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Agnostic phase II, multicenter, single-arm study with *DURVA*lumab plus carboplatin or cisplatin and etoposide as first-line treatment in extensive stage - Extrapulmonary Small Cell Carcinoma (EP*SCC*) patients – *DURVASCC* trial (GOIRC-01-2021)

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Abstract

Background EPSCCs represent rare and extremely aggressive tumors. In most cases, with widespread metastatic disease, the incidence rate is between 0.1% and 0.4%, and the median survival of less than one year. At present, chemotherapy is considered the only therapeutic strategy in the extensive stage of EPSCC.

Methods/design This is an open-label, multicenter, Italian phase II single-arm trial in which patients with extensive-stage EPSCC will receive first-line therapy with intravenously durvalumab (day 1) plus carboplatin or cisplatin, and etoposide (day 1–3) every 3 weeks for 4 or 6 cycles, as investigator's choice, followed by maintenance with durvalumab every 4 weeks for a maximum of 24 months. Durvalumab will be administered at a fixed dose of 1500 mg, cisplatin at 75 to 80 mg/m2 (day 1), carboplatin AUC 5–6 (day 1), and etoposide at 80–100 mg/m2 daily on days 1 to 3 every 3 weeks. The primary endpoint is the 12-month PFS. The study hypothesis is to detect an increase of at least 10% points compared to standard chemotherapy alone. Secondary endpoints include ORR, DoR, safety, and QoL. Collateral translational studies evaluate (i) whole-exome sequencing and gene expression profiling, and (ii) genetic alterations by circulating free DNA obtained from plasma samples. The trial is an ongoing enrollment; 21 of 66 planned patients have been enrolled.

Discussion Considering the efficacy of immunotherapy plus chemotherapy in extensive SCLC and the low incidence of EPSCCs that limits the conduct of randomized trials, this therapeutic approach could be considered for the first

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time as an agnostic indication based on tumor histology, regardless of the tumor site. The DURVASCC study aims to demonstrate the role of anti-PDL1 antibody in combination with chemotherapy in first-line therapy of ES-EPSCC patients as a histology-related agnostic choice.

Trial registration ClinicalTrials.gov: NCT06464068, June 18, 2024.

Keywords Extrapulmonary small cell carcinoma, Extensive stage, Anti-PDL1 antibody, Durvalumab, Chemotherapy

Background

Small cell carcinomas (SCCs) are poorly differentiated neuroendocrine tumors that can occur from a variety of epithelial tissues, with the most recurrent being the bronchial tree, representing up to 15% of lung cancers [1]. Among all SCCs, extra-pulmonary SCCs (EPSCCs) represent 2.5–5.5%, with a global incidence rate of only 0.1–0.4% [2]. They are extremely aggressive tumors with poor survival outcomes and, in most cases, with widespread metastatic disease. According to the Veterans Administration Lung Group (VALSG), the EPSCC is classified as a limited stage or extensive stage (ES) with a median survival of about 1.4–3.5 years and less than one year, respectively [3].

As mentioned above, these tumors can arise from many different organs [4, 5] and the gastrointestinal district, especially the esophagus, is the most affected (comprising 53.0% to 71.0%) [6, 7], followed by the genitourinary system (the bladder and prostate are the most frequent sites) with a median overall survival of approximately 10.6 months [8, 9]. A low incidence (< 2%) of EPSCC accounts in the cervix with a high rate of recurrence [10, 11].

Although EPSCC is often considered to be like small cell lung cancer (SCLC) in terms of histopathological features and aggressiveness, the presence of meaningful biological differences between these disorders could lead to changes in therapeutic approaches.

To date, in the absence of prospective clinical trials due to rarity and unfavorable prognosis, only retrospective studies are available, making it tough to decide the treatment for these rare cancers. Based on weak evidence, it was reasonable in the past to manage EPSCCs similarly to SCLC [12, 13], until the recent approval of atezolizumab or durvalumab in combination with a platinum agent/etoposide combination that became the preferred first-line regimen only for ES-SCLC [14, 15].

The main chemotherapy regimen used in clinical practice as a first-line choice for ES-EPSCC includes platinum-derived drugs (cisplatin or carboplatin) in combination with etoposide. Unfortunately, this regimen does not report optimal survival data, as shown by a retrospective study with 35 patients affected by ES-EPSCCs, in which the median overall survival was 5 months [13]. Another retrospective study evaluated 120 patients with EPSCC with variable primary tumor sites, and 30% of patients had extensive disease, reaching a median survival of 0.7 years [12].

Therefore, there is a significant need to improve treatment options for patients with ES-EPSCC. For this purpose, immune checkpoint inhibitors could offer a novel treatment approach that could potentially improve the prognosis of patients with these rare and aggressive diseases.

Few case reports were published in this setting; a patient with ES-EPSCC of the cervix, pretreated with chemotherapy, exhibited a radiological decrease of all target lesions after two doses of nivolumab despite being PD-L1 negative [16].

In a similar case, a patient with ES-EPSCC of the pancreas after the first-line treatment with carboplatin and etoposide, and second-line with topotecan, nivolumab, showed a significant reduction in tumor sizes after four cycles [17].

On the contrary, an investigator-initiated phase II basket trial with pembrolizumab alone for patients with rare tumors, including different ES-EPSCC cohorts, showed minimal activity with only one stable disease in 6 patients with cervix primary tumor site; additionally, no one was progression-free at 27 weeks [18].

Tumor-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone [19, 20], and this may reasonably occur in tumors regardless of PD-L1 expression.

Targeting the PD-L1 pathway with durvalumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. The addition of durvalumab to carboplatin or cisplatin and etoposide resulted in significantly longer overall and progression-free survival than chemotherapy alone in ES-SCLC, with a manageable safety profile [14].

Phase I or II clinical trials are currently ongoing (Table 1), evaluating the effectiveness of immune checkpoint inhibitors in combination with other therapies (chemotherapy, tyrosine kinase inhibitors), and others exploring new small molecules in EPSCC tumors.

We designed the agnostic DURVASCC study to evaluate the preliminary efficacy and safety of durvalumab in combination with carboplatin or cisplatin plus etoposide

Table 1 Active and recruiting clinical trials in EPSCCs

Drugs	Trial	Setting	Outcomes
Nivolumab and Ipilimumab in combination with Cabozantinib [21]	Phase II NCT03866382	1 L and 2 L	Primary: ORR Secondary: safety; PFS
LSD-1 Inhibitor (Iadademstat) in combination with Paclitaxel [22]	Phase II NCT05420636	≥ 2 L	Primary: ORR Secondary: DoR; PFS; OS; safety; clinical benefit rate (CBR)
CDK 4/6 inhibitors (Abemaciclib) [23]	Phase II NCT04010357	≥ 2 L	Primary: ORR Secondary: DoR; 6-months PFS; OS; safety
Topotecan in combination with ATR kinase inhibitor (Berzosertib) [24]	Phase I/II NCT02487095	≥ 2 L	Primary: Maximum Tolerated Dose (MTD)/ Recommended Phase 2 Dose (RP2D); clinical response; safety Secondary: DOR; PFS; OS
Dipeptidyl peptidases—primarily DPP8/9 inhibitor (Talabostat) plus Pembrolizumab or Talabostat alone [25]	Phase Ib/II NCT03910660	1 L and ≥ 2 L	Primary: ORR; CTC conversion; ≥50% PSA decline Secondary: rPFS; PSA PFS; OS; DoR

in untreated ES-EPSCC patients based on agnostic histology regardless of the disease location.

Methods

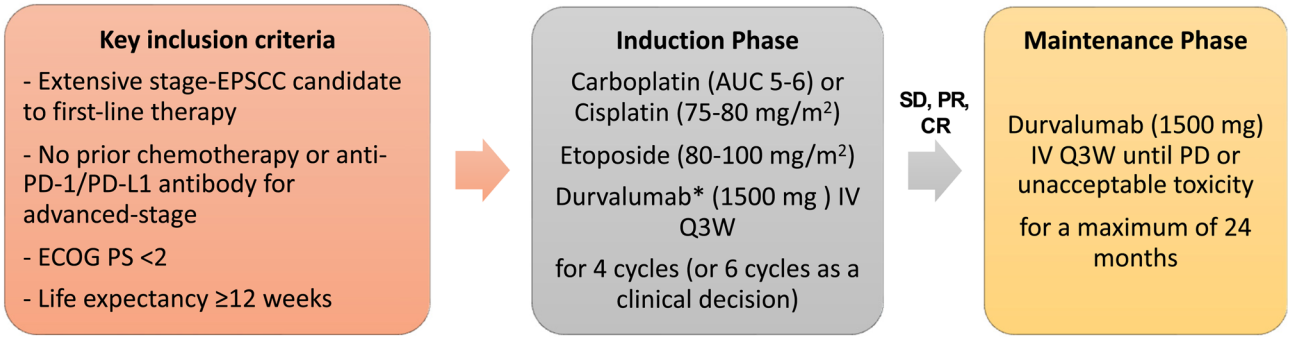
Protocol overview/study treatment

This is an open-label, multicentric phase II single-arm trial in which patients with ES-EPSCC will receive standard chemotherapy with carboplatin or cisplatin and etoposide in combination with durvalumab as the first line of treatment. Study screening will take place within 21 days before starting the study treatment. Eligible patients will be enrolled and treated with induction of 4 (or 6) cycles, based on the physician's decision, with intravenous etoposide at a dose of 80–100 mg/m² (administered on days 1–3 of each 21-day cycle), investigator's choice of either carboplatin area under the curve 5–6 mg/mL per min or cisplatin 75–80 mg/m² (administered on day 1 of each 21-day cycle) in combination with durvalumab flat dose of 1500 mg every 3 weeks (except for patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg). After that, in patients who achieved a response to the disease, maintenance with durvalumab flat dose of 1500 mg every 4 weeks will be administered (Fig. 1). Patients will continue treatment until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria. Extension of study treatment after disease progression will be permitted if there is evidence of clinical benefit for a maximum of 24 months.

During the protocol's treatment, patients will be followed for safety based on Adverse Event (AE) assessments, including vital signs, physical findings, and clinical laboratory test results. An interim analysis will be performed when the 10th patient is enrolled by an internal assessment committee that will review AE profiles, serious AEs, relevant laboratory data, and dose modifications stated.

A radiological assessment with abdomen/pelvis, chest, and brain CT scan (if contraindicated, an MRI of the abdomen/pelvis/brain and a spiral CT scan of the chest are required) will be carried out every 6 weeks for the first two months and then every 8 weeks during the treatment. If clinically indicated, a CT scan of the neck or extremities should also be performed. After the progression of the disease, if feasible, at least one follow-up scan will be required.

The disease response will be assessed by the investigator using the RECIST v1.1 criteria. An independent



EPSCC: Extra-pulmonary Small Cell Carcinoma; SD: stable disease; PR: partial response; CR: complete response; Q3W: every 3 weeks; IV: intravenously

*Patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q3W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

Fig. 1 Study Design of DURVASCC Trial

review of all data related to tumor assessment will be conducted at the end of the study by an Independent Monitoring Committee.

Before starting the study treatment, tumor blocks will be collected as primary or metastatic tissue. Moreover, blood samples will be gathered at different time points (baseline, before maintenance treatment, and at the progression of the disease) to investigate the occurrence of genetic alterations by analyzing the cfDNA associated with acquired resistance to immune checkpoint inhibitors.

Quality of life using a validated EORTC QLQ-C30 questionnaire will be assessed at baseline, every 4 cycles of treatment, and at the study discontinuation visits.

Following discontinuation of the treatment, follow-up visits will occur every three months for a maximum of 2 years from the first dose of therapy.

A list of participating centers is provided in Table 2.

Main inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled: (i) Histologically or cytologically confirmed small cell carcinoma; (ii) unresectable extensive stage extrapulmonary small cell carcinoma not previously treated with chemotherapy or immunotherapy for metastatic disease; (iii) asymptomatic or treated and stable off steroids and anti-convulsant brain metastases at least 1 month before study treatment; (iv) no prior exposure to immune-mediated therapy, including durvalumab excluding therapeutic anticancer vaccines; (v) no prior exposure to chemotherapy for advanced disease; (vi) life expectancy ≥ 12 weeks at enrollment; (vii) age ≥ 18 years; (vi) ECOG performance status 0–1; (viii) adequate organ and marrow function; (ix) patients suitable to receive a platinum-based chemotherapy; (x) creatinine clearance (CL) > 40 mL/min or calculated creatinine CL > 40 mL/min by the Cockcroft-Gault formula; (xi) availability of an archived tumor tissue block at baseline; (xii) evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients; (xiii) at least 1 lesion, not previously irradiated, that can be accurately measured at baseline; (xiv) signed written informed consent obtained before any study-specific screening procedures.

Table 2 Participating Italian cancer centers

Principal Investigator	Site	City
Angela Damato	Azienda USL – IRCCS Reggio Emilia	Reggio Emilia
Lorenzo Antonuzzo	Azienda Ospedaliero - Universitaria Careggi	Firenze
Rossana Berardi	Università Politecnica delle Marche – AOU delle Marche	Ancona
Angela Buonadonna	IRCCS – CRO Aviano	Aviano
Nicole Brighi	IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori"	Meldola
Saverio Cinieri	Presidio Ospedaliero "Senatore Antonio Perrino"	Brindisi
Concetta Di Micco	Ospedale "Casa Sollievo della Sofferenza"	San Giovanni Rotondo
Fabio Gelsomino	Azienda Ospedaliero-Universitaria	Modena
Federico Grossi	ASTT Sette Laghi	Varese
Erika Martinelli	Università degli Studi della Campania "Luigi Vanvitelli"	Napoli
Gianluca Masi	Azienda Ospedaliero – Universitaria Pisana	Pisa
Sara Pusceddu	Istituto Nazionale dei Tumori	Milano
Francesca Spada	Istituto Europeo di Oncologia	Milano

Main exclusion criteria

Patients are not eligible for this study if any of the following exclusion criteria apply: (i) any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment; (ii) radiotherapy to any site within 4 weeks before the study (radiation therapy for palliative care is allowed); (iii) active, known, or suspected autoimmune disease requiring systemic treatment including steroids prior 14 days before the first dose of durvalumab; (iv) active or prior documented autoimmune or inflammatory disorders, diverticulitis, systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome; (v) additional malignancy in the last 5 years (exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy); (vi) history of leptomeningeal carcinomatosis; (vii) history of HIV infection; (viii) active Hepatitis B or Hepatitis C; (ix) history of allogenic organ transplantation; (x) live, attenuated vaccine within 30 days before the first dose of treatment; (xi) major surgical procedure within 28 days prior to the first dose of investigational product; (xii) female patients with a positive pregnancy test at enrollment or before administration of study medication; (xiii) pregnancy or breast-feeding period; (xiv) mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms; (xv) uncontrolled intercurrent illness that would limit compliance with study requirement, increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

Study endpoints

The present trial will determine if adding durvalumab to the first-line therapy with carboplatin or cisplatin and etoposide in ES-EPSCC is effective in terms of 12-month progression-free survival (PFS), defined as the time from the beginning of study treatment to the first occurrence

of disease progression or death from any cause, whichever occurs first.

Secondary endpoints are the following: (i) Objective Response Rate (ORR), defined as the percentage of patients who obtain complete response (CR) or partial response (PR) according to RECIST v1.1 criteria; (ii) Disease control rate (DCR) measured as the percentage of patients who have archived CR, PR, and stable disease (SD); (iii) Overall survival (OS), defined as the time from the beginning of study-drug administration to the date of death from any cause; (iv) Duration of response (DOR), defined as the time from initial response to disease progression or death among patients who have experienced a CR or PR (unconfirmed) during the study evaluated by the investigator according to RECIST v1.1 criteria; (v) safety profile of carboplatin or cisplatin and etoposide plus durvalumab defined in terms of incidence, nature, frequency, and severity of AEs and laboratory abnormalities graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0; (vi) quality of life (QoL) of patients measured as predefined PRO endpoints meaning change from baseline in EORTC QLQ-C30 questionnaire consists of 30 questions to assess five aspects of patient functions (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health and/or quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). Scale scores can be obtained for the multi-item scales.

Explorative and collateral studies aim to identify possible biomarkers associated with sensitivity or resistance to immune checkpoint inhibitors (e.g., PD-L1, Tumor Mutational Burden, somatic mutations/genomic alterations, Delta-like canonical Notch ligand 3 (DLL3) expression). Formalin-fixed and paraffin-embedded (FFPE) tumor samples will be collected before starting the treatment (at baseline), as primary or metastatic tumor tissue blocks, or as fifteen 5-micron unstained slides. The neoplastic cell content of each tumor sample will be assessed and, if possible, in cases with neoplastic cells < 50% a macrodissection of the specimen will be performed. Tumor samples will undergo whole-exome sequencing (WES) and gene expression profiling by using a 3' RNA-seq approach. Moreover, in all patients enrolled to investigate the occurrence of genetic alterations that might be associated with acquired resistance to immune checkpoint inhibitors, venous blood will be obtained by standard phlebotomy technique from a peripheral access point or a central line into two 10.0 mL K2-EDTA Vacutainers by trained personnel. Blood samples will be collected by analyzing the cfDNA using targeted sequencing panels at different time points: at baseline, before the maintenance treatment, and at disease progression.

Data collection and follow-up

Study drug administration occurs on Day 1 (± 3 days) for carboplatin or cisplatin and durvalumab and on Day 1–3 (± 3 days) for etoposide of each cycle. Each cycle lasts 21 days. Cycle 1 should occur within 3 days from registration of patients. All procedures during the study treatment must occur within 3 days before the administration, except for radiological assessment required for baseline, within 21 days before initiation of the study treatment. All radiological assessments will be performed at week 6 (± 1 week) and week 12 (± 1 week), and then every 8 weeks (± 1 week). The end of the study treatment visit should occur within 30 days after the last dose of study treatment. The post-treatment follow-up visits will occur every 3 months (± 14 days) for a maximum of 2 years from the first dose (Table 3).

Statistical analysis and sample size

The primary objective of this study is to evaluate the preliminary efficacy of durvalumab in association with carboplatin or cisplatin and etoposide in first-line patients affected by extensive-stage EPSCC, in terms of the percentage of patients at 12-month PFS. According to CASPIAN trial results [14], in which was observed a 12-month PFS rate of 5% (2.4–8.0) for patients treated with Platinum–etoposide is expected to detect an increase of at least 10% points (to 15%) with durvalumab association. Using a two-sided one-sample log-rank test, and fixing alpha and beta probabilities to 0.05 and 0.1, respectively, 60 patients must be enrolled for 18 months and followed up for 24 months. Considering that a drop-out rate of 10% is estimated due to this type of tumor and patient conditions, and the endpoint is PFS, we assume that the observation of 60 patients of interest is exponentially distributed with lambda parameter (the rate of drop-out for each month) = 0.0059 [-ln (0.9)/18]. Each subject has a probability of 0.07 to leave before 12 months early, and so on; out of 60 subjects, it should mean 4 of them could be observed for less than 12 months. Conservatively, to manage a drop-out rate swing among 10–15%, a further 6 patients will be enrolled for a total of 66.

Interim analysis

Safety assessment will start after the enrollment of the 10th patient. An internal assessment committee will review AE profiles, serious AEs, relevant laboratory data, and dose modifications reported.

The assessment will be defined according to a continuous toxicity monitoring approach, giving priority to the alternative hypothesis, based on the Pocock group sequential method (delta = 0.0). Fixing a probability of stopping early the trial of about 5% when the true toxicity rate is ≤ 10% and a power equal to 80%, assuming a maximum level of accepted toxicity equal to 30%, the

Table 3 Study assessments

ProcedureS	Screening (−21 days)	Cycle 1 (± 3 days)[a]	Cycle 2 (+ 3 days)	Cycle 3 (+ 3 days)	Cycle 4 (+ 3 days)[a]	Maintenance Cycles[a]	End of treatment[a]	Post treatment Follow-Up[a]
Informed consent including biomarker sample collection	X							
Medical history and baseline conditions	X							
Physical examination	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	
Vital signs[b]	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Hematology, serum chemistry[c]	X	X	X	X	X	X	X	
TSH, T3, T4, amylase, lipase[d]	X	X	X	X	X	X[d]	X	
Pregnancy test[e]	X	See note e			See note e	See note e		
Radiological assessment[f]	X	Tumor assessments should be performed at week 6 (± 1 week), at week 12 (± 1 week), and then every 8 weeks (± 1 week) until RECIST 1.1 criteria defined progression disease. All patients require one follow up scan post initial progression where possible.						
QLQ-C30 questionnaire[g]	X[g]				X[g]	X[g]	X[g]	
Blood samples[h]	X[h]					X[h]	X[h]	
Carboplatin/Cisplatin and Etoposide administration[i]		X	X	X	X			
Durvalumab administration[i]		X	X	X	X	X		
Survival follow-up								X

[a]Each cycle lasts 21 days. Study drug administration occurs on Day 1 (± 3 days) of each cycle for carboplatin or cisplatin, and durvalumab; on Day 1–3 (± 3 days) for etoposide. Cycle 1 should occur within 3 days from the registration of the patient. All other events and assessments during the study treatment must occur within 3 days before the administration, except for the radiological evaluation. The end of the study treatment visit should occur within 30 days after the last dose of study treatment is administered. The post-treatment follow-up visits will occur every three months (± 14 days) for a maximum of 2 years from the first dose

[b]Vital signs will include weight measurements, respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure. At baseline also height and BSA are required

[c]Baseline analysis will not be repeated if performed within 7 days before Cycle 1 Day 1. Hematology consists of CBC, including hemoglobin, WBC count with differential and platelet count. Serum chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, potassium, sodium, total bilirubin, direct and indirect bilirubin, total protein, urea o blood urea nitrogen (BUN)

[d]Amylase, lipase, TSH, fT3, and fT4 will be done every other cycle

[e]Serum pregnancy test to be done within 24 h before first dose; after that serum or urine pregnancy test to be done, every 4 weeks (± 7 days) regardless of dosing schedule

[f]All radiological assessments with CT scan (or MRI) will be performed at Week 6 (± 1 week), at Week 12 (± 1 week), and then every 8 weeks (± 1 week). An initial CT scan of the chest, abdomen, pelvis, and brain or MRI is required for baseline within 21 days before initiation of the study treatment. Evaluation using the same modality should be repeated

[g]Questionnaire will be completed at baseline, at cycles 4, every 4 cycles during maintenance treatment, and at the end of the treatment visit

[h]Blood samples will be collected at baseline, before maintenance treatment, and at the time of progression

[i]Carboplatin or cisplatin and etoposide plus durvalumab in the induction phase will be administered for 4 cycles or 6 cycles, as clinical decision. Durvalumab will be administrated in the maintenance phase for a maximum of 24 months. Durvalumab will be administrated in the maintenance phase for a maximum of 24 months

data will be analyzed after the enrollment of 10, 20, 30 patients. The trial will be stopped if dose-limiting toxicity, defined as lung toxicity of any grade, is observed in 4, 6, 7, or more patients, respectively.

At the enrollment of the 30th patient, approximately 50% of the overall sample size, no formal 12-month PFS will be conducted by the Independent Monitoring Committee (IDMC) for the exploratory purpose of evaluating the plausibility of an evident efficacy.

Coordinating site

On behalf of Gruppo Oncologico Italiano Ricerca Clinica (GOIRC) Cooperative Group, Azienda Unità Sanitaria Locale di Reggio Emilia – IRCCS is responsible for coordinating and managing the study.

Discussion

Due to histological, immunohistochemical and genetic similarity with SCLC highly enriched for the genetic inactivation of the tumor suppressive genes TP53 and RB1, which upregulate the DNA damage repair pathway, and normal cells can proliferate indefinitely [26, 27],

extrapulmonary small cell tumors have always been considered on par with SCLC, although they differ in tumorigenesis, and many aspects of oncogenesis still need to be clarified.

Recently, one hundred and seventy-one EP-SCC were enrolled in a multicenter study, and all tissue samples underwent an immunohistochemical p53 analysis [28]. This study showed that the TP53 mutation was prognostic and associated with shorter overall survival (p = 0.041), and the incidence of aberrant p53 expression/TP53 molecular alteration was.

noticeably lower in EP-SCC than in small-cell lung carcinomas. Moreover, the multivariate analysis of p53 and TP53 mutational status found that it impacted overall survival relative to distinct sites of tumor locations, especially for gastrointestinal tumors, which were a significant negative prognostic factor (p = 0.001).

Targeting the PD-L1 pathway with durvalumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Tumor-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone [19, 20]. Given the rarity and aggressiveness of extrapulmonary small cell tumors, unfortunately, there are no randomized, prospective studies supporting the use of immunotherapy as a single agent or in combination with other drugs in this setting of disease.

Nowadays, there are no clinical guidelines or consensus to standardize the management in clinical practice of ES-EPSCC. The systemic chemotherapy based on platinum derivatives and etoposide remains the standard of care, but survival remains poor, and is less than one year. In those chemotherapy-ineligible patients, due to underlying frailty or a poor performance status, the best supportive care is indicated.

Recently, several phase II and III clinical trials have led to revolutionary changes in the first-line treatment for the extensive stage of SCLC, adding immunotherapy to standard chemotherapy. Specifically, the phase III, double-blind, placebo-controlled Impower-133 trial [15], showed that the combination of atezolizumab plus chemotherapy significantly prolonged median OS (12.3 months versus 10.3 months; p = 0.007), while PFS was 5.2 months versus 4.3 months, respectively (p = 0.02); an updated OS analysis with an additional 9 months of follow-up was 22.9 months and ORR was 60.2% in the experimental arm. In the second trial, a randomized, open-label CASPIAN study [14], patients with ES-SCLC were treated with durvalumab plus carboplatin or cisplatin and etoposide for 4 cycles or durvalumab plus tremelimumab plus chemotherapy for 4 cycles versus chemotherapy alone for up to 6 cycles. Durvalumab was continued as maintenance therapy until the progression of disease. Durvalumab plus chemotherapy significantly improved median OS compared with the chemotherapy arm (13.0 versus 10.3 months; p = 0.0047), and median PFS was 5.1 versus 5.4 months with durvalumab plus chemotherapy compared to platinum–etoposide alone. An updated analysis showed 22.2% versus 14.4% of patients alive at 24 months [29]. Instead, the combination of tremelimumab, durvalumab, and chemotherapy did not improve OS compared with chemotherapy alone. Grade 3–4 adverse events were observed in 62.3% of patients treated with durvalumab plus chemotherapy.

Based on these results, durvalumab and atezolizumab plus platinum-based and etoposide chemotherapy have become a new standard in the first-line treatment of ES-SCLC. No biomarkers were identified as predictors of response or resistance to immunotherapy treatment.

Likewise, other ongoing studies are testing new bispecific antibodies in patients with recurrent SCLC, with promising preliminary results [30].

To implement data to support the use of immunotherapy also in EPSCCs, in addition to the plethora of case reports, small phase 2 basket trials are finally emerging. Although the data of pembrolizumab as monotherapy in SCC of the cervix were not encouraging [18], a basket study tested, in a cohort with six primary SCC gastrointestinal tumors, dual anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) blockade showing four confirmed partial responses, an overall 6-month PFS rate of 32% with a median PFS of 2.0 months, and a median OS of 8.9 months; the safety profile was manageable with a 37% of Grade 3/4 immune-related adverse events [31].

Pending results from the ongoing phase 2 trials, the DURVASCC study also aims to demonstrate the role of immunotherapy in combination with standard chemotherapy as agnostic first-line therapy in patients with extensive-stage EPSCC disease.

Abbreviations

AE	Adverse Event
AUC	Area Under Curve
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CI	Confidence Interval
CR	complete response
DoR	Duration of response
DCR	Disease control rate
EPSCC	Extrapulmonary Small Cell Carcinoma
ES	Extensive Stage
ECOG PS	Eastern Cooperative Oncology Group – performance status
HIV	Human immunodeficiency virus
HR	Hazard Ratio
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
OS	Overall survival
PD-L1/PD-1	Programmed death-1/ligand 1
PFS	Progression-free survival

PR	partial response
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SCC	small cell carcinoma
SCLC	small cell lung carcinoma

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15112-w.

Supplementary Material 1

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Authors' contributions
CP, AD, and GM designed the study and wrote the original protocol. AD and CP drafted the manuscript. All the other authors directly contributed, read, and approved the final manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
This study is conducted in agreement with either the Declaration of Helsinki or the laws and regulations of the country, whichever provides the greatest protection for the patient. The protocol has been written, and the study is conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The study (Protocol version 1.0, February 22, 2022) was approved for all participating centers by AIFA, the Italian health authority (Agenzia Italiana del Farmaco) on December 1 st, 2023, and registered at Clinicaltrials.gov (NCT06464068) on June 16, 2024. IEC(s)/IRB(s) approved the submitted documents for each center. Company QBE Insurance was appointed by GOIRC for an insurance policy to reimburse patients for any injury associated with the study. Changes to eligibility criteria, outcomes, analysis, or other important protocol modifications will be notified to the IEC/IRB for approval and will be forwarded to the Sponsor. Informed consent to study procedures before enrollment in the study was signed by all candidates. Moreover, those will be informed about the study purpose, the activities involved, the expected duration, and the potential risks and benefits by the investigators (or legally authorized representatives).

Consent for publication
Not applicable.

Competing interests
A.D.: outside the submitted work, has received personal fees for the advisory role, speaker engagements, and travel and accommodation expenses from Ipsen, Servier, BMS, Merck Serono, Amgen, and Daichii Sankyo.C.P.: outside the submitted work personal fees for the advisory role, speaker engagements, and travel and accommodation expenses from Amgen, Astellas, AstraZeneca, Bayer, Bristol Meyer Squibb, Celgene, Daiichi Sankyo, Eisai, Ipsen, Janssen, Incyte, Merck-Serono, Merck Sharp and Dohme, Novartis, Roche, Sandoz, Sanofi, and Servier.N.B.: outside the submitted work, has received travel support from Ipsen, Novartis, Janssen-Cilag, Pfizer, Advanced Accelerator Applications, and speaker honoraria from Bristol-Myers Squibb, Gentili Oncology, and Johnson & Johnson.F.G.: outside the submitted work, has received honoraria for Advisory board/Speaker's bureau from Servier, Eli Lilly, Bristol-Myers Squibb, Iqvia, Merck Serono, Amgen, Pierre-Fabre.F.S.: outside the submitted work, has received honoraria for Writing Engagement/invited speaker/educational activities from Ipsen, Merck, SAS SPA, and Novartis.E.M.: Receipt of honoraria or consultation fees for speaker, consultancy, or advisory roles from Amgen, Bayer, Eisai, Merck Serono, Pierre Fabre, Roche, Servier, Incyte, ESMO, MSD. Travel grant: AstraZeneca, Pierre Fabre.

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