ETOP 6-14 NICOLAS

A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma

NICOLAS: NIvolumab COmbination with standard first-line chemotherapy and radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma

Sponsor: European Thoracic Oncology Platform (ETOP)

EudraCT number: 2014-005097-11

BMS number: CA209-208

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Version 3.0

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In collaboration with Bristol-Myers Squibb

Protocol signature page amendment 2

A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma

ETOP 6-14 NICOLAS

Approved by:

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Trial Co-Chair

22/08/2017
Date

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23/8/2017
Date

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9.8.17
Date

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31/7/17
Date

Principal Investigator protocol signature page amendment 2

A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to
standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma

ETOP 6-14 NICOLAS

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with 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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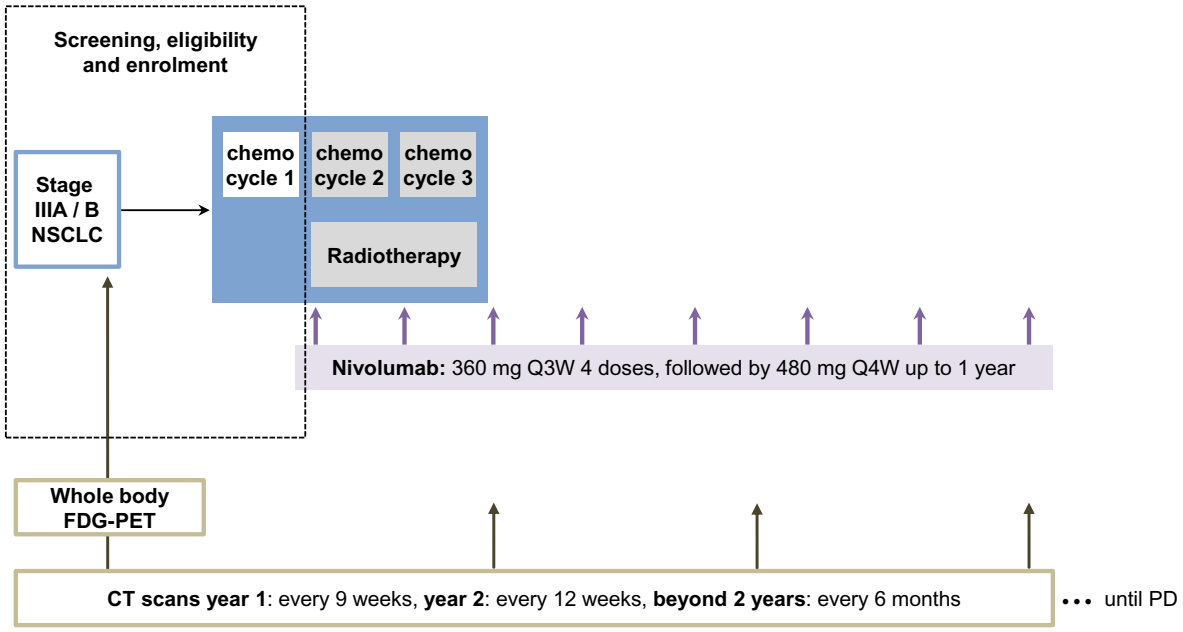
A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma

Sponsor: European Thoracic Oncology Platform (ETOP)

Pharma Partner: Bristol-Myers Squibb

Population: Documented stage IIIA/B NSCLC, amenable to concurrent chemo-radiotherapy.

Design: A single arm multicenter phase II trial



Sample size: 78 patients

Rationale: Over the past decade, concomitant chemotherapy and radiotherapy has become the first choice treatment for most patients with stage III non-small-cell lung carcinoma (NSCLC).

However, only about 30% of patients are alive 5 years after concomitant therapy. These figures remain approximately the same with the addition of surgery. After chemo-radiotherapy, at least 30-40% of the patients show local tumour progression on CT scans as first site of relapse. Also after surgery, about 30% of patients fail locally as a first site of recurrence. In addition, more than half of the patients eventually develop distant metastases that may have been present but undetected at the time of staging or that may have come from persistent or recurring local disease. It is thus obvious that new approaches that preferentially tackle both local and distant disease sites are needed to improve long-term survival and cure rates.

Dose-limiting toxicity of thoracic radiotherapy includes radiation pneumonitis (RP). Starting from two months after the end of radiotherapy, about 15% of the patients develop increasing dyspnoea and cough, provoked by a mixed T-lymphocyte infiltrate in lung areas that have been irradiated. RP may happen up to 6 months post-treatment, however about three quarters of RP cases occur 3 months after radiotherapy. Besides dose and volume parameters of the radiotherapy, such as the mean lung dose (MLD) or the V_{20} (that is the percentage of the lungs that received more than 20 Gy), the most important risk factor for developing RP is the inflammatory status of the lungs before therapy. The more baseline inflammation, the higher is the risk of RP. Inflammation in the lungs can be visualized and quantified by measuring the ^{18}F-fluoro-D-deoxyglucose (FDG) in the lung parenchyma by standard FDG-PET-CT scans obtained at the time of staging. As the relative FDG uptake in the lung vs. the aorta is used, no specific calibration of the PET-scanner is required.

Attempts to improve the long-term survival include radiotherapy dose escalation/acceleration, new chemotherapy combinations, and adding biological agents and cancer vaccines to standard regimens. At present, none of these have demonstrated an improved outcome.

Improved understanding of the immune profile of NSCLC has led to immunotherapeutic strategies, including inhibitory molecules responsible for abrogating an anti-cancer immune response such as PD-1 and CTLA-4. Bristol-Myers Squibb's nivolumab, an investigational monoclonal antibody that inhibits the immune checkpoint receptor PD-1 expressed on activated T cells, has demonstrated positive results in several trials in previously treated patients with advanced NSCLC. However, rare cases of severe or fatal pneumonitis have been reported throughout clinical trials using anti-PD-1 or anti-PD-L1 compounds.

Pre-clinical data consistently show a clear beneficial effect by combining local radiotherapy and anti-PD-1.[1] Not only was the local tumour control increased, but an "abscopal" effect on distant metastases could be observed. Radiotherapy clearly acted as an "in situ" tumour vaccination resulting in the induction of specific anti-tumour immunity in all sites of the body that could result in a clinical anti-tumour effect because of the combination with anti-PD-1. In these models, the concurrent administration of anti-PD-1/PD-L1 antibodies was more efficient to provoke an anti-tumour immune response than the sequential approach.

The initial dose and schedule of nivolumab while combined with chemotherapy will be 360 mg *i.v.*. The rationale for flat dosing is based on the expected similarity of safety and efficacy to the approved 3 mg/kg dose. Based on a wide therapeutic window of nivolumab monotherapy, the range of exposures with flat dosing are not expected to affect the efficacy because the exposures predicted for the 360 mg Q3W dose is on the flat part of the exposure response curve. For safety, doses up to 10 mg/kg nivolumab Q2W have been well tolerated across multiple tumours and an increase in exposure is not associated with a probability of increasing adverse events. Therefore, the flat dose (360 mg Q3W) for nivolumab monotherapy is recommended for further invetion in this trial.

From nivolumab cycle five on, nivolumab will be administered at 480 mg Q4W for up to 1 year from commencement of nivolumab treatment. Based on pharmacokinetic modelling, the 480 mg Q4W will provide similar steady-state average concentrations as 3 mg/kg or 240 mg Q2W for 4 months. The 4-weekly schedule will be more convenient for patients.

While the role of immunotherapy is currently being evaluated as monotherapy or in combination with chemotherapy or tyrosine kinase inhibitors in all lines of treatment of advanced NSCLC, as monotherapy in early NSCLC adjuvant setting as well as monotherapy in consolidation after completion of definitive chemo-radiotherapy, it has not yet been assessed in combination with radiotherapy. Anecdotal data of concurrent treatment in the palliative setting suggest acceptable safety and a good tolerability of such combination. The NICOLAS trial was initially developed to prospectively assess the safety of checkpoint inhibition concurrently with chemo-radiotherapy.

In summary, there is a definite unmet need in the multidisciplinary care to improve the prognosis of patients diagnosed with stage III NSCLC, with a strong rationale supporting the combination of chemo-radiotherapy with anti-PD-1. A major theoretical concern is the development of pneumonitis, a rare toxicity of both radiotherapy and checkpoint inhibitors. The main aim of the ongoing current trial is therefore to evaluate the pneumonitis rate in patients being treated with chemo-radiotherapy in combination with nivolumab treatment.

Rationale for protocol amendment 2

Since the NICOLAS trial was initiated, the landscape of combining chemo-radiotherapy with immune-checkpoint inhibition, such as anti-PD-1 antibodies, has changed rapidly, opening a new window of opportunity.

There is a very strong interest of the multidisciplinary lung cancer community to investigate the optimal integration of anti-PD-1 treatment into chemo-radiotherapy. Currently, 11 sites from 5 countries are activated for the NICOLAS trial and recruiting strongly (ahead of schedule). Using this momentum will allow us to rapidly recruit additional patients in order to reach the power to not only determine the feasibility in terms of pneumonitis grade 2 and abouve, but also to evaluate the efficacy of the concurrent treatment.

So far, during the regular safety review, the ETOP IDMC did not observe any additional toxicity compared the chemo-radiotherapy alone.

Additionally, a first planned analysis of the PACIFIC trial (stage III NSCLC treated with concurrent chemotherapy and radiotherapy, followed by the anti-PD-L1 durvalumab or observation, NCT02125461) showed an increased progression-free survival (PFS), which was co-primary endpoint together with overall survival (OS). The full details are not known, yet, but it appears that the pre-clinical rationales of combined chemo-radiotherapy and anti-PD-1 treatment can be successfully transferred into clinical trials, without serious toxicities.

A recent secondary analysis of the Keynote 001 trial indicates synergistic affects of radiotherapy and immunotherapy.[2] This international, multicentre phase I trial assessed the effect of pembrolizumab monotherapy in patients with progressive locally advanced or metastatic NSCLC. Patients were assigned to multiple expansion cohorts to allow for the inclusion of patients who were naïve to systemic therapy and those who had progression after one or two previous regimens.

The results from this study showed that the effect of pembrolizumab was significantly higher in patients who received previous radiotherapy than in patients without previous radiotherapy

(median PFS: 4.4 months versus 2.1 months, hazard ratio 0.56, p=0.019; median OS: 10.7 months versus 5.3 months, hazard ratio 0.58, p=0.026).

These findings were well in line with pre-clinical studies that underlined the ability of radiotherapy to enhance antitumour immune response.[2]

In the absence of of serious pulmonary toxicity, the apperant benefit of chemo-radiotherapy and anti-PD-1 and the high interest of the NICOLAS study group, we propose to amend the NICOLAS trial protocol to expand on the number of patients in order to reach sufficient power for an efficacy readout (progression-free survival).

Objectives and endpoints: To assess the safety and efficacy of nivolumab administration to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC, as defined by the rate of grade ≥3 pneumonitis (CTCAE V4.0) 6 months post-radiotherapy and, if safety is proven, to assess the progression-free survival.

Primary endpoint:

- Grade ≥3 pneumonitis (CTCAE V4.0) observed any time during 6 months from the end of radiotherapy

Key secondary endpoint:

- 1-Year progression-free survival

Other secondary endpoints:

- Time to first pneumonitis of grade ≥3
- Objective response rate by RECIST v1.1
- Time to treatment failure
- Overall survival
- 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 locally advanced stage IIIA or III B (T0-3 N2-3 or T4 N0-3 M0) non-small cell lung carcinoma (NSCLC), according to 7th TNM classification.
- Nodal status N2 or N3 need to be proven (by biopsy, EBUS, mediastinoscopy or thoracoscopy) except for overt cT4 disease
- Measurable disease according to RECIST v1.1
- Previous delivery of a maximum of one 3-weekly cycle of platinum-based chemotherapy
- ECOG performance status 0-1
- Adequate hepatic, haematological and renal function
- All AEs from previous therapies (including the first chemotherapy cycle in the context of this trial) resolved to grade <2 (except fatigue, alopecia, nausea lack of appetite or peripheral neuropathy)

Exclusion criteria at enrolment:

- Metastatic disease (as determined by PET-CT and brain MRI (preferred) or high-quality brain CT with intravenous contrast at the time of staging, performed within 35 days before the beginning of first chemotherapy cycle)
- Previous radiotherapy to the chest, including radiotherapy for breast cancer
- Prior chemotherapy, radiotherapy or molecular targeted therapy for NSCLC (with the exception of one cycle of chemotherapy given prior to enrolment into this trial)
- Active, known or suspected autoimmune disease

Treatment:

Chemotherapy consists of 3 cycles of cisplatin* in combination with vinorelbine, etoposide or pemetrexed.

Option	Drug		Dose	Dose frequency
1	**Cisplatin plus vinorelbine**			
	Cisplatin*		80 mg/m^2	d1, Q3W, 3 cycles**
	Vinorelbine	chemo-radiotherapy	30 mg/m^2	d1 + d8 cycle 1
			20 mg/m^2	d1 + d8 cycles 2 & 3
2	**Cisplatin plus etoposide**			
	Cisplatin*		80 mg/m^2	d1, Q3W, 3 cycles**
	Etoposide		100 mg/m^2	d1-d3, Q3W, 3 cycles**
3	**Cisplatin plus pemetrexed** (for non-squamous histological subtypes)			
	Cisplatin*		75 mg/m^2	d1, Q3W, 3 cycles**
	Pemetrexed		500 mg/m^2	d1, Q3W, 3 cycles**

* If cisplatin cannot be used, it can be replaced by carboplatin AUC5 at d1.

** The first chemotherapy cycle is administered before enrolment.

<u>Concurrent radiotherapy and nivolumab treatment</u>

Patients must be enrolled before the start of chemotherapy cycle 2 and prior to the start of radiotherapy and nivolumab treatment.

<u>Radiotherapy</u>

Radiotherapy will consist of a physical dose of at least 60 Gy delivered concurrently with chemotherapy cycles 2 and 3 (see ESMO 2013 and EORTC radiotherapy guidelines).

<u>Nivolumab treatment</u>

Nivolumab therapy will start concurrently with radiotherapy.

The first four doses of nivolumab are administered at 360 mg as intravenous infusion (approx. 30 minutes) every 3-weeks with the first two doses given on day 1 of chemotherapy cycle 2 and on day 1 of chemotherapy cycle 3. Thereafter, nivolumab is administered at 480 mg every 4 weeks for up to 1 year from start of nivolumab treatment, unless treatment stops earlier due to unacceptable toxicity, disease progression, withdrawal of consent or the trial is terminated by the sponsor.

Statistical considerations:

A total sample size of 78 patients, receiving concurrent therapy is needed for the study, assuming a 5% loss-of-follow-up rate. First, testing for safety will be performed to evaluate

the 6-month post-radiotherapy pneumonitis-free rate and if the safety endpoint is met, an efficacy analysis will be performed regarding the one-year PFS.

The primary safety hypothesis corresponds to the 6-month pneumonitis-free rate of grade ≥3:

Null hypothesis states that 6-month pneumonitis-free rate of grade ≥3 is less than or equal to π_0=67%, vs the one-sided alternative that the rate is above 67%, tested at π_1=85%:

$$H_0: \pi_0 \leq 67\% \text{ vs } H_1: \pi_1 > \pi_0, \text{ at } \pi_1 = 85\%$$

For a one-sided alpha of 0.05 and power of 83%, the required sample size for the safety evaluation is 41 evaluable patients allowing for one interim safety analysis at 21 patients without any requirement for trial interruption. In the safety evaluation phase of the trial 43 patients will be recruited allowing for around 5% competing risk rate. If additional patients are non-evaluable for the primary endpoint, up to 3 patients will be replaced.

An interim safety analysis will be performed when 21 patients have completed a 3-month follow-up on nivolumab after chemotherapy and radiotherapy, assuming approximately 70% of the cases of pneumonitis occur by 3 months after the end of radiotherapy.

If at the safety interim analysis, none of the 21 patients has developed pneumonitis of grade ≥3 by 3 months, then the safety phase of the trial could stop early with the conclusion that the treatment is feasible and safe. The trial will continue to reach the total sample size required to test the efficacy hypothesis. If the only patients developing pneumonitis of grade ≥3 by 3 months have done so before starting nivolumab, the Independent Data Monitoring Committee (IDMC) could choose to focus on the patients who started nivolumab for claiming feasibility.

If the trial does not reach the safety conclusion at the interim, the final safety analysis will be performed when 41 patients have completed the 6-month follow-up. If at least 33 out of 41 patients reach 6 months pneumonitis-free, the 6-month pneumonitis-free rate will be considered as promising, and the trial will continue to allow for the treatment to be tested for efficacy.

Based on a hierarchical design,[3] a secondary efficacy hypothesis (secondary-Hs) is tested after the pneumonitis null hypothesis (primary-Hp) is rejected.

Based on preliminary baseline information regarding stage, it is believed that for the observed case-mix, the 1-year PFS rate that could be achieved with current best provided care is estimated to be around 45%.[4, 5] The aim of the combination under investigation will be to improve the 1-year PFS by at least 15%, that is, to achieve a 1-year PFS rate of at least 60%.

Efficacy hypothesis (Hs):

$$H_{s0}: PFS_0 \leq 45\% \text{ vs } H_{s1}: PFS_1 > PFS_0, \text{ at } PFS_1 = 60\%$$

A sample size of 74 evaluable patients will provide a power of 83%, for testing the above efficacy hypothesis, using an exact test for a single proportion, at the one-sided alpha of 0.05. Assuming 5% non-evaluable patients, a total sample size of 78 patients need to enter the study.

The final efficacy hypothesis is tested after the safety null hypothesis is rejected either at the interim or the final safety analysis, when 74 evaluable patients under concurrent chemo-

radiotherapy have reached one-year follow-up (from time of enrolment into the trial) or have experienced PD.

The 78 patients will be enrolled under the protocol amendments (protocol versions 2.0 and 3.0). Patients included under the original protocol (version 1.0) will be evaluated separately.

A detailed statistical analysis plan (SAP) will be produced as a separate document.

Safety evaluations will be reviewed by the IDMC at their regular meeting every three months.

Total trial duration (for amendment 2):

After a run-in period of 3 months for the activation of the centres, patient accrual is expected to be completed within 7 months. The trial will end with the preparation of the final report, scheduled at 2.5 years after the inclusion of the first patient.

2. Trial schedule

	Baseline before enrolment [0(2)]	**Chemotherapy** [(3)]	**Radiotherapy** [(4)] **and nivolumab** [(5)] **treatment**	**End of treatment** [(6)]	**Post-treatment visits** [(7)]	
					before PD [(8)]	after PD [(8)]
Written informed consent: [(9)]						
Medical history						
Physical exam: PS, blood pressure, weight, height (at baseline)		Every cycle [(17)]	Every dose [(18)]		According to local standards	
Adverse events [(10)]	Baseline symptoms	Every cycle [(17)]	Every dose [(18)]			
Concomitant medication		Every cycle [(17)]	Every dose [(18)]			
Further-line therapy						
Survival						
HIV status, hepatitis B/C						
Pregnancy test if applicable [(11)]			At dose 1, then every 2nd dose			
TSH, with reflex free T3 and T4 [(12)]			At dose 1, then every 2nd dose			
Haematology: haemoglobin, platelets, leukocytes, neutrophils		Every cycle [(17)]	Every dose [(18)]			
Renal function: serum creatinine, calculated creatinine clearance [(13)]		Every cycle [(17)]	Every dose [(18)]			
Serum urea level			Every dose [(18)]			
Hepatic function: ALT, AST, AP, total bilirubin		Every cycle [(17)]	Every dose [(18)]			
Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase			Every dose [(18)]			
Pulmonary function: FEV1, DL_{co} (%)						
Electrocardiogram						
Whole body FDG-PET CT [(14)]						
Brain MRI or CT [(15)]						
Tumour assessment by CT scans [(16)]			**Year 1**: every 9 weeks, **year 2**: every 12 weeks, thereafter every 6 months			
Chemotherapy [(3)]						
Radiotherapy [(4)]						
Nivolumab [(5)]						

Mandatory

(1) Baseline: to be done within 28 days prior to enrolment

(2) Patients must be enroled prior to the start of radiotherapy and nivolumab treatment, e.g. between chemotherapy cycle one and two, **ideally on day 1 of chemotherapy cycle 2**

(3) Chemotherapy consists of 3 cycles of cisplatin in combination with vinorelbine, etoposide or pemetrexed administered in 3-week (±3 days) cycles. If cisplatin cannot be used, it can be replaced by carboplatin (AUC5). The first cycle is given prior to enrolment into the trial. After enrolment, the chemotherapy cycle 2 must start 21 days (±3 days) after the start of cycle 1. Enrolment must occur before the start of concurrent radiotherapy and nivolumab treatment.

(4) Radiotherapy consists of a physical dose of at least 60 Gy delivered concurrently with nivolumab and chemotherapy cycles 2 and 3. Please note that patients must be enrolled before radiotherapy starts. If the administration of chemotherapy is delayed due to toxicity, radiotherapy should start within 3 days of the start of chemotherapy cycle 2 in the.

(5) Nivolumab treatment: The initial 4 doses of nivolumab will be administered at 360 mg as intravenous infusion (approx. 30 minutes) every 3-weeks (±3 days). The first 2 doses are administered concurrently with the last two chemotherapy cycles. From dose 5 on, nivolumab is administered at 480 mg every 4 weeks (±3 days) for up to 1 year from start of nivolumab treatment, unless nivolumab treatment stops earlier due to unacceptable toxicity, disease progression, withdrawal of consent or the trial is terminated by the sponsor. **Please note that dose 5 will start 3 weeks (±3 days) after dose 4.**

(6) End of treatment visit: to be scheduled within 30 days following the decision to stop nivolumab treatment or within 30 days after planned treatment start if treatment never started.

(7) Post treatment follow-up will continue for 2 years after the last patient started nivolumab treatment. Up to progression these visits should be scheduled to be done at the same time as the CT scans. After progression the post treatment visits will be every 6 months (±4 weeks).

(8) Treatment beyond PD: Patients with tumour volume increase detected after nivolumab treatment start but without appearance of new lesions or rapid clinical deterioration should continue to be treated with nivolumab and clinically observed with an imaging scheduled 6 weeks (±1 week) later to allow detection of a subsequent tumour response (see section 10.7) for more information).

(9) Written informed consent must be obtained prior to any trial specific evaluations and intervention within 7 weeks before enrolment.

(10) Adverse events: Symptoms present at baseline will be recorded on the adverse event form. Adverse events should be documented until 100 days following the last dose of nivolumab. For more information please refer to section 12.

(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 study enrolment. The test must be repeated within 24 hours before beginning nivolumab treatment and then before every 2nd nivolumab administration. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stops.

(12) TSH, free T3 and T4 to be done before the first nivolumab administration. TSH must be repeated before every 2nd nivolumab administration. Free T3 and T4 have only to be repeated in case of abnormal TSH value.

(13) Calculated according to the formula of Cockroft-Gault.

(14) Whole body FDG-PET (with max SUV measurements) at baseline within 35 days before beginning of the first chemotherapy cycle. Contrast enhanced CT of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) is needed in addition to or in combination with PET.

(15) Brain MRI (preferred) or high-quality CT with intravenous contrast at the time of staging mandatory within 35 days before beginning of first chemotherapy cycle.

(16) Tumour assessment: CT of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively CT of thorax and ultrasonography of upper abdomen every 9 weeks (±1 week) from enrolment in the first year, every 12 weeks (±2 weeks) in the second year and thereafter every 6 month (±4 weeks), until progression of disease. First CT scan will be done at baseline within 35 days before start of chemotherapy (in combination with the whole body FDG-PET see footnote (14)).

(17) Evaluations during chemotherapy: To be done within 24 hours prior to chemotherapy administration.

(18) Evaluations during nivolumab therapy: To be done within 3 days before administration of the next nivolumab dose.

3. List of abbreviations

AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APL	Acute Promyelocytic Leukaemia
AST	Aspartate Transaminase
AUC	Area Under the Curve
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CD279	Cluster of Differentiation 279
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
CTV	Clinical Target Volume
DILI	Drug-Induced Liver Injury
DL_{CO}	Diffusing Capacity for Carbon Monoxide
DVH	Dose Volume Histogram
EBUS	Endobronchial Ultrasound
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
ERB	Ethical Review Board
ESMO	European Society for Medical Oncology
ETOP	European Thoracic Oncology Platform
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FEV1	Forced Expiratory Volume in 1 Second
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GTV	Gross Tumour Volume
Hb	Haemoglobin

HIV	Human Immunodeficiency Virus
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy
IRB	Institutional Review Board
ITV	Intratracheal ventilation
IUD	Intrauterine Device
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LFU	Lost to Follow-Up
MEL	Melanoma
MIP	Maximum Intensity Projection
MLD	Mean Lung Dose
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NSCC	Non-Squamous-Cell Carcinoma
NSCLC	Non-Small Cell Lung Carcinoma
OAR	Organs at Risk
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
PTV	Planning Target Volume
RCC	Renal Cell Carcinoma
RDE	Remote Data Entry
RECIST	Response Evaluation Criteria in Solid Tumours
RP	Radiation Pneumonitis
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

SCC	Squamous-Cell Carcinoma
SCLC	Small Cell Lung Carcinoma
SD	Stable Disease
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standard Uptake Volume
TFP3	Time to first grade ≥3 pneumonitis
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour, Nodes, Metastasis
TTF	Time to treatment failure
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal Lab Value
VMAT	Volumetric Arc Therapy
WBC	White Blood Cell
WC	Withdrawal of Consent
4DCT	Four-Dimensional Computed Tomography
5-HT	5-Hydroxytryptamin

4. Background and rationale

4.1. Disease background

Primary lung cancer is the most common malignancy after non-melanocytic skin cancer with deaths from lung cancer exceeding those from any other type of malignancy worldwide [6]. While it has been the most important cause of cancer mortality in men since the 1960s, it has equalled breast cancer as a cause of mortality in women since the 1990s.

Lung cancer accounts for 12% of all incident cases of cancer. Non-small cell lung carcinoma (NSCLC) account for 80-85% of lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the last two decades [7].

Stage III NSCLC represents a heterogeneous group of patients even in the revised new version of the IASLC/TNM staging system 7. This stage includes either locally advanced primary tumours (T4-situation) with local infiltration of vital mediastinal organs or involvement of loco regional mediastinal lymph nodes (N2 or N3-nodes). Consecutively, the IIIA subset remains to be differentiated from the IIIB subset of NSCLC. Definitive cure rates and long-term prognosis also differ significantly between substages IIIA and IIIB [8].

Based on the underlying aetiology for developing lung cancer, patients in stage III present with variable clinical conditions and physical status. Long-term smokers – still the majority of the lung cancer population – typically harbour significant smoking induced comorbidities such as reduced pulmonary function due to chronic obstructive pulmonary disease (COPD), significant cardiac problems related to coronary heart disease as well as vascular problems due to smoking-induced arteriosclerosis (peripheral and cerebral extension). Thus the comorbidity profile of the mostly elderly lung cancer patients in stage III may significantly hamper curative-intent radical treatment strategies.

Over the past decade, concomitant chemotherapy and radiotherapy has become the first choice treatment for stage III NSCLC.

However, only about 30% of patients are alive 5 years after concomitant therapy. These figures remain approximately the same with the addition of surgery. After chemo-radiotherapy at least 30-40% of the patients show local tumour progression. Also, after surgery about 30% of patients fail locally as a first site of recurrence. On top of these figures, more than half of the patients develop distant metastases that may have been present but undetected at the time of staging or that may have come from persistent or recurring local disease. It is clear that novel approaches that preferentially address both local and distant disease sites are needed to improve long-term survival and cure rates.

4.2. Chemo-radiotherapy

Some patients are defined as having potentially resectable stage III NSCLC when a dedicated multidisciplinary assessment, including an experienced thoracic surgeon, judges a complete resection (R0) may be feasible after induction treatment.

The role of surgery was initially investigated in two phase III trials: EORTC 0841 and INT-0139/RTOG-9309. In the EORTC trial, patients with stage IIIA-N2, deemed unresectable at

baseline evaluation, received cisplatin-based induction chemotherapy followed by either surgery or radiotherapy (60 Gy/ 30 fractions) in responding patients [9]. In this trial, in which no FDG-PET staging was used, there was no significant difference in OS (overall survival), being about 15% in both groups. In the INT/RTOG trial, patients with resectable stage IIIA-N2 at the time of staging received two cycles of cisplatin-etoposide concurrent with radiotherapy to a dose of 45 Gy/25 fractions followed by either surgery or completion to so-called full dose radiotherapy (61 Gy) [10]. Again, in this trial without FDG-PET-CT staging, no significant difference in OS was observed (5-year OS in the surgery arm 27% vs. 20% in the non-surgery group, p=0.10), but due to the better disease-free survival in the surgery arm, the exceptionally high mortality in right-sided pneumonectomy patients and the higher OS in the unplanned "matched" lobectomy subgroup analysis, the debate on the role of surgery in the treatment of stage III disease continued.

The two recent randomised trials investigated different questions: Does sequential chemotherapy plus radiotherapy (44 Gy / 22 fractions / 3 weeks) before surgery improve the event-free survival compared to induction chemotherapy followed by surgery (the SAKK SAKK 16/00 trial) [11] or does surgery improve the OS when added to induction chemotherapy followed by concurrent chemo-radiotherapy (45 Gy/30 fractions every 3 weeks; 1.5 Gy twice-daily) vs induction chemotherapy followed by full-dose concurrent chemo-radiotherapy (45 Gy/30 fractions every 3 weeks, followed by 2 Gy once-daily) in an isotoxic, accelerated way (total dose 65 Gy-71 Gy) (the ESPATUE trial [5]). In both studies, contemporary staging such as brain imaging and FDG-PET-CT was used.

Neither trial showed a difference in the primary endpoint between both arms. At first glance, this would imply that for patients with resectable stage IIIA-N2 NSCLC at diagnosis, either induction chemotherapy followed by surgery or definitive concurrent chemo-radiotherapy are equal options. In unresectable or inoperable disease, concurrent chemo-radiotherapy remains the first choice [12].

Based on the non-significant difference in the primary endpoint result in these randomized trials, the choice of treatment varies across countries and centres. The optimal treatment plan is discussed in a multidisciplinary tumour board, taking into account the local treatment expertise. Both definitive chemo-radiotherapy as well as induction therapy followed by surgery or in some cases preoperative chemo-radiotherapy are options.

Altogether, for the majority of stage III NSCLC, definitive chemo-radiotherapy will be preferred. Induction chemotherapy followed by radiotherapy, mostly to a dose of 60-66 Gy in 30-33 fractions in 6-7 weeks, so-called sequential chemo-radiation, was compared to concurrent chemo-radiotherapy at the same dose in many phase III trials and in a meta-analysis [13, 14]. Concurrent chemotherapy and radiotherapy lead to higher 5-year survival rates at the cost of a higher rate of reversible oesophagitis. In fit patients, this is the standard treatment [13-16]. A detailed look at the relationship of overall treatment duration and outcome in these studies has confirmed that prolonged treatment time is an issue in this setting, as it is in other tumour types. Overall treatment times over 4 weeks lead to a worse long-term survival. For concurrent radiochemotherapy protocols, a prolonged treatment time exceeding seven weeks would be perceived as suboptimal.

Chemotherapy is an integral part of the treatment of locally advanced NSCLC as it improves survival in all subgroups of patients, whether treatment included surgery or radiotherapy, as shown in meta-analyses based on individual patient data [20, 21].

In the absence of randomized studies defining an optimal chemotherapy regimen, no strict recommendation can be given as to a preferable combination. Of the six randomized studies in the meta-analyses, five used cisplatin-based schedules and only one carboplatin. In the latter study, a weekly infusion was used, but this relates to only 91 patients out of a total of 1205 in the meta-analysis. Cisplatin-based schedules are therefore recommended [16]. Moreover, in a recent meta-analysis on risk factors for symptomatic radiation pneumonitis, elderly patients who received carboplatin-paclitaxel chemotherapy were at highest risk [22]. Of the five phase III studies that used cisplatin concurrently with radiotherapy, two used only 2 cycles of platin combinations during radiotherapy, one trial used 2 cycles of platin combinations concomitantly during radiotherapy followed by 2 cycles of consolidation chemotherapy and two used daily cisplatin alone. There was no significant heterogeneity in the benefit between these schedules, although the daily administration of cisplatin has not been adopted widely because of practical issues. Therefore, 2 (to a maximum of 4) cycles of cisplatin-based doublet chemotherapy are recommended. The most commonly used drugs together with cisplatin are etoposide (at full systemic dose 100-120 mg/m²) and vinorelbine (at 60% of systemic dose, 15 mg/m²).

In the PROCLAIM trial, cisplatin-etoposide was compared to cisplatin-pemetrexed given concurrently with 66 Gy in 33 fractions of thoracic radiotherapy [23, 24]. No differences in PFS and OS were observed. Cisplatin-pemetrexed concurrent with radiotherapy was well tolerated.

In all trials an average cisplatin dose of 80 mg/m^2 per cycle was administered. There is no evidence for extended induction or consolidation chemotherapy [25-28].

Attempts to improve the long-term survival include radiotherapy dose escalation / acceleration [4], new chemotherapy combinations, and the addition of biological agents and cancer vaccines to standard regimens. Technical radiotherapy modifications, including intensity-modulated radiotherapy have also been investigated. However, none of these have thus far improved the OS of patients with stage III NSCLC, except for acceleration of radiotherapy in the non-concurrent setting [17].

4.3. Radiation pneumonitis

Dose-limiting toxicity of thoracic radiotherapy includes radiation pneumonitis (RP). Starting from two months after the end of radiotherapy, about 15% of the patients develop increasing dyspnoea and cough, provoked by a mixed T-lymphocyte infiltrate in lung areas that have been irradiated. RP typically may happen up to 6 months post-treatment, but about three quarters of RP cases have already occurred within 3 months after radiotherapy.

Besides dose and volume parameters of the radiotherapy such as the mean lung dose (MLD) or the V_{20} (i.e., the percentage of the lungs that received more than 20 Gy), the most important risk factor for developing RP is the inflammatory status of the lungs before therapy. The more baseline inflammation, the higher is the risk of RP. Inflammation in the lungs can be visualized

and quantified by measuring the ^{18}F-fluoro-D-deoxyglucose (FDG) in the lungs by standard FDG-PET-CT scans obtained at the time of staging. As the relative FDG uptake in the lung vs. the aorta is used, no specific calibration of the PET-scanner is required.

4.4. Targeted agents in non-small cell lung carcinoma

In metastatic NSCLC several chemotherapy regimens have shown comparable efficacy with different toxicity profiles that are taken into account for treatment selection. Targeted agents are now among the therapeutic options for patients with NSCLC and specific molecular characteristics. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors attain high response rates in patients whose tumours have activating EGFR mutations. Crizotinib also achieves high response rates in anaplastic lymphoma kinase (ALK)-translocated and ROS1-translocated NSCLC patients.

More recently, promising results have been reported with immune-checkpoint blockers (targeting cytotoxic T-lymphocyte–associated antigen 4 [CTLA4], programmed cell death protein 1 [PD-1] or its ligand PD-L1) in advanced NSCLC with objective responses in around 20% of patients. Clinical results obtained with immune-checkpoint inhibitors illustrate how immunotherapy can induce long-lasting disease control.

4.5. Immunotherapy for non-small cell lung carcinoma

Improved understanding of the immune profile of NSCLC has led to immunotherapeutic strategies, including inhibitory molecules such as PD-1 and CTLA-4 responsible for abrogating an anti-cancer immune response.

PD-1 is a key immune-checkpoint receptor expressed by activated T cells. Compared with CTLA4, 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 the surface of the activated Treg lymphocytes and also on B lymphocytes or 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 also on cancer cells.

Indeed, one important mechanism for tumour cells to escape the immune system is by overexpressing PD-1 ligands on their surface. Expression of immune-checkpoint ligands can be innate through constitutive oncogenic signalling or induced in response to inflammatory signals, such as interferon gamma, that are produced by an active antitumour immune response. PD-L1 expression was described in many histological cancer types and in particular in lung cancer where approximately 50% of NSCLCs are reported to express PD-L1.

Several trials using anti-PD-1 and anti-PD-L1 antibodies from different pharma companies are ongoing and a significant amount of additional clinical data will be available soon.

4.6. Nivolumab

Nivolumab (BMS-936558; anti-PD-1) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that targets the programmed cell death protein 1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. 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 [29, 30]. Nivolumab abrogates this interaction between PD-1 and its ligands.

Monoclonal antibodies targeting both PD-1 and PD-L1 are being developed, which have demonstrated significant clinical activity against several tumour types. Nivolumab (BMS-936558) is a fully humanized antibody that targets the PD-1 receptor, preventing its activation by PD-L1 or PD-L2.

A phase I trial tested nivolumab in 296 patients with advanced solid cancers, including 129 NSCLC patients [31, 32]. Nivolumab was administered intravenously once every 2 weeks at doses of 1, 3 or 10 mg/kg. The majority of patients were heavily pre-treated (54% of NSCLC patients had already received 3 lines of chemotherapy). Previous treatments included platinum-based chemotherapy (99%) and tyrosine kinase inhibitors (28%). Of the 129 NSCLC patients, 17% had objective responses (n =22). Responses in NSCLCs were seen at all dose levels, but were higher with higher doses: 3% at 1 mg/kg, 24% at 3 mg/kg, and 20% at 10 mg/kg.

Objective responses were observed in squamous and nonsquamous NSCLCs: 17% of squamous-cell carcinoma (SCC; n =9 of 54) and 18% of nonsquamous-cell carcinoma (NSCC; n =13 of 74). Median OS across all dose cohorts was 9.2 months for SCC and 9.6 months for NSCC. Prolonged responses were reported in both histologies with sustained OS: 44% / 41% SCC and 44% / 17% NSCC were alive at 1 and 2 years, respectively.

Toxicity was mild, consisting mainly of fatigue, skin rash, GI toxicity (diarrhoea) or endocrinopathy. Grade 3-4 toxicities were extremely rarely observed, and described to potentially affect lung or GI tract including hepatitis. Rare cases of fatal pneumonits were reported.

The probability of severe pneumonitis is less than 5% with nivolumab alone. After radiotherapy with or without chemotherapy, the incidence of severe pneumonitis is approximately 15%. It is unknown if nivolumab influences the incidence of pneumonitis after radiotherapy.

In addition, two phase III trials showed an OS benefit against docetaxel in the second-line setting.

The first one (CheckMate 017) focussed on squamous histology advanced NSCLC patients. 272 patients were assigned to receive nivolumab at a dose of 3 mg/kg of body weight every 2 weeks, or docetaxel at a dose of 75 mg/m^2 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 [33, 34].

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 [35]. 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 [35].

4.7. Biomarker research for nivolumab

Biomarker efforts within the nivolumab (BMS-936558, anti-PD-1) program include identification of predictive biomarkers for patient stratification or enrichment in order to maximize the therapeutic index of the drug. Currently, the lead candidate predictive biomarker for nivolumab is PD-L1 (B7-H1) expression as assessed by immunohistochemistry (IHC) based on a preliminary, retrospective analysis of a subset of subjects from the nivolumab monotherapy study CA209-003, which included NSCLC, melanoma (MEL) and renal cell carcinoma (RCC) subjects. Based on this initial data [36], Bristol-Myer Squibb (BMS) is partnering with Dako to develop a diagnostic IHC assay to reliably and reproducibly measure PD-L1 expression in NSCLC, MEL, and RCC tumour tissue samples. The Phase III NSCLC program, currently including studies CA209-017 (second-line, squamous NSCLC, vs docetaxel) and CA209-057 (second/third-line, non-squamous NSCLC, vs docetaxel) incorporate mandatory tumour tissue collection and pre-specified, retrospective assessment of PD-L1 IHC expression.

Historically, different antibodies and scoring methods have been used to assess PD-L1 status by IHC, which has provided a broad range of positivity rates in the tumour types of interest. Most reports suggest that PD-L1 positivity is linked to a poor prognosis, although there are conflicting reports suggesting that PD-L1 positive status portends a good prognosis. There is a priority in understanding the prognostic role of PD-L1 in NSCLC, while providing additional information around the rate of positivity in this tumour type, notably using the Dako-developed assay for nivolumab.

4.8. Overall risk/benefit assessment

Radiochemotherapy is a curative intent strategy in locally advanced NSCLC. However despite optimal delivery of therapy either local or distant relapse will be observed in the majority of patients in the first two years following completion of treatment. Several strategies have failed

to improve the prognosis of these patients: induction or consolidation chemotherapy, EGFR tyrosine kinase inhibitor maintenance treatment, consolidation vaccination as well as higher dose of daily fractionated radiotherapy up to 70 Gy.

There is an urgent need to identify new ways to improve the cure rate in locally advanced NSCLC. As seen in advanced disease, immunotherapy looks a very promising approach. Additionally, the setting of minimal residual disease after chemo-radiotherapy probably offers a good opportunity for immune modulation.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in trial CA209012. Nivolumab 10 mg/kg was combined with gemcitabine plus cisplatin and pemetrexed plus cisplatin. Nivolumab doses of 5 mg/kg and 10 mg/kg were combined with paclitaxel and carboplatin [37].

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines.

Nivolumab has not been tested in the context of definitive chemo-radiotherapy for stage III disease. To date there is no data concerning an interaction with palliative radiotherapy in the stage IV setting.

The unmet need in this curative context presents a very favourable risk/benefit ratio; the major concerns are the cumulative risk of radiotherapy induced pneumonitis and reported rare cases of nivolumab-related pneumonitis.

4.9. Rationale for trial design

Most comparative studies of concurrent chemo-radiotherapy vs sequential administration used cisplatin/etoposide or cisplatin/vinca alkaloid (typically: cisplatin plus vinorelbine) combination chemotherapy. There are no comparative phase III trials using the paclitaxel/carboplatin regimen. Thus, when delivered perioperatively, cisplatin based combinations are considered the treatment of choice, in the absence of contra-indication – with vinorelbine and etoposide as the best standard combination.

Pre-clinical data show a clear beneficial effect of combining local radiotherapy and anti-PD-1. This led not only to an increase in the local tumour control but to an “abscopal” effect on distant metastases. Radiotherapy acted as an “in situ” tumour vaccination resulting in the induction of specific anti-tumour immunity in all sites of the body that could result in a clinical anti-tumour effect because of the combination with an anti-PD-1 agent like nivolumab.

There is a need to improve the prognosis of patients with stage III NSCLC, and a strong rationale to combine chemo-radiotherapy with anti-PD-1. A major theoretical concern is the development of pneumonitis. The main aim of the current trial proposal is therefore to evaluate the pneumonitis rate in patients being treated with concurrent chemo-radiotherapy and nivolumab treatment.

The initial dose and schedule of nivolumab while combined with chemotherapy will be 360 mg *i.v.* Q3W. The rationale for the flat dose is based on the expected similarity of safety and efficacy to the approved 3 mg/kg dose. Based on a wide therapeutic window of nivolumab monotherapy, the range of exposures with flat dosing are not expected to affect efficacy because

the exposures predicted for the 360 mg Q3W dose is on the flat part of the exposure response curve. For safety, doses up to 10 mg/kg nivolumab Q2W have been well tolerated across multiple tumours and an increase in exposure is not associated with a probability of increasing adverse events. Therefore, a flat dose of 360 mg Q3W for nivolumab monotherapy will be investigated in this trial.

From cycle 5 on, nivolumab will be administered at 480 mg Q4W for up to 1 year. Based on pharmacokinetic modelling, the 480 mg Q4W dose will provide similar steady-state average concentrations as 3 mg/kg or 240 mg Q2W dose. The every 4-week schedule will be more convenient for patients.

While the role of immunotherapy is currently being evaluated as monotherapy or in combination with chemotherapy or TKIs in all lines of treatment of advanced NSCLC, as monotherapy in early NSCLC adjuvant setting as well as monotherapy in consolidation after completion of definitive chemo-radiotherapy, it is not to date being assessed in combination with radiotherapy. While anecdotal data of concurrent treatment in the palliative setting suggest safety and a good tolerability of such a combination, a formal prospective assessment is required before embarking on any trial comparing concurrent versus sequential checkpoint inhibitors and radiotherapy designs.

The rationale for concurrent checkpoints and radiotherapy resides in the description of cases of unexpected immune sensitization offered by such a combination, with the demonstration of tumour responses to localized radiotherapy after immune simulation in non-irradiated sites – called the abscopal effect. A strong rationale is also provided by pre-clinical models, showing a synergistic effect of such approaches in various in vitro and in vivo models [38].

4.9.1. Rational for protocol amendment 2

Since the NICOLAS trial has been initiated, the landscape of combining chemo-radiotherapy with immune-checkpoint inhibition, such as anti-PD-1 antibodies, has changed rapidly, opening a new window of opportunity.

There is a very strong interest within multidisciplinary lung cancer community to investigate the optimal integration of anti-PD-1 treatment into chemo-radiotherapy. Currently, 11 sites from 5 countries are activated for the NICOLAS trial and recruiting strongly (ahead of schedule). Using this momentum will allow us to rapidly recruit additional patients in order to reach the power to not only investigate toxicity, but also to evaluate the efficacy of the concurrent treatment.

So far, during the regular safety review, the ETOP IDMC did observe any additional toxicit compared the chemo-radiotherapy alone.

Additionally, a first planned analysis of the PACIFIC trial (stage III NSCLC treated with concurrent chemotherapy and radiotherapy, followed by the anti-PD-L1 durvalumab or observation, NCT02125461) showed an increased progression-free survival (PFS), which was co-primary endpoint together with overall survival (OS). The full details are not yet known, but it appears that the pre-clinical rationales of combined chemo-radiotherapy and anti-PD-1 treatment are successfully transferred into clinical trials, without serious toxicities.

A recent secondary analysis of the Keynote 001 trial indicates synergistic affects of radiotherapy and immunotherapy.[2] This international, multicentre phase I trial assessed the effect of pembrolizumab monotherapy in patients with progressive locally advanced or metastatic NSCLC. Patients were assigned to multiple expansion cohorts to allow for the inclusion of patients who were naïve to systemic therapy and those who had progression after one or two previous regimens.

The results from this study showed that the effect of pembrolizumab was significantly higher in patients who received previous radiotherapy than in patients without previous radiotherapy (median PFS: 4.4 months versus 2.1 months, hazard ratio 0.56, p=0.019; median OS: 10.7 months versus 5.3 months, hazard ratio 0.58, p=0.026).

These findings were well in line with preclinical studies that demonstrated the ability of radiotherapy to enhance antitumour immune response.[2]

In the absence of of serious pulmonary toxicity, the apparent benefit of chemo-radiotherapy and anti-PD-1 and the high interest of the NICOLAS study group, we propose to amend the NICOLAS trial protocol to expand on the number of patients in order to reach sufficient power for an efficacy readout (progression-free survival).

5. Objectives and endpoints

5.1. Primary objective

To assess the safety and efficacy of the concurrent nivolumab administration with standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC, as defined by the rate of grade ≥3 pneumonitis (CTCAE V4.0) 6 months post-radiotherapy and, if safety is proven, to assess the progression-free survival (see section 17: Statistical Considerations).

5.2. Secondary objectives

5.2.1. To evaluate secondary measures of clinical efficacy including time to first grade ≥3 pneumonitis (TFP3), objective response rate (ORR), time to treatment failure (TTF) and overall survival (OS).

5.2.2. To assess the safety and the tolerability of the treatment.

5.3. Primary endpoint

5.3.1. Grade ≥3 pneumonitis (CTCAE V4.0) observed any time during 6 months from end of radiotherapy; for definition, see section 14.1.

5.4. Key secondary endpoint

5.4.1. 1-Year progression-free survival by RECIST v1.1

5.5. Other secondary endpoints

5.5.1. Time to first grade ≥3 pneumonitis

5.5.2. Objective response determined by RECIST v1.1

5.5.3. Time to treatment failure

5.5.4. Overall survival

5.5.5. Adverse events graded according to CTCAE V4.0

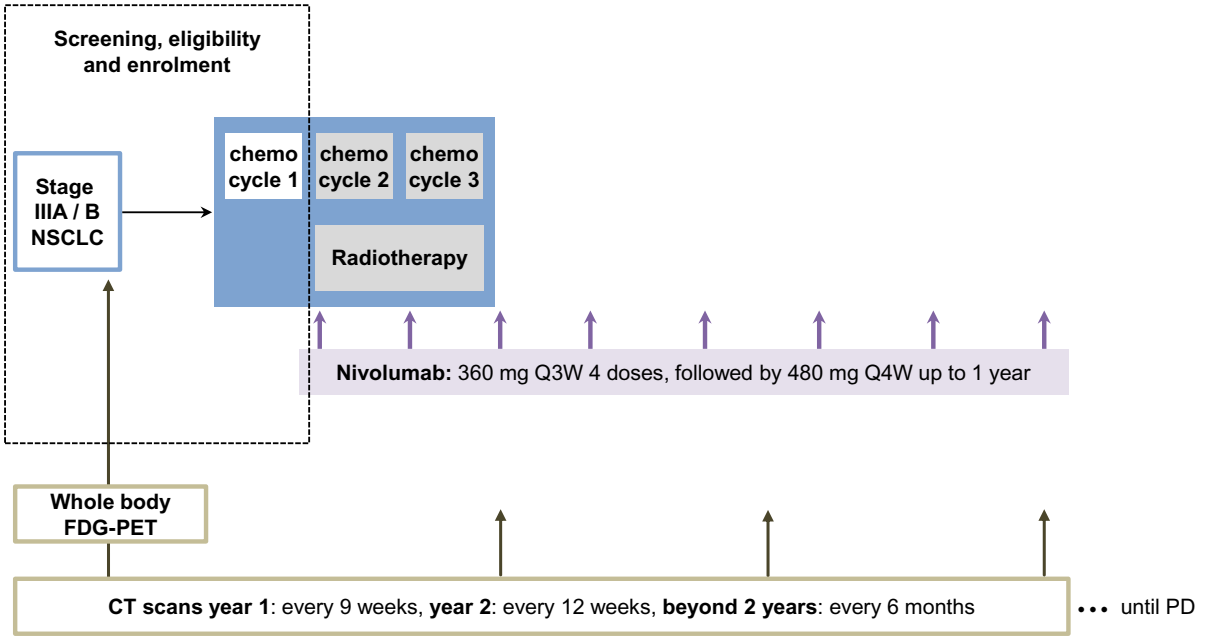
For definitions, see section 14.

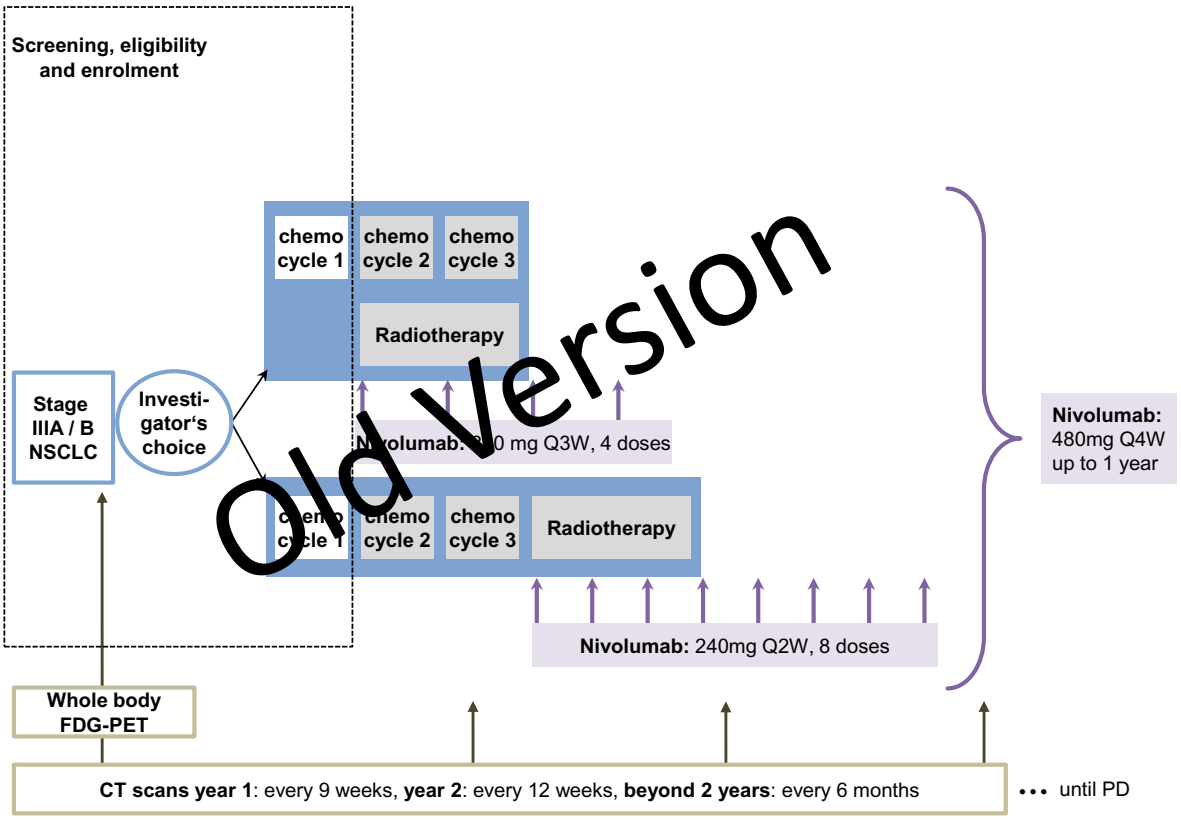
6. Trial design, duration and termination

This phase II trial aims at evaluating the addition of anti-PD-1 nivolumab consolidation to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC with safety as primary endpoint and efficacy as key secondary endpoint.

Patients will receive 4 doses of nivolumab 360 mg Q3W, concurrently with standard chemo-radiotherapy, followed by 480 mg Q4W for up to 1 year from start of nivolumab treatment, unless treatment stops earlier due to unacceptable toxicity, disease progression, withdrawal of consent or the trial is terminated by the sponsor.

After a run-in period of 3 months for the activation of the centres, patient accrual is expected to be completed within 9 months. Follow-up will continue until 2 years from start of nivolumab treatment of the last recruited patient. The trial will end with the preparation of the final report, scheduled at 2.5 years after the inclusion of the first patient.





Eleven sites from five 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 evaluation and/or intervention.

7.1. Inclusion criteria

7.1.1. Histologically or cytologically confirmed non-small cell lung carcinoma

7.1.2. Locally advanced stage IIIA or IIIB (T0-3 N2-3 or T4N0-3 M0) NSCLC, according to 7th TNM classification.
Within 35 days before beginning of first platinum-based chemotherapy cycle:

- Nodal status N2 or N3 must be proven (by biopsy, EBUS, mediastinoscopy or thoracoscopy) except for overt cT4 disease.
- Whole body FDG-PET plus contrast enhanced CT of thorax / upper abdomen (from top of thorax until adrenal glands, and full liver and kidney included) in addition to or in combination with PET.
- brain MRI (preferred) or high-quality brain CT with intravenous contrast at the time of staging mandatory.

7.1.3. Measurable disease (according to RECIST v1.1 criteria)

7.1.4. Age ≥18 years

7.1.5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (see Table 1)

7.1.6. Life expectancy >3 months

7.1.7. Previous delivery of a maximum of one 3-weekly cycle of platinum-based chemotherapy

7.1.8. All AEs from previous therapies (including the first chemotherapy cycle in the context of this trial) resolved to grade <2 (except fatigue, alopecia, nausea, lack of appetite and peripheral neuropathy).

7.1.9. Adequate haematological function:

- WBC ≥2000/µL
- haemoglobin ≥9 g/dL
- neutrophil count $\geq 1 \times 10^9$/L
- platelet count $\geq 100 \times 10^9$/L

7.1.10. Adequate liver function:

- Total bilirubin ≤2 x ULN (except patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dl)
- ALT ≤3 × ULN
- Alkaline phosphatase ≤5 x ULN.

7.1.11. Adequate renal function: Calculated creatinine clearance (according to Cockroft-

Gault, see 10.2):
- ≥60ml/min for patient receiving cisplatin
- ≥30ml/min for patient receiving carboplatin

7.1.12. Pulmonary function FEV1 of 1.0 L or >40% predicted value and DL_{CO} >30% predicted value

7.1.13. Patient capable of proper therapeutic compliance, and accessible to correct follow-up.

7.1.14. 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 trial enrolment. The test must be repeated within 24 hours before beginning nivolumab treatment and then before every 2nd nivolumab administration. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stops.

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

Table 1: ECOG Performance Status:

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
PS 3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2. Exclusion criteria

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

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

7.2.3. Prior chemotherapy, radiotherapy or molecular targeted therapy for NSCLC (with the exception of one cycle of chemotherapy given prior to enrolment into this trial, see 7.1.7)

7.2.4. Patients with an active, known or suspected autoimmune disease. Patients are permitted to enrol if they have vitiligo, type I diabetes mellitus, residual hypo-thyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

7.2.5. Patient who has had in the past 3 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.

7.2.6. Patient 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 trial.

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

7.2.8. Known or suspected hypersensitivity to nivolumab or any of its excipients

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

7.2.10. Established pathological diagnosis of underlying 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 (see section 10.8) during the trial treatment and for a period of at least 7 months (male participants) and 5 months (female participants) following the last administration of nivolumab.

7.2.13. Patients receiving any concurrent anticancer systemic therapy

7.2.14. HIV, active Hepatitis B or Hepatitis C infection

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

7.2.16. Planned radiotherapy to lung of mean dose >20 Gy or V_{20} >35%

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

7.2.18. Metastatic disease (mandatory assessment of the brain either by MRI or high-quality CT with intravenous contrast at the time of staging as well as systemic PET and CT scan)

7.2.19. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways

Please refer to section 10.6 for prohibited and restricted therapies during trial treatment.

8. Patient screening and enrolment

This trial will use a web-based registration system. Each participating centre will access the system directly to enrol patients. Specific details for enrolment of patients are in the ***ETOPdata User Manual*** which will be available on the trial specific section on the ETOP website (http://www.etop-eu.org).

8.1. Screening

Note that written informed consent must be obtained from the patient prior to any trial-related evaluation and/or intervention (with the exception of the first chemotherapy cycle that is administered before enrolment into the trial). Detailed trial procedures are described in section 15.

8.2. Enrolment

Patients must be enrolled prior to the start of radiotherapy and nivolumab treatment, e.g. between chemotherapy cycle one and two, **ideally on day 1 of chemotherapy cycle 2**.

Verify eligibility and enrol the patient in the RDE facility ETOPdata according to the information in the ***ETOPdata User Manual*** (available on the trial specific section on the ETOP website). The date the Informed Consent was signed by the patient and the date signed by the investigator are both required to complete the eligibility checklist.

Please complete and submit the Eligibility for Enrolment tab. Then submit the eCRF in ETOPdata in order to enrol the patient. Detailed trial procedures are described in section 15.

8.3. Start of chemo-radiotherapy

Chemotherapy consists of 3 cycles. The first cycle is given prior to enrolment into the trial. After enrolment, the second chemotherapy cycle should start 21 (±3) days after day 1 of cycle 1, except for delay due to chemotherapy toxicities from first cycle (see section 10.3).

Radiotherapy is applied concurrently and must start at the same time as chemotherapy cycle 2. In case the administration of chemotherapy is delayed due to toxicity, radiotherapy should start within 3 days of start of chemotherapy cycle 2.

8.4. Start of nivolumab

Nivolumab treatment will start concurrently with radiotherapy and starts on the same day as chemotherapy cycle 2. In case of chemotherapy delays due to toxicity, nivolumab will be administered when chemotherapy recommences. Nivolumab is always administered at the same time as chemotherapy, i.e. the same delay will apply for both chemotherapy and nivolumab.

9. Investigational product

Nivolumab is the Investigational Medicinal Product (IMP) used in this trial. BMS will provide the IMP at no cost for the entire duration of this trial.

The ***Drug Supply Manual*** (available on the trial specific section on the ETOP website) will describe detailed drug supply logistics as well as labelling, packaging, handling, drug accountability and destruction of unused drugs.

9.1. Description of investigational drug

Nivolumab (also referred to as BMS-936558 or MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4-S228P) antibody (HuMAb) that targets the programmed cell death protein 1 (PD-1) cell surface membrane receptor.

PD-1, a transmembrane protein, is a member of the CD28 family of T-cell costimulatory 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. PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1. Binding of PD-1 to its ligands results in the down-regulation of lymphocyte activation. 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. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies.

The clinical study product is a sterile solution for intravenous administration.

9.2. Packaging and labelling

Nivolumab is available in concentrations of 100 mg/vial (10 mg/ml). Nivolumab is administered via intravenous (*i.v.*) infusion only.

9.3. Receipt of the drug

Nivolumab will be supplied by BMS directly to the sites. The investigational site will check the condition of nivolumab upon arrival. Any damaged shipments will be replaced. See the ***Drug Supply Manual*** for details.

Accurate records of nivolumab 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 nivolumab is destroyed at site a certification of destruction form should be generated and retained in the Trial Master File.

9.4. Storage and handling

Nivolumab must be stored at 2°- 8°C, protected from light and freezing. Nivolumab must be stored in a secure area according to local regulations. See ***Drug Supply Manual*** for details.

9.5. Unused trial drug supplies

If nivolumab 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. Please refer to the ***Drug Supply Manual*** for details.

10. Trial treatments

10.1. Overview of treatment

Trial treatment consists of chemotherapy (cisplatin in combination with vinorelbine, etoposide or pemetrexed) concurrently with radiotherapy and anti PD-1 nivolumab treatment.

10.2. Chemotherapy dosage, administration and schedule

Chemotherapy consists of 3 cycles of cisplatin in combination with vinorelbine, etoposide or pemetrexed. The first cycle is given prior to enrolment into the trial. After enrolment, the second chemotherapy cycle must start 21 days (±3 days) after the start of cycle 1, except for delay due to chemotherapy toxicities from first cycle (see section 10.3).

Radiotherapy is given concurrently with chemotherapy cycle two and three (see Section 10.4) Chemotherapy is administered according to local guidelines. The chemotherapy doses should be based on the patient's calculated pre-treatment body surface area (BSA) using actual body weight.

Table 2: Overview chemotherapy options

Option	Drug		Dose	Dose frequency
1	**Cisplatin plus vinorelbin**			
	Cisplatin*		80 mg/m^2	d1, Q3W, 3 cycles**
	Vinorelbine	chemo-radiotherapy	30 mg/m^2	d1 + d8 cycle 1**
			20 mg/m^2	d1 + d8 cycles 2 & 3
2	**Cisplatin plus etoposide**			
	Cisplatin*		80 mg/m^2	d1, Q3W, 3 cycles**
	Etoposide		100 mg/m^2	d1-d3, Q3W, 3 cycles**
3	**Cisplatin plus pemetrexed** (for non-squamous histological subtypes)			
	Cisplatin*		75 mg/m^2	d1, Q3W, 3 cycles**
	Pemetrexed		500 mg/m^2	d1, Q3W, 3 cycles**

* If cisplatin cannot be used, it can be replaced by carboplatin AUC5 at d1.

** The first chemotherapy cycle is administered before enrolment.

Carboplatin dose must be calculated according to Calvert formula and calculated creatinine clearance (CrCl) according to the formula of Cockroft-Gault (see below).

Calvert Formula: Dose (in mg) = Target AUC × (GFR+ 25)

Cockroft-Gault:

$$\mathrm{CrCl}\left(\frac{\mathrm{mL}}{\mathrm{min}}\right)=\frac{[140\text{-age (years)}\times\text{actual body weight (kg)}]}{72\times\text{serum creatinine }\left(\frac{\mathrm{mg}}{\mathrm{dL}}\right)}\times\{0.85\text{ if female}\}$$

AUC: Area under curve; GFR: Glomerular filtration rate (calculated creatinine clearance)

10.3. Chemotherapy delay and dose modification for toxicity

Chemotherapy toxicity should be managed according to local standards.

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. - 11.6.

Nivolumab administration will follow any chemotherapy delay.

Repeated dose delays are allowed as required, but the sum of all delays should not exceed 6 weeks. If chemotherapy cannot be administered after a three-week delay, chemotherapy should be discontinued. Note: patients who cannot complete chemotherapy due to toxicity may continue trial treatment if radiotherapy can be given at a curative dose. In such a case, nivolumab administration will continue concurrently with radiotherapy.

10.3.1. Haematological toxicity

Dose modifications are based on each pre-treatment blood count.

Table 3: Chemotherapy dose modifications for haematological toxicity

ANC x 10^9/l		Platelets x 10^9/l	Cisplatin + etoposide or vinorelbine + pemetrexed or carboplatin + etoposide or vinorelbine + pemetrexed
>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 of both drugs and continuing G-CSF support.
		Grade 4 thrombocyto-penia requiring medical intervention or grade ≥2 bleeding with thrombocytopenia	First event: 20% dose reduction of both drugs Second event: 35% dose reduction of both drugs

10.3.2. Hepatic toxicity

Table 4: Chemotherapy dose modifications for hepatic toxicity

AST/ALT		Bilirubin	Cisplatin or carboplatin	Etoposide, vinorelbine or pemetrexed
2-5 x ULN at day 1 of cycle	and	≤2 x ULN	Full dose	Full dose
>5 x ULN at day 1 of cycle	or	>2 x ULN	Delay one week then reassess using the same criteria. A delay up to three weeks is allowed (if a longer delay is necessary trial treatment must be stopped). First event: 20% dose reduction of etoposide at cycle 2, no reduction in vinorelbine or carboplatin. Second event: 35% dose reduction of etoposide at cycle 3, 25% reduction vinorelbine.	

10.3.3. Renal toxicity

Request calculated creatinine clearance before each course of chemotherapy.

Table 5: Cisplatin dose modifications for renal toxicity

Calculated creatinine clearance at day 1 of cycle	Cisplatin	Etoposide, vinorelbine or pemetrexed
>50 ml/min	Full dose	Full dose
<45 ml/min	Switch to carboplatin AUC5	If pemetrexed is used, switch to vinorelbine or etoposide with 20% dose reduction
25-50 ml/min	Switch to carboplatin AUC5	20% dose reduction
<25 ml/min	Off trial treatment	Off trial treatment

Carboplatin dosing:

If carboplatin is to be used, the dose uses target area under the curve (AUC) of 5 and must be calculated according to the Calvert formula:

Dose (in mg) = Target area under curve × (GFR+ 25)

Carboplatin, pemetrexed and etoposide will be given 3-weekly.

Table 6: Carboplatin dose modifications for renal toxicity

Calculated creatinine clearance at day 1 of cycle	Carboplatin	Etoposide, vinorelbine or pemetrexed
>50 ml/min	Full dose	Full dose
<45 ml/min	Full dose	If pemetrexed is used, switch to vinorelbine or etoposide with 20% dose reduction
25-50 ml/min	Full dose	20% dose reduction
<25 ml/min	Off trial treatment	Off trial treatment

10.3.4. Other toxicities at any time during chemo-radiotherapy treatment

Table 7: Chemotherapy dose modifications for other toxicities

Peripheral neuropathy grade >2	Switch to carboplatin AUC5 100% dose of etoposide 25% dose reduction vinorelbine
Any grade 3-4 toxicities other than mucositis, nausea/vomiting, fatigue or alopecia	25% dose reduction for cisplatin/carboplatin and etoposide, vinorelbine or pemetrexed after recovery to grade ≤1. A delay up to three weeks is allowed (if a longer delay is necessary trial treatment must be stopped).

10.4. Thoracic radiation

Radiotherapy will consist of a physical dose of at least 60 Gy delivered concurrently with the chemotherapy cycles two and three (see ESMO 2013 [16] and EORTC radiotherapy [19] guidelines) and must start at the same time as chemotherapy cycle 2. In case the administration of chemotherapy must be delayed due to toxicity, radiotherapy should start ±3 days of start of chemotherapy cycle 2.

10.4.1. Doses, fractionation and treatment techniques

As there is an ongoing debate about the optimal radiotherapy dose and scheduling, the only requirement in this trial is that each individual patient should have received a radiotherapy dose that is considered to be able to eradicate the primary tumour and the involved lymph nodes. A physical dose of at least 60 Gy is required.

The fractionation schedule and the treatment techniques are left over to the discretion of the clinician, but it is recommended to use the ESMO guidelines [16] and the EORTC technical recommendations [19].

10.4.2. Organs at risk (OAR)

In order to be able to correlate toxicity with doses to the OARs, the following OAR should be contoured and some dose-volume histogram (DVH) parameters recorded (see below):

Mandatory

Lungs: The mean lung dose is calculated using the total (left and right) lung volume minus the total (primary tumour plus lymph nodes) gross tumour volume (GTV).

Optional

Oesophagus: the outer contour being delineated from the cricoid to the gastro-oesophageal junction. The mean and the maximal dose will be recorded.

Heart. Contouring done according to the RTOG guidelines by Kong et al (www.rtog.org). The mean and the maximal dose will be recorded.

10.5. Nivolumab treatment

10.5.1. Start of nivolumab treatment

Patients may only start nivolumab treatment if all adverse events from previous chemotherapy have resolved to grade <2 (except fatigue, alopecia, nausea, lack of appetite or peripheral neuropathy).

Nivolumab treatment starts together with radiotherapy, 21 (±3) days after start of the first chemotherapy cycle. The first two nivolumab doses are administered concurrently with chemotherapy cycles 2 and 3. In case of chemotherapy delays due to toxicity, nivolumab will be administered when chemotherapy recommences.

10.5.2. Nivolumab dose and schedule

The initial 4 doses of nivolumab will be administered at 360 mg as intravenous infusion (approx. 30 minutes) every 3-weeks (±3 days). The first 2 doses are administered concurrently with the last two chemotherapy cycles.

Separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first and the infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the chemotherapy infusion, no sooner than 30 minutes after completion of the nivolumab infusion.

From dose 5 on, nivolumab is administered at 480 mg every 4 weeks (±3 days) for up to 1 year from start of nivolumab treatment, unless nivolumab treatment stops earlier due to unacceptable toxicity, disease progression, withdrawal of consent or the trial is terminated by the sponsor. **Please note that dose 5 will start 3 weeks (±3 days) after dose 4**.

10.5.3. Nivolumab administration

Nivolumab may be diluted in normal saline or 5% dextrose solution. It is to be administered as *i.v.* infusion (approx. 30 minutes). It is not to be administered as an *i.v.* push or bolus injection. At the end of the infusion, the line must be flushed with a sufficient quantity of normal saline.

10.5.4. Dose Modifications

Dose reductions or dose escalations of nivolumab are not permitted.

10.5.5. Nivolumab delay and discontinuation for toxicity

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. (See current Investigator Brochure (IB) [39], available on the trial specific section on the ETOP website. IB udpates will be distributed by ETOP whenever an update is available.)

The next nivolumab dose must be delayed in case of persisting drug-related adverse event of grade ≥2.

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab).

If treatment is delayed >6 weeks (i.e., more than 9 weeks since the last dose for Q3W and 10 weeks for Q4W schedules), the patient must permanently discontinue nivolumab treatment, except as specified below in section 10.5.7.

Nivolumab is always administered at the same time as chemotherapy, i.e. the same delay will apply for both chemotherapy and nivolumab.

10.5.6. Criteria to resume nivolumab treatment

Patients may resume treatment, if treatment interruption was ≤6 weeks, with study drug when the drug-related AE(s) resolve to Grade ≤1, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue, increased creatinine, lack of appetite, peripheral neuropathy or alopecia
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- 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 may resume treatment

If the above criteria to resume treatment are met, the patient should restart treatment at the time point when the next dose would have been administered had there been no interruption.

10.5.7. Criteria to discontinue nivolumab treatment

Treatment must be permanently discontinued for the following:

- Patients with combined Grade ≥2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks after last dose OR requires systemic treatment
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 non-skin, drug-related adverse event lasting >7 days require discontinuation, except grade 3 drug-related laboratory abnormalities not listed below.
- 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 requires discontinuation:
    - AST or ALT >8 x ULN
    - Total bilirubin >5 x ULN
    - Concurrent AST or ALT >3 x ULN and total bilirubin >3 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade <4 within 1 week of onset.
    - 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
- Any nivolumab dosing interruption lasting >6 weeks (i.e., more than 9 weeks since the last dose Q3W and 10 weeks for Q4W), with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapering to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing interruption lasting >6 weeks, ETOP (NICOLAS@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. Prior to re-initiating treatment in a patient with a dosing interruption lasting >6 weeks, ETOP (NICOLAS@etop-eu.org) must be consulted. Tumour assessments should continue as per protocol even if dosing is interrupted.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing

10.5.8. Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, 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 CTCAE v.4 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 administrations.

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

Stop the nivolumab 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, then 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 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 study drug 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 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 (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization 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. 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 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 localized or generalized pruritus 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 IB [39] and in separate guidelines for management algorithms which can be downloaded from the trial specific section of the ETOP website.

10.6. Prohibited and restricted therapies during trial treatment

10.6.1. Accepted treatment during trial treatment (chemo-radiotherapy and nivolumab treatment)

- 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.
- Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

10.6.2. Prohibited treatments during trial treatment (chemo-radiotherapy and nivolumab treatment)

- Any non-trial cytotoxic or immunotherapy anticancer treatment
- Treatment with inhibitor or agonist of T-cell costimulation
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of nivolumab administration.
- Live vaccines within 30 days prior to the first dose of nivolumab treatment and during nivolumab treatment.
- GM-CSF
- Immune check-point blockers (PD-1; PD-L1, CTLA-4)
- Immunosuppressive agents

10.6.3. Precautions

Women of childbearing potential and sexually active men must use effective contraception from the start of the trial treatment throughout the trial period up to 7 months (male participants) and 5 months (female participants) after the last dose of any trial treatment. Please refer to section 10.8 for highly effective contraception methods.

10.7. Treatment duration

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

- Documented progression according to RECIST v1.1 (except at local progression after nivolumab treatment start until confirmation by CT scan after 6 (±2) weeks, see below)
- Secondary malignancy resulting in need for systemic treatment
- Unacceptable toxicity
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant
- 1 year of nivolumab treatment has been completed, or stopped early due to unacceptable toxicity, disease progression, withdrawal of consent or the study is stopped by the sponsor

Nivolumab is 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 tumour lesions following the start of nivolumab 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 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 after start of nivolumab (IMP) treatment but without appearance of new lesions or rapid clinical deterioration (see below) should continue to be treated with IMP and CT scan should be repeated after 6 (±1) weeks to allow detection of a subsequent tumour response. This will improve the overall assessment of the clinical activity of IMP and more likely capture its true potential to induce clinical responses. This must follow the definition below:

Treatment beyond disease progression

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

Patients treated with IMP will be permitted to continue treatment beyond initial RECIST v1.1 defined PD after nivolumab treatment start if they meet all of the following criteria:

1. Investigator-assessed clinical benefit, and no rapid disease progression
2. All other study protocol eligibility criteria met
3. Tolerance of study drug
4. Stable performance status
5. Only local progressive disease of known stage III-defining NSCLC lesions (absence of new lesion)

A radiographic assessment / scan should be performed 6 (±1) weeks from this original PD scan to determine whether there has been a decrease in the tumour size or disease stabilization, or alternatively continued PD which would terminate the trial treatment.

For the patients who continue nivolumab beyond progression, further progression is defined as an additional >10% increase in tumour dimension or new lesions as assessed per RECIST v1.1 criteria from time of initial PD. Patients who continue treatment beyond initial investigator-assessed, RECIST v1.1-defined progression will be considered to have had progressive disease at the time of the initial progression event.

If nivolumab has 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 CRF.

10.8. Contraception, nursing, pregnancy

10.8.1. Contraception

Female patients who are not of childbearing potential due to being postmenopausal (2 year without menstruation) 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 from the start of trial treatment throughout the trial period up to 7 months (male participants) and 5 months (female participants) after the last dose of any trial treatment.

The following contraception methods are considered highly effective:

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

Patients should start using birth control from the start of trial treatment throughout the trial period up to 7 months (male participants) and 5 months (female participants) after the last dose of any trial treatment.

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 trial participant must be reported.

Patients should be informed that taking the trial medication may involve unknown risks to the fetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above). If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

10.8.2. Use in pregnancy

If a patient inadvertently becomes pregnant while on treatment with nivolumab, trial treatment will be stopped immediately for the patient and the event reported immediately, see Section 12.9. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to ETOP without delay and within 24 hours if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to ETOP.

10.8.3. Use in nursing women

It is unknown whether nivolumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for this trial.

11. Safety of investigational products

The chemotherapy regimens constitute standard chemotherapy, and are not investigational.

11.1. Nivolumab

11.1.1. Safety profile of nivolumab

The overall safety experience with nivolumab is based on experience in approximately 4,000 patients as either a monotherapy or in combination with other therapeutics. In general for monotherapy, the safety profile is similar across tumour types. The only exception is pulmonary inflammation AEs which may be numerically greater in patients with NSCLC possibly because in some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment related AE, fatigue is almost always low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues/organs. These include the following: pulmonary, gastrointestinal, hepatic, skin, endocrine, and renal AEs as well as hypersensitivity/infusion reaction.

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Safety management algorithms for organ-specific AEs are found in guidance document on specific management principles (IB Appendix 2) [39]. Patients should have a thorough diagnostic work-up to evaluate potential drug and non-drug related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate and high-grade AEs immunosuppresion with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3-6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms. Rarely, a patient receiving immunosuppression for nivolumab-related AEs may develop an opportunistic infection. Patients with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the adverse event should be considered for antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as pneumocystis jiroveci (formerly P carinii) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent adverse events in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in patients with active autoimmune disease given the mechanism of action of the antibody.

11.1.2. Safety when combining nivolumab with chemotherapy

The interaction of a tumour with the immune system is complex. Tumors and the tumour microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumour. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumour infiltrating T-cells (e.g., PD-L1 expression; TGF-beta). In addition, some tumour-derived factors are able to enhance immune system counter-regulatory systems (e.g., increased T-regulatory cells). Finally, suboptimal tumour antigen delivery and presentation has been postulated as another mechanism by which tumours can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumour/immune-system interactions in favor of the immune system. Chemotherapy can result in tumour cell death with a resultant increase in tumour antigen delivery to antigen-presenting cells. Tumour cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumour-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine plus cisplatin and pemetrexed plus cisplatin. Nivolumab 10 mg/kg, and 5 mg/kg, was combined with paclitaxel and carboplatin [37].

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. No dose-limiting toxicities were observed during the first 6 weeks of treatment. The frequency of most immune-related AEs was higher than what had been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths. Pneumonitis of any grade was reported in 7 patients (13%); Grade 3-4 in 4 subjects (7%). Twelve (21%) patients discontinued due to treatment-related AEs.

The observed response rates of nivolumab and chemotherapy were similar to that of platinum-doublet chemotherapy alone, though the duration of responses was longer. The median duration of response across all the nivolumab plus chemotherapy cohorts was 27.3 weeks. The 1-year survival rate for all cohorts combined was 71% [37].

Table 8 Treatment-related AEs in first-line treatment of nivolumab / chemotherapy in CA209012

	Total (N=56)		
	All Grades	**Grade 3**	**Grade 4**
Subjects with any treatment-related AE, % (n)	95 (53)	41 (23)	4 (2)

Treatment-related AE, % (n)			
Fatigue	71(40)	5 (3)	0
Nausea	46 (26)	2 (1)	0
Decreased Appetite	36 (20)	2 (1)	0
Alopecia	30 (17)	0	0
Anemia	27 (15)	4 (2)	0
Rash	27 (15)	2 (1)	0
Arthralgia	21 (12)	0	0
Diarrhea	21 (12)	2 (1)	0
Constipation	20 (11)	0	0
Peripheral Neuropathy	20 (11)	0	0

Table 9 Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012

	Nivolumab 10 mg/kg			**Nivolumab 5 mg/kg**
	Gem/Cis (n=12)	**Pem/Cis (n=15)**	**Pac/Carb (n=15)**	**Pac/Carb (n=14)**
ORR, %	33	47	47	43
SD, %	58	47	27	43
Median Duration of Response, Weeks	45	24.4	27.3	27.3
12-mo OS rate, %	50	87	72	86
18-mo OS Rate, %	33	60	40	62
Median OS, Weeks	51	83	65	Not Reached

11.2. Cisplatin

The most frequently reported adverse events (>10%) of cisplatin were haematological (leucopenia, 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/m^2. 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/mm^2 and white cells greater than 4,000/mm^2. 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.

11.3. 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 >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 baseline 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 one third 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, pruritus

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 one third 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.

11.4. Etoposide

The following adverse reactions have been reported:

Table 10: Adverse reactions 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 chemo-therapy*				Acute promyelo-cytic leukaemia

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
Blood and lymphatic systems disorders	Myelosuppression **, leucopenia, thrombo-cytopenia, anaemia					
Immune system disorders		Anaphylactic-like reactions***				
Metabolism and nutrition disorders	Anorexia			Hyperuri-caemia		
Nervous system disorders	Central nervous system disorders (fatigue, drowsiness)		Peripheral neuropathies	Insults, paresthesiae, optic neuritis, taste disturbance		
Eye disorders				Reversible loss of vision, transient cortical blindness		
Cardiac disorders			Arrhythmia, myocardial infarction, cyanosis			
Vascular disorders		Hypotension[%], haemorrhage (in patients with severe myelosuppression)		Phlebitis[+]		
Respiratory, thoracic and mediastinal disorders			Bronchospasm, coughing, laryngospasm	Apnoea, interstitial pneumonitis or pulmonary fibrosis		
Gastrointestinal disorders	Nausea, vomiting	Abdominal pain, diarrhoea, stomatitis	Mucositis, oesophagitis	Constipation, swallowing disorders (dysphagia)		
Hepatobiliary disorders		Hepatic dysfunction				

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
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 inflam-mation 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/m^2) 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.

11.5. Vinorelbine

Please refer to the latest version of the Summary of Product Characteristics (SPC) at:

http://www.medicines.org.uk/emc/medicine/16029

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, leukopenia and anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

11.6. Pemetrexed

Please refer to the latest version of the Summary of Product Characteristics (SPC) at:

http://www.medicines.org.uk/emc/medicine/31354

The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Rarely seen events include Stevens-Johnson syndrome and Toxic epidermal necrolysis.

12. Adverse events and reporting

12.1. Adverse event definition and reporting

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

An adverse event in this trial is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition that occurs from the day of signing informed consent until 100 days after the final dose of nivolumab, regardless of whether it is considered related to the trial treatment. After the last dose, only AEs considered possibly related to nivolumab by the Investigator have to be reported.

The causal relationship to study drug is determined by a physician and should be used to assess and report all adverse events (AE). The causal relationship can be one of the following:

Related (possible, probable, definite): There is a reasonable causal relationship between study drug administration and the AE.

Not related (unrelated, unlikely): There is not a reasonable causal relationship between study drug administration and the AE.

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 patient. 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 CRF 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 CRF from grade ≥3 only
- AEs should not be reported in a narrative description.
- Status of pneumonitis will be specially recorded in the eCRFs.

12.2. Definition of Serious Adverse Event (SAE)

12.2.1. SAEs during trial treatment

An SAE is defined in this trial as any undesirable medical occurrence/adverse drug experience that occurs from the provision of informed consent or within 100 days after the final dose of nivolumab that, at any dose, results in any of the following:

- is fatal (any cause)
- life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect
- is a secondary malignancy
- is a medically important event
- Although overdose is not always serious by regulatory definition, this event must be handled as SAE.
- Pregnancy (see section 12.8).

Second (non-NSCLC) malignancies are always considered SAEs, no matter when they are diagnosed. These events should be reported on the Serious Adverse Event Forms.

Other significant/important medical events which may jeopardise the patient are also considered serious adverse events.

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.

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the patient to have study drug discontinued or interrupted, as well as dose modifications during chemo-radiotherapy
- any laboratory abnormality that required the patient to receive specific corrective therapy.

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 and in the IB.

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 serious adverse events are hospitalizations occurring under the following circumstances:

- elective surgery
- occur on an outpatient basis and do not result in admission (hospitalization <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).

12.2.2. SAEs after end of trial treatment

During the follow-up phase (beyond 100 days of discontinuation of dosing), the following events always 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 12.8)

12.3. Definition of Serious Adverse Reaction (SAR)

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

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

The expectedness assessment is the responsibility of the sponsor of the trial. A SUSAR is a serious adverse reaction that is assessed as unexpected on the basis of the following reference documents:

- For cisplatin, carboplatin, vinorelbine, etoposide: European Summary of Product Characteristics (SmPC)
- For nivolumab: Investigator's Brochure.

12.5. Protocol-specified significant events

12.5.1. 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 drug-induced liver injury 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 to the IB) for appropriate management of drug-induced liver injury (DILI) cases.

12.5.2. Reporting protocol specified significant events

Protocol Specified Significant Events must be documented and reported by submitting the completed SAE Report Tab (initial and follow-up) in the RDE system

- Within 24 hours after knowledge of the event if the event is serious
- Within 5 days after knowledge of the event if the event is not serious (Indicate in "Description" section that this is a "non-serious adverse event of special interest")

12.6. Reporting SAEs and protocol specified significant events

Following the patient's written consent to participate in the study, all SAEs, whether related or not related 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 trial medication.

If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is suspected to be related to study drug or protocol-specified procedure.

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

Protocol Specified Significant Events are to be reported by submitting the completed SAE Initial Report Tab in the RDE system, even if they do not meet any of the seriousness criteria. Please submit the completed SAE Report Tab (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 knowledge of the event. Indicate in "Description" section if "non-serious adverse event of special interest" yes or no.

Submission 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

The SAE outcome must be reported within 14 days after onset by submitting the SAE Follow-up Report eCRF online. 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 notify principal investigators of any SAR 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) on all SAEs regardless of relatedness, and other appropriate persons about all SAEs at least possibly related to trial medication (per either investigator or ETOP Safety Office review) within 24 hours of receipt.

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

12.7. Non-serious adverse event definition and reporting

A nonserious adverse event is an AE not classified as serious.

The collection of nonserious AE information should begin after patient has signed informed consent. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

12.8. 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.

Women of childbearing potential and sexually active men must use highly effective contraception from the start of trial treatment throughout the trial period up to 7 months (male participants) and 5 months (female participants) after the last dose of any trial treatment. Please refer to section 10.8 for approved contraception methods.

In the case of pregnancy occurring during the course of the trial or within 1 year 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.

All neonatal deaths that occur within 28 days of birth should be reported, irrespective of causality, as SAEs. In addition, any infant death after 28 days, irrespective of causality should also be reported within 24 hours of the investigator's knowledge of the event using the SAE forms.

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

13. Response evaluation

13.1. RECIST v1.1 criteria

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done according to the schedule indicated below, until tumour progression is determined according to RECIST v1.1 criteria. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

At baseline:	within 28 days before start of first chemotherapy cycle
Year 1:	every 9 weeks (±1 week) from enrolment
Year 2:	every 12 weeks (±2 weeks)
Beyond 2 years:	every 6 months (±4 weeks) until 2 years after the last patient started nivolumab treatment

The patient's response to chemo-radiotherapy treatment and nivolumab consolidation treatment will be assessed by RECIST v1.1 criteria [40] (see appendix 2). The response assessment according to RECIST v1.1 should be done by the local radiologist and reported on the CRF.

13.2. Determination of time point response

Table 11: Determination of time point response

Target lesions	Non-target lesions	New lesions	Resulting 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
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 reference [40]: 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 50mm with three measured lesions and at follow-up only two 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.

13.3. 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.

14. Endpoints definition

14.1. Grade ≥3 pneumonitis (CTCAE v4.0) observed any time during 6 months from the end of radiotherapy

This is the primary endpoint. It is defined as the number of patients reaching up to 6 months post chemo-radiation treatment without any episode of CTCAE v4.0 grade ≥3 pneumonitis. It will be used as the primary endpoint for all patients followed for at least 6 months beyond radiotherapy.

14.2. Progression-free survival

This is the key secondary endpoint. It is defined as the time from the date of enrolment 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. Patients who continue treatment beyond initial investigator-assessed, RECIST v1.1-defined progression will be considered to have had progressive disease at the time of the initial progression event [40]. For patients receiving nivolumab treatment, PFS will be evaluated both from date of enrolment and from date of first nivolumab dose.

14.3. Time to first pneumonitis of grade ≥3

TFP3 is defined as the time from the date of enrolment until first documented pneumonitis of grade ≥3. Censoring will occur at the last assessment only if patient is lost to follow-up or has died.

14.4. Objective response

Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from enrolment to termination of trial treatment. Objective response to nivolumab treatment will be determined using RECIST v1.1 criteria (see section 13).

14.5. Time to treatment failure

Time to treatment failure (TTF) is defined as time from enrolment to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Censoring will occur at the time of last tumour assessment only if the patient is lost to follow-up.

14.6. Overall survival

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

14.7. Toxicity

Adverse events classified according to CTCAE version 4.

15. Trial procedures

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

15.1. Baseline evaluations before enrolment

The following examinations must be done within 35 days before start of chemotherapy treatment:

15.1.1. Whole body FDG-PET

15.1.2. Contrast enhanced CT of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) is needed in addition to or in combination with PET-CT

15.1.3. Brain MRI or contrast enhanced CT

15.1.4. TNM categories

The following examinations must be done within 28 days before enrolment. If examinations were done prior to 28 days before enrolment, they have to be repeated.

15.1.5. Obtain written informed consent prior to any trial-related evaluation and/or intervention (within 7 weeks before enrolment)

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

15.1.7. Physical examination according to local standards, including blood pressure [mmHg], ECOG performance status, body weight [kg] and height

15.1.8. Haematology: haemoglobin, platelets, leukocytes, neutrophils

15.1.9. HIV, hepatitis B and C status

15.1.10. Renal function: serum creatinine and creatinine clearance calculated according to Cockroft-Gault (see section 10.2)

15.1.11. Hepatic function: ALT, AST, AP, total bilirubin

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

15.1.13. Electrocardiogram

15.1.14. Pregnancy test for women with childbearing potential within 7 days before enrolment.

15.1.15. Record all concomitant medications

15.2. CT schedule for disease evaluation

All patients will have a CT of thorax and upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively (and only after the first CT at baseline) CT of thorax and ultrasonography of upper abdomen until progression:

At baseline:	Whole body FDG-PET within 35 days before start of first chemotherapy cycle. CT is needed in addition to or in combination with PET.
Year 1:	every 9 weeks (±1 week) from enrolment
Year 2:	every 12 weeks (±2 weeks)
Beyond 2 years:	every 6 months (±4 weeks) until 2 years after the last recruited patient started nivolumab treatment

Also refer to section 10.7 for the management of patients with tumour volume increase after start of nivolumab dosing.

15.3. During chemotherapy

Tumour assessment will be done according to the schedule indicated in section 15.2.

Patients will be assessed clinically prior to each cycle of chemotherapy, within 24 hours before the first dose of the next cycle of chemotherapy:

15.3.1. Physical examination according to local standards, including blood pressure, performance status, and body weight

15.3.2. Recording of symptoms / adverse events

15.3.3. Record all changes in concomitant medications

15.3.4. Haematology (haemoglobin, platelets, leukocytes, neutrophils).

15.3.5. Serum creatinine and creatinine clearance calculated according to Cockroft-Gault (see section 10.2)

15.3.6. Hepatic function: ALT, AST, AP, total bilirubin

15.4. During nivolumab treatment and radiotherapy

15.4.1. Tumour assessment will be done according to the schedule indicated in section 15.2.

15.4.2. Pregnancy test for women with childbearing potential must be repeated within 24 hours before beginning nivolumab treatment and then every 2nd dose during nivolumab treatment. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stop.

The evaluations listed below will be done within 3 days before the administration of every dose of nivolumab

15.4.3. Recording of symptoms / adverse events

15.4.4. Physical examination according to local standards, including blood pressure, performance status, and body weight

15.4.5. Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase

15.4.6. Serum urea level

15.4.7. Haematology: haemoglobin, platelets, leukocytes, neutrophils

15.4.8. Serum creatinine and creatinine clearance calculated according to Cockroft-Gault (see section 10.2)

15.4.9. Hepatic function: ALT, AST, AP, total bilirubin

15.4.10. TSH, free T3 and T4 before the first nivolumab administration. TSH must be repeated before every 2nd nivolumab administration. Free T3 and T4 have only to be repeated in case of abnormal TSH value.

15.4.11. Record all changes in concomitant medications

15.5. End of treatment visit

At the end of all trial treatment and **irrespective of the reason for stopping treatment**, an end of treatment visit at the centre is to be scheduled within 30 days following the decision to stop nivolumab treatment or within 30 days after planned treatment start if treatment never started. In case treatment was delayed due to AEs and could not be resumed, the end of treatment visit should be performed within 10 weeks after the last dose. The following procedures should be performed:

15.5.1. Recording of symptoms / adverse events

15.5.2. Physical examination according to local standards, including performance status, blood pressure and weight

15.5.3. Haematology: haemoglobin, platelets, leukocytes, neutrophils

15.5.4. Hepatic function: ALT, AST, AP, total bilirubin

15.5.5. Serum creatinine and creatinine clearance calculated according to Cockroft-Gault (see section 10.2)

15.5.6. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stops.

15.5.7. CT thorax and upper abdomen, if not done within the last 6 weeks

15.5.8. Record all changes in concomitant medications

15.6. Evaluations in the follow-up phase before progression

Follow up visits after trial treatment stop will take place at the time of the CT scans (see section 15.2) and the following evaluations will be done:

15.6.1. Physical examination according to local standards, including performance status

15.6.2. CT thorax / upper abdomen (see section 15.2)

15.6.3. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stop

15.7. Evaluations after progression in follow-up

Follow up visits after progression will take place every 6 months (starting from date of progression, ±4 weeks).

The following evaluations will be done:

15.7.1. Pregnancy tests should be repeated at approximately 30 days and approximately 70 days after nivolumab treatment stops

15.7.2. Survival

15.7.3. Further lines of treatment

Patients who do not start nivolumab treatment will be followed up for survival alone (please complete the follow up tab in ETOPdata), no further CT scans need to be reported. Follow up visits can take place at the standard visits of the patient to the hospital but should ideally be reported within similar timelines as stated above for patients who started nivolumab treatment.

Follow-up will continue until 2 years from the start of nivolumab treatment of the last recruited patient.

16. Case report forms and documentation

16.1. Case report forms schedule

CRFs 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 12: Case report forms

Tab in ETOPdata	To be completed
Eligibility for Enrolment	Within 28 days of start of baseline assessments
Baseline	Within 14 days after enrolment

Tab in ETOPdata	To be completed
Tumour Assessments	Baseline: Within 14 days after enrolment; Year 1: within 14 days after each CT thorax and upper abdomen is performed [every 9 weeks starting from enrolment, (+/- 1 week)]; Year 2: within 14 days after each CT thorax and upper abdomen is performed [every 12 weeks (+/-2 weeks)]; Beyond year 2: within 14 days of end of each 6 month period (+/-4 weeks), until documented progression or until 2 years from start of nivolumab treatment of the last recruited patient
Concomitant Medications	Continuously from date of enrolment to 30 days after end of trial treatment. In case of any change in concomitant medications (new medication, stop medication): Within 14 days after each chemotherapy cycle. Within 14 days after each nivolumab cycle. Within 14 days after end-of-treatment visit.
Trial Treatments	Within 14 days after end of each chemotherapy and/or nivolumab administration. Please also don't forget to complete the Concomitant Medications and the Adverse Events CRFs at the end of each cycle.
Thoracic Radiotherapy	Within 14 days after end of radiotherapy
Nivolumab Treatments	Within 14 days after each administration
Adverse Events	Continuously from date of enrolment up to 100 days after end of nivolumab treatment, in case of any changes in adverse events (new events, change in severity grade of an event, end of an event). Within 14 days after enrolment (to record symptoms present at enrolment). Within 14 days after end of each chemotherapy cycle. Within 14 days after each nivolumab dose. Within 14 days after end-of-treatment visit. Within 14 days after follow-up visits.

Tab in ETOPdata	To be completed
SAE Initial Reports	Within 24h of awareness of SAE; Can be submitted via ETOPdata or via fax to ETOP safety office in case of unavailability of ETOPdata.
SAE Follow-up Reports	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.
End of Treatment	Within 14 days after end-of-treatment visit (which is to take place within 30 days following the decision to stop trial treatment)
Follow-up	Before progression: Year 1: after completion of chemo-radiotherapy: Within 14 days after follow-up visits [performed every 9 weeks (±1 week)]. Year 2: after completion of chemo-radiotherapy: Within 14 days after follow-up visits [performed every 12 weeks(±2 weeks)]; Beyond 2 years: after completion of chemo-radiotherapy: Within 14 days after follow-up visits (which take place every 6 months (+/- 4 weeks), until death, for a maximum of 2 years from start of nivolumab treatment of the last recruited patient; After progression: Within14 days after follow-up visits, which take place every 6 months (+/- 4 weeks), until death, for a maximum of 2 years from start of nivolumab treatment of the last recruited patient; To be completed at death.
Pregnancy	Within 24 hours of first documentation of pregnancy; Within 14 days of end of pregnancy.
WC/LFU (Withdrawal of consent / Lost to follow-up)	Within 14 days of awareness of withdrawal of consent or loss to follow-up.

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

17. Statistical considerations

17.1. Primary and key secondary objectives

To assess the safety and efficacy of the concurrent administration of nivolumab with standard first-line chemotherapy and radiotherapy for locally advanced stage IIIA/B NSCLC. Safety is defined by an adequately high 6-month pneumonitis-free rate of grade ≥3, or equivalently by an acceptably low rate of grade ≥3 pneumonitis (CTCAE V.4) observed any time within 6 months post-radiotherapy. If safety is proven then the one-year PFS is evaluated as key secondary endpoint.

17.2. Sample size determination

17.2.1. Safety evaluation

A 6-month post-radiotherapy rate of grade ≥3 pneumonitis (CTCAE V.4) of 15% is the expected rate after chemo-radiotherapy alone, while a rate above 33% is deemed unacceptably high. Thus, the interest is to reject a ≤67% 6-month pneumonitis-free rate of grade ≥3, targeting a 6-month pneumonitis-free rate of 85%.

The design of the safety evaluation is based on an exact group sequential test of the proportion π (6-month pneumonitis-free rate of grade ≥3) and estimation of the sample size uses the binomial probability distribution of number of successes, where success for a patient is defined as reaching 6 months post radiation treatment pneumonitis-free [41-44]. Using the exact group sequential test (with O'Brien-Fleming boundaries) [45], we incorporate in the design one interim look to have the opportunity of reaching an early conclusion on the feasibility of the treatment. At the interim look, the 3-month pneumonitis rate of grade ≥3 is evaluated (pneumonitis defined as having occurred up to 3 months after end of RT), while at the final analysis, the 6-month pneumonitis rate of grade ≥3 is of interest.

The primary safety hypothesis corresponds to the 6 months without pneumonitis of grade ≥3:

The null hypothesis states that 6-month pneumonitis-free rate of grade ≥3 is less than or equal to 67%, vs the one-sided alternative that the rate is above 67%, tested at π_1=85%:

$$H_0: \pi_0 \leqslant 67\% \text{ vs } H_1: \pi_1 > \pi_0, \text{ at } \pi_1 = 85\%$$

For a one-sided alpha of 0.05 and power of 83%, the required sample size for the safety evaluation is 41 patients evaluable for pneumonitis 6 months after end of RT, allowing for one interim safety analysis on the first 21 patients without any requirement for trial interruption. In the safety evaluation phase of the trial, 43 patients will be recruited allowing for about 5% competing risk rate rendering the patient not evaluable for pneumonitis. The 5% competing risk rate includes patients who are lost to follow-up or die without evidence of pneumonitis of grade ≥3.

As approximately 70% of the cases of pneumonitis are expected to occur by 3 months after the end of radiotherapy, a planned interim safety analysis on 21 patients will be performed at 3-months evaluating the pneumonitis-free rate at this time point.

In addition, a hierarchical design [3] is adopted that allows the examination of a secondary efficacy hypothesis (secondary-Hs) after the pneumonitis null hypothesis (primary-Hp) is rejected. This strategy allows testing for efficacy in this study cohort (Hs), while keeping the Family Wise Error (FWER) strongly at the desired level alpha. The hypothesis of treatment efficacy will be of interest only if the pneumonitis toxicity is acceptable either at the scheduled interim or at the end of the safety phase of the study. If the pneumonitis null hypothesis (Hp) is rejected either at the interim or the final primary safety analysis, the study will continue to include all required patients to test the efficacy hypothesis (Hs).

17.2.2. Efficacy evaluation

Based on preliminary baseline information regarding stage, it is believed that for the observed case-mix, the one-year PFS rate that could be achieved with current best provided care is estimated to be around 45%.[4, 5] The aim of the combination under investigation will be to improve the one-year PFS by at least 15%, that is, to achieve a one-year PFS rate of at least 60%.

Efficacy hypothesis (Hs):

$$H_{s0}: PFS_0 \leq 45\% \text{ vs } H_{s1}: PFS_1 > PFS_0, \text{ at } PFS_1 = 60\%$$

A sample size of 74 evaluable patients will provide a power of 83%, for testing the above efficacy hypothesis, using an exact test for a single proportion, at the one-sided alpha of 0.05. Assuming 5% non-evaluable patients, a total sample size of 78 patients need to enter the study.

17.3. Evaluation of primary and secondary endpoints

17.3.1. Overview of planned analyses and statistical methods

The total study duration for the primary safety endpoint analysis will be approximately 20 months including a 3-month start-up period, 9 months accrual (of the first 43 pateints), two months for completing radiotherapy and 6 months follow-up after radiotherapy.

The study duration for the key secondary efficacy endpoint will be approximately 22 months, including a 3-month start-up period, 7 months accrual (of the additional patients) and 12 months follow-up for evaluating the one-year PFS rate.

The overall testing strategy can be described as follows:

Interim analysis for grade ≥3 pneumonitis 3 months after nivolumab start (N=21 patients).

If pneumonitis null hypothesis is not rejected = no decision reached → trial continues to final analysis for safety (pneumonitis grade ≥3) with a total of 41 patients.

→ Safety analysis for grade ≥3 pneumonitis 6 months after completion of radiotherapy (N=41 patients)

If pneumonitis null hypothesis is not rejected, toxicity is of concern and trial will end.

If pneumonitis null hypothesis is rejected, there is no toxicity concern and trial continues to efficacy analysis.

If pneumonitis null hypothesis is rejected → trial continues to final analysis for efficacy evaluation with a total of 74 patients.

The efficacy analysis will be performed on patients receiving concurrent treatment under protocol versions 2.0 and 3.0. Information on patients on sequential treatment and/or enrolled under the original protocol (version 1) will be presented separately (see 17.3.6).

The binomial exact one-sample test will be used for both the interim and the final safety analysis, as well as the efficacy evaluation (if trial continues) [41-44]. The safety conclusion will be based on examining whether or not the observed number of pneumonitis-free patients crossed the corresponding O'Brien-Fleming boundary.

The 6-month pneumonitis-free rate of grade ≥3 along with corresponding exact binomial two-sided 90% confidence intervals will be presented.

Kaplan-Meier estimates will be provided for Progression-free Survival, Overall Survival, Time to Pneumonitis of grade ≥3 and Time to Treatment Failure.

Other toxicities will be presented. The worst grade of toxicity/ adverse events observed over the whole treatment period according to CTCAE v.4 will be displayed.

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

17.3.2. Interim safety analysis

The expectation for the safety interim analysis is that approximately 70% of pneumonitis (grade ≥3) cases have already occurred by 3 months after chemo-radiotherapy, the null and alternative hypothesis for the interim analysis are formulated as follows:

Null hypothesis states that the 3-month pneumonitis-free rate of grade ≥3 is less than or equal to 76.9%, vs the one-sided alternative that the rate is above 76.9%, tested at π_1=89.5%:

$$H_0: \pi_0^{Interim} \leq 76.9\% \text{ vs } H_1: \pi_1^{Interim} > \pi_0^{Interim}, \text{ at } \pi_1^{Interim} = 89.5\%$$

To take into account that the interim safety analysis considers a modified hypothesis (the focus is on the 3-month pneumonitis-free rate of grade ≥3 instead of the corresponding 6-month rate), a piecewise exponential model is assumed for the 6-month pneumonitis-free rate of grade ≥3. In 100,000 simulations based on the above assumptions, a one-sided alpha of 0.044 and power of at least 83% are achieved with an interim analysis on the first 21 patients reaching the 3-month post chemo-radiotherapy follow-up time point. If at this interim analysis none of the 21 patients has developed pneumonitis of grade ≥3, then the safety phase of the trial will be stopped early (interim alpha is 0.004). In that case, the interim null hypothesis for safety that the 3-month pneumonitis-free rate is ≤76.9% can be rejected and the conclusion that the treatment is safe can be reached early. Otherwise it is decided that the trial continues and the final safety analysis will be performed when 41 patients reach the 6-month follow-up time point.

The EAST Design package [41] was used for calculations and simulations were run in the R statistical package.

17.3.3. Final safety evaluation

The primary safety hypothesis evaluates the 6-month post-radiotherapy rate of grade ≥3 pneumonitis (CTCAE V.4):

The null hypothesis states that 6-month pneumonitis-free rate of grade ≥3 is less than or equal to 67%, vs the one-sided alternative that the rate is above 67%, tested at π_1=85%:

$$H_0: \pi_0 \leqslant 67\% \text{ vs } H_1: \pi_1 > \pi_0, \text{ at } \pi_1 = 85\%$$

If at least 33 out of the 41 patients are pneumonitis-free up to 6 months, the final null hypothesis for safety of a 6-month pneumonitis-free rate of ≤67% will be rejected, and the treatment will be accepted as feasible and therefore eligible to be further tested for efficacy.

17.3.4. Regular safety evaluation

Safety evaluations will be performed 4 times per year and submitted to the IDMC for advice. The trial will continue while safety is being evaluated.

17.3.5. Final efficacy analysis

The final efficacy hypothesis is tested after the safety null hypothesis is rejected either at the interim or the final safety analysis, when 74 evaluable patients receiving concurrent therapy have reached one-year follow-up (from time of enrolment into the trial) or have experienced PD.

The 78 patients will be enrolled under the protocol amendmens (v2.0 and v3.0). Patients included under the original protocol (v1.0) will be evaluated separately.

A detailed SAP will be produced as a separate document.

17.3.6. Evaluation of patients enrolled under the original protocol

The follow-up of patients enrolled under the original trial protocol (v1.0) will continue as originally planned, that is until 2 years from start of nivolumab treatment of the last recruited patient. These patients will only be evaluated in terms of safety and toxicity and the evaluation results will be reported separately. More specifically, patients included under the original trial protocol will be evaluated for adverse events, disease progression, death and treatment discontinuation. Results will be presented in terms of absolute and relative frequencies. Because of the low accrual reached by the time of protocol amendment 1 activation no formal statistical test will be performed.

Patients that were enroled under protocol v2.0 (amendment 1) will be included in the final safety and efficacy analysis as decribed in sections 17.3.3 and 17.3.5 above.

18. Criteria for termination of the trial

18.1. 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 authorization and approval to conduct the trial is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

18.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression according to RECIST v 1.1. Except patients with tumour volume increase detected after nivolumab treatment start but without appearance of new lesions or rapid clinical deterioration (see section 10.7 for more information), who are allowed to continue nivolumab treatment.
- Occurrence of unacceptable toxicities of radiotherapy or nivolumab. Stopping protocol treatment is determined by medical judgment of the treating physician. Note: patients who cannot complete chemotherapy at the full dose due to toxicity may continue trial treatment if radiotherapy can be given at a curative dose.
- 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 the 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 the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

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

18.3. 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 time point 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 ***CRF completion guidelines***, if the patient accepts to be contacted for survival status despite withdrawal trial consent. For the patient's safety, an end of treatment visit should be performed and documented in the eCRF if the patient agrees to this.

19. Ethics aspects, regulatory approval, and Patient Informed Consent

The Investigator will ensure that this trial 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 trial 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).

19.1. 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.

19.2. 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.

19.3. 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 inclusion 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 process of obtaining the informed consent must be documented in the patient record.

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. 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 (PIS/IC) 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 needs to receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centres need to send their locally modified PIS/IC to ETOP for review and approval before submitting to their Ethics Committee.

20. Governance and administrative issues

20.1. Final report

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

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

20.3. 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.

20.4. Publication

The results of the trial will be published according to the ETOP publication guidelines.

20.5. 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 institution should report all alleged claims immediately to the ETOP Coordinating Office.

20.6. Quality assurance and quality control

ETOP conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial Data Manager reviews each CRF as it is received. In addition, the ETOP Medical Reviewer reviews each case at specific time points. 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 trial 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 and quality of data.

20.7. 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/REB it cannot be implemented. All protocol deviations will be recorded.

20.8. 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.

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.

20.9. 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 one month in advance.

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