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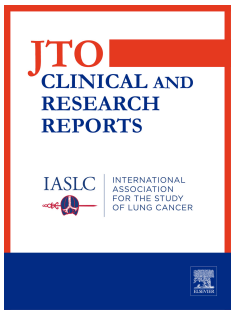

Efficacy and Safety of Anti-PD-L1 Monoclonal Antibody Socazolimab with Carboplatin and Etoposide for Extensive-Stage Small Cell Lung Cancer: Results from the Phase Ib Clinical Trial

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Efficacy and Safety of Anti-PD-L1 Monoclonal Antibody Socazolimab with Carboplatin and Etoposide for Extensive-Stage Small Cell Lung Cancer: Results from the Phase Ib Clinical Trial

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Supplementary data: Two supplementary tables

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Conflicts of interest

Author Benjamin Xiaoyi Li and Xiangrong Dai are employed by Lee's Pharmaceutical Holdings Limited. This study received funding from Lee's Pharmaceutical Holdings Limited. The funder had the following involvement with the study Efficacy and Safety of Socazolimab with Carboplatin and Etoposide for ES-SCLC. All authors declare no other competing interests.

ABSTRACT

Purpose: The study (ClinicalTrials.gov, NCT04346914) is an open label, single-arm phase Ib clinical trial investigating the safety, tolerability, and efficacy of the recombinant human anti-programmed death-ligand 1 (PD-L1) monoclonal antibody Socazolimab in combination with carboplatin and etoposide in the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC). Good safety and efficacy were demonstrated in previous phase I clinical trials of other cancers like cervix cancer.

Experimental Design: Patients received Socazolimab (5mg/kg) every three weeks until disease progression or physician decision. Carboplatin(AUC 5) was also administered every three weeks, and etoposide (100mg/m^2) on days 1, 2, and 3 of the treatment cycle. The primary purpose of the study was safety mesured by CTCAE. Secondary purposes included the objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

Results: From 15th April 2020 (enrollment date) to 30th December 2021 (data cutoff), 20 patients with ES-SCLC were administered with Socazolimab, carboplatin and etoposide. ORR was 70.0% (95% CI: 45.72%, 88.11%). Median PFS was 5.65 months (95% CI: 4.14, 6.54), and the median DOR was 4.29 months (95% CI: 2.76, 5.85). Median OS was 14.88 months (95% CI: 10.09, NE). The highest incidence of TRAEs included anemia (100%), decreased neutrophil count (95%), decreased platelet count (95%) and decreased white blood cell count (95%) which occurred during combination therapy. The most common grade 3 or 4 TRAEs were neutropenia (90%), decreased white blood cell count (65%), decreased platelet count (50%) and anemia (30%) which were also common adverse reaction of chemotherapy. No adverse events leading to death had occurred.

Conclusions: Results revealed that the combination therapy of Socazolimab, carboplatin and etoposide had preliminarily confirmed the safety of

Socazolimab in the first-line treatment of SCLC combined with EC chemotherapy. Currently, a phase III, randomized, placebo-controlled trial (ClinicalTrials.gov, NCT04878016) is being conducted with 498 patients.

Keywords: Socazolimab, extensive-stage small cell lung cancer (ES-SCLC), Carboplatin, Etoposide, PD-L1

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 15%-20% of lung cancer cases [1,2], and is the most aggressive subtype of lung cancer. 90% of SCLCs have distant metastasis at the time of diagnosis, with approximately 30-40% in limited-stage and 60-70% in extensive-stage. With poor prognosis, the average five-year overall survival rate is only 5% [3].

Etoposide or irinotecan, plus cisplatin or carboplatin regimens (EP/EC/IP/IC) are the preferred regimens for patients with extensive-stage SCLC (ES-SCLC). The EP regimen (etoposide plus cisplatin), in particular, is the most commonly used chemotherapy regimen for initial treatment [4]. Carboplatin is also commonly used clinically as a replacement of cisplatin to reduce vomiting, neurotoxicity, and nephrotoxicity, but similarly increases the risk of myelosuppression. In addition, maintenance or consolidation chemotherapy generally does not exceed four to six cycles, and long-term chemotherapy only slightly prolongs remission time without improving survival, and increases the risk of cumulative toxicity [5].

A majority of chemotherapeutic drugs play an active role in anti-tumor immune responses, including immunogenicity to tumor cells, antigen presentation, suppressor cells, and effector responses [6]. Cytotoxic drugs that damage DNA can activate immunogenic cell death, alter the tumor inflammatory microenvironment, and stimulate neoantigen production, thereby activating antitumor immunity [7]. Chemotherapy can also induce the production of neoantigens and increase tumor mutations, thereby stimulating T-cell immune responses and enhancing the sensitivity of immune checkpoint inhibitors, and provide a theoretical basis for chemotherapy drugs combined with immune checkpoint inhibitors [8].

Recently, in the IMPOWER133 study of PD-L1 inhibitor atezolizumab, 403 newly diagnosed patients with ES-SCLC were randomly divided into two groups at 1:1. The study group was given four cycles of induction

chemotherapy with atezolizumab+EC regimen and sequential atezolizumab maintenance therapy. The control group was given placebo plus EC regimen for four cycles of induction chemotherapy and sequential placebo maintenance. Both groups were treated until the disease progresses or there are intolerable adverse reactions or no longer clinical benefits until disease progression, intolerable adverse reactions or no observed clinical benefit. Results revealed that atezolizumab significantly prolonged OS (median OS, 12.3m vs. 10.3m, HR=0.70), with median PFS of 5.2 m and 4.3m (HR=0.77), respectively[9]. Another similar study, CASPIAN, which aimed to explore the efficacy of the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab combined with chemotherapy in the first-line treatment of patients with ES-SCLC. The study included patients with untreated ES-SCLC who were randomly allocated into three groups to receive durvalumab±tremelimumab combined with EP chemotherapy. In the durvalumab group, patients received up to four cycles of chemotherapy, while the chemotherapy group allowed up to six cycles of chemotherapy and prophylactic intracranial irradiation. In the CASPIAN study, 268 and 269 patients were enrolled in the durvalumab group and the chemotherapy group, respectively. The OS of the durvalumab plus chemotherapy group was 13.0 months (HR=0.73, p=0.0047), in contrast to the OS of the chemotherapy group (10.3 months). The safety and tolerability of durvalumab in combination with chemotherapy were consistent with the known safety profile of the drug, providing good evidence that the regimen is safe and feasible[10]. These two studies confirmed the effectiveness of PDL1 antibody in the treatment of highly immunogenic tumors such as small cell lung cancer and the beneficial effect of chemotherapy on immunotherapy. Based on the results of these two studies, both atezolizumab and durvalumab have been approved for the first-line treatment of ES-SCLC.

Socazolimab, screened from the human G-MAB^{TM} antibody library, has

high specificity and affinity for human PD-L1 proteins. Upon binding PD-L1, the PD-1/PD-L1 signaling pathway is blocked and eliminates the tumor immune escape mechanism, which enables T cells to respond normally and inhibit tumor growth. In addition, Socazolimab has an intact IgG1 Fc segment that is recognized by Fc receptors on NK cells. Once Fc receptors bind to the Fc region of IgG, NK cells release cytokines (such as IFN-γ) and cytotoxic granules, including perforin and granzymes, resulting in antibody-dependent cell-mediated cytotoxicity (ADCC). Socazolimab binds to PD-L1 on the surface of tumor cells, and guides NK cells to attach to the tumor region through its Fc component, achieving the ADCC effect for tumor inhibition. Socazolimab is intended for the treatment of recurrent or metastatic solid tumors. Currently completed or ongoing clinical trials of Socazolimab include small cell lung cancer, cervical cancer, osteosarcoma, and urothelial tumors. Phase I trials were conducted for the pharmacokinetic characteristics and recommended phase II dose(RP2D) of Socazolimab in cervical cancer, osteosarcoma and uroepithelial cancer. Complete PD-L1 receptor occupancy was observed in all patients with the recommended 5mg/kg dose and the mean serum half-life of Socazolimab was 317.0 h (13.2 days). The 5mg group has observed a good response with ORR of 18.1% (95% CI, 10.9 27.4%) [11]. Based on the above studies，the RP2D was determined with 5mg/kg, and the administration cycle is once every 2 to 3 weeks. The relevant study results are being published. Therefore, this study of SCLC will no longer conduct pharmacokinetic or RP2D studies, but only observe the preliminary safety and efficacy of Socazolimab in domestic patients with SCLC, and take this as a basis for judging whether to continue the III phase study.

METHODS

Study Design

This phase Ib study (ClinicalTrials.gov, NCT04346914), as a lead-in study for the phase III clinical study, included a total of 20 patients in three centers in China, which investigated the safety and tolerability of the PD-L1 monoclonal antibody Socazolimab combined with etoposide and carboplatin (EC) for the first-line treatment of ES-SCLC. The study followed the ICH GCP and the Declaration of Helsinki, and the study protocol and amendments were approved by the independent ethics committee. All patients signed written informed consent to participate.

Safety was the primary objective of the study, which will be mesured by incidence and severity of adverse events (AEs) and serious adverse events (SAEs) as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Safety observation period lasted throughout the period of Socazolimab treatment. Secondary endpoints included investigator-assessed ORR, PFS(defined as time from enrollment to the date of first documented radiographic tumor progression or death due to any cause, whichever occurs first), disease control rate (DCR), OS(defined as time from date of randomization to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact), and DOR based on RECIST v1.1 criteria.

Tissue samples for PD-L1 expression were made into formalin-fixed and paraffin embedded （FFPE） blocks. The PD‑L1 expression tests were carried out on the cancer tissue samples with immunohistochemistry (IHC) staining by using antibody of PD-L1 and Avidin-Biotin Complex (ABC) methods. Tumor proportion score （TPS） and were calculated for the evaluation of PD‑L1 expression. The group was categorized as strong positive if more than 50% of tumor cells were expressed, whereas the weak positive was recorded when 1 % to 50 % and cells with less than 1% were grouped as negative. Positive rate of anti-drug antibodies (ADA) judged by

electrochemiluminescence method.

Study Population

All enrolled patients must meet the following inclusion criteria: age ≥18 years and ≤75 years, regardless of gender; histologically confirmed SCLC; extensive-stage SCLC (ES-SCLC) according to the American Veterans Lung Cancer Association (VALG); did not receive any prior first-line systemic therapy for ES-SCLC; Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; estimated survival time > 12 weeks; at least one measurable lesion according to RECIST v1.1; suitable liver and kidney function and bone marrow reserve; and can provide tumor tissue specimens that meet the detection requirements for PD-L1 expression.

Major exclusion criteria included: prior treatment with other immune checkpoint inhibitors; active brain or meningeal metastases; history of autoimmune disease; use of corticosteroids (>10 mg/day prednisone or equivalent dose) or other immunosuppressive agents within 14 days before the first dose of the Socazolimab combination therapy; clinical cardiovascular symptoms/diseases that cannot be well-controlled; uncontrollable active infection; and other malignancies ≤5 years before the first dose.

Study Procedure

Socazolimab was administered intravenously at 5 mg/kg every 21 days as a treatment cycle until an event that met the termination criteria, or for a maximum of two years. In the chemotherapy regimen, carboplatin was administered at AUC 5 once every 21 days per treatment cycle. The carboplatin dose of AUC 5 will be calculated using the Calvert formula: Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25). For the purposes of this study, the GFR is considered to be equivalent to the creatinine clearance (CRCL). The CRCL is calculated by the method of

Cockcroft and Gault using the following formula:[(140 – age in years) × (weight in kg)]÷[(72×serum creatinine in mg/dL)] × (0.85 if female). Etoposide was administered continuously at 100 mg/m^2 on days 1, 2, and 3, with a treatment cycle every 21 days. Carboplatin and etoposide were administered until an event meeting the termination criteria, or up to four cycles. The order of medication in each cycle was Socazolimab, carboplatin, and etoposide.

Tumor efficacy evaluations were carried out every six weeks, or according to clinical needs, to assess whether to continue the treatment. Patients will continue to receive treatment until a study-related intolerable adverse event occurs, the prescribed maximum dosing cycle is reached, confirmation of progressive disease (PD), or disease-related clinical deterioration occurs even in the absence of radiographic progression. Patients may be terminated early due to investigator discretion on medical considerations, or upon patient request.

Statistical Methods

All data were analysed using appropriate statistical methods according to the data type: continuous variables use mean, standard deviation, median, minimum, and maximum values; and categorical variables use frequency and percentage, for descriptive statistical summary. Analysis of the primary efficacy endpoints will be based on the FAS(full analysis set). Objective response rate (ORR), will be estimated for the rate and the two-sided 95% confidence interval (CI) (normal approximation). Descriptive statistics will be used for the duration of response (DOR). In addition, the Kaplan-Meier method was used to estimate PFS and OS, and the survival curve was drawn to estimate the median PFS, OS and the 95% CI.

All efficacy and safety analyses were conducted on all patients who received at least one dose of the Socazolimab combination therapy and had at least one follow-up assessment. The data cutoff for this study was

December 30, 2021.

RESULTS

Patient Demographics and Baseline Characteristics

From April 15, 2020, to January 18, 2021, a total of 29 patients were screened, of which 20 were successfully enrolled into the study. The reasons for screening failure included symptomatic brain metastases in 2 cases, autoimmune disease in 1 case, ascending aortic aneurysm in 1 case, limited stage in 1 case, and elevated HBV-DNA in 1 case. Besides, another 3 cases withdrew with informed consent during the screening phase. A summary of patient disposition is shown in Figure 1. At the time of data analysis, two patients remained in response and were still receiving treatment. Sixteen patients discontinued treatment due to disease progression, and an additional two patients discontinued treatment due to intolerable toxicity. A summary of patient demographics and baseline characteristics is shown in Table 1. Mean age of enrolled patients was 63 years, with 16 male patients. All patients had ES-SCLC based on VALG staging, including 13 patients with IV stage based on TNM staging. The ECOG performance status was 1 for all patients.

Nineteen patients were PD-L1 positive except for one patient who could not be detected because of insufficient tumor samples (Table 1). Among them, strong positive and weak positive 9 patients and 10 patients respectively.

Safety Results

Patients received treatment cycles ranging from one to 33 cycles, with an average of 8.8 cycles of treatment. In addition to discontinuation due to disease progression, one patient withdrew due to multiple infusion reactions and another patient discontinued due to arrhythmia requiring treatment.

All patients reported treatment-related adverse events (TRAEs), defined as adverse events related to Socazolimab and/or chemotherapy. Table 2 lists the type and incidence of all-grade TRAEs occurring in more than 10% of patients. Most TRAEs occurred during combination therapy. The most common TRAEs included anemia (100%), decreased neutrophil count (95%), decreased platelet count (95%), decreased white blood cell count (95%), hypoalbuminemia (35%), infusion-related reactions (25%), increased alanine aminotransferase (20%), increased blood bilirubin (20%), hyperuricemia (20%), hyperglycemia (15%), increased aspartate aminotransferase (15%), alopecia (15%), weight loss (15%), premature atrial contractions (15%), and prolongation of QTC interval on electrocardiogram (15%).

The most common grade 3 and higher TRAEs were decreased neutrophil count (90%), decreased white blood cell count (65%), decreased platelet count (50%), anemia (30%) .Nearly all Grade 3 and higher TRAEs occurred during combination therapy and related to chemotherapy. Only one case of impetigo and one case of diabetic ketosis occurred during maintenance treatment with Socazolimab.

The AEs that led to drug suspension included myelosuppression during chemotherapy (Supplementary Table 1). Combination therapy can be resumed after reaching 80% or 50% of the previous dose, and after symptomatic and supportive treatment. Discontinuation of treatment included one case of Grade 2 anaphylaxis (during etoposide infusion) during combination therapy in the beginning of the first cycle, and one case of Grade 2 arrhythmia during maintenance therapy in the 6th cycle that relapsed despite symptomatic treatment and/or pretreatment. No adverse events leading to death had occurred.

A total of 40% of patients reported immune-related adverse events (irAEs) during the study period (Supplementary Table 2). Apart from one case of QTC interval prolongation and one case of impetigo that were Grade

3 irAEs, the rest were Grade 1/2 irAEs, with most common irAEs including hypothyroidism (10%), hyperglycemia (10%) and elevated alanine aminotransferase (10%).

The ADA test found that five of 20 patients had ten positives within a given testing cycle (every two cycles until withdrawal), with one patient remaining positive throughout the entire test. ADA were first detected in cycle 1 with two patients and in cycle 3 with another two patients, and one patients was first detected in cycle 5.

Efficacy Results

At the time of data analysis, the ORR, according to RECIST v.1.1, was 70.0% (95% CI: 45.72%, 88.11%). No patient experienced a complete response (CR), but 14 patients (70%) had partial responses and two patients remained on treatment with ongoing responses at the time of data cutoff (Figure 2, Table 3). Median DOR was 4.29 months (95% CI: 2.76, 5.85). Median PFS was 5.65 months (95% CI: 4.14, 6.54) (Figure 3A), and the median OS was 14.88 months (95% CI: 10.09, NE). The Kaplan-Meier curve of patient overall survival is shown in Figure 3B.

As exploratory objectives, PD-L1 expression levels were retrospectively evaluated as potential biomarkers. The OS of strong positive and weak positive are 16.6months (95% CI: 4.14,NE) and 13.1 months (95% CI: 7.39,14.88), respectively. The PFS of strong positive and weak positive are 5.72 months (95% CI: 1.77, NE) and 5.65 months (95% CI:1.35, 6.93), respectively(Table 3).

DISCUSSION

The approval of Atezolizumab for SCLC treatment has brought great encouragement to the research of similar drugs for the same indication. Because the pharmacokinetics and RP2D of Socazolimab have been studied in other tumors, this study is only a preliminary study of the safety and

efficacy of drugs in small cell lung cancer, so it is called Ib study.This phase Ib study was conducted as a phase III and placebo-controlled lead-in study.

This study preliminarily explored the efficacy of Socazolimab in the first-line treatment of small cell lung cancer combined with EC regimen. The median progression-free survival (mPFS) was 5.65 months (95% CI: 4.14, 6.54). and median OS was 14.88 months (95% CI: 10.09, NE). Three patients with asymptomatic brain metastasis were enrolled, but they did not seem to receive significant benefits from treatment, and both PFS and OS were shorter than those without brain metastasis. Although the sample size was limited, this study preliminarily suggests that Socazolimab combined with chemotherapy may have a survival benefit in the first-line treatment of ES-SCLC.

All patients provided tissue samples for detecting PD-L1 expression, of which 19 samples were tested, and 19 of them were all positive. Therefore, we re-set 50% as the cutoff value in all 19 positive patients, with TPS ≥ 50% as strong positive and < 50% as weak positive. Due to the small sample size, we can not determine the correlation between PDL1 expression with OS or PFS. This is consistent with the results of the phase I study of atezolizumab [12]. However, strong positive patients seem to have a longer survival than weakly positive patients. In the ongoing phase III study, the relationship between PD-L1 expression and efficacy will continue to be explored.

Monoclonal antibody itself can also be recognised as an antigen by the human immune system, so it has immunogenicity, and the immune system may produce anti-drug antibodies(ADA). PD-1/PD-L1 inhibitors are humanized or completely human monoclonal antibodies and have certain immunogenicity. Some of the major safety events such as anaphylaxis, infusion reaction, cytokine release syndrome, and other acute reactions or delayed hypersensitivity (i.e., serum sickness) were thought to be related with immunogenicity[13], we detected the immunogenicity of Socazolimab by

(ADA) for all patients. ADA has been detected in trials of Socazolimab as a single drug for cervical cancer, osteosarcoma and uroepithelial cancer. ADA were detected in 11 of 104 evaluable patients (10.6%) in the cervical cancer patients[11]. Considering that this study is a combination of Socazolimab and chemotherapy, and to better capture the occurrence of ADA in the combination, we performed ADA testing every 2 cycles (6 weeks). ADA were found in five patients to varying degrees following Socazolimab administration. In this study, ADA incidence was higher than that of other types of PD-1/PD-L1 monoclonal antibodies, but with similar ADA incidences as atezolizumab [14]. There was no significant difference in safety or response time between ADA-positive patients and -negative patients. Only one ADA positive patient had transfusion reaction, but the ADA test was negative when the transfusion reaction occurred. Based on this, later studies should reduce the frequency of ADA detection, for example, only once in cycle 3 (2 months after treatment).

TRAE incidence in this study, especially Grade 3 or 4 TRAEs, was significantly higher than that of foreign studies of similar drugs. A majority of grade 3 or 4 TRAEs occurred in the combination treatment period of Socazolimab and chemotherapy, with most cases being myelosupression that is common for chemotherapy patients. Therefore, differences in safety results due to racial differences were considered, and were similar to those reported in the literature [15]. During single-agent maintenance therapy, grade 3 or 4 TRAEs were rare, indicating that Socazolimab has a good safety profile. Patients with grade 3 or 4 myelosuppression were able to complete all the treatment of the follow-up combined treatment cycles after the dose reduction of chemotherapy.

The most common irAE in the study was endocrine toxicity, and a majority of patients continued to receive Socazolimab without treatment or just replacement therapy. Two cases of grade 3 irAE were treated

continuously after symptomatic treatment. One of the patients had a transient QTC prolongation of grade 3 during the 7th cycle of Socazolimab. The patient's previous electrocardiogram showed low and flat t-wave, which may be due to myocardial ischemia. However, this prolongation of QTC is not accompanied by other ECG abnormalities or symptoms, nor is it accompanied by other drug treatments that may affect the heart. Considering that prolonged QTC may be one of the manifestations of myocarditis[16,17], this adverse event is classified as irAE.

Adverse events of particular concern in this study were infusion reactions (allergies), which occurred in six patients. All infusion reactions occurred at the start of etoposide infusion, which were alleviated after symptomatic treatment and a decreased infusion rate, and did not occur after pretreatment with low-dose corticosteroids in subsequent treatment cycles. However, one patient was terminated due to a first-time experience of infusion reactions, which persisted even after subsequent cycles of corticosteroid pretreatment. However, the infusion reaction did not occur again after chemotherapy alone. None of the patients experienced infusion reactions during Socazolimab single-agent maintenance therapy, even without pretreatment. Considering that etoposide itself can result in infusion reactions [18], the immunostimulatory activity of PD-1/L1 inhibitors can lead to the aggravation of allergic reactions or inflammatory adverse events (such as dermatitis, infusion-related symptoms, etc.) related to chemotherapy. Besides, PD-L1 antibodies possess PD-1/PD-L1 blockade activity with or without ADCC activity. For example, both Atezolizumab and Durvalumab eliminated the effect of ADCC through structure modification[14], while Avelumab retained a strong ADCC effect[19].The design of Socazolimab is similar to that of Avelumab,thus enhancing the anti-tumor, but at the same time, the infusion reaction of Aveluzumab was the highest of all PD-L1 antibodies, up to more than 20%[20]. Fortunately, the infusion reaction is

considered to be mild and manageable [21]. Therefore, follow-up treatment and further study could include giving patients oral nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesic drugs and antihistamines, or adding low-dose corticosteroids after the completion of Socazolimab infusion and before the use of chemotherapy drugs. For infusion reactions still occurring after symptomatic treatment or prophylaxis, we can consider only continuing chemotherapy and maintaining Socazolimab after the completion of chemotherapy.

Another patient discontinued treatment due to grade 2 arrhythmia. Although the patient had a normal electrocardiogram before medication, arrhythmia occurred during maintenance therapy, without any further cardiac damage. Treatment termination was considered when no recovery had been observed after treatment suspension and symptomatic treatment. In addition to mild ECG changes observed in other patients, it suggests that Socazolimab has certain cardiotoxicity, but at the same time, it cannot be ruled out that because most of the patients are elderly patients, who already experience reduced cardiac function. Above all, the grade 3 or 4 TRAEs during the combination treatment and the TRAEs leading to the discontinuation of treatment were manageable. There were no serious unanticipated adverse events.

This study preliminarily confirmed the safety of Socazolimab in the first-line treatment of SCLC combined with EC chemotherapy, and suggested that this treatment has the potential to achieve survival benefits. It is expected that the ongoing phase III study (ClinicalTrials.gov, NCT04878016) will verify the above results.

Author contributions

Zhiwei Chen and Shun Lu: Conceptualization, Methodology; Zhiwei Chen, Jiuwei Cui, Renhua Guo,and Ziming Li: Investigation, Resources;

Zhiwei Chen: Writing - Original Draft; Shun Lu: Writing - Review & Editing, Supervision, Project administration. Benjamin Xiaoyi Li, Xiangrong Dai: Project administration, Funding acquisition.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017.
2. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006; 24:4539-4544.
3. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143:e400S-419S.
4. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol 1985; 3:1471-1477.
5. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer:E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2001; 19:2114-2122.
6. Lesterhuis WJ, Nowak AK, Lake RA. Immune stimulatory features of classical chemotherapy. In: Cancer Immunotherapy – Immune Suppression and Tumor Growth. Prendergast GC, Jaffee EM (Eds). Academic Press, UK, 395–416 (2013).
7. Brown JS, et al. Combining DNA damaging therapeutics with immunotherapy: more haste，less speed. J Br J Cancer, 2018,118 (3): 312-324.
8. McGranahanN, et al. Clonal neoantigens elicit T Cell immunoreactivity and sensitivity to immune checkpoint blockade. J Science, 2016,351(6280):1463-1469.

9. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec 6;379(23):2220-2229.
10. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1929-1939.
11. An J, Tang J, Li BX, et al. Efficacy and Safety of the Anti-PD-L1 mAb Socazolimab for Recurrent or Metastatic Cervical Cancer: a Phase I Dose-Escalation and Expansion Study. Clin Cancer Res. 2022 Dec 1;28(23):5098-5106.
12. Sequist LV, Chiang A, Gilbert J, et al. Clinical activity, safety and predictive biomarkers results from a phase Ia atezolizumab(atezo) trial in extensive-stage small cell lung cancer (ES-SCLC). Ann Oncol 2016; 27: Suppl 6: 1425PD. abstract.
13. Food and Drug Administration. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. 2014.8
14. Zhao, Q, Yang L & Xie R. Characteristic review of 9 approved anti-PD-1/PD-L1 monoclonal antibody drugs. [J] China Pharmacy 2020 31 (18).2294-2299
15. Hu J. JCSE01.03 Any Difference on Efficacy and Toxicity Between East and West? [J]. Journal of Thoracic Oncology, 2019, 14(10):S125.
16. Wu S, Bai H, Zhang L, He J, et al. Cardiovascular adverse events induced by immune checkpoint inhibitors: A real world study from 2018 to 2022. Front Cardiovasc Med. 2022 Aug 10;9:969-942.
17. Zlotoff DA, Hassan MZO, Zafar A, et al. Electrocardiographic features of immune checkpoint inhibitor associated myocarditis. J Immunother Cancer. 2021 Mar;9(3):e002-007.
18. Zhang L, Qu S, Bai H, et al. Report on two cases of allergic reactions

caused by etoposide J. Clinical Misdiagnosis and Mistreatment, 2006, 19(1):82-82

19. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opin Biol Ther. 2017 Apr;17(4):515-523.
20. BAVENCIO- avelumab injection, solution, concentrate. EMD Serono, Inc.2017
21. Gulley JL, Kelly K. Infusion-related reactions with administration of avelumab: mild and manageable side effects. Transl Cancer Res. 2017 Oct;6(Suppl 7):S1296-S1298.

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FIG 1. Patient Disposition

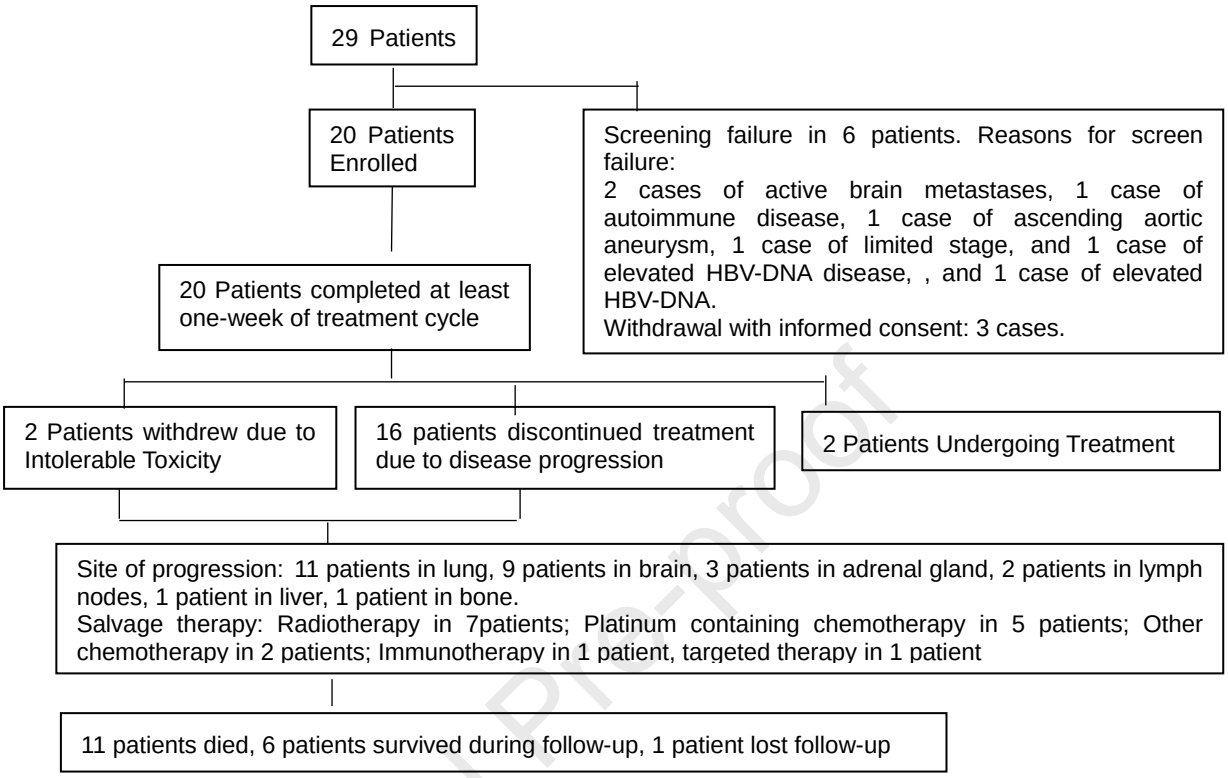

FIG 2. (A)

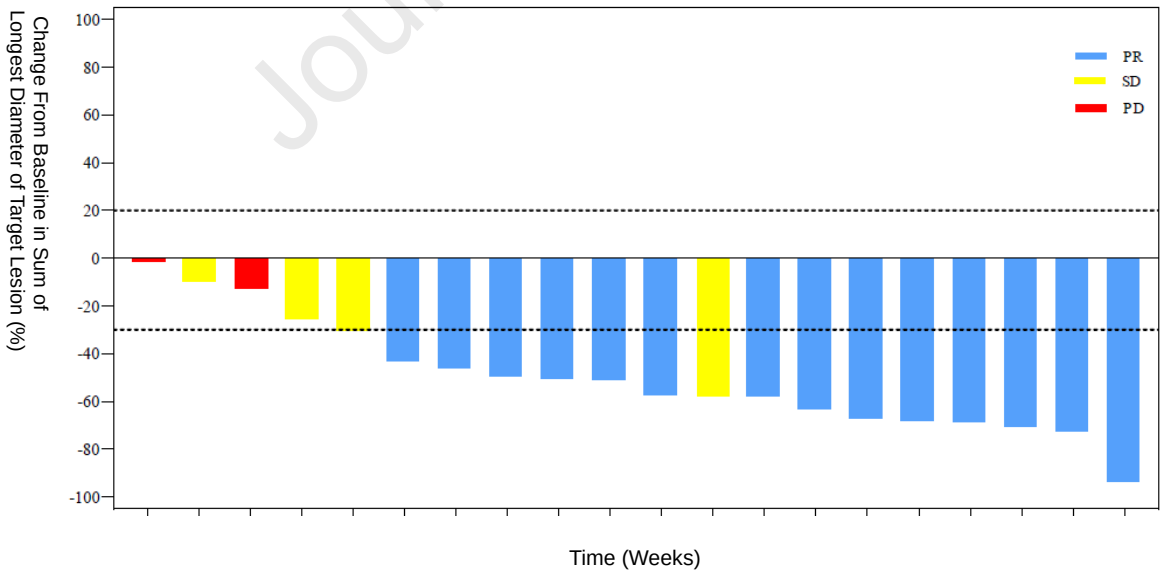

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FIG 2. (B)

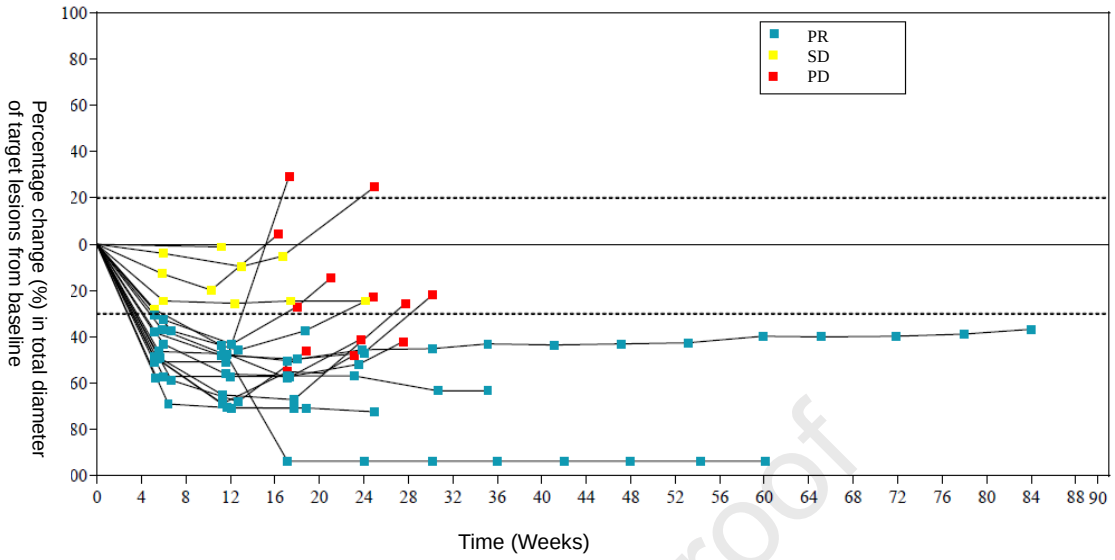

FIG 2. (C)

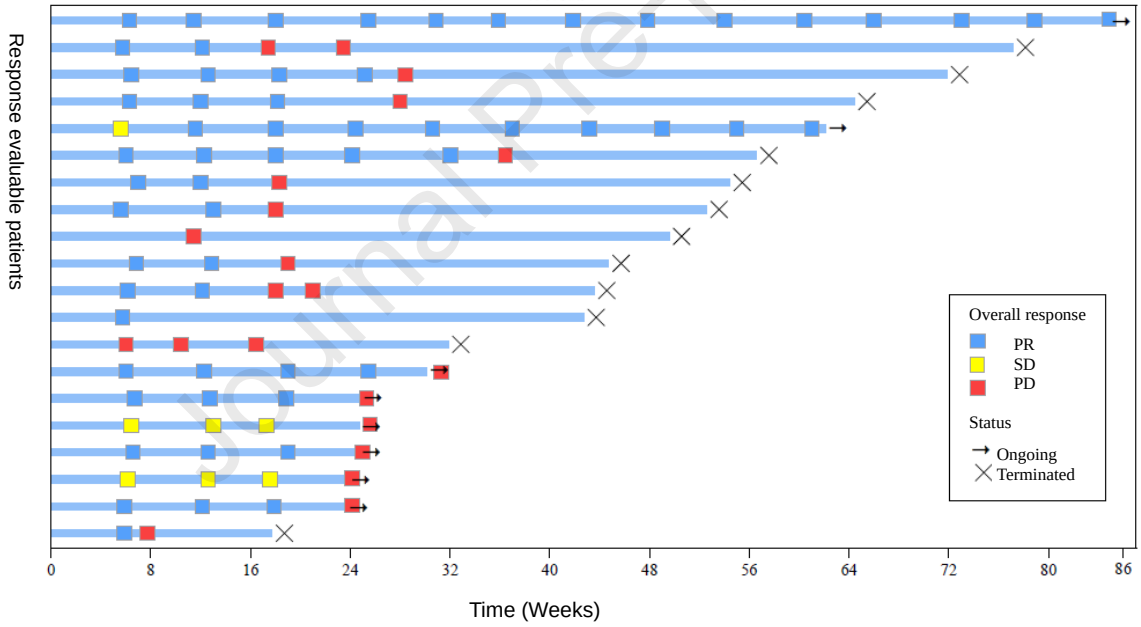

FIG 2. (A) Change of tumor burden from baseline (investigator assessed; n = 20). Bar length is decrease/increase in target lesion size. Bar color is best overall response. (B) Change from baseline over time (investigator assessed; n = 20) for each individual. (C) Treatment exposure and response duration (by RECIST v1.1; investigator assessed; n = 20). The length of each bar corresponds to the duration of treatment. Response symbols represent time to first report and not best overall. CR, complete response; PD, progressive

disease; PR, partial response; SD, stable disease.

FIG 3. (A)

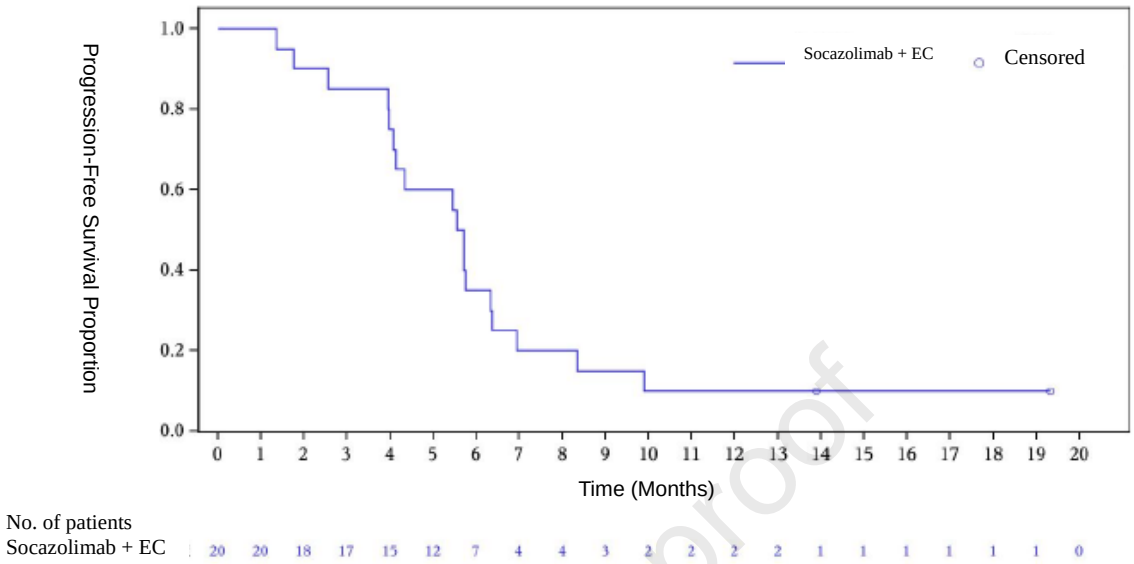

FIG 3. (B)

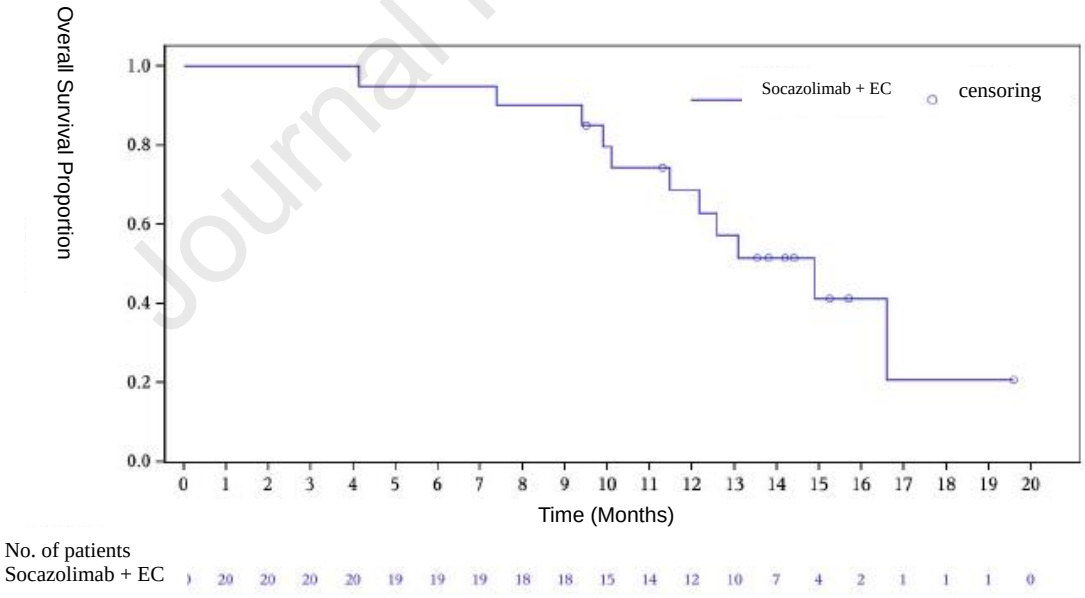

FIG 3. (A) Kaplan-Meier curve for patient progression-free survival (full analysis set). (B) Kaplan-Meier curve for overall survival (full analysis set).

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TABLE 1. Patient Demographics and Baseline Characteristics

Age (years)	N=20
Mean (standard deviation)	63.0 (6.00)
Minimum - maximum	48 - 74
<60	5 (25%)
>=60	15 (75%)
Gender	
Male	16 (80%)
Female	4 (20%)
Body mass index (m^2)	
Median	1.77
Minimum - maximum	1.45 - 2.03
TNM staging	
IV	16 (80%)
Other	4(20%)
Site of metastasis	
Nonregional lymph nodes	15(75%)
Pleural or pericardial effusion	6(30%)
Liver	4(20%)
Brain	3(15%)
Lung	3(15%)
Pleura	3()15%
Adrenal gland	1(5%)
Colon	1(5%)
Baseline ECOG performance status	
1 point	20 (100%)
0 points	0
Baseline PD-L1 Expression Level (Tumor Proportion Score)	
<1%	0
1-49%	10 (30%)
≥50%	7 (35%)
Unreported	1 (5%)

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TABLE 2. Summary of Patient AEs (N = 20)

Adverse Events	Grade 1/2 (n, %)	Grade 3/4 (n, %)	Socazolimab-Related Grade 1/2	Socazolimab-Related Grade 3/4	Total (N=20)
TRAEs	**20, 100%**	**19, 95%**	**18, 90%**	**7, 35%**	**20, 100%**
Anemia	14, 70%	6, 30%	5, 25%	-	20, 100%
Decreased neutrophil count	1, 5%	18, 90%	1, 5%	3, 15%	19, 95%
Decreased platelet count	9, 45%	10, 50%	5, 25%	2, 10%	19, 95%
Decreased white blood cell count	6, 30%	13, 65%	2, 10%	2, 10%	19, 95%
Hypoalbuminemia	7, 35%	-	3, 15%	-	7, 35%
Infusion-related reactions	5, 25%	-	2, 10%	-	5, 25%
Elevated alanine aminotransferase	4, 20%	-	1, 5%	-	4, 20%
Elevated blood bilirubin	4, 20%	-	3, 15%	-	4, 20%
Hyperuricemia	4, 20%	-	2, 10%	-	4, 20%
Hyperglycemia	4, 20%	-	4, 20%	-	4, 15%
Elevated aspartate aminotransferase	3, 15%	-	1, 5%	-	3, 15%
Weight loss	3, 15%	-	1, 5%	-	3, 15%
Hair loss	3, 15%	-	-	-	3, 15%
Atrial premature beat	3, 15%	-	-	-	3, 15%
ECG QTC interval prolongation	2, 10%	-	1, 5%	-	3, 15%
Weight increase	2, 10%	-	1, 5%	-	2, 10%
Elevated alkaline phosphatase	2, 10%	-	-	-	2, 10%
ECG ST segment changes	2, 10%	-	-	-	2, 10%
Loss of appetite	2, 10%	-	2, 10%	-	2, 10%
Pruritus	2, 10%	-	1, 5%	-	2, 10%
Sinus bradycardia	2, 10%	-	2, 10%	-	2, 10%
Nausea	2, 10%	-	1, 5%	-	2, 10%
Hypothyroidism	2, 10%	-	2, 10%	-	2, 10%
Hypersensitivity	2, 10%	-	2, 10%	-	2, 10%

All TRAEs (with ≥ 10% incidence rates) were noted. For irAEs, apart from one case of Grade 3 QTC interval prolongation and one case of Grade 3 impetigo, the rest were Grade 1/2 irAEs.

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TABLE 3. Anti-Tumor Efficacy Assessment by Investigator Evaluation (N = 20)

Efficacy	Total Patients（N=20）
Objective response, n(%)	
Best overall response, n(%)	14(70.0, 45.72%,88.11%)
CR	0
PR	14(70.0)
SD	2(10.0)
PD	3(15.0)
Not evaluated	1(5.0)
median Duration of response	4.29 m (2.76, 5.85)
median PFS	5.65 m(4.14, 6.54)
PD-L1≥50%(n=9)	5.72 (1.77, NE)
PD-L1＜50%(n=10)	5.65 (1.35, 6.93)
With brain metastasis	2.56(1.35 ~ 4.34)
Without brain metastasis	5.72 (4.07 ~ 6.93）
median Overall survival	14.88 m (10.09, NE)
PD-L1≥50%(n=9)	16.6 (4.14,NE)
PD-L1＜50%(n=10)	13.1 (7.39,14.88)
With brain metastasis	4.90(3.94 ~ 5.72)
Without brain metastasis	6.65(6.34 ~ NE)

Unless otherwise indicated, m=months; n % (95% CI); CR=complete response; PR=partial response; SD=stable disease; PD=progression disease; NE=not evaluated; PFS=progression free survival; OS=overall survival.

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CRediT Statement

Zhiwei Chen and Shun Lu: Conceptualization, Methodology；Zhiwei Chen, Jiuwei Cui, Renhua Guo,and Ziming Li: Investigation, Resources; Zhiwei Chen: Writing - Original Draft; Shun Lu: Writing - Review & Editing, Supervision, Project administration. Benjamin Xiaoyi Li, Xiangrong Dai: Project administration, Funding acquisition.

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