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Information | Research

EMPHASIS-lung

ETOP 3-12

A randomized phase III trial of erlotinib versus docetaxel in patients with advanced squamous cell non-small cell lung cancer who failed first line platinum-based doublet chemotherapy stratified by VeriStrat Good vs VeriStrat Poor

Erlotinib **M**aldi TOF **Pha**se III **Si**gnature in **S**quamous cell non-small cell lung cancer

A clinical trial of ETOP

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1. ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
EGFR	Epidermal Growth Factor Receptor
HR	Hazard Ratio
KM	Kaplan - Meier
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PH	Proportional Hazards
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal lab value
VSG	VeriStrat Good
VSP	VeriStrat Poor

2. INTRODUCTION

2.1 Preface

The current project aims to assess the predictive ability of the VeriStrat signature, a recently developed blood-based proteomic test that appears to be both predictive and prognostic for outcome in patients with non-small cell lung cancer (NSCLC). VeriStrat assigns each sample a "good" (VSG) or "poor" (VSP) label and previous studies have confirmed that patients classified as VSG had better progression free survival (PFS) and overall survival (OS) than patients classified as VSP. In the present trial, patients with relapsed squamous cell lung cancer in both strata of the VeriStrat signature (VSG and VSP) are randomized between an EGFR-TKI and chemotherapy. As both erlotinib and docetaxel are currently approved for this indication, these drugs are used in the trial. Our main purpose is to explore the predictive ability of the VeriStrat signature regarding the benefit of treatment with erlotinib vs docetaxel.

2.2 Hypotheses

The VeriStrat signature is expected to be able to predict the benefit of treatment with erlotinib vs docetaxel as measured by a significant improvement in median PFS for VSG patients with squamous cell advanced NSCLC, when treated with an EGFR-TKI, and without significant improvement in VSP patients who receive the same treatment.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

Primary Objective

Explore the predictive ability of the VeriStrat signature, by testing for interaction between treatment arms (Arm A: erlotinib vs Arm B: docetaxel) and VeriStrat status (Good vs Poor) using progression free survival as outcome.

Secondary Objectives

i. Explore whether treatment with erlotinib provides progression free survival benefit as compared to docetaxel in the VSG group.
ii. Compare progression free survival in the two treatment arms (Arm A: erlotinib vs Arm B: docetaxel) in the VSP group.

iii. Explore the prognostic ability of the VeriStrat signature by testing for an overall difference in progression free survival between the two VeriStrat groups (in case of no significant interaction).

iv. Explore the predictive ability of the VeriStrat signature using the secondary measures of clinical efficacy including overall survival, objective response rate, and disease control rate.

v. Compare overall survival, objective response rate and disease control rate between treatment groups separately in the VSG and VSP groups.

vi. Explore the prognostic ability of the VeriStrat signature by testing for an overall difference in overall survival, objective response rate and disease control rate between the two VeriStrat groups (in case of no significant interaction).

vii. Assess the safety and the tolerability of the two treatments separately in each VeriStrat group and overall.

3.2 Endpoints

Primary Endpoint

The primary endpoint of the study is Progression-free Survival (PFS), defined as the time from randomization until documented progression or death without documented progression or up to last day of follow-up if event has not occurred.

Secondary Endpoints

Secondary endpoints include Overall Survival (OS), Time to Treatment Discontinuation (TTD), Objective Response (OR), Disease Control (DC) and toxicities of treatment. More specifically OS is defined as the time from randomization until death, or up to last day of follow-up if event has not occurred. Regarding TTD, two different definitions of treatment discontinuation are considered:

i) all cause treatment discontinuation, and

ii) discontinuation of treatment for patient decision.

In addition, OR is defined as the best overall response (CR or PR) across all assessment time-points according to RECIST Criteria 1.1, during the period from randomization to termination of trial treatment. DC is defined as achieving objective response or stable disease for at least 6 weeks. Finally, toxicities of treatment refer to all adverse events classified according to NCI CTCAE version 4.

3.3 Statistical Hypotheses

The specific statistical hypotheses that are to be tested in order to assess the primary and secondary objectives of the study, as described in Section 3.1, are listed below.
All tests will be performed using a 2-sided significance level of 0.05.

Primary Objective

H_0: The difference on median PFS when treated with erlotinib vs docetaxel is independent of VeriStrat status.

H_1: The difference on median PFS when treated with erlotinib vs docetaxel is not independent of VeriStrat status.

It is assumed that the PFS Hazard Ratio of erlotinib versus docetaxel will be HR=0.675 for the VSG patients (median PFS of 4 months for erlotinib and of 2.7 months for docetaxel), while HR=1.23 for the VSP patients (median PFS of 2.2 and 2.7 months, respectively).

Secondary Objectives

i. H_0: The median PFS does not differ significantly between the two treatment arms in the VSG group.
H_1: There is a significant difference in the median PFS between the two treatment arms in the VSG group.

ii. H_0: The median PFS does not differ significantly between the two treatment arms in the VSP group.
H_1: There is a significant difference in the median PFS between the two treatment arms in the VSP group.

iii. H_0: The median PFS does not differ significantly between the two VeriStrat groups.
H_1: There is a significant difference in the median PFS between the two VeriStrat groups.

iv. H_0: The difference on median OS (ORR / DCR) when treated with erlotinib vs docetaxel is independent of VeriStrat status.
H_1: The difference on median OS (ORR / DCR) when treated with erlotinib vs docetaxel is not independent of VeriStrat status.

v. H_0: The median OS (ORR / DCR) does not differ significantly between the two treatment arms in the VSG group.

H_1: There is a significant difference in the median OS (ORR / DCR) between the two treatment arms in the VSG group.

H_0: The median OS (ORR / DCR) does not differ significantly between the two treatment arms in the VSP group.

H_1: There is a significant difference in the median OS (ORR / DCR) between the two treatment arms in the VSP group.

vi. H_0: The median OS (ORR / DCR) does not differ significantly between the two VeriStrat groups.

H_1: There is a significant difference in the median OS (ORR / DCR) between the two VeriStrat groups.

4. STUDY METHODS

4.1 General Study Design and Plan

The study is designed as a Phase III trial to explore the differential activity of erlotinib vs docetaxel in VSG vs VSP squamous cell NSCLC patients who relapsed after first line platinum-based chemotherapy. Patients in both VeriStrat strata, i.e. VSG and VSP, will be randomized to receive erlotinib or docetaxel, and treatment must start within 7 days after randomization. The investigator will be blinded to the result of the VeriStrat test.

Patient accrual is expected to be completed within 18 months after first patient randomization. The combined run period, treatment and follow-up for PFS (primary endpoint) is expected to extend the study duration to a total of 24 months (i.e., 6 months after the last patient is randomized). All patients will be followed for survival status every 12 weeks thereafter, until death or up to 24 months after the last patient is randomized, at which time the study will formally end.

The preparation of the study report is scheduled for 26 months after the first patient is enrolled.

4.2 Patient Selection

Patients should only be selected and consented for screening if they fulfill the inclusion and exclusion criteria (EMPHASIS Protocol, Sections 7.1 – 7.2), within 14 days prior to registration, except where otherwise noted. Written informed consent needs to be obtained prior to undertaking any study-specific procedure, including blood collection for VeriStrat testing.

4.3 Patient Randomization

This trial will use the web-based randomization and RDE (Remote Data Entry) system called ETOPdata. Each participating center will access the system directly. Specific details for randomization of patients are described in the document "*EMPHASIS Randomization Procedure*".

Block stratified randomization balanced by center using a minimization algorithm (Pocock and Simon, 1975; Pocock, 1979) will be used in the study. Patients will be stratified based on VeriStrat status (VSG vs VSP) and Performance Status (0-1 vs 2).

4.4 Study Variables

Trial schedule of events

	Screening	Treatment period[5]					At PD	End of treatment	Follow-up
Timepoint	Up to 14 days before Registration (except where noted)	Cycle 1 day 1	Cycle 2 day 1	Cycle 3 day 1	Even cycle 4/6/8… day 1	Odd cycle 5/7/9… day 1		30-45 days after last dose	every 3 months
Informed consent	X								
VeriStrat blood sample	X								
Demographics	X								
Medical history	X								
Concomitant medication	X								
Physical examination / PS	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X	X	X	X	X			
Complete blood count + diff.	X	X	X	X	X	X		X	
Blood chemistry	X	X	X	X	X	X		X	
Pregnancy test	X[1]								
Tumor assessment[2]	X[3]			X		X	X	X	
Adverse events	X	X	X	X	X	X		X[4]	
Survival[6]									X

1. Female patients with childbearing potential must have a negative serum or urin pregnancy test within 7 days prior to study registration. Non-childbearing potential is defined as surgically sterile or post-menopausal (defined as ≥24 months since last menses).
2. Thoraco-abdominal CT scan; brain imaging (CT scan or MRI) if clinical suspicion of brain metastasis. To be done within 2 weeks prior to registration and within 5 days prior to cycles 3, 5, 7, …
3. May be performed within 4 weeks prior to treatment start, regardless of registration date.
4. For patients who cease study treatment for reasons other than progression, tumor assessment should be performed 30 (to 45) days after stop of study treatment and every 6 weeks until documented progression.
5. Treatment must start within 7 days after randomization.
6. Survival status may be collected by patient visit or documented phone call.

Baseline evaluations (within 14 days prior to registration)

- Medical history including symptoms, smoking history, medications, comorbidities and allergies.

- Physical examination including blood pressure [mmHg], ECOG performance status (see definition in *EMPHASIS-lung procedures manual*), and body weight [kg] and height [cm].
- Hematology: hemoglobin, neutrophils, platelets.
- Renal function: serum creatinine and creatinine clearance calculated according to Cockroft-Gault.
- Hepatic function: ALT, AP, Bilirubin.
- Serum or urine pregnancy test for women of reproductive potential, within 7 days prior to registration.
- CT scan of thorax and abdomen, within 2 weeks before registration, with i.v. contrast (alone or in combination with PET) to determine measurable disease according to RECIST v1.1 (at least one lesion outside of irradiated areas that can be measured in at least one dimension as ≥ 10 mm, or ≥ 15 mm in case of lymph nodes). In the presence of clinically suspected metastases outside of these fields, additional imaging of the affected body part is recommended.
- CT scan of brain is not mandatory and only recommended in case of clinically suspected brain metastasis.

Before Randomization

For VeriStrat testing collect, process and ship serum sample according instructions in the kits and in the *EMPHASIS-lung Procedures Manual*.

Routine evaluations before and during trial treatment

On day 1 of every 3-week treatment cycle:

- Recording of symptoms / adverse events
- Physical examination including blood pressure, performance status, and body weight
- Hematology: hemoglobin, neutrophils, platelets
- Serum creatinine
- Hepatic function: ALT, AP, Bilirubin

Tumor evaluations during treatment

These evaluations will occur prior to the start of odd cycles (3, 5, 7, 9, ...) until progression. They should be performed within 5 days before the start of the subsequent cycle:

- CT thorax and abdomen

Evaluations in the follow-up phase before progression

Patients who discontinue treatment before progression should have the following assessments 30-45 days after study treatment stop and every 6 weeks thereafter:

- Physical examination
- CT thorax and abdomen (plus further imaging, repeating former disease evaluation imaging techniques, if applicable)
- Documentation of further treatments

Evaluations at progression

Each patient will receive trial treatment until documented progression. At progression, do the following:

- CT thorax and abdomen, document progression on the respective CRF
- Documentation of further treatments

End of treatment visit

At the end of the trial treatment and **irrespective of the reason for stopping treatment**, a post treatment visit at the center is to be scheduled after 30 to 45 days following last treatment day. The following procedures should be performed:

- Recording of symptoms
- Physical examination including blood pressure
- Hematology: hemoglobin, neutrophils, platelets
- Hepatic function: ALT, AP, Bilirubin
- Serum creatinine
- CT thorax and abdomen, if not done within the last 30 days

Evaluations after progression

Patients with progression will end trial treatment and should have documented survival every 12 weeks until death. Survival status can be collected by patient visit or documented phone calls.

4.5 Primary Comparisons

The main comparison involves exploring the ability of the VeriStrat signature to predict response to treatment (Arm A: erlotinib vs Arm B: docetaxel). The primary comparison will be based on PFS, and in particular the predictive ability of the VeriStrat signature will be tested by studying the interaction between VeriStrat status and treatment arm in a Cox proportional hazards (PH) model.

5. PLANNED ANALYSIS

The total study duration will be approximately 23 months: 18 months recruitment period, and at least 2 months treatment and follow-up period for the last randomized patient. The final evaluation will be done within 6 months after the two-month visit of the last entered patient, approximately 26 months after the inclusion of the first patient. The planned analysis in terms of methods, reporting conventions and formats is described in detail in Sections 9-13.

6. SAMPLE SIZE

For a sample size of 500, accrued in 18 months and an additional follow-up of 2 months, 86% power is achieved for testing at a two-sided significance level of 0.05, the null hypothesis that the difference on median PFS when treated with erlotinib vs docetaxel is independent of VeriStrat status, under the above stated assumptions of HR=0.675 for VSG patients and HR=1.23 for VSP patients, assuming a hazard for censoring of 0.01 (power of 82% is achieved for a hazard for censoring of 0.05).

In the case the median PFS for erlotinib treated VeriStrat Poor patients is as high as 2.4, (HR=1.125), with all other assumptions the same, we retain a power of 74%.

Simulations are run with the R software package and used for sample size calculations, along with the Interaction Survival Power/Sample Size program from the Southwest Oncology Group, SWOG (http://www.swogstat.org/stat/public/Help/survivalint.html).

Secondary objective: Test for significant difference in PFS between treatment arms in the VSG group.

For the sample size of 250 patients accrued in 18 months in the VSG group, and with a total study duration of 20 months (total events 204), a power of 80% is achieved to detect with a two-sided logrank test at a significance level of 0.05, a 32.5% difference in median PFS (HR=0.675) between the two treatment groups.

The EAST software package is used for sample size calculations in the VSG patient group (EAST 5, Version 5.4.0.0, Cytel Inc. 2010).

7. GENERAL CONSIDERATIONS

7.1 Timing of Analyses

The preparation of the study report is scheduled for 26 months after the first patient is enrolled.

7.2 Analysis Populations

Efficacy Cohort

The efficacy cohort will include all eligible patients with a VSG or VSP signature entering the study (see Figure 1).

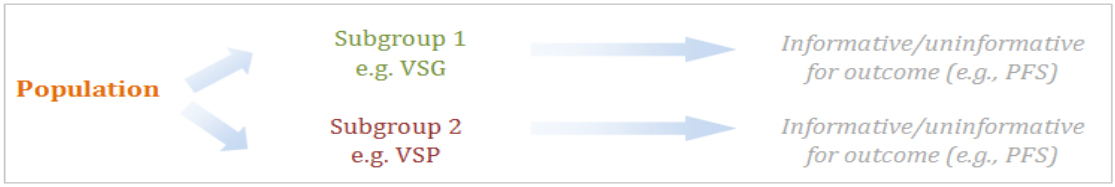

Figure 1. Predictive signature representation

Safety Cohort

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

7.3 Missing Data

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

8. EFFICACY ANALYSIS

The primary efficacy analysis will include all eligible patients with a VSG or VSP signature entering the study (efficacy cohort – see Figure 1).

Baseline characteristics will be summarized and presented both overall and by treatment arm. 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.

In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Treatment A: erlotinib, Treatment B: docetaxel) and a column for the total population.

Information on outcome (PFS & OS) will be as well presented, overall and within the two treatment groups. Observed differences by i) treatment arm and ii) VeriStrat status will be graphically depicted via Kaplan-Meier curves. Moreover, the median follow-up time will be calculated using the reverse censoring method for OS. Clinical efficacy will be further described by objective response rate (ORR) and disease control rate (DCR).

9. SAFETY ANALYSIS

The safety cohort will encompass all patients who have received at least one dose of trial treatment. Safety and tolerability of the docetaxel and erlotinib treatments will be described overall and separately in each VeriStrat subgroup (Figure 1) by tabulation of the CTCAE V4 grade and graphical representation of the corresponding distributions using bar charts. In particular, safety analysis will include assessment of the experience of adverse events (AE) and serious adverse events (SAE), the frequency of AEs (overall and separately for targeted and non-targeted AEs) and their distribution by CTCAE V4 grade. The numbers of patients experiencing specific number of adverse events will also be reported.

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 its relation to treatment, the treatment arm each patient belongs to and his/ her specific outcome. Bar charts will be used to depict the maximum severity of AE per patient, overall and by treatment arm.

9.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after the final dose, regardless of whether it is considered related to a medication. In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the protocol treatment should be considered an adverse event.

9.2 Severity Grade

The adverse events severity grade (NCI CTCAE Version 4) provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study drug.

Severity grade for other adverse events not covered in the toxicity grading scale:

1=Grade 1	Mild
2=Grade 2	Moderate
3=Grade 3	Severe
4=Grade 4	Life- threatening
5=Grade 5	Fatal

9.3 Serious Adverse Events (SAE)

SAEs during trial treatment

A SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occur during or within 30 days after stopping study treatment and which, at any dose, results in any of the following:

- is fatal (any cause),
- life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly or birth defect
- is a secondary malignancy,
- requires significant medical intervention.

Second (non-NSCLC) malignancies are always considered SAEs, no matter when they are diagnosed. These events should be reported on the Serious Adverse Event Forms. Other significant/important medical events which may jeopardize the patient are also considered serious adverse events.

Serious also includes any other event that the investigator or the ETOP Safety Office judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred. An unexpected adverse event is one that is not listed as a known toxicity in the summary of product characteristics.

A related adverse event is one for which the investigator assesses that there is a reasonable possibility that the event is related to the drug. All adverse events judged as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Events not considered to be serious adverse events are hospitalizations occurring under the following circumstances:

- elective surgery;
- occur on an outpatient basis and do not result in admission (hospitalization<24h);
- are part of the normal treatment or monitoring of the studied treatment;
- progression of disease.

SAEs after end of trial treatment

During the follow-up phase (starting 30 days after end of trial treatment), the following events have to be reported as SAE:

- fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment
- disabling events
- second primary cancer
- congenital anomaly
- pregnancy

In the case of pregnancy (involving a treated female or male patient) occurring during trial treatment or within 1 year after treatment discontinuation, the investigator shall immediately notify the ETOP Safety Office by completing the pregnancy reporting form. The investigator shall ensure that the case is followed up to the end of the pregnancy and supply a final report on the outcome.

10. REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values >0.010 will be reported with two significant digits; 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 significant figures.

11. TECHNICAL DETAILS

Data will be analyzed using the SAS software package (version 9.3).

A second review 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.

12. 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
- Covariates used to define facets or sub-plots

Table 1. Listing of Tables

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics
Accrual by center	1	Efficacy cohort	Accrual	NA	center	n (%)
Balance of treatment allocation per stratification factor combination	2	Efficacy cohort	Treatment allocation	NA	Treatment arm, ECOG performance status, VeriStrat status	n (%)
Patient baseline characteristics	3a, 3b	Efficacy cohort	Gender	Baseline	Treatment arm	n (%)
			Smoking status	Baseline	Treatment arm	n (%)
			Tumor histology	Baseline	Treatment arm	n (%)
			ECOG performance status	Baseline	Treatment arm	n (%)
			VeriStrat status	Baseline	Treatment arm	n (%)
			Age	Baseline	Treatment arm	Mean, 95% CI, median, min, max
Time on follow-up & time on treatment	4a, 4b	Efficacy cohort	No. of patients still on f-up, no. of discontinuations	End of f-up	Treatment arm	n (%) median, iterq. range
Adverse event overview	5a, 5b	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%) of persons who have experienced >=1 AE
Serious adverse event overview	6a, 6b	Safety cohort	SAE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%) of persons who have experienced >=1 SAE
Serious adverse events overview by center	7	Safety cohort	SAE	On day 1 of every 3-week treatment cycle	Center	n (%) of persons who have experienced >=1 SAE, incidence
Frequency of serious adverse events	8a, 8b	Safety cohort	SAE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of serious adverse events according to CTCAE Version 4	9a, 9b	Safety cohort	SAE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Number of patients experiencing specific number of serious adverse events	10	Safety cohort	SAE	On day 1 of every 3-week treatment cycle		n
Number of patients experiencing specific number of serious adverse events according to CTCAE Version 4	11	Safety cohort	SAE	On day 1 of every 3-week treatment cycle		n

Table title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics
Distribution of adverse events by Grade	12	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Severity grade	n (%)
Distribution of adverse events by Grade according to CTCAE Version 4	13	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Severity grade	n (%)
Frequency of adverse events	14a, 14b	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of adverse events according to CTCAE Version 4	15a, 15b	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Number of patients experiencing specific number of adverse events	16	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Number of patients experiencing specific number of adverse events according to CTCAE Version 4	17	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of targeted adverse events	18a	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of non-targeted adverse events	18b	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of targeted adverse events according to CTCAE Version 4	19a	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Frequency of non-targeted adverse events according to CTCAE Version 4	19b	Safety cohort	AE	On day 1 of every 3-week treatment cycle	Treatment arm	n (%)
Treatment A: Adverse event information by patient (any AE & SAE)	20a	Safety cohort	AE / SAE	On day 1 of every 3-week treatment cycle	Treatment A	NA
Treatment B: Adverse event information by patient (any AE & SAE)	20b	Safety cohort	AE / SAE	On day 1 of every 3-week treatment cycle	Treatment B	NA
Narratives of patients with a SAE	21	Safety cohort	SAE	On day 1 of every 3-week treatment cycle		NA
Adverse events experienced by patients with progression of disease / death	22	Safety cohort	AE	On day 1 of every 3-week treatment cycle		NA
Adverse events experienced by patients with progression of disease / death according to CTCAE Version 4	23	Safety cohort	AE	On day 1 of every 3-week treatment cycle		NA

Table 2. Listing of Figures

Title	**Number**	**Population**	**Type of graph**	**Horizontal Variables**	**Vertical Variables**	**Groupings**	**Statistics**
Patients flowchart	1	Efficacy cohort	Flowchart	NA	NA		NA
Expected vs observed accrual	2a	Efficacy cohort	Line graph	time	cumulative number of patients		NA
Cumulative accrual by treatment arm	2b	Efficacy cohort	Line graph	time	cumulative number of patients	Treatment arm	NA
Time on follow-up by treatment arm	3	Efficacy cohort	KM	time	probability	Treatment arm	Survival estimates
Time on treatment by treatment arm	4	Efficacy cohort	KM	time	probability	Treatment arm	Survival estimates
Distribution of adverse events	5a, 5b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Distribution of serious adverse events	6a, 6b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Distribution of serious adverse events (nominal)	7a, 7b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Distribution of serious adverse events according to CTCAE Version 4 (nominal)	8a, 8b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Severity of adverse events	9a, 9b	Safety cohort	Bar chart	NA	percentage	Severity grade, Treatment arm	percentage
Severity of adverse events according to CTCAE Version 4	10a, 10b	Safety cohort	Bar chart	NA	percentage	Severity grade, Treatment arm	percentage
Maximum severity of adverse events per patient	11a, 11b	Safety cohort	Bar chart	NA	percentage	Severity grade, Treatment arm	percentage
Distribution of adverse events (nominal)	12a, 12b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Distribution of adverse events according to CTCAE Version 4 (nominal)	13a, 13b	Safety cohort	Bar chart	NA	percentage	Treatment arm	percentage
Progression-free survival	14, 15	Efficacy cohort	KM	time	probability	VeriStrat status	Survival estimates
Overall survival	16, 17	Efficacy cohort	KM	time	probability	VeriStrat status	Survival estimates

References

SJ Pocock (1979). Allocation of patients to treatment in clinical trials. Biometrics, 35: 183 - 187.

SJ Pocock and R Simon (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. Biometrics, 31: 103 -115.