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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 Maldi TOF Phase III Signature in Squamous cell non-small cell lung cancer

A clinical trial of ETOP

EudraCT number:
2012-001896-35

ETOP c/o IBCSG Coordinating Center, Effingerstrasse 40, CH- 3008 Bern
Phone: +41 31 389 93 91 Fax: +41 31 389 93 92

Version 1.0

Contacts

Trial Co-Chair	Egbert Smit. MD-PhD	Address Tel: Fax: Email:	Vrije Universiteit VU Medical Centre, PO Box 7057 1007MB Amsterdam, The Netherlands +31204444782 +31204444328 ef.smit@vumc.nl
Trial Co-Chair	Solange Peters, MD-PhD	Address Tel: Fax: Email:	Centre Pluridisciplinaire d'Oncologie Centre Hospitalier Universitaire Vaudois 1011 Lausanne, Switzerland +41 79 556 01 92 +41 21 314 67 89 (assistant) +41 21 314 01 67 solange.peters@etop-eu.org
Chairman ETOP	Rolf Stahel, MD	Address Tel: Fax: Email:	Laboratory of Molecular Oncology Clinic of Oncology University Hospital Zuerich Häldeliweg 4 8044 Zürich, Switzerland +41 44 634 28 71 +41 44 634 28 72 rolf.stahel@usz.ch
Statistics	Urania Dafni, ScD	Address Tel: Fax: Email:	Frontier Science Foundation - Hellas 70 Mikras Asias Str. 11527, Athens, Greece +302107710902 +302107710903 udafni@frontier-science.gr
Data Management	ETOP Coordinating Office	Address Tel: Fax: Email:	ETOP Coordinating Office c/o IBCSG Coordinating Center Effingerstrasse 40 3008 Bern, Switzerland +41 31 389 93 91 +41 31 389 92 29 EMPHASIS@etop-eu.org
Safety and Regulatory Affairs	Barbara Ruepp, PhD	Address Tel: Fax: Email:	ETOP Safety and Regulatory Office c/o IBCSG Coordinating Center Effingerstrasse 40 3008 Bern, Switzerland +41 31 389 93 91 +41 31 389 92 29 regulatoryoffice@etop-eu.org
ETOP Coordinating Office Team	Anita Hiltbrunner Rudolf Maibach, PhD Susanne Roux Marc Marbot	Address Tel: Fax: Email:	c/o IBCSG Coordinating Center Effingerstrasse 40 3008 Bern, Switzerland +41 31 389 93 91 +41 31 389 92 29 anita.hiltbrunner@etop-eu.org rudolf.maibach@etop-eu.org susanne.roux@etop-eu.org marc.marbot@etop-eu.org

In collaboration with Biodesix, Inc.

Protocol Signature Page

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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

Approved by:

Egbert Smit
Trial Co-Chair

_____signature on file_____

Solange Peters
Trial Co-Chair

_____signature on file_____

Rolf Stahel
Chairman of ETOP

_____signature on file_____

Principal Investigator Protocol Signature Page

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EMPHASIS-lung

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

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP). I will provide copies of this protocol version, furnished to me by ETOP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the study drugs and VeriStrat, and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, VeriStrat kit and sample shipment and all other information collected during the trial for a minimum period of 15 years after trial closure.

Printed Name of Principal Investigator:

_____

Printed Name and Place of Institution:

_____

_____ _____

Signature Date

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1. Protocol Summary

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

Rationale:

In the Western world lung cancer remains the first cause of cancer related deaths in men and is surpassing the deaths due to breast cancer in women. About 20% of non-small cell lung cancer (NSCLC) patients present with localized disease amenable to therapy with curative intent, while the remaining patients suffer from advanced disease for which treatment with palliative intent is delivered. Platinum containing chemotherapy has become the cornerstone of treatment for these patients and is associated with modest prolongation of life span and improvement of quality of life (QoL). Approximately 25-30% of patients will show a major response and 40% will have disease stabilization for some time. However, inevitably these patients will experience tumor progression and qualify for second line treatments.

Based on data from phase III trials showing superior survival with chemotherapy as compared to best supportive care (BSC), equal therapeutic efficacy of evaluated drugs, and no benefit of drug combinations as compared to monotherapy, single agent chemotherapy is the standard of care for patients with relapsed NSCLC following platinum based, first line chemotherapy(1). Several agents are now approved for use as second line treatment in advanced NSCLC.

The first agent to enter the second line arena was docetaxel. A phase III trial led by Canadian investigators randomized 104 patients with relapsed advanced NSCLC to either docetaxel or BSC. A survival advantage for the docetaxel treated patients was observed (7.0 months vs 4.6 months, p = 0.010, log-rank test). Also, progression free survival was superior in the docetaxel arm. In addition, QoL measures all favored treatment with docetaxel. An analysis per histology was not provided (2).

Next, erlotinib was found to produce superior patient outcomes as compared to BSC in the same patient population in 2nd or 3rd line of treatment in the BR21 study (3). Here, 731 patients were randomized in a 2:1 fashion to treatment with erlotinib or placebo. Both overall survival (OS) and progression free survival (PFS) were significantly longer in the active treatment arm (6.7 vs 4.7 months and 2.2 vs 1.8 months, respectively). Although subgroup analysis favored patients with adenocarcinoma or those who never smoked, the treatment effects did extend to patients having squamous cell carcinoma.

Currently there are no accepted baseline criteria to allow choosing between docetaxel or erlotinib, except for the presence of an activating epidermal growth factor receptor (EGFR) mutation, provided patients did not receive an EGFR-tyrosine kinase inhibitor (TKI) as first line therapy. In fact, the INTEREST trial that randomized NSCLC patients with all histologies between gefitinib and docetaxel in the second line setting, showed no difference in PFS and OS in the EGFR wild-type (WT) population. In a subgroup analysis, patients

with squamous cell carcinomas did not present any difference in PFS or OS between both treatment groups.

One way to move forward is to select patients for treatment based upon (predictive) biomarkers. The prime example of a predictive biomarker is the presence of an activating EGFR mutation, as patients with this genetic aberration respond dramatically to EGFR-TKIs. Unfortunately, the incidence of activating EGFR mutations in patients with squamous cell lung cancer is very low, rendering this biomarker of little use for most of these patients.

Recently, a blood-based proteomic test, VeriStrat®, that appears to be both predictive and prognostic for outcome in patients with NSCLC, has become available. VeriStrat was developed and validated in a multi-institutional study of advanced NSCLC patients treated with gefitinib (4). The VeriStrat algorithm was developed using a training set of pre-treatment serum samples from patients who experienced either long term stable disease or early progression on gefitinib therapy. Mass spectra from these patients' serum samples were used to define eight mass spectrometry (MS) features (i.e. peaks), differentiating these two outcome groups. An algorithm utilizing these features and based on a k-nearest neighbors (KNN) classification scheme was created and its parameters were optimized using additional spectra from the training set. VeriStrat assigns each sample a "good" (VSG) or "poor" (VSP) label. In approximately 2% of cases, an unequivocal label cannot be assigned and an indeterminate classification is reported. The test was validated in a blinded fashion in two independent cohorts of patients who were treated with gefitinib or erlotinib. These studies confirmed that patients classified as VSG had better PFS and OS outcome than patients classified as VSP (hazard ratio [HR] of death=0.47, p=0.0094 in one cohort; HR=0.33 and p=0.0007 in the other). VeriStrat demonstrated outstanding reproducibility, confirmed in the comparative analysis between data obtained on identical samples in two different institutions (Vanderbilt University and University of Colorado, USA). The overall concordance of the classification results was 97% (4). Retrospective analysis of VeriStrat performed on available serum samples of patients from the randomized NCIC CTG BR.21 trial of erlotinib versus placebo confirmed the above results for the treatment arms(5). In this last study it was found that patients with the VSG classification had a significantly longer overall survival under erlotinib as compared to placebo (10.5 vs 6.6 months). VSG patients showed a better OS than VSP patients in the group treated with erlotinib (10.5 vs 4.0 months), independent of EGFR mutation status. There was a significant prognostic component indicating that VeriStrat measures an innate property of the disease. Further, the BR.21 sub-study showed a strong, statistically significant correlation of VeriStrat classification with objective response rate (ORR) and disease control rate (DCR) in evaluable patients in the erlotinib arm (Fisher exact test 2-sided p=0.0022 for ORR and p<0.001 for DCR).

In the initial evaluation of VeriStrat it was found that patients with relapsed squamous cell lung carcinoma and designated to the VSG population had an unexpectedly favorable outcome following treatment with gefitinib. The test does not seem to discriminate between patients who receive cytotoxic chemotherapy, including standard treatment with standard doses of docetaxel (Biodesix, data on file), as both VeriStrat groups presented similar survival outcomes for chemotherapy.

Thus, one rational approach for using the VeriStrat test is a trial design where patients with relapsed squamous cell lung cancer in both strata (VSG and VSP) are randomized between an EGFR-TKI and chemotherapy. As both erlotinib and docetaxel are currently approved for this indication, these drugs will be used in the proposed trial.

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.

Objectives:

1. 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 (VSG vs VSP) using as outcome progression free survival.
2. Explore whether treatment with erlotinib provides progression free survival benefit as compared to docetaxel in the VSG group.
3. Compare progression free survival in the two treatment arms (Arm A: erlotinib vs Arm B: docetaxel) in the VSP group.
4. 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).
5. 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.
6. Compare overall survival, objective response rate and disease control rate between treatment groups separately in the VSG and VSP groups.
7. 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).
8. Assess the safety and the tolerability of the two treatments separately in each VeriStrat group and overall.

Endpoints:

1. Primary endpoint: Progression free Survival
2. Secondary endpoints:
    a. Overall Survival
    b. Toxicities of treatment
    c. Objective Response
    d. Disease control

Patient selection criteria:

Patients are eligible only if they meet all of the following criteria within 14 days prior to registration, except where otherwise noted:

1. Histologically or cytologically confirmed locally advanced stage IIIB, not amenable to radical radiotherapy, or metastatic stage IV non-small cell lung cancer (NSCLC) of predominant squamous subtype, according to the 7th edition of the TNM classification, including M1a (separate tumor nodule in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion) and/or M1b (distant metastasis).

2. Progressive disease upon or after previous chemotherapy including at least one line of platinum-based chemotherapy.
3. Measurable or evaluable disease according to RECIST v1.1 (Appendix 2).
4. ECOG PS 0-2.
5. Age ≥ 18 years.
6. Adequate organ function, including:

   Adequate bone marrow reserve: ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L.

   Hepatic: bilirubin <1.5 x ULN; AP, ALT < 3.0 x ULN; AP, ALT <5 x ULN is acceptable in case of liver metastasis.

   Renal: calculated creatinine clearance > 40 ml/min based on the Cockroft and Gault formula.
7. Signed and dated informed consent form.
8. Male and female patients with reproductive potential must use an approved contraceptive method, during the trial and 12 months thereafter. Female patients with reproductive potential must have a negative pregnancy test within 7 days prior to study registration.
9. Estimated life expectancy >12 weeks.
10. Patient compliance and geographical proximity that allow adequate follow-up.

Patients will be excluded if they meet any of the following criteria:

1. Evidence of other medical condition which would impair the ability of the patient to participate in the trial or might preclude therapy with trial drugs (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease, active infection, uncontrolled diabetes mellitus).
2. Previous treatment with any EGFR-TKI or docetaxel.
3. Documented brain metastases unless the patient has completed local therapy for central nervous system metastases and has been off corticosteroids for at least 14 days prior to study registration.
4. Documented presence of activating EGFR mutations, if the patient was tested for EGFR mutations.
5. Previous malignancy within the past 5 years with the exception of adequately treated cervical carcinoma in situ, breast cancer in situ or localized non-melanoma skin cancer.
6. Psychiatric disorder precluding understanding of information on trial related topics, giving informed consent, or interfering with compliance for oral drug intake.
7. Concurrent treatment with experimental drugs or other anti-cancer therapy treatment in a clinical trial within 21 days prior to study registration.
8. Known hypersensitivity to trial drugs or hypersensitivity to any other component of the trial drugs or any concomitant drugs contraindicated.

Trial design and treatments administered:

Patients in both VeriStrat strata, i.e., VSG and VSP, will be randomized to receive erlotinib or docetaxel. The investigative site and their personnel will be blinded to the result of the VeriStrat test.

Arm A: erlotinib 150 mg/day p.o. continuously with 21 days cycle

Arm B: docetaxel 75 mg/m^2 as an IV infusion Day 1 every 21 days

Dose adjustments: Dose adjustments for assigned treatment may be made according to Sections 10.2 and 10.5, and the judgment of the treating physician.

Duration of treatment: Treatment with erlotinib or docetaxel will be continued until progressive disease (PD) occurs, documented by clinical or radiographic progression. In case of unacceptable toxicity patients will be withdrawn from protocol therapy although study follow-up will continue for collection of progression and survival data as described in Section 10.6.

Concomitant treatments: The protocol allows patients to receive the following concomitant treatments:

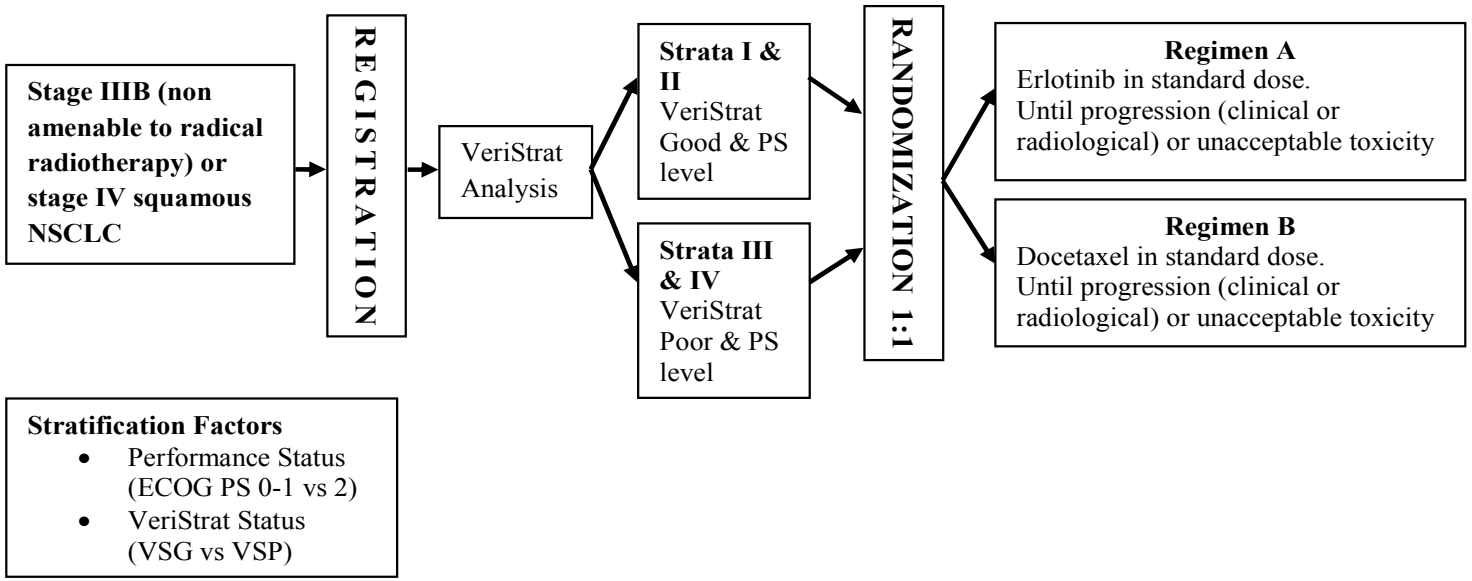
1. Antiemetic therapy at the investigator's discretion.
2. Full supportive-care therapies during the study according to local standards of care.
3. Palliative radiation therapy.

Restricted treatments: Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation of study therapy, but patients will continue to be followed for progression and survival. No other anticancer therapy, immunotherapy, hormonal cancer therapy, curative radiation, or experimental medications will be permitted while the patients are on trial treatment.

Recruitment period: 18 months
Sample Size: 500

2. Trial Design and Schedule

2.1. Graphical trial design



2.2. 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.

3. List of abbreviations

ALT	alanine transaminase
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST	aspartate transaminase
BSC	best supportive care
DCR	disease control rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	epidermal growth factor receptor
GCP	Good Clinical Practice
HR	hazard ratio
ICH	International Conference on Harmonization
LLN	lower limit of normal lab value
KNN	k-nearest neighbor's classification scheme
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression free survival
PS	performance status
RDE	remote data entry
RECIST	Response Evaluation Criteria In Solid Tumors
TKI	tyrosine kinase inhibitor
QoL	Quality of Life
ULN	upper limit of normal lab value
VSG	VeriStrat Good
VSP	VeriStrat Poor
WT	wild type

4. Background and Rationale

4.1. Non-small cell lung cancer

In the Western world lung cancer remains the first cause of cancer related deaths in men and is surpassing the deaths due to breast cancer in women. About 20% of NSCLC patients present with localized disease amenable to therapy with curative intent, while the remaining patients suffer from advanced disease for which treatment with palliative intent is delivered. Platinum containing chemotherapy has become the cornerstone of treatment for these patients; it is associated with modest prolongation of life span and improvement of QoL. Approximately 25-30% of patients will show a major response and 40% will have disease stabilization for some time. However, inevitably these patients will experience tumor progression and qualify for second line treatments.

4.2. Treatment of non-small cell lung cancer

Based on data from phase III trials showing superior survival with chemotherapy as compared to best supportive care, equal therapeutic efficacy between evaluated drugs, and no benefit of drug combinations as compared to monotherapy, single agent chemotherapy is the standard of care for patients with relapsed NSCLC following platinum based, first line chemotherapy (1). Several agents are now approved for use as second line treatment in advanced NSCLC.

The first agent to enter the second line arena was docetaxel. A phase III trial led by Canadian investigators randomized 104 patients with relapsed advanced NSCLC to either docetaxel or BSC. A survival advantage for the docetaxel treated patients was observed (7.0 months vs 4.6 months, $p = 0.010$, log-rank test). Also, progression free survival was superior in the docetaxel arm. In addition, QoL measures all favored treatment with docetaxel. An analysis per histology was not provided (2).

Next, erlotinib was found to produce superior patient outcomes as compared to BSC in the same patient population in 2nd or 3rd line of treatment in the BR21 study (3). Here, 731 patients were randomized in a 2:1 fashion to treatment with erlotinib or placebo. Both OS and PFS were significantly longer in the active treatment arm (6.7 vs 4.7 months and 2.2 vs 1.8 months respectively). Although subgroup analysis favored patients with adenocarcinoma or those who never smoked, the treatment effects did extend to patients having squamous cell carcinoma.

Currently there are no accepted baseline criteria that allow choosing between docetaxel or erlotinib, except for the presence of an activating EGFR mutation, provided patients did not receive an EGFR-TKI as first line therapy. In fact, the INTEREST trial, randomizing NSCLC patients with all histologies between gefitinib and docetaxel in the second line setting, showed no difference in PFS and OS in the EGFR WT population. In subgroup analysis, patients with squamous cell carcinomas did not present any difference in PFS or OS between both treatment groups.

One way to move forward is to select patients for treatment based upon (predictive) biomarkers. The prime example of a predictive biomarker is the presence of an activating EGFR mutation, as patients with this genetic aberration respond dramatically to EGFR-TKIs. Unfortunately, the incidence of activating EGFR mutations in patients with squamous cell lung cancer is very low, rendering this biomarker of little use for most of these patients.

4.3. VeriStrat Test

Recently, a blood-based proteomic test, VeriStrat, that appears to be both predictive and prognostic for outcome in patients with NSCLC, has become available. VeriStrat was developed and validated in a multi-institutional study of advanced NSCLC patients treated with gefitinib (4). The VeriStrat algorithm was developed using a training set of pre-treatment serum samples from patients who experienced either long term stable disease or early progression on gefitinib therapy. Mass spectra from these patients' serum samples were used to define eight MS features (i.e. peaks), differentiating these two outcome groups. An algorithm utilizing these features and based on a k-nearest neighbors (KNN) classification scheme was created and its parameters were optimized using additional spectra from the training set. VeriStrat assigns each sample a "good" (VSG) or "poor" (VSP) label. In approximately 2% of cases, an unequivocal label cannot be assigned and an indeterminate classification is reported. The test was validated in a blinded fashion in two independent cohorts of patients who were treated with gefitinib or erlotinib. These studies confirmed that patients classified as VSG had better PFS and OS outcome than patients classified as VSP (hazard ratio (HR) of death=0.47, p=0.0094 in one cohort; HR=0.33 and p=0.0007 in the other). VeriStrat also demonstrated outstanding reproducibility, confirmed in the comparative analysis between data obtained on identical samples in two different institutions (Vanderbilt University and University of Colorado, USA). The overall concordance of the classification results was 97% (4). Retrospective analysis of VeriStrat performed on available serum samples of patients from the randomized NCIC CTG BR.21 trial of erlotinib versus placebo confirmed the above results for the treatment arms (5). In this last study it was found that patients with the VSG classification had a significantly longer overall survival under erlotinib as compared to placebo (10.5 vs 6.6 months). VSG patients showed a better survival than VSP patients in the group treated with erlotinib (10.5 vs 4.0 months), independent of EGFR mutation status. There was a significant prognostic component indicating that VeriStrat measures an innate property of the disease. Further, the BR.21 sub-study showed a strong statistically significant correlation of VeriStrat classification with ORR and DCR in evaluable patients in the erlotinib arm (Fisher's exact test 2-sided p=0.0022 for ORR and p=<0.001 for DCR).

In the initial evaluation of VeriStrat it was found that patients with relapsed squamous cell lung carcinoma and designated to the VSG population had an unexpectedly favorable outcome following treatment with gefitinib. The test does not seem to discriminate between patients who receive cytotoxic chemotherapy, including standard treatment with standard doses of docetaxel (Biodesix, data on file), as both VeriStrat groups present similar outcome under chemotherapy.

Thus, one rational approach using the VeriStrat test is a trial design where patients with relapsed squamous cell lung cancer in both strata (VSG and VSP) are randomized between an EGFR-TKI and chemotherapy. As both erlotinib and docetaxel are currently approved for this indication, these drugs will be used in the proposed trial.

4.4. Hypothesis for a prospective evaluation

The VeriStrat signature will be able to predict the benefit of treatment with erlotinib vs docetaxel 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.

5. Objectives and endpoints

5.1. 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.

5.2. Secondary objectives

5.2.1. Explore whether treatment with erlotinib provides progression free survival benefit as compared to docetaxel in the VSG group.

5.2.2. Compare progression free survival in the two treatment arms (Arm A: erlotinib vs Arm B: docetaxel) in the VSP group.

5.2.3. 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).

5.2.4. 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.

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

5.2.6. 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).

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

5.3. Primary endpoint

Progression free Survival. For definition, see Section 13.1.

5.4. Secondary endpoints

5.4.1. Overall Survival

5.4.2. Toxicities of treatment

5.4.3. Objective Response

5.4.4. Disease Control

For definitions, see section 13.

6. Trial design, duration and termination

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. The primary endpoint of the study is PFS. 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 in period, treatment and follow-up for PFS 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.

7. Patient selection

Patients should only be selected and consented for screening if they fulfill the inclusion and exclusion criteria in Sections 7.1 and 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.

7.1. Inclusion criteria

7.1.1. Histologically or cytologically confirmed locally advanced stage IIIB, not amenable to radical radiotherapy, or metastatic stage IV non-small cell lung cancer (NSCLC) of predominant squamous subtype, according to the 7th edition of the TNM classification, including M1a (separate tumor nodule in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion) and/or M1b (distant metastasis).

7.1.2. Progressive disease upon or after previous chemotherapy including at least one line of platinum-based chemotherapy.

- Adjuvant platinum-based chemotherapy can be considered as platinum-based chemotherapy line if administration ended in the 6 months before registration.
- Platinum-based chemotherapy combined with definitive radiotherapy can be considered as platinum-based chemotherapy line if administration ended in the 6 months before registration.

7.1.3. Measurable or evaluable disease according to RECIST v1.1 (Appendix 2).

7.1.4. ECOG performance status 0-2.

7.1.5. Age $\geq$ 18 years.

7.1.6. Adequate organ function, including:

- Adequate bone marrow reserve: ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L.
- Hepatic: bilirubin <1.5 x ULN; AP, ALT < 3.0 x ULN; AP, ALT <5 x ULN is acceptable in case of liver metastasis.
- Renal: calculated creatinine clearance > 40 ml/min based on the Cockroft and Gault formula.

7.1.7. Signed and dated informed consent form.

7.1.8. Male and female patients with reproductive potential must use an approved contraceptive method, if appropriate. Female patients with reproductive potential

must have a negative serum or urin pregnancy test within 7 days prior to study registration. Non-reproductive potential for females is defined as surgically sterile or post-menopausal defined as ≥24 months since last menses. Male patients are considered to have reproductive potential unless they are surgically sterile. Not eligible: Women who are in the period of lactation.

7.1.9. Estimated life expectancy >12 weeks.

7.1.10. Patient compliance and geographical proximity that allow adequate follow-up.

7.2. Exclusion criteria

7.2.1. Evidence of other medical conditions which would impair the ability of the patient to participate in the trial or might preclude therapy with trial drugs (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease, active infection, uncontrolled diabetes mellitus).

7.2.2. Previous treatment with any EGFR-TKI or docetaxel.

7.2.3. Documented brain metastases unless the patient has completed local therapy for central nervous system metastases and has been off corticosteroids for at least 14 days prior to registration.

7.2.4. Documented presence of activating EGFR mutations, if patient was tested for EGFR mutations.

7.2.5. Previous malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ, breast cancer in situ or localized non-melanoma skin cancer.

7.2.6. Psychiatric disorder precluding understanding of information on trial related topics, giving informed consent, or interfering with compliance for oral drug intake.

7.2.7. Concurrent treatment with experimental drugs or other anti-cancer therapy treatment in a clinical trial within 21 days prior to registration.

7.2.8. Known hypersensitivity to trial drugs or hypersensitivity to any other component of the trial drugs or any concomitant drugs contraindicated.

8. Patient Randomization

8.1. Randomization principles

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 "*EMPHASIS-lung Procedures Manual*" which will be available on the ETOP website (www.etop-eu.org).

Block stratified randomization balanced by center using a minimization algorithm (6) will be used in the study. Patients will be stratified based on VeriStrat status (VSG vs VSP) and Performance Status (0-1 vs 2).

8.2. Randomization steps

Complete the following steps to randomize a patient on this trial. Please consult the *EMPHASIS-lung Procedures Manual* for detailed instructions.

Note that written informed consent needs to be obtained prior to undertaking any study-specific procedures, including blood collection for VeriStrat testing.

8.2.1. Screening: Verify eligibility and register the patient in the RDE facility by completing the Identification Tab and the Eligibility Tab.

8.2.2. VeriStrat Collection, Shipment, and Testing

- Collect blood from patient and process to generate serum.
- Spot serum onto the Serum Collection Card and label card with ETOPdata assigned Patient ID.
- Send serum sample card to Biodesix Inc.
- Biodesix will enter results into RDE (results will not be visible to the investigative staff). Upon generation of VeriStrat results, the RDE will send an automatic confirmation email to the site.

8.2.3. Randomization: After receipt of the VeriStrat confirmation, the investigator will randomize the patient through the RDE according to the instructions in the *EMPHASIS-lung Procedures Manual* as well as the *ETOPdata User Manual*. The assigned treatment information will be displayed on the RDE screen and sent to the investigator by email.

9. Central VeriStrat testing

As described in Section 8.1.2, a serum sample from each patient must be collected prior to randomization, and must be sent to Biodesix, the central laboratory for VeriStrat testing.

The results of the VeriStrat test will be used only for the purposes of randomization. The investigative site and their personnel will be blinded to the result of the VeriStrat test.

9.1. Collection of the serum sample for VeriStrat

Upon activation, the center will receive ***EMPHASIS-lung*** VeriStrat kits containing blood collection materials, including the Serum Collection Card, labels, and shipping materials.

After obtaining signed informed consent from the patient, 3.5ml of venous blood will be collected into the SST tube provided. Serum will be processed and shipped according to the instructions in the kit (see the *EMPHASIS-lung Procedures Manual* for more information).

9.2. Shipping of samples to central laboratory

Within 24 hours of collection, the serum sample will be shipped to Biodesix Inc. following the kit instructions and the *EMPHASIS-lung Procedures Manual,* and using the pre-printed airbills provided**.**

9.3. Central laboratory evaluation

Within 72 hours of receipt of the serum sample, the central laboratory will record the result of the VeriStrat test in the RDE system. As soon as the result is in the system, the site will

be notified and the patient is ready to be randomized, see the *EMPHASIS-lung Procedures Manual* for details.

9.4. Indeterminate VeriStrat result

In approximately 2% of the cases the VeriStrat Test result will be indeterminate, and the patient cannot be allocated into either the VSG or the VSP group. These patients will also be randomized and followed according to protocol. They will not contribute in the interaction analysis but their outcome will be reported.

9.5. VeriStrat test not feasible

In the rare case that a sample cannot be analyzed by Biodesix, the enrolling site will be informed immediately by email and asked to redraw a new blood sample from the patient for retesting. If the new sample cannot be analyzed, the patient is considered ineligible and will not be randomized. No further information has to be entered into the ETOPdata System for these patients.

10. Trial treatments

Erlotinib and docetaxel are the drugs used in this trial. Both drugs are standard of care in second line treatment of NSCLC and will be locally sourced and paid.

Drug therapy is to begin within 7 days after randomization.

10.1. Sequence of treatments

Patients in both VeriStrat strata, i.e. VSG and VSP, will be randomized to receive erlotinib or docetaxel. The investigative site and their personnel will be blinded to the result of the VeriStrat test.

Arm A: erlotinib 150 mg/day p.o. continuously with 21 days cycle.

Arm B: docetaxel 75 mg/m^2 as an IV infusion Day 1 every 21 days.

10.2. Dosage, administration and schedule

10.2.1. Docetaxel dose / route / regimen

Docetaxel is given 75 mg/m^2 as an IV infusion Day 1 every 21 days.

All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

In case of relevant toxicity, dose reductions are recommended to improve the tolerance according to Section 10.5.

10.2.2. Erlotinib dose / route / regimen

Erlotinib is started at a fixed oral dose of 150 mg per day.

Tablets should be taken at a fixed time each day and at least 1 hour before, or 2 hours after the ingestion of food.

No routine premedication (e.g. to prevent skin toxicity) is recommended for erlotinib. Systemic or local tetracyclines, systemic or local corticosteroids and loperamide in case of diarrhea are strongly recommended if significant toxicity occurs.

Smokers have reduced plasma levels and should be counseled for smoking reduction or cessation, the dose of 150 mg must never be increased.

In case of relevant toxicity, dose reductions are recommended to improve the tolerance according to Section 10.5.

10.3. Precautions

Male and female patients with reproductive potential must use an approved contraceptive method, if applicable during the trial treatment and 12 months thereafter.

Female patients are considered to have reproductive potential unless they are surgically sterile or are post-menopausal and have not had menses for ≥24 months. Male patients are considered to have reproductive potential unless they are surgically sterile.

10.4. Concomitant treatment

The following treatments **are allowed** during the treatment phase of the trial:

1. Antiemetic therapy at the investigator's discretion.
2. Full supportive-care therapies during the trial according to local standards of care.
3. Palliative radiation therapy for irradiating areas of metastasis that cannot be managed adequately using systemic or local analgesics.

The following concurrent treatments are **NOT allowed in either arm**:

Other anticancer therapy, immunotherapy, hormonal cancer therapy, curative radiation, or experimental medications are **NOT allowed** while the patient is on trial treatment.

Medications, herbal extracts or food which can interact with erlotinib (CYP3A4 inducers/inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice) are **NOT allowed** while **a patient randomized to erlotinib** is on trial treatment.

10.5. Treatment delay and dose modification for toxicity

Treatment with erlotinib or docetaxel will be continued until progression has been documented by RECIST V1.1 (see appendix 2).

In case of toxicity, treatment interruptions should be used according to the following sections. Docetaxel treatment delay or erlotinib dose interruptions are allowed as required, for a maximum of 21 days per occasion. In case of unacceptable toxicity patients should be withdrawn from trial treatment.

10.5.1. Docetaxel

Patients who experience any of the following toxicities while on docetaxel should have treatment withheld until resolution of the toxicity to grade ≤1 and then resumed at a dose of 55 mg/m2.

- febrile neutropenia
- neutrophils <500 cells/mm3 for > one week

- other grade 3/4 non-hematological toxicities (except alopecia and fatigue).

Upon second occurrence of grade 3/4 non-hematological toxicities, docetaxel should be permanently discontinued.

Patients who develop ≥grade 3 peripheral neuropathy should have docetaxel treatment discontinued permanently.

10.5.2. Erlotinib

Patients who experience any of the following toxicities while on erlotinib should have treatment withheld until resolution of the toxicity to grade <1 and then resumed at a dose of 100mg/day.

- Grade 4 acneiform rash
- Grade 3/4 diarrhea despite maximal supportive care
- Grade 3/4 creatinine elevation
- Grade 3/4 elevations of hepatic tests (AP, ALT, bilirubin)
- Any other grade 3/4 toxicities (except alopecia and fatigue)

Upon second occurrence of aforementioned toxicities, erlotinib should be permanently discontinued.

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with erlotinib should be interrupted pending diagnostic evaluation.

Erlotinib **must be permanently discontinued** in case of:

- Clinically diagnosed interstitial Lung Disease (ILD)
- Hepatic failure
- Gastrointestinal perforation

10.6. Treatment duration

Patients remain on trial treatment until one of the following events:

- Documented progression according to RECIST v1.1 (Appendix 2).
- Unacceptable toxicity
- Any interruption of erlotinib of more than 3 weeks or treatment delay for docetaxel of more than 3 weeks.
- Medical condition that prevents further treatment
- Significant protocol violation
- Patient withdraws consent
- Patient becomes pregnant

If study drug has been stopped for any reason, the patient enters the follow-up phase of the trial. **Regardless of whether or not the patient continues to receive trial treatment, the "on treatment" schedule of evaluations must be followed until disease progression has been confirmed.** Patients who discontinue trial treatment should be assessed by the

investigator who must document the case on the appropriate case report form (CRF). Remaining erlotinib tablets should be returned to the investigative site by the patient to enable the staff to assess compliance.

11. Safety

11.1. Docetaxel

11.1.1. Known adverse reactions

Very common (> 10%):

- Allergy/immunology: Fever, chills, bronchospasm, anaphylactoid type reactions, hypersensitivity reactions
- Blood/bone marrow: Neutropenia, anemia, thrombocytopenia
- Constitutional Symptoms: Anorexia, asthenia, fever
- Dermatology/skin: Alopecia, erythema, nail disorders
- Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting
- Infection: Infections, pharyngitis, rhinorrhea
- Lymphatics: Peripheral edema, fluid retention
- Neurology: Neuropathy, insomnia
- Ocular/visual: Conjunctivitis, hyperlacrimation
- Pain: Myalgia, Headache
- Pulmonary: Dyspnea
- Syndromes: Flu-like syndrome

Common (1-10%):

- Cardiac general: Hypotension, tachycardia
- Dermatology/skin: Dry skin, injection site reaction
- Gastrointestinal: Constipation, abdominal pain, oesophagitis, dysphagia, odynophagia
- Hemorrhage/bleeding: Epistaxis
- Infection: Oral thrush, febrile neutropenia
- Metabolic/Laboratory: Elevated bilirubin, AP, AST, ALT
- Neurology: Depression, loss of taste
- Ocular/visual: Conjunctivitis
- Pain: Arthralgia

11.1.2. Warnings and precautions

Surveillance during 1st and 2nd treatment of docetaxel:

In case a docetaxel hypersensitivity reaction occurs despite premedication, it is very likely to occur within a few minutes from start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusion, a careful evaluation of general sense of well-being should be performed. Whenever possible, monitoring of blood pressure and heart rate has to be performed by a physician or nurse for at least the first 10 minutes, so that immediate intervention could occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation should be immediately available: antihistamine, corticosteroids, aminophylline and epinephrine.

11.1.3. Contraindications

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm^3.

11.2. Erlotinib

11.2.1. Known adverse reactions

The most common adverse reactions (>20%) in patients with non-small cell lung cancer are rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting.

11.2.2. Interstitial Lung Disease (ILD)

There have been infrequent reports of serious ILD-like events (including fatalities) in patients receiving erlotinib for the treatment of NSCLC, pancreatic cancer, or other advanced solid tumors. In the single-agent study in patients with NSCLC, Study BR.21, the incidence of serious ILD-like events (0.8%) was the same in the placebo and erlotinib groups. No imbalance was noted in the incidence of serious ILD-like events in the 2 large first-line NSCLC studies (Studies OSI2298g and BO16411), which utilized a standard platinum-based regimen with or without erlotinib. In the combination study with gemcitabine in patients with pancreatic cancer, Study PA.3, the incidence of ILD-like events was 2.5% versus 0.4% in the erlotinib plus gemcitabine versus the placebo plus gemcitabine groups, respectively. The overall incidence of ILD-like events in approximately 32,000 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%. When cases from a postmarketing surveillance study from Japan are excluded (N = 5860; 3.4% incidence), the incidence from rest of world was approximately 0.6%. Some examples of reported diagnoses included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as necessary, including corticosteroids.

11.2.3. Diarrhea

Diarrhea (sometimes severe) has occurred in patients receiving erlotinib and was usually managed by loperamide; however, reduction in the dose of erlotinib was occasionally necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting

associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to intensively treat the dehydration. Since there have been rare reports of hypokalemia and/or acute renal failure (including fatalities), secondary to severe dehydration, renal function and serum electrolytes (including potassium) should be monitored in this setting.

11.2.4. Gastrointestinal Perforation

Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation (including fatalities), which was observed uncommonly. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

11.2.5. Renal Failure

Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with significant dehydration due to diarrhea, vomiting, and/or anorexia. Other possible contributing factors have included concomitant medications and/or chemotherapy, pre-existing renal disease, or other medical conditions associated with renal disease. Periodic monitoring of renal function in patients with these risk factors is recommended.

11.2.6. Myocardial Infarction/Cerebral Vascular Accident

In the pancreatic cancer Study PA.3, small numerical imbalances in the incidence of stroke and myocardial infarction (including fatalities) were noted in patients receiving erlotinib in combination with gemcitabine. A causal relationship to erlotinib has not been established.

11.2.7. Hepatotoxicity

Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent erlotinib and occasionally with erlotinib in combination with concomitant chemotherapy, e.g. gemcitabine. Rare cases of hepatic failure (including fatalities) have been reported during postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs. Periodic monitoring of liver function is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe.

11.2.8. Patients with Hepatic Impairment

In a pharmacokinetic study (Study OSI-774-104) in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of 15 patients died on treatment or within 30 days of the last erlotinib dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. None of the deaths were considered to be related to erlotinib treatment by the investigators. However, treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh B or C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.

11.2.9. Thrombotic Microangiopathy/Microangiopathic Hemolytic Anemia with

Thrombocytopenia/Hemolytic Uremic Syndrome

Isolated reports of microangiopathic haemolytic anemia with thrombocytopenia and hemolytic uremia syndrome (HUS) have been received. All patients received erlotinib and gemcitabine concurrently. A causal relationship to erlotinib has not been established.

11.2.10. Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

11.2.11. Ocular Disorders

Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and may be potential risk factors. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Infrequent occurrences of keratitis have been observed during erlotinib treatment. Isolated reports of uveitis and orbital cellulitis have been reported in patients receiving erlotinib therapy.

Patients who develop irregular or excessive eyelash growth should be monitored for eye symptoms such as eye pain. Careful removal of in-growing/abnormal/elongated eyelashes should be considered if increased growth leads to scratching and/or irritation of the cornea. Patients with a prior history of ocular disorders or additional identifiable risk factors should be closely monitored by a physician.

12. Adverse events and reporting

12.1. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 4. The CTCAE is available for downloading on the internet, see Appendix 3 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

An adverse event (AE) 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.

Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

The adverse event severity grade 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

Note:

- Report the highest grade observed within one period.
- Baseline symptoms will be recorded on the CRF and will continue to be followed up during treatment.
- Laboratory abnormalities for non-safety parameters will be documented on the Adverse Event Form only for grades 3 and higher.
- AEs should not be reported in a narrative description.

12.2. Definition of Serious Adverse Event (SAE)

12.2.1. SAEs during trial treatment

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs 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.

12.2.2. 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.

12.3. Definition of Serious Adverse Drug Reaction (SADR)

SADRs are all SAEs considered to be related (possibly, probably, definitely) to the trial treatment.

12.4. Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction that is assessed as unexpected on the basis of the applicable Swiss product information and/or the European summary of product characteristics.

12.5. Reporting SAEs

Any SAE must be reported by submitting the completed SAE Initial Report Tab in the RDE system within 24 hours.

Submission is done via the electronic data capture system, or in case of unavailability, by sending the paper version of the SAE form by fax to the ETOP Safety Office:

+41 31 389 92 29

The SAE outcome must be reported within 14 days after onset by completing the SAE Follow-up Report Tab. In case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome.

The ETOP Safety Office will forward each SAE to the trial chairs and notify principal investigators of any SADR meeting the criteria for expedited reporting (SUSAR) within the timelines specified in GCP.

The local Ethics committee must be informed by the principal investigator about local SAEs.

The ETOP Safety Office will inform appropriate persons about all SAEs related to trial medication (per either investigator or ETOP Safety Office review) within 24 hours of receipt.

The ETOP Safety Office will record the SAE and prepare a periodic summary report of all SAEs received. Principal Investigators will receive the summary report on a regular basis.

13. Endpoints definition

13.1. Progression free survival

This is the primary endpoint. It is defined as the time from the date of randomization until documented progression or death without documented progression.

13.2. Overall survival

Defined as time from the date of randomization until death from any cause.

13.3. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST Criteria 1.1 (Appendix 2), during the period from randomization to termination of trial treatment.

13.4. Disease control

Disease control is defined as achieving objective response or stable disease for at least 6 weeks.

13.5. Toxicities of treatment

Adverse events classified according to NCI CTCAE version 4.

14. Trial procedures

This section gives an overview of procedures, clinical and laboratory evaluations and follow-up investigations.

14.1. Trial stages

The trial consists of the following stages:

- Screening: the screening period must occur no longer than 14 days before registration in the RDE system. Baseline evaluations must be done within 14 days prior to registration. Please consult the *EMPHASIS-lung procedures manual* for more information.

- VeriStrat Testing: The serum for the VeriStrat testing has to be collected and sent to Biodesix within 3 working days after registration and before randomization.
- Treatment phase: Drug therapy is to begin within 7 days of randomization.
- End of treatment will be the date of the end of treatment visit that will occur 30 - 40 days following the last dose of study drug.
- Follow-up period: every 3 months following end of treatment visit until death, patients will be followed up to document outcome. Between end of treatment and progression, the visit schedule needs to follow the one corresponding to the treatment phase, see section 14.6.

14.2. Baseline evaluations (within 14 days prior to registration)

- Medical history including symptoms, smoking history, medications, co-morbidities 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 urin 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.

14.3. Before Randomization

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

14.4. 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

14.5. 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

14.6. 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

14.7. 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

14.8. 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

14.9. 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.

15. Case report forms and documentation

15.1. Case report forms schedule

CRFs will only be available on-line at the ETOPdata Remote Data Entry (RDE) facility. No paper forms will be used, with the exception of a paper SAE form in case of system unavailability.

Tab in the RDE	**To be completed**
Identification	At screening, prior to randomization
Eligibility	At screening, prior to randomization
Baseline	At randomization
Cycle	At the end of each cycle and 30 days post trial treatment
Tumor assessment	At baseline and at start of odd cycles 3, 5, 7, ...; every 6 weeks until progression in case of treatment discontinuation; at progression
Adverse event	At baseline; At the end of each cycle; At end of treatment visit
Pregnancy	At first documentation of pregnancy; At end of pregnancy
Serious adverse event	Within 24h of occurrence of SAE to RDE, or via fax to ETOP safety office in case of system unavailability
Follow-up	Patients who discontinue treatment before progression: every 6 weeks; After progression: At every follow-up visit, every 12 weeks until death.

Consult the *EMPHASIS-lung Procedures Manual* as well as the *ETOPdata User Manual* for detailed instructions on how to complete, save and submit the electronic CRFs.

16. Statistical considerations

The study is designed as a phase III trial to explore the differential activity on PFS of erlotinib vs docetaxel in VSG vs VSP squamous cell lung cancer patients who relapsed after first line platinum based chemotherapy (7). The main endpoint of the study is PFS.

At an accrual rate of 28 patients per month and a study accrual period of 18 months, 500 patients will be randomized to the two treatment arms. An approximately equal number of VSG and VSP patients are expected to enter the study (ratio 50/50). 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)

16.1. Primary objective

Explore differential activity of treatment effect on PFS in the two VeriStrat groups by testing for interaction between treatment arms (Arm A: erlotinib vs Arm B: docetaxel) and VeriStrat status (Good vs Poor).

16.2. Secondary objective

- Test for significant difference in PFS (and other secondary endpoints) between treatment arms in the VSG group.
- Test for significant difference in PFS (and other secondary endpoints) between treatment arms in the VSP group and overall (in case of no significant interaction).
- Test for significant difference in PFS (and other secondary endpoints) between VeriStrat groups (in case of no significant interaction) adjusting for treatment if necessary.
- Explore differential activity of treatment effect on the secondary endpoints in the two VeriStrat groups by test for interaction between treatment arms and VeriStrat status.
- Assess the safety and the tolerability of the two treatments separately in each VeriStrat group and overall.

16.3. Sample size determination

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).

Intermediate evaluation of the VeriStrat actual partition observed in the trial (Poor vs Good) will be performed after 200 patients have been randomized, with the possibility to increase the sample size by 50 patients if needed to retain at least 80% power. In addition, the number of patients with indeterminate VeriStrat result will be assessed and if deemed necessary, the total sample size will be increased by this number, which is expected to be not higher than 10 patients (2% indeterminates).

16.4. Evaluation of primary and secondary objectives

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 primary efficacy analysis will include all eligible patients with a VSG or VSP signature entering the study (efficacy cohort). The significance of an interaction term included in a Cox proportional hazards regression model for PFS, will be explored. The test will be performed at the 0.05 significance level. The VeriStrat status indicator and a randomized treatment indicator will be included in the model for PFS along with the interaction term.

In case the interaction term is not significant, a Cox regression analysis exploring the treatment effect adjusted for VeriStrat status will be performed. The prognostic significance of the VeriStrat status adjusted for treatment will also be explored in this Cox model.

Progression free survival (PFS) and overall survival (OS) will be estimated by the Kaplan Meier method and compared between the treatments in the full cohort and in each VeriStrat subgroup by means of the logrank test, stratified when appropriate.

The analyses will be repeated for OS, and the other secondary endpoints for the whole cohort and the two VeriStrat subgroups separately. Clinical efficacy will be further described by objective response rate (ORR) and disease control rate (DCR).

Safety and the tolerability of the docetaxel and erlotinib treatments will be described overall and separately in each VeriStrat subgroup by tabulation of the CTCAE V4 grades. The safety cohort will encompass all patients who have received at least one dose of trial treatment.

17. Criteria for termination of the trial

17.1. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation of protocol therapy.

Note: Diagnosis of another neoplastic disease (second malignant tumor) does not mandate a stop of trial therapy, patients may continue to receive protocol treatment after appearance of a second primary tumor, stopping protocol treatment is determined by the medical judgment of the treating physician.

- Request by the patient.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

The decision for discontinuation of protocol treatment of individual patients is taken by the treating physician based on his medical evaluation and taking into account the patient's individual situation.

17.2. General criteria for termination of the trial

The trial will be stopped if early analyses of the study data show a significant harm, by decision of ETOP or Trial Steering Committee.

18. Ethics approval procedures and Patient Informed Consent

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

18.1. Ethical Review Board/Ethics Committee

The protocol and the use of biological samples from patients must have the approval of a properly constituted committee or committees responsible for approving clinical studies.

The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP Coordinating Office prior to center activation.

18.2. Regulatory approval procedures

There will be local, regional and country specific differences in the regulations concerning the use of biological samples for research. Each site will be expected to notify ETOP of the local regulations and seek the relevant approvals.

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP Coordinating Office prior to participating center activation.

18.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “Patient Information and Informed Consent".

One signed and dated copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for inclusion to this trial.

18.4. Confidentiality

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the ETOPdata RDE facility. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central labs.

Biological material will be transferred outside the treating institution for central testing. Results of the assays will be coded only by the patient identifier.

18.5. Duration of study

Data will be kept in the central database for an unlimited time. The ETOP Foundation Council will decide about the eventual discontinuation of this study and deletion of data.

19. Governance and administrative issues

19.1. Steering Committee

A Steering Committee will be constituted for this trial. The Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial co-chairs, trial statistician, ETOP officials, representatives from some participating institutions and groups, and a representative from Biodesix.

19.2. Publication

The results of the trial will be published according to the ETOP publication guidelines (appendix 4).

19.3. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP Coordinating Office.

20. References

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