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

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Summary

Background There are no data from prospective studies focused exclusively on patients with advanced lung and thymic carcinoids.

Methods LUNA was a prospective, multicentre, randomised, open-label, 3-arm, phase 2 trial. Patients with advanced, progressive, carcinoid tumours of the lung/thymus were enrolled from 36 centres in nine countries. Eligible patients were randomised in a 1:1:1 ratio to receive treatment with long-acting pasireotide (60 mg intramuscularly every 28 days), everolimus alone (10 mg orally once daily), or in combination, for the core 12-month treatment period. Patients were stratified by carcinoid type (typical *vs* atypical) and line of study treatment (first line *vs* others). Radiological assessments were performed every 3 months. The primary endpoint was the proportion of patients progression-free at month 9, which was defined as the proportion of patients with overall lesion assessment at month 9 being complete response (CR), partial response (PR), or stable disease (SD) according to local Response Evaluation Criteria in Solid Tumours, version 1·1, assessed in the intention-to-treat population. Progression-free survival (PFS) and safety were secondary endpoints. Safety was assessed in all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The trial is registered with ClinicalTrials.gov, NCT01563354; the extension phase of the study is ongoing.

Findings Between Aug 16, 2013, and Sept 30, 2014, a total of 124 patients were enrolled; 41 were allocated to long-acting pasireotide (P arm), 42 to everolimus (E arm), and 41 to combination treatment (EP arm). At month 9, the proportion of patients with an overall lesion assessment of CR, PR, or SD in the P arm, E arm, or EP arm, were 16/41 (39·0%; 95% CI 24·2–55·5), 14/42 (33·3%; 95% CI 19·6–49·5), and 24/41 (58·5%; 95% CI 42·1–73·7), respectively. The most common grade 1/2 adverse events with a suspected relationship to treatment with long-acting pasireotide monotherapy or long-acting pasireotide + everolimus

were diarrhoea (36·6% [15/41] and 46·3% [19/41], respectively) and hyperglycaemia (41·5% [17/41] and 65·9% [27/41]); for everolimus, they were stomatitis (61·9% [26/42]) and diarrhoea (38·1% [16/42]). Eleven patients died during the core 12-month treatment phase or up to 56 days after the last study treatment exposure date: 2/41 (4·9%) in the P arm, 6/42 (14·3%) in the E arm, and 3/41 (7·3%) in the EP arm. No deaths were suspected to be related to long-acting pasireotide treatment. One death in the E arm, due to acute kidney injury associated with diarrhoea, and 2 deaths in the EP arm, due to diarrhoea/urinary sepsis in one patient and acute renal failure/respiratory failure in the other patient, were suspected to be related to everolimus treatment. In the latter patient, acute renal failure was not suspected to be related, while respiratory failure was suspected to be related to everolimus treatment.

Interpretation The study met the primary endpoint in all three treatment arms. Safety profiles were consistent with the known safety profiles of these agents. Further studies are needed to confirm the antitumour efficacy of the combination of a somatostatin analogue with everolimus in lung and thymic carcinoids.

Funding Novartis Pharma AG.

Introduction

Neuroendocrine tumours (NET) are relatively rare and heterogeneous tumours that arise from neuroendocrine cells, often arising in the gastrointestinal (GI) tract, lung, and pancreas.[1] The World Health Organization (WHO) classifies lung and thymic NET into four major subtypes: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma, and small cell carcinoma.[2]

Given the lack of prospective clinical trial data from large numbers of patients with advanced lung and thymic carcinoids, the majority of treatment recommendations are based on results of studies in GI NET and mixed primary NET populations that include lung and thymic carcinoids[3,4]; until recently, there has been an absence of approved drugs for this indication.[4] Based on the results of the phase 3 RADIANT-4 study, the mammalian target of rapamycin (mTOR) inhibitor everolimus recently received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of patients with advanced (unresectable, locally advanced, or metastatic), progressive, well-differentiated, non-functional NET of lung and GI origin, in addition to the previous approval in pancreatic NET.[5,6] In RADIANT-4, median progression-free survival (PFS) of patients with advanced, well-differentiated NET of GI or lung origin was significantly improved: 11·0 months for patients receiving everolimus, compared with 3·9 months among patients receiving placebo (hazard ratio [HR] 0·48; 95% confidence interval [CI] 0·35–0·67; p<0·0001).[7] In a subgroup analysis of patients with advanced lung carcinoids, everolimus improved median PFS by 5·6 months *vs* placebo (9·2 *vs* 3·6 months), as assessed by central review.[8]

Current European Neuroendocrine Tumor Society (ENETS) consensus guidelines recommend everolimus as a first-line therapy for progressive, advanced lung carcinoids, unless a somatostatin analogue (SSA; long-acting octreotide or lanreotide) may be considered as first-line therapy for tumours with low proliferative activity (i.e., TC) and somatostatin receptor (SSTR) expression on imaging.[4] The recommendation for SSA treatment is based on the expectation that TC will respond in a similar manner to grade 1

NET of other sites, such as the GI tract,[4] as well as data from a few retrospective analyses of lung NET.[9]

Pasireotide is a novel multireceptor ligand SSA with higher affinity for somatostatin receptors 1 (SSTR1), 3 (SSTR3), and 5 (SSTR5) compared with octreotide, but a slightly lower affinity for SSTR2.[10] The antitumour activity of pasireotide (long-acting or short-acting subcutaneous) has been investigated in phase 2 and 3 trials of patients with advanced NET who have symptoms refractory to standard long-acting octreotide dosing,[11,12] along with a phase 2 trial of treatment-naive patients with metastatic grade 1 or 2 NET.[13] It is hypothesised that the combined action of long-acting pasireotide on SSTR and inhibition of insulin-like growth factor 1 receptor (IGF-1R), along with the mTOR inhibitor everolimus, may control tumour growth more effectively than either treatment alone.[14]

The phase 2 LUNA trial aimed to assess the efficacy and safety of long-acting pasireotide and everolimus, administered alone or in combination, in patients with advanced carcinoids of the lung or thymus. LUNA is the first prospective, randomised clinical trial to focus exclusively on this specific patient population.

Methods

Study design and participants

LUNA was a prospective, single-stage, multicentre, randomised, open-label, phase 2 trial conducted at 36 centres across nine countries (appendix, p 1). The study comprised a 12-month core study period, followed by an extension phase that continued until all patients had progressed. Adult patients (aged >18 years) with pathologically confirmed advanced (unresectable or metastatic), well-differentiated, TC or AC of the lung or thymus were eligible. Histopathologic classification was determined using the WHO 2004 classification of tumours of the lung, pleura, thymus, and heart;[15] cytology by endobronchial ultrasound-guided fine needle aspiration alone was not sufficient for classification. Patients of any treatment line (naive or pre-treated) and progressive within 12 months according to

Response Evaluation Criteria In Solid Tumours, version 1·1 (RECIST v1·1) were eligible. Additional key inclusion criteria included: measurable disease according to computed tomography (CT) scan or magnetic resonance imaging (MRI) as defined by RECIST v1·1; WHO performance status ≤2; and adequate bone marrow, liver, and kidney function. Due to the potential for other SSA or mTOR inhibitors to interfere with the antitumour efficacy observed in this study, patients were ineligible if they had any of the following: severe functional disease (ie, carcinoid syndrome) requiring symptomatic treatment with SSA (judgement made by study clinicians); previous treatment with any long-acting SSA within 1 month of randomisation; or treatment with mTOR inhibitors (sirolimus, temsirolimus, or everolimus). Patients were also ineligible if they had any of the following: radiotherapy within 4 weeks of randomisation; Cushing's syndrome requiring treatment within 3 months; radioligand therapy (peptide receptor radionuclide therapy) within 6 months of randomisation; hepatic artery embolisation, cryoablation, or radiofrequency ablation of hepatic metastasis within 3 months of randomisation; participation in a clinical trial testing an investigational drug within 4 weeks or 5 half-lives (whichever is longer) of randomisation; uncontrolled diabetes mellitus (haemoglobin A1C of at least 8%) despite adequate therapy; presence of active or suspected acute or chronic uncontrolled infection; or signs of recurrence of previous or concomitant malignancies within the last 3 years or requiring active treatment. The estimated life expectancy of eligible patients was 24-40 months.[1,16]

The study was conducted in accordance with Good Clinical Practice, the ethical principles of the Declaration of Helsinki, and local regulations. Institutional review boards, independent ethics committee, and the research ethics board reviewed and approved the study and all amendments to the protocol. All patients provided written informed consent. Further details of the protocol are available on clinicaltrials.gov.

Randomisation and masking

Patients were randomised (1:1:1) to receive long-acting pasireotide monotherapy (P arm), everolimus monotherapy (E arm), or everolimus and long-acting pasireotide in combination

(EP arm). The planned number of patients enrolled was 120, with 40 patients randomised to each treatment arm. At the screening visit, the investigator or their designee assigned a unique number to each patient being considered for the study. Once the eligibility of each patient was confirmed, the investigator or their designee registered the patient using an interactive voice recognition system into one of the three treatment arms. The randomisation allocation sequence was generated by an external company (Perceptive Informatics, Nottingham, UK). Patients were stratified by TC *vs* AC according to the WHO classification and line of study treatment (first line of systemic medical treatment *vs* other). Patients and investigators were not masked to treatment allocation.

Procedures

Patients randomised to the P arm received long-acting pasireotide at a dose of 60 mg intramuscularly (IM) every 28 days; patients randomised to the E arm received everolimus at a dose of 10 mg taken orally (PO) once daily (QD); and patients randomised to the EP arm received everolimus and long-acting pasireotide at a dose of 10 mg everolimus PO QD and 60 mg long-acting pasireotide IM every 28 days. Dose reductions and treatment interruptions for less than 56 days for long-acting pasireotide and less than 28 days for everolimus were allowed for patients who did not tolerate therapy, or to manage treatment-related adverse events (AEs). Two dose reductions were allowed for everolimus: from 10 mg per day to 5 mg per day, with a subsequent reduction to 5 mg every other day. A dose reduction from 60 mg to 40 mg long-acting pasireotide every 28 days was allowed with a subsequent, but transient, reduction to 20 mg. Re-escalation to 40 mg was required within 56 days; otherwise, the patient was discontinued from study.

All patients who underwent randomisation were locally assessed for efficacy by triphasic CT or MRI every 3 months for the duration of the treatment phase (12 months) and, if the patient continued into the extension phase, every 3 months thereafter. Safety was monitored by assessing haematology (baseline and weeks 2, 4, and every 4 weeks (q4w) from weeks 8-52), coagulation (weeks 0, 4, 8, and every 8 weeks (q8w) from weeks 12-52; additionally at 3

and 7 weeks for those treated with pasireotide), biochemistry (weeks 0, 2, 4, and q4w from weeks 8-52), fasting glucose (weeks 0, 2-4, and q4w from weeks 7-52), liver function tests (weeks 0, 2, 4, and q4w from weeks 8-52; additionally at 3 and 7 weeks for those treated with pasireotide), serum lipid profile (weeks 2, 4, and q4w from weeks 8-52), thyroid function test (weeks 12, 24, and 52), urinalysis (weeks 0, 2, 4, and q4w from weeks 8-52), chromogranin-A and 5-hydroxyindoleacetic acid measurement (weeks 12, 24, 36, 48, and 52), electrocardiogram (weeks 0, 3, 8, 16, 28, 40, and 52), gallbladder assessment (only those treated with pasireotide; weeks 12, 24, 36, 48, 52), and WHO performance status and vital signs (weeks 0, 2, 4, and q4w from weeks 8-52). Adverse events were assessed continuously throughout the study and were evaluated for severity grade and duration, suspected relationship to treatment, whether a dose adjustment, interruption, or discontinuation was required, outcome, and whether concomitant medication was required. Study treatment continued for 12 months or until disease progression, intolerable toxicity, start of new cancer therapy, withdrawal of consent, or discontinuation for any other reason. Patients who demonstrated clinical benefit, and who were not experiencing unacceptable toxicity, were allowed to continue treatment in an extension phase until disease progression, intolerable toxicity, start of new cancer therapy, withdrawal of consent, or discontinuation for any other reason. The end of the study was defined as the final study visit 2 years after the start of the last randomised patient, or when all patients had progressed (whichever came first). All patients were requested to participate in a safety follow-up 56 days after their last dose of study treatment to assess AEs.

Outcomes

The primary efficacy endpoint was the progression-free rate at month 9, defined as the proportion of patients with overall response at month 9, including complete response (CR), partial response (PR), or stable disease (SD) according to local RECIST v1·1. Patients with a missing or unknown tumour assessment at month 9, and with CR, PR, or SD at month 11 or 12, were considered as progression free at month 9. Patients with no tumour assessment

performed in the 211-294 study day period (9 month window) were classified as not assessed at month 9. Patients with progressive disease, not assessed, or unknown response at month 9 were classified as non-progression free.

Overall PFS, defined as the time from first study drug administration to tumour progression or death from any cause according to RECIST v1·1, was a secondary endpoint. Patients who did not experience a PFS event were censored at the date of the patient's last adequate tumour assessment. The probability of patients remaining event free (i.e., no objective tumour progression or death from any cause) up to the specified timepoint were obtained from the Kaplan-Meier survival estimates for all treatment groups; the Greenwood formula was used for confidence intervals of Kaplan-Meier estimates. Tumour shrinkage was evaluated according to best response per RECIST v1·1.

The safety and tolerability of long-acting pasireotide and everolimus alone or in combination was assessed by measuring the rate and severity of AEs, which were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4·0 (CTCAE grade 5 [death] was not used in this study). The relationship of AEs to treatment was assessed per investigator decision.

Statistical analysis

All randomised patients who received at least one dose of study drug constituted the full analysis set (FAS). Following the intention-to-treat principle, patients were analysed according to the treatment and stratum they were assigned to at randomisation. Primary efficacy analyses were assessed on the FAS. The safety set included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

For the primary endpoint, a Fleming single-stage design was employed for each treatment arm, where p_0 (the null hypothesis) represents the highest proportion of patients progression free at 9 months that indicated the treatment is clearly ineffective, and p_1 (the alternative hypothesis) represented the minimum required proportion of patients who were progression

free to show that the treatment is effective. The trial tested the null hypothesis H_0 that the observed proportion of patients who were progression free, p, was less than or equal to p_0 against the alternative hypothesis H_1 that p was greater than or equal to p_1. It consisted of entering a predetermined number of patients and deciding in favour of p_0 or p_1 based on the success rate observed by using an appropriate cutoff between p_0 and p_1. If the number of responses was greater than or equal to R+1, p_0 was rejected. If the number of responses was less than or equal to R, p_1 was rejected. In this trial, p_0 and p_1 were set equal to 0·20 and 0·45, respectively, and target alpha and beta were 5% and 10%, respectively. The number of patients required per treatment arm to determine whether the proportion responding was less than or equal to p_0 or greater than or equal to p_1 was determined to be 40. If the number of responses was 13 or more, the hypothesis that $p \leq p_0$=20% was rejected with a target alpha error rate of 5% and an actual alpha error rate of 4·3%; if the number of responses was 12 or less, the hypothesis that $p \geq p_1$=45% was rejected with an actual beta error rate of 4%. No dropout percentage was considered in this calculation.

The 95% confidence interval (CI) for the progression-free rate at 9 months was computed using an exact binomial method. PFS was estimated using the Kaplan-Meier method, with a 95% CI. Tumour shrinkage data were presented as waterfall plots by treatment arm. All data were analysed using SAS version 9.4.

An independent data monitoring committee reviewed safety-related issues and provided oversight in study conduct. This study was registered with the EU Clinical Trials Register, number EudraCT 2011-002872-17, protocol CSOM230DIC03, and with ClinicalTrials.gov, number NCT01563354.

Role of the funding source

The study was designed by academic investigators and representatives of the funder (Novartis Pharma AG). The first draft of the report was prepared by PF, GG, NS, MS, KÖ, EB, and a medical writer employed by the funder. All authors vouch for the accuracy and completeness of the data and attest that the study conformed to the protocol and statistical

analysis plan. The corresponding author had full access to all data in the study and had final responsibility, along with KÖ and EB, for the decision to submit for publication.

Results

Between Aug 16, 2013, and Sept 30, 2014, a total of 124 patients with advanced, progressive, TC or AC of the lung or thymus were enrolled and randomly assigned to receive treatment with either long-acting pasireotide (P arm; n=41), everolimus (E arm; n=42), or everolimus and long-acting pasireotide (EP arm; n=41) (figure 1). The core 12-month treatment phase was completed on Dec 30, 2015. All randomised patients received at least one dose of study drug and constituted the FAS used for efficacy analyses (n=124). All patients received at least one dose of medication and had at least one post-baseline safety assessment, and therefore were all included in the safety set (n=124). Baseline demographics and disease characteristics at baseline are summarised in table 1. The median age of the patients was 64 years, 62·1% (77/124) were male, the majority (98·4%; 122/124) were Caucasian and 63·7% (79/124) had an Eastern Cooperative Oncology Group performance status of 0. The vast majority (116/124; 93·5%) of patients presented with primary tumours in the lung, around two-thirds (85/124; 68·5%) of patients presented with AC, and 77·4% (96/124) had non-functional disease. The most common metastatic sites were the liver (95/124; 76·6%), bone (69/124; 55·6%), lung (48/124; 38·7%), cervical/thoracic lymph nodes (38/124; 30·6%), and pleura (10/124; 8·1%). Characteristics were generally well balanced across treatment arms, with the exception of bone metastases, which were more frequently reported in the long-acting pasireotide treatment arm.

Prior therapies are presented in the appendix (p 2). Approximately a third (40/124; 32·3%) of patients were treated for advanced disease in the first line. Prior SSA use was well balanced among the treatment groups; 48·4% (60/124) of patients had received prior SSAs, with the length of SSA exposure ranging from less than 6 months to 5 or more years. Prior antineoplastic therapy was more frequently reported in the EP arm.

During the core 12-month treatment phase, 65·3% (81/124) of randomised patients discontinued treatment, mainly due to AEs (n=33) and disease progression (n=33) (figure 1). In the P arm, 68·3% (28/41) of patients discontinued treatment, with 18/28 due to disease progression and 5/28 due to AEs as the primary reason. In the E arm, 64·3% (27/42) discontinued treatment, with 15/27 due to AEs as the primary reason and 7/27 due to disease progression. In the EP arm, 63·4% (26/41) discontinued treatment, with 13/26 due to AEs as the primary reason and 8/26 due to disease progression. Of the 43 patients who completed the core phase of the study, 41 entered the extension phase (figure 1).

The proportions of patients with overall lesion assessment at month 9 being CR, PR, or SD according to RECIST v1·1 (i.e., progression-free) in the P arm, E arm, or EP arm were 16/41 (39·0%; 95% CI 24·2–55·5), 14/42 (33·3%; 95% CI 19·6–49·5), and 24/41 (58·5%; 95% CI 42·1–73·7), respectively (table 2). As noted in table 2, the minimum number of patients required to be progression free at month 9 in order to consider the treatment as effective was 13 patients for the P arm, 14 patients for the E arm, and 13 patients for the EP arm. Overall lesion response at month 9 was mostly SD among the 3 treatment groups; 34·1% (14/41) in the P arm, 31·0% (13/42) in the E arm, and 48·8% (20/41) in the EP arm. Progressive disease at 9 months was observed in 7/41 (17·1%), 1/42 (2·4%), and 0/41 (0%) patients in the P arm, E arm, or EP arm, respectively. Patients with progressive disease, not assessed, or unknown response at month 9 were classified as non-progression free. The proportions of patients with no tumour assessment performed at 9 months were classified as 'not assessed' but were not excluded from the analysis; 18/41 (43·9%), 25/42 (59·5%), and 17/41 (41·5%) in the P arm, E arm, or EP arm, respectively. This was mostly due to AEs leading to withdrawal in 3/41 (7·3%), 15/42 (35·7%), and 10/41 (24·4%) of those in the P arm, E arm, and EP arm, respectively, or due to disease progression prior to month 9 tumour assessment in 10/41 (24·4%), 4/42 (9·5%), and 2/41 (4·9%), respectively. Overall, 11/36 (30·6%) patients in the P arm, 16/33 (48·5%) in the E arm, and 24/33 (72·7%) in the EP arm experienced some degree of tumour shrinkage (figure 2).

The median PFS by investigator-assessed radiological review was 8·51 months (95% CI 5·68–not estimable [NE]), 12·48 months (95% CI 5·55–NE), and 11·79 months (95% CI 11·10–NE) in the P arm, E arm, and EP arm, respectively (figure 3). The probability of patients remaining event-free (i.e., no objective tumour progression or death from any cause) until 9 months (table 3) was 49·6% (95% CI 31·9–65·1) for those in the P arm, 56·9% (95% CI 38·1–71·9) in the E arm, and 79·2% (95% CI 61·1–89·5) in the EP arm.

During the core treatment phase, median patient exposures to long-acting pasireotide in the P arm and everolimus in the E arm were 38·9 weeks (interquartile range [IQR] 20·00–52·14) and 26·9 weeks (IQR 10·43–52·00), respectively. In the EP arm, median patient exposure to long-acting pasireotide was 48·4 weeks (IQR 12·57–52·14) and 49·0 weeks (IQR 12·14–52·14) to everolimus; the median exposure to both drugs combined was 49·0 weeks (IQR 12·57–52·14). The median relative dose intensity of long-acting pasireotide was 100% in both the P arm (IQR 97·1%–102·0%) and EP arm (IQR 89·2%–107·1%). The median relative dose intensity of everolimus was 93·6% (IQR 63·0%–100·0%) and 84·1% (IQR 53·6%–100·0%) in the E arm and EP arm, respectively.

Treatment interruptions or dose reductions occurred in 48·8% (20/41) of patients in the P arm, 66·7% (28/42) of patients in the E arm, 48·8% (20/41) of patients treated with long-acting pasireotide in the EP arm, and 53·7% (22/41) of patients treated with everolimus in the EP arm. The most common reasons for treatment interruptions or dose reductions were ‘as per protocol’ due to emergent safety concerns (95·0% [19/20], 25·0% [7/28], 65·0% [13/20], and 36·4% [8/22] of patients treated with long-acting pasireotide in the P arm, everolimus in the E arm, long-acting pasireotide in the EP arm, and everolimus in the EP arm, respectively) and ‘any other adverse event’ (40·0% [8/20], 82·1% [23/28], 65·0% [13/20], and 100·0% [22/22], respectively).

Grade 1/2 treatment-emergent AEs with a frequency of ≥10% in at least one treatment group are summarised in table 4. Grade 1/2 AEs were reported in all patients in all treatment arms. The most common grade 1/2 AEs, regardless of drug relationship, reported in the P arm and the EP arm were hyperglycaemia (43·9% [18/41] and 82·9% [34/41], respectively), diarrhoea

(39·0% [16/41] and 75·6% [31/41]), and weight decreased (43·9% [18/41] and 56·1% [23/41]). A higher incidence of grade 1/2 stomatitis (61·9% [26/42]) was reported for patients treated in the E arm vs the P arm, which was consistent with the established safety profile of everolimus; the incidence of grade 1/2 stomatitis was lower (31·7% [13/41]) in patients receiving combination therapy in the EP arm. The most common grade 3 treatment-emergent AEs reported in the P arm were increased gamma glutamyltransferase (12·2% [5/41]) and dyspnoea (9·8% [4/41]); in the E arm were hyperglycaemia (16·7% [7/42]) and stomatitis (9·5% [4/42]); and in the EP arm were hyperglycaemia (24·4%, [10/41]), diarrhoea (17·1%, [7/41]), and fatigue (9·8%, [4/41]) (table 4). Grade 4 treatment-emergent AEs occurred in 12·2% (5/41) of those in the P arm, 19·0% (8/42) in the E arm, and 9·8% (4/41) in the EP arm. A complete listing of all grade 3 and 4 treatment-emergent AEs is provided in the appendix (p 3).

The most common grade 1/2 AEs with a suspected relationship to treatment with long-acting pasireotide (P arm; EP arm) were diarrhoea (36·6% [15/41]; 22·0% [9/41]), hyperglycaemia (41·5% [17/41]; 7·3% [3/41]), and weight loss (19·5% [8/41]; 2·4% [1/41]); for everolimus (E arm; EP arm), they were stomatitis (61·9% [26/42]; 22·0% [9/41]) and diarrhoea (38·1% [16/42]; 22·0% [9/41]); and for the combination treatment they were hyperglycaemia (65·9% [27/41]), diarrhoea (46·3% [19/41]), and asthenia (19·5% [8/41]) (appendix, pp 8-13). A complete listing of all grade 3 and 4 AEs with a suspected relationship to treatment are provided in the appendix, pp 8-13.

Adverse events requiring study dose adjustment or interruption regardless of study treatment relationship were reported in 24·4% (10/41) of patients in the P arm, 52·4% (22/42) of patients in the E arm, and 61·0% (25/41) patients in the EP arm. Treatment-emergent serious AEs occurred in 39·0% (16/41) of patients in the P arm, 42·9% (18/42) of patients in the E arm, and 31·7% (13/41) of patients in the EP arm. Eleven patients died during the core 12-month treatment phase or up to 56 days after the last study treatment exposure date: 2/41 (4·9%) in the P arm, 6/42 (14·3%) in the E arm, and 3/41 (7·3%) in the EP arm. In the P arm, one patient died of disease progression and one died due to pneumonia. Neither death

was suspected to be related with pasireotide treatment. In the E arm, five deaths were not considered related to study drug: two due to disease progression and one each due to respiratory failure, pneumonia, and cardiac failure. One patient died of acute kidney injury associated with diarrhoea, which was considered related to everolimus therapy. In the EP arm, one death due to disease progression was not considered related to study drug. One patient died from diarrhoea and urinary sepsis which was suspected to be associated with everolimus and one patient died due to acute renal failure and also respiratory failure. For the latter patient, acute renal failure was not suspected to be related with study treatment, while respiratory failure was suspected to be related to everolimus.

Discussion

To our knowledge, LUNA is the first prospective, randomised clinical trial dedicated specifically to patients with advanced carcinoid tumours of the lung and thymus, demonstrating the feasibility of conducting clinical trials in this rare NET subpopulation. Results of the current phase 2 study suggest that long-acting pasireotide, everolimus, or combination therapy with both agents is associated with antitumour activity, as the null hypothesis was rejected for all three treatment arms. The 2-year extension phase of this trial is ongoing, with all patients who benefited from treatment at 12 months; mature data on PFS will be available when the extension phase of the trial is completed.

To date, the clinical investigation of exclusive pulmonary NET patient populations have been limited to small retrospective studies.[9,17-19] Subgroup analyses of mixed NET populations have also been conducted, with everolimus being the most studied drug in the setting of lung NETs.[8,20] In the current study, the patient population enrolled had relatively aggressive tumours; 68·5% of patients were classified as having AC, 67·7% were post first-line therapy, and 100% had documented disease progression within the previous year according to RECIST v1·1 criteria. Functional disease was present in 22·6% (28/124) of patients; this is an interesting additional finding as this is the first and largest prospective clinical trial

379 conducted exclusively in this patient population. A recent retrospective US population-based
380 analysis of patients diagnosed with well-differentiated grade 1 or 2 NET of the lung or other
381 respiratory organ between 2000-2011 (from the Surveillance, Epidemiology, and End
382 Results-Medicare database) revealed that carcinoid syndrome was present in 8·0%
383 (83/1044), 7·9% (19/239), and 15·3% (30/196) of localised, regional, and distant stage
384 disease.[21] Previous estimates of carcinoid syndrome in lung carcinoids have been much
385 lower (2%) and carcinoid syndrome is rare in thymic carcinoids.[22] Other functional
386 syndromes observed in thoracic carcinoids include Cushing syndrome, caused by ectopic
387 adrenocorticotropic hormone production, with an incidence of 2% in bronchial carcinoids and
388 up to 50% in thymic carcinoids, and acromegaly, which occurs rarely in both bronchial and
389 thymic carcinoids and is caused by ectopic growth hormone–releasing hormone.[22]
390 The 'conservative' 9-month timepoint was selected to assess the primary endpoint in this
391 study in order to minimise bias; this timepoint was considered to be acceptable based on the
392 clinical experience and known biological behaviour of lung NET at the time of study design.
393 In addition, uncertainties surrounding the management of pulmonary NET with these novel
394 agents, along with the unknown rate and evolution of functioning syndromes in this NET
395 subpopulation, were taken into account.
396 Treatment guidelines as of 2016 recommend everolimus as a first-line therapy for
397 progressive, advanced lung carcinoids.[4] The efficacy of everolimus in non-functional well-
398 differentiated NET of GI and lung origin was recently established in the RADIANT-4 trial.[7] A
399 subgroup analysis of patients with lung NET in RADIANT-4 showed a median PFS of 9·2
400 months with everolimus *vs* 3·6 months with placebo by central review, and a median PFS of
401 13·8 months with everolimus *vs* 3·5 months with placebo by investigator assessment.[8] In
402 addition, an exploratory analysis of the RADIANT-2 trial reported a median PFS of 13·6
403 months with everolimus and long-acting octreotide *vs* 5·6 months with long-acting octreotide
404 in patients with low or intermediate grade lung NET and carcinoid syndrome.[20] In the current
405 study, the median PFS of patients with functional or non-functional thoracic carcinoids
406 treated with everolimus alone and in combination with long-acting pasireotide was 12·5 and

11·8 months, respectively. This confirms the efficacy of everolimus that was demonstrated in the lung subgroup of the RADIANT-4 study.

Long-acting pasireotide has previously been investigated in clinical trials of patients with advanced, grade 1 or 2 NET, primarily in patients with primary tumours of the small intestine or pancreas, with a median PFS of 11·0–11·8 months reported for monotherapy.[12,13,23] In this study of patients with lung or thymic carcinoids, the median PFS of patients treated with long-acting pasireotide monotherapy was 8·5 months and the combination of everolimus and long-acting pasireotide was associated with a median PFS of 11·8 months. In the phase 2 COOPERATE-2 study, the addition of long-acting pasireotide to everolimus did not significantly improve median PFS *vs* everolimus in patients with non-functional pancreatic NET (16·8 vs 16·6 months, respectively; hazard ratio 0·99; 95% CI 0·6–1·5, p=0·49). However, combined treatment with everolimus and long-acting pasireotide demonstrated a trend toward a higher objective response rate—20·3%, vs 6·2% treated with everolimus monotherapy.[23]

The most common grade 1/2 AEs with a suspected relationship to treatment with long-acting pasireotide monotherapy or everolimus and long-acting pasireotide were diarrhoea (36·6% and 46·3%) and hyperglycaemia (41·5% and 65·9%). Most AEs were manageable through dose modification or interruption, with no new safety signals being reported in this study. The safety profiles observed in the monotherapy and the combination treatment arms were similar to that of previous studies,[8,11,24] indicating the feasibility of combination therapy with long-acting pasireotide and everolimus. Although discontinuations due to AEs and dose modifications were frequently reported, the median relative dose intensity remained high in all treatment groups. Hyperglycaemia has been observed as an AE in other studies with everolimus and pasireotide monotherapy, albeit at lower frequencies.[8,11] The high levels of hyperglycaemia reported in a phase 1 study[24] and in our study of everolimus and long-acting pasireotide in combination, appears to indicate an additive effect, highlighting the importance of close monitoring of fasting serum glucose. Achievement of optimal glycaemic control before initiation of therapy is required.[25] Hyperglycaemia is, however, manageable in the

context of a multidisciplinary centre, thus avoiding the need for treatment discontinuation, particularly in patients responding to treatment.[25] The everolimus dose may be reduced to 5 mg/day or interrupted until the fasting serum glucose has normalized, as per the protocol used in this study; however, considering the high number of treatment interruptions (52·4%) or dose reductions (61·1%) due to AEs in this study, it is difficult to state definitively whether hyperglycaemia will be manageable in all patients without exploratory analyses of the dose-exposure relationship. A limited number of deaths in this study were classified as drug-related per investigator review, but based on the analysis of causes of death, close observation is recommended for patients undergoing treatment for pulmonary function, as well as cardiac and kidney function, especially in case of dyspnoea with normal lung imaging or associated diarrhoea or diabetes.

This study has a number of limitations. The small size and lack of a placebo control arm limits the comparisons, and the conclusions of the study should be considered exploratory. No subanalyses of efficacy by primary site (lung vs thymus), carcinoid subtype (TC vs AC), Ki-67 index (high vs low), or median time from radiological disease progression at baseline were performed, which may have provided useful information in this rarely studied population. However, these subanalyses were not appropriate, given the small sample size and imbalance between groups (eg, only 8 patients with thymic carcinoids), or were not possible due to the lack of recorded time from disease progression at baseline or Ki-67 indices for each patient. Ki-67 indices were not reported for each patient because the pathologic assessment in this study was based on the 2004 WHO classification of tumours of the lung and thymus, which did not include Ki-67.[15] It would have been unethical to select patients based on Ki-67, since the 2004 WHO classification was the only clinical method recognized by regulatory authorities for the classification of thoracic NET at the time of enrolment. Another limitation of the study is that only 43/124 (34·7%) patients completed the 12-month core treatment phase. However, the completion and discontinuation rates were consistent across the treatment groups (figure 1). For the primary endpoint, a single-stage

Fleming design was employed for each treatment arm; this design has no provision for early termination if the observed response rate is unacceptably low. Furthermore, for the primary endpoint (progression-free rate at 9 months), ideally a Kaplan-Meier analysis should be employed rather than the responder and non-responder analysis that was performed in this study. In this study, it was not appropriate to alter the primary endpoint to a Kaplan-Meier analysis after patients had been recruited because the sample size was determined based on the responder and non-responder analysis. The handling of missing data, such as patients with a missing tumour assessment at 9 months being classified as non–progression free, may have led to an underestimation of tumour response rates included in the analysis of the primary endpoint. However, exclusion of these patients from the primary endpoint analysis would have led to bias in the results by selecting patients who likely had improved outcomes. In addition, the lack of blinded central radiological review of tumour response may have introduced bias in the assessment of response.

In summary, the treatment of patients with advanced carcinoid tumours of the lung and thymus with long-acting pasireotide alone or in combination with everolimus showed preliminary evidence of efficacy and an acceptable safety profile. Further studies would be needed to confirm the antitumour efficacy of combination therapy consisting of an SSA with everolimus in this subset of patients with NET. Future research may improve prognostic stratification, identify predictors of response, and determine the anti-secretory impact of the treatment combination of an SSA with everolimus in the thoracic NET setting. While beyond the scope of this study, the process toward personalized and precision medicine will be a priority over the next two decades.

Research in context

Evidence before this study

We searched PubMed/MEDLINE for published reports on clinical trials in lung and thymic neuroendocrine tumours (NET), with ‘lung’, ‘thymic’ or ‘thymus’, ‘NET’, and ‘carcinoid’ as our primary search terms, limiting our findings to include studies evaluating the treatment of lung/thymic NET or carcinoid tumours. We did not limit our search by date, but only searched for articles published in English. We identified no prospective clinical trials specifically investigating the treatment of advanced lung/thymic NET or carcinoids. However, prospective studies (e.g., RADIANT-2 and RADIANT-4) in mixed NET populations and small retrospective studies focusing on lung/thymic NET were identified. A subgroup analysis of the RADIANT-4 trial was presented at the ENETS 13th Annual Conference in 2016, and reported a clinically meaningful improvement in median progression-free survival (PFS) following treatment with everolimus in patients with advanced, progressive, well-differentiated, non-functional lung NET. The findings of a subgroup analysis of RADIANT-2 also reported an improvement in median PFS following treatment with everolimus plus octreotide long-acting repeatable. These exploratory subgroup analyses highlight the potential benefit of combination therapy with a somatostatin analogue (SSA) and everolimus.

Added value of this study

Preclinical data suggest that the SSA pasireotide may be associated with more potent antiproliferative effects than octreotide, thus providing the rationale for combining long-acting pasireotide with everolimus. To our knowledge, LUNA is the first prospective, randomised, phase 2 clinical trial investigating an exclusive population of patients with advanced carcinoid tumours of the lung and thymus. Patients were randomised to treatment with long-acting pasireotide, everolimus, or a combination of the two agents. Our study indicates that long-acting pasireotide with or without everolimus provides preliminary evidence of antitumour activity, may improve PFS, and has an acceptable safety profile. Following confirmation of superiority in phase 3 testing, combination of an SSA with everolimus may be

useful in the treatment of patients with advanced lung/thymic carcinoid tumours and demonstrates the feasibility of conducting clinical trials in this rare NET subpopulation.

Implications of all the available evidence

Prospective clinical data on lung/thymic carcinoid tumours are limited. The results of this randomised trial indicate that combination therapy of an SSA with everolimus would need further clinical investigation in this rare subset of patients with NET. Additional well-designed, adequately powered, randomised controlled clinical trials are required to expand on these findings and establish the efficacy and safety of this treatment strategy.

Contributors

MS was the Clinical Trial Head. PF, GG, MS, KÖ, and EB were responsible for designing the study. GG was responsible for trial management. WM, VD, CL-B, CG, HG, JDC, NR, GG, KÖ, and EB participated in patient recruitment/inclusion. MPB, TM, JM, CDC, HL, AB, WB, CG, HG, MT, JDC, and GG participated in data collection/acquisition. PF, WM, JM, HL, GG, NS, MS, and EB performed the data analyses. PF, MPB, TM, WM, WB, VM, GG, NS, MS, and EB interpreted the data. PF, MS, and EB conducted the literature search. GG was the trial's statistician. KÖ performed a statistical evaluation. PF, WM, JM, WB, VM, NR, GG, MS, KÖ, and EB wrote the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

PF reports other fees from Novartis, during the conduct of the study; other fees from Novartis, Merck, Ipsen, Pfizer, and Lexicon, outside the submitted work. TM reports personal fees from Bristol-Myers Squibb, Bayer, Eisai, Ipsen, and Merck, outside the submitted work. HL reports personal fees from Novartis, during the conduct of the study; personal fees and non-financial support from Bristol-Myers Squibb, Lilly, Pierre Fabre Oncologie, Pfizer, AstraZeneca, and Boehringer Ingelheim, and non-financial support from MSD, Roche, and Amgen, outside the submitted work. AB reports personal fees from Novartis and Ipsen,

outside the submitted work. HG reports grants from Ipsen, Novartis, AbbVie, and Intercept Pharma, outside the submitted work. NR reports grants, personal fees, and non-financial support from Novartis and Ipsen, outside the submitted work. GG and MS were Novartis Farma S.p.A. employees during the conduct of the study. KÖ reports grants and other fees from Novartis, and other fees from Ipsen, outside the submitted work. EB reports grants, personal fees and non-financial support from Novartis, Ipsen, and Pfizer, and grants and non-financial support from AAA, during the conduct of the study; grants, personal fees and non-financial support from Novartis and Ipsen and non-financial support from AAA, outside the submitted work. All other authors declare no competing interests.

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636 ***Table 1:*** **Baseline demographics and disease characteristics (full analysis set)**

	P arm (n=41)	**E arm (n=42)**	**EP arm (n=41)**	**All patients (N=124)**
Age, years				
<65	21 (51·2%)	18 (42·9%)	24 (58·5%)	63 (50·8%)
≥65	20 (48·8%)	24 (57·1%)	17 (41·5%)	61 (49·2%)
Median	64	66	61	64
IQR	51–69	61–73	56–69	56-70
Sex				
Female	15 (36·6%)	19 (45·2%)	13 (31·7%)	47 (37·9%)
Male	26 (63·4%)	23 (54·8%)	28 (68·3%)	77 (62·1%)
Race				
Caucasian	40 (97·6%)	42 (100%)	40 (97·6%)	122 (98·4%)
Black/African American	1 (2·4%)	0	0	1 (0·8%)
Asian	0	0	1 (2·4%)	1 (0·8%)
Other	0	0	0	0
ECOG performance status				
0	28 (68·3%)	24 (57·1%)	27 (65·9%)	79 (63·7%)
1	11 (26·8%)	17 (40·5%)	14 (34·1%)	42 (33·9%)
2	2 (4·9%)	1 (2·4%)	0	3 (2·4%)
Histological grade*				
Typical	14 (34·1%)	12 (28·6%)	13 (31·7%)	39 (31·5%)
Atypical	27 (65·9%)	30 (71·4%)	28 (68·3%)	85 (68·5%)
Primary site of cancer				
Lung	38 (92·7%)	39 (92·9%)	39 (95·1%)	116 (93·5%)
Thymus	3 (7·3%)	3 (7·1%)	2 (4·9%)	8 (6·5%)
Functional status of tumour				
Functional	12 (29·3%)	7 (16·7%)	9 (22·0%)	28 (22·6%)
Non-functional	29 (70·7%)	35 (83·3%)	32 (78·0%)	96 (77·4%)
Current metastatic extent†				
Liver	30 (73·2%)	34 (81·0%)	31 (75·6%)	95 (76·6%)
Bone	32 (78·0%)	15 (35·7%)	22 (53·7%)	69 (55·6%)

Lung	15 (36·6%)	13 (31·1%)	20 (48·8%)	48 (38·7%)
Cervical/thoracic lymph nodes	14 (34·1%)	15 (35·7%)	9 (22·0%)	38 (30·6%)
Pleura	2 (4·9%)	2 (4·8%)	6 (14·6%)	10 (8·1%)
Other‡	28 (68·3%)	24 (57·1%)	27 (65·8%)	79 (63·7%)

637

638 Data are n (%) unless otherwise stated. P arm=long-acting pasireotide treatment arm. E
639 arm=everolimus treatment arm. EP arm=everolimus and long-acting pasireotide treatment
640 arm. ECOG=Eastern Cooperative Oncology Group. IQR=interquartile range. *Reconciled
641 rates. During the randomisation process, seven patients were misstratified by the
642 investigational sites with respect to histologic grade. †Including individual sites with more
643 than 10% involvement in at least one treatment group. ‡Including skin, thyroid, kidney,
644 adrenal glands, testis, ovary, breast, ascites (malignant), peritoneum, para-aortic abdominal
645 lymph nodes, pancreas, spleen, brain, bone marrow, abdomen lymph node, paravertebral
646 lymph node, subcutaneous lesions, supraclavicular lymph nodes, mediastinum, lung nodes,
647 left supraclavicular adenopathy, right retrocrural lymph node, or soft tissue on anterior
648 abdominal wall.

Table 2: **Proportion of patients progression-free at month 9 (full analysis set)**

	P arm (n=41)		**E arm (n=42)**		**EP arm (n=41)**	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Overall lesion response at month 9*						
CR	0	0·0%–8·6%	0	0·0%–8·4%	0	0·0%–8·6%
PR	1 (2·4%)	0·1%–12·9%	1 (2·4%)	0·1%–12·6%	1 (2·4%)	0·1%–12·9%
SD	14 (34·1%)	20·1%–50·6%	13 (31·0%)	17·6%–47·1%	20 (48·8%)	32·9%–64·9%
PD	7 (17·1%)		1 (2·4%)		0	
Unknown†	1 (2·4%)		2 (4·8%)		3 (7·3%)	
Not assessed‡	18 (43·9%)		25 (59·5%)		17 (41·5%)	
Discontinued before Month 9	20 (48·8%)		24 (57·1%)		16 (39·0%)	
Progression-free rate at month 9§	16 (39·0%)	24·2%–55·5%	14 (33·3%)	19·6%–49·5%	24 (58·5%)	42·1%–73·7%
Minimum number of progression-free patients to reject H_0‖	13		14		13	

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm. EP arm=everolimus and long-acting pasireotide treatment arm. CI=confidence interval. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *Overall lesion response at month 9 is the investigator-reported overall lesion response at the week 36 visit. The 95% CI for the responses are computed using an exact binomial method. †If progression is not documented and one or more lesions have not been assessed or have been assessed using a different method from baseline, then the overall lesion response at month 9 is ‘unknown’. ‡If a patient does not have any tumour assessments made in the study day 211-294 window, then the overall lesion response at month 9 is 'not assessed'. §The progression-free rate at month 9 is defined as the proportion of patients with overall lesion assessment at month 9 being CR, PR, or SD according to Response Evaluation Criteria in Solid Tumours, version 1·1. Patients with missing or unknown month 9 assessment and with CR, PR, or SD at any of the following assessments at month 11 or 12 are considered as progression free at month 9. ‖H_0: a progression-free rate ≤20% is the null hypothesis on the progression-free rates at month 9. The minimum number of progression-free patients to reject H_0 is calculated according to the Fleming single-stage design.

Table 3: **Progression-free survival per investigator radiological review (full analysis set)**

	P arm (n=41)	**E arm (n=42)**	**EP arm (n=41)**
Patients, n (%)			
With events	20 (48·8%)	17 (40·5%)	14 (34·1%)
With censorings	21 (51·2%)	25 (59·5%)	27 (65·9%)
Censored at day 1	1 (2·4%)	5 (11·9%)	5 (12·2%)
PFS, months, median (95% CI)	8·5 (5·7–NE)	12·5 (5·6–NE)	11·8 (11·1–NE)
Event-free probability estimate,* % (95% CI)			
3-month	83·6% (67·1%–92·3%)	91·2% (75·1%–97·1%)	88·6% (72·4%–95·5%)
6-month	68·2% (49·8%–81·1%)	63·5% (44·7%–77·4%)	85·5% (68·6%–93·7%)
9-month	49·6% (31·9%–65·1%)	56·9% (38·1%–71·9%)	79·2% (61·1%–89·5%)
12-month	35·9% (18·3%–53·9%)	50·2% (31·9%–66·0%)	39·4% (17·0%–61·2%)

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm. EP arm=everolimus and long-acting pasireotide treatment arm. PFS=progression-free survival. CI=confidence interval. NE=not estimable; *Percentage event-free probability estimate is the estimated probability that a patient will remain without objective tumour progression or death from any cause up to the specified timepoint. These estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; the Greenwood formula is used for confidence intervals of Kaplan-Meier estimates.

Table 4: **Treatment-emergent adverse events, regardless of study drug relationship, by preferred term and treatment (safety set)**

	P arm (n=41)			**E arm (n=42)**			**EP arm (n=41)**		
Preferred term*	**Grade 1 or 2, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**	**Grade 1 or 2, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**	**Grade 1 or 2, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**
Total	41 (100·0%)	23 (56·1%)	5 (12·2%)	42 (100·0%)	29 (69·0%)	8 (19·0%)	41 (100·0%)	33 (80·5%)	4 (9·8%)
Hyperglycaemia	18 (43·9%)	3 (7·3%)	0	12 (28·6%)	7 (16·7%)	0	34 (82·9%)	10 (24·4%)	0
Diarrhoea	16 (39·0%)	3 (7·3%)	1 (2·4%)	18 (42·9%)	2 (4·8%)	1 (2·4%)	31 (75·6%)	7 (17·1%)	1 (2·4%)
Stomatitis	2 (4·9%)	0	0	26 (61·9%)	4 (9·5%)	0	13 (31·7%)	2 (4·9%)	0
Weight decreased	18 (43·9%)	0	0	17 (40·5%)	1 (2·4%)	0	23 (56·1%)	3 (7·3%)	0
Asthenia	10 (24·4%)	0	0	12 (28·6%)	1 (2·4%)	0	15 (36·6%)	1 (2·4%)	0
Abdominal pain	13 (31·7%)	1 (2·4%)	0	4 (9·5%)	0	0	5 (12·2%)	0	0
Decreased appetite	10 (24·4%)	0	0	13 (31·0%)	2 (4·8%)	0	12 (29·3%)	2 (4·9%)	0
Cough	6 (14·6%)	0	0	12 (28·6%)	0	0	11 (26·8%)	0	0
Oedema peripheral	7 (17·1%)	0	0	12 (28·6%)	1 (2·4%)	0	10 (24·4%)	1 (2·4%)	0

Anaemia	8 (19·5%)	3 (7·3%)	0	12 (28·6%)	1 (2·4%)	0	8 (19·5%)	2 (4·9%)	0
Dyspnoea	6 (14·6%)	4 (9·8%)	1 (2·4%)	12 (28·6%)	2 (4·8%)	0	3 (7·3%)	2 (4·9%)	0
Rash	1 (2·4%)	0	0	11 (26·2%)	3 (7·1%)	0	5 (12·2%)	0	0
Nausea	10 (24·4%)	0	0	10 (23·8%)	1 (2·4%)	0	8 (19·5%)	0	0
Fatigue	6 (14·6%)	1 (2·4%)	0	7 (16·7%)	1 (2·4%)	0	10 (24·4%)	4 (9·8%)	0
Constipation	9 (22·0%)	0	0	6 (14·3%)	1 (2·4%)	0	0	0	0
Thrombocytopaenia	0	0	0	9 (21·4%)	1 (2·4%)	0	7 (17·1%)	0	0
Pyrexia	7 (17·1%)	0	0	7 (16·7%)	1 (2·4%)	0	6 (14·6%)	0	0
Headache	7 (17·1%)	0	0	5 (11·9%)	0	0	6 (14·6%)	0	0
Back pain	7 (17·1%)	1 (2·4%)	1 (2·4%)	6 (14·3%)	0	0	4 (9·8%)	0	0
Diabetes mellitus	7 (17·1%)	3 (7·3%)	0	3 (7·1%)	0	0	5 (12·2%)	3 (7·3%)	0
Blood alkaline phosphatase increased	7 (17·1%)	1 (2·4%)	0	2 (4·8%)	1 (2·4%)	0	2 (4·9%)	1 (2·4%)	0
Dysgeusia	4 (9·8%)	0	0	4 (9·5%)	0	0	7 (17·1%)	0	0
Pruritus	2 (4·9%)	0	0	2 (4·8%)	0	0	7 (17·1%)	0	0
Hypertriglyceridaemia	3 (7·3%)	0	0	7 (16·7%)	0	0	5 (12·2%)	1 (2·4%)	0

Vomiting	6 (14·6%)	0	0	4 (9·5%)	0	0	4 (9·8%)	1 (2·4%)	0
Gamma-glutamyltransferase increased	6 (14·6%)	5 (12·2%)	1 (2·4%)	2 (4·8%)	2 (4·8%)	1 (2·4%)	2 (4·9%)	3 (7·3%)	0
Productive cough	0	0	0	3 (7·1%)	0	0	6 (14·6%)	0	0
Chest pain	3 (7·3%)	1 (2·4%)	0	6 (14·3%)	0	0	4 (9·8%)	1 (2·4%)	0
Hypercholesterolaemia	1 (2·4%)	0	0	6 (14·3%)	0	0	5 (12·2%)	0	0
Urinary tract infection	3 (7·3%)	2 (4·9%)	0	2 (4·8%)	0	0	5 (12·2%)	0	0
Hypophosphataemia	1 (2·4%)	0	0	2 (4·8%)	2 (4·8%)	0	5 (12·2%)	1 (2·4%)	0
Mouth ulceration	0	0	0	2 (4·8%)	1 (2·4%)	0	5 (12·2%)	1 (2·4%)	0
Epistaxis	0	0	0	5 (11·9%)	0	0	2 (4·9%)	0	0
Abdominal pain upper	4 (9·8%)	0	0	2 (4·8%)	0	0	3 (7·3%)	0	0
Hypomagnesaemia	4 (9·8%)	0	0	2 (4·8%)	0	0	3 (7·3%)	0	0
Dizziness	4 (9·8%)	0	0	2 (4·8%)	0	0	2 (4·9%)	0	0
Musculoskeletal pain	4 (9·8%)	0	0	1 (2·4%)	0	0	2 (4·9%)	0	0
Musculoskeletal chest pain	4 (9·8%)	0	0	0	0	0	2 (4·9%)	0	0
Muscle spasms	4 (9·8%)	0	0	2 (4·8%)	0	0	1 (2·4%)	0	0

Aspartate aminotransferase increased	4 (9·8%)	0	0	2 (4·8%)	0	0	0	1 (2·4%)	0
Pneumonia	4 (9·8%)	1 (2·4%)	1 (2·4%)	1 (2·4%)	1 (2·4%)	0	0	0	0
Chills	4 (9·8%)	0	0	0	0	0	0	0	0
Hypokalaemia	1 (2·4%)	1 (2·4%)	0	3 (7·1%)	0	0	4 (9·8%)	0	0
Haemorrhoids	1 (2·4%)	0	0	1 (2·4%)	1 (2·4%)	0	4 (9·8%)	0	0
Toothache	1 (2·4%)	0	0	1 (2·4%)	0	0	4 (9·8%)	0	0
Flushing	1 (2·4%)	0	0	0	1 (2·4%)	0	4 (9·8%)	0	0
Pneumonitis	0	0	0	2 (4·8%)	2 (4·8%)	0	4 (9·8%)	2 (4·9%)	0
Dysphagia	0	0	0	4 (9·5%)	2 (4·8%)	0	0	0	0

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm; EP arm=everolimus and long-acting pasireotide treatment arm.

*Presented for those with grade 1 or 2 adverse events occurring with a frequency of ≥10% in at least one treatment group.

Figure Legends

Figure 1: **Trial profile**

*Two patients completed the core phase of the study but did not enter the extension phase: one patient in the P arm due to worsening clinical condition and one patient in the E arm by investigator decision.

Figure 2: **Best percentage change from baseline in sum of longest diameters of target lesions (full analysis set)**

Percentages are calculated based on n (number of patients included in the analysis). Contradiction refers to a percentage change in target lesion available, but contradicted by overall lesion response (progressive disease). †N is the number of randomised patients; n is the number of patients with valid postbaseline assessments, excluding patients for whom target lesion and overall response is 'unknown'.

Figure 3: **Progression-free survival per investigator radiological review (full analysis set)**