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Sponsor / Company: Sanofi **Drug substance(s):** XRP6976 (docetaxel)	**Study Identifiers:** NCT01266512, UTN U1111-1115-3573 **Study code:** DOCET_L_05158
Title of the study: Phase II study of concurrent chemoradiotherapy using IMRT (with SPECT-CT to define functional lung volume and PET to define GTV) and docetaxel-cisplatin followed by adjuvant chemotherapy for inoperable stage III non-small-cell lung cancer (NSCLC)	
Study center(s): 3 centers in Hong Kong (Queen Elizabeth Hospital, Pamela Youde Nethersole Eastern Hospital, Princess Margaret Hospital)	
Study period: Date first patient enrolled: 09/Dec/2010 Date last patient completed: 17/Mar/2014	
Phase of development: Phase 2	
Objectives: To evaluate the response rate (CR/PR/SD/PD) of concurrent chemoradiotherapy using IMRT (with SPECT-CT to define functional lung volume and PET to define GTV) and docetaxel-cisplatin (or carboplatin) followed by adjuvant chemotherapy for inoperable stage III non-small-cell lung cancer. To evaluate the progression-free survival (PFS) and overall survival (OS) of patients post chemoradiotherapy (IMRT with concurrent docetaxel-cisplatin/carboplatin) and adjuvant docetaxel-cisplatin. To evaluate the adverse events (AE, including hematological, gastrointestinal, esophageal, and pulmonary toxicities) during the treatment period of concurrent chemoradiotherapy and adjuvant chemotherapy. *Abbreviations: CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; IMRT: Intensity-modulated radiation therapy; SPECT-CT: Single-photon emission computerized tomography-computerized tomography; PET: positron emission tomography; GTV: Gross tumor volume*	
Methodology: Phase 2, multicenter, non-comparative, open-label, single arm aimed to determine the efficacy and safety of concurrent chemoradiotherapy (IMRT and docetaxel/carboplatin) with adjuvant docetaxel-cisplatin for the treatment of patients with inoperable stage III non-small cell lung cancer.	
Number of patients**:**	Planned: 43 Recruited: 34 Treated: 27 Evaluated: 27

Diagnosis and criteria for inclusion:

Inclusion Criteria:

Patients aged 18 years or older with the following characteristics were eligible:

- Pathologically proven locally advanced, inoperable, confirmed by PET scan (thorax/upper abdomen) to be International stage III (2009) NSCLC and without multifocal tumors in the lung
- Disease volume encompassible within a tolerable Planning Target Volume treated to 66 Gy
- Forced expiratory volume in 1 second (FEV_1) >1000 mL
- Hemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100 000/mm^3
- Total bilirubin ≥1.5 times the upper limit of normal
- Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤2.5 × upper limit of normal (≤5 × upper limit of normal for patients with liver derangement)
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1

Exclusion criteria:

- Previous treatment with chest radiotherapy, chemotherapy, or molecularly targeted agents
- Inadequate lung function (exercise tolerance less than 1 flight of stairs [FOS], FEV_1 <1 L/sec, or raised partial pressure of carbon dioxide [pCO_2])
- History of hypersensitivity or contraindication to the study drugs or premedications or products formulated in polysorbate 80
- Pregnant or breastfeeding women, or women with childbearing potential who are not following an effective method of contraception and/or who are unwilling or unable to be tested for pregnancy (either by serum or urine pregnancy test before study entry)
- Participation in a clinical trial with any investigational drug used and within 30 days prior to study entry

The study protocol was reviewed and approved by all responsible local ethics committees. Written informed consent was obtained before participation into the study. The conduct of the trial was supervised by an independent data monitoring committee (IDMC).

Study treatments

Investigational medicinal product(s): Docetaxel, carboplatin or cisplatin

Formulation: Docetaxel 20 mg or 80 mg concentrate for solution for infusion

Route(s) of administration: intravenous (IV)

Dose regimen:

Concurrent chemoradiotherapy:

- Radiotherapy: IMRT (66 Gy/6.5 weeks over 33 fraction; ie, 2 Gy per fraction)
- Docetaxel 20 mg/m^2 + cisplatin 20 mg/m^2 (or carboplatin area under the curve [AUC] 2 instead if creatinine clearance [CrCl] <60 mL/min) weekly for 6 weeks.
- Dexamethasone for a total of 3 doses is to be given at a dose of 4 mg at 12 hours, 1 hour before and 12 hours after every docetaxel administration.

Adjuvant chemotherapy Q3 weeks for 2 cycles:

Adjuvant chemotherapy will be started 2 weeks after completion of concurrent chemoradiotherapy and is to be given every 3 weeks for 2 cycles:

- Docetaxel 35 mg/m² IV infusion for 1 hour on Days 1 and 8
- Cisplatin 35 mg/m² on Days 1 and 8 (or carboplatin AUC 5 on Day 1 instead, if CrCl <60 mL/min)
- Dexamethasone for a total of 3 doses is to be given at a dose of 4 mg at 12 hours, 1 hour before and 12 hours after every docetaxel administration.

Duration of treatment: 12 weeks treatment phase (including a resting period of 2 weeks)

Duration of observation: 2 years long-term follow-up

Criteria for evaluation:

Patients were recruited within 4 weeks before the concurrent chemoradiotherapy was planned. The first PET scan was to be taken ≤6 weeks and the first SPECT scan and contrast CT scan (thorax and upper abdomen) to be taken ≤4 weeks before the start of concurrent chemoradiotherapy. The concurrent chemoradiotherapy was to take 6 to 7 weeks followed by a resting period of 2 weeks. Then, a 3-weekly regimen (2 cycles) of adjuvant chemotherapy was to be followed.

The patient was to have a second SPECT scan, PET scan, and contrast CT scan 12 weeks (±1 week) after the completion of adjuvant chemotherapy, or within 4 weeks after premature study discontinuation.

After completion of treatment, patient was to be followed up and to have a CT scan performed every 12 weeks (±4 weeks) until death. A third PET scan was to be done if an objective disease progression was observed.

Objective response rate (ORR) was defined as the proportion of patients who achieved clinical tumor response (complete response [CR] and partial response [PR]) assessed according to the World Health Organization criteria by Investigators.

Overall survival (OS) was assessed from Day 1 of treatment to the date of subject death, due to any cause, or to the last date the subject was known to be alive.

Progression-free survival (PFS) was assessed from Day 1 of treatment to the date when an objective disease progression is observed. Death will be regarded as a progression event in those subjects who die before disease progression. Subjects without documented objective progression at the time of the final analysis will be censored at the date of their last tumor assessment.

Safety: Safety was monitored by physical examination, vital signs, hematology, esophageal and pulmonary toxicities, and AE assessments at the end of each cycle of chemotherapy since commencement of chemoradiotherapy. Severity of AEs was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical methods:

The primary endpoint of the study was the response rate. Kaplan-Meier analysis was used to evaluate OS.

The Fisher's exact test or chi-squared test was used to compare categorical variables. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) 13.0. All statistical tests were two-sided, and a p-value of less than 0.05 was considered as statistically significant.

For OS, analysis was performed in two different populations. The intent-to-treat (ITT) population included all randomized patients in the study regardless of compliance with the protocol or completion of the study. The per-protocol (PP) population was defined as a subset of the ITT population who completed the study without any major protocol violations.

Summary: A total of 34 patients were recruited from 09 December 2010 to 27 August 2013. The male:female ratio was 30:4. Median age was 63 years (42 to 77 years). Histology distribution: adeno 11, squamous 11, nonsmall cell carcinoma NOS 11, large cell neuroendocrine carcinoma 1. Group stage IIIA (22): Group IIIB (12). Six were never-smokers. Seven patients did not complete protocol treatments (3 withdrew consent, 2 died of chest infections, 1 died of PD, 1 stopped due to brain metastases). Of the 27 patients evaluable for primary endpoint, the ORR was 77.8% (CR/PR/SD/PD: 5/16/2/4). Median OS was 25.5 months for the ITT population and 35.5 months for the PP population.

The treatments were generally well tolerated. Three deaths occurred during the course of treatment (2 due to chest infection, 1 due to progressive disease), 4 stopped treatment prematurely (1 due to development of brain metastases, 3 withdrew consent). Severe adverse events occurred in 15 patients (44.1%). Serious adverse events (G3 or G4) included anemia (6 patients), hyponatremia (3 patients), esophagitis (3 patients), intestinal obstruction (1 patient), gastric ulceration (1 patient), pneumonia (1 patient), septic shock (1 patient), atrial fibrillation (1 patient), and worsening of preexisting COPD (1 patient). The treatment was generally well tolerated, and 27 patients (73%) could complete the protocol treatment.

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