SPLENDOUR
Synopsis

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

Achtung: Diese initiale Version berücksichtigt nicht allfällige Protokoll-Amendments!

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:

Screening, eligibility and enrolment 

First-line Stage IV NSCLC

Stratify: 
- Bone mets 
- Region 
- ECOG PS 
- Histology

RANDOMISE

A

4-6 cycles chemotherapy every 3 weeks + BSC

ARM A:

4-6 cycles chemotherapy every 3 weeks

Denosumab every 3-4 weeks

ARM B:

Trial treatment

Progression Follow-up

Blood 

Blood 

Blood 

FFPE FFPE FFPE

Translational research:

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/m², i.v. day 1, plus gemcitabine 1250 mg/m², i.v., days 1 and 8
**CarboGem**: carboplatin AUC 5, i.v. day 1, plus gemcitabine 1250 mg/m², 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/m², i.v. day 1, plus pemetrexed 500 mg/m² i.v. day 1

**CarboPem**: carboplatin AUC 5, i.v. day 1, plus pemetrexed 500 mg/m² 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=.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 ≥ 1.5×10^9/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×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 investigative 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 \( \geq 150/100 \) 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 \( \geq 2 \) 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.