STUDY PROTOCOL

Establishment of a prospective multicenter cohort for advanced non-small cell lung cancer in China (CAPTRA-Lung study)

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Abstract

The CAPTRA-Lung study (NCT03334864) is a prospective observational study that will capture real-world data of patients with advanced or metastatic non-small cell lung cancer (NSCLC) across China. The study aims to complement the results from current therapeutic regimens to improve the standard of diagnosis and treatment, evaluate the effectiveness and safety of systemic therapy, and determine the factors influencing the outcomes and responses to treatment. From January 2018 to December 2023, eligible patients with advanced or metastatic NSCLC who are receiving treatment and participating in follow-up at 16 institutions in China, will be enrolled. The demographic, clinical, laboratory, and treatment characteristics and responses to treatment will be recorded in a case report form and transcribed into an electronic data capture system. Overall survival, progression-free survival, overall response rate, and incidence of adverse events will be calculated from the time of initial enrolment until progression evaluated by physicians, last contact, date of death, or analysis cutoff date, respectively. Based on the disease characteristics and treatment strategies, four sub-cohorts will also be established. This study cohort could serve as a pool of patients with advanced or metastatic NSCLC to support further research.

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer death in China. The incidence rate in China is high and is increasing at a more rapid rate than in Western countries.[1] There are an estimated 733 000 new cases of lung cancer in China per year.[2] Among these, non-small cell lung cancer (NSCLC) accounts for approximately 85–90% of all lung cancer cases.[3] Most NSCLC patients are diagnosed at advanced or metastatic stage, with only 20% eligible for surgical treatment with a curative intent.[1]

Over the last decade, the therapeutic regimen options for advanced NSCLC have greatly increased. The standard care for the first-line treatment of advanced NSCLC without treatable oncogenic alterations is a platinum-based doublet, which includes third-generation cytotoxic agents (i.e. gemcitabine, pemetrexed, docetaxel, or paclitaxel).[4,5]

With the rapid evolution of tumor genotyping technologies, late-stage NSCLC patients are recommended to undergo molecular and biomarker analysis before treatment is administered. The cancer-specific oncogenic driver gene mutations include *EGFR, BRAF* p.V600E, and *KRAS* gene mutations; *ALK, ROS1, RET*, and *NTRK* gene rearrangements; and *MET* and *ERBB2* gene mutations or amplifications[6,7] Genetic information greatly helps to make treatment decisions for advanced NSCLC patients. Moreover, the approach for treating NSCLC has evolved rapidly with the increasingly widespread application of molecular agents targeting these mutations. Several United States Food and Drug Administration approved molecular agents, such as EGFR and ALK TKIs, are now widely used in first-line and/or second-line NSCLC treatments, and have shown significant efficacy.[8]

VEGF is an important mediator in tumor-associated growth and angiogenesis.[9] Therapeutic intervention aimed at the VEGF pathway has become a mainstay of cancer treatment.[10] Bevacizumab plus platinum-based doublet chemotherapy is recommended by the National Comprehensive Cancer Network as a category 1 regimen and is widely used for advanced NSCLC. In 2015, based on a China-specific phase III trial (BEYOND), the China Food and Drug Administration (CFDA) approved bevacizumab, a humanized VEGF receptor monoclonal antibody, combined with carboplatin and paclitaxel, as a first-line therapy for metastatic non-squamous NSCLC.[11]

With the recent identification of immune-based cellular targets and the development of novel approaches aiming to stimulate the immune system, cancer immunotherapy has made substantial progress in recent years. The clinical success of immune checkpoint blockades (antagonists of CTLA-4, PD-1, and PD-L1) indicates that immunotherapy may become one of the pillars of cancer therapy.

Encouraging data have been obtained from pembrolizumab (anti-PD-1) trials assessing both monotherapy[12] and chemotherapy combinations to treat NSCLC.[13] More recently, based on data from the pivotal phase 3 CheckMate−078 trial (NCT02613507), the CFDA approved the use of nivolumab (anti-PD-1) for the treatment of locally advanced or metastatic NSCLC after prior platinum-based chemotherapy in Chinese adult patients.

However, despite the encouraging results from these recent clinical trials, real-world prospective observational studies with large study populations and long follow-up periods are required to confirm the effectiveness of these treatments, which may be more representative with an unselected population than in clinical randomized controlled trials. In particular, real-world prospective observational studies can provide information on treatment practices in specific populations that are usually excluded from randomized controlled trials.[14]

Study aims

In order to gain greater insights from current therapeutic regimens in advanced NSCLC, we launched the CAPTRA-Lung study, a multi-center prospective observational cohort in China. This study will evaluate the effectiveness and safety of current therapeutic regimens and explore factors associated with outcomes to understand treatment responses in real-world settings. Moreover, this study cohort could also serve as a pool of patients with advanced or metastatic NSCLC to support further research.

Methods

Objectives

The primary objective of this study is to establish and maintain a cohort of patients with advanced NSCLC, which could provide sufficient data to help us better understand the factors associated with disease progression and outcomes.

The secondary objective of this study is to understand disease characteristics, treatment patterns, prognosis, and influential factors in various patient populations in a real-world setting.

Study design

The study is designed as a multi-center prospective observational cohort (NCT03334864). Newly diagnosed advanced NSCLC patients and treated advanced NSCLC patients receiving further anti-cancer treatment will be recruited from the date informed consent is provided, and will be prospectively followed until death, the date of

informed consent withdrawal, loss to follow-up, or the analysis cutoff, whichever occurs first. Medical records before and after the study launch will be collected and analyzed.

Depending on the disease characteristics and treatment options, a total of four sub-cohorts will be involved prospectively:

1 Sub-cohort A: Advanced NSCLC patients with driver oncogene mutations, including *EGFR*, *BRAF* p.V600E, and *KRAS* gene mutations; *ALK*, *ROS1*, and *RET* gene rearrangements; and *MET* or *ERBB2* gene mutations or amplifications.
2 Sub-cohort B: Advanced NSCLC patients who have received immunotherapy.
3 Sub-cohort C: Advanced NSCLC patients without definite driver oncogene mutations/fusions or unknown driven gene status.
4 Sub-cohort D: Advanced non-squamous NSCLC patients receiving anti-VEGF therapy.

Given the fact that treatment/mutation criteria are not mutually exclusive, the same patient maybe be categorized into more than one sub-cohort.

Institutions

This prospective multicenter observational cohort study was launched on 3 January 2018, with Peking Union Medical College Hospital as the principal investigator (PI) institute. Sixteen hospitals across China are currently participating; however, more institutions may be involved as the study progresses. In such a case, applications will be submitted for approval to amend the research protocol. The 16 hospitals currently participating are: Peking Union Medical College Hospital (PI institute); Beijing Cancer Hospital; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital; Beijing Hospital; Peking University First Hospital; Peking University People's Hospital; Peking University Third Hospital; Beijing Chest Hospital; Beijing Chaoyang Hospital; Beijing Shijitan Hospital; Shanxi Cancer Hospital; West China Hospital, Sichuan University; Second Affiliated Hospital of Harbin Medical University; First Affiliated Hospital of China Medical University; Fourth Affiliated Hospital of Hebei Medical University; and North Hospital.

Eligibility criteria

Patients eligible for the study include those: (i) pathologically or cytologically diagnosed with NSCLC (newly or previously diagnosed); (ii) at stage IIIb/c or IV local advanced or metastatic NSCLC, according to the 8th edition International Association for Lung Cancer staging system;

(iii) aged ≥ 18 at the time of diagnosis; (iv) who provide written informed consent; and (v) receiving anti-cancer treatments.

The exclusion criteria are: (i) pathologically confirmed small cell lung cancer (SCLC) or mixed SCLC patients; and (ii) early-stage NSCLC patients who have not developed metastasis or recurrence.

Sample size

As this an observational study without any statistical assumptions or hypothesis testing, no statistical hypothesis-based sample size calculation is needed. All eligible patients will be included. The actual sample size will depend on the size of the patient pool and response rate at each site.

Study parameters

All important patient information will be collected, including baseline demographic information, disease characteristics, laboratory and pathology tests, imaging, treatment information, and disease outcomes.

Main outcomes

The main outcomes of the study are overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and safety outcomes. OS, depending on research interest, is defined as the interval from disease diagnosis or the initiation of certain treatment until death from any cause. PFS, depending on the research interest, is defined as the interval from disease diagnosis or the initiation of certain treatment until objective tumor progression or death. The ORR is defined as the proportion of patients with tumor reduction of a predefined amount and for a minimum time period. More specifically, ORR will be the sum of partial plus complete responses under Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The safety outcomes will be measured as the proportion or incidence of adverse events (AE).

Patient enrollment

From January 2018 to December 2023, eligible advanced or metastatic NSCLC patients receiving treatment and participating in follow-up will be enrolled in this study. The study timeline is shown in Figure 1. Patient recruitment will be conducted at inpatient/outpatient departments during hospital visits. A trained physician at the study hospital will determine patient eligibility.
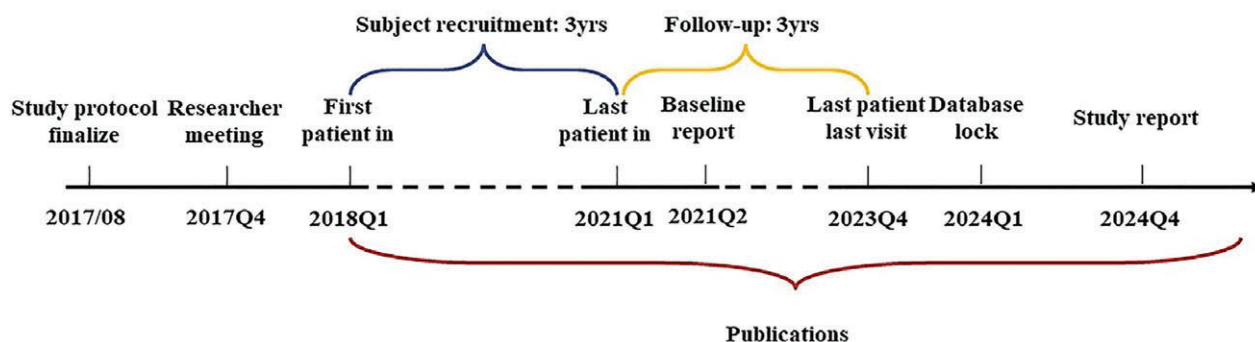
Figure 1 Study timeline and milestones.

Ethics, patient protection, and dissemination

The Peking Union Medical College Hospital institutional review board (IRB) approved the study proposal (Approval Number: JS-1410). Separate IRB approval may be required by corresponding institutes. In order to officially launch the study and collect data, each site must receive approval from either a central or local IRB. The enrolled patients must sign written informed consent in accordance with institutional guidelines. Participation in this study is completely voluntary and patients reserve the right to withdraw their consent at any time during the study without affecting their medical care.

No personal information will be disclosed. A unique study ID number will be assigned to each participant, and the corresponding clinical data will be registered pseudonymously via Research Manager software. Each institution will record a separate file containing personal information for management only, which will not be collected and analyzed as research data.

Data collection

The overall baseline characteristics, pathology results, molecular and biomarker analysis results for cancer-specific oncogenic driver genes, lung cancer clinical staging, effectiveness and safety data of therapeutic regimens, locoregional therapy information, and follow-up data will be collected.
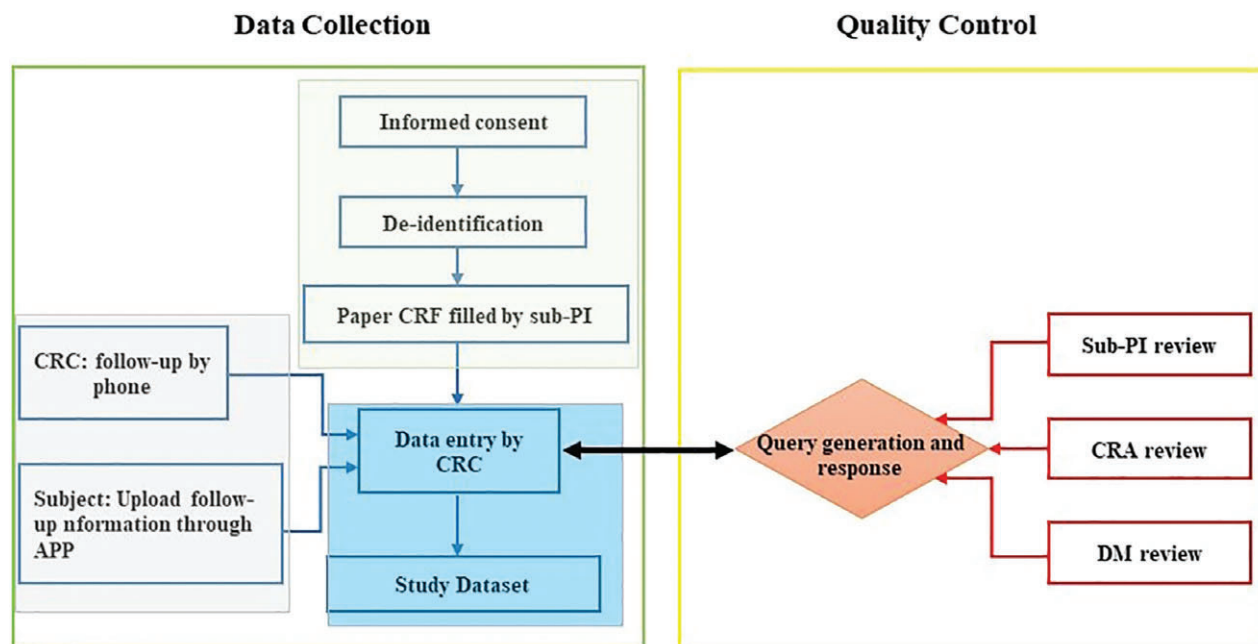

Figure 2 Flowchart for data collection and quality control. CRA, clinical research assistant; CRC, clinical research coordinator; CRF, case report form; DM, data manager; PI, principal investigator.

A flowchart of data collection and quality control is shown in Figure 2. Medical records will be the source of all study data, as recorded by physicians in study hospitals during their daily practice. The medical records of each study subject will be reviewed and a paper case report form (CRF) completed by well-trained study physicians (Sub-PIs) and updated manually. Professional data entry staff or clinical research coordinators (CRCs) will hereafter manually review the CRF and transcribe all data into an electronic data capture (EDC) system specifically designed for this study. In cases of data uncertainty, professional oncologists or physicians at the study hospital will be consulted as necessary. Prospective data will be updated every three months. Sub-PIs at each institution will review each complete EDC case report and sign a supervision form annually.

Data management

The CRF was designed based on the study protocol to collect all key information, and the EDC system was developed accordingly with support from Medbanks Network Technology Co., Ltd. (Beijing, China) to store and manage all study data. The system is a cloud based electronic database specifically designed to collect real world medical data in oncology. To ensure the integrity and consistency of data, logic rules were built in as a module of the system and queries will be automatically generated for any logic inconsistencies or missing key information. Clinical research assistants (CRAs), data administrators, and research medical teams can also generate manual queries. The data sets are downloaded and backed up quarterly to support various research topics. Prior to any data analysis, all queries must be resolved and closed. During data analysis, source documents will be retrieved and reviewed to resolve any possible queries.

To ensure data safety, all study data stored in the EDC system will be encrypted, and only authorized personnel will have access to the data. Hyper Text Transfer Protocol over Secure Socket Layer (HTTPS) will be used to ensure safety during data transmission through the internet, and both cloud and local servers will be used to perform data backup on a daily basis.

All centers will be visited three months after registration of 50 patients. Additional monitoring visits will be made if the center has higher or lower registration rates or queries with data management, and special attention will be paid to the integrity of informed consent, data monitoring, and case records. CRAs, data administrators, or research medical teams will conduct local data management.

Given that CAPTRA-Lung is a trial of general care to evaluate diagnostic and existing treatment strategies, the incidence of complications will not be covered in this study. Thus, a safety data monitoring board will not be established.

Research data can only be presented or published under an agreement with the CAPTRA-Lung data committee. Any research data traceable to individuals will not be submitted or published. The research data will be reported following CONSORT guidelines.

Statistical methods

Statistical analysis will be performed after the completion of data collection and verification. If data is missing, it will be recorded as "missing." Full patient demographic information and baseline characteristics will be tabulated, analyzed, and reported. For continuous variables, mean/median $\pm$ standard deviation will be reported. For categorical variables, the percentage will be reported. According to the type of variables, chi-square /Fisher's exact tests or *T*-test/ *F*-test will be used to detect differences among groups, and linear/logistic regression will be used for the correlations among factors. A survival analysis method will be applied to obtain survival curve and hazard ratio estimates. Stratified analysis of the potential confounding factors may be applied if needed. Unless specified, all statistical testing will be two-tailed at a 5% significance level.

Discussion

The primary objective of this study is to establish a multicenter cohort of patients with NSCLC across China. The results will complement and improve the current understanding of the real status of diagnosis and prognosis of advanced NSCLC in China. The secondary objective is to confirm the effectiveness of various novel treatment regimens in a real-world setting and explore the related influencing factors.

An advantage of this observational study is the high external validity that will be achieved by enrolling a wide range of patients across different treatment settings, providing evidence of the effectiveness of treatment strategies and ensuring drug safety in a broad population of patients. Moreover, because of the wide coverage and prospective design, the CAPTRA-Lung study will establish and maintain a pool of patients with advanced NSCLC in China. Therefore, it will also serve as a platform to support further research based on this population.

However, attention should be paid to the potential limitations, including the inconsistency and incompleteness of data sources in clinical practice; the effects of potential confounding by diagnosis bias across different institutions; the fact that blinding is not performed in a real-world study; and the intervention from potential external clinical trial participants. Attrition may be another source of bias

affecting the strength of the conclusions. To reduce such bias, additional methods with higher statistical power will be applied when dealing with the large number of covariates in this study.

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Disclosure

No authors report any conflict of interest.

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