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Evaluation of clinical clinical diseases and Mechanism of acupuncture-Acupuncture improves the clinical efficacy evaluation of the immune response in cervical cancer patients

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The Affiliated Cancer Hospital of Chongqing University

Study years: November 2023-November 2026

Version number: 2.0

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catalogue

scenario summary

project name	Clinical efficacy evaluation and action mechanism of acupuncture and moxibustion-Evaluation of acupuncture to improve the response rate of immunotherapy in cervical cancer patients.
purpose of research	1. Clarify the synergistic effect and safety of acupuncture therapy on immunotherapy for cervical cancer patients, and provide evidence-based medical evidence for the clinical efficacy of acupuncture therapy in immunotherapy for cervical cancer; 2. Patients' blood, stool and tongue coating samples were retained for cytokine and 16S rDNA / metagenomic testing, and then further explored the mechanism of acupuncture therapy to improve the immune response of patients through microflora.
research design	Prospective, multicenter, randomized controlled clinical study
Total number of cases	90 Cases
Case selection	**Inclusion criteria:** (1) Patients with metastatic, recurrent or persistent squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or cervical cancer unsuitable for surgery and / or radiation therapy; (2) Age: 18-70 years old; (3) Having at least one measurable lesion according to RECIST 1.1; (4) The ECOG score is 0 or 1 point; (5) The life expectancy exceeds 3 months; (6) The patient has normal important organ function, specifically as follows: ① Absolute neutrophil count (ANC) 1.510 ^ 9 / L; ② Platelet count: 8010 ^ 9 / L; ③ Hemoglobin: 90g / L; ④ Total bilirubin 1.5 upper limit of normal (ULN); ⑤ Asparpartate aminotransferase (AST) and alanine aminotransferase (ALT) 2.5 ULN; Note: If the patient has liver metastasis, the AST and ALT levels are 5

	ULN; ⑥ Creatinine 1.5 ULN or creatinine clearance 60 ml/min (Cockcroft-Gault formula); ⑦ Baseline albumin: 28g / L; (7) Thyroid-stimulating hormone (TSH) level of 1 ULN; (8) Patients may sign a written informed consent form.
	Exclusion criteria: (1) Histopathological diagnosis of tumors other than squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma; (2) Participated in other clinical trials, or completed other clinical trials within 4 weeks; (3) Previous use of immune checkpoint inhibitors, including but not limited to other anti-PD-1 and anti-PD-L1 antibodies; (4) known history of allergy to any component of carlizumab or other monoclonal antibodies; (5) The current need to use immunosuppressive drugs; (6) patients with any history of active autoimmune disease or autoimmune diseases, including but not limited to the following diseases: hepatitis, pneumonia, uveitis, colitis (inflammatory bowel disease), hypophysitis, vasculitis, nephritis, hyperthyroidism and hypothyroidism, need intermittent use of bronchodilators or other medical intervention of asthma patients; (7) Clinically significant cardiovascular disease, including but not limited to congestive heart failure (New York Heart Association (NYHA) grade> 2), unstable or severe angina, severe acute myocardial infarction within 1 year prior to enrollment, supraventricular or ventricular arrhythmias requiring medical intervention, or QT interval 470 milliseconds (female); (8) arterial thrombosis or venous thrombosis occurs within 6 months; (9) Hypertension drugs are not well controlled by hypertension (systolic blood pressure 140 mmHg and / or diastolic blood pressure 90 mmHg); (10) Proteinuria (+ +) or total urine protein in 24 hours> 1.0 g; (11) Coagulation abnormalities (INR> 2.0, PT> 16s), have a bleeding tendency or are receiving thrombolysis or anticoagulant therapy; (12) No recovery from previously administered adverse events (except

	alopecia) (i. e., grade 1 or baseline); (13) Known as having active central nervous system metastases; (14) Patients with a previous invasive malignancy and with any evidence of disease within the past 5 years; (15) Active infection that requires systemic treatment; (16) History of immunodeficiency, including seropositivity for human immunodeficiency virus (HIV) or other acquired or congenital immunodeficiency diseases; (17) Hepatitis B virus (HBV)> 2000 IU / ml or DNA 110 ^ 4 / ml; or hepatitis C virus (HCV) RNA 110 ^ 3 / ml); (18) Live vaccine was received within 4 weeks before the first trial treatment; (19) Patients with suspected intestinal obstruction or risk of vaginorectal fistula or vaginal vesical fistula; (20) Any other medical, mental or social condition whose rights, safety, welfare, or ability to sign informed consent, collaboration and study participation or may interfere with the interpretation of the results.
therapeutic regimen	Trial group: acupuncture therapy + immunotherapy + targeted therapy / acupuncture therapy + immunotherapy + chemotherapy Control group: immunotherapy + targeted therapy / immunotherapy + chemotherapy
Efficacy assessment	Evaluation criteria and time: 1.1 Evaluation criteria: Treatment response was evaluated according to the Efficacy Evaluation criteria for Solid Tumors version 1.1 (RECIST 1.1) (see Annex 1); 1.2 Evaluation time: Start of treatment until 40 weeks, every 8 weeks ± 2 weeks, and then every 12 weeks ± 2 weeks until the end of treatment; patient efficacy evaluation results should be maintained for at least 4 weeks. 2. Efficacy evaluation items: 2.1 Objective response rate (Objective response rate, ORR): including comple teresponse (comple teresponse, CR), partial response (partial response, PR); ORR = (CR + PR) / 100% total. 2.2 Disease control rate (disease control rate, DCR): including comple

	teresponse (comple teresponse, CR), partial response (partial response, PR), and stable disease (stable disease, SD). DCR = (CR + PR + SD) / 100% of total cases. 2.3 Progression-free survival time (progression free survival, PFS): PFS is defined as the time from initiation of this regimen and the first onset of disease progression or death from any cause. 2.4 Overall survival (Overall survival, OS): the time from randomization to death due to any cause. 2.5T lymphoid subset and NK cells: including CD3 +, CD4 +, CD8 +, CD4 + / CD8 + and NK cells. 2.6 Level of tumor markers: SCC, CA125. 2.7 Quality of Life: This study used the QLQ-C30 quality of life questionnaire (see Annex 2) developed by the European Center for Cancer Research and Treatment (EORTC), the Quality of Life questionnaire for Cervical Cancer Patients EORCT QLQ CX24 (see Annex 3), and the Chinese version of the Simple Fatigue Scale (Brief Fatigue Inventory, BFI-C) (see Annex 4), quantity tables (Insomnia Severity Index, ISI) (see attachment 5), the Brief Pain Assessment Scale (Chinese Version of the Brief Fatigue Inventory, BPI-C) (see Attachment 6), the Hamilton Depression Scale (Hamilton Depression Scale, HAMD) (see Attachment 7), the Hamilton Anxiety Scale (Hamilton Anxiety Scale, HAMA) (see Attachment 8) 2.8 Adverse events related to immunotherapy and targeted therapy and their severity: Evaluation according to the evaluation criteria of adverse reaction events in version NCI CTCAE V5.0, including but not limited to skin reactions, pneumonia, colitis, nephritis, endocrine diseases, etc. 2.9 Safety indicators: including blood, urine, stool routine, liver function (ALT, AST), renal function (Cr, BUN) examination, check at any time when necessary.
statistical method	**1. Statistical software:** SAS 9.2 statistical software, efficacy indicators with full analysis set (FAS) analysis and compliance protocol set (PPS) analysis, adverse reactions should be safety data set (SS) analysis. **2. Statistical methods:**

	All statistical tests were two-sided and P 0.05 will be considered to be statistically significant. The proportion of shedding cases should not be greater than 20%. Metering data description mean, standard deviation, median, minimum value, maximum value, etc., count data description frequency, percentage, etc. Measurement data were analyzed by t-test and rank sum test, chi-square test and Ridit analysis, and survival data by Kaplan-Meier method, Wilcoxon rank sum test or log-rank test. Multivariate survival analysis was performed using a Cox proportional hazards regression model.
The study period	November 2023-November 2026

1. research background

1. Current status of modern medical treatment of cervical cancer

Cervical cancer is one of the most common gynecological malignant tumors. According to the data of the National Cancer Center in 2022, [1], the incidence and mortality rate of cervical cancer rank fourth among female tumors. In China, the incidence rate and mortality rate of cervical cancer are relatively high. In 2020, there are about 110,000 new cases and 60,000 death cases in China, [2], and the trend is younger. Despite significant progress in the screening and prevention of cervical cancer in recent years, its five-year overall survival rate has only been maintained at around 60%. The recurrence rate of advanced cervical cancer was as high as 70%, with a median survival of only 16.8 months [3].

For recurrent / metastatic cervical cancer, treatment modalities are limited and ineffective, and studies show that the 5-year survival rate for patients with recurrent / metastatic cervical cancer is only about 17% [4-5]. For metastatic / recurrent cervical cancer patients, (2020 before) NCCN guidelines have recommended: first-line treatment for paclitaxel and platinum and combined bevacizumab chemotherapy, including overall survival (OS) is about 13 months, second-line treatment for bevacizumab, topotecan, docetaxel, albumin paclitaxel and other single agent chemotherapy, its progression free survival (PFS) is not more than 5 months, OS only about 10 months [6-7].

Moreover, because the disease itself, long-term treatment and complications seriously threaten women's physical and mental health, the long-term quality of life of patients is generally low. Therefore, how to reduce the rate of cervical cancer recurrence and metastasis and improve the survival of advanced cervical cancer patients is an urgent clinical problem to be solved.

2. Advantages and limitations of immunotherapy for cervical cancer

Tumor immunotherapy is a therapeutic method to control and clear tumor by restoring the normal anti-tumor immune response by initiating and maintaining the tumor-immune circulation. At present, immunotherapy methods mainly include monoclonal antibodies, immune checkpoint inhibitors, therapeutic antibodies, cancer vaccines, cell therapy, small molecule inhibitors and so on.

The results of the KEYNOTE-826 study published in The New England Journal of Medicine in 2021 show, The combination of pabolizumab compared with chemotherapy ± bevacizumab was more than 15% in patients with persistent, recurrent / metastatic cervical cancer, Median PFS increased by over 2 months of [8], Based on this study, The FDA approved pabolizumab in combination with platinum-based chemotherapy ± bevacizumab as the first-line treatment for PD-L1 positive (CPS 1) persistent, recurrent / metastatic cervical cancer. Opened a new chapter in

immunotherapy for cervical cancer. For the second-line treatment of recurrent metastatic cervical cancer, NCCN guidelines recommended pabolizumab or navulimumab monotherapy use, KEYNOTE-158 study is a clinical trial of pabolizumab monotherapy for second-line cervical cancer and included 98 cervical cancer patients, the results showed that the ORR of the overall population was only 12.2%, the overall population median PFS and median OS were 2.1 and 9.4 months [9], respectively.

Based on the above results, it can be seen that for advanced recurrent and metastatic cervical cancer, although ICI alone lasts for a long time, but the remission rate is low, especially for patients with failed first-line treatment failure, its clinical efficacy is not satisfactory. Therefore, many joint programmes have been explored in recent years. The CLAP study was a single arm and phase clinical study of immunosuppressive agents combined with small molecule tyrosine kinase inhibitors (tyrosine kinase inhibitor, TKI), namely carilizumab and apatinib mesylate for second-line treatment of recurrent and metastatic cervical cancer. A total of 45 patients were included, with an overall ORR of 55.6% and an overall median PFS of 8.8 months [10].

Although immunotherapy partly improves survival in patients with recurrent / metastatic advanced cervical cancer, there is still a low response to immunotherapy in cervical cancer. The reason may be that tumor cells secrete immunosuppressive factors such as TGF- β and IL-10 that attract immunosuppressive cells (such as regulatory T cells and bone marrow-derived inhibitory cells) into the tumor microenvironment leading to immune tolerance [11]. Meanwhile, long-term immune checkpoint blockade therapy may lead to T cell depletion and weaken the immune response leading to immunoresistant [12]. Tumor-associated fibroblasts and macrophages in the tumor microenvironment can also inhibit the immune response into the tumor and prevent the immune cells from entering the tumor, leading to the inhibition of [13] by the tumor microenvironment. At the same time, as activated T cells attack normal tissues, increase inflammatory cytokines and autoantibodies [14], their immune-related adverse events could not be ignored, including hypothyroidism (10.2%), appetite loss (9.2%), fatigue (9.2%), diarrhea (21%) and other [15-16].

The above research results suggest that for second-line recurrent / metastatic cervical cancer patients in line and above have entered the era of "dechemotherapy", despite the low response to immunotherapy and epidemic-related adverse events, its application prospect is still very broad.

3. Acupuncture therapy can regulate the immune function of tumor patients

Acupuncture therapy can improve the body's immune function. On the one hand, acupuncture can regulate the balance of Yin and Yang and the function of viscera and meridians of the human body, but also can strengthen and dispel evil, and maintain the balance of the internal and external

environment of the human body [17]. The subtle balance between T cell subsets is the central link to maintaining the stability of the internal environment of the immune system, so it is an important indicator to reflect the anti-tumor immune function of the body [18]. The study shows that acupuncture treatment can increase the content of IL-2, IL-18, TNF-a and INF-A in tumor patients and animal tumor-bearing models, increase the number of NK cells, macrophages, CD4 +, CD8 + T cells, and B lymphocytes, activate and enhance innate and adaptive immunity, and at the same time, reduce the content of IL 4, IL-6 and IL 10, so as to inhibit Th 2, cells and Treg cells, relieve tumor immune suppression, and inhibit tumor growth [19-20]. The regulation mechanism of acupuncture on the immune system of the body may be strengthening the foundation, so acupuncture mostly focuses on the acupoints of the spleen and stomach and the acupoints of the veins. Many scholars at home and abroad found that compared with the conventional treatment of western medicine, acupuncture on acupoints, including Sanli, Guan Yuan, Tianhai and Sanyang, can improve the T cell subsets such as CD4 +, CD8 + and CD4 + / CD8 + and NK cells, and weaken the pro-inflammatory cytokines such as IL-1 β and TNF- α, thus improving the body's immune function of the body to delay tumor growth [21-23]. The results of the above studies suggest that acupuncture may have some synergistic potential for anti-tumor immunotherapy.

4. Research status and application prospect of acupuncture synergistic immunotherapy for cervical cancer

Previous studies have demonstrated the efficacy and advantages of acupuncture in regulating the immune function. Therefore, can acupuncture improve the immune status of cervical cancer patients to improve the response rate of immunotherapy? At present, most studies focus on the synergistic immune efficiency [24] of TCM therapy, and there are few research records on whether acupuncture can be synergistic immunotherapy and reduce toxic and side effects. Moreover, most cases were reported, with limited [25], mostly concentrated in the basic research stage. At present, the clinical application of acupuncture combined with immunotherapy for cervical cancer patients is not extensive, the preliminary basic research is weak, there is a lack of large-scale multi-center clinical trials, and there is no high-level evidence to support the role of acupuncture in cervical cancer immunotherapy. This study can fill the gap in the efficacy of acupuncture combined with immunotherapy in cervical cancer patients, explore the mechanism of the synergistic effect of acupuncture on immunotherapy in cervical cancer patients, and provide evidence-based medical evidence for their treatment. To fill the gap of acupuncture in the treatment of cervical cancer.

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2. purpose of research

1. Main purpose:

2. Secondary objectives:

Blood, stool and tongue coating samples were retained for cytokines and 16S rDNA / metagenomic testing, and the mechanism of acupuncture treatment to improve patients' immune response through microflora was further explored.

3. Type and principles of the study design

1. Study design type:

Prospective, multicenter, randomized controlled clinical study.

2. Random method:

For this study, using the central randomization method, 90 patients with recurrent / metastatic cervical cancer were included and divided into 8 study centers. In each research center, pathological type, PD-L1 expression level, and immunotherapy combined with targeted therapy / immunotherapy combined with chemotherapy were used as stratification factors. The patients were divided into control group (Group A) and test group (Group B), and the length of the group was 6 and the allocation ratio of 1 ： 1.

3. Comparative method:

This trial includes control group and trial group, trial group intervention measures: acupuncture therapy + immunotherapy + targeted therapy / acupuncture therapy + immunotherapy + chemotherapy; control group intervention measures: immunotherapy + targeted therapy / immunotherapy + chemotherapy.

4. Sample size calculation:

This study intends to conduct a preliminary exploratory study, using small samples for clinical observation and literature review[1]The sample size of each group in the exploratory study should be greater than 30.90 patients to be included in this exploratory study should be assigned to the test group and the control group according to 1:1, with 45 cases in each group, which meets the sample size of the small exploratory study。

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四、Case selection

1. Inclusion criteria:

(1) Patients with metastatic, recurrent or persistent squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or cervical cancer unsuitable for surgery and / or radiation therapy;

(2) Age: 18-70 years old;

(3) Having at least one measurable lesion according to RECIST 1.1;

Note: Measurable lesions are defined as lesions that can be accurately measured in at least one dimension (the longest diameter recorded by computed tomography (CT) scan, magnetic

resonance imaging (MRI) is 10mm; lymph nodes must be 15mm on the short axis. Tumors within the previously irradiated area will be designated as "nontarget" lesions unless progression is recorded at least 90 days after completion of radiotherapy or a biopsy is performed to confirm persistence.

(4) The ECOG score is 0 or 1 point;

(5) The life expectancy exceeds 3 months;

(6) The patient has normal important organ function, specifically as follows:

① Absolute neutrophil count (ANC) 1.510 ^ 9 / L;

② Platelet count: 8010 ^ 9 / L;

③ Hemoglobin: 90g / L;

④ Total bilirubin 1.5 upper limit of normal (ULN);

⑤ Asparpartate aminotransferase (AST) and alanine aminotransferase (ALT) 2.5 ULN;

Note: If the patient has liver metastasis, the AST and ALT levels are 5 ULN;

⑥ Creatinine 1.5 ULN or creatinine clearance 60 ml/min (Cockcroft-Gault formula);

⑦ Baseline albumin: 28g / L;

(7) Thyroid-stimulating hormone (TSH) level of 1 ULN;

Note: Patients with a free triiodothyronine [FT3] or a free thyroxine [FT4] level of 1 ULN may be included.

(8) Patients may sign a written informed consent form.

2. Exclusion criteria:

(1) Histopathological diagnosis of tumors other than squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma;

(2) Participated in other clinical trials, or completed other clinical trials within 4 weeks;

(3) Previous use of immune checkpoint inhibitors, including but not limited to other anti-PD-1 and anti-PD-L1 antibodies;

(4) known history of allergy to any component of carlizumab or other monoclonal antibodies;

(5) The current need to use immunosuppressive drugs;

Note:> 10 mg/d prednisone or equivalent dose were prohibited for 2 weeks prior to study drug administration.

(6) patients with any history of active autoimmune disease or autoimmune diseases, including but not limited to the following diseases: hepatitis, pneumonia, uveitis, colitis (inflammatory bowel disease), hypophysitis, vasculitis, nephritis, hyperthyroidism and hypothyroidism, need intermittent use of bronchodilators or other medical intervention of asthma patients;

Note: except for vitiligo, resolved pediatric asthma / atopic subjects.

(7) Clinically significant cardiovascular disease, including but not limited to congestive heart failure (New York Heart Association (NYHA) grade> 2), unstable or severe angina, severe acute myocardial infarction within 1 year prior to enrollment, supraventricular or ventricular arrhythmias requiring medical intervention, or QT interval 470 milliseconds (female);

(8) arterial thrombosis or venous thrombosis occurs within 6 months;

(9) Hypertension drugs are not well controlled by hypertension (systolic blood pressure 140 mmHg and / or diastolic blood pressure 90 mmHg);

(10) Proteinuria (+ +) or total urine protein in 24 hours> 1.0 g;

(11) Coagulation abnormalities (INR> 2.0, PT> 16s), have a bleeding tendency or are receiving thrombolysis or anticoagulant therapy;

(12) No recovery from previously administered adverse events (except alopecia) (i. e., grade 1 or baseline);

(13) Known as having active central nervous system metastases;

(14) Patients with a previous invasive malignancy and with any evidence of disease within the past 5 years;

Note: Skin basal cell carcinoma, skin squamous cell carcinoma or cervical cancer in situ with potentially curative treatment.

(15) Active infection that requires systemic treatment;

(16) History of immunodeficiency, including seropositivity for human immunodeficiency virus (HIV) or other acquired or congenital immunodeficiency diseases;

(17) Hepatitis B virus (HBV)> 2000 IU / ml or DNA 110 ^ 4 / ml; or hepatitis C virus (HCV) RNA 110 ^ 3 / ml);

(18) Live vaccine was received within 4 weeks before the first trial treatment;

Note: Administration of an inactivated virus vaccine against seasonal influenza is allowed.

(19) Patients with suspected intestinal obstruction or risk of vaginorectal fistula or vaginal vesical fistula;

(20) Any other medical, mental or social condition whose rights, safety, welfare, or ability to sign informed consent, collaboration and study participation or may interfere with the interpretation of the results.

3. Loss standards:

① Poor compliance, do not cooperate with the treatment;

② Those who cannot adhere to the treatment if an accident occurs during the treatment process;

③ Self-withdrawal of patients during the trial;

④ Lost to visit;

4. Termination of the study criteria:

① The subject volunteered to withdraw;

② The subject has poor compliance and the investigator cannot not continue the clinical investigator;

③ Subject experienced pregnancy, death, or was lost to follow-up;

④ The Sponsor terminates the study;

⑤ The competent administrative department cancels the test;

⑥ Other circumstances deemed necessary to withdraw from the study.

The investigators should do their best effort to enable each subject to continue the appropriate treatment unless stopping participation in the study is most beneficial. If the subject's study treatment stops, the investigator should do his best to evaluate the subject's study results.

Subjects should also enter the follow-up period after treatment termination or withdrawal from the study. The subject will receive periodic follow-up (once every 2 months, telephone or outpatient follow-up) to learn about survival status, follow-up, the endpoint event (i. e. patient death or follow-up after 2 years).

5. End of treatment and entry to follow-up phase criteria:

Treatment is stopped prior to follow-up in one of the following cases:

① Treatment cycle is up to 2 years;

② Patients with disease progression;

③ Unacceptable toxic effects occur in patients;

④ The use of contraindicated therapy, such as non-palliative radiotherapy or anticancer effect of traditional Chinese medicine decoction and proprietary Chinese patent medicine oral, injection;

⑤ The investigator decides to stop the protocol or the patient withdrew consent;

⑥ Treatment can be discontinued if a patient with a confirmed complete response has received at least 8 cycles of immunotherapy, including at least 2 cycles beyond the complete response.

6. Early study termination / site closure:

Upon termination of the study, the Ethics committee and the regulatory B are reported. In the event of early study termination or site closure, all study materials (except documents that must be retained at the site) must be returned to the investigator. The investigator must keep the relevant

documents until notified of the destruction. Reasons for early termination of the trial or site closure may be but not limited to the following reasons: discovery of new drug toxicity, results of any interim analysis, subject enrollment and follow-up completion, non-protocol compliance, changes to the study schedule, slow enrollment, or poor quality of clinical data.

5. Research methods and technical routes

1. Treatment plan:

1.1 Treatment regimen of the trial group: acupuncture therapy + immunotherapy + targeted therapy / acupuncture therapy + immunotherapy + chemotherapy

1.1.1 Acupuncture therapy:

(1) Needle: disposable acupuncture needle (p0.340mm, 1.5 inch) and fixed pad specially made by Suzhou Medical Supplies Factory Co., LTD., and low frequency electronic pulse therapy instrument (G6805-1A) produced by Shanghai Huayi Medical Instrument Co., LTD., are selected.

(2) Point selection and positioning: (refer to the planning textbook of National Traditional Chinese Medicine Colleges in Acupuncture (10th edition)):

main point:

Bilateral foot li: stomach meridian acupoint, located outside the calf, 3 inches below the calf nose, 1 transverse finger outside the anterior tibial crest, the calf nose and exi connection.

Bilateral three Yin intersection: the spleen through the meridian acupoint, located in the inner side of the calf, 3 inches above the medial malleolus, the medial edge of the tibia.

Guan Yuan: Ren Mai meridian acupoint, located in the lower abdomen, 3 inches below the umbilical cord, on the front midline.

Qi sea: Ren meridian acupoint, located in the lower abdomen, 1.5 inches below the umbilical cord, on the front midline.

Baihui: Du meridian acupoint, located in the head, before the middle of the hairline straight up 5 inches.

Yintang: Du meridian acupoint, located in the head, the middle of the inner end of the two eyebrows.

adjunct acupuncture points:

① Pain: bilateral, Hetian point, bilateral Tachong point.

Hepoint: large intestine, located in the back of the hand, the middle point of the radial side of the second metacarpal.0.5-1 inch.

Taichong point: the liver meridian acupoint, located in the back of the foot, the first, the second metatarsal bone, the base of the metatarsal bone and the front of the depression, or touch

the arterial beat.0.5-1 inch.

② Insomnia, anxiety, depression: temple temple, bilateral temples:

Temple point: Du meridian acupoint, located in the head, the middle of the hairline straight 0.5 inches.

Temple: through the outer strange hole, located in the head, when the brow tip and the eye outer canthus, back about 1 horizontal finger in the depression.

③ God fatigue: Zhongwan point, bilateral Shenmen point:

Zhongwan point: Ren meridian point, located in the upper abdomen, 4 inches in the umbilical cord, on the front midline.

Shenmu point: heart meridian acupoint, in the anterior wrist area, the distal palar side, the radial end of the flexor carpal tendon on the ulnar side.

④ If the patient has urinary symptoms such as frequent urination, nocturia, urinary incontinence, dysuria, discomfort in lower abdomen, perineal pain, after getting qi, the electrodes are horizontally connected to the bilateral three yin crossing point.

(3) Operation method

The patient was placed in the supine position, and the local skin was routinely disinfected.

Zusanli: after vertically stabbing 0.5-1 inch with 0.3 40mm millineedle, uniform small lifting twist 3 times, with the patient local acid, numbness and other qi feeling as the degree. After obtaining gas, the electrodes of the electric needle instrument were connected laterally to the needle handle of both sides, and the continuous wave was selected, the adjustment frequency was 2 Hz, and the current size was 0.5-2 mA.

Sanyin intersection: avoid nerves, slowly lower into 0.5-1 inch. If there is no electric shock needle after puncture, turn for 3 times in the direction of needle, adjust the needle under the skin, enter the needle tip again, and turn for 3 times later. If the patient has urinary symptoms such as frequent urination, nocturia, urinary incontinence, dysuria, lower abdominal discomfort, perineal pain, after getting gas, the electrode is horizontally connected to the needle handle of the bilateral side, the continuous wave is selected, the adjustment frequency is 2 Hz, and the current size is 0.5-2 mA.

Guan Yuan point, gas sea point: straight stab 0.5-1 inch, uniform small range of lifting twist 3 times, to the patient's local acid, numbness and other qi feeling degree.

Baihui: flat thorn 0.5-0.8 inches, no technique.

Yintang: 1 inch from the middle depression of the inner section of the two eyebrows slightly left or right to avoid the vein into the needle, puncture under the periosteum, the tip of the needle

down flat stab 0.5-1 inch.

If the patient has pain symptoms, Heu point straight stab 0.5-1 inch, Taichong point straight stab 0.5-1 inch, uniform small range of lifting twist 3 times, to the patient local acid, numbness and other gas feeling degree.

If the patient has insomnia or anxiety, depression of mood disorders, ting point, flat thorn 0.5-0.8 inches, not technique, bilateral temples straight or oblique stab 0.3-0.5 inches, uniform small range of lifting twist turn 3 times, to the patient local acid, numbness and other gas feeling degree.

If the patient is tired, Zhongwan point straight stab 1-1.5 inches, bilateral men point straight stab 0.3-0.5 inches, uniform small range of twist 3 times, to the patient locally produce acid, numbness and other gas feeling as the degree.

(4) Cycle and frequency:

Start simultaneously with immunotherapy, 1 cycle every 4 weeks, 1-2 injections per week, and at least 4 injections per cycle. Each needle was left for 30 minutes.

1.1.2 Immunotherapy: Carrelizumab

① Usage and dosage: Carizumab (Carizumab for injection, manufacturer: Suzhou Shengdia Biomedical Co., LTD., No. Approval number: S20190027), 200mg / time, intravenous injection, once every 2 weeks)

② Frequency and course of treatment: use once for every 2 weeks, 1 cycle for every 4 weeks;

③ Treatment cessation duration: use up to 2 years, patient disease progression, unacceptable toxic effects, use of prohibited therapy, investigator decision to stop the regimen or patient withdrawal of consent. Treatment could be discontinued if a patient with a confirmed complete response had received at least 8 cycles of immunotherapy, including at least 2 cycles beyond the complete response.

1.1.3 Targeted therapy: apatinib

① Usage and dosage: Apatinib (apatinib mesylate tablets, manufacturer: Jiangsu Hengrui Pharmaceutical Co., LTD., approval number: H20140103), 250mg / time, orally, once a day.

② Drug reduction: If the patient has treatment-related adverse events, the amount of apatinib can be reduced as follows:

Dose grade	dosage
initial dose	250mg, qd (250mg / 1 day)
Grade 1 dose	250mg, oral 2 days off 1 day (500mg / 3

reduction	days)
Grade 2 dose reduction	250mg, 1 day off 1 day (250mg / 2 day)

Note: carilizumab is not allowed; apatinib is not allowed to increase the dose again after the reduction.

1.1.4 Chemical therapy:

The specific chemotherapy regimen, drug usage and dosage, and the frequency of chemotherapy should be determined by the oncology clinicians according to the NCCN guidelines (2023) and the patient's condition.

1.2, Treatment regimen of the control group: immunotherapy + targeted therapy / immunotherapy + chemotherapy

.11.2 Immunotherapy: Carrelizumab

① Usage and dosage: Carizumab (Carizumab for injection, manufacturer: Suzhou Shengdia Biomedical Co., LTD., No. Approval number: S20190027), 200mg / time, intravenous injection, once every 2 weeks)

② Frequency and course of treatment: once for every 2 weeks, and 1 cycle for every 4 weeks;

③ Treatment cessation duration: use up to 2 years, patient disease progression, unacceptable toxic effects, use of prohibited therapy, investigator decision to stop the regimen or patient withdrawal of consent. Treatment could be discontinued if a patient with a confirmed complete response had received at least 8 cycles of immunotherapy, including at least 2 cycles beyond the complete response.

1.2.2 Targeted therapy: apatinib

① Usage and dosage: Apatinib (apatinib mesylate tablets, manufacturer: Jiangsu Hengrui Pharmaceutical Co., LTD., approval number: H20140103), 250mg / time, orally, once a day. The 4 weeks is 1 cycle.

② Drug reduction: If the patient has treatment-related adverse events, the amount of apatinib can be reduced as follows:

Dose grade	dosage
initial dose	250mg, qd (250mg / 1 day)
Grade 1 dose reduction	250mg, oral 2 days off 1 day (500mg / 3 days)
Grade 2 dose	250mg, 1 day off 1 day (250mg / 2 day)

reduction	

Note: carilizumab is not allowed; apatinib is not allowed to increase the dose again after the reduction.

1.2.3 Chemical therapy:

The specific chemotherapy regimen, drug usage and dosage, and the frequency of chemotherapy should be determined by the oncology clinicians according to the NCCN guidelines (2023) and the patient's condition.

1.3 Other Therapy:

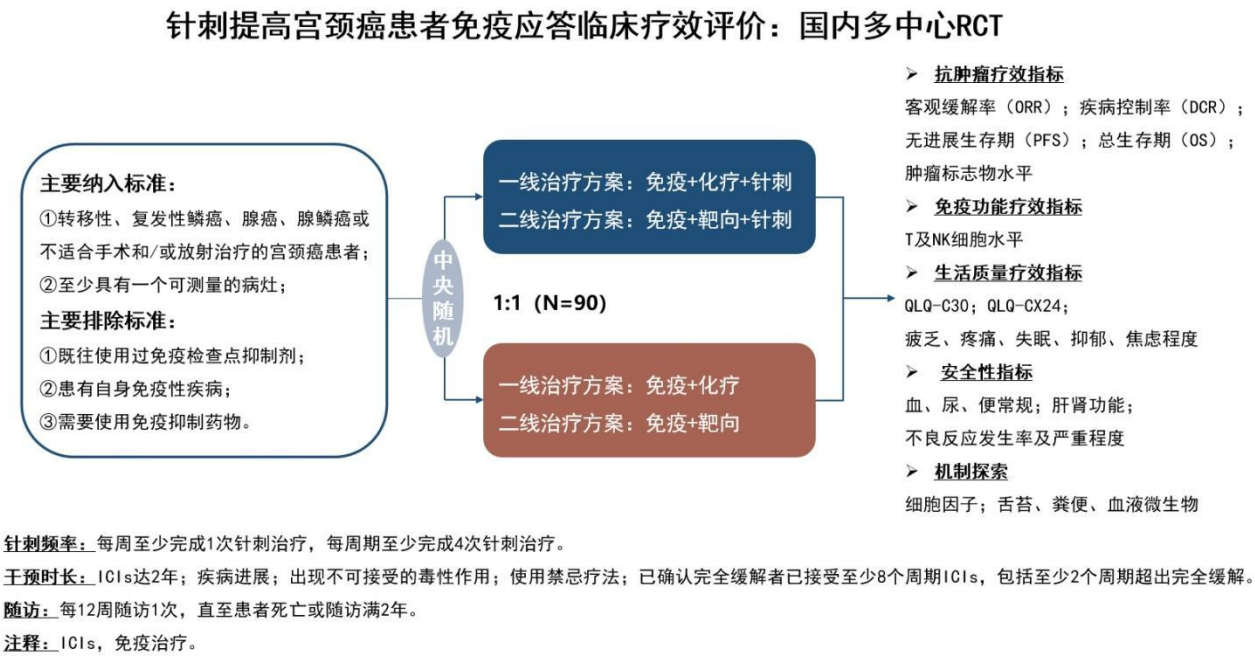
Both groups may be treated with symptomatic supportive care according on their disease. The investigator should record in detail the treatment of both groups, including the following aspects: ① pain management; ② nutritional support; ③ psychopsychological intervention; ④ tumor treatment prevention and side effects.

2. No medication use and treatment:

The use of other antitumor therapy except carilzuzumab + apatinib / carilzumab + chemical therapy, including non-palliative radiotherapy, other Chinese medicine injections with anti-tumor effect, TCM decoction, proprietary Chinese medicine, other anti-tumor drugs or treatments as specified by the protocol, is prohibited.

3. Drug distribution:

First, the appropriate amount of drugs is delivered to the research centers according to the expected progress of the trial, and then distribute the drugs during the trial according to the actual progress. Distribued by the site site s at the site to authorized staff. The drug distribution process should be recorded accordingly, and the researcher must sign the drug distribution sheet and record the use and recovery of the drug. In order to ensure the timely supply of drugs, the drug alert quantity is set in advance, and once the stock is insufficient, timely distribution.



针刺频率：每周至少完成1次针刺治疗，每周期至少完成4次针刺治疗。

干预时长：ICIs达2年；疾病进展；出现不可接受的毒性作用；使用禁忌疗法；已确认完全缓解者已接受至少8个周期ICIs，包括至少2个周期超出完全缓解。

随访：每12周随访1次，直至患者死亡或随访满2年。

注释：ICIs，免疫治疗。

4. Technology roadmap: Vi. Observation items and test time

1. Observation items:

1.1 Demographic data:

Name, date of birth, contact information, residence, occupation, smoking history, alcohol consumption, personal history, family genetic history, history of drug and food allergy.

1.2 Diagnostic data:

Time to diagnosis of cervical cancer, unit of diagnosis, pathology type, pathological grade, site of metastasis, previous treatment, PD-L1 expression, TNM stage; past history and complicated disease.

1.3 Efficacy indicators:

Evaluation criteria and evaluation points: The target lesions were evaluated according to the treatment response according to the efficacy evaluation criteria for solid tumors, version 1.1 (RECIST 1.1) (see Annex 1); every 8 weeks until 40 weeks, and then every 12 weeks until the end of treatment; the patient efficacy evaluation results should be maintained for at least 4 weeks.

ORR = (number of CR cases + number of PR cases) / 100% of total cases.

1.3.2 Disease control rate (disease control rate, DCR): DCR refers to the proportion of patients whose tumor volume decreases or stabilizes the prespecified value and can maintain the minimum time limit requirements. Cases that include a comple teresponse (comple teresponse, CR), partial response (partial response, PR), and stable disease (stable disease, SD).

DCR = (CR + PR + SD) / 100% of total cases.

1.3.3 Progression-free survival time (Progression Free Survival, PFS): PFS is the time from

randomization to the onset of tumor progression or death.

1.3.4 Overall survival (Overall survival, OS): the time from randomization to death from any cause.

1.3.5T Lymphoid subset and NK cells: including the levels of CD3 +, CD4 +, CD8 +, CD4 + / CD8 +, and NK cells.

1.3.6 Tumor markers: including: SCC, CA125.

1.3.7 Quality of Life: This study used the QLQ-C30 quality of life questionnaire (see Annex 2) developed by the European Center for Cancer Research and Treatment (EORTC), the Quality of Life questionnaire for Cervical Cancer Patients EORCT QLQ CX24 (see Annex 3), and the Chinese version of the Simple Fatigue Scale (Brief Fatigue Inventory, BFI-C) (see attachment 4), insomnia severity, count tables (Insomnia Severity Index, ISI) (see attachment 5), the Brief Pain Assessment Scale (Chinese Version of the Brief Fatigue Inventory, BPI-C) (see Attachment 6), the Hamilton Depression Scale (Hamilton Depression Scale, HAMD) (see Attachment 7), the Hamilton Anxiety Scale (Hamilton Anxiety Scale, HAMA) (see Attachment 8).

(According to the evaluation criteria of adverse reaction events in NCI CTCAE V5.0): routine blood, urine and stool tests before treatment and every two cycles; electrocardiogram, liver function (ALT, AST), renal function (Cr, BUN) tests, if necessary.

1.3.8 Adverse events and their severity related to immunization, treatment and targeted therapy: Evaluation according to the evaluation criteria of adverse reaction events in NCI CTCAE V5.0, including but not limited to skin reactions, pneumonia, colitis, nephritis, endocrine diseases, etc.

1.3.9 Safety indicators: blood, urine, routine stool test, liver function (ALT, AST), and renal function (Cr, BUN) test.

1.4 Blood Samples:

After the patients signed the informed consent, 6ml + 2ml, 5g, and tongue coating samples were kept within 4 weeks, every 6 weeks / 12 weeks before enrollment, at disease progression, including 6ml blood samples for cytokine detection.2ml blood sample, stool sample 5g and tongue coating sample were used for 16S rDNA / metagenome technology to complete the intestinal, blood and oral microbial examination to explore the mechanism of action.

2. Observation time point:

2.1 Pre-enrollment examination-Domestic Demand completed 4 weeks before the start of treatment:

① General information collection: name, date of birth, contact information, residence, occupation, smoking history, drinking history, personal history, family genetic history, history of

drug and food allergy;

② Collection of disease information and diagnosis data: time of diagnosis of cervical cancer, unit of diagnosis, pathological type, pathological grade, the site of metastasis, previous treatment, PD-L1 expression, TNM stage; past history and comorbid disease;

③ Vital signs: heart rate, respiration, blood pressure, and body temperature;

④ Physical examination, clinical symptoms, patient tongue coating, pulse image and traditional Chinese medicine syndrome;

⑤ ECOG score, EORTC QLQ-C30, EORCT QLQ CX24, and MDASI-TCM questionnaires;

⑤ Blood routine, urine routine, stool routine, liver and kidney function, electrocardiogram;

⑥ Tumor markers, T lymphoid subsets and NK cell levels, cytokines detection;

⑦ Imaging examination: chest, abdomen, pelvic enhanced CT, if contrast allergy, plain chest CT, abdominal, pelvic MRI or CT; brain CT or MRI, whole body bone scan or PET-CT examination.

⑧ Keep biological samples from patients, including: blood sample 6ml + 2ml, stool sample 5g, and tongue coating sample.

2.2 Examination during the treatment period:

2.2.1 Every 8 weeks / 12 weeks ± 2 weeks, completion is required:

① Vital signs: heart rate, respiration, blood pressure, and body temperature;

② Physical examination, clinical symptoms, patient tongue coating, pulse image and traditional Chinese medicine syndrome;

③ ECOG score, EORTC QLQ-C30, EORCT QLQ CX24, and MDASI-TCM questionnaires;

④ Blood routine, urine routine, stool routine, liver and kidney function, electrocardiogram;

⑤ Tumor markers, T lymphoid subsets and NK cell levels, cytokines detection;

⑥ Chest, abdomen, ministry, pelvic CT / MRI examination according to the needs of the disease: the efficacy evaluation is confirmed at least 4 weeks after the study of PR and CR, and the subsequent PFS and imaging examination should be the same as the examination method when entering the group, and the same examination method must be adopted;

⑦ Keep biological samples from patients, including: blood sample 6ml + 2ml, stool sample 5g, and tongue coating sample.

2.4 Follow-up visit:

① Follow-up of all the subjects in this study;

② Start-up time of follow-up: follow-up started after treatment, follow-up to end point event (i. e. patient death or follow-up after 2 years);

③ Frequency and content of follow-up: follow-up once every 12 weeks ± 1 week, and observe the patients' medication category, physical condition score, tumor markers and imaging examination. Among them, tumor markers and imaging examination can be selected. For subjects who did not have disease progression at the time of withdrawal from this clinical study, imaging follow-up was required every 8 weeks (± 1 week) until disease progression or the subject received other treatments.

七、Evaluation method of the main indicators

Evaluation of effectiveness: CT, ultrasound, and tumor markers were performed before treatment, every 8 / 12 weeks after ± 1 week of treatment. When necessary, brain MRI and bone scan were performed as evaluation methods. During the follow-up period, patients were followed up once every 12 weeks ± 1 week to record the survival status, including optional CT, ultrasound, tumor markers, brain MRI, etc.;

Safety evaluation: blood routine, urine routine, stool routine, liver and kidney function, and electrocardiogram were used as the evaluation methods.

Viii. Observation of adverse events

1. Adverse event definition:

Adverse event (AdverseEvent, AE) is an adverse medical event after a patient or a clinical trial subject receives a drug but not necessarily causally related to treatment. Adverse events are the main factors affecting the safety of drugs and should be emphasized in the process of clinical trials.

Any adverse medical event since the subject voluntarily signed the informed consent and entered the trial until the last follow-up should be attributed to the trial drug. An adverse event can be any adverse and undesirable signs (including abnormal laboratory findings), symptomatic or temporal medication-related disease regardless of a causal relationship to treatment. Changes due to normal growth and development without frequency or severity above the normal range were not considered adverse events. Adverse events include the following:

① All suspected adverse drug reactions;

② All reactions due to drug overdose, abuse, withdrawal, allergy, toxicity, or "no expected pharmacological effects of the drug";

③ Obviously unrelated diseases;

④ Injury or accident (it must be a medical event). Note: If a medical condition is known to cause an injury or accident (e. g., a fall caused by vertigo), then the medical condition (vertigo) and an accident (fall) should be reported as two different adverse events. The result of this incident (e. g. hip fracture with a fall) should be recorded under notes;

⑤ Abnormal findings during physical examination or laboratory examination. If the physical examination and laboratory numerical treatment are normal before and after, there will be no such adverse events occurring; if abnormal before treatment and normal after treatment, the causes before and after normal should be analyzed according to the study needs, not an adverse event; but if normal before treatment and abnormal after clinical treatment and the abnormal are adverse event; abnormal before and after treatment, the doctor experience and the industry should have clinical significance, or take further examination (except for review).

2. Obtaining the adverse event information:

① AEs were learned from the subject's self-description (e. g. visit visits, log cards, etc.).

After each visit of the treatment, the subject will be asked about the adverse event. The question at the first visit could be: " Are there any health problems ever since you started taking the study medication?"Can you ask any health problems since your last visit?”。

② Adverse events are informed from the visit examinations and laboratory results.

Although this approach has the advantages of sufficient judgment basis, intuition and data traceability, whether the design of safety in the test protocol is complete is an important influencing factor of the informed route. The study physician applied concise medical terms to report all adverse events found.

③ Tracing that adverse events originated from concomitant medication.

Concomitant drugs in large-scale clinical trials with long study periods are often complicated, and the emergence of new synergistic drugs and replacement drugs often indicates the occurrence of AEs. For example, during a follow-up visit, the patient told the doctor that "amoxicillin" was used during a recent observation period. When recording the combined medication information, it is important to ask the patient about the reason why he is taking amoxicillin, because the patient may have had an adverse event of "upper respiratory tract infection".

3. Observation and recording of Adverse events:

When filling in the AE report form, specifically describe the occurrence of adverse events, including the time, severity, duration, measures taken and outcome. All adverse events shall be recorded in the designated CRF adverse event table. Try to fill in the medical diagnosis, do not list the symptoms, if the disease name can not be confirmed, try to write a symptom form.

Collection of adverse events based on physical examination and laboratory indicators often requires comparison with the baseline specified in the test protocol. If the data change is within the baseline range specified in the protocol, it is not an adverse event; if the data change (rise or decrease) is significant, it is an adverse event to be recorded; if the change is large, the start and termination time, and the clinical trial.

All adverse events including any symptoms and laboratory abnormalities during the clinical trial should be followed until the adverse event disappears or further follow-up as the investigator is no longer necessary.

4. Possible adverse events and treatment:

4.1 Possible adverse events and management:

Apatinib mesylate: may appear hypertension, bone marrow suppression, diarrhea, vomiting, proteinuria, abnormal liver function, appetite, rash, fatigue, such as adverse reactions, if patients with adverse reactions, should be evaluated by the researchers and oncology clinicians, pause or reduce medication, at the same time can be symptomatic treatment for patients.

Carilizumab: adverse reactions may be hepatitis, abnormal liver function, pneumonia, reactive capillary hyperplasia, nephritis, hypothyroidism, thrombocytopenia and other reactions. If the patient has adverse reactions, the drug should be suspended after evaluation by the investigator and oncology clinician, and the patient can be given symptomatic treatment.

Chemotherapy possible adverse events and treatment: there may be bone marrow suppression, nausea, alopecia, hair loss, neurotoxicity, neurotoxicity and urinary toxicity adverse reactions, if patients with adverse reactions, should be evaluated by the researchers and oncology clinicians, decided to suspend medication, reduce dosage or change chemotherapy regimen, etc., can give patients symptomatic treatment at the same time.

4.2 Possible adverse events and management of acupuncture:

Acupuncture therapy may have adverse reactions, such as acupuncture, injection, needle bending, folding, pain, hematoma, infection, etc. If the patient has adverse reactions, the treatment should be stopped immediately, all needles should be pulled out, and the patient can be given symptomatic treatment. After evaluation by the investigator and acupuncture clinicians, it is decided whether the next acupuncture treatment is feasible.

If any adverse event occurs in the clinical trial, whether the trial drug is causal, the responsible doctor should take the necessary measures to give treatment and rescue. For the adverse events occurring during the trial, the type, degree, occurrence time, duration, treatment measures and treatment process should be recorded in the CRF, and whether they are related to the test drug used and the control drug. After the adverse event occurs, the investigator may decide

whether the subject will discontinue the clinical trial according to the condition. Cases discontinued due to serious adverse events should be followed up and the outcome should be recorded.

5. Assessment of adverse events:

5.1 Date of occurrence of the adverse event:

The date of the first adverse symptoms or signs or abnormal laboratory parameters (the date of examination showing a clinically significant abnormal result) can be considered as the date of occurrence. For asymptomatic / complication / concomitant disease, the date of diagnosis is the date of occurrence (date of diagnostic examination).

5.2 Severity of adverse events:

When completing the adverse event form for the CRF, the investigator should use the NCRC Common Adverse Event Evaluation criteria to describe the intensity of version 5.0).

All the causal analysis of the relationship between adverse events and trial drugs, "definitely related", "very likely related", "probably related", "probably related", "definitely unrelated" five levels, the first three drugs. Causal analysis consideration has the following five aspects:

① Whether there is a reasonable sequence relationship between the time of drug initiation and the time of suspected adverse drug reactions (Adverse Drug Reaction, ADR) (drug occurrence));

② Whether the suspected ADR meets the known ADR of the drug (literature);

③ Whether the suspected ADR can be explained by concomitant medication, previous medication, patient clinical conditions, or other therapies (other explanations);

④ Whether the suspected ADR disappears or decreases after withdrawal or reduction (withdrawal reaction);

⑤ After reexposure to the same drug, whether the suspicious ADR appears again (reuse).

The investigator assessed the possible association between adverse events and trial drug and concomitant medication, according to the table below.

Consider factors	Drug use	In accordance with the literature	Other explanations	Stop the drug disappear	Again with reproduction
Certainly related	+	+	−	+	−
It's likely to be relevant	+	+	−	+	?

Probably about	+	+	±	±	?
It may not matter	+	−	±	±	?
Certainly irrelevant	−	−	+	−	−

Note: "+" indicates positive; "-" indicates no; "±" indicates difficult positive or negative; "?"Shall not know.

5.3 Return of Adverse Events:

Evaluation of adverse signs and symptoms and progression of abnormal changes seen in the laboratory using the following categories:

① Recovery: recovery signs and symptoms disappear or the subject recovers; examination values return to normal or return to baseline;

② Relief: the severity of improvement was reduced by a grade or more, or mild symptoms and disappearance, or the indicators returned to the level before the trial treatment;

③ Not recovered / no disappeared: no recovered symptoms, seen and various indicators did not improve; according to the data of the last visit during the observation period, the severity relative to the first occurred caused irreversible abnormalities;

④ Recovery but with sequelae: some symptoms and seen recovery, some of the seen into sequelae;

⑤ Death: Death has a direct causal relationship to the adverse events discussed."A direct causal relationship" means that the adverse event discussed is the cause of death or the adverse event is indeed related to death;

⑥ Unknown: not during the unknown administration of the test medication or at the end of the trial according to the protocol.

5.4 Date of adverse event conclusion:

Record the conclusion date of "recovery", "improvement", "not recovery", "recovery but with sequelae" or "death". When the date of the conclusion cannot be clearly recorded, the content date of the conclusion or the date of the judgment may be taken as the conclusion date. In principle, except for permanent, irreversible adverse events or any preexisting chronic complication, the

events deemed "not recovered" should be visited until the subject recovers. The conclusion date should be described in the notes. Given the permanent, irreversible adverse event or worsening of any pre-existing chronic complication until the subject recovers, this fact and the date of judgment.

6. Serious Adverse Events:

6.1 Definition of serious adverse events:

Serious adverse events are those occurring during the study phase meeting one or more of the following criteria:

① die;

② threat to life;

③ Need hospitalization or prolonged hospitalization;

④ Permanent or serious disability;

⑤ Leading to congenital malformation defects.

Some medical events that have not caused death, life danger or hospitalization should be considered serious adverse events after appropriate medical judgment to the subject or to avoid medical or surgical treatment.

6.2 Record and reporting of serious adverse events:

In case of serious adverse event during the test, whether related to the test drug, emergency treatment should be taken immediately. The investigator must report to the State Medical Products Administration, the National Health Commission, Jiangsu Henrui Pharmaceutical Co., Ltd., Suzhou Shengdiya Biological Pharmaceutical Co., Ltd., and the provincial drug administration authorities within 24 hours of knowing the serious adverse events. And at the same time (24 hours) report to the branch of research unit, and by the branch of the research unit immediately report to the responsible unit (China academy of Chinese medicine sciences cross gate hospital), then by subject responsible unit reported to the unit ethics committee, and within 30 days in other research center. See the contact number in the table below.

unit	contacts	contact number
Research Group of Guang'anmen Hospital, China Academy of Chinese Medical Sciences	Wang Yan	18435227044
Ethics Committee of Guang'anmen Hospital, Chinese Academy of Chinese Medical Sciences	Qiao Jie	010-88001552

7. Abnormal clinical test results and other abnormal indicators as adverse events

or serious adverse events:

If some abnormal laboratory findings (e. g., clinical biochemistry, hematology, urinalysis), or other abnormal indicators (e. g., electrocardiogram, vital signs, etc.) are clinically significant and meet the definition of some or some serious adverse events, they must be recorded as adverse events or serious adverse events. Clinically significant abnormal laboratory findings and other abnormalities found after medication, or present at baseline assessment and aggravated after study entry, should be considered as an adverse event or serious adverse event.

However, clinically significant abnormal laboratory findings or other abnormalities regarding the studied disease were found unless the investigator determines that the subject is more severe than expected and is not included in adverse events or serious adverse events. Abnormal laboratory findings or other abnormalities present at the beginning of the study but not aggravated were also not included in adverse events and serious adverse events.

Death due to disease progression was not reported as a serious adverse event.

IX. Research quality control and quality assurance

1. Establish a project research office:

The project research office is set up by the project leading unit, which is responsible for the implementation of the project funds and the coordination between the project participating units. The research office is composed of the person in charge of the undertaking unit and the core research members, who are responsible for the design of the research objectives, contents and technical routes of the subject task, the training of researchers, and the coordination and communication with the cooperative unit. Hold regular project meetings to coordinate the project progress and solve the practical problems in the project implementation process.

2. Project objectives and task management:

With the project undertaking unit as the core, the oncology departments of major hospitals across the country were evaluated, and the units with sufficient disease sources and certain clinical research experience were selected as the cooperative units, and the national clinical research base of TCM was mainly selected. Implement procedural and network management for the participating units. Establish a special task management mechanism to supervise the completion of tasks in the stage. Establish a file management system for the original research data. Implement the performance evaluation system of mainly management by objectives and combining process management with management by objectives. Clear responsibilities and rights, clear division of labor, and regular feedback on the progress of the project.

3. Use and management of project funds:

Establish the project funds supervision group, set up the secondary financial review system, composed of the financial personnel of the project undertaking unit and the participating unit; supervise and review the use way and progress of the project funds irregularly, and urge the participating units to calculate the funds for special purposes.

4. Project quality control and management:

Introduction and promotion of "ISO" quality management system, personnel at all levels accept necessary management consciousness and quality awareness training, establish quality control system in the project implementation process, formulate relevant quality control measures and evaluation scheme, select CRO this research quality control and supervision, such as clinical data collection specification, data verification quality control measures, and task completion of task verification and quality control, form the quality verification document report and archive management.

5. Blood sample management:

Keep blood samples for coding, encryption, after the study did not use blood samples for at least 8 years, anonymous stored in China academy of Chinese medicine sciences cross hospital biological library, and send personnel to watch, during and without the consent of the study, no anyone to borrow, transfer samples, if using the blood samples, submit the relevant application to explain the purpose, the use of blood samples, to eliminate the use of blood samples collected in illegal and harm the interests of patients.

X. Statistical treatment

Statistical software: Using SAS 9.2 statistical software, the full analysis set (FAS) analysis, and safety data set (SS) analysis should be performed for adverse reactions. Statistical method: All statistical tests are two-sided, and P 0.05 will be considered statistically significant. The proportion of shedding cases should not be greater than 20%. Metering data description mean, standard deviation, median, minimum value, maximum value, etc., count data description frequency, percentage, etc. Measurement data were analyzed by t-test and rank sum test, chi-square test and Ridit analysis, and survival data by Kaplan-Meier method, Wilcoxon rank sum test or log-rank test. Multivariate survival analysis was performed using a Cox proportional hazards regression model.

Xi. Ethics of clinical research

Clinical research will follow the provisions of the Declaration of Helsinki. The clinical study was performed after ethics committee approval of the trial protocol prior to study initiation. Before each subject is included in the study, the investigator has the responsibility to present the subject or his agent about the purpose and procedures and possible risks to the study and sign a written

informed consent to inform the subject that they have the right to withdraw from the study at any time, and the informed consent shall be retained as a clinical study document for future reference. During the study, the personal privacy and data confidentiality of the subjects will be protected, and the subject's personal information will not be disclosed. The positive or negative results of this study will be published, and the personal privacy of the patients will not be disclosed in the published articles.

Xii. Research progress

From February 2024 to March 2024, a clinical research database will be established, and researcher training will be conducted through ethical approval, and the project task assignment and launch meeting will be held.

From April 2024 to September 2024,50% of cases were collected, the enrolled cases were followed up, clinical observation form, follow-up form, data entry and verification, and regular monitoring. Data were collected for an interim summary. Hold the subject treatment control and supervision meeting to improve the quality and efficiency of enrollment.

From October 2024 to March 2025, the enrolled cases were follow-up, fill in the clinical observation form, follow-up form, data entry and check, and regular monitoring. Hold the project conclusion and evaluation meeting to prepare for the conclusion. Completed CRF tables and follow-up tables were recovered.

From April 2025 to December 2025, complete all data follow-up, data entry, cleaning, and submit to clean database of statistical experts for statistical analysis; statistical analysis data, outcome measurement, determine the efficacy after treatment, adverse reactions, and summarize; summarize data, and prepare for project acceptance.

Attachment 1 Efficacy Evaluation of Solid Tumors Version 1.1 (RECIST1.1)

The treatment response was evaluated according to the efficacy evaluation criteria of solid tumors, version 1.1 (RECIST1.1), and the target lesions were evaluated as follows:

	CR complete remission	PR partial remission	SD disease is stable	PD PD
Quantitation of target lesions estimate	All target lesions were lost and lasted no less than 4 weeks; all pathological lymph nodes were <10mm and lasted no less than 4 weeks.	The sum of diameters of all target lesions showed a baseline reduction of at least 30% and duration not less than 4 weeks.	PR was not achieved, nor PD, and lasted no less than 4 weeks.	The sum of the diameter of all target lesions increases by at least 20% (the smallest sum of the comparison study, and the absolute value of the sum of the diameters must increase by at least 5mm for no less than 4 weeks.
Qualitative assessment of non-target lesions	Disdisappearance of non-target lesions.	Non-CR / non-PD; One or more non-target foci persisted.		
New lesions	not have	not have		The appearance of one or more new lesions
Tumor biomarkers	epistrophy	Tumor marker levels were not in the normal range		
Other instructions	Record of lymph nodes as target lesions: even if the short diameter shrinks to <10mm, it needs to be recorded and counted as the sum of the diameters. Therefore lymph nodes need to be recorded separately for facilitate assessment of CR. The target lesion is too small to measure: if the radiography suggests that the target lesion disappear, it can be recorded as 0mm; if the target lesion is indeed present but only too small to measure, the default record is 5mm. Divided or combined lesions during treatment: record the sum of the longest diameter of all divided lesions, and record the longest diameter of the combined lesions. If the non-target lesion is assessed as definite progression, there must be a global			

	level of severe change, even if the target lesion is assessed as SD or PR, the overall tumor burden needs to be increased enough to stop treatment before discontinuing treatment.

Attachment 2 EORTC QLQ-C 30 scale (Chinese version)

EORTC L Scale QLQ-C 30 (V3.0) Chinese version of the questionnaire target date:				
Note: We want to know something about you and your health, please answer all the following questions by yourself. The answer here is not "right" or "wrong", only required to hit the number that best reflects your situation. The information you provide will be kept strictly confidential.				
	not have	some	match	extraordinary
1. Do you have difficulty in doing some strenuous activities, such as carrying heavy shopping bags or suitcases?				
2. Is it very difficult for you to walk over long distances?				
3. Is it difficult for you to walk in a short distance outdoors?				
4. Do you need to stay in bed or in a chair during the day?				
5. Do you need help when eating, dressing, bathing or going to the bathroom?				
In the past one week:				
6. Are you restricted in your work and daily activities?				
7. Are you restricted in pursuing your hobbies or leisure activities?				
8. Do you have any shortness of breath?				
9. Do you have any pain?				
Do you need a break?				
11. Have you had trouble sleeping?				

12. Do you feel weak?				
13. Do you lose your appetite (do you have no appetite)?				
14. Do you feel sick?				
15. Did you ever vomit?				
16. Do you have constipation?				
17. Do you have diarrhea?				
18. Are you feeling tired?				
19. Does the pain affect your daily activities?				
20. Do you have difficulty concentrating on doing things, such as reading a newspaper or watching TV?				
21. Are you feeling nervous?				
22. Are you worried?				
23. Do you feel irritable?				
24. Do you feel depressed (depressed)?				
Do you have trouble remembering it?				
26. Does your physical condition or treatment affect your family life?				
27. Does your physical condition or treatment affect your social activities?				
28. Does your physical condition or treatment put you into financial difficulties?				
For the following questions, select a number between 1 and 7.				
29. How do you evaluate your overall health in the past week? 1 2 3 4 5 6 7 Very poor, very good				
30. How do you evaluate your total quality of life in the past week? 1 2 3 4 5 6 7				

Very poor, very good

Attachment 3 EORTC QLQ CX24 Questionnaire (Chinese version)

EORTC QLQ-C X24 (V3.0) Chinese version questionnaire target date:				
Note: We want to know something about you and your health, please answer all the following questions by yourself. The answer here is not "right" or "wrong", only required to hit the number that best reflects your situation. The information you provide will be kept strictly confidential.				
	not have	some	match	extraordinary
1. Have you ever smoked any tendons in your stomach?				
2. Do you have a problem with your visceral activity?				
3. Is there any blood in your stool?				
4. Do you have any symptoms of frequent urination?				
5. Do you feel pain or burning when you urinate?				
6. Do you have any urine leakage?				
7. Is there a problem with you?				
8. Do your legs have any oedema?				
9. Do you feel any pain in your lower back?				
10. Do you feel numbness or pain in your hands or feet?				
11. Do you have pain in your vagina or vagina?				
12. Will your vagina remove a foreign body?				
13. Do you have bleeding from your vagina?				

14. Do you have a red flush or a sweat in your vagina?				
15. Do you feel unattractive because of your illness or treatment?				
16. Do you feel the lack of young women because of your illness or treatment?				
17. Are you not satisfied with your body?				
In the last 4 weeks:				
18. Have you ever been worried that having sex can be very painful?				
19. Are you sexually active?				
If you have been sexually active in the past four weeks, please answer the following questions:				
20. Does your penis feel dry during sexual activity?				
21. Does your vagina feel shorter?				
22. Does your vagina feel very tight?				
23. Do you feel pain during sex or other sexual activities?				
24. Do you enjoy sexual activities?				

Attachment 4 Simple Fatigue Scale Chinese Version (BFI-C)

Simple Fatigue Scale BFI-C, Chinese version of the questionnaire target date:											
Note: In order to give us a better service for you, you are invited to fill in this scale. In our life, most of us will have time to feel very tired or tired, the 0 in the table represents no fatigue, the larger the number, the heavier the degree of fatigue, 10 represents the most tired you can imagine. The information you provide will be kept strictly confidential.											
	0	1	2	3	4	5	6	7	8	9	10

1. Please choose a numerical value that can describe how much you are getting tired right now.											
2. Please choose a value that describes how tired you were in the past 24 hours.											
3. Please choose a value that describes your worst fatigue in the past 24 hours.											
4. Please choose the way of fatigue in the past 24 hours											
A. Effects on the daily activities											
B . Influence on emotions											
C . Effect on the ability to walk											
D. Impact on daily life (including daily housework and normal work)											
E. Influence on the relationships between others											
F. Effects on everyday interests											

Attachment 5 Insomnia severity Quantity Table (ISI)

Insomnia severity Quantity Table (ISI) target date:					
Note: In order to give us a better service for you, you are invited to fill in this scale. The scale is a simple tool for screening for insomnia and includes seven items to assess the nature and symptoms of sleep disturbances in subjects. For sed in people aged 17 – 84 years. For each of the following questions, choose the most appropriate answer.					
	not have	a little	some	more	a great many
1. Describe the severity of your most recent (e. g., the last 2 weeks) insomnia problem.					
A.difficulty falling asleep					
B. Maintain sleep difficulties					
C.early awakening					
2. Your satisfaction with your current sleep patterns					
3. To what extent do you think your sleep problems interfere with your daytime functions (e. g., daytime fatigue, ability to handle work and daily tasks, attention, memory, mood, etc.):					
4.4. How much does your insomnia affect or damage your quality of life compared with others:					
5. How much concern / frustration do you have about your current					

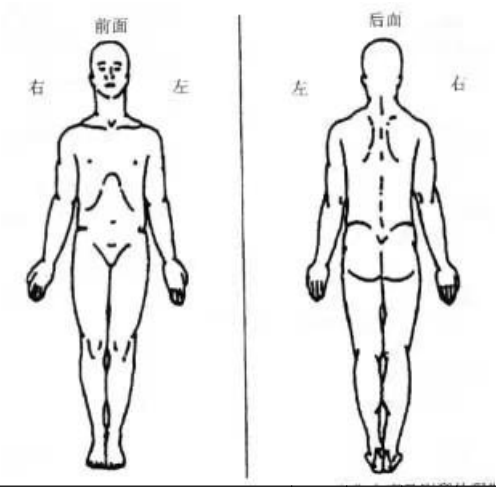
sleep problems:						

Attachment 6 Brief Pain Assessment Scale (BPI-C)

Concise Pain Assessment Scale (BPI-C)

target date:

Note: In order to give us a better service for you, you are invited to fill in this scale. The 0 in this table represents no pain, and the larger the number is, the heavier the pain is, and the 10 is the most pain you can imagine. The information you provide will be kept strictly confidential. For each of the following questions, choose the most appropriate answer.

	0	1	2	3	4	5	6	7	8	9	10
1. Most people have experienced pain throughout their lives (such as mild headaches, post-sprain pain, toothache). Do you now feel other types of pain? whether or not☐☐											
2. Please select the part of your pain in the figure below, and express the part of the most severe pain in X:  											
	0	1	2	3	4	5	6	7	8	9	10
3. Please select a number to indicate your most severe pain in the past 24 hours.											
4. Please select a number to indicate the slightest degree of your pain in the past 24 hours.											
5. Please select a number to indicate the average level of your pain over the past 24 hours.											
6. Please select a number to indicate your current pain level.											

7. How much has your pain relieved in the past 24 hours due to medication or treatment? Please select a percentage below to indicate the degree of pain relief.

0	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

8. Please select a number below to indicate the impact of pain on you in the past 24 hours.	0	1	2	3	4	5	6	7	8	9	10
A. Impact on daily life.											
B . The effect on the mood.											
C . Effect on the ability to walk.											
D. Impact on daily life (including outside of work and housework).											
E. Influence on the relationships between others.											
F. Effects on sleep.											
G. Impact on an interest in life.											

Attachment 7 The Hamilton Depression Scale (HAMD)

The Hamilton Depression Scale (HAM D) target date:				
Note: In order to give us a better service for you, you are invited to fill in this scale. For each of the following questions, choose the most appropriate answer.(1. asymptomatic; 2. light; 3. medium; 4. heavy; 5. Very heavy.)				
order number	project	specific description	grade	Patient score
1	Depression	do not appear	0	
		The complaint is only when asked	1	
		Express it spontaneously in speech;	2	
		This emotion can be expressed from expression, posture, voice, or crying without words	3	
		The patient's spontaneous and non-spontaneous language (expressions, movements) are almost completely manifested by this emotion	4	
2	feeling of guilty	do not appear	0	
		Blame yourself and feel that you have affected others	1	
		Think you have committed a crime, or think about past mistakes and mistakes	2	
		That the current disease is a punishment for their own mistakes, or a criminal delusion	3	
		Criminal delusion is accompanied by accusations or threatening hallucinations.	4	
3	idioctonia	do not appear	0	
		I feel alive	1	
		I hope I have died, or I often think of something	2	

		related to death		
		Negative perception (suicidal thoughts)	3	
		Serious suicidal behavior	4	
4	difficulty falling asleep	do not appear	0 1 2	
		The chief complaint sometimes has difficulty falling asleep, that is, half an hour after going to bed		
		The chief complaint had difficulty falling asleep every night		
5	Sleep is not deep	do not appear	0 1 2	
		Sleep shallow many evil dreams		
		Wake up in the middle of the night (before 12 pm) (excluding bathroom use)		
6	early awakening	do not appear	0 1 2	
		Wake up early, an hour earlier than usual, but you can fall asleep again		
		I can't fall asleep again after waking up early		
7	Work and interest	do not appear	0 1 2 3 4	
		Ask questions and tell them		
		Spontaneously directly or indirectly express the loss of interest in activities, work or study, such as feeling listless, hesitant, unable to insist or need to force yourself to work or activities		
		Hospital labor or entertainment for less than 3 hours		
		Stop working due to the current illness, inpatients do not participate in any activities or without the help of others		
8	slow	do not appear	0	
		Mild delay was noted on the psychiatric examination	1	
		Significant mental retardation was found on the mental examination	2	
		Mental examination is difficult to conduct	3	
		Unable to answer questions (stiff)	4	
9	intense	do not appear	0	
		Check the examination	1	
		Obviously mental distracted or small movements	2	
		Can not sit still, ever standing during the examination	3	
		Rub your hands, bite your fingers, pull your hair, and bite your lips	4	
10	Mental anxiety	do not appear	0	
		When asked, he complained	1	
		Spontaneous expression	2	
		The expression and speech reveal obvious anxiety	3	
		Apparently frightened	4	
11	somatic anxiety	do not appear	0	
		mild	1	

	*	Moderate, with positive above symptoms	2	
		Severe, the above symptoms are serious, affect the life or need to be treated	3	
		Seriously affect life and activities	4	
12	gastrointestinal symptom	do not appear	0	
		Loss of appetite, but eat by yourself without encouragement	1	
		Eating requires urging or requests or laxatives or digestive aids	2	
13	constitutional symptom	do not appear	0	
		heaviness in the limbs, back, or neck, backache, headache, muscle pain, general fatigue or fatigue	1	
		The above symptoms are obvious	2	
14	Sexual symptoms (decreased libido, menstrual disorder, etc.)	do not appear	0	
		mild	1	
		severe	2	
		Can not be sure, or this item is not suitable for the candidate.(Not included in the total score)		
15	hypo	do not appear	0	
		Too much attention to the body	1	
		Think repeatedly consider health issues	2	
		Suspicion	3	
		A suspected disease delusion with hallucinations	4	
16	lose weight	do not appear	0	
		Weight loss of more than 1 kg within a week	1	
		Weight loss of more than 2 kg within a week	2	
17	insight	Know oneself sick, the performance is melancholy	0	
		Know you are sick, but due to poor food, environmental problems, busy work, virus infection or need to rest	1	
		Completely deny illness	2	

* Physiological symptoms of anxiety, including dry mouth, abdominal bloating, diarrhea, beating, abdominal cramps, palpitations, headache, excessive ventilation and sighs, and frequent urination and sweating.

Attachment 8: The Hamilton Anxiety Scale (HAMA)

Hamilton Anxiety Scale (HAMA) target date:
Note: In order to give us a better service for you, you are invited to fill in this scale. For each of the following questions, choose the most appropriate answer.(1. asymptomatic; 2. light; 3. medium; 4. heavy; 5.

Very heavy.)					
	1	2	3	4	5
1. Anxiety: worry, worry, feel that the worst thing is going to happen, easy to provoke					
2. Tension: nervous, easy to fatigue, can not relax, emotional reaction, easy to cry, shake, feel uneasy					
3. Fear: fear of the darkness, strangers, solitude, animals, rides or travel and crowded occasions					
4. Insomnia: difficult to fall asleep, easy to wake up, dream, nightmare, night shock, feel tired after waking up					
5. Cognitive function: or memory and attention disorders. Unable to focus on attention, poor memory					
6. Depression mood: loss of interest, lack of pleasure to the previous hobbies, melancholy, early wake up, heavy day and light night					
7. Muscle system symptoms: muscle soreness, twitching, inflexible, teeth beating, voice shaking					
8. Sensory system symptoms: blurred vision, chills, fever, weakness, and tingling					
9. Cardiovascular system symptoms: tachycardia, palpitations, chest pain, vascular beating, fainting, cardiac leakage					
10. Respiratory symptoms: chest tightness, suffocation, sigh, and dyspnea					
11. Gastrointestinal symptoms: dysphagia, indigestion, intestinal movement, diarrhea, low weight sensation, constipation					
12. Genitourinary symptoms: urinary frequency, urgency, menopause, apathy, impotence					
13. Plant nervous system symptoms: dry mouth, flushing, pale, easy to sweat, "goose bumps", etc					
14. Meeting behavior performance: (1) general performance: tension, facial tension, restless feet, hands shaking, frown, high muscle tension, sigh breathing, pale: (2) physiological performance: swallowing, well, quiet heart rate, breathing fast (20 times / points), tendon reflex, tremor, pupil amplification, eyelid beating easy to sweat, eyeball.					