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A PHASE II, SINGLE ARM STUDY OF CARBOPLATIN PLUS ETOPOSIDE WITH BEVACIZUMAB AND ATEZOLIZUMAB IN PATIENTS WITH EXTENDED-DISEASE SMALL-CELL LUNG CANCER (SCLC) – CELEBRATE TRIAL

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Abstract

Small cell lung cancer (SCLC) is an aggressive type of neuroendocrine tumor with the majority of patients being diagnosed at extended disease SCLC (ES-SCLC) stage. The new standard of treatment for patients with ES-SCLC is a combination of chemotherapy (either cisplatin or carboplatin and etoposide) and atezolizumab or durvalumab, two programmed cell death ligand 1 (PD-L1) inhibitory monoclonal antibodies (mAb). However, the benefit derived from the addition of PD-L1 inhibitors to chemotherapy in ES-SCLC was limited and restricted to a subset of patients. The vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor implicated in cancer angiogenesis, which is abundant in SCLC and associated with poor prognosis. Antiangiogenic agents, such as bevacizumab, a humanized mAb against VEGF, added to platinum-etoposide chemotherapy improved progression-free survival in SCLC in two trials, but it did not translate into a benefit in overall survival. Nevertheless, VEGF has been recently shown to act as a mediator of an immunosuppressive microenvironment and its inhibition can revert the immune - suppressive tumor microenvironment and potentially enhance the efficacy of immunotherapies. Based on available preclinical data, we hypothesized that VEGF inhibition by bevacizumab could improve atezolizumab efficacy in a synergistic way and designed a phase II single-arm trial of bevacizumab in combination with carboplatin, etoposide, and atezolizumab as first-line treatment in ES-SCLC to test this hypothesis. The trial, which is still ongoing, enrolled 53 patients, including those with treated or untreated asymptomatic brain metastases (provided criteria are met), who received atezolizumab, bevacizumab, carboplatin and etoposide for 4-6 cycles (induction phase), followed by maintenance with atezolizumab and bevacizumab for a maximum of 18 total cycles or until disease progression, patient refusal, unacceptable toxicity. The evaluation of efficacy of the experimental combination in terms of 1-year overall survival rate is not yet mature (primary objective of the trial). The combination was feasible and the toxicity profile manageable (secondary objective of the trial).

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Background

Introduction to small-cell lung cancer

Neuroendocrine tumors arise from the enterochromaffin-like cells scattered throughout the body, the most commonly originating from the lung, pancreas, and gastrointestinal tract. Small-cell lung cancer (SCLC) is the most common type of neuroendocrine lung tumor and the most common among all neuroendocrine tumors.[1] Worldwide, 250,000 new cases and at least 200,000 deaths attributable to SCLC each year are estimated, mostly in patients with a heavy smoking history (≥30 pack-years).[2] Indeed, less that 2% of SCLC are diagnosed in never-smokers, even though this proportion is as high as 20% in the Asiatic population.[3] Despite inherited genetic factors have been thought to have a minor role in susceptibility to develop SCLC, some studies report a higher prevalence of germline mutations in DNA damage response genes (DDR) in non-smoker patients with SCLC, as well as pollution or radon exposure.[4,5] Nevertheless, because SCLC is a highly smoke-related tumor, its incidence has been decreasing over the last decades, with a more marked decline in men than in women, as it tracked with tobacco use trends, according to data from the Surveillance, Epidemiology, and End Results (SEER) database (**Figure 1A**).[1] Current estimates report that SCLC accounts for 13-15% of all lung cancers (**Figure 1B**). [6–8]

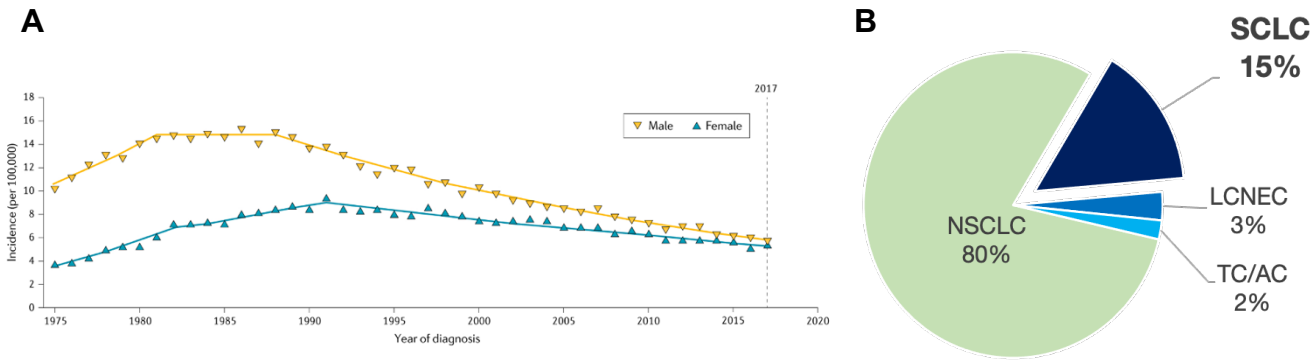

Figure 1. (**A**) Age-adjusted incidence of SCLC by sex in the USA between 1975 and 2017 according to data in the Surveillance, Epidemiology, and End Results (SEER) database (from: Rudin et al., *Nat Rev Dis Primers* 2021)[1]. (**B**) Relative incidence of lung tumors. Neuroendocrine tumors are represented in shades of blue. SCLC: small-cell lung cancer; LCNEC: large-cell neuroendocrine carcinoma; TC/AC: typical/atypical carcinoid; NSCLC: non-small cell lung cancer.

SCLC is clinically characterized by an aggressive behavior, due to its high growth fraction and early development of metastases[9,10], therefore up to 70% of patients is diagnosed with SCLC at advanced stage of disease, also referred to as extensive-stage (ES-SCLC) according to the Veterans Administration Lung Study Group (VALG) classification, and has a dismal prognosis, with a survival rate at 5 years of <5%.[11]

Treatment of ES-SCLC – from chemotherapy to chemo-immunotherapy

Since 1980s, the standard treatment of patients with ES-SCLC has been a combination chemotherapy of a platinum salt (either cisplatin or carboplatin) and etoposide (PE).[12–14] Radiological objective responses to PE chemotherapy occur in a high percentage of cases (50-70%), but are short in duration.[15,16] As SCLC invariably recur, prognosis is dismal, with a median survival of 9-11 months.

The advances in the insight in the cancer-immune system interplay have shed light on the paramount role of immune response in cancer biology and have brought into the clinic a new immunotherapy strategy, i.e., the inhibition of negative regulators of T-cell activation, the so-called "immune-checkpoints".[17] Inhibitory monoclonal antibodies, referred to as immune checkpoints inhibitors (ICIs), which target the programmed cell death protein-1 (PD-1) - programmed death-ligand-1 (PD-L1) axis improved survival outcomes in many cancer types by restoring the T-cell immune response against tumor cells.[17,18] Molecular biomarkers, such as PD-L1 expression on tumor cells and tumor mutation burden (TMB), may help identify subgroup of patients with different cancer types which are more likely to benefit from ICIs, although these are "imperfect" biomarkers as also tumors with no PD-L1 expression or low TMB might respond to treatment, and vice versa.[19–24] Despite SCLC has overall high TMB and genomic instability, which track with a high rate of tumor-associated antigens (TAAs) and thus to an increased probability to respond to immunotherapy,[25–27] ICIs as single-agent or in combination provided no benefit or limited benefit in a small proportion of

patients with SCLC[28,29], who can't be identified due to a lack of predictive biomarkers.[30,31] Nevertheless, an international multicenter retrospective study showed that the development of immune-related adverse events (irAEs) was associated with improved clinical outcomes to ICIs in patients with ES-SCLC.[32] Recently, the addition of PD-L1 inhibition to chemotherapy improved survival outcomes in ES-SCLC as shown by two phase III clinical trials, the IMpower133 and the CASPIAN trial of atezolizumab and durvalumab, respectively.[33–36] Atezolizumab is a fully humanized G1 immunoglobulin directed against PD-L1 which prevents its interaction with PD-1 expressed predominantly on T cells, thereby leading to activation of tumor-specific T-cell responses.[37] The randomized placebo-controlled phase III IMpower133 trial investigated the efficacy of atezolizumab in association with carboplatin and etoposide in patients with untreated ES-SCLC.[33] The co-primary endpoints of the study were overall survival (OS) and progression-free survival (PFS) and were both met as the median OS was 12.3 months vs. 10.3 months, whereas the median PFS was 5.2 months vs. 4.3 months in the atezolizumab and in the placebo arm, respectively. The 12-month OS rate was 51.7% in the atezolizumab arm and 38.2% in the placebo arm. Update survival data confirmed these findings and showed that atezolizumab improved survival irrespective TMB or PD-L1 expression.[34] In the randomized controlled phase III CASPIAN trial, durvalumab, a fully-human anti-PD-L1 monoclonal antibody, with PE improved OS, the primary endpoint, compared to PE alone in treatment-naïve ES-SCLC patients (12.9 vs. 10.5 months, respectively, according to the most recent update).[35] The addition of PD-L1 inhibition with either atezolizumab or durvalumab to PE was safe, with a manageable toxicity profile consistent with what previously reported, and did not negatively affect patients' quality of life.[38,39] A recent meta-analysis including also two more trials of the combination of PD-1 inhibitors and PE[40,41] confirmed that the addition of PD-1/PD-L1 inhibitors to chemotherapy improves all activity and efficacy outcomes in patients with ES-SCLC compared to PE alone, with a manageable safety profile.[42] Also, the OS benefit was also more marked when considering long-term analysis, compared to the median estimations. This data led to the approval of

PE combined with a PD-L1 inhibitor, either atezolizumab or durvalumab, as the new standard first-line treatment for patients with ES-SCLC.

Angiogenesis inhibition in the treatment of patients with ES-SCLC

Angiogenesis is one of the hallmarks of cancer, as it sustains tumor growth and facilitates metastatic spread of tumor.[43] One of the key factors in the angiogenesis process is the vascular endothelial growth factor (VEGF), that binds the VEGF receptor (VEGFR) on endothelial cells, which are stimulated to form new vessels.

SCLC is a highly vascularized tumor as angiogenesis is crucial to foster its high growth rate and invasiveness. Furthermore, a high microvessel count and the over-expression of VEGF in the tumor are associated with a poorer prognosis in patients with SCLC.[44] Bevacizumab is a recombinant humanized G1 immunoglobulin directed against VEGF-A, which prevents its interaction with the VEGFR, thus inhibiting VEGF-mediated neo-angiogenesis.[45] Safety and activity of bevacizumab in combination with chemotherapy in ES-SCLC have been investigated in two phase II randomized clinical trials.[46,47] The American randomized phase II SALUTE trial evaluated safety and activity of adding bevacizumab to PE as first-line treatment of patients with ES-SCLC.[46] In this study, the addition of bevacizumab to chemotherapy showed an acceptable safety profile with a significant improvement in PFS, the primary endpoint of the study: 5.5 months in the combination arm compared to 4.4 months in the control arm. However, no improvement in OS was observed. In the phase III FARM6PMFJM trial, performed by our GOIRC Group, the combination of PE with bevacizumab in patients with ES-SCLC improved PFS as compared to chemotherapy alone (6.7 months vs 5.7 months, respectively), with a manageable safety profile.[47] However, the PFS improvement did not translate into an improvement in OS, which was the primary endpoint of the study.

Angiogenesis and anti-tumor immune response – rationale for the CeLEBrATE trial

The role of VEGF is not limited to stimulation of angiogenesis alone as there is a complex relationship between angiogenesis itself and the immune system.[48,49] Indeed, VEGF has pleiotropic effects on endothelial cells, dendritic cells, CD8+ effector T cells, tumor associated macrophages and Treg cells in an immune-suppressive and tumor-promoting way (**Figure 2**).[48] As a consequence, angiogenic stimuli lead to decreased anti-tumor immune response through the promotion of an immunosuppressive tumor microenvironment, as opposed to angiogenesis inhibition that facilitates anti-tumor immune response, and could thus enhance immunotherapy T-cell-mediated cancer cell killing, and translate into synergic antitumor activity with ICIs, as shown in some preclinical models.[50,51]

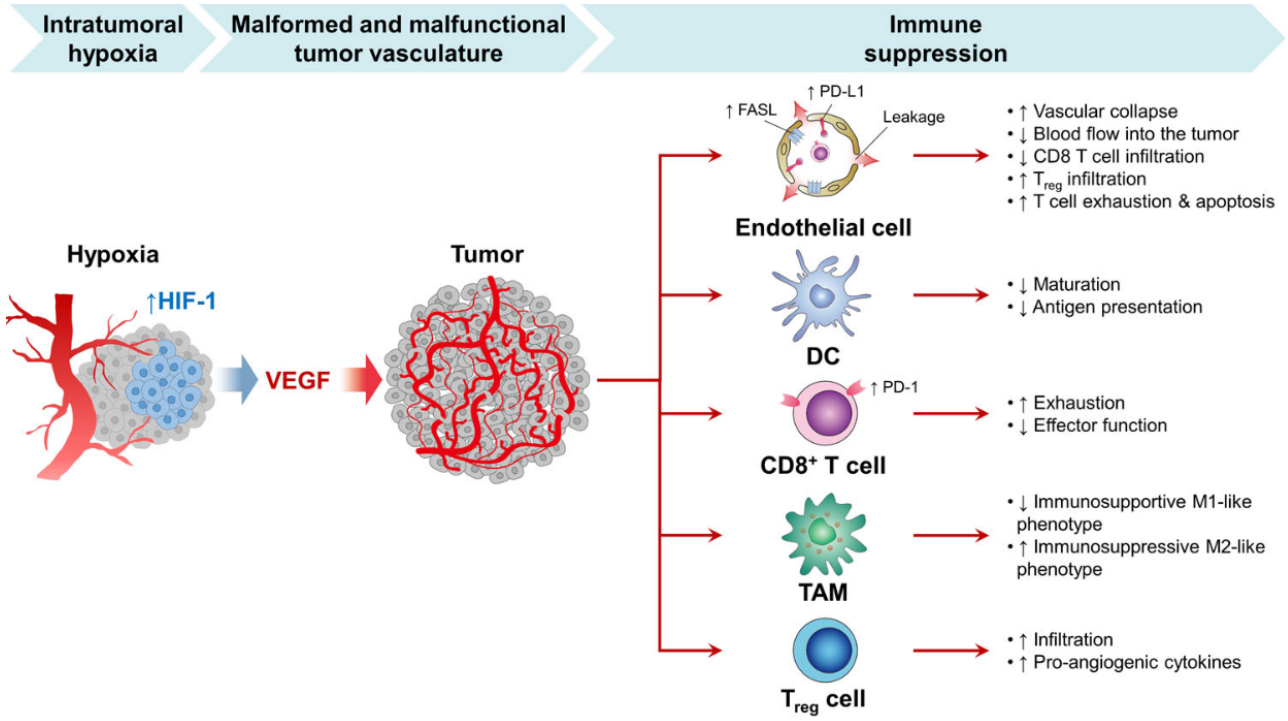

Figure 2. Schematic representation of the effects of factors implicated in angiogenesis on immune system. VEGF, a key factor in this process, exerts its pleiotropic immune suppressive effects on different cells, including endothelial cells, DCs, CD8+ cells, TAMs and Treg cells (from: Lee W. et al., *Exp Mol Med* 2020).[48]
HIF-1: hypoxia-induced factor-1; VEGF: vascular endothelial growth factor; PD-L1: programmed-death ligand 1; FASL: FAS

As a combination of VEGF and PD-L1 inhibition synergistically improved outcomes compared to either inhibition alone in an autochthonous mouse model of SCLC, such combination could be an appealing strategy in patients with SCLC as well.[51] Furthermore, the contemporary delivery of chemotherapy can cause release of TAAs which can further boost anti-tumor immune

response.[52] A combination of platinum-based chemotherapy with atezolizumab and bevacizumab was investigated in the phase III IMpower 150 trial in the first-line treatment of patients with non-small cell lung cancer (NSCLC), and has been shown to be feasible in terms of toxicity, with a safety profile consistent with those of the individual drugs.[53,54] A phase II trial of anlotinib, a multi-targeted tyrosine kinase inhibitor with anti-angiogenesis activity, plus durvalumab and PE in first-line treatment of ES-SCLC is also currently ongoing (NCT04660097).

We thus hypothesized that the addition of bevacizumab to PE and atezolizumab could improve outcome in untreated patients with ES-SCLC by increasing the proportion of patients that benefit from treatment thanks to synergy among its components (**Figure 3)**, and designed the a phase II, single arm study of CarbopLatin plus Etoposide with Bevacizumab and Atezolizumab in patients with exTEnded-disease small-cell lung cancer (SCLC) – the CeLEBrATE trial (Eudract Number: 019-003798-25) to evaluate the efficacy and safety of this strategy.[55]

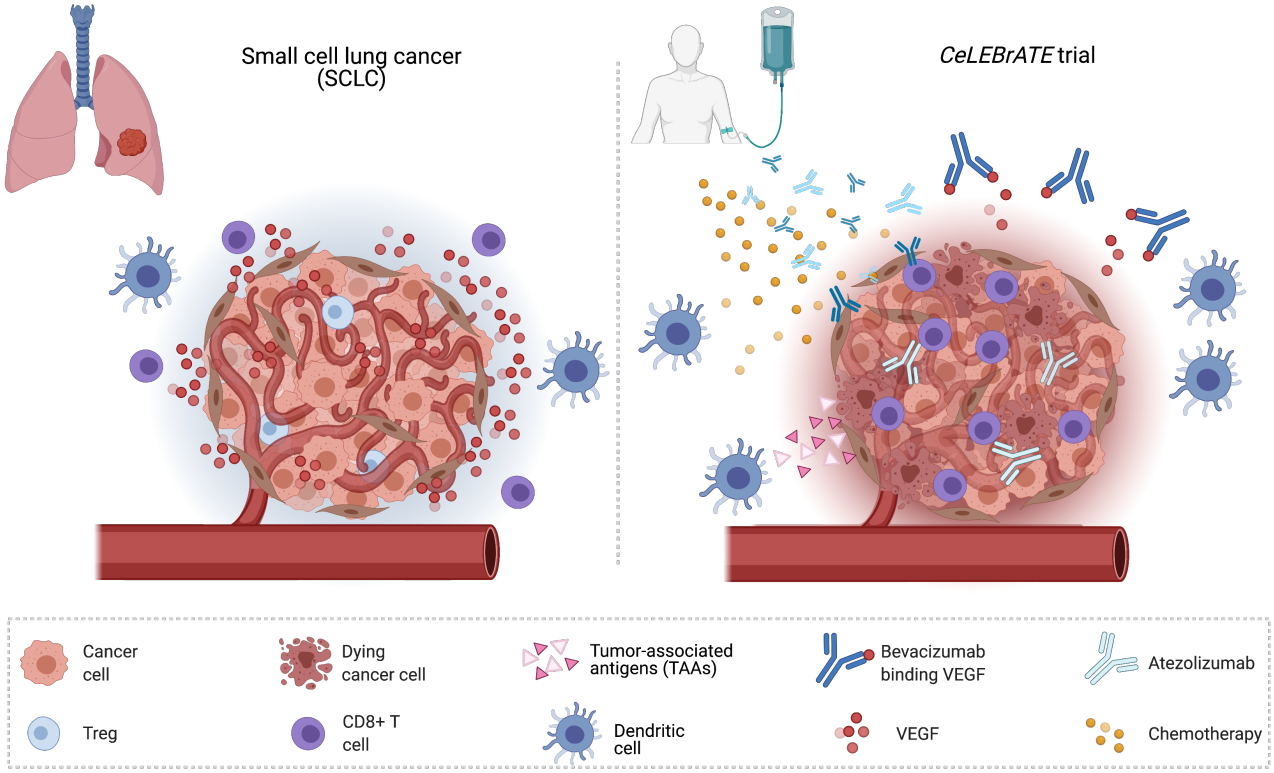

Figure 3. Rationale behind the CeLEBrATE study. In the left panel, VEGF promotes angiogenesis, that fosters tumor growth, and induces an immune-suppressive microenvironment that prevents immune cells infiltration, except for Treg cells. On the right panel, the hypothesized synergistic effect of drugs combined in the CeLEBrATE trial: chemotherapy kills cancer cells and causes release of TAAs, which are recognized by DCs that activate CD8+ T cells. T cells exhaustion and tolerance is overcome through PD-L1 inhibition by atezolizumab. Bevacizumab sequestrate VEGF from the tumor microenvironment which facilitates immune infiltration and cancer cell killing by CD8+ T cells. From: Andrini E. et al., *Future Oncol* 2022.[55]

Materials and methods

Study design

The CeLEBrATE study is an open-label, multicenter, phase II trial designed to assess the efficacy and safety of the combination of carboplatin, etoposide, atezolizumab, and bevacizumab in treatment-naïve patients with ES-SCLC. Patients enrolled from 15 Italian centers received carboplatin (AUC 5 on day 1), etoposide (100 mg/sqm on days 1-3), bevacizumab (7.5 mg/kg on day 1) and atezolizumab (1200 mg on day 1) administered every three weeks for 4-6 courses (induction phase), followed by bevacizumab and atezolizumab every 3 weeks (maintenance phase) for a maximum of 18 total cycles or until disease progression, unacceptable toxicity, patient refusal or loss of clinical benefit (for atezolizumab) (**Figure 4**). Treatment with atezolizumab beyond radiological disease progression (PD) as defined by response evaluation criteria in solid tumors (RECIST) version 1.1,[56] was allowed, provided that the patient was still deriving clinical benefit as assessed by local investigator (i.e. absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression), good tolerance of study drug, and stable performance status.

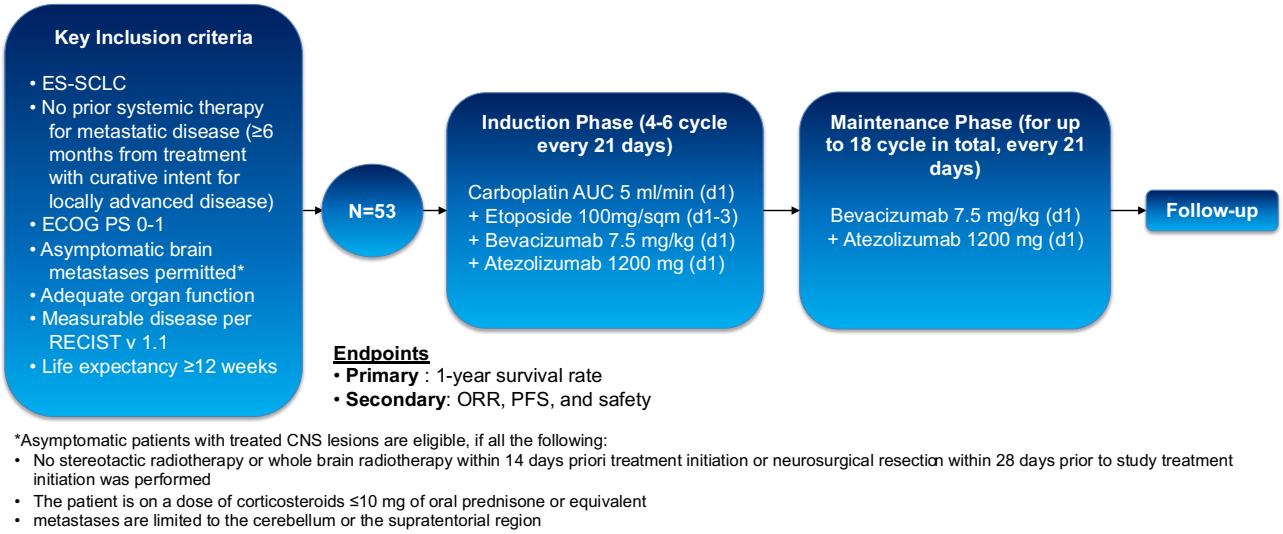

Figure 4. Study design of the CeLEBrATE trial. From: Andrini E. et al., *Future Oncol* 2022.[55]
ES-SCLC: extensive stage small-cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; RECIST: response criteria in solid tumor; AUC: area under the curve; ORR: objective response rate; PFS: progression-free survival; CNS: central nervous system.

Key eligibility criteria

Eligible patients had to be ≥18 years old and have histologically or cytological documented ES-SCLC, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, have an estimated life expectancy >12 weeks and not received prior anti-cancer treatment. Patients were excluded if they had grade ≥ 3 gastrointestinal bleeding or a history of significant thromboembolism (e.g. deep vein thrombosis or pulmonary embolism) within 3 months prior to therapy start, experienced hemoptysis within 2 months prior to first dose of therapy, radiographic evidence of intratumor cavitation, uncontrolled hypertension, risk factors for gastrointestinal perforation, evidence of bleeding diathesis or coagulopathy, active autoimmune disease, symptomatic brain metastases or spinal cord compression requiring immediate radiotherapy for palliation. Notably, patients with asymptomatic treated or untreated brain metastases were eligible if radiotherapy (either stereotactic or whole brain) or neurosurgical resection had been performed at least 14 or 28 days prior to study treatment initiation, respectively, and there had been no evidence of interval progression in the brain between the end of radiotherapy or surgery and treatment start, the patient were on a dose of corticosteroids ≤10 mg of oral prednisone or equivalent, and metastases were limited to the cerebellum or the supratentorial region.

Study objectives and endpoints

The primary objective of the study was to evaluate the efficacy of carboplatin, etoposide, atezolizumab, and bevacizumab as first-line treatment of patients with ES-SCLC. The primary endpoint was OS rate at 1 year, calculated from the date of enrolment to the date of death, by any cause.

The secondary objectives of the study included evaluation of activity and safety of the studied regimen. The secondary endpoints were overall response rate (ORR), defined as the sum of complete

responses (CR) + partial responses (PR) and evaluated according to RECIST v1.1; PFS, defined as the interval between the date of enrolment and the date of progression or death; and safety, evaluated through the monitoring of all non-serious adverse events (AEs) and serious AEs (SAEs), defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Study assessments

Objective tumor response was assessed by the investigator using RECIST criteria v1.1. Tumor response assessments were performed at screening (within 28 days before starting treatment) and every 9 weeks for 54 weeks following day 1 of first cycle, and then every 12 weeks until PD. Among patients who continued atezolizumab beyond radiological PD, a radiologic reassessment had to be performed within 9 weeks of initial investigator-assessed progression and further progression was defined as an additional 10% increase (in the sum of diameters of all target lesions and/or the development of new measurable lesions) from time of initial PD. In case of confirmed PD, atezolizumab was permanently discontinued. All AEs were graded according to CTCAE version 5.0 and were reported if occurring during the trial and until 30 days after the last dose of study treatment.

Statistical analysis

For the primary endpoint and all secondary endpoints, the modified intention to treat population (including all patients who have received at least one dose of study treatment, mITT) has been analyzed. Kaplan-Meier method were used to estimate PFS, OS and the 1-year cumulative probability of OS. The two-sided 90% confidence interval of the crude estimate and the hypothesis test were conducted according to Brookmeyer and Crowley. The hypothesis was that the study regimen was associated with a probability of 1-year OS equal to 70%. The null hypothesis that true 1-year probability of OS is <50% was tested against a one-sided alternative. This design yields a type

I error rate of 5% and power of 90% when the true 1-year probability of OS is > 70%. The overall complexity and costs of the trial justified the ambitious endpoint and the statistical design; positive results were considered achievable also based on the strict selection of eligible patients. Toxicity descriptive tables were generated, providing the worst degree of toxicity registered during all cycles of study treatment, according to CTCAE version 5.0.

Ethical considerations

The study has been conducted according to the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP). The Local Ethics Committees of all participating sites approved the study protocol. All patients provided written informed consent before study enrollment.

Results

Patient characteristics

Between 24/08/2020 and 21/03/2022, 66 patients were screened across 15 centers in Italy, and 53 were eligible and received at least one dose of study treatment (**Figure 5**).

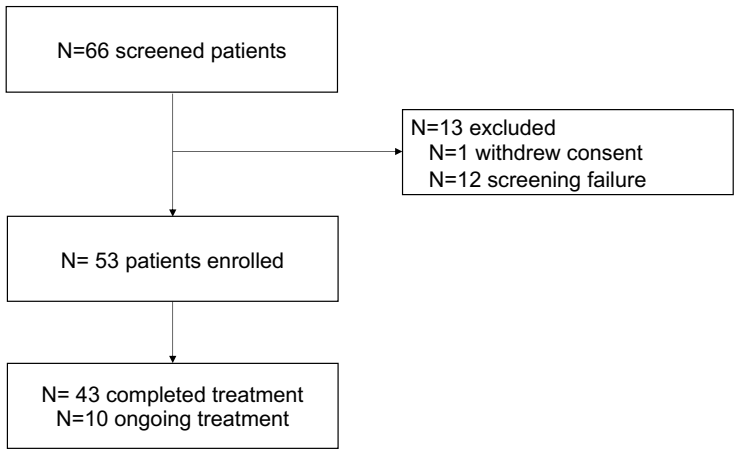

Figure 5. CONSORT diagram.

Among the enrolled patients, 24 (45.3%) were women, median age was 65 years (range: 46-79), 24 (47.1%) were smokers, 26 (51.0%) former smokers and 1 (1.9%) never smoker, 31 patients (58.5%) had an ECOG PS of 0 and 22 (41.5%) an ECOG PS of 1. Patient characteristics are summarized in **Table 1**.

Outcomes

At the 30/09/2022 data cutoff, at a median follow-up time of 10.0 months (95%CI: 6.8-13.6), 20 patients died (37.7%), while 33 were still alive; the study was still ongoing, thus survival data were still immature and primary endpoint weren't evaluated. During treatment, 37 patients had PD, 6 died without radiological evidence of PD, while treatment was still ongoing in 10 patients.

Table 1. Patient characteristics.

Variable		N	(%)
Total		53	(100%)
Sex	Male	29	(54.7%)
	Female	24	(45.3%)
Age	Median (range)	65	(46-79)
Smoking status	Current smoker	24	(47.1%)
	Former smoker	26	(51.0%)
	Never smoker	1	(1.9%)
	Unknown	2	
ECOG PS	0	31	(58.5%)
	1	22	(41.5%)
T stage	T1	5	(9.4%)
	T2	6	(11.3%)
	T3	10	(18.9%)
	T4	28	(52.8%)
	Tx	4	(7.6%)
N stage	N1	4	(7.6%)
	N2	17	(32.1%)
	N3	25	(47.2%)
	Nx	7	(13.2%)
M stage	M0	6	(11.3%)
	M1	47	(88.7%)
Metastatic sites	Liver	14	(26.4%)
	Bone	11	(20.8%)
	Brain	10	(18.9%)
	Adrenal gland	7	(13.2%)
Sum of longest diameters	Median (range)	119.5 mm	(17-240)

Among 44 patients with available data, best radiological response was PR in 32 patients, SD in 4, PD in 4, while 4 patients were not evaluated and considered treatment failures, accounting for an ORR of 72.7% (N=32/44, 95%CI: 57.2-85.0).

Treatment exposure

Treatment exposure data was available in 44 patients and is summarized in **Table 2**. During the induction phase, 220 courses were administered in total, and a median of 4 cycles (interquartile range [IQR]: 4-4.5) per patient. Thirty-seven patients (84.1%) received at least 4 cycles during the induction phase and received at least 1 cycle of maintenance with atezolizumab and bevacizumab. A total of 245 cycles and a median of 5 courses (IQR: 3-7) per patient have been administered during the maintenance phase. Considering the overall study treatment, 465 courses have been delivered in total and a median of 9 therapy cycles (IQR: 7-11) per patient until the data cutoff date. Study therapy was discontinued in 43 patients because of radiological PD (N=33), death without radiological progression (N=6), patient refusal (N=1), or other reasons (N=3).

Table 2. Treatment exposure by induction phase, maintenance phase, and in total. IQR: interquartile range; PD: progressive disease.

		N	(%)
Patients with available data		44	(83.0%)
Induction			
	Total courses	220	
	Median (IQR)	4	(4-4.5)
	≥4 courses	43	(84.1%)
Maintenance			
	Total courses	245	
	Median (IQR)	5	(3-7)
Total			
	Total courses	465	
	Median (IQR)	9	(7-11)
Treatment discontinuation		43	(97.7%)
	Radiological PD	33	(76.7%)
	Death without radiological PD	6	(14.0%)
	Patient refusal	1	(2.3%)
	Other	3	(7.0%)

Safety

Safety data wes available in 51 patients who received a total of 224 courses during the induction phase and in 43 patients who received a total of 251 cycles during the maintenance phase. The most commonly reported AEs irrespective of grade during the induction phase were neutropenia (70.6%), anemia (43.1%), fatigue (43.1%), leucopenia (29.4%), and nausea (27.5%), while the most frequently reported grade 3-5 AE was neutropenia (54.9%) followed by febrile neutropenia (7.8%), anemia (7.8%), and thrombocytopenia (5.9%) (**Table 3**).

Table 3. Adverse events reported during the induction phase in the N=51 patients with available safety data.

Adverse event	Any grade	(%)	Grade 1-2	(%)	Grade 3-5	(%)
Anemia	22	(43.1%)	18	(35.3%)	4	(7.8%)
Leucopenia	15	(29.4%)	12	(23.5%)	3	(5.9%)
Neutropenia	36	(70.6%)	8	(15.7%)	28	(54.9%)
Thrombocytopenia	9	(17.7%)	6	(11.8%)	3	(5.9%)
Nausea	14	(27.5%)	14	(27.5%)	0	(0%)
Vomiting	6	(11.8%)	6	(11.8%)	0	(0%)
Diarrhea	8	(15.7%)	8	(15.7%)	0	(0%)
Mucositis	7	(13.7%)	7	(13.7%)	0	(0%)
Fatigue	22	(43.1%)	20	(39.2%)	2	(3.9%)
Arthralgia	1	(1.9%)	1	(1.9%)	0	(0%)
Fever without neutropenia	6	(11.8%)	5	(9.8%)	1	(1.9%)
Febrile neutropenia	4	(7.8%)	0	(0%)	4	(7.8%)
Pulmonary toxicity	1	(1.9%)	1	(1.9%)	0	(0%)
Skin toxicity	5	(9.8%)	5	(9.8%)	0	(0%)
Hypothyroidism	2	(3.9%)	2	(3.9%)	0	(0%)
Hyperthyroidism	6	(11.8%)	6	(11.8%)	0	(0%)
Other endocrine disorders	1	(1.9%)	1	(1.9%)	0	(0%)
Hepatic toxicity	4	(7.8%)	4	(7.8%)	0	(0%)
Renal toxicity	4	(7.8%)	3	(5.9%)	1	(1.9%)

During the maintenance phase, the most commonly reported AEs irrespective of grade were fatigue (32.5%), anemia (23.3%), nausea (20.9%), arthralgia (11.6%), and hypothyroidism (11.6%), while leucopenia (4.7%) was the most commonly reported grade 3-5 AE (**Table 4**). As expected, hematological AEs were more common in the induction phase in which chemotherapy was administered, while immune-related AEs were more evenly distributed between the two phases, with a slight predominance during the maintenance phase. No patient discontinued treatment due to toxicity. SAEs were reported in 26 cases irrespective of causality, of which 16 are under investigation for potential correlation with study treatment. Of these, 4 resulted in patient death: N=2 cases of febrile neutropenia, N=1 case of pancreatitis, and N=1 case of internal bleeding. Among the AE of special interest (AESI), two non-fatal cases of thromboembolism have been reported which might be correlated to bevacizumab treatment.

Table 4. Adverse events reported during the maintenance phase in the N=43 patients with available safety data.

Adverse event	Any grade	(%)	Grade 1-2	(%)	Grade 3-5	(%)
Anemia	10	(23.3%)	10	(23.3%)	0	(0%)
Leucopenia	3	(7.0%)	1	(2.3%)	2	(4.7%)
Neutropenia	3	(7.0%)	2	(4.7%)	1	(2.3%)
Nausea	9	(20.9%)	9	(20.9%)	0	(0%)
Vomiting	3	(7.0%)	3	(7.0%)	0	(0%)
Diarrhea	4	(9.3%)	3	(7.0%)	1	(2.3%)
Mucositis	1	(2.3%)	1	(2.3%)	0	(0%)
Fatigue	14	(32.5%)	13	(30.2%)	1	(2.3%)
Arthralgia	5	(11.6%)	5	(11.6%)	0	(0%)
Fever without neutropenia	4	(9.3%)	4	(9.3%)	0	(0%)
Pulmonary toxicity	3	(7.0%)	2	(4.7%)	1	(2.3%)
Skin toxicity	2	(4.7%)	2	(4.7%)	0	(0%)
Hypothyroidism	5	(11.6%)	5	(11.6%)	0	(0%)
Hyperthyroidism	2	(4.7%)	2	(4.7%)	0	(0%)
Hepatic toxicity	1	(2.3%)	1	(2.3%)	0	(0%)
Pancreatic toxicity	1	(2.3%)	0	(0%)	1	(2.3%)
Renal toxicity	2	(4.7%)	1	(2.3%)	1	(2.3%)

Discussion

The phase II CeLEBrATE study was designed to evaluate the efficacy and safety of the combination of carboplatin, etoposide, bevacizumab, and atezolizumab in patients with treatment-naïve ES-SCLC. The enrollment was completed but the study is still ongoing as 10 patients are still on treatment, which is promising and might hopefully anticipate a positive result in respect to the primary outcome. Results from this trial will inform whether the addition of bevacizumab can increase efficacy of PE and atezolizumab and is thus worth a phase III trial to establish its effectiveness as first-line treatment of ES-SCLC. Based on preliminary data, this combination appears to be feasible, as there were no additive toxicity or new safety signals.

Because of the dismal prognosis and the lack of available therapeutic options, new effective treatments for SCLC are an acknowledged unmet need. The IMpower133 and the CASPIAN trial of atezolizumab and durvalumab, respectively, added to PE set the new first-line treatment standard in patients with ES-SCLC and marked the first improvement in this setting in almost 40 years.[33,35] Nevertheless, the benefit appears to be limited to a small subset of patients. To date, several trials have investigated the role of combining ICIs with other agents, such as DDR inhibitors (e.g., olaparib), in an attempt to expand the proportion of patients with ES-SCLC that respond to immunotherapy, but with limited results.[57,58] Despite most trials in SCLC have been performed in unselected patients, recent data suggested that SCLC is not a homogenous entity but that four molecular subtypes can be rather identified.[59,60] SCLC belonging to each of these molecular subgroups have distinct therapeutic vulnerabilities that could be exploited with specific agents. In particular, the “inflamed” subtype (SCLC-I), that accounts for 15-20% of SCLCs, could be the most sensitive to the addition of PD-L1 blockade to chemotherapy, although prospective data are lacking.[60] Nevertheless, the combination of drugs that positively affect tumor immune microenvironment, such as anti-angiogenic agents, might also expand the proportion of patients who benefit from chemoimmunotherapy beyond the SCLC-I subgroup. In fact, subgroups are defined by transcription

factor expression and group shifting during treatment have been observed. The rationale of the CeLEBrATE study was based on the growing evidence about the complex relationship between angiogenesis and immune system, also supported by pre-clinical evidence of synergistic activity of the combination of VEGF and PD-L1 in SCLC models.[51]. Also, our GOIRC group, as well as the American one, have previously shown that the addition of bevacizumab to PE is active and safe in ES-SCLC.[46,47] The combination of an antiangiogenetic agent with chemoimmunotherapy has not been explored in ES-SCLC patients yet, but a similar four-drug regimen with a platinum doublet chemotherapy, atezolizumab, and bevacizumab has been proved feasible in the IMpower 150 study, a phase III randomized clinical trial in patients with metastatic untreated NSCLC.[53] Preliminary data from the CeLEBrATE trial seems to confirm the safety of carboplatin, etoposide, atezolizumab, and bevacizumab also in patients with SCLC, but survival data are still immature to evaluate efficacy, the primary endpoint.

Novel therapeutic strategies are urgently needed to improve outcomes of patients with ES-SCLC. The combination of carboplatin, etoposide, atezolizumab, and bevacizumab appears to be safe, and the proportion of patients still on treatment is a positive signal that could possibly translate into a positive survival outcome. Primary endpoint data will be available during the first half of 2023.

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