Current Trial Report

A Phase I/II Study of Necitumumab Plus Pembrolizumab, Nab-Paclitaxel, and Carboplatin for Previously Untreated Advanced Squamous Non–Small Cell Lung Cancer Study: (NEJ048A/NEXUS)

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Abstract

Background: Platinum-based combination therapy plus a programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitor is a standard treatment for patients with stage IV non–small cell lung cancer. However, necitumumab is used with gemcitabine and cisplatin as a first-line treatment option for squamous cell lung cancer (SqCLC). Furthermore, the combination of necitumumab with immune checkpoint inhibitors has the potential to enhance tumor immunity and improve the therapeutic effect. Thus, we planned and initiated this phase I/II study to evaluate the safety and efficacy of necitumumab plus pembrolizumab, nanoparticle albumin–bound (nab)-paclitaxel), and carboplatin therapy for patients with previously untreated SqCLC. **Patients and Methods:** In phase I, the primary endpoint is the tolerability and recommended dose of necitumumab combined with pembrolizumab plus nab-paclitaxel and carboplatin. In phase II, the primary endpoint is the overall response rate. Secondary endpoints are disease control rate, progression-free survival, overall survival, and safety. Forty-two patients will be enrolled in phase II. **Conclusion:** This is the first study to investigate the efficacy and safety of necitumumab plus pembrolizumab combined with platinum-based chemotherapy in patients with previously untreated SqCLC.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. The choice of treatment for advanced NSCLC is based on factors such as the patient's Eastern Cooperative Oncology Group performance status, histology, and type of gene mutation. For squamous cell lung cancer (SqCLC), treatment with pemetrexed or bevacizumab is not recommended due to limited efficacy and toxicity. In addition, treatment of SqCLC with tyrosine

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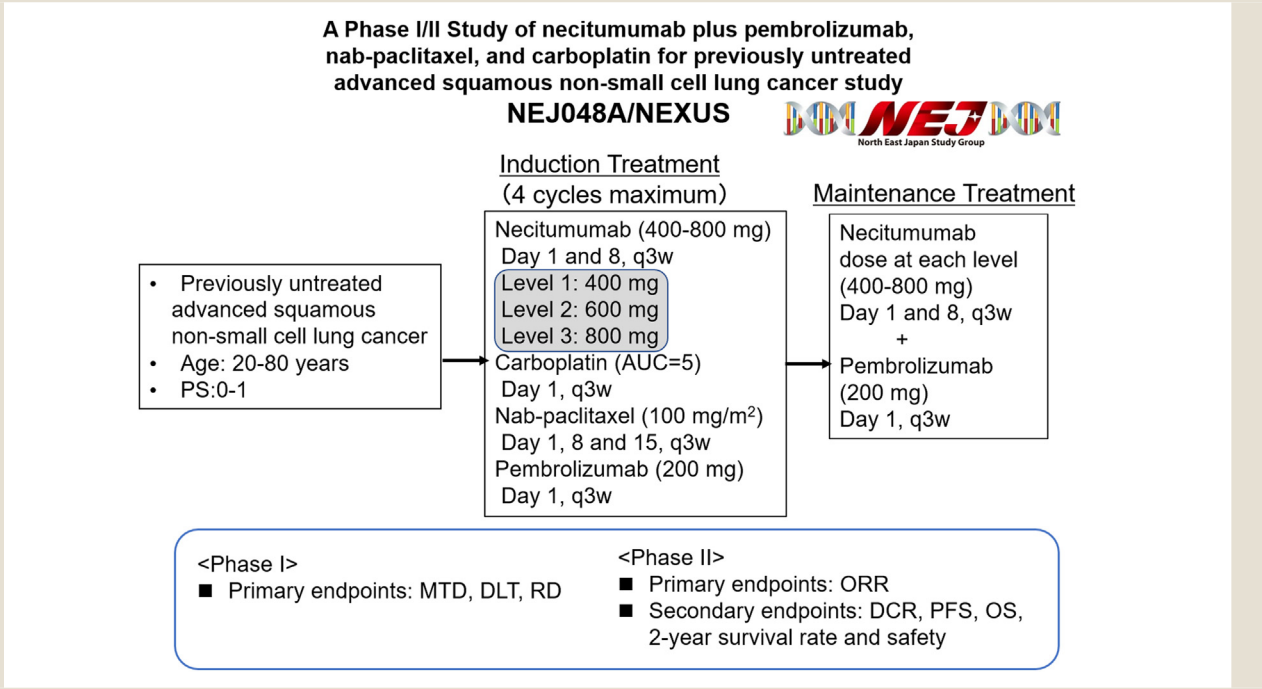
Figure 1 Schema of the trial design.



kinase inhibitors, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and anaplastic lymphoma kinase (ALK) inhibitors, is rarely indicated. This is because cases with driver gene mutations that can be targeted for treatment are rare.[1, 2] Therefore, there are limited treatment options for patients with SqCLC versus those with non-SqCLC.

The clinical use of necitumumab in combination with gemcitabine and cisplatin has been approved as a first-line treatment option for SqCLC. On the other hand, platinum-based combination therapy plus a programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitor is recommended for patients with stage IV NSCLC (naïve EGFR mutation and ALK translocation negative) and performance status 0 to 1. The combination of pembrolizumab, nanoparticle albumin–bound (nab)-paclitaxel, and carboplatin is mainly used for the treatment of SqCLC.[3] Blockage of EGFR signaling enhances the expression of major histocompatibility complex class I and interferon-gamma (IFN-γ) receptor, leading to activation of antitumor immunity. In antitumor activity of PD-1 blockade by EGFR inhibition, pembrolizumab combined with cetuximab shows promising clinical activity for recurrent or metastatic head and neck squamous cell carcinoma.[4] Hence, the use of necitumumab in combination with chemotherapeutic agents other than gemcitabine and cisplatin should also be considered. Necitumumab/nab-paclitaxel/carboplatin first-line therapy showed favorable efficacy outcomes with manageable toxicity in patients with stage IV SqCLC.[5] Examples of such drugs include pembrolizumab, nab-paclitaxel, and carboplatin, which are standard agents for the treatment of SqCLC. The addition of necitumumab to the current standard combination has the potential to improve response rates and prolong progression-free survival and overall survival (OS).

In the overseas phase III SQUIRE study and Japanese phase I/IIb JFCM study of necitumumab, the investigators reported hypomagnesemia, arterial thromboembolism, venous thromboembolism, skin disorders, etc., which are common adverse events associated with anti-EGFR antibody drugs.[6,7] Since 4 drugs are used in combination, it is considered necessary to monitor the potential development of myelosuppression, (eg, leukopenia), interstitial lung disease, peripheral neuropathy, and thyroid dysfunction, which are specifically linked to these agents.

Based on these data, we planned and initiated this phase I/II study to evaluate the safety and efficacy of necitumumab plus pembrolizumab, nab-paclitaxel, and carboplatin therapy for patients with previously untreated SqCLC.

Study Protocol

Study Design and Clinical Endpoints. This is a multicenter, prospective study consisting of 2 phases. In phase I, patients will be enrolled in a 3-plus-3 design, with dose escalation permitted according to the incidence of dose-limiting toxicity (DLT). DLT is defined as the development of one of the following adverse events, if considered definitely, probably, or possibly related to necitumumab. The grading of DLT is as follows: grade 4 neutropenia lasting >7 days; grade ≥3 thrombocytopenia with signs of bleeding or requirement of platelet transfusions; grade ≥3 neutropenia associated with fever; grade ≥3 skin toxicity despite best preemptive and supportive care; grade ≥3 nausea, diarrhea, or vomiting despite best preemptive and supportive care; grade 3 to 4 nonhematologic toxicity other than the

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Table 1 Eligibility Criteria.

Key inclusion	
1)	Histologically or cytologically proven squamous non–small-cell lung cancer
2)	Stage IIIB who cannot receive curative radiation, IIIC, IVA, IVB, or postoperative recurrence
3)	Measurable lesions based on RECIST Ver.1.1
4)	Previously untreated
5)	Age 20 to 80 years
6)	ECOG PS, 0 or 1
7)	Adequate organ function within 14 days prior to registration
8)	Written informed consents
Key exclusion	
1)	Interstitial lung disease (ILD), drug-induced ILD, history of radiation pneumonitis requiring steroid therapy
2)	Unstable brain metastasis or spinal cord compression
	(Brain metastasis is allowed if the patient is asymptomatic at the time of registration.
	Patients who received radiotherapy to the brain can participate,
	but are required to have an interval 14 days between the last days of radiotherapy and study treatment.)
3)	Received radiation to the primary lesion and the evaluated lesion
4)	Serious complications (such as poorly controlled pulmonary, hepatic, or renal disease)
5)	Active hepatitis B virus
6)	Pleural effusion, pericardial effusion, and ascites requiring drainage by drains
7)	Concurrent multiple cancers or heterogeneous multiple cancers with a disease-free interval of 5 years or less
8)	An expected life expectancy of 12 wk or less
9)	Conjunctivitis, hypomagnesemia, or skin disorders that require treatment
10)	Uncontrolled hypertension
11)	Superior vena cava syndrome
12)	Grade 2 or higher peripheral neuropathy
13)	Active autoimmune diseases that required systemic treatment within the past 2 y
14)	Taking corticosteroids
15)	Significant cardiac disease, uncontrolled congestive heart failure (NYHA III or IV degrees), or uncontrolled arrhythmia due to medication

above (excluding electrolyte abnormality); failure to initiate dosing within 21 days of the scheduled start date of the second course (day 22) due to an adverse event; and occurrence of any adverse events resulting in the nonadministration of at least 2 infusions of necitumumab. Figure 1 shows the study schema.

Objectives

In phase I, the main objective was to assess the tolerability and recommended dose of necitumumab plus pembrolizumab, nab-paclitaxel, and carboplatin. The aim of phase II is to explore the efficacy and safety of the 4-drug combination therapy in 42 patients.

Endpoints

In phase I, the primary endpoint is the assessment of the maximum tolerated dose, DLT, and recommended dose of necitumumab plus pembrolizumab, nab-paclitaxel, and carboplatin. In phase II, the primary endpoint is the overall response rate (ORR). Secondary endpoints are disease control rate, PFS, OS, 2-year survival rate, and safety.

Eligibility Criteria

The key inclusion and exclusion criteria are listed in Table 1.

Treatment Plan

Patients will receive necitumumab at each level (400-800 mg) on days 1 and 8 of a 3-week cycle, while carboplatin (area under the curve: 5.0 on day 1), nab-paclitaxel (100 mg/m^2 on days 1 and 8), and pembrolizumab (200 mg on day 1) will be administered intravenously every 3 weeks for a maximum of 4 cycles. Patients without disease progression after 4 cycles of induction therapy will continue treatment with necitumumab at each level (400-800 mg) on days 1 and 8 of a 3-week cycle plus pembrolizumab (200 mg on day 1) every 3 weeks until the occurrence of disease progression or unacceptable toxicity.

Follow-up and assessment

Patients will be followed up for at least 2 years from the time of enrollment. Radiographic and computed tomographic evaluations of tumors are performed and analyzed according to the response evaluation criteria in solid tumors (version 1.1) by each investigator every 6 weeks for the first 48 weeks, and every 12 weeks for the remaining follow-up period. Each patient is followed up every 6 months after the discontinuation of protocol treatment.

Statistical Analyses

This study will include an adequate number of patients for the assessment of treatment safety and efficacy. In an international,

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randomized, double-blind, phase III study of pembrolizumab plus paclitaxel or nab-paclitaxel and carboplatin (hereafter referred to as chemotherapy) versus chemotherapy in chemotherapy-naïve patients with advanced or recurrent SqCLC, the ORR in the pembrolizumab combination group was 62.6% (95% confidence interval [CI]: 56.6-68.3).[3] We referenced the ORR of 51% in a previous phase II trial of necitumumab/nab-paclitaxel/carboplatin first-line therapy in patients with SqCLC to set the efficacy threshold.[5]

Based on the above findings, it was estimated that 38 eligible patients with a threshold response rate of 50% and an expected ORR of 67% will be required to ensure statistical power of 0.80 at a 1-sided alpha error of 0.10. Assuming a drop-out rate of 8%, a total of 42 patients need to be enrolled in the study.

The safety analysis set will include patients who received the protocol treatment at least once. For the safety analysis, we will calculate the proportion of patients in the safety analysis set who discontinue the protocol treatment due to toxicity. We will also document the frequency of the worst grade for each reported adverse event during the treatment course using the common terminology criteria for adverse events, version 5.0. This will be represented as the proportion of patients who experience grade 4 hematologic toxicity or grade 3 nonhematologic toxicity. For the efficacy analysis, we will determine point estimates of the ORR, complete response rate, and disease control rate using the response evaluation criteria in solid tumors, version 1.1, and the 95% CIs using the Clopper–Pearson method. The difference in ORR and the associated 95% CIs will also be estimated. The Kaplan–Meier method will be used to estimate the PFS and OS.

Discussion and Conclusions

This is the first study to investigate the efficacy and safety of necitumumab plus pembrolizumab combined with platinum-based chemotherapy in patients with previously untreated SqCLC. Previously, a combination of immune checkpoint inhibitors (ICI) and chemotherapy was used for the first-line treatment of SqCLC; however, this treatment did not demonstrate sufficient efficacy in some patients.[3] Necitumumab is an antibody against EGFR, inhibiting tumor growth by blocking EGFR-mediated signaling. EGFR is also involved in the activation of regulatory T cells, suppressing tumor immunity and the expression of PD-L1, which is involved in immune evasion in tumor tissues.[8,9] The mechanisms underlying these effects differ from those by which ICI affects tumor immunity. Hence, the combination of necitumumab with ICI may enhance tumor immunity and improve the therapeutic effect. We think that the results of this phase I/II NEXUS study will provide valuable information regarding the safety and preliminary efficacy of treatment with necitumumab plus ICI. These findings may influence the future treatment strategy and improve the outcomes of many patients with untreated SqCLC.

Disclosure

Nippon Kayaku Co., Ltd. provides necitumumab for the clinical trial; A.M., H.A., S.W., T.S., Y.T., Y.H., S.S, T.O., S.M., K.K., and M.S. received honoraria from AstraZeneca; H.A., S.W., Y.H., S.S, T.O., S.M., and M.S. received honoraria from Eli Lilly Japan; H.A., S.W., T.S., Y.H., S.S, T.O., S.M., and M.S. received honoraria from Taiho Pharmaceutical Co. Ltd; H.A., S.W., T.S., Y.T., Y.H., S.S, T.O., S.M., and M.S. received honoraria from Chugai Pharmaceutical Co. Ltd; H.A., S.W., T.S., Y.H., S.S, and M.S. received honoraria from Ono Pharmaceutical; S.W., T.S., Y.H., S.S, T.O., S.M., and M.S. received honoraria from Bristol-Myers Squibb; A.M., H.A., Y.H., S.S, K.M., and M.S. received honoraria from Kyowa Kirin; A.M., S.W., T.S., Y.T., Y.H., S.S, M.M, and M.S. received honoraria from Nippon Kayaku Co., Ltd; Y.H., S.S, T.O., K.K., and M.S. received honoraria from Takeda Pharmaceutical; H.A., S.W., T.S., S.S, S.M., and M.S. received honoraria from MSD K.K; S.W., T.S., Y.H., S.S, and M.S. received honoraria from Novartis Pharmaceutical Co. Ltd; S.W., T.S., S.S, T.O., K.M., and M.S. received honoraria from Nippon Boehringer Ingelheim Co. Ltd; S.W., T.S., and M.S. received honoraria from Daiichi-Sankyo; K.M. received honoraria from Astellas; Y.H., S.M. received honoraria from Eisai; A.M., S.W., T.S., Y.H., S.S, S.M., received honoraria from Phizer Japan Inc; S.S, received honoraria from Yakult Honsha; H.A., S.S, received honoraria from Merck; S.S, received honoraria from Amgen, AbbVie, Otsuka, Thermo Fisher Scientific and Towa Pharmaceutical; T.S. received research funding from AstraZeneca, Chugai Pharmaceutical Co Ltd, Nippon Boehringer Ingelheim Co Ltd, MSD K.K, and Novartis Pharmaceutical Co Ltd; Y.T. received research funding from Ono Pharmaceutical and Phizer Japan Inc; S.M. received research funding from Eisai; K.M. received consulting fees from Nippon Kayaku Co., Ltd; M.S. received research funding from Taiho Pharmaceutical, Chugai Pharmaceutical Co. Ltd, Eli Lilly, MSD K.K, and Nippon Boehringer Ingelheim Co. Ltd.

CRediT authorship contribution statement

Akihiko Miyanaga: Conceptualization, Methodology, Writing – original draft. **Hajime Asahina:** Supervision, Writing – review & editing. **Satoshi Watanabe:** Supervision, Writing – review & editing. **Takehito Shukuya:** Supervision, Writing – review & editing. **Yukari Tsubata:** Supervision, Writing – review & editing. **Yukio Hosomi:** Supervision, Writing – review & editing. **Shunichi Sugawara:** Supervision, Writing – review & editing. **Makoto Maemondo:** Supervision, Writing – review & editing. **Tetsuya Okano:** Supervision, Writing – review & editing. **Satoshi Morita:** Methodology, Formal analysis, Writing – review & editing. **Kotone Matsuyama:** Supervision, Writing – review & editing. **Kunihiko Kobayashi:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Masahiro Seike:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

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This investigation is a physician-led clinical trial conducted based on a contract between Nippon Kayaku Co., Ltd. and Nippon Medical School Hospital. Nippon Kayaku Co., Ltd. Is the party to the contract with Nippon Medical School Hospital and the payment of the expenses for this clinical trial to Nippon Medical School hospital. The clinical trial coordinating investigator of this study is responsible for decisions regarding the planning, conduct, and presentation of this clinical trial. The clinical trial is conducted

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while ensuring the transparency and reliability of the data to avoid bias introduced by Nippon Kayaku Co., Ltd. In accordance with the transparency guidelines stipulated by the Japan Pharmaceutical Manufacturers Association and based on the "Guidelines for Transparency in Relationships between Nippon Kayaku Co., Ltd. and Medical Institutions," Nippon Kayaku Co., Ltd. makes appropriate disclosure regarding funding and other matters. Nippon Kayaku Co., Ltd. does not induce commercially advantageous positioning in funding this clinical trial.

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