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24 February 2010

**Erlotinib for maintenance treatment of non small-cell lung cancer. Clarification questions**

Dear Kate,

Thank you very much for your Email dated 10th February 2010.

Please find below answers to the clarification questions raised regarding the use of erlotinib for the maintenance treatment of non small-cell lung cancer. Roche welcomes the opportunity to provide further clarification around our submission and would be pleased to answer any additional questions which might arise.

Best wishes.

Yours sincerely,

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## Section A: Clinical Effectiveness:

A1. **Protocol and Clinical Study Report (CSR) - Current study details are available within the manufacturer's submission and a variety of conference abstracts, some of which present interim analysis. In order to more clearly understand the planning and conduct of the trial the ERG request copies of the SATURN trial protocol and the Clinical Study Report including all of its appendices. It would be most helpful if these could be sent electronically and if possible ahead of the other requested analysis to assist the review team with the information previously submitted.**

Answer: due to the size of the CSR, a copy has been provided in a CD format. PLEASE NOTE THAT THE CSR IS CIC.

**Clinical results**

PLEASE NOTE THAT ALL DATA SETS GIVEN IN QUESTION A2 (A2I, A2II, A2III AND A2IV) ARE CIC

A2. **Clinical results in the submission do not allow for exploration of issues related to time to events. Therefore the following clinical result analyses are requested (a sample table structure for responses is included at the end of this document):**

**I. Please provide Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the SATURN trial data for the following populations and outputs (i.e. 3 x 2 x 2 = 12 sets of output):**

- **ITT, Stable Disease and Non-Squamous populations**

**By**

- **Time to progression (PFS) and time to death (OS)**

**By**

- **Erlotinib maintenance therapy and placebo**

**In each case please provide a table of results showing for each event time:**

- **Time of event from baseline (days)**
- **Product-limit estimate of survival proportion**
- **Standard error of survival proportion**
- **Number of patients failed**
- **Number of patients remaining at risk**

**In addition, please provide for each set of outputs the estimated mean survival time from baseline up to the time of last event, together with the standard error of the mean estimate.**

Answer: The data for above requests has been attached to this letter.

**II. Please provide Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the SATURN trial data for the following populations and outputs (i.e. 3 x 1 x 2 x 2 = 12 sets of output):**

- **ITT, Stable Disease and Non-Squamous populations**

**By**

- **Time from progression to time of death (PPS)**

**By**

- **Erlotinib maintenance therapy and placebo**

**Stratified by**

- **Duration of trial medication (erlotinib or placebo) between those treated for up to 12 months and those treated for more than twelve months**

**Please provide the same table of results, and the estimated mean survival time from progression to death (with standard error) for each analysis as specified in (I).**

Answer: The data for above requests has been attached to this letter.

**III. For each of the 12 sets of output from (II) please provide a patient-level scatterplot of PFS (x-axis) versus PPS, and the results of performing a linear regression of y as a function of x with regression coefficient and confidence intervals for model parameters.**

Answer: The data for above requests has been attached to this letter.

**IV. Please provide Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the SATURN trial data for the following populations and outputs (i.e. 3 x 1 x 2 x 2 = 12 sets of output):**

- **ITT, Stable Disease and Non-Squamous populations**

**By**

- **Time from progression to time of death (PPS)**

**By**

- **Erlotinib maintenance therapy and placebo**

**Stratified by**

- **Whether patients did or did not receive any 2nd line chemotherapy**

**Please provide the same table of results, and the estimated mean survival time from progression to death (with standard error) for each analysis as specified in (I).**

**A number of the following information points may be readily available in the trial protocol or CSR when we receive it. It would be helpful when this is the case if the manufacturer could also specify the location of the information within these documents.**

Answer: The data for above requests has been attached to this letter.

**Indirect comparisons**

A3. **The submission currently contains an indirect comparison for pemetrexed vs erlotinib. Although methods are identified for the identification of studies used in the comparison no methods on how the comparison was carried out are provided. Please provide a detailed methodology and assumptions on how the indirect comparison for pemetrexed versus erlotinib was estimated. Please provide the data points used in the comparisons.**

As has been explained in Roche's original submission the data available for pemetrexed and erlotinib in the maintenance setting is limited to that from two clinical trials. These trials share a common comparator i.e. no treatment until disease progression in patients achieving at least stable disease after first-line chemotherapy.

Under these circumstances efficacy was compared by means of a simple indirect comparison of hazard ratios for PFS and OS for the interventions versus the common control as shown in Table 11 of our original submission. As explained in Section 6.6.10 of Roche's original submission, this approach has limitations, primarily because of the different baseline characteristics of the patients in the two studies, though it is difficult to see how this can be overcome given the information available.

Safety was compared by a simple comparison of adverse event rates between study arms.

Further details could be found in section 7.2.7.2 of the manufacturer's original submission and in addition calculations can be found in the "Non Squam Tarceva 1$^{st}$ lin Maint mNSCLC Saturn_i18192 FINAL.xls" model (sheet called "Indirect Comparison(s))".

**Stratification**

**A4. Please provide stratified analysis for PFS and OS by EGFR status, stage of disease, ECOGPS, chemotherapy regimen, smoking status and region.**

In a stratified analysis incorporating the above factors the adjusted HR for the primary PFS endpoint in the erlotinib group relative to the placebo group was 0.70 (95% CI 0.59 to 0.84, p<0.0001). Similar results were obtained for the EGFR IHC positive population (0.69 [95% CI 0.57 to 0.84], p=0.0003.

For overall survival in the stratified log rank test for OS for all patients the HR was higher (0.85) than for the non stratified analysis (0.81) and the p-value became non-significant (p=0.0839). This difference is due to the high number of strata (540 maximum), many of which had only a few patients and more than 10% of had no events. An alternative analysis to adjust for the stratification factors, a multiple Cox regression, was therefore performed. It can be seen from this analysis that the treatment effect adjusted for stratification factors was similar to the non-stratified analysis (HR=0.82, p=0.0103). Significant factors in the model, other than treatment, were ECOG performance status and smoking status.
In the stratified log rank test for OS for the EGFR IHC positive population there are considerably less strata (180 maximum, since IHC status was no longer considered) and so there was not an issue with the stratified analysis. The HR was the same as for the non stratified analysis (0.77) and the p-value remained statistically significant (p=0.0122). For consistency with the overall population analysis a multiple Cox regression analysis was performed. In this analysis the treatment effect adjusted for stratification factors was similar to both the stratified and non-stratified analyses (HR 0.76, p=0.0043). Significant factors in this model, other than treatment, were again ECOG performance status and smoking status.

**Proportion of patients receiving 2nd line treatment**

**A5. The reported proportion of patients estimated to receive 2nd line treatment varies in the document (one third, 28% and 40%). Please clarify the sources used to estimate these figures and also clarify the total number of patients that would be expected to be treated annually in England and Wales.**

We apologise for the confusion on this issue. Firstly, it must be noted that there is no definitive source of information available on second-line treatment rates. The National Lung Cancer audit does not yet include second-line treatment rates in its annual report and assuming that centre-to -entre variability is similar to that in first-line treatment rates (which is reported by the National Lung Cancer Audit to range from 0-100% for PS 0-1, Stage IIB/IV NSCLC patients), single centre audit data is unlikely provide great accuracy in this area.

Based on a succession of market research exercises, Roche has always adopted the working hypothesis that around one-third of patients receiving first-line chemotherapy receive second-line systemic therapy and that if all those suitable were to receive it the figure might rise to around 40%.

In preparing this submission we were keen to provide a figure with rather more external validation and approached Dr Mick Peak, as Director of the National Lung Cancer Audit for any information available on second-line systemic treatment rates. He confirmed that although data returns on second-line treatments were less complete than those on first-line

he did have information from the audit that the second-line systemic treatment rate was 28%. Given the problems with Market Research (in the first-line setting clinicians seem to routinely overestimate treatment rates relative to National Lung Cancer Audit figures) this figure is pretty close to the "one-third" traditionally used by Roche. Since it has external validation, 28% would seem a reasonable figure to use.

As per Figure 1 of Roche's original submission, applying the 28% second-line treatment rate to a treatment pathway describing the disposition of lung cancer patients in England and Wales yields a pool of 1,750 patients receiving second-line systemic therapy for NSCLC in England and Wales each year**.**

**Compliance**

A6. **Please provide detailed information on the interim analysis plan and timing of the actual interim analyses for SATURN trial.**

An interim analysis of efficacy and safety was planned after approximately 365 events (disease progressions or deaths) had occurred (50% of events). At this point it was estimated that approximately 200 deaths would have occurred, allowing for an evaluation of differences between erlotinib and placebo for OS. The main purpose of the interim analysis was to terminate the study early if 1) the Data and Safety Monitoring Board (DSMB) had safety concerns, or 2) robust efficacy had been demonstrated.

The interim analysis was performed on 2 different patient populations, (1) all patients and (2) patients with EGFR IHC positive tumors. As a separate analysis, K-ras mutation status was correlated with clinical outcome.

Safety concerns were addressed by testing for a detrimental effect of erlotinib, compared to placebo, on survival and on PFS, based on a one- sided log-rank test at a 5% significance level. In case of a significant result, for either survival or PFS in favor of placebo, early stopping or amendment of enrollment for detrimental effect was to be considered. At the interim analysis, communication between the DSMB and the sponsor was limited to the recommendation on whether or not to continue or amend the study.

Robust efficacy was assessed by testing for overwhelming efficacy of erlotinib with respect to PFS. A Lan-DeMets alpha spending function with an O'Brien-Fleming boundary was used to maintain an overall alpha of 0.05. At no time did any of the erlotinib project team members have access to unblinded data and the results of the interim analysis were not displayed to anyone outside the DSMB.

The cut-off date for the interim analysis was 30 July 2007, the estimated date of the occurrence of the 365$^{th}$ event. After data cleaning, there were 399 events for the Full Analysis Set (FAS) population (610 patients), ie, 54.6% of the total required number of events, instead of 50%. Therefore the alpha was recalculated according to the Lan-De Mets alpha-spending function with an O'Brien-Fleming boundary to maintain an overall alpha of 0.05, with the software East v4.1, with the same assumptions as

in the original protocol (HR and power of the Full Analysis Set [ITT] analysis), with no impact on the total required number of events for the final analysis. The alpha was also recalculated for the EGFR IHC positive population with the assumption that 54.6% of the total number of events were observed in the interim analysis. The resulting significance levels are given in Table 1.

**Table 1. Significance levels for interim and final analyses**

| Population | Significance level at interim analysis | Significance level at final analysis | Total alpha spent |
|---|---|---|---|
| Full Analysis Set (ITT) | 0.00199 | 0.02934 | 0.03 |
| EGFR IHC +ve population | 0.00098 | 0.01967 | 0.02 |

Following their review of the interim efficacy and safety data, the DSMB recommended that the study continue.

**A7. Please clarify how patient compliance with erlotinib therapy was monitored during the SATURN trial. Please clarify the rate of patient compliance for both arms during the SATURN trial.**

Accountability and patient compliance was assessed by maintaining adequate “drug dispensing” and return records.

Patients were asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

A drug dispensing log was kept current and contained the following information:

• the identification of the patient to whom the study medication was dispensed;

• the date(s), quantity of the study medication dispensed to the patient;

• the date(s) and quantity of the study medication returned by the patient.

This inventory was made available for inspection by the Covance Monitor or designee.

All supplies, including partially used or empty containers and the dispensing logs, were returned to the sponsor or designee at the end of the study.

The CSR does not contain any information on compliance and we have been unable to obtain further information within the timescale required for this response though information on treatment exposure based on dispensed treatment is included as in Table 2.

**Table 2 Treatment exposure in the SATURN study**

| | PLACEBO N = 442 No. (%) | ERLOTINIB N = 430 No. (%) |
|---|---|---|
| TRIAL DRUG MG | | |
| Treatment Duration (months) | | |
| 0 - 0.9 | 16 ( 4) | 21 ( 5) |
| 1 - 1.9 | 179 ( 40) | 142 ( 33) |
| 2 - 2.9 | 99 ( 22) | 60 ( 14) |
| 3 - 3.9 | 27 ( 6) | 30 ( 7) |
| 4 - 4.9 | 40 ( 9) | 46 ( 11) |
| 5 - 5.9 | 23 ( 5) | 35 ( 8) |
| 6 - 6.9 | 10 ( 2) | 13 ( 3) |
| 7 - 7.9 | 13 ( 3) | 22 ( 5) |
| 8 - 8.9 | 8 ( 2) | 16 ( 4) |
| 9 - 9.9 | 4 ( <1) | 7 ( 2) |
| 10 - 999 | 23 ( 5) | 37 ( 9) |
| Total Cumulative Dose (MG) | | |
| Mean | 15273.8 | 18509.4 |
| SD | 14029.16 | 16418.57 |
| SEM | 667.30 | 791.77 |
| Median | 12300.0 | 12750.0 |
| Min | 750 | 0 |
| Max | 88500 | 89400 |
| n | 442 | 430 |

Percentages are based on N.
Patients for whom inadvertently both study drugs were dispensed are excluded from this analysis.
Cut-off for statistical analysis: 17MAY2008
MT11 17NOV2008:18:27:56 (1 of 1)

dm16durtrt Summary of Treatment Duration
Protocol(s): BO18192 (I18192U)
Analysis: SAFETY ANALYSIS POPULATION Center: ALL CENTERS

| | PLACEBO N = 442 | ERLOTINIB N = 430 |
|---|---|---|
| Treatment Duration [weeks] | | |
| Mean | 14.70 | 18.59 |
| SD | 13.754 | 16.678 |
| SEM | 0.654 | 0.805 |
| Median | 11.71 | 12.29 |
| Min-Max | 0.9 - 92.7 | 0.6 - 85.1 |
| n | 442 | 429 |

n represents number of patients contributing to summary statistics.
Patients for whom inadvertently both study drugs were dispensed are excluded from this analysis.
Cut-off for statistical analysis: 17MAY2008
DM16 17DEC2008:12:52:53 (1 of 1)

It is unclear how compliance information impacts on this appraisal. The efficacy and tolerability seen in the study were seen with the degree of compliance that patients are able and willing to give. There is no reason to believe that this is any different to that which

would prevail in clinical practice and that any outcomes in the trial that had been influenced by compliance issues would be different in clinical practice. Assuming that under-compliance resulting from patients forgetting to take tablets or choosing not to is more likely than over-compliance. In a trial patients return unused tablets at each treatment visit and are issued with a fresh supply based on their theoretical requirement until their next treatment visit. In clinical practice, any tablets the patient has in hand at the time of repeat prescribing will be left with them for future use rather than returned and destroyed, thus reducing medication wastage.

**Patient treatment and deviations**

**A8. Please provide details of the 1st line treatment provided to patients listed by ITT, non-squamous and stable disease (SD) populations.**

Answer: The data for above request has been attached to this letter.

**A9. Please specify the post-progression chemotherapies/TK inhibitors given in each treatment arm in the SATURN trial and the proportions of patients receiving each of these post-progression chemotherapies listed by 1st line treatment as well as by ITT, non-squamous and SD populations**

Answer: The data for above request has been attached to this letter.

**A10. Please provide a full list of protocol deviations for the SATURN trial.**

Major protocol violations causing exclusion from the per protocol (PP) analysis of efficacy were specified in the study Data Reporting and Analysis Manual as:
1. Failure to receive at least 1 dose of study medication.
2. Incorrect study medication given versus randomized treatment arm (crossover from erlotinib to placebo or vice versa).
3. Failure to receive 4 cycles of platinum-based chemotherapy.
4. Failure to undergo at least 1 post-baseline efficacy assessment (unless patient died before first post-baseline tumor assessment).
5. Receipt of previous anti-cancer treatments specifically listed in the exclusion criteria of the protocol.
6. Absence of measurable disease at screening.
7. Absence of CR, PR or SD at baseline.
8. Absence of histologically documented Stage IIIb or IV NSCLC.
9. Presence of malignancy other than carcinoma in situ of the cervix or basal or squamous cell skin cancer.
10. Lung tumor resection following response to chemotherapy before baseline.

11. Not randomized.
12. Breaking blinding by chemical analysis of study medication.

**A11. Please provide the number of patients in each arm of the SATURN trial broken down by type of protocol deviation**

A similar number of patients in each treatment group had at least 1 major protocol violation from the list provided in response to Question A10 (19 patients in the erlotinib group versus 17 patients in the placebo group, as shown in Table 3). The most common protocol violations were missing post-baseline tumor assessments and PD at baseline. Eight patients (6 in the placebo group and 2 in the erlotinib group) had PD or no evaluable tumor assessment at baseline. Other protocol violations such as failure to receive at least 1 dose of study drug or incorrect study drug given versus randomised treatment arm occurred in less than 1% of patients in both treatment groups.

**Table 3. Protocol violations resulting in exclusion from the Per Protocol analysis by trial treatment in the SATURN study**

| | Placebo | Erlotinib |
|---|---|---|
| Number of patients randomized | 451 | 438 |
| Number of patients included in per protocol analysis | 434 | 419 |
| Number of patients excluded from per protocol analysis | 17 | 19 |
| Reasons for exclusion | | |
| No post-baseline tumour assessment | 6 | 11 |
| Absence of CR, PR or SD at baseline | 6 | 2 |
| No trial treatment | 4 | 3 |
| Previous platinum-based chemotherapy not according to protocol | 3 | 3 |
| Absence of measurable disease at screening | 2 | 2 |
| Blinding broken by patient chemically analyzing trial treatment | 1 | - |
| Presence of another malignancy excluded by protocol | 1 | - |

**Patients**

**A12. Please clarify the assumptions undertaken to incorporate data points from patients who deviated from the SATURN trial protocol.**

Roche are unclear what information is being sought here. The primary analysis in this study was, as is good practice in an RCT with a superiority end-point conducted on an ITT basis with all available data from all randomised patients included. This was supported by a per protocol (PP) analysis excluding from both study arms patients who were major protocol violators. Results from the ITT and PP analyses were similar.

**Quality of Life**

**A13. Please provide reasons and characteristics of patients (number (%) per arms) with missing responses for the Fact-L subscales that were excluded when transforming**

**FACT-L scores into EQ5D utilities.**

Answer: The response for above requests has been attached to this letter.

**EGFR status**

**A14. Please provide reasons and characteristics of patients (number (%) per arms) with missing EGFR IHC status.**

Table 3 shows the reasons given for not reporting EGFR IHC status for patients in the SATURN study

**Table 3 Reasons for missing EGFR IHC status in the SATURN study**

| Consolidated Comment | EGFR IHC (n/%) |
|---|---|
| NOT ENOUGH TUMOR/SLIDES | 53/36% |
| NO TUMOR | 43/29% |
| INAPROPRIATE TISSUE | 16/11% |
| NO SAMPLE | 15/10% |
| ARTIFACTS | 9/6% |
| WASHED OFF | 6/4% |
| STAINED SLIDES RECEIVED | 3/2% |
| NECROSIS | 2/1% |
| Total | 147/100% |

It is clear from Table 3 that although a variety of wording was used to describe the reason for missing IHC status in most cases this was due to a lack of testable tumour tissue. This is not unexpected – lung biopsies are typically small (they are NOT resection specimens) tissue fragments taken from tumours that are intermingled with normal lung tissue. What may appear to be a an adequate biopsy sample at the time may, on subsequent examination, contain no tumour.

It was not possible within the timescale of this response to provide the data in Table 3 organized by study arm. However, as shown in Table 4, the number of missing results and the characteristics of patients within missing results is similar between study arms indicating that the missing results are unlikely to have led to any bias in the results in IHC positive patients.

**Table 4 Characteristics of patients with missing EGFR IHC status in SATURN study**

| All | PLACEBO (n=55) | ERLOTINIB (n=52) |
|---|---|---|
| Gender | | |
| - Male | 44 | 41 |
| - Female | 11 | 11 |

| | | |
|---|---|---|
| Race | | |
| - Caucasian | 52 | 44 |
| - Asian | 3 | 7 |
| - Black | 0 | 1 |
| | | |
| Smoking Status | | |
| - Ever | 48 | 45 |
| - Never | 7 | 7 |
| | | |
| Histology | | |
| - Adenocarcinoma | 22 | 19 |
| - Squamous Cell Carcinoma | 26 | 22 |
| - Other | 7 | 11 |
| | | |
| Response | | |
| - PR | 1 | 6 |
| -SD | 29 | 29 |
| -PD | 20 | 16 |
| -NA | 5 | 1 |
| | | |

It is also appropriate to emphasis that the SATURN data do not provide a rationale for using EGFR IHC status for selecting patients, Roche is not proposing IHC status as a basis for patients selection and does not believe that the anticipated Marketing Authorisation for erlotinib in maintenance will be restricted based on IHC status, as such the significance of the requested information is unclear.

**Trial flow**

**A15. Please provide consort type patient flow diagram for SATURN trial.**

You are referred to Figure 5 in Roche's original submission

**Comparison to 2nd line treatment**

**A16. On page 11 of the MS it states: 'Since mean treatment durations are similar in maintenance and second-line, where erlotinib is now the dominant treatment in the**

**UK (130 and 125 days, respectively), there will be little net increase in erlotinib usage as a result of its use as a maintenance therapy'. Please provide clarification of the evidence base regarding 130 and 125 days.**

130 days and 125 days are the mean durations of treatment in the BR21 ($2^{nd}$/$3^{rd}$-line treatment) and SATURN (maintenance therapy) trials, respectively.

**Pemetrexed dominance for 1st line treatment**

**A17. The document states (page 14) that pemetrexed now dominates in terms of use for 1st line treatment. Please provide the source for this conclusion.**

Page 14 of the Roche submission states that "This [Maintenance] indication for pemetrexed is currently being appraised by NICE and although the drug is clearly active as a maintenance agent its uptake is likely to be limited by the desire of clinicians to use pemetrexed as part of first-line chemotherapy for patients with non-squamous tumours, following NICE's recent endorsement of its use in this way". This is clearly a speculative statement and not a claim of dominance. Having said this Roche strongly believes through its regular interaction with clinicians treating NSCLC that pemetrexed will come to dominate in this area. For more than a decade clinicians have had to choose between a variety of platinum doublet regimens none of which offer clear efficacy advantages in first-line treatment of NSCLC. NICE's recent endorsement of pemetrexed/cisplatin for most non-squamous tumours gives them access to a regimen that, in this group, is more active, somewhat less toxic and requires less hospital visits than the regimens that they are currently using. Under these circumstances, it is difficult to see why they would not make the change to using pemetrexed/platinum first-line. This view is endorsed almost universally by the clinicians we have spoken to and supported by our market intelligence reports which have shown a sharp uplift in UK pemetrexed sales that started following promulgation of the positive NICE guidance.

**FDA analysis**

**A18. The report by the FDA includes a non-significant stratified log rank of overall survival in the SATURN study. Would Roche like to comment on this analysis as it provides an outcome that is not described in their submission? http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM195716.pdf**

See response to Question A4