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ETOP 7-14 NICHE

Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

Sponsor: European Thoracic Oncology Platform (ETOP)

STATISTICAL ANALYSIS PLAN – FINAL ANALYSIS

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1. INTRODUCTION

1.1 Preface

Afatinib presents a manageable toxicity profile and potentially offers a significant activity in terms of disease control and long-term outcome. Therefore this treatment option offers a good benefit to risk ratio in patients with HER2-mutate advanced NSCLC.

The primary objective of the study is to evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations. More particularly, the primary endpoint is disease control at 12 weeks.

The secondary objectives of the study are:

- To evaluate secondary measures of clinical efficacy including progression-free survival (PFS),
- To assess the safety and the tolerability of the treatment.

1.2 History of the Study

ETOP/7-14 NICHE trial was activated in December 2014 and the first patient was enrolled on September 2015.

The ETOP IDMC reviewed the trial safety data during its scheduled bi-annually meetings, in April 2016 (n=5 patients enrolled; no safety issues identified) and October 2016 (n=13) when the interim analysis was presented. Follow-up was suspended based on the interim analysis and an unscheduled follow-up IDMC meeting in November 2016 on the 13 enrolled patients enrolled).

At the IDMC meeting of October 2016, the interim analysis (1st stage of Simon's two-stage design) was presented. Among the first 9 patients, 5 patients (55.6%) had not reached week 12 free of progression. Thus, the stopping threshold of the 1st stage of Simon's two-stage design was reached, since more than the maximum allowed of 3 patients had a progression by 12 weeks. Based on these results, the IDMC recommended suspending further recruitment into the trial while continuing the treatment and close follow-up for the enrolled patients.

A follow-up analysis, once all enrolled patients reached the 12-week assessment, was performed in November 2016. Among all 13 enrolled patients, 6 patients (46.2%) had not reached week-12 free of progression.

Based on the data and results of the interim analysis and considering the protocol specified early stopping rule, the IDMC recommended that:

- The ETOP 7-14 NICHE trial should be permanently closed to accrual.
- Treatment and follow-up of enrolled patients may continue based on the judgement of the treating physician.
- Patients should be informed.

1.3 Purpose of the present Statistical Analysis Plan

The purpose of the present Statistical Analysis Plan (SAP) is to provide an analytic and solid framework for the final analysis of the patients enrolled in the NICHE study.

More details on the planned final evaluation in terms of methods, reporting conventions and formats are described in detail in the following sections.

The overall objectives and methods of the study, as dictated by its protocol, may be found in the Appendix.

2. GENERAL CONSIDERATIONS FOR THE ANALYSIS

2.1 Timing of Analysis

The final analysis will be performed at least six months after the last patient was enrolled and as soon as the database is formally locked.

2.2 Analysis Populations

Interim evaluation Cohort

The interim evaluation cohort will include the first 9 patients enrolled in the study, which were used for the evaluation of Simon's stage one.

Efficacy Cohort

The efficacy cohort will include all eligible patients enrolled in the study until trial termination.

Safety Cohort

The safety cohort will encompass all eligible enrolled patients who have received at least one dose of trial treatment.

2.3 Statistical Considerations

Primary endpoint is disease control (DC), defined as complete (CR) or partial response (PR), or disease stabilisation (SD) lasting at least 12 weeks.

Simon's two stage phase II design has been adopted. A Disease Control Rate (DCR) of 50% was considered as unacceptable, targeting a DCR of 75%. Hence the null hypothesis under consideration was that the DCR≤50% versus the alternative that DCR≥75%. For a one-sided type I error of 10% and power of 80%, a total of 22 patients were needed, with 9 patients in the first stage. If in the first stage, 6 out of the 9 patients achieved Disease Control, then the trial would proceed to the second stage and recruit an additional 13 patients for a total of 22 patients. If at least 14 out of the 22 patients achieved Disease Control, then this finding would indicate that it would be reasonable to proceed to a Phase III trial.

Secondary endpoints include objective response (OR), defined as best overall response (CR or PR, using RECIST 1.1 criteria) across all assessment time-points during the period from enrolment to termination of trial treatment, progression-free survival (PFS), defined as the time from the date of enrolment until documented progression or death, overall survival (OS), defined as time from the date of enrolment until death from any cause (censoring occurring at the last follow-up date), and toxicity as specified by the adverse events classified according to NCI CTCAE version 4.

2.4 Missing Data

Missing values will not be replaced by any statistics calculated over non-missing data.

3. SUMMARY OF STUDY DATA

3.1 MAIN OUTCOME

The primary endpoint according to study's protocol, is the **DCR**.

DCR will be calculated along with 90% exact binomial confidence interval (CI) for the efficacy cohort.

PFS and OS (medians and rates) will be estimated based on the product-limit Kaplan-Meier method, while the corresponding 95% CIs for the median values will be based on the complementary log–log transformation.

3.2 Baseline characteristics

Baseline characteristics will be summarized and presented overall **for all enrolled patients.**

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, 95% CI for the mean, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

3.3 Follow-up and treatment administration

Follow-up time will be defined as time between the minimum of enrolment and start treatment date and last contact date. The median follow-up will be estimated based on reverse censoring of overall survival.

Time-to-Treatment Failure (TTF) will also be calculated based on the Kaplan-Meier method, and the specific reasons of treatment failures will be provided.

3.4 Translational results

The results of all translational analyses (of the tests performed centrally) in the frame of the study we be analytically presented in tabular format.

4. EFFICACY ANALYSIS

The primary efficacy analysis will include all eligible enrolled patients.

The primary endpoint is disease control, defined as complete or partial response or disease stabilisation lasting at least 12 weeks.

Results on the primary endpoint will be presented for the whole efficacy cohort as well as for the 'interim analysis' cohort.

Objective response, progression-free survival and overall survival, the secondary efficacy endpoints of the NICHE trial, will also be evaluated for the whole efficacy cohort.

Best overall response, defined as best response across all assessment time-points, during the period from enrolment to termination of trial treatment, and objective response rate, defined as the best overall response (complete or partial response) will be summarized in table format.

PFS (defined as the time between the minimum of enrolment and start treatment date until documented progression or death) and OS (defined as the time between the minimum of enrolment and start treatment date until death or last contact date for censored patients) will be summarized through tables as well as graphically depicted via Kaplan-Meier curves and alternative graphical illustrations if possible (spider plot, swimmer plot).

As an exploratory analysis, the association of the primary endpoint (Disease control at 12 weeks) with patients' baseline characteristics, prior treatments received as well as with translational results will be also investigated.

More particularly, the distribution of patients' baseline characteristics and prior treatments will be presented separately for the group of patients that achieved disease control at 12th week versus the group of patients that did not achieve disease control and corresponding Fisher's exact tests will be provided.

In a similar manner, all translational results will be presented separately for the groups of patients that achieved or not disease control. Also, PFS and OS results will be provided for selected subgroups of patients with particular interest (type of ERBB2 mutation, Gender and Smoking status). Log-rank test comparing the survival curves between subgroups will be also presented.

5. SAFETY ANALYSIS

The safety cohort will encompass all patients who have received at least one dose of trial treatment. Safety and tolerability of the afatinib treatments will be described by tabulation of the CTCAE V4 grade. In particular, safety analysis will include assessment of the experience of adverse events (AE) and serious adverse events (SAE), the frequency of AEs, the numbers of patients experiencing specific number of adverse events and their distribution by CTCAE V4 grade. Further exploration on AEs, with respect to their grade will include the presentation of maximum severity of AEs for each patient as well as the distribution of worst degree of severity by patient.

Note: If the same adverse event is recorded more than once for a specific patient, it will be counted only once keeping the one with the higher grade.

For a closer investigation and for purposes of medical review, information on AEs will also be provided by patient. This information will consist of AE description and grade, date of AE onset and end date (if the event is resolved), its potential relation to treatment and his/ her specific outcome.

A summary table of all the narratives of patients with SAE will also be provided.

Furthermore, the baseline symptoms experienced by some of the patients, which are not counted as adverse events –unless their grade was increased or they appeared as new events at a later period of time- will be presented separately.

6. REPORTING CONVENTIONS

P-values≥0.001 will be reported with two significant digits (e.g. p=0.26, p=0.026, p=0.003); p-values less than 0.001 will be reported as "<0.001". The mean, 95% confidence limits, quantiles, and any other statistics, will be reported to one decimal. Hazard ratios (HRs) and their 95% CI's will be reported to two decimals. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 decimals.

7. TECHNICAL DETAILS

Data will be analyzed using the SAS software package (version 9.4). The use of R language will also be considered for the production of specific plots.

A second statistician, the **reviewing statistician** will independently reproduce all analysis and summary statistics. The **reviewing statistician** will have an overview of the entire analysis and will explicitly check the code producing tables and figures as well as any other pieces of code as desired.

8. LISTING OF TABLES AND FIGURES

Table 1 gives a tabulation of the following aspects unique to each table:

- Title
- Numbering
- Population
- Endpoint(s)

- Time Points or details of how to conglomerate multiple observations
- Covariates or Subgroups used to break down summary statistics
- Which summary statistics will be calculated

For figures the equivalent information is summarized in Table 2 and includes the following:

- Title
- Numbering
- Population
- Type of figure
- Endpoint(s), and which is used for horizontal and vertical co-ordinates
- Statistic(s) used in calculating co-ordinate values used in the figure
- Covariates used within the figure used to determine colours or symbols

Table 1. Listing of Tables

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis	Notes
Section I: Patient Accrual & Baseline Characteristics								
Accrual by center	1	Efficacy cohort	Accrual	NA	center	n (%)	NA	Sorted by descending "n"
Patient and tumor baseline characteristics	2	Efficacy cohort	Gender Smoking history ECOG Performance status (at enrolment) TNM staging Age (yrs at enrollment)	Baseline	-	n (%)	NA	
Information on previous and subsequent lines of treatment	3	Efficacy cohort	Type of prior platinum treatment Afatinib Treatment Line Further treatment Type of further treatment	Baseline, Follow-up	-	n (%)	NA	
History of previous diseases/conditions	4	Efficacy cohort	Types of previous diseases and conditions	Baseline	-	n (%)	NA	
Results of HER2 central testing	5	Efficacy cohort	HER2 (ERBB2) mutation	Baseline	-	n (%)	NA	
Section II: Follow-up & Treatment Administration								
Time on follow-up and Time on treatment	6	Efficacy cohort	No. of patients still on f-up, no. of discontinuations	End of follow-up	-	n (%) median, interq. range	Reverse Censoring based on OS (f-up) Kaplan – Meier analysis (both)	
Reasons of treatment failures	7	Efficacy cohort	Reasons of treatment failures			n (%)	NA	
Section III: Analysis of Primary Endpoint								

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis	Notes
Disease Control Rate (DCR) at 12 weeks	8	Interim evaluation cohort & Efficacy cohort	Disease Control (Yes / No)	12-week evaluation (tumor assessment)	-	n (%)	NA	
Section IV: Analysis of Secondary Efficacy Endpoints								
Best Overall Response and Objective Response Rate (ORR) for all enrolled patients (N=13)	9	Efficacy cohort	Best Overall Response, ORR	*OR*: The best overall response (CR or PR) across all assessment time-points according to RECIST Criteria 1.1, during the period from enrolment to termination of trial treatment.		n (%)		
Progression-free Survival (PFS) for all enrolled patients (N=13)	10	Efficacy cohort	PFS	*PFS*: time from the date of enrolment until documented progression or death without documented progression	-	KM estimates: no. of patients, n(%) of PFS events, 12-week PFS (%) (95% CI), median PFS (in weekw)	Kaplan – Meier analysis	
Overall Survival (OS) for all enrolled patients (N=13)	11	Efficacy cohort	OS	*OS*: time from the date of enrolment until death	-	KM estimates: no. of patients, n(%) of deaths, xx-weeks OS	Kaplan – Meier analysis	

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis	Notes
				from any cause		(%) (95% CI), median OS (in weeks)		
Section V: Translational Results								
Translational results of central testing	12	Efficacy cohort	All biomarkers included in the central testing (wild-type, mutation detected, type of mutation detected)	Baseline	-	n (%)		
Section VI: Exploratory Analysis of Efficacy Endpoints								
Primary endpoint by baseline characteristics	13	Efficacy cohort	DC at 12w achieved or not for each value of baseline characteristics	12-week assessment	Different values of baseline characteristics	n (%)	Fisher's exact test	
Primary endpoint by prior treatment	14	Efficacy cohort	DC at 12w achieved or not for each value of prior treatment	12-week assessment	Different types of prior treatment	n (%)	Fisher's exact test	
Primary endpoint by translational results	15	Efficacy cohort	DC at 12w achieved or not for each value of biomarkers centrally tested	12-week assessment	Different status of biomarkers tested	n (%)	Fisher's exact test	
Progression-free survival (PFS) for selected subgroups of patients	16	Efficacy cohort	PFS	*PFS*: time from the date of enrolment until documented progression or death without documented progression	ERBB2, gender, smoking status	KM estimates: no. of patients, n(%) of PFS events, 12-week PFS (%) (95% CI), median PFS (in weekw)	Kaplan – Meier analysis	
Overall survival (OS) for selected subgroups of patients	17	Efficacy cohort	OS	*OS*: time from the date of enrolment until death from any cause	ERBB2, gender, smoking status	KM estimates: no. of patients, n(%) of deaths, xx-weeks OS (%) (95% CI), median OS (in weeks)	Kaplan – Meier analysis	

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis	Notes
Section VII: Safety Analysis								
(Serious) Adverse event overview	18	Safety cohort	AE / SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	-	n (%) of persons who have experienced >=1 AE or SAE	-	
Number of patients experiencing specific number of adverse events	19	Safety cohort	AE	At the end of each treatment visit	-	n (%)	-	
Number of patients experiencing specific number of serious adverse events	20	Safety cohort	SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	-	n (%)	-	
Maximum severity of adverse events (AE/SAE) per patient	21	Safety cohort	AE / SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	-	n (%)		
Distribution of adverse events (AE/SAE) by Grade	22	Safety cohort	AE / SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	Severity grade (NCI CTCAE version 4)	n (%)	-	In case of multiple reports of the same AE/SAE (grouped according to CTCAE V4) for a particular patient, the

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis	Notes
								event is counted once.
Baseline symptoms by patient	23	Safety cohort	AE	At baseline	-	-	-	Patients ordered by enrolment date
Adverse event information by patient	24	Safety cohort	AE / SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	-	-	-	Patients ordered by enrolment date
Narratives of patients with SAE	25	Safety cohort	SAE	At the end of each treatment visit, Within 24h of occurrence of SAE	-	-	-	Patients ordered by enrolment date

Table 2. Listing of Figures

Title	Number	Population	Type of graph	Horizontal Variables	Vertical Variables	Groupings	Notes
Section I: Patient Accrual & Baseline Characteristics							
Expected vs Observed Accrual	1	Efficacy cohort	Line graph	time	cumulative number of patients	-	-
Section II: Follow-up & Treatment Administration							
Kaplan Meir plot for Time-to-Treatment Failure (TTF)	2	Efficacy cohort	KM	time	probability	-	-
Section IV: Analysis of Secondary Efficacy Endpoints							
Plot of tumor response	3	patients in efficacy cohort evaluable for tumor-response	Spider plot	time	% change (in sum of diameter of target lesions) from baseline		It depends on the data whether it will be feasible to produce it
Plot of duration of tumor response	4	patients in efficacy cohort evaluable for tumor-response	Swimmer plot	Duration of response (in weeks)	Patient id	-	It depends on the data whether it will be feasible to produce it
Kaplan Meir plot for Progression Free Survival (PFS)	5	Efficacy cohort	KM	time	probability	-	-
Plot of Progression-free Survival by patient, according to primary endpoint (disease achieved at 12 weeks)	6	Efficacy cohort	Bar-plot	Patient id	PFS (in weeks)	-	Additional patients' characteristics will be shown below the bars
Kaplan Meir plot for Overall Survival (OS)	7	Efficacy cohort	KM	time	probability	-	-

APPENDIX

IMPORTANT INFORMATION AS DESCRIBED IN THE PROTOCOL

Objectives

The primary objective of the study is to evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations. More particularly, the primary endpoint is disease control at 12 weeks.

Secondary objectives

The secondary objectives of the study are:

- To evaluate secondary measures of clinical efficacy including progression-free survival (PFS),
- To assess the safety and the tolerability of the treatment.

Endpoints

1. Primary endpoint: Disease control at 12 weeks
2. Secondary endpoints:
    a. Progression-free survival by RECIST v1.1
    b. Objective response rate by RECIST v1.1
    c. Overall survival
    d. Adverse events graded according to CTCAE V4.0

Most important eligibility criteria

Inclusion criteria at enrolment:

- Histologically or cytologically confirmed, non-predominant squamous subtype,
- Stage IIIB (non amenable to curative-intent multimodal treatment) or IV NSCLC, according to 7th TNM classification
- Tumour is platinum-refractory
- Measurable or evaluable disease (according to RECIST 1.1 criteria)
- Locally documented HER2 mutation
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
- Life expectancy >3 months
- Adequate haematological, renal and hepatic function
- Effective contraception, no pregnancy

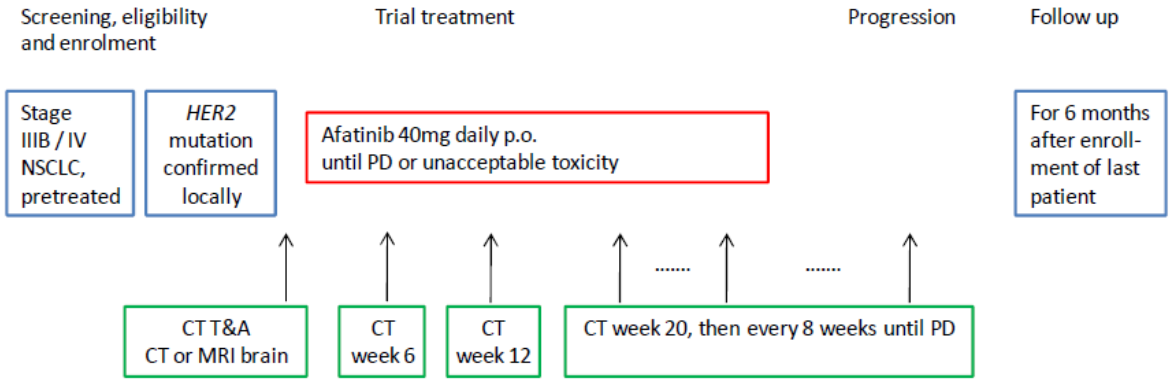
Exclusion criteria at enrolment:

- Mixed small-cell and non-small-cell histologic features
- Uncontrolled lepto-meningeal metastatic disease
- Previous treatment with HER2 targeted antibody or tyrosine kinase inhibitor
- Any previous (in the past 3 years) or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ ductal carcinoma of the breast
- History or presence of clinically relevant cardiovascular abnormalities

- Other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient's capacity to participate in the trial
- Interstitial lung disease or pulmonary fibrosis
- Any concurrent systemic anticancer therapy

Treatment

Afatinib 40 mg p.o./day until tumour progression or lack of tolerability



SCHEMA 1. Trial design

Population: Advanced stage NSCLC, harbouring *HER2* exon 20 mutations.

Design: A Phase II single-arm multicenter trial

Planned sample size: 22 patients

Total trial duration: 40 months from enrolment of the first patient, including 6 months of follow-up from enrolment of the last patient

Statistical considerations

Simon's two stage phase II design is adopted. A Disease Control Rate (DCR) of 50% is considered as unacceptable, targeting a DCR of 75%. Hence the null hypothesis under consideration is that the DCR≤50% versus the alternative that DCR≥75%. For a one-sided type I error of 10% and power of 80%, a total of 22 patients are needed, with 9 patients in the first stage. If in the first stage, 6 out of the 9 patients achieve Disease Control, then the trial will proceed to the second stage and recruit an additional 13 patients for a total of 22 patients. If at least 14 out of the 22 patients achieve Disease Control, then this finding will indicate that it would be reasonable to proceed to a Phase III trial.