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Preoperative nivolumab to evaluate pathological response in patients with stage I non-small cell lung cancer: a study protocol of phase II trial (POTENTIAL)

Atsushi Kagimoto ,[1] Yasuhiro Tsutani ,[1] Takahiro Mimae,[1] Yoshihiro Miyata,[1] Norihiko Ikeda,[2] Hiroyuki Ito,[3] Yoshimasa Maniwa,[4] Kenji Suzuki,[5] Masahiro Tsuboi,[6] Kenichi Yoshimura,[7] Seiji Umemoto,[7] Morihito Okada[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Yasuhiro Tsutani;
tsutani@hiroshima-u.ac.jp

ABSTRACT

Introduction Recently, inhibition of programmed cell death 1 or its ligand has shown therapeutic effects on non-small cell lung cancer (NSCLC). However, the effectiveness of preoperative nivolumab monotherapy for stage I NSCLC remains unknown. The present study aimed to investigate the pathological response of preoperative treatment with nivolumab for clinically node negative but having a high risk of NSCLC recurrence.

Methods and analysis The Preoperative Nivolumab (Opdivo) to evaluate pathologic response in patients with stage I non-small cell lung cancer: a phase 2 trial (POTENTIAL) study is a multicentre phase II trial investigating efficacy of preoperative nivolumab for clinical stage I patients at high risk of recurrence. This study includes histologically or cytologically confirmed NSCLC patients with clinical N0 who were found on preoperative high-resolution CT to have a pure solid tumour without a ground-glass opacity component (clinical T1b, T1c or T2a) or a solid component measuring 2–4 cm in size (clinical T1c or T2a). Patients with epidermal growth factor receptor (EGFR) mutation (deletion of exon 19 or point mutation on exon21, L858R), anaplastic lymphoma kinase (ALK) translocation or c-ros oncogene 1 (ROS-1) translocation are excluded from this study. Nivolumab (240 mg/body) is administrated intravenously as preoperative therapy every 2 weeks for three cycles. Afterward, lobectomy and mediastinal lymph node dissection (ND 2a-1 or ND 2a-2) are performed. The primary endpoint is a pathological complete response in the resected specimens. The secondary endpoints are safety, response rates and major pathological response. The planed sample size is 50 patients. Patients have been enrolled since April 2019.

Ethics and dissemination This trial was approved by the Institutional Review Board of Hiroshima University Hospital and other participating institutions. This trial will help examine the efficacy of preoperative nivolumab therapy for clinical stage I NSCLC.

Trial registration number jRCT2061180016.

Strengths and limitations of this study

- This study is a multi-institutional phase II trial to investigate the efficacy of preoperative nivolumab in patients with stage I non-small cell lung cancer (NSCLC).
- In patients with clinical stage IB–IIIA NSCLC, favourable pathological responses have been reported after preoperative nivolumab monotherapy.
- There are no studies focused on patients with stage I investigating efficacy of preoperative immune check point inhibitor.
- If favourable pathological responses have been achieved by nivolumab for included patients, preoperative nivolumab can be a standard therapy for clinical N0 NSCLC with high risk of recurrence.

INTRODUCTION

With the recent advancements in high-resolution CT (HRCT) or 18-fluorodeoxyglucose positron emission tomography/CT (18F-FDG-PET/CT), early-stage lung cancer is becoming more frequently detected.[1] The standard treatment strategy for clinical stage I non-small cell lung cancer (NSCLC) is radical resection. The prognosis of stage I NSCLC after complete resection is expected to be favourable. However, a large number of patients experience recurrence after complete resection, such that the 5-year disease-free survival rate is 84.3% for clinical stage IA and 65.8% for stage IB.[2] To improve postresection prognosis, adjuvant chemotherapy has been considered for patients with lymph node metastases[3 4] or large-sized primary tumors[5]; nonetheless, this method has not yet achieved sufficiently satisfactory survival outcomes.

Comparable outcome between preoperative and adjuvant chemotherapies has been shown in a meta-analysis.[6] One of the benefits of neoadjuvant chemotherapy is its potential for preoperative identification of clinical and biological surrogate markers that may correlate with responses to therapy and potential long-term outcomes.

Recently, inhibition of programmed cell death 1 (PD-1) or its ligand (PD-L1) has shown therapeutic effects on NSCLC, coupled with other immunological mechanisms that may be more common.[7] Pembrolizumab monotherapy, for example, represents the standard of care as first-line treatment for stage IV or relapsed NSCLC.[8 9] Furthermore, the combination of chemotherapy and PD-1 or PD-L1 inhibitors have shown survival advantages over chemotherapy alone.[10 11] In patients with clinical stage IB–IIIA NSCLC, favourable pathological responses have been reported after preoperative nivolumab monotherapy.[12] Nevertheless, the majority of the patients in this study had stage IIA or more NSCLC with lymph node metastasis. Therefore, the effectiveness of preoperative monotherapy of immune checkpoint inhibitor for stage I NSCLC has still remained unknown. Moreover, a slight benefit of anti-PD-1 inhibitor is seen compared with anti-PD-L1 inhibitor.[13] The present study aimed to investigate the pathological response to preoperative nivolumab, anti-PD-1 inhibitor and therapy for clinical stage I NSCLC in patients at high risk for recurrence.

Study design

Protocol V.7.0, modified 24 November 2020.)

Objective of potential trial

The aim of this study was to investigate the efficacy of preoperative nivolumab in patients with stage I NSCLC. The graphic digest of this trial is shown in figure 1, and summary data are shown in online supplemental materials 1.

Study setting of potential trial

This study is a multi-institutional, non-blinded single-arm phase II trial. Because this study is not a randomised trial, there will be no concealment and comparators. The chief investigator is MO, and the trial statistician is KY.

Resources

This study is funded by Ono Pharmaceutical Co, Ltd (Osaka, Japan, https://www.ono.co.jp/eng/). However, the sponsors are not involved in patient aggregation or analysis.

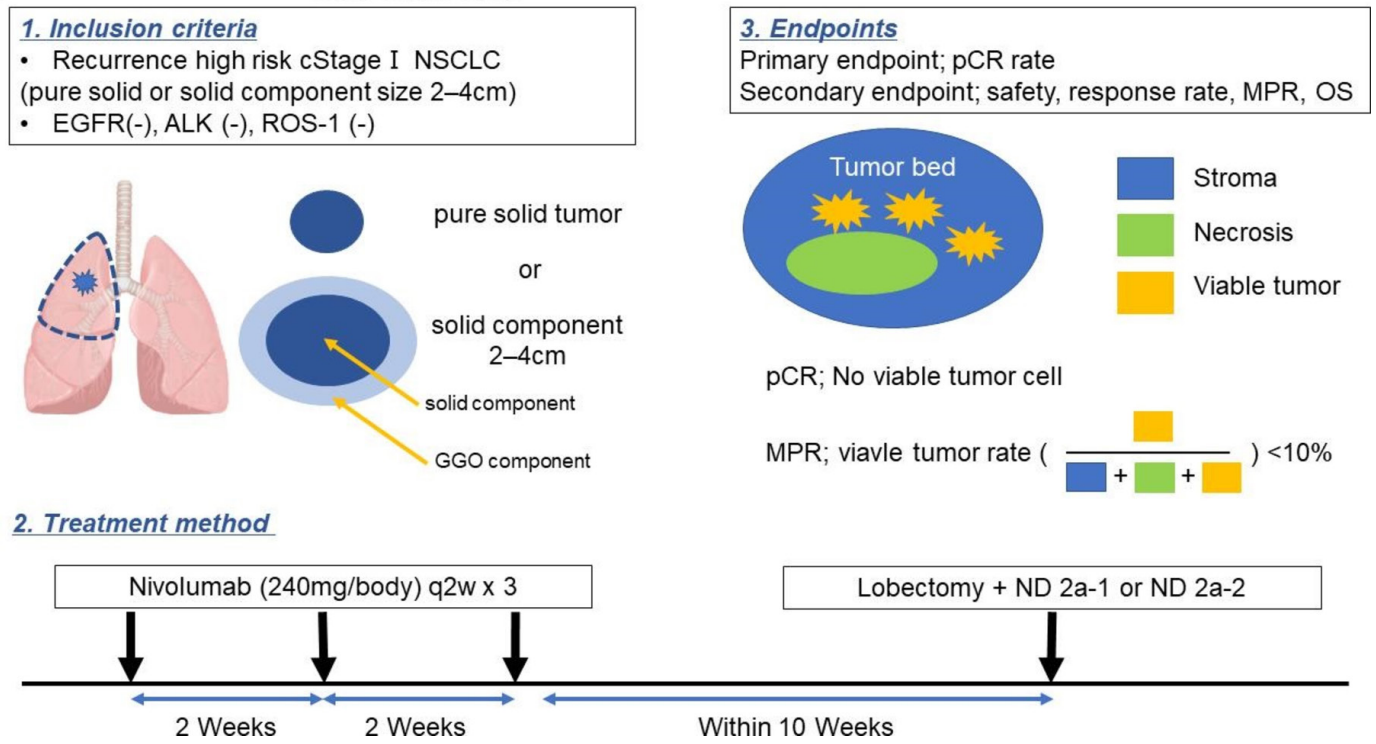

Figure 1 Graphic summary of POTENTIAL trial. This trial includes stage I non-small cell lung cancer (NSCLC) having a high risk of recurrence (pure solid or containing a solid component 2–4 mm in size) without epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) translocation or c-ros oncogene 1 (ROS-1) translocation tests. Nivolumab (240 mg/body) is administrated intravenously as preoperative therapy on day 1 of each 2-week cycle for a total of three cycles. After preoperative therapy termination, lobectomy and mediastinal lymph node dissection are performed in all operable patients. The primary endpoint is the pCR rate in the resected specimens. The secondary endpoints are: (1) safety, (2) response rates and (3) major pathological response. MPR, major pathological response rate; OS, overall survival; pCR, pathological complete response.

Patients

All patients with histologically or cytologically confirmed NSCLC with clinical N0 who were identified to have a pure solid tumour without a ground-glass opacity component (clinical T1b, T1c, or T2a) or a solid component measuring 2–4 cm in size (clinical T1c or T2a) on a preoperative HRCT are determined eligible. Patients who have tumour with clinical T1a are excluded because it is difficult to measure therapeutic effect. After obtaining informed consent by registered clinical investigators of each institute (informed consent form written in Japanese is shown in online supplemental materials 2), baseline data (Eastern Cooperative Oncology Group Performance status, vital signs, ECG, blood examination, urine examination, chest X-ray, pulmonary function test, HRCT, 18F-FDG-PET/CT and MRI of brain) is captured to judge eligibility. These data are also captured before resection. Patients with EGFR mutation (deletion of exon 19 or point mutation on exon21, L858R), ALK translocation or ROS 1 translocation tests are excluded from this study. All eligibility criteria are shown in box 1. Patients have been enrolled since April 2019. Registration is scheduled to run until September 2022.

Treatment method

Nivolumab (240 mg/body) is administrated intravenously every 2 weeks as preoperative therapy on day 1 of the cycle for a total of three cycles.

Reduction of nivolumab is not set, and administration of nivolumab is postponed in the following cases with adverse events (AEs) evaluated on Common Terminology Criteria for Adverse Events (CTCAE) (V.4.0): (1) grade 2 non-skin AEs related to nivolumab other than fatigue; (2) grade 2 abnormalities in creatinine, AST, ALT and/or total bilirubin that are related to nivolumab; (3) grade 3 skin AE related to nivolumab; and (4) other grade 3 laboratory abnormalities related to nivolumab. If the AE returns to grade 1 or to baseline status, nivolumab can be restarted. However, if the AE does not return to grade 1 within 6 weeks from last administration of nivolumab, preoperative therapy is discontinued.

After the preoperative therapy period, including discontinuation of nivolumab administration, radical surgery (lobectomy and mediastinal lymph node dissection, ND2a-1 or ND2a-2) is performed for all operable patients. Surgery is supposed to be performed within 10 weeks of the preoperative therapy completion, but in cases of nivolumab-related AEs, surgery has to be performed after recovery from the AE. The use of immunosuppressants, systemic corticosteroids (>10 mg/day of prednisolone or equivalent) and all kinds of anti-tumour therapy are forbidden. Postoperative adjuvant treatment is neither prescribed nor prohibited.

Serum samples are stored in Hiroshima University Hospital. The specimens used for diagnosis at enrolment, and resected specimens used for diagnosis are also stored in Hiroshima University after central review.

Box 1 Inclusion and exclusion criteria of potential trial

Inclusion criteria

Patients are required to fulfil all of the following inclusion criteria.

1. Histologically or cytologically confirmed non-small cell lung cancer (NSCLC).
2. Resectable NSCLC patients with clinical stage I (by Union for International Cancer Control-TNM classification V.8), defined as having a high risk of recurrence (pure solid without ground-glass opacity component or solid tumour size: 2–4 cm).
3. Eastern Cooperative Oncology Group Performance status 0–1.
4. Have a measurable target lesion, designated by Response Evaluation Criteria in Solid Tumors V.1.1.
5. Patients with no serious disease that make the surgery to be impossible to do.
6. Patient who is considered capable of lobectomy.
   a. Postoperative predicted forced expiratory volume in 1 s (FEV1.0) ≥800 mL * postoperative predicted FEV1.0=preoperative FEV1.0 × (total lung segments − numbers of segments to be resected) / total lung segments.
   b. Saturation of percutaneous oxygen (SpO_2)≥93% (room air).
7. Age: more than 20 years old.
8. Meet the defined criteria of the results of laboratory tests on screening visit.
   a. White cell count ≥2000/mm^3.
   b. Neutrophil count ≥1500/mm^3.
   c. The number of the platelets ≥10 × 10^4/mm^3.
   d. Haemoglobin ≥9.0 g/dL.
   e. Serum creatinine ≤1.5 × upper limit of normal (ULN) or creatinine clearance ≥50 mL/min/1.73 m^2 by Cockcoft-Gault estimation.
   f. AST ≤3.0 × ULN.
   g. ALT ≤3.0 × ULN.
   h. Total bilirubin ≤1.5 × ULN (patients with Gilbert's disease: ≤3 × ULN).
9. For women of childbearing potential (WOCBP), the result of pregnancy test (14 or less days before enrolment) is negative.
10. WOCBP who has agreed with contraception until 5 months after last administration of nivolumab.
11. Patient of aspermia did not need contraception.
12. Patient with written informed consent for participation of the study.
13. Patient who observed the rules about scheduled visit, study schedule and laboratory tests.

Exclusion criteria

Patients who meet any of the following exclusion criteria cannot be registered to this study.

1. Positive for epidermal growth factor (EGFR) mutation (deletion of exon 19, or point mutation on exon21, L858R), anaplastic lymphoma kinase (ALK) translocation or translocation or c-ros oncogene 1 (ROS-1) translocation tests.
2. Known or suspected autoimmune disease.
3. Patients requiring treatment with systemic corticosteroids (over 10 mg/day dose) or immunosuppressants within 14 days before enrolment.
4. Receive or plan to receive live or attenuated vaccine within 28 days prior to registration.
5. Patients who have obvious interstitial lung disease or pulmonary fibrosis by chest CT test.
6. Patients with concomitant or a history of tuberculosis.
7. Patients who have serious or uncontrollable disease.
8. Patients who have prior therapy with chemotherapy or any other anticancer therapy for early stage of NSCLC.

Continued

Box 1 Continued

9. Patients who have medical history of treatment with antiprogrammed cell death 1 antibody, antiprogrammed cell death ligand 1/programmed cell death 2 antibody, anti-CTLA-4 antibody or any other antibody for inhibition or modulation of T cell costimulatory pathway.
10. Positive for hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody, HIV antibody or human T-cell leukemia virus type 1 (HTLV-1) antibody tests.
11. Negative for HBs antigen test, but positive for HBs or hepatitis B core (HBc) antibody test and positive for hepatitis B virus (HBV)-DNA quantitative test.
12. Females who are pregnant, lactating or suspected pregnancy.
13. Patients who have a treatment history of active malignant tumour within 3 years before enrolment.
14. Patients who have a medical history of allergy or hypersensitivity to ingredients of nivolumab.
15. Patients with psychosis or dementia to interfere to obtain informed consent appropriately.
16. Patients who have diverticulitis or symptomatic peptic ulcer disease.
17. Patients who have medical history of haematopoietic stem cell transplantation.
18. Patients whom the physicians in the study consider inappropriate for entry.

Endpoints

The primary endpoint is the pathological complete response (pCR) rate in the resected specimens. The secondary endpoints are safety (AE within 90 days of surgery), response rates (Response Evaluation Criteria in Solid Tumors V.1.1), major pathological response rate (MPR) and overall survival (OS).

The pathological responses (pCR and MPR) of resected specimens are evaluated by central review. The average percentage of viable tumour tissue for each patient was calculated. The entire tumour bed was examined histologically in patients who had a pCR, defined as the absence of viable tumour cells in all slides. Major pathological response was defined as the presence of 10% or less of viable residual tumour cells. AE occurring from the day of first administration of nivolumab to 90 days from surgery is evaluated using the CTCAE (V.4.0). Postoperative complications are classified according to the Clavien–Dindo classification.[14] OS was defined as the time interval from the date of surgery until the date of death due to any cause or until the last follow-up visit. Because main subject of this study is pathological response of resected specimens, survival is analysed at the 6 months from surgery and more long-term survival is going to be analysed as a different observational study. When other studies are planned using specimens collected in this study, review by Hiroshima University Hospital Institutional Review Board will be done again.

Postoperative follow-up

The clinical trial period lasts up to postoperative day (POD) 90, with the subsequent follow-up left to clinical practice at each facility. Physical examination and measurement of vital signs are required on PODs 1, 3, 7, 30, 60 and 90 (at trial termination). Besides, blood sampling is required on PODs 30, 60 and 90, whole body enhanced CT on POD 90 (at trial termination) and ECG on PODs 1 and 7.

Study design and statistical analysis

This trial is conducted as a single-arm trial, not as a randomised clinical trial. In a clinical trial of two doses of preoperative nivolumab for clinical stage IB-IIIA NSCLC, 2 of the 21 patients scheduled for resection showed a pCR.[11] In the present study, the threshold for the pCR rate is set at 10%, and the expected value is 23%, because preoperative nivolumab is administered in three doses, and the study includes patients with earlier stage NSCLC. With an alpha error (one sided) of 0.05 and a power of 0.8, the required number of patients is 48. Therefore, the number of cases in the study is limited to 50. The study is validated if 10 of the 50 patients have a pCR. Patients who cannot undergo surgery are going to be counted as non-pCR.

Interim analysis, data handling and other provisions

No interim analysis is planned for this trial. The in-house monitoring will be performed by EP-Force Co, Ltd (Tokyo, Japan) to evaluate and improve study progress and quality. In order to evaluate the accuracy of preoperative diagnosis and pathological evaluation, we will centrally review the preoperative imaging studies and resected specimens in all the registered patients.

The results of this article will be shared immediately via publication in appropriate journal and meeting. Authorship eligibility is in chief investigator. There are no plans to release the dataset or raw data to the public. The changes made to the protocol will be communicated to the ethics committee and also be included in the clinical trial register. Each case of missing data will be discussed with a statistician to determine the best way to handle it. Protocol revisions and termination of this study will be decided in consultation with the chief investigator and other participants when necessary based on propose from safety evaluation committee. The patient's personal information will be collected in an anonymised form and managed by the case registration centre operated by FiveRings Co, Ltd (Osaka, Japan). The statistical analysis will be performed by Clinical Study Support Co, Ltd (Nagoya, Japan), and all investigators will not be able to access the data. In addition, compensation for health damage caused by this clinical trial will be paid.

Patients and public involvement

Neither patients nor members of the public were directly involved in construction of this study.

Participating institutions (from north to south)

National Cancer Center Hospital East, Tokyo Medical University Hospital, Juntendo University Hospital,

Kanagawa Cancer Centre, Kobe University Hospital and Hiroshima University Hospital.

ETHICS AND DISSEMINATION

This trial was approved by the ethics committee of all participating institutions (Hiroshima University Hospital Institutional Review Board, National Cancer Center Hospital East Certified Review Board, Institutional Review Board of Tokyo Medical University, Juntendo Hospital, Institutional Review Board, Kanagawa Cancer Center Institutional Review Board and Institutional Review Board for Kobe University Hospital). The POTENTIAL study is a multicentre phase II trial investigating efficacy of preoperative nivolumab for clinical stage I patients at high risk of recurrence. If favourable pathological responses are achieved by nivolumab for included patients, preoperative nivolumab can be a standard therapy for clinical N0 NSCLC with high risk of recurrence.

Author affiliations
[1]Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan
[2]Department of Surgery, Tokyo Medical University, Shinjuku-ku, Tokyo, Japan
[3]Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan
[4]Division of Thoracic Surgery, Kobe University Graduate School of Medicine School of Medicine, Kobe, Hyogo, Japan
[5]Department of General Thoracic Surgery, Juntendo University School of Medicine Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
[6]Division of Thoracic Surgery, National Cancer Center-Hospital East, Kashiwa, Chiba, Japan
[7]Center for Integrated Medical Research, Hiroshima University, Hiroshima, Japan

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ORCID iDs
Atsushi Kagimoto http://orcid.org/0000-0002-6189-4349
Yasuhiro Tsutani http://orcid.org/0000-0001-8836-1027

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