A randomized phase II clinical trial of nab-paclitaxel and carboplatin compared with gemcitabine and carboplatin as first-line therapy in locally advanced or metastatic squamous cell carcinoma of lung

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Abstract
Background: Recent advances have shown that histology and genetic biomarkers are important in patient selection, which have led to significantly better outcomes for lung cancer patients. However, most new treatments only apply to adenocarcinoma or non-squamous, and in squamous carcinoma there is little breakthrough. In a phase III trial nab-paclitaxel plus carboplatin showed superior response rate over paclitaxel and carboplatin. In subgroup analysis the squamous histology appeared to be a predictive factor to nab-paclitaxel treatment.

Methods/Design: This is an open-label, randomized, active controlled phase II trial. A total of 120 untreated advanced squamous lung cancer patients are randomized at a 1:1 ratio to receive nab-paclitaxel (135 mg/m², d1, 8, q3w) plus carboplatin (AUC 5, d1, q3w) or gemcitabine (1,250 mg/m², d1, 8, q3w) and carboplatin (AUC 5, d1, q3w). The primary endpoint is objective response rate and the second endpoints are progression free survival, overall survival, safety and biomarkers associated with nab-paclitaxel. The treatment will continue up to six cycles or intolerable toxicity.

Discussion: This ongoing trial will be the first prospective randomized trial to explore the efficacy of nab-paclitaxel as the first-line treatment specifically in squamous carcinoma of lung.

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Trial Registration: Clinicaltrials.gov reference: NCT01236716
Keywords: Nab-paclitaxel, Carboplatin, Gemcitabine, Squamous, Carcinoma, Lung

Background
For both men and women, lung cancer is the leading cause of death and non-small cell lung cancer (NSCLC) represents more than 80% of all lung cancer cases [1]. Compared with best supportive care, platinum-based doublet chemotherapy not only prolongs the survival, but also improves symptom control and the quality of life. It has been the standard of care for advanced NSCLC [2]. Available data suggest that different platinum/third generation chemotherapy agent combinations have similar efficacy in the first line setting [3].

Traditionally, the choice of chemotherapy is based on performance status, age, etc, and histology has not influenced the treatment options. Recent years, personalized treatment has developed rapidly with the emerging of new chemotherapy agents and targeted therapies. Pemetrexed has favorable efficacy and safety profiles in non-squamous NSCLC but not in squamous population [4]. The benefit of bevacizumab is also limited to the non-squamous subtypes [5]. Moreover, most targeted drugs need molecular markers to distinguish patients who would likely to gain survival advantage from treatment, such as epidermal growth factor receptor (EGFR) mutation for EGFR tyrosine kinase inhibitors (TKIs) [6,7], EGFR amplification for cetuximab.
All patients before any trial-related procedures are carried out. 120 patients are randomly assigned to treatment group A: receiving nab-paclitaxel 135 mg/m², d1, 8 and carboplatin AUC 5, d1 every three weeks; or group B: receiving gemcitabine 1,250 mg/m², plus carboplatin AUC 5, d1 every three weeks. Both group A and B receive up to six cycles of chemotherapy.

**Study objectives**

The primary objective of this study is to compare the ORR of Abraxane plus carboplatin to gemcitabine plus carboplatin. Secondary objectives include PFS, OS, safety and biomarker parameters. Exploratory endpoints include expression of secreted protein acid rich in cysteine (SPARC) and caveolin-1 in NSCLC tissue and their predictive value in PFS and OS. Tumor samples will be collected from all randomized patients and tested in the central lab of Guangdong Lung Cancer Institute, Guangdong Academy of Medical Sciences.

**Statistics**

The sample size calculation assumes that in advanced squamous lung cancer, Abraxane + carboplatin has an ORR of 40% [11] while gemcitabine + carboplatin has an ORR of 19% [3]. With inequality test using ratios of two independent proportions, the sample size is 120 patients in total, which will be randomly assigned at a 1:1 ratio between two treatment arms (60 in each). This sample size will provide 80% power with two-sided type I error of 0.05 to reject the primary efficacy null hypothesis that Abraxane + carboplatin/gemcitabine + carboplatin hazard ratio for ORR is equal to 1.0.

The primary objective will be analyzed by chi-square test. Secondary endpoints of PFS and OS will be evaluated by Kaplan-Meier method with a 95% confidence interval. The log-rank method will be used to compare the difference between the survival curves of two arms. Multifactorial Cox regression analysis will be used to determine the prognostic factors of the survivals including PFS and OS.

**Ethical considerations**

Prior to initiation of the study, each of the participating sites must obtain local or central ethics committee approval from the appropriate body. All research will conform to the Declaration of Helsinki, as well as local legal and ethical requirements.

**Discussion**

Previous researches have shown comparable efficacy and good safety profile of Abraxane-based chemotherapy in the first-line treatment of advanced NSCLC, compared to other standard platinum-based doublets. In a phase III trial, the ORR of Abraxane plus carboplatin is significantly higher than solvent-based paclitaxel and the survival time is equivalent in two groups [11]. The most
The incidence of Grade 3-4 thrombocytopenia and anemia are higher in Abraxane group than solvent-based paclitaxel arm, while the incidence of neutropenia is higher in solvent-based paclitaxel arm. But patients who have received chemotherapy for neoadjuvant or adjuvant treatment at least 12 months before the study treatment are eligible.

Patients' blood test must meet the following requirements:
- ANC ≥ 1.5 x 10⁹/L
- Platelets ≥ 100 x 10⁹/L
- Hb ≥ 90 g/L (9 g/dL)

Patients' clinical biochemistry examination must meet the following requirements:
- ALT and AST ≤ 2.5 x upper limit of normal (ULN) without liver metastasis, ALT and AST ≤ 5 x ULN with liver metastases
- Serum creatinine ≤ 1.5 x ULN
- Total bilirubin ≤ 1.5 x ULN

Urine pregnancy test is negative for women, within 14 days before study treatment.

Estimated life expectancy of at least 3 months.

Patients will comply with the clinical trial protocol.

Patients voluntarily participate in clinical trial and the informed consent must be signed.

Primary brain tumor or central nervous system metastatic tumor.

Serious mental disorder.

Serious dysgnosia or cognitive dysfunction.

Other serious comorbidities.

Alcohol or drug dependence.

Previously allergic to drugs used in the study.

Patients who are deemed unsuitable to participate in the study.

Table 1 Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| Previously untreated, histologically documented stage IIIB to stage IV or stage IIIA that is not amenable to regional therapy (7th Edition of TNM Staging Criteria) squamous cell carcinoma of lung. Previously untreated, histologically documented squamous cell carcinoma of lung with stage IV or locally advanced disease that is not amenable to radical regional therapy (7th Edition of TNM Staging Criteria). | Patients who are currently undergoing other anti-tumor therapies. |
| At least one measurable tumor lesion as defined by RECIST criteria. | Patients who were enrolled into any other clinical trial within 4 weeks of study entry. |
| 18 to 85 years of age. | Any clinical laboratory findings give reasonable suspicion of a disease or condition that contraindicates the use of any study medication or render the subject at high risk from treatment. |
| ECOG performance status 0-1. | Primary brain tumor or central nervous system metastatic tumor. |
| Patients have no previously malignant tumors or history except cured cervical carcinoma in situ, basal cell carcinoma or superficial bladder cancer (T<sub>1a</sub>, T<sub>1b</sub>, or T<sub>1</sub>). | Serious mental disorder. |
| Patients should not have been treated with chemotherapy such as gemcitabine, platinum and taxane. But patients who have received chemotherapy for neoadjuvant or adjuvant treatment at least 12 months before the study treatment are eligible. | Serious dysgnosia or cognitive dysfunction. |
| Patients’ blood test must meet the following requirements: | Other serious comorbidities. |
| Patients’ clinical biochemistry examination must meet the following requirements: | Alcohol or drug dependence. |
| Patients voluntarily participate in clinical trial and the informed consent must be signed. | Previously allergic to drugs used in the study. |
| Patients who are deemed unsuitable to participate in the study. | |

Thus Abraxane seems an optimal choice of third generation chemotherapy agents to be combined with platinum as the standard treatment due to its high activity and favorable safety profile. Moreover, retrospective subgroup analyses showed that in squamous histology group, there were more significant ORR benefit and OS improvement trend. Squamous cell carcinoma consists approximately 30% of all NSCLC but new treatment options are few. There is huge unmet medical need to increase the prognosis of this patient population. Abraxane has the active agent of paclitaxel, which is an approved agent for treatment of squamous cell carcinoma.
squamous cell lung cancer, as well as the albumin-bound property which increases the drug distribution and concentration to a new level. Furthermore, studies have shown that SPARC is an albumin-bound protein that is rich in tumor matrix and may play an important role in absorbing Abraxane into the tumor site [12]. SPARC may serve as a predictive or prognostic biomarker of Abraxane-based therapy. Thus Abraxane has the potential to be the optimal treatment choice in squamous carcinoma of lung to achieve better response and survival.

This trial will be the first study to prospectively compare Abraxane-based regimen with a currently standard treatment for squamous histology patients. A total of 120 patients will be randomized at a 1:1 ratio to receive Abraxane 135 mg/m², d1,8 plus carboplatin AUC 5, d1, or gemcitabine 1,250 mg/m² plus carboplatin AUC 5, d1, both in a cycle of three weeks and up to six cycles. The choice of Abraxane dosage and schedule is based on previous researches and the phase III trial result. Weekly Abraxane has been proved to have better efficacy and safety than every three week schedule [13]. Compared to 100 mg/m² d1, 8, 15 in a four-week cycle in the phase III trial, we implement a modified 135 mg/m² d1, 8 in a three-week cycle schedule to ensure a similar dose intensity but more timely treatment break in order to further reduce toxicity.

This study, together with findings from other phase I/II/III studies of Abraxane in NSCLC, will provide valuable insight to the role of Abraxane in the optimal treatment choice for squamous carcinoma of lung.

Competing interests
This study received research grant from Celgene Corporation.

Authors’ contributions
All authors have been involved in critically revising the drafts of the manuscript and read and approved the final manuscript. YJY was involved in manuscript drafting. All authors have been involved in the development of the study design. All authors read and approved the final manuscript.

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References
1. National Office for Cancer Prevention and Control & National Central Cancer Registry, Disease Prevention and Control Bureau, Ministry of Health: Chinese Cancer Registry Annual Report 2010: Cancer Incidence and Mortality in Chinese Cancer Registration Areas in 2007. No. 27 Taiping Road Haidian District, Beijing, China (Postcode: 100850): Military Medical Science Publishing House; 2011.

2. National Comprehensive Cancer Network (NCCN) NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Fort Washington, PA: NCCN; 2011. Ver. 2.2012. [In http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf]

3. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002, 346:92–98.

4. Scaglotti G, Parikh P, von Pawel J, Risea G, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digimart R, Zukin M, Lee JS, Mellingerd A, Park K, Pali S, Robiki J, Goelos T, de Marinis F, Simms L, Sugerman RP, Gandara D: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008, 26:3543–3551.

5. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH: Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006, 355:2562–2550.

6. Ma X, Wu YL, Thongprasert S, Yang CH, Chu DT, Saigusa N, Supawaratrong P, Han B, Margono B, Khinson Y, Nichikawa O, Yhe Y, Yang JI, Chiewkisulgong B, Jhang H, Duffield EL, Watkins CL, Armour AA, Fukuka M, Goffinib or carboplatin-paclitaxel in pulmonary adencarcinoma. N Engl J Med 2009, 361:947–957.

7. Rosell R, Caproncy E, Gervais R, Vergnergere A, Massuti B, Felp P, Palermo R, Garcia-Gomez, Pallares C, Sanchez JIM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Millea M, Reguat N, Altavilla G, Jimenez U, Provemico M, Moreno MA, Terraera J, Muñoz-Langa J, et al: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicenter, open-label, randomised phase 3 trial. Lancet Oncol 2012, 13:239–246.

8. Parker R, Pereira JR, Szcesna A, von Pawel J, Kizkowitz M, Ramli R, Vynnycheno I, Park K, Yu CT, Ganul V, Rohl JK, Bajetta E, O’Byrne K, de Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U, FLEX Study Team: Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009, 373:1525–1531.

9. Kwak EL, Bang YJ, Camdge DR, Shaw AT, Solomon B, Ou SH, Debeur BJ, Jänecke PA, Costa DB, Varella-Garcia M, Kim WH, Lynch T, Fidias P, Stubbis H, Engelman JA, Sequist LV, Ban W, Gandul F, Mingo-Kenudon M, Wei GC, Shreeve SW, Ratan MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Saliga R, Pham GI, Clark GW, et al: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010, 363:1693–1703.

10. Forbes SA, Sharma G, Bamford S, Dawson E, Kom C, Dementis J, Mezina Z, Teagut JW, Fyreal PA: The catalogue of somatic mutations in cancer (COSMICS).Curr Protoc Hum Genet 2008, 41–52: chapter 10: unit 10.11.

11. Sociinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnycheno I, Okamoto I, Hon JK, Hinh V, Bahr P, Zhang H, Iglesias A, Renschler MF, Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012, 30:2055–2062.

12. Kourkourakis M, Girotomanolaki A, Breikmen R, Sviridov E, Gatter KC, Harris AL, Siegel EH: Enhanced expression of SPARC/osteonectin in the tumor-associated stroma of non-small cell lung cancer correlated with markers of hypoxia/ acidity and with poor prognosis of patients. Cancer Res 2003, 63:3576–3580.

13. Sociinski MA, Manikhas GM, Strozyakovskiy DL, Makhson AN, Chepovov SV, Orlov SV, Yablonsky PK, Bahr P, Iglesias A: A dose finding study of weekly and every-3-week nab-paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol 2010, 5:862–861.

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