ENERGY

Randomised phase III study testing nivolumab and ipilimumab versus a carboplatin based doublet in first line treatment of PS 2 or elderly (more than 70 years old) patients with advanced non-small cell lung cancer.

Sponsor
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Coordinating investigator
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Methodology and Data management Centre
Methodologist:
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Biostatistician:
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Coordination and monitoring of study
Direction de la Recherche et de l'Innovation, CHU de Rennes - 2, rue Henri le Guilloux, 35033 Rennes cedex 9
Groupe Français de Pneumo-Cancérologie

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Version submitted to the authorities: Version 1.0 du 03/07/2017
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SPONSOR :	**CHU Rennes (Rennes University Hospital Centre)**
TRIAL CODE :	SPONSOR 35RC16_9734 GFPC 08-2015 BMS CA209-449
EudraCT no. :	**2017-002842-60**
PRODUCT/COMPOUND	Nivolumab / Ipilimumab
COMPLETE TITLE	Etude randomisée de phase III testant l'association du nivolumab et de l'ipilimumab versus un doublet à base de carboplatine dans le traitement de première ligne du CBNPC chez des patients PS 2 ou de plus de 70 ans. Randomised phase III study testing nivolumab and ipilimumab versus a carboplatin based doublet in first line treatment of PS 2 or elderly (more than 70 years old) patients with advanced non-small cell lung cancer.
CLINICAL PHASE	III
INDICATION(S) (TARGET)	Advanced non small cell lung cancer
COORDINATING INVESTIGATOR	Dr Herve Lena Service de pneumologie CHU of Rennes - Hôpital Pontchaillou 2 rue Henri Le Guilloux 35033 Rennes Cedex 9 France
PROTOCOL VERSION NO.	2.0
DATE OF PROTOCOL	06/11/2017
CPP	Approved on 28/09/2017 By the Committee for the Protection of Persons SOOM IV of Limoges
ANSM	Date of authorisation: 12/09/2017 Authorisation no.: 170472A-12

TABLE OF CONTENTS

SIGNATURES

INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical trial protocol for which the CHU of Rennes is the sponsor. I confirm that it contains all information necessary for the correct conduct of the study. I agree to conduct the study in compliance with the protocol and terms of conditions which are defined in it. I agree to conduct the study while complying with the conditions of:

- Principles of the "Declaration of Helsinki",
- The rules and recommendations of international good clinical practice ((ICH-E6) and French good clinical practice (rules of good clinical practice for biomedical research studies of medicinal products for human use - decisions of 24 November 2006),
- National legislation and regulations pertaining to clinical trials,
- Compliance with the Clinical Trials Directive of the EU [2001/20/EC].

I also agree that investigators and other qualified members of my team may have access to copies of this protocol and documents pertaining to the correct conduct of the study enabling them to work in compliance with conditions contained in these documents.

NAME : Docteur Hervé Léna

Signature : Date : 6 novembre 2017

SPONSOR'S SIGNATURE

Sponsor : CHU de Rennes

NAME : Monsieur Pascal Gaudron

Signature : Date : 6 novembre 2017

SYNOPSIS

TITLE	eNERGY Nivolumab Ipilimumab EldeRly GFPC 08-2015 Etude randomisée de phase III étudiant l'association du nivolumab et de l'ipilimumab versus un doublet à base de carboplatinedans le traitement de première ligne du CBNPC avancé chez des patients PS 2 ou de plus de 70 ans. Randomized phase III study testing nivolumab and ipilimumab versus a carboplatin based doublet in 1st line treatment of PS 2 patients or elderly (more than 70 years old) with advanced non-small cell lung cancer.
SPONSOR	CHU of Rennes
COORDINATING INVESTIGATOR	Dr Hervé Lena Service de pneumologie CHU de Rennes - Hôpital Pontchaillou 2 rue Henri Le Guilloux 35033 Rennes Cedex 9 France
PROTOCOL VERSION	2.0
RATIONALE / CONTEXT	Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Western countries (1). Unfortunately, at the time of diagnosis, the majority of patients already have metastatic disease and a systemic, palliative treatment is the primary therapeutic option. Guidelines for PS 2 patients or older than 75 years old patients at the time of diagnosis recommend for fit patients a carboplatin doublet chemotherapy. Nivolumab has proven efficacy in 3rd line squamous cell lung carcinoma and is superior to chemotherapy in 2nd line treatment of squamous and non-squamous lung cancer in term of overall survival. In 1st line, nivolumab failed to show superiority compared to a platin based doublet in terms of progression free survival and overall survival in tumors ≥ 5% PD-L1 expression. The association Nivolumab plus Ipilimumab showed encouraging results in first line setting in phase 1 study. We think that with regard to the manageable toxicity of nivolumab in lung cancer population and the possibility to obtain long responses, this association could be a valid option for this population of elderly and/or PS2 patients in term of overall survival.
ORIGINALITY AND INNOVATIVE ASPECTS	It will be the first trial to test the efficacy of the association nivolumab and ipilimumab in PS2 and elderly in advanced NSCLC patients.
PRIMARY OBJECTIVE	To compare overall survival of patients in experimental arm versus chemotherapy
SECONDARY OBJECTIVES	To evaluate : • survival at one year of patients treated with nivolumab and ipilimumab versus patients treated with chemotherapy, • the objective response rate, • the progression free survival, • the safety and the tolerability of nivolumab and ipilimumab versus chemotherapy, • the QOL, • the prognostic impact of PD-L1 expression by immunochemistery (IHC) on OS and PFS, • the predictive impact of a geriatric mini data set on OS, PFS and toxicity and its evolution under treatment, this analysis will be restricted to patients ≥70 years old.
PRIMARY EVALUATION CRITERION	Overall survival
SECONDARY EVALUATION CRITERIA	• Percentage of patients alive one year after inclusion in the trial,

	• Objective response rate according to Recist 1.1, • Progression free survival time, • Safety tolerability according to CTCAE 4.0, • QOL evaluated by EQ5D and EORTC QLQ-ELD14 every 6 weeks, • PD-L1 testing by immunochemistery assessed by a central laboratory, • Geriatric mini data set (restricted to patients ≥70 years old)
METHODOLOGY / STUDY SCHEDULE	Open label Phase III randomized study
CRITERIA FOR INCLUSION OF PATIENTS	• Signed written informed consent • Cytologically or histologically proven NSCLC (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma) • Stage IV or non-treatable by radiotherapy or surgery stage III (7th classification) • No previous systemic chemotherapy for lung cancer, except in case of relapse after adjuvant treatment for localized disease with 6 months or more between end of previous chemotherapy and relapse • Patients less than 70 years old and PS 2 or 70 years older PS 0 to 2 • Judged fit enough to receive a carboplatin based doublet according to ESMO guidelines • Presence of at least one measurable target lesion (RECIST 1.1 rules) in a non-irradiated region and analysable by CT • Life expectancy >12 weeks • Prior radiation therapy is authorized if it involved less than 25% of the total bone marrow volume and finished 14 days before D1 of planned treatment • Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization/registration ▪ WBC ≥ 2000/µL ▪ Neutrophils ≥ 1500/µL ▪ Platelets ≥ 100 x10^3/µL ▪ Hemoglobin > 10.0 g/dL ▪ Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 45 mL/min (if using the Cockcroft-Gault formula below): *Female* CrCl = [(140 - age in years) x weight in kg x 0.85] / [72 x serum creatinine in mg/dL] *Male* CrCl = [(140 - age in years) x weight in kg x 1.00] / [72 x serum creatinine in mg/dL] ▪ AST/ALT ≤ 3 x ULN ▪ Total Bilirubin ≤ 1.5 x ULN (except Patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) • Availability of adequate FFPE tumor-derived material (tumor blocks or slides) from a biopsy, surgery or fine needle aspirate for analysis of PD-L1 testing by IHC Age and Reproductive Status • Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception during treatment. WOCBP should use an adequate method to avoid pregnancy : o For 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab + ipilimumab, o For 4 weeks after the last dose of carboplatine + pemetrexed, o For 5 weeks after the last dose of carboplatine + paclitaxel. • Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)

	within 24 hours prior to the start of treatment • Women must not be breastfeeding • Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year during treatment Men will be instructed to adhere to contraception for a period of 31 weeks after the last dose of nivolumab + ipilimumab and with carboplatine +pemetrexed or carboplatine + paclitaxel up to 6 months thereafter.
NON-INCLUSION CRITERIA OF PATIENTS	• Patients with other severe concurrent disorders that occurred during the prior six months before enrollment (myocardial infection, severe or unstable angor, coronarian or peripheric arterial bypass operation, NYHA class 3 or 4 congestive heart failure, transient or constituted cerebral ischemic attack, at least grade 2 peripheral neuropathy, psychiatric or neurological disorders preventing the patient from understanding the trial, uncontrolled infections) are not eligible. • Serious or uncontrolled systemic disease judged as incompatible with the protocol by the investigator • Another previous or concomitant cancer, except for basocellular cancer of the skin or treated cervical cancer in situ, or appropriately treated localized low-grade prostate cancer (Gleason score < 6), unless the initial tumor was diagnosed and definitively treated more than 5 years previously, with no evidence of relapse. • Known activating mutation of EGFR (del LREA exon 19, mutation L858R or L861X of exon 21, mutation G719A/S in exon 18) or EML4-ALK or ROS-1 translocation • Superior caval syndrome • Uncontrolled infectious status • All concurrent radiotherapy • Concurrent administration of one or several other anti-tumor therapies. • Psychological, familial, social or geographic difficulties preventing follow-up as defined by the protocol. • Protected person (adults legally protected (under judicial protection, guardianship or supervision), person deprived of their liberty, pregnant woman, lactating woman and minor), • Concurrent participation in another clinical trial • Patients are excluded if they have active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for [lowest minimum is 4 weeks or more] after treatment is complete and within 28 days prior to the first dose of nivolumab and ipilimumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. • Patients should be excluded if they have an active, known or suspected autoimmune disease. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism 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 • Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

	• Patients should be excluded if they are positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection • Patients should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Patients should be excluded if they have a lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity • Allergies and Adverse Drug Reaction • History of allergy to study drug components • Severe spinal hypoplasia and / or hemorrhagic tumors
TREATMENTS/STRATEGIES/ PROCEDURES	The investigator will declare before randomization the treatment in control arm (ie the choice of the second drug associated to carboplatin). Patients will be randomized 1:1 into one of the two treatment arms and stratified by age (70 years old versus less than 70 years old), by PS (PS 0/1 versus PS2) and by histology (squamous versus non-squamous). **Experimental arm:** Nivolumab (BMS-936558) dosed intravenously over 30 minutes at 240 mg every 2 weeks combined with Ipilimumab dosed intravenously over 30 minutes at 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or other reasons specified in the protocol. Nivolumab and Ipilimumab can be continued beyond progression according to RECIST 1.1 if the investigator assesses a clinical benefit (defined paragraph) **Control arm :** the investigator will declare before randomization the treatment **among:** Doublet of chemotherapy according to standard of care carboplatin (AUC 5) with a dose that will be capped to 700 mg and pemetrexed (500 mg/m²) over 4 to 6 hours every three weeks (restricted to non-squamous histology) or carboplatin (AUC 6) with a dose that will be capped to 700 mg and paclitaxel (90 mg/m²) D1 D8 D15 over 4 to 6 hours every 4 weeks, with a maximum of 4 cycles of carboplatin based doublet, and the possibility to use maintenance with pemetrexed. Follow up will be done over 30 minutes every 6 weeks in both arms, until progression. Patients treated by the association nivolumab plus ipilimumab in experimental arm and who did not discontinue for progression or toxicity will be treated up to 2 years. In case of subsequent progression a rechallenge with additional one year of treatment by the association nivolumab plus ipilimumab will be proposed. For patients treated by chemotherapy in control arm, after progression, a second line therapy will be proposed according to standard of care. OS will be followed continuously while patients are on the study drug and every 3 months via in-person or phone contact after patients discontinue the study drug. All randomized patients will be evaluated. Subsequent therapies will be recorded during one year after inclusion.
NUMBER OF PATIENTS	The primary endpoint of the phase III is overall survival. The study is calibrated to detect a treatment effect hazard ratio (HR) of 0.65, translating in an improvement of 1-year OS rate from 40% (control arm) to 55% (Nivolumab and Ipilimumab arm). A total of 199 events observed at the time of the final analysis would have 85% power to show statistically significant log-rank test at a 2-sided alpha level of 5%. Considering a recruitment duration of 24 months and a18 months follow-up for the last included patient (estimated total duration of the study: 42 months), **242 patients** will be randomized in the study (121 by arm).

Randomization ratio 1:1 will be stratified according to Age (< 70 vs. ≥ 70 years),ECOG-PS status (0/1 vs. 2) and histology status (squamous vs non-squamous).

Interim analyses During the trial, one interim analysis for futility will be performed, permitting to early stop the trial, if no sufficient efficacy is shown. This analysis will be performed after that 33% of the expected events have occurred. Using planned enrollment rate, this analysis should be performed after inclusion of 171 patients (17 months after first included patient). No adjustment of type I error was required. Stopping boundaries were defined according to Lan-DeMets spending function to control type II error. Table 1 shows the futility boundaries.
An independent Data Safety Monitoring Board will be organized to discuss the conduct of the study after analysis performed.
Sample size calculation and interim analysis planning were performed using East® software (Cytel Inc. 1994-2014), version 6.3.1

Table1: Futility boundaries

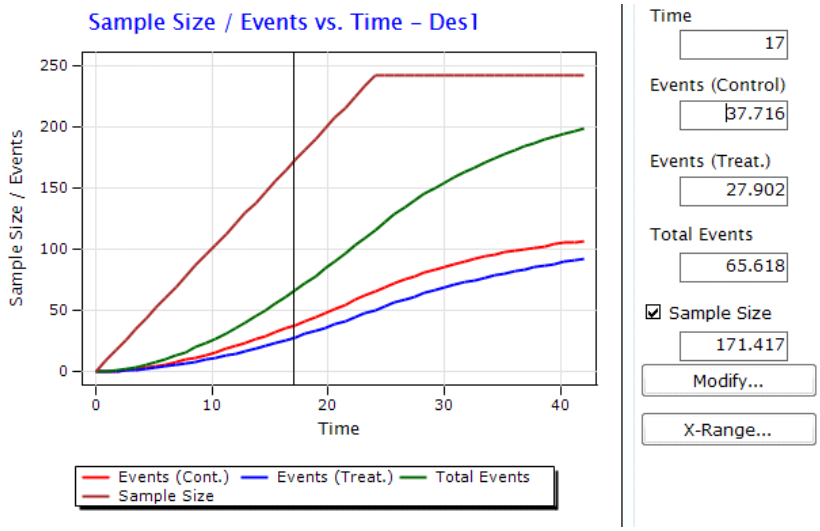

Table1: Futility boundaries

Look	Fraction of information	Cumulative spent	P value	HR futility bound
1	0.33	0.012	0.698	1.137
2	1	0.15	0.0025	

DURATION OF STUDY	Recruitment period : 24 months Duration of patient monitoring : 18 months or until end of study treatment in both arms Estimated total duration of study : 42 months
EXPECTED FINDINGS AND IMPACT	Superiority of nivolumab and ipilimumab versus a carboplatin based-doublet in specific populations of elderly or PS2 NSCLC

LIST OF ABBREVIATIONS

Term	Definition
21CFR50	United States Code of Federal Regulations, Title 21, Part 50
ANC	absolute neutrophil count
AIDS	acquired immunodeficiency syndrome
aPTT	activated partial thromboplastin time
AE	adverse event
ALT	alanine aminotransferase
AT	aminotransaminases
ANOVA	analysis of variance
ADA	Anti-drug antibody
APC	Antigen Presenting Cell
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
AST	aspartate aminotransferase
A-V	atrioventricular
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
Cavg	average concentration
BLQ	below limit of quantification
BOR	best overall response
b-HCG	beta-human chorionic gonadotrophin
HCO3-	bicarbonate
BA/BE	bioavailability/bioequivalence
BID, bid	bis in die, twice daily
BP	blood pressure
BUN	blood urea nitrogen
BMI	body mass index
BMS	Bristol-Myers Squibb
Ca++	calcium
CBNPC	cancer bronchique non-à-petites cellules
CRF	Case Report Form, paper or electronic
C	celcius
cm	centimeter
CNS	central nervous system

Cl-	chloride
CL	clearance
CRC	clinical research center
TR_Cmax	cmax treatment ratio
CFR	code of federal regulations
CV	coefficient of variation
CTCAE v4	common terminology criteria for adverse events version 4
CBC	complete blood count
CR	complete response
CT	computed tomography
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CI	confidence interval
CrCl	creatinine clearance
C	cycle
CMV	cytomegalovirus
CTLA-4	cytotoxic t lymphocyte-associated antigen 4
D	day
dL	deciliter
D/C	discontinue
ECOG	eastern cooperative oncology group
T-HALFeff_AUC	effective elimination half life that explains the degree of auc accumulation observed
T-HALFeff_Cmax	effective elimination half life that explains the degree of cmax accumulation observed)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EP	endpoint
EGFR	epidermal growth factor receptor
q	every
eg	exempli gratia (for example)
Ct	expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
ESR	expedited safety report
FISH	fluorescent in situ hybridization
FSH	follicle stimulating hormone
FDA	food and drug administration
FFPET	formalin fixed paraffin embedded tissue
FFPE	formalin fixed paraffin-embedded
GGT	gamma-glutamyl transferase

GFPC	groupe français de pneumo-cancérologie
GFR	glomerular filtration rate
GCP	good clinical practice
g	gram
T-HALF	half life
HR	hazard ratio
HIPAA	health information portability and accountability act
HR	heart rate
HBsAg	hepatitis b surface antigen
HBV	hepatitis b virus
HCV AB	hepatitis c antibody
HCV RNA	hepatitis c rna
HCV	hepatitis c virus
HRT	hormone replacement therapy
h	hour
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ie	id est (that is)
IHC	immunohistochemistry
IEC	independent ethics committee
IRRC	independent radiology review committee
ICF	informed consent form
IRB	institutional review board
IVRS	interactive voice response system
ICH	international conference on harmonisation
IU	international unit
IU/L	international unit per liter
IU/mL	international unit per milliliter
IV	intravenous
IMP	investigational medicinal products
IND	investigational new drug exemption
IB	investigator brochure
KM	kaplan-meier
kg	kilogram
LDH	lactate dehydrogenase
L	liter
LCSS	lung cancer symptom scale
Mg++	magnesium

MRI	magnetic resonance maging
Cmax, CMAX	maximum observed concentration
MTD	maximum tolerated dose
mCRPC	metastatic castration-resistant prostate cancer
m	meter
mcg	microgram
miRNA	microrna (micro ribonucleic acid)
mg	milligram
mL	milliliter
mL/min	milliliters per minute
mm	millimeter
mmHg	millimeters of mercury
MIC	minimum inhibitory concentration
min	minute
mo	month
MDSC	myeloid derived suppressor cells
NIMP	non-investigational medicinal products
NSCLC	non-small cell lung cancer
NSAID	nonsteroidal anti-inflammatory drug
N/A	not applicable
NE	not evaluable
N	number of patients or observations
ORR	overall response rate
OS	overall survival
PR	partial response
PRO	patient reported outcomes
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PK	pharmacokinetics
PPK	population pharmacokinetic
K+	potassium
K3EDTA	potassium ethylenediaminetetraacetic acid
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression free survival
PD	progressive disease
PS	performance status

QC	quality control
QOL	Quality of life
QPCR	quantitative polymerase chain reaction
QD, qd	quaque die, once daily
RBC	red blood cell
RCC	renal cell carcinoma
CLR	renal clearance
RECIST 1.1	response evaluation criteria in solid tumors version 1.1
SAE	serious adverse event
SNP	single nucleotide polymorphism
Na+	sodium
SD	stable disease
SD	standard deviation
SOP	standard operating procedures
SmPC	summary of product characteristics
t	temperature
TID, tid	ter in die, three times a day
TSH	thyroid stimulating hormone
T	time
Tmax, TMAX	time of maximum observed concentration
TAO	trial access online, the bms implementation of an edc capability
Cmin, CMIN	trough observed concentration
TILs	tumor infiltrating lymphocytes
UV	ultraviolet
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WOCBP	women of childbearing potential
WHO	world health organization

1 GENERAL INFORMATION

1.1. Title

eNERGY

Etude randomisée de phase III testant l'association du nivolumab et l'ipilimumab versus un doublet à base de platine dans le traitement de première ligne du CBNPC chez des patients PS 2 ou de plus de 70 ans.

Randomised phase III study testing nivolumab and ipilimumab versus a carboplatin based doublet in first line treatment of PS 2 or elderly (more than 70 years old) patients with advanced non-small cell lung cancer.

1.2. Sponsor

Identification
CHU of Rennes
2, rue Henri le Guilloux
35033 Rennes cedex 9

Signature of protocol on behalf of the sponsor
Pascal Gaudron, Director of Research
CHU of Rennes
2, rue Henri le Guilloux
35033 Rennes cedex 9

Person responsible for study on the side of the sponsor
Pascal Gaudron, Director of Research
CHU of Rennes
2, rue Henri le Guilloux
35033 Rennes cedex 9

1.3. Coordination and monitoring of study

Direction of Research
CHU of Rennes
2, rue Henri le Guilloux
35033 Rennes cedex 9

1.4. Investigators

Coordinating investigator
Dr Hervé Léna
Service de pneumologie
CHU of Rennes- Hôpital de Pontchaillou
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35033 Rennes Cedex 9

Associated investigators (see appendix 1)

1.5. Pharmacy

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Pharmacie
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1.6. Pharmacovigilance

Dr Catherine Mouchel
Service de Pharmacologie et Centre d'Investigation Clinique - INSERM 0203
CHU of Rennes – Hôpital de Pontchaillou

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35033 Rennes cedex 9

1.7. Methodologist – biostatistician

- **Methodologist :**

Dr David Pérol
Unité de Biostatistique et d'Evaluation des Thérapeutiques
Direction de la Recherche et de l'Innovation
Centre Léon Bérard
28, rue Laënnec - 69373 Lyon Cedex 08

- **Biostatistician :**

Sylvie Chabaud
Biostatisticienne - Responsable pôle statistique
Unité de Biostatistique et d'Evaluation des Thérapeutiques
Direction de la Recherche et de l'Innovation
Centre Léon Bérard
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1.8. Referent for geriatric analysis based on mini data set assessment

Pr Elena Paillaud
Département de gériatrie CHU Henri Mondor
51 Avenue du Maréchal de Lattre de Tassigny
94010 Créteil Cedex

1.9. Referent for PD-L1 testing by immunochemistery (IHC) assessed by the central laboratory

Pr Diane Damotte
Service d'anatomie et cytologie pathologiques
HU-PARIS OUEST SITE G.POMPIDOU APHP
20 Rue Leblanc
75015 Paris

1.10. Efficacy evaluation committee

The efficacy evaluation committee will review all available tumor assessment scans to determine response (RECIST 1.1). The determined response will be used in the analyses of ORR and PFS.

The members are:
Dr Gilles Robinet, service d'oncologie thoracique, CHU Brest
Dr Maurice Pérol, service d'oncologie médicale, Centre Léon Bérard Lyon
Pr Christos Chouaid, service de pneumologie Centre Hospitalier Intercommunal Créteil
Pr Alain Vergnenègre, service de pneumologie, CHU Limoges
Dr Hervé Léna, service de pneumologie, CHU Rennes

This committee will meet three times a year to follow inclusion rates, primary and secondary endpoints of the study. Conference call will be organized if necessary.

1.11. Data monitoring committee

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol Energy, and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of patients enrolled in the trial. The DMC will monitor patient safety and evaluate the available efficacy data for the study. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes in study conduct are required. After meeting, the DMC will notify the clinical study leadership group that it has met and will provide recommendations about the study by telephone or email. Any recommendation by

the DMC regarding study modification will be submitted to the clinical study leadership team within pre-specified business days of the DMC meeting.

Members of the DMC are:
Thoracic oncologists :
Pr A Cortot, Service de pneumologie, CHU Lille
Dr B Mennecier, Service de pneumologie, CHU Strasbourg

Pharmacovigilance :
Dr Sophie Duranton, Direction de la Recherche, CHU Poitiers

Méthodologist :
Bruno Giraudeau, CIC Inserm 1415, CHU Tours

2 SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION OF STUDY

2.1. Name and description of investigational medicinal products

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

2.2. Summary of results of non-clinical trials and clinical trials available and relevant regarding the research involving the human person study concerned

Control arm
Chemotherapy is feasible and beneficial for elderly NSCLC patients with advanced/metastatic disease [1–4]. On the other hand, it should be noted that elderly had higher rates of adverse events during chemotherapy compared with patients younger than 55 years and this observation was independent of comorbidity [5]. This could be the reason for the significant under-treatment of elderly patients in clinical practice.
Prospective trials support the use of carboplatin-based doublets in fit elderly patients [6-7]. For less fit patients, single-agent treatment (gemcitabine, vinorelbine, taxanes) represents a valid option according to ESMO guidelines published in 2014 [8]. There are no data to support any single agent offering an OS benefit, very limited data are available for octogenarians and, therefore, no specific recommendations can be made for this group. Performance status, comorbidities, life expectancy and patient's preference should be taken into account when developing a treatment strategy.
For patients PS 2 with advanced NSCLC, the updated systematic review performed by the ASCO clinical practice guideline update and published in oct 2015 [9] identified two small trials specifically comparing single agent versus combination chemotherapy in patients with PS 2. The first trial which included 205 participants, compared carboplatin plus pemetrexed with pemetrexed alone[10]. In the results, OS and PFS were statistically significantly longer with the combination. Adverse events were slightly more frequent with the combination, but the results were not statistically significant. One trial with 56 participants compared cisplatin plus gemcitabine with gemcitabine and found that OS and QoL was also higher; however, the study was stopped early and had few participants [11]. The Cochrane systematic review on chemotherapy and supportive care, updated in 2012, continued to show that chemotherapy and best supportive care versus supportive care alone benefit patients, including those who have PS 2 [12]. PFS were statistically significantly longer with the combination.

Trials limited to patients with PS 2 have typically not reported the cause for designation of PS 2 (ie, cancer-related symptoms secondary to large tumor burden v poor PS designation because of multiple chronic conditions). That's why ASCO guidelines concluded in 2015, that the data informing chemotherapy decisions for patients with PS 2 are insufficient to make a strong recommendation favoring combination chemotherapy. Patients and clinicians should discuss the risks and benefits of combination chemotherapy. Some patients may choose single-agent chemotherapy if their perception of risk outweighs perceived benefits of combination therapy. There is no effective tool to determine which patients will tolerate doublet therapy and experience an improvement in PS with a reduction of symptoms and which patients will experience an acceleration of their decline with treatment [9].

Experimental arm

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer [13]. Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab is now approved in Europe to treat patients with metastatic squamous cell NSCLC with progression on or after platinum-based chemotherapy.

The approval was based on the results of CA209017 [14], a randomized trial of nivolumab versus docetaxel. The median overall survival (OS) for Patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend for better efficacy for those with PD-L1 expressing tumors. A single arm trial (CA209063) of 117 Patients with metastatic squamous cell NSCLC, with progression after platinum-based chemotherapy and at least one additional systemic regimen, showed a 15% overall response rate (ORR), of whom 59% had response durations of 6 months or longer [15].

A second phase 3 study, CA209057 [16], stopped at a preplanned interim analysis by the independent Data Monitoring Committee (DMC), met its primary endpoint of superior overall survival of nivolumab versus docetaxel in Patients with previously-treated non-squamous NSCLC. Patients in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction p-values, reported for PD-L1 expression subgroups by each of the predefined expression levels, suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36% in Patients with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs docetaxel across the PD-L1 expression continuum. In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor. Nivolumab monotherapy has also been evaluated in first-line NSCLC, where it showed promising activity regardless of histology. As in pretreated NSCLC, activity with nivolumab monotherapy is pronounced in PD-L1 expressing NSCLC. The recruitment of the trial comparing nivolumab to chemotherapy in 1st line at the investigator's choice is closed to inclusions. In general, nivolumab also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.

Nivolumab monotherapy has also been evaluated in first-line NSCLC, where it showed promising activity regardless of histology [17]. But study Checkmate 026 failed to demonstrate a PFS nor OS benefit in favor of Nivolumab versus a platin-based doublet in first line treatment of stage IV NSCLC ≥ 5% PD-L1 expression [18].

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-ɤ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodiesincreased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone [19].

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a phase 1b multiple ascending dose study in Patients with treatment-naive and previously treated advanced melanoma. Results showed promising activity, with higher, but tolerable toxicity than ipilimumab alone [20]. Based on these data, CA209069, a

phase 2 study, compared the combination to ipilimumab alone in treatment-naïve patients with advanced melanoma: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks x4 followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks x 4 [21]. In patients with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) complete responses (CR) in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR=0.4). It should be noted that in the combination group, the ORR was independent of PD-L1 expression. In this group, ORR was 58% among patients with PD-L1+ tumors and 55% among those with PD-L1- tumors. In contrast, in the ipilimumab alone group, the ORR was numerically higher among patients with PD-L1+ tumors (18%) compared to those with PD-L1- tumors (4%). Grade 3-4 treatment-related AEs were reported in 54% of patients receiving the combination compared to 24% for ipilimumab alone.

Ipilimumab has been shown to have activity in lung cancer. A Phase 2 study (CA184041) in Patients with NSCLC or small cell lung cancer (SCLC) investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased). The phased schedule demonstrated a significant improvement of immune-related progression-free survival as well as progression-free survival by modified WHO criteria compared to chemotherapy alone, in both NSCLC and SCLC [22].

Based on the initial data in melanoma, and the activity observed with nivolumab and ipilimumab in lung cancer, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in patients with advanced NSCLC. In CA209012, early combination cohorts evaluated 2 dosing schedules that were studied in the CA209004 study in melanoma:

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms G and H, n=24);
-nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms I and J, n=25)

These regimens resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related adverse event.

Thus, additional combination cohorts were initiated, using lower doses of both nivolumab and ipilimumab, or less frequent dosing of ipilimumab. Data from these cohorts demonstrate that both nivolumab 1 mg/kg + ipilimumab 1 mg/kg q 3 weeks with nivolumab maintenance 3 mg/kg q2w (arm N in study CA209012), as well as ipilimumab at 1 mg/kg q6w is tolerable, when given with nivolumab 3 mg/kg q2w (arm Q in study CA209012). Overall, the safety data are not dissimilar to what has been observed in the nivolumab arm (arm F in CA209012). Of particular note, the rate of discontinuation due to drug-related AEs was 13% in arm N and 11% in arm Q compared to 10% in the nivolumab monotherapy arm (arm F) [17].

Table1: Treatment-related immune adverse events from selected cohorts in C209012 [17].

Table 5.5.1.1-2: Summary of Safety in Subjects Treated with Nivolumab + Ipilimumab (New Cohorts) by Worst CTC Grade - CA209012

Category	Arm N Nivo 1 mg/kg + Ipi 1 mg/kg Q3W N = 31[a] n (%)		Arm O Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 40 n (%)		Arm P Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W N = 39 n (%)		Arm Q Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 39 n (%)	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
AEs	31 (100.0)	16 (51.6)	37 (92.5)	24 (60.0)	37 (97.4)	15 (39.5)	36 (92.3)	18 (46.2)
Drug-related AEs	26 (83.9)	9 (29.0)	29 (72.5)	16 (40.0)	31 (81.6)	14 (36.8)	28 (71.8)	13 (33.3)
Drug-related AEs in ≥ 10% of Subjects								
Fatigue	9 (29.0)	0	9 (22.5)	1 (2.5)	6 (15.8)	1 (2.6)	9 (23.1)	1 (2.6)
Rash	9 (29.0)	4 (12.9)	10 (25.0)	2 (5.0)	6 (15.8)	1 (2.6)	4 (10.3)	1 (2.6)
Diarrhea	6 (19.4)	0	10 (25.0)	2 (5.0)	8 (21.1)	1 (2.6)	8 (20.5)	0
Pruritus	6 (19.4)	0	4 (10.0)	0	9 (23.7)	0	5 (12.8)	0
Lipase Increased	4 (12.9)	2 (6.5)	3 (7.5)	1 (2.5)	6 (15.8)	3 (7.9)	0	0
Arthralgia	4 (12.9)	0	2 (5.0)	0	4 (10.5)	0	0	0
Nausea	4 (12.9)	0	3 (7.5)	0	6 (15.8)	0	6 (15.4)	1 (2.6)
Pneumonitis	3 (9.7)	1(3.2)	3 (7.5)	0	4 (10.5)	2 (5.3)	2 (5.1)	1 (2.6)
Amylase Increased	3 (9.7)	2 (6.5)	2 (5.0)	0	6 (15.8)	1 (2.6)	0	0
Rash Maculo-papular	3 (9.7)	0	1 (2.5)	0	5 (13.2)	0	4 (10.3)	1 (2.6)
Adrenal Insufficiency	2 (6.5)	2 (6.5)	3 (7.5)	2 (5.0)	1 (2.6)	1 (2.6)	5 (12.8)	2 (5.1)
Decreased Appetite	2 (6.5)	0	3 (7.5)	0	4 (10.5)	0	5 (12.8)	0
Hypothyroidism	2 (6.5)	0	6 (15.0)	0	2 (5.3)	0	1 (2.6)	0
ALT Increased	2 (6.5)	1 (3.2)	8 (20.0)	4 (10.0)	1 (2.6)	0	1 (2.6)	1 (2.6)
AST Increased	2 (6.5)	1 (3.2)	8 (20.0)	5 (12.5)	1 (2.6)	0	1 (2.6)	1 (2.6)
Hyperthyroidism	2 (6.5)	0	3 (7.5)	0	0	0	4 (10.3)	0
Pyrexia	2 (6.5)	0	1 (2.5)	0	5 (13.2)	0	2 (5.1)	0
Dry mouth	2 (6.5)	0	4 (10.0)	0	2 (5.3)	0	1 (2.6)	0
Rash generalized	0	0	2 (5.0)	0	0	0	4 (10.3)	0
Transaminases Increased	1 (3.2)	0	0	0	0	0	1 (2.6)	1 (2.6)

Table 5.5.1.1-2: Summary of Safety in Subjects Treated with Nivolumab + Ipilimumab (New Cohorts) by Worst CTC Grade - CA209012

Category	Arm N Nivo 1 mg/kg + Ipi 1 mg/kg Q3W N = 31[a] n (%)		Arm O Nivo 1 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 40 n (%)		Arm P Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q12W N = 39 n (%)		Arm Q Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 39 n (%)	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
SAEs	13 (41.9)	11 (35.5)	26 (65.0)	18 (45.0)	23 (60.5)	12 (31.6)	24 (61.5)	14 (35.9)
Drug-related SAEs	6 (19.4)	5 (16.1)	15 (37.5)	11 (27.5)	12 (31.6)	9 (23.7)	11 (28.2)	9 (23.1)
Drug-related SAEs in > 1 Subject								
Adrenal Insufficiency	2 (6.5)	2 (6.5)	3 (7.5)	2 (5.0)	1 (2.6)	1 (2.6)	2 (5.1)	2 (5.1)
Hypophysitis	2 (6.5)	2 (6.5)	1 (2.5)	0	0	0	0	0
Pneumonitis	2 (6.5)	1 (3.2)	2 (5.0)	0	2 (5.3)	2 (5.3)	1 (2.6)	1 (2.6)
Autoimmune hepatitis	1 (3.2)	1 (3.2)	3 (7.5)	3 (7.5)	0	0	0	0
Colitis	0	0	1 (2.5)	1 (2.5)	1 (2.6)	1 (2.6)	3 (7.7)	2 (5.1)
Diarrhea	1 (3.2)	0	2 (5.0)	2 (5.0)	2 (5.3)	1 (2.6)	0	0
Acute kidney injury	0	0	1 (2.5)	0	2 (5.3)	1 (2.6)	0	0
AEs Leading to Discontinuation	4 (12.9)	3 (9.7)	5 (12.5)	5 (12.5)	8 (21.1)	4 (10.5)	7 (17.9)	3 (7.7)
Drug-related AEs Leading to Discontinuation	4 (12.9)	3 (9.7)	3 (7.5)	3 (7.5)	4 (10.5)	2 (5.3)	5 (12.8)	3 (7.7)
Drug-related AEs Leading to Discontinuation in > 1 Subject								
Pneumonitis	1 (3.2)	1 (3.2)	0	0	2 (5.3)	1 (2.6)	2 (5.1)	1 (2.6)
Autoimmune hepatitis	0	0	2 (5.0)	2 (5.0)	0	0	0	0

[a] Analysis of safety in the nivolumab monotherapy group focused on the initial cohort (N = 20) whose safety data is sufficiently mature.

Source: Preliminary data for CA209012, database lock date, 18-Feb-2016

Note: Safety events were reported between the first dose and 100 days after the last dose of study drug.

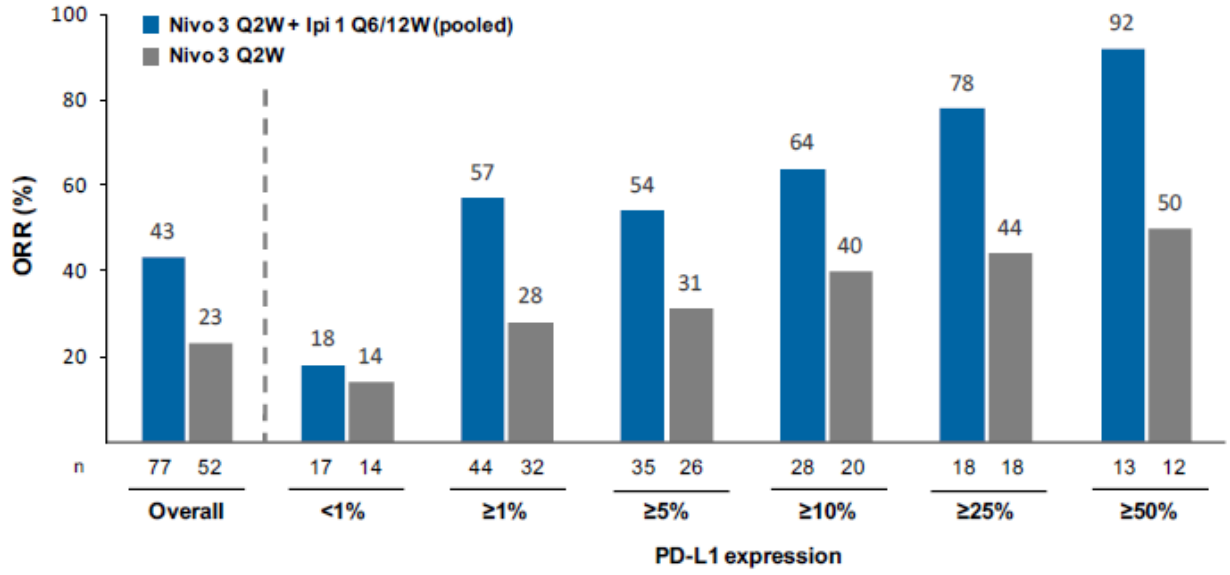
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Nivo = nivolumab; Ipi = ipilimumab

The toxicity rate was higher with the combination compare to nivolumab alone. Nevertheless it was a majority of grade 1-2 toxicities.

Table 2: Clinical activity of nivolumab/ipilimumab combination and nivolumab alone[17].

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

Table 3: Clinical activity of nivolumab/ipilimumab combination compared to nivolumab alone by PD-L1 status, using 1% cutoff [17].



Flat dose regimens of nivolumab

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to3 mg/kg Q2W dosing regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for patients weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation.

Shorter Infusion Duration

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in CA209153 in patients (n=322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in patients administered nivolumab over a 30 min infusion compared with that reported for patients with the 60 min infusion. Thus, it was shown that nivolumab can be safely infused over 30 min.

Based on these data, the following schedule will be evaluated in Inergy:

- Nivolumab (3 mg/kg every 2 weeks) + ipilimumab (1 mg/kg every 6 weeks) will be evaluated in both PD-L1+ and PD-L1- patients.

Of note, all patients included in the trials with nivolumab and ipilimumab were in good general status PS 0 to 1 (inclusion criteria). Number of elderly patients included in CA209 057 and CA 209 017 was very low even if there was no limitation of age in inclusion criteria. Median age for example in 057 study was 61 years old with only 7% older than 75.

Energy is planned to compare the efficacy and safety of nivolumab and ipilimumab versus carboplatin-based doublet in advanced NSCLC in first line in patients ≥70 years old or PS2.

2.3 Summary of benefits and of foreseeable and known risks for the person who is a Patient in the research study

2.3.1 Benefits

2.3.1.1 Individual benefits

Regard to the low toxicity of nivolumab and ipilimumab in lung cancer population, the possibility to obtain long responses, nivolumab and ipilimumab could be a valid option for this frail population of patients.

2.3.1.2 Collective benefit

Evaluation of new treatments in these specific populations of frail or elderly lung cancer patients will potentially increase the therapeutic possibilities for these specific populations.

2.3.2 Risks

Individual risks

- Physical risks and constraints

The main risk in this frail population could be the delay to cytotoxic chemotherapy. First evaluation will be done at 6 weeks, allowing a rapid crossover in case of progression under nivolumab and ipilimumab. In case of clinical progression, a rapid evaluation will be asked to confirm progression and beginning of chemotherapy. The association of nivolumab and ipilimumabincrease toxicity compared to nivolumab alone but at the doses of nivolumab plus ipilimumab that will be used in this study we don't expect to observe a higher rate of discontinuation due to drug-related AEs than with nivolumab alone. This association appears tolerable even for a frail population.

- Psychological risks and constraints

Not applicable. Cancer patients benefit of specific support according to plans cancers 1 to 3. All research sites have an agreement for treatment of advanced cancer patients and psychological support is part of this agreement.

- Socio-economic risks and constraints

Nivolumab and ipilimumab will be supplied by BMS. All other drugs are registered and used in this indication and are included in national and international recommendations.

2.4. Description and rationale for route of administration, dosage, administration regimen and duration of treatment

Experimental arm:

Patients will receive treatment with nivolumab as a 30 minutes infusion at 240 mg every 2 weeks and ipilimumab as a 30 minutes infusion at 1 mg/kg every 6 weeks, starting on Day 1, until disease progression, unacceptable toxicity, or other reasons specified in the protocol section 4.6.

All decisions to continue treatment beyond initial progression documented in the study record, discussed and agreed to by the study coordinator. Patients should be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

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

Patients will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria determined by the investigator:

- Investigator-assessed clinical benefit and Patient is tolerating study drug.
- Tolerance of study drug
- Stable performance status

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

Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab + ipilimumab.
For the patients who continue nivolumab + ipilimumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab+ ipilimumab treatment should be discontinued permanently upon documentation of further progression.
New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.
For statistical analyses, this will need to be described in patient population information. E.g. Patients who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

Control arm:
Patients will receive according to standard practice and local guidelines:

- carboplatine AUC 5 with a dose that will be capped to 700 mg I.V D1 and pemetrexed (500 mg/m²) I.V D1 over 4 to 6 hours every 3 weeks for 4 cycles (restricted to non-squamous histology)
- or carboplatine AUC 6 with a dose that will be capped to 700 mg I.V D1 and paclitaxel (90 mg/m²) I.V D1 D8 D15 over 4 to 6 hours every 4 weeks for 4 cycles (allowed in squamous and non-squamous histologies).

Premedication (steroids for pemetrexed and paclitaxel, folic acid and vitamin B12 for pemetrexed) and emesis prevention therapy are required and will be used as standard practice. Treatment will be given for 4 cycles except in case of progression or toxicity.
See chapter 6 for more detailed description.

In cases of patient with a body surface area≥2m², all the chemotherapies doses will be capped at 2m² of body surface area.

2.5. Statement indicating that the study will be conducted in compliance with the protocol as well as with good clinical practices and legislative and regulatory conditions in force

The sponsor and the investigator also agree that this study will be conducted:

- in compliance with the protocol,
- in compliance with local and international good clinical practice currently in force,
- in compliance with legislative and regulatory conditions currently in force in participating countries.

2.6. Description of the studied population

Patients with untreated non-small cell lung cancer, patients less than 70 years old with PS2 or older than 70 years old with PS 0, 1 or 2 or at diagnosis. The selection procedures are described in chapter 5.

2.7. References to the scientific literature and to relevant data used as a reference for the study

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3 STUDY OBJECTIVES

3.1. Primary objective

To compare overall survival of patients treated with nivolumab + ipilimumab versus patients treated with chemotherapy.

3.2. Secondary objectives

To compare:

- survival rate at one year of patients treated with nivolumab + ipilimumab versus patients treated with chemotherapy,
- the objective response rate,
- the Progression free survival,
- the safety and the tolerability of nivolumab + ipilimumab versus chemotherapy,
- the QOL,
- the prognostic impact of PD-L1 expression by immunochemistery (IHC) on OS and PFS,
- the prognostic impact of a geriatric mini data set on OS, PFS and toxicity and its evolution under treatment restricted to patients ≥70 years old.

4 STUDY DESIGN

4.1 Evaluation criteria

4.1.1 Primary evaluation criteria

Overall survival

4.1.2. Secondary evaluation criteria

- Survival rate at one year,
- Objective response rate according to RECIST 1.1,
- Progression free survival,
- Safety tolerability according to CTCAE version 4.0,
- Quality of life according to EQ-5D and EORTC QLQ-ELD14 questionnaires every 6 weeks,
- PD-L1 expression by immunochemistery (IHC) as a predictive factor of OS and PFS,
- Geriatric mini data set restricted to patients ≥70 years old.

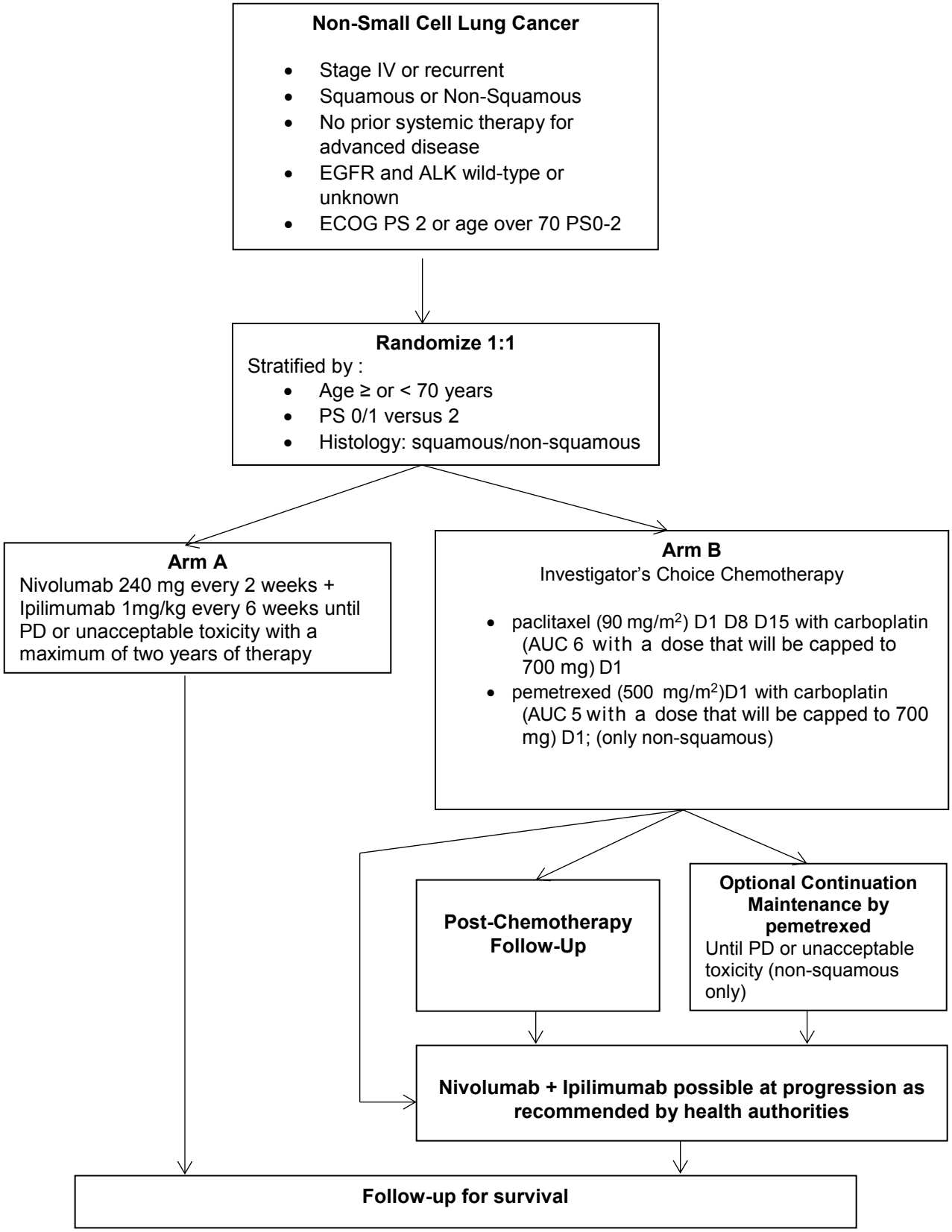
4.2. Description of study methodology

4.2.1. Experimental design

Open label phase III randomised study

4.2.2. Conduct of study

Figure 1: Study Schema



4.2.2.1. Inclusion Assessments and Procedures

Within 28 days before treatment:

- Informed consent must be obtained prior to any specific procedure to the trial
- Checking inclusion/ exclusion criteria
- A complete medical history and concomitant medications
- Physical measurements including height, and weight (calculated BMI, calculated BSA for Patients randomized to treatment Arm B). Focused physical examination may be performed as clinically indicated
- ECOG performance status
- Vital signs (including heart rate, blood pressure) within 72 hours of dosing
- Oxygen saturation by pulse oximetry at rest, (also monitor amount of supplemental O2 if applicable) within 72 hour of dosing
- A serum or urine pregnancy testing for WOCBP will be collected within **24** hours prior to start of study therapy
- Laboratory tests include (performed within 7 days prior to randomization unless otherwise specified)
  - Blood for complete blood count (CBC) with differential, including neutrophil and lymphocyte count
  - Serum chemistry tests : urea level, serum creatinine, sodium, potassium, calcium, phosphate, chloride, glucose, LDH)
  - AST, ALT, albumin, total bilirubin, alkaline phosphatase
  - TSH, free T3 and free T4 (within 28 days of randomization)
  - Hepatitis B surface antigen (HBV sAG), Hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA),HIV and CMV serology testing within 28 days prior to randomization
- Signs and symptoms present prior to randomization (regardless of relationship to disease) will be recorded. Additionally, record any concomitant medications taken within 14 days of randomization.
- Disease evaluation (chest abdomen CT scan, PET scan or bone scan if suspicion of bone disease, brain or MRI if clinically indicated)
- QOL evaluated with EQ5D and EORTC QLQ-ELD14
- Geriatric mini data set only for patients ≥70 years old (appendix 9)
- Electrocardiogram
- Availability of adequate FFPE tumor-derived material (tumor blocks or slides) from a biopsy, surgery or fine needle aspirate for analysis of PD-L1 testing by IHC. The tumor blocks or slides will be secondary sent to Pr Diane Damotte, service d'anatomie et cytologie pathologiques Hôpital Européen Georges-Pompidou H.E.G.P. 20 Rue Leblanc (Paris 15 - Vaugirard) 75015 Paris.

4.2.2.2. On-Study Assessments and Procedures

Before every infusion of treatment (experimental and control arm):

- Adverse Events and Serious Adverse Events
- Concomitant medications taken through course of study should be recorded
- Blood for CBC with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results to be obtained within 72 hours prior to dosing on infusion days).
- Serum chemistry tests: urea level, serum creatinine, albumin, sodium, potassium, calcium, phosphate, chloride, glucose, and LDH.
- Liver function tests including AST, ALT, total bilirubin, and alkaline phosphatase
- Vital signs (heart rate, blood pressure)
- Physical measurements including weight (and calculated BSA for Patients randomized to treatment Arm B), and ECOG performance status
- For nivolumab + ipilimumab arm, oxygen saturation by pulse oximetry at rest (obtained within 72 hours of dosing and at any time a Patient has any new or worsening respiratory symptoms. also monitor amount of supplemental oxygen if applicable) If a Patient shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient

should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm contained within the Investigator's Brochure.

Every 6 weeks :

- Tumor evaluation with chest and abdmen CT scan until disease progression even if study treatment is discontinued. If a cycle is delayed, tumor evaluation must not be delayed.
  If clinical progression occurs outside tumor evaluation, all efforts must be made to document this progression by CT scan or appropriate imaging methods.
- Thyroid function testing should be done every 6 weeks (every 3 cycles) for patients receiving nivolumab: free T3 and T4 if TSH is abnormal or if pts have symptoms.
- A serum or urine pregnancy testing is required every 6 weeks.
- QOL evaluated with EQ5D and EORTC QLQ-ELD14.
  At 8 weeks or before in case of progression or withdrawal of the study and restricted to patients ≥70 years old:
- Geriatric mini data set

4.2.2.3 Post progression Assessments and Procedures

- After discontinuation from nivolumab + ipilimumab, a serum or urine pregnancy testing should be repeated at approximately 30 days and approximately 70 days.
- Chemotherapy / nivolumab + ipilimumab according to INCA standards should be proposed according to the patient's condition and decision. The data on post progression therapy will be recorded in the CRF.
- AE possibly related to nivolumab and/or ipilimumab must be followed 100 days after last dosing.
- OS will be followed every 3 months via in-person or phone contact after patients discontinue the study drug. All randomized patients will be evaluated. Patients will be followed for one year after inclusion.
- Initial follow-up visits 1 and 2
- After discontinuation from treatment, the patient will come to the hospital for the first 2 follow-up visits. The first visit will take place approximately one month after cessation of treatment and the second approximately two months later. During this time, the patient's condition will be assessed.
- Additional follow-up visits (after the follow-up visit 2)
- This monitoring will be followed every 3 months via in-person or phone. During this time, the patient's condition will be assessed.

4.2.2.4 Study Flow-chart

Procedure	Screening visit (Within 28 days before treatment)	On-treatment (D1 of each cycle if not otherwise specified)	Post progression	
Eligibility Assessments				
Informed Consent	x			
Inclusion/Exclusion Criteria	x			
Medical History	x			
Safety Assessments				
Vital Signs and Oxygen saturation	x			Vital signs include heart rate, blood pressure. For Nivolumab + ipilimumab arm only, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing.
Physical Measurements (including Performance Status)	x	x		Physical measurements include height (at screening only), weight (calculated BSA for Patients randomized to treatment Arm B) and Performance Status. Focused physical examination may be performed as clinically indicated
ECG	x			
Hepatitis B,C, HIV and CMV testing	x			Within 28 days before treatment: Hepatitis B,C (HBV sAg and HCV Ab or HCV RNA), HIV and CMV testing
Complete blood counts (CBCs)	x	x		Within 7 days before C1D1, and within 72 hours before each cycle: Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	x	x		Within 7 days before C1D1, and within 72 hours before each cycle: serum urea level, creatinine, Ca, Na, K, Cl, LDH, Glucose
Liver Function testing	x	x		Within 7 days before C1D1, and within 72 hours before each cycle: ALT, AST, total bilirubin, alkaline phosphatase
Endocrine testing	x	x		Within 28 days before treatment and every 6 weeks (every 3 cycles) for Patients receiving nivolumab+ ipilimumab : TSH (with Free T4 and Free T3)
Pregnancy Test	x	x	x	A serum or urine pregnancy testing is required within 24 hrs of study enrollment or randomization, then every 6 weeks for WOCBP prior to dosing nivolumab + ipilimumab. After discontinuation from nivolumab + ipilimumab these should be repeated at approximately 30 days and approximately 70 days.

Adverse Events (AE) and Serious Adverse Event (SAE) assessment (of signs and symptoms)	x	x	x	AE possibly related to nivolumab and/or ipilimuamb must be followed 100 days after last dosing
Concomitant Medication collection	x	x	x	Post-progression therapy should be recorded in CRF
Efficacy Assessments				
Radiographic Tumor Assessment (Chest and abdomen)	x	x		Within 28 days before treatment: chest abdomen CT scan, PET scan or bone scan if suspicion of bone disease, brain or MRI if clinically indicated Every 6 weeks: tumor evaluation with chest and abdomen CT scan until disease progression. If clinical progression occurs outside tumor evaluation, all efforts must be made to document this progression by CT scan or appropriate imaging methods
EQ5D and EORTC QLQ-ELD14 questionnaires	x	x		At screening and then Every 6 weeks until disease progression
Collection of Survival Information			x	Every 3 months, until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.
Geriatric assessment				
Geriatric mini data set (restricted to patients ≥70 years old.)	x	x At week 8		To repeat at 8 weeks or before in case of progression or withdrawal of the study
Clinical Drug Supplies				
Study drug administration		x		
Tumor blocks or slides				
		x		Sent to Pr Diane Damotte, service d'anatomie et cytologie pathologiques Hôpital Européen Georges-Pompidou H.E.G.P. 20 Rue Leblanc (Paris 15 - Vaugirard) 75015 Paris for PDL1 testing by IHC

4.3. Description of the measures taken to reduce and prevent bias

4.3.1. Randomisation

After the Patient's eligibility is established and informed consent has been obtained, the Patient will be enrolled and a number will be assigned through the eCRF. Every Patient who signs informed consent must be assigned a Patient number in eCRF.

The investigator (or designee) will register the Patient for enrollment by following the enrollment procedures established by the CHU de Rennes. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth

Once enrolled in eCRF, enrolled Patients that have signed informed consent and met all eligibility criteria will be ready to be randomized through the eCRF. The following information is required for Patient randomization:

- Patient number
- Date of birth
- Gender at birth
- Diagnosis
- Date of informed consent
- PS

4.3.2. Methods of blinding

Not applicable

4.4. Description of dosage and methods of administration of the investigational medicinal products. Description of dose unit form, packaging and labelling of the investigational medicinal product(s)

The description of the medicinal product (Dosage and methods of administration, Unit form, packaging and labelling) is detailed in Section 6.

4.5. Expected duration of participation of persons and description of chronology and of duration of all study periods including monitoring

- Recruitment period: 24 months
- Duration of patient monitoring: 18 months or until end of study treatment in both arms
- Estimated total duration of study: 42 months

Starting with inclusion of the first patient, the sponsor has to inform without delay the local health agency and the ethics committee of the actual date of start-up of the study. The actual date of start-up = date of signature of consent form by the first person who is a Patient in the study.

The date of end of the study will be transmitted by the sponsor to the ethics committee and to the local health agency within 90 days or earlier according to local regulations**.** The date of end of the study corresponds to the last visit of the last person who is a Patient in the study.

4.6. Description of rules for permanent or temporary discontinuation

4.6.1. Discontinuation of participation of a person in study

Patients can withdraw their consent and ask to withdraw from the study at any time and for whatever reason. If a Patient discontinues the study before its completion, the investigator must document the reasons as completely as possible.

In fact, the investigator can temporarily or permanently discontinue the study treatment for any reason which is in the best interest of the Patient.

If a Patient is lost to follow-up, the investigator will make every effort to resume contact with that person.

4.6.2. Discontinuation of part or of the entire study

Unexpected events or new information pertaining to the product, in light of which the study objectives or clinical programme probably would not be achieved, can lead the sponsor to terminate the study.

In case of early permanent discontinuation of the study, the information will be sent by the sponsor within 15 days to the relevant country health agency and to the ethics committee or earlier according to local regulations.

5 SCREENING AND EXCLUSION OF PERSONS FROM THE STUDY

5.1. Inclusion criteria for persons who are Patients in the study

Target Population

- Signed written informed consent
- Cytologically or histologically proven NSCLC (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma)
- Stage IV or non-treatable by radiotherapy or surgery stage III (7th classification)
- No previous systemic chemotherapy for lung cancer, except in case of relapse after adjuvant treatment for localized disease with 6 months or more between end of previous chemotherapy and relapse
- Patients PS 2 less than 70 years old or 70 years older PS 0 to 2
- Judged fit enough to receive a carboplatin-based doublet according to ESMO guidelines
- Presence of at least one measurable target lesion (RECIST 1.1 rules) in a non-irradiated region and analysable by CT
- Life expectancy >12 weeks
- Prior radiation therapy is authorized if it involved less than 25% of the total bone marrow volume and finished 14 days before D1 of planned treatment
- Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization/registration
    - WBC $\geq 2000/\mu L$
    - Neutrophils $\geq 1500/\mu L$
    - Platelets $\geq 100 \times 10^3/\mu L$
    - Hemoglobin > 10.0 g/dL
    - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 45 mL/min (if using the Cockcroft-Gault formula below):
      Female CrCl = [(140 - age in years) x weight in kg x 0.85] / [72 x serum creatinine in mg/dL]
      Male CrCl = [(140 - age in years) x weight in kg x 1.00] / [72 x serum creatinine in mg/dL]
    - AST/ALT ≤ 3 x ULN
    - Total Bilirubin ≤ 1.5 x ULN (except Patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

Age and Reproductive Status

- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception during treatment. WOCBP should use an adequate method to avoid pregnancy :
    - For 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab + ipilimumab,
    - For 4 weeks after the last dose of carboplatine + pemetrexed,
    - For 5 weeks after the last dose of carboplatine + paclitaxel.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of treatment
- Women must not be breastfeeding
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year during treatment
- Men will be instructed to adhere to contraception for a period of 31 weeks after the last dose of nivolumab + ipilimumab and with carboplatine + pemetrexed or carboplatine + paclitaxel up to 6 months thereafter
- Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

5.2. Non-inclusion criteria for persons who are patients in the study

- Patients with other severe concurrent disorders that occurred during the prior six months before enrollment (myocardial infection, severe or unstable angor, coronarian or peripheric arterial bypass operation, NYHA class 3 or 4 congestive heart failure, transient or constituted cerebral ischemic attack, at least grade 2 peripheral neuropathy, psychiatric or neurological disorders preventing the patient from understanding the trial, uncontrolled infections) are not eligible
- Serious or uncontrolled systemic disease judged as incompatible with the protocol by the investigator
- Another previous or concomitant cancer, except for basocellular cancer of the skin or treated cervical cancer in situ, or appropriately treated localized low-grade prostate cancer (Gleason score < 6), unless the initial tumor was diagnosed and definitively treated more than 5 years previously, with no evidence of relapse.
- Known activating mutation of EGFR (del LREA exon 19, mutation L858R or L861X of exon 21, mutation G719A/S in exon 18) or EML4-ALK or ROS-1 translocation
- Superior caval syndrome
- Uncontrolled infectious status
- All concurrent radiotherapy
- Concurrent administration of one or several other anti-tumor therapies
- Psychological, familial, social or geographic difficulties preventing follow-up as defined by the protocol.
- Protected person (adults legally protected (under judicial protection, guardianship or supervision), person deprived of their liberty, pregnant woman, lactating woman and minor)
- Concurrent participation in another clinical trial
- Patients are excluded if they have active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for [lowest minimum is 4 weeks or more] after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration
- Patients should be excluded if they have an active, known or suspected autoimmune disease. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism 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
- Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease
- Patients should be excluded if they are positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
- Patients should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Patients should be excluded if they have a lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
- Allergies and Adverse Drug Reaction
- History of allergy to study drug components
- Severe spinal hypoplasia and / or hemorrhagic tumors

5.3. Methods of recruitment

Recruitment will come from GFPC centers. Treatment decision for new cancers patients are made in multidisciplinary meetings and proposal for inclusion in clinical trials are part of these meetings.

6 TREATMENTS ADMINISTERED TO PERSONS WHO ARE PATIENTS IN THE STUDY

6.1. Description of the treatments necessary for conduct of the study

6.1.1. Nivolumab - Ipilimumab

6.1.1.1 Description

NIVOLUMAB AND IPILIMUMAB INFORMATION TABLE: Please also see Drug Information (Appendix 7)

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/ml)	IP	Open label	Clear to opalescent colorless to pale yellow liquid. May contain particles. 240 mg kit contains: 2 x 100 mg vials (10 mL/vial) and 1 x 40 mg vial (4 mL/vial) or carton containing 5 vials of 100 mg	2-8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200mg (5mg/mL)	IP	Open label	Clear to slightly opalescent colorless to pale yellow liquid. May contain particles. Carton containing 4 vials of 200mg	2-8°C. Protect from light and freezing.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.
For additional details on prepared drug storage and use time of nivolumab and ipilimumab under room temperature/light and refrigeration, please refer to the BMSInvestigator Brochure section for "Recommended Storage and Use Conditions"
The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately. Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information

6.1.1.2 Dosing schedule and Administration

	Week 1 +/- 3 days	Week 2	Week 3 +/- 3 days	Week 4	Week 5 +/- 3 days	Week 6
Nivolumab 240 mg q2 weeks + Ipilimumab 1 mg/kg q 6 weeks	Day 1 Nivolumab + Ipilimumab		Day 1 Nivolumab		Day 1 Nivolumab	

Patients randomized to experimental arm will receive treatment with Nivolumab as a 30 minutes infusion 240 mg every 2 weeks and ipilimumab as a 30 minutes infusion 1 mg/kg every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. When nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations should be based on the body weight assessed as per Table 5.1-4. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Patients may be dosed with nivolumab no less than 12 days from the previous dose. There are no premedications recommended.
Patients should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, Patients should be managed according to Protocol Section 4.5.11.
Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the Patient tolerates the treatment. See Sections 4.5.5, 4.5.7, and 4.5.8, for more details regarding dose delays, retreatment, and discontinuations.

6.1.1.3 Dosage adjustment
Dose reductions or dose escalations are not permitted.

6.1.2. Comparator

Table 6.1.2-1:	**Product Description - Treatment Phase**				
Product Description and Dosage	**Potency**	**Primary Packaging (Volume)/**	**Secondary Packaging (Qty) /Label**	**Appearance**	**Storage Conditions (per**
Carboplatin Solution for Injection	450 mg/vial (10 mg/mL)	45 mL per vial/	4 vials per carton/Open-label	Clear, colorless or slightly yellow solution	Store at or below 25°C. Protect from
Pemetrexed Powder for Concentrate for Solution for	500 mg/vial	500 mg per vial/ Open-	1 vial per carton/ Open-label	White to either light yellow or	Store at 25°C. Excursions permitted
Paclitaxel Solution for Injection	100 mg/vial (6	16.7 mL vial/ Open-label	4 vials per carton/Open-label	Clear, colorless or slightly yellow viscous solution	Store at 15°C-30°C. Protect from light.

6.1.2.1 Dose Reductions for Investigator's Choice Chemotherapy
To receive chemotherapy patient must have:
Neutrophils count >= 1500/mm3
Platelets >=100000/mm3
Back to grade≤1 non-hematological toxicity
A maximum delay of two weeks is accepted. If D1 cannot be administered, chemotherapy will be stopped. Some exceptions can be discussed with the principal investigator

Dose reductions of investigator's choice chemotherapy may be required, and will be performed according to Table 6.1.2-2. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent combination cycles. The dose reductions for each agent in the investigator's choice chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 6.1.2-2	**Dose Modifications of Chemotherapeutic Agents**		
Dose Level	**Pemetrexed**	**Carboplatin**	**Paclitaxel**
Starting dose	500 mg/m²	AUC 6 (with Paclitaxel) AUC 5 (with Pemetrexed)	90 mg/m²
First dose reduction	375 mg/m²	AUC 5 (with paclitaxel) AUC 4 (with Pemetrexed)	80 mg/m²
Second dose reduction	185 mg/ m²	AUC 4 (with paclitaxel) AUC 3 (with Pemetrexed)	70 mg/m²
Third dose reduction	Discontinue	Discontinue	Discontinue

Any Patients with two prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Investigator's Choice Chemotherapy - Dose Reductions for Hematologic Toxicity
Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for investigator's choice chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the investigator's choice chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 6.1.2-3: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)			
Toxicity	**Pemetrexed**	**Cisplatin**	**Paclitaxel**
Neutrophil Count Decreased			
Grade 4 durig at least 7 days (< 500/mm^3 or < 0.5 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 3 or 4 febrile neutropenia (< 1000/mm^3 or < 1.0 x 10^9/L and fever≥ 38°5C)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Anemia			

Grade 4 (< 6,5 g/dl)	Reduce one dose level	Reduce one dose level	Reduce one dose level
Platelet Count Decreased			
Grade 3 (25,000 - < 50,000/mm^3; 25.0 -< 50.0 x 10^9/L) or bleeding requiring transfusion	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 (< 25,000/mm^3; < 25.0 x 10^9/L) or bleeding requiring transfusion	Reduce one dose level	Reduce one dose level	Reduce one dose level

Investigator's Choice Chemotherapy – Dose Reductions for Non-Hematologic Toxicities
Dose adjustments for investigator's choice chemotherapy for non-hematologic toxicities during treatment are described in Table 4.3.4.3-1. All dose reductions should be made based on the worst grade toxicity. Patients experiencing any of the toxicities detailed in Table 6.1.2-4 during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 4.3.5.2) and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the two drugs in the investigator's choice chemotherapy regimen are not linked and may be reduced independently, as summarized in the table below.

Table 6.1.2-4: Dose Modifications for Non-hematologic Toxicity

Toxicity	Pemetrexed	Carboplatin	Paclitaxel
Diarrhea Grade □ 3	Reduce one dose level	No change	Reduce one dose level
Allergic reaction Grade □ 3	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	No change	Reduce one dose level
Neuropathy Grade □ 3	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 45 mL/min	Discontinue	No change	No change
Other Grade □ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

[a] Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (□ Grade 3) require(s) discontinuation. All other drugs may be continued

- Carboplatin/pemetrexed

Pemetrexed 500 mg/m² on D1 + carboplatin AUC 5 with a dose that will be capped to 700 mg on D1, the cycles being repeated every 21 days. The reconstitution of the cytostatics should be ideally realized in central units. In all cases, the traceability of the products must be assumed for all enrolled patients. The drugs will be administered as follows.
Pemetrexed will be given at a dose of 500 mg/m² as an IV infusion lasting about 10 min on D1 of each 21-day cycle.

Premedication regimen
To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.
To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

Pemetrexed should not be administered to dehydrated patients.

Dosage adjustment
The dose at the beginning of each cycle will be adjusted to the polymorphonuclear neutrophil (PNN) nadir and the platelet nadir of the previous cycle.
The PNN must be >1500/mm³ and the platelet count >100 000/mm³ before starting each treatment cycle.

Dose adjustment according to cell counts during each previous cycle

CBC D22, D43, D64		
Polymorphonuclear neutrophils (/mm 3)	Platelets (/mm3)	Doses and postponements
≥ 1500	≥ 100 000	Treatment dates as planned, dose adjustment according to the nadir
< 1 500	and/or < 100 000	Treatment postponed for a week*, dose adjusted to the nadir of the previous cycle

* no more than two one-week postponements are authorized; otherwise, treatment will be stopped.

Dose adjustment according to the nadir during each cycle: **cf Table 6.1.2-3**

Dose adjustment of the carboplatin–pemetrexed combination for non-hematologic toxicity
Diarrhea
In case of grade III or IV diarrhea (CTCAE), the following measures are authorized: hydration, octreotide and antidiarrhoeal agents. A 25% reduction in the dose of the two drugs is recommended.
In case of severe diarrhea necessitating IV rehydration and/or associated with fever or severe grade III or IV neutropenia, broad-spectrum antibiotic therapy must be prescribed. Patients with severe diarrhea or diarrhea associated with nausea or vomiting must be hospitalized for IV hydration and correction of electrolytic imbalance.
In the case of diarrhea necessitating hospitalization, chemotherapy must not be administered until the diarrhea has resolved, and the dose must be reduced to 75% of the previous dose.

Other non-hematologic toxicity
In case of grade >3 toxicity (excepting neurotoxicity), treatment must be interrupted until the disorder subsides to grade <1 or to the grade observed at enrollment in the study. A 25% reduction in the dose of the two drugs can be made if considered appropriate by the clinician.

Stomatitis: in case of stomatitis, only the pemetrexed dose will be adjusted, as described in the following table:

CTCAE	Pemetrexed	Carboplatin
CTC Grade 0 – 2	100% of the planned dose	100% of the planned dose
CTC Grade 3-4	50% of the planned dose	100% of the planned dose
Recurrent grade >3 stomatitis after two dose reductions	Study exit	Study exit

Neurotoxicity: in case of neurotoxicity, only the carboplatin dose will be adjusted, as described in the following table:

CTCAE grade	Carboplatin dose	Pemetrexed dose (mg/m2)
0-1	100% of the planned dose	100% of the planned dose
2	50% of the previous dose	100% of the planned dose
3–4	Study exit	Study exit

Renal failure: Before beginning a new cycle, creatinine clearance, calculated with the Cockcroft-Gault formula, must be >45 ml/min. Chemotherapy can be postponed up to 2 weeks while waiting for the adverse event to resolve. Beyond D36, if the creatinine clearance is not >45 ml/min, the patient will leave the study.
All other grade III or IV toxicity: the dose must be reduced to 75% of the previous dose. Treatment must be postponed until the adverse event resolves. The patient will leave the study after a maximum of two dose reductions.
Protocol rescue
In case of severe hematologic toxicities like grade IV leucopenia, neutropenia, myelosuppression during more than 3 days and with complications, or grade IV thrombopenia with bleeding or grade III or IV mucitis, the following protocol can be used:

- Ac Folinic (leucovorin®) 100 mg/m² IV followed by
- Ac Folinic (leucovorin®) 50 mg/m² IV every 6 hours during 8 days. (an oral form can also be used)

- Carboplatin-paclitaxel

4 cycles of carboplatin AUC6 D1 + paclitaxel 90 mg/m² D1, D8, D15 4 cycles every 28days. Carboplatin dosage will be made according to Calvert formula.

All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to Paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before Paclitaxel.
The reconstitution of the cytostatics should be ideally realized in central units. In all cases, the traceability of the products must be assumed for all enrolled patients. The drugs will be administered as follows.
Institutions should follow their standard administration regimens for paclitaxel. In general, paclitaxel will be administered intravenously at a dose of 90 mg/m2 over 3 hours followed by carboplatin at day one. At day 8 and day 15, paclitaxel alone will be administered.

Dosage adjustment
The dose at the beginning of each cycle will be adjusted to the polymorphonuclear neutrophil (PNN) nadir and the platelet nadir of the previous cycle.
At D1, the PNN must be >1500/mm³ and the platelet count >100 000/mm³ before starting each treatment cycle.

Dose adjustment at D1 according to cell counts during each previous cycle

CBC D22, D43, D64		
Polymorphonuclear neutrophils (/mm 3)	Platelets (/mm3)	Doses and postponements
≥ 1500	≥ 100 000	Treatment dates as planned, dose adjustment according to the nadir
< 1 500	and/or < 100 000	Treatment postponed for a week*, dose adjusted to the nadir of the previous cycle

* no more than two one-week postponements are authorized; otherwise, treatment will be stopped

Dose adjustment according to the nadir during each cycle: **cf Table 6.1.2-3**

Dose adjustment of the carboplatin–paclitaxel combination for non-hematologic toxicity

ORGANS	TOXICITIES	GRADE	ACTIONS
Ears	hearing/inner ear	≥2	Discontinue carboplatin Pursue paclitaxel according to investigator's choice
Cardiovascular	Asymptomatic sinus bradycardia Asymptomatic ventricular arrhythmia	1	No dose change ECG before each cycle
	Asymptomatic ventricular arrhythmia Atrio ventricular block (except of first degree) Other blocks	≥2	Discontinue chemotherapy
Gastrointestinal	mucositis	≥3	Reduce one dose level for the two drugs
Liver	Bilirubin>3× ULN AST/ALT>2.5× ULN In cas of liver metastasis:≥5× ULN	≥3 ≥2	Discontinue chemotherapy
Infection	Infection without neutropenia	≥3	Reduce one dose level for the two drugs
Neurological	Sensitive neuropathy	1 2 *2 ≥3	No change Reduce one dose level for the two drugs If persistence despite dose reduction, one more level reduction Discontinue chemotherapy
Pain	Arthralgia/myalgia During more than 7 days	≥3 ≥3	Reduce one dose level for paclitaxel only Discontinue chemotherapy
Kidneys	Creatinin>1.5 × ULN	≥2	Discontinue carboplatin Pursue paclitaxel according to investigator's choice
Other toxicities excluding nausea, vomiting and asthenia		≥3	Reduce two doses levels or stop according to investigator's choice

Dose adjustment at day 8 and 15 of paclitaxel
At D8 and D15 infusions of paclitaxel will be done only if ANC is≥1500/mm3, platelets ≥100000/mm3. Infusion will be omitted if CBC does not allow infusion. If D8 and D15 must have been cancelled, next cycle will start at D29 in respect of planned dose level reduction.
The dose of paclitaxel will be the same at D8 or D15 than at D1 except if a non-hematological toxicity requiring a dose level reduction is occurred between D1 and D8 or D8 and D15.

- **Allergic Reaction/Hypersensitivity (Paclitaxel Only)**

CAUTION: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but the administration of prophylactic medication (see below) and intensive monitoring of vital signs is recommended.

• Mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No treatment required.
• Moderate symptoms: Stop paclitaxel infusion. Give IV diphenhydramine 25−50 mg and IV dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hour for 15 minutes, then 40 mL/hour for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. If symptoms reoccur, stop paclitaxel infusion. Paclitaxel treatment will be discontinued.
• Severe life-threatening symptoms: Stop paclitaxel infusion. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel treatment will be discontinued.

Moderate or severe hypersensitivity reactions should be recorded as an adverse event.

6.2. Packaging and labelling

The reconstitution of the cytostatics should be ideally realized in central units a specific label for a clinical trial in compliance with applicable regulatory requirements including European regulations; mentioning at least:

- Name of study
- Name of product,
- Dosage,
- Route of administration,
- Conditions for storage,
- The expiry date for use,
- Batch number,
- Sponsor's name and address,
- "for clinical trial use only"

Labels will be translated in French. The sponsor ensures a proper labelling and the sponsor ensures via the clinical research organization the good distribution of the drugs to all sites.

6.3 Drug ordering and accountability

BMS is supplying study drug.

The sponsor is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity).

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately. If commercial investigational product is used, it should be stored in accordance with the appropriate local labeling.

If the study drug(s) are 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.

6.4 Authorised and unauthorised medicinal products and treatments in the setting of the protocol, including emergency medicinal products

6.4.1. Authorised treatments

Experimental arm: 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 (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatoxicity should be used with caution.

Control arm: all support treatment (emesis prevention, GCSF if judged necessary by investigato) are allowed as standard of care.

6.4.2. Unauthorised treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.4.1)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)

Investigators should refer to the local product labeling for the chemotherapy drugs selected for use in each Arm B Patient for additional prohibited and restricted concomitant medications.

Except for the permitted procedures specified as palliative local therapies, all other radiation therapy or surgery to any tumor lesion is not permitted during study treatment. Patients who require such non-palliative procedures must be discontinued from study treatment.

6.4.3. Interaction with other medicinal products

Pemetrexed

Concomitant use contraindicated: Yellow fever vaccine: risk of fatal generalised vaccinale disease

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration.
In patients with mild to moderate renal insufficiency eligible for pemetrexed therapy NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Carboplatin
Concomitant use contraindicated: Yellow fever vaccine: risk of generalised disease mortal
Concomitant use not recommended:
- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This risk is increased in patients who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

6.4.4. Emergency treatment
Carboplatin pemetrexed
In case of severe hematologic toxicities like grade IV leucopenia, neutropenia, myelosuppression during more than 3 days and with complications, or grade IV thrombopenia with bleeding or grade III or IV mucitis, the following protocol can be used:

- Ac Folinic (leucovorin®) 100 mg/m² IV followed by
- Ac Folinic (leucovorin®) 50 mg/m² IV every 6 hours during 8 days. (an oral form can also be used)

Carboplatin paclitaxel

- Cases of severe hypersensitivity characterized by hypotension, dyspnea, angioedema or generalized urticaria have been reported in 2% of patients receiving paclitaxel.

In case of hypersensitivity reactions, appropriate measures must be taken by the investigator based on the severity of the event.

- CTC Grade 1: transient rash, fever <38 ° C: further infusion monitoring. No treatment needed.
- CTC Grade 2: hives, fever> = 38 ° C and / or symptomatic bronchospasm: stopping the paclitaxel infusion, administration of 2.5 mg of methylprednisolone dexchloropheniramine and 60 mg. Resume paclitaxel infusion after sedation of symptoms at a slower rate: 20 ml / h for 15 min and 50 ml / h for 15 minutes then there are no other symptoms at the initial pace until the end of infusion. Particular attention monitored should be monitored during the next administration of paclitaxel.
- CTC Grade 3 or 4: severe symptoms and even life threatening: Major bronchospasm requiring intravenous treatment, with or without urticaria, edema / angioedema, anaphylactic shock: stopping the paclitaxel infusion. Administration of diphenhydramine and methylprednisolone as above. Add adrenaline if necessary. Mention the incident as a Junk Grave Event (SAE). Definitely stop chemotherapy.

6.5. Conditions for storage of the investigational medicinal product
The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.
Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.
Treatments used in the study will be stored at the pharmacies of participating center.

6.6. Management of Nivolumab and Ipilumumab, resupply and dispensing of Nivolumab and Ipilumumab

Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.
Ipilimumab has a concentration of 5 mg/mL and is provided in a 40 mL vial. Four vials are provided in a carton.

6.6.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of nivolumab and/or Ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient.
The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab or ipilimumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing.

6.6.2 Re-Supply

Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

6.6.3 Drug Excursions

Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form.

6.6.4 Handling and Dispensing

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.
Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

6.6.5 Destruction

Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures can be consulted by sponsor upon request.
- Records are maintained that allow for traceability of each IP, including the date disposed of, quantity disposed, and identification of the person disposing the IP. The method of disposal must be documented.
- Accountability and disposal records are complete, up-to-date, and available for sponsor to review throughout the clinical trial period as per the study agreement.

Please refer to the most recent version of the Investigator Brochure for additional information.

7 EVALUATION OF SAFETY

7.1 Definitions

7.1.1 Adverse event (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation Patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended

sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

Related: There is a reasonable causal relationship between study drug administration and the AE.
Not related: There is not a reasonable causal relationship between study drug administration and the AE.
The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

7.1.2 Adverse reaction of an investigational medicinal product (AR)

Any untoward and unintended responses to an investigational medicinal product related to any dose administered. In other wise, that means all adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product, qualify as adverse reactions.

7.1.3 Serious adverse event or serious adverse reaction (SAE/SAR)

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the Patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the Patient or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

Potential drug induced liver injury (DILI) is also considered as an important medical event.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

A Serious Adverse Reaction (SAR) is a serious adverse event with a causal relationship to an investigational medicinal product.

7.2 Investigator's role

7.2.1 Adverse Events to be immediately notified to the sponsor

7.2.1.1 Serious Adverse Events

Every serious adverse event, related to study drugs or not, must be reported immediately by the investigator to the sponsor on a "SAE form" mentioning the date of occurrence, criterion of seriousness, relationship with the study drugs (or the study), and the outcome.
Follow-up information must be completed if needed and sent to the sponsor as soon as new relevant information is obtained. Copies of the patient's medical record must be attached as well as results of laboratory tests. Whenever a serious event persists at the end of the study, the investigator must follow the patient until the event is considered resolved.

7.2.1.2. Potential Drug Induced Liver Injury (DILI)

Potential Drug Induced Liver Injury (DILI) is considered as an important medical event and must be reported immediately by the investigator to the sponsor on a "SAE form".
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.

7.2.1.3 Suspected transmission of an infectious agent
Suspected transmission of an infectious agent (pathogenic or nonpathogenic) must be reported immediately by the investigator to the sponsor on a "SAE form".

7.2.1.4 Non serious adverse event but critical to safety evaluation
Pregnancy
If, following initiation of the investigational product, it is subsequently discovered that a study Patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after Nivolumab or Ipilimumab administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for Patient safety).
The investigator must immediately notify the sponsor of this event via the Pregnancy Surveillance Form.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.
Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose
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.

Laboratory Test Abnormalities considered as SAE
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
- any laboratory abnormality that required the Patient to receive specific corrective therapy.

Other Safety Considerations
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.

7.2.2 Notification to the sponsor and time frame reporting
- **Following the Patient's written consent** to participate in the study, all SAEs and other events listed above, 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 discontinuation of dosing.
- The investigator should report **any SAE** that occurs **after these time periods** that is believed to be **related** to study drug or protocol-specified procedure.
- All SAE and other events listed above must be reported to the sponsor **immediately or within 24 hours** from the time the investigator becomes aware of them.
- The Investigator must complete, sign, and date the SAE form, verify the accuracy of the information recorded on the SAE form with the corresponding source documents, and send a copy via fax to Sponsors' Clinical Trial Vigilance Office (Catherine Mouchel - catherine.mouchel@chu-rennes.fr) which contacts information provided below:
  Fax number: 02 99 28 40 10/ Phone number: 02 99 28 91 96
  E-mail: vigilance.essais@chu-rennes.fr
- When further information or additional follow-up information becomes available, the SAE form should be updated with the new information and reported to the sponsor immediately or within 24 hours via the same contacts information.
- All SAEs should be followed to **resolution** or **stabilization**.

7.2.2.1 Events not to be notified immediately to the sponsor

- Specific hospitalizations

The following hospitalizations are not considered SAEs and will not be collected:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

- Specific events related to non-small cell lung cancer progression

Disease progression can be considered as worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not AE.

➔ Events, which are unequivocally due to disease progression, should not be reported as an Adverse Event (AE) during the study and will not be collected.

- Non serious adverse events

- The collection of non-serious AEs information should begin at initiation of study drug. The information regarding non-serious AE must be reported in the CRF.

- All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of **30 days** following the last dose of study treatment.

- Seven specific types of non-serious AEs must be collected that occur within **100 days** of discontinuation of dosing:
  - Renal adverse event
  - Endocrinopathy
  - Gastro-intestinal adverse event
  - Hepatic adverse event
  - Neurological adverse event
  - Pulmonary adverse event
  - Skin adverse event

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious.

- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

7.3 Sponsor's role

7.3.1 Analysis of serious adverse events

The sponsor must evaluate the following:

- the causal relationship of serious adverse events (all adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered, are considered as suspected adverse reactions. If the sponsor's evaluation of the event differs from the investigator's, both opinions are mentioned in the statement sent to the competent authority if this statement is necessary),
- and their expected or unexpected feature, using the reference document in force. All SAEs will be followed to resolution or stabilization.

7.3.2 Method of relationship assessment

The method used by the sponsor in evaluating the relationship of the event is as follows:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship; the adverse event is therefore qualified as an adverse reaction.
If the adverse reaction is unexpected, it is qualified as being Suspected Unexpected SAR (SUSAR) and must be declared in a report by the sponsor to the competent authorities and to the ethic committee.

7.3.3 Declaration of unexpected serious adverse events
The sponsor reports all suspected unexpected serious adverse reactions (SUSAR) to Eudravigilance (European pharmacovigilance database), to local regulatory agency (ANSM), to the ethic committee and to investigators within the regulatory time periods for reporting.

7.3.4 Transmission of annual safety reports
On the anniversary date of authorisation of the study delivered by the Health Authorities, the sponsor writes a Data Safety Update Report (DSUR) report containing:
- the list of serious adverse events which may be related to the investigational medicinal products studied, including expected and unexpected serious effects,
- a critical analysis of safety of patients who are Patients in the study.

It is sent to local regulatory agency and to the ethics committee within 60 days following the anniversary of authorisation of the trial.

7.3.5 Declaration of other safety data
Every safety finding that can alter the benefit/risk ratio of an investigational medicinal product or sufficient to consider changes in administration of the study product or changes in conduct of the trial must immediately be notified to the sponsor. The former will be the Patient of a report to the competent authorities and ethic committee.

7.3.6 Transmission of Safety Data to BMS
SAEs and pregnancies will be reported to BMS within 24 hours. SAEs will be recorded on CIOMS Form; pregnancies will be reported on a Pregnancy Surveillance Form.
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804
If only limited information is initially available, follow-up reports will be required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report will be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report.

7.4 Expected adverse reactions specific to the present study
7.4.1 Adverse reactions related to Nivolumab or Ipilimumab

Infections and infestations	
Uncommon	bronchitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	histocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Immune system disorders	
Uncommon	anaphylactic reaction, hypersensitivity, infusion related reaction
Endocrine disorders	
Common	hypothyroidism
Uncommon	adrenal insufficiency, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Nervous system disorders	
Common	peripheral neuropathy, headache, dizziness
Uncommon	myasthenic syndrome, polyneuropathy
Cardiac disorders	
Uncommon	tachycardia
Vascular disorders	
Uncommon	vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis, dyspnoea, cough

Uncommon	lung infiltration
Gastrointestinal disorders	
Very common	nausea
Common	diarrhoea, stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	colitis, duodenal ulcer
Skin and subcutaneous tissue disorders	
Common	rash, pruritus
Uncommon	urticaria
Musculoskeletal and connective tissue disorders	
Common	musculoskeletal pain,a arthralgia
Uncommon	polymyalgia rheumatica
Renal and urinary disorders	
Uncommon	tubulointerstitial nephritis, renal failure
General disorders and administration site conditions	
Very common	fatigue
Common	pyrexia, oedema
Investigations	
Very common	increased AST,bincreased ALT,b increased alkaline phosphatase,b increased creatinine,b decreased lymphocytes,b decreased platelet count,b decreased haemoglobin,b hypercalcaemia,b hypocalcaemia,b hyperkalaemia,b hypokalaemia,b hypomagnesaemia,b hyponatraemiab
Common	increased total bilirubin,b decreased absolute neutrophil count,b hypermagnesaemia,b, hypernatraemiab
Uncommon	Increased lipase, increased amylase

a Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, spinal pain.
b Frequencies reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

Management Algorithms for Immuno-Oncology Agents
Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:
Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.
While the ipilimumab investigator brochure contains very similar safety management algorithms for these adverse events, the recommendation is to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management across the three blinded treatment arms.
The algorithms are found in the Nivolumab IB and in Appendix 8 of this protocol.

Dose Delay for experimental Arm (Nivolumab plus Ipilimumab)
Tumor assessments for all Patients should continue as per protocol even if dosing is delayed.
Nivolumab and ipilimumab administration should be delayed for the following:
Any Grade ≥ 2 non-skin, drug-related AE except forfatigue or laboratory abnormalities
- Any Grade 3 skin, drug-related AE

Any Grade 3 drug-related laboratory abnormality, with the following exceptions AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
-
- If a Patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a Patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Patients that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met.

Criteria to Resume Nivolumab and Ipilimumab Dosing

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

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Patients with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.5.8.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Patients who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone +/-10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 6.1.1.7.

Ipilimumab may not be resumed sooner than 6 weeks (+/- 5days) after the prior ipilimumab dose.
In general, Patients who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
One exception to note is when ipilimumab and nivolumab doses are delayed due to drug related Grade ≥3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline.
Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the patient's medical chart. The Medical Monitor should be consulted prior to resuming nivolumab in such Patients.

Nivolumab and Ipilimumab discontinuation

Nivolumab Dose Discontinuation
Treatment with nivolumab should be permanently discontinued for the following:

- 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 the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted 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 require discontinuation:
            - AST or ALT > 8 x ULN

    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤7 days
    - Grade 4 lymphopenia or leucopenia
    - 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. The Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a Patient with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor 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.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.
If a patient meets the criteria for discontinuation of ipilimumab but not nivolumab prior to completion of the first 4 cycles, treatment with nivolumab may not resume until the adverse event has fully resolved, and the patient has discontinued steroids, if they were required for treatment of the adverse event. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at 240 mg every 2 weeks.
If a patient in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Ipilimumab Dose Discontinuation
Ipilimumab should be permanently discontinued if any of the following criteria are met:

- 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 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 8x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

  - Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 12 weeks, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drugrelated reasons may be allowed if approved by the BMS medical monitor. Prior to reinitiating treatment in a patient with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- 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.
- The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.
- If a patient meets the criteria for discontinuation of ipilimumab but not nivolumab, treatment with nivolumab may not resume until the adverse event has fully resolved and the patient has discontinued steroids, if they were required for treatment of the adverse event. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at 240 mg every 2 weeks. If a patient in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of Patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD). Patients will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as all of the following criteria are met and clearly documented:

• Investigator-assessed clinical benefit and no rapid disease progression;

• Tolerating blinded study drug(s);

• Stable performance status;

• Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases);

• Patient provides written informed consent prior to receiving additional study therapy, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued study therapy.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. For the Patients who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. For Patients with evaluable disease only, further progression is defined as unequivocal disease progression of non-target lesions or the development of new lesions from time of initial PD. Treatment should be discontinued permanently upon documentation of further disease progression.

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

measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, Patients who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For Patients in all treatment arms, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document.

Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab 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, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Insert version e.g.: 4.0) guidelines.

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

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

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

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the Patient with diphenhydramine 50 mg IV (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 IV, 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 IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion of nivolumab. Begin an IV 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 IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (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 (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7.4.2 Adverse reactions related to Carboplatin

The reference document for definition of expectedness is the the European Union (EU) Summary of Product Characteristics (SPC) CARBOPLATINE HOSPIRA 10 mg/ml sol inj p perf. The expected adverse reactions related to Carboplatin are listed in this document.

7.4.3 Adverse reactions related to Pemetrexed

The reference document for definition of expectedness is the the European Union (EU) Summary of Product Characteristics (SPC) ALIMTA 100 mg pdre p sol diluer p perf. The expected adverse reactions related to Pemetrexed are listed in this document.

7.4.4 Adverse reactions related to Paclitaxel

The reference document for definition of expectedness is the the European Union (EU) Summary of Product Characteristics (SPC) TAXOL 6 mg/ml sol diluer p perf. The expected adverse reactions related to Paclitaxel are listed in this document.

8 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A comprehensive Statistical analysis plan (SAP) for the trial will be prepared before any statistical analysis. It will include detailed information on the analysis of primary and secondary outcome measures and the definitions of major protocol deviations.

Sample size consideration

The primary endpoint of the phase III is overall survival. The study is calibrated to detect a treatment effect hazard ratio (HR) of 0.65, translating in an improvement of 1-year OS rate from 40% (control arm) to 55% (Nivolumab + Ipilimumab arm).

A total of 199 events observed at the time of the final analysis would have 85% power to show statistically significant log-rank test at a 2-sided alpha level of 5%. Considering a recruitment duration of 24 months and a 18 months follow-up for the last included patient (estimated total duration of the study: 42 months), 242 patients will be randomized in the study (121 by arm).

Randomization ratio 1:1 will be stratified according to Age (< 70 vs. ≥ 70 years),ECOG-PS status (0/1 vs. 2) and by histology (squamous versus non-squamous).

Interim analyses

During the trial, one interim analysis for futility will be performed, permitting to early stop the trial, if no sufficient efficacy is shown. This analysis will be performed after that 33% of the expected events have occurred. Using planned enrollment rate, this analysis should be performed after inclusion of 171 patients (17 months after first included patient) (fig. 1). No adjustment of type I error was required. Stopping boundaries were defined according to Lan-DeMets spending function to control type II error. Table 1 shows the futility boundaries.

An independent Data Safety Monitoring Board will be organized to discuss the conduct of the study after analysis performed.

Sample size calculation and interim analysis planning were performed using East® software (Cytel Inc. 1994-2014), version 6.3.1

Table1: Futility boundaries

Look	Fraction of information	Cumulative □ spent	P value	HR futility bound
1	0.33	0.012	0.698	1.137
2	1	0.15	0.0025	

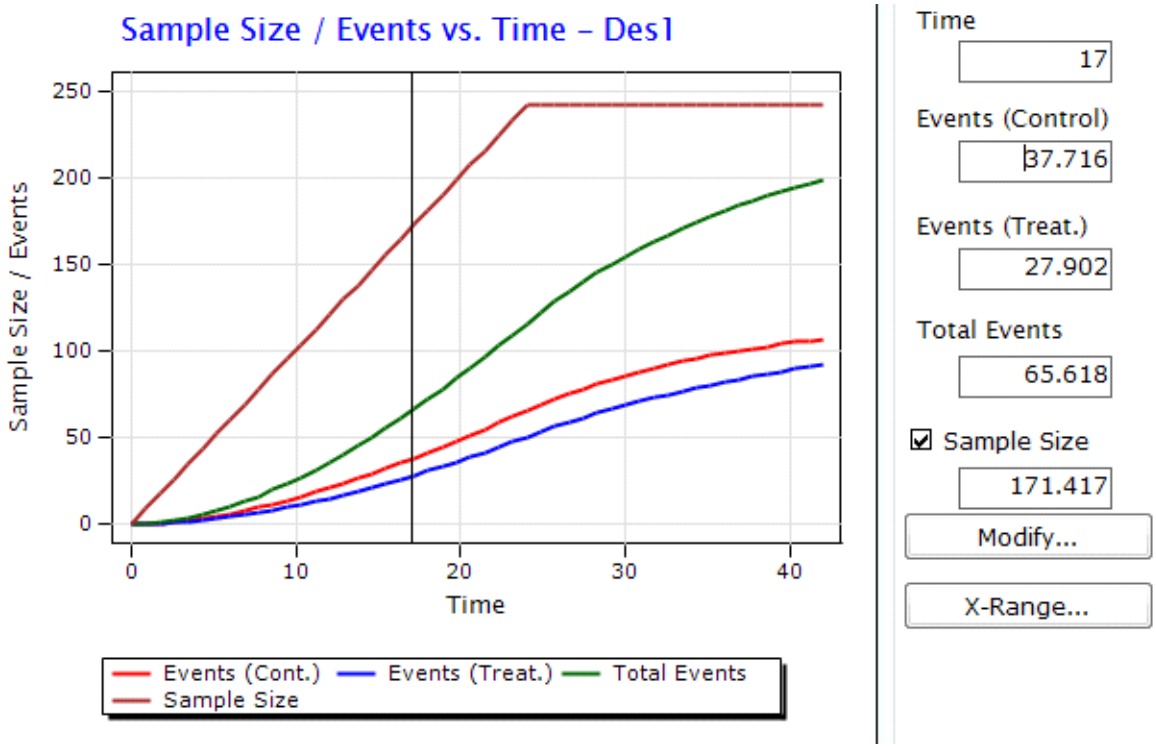


Figure 1: Estimated Sample size / events during study period.

Definition of population

- The Intent-to-treat (ITT) population is defined as all patients randomized in the trial, regardless of whether they actually received treatment. The treatment groups will be analyzed as randomized.
- The Per Protocol (PP) population is a subgroup of the ITT population containing all patients who do not have any major protocol violation and received study treatment at least once. Major protocol violations will be defined in the Statistical Analysis Plan (SAP).
- The Safety population will include all randomized patients having received at least one dose of study treatment and one safety follow-up, whether withdrawn prematurely or not.

All efficacy analysis will be performed on the ITT population. The safety data will be analyzed on the safety analysis set

Endpoints

- **Primary endpoint : Overall survival**

Overall survival is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
OS will be estimated using the Kaplan-Meier method, and will be compared between arms at a 2-sided significance level of 5% (Log-Rank test supported by a stratified Cox regression adjusted on randomization strata). Median OS per arm associated with its 95% confidence interval with be presented.

- **Secondary endpoint :**

- **Survival rate at one year** will be presented per arm. Associated 2-sided 95% CI will be provided.
- **Objective response rate according to RECIST 1.1:** ORR is defined as the rate of patients with an observed tumor response (CR or PR) as best response seen during all over the study treatment period and evaluated according to RECIST 1.1. Patients without any tumor assessment following study treatment initiation and not died of neoplasic cause will be considered as non-evaluable patients. ORR rate will be presented by arm associated with its corresponding 95% CI and compared between arms using chi² or Fisher exact test if needed. Definition RECIST 1.1: Appendix 4.
- **Progression free survival**: PFS is defined as the time from randomization until the date of the first progression assessment according to RECIST version 1.1 or death (by any cause in the absence of progression). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

The first progression assessment will be based on investigator-recorded assessments. or on central review of the radiological scans.

As for OS, PFS will be estimated using the Kaplan-Meier method, and will be compared between arms at a 2-sided 5% significance level Log-Rank test.

- **Safety tolerability according to CTCAE version 4.0:** The assessment of safety will be based mainly on the frequency of adverse events (AE).

  Descriptive statistics will be provided to evaluate the number of patients with at least:
  - One adverse events and the number of adverse events by arm,
  - One Serious AE,
  - One AE with grade 3 or above.

  Comparison between arms will be performed using chi² test or fisher exact test if needed.

  Adverse events of special interest should be described in addition to safety analysis based on system organ class and preferred term classifications
- **Quality of life according to EQ-5D and EORTC QLQ-ELD14 questionnaires every 6 weeks:** Quality of Life will be analyzed descriptively and according to the scoring manual. Absolute and relative variation compared to randomization time point will be calculated by patient. Evolution during time will be compared between treatment arms
- **PD-L1 testing by immunochemistery (IHC) by local and central laboratories**: Pronostic impact of PD-L1 on OS and PFS will be tested. Univariate and multivariate analysis will be implemented. Sub group analysis depending on PD-L1 level will be performed.
- **Geriatric mini data set (**restricted to patients ≥70 years old.): predictive impact of geriatric mini data set and its evolution over time on OS, PFS and toxicity. Univariate and multivariate analysis will be implemented. This analysis will be performed, using baseline geriatric characteristics included in the geriatric mini data set as stratification variables. To identify factors potentially influencing OS, PFS or toxicity, a multivariate Cox model will be constructed with stepwise variable selection. We'll use univariate Cox models to select baseline variables (p=0·20) for the multivariate analysis.

9 RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

9.1. Access to data

In compliance with GCP:

- the sponsor is in charge of obtaining the agreement of all parties involved in the study to ensure direct access to all sites of study conduct, source data, source documents and reports with the aim of checking quality and of an audit by the sponsor,
- investigators will make available to persons in charge of monitoring, checking of quality or audit of the study documents and individual data which are strictly necessary for such checking, in compliance with legislative and regulatory conditions in force (articles L.1121-3 and R.5121-13 of the French public health code).

9.2. Source documents

Source data defined as all documents or original items which make it possible to demonstrate the existence or accuracy of data or of a finding recorded in the clinical study will be kept for 15 years by the investigator or by the hospital if it involves a hospital medical dossier.

Source documents consist of a medical dossier, originals of laboratory test results, imaging examination reports, etc.

9.3. Confidentiality of data

In compliance with conditions concerning confidentiality of data to which persons in charge of quality control of the research involving the human person study have access (article L.1121-3 of the French public health code), in compliance with conditions pertaining to confidentiality of information in particular concerning the type of investigational medicinal products, the tests, persons who are Patients in the study and results obtained (article R. 5121-13 of the French public health code), persons having direct access will take all necessary precautions with the aim of ensuring confidentiality of information pertaining to the investigational medicinal products, tests, the persons who are Patients in the study and in particular concerning their identity as well as that of results obtained.

These persons, in the same capacity as the investigators themselves, are Patient to professional secrecy (according to conditions defined by articles 226-13 and 226-14 of the French penal code).

During the study or at its end, data collected on persons who are Patients in the study and forwarded to the sponsor by the investigators (or all other specialised participants) will be made anonymous (deletion of Patients' names).

They must not in any event clearly reveal the names of the persons concerned or their address.

Only the first letter of the surname and of the first name of the Patient are recorded, together with the code number specific for the study indicating the order of inclusion of Patients.
The sponsor will make certain that each person who is a Patient in the study has provided his or her written agreement for access to his/her personal individual data and strictly necessary for quality control of the study.

10 QUALITY CONTROL AND ASSURANCE

A Clinical Research Associate (CRA) designated by the sponsor will ensure proper conduct of the study and the quality of data collected, in agreement with the Standard Operating Procedures applied in the CHU of Rennes and in compliance with Good Clinical Practice as well as legislative and regulatory conditions in force.
The investigator and members of his team agree to make themselves available at Quality Control visits carried out at regular intervals by the Clinical Research Associate. At these visits the following items will be reviewed:

- informed consent,
- compliance with study protocol and procedures defined in it,
- quality of data collected in the case report forms: accuracy, missing data, consistency of data with "source" documents (medical dossiers, appointment diaries, originals of laboratory test results, etc.),
- management of possible products.

In addition, the investigators agree to receive quality assurance audits performed by the sponsor as well as inspections performed by the Competent Authorities. All data, all documents and reports can be Patiented to audits and regulatory inspections without being opposed by medical secrecy.

11 ETHICAL CONSIDERATIONS

11.1. Regulatory and institutional review

The protocol, information form and certificate of consent of the study will be submitted to the relevant independent ethics committee (IEC) for review.
Notification of a favourable opinion from the IEC will be transmitted to the sponsor of the study and to the competent Authority. An application for authorisation will be sent by the sponsor to local regulatory authority prior to start of study.

11.2. Substantial changes

In case of a substantial change made to the study protocol by the investigator, it will be approved by the sponsor. The latter must obtain prior to start of study a favourable opinion from the ethics committee and authorisation from the relevant health authority in the setting of their respective competence. Additional consent from persons participating in the study will be collected if necessary.

11.3. Information for patients and written informed consent form

Patients will be completely and truly informed in terms which are understandable to them of the objectives and constraints of the study, the possible risks incurred measures of supervision and safety necessary, of their right to refuse to participate in the study or of the possibility of retracting their agreement at any time.
All this information is contained in an information and consent form given to the patient. Free, informed and written consent from the patient will be collected by the investigator, or a doctor representing him prior to final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient; the investigator will keep the original of it.

12 DATA PROCESSING AND RETENTION OF DOCUMENTS AND DATA

12.1. Case report forms and data entry

All information required by the study protocol must be recorded in the case report forms and an explanation must be provided for any missing data. Data must be collected progressively as obtained and recorded explicitly in the case report forms.
An electronic case report form (e-CRF) will be made available and data entry will be made in centres through a WEB interface (Clinsight software, Ennov, Paris (75), France). It solely requires an internet connection and a browser. An aid document for use of this tool will be provided to investigators. The interface between the CRA and the investigator thus will be promoted, making possible the collection and control of data at a distance. Tests of control of consistency of data will be incorporated in electronic format. An audit function is incorporated in the e-CRF thus making it possible to follow any change in study data. This function also makes it possible to clearly identify the person who made a change as well as the date. A justification possibly can be incorporated in comment.

If requested, a paper copy will be printed at the end of the study, authenticated (dated and signed) by the investigator and a copy will be sent to the sponsor and archived.
Data analysis will be carried out by statisticians of the Biostatistics Unit Department of Pharmacoly of Rennes.

12.2. CNIL

This study falls within the scope of the "Methodology of Reference" (MR-001) in application of conditions of article 54 line 5 of French law no. 78-17 of 6 January 1978 modified pertaining to data processing, computer files and liberties. This change has been authorised by the decision of 5 January 2006. The CHU of Rennes, sponsor of the study, has signed an agreement of compliance with this "Methodology of Reference".

12.3. Archiving

The following documents will be kept in the respective departments until the end of the period of practical utility.
These documents are:

- The study protocol and its annexes, and possible amendments,
- The original signed informed information and consent forms,
- Individual data (authenticated copies of raw data),
- Monitoring documents,
- Statistical analyses,
- The study final report.

At the end of the period of practical utility, the documents will be archived by the sponsor for at least 25 years after the end of the study or its early discontinuation, in compliance with institutional practices.
Archived documents cannot be moved or destroyed without agreement of the sponsor. All data, all documents and reports can be patiented to an audit or inspection.

13 INSURANCE

The Sponsor will take out, for the duration of the study, insurance covering his own civil responsibility as well as that of all doctors involved in conduct of the study. He will also insure the total compensation of all harmful consequences of the study for persons who are Patients in it and his heirs, except for evidence to be provided that the harm is not causally related to his fault or that of any participant, without it being possible to oppose the intervention of a third party or the voluntary withdrawal of a person who had initially consented to be a Patient in the study.

14 STUDY FEASIBILITY

The Groupe Français de Pneumocancérologie performed multiples studies in non small cell lung cancer, some of them focused on elderly patients. ESOGIA, a phase III randomized study included 495 patients in less than 3 years, TARSEQ, randomized phase II 132 inclusions in 1 year.

15 RULES PERTAINING TO PUBLICATION

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the responsible investigators. The co-authors of the report and of publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers.
Rules on publication will follow international recommendations (N Engl J Med, 1997; 336:309-315).
The study will be recorded on a freely accessible website (Clinical Trials) prior to inclusion of the first patient in the study.

16 LIST OF APPENDIX

Appendix 1 : List of investigators
Appendix 2: Notes d'information et formulaires de consentement
Appendix 3: American Joint Committee on Cancer Staging Criteria for Lung Cancer
Appendix 4: RECIST (version 1.1) for Tumor Response
Appendix 5: Eastern Cooperative Oncology Group Performance Status
Appendix 6 : Echelles de qualité de vie EQ5D et EORTC QLQ-ELD14
Appendix 7 : Information on NIVOLUMAB
Appendix 8 : Nivolumab and Ipilimumab Management Algorithms
Appendix 9: Geriatric mini data set