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STIMULI

ETOP/IFCT 4-12

A randomized open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

Statistical Analysis Plan (SAP) for
Final analysis

NCT02046733

A clinical trial of ETOP

SAP VERSION & DATE: 1.0 – MAY 2020

Contents

INTRODUCTION

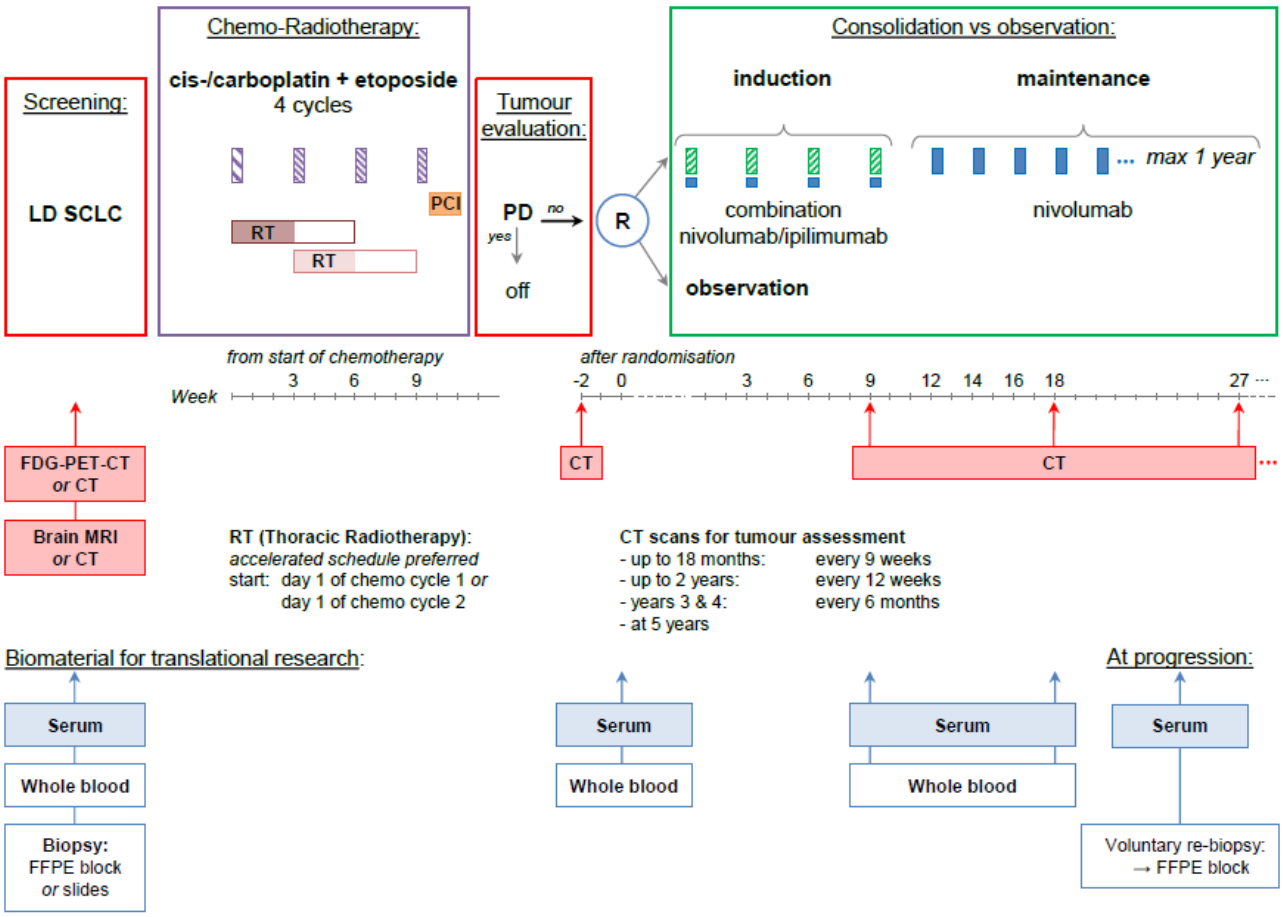
The aim of this Statistical Analysis Plan (SAP) is to describe an analytic and solid framework that will be followed in order for the **final efficacy analysis** of the STIMULI trial to be implemented (based on protocol amendment-1 [AM1]).

A short description of the contents of this statistical analysis plan is provided below:

1. **Trial outline/oversight:** trial's schema, objectives and trial endpoints, eligibility criteria, trial treatment, statistical design (sample size and power), trial duration, previous protocol versions
2. **Statistical considerations for final analysis:** analysis timing, definition of primary, secondary and exploratory endpoints, (serious) adverse events definition, analysis populations
3. **Primary efficacy analysis of Progression free-survival (PFS)**
4. **Additional secondary analysis:** accrual and baseline characteristics, treatment administration and follow-up, secondary and exploratory analysis
5. **Technical issues:** data retrieval, testing, handling of missing data, reporting conventions

Trial oversight (as per protocol version 2.0, Amendement1; AM1)

STIMUI is a randomized open-label phase II international multicentre clinical trial aiming to demonstrate superiority of consolidation with nivolumab and ipilimumab versus observation after chemo-radiotherapy and prophylactic cranial irradiation (PCI), in patients with radically treated limited-stage small cell lung cancer (SCLC).



SCHEMA 1. Trial design under protocol AM1

STIMULI is a trial with block stratified randomization balanced by institution. After completion of the 4 cycles of chemotherapy, thoracic radiotherapy and PCI, patients who have not progressed can be randomized to one of the two treatment arms. The two stratification factors are: number of fractions of radiotherapy (twice-daily vs once-daily) and positron emission tomography–computed tomography (PET-CT) (done vs not done)

1.1 Objectives and Endpoints

Primary objective

According to protocol AM1, the **primary objective** of the study is to evaluate if patients treated with chemo-radiotherapy and PCI followed by consolidation treatment (nivolumab plus ipilimumab) have a better outcome in terms of progression-free survival (PFS) and overall survival (OS) compared to patients treated with chemo-radiotherapy and prophylactic cranial irradiation without consolidation treatment.

Co-primary endpoints:

- Progression-free survival (PFS) according to RECIST 1.1 criteria based on the local radiologist assessment
- Overall survival (OS)

Important notes:

- Following a subsequent modification in trial design, without requiring protocol amendment, PFS alone was set to be the primary endpoint of the trial, with OS becoming a secondary endpoint. This is further described in section 1.4.2.
- PFS (measured from randomization) are compared between treatment arms only for randomized patients.
- Patients randomized to ipilimumab monotherapy before the protocol AM1, i.e., under the original protocol version, will be excluded from the present final efficacy analysis, and will be evaluated separately.

Secondary endpoints:

- Objective response determined by RECIST 1.1 criteria
- Time to treatment failure (TTF)
- Adverse events graded according to CTCAE v4.0

Exploratory endpoints:

- Time to treatment discontinuation (TTD)
- Duration of response (DoR)

Details on the calculation of endpoints are provided in section 2.2.

1.2 Most important eligibility criteria

Inclusion criteria at enrolment:

- Histologically or cytologically confirmed small cell lung carcinoma
- Untreated (with the exception of 1 cycle of chemotherapy given prior to enrolment) limited stage disease (LD) as defined by stage I-IIIB based on 7th TNM classification (IASLC classification for SCLC proposal). M0 proven by
    - Whole body FDG-PET CT including a contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals); OR contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan;
      AND
    - Brain MRI (or contrast enhanced CT of the brain).
      Within 28 days before start of chemotherapy
- Age ≥18 years
- ECOG performance status 0-1
- Adequate hematological, renal, hepatic and liver function
- Pulmonary function FEV1 of 1.0L or >40% predicted value and DL_{CO} >40% predicted value

Exclusion criteria at enrolment:

- Patients with mixed small-cell and non-small-cell histologic features
- Patients with pleural or pericardial effusions proven to be malignant
- Documented history of severe autoimmune or immune mediated symptomatic disease that required prolonged (>2 months) systemic immunosuppressive treatment (e.g. steroids) such as ulcerative colitis and Crohn´s disease, rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, or autoimmune vasculitis (eg, Wegener's granulomatosis)
- Patients with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment
- Interstitial lung disease or pulmonary fibrosis
- Women who are pregnant or in the period of lactation
- Patients with any concurrent anticancer systemic therapy (except for chemotherapy cycle 1)
- HIV, Hepatitis B or Hepatitis C infection
- Patients who have had in the past 5 years any previous or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ ductal carcinoma of the breast
- Previous radiotherapy to the thorax (prior to inclusion)
- Planned mean lung dose >20 Gy or V20 >35%

Inclusion criteria at randomization:

- Chemo-radiotherapy completed per protocol: 4 cycles of chemotherapy, 85% of PTV of thoracic radiotherapy, as well as completed, mandatory PCI
- Non-PD after chemo-radiotherapy and PCI

1.3 Trial treatment

After enrolment, the patient will receive or, if included after the first chemotherapy cycle, continue receiving standard of care treatment for limited disease SCLC consisting of chemo-radiotherapy and PCI.

- Chemotherapy: will be started in the week following enrolment (alternatively, maximum 1 cycle of chemotherapy may be administered before enrolment), and consists of a total of 4 cycles of cisplatin (25 mg/m2 i.v. on days 1 – 3 or 75 mg/ m2 on day 1) or carboplatin (AUC 5-6, calculated according Calvert formula, i.v. on day 1), plus etoposide (100 mg/ m2 i.v. days 1 – 3), repeated every 3 weeks (+/- 3 days without cycle delay).

- Concomitant Thoracic Radiotherapy: Accelerated twice-daily administration of 45 Gy in 30 twice-daily fractions of 1.5 Gy (6-8 hours apart), 5 days per week for 3 weeks, or an allowed, but not-recommended schedule of 56 Gy, given in 28 once-daily fractions of 2 Gy, 5 days per week for 6 weeks. Two options are allowed: Thoracic radiotherapy MUST start either from day 1 of cycle 1 or day 1 of cycle 2. Radiotherapy start at day 1 of cycle 3 is allowed if patient is enrolled after the first cycle only but should be exceptional. Optimally, radiotherapy should start at the latest on day 1 of cycle 2.

- PCI: 25 Gy in 10 fractions starting between day 8 and day 15 of chemotherapy cycle 4 and finished not later than day 29 from start of cycle 4.

After randomization, which should take place within 5-6 weeks after day 1 of cycle 4 (between days 35 and 42 of cycle 4)

Experimental arm

Induction phase:

To start within 6-8 weeks (42-56 days) after the start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomization.

- Nivolumab at a dose of 1 mg/kg i.v. over a period of 30 minutes,
  followed (on the same day) by
- Ipilimumab at a dose of 3 mg/kg i.v. over a period of 90 minutes, once every 3 weeks (+/- 3 days, without dosing delay), 4 cycles

Maintenance phase:

To start 3 weeks (21 days) after the last Investigational Medical Product (IMP) dose of induction phase.

- Nivolumab 240 mg i.v. over a period of 30 minutes, once every 2 weeks (+/- 2 days, without dosing delay), for a maximum of 12 months from start of maintenance phase.

Observation arm

No further treatment.

1.4 Statistical design, sample size and power

1.4.1 Based on protocol AM1

This is a 1:1 randomized phase II trial (stratified by twice-daily vs once-daily radiotherapy and PET-CT done vs not done) with co-primary endpoints PFS and OS. The **overall one-sided significance level of 0.05** is split to 0**.01 for PFS** and 0.**04 for OS**. A total of 325 patients are expected to be enrolled in 36 months of accrual time, leading to **260 patients randomized** to the two arms based on a 20% attrition rate due mainly to early progression events during the first 4 months after enrolment. An additional 3% loss to follow-up is assumed during the trial after randomization. A trial duration of 87 months is necessary for the **required 212 deaths** to be observed, while the main analysis of PFS will be performed when **148 PFS events** have occurred, which is expected at approximately 45 months. Using the log-rank test, the achieved power is 80% for PFS at the 45-months evaluation and 78% for OS at the end of the trial.

Median PFS and OS for the observation arm are expected to be 13.1 and 20.7 months, as measured of randomization. Taking into account that the patients randomized are of better prognosis than the total patients enrolled, **the expected increase in medians for the cohort of patients in the experimental arm is 9.7 months and 9 months for PFS and OS respectively. This translated to a PFS HR of 0.57 and OS HR of 0.70.**

The trial will end when either the total number of 212 deaths has been observed or at a maximum of 7.5 years from the first patient enrolment date.

Calculations are performed using the EAST package and simulations were run in the R statistical package.

1.4.2 Modifications after premature accrual closure

Because of the low accrual rate as well as additional strategic considerations unrelated to the scientific rational of the trial design, trial's funding source (Bristol-Myers Squibb, BMS) informed ETOP on 18 March 2019 that cannot continue funding the STIMULI trial. Therefore, the Trial Steering Committee decided to close the accrual into the trial prematurely as of 30 April 2019. Note that no safety concerns led to the decision of accrual closing.

Patients who already consented were still allowed to be enrolled until 30 April 2019. After this date, no new patients would be allowed to be enrolled into the trial. Treatment and follow-up for

all included patients continued as per protocol. Patients in the chemoradiotherapy phase who meet the criteria, would be still allowed to be randomized.

Thus, taking into account the reduced number of randomized patients and the corresponding initially required events (148 PFS events, 212 OS events) which were not possible to be observed anymore, the statistical design was modified.

According to this latest statistical modification, the primary endpoint of the trial is now defined as only the PFS (previous: co-primary PFS and OS) using the overall one-sided significance level of 0.05 (previous: 0.04 for PFS and 0.01 for OS). The hypotheses for PFS remain the same (PFS HR=0.57, with 13.1 months median PFS assumed in the observation arm versus 22.8 in the experimental). In this setting, the number of the required PFS events, for testing the PFS hypothesis with 80% power, at 5% significance level, is 81 (in: 148 events).

1.5 Total trial duration

Patient accrual was expected to be completed within 3 years including a run-in-period of 3 months. The total trial duration would be approximately 7.5 years including the 36 months recruitment period. Patients would be followed until death – thus follow-up was estimated to last up to 4.5 years following the enrolment of the last patient.

The trial will end with the preparation of the final report, initially scheduled for 7.5 years after the inclusion of the first patient. However due to premature accrual closure the final report will be prepared earlier, expected approximately 4.5 years after the inclusion of the first patient.

1.6 Previous protocol version (original protocol)

STIMULI trial, original protocol v1.0, was activated in December 2013 and the first patient was enrolled on the 28th of July 2014.

The low accrual rate experienced in the first few months of the STIMULI study, along with recently presented results showing significant benefits with Nivolumab treatment with or without Ipilimumab [Antonia S.J., JCO 2015; Larkin J., NEJM 2015; Postow M.A., NEJM 2015], led the protocol team to decide to procced to protocol amendment (AM1). The protocol amendment has been completed and distributed to the sites (21st of September 2015) for submission to the corresponding authorities. The first subject was enrolled under AM1 on the 18th of December 2015.

The main modifications introduced by the amendment were:

- the addition of Nivolumab to consolidation therapy

- the addition of carboplatin to standard therapy as an alternative to cisplatin
- addition of PFS as co-primary endpoint
- the option of contrast enhanced CT of the brain as an alternative to MRI at screening
- allowing one cycle of chemotherapy before enrolment of patient.

2 Statistical considerations for final analysis

2.1 Analysis timing

According to the modified statistical design, the final efficacy analysis will be performed when the 81 required PFS events have been observed among all STIMULI patients randomized under AM1.

2.2 Study's endpoints

2.2.1 Primary endpoint

The primary endpoint of the analysis is PFS, defined as the time from the **date of randomization** until documented progression (based on RECIST 1.1 criteria) or death, if progression is not documented. Censoring (patients without progression/death) for PFS will occur at the last tumour assessment. In the frame of a sensitivity analysis, if the last tumour assessment is «Non evaluable», censoring will occur to the more recent tumour assessment where an overall evaluable result is recorded.

2.2.2 Secondary endpoints

Secondary endpoints include OS, ORR, TTF and adverse events (AEs) graded according to CTCAE v4.0. More specifically:

- OS is defined as the time from the date of randomization until death from any cause. Censoring (patients without death) for OS will occur at the last follow-up date.
- ORR is defined as the rate of best overall response (complete or partial response) according to RECIST 1.1 criteria across all assessment time-points, during the period from randomization to termination of trial treatment. Of note, the determination of ORR will be restricted to patients who have not attained a CR during chemo-radiotherapy.
- TTF is defined as the time from the date of randomization to treatment failure for any reason (including progression of disease, treatment toxicity, refusal, lost to follow-up and death). Censoring for TTF (patients without failure) will occur at the last-follow-up date.
- Toxicity, defined as adverse events classified according to CTCAE v4.0.

2.2.3 Exploratory endpoints

- TTD is defined as the time from the randomization to treatment discontinuation for any reason (including progression of disease, treatment toxicity, refusal, lost to follow-up and death). Censoring for TTD (patients on treatment or completed treatment), will occur at the last-follow-up date

– DoR is defined as the time from the documentation of tumour response (either partial or complete response) to disease progression or death. Censoring will occur at the last tumour assessment with response other than progression.

2.2.4 (Serious) Adverse Events

Adverse Events (AEs)

The main criterion for treatment tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE version 4 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

An adverse event is defined as any untoward medical occurrence that occurs from the day of enrolment in the Remote Data Entry (RDE) until 100 days after the final dose of IMP regardless of whether it is considered related to a medication. The relation of the adverse event with the administered trial treatment has to be indicated as: unrelated, unlikely, possible, probable or definite. 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.

Immune-related Adverse Events (irAEs)

The following adverse events are of special interest and must be documented after randomization in both treatment arms:

CTCAE Version 4.0 system organ class / preferred terms:

Nervous system disorders:

- Peripheral motor neuropathy
- Peripheral sensory neuropathy
- Meningismus
- Limbic Encephalitis
- Nervous system disorders - Other, specify (Guillain-Barré, myasthenia gravis, aseptic or non-infectious meningitis)

Skin and subcutaneous tissue disorders:

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Bullous dermatitis
- Rash acneiform
- Rash maculo-papular
- Pruritus
- Skin and subcutaneous tissue disorders - Other, specify

Gastrointestinal disorders:

- Colitis

- Diarrhea
- Colonic perforation
- Small intestinal perforation
- Gastric perforation
- Gastrointestinal disorders - Other, specify

Hepatobiliary disorders:

- Hepatic failure
- Hepatitis viral
- Drug-induced liver injury (DILI)

Investigations:

- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood bilirubin increased

Endocrine:

- Adrenal insufficiency
- Hypothyroidism
- Endocrine disorders - Other, specify (hypopituitarism, hypophysitis)

Respiratory, thoracic and mediastinal disorders:

- Pneumonitis

Renal and urinary disorders:

- Renal and urinary disorders - Other, specify (nephritis)

Eye disorders:

- Uveitis
- Eye disorders - Other, specify (iritis)

Blood and lymphatic system disorders:

- Blood and lymphatic system disorders- Other, specify (haemolytic anaemia)

Cardiac disorders:

- Myocarditis

Serious Adverse Events (SAEs)

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 100 days after stopping study treatment that, 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
- is a medically important event
- overdose (although this event is not always serious by regulatory definition, overdose must be handled as SAE)

- pregnancy

Second (non-SCLC) malignancies are always considered SAEs, no matter when they are diagnosed. Other significant/important medical events which may jeopardize the patient are also considered SAEs. 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.

Severity Grade

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 patients. *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:

Grade 1	Mild- transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade 2	Moderate- mild to tolerate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe- marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
Grade 4	Life-threatening- extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
Grade 5	Fatal- the event results in death

2.3 Analysis population

Efficacy cohort: The efficacy cohort is the Intention-to-treat (ITT) population of the trial and includes all randomized subjects under protocol AM1. Patients will be evaluated in the treatment arms to which they were randomly assigned, regardless of the treatment actually received, including patients who were randomized but did not receive any trial treatment.

Safety cohort: The safety cohort consists of all subjects who have received at least one dose of IMP treatment plus all patients randomized to observation arm (under protocol AM1).

Patients will be evaluated according to the treatment they actually received, irrespective of their allocated treatment at randomization.

Per-Protocol cohort: Per-protocol cohort includes all patients enrolled under protocol AM1.

Per-Protocol safety cohort: Per-protocol safety cohort includes all patients enrolled under protocol AM1, who received at least one dose of chemo-radiotherapy after enrollment.

3 Primary efficacy analysis of PFS

Primary efficacy analysis of PFS (primary endpoint) will be performed on **all randomized patients under AM1 protocol, based on their initial treatment assignment (ITT, efficacy cohort)**. PFS time is measured from time of randomization.

Formal hypothesis testing

Based on the protocol AM1 and after the modifications arose from the premature study accrual termination, the trial is designed to test the hypotheses that treatment with chemoradiotherapy and PCI followed by consolidation treatment (nivolumab plus ipilimumab) will lead to an increase in median PFS to 22.8 months, from 13.1 months under treatment with chemoradiotherapy and PCI without consolidation treatment. **According to the study design, this corresponds to a PFS HR of 0.57**. Using **80% power** and a **one-sided type I error of 5%**, a total of **81 PFS events** are needed to observed in order to achieve the trial goal.

In the frame of final efficacy analysis, the **formal comparison** of the PFS between the two treatment arms, will be based on **stratified log-rank test** (with number of fractions of radiotherapy [1/2] and administration of FDG-PET-CT [Yes/No] being the stratification factors). Unstratified log-rank test will be also calculated. This would be of particular value in case at least one stratum level has very low number of patients.

Further PFS analyses

The following **PFS analyses** will also be performed and presented

- The total number (%) of PFS events observed, overall and by treatment arm will be presented. In addition, 6-month and 1/2-year PFS estimates, median PFS and respective 95% CI will be provided. Respective results by stratifications factors will be also presented.
- Kaplan-Meier plots by treatment arm as well as by treatment arm within each stratification factor will be created.
- Number of PFS events, median PFS and unstratified/unadjusted HRs (along with 95% CI) will be summarized for the **subgroups** defined by the following clinicopathological variables of interest: gender, smoking history, ECOG performance status at randomization, stage of tumour, age (appropriately categorized) and biological markers (if available). This information will be depicted in a tabular format in the report (a corresponding forest plot will be subsequently produced for presentation/publication).

- To assess the effect of trial treatment and other clinicopathological variables on PFS, Cox proportional hazard models will be fitted.
    - Initially a univariate (stratified and unstratified) Cox model will be fitted in the model and the statistical significance of trial treatment will be tested at the 5% significance level.
    - Subsequently, multivariate Cox models (stratified and unstratified) will be estimated, adjusted for the clinicopathological variables of interest as defined above (in case of unstratified model, the stratification factors will be also included in the covariates of the model). The backward elimination method, with a removal criterion at 10% will be used to conclude on the statistically significant variables of the model. The HRs along with the corresponding 95% CIs for all significant predictors (in the multivariate Cox model) will be summarized in a tabular format in the report (a corresponding forest plot will be subsequently produced for presentation/publication).
    - The proportionality assumption of Cox model will be explored by Schoenfeld's residuals and by testing for time-dependent effect of covariates in extended Cox models. In cases that non-proportionality is detected further appropriate measures will be used
        - Use of variable(s), for which proportionality assumption is violated, as stratification factor(s)
        - Use of weighted tests, alternatives to log-rank for the comparison of survivals, such as the Wilcoxon test
        - Estimation of Restricted Mean Survival Time (RMST) at specific time points (close to median follow and covering the full follow-up time for the majority of patients)
        - Calculation of HR for separate time intervals

4 Additional secondary analysis

In this section, we present in detail the additional analysis that will be performed in the frame of final efficacy analysis for STIMULI trial.

4.1 Patient accrual, balance of stratifications factors & baseline characteristics

- A consort diagram will be created to graphically depict the flow of patients and the phases of the trial.
- Patient accrual by center and country will be presented in tabular format (including enrolled, randomized and ineligible patients)
- For patients deemed ineligible a table summarizing the reasons for non-enrolment will be provided[1]
- Observed vs. expected accrual over time will be graphically displayed.
- Balance of treatment allocation by center and by stratification factors will be summarized
- Patient and tumour baseline characteristics at enrolment (categorical: gender, smoking history, ECOG performance status at diagnosis, stage (based on 7th TNM classification), TNM stage and continuous: age at enrolment), will be presented for the full cohort of enrolled patients. The same characteristics will be presented for the cohort of randomized patients overall and separately by treatment arm. Note that the ECOG PS reported for the randomized patients is the PS recorded just before the randomization. Frequencies and corresponding percentages will be presented for categorical variables (if missing cases exist, a separate category named "*Missing*" will be created.), while the following descriptive measures will be considered for the continuous ones: n (non-missing sample size), mean, 95% CI for the mean, median, maximum and minimum values. Balance of baseline characteristics (at randomization) by treatment arm will be assessed via the Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous.
- Available information on medical history will be summarised, by treatment arm.

4.2 Follow-up information and Treatment administration

Follow-up time of the patients will be presented as:

- Median follow-up (FU) of the randomized patients (overall and by treatment arm) along with the respective interquartile range (IQR) and the number (%) of patients that are still on FU.

[1] Note: This table includes the number of patients registered in the database and characterized as ineligible, but this does not represent the full set of screened patients since, it is not mandatory by the protocol to enter in the database all screened patients, even if not eligible.

- A Kaplan-Meier (K-M) plot will be provided for a graphical representation of follow-up time, overall and by treatment arm.

Treatment information will be summarized first for the chemo-radiotherapy phase and then for the randomization phase overall and separately by treatment arm. More specifically the following information will be presented:

- No. of patients enrolled (under protocol AM1)
- No. of patients stopped the trial before starting any treatment
- No. of patients started chemo-radiotherapy treatment
- No. of treatment failures during chemo-radiotherapy treatment (including failure reasons)
- No. of patients completed chemo-radiotherapy phase
- No. of patients not completed PCI for specific reasons
- No. of patients received (and completed) PCI after chemo-radio therapy phase
- No. of unrandomizable patients
- No. of randomized patients (by arm)
- No. of patients that started treatment with the IMP
- No. of patients that completed treatment
- No. and reasons of treatment failures during randomization phase (by arm)
- No. of patients that completed treatment and they experienced a failure afterwards.
- 6-month, 1/2-year TTF rate (%) and median TTF estimates, along with corresponding 95%CI and log-rank test p-value for comparison of the two treatment arms
- A Kaplan Meier curve for TTF by treatment arm
- For those patients who progressed, information on further lines of treatment (if available) will be provided by treatment arm.

4.3 Secondary (efficacy) and exploratory endpoints

4.3.1 Overall survival

Similar to PFS the following will be presented for OS:

- Total number (%) of OS events, overall and by treatment arm (as well as by stratification factor)
- 1-year/2-year OS estimates, median and respective 95% CIs (comparison between treatment arms based on stratified and unstratified log-rank).
- Kaplan- Meier plot by treatment arm

- Subgroup analysis (number of events, median time and unstratified/unadjusted HRs (along with 95% CIs) and variables of interest)
- Univariate and multivariate Cox proportional hazards model, adjusted for the stratification factors and clinicopathological variables of interest; HRs and corresponding 95% CIs for all significant predictors will be presented in a table.
- Summary table of the death causes overall and by treatment arm (e.g., lung cancer, toxicity, other, etc)

4.3.2 Time to treatment discontinuation

- Total number (%) of TTD events, overall and by treatment arm
- 6-month and 1/2-year TTD estimates, median and respective 95% CIs (comparison between the arms based on stratified log-rank).
- Kaplan- Meier plot by treatment arm
- Summary table of the reason of (permanent) treatment discontinuations overall and by treatment arm (e.g., lung cancer, toxicity, other, etc)

4.3.3 Objective response rate

- Overall best responses and objective response rate (ORR) will be presented overall and separately for the two treatment arms, along with a 95% exact binomial CI. ORR will be compared between the two treatment groups using Fisher's exact test and Cochran-Mantel-Haenszel test stratified by the stratification factors of the trial.
- Logistic regression models will be further applied to investigate the treatment effect on ORR, adjusting for stratification factors and variables of clinical interest.
- Note: ORR will be calculated based on the randomized patients who have not attained complete response during chemo-radio therapy.

4.3.4 Graphical illustration of tumour responses

- A waterfall plot will be created by treatment arm to present the best percentage change in tumour size from the baseline tumour assessment before randomization (sum of target lesions diameters).
- The percentage changes in tumour size from the baseline tumour assessment before randomization (sum of target lesions diameters) over the time will be depicted graphically by a spider plot

4.3.5 Duration of response

- Median DOR, along with 95% CI will be presented, for all responders and separately for the two treatment groups.
- Duration of response will be compared between the two treatment arms using the log-rank testing and graphically illustrated by Kaplan-Meier curves.
- Graphical representation of duration of response will be also performed via swimmer plot.

4.4 Subgroup analysis

To determine whether the treatment effect is consistent across various subgroups the between-group treatment effect for the primary and secondary efficacy endpoints will be estimated within each category of the following pre-specified variables.

Main subgroup analyses:

- Number of radiotherapy fractions per day (once or twice per day)
- Tumour stage (I/II/III by 7th TNM classification)
- Gender

Other pre-planned subgroup analyses:

- Age group
- ECOG performance status (at randomization)
- Smoking history
- Status according to biological markers (if available)

Notes:

1. In case of imbalance in number of patients with the subgroups created by treatment and the variables of interest, this subgroup analysis will not count in the multiple comparison adjustment.
2. These analyses are also described above in the description of PFS, OS analyses.

4.5 Sensitivity analysis

In a sensitivity analysis framework, PFS, OS and TTF (efficacy cohort) will be evaluated having as start date the date of enrolment. In case of patients enrolled after their first chemotherapy cycle, further adjustment will be made to the start date (start date will be the date of 2nd chemotherapy cycle minus 21 days).

4.6 Descriptive analysis of the per-protocol cohort

For all patients enrolled under protocol AM1, irrespective of whether they were subsequently randomized or not, the following will be presented:

- Objective response to chemo-radiotherapy based on the tumour assessment performed before randomization.
- All reasons for non-randomization (included in section 4.2).
- OS analysis (KM plot, median OS, 1 and 2-year rates with 95% CIs) with start date the enrolment date, further adjusted for patients enrolled after the first chemotherapy cycle.

4.7 Safety analysis

The safety analysis will be based on the safety cohort, i.e.., all patients who have received at least 1 dose of IMP treatment (experimental arm) plus all patients randomized to observation arm, and will include the following:

- Overview of the number of patients who experienced an AE and/or a SAE, as well as the number of patients in the safety cohort who did not experience an event, along with respective percentages will be shown. This information will be presented overall and by treatment arm. Also, number of patients that entered the study with baseline symptoms will be reported.
- Number of AEs/SAEs will be presented overall and by treatment arm.
- Number of patients experiencing a specific number of AEs/SAEs, overall and by treatment arm.
- Distribution of (S)AEs by grade and CTCAE category, separately for the two treatment arms. Six columns, one for each grade and one for all (any) grades, will be shown (for each arm). An additional column (by arm) indicating which events were also SAEs will be also available. In this column, the frequency of the SAEs and the severity grade will be given. The percentages that will accompany the frequencies will be based on the respective frequency of an event over the total number of patients in the safety cohort and specific treatment arm. This table will include all (S)AEs irrespective of their relation to the trial treatment.
- Analogous table focusing only on the treatment related (S)AEs.
- Number and corresponding percentages of treatment related (S)AEs by grade, leading either to treatment discontinuation or death will be summarized for the two treatment arms.

- Maximum severity of adverse events (AE/SAE) for patients, overall and by treatment arm.
- Number of SAEs by center
- Detailed information of pulmonary AEs/SAEs of grade ≥3 will be summarized for the two treatment arms.
- The risk difference between the two treatment arms, along with corresponding 95% CIs for specific adverse evets (most frequent i.e. ≥15%, of any grade, or perhaps focus on grade ≥3, irrespective of relation to treatment or treatment-related).

Analogous (more concise) information will be reported for the adverse events during the chemo-radiotherapy phase of all enrolled patients who received at least one dose of chemo-radiotherapy (per-protocol safety cohort).

5 Technical details

Data will be primarily analysed using the SAS software package (version 9.4), while the R statistical software will be also used for specific analysis and plots.

All analysis and reviews will be performed according to the Standard Operating Procedures (SOPs) of FSFH statistical team for the final analysis. A second statistician, the reviewing statistician, will independently reproduce all analysis and summary statistics. The reviewing statistician will have an overview of the entire analysis and will explicitly check the code producing tables and figures, as well as any other pieces of code as desired.

Data retrieval information

The final analysis will be based on the database download, that will take place, as soon as the total number of 81 PFS events required according to the statistical design of the trial are observed. Using this database extraction, a set of queries will be produced and forwarded to trial's data manager with the expectation to be answered in a pre-specified time period (approximately four weeks). Corrections and responses based on these queries, will be used for correcting the previously downloaded database, in order to create the final clean dataset to be used for the analysis.

Missing data

- Baseline characteristics

For categorical baseline characteristics if missing cases exist, a separate category named "*Missing*" will be created. As far as continuous values, missing cases will not be replaced by any statistics calculated over non-missing data.

- Dates:

If the day of the month is missing for any date used in the analysis, the 15th of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in one day of duration will be used. If the day of the month and the month are missing for any date used in a calculation, i.e., January 1 will be used to replace the missing date. Missing dates for adverse events will be imputed based on the similar principle.

- Incomplete tumour assessment information

In patients who have no on-study assessments:

- If death is recorded prior to the first planned tumour assessment, the death date will be considered as the date of the PFS event.
- If clinical progression is recorded prior to the first planned tumour assessment, the date of the reported clinical progression will be considered as the date of the PFS event.
- In all other cases, the patient will be censored at the date of randomization plus 1 day.

Reporting conventions

Regarding the estimates presented in the report, the following rules will be adopted:

- P-values ≥0.001 will be reported with three decimal places
- P-values >0.010 will be reported with two significant demical digits
- P-values less than 0.001 will be reported as "<0.001"
- Means, medians, 95% confidence limits (Cis), quantiles, and any other summary statistics, will be reported with one decimal digit
- Hazard ratios (HRs) and their 95% CI's will be reported to two decimals
- Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to three significant figures.

Multiple recordings of an event for the same patient

There are some cases where a patient may experience the same event (AE/SAE) more than once. In such cases, the event will be counted only once for the calculation of the total number of events reported for the overall safety cohort.

Presentation of results

The results will be presented through tables and figures. A summary of the results will also accompany the main report. First, a short synopsis of the results will be presented through bullets, where only the most important findings will be shown. Following that, a more detailed description of the results will be provided, sectioned in the following order:

- Patient accrual and baseline characteristics
- Follow-up and Treatment administration

- Efficacy analysis
- Safety analysis

All tables and figures will be included in an appendix.