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A MULTICENTER PHASE II, SINGLE ARM STUDY OF DURVALUMAB WITH CARBOPLATIN PLUS ETOPOSIDE FOR 4 CYCLES FOLLOWED BY DURVALUMAB MAINTENANCE IN PATIENTS WITH METASTATIC PULMONARY LARGE-CELL NEUROENDOCRINE CARCINOMA (LCNEC) – DUPLE TRIAL

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and highly aggressive type of lung cancer, that shares biologic and clinical features with both small-cell lung cancer (SCLC), also of neuroendocrine derivation, and non-small-cell lung cancer (NSCLC), of epithelial origin. Recent genomic profiling has identified two molecular LCNEC subtypes with potential prognostic and therapeutic implications: type I ("NSCLC-like"), characterized by a more epithelial profile, and type II ("SCLC-like"), with predominant neuroendocrine features. Whether these molecular profiles are associated with different clinical behavior is currently unknown. Because of LCNEC rarity, most evidence comes from small retrospective studies and treatment strategies are extrapolated from those adopted in SCLC and NSCLC.

Addition of programmed death-1 (PD-1) and its ligand (PD-L1) blockade to standard first-line platinum-etoposide chemotherapy improved outcomes in SCLC. Based on the hypothesis that the same strategy will be similarly effective in LCNEC, a phase II multicenter single-arm clinical trial of combination of durvalumab, an anti-PD-L1 monoclonal antibody, with carboplatin-etoposide chemotherapy in treatment-naïve metastatic pulmonary LCNEC patients, was designed (DUPLE trial). The trial, which is still ongoing, enrolled 46 patients, who received a combination of intravenous carboplatin (AUC 5 on day 1), etoposide (100 mg/sqm on days 1-3), and durvalumab (1500 mg on day 1) administered every three weeks for a total of 4 courses (induction phase), followed by durvalumab (1500 mg on day 1) every 4 weeks (maintenance phase) until completion of 24 courses (for a total of 28 courses, including the 4 courses of induction phase) or 2 years of treatment whichever occurs first, disease progression, unacceptable toxicity, patient refusal or loss of clinical benefit. 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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Introduction

Neuroendocrine tumors of the lung comprise a heterogeneous spectrum of malignancies that include typical carcinoids, atypical carcinoids, pulmonary large cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC). Among these, LCNEC represents a rare and highly aggressive entity, accounting for approximately 2-3% of all lung cancers (1,2).

LCNEC shares biologic and clinical features with both SCLC, also of neuroendocrine derivation, and non-small-cell lung cancer (NSCLC), of epithelial origin. However, LCNEC exhibits distinct pathological and molecular features that set it apart from both categories. Compared to SCLC, LCNEC is typically located more peripherally, is more often resectable at diagnosis and is often combined with another histological subtype, including SCLC (more commonly), as well as adenocarcinoma and squamous carcinomas.

Given its rarity, there are no randomized trial available to guide treatment, so that therapeutic options mirror those of SCLC and NSCLC (3). As a consequence, treatment selection remains controversial, and clinical outcomes are generally poor, highlighting a major unmet need for more effective and biologically informed treatment strategies.

In the last few years, the introduction of next-generation sequencing allowed the identification of two different molecular subtypes of LCNECs, with prognostic and potential therapeutic implications (3,4). Type I LCNECs ("NSCLC-like") are characterized by mutations in *TP53*, *STK11* and *KEAP1* and a neuroendocrine-like expression profile (high *ASCL1* and *DLL3* expression, low *NOTCH1* expression), whereas type II LCNECs ("SCLC-like") harbor mutations in both *TP53* and *RB1* and a reduced expression of neuroendocrine markers (low *ASCL1* and *DLL3* expression, high *NOTCH1* expression) but also an increased expression of immune response genes (3). Whether these molecular profiles are associated with differential clinical behavior and susceptibility to treatments is currently unknown. Nevertheless, a significant proportion of patients do not respond to platinum-etoposide chemotherapy, possibly because of tumor molecular heterogeneity.

Clinical management of LCNEC is currently controversial and treatment strategies are not standardized due to the lack of definitive evidence supporting a specific approach, so that definition of the optimal therapeutic strategy for this aggressive disease represents an unmet clinical need.

Background

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and highly aggressive type of lung cancer, which accounts for approximately 2-3% of NSCLC (2). Even though LCNEC is diagnosed at an early stage more often than SCLC (about 25% vs 5%, respectively), median survival of advanced stage LCNEC patients is worse compared to NSCLC but not significantly different to extensive-disease (ES) SCLC patients, ranging from 10 to 16 months (2,5). In particular, in a phase II trial of platinum-etoposide chemotherapy in 42 LCNEC, median survival was 7.7 months and 12-month survival rate was 27% (6). However, after central pathology review, only 29 cases were confirmed as LCNEC, among whom median survival was 8.0 months, while the 12-month survival rate was not reported. These findings highlight both the aggressiveness of LCNEC and the challenges associated with accurate pathological diagnosis and treatment standardization. In recent years, immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) or its ligand PD-L1 have changed the therapeutic landscape of thoracic oncology. In the randomized phase III placebo-controlled IMpower 133 trial comparing atezolizumab or placebo plus carboplatin and etoposide in ES-SCLC, both overall survival (OS) and progression-free survival (PFS) (co-primary endpoints) were improved in the atezolizumab arm compared to the placebo arm: median OS was 12.3 versus 10.3 months and PFS was 5.2 vs 4.3 months, in the atezolizumab and in the placebo arm, respectively (7). Similarly, the randomized phase III open-label CASPIAN trial demonstrated that the addition of durvalumab to platinum–etoposide chemotherapy improved OS compared with chemotherapy alone (median OS 13.0 vs 10.3 months; 12-month OS rate 54% vs 40%) (8). These pivotal studies established chemo-immunotherapy as the new standard first-line treatment for ES-SCLC. Given the

biological similarity between SCLC and LCNEC, it is plausible that LCNEC may derive comparable benefit from the addition of ICIs to platinum–etoposide chemotherapy. However, this hypothesis has yet to be tested in dedicated, prospective clinical trials.

Preliminary data on durvalumab and immunotherapy in pulmonary large-cell neuroendocrine carcinoma

Lung cancer can evade immune surveillance using different immunosuppressive mechanisms, including activation of inhibitory "immune checkpoints", such as PD-1 and PD-L1 (9). In non-NSCLC, a high tumor mutational burden (TMB) has been associated with improved responsiveness to ICIs, providing a strong biological rationale for immunotherapy in other thoracic malignancies, including SCLC (10,11). Tumors with high TMB are inherently more likely to generate tumor-specific neoantigens, enhancing recognition by cytotoxic T cells and promoting antitumor immune response (10,12). LCNEC genome, just like SCLC one, is notable for high TMB and genomic instability. In fact, reported mutation burden is between 8.5 and 10.5 mutations/Mb, with a predominance of transversion mutations, which are typically associated with tobacco exposure (13,14). The immune checkpoint PD-L1, whose interaction with PD-1 and CD80 is disrupted by durvalumab, is expressed in approximately 10 to 20% of LCNEC cases, a rate similar to that observed in SCLC. PD-L1 expression in LCNEC is also more frequently associated with tumor-infiltrating immune cells than in SCLC (15). In addition, in a subset of cases (39 LCNEC and 63 SCLC) with tumor evaluable for both PD-L1 by immunohistochemistry and mutation burden from targeted next-generation sequencing, PD-L1 expression was positively correlated with TMB in LCNEC, as well as SCLC (5,16).
Durvalumab is a Fc-optimized human immunoglobulin G1 kappa (IgG1k) monoclonal antibody which can disrupt the interaction between PD-1 and PD-L1 leading to the recognition of cancer cells by cytotoxic T cells. Durvalumab as monotherapy is now approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 on ≥ 1% of tumor

cells and whose disease has not progressed following platinum-based chemoradiation therapy. Data from the SCLC expansion cohort of a phase I/II study of durvalumab showed a response rate of 9.5% (N=2/21) with a duration of response of 14.6 and 29.5 months, respectively, in unselected pretreated ES-SCLC (17). The median PFS was 1.5 months, the median OS was 4.8 months and the OS rate at 12 months was 27.6%. More compelling evidence for the efficacy of durvalumab in SCLC came from the phase III CASPIAN trial, a randomized open-label multicenter phase III trial designed to evaluate durvalumab with and without tremelimumab, an anti-CTLA4 monoclonal antibody, plus carboplatin and etoposide in untreated patients with ES-SCLC. Patients were randomly assigned in a 1:1:1 ratio to receive platinum-based chemotherapy and etoposide alone or with either durvalumab or durvalumab + tremelimumab for up to six 21-day cycles (induction phase), followed by a maintenance phase during which they received durvalumab (in both the durvalumab monotherapy or the durvalumab + tremelimumab arm) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or no additional clinical benefit. A total of 268 patients were randomly assigned to the durvalumab group, and 269 patients to the chemotherapy only group. At a median follow-up of 39.4 months, the addition of durvalumab significantly improved OS compared with chemotherapy alone (median OS 13.0 vs. 10.3 months; HR 0.71), with a 3-year OS rate of 17.6% versus 5.8% (18). The safety profile of durvalumab plus platinum-based chemotherapy was consistent with the previously reported safety profile of the individual agents, with no new findings observed.

Although no prospective trials have specifically evaluated ICIs in LCNEC, emerging retrospective evidence is encouraging. Overall, 16 cases of LCNEC patients receiving ICIs have been reported (19), with a response rate of 60% and a median PFS of 57 weeks in the largest series (N=10) (20). A recent retrospective study, including 87 patients with advanced LCNEC of the lung, showed that the combination of chemo-immunotherapy significantly improved outcomes compared to chemotherapy alone, improving median OS from 7.1 to 15.0 months (p =

0.001) and PFS from 3.1 to 6.7 months, with benefits confirmed after propensity score matching (21). Furthermore, a recent systematic review and meta-analysis including 470 patients with advanced LCNEC reported that ICIs, used either alone or in combination, achieved a pooled overall response rate (ORR) of 34.7% and a DCR of 71.9% (22). A subgroup analysis of three double-arm studies comparing chemotherapy alone (n=42) versus chemo-immunotherapy (n=42) as first-line treatment showed a trend toward higher ORR for the combination over chemotherapy alone (RR=1.58, 95% CI: 0.92-2.70; p=0.095), although non-significant, and a significantly improved DCR (RR=1.32, 95% CI: 1.04-1.68; p=0.021), supporting the potential role of chemo-immunotherapy in this rare entity. Collectively, these findings suggest that immune checkpoint inhibition represents a promising therapeutic strategy in LCNEC.
Adding PD-L1 blockade to first-line platinum-etoposide chemotherapy in ES-SCLC yielded consistent benefit across different trials. Similarly, addition of PD-1 blockade to platinum-based chemotherapy in treatment naïve advanced NSCLC, improved outcomes. Since LCNEC shares biological and clinical features with both SCLC and NSCLC, we hypothesized that the addition of durvalumab to carboplatin and etoposide as first-line treatment of metastatic pulmonary LCNEC yields the same OS benefit observed in SCLC. Given the low incidence of pulmonary LCNEC, we designed a multicenter single-arm phase II study to reduce sample size and to expose all subjects to the experimental, potentially more effective, treatment.

Materials and methods

Study Design

This is a multicenter single-arm phase II study seeking to evaluate efficacy of addition of durvalumab to standard carboplatin and etoposide chemotherapy as first-line treatment of metastatic LCNEC of the lung. Patients enrolled from 15 Italian centers received a combination of intravenous carboplatin (AUC 5 on day 1), etoposide (100 mg/sqm on days 1-3), and durvalumab (1500 mg on day 1) administered every three weeks for a total of 4 courses

(induction phase), followed by durvalumab (1500 mg on day 1) every 4 weeks (maintenance phase) until completion of 24 courses (for a total of 28 courses, including the 4 courses of induction phase) or 2 years of treatment whichever occurs first, disease progression, unacceptable toxicity, patient refusal or loss of clinical benefit (**Figure 1**). Treatment with durvalumab beyond radiological disease progression (PD) according to RECIST version 1.1, 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.

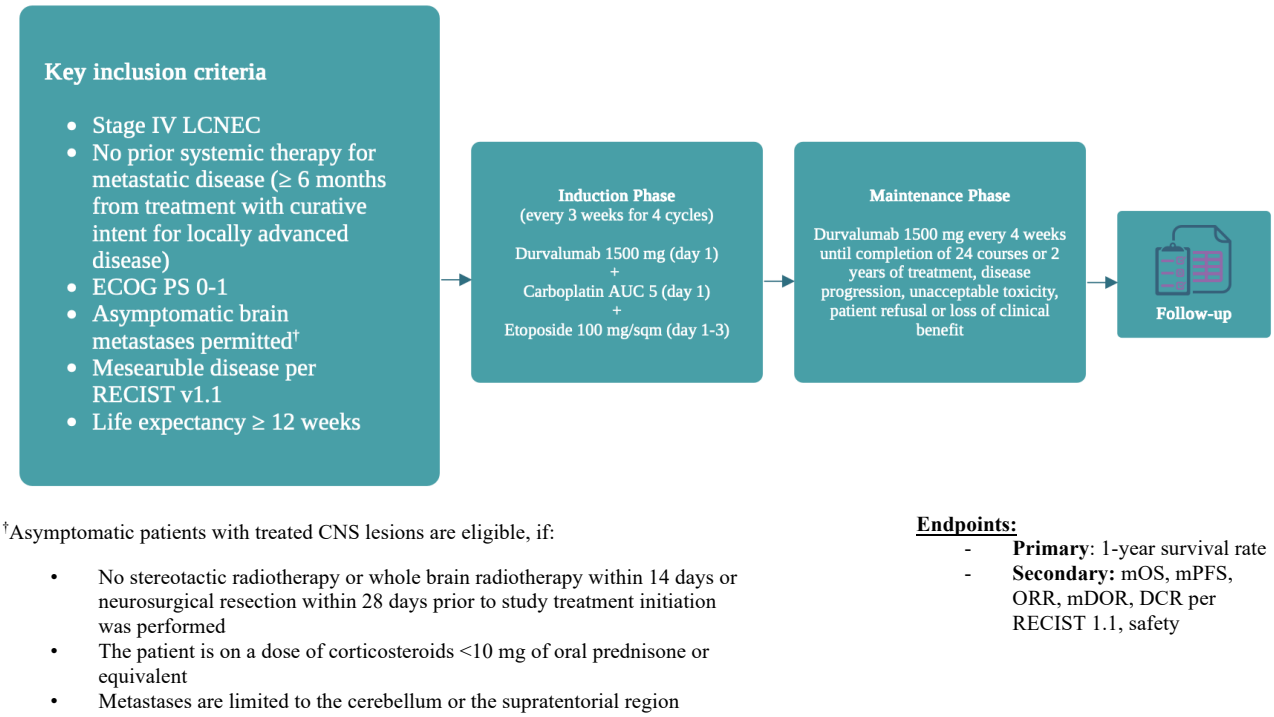

Figure 1. DUPLE study design

LCNEC: large cell neuroendocrine carcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; RECIST: response criteria in solid tumor; AUC: area under the curve; CNS: central nervous system; OS: overall survival; ORR: objective response rate; PFS: progression-free survival; DOR: duration of response; DCR: disease control rate.

Key eligibility criteria

Eligible patients were required to be ≥18 years old and to have unresectable stage IIIB or stage IV pulmonary LCNEC (histologically or cytologically documented). Additional inclusion criteria

included an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, an estimated life expectancy >12 weeks and no prior systemic anti-cancer treatment for advanced disease. Patients previously treated with chemoradiotherapy for locally advanced pulmonary LCNEC were eligible if they had received treatment with curative intent and experienced a treatment-free interval of at least 6 months from the last chemotherapy, radiotherapy, or chemoradiotherapy cycle to disease relapse, progression, or diagnosis of metastatic LCNEC. Patients were excluded if they had symptomatic brain metastases or spinal cord compression requiring immediate radiotherapy for palliation, history of leptomeningeal disease, uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. Notably, patients with asymptomatic brain metastases were eligible provided that they had no history of intracranial or spinal hemorrhage, had received adequate local therapy (≥14 days after radiotherapy or ≥28 days after surgery), were on ≤10 mg/day prednisone (or equivalent), had stable anticonvulsant therapy, and had non-progressive supratentorial or cerebellar metastases only.

Additional exclusion criteria included active autoimmune disease (e.g., inflammatory bowel disease, systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, Graves' disease, Wegener's granulomatosis, or hypophysitis) and a history of idiopathic pulmonary fibrosis. Exceptions were patients with vitiligo, alopecia, hypothyroidism stable on hormone replacement, chronic skin conditions not requiring systemic therapy, celiac disease controlled by diet, or inactive autoimmune disease for ≥5 years after evaluation by the study physician. Patients with autoimmune neurologic paraneoplastic syndromes (e.g., non-infectious encephalitis or Lambert–Eaton syndrome) were also excluded, while those with SIADH or ectopic ACTH production were eligible for inclusion.

Study objectives and endpoints

The primary objective of the study was to assess the efficacy of the combination of carboplatin, etoposide, and durvalumab in treatment-naïve patients with metastatic pulmonary LCNEC. 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 included evaluation of activity and safety of the studied regimen. The secondary endpoints were median OS, calculated from the date of registration to the date of death by any cause; 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; median Duration of Response (DoR), measured from the date of first radiological evidence PR or CR to the date of first evidence of PD, according to standard RECIST 1.1 criteria; disease control rate (DCR), considered as the sum of complete responses (CRs), partial responses (PRs) and stable disease (SD), according to standard RECIST 1.1 criteria; and safety, evaluated through the monitoring of all non-serious adverse events (AEs) and serious AEs (SAEs), defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Study assessments

Objective tumor response was assessed by investigators according to RECIST criteria v1.1. Tumor response assessments were performed at screening (within 28 days before starting treatment), at week 6 and at week 12 following Cycle 1 Day 1, and then every 12 weeks until disease progression.

For patients who continued durvalumab beyond radiological PD, a radiologic reassessment had to be performed within 8 weeks from initial investigator-assessed progression to determine whether tumor shrinkage or further progression had occurred. In case of confirmed PD, durvalumab was permanently discontinued.

All AEs were graded according to CTCAE v5.0, and were recorded from treatment initiation until 30 days after the last dose of study therapy.

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 null hypothesis that the true 1-year probability of OS was <30% was tested against a one-sided alternative. This design yields a type I error rate of 10% and power of 80% when the true 1-year probability of OS is > 45%. 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 27/05/2022 and 31/03/2025, 54 patients were screened across 15 Centers in Italy, and 46 were eligible and received at least one dose of study treatment (**Figure 2**). At the data cutoff (31/08/2025), 15 patients were still receiving treatment, whereas 31 had discontinued therapy.

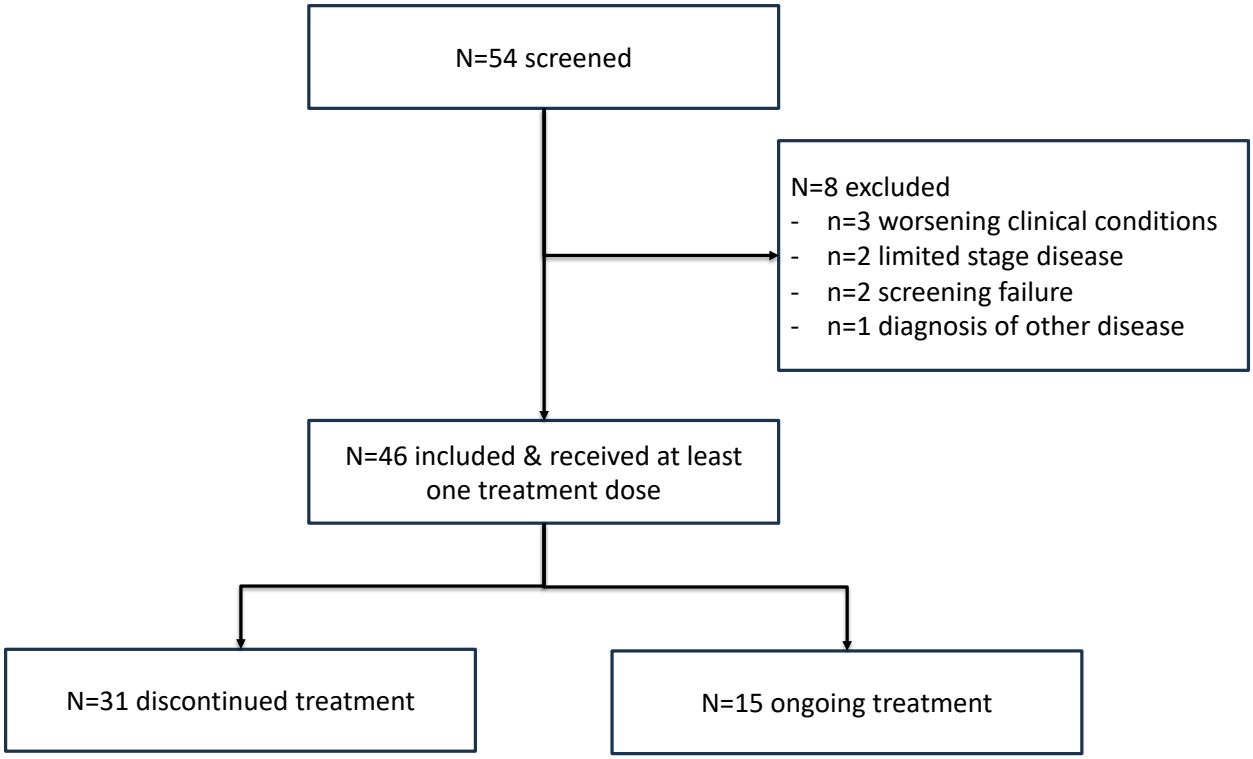

Figure 2.

Consolidated Standards of Reporting Trials diagram of the study.

Among the enrolled patients, the median age at diagnosis was 63.5 years (range, 35–82), and 18 patients (39%) were female. Regarding smoking history, 18 patients (40%) were smokers, 22 (49%) former smokers and 5 (11%) never smoker. Twenty-three patients (50%) had an ECOG PS of 0 and 23 (50%) an ECOG PS of 1. At diagnosis, 10 patients (22%) presented with stage III disease, whereas 36 patients (78%) had stage IV disease. Five patients (11%) underwent surgical treatment, and 4 patients (9%) received concurrent or sequential chemoradiotherapy.

Table 1. Demographic and disease characteristics of the patients at baseline

Variable	Category	n. (%)
Sex	Female	18 (39%)
	Male	28 (41%)
Age, years	Median (range)	63.5 (35-82)
Smoking status	Smoker	18 (40%)
	Former smoker	22 (49%)
	Never smoker	5 (11%)
	Unknown	1
ECOG PS	0	23 (50%)
	1	23 (50%)
Stage	III	10 (22%)
	IV	36 (78%)
Previous treatments	CT-RT	4 (9%)
	Surgery	5 (11%)

Outcomes

The study completed enrollment on 31/03/2025 and is currently ongoing.

At the 31/08/2025 data cutoff, survival data were not yet mature, as a minimum follow-up of one year per patient was required. Among the 35 evaluable patients (76%), the ORR was 26% (95% CI: 12–43%), corresponding to 9 patients who achieved a PR. Progressive disease was documented in 11 patients (31%), while 15 patients (43%) achieved stable disease, resulting in a DCR of 69% (24 out of 35 evaluable patients) (**Table 3, Figure 4**).

Table 3. Objective response according to RECIST criteria. ORR: objective response rate; DCR: disease control rate; PR: partial response; SD: stable disease; PD: progressive disease.

Best response (overall)	Evaluable	35/46 (76%)
	ORR	9 (26% [95%CI: 12-43%])
	DCR	24 (69% [95%CI: 51-83%])
	PR	9 (26%)
	SD	15 (43%)
	PD	11 (31%)

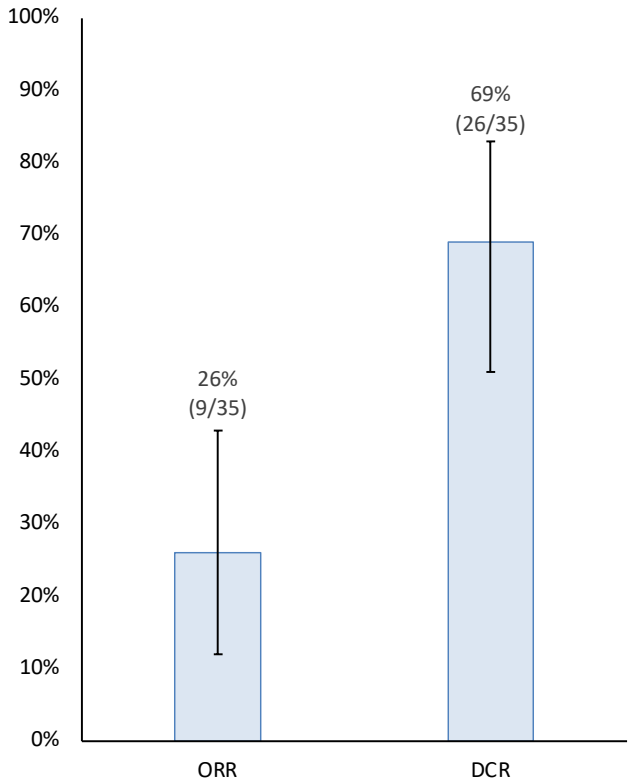

Figure 4. Objective response rate and Disease control among the evaluable patients.

Treatment exposure

Treatment exposure data was evaluable in 42 patients (91%) during the induction phase and in 22 patients (48%) during the maintenance phase, as summarized in **Table 2**.

A total of 32 patients (76%) completed induction phase, with a median of 4 cycles administered (range 1–4). Sixteen patients (73%) proceeded to the maintenance phase per protocol, receiving a median of 3 cycles (range 1–9).

Table 2.

Treatment exposure by induction phase and maintenance phase.

		N. (%)
Induction phase	Available	**42**/46 (91%)
	Completed induction	**32** (76%)
	Median n. of cycles (range)	4 (1-4)
Maintenance phase	Available	**22**/46 (48%)
	Started Maintenance	**16** (73%)
	Median n. of cycles (range)	3 (1-9)

Data on the duration of treatment were available for 28 out of 46 patients (61%). The median treatment duration was 4.77 months (range 0-18.5 months) (**Figure 3**).

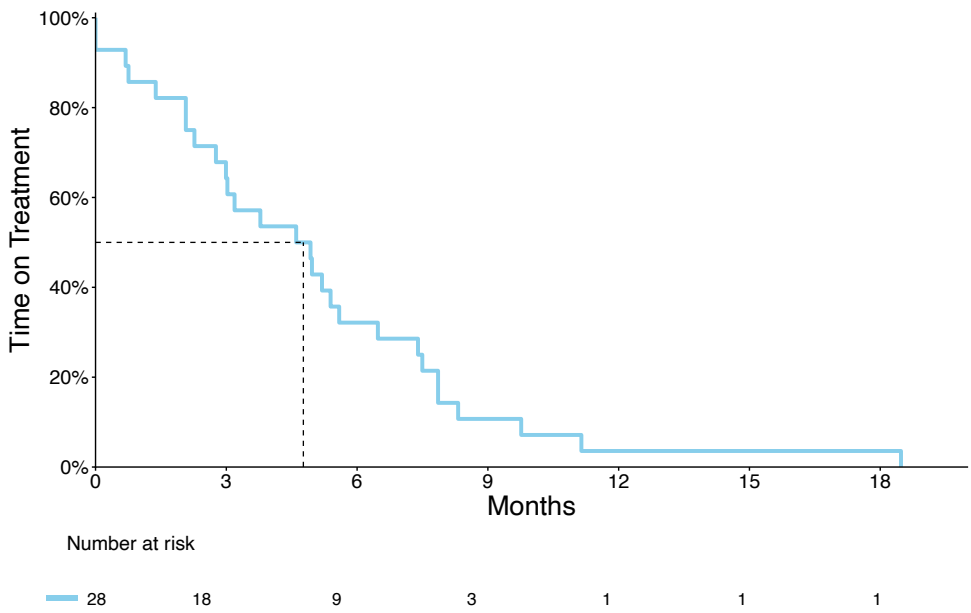

Figure 3. Median treatment duration

Safety

Safety data were available in 23 patients during both the induction and the maintenance phase. The most commonly reported AEs, irrespective of grade, were anemia (56%), neutropenia (43%) and asthenia (48%), whereas the most frequently observed grade 3–5 AE was neutropenia (43%), followed by anemia (4%) and thrombocytopenia (4%). Among the non-hematologic AEs

(83%), the most frequent were nausea (39%), asthenia (48%) and skin rash (26%) (**Table 4**). No patient discontinued treatment due to toxicity.

Table 4. Adverse events in the N = 23 patients with available safety data.

Toxicity	All grades	Grade ≥3
Hematologic toxicity	16 (70%)	10 (43%)
Anemia	13 (56%)	1 (4%)
Neutropenia	10 (43%)	10 (43%)
Thrombocytopenia	3 (13%)	1 (4%)
Non-hematologic toxicity	19 (83%)	0 (0%)
Nausea	9 (39%)	0 (0%)
Vomit	2 (9%)	0 (0%)
Diarrhea	2 (9%)	0 (0%)
Mucositis	2 (9%)	0 (0%)
Anorexia	2 (9%)	0 (0%)
Asthenia	11 (48%)	0 (0%)
Arthralgia	1 (4%)	0 (0%)
Lung toxicity	2 (9%)	0 (0%)
Skin rash	6 (26%)	0 (0%)
Hypothyroidism	2 (9%)	0 (0%)
Liver toxicity	1 (4%)	0 (0%)
Pancreatic toxicity	1 (4%)	0 (0%)

Discussion

The DUPLE study was a prospective, multicenter, phase II trial designed to evaluate the efficacy and safety of adding durvalumab to standard carboplatin-etoposide chemotherapy as first-line treatment for patients with metastatic pulmonary LCNEC. The study design was based on the demonstrated survival benefit of chemo-immunotherapy in ES-SCLC, as observed in both IMpower133 and CASPIAN phase III trials, where the addition of atezolizumab or durvalumab to platinum–etoposide significantly improved overall survival. By mirroring the SCLC paradigm, the DUPLE trial aimed to verify whether this benefit could extend to LCNEC, a rare and aggressive disease that shares similar biological features but remains clinically orphan of

evidence-based therapeutic standards. The trial enrolled 46 patients across 15 Italian Centers, representing one of the largest prospective efforts to date in this disease setting. The study completed accrual on 31/03/2025 and is currently ongoing. At the 31/08/2025 data cutoff, 15 patients were still receiving treatment, whereas 31 had discontinued therapy. Although the study is still ongoing and survival data remain immature due to the required minimum follow-up of one year per patient, the results reported here provide valuable preliminary insights into treatment exposure, antitumor activity, and safety profile of the chemo-immunotherapy combination. The baseline characteristics of the enrolled patients reflect the epidemiologic and clinical profile typically observed in pulmonary LCNEC, with a predominance of elderly male smokers and a substantial proportion of patients presenting with stage IV disease at diagnosis. Approximately half of the patients had an ECOG performance status of 1, consistent with the rapid clinical deterioration frequently associated with this malignancy. The inclusion of a small proportion of patients with stage III disease mirrors real-world clinical practice, where systemic therapy is frequently administered in the presence of unresectable or oligometastatic disease. Treatment exposure data indicate that the regimen was generally well tolerated and feasible. The majority of patients (76%) completed all four induction cycles, and nearly three quarters of those were eligible to procede to the maintenance phase, receiving a median of three cycles of durvalumab. These findings suggest that treatment adherence was satisfactory and comparable to that reported in studies of SCLC adopting similar chemo-immunotherapy schedules (7,23). Although survival outcomes are not yet mature, preliminary efficacy data are encouraging. An ORR of 26% and a DCR of 69% were observed among evaluable patients. These results, consistent with historical data in SCLC, are slightly superior to those reported with platinum–etoposide chemotherapy alone in retrospective LCNEC series, where ORR typically range from 20% to 30% and DCR rarely exceed 60% (6). These findings suggest a potential added value of durvalumab in improving tumor control in this setting. The biological rationale for this finding is strong. Molecular profiling studies have demonstrated that a subset of LCNECs shares genomic

and transcriptomic features with SCLC, including *TP53* and *RB1* co-alterations, high proliferative index, and elevated TMB. These molecular hallmarks indicate an intrinsically immunogenic tumor microenvironment that may render LCNEC susceptible to immune checkpoint blockade. The encouraging disease control observed in this trial, together with the absence of major safety concerns, supports further investigation of immunotherapy-based combinations in this rare and heterogeneous histology.

The combination of durvalumab with carboplatin–etoposide was generally well tolerated, with no treatment discontinuations due to toxicity. The most frequent AEs were hematologic, particularly anemia (56%) and neutropenia (43%), in line with the known safety profile of platinum–etoposide. Grade 3–5 neutropenia occurred in 43% of patients, a rate comparable to that seen in prior SCLC studies combining chemotherapy with PD-L1 inhibitors. Non-hematologic toxicities were mainly mild to moderate, with asthenia, nausea, and skin rash being the most common. Importantly, immune-related AEs were limited and manageable, with no cases of treatment-related death. These data confirm the overall favorable safety profile of the regimen and support its feasibility even in frail patient population, often characterized by advanced age, several comorbidities and poor performance status.

Given the historically poor prognosis and limited therapeutic options available for this disease, the observed disease control rate and manageable toxicity profile are clinically meaningful, supporting the feasibility and potential efficacy of integrating durvalumab into the standard platinum–etoposide regimen for advanced pulmonary LCNEC. The ongoing follow-up will be critical to determine whether these early signs of activity translate into improvements in survival outcomes. This trial also highlights the importance of conducting prospective, histology-specific studies in rare thoracic malignancies. The accrual of 46 patients across 15 centers within less than three years demonstrates that cooperative, network-based clinical research is feasible even in rare cancers. Future efforts should incorporate molecular stratification, as emerging evidence suggests that LCNEC comprises distinct subgroups—one resembling SCLC and another

NSCLC—potentially associated with differential sensitivity to immunotherapy (3).

The main limitation of this analysis is the immaturity of survival data, which prevents definitive conclusions on long-term efficacy. Additionally, the relatively small sample size and the lack of a control arm preclude formal comparisons with standard chemotherapy. Nonetheless, the prospective design, centralized data collection, and multicenter participation strengthen the reliability of these preliminary findings.

Conclusion

The addition of durvalumab to carboplatin–etoposide demonstrated a manageable safety profile and promising antitumor activity in patients with advanced pulmonary LCNEC. While survival data are awaited, these results suggest that immune checkpoint blockade may enhance the efficacy of platinum-based chemotherapy. The final analysis of the DUPLE study will help to define the role of chemo-immunotherapy as a potential new standard for this rare but challenging malignancy.

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