Bevacizumab plus nab-paclitaxel and platinum as second-line therapy for driver-gene-negative non-squamous non-small cell lung cancer progressed after first-line immune checkpoint inhibitor-based regimen: a phase 2 single-arm single-center study (BETTER trial)

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Protocol Version No.: 2.0

Protocol No.: BETTER-NSCLC-2021

Protocol Version Date: March 2022

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1 Background

1.1 Overview of Non-Small Cell Lung Cancer

According to GLOBOCAN statistics, both globally and in China, the incidence and mortality of lung cancer ranked among the top three among all tumor types in 2020 [1], making it one of the diseases that seriously threaten people's life and health.

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is the main subtype of lung cancer, which can be divided into non-squamous cell carcinoma (including adenocarcinoma, large cell carcinoma and other subtypes) and squamous cell carcinoma [2].

1.2 Current Treatment Status of NSCLC

Genetic changes with prognostic and/or predictive significance for NSCLC include EGFR mutation, ALK gene rearrangement, ROS1 gene rearrangement, etc. [3]. These genetic alterations are considered drivers of lung cancer development, and various tyrosine kinase inhibitors have been developed for targeted therapy of driver-gene-positive NSCLC.

For driver-gene-negative NSCLC, the previous treatment mainly adopted platinum-containing doublet chemotherapy, and for non-squamous NSCLC, chemotherapy combined with bevacizumab anti-angiogenic therapy could be considered. The overall response rate (ORR) of platinum-containing doublet drugs is about 25%, the progression-free survival (PFS) is maintained at about 4 to 5.5 months, and the overall survival (OS) is about 9 to 11 months. Although bevacizumab, an anti-angiogenic drug, can be considered for driver-gene-negative non-squamous NSCLC, according to studies such as BEYOND and PointBreak, PFS and OS can be increased to about half a year and two years, respectively, but the benefit may have reached a plateau [4-6].

Recently, great progress has been made in immunotherapy, mainly focusing on CTLA-4 inhibitors and PD-1/PD-L1 inhibitors [7]. CTLA-4 is an activation-induced surface molecule of T cells that mediates inhibitory signaling pathways and can turn off T cell-dependent immune responses [7]. Ipilimumab can bind to the CTLA-4 antigen expressed on T cells, interfere with the interaction between CTLA-4 and B7 molecules on antigen-presenting cells, and then block the inhibition of T cell activation caused by CTLA-4/B7 binding [7]. The results of the CHECKMATE-227 study showed that ipilimumab combined with nivolumab showed longer survival time than nivolumab monotherapy and chemotherapy alone in the first-line treatment of advanced driver-gene-negative NSCLC [8]. PD-L1 is a co-regulatory molecule that can be expressed on tumor cells, inhibiting T cell activation, proliferation of previously activated cells, and T cell-mediated cell death [7]. PD-1/PD-L1 inhibitors enhance endogenous T cell anti-tumor effects by blocking the interaction between PD-L1 and PD-1 [7]. Clinical studies of various PD-1/PD-L1 inhibitors at home and abroad have confirmed that PD-1/PD-L1 inhibitors combined with chemotherapy can significantly improve the progression-free survival time of advanced driver-gene-negative NSCLC compared with chemotherapy alone. A variety of drugs including pembrolizumab, camrelizumab, tislelizumab, and sintilimab have been approved by the National Medical Products Administration (NMPA) of China for first-line treatment of advanced driver-gene-negative NSCLC patients in combination with platinum-containing doublet chemotherapy. Among them, pembrolizumab has also obtained the NMPA indication for monotherapy of advanced NSCLC with high PD-L1 expression (PD-L1 TPS $\geq$ 50%) [9-14]. According to the overall survival data of the phase III Keynote-189 clinical trial, pembrolizumab combined with chemotherapy increased the OS of advanced non-squamous NSCLC from 10.6 months to 22 months, and the 3-year overall survival rate from 17.4% to 31.3% [9, 10]. In addition, subgroup analyses of the Keynote-189 clinical trial showed that pembrolizumab combined with chemotherapy significantly improved PFS and OS compared with chemotherapy alone in both PD-L1 positive and negative patients [9, 10]. However, despite this, more than two-thirds of patients with

advanced NSCLC have a survival time of less than 3 years.

1.3 Unmet Treatment Needs in the Second-Line and Beyond Treatment of NSCLC

At present, immunotherapy alone or in combination has been widely used in the first-line treatment of patients with advanced driver-gene-negative non-squamous NSCLC. For the choice of combined chemotherapy regimens, compared with taxane combined with platinum, oncologists now more widely use pemetrexed combined with platinum because of its good drug tolerance. However, for the second-line treatment of such patients after progression, the current guidelines still follow the recommendations of the pre-immunotherapy era. Considering the patient's general condition and quality of life, monotherapy chemotherapy is generally recommended, including single-agent docetaxel, etc. However, the effect of the second-line treatment recommended by the guidelines is limited. For example, the median PFS of docetaxel is only 2.9 months, and the OS is only 8 months [15]. Therefore, there is an urgent need to explore the second-line treatment regimens for patients with advanced driver-gene-negative non-squamous NSCLC who progress after first-line immunotherapy, so as to bring more survival benefits to patients.

1.4 Bevacizumab Combined with Nab-Paclitaxel and Platinum is One of the Effective Treatment Regimens for Advanced nsq NSCLC

Before the era of immunotherapy, bevacizumab combined with paclitaxel/pemetrexed and platinum could be used as a first-line treatment option for advanced non-squamous NSCLC. The results of the phase III randomized trial of ECOG4599 and the confirmatory study in Chinese population (BEYOND study) both suggested that compared with chemotherapy alone with carboplatin combined with paclitaxel, bevacizumab combined with carboplatin and paclitaxel significantly improved objective response rate (ORR), PFS and OS [5, 6]. Since the ECOG4599 and

BEYOND studies were conducted earlier, the paclitaxel used in them was conventional paclitaxel. As a new paclitaxel formulation, nab-paclitaxel wraps paclitaxel particles through nano-sized albumin particles, improving its water solubility and avoiding the use of polyoxyethylene castor oil as a solvent, thereby reducing the common hypersensitivity reactions of conventional paclitaxel [16]. The CA031 study was a phase III randomized trial comparing nab-paclitaxel combined with carboplatin versus conventional paclitaxel combined with carboplatin in advanced NSCLC. The results showed that compared with conventional paclitaxel combined with carboplatin, nab-paclitaxel combined with carboplatin significantly improved ORR (33% vs. 25%, P=0.005), and the absolute values of PFS and OS increased by 10%, although there was no statistical difference (median PFS: 6.3 vs. 5.8 months, P=0.214; median OS: 12.1 vs. 11.2 months, P=0.271) [16]. Compared with conventional paclitaxel, nab-paclitaxel not only avoids hormone pre-treatment, but also significantly reduces hematological toxicity and gastrointestinal toxicity, improving drug safety [16]. The results of the CA031 study showed that in the treatment of advanced NSCLC, the efficacy of nab-paclitaxel is not inferior to or may be slightly superior to conventional paclitaxel, and there is a great improvement in safety. A phase II clinical study explored the efficacy and safety of bevacizumab combined with nab-paclitaxel and carboplatin as first-line treatment for advanced non-squamous NSCLC. The results showed that the ORR of this combination was 31%, and the median PFS and OS were 9.8 months and 16.8 months [17]. The absolute values of ORR, PFS and OS in this study had certain advantages compared with the CA031 study, showing the potential efficacy of the three-drug combination and demonstrating the safety of the three-drug combination.

In the era of immunotherapy, most patients with non-squamous NSCLC did not receive anti-angiogenic drugs or nab-paclitaxel during first-line immunotherapy. Therefore, it is speculated that the second-line use of bevacizumab combined with nab-paclitaxel and platinum is still effective for advanced non-squamous NSCLC, and may be superior to the standard docetaxel treatment.

1.5 Design and Significance

This study explores the efficacy and safety of bevacizumab combined with nab-paclitaxel and platinum as second-line treatment for advanced driver-gene-negative non-squamous NSCLC that failed immune checkpoint inhibitor ± chemotherapy. It is expected to achieve efficacy superior to the current standard second-line docetaxel treatment, provide more clinical benefits for the second-line and beyond treatment of advanced non-squamous NSCLC, and has important significance that may change the guidelines.

2 Objectives

This study will evaluate the efficacy and safety of bevacizumab combined with nab-paclitaxel and cisplatin/carboplatin as second-line treatment for advanced non-squamous NSCLC that failed immune checkpoint inhibitor ± chemotherapy.

2.1 Primary Study Objective

The primary study objective is to evaluate the objective response rate (ORR) of bevacizumab combined with nab-paclitaxel and cisplatin/carboplatin as second-line treatment for advanced non-squamous NSCLC that failed immune checkpoint inhibitor ± chemotherapy. ORR is defined as the proportion of patients whose best response is complete response (CR) or partial response (PR), as determined by the investigator according to RECIST v1.1.

2.2 Secondary Study Objectives

The secondary study objectives are as follows.

Progression-Free Survival (PFS), defined as the time from signing the informed consent form to the first occurrence of disease progression (determined by the

investigator according to RECIST v1.1) or death from any cause (whichever occurs first).

Overall Survival (OS), defined as the time from signing the informed consent form to death from any cause.

Safety, evaluating the incidence and severity of adverse events (AE), with severity determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

2.3 Exploratory Study Objectives

This study intends to conduct subgroup analyses based on demographic data (such as age, gender, etc.), baseline prognostic characteristics (such as ECOG performance status), first-line treatment resistance status (primary resistance, secondary resistance), etc., to explore the differences in efficacy of bevacizumab combined with chemotherapy in the second line among various subgroups.

3 Study design

3.1 Overview

This study plans to enroll 56 patients with advanced EGFR, ALK and ROS1 gene mutation-negative non-squamous NSCLC who progressed after first-line treatment with immune checkpoint inhibitor ± chemotherapy between March 2022 and September 2023. The enrolled patients will receive treatment with bevacizumab combined with nab-paclitaxel and cisplatin/carboplatin. This is a single-center, single-arm phase II clinical study without randomization.

3.2 Inclusion Criteria

1. Patients voluntarily participate in this study and sign the informed consent form.

2. Aged 18 to 75 years old.

3. Histologically or cytologically confirmed stage IIIB to IV non-squamous non-small cell lung cancer that cannot be treated with curative chemoradiotherapy, according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging.

4. No sensitive EGFR mutation, ALK gene rearrangement or ROS1 gene rearrangement.

5. Previous first-line treatment must have included an immune checkpoint inhibitor (anti-CTLA-4, anti-PD-1/PD-L1) as monotherapy or in combination with/without chemotherapy, with documented disease progression. If the first-line treatment was stopped due to adverse reactions, and no other anti-tumor treatment was given after drug withdrawal, patients who developed disease progression can still be enrolled.

6. Patients who received prior neoadjuvant/adjuvant immunotherapy may be eligible if they subsequently received first-line immunotherapy-based treatment for metastatic disease and meet all other criteria.

7. At least one measurable lesion according to RECIST 1.1 criteria. A previously irradiated lesion can be considered a measurable lesion only if it shows clear disease progression after radiotherapy and is not the only lesion.

8. ECOG PS score: 0 to 1.

9. Expected survival time exceeds 3 months.

10. Sufficient hematological and terminal organ function, as defined by the following laboratory test results, which must be within 14 days before the first treatment and meet the following criteria:

(1) Routine blood test (without blood transfusion or use of hematopoietic stimulating factors to correct the status within 14 days):

a) Hemoglobin (Hb) ≥ 90g/L;

b) White blood cell count (WBC) ≥ 3.0 × 10^9/L;

c) Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L;

d) Platelet (PLT) ≥ 80 × 10^9/L.

(2) Biochemical examination:

a) Total bilirubin (TBIL) ≤ 1.5 times the upper limit of normal (ULN);

b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 ULN; for patients with liver metastasis, ALT and AST ≤ 5 ULN;

c) Alkaline phosphatase (ALP) ≤ 2.5 ULN (for patients with liver metastasis, ALP ≤ 5 ULN; for patients with bone metastasis, ALP ≤ 10 ULN;

d) Serum creatinine (Cr) ≤ 1.5 ULN or creatinine clearance rate (CCr) ≥ 45ml/min;

e) Serum albumin ≥ 25 g/L (2.5 g/dL). To meet this standard, symptomatic infusion of human albumin and other nutritional support treatments are allowed.

(3) Urine examination:

Urine dipstick test for proteinuria < 2+;

If the baseline urine analysis of patients with proteinuria is ≥ 2+, a 24-hour urine sample must be collected, and the 24-hour urinary protein must be ≤ 1 g.

(3) Coagulation function test:

For patients not receiving anticoagulant therapy: INR or aPTT ≤ 1.5 × ULN.

11. Patients with asymptomatic central nervous system (CNS) metastases can be enrolled. Patients with symptomatic CNS metastases can also participate in this study if their symptoms are controlled by local treatment as determined by clinicians and meet the following conditions: a) stable condition within 14 days before enrollment after receiving steroid and anticonvulsant treatment; b) completion of radiotherapy within at least 14 days before enrollment; c) no CNS progression found on imaging examination during the screening period after the end of radiotherapy. If the CNS has received local treatment before enrollment, there must be measurable lesions confirmed according to RECIST v1.1 outside the CNS.

12. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to enrollment and must agree to use adequate contraception during the study and for 6 months after the last dose of study treatment.

13. Able to comply with the study and follow-up procedures.

3.3 Exclusion Criteria

Patients with any of the following conditions will not be able to enroll in this study:

1. Histologically mixed small cell and non-small cell lung cancer or mixed squamous and non-squamous non-small cell lung cancer.

2. Patients who have previously received anti-angiogenic drugs (including bevacizumab, anlotinib, apatinib, etc.) and/or paclitaxel preparations (including conventional paclitaxel, paclitaxel liposome, nab-paclitaxel and other paclitaxel preparations) for advanced NSCLC are excluded. If paclitaxel preparations (including conventional paclitaxel, paclitaxel liposome, nab-paclitaxel and other paclitaxel preparations) were used during the adjuvant treatment of NSCLC, patients whose disease recurrence occurred more than 6 months after the end of adjuvant treatment can be enrolled.

3. Patients with a history of other malignancies within 5 years prior to enrollment,

except cured carcinoma in situ of the cervix, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1 (tumor invading basement membrane)], basal or squamous cell skin cancer, localized prostate cancer treated with radical surgery, and ductal carcinoma in situ of the breast treated with radical surgery.

4. Patients with leptomeningeal metastasis or untreated symptomatic or rapidly progressing CNS metastasis are excluded.

5. Unresolved toxic reactions above grade 2 according to CTCAE (5.0) caused by any previous treatment, except alopecia, nausea and vomiting.

Uncontrollable tumor-related pain. Patients requiring analgesic treatment must have a stable analgesic treatment plan when entering the study. If there are symptomatic lesions suitable for palliative radiotherapy (such as bone metastasis or metastasis invading nerves), treatment should be completed before enrollment. Patients should recover from the effects of radiation, and no minimum recovery period is required. Asymptomatic metastatic lesions, if the investigator believes that their further growth may lead to dysfunction or intractable pain (such as epidural metastasis not currently associated with spinal cord compression), local regional treatment should be considered before enrollment.

7. Major surgery other than diagnosis within 4 weeks before the start of study treatment, or expected to require major surgery during the study.

8. Severe infection occurring within 4 weeks before the start of study treatment, including but not limited to hospitalization due to complications of infection, bacteremia or severe pneumonia, or any active infection that the investigator believes may affect patient safety.

9. Patients with any severe and/or uncontrolled diseases, including:

(1) Patients with poorly controlled blood pressure (systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg), with hypertensive crisis or

hypertensive encephalopathy;

(2) Major cardiovascular diseases, including but not limited to: grade I or above myocardial ischemia or myocardial infarction, arrhythmia (including QTc ≥ 440ms) and grade ≥ 2 congestive heart failure (New York Heart Association (NYHA) classification);

(3) Active or uncontrolled severe infection (≥ CTCAE grade 2 infection);

(4) History of immunodeficiency, including HIV positivity or other acquired or congenital immunodeficiency diseases, or history of organ transplantation;

(5) Uncontrolled pleural effusion, pericardial effusion and ascites requiring repeated drainage (once a month or more frequently);

(6) Poorly controlled diabetes [fasting blood glucose (FBG) > 10mmol/L];

(7) Urine routine indicates urinary protein ≥ ++, and 24-hour urinary protein > 1.0 g;

(8) Patients with epilepsy who require treatment;

(9) Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN).

10. Arterial/venous thrombotic events occurring currently or within 6 months, such as cerebrovascular accident (including transient ischemic attack), deep vein thrombosis and pulmonary embolism.

11. History of grade ≥ 2 hemoptysis within 3 months before the start of study treatment (defined as ≥ 2.5 mL of bright red blood each time).

12. Evidence of bleeding tendency or coagulation in the absence of therapeutic anticoagulation..

13. Evidence of tumor infiltration or adjacency to large blood vessels.

14. History of abdominal fistula, gastrointestinal (GI) perforation, abdominal abscess or active gastrointestinal bleeding within 6 months before the start of study treatment.

15. Current or recent (within 10 days before the start of study treatment) use of aspirin (> 325 mg/d) or clopidogrel (> 75 mg/d). Prophylactic use of anticoagulants is allowed.

16. Active pulmonary tuberculosis (TB) or a history of active pulmonary tuberculosis infection within 48 weeks before screening, whether treated or not.

17. History of idiopathic pulmonary fibrosis, organizing pneumonia (such as bronchiolitis obliterans), drug-induced pneumonia, radiation pneumonitis requiring steroid treatment, or active pneumonia with clinical symptoms; or other moderate to severe pulmonary diseases that seriously affect lung function.

18. History of psychoactive substance abuse that cannot be abandoned or mental disorders.

19. Known allergy or hypersensitivity to any component of carboplatin/cisplatin or bevacizumab preparation, and there are no other alternative drugs allowed by this protocol. Patients with known allergy to any component of conventional paclitaxel preparation can be enrolled if they can try nab-paclitaxel treatment after evaluation and judgment by the investigator.

20. Pregnant or lactating women.

21. According to the investigator's judgment, there are comorbid diseases that seriously endanger patient safety or affect the patient's completion of the study.

3.4 Criteria for Discontinuation of Study Treatment

1. Disease progression (PD) or significant deterioration of symptoms determined according to efficacy evaluation criteria.

2. Occurrence of intolerable adverse reactions or serious adverse events, confirmed by the investigator.

3. Patients withdraw informed consent.

4. Patients have severe allergic reactions or hypersensitivity reactions to study drugs during treatment, and the investigator believes that there are no alternative drugs allowed by this protocol or does not recommend continuing this study.

5. Occurrence of concurrent diseases that seriously affect clinical evaluation.

6. Receiving other non-study systemic treatment or using drugs prohibited by this study.

7. Unexpected pregnancy.

8. Death

4 Study Protocol

4.1 Treatment

4.1.1 Treatment Allocation

This is a single-arm, single-center clinical study. After obtaining written informed consent, completing all screening procedures and evaluations, patients who meet the inclusion criteria and do not meet the exclusion criteria will receive treatment with bevacizumab combined with nab-paclitaxel and platinum.

4.1.2 Study Drug Administration

The study drug administration includes induction treatment and maintenance treatment. Among them, platinum includes carboplatin and cisplatin, and its selection is determined by the investigator according to the patient's general condition and previous medication history.

Induction (4 cycles of 21 days)	Maintenance (cycles of 21 days)
Bevacizumab + Nab-Paclitaxel + Carboplatin/Cisplatin	Bevacizumab

Induction treatment includes 4 cycles of 21 days. On day 1 of each cycle, patients receive drug infusion through intravenous injection. The specific doses are as follows:

Bevacizumab is administered at a dose of 15mg/kg.

Nab-paclitaxel is administered at a dose of 260 mg/m².

The initial target value of the area under the concentration-time curve (AUC) for carboplatin is 4~6mg/mL•min (administered according to the Calvert formula; Calvert et al.1989). For a target AUC = 6, the maximum dose is 6×150 = 900 mg. For a target AUC = 5, the maximum dose is 5×150 = 750 mg. For a target AUC = 4, the maximum dose is 4×150 = 600 mg.

Cisplatin is administered at a dose of 75 mg/m².

Pre-medication, prophylactic antiemetic, hydration, infusion methods and infusion time are all implemented according to the routine of the study center. The actual dose of the study drug is allowed to be adjusted by ±5% on the basis of the theoretically calculated dose.

After the induction phase is completed, patients will enter the maintenance treatment phase, maintained with bevacizumab at a dose of 15mg/kg.

All drugs used in this study are marketed drugs. For information on the manufacturer, formulation specifications, packaging and preparation methods of each drug, please refer to the local prescribing information of each drug. There is no free

drug supply in this study, and the cost of all drugs used shall be borne by the patients themselves; the cost of all examinations involved in the study shall be borne by the patients themselves.

4.2 Concomitant Treatment

No other drugs with anti-tumor effects can be used during the study, including prescription drugs, over-the-counter drugs, vaccines, Chinese herbal medicines or homeopathy, nutritional supplements, etc.

Patients are allowed to receive the following treatments during the study:

Oral contraceptives.

Hormone replacement therapy.

Prophylactic or therapeutic anticoagulant therapy (such as stable dose warfarin or low molecular weight heparin): During treatment with bevacizumab, due to the risk of bleeding, patients should not use more than 325 mg of aspirin per day (or no more than 75 mg of clopidogrel per day or equivalent dose) at least until bevacizumab treatment is stopped. Concurrent direct oral anticoagulants are not recommended.

Prophylactic granulocyte colony-stimulating factor treatment.

Vaccination with inactivated influenza vaccine.

Use of megestrol acetate to stimulate appetite.

Palliative radiotherapy (for example, treatment of known bone metastases or relief of symptomatic pain) can be performed after chemotherapy is completed, provided that it does not interfere with the evaluation of tumor target lesions (for example, the lesion to be irradiated cannot be the only site of measurable lesions). During palliative radiotherapy, bevacizumab can be continued.

Local treatment methods (such as surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) are as follows: If the response of different lesions in patients is inconsistent, and local treatment is needed to control three or fewer lesions, after the decision of the investigator, the study treatment can still be continued. Patients whose target lesions receive direct local treatment cannot undergo imaging response evaluation, but can still undergo disease progression evaluation.

Other symptomatic supportive treatments deemed necessary by the investigator.

4.3 Treatment Delay and Dose Adjustment

4.3.1 General Principles for Management of Toxic and Adverse Reactions and Dose Adjustment

Dose reduction of bevacizumab is not allowed. If an adverse event is considered related to bevacizumab, drug administration can be suspended or permanently discontinued.

The general principles for dose adjustment of chemotherapy drugs are as follows. Dose suspension and dose reduction are only allowed when hematological toxicity reaches grade 3; if ANC $\leq$ 1.5 x 10^9/L and PLT $\leq$ 100 x 10^9/L on day 1 of the course, drug administration shall be postponed. Dose suspension and dose reduction are only allowed when non-hematological toxicity reaches grade 2; among them, controllable nausea, vomiting, alopecia, fever with definite cause (such as infection or tumor), and grade 3/4 ALP elevation can be actively treated symptomatically, and dose suspension and dose reduction are not performed temporarily; except for alopecia, nausea and vomiting, other grade 2 and above non-hematological toxicity must return to grade 0 to 1 before the next course of treatment. The maximum delay is 14 days to recover from hematological and non-hematological toxicity. A maximum of two dose reductions is allowed. Dose reduction shall be based on the most severe toxicity grade of the previous course, with each reduction of 20-25% of the original dose.

If an adverse event requires dose adjustment or interruption or termination of treatment, please refer to the following and Appendix 5 for specific rules. For unlisted adverse events, the investigator shall refer to the corresponding local prescribing information (if any) or product characteristics, and make dose adjustment according to the general principles based on the investigator's best medical judgment.

4.3.2 Hematological Toxicity

If grade 3/4 neutropenia with fever (≥38.5°C) occurs; or grade 4 neutropenia persists for ≥7 days, the dose of chemotherapy drugs needs to be reduced.

4.3.3 Peripheral Neurotoxicity

Both nab-paclitaxel and platinum may cause peripheral neurotoxicity. If grade III/IV peripheral neurotoxicity occurs in any limb, drug administration should be suspended, and the dose should be reduced after the peripheral neurotoxicity returns to ≤ grade II. The first dose reduction of nab-paclitaxel is adjusted to 220mg/m², and the second dose reduction is adjusted to 180mg/m².

4.3.4 Liver Function Impairment

Degree of Impairment	Degree of Impairment	Degree of Impairment	Recommended Dose of Nab-Paclitaxel
Liver Transaminase		Bilirubin Level	
<10×ULN	and	1.0-1.5×ULN	260mg/m²
<10×ULN	and	1.51-3.0×ULN	200mg/m²
<10×ULN	and	3.1-5.0×ULN	200mg/m²
≥10×ULN	or	>5.0×ULN	Not Recommended

4.3.5 Renal Function Impairment

No dose adjustment of nab-paclitaxel is required for patients with estimated creatinine clearance ≥30ml/min, and it is not recommended to continue using nab-paclitaxel for patients with estimated creatinine clearance <30ml/min.

The dose of carboplatin needs to be reduced for patients with estimated creatinine clearance <60ml/min.

When 45ml/min ≤ estimated creatinine clearance <60ml/min, cisplatin is reduced by 25%; when 30ml/min ≤ estimated creatinine clearance <45ml/min, cisplatin is reduced by 50%; when estimated creatinine clearance <30ml/min, cisplatin administration should be suspended.

4.3.6 Weight Change

Patients with a weight change of more than 10% compared with the baseline need dose adjustment.

4.4 Efficacy Assessment

Patients will undergo tumor assessment at baseline, every 2 treatment cycles in the first 12 months after the start of treatment, and then the investigator may choose to perform tumor assessment every 3 treatment cycles until the investigator determines the occurrence of imaging disease progression or loss of clinical benefit according to RECIST v1.1 criteria. According to the investigator's judgment, tumor assessment can be repeated at any time if disease progression is suspected in the patient.

At screening, all measurable and evaluable lesions should be assessed and recorded. Tumor assessment results obtained according to treatment standards before signing the informed consent form and within 28 days before the start of study treatment do not need to be re-tested during screening.

Screening assessment must include chest, abdomen, pelvic, head CT scan or magnetic resonance imaging (MRI) scan, bone scan imaging. Positron emission tomography (PET) CT scan can replace bone scan imaging. If contrast-enhanced scanning is contraindicated (i.e., for patients with impaired renal clearance or contrast medium allergy), non-contrast-enhanced scanning can be performed. If there are clinical indications, bone scan and neck CT scan should be performed. According to the

investigator's judgment, other methods can be used to assess measurable lesions (determined according to RECIST v1.1 criteria). In tumor assessment, if the investigator agrees, a PET-CT scanner can be used for CT scanning. In subsequent tumor assessments, the same radiological examination method used for detecting lesion sites during screening should be used for subsequent tumor assessments. For patients who continue to receive treatment after progression, tumor assessment must be continued according to RECIST v1.1 after disease progression. This includes continuous measurement of target lesions in all subsequent assessments, assessment of non-target lesions (including monitoring of further deterioration of any clearly progressive non-target lesions), and assessment of any newly discovered lesions (including measurement, if the lesion is measurable; see Appendix 2).

Disease Control Rate (DCR) is defined as the proportion of patients whose disease is controlled, including cases of Complete Response (CR) + Partial Response (PR) + Stable Disease (SD). Objective Response Rate (ORR) is defined as the proportion of patients whose tumors shrink to a certain extent and maintain for a certain time, including cases of CR and PR. Subjects who discontinue the trial for reasons other than disease progression (without subsequent imaging examination) and subjects who receive post-trial treatment will have their data censored at the time of trial discontinuation or the time of starting post-trial treatment. New secondary primary tumors are not considered disease progression events and are not used as data censoring. For lost-to-follow-up subjects, their OS is censored at the last confirmed survival time before lost to follow-up. OS with data censoring is defined as the time from enrollment to censoring.

4.5 Study Termination and Study Duration

The study termination date is 6 months after the enrollment of the last patient.

4.6 Sample Size Calculation

According to historical data, the ORR of docetaxel monotherapy as second-line treatment for advanced NSCLC is about 15%. The sample size is estimated to be 56 people based on the following assumptions:

• Expected ORR of second-line bevacizumab/nab-paclitaxel/platinum is 30%;

• Two-sided test significance level is 0.05;

• Test power is 80%;

• Attrition rate is 5%.

The expected recruitment period is about 12 months, and the preliminary analysis of ORR is expected to be performed 15 months after the enrollment of the first patient.

4.7 Efficacy Analysis

Intention-To-Treat (ITT) Population: All patients who signed the informed consent form.

Per Protocol (PP) Population: All patients who completed the treatment according to the protocol.

Safety Analysis Population (Safety Set, SS): All patients who have signed the informed consent form.

4.7.1 Primary Endpoint Analysis

The primary endpoint ORR analysis will include all patients in the ITT population. Data of patients without post-baseline tumor assessment will be recorded as NE.

4.7.2 Secondary Endpoint Analysis

PFS and OS analyses will include all patients in the ITT population. Kaplan-Meier

method will be used to estimate median PFS and OS, and Kaplan-Meier curves will be constructed. In PFS analysis, data of patients who did not experience disease progression or died at the time of analysis will be censored at the date of the last tumor assessment or survival follow-up (whichever occurs later). Data of patients without post-baseline tumor assessment will be censored at the last known survival date. In OS analysis, patients who did not have disease progression and did not die will be censored at the date of the last tumor assessment or survival follow-up (whichever occurs later).

Safety analysis will be performed on the SS. AEs will be described verbatim with terms from the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and graded according to NCI CTCAE v5.0. Severe adverse events (≥ grade 3), adverse events of special interest, and adverse events leading to discontinuation or suspension of study drug treatment will also be summarized accordingly. For the same event occurring multiple times, it will be recorded as one event according to the maximum severity.

4.7.3 Exploratory Endpoint Analysis

Subgroup analysis will be stratified by demographic data (such as age, gender, etc.), baseline prognostic characteristics (such as ECOG performance status), first-line treatment resistance status (primary resistance, secondary resistance) factors, and the ORR, PFS and OS among subgroups will be summarized and compared. In the exploratory analysis, chi-square test will be used to compare the differences in ORR among subgroups, Kaplan-Meier method will be used to calculate the median PFS and OS of each subgroup, and Kaplan-Meier curves will be constructed to provide a visual description of the differences between treatment groups, and log-rank test will be used to compare PFS and OS between the two treatment groups. Exploratory analysis can conduct retrospective analysis on unprespecified stratification factors.

The different resistance phenotypes (primary resistance and secondary resistance) of first-line immune checkpoint inhibitor ± chemotherapy are defined as follows.

Primary resistance is defined as patients with best response of PD or SD duration < 6 months according to RECIST v1.1 under the condition of immune checkpoint inhibitor ± chemotherapy exposure ≥ 6 weeks [18]. Secondary resistance is defined as patients with best response of CR, PR or SD duration > 6 months according to RECIST v1.1 under the condition of immune checkpoint inhibitor ± chemotherapy exposure ≥ 6 months [18]. Patients with PD in efficacy assessment need to be confirmed by efficacy, that is, after the first assessment of PD (IUPD), imaging examination is performed again at an interval of at least 4 weeks, and patients with PD in the second assessment are confirmed as PD (ICPD), unless the disease progresses rapidly and the investigator clinically judges that the patient cannot tolerate waiting for the second assessment [18].

5 References

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