFR mutation, EGFR gene copy number, PTEN protein expression, EGFR polymorphism, EGF polymorphism, CCND1 polymorphism), biomarkers relating to immune effector function (FCGR2A and FCGR3A polymorphisms) and biomarkers relating to acne like rash (EGFR polymorphism). In most cases (apart from EGFR and FCGR2A/3A) the sample sizes were small and the confidence intervals wide. None of the biomarkers assessed were found to provide any predictive value for establishing which tumours may be more responsive to cetuximab. This included EGFR gene copy number assessed by FISH which was found to be increased in 37% (n=102) and 52% (n=54) of the available samples in EMR 62202-046 and CA225099, respectively. In contrast to EMR 62202-046 where the OS HR was 0.84 (p=0.43) in the EGFR FISH positive subgroup, in CA225099 there was a reduction in OS (HR 1.92, p=0.03) in the EGFR FISH positive group.

Supplementary Clinical Evaluation – Safety

Introduction

Data from the 6 clinical trials in NSCLC were used in the initial application safety evaluation, with a total of 2036 subjects of whom 1045 were exposed to cetuximab. With the supplementary data, safety was evaluated from studies EMR 62202-046 and CA225-099 by low and high EGFR expression and compared to the overall safety population. The data were not pooled for analysis as different chemotherapy regimens were used in the trials.

Patient exposure

In study EMR 62202-046, the safety population for this study by EGFR IHC score is summarised in Table 23. There were 175 high EGFR expressing subjects exposed to cetuximab+CTX.

Table 23: EMR62202-046. Safety population, number of subjects by IHC score and treatment group

EMR62202-046	Total	Cetuximab+CTX	CTX
Overall safety population	1110*	548	562
EGFR expression evaluated	1106	546	560
Low EGFR expression	763	371	392
High EGFR expression	343	175	168

*IHC score not available for 4 subjects

In CA225099, there were 39 subjects with high EGFR expression exposed to cetuximab in this study (Table 24).

Table 24: CA225099. Safety population, number of subjects by IHC score and treatment group

CA225099	Total	Cetuximab+CTX	CTX
Overall safety population	645	325	320
EGFR expression evaluated	136	74	62
Low EGFR expression	59	35	24
High EGFR expression	77	39	38

Adverse Events

In study EMR 62202-046 for the overall safety population, Grade 3 or 4 AEs were more common in the cetuximab+CTX group compared to CTX (91.1% vs 86.3%) with Grade 4 AEs occurring in 62.4% and 52.3%, respectively. In the high EGFR expressing group, the rate of Grade 3 or 4 AEs was similar between treatment groups (87.4% vs 89.9%) and Grade 4 AEs were slightly higher with cetuximab+CTX (59.4% vs 57.1%) (Table 25).

Table 25: AE frequencies by EGFR expression

Adverse event (AE)	EMR 62202-046 (Safety population)					
	All		Low EGFR expression IHC <200		High EGFR expression IHC ≥200	
	Cetuximab + CT (n=548)	CT (n=562)	Cetuximab + CT (n=371)	CT (n=392)	Cetuximab + CT (n=175)	CT (n=168)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Grade 3 or 4 AE	499 (91.1)	485 (86.3)	345 (93.0)	333 (84.9)	153 (87.4)	151 (89.9)
Grade 4 AE	342 (62.4)	294 (52.3)	237 (63.9)	198 (50.5)	104 (59.4)	96 (57.1)
Any serious AE	325 (59.3)	244 (43.4)	227 (61.2)	168 (42.9)	97 (55.4)	76 (45.2)
AE with fatal outcome*	81 (14.8)	52 (9.3)	57 (15.4)	31 (7.9)	23 (13.1)	21 (12.5)

*AEs for whom the investigator documented the outcome "death". This does not imply a causal relationship with the study treatment.

On examination, AEs that had a rate of at least 5% higher in the cetuximab+CTX group in the safety population, febrile neutropenia (23.4% vs 16.7%) and pyrexia (22.3% vs

14.3%) were again notably higher in those with high EGFR expression. For the Grade 3 and 4 AEs, as seen with the safety population, the high EGFR group treated with cetuximab had higher rates of febrile neutropenia (22.3% vs 16.1%), leukopenia (28.0% vs 19.6%), neutropenic infection (3.4% vs 1.2%), pneumonia (4.0% vs 3.0%) and hypomagnesaemia (1.7% vs 0.6%). AEs of special interest, such as acne-like rash, mucositis, thromboembolic events and septic events, were greater in patients treated with cetuximab irrespective of EGFR status and did not occur at a higher rate in the high EGFR expressing group than the safety population.

In study CA225099, the frequency of Grade 3 or 4 AEs was higher with cetuximab treatment irrespective of EGFR status. For AEs of any grade with a rate difference of at least 5% in the safety population, nausea, constipation, diarrhoea, weight decreased, hypomagnesaemia and epistaxis all remained more frequent in the high EGFR expressing subgroup when treated with cetuximab+CTX. Grade 3 and 4 AEs of fatigue, pneumonia, dehydration, acute renal failure and dizziness were all more frequent in those treated with cetuximab in both the low and high EGFR expressing groups. For AEs of special interest in CA225099, the pattern was similar between the high EGFR expressing group and the safety population, apart from a higher rate of mucositis (43.6% vs 34.5%) and infusion related reactions (20.5% vs 16.0%), respectively.

In the overall safety set (4 randomised controlled trials), the AEs of special interest with the observation period standardised were also presented. Severe infectious complications (febrile neutropenia, pneumonia or septic events) with an outcome of patient death occurred in 9.8% and 8.0% of the cetuximab+CTX and CTX groups, respectively. For thromboembolic complications, the rates were 6.8% vs 4.8% for Grade 3 and 4 events, 3.4% vs 2.3% for pulmonary embolism and 2.2% vs 1.5% for deep venous thrombosis in the cetuximab+CTX and CTX groups, respectively. For renal failure there was a higher rate in cetuximab+CTX treated patients in CA225099 (4% vs 0.6%) with no cases of Grade 4 renal failure and Grade 3 renal failure being less frequent (0.9% vs 0.3%). The increased frequency of renal failure was not noted in the other 3 studies.

Serious Adverse Events and Deaths

Deaths

In all studies combined, when examining the same follow up period (up to 30 day post CTX) there were 126/979 (12.9%) deaths in the cetuximab+CTX group compared to 115/991 (11.6%) in the CTX group.

In the supplementary data AEs with fatal outcome were presented. In study EMR 62202-046, there was a higher rate of fatal AEs in the cetuximab+CTX group compared to the CTX group (14.8% vs 9.3%). For those with high EGFR expression the fatal AE rates were similar (13.1% and 12.5%). In study CA225099, the fatal AE rate was higher in patients treated with cetuximab+CTX than CTX (12.0% vs 8.8%), though was less than this in the high EGFR expressing group (2.6% vs 7.9%)

SAEs

Overall, there were more SAEs and more treatment related SAEs, in subjects treated with cetuximab+CTX than in those treated with CTX alone. In the Phase III studies, SAEs occurred in 59.3% vs 43.4% (EMR 62202-046) and 55.4% vs 37.8% (CA225099) in the cetuximab+CTX and CTX groups, respectively. A reanalysis of SAEs was undertaken, as requested by the evaluator, which adjusted for differences in the observation period between treatment groups. In the 4 main studies which comprised the main safety set, the SAE rate was 49.9% and 39.0% in the cetuximab+CTX and CTX groups, respectively.

For those with high EGFR expression, the SAE rate remained higher when treated with cetuximab+CTX (55.4% vs 45.2% in EMR 62202-046 and 64.1% vs 31.6% in CA225099). In the high EGFR expressing subgroup, the SAEs with a higher rate in the cetuximab+CTX treatment group were neutropenia, leukopenia, pneumonia and sepsis, which are similar to the overall population.

Safety in special populations

Safety was assessed by age and EGFR expression status in study EMR 62202-046. This found that in patients aged ≥ 65 years there was a higher rate of Grade 3 and 4 AEs, SAEs and fatal AEs and this was still noticeable in those with high EGFR expression.

Evaluator's overall conclusions on clinical safety

Data from the 6 clinical trials in NSCLC were used in the initial application safety evaluation and included 2036 subjects of whom 1045 were exposed to cetuximab. From this population there were 175 and 39 high EGFR expressing subjects exposed to cetuximab+CTX in studies EMR 62202-046 and CA225099, respectively. Safety data were not pooled from these studies.

In EMR 62202-046, for the high EGFR expressing group the rate of Grade 3 or 4 AEs was comparable between treatment groups (87.4% vs 89.9%) and Grade 4 AEs were slightly higher with cetuximab+CTX (59.4% vs 57.1%). As with the safety population, the high EGFR group treated with cetuximab had higher rates of Grade 3 and 4 febrile neutropenia (22.3% vs 16.1%), leukopenia (28.0% vs 19.6%), neutropenic infection (3.4% vs 1.2%), pneumonia (4.0% vs 3.0%) and hypomagnesaemia (1.7% vs 0.6%). Acne-like rash, mucositis, thromboembolic events and septic events, were greater in patients treated with cetuximab irrespective of EGFR status. Data from the small group in CA225099, found the frequency of Grade 3 or 4 AEs was higher with cetuximab treatment irrespective of EGFR status with a similar nature AEs.

In EMR 62202-046, the fatal AE rate in the high EGFR expressing group (13.1% vs 12.5%) was in line with the overall population (14.8% vs 9.3%) and remained higher in those treated with cetuximab+CTX compared to CTX alone. For those with high EGFR expression, the SAE rate was notably higher when treated with cetuximab+CTX (55.4% vs 45.2% in EMR 62202-046 and 64.1% vs 31.6% in CA225099) though the rate difference of 10.2% in EMR 62202-046 was in line with the safety population (10.9%). The SAEs with a higher rate were neutropenia, leukopenia, pneumonia and sepsis, which was comparable to the safety population.

The safety data in those with high EGFR expressing tumours was in line with the overall safety population in terms of rates of AEs and nature of AEs with no remarkable safety signals. The subgroup exposure however is only 214 patients (compared to 1045), so rarer events may not be detected.

The sponsor presented data from the overall safety set (4 randomised controlled trials) with the observation period standardised as the issue of differing observation periods between treatment groups was raised in the initial evaluation. In all studies combined, up to 30 day post CTX, the death rates were 12.9% and 11.6 % in the cetuximab+CTX and CTX groups, respectively. The adjusted SAE rate was 49.9% in the cetuximab+CTX compared to 39.0% in the CTX group.

Supplementary Clinical Evaluation – List of Questions

There were three questions raised by the evaluator in the initial data package evaluation. The sponsor provided answers in the supplementary data package. These are summarised below together with new questions relating to the supplementary data.

Pharmacokinetics

Question: It was noted that the application submitted in the USA was withdrawn in 2009 due to issues raised by the FDA regarding PK comparability of the US-marketed product and the product used in clinical trials.

Sponsor's response: The pivotal Phase III trial EMR 62202-046 used PBS 2 mg/mL formulated material manufactured by Boehringer Ingelheim (EU). Since this material is not registered in the US the FDA requested further comparability studies. A safety study comparing EU and US material in SCCHN was conducted and a small safety study using US material in NSCLC is currently ongoing. Study CS225099 used 2 mg/mL PBS formulated material from ImClone which is US registered. In the EU and Australia comparability has previously been demonstrated for both PBS 2 mg/mL and GCTS 5 mg/mL formulated material from both manufacturers.

Evaluator's comments: *This explanation was acceptable*.

Efficacy

- The supplementary data package stated the EGFR staining in EMR 62202-011 was ongoing and that the availability of tumour slides in CA225100 was under evaluation. Are these data available? If so, please provide results and commentary.
- Is the DAKO PharmDx kit validated for use in NSCLC? The manual refers only to use in colorectal carcinoma.

Question: A study report for the meta-analysis data provided in the PowerPoint presentation should be provided.

Sponsor's response: The sponsor stated that the new data presented in the supplementary submission supersede the meta-analysis efficacy data.

Evaluator's comments: *The evaluator agreed with this.*

Safety

- It is noted that aseptic meningitis is a newly identified risk of cetuximab treatment. Are there any other risks that should be added to the product information? Has the review of acute renal failure been completed and, if so, are there any data that should be included in the PI?

Question: Data on the frequency of SAEs and Grade 4 AEs during the chemotherapy phase of the 4 controlled trials (that is, after adjustment for similar observation periods) should be provided.

Sponsor's response: The sponsor provided supportive safety analyses as requested.

Evaluator's comments: *The safety results with adjusted observation periods show a tendency to reduce the magnitude of additional adverse event rates when treated with cetuximab. However, there still remains a noticeable poorer safety profile.*

Product Information/Consumer Medicine Information

There were also questions relating to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Supplementary Clinical Evaluation – Conclusion

Clinical Aspects

Clinical Efficacy

The initial evaluation noted that, while there is evidence of activity of cetuximab against NSCLC through positive results in ORRs in all 4 trials, the overall efficacy results, as measured by the clinically relevant endpoints of OS and PFS, were found to be marginal and discordant between trials. In EMR 62202-046, there was a modest benefit in OS of 1.2 months (HR=0.87, 95% CI: 0.76, 0.99, p=0.044) but there was no significant improvement in PFS. In CA225099, the primary endpoint of PFS as assessed by an IRRC, was not met and OS was not improved. Neither OS nor PFS were significantly improved in the 2 Phase II trials.

In this submission, new biomarker data from the two pivotal Phase III studies were presented. An IHC composite score was generated ranging from 0 (no staining) to 300 (100% of cells with strong staining) with a cut-off of 200, based on the ORR, for low and high EGFR expression.

In EMR 62202-046, of the 1125 subjects randomised 99.6% had samples available for testing and 31% (345) were high EGFR expressing. As EGFR expression was not an inclusion criteria in CA225099, of the 676 patients randomised, there were evaluable samples from only 20.1% (136) patients and 56.6% (77) of these were high EGFR-expressing. The means that the efficacy data are based on a subgroup of 422 patients.

In EMR 62202-046, the high EGFR expressing group treated with cetuximab+CTX had an increase in median OS time of 2.4 months (12.0 vs 9.6 months) with a significant HR of 0.73 (95% CI: 0.58, 0.93, p=0.011). In contrast, the low EGFR expressing group had no improvement in OS (9.8 vs 10.3 months, HR=0.99, 95% CI: 0.84, 1.16 p=0.879). The median PFS time was still not significantly improved (HR=0.86, 95% CI: 0.68,1.09, p=0.216), though there was a minor increase in PFS time of 0.4 months compared to no difference in the ITT population.

Study CA225099 was used for validation as there was a small group with EGFR expression data. Due to imbalance between the treatment groups for age in this subgroup, adjusted rates were provided. For those with high EGFR expression, the age adjusted PFS was 4.6 months for cetuximab+CTX compared to 4.2 months for CTX alone (HR 0.84, 95% CI: 0.47,1.51) and age adjusted OS was 9.3 months and 7.6 months, respectively (HR 0.77, 95% CI: 0.46, 1.30). Neither results reached statistical significance, though there are signs of modest improvement in PFS (0.4 vs 0.2 months) and OS (1.7 vs 1.3 months) in the high EGFR expressing compared to the ITT population. These results need to be interpreted with caution due to the small numbers, the possibility of a non-representative group and the fact this was a *post hoc* subgroup analysis of a study that was negative.

For those with high EGFR expression, the benefit in OS was seen across the subgroups of <65 years, Caucasians, squamous cell carcinoma and Stage IV, while no benefit was found in Asian patients, though numbers were low (n=49).

A variety of other biomarkers were assessed from available samples from the two studies. None of these biomarkers, including EGFR gene copy number assessed by FISH, were found to provide any predictive value for establishing which tumours may be more responsive to cetuximab.

Clinical Safety

Data from the 6 clinical trials in NSCLC were used in the initial application safety evaluation and included 2036 subjects of whom 1045 were exposed to cetuximab. There

were 175 and 39 high EGFR expressing subjects exposed to cetuximab+CTX in studies EMR 62202-046 and CA225099, respectively. Safety data were not pooled from these studies.

The safety profile was similar in the high EGFR expressing group to the overall safety population. The rate of Grade 3 or 4 AEs was similar between treatment groups (87.5% vs 89.9%) and Grade 4 AEs were slightly higher with cetuximab+CTX (59.4% vs 57.1%). For Grade 3 and 4 AEs, the high EGFR group treated with cetuximab had higher rates of febrile neutropenia (22.3% vs 16.1%), leukopenia (28.0% vs 19.6%), neutropenic infection (3.4% vs 1.2%), pneumonia (4.0% vs 3.0%) and hypomagnesaemia (1.7% vs 0.6%). Acne-like rash, mucositis, thromboembolic events and septic events, were greater in patients treated with cetuximab irrespective of EGFR status. Data from CA225099 supported these findings, though was limited by small numbers.

In EMR 62202-046, the fatal AE rate was higher in those treated with cetuximab, though this was more marked in the overall population (14.8% vs 9.3%) than in the high EGFR expressing group (13.1% and 12.5%). For those with high EGFR expression, the SAE rate remained higher when treated with cetuximab (55.4% vs 45.2% in EMR 62202-046 and 64.1% vs 31.6% in CA225099) and the rate difference in EMR 62202-046 was in line with the overall safety population (10.2% vs 10.9%). The SAEs with a higher rate remained neutropenia, leukopenia, pneumonia and sepsis.

As the issue of differing observation periods between treatment groups was raised in the initial evaluation, the sponsor presented data from the overall safety set (4 randomised controlled trials) with the observation period standardised. In all studies combined, up to 30 day post CTX, the death rates were 12.9% and 11.6 % and the adjusted SAE rate was 49.9% and 39.0% in the cetuximab+CTX and CTX groups, respectively.

Benefit Risk Assessment

Benefits

The initial evaluation of cetuximab in NSCLC found a modest improvement in median OS of 1.2 months with an HR of 0.87 (95% CI: 0.76, 0.99, p=0.044) in the main trial and modest evidence of activity against NSCLC on ORR across the 4 controlled studies. For the subgroup of patients with high EGFR expression, the improvement in OS increased to 2.4 months (HR 0.73, 95% CI: 0.58, 0.93, p=0.011) while there was no benefit found with cetuximab for those with low EGFR expression levels (HR 0.98, 95% CI: 0.73, 1.30 p=0.879). Despite this improvement in OS, PFS was not significantly improved in the high EGFR expressing group, though there was a minor change to 0.4 months from no difference in the ITT population. The second Phase III study had negative results on PFS and OS, however, in the small validation set, subjects with high EGFR expressing tumours showed a non-significant trend towards improvement in these outcomes.

The benefit of cetuximab treatment on OS of 1.2 months was of borderline statistical significance and not supported by the secondary endpoint of PFS or the results in the other 3 trials and so did not appear convincing. However, in the subgroup of patients with high EGFR expressing tumours, cetuximab appears to have greater activity with OS doubling to 2.4 months together with a reduction in the hazard ratio from 0.87 to 0.73 and an improvement in the degree of statistical significance. This finding is in line with benefits seen with other agents.

The efficacy findings were consistent across subgroups of gender, age, staging and performance status. For histology, SCC showed the highest response and the result was statistically significant.

Risks

The risks of cetuximab treatment in advanced NSCLC patients were outlined in the initial evaluation. This noted that adverse events were virtually universal in this patient group and resulted in about 25% of subjects ceasing cetuximab treatment. Many of the AEs were consistent with the current product labelling for cetuximab, such as infusion related reactions, skin reactions, mucositis, thromboembolic events and electrolyte disturbances. The sponsor has now also proposed to include the risk of cardiac events, that was highlighted in the initial evaluation, in the product information.

The major additional concern with cetuximab, when used concurrently with platinum based chemotherapy in NSCLC, is the notably increased rate of Grade 3 or 4 AEs and of SAEs. Events of concern were leukopenia and neutropenia and their infectious complications (febrile neutropenia, pneumonia and sepsis).

The evaluation of safety data for the subgroup of patients with high EGFR expression found a similar AE profile, with no notable increase in the AE rates, compared to the overall safety population.

The safety subpopulation consisted of only 214 patients with high EGFR expressing tumours exposed to cetuximab. With such a small group, the risk of undetected, rarer events remains present, although it is expected that safety in this subgroup would remain in line with the broader NSCLC population.

The efficacy subpopulation was modest (422 patients) and the weight of evidence comes from one pivotal trial without confirmatory evidence from the second study.

Subgroup analysis indicated a detrimental effect in Asian patients, though the numbers were small.

Balance

It is well known that lung cancer has a low 5 year survival and the treatment options are limited for advanced stage disease. The mainstay of first line treatment is cytotoxic platinum based chemotherapy doublets and more recently there has been the addition of bevacizumab and small molecule inhibitors of EGFR tyrosine kinase (erlotinib and gefitinib). As such treatments are only providing small incremental benefits and overall survival, regrettably, remains short, there is an obvious unmet medical need in the treatment of advanced NSCLC.

The initial evaluation of cetuximab treatment in advanced NSCLC found a negative benefit risk balance. The marginal benefit on OS of 1.2 months from one positive Phase III study was outweighed by discordant results between OS and PFS, a negative second Phase III study and a significant risk of severe side effects.

The pivotal Phase III trial required EGFR expression for inclusion and so had prospective collection of tumour samples. This study, where 31% of tumours had high EGFR expression, provides the weight of evidence for a statistically significant benefit of cetuximab on OS (median 2.4 months, HR 0.73, p=0.01) in the high EGFR expressing group, the level of which is in line with other treatments for advanced NSCLC. For those with low EGFR expression, no significant improvements were found. In the small, retrospective subset from the second Phase III trial, where 57% of available samples had high EGFR expression, no significant results were found, however efficacy parameters trended in the direction of improved outcome and so provided some tenuous supportive evidence.

The difference in high EGFR expression rates in the two Phase III trials has not been fully explained though may be related to the different trial inclusion criteria. The sponsor

estimated that approximately 25% of NSCLC will meet the criteria for high tumour expression of EGFR.

The analysis of a number of other tumour biomarkers relating to EGFR protein expression, EGFR gene copies, or EGFR mutations, only found high EGFR expression to be predictive of response to cetuximab. An EGFR positive FISH status, found in 37% of tumours, was not associated with improved outcomes with cetuximab. It is noted, however, that many of these analyses were of small numbers so the ability to extrapolate results is limited. While FISH status is used for identifying breast cancer patients who will benefit from trastuzumab, this was not found predictive for cetuximab in NSCLC and the sponsor is not advocating routine testing.

The composite IHC scoring used to identify the high EGFR expressing subgroup used the DAKO PharmDx kit which is available in Australia, validated and FDA approved. As the manual refers only to colorectal cancer it remains to be confirmed that the validation extends to NSCLC.

Cetuximab is a treatment which has considerable serious risks and in the broad NSCLC population the benefit risk balance was found to be negative. In the subgroup of patients with high EGFR expressing tumours, there was a noticeable and statistically significant increase in overall survival which was combined with no deterioration in the safety profile. The results are based on small numbers from one trial, there is ongoing discrepancy with PFS and a lack of available data from the supportive trial. However, the pivotal trial was well designed and conducted and the non-significant results from the second trial were trending in favour of cetuximab treatment.

The TGA-adopted EU guideline recommends that if licensing is to be based on one pivotal study, it requires demonstration of efficacy at levels beyond standard criteria for statistical significance.[21] Study EMR 62202-046 had a suitable population from which to extrapolate data, a clinically relevant effect size on a key outcome of interest, an improvement in statistical significance level in the targeted subgroup, a plausible hypothesis and consistent finding across subgroups.

Taking these factors into account, the evaluator believed that the increase in the clinically relevant outcome of overall survival, in a patient group who have a potentially fatal disease with limited treatment options, outweighs the lack of confirmatory evidence and the adverse safety profile. In addition, excluding patients with low EGFR expression, where no beneficial effects were seen, has been important in improving the benefit risk balance for this treatment.

Given the poor prognosis for patients with advanced NSCLC, and the limited number of treatment options, the evaluator recommended that there is place for the use of cetuximab in patients with high EGFR expressing tumours as defined by an IHC composite score of over 200. The risks of treatment need to be thoroughly outlined in the product information and subject to a careful risk management system.

Conclusions

After considering the responses to the initial questions and evaluating the supplementary data provided, it was concluded that the overall benefit risk balance of cetuximab is favourable for the indication of:

[21] EMEA, Committee for Proprietary Medicinal Products (CPMP), 31 May 2001. Points to Consider on Application with 1. Meta-analyses, 2. One Pivotal Study, CPMP/EWP/2330/99.

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR-expressing tumours.

This recommendation assumes there is no change to the risk benefit balance after provision of responses to the questions described in this AusPAR. In addition, the RMP provided in the initial evaluation was dated July 2008 and should be updated in relation to the high EGFR expressing subgroup and more recent information.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor identified the following safety concerns (Table 26) which were described in an updated RMP which was provided after the supplementary clinical evaluation

Table 26: Safety Concerns for Erbitux

Important identified risks	• Infusion-related reactions
	• Skin reactions
	  • Superinfections of skin lesion and subsequent complications
	  • Radiation dermatitis
	• Hypomagnesemia
	• Deep vein thrombosis
	• Pulmonary embolism
	• Diarrhoea
	• Increase in liver enzyme levels (ASAT, ALAT, AP)
	• Dehydration, in particular secondary to diarrhoea and mucositis
	• Cardiac ischemia including myocardial infarction and congestive heart failure (in combination with fluoropyrimidines)
	• Palmar-plantar erythrodysesthesia syndrome (in combination with fluoropyrimidines)
	• Severe leukopenia or severe neutropenia, and infectious complications such as febrile neutropenia, pneumonia and sepsis (in combination with platinum-based chemotherapy)

Important potential risks	• Interstitial pneumonitis • Reversible posterior leukencephalopathy syndrome (RPLS) • Haemolytic disorders and disseminated intravascular coagulation (DIC) • Transplant rejection • Thrombotic thrombocytopenic purpura • (Acute) renal failure • Toxic epidermal necrolysis/Stevens-Johnson syndrome • Gastrointestinal perforation
Important missing information	None Since its marketing authorisation the cumulative number of patients exposed worldwide to Erbitux is estimated to be 317,838 (PSUR 9, period 01 December 2003 to 30 September 2010) which enables a comprehensive evaluation of the safety profile of Erbitux.

Clinical review

The clinical evaluator noted that from the NSCLC studies in the initial clinical evaluation, the newly identified safety concerns included in the RMP were severe leukopenia and neutropenia, dehydration (in particular secondary to diarrhoea) and mucositis, and (acute) renal failure. Interaction with platinum based chemotherapy was noted to result in an increased risk of severe leukopenia and neutropenia and consequent infectious complications. An in depth review of the acute renal failure cases in CA225099 was proposed to be undertaken.

The increased frequency of cardiac events in those with a history of cardiac disease was not included in the RMP. The RMP should be updated to reflect this additional safety signal. It was noted that this information has also been requested by the EMA. The data pertaining to the review of acute renal failure should also be provided.

Upon review of the supplementary clinical evaluation report, the evaluator noted that aseptic meningitis was a newly identified risk and that careful monitoring of gastrointestinal perforation and radiation dermatitis has been proposed in EU. A review of acute renal failure cases was also previously proposed. Subgroup analysis found a non-significant detrimental effect in Asian patients and this should be monitored. It was recommended the RMP be updated to include these findings.

The sponsor stated that aseptic meningitis was included as a potential risk in the previous RMP version and the sponsor considered that updating the product labelling was sufficient to address this. As such aseptic meningitis was removed from the RMP. The OPR reviewer noted that an updated PI was not available to review but consistent with the clinical evaluators request, the PI should include an appropriate statement regarding aseptic meningitis.

Additional important potential risks that have been added are toxic epidermal necrolysis and gastrointestinal perforation.

Pharmacovigilance Plan

The sponsor proposed routine pharmacovigilance (PV) activities for all identified and potential risks.[22] The sponsor proposed additional pharmacovigilance activities for the following risks:

- Radiation dermatitis
- Severe leukopenia or severe neutropenia, infectious complications and sepsis (when used in combination with platinum based chemotherapy)
- Acute renal failure
- Gastrointestinal perforation

Neutropenia – The ongoing study from the previous evaluation has now been completed. The findings, as reported by the sponsor, confirmed the greater risk of this outcome associated with treatment. This will continue to be included as an identified risk, with monitoring via routine PV.

Acute renal failure (ARF) – a review of ARF was conducted throughout PSURs, and it was determined to be rarely reported. This will continue as a potential risk, with monitoring via routine PV.

Gastrointestinal perforation– careful monitoring as part of routine PV is considered adequate, with specific updates provided in PSURs.

The clinical evaluation included a statement regarding a potential detrimental effect in Asian patients. The sponsor was therefore requested to provide analysis or comment in subsequent Periodic Safety Update Reports (PSURs).

[22] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Risk Minimisation Activities

The sponsor proposed routine risk minimisation activities (product labelling) for all identified risks and additional activities for radiation dermatitis.[23]

The RMP reviewer noted that the additional activity is a health care professional and patient educational program on a country specific basis to address the risk of radiation dermatitis. The program objectives are to ensure adequate training to providers about prophylactic measures and treatment guidelines as a pre-requisite for administering cetuximab. As this is the EU RMP, the sponsor was asked to clarify the details of this educational program as it would relate to Australia.

Regarding the specific risk of neutropenia/leukopenia with combined risk with platinum containing agents, it was noted that a further update to the PI is proposed as appropriate depending on the results from an ongoing study. The proposed PI statements were considered satisfactory is terms of understanding of this risk, however the sponsor was requested to consider enhancing the wording to better instruct physicians regarding what actions to take with cetuximab once the identified risk is detected.

Summary

The pharmacovigilance plan and application of risk minimisation activities as proposed by the sponsor was considered acceptable with the following assurances:

- The approved PI includes an appropriate statement regarding aseptic meningitis,
- PSURs will include comments on:
    - Radiation dermatitis
    - Neutropenia
    - Aseptic meningitis (if present)
    - Acute renal failure
    - Gastrointestinal perforation, and
    - Potential detrimental effect in Asian patients.

It was recommended to the Delegate that the implementation of RMP version 14.1, including the sponsor's commitment to address specific safety concerns in PSURs and any future updates, be imposed as a condition of registration if this product is approved.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The submission included some published preclinical efficacy data. Cetuximab demonstrated anti-NSCLC tumour activity in a variety of *in vitro* models and in *in vivo* models using NSCLC xenografts in athymic mice. No new nonclinical safety data were submitted.

[23] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The nonclinical evaluator had no objections to registration.

Initial Clinical Submission

Pharmacokinetics

PK data were collected using frequent sampling in one phase II trial in NSCLC patients (study 6202-011/LUCAS). Coadministration of cisplatin and vinorelbine did not affect the PK of cetuximab and the cetuximab PK parameters were consistent with those observed in the currently approved indications.

Peak and trough levels were measured in four studies. Levels remained reasonably constant over time. A population PK analysis was also submitted. Values obtained for clearance and volume were consistent with those previously observed.

Efficacy

The submission included two pivotal randomised controlled trials:

- Study 62202-046 (the FLEX trial); and
- Study CA225-099 (the BMS099 trial).

Both studies have been published (Lancet 2009 and JCO 2010 respectively).[24,25]

Study -046 (FLEX)

This trial enrolled subjects with previously untreated advanced NSCLC. The study only included subjects with tumours with immunohistochemical evidence of EGFR expression. All subjects were treated with 6 cycles of cisplatin and vinorelbine, and subjects were randomised to receive cetuximab or no additional treatment. The study was not blinded.

The primary endpoint was overall survival. Cetuximab therapy was associated with a statistically significant improvement in overall survival - HR 0.871 (95%CI: 0.762 – 0.996; p = 0.0441). Median survival was prolonged by 1.2 months (11.3 vs 10.1). One year survival was increased by 5 % (47% vs 42%) and two year survival by 3% (20% vs 17%). The Kaplan-Meier curve is shown at Figure 2.

For secondary endpoints, cetuximab therapy was also associated with statistically significant improvements in overall response rate and time to treatment failure. However there was no significant benefit in terms of progression free survival. There was some evidence of deterioration of overall quality of life in the cetuximab arm during treatment but not in the longer term.

Study CA225-099

This study also enrolled subjects with previously untreated NSCLC but did not require immunohistochemical evidence of EGFR expression on tumours. All subjects were treated with 6 cycles of carboplatin and a taxane with and without cetuximab.

The primary endpoint was PFS as assessed by a blinded independent radiology review committee (IRRC). There was no significant difference between the treatment arms.

For secondary endpoints, there was a significant benefit associated with cetuximab treatment in terms of response rate (25.7% vs 17.2%) but no significant benefit in terms

[24] Pirker R, Pereira JR, Szczesna A. Cetuximab plus chemotherapy in patients with advance non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009; 373: 1525-31.

[25] Lynch TJ, Patel T, Driesbach L et al. Cetuximab and First-Line Taxane/Carboplatin Chemotherapy in Advanced Non–Small-Cell Lung Cancer: Results of the Randomized Multicenter Phase III Trial BMS099. J Clin Oncol 2010; 28: 911-917.

of overall survival. According to the published version of the study there were no differences between groups in terms of lung cancer symptoms.

Supportive studies

The submission included two earlier randomised controlled phase II trials (CA225-100 and EMR 62 2010-011/LUCAS) which compared cetuximab added to platinum based doublet therapy against platinum based doublet therapy alone. In both studies cetuximab therapy was associated with a non-significant trend towards improved response rates.

Safety

A total of 1045 NSCLC patients were exposed to cetuximab in the submitted studies. The pattern of toxicity of cetuximab observed in the randomised controlled trials in NSCLC was generally consistent with that previously observed in colon cancer and SCCHN. Prominent toxicities included:

- Skin toxicity – rash, dry skin, dermatitis acneiform;
- GIT toxicity – diarrhoea, stomatitis, mucosal inflammation, nausea, constipation, anorexia, etc;
- Electrolyte disturbances – hypomagnesaemia, hypocalcaemia, hypokalaemia;
- Infusion reactions;
- Abnormal LFTs;
- Thromboembolic events;

Observed toxicities not previously associated with cetuximab included:

- An increase in the incidence of neutropenia (including Grade 3 or 4) and its associated complications such as febrile neutropenia, septic events, pneumonia;
- An increase in the incidence of cardiac adverse events (principally arrhythmias) was observed in one of the pivotal studies (CA225-099);

As shown in Table 27, the addition of cetuximab to chemotherapy was associated with a notable increase in the incidence of Grade 3 or 4 toxicity and serious adverse events. Approximately 20-30% of subjects discontinued treatment with cetuximab due to adverse events. There was no apparent increase in the incidence of study drug related deaths.

Table 27: Incidence of various adverse events

	Incidence	
	Cetuximab + CTX	CTX alone
Adverse events - Study -046 - Study -099	 99.5 % 99.7 %	 97.7 % 99.7 %
Grade III or IV adverse events - Study -046 - Study -099	 91.1 % 79.1 %	 86.3 % 61.3 %
Serious adverse events - Study -046 - Study -099	 59.3 % 55.4 %	 43.4 % 37.8 %
AEs leading to discontinuation of cetuximab - Study -046 - Study -099	 19.9 % 30.5 %	 - -

Antibodies to cetuximab were not detected in the 176 NSCLC subjects who were tested.

Evaluator's conclusion

The evaluator considered that the benefits obtained from adding cetuximab to chemotherapy were modest (a prolongation of median survival of only 1.2 months) and efficacy was not consistently demonstrated in both pivotal studies, and the benefits of the drug were outweighed by the additional toxicity produced. The evaluator therefore recommended rejection of the application.

Supplementary Clinical Submission

Efficacy

In response to the initial negative clinical evaluation report the sponsor proposed a revised indication, which limited use of the product to patients with tumours that have high levels of EGFR expression as assessed by immunohistochemistry. Efficacy for this revised indication was supported by a retrospectively conducted subgroup analysis of study -046 (FLEX). At the time of writing this subgroup analysis had not been published.

All patients enrolled in study -046 were required to have immunohistochemical evidence of tumour EGFR expression. Hence data on the EGFR expression were collected prospectively. A total of 31% of subjects enrolled in the trial were determined to have tumours that had high levels of EGFR expression.

The efficacy benefit produced by the addition of cetuximab to chemotherapy was greater in the high EGFR population (hazard ratio 0.73 vs 0.87; difference in median survival 2.4 vs 1.2 months). A greater benefit was also seen on the secondary endpoints of response rate and time to treatment failure but not in terms of progression free survival (PFS).

EGFR expression was not an inclusion criterion for the second Phase III trial (study CA225-099) and hence only 20% of patients (n = 136) had evaluable tumour samples. Of these subjects, approximately 57% of subjects (n= 77) had tumours with high EGFR expression. There was no significant benefit associated with cetuximab in terms of PFS or overall survival.

Other biomarkers

In colon cancer, cetuximab (and the related product panitumumab) are only effective in patients without mutations of the KRAS gene. Analyses of efficacy according to KRAS mutation status were conducted for both the pivotal studies. There was no evidence of improved efficacy in patients with wild type KRAS mutation status. In addition, a number of other biomarkers were assessed, including EGFR gene copy number by FISH, and EGFR mutation status. None of the other biomarkers were found to be predictive of efficacy.

Safety

Analysis of the safety data from the pivotal studies according to level of EGFR expression, did not suggest any differences in toxicity in patients with high EGFR tumours compared to the ITT population.

Risk Management Plan

The most recent Risk Management Plan proposed by the sponsor was found to be acceptable by the TGA's Office of Product Review (OPR).

Risk-Benefit Analysis

Delegate Considerations

Overall risk benefit

The addition of cetuximab to chemotherapy resulted in a prolongation of median survival of 2.4 months in patients with tumours with high expression of EGFR. As noted by the clinical evaluator this level of efficacy has previously been accepted as being clinically significant in the first line treatment of NSCLC (for example, with bevacizumab). The addition of cetuximab resulted in approximately a 15% increase in the incidence of Grade III/IV adverse events and serious adverse events and a deterioration in quality of life during chemotherapy. Up to 30% of patients discontinued cetuximab due to adverse events. The pattern of adverse events was generally consistent with that previously seen with the drug, although neutropenia and its complications was a new finding. If the overall risk benefit is positive, it would appear to be only marginally so.

Validity/reliability of the subgroup analysis

The subgroup analysis on which the proposed indication is based was defined retrospectively. The efficacy findings should therefore perhaps be considered as hypothesis generating and needing to be confirmed by a further randomised controlled trial. However, the sponsor has indicated that it does not intend to conduct any further trials in this population for reasons relating to patent expiry.

In addition, significant efficacy has only been demonstrated in one study. The TGA-adopted EU guideline addresses this as follows:[21]

"*In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, ... " and:*

"Statistical evidence considerably stronger than p < 0.05 is usually required."

The p-value achieved in the subgroup analysis was 0.01 but it appears that no adjustment was applied for multiplicity of statistical testing.

Overall, given the marginal risk benefit ratio, the Delegate expressed concerns that the retrospectively conducted subgroup analysis is not a scientifically robust basis for approval. The Delegate was therefore inclined to reject the application.

Indication

If the advisory committee considers that the application could be approved, advice was sought as to whether the indication should be restricted to the specific chemotherapy combination for which significant evidence of efficacy is available, for example:

Erbitux in combination with ~~platinum-based chemotherapy~~ cisplatin and vinorelbine, is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with high EGFR-expressing tumours.

Diagnostic test

In the second clinical evaluation, the evaluator raised the issue of whether the EGFR testing kit used in the FLEX study has been validated for use on NSCLC specimens. The sponsor was requested to comment on this issue in the pre-ACPM response.

The Delegate was inclined to reject the application due to concerns regarding the validity/reliability of the evidence provided for efficacy.

Response from Sponsor

The sponsor noted it had applied to extend the approved indications for Erbitux (cetuximab) to include treatment of advanced, or metastatic non-small cell lung cancer (NSCLC). The proposed indication was revised based on the availability of new biomarker data capable of identifying patients with the largest benefit in the target population. The clinical evaluator was in agreement and concluded that the overall benefit risk balance of Erbitux was favourable for the following indication:

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR-expressing tumours.

The sponsor understood that the Delegate nevertheless remains concerned about overall risk benefit ratio and the validity/reliability of the subgroup analysis.

In this submission, the sponsor outlined why it believed that the indication proposed and recommended for approval by the clinical evaluator remains the most appropriate for Australian patients.

Unmet medical need in advanced or metastatic non-small cell lung cancer

The Australian Institute of Health and Welfare lists NSCLC as the leading cause of cancer death in Australia (AIHW, 2008).[19] Among the various types of cancer, advanced or metastatic NSCLC remains one of the most difficult tumours types to treat. As noted by the clinical evaluator in the first clinical evaluation report: "Treatment options are limited for advanced stage disease. The main stay of first line treatment is cytotoxic platinum chemotherapy doublets. The addition of bevacizumab to chemotherapy has shown a statistically significant 2 month improvement in median OS (12.3 vs 10.3 months) for patients with non-squamous NSCLC. Second line treatment options include the small molecule inhibitors of EGFR tyrosine kinase (erlotinib and gefitinib). For NSCLC patients after failure of at least one CTX regimen, erlotinib improved overall survival by 2 months (6.7 vs 4.7 months) with a significant HR of 0.73 (p=0.001). Gefitinib did not significantly improve OS (HR=0.98, 5.6 versus 5.1 months) in patients with advanced or metastatic NSCLC who had failed chemotherapy and is only approved for use in such patients who have never smoked or who have already had some benefit from this treatment."

The use of cetuximab in high EGFR expressing NSCLC compares favourably to other agents: statistically significant benefits including overall survival (OS) in ITT population, and clinically meaningful increase in OS of 2.4 months (HR 0.73) in the high EGFR group (Study 046). In addition, it is important to appreciate that NSCLC is a heterogeneous disease and the cetuximab studies:

- Included all histologies and Performance Score (PS) 0, 1 and 2 (unlike other targeted therapies)
- Demonstrated benefits when combined with chemotherapy (CTX) (unlike erlotinib and gefitinib)
- Benefited across tumour types, for example, high EGFR adenocarcinoma (median OS 20.2 vs 13.6 months, HR 0.74) and squamous cell carcinoma (median OS 11.2 vs 8.9 months, HR 0.62) (unlike bevacizumab, which has a risk of potentially fatal pulmonary haemorrhage with tumours of SCC morphology)

Since EGFR mutations have never been described in SCC, this range supports the existence of a ligand dependent mechanism in NSCLC amenable to inhibition with EGFR monoclonal antibodies, such as cetuximab, rather than tyrosine kinase inhibitors, such as erlotinib and gefitinib.

Overall risk benefit

The sponsor proposed an indication restricted to patients empirically stratified to identify those most likely to benefit from the addition of cetuximab to CTX. The incremental benefit in median overall survival time demonstrated for the addition of cetuximab to CTX compared to CTX alone in the target high EGFR NSCLC population was 2.4 months, which is double the benefit seen in the ITT population (1.2 months) (Table 21). The result in the high EGFR group represents significant clinical benefit relative to existing therapies.

It should be noted that the FDA recommends OS as the primary endpoint in late phase clinical studies of oncology medicines particularly where the OS is relatively short and therefore the predictive value of progression free survival (PFS) is lessened (FDA guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics, May 2007).

Except for PFS, the efficacy benefit for cetuximab in the target high EGFR population is both statistically and clinically significant, particularly in a treatment area acknowledged to have a high unmet clinical need. The survival increment is at least as good as both bevacizumab and erlotinib. The Delegate noted that "this level of efficacy has previously been accepted as being clinically significant in the first line treatment of NSCLC (for example, with bevacizumab)".

Safety

"The major concern with cetuximab when used concurrently with platinum based chemotherapy in NSCLC is the notably increased rate of Grade 3 or 4 AEs and of SAEs. In the 4 controlled studies there was a 15.5% increased rate of SAEs."

However, in the high EGFR group currently under consideration, the proportion of patients who experienced a Grade 3 or 4 AE or AE with fatal outcome, were balanced between the treatment arms (Table 25).

Differences between the treatment groups are mainly attributable to the combination of cetuximab with platinum based CTX which may lead to an increased frequency of Grade 3 and/or 4 neutropenia or leukopenia or increased SAEs including (febrile) neutropenia and pneumonia. The overall frequencies of SAEs in the high EGFR expression group were

similar to those in the safety population (high EGFR expression group 55.4% vs 45.2%, safety population 59.3% vs 43.4%). The AE profile – in particular in combination with platinum based regimens - is in line with the proposed PI and there is no evidence for an increased toxicity in the target population of the high EGFR group.

In regard to neutropenia and associated AEs, it should be noted that febrile neutropenia was the most common SAE in both treatment groups in Study 046 (safety population 17.5% v 11.9%, high EGFR group 17.7% v 11.9%). When only those SAEs considered to be related to treatment with cetuximab are considered, the incidence is greatly reduced (Table 28)

Table 28: Incidence of neutropenia and associated AEs

Safety Population	SAE	Cetuximab related SAE
Neutropenia	8.6%	1.8%
Febrile neutropenia	17.5%	2.0%
Neutropenic sepsis	1.6%	0.5%
Pneumonia	3.5%	0.5%
Pyrexia	2.9%	0.7%

In terms of clinical consequences of febrile neutropenia in the ITT population, the primary publication of the Study 046 "FLEX" trial (Pirker 2009) noted that "The recorded rates of febrile neutropenia, including sepsis, did not affect the administration of chemotherapy and, most importantly, did not result in an increase in treatment-related deaths".[24]

Concerns have been raised in regard to an increased risk of cardiac AEs, principally arrhythmias, in BMS099. The first TGA clinical evaluation noted that the increase in cardiac events was limited to this trial: "cardiac events (including arrest, arrhythmia, congestive heart failure, infarction/ischemia, and sudden death) occurred at a similar frequency in 3 of the trials". In Study 046, frequencies of Grade 3 or 4 cardiac events were comparable between the study arms (5.7% vs 5.0%) but Grade 3 or 4 AEs belonging to the medical concept "infarction/ischaemia" tended to occur more frequently in subjects treated with cetuximab + CTX (1.5% vs 0.7%). All but one subject had a medical history of coronary artery disease and/or cardiovascular risk factors. A similar trend was seen in the low but not in the high EGFR expression group.

The increased rate of AEs with an outcome of death reported in the four NSCLC trials in elderly patients (≥65 years) treated with cetuximab, and largely accounted for by cardiac events, was not evident in the high EGFR group. Indeed the incidence of these events was actually lower in the cetuximab treatment group of the high EGFR target population.

These observations are difficult to interpret, as an increased risk for cardiac events would normally be expected to be irrespective of the EGFR expression level on the tumour. It cannot be excluded that the balanced result for cardiac events between treatment arms in the high EGFR expression group is a chance finding as the number of patients with events per age group is low. The sponsor therefore already included an appropriate statement in the "Precautions" section of the PI.

The Delegate also noted that "Up to 30% of patients discontinued cetuximab due to adverse events." However, discontinuation rates for CTX in the study control arms are also high, ranging from 12.1% to 30.2% in the supportive studies and 17.2% to 18.9% in the pivotal trials. In Study 046, cetuximab and CTX discontinuations due to AEs were similar

(19.9% cetuximab vs 18.9% CTX in the control arm). The AEs leading to discontinuation of study drugs were consistent with the known safety profiles of the individual study drugs.

Importantly in Study 046, the addition of cetuximab did not appear to increase the proportion of patients discontinuing CTX due to AEs (safety population cetuximab + CTX vs CTX 20.3% vs 18.9%) although variable results were seen in the other studies. As requested by the clinical evaluator and the Delegate, discontinuation rates due to AEs have been added to the 'Clinical Trials' section of the PI for all four NSCLC studies.

In all 4 studies, cetuximab could be continued as monotherapy following the six cycles in combination with chemotherapy, until disease progression or unacceptable toxicity occurred. It can therefore be partly explained by the trial design that more patients discontinued any study drug due to AEs in the cetuximab arm. The clinical evaluation report for the ITT population notes the inherent imbalance in the evaluation of AEs and in relation to Study 046 also notes that "Adding cetuximab did not impact on CTX (cisplatin and vinorelbine) treatment as the number of infusions, median duration of treatment, cumulative dose, dose intensity, and relative dose intensity in the 2 treatment groups were similar". Indeed, 44% of patients continued on cetuximab as monotherapy following the completion of the chemotherapy phase, over half of these patients for more than 9 additional weeks, indicating the acceptability of treatment with cetuximab.

The Delegate also noted "a deterioration in quality of life during chemotherapy" in Study 046. As stated in the clinical evaluation of the ITT population "It was noted that there was a temporary decrease in QoL across a number of scales during Cycle 3 of treatment in subjects receiving cetuximab+CTX. The sponsor proposed that this may be due to skin reactions occurring at this time." This was indeed the case. As noted in the *Clinical Study Report*, "The report (on Quality of Life) concludes that when employing longitudinal models over the whole treatment period, no significant differences in QoL between the study groups were observed. The scales for social, physical and role functioning tended to be lower in subjects treated with cetuximab after treatment in Cycle 3. This is consistent with the occurrence of skin reactions at this time point. An additional confounding factor is the different return rate of QoL questionnaires at this time point. Overall, and taking all possible biases into account, there was no apparent long term effect of cetuximab on QoL." Therefore, whilst there was a decrease in QoL associated with cetuximab therapy, it was only temporary. Overall, treatment with cetuximab did not negatively impact patient QoL.

Validity/reliability of the subgroup analysis

There is a strong biological rationale that EGFR expression level plays a major role in NSCLC and EGRF expression was accordingly an inclusion criterion for the pivotal FLEX study. The Delegate was concerned by the subgroup analysis on which the proposed indication is based being defined retrospectively, even though the data on EGFR expression were collected prospectively. The FLEX protocol defines, under subgroup analysis, the following subgroups: EGFR % stained cells (0%, > 0-<10%, 10-<20%, 20-<30%, 30-<40%, or ≥40%) and EGFR staining intensity (1+ (faint), 2+ (moderate), 3+ (strong)). These subgroups were therefore prospectively identified in the protocol. It therefore was a defined intention of Study 046 to investigate the association of EGFR expression status and efficacy of cetuximab.

FLEX (Study 046) has provided the largest tumour sample set of any NSCLC trial to date with 1121 patient EGFR IHC scores out of 1125 being available for analysis - 99.6% of patients. Baseline characteristics were generally similar between treatment arms in each EGFR expression subgroup, and the observed survival benefit in patients with high tumour EGFR expression is not therefore related to the selection of a subgroup of patients with favourable prognostic factors. This conclusion was further supported by a sensitivity

analysis of overall survival with adjustment for prognostic baseline factors. This analysis used the Cox proportional hazards model with adjustment for selected baseline variables and resulted in an HR of 0.67 for the high EGFR expression group (95% CI 0.52, 0.87; p = 0.002), giving further support to the high EGFR expression subgroup analysis results.

The effect seen in the high EGFR expression group was consistent across clinical subgroups with the exception of the Asian population (121 patients overall, 49 in the high EGFR group). This is described in the 'Clinical Trials' section of the PI.

Starting with the overall positive result of the Study 046 in the sense of a statistically significant improvement of OS, the biomarker analysis provides strong evidence for a predictive value of EGFR expression in the sense of a substantial benefit for patients with high but not low EGFR expression. This predictive value was assessed specifically with a treatment interaction test (p = 0.044 for OS). The hypothesis that EGFR expression is a predictive biomarker was then tested in an analysis of data from the BMS099 trial, which confirmed the hypothesis with statistically significant results (treatment interaction test for OS: p = 0.042 for OS).

Predictive biomarkers are an exciting science that is evolving more rapidly than can usually be accommodated for in large, pivotal clinical trials, whose prospective designs must be finalised years before the trial data will be analysed by regulatory authorities. Retrospective analysis is therefore a common, and necessary, occurrence. There is precedent in this regard in relation to current product indications approved by the TGA for the Australian market. Examples include the pivotal IPASS study for Iressa (gefitinib) for NSCLC. In this study, evaluations of efficacy according to the baseline biomarker status of EGFR were planned exploratory objectives, in a similar vein to the cetuximab EGFR determination, however the current indication for NSCLC was nevertheless a retrospective analysis.

Moreover, only 437 patient samples (36%) could be evaluated. The sample size that led to this indication for gefitinib is therefore substantially smaller than the data provided in this submission for cetuximab.

The Delegate noted that the high EGFR subgroup analysis has not been published. Three posters relating to information in the sponsor's response (high EGFR clinical outcomes, safety analysis and RRT of the EGFR test kit – see below) were presented at the 14th World Conference on Lung Cancer (WCLC), 3-7 July 2011. They were provided with the response. Attention was also drawn to the letter of support from an Australian molecular pathologist with an international reputation in the use of predictive biomarkers to select cancer patients for clinical trials of targeted therapies.

Validation of EGFR testing kit

The EGFR expression analysis that was prospectively performed in FLEX applied the DAKO EGFR pharmDx kit. The kit is suitable for laboratory use to identify by immunohistochemistry (IHC) the expression of EGFR in tissues of a wide range of tumour types. The reproducibility of the semi quantitative IHC detection of EGFR protein in NSCLC has now been validated in an international round robin test (RRT). The RRT was performed after a feasibility study was undertaken that identified factors impacting on reproducibility. The RRT showed a high inter-observer agreement in EGFR IHC scoring among study participants, with an overall concordance rate of 91% and a mean kappa coefficient of 0.81. The RRT demonstrated that assessing EGFR expression by the EGFR IHC score allowed a highly reproducible allocation of NSCLCs into high or low EGFR expression groups, based on a cut-off score of 200. Further details are in the WCLC poster. A full report was also available.

Indication

The Delegate sought ACPM advice on limiting the indication to the specific CTX regimen used in Study 046. It should be noted that the combination of cetuximab and platinum based doublets prolonged OS time and resulted in a consistent benefit in the ITT population of all 4 studies presented in the application. New analyses based on EGFR expression showed a consistent benefit in OS for the cetuximab + CTX group compared to the CTX group in the high EGFR expression groups of the 3 randomised, controlled studies in which EGFR data are available (HRs ranging from 0.71 to 0.76).

In assessing the medical significance of these results, it is important to remember that:

1. Over-expression of EGFR in NSCLC tumours is correlated with a poor prognosis.[26,27]

2. EGFR can confer resistance against platinum based chemotherapy. Sensitisation to platinum based CTX by anti-EGFR therapy is particularly pronounced in tumours with high EGFR expression.[28,29,30,31]

For these reasons, the sponsor submitted that the optimum way to identify patients most likely to benefit from use of cetuximab is on the basis of EGFR expression and not by limiting treatment options based on CTX regimen. This is particularly so in NSCLC where platinum based CTX doublets are considered to be of equivalent efficacy and selection is made by the oncologist based on individual patient considerations.[32,33]

In line with the clinical evaluator's conclusion, the sponsor therefore concludes the overall benefit risk balance of cetuximab to be favourable for the indication of:

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR-expressing tumours.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), 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.

In expressing its view that the submission should be considered for rejection, the ACPM considered the following matters:

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[26] Ray M, Salgia R, Vokes EE. The role of EGFR inhibition in the treatment of non-small cell lung cancer. The Oncol 2009; 14: 1116-1130.

[27] Sharma SV, Bell DW, Settleman J et al. Epidermal growth factor receptor mutations in lung cancer. Nat Rev 2007; 7: 169-81.

[28] Hasegawa Y, Goto M, Hanai N et al. Prediction of chemosensitivity using multigene analysis in head and neck squamous cell carcinoma. Oncology 2007; 73: 104–11.

[29] Coley HM, Shotton CF, Ajose-Adeogun A et al. Receptor tyrosine kinase (RTK) inhibition is effective in chemosensitising EGFR-expressing drug resistant human ovarian cancer cell lines when used in combination with cytotoxicagents. Biochem Pharmacol 2006; 72: 941-8.

[30] Dai Q, Ling YH, Lia M et al. Enhanced sensitivity to the HER1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib hydrochloride in chemotherapy-resistant tumour cell lines. Clin Cancer Res 2005; 11: 1572-8.

[31] Lei W, Mayotte YE, Levitt ML. Enhancement of chemosensitivity and programmed cell death by tyrosine kinase inhibitors correlates with EGFR expression in non-small cell lung cancer cells. Anticancer Res 1999; 19: 221-228(19989).

[32] National Comprehensive Cancer Network (NCCN) Guidelines (Version 2.2011).

[33] American Society of Clinical Oncology (ASCO) Guidelines (Update 2009).

Efficacy: Of the two studies submitted, the FLEX study (62202-046) was considered not entirely pertinent to the Australian population as the chemotherapy regimen (cisplatin with vinorelbine) is not currently standard clinical practice in this condition in Australia. It was conducted in a patient population that had a higher smoking rate and a younger age than the typical NSCLC population in Australia. This study did demonstrate efficacy in terms of overall survival and response rates in the subgroup of patients with high EGFR expressing tumours. The lack of increase in progression free survival may suggest that subsequent treatments were responsible for the improvement in overall survival. The subgroup analysis based on degree of EGFR expression was defined retrospectively.

The second study (CA225-099), notably in a more relevant population and using a chemotherapy regimen more common in Australia, failed to confirm efficacy. There was no improvement in progression free survival, despite an increase in response rates. There was no significant benefit in terms of overall survival.

Safety: A significant increase in toxicity was reported with the addition of cetuximab to chemotherapy. The pattern of toxicity of cetuximab observed in the randomised controlled trials in NSCLC was generally consistent with that previously observed in colon cancer and SCCH&N. However, there were reports of an increase in the incidence of febrile neutropenia and of cardiac adverse events which were not reported previously.

The benefits obtained from adding cetuximab to chemotherapy were modest and efficacy was not consistently demonstrated in both pivotal studies. The benefits of the addition of cetuximab were outweighed by the additional toxicity produced. In addition, the retrospectively defined subgroup analysis was not considered a sufficiently robust evidence base to support approval. While the Delegate considered the risk benefit was marginal, the ACPM, taking into account the submitted evidence of safety and efficacy, were of the view there was an unfavourable benefit risk profile for this product for the proposed indication.

Outcome

The application was withdrawn by the sponsor before a decision was made.

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Reference/Publication #