Supplemental Online Content

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eMethods

Inclusion and Exclusion Criteria

Inclusion Criteria

1) Voluntary participation in clinical studies; fully understand, be informed about the study and have signed the informed consent form (ICF); willingness to follow and ability to complete all trial procedures.
2) Male or female aged ≥18 years at the time of signing the ICF.
3) Histologically or cytologically diagnosed with extensive-stage small cell lung cancer (ES-SCLC) according to the Veterans Administration Lung Study Group staging system.
4) No prior systemic therapy for ES-SCLC (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies).
5) Patients who have received chemoradiotherapy for previous limited-stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive-stage SCLC.
6) At least 1 measurable lesion as assessed by the independent radiology review committee (IRRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 within 4 weeks prior to randomization.
    - *Note*: Measurable lesions are not from previously irradiated sites. If the lesion at the previously irradiated site is the only selectable target lesion, a radiological assessment showing significant progression of the irradiated lesion should be provided by the investigator.
7) Patients must provide tumor tissues that meet the requirements for the determination of programmed death-ligand 1 (PD-L1) expression levels. Patients are assessed for an evaluable PD-L1 expression category (negative: TPS <1%, positive: TPS ≥1%, or not evaluable/not available) by the central laboratory for randomization.
    - *Note*: It is recommended to provide formalin-fixed tumor tissue samples, paraffin-embedded tumor specimens (preferred), formalin-fixed paraffin-embedded (FFPE), tumor specimens or newly prepared unstained serial tissue sections (preferably adhesive slides) within 6 months prior to the first dose of study medication. A relevant pathology report must also be provided for the above specimens. Freshly collected specimens, radical resections, core needle biopsy, excisions, incisions, punch or clamp biopsies are acceptable (newly obtained tissues are preferred). Fine-needle aspirations (i.e., samples that lack a complete tissue structure and provide only cell suspension and/or cell smear), brush biopsies, and cell pellet samples from pleural or peritoneal effusions are unacceptable. For detailed requirements for tissue samples, see the laboratory manual.
8) Prior antineoplastic therapy must have been ≥2 weeks from the first dose in this study with treatment-related adverse events resolved to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≤1 (except for grade 2 alopecia).
9) An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1.
10) An expected survival ≥12 weeks.
11) Subjects with prior denosumab use that can and agree to switch to bisphosphonate therapy for bone metastases starting prior to randomization and throughout treatment.

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12) Normal major organ functions as defined by the following criteria (no blood transfusions, or treatment with albumin, recombinant human thrombopoietin or colony-stimulating factor within 14 days prior to the first dose in this study):

Hematologic system	
Absolute neutrophil count (ANC)	$\geq 1.5\times10^9$/L
Lymphocyte	$\geq 0.5\times10^9$/L
Platelet (PLT)	$\geq 100\times10^9$/L
Hemoglobin (Hb)	≥90 g/L
Hepatic functions	
Total bilirubin (TB)	≤1.5×upper limit of normal (ULN) For patients with Gilbert's syndrome, total bilirubin ≤3×ULN is acceptable
Alanine transaminase (ALT)	≤2.5×ULN; ≤5×ULN for patients with liver metastases
Aspartic transaminase (AST)	≤2.5×ULN; ≤5×ULN for patients with liver metastases
Alkaline phosphatase (ALP)	≤2.5×ULN; ≤5.0×ULN for patients with liver or bone metastases
Renal functions	
Creatinine (Cr)	≤1.5×ULN; In case of >1.5×ULN, creatinine clearance ≥50 mL/min (calculated from Cockcroft-Gault formula)
Coagulation functions	
Activated partial prothrombin time (APTT)	≤1.5×ULN
Prothrombin time (PT) or International normalized ratio (INR)	≤1.5×ULN
The above requirements apply only to subjects who are not receiving anticoagulant therapy; subjects who are receiving anticoagulant therapy must maintain a stable dose of anticoagulants.	

13) Female patients must meet 1 of the following conditions:
   a) Menopause (defined as no menses for at least 1 year and no confirmed cause other than menopause), or
   b) Surgically sterilized (removal of the ovaries and/or uterus), or
   c) Of child-bearing potential, but must meet the following:
      i) Serum pregnancy test must be negative within 7 days prior to randomization, and
      ii) Agree to use birth control methods with an annual failure rate of <1% or maintain abstinence (avoid heterosexual intercourse) (from the signing of ICF to at least 6 months after the final dose of study drug) (birth control methods with an annual failure rate of <1% include bilateral tubal ligation, male sterilization, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine contraceptive devices and copper-containing intrauterine contraceptive devices or condoms), and
      iii) Must not be breast-feeding.

14) Male patients must: agree to abstinence (avoid heterosexual intercourse) or take contraception measures as follows: male patients with a pregnant partner or a partner of child-bearing potential must remain abstinent or use a condom to prevent embryonic exposure during study treatment and for at least 6 months after the last dose of study drug. Periodic abstinence (e.g., contraceptive methods based on calendar day, ovulation, basal body temperature or post-ovulation) and external ejaculation are ineligible methods of contraception.

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Exclusion Criteria

1) Histologically or cytologically confirmed mixed SCLC.
2) Other active malignancies within 5 years or at the same time. Localized tumors that have been cured, such as basal cell carcinoma, squamous-cell skin cancer, superficial bladder cancer, prostate carcinoma in situ, cervical cancer in situ and breast cancer in situ are acceptable.
3) Patients who are preparing for or have received an organ or bone marrow transplant.
4) Pleural or pericardial effusion requiring clinical intervention, or ascites.
5) Patients with known or documented active central nervous system metastases and/or carcinomatous meningitis at screening. However, the following subjects are allowed to be enrolled: 1) Subjects with asymptomatic brain metastases (i.e., no progressive central nervous system symptoms caused by brain metastases, no requirement for corticosteroids, and lesion size ≤1.5 cm) may be included but are required to receive regular brain imaging as a site of lesion. 2) Subjects with treated brain metastases which have been stable for at least 2 months (as confirmed by 2 radiological examinations at least 4 weeks apart after treatment of brain metastases), with no evidence of new or enlarging brain metastases, and with discontinued steroids 3 days prior to study drug administration. Stable brain metastases here should be confirmed before the first dose of the study drug.
6) Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy.
7) Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥450 ms for males and ≥470 ms for females) (QTc intervals are calculated by Fridericia's formula).
8) Class III to IV cardiac insufficiency according to New York Heart Association (NYHA) classification or a left ventricular ejection fraction <50% by cardiac color Doppler.
9) Subject has uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN).
10) Subject with peripheral neuropathy grade ≥2 by CTCAE.
11) Human immunodeficiency virus (HIV) infection, positive test for HIV antibody.
12) Active or latent pulmonary tuberculosis.
13) Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity, as judged by the investigator.
14) Hepatitis B (positive test for HBsAg or HBcAb and positive test for HBV-DNA) or Hepatitis C (positive tests for HCV antibody and HCV-RNA). Hepatitis B and C coinfection (positive test for HBsAg or HBcAb and positive test for HCV antibody).
15) Known active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to enroll.
16) Treatment with live vaccines and all COVID-19 vaccines (fully administered to the required number of doses) within 28 days prior to study drug administration; inactivated viral vaccines for seasonal influenza are allowed.
17) Subjects requiring treatment with systemic corticosteroids (>10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study. However, in the absence of active autoimmune disease, subjects are allowed to use topical or inhaled steroids and adrenal hormone replacement therapy at doses equivalent to ≤10 mg/day of prednisone efficacy.
18) Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration or subjects with a positive RT-PCR test for SARS-CoV-2 infection at randomization. Subjects with a history of COVID-19 infection must have a negative RT-PCR test prior to the first dose of the study drug.
19) Major surgery within 28 days prior to the first dose of the study drug, defined as: surgeries requiring at least 3 weeks of recovery to be able to receive treatment in this study.
20) Radical radiation therapy within 3 months prior to study medications.
    - *Note*: Palliative radiotherapy to bone or palliative radiotherapy to superficial lesions is allowed according to local standards 14 days prior to the first dose. Radiotherapy covering more than 30% of the bone marrow area within 28 days prior to the first dose is not allowed.
21) The subject has previously received other antibodies/drugs against immune checkpoints, such as programmed death 1 (PD-1), PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA4).

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22) Participation in any other ongoing clinical studies, or less than 14 days from the end of the previous clinical study treatment to the start of this trial.
23) Known history of severe allergy to any monoclonal antibody.
24) Known hypersensitivity to carboplatin or etoposide.
25) Pregnant or lactating women.
26) Known history of psychotropics abuse or drug abuse.
27) In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.

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Definitions of Efficacy Outcomes

Outcome	Definition
Overall survival	Time from randomization to death from any cause
Progression-free survival	Time from randomization to first disease progression or death from any cause
Objective response rate	Proportion of patients achieving complete or partial response
Duration of response	Time from first complete or partial response to disease progression or death from any cause

Treatment After Disease Progression

Patients with first documented disease progression per RECIST version 1.1 were allowed to continue assigned treatment at the discretion of investigators if they were clinically stable and subsequent therapy would be chemotherapy according to treatment guidelines (the National Comprehensive Cancer Network guidelines or European Society for Medical Oncology guidelines). Study treatment continued until second disease progression, unacceptable toxicity, death, withdrawal of consent, or lost to follow-up. Patients who discontinued study treatment due to unacceptable toxicity, withdrawal of consent, or reasons other than disease progression were not eligible for continuing study treatment after disease progression.

PD-L1 Assessment

PD-L1 expression was analyzed in archival FFPE tumor samples collected within 6 months before initiating study treatment, or if not available, in fresh biopsy samples collected during screening. PD-L1 expression was assessed using PD-L1 IHC 22C3 PharmDx kit (catalog# SK006) by Labcorp Drug Development. PD-L1-positive was defined as a tumor proportion score of ≥1%.

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eTable 1. Detailed Reasons for Excluding Patients Who Did Not Meet Eligibility Criteria

Criteria No.	Eligibility criteria[a]	No. of patients
Total		302
Did not meet inclusion criteria		**170**
Inclusion 01	Voluntary participation in clinical studies; fully understand, be informed about the study and have signed the informed consent form (ICF); willingness to follow and ability to complete all trial procedures.	67
Inclusion 02	Male or female aged ≥18 years at the time of signing the ICF.	1
Inclusion 03	Histologically or cytologically diagnosed with extensive-stage small cell lung cancer (ES-SCLC) according to the Veterans Administration Lung Study Group staging system.	17
Inclusion 04	No prior systemic therapy for ES-SCLC.	1
Inclusion 05	Patients who have received chemoradiotherapy for previous limited-stage SCLC must be treated with curative intent and have a treatment-free interval of at least 6 months from the last course of chemotherapy, radiotherapy, or chemoradiotherapy to the diagnosis of extensive-stage SCLC.	3
Inclusion 06	At least 1 measurable lesion as assessed by the independent radiology review committee (IRRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 within 4 weeks prior to randomization.	3
Inclusion 07	Patients must provide tumor tissues that meet the requirements for the determination of programmed death-ligand 1 (PD-L1) expression levels.	22
Inclusion 09	An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1.	18
Inclusion 10	An expected survival ≥12 weeks.	5
Inclusion 12	Normal major organ functions.	29
Inclusion 13	Female patients must meet 1 of the following conditions: a) Menopause, or b) Surgically sterilized, or c) Of child-bearing potential, but must meet the following: i) Serum pregnancy test must be negative within 7 days prior to randomization, and ii) Agree to use birth control methods with an annual failure rate of <1% or maintain abstinence from the signing of ICF to at least 6 months after the final dose of study drug, and iii) Must not be breast-feeding.	1
Inclusion 09; Inclusion 10	An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1; An expected survival ≥12 weeks.	2
Inclusion 09; Inclusion 12	An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1; Normal major organ functions.	1
Met exclusion criteria		**131**
Exclusion 01	Histologically or cytologically confirmed mixed SCLC.	3
Exclusion 02	Other active malignancies within 5 years or at the same time. Localized tumors that have been cured are acceptable.	5
Exclusion 04	Pleural or pericardial effusion requiring clinical intervention, or ascites.	3
Exclusion 05	Patients with known or documented active central nervous system metastases and/or carcinomatous meningitis at screening.	37
Exclusion 06	Subjects with spinal cord compression that has not been radically treated with surgery and/or radiotherapy.	1

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Criteria No.	Eligibility criteria[a]	No. of patients
Exclusion 07	Patients with myocardial infarction within half a year before the first dose of the study drug, poorly controlled arrhythmia (including QTc intervals ≥450 ms for males and ≥470 ms for females) (QTc intervals are calculated by Fridericia's formula).	6
Exclusion 08	Class III to IV cardiac insufficiency according to New York Heart Association (NYHA) classification or a left ventricular ejection fraction <50% by cardiac color Doppler.	6
Exclusion 09	Subject has uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN).	1
Exclusion 13	Subjects with previous and concurrent interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity, as judged by the investigator.	2
Exclusion 14	Hepatitis B or Hepatitis C. Hepatitis B and C coinfection.	17
Exclusion 17	Subjects requiring treatment with systemic corticosteroids (>10 mg/day prednisone efficacy dose) or other immunosuppressive drugs within 14 days prior to the first dose or during the study.	1
Exclusion 18	Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration or subjects with a positive RT-PCR test for SARS-CoV-2 infection at randomization. Subjects with a history of COVID-19 infection must have a negative RT-PCR test prior to the first dose of the study drug.	12
Exclusion 27	In the judgment of the investigator, the subject has any other factors that may lead to a premature discontinuation.	36
Exclusion 09; Exclusion 14	Subject has uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN); Hepatitis B or Hepatitis C. Hepatitis B and C coinfection.	1
Did not meet inclusion criteria and met exclusion criteria		1
Inclusion 09; Exclusion 05	An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1; Patients with known or documented active central nervous system metastases and/or carcinomatous meningitis at screening.	1

[a] For full eligibility criteria, please refer to Inclusion and Exclusion Criteria in eMETHODS.

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eTable 2. Summary of Subsequent Anticancer Treatment After First Disease Progression

	No. (%)	
	Serplulimab group (n = 389)	**Placebo group (n = 196)**
Number of patients with ≥1 treatment after first disease progression	172 (44.2)	85 (43.4)
Line of therapy		
2	165 (42.4)	83 (42.3)
3	24 (6.2)	16 (8.2)
4	5 (1.3)	5 (2.6)
5 and other[a]	15 (3.9)	10 (5.1)
Therapy type		
Chemotherapy	126 (32.4)	75 (38.3)
Irinotecan	65 (16.7)	43 (21.9)
Carboplatin	40 (10.3)	23 (11.7)
Etoposide	40 (10.3)	20 (10.2)
Paclitaxel	28 (7.2)	14 (7.1)
Cisplatin	24 (6.2)	14 (7.1)
Docetaxel	11 (2.8)	6 (3.1)
Topotecan	7 (1.8)	4 (2.0)
Lobaplatin	8 (2.1)	1 (0.5)
Nedaplatin	3 (0.8)	5 (2.6)
Temozolomide	2 (0.5)	2 (1.0)
Vinorelbine	3 (0.8)	0
Gemcitabine	0	3 (1.5)
Cyclophosphamide	2 (0.5)	0
Doxorubicin	2 (0.5)	0
Ifosfamide	2 (0.5)	0
Vincristine	2 (0.5)	0
Lomustine	1 (0.3)	0
Mitoxantrone	1 (0.3)	0
Oxaliplatin	1 (0.3)	0
Immunotherapy	108 (27.8)	19 (9.7)
Serplulimab	95 (24.4)	0
Sintilimab	10 (2.6)	7 (3.6)
Atezolizumab	2 (0.5)	2 (1.0)
Camrelizumab	2 (0.5)	2 (1.0)
Tislelizumab	2 (0.5)	2 (1.0)
Toripalimab	1 (0.3)	3 (1.5)
Durvalumab	1 (0.3)	0
Nivolumab	0	1 (0.5)
Penpulimab	0	1 (0.5)
Pianprizumab	0	1 (0.5)
Immunotherapy (unknown)	0	1 (0.5)
Targeted therapy	38 (9.8)	28 (14.3)
Catequentinib	37 (9.5)	24 (12.2)
Apatinib	2 (0.5)	2 (1.0)
Bevacizumab	0	3 (1.5)
Other	32 (8.2)	27 (13.8)
Herbal or Traditional Chinese Medicine	19 (4.9)	23 (11.7)
Immunomodulator[b]	6 (1.5)	7 (3.6)

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	No. (%)	
	Serplulimab group (n = 389)	Placebo group (n = 196)
Antineoplastic agent (unknown)	4 (1.0)	2 (1.0)
Other clinical trial	5 (1.3)	0

[a] Other lines of therapy included herbal or Traditional Chinese Medicine, thermo-chemotherapy perfusion, and non-systemic treatment, among others.

[b] Immunomodulators included lentinan, thalidomide, spleen aminopeptide oral lyophilized powder, thymopolypeptides for injection, etc.

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eTable 3. Tumor Response According to Investigator Assessments per RECIST Version 1.1

	Serplulimab group (n = 389)	**Placebo group (n = 196)**
Objective response rate[a]		
No. of patients	299	135
% (95% CI)	76.9 (72.4-81.0)	68.9 (61.9-75.3)
Best response, no. (%)		
Complete response	11 (2.8)	1 (0.5)
Partial response	288 (74.0)	134 (68.4)
Stable disease	44 (11.3)	34 (17.3)
Progressive disease	30 (7.7)	16 (8.2)
Non-evaluable or missing	16 (4.1)	11 (5.6)
Median duration of response[b] (95% CI), mo	4.4 (4.2-5.6)	3.0 (2.9-4.0)
Response duration ≥12 months (95% CI), %	21.0 (15.6-27.0)	3.5 (0.8-9.4)

Abbreviations: CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Defined as proportion of patients achieving complete or partial response.

[b] Assessed in patients who achieved complete or partial response and defined as time from first objective response to disease progression or death from any cause.

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eTable 4. Summary of Treatment-emergent Adverse Events

	No. (%)	
	Serplulimab group (n = 389)	**Placebo group (n = 196)**
Any treatment-emergent adverse events	372 (95.6)	191 (97.4)
Grade ≥3	321 (82.5)	157 (80.1)
Grade 5	30 (7.7)	20 (10.2)
Serious	136 (35.0)	69 (35.2)
Leading to treatment discontinuation	31 (8.0)	15 (7.7)
Serplulimab or placebo-related adverse events	272 (69.9)	110 (56.1)
Grade ≥3	129 (33.2)	54 (27.6)
Grade 5	3 (0.8)	1 (0.5)
Serious	66 (17.0)	27 (13.8)
Leading to treatment discontinuation	19 (4.9)	8 (4.1)
Immune-related adverse events[a]	144 (37.0)[b]	36 (18.4)

[a] Defined as an adverse event related to drug exposure and consistent with an immune-mediated mechanism of action without any other definitive pathological factor.

[b] According to investigator assessment, 1 patient in the serplulimab group experienced a grade 5 immune-related sepsis that was considered unrelated to serplulimab by both the investigator and the sponsor. The sponsor suggested that the investigator should consider reclassifying this as an immune-related adverse event.

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eTable 5. Common Treatment-emergent Adverse Events Reported by ≥10% Patients in the Adverse Event Set

	No. (%)	
	Serplulimab group (n = 389)	**Placebo group (n = 196)**
Blood and lymphatic system disorders	324 (83.3)	165 (84.2)
Anemia	278 (71.5)	138 (70.4)
Neutropenia	114 (29.3)	62 (31.6)
Leukopenia	95 (24.4)	40 (20.4)
Thrombocytopenia	71 (18.3)	29 (14.8)
Investigations	312 (80.2)	151 (77.0)
Neutrophil count decreased	218 (56.0)	100 (51.0)
White blood cell count decreased	208 (53.5)	100 (51.0)
Platelet count decreased	157 (40.4)	88 (44.9)
ALT increased	70 (18.0)	37 (18.9)
Lymphocyte count decreased	69 (17.7)	29 (14.8)
AST increased	62 (15.9)	33 (16.8)
Blood alkaline phosphatase increased	46 (11.8)	17 (8.7)
Blood lactate dehydrogenase increased	42 (10.8)	17 (8.7)
Weight increased	40 (10.3)	14 (7.1)
Metabolism and nutrition disorders	253 (65.0)	111 (56.6)
Decreased appetite	103 (26.5)	56 (28.6)
Hyponatremia	93 (23.9)	26 (13.3)
Hypoalbuminemia	71 (18.3)	28 (14.3)
Hypotriglyceridemia	64 (16.5)	24 (12.2)
Hypokalemia	55 (14.1)	14 (7.1)
Hyperglycemia	48 (12.3)	15 (7.7)
Hypercholesterolemia	43 (11.1)	18 (9.2)
Hyperuricemia	40 (10.3)	17 (8.7)
Hypocalcemia	39 (10.0)	10 (5.1)
Gastrointestinal disorders	233 (59.9)	127 (64.8)
Nausea	138 (35.5)	85 (43.4)
Constipation	93 (23.9)	56 (28.6)
Vomiting	75 (19.3)	58 (29.6)
Skin and subcutaneous tissue disorders	234 (60.2)	115 (58.7)
Alopecia	210 (54.0)	111 (56.6)
General disorders and administration site conditions	169 (43.4)	91 (46.4)
Pyrexia	56 (14.4)	26 (13.3)
Asthenia	40 (10.3)	25 (12.8)
Respiratory, thoracic, and mediastinal disorders	115 (29.6)	65 (33.2)
Cough	42 (10.8)	23 (11.7)
Dyspnea	26 (6.7)	27 (13.8)
Infections and infestations	97 (24.9)	46 (23.5)
Musculoskeletal and connective tissue disorders	93 (23.9)	40 (20.4)
Cardiac disorders	82 (21.1)	33 (16.8)
Nervous system disorders	82 (21.1)	33 (16.8)
Endocrine disorders	93 (23.9)	16 (8.2)
Hypothyroidism	63 (16.2)	7 (3.6)
Hyperthyroidism	44 (11.3)	6 (3.1)
Psychiatric disorders	58 (14.9)	30 (15.3)
Insomnia	43 (11.1)	17 (8.7)
Renal and urinary disorders	49 (12.6)	21 (10.7)

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	No. (%)	
	Serplulimab group (n = 389)	**Placebo group (n = 196)**
Vascular disorders	34 (8.7)	21 (10.7)
Hepatobiliary disorders	29 (7.5)	20 (10.2)

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eTable 6. Immune-related Adverse Events

	No. (%)			
	Serplulimab group (n = 389)		Placebo group (n = 196)	
	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3
Any immune-related adverse event[a]	107 (27.5)	37 (9.5)	25 (12.8)	11 (5.6)
Immune-related adverse events with an incidence of ≥2% in any grade category or events of grade ≥3 in either group				
Hypothyroidism	44 (11.3)	1 (0.3)	3 (1.5)	0
Hyperthyroidism	35 (9.0)	0	6 (3.1)	0
Alanine aminotransferase increased	6 (1.5)	3 (0.8)	4 (2.0)	0
Aspartate aminotransferase increased	6 (1.5)	1 (0.3)	4 (2.0)	0
Gamma-glutamyl transferase increased	5 (1.3)	1 (0.3)	3 (1.5)	0
Platelet count decreased	3 (0.8)	3 (0.8)[b]	1 (0.5)	2 (1.0)
White blood cell count decreased	5 (1.3)	0	0	3 (1.5)
Neutrophil count decreased	2 (0.5)	2 (0.5)	0	4 (2.0)
Blood lactate dehydrogenase increased	0	0	5 (2.6)	0
Blood cholesterol increased	0	1 (0.3)	0	0
Lymphocyte count decreased	0	0	0	1 (0.5)
Rash	11 (2.8)	1 (0.3)	2 (1.0)	0
Dermatitis bullous	0	1 (0.3)	0	0
Asthenia	5 (1.3)	0	0	1 (0.5)
Fatigue	4 (1.0)	1 (0.3)	1 (0.5)	0
Pyrexia	2 (0.5)	1 (0.3)[b]	1 (0.5)	0
Hyperglycemia	1 (0.3)	4 (1.0)	1 (0.5)	0
Diabetic ketoacidosis	0	2 (0.5)	0	0
Hyponatremia	0	0	0	2 (1.0)
Diabetes mellitus	0	1 (0.3)	0	0
Hypertriglyceridemia	0	1 (0.3)	0	0
Anemia	9 (2.3)	0	3 (1.5)	1 (0.5)
Leukopenia	1 (0.3)	1 (0.3)	0	0
Thrombocytopenia	0	1 (0.3)	0	1 (0.5)[b]
Neutropenia	0	1 (0.3)	0	0
Diarrhea	6 (1.5)	1 (0.3)	0	0
Immune-mediated pancreatitis	0	1 (0.3)	0	0
Vomiting	0	1 (0.3)	0	0
Oral pain	0	0	0	1 (0.5)
Immune-mediated encephalitis	0	2 (0.5)	0	0
Neuropathy peripheral	1 (0.3)	1 (0.3)	0	0
Encephalitis autoimmune	0	1 (0.3)	0	0
Peripheral sensorimotor neuropathy	0	1 (0.3)	0	0
Immune-mediated lung disease	1 (0.3)	1 (0.3)	2 (1.0)	0
Chronic obstructive pulmonary disease	0	1 (0.3)	0	0
Acute coronary syndrome	0	1 (0.3)[b]	0	0
Acute myocardial infarction	0	1 (0.3)	0	0
Cardiac failure acute	0	1 (0.3)	0	0
Pneumonia	2 (0.5)	1 (0.3)	0	1 (0.5)
Sepsis	0	1 (0.3)[c]	0	0
Hepatic function abnormal	1 (0.3)	0	0	1 (0.5)
Immune-mediated hepatitis	0	1 (0.3)	0	0
Drug-induced liver injury	0	0	0	1 (0.5)

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	No. (%)			
	Serplulimab group (n = 389)		Placebo group (n = 196)	
	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3
Panic disorder	0	1 (0.3)	0	0
Vision blurred	0	1 (0.3)	0	0
Anaphylactic reaction	0	1 (0.3)	0	0

[a] Defined as an adverse event related to drug exposure and consistent with an immune-mediated mechanism of action without any other definitive pathological factor.

[b] In total, 3 and 1 grade 5 immune-related adverse events were observed in the serplulimab group (1 platelet count decreased, 1 pyrexia, and 1 acute coronary syndrome) and the placebo group (1 thrombocytopenia), respectively.

[c] According to investigator assessment, 1 patient in the serplulimab group experienced a grade 5 immune-related sepsis that was considered unrelated to serplulimab by both the investigator and the sponsor. The sponsor suggested that the investigator should consider reclassifying this as an immune-related adverse event.

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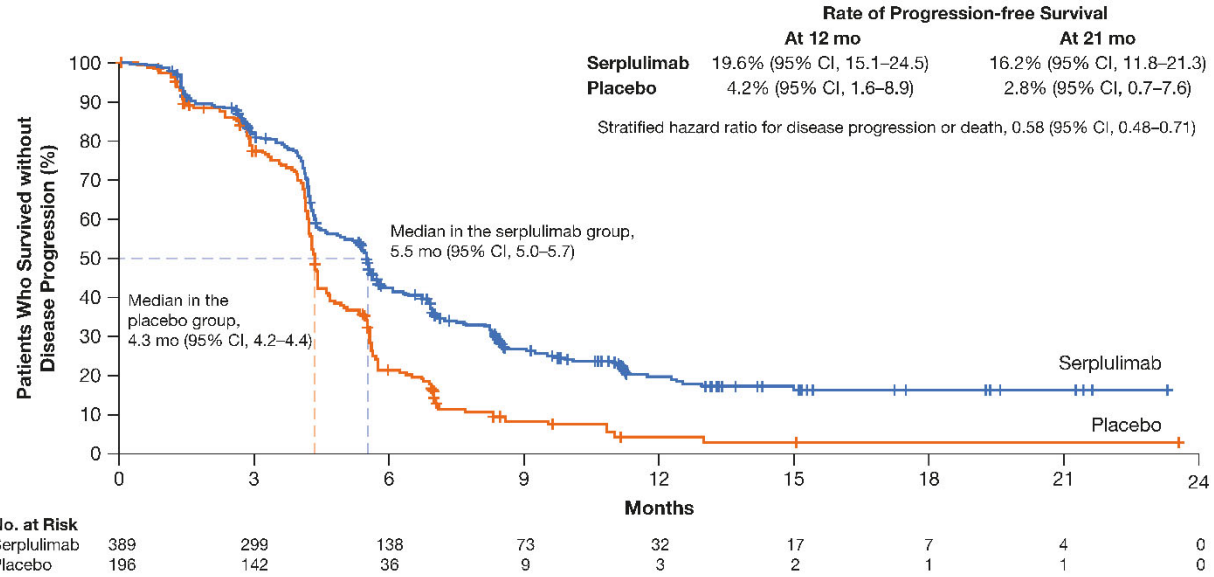
eFigure. Progression-free Survival According to Investigator Assessments per RECIST Version 1.1



Abbreviations: CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.

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