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***ETOP 5-12 EORTC-08111 protocol***

# *Splendour: Survival imProvement in Lung cancEr iNduced by DenOsUmab theRapy*

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***The contents of this plan are confidential.***

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## PURPOSE

This document contains a description of how the final analysis for the ETOP 5-12 EORTC 08111 Phase III study will be performed. All abstracts, presentations and publications for the primary results will be based on the analyses described here. This document is to be used in conjunction with the protocol which contains a detailed description of the clinical aspects of this study, the EORTC standard operating procedure (ST-005-SOP version 1.02 entitled 'Statistical Analyses'), working instructions (ST-005-WIN-01 version 1.00 entitled 'Statistical Inference'), the data validation and update plan (UVP) and the recommendations from the EORTC IDMC (upon performing the planned interim analysis described in the protocol).

## ABBREVIATIONS

**RT**: radiotherapy;
**CTx** chemotherapy;
**trt**: treatment

**KM**: Kaplan-Meier curve
**HR**: hazard ratio
**CI**: confidence interval
**P**: p-value

## CONVENTIONS

In the analysis we will use the coding of the variables which is used on the CRF (case report form) and in the clinical database unless otherwise specified.
Solid bullets (•) refer to variables that will be reported, circles (o) to categories. Variables in grey are on the CRF, but will not be reported.
In case more than one version of CRF exists, only variables that exist on the last version which are consistently cleaned will be used in the analysis.

# 1 Statistical considerations

## 1.1 Sample size and objectives (copied from protocol)

The primary objective is to evaluate whether the addition of denosumab to standard firstline chemotherapy in advanced NSCLC improves overall survival.

Using 90% power and a one-sided type I error of 2.5%, demonstration of an increase in median overall survival to 11.25 months in the experimental arm relative to 9 months in the control arm (equivalent to HR = 0.80) requires observation of 847 deaths. Assuming an accrual rate of 15 patients/month for the first 6 months and 30 patients/month thereafter, an accrual of 1000 patients would be required with corresponding accrual period of 37 months and an extra 14 months follow up time after the last patient entry to reach the above required number of events. The accrual in the bone mets stratum is expected around 30% of the total, with the rest of the patients (70%) for the non-bone mets stratum. The same median OS and improvement in the experimental arm is assumed for both strata.

The trial is designed with a futility interim analysis (IA), to be performed at 30% of the information time. If the trial is completed with full accrual, the maximum overall duration is expected to be 51 months.

## 1.2 Implementation of clinical cut-off date

The clinical cut-off date for the final analysis will be determined before data base lock. The maturity of the primary analysis as described in the above should determine the cut-off date.

**Follow-up and follow up measurement forms**

'survival status' section of the FU form will be cleaned and reviewed/included in the final analysis when the date last known to be alive or date of death ≤ clinical cut-off date.

'disease/progression' sections of the FU, FUM forms will be cleaned and reviewed/included in the final analysis when the date of visit ≤ clinical cut-off date.

**All other forms are included.**

# 2 Patient populations

## 2.1 Patient populations used in the analyses

2 populations will be used in the analysis of this study. They are described below along with sections of this statistical analysis plan where they are applicable.

**Population 1: Intention-to-treat population (ITT)**

- All randomized patients will be analyzed in the arm they were allocated by randomisation. This dataset will be analyzed by randomized treatment arm. It will be used for:
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    - All tabulations of baseline characteristics, accrual, eligibility
    - Tabulations of off-study reasons
    - All efficacy analyses. Some sensitivity analyses may be performed, but will explicitly mention the population, and be marked as sensitivity analysis.

**Population 2: Safety population**

- All patients who have started their allocated treatment (at least one dose of the study drug(s)). Start of treatment is determined by checking the chemotherapy form (TRTCTX) box 2 (*dtsttrtctx*) and denosumab form (TRTDEN) box 6 (*dtst1den*). It will be used for:

    - All safety tables.
    - All dosing tables.

Note: Patients who started with the other treatment arm will not be included in the safety dataset. Their safety and dosing will be reported separately

Presence vs absence of bone metastases, Geographical regions, ECOG performance status (0 or 1 vs 2), Histology (Squamous vs other histology) were used as stratification factors at the time of randomization.

Serious Adverse Events will be reported for all patients, regardless of the related from non-related status.

TR analysis is not included in this SAP. The TR population will normally follow ITT, but depending on the nature of the analysis may include sub-groups according to the investigated markers. Simple SAP will be written separately before conducting the TR analysis.

# 3 Descriptive Statistics

## 3.1 Accrual by center and treatment group

The number of patients randomised to each of the two treatment groups in the different centers will be presented in a table. A second table will provide the total number of patients randomized each year.

## 3.2 Eligibility by treatment group

The eligibility status of the patients as assessed by the Clinical Research Physician and the Study Coordinators (form DM01) will be summarized per treatment group. A list of the ineligible patients and the reason for ineligibility will be presented by treatment group.

## 3.3 Patient characteristics

A table will be provided with the distribution of the following patients characteristics by treatment group. The data will be taken from the on study form. All stratification factors used at the randomization will be taken from the randomization form (as available/applicable). The coding is that which is used on the randomization form.

Age (≤40, 41-≤ 50, 51 – ≤60, 61 – ≤ 70, 71 – ≤75, > 75 years; median and range)

ECOG performance status at baseline

Histology

Bone metastases

Region

Measurable or evaluable disease

Life expectancy of at least 3 months

Prior surgery for early stage NSCLC

Stage at diagnosis and at study entry of NSCLC ($7^{th}$ and $8^{th}$ TNM)

EGFR and ALK Status

History of allergy

Prior malignancy

Smoking habit

Prior chemotherapy or molecular targeted therapy

If yes:

- Prior radio-chemotherapy
- Prior neo-adjuvant/adjuvant chemotherapy or molecular targeted therapy

Time between prior chemo/molecular therapy and randomization (in weeks)

- Time between prior radio-chemotherapy and randomization (in weeks)
- Time between prior adjuvant/neoadjuvant and randomization (in weeks)

Other investigational agent(s) within 30 days of Randomization

Concurrent bisphosphonate use

Prior history or current evidence of osteomyelitis/osteonecrosis

Evidence of any medical condition impairing patient participation in the trial

Active hepatitis B, C and HIV infection

Hypersensitivity to any components of the treatment

Legal incapacity

Medical or psychological condition would not permit patient to complete trial

Previous exposure to denosumab

Previous bisphosphonate exposure

Women of child-bearing potential

Agree to use an effective contraception

Women:

- Pregnant or breast feeding

Pregnancy test

Baseline laboratory tests (see hereafter for methodology)

Time between initial diagnosis and randomization (in weeks)

Time between stage IV diagnosis and randomization (in weeks)

Histology

Time between prior surgery and randomization (in weeks)

Prior history of malignant disease

Malignant disease type(s)

Sites of metastasis disease

Time(s) between prior malignant disease(s) and randomization (in weeks)

## 3.4 Treatment received

Tables of dosing will be by regimen: for the control arm, these will be split by regimen type (CISPlatin/CARBoplatin, PEMetrexed, GEMcitabine). For the treatment arm, apart from the above, DENosumab dose will be calculated.

Some patients in standard arm receive zoledronic acid. These patients will be tabulated separately.

Tabulations will also include:

- The number of patients who received Folic acid
- The number of patients who received vitamin B12, D, and Calcium
- Number of cycles received
- Dose intensity and relative dose intensity (<70%, 70-90%, 90-110%, >110%) of CISPlatin/CARBoplatin, PEMetrexed, GEMcitabine, DENosumab. Calculation rules will be as per EORTC work procedures. Body surface areas will be recalculated on the basis of height and last prior reported weight.
- The duration of treatment (in days) for a patient will be calculated as the difference between the start of the last administered cycle + 3 weeks and the first date of treatment. The distribution of the duration of treatment along with the reason for stopping treatment will be tabulated by treatment group.
- Dose modifications (as calculated being 15% below the per protocol dose) and discontinuations (as calculated), and reasons for modifications.

- Maximum cycle delay by patient, and by cycle (0-3 days, 4-7 days, 8-14 days, > 14 days), and reasons for delay.

## 3.5 Compliance to treatment (Compliance form and Medical review form)

The compliance to protocol treatment, will be tabulated and listed, by treatment arm both from compliance form and medical review form (as reviewed by the SCs and the CRP).

## 3.6 Treatment toxicity (AE form)

All grading of adverse events and laboratory values was and will be done according to CTC version 4.0. Toxicity will be tabulated by treatment arm. Patients receiving wrong regimen will be listed separately.

### 3.6.1 Adverse events

Adverse events will be categorized by their CRF preprinted category.

Tabulations by treatment arm will include:

- Grade at baseline
- Worst grade on treatment. This includes all adverse events post baseline

### 3.6.2 Hematology/Biochemistry (hematology form and biochemistry form)

The worst degree of toxicity for the haematological and biochemical parameters on the laboratory form will be calculated. Tables will presented by treatment group:

- Hematology/Biochemistry grades at baseline
- Worst grade for hematology on treatment. This includes all lab tests post baseline ( hematology form, boxes 6-17).
- Worst grade for biochemistry on treatment. This includes all lab tests post baseline (biochemistry form, boxes 6-29).

All serious adverse events will be summarized on a per patient basis. A narrative of all toxic deaths will be provided.

## 3.7 Reason off treatment (end of treatment form)

The reason for going off doublet chemotherapy treatment will be tabulated, with additional listings of specifications.

For the treatment arm, the reason for going off Denosumab protocol treatment will be tabulated, with additional listings of specifications.

# 4 Efficacy analysis

## 4.1 Endpoints

### 4.1.1 Intent to treat

#### 4.1.1.1 Primary endpoint

- Overall survival (OS)

#### 4.1.1.2 Secondary end points

- Progression free survival (PFS) based on RECIST 1.1

- Response based on RECIST 1.1

- Toxicity profile of denosumab; toxicities will be assessed and graded according to CTCAE v. 4 (Please see above 3.6)

### 4.1.2 Overall Survival (Primary endpoint)

In the overall survival analysis, events are deaths from any cause found at any form in the database. Prior to locking the database, utmost care will be taken to ensure any death is documented on forms (end of treatment form, boxes 25 and 27, follow up form boxes 33, 35). Date of last known to be alive is the maximum date calculated from the following dates:

- End of Treatment form (EOT, boxes: 1, 19, 20, 22, 27 )
- Follow up form (FU, boxes: 1, 3, 6, 12, 13, 16, 17, 20, 23, 24, 27, 28, 31, 32, 35 )
- Follow up Measurement form (FUM, boxes: 1, 66)
- Treatment from (TRTCTX, boxes: 7, 12, 17, 22, 43, 48)
- Denosumab form (TRTDEN, boxes: 6, 11)
- Hematology form (LBHEM, box: 2, if box 3 =1 )
- Biochemistry form (LBBIO, box: 2, if box 3 =1)

For patient who died, the last date of known to be alive will be assigned to the date of death. Patient who did not die will be censored at the date they were last known to be alive. The overall duration of survival is defined as the time from the date of randomisation to the date of death/date of censoring.

The frequency and cause of death will be tabulated by treatment group.

### 4.1.3 Progression Free Survival (secondary endpoint)

Events for progression-free survival are defined as: (1) progression based on RECIST 1.1 or (2) death from any cause. Patients who did not experience an event (as described above) will be censored at the date of the last follow-up examination. The period of PFS is counted from the date of

randomization. Date of the last follow-up examination is calculated to be the maximum date in follow up measurement form (FUM, box 1).

The date of progression will be as documented on the follow-up measurement form (boxes 65, 66) on the follow-up form (boxes 2,3).

#### 4.1.4 Overall Response (based on RECIST 1.1, secondary endpoint)

Overall response to the treatment is obtained from the medical review form (box 21) and if missing, it should be taken from the follow-up measurement form (box 65). The number and percent of patients who achieved a complete response, partial response, stable disease, progression or are not assessable will be presented by treatment group. Reason for not assessable response will be summarized.

Patients who were not assessable will be counted as non-responders in all comparisons (CR+PR vs. all other cases).

Timing of reaching the best response (at midpoint of neo-adjuvant treatment or at the end) will be tabulated by treatment arm and response outcome.

## 4.2 Comparison of the two treatment groups for efficacy

### 4.2.1 Main analyses

#### 4.2.1.1 Primary endpoint

The analysis on the primary endpoint will be based on intent to treat (ITT). Recent introduction of anti PD-1/PD-L1 immunotherapy may change the expectation of overall survival in the patient population, given the anticipated effect of such immunotherapy on survival and the changes made to the inclusion criteria. The primary analysis to compare the experimental versus the control arms for the time-to-event endpoints will be based on Cox regression adjusted for the stratification factors, receiving prior anti PD-1/PD-L1 immunotherapy administration (Yes vs No) and an indicator whether the patient was included in the pre- or post-amendment protocol (Yes vs No).

As a sensitivity analysis, a one-sided log rank test stratified by the factors used as stratification at randomisation, comparing the two treatment arms (as randomized) at a specific 1-sided overall alpha = 0.025, will be performed.

At the interim look, futility analysis will be conducted using the Lan-Demets approach with an O'Brien-Fleming stopping boundary. The calculation of the boundary will be made by East 6 (version 6.4 or the latest), and the applicable boundary will be determined using the available

information (number of events) at the time of the interim analysis. As an example, with 30% events, a 2-sided $p > 0.8423$ would be used as a criterion to declare futility.

#### 4.2.1.2 Secondary endpoints

##### *4.2.1.2.1 Time-to-event endpoints*

For PFS, inference will be based on the Cox Regression as in the analysis of the primary endpoint OS.

##### *4.2.1.2.2 Overall response rate*

The analysis will compare treatment arms for overall response rate on ITT population by Fisher's Exact test.

### 4.2.2 Preplanned sensitivity, subgroup and exploratory analyses

#### 4.2.2.1 PFS and OS

As a sensitivity analysis, other baseline disease factors namely gender, smoking status, age, PS, mutational status (EGFR, ALK) and back bone chemo (carboplatin versus cisplatin) will be used as adjustment factors in a multivariate Cox regression analysis, in addition to the stratification factors used for randomisation. A log rank test with no adjustment factors to compare the two arms will also be performed as a sensitivity analysis.

The proportional hazards assumption will be checked using the method described by Grambsch and Therneau. If the data clearly do not follow proportional hazards as indicated by the significance of the above test of Grambsch and Therneau, medical explanations should be identified and alternative statistical methods will be explored.

Subgroup-analysis by stratification factors used in randomisation will be conducted. In particular, analysis according to the existence/non-existence of bone metastasis will be emphasized to ensure that patients without bone metastasis at randomization are not exposed to an inferior treatment. This concern is triggered by the results of the Amgen **study *'A randomized, Double-blind, Multi center Phase 2 trial of Denosumab in combination with chemotherapy as first line treatment of metastatic NSCLC'*** where the subgroup analysis showed that in patients without bone metastatis at baseline, the HR for OS is 1.25 (95% CI 0.78, 2.02) in favour of placebo. The analysis was based on 126 patients (43 and 83 patients in placebo and denosumab arm respectively) with a total number of events/deaths = 86.

**Of the above sensitivity analyses, subgroup analysis by stratification factors used in randomisation will be performed at the interim analysis. Particular attention will be focused on the analysis of primary endpoint OS with respect to the presence and absence of brain metastasis. Comparison of the primary endpoint will be made in the subgroups of patients with brain metastasis and non-brain metastasis at randomization. HRs and their 95% CIs will be estimated and p-values from the multivariate Cox regression analysis adjusted by the stratification factors used for randomisation as described in 4.2.1.1, as well as for the presence vs absence of bone metastases will be calculated. A log rank test with no adjustment factors to compare the two arms will also be performed.**

# 5 Translational research analyses

All additional translational research subprojects will need to be described in separate analysis plans prior to being performed.

# 6 Appendices

- recommendations from the ETOP IDMC