Study of the safety and efficacy of CAR-T cell therapy after standard treatment of advanced lung cancer: a single-arm, single-center phase I clinical study

Study plan

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Study of the safety and efficacy of CAR-T cell therapy after standard treatment of advanced lung cancer: a single-arm, single-center phase I clinical study

1. Background

1.1 Introduction

Chimeric antigen receptor modified T lymphocyte therapy (CAR-T) is a combination of high affinity of chimeric antigen receptor for tumor antigen and T cell killing mechanism, through gene transduction of T Cells, to obtain the ability to specifically kill tumor cells, without MHC restriction. CAR-T cell therapy has shown high specificity, lethality and durability in clinical trials, providing new avenues for immune cell therapy and showing huge development potential and application prospects.

2. Significance

2.1 Main objective

To study the safety and effectiveness of PD-L1 CAR-T cells in the treatment of patients with advanced non-small cell lung cancer (NSCLC).

2.2 Secondary objectives

1) Perform baseline WGS / WES on the biopsy tissues, TCR library analysis on the baseline and post-treatment plasma / blood cells, and perform intestinal flora metagene analysis on the fecal specimens at baseline and after treatment. ORR, disease control rate (DCR) correlation analysis, preliminary study of predictive factors for efficacy.

2) Perform baseline WGS / WES on biopsy tissues, TCR analysis on plasma and blood cells at baseline and after treatment, and perform metabolic analysis of gut microbiota on fecal specimens at baseline and after treatment. Period PFS, overall survival (OS) association analysis, preliminary study of survival predictors.
3. Subjects

3.1 Inclusion criteria:

The number of cases to be enrolled in clinical trial was 20. Considering the 10% dropout rate during the study period, the number of lung cancer patients that met the inclusion criteria and were not included in the exclusion criteria should be 22 in this study.

1) Pathological or cytological diagnosis of NSCLC, with stage IIIB / stage IV tumors (according to UICC / AJCC staging system version 8).

2) Relapsed NSCLC or progression after standard treatment (surgery, radiotherapy, chemotherapy and targeted therapy, excluding PD-1 / PD-L1 immune checkpoint inhibitor treatment), or the patient refuse to receive chemotherapy.

3) Before enrollment in the study, the patient needs to perform a second biopsy, retaining at least one biopsy, or at least 10 unstained sections.

4) TKI and chemotherapy drugs must be discontinued before $\geq 21$ days of the first day of infusion. Pulmonary radiotherapy must be discontinued $\geq 6$ months before the first day of infusion. After discontinuing previous treatment, a baseline imaging scan must be obtained.

5) According to the RECIST 1.1 standard, subjects must have measurable lesions that are examined by CT or MRI. Tumor imaging evaluation was performed within 28 days before CAR T cell therapy.

6) Age $\geq 18$ years old, weight $\geq 40$kg.

7) IHC detection of lung cancer biopsy tissue after standard treatment is positive for PD-L1 ($> 10\%$).

Roche Ventana rabbit monoclonal antibody SP142 approved by the FDA was used to detect the expression level of PD-L1 in lung cancer sections of patients enrolled in this project.

8) Estimated survival time $\geq 12$ weeks;

9) ECOG score $\leq 2$ points
10) Women of childbearing age must have a negative pregnancy test within 14 days before starting treatment and agree to take contraceptive measures with a failure rate of <1% per year during the study until the last follow-up.

Contraceptive measures with a failure rate of <1% per year include bilateral fallopian tube ligation, male sterilization, correct use of hormonal contraceptives that suppress ovulation, intrauterine hormone release systems, and intrauterine copper birth control devices.

11) The subject must have sufficient hematology and end-organ function and meet the laboratory values in the table below. These test results must be completed within 7 days before the first cell application.

<table>
<thead>
<tr>
<th>System</th>
<th>Laboratory value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Leukocyte (WBC)</td>
<td>&gt;=3.5*10^9/L</td>
</tr>
<tr>
<td>Neutrophil (ANC)</td>
<td>&gt;=1.5*10^9/L</td>
</tr>
<tr>
<td>Hemoglobin (HGB)</td>
<td>&gt;=90g/L</td>
</tr>
<tr>
<td>Platelets (PLT)</td>
<td>&gt;=80*10^9/L</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, Partial thromboplastin time, Plasma fibrinogen, Thrombin time</td>
<td>Within normal range</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>&lt;2.5 * normal upper limit (ULN)</td>
</tr>
<tr>
<td></td>
<td>ECOG score of 0-1 points for liver metastasis &lt;5 * ULN</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>&lt;2.5 * ULN</td>
</tr>
<tr>
<td></td>
<td>ECOG score of 0-1 points for liver metastasis &lt;5 * ULN</td>
</tr>
<tr>
<td>Total bilirubin (TIBC)</td>
<td>&lt;1.5*ULN</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (CR)</td>
<td>&lt;1.0*ULN</td>
</tr>
</tbody>
</table>

12) Participate voluntarily in this experiment and sign the informed consent.

3.2 Exclusion criteria:

1) Subjects receiving systemic steroid therapy within <= 3 days before the first cell
therapy.

Note: a. Corticosteroids can be used to treat AE, SAE, and ECI after the study of cell therapy.

b. Not including subjects who are receiving steroid replacement therapy every day. A daily dose of 5-7.5 mg of prednisone is an alternative therapy.

c. An equivalent dose of hydrocortisone therapy may also be admitted into the trial as an alternative therapy.

2) Subjects who have received previous systemic cytotoxic chemotherapy, biological therapy or major surgery within 3 weeks before the application of the first dose of test cells, and received lung radiotherapy> 30Gy within 6 months before the application of the first cell infusion.

3) Subjects who have received CAR-T, CIK and other cell therapies, anti-PD-1, anti-PD-L1 antibody therapy.

4) Subjects with known central nervous system metastases and / or cancerous meningitis.

Note: Subjects who have previously received brain metastasis treatment can also participate in this study, as long as the patient is stable (no neurological symptoms) and no new brain metastases are found at least 4 weeks after brain metastasis treatment (such as surgery, RT); Imaging evidence of no metastasis and discontinuation of hormone therapy at least 3 days before the first application of the cells.

5) In the past 2 years, have active autoimmune diseases that require systemic treatment (such as the use of disease-modifying drugs, corticosteroids or immunosuppressants).

Note: Alternative therapy (i.e., thyroxine, insulin, or physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a systemic treatment. Subjects requiring inhaled glucocorticoid therapy need not be excluded from this study. Subjects with vitiligo or cured childhood asthma / allergic disease can participate in the study. Subjects who need local steroid injections can participate in the study.

6) Subjects with interstitial pneumonia or a history of pneumonia requiring oral or intravenous steroid therapy.
7) Difficulties in transduction of the patient’s lymphocyte with lentiviral vectors (<20%) or inability to effectively expand (<5 times) during evaluation.

8) Subjects who have received allogeneic tissue / solid organ transplantation.

9) Subjects who have been vaccinated or will be vaccinated with live vaccines within 30 days before the application of the first cells. Seasonal influenza vaccines that do not contain live vaccines are allowed.

10) Subjects with active infections requiring intravenous systemic treatment.

11) Subjects with a history of human immunodeficiency virus (HIV) (HIV1 / 2 antibody) infection.

12) Active hepatitis B or hepatitis C is known. Subjects with positive HBsAg need to be excluded. Active hepatitis C is defined as positive for hepatitis C antibodies, and it is known that quantitative HCV RNA results exceed the detection limit of analysis.

13) The history of mental illness or drug abuse that can’t comply with the requirements of the experiment.

14) Pregnant or breastfeeding, or male subjects whose spouses are expected to become pregnant during the study period (from screening visit to 60 days after the last application of the cells).

4. Study design and test methods

4.1 Study design

1) For patients with non-small cell lung cancer that progressed after standard treatment and meet the recruitment criteria for the protocol, they must provide tumor biopsy tissue specimens and unstained paraffin tissue sections during the screening period.

2) Intravenously infuse the cells according to the protocol. Before the infusion, take 10 ml of the peripheral blood of the patient for baseline laboratory tests; take the fecal specimen of the patient for baseline flora metagene analysis. During the patient’s follow up the efficacy evaluation (CT / MRI re-examination) was performed, each time 10 ml of peripheral blood and stool samples were collected. If the patient meets the withdrawal criteria (such as disease progression PD, DLT out of the group,
etc.), the investigator decides that the patient needs to withdraw from the clinical trial and needs to retain 10 ml of peripheral blood and feces before exiting the clinical trial.

3) After the patient receives the infusions, the doctor decides if the treatment is effective during the follow-up, the patient won’t receive other treatments; if the treatment is ineffective, the patient will be observed for one month according to the patient’s wishes. No other drugs can be used for treatment, and the patient will be out of the group after the treatment is evaluated again within 1 month; if the third (5th month) follow up evaluation is still effective, that is, all three evaluations are PR or SD. The patient can be receive one more free treatment; regardless of whether it is effective, patients can decide to withdraw at any time during the study according to their own wishes. If the treatment is effective (stable SD, partial or complete remission PR / CR), the follow-up will continue for up to 2 years.

4.2 Genomic analyses

1) Next generation sequencing (NGS)
   - Whole genome sequencing (WGS)
   - Whole Exons Sequencing (WES)

2) Dynamic detection of TCR library

3) Dynamic analysis of intestinal flora metagenes

5. Study plan

5.1. Pre-examination and evaluation of patients before treatment

Within 48 hours after the patient signed the informed consent form, the patient’s blood samples were drawn and was tested for hepatitis B, hepatitis C and HIV. It takes about 4 days to assess whether the subject’s PBMCs are suitable for producing PD-L1 CAR-T cells.

5.2. Production of PD-L1 CAR vector lentivirus

PD-L1 CAR lentiviruses were packaged in 293T cells, and the collected viruses were concentrated and purified, their titers were determination, and frozen at -80°C and used for the transduction of autologous T cells.
5.3. Transduction of autologous T cells

According to the following table, collect a certain amount of blood from the patient, isolate PBMC cells by Ficoll density gradient centrifugation. The T cells were further purified and activated by CD3/CD28 beads. Then PD-L1 CAR lentiviruses were added with the predetermined MOI ratio. Culture and expand the transduced cells. The blood collection volume corresponding to the absolute counts of lymphocytes is shown in the table below:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Lymphocyte Count ($\times 10^9$/L)</th>
<th>Blood volume required (ml)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50kg</td>
<td>1-2×10^9/L</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3×10^9/L</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-4×10^9/L</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>50-60kg</td>
<td>1-2×10^9/L</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3×10^9/L</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-4×10^9/L</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>60-70kg</td>
<td>1-2×10^9/L</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3×10^9/L</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-4×10^9/L</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>70-80kg</td>
<td>1-2×10^9/L</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3×10^9/L</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-4×10^9/L</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>80-90kg</td>
<td>1-2×10^9/L</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3×10^9/L</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-4×10^9/L</td>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

5.4. Quality control before CAR-T cell transfusion

The live cell count, transduction efficiency, T cell phenotype, endotoxin, bacteria, and mycoplasma of PD-L1 CAR-T cells are vigorously tested, and the replication-competent lentiviruses are also tested by PCR. All of these tests will determine whether they meet the clinical application standards. The batches that do not meet the standard will be discarded and recorded.

5.5. Infusion of PD-L1 CAR-T cells

The cells will be infused into the patient if the cells are not contaminated with any pathogenic microorganisms, and the patients are treated with chemotherapy (cyclophosphamide: 250mg / m2 × 3days; fludarabine: 25mg / m2 × 3days) to remove Treg cells and reduce lymphocytes. It is beneficial for the expansion of PD-L1
CAR-T cells in vivo to enhance the anti-tumor effect of CAR-T cells. After the chemotherapy, the peripheral blood will be collected the day before the CAR-T infusion and the blood routine tests will be carried out. The effect of chemotherapy was evaluated according to the number of lymphocytes and T cell subsets.

To ensure safety, PD-L1 CAR-T cells were infused at three different times, 10%, 30%, and 60% of the total infusion on Day 0, Day 3, and Day 7, respectively. The total amount of cell infusion is \((1-2) \times 10^6\) PD-L1 CAR-T cells / kg. The cells are suspended in 100ml of normal saline and infused into the body at a rate of about 50 drops / minute. After being infused to patients, the remaining cells are kept frozen (-80°C) for later tests if severe adverse reactions happen.

5.6. Clinical safety monitoring and evaluation

(1) All adverse events were recorded according to nci-ctcae (v4.02):

Adverse events are defined as any unexpected medical events that occur after medication, regardless of whether there is a causal relationship between the event and the treatment. The lack of efficacy in clinical trials cannot be regarded as an adverse event, because the purpose of clinical trials is to evaluate the efficacy of treatment:

1) Fever: including agranulocytosis fever. It is necessary to take imaging examination and determine etiology, find the source of infection, and empirically treat with broad-spectrum antibiotics.

2) Abnormal liver and kidney functions: administer liver protection treatment; determine the causes of renal function abnormality (prerenal, renal, postrenal), and corresponding support treatment.

3) Muscle pain and bone pain: except for mechanical injury, analgesic treatment (NSAIDs, weak opioids or strong opioids) can be given.

4) Respiratory insufficiency (hypoxemia): Patients with mild symptoms should be given oxygen inhalation by nasal catheter, while patients with severe symptoms should contact ICU for mechanical ventilation and assisted respiration. Except for pulmonary infection (imaging and etiology), it can be treated with hormone anti-inflammatory therapy.

5) Hypotension: in addition to infection, it is considered to be related to the vascular leakage reaction caused by cytokine. Fluids should be supplemented adequately, and
vasopressors (dopamine, adrenaline) should be used properly for severe cases. If necessary, anti-IL-6 antibody (tocilizumab for IL-6 receptor or siltuximab for IL-6) will be applied [47].

6) Other adverse events are evaluated accordance with nci-ctcae4. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (2013)) to be graded and actively treated.

(2) Monitoring and evaluation of cytokine release syndrome (CRS)

1) Definition of cytokine release syndrome (CRS)

According to the NCI-CTCAE (v4.02) evaluation criteria for common adverse events, CRS is defined as a group of clinical disorders with characteristics of fever, nausea, headache, tachycardia, hypotension, rash and dyspnea.

2) Clinical manifestations / evaluation criteria of cytokine release syndrome (CRS)

a) Fever for three consecutive days;

b) The maximum value of two cytokines is 75 times higher than the standard or the maximum value of one cytokine is 250 times higher than the standard;

c) At least one toxicity-related clinical symptom occurs, such as hypotension that (requires at least one vasopressor), hypoxia (PO2 <90%), neurological symptoms.

d) CRP level ≥20mg / dl.

3) The grading standards for cytokine release syndrome are set forth according to the revised version of NCI-CTCAE (v4.02)

a) Level 1: Mild reaction, treatment can be continued without special intervention treatment;

b) Level 2: Intervention or interruption of treatment is required, the treatment needs to be given quickly (such as the use of antihistamines, NSAIDs, narcotic drugs, intravenous administration), and preventive medical measures should be taken ≤24h;

c) Grade 3: Any one or more of the following severe symptom signs: the patient’s baseline blood pressure level drops by ≥20% (systolic, diastolic, or average arterial pressure), and the person cannot quickly improve after treatment and / or infusion intervention within 24 hours; Grade 3 respiratory dysfunction; Grade 3 renal dysfunction; Grade 3 neurological dysfunction;

d) Level 4: requires positive pressure breathing or mechanical ventilation.
4) Treatment of cytokine release syndrome (CRS)

a) In view of the potential clinical risks of CART treatment, we will closely monitor the patient's vital signs after CART infusion; if fever occurs, blood is drawn for C-reactive protein, serum ferritin, serum IL-6 and sIL. Early detection of potential cytokine release syndrome, and active supportive treatment.

b) If necessary, use IL-6R blocking monoclonal antibody (tocilizumab) as early as possible in the treatment of suspected severe patients. The dose is 4 mg / kg, which can be repeated once. The use of tocilizumab alone can relieve fever and CRS symptoms without inhibiting the proliferation of CAR-T cells. IL-6R blocking monoclonal antibody (Yamero tocilizumab) is a prescription drug produced by Roche can be provided adequately by the hospital.

c) The use of high-dose steroid hormones equivalent to or above the doses of 100 mg prednisone per day can quickly reverse the clinical symptoms of CRS. However, corticosteroid drugs can also inhibit the proliferation of CAR-T in vivo, so that patients with CRS treated with steroid drugs have a higher recurrence rate and affect the efficacy of CAR-T treatment.

(3) Treatment of unspecific tissue damage

Lung cancer cells and myeloid-derived immunosuppressive cells (MDSCs) in cancer tissues, although specifically express PD-L1, can be killed by PD-L1 CAR-T cells, but normal cells in the inflammatory site are also expressed under IFNγ induction, and there exists the possibility that normal tissues can be damaged by PD-L1 CAR-T cells (on-target, off-tumor toxicities). After receiving PD-L1 CAR-T cell infusion, patients need to be observed closely, especially the functions of brain, heart, lung, liver, kidney and other important organs.

(4) If the patient has serious side effects after treatment, high-dose corticosteroid therapy is required; the incidence of adverse events in clinical studies > 1/3; the progress of the disease, etc., can be regarded as a criterion for the termination of study.

6. Subject withdrawal criteria

Patients can withdraw from treatment and evaluation at any stage of the study, but as long as the patients treated with CAR-T they will participate in safety and efficacy evaluation. The reasons for withdrawal are as follows:
1. Voluntary withdrawal, patients can freely withdraw from the trial at any time, and will not affect future treatment;

2. The investigator believes that the patient's compliance with the study is poor;

3. Missing follow-up;

4. Those who have disease progression or intolerable adverse reactions, and the doctor determines that it is not appropriate to continue the study.

7. Criteria and evaluation methods for efficacy

1) Use flow cytometry or quantitative PCR to monitor the proliferation and survival of PD-L1 CAR-T cells in vivo. CAR-T cell proliferation and survival in vivo will be monitored regularly by flow cytometry or quantitative PCR after the last (day 7) infusion of CAR-T cells. Observe and test every 2 months for 1 year, and then every quarter for 2 years after infusion.

2) Record the anti-tumor effect every follow up after infusion of PD-L1 CAR-T.

We will adopt RECIST (Response Evaluation Criteria in Solid Tumors version 1.1) [48] and Immune-Related Response Criteria [49] to evaluate the anti-tumor efficacy of PD-L1CAR-T cells.

a. If effective, determine whether they are partial response (PR) or complete response (CR). Due to the small number of subjects, the response should be recorded in detail.

b. At the same time, record their progression-free survival (PFS).

3) Record the secondary tumors.

4) Record the overall survival and cause of death.

5) For patients with preserved tumor cells, determine the correlation between the activity of CAR-T cells to kill tumor cells in vitro and clinical response.

6) Check whether the host produces cellular and humoral immunity against PD-L1 CAR T cells, determine the host's production of antibodies against PD-L1 CAR or other transgenic genes.

7) Determine the cell subsets of PD-L1 CAR-T cells (CD3, CD4, CD8, Tcm, Tem, and
8. Set up of the sample size

According to the number of cases of the phase I clinical trial, the number of the patients with advanced lung cancer receiving PD-L1 CAR-T cell therapy was determined as follows:

The number of cases to enroll in this clinical trial was 20. Considering the 10% dropout rate during the study period, the number of cases of lung cancer that met the inclusion criteria and were not included in the exclusion criteria was 22 in this study:

The study was of exploratory nature, so the sample size was set to include all available patients who received PD-L1 CAR-T treatment.

8.1 Data set

Intention-to-treat population (ITTP): Refers to all cases that express an intention to receive treatment and sign an informed consent.

Adjusted intention-to-treat population (MITTP): refers to signing an informed consent form and having at least one effective data record on the main efficacy indicators after receiving treatment. Baseline data analysis is based on MITTP. The efficacy analysis is based on the results of MITTP analysis.

People who meet the protocol (PPP): refer to the cases that meet the inclusion criteria, do not belong to the exclusion criteria, and complete the treatment plan, that is, analyze the cases that complete the trial plan, have good compliance, and complete the CRF regulations (PP analysis). PP analysis is mainly used for the main therapeutic indexes. PPP needs to meet a series of conditions:

(1) Join the plan. Complete all evaluations without violating the selection and exclusion criteria specified in the plan;

(2) Complete at least one course of autologous CAR T cell infusion;

(3) No other drugs that affect the evaluation of efficacy are used.

8.2 Missing data

Use LOCF estimation (last observation carry forward) for missing data of important indicators.

8.3 Statistical analysis methods

Statisticians and main researchers formulate statistical analysis plans based on the research plan and complete the documentation before the data is locked. Statistical analysis was performed using SPSS 20.0 statistical analysis software.

The curative effect evaluation used the solid tumor curative effect evaluation standard RECIST1.1 to evaluate the objective response rate ORR and disease control rate DCR. The dose data is expressed by x ± s, and the comparison of different time points is by repeated measurement analysis of variance. The description of classification indicators uses various types of cases and percentages. Descriptive statistics of the completion of the study and the efficacy indicators. The demographic data is grouped into other statistical descriptions. Patients who withdrew or died before treatment and patients who did not complete the required safety observation evaluation will be evaluated separately.

The safety assessment will be descriptive, and safety indicators include adverse events, laboratory examination data, and vital signs. The type, severity, frequency and relationship with the test substance of all adverse events that occurred during the study will be listed. Specially note the cases where the study was terminated due to adverse events and serious adverse events occurred. For laboratory tests, list the completed items in the form of cross-tabs before and after treatment. Examination items with abnormal values and clinical significance should be listed.

9. Ethics

9.1 Regulatory and ethical compliance

Design, execute, and report this clinical trial in accordance with Chinese GCP and other locally applicable regulations, and the ethical rules stipulated in the Declaration of Helsinki
9.2 Responsibilities of researchers and ethic committees

Before the start of the study, the research protocol and the written informed consent must be reviewed and approved by the ethics committee of a formal research institution. The investigator agreed to conduct the study in accordance with these documents and all instructions and operations shown in this test protocol.

9.3 Informed consent process

Qualified patients can only be enrolled in this study after providing written EC-approved informed consent.

10. Implementation plan

<table>
<thead>
<tr>
<th>Period</th>
<th>Content and goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017/9-2018/9</td>
<td>Collection of tumor tissue and peripheral blood samples of all enrolled patients and corresponding clinical information collection. Immediately carry out clinical trial treatment to evaluate safety and efficacy.</td>
</tr>
<tr>
<td>2018/10-2019/3</td>
<td>The collected clinical samples are collected for sequencing and basic data analysis.</td>
</tr>
<tr>
<td>2019/4-2019/9</td>
<td>Analyze data, draw conclusions, write papers, submit articles and publish articles.</td>
</tr>
</tbody>
</table>

11. References