SCIENTIFIC DISCUSSION

1. Introduction

Tarceva (erlotinib) is a human epidermal growth factor receptor type 1 (HER1, also known as EGFR) tyrosine kinase inhibitor.
Tarceva has been authorised in the EU for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen, on 19 September 2005. The approval was based on data from Study BR.21, a randomised, double-blinded, placebo-controlled Phase III study of single-agent erlotinib at 150 mg daily versus best supportive care in patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen.
The MAH subsequently applied for the approval of Tarceva (erlotinib hydrochloride) at the following indication (as originally proposed): *first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer* at a recommended daily dose of 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with the approved standard regimen of gemcitabine.

Pancreatic cancer is the sixth leading cause of cancer death in Europe. There are few signs or symptoms associated with early stage pancreatic cancer and up to 90% of patients present with locally advanced or metastatic disease. The 5-year survival rate is less than 5% and of the 10% of patients with possibly resectable disease only about 20% will survive for 5 years. Patients have usually only a few months to live, usually with a rapidly deteriorating state of health. Besides cancer pain and the distress of suffering from an uncurable and deadly disease the main clinical problems are related to the gastrointestinal tract like nausea, vomiting, both constipation and diarrhoea, jaundice, intestinal stenosis and often severe weight loss. For treatment purposes tumours are divided into resectable, locally advanced, unresectable, and metastatic.
Historically, treatment of patients with locally advanced, unresectable pancreatic cancer with 5-fluorouracil (5-FU) in combination with radiation was shown to improve survival over radiotherapy alone. However, it is still not clear whether radiation is an essential element of treatment for patients with locally advanced disease.
The current standard and only approved therapy for patients who have advanced, metastatic or unresectable pancreatic cancer is gemcitabine, which offers improvement in survival and amelioration of symptoms. In a Phase III randomized (1:1) trial in 126 previously untreated patients with pancreatic cancer, gemcitabine improved survival in comparison to 5-FU by approximately 4-5 weeks. In that study, patients who received gemcitabine also reported a greater effect on disease-related symptoms such as pain, performance status (PS), and weight changes than those who received 5-FU.
Other cytotoxic agents such as cisplatin, irinotecan, and oxaliplatin have been studied in this patient population in randomized Phase III clinical trials in combination with gemcitabine, none of the combinations has demonstrated a statistically significant survival benefit over gemcitabine alone.
Despite the use of chemotherapy, the overall survival of patients with pancreatic cancer remains dismal and treatment is palliative.

3.2. Clinical aspects

The clinical development program of erlotinib in pancreatic cancer consists of one large pivotal phase III study (study PA.3) including 569 patients.
Pharmacokinetics of erlotinib in combination with gemcitabine were investigated in a phase Ib study (OSI-774-155) including patients with pancreatic cancer or other malignancies (N=26).
Furthermore a phase 1 open-label study (OSI-774-103) has been conducted to characterize the pharmacokinetics of erlotinib in non-smoking and currently smoking healthy male subjects.
All studies in the erlotinib clinical development program were performed in concordance with current standards for the design, conduct, and analysis of clinical research, including ICH GCP and all region-specific requirements.

Pharmacokinetics
Two studies have evaluated the pharmacokinetics of erlotinib and gemcitabine when administered in combination: the Phase Ib Study OSI-774-155 and a population pharmacokinetic analysis 05-0140-1219 that included data from clinical Study PA.3. The population pharmacokinetic model was based on study 04-0143-1219, which was discussed in the original application for Tarceva.

Study OSI-774-155
This was an open-label Phase 1b study in patients with advanced solid, mainly pancreatic tumours.
A total of 26 patients were enrolled and treated. There were 13 males and 13 females, with a median age of 63 (range 29 to 82). All but 2 patients were Caucasian. At study entry, patients had KPS reported at 100% (7 patients), 90% (8 patients), and 80% (11 patients). Per the protocol, the primary diagnosis in the majority of patients (15 of 26 patients) was pancreatic carcinoma; in addition there were 2 patients with breast carcinoma, 2 patients with non-small cell lung carcinoma, and single cases of bladder, colon, gastric, prostate, renal, thyroid, and cholangiocarcinoma. A standard dose escalation scheme was used to determine the safety and tolerability of 100 and 150 mg doses of oral erlotinib, administered daily, with gemcitabine, 1000 mg/m^2 30 minute IV infusion administered weekly x 7, with 1 week off (Cycle 1), followed by weekly x 3 with 1 week off (subsequent cycles).

Results from this study indicate that erlotinib does not affect gemcitabine exposure in a clinically significant manner, and vice versa, gemcitabine does not affect erlotinib pharmacokinetics, under clinically relevant conditions. These results are in line with data from clinical studies BO16411 and OSI-774-154, which were discussed in the original application. Also in these studies, no clinically relevant difference was observed for erlotinib in the absence or presence of gemcitabine, not for gemcitabine in the absence or presence of erlotinib and cisplatin.

Population pharmacokinetic analysis 05-0140-1219
A population pharmacokinetics analysis was performed to compare the pharmacokinetics of single-agent erlotinib with those obtained when erlotinib is used in combination with gemcitabine (combined dataset). The analysis included 4 Phase II studies and 2 Phase III studies with the following PK designs: full screen (randomized sampling windows) and multiple troughs. Full screen typically refers to designs in which a limited number of samples were collected from each patient, but sampling times varied across patients to allow assessment of the full profile in the population

This population pharmacokinetics analysis demonstrated that the covariates affecting erlotinib disposition in patients from Study PA.3 were very similar to those previously reported and no new covariate effects were identified. The covariate effects previously identified as affecting erlotinib apparent oral clearance (CL/F) were total bilirubin, α-1-acid glycoprotein (AAG), and smoking status. The SmPC already includes a recommendation for smokers to stop smoking. Data on smoking history were not collected from patients in Study PA.3.

In conclusion, this population PK analysis demonstrated that the covariates affecting erlotinib disposition in patients from Study PA.3 were very similar to those previously reported. No additional covariate effects were observed. Co-administration of gemcitabine had no effect on erlotinib CL/F.
The data obtained in the present study 05-0140-1219 can be considered supportive to those derived form the clinical studies OSI-774-155**,** BO16411 and OSI-774-154. In all of these studies, erlotinib and gemcitabine appeared not to influence each other's pharmacokinetic behaviour in a clinically relevant manner.

Pharmacodynamics
In Study BR.21, which was the pivotal trial in the initial application, tumour samples were evaluated for EGFR expression in 31 % of erlotinib treated patients. Results suggested that tumoural EGFR-expression may be a prognostic biomarker for treatment response to erlotinib.

Within the pancreatic cancer study PA.3, data regarding EGFR expression status (determined by IHC) were only available for 27% of the patients in the erlotinib arm and for 24% of the patients in the placebo arm. The number of samples available was limited due to the advanced stage of pancreatic cancer at primary diagnosis and the method used for diagnosis, which is usually fine-needle aspiration

rather than surgery. Patients with a positive EGFR status (≥ 10% staining) in the placebo group had a worse median survival (5.32 months) than patients with EGFR negative tumours (6.11 months), suggesting that an EGFR positive status might be a weak negative prognostic factor for survival in patients with pancreatic cancer. The survival HRs for patients with a positive EGFR status were very similar to those with a negative EGFR status (0.79 and 0.80, respectively), suggesting the survival benefit from erlotinib with gemcitabine relative to gemcitabine alone was *not* related to EGFR expression status. Caution must be taken in the interpretation of these results, however, because of the small number of patients with known EGFR status and the fact that this was only designed as an exploratory analysis. Availability of tissue for determination of EGFR protein expression status was not an entry requirement for this study and patients were required to sign a separate consent form to allow for their tissue to be used for this analysis.

Overall, the association between EGFR expression and clinical benefit from erlotinib is still unknown, and the translational work done in study PA.3 also does not clarify this, as only about a fourth of tumour samples were available for EGFR expression, and no correlation was found for erlotinib treatment and clinical benefit. The reliability of EGFR expression assessments is influenced by the homogeneity of the tumour sample and whether that tumour sample is indeed representative of the tumour as a whole. Additionally, clinical benefit in study PA.3 is a composite of treatment response to two purportedly active agents, i.e. gemcitabine and erlotinib, and a possible correlation between EGFR expression and treatment response to erlotinib might be masked by gemcitabine-associated response patterns.

One phase Ib study (OSI-774-155) has been performed to determine the safety, tolerance, and preliminary antineoplastic activity of gemcitabine administered in combination with escalating oral doses of erlotinib to patients with recently diagnosed, gemcitabine-naïve, advanced pancreatic carcinoma or other potentially responsive malignancies. There were no significant effects of daily erlotinib administration on the pharmacokinetic parameters of gemcitabine and vice versa.

While there was a borderline statistical significance for the correlation of single dose erlotinib C_{max} with patients' best response to erlotinib treatment in study 248-004, no correlation has been reported for erlotinib or gemcitabine pharmacokinetic parameters (C_{max}, AUC, drug clearance) with treatment response in the concurrent gemcitabine/erlotinib regimen studies PA.3 and OSI-774-155. While the concurrent treatment with two purportedly active compounds makes such analyses more burdensome, it could give more insight into the optimal treatment schedule to eventually increase treatment response and/or dampen toxicity.

Clinical efficacy

Dose-response study

No new studies were required to support this indication. Formal dose-response studies of erlotinib were included in the original Marketing Authorisation Application.

No data on treatment with erlotinib in combination with gemcitabine in patients with advanced pancreatic cancer were available prior to the initiation of the Study PA.3, therefore the starting dose of erlotinib for the study was 100 mg and safety was strictly monitored.

At the initiation of PA.3, the dose-finding and safety study OSI-774-155 was in progress. OSI-774-155 looked at two escalating doses of erlotinib (100 mg and 150 mg daily) concurrently with standard-dosed gemcitabine, concluding 150 mg erlotinib daily could safely be given together with gemcitabine in patients with advanced pancreatic cancer or other potentially responsive tumours.

A safety analysis, blinded to treatment assignment, of the first 16 patients treated with erlotinib/placebo at 100 mg daily in combination with gemcitabine in study PA.3 was conducted. Due to transaminase elevations in 3/16 patients in the combined treatment arms, it was decided to expand the 100 mg cohort to up to 50 patients. A safety evaluation of the first 50 patients treated with 100 mg erlotinib/placebo concluded that the dose was tolerated. A safety evaluation of 16 patients enrolled at selected Canadian centres at the 150 mg erlotinib/placebo dose in combination with gemcitabine also concluded that this combination was adequately tolerated to permit further recruitment. At that time, however, accrual to the study was so advanced (405 patients) that too few patients entered the 150 mg (n=48) cohort for a proper subgroup analysis.

More “class-specific” adverse events as seen in the 150 mg erlotinib cohort in PA.3 may also mean more activity, as a correlation between TKI-associated rash and treatment response has repeatedly been shown. Although the 100 mg daily dose of erlotinib led to a statistically significant survival benefit in these patients, the true optimal dose of erlotinib if given concurrently with gemcitabine might be higher.

Main study

One large randomised, double-blind, placebo-controlled pivotal phase III study (PA.3) including 569 patients was submitted to support the claimed indication. Study PA.3 was conducted in patients with locally advanced, unresectable or metastatic pancreatic cancer.

The 569 patients were randomized (1:1) to daily erlotinib or placebo in combination with the standard dose (1000 mg/m^2) and schedule of gemcitabine. 285 patients were randomised to receive gemcitabine with erlotinib (261 at 100 mg dose and 24 at 150 mg dose) and 284 to receive gemcitabine with placebo (260 at 100 mg dose and 24 at 150 mg dose).

Primary Objective:

- To compare overall survival rates in patients with locally advanced, unresectable or metastatic pancreatic cancer treated with erlotinib and gemcitabine or placebo and gemcitabine

Secondary Objectives:

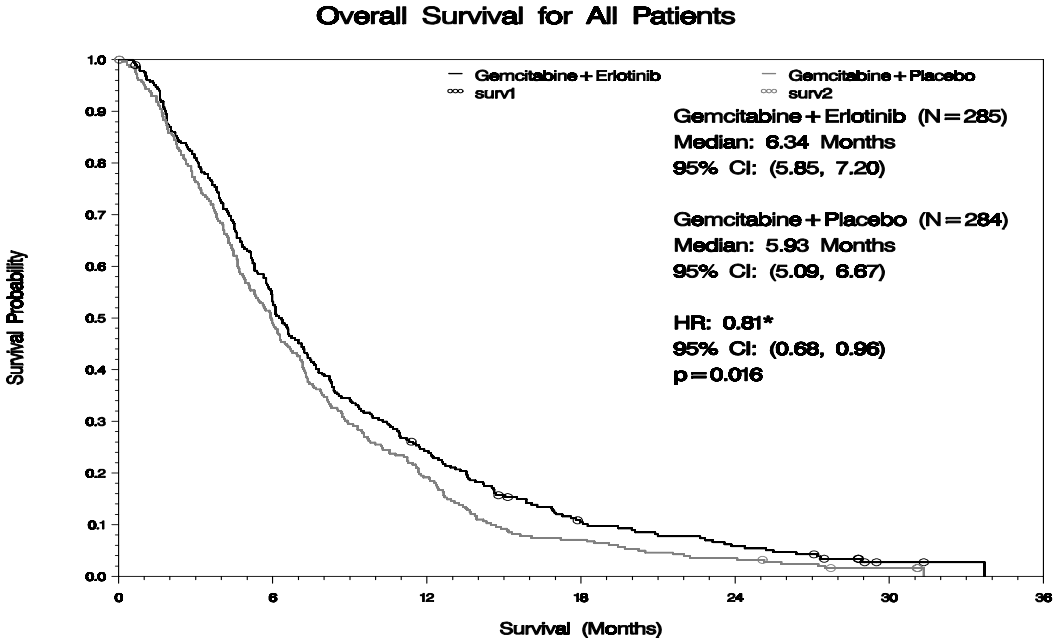
- To compare PFS in this patient group
- To compare the effects of these treatments on measures of quality of life in this patient group using the EORTC QLQ-C30
- To compare response rates in this patient group (CR, PR)
- To estimate and compare response duration in this patient group
- To compare the nature, severity, and frequency of toxicities between the two arms
- To correlate the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment
- To measure trough levels of erlotinib to define population pharmacokinetics

Primary Outcome:

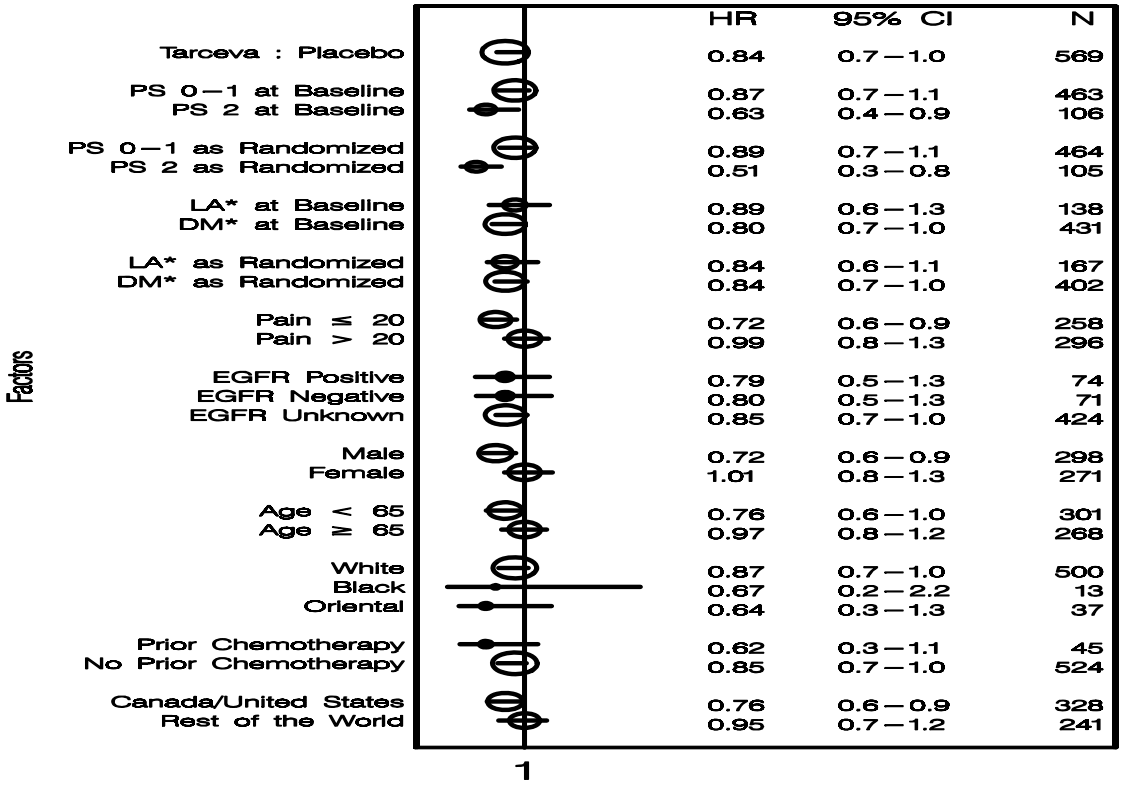
The median overall survival of the combined dose cohorts, estimated from univariate Kaplan-Meier curves, was 6.37 months (95% CI : [5.85, 7.20]) in the erlotinib arm compared with 5.91 months (95% CI : [5.09, 6.67]) in the placebo arm. The mean survival for the erlotinib arm was 8.8 months and for the placebo arm was 7.6 months (absolute mean survival benefit of 5 weeks). The estimated 1-year survival rates were 23.8% for the erlotinib arm and 16.8% for the placebo arm. The median overall survival of the 100 mg dose cohort was 6.47 months compared with 5.95 months, and the estimated 1-year survival rates were 23.2% and 17.4%, respectively.

The adjusted HR for death for erlotinib and gemcitabine relative to placebo and gemcitabine estimated from the primary analysis was 0.79, 95% (CI 0.66 to 0.95) (p = 0.011) using a Log Rank test including the stratification factors as reported at the time of randomization (ECOG PS, extent of disease). When the analysis was restricted to patients in the 100 mg cohort, the HR was essentially unchanged, 0.79 (95% CI 0.66 to 0.96, p = 0.017), confirming that the main statistically significant effect was maintained at this dose level. The number of patients in the 150 mg dose cohort was too small to draw any definitive conclusions regarding the efficacy of erlotinib at this dose level.

ECOG PS 2 and the presence of distant metastases were found to be significant predictors of overall survival in the study population, in accordance to what is known in the literature. Subgroup analysis did not identify any erlotinib-exposed subgroup with worse outcome as compared to the respective placebo subgroup. These subgroup analyses however were made post-hoc, with quite small patient number per subgroup, and the respective results have therefore to be interpreted cautiously. Smoking history again has not been assessed in correlation with overall survival, despite its purported influence on tumour biology and response to anticancer treatment.



Survival by Pre-treatment Characteristics – All Patients



Secondary Outcomes:

- **Progression-Free Survival**

The adjusted HR for progression in the erlotinib arm relative to the placebo arm was 0.77 (95% CI 0.64 to 0.92, p = 0.004) using a log rank test including the stratification factors at randomization. For the 100 mg dose cohort, the adjusted HR was 0.77 (95% CI 0.64 to 0.93, p = 0.006).

The median PFS was 3.75 months (95% CI 3.58 to 4.83) in the erlotinib arm and 3.55 months (95% CI 3.22 to 3.71) in the placebo arm. In the 100 mg dose cohort, the median PFS was 3.81 months (95% CI 3.58 to 4.93) and 3.55 months (95% CI 3.29 to 3.75), respectively.

The prolongation of disease-free survival however is 0.2 months or about a theoretical 6 days, which cannot be seen as clinically meaningful. ECOG performance status and distant metastasis status are identified as prognostic factors, which is in accordance to what is known from the literature.

- **Quality of Life**

In regards to quality of life, no statistically significant differences were observed between the 2 treatment arms for the change from baseline at each assessment in the EORTC QLQ-C30 domains, except for significantly more diarrhoea in the erlotinib arm. Overall, the addition of erlotinib to gemcitabine did not decrease quality of life, except for the fact that, as expected, the QoL category for "Diarrhoea" was worse for the patients treated with erlotinib. This was consistent with what was reported as adverse events in the CRF, although the severity of most diarrhoea events was mild to moderate.

- **Tumour response**

A total of 1 CR and 22 PRs were observed in the erlotinib arm and a similar number, 3 CRs and 18 PRs, were observed in the placebo arm, for an overall objective response rate of 8.6% (95% CI 5.5 to 12.6) in the erlotinib arm and 8.0% (95% CI 5.0 to 12.0) in the placebo arm ($p = 0.875$). In the 100 mg dose cohort, the objective response rate was also 8.6% (95% CI 5.4 to 12.9) in the erlotinib arm and 7.9% (95% CI 4.8 to 12.0) in the placebo arm ($p = 0.869$). The responses for the patients with measurable disease were durable, as the median response duration was 23.3 weeks in both study arms. In the 100 mg dose cohort, the duration was also similar in both arms. Overall, patients with a positive EGFR status had lower response rates and response plus SD rates than patients with EGFR negative tumours or patients for whom the EGFR status was unknown. Of note, however, since there were only a small number of patients in the group who had a known positive or negative status, this resulted in very wide confidence intervals.

- **Duration of response and Duration of stable disease**

No differences in duration of response or stable disease were observed between the 2 treatment arms, either in the overall population or in the 100 mg cohort. The overall median duration of the objective responses (CR and PR) for the patients in the erlotinib arm was 23.3 weeks (95% CI 16.29 to 29.57), ranging from 3.71 to 56.00+ weeks. In the placebo arm, median duration was also 23.3 weeks (95% CI 16.14 to 32.43), ranging from 6.71+ to 65.29+ weeks.

Clinical safety

The pivotal Phase III Study PA.3 together with a Phase Ib dose-escalation study (Study OSI-774-155) form the basis for the safety evaluation of erlotinib given in combination with gemcitabine 1000 mg/m^2 administered weekly for 7 weeks of an 8-week cycle followed by weekly administrations for 3 weeks of a 4-week cycle. A total of 308 patients were exposed to erlotinib 100 mg or 150 mg in these 2 studies.

The adverse event profile of erlotinib is characterised by rash and diarrhoea. Rash occurred in 75% to 85% of erlotinib-treated patients, and diarrhoea occurred in approximately half of the patients. These adverse events were usually mild or moderate in severity and few patients discontinued medication due to these adverse events. Grade 3 rash can generally be handled with dose reductions. The frequency of rash is biased by concurrent administration of gemcitabine. Grade 3 diarrhoea may respond to loperamide without the need for dose reduction, but doses may have to be reduced if loperamide therapy is not sufficient.

Interstitial lung disease (ILD) with fatal outcome has been raised as a potential concern for this class of drugs. In Study BR.21, the incidence of serious ILD-like events was balanced between the erlotinib and placebo groups: 0.8% in each treatment arm.

A conservative estimate of the incidence of ILD-like serious adverse events in study PA.3 was 2.5% (7/282 patients) in the combined erlotinib cohorts and 0.4% (1/280 patients) in the combined placebo cohorts. Events in the erlotinib-exposed patients were fatal in three out of the seven patients, for a mortality rate of 43%. There might be the potential for significantly more pulmonary toxicity when

erlotinib is given concurrently with gemcitabine, both infrequently associated with pulmonary toxicity when given as single agents.

Adverse events regardless of causality occurring more frequently (≥ 3%) in the erlotinib 100 mg group than in the placebo group are described in this section and summarized in the following table by decreasing frequency in the erlotinib group.

Study PA.3 Incidence of Patients with Adverse Events Regardless of Causality — 100 mg Cohort Erlotinib Arm ≥ 3% Higher than Placebo Arm

	Gemcitabine+Erlotinib 100 mg (N=259)						Gemcitabine+Placebo 100 mg (N=256)					
	Any		3		4		Any		3		4	
MedDRA Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total patients with any AE	256	(99)	124	(48)	56	(22)	248	(97)	123	(48)	40	(16)
Fatigue	188	(73)	35	(14)	5	(2)	178	(70)	34	(13)	6	(2)
Rash	180	(69)	12	(5)	0	(0)	76	(30)	3	(1)	0	(0)
Diarrhoea	125	(48)	14	(5)	1	(<1)	91	(36)	5	(2)	0	(0)
Weight decreased	101	(39)	5	(2)	0	(0)	74	(29)	2	(<1)	0	(0)
Pyrexia	93	(36)	7	(3)	0	(0)	78	(30)	9	(4)	0	(0)
Infection	80	(31)	9	(3)	1	(<1)	62	(24)	15	(6)	2	(<1)
Stomatitis	56	(22)	1	(<1)	0	(0)	31	(12)	0	(0)	0	(0)
Depression	50	(19)	5	(2)	0	(0)	37	(14)	2	(<1)	0	(0)
Dyspepsia	43	(17)	2	(<1)	0	(0)	34	(13)	1	(<1)	0	(0)
Cough	42	(16)	0	(0)	0	(0)	29	(11)	0	(0)	0	(0)
Headache	39	(15)	2	(<1)	0	(0)	26	(10)	0	(0)	0	(0)
Neuropathy	34	(13)	3	(1)	1	(<1)	25	(10)	1	(<1)	0	(0)
Flatulence	33	(13)	0	(0)	0	(0)	22	(9)	2	(<1)	0	(0)
Rigors	31	(12)	0	(0)	0	(0)	22	(9)	0	(0)	0	(0)
Dry skin	24	(9)	0	(0)	0	(0)	7	(3)	0	(0)	0	(0)
Epistaxis	18	(7)	0	(0)	0	(0)	2	(<1)	0	(0)	0	(0)
Chest pain	17	(7)	2	(<1)	0	(0)	9	(4)	1	(<1)	0	(0)
Dysgeusia	16	(6)	0	(0)	0	(0)	8	(3)	0	(0)	0	(0)

Serious Adverse Events study PA.3

The incidence of serious adverse events regardless of causality in the 100 mg dose cohort (see the following table) was higher in the erlotinib arm compared with the placebo arm (51% vs. 39%). This imbalance was mainly due to minor differences in the following SOCs: infections and infestations (16% vs. 11%), general disorders and administration site conditions (13% vs. 10%), respiratory, thoracic, and mediastinal disorders (7% vs. 4%), nervous system disorders (4% vs. < 1%), hepatic disorders (4% vs. 2%), and renal and urinary disorders (2% vs. 0%). There was no difference in the incidence of serious adverse events in the gastrointestinal SOC despite the higher incidence of diarrhoea observed with erlotinib.

Study PA.3 Serious Adverse Events Occurring in ≥ 2% of Patients Regardless of Causality – 100 mg Cohort

	Gemcitabine+Erlotinib 100 mg (N=259)						Gemcitabine+Placebo 100 mg (N=256)					
	Any		1	2	3	4	Any		1	2	3	4
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**n**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Total patients with any SAE	131	(51)	(2)	(5)	(28)	(17)	99	(39)	(<1)	(3)	(24)	(11)
Infections and infestations	41	(16)	(0)	(2)	(11)	(3)	29	(11)	(0)	(1)	(8)	(2)
Sepsis	11	(4)	(0)	(0)	(3)	(<1)	5	(2)	(0)	(0)	(1)	(<1)
Pneumonia	10	(4)	(0)	(0)	(3)	(1)	7	(3)	(0)	(<1)	(2)	(<1)
Cellulitis	6	(2)	(0)	(1)	(1)	(0)	0	(0)	(0)	(0)	(0)	(0)
Gastrointestinal disorders	37	(14)	(<1)	(2)	(8)	(3)	35	(14)	(0)	(2)	(9)	(2)
Vomiting	9	(3)	(0)	(2)	(2)	(0)	11	(4)	(0)	(<1)	(4)	(0)
Gastrointestinal haemorrhage	8	(3)	(0)	(0)	(3)	(<1)	7	(3)	(<1)	(0)	(2)	(<1)
General disorders and administration site conditions	33	(13)	(4)	(4)	(3)	(<1)	25	(10)	(3)	(4)	(3)	(<1)
Pyrexia	21	(8)	(4)	(3)	(<1)	(0)	18	(7)	(3)	(2)	(2)	(0)
Fatigue	8	(3)	(0)	(<1)	(2)	(<1)	7	(3)	(<1)	(<1)	(<1)	(<1)
Respiratory, thoracic and mediastinal disorders	17	(7)	(<1)	(<1)	(3)	(3)	11	(4)	(0)	(<1)	(2)	(2)
Pulmonary embolism	6	(2)	(0)	(0)	(<1)	(2)	5	(2)	(0)	(0)	(0)	(2)
Vascular disorders	16	(6)	(0)	(0)	(6)	(0)	14	(5)	(<1)	(<1)	(3)	(2)
Deep vein thrombosis	7	(3)	(0)	(0)	(3)	(0)	3	(1)	(0)	(<1)	(<1)	(0)
Thrombosis	6	(2)	(0)	(0)	(2)	(0)	5	(2)	(0)	(0)	(1)	(<1)

Note: Excludes Progressive Disease
Data Source: Study PA.3 Clinical Study Report

Deaths, Study PA.3

Five patients (2%) died of toxicity attributed to protocol therapy (i.e., erlotinib and/or gemcitabine) within 30 days of last dose, all in the erlotinib 100 mg dose cohort. The relationship of these events to erlotinib could not be concluded.

Overall Discussion and Benefit Risk assessment

One large randomised, double-blind, placebo-controlled pivotal phase III study (PA.3) including 569 patients was submitted to support the claimed indication. The design of the study PA.3 is considered adequate, as are the chosen primary study outcome, i.e. overall survival. Although it was a controlled, blinded study, the high frequency of erlotinib-associated (typical) skin and gastrointestinal toxicity may have diluted blinding in a significant share of patients. However, almost all occurrences of rash in both treatment groups were ascribed by the investigators to erlotinib. In the placebo plus gemcitabine group, 30% of the patients experienced rash– in 26% of the group the event was ascribed either to erlotinib alone or to both erlotinib plus gemcitabine. These facts testify against the notion of "dilution of blinding.

The inclusion of two erlotinib/placebo dose groups into the phase III-controlled trial design is unusual, and did not in fact contribute to the finding of the optimal dose of erlotinib if given concurrently with gemcitabine, but is not suggested to impair the primary study objective or secondary study objectives. Due to the design of study PA.3, the 150 mg patient cohort remained too small for subgroup analysis, resulting in the recommendation for 100 mg daily erlotinib together with standard-dosed gemcitabine. Treatment groups are well balanced for known prognostic factors in metastatic pancreatic cancer, especially ECOG PS, age and distant metastases.

Regarding the primary objective a statistical significant difference of overall survival has been demonstrated. The median overall survival of the combined intervention arm (erlotinib 100mg/150mg) was 6.34 months (95% CI: 5.86, 7.20) compared with 5.93 months (95% CI: 5.09, 6.67) in the placebo arm. This corresponded to a median survival difference of 0.41 months or approximately 12 days in favour of the erlotinib arm. Another perhaps more appropriate measure of overall survival in rapidly progressive diseases such as pancreatic cancer is the hazard ratio (HR). In the updated database, the observed HR in the 100 mg cohort was 0.82. This translates into an 18% reduction (1 – 0.82) in the risk of death for patients in the gemcitabine plus erlotinib arm, or a 22% improvement (1/0.82 – 1) in overall survival. Thus the true benefit provided by erlotinib is an increase in overall survival of 22%, which can be thought of as an average improvement over the whole survival curve since there was no evidence that the hazard ratio varied with time. Both the hazard ratio and the calculated mean survival

difference correspond to an improvement in overall survival of approximately 5 weeks (i.e. an improvement in the same magnitude observed for gemcitabine monotherapy compared to the classical palliative treatment with 5-FU). The 1-year survival rates were 19.4% on placebo compared to 23.8% on erlotinib.

Although a statistically significant survival difference has been demonstrated in this single large phase III study, a modest survival difference may not be considered clinically meaningful for the following clinical reasons. Although the two Kaplan-Meier curves (erlotinib versus placebo) separate slightly from the beginning, about 2/3 of the patients die, before an at best moderate difference can be observed. The quality of life analyses did not show any improvements of treatment but a significant deterioration regarding diarrhoea. Amelioration of symptoms has not been demonstrated. It should be noted that the study was not powered to detect differences in QOL. Superior efficacy has not been demonstrated for other secondary efficacy results such as tumour response and duration of response. Progression-free survival was prolonged statistically significant by approximately median 6 days in the erlotinib arm (mean difference 3.9 weeks)

It is accepted, that the most appropriate measure of overall survival in rapidly progressive diseases such as pancreatic cancer is the hazard ratio (HR). Both the hazard ratio and the calculated mean survival difference correspond to an improvement in overall survival of approximately 5 weeks. The observed median survival difference of 12 days presents the overall survival in an unfavourable way; however, also individual point estimates give useful information. Although the two curves (Figure 1) in the erlotinib and placebo groups separate slightly from the beginning, about 2/3 of the patients die, before an at best moderate difference can be observed.

There was no difference in tumour response in the two arms. The objective response-rate with gemcitabine single-agent (patients in the placebo group) is in accordance with literature data, but higher than typical objective response-rates with 5-FU single-agent treatment (typically <5%). It is increasingly noticed that clinical benefit from erlotinib might not be correlated with objective tumour response. There are no data provided as to the objective tumour response in patients administered 150 mg daily erlotinib concurrently with gemcitabine.
Furthermore, there are no data on the impact of smoking history on the objective response rate in study PA.3. Smoking is not only a risk factor for pancreatic cancer, but might also influence the tumour biology and subsequently the response to anticancer treatment.

Treatment with erlotinib in study PA.3 did not improve overall quality-of-life, but demonstrated a deterioration of diarrhoea. Single QoL items “Social functioning” and “sleep” improved with borderline statistical significance. The QoL item “pain” improved in 57% of patients in the erlotinib arm compared to 50% in the placebo, this was however not statistically significant.

The adverse event profile of erlotinib is characterised by rash and diarrhoea. Rash occurred in 75% to 85% of erlotinib-treated patients, and diarrhoea occurred in approximately half of the patients. These adverse events were usually mild or moderate in severity and few patients discontinued medication due to these adverse events.
The incidence of serious adverse events regardless of causality in the 100 mg dose cohort was higher in the erlotinib arm compared with the placebo arm (51% vs. 39%). Grade 3 rash can generally be handled with dose reductions. The frequency of rash is biased by concurrent administration of gemcitabine. Grade 3 diarrhoea may respond to loperamide without the need for dose reduction, but doses may have to be reduced if loperamide therapy is not sufficient.

Although the MAH has shown a clear statistical survival advantage for the combination gemcitabine/erlotinib, the CHMP was of the opinion that the clinical relevance of the survival gain is doubtful bearing in mind that the toxicity is more pronounced for the combination than for gemcitabine as monotherapy.

Report from the Scientific Advisory group meeting of 7 July 2006

The CHMP consulted the Scientific Advisory Group – Oncology on the following questions:

Q1: *In terms of clinical benefit, what can be concluded about the value of the efficacy results associated with treatment with gemcitabine+erlotinib in the proposed indication?*

Whether looking at median survival or other quantiles, at the Kaplan-Maier survival estimators, or at the hazard ratio, the observed effect for the combination treatment of erlotinib+gemcitabine *v.* gemcitabine alone in terms of overall survival, is very small. Concerning other efficacy endpoints, including quality of life, progression-free survival, and objective response rate, the effect is similarly small, or not detectable, despite the large sample size. Considering all the available efficacy data presented, the observed effect size does not allow to conclude that there is a clinical benefit in the claimed indication. Rather, failure to detect a relevant effect in the large study PA.3 suggests that the existence of a meaningful effect in the population is unlikely.
It is possible that the observed activity might be of some benefit in certain subpopulations but this remains a hypothesis at this stage. Based on the data and subgroup analyses presented, there are no clear hints as to whether such subgroups exist and how they might be identified.

Q2: *From a clinical perspective, how does the magnitude of the clinical benefit compare to the observed harms and risks associated with gemcitabine+erlotinib in the proposed indication?*

The observed efficacy results, and the lack of a clinical benefit (see answer to Q1) do not compare favourably with the observed toxicity for the combination erlotinib+gemcitabine compared to gemcitabine alone. Although there are no striking differences in terms of severe and life-threatening toxicity, there are frequent and significantly higher grade 1-2 toxicity such as diarrhoea and rash which cumulatively over the duration of treatment can represent a significant burden for the patient. There are no convincing quality of life data to show that this would not be the case. The absolute level of grade 3-4 toxicity is not a concern, but a relatively high rate of possibly treatment-related deaths has been observed for the combination arm. Overall, from a clinical perspective, the toxicity observed for the combination compares unfavourably with the very small effect observed on clinical efficacy endpoints.

Q3: *No reasonably well justified prognostic factors enabling enrichment of the target population have been identified at baseline. The predictive value of on-therapy rash grade 2/3, however, is again suggested by the data and suggests that this could be used to guide the physicians as regards withdrawal from erlotinib therapy.*

There are no data to suggest what subgroups, if any, may have a clear clinical benefit from the treatment with erlotinib+gemcitabine. Further studies would have to be conducted in order to study this aspect. The development of rash does not seem to provide useful information as to what patients might respond to therapy.

Q4: *Is it reasonable to suspect that there might be antagonistic interaction between chemotherapy and erlotinib in certain groups of patients?*

Based on the data presented, there are no reasons to suspect an antagonistic interaction between erlotinib and gemcitabine in certain subgroups of patients.

Q5: *To what extent would studies be warranted or urgently needed in order to ensure that populations with clearly negative benefit-risk profile are identified, and what types of studies would be needed?*

Overall, the benefit-risk balance is considered negative in the claimed indication (see answer to Q1 and Q2). Whether there exist subpopulations in which the balance is positive is unknown at this stage (see answer to Q3).

CHMP opinion of 27 July 2007

On 27 July 2006 the CHMP considered this Type II variation and agreed that the changes to the terms of the Marketing Authorisation should be refused on the following grounds:

– The effect in terms of overall survival was too marginal to constitute a clinical benefit in the population treated with the combination of erlotinib + gemcitabine given the toxicity profile of the combination treatment in patients with locally advanced, unresectable or metastatic pancreatic cancer.

– Concerning other efficacy endpoints, including quality of life, progression-free survival, and objective response rate, the effect is similarly small, despite the large sample size of the trial PA3.

Discussion on the MAH's grounds for Re-examination of the negative opinion.

On 16 October the MAH submitted the grounds supporting a request for a re-examination of the negative opinion. As the basis for this re-examination, each of the above grounds for refusal was addressed by the MAH as summarised here.

- Erlotinib has demonstrated a significant and clinically relevant survival benefit in patients with pancreatic cancer in a well designed, placebo controlled trial,
- Pancreatic cancer is a rapidly fatal condition with a median survival of 6 months only. Given such a poor outlook even modest improvements in survival should be regarded as clinically meaningful.
- The secondary efficacy endpoints are consistent with and support the overall survival benefit observed in the PA3 trial.
- The added toxicity of erlotinib is moderate and acceptable in this uniformly fatal disease, especially when viewed in the context of the survival benefit. This is supported by the QoL analyses.

The rapporteurs during the review of the detailed ground for the re-examination discussed a number of outstanding points as follows.

Clinical benefit
Survival was the primary endpoint and the study was designed as a double blind study. The assessment benefit of erlotinib add-on to gemcitabine in the treatment of pancreatic cancer refers to prolonged overall survival (mean 5 weeks). Tumour response and progression were not independently assessed. As such this is acceptable. With respect to the supportive value of tumour-related endpoints, possible unblinding due to rash and other characteristic adverse events, is of relevance, however. With respect to the statistical robustness of survival benefit data, the requirements set forth in CPMP/2330/99 are not fulfilled. The p-value is about 0.02 and the supportive value of PFS data is limited due to methodological concerns.

Safety
The overall incidence of diarrhoea was 36% in the placebo plus gemcitabine arm and 48% in the arm receiving erlotinib plus gemcitabine. Most events were by severity of Grade 1 or 2 while 5% in the erlotinib arm experienced Grade 3 severity compared to 2% in the placebo arm. The frequency of hospitalization due to diarrhoea could be described as balanced between the arms – three in the placebo arm and four in the erlotinib arm. The diarrhoea could be managed with the usual medical therapy (loperamide) in most patients. Two erlotinib-treated patients discontinued treatment due to diarrhoea. Thus, although the proportion of patients experiencing diarrhoea was higher in the erlotinib plus gemcitabine arm, patients in both treatment arms suffered from diarrhoea during a short time during the treatment period.

Rash occurred in 75% to 85% of erlotinib-treated patients. These adverse events were usually mild or moderate in severity. Erlotinib rash responds well to moisturising agents and topical antibiotics where inflammation occurs. Also other EGFR affecting substances have shown a high percentage of this type of rash and this correlates with favourable outcome, as analysed later.
With respect to severe and serious adverse reactions, the safety profile is considered acceptable and as regards common reactions such as rash and diarrhoea.

Quality of Life
The pivotal study PA.3 was not powered or designed to demonstrate an improvement in quality of life (QoL) of the participating patients, and it is acknowledged that it is difficult to detect an improvement in quality of life when two anticancer agents are combined in such a rapidly fatal disease. Therefore conclusions concerning QoL aspects in this study have a lot of limitations. Nevertheless, although the value of the QoL assessment in this study is limited, it seems notable that with the exception of the occurrence of diarrhoea and rash the add-on therapy has no significantly negative impact on the quality of life of the patients in this trial. Furthermore the data do not indicate a relevant influence of the development of rash on QoL. Whether the submitted post hoc-analysis of the time to 5 % deterioration in global quality of life score really demonstrates positive signal as a significant and valid effect with regard to prolonged time to deterioration seems to be doubtful out of methodological reasons.

Identification of a sub-population that may derive greater benefit
The only current options for identification of subgroups of patients who may achieve greater benefit are currently based on exploratory sub-population analyses of the study data.
Patients, whose pancreatic cancer-related symptoms are still modest and whose quality of life and performance status is favourable, are likely to derive more benefit from erlotinib treatment, based on a post-hoc analysis of the PA.3 study data. These patients who still have a good quality of life and only moderate pain achieve an HR of 0.63, regardless of performance status. The result is that these patients, whose life expectancy is already greater than the overall population, achieved a median increase in survival of two months. Low pain intensity at baseline appears to be the main driver, rather than quality of life score or ECOG status, as with low pain intensity alone the apparent survival benefit approached that achieved when the three criteria were combined.

Another subgroup, which appears to derive benefit, is patients with distant metastases, compared to those with just locally advanced disease. Such a distinction has also previously been reported.

Patients who develop rash

Rash has been considered to be an indicator of the desirable pharmacodynamic effect of the drug, indicative of the necessary and required systemic exposure to erlotinib. Survival outcome by grade of rash is presented in the table below.

Survival Outcomes, by Grade of Rash

	Gemcitabine + erlotinib		**Gemcitabine + placebo**	
Rash	N	Median (months)	N	Median (months)
None	79	4.99	180	5.91
Grade 1	91	5.78	50	6.29
Grade 2/3	89	10.68	26	7.05
	HR* = 0.68, p < 0.0001		HR* = 0.92, p = 0.402	
	Univariate interaction p = 0.016			
	Multivariate interaction p = 0.108			

* HR of Grade 2/3 vs. Grade 0/1

Erlotinib-related rash generally occurs early during treatment in those patients who develop it. As shown below, the median time to the first occurrence of rash (any Grade) was 10 days (in both treatment groups) and the 90th percentile for onset of rash in the erlotinib plus gemcitabine group was 44 days.

The results of a recently reported, randomised study conducted with cetuximab in patients with colorectal cancer is compatible with the notion that dose individualisation using rash as a "biomarker" for dose adjustments might enhance the activity of cetuximab. Whether this would be the case in pancreatic cancer and for erlotinib is obviously an open question. A study exploring this and other pertinent questions related to optimised patient selection based on tumour geno/phenotype data would be of major clinical interest. In this context it is noted that exploratory data from Study PA.3 are yet not available.

With respect to the estimated treatment effect, the relative survival benefit is small (hazard ratio 0.8) in comparison with what is often seen in add-on studies within the field of oncology. The absolute added benefit (mean 5 weeks) is moderate. In an attempt to identify subpopulations that benefit, EGFR IHC has not proved helpful. Exploratory subpopulation analyses suggest that patients in generally good condition (low pain intensity, good quality of life at baseline, good PS) or distant metastases may derive enhanced survival benefit. There is a correlation between grade of rash and survival.

Assuming that the point estimate for survival benefit accurately estimates the magnitude of the treatment effect in the full study population and if, in clinical practice, the individual patient's prognostic factors are taken into account in the decision whether and how to treat, then it can be considers that the benefit of add-on therapy with erlotinib outweighs the risk. The issue of correlation of rash incidence with outcome was also debated. One option could be that in the absence of erlotinib-related rash until after about 4 weeks, erlotinib therapy could be reconsidered. Available data indicate that quality of life is not relevantly impaired. It is acknowledged, however, that there are uncertainties related to this assessment.

Report from the Scientific Advisory Group Meeting of 30 November 2006

Since several issues still remained open, the CHMP considered that the Scientific Advisory Group should be convened and the following questions were adopted by the CHMP to be addressed by the SAG- Oncology at the meeting of 30 November 2006:

1. What is the SAG position of the rapporteurs' assessment of efficacy concluding that the modest effect on survival seen in the study PA.3 is meaningful?

The SAG has extensively discussed this open question and a number of different views were put forward showing substantial divergence of views. There are at least two issues that need to be considered jointly, namely, validity of the results and the meaningfulness of the treatment effect.

Validity of results

Study design, one single pivotal study

The demonstration of efficacy is based on a single pivotal trial, PA.3. Supporting the validity of the results is the fact that the trial was a well designed, large double blind randomized controlled trial. Purely looking at trial design, one could argue that a large randomized controlled trial could in principle provide sufficient evidence to establish efficacy. It was claimed that there were no striking imbalances in important prognostic factors, and that the observed effects are unlikely to be due to chance alone.

Against the validity of the results was the consideration that the statistical evidence from PA.3 that the efficacy findings are not due to chance is not overwhelming, based on the moderate significance level for the updated study data P=0.028. A second randomized controlled trial would be recommended to provide additional statistical evidence (although its additive contribution if results were identical or similar was questioned).

Internal validity, effect across subgroups

In support of internal validity is the fact that the effect on progression-free survival (PFS) was consistent with the effect on survival. The effect was generally consistent across different subgroups, adding to the validity of the observed effect. Internal consistency is also reinforced by the effect of usual predictive factors including poor performance status and highly symptomatic patients and better effect in patients with rash.

However, doubts on internal validity were raised because the response rate (RR) was exactly the same in the two arms. It was argued that when identical RR but different PFS are seen in different arms of a randomized controlled trial this may be due to a *bona fide* cytostatic effect, but equally may be due to prognostic imbalances in the populations. The effect was not always consistent across subgroups. Patients with lower pain score and better baseline QL, of which there were 158 in the study (28% of the trial population) appeared to have a large benefit so it is likely the remaining patients had little or no benefit. Also, acknowledging the pitfalls of exploratory subgroup analyses, there was no evidence of benefit in patients with locally advanced disease and the unexpected observation of a HR close to 1.0 for women, for patients aged >65 years, and for non-North Americans.

Meaningful treatment effect

Speaking for the meaningfulness of the effect is the estimated 20% improvement in the hazard rate in a population with very poor prognosis. Looking at average survival the treatment effect is approximately 5 weeks. The estimate is claimed to be unbiased in terms of right-censoring. The hazard rate was claimed to be approximately proportional for the entire duration of follow-up and it was claimed that there are no apparent outlying observations that may individually explain the observed effect. A true effect of 5 weeks would generally be considered as clinically meaningful. A risk reduction of 20% with 4% absolute difference in the long term survivors is in line with the effects of a number of anticancer agents in different settings.

Against the conclusion of a meaningful effect, the concern was raised that the Kaplan-Meier survival curves are very similar and the proportion of deaths between the two groups only differs by a few events for a very short time period. As an example, the difference in median survival is approximately 12 days and this is can be considered to be a futile effect. The average is sensitive to outliers, and it is difficult to assess whether this is a homogenous effect across the entire population or if it is due to a few outlying observations. The curves track very close up to 8 months and the mean difference of 5 weeks is seen because of the larger separation in the tail. About 2/3 of the patients die, before an at best moderate difference can be observed. Accordingly, one could argue that any benefit is confined to patients with a prognosis of >9 months on gemcitabine alone. The considerable difference between mean and median prolongation of overall survival are of concern. Similarly, progression-free survival (PFS) was prolonged by approximately median 6 days in the erlotinib arm, with a mean difference of 3.9 weeks. Again, the difference is not considered clinically relevant, although statistically significant. As a consequence, the requirements set forth in CPMP Points to Consider On Application With One Pivotal Study (CPMP/2330/99) cannot be seen as fulfilled. It was also reminded that the benefit of gemcitabine as compared to single-agent 5-fluorouracil in the gemcitabine registration study was in the range of 4-5 weeks, but most importantly, it was accompanied by an improvement in quality of life issues. On the contrary, study PA.3 was not able to show any improvements in quality of life issues. Amelioration of symptoms has not been demonstrated. In conclusion, according to this view, although the applicant has shown a statistical survival advantage for the combination gemcitabine/erlotinib as compared to gemcitabine/placebo in patients with advanced pancreatic cancer, the clinical relevance of the survival gain was considered doubtful, bearing in mind that the median survival difference is only 12 days.

Conclusions

There has been intense and comprehensive discussion on this topic. No consensus among the experts was reached and this was certainly influenced by the lack of even preliminary results from biomarker studies, thus relying only on exploration of clinical data. In summary, concerning this question there were three main different positions:

1) The effect observed is unlikely to be due to chance and is clinically meaningful in this situation.

2) It is not possible to conclude that the effect is unlikely to be due to chance and an additional study – for instance testing increased dosing in patients without side effect should be conducted to confirm the effect.

3) Whether the effect is due to chance or not, the observed effect is so small that it is of no clinical relevance, the effect compares unfavourably to the observed toxicity, and based on the data provided, it is not possible to identify a subpopulation likely to derive any meaningful clinical benefit.

2. From a pharmacodynamic perspective, activation of EGFR signalling pathways (irrespective of cause) appears to be a likely prerequisite for the therapeutic activity of erlotinib.

2.1 To what extent is heterogeneity (within sample and between sources, e.g. primary *v.* metastases) with respect to EGFR activations known to influence erlotinib (or gefetinib) activity?

EGFR signalling activation is a possible biomarker but regrettably there are no comprehensive data to address this issue in the context of the PA.3 trial nor in any other ongoing or planned trials. However, it is possible that EGFR may not explain all or even most of the effect observed, as the true mechanism of action for this tyrosine-kinase inhibitor (TKI) *in vivo* remains to be elucidated.

2.2 Irrespective of measure, is it possible to meaningfully define a sample as "negative" or. "positive" with respect to receptor status and or EGFR activation?

No study allows for a precise definition of the cut-off value to consider a pancreatic cancer as positive or negative for EGFR expression (or amplification). Furthermore a number of data suggest that Ki-ras mutation, which is frequent in pancreatic cancer, could bypass the transduction pathway and lead to insensitivity to EGFR inhibitors.

2.3 Is EGFR signalling activation (or any other measure) possible to estimate with valid technology in clinical practice prior to treatment with erlotinib?

In view of the diagnostic tools (CT, US guided biopsies), small size of the samples and frequent heterogeneity in terms of pathology, one can consider that no measure has been validated in clinical practice.

2.4 Are there data indicating that the use of erlotinib would be of benefit to specific subgroups of patients (low pain, incidence of rash…) ?

There was agreement that based on theoretical arguments and the claimed pharmacodynamic effect, patients for whom the tumour did not express EGFR could not be considered candidates for such treatment. However, the lack of a biomarker study was considered as a major deficiency in the application and there is a compelling rationale for conducting such studies in parallel with further clinical studies (e.g., randomised study of standard dose erlotinib *v.* tailoring to rash in the other arm, with collection of tumour material for all patients).

Based on the available data there are no confirmatory data indicating that the use of erlotinib would be of benefit to specific subgroups of patients (low pain, incidence of rash…). However it was aknowledged that in a variety of tumour and with different EGFR inhibitors (MoAB or TKI) patients experiencing a rash were the most likely to benefit from the agent to the extent that dose escalation with another agent has been tested in patients without rash with achievement of further responses. The subgroup analysis provided also suggest that most of the apparent effect was accounted for by patients who developed a grade >1 rash while receiving erlotinib. Thus one could in theory hypothesize that the efficacy might be increased in asymptomatic or mildly symptomatic patients with good performance status, and that treatment should not be continued in patients without evidence of skin rash. However, such claims remain hypothetical and would require confirmatory evidence from prospectively conducted clinical trials.

There is no clinically useful guidance for patient selection, in order to prevent significant overexposure of the population of patients with pancreatic cancer. Selection based on development of rash means that 100% of patients will be treated. It will be very difficult to discontinue therapy if no or

just little rash develops, and it would be difficult to define clear thresholds. Furthermore, there are no known dose-effect relationships for rash, i.e. useful dose-adaptation is an undeveloped strategy.

Regardless of approval status, further studies are warranted. A second randomised controlled trial should be conducted, for example looking comparing a dose increase in patients without rash at 2 weeks, *v.* standard dose. Such a study should also include systematic biomarker studies (HER1 transduction patway and Ki-ras mutations).

3. In the context of the indication, can the safety profile be considered acceptable? As regards common reactions such as rash and diarrhoea, are these manageable and reversible?

Yes. In the context of the indication, compared to the toxicity profile of 5-FU and gemcitabine, the safety profile can be considered acceptable. As regards common reactions such as rash and diarrhoea, these are manageable and reversible.

Benefit-risk balance

On the issue of balance of observed effect and toxicity there was considerable divergence of views.

In favour of a conclusion of positive benefit-risk, considering the severity and the general poor prognosis of the disease, the observed benefit of 20% increase in the hazard ratio for overall survival clearly outweighs the toxicity and any risks. The excess toxicity in terms of diarrhoea and rash is primarily grade 1 and 2 toxicity which are of no relevance in the context of the clinical picture.
According to a contrary view, the increase in toxicity for erlotinib + gemcitabine is small but not negligible. The toxicity is markedly increased for diarrhoea and rash with the combination of gemcitabine/erlotinib as compared to gemcitabine/placebo. A significant deterioration regarding diarrhoea has been observed in the quality of life questionnaire. There have been fatalities attributed to toxicity of erlotinib + gemcitabine. Given the small treatment effect, which is further weakened by uncertainties about the validity of the data, the toxicity is considered unacceptable and that the benefit risk balance is negative or neutral at best in the claimed indication.

Restricted indication: Metastatic pancreatic cancer

As discussed in the initial assessment and during the re-examination, the HR for overall survival for locally advanced pancreatic cancer patients is 0.93 with a CI of 0.65 to 1.35. During the MAH's oral explanation, the benefit of erlotinib in these patients was questioned. The biologic/ clinical basis for this discrepancy needs further explanation, which was provided from the MAH during the meeting.

Supporting evidence from other trials:

In the original trial comparing the treatment with gemcitabine and 5FU (Burris et al) data were not analysed by extent of disease.
In the trial by Louvet et al., which compared treatment with gemcitabine +/- oxaliplatin, the median OS time for the whole population was not significantly different (6.9 months for Gem alone and 8.8 months for GemOx; p = 0.15; HR, 1.18; 95% CI, 0.94 to 1.51). For the subpopulation of locally advanced patients, median survival times were identical in both arms (10.3 months), whereas for metastatic patients, the median survival time was 6.7 months in the Gem arm and 8.5 months in the GemOx arm (p = 0.17; HR, 1.21; 95% CI, 0.91 to 1.63).
Based on the results presented at the annual ASCO meeting, (Saif MW.: Pancreatic cancer: highlights from the 42nd annual meeting of the American Society of Clinical Oncology, 2006. JOP. 2006 Jul 10;7(4):337-48) it is concluded that patients with locally advanced vs. metastatic pancreatic cancer should be studied separately, for the better understanding of the biology of pancreatic cancer and evaluation of novel agents.

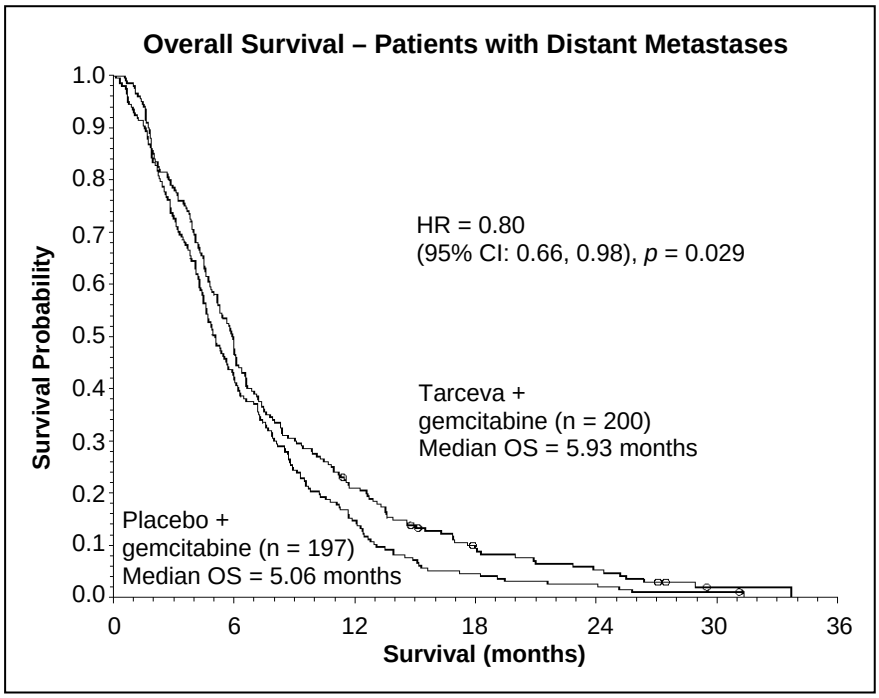
Possible biological rationale

The biological basis for the lack of efficacy in locally advanced disease in these trials is not known. Potential explanation cited by Louvet is the use of concomitant radiotherapy. However, the number of patients in the PA3 trial who received radiotherapy is too small to explain this (please see enclosed table). In the literature, no meaningful data can show that the molecular genetic alterations or the growth control mechanisms in locally advanced pancreatic cancer are different than those operative in

metastatic pancreatic cancer. Therefore, the greater likelihood of locally invasive complications resulting from small increases in tumor mass in patients with locally advanced pancreatic cancer may be the key factor leading to inability to demonstrate a survival benefit of erlotinib.

Discussion on the results of erlotinib + gemcitabine in metastatic pancreatic cancer

An exploratory analysis compared overall survival in the metastatic pancreatic cancer patient subset treated with erlotinib + gemcitabine (n=200) to the those who received gencitabine + placebo (n=197). The Median overall survival was 5.93 months versus 5.06 months, the mean was 8.10 months versus 6.67 months. The hazard ratio of 0.80 with a CI of 0.656-0.978 is as previously estimated for the overall population (0.82) translating in 25 % improvement. The Kaplan- Meier curve for the metastatic population is presented below.



Following discussion on this analysis, it was considered that an indication could be granted for metastatic pancreatic patients. Given the very short life-expectancy of patients with pancreatic cancer, even apparently modest improvements in survival are considered critical by patients, their families, and treating physicians. As regards to safety of erlotinib in the context of the indication, the safety profile is acceptable. Common reactions such as rash and diarrhoea are manageable and reversible. Having now restricted the indication to patients with metastatic pancreatic cancer, the CHMP agreed that the benefit –risk ratio in this population is positive.

The MAH agreed with the CHMP on post-approval commitments: A study addressing the issue whether advanced pancreatic patients treated with Tarceva and gemcitabine and do not have rash could benefit from dose escalation of erlotinib. A second study will be designed addressing the issue of patient selection with advanced pancreatic cancer for treatment with erlotinib based on predictive genetic and / or other biomarkers.

IV. CONCLUSION

On 14 December 2006 the CHMP considered the grounds for the re-examination on the negative opinion on this Type II variation and recommended by a majority of 20 out of 26 votes that its opinion of July 2006 should be revised, accepting the following restricted indication:

Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival advantage could be shown for patients with locally advanced disease.

- The divergent opinion expressed by some CHMP members was:

The demonstration of efficacy is based on the single pivotal trial PA.3. The prerequisites for a single confirmatory trial to be used for registration set forth in CPMP Points to Consider On Application With One Pivotal Study (CPMP/2330/99) include that the estimated size of clinical benefit must be large enough to be clinically valuable, and that the statistical evidence should be considerably stronger than $P<.05$. Concerning clinical benefit, the estimated effect on survival is small and its clinical value is questionable. Furthermore, the statistical evidence from PA.3 is not very strong ($P=0.028$). In addition, the proposed indication "metastatic cancer of the pancreas" is based on a post hoc analysis. A marked increase in toxicity in terms of diarrhoea and rash has been associated with erlotinib combination treatment. Given the non compelling efficacy results, the lack of a sizeable clinical benefit, the weak statistical evidence, and the non-negligible toxicity, we believe that the benefit-risk balance of erlotinib in combination with gemcitabine for the indication of advanced pancreatic cancer is not established.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

- Study addressing the issue whether patients without rash could benefit from the addition of Tarceva to gemcitabine in advanced pancreatic cancer (e.g. by dose escalation)
- Study addressing the issue of patient selection with advanced pancreatic cancer for treatment with erlotinib based on predictive genetic and / or other biomarkers