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Development of an externally controlled trial from a single-arm study to assess first-line immunochemotherapy in advanced large cell neuroendocrine lung carcinomas: a study protocol from the FIRST-NEC GFPC 01-2022 trial

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ABSTRACT

Background Large-cell neuroendocrine carcinomas (LCNECs) of the lung are rare tumours with poor prognosis. A platinum-based regimen is currently the recommended first-line treatment for advanced LCNECs. Retrospective studies suggest potential benefit from immune checkpoint inhibitors (ICIs) but prospective data is lacking.

Methods and analysis The ongoing phase II FIRST-NEC (First-line treatment for NeuroEndocrine Carcinoma) externally-controlled trial evaluates the efficacy and safety of durvalumab combined with platinum-etoposide as first-line treatment in locally advanced, ineligible for local therapy or patients with metastatic LCNEC. Histopathological diagnosis is centrally confirmed. All patients receive four induction cycles once every 3 weeks with durvalumab 1500 mg and platinum-etoposide. Durvalumab is maintained once every four weeks for up to 24 additional cycles. The primary endpoint is the 12-month progression-free rate (12M-PFR) as per central radiological review. Secondary endpoints include progression-free survival (PFS), overall survival (OS) and safety. Efficacy is assessed every 10 patients using a Bayesian approach, with a futility rule stopping the trial if the probability that 12M-PFR ≤15% exceeds 80%. Based on an A'Hern-Fleming design, 51 evaluable patients are required. Given the rarity of LCNEC, we developed an innovative approach based on target trial emulation to compare the survival outcomes of ICI plus chemotherapy (PFS and OS) to an external control arm (real-world PFS and OS), using real-world data from the Epidemiological Strategy and Medical Economics-Advanced and Metastatic Lung Cancer database.

Ethics and dissemination This clinical trial received approval from the competent authorities on 14 March 2024. The results from the final clinical report will be published in medical journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This externally-controlled prospective phase II trial evaluates first-line immune-checkpoint inhibitors combined with standard chemotherapy in advanced large cell neuroendocrine lung carcinomas.
⇒ The study leverages a nationwide external comparator derived from the French Epidemiological Strategy and Medical Economics-Advanced and Metastatic Lung Cancer database using prespecified eligibility criteria aligned with the target trial population.
⇒ A target trial emulation framework, combined with causal inference methods, is used to compare efficacy estimates, including overall survival and real-world progression-free survival.
⇒ Centralised histopathological confirmation by expert thoracic pathologists ensures diagnostic accuracy.
⇒ Residual confounding cannot be excluded and is addressed through planned sensitivity analyses designed to quantify the potential magnitude of bias.

Protocol identifier V.2.0 dated 11 December 2024.
Trial registration number NCT06393816

INTRODUCTION

Large-cell neuroendocrine carcinomas (LCNECs) of the lung are rare and aggressive epithelial tumours accounting for 2–3% of lung cancers.[1] The WHO classification defined in 2021 LCNECs and small-cell lung cancers (SCLCs) as primary pulmonary neuroendocrine neoplasms.[2] The diagnosis of LCNECs remains challenging and ideally requires a central pathological review, with confirmation by a pathologist expert. Indeed, only 70% of the suspected cases are confirmed.[3 4] In line with the former

SCLC standard of care, the first-line treatment for metastatic LCNEC remains a combination of etoposide and platinum.[5]

To date, only three prospective phase II trials investigated first-line chemotherapy (CT) in patients with metastatic LCNEC[5–7] and reported median progression-free survival (PFS) ranging from 4.0 to 5.2 months and a poor median overall survival (OS) of approximately 8–10 months, prompting the critical need for effective treatments in patients with LCNEC.

Cancer immunotherapy (IO) revolutionised the field of oncology in the last decade. Recent retrospective series supported the promising clinical efficacy of IO in lung LCNECs.[8–13] Furthermore, a recent meta-analysis further supports the use of IO in this aggressive disease.[14] However, to date, disease scarcity prevents evidence studies from being conducted and notably prospective randomised trials with large sample sizes are lacking.

The immune checkpoint inhibitor (ICI) durvalumab targeting programmed death-ligand 1 (PD-L1) has been approved in combination with platinum-etoposide in patients with stage IV SCLC. Considering the similarities in the current management of patients with LCNEC and SCLC, combining durvalumab with platinum-etoposide CT appeared as a promising option in patients with advanced LCNEC. The First-line treatment for Neuro-Endocrine Carcinoma (FIRST-NEC) trial aims to assess prospectively the efficacy of durvalumab combined with etoposide and platinum-based CT as a first-line treatment in patients with advanced LCNEC.

Faced with the rarity of LCNECs, the implementation of randomised controlled trials (RCTs) at a national level in a reasonable timeframe is inevitably limited. Overcoming these constraints required dedicated methodology. The FIRST-NEC trial therefore developed an innovative design and included an externally controlled arm (ECA) that emulates an RCT from observational data. In this report, we describe the methodology that will be applied in the FIRST-NEC trial to provide a robust comparison of survival outcomes between patients treated with the experimental treatment and real-world patients exclusively treated with CT. This analysis will leverage the real-world data experience to provide a reliable ECA and to assess real-world PFS (rwPFS) and OS.

METHODS AND ANALYSIS

Study design and objectives

The FIRST-NEC trial is an open-label, externally controlled phase II study designed to assess the efficacy of durvalumab combined with CT (etoposide and platinum, either cisplatin or carboplatin) as a first-line treatment for patients with advanced LCNEC, as confirmed by centralised expert-pathologist review (figure 1).

The primary objective is to determine the efficacy of the combination, as measured by progression-free rate at 12 months (12M-PFR) in patients with a centrally confirmed LCNEC. In the CASPIAN trial comparing the combination of platinum-etoposide with platinum-etoposide plus durvalumab in patients with SCLC, the median PFS was similar between the two groups (5.4 vs 5.1 months). As the median PFS reflects the time point at which 50% of patients have progressed, it may be influenced by early events and delayed treatment benefits may be overlooked. Indeed, the separation of the PFS curves occurred only beyond 6 months, and at 12 months, the curves diverged significantly (12M-PFS: 5% vs 18%).[15] This pattern suggests that a subgroup of long-term responders highly benefits from IO. By analogy with SCLC, the 12-month PFR rate was chosen as a clinically relevant measure of durable disease control when adding IO to the standard CT regimen. The secondary objectives are, in confirmed patients with LCNEC: the 12-week objective response rate (12W-ORR), the 12-week disease control rate (12W-DCR), PFS, OS and the safety profile as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.5.0. The 12-week time point selected for the secondary endpoints (12W-ORR and 12W-DCR) reflects early antitumour activity at a predefined and clinically meaningful time point (after the two first scheduled radiological assessments). Efficacy

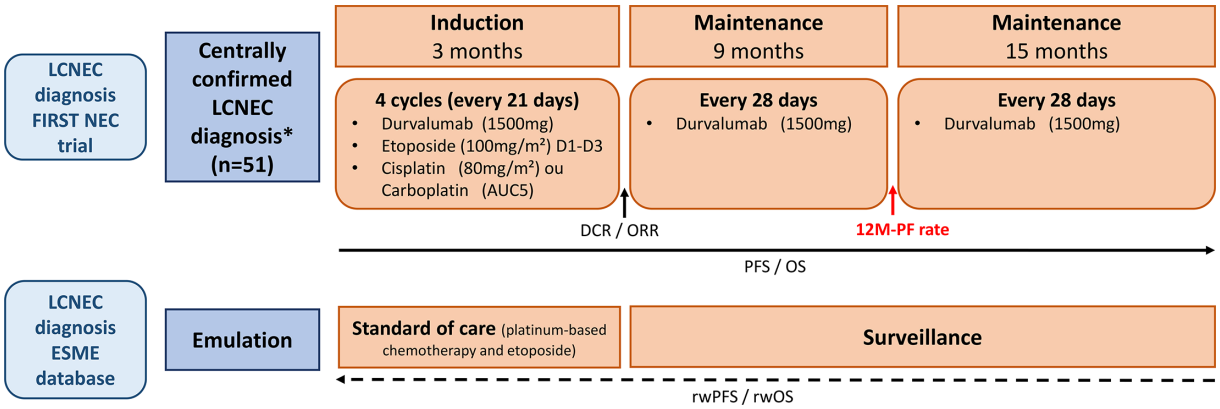

Figure 1 FIRST-NEC study flow chart and its exploratory effectiveness analysis. AUC, area under the curve; DCR, disease control rate; ESME, Epidemiological Strategy and Medical Economics; FIRST-NEC, First-line treatment for NeuroEndocrine Carcinoma; LCNEC, large-cell neuroendocrine carcinoma; 12M-PF; 12-month progression-free; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; rwOS, real-world OS; rwPFS, real-world PFS.

endpoints will be assessed using the Response Evaluation Criteria In Solid Tumor (RECIST) V.1.1.[16]

The first exploratory objective is to assess the efficacy of the combo CT-IO versus CT alone in the first-line treatment of patients with LCNEC. Survival outcomes (PFS and OS) of the FIRST-NEC trial population will be compared with rwPFS and OS of an ECA derived from the Epidemiological Strategy and Medical Economics-Advanced and Metastatic Lung Cancer (ESME-AMLC) database, using a target trial emulation (TTE) approach. Additional exploratory objectives include assessing the concordance rate of histopathological diagnoses between local analysis and centralised pathological review. Finally, immunohistochemical (like PD-L1 expression on tumour and immune cells, and retinoblastoma protein Rb expression) and molecular biomarkers will be studied as predictive (12M-PFR and ORR) and prognostic (OS) factors of efficacy.

Current study status

The FIRST-NEC trial is sponsored by the Comprehensive Cancer Centre Léon Bérard in Lyon, France, in partnership with the French Pneumo-Oncology Group (GFPC). The trial has been registered on ClinicalTrials.gov (NCT06393816). FIRST-NEC has been activated in 30 sites in the GFPC ('Groupe Français de Pneumo-Cancérologie'), a French cooperative group of thoracic oncology. Recruitment began in June 2024 and is expected to last 36 months. Between June 2024 and November 2025, 40 patients were enrolled, including 24 patients with confirmed diagnosis, 7 unconfirmed and 9 screen failures or with ongoing diagnoses. The protocol was presented during the 2025 American Society of Clinical Oncology meeting (poster session).[17] The FIRST-NEC trial is partly funded by a French governmental funding programme dedicated to clinical research Programme Hospitalier de Recherche Clinique. Durvalumab is provided by AstraZeneca.

Study population

The population in the FIRST-NEC trial is defined by the following main selection criteria (a comprehensive list of selection criteria is available in online supplemental S1): patients aged ≥18 years at the time of study entry; locally documented histological diagnosis of LCNEC (2021 WHO Classification of Lung Tumors[18]); sufficient tissue material to achieve central histological confirmation and exploratory analyses (one representative formalin-fixed paraffin-embedded (FFPE) block or at least 10 unstained slides); locally advanced disease (Stage III) not eligible for locoregional therapy or metastatic disease (Stage IV) in first line treatment (eighth tumour, node, metastasis classification); measurable disease as per the RECIST V.1.1; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1; absence of previous treatment for LCNEC in a metastatic setting; no previous treatment with a programmed cell death protein 1 or PD-L1 inhibitor, including durvalumab.

All patients must give their written informed consent prior to any procedure specific to the FIRST-NEC trial.

The construction of the ECA, composed of patients identified through real-world data sources, aligns with regulatory expectations and methodological guidance,[19] providing that key design elements—such as inclusion/exclusion criteria, baseline characteristics and outcome definitions—are closely matched between the experimental arm and the real-world cohort.[20 21]

In a first step, a targeted literature review identified two suitable data sources involving CT in the relevant indication: the French ESME-AMLC database[20] and the US FLATIRON programme.[21] Both potential data sources met a set of key eligibility criteria, making them suitable for constructing an ECA. These criteria included: a sufficiently large sample of patients treated with CT within the relevant indication (with prior power calculations based on a calibration approach); comparable definitions of outcomes and adjustment covariates to those collected in FIRST-NEC; the availability and completeness of baseline characteristics, particularly for identified confounding factors; sufficient overlap between populations on key characteristics; and timely access compatible with the planned analysis timelines. This data qualification phase aimed to assess the feasibility of constructing the ECA from the ESME-AMLC database, which was ultimately deemed to best meet the selection criteria.

The ongoing ambispective UNICANCER ESME-AMLC real-world data cohort (ClinicalTrials.gov NCT03848052) is derived from electronic health records of consecutive patients who have been treated for lung cancer since 2015 at one of the 38 participating sites (private non-profit comprehensive cancer centres and public hospitals). The ESME-AMLC cohort has been authorised by the French data protection authority (initial authorisation no. DE-2017-397 and subsequent amendment in accordance with the General Data Protection Regulation). In accordance with the authorisations issued by the French authorities, no formal, dedicated informed consent is required; however, all patients have approved the use of their data. Data are routinely collected by continuously trained operators using an electronic data collection tool. Online consistency checks enable continuous data monitoring. This dynamic cohort is prospectively updated annually on vital status and includes newly diagnosed patients undergoing treatment. Approval for the use of data from patients with LCNEC was granted by the scientific committee of ESME-AMLC data platform (ref. ESME CBP 2023–03). From 2015 (date of diagnosis of the first patients included in the database) to 2023, 61 139 patients with lung cancer, including 1020 with LCNEC all stages combined, followed for a median duration of 58 months, were included in this database. These numbers will be updated at the time of the analysis.

The emulation process using the ESME database to construct a robust real-world external control arm follows an approach successfully applied in another tumour

type,[22] thereby reinforcing the comparative validity of survival outcomes.

The comparison with the ECA will be conducted using the TTE framework to prevent common design-related biases, including bias related to selection and treatment misclassification.[23] Eligibility criteria for the phase 2 trial will be applied to the ECA to ensure comparability of the two arms. All inclusion and exclusion criteria specified in the trial protocol will be replicated in the ECA when possible. Variables not directly available in the real-world database will be approximated using proxy measures. The final ECA will be defined as patients meeting these harmonised criteria (table 1).

Outcomes

FIRST-NEC trial outcomes

The primary endpoint, 12M-PFR, will be defined as the proportion of patients in complete response (CR), partial response (PR) or stable disease (SD) status, as determined by central review based on radiological evaluation performed 12 months±2 weeks after treatment initiation. Patients who die due to disease progression or

Table 1 Main inclusion/exclusion criteria and application in the ESME-AMLC data platform

	Criterion	FIRST-NEC trial arm definition	ECA application in ESME-AMLC data platform
Inclusion criteria	Age	≥18 years.	Directly applied.
	Histology	Locally documented histological diagnosis of LCNEC of the lung.	Histological type: neuroendocrine large cell carcinoma. Date of diagnosis: Since 1 January 2015 (database entry) to September 2025. Histological diagnosis only.
		Patient must have sufficient tissue material to achieve central histological confirmation and exploratory analyses.	Not available.
	Setting of the disease and treatments	Locally advanced (Stage III) not eligible for locoregional therapy or metastatic (Stage IV) in first line treatment. *Nota Bene*: patients with recurrence of local or locally advanced LCNEC are eligible to the trial provided that recurrence occurs beyond 3 months after the last chemotherapy administration.	- Stage III (without radiotherapy or surgery) and stage IV. First line treatment: platinum-based chemotherapy (carboplatin or cisplatin) AND etoposide (≥1 cycle). - Exclusion of other platin-salt bitherapy (ex: carbo/paclitaxel) Immunotherapy-naïve (neither before, nor during, nor after chemotherapy).
	Tumour	Measurable disease as per the RECIST 1.1.	Not available.
	ECOG Performance Status	≤1.	≤1 (approximated: 1 month before C1D1).
Exclusion criteria	Previous treatments	Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.	Directly applied as a criterion used for defining the disease setting.
	Brain metastases	CNS metastases, unless asymptomatic or previously treated and stable and asymptomatic at the time of randomisation for at least 15 days.	Exclusion of symptomatic CNS metastases at the first cycle of chemotherapy.
	Allogenic organ transplantation	History of allogenic organ transplantation.	Not available.

CNS, central nervous system; ECA, externally controlled arm; ECOG, Eastern Cooperative Oncology Group; ESME-AMLC, Epidemiological Strategy and Medical Economics-Advanced and Metastatic Lung Cancer; FIRST-NEC, First-line treatment for NeuroEndocrine Carcinoma; LCNEC, large-cell neuroendocrine carcinoma; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumor.

toxicity before any tumour evaluation will be considered in failure.

The secondary efficacy endpoints include the 12-week objective response rate (12W-ORR), defined as the proportion of patients with a CR or PR at 12 weeks±2 weeks, and the 12W-DCR, defined as the proportion of patients with a CR or PR or SD at 12 weeks±2 weeks. The survival endpoints are PFS, defined as the time from the date of the first administration of the study treatment to the date of the first documented disease progression (reviewed centrally and according to investigators) or the date of death from any cause, and OS, defined as the time from the date of the first administration of the study treatment to the date of death from any cause.

Real life ESME database outcomes

For the external control arm (patients from ESME-AMLC database), rwPFS will be determined using two different approximation approaches. rwPFS will be either defined as the time from the start date of the platinum-based regimen treatment for advanced LCNECs to the date of disease progression or death (any cause), whichever came first; or to the time to first subsequent therapy or death (any cause), whichever came first.

The OS using the ESME-AMLC database is defined as the time from the start date of the platinum-based regimen treatment for advanced LCNECs to the date of death from any cause, measured using observational data sources such as electronic health records, registries or claims database.

Study objectives and endpoints are listed in online supplemental S2.

Study treatments

All eligible patients will be treated with experimental therapy, regardless of whether the local diagnosis has been confirmed. During the 3-month induction period, durvalumab 1500 mg is administered concomitantly to etoposide (100 mg/m^2) and either cisplatin (80 mg/m^2) or carboplatin (area under the curve 5), according to the renal function. The regimen is repeated on a 21-day cycle. All patients receive granulocyte-colony stimulating factors 24 hours after each CT cycle. Erythropoietin is allowed in cases of anaemia, and patients may be premedicated with anti-emetics in accordance with local practices. Durvalumab 1500 mg is then administered every 28 days as maintenance therapy for 24 additional months. Toxicity management guidelines follow the Reference Safety Information for the respective study drugs (summary of product characteristics of chemotherapies and investigator's brochure of durvalumab). Study treatments are continued until the end of the 24-month maintenance period (for a total of 27 months), unless disease progression, clinical deterioration, unacceptable toxicity or patient refusal occurs. For patients whose diagnosis is not confirmed by central pathological review, the experimental treatment may continue in case of clinical benefit.

As shown in table 1, eligible patients in the ECA must have received first-line platinum-based CT (carboplatin or cisplatin) in combination with etoposide, with at least one cycle required. Patients treated with other platinum doublets (eg, carboplatin/paclitaxel) were excluded, and no IO was permitted before, during or after CT.

Study procedures in FIRST-NEC

Central pathological review

A central pathological review of the initial diagnosis has been implemented for all patients included in the single-arm phase II trial. To achieve central histological confirmation and exploratory analyses, sufficient tumour tissue material must be made available (one representative FFPE block or at least 10 unstained slides). Tumour samples are sent to the central expert pathologists at the time of inclusion. Central confirmation is based on the WHO classification criteria, using immunohistochemistry markers (Chromogranin A, Synaptophysin, ±CD56 and INSM1, TTF1, p40, Rb, BRG1 and Ki67).

Additional biological analyses are conducted in patients with a centrally confirmed diagnosis of LCNEC who have consented to optional ancillary studies.

These analyses include additional immunohistochemistry markers such as PD-L1 (evaluated using three scores: Tumor Proportion Score, Immune Cell and combined Positive Score, DLL3, ASCL1 and NEUROD1, as well as molecular analyses, including whole-transcriptome gene expression and mutational analysis of the tumour. Other analyses may be performed based on the evolving knowledge at the time of analysis.

Experimental study treatments may be introduced before the expert pathologist reaches a conclusion; these are administered to all patients, regardless of the central confirmation.

Study procedures

Throughout the treatment period, patients are monitored according to the treatment schedule. Before each infusion of treatment, patients undergo a full physical examination (including determination of the ECOG PS and vital signs) and laboratory assessments (haematology, biochemistry, thyroid function tests and serum pregnancy tests). If clinically indicated, urinalysis and cardiac assessment (12-lead ECG and left ventricular ejection fraction) may be performed. The primary endpoint (12m-PFR) is assessed using RECIST V.1.1 criteria, with brain, chest, abdomen and pelvis imaging (either CT scan or MRI) performed every 6 weeks for the first 13 cycles and then every 12 weeks thereafter (relative to the start of treatment). Tolerance (NCI-CTCAE V.5.0) is continuously assessed throughout the patient's participation. After treatment ends, a safety follow-up is arranged for up to 90 days after the last treatment administration, during which all the above-described study assessments are repeated. Vital status will be updated for all patients once at the end of the study to describe OS.

Central radiological review

To ensure a standardised assessment of the primary endpoint, a central radiological review has been implemented. The GFPC constituted a panel of experts to review the imaging of all participants from the time of inclusion until the first documented disease progression (RECIST V.1.1).

Statistical methods

Generalities

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document 'Statistical Principles for Clinical Trials'. Statistical analyses will be performed using SAS software V.9.4 or later.

Descriptive statistics will be provided for characterising and assessing patient tolerance to treatment. Adverse events (AEs) will be described using the NCI-CTCAE V.5.0, by System Organ Class and Preferred Term and Grade. Number of patients with any grade of AE, immune-mediated AE, treatment-related AE, AE leading to premature treatment discontinuation as well as serious AE will be described.

The Kaplan-Meier method will be used to estimate survival endpoints, and a survival curve will be plotted over time.

FIRST-NEC trial sample size calculation

No formal sample size is required with the Bayesian approach followed in this study. By analogy with a frequentist approach based on a single-stage phase II design (A'Hern-Fleming) with P_0 = 15%,[3] P_1=30%, 85% power and a one-sided 5% alpha risk, 51 evaluable patients with a centrally confirmed diagnosis of LCNEC have to be included. Assuming that in 30% of the cases the diagnosis of LCNEC will not be confirmed,[7] 80 patients should be included in the study.

The whole population will be composed of all included patients, regardless of central review. The 'efficacy-evaluable' population (n=51) will be composed of the subgroup of patients without major protocol violation regarding inclusion/exclusion criteria having:

- Central histopathological confirmation of the diagnosis.
- At least one dose of study drug administered (durvalumab and CT).

External control arm sample size calculation

As the ECA is derived retrospectively from ESME-AMLC database, its sample size is determined by the availability of suitable patients (regarding FIRST-NEC eligibility criteria). Therefore, no formal prospective calculation was performed for this arm. However, we anticipate identifying approximately 400 patients in the ECA, yielding an allocation ratio of approximately 1:8.

Assuming the hypotheses (p0=15% and p1=30%, transferable to the ECA and experimental arms, respectively), using Schoenfeld's method and assuming a two-sided alpha level of 5%, the estimated statistical power to detect this difference is approximately 85%, based on the total sample size and expected number of events (436 events). This level of power is considered sufficient to support the comparative analysis between the investigational treatment and the ECA.

Bayesian approach

Efficacy will be evaluated sequentially after inclusion of 10, 20, 30 and 40 patients with a centrally confirmed diagnosis of LCNEC in the study. If poor clinical activity is observed at each stage, the study will be stopped to enrolment. Less than P_0=15% of 12M-PFR is considered as the inefficacy boundary. A posterior probability higher than 80% to have a 12M-PFR lower than P_0 can be considered as limit for inefficacy. Figure 2 illustrates the probability that the distribution density of 12M-PFR is lower than 15%. Recommendation to stop the study for inefficacy should be proposed if Pr(12M-PFR <15%) >80%. If there is no early stopping, the final probability (ie, Pr(12M-PFR >15%)) will be updated with its 95% CI (called the 95% credibility interval).

12M-PFR will be considered a random variable following a binomial distribution Bin(n, p) where n is the sample size and p is the underlying true 12M-PFR. The a priori distribution of p (representing knowledge of the probability of non-progression observing the data) will be prespecified. As there is very little information available in the literature on which to define the prior distribution,

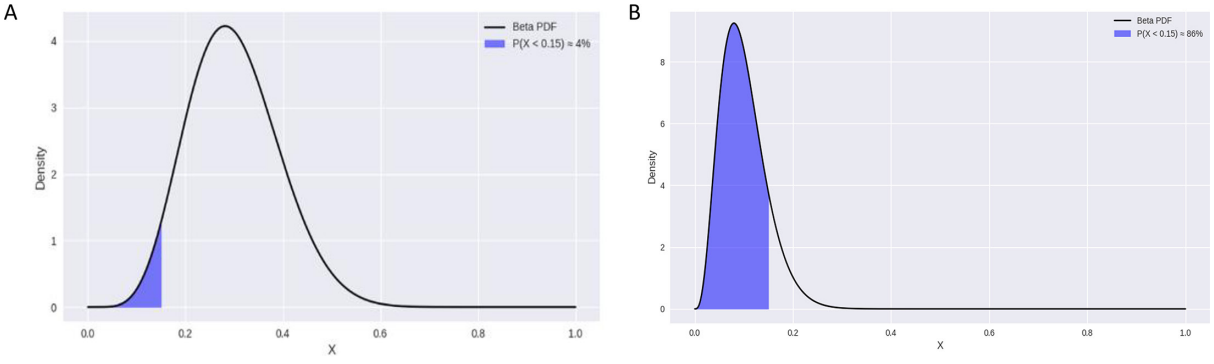

Figure 2 Representation of the posterior distribution of the 12M-PFR with the futility zone in blue. (A) A low probability (4%) that 12m-PFR <15%, (B) high probability (86%) that 12M-PFR <15%. 12M-PFR; 12-month progression-free rate; PDF, Probability Density Function.

an uninformative a priori distribution Beta (1,1) will be considered.

An independent monitoring committee, comprising two medical oncologists who are not involved in this trial and a methodologist, will be responsible for interpreting these interim results, monitoring patient safety and ensuring that an acceptable benefit/risk ratio is maintained throughout the study. The first meeting was scheduled 6 months after accrual begins (January 2025). Thereafter, meetings will be scheduled in line with interim analyses, or more frequently in the event of major safety issues. The committee will make recommendations on whether to continue the study and communicate these to the study's scientific committee. The sponsor may convene the independent committee at any time if necessary.

EXPLORATORY ANALYSIS: TARGET TRIAL EMULATION

An exploratory comparative analysis will be conducted to assess PFS and OS from the FIRST-NEC trial in comparison with the ECA derived from the ESME-AMLC database. This externally-controlled trial (ECT) approach uses the methodological framework of TTE, as theorised by Hernan and Robins.[24 25] When applied to the FIRST-NEC trial, this will first involve specifying the protocol for a hypothetical randomised pragmatic trial that would address the causal question of interest (ie, demonstrating the superiority of the durvalumab plus platinum-etoposide combination over a platinum-based regimen alone in patients with first-line advanced lung LCNEC). This will then be attempted using the ESME-AMLC cohort.

ECT, by explicitly emulating a clinical trial is a useful approach for providing robust efficacy estimates, as it minimises common design-related biases. These biases include those related to selection and treatment misclassification, which result from misalignment of the times at which eligibility is ascertained, treatment is assigned and follow-up begins.[26] TTE will be combined with the relevant statistical adjustment techniques to control for confounding biases and achieve causal inference. The classification of the confounders will be supported by a literature review, and the corresponding hypotheses will be modelled using a causal directed acyclic graph.[24]

To control for differences in baseline clinical characteristics across the treatment arms, the following strategy will be employed. First, to reduce confounding and improve comparability between the single-arm trial population and the external control cohort, the characteristics of patients identified as confounders will be included in a propensity-score model. Common propensity-score overlap and covariate balance between treatment arms before and after weighting will be assessed using standardised mean differences. Second, the efficacy of the experimental combination will be estimated and compared with CT alone using weighted Cox regressions with stabilised inverse-probability weighting, with calculation of PFS and OS HR. As a sensitivity analysis, HR will also be estimated using the G-computation approach.[27]

Finally, two complementary approaches will be employed to investigate unmeasured confounding factors: First, a quantitative bias analysis, followed by a method based on E-value calculation.[28 29] If these methods fail to conclusively detect the presence and/or magnitude of uncontrolled confounding factors, or to assess the robustness of the study results with respect to alternative assumptions, negative controls could be employed by linking ESME-AMLC to Système National des Données de Santé to obtain variables unrelated to cancer.[30]

Given the absence of centralised pathological review for LCNEC diagnoses within the ESME-AMLC database, a comparison of rwPFS will be performed on confirmed diagnoses (target population n=51) as well as on the total cohort of patients included prior to centralised review (theoretically n=80) as sensitivity analysis. Similarly, the OS in the ESME-AMLC database will be compared with that of patients in whom a diagnosis of LCNEC has been centrally confirmed in FIRST-NEC trial and with that of the total cohort (confirmed and not confirmed).

Patient and public involvement

The patients and the public were not involved in the design or dissemination plan of the study.

ETHICS AND DISSEMINATION

This clinical trial is conducted in accordance with the ethical principles laid down in the Declaration of Helsinki and the ICH guidelines for Good Clinical Practices. The trial was registered on the European Medicines Agency database, number 2023–506590-35-00 and on ClinicalTrials.gov, number NCT06393816. The trial protocol received approval from the competent authorities on 14 March 2024. With the change in European Union (EU) clinical trial regulation, all clinical trial processes in the EU are now centralised through the Clinical Trials Information System (CTIS) platform that replaces the previous submissions to national competent authorities and ethics committees. As a result, ethics committees no longer provide individual reference numbers. Instead, the CTIS assigns a single EU CT number that covers all regulatory and ethics evaluation. The reference of the FIRST-NEC trial is: 2023–506590-35-00. The Ethics Committee that reviewed and approved the study was the CPP Sud-Méditerranée IV (cppsudmed4@chu-montpellier.fr).

All patients from the FIRST-NEC trial must provide written informed consent. Personal data collection and processing will comply with the reference methodology (MR-001) of the *Commission Nationale de l'Informatique et des Libertés* (approval reference number 1994173 v 0).

The ESME-AMLC cohort was authorised by the French data protection authority (ref DE-2017-397) and approval for the use of data was granted by the scientific committee of the ESME-AMLC data platform (ref. ESME CBP 2023–03). An independent monitoring committee will monitor

patient safety and the benefit/risk ratio throughout the study.

The data and results of this research will be available on reasonable request from the corresponding author and results from the final report will be published in medical journals. Any author with a significant contribution to trial design, execution, analysis and reporting will be cited.

DISCUSSION

The current standard of care for treating patients with advanced pulmonary LCNEC is a regimen combining etoposide with a platinum-based drug (either carboplatin or cisplatin, depending on renal function). However, despite the limited efficacy of CT in this situation, the recommended treatment has remained unchanged for years, pointing to an urgent medical need for new and effective anticancer treatments.

FIRST-NEC is an externally-controlled phase II trial evaluating the efficacy of combining durvalumab with the standard of care for the initial treatment of patients with advanced pulmonary LCNEC. According to the clinicaltrials.gov website, there are currently some prospective clinical trials evaluating the efficacy of an ICI in combination with CT (NCT06049966; NCT05470595). However, none of these trials have published results to date and none have central pathological confirmation of the diagnosis. Indeed, FIRST-NEC is the first trial to assess the efficacy and safety of ICIs combined with standard CT in patients whose diagnosis of pulmonary LCNEC has been centrally confirmed by expert pathologists. Compared with previous and current trials, this central confirmation of the histopathological diagnosis is a major strength; assuming that 30% of patients with a local diagnosis of pulmonary LCNEC have another tumour type (mainly SCLC),[3] the other ongoing trials will not provide accurate clinical efficacy data specific to the LCNEC population. Furthermore, the availability of mandatory pathological material on inclusion in this trial will enable attempts to identify potential predictive factors for response to IO.

In the case of rare cancers, the low incidence rate makes it unfeasible to conduct large RCTs at a national level within a reasonable timeframe. Although the new European Clinical Trial Regulation permits a single centralised regulatory submission via the CTIS, launching international trials remains challenging in terms of logistics and funding. In this context, support from a medical society or network of investigators is crucial for selecting participating sites and ensuring their adherence to the project. In this trial, the GFPC is responsible for selecting and activating the investigational sites, and will ensure the quality control of study data. The selected sites are accustomed to collaborating with the GFPC, so it is expected that their interactions will be more effective than with other coordinating centres. Furthermore, all investigators at the selected sites are committed to including patients in GFPC-labelled studies.

The study was designed using a sequential Bayesian approach to enable continuous monitoring of the primary efficacy outcome. This adaptive design uses data obtained during the trial to update the results. It provides great flexibility regarding the number and frequency of interim analyses, enabling the study to be closed for evaluation as early as possible if sufficient promising activity is not demonstrated. The Bayesian method is a probabilistic approach that enables endpoint distribution to be estimated without the need for formal testing. This avoids the methodological bias associated with multiple testing.

FIRST-NEC is a single-arm phase II trial. Therefore, while the efficacy results can be described in relation to historic controls, a statistical comparative analysis between the experimental treatment and the standard of care is not possible. However, the use of an ECA enables exploratory comparisons of survival outcomes (rwPFS and OS) between combination ICI-CT and CT alone. Several factors support the robustness of the methodology used to construct and analyse this ECA. First, data were collected from the ESME-AMLC database from patients treated since 2015, and the CT regimen used in the FIRST-NEC trial (etoposide and platinum) has remained unchanged since 2013.[5] Second, applying the design principles of the TTE framework can prevent common design-related biases. However, it is important to note that TTE does not eliminate biases such as confounding bias. The FIRST-NEC trial will address the identification and mitigation of measured and residual confounding biases using the appropriate analytical techniques already employed by the statistical study team.[31 32] Finally, in the context of rare diseases with significant unmet clinical needs, an ECA may provide additional information on the accuracy of the results and how they compare with standard treatments. This study, designed with a rigorous and innovative methodology, aims to generate high-quality evidence supported by a TTE that could help redefine therapeutic strategies and improve the outcomes in this underrepresented population.

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