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A Randomized clinical trial evaluating the impact on survival and quality of life of ^{177}Lutetium[Lu]-edotreotide versus everolimus in patients with neuroendocrine tumors of the lung and thymus: the LEVEL study (GETNE T-2217)

Jaume Capdevila[1*], Virginia Pubul[2], Urbano Anido[3], Thomas Walter[4], Javier Molina-Cerrillo[5], Teresa Alonso-Gordoa[5], Rocio Garcia-Carbonero[6,7,8], Maria San-Roman-Gil[6], Belen Llana[9], Paula Jimenez-Fonseca[10], Marta Benavent Viñuales[11], Catherine Ansquer[12], Eric Baudin[13], Come Lepage[14], Maribel del Olmo-García[15,16], José Carlos Ruffinelli[17], Amandine Beron[18], Magalie Haissaguerre[19], Emmanuel Deshayes[20], David Taïeb[21], Sergio Baldari[22], Maddalena Sansovini[23], Sara Cingarlini[24], Angelina Filice[25], Francesco Panzuto[26], Rosa Álvarez-Álvarez[27], Laurence Lousberg[28], Frank Aboubakar Nana[29,30], Jorge Hernando[1], Alejando García-Álvarez[1], Amparo García-Burillo[1], Guillermo Villacampa[31], Timon Vandamme[32,33], Nicola Fazio[34] and Alice Durand[4]

Abstract

Background Everolimus is the only approved therapy for patients with advanced neuroendocrine tumors (NET) of lung and thymus and new treatment options are urgently needed. Expression of somatostatin receptor 2 (SSTR2) is frequently seen in functional imaging in lung-NETs opening the opportunity to treat SSTR2 positive patients with radioligand therapies (RLT). Retrospective data suggest a potential meaningful benefit of RLT directed to SSTR2 in lung-NET patients.

Methods The LEVEL trial is a randomized, open-label, phase III international trial of ^{177}Lu-edotreotide versus everolimus in patients with progressive, locally advanced or metastatic, and well/moderately differentiated NETs of lung (typical/atypical) or thymic origin. Patients could be treatment-naïve or have progressed (PD) on somatostatin analogues or ≤ 2 additional systemic treatments. Prior RLT or mTOR inhibitors are not permitted.

Eligible patients are randomly assigned 3:2 to 6 cycles of ^{177}Lu-edotreotide (total administered activity 7.5 ± 0.7 GBq / cycle) or to oral everolimus 10 mg once daily until PD or unacceptable toxicity. Only patients with positivity in somatostatin receptor imaging will be included. CT or MRI scans are performed every 12 weeks until PD. Blood samples

*Correspondence:
Jaume Capdevila
jcapdevila@vhio.net
Full list of author information is available at the end of the article

are analyzed at baseline, at 1st tumor assessment, and at PD for pharmacodynamic endpoints. Archival tumor tissue samples will be analyzed for ancillary studies.

The primary endpoint is progression-free survival (PFS) according to RECIST v1.1 based on local investigator assessment. Secondary endpoints include overall survival, overall response rate, safety, and quality of life (EORTC QLQ-C30).

The expected sample size is 120 patients to demonstrate statistical significant risk reduction of 46.4% (HR = 0.536) in PFS with the experimental treatment using an overall 5% two-sided alpha error with 80% power. An interim PFS analysis was included using the Lan-DeMets with O'Brian-Fleming-like boundaries.

Discussion The LEVEL trial will investigate if ^{177}Lu-edotreotide has the potential to be incorporated as a standard treatment option for patients with NETs from the lung and Thymus.

Trial Registration EU CT: 2022–502154-13–00 / www.clinicaltrials.gov: NCT05918302 (June 23rd, 2023).

Keywords Neuroendocrine tumors, Lung and Thymus, Everolimus, ^{177}Lu-edotreotide, Targeted Radioligand Therapy

Background

Neuroendocrine tumors (NET) are rare malignancies originating from the neuroendocrine system and characterized by a well-differentiated histology [1]. The main primary tumor origin is the digestive tract, followed by the lung, which comprises approximately one-quarter to one-third of NETs with an incidence ranging from 2 to 20 cases per million people per year, based on data from the US and Europe [2, 3]. The incidence of lung-NETs has increased in the last years, likely influenced by the rising awareness and improved diagnostic techniques. Lung-NETs are classified by the World Health Organization (WHO) into typical and atypical carcinoid, corresponding to low- and intermediate-grade tumors, respectively, based on the histological differentiation and mitotic index [4]. Other thoracic NETs include thymic carcinoid (ThC) with an incidence accounting for 2 per million people per year in the European population [5, 6].

Thoracic NETs are most often diagnosed as a consequence of non-specific tumor-related respiratory symptoms (mainly central forms) or incidentally (mainly peripheral forms) [7]. Approximately 80% of lung-NET cases are diagnosed at an early stage [8]. In contrast, most ThCs are diagnosed at advanced-stage [9]. Lung-NETs are more common in women and the most common age of onset ranges from 50 to 60 years [10]. A minority of cases present with symptoms related to hormonal hypersecretion [11]. The prognosis of patients with lung-NETs is mild with a 5-year overall survival (OS) of 60% [12]. Conversely, the prognosis of ThC remains poor, with an estimated 5-year OS of 26%–60% [5, 12].

Control of tumor growth and functioning syndromes are the main goals of therapeutic management, with the aims of improving both the quality of life (QoL) and survival. Systemic antitumor therapies for patients with advanced thoracic NETs include somatostatin analogues (SSAs), which allow control of tumor growth and palliate hormone-related symptoms [13–16], chemotherapy [17–19], and everolimus [20, 21]. The RADIANT-4 study comprises the largest series of lung-NETs ever included in a phase III trial, showing a median progression-free survival (PFS) of 9.2 months in the everolimus arm vs 3.6 months in the placebo arm, being the only drug approved by regulatory agencies to treat patients with advanced lung-NETs [20, 21]. The SPINET trial was designed to demonstrate the efficacy of SSAs in somatostatin receptor 2 (SSTR2) positive advanced lung-NETs, but failed to recruit enough patients, likely because this treatment option is already included in all guidelines despite the lack of a prospective study that demonstrates it role [22]. The heterogeneity of the disease, together with the relatively low incidence of advanced cases have transformed the design and completion of a phase III trial in this setting into a real challenge.

Radioligand therapy (RLT) targeting SSTR2 is arising as one of the most promising treatment strategies for the management of NETs in advanced / metastatic stages [23–26]. ^{177}Lu-oxodotreotide (^{177}Lu-Dotatate) has been approved in Europe and the United States for the treatment of unresectable or metastatic progressive, well-differentiated (G1 and G2), SSTR2-positive gastroenteropancreatic (GEP)-NETs [26]. ^{177}Lu-Dotatate is effective and maintains QoL, with a well-established safety profile [27]. Several studies showed that RLT is also effective in small retrospective cohorts of patients with lung-NETs [28–32]. In these studies, ^{177}Lu-Dotatate showed an objective response rate (ORR) of 30% and a median PFS of 20 months.

The aim of this trial is the comparison between ^{177}Lu-Edotreotide (^{177}Lu-Dotatoc) and everolimus. It is hypothesized that ^{177}Lu-Edotreotide may significantly increase the PFS in comparison with everolimus in lung-NETs and ThC.

Methods/design

Design

The LEVEL trial is a randomized, prospective, international, open-label, phase III study comparing everolimus and ^{177}Lu-edotreotide in advanced SSTR2-positive lung-NETs and ThC. The primary objective of the study is to evaluate the efficacy of ^{177}Lu-edotreotide in terms of PFS and its safety profile. Secondary endpoints include parameters of morphological and functional tumor response, such as ORR, duration of response (DoR), disease control rate (DCR), as well as OS. In addition, the current trial includes QoL and translational research. The study is planning to recruit patients in Spain, France, Belgium and Italy.

Target population and allocation

In total, 120 patients with NETs of lung or thymic origin will be randomized in a 3:2 proportion to either experimental or control arms, respectively (Fig. 1). Randomization will be stratified according to prior medical therapy (treatment-naïve [patients who have not received any prior systemic anticancer therapy] versus non-treatment-naïve [patients who have received prior systemic anticancer therapy]) and histological differentiation (typical versus atypical).

Inclusion criteria

1. Independent Ethics Committee (IEC) approved written informed consent.
2. Patients ≥ 18 years of age.
3. Patients who have histologically confirmed metastatic or locally advanced unresectable, well/moderately differentiated NETs (WHO 2015 criteria) of lung (typical and atypical carcinoids) or thymus origin whether functioning or non-functioning who are candidates to receive everolimus or RLT.
4. Patients must have the appropriate pathological features based on WHO classification (well/moderately differentiated), and description of proliferation activity as indicated by mitotic count per 10 high-power fields (HPF) and presence of necrosis, or Ki67 index (locally assessed).
5. In somatostatin receptor imaging (SRI) all Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 selected target lesions and all other lesions considered dominant by the investigator should be STR-positive.
6. Lesions must have shown radiological evidence of disease progression in the 12 months prior to inclusion in the study.
7. Patients may be included in first-line therapy (systemic treatment-naïve) or may have experienced progression on SSAs or additional systemic treatments, which may include, but are not limited to, chemotherapy, targeted agents, or immunotherapy (maximum of 2 prior systemic anti-tumor treatments).

NOTE: SSAs for patients with functioning tumors are allowed.

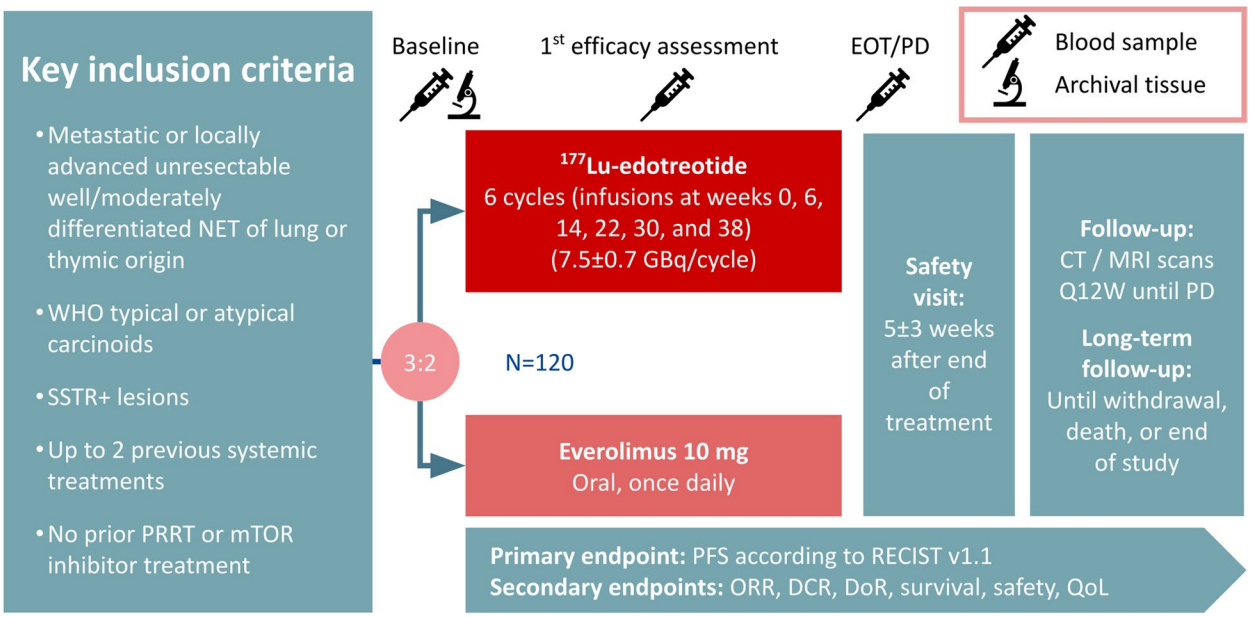

Fig. 1 The LEVEL study protocol design

8. Patients have radiographically documented and measurable metastatic or locally advanced disease at baseline according to RECIST v1.1.
9. An archival tumor tissue sample should be available for submission to the central laboratory prior to study treatment (samples obtained for up to 36 months prior to initiation of study treatment are considered valid for this purpose). If an archival tumor tissue sample is not available, a new biopsy tissue sample should be provided if feasible.

Note: These samples will be used for consistency analysis of histology and translational research but not for the assessment of eligibility.

10. Patients who have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
11. Adequate organ and bone marrow function:

    a. Neutrophil count (ANC) $\geq 1{,}500/mm.^3$
    b. Platelet count $\geq 75 \times 10^9/L$
    c. Hemoglobin (Hb) ≥ 8 g/dL
    d. Serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) or $\leq 3 \times$ ULN for subjects with Gilbert's disease or liver metastases
    e. Creatinine clearance (CrCl) ≥ 40 mL/min as estimated by the Cockroft-Gault formula or as measured by 24-h urine collection.
    f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN for subjects with liver metastases

12. Female subjects must provide a negative urine pregnancy test at screening, and must agree to use a medically accepted and highly effective birth control method (i.e. those with a failure rate less than 1%) for the duration of the study treatment and for 6 months after the final dose of study treatment.
13. Female patients must agree not to breastfeed or donate ovules starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
14. Male patients must agree not to donate sperm starting at screening and throughout the study period, and for at least 6 months after the final study drug administration.
15. Male patients must agree to abstinence or use a condom for the duration of the study period and for at least 6 months after the final study drug administration.
16. Subject agrees not to participate in another interventional study while on treatment in the present study.

Exclusion criteria

1. Patients who are not able to swallow tablets.
2. Patients with poorly-differentiated or high-grade neuroendocrine carcinoma (i.e. large cell neuroendocrine carcinoma of lung, small cell lung cancer) or mixed tumors (i.e. adenocarcinoid tumor) are not eligible.
3. Patients with brain mets unless stable on treatment for > 12 weeks and with no evidence of raised intracranial pressure or mass effect,
4. Patients who have ongoing clinically significant toxicity (grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery).
5. Patients who have a recent diagnosis of another malignancy (within 12 months prior to inclusion); patients who are on active treatment for other cancer before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy..
6. Patients who have a known active Hepatitis B (e.g., HBsAg reactive) or active hepatitis C (e.g., HCV RNA [qualitative] is detected). Patients who have a known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).
7. Patients who have received a live vaccine up to 4 weeks prior to the first dose of trial treatment.

Note: Live attenuated vaccines should not be administered during the trial treatment and over the next 3 months after the last treatment dose.

8. Patients who have documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug.
9. Prior RLT or mammalian target of rapamycin (mTOR) inhibitors (e.g. deforolimus, everolimus, sirolimus, temsirolimus, etc.); or hepatic radioembolization (within 6 months prior to first dose of study treatment).

10. Prior radiotherapy or major surgery within 12 weeks prior to the first dose of study drug.
11. Patients who have had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 4 weeks prior to the first dose of study drug.
12. Patients who have known hypersensitivity to everolimus or to any excipient contained in the drug formulation of everolimus. Patients who have hypersensitivity to other rapamycin derivatives.
13. Patients who have known hypersensitivity to ^{177}Lu-edotreotide or to any excipient contained in the drug formulation of ^{177}Lu-edotreotide or the nephroprotective amino acid solution (AAS).
14. Current spontaneous urinary incontinence that, in the investigator's opinion, prevents the safe administration of the investigational medicinal product (IMP).
15. Patients who have other underlying medical conditions that, in the opinion of the investigator, would impair the ability of the subject to receive or tolerate the planned treatment and follow-up.
16. Patients who have limited their capability to freely decide to participate (patients under guardianship / curatorship), or are in a situation of institutional or hierarchical dependency that could inappropriately influence their decision to participate.

Study treatment

Patients randomized to the experimental arm will receive treatment with 6 cycles of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide. The prescribed treatment administration is as follows: a 6 (+2) weeks interval between cycles 1 and 2 followed by all remaining cycles (3– 6) given 8 (± 1) weeks after the previous cycle, where possible, or until disease progression, intolerable toxicity or death, whichever occurs first (Fig. 2). The selected dose was based on COMPOSE studies and the dosimetry data showing that the administered activity of 7.5 ± 0.7 GBq does not exceed

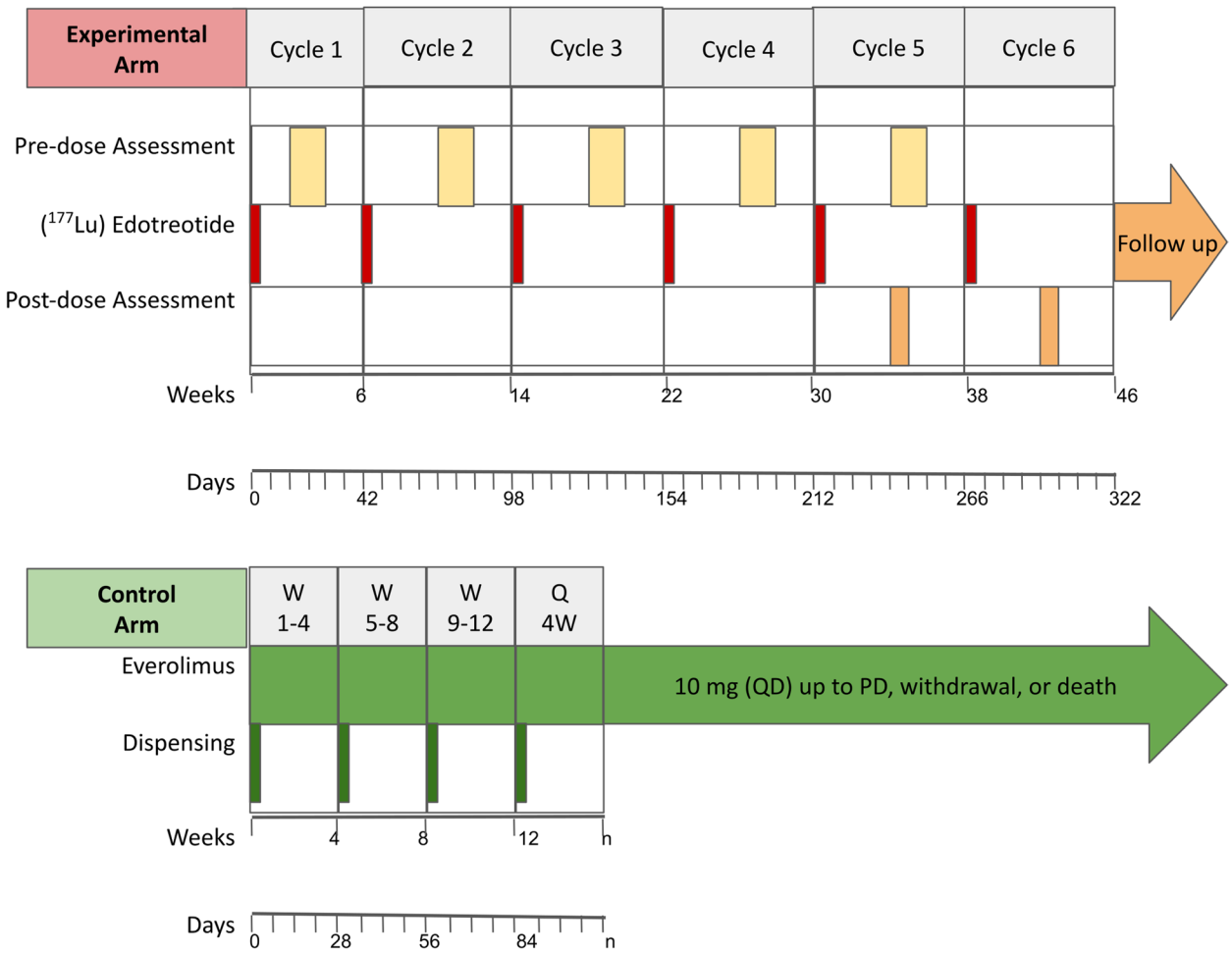

Fig. 2 Treatment Schedule

an average cumulative renal absorbed dose of 23 Gy. The dose is chosen also based on the worse prognosis of progressive lung disease, justifying the use of COMPOSE with two more cycles than COMPETE and NETTER trials. The LEVEL trial does not include dosimetry.

Patients will be required to have Hb concentration ≥ 5.0 mmol/L (≥ 8.0 g/dL); ANC $\geq 1.5 \times 10^9$ cells/L; platelets $> 75 \times 10^9$ cells/L, total bilirubin $\leq 3 \times$ ULN, albumin ≥ 30 g/L, ECOG < 3, and CrCl ≥ 40 mL/min before each IMP administration. Dosing may be delayed by up to a maximum of 4 additional weeks and no dose reductions are allowed. The administration of ^{177}Lu-edotreotide requires the coadministration of a nephroprotective AAS containing a mixture of 25 g lysine-hydrochloric acid (HCl) and 25 g arginine-HCl diluted in 2000 mL of electrolyte solution. The AAS is infused over 4 to 6 h, starting 30 to 60 min before RLT administration via a peripheral or central line as considered more appropriate.

Patients randomized to the control arm will receive everolimus 10 mg orally once daily (QD) until disease progression or intolerable toxicity or death, whichever occurs first (Fig. 2). Posology and treatment schedule modifications will be according to physician criteria and latest local Prescribing Information.

Objectives and endpoints

The primary objective is to evaluate PFS, defined as the time from randomization until adequately documented progression of the disease (PD) according to RECIST v1.1 or death, whichever occurs first.

Secondary objectives include:

- To evaluate ORR, defined as the proportion of randomized patients with confirmed complete response (CR) or partial response (PR) (RECIST v1.1).
- To evaluate DCR, defined as the proportion of randomized patients with CR, PR or stable disease (SD; maintained > 4 months) (RECIST v1.1).
- To evaluate DoR, defined as the time from experiencing the first CR or PR until PD (RECIST v1.1).
- To evaluate OS, defined as the time from randomization until death.
- To evaluate safety of the intended treatment regimen based on the frequency and severity of adverse events (AEs) and Treatment-emergent adverse events (TEAEs) assessed by NCI CTCAE v5.0.
- QoL, assessed through the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3 and lung cancer-specific extension module LC-13.
- To determine molecular or clinical predictive biomarkers of response to ^{177}Lu-edotreotide.

Assessments

Informed consent is obtained prior to the start of the specified screening window (90 days). Procedures conducted as part of the subject's routine clinical management prior to signing of ICF may be used, provided these procedures are conducted as specified in the protocol. During the screening phase patients undergo the following assessments to determine their eligibility: tumor histology, electrocardiogram, recording AEs Physical exam, ECOG performance status, vital signs, body mass index, and symptom control, ^{68} Ga-based or ^{64}Cu-based SRI, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan (*optional*), laboratory determinations (blood chemistry and hematology, serology, urinalysis, and pregnancy test), concomitant medication, biological samples (archival tumor tissue and blood samples), magnetic resonance imaging (MRI) and/or computed tomography (CT) and prior medical therapy.

During the treatment phase patients in the experimental arm are monitored at dosing visits, at pre-treatment evaluations performed 2 to 3 weeks before each subsequent dose, and at post-dose visits, performed 4 ± 1 weeks after the administration of cycle 5 and 6. In the control arm, patients are monitored every 4 weeks, coincident with drug dispensing. A patient diary is provided to patients in the control arm to aid in the assessment of everolimus compliance. See Tables 1 and 2 for the specific schedule of assessments in the experimental and control arms respectively.

Efficacy assessments including diagnosis of progression and tumor burden is established based on radiological information from morphological imaging (MRI/CT) according to RECIST v1.1. Tumor assessments are scheduled every 12 ± 2 weeks from randomization (the first scan will be performed after cycle 2 for the ^{177}Lu-edotreotide until radiologically confirmed PD, initiation of new subsequent anticancer therapy, or death; whichever comes first). The scanning modality and protocol should be consistent with the baseline scan. Diagnosis of RECIST v1.1 progression will be made by the local investigator. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration).

Safety is assessed continuously, with records of the type of AEs, their incidence, severity, seriousness, and relatedness to the treatment under study.

The QoL will be assessed on cycle 1 day 1, every 12 ± 2 weeks from randomization coincident with tumor assessments, and at PD.

After progression, the patient will be followed to assess survival status and subsequent anticancer treatments until death, loss of follow-up, total patient consent

Table 1 Study determinations in the experimental arm ^{177}Lu-edotreotide

Visit	**SCR**	**Randomization**	**Cycle 1**	**Cycle 2**		**Cycle 3–4**		**Cycle 5–6**			**Safety Visit / EOT**	**PFS FU**	**EOS FU**
Timeline	**≤ 90 d**	**−7 d to 0 d**	**Day 1**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Post dose**	**within 5S after EOT**	**Q12 weeks**	**Q6 months**
Visit. window				2–3 Weeks Prior Planned Cycle Dosing	6 (+ 2) Weeks After Cycle 1	2–3 Weeks Prior Planned Cycle Dosing	8 (± 1) Weeks After Previous Cycle	2–3 Weeks Prior Planned Cycle Dosing	8 (± 1) Weeks After Previous Cycle	4 ± 1 Weeks After Dosing	Within 5 ± 3 Weeks After Treatment Discontinuation	± 7d	± 1 m
Clinical Assessments													
Informed consent	Prior to any study specific determination												
Review inclusion / Exclusion criteria	X	X											
Medical History (Medical and oncology specific)	X	X											
Physical Exam		X	X	X	X	X	X	X	X	X	X		
Vital signs		X	X	X	X	X	X	X	X	X	X		
ECOG		X	X	X	X	X	X	X	X	X	X		
Contraception check		X	*According to investigator's criteria*										
Laboratory Assessments (*Analytics should be performed within 72 h previous to the visit, and available by the time of the visit*)													
Coagulation		X	X	X	X	X	X	X	X	X	X		
Hematology		X	X	X	X	X	X	X	X	X	X		
Blood chemistry		X	X	X	X	X	X	X	X	X	X		
Serology		X											
Pregnancy test		X	X	X	X	X	X	X	X				
Urinalysis		X	X	X	X	X	X	X	X	X	X		
Cardiac Assessments													
Electrocardiogram		X	X		X		X		X				
Efficacy Assessments													

Table 1 (continued)

Visit	**SCR**	**Randomization**	**Cycle 1**	**Cycle 2**		**Cycle 3–4**		**Cycle 5–6**			**Safety Visit / EOT**	**PFS FU**	**EOS FU**
Timeline	**≤ 90 d**	**−7 d to 0 d**	**Day 1**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Post dose**	**within 5S after EOT**	**Q12 weeks**	**Q6 months**
SRI imaging (^{68}Ga-based or ^{64}Cu-based)	within 4 months prior to randomization												
FDG PET scan (*Optional*)	within 4 months prior to randomization												
Tumor assessment (CT / MRI scan) with RECIST v1.1		*Every 12 Weeks (Q12W) ± 2 weeks from randomization until adequately documented disease progression (Can be coupled with other visits when possible)*											
Treatment Assessments													
Eligibility for RLT	X	X	X	X	X	X	X	X	X				
^{177}Lu-edotreotide ordering		X		X		X		X					
Kidney protect infusion			X		X		X		X				
^{177}Lu-edotreotide administration			X		X		X		X				
Safety Assessment													
Adverse events	*To be reviewed and collected at each patient visits*											SARs only	
Concomitant medications	*To be reviewed and collected at each patient visits*												
Patient reported outcomes		X	Q12W									X (PD)	
Other Assessments													
Archival tumor block		X											

Table 1 (continued)

Visit	**SCR**	**Randomization**	**Cycle 1**	**Cycle 2**		**Cycle 3–4**		**Cycle 5–6**			**Safety Visit / EOT**	**PFS FU**	**EOS FU**
Timeline	**≤90 d**	**−7 d to 0 d**	**Day 1**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Pre dose**	**Dosing**	**Post dose**	**within 5S after EOT**	**Q12 weeks**	**Q6 months**
Blood for biomarkers		X	*At first efficacy assessment*								X (EOT & PD)		
New cancer treatment												X	X
Survival assessment													X

Table 2 Study determinations in the control arm (Everolimus)

Visit	**SCR**	**Randomization**	**Treatment and PFS period**			**Safety Visit / EOT**	**PFS FU**	**EOS FU**
Timeline	**≤ 90 d**	**−7 d to 0 d**	**Daily**	**Safety**	**Efficacy**	**within 5S after EOT**	**Q12 weeks**	**Q6 months**
Visit. window			Within 4 Weeks After Random	Q4W or according to institutional protocols	Every 12 ± 2 Weeks from Random. until PD	Within 5 ± 3 Weeks After Treatment Discontinuation	± 7d	± 1 m
Clinical Assessments								
Informed consent	Prior to any study specific determination							
Review inclusion / Exclusion criteria	X	X						
Medical History (Medical and oncology specific)	X	X						
Physical Exam		X		X		X		
Vital signs		X		X		X		
ECOG		X		X		X		
Contraception check		X	*According to investigator's criteria*					
Laboratory Assessments (*Analytics should be performed within 72 h previous to the visit, and available by the time of the visit*)								
Coagulation		X		X		X		
Hematology		X		X		X		
Blood chemistry		X		X		X		
Serology		X						
Pregnancy test		X		X				
Urinalysis		X		X		X		
Cardiac Assessments								
Electrocardiogram		X		X				
Efficacy Assessments								
SRI imaging (^{68}Ga-based or ^{64}Cu-based)	within 4 months prior to randomization							
FDG PET scan	within 4 months prior to randomization							
Tumor assessment (CT / MRI scan) with RECIST v1.1	X				X		X (at PD)	
Treatment Assessments								
Everolimus dispensing			X *every 4 weeks (Q4W)*					
Everolimus administration			X					
Treatment compliance			X *every 4 weeks (Q4W)*			X		
Safety Assessment								
Adverse events	*To be reviewed and collected at each patient visits*						SARs only	
Concomitant medications	*To be reviewed and collected at each patient visits*							
Patient reported outcomes		X			X		X (at PD)	

Table 2 (continued)

Visit	SCR	Randomization	Treatment and PFS period			Safety Visit / EOT	PFS FU	EOS FU
Timeline	**≤ 90 d**	**−7 d to 0 d**	**Daily**	**Safety**	**Efficacy**	**within 5S after EOT**	**Q12 weeks**	**Q6 months**
Other Assessments								
Archival tumor block		X						
Blood for biomarkers		X	*At first efficacy assessment*			X (at EOT and PD)		
New cancer treatment							X	X
Survival assessment								X

withdrawal (refusing any trial procedure), or end of study. The end of study is defined as the Last Patient Last Visit (LPLV) and will be estimated at 60 months after the first patient first visit (FPFV).

Statistical planning

The study uses an event-driven analysis. The analysis will be performed once the prespecified number of events is reached. The median PFS in the everolimus arm is assumed to be 10 months (based on the RADIANT-4 lung subgroup analysis) [20, 21] while an improvement to median PFS of 18.66 months is expected with ^{177}Lu-edotreotide. Therefore, a risk reduction by 46.4% (a hazard ratio (HR) of 0.536) is considered important to detect. The study is based on a 3:2 randomization to have 80% power to detect a PFS HR of 0.536 in favor of ^{177}Lu-edotreotide using a two-sided log-rank test at a significance level of 0.05. Assuming a 5% drop-out rate on either treatment arm, uniform recruitment over a 24-month accrual period, and approximately 42 months from the inclusion of the first patient to the final PFS analysis, a total sample size of 120 patients is required.

To assess the null hypothesis, the study is designed with a group sequential approach for testing superiority of ^{177}Lu-edotreotide with respect to PFS endpoint. The decision criterion to make a superiority claim at the interim analysis is based on the alpha-spending function according to Lan-DeMets with O'Brien-Fleming-like boundaries. The sample size was calculated using the *gsDesign* R package and by means of simulation with the R software version 4.1.2.

An interim analysis will be conducted after, but as close as possible to, 60 PFS are observed. The goal of the interim analysis is the early reporting of superior efficacy results in the ^{177}Lu-edotreotide arm. No formal futility analysis is planned. The final analysis will be conducted after, but as close as possible to, the observation of 87 PFS events.

Demographic and other baseline data (including disease characteristics) will be summarized by treatment arm using the full analysis set (FAS) population, comprising all patients randomized to treatment analyzed according to the treatment arm to which they were randomized.

Time-to-event variables (PFS, OS, DoR) will be analyzed according to the Kaplan–Meier method. Kaplan–Meier survival curves and the 50th percentile (median) will be reported using FAS population by treatment arm, along with associated 95% confidence intervals (CIs) calculated using the standard error derived from Greenwood's formula. Cox regression on univariate models using the FAS population will calculate the risk reduction and HR with 95% CIs in the time-to-event variables. For categorical endpoints (i.e., ORR, CBR), counts and percentages, with 95% CIs, will be calculated by treatment arm. CIs will be calculated with the exact binomial two-sided 95% CI according to Clopper-Pearson.

The incidence of AEs and TEAEs will be reported by type and severity in each arm using the safety population, comprising all patients receiving at least one dose of study treatment analyzed according to the treatment they actually received.

For QoL assessments, normalized total scores will be calculated for every assessment time point. To estimate change from baseline, a longitudinal analysis of the scores will be performed using linear mixed models adjusting with random effects to account for correlation of repeated measures within an individual. The time to 10% deterioration in the global score will be estimated as a survival outcome using Cox models.

Translational research

The study includes the collection of archival tumor tissue at baseline and up to 4 blood samples (50 ml each), at baseline, after 1st dose of study treatment, at the end of treatment and after PD.

Samples will be used to determine somatic alterations in tumors including proteomics, transcriptomics, and metabolomics.

Discussion

The design and execution of an international phase III study in lung-NET patients is challenging, as evidenced by the fact that only one previous trial successfully completed recruitment. Although lung-NETs express SSTR2, their expression is less frequent and more heterogeneous, complicating the selection of potential candidates for RLT. Another study specifically assessing the role of RLT in thoracic NETs in the United States started accrual in February 2023 and is still ongoing to complete the expected sample size (n = 108) [33]. Only one phase II study with RLT in this pathology completed the accrual with 34 patients [29].

Our study will provide head to head evidence of the potential improvement in efficacy and QoL of ^{177}Lu-edotreotide over the standard of care in lung-NETs, similar to the COMETE trial which will inform the same treatment comparison in GEP-NETs.

Patients with thoracic NETs still have a mild prognosis and the available therapeutic options do not achieve long term disease control for all patients [1, 12–20]. Therefore, analyzing if RLT is superior to standard treatment options for patients with thoracic NETs is of scientific interest. This is specially relevant, taking into account the results obtained by RLT in patients with GEP-NETs which led to their approval as standard of care [26] and the promising preliminary data in lung-NETs [28–32]. Responses are observed early after treatment initiation. The majority of patients who responded to ^{177}Lu-oxodotreotide treatment, approximately 92%, had their first response after the first RLT cycle [25, 26]. Despite similar therapeutic strategy, dotatate still has structural differences with dotatoc which may lead to different treatment outcomes. In SRI, ^{68} Ga-dotatoc shows significantly higher uptake in GEP-NETs [34].

Everolimus was chosen as the control arm over chemotherapy because it is the only approved standard treatment for lung NETs in the first-line setting [20, 21]. Since STR expression can be lost or reduced over time, it makes sense to move RLT upfront, following the examples of NETTER1 and NETTER2 trials [26, 35]. Moreover, everolimus combined with SSAs has shown a good symptom control in NETs associated with carcinoid syndrome [20, 21]. Chemotherapy regimens are diverse and there is not a well established standard regimen, being discarded as potential treatments for control arm despite their use might be recommended by clinical guidelines for second or subsequent treatment lines [16–20]. Considering that there are already approved therapies for LCs and ThC, a placebo controlled design was considered inadequate from an ethical or medical perspective.

The study was designed as an open-label trial, which may induce observational bias. This is required because control and experimental treatments have very different administration schedules and routes and therefore it was not ethically acceptable to expose the patients to placebo. The NETTER trials were designed as open-label based on the same constraints and ethical concerns [26, 35]. The logistic and safety measures for ^{177}Lu-edotreotide make blinding difficult. Also, this is a non commercial study sponsored by a non-profitable group of physicians and the blinding and placebo logistics would have increased the costs. The use of a blinded statistician for the scheduled analysis of safety and efficacy would be a potential improvement to minimize bias and is encouraged.

The treatment with ^{177}Lu-edotreotide was scheduled for 6 cycles, with a smaller treatment interval between cycle 1 and 2, based on the design of the COMPOSE study [24], in contrast with the 4 cycles scheduled for NETTER trials [26, 35]. The 6-cycles schedule was considered adequate as progressive lung-NETs tend to exhibit more aggressive behavior than GEP-NETs.

Randomization is stratified by the two main prognostic factors described in patients with NETs and associated with RLT activity in other tumor types, the PD to previous treatments and the tumor grade [7, 8, 17]. Stratification according to the functional status is not foreseen considering the poor predictive and prognostic relevance of this criteria on RLT in the literature [36].

The formal sample size calculations ensure that the trial will provide clinically meaningful and statistically significant results. The expected sample size will represent the largest cohort of patients with lung-NETs recruited in a clinical trial to date. The trial is conducted in 4 European countries, which is expected to provide a sufficient number of patients based on the incidence of the disease under study. Other European countries may be opened in the future to boost accrual if required. The inclusion of self-reported QoL endpoints is a novel and key goal of the LEVEL trial, which aims to determine whether the potential clinical benefit translates into improved patient well-being and daily life.

In conclusion, the LEVEL trial will elucidate if ^{177}Lu-edotreotide has the potential to be incorporated as a standard treatment option for patients with NETs from the lung and thymus.

Abbreviations

AAS	Amino Acid Solution
AEs	Adverse Events
ALT	Alanine Aminotransferase
ANC	Neutrophil Count
AST	Aspartate Aminotransferase
CIs	Confidence Intervals
CrCl	Creatinine Clearance
CT	Computed Tomography
DCR	Disease Control Rate
DoR	Duration Of Response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization For Research And Treatment Of Cancer
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FPFV	First Patient First Visit
GEP	Gastroenteropancreatic
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPF	High-Power Fields
HR	Hazard Ratio
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LPLV	Last Patient Last Visit
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target Of Rapamycin
NET	Neuroendocrine Tumors
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Of The Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
QLQ	Quality Of Life Questionnaire
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
RLT	Radioligand Therapies
RNA	Ribonucleic Acid
SRI	Somatostatin Receptor Imaging
SSA	Somatostatin Analogues
SSTR	Somatostatin Receptor
TEAEs	Treatment-Emergent Adverse Events
ThC	Thymic Carcinoid
ULN	Upper Limit Of Normal
WHO	World Health Organization

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Authors' contributions
This study was designed by JC. JC is the coordinating investigator of the trial. NF and TW are the national coordinators for Italy and France, respectively. All co-authors: JC, VP, UA, TW, JM-C, TA-G, RG-C, MS-R-G, BLI, PJ-F, MBV, CA, EB, CL, MdO-G, JCR, AB, MH, ED, DT, SB, MS, SC, AF, FP, RÁ-Á, LL, FAN, JH, AG-Á, AG-B, GV, TV, NF, and AD made substantial contributions, have read and approved this manuscript.

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Data availability
The study is reported in accordance with the CONSORT guidelines. The full protocol is attached to this manuscript. All data will be handled confidentially, coded with a pseudoanonymization code and without providing identifiable patient data. Only the team at the site will be able to identify the patients. The study results will be published in scientific manuscripts and conferences.

Declarations

Ethics approval and consent to participate
The study is being conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Guidelines for Good Clinical Practice and the local regulations. The study protocol was approved by the IEC of Hospital Universitari Vall D'Hebron on June 19th, 2023 (Ref: 2023/578) and the competent authorities of the European member states concerned (Spain: July 14th, 2023, France: October 10th, 2023, Italy: November 8th, 2023). All patients are providing written informed consent.

Consent for publication
Not applicable.

Competing interests
RGC has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from: AAA-Novartis, Advanz Pharma, Astellas, Bayer, BMS, Boehringer, Esteve, GSK, Hutchmed, Ipsen, ITM, MSD, PharmaMar, Pierre Fabre, Sanofi, Servier, Takeda.PJF has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from: Astellas, AstraZeneca, Bristol-Myers Squibb (BMS), Esteve, Merck Sharp & Dohme (MSD), Novartis, Nutricia, Pfizer, Rovi, Takeda, Viatris.TW has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from: Novartis, MSD, Esteve, Ipsen, ITM, Terumo, Pierre Fabre, Sanofi, OranoMed, Sirtex.CL has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from: Pierre Fabre, AMGEN, Takeda, Ipsen, AAA.ED has received fees from AAA-Novartis, Janssen and GE.JCR has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from: AMGEN, MSD, AAA.TV has received honoraria for speaker engagements, advisory roles or funding for continuous medical education from from AstraZeneca, Astellas, Bayer, Bristol Myers Squibb, Eisai, Elmedix, Ipsen, MyNeoTx, Nordic Pharma, Novartis, Roche, Sirtex, Servier, Takeda. TV is a senior clinical investigator at the Research Foundation-Flanders (FWO), project number 1803723N.The remaining authors declare that they have no competing interests.GV has received a speaker's fee from Pfizer, MSD, GSK and Pierre Fabrer, has held an advisory role with AstraZeneca and received consultant fees from Reveal Genomics.TAG reports Advisory role or speaker & fee from Lilly, Bayer, Johnson & Johnson, Astellas, Eisai, Roche, Ipsen, MSD and Adacap. Research Grant from Johnson & Johnson and IPSEN.All the other co-authors confirmed that they had no competing interests to be declared.

Author details
[1]Medical Oncology Department. Vall, Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain. [2]Department of Nuclear Medicine, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain. [3]Molecular Imaging Research Group, Nuclear Medicine Department, University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain. [4]Medical Oncology Department, Edouard Herriot Hospital, Lyon, France. [5]Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain. [6]Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain. [7]Center of Experimental Oncology. Gastrointestinal and Neuroendrocrine Tumors Research Group. Hospital 12 de Octubre Research Institute (Imas12), Madrid, Spain. [8]Facultad de Medicina, Departamento de Medicina, Universidad Complutense de Madrid (UCM), Madrid, Spain. [9]Nuclear Medicine Department, Hospital Universitario Central de Asturias, Oviedo, Spain. [10]Medical Oncology Department, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain. [11]Medical Oncology Department, University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS), Seville, Spain. [12]Service de Médecine Nucléaire, CHU de Nantes, Nantes Université, Nantes, France. [13]Department of Endocrine Oncology and Nuclear Medicine, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France. [14]Department of Digestive Oncology, University Hospital Dijon, University of Burgundy and Franche Comté, Dijon, France. [15]Endocrinology and Nutrition Department, Endocrinology, Nutrition and Diet Therapy Research Unit, University and Polytechnic Hospital La Fe, Valencia, Spain. [16]Departamento de Medicina, Universidad de Valencia, Valencia, Spain. [17]Medical Oncology Department, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain. [18]Service de Médecine Nucléaire, Hôpital Claude Huriez, CHU Lille, Lille, France. [19]Department of Endocrinology, University

of Bordeaux, Bordeaux, France. [20]Department of Nuclear Medicine, Institut du Cancer de Montpellier, Université de Montpellier, Cedex 5 Montpellier, France. [21]Department of Nuclear Medicine, Aix-Marseille University, La Timone University Hospital, Marseille, France. [22]Nuclear Medicine Unit, Department of Biomedical and Dental Sciences and of Morpho-Functional Imaging, University of Messina, Messina, Italy. [23]Therapeutic Nuclear Medicine, IRCCS Istituto Romagnolo Per Lo Studio Dei Tumori (IRST) "Dino Amadori", Meldola, Italy. [24]Medical Oncology, University and Hospital Trust of Verona, Verona, Italy. [25]Servizio Di Medicina Nucleare, Azienda USL-IRCCS Di Reggio Emilia, Reggio Emilia, Italy. [26]Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Digestive Disease Unit, ENETS Center of Excellence, Sant'Andrea University Hospital, Rome, Italy. [27]Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain. [28]Service d'Oncologie Médicale CHU Liège, Liège, Belgium. [29]Department of Pulmonology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 1200 Brussels, Belgium. [30]Institut de Recherche Expérimentale Et Clinique (IREC), Université Catholique de Louvain, 1200 Brussels, Belgium. [31]Statistics Unit, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [32]Department of Oncology and Netwerk, University Hospital Antwerp, Edegem, Belgium. [33]Center for Oncological Research, Integrated Personalized &Precision Oncology Network (IPPON), University of Antwerp, Wilrijk, Belgium. [34]Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IEO, IRCCS, Milan, Italy.

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References

1. Baudin E, Caplin M, Garcia-Carbonero R, Fazio N, Ferolla P, Filosso PL, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol Off J Eur Soc Med Oncol. 2021;32(4):439–51.
2. Broder MS, Cai B, Chang E, Neary MP. Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database. BMC Pulm Med. 2018;18(1):135.
3. Korse CM, Taal BG, van Velthuysen MLF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer Oxf Engl 1990. 2013;49(8):1975–83.
4. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2015;10(9):1243–60.
5. de Laat JM, Pieterman CR, van den Broek MF, Twisk JW, Hermus AR, Dekkers OM, et al. Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients. J Clin Endocrinol Metab. 2014;99(9):3325–33.
6. Sullivan JL, Weksler B. Neuroendocrine tumors of the thymus: analysis of factors affecting survival in 254 patients. Ann Thorac Surg. 2017;103(3):935–9.
7. Daddi N, Schiavon M, Filosso PL, Cardillo G, Ambrogi MC, De Palma A, et al. Prognostic factors in a multicentre study of 247 atypical pulmonary carcinoids. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2014;45(4):677–86.
8. Yoon JY, Sigel K, Martin J, Jordan R, Beasley MB, Smith C, et al. Evaluation of the prognostic significance of TNM staging guidelines in lung carcinoid tumors. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2019;14(2):184–92.
9. Zhao Y, Gu H, Fan L, Han K, Yang J, Zhao H. Comparison of clinical features and survival between thymic carcinoma and thymic carcinoid patients. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2017;52(1):33–8.
10. García-Yuste M, Matilla JM, Cañizares MA, Molins L, Guijarro R. Surgical treatment of low and intermediate grade lung net. J Thorac Dis. 2017;9(Suppl 15):S1435–41.
11. Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18(4):525–34.
12. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol. 2000;114(1):100–10.
13. Ferolla P, Brizzi MP, Meyer T, Mansoor W, Mazieres J, Do Cao C, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 2017;18(12):1652–64.
14. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2020;31(7):844–60.
15. Sullivan I, Le Teuff G, Guigay J, Caramella C, Berdelou A, Leboulleux S, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. Eur J Cancer. 2017;1(75):259–67.
16. Bongiovanni A, Recine F, Riva N, Foca F, Liverani C, Mercatali L, et al. Outcome analysis of first-line somatostatin analog treatment in metastatic pulmonary neuroendocrine tumors and prognostic significance of 18FDG-PET/CT. Clin Lung Cancer. 2017;18(4):415–20.
17. Robelin P, Hadoux J, Forestier J, Planchard D, Hervieu V, Berdelou A, et al. Characterization, prognosis, and treatment of patients with metastatic lung carcinoid tumors. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2019;14(6):993–1002.
18. Spada F, Antonuzzo L, Marconcini R, Radice D, Antonuzzo A, Ricci S, et al. Oxaliplatin-based chemotherapy in advanced neuroendocrine tumors: clinical outcomes and preliminary correlation with biological factors. Neuroendocrinology. 2016;103(6):806–14.
19. Al-Toubah T, Morse B, Strosberg J. Capecitabine and temozolomide in advanced lung neuroendocrine neoplasms. Oncologist. 2020;25(1):e48-52.
20. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968–77.
21. Fazio N, Buzzoni R, Delle Fave G, Tesselaar ME, Wolin E, Van Cutsem E, et al. Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. Cancer Sci. 2018;109(1):174–81.
22. Baudin E, Capdevila J, Hörsch D, Singh S, Caplin ME, Wolin EM, et al. Treatment of advanced BP-NETS with lanreotide autogel/depot vs placebo: the phase III SPINET study. Endocr Relat Cancer. 2024;31(9):e230337.
23. Pavel ME, Rinke A, Baum RP. COMPETE trial: Peptide receptor radionuclide therapy (PRRT) with 177Lu-edotreotide vs. everolimus in progressive GEP-NET. Ann Oncol. 2018;29:viii478.
24. Halfdanarson TR, Halperin D, Reidy-Lagunes D, Kong G, Mailman J, Hermann K, et al. 902TiP COMPOSE: pivotal phase III trial to compare 177Lu-edotreotide with best standard of care for well-differentiated aggressive grade 2 and grade 3 gastroenteropancreatic neuroendocrine tumours. Ann Oncol. 2022;1(33):S960.
25. Baum RP, Kluge AW, Kulkarni H, Schorr-Neufing U, Niepsch K, Bitterlich N, et al. [177Lu-DOTA]0-D-Phe1-Tyr3-Octreotide (177Lu-DOTATOC) for peptide receptor radiotherapy in patients with advanced neuroendocrine tumours: a phase-II study. Theranostics. 2016;6(4):501–10.
26. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35.
27. Strosberg JR, Srirajaskanthan R, El-Haddad G, Wolin EM, Chasen BR, Kulke MH, et al. Symptom diaries of patients with midgut neuroendocrine tumors treated with 177Lu-DOTATATE. J Nucl Med Off Publ Soc Nucl Med. 2021;62(12):1712–8.
28. Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology. 2017;105(3):295–309.
29. Ianniello A, Sansovini M, Severi S, Nicolini S, Grana CM, Massri K, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced

bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur J Nucl Med Mol Imaging. 2016;43(6):1040–6.
30. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA0, Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res Off J Am Assoc Cancer Res. 2017;23(16):4617–24.
31. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(17):2416–23.
32. Sabet A, Haug AR, Eiden C, Auernhammer CJ, Simon B, Bartenstein P, et al. Efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in metastatic pulmonary neuroendocrine tumors: a dual-centre analysis. Am J Nucl Med Mol Imaging. 2017;7(2):74–83.
33. Study Details | Testing Lutetium Lu 177 Dotatate in Patients With Somatostatin Receptor Positive Advanced Bronchial Neuroendocrine Tumors | ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT04665739?term=typical%20carcinoid%20dotatate&rank=4. Cited 2024 Sep 9.
34. Todorović-Tirnanić MV, van Echteld CJA, Gajić MM, Baum RP. Uptake of 68Ga-DOTATATE and 68Ga-DOTATOC in primary neuroendocrine tumors, metastases, and normal liver tissue: is there a significant difference? In: Prasad V, editor. Beyond Becquerel and biology to precision radiomolecular oncology: Festschrift in HONOr of Richard P Baum. Cham: Springer International Publishing; 2024. p. 337–48. https://doi.org/10.1007/978-3-031-33533-4_34. Available from: Cited 2024 Oct 16.
35. Singh S, Halperin D, Myrehaug S, Herrmann K, Pavel M, Kunz PL, et al. [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. Lancet. 2024;403(10446):2807–17.
36. Zandee WT, Brabander T, Blažević A, Minczeles NS, Feelders RA, de Herder WW, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for symptomatic control of refractory carcinoid syndrome. J Clin Endocrinol Metab. 2021;106(9):e3665–72.

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