SPLENDOUR

ETOP 5-12
EORTC 08111

A randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC

Survival imProvement in Lung cancEr iNduced by DenOsUmab theRapy

Sponsor: European Thoracic Oncology Platform (ETOP)

Coordinated by European Organization for Research and Treatment of Cancer (EORTC)

In collaboration with

CECOG
Central European Cooperative Oncology Group

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In collaboration with Amgen.

Protocol Signature Page

SPLENDOUR

Approved by:

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25-APR-2014

Date

Rolf Stahel
Trial Co-Chair and Chairman of ETOP

F.S. 15

Date

Principal Investigator Protocol Signature Page

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I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by ETOP and EORTC, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drugs and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator:_____

Institution's name and place:_____

_____ _____

Signature Date

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1. Protocol Summary

SPLENDOUR

A randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC

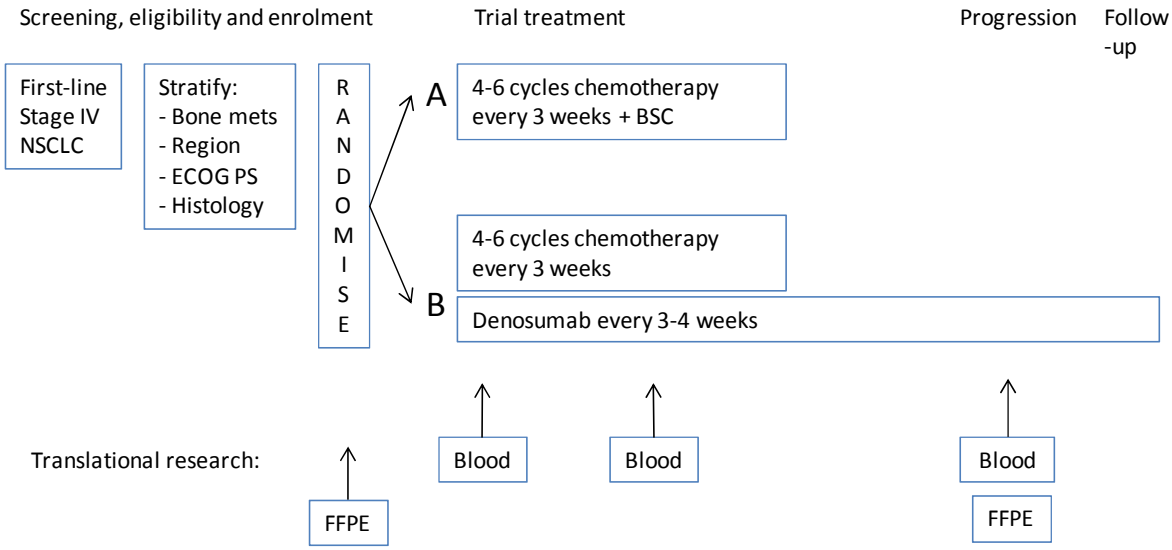
Sponsor: European Thoracic Oncology Platform (ETOP)

Trial Coordinator: European Organization for Research and Treatment of Cancer (EORTC)

Pharma Partner: AMGEN

Population: Patients with untreated advanced NSCLC, PS 0-2, with or without bone metastasis at diagnosis

Design:



Sample size: 1000

Trial treatment:

ARM A: 4 – 6 cycles of doublet chemotherapy + best supportive care

ARM B: 4 – 6 cycles of doublet chemotherapy + denosumab 120 mg, s.c. every 3-4 weeks until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued upon tumour progression and concomitantly to

subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Doublet chemotherapy (3 week cycles):

CisGem: cisplatin 75 mg/m^2, i.v. day 1, plus gemcitabine 1250 mg/m^2, i.v., days 1 and 8

CarboGem: carboplatin AUC 5 , i.v. day 1, plus gemcitabine 1250 mg/m^2, i.v. days 1 and 8

In patients with non-squamous cell histology only, pemetrexed may be administered instead of gemcitabine:

CisPem: cisplatin 75 mg/m^2, i.v. day 1, plus pemetrexed 500 mg/m^2 i.v. day 1

CarboPem: carboplatin AUC 5 , i.v. day 1, plus pemetrexed 500 mg/m^2 i.v. day 1

Daily supplementation with calcium (500 mg) and vitamin D (≥400U) will be administered to all patients (mandatory for pts in arm B (denosumab) and recommended in arm A if they receive zoledronic acid according to local guidelines). Patients treated with pemetrexed will receive folic acid 0.4 – 1 mg/day and vit B12 1000 IU s.c. 1 week before first dose and then every 3 cycles.

Rationale:

Denosumab is a fully human monoclonal IgG2 antibody binding with a high affinity to RANKL. In a pivotal phase III trial in patients with solid tumors (other than breast or prostate) or multiple myeloma and bone metastasis, denosumab was shown to be non inferior – with a trend toward superiority – to zoledronic acid in delaying time to first SRE (HR, 0.84; 95% CI, 0.71 to 0.98; non-inferiority P= .0007, representing 16% reduction in hazard). Regarding non-small cell lung cancer (NSCLC), the effect of denosumab on time to first on-study SRE relative to zoledronic acid by tumour stratification factors resulted in a HR of 0.84 for NSCLC (n=702; 95% CI, 0.64 to 1.10; P=0.20). Overall survival was similar between both treatment groups. Interestingly, an ad hoc analysis examining overall survival was performed for distinct strata, demonstrating an OS HR of 2.26 for myeloma (n=180; 95% CI, 1.13 to 4.50), and 1.08 for other solid tumours (95% CI, 0.90 to 1.30).

In the 811 patients with lung cancer, including non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), denosumab treatment was associated with significantly improved overall survival versus zoledronic acid (8.9 vs 7.7 mos., HR=0.80 (95% CI, 0.67–0.95), P = 0.01). Specifically, in NSCLC, a HR of 0.79 (9.5 vs. 8.1 mos., 95% CI, 0.65 to 0.95) was described. Further subgroup analysis could demonstrate this OS difference through distinct NSCLC histologic subtypes, maybe to some higher extent in squamous histology (adenocarcinoma 9.6 vs. 8.2 mos., HR=0.80 (95% CI, 0.62–1.02), P = 0.0751, and squamous 8.6 vs. 6.4, HR=0.68 (95% CI, 0.47–0.97), P = 0.0350).

Cancer metastasis to the bone results from the active engagement and interaction with the bone microenvironment. RANKL-mediated increased bone turnover and osteoclast activity may mechanically enhance tumour growth. RANK and RANKL expressions have been observed in some tumour types with early clinical data, suggesting a potential anti-tumour effect of RANK pathway inhibitors.

This phase III prospective trial will evaluate the potential of denosumab - as an antitumour agent - to increase survival of advanced NSCLC with or without bone metastasis.

Objectives and endpoints:

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

Secondary objectives are to compare progression free survival (PFS) and response rate (RR, based on RECIST 1.1) in patients treated with standard first-line chemotherapy with or without denosumab, and to assess the tolerability of the two regimens.

The translational research objective is to evaluate potential predictive biomarkers for denosumab activity.

Primary endpoint: overall survival

Secondary endpoints:

- Progression free survival (PFS) based on RECIST 1.1
- Response based on RECIST 1.1
- Toxicity profile of denosumab; toxicities will be assessed and graded according to CTCAE v 4.
- Evaluation of potential predictive biomarkers for denosumab activity

Eligibility criteria:

Inclusion criteria:

- Histologically or cytologically confirmed advanced stage IV non-small cell lung carcinoma (NSCLC), according to 7th TNM classification
- Age ≥ 18 years
- ECOG performance status 0-2
- Measurable or evaluable disease (according to RECIST 1.1 criteria).
- Availability of tumour tissue for translational research:
  - preferred: FFPE block from primary tumour or metastasis,
  - alternatively: cell block
  - if no block available: 10 unstained slides with wax protection
- Adequate haematological function: neutrophils ≥ 1.5 $\times 10^9$/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL
- Adequate liver function:
  - ALT ≤ 3 × ULN (≤ 5 × ULN if liver metastasis are present)
  - Total bilirubin < 2 x ULN
- Adequate renal function: calculated creatinine clearance ≥ 30 mL/min (according to the formula of Cockroft-Gault)
- Life expectancy of at least 3 months.

- Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 14 days before beginning treatment.
- All sexually active men and women of childbearing potential must use an effective contraceptive method during the study treatment and for a period of at least 5 months following the last administration of trial treatment.
- Written Informed Consent must be signed and dated by the patient and the investigator prior to any trial-related intervention for
  a) Trial treatment
  b) Submission of biomaterial for central testing

Exclusion criteria:

- Patients with presence of documented sensitizing EGFR activating mutation or ALK rearrangements (screening following local standards is optional, but strongly encouraged in non-squamous histology)
- Patients with documented brain metastases (systematic screening of patients not mandatory)
- Prior chemotherapy or molecular targeted therapy for metastatic disease, with the exception of neoadjuvant or adjuvant chemotherapy or definitive radio-chemotherapy, if terminated more than 6 months before registration.
- Any investigational agent(s) within 30 days prior to randomisation
- Concurrent bisphosphonate administration
- Oral/ dental conditions (by visual inspection):
  - Prior history or current evidence of osteomyelitis / osteonecrosis of the jaw
  - Active dental or jaw condition which requires oral surgery
  - Planned invasive dental procedure for the course of the trial
  - Non-healed dental or oral surgery
- Evidence of any medical condition which would impair the ability of the patient to participate in the trial or might preclude therapy with trial drugs (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease, active infection, uncontrolled diabetes mellitus; uncontrolled arterial hypertension ≥ 150/100 mmHg, history of myocardial infarction in the last 3 months.)
- Documented active infection with Hepatitis B virus or Hepatitis C virus, known infection with human immunodeficiency virus (HIV)
- Known hypersensitivity to any of the components of the treatment
- Severe, uncorrected hypocalcaemia or hypercalcaemia
  - hypercalcaemia: total calcium >3.1 mmol/l, corrected calcium (with albumin level) >3 mmol/l
  - hypocalcaemia: total calcium <2 mmol/l, corrected calcium (with albumin level) < 1.9 mmol/l
- Legal incapacity or limited legal capacity

- Medical or psychological condition which in the opinion of the investigator would not permit the patient to complete the trial or sign meaningful informed consent
- Women who are pregnant or breastfeeding
- Any concurrent malignancy other than adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ breast carcinoma. (Patients with a previous malignancy but without evidence of disease for ≥ 2 years will be allowed to enter the trial).
- Any previous exposure to denosumab, with the exception of a maximum of 2 previous doses of denosumab (Prolia®) more than 6 month before enrolment for osteoporosis treatment/prevention
- Previous bisphosphonate exposure which
  - exceeds 2 prior doses of i.v. bisphosphonates

  AND/OR
  - exceeds a cumulative exposure of 1 year oral bisphosphonates.

Statistical considerations:

Phase III trial, with futility Interim Analysis (IA).

Primary endpoint: Overall Survival (OS)

Patient population: All randomised patients (ITT)

Power, sample size and trial duration:

Using 90% power and a one-sided type I error of 2.5%, demonstration of an increase in overall survival to 11.25 months in the experimental arm relative to 9 months in the control arm (equivalent to HR = 0.80) requires observation of 847 deaths. The total sample size is 1000 patients, which could increase in case the event rate is lower than expected.

Interim Futility Analysis (IA):

The trial is designed with a futility IA, based on a non-binding O'Brien-Fleming boundary, at 30% of the overall trial information time. This will be an event driven IA, when 254 deaths have been observed overall, and is expected to occur by 22.5 months from the date the first patient is randomised. At this time accrual is expected to have reached approximately 58% of the total.

Duration: If the trial is completed with full accrual, the maximum overall duration is expected to be approximately 51 months.

Translational research:

The collection of tumor and serum samples is required in this trial. This material will constitute an invaluable and precious source for biological research in the context of this trial.

Translational research looking at potential predictive biomarkers of denosumab activity will be performed on serum and tumor tissue.

Analysis of serum samples by ELISA includes CTX, osteoprotegerin (OPG), propeptide of type I procollagen (PINP), osteopontin (OPN), free RANKL and RANKL-OPG. These may

be changed and the panel of serum biomarkers will include best candidates at the time of analysis.

The following evaluations are proposed for translational research on FFPE tumor tissue: IHC (and/or RT-PCR) for RANKL & RANK, and potentially NF-kappaB activation evaluation (RT-PCR and/or IHC) and bone sialoprotein (BSP) which in tumour has been correlated with bone metastasis progression and high levels are associated with poor prognosis; and osteopontin (OPN) levels in primary tumour may correlate with tumour aggressiveness. Again, these may be adapted in the future to include best candidates available at the time of evaluation.

Trial schedule

	≤ 28 days prior rando	At rando	Cyc 1	Cyc 2	Cyc 3	Cyc 4	Cyc 5*)	Cyc 6*)	30 (+/- 5) days after stop of first line chemotherapy	After stop of first line chemotherapy, before first progression [17]	At first pro-gression	After first progres-sion	Arm B: 30 (+/- 5) days after stop of denosumab	Follow-up: every 8 weeks[18]
Written informed consent [1]	X													
Medical history	X													
Tumour material [2]		X												
Blood sample [3]			X		X						X			
Physical exam, PS, blood pressure, weight	X		X	X	X	X	X	X	X	X	X		X	
Baseline symptoms	X													
Haematology [4]	X		X	X	X	X	X	X	X		X		X	
Chemistry [5]	X		X	X	X	X	X	X	X	X [16]	X	X [16]	X	
Pregnancy test [6]	X													
PET-CT or CT [7]	X													
CT scan [8]						X			X [11]	X [11]	X			
Bone scan [9]	X					√			√ [11]	√ [11]	√			
Brain CT or MRI [10]	√					√			√ [11]	√ [11]	√			
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X
Cis or Carbo[12]			X	X	X	X	X	X						
Gemcitabine[13]			X	X	X	X	X	X						
Pemetrexed (non squamous only) [14]			X	X	X	X	X	X						
Arm B: Denosumab [15]			X [15]	X	X	X	X	X	X	X		X		
Survival status and further lines of treatment									X	X	X	X		X

X = mandatory; √ = if clinically indicated

*) Administration of cycles 5 and 6 follows local investigator decision

Legend for schedule:

1 – before any trial-specific intervention; maximum two weeks before randomisation

2 – submit tumour material from biopsy: FFPE block or cell block; or at least 10 unstained slides

3 – A blood sample for translational research should be taken at baseline, on day 1 of cycle 3, and at the time of first progression (within 4 weeks of PD).

4 – Haematology: haemoglobin, neutrophils, platelets

5 – Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

6 – Pregnancy test for women of childbearing potential within 14 days before start of treatment

7 – PET-CT or CT of thorax and abdomen at screening.

8 – CT of thorax and abdomen on day 1 of cycle 4, then every 12 weeks until first progression has been fully documented (see also footnote 10); thereafter according to local standard of care.

9 – In the event of equivocal results, further confirmation using bone MRI, CT, X-Ray or biopsy is recommended. Bone scan at baseline not required for patients who have undergone a PET-CT at baseline; Bone imaging (including bone scan) during treatment only in case of suspected bone metastases.

10 – Brain CT or MRI in case of clinically suspected brain metastasis.

11 – For patients who discontinued per-protocol first-line chemotherapy trial treatment due to toxicity rather than progressive disease, restaging (CT scan chest and abdomen, brain scan if applicable) should be repeated if not already performed within 30 days prior to the last dose of trial treatment, and then every 12 weeks until progression.

12 – Choice of the investigator

13 – Gemcitabine (on days 1 and 8 of cycle) OR pemetrexed on day 1 of cycle will be delivered in addition to the platinum compound according to local investigator.

14 – Pemetrexed option is restricted to non-squamous histology.

15 – Denosumab is administered every 3-4 weeks until unacceptable toxicity or patient refusal. In cycle 1, an additional dose will be given on day 8. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment.

16 – After first-line chemotherapy, while still on denosumab treatment: only total calcium, albumin

17 - After first line per protocol chemotherapy, clinical FU including physical exam should be according to local standard of care, according to denosumab schedule and subsequent anticancer treatment schedules, every 6-8 weeks, until first progression. In the observation arm, adverse events have to be documented at the same schedule.

18 – After first progression has been fully documented, visits and imaging (CT) will be done according to local standard of care. Survival status and adverse events will be captured every 8 weeks until death. In arm B denosumab treatment continues for an unlimited time.

2. List of abbreviations

ALT	Alanine transaminase
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	Epidermal growth factor receptor
FFPE	Formalin fixed, paraffin embedded
GCP	Good Clinical Practice
IB	Investigator brochure
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
IP	Investigational Product
ITT	Intention to treat
HR	Hazard ratio
LLN	Lower limit of normal lab value
NSCLC	Non-small cell lung cancer
OPG	Osteoprotegerin
ORTA	Online Randomised Trials Access
OS	Overall survival
PFS	Progression free suvival
PINP	Propeptide of type 1 procollagen
RANK	Receptor activator of nuclear factor-KappaB
RANKL	Receptor activator of nuclear factor-KappaB ligand
RDC	Remote data capture
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SmPC	Summary of product characteristics
SRE	Skeletal related event
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal lab value
VEGF	Vascular endothelial growth factor

3. Background and Rationale

3.1. Bone metastasis in lung cancer

Lung cancer is the most common neoplasm worldwide, and overall survival rates are poor, with a median and 5-year survival expectations in advanced disease of about one year and less than 5% of patients, respectively. As the life expectancy of individuals with lung cancer increases, symptom control measures are growing in importance. Bone metastases represent a significant cause of morbidity in patients with advanced cancer and are common in lung cancer. Notably, about 30-50% of patients suffering from lung cancer develop bone metastases at some point, affecting 2/3 of them already at the time of diagnosis.

3.2. Skeletal Related Events (SREs) in lung cancer

Patients with metastatic bone disease may suffer from skeletal-related events (SREs), such as fractures, pain requiring radiation or bone surgery, spinal cord compression, – severely affecting their quality of life as well as absorbing significant hospital and financial resources. Owing to short survival times, data on the incidences of SREs are limited. Lung cancer patients are known to present with a high frequency of SREs, comparable to other solid tumours often metastasizing to bone, like breast and prostate cancers [1,2], while the occurrence of NSCLC SRE was shown to predict an unexpectedly short life expectancy for these patients [3].

3.3. Prevention of SREs

3.3.1. Zoledronic acid

Zoledronic acid acts on bone metabolism by disrupting the HMG-CoA reductase pathway and blocking osteoclastogenesis, as well as osteoclast cytoskeletal arrangement. Bisphosphonates have shown efficacy in randomised placebo-controlled trials for preventing and delaying SREs and improving QoL in patients with solid tumours, including NSCLC, while concomitantly preventing the increase in pain that accompanies progression of malignant bone disease [1,2,4]. Clinical experience suggests that bisphosphonates are rarely used in treatment regimens for NSCLC despite evidence that they are an effective treatment of bone metastases and prevention of SREs in this population [1]. One of the reasons for this may be the potential adverse effects of these agents. Orally administered bisphosphonates are associated with gastrointestinal intolerance, while nephrotoxicity and osteonecrosis of the jaw are usually linked with i.v. agents [5-7].

3.3.2. Targeting Receptor Activator of NF-KappaB (RANK) pathway

Recently, targeting the osteoprotegerin (OPG)/receptor activator of nuclear factor-KappaB ligand (RANKL)/(RANK) pathway was demonstrated to be an interesting strategy in patients suffering from virtually all bone-metastatic advanced solid tumours [8-10].

The RANK pathway plays a major role in osteoclasts function and therefore contributes to the subtle regulation of bone turnover. RANK is a member of the tumour necrosis factor receptor (TNFR) superfamily. RANK and OPG are both receptors for RANKL. However, whereas RANK signaling is stimulated upon RANKL binding, OPG is a secreted decoy receptor that acts as a natural inhibitor of the pathway [11]. Biologically, RANKL is a potent osteoclastogenic factor expressed on osteoblasts and osteocytes, promoting survival, proliferation, differentiation, and activation of mature osteoclasts. While the RANK

pathway is specifically involved in bone homeostasis, its deregulation was shown to be an initiator of SREs in cancer.

3.4. Denosumab

Denosumab is a fully human monoclonal IgG2 antibody binding with a high affinity to RANKL. It is specific and does not demonstrate significant binding to other members of the TNF ligand superfamily. As a result of its specific mechanism of action on the bone matrix, denosumab has become a new option for the treatment of osteoporosis [12].

In breast cancer, denosumab was demonstrated superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; P = .01 superiority), associated with a greater reduction in bone turnover markers. Overall survival, disease progression, and rates of adverse events were similar between groups [10].

In a pivotal phase 3 trial in patients with solid tumours and multiple myeloma (other than breast or prostate) and bone metastasis, denosumab was shown to be non-inferior – with a trend toward superiority – to zoledronic acid in delaying time to first SRE (HR, 0.84; 95% CI, 0.71 to 0.98; P= .0007, representing 16% reduction in hazard). Regarding NSCLC, the effect of denosumab on time to first on-study SRE relative to zoledronic acid by tumour stratification factors resulted in an HR of 0.84 for NSCLC (95% CI, 0.64 to 1.10; P=0.20) [9].

3.5. Survival impact of denosumab treatment

Overall survival in solid tumours was similar between both treatment groups. Interestingly, an ad hoc analysis examining overall survival was performed for three distinct strata, demonstrating an OS HR of 2.26 for myeloma (95% CI, 1.13 to 4.50), and 1.08 for other solid tumours (95% CI, 0.90 to 1.30). In the 811 patients with lung cancer, including non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), denosumab treatment was associated with significantly improved overall survival versus zoledronic acid (8.9 vs 7.7 mos., HR, 0.80 (95% CI, 0.67–0.95), P = 0.01). Specifically, in NSCLC, a HR of 0.78 (9.5 vs. 8.0 mos., 95% CI, 0.65 to 0.94) was described, while the same trend remained in a statistically non-significant way in SCLC (7.6 vs. 5.1 mos., HR, 0.81 (95% CI, 0.52–1.26), P = 0.3580). Further subgroup analysis could demonstrate this OS difference through distinct NSCLC histological subtypes, maybe to some higher extent in squamous histology (adenocarcinoma 9.6 vs. 8.2 mos., HR 0.80 (95% CI, 0.62–1.02, P = 0.0751 and squamous 8.6 vs. 6.4 mos., HR 0.68 (95% CI, 0.47–0.97) P = 0.0350) [9].

3.6. Biological hypothesis for direct antitumor effect of denosumab

Apart from bone matrix cells, the transmembrane RANK protein is strongly expressed on lymphocytes, dendritic cells, fibroblasts, and mammary gland and RANK mRNA is also found in skeletal muscle, liver, small and large intestine and adrenal gland [13]. Of therapeutic interest, its presence was also demonstrated in some specific types of cancer cells, notably in NSCLC, osteosarcoma as well as in breast and prostate cancer [14-16].

A direct impact of RANK and RANKL on tumour cell proliferation has been hypothesized, with a potential similar stimulatory effect as observed on osteoclasts. RANK signalling accelerated tumorigenesis in mouse mammary tumour virus (MMTV)-RANK transgenic mice as well as in the MMTV-Neu transgenic mouse model [17,18]. In animal models, RANKL was shown to increase invasiveness of mammary and prostate cancer as measured by the propensity of the tumours to generate metastatic spread, notably to the lung [19]. Promotion of cell migration was also consistently demonstrated in xenograft models using other breast, prostate and melanoma cancer cell lines [20,21].

Interestingly, the implication of NF-κB – a crucial component of RANK signalling – in lung tumour development is progressively being recognized. Notably, using genetically-engineered mouse models of lung adenocarcinoma, in which the tumours are initiated by oncogenic KRAS activation in lung epithelial cells, the NF-κB pathway, both in tumour epithelial cells and in myeloid cells, was recently shown to participate in tumour development [22-27].

3.7. Biomarkers in RANK pathway inhibitor trial

3.7.1. RANK and RANKL tumour cell expression

Very few data are available about RANK and RANKL expression prevalence in NSCLC. IHC methodological limitations make the testing process very delicate and hardly reproducible to date. The available IHC data in 42 NSCLC demonstrate a positivity of RANK and RANKL in respectively 56% and 75% among lung adenocarcinoma and 34% and 19% among squamous cell carcinoma [28]. In addition, RT-PCR data presented in a poster by Tometsko in 2006 show that RANK mRNA expression was significantly higher in primary human lung tumours than in normal lung tissue, and is detectable on human lung cell lines isolated from various metastatic sites. By flow cytometry, high RANK surface protein expression was detected on cell lines that were isolated from bone metastases while it was low on cell lines isolated from metastases in the pleural cavity.

Serum measurement of RANKL can be done through a quantitative determination of total (free RANKL and RANKL complexed to OPG) soluble RANKL in serum and osteoprotegerin (OPG) levels to provide surrogate measurement of baseline status of the RANKL-RANK-OPG pathway.

3.7.2. Bone resorption markers

The osteoclasts cause breakdown of type I collagen transverse cross-links, the main constituent of the bone's organic matrix, resulting in the release of degradation molecules such as pyridinoline, deoxypyridinoline, N-telopeptides (NTX) and C-telopeptides (CTX). N-telopeptide is one of several unique breakdown products of type I collagen released into circulation with degradation of bone. These products are released into the blood and excreted in the urine, and constitute markers of bone resorption and formation. Urinary N-telopeptide levels have been shown to be extremely sensitive measures of bone resorption when corrected by urinary creatinine levels [29].

Zoledronic acid and denosumab treatments immediately and consistently reduced urinary N-telopeptide/creatinine ratios. The detection of the recent CTX markers in blood is associated with the presence and progression of bone metastases and is linked to the prognosis and the response to pharmacological treatment [30]. Normalisation of NTX levels with zoledronic acid is associated with improved survival in NSCLC [31]. Osteopontin (OPN) levels in advanced NSCLC correlate with therapeutic response and survival [32]. Propeptide of type 1 procollagen (PINP) is raised in the serum of lung cancer patients compared to normal sera [33].

3.8. Trial hypothesis

Although both the HMG-CoA reductase and RANK pathways are physiologically involved in bone turnover, the RANK pathway was specifically highlighted in preclinical and clinical studies that reported an increased expression of the RANK/RANKL proteins and abnormal OPG/RANKL ratios in patients having cancer with bone metastases. Cancer metastasis to

the bone results from the active engagement and interaction with the bone microenvironment. RANKL-mediated increased bone turnover and osteoclast activity may enhance tumour growth in bone by mechanically facilitating cancer cell establishment. In addition, RANK/RANKL expression per se has been observed in some tumour types, and RANK inhibitors might reduce tumour aggressiveness and metastatic capabilities via distinct mechanisms.

The retrospective, unplanned nature of lung cancer survival data imposes some limitations in interpreting these data and implies bias risks. However, based on previous data involving the RANK pathway in tumour biology, it is obvious that this warrants further pre-clinical and prospective clinical investigation. This trial aims at evaluating the potential of denosumab – as an antitumor agent – to increase survival of advanced NSCLC with or without bone metastasis, in the context of a strong and unique European collaboration.

3.9. Trial treatment

All patients will receive standard, platinum-based chemotherapy combined with pemetrexed or gemcitabine for first-line NSCLC. The number of cycles of doublet chemotherapy will be between 4 and 6 cycles, according to the institution's policy. Similarly, pemetrexed or erlotinib maintenance treatment after doublet chemotherapy is allowed in both arms. Patients will be randomised between Arm A, chemotherapy plus best supportive care (BSC), and Arm B, chemotherapy plus denosumab. Denosumab will be administered every 3-4 weeks, and should be continued beyond chemotherapy lifelong or until unacceptable toxicity or patient refusal.

3.10. Overall risk/benefit assessment

All patients will receive standard first-line treatment for NSCLC. The addition of denosumab to the standard treatment poses only a small risk for toxic effects, and the protocol prescribes precautions to be taken to avoid these. Denosumab has potential to prolong overall survival in these patients. Overall, the trial design offers a favourable benefit to risk ratio.

3.11. Rationale for trial design

The hypothesis underlying the trial is that the addition of denosumab will significantly prolong overall survival. Both survival being primary endpoint and thus not subjected to bias, as well as denosumab being continued over a long period of time justify an open-labelled strategy. An open-label randomisation is justified since denosumab will be administered at a 3- or 4-week schedule as opposed to the 3-week chemotherapy, and since denosumab can be continued for an unlimited time after stop of chemotherapy.

4. Objectives and endpoints

4.1. General objectives

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

Secondary objectives are to compare progression free survival (PFS) and response rate (RR, based on RECIST 1.1) in patients treated with standard first-line chemotherapy with or without denosumab, and to assess the tolerability of the two regimens.

The translational research objective is to evaluate potential predictive biomarkers for denosumab activity.

Translational research looking at potential predictive biomarkers of denosumab activity will be performed in an exploratory manner on blood and tumor tissue.

4.2. Primary endpoint

Overall Survival (OS). For definition, see section 13.1

4.3. Secondary endpoints

4.3.1. Progression free survival (PFS) based on RECIST 1.1

4.3.2. Response based on RECIST 1.1

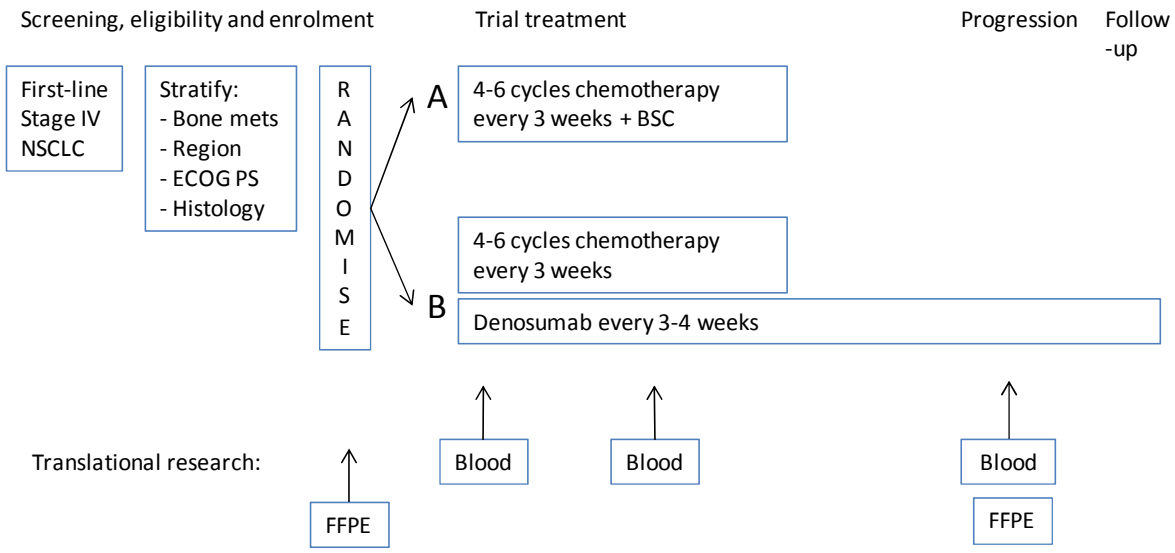
4.3.3. Toxicity profile of denosumab; toxicities will be assessed and graded according to CTCAE v 4.

4.3.4. Evaluation of potential predictive biomarkers for denosumab activity (see section 14 on biomaterial and translational research).

5. Trial design, duration and termination

This is a multinational, multi-center, randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC. The primary endpoint is overall survival (OS) measured from the date of randomisation.

Trial design:



Doublet chemotherapy cycles last 3 weeks:

CisGem: cisplatin 75 mg/m^2, i.v. day 1, plus gemcitabine 1250 mg/m^2, i.v., days 1 and 8

CarboGem: carboplatin AUC 5 , i.v. day 1, plus gemcitabine 1250 mg/m^2, i.v., days 1 and 8

In patients with non-squamous cell histology only, pemetrexed may be administered instead of gemcitabine:

CisPem: cisplatin 75 mg/m^2, i.v. day 1, plus pemetrexed 500 mg/m^2 i.v. day 1

CarboPem: carboplatin AUC 5 , i.v. day 1, plus pemetrexed 500 mg/m^2 i.v. day 1

Patients will be randomised to one of two treatment regimens as follows:

ARM A : 4 – 6 cycles of one of the above combinations + best supportive care

ARM B : 4 – 6 cycles of one of the above combinations + **denosumab 120 mg, s.c. every 3-4 weeks** until unacceptable toxicity, patient refusal or patient's death. Denosumab will be continued every 3-4 weeks upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Frequency of administration is 3-4 weeks and is left to investigator's preference. For practical reasons, it is encouraged to consider 3-weekly administration during first-line chemotherapy and 4-weekly schedule after first-line chemotherapy, in particular when no chemotherapy is delivered or when chemotherapy is not cycled on a 3-weeks basis.

Beyond primary analysis, all subjects randomised to ARM B and still benefitting from the drug will be offered denosumab at a dose of 120 mg s.c. until patient or physician elect to discontinue denosumab for any reason, and for a maximum of 2 years after the required number of 847 deaths for the final analysis has been reached.

Daily supplementation with calcium (500 mg) and vitamin D (≥400U) will be administered to all patients (mandatory for pts in arm B (denosumab) and recommended in arm A if they receive zoledronic acid according to local guidelines). Patients treated with pemetrexed will receive folic acid 0.4 – 1 mg/day and vit B12 1000 IU s.c. 1 week before first dose and then every 3 cycles.

Patient accrual is expected to be completed within 37 months including a run-in-period of 6 months. Treatment and follow-up is expected to extend the trial duration to a total of 51 months. All patients will be followed until death – thus follow-up estimated up to 3 years following the enrolment of the last patient.

The trial will end with the preparation of the final report, scheduled for month 56 after the inclusion of the first patient.

Systemic therapy beyond first-line trial treatment will be delivered according to local standards (including maintenance). Locoregional therapy is left to the investigator's discretion according to medical need.

6. Patient selection

Written informed consent needs to be obtained prior to any trial specific intervention.

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

6.1. Inclusion criteria

6.1.1. Histologically or cytologically confirmed advanced stage IV non-small cell lung carcinoma (NSCLC), according to 7th TNM classification

6.1.2. Age ≥ 18 years

6.1.3. ECOG performance status 0-2 (see below *)

6.1.4. Measurable or evaluable disease (according to RECIST 1.1 criteria).

6.1.5. Availability of tumour tissue for translational research:

- preferred: FFPE block from primary tumour or metastasis,
- alternatively: cell block
- if no block available: 10 unstained slides with wax protection

6.1.6. Adequate haematological function: neutrophils ≥ 1.5 $\times 10^9$/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL

6.1.7. Adequate liver function:

- ALT ≤ 3 × ULN (≤ 5 × ULN if liver metastasis are present)
- Total bilirubin < 2 x ULN

6.1.8. Adequate renal function: calculated creatinine clearance ≥ 30 mL/min (according to the formula of Cockroft-Gault)

6.1.9. Life expectancy of at least 3 months.

6.1.10. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 14 days before beginning treatment.

6.1.11. All sexually active men and women of childbearing potential must use an effective contraceptive method during the study treatment and for a period of at least 5 months following the last administration of trial treatment.

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

a) Trial treatment

b) Submission of biomaterial for central testing

* ECOG Performance Status:

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

6.2. Exclusion criteria

6.2.1. Patients with presence of documented sensitizing EGFR activating mutation or ALK rearrangements (screening following local standards is optional, but strongly encouraged in non-squamous histology)

6.2.2. Patients with documented brain metastases (systematic screening of patients not mandatory)

6.2.3. Prior chemotherapy or molecular targeted therapy for metastatic disease, with the exception of neoadjuvant or adjuvant chemotherapy or definitive radio-chemotherapy, if terminated more than 6 months before registration.

6.2.4. Any investigational agent(s) within 30 days prior to randomisation

6.2.5. Concurrent bisphosphonate administration

6.2.6. Oral/ dental conditions (by visual inspection):

- Prior history or current evidence of osteomyelitis / osteonecrosis of the jaw
- Active dental or jaw condition which requires oral surgery
- Planned invasive dental procedure for the course of the trial
- Non-healed dental or oral surgery

6.2.7. Evidence of any medical condition which would impair the ability of the patient to participate in the trial or might preclude therapy with trial drugs (e.g. unstable or uncompensated respiratory, cardiac, hepatic or renal disease, active infection, uncontrolled diabetes mellitus; uncontrolled arterial hypertension $\geq$ 150/100 mmHg, history of myocardial infarction in the last 3 months.)

6.2.8. Documented active infection with Hepatitis B virus or Hepatitis C virus, known infection with human immunodeficiency virus (HIV)

6.2.9. Known hypersensitivity to any of the components of the treatment

6.2.10. Severe, uncorrected hypocalcaemia or hypercalcaemia

- hypercalcaemia: total calcium >3.1 mmol/l, corrected calcium (with albumin level) >3 mmol/l
- hypocalcaemia: total calcium <2 mmol/l, corrected calcium (with albumin level) < 1.9 mmol/l

6.2.11. Legal incapacity or limited legal capacity

6.2.12. Medical or psychological condition which in the opinion of the investigator would not permit the patient to complete the trial or sign meaningful informed consent

6.2.13. Women who are pregnant or breastfeeding

6.2.14. Any concurrent malignancy other than adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ breast carcinoma. (Patients with a previous malignancy but without evidence of disease for ≥ 2 years will be allowed to enter the trial).

6.2.15. Any previous exposure to denosumab, with the exception of a maximum of 2 previous doses of denosumab (Prolia®) more than 6 month before enrolment for osteoporosis treatment/prevention.

6.2.16. Previous bisphosphonate exposure which

- exceeds 2 prior doses of i.v. bisphosphonates

AND/OR

- exceeds a cumulative exposure of 1 year oral bisphosphonates.

7. Investigator authorisation procedure

Investigators will be authorised to randomise patients in this trial only once they have returned the following documents to the ETOP/EORTC Headquarters:

7.1.1. The updated signed and dated curriculum vitae of the Principal Investigator in English with proof of GCP training.

7.1.2. The (updated) list of normal ranges for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.

7.1.3. The signed Confirmation of Interest by the investigator form (EORTC sites) stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Confirmation of Interest by the investigator form.

7.1.4. A copy of the favourable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the

version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.

7.1.5. A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.

7.1.6. The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the ETOP/EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the ETOP/EORTC Headquarters.

7.1.7. The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication.

7.1.8. An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorisation list", and will be allowed to register/randomise patients in the trial as soon as

7.1.9. All the above mentioned documents are available at the ETOP/EORTC Headquarters.

7.1.10. All applicable national legal and regulatory requirements are fulfilled.

Patient randomisation from centers not (yet) included on the authorisation list will not be accepted.

8. Patient screening and registration/randomisation

8.1. Screening

Complete the following steps to screen and enroll a patient on this trial.

8.1.1. Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention including submission of tissue for translational research.

8.1.2. Screening: Verify eligibility (including absence of EGFR mutation if tested) and register the patient in ORTA immediately after having signed informed consent. The date the Informed Consent Form and the consent to biological material submission section of the Informed Consent Form were signed by the patient and the date signed by the investigator are both required to complete the eligibility checklist.

8.1.3. Patients have to be randomised maximum two weeks after informed consent.

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomisation must be done before the start of the protocol treatment.

Patients should be registered immediately after signing informed consent directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive registration program, the investigator needs a username and a password (which can be requested at www.eortc.be/random).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to register patients via the EORTC call center. Registration via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (www.eortc.be/random) and it is updated annually.

Through Internet: www.eortc.be/random
If no connection available by phone: +32 2 774 16 00

8.2. Registration procedure for screening (step 1)

Standard information requested:

- EORTC institution number
- EORTC protocol number
- step number: 1
- name of the responsible investigator
- patient's code (maximum 4 alphanumerics)
- patient's birth date (day/month/year)

Protocol specific questions:

- date of written informed consent (day/month/year) signed by the patient and the date signed by the investigator are both required

At the end of the procedure, a patient sequential identification (SeqID) number will be assigned. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

8.3. Randomisation procedure (step 2)

Patients have to be randomised as soon as possible, but not later than 2 weeks after having obtained written informed consent.

A patient can only be randomised after verification of eligibility. Both the eligibility check and randomisation must be done before the start of the protocol treatment

Standard information requested:

- institution number
- protocol number
- name of the responsible investigator
- step number: 2
- choose the seqID of the patient from drop-down list
- patient's birth date (day/month/year)
- for EORTC sites: group affiliation
  - primary group affiliation
  - secondary group affiliation

Protocol specific questions:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- stratification factors
- date foreseen for protocol treatment start

Once eligibility has been verified, the treatment will be randomly allocated to the patient.

8.4. Stratification

Patients will be centrally randomised. A block design technique will be used for random treatment allocation stratifying by:

- Presence vs absence of bone metastases as assessed by bone scan or alternatively by PET-scan
- Geographical region according to pemetrexed availability, maintenance strategy, and standard of care
- ECOG performance status 0 or 1 vs 2
- Squamous vs other histology

Treatment allocation is not blinded (open label).

9. Investigational drug

Denosumab is the investigational drug used in this trial. Denosumab will be supplied.

Please consult the ***Drug Supply Manual*** for a description of drug supply logistics as well as labelling, packaging, handling, drug accountability and destruction of unused drugs.

9.1. Description of investigational drug

Denosumab (XGEVA®) is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology. It is indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

9.2. Packaging and labelling

Each vial contains 120 mg of denosumab in 1.7 ml of solution (70 mg/ml). Each 1.7 ml of solution contains 78 mg sorbitol (E420).

Pharmaceutical form: Solution for injection (injection). Clear, colourless to slightly yellow solution; may contain trace amounts of translucent to white proteinaceous particles.

9.3. Receipt of the drug

Denosumab will be supplied by Amgen directly to the sites. The investigational site will check the condition of denosumab upon arrival and sign a proof of delivery form. Any damaged shipments will be replaced. See the ***Drug Supply Manual*** for details.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Accountability Log. In the event that denosumab is destroyed at site a certification of destruction form should be generated and retained in the Trial Master File

9.4. Storage and handling

Store denosumab in a refrigerator between 2°C and 8°C. See the ***Drug Supply Manual*** for details.

9.5. Unused trial drugs supplies

At the close of the trial, any quantities of the IP which remain unused will either be disposed of at the study site or returned to Amgen with the appropriate documentation. See the ***Drug Supply Manual*** for details.

10. Trial treatments

Drug therapy is to begin within 10 days of randomisation.

10.1. Drug combinations

The following chemotherapy combinations may be used in **cycles lasting 3 weeks each:**

In patients with all histologies:

CisGem: Cisplatin 75 mg/m^2, i.v. day 1, plus Gemcitabine 1250 mg/m^2, i.v., days 1 and 8

CarboGem: Carboplatin AUC 5 , i.v. day 1, plus Gemcitabine 1250 mg/m^2, i.v., days 1 and 8

In patients with non-squamous cell histology only, pemetrexed may be administered instead of gemcitabine:

CisPem: Cisplatin 75 mg/m^2, i.v. day 1, plus Pemetrexed 500 mg/m^2 i.v. day 1

CarboPem: Carboplatin AUC 5 , i.v. day 1, plus Pemetrexed 500 mg/m^2 i.v. day 1

Patients will be randomised to one of two treatment regimens as follows:

ARM A : 4 – 6 cycles of one of the above combinations + best supportive care

ARM B : 4 – 6 cycles of one of the above combinations + denosumab 120 mg, s.c. every 3-4 weeks until unacceptable toxicity, patient refusal, or patient's death. Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient. In cycle 1, an additional dose will be given on day 8.

Frequency of administration is 3-4 weeks and is left to investigator's preference. For practical reasons, it is encouraged to consider 3-weekly administration during first-line chemotherapy and 4-weekly schedule after first-line chemotherapy, in particular when no chemotherapy is delivered or when chemotherapy is not cycled on a 3-weeks basis.

Beyond primary analysis, all subjects randomised to ARM B and still benefitting from the drug will be offered denosumab at a dose of 120 mg s.c. until patient or physician elect to discontinue denosumab for any reason, and for a maximum of 2 years after the required number of 847 deaths for the final analysis has been reached.

Cisplatin, carboplatin, gemcitabine and pemetrexed are standard treatment for NSCLC and have to be sourced locally and will not be reimbursed.

Daily supplementation with calcium (500 mg) and vitamin D (≥400U) will be administered to all patients (mandatory for pts in arm B (denosumab) and recommended in arm A if they receive zoledronic acid according to local guidelines). Patients treated with pemetrexed will receive folic acid 0.4 – 1 mg/day and vit B12 1000 IU s.c. 1 week before first dose and then every 3 cycles. These supplements will have to be sourced locally and will not be reimbursed.

Notes:

- In arm A, in patients with bone metastasis, zoledronic acid is recommended to be administered concomitantly to first line platinum doublet and thereafter continued as a bone protective drug after progression even if chemotherapy has to be changed to second-line, until unacceptable toxicity, patient refusal or patient's death. Administration schedule and duration is left to investigator's discretion.
- The addition of bevacizumab to platinum-based chemotherapy is not allowed
- Maintenance chemotherapy with pemetrexed (non squamous histology only) or erlotinib is allowed
- Pemetrexed should only be administered if calculated creatinine clearance ≥ 45 mL/min
- After disease progression to first-line chemotherapy, further treatment is up to investigator's choice in both arms
- Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient.
- Maintenance is allowed (pemetrexed or erlotinib, according to local standard of care).
- Crossover of treatment arms is not allowed in this trial.

10.2. Pemetrexed

10.2.1. Premedication and dosing of pemetrexed

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 each 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. Patients must take oral folic acid or a multivitamin containing folic acid (400 to 1000 µg) 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 µg) 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. The dosing of pemetrexed is based on the patient's total body surface area (m^2).

10.3. Cisplatin, Carboplatin and/or Gemcitabine

The combinations should be administered according to local guidelines including premedication.

Antiemetic prophylaxis and therapy is recommended to be administered according to local rules.

Hydration is left open as some centers are performing cisplatin therapy in an ambulatory setting. Standard i.v. hydration is however recommended before and after cisplatin treatment, e.g. 1000 ml NaCl 0.9% i.v. over 2 hours before and 2000 ml NaCl 0.9% i.v. after cisplatin.

10.4. Denosumab

Administration by subcutaneous injection should be performed by an individual who has been adequately trained in injection techniques.

10.5. Precautions

Women of childbearing potential and sexually active men must use effective contraception during the trial and 5 months thereafter.

10.6. Concomitant treatment

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

- Approved drugs for other medical indications than cancer
- Palliative and supportive care, including analgesic radiotherapy, antiemetics as well as G-CSF according to standard guidelines
- Safe alternative medicine if potential interactions with trial drugs can be excluded

The following treatments are **NOT allowed**:

- For first-line chemotherapy treatment: Investigational drugs

- Denosumab is not allowed in Arm A
- Bisphosphonates are not allowed in Arm B
- Non-IP denosumab

10.7. Treatment delay and dose modification for toxicity

10.7.1. General remarks on dose modifications

In general:

- In cases of conflicting recommendations, use the most restrictive treatment adjustment
- In case of missing recommendations, adaptations must be made according to local standards of care
- No dose re-escalation is allowed after reduction
- After a dose/drug modification has been done, it should be maintained for the subsequent cycles (e.g. switch from cisplatin to carboplatin or from pemetrexed to gemcitabine).

The trial chair should be contacted in case the investigator has any doubts about treatment delays and/or dose reductions.

10.7.2. CisGem dose reductions and delays

	Grade/count	Cisplatin	Gemcitabine
Platelet count decreased	At day 1 of cycle <100×10^9/L	Delay* cycle start until recovery to >100×10^9/L	
	If <50×10^9/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence <50×10^9/L	No change at start of next cycle	Start next cycle at 50% of dose
	Third occurrence <50×10^9/L	Next cycle with 75% dose	Omit day 8
Neutrophil count decreased	<1.0 ×10^9/L at day 1 of cycle	Delay* until recovery to >1.0 ×10^9/L And no change at start of next cycle	Delay* until recovery to >1.0 ×10^9/L
	<0 .5 ×10^9/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence <0.5 ×10^9/L at any time during cycle	Reduce to 75% of dose	Reduce to 50% of dose
	Third occurrence <0.5 ×10^9/L at any time during cycle	Reduce to 50% of dose	Reduce to 50% of dose
Febrile neutropenia	3, 4	Add G-CSF at day 3-4 for a minimum of 3 days in all subsequent cycles	
Renal impairment	Creatinine clearance <60ml/min at day 1 of cycle	Replace by carboplatin AUC 5	No change
	Creatinine clearance <30ml/min at day 1 of cycle	Discontinue	No change
Ototoxicity	Grade 3 or 4 on day 1 of cycle	Replace by carboplatin AUC 5	No change
Other toxicities (except specific AEs above, nausea, alopecia and fatigue) *	First occurrence of grade 3 or 4	Reduce to 75% of dose	Reduce to 75% of dose
	second occurrence of grade 3 or 4	Replace by carboplatin AUC 5	Reduce to 50% of dose

* Delay for a maximum of 4 weeks until recovery to ≤ grade 2. If no recovery within 4 weeks, the patient stops chemotherapy and is treated according to local recommendations. Denosumab should be continued in arm B.

10.7.3. CisPem dose reductions and delays

	Grade/count	Cisplatin	Pemetrexed
Platelet count decreased	At day 1 of cycle $<100\times10^9$/L	Delay* cycle start until recovery to $>100\times10^9$/L	
	If $<50\times10^9$/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence $<50\times10^9$/L	No change at start of next cycle	Start next cycle at 50% of dose
	Third occurrence $<50\times10^9$/L	Next cycle with 75% dose	No change
neutrophil count decreased	$<1.0\times10^9$/L at day 1 of cycle	Delay* until recovery to $>1.0\times10^9$/L	Delay* until recovery to $>1.0\times10^9$/L
	$< 0.5\times10^9$/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence $<0.5\times10^9$/L at any time during cycle	Reduce to 75% of dose	Reduce to 50% of dose
	Third occurrence $<0.5\times10^9$/L at any time during cycle	Reduce to 50% of dose	Reduce to 50% of dose
Febrile neutropenia	3, 4	Add G-CSF at day 3-4 for a minimum of 3 days in all subsequent cycles	Add G-CSF at day 3-4 for a minimum of 3 days in all subsequent cycles
Renal impairment	Creatinine clearance <60 and >45ml/min at day 1 of cycle	Replace by carboplatin AUC 5	No change
	Creatinine clearance <45ml/min at day 1 of cycle	Replace by carboplatin AUC 5	Replace by gemcitabine
	Creatinine clearance <30ml/min at day 1 of cycle	Discontinue	Replace by gemcitabine
Ototoxicity	3,4 on day 1 of cycle	Replace by carboplatin AUC 5	No change
Neurotoxicity	Grade 2	Replace by carboplatin AUC 5	No change
	Grade 3, 4	Replace by carboplatin AUC 5	Replace by gemcitabine
Other toxicities (except specific AEs above, nausea, alopecia and fatigue) *	First occurrence of grade 3 or 4	Reduce to 75% of dose	Reduce to 75% of dose Reduce to 50% of dose in case of grade 3/4 mucositis
	second occurrence of grade 3 or 4	Replace by carboplatin AUC 5	Reduce to 50% of dose

* Delay for a maximum of 4 weeks until recovery to ≤ grade 2. If no recovery within 4 weeks, the patient stops chemotherapy and is treated according to local recommendations. Denosumab should be continued in arm B.

10.7.4. CarboGem dose reductions and delays

	Grade/count	Carboplatin	Gemcitabine
Platelet count decreased	At day 1 of cycle $<100\times10^9$/L	Delay* cycle start until recovery to $>100\times10^9$/L	
	If $<50\times10^9$/L at any time during cycle	Start next cycle at 75% of dose	Start next cycle at 75% of dose
	Second occurrence $<50\times10^9$/L	No change at start of next cycle	Start next cycle at 50% of dose
	Third occurrence $<50\times10^9$/L	Next cycle with 50% dose	No change
Neutrophil count decreased	$<1.0\times10^9$/L at day 1 of cycle	Delay* until recovery to $>1.0\times10^9$/L	Delay* until recovery to $>1.0\times10^9$/L
	$<0.5\times10^9$/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence $<.5\times10^9$/L at any time during cycle	Start next cycle at 75% of dose	No change
	Third occurrence $<.5\times10^9$/L at any time during cycle	Start next cycle at 75% of dose	Reduce to 50% of dose
	Fourth occurrence $<.5\times10^9$/L at any time during cycle	Reduce to 50% of dose	Reduce to 50% of dose
Febrile neutropenia	3, 4	Add G-CSF at day 3-4 for a minimum of 3 days in all subsequent cycles	
Renal impairment	Creatinine clearance <30ml/min at day 1 of cycle	no change	no change
Other toxicities (except specific AEs above, nausea, alopecia and fatigue) *	First occurrence of grade 3 or 4	Reduce to 75% of dose	Reduce to 75% of dose
	second occurrence of grade 3 or 4	No change	Reduce to 50% of dose
	Third occurrence of grade 3 or 4	Reduce to 50% of dose	No change

* Delay for a maximum of 4 weeks until recovery to ≤ grade 2. If no recovery within 4 weeks, the patient stops chemotherapy and is treated according to local recommendations. Denosumab should be continued in arm B.

10.7.5. CarboPem dose reductions and delays

	Grade/count	Carboplatin	Pemetrexed
Platelet count decreased	At day 1 of cycle <100×10^9/L	Delay* cycle start until recovery to >100×10^9/L	
	If <50×10^9/L at any time during cycle	Start next cycle at 75% of dose	Start next cycle at 75% of dose
	Second occurrence <50×10^9/L	No change at start of next cycle	Start next cycle at 50% of dose
	Third occurrence <50×10^9/L	Next cycle with 50% dose	No change
neutrophil count decreased	<1.0 ×10^9/L at day 1 of cycle	Delay* cycle start until recovery to >1.0 ×10^9/L	
	<0 .5 ×10^9/L at any time during cycle	No change at start of next cycle	Start next cycle at 75% of dose
	Second occurrence <0.5 ×10^9/L at any time during cycle	Start next cycle at 75% of dose	No change
	Third occurrence <0.5 ×10^9/L at any time during cycle	Start next cycle at 75% of dose	Start next cycle at 50% of dose
	Fourth occurrence <0.5 ×10^9/L at any time during cycle	Start next cycle at 50% of dose	Start next cycle at 50% of dose
Febrile neutropenia	3, 4	Add G-CSF at day 3-4 for a minimum of 3 days in all subsequent cycles	
Renal impairment	Creatinine clearance <45ml/min at day 1 of cycle	No change	Replace by gemcitabine
	Creatinine clearance <30ml/min at day 1 of cycle	Discontinue	Replace by gemcitabine
Neurotoxicity	Grade 2	No change	No change
	Grade 3, 4	No change	Replace by gemcitabine
Other toxicities (except specific AEs above, nausea, alopecia and fatigue) *	First occurrence of Grade 3, 4	Reduce to 75% of dose	Reduce to 75% of dose Reduce to 50% of dose in case of grade 3/4 mucositis
	Second occurrence of grade 3 or 4	No change	Reduce to 50% of dose
	Third occurrence of grade 3 or 4	Reduce to 50% of dose	no change

* Delay for a maximum of 4 weeks until recovery to ≤ grade 2. If no recovery within 4 weeks, the patient stops chemotherapy and is treated according to local recommendations. Denosumab should be continued in arm B.

10.8. Treatment duration

Patients remain on trial-specified chemotherapy until one of the following events:

- Chemotherapy: Maximum of 6 cycles
- Documented progression according to RECIST v1.1
- Unacceptable toxicity
- Medical condition that prevents further treatment
- Patient refuses further treatment
- Patient withdraws consent
- Patient becomes pregnant

Patients in Arm B remain on denosumab treatment through trial-specified chemotherapy and further lines of treatment until one of the following events:

- Unacceptable toxicity attributed to denosumab
- Medical condition that prevents further treatment
- Patient refuses further treatment
- Patient withdraws consent
- Patient becomes pregnant
- Beyond primary analysis, all subjects randomised to ARM B and still benefitting from the drug will be offered denosumab at a dose of 120 mg s.c. until patient or physician elect to discontinue denosumab for any reason, and for a maximum of 2 years after the required number of 847 deaths for the final analysis has been reached.

11. Safety of chemotherapy and investigational product

11.1. Cisplatin

11.1.1. Known adverse reactions

Please refer to the latest version of the SmPC.

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

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

11.2. Carboplatin

11.2.1. Known adverse reactions

The following adverse events have been reported; please refer to the latest version of the SmPC for details.

Cardiac disorders

Cardiovascular events (cardiac failure, embolism), cerebrovascular events (apoplexy), hypertension.

Blood and lymphatic system disorders

Myelosuppression, leukopenia, haemorrhagic complications, infectious complications, febrile neutropenia.

Single cases of life-threatening infections and bleeding have occurred.

Myelosuppression is the dose-limiting toxicity of carboplatin.

Respiratory, thoracic and mediastinal disorders

Pulmonary fibrosis manifested by tightness of the chest and dyspnoea.

Nervous system disorders

Peripheral neuropathies, central nervous symptoms

Eye disorders

Transient visual disturbances, sometimes including transient sight loss, optic neuritis

Ear and labyrinth disorders

Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss determined by audiogram, clinical ototoxicity.

Gastrointestinal disorders

Nausea, vomiting, painful gastro-intestinal disorders, diarrhoea, constipation, mucositis, taste alteration, anorexia.

Renal and urinary disorders

Renal toxicity, renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min, may also be observed.

Skin and subcutaneous tissue disorders

Alopecia.

Metabolism and nutrition disorders

Decreases in serum electrolytes (sodium, magnesium, potassium and calcium), hyponatraemia.

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

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

General disorders and administration site conditions

Hyperuricaemia, asthenia, malaise, urticaria. flu-like syndrome, erythematous rash, pruritis, fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis; haemolytic uraemic syndrome.

Immune system disorders

Allergic reactions (e.g. skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus), anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial oedema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia.

Hepatobiliary disorders

Abnormalities of liver function tests, severe hepatic dysfunction (including acute liver necrosis).

11.3. Gemcitabine

11.3.1. Known adverse reactions

Please refer to the latest version of the SmPC.

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

The most commonly reported adverse drug reactions associated with Gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% of patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients.

11.4. Pemetrexed

11.4.1. Known adverse reactions

Please refer to the latest version of the SmPC.

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

11.5. Denosumab

11.5.1. Known adverse reactions

Infections and infestations: uncommon: cellulitis (see below)

Immune system disorder: uncommon: drug hypersensitivity

Metabolism and nutrition disorders: common: hypocalcaemia, hypophosphataemia.

Respiratory, thoracic and mediastinal disorders: very common: dyspnoea

Gastrointestinal disorders: very common: diarrhea; common: tooth extraction

Skin and subcutaneous tissues: common: hyperhidrosis

Musculoskeletal and connective tissue disorders: common: osteonecrosis of the jaw (see below); musculoskeletal pain.

Please also refer to the latest version of the IB.

Description of selected adverse reactions:

Hypersensitivity Reactions

All monoclonal antibodies have the potential to be associated with hypersensitivity reactions, including anaphylactic reactions. In pivotal clinical studies evaluating prevention of skeletal-related events (SREs) in subjects with advanced malignancies involving bone, drug hypersensitivity events (preferred term) were reported in 0.9% of subjects in the denosumab group and 0.4% of subjects in the zoledronic acid group. An imbalance for events potentially associated with hypersensitivity disfavoring denosumab compared with zoledronic acid was observed in these clinical studies (5.4% denosumab, 3.8% zoledronic acid).

A comprehensive safety assessment of anaphylactic reactions with denosumab treatment was performed. The assessment included a medical review of clinical trial adverse events and postmarketing cases. Two nonstudy cases of anaphylactic reaction in the postmarketing setting were assessed as causally related to denosumab ; both had a positive rechallenge. Time to onset for each case was consistent with anaphylactic reaction events subsequent to denosumab 120 mg q4w administration. None of these cases was fatal. As a result hypersensitivity, including anaphylactic reactions, has been added as an identified risk for denosumab .

Atypical Femoral Fracture

Atypical femoral fractures are defined as fractures occurring with no trauma or minimal trauma, such as a fall from a standing height or less, that result in subtrochanteric or proximal diaphyseal fractures anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare. These fractures usually have a characteristic appearance on imaging studies of a simple transverse or oblique fracture, often with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft. Subtrochanteric and diaphyseal fractures together account for about 5% to 10% of all hip/femoral fractures; of these, a subset of approximately 17% to 29% is atypical. The causes of atypical femoral fracture are likely multi-factorial. Atypical femoral fractures have been reported in patients with certain co-morbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and in patients receiving certain pharmaceutical agents (eg, bisphosphonates, glucocorticoids, proton pump inhibitors). Events also have

occurred in patients not receiving any antiresorptive therapy. Epidemiologic evidence suggests an association of atypical femoral fracture with long-term bisphosphonate (antiresorptive) therapy.

An assessment of events of atypical femoral fracture in cancer patients administered denosumab was performed. One case from clinical trials with denosumab 120 mg q4w was positively adjudicated as atypical femoral fracture. As a result atypical femoral fracture has been added as an identified risk for denosumab.

Hypocalcaemia:

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcaemia was reported in 9.6% of patients treated with denosumab and 5.0% of patients treated with zoledronic acid.

A grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with denosumab and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with denosumab and 0.2% of patients treated with zoledronic acid

In the postmarketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported.

Osteonecrosis of the jaw (ONJ):

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with denosumab and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most (81% in both treatment groups) had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. In addition most subjects were receiving or had received chemotherapy . Patients with certain identified risk factors for ONJ were excluded from participation in the pivotal studies.

ONJ is an identified risk for denosumab and is addressed in several sections of the XGEVA (denosumab 120 mg Q4W) core safety information, including the warnings and adverse reactions sections. The current risk minimization language in the denosumab core safety information includes the following instructions:

- A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with risk factors for ONJ.
- Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon.

Incidence of ONJ was higher with longer duration of exposure. In Henry trial [9], positively adjudicated ONJ occurred with cumulative incidence rates in the zoledronic acid and denosumab groups of, respectively, 0.6% and 0.5% at 1 year, 0.9% and 1.1% at 2 years, and 1.3% and 1.1% at 3 years.

Skin infections (predominantly cellulitis) leading to hospitalization:

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving denosumab (0.9%) compared with zoledronic acid (0.7%).

In postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported for 0.4% women receiving Prolia (denosumab 60 mg every 6 months) and for 0.1% women receiving placebo.

Other special populations:

In a clinical study of patients without advanced cancer with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis, there was a greater risk of developing hypocalcaemia in the absence of calcium supplementation.

11.5.2. Contraindications and special warnings

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe, untreated hypocalcaemia.

Special warnings and precautions for use

Calcium and Vitamin D supplementation:

Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.

Hypocalcaemia:

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with denosumab. Hypocalcaemia can occur at any time during therapy with denosumab and most commonly occurs within the first 6 months of dosing. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Monitoring of calcium levels in these patients is recommended. If hypocalcaemia occurs while receiving denosumab, additional calcium supplementation may be necessary. In the post marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported.

Osteonecrosis of the jaw:

Osteonecrosis of the jaw (ONJ) was reported in patients treated with denosumab, predominantly in patients with advanced malignancies involving bone. Patients who developed ONJ in clinical studies generally had known risk factors for ONJ, including invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease, advanced malignancies, infections, or concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck). A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with active dental and jaw conditions (as listed above). While on treatment, patients should avoid invasive dental procedures if possible. Good oral hygiene practices should be maintained during treatment with denosumab. Patients who are suspected of having or who develop ONJ while on denosumab therapy should receive care by a dentist or oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Administration of investigational product will also be withheld 30 days prior to any elective invasive oral/ dental procedure. Investigational product administration will be withheld until documented evidence of complete mucosal healing following any invasive oral/ dental procedure.

12. Serious adverse events reporting

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

12.1. Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as "any noxious and unintended response to a medicinal product related to any dose administered".

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. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is "any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

12.2. Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for trial participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

By convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

12.3. Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc or http://evs.nci.nih.gov/ftp1/CTCAE/About.html

12.4. Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

12.5. Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the trial. The expectedness assessment will be performed against the following reference documents:

- For cisplatin: Summary of Product Characteristics (SmPC)
- For carboplatin: Summary of Product Characteristics (SmPC)
- For gemcitabine: Summary of Product Characteristics (SmPC)
- For pemetrexed: Summary of Product Characteristics (SmPC)
- For denosumab: Investigator's Brochure.

12.6. Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject has signed informed consent until 30 days after last protocol treatment administration and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or trial participation.

From date of informed consent till 30 days after last dose of first-line chemotherapy or IP, whichever occurs later :	All SAEs
From day 31 after last dose of first-line chemotherapy or dose of IP, whichever occurs later:	Only related SAEs and second primary cancer

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

- All reporting must be done by the principal investigator or authorised staff member (i.e. on the signature list) to confirm the accuracy of the report.
- All SAE data must be collected on the trial-specific SAE form.
- All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.
- All SAE-related information needs to be provided in English.
- All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.
- All SAE-related information has to be faxed to EORTC Pharmacovigilance Unit:

  Fax No. +32 2 772 8027

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorised staff member (i.e. on the signature list).

12.7. Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters, ETOP and to Amgen

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators.

12.8. Pregnancy and lactation reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should

be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case as specified below. In addition to reporting a lactation case during the trial treatment, Investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 7 months.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 7 months after trial treatment discontinuation must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

13. Endpoints definition

13.1. Overall survival

Defined as time from the date of randomisation until death from any cause. Patients who are still alive at last contact are censored at the date of last follow up.

13.2. Progression-free survival

Progression-free survival (PFS) is defined as time from date of randomisation until objective disease progression or death, whichever occurs first. Disease progression and its evaluation are defined based on RECIST 1.1 (see Appendix 2). If neither event has been observed, then the patient is censored at the date of the last follow up examination

Patients with new non-lung cancer malignancy must continue to be followed for progression of the original lung cancer.

Patients who discontinue treatment prior to documented disease progression (see section 10.8), including those who initiate non-protocol therapy prior to progression, will be followed for disease progression and death.

13.3. Response

The response of the tumour is defined according to RECIST 1.1 criteria, see appendix 2.

13.4. Toxicity

Adverse events classified according to NCI CTCAE version 4. Electronic versions are available on www.eortc.org\investigators-area\ctc or http://evs.nci.nih.gov/ftp1/CTCAE/About.html

14. Biological material and translational research

The collection of tumour and serum samples is required in this trial. This material will constitute an invaluable and precious source for biological research in the context of this trial.

14.1. Serum

14.1.1. Serum samples

Mandatory serial serum samples will be collected at baseline (prior to the start of chemotherapy), on day 1 of cycle 3 and at progression.

Analysis of serum samples by ELISA includes CTX, osteoprotegerin (OPG), propeptide of type I procollagen (PINP), osteopontin (OPN), free RANKL and RANKL-OPG. These may be changed and the panel of serum biomarkers will include best candidates at the time of analysis.

14.1.2. Collection, storage and submission of serum samples

Serum samples must be collected at baseline (prior to the start of chemotherapy), on day 1 of cycle 3 and at progression. Blood collection and serum preparation: see ***SPLENDOUR biological samples manual.*** Serum will be aliquoted into cryovials and must be immediately frozen at -80ºC and kept at the participating site until shipment. Shipments will be organized centrally.

Serum samples will be sent to Sheffield biorepository, UK;

Kevin Corke, Room EU17
Sheffield Medical School
Beech Hill Road, Sheffield
S10 2RX, United Kingdom

and analysed at Northern General Hospital, Sheffield.

14.2. Tumour tissue

Availability of a sample of tumour tissue is an eligibility criterium. The samples will be collected after the patient has been randomised:

- The preferred option is an FFPE block from a recent biopsy of the primary tumour or metastasis; archival tissue from tumour resection is also an option;
- If a tissue block is not available, a paraffin-embedded cell block (cytoblock) is a valuable alternative to an FFPE tumour block. Cytology smears alone are not accepted in this trial;
- If neither a tumour block nor a cell block is available: 10 unstained slides with wax protection.

There is no limitation regarding the age of the tumour sample in this trial. However, recent samples are preferred and investigators should consider a new biopsy in patients relapsing after surgery.

Please consult the ***SPLENDOUR biological samples manual*** for instructions on how to prepare and ship block or slides.

The following evaluations are proposed for translational research: IHC (and/or RT-PCR) for RANKL & RANK, and potentially NF-kappaB activation evaluation (RT-PCR and/or IHC) and bone sialoprotein (BSP) which in tumour has been correlated with bone metastasis progression and high levels are associated with poor prognosis [34]; and osteopontin (OPN) levels in primary tumour may correlate with tumour aggressiveness [35]. These may be adapted in the future to include best candidates available at the time of evaluation.

14.2.1. Submission of FFPE material

The following items must be submitted for all patients:

1. FFPE material as described above
2. Pertinent pathology report (please black out name and any other identifier, and add the seqID issued by the ORTA system, see section 8.2)

Highly desirable:

3. Tumour or cell block and pathology report from re-biopsy at progression

The FFPE tissue blocks may be returned to the site upon request after samples have been removed for analysis.

Slides should be covered with wax immediately after cutting. They will be stored at 4°C in the dark to avoid any degrading.

Samples have to be sent to the ISREC lab

Swiss Institute for Experimental Cancer Research (ISREC)
EPFL-SV-ISREC
Dr. Etienne Meylan
EPFL SV ISREC UPMEYLAN
Station 19
CH-1015 Lausanne, Switzerland

according to specific instructions in the ***SPLENDOUR procedures manual***.

14.3. Banking of biological material

The ETOP and EORTC have established a central repository for tissue blocks/slides and serum samples from every patient enrolled in this trial. The required tissue material (described in the previous sections) is submitted to, catalogued, and maintained in the ISREC lab. Serum samples are submitted to the Sheffield biorepository.

15. Trial procedures

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

The trial consists of the following stages:

15.1.1. Screening: the screening period must occur within 28 days before randomisation in ORTA. Baseline evaluations must be done within 28 days prior to randomisation**.** Trial specific examinations may only be done after informed consent has been signed by the patient, and within 14 days before randomisation.

15.1.2. Treatment phase:

Drug therapy is to begin within 10 days after randomisation.

Upon first disease progression or completion of first-line per protocol chemotherapy treatment, further therapy will be at the discretion of the treating physician.

In arm B, Denosumab will be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment, as long as tolerable for the patient.

15.1.3. End of per protocol first-line chemotherapy: an end of treatment visit will occur 30 +/-5 days following the last dose of first-line chemotherapy.

15.1.4. Arm B: End of denosumab treatment: an end of treatment visit will occur 30 +/-5 days following the last dose of denosumab.

15.1.5. Follow-up period: every 6-8 weeks following end of treatment visit until death, patients will be followed up to document outcome and further lines of treatment. Between end of treatment and progression, the visit schedule needs to follow the one corresponding to the treatment phase, see section 15.6.

15.2. Baseline evaluations (within 28 days prior to registration)

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

15.2.2. Physical examination including blood pressure [mmHg], ECOG performance status (see text box in section 6.1), and body weight [kg]

15.2.3. Haematology: haemoglobin, neutrophils, platelets

15.2.4. Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

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

15.2.6. Hepatic function: ALT, bilirubin

15.2.7. Pregnancy test for women of childbearing potential within 14 days before start of treatment

15.2.8. Bone scan: Bone scan at baseline not requested for patients who have undergone a PET-CT at baseline; In the event of equivocal results of the bone scan, further confirmation using bone MRI, CT, X-Ray or biopsy is recommended.

15.2.9. CT scan of thorax and upper abdomen with i.v. contrast (alone or in combination with PET). In the presence of clinically suspected metastases outside the thorax (e.g. brain, bone or lower abdomen), additional CT of the affected body part is recommended.

15.2.10. CT scan or MRI of brain is not mandatory and only recommended in case of clinically suspected brain metastasis

15.3. Before start of treatment

15.3.1. Take baseline samples for translational research

- 1 block of FFPE tissue from biopsy, surgery or cytology
- Pathology report
- Blood sample

send the FFPE samples to the central lab within 12 weeks after randomisation.

15.4. Evaluations before and during per protocol first-line chemotherapy

On day 1 of every 3-week treatment cycle:

15.4.1. Recording of adverse events

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

15.4.3. Haematology: haemoglobin, neutrophils, platelets

15.4.4. Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

15.4.5. CT thorax and upper abdomen on day 1 of cycle 4, then every 12 weeks **until first progression has been fully documented**. Additional exams (MRI, PET-CT, etc,) might be performed upon symptoms or suspicion of progression, according to local standards and can serve as documentation of progression according to RECIST.

15.4.6. On day 1 of cycle 3: Blood sample for translational research

15.5. End of first-line chemotherapy treatment visit

At the end of first-line chemotherapy and **irrespective of the reason for stopping**, an end-of-treatment visit at the center is to be scheduled after 30 (+/- 5) days following last chemotherapy treatment day. The following procedures should be performed:

15.5.1. Recording adverse events

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

15.5.3. Haematology: haemoglobin, neutrophils, platelets

15.5.4. Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

15.6. Evaluations after per protocol first-line chemotherapy and before first progression

For patients who discontinue chemotherapy without documented progression, clinical follow-up should be done every 6-8 weeks according to local standard of care and subsequent anticancer treatment schedules, and in Arm B according to denosumab treatment:

15.6.1. Documentation of further treatments

15.6.2. Adverse events every 6-8 weeks

15.6.3. Arm B: Total calcium, albumin at every denosumab administration (q3 or 4 weeks)

15.6.4. **Every 12 weeks**: CT thorax and upper abdomen (Additional exams (MRI, PET-CT, etc) might be performed upon symptoms or suspicion of progression, according to standard of care and can serve as documentation of progression according to RECIST.).

15.7. Evaluations at first documented progression

15.7.1. CT thorax and upper abdomen, document progression on the respective CRF

15.7.2. Physical examination including blood pressure and performance status

15.7.3. Haematology: haemoglobin, neutrophils, platelets

15.7.4. Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

15.7.5. Documentation of further treatments

15.7.6. Blood sample for translational research

15.7.7. Tumour re-biopsy is encouraged for testing of further predictive markers and translational research at the central reference laboratory

15.8. Evaluations after first progression

After documented first progression, patients should be documented every 8 weeks for

15.8.1. Survival information until death

15.8.2. Further lines of treatment every 6-8 weeks until death

15.8.3. Adverse events every 6-8 weeks

15.9. Arm B: End of denosumab treatment visit

At the end of denosumab treatment and **irrespective of the reason for stopping**, an end-of-treatment visit at the center is to be scheduled after 30 (+/- 5) days following last denosumab treatment day. In the unlikely case that denosumab treatment is stopped before first-line chemotherapy, this visit should take place after stop of first-line chemotherapy. The following procedures should be performed:

15.9.1. Recording adverse events

15.9.2. Physical examination including blood pressure and performance status

15.9.3. Haematology: haemoglobin, neutrophils, platelets

15.9.4. Blood chemistry: serum creatinine, ALT, bilirubin, total calcium, albumin

16. Case report forms and documentation

16.1. Case report forms

Data will be reported on the forms specifically designed by the ETOP/EORTC Headquarters for this trial. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form, paper lactation form and paper pregnancy notification form which are a paper CRF.

Serious adverse events and pregnancies should be reported immediately according to the procedures detailed in this protocol (see section 12.6).

A. Before the treatment starts:

The patient must be registered and randomised in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the registration/randomisation on http://rdc.eortc.be/ or on http://www.eortc.be/ in the section for investigators.

The paper CRF (only SAE form, lactation form and pregnancy notification form) will be made available to the institution at the time the institution is authorised.

B. During/after treatment

The list of forms to be completed for this trial and their submission schedule are available on the VISTA/RDC website and are also described in the "Guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorised staff members.

16.2. CRF submission schedule

CRFs will only be available on-line on the VISTA/RDC website. No paper forms will be used, with the exception of a paper SAE form and of a paper lactation and a paper pregnancy notification form.

CRF forms	**To be completed**
Eligibility checklist	At randomisation of the patient.
On-study form	At baseline, within 1 week after randomisation of the patient.
Assessment form	At baseline; At D1 of each cycle; At end of treatment visit.
Initial measurements form	At baseline, within 1 week after randomisation of the patient.
Biochemistry form	At D1 of each cycle; At end of treatment visit.
Hematology form	At D1 of each cycle; At end of treatment visit.
Treatment form	At the end of each cycle.
Adverse events form	At baseline; At the end of each cycle; At end of treatment visit
Follow-up measurements form	Every 12 weeks until progression; Patients who discontinue treatment before progression: every 12 weeks until progression
Pregnancy form	Paper form; by Fax, within 24 hours of first becoming aware of the pregnancy to EORTC Pharmacovigilance Unit
Lactation form	Paper form; by Fax, within 24 hours of first becoming aware of the lactation to EORTC Pharmacovigilance Unit
Serious adverse event form	Paper form; **by Fax**, within 24h of first becoming aware of SAE to EORTC Pharmacovigilance Unit
Follow-up form	Every 8 weeks after treatment discontinuation until death.

Consult the “Guidelines for completion of case report forms" for detailed instructions on how to complete, save and submit the electronic and paper CRFs.

16.3. Data flow

The forms must be completed electronically, with the exception of the paper SAE forms, according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorised to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the trial. To enter the RDC system, the investigator or authorised staff member needs to use the same username and password that are used to access the interactive randomisation program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other trial related issues.

If an investigator (or an authorised staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

17. Statistical considerations

17.1. Primary Objective

This randomised phase III trial will evaluate the potential of denosumab – as an antitumour agent – to increase survival in patients with stage IV NSCLC with or without bone metastasis.

17.2. Sample size

Using 90% power and a one-sided type I error of 2.5%, demonstration of an increase in median overall survival to 11.25 months in the experimental arm relative to 9 months in the control arm (equivalent to HR = 0.80) requires observation of 847 deaths. Assuming an accrual rate of 15 patients/month for the first 6 months and 30 patients/month thereafter, an accrual of 1000 patients would be required with corresponding accrual period of 37 months and an extra 14 months follow up time after the last patient entry to reach the above required number of events. The accrual in the bone mets stratum is expected to be 300 patients (30% of the total), with 700 for the non-bone mets stratum. The same median OS and improvement in the experimental arm is assumed for both strata.

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

17.3. Statistical analysis plan

17.3.1. Analysis populations

- **Intention-to-treat population (ITT)**: All randomized patients will be analyzed in the arm they were allocated by randomisation.
- **Per protocol population**: All patients who do not have any major deviation from eligibility criteria and have started their allocated treatment (at least one dose of the study drug(s))
- **Safety population**: All patients who have started their allocated treatment (at least one dose of the study drug(s))

A patient will be considered to be eligible if he/she did not have any major deviation from the patient entry criteria listed in section 6 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

17.3.2. Statistical methods

Time to event endpoints

The analyses of the primary and secondary endpoints (OS, PFS) will be performed on all randomised patients according to the intention to treat principle.

The null hypothesis for the primary endpoint will be tested at a significance level of 0.05 (or 0.025 if based on one-sided test). If the primary hypothesis is rejected, the null hypothesis for the secondary endpoint of progression free survival will be tested at a significance level of 0.05 (or 0.025 if based on one-sided test). To preserve the Type I error for other secondary analyses, the Hommel procedure will be used to account for multiple testing.

Estimates and confidence intervals

Estimates of the median PFS and OS are obtained by the Kaplan Meier technique. The (1-α) confidence interval (CI) for the median will be calculated using the reflected CI method.

Follow-up time will be estimated based on the reverse Kaplan Meier method.

Estimates of the event-free rate at a fixed time point will be obtained using the Kaplan Meier technique and (1-α) CI will be calculated by Greenwood's estimation of the standard deviation. Estimates of hazard ratios and their (1-α) CI will be obtained by Cox regression. Kaplan Meier Curves will be drawn for both the experimental and control arms on the same plot.

Response rate (objective; complete and partial response) will be analyzed for all eligible patients according to the treatment assigned at randomization (intention-to-treat analysis population).

Inference: Test statistics for comparisons

A log-rank test stratified by the randomisation stratification factors will be used to compare the experimental versus the control arms for the time to event endpoints.

Fisher's exact test will be used to compare the differences in overall response rate between the two groups.

Toxicity

Analysis for toxicity is based on the safety population. The worst grade of toxicity/adverse events observed over the whole treatment period according to CTCAE version 4 will be displayed. In the primary analysis, no formal statistical analysis will be performed to compare toxicity in both arms.

17.3.3. Pre-planned sensitivity or exploratory analyses

As a sensitivity analysis, other baseline disease factors namely gender, smoking status, age, carboplatin versus cisplatin will be used as adjustment factors in Cox regression analysis, in addition to the stratification factors used for randomisation. A log rank test with no adjustment factors to compare the two arms will also be performed as a sensitivity analysis. For the secondary endpoint PFS, due to possible variation in time window used by centre for disease assessment, a method based on interval censoring will be used in the sensitivity analysis [36]. Proportional hazards assumption will be checked using the method described by Grambsch and Therneau [37]. If the data clearly do not follow proportional hazards, medical explanations should be identified and alternative statistical methods will be explored.

Subgroup-analysis by stratification factors used in randomisation will be conducted.

17.3.4. Prognostic factor analyses

Except for the analyses described in the previous sub-section, there are no other prognostic factor analyses foreseen in the current protocol.

17.3.5. Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomisation – date of past event + 1) and presented using the median and range. For example, on the randomisation checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on trial (date of randomisation – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the CTCAE v.4 grading scale will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value across all cycles.

Other continuous variables (for example age, dose) are presented using the median and range (minimum, maximum).

$$\text{DI observed}\left[\frac{mg}{m^2 \times weeks}\right] = \frac{total\ \ dose\ \left[\frac{mg}{m^2}\right]}{total\ \ duration\ \left[weeks\right]}$$

The relative dose intensity is calculated as the ratio of the dose intensity as calculated above to the dose intensity indicated in the protocol. The dose intensity indicated in the protocol is obtained as the dose specified per cycle (in mg/m²).

The dose intensity and the relative dose intensity are presented using median and ranges. The relative dose intensity can also be presented in categories (≤70%, >70-90%, >90-110%, >110-120%, >120%.

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

17.4. Interim analyses

The trial is designed with a futility IA, at 30% of the overall trial information time. This will be an event driven IA, when 254 deaths have been observed overall, expected to occur by 22.5 months from the date the first patient is randomised. At this time accrual is expected to have reached 58% of the total.

The Lan-Demets spending function with O'Brien-Fleming-type stopping boundary is used to determine the futility boundary at IA.

If the futility boundary is crossed, i.e. p>0.8423, the trial may be closed based on the recommendation of the Independent Data Monitoring Committee (IDMC). If the futility boundary is not crossed, the trial will continue to completion. The final analysis will be performed in the overall trial population at one-sided alpha of 0.025, when the required number of 847 events is observed at the estimated maximum trial duration of 51 months.

The Interim Analysis Report is confidential and will be reviewed by the IDMC which will make a recommendation to continue or stop the trial based on the interim analysis results.

17.5. End of trial

End of trial occurs when all of the following criteria have been satisfied:

- All patients have been off protocol-specified treatment (first-line chemotherapy or denosumab, whichever occurs later) for at least thirty days, or a maximum of 2 years after the final analysis, estimated to be done at month 56 after inclusion of the first patient.
- The trial is mature for the analysis of the primary endpoint as defined above.
- The database has been fully cleaned and frozen for the final analysis

Note: follow-up will be life-long for all patients.

18. Criteria for termination of the trial

18.1. Discontinuation of protocol treatment for individual patients

First-line chemotherapy should be stopped in the following situations:

- Disease progression
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.

- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation of protocol therapy. Note: Diagnosis of another neoplastic disease (second malignant tumour) does not mandate a stop of trial therapy, patients may continue to receive protocol treatment after appearance of a second primary tumour, stopping protocol treatment is determined by the medical judgment of the treating physician
- Request by the patient (see also section 19.4)
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective
- Patient becomes pregnant

Denosumab (arm B) should be continued upon tumour progression and concomitantly to subsequent lines of systemic treatment. Denosumab should be stopped in the following situations:

- Occurrence of unacceptable toxicities attributed to denosumab. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Request by the patient
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective
- Patient becomes pregnant

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

Beyond primary analysis, all subjects randomised to ARM B and still benefitting from the drug will be offered denosumab at a dose of 120 mg s.c. until patient or physician elect to discontinue denosumab for any reason, and for a maximum of 2 years after the required number of 847 deaths for the final analysis has been reached.

18.2. General criteria for termination of the trial

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

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

The Investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

19.1. Ethics Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials.

The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP Coordinating Office/EORTC HQ prior to participating center activation .

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

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

19.2. Regulatory approval procedures

There will be local, regional and country specific differences in the regulations concerning the use of biological samples for research.

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP Coordinating Office/EORTC HQ prior to Participating Center activation.

19.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “Patient Information and Informed Consent" (see Appendix 1). One signed and dated copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for randomisation to this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician (http://www.wma.net/en/30publications/10policies/b3/index.html). The potential patient should also be informed of her right to not participate or to withdraw from the trial at any time. The patient should be told that material from her tumour will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. By signing this protocol, the investigator agrees to conduct the trial in accordance with Good Clinical Practice and the "Declaration of Helsinki."

ETOP recognizes that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (Appendix 1), which can be edited to incorporate information specific to your institution. The template Patient Information Sheet

and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki". The final version should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centers should send their locally modified patient information sheet and informed consent form to ETOP/EORTC HQ for review and approval before submitting to their Ethics Committee.

19.4. Premature withdrawal

Patients have the right to refuse further treatment for any reason and at any time. Patients who decide to withdraw from the trial should be asked whether they also want to withdraw their consent for their data to be used for the follow-up assessments, and whether they want to withdraw consent for the use of biological samples. For the patient's safety, a last examination should be performed.

Patients may be withdrawn at any time from trial treatment at the discretion of the investigator due to a serious adverse event, or based on any other relevant medical condition. The patient will then be transferred to the follow-up phase and will be documented as planned.

For criteria on early stop of trial treatment see section 18.1.

20. Governance and administrative issues

20.1. Steering Committee

A Steering Committee will be constituted for this trial. The Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial chair and co-chair, trial coordinators, trial statisticians, EORTC and ETOP officials, representatives from some participating institutions and groups, and maybe a representative from Amgen. Steering Committee guidelines are available.

20.2. Independent Data Monitoring Committee

The trial will be presented for review to the ETOP IDMC at each of their semi-annual meetings. Accrual and safety will be monitored. The Interim Analysis Report will be reviewed by the IDMC which will make a recommendation to continue or stop the trial based on the interim analysis results.

20.3. Publication

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

20.4. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP Coordinating Office.

20.5. Quality Assurance/Quality control

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

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

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

20.6. Protocol adherence

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

20.7. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by ORTA. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central labs.

Biological material will be transferred outside the treating institution for central screening and review. Results of the assays will be coded only by the patient identifier.

20.8. Record Retention

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

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

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

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