ETOP/IFCT 4-12 STIMULI

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

STIMULI: Small cell lung carcinoma Trial with nivolumab and Ipili-MUmab in LImited disease

Sponsor: European Thoracic Oncology Platform (ETOP)

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In collaboration with Bristol-Myers Squibb

Protocol Amendment 1 Signature Page

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

ETOP/IFCT 4-12 STIMULI

Approved by:

Solange Peters
Trial Chair

22/9/15
Date

Dirk De Ruysscher
Trial Chair

Sept. 18, 2015
Date

Rolf Stahel
ETOP Chairman

2/9/15
Date

Protocol Signature Page

A randomised open-label phase II trial of consolidation ipilimumab in limited-stage SCLC after chemo-radiotherapy

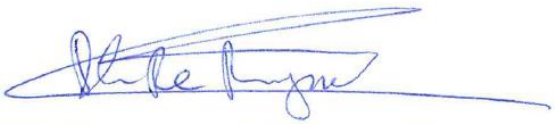
ETOP/IFCT 4-12 STIMULI

Approved by:

Solange Peters
Trial Co-Chair

12.12.13
Date

Dirk De Ruysscher
Trial Co-Chair



18.12.2013
Date

Rolf Stahel
ETOP Chairman

4.12.13
Date

Principal Investigator Protocol Amendment 1 Signature Page

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

ETOP/IFCT 4-12 STIMULI

I have read the amended 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 GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience 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 drug and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator:_____

Institution’s name and place:_____

_____ _____

Signature Date

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ETOP/IFCT 4-12 STIMULI

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

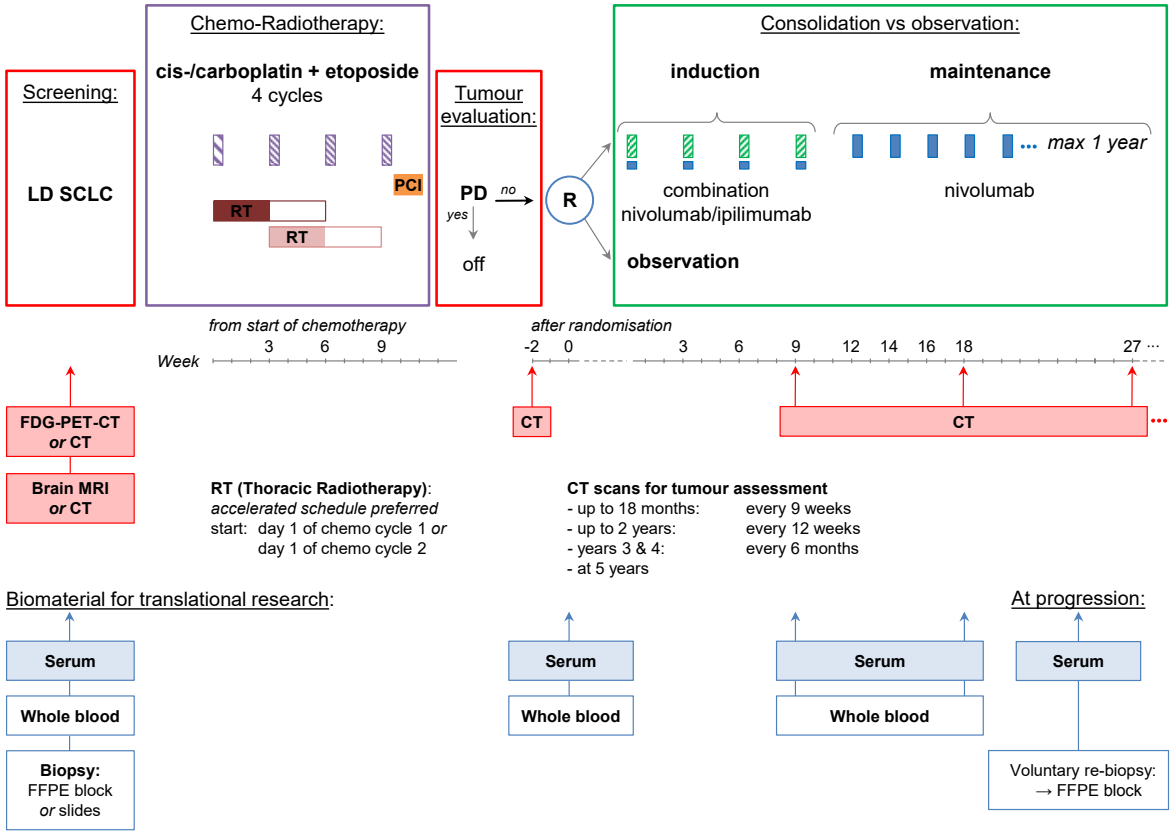
Small cell lung carcinoma Trial with nivolumab and IpiliMUmab in LImited disease

Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: Bristol-Myers Squibb

Population: Radically treated limited-stage SCLC following completion of thoracic radiotherapy concomitant to chemotherapy and PCI

Design: Open-label, randomised, two-arm, phase II international multi-centre clinical trial with early interim analysis for safety



Sample size: 260 randomised under the amendment 1, approximately 325 enroled in chemo-radiotherapy part.

Randomisation: stratified by twice-daily vs once-daily radiotherapy and PET-CT done vs not done.

Rationale:

At the time of diagnosis, 30% of patients with small cell lung carcinoma (SCLC) will have limited stage disease, now called stage I-IIIB (IASLC). The outcome of limited disease SCLC is still poor, with a median survival of 16 to 24 months with current forms of treatment and only 15-25% long term survivors.

Combining chemotherapy and thoracic radiotherapy is the standard treatment approach in limited-stage SCLC with a combination of platinum compounds (cis- or carboplatin) and etoposide as the backbone regimen. Concurrent chemo-radiotherapy is superior to sequential treatment and early thoracic irradiation starting with first or second cycle of chemotherapy appears beneficial. Hyperfractionated accelerated radiotherapy has been shown to be more efficacious than radiotherapy given in a long overall treatment time. However, availability and routine-use of hyperfractionated radiotherapy remains a matter of debate. Therefore, in this trial, both radiotherapy schedules of accelerated twice-daily administration or once-daily radiotherapy are accepted. The choice of schedule is a stratification factor for randomisation.

Several studies in patients with NSCLC suggested an association of increased tumour infiltration of immune cells with improved survival. In recent years, a continuously improved identification of antigenic targets, the addition of immunoadjuvants, and the production of more efficient delivery systems have resulted in more efficient vaccines, able to elicit a potent immune response, leading to the development of immunotherapy as a fundamentally new treatment of NSCLC.

The adaptive immune response is triggered via effector T-cells, antigen-presenting cells (APCs) and co-stimulatory signals mediated by T-cell receptors such as CD28. The interplay of these signals results in the activation and clonal proliferation of T-cells.

T-cell proliferation is tightly regulated in order to avoid autoimmunity. The balance between co-stimulatory signals mediated by CD28 and co-inhibitory signals via so called immune checkpoint receptors is crucial for the maintenance of self-tolerance and to protect tissues from damage during normal immune response. After activation, T-cells express the immune checkpoint receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1).

CTLA-4- and PD-1 expressing T-cells play a critical role in maintaining self-tolerance but are also responsible for non-responsiveness to tumour antigens. Cancer cells escape from immune surveillance by expressing immune checkpoint receptors. The goal of immune checkpoint inhibitor therapies is not to activate the immune system to attack particular targets on tumour cells, but rather to remove inhibitory pathways that block effective antitumour T-cell responses.

Ipilimumab is a monoclonal antibody that binds to CTLA-4 and inhibits the interactions with the ligands B7.1 and B7.2,

Nivolumab is a monoclonal antibody that targets PD-1. Engagement of PD-1 by its natural ligands, PD-L1 and PD-L2, results in an inhibition of T-cell proliferation, survival and cytokine secretion. Nivolumab abrogates this interaction between PD-1 and its ligands.

The two antibodies, nivolumab and ipilimumab, do not only target different immune cell receptors, they also regulate distinct inhibitory pathways and have therefore non-overlapping mechanisms of action. Anti-CTLA-4 therapies seem to drive T-cells into tumours, resulting in an increased number of intratumour T-cells and a concomitant increase in IFN-γ. This in turn can induce the expression of PD-L1 in the tumour microenvironment, with subsequent inhibition of antitumour T-cell responses, but may also increase the chance of benefit from anti-PD-1 and anti-PD-L1 therapies. A combination treatment with anti-CTLA-4 (e.g. ipilimumab) plus anti-PD-1 (e.g. nivolumab) or anti-PD-L1 antibodies should enable the creation of an immunogenic tumour microenvironment with subsequent clinical benefit for patients.

Nivolumab monotherapy has been approved for the treatment of advanced melanoma (FDA, EMA, and Japan) and previously treated squamous NSCLC (FDA, positive CHMP opinion). Nivolumab and ipilimumab improved PFS compared to nivolumab or ipilimumab alone in a study in melanoma (CA209067).

In a randomised open-label phase I/II trial (CheckMate 032), evaluating nivolumab with or without ipilimumab in pretreated SCLC patients with progressive disease and sensitive or refractory to platinum based chemotherapy, based on an interim analysis a response rate of 33% and disease stabilisation in 22% was observed for the combination of nivolumab and ipilimumab compared to 18% response rate and 20% stable disease with nivolumab monotherapy.

Both, nivolumab monotherapy and nivolumab plus ipilimumab combination treatment were tolerable for the treatment of SCLC, and no new safety profile was identified compared to the profile of nivolumab with or without ipilimumab in other anti-cancer therapies.

Nivolumab plus ipilimumab will be administered as a consolidation treatment after completion of a standard treatment including chemo-radiotherapy and prophylactic cranial irradiation (PCI).

Objectives and endpoints:

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

Co-primary endpoints:

- Overall survival
- Progression-free survival determined by RECIST 1.1

Secondary endpoints:

- Objective response determined by RECIST 1.1
- Time to treatment failure
- Adverse events graded according to CTCAE V4.0

Most important eligibility criteria (see protocol section 7 for complete list)**:**

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 haematological, renal, hepatic and lung 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 (more than 2 months) systemic immunosuppressive treatment (e.g steroids) such as ulcerative colitis and Crohn´s disease, rheumathoid 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 are excluded.
- 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 randomisation:

- 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

Treatment arms:

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 randomisation

- 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 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

Statistical considerations:

Hyperfractionated accelerated radiotherapy has been shown to be more efficacious than radiotherapy given in a long overall treatment time. By giving twice-daily fractionation (BID), late reacting normal tissues are spared compared to the tumour, with as a consequence more temporarily acute oesophagitis.

The value of twice daily (BID) radiotherapy given early and concurrently to chemotherapy was examined in landmark trials and in a meta-analysis which will be our benchmark data. After a median follow-up of over 8 years, 2-year overall survival (OS) for BID and QD radiotherapy, respectively, were 47% and 41%. Assuming that half of included patients will receive BID and QD respectively, the median OS is therefore expected to be 20.7 months in the observation. Median progression-free survival (PFS) is expected to be 13.1 months.

PFS and OS will be evaluated as co-primary endpoints. Hazard ratios of 0.70 for OS and 0.57 for PFS are to be detected with adequate power. The overall one-sided significance level of 0.05 for the logrank test is divided into 0.04 for OS and 0.01 for PFS.

A trial duration of 7.5 years from enrolment of the first patient is necessary for the required 212 deaths to be observed. The main analysis of PFS will be performed when 148 PFS events have occurred, which is expected at approximately 45 months. The achieved power is 78%

for OS at the end of the study, and 80% for PFS at 45 months. A total number of 260 patients is required to be randomised.

It is expected that after the chemo-radiotherapy phase, about 20% of treated patients will have progressed or will not receive PCI and can therefore not be randomised. Thus, approximately 325 patients will be enroled in order to randomise 260 patients under amendment 1, at an estimated accrual time of 3 years.

Total trial duration: 7.5 years from enrolment of the first patient

Translational research:

Serum levels of TNF α/β, IL6 and circulating antibodies will be determined centrally in every patient at enrolment, at the time of randomisation, 9 and 18 weeks after randomisation and at the time of progression.

A biobank will be created with centralised samples for translational research.

Whole blood, PBMCs (in selected centres) and diagnostic FFPE blocks will be collected from patients consenting to translational research. If no blocks can be submitted, 5-10 sections with a minimum thickness of 15-20µm from the tumour block or cell block can be submitted instead, and, when feasible, also 5 freshly cut sections at 4-5 µm thickness. Immune-related gene expression profile and deep sequencing will be considered in peripheral blood and tumours, and immunohistochemistry will allow characterising tumour microenvironment. Immunomonitoring with blood cell subtyping and quantification, including FACS analysis, will be performed on PBMCs (selected centres only).

Progressing patients will be asked for a voluntary biopsy.

Pre-chemo-radiotherapy FDG-PET to assess background FDG avidity in the tumour, the hilar and mediastinal lymph nodes (if involved at staging) and the lungs will be optional.

2. Trial schedule

	Screening[1]	Enrolment	Chemo-radiotherapy[2]	Before randomisation[3]	Consolidation treatment[4]		PD	End of Treatment visit	Follow-up[8]	
					Induction[5,7]	Maintenance[6,7]			Before PD	After PD
Written informed consent before any trial specific evaluations and intervention										
Medical history										
FFPE tumour material	**optional**						**optional** (encouraged) re-biopsy			
Serum samples for translational research TNF α/β, IL6, circulating antibodies					9 weeks after randomisation	18 weeks after randomisation				
Whole blood for translational research: RNA profiling (all sites), PBMCs (selected sites)		**optional**		**optional**	**optional** 9 weeks after randomisation	**optional** 18 weeks after randomisation				
Physical exam: PS / blood pressure / body weight / height			**every cycle**		**every cycle**	**every cycle**				
Pulmonary function: FEV1 / DL_{CO}										
HIV / Hepatitis B/C										
Haematology[9]			**every cycle** only haemoglobin, platelets, neutrophils		**every cycle**	**every cycle**				
Renal function: serum creatinine, calculated creatinine clearance			**every cycle**		**every cycle**	**every cycle**				
Hepatic function: ALT, AST, AP, bilirubin			only AST & bilirubin		**every cycle**	**every cycle**				
Na, K					**every cycle**	**every cycle**				
TSH, with reflex free T3/4[10]					**1st and 3rd cycle**	**at 1st cycle, then every 3 cycles**				

	Screening[1]	Enrolment	Chemo-radiotherapy[2]	Before randomisation[3]	Consolidation treatment[4]		PD	End of Treatment visit	Follow-up[8]	
					Induction[5,7]	Maintenance[6,7]			Before PD	After PD
Ca, LDH, glucose, amylase, lipase[10]					**every cycle**	**every 3 cycles**				
Pregnancy test [11]**:**					**every 6 weeks**	**every 6 weeks**				
Tumour assessments before randomisation[12]										
Tumour assessments after randomisation[13]										
Adverse events[14]										
Concomitant medications										
Cis- or carboplatin + etoposide										
Radiotherapy[15]										
Prophylatic cranial irradiation			**cycle 4**							
Nivolumab plus ipilimumab										
Nivolumab										
Second-line therapy and survival										

Mandatory evaluation / intervention

1 ⩽ 28 days prior enrolment; if the first chemotherapy cycle has been administered before enrolment, baseline evaluations must have been done within 35 days before start of first chemotherapy cycle.

2 **Chemotherapy** consists of platinum compound (cis- or carboplatin) and etoposide combination and is given for 4 cycles (1 cycle = 21 days). Chemotherapy should start within 7 days after enrolment. If the start of chemotherapy cannot be delayed, a maximum of 1 chemotherapy cycle can be administered before enrolment.

3 R**andomisation** should take place 5 - 6 weeks from day 1 of chemotherapy cycle 4 (between days 35 and 42 of cycle 4). All examinations have to be done within 7 days prior randomisation (except for tumour assessment, which has to be done within 14 days before randomisation).

4 **Consolidation treatment** should start 6-8 weeks (42-56 day) from start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation.

5 **Induction phase**: nivolumab (1 mg/kg i.v. over a period of 30 minutes) followed (on the same day) by ipilimumab (3 mg/kg i.v. over a period of 90 minutes), once every 3 weeks (+/- 3 days, without dosing delay), for 4 cycles.

6 **Maintenance phase**: nivolumab (240 mg i.v. over a period of 30 minutes), once every 2 weeks (+/- 2 days, without dosing delay) until PD, for a maximum of 1 year from start of maintenance phase. The first dose of maintenance nivolumab will be administered 3 weeks after the last IMP doses of induction phase.

7 **Observation arm**: patients should be documented 9 and 18 weeks (+/- 3 days) after randomisation and thereafter every 18 weeks (+/- 1 week), according to local standard of follow-up, until PD or for maximum15 months after randomisation. The following laboratory values are to be measured: haematology, renal function, hepatic function, Na and K. Beyond 15 months after randomisation or upon PD patients will enter the follow-up phase.

CT scans for tumour assessment are done at the same schedule as for patient in the experimental arm (see footnote 13).

8 **Follow-up:**

Before PD: Patients who completed consolidation treatment (in the observation arm this corresponds to 15 months after randomisation) or discontinue IMP treatment before tumour progression should have physical examination at regular intervals (blood pressure, performance status and weight). In the first 18 months after randomisation this has to be done together with the CT scans according to the schedule indicated in footnote 13, then every 12 (+/- 1) weeks until PD for a maximum of 4.5 years after the enrolment of the last patient.

After PD: Patients with tumour progression will end trial treatment and should have documented survival, and further lines of treatment every 12 weeks (+/-1 week) starting from date of progression during the first year after randomisation, then every 6 months (+/- 4 weeks) up to 4.5 years after the enrolment of the last patient.

9 **Haematology**: haemoglobin, platelets, complete white blood cell count [leucocytes, neutrophils, eosinophils, basophils (or total granulocytes), lymphocytes, monocytes]

10 **Only patients in experimental arm**. In case of abnormal TSH value, also free T3 and T4 has to be measured.

11 **Pregnancy test:** Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before beginning of chemotherapy. The test has to be repeated within 7 days before randomization and then every 6 weeks during consolidation treatment. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after consolidation treatment stop.

12 **Tumour assessments before randomisation**

At baseline: brain MRI (or contrast enhanced CT of the brain), *AND* whole body FDG-PET CT including a contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals). If FDG-PET CT is not available, contrast enhanced CT of the thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan is required for tumour assessment at baseline.

Within 14 days prior to randomisation: contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals)

13 **Tumour assessments after randomisation**

For both treatment arms, CT of thorax and upper abdomen (incl. liver, kidney, adrenals) have to be done as indicated below:

- up to 18 months:	every 9 weeks	weeks after randomisation:	9, 18, 27, 36, 45, 54, 63, 72, 81 (+/- 1 week)
- up to 2 years:	every 12 weeks	"	93, 105 (+/- 1 week)
- years 3 and 4:	every 6 months (26 weeks)	"	131, 157, 183, 209 (+/- 1 week)
- at 5 years:		"	260 (+/- 1 week)

In case of clinical suspicion of distant metastases, immediate adequate diagnostic procedures including CT-scan, whole body PET-CT, bone scans and MRI (as appropriate) should be used.

Early progression at 9 weeks: Patients with tumour volume increase documented by CT scan 9 weeks after randomisation, but without appearance of new lesions or rapid clinical deterioration should continue to be treated with IMP and clinically observed with a stringent imaging schedule 4 weeks later to determine whether there has been a decrease in the tumour size or disease stabilisation, or alternatively continued PD which would terminate the trial treatment.

Patients who discontinue study treatment for reasons other than progressive disease: Restaging should be repeated at time of discontinuation, except if already performed within 6 weeks prior to the last dose of study treatment.

14 **Adverse events:** All adverse events that occur within 100 days of the last administered study medication or within 100 days after the last visit in the observation arm must be documented. Symptoms present at baseline and at randomisation will be recorded on the adverse event forms as well.

15 **Thoracic radiation** will be administered concurrently to chemotherapy and should preferentially start at the same time as the first chemotherapy cycle (e.g. day 1 of cycle 1), if the patient can be enroled before chemotherapy start. Otherwise, radiotherapy should optimally start at day 1 of cycle 2, i.e. in treatment week 4. As a latest start of radiotherapy day 1 of cycle 3 is allowed, but should be exceptional.

3. List of abbreviations

AE	Adverse Event
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
APC	Antigen presenting cell
AST	Aspartate transaminase
AUC	Area Under the Curve
BID	Bis In Die (lat.), twice-daily
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BORR	Best Overall Response Rate
CNS	Central Nervous System
CR	Complete response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
CTV	Clinical Target Volume
DL_{CO}	Diffusing Capacity for Carbon Monoxide
DVH	Dose Volume Histogramm
EC	Ethics Committee
ECL	Electrochemiluminescent
eCRF	Electronic Case Report Form
ED	Extensive Stage Disease
EGFR	epidermal growth factor receptor
EP	Etoposide - Cisplatinum
ERB	Ethical Review Board
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed, Paraffin Embedded
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GTV	Gross Tumour Volume
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	Informed Consent
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
IMRT	Intensity Modulated Radiotherapy

INR	International Normalised Ratio
IMP	Investigational Medicinal Product
irAE	Immune-related Adverse Events
irBORR	Best Overall Response Rate by irRC
irPFS	Immune-related Progression Free Survival
irRC	Immune-related Response Criteria
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Hb	Hemoglobin
LD	Limited Stage Disease
LF	Lost to Follow-up
LFT	Liver Function Test
LLN	Lower Limit of Normal Lab Value
LS	Limited Stage
MIP	Maximum Intensity Projection
MLD	Mean Lung Dose
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NCCN	National Comprehensive Cancer Network
NSCC	Nonsquamous-Cell Carcinoma
NSCLC	Non-Small Cell Lung Carcinoma
OAR	Organs at Risk
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell
PCI	Prophylactic Cranial Irradiation
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Ligand 1
PE	Cisplatin/Etoposide
PFS	Progression Free Survival
PK	Pharmacokinetics
PPK	Population Pharmacokinetic
PR	Partial Response
PS	Performance Status
QD	Quaque Die, once daily
PTV	Planning Target Volume
RDE	Remote Data Entry
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy

SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SCC	Squamous-Cell Carcinoma
SCLC	Small cell lung carcinoma
SD	Stable Disease
SER	Start of any Treatment to the End of Radiotherapy
SIAD	Syndrome of Inappropriate Diuresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standard uptake volume
TIL	Tumour Infiltrating Lymphocyte
Treg	Regulatory T-cells ($CD4^+CD25^+$)
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal lab value
VALG	Veterans Administration Lung Study Group
VEGF	Vascular endothelial growth factor
WBRT	Whole Brain Radiotherapy
WC	Withdrawal of Consent

4. Background and rationale

4.1. Disease background

Lung cancer accounts for 12% of all incident cases of cancer. 13% of these lung cancer cases are small cell lung carcinoma (SCLC) [1]. Over 90% of SCLC patients are current or past smokers, although some very exceptional cases have been described in never-smokers [2, 3]. The median age at diagnosis exceeds 70 years and most patients have at least one cardiovascular, respiratory, or metabolic co-morbidity [4]. The incidence of SCLC has been decreasing over the past 30 years in developed countries, most probably related to changes in smoking pattern [5].

SCLC is defined as "a malignant epithelial tumour consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli" [6]. There are two categories: more than 90% is 'typical', the others being 'combined' when at least 10% large cells are admixed.

Cytogenetic analysis of SCLC has identified several abnormalities in DNA copy number. Several important genetic and molecular changes have been described, including the identification of autocrine growth loops, proto-oncogene activation, and loss or inactivation of tumour-suppressor genes [7]. One of the most frequent genetic alterations in SCLC is the deletion of the chromosome region 3p(14-23) occurring in virtually all SCLCs. This region of deletion includes the tumour suppressor gene FHIT. The mutational pattern evident in SCLC is distinct from that in NSCLC with a near universal loss of the tumour suppressor retinoblastoma gene RB1 and more frequent mutation of TP53. Tyrosine kinase signalling genes including K-RAS and EGFR are rarely mutated.

The typical SCLC patient is a 70 year old male heavy (ex-)smoker with pulmonary and cardiovascular comorbidity, presenting with rapid onset symptoms due to either local tumour growth (cough, wheezing, dyspnoea, haemoptysis), invasion in either chest wall, superior vena cava, oesophagus or recurrent nerve, distant spread (pain, fatigue, anorexia, neurological complaints) or a paraneoplastic syndrome [8, 9]. The duration of symptoms is short, being approximately 8–12 weeks prior to presentation. Preferential metastatic sites of dissemination are the brain, liver, adrenal glands, bone and bone marrow. SCLC is the most frequent cause of paraneoplastic syndromes, most commonly the syndrome of inappropriate diuresis (SIAD) and Cushing syndrome.

In 1957, the Veterans Administration Lung Study Group (VALG) adopted a dichotomized staging classification [10]. Limited stage (LS) was defined as a tumour volume encompassable in a single radiation portal. All other disease spread was classified as extensive stage. Of course, this definition dates from before the CT-era, contemporary staging and radiotherapy techniques. The International Association for the Study of Lung Cancer recommends staging of SCLC according to the 7th edition of the TNM-classification of lung cancer [11]. This recommendation is based on a retrospective analysis of data from 8000 SCLC patients, showing that survival of LS-patients with mediastinal lymph node involvement (stage III) significantly differs from those without (stage I) or with N1-lymph node involvement (stage II) [12]. Patients with pleural effusion have an intermediate prognosis between stage III and those with

haematogenous spread (stage IV). The implication of this recommendation is that patients with cytologically negative effusions are now classified as having stage III. Although its simplicity makes the VALG-classification attractive for use in routine clinical practice, clinicians and cancer registrars are nevertheless strongly encouraged to use the TNM-classification. Moreover, it should be emphasised that the definition of "limited stage" also differs significantly between clinical studies, and that most series did not use the strict VALG-classification.

4.2. Treatment of stage I-III SCLC

Because SCLC is a systemic disease, chemotherapy is and remains the backbone of the treatment. Adequate local therapy nevertheless improves long-term survival significantly when delivered together with systemic treatment. Importantly, the COCIS meta-analysis [13] of individual patient data showed that carboplatin-based regimens appear to be equally effective in terms of OS, PFS, and ORR compared with cisplatin-based combinations for the first-line therapy of SCLC, differing only in their toxicity profiles. Carboplatin-based regimens were associated with more cases of Grade 3 to 4 haematologic toxicities. Cisplatin-based therapies were associated with more nonhaematologic toxicities of any grade. No evidence of significant differences in OS between cisplatin and carboplatin according to sex, stage, performance status, or age were apparent. Despite the fact that only a small group of patients had limited disease in the trials considered in COCIS, and that probably no definite conclusions can be drawn in this subgroup of patients with a rather poor prognostic profile, carboplatin is widely accepted as an option in extensive and limited disease SCLC, as evidenced for example in the NCCN guidelines (www.nccn.org).

4.2.1. Resection

Immediate surgery may be considered in the rare biopsy-proven T1N0M0 tumours, but only after thorough mediastinal staging confirming node negativity before proceeding with resection. Most patients with resected SCLC presented with a solitary pulmonary nodule without pathological diagnosis and thus had small volume disease. Adjuvant chemotherapy is recommended and is followed by prophylactic cranial irradiation (PCI) in most of the retrospective series, with 5-year survival rates up to 57% [14]. The role of post-induction surgery has never been fully developed because the overwhelming majority of patients with non-metastatic SCLC present with irresectable stage III.

4.2.2. Chest radiotherapy

A meta-analysis from individual patient data provided evidence that the addition of chest radiotherapy to chemotherapy improved survival [15]. An improvement of 5.4% in the absolute survival at three years was observed in favour of groups having received chest irradiation. The 5-year survival rate remained disappointingly low at 10-15%. The question which chemotherapy should be combined with chest radiotherapy was investigated in randomised trials. Etoposide-cisplatinum (EP) was compared to a combination of cyclophosphamide, etoposide and vincristine [16]. Among stage I-III patients, a significant superior survival was observed with EP. In a small randomised study, the substitution of cisplatin by carboplatin – both in combination with etoposide and chest radiotherapy – resulted in the same survival [17]. As in

stage IV SCLC, several drugs have been added to EP or new regimens explored, including irinotecan, without improving the outcome [18-22].

Data on the optimal radiation dose and fractionation comes mostly from retrospective and phase II prospective studies. In patients receiving either sequential chemo-radiation or alternating schedules, in non-randomised studies, a major improvement in local control may be achieved when the dose was increased from 35 to 40 Gy, with possibly a modest further gain with an escalation to 50 Gy [23]. However, it is unclear whether also in the setting of concurrent chemo- and radiotherapy, radiation dose escalation above 45-50 Gy is beneficial. The current standard of a dose of 45 Gy in 30 twice-daily fractions of 1.5 Gy, delivered concurrently with chest radiotherapy [24, 25] is at present being compared to higher doses in two on-going phase III trials in the US and Europe (CONVERT).

The definition of the target volumes for radiotherapy is important, for decreasing the volume of the organs at risk (OAR) which are irradiated will also reduce the side-effects. In a prospective study in stage I-III SCLC in which only CT-positive mediastinal lymph nodes were included in the target volume, a higher than expected isolated recurrence rate of 11% was observed [26]. Irradiation of only FDG-PET positive nodes was tested in a phase II study [27]. Only 3% isolated nodal failures were observed, with intriguingly only 13% of Grade 3 esophagitis, which compares favourably with the expected 30%. These results were subsequently confirmed in a retrospective series from MD Anderson [28].

Many phase III trials have investigated the optimal timing of chest radiation (reviewed in [29]). At 5 years, the survival was significantly higher when chest radiotherapy was given early, i.e. within 30 days after the initiation of platinum-based chemotherapy, representing a 5-year survival rate of 20% for early versus 14% for late thoracic radiotherapy. In a pivotal phase III trial [30], decreasing the overall treatment time of chest radiotherapy from 5 weeks (2 Gy once-daily) to 3 weeks (1.5 Gy twice-daily), whilst keeping the total radiation dose to 45 Gy, increased the 5-year survival from 16 to 26%. In both arms of the trial, chest radiotherapy was delivered concurrently with cisplatin and etoposide chemotherapy. Early concurrent chemotherapy with accelerated radiation resulted in approximately 30% Grade 3 acute esophagitis, which contrasts with about 15% in early concurrent non-accelerated radiotherapy and approximately 5% in sequential schedules. In this trial, elective mediastinal radiotherapy was used. It should be stressed that lung toxicity was not different according to the timing of radiotherapy. Because a time-interaction between chest radiation and chemotherapy was suspected, it was hypothesised that accelerated repopulation was triggered by the first dose of any effective cytotoxic agent and that in order to obtain local tumour control, the last tumour clonogen should be killed by the end of radiotherapy. It follows from these two assumptions that the long-term survival should decrease with increasing time between the Start of any treatment to the End of Radiotherapy (SER). A meta-analysis of published data, which was subsequently updated, showed superior long-term survival if the SER was kept below 30 days [31, 32]. These results are consistent with the hypothesis that there is accelerated proliferation of tumour clonogens triggered by radiotherapy and/or chemotherapy.

In conclusion, for stage I-III SCLC, current evidence supports early administration of 45 Gy with concurrent EP at systemic doses. If for reasons of fitness or availability, this scheme cannot be offered, chest radiotherapy should follow induction chemotherapy.

4.2.3. Prophylactic Cranial Irradiation (PCI)

As whole brain radiotherapy (WBRT) for symptomatic brain metastases for patients with SCLC yields a response rate of 50% and a median survival of 4-5 months [33], several phase III studies have been undertaken to investigate the effect of PCI on brain recurrence and survival in patients with stage I-III SCLC. In a meta-analysis based on individual patient data, it was shown that the addition of PCI resulted in a significant increase in the 3-year survival rate (15% without PCI versus 21% with PCI) [34]. PCI also increased the disease-free survival and reduced the cumulative incidence of brain metastases. There was a trend toward a greater effect in patients with shorter time intervals between induction therapy and PCI, suggestive of a benefit of early versus late administration of PCI. In this meta-analysis, only patients with a complete remission on a chest X-ray were included. Because at the present time, combined chemotherapy and radiotherapy has become standard treatment and therefore radiological assessment of response is notoriously inaccurate for post-radiation changes cannot be distinguished from active tumour. In currently ongoing phase III trials, patients without progressive disease are therefore being offered PCI. From this meta-analysis, a PCI dose and fractionation of 25 Gy delivered in 10 once-daily fractions became standard. In a large phase III trial, patients with stage I-III SCLC in complete remission on the basis of chest X-rays after induction chemotherapy were randomised to either this standard or a higher PCI-dose (36 Gy) [35]. No beneficial effect on survival of the higher dose was observed, but neurotoxicity was increased [36]. Based on these results, the current recommendation of 25 Gy in ten 2.5 Gy fractions remains the standard of care of PCI.

In summary, PCI should be planned for all SCLC patients not-progressing after induction therapy. However, it should be used with caution in patients with significant medical comorbidities, poor performance status, or impaired neurocognitive function.

4.3. Targeted agents in small cell lung carcinoma

Many targeted therapies have been evaluated in the treatment of SCLC, but, in contrast to advanced-stage NSCLC, none of these have been successful (reviewed in [37]). Small molecule inhibitors of different receptor tyrosine kinases (EGFR, c-kit, VEGFR) were studied in phase II trials with or without chemotherapy but did not show significant activity. Two large randomised phase III trials failed to show a significant benefit of adding thalidomide to standard chemotherapy. Adding two different matrix metalloproteinase inhibitors to standard chemotherapy demonstrated no improved survival, and even decreased quality of life. Vaccine therapy targeted against the ganglioside family of antigens on the SCLC surface has failed to show any benefit.

4.4. Immunotherapy

Several studies in patients with NSCLC suggested an association of increased immune cell infiltration into tumours with improved survival. In recent years, improved identification of

antigenic targets, the addition of immunoadjuvants, and the production of more efficient delivery systems have resulted in more efficient vaccines, able to elicit a potent immune response, leading to the development of immunotherapy for the treatment of NSCLC [38]. Different vaccines are in late-stage development in different NSCLC treatment settings. For early-stage NSCLC, the MAGE-A3 vaccine is in phase III testing and results from the completed trial are awaited. For locally advanced stage, the L-BLP25 vaccine has been tested as a consolidation treatment after chemo- radiotherapy in stage III. Butts and colleagues have reported at ASCO 2013 the absence of a survival benefit related to vaccination in the whole population, but identified a potential survival benefit in the subgroup of patients having benefitted of a concomitant strategy of chemo-radiotherapy (as compared to sequential), deserving a confirmatory trial. For advanced NSCLC, several compounds are currently investigated in randomised controlled trials: belagenpumatucel-L, the EGF vaccine, and the TG4010 vaccine [39, 40].

4.5. Immune checkpoint receptors

The adaptive immune response requires two signals between the antigen-presenting cells (APCs) and the effector T-cells. The first signal is mediated by the T-cell receptor and the major histocompatibility complex classes I or II antigenic peptide. The second signal is a co-stimulatory signal mediated by CD28 on the T-cell surface through binding of the B7 family members on APCs. Both signals result in the activation and clonal proliferation of T-cells.

In order to avoid autoimmunity, T-cell proliferation is tightly regulated. The balance between co-stimulatory signals mediated by CD28 and co-inhibitory signals via so called immune checkpoint receptors is crucial for the maintenance of self-tolerance and to protect tissues from damage during normal immune response. After activation, T-cells express cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1, cluster of differentiation 279 [CD279]), both so called immune checkpoint receptors.

CTLA-4 binds members of the B7 family with a much higher affinity than CD28 and down-regulates the T-cell response. It has been shown in pre-clinical models that one reason for the poor immunogenicity of many tumours such as lung cancer is CTLA-4 activity and that *in vivo* administration of antibodies to CTLA-4 can enhance antitumour immunity [41].

CD4+CD25+ regulatory T-cells (Treg) that express FOXP3 represent a group of T lymphocytes that is essential for maintaining self-tolerance [42]. The transcription factor FOXP3 represses IL2 transcription and up-regulates expression of CTLA-4. FOXP3+CD25+CD4+ Treg cells constitutively express cell surface CTLA-4. CTLA4 thus maintains the immune system homeostasis by functioning as a major feedback inhibitor of T-cell activation.

PD-1 is another immune checkpoint receptor expressed on activated T-cells. Its physiological role is to dampen the immune response in order to protect against excessive inflammation and development of autoimmunity. PD-1 is expressed in response to inflammation and is found in many tumours. Compared with CTLA-4, PD-1 modulates a later stage of the immune response. Instead of affecting the initial stage of T-cell activation (priming) in the regional lymph node, PD-1 regulates the activation of T-cells in peripheral tissues. Like CTLA-4, PD-1 can be found on Treg lymphocytes and also on B lymphocytes and natural killer cells. PD-

1 binds to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed on antigen presenting cells but more importanly, also on cancer cells.

While CTLA-4- and PD-1 expressing Tregs may play a critical role in maintaining self-tolerance, they also play a role in non-responsiveness to tumour antigens.

It is a recognised feature of cancer cells to escape immune surveillance by expressing ligands binding to immune checkpoint receptors and the development of therapies to enhance immunogenic activity towards tumours is a rational treatment strategy. The goal of checkpoint inhibitor therapies is not to activate the immune system to attack particular targets on tumour cells, but rather to remove inhibitory pathways that block effective antitumour T-cell responses.

Tregs have been shown to be present in tumours and coexist with primed effector T-cells. Blockade of Tregs function *via* anti-CTLA-4 and anti-PD-1 has the potential to remove Tregs suppression and enhance antitumour immunogenicity [43, 44].

The abscopal effect, a systemic antitumour response, describes an immune-mediated phenomenon where localised irradiation causes tumour response not only in the treated tumour but also in tumours outside the radiation therapy field. Local radiotherapy causes the tumour-cell to undergo apoptosis or necrosis and to subsequently release tumour antigens. But especially in poorly immunogenic cancer this radiation alone is not sufficient to trigger antigenic signals, and a second co-stimulatory signal is required to elicit systemic antitumour immune responses [45]. The combination of radiotherapy with immune modulators such as checkpoint inhibitors may have the capability to escalate antitumour responses to a level that could suppress or eliminate systemic metastasis [46-53].

4.6. Immune checkpoint inhibitors

4.6.1. Ipilimumab

Ipilimumab is a fully human monoclonal anti-CTLA-4-antibody. It has already been approved by the US Food and Drug Administration for the treatment of metastatic melanoma. Ipilimumab showed promising results in a first-line NSCLC phase II study combining carboplatin/paclitaxel chemotherapy with ipilimumab [54]. In that randomised, double-blind phase II trial, 204 chemotherapy-naive non-small-cell lung carcinoma patients were randomly assigned to receive paclitaxel and carboplatin with either placebo (control) or ipilimumab in one of the following two regimens: concurrent ipilimumab (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin) or phased ipilimumab (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin). Phased ipilimumab, concurrent ipilimumab, and control treatments were associated with a median immune-related progression-free survival (irPFS) of 5.7, 5.5, and 4.6 months, respectively, a median PFS of 5.1, 4.1, and 4.2 months, respectively, and a median OS of 12.2, 9.7, and 8.3 months. Overall rates of Grade 3 and 4 immune-related adverse-events (AEs) were 15%, 20%, and 6% for phased ipilimumab, concurrent ipilimumab, and the control, respectively. Two patients (concurrent,

one patient; control, one patient) died from treatment-related toxicity. The study met its primary end point of improved irPFS for phased ipilimumab versus the control (hazard ratio [HR], 0.72; P = 0.05), but not for concurrent ipilimumab (HR, 0.81; P = 0.13).

The results are in accordance with preclinical work, showing the best results for immune therapy by adding this in patients where immunogenic cell death have been induced with massive release of tumour associated antigens by certain drugs and – very consistently over several tumour models – by radiotherapy.

In patients with stage IV SCLC, 130 patients were enroled in the randomised phase II study comparing concurrent or phased ipilimumab plus paclitaxel and carboplatin [55]. Phased ipilimumab plus chemotherapy appeared to show improved efficacy as shown by an improvement in irPFS (6.4 vs. 5.3 months, p = 0.03), a numerically higher irBORR (best overall response rate by irRC) (71% vs. 53%) and a trend for improved overall survival (12.9 vs. 9.9 months, p = 0.13). The concurrent-ipilimumab regimen showed no such activity.

Ipilimumab did not appear to exacerbate toxicities observed with chemotherapy alone and observed toxicities (see Table 1) were generally manageable using protocol-defined treatment guidelines.

Table 1: AEs in a randomised placebo-controlled phase II trial in stage IV SCLC comparing chemotherapy to concurrent or sequential chemotherapy and ipilimumab

Events	Control: Placebo + chemo		Concurrent Ipilimumab + chemo		Phased Ipilimumab + chemo	
	Any grade %	G 3/4 %	Any grade %	G 3/4 %	Any grade %	G 3/4 %
Fatigue	25	5	31	7	29	12
Arthralgia	32	-	24	-	45	10
Alopecia	59	n.a.	57	n.a.	67	n.a.
Rash	2	-	36	5	24	-
Pruritus	5	-	24	-	19	2
Diarrhoea	16	5	26	4	33	10
Nausea	23	2	24	-	29	-
Decreased appetite	9	-	19	2	10	-
Peripheral neuropathy	11	-	14	-	24	-
Peripheral neuropathy, sensory	32	-	24	-	33	-

The results of this study were considered worth to support further investigation of the phased-ipilimumab regimen in previously untreated stage IV SCLC in an ongoing phase III trial.

4.6.2. Nivolumab

Nivolumab (BMS-936558; anti-PD-1) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that targets the cell surface membrane receptor PD-1. The co-inhibitory receptor PD-1, a member of the CD28 superfamily of molecules, has important T-cell regulatory functions. It is inducibly expressed on activated T-cells, B-cells, a subset of myeloid cells and a fraction of T-memory cells, and it has been shown to mediate inhibition of T-cell responses in peripheral tissues and tumours. Engagement of PD-1 by its natural ligands, PD-L1 and PD-L2, results in an inhibition of T-cell proliferation, survival and cytokine secretion [56, 57]. Nivolumab abrogates this interaction between PD-1 and its ligands.

Nivolumab monotherapy has been approved for the treatment of advanced melanoma (FDA, EMA, and Japan) and previously treated squamous NSCLC (FDA, positive CHMP opinion). Nivolumab and ipilimumab improved PFS compared to nivolumab or ipilimumab alone in a study in melanoma (CA209067).

A phase I trial tested nivolumab in 296 patients with advanced solid cancers, including 129 NSCLC patients [58, 59]. Nivolumab was administered intravenously once every 2 weeks at doses of 1, 3 or 10 mg/kg. Patients continued treatment for up to 96 weeks (12 cycles) or until unacceptable toxicity, confirmed complete response, confirmed disease progression, or withdrawal of consent. In the absence of clinical deterioration, patients could continue treatment after initial disease progression to allow for patterns of response consistent with immune-related response criteria. In the NSCLC cohort, with a long term median follow-up of 27.5 months (range, 21 to 54 months), median overall survival (OS) across nivolumab doses was 9.9 months. One- and 2-year OS rates were 42% and 24%, respectively, across doses and 56% and 45%, respectively, at the 3 mg/kg dose (n=37) being used for further clinical development. Among 22 (17%) patients with objective responses, estimated median response duration was 17.0 months. Response rates were similar in squamous and non-squamous NSCLC and in patients who received 3 or more prior therapies. Sixteen responding patients discontinued nivolumab for reasons other than progressive disease and 6 (38%) had responses lasting >30 weeks after their last dose. Grade 3-4 treatment-related adverse events occurred in 14% of patients. Three treatment-related deaths (2% of patients) occurred, each associated with pneumonitis [58].

Recently, the first randomized trials using nivolumab in comparison to standard of care docetaxel in the second line setting have been reported [60, 61].

The first one (checkmate 017) was focusing on squamous histology advanced NSCLC patients. 272 patients were assigned to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks, or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (hazard ratio, 0.59; 95% CI, 0.44 to 0.79; P<0.001). At 1 year, the overall survival rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (P=0.008). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (hazard ratio for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; P<0.001). The expression of the PD-1 ligand (PD-L1) was neither

prognostic nor predictive of benefit. Treatment-related adverse events of Grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group [60].

The second trial, checkmate 057 used the same design in the non-squamous subgroup. Patients in the CheckMate 057 study had progressed after treatment with platinum-based doublet chemotherapy (and, if eligible, a tyrosine kinase inhibitor), a guideline-recommended first-line therapy for nonsquamous NSCLC. They were randomly assigned to subsequent treatment with nivolumab (3 mg/kg every 2 weeks; 292 patients) or docetaxel (75 mg/m2 every 3 weeks; 290 patients); both drugs were continued until progression or discontinuation due to toxicity.

The primary efficacy endpoint of the study was overall survival (OS). Treatment with nivolumab significantly improved median OS, with a hazard ratio for death of 0.73 (95% CI: 0.59, 0.89; P=0.00155) compared with docetaxel. One-year OS was 50.5% with nivolumab versus 39.0% with docetaxel. Other study endpoints included PFS, ORR, and nivolumab efficacy by PD-L1 expression.

Significantly more patients had an objective response (19.2% vs. 12.4%; P=0.0235). At the time of the analysis, the median duration of response to nivolumab was 17.1 months, compared with 5.6 months for docetaxel. No difference between nivolumab and docetaxel was observed in median PFS (2.3 months vs. 4.2 months; P=0.393). PD-L1 expression was associated with improved efficacy for patients treated with nivolumab, an effect most dramatically seen in patients with PD-L1 expression 5% or higher and 10% or higher, but evident at PD-L1 expression levels as low as 1% or higher.

Also of note, subgroup analysis favoured nivolumab over docetaxel in all categories, except patients 75 years of age or older, never smokers, and those positive for EGFR mutations. Treatment-related adverse reactions of grade 3 to 5 severity occurred at a higher rate with docetaxel (53.7%) than with nivolumab (10.5%).

Regarding toxicity, and as a summary, across all clinical trials perfomred to date using anti-PD-1 drug monotherapy and in particular nivolumab, the observed incidence of severe pneumonitis is less than 5% with nivolumab monotherapy. Of note, after thoracic definitive radiotherapy (of 60-70 Gy) with or without chemotherapy, the incidence of severe pneumonitis is approximately 15%. It is unknown if nivolumab influences the incidence of pneumonitis after radiotherapy [61].

4.6.3. Dual blockade of CTLA-4 and PD-1 with ipilimumab and nivolumab

The two monoclonal antibodies nivolumab and ipilimumab bind to different cell receptors in immune cells and target different pathways in the activation of anticancer immune response. CTLA-4 and PD-1/PD-L1 regulate distinct inhibitory pathways and have non-overlapping mechanisms of action. Anti-CTLA-4 therapies seem to drive T-cells into tumours, resulting in an increased number of T-cells and a concomitant increase in IFN-γ. This in turn can induce the expression of PD-L1 in the tumour microenvironment, with subsequent inhibition of anti-tumour T-cell responses, but may also increase the chance of benefit from anti-PD-1 and anti-PD-L1 therapies. A combination treatment with anti-CTLA-4 (e.g. ipilimumab) plus

anti-PD-1 (e.g. nivolumab) or anti-PD-L1 antibodies should enable the creation of an immunogenic tumour microenvironment with subsequent clinical benefit for patients [44, 62, 63].

Preclinical data suggest that combining PD-1 and CTLA-4 blockade may indeed improve antitumour activity over blocking either receptor alone [62, 64, 65].

In tumour models, dual blockade led to tumour rejection in two thirds of mice and was associated with increased proliferation of effector CD8+ and CD4+ T-cells, increased cytokine release, inhibition of suppressive functions of Tregs, and upregulation of key signaling molecules critical for T-cell function, compared with single pathway blockade.

Nivolumab plus ipilimumab in advanced melanoma has shown higher response rates than those seen with monotherapy, with early responses and an encouraging survival profile [63, 65].

The safety and efficacy of the combined CTLA-4 and PD-1 blockage with nivolumab and ipilimumab has been tested in a phase I dose escalation study in patients with advanced melanoma. In this study a high rate of objective response (including complete responses), a prolonged duration of response, and a favourable overall survival rate of 79% at 2 years were observed[63, 65, 66].

In a second, randomised, double-blind trial comparing nivolumab in combination with ipilimumab with standard-of-care ipilimumab monotherapy as first-line treatment in patients with advanced melanoma, it was shown that the objective-response rate and the progression-free survival were significantly higher in the combination than with ipilimumab monotherapy. The incidence of Grade 3 or 4 adverse events was higher with combination therapy, but most of these toxicities were reversible and were generally manageable when established safety guidelines were used [66].

Collectively, the results of both studies suggest that nivolumab and ipilimumab can be administered concurrently with a manageable safety profile. Nevertheless, the risk–benefit profile of combined PD-1 and CTLA-4 blockade, as compared with monotherapy, will be further clarified by data from ongoing phase III double-blind, randomised trials, such as the CheckMate 067 study [66].

4.6.4. Immune check point inhibitors in SCLC

In SCLC, a phase I/II trial evaluating nivolumab with or without ipilimumab in pretreated ED SCLC patients (CheckMate 032) has been recently presented [67].

In this open-label trial, SCLC patients with progressive disease and sensitive or refractory to platinum based chemotherapy were enroled, independent of the tumour PD-L1 status. Patients were randomised to either nivolumab monotherapy (3 mg/kg i.v. every 2 weeks) or to nivolumab plus ipilimumab combination therapy (1 mg/kg ipilimumab plus 1 mg/kg nivolumab vs 3 mg/kg ipilimumab plus 1 mg/kg nivolumab vs 1 mg/kg ipilimumab plus 1 mg/kg nivolumab i.v. every 3 weeks for 4 cycles followed by nivolumab 2 mg/kg i.v. every 2 weeks for 1 year). Primary objective was overall response. Other objectives were safety, PFS, OS and biomarker analysis.

At last database lock, the trial reported a response rate of 18% and SD in 20% with nivolumab monotherapy while the combination of ipilimumab and nivolumab yielded 33% response and 22% stabilisation.

Interestingly, activity was observed in platinum-sensitive and resistant/refractory patients. A preliminary analysis showed that clinical responses occurred in patients regardless of PD-L1 expression.

The safety profiles of nivolumab monotherapy and nivolumab and ipilimumab combination are consistent with other tumour types, mainly fatigue, diarrhoea, rash and nausea and were managed with established safety guidelines. One drug-related death in the nivolumab 1 mg/kg / ipilimumab 3 mg/kg cohort occurred. This patient developed myasthenia gravis (reported as Grade 4) after treatment start and suffered from complications causing the patient's death.

Paraneoplastic syndromes (limbic encephalitis) and autoimmune diseases (myasthenia gravis) have been reported in clinical trials with nivolumab. Limbic encephalitis of Grade 2 occurred in 2 patients (nivolumab, n = 1; nivolumab 1 mg/kg + ipilimumab 3 mg/kg, n = 1) and resolved with immunosuppressive treatment. One patient on nivolumab had Grade 4 limbic encephalitis that did not resolve with immunosuppressive treatment.

Of note, early results from another early phase I trial using anti-PD-1 drug monotherapy (pembrolizumab)[68], confirmed a promising RR of 35% (SD of 5%) in 20 patients selected at enrolment for expression of PD-L1. The safety profile was manageable and in line with anti-PD-1 usual toxicities with no pneumonitis or paraneoplastic syndrome reported.

4.7. Overall risk/benefit assessment

Ipilimumab is the first drug to demonstrate prolonged survival in patients with pre-treated advanced melanoma, based on a large, multinational, double-blind, pivotal, Phase III study supported by a comprehensive Phase II program.

In the recent subsequent large, randomised, double-blind, phase II study involving patients with previously untreated advanced melanoma, treatment with nivolumab alone or with the combination of nivolumab and ipilimumab resulted in significantly longer PFS and higher ORR than did treatment with ipilimumab alone. In the two nivolumab-treated groups, as compared with ipilimumab, these results were observed independently of PD-L1 tumour status, *BRAF* mutation status, or metastasis stage [65]. Early clinical trials data show promising results of anti-PD-1 nivolumab or pembrolizumab monotherapy and suggest improved activity by combining nivolumab and ipilimumab in this disease too. Refinement of treatment doses and schedules is currently ongoing and larger randomised extensive stage SCLC confirmatory trials recently started or are planned to be started soon.

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Nivolumab and ipilimumab impact tumour cells indirectly, and measurable clinical effects emerge after the immunological effects. Tumour infiltration with lymphocytes and the associated inflammation (documented by biopsy in some patients) is likely the cornerstone of the effect of ipilimumab and nivolumab and can manifest in various patterns of clinical activity leading to tumour control. In some cases, inflammation may

not be noted by radiological examination and objective response is observed with the first tumour assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumour volume and/or the appearance of new lesions due to lymphocyte infiltration and inflammation, which may be mistaken for tumour progression on radiological evaluations.

In metastatic disease, stabilisation is more common than response, and in some instances is associated with slow, steady decline in tumour burden over many months, sometimes improving to partial and/or complete responses. The immune-based mechanism of action of ipilimumab may result in durable disease control, sometimes with novel patterns of response, which contribute to its improvement in OS.

The immune-based mechanism of action is also reflected in the safety profile. The most common drug-related AEs are immune-related, consistent with the mechanism of action of the drugs and generally medically manageable with topical and/or systemic immunosuppressants. As previously discussed, the immune-related adverse reactions primarily involve the GI tract, skin, liver, endocrine glands, and nervous system.

The early diagnosis of immune- related adverse reactions is important to initiate therapy and minimise complications. Immune- related adverse reactions are generally manageable using symptomatic or immunosuppressive therapy as recommended through detailed diagnosis and management guidelines, as described fully in the current IBs for nivolumab and ipilimumab. The management guidelines for general immune- related adverse reactions and ipilimumab- as well as nivolumab-related GI toxicities, hepatotoxicity, skin toxicity, endocrinopathy, and neuropathy are provided in the appendices of the current IBs and as supplementary material to this protocol.

A safety concern in this trial is the possible enhancement of radiation pneumonitis due to the nivolumab and ipilimumab combination. Radiation pneumonitis may occur in 15-20% of patients being treated with concurrent chemo-radiotherapy for stage I-III SCLC, mostly 2-6 months after radiation. Thereafter, irreversible lung fibrosis, which is mostly asymptomatic, will occur in lung areas that have received high radiation doses.

Pre-clinical observations show that $CD4^+CD25^+IL\text{-}17^+$ and $CD4^+CD25^+Foxp3^+$ expressing cells are recruited to the lung tissue of irradiated mice [69]. Interestingly, RAG-$2^{-/-}$ mice, who fail to generate mature T- and B-lymphocytes due to a total inability to initiate V(D)J rearrangement, had an increased sensitivity for radiation-induced lung fibrosis compared to wild-type mice.

An important question of this trial will thus be the pulmonary toxicity, both acute (pneumonitis) and fibrosis (scored on CT-scans). In order to exclude an exacerbation by nivolumab and ipilimumab treatment, a safety evaluation will take place 12 weeks after the first 30 patients have been randomised to the experimental arm (total of 60 pts, 30 in the nivolumab plus ipilimumab combination and 30 in observation arm). This first safety evaluation will be submitted to the IDMC for advice.

In summary, the combination of nivolumab and ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with advanced melanoma and evidence of

clinical activity in early or randomised studies in other tumour types, including SCLC. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-mediated toxicities, suggest a favourable benefit to risk ratio.

4.8. Rationale for trial design

As previously discussed, even in the best series, the 5-year survival rate of patients with stage I-III ("limited stage") SCLC is only about 25%, with median survival rates of 2 years. Both distant metastases and local recurrences remain problematic even after concurrent chemo-radiotherapy and PCI.

CTLA-4 inhibition as a single agent immuno-oncology approach for the treatment of SCLC patients might not be potent enough to result in clinically meaningful results. Recently, results from study CA184-156 (A Randomized, Multicenter, Double-Blind, Phase III Trial Comparing the Efficacy of Ipilimumab plus Etoposide/Platinum versus Etoposide/Platinum in Subjects with Newly Diagnosed Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) became available. This study did not achieve its primary objective and did not demonstrate a statistically significant improvement in overall survival in subjects with newly diagnosed ED SCLC receiving ipilimumab plus etoposide/platinum versus etoposide/platinum alone. The overall safety profile of ipilimumab plus etoposide/platinum, was consistent with expectations based on prior data, in terms of type, frequency and severity of reported events. No new safety concerns with ipilimumab in combination with etoposide/platinum treatment were identified. Although this study was conducted in SCLC patients with extensive disease stadium and with sequentially administered ipilimumab as a component of the platinum based induction treatment, it appears questionable if an ipilimumab maintenance therapy alone in the limited disease setting will result in a clinically meaningful overall survival prolongation [70] and internal communication BMS.

As described above, preliminary phase I/II data from study CA209-032 showed an encouraging overall response rate of 33% for the combination of nivolumab with ipilimumab in heavily pretreated SCLC patients with extensive disease status. Objective responses were long lasting. Combining nivolumab and ipilimumab therefore represents a very promising treatment option worth exploring, to be evaluated prospectively in a consolidation/maintenance setting within the curative intent treatment strategy used for LD SCLC. The observation that nivolumab combined with ipilimumab shows activity in ED SCLC is consistent with pre-clinical data and support the use of these drugs after definitive treatment. Moreover, radiotherapy is not only part of standard therapy of stage I-III SCLC, but it consistently induces up-regulation of tumour antigens or of tumour-associated antigens irrespective of the histology of the tumour. Fractionated irradiation of the tumour in combination with CTLA-4-blockage was shown to induce regression of distant metastases.

The combination of nivolumab and ipilimumab will be delivered as a consolidation treatment after a standard schedule consisting of chemo-radiotherapy and PCI. Importantly, in CA184042, the first study to evaluate ipilimumab monotherapy among patients with advanced stage IV melanoma and active brain metastases [71], the safety profile observed in the subset

of 31 patients having received prior radiation therapy for CNS metastases was not different from the one regarding the whole 72 patients study population.

These observations support this open-label randomised phase II trial in patients with stage I-III SCLC which aims at improving the treatment outcome by delivering the combination of nivolumab and ipilimumab after concurrent cis- or carboplatin-etoposide, chest radiotherapy and PCI.

5. Objectives and endpoints

5.1. Primary objective

To evaluate whether patients treated with chemo-radiotherapy and prophylactic cranial irradiation followed by nivolumab plus ipilimumab consolidation treatment 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.

5.2. Secondary objectives

5.2.1. To evaluate secondary measures of clinical efficacy including objective response rate (ORR), and time to treatment failure.

5.2.2. To assess the safety and the tolerability of the treatment in both arms.

5.3. Co-primary endpoints

5.3.1. Progression-free survival (PFS) according to RECIST 1.1

5.3.2. Overall survival (OS)

For definition, see section 14.1

5.4. Secondary endpoints

5.4.1. Objective response determined by RECIST 1.1

5.4.2. Time to treatment failure

5.4.3. Adverse events graded according to CTCAE V4.0

For definitions, see section 14.

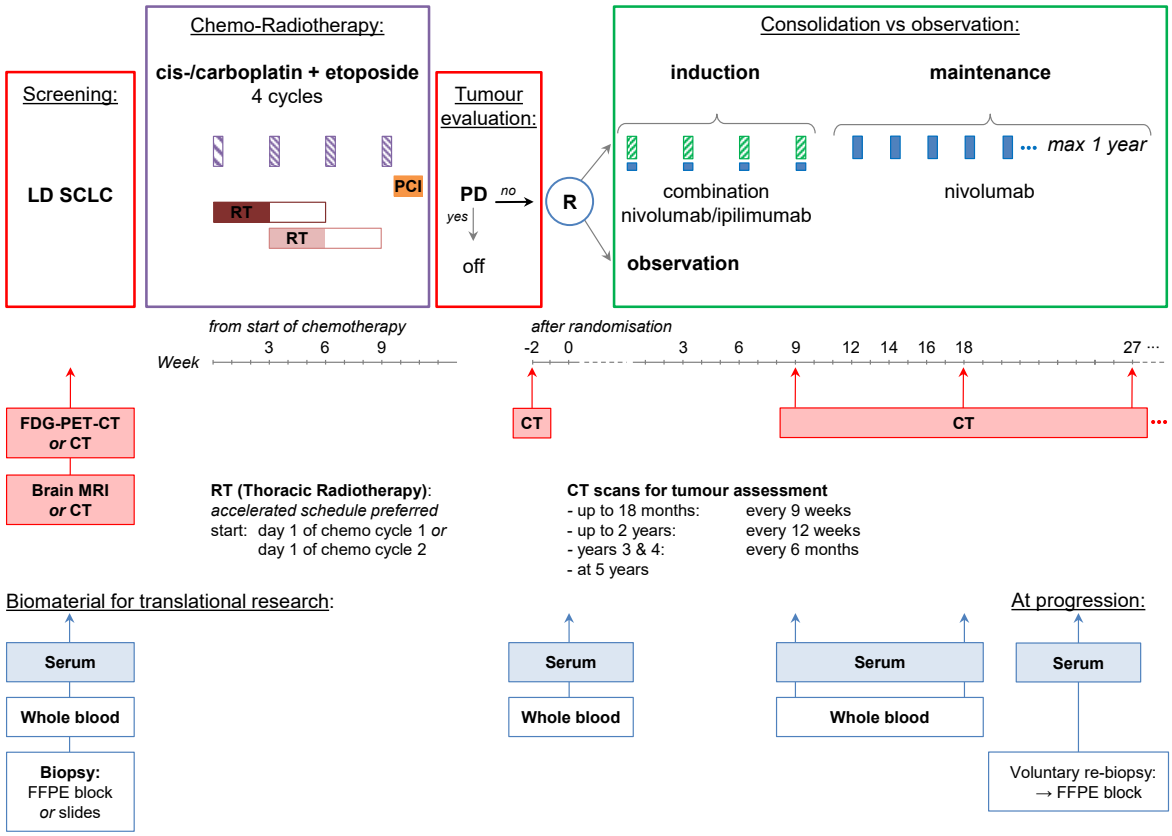
6. Trial design, duration and termination

This is an open-label, randomised, two-arm, phase II international multi-centre clinical trial with early interim analysis for safety in patients with radically treated limited-stage SCLC following completion of thoracic radiotherapy concomitant to chemotherapy and PCI.

Patients randomised to the experimental arm will receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg combination as induction, 4 cycles every 3 weeks, followed by maintenance with nivolumab 240 mg every 2 weeks for maximum 12 months from start of maintenance (see section 0 for rational to support "flat" dose of nivolumab).

Patient accrual is expected to be completed within 3 years including a run-in-period of 3 months. Treatment and follow-up is expected to extend the study duration to a total of 7.0 – 7.5 years. Patients will be followed until death – thus follow-up is 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, scheduled for 7.5 years after the inclusion of the first patient.



It is expected that after the chemo-radiotherapy phase, about 20% of treated patients will present with progressive disease or will not have completed chemo-radiotherapy per protocol definition (4 cycles of chemotherapy, 85% of PTV of thoracic radiotherapy) and/or completed mandatory PCI and will therefore not be randomised. Thus, at least 325 patients will have to be enroled in order to randomise 260 patients under the amendment 1. Patients who are not randomised will be followed up for survival and documentation of type of further lines of therapy until death. Approximately 30 - 60 sites from several European countries will participate.

7. Patient selection

Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention (with the exception of one cycle of chemotherapy given prior to enrolment) for trial treatment and biomaterial submission for central review and testing.

Patients should only be selected and consented for screening if they fulfil the criteria in the next section:

7.1. Inclusion criteria for enrolment

7.1.1. Histologically or cytologically confirmed small cell lung carcinoma

7.1.2. Untreated limited stage disease (with the exception of one cycle of chemotherapy given prior to enrolment) 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.

7.1.3. Age ≥18 years

7.1.4. ECOG performance status 0-1

7.1.5. Adequate haematological function:

- haemoglobin >9 g/dL
- neutrophils count >1.5×10^9/L
- platelet count >100 × 10^9/L

7.1.6. Adequate liver function:

- Total bilirubin <2.5 × ULN
- ALT and/or AST <2.5 × ULN
- alkaline phosphatase <5 × ULN.

7.1.7. Adequate renal function: Calculated creatinine clearance ≥30 mL/min (Cockroft-Gault).

7.1.8. Pulmonary function FEV1 of 1.0L or >40% predicted value and DL_{CO} >40% predicted value.

7.1.9. Patient capable of proper therapeutic compliance, and accessible for correct follow-up.

7.1.10. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before beginning of chemotherapy. The test has to be repeated within 7 days before randomisation and then every 6 weeks during consolidation treatment. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after consolidation treatment stop.

7.1.11. All sexually active men and women of childbearing potential must use an effective contraceptive method (two barrier methods or a barrier method plus a hormonal method) during the study treatment and for a period of at least 12 months following the last administration of trial drugs.

7.1.12. Measurable or evaluable disease (according to RECIST 1.1 criteria). Not eligible: patients with only one measurable or evaluable tumour lesion which was resected or irradiated prior to enrolment.

7.1.13. Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention for

a) Chemo-radiotherapy treatment, PCI, and subsequent randomisation, including mandatory biological samples

b) Optional biological material collection, long-term storage and future use of biological material for translational research

7.2. Exclusion criteria for enrolment

7.2.1. Patient with mixed small-cell and non-small-cell histologic features

7.2.2. Patient with pleural or pericardial effusions proven to be malignant

7.2.3. 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 (if no RT was involved).

7.2.4. Patients with other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient's capacity to participate in the study.

7.2.5. Ongoing clinically serious infections requiring systemic antibiotic or antiviral, antimicrobial, or antifungal therapy.

7.2.6. Known or suspected hypersensitivity to nivolumab or ipilimumab or any of their excipients.

7.2.7. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

7.2.8. Documented history of severe autoimmune or immune mediated symptomatic

disease that required prolonged (more than 2 months) systemic immunosuppressive treatment (e.g. steroids), such as but not limited to ulcerative colitis and Crohn´s disease, rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, or autoimmune vasculitis (e.g. Wegener's granulomatosis).

7.2.9. Subjects with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment.

7.2.10. Interstitial lung disease or pulmonary fibrosis.

7.2.11. Women who are pregnant or in the period of lactation.

7.2.12. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the study.

7.2.13. Patients with any concurrent anticancer systemic therapy (except for chemotherapy cycle 1).

7.2.14. HIV, active Hepatitis B or Hepatitis C infection

7.2.15. Previous radiotherapy to the thorax (prior to inclusion), including RT for breast cancer

7.2.16. Planned radiotherapy to lung of mean dose >20 Gy or V20 >35%

7.2.17. Patients who received treatment with an investigational drug agent during the 3 weeks before enrolment in the study.

7.2.18. Prior chemotherapy or radiotherapy for SCLC. Exception: one cycle of chemotherapy (as specified to section 10.2) may be administered prior to enrolment.

7.3. Inclusion criteria for randomisation

7.3.1. Chemo-radiotherapy completed per protocol: 4 cycles of chemotherapy, ≥85% of PTV of thoracic radiotherapy, as well as completed, mandatory PCI

7.3.2. Non-PD after chemo-radiotherapy and PCI

7.3.3. ECOG performance status 0-2

7.3.4. Recovery of all adverse events to a Grade ≤1, except for fatigue, appetite, oesophagitis and renal impairment (where ≤2 is allowed) and alopecia (any grade)

7.3.5. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before randomisation.

7.4. Exclusion criteria for randomisation

7.4.1. Less than 4 cycles of chemotherapy administered, less than 85% PTV of thoracic radiotherapy delivered, or PCI not completed

7.4.2. Progressive disease after chemo-radiotherapy and PCI

8. Patient screening, enrolment and randomisation

This trial will use a web-based registration and randomisation system. Each participating centre will access the system directly to enrol and later to randomise patients. Specific details for enrolment of patients are in the ***STIMULI Procedures Manual*** which will be available on the trial documentation download section of the ETOP website (www.etop-eu.org).

8.1. Screening

Complete the following steps to screen and enrol a patient on this trial. Please consult the ***STIMULI Procedures Manual*** for detailed instructions.

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention.

Verify eligibility and enrol the patient in the RDE facility ETOPdata according to the information in the ETOPdata User Manual. The dates the Informed Consent Form and the consent to pathology material submission section of the Informed Consent Form were signed by the patient as well as the dates the investigator signed those forms are all required to complete the eligibility checklist.

Patients should preferably be enroled before start of chemotherapy, and chemotherapy should start within 7 days after enrolment. If the start of chemotherapy cannot be delayed, a maximum of 1 chemotherapy cycle can be administered before enrolment (according to section 10.2). Patients must be enroled prior to chemotherapy cycle 2 and prior to start of thoracic radiotherapy (section 10.4).

8.2. Randomisation and stratification

After completion of the 4 cycles of chemotherapy, thoracic radiotherapy and prophylactic cranial irradiation (see section 10.5) patients who have not progressed can be randomised to one of the 2 treatment arms. Patient eligibility needs to be checked before randomisation (see sections 7.3 and 7.4). Randomisation should take place within 5-6 weeks after day 1 of chemotherapy cycle 4 (between days 35 and 42 of cycle 4). Please complete and submit the Eligibility Check and Randomisation eCRF (see sections 7.3 and 7.4). Then submit the Randomisation eCRF in ETOPdata in order to randomise the patient. Nivolumab and ipilimumab combination treatment has to start within 6-8 weeks (42-56 days) from start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation.

Block stratified randomisation balanced by institution will be performed, stratified by radiotherapy schedule (twice-daily vs once-daily) and PET-CT done vs not done [72].

9. Investigational Medicinal Products

Nivolumab and ipilimumab are the Investigational Medicinal Products (IMPs) used in this trial. BMS will provide both IMPs at no cost for this trial.

Complete details of the trial drug logistics, distribution, packaging, labeling, storage and handling as well as accountability are described in the ***STIMULI drug supply manual***, which is available on the trial documentation download section of the ETOP website (www.etop-eu.org).

9.1. Description of the Investigational Medicinal Products

9.1.1. Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys. The clinical study product is a sterile solution for intravenous administration.

9.1.2. Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4-S228P) antibody (HuMAb) that targets PD-1, a transmembrane protein from the CD28 family of receptors. PD-1 is highly expressed on activated T-cells and B cells. Two ligands specific for PD-1 have been identified: PD-L1 and PD-L2. Both ligands have been shown to down-regulate T-cell activation upon binding to PD-1. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self antigens. The clinical study product is a sterile solution for intravenous administration.

9.2. Packaging and labelling

BMS will provide the IMPs (nivolumab and ipilimumab) at no cost for this study. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Ipilimumab is available at a concentration of 5 mg/mL(200 mg in 40 mL per vial).

Nivolumab is available at a concentration of 10 mg/mL (100 mg in 10 mL per vial).

The pharmaceutical form of both IMPs is a sterile solution for intravenous injection. The liquid is clear, colourless to pale yellow and may contain trace amounts of proteinaceous particles.

9.3. Receipt of the drugs

Both IMPs will be supplied by BMS directly to the sites. See the ***STIMULI drug supply manual*** for details.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Accountability Log. In the event that either of the

IMPs is destroyed at site a certification of destruction form should be generated and retained in the Investigator Site File.

9.4. Storage and handling

9.4.1. Storage

Both IMPs must be stored in a secure area according to local regulations. The investigator must ensure that IMPs are stored refrigerated at 2-8^{0}C, protected from light and freezing, see the ***STIMULI drug supply manual*** for details.

9.4.2. Handling

Both, nivolumab and ipilimumab are to be administered on the same day. Separate infusion bags and filters must be used for each infusion. Nivolumab infusion has to be administered over 30 min and ipilimumab infusion has to be administered over 90 min. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion. See respective IBs for ipilimumab and nivolumab and the ***STIMULI drug supply manual*** for details.

9.5. Unused trial drug supplies

If either of the IMPs is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained. Provide a certificate of destruction to ETOP upon disposal. See the ***STIMULI drug supply manual*** for details.

10. Trial treatments

10.1. Overview of treatment sequence

10.1.1. **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/m^2 i.v. on days 1 – 3 or 75 mg/ m^2 on day 1) or carboplatin (AUC 5-6, calculated according Calvert formula, i.v. on day 1), plus etoposide (100 mg/ m^2 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 enroled after the first cycle only but should be exceptional. Optimally, radiotherapy should start at the latest on day 1 of cycle 2.

- **Prophylactic Cranial Irradiation** (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.

10.1.2. **After randomisation**, 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) from start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation**:**
  - 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 dose delays), 4 cycles

- **Maintenance phase:**
  Nivolumab 240 mg i.v. over a period of 30 minutes, once every 2 weeks (+/- 2 days, without dose delays), for a maximum of 12 months from start of maintenance. The first dose of maintenance nivolumab will be administered 3 weeks (21 days) after the last IMP doses of induction phase.

Observation arm: no further treatment

10.2. Chemotherapy dosage, administration and schedule

Patients should preferably be enroled before start of chemotherapy, and chemotherapy should start within 7 days after enrolment. If the start of chemotherapy cannot be delayed, a maximum of 1 chemotherapy cycle can be administered before enrolment. Patients must be enroled prior to start of thoracic radiotherapy. Maximum 1 chemotherapy cycle may be given prior to radiotherapy start (exception for patients enroled after chemotherapy start is described in section 8.1).

Chemotherapy consists of the standard combination of platinum compound (cis- or carboplatin) and etoposide and is given for 4 cycles. The cisplatin and etoposide doses should be based on the patient's calculated pre-treatment body surface area (BSA) using actual body weight. Carboplatin doses must be calculated according to the Calvert formula:

Dose (in mg) = Target AUC × (GFR+ 25)

AUC : Area under curve ; GFR: Creatinine Clearance must be calculated according to the formula of Cockroft-Gault.

There will be no dose capping. A detailed plan for administering a cycle of chemotherapy is given below. Centres can opt for one of the 3 chemotherapy regimens. Cycles are given at 3 week intervals:

- Option 1: cisplatin 75 mg/ m^2 i.v. day 1 and etoposide 100 mg/m^2 i.v. days 1-3 (see Table 2)

OR

- Option 2: cisplatin 25 mg/ m^2 i.v. days 1-3 and etoposide 100 mg/m^2 i.v. days 1-3 (see Table 3)

OR

- Option 3: carboplatin AUC 5-6 (calculated according Calvert formula) i.v. day 1 and etoposide 100 mg/m^2 i.v. days 1-3 (see Table 4)

Centres have the choice to give cisplatin (at a dose of 75 mg/m^2 on day 1 at a dose of 25 mg/ m^2 on days 1-3 every 21 days) or carboplatin (at a dose of AUC 5-6, calculated according Calvert formula, on day 1 every 21 days).

Etoposide will be administered as 100 mg/m^2 on days 1-3, daily administered as an intravenous infusion over 1 hour every 3 weeks.

Cisplatin will be administered as 75 mg/m^2 on day 1 or as 25 mg/m^2 on days 1-3, as an intravenous infusion over 1-2 hours every 3 weeks.

Carboplatin will be administered at a dose of AUC 5-6 on day 1, as an intravenous infusion over 2 hours every 3 weeks.

Cis- or carboplatin and etoposide will be administered as per local guidelines and schedule, including local anti-emetics, prophylactic antibiotics and G-CSF co-medications as well as hydration standards. Patients should be encouraged to take a high oral fluid intake on the day prior to cis- or carboplatin chemotherapy. Below are suggested schemes of administration of chemotherapy cycles.

Table 2: Chemotherapy administration using option 1 schedule (cisplatin day 1 only)

Day 1		
Administer anti-emetics according to local guidelines		
Time	**Drug**	**Fluid**
0.00	Pre – cisplatin hydration	1 L i.v. 0.9% NaCl over 2 hours with 20 mmol KCl
When urine output ≥100mL per hour		
2.00	Cisplatin 75 mg/m^2	1 L 0.9% NaCl with 1 g MgCl 20 mmol over 1-2 hours
3.00 - 4.00	Etoposide 100 mg/m^2	1 L i.v. 0.9% NaCl over 1 hour
4.30 - 5.30	Post – cisplatin hydration	1 L i.v. 0.9% NaCl with 20 mmol KCl and 10 mmol $MgSO_4$ sulphate over 2 hours

Maintain oral intake of 1-2 litres of fluid for 6 hours after iv fluids discontinued		
Days 2 and 3		
Administer anti-emetics according to local guidelines		
0.00	Etoposide 100 mg/m^2	1 L i.v. 0.9% NaCl over 1 hour

Table 3: Chemotherapy administration using option 2 schedule (cisplatin days 1-3)

Days 1-3		
Administer anti-emetics according to local guidelines		
Time	**Drug**	**Fluid**
0.00	Cisplatin 25 mg/m^2 dL^{-3}	500mL i.v. 0.9% NaCl over 1 hour
1.00	Etoposide 100 mg/m^2 dL^{-3}	500mL i.v. 0.9% NaCl over 1 hour
Patients to have an oral intake of 2 litres of fluid days 1 to 3		

Table 4: Chemotherapy administration using option 3 schedule (carboplatin day 1 only)

Day 1		
Administer anti-emetics and hydration according to local guidelines		
Time	**Drug**	**Fluid**
0.00	Carboplatin AUC 5-6	1 L i.v. 0.9% NaCl 1 g MgCl 20 mmol over 1-2 hours, according to local standards
1.00 - 2.00	Etoposide 100 mg/m^2	1 L i.v. 0.9% NaCl over 1 hour
Days 2 and 3		
Administer anti-emetics according to local guidelines		
0.00	Etoposide 100 mg/m^2	1 L i.v. 0.9% NaCl over 1 hour

Prophylactic antibiotics with fluoroquinolones (choice left to local investigator) are recommended to start on day 8 of cycle 1 chemotherapy and to continue for 7 days to minimise the risk of neutropenic sepsis and respiratory infection. Consideration should be given to continuing prophylactic antibiotics after subsequent cycles if bronchial obstruction is present.

Anti-emetics will be routinely used using a combination of a steroid, aprepitant, and a 5-HT3 antagonist.

- The use of G-CSF is optional:
    - G-CSF will be prescribed, if clinically indicated, as per ASCO 2006 guidelines or in line with local policy / guidelines for treatment of febrile or prolonged neutropenia.
    - Secondary prophylaxis with G-CSF is recommended.
    - GM-CSF is not allowed.
- The use of erythropoietin for the treatment of anaemia is prohibited. If Hb<10, blood transfusions will be required.

10.3. Chemotherapy delay and dose modification for toxicity

In case of toxicity, symptomatic treatment and dose interruptions should be used according to the following sections. Repeated dose delays are allowed as required, but the sum of all delays should not exceed 6 weeks.

The policy should be to delay and give at full dose, rather than reduced dose. The dose modification schedule should be followed, but clinical judgment and local standards should be used in individual cases. Common side effects are listed in sections 11.2 − 11.7.

10.3.1. Haematological toxicity

Table 5: Dose modifications of cisplatin/etoposide for haematological toxicity

Dose modifications are based on pre-chemotherapy blood count.

ANC x 10^9/ L		**Platelets x 10^9/L**	**Cisplatin /Etoposide**
>1.5 at day 1 of cycle	and	>100	Full dose
≤1.5 at day 1 of cycle	or	≤100	Delay until recovery ANC >1.5 and Platelets >100
Febrile neutropenia episode or treatment delay for Grade 4 neutropenia >7 days			First event: full dose and G-CSF support is recommended. Second event or if G-CSF support was already delivered: 20% dose reduction and continuing G-CSF support. Third event despite 20% dose reduction and G-CSFsupport: 35% dose reduction Subsequent event: off trial
		Grade 4 thrombocytopenia requiring medical intervention or ≥ Grade 2 bleeding with thrombocytopenia	First event: 20% dose reduction Second event: 35% dose reduction Subsequent event: off trial

Table 6: Dose modifications of carboplatin/etoposide for haematological toxicity

Dose modifications are based on pre-chemotherapy blood count.

ANC x 10^9/ L		**Platelets x 10^9/L**	**Carboplatin /Etoposide**
≥ 1.5 at day 1 of cycle	and	≥100	Full dose
<1.5 at day 1 of cycle	or	<100	Delay until recovery ANC ≥ 1.5 and Platelets >100

ANC x 10^9/ L		Platelets x 10^9/L	Carboplatin /Etoposide
Febrile neutropenia episode or treatment delay for Grade 4 neutropenia >7 days			First event: full dose and G-CSF support is recommended. Second event or if G-CSF support was already delivered: 20% dose reduction and continuing G-CSF support. Third event despite 20% dose reduction and G-CSFsupport: 35% dose reduction Subsequent event: off trial
		Grade 4 thrombocytopenia requiring medical intervention or ⩾ Grade 2 bleeding with thrombocytopenia	First event: 20% dose reduction Second event: 35% dose reduction Subsequent event: off trial

If chemotherapy cannot be administered after a 3-week delay because of haematological toxicity, chemotherapy should be discontinued. If Hb<10, blood transfusions will be required.

10.3.2. Hepatic toxicity

Table 7: Dose modifications of cisplatin/etoposide for hepatic toxicity

Dose modifications are based on pre-chemotherapy laboratory values

AST		Bilirubin	Cisplatin	Etoposide
2-5 x ULN at day 1 of cycle	And	≤ 1.5 x ULN	Full dose	Full dose
>5 x ULN at day 1 of cycle	Or	>1.5 x ULN	Delay 1 week then reassess using the same criteria; A delay up to 3 weeks is allowed	

Table 8: Dose modifications of carboplatin/etoposide for hepatic toxicity

Dose modifications are based on pre-chemotherapy laboratory values

AST		Bilirubin	Carboplatin	Etoposide
2-5 x ULN at day 1 of cycle	And	⩽ 1.5 x ULN	Full dose	Full dose
>5 x ULN at day 1 of cycle	Or	>1.5 x ULN	Delay 1 week then reassess using the same criteria; A delay up to 3 weeks is allowed	

10.3.3. Renal toxicity

Request calculated creatinine clearance (according to Cockroft-Gault) before each course of chemotherapy.

Table 9: Dose modifications of cisplatin/etoposide for renal toxicity

Dose modifications are based on pre-chemotherapy laboratory values

Calculated creatinine clearance at day 1 of cycle	Cisplatin	Etoposide
>50 mL/min	Full dose	Full dose
30-50 mL/min	Switch to carboplatin	20% dose reduction
<30 mL/min	Off trial treatment	Off trial treatment

Table 10: Dose modifications of carboplatin/etoposide for renal toxicity

Dose modifications are based on pre-chemotherapy laboratory values

Calculated creatinine clearance at day 1 of cycle	Carboplatin	Etoposide
>50 mL/min	Full dose	Full dose
30-50 mL/min	Full dose	20% dose reduction
<30 mL/min	Off trial treatment	Off trial treatment

10.4. Thoracic radiation

Thoracic radiation will be administered concurrently to chemotherapy and should preferentially start at the same time as the first chemotherapy cycle (e.g. day 1 of cycle 1), see also ref. [73], if the patient can be enroled before the first chemotherapy cycle. Otherwise, radiotherapy should optimally start at day 1 of cycle 2, i.e. in treatment week 4. As a latest start of radiotherapy day 1 of cycle 3 is allowed, but should be exceptional.

10.4.1. Doses and fractionation

Two different radiation doses are allowed: the recommended schedule is 45 Gy in 30 twice-daily fractions of 1.5 Gy (6-8 hours apart), in 30 treatments on 5 days per week over 3 weeks (preferred). The alternative, but not-recommended schedule is 56 Gy, given in 28 once-daily fractions of 2 Gy, 5 days per week over 6 weeks. In case the twice-daily fractionation is used, the treatment times (a.m./p.m.) must be documented in the daily record.

Treatment is administered 5 days/week. A minimum of 3 days concurrent chemotherapy with chest radiotherapy is required.

In case of interruptions of radiotherapy, 4 treatment days per week are allowed, as long as the foreseen overall treatment time is not exceeded by more than 4 days.

10.4.2. Treatment techniques

Normalisation of the treatment plan will cover 95% of the planning target volume (PTV) with the prescription dose. The minimum PTV dose must not fall below 90% of the prescription dose, the maximal dose must not exceed 115% PTV. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (i.e., air in the lung and bone). The maximum, mean and minimum point doses (within the PTV) will be reported.

10.4.3. Variations of dose prescription:

No deviation: ≥99% of the PTV receives ≥90% of the prescribed dose, and a contiguous volume of no more than 2cc inside PTV exceeds 20% of the prescribed dose.

Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage that is equal to 90% of the prescribed dose and falls between 99% and 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 20-25% of the prescribed dose.

Major deviation: Doses in this region are not acceptable. More than 1 cm^3 of tissue outside the PTV receives ≥120% of the prescribed dose, or 90% of the prescribed dose falls below 90% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 25% of the prescribed dose.

10.4.4. Heterogeneous dose calculations

In order to calculate the radiation dose to the PTV and the organs at risk, advanced dose calculation algorithms that take into account the secondary electron range, should preferentially be used. Examples include a superposition/ convolution and an AAA algorithm. Simple, so-called "type A dose calculation algorithms" such as Clarkson or pencil beam are thus allowed, when no Intensity Modulated RadioTherapy (IMRT) or Volumetric Arc Therapy (VMAT) is used.

10.4.5. Technical factors

Beam Energy: 6 - 18 MV are to be used.

3D-conformal techniques, as well as Intensity Modulated RadioTherapy (IMRT) and Arc treatments are all accepted, provided the PTV dose criteria and the constraints for the Organs at Risk (OAR) are met.

10.4.6. Localisation, simulation, and immobilisation

A volumetric treatment planning CT study will be required to define gross tumour volume (GTV), clinical target volume (CTV), and planning target volume (PTV). Each patient will be positioned in an immobilisation device in the treatment position on a flat table.

Contiguous CT slices, having at maximum 3 mm thickness starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume will be obtained. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices.

Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT. If contrast is used, the densities can be over-ridden or the contrast scan must be registered to a non-contrast scan for planning purposes.

Optimal immobilisation is critical for this protocol. Immobilisation to assure reproducibility of the setup is necessary.

The use of 4-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumour motion include: design of the PTV to cover the excursion of the lung primary cancer and nodes during breathing such as an ITV approach, a maximum intensity projection (MIP) approach, automatic breath-hold (e.g. Elekta ABC device) or a gating approach (e.g. Varian RPM system).

10.4.7. Target Volumes

The definitions of target volumes will be in accordance with ICRU Reports 50, 62 and 83 Definition of the GTV [74].

The primary tumour and clinically positive lymph nodes seen either on the planning CT (>1 cm short axis diameter) or pre-treatment PET scan (SUV >3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumour from fluid/atelectasis is encouraged. The ITV includes the envelope that encompasses the tumour motion for a complete respiratory cycle.

10.4.7.1. Definition of the CTV

The CTV is defined to be the GTV plus a 0.5 cm margin as appropriate to account for microscopic tumour extension. CTV expansion can be edited to exclude anatomic structures such as vertebrae. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

10.4.7.2. Definition of the PTV

The CTV-PTV margins should be determined according to international guidelines and may thus differ according to the techniques used.

For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged.

For institutions with gating technology, the use of respiratory gating is encouraged.

10.4.7.3. Normal anatomy to be identified

The normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, skin, oesophagus and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The oesophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The skin and spinal cord should be contoured on each CT slice. The spinal cord should be contoured based on the bony limits of the spinal canal.

10.4.8. Treatment Planning

10.4.8.1. 3D Conformal Therapy

The PTV is to be treated with any combination of coplanar or Non-coplanar 3D conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based

on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. Each field is to be treated daily.

10.4.8.2. Intensity Modulated Radiation Therapy (IMRT) or Arc treatments

IMRT or Arc techniques are allowed as long as the participating institution is credentialed by an official organisation, such as the EORTC, the RTOG, or in some countries local or national accreditation bodies.

10.4.8.3. Organs at risk (OAR)

Normal tissue constraints shall be prioritised in the following order for treatment planning:

1=spinal cord, 2=lungs, 3=oesophagus, 4=brachial plexus, and 5=heart.

1. Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 50.5 Gy.
2. Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of both lungs that receive more than 20 Gy (the V20) should not exceed 35% of the total. Alternatively, the mean lung dose should optimally be ≤ 20 Gy. (By total lung volume we mean the total lung minus the GTV both for V20 and MLD).

   When using Arc techniques, on top of these pulmonary constraints, the V5 of the contralateral lung should be less than 60% and the V5 of both lungs together less than 75%.
3. Brachial Plexus: Brachial plexus doses should be kept ≤ 70 Gy. In this trial, because of the low PTV doses, this constraint will not be reached.
4. Oesophagus: The mean dose to the oesophagus is optimally kept below 34 Gy. This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force the situation.
5. Heart: The mean dose should not exceed 46 Gy.

10.4.9. Documentation requirements

- Portal image of each field of 3D radiotherapy or orthogonal images that localise the isocentre placement of IMRT must be obtained on the first day of therapy but should not be submitted.
- Weekly verification or orthogonal images are required to be taken, but not submitted. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.
- DVHs of GTV, CTVs, and critical normal structures for IMRT.

10.5. Prophylactic cranial irradiation (PCI)

Patients without clinical evidence of disease progression and after completion of concurrent chemo-radiotherapy per protocol (4 cycles of chemotherapy, 85% of PTV of thoracic radiotherapy), and with an ECOG performance status of 0-2 should be offered PCI.

All patients will receive PCI in 10 daily fractions of 2.5 Gy, 5 days per week, to a total dose of 25 Gy. Treatment will be delivered with right and left lateral equally weighted fields with the dose calculated on the central ray at mid-separation of the beams.

All efforts should be made to initiate PCI between day 8 and no later than day 15 of cycle 4. PCI should be completed no later than day 29 from the start of cycle 4.

10.5.1. Technical factors

Beam Energy: 4-6 MV beam energy is to be used for PCI

10.5.2. Localisation, simulation, and immobilisation

Simulation must be done prior to the start of PCI. Patients will be supine with radio-opaque markers placed at the lateral orbital canthi to assist in blocking the lenses in case no CT-simulation is used. Aquaplast or similar immobilisation per institution standard must be used.

10.5.3. Treatment planning/target volumes

The target volume is the entire intracranial contents. There should be at least a 1 cm margin around the bony skull superiorly, inferiorly, anteriorly and posteriorly. The inferior border at the cervical vertebral bodies should be at the C1-C2 interspace.

Individual shaped ports with tailor-made blocks or multileaf collimator must define the irradiation target volume.

IMRT techniques are also allowed.

10.6. Nivolumab and ipilimumab combination treatment

The IMPs (ipilimumab and nivolumab) will be administered according to the following schedule:

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 randomisation):

- 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), for 4 cycles

Nivolumab is to be administered as a 30 minute i.v. infusion and ipilimumab is to be administered as a 90 minute i.v. infusion. It is not to be administered as an i.v. push or bolus injection. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a flush of normal saline to clear the line of nivolumab before starting the ipilimumab

infusion. The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Maintenance phase (to start 3 weeks (21days) after the last IMP doses of induction phase):

- Nivolumab at a dose of 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 . Patients should not be dosed less than 12 days from the previous dose of nivolumab.

10.7. Nivolumab and ipilimumab delay and discontinuation for toxicity during consolidation phase

Dose delay criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both. **Nivolumab and ipilimumab must both be delayed** until treatment can resume.

Note: There will be no nivolumab and ipilimumab dose modifications allowed for the management of toxicities of individual patients. Doses for both, nivolumab and ipilimumab may be delayed or "withheld" for a specific time.

Please refer to the management algorithms for pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity in the appendices of the respective IBs for nivolumab and ipilimumab.

10.7.1. Dose delay criteria due to toxicities likely attributable to either nivolumab or ipilimumab

Nivolumab and ipilimumab administration should be delayed for the following reasons:

- Any Grade ≥2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis do not require a dose delay. It is recommended to consult with the ETOP Medical Reviewer for Grade 3 amylase or lipase abnormalities.
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
  - If a patient has baseline Grade 1 AST, ALT, or total bilirubin elevation, delay dosing for drug-related Grade ≥3 toxicity

- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for nivolumab- or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity. Adverse event treatment management algorithms included in the appendices of the IBs for nivolumab or ipilimumab should be considered for individual cases.

10.7.2. Dose modification

Nivolumab and/or ipilimumab dose reductions for the management of toxicities of individual patients or dose escalations **are not permitted**.

10.7.3. Criteria to resume treatment

Patients may resume treatment with study drugs when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT *OR* total bilirubin. Patients with combined Grade 2 AST/ALT *AND* total bilirubin values meeting discontinuation criteria (section 10.7.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhoea, or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement or glucose controlling agents may resume treatment.

If the criteria to resume treatment are met, the patients should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the scheduled timepoint per protocol, the next scheduled timepoint will be delayed, but not skipped, until dosing resumes. In particular, this is to ensure that patients in the experimental arm will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for patients in the experimental arm during week 1-12, both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed >6 weeks, the patients must be permanently discontinued from study therapy, except as specified in section 10.7.4.4.

10.7.4. Discontinuation criteria

Discontinuation criteria apply for all drug-related adverse events attributed to either nivolumab or ipilimumab.

Treatment should be permanently discontinued for the following:

10.7.4.1. Any Grade 2 drug-related uveitis, eye pain, or blurred vision that

- does not respond to topical therapy and does not improve to Grade 1 severity within the maximum allowed treatment delay of 6 week
- requires systemic treatment

10.7.4.2. Any Grade 3 non-skin, drug-related adverse event lasting >7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT >8 x ULN
    - Total bilirubin >5 x ULN
    - Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN

10.7.4.3. Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:

- Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. It is recommended to consult with the ETOP Medical Reviewer for Grade 4 amylase or lipase abnormalities.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which re-

solve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered after discussion with the ETOP Medical Reviewer.

10.7.4.4. Any dosing interruption lasting >6 weeks with the following exceptions:

- Dosing interruptions to allow for prolonged steroid tapers to manage drug related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing interruption lasting >6 weeks, the ETOP Medical Reviewer (STIMULI@etop-eu.org) must be consulted. Tumour assessments should continue as per protocol even if dosing is interrupted.
- Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by ETOP (STIMULI@etop-eu.org). Prior to re-initiating treatment in a patient with a dosing interruption lasting >6 weeks, ETOP (STIMULI@etop-eu.org) must be consulted. Tumour assessments should continue as per protocol even if dosing is interrupted.

10.7.4.5. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants discontinuation of study medication.

If a patient in the experimental arm meets criteria for discontinuation of nivolumab, the patient should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the trial entirely. However, if the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the patient meets criteria to resume nivolumab treatment (specified section 10.7.3). Nivolumab would be continued at 240 mg with 2 week dosing interval. The relationship to ipilimumab and nivolumab should be well documented in the source documents and the eCRFs. The ETOP Medical Reviewer needs to be contacted prior to continuation with nivolumab therapy.

10.8. Immune-related Adverse Events (irAEs): definition, monitoring and treatment

Blocking the function of immune checkpoint receptors may permit the emergence of autoreactive T-cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhoea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed immune-mediated adverse reactions, noted in previous nivolumab and ipilimumab studies.

For the purposes of this study, an immune-related adverse reaction (irAE) is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an immune-related adverse reaction. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE and/or SAE form, see section 12.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-related adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-related adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-related adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on nivolumab or ipilimumab activity. However, clinical anti-tumour responses have been maintained in patients treated with corticosteroids and discontinued from nivolumab and ipilimumab. If utilised, corticosteroid therapy should be individualised for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhoea requires corticosteroid treatment.

Specific management algorithms for immune-related gastro-intestinal, hepatic, skin, endocrine and neurological adverse events are included as appendices in the IB and in separate guidelines for management algorithms for gastro-intestinal, hepatic, skin, endocrine and neurological toxicities.

10.8.1. Treatment of nivolumab- or ipilimumab-related infusion reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigours, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti inflammatory drugs, narcotics, corticosteroids, bronchodilators, i.v. fluids]; prophylactic medications indicated for ≤24 hours):

Stop the nivolumab or ipilimumab infusion, begin an i.v. infusion of normal saline, and treat the patient with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms

resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg i.v., and remain at bedside and monitor the patient until resolution of symptoms. The amount of IMP infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of i.v. hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae [e.g. renal impairment, pulmonary infiltrates]; Grade 4: (life threatening; pressor or ventilatory support indicated):

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an i.v. infusion of normal saline, and treat the patient as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localised or generalised pruritis within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine, or corticosteroids).

Specific management algorithms for immune-related gastro-intestinal, renal, pulmonary, hepatic, skin, endocrine and neurological adverse events are included as appendices in the respective IBs of the IMPs and in separate guidelines for management algorithms which can be accessed on the trial documentation download section of the ETOP website (www.etop-eu.org).

10.8.2. Treatment of ipilimumab-related isolated drug fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with anti-pyretic or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subse-

quent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate reduction, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

10.8.3. Liver function test (LFT) assessments required before administration of nivolumab and ipilimumab

Liver function tests (AST, ALT, total bilirubin) will be evaluated for every patient within 3 days prior to administration of nivolumab or ipilimumab. Results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: ⩽2.5 x ULN for AST, and/or ALT, ⩽2.5 x ULN for alkaline phosphatase, and ⩽1.5 x ULN for total bilirubin.

If, during the course of treatment abnormal LFT values are detected, the patient must be managed using the hepatotoxicity algorithm section of the separate guidelines for toxicity management algorithms.

10.9. Prohibited and restricted therapies during trial treatment

10.9.1. Accepted and prohibited treatment during chemo-radiotherapy treatment

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

- G-CSF is allowed according to local standards
- Use of corticosteroids is allowed if used as premedication for chemotherapy/radiotherapy or on study management of an AE.
- Safe alternative medicine if potential interactions with trial drugs can be excluded.

The following treatments are **NOT allowed**:

- Chronic use of immune suppressive drugs.
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of IMP administration.
- Any non-trial cytotoxic or immunotherapy anti-cancer treatment
- Treatment with inhibitor or agonist of T-cell costimulation.
- GM-CSF
- Erythropoietin (for the treatment of anaemia)

10.9.2. Prohibited Therapies during treatment with IMP

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving nivolumab and/or ipilimumab treatments. Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents

- Anti-PD-1 / PD-L1immune check-point blockers (except for nivolumab)
- Immunosuppressive agents
- Chronic systemic corticosteroids (more than prednisone 10 mg/day continuous or equivalent)

10.10. Pregnancy prevention

Female patients who are not of childbearing potential due to being postmenopausal (1 year without menstruations without an alternative medical cause or at least 2 years without menstruation following chemotherapy) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential.

Women of childbearing potential and sexually active men must use highly effective contraception during treatment with nivolumab and ipilimumab and until 12 months thereafter. The following contraception methods are considered highly effective:

- Hormonal (estrogen and progesterone) contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation
- Progesteron-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- Intrauterine deviced (IUD) or intrauterine hormone releasing systems (IUS)
- Bilateral tubal occlusion
- Vasectomised partner

Women who become pregnant while participating in the trial must discontinue trial medication immediately. The pregnancy must be reported following procedures detailed in section 12.9. Also any pregnancy that occurs in a female partner of a male study participant must be reported.

10.11. Treatment duration

Patients remain on treatment until one of the following events, whichever occurs first:

- Documented progression according to RECIST v1.1 in chemo-radiotherapy phase
- Documented progression according to RECIST v1.1 in randomised consolidation phase
- Secondary malignancy resulting in need of systemic treatment
- Unacceptable toxicity
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant

- One year of maintenance treatment has been completed

Nivolumab and ipilimumab are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of SCLC tumour lesions within 9 weeks following the start of nivolumab and ipilimumab dosing. In some patients, tumour volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumour or blood. In conventional studies, such tumour volume or relevant laboratory parameter increases during the first 9 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumour volume increase detected up to week 9 of IMP treatment but without appearance of new lesions or rapid clinical deterioration should continue to be treated with IMPs and be clinically observed with a stringent imaging schedule 4 weeks later to allow detection of a subsequent tumour response. This will improve the overall assessment of the clinical activity of IMPs and more likely capture its true potential to induce clinical responses. This must follow the definitions below:

10.11.1. Treatment beyond disease progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Patients should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumour burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumour burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

Patients treated with IMPs will be permitted to continue treatment beyond initial RECIST 1.1 defined PD – at 9 weeks CT scan assessment – if they meet all of the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of study drug
4. Stable performance status
5. Only local progressive disease of known LD SCLC (absence of new lesion)

After the 9 week scan, a radiographic assessment / scan should be performed at least 4 weeks after the original PD scan to determine whether there has been a decrease in the tumour size or disease stabilisation, or alternatively continued PD which would terminate the trial treatment.

If the IMPs have been stopped for any reason, the patient enters the follow-up phase of the trial. Patients who discontinue trial treatment should be assessed by the investigator who must document the case on the appropriate eCRF.

11. Safety of Investigational Medicinal Products

Please note that both nivolumab and ipilimumab are considered as Investigational Medicinal Product (IMP). Cisplatin, carboplatin and etoposide constitute the required chemotherapy, but are not investigational.

11.1. Ipilimumab

11.1.1. Safety profile of ipilimumab

The safety profile of ipilimumab at a dose of 10 mg/kg was characterised in a total of 325 patients who received multiple doses of 10 mg/kg ipilimumab as monotherapy in the 4 completed melanoma studies (CA184004, -007, -008, and -022). Overall, the incidence of Grade 3/4 AEs attributable to study drug was 31%. The target organ system, the incidence and the severity of the most commonly observed irAEs are displayed in Table 11.

Table 11: Summary of irAE safety data for 10 mg/kg ipilimumab in melanoma

	Total (%)	**Low-grade (Grade 1 - 2) (%)**	**High-grade (Grade 3 - 4) (%)**	**Median Time to Resolution of Grade 2 - 4 irAEs (weeks)**
All irAEs	72.3	46.2	25.2	-
Skin (eg, rash, pruritus)	52.0	49.2	2.8	6.14
GI (eg, colitis, diarrhoea)	37.2	24.9	12.3	2.29
Liver (eg, LFT elevations)	8.0	0.9	6.8	4.0
Endocrine (eg, hypophysitis, hypothyroid)	6.2	3.7	2.5	20.1

Overall, the 10 mg/kg had an acceptable safety regimen, while being the most active dose. The study drug-related deaths across the program are in section 5 of the IB.

Across clinical studies that utilised ipilimumab doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, oesophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

11.1.2. Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralising antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ipilimumab with the incidences of antibodies to other products may be misleading.

11.1.3. Pregnancy outcomes

The use of ipilimumab during human pregnancy has not been formally studied in clinical trials.

As of Jan 2013, 20 healthcare professional confirmed reports of exposure to ipilimumab during pregnancy. Of these, 17 were clinical trial cases and 2 were spontaneous cases. Thirteen of the 20 cases were paternal exposure to blinded therapy (8) or open-label ipilimumab (4) from clinical trials or spontaneously reported (1). The outcome of these 13 cases was normal infant (7), spontaneous abortion (1), full term baby with “small ureters” that was expected by the paediatrician to disappear as baby grows (1), unknown (4). In the remaining 7 maternal exposure cases (2 on blinded study), outcome was elective abortion (4), unknown (2), premature baby (1) at 36 gestational weeks with respiratory distress that resolved by birth week 16

11.1.4. Immune-related adverse reactions with ipilimumab

Ipilimumab can result in severe and fatal immune-related reactions due to T-cell activation and proliferation.

11.1.4.1. Immune-related gastrointestinal events

As of 24-Jan-2013, 78 patients (<1%) reported a bowel wall perforations deemed as related to ipilimumab in open-label and completed clinical trials. Of the 78 patients with bowel wall

perforations, 61 had surgical intervention (colectomy). Twenty-four of the 78 patients died of complications associated with the bowel wall perforations.

GI perforation in association with narcotic use:

A review of the ipilimumab safety data showed that intestinal perforation in association with narcotic use reported in isolated cases is a potential safety concern. While the diarrhoea and colitis management algorithm has been effectively used for minimising the risk of complications such as immune-related events, the use of narcotics may potentially mask the GI symptoms or delay detection of their relevant complications, such as bowel perforation. Therefore, it is recommended that:

- In general, use of narcotics during the treatment with ipilimumab should be approached with caution. Extra caution should be exercised for those patients on narcotics with respect to any GI signs or symptoms. Even minor diarrhoea may indicate a more severe colitis requiring immediate attention.
- For patients already experiencing diarrhoea or abdominal pain while on ipilimumab therapy, narcotic use should be avoided. In rare cases where the use of narcotics is medically required, the patients should be closely monitored for potential intestinal perforation.

11.1.4.2. Immune-related hepatotoxicity

Hepatic immune-related AEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis. Elevations in liver function tests (LFTs) may develop in the absence of clinical symptoms. Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

11.1.4.3. Immune-related skin toxicity

Skin immune-related AEs presented mostly as a rash and/or pruritus. Some patients reported vitiligo associated with ipilimumab administration. Severe reaction such as Stevens Johnson syndrome and toxic epidermal necrolysis are rarely seen. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

11.1.4.4. Immune-related endocrinopathy

Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, and adrenal insufficiency and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease.

Close monitoring of symptoms and laboratory values before each administration are important. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioural changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the patients symptomatically improved with hormone replacement therapy. It is possible that long-term hormone replacement therapy will be required for patients developing hypophysitis/hypopituitarism after treatment with ipilimumab.

11.1.4.5. Immune-related neurological events

Such events have been reported in up to 0.3% with ipilimumab monotherapy, mostly with low grade. Neurological manifestations included muscle weakness and sensory neuropathy. Fatal Guillain-Barré syndrome has been reported in clinical trials of ipilimumab. Patients may present with unilateral or bilateral muscle weakness, sensory alterations and paresthesias. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, and medications should be excluded.

11.1.4.6. Other immune-related AEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhoea in a few patients (<1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed immune-related AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, which were individually reported for <1% of patients.

Overall, immune-related AEs commonly started within 3 to 10 weeks from first dose, were successfully managed in most instances by omitting doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned above and detailed in section 10.8. Immune-related AEs generally resolved within days to weeks in the majority of patients.

11.1.5. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

11.2. Nivolumab

In a Phase I/II study of nivolumab and nivolumab combined with ipilimumab for treatment of recurrent SCLC (CA209032), patients who were platinum sensitive or refractory, and had progressive disease were enroled regardless of tumour PD-L1 status or number of prior chemotherapy regimens. This open-label study randomised patients to nivolumab 3 mg/kg i.v. every 2 weeks or nivolumab + ipilimumab (1 + 1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) i.v.

every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. The primary objective was objective response rate. Other objectives were safety, PFS, OS and biomarker analysis. The CA209032 data shown here are based on an interim database lock date of 16-Feb-2015 and focus on the treatments groups nivolumab monotherapy (3 mg/kg: N = 40) and nivolumab / ipilimumab combination (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg: N = 3; nivolumab 1 mg/kg plus ipilimumab 3 mg/kg: N = 47) which represent the groups with the longest follow up.

11.2.1. Demographics and Baseline Characteristics

All patients had prior platinum-based first-line treatment and progression after the most recent treatment regimen. Baseline characteristics were typical for a SCLC population in respect to age, smoking history and gender. 35% of patients (nivolumab monotherapy) and 56% (nivolumab/ipilimumab combination) had one prior chemotherapy treatment regimen. 35% of patients (nivolumab monotherapy) and 34% (nivolumab/ipilimumab combination) had platinum-resistant or refractory disease.

11.2.2. Exposure and Disposition

As of the 16-Feb-2015 database lock, 20% of patients (nivolumab monotherapy), 33% (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg), and 43% (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) were continuing study treatment. Patients in the different cohorts were in part sequentially enroled with patients in the combination cohorts in general at later timepoints, resulting in a shorter follow up for patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group. 7.5% of patients (nivolumab monotherapy) and 11% (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) permanently discontinued treatment because of treatment related AEs.

11.2.3. Safety

Nivolumab monotherapy in patients with SCLC was well tolerated. 52.5% of the patients had drug-related AEs of any grade, 15.0% with Grade 3-4 events (Table 12). There were no drug related adverse AEs leading to death. The most frequent (≥10%, any grade) drug-related AEs were fatigue, diarrhoea, nausea, and decreased appetite (Table 12). A total of 7.5% of patients permanently discontinued treatment because of treatment related AEs (N = 3, limbic encephalitis, hyperglycemia, and stomatitis).

Nivolumab plus ipilimumab combination therapy showed a manageable safety profile. While the incidence of drug-related AEs (nivolumab 1 mg kg plus ipilimumab 3 mg/kg: 76.6% any grade, 34% Grade 3-4) was higher than in the nivolumab monotherapy group (Table 12), the treatment discontinuation rate for treatment related AEs was 11% (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg): N = 5, diarrhoea, myasthenia gravis [subsequently developing complications with fatal outcome], pneumonitis, cardiomyopathy, one patient with hypothyroidism, hyperglycemia and increased ALT). The most frequent (≥10%, any grade) drug-related AEs

were diarrhoea, fatigue, rash, pruritus, hypothyroidism, rash maculo-papular, nausea, hyperthyroidism, and lipase increased (Table 12).

One treatment-related death in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort occurred. This patient developed myasthenia gravis (reported as Grade 4) after treatment start and suffered from complications causing the patient's death.

Limbic encephalitis was reported in 3 patients and resolved with immunosuppressive treatment in 2 cases. Another patient had a minor response to immunosuppressive treatment and eventually died due to the underlying tumour disease.

Table 12: Drug-related AEs ⩾5% (any grade) and all Grade 3-5 AEs – SCLC patients treated with nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg combination therapy

System organ class (%)	Nivolumab (N = 40)			Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N = 47)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Total patients with an event	21 (52.5)	6 (15.0)	0	36 (76.6)	16 (34.0)	0
Gastrointestinal disorder	10 (25.0)	1 (2.5)	0	19 (40.4)	6 (12.8)	0
Skin and subcutaneous tissue disorder	6 (15.0)	0	0	21 (44.7)	4 (8.5)	0
General disorders and administration site conditions	7 (17.5)	1 (2.5)	0	11 (23.4)	0	0
Endocrine disorders	2 (5.0)	0	0	10 (21.3)	0	0
Metabolism and nutrition disorder	6 (15.0)	1 (2.5)	0	7 (14.9)	1 (2.1)	0
Nervous system disorder	3 (7.5)	0	0	6 (12.8)	1 (2.1)	0
Respiratory, thoracic and mediastinal disorders	3 (7.5)	0	0	4 (8.5)	2 (4.3)	0
Musculoskeletal and connective tissue disorders	4 (10.0)	0	0	2 (4.3)	0	0
Cardiac disorders	0	0	0	3 (6.4)	1 (2.1)	0
Infections and infestations	3 (7.5)	1 (2.5)	0	2 (4.3)	0	0
Hepatobiliary disorders	0	0	0	1 (2.1)	1 (2.1)	0
Injury, poisoning and procedural complications	2 (5.0)	0	0	1 (2.1)	0	0

11.2.4. Rationale to support nivolumab monotherapy "flat" dose of 240 mg

Nivolumab monotherapy has been extensively studied in NSCLC patient population and other solid tumour indications with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of patients in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected in these studies, together with PK data from several Phase I, II and III clinical studies of nivolumab monotherapy in solid tumours. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that an mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients. Table 13 presents summary statistics of the estimated nivolumab steady state trough, peak and time-averaged concentration (C_{minss}, C_{maxss}, and C_{avgss}, respectively) in NSCLC patients receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a "flat" nivolumab dose of 240 mg. It should be noted that a dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for patients weighing 80 kg, which is the approximate median body weight of NSCLC patients in the 3 Phase II and III clinical studies of nivolumab monotherapy in NSCLC patients (CA209017, CA209057, and CA209063). As evident from the data presented in Table 13, the geometric mean values of C_{minss}, C_{maxss}, and C_{avgss} with flat dosing are slightly (<15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv %) in these measures of exposure are only slightly (<10%) greater than that of 3 mg/kg dosing.

Table 13: Summary statistics of nivolumab steady-state exposure

Nivolumab Dose	**C_{minss} Geo. Mean** [μg/mL] (cv %)	**C_{maxss} Geo. Mean** [μg/mL] (cv %)	**C_{avgss} Geo Mean** [μg/mL] (cv %)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)
240 mg	61.5 (44.6)	133.7 (35.0)	84.2 (38.2)

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

11.3. Safety profile of nivolumab and ipilimumab combination therapy

The CA209067 study was conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in patients with previously untreated metastatic melanoma [65]. Eligible patients had histologically confirmed stage III (unresectable) or stage IV melanoma and had received no prior systemic treatment for advanced disease. In this double-blind, phase III study, enroled patients were randomly assigned in a 1:1:1 ratio to receive one of the following regimens: 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo); 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond; or 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo). Overall, 945 patients were enroled (nivolumab: n = 316; ipilimumab: n = 315; nivolumab plus ipilimumab n = 314).

Treatment-related adverse events of any grade occurred in 82.1% of the patients in the nivolumab group, 95.5% of those in the nivolumab-plus-ipilimumab group, and 86.2% of those in the ipilimumab group. The most common adverse events in the nivolumab-plus-ipilimumab group were diarrhoea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%). The incidence of treatment-related adverse events of Grade 3 or 4 was also higher in the nivolumab plus-ipilimumab group (55.0%) than in the nivolumab group (16.3%) or the ipilimumab group (27.3%).

Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the patients in the nivolumab group, 36.4% of those in the nivolumab-plus-ipilimumab group, and 14.8% of those in the ipilimumab group, with the most common events being diarrhoea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively). One death due to toxic effects of the study drug was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest); none were reported in the nivolumab-plus-ipilimumab group.

Immune modulatory agents, including topical agents, to manage adverse events were used in 47.0% of the patients in the nivolumab group, 83.4% of those in the nivolumab-plus-ipilimumab group, and 55.9% of those in the ipilimumab group, with secondary immunosuppressive agents (e.g., infliximab) used in 0.6%, 6.1%, and 5.1% of the patients, respectively. Resolution rates for select adverse events of Grade 3 or 4 were between 85 and 100% in the nivolumab-plus-ipilimumab group for most organ categories. As in prior studies, most endocrine events did not resolve and patients continued on physiological hormone substitution.

In general, the safety profile of the combination therapy was consistent with previous experience with nivolumab or ipilimumab alone. No new safety signals were identified, and there were no drug-related deaths in the combination group. Adverse events were manageable with established treatment guidelines, and most select adverse events resolved with the use of immune-modulatory agents.

11.4. Early analysis for treatment related pneumonitis

Pneumonitis related to radiation has been observed in 15-20% of patients treated with chemo-radiotherapy. In order to exclude an exacerbation by nivolumab and ipilimumab treatment, a safety evaluation will take place 12 weeks after the first 30 patients have been randomised to the experimental arm (total of 60 pts, 30 in the nivolumab plus ipilimumab combination and 30 in observation arm). This first safety evaluation will be submitted to the IDMC for advice (see also sections 4.7 and 18.5).

11.5. Cisplatin

The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricaemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Nephrotoxicity: Renal toxicity has been noted in about one third of patients given a single dose of cisplatin when prior hydration has not been employed. It is first noted during the second week after a dose and is manifested by elevations in plasma urea and serum creatinine, serum uric acid and/or decrease in creatinine clearance.

Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to acceptable levels before another dose of cisplatin can be given.

Renal function impairment has been associated with renal tubular damage. The administration of cisplatin using a 6-8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity. However renal toxicity still can occur after utilisation of these procedures.

Gastrointestinal toxicity: Nausea and vomiting occur in the majority of patients, usually starting within 1 hour of treatment and lasting up to 24 hours. Anorexia, nausea and occasional vomiting may persist for up to a week.

Ocular toxicity: There have been reports of optic neuritis, papilloedema and cerebral blindness following treatment with cisplatin. Improvement and/or total recovery usually occurs following immediate discontinuation. Blurred vision and altered colour perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended.

Ototoxicity: Ototoxicity has occurred in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2. Ototoxicity may be more severe in children and more frequent and severe with repeated doses.

Careful monitoring should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Unilateral or bilateral tinnitus, which is usually reversible, and/or hearing loss in the high frequency range may occur.

The overall incidence of audiogram abnormalities is 24%, but large variations exist. These abnormalities usually appear within 4 days after drug administration and consist of at least a 15 decibel loss in pure tone threshold. The damage seems to be cumulative and is not reversible. The audiogram abnormalities are most common in the 4000-8000 Hz frequencies.

Haemotoxicity: Myelosuppression is observed in about 30% of patients treated with cisplatin. Leucopenia and thrombocytopenia are more pronounced at higher doses. The nadirs in circulating platelets and leucocytes generally occur between days 18-23 (range 7.3 to 45) with most patients recovering by day 39 (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/m2. Anaemia (decreases of greater than 2 g% haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leucopenia and thrombocytopenia. Subsequent courses of cisplatin should not be instituted until platelets are present at levels greater than 100,000/mm2 and white cells greater than 4,000/mm2. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin.

Anaphylaxis: Reactions possibly secondary to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Serious reactions seem to be controlled by i.v. adrenaline, corticosteroids or antihistamines.

Serum electrolyte disturbances: Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia and hypophosphataemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Hypomagnesaemia and hypocalcaemia may result in tetany. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate antidiuretic hormone syndrome has also been reported.

Neurotoxicity: Usually characterised by peripheral neuropathies and paresthesia in both upper and lower extremities. Peripheral neuropathy, while reversible, may take a year or more to recover. Loss of taste and seizures have also been reported. Neuropathies resulting from cisplatin treatment may occur after prolonged therapy; however, neurological symptoms have

been reported to occur after a single dose. The neuropathy may progress after stopping treatment.

Hyperuricaemia: Hyperuricaemia occurring with cisplatin is more pronounced with doses greater than 50 mg/m^2. Allopurinol effectively reduces uric acid levels.

Other toxicities: Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (haemolytic uraemic syndrome) or cerebral arteritis. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesaemia developing coincident with the use of cisplatin may be an added, although not essential factor, associated with this event. However the cause of this Raynaud's phenomenon is currently unknown.

Other toxicities reported to occur infrequently are cardiac abnormalities including tachycardia and arrhythmia.

Local soft tissue toxicity has been reported rarely following extravasation of cisplatin. Infiltration of solutions of cisplatin may result in tissue cellulitis, fibrosis and necrosis.

11.6. Carboplatin

The following adverse reactions have been reported:

Frequency definition:

Very common (≥1/10)

Common (≥1/100, <1/10)

Uncommon (≥1/1,000, <1/100)

Rare (≥1/10,000, <1/1,000)

Very rare (<1/10,000), not known (cannot be estimated from the available data)

Cardiac and vascular disorders

Very rare: Cardiovascular events (cardiac failure, embolism) as well as cerebrovascular events (apoplexy) have been reported in single cases (causal relationship with carboplatin not established). Single cases of hypertension have been reported.

Blood and lymphatic system disorders

Very common: Myelosuppression is the dose-limiting toxicity of carboplatin. Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65. Myelosuppression is also worsened by therapy combining carboplatin with other compounds that are myelosuppressive.

Myelosuppression is usually reversible and not cumulative when carboplatin is used as a single agent and at the recommended dosages and frequencies of administration.

At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50 x 10^9/L, occurs in about a third of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy.

Leucopenia has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14-28) may be slower and usually occurs within 42 days from the start of therapy. Neutropenia with granulocyte counts below 1 x 10^9/L occurs in approximately 1/5 of patients. Haemoglobin values below 9.5 mg/100 mL have been observed in 48% of patients with normal base-line values. Anaemia occurs frequently and may be cumulative.

Common: Haemorrhagic complications, usually minor, have also been reported.

Uncommon: Infectious complications have occasionally been reported.

Rare: Cases of febrile neutropenia have been reported. Single cases of life-threatening infections and bleeding have occurred.

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary fibrosis manifested by tightness of the chest and dyspnoea. This should be considered if a pulmonary hypersensitivity state is excluded (see General disorders below). Interstitial pneumonitis under high dose therapy.

Nervous system disorders

Common: The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in elderly patients and those previously treated with cisplatin. Paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin.

Uncommon: Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy.

On prolonged therapy with carboplatin: convulsions, peripheral neuropathies have been reported.

Eye disorders

Rare: Transient visual disturbances, sometimes including transient sight loss, have been reported rarely with platinum therapy. This is usually associated with high dose therapy in renally impaired patients. Optic neuritis has been reported in post marketing surveillance.

Ear and labyrinth disorders

Very common: Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.

Common: Clinical ototoxicity (clinical hearing deficits). Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen.

At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin was administered.

Gastrointestinal disorders

Very common: Nausea without vomiting occurs in about a quarter of patients receiving carboplatin vomiting has been reported in over half of the patients and about 1/3 of these suffer severe emesis. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of carboplatin, usually disappear within 24 hours after treatment and are usually responsive to (and may be prevented by) anti-emetic medication. A quarter of patients experience no nausea or vomiting. Vomiting that could not be controlled by drugs was observed in only 1% of patients. Vomiting seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin.

Painful gastrointestinal disorders occurred in 17% of patients.

Common: Diarrhoea (6%), constipation (4%), mucositis.

Rare: Taste alteration. Cases of anorexia have been reported. Haemorrhagic colitis under high dose therapy.

Renal and urinary disorders

Very common: Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as high volume fluid hydration or forced diuresis. Nevertheless, increasing uric acid and blood urea nitrogen levels or serum creatinine levels can occur.

Common: Renal function impairment, as defined by a decrease in the creatinine clearance below 60 mL/min, may also be observed. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy.

It is not clear whether an appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41-59 mL/min) or severe renal impairment

(creatinine clearance 21-40 mL/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 mL/min.

Skin and subcutaneous tissue disorders

Common: Alopecia, rash, skin irritation.

Metabolism and nutrition disorders

Very common: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms.

Rare: Cases of hyponatraemia have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Secondary malignancies (including promyelocytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).

General disorders and administration site conditions

Very common: Hyperuricaemia is observed in about 1/4 of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia.

Common: Malaise, urticaria, flu-like syndrome, erythematous rash, pruritis,

Uncommon: Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis

Rare: Haemolytic uraemic syndrome.

Immune system disorders

Common: Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum containing compounds and should be managed with appropriate supportive therapy.

Rare: Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial oedema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia have occurred. These were reactions similar to those seen after cisplatin therapy, but in a few cases no cross-reactivity was present.

Hepatobiliary disorders

Very common: Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about 1/3 of the patients with normal baseline values. The alkaline

phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.

Rare: Severe hepatic dysfunction (including acute liver necrosis) has been reported after administration of higher than recommended carboplatin dosages.

11.7. Etoposide

The following adverse reactions have been reported:

Table 14: Summary of AE safety data for etoposide

System Organ Class	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)	Not known
Infections and infestations						Infections have been reported in patients with bone marrow depression
Neoplasms benign and malignant		Leukaemia secondary to oncology chemotherapy*				Acute promyelocytic leukemia
Blood and lymphatic systems disorders	Myelosuppression**, leucopenia, thrombocytopenia, anaemia					
Immune system disorders		Anaphylactic-like reactions***				
Metabolism and nutrition disorders	Anorexia			Hyperuricaemia		
Nervous system disorders	Central nervous system disorders (fatigue, drowsiness)		Peripheral neuropathies	Insults, paraesthesiae, optic neuritis, taste disturbance		
Eye disorders				Reversible loss of vision, transient		
Cardiac disorders			Arrhythmia, myocardial infarction, cyanosis			

System Organ Class	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)	Not known
Vascular disorders		Hypotension[%], haemorrhage (in patients with severe myelosuppression)		Phlebitis		
Respiratory, thoracic and mediastinal disorder			Bronchospasm, coughing, laryngospasm	Apnoea, interstitial pneumonitis or pulmonary fibrosis		
Gastrointestinal disorder	Nausea, vomiting	Abdominal pain, diarrhoea, stomatitis	Mucositis, oesophagitis	Constipation, swallowing disorders (dysphagia		
Hepatobiliary disorders		Hepatic dysfunction				
Skin and subcutaneous tissue disorders	Reversible alopecia (sometimes progressing to total baldness)		Rash, urticaria, pigmentation and pruritus		Toxic epidermal necrolysis, radiation "recall" dermatitis, hand-foot syndrome	
Renal and urinary disorders	Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment					
General disorders and administration site conditions		Fatigue		Asthenia; after extra-vasation, irritation of soft tissue and inflammation occur occasionally		
Investigations		Bilirubin increased, SGOT increased, alkaline phosphatase increased				

* The risk of secondary leukaemia among patients with germ-cell tumours after treatment with etoposide is about 1%. This leukaemia is characterised with a relatively short latency period (mean 35 months), monocytic or myelomonocytic FAB subtype, chromosomal abnormalities at 11q23 in about 50% and a good response to chemotherapy. A total cumulative dose (etoposide >2 g/m²) is associated with increased risk.

Etoposide is also associated with development of acute promyelocytic leukaemia (APL). High doses of etoposide (>4,000 mg/m2) appear to increase the risk of APL.

** Myelosuppression is dose limiting, with granulocyte nadirs occurring 5 to 15 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported.

Fatal cases of myelosuppression have been reported.

Infections have been reported in patients with bone marrow depression.

*** Anaphylactic-like reactions characterised by fever, flushing, tachycardia, bronchospasm, and hypotension have been reported (incidence 0.7-2%), also apnoea followed by spontaneous recurrence of breathing after withdrawal of etoposide infusion, increase in blood pressure. The reactions can be managed by cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines and/ or volume expanders as appropriate.

Anaphylactoid-like reactions may occur after the first intravenous administration of etoposide.

Erythema, facial and tongue oedema, coughing, sweating, cyanosis, convulsions, laryngospasm and hypertension have also been observed. The blood pressure usually returns to normal within few hours following cessation of therapy.

% Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to supportive therapy after cessation of the administration. When restarting the infusion, a slower administration rate should be used.

\+ Phlebitis has been observed following bolus injection of etoposide. This adverse reaction can be avoided by i.v. infusion over 30 to 60 minutes.

Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.

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 is defined as any untoward medical occurrence that occurs from the day of enrolment in the RDE until 100 days after the final dose of IMP, regardless of whether it is considered related to the trial treatment. The relationship of the adverse event with the administered trial treatment has to be indicated (unrelated – unlikely – possible – probable – 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.

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 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:

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

Note:

- Baseline symptoms will be recorded on the eCRF and changes in grade as well as resolution of an AE during treatment have to be reported
- Laboratory abnormalities for non-safety parameters will be documented on the AE eCRF from Grade ≥3 only
- AEs should not be reported in a narrative description.

12.2. Targeted Adverse Events for chemo-radiotherapy

The following adverse events must be documented if observed during the chemo-radiotherapy phase of trial treatment:

CTCAE Version 4.0 system organ class / preferred terms:

Blood and lymphatic system disorders

Anaemia

Febrile neutropenia

Ear and labyrinth disorder

Tinnitus

Infections and infestations

Infections and infestations - Other, specify

Investigations:

Platelet count decreased

Neutrophil count decreased

Renal and urinary disorders

Acute kidney injury

Respiratory, thoracic and mediastinal disorders

Pneumonitis

12.3. Definition of immune-related Adverse Events (irAE)

The following adverse events are of special interest and must be documented after randomisation 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

Diarrhoea

Colonic perforation

Small intestinal perforation

Gastric perforation

Gastrointestinal disorders - Other, specify

Hepatobiliary disorders

Hepatic failure

Hepatitis viral

Drug-induced liver injury (DILI) (see section 12.4)

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

12.4. Drug-induced liver injury (DILI):

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential DILI is defined as:

1) ALT or AST elevation >3 times upper limit of normal (ULN)

AND

2) Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

A hepatic AE management algorithm has been established (appendix 2 to the nivolumab IB) for appropriate management of DILI cases.

12.5. Definition of Serious Adverse Event (SAE)

12.5.1. SAEs during trial treatment

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 hospitalisation,
- 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 (see section 12.9)

Second (non-SCLC) 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 jeopardise the patient are also considered SAEs. An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

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 of the investigational drug 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 investigational 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 SAEs are hospitalisations occurring under the following circumstances:

- elective surgery;

- occur on an outpatient basis and do not result in admission (hospitalisation <24 h);
- are part of the normal treatment or monitoring of the studied treatment;
- progression of disease (by convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting).

12.5.2. SAEs after end of trial treatment

During the follow-up phase (starting 100 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 (see section 12.9)

12.6. Definition of Serious Adverse Drug Reaction (SADR)

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

12.7. 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, the European summary of product characteristics, and the relevant IBs.

12.8. Reporting SAEs and protocol-specified significant events

Following the patient's written consent to participate in the study, all SAEs, whether related or not to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of the last administered study medication or within 100 days after the last visit in the observation arm.

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

DILI are to be reported by submitting the completed SAE Initial Report eCRF in the RDE system, even if they do not meet any of the seriousness criteria. Please submit the completed SAE Report eCRF (initial and follow-up) in the RDE system within 24 hours if the event is serious, or within 5 days, if the event is non serious, after awareness of the event. Indiate in "Description" section if "non-serious adverse event of special interest" yes or no

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

+41 31 389 92 29

Once the RDE system is available again, the SAE eCRF has to be completed and submitted by the site.

The SAE outcome must be reported within 14 days after initial reporting by online submitting the SAE Follow-up Report eCRF. 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 (if applicable by local law).

The ETOP Safety Office will inform Bristol-Myers Squibb (by e-mail to worldwide.safety@bms.com) of all SAEs – regardless of relatedness – and other appropriate persons (per either investigator or ETOP Safety Office review) within 24 hours of receipt.

The ETOP Safety Office will record the SAE and prepare a summary report of all SAEs received. Listings of SAEs will be prepared as required.

12.9. Pregnancy

Patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential.

Women of childbearing potential and sexually active men must use highly effective contraception during treatment with nivolumab and ipilimumab and until 12 months thereafter. Please refer to section 10.10 for highly effective contraception methods.

In the case of pregnancy occurring during the course of the trial or within 12 month after treatment discontinuation, the investigator shall immediately (within 24 hours after awareness of pregnancy) notify ETOP by completing the pregnancy form in ETOPdata in accordance with the SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported (within 14 days) on the Pregnancy Form in ETOPdata.

Any pregnancy that occurs in a female partner of a male study participant should be reported to ETOP. Information on this pregnancy will be collected on the Pregnancy Form.

13. Response evaluation

13.1. RECIST 1.1 criteria

The patient's response to chemo-radiotherapy treatment and to nivolumab plus ipilimumab consolidation treatment will be assessed by RECIST 1.1 criteria (see appendix 2). Only patients with stable or responding disease will be eligible for randomisation. The response assessment according to RECIST 1.1 should be done by the local radiologist and reported on the eCRF.

For exploratory purposes, the response in the randomised nivolumab plus ipilimumab consolidation phase of the trial will also be assessed post-hoc centrally by immune-related response criteria based on RECIST 1.1.

13.2. CT Schedule for tumour assessment

Before randomisation:

At baseline: brain MRI (or contrast enhanced CT of the brain), and whole body FDG-PET CT including a contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals). If FDG-PET CT is not available, contrast enhanced CT of the thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan is required for tumour assessment at baseline.

Within 14 days prior to randomisation: contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals)

After randomisation:

For both treatment arms, post randomisation CT scans of thorax and upper abdomen will be repeated according to the schedule indicated below, until tumour progression:

- up to 18 months:	every 9 weeks	9, 18, 27, 36, 45, 54, 63, 72, 81 (+/- 1 week)
- up to 2 years:	every 12 weeks	93, 105 (+/- 1 week)
- years 3 and 4:	every 6 months (26 weeks)	131, 157, 183, 209 (+/- 1 week)
- at 5 years:		260 (+/- 1 week)

13.3. Determination of time point response

Table 15: Determination of time point response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD

Target lesions	Non-target lesions	New lesions	Overall response
Not all evaluated	Non-PD	No	NE unless the sum of diam. of *evaluated* lesions indicates PD [1)]
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

1) From ref. 1 in appendix 2, p.234: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

13.4. Determination of best overall response

Best overall response is defined as best response across all time points. Confirmation of partial or complete response by an additional scan is not requested in this trial.

13.5. Storage of imaging

All CT, FDG-PET-CT scans and MRI images must be stored locally in electronic format for later central review, please consult the ***STIMULI procedures manual*** for detail.

14. Endpoints definition

14.1. Progression-free survival

It is defined as the time from the date of randomisation until documented progression or death, if progression is not documented. Censoring will occur at the last tumour assessment only if patient is lost to follow-up.

14.2. Overall survival

Defined as time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

14.3. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from randomisation to termination of trial treatment. Objective response to chemo-radiotherapy will be determined by tumour assessment around week 15 (see trial schedule in section 2).

Objective response to IMP treatment will be determined using RECIST 1.1 criteria (see section 13).

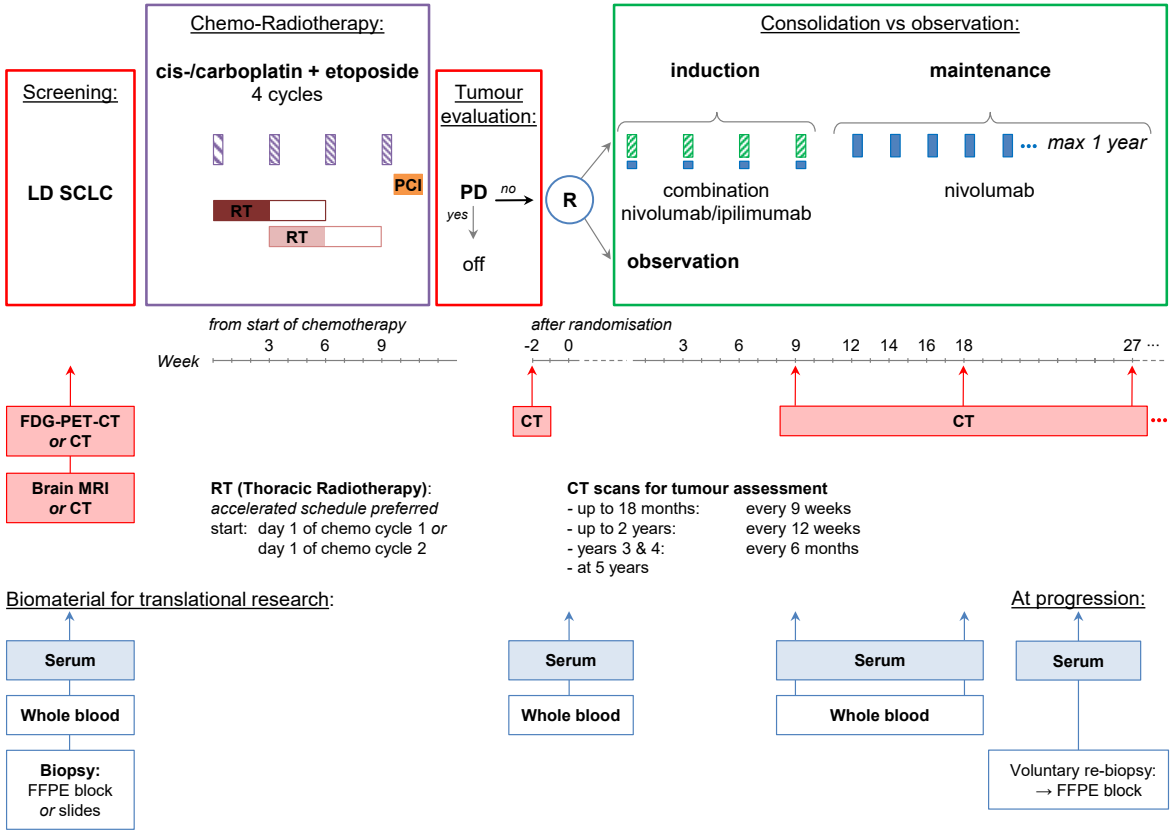
14.4. Time to treatment failure

Defined as time from the date of randomisation to discontinuation of treatment for any reason (including progression of disease, treatment toxicity, refusal and death). Censoring will occur at the last follow-up date.

14.5. Toxicity

Adverse events classified according to NCI CTCAE Version 4.

15. Biological material and translational research



15.1. Mandatory evaluations

Serum levels of TNF α/β and IL6, and circulating antibodies will be determined centrally in every patient from samples taken prior to or at enrolment, at the time of randomisation, 9 and 18 weeks (+/- 3 days) after randomisation and at the time of progression.

15.2. FDG-PET CT

A pre-chemo-radiotherapy whole body FDG-PET-CT will be taken before enrolment to assess background FDG avidity in the tumour, the hilar and mediastinal lymph nodes (if involved at staging), and the lungs. If FDG-PET CT is not available, contrast enhanced CT of the thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan is required for tumour assessment at baseline.

FDG-PET CT images must be stored locally in electronic format for later central review, please consult the ***STIMULI procedures manual*** for detail.

15.3. Optional evaluations

A biobank will be created with centralised samples for translational research. Tumour blocks, PBMCs (selected centres only), whole blood and mandatory serum sample will be centrally collected and biobanked at the Ludwig Institute for Cancer Research at University of Lausanne, Switzerland.

15.3.1. Blood sample

Whole blood samples will be taken at baseline, at randomisation and 9 and 18 weeks (+/- 3 days) after randomisation, as follows:

- 2.5 mL in PAXgene tubes for RNA profiling;
- At selected sites: 50 mL in lithium heparin tubes for immunomonitoring with blood cell subtyping and quantification, including FACS analysis.

  For details on blood collection and processing of samples, please consult the ***STIMULI procedures manual.***

15.3.2. FFPE material

A diagnostic tumour FFPE block, or a cell block if the diagnosis is done by cytology, will be collected from all consenting patients. If requested, these blocks can be returned to the submitting site after the slides for the analyses have been cut. If no blocks can be submitted, 5-10 sections with a minimum thickness of 15-20µm from the tumour block or cell blockcan be submitted instead. If further slides can be be provided, 5 sections at 4-5 µm thickness should also be submitted for immunohistochemistry characterization. All slides should be freshly cut.

Progressing patients will be asked for a voluntary re-biopsy, if possible not in an irradiated area to avoid fibrotic tissue.

15.3.3. Translational research

The following projects will be considered, at least, and subsequently adapted according to the growing knowledge about immunological modification observed and potential biomarkers of nivolumab plus ipilimumab immunotherapy:

- Presence of infiltrating lymphocytes in tumour (TILs) will be evaluated. Study and characterisation of TILs in detail will be performed using flow cytometry and functional in vitro assays.
- Tregs and T effectors quantitative analyses by FACS
- Immune modulation on respective lymphocyte subtypes by FACS
- Measurement and characterisation of T-cell infiltration, T-cell subsets and activation, and immune activation using multispectral immunohistochemistry (IHC) to quantify immune cell subsets. Immunohistochemistry on tumour micro-environment for immune cell infiltration description.
- Gene expression profile (targeting selected panel of immune-related genes) will be analysed by deep sequencing, using Next Generation Sequencing technology including TCR sequencing to capture clonal expansion of TILs.
- Multiple tumour, inflammatory- and immune-related genes will be analysed by multiplex Nanostring technology.
- PD-L1 expression

15.4. Submission of material

The tissue and blood samples collected during the conduct of the trial must be marked with the patient identifier issued by the RDE system and shipped to the central reference laboratory (Ludwig Institute for Cancer Research, University of Lausanne, Switzerland) and will be stored there for an unlimited time. This precious material will be used for central quality assurance and made available for translational research projects.

15.4.1. Submission of FFPE material

The following items should be submitted for all patients:

1. Pathology Report from diagnostic biopsy (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed)
2. Tumour block or cell block from diagnostic biopsy, or alternatively 5-10 sections of at least 15-20 µm from the tumour block or cell block, and, when feasible, also 5 freshly cut sections at 4-5 µm thickness.

Recommended, but not required:

3. Pathology report from re-biopsy at progression (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed)
4. Tumour or cell block from re-biopsy at progression, or alternatively 5-10 sections of at least 15-20 µm from the tumour block or cell block, and, when feasible, also 5 freshly cut sections at 4-5 µm thickness.

Paraffin-embedded cell blocks are a valuable alternative to tumour blocks. Cytology smears alone are not accepted in this trial. Tumour material should be submitted as soon as obtained, and documented in the Biological Material Tracking eCRF in the database. If requested, these blocks can be returned to the submitting site after the slides for the analyses have been cut.

Alternatively, 5-10 sections of at least 15-20µm will be acceptable if the tumour block is not available for banking. If further slides can be provided, 5 freshly cut sections at 4-5 µm thickness should also be submitted.

All reports, slides, and blocks must be marked with the patient identification number issued by the RDE system. The pathology number, and any other identification should be removed or blackened.

Please ensure that the blocks and/or slides are carefully packaged as otherwise they could easily get damaged during transport.

Samples have to be sent to:

Ludwig Center for Cancer Research
Hôpital Orthopédique HO 05/1552
Av. P-Decker 4
CH-1011 Lausanne, Switzerland

Anonymised pathology reports should be uploaded via the RDE system. Please consult the ***STIMULI procedures manual*** for specific instructions.

15.4.2. Submission of blood and serum samples

Blood collection and serum preparation (see ***STIMULI procedures manual)***:

- 2.5 mL whole blood will be put into PAXgene tubes (Qiagen; for gene profiling) and stored locally at -80°C.
- Serum samples taken from 5mL blood should be immediately frozen at -80ºC
- 50 mL blood will be collected to isolate PBMCs (in selected centers only)

Samples will be kept at the participating site until shipment. Shipments will be arranged centrally. Samples have to be sent to the same address as indicated above (section 15.4.1).

15.5. Banking of biological material

ETOP has established a central repository for tissue blocks/slides, PBMCs, whole blood and serum samples from every patient enroled in this trial. The required pathological material (described in the previous section) is submitted to, catalogued, and maintained at the Ludwig Institute for Cancer Research, University of Lausanne, Switzerland, and will be made available for translational research, following completion of the primary trial translational research objectives.

16. Trial procedures

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

16.1. Trial phases

The trial consists of the following phases:

16.1.1. **Screening**: Baseline evaluations must be done within 28 days prior to enrolment (if the first chemotherapy cycle has been administered before enrolment, baseline evaluations must have been done within 35 days before start of first chemotherapy cycle). Please consult the ***STIMULI procedures manual*** for details.

16.1.2. **Chemotherapy-radiotherapy**:
Chemotherapy: will be started in the week following enrolment (alternatively, maximum 1 cycle of chemotherapy may be administered before enrolment) and consists of 4 cycles of cisplatin (25 mg/m^2 i.v. on days 1 - 3 or 75 mg/ m^2 on day 1) or carboplatin (AUC 5-6, calculated according Calvert formula, i.v. on day 1), plus etoposide (100 mg/ m^2 i.v. on days 1 – 3), repeated every 3 weeks (+/- 3 days without cycle delay).

Thoracic radiotherapy: Two different radiation doses are allowed: the recommended schedule is 45 Gy in 30 twice-daily fractions of 1.5 Gy (6-8 hours apart), in 30 treatments on 5 days per week over 3 weeks (preferred). The alternative, but not-recommended schedule is 56 Gy, given in 28 once-daily fractions of 2 Gy, 5 days per week over 6 weeks. Radiotherapy should start on day 1 of chemotherapy cycle 1 or on day 1 of chemotherapy cycle 2. Radiotherapy start on day 1 of cycle 3 is allowed as an exception if patient is enroled after the first cycle only.

Prophylactic cranial irradiation (PCI): 25 Gy in 10 fractions starting between day 8 and day 15 of first day of chemotherapy cycle 4 and finished not later than day 29 from start of cycle 4.

16.1.3. **Consolidation phase**: Nivolumab plus ipilimumab combination therapy (induction) is to start within 6-8 weeks (42-56 days) from start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation.

a) **Induction:**
- 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), for 4 cycles

b) **Maintenance:**
Nivolumab at a dose of 240 mg i.v. over a period of 30 minutes, once every 2 weeks (+/- 2 days, without dosing delay) for maximum 12 months from start of maintenance phase. The first dose of maintenance nivolumab will be administered 3 weeks after the last IMP doses of induction phase

Upon disease progression or completion of trial treatment, further therapy will be at the discretion of the treating physician.

16.1.4. **End of treatment**: an end of treatment visit will occur within 30 days following the last administered dose of trial treatment. For patients in the observation arm the end of treatment visit is to be scheduled within 30 days following PD or 15 months after randomisation. For patients who have not been randomised the end of treatment visit is to be scheduled within 30 days following PD or within 30 days following the last chemotherapy cycle.

16.1.5. **Follow-up period**

16.1.5.1. Before tumour progression: In the first 18 months after randomisation follow-up visits will occur together with the CT scans according to the schedule indicated in section 13.2, then every 12 (+/- 1) weeks until PD for a maximum of 4.5 years after the enrolment of the last patient.

16.1.5.2. After tumour progression: follow-up visits will occur every 12 weeks in the first year after randomisation starting from date of progression, then every 6 months up to 4.5 years after the enrolment of the last patient. This applies also to patients who have been enroled but not randomised (see section 18.4).

16.2. Baseline evaluations

To be done within 28 days prior to enrolment. If the first chemotherapy cycle has been administered before enrolment, baseline evaluations must have been done within 35 days before start of first chemotherapy cycle.

16.2.1. Obtain written informed consent prior to any trial-specific evaluations or interventions

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

16.2.3. Physical examination including blood pressure [mmHg], ECOG performance status (see definition in ***STIMULI procedures manual)***, and body weight [kg], height [cm]

16.2.4. Haematology: haemoglobin, platelets, complete white blood cell count (leukocytes, neutrophils, eosinophils, basophils (or total granulocytes), lymphocytes and monocytes)

16.2.5. HIV, hepatitis B and C status

16.2.6. Renal function: serum creatinine and creatinine clearance calculated according to Cockroft-Gault

16.2.7. Hepatic function: ALT, AST, AP, bilirubin

16.2.8. Pulmonary function: relative FEV1 and DL_{CO} (%)

16.2.9. Pregnancy test for women with childbearing potential within 7 days before chemotherapy start.

16.2.10. Whole body FDG-PET-CT (with max SUV measurements) including a contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals), see procedure manual and ***STIMULI CRF completion guidelines*** for details;

OR

contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan;

16.2.11. TNM categories

16.2.12. Brain MRI (or contrast enhanced CT of the brain)

16.2.13. FFPE block from diagnosis available for biobanking (subject to additional consent). If no blocks can be submitted, 5-10 sections with a minimum thickness of 15-20µm from the tumour block or cell block can be submitted instead. Submission of additional 5 freshly cut sections at 4-5 µm thickness is desired.

16.2.14. Mandatory serum sample, whole blood sample (subject to additional consent).

16.3. During chemo-radiotherapy

To be done within 24 hours of each chemotherapy administration

16.3.1. Physical exam: blood pressure, performance status and body weight

16.3.2. Haematology: haemoglobin, platelets neutrophils

16.3.3. Hepatic function: AST, bilirubin

16.3.4. Renal function: serum creatinine and creatinine clearance (calculated according to Cockroft-Gault)

Recording symptoms, adverse events, concomitant medications.

16.4. Before randomisation

Contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals) should take place within 14 days before randomisation.

All other examinations, listed below, should take place within 7 days before randomisation:

16.4.1. Physical examination including blood pressure, performance status, and body weight

16.4.2. Haematology: haemoglobin, platelets, complete white blood cell count (leukocytes, neutrophils, eosinophils, basophils (or total granulocytes), lymphocytes and monocytes)

16.4.3. Hepatic function: AST, ALT, AP, bilirubin

16.4.4. Renal function: serum creatinine plus creatinine clearance (calculated according to

Cockroft-Gault)

16.4.5. Recording of symptoms, adverse events and concomitant medications

16.4.6. Pregnancy test

16.5. Before start of consolidation phase

16.5.1. Serum sample; whole blood sample (subject to additional consent);

16.6. During consolidation phase (induction and maintenance)

Within 3 days before the administration of the next dose, the following evaluations will be done.

In the observation arm, these evaluations should be done 9 and 18 weeks (+/- 3 days) after randomisation and thereafter every 18 weeks (+/- 1 week), according to local standard of follow-up, until PD or for maximum 15 months after randomisation. Beyond these 15 months or upon PD patients will enter the follow-up phase..

16.6.1. Recording of symptoms, adverse events and concomitant medications.

16.6.2. Physical examination including blood pressure, performance status, and body weight

16.6.3. Haematology: haemoglobin, platelets, complete white blood cell count (leukocytes, neutrophils, eosinophils, basophils (or total granulocytes), lymphocytes and monocytes)

16.6.4. Renal function: serum creatinine and creatinine clearance (calculated according to Cockroft-Gault)

16.6.5. Hepatic function: ALT, AST, AP, Bilirubin

16.6.6. Na, K

16.6.7. Serum sample; whole blood (subject to additional consent) at 9 and 18 weeks (+/- 3 days) after randomisation.

16.6.8. A serum or urine pregnancy testing is required every 6 weeks during consolidation treatment (only in experimental arm).

16.6.9. Ca, LDH, Glucose, amylase, lipase (only in experimental arm). To be done before each administration of nivolumab and ipilimumab during induction phase and then before every 3rd administration of nivolumab during maintenance phase.

16.6.10. TSH (only in the experimental arm). To be done before the 1st and the 3rd administration of nivolumab and ipilimumab during induction phase and before the 1st and then every 3rd administration of nivolumab in the maintenance phase (always within 3 days prior to next IMP dose). In case of abnormal TSH, also free T3 / T4 have to be mearured. In case a value is abnormal then free T3/T4 needs to be repeated before the next administration.

Note: For both treatment arms, post randomisation CT scans of thorax and upper abdomen

(incl. liver, kidney, adrenals) have to be repeated as indicated below, until tumour progression:

- up to 18 months:	every 9 weeks	9, 18, 27, 36, 45, 54, 63, 72, 81 (+/- 1 week)
- up to 2 years:	every 12 weeks	93, 105 (+/- 1 week)
- years 3 and 4:	every 6 months (26 weeks)	131, 157, 183, 209 (+/- 1 week)
- at 5 years:		260 (+/- 1 week)

In case of early local tumour progression documented by CT scan 9 weeks after randomisation, a radiographic assessment / scan should be performed at least 4 weeks after the original PD scan to determine whether there has been a decrease in the tumour size or disease stabilisation, or alternatively continued PD which would terminate the trial treatment. Please consult the ***STIMULI procedures manual*** for a detailed schedule.

16.7. Evaluations at progression

At progression, the following assessments are required:

16.7.1. CT thorax and upper abdomen, document progression on the respective eCRF

16.7.2. Serum sample

16.7.3. Tumour re-biopsy is strongly encouraged

16.8. 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 centre is to be scheduled within 30 days following the last dose of treatment. For patients in the observation arm the end of treatment visit is to be scheduled within 30 days following PD or 15 months after randomisation. For patients who have not been randomised the end of treatment visit is to be scheduled 30 days following PD or 30 days following the last chemotherapy cycle. The following procedures should be performed:

16.8.1. Recording of symptoms / adverse events / concomitant medications

16.8.2. Physical examination including blood pressure, performance status and body weight

16.8.3. Haematology: haemoglobin, platelets, complete white blood cell count [leukocytes, neutrophils, eosinophils, basophils (or total granulocytes), lymphocytes and monocytes]

16.8.4. Hepatic function: ALT, AST, AP, bilirubin

16.8.5. Renal function: serum creatinine and calculated creatinine clearance (according to Cockroft-Gault)

16.8.6. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after consolidation treatment stop.

16.8.7. CT thorax and upper abdomen, if not done within the last 6 weeks, and thereafter adhere to the schedule described in section 16.9, if reason for treatment discontinuation is oher than PD.

16.9. Evaluations in the follow-up phase before progression

Patients who completed consolidation treatment (this corresponds to 15 months after randomisation in the observation arm) or discontinue IMP treatment before progression should have a regular physical examination (blood pressure, performance status and weight). In the first 18 months after randomisation this has to be done together with the CT scans according to the schedule below, then every 12 (+/- 1) weeks until PD or up to 4.5 years after the enrolment of the last patient.

For both treatment arms, post randomisation CT scans of thorax and upper abdomen will be repeated according to the schedule indicated below, until tumour progression:

- up to 18 months:	every 9 weeks	9, 18, 27, 36, 45, 54, 63, 72, 81 (+/- 1 week)
- up to 2 years:	every 12 weeks	93, 105 (+/- 1 week)
- years 3 and 4:	every 6 months (26 weeks)	131, 157, 183, 209 (+/- 1 week)
- at 5 years:		260 (+/- 1 week)

16.10. Evaluations after progression / in follow-up

Patients with progression will end trial treatment and should have documented

- survival and
- further lines of treatment

every 12 weeks (+/-1 week) starting from date of progression during the first year after randomisation, then every 6 months (+/- 4 weeks) up to 4.5 years after the enrolment of the last patient.

17. Case report forms and documentation

17.1. Case report forms schedule

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

Table 16: Case report forms

CRF in ETOPdata	**To be completed**
Eligibility for Enrolment	Within 28 days after start of baseline assessments. Prior to start of 2nd cycle of chemotherapy and thoracic radiotherapy if the patient could not be enroled before the 1st cycle of chemotherapy.
Baseline for Chemotherapy	Within 14 days after enrolment
Tumour Assessment	*Before randomisation* Baseline before enrolment: within 14 days after enrolment; Baseline before randomisation: between 3-6 weeks after day 1 of chemotherapy cycle 4; After randomisation: within 14 days of date of CT scans, which take place as follows until tumour progression: - up to 18 months: every 9 (+/- 1) weeks - up to 2 years: every 12 (+/- 1) weeks - years 3 and 4: every 26 (+/- 1) weeks - at 5 years: week 260 (+/- 1)
Concomitant Medication	Continuously from date of enrolment to 30 days after end of trial treatment (100 days if applied for the treatment of AEs and/or SAEs).
Chemotherapy Cycles	Within 14 days after the last administration of chemotherapy in each cycle. For patients that have been enroled after the first chemotherapy cycle, an eCRF providing information about the 1st chemotherapy cycle has to be submitted within 14 days after enrolment.
Thoracic Radiotherapy and PCI	Within 14 days of last day of each radiotherapy
Adverse Events Chemo-radiotherapy	At baseline: within 14 days after enrolment (to record symptoms present at baseline); Within 14 days of end of each cycle of chemo-radiotherapy; Within 14 days after randomisation; Within 14 days of end-of-treatment visit if patient does not proceed to randomisation.

CRF in ETOPdata	**To be completed**
Biological Material Tracking	This eCRF is to be completed incrementally. Entries are to be made: - immediately after local storage of blood/serum samples (on same day). - immediately after submission of material (FFPE and blood/serum) for central biobanking (on same day).
Baseline before Randomisation	Within 14 days after randomisation
Eligibility Check and Randomisation	After end of chemo-radiotherapy, for randomisation
Experimental Arm / Observation Arm	Experimental arm: within 7 days of the end of each consolidation cycle (every 3 weeks during 4 induction cycles and every 2 weeks during maintenance) Observation Arm: within 7 days of each visit, which takes place at weeks 9 and 18 (+/- 3 days) after randomisation, and thereafter every 18 weeks (+/- 1 week) for 15 months after randomisation.
Adverse Events after Randomisation	After randomisation: within 14 days after randomisation (to record ongoing events present at randomisation); Experimental arm: within 7 days of end of each cycle of IMP treatment; Observation arm: to be completed within 7 days of weeks 9 and 18 and every 18 weeks thereafter; End of treatment: within 7 days after end-of-treatment visit 100 days period after last treatment / last visit in observation arm: within 14 days after follow-up visits
End of Treatment	Within 7 days after end of treatment visit (which is to take place as soon as possible after decision to end treatment/observation, but at the latest 30 days after the last dose of treatment/progression of disease)

CRF in ETOPdata	To be completed
Follow-up	Follow-up before progression: **Within 14 days** of clinical follow-up visits. In the first 18 months after randomisation these visits take place together with the CT scans (see above) and then at 3-monthly intervals until PD, for a maximum of 4.5 years after the enrolment of the last patient Follow-up after progression: <12 months post randomisation: **within 14 days** of clinical follow-up visits (which take place at 3-monthly intervals from date of progression); >12 months post randomisation: **within 14 days** of clinical follow-up visits (which take place at 6-monthly intervals from date of progression) until death, for a maximum of 4.5 years after the enrolment of the last patient. Follow-up on death: To be completed within 14 days upon awareness of death.
Serious Adverse Event Initial Report	Within 24h of awareness of SAE; Must be submitted via ETOPDdata, submission via fax to ETOP safety office only in case of inavailability of ETOPdata.
Serious Adverse Event Follow-up Report	Within 14 days of completion of initial report. If event was not resolved after 14 days, submit an additional report again within 7 days of resolution of event.
Pregnancy	Within 24h of first documentation of pregnancy; Within 14 days of end of pregnancy.
WC/LFU	Within 14 days of awareness of withdrawal of consent or loss to follow-up

Consult the ***STIMULI CRF completion guideline*** for detailed instructions on how to complete, save and submit the eCRFs.

18. Statistical considerations

18.1. Primary objective

To evaluate whether patients treated with chemo-radiotherapy and prophylactic cranial irradiation followed by nivolumab plus ipilimumab consolidation treatment have a better outcome as measured by the co-primary endpoints of overall survival and progression-free survival, compared to patients without nivolumab plus ipilimumab consolidation treatment. OS and PFS (measured from randomisation) are compared between treatment arms only for randomised patients.

Patients randomised to ipilimumab monotherapy before the protocol amendment 1 will be excluded from the efficacy analyses, and will be evaluated separately.

18.2. Sample size determination

Hyperfractionated accelerated radiotherapy has been shown to be more efficacious than radiotherapy given in a long overall treatment time. By giving twice-daily fractionation (BID), late reacting normal tissues are spared compared to the tumour, with as a consequence more temporarily acute esophagitis.

The value of twice daily (BID) radiotherapy given early and concurrently to chemotherapy was examined in a landmark trial [24] and confirmed in two meta-analyses [25, 29], which will be our benchmark data.

After a median FU of over 8 years, 2-year OS for respectively BID and QD radiotherapy was 47% and 41%, and 5-year OS was 26 % and 16 %, respectively. Median PFS was approximately 13-14 months.

18.3. Co-primary endpoint: OS and PFS

OS and PFS will be measured from randomisation and compared between treatment arms only in the cohort randomised under amendment 1.

The 2-year survival rate for the observation arm is estimated to be approximately 44% (47% for BID and 41% for QD radiotherapy, assuming half of included patients will receive BID and QD respectively). Median PFS and OS are expected to be 13.1 and 20.7 months.

For the experimental arm, medians as measured from randomisation are assumed to be 29.7 and 22.8 months for OS and PFS respectively (OS HR=0.70; PFS HR=0.57), taking into account that the patients randomised are of better prognosis than the total patients enrolled.

The overall one-sided significance level of 0.05 is split to 0.04 for OS and 0.01 for PFS. A total of 325 patients are expected to be enroled in 36 months of accrual time, leading to 260 patients randomised to 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 randomisation.

A trial duration of 87 months is necessary for the required 212 deaths to be observed, while on 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 78% for OS at the end of the trial, and 80% for PFS at the 45-months evaluation.

Total trial duration: 7.5 years

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.

Alternative scenarios for the co-primary endpoint of PFS and OS were run each in 10,000 simulations. The overall one-sided alpha level of 0.05 was split to 0.04 for OS and 0.01 for PFS. The alternative hypothesis of treatment benefit corresponds to an HR for PFS equal to 0.55, 0.60 and 0.65 and an OS HR of 0.7. A piecewise exponential survival distribution was assumed based on the above assumptions, omitting the lower end of the distribution time, i.e., events occurring before randomisation. The follow-up after randomisation was simulated according to the alternative of interest.

Power of 78% for testing OS from randomisation to end of trial and of 80% for testing PFS were generally aimed and achieved for the different scenarios. The probability of rejecting the null hypothesis regarding OS given that the null hypothesis regarding PFS was rejected was of the order of 85%-87%, while at least one rejection was achieved (power for co-primary) from 88% to 91% of the time, with 67-68% observed joint rejection.

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

18.4. Evaluation of primary and secondary objectives

The total study duration will be approximately 7.5 years including the 36 months recruitment period. The primary analyses on PFS and OS will be performed overall and stratified by radiotherapy schedule. An intent to treat primary efficacy analysis will be performed, including all eligible patients randomised (= efficacy cohort).

PFS and OS will be estimated by the Kaplan Meier method and compared between the two treatment arms by a stratified logrank test. In addition, stratified (by the randomisation stratification factors) and multivariate Cox models will be used for exploring the association of PFS and OS with treatment in the presence of prognostic factors.

The two treatment groups will also be compared with respect to secondary efficacy and tolerability endpoints. No multiplicity adjustment will be performed for these analyses.

Time to treatment failure (TTF) will be estimated by the Kaplan Meier method and compared between the two treatment arms based on the logrank test stratified by the randomisation stratification factors. Cox proportional hazards regression adjusting for prognostic factors will also be performed for this secondary endpoint.

All time-to-event endpoints will be presented and evaluated from date of randomisation, with secondary presentation from date of enrolment.

Clinical efficacy will be further described by objective response rate (ORR, defined as percentage of patients reaching a complete or partial response) based on RECIST 1.1 response

criteria. The determination of ORR will be restricted to patients who have not attained a CR during chemo-radiotherapy.

Assessment of response by immune-related response criteria based on RECIST 1.1 will be explored post-hoc, centrally, in the randomised consolidation phase of the trial.

Safety and the tolerability of the nivolumab plus ipilimumab consolidation therapy will be described by tabulation of the CTCAE Version 4 grade. The safety cohort will encompass all patients who have received at least 1 dose of IMP treatment plus all patients randomised to observation.

The correlation of biological markers with OS and PFS will be evaluated by univariate and multivariate Cox proportional hazards regression.

OS analysis will also be performed for the full cohort of 325 patients for descriptive purposes. The survival time for the full cohort will be defined as the time from enrolment into the trial until death.

Statistical analysis for the primary, secondary endpoints and translational research will be described in detail in the Statistical Analysis Plan (SAP) document.

18.5. Early safety evaluation

Pneumonitis related to radiation has been observed in 15-20% of patients treated with chemo-radiotherapy. In order to exclude an exacerbation by IMP treatment, a safety evaluation will take place 12 weeks after the first 30 patients have been randomised to the experimental arm (total of 60 pts, 30 in the nivolumab plus ipilimumab combination and 30 in observation arm). This first safety evaluation will be submitted to the IDMC for advice. The trial will continue while safety is evaluated.

Safety evaluations will be performed 4 times a year and submitted to the IDMC at their regular meeting.

19. Criteria for termination of the trial

19.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the product leads to doubt as to the benefit/risk ratio, by decision of ETOP or Trial Steering Committee, or at the suggestion of the IDMC based on the interim safety evaluations.

The trial can be terminated at any time if the authorisation and approval to conduct the Study is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or on ethical grounds.

19.2. 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 tumour) does not mandate a stop of trial therapy, patients may continue to receive protocol treatment after appearance of a second primary tumour, stopping protocol treatment is determined by the medical judgment of the treating physician.
- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have 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.

The patient will be followed for survival irrespective of whether treatment is discontinued (required provisions outlined in section 19.3).

19.3. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the timepoint of withdrawal will continue to be evaluated in the trial. The investigator should ask the patient for consent to continue to collect information on her/his disease and survival status.

It should be documented in both the medical records and in the eCRF, according to the instructions in the ***STIMULI CRF completion guidelines***, if the patient accepts to be contacted for survival status despite withdrawing the trial consent. For the patient's safety, an end of treatment visit should be performed and documented in the eCRF.

20. Ethics aspects, regulatory approval, 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).

20.1. Ethical Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

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 enrolment of the first patient.

Any modifications made to the protocol must be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

20.2. Regulatory approval procedures

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 Centre activation.

20.3. 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" (See appendix 1). 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 enrolment to this trial.

The “Declaration of Helsinki” recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material from her/his tumour and blood and serum samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e., a minor, or mentally incompetent), informed consent must be obtained from

the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with Good Clinical Practice and the "Declaration of Helsinki".

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (appendix 1), which can be edited to incorporate information specific to your institution. The template Patient Information Sheet and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the “Declaration of Helsinki”. The final version should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their Ethics Committee.

21. Governance and administrative issues

21.1. Final report

A final clinical trial report will be written and distributed to Health Authorities as required by applicable regulatory requirements

21.2. 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 chair and co-chair, trial coordinators, trial statisticians, ETOP officials, representatives from some participating institutions and groups, and a representative from Bristol-Myers Squibb.

21.3. Independent Data Monitoring Committee

The trial will be presented for review to the ETOP IDMC at each of their meetings which take place 4 times a year. Accrual and safety will be monitored.

21.4. Publication

The results of the trial will be published according to the ETOP publication policy (appendix 3).

21.5. 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.

21.6. Quality assurance

ETOP conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial Data Manager reviews each eCRF as it is received. In addition, the ETOP Medical Reviewer reviews each case at specific timepoints. ETOP conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from ETOP or its designees, or to ethics committee and health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the Centre will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing IMP, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood and serum samples.

21.7. Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact ETOP or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any deviations to the Sponsor and to the EC concerned in accordance with the applicable EC policies and procedures. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by the sponsor and approved by the IRB/IEC/ERB it cannot be implemented. All protocol deviations will be recorded.

21.8. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the RDE facility ETOPdata. 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 screening and review. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and pertinent Ethics Committees (IRB/ERB) may have access to patient data on-site. ETOP audit or monitoring personnel will also have access to such data on-site.

21.9. Record retention

The centre must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. ETOP guarantees access and availability of the data entered into ETOPdata for at least 15 years after the termination of the trial.

Longer retention may be required for participating centres according to national regulations.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to ETOP and the local Ethics Committee at least 1 month in advance.

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