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Carboplatin, etoposide, atezolizumab, and bevacizumab in the first-line treatment of patients with extensive stage small-cell lung cancer: the GOIRC-01-2019 CeLEBrATE study

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ABSTRACT

Background The addition of a programmed death-ligand 1 (PD-L1) inhibitor, either atezolizumab or durvalumab, to platinum-etoposide prolonged survival in a limited subset of patients with extensive-stage small-cell lung cancer (ES-SCLC). Preclinical studies demonstrated synergistic antitumor activity of combined vascular endothelial growth factor receptor and PD-L1 inhibition in SCLC. Since bevacizumab added to platinum-etoposide was safe and active in ES-SCLC, we investigated the efficacy of atezolizumab, bevacizumab, carboplatin, and etoposide as first-line treatment of ES-SCLC.

Methods The CeLEBrATE study is an Italian multicentric single-arm phase II trial of carboplatin (area under the curve 5 ml/min), etoposide (100 mg/sqm), bevacizumab (7.5 mg/kg), and atezolizumab (1,200 mg) every 3 weeks (q3w) for four to six courses, followed by bevacizumab and atezolizumab maintenance q3w in patients with ES-SCLC and no contraindications to immunotherapy or antiangiogenic therapy. Patients with asymptomatic brain metastases were eligible. Prophylactic cranial irradiation and consolidation thoracic external radiotherapy were not permitted while on study treatment. Primary endpoint was overall survival (OS) rate at 1 year.

Results 53 patients were enrolled (45.3% women, median age 65 years) and received at least one dose of study treatment. At a median follow-up time of 23.4 months (95% CI: 21.1 to 26.0), the 1-year OS rate was 61.8% (90% CI: 50.7% to 72.8%; p=0.04), with a median OS of 12.9 months (95% CI: 11.6 to 17.5). Median progression-free survival was 6.2 months (95% CI: 5.4 to 6.6) and objective response rate was 83.3% (95% CI: 69.8% to 92.5%). Grade 3–4 adverse events were reported in 34 patients (64.2%) leading to dose reductions in 24 (45.3%), and dose delays in 39 (73.9%) and 32 (69.6%) during the induction and maintenance phase, respectively. 19 (35.8%) treatment-related serious adverse events were reported.

Conclusion The CeLEBrATE study met its primary objective demonstrating a signal of efficacy of bevacizumab, atezolizumab, carboplatin, and etoposide in the first-line treatment of patients with ES-SCLC.

Trial registration number GOIRC-01–2019 ML41241, Eudract Number: 2019-003798-2.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Addition of programmed death-ligand 1 (PD-L1) inhibition to platinum-etoposide chemotherapy extends survival in patients with extensive-stage small-cell lung cancer (ES-SCLC) in a limited subset of patients which we are not able to identify. Combined PD-L1 and vascular endothelial growth factor receptor (VEGF) inhibition have synergistic antitumor activity in mouse models of SCLC.

WHAT THIS STUDY ADDS

⇒ The CeLEBrATE study provides proof-of-concept data that combined VEGF inhibition with bevacizumab and PD-L1 inhibition with atezolizumab added to platinum-based chemotherapy may extend survival as first-line treatment of patients with ES-SCLC. This is the first study with this therapeutic strategy to enroll Western patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings demonstrate that combined VEGF and PD-L1 inhibition is a promising strategy to improve outcomes of patients with SCLC and that should be optimized also considering data from trials with other molecules in similar settings.

INTRODUCTION

Small-cell lung cancer (SCLC) is a poorly differentiated malignant epithelial tumor which is categorized as a high-grade

neuroendocrine carcinoma and represents approximately 13–15% of all lung cancers.[1 2] Being characterized by rapid proliferation, high vascularity, and early metastatic spread, it remains one of the most aggressive and lethal malignancies with a 5-year survival rate <7%. Only a small fraction of patients is amenable to potentially curative-intent multimodality therapy whereas the majority of patients with SCLC (about 60–70%) are diagnosed in extended-stage (ES-SCLC), defined as a disease that has spread beyond a single radiation port.[3 4]

In contrast with the dramatic therapeutic improvements achieved for patients with non-small cell lung cancer (NSCLC), the combination of platinum (either cisplatin or carboplatin) and etoposide has been the cornerstone of first-line treatment for patients with ES-SCLC for almost 40 years. Such combination yields an objective response rate in 50–70% of cases,[5 6] but the duration of response is limited, and the majority of patients progress within a few months, with a median overall survival (mOS) of 9–11 months.[7] As of today, no other chemotherapy strategy has surpassed platinum-etoposide performance. However, after decades without significant changes in the standard of care, in 2019 US Food and Drug Administration (FDA) approved the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab in combination with first-line platinum doublet chemotherapy for patients with extensive-stage disease.

Despite the substantial progress in the understanding of SCLC biology and tumor heterogeneity, there is a need for novel therapeutic strategies to improve disease outcome. The programmed cell death protein-1 (PD-1)/PD-L1 axis inhibition by immune checkpoint inhibitors (ICIs) improved survival in many cancer types, by restoring the T-cell immune response against tumor cells.[8 9] Because SCLC is almost always associated with the chemical mutagenic effects of tobacco exposure, it is characterized by high mutational burden and genomic instability, which are associated with the generation of tumor-associated antigens (TAAs), providing an increased response to ICIs in tumor types other than SCLC.[10–12] However, ICIs as single agents or in combination provided benefit only in a small proportion of patients with SCLC,[13 14] who we are still unable to identify due to a lack of predictive biomarkers of response in this setting.[15 16] Recently, the addition of PD-L1 inhibition to chemotherapy improved survival outcomes in ES-SCLC as shown by two phase III clinical trials.[17 18]

The phase III IMpower133 trial randomized patients with ES-SCLC in the first-line setting to receive a combination of carboplatin and etoposide plus atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo.[17] Atezolizumab is a humanized immunoglobulin monoclonal antibody directed against PD-L1, which prevents the interaction with PD-1, leading to activation of tumor-specific T-cell responses.[19] Co-primary endpoints of the IMpower133 study were OS and progression-free survival (PFS) and were both met as the mOS was 12.3 months compared with 10.3 months, whereas the median PFS (mPFS) was 5.2 months and 4.3 months in the atezolizumab arm and in the placebo arm, respectively.[17] In addition, both 1-year and 1.5-year survival rates were higher in patients who received atezolizumab compared with the placebo group. Updated survival data confirmed these findings and showed that atezolizumab improved survival regardless of tumor mutational burden or PD-L1 expression.[20 21]

In the phase III CASPIAN trial, durvalumab, a fully-human anti-PD-L1 monoclonal antibody, was combined with platinum-etoposide in treatment-naïve patients with ES-SCLC showing an improved OS, the primary endpoint of the study, compared with platinum-etoposide alone (12.9 vs 10.5 months, respectively).[18 22] The addition of PD-L1 inhibition with either atezolizumab or durvalumab to platinum-etoposide chemotherapy was safe, with a manageable toxicity profile consistent with what was previously reported, and did not negatively affect the patient's quality of life.[23 24] A meta-analysis including two additional trials confirmed that the addition of PD-1/PD-L1 inhibitors to chemotherapy improves all activity and efficacy outcomes, with a good safety profile.[25–27] The FDA approved the use of durvalumab for extensive-stage SCLC in the first-line setting shortly thereafter.

Interestingly, the approximately 2-month extension of median survival seen in these studies may seem modest; however, OS benefit is more evident when considering long-term analysis, compared with median estimations, especially looking at the tail of survival curves where it becomes evident that the addition of ICIs to platinum-based chemotherapy can lead to an approximate tripling of 3-year survival.[25]

Angiogenesis is a hallmark of cancer and plays a crucial role in sustaining the high growth rate and invasiveness typical of SCLC.[28] Furthermore, microvessel count and overexpression of vascular endothelial growth factor (VEGF) are associated with poor prognosis in SCLC.[29] Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF-A, which prevents its interaction with VEGF receptor (VEGFR), thus inhibiting VEGF-mediated neoangiogenesis.[30] Safety and activity of bevacizumab in combination with chemotherapy in ES-SCLC have been studied in several trials and in particular in two randomized ones.[31–33]

The first randomized phase II study assessing the addition of bevacizumab to platinum-based chemotherapy in previously untreated patients with ES-SCLC was the SALUTE trial.[31] The primary endpoint was the PFS, and patients were randomly assigned to receive bevacizumab or placebo plus chemotherapy. The results showed an improvement in PFS, which was 5.5 months in the combination arm compared with 4.4 months in the control arm. However, no improvement in OS was observed. These data were also confirmed in the phase III FARM6PMFJM trial, performed by our Group—Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)—a study comparing the combination of platinum-etoposide with bevacizumab to

chemotherapy alone (median PFS of 6.7 months vs 5.7 months, respectively).[32] However, the study did not reach its primary endpoint (OS).

Several studies reported a complex relationship between angiogenesis and the immune system.[34–36] Indeed, VEGF pathway activation leads to decreased antitumor response through inhibition of dendritic cells maturation and T cells activation, resulting in an immunosuppressive microenvironment.[34] This evidence suggests that the combination of ICIs with anti-angiogenic agents could increase T cell infiltration in the tumor microenvironment, enhance immunotherapy T cell-mediated cancer cell killing, and translate into synergistic antitumor activity.[37] Moreover, cancer cell killing by chemotherapy releases TAAs, which can further boost immune response.[38] The combination of platinum-based chemotherapy with atezolizumab and bevacizumab was investigated in the phase III trial IMpower150 in first-line treatment of patients with NSCLC, resulting feasible in terms of toxicity, with a safety profile consistent with those of the individual drugs.[39 40] Because combining PD-L1 and VEGF inhibition has a synergistic antitumor effect in SCLC models, we hypothesized that adding bevacizumab to atezolizumab, carboplatin and etoposide would improve survival in patients with ES-SCLC.

MATERIAL AND METHODS

Patients

As previously published,[41] eligible patients were adults with histologically or cytologically confirmed ES-SCLC, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST),[42] V.1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 and had not received previous systemic treatment for ES-SCLC. Patients with asymptomatic treated or untreated brain metastases were eligible if no stereotactic radiotherapy or whole brain radiotherapy within 14 days prior to study treatment initiation or neurosurgical resection within 28 days prior to study treatment initiation was performed, the patient was on a dose of corticosteroids ≤10 mg of oral prednisone or equivalent, and metastases were limited to the cerebellum or the supratentorial region.[41] Key exclusion criteria included grade ≥3 gastrointestinal bleeding or a history of significant thromboembolism (eg, deep vein thrombosis or pulmonary embolism) within 3 months prior to therapy start, 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.[41]

Trial design and interventions

The CeLEBrATE trial (GOIRC-01–2019 ML41241, Eudract Number: 2019-003798-25) is an investigator-initiated multicenter phase II single-arm trial sponsored by GOIRC and partially supported by Roche of bevacizumab, atezolizumab, carboplatin, and etoposide as first-line treatment of patients with ES-SCLC. Patients received carboplatin (area under the curve 5 ml/min day 1), etoposide (100 mg/sqm days 1–3), bevacizumab (7.5 mg/kg day 1), and atezolizumab (1,200 mg day 1) every 3 weeks for four to six courses (induction phase), followed by bevacizumab and atezolizumab every 3 weeks (maintenance phase) for up to 18 total cycles or until disease progression, unacceptable toxicity, patient refusal or loss of clinical benefit (for atezolizumab) (figure 1).[41] Treatment with atezolizumab beyond radiological progression as defined by RECIST V.1.1[42] was allowed, provided that

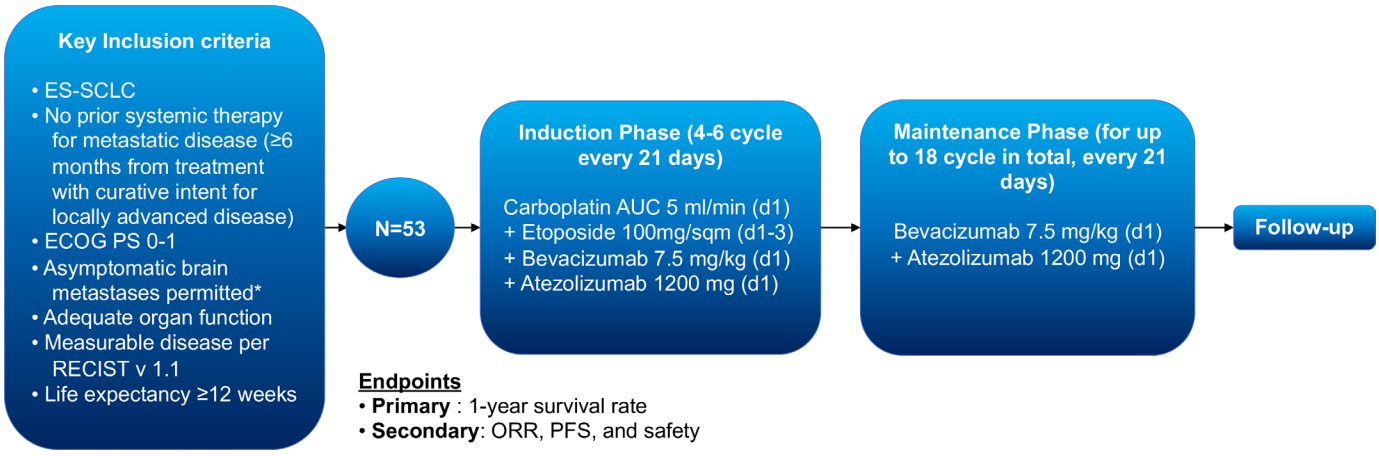

Figure 1 CeLEBrATE study flow chart. AUC, area under the curve; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. *Asymptomatic patients with treated CNS lesions are eligible, if all the following: No stereotactic radiotherapy or whole brain radiotherapy within 14 days priori treatment initiation or neurosurgical resection within 28 days prior to study treatment initiation was performed. The patient is on a dose of corticosteroids ≤10 mg of oral prednisone or equivalent. metastases are limited to the cerebellum or the supratentorial region.

the patient still had clinical benefit as assessed by the investigator (ie, absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression), good tolerance of study drug and stable performance status. Prophylactic cranial irradiation (PCI) and consolidation thoracic external radiotherapy were not allowed during the study treatment, as at the time of study design, there was little evidence regarding the safety of concomitant administration of ICIs and bevacizumab. In particular, PCI was not allowed in the experimental arm of the CASPIAN study, whereas it was permitted only during the maintenance phase in the IMPower133 study. Furthermore, a subsequent analysis from the IMPower133 reported a comparable rate of central-nervous system-related adverse events (AEs) in the 23 patients (11%) who received PCI in the atezolizumab arm compared with the 21 patients (10%) in the control arm.[43] Because in the included population the expected rate of febrile neutropenia was below 20%, primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was not permitted.[44] The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice.

Endpoints and assessments

The primary endpoint was OS rate at 1 year, calculated from the date of enrollment to the date of death, for any cause. The secondary endpoints are overall response rate (ORR), defined as the sum of complete responses+partial responses (PR) and evaluated according to RECIST V.1.1; PFS, defined as the interval between the date of enrollment and the date of progression or death; safety, evaluated through the monitoring of all serious and non-serious AEs (SAEs), defined and graded according to Common Terminology Criteria for Adverse Events V.5.0.[41]

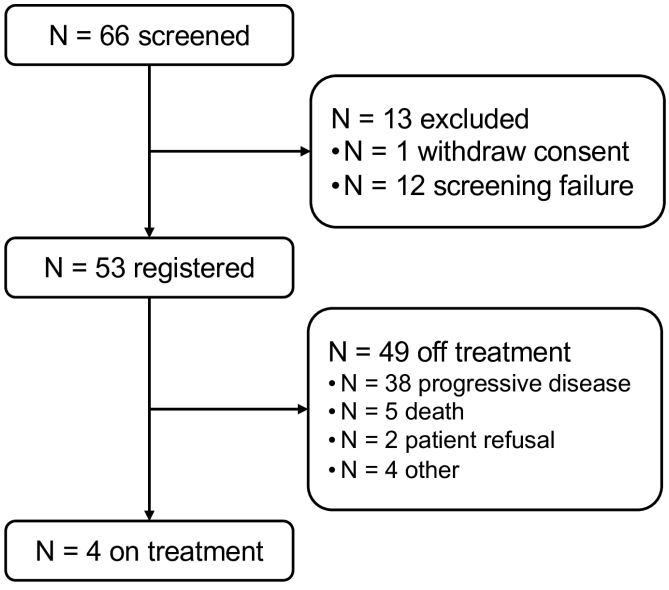

Figure 2 Consolidated Standards of Reporting Trials diagram of the study.

Tumor assessments were conducted at screening (within 28 days before starting treatment) and every 9 weeks for the first 54 weeks starting from day 1 of cycle 1, and every 12 weeks thereafter until the occurrence of disease progression (PD) according to RECIST. Among patients who continued atezolizumab beyond radiological disease progression, a radiologic reassessment has been 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 the time of initial PD.[41] In case of confirmed PD, atezolizumab was to be permanently discontinued. AEs were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, V.5.0. The investigators determined whether AEs were related to the trial regimen.

Statistical analysis

The primary endpoints were assessed in the modified intention-to-treat population (including all patients who have received at least one dose of study treatment). For the analysis of PFS, data for patients who were alive and had no disease progression were censored at the time of the last tumor assessment. For the analysis of OS, data for patients who were alive were censored at the time of the last contact. The Kaplan-Meier method was used to estimate PFS, OS and the 1-year cumulative probability of OS. The two-sided 90% CI of the crude estimate and the hypothesis test was conducted according to Brookmeyer and Crowley. The hypothesis is that the study regimen is associated with a probability of 1-year OS equal to 70%. The null hypothesis that the true 1-year probability of OS is <50% will be 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%.[41]

RESULTS

Patient characteristics

Between August 2020 and March 2022, among 66 ES-SCLC screened patients, 13 were excluded because of consent withdrawal (N=1) or screening failure (N=12) and 53 were finally registered in the study and started study treatment (figure 2). At the data cut-off date of December 31, 2023, four patients were still on treatment.

Of the 53 registered patients, 24 (45.3%) were women, median age was 65 years (range 46–79), 24 (45.3%) were active smokers, 26 (49.1% were former smokers, 1 never smoked (1.9%, table 1). ECOG PS was 1 in 22 patients (41.5%), while at treatment start there were brain metastases in 10 patients (18.9%), liver metastases in 13 (24.5%), and bone metastases in 12 (22.6%). The median sum of longest diameter of target lesions was 118 mm (range 17–240).

Table 1 Patient characteristics and treatment exposure

Patient characteristics	N=53	(%)
Sex		
Female	24	(45.3)
Male	29	(54.7)
Age		
Median (range)	65 years	(46–79)
Smoking status		
Active	24	(45.3)
Former	26	(49.1)
Never	1	(1.9)
Unknown	2	(3.8)
ECOG PS		
0	31	(58.5)
1	22	(41.5)
Metastatic sites		
Brain	10	(18.9)
Liver	13	(24.5)
Bone	12	(22.6)
Sum of longest diameter*		
Median (range)	118 mm	(17–240)
Induction		
Number of cycles, median (range)	4	(1–6)
<4 cycles	7	(13.2)
4 cycles	31	(58.5)
>4 cycles	15	(28.3)
Maintenance		
Started maintenance	46	(86.8)
Number of cycles, median (range)	5.5	(1–37)
Total cycles		
Median (range)	9	(1-41)
Treatment beyond PD	17	(32.1)
Number of cycles, median (range)	2	(1–10)

*The "sum of longest diameter" is the sum of the diameter of target lesions identified according to RECIST V.1.1 criteria at baseline.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary objective analysis

At a median follow-up time of 23.4 months (95% CI: 21.1 to 26.0), 41 patients had died (77.4%): 36 because of disease progression, 4 because of toxicity (n=2 septic shock during febrile neutropenia, n=1 pancytopenia, n=1 pancreatitis) and 1 for other reasons (n=1 massive bleeding). The primary objective of the study was met, the primary endpoint of 1-year OS rate being 61.8% (90% CI: 50.7% to 72.8%; p=0.04), with a median OS of 12.9 months (95% CI: 11.6 to 17.5; figure 3).

Secondary objectives analysis

PD was observed in 43 patients, while 7 had died without radiological evidence of disease progression, with a median PFS of 6.2 months (95% CI: 5.4 to 6.6, figure 4). Among the 48 response-assessable patients, PR was observed in 40 (ORR: 83.3% (95% CI: 69.8% to 92.5%)), stable disease in 4 cases, and PD as best response in 4 cases. Median duration of response was 4.2 months (95% CI: 4 to 5.8).

11 patients (20.8%) received atezolizumab beyond the RECIST-defined PD. Median number of atezolizumab courses received beyond PD was 2 (range: 1–24), for a median post-progression PFS of 1.8 months (95% CI: 1.0 to not estimable).

Safety

The safety population included 53 patients who received at least one dose of study treatment, of whom 46 patients (86.8%) received at least four induction courses (median 4, range 1–6), and the median number of maintenance cycles was 5.5 (range 1–37). 49 patients discontinued study treatment: 38 (71.7%) because of PD, 5 (9.4%) because of death without radiological progression (n=4 because of G5 toxicity and n=1 because of bleeding), 2 (3.8%) because of patient's refusal, and 4 (7.6%) for other reasons. Summary of AEs is reported in table 2. Overall, grade 3–4 AEs have been reported in 34 patients (64.2%). Grade 3–4 hematological AEs occurred in 30 patients (56.6%), the most common being neutropenia (n=28, 52.8%), followed by anemia (n=4, 7.6%), leukopenia, thrombocytopenia and febrile neutropenia (n=3, 5.7% each). Grade 3–4 non-hematological AEs have been reported in 10 patients (18.9%), the most common being hyponatremia (n=6, 11.3%) and arterial hypertension, thromboembolism, and fatigue (n=3 each, 5.7%). AEs related to the treatment with bevacizumab included arterial hypertension (G3-4 N=3, 5.7%), thromboembolism (G3-4 n=3, 5.7%), bleeding and proteinuria (G3-4 n=1 each, 1.9%).

Toxicity required dose reduction in 24 patients (45.3%) during the induction phase, while 39 (73.6%) and 32 (69.6%) delayed at least one treatment course of the induction and maintenance phase, respectively. No patient discontinued treatment because of toxicity.

Any-cause SAEs were reported in 31 patients (58.5%), 19 (35.8%) of which were related to study treatment. Among them, four grade 5 AEs occurred: two septic shocks during febrile neutropenia, one pancytopenia, and one pancreatitis.

DISCUSSION

The CeLEBrATE study suggests that VEGF inhibition, in this case with bevacizumab, may have a potential role in enhancing the efficacy of the standard carboplatin-etoposide-atezolizumab first-line treatment of patients with ES-SCLC, while maintaining a generally manageable safety profile.

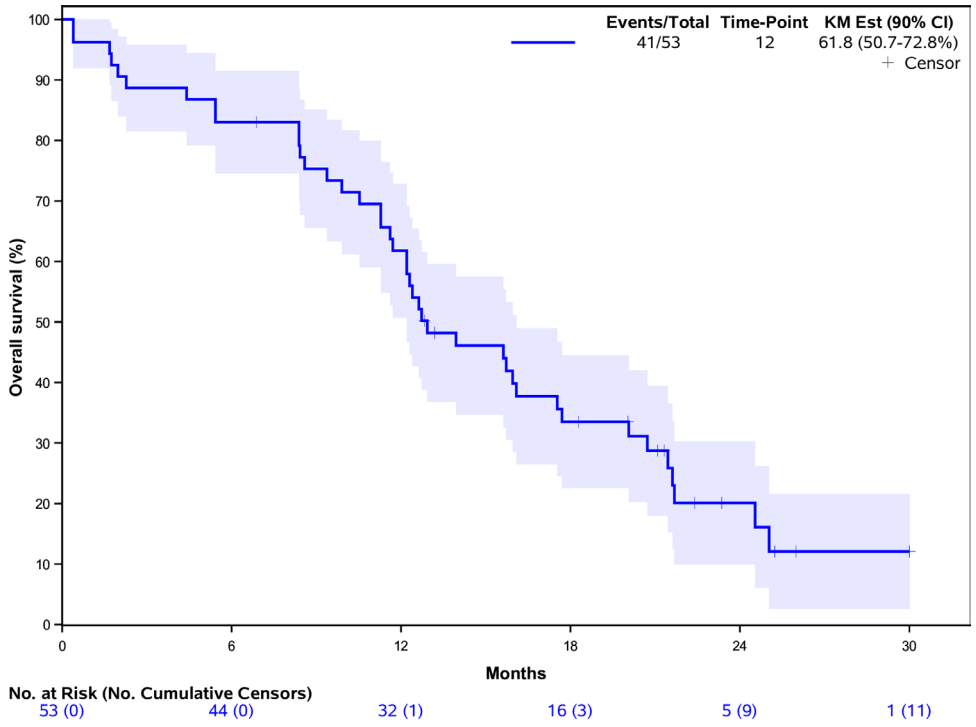

Figure 3 Kaplan-Meier estimates (KM Est) of overall survival.

Although the study is formally positive, the observed 1-year OS of 61.8% was lower than the hypothesized level of efficacy (1-year OS 70%). The expected survival improvement with the experimental treatment was probably too ambitious but justified by the adoption of strict inclusion criteria required to guarantee patients' safety on bevacizumab as well as to offset the economic cost and potential toxicity of the investigated four-drug scheme.

Despite a higher 1-year OS in the CeLEBrATE study compared with the phase randomized-controlled trials with platinum-etoposide and a PD-L1 inhibitor (eg, IMpower133 and CASPIAN), the mOS was similar to that observed in these studies (12.9 months vs 12.3–13.0 months). This could be due to the lack of actual efficacy of adding bevacizumab in our study, the limitations of cross-trial comparisons, or a potential immune activation

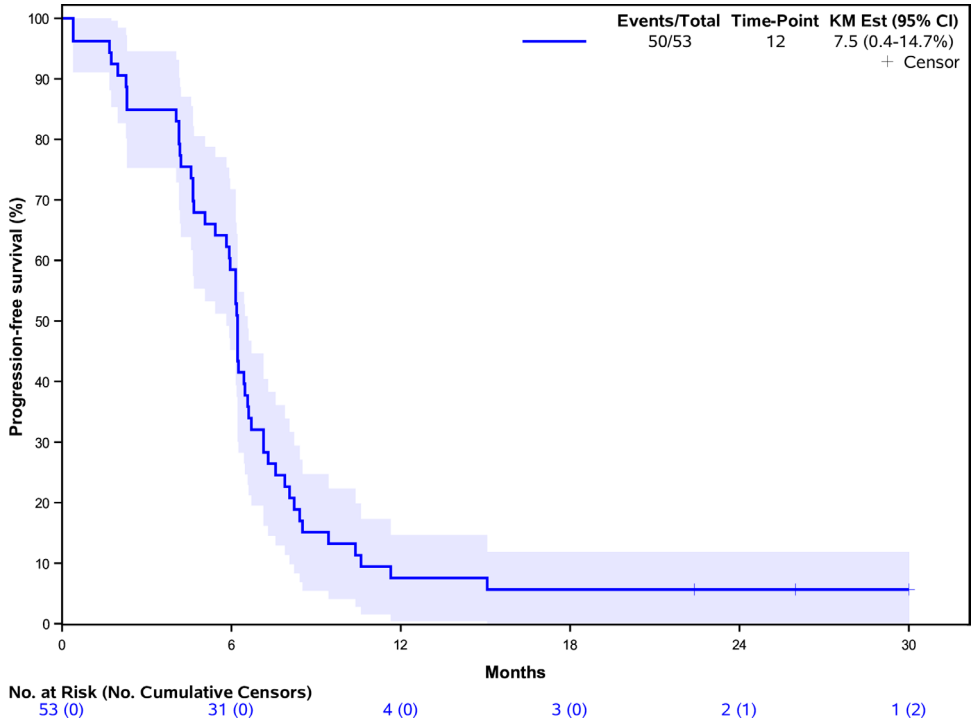

Figure 4 Kaplan-Meier estimates (KM Est) of progression-free survival.

Table 2 Summary of adverse events

Adverse event	Grade 1–2	%	Grade 3–4	%
Any type toxicity	14	26.4	34	64.2
Hematological toxicity	12	22.6	30	56.6
Neutropenia	9	17.0	28	52.8
Anemia	21	39.6	4	7.6
Leukopenia	12	22.6	3	5.7
Thrombocytopenia	8	15.1	3	5.7
Febrile Neutropenia	0	0	3	5.7
Non-hematological toxicity	35	66.0	10	18.9
Fatigue	25	47.2	3	5.7
Nausea	19	35.9	0	0
Diarrhea	12	22.6	1	1.9
Thromboembolism	9	17.0	3	5.7
Cough	9	17.0	0	0
Arterial hypertension	5	9.4	3	5.7
Fever w/o neutropenia	7	13.2	1	1.9
Mucositis	8	15.1	0	0
Vomiting	8	15.1	0	0
Skin toxicity	9	17.0	0	0
Hypothyroidism	8	15.1	0	0
Hyponatremia	2	3.8	6	11.3
Hyperthyroidism	7	13.2	0	0
Bleeding	5	9.4	1	1.9
GGT elevation	4	7.6	2	3.8
Amylase/lipase elevation	4	7.6	2	3.8
Renal toxicity	4	7.6	1	1.9
Arthralgia	5	9.4	0	0
Transaminase elevation	5	9.4	0	0
Proteinuria	3	5.7	1	1.9
Pulmonary toxicity	3	5.7	1	1.9
Other endocrine disorders	2	3.8	0	0
Pancreatitis	0	0	1	1.9

GGT, Gamma-glutamyl transferase.

effect. The latter might not lead to a clear improvement in mOS but could benefit a subset of patients in the long term, as suggested by the "tail" of the survival curves, similar to the ~10–12% long-term survivors observed with PD-L1 inhibition plus platinum-etoposide chemotherapy in registration studies.[20 22 45 46] Because of this, strategies to improve outcomes of patients with ES-SCLC and to expand the proportion of patients who benefit from ICIs are a highly unmet need in SCLC. The combination of other different ICIs, namely Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), to PD-L1 inhibition has been disappointing.[47–49] Given its pleiotropic immunosuppressive effects, combined inhibition of the VEGF pathway together with PD-L1 inhibition is an appealing strategy as it is hypothesized to enhance the antitumor immune system activation unleashed by ICIs,[34 35] in keeping with preclinical relevant in vivo models of SCLC.[37] Indeed, angiogenesis inhibition with the addition of bevacizumab to carboplatin-etoposide chemotherapy has proved to be active and safe in two independent randomized clinical trials (mPFS 5.5–6.7 months and mOS 9.4–9.8 months).[31 32] In a single-arm phase II Chinese trial of anlotinib, a small molecule VEGFR 2 inhibitor, and platinum-etoposide chemotherapy, a PFS of 10.3 months and an OS of 17.1 months have been reported.[50] In respect to combined PD-L1 and angiogenesis inhibition, results of a three-arm phase III randomized placebo-controlled clinical trial of the PD-L1 inhibitor benmelstobart, anlotinib, carboplatin,

and etoposide have been recently presented.[51] An improvement in PFS (primary endpoint, 6.93 vs 4.21 months), and OS (19.3 vs 11.9 months) was observed in the four-drug experimental arm compared with the chemotherapy-only arm. However, data from the placebo-anlotinib-chemotherapy arm were not reported, while a chemo-immunotherapy arm without anlotinib was not present by study design. Furthermore, the BEAT-SC study, a phase III randomized placebo-controlled trial of bevacizumab or placebo in combination with atezolizumab and platinum-etoposide chemotherapy is ongoing in China and Japan.[52] The study demonstrated that median PFS, the primary endpoint of the study, was significantly longer in the bevacizumab than in the placebo arm (5.7 vs 4.4 months, HR 0.70). However, the third interim analysis for OS failed to demonstrate a benefit from the addition of bevacizumab to atezolizumab-carboplatin-etoposide (14.1 vs 16.0 months, respectively, HR: 1.07). Notably, in both these trials, grade ≥3 neutropenia was reported in 60–70% of patients, SAE in 35–47%, and treatment-related deaths in 3.0–4.5%.

Limitations of our study include its design and toxicity rates. Because the CeLEBrATE study is a phase II single-arm study, its aim was to provide a signal of activity of the addition of bevacizumab to atezolizumab-carboplatin-etoposide, thus preventing us from making any definitive conclusion. Moreover, the interim results of the BEAT-SC study warrant caution in the interpretation of our study results.

Regarding toxicity, no new safety concerns emerged during treatment with the drugs under study. Hematologic toxicity, namely neutropenia, febrile neutropenia, and thrombocytopenia, was not significantly more commonly reported than in other trials with combinations of chemotherapy with immune checkpoint inhibitors and/or angiogenesis inhibitors in the same setting.[17 18 31 32 50 51] Nevertheless, two deaths of sepsis in febrile neutropenia and one of pancytopenia were observed likely because G-CSF as primary prophylaxis was not permitted per-protocol on trial. Overall, death from toxicity occurred in 7.5% of patients (n=4/53), slightly higher than what was observed in the CASPIAN study and in other trials of combined angiogenesis and immune checkpoint inhibition (3.0–4.5%).[17 45 52 53]

In conclusion, the combination of bevacizumab, atezolizumab, carboplatin, and etoposide is feasible and active in the first-line treatment of patients with ES-SCLC. Though toxicity must be carefully managed through adequate patient selection and proper use of G-CSF prophylaxis, data from the CeLEBraTE study suggest that the combined inhibition of angiogenesis and immune checkpoints may be effective in a challenging disease setting such as ES-SCLC.

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Ethics approval According to the Italian laws at the time of study design and submission, the study has been approved by the institutional review board (IRB) of each participating center. The primary IRB was the Comitato Etico Area Vasta Emilia Centro (CE-AVEC) - in Bologna (Italy) with approval number 3/2020/Farm/AOUBo. Participants gave informed consent to participate in the study before taking part.

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